Novel Vanilloid Receptor-1 Antagonists: 1. Conformationally Restricted Analogues of *trans*-Cinnamides†

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The vanilloid receptor-1 (VR1 or TRPV1) is a member of the transient receptor potential (TRP) family of ion channels and plays a role as an integrator of multiple pain-producing stimuli. From a high-throughput screening assay, measuring calcium uptake in TRPV1-expressing cells, we identified an *N*-aryl *trans*-cinnamide (AMG9810, compound **9**) that acts as a potent TRPV1 antagonist. We have demonstrated the antihyperalgesic properties of **9** in vivo and have also reported the discovery of novel, orally bioavailable cinnamides derived from this lead. Herein, we expand our investigations and describe the synthesis and biological evaluation of a series of conformationally constrained analogues of the s-*cis* conformer of compound **9**. These investigations resulted in the identification of 4-amino- and 4-oxopyrimidine cores as suitable isosteric replacements for the *trans*-acrylamide moiety. The best examples from this series, pyrimidines **79** and **74**, were orally bioavailable and exhibited potent antagonism of both rat (IC_{50} = 4.5 and 0.6 nM, respectively) and human TRPV1 (IC_{50} = 7.4 and 3.7 nM, respectively). In addition, compound **74** was shown to be efficacious at blocking a TRPV1-mediated physiological response in vivo in the capsaicin-induced hypothermia model in rats; however, it was ineffective at preventing thermal hyperalgesia induced by complete Freund's adjuvant in rats.

Introduction

Pain is a complex perceptual experience that can have a profound impact on the quality of a person's life. From the beginning of human existence, man has endured pain in all its many forms and for centuries has sought methods to relieve it. For example, ancient civilizations recorded accounts of pain on stone tablets and illustrated various treatments, such as pressure, heat, water, and sun. Pharmaceutical intervention also dates as far back as 5000 years ago when Sumerian texts report the effect of the poppy plant (opium) for treating pain and Egyptians used willow extracts (salicylic acid) to reduce the redness and pain of inflamed joints.[1−3] In the intervening years, physicians and scientists have discovered and developed many analgesic agents that have dramatically improved peoples lives. However, despite the many years of effort to effectively manage pain, individuals still suffer from its physical and emotional consequences, and improved treatments are still needed today.[4]

Ironically, one of the most recent pain targets has also been modulated unknowingly for centuries.[5] This pain target is linked to the natural product capsaicin (**1**, Figure 1), the pungent component of chili peppers.[6] For example, early European folk medicine employed hot pepper extracts (hence capsaicin) to relieve toothaches, and native Americans were also known to have massaged chili pods onto their inflamed gums to ease dental pain.[7] Capsaicin is still in wide use today and is the active pharmacological ingredient of several topical analgesic creams used to relieve minor aches and pains of muscles and joints associated with arthritis.[8] The analgesic effects of capsaicin, when delivered topically, come from its selective action on a certain population of unmyelinated primary sensory neurons. In small doses, capsaicin stimulates these neurons and induces the release of neurotransmitters such as substance P. Upon continued stimulation, the neurotransmitters are depleted causing selective damage of the nerves and, thereby, desensitizing them toward further stimulus. The nerve damage and analgesic actions of capsaicin are preceded by an intense painful hyperalgesia caused by activation of an ion channel known as the vanilloid receptor 1 (VR1 or TRPV1), which is selectively expressed in sensory neurons.[9] TRPV1 was first cloned and characterized in late 1997 by David Julius and co-workers.[10]

Over the last several years, an elegant series of experiments, both genetic and pharmacological, have positioned TRPV1 as a key target for developing novel pain therapeutics.[11] The approach followed by several groups, including the effort conducted in our laboratories, has been directed toward identifying selective antagonists of TRPV1.[12,13] The concept is that these molecules would be able to produce analgesia without the associated nerve damage seen with capsaicin. Early support of this approach came from the study of capsaicin derivatives. For example, capsazepine (**2**), an analogue of capsaicin and the first reported antagonist of TRPV1, reversed hyperalgesia associated with inflammatory and neuropathic pain in the guinea pig.[14] Other evidence for the role of TRPV1 in pain sensation has come from studies with TRPV1 knock-out mice.[15,16] These TRPV1-deficient mice had a decreased sensitivity to painful heat in inflammatory pain models.

During the past few years, several other classes of TRPV1 antagonists structurally unrelated to the exogenous agonist capsaicin have been described in the literature, and their chemistry and pharmacology have been reviewed.[11−13,17,18] Some of the most frequently reported structural classes of TRPV1 antagonists

† Dedicated to the memory of our friend and colleague, Vassil I. Ognyanov.

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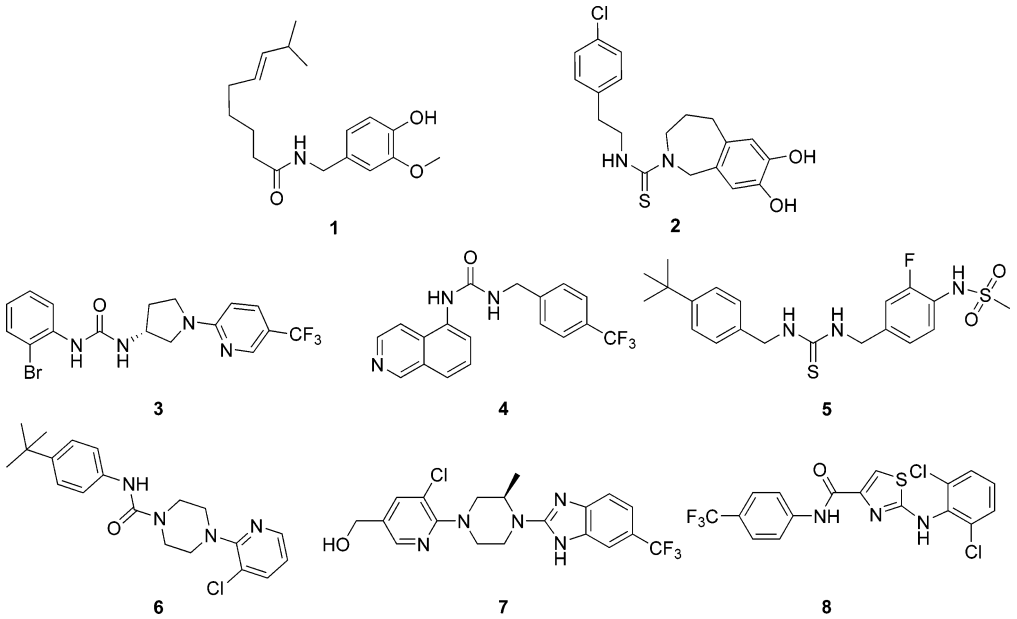


Figure 1. The TRPV1 agonist, capsaicin (**1**), and representative examples of TRPV1 antagonists (**2**−**8**).

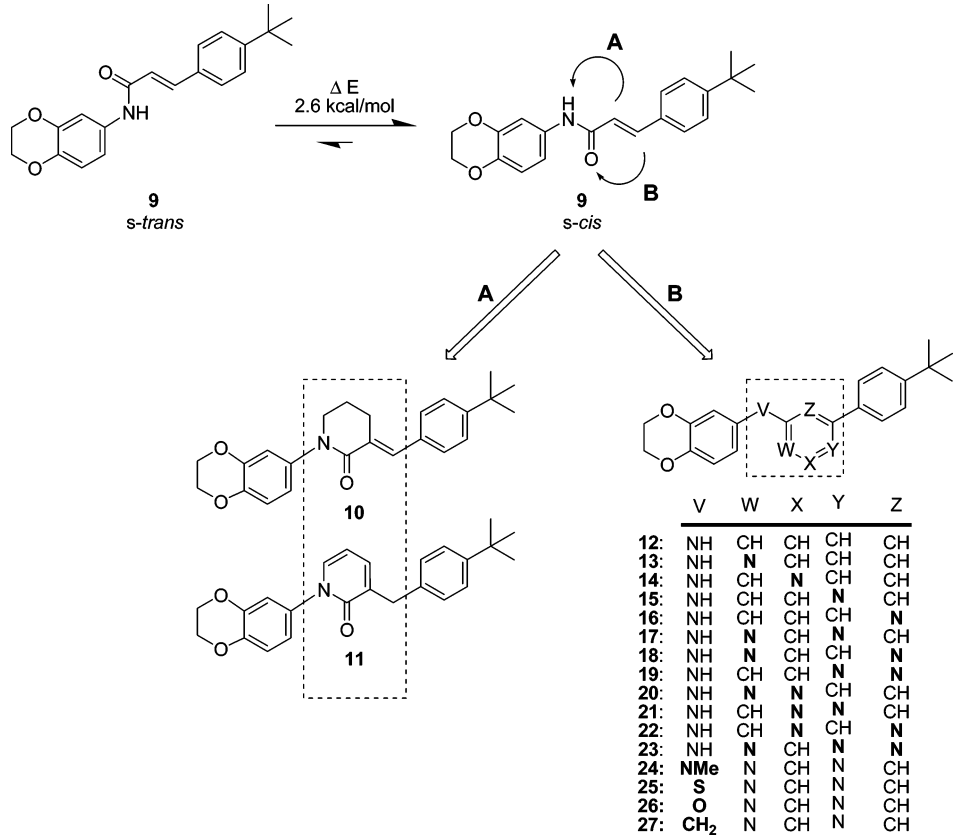


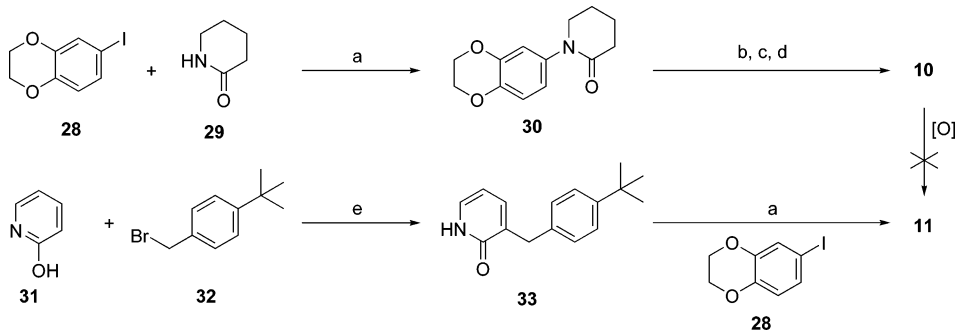
Figure 2. Conformationally restricted analogues of the proposed bioactive s-*cis* conformer of cinnamide **9**.

have been ureas,[19] thio-ureas,[20] amides,[19a,c,21−23] benzimidazoles,[24] and piperazine carboxamides,[21b,c,25] and are exemplified by compounds **3**−**8** shown in Figure 1.

In addition to these structural classes, we have recently described the discovery of a series of *N*-aryl-cinnamides as potent TRPV1 antagonists.[22,26,27] In these investigations, we identified the *N*-aryl cinnamide AMG9810 (**9**, Figure 2) as a potent, competitive antagonist that blocks the capsaicin-, heat-, and pH-induced uptake of $^{45}Ca^{2+}$ in TRPV1-expressing Chinese hamster ovary (CHO) cells.[22a] Furthermore, we demonstrated that cinnamide **9** was effective at preventing a capsaicin-induced eye wiping response in a dose-dependent manner as well as reversing thermal and mechanical hyperalgesia in a model of inflammatory pain induced by intraplantar injection of complete Freund's adjuvant (CFA) in rats.[26]

To further advance our understanding of this series, we have conducted a conformational analysis of several *N*-aryl-cinnamides to gain insights into the optimum orientation of the pharmacophoric elements required for TRPV1 inhibitory activity.[28] In these studies, we examined the conformational preferences of several *N*-aryl cinnamides using Monte Carlo searching and ab initio quantum mechanical calculations at 6-31G* level.[29]

Scheme 1[a]



[a] Reagents and conditions: (a) *N*,*N*′-dimethylethylenediamine, CuI, K_3PO_4, dioxane, 85 °C; (b) LDA, THF, 4-*t*-butylbenzaldehyde; (c) MsCl, CH_2Cl_2; (d) DBU, THF; (e) neat, 190 °C, 5 min, microwave.

We found that the s-*cis* conformation of compound **9** (Figure 2) was preferred over the s-*trans* conformation by 2.6 kcal/mol and that analogues that were better able to adopt the s-*cis* conformation were more potent TRPV1 antagonists. Based on this conformational analysis, we proposed that the bioactive conformer of the *N*-aryl cinnamide of compound **9** was s-*cis*, with a coplanar arrangement of the amide carbonyl, the cinnamide double bond, and the β-substituted aryl group being optimal.

To test this hypothesis and to extend our study of the structure−activity relationships (SAR) of this chemical class, we have investigated a variety of replacements of the acrylamide core (**10**−**27**; Figure 2).[30] In the initial phase of the investigation, we examined the effect of restricting the s-*cis* conformer of cinnamide **9** in two general ways: (1) by connecting the amide nitrogen to the α-position of the cinnamide to form lactam **10** and the corresponding dihydro-isomer, pyridone **11** [cyclization **A**, Figure 2]; and (2) by incorporating the β-position of the cinnamide and the amide carbonyl into various six-membered aromatic rings to give compounds **12**−**23** [cyclization **B**, Figure 2]. Constraining cinnamide **9** in these two ways allowed for the thorough evaluation of 14 different core replacements in which the position of the ring heteroatoms were systematically varied (W, X, Y, and Z; Figure 2), while the position of the *t*-butylphenyl and the benzodioxane groups remained constant. As a second phase of this study, we modified the nature of the "linker" group (V, Figure 2) between the pyrimidine heterocyclic core and the benzodioxane moiety to give compounds **24**−**27**.

The synthesis and biological evaluation of lactam **10**, pyridone **11**, and substituted heterocycles **12**−**27** are described herein. This study culminated in the identification of isosteric replacements for the acrylamide moiety (e.g., 4-amino- and 4-oxopyrimidine) and has provided us with a novel class of TRPV1 antagonists for further investigation.[31]

Chemistry

The syntheses of lactam **10** and pyridone **11** are illustrated in Scheme 1. Commercially available 3,4-ethylenedioxyiodobenzene (**28**) was coupled with δ-valerolactam (**29**) under copper-mediated amidation conditions[32] to provide lactam **30** in moderate yield. The desired pyridone **10** was obtained from the aldol condensation of lactam **30** with 4-*t*-butylbenzaldehyde followed by dehydration of the resulting benzyl alcohol.[33]

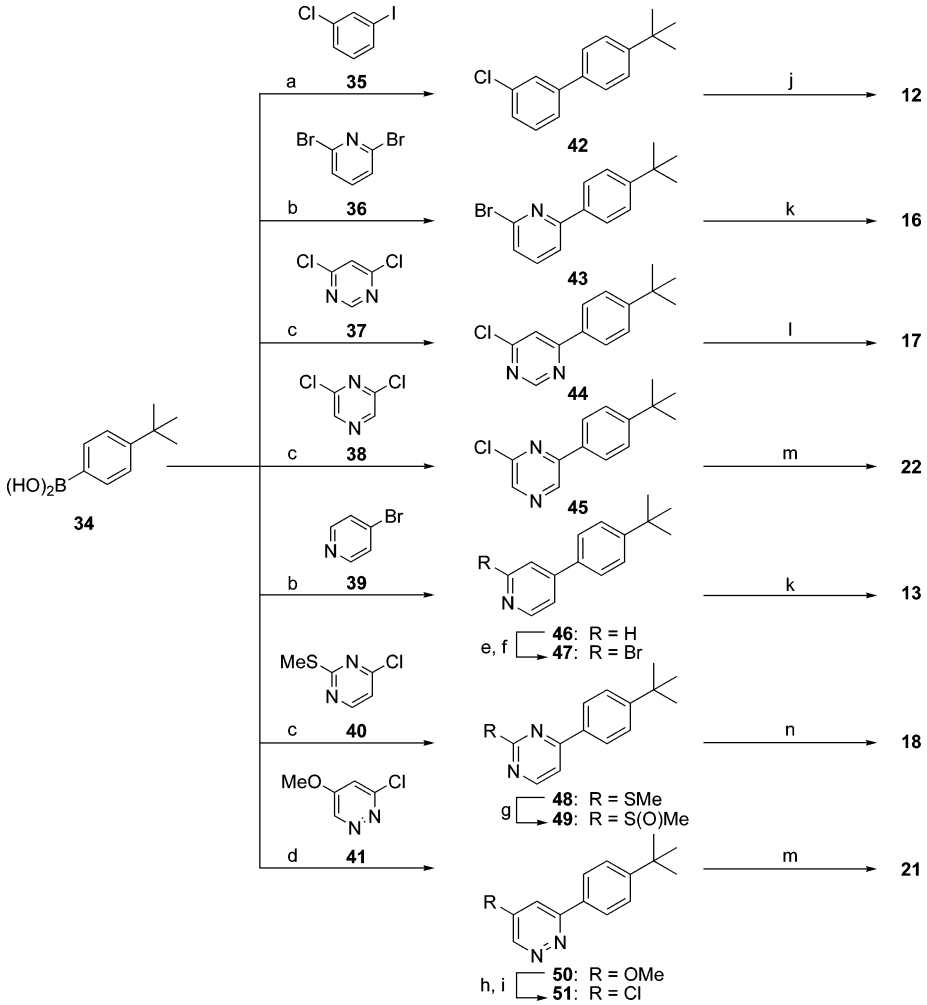
Attempts to convert lactam **10** to give pyridone **11** directly with dichlorodicyanobenzoquinone (DDQ) or by catalytic dehydrogenation with Pd/C were unsuccessful and, therefore, an alternative synthetic route was required. Ultimately, pyridone **11** was prepared in a two-step sequence by a regioselective, solvent-free, thermal C-benzylation reaction[34] of 2-hydroxypyridine (**31**) with 4-(*t*-butyl)benzyl bromide (**32**) followed by a copper-catalyzed aryl amidation of the resulting pyridone (**33**) with 3,4-ethylenedioxyiodobenzene (**28**).[35]

The next series of compounds examined contained various six-membered aromatic and heteroaromatic rings in place of the acrylamide core of compound **9**. The replacement cores included phenyl (**12**), each of the four pyridyl (**13**−**16**), three pyrimidinyl (**17**−**19**), and two pyridazinyl (**20**−**21**) regioisomers, as well as the pyrazine (**22**) and triazine (**23**) ring systems. The majority of these derivatives were prepared by one of two general methods: (1) by the addition of the *t*-butylphenyl group to the core system by a Suzuki coupling[36] followed by introduction of the aminobenzodioxane group (Scheme 2); or (2) by reversing the sequence and coupling the heterocyclic core with 7-aminobenzodioxane first, followed by a Suzuki coupling to incorporate the *t*-butylphenyl group (Scheme 3). Both methods proved to be useful in providing the appropriately substituted derivatives, and the synthetic method chosen was dictated mainly by the availability of starting materials.

The first general method is outlined in Scheme 2 and provided target compounds **12**, **13**, **16**−**18**, **21**, and **22** in two to four steps from readily available starting materials. For example, Suzuki palladium-mediated coupling of 4-*t*-butylphenylboronic acid (**34**) to 1-chloro-3-iodobenzene (**35**), 2,6-dibromopyridine (**36**), 4,6-dichloropyrimidine (**37**), and 2,6-dichloropyrazine (**38**) gave halo-intermediates **42**−**45**, respectively. The corresponding phenyl (**12**), pyridinyl (**16**), pyrimidinyl (**17**), and pyrazinyl (**22**) target compounds were obtained by treatment of intermediates **42**−**45** with 1,4-benzodioxan-6-amine (**52**) under palladium-mediated or thermal coupling conditions.[37]

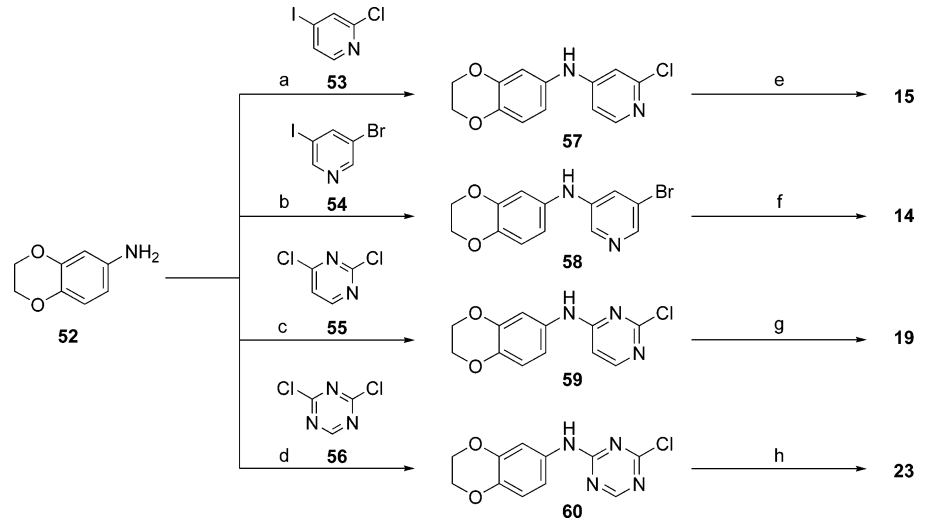
The remaining three compounds illustrated in Scheme 2 (**13**, **18**, and **21**) required additional modifications of the initial intermediates to produce leaving groups that would allow for the final addition of the aminobenzodioxane moiety. For example, Suzuki coupling of 4-*t*-butylphenylboronic acid (**34**) with 4-bromopyridine (**39**), 4-chloro-2-(methylthio)pyrimidine (**40**), and 3-chloro-5-methoxypyridazine (**41**)[38] gave intermediates **46**, **48**, and **50**, respectively. Following the Suzuki coupling, the pyridine *N*-oxide of **46** was generated by treatment with methylrhenium trioxide and hydrogen peroxide,[39] and the intermediate *N*-oxide was converted to 2-bromopyridine, **47**, by reaction with triphenylphosphonium bromide. Palladium-mediated coupling of **47** with 1,4-benzodioxan-6-amine (**52**) provided the desired pyridine analogue, **13**. To prepare the 2,4-pyrimidine derivative, **18**, the initial sulfide intermediate **48** was first oxidized to sulfoxide **49** with *m*-chloroperoxybenzoic acid, and the sulfoxide group was then displaced with 1,4-benzodioxan-6-amine (**52**). In the case of pyridazine derivative **21**, the initial methoxy intermediate **50** was demethylated by treat-

Scheme 2[a]



[a] Reagents and conditions: (a) PS−Pd(PPh$_3$)$_4$, Na$_2$CO$_3$; (b) Pd(PPh$_3$)$_4$, aq Na$_2$CO$_3$, DME, 90 °C; (c) Pd(PPh$_3$)$_4$, aq Na$_2$CO$_3$, CH$_3$CN, 90 °C; (d) Pd(PPh$_3$)$_4$, aq K$_2$CO$_3$, DME, 90 °C; (e) CH$_3$ReO$_3$, H$_2$O$_2$, CH$_2$Cl$_2$; (f) Ph$_3$P, Br$_2$, NEt$_3$, CH$_2$Cl$_2$; (g) *m*-CPBA, CH$_2$Cl$_2$; (h) 47% HI, 150 °C; (i) POCl$_3$; (j) 1,4-benzodioxan-6-amine, Pd$_2$(dba)$_3$, dppf, NaO*t*-Bu, toluene, reflux; (k) 1,4-benzodioxan-6-amine, Pd(OAc)$_2$, BINAP, NaO*t*-Bu, toluene, DMF, 90 °C; (l) 1,4-benzodioxan-6-amine, 1,4-dioxane, reflux; (m) 1,4-benzodioxan-6-amine, EtOH, 180 °C, microwave; (n) 1,4-benzodioxan-6-amine, 1,4-dioxane, EtOH, reflux.

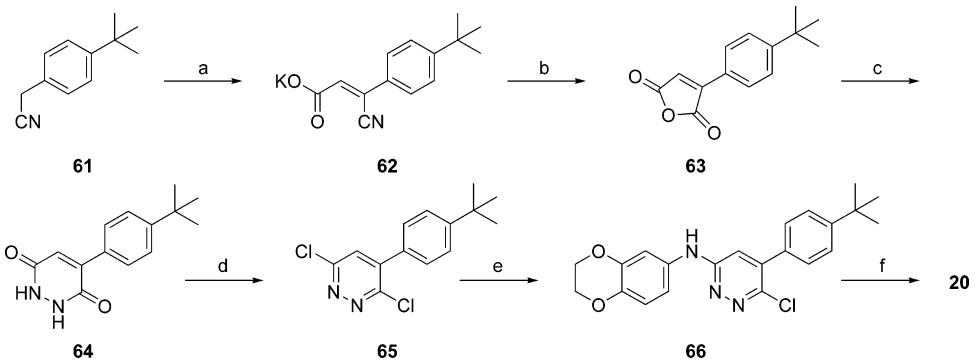
Scheme 3[a]



[a] Reagents and conditions: (a) Pd(OAc)$_2$, 2-(di-*t*-butylphosphino)biphenyl, K$_3$PO$_4$, toluene, reflux; (b) Pd$_2$(dba)$_3$, dppf, NaO*t*-Bu, toluene, 150 °C, microwave; (c) EtOH, rt; (d) *t*-BuOH, NaHCO$_3$, rt; (e) 4-*t*-butylphenylboronic acid, Pd(PPh$_3$)$_4$, aq Na$_2$CO$_3$, CH$_3$CN, 90 °C, 8 h; (f) 4-*t*-butylphenylboronic acid, PS-resin-bound Pd(PPh$_3$)$_4$, aq Na$_2$CO$_3$, DME/EtOH, 120 °C, microwave; (g) 4-*t*-butylphenylboronic acid, Pd(PPh$_3$)$_4$, aq Na$_2$CO$_3$, CH$_3$CN, 90 °C, 14 h; (h) 4-*t*-butylphenylboronic acid, 1,4-dioxane, Pd(PPh$_3$)$_4$, aq K$_2$CO$_3$, 130 °C, microwave.

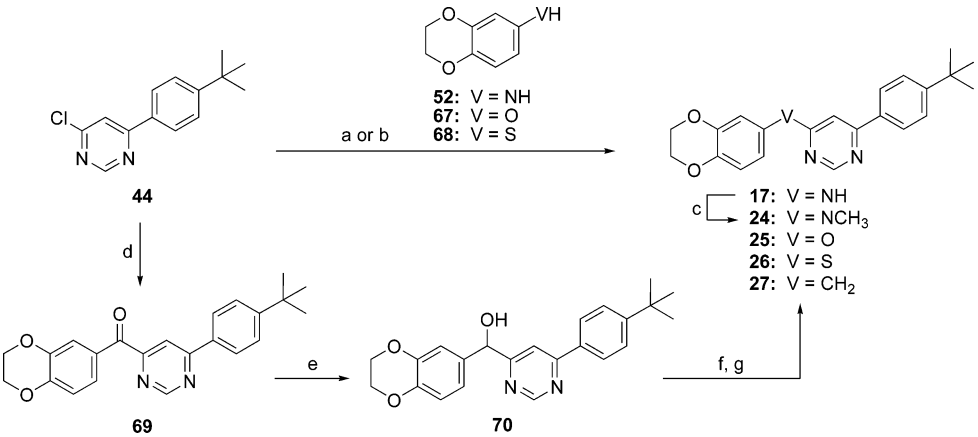
ment with hydroiodic acid, and the resulting pyridazinol was converted to chloropyridazine **51** by treatment with phosphorus oxychloride. Direct addition of 1,4-benzodioxan-6-amine (**52**) to chloropyridazine **51** provided the desired pyridazine **21**.

Scheme 4[a]



[a] Reagents and conditions: (a) glyoxilic acid, K_2CO_3, MeOH; (b) H_2SO_4, HCOOH; (c) NH_2NH_2, H_2O, AcOH, reflux; (d) $POCl_3$; (e) 1,4-benzodioxan-6-amine (**52**), EtOH, 180 °C, microwave; (f) Rieke Zn, EtOH, 72 °C.

Scheme 5[a]



[a] Reagents and conditions: (a) 1,4-dioxane, reflux; (b) Cs_2CO_3, DMF, 65 °C; (c) CH_3I, MP-carbonate, acetone; (d) NaH, 2,3-dihydrobenzo[*b*][1,4]dioxine-6-carbaldehyde, 1,3-dimethylimidazolium iodide, dioxane; (e) $NaBH_4$, MeOH, rt; (f) benzoyl chloride, pyridine, THF; (g) Pd/C, H_2.

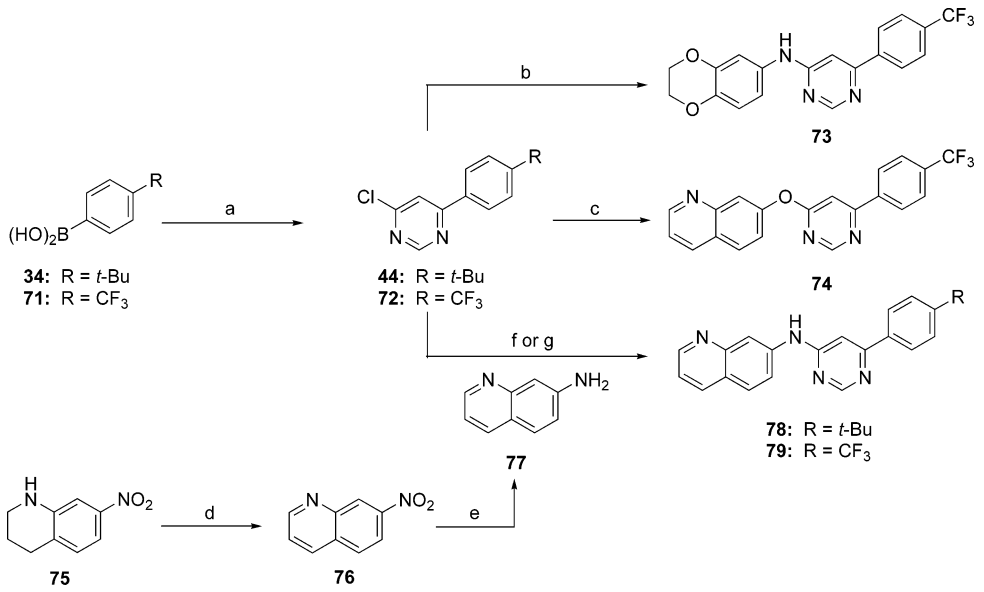
The second general synthetic method allowed for the preparation of compounds **14**, **15**, **19**, and **23** and is illustrated in Scheme 3. In this method, 1,4-benzodioxan-6-amine (**52**) was coupled with 2-chloro-4-iodopyridine (**53**), 3-bromo-5-iodopyridine (**54**), 2,4-dichloropyrimidine (**55**), or 2,4-dicholoro-1,3,5-triazine (**56**) under palladium-mediated coupling conditions to give intermediates **57**−**60**, respectively. The desired target compounds (**15**, **14**, **19**, and **23**) were obtained from the Suzuki coupling of **57**−**60** with 4-*t*-butylphenylboronic acid. The regiochemical assignment of pyridine **15** was confirmed based on comparison of the ^{1}H NMR and NOESY correlations with its isomeric pyridine analogue, **13**.

A longer synthetic route was needed to prepare the last isomeric pyridazine isomer required for this investigation (compound **20**, Scheme 4). Following the method described by Dean and co-workers, 4-*t*-butylphenylacetonitrile (**61**) was condensed with glyoxylic acid under basic conditions to provide potassium (*Z*)-3-aryl-cyanopropenoate (**62**).[40] Cyanopropenoate **62** was converted to the aryl maleic anhydride **63** under acidic conditions, which was then reacted with hydrazine to provide pyridazinedione **64**. Compound **64** was converted to dichloropyridazine **65** by treatment with phosphorus oxychloride. The reaction of dichloropyridazine **65** with 1,4-benzodioxan-6-amine (**52**) provided chloropyridazine **66** in moderate yield. A small amount (3%) of the bis-addition product was isolated; however, the regioisomeric product resulting from the displacement of the 3-chloro group was not observed. Chloropyridazine **66** was dehalogenated with Rieke Zn to provide the targeted pyridazine **20**.

Pyrimidine derivatives with alternative linking groups (V) were prepared as outlined in Scheme 5 (compounds **24**−**27**). The *N*-methyl analogue (**24**) was prepared by alkylation of pyrimidine **17** with methyl iodide. Displacement of the chloro group of intermediate **44** with 3,4-(ethylenedioxy)phenol (**67**)[41] or 3,4-(ethylenedioxy)thiophenol (**68**) provided pyrimidines **25** and **26**, respectively. The methylene-linked derivative (**27**) was prepared in a four-step sequence starting from chloropyrimidine **44** according to an analogous procedure described by Miyashita and co-workers.[42] Treatment of **44** with 2,3-dihydrobenzo[*b*]-[1,4]dioxine-6-carbaldehyde, 1,3-dimethylimidazolium iodide, and sodium hydride provided ketone **69**, which was reduced with sodium borohydride to give benzylic alcohol **70** in good yield. Finally, dehydration of **70** was accomplished by acylation of the benzylic alcohol with benzoyl chloride followed by hydrogenation of the resulting ester to give compound **27**.

The synthesis of the final set of compounds is illustrated in Scheme 6 (pyrimidines **73**, **74**, **78**, and **79**). These compounds were prepared to examine the effect of incorporating the pyrimidine core with two of the best flanking groups identified from our earlier SAR investigations in the cinnamide series, 7-substituted quinoline and 4-trifluoromethylphenyl.[22a] The trifluoromethyl derivative (**73**) was prepared by the Suzuki coupling of 4-trifluoromethylphenylboronic acid (**71**) to 4,6-dichloropyrimidine followed by the treatment of the resulting chloropyrimidine intermediate **72** with 1,4-benzodioxan-6-amine. Similarly, the O-linked quinoline analogue, pyrimidine **74**, was prepared by the treatment of chloropyrimidine **72** with the alkoxide of commercially available 7-hydroxyquinoline.

Scheme 6[a]



[a] Reagents and conditions: (a) 4,6-dichloropyrimidine (**37**), $Pd(PPh_3)_4$, aq Na_2CO_3, CH_3CN, 80 °C; (b) 1,4-benzodioxan-6-amine (**52**), EtOH, 180 °C, microwave; (c) 7-hydroxyquinoline, DMF, NaH, rt; (d) DDQ, CH_2Cl_2, rt; (e) Pd/C, H_2, MeOH; (f) $Pd_2(dba)_3$, dppf, NaO*t*-Bu, toluene, microwave, 200 °C; (g) neat, 200 °C, microwave.

Oxidation of 7-nitrotetrahydroquinoline (**75**)[43] with DDQ provided quinoline **76**, and subsequent reduction of the nitro group cleanly gave intermediate **77**. Reaction of 7-aminoquinoline (**77**) with chloropyrimidines **44** and **72** gave the final two target pyrimidines **78** and **79**, respectively.[44]

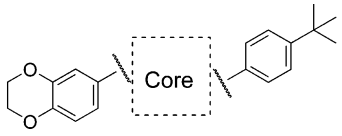
Results and Discussion

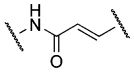
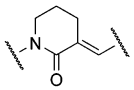
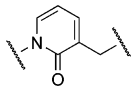
Based on our previous SAR investigations in the cinnamide series, we postulated that the s-*cis* conformer of compound **9** was the conformational isomer responsible for optimum potency at the TRPV1 channel.[28] In an attempt to lock the flanking *t*-butylphenyl and benzodioxane groups of compound **9** into this preferred conformation, we replaced the olefin double bond and the carbonyl of the acrylamide moiety with 18 different cyclic cores (**10**−**27**). We envisaged that confining the groups in this way would reduce rotational degrees of freedom and translate into increased inhibitory activity at the receptor. In addition to locking the orientation of the *t*-butylphenyl and benzodioxane groups into preferred positions, the diverse heterocycles examined would help increase our understanding of the key structural features required for activity in the core region of these TRPV1 antagonists and may also provide derivatives with improved pharmacokinetic properties.

The derivatives prepared in this study were evaluated for their ability to inhibit capsaicin (CAP)- and acid (pH 5)-induced influx of $^{45}Ca^{2+}$ into rat TRPV1-expressing CHO cells. IC_{50} values obtained for the conformationally constrained derivatives **10**−**27** are summarized in Tables 1−4, and the activity of cinnamide **9** is included for comparison. It should be noted that all compounds tested in this study were full antagonists and had EC_{50} values >4 μM in a separate assay measuring agonist activity.

The first two core replacements examined the effect of linking the amide nitrogen of cinnamide **9** to the α-position to form lactam **10** and pyridone **11** (Table 1). In lactam **10**, the position of both the carbonyl and the double bond are maintained, whereas only the position of the carbonyl is conserved in pyridone **11** (relative to compound **9**). In both cases, however, a dramatic loss in activity was observed, with lactam **10** and pyridone **11** giving IC_{50} values of >4 μM in both the capsaicin- and the acid-mediated assays. These results are consistent with our earlier SAR studies in the cinnamide series, where we found that alkylation of the amide nitrogen of compound **9** led to a significant decrease in TRPV1 inhibitory activity.

Table 1. In Vitro TRPV1 Activities for Cinnamide **9** and Compounds **10** and **11**[a]

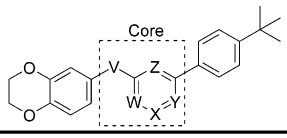


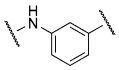
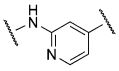
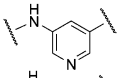
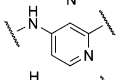
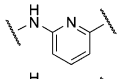
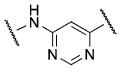
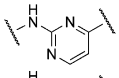
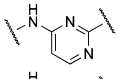
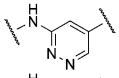
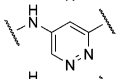
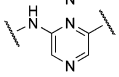
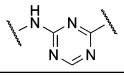
Compound No.	Core	rTRPV1 (CAP)[b] IC_{50} (nM)	rTRPV1 (acid)[b] IC_{50} (nM)
9		79 ± 45	350 ± 230
10		>4000	>4000
11		>4000	>4000

[a] Constrained derivatives resulting from cyclization route **A**, Figure 2. [b] IC_{50} values based on inhibition of capsaicin- (500 nM) or acid- (pH 5) induced influx of $^{45}Ca^{2+}$ into rat TRPV1-expressing CHO cells. (Each IC_{50} value reported represents an average of at least two independent experiments with three replicates at each concentration (±SEM).)

The next series of derivatives investigated in this study examined the effect of incorporating the β-position of cinnamide **9** and its amide carbonyl into various six-membered aromatic rings (compounds **12**−**23**; Table 2). Unlike the first two constrained derivatives (lactam **10** and pyridone **11**), this series of compounds maintained the NH group found to be important for the TRPV1 activity of cinnamide **9**. In addition to the amide NH, our earlier SAR studies indicated that the amide carbonyl of cinnamide **9** was also critical for activity. For example, we found that all TRPV1 activity was lost when the amide of compound **9** was reduced to the corresponding secondary amine.[22a] Therefore, it was not surprising that the phenyl derivative (**12**), which eliminates the corresponding heteroatom

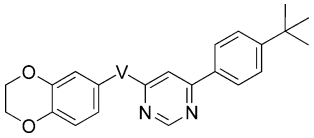
Table 2. In Vitro TRPV1 Activities for Cinnamide **9** and Compounds **12**−**23**[a]



Compound No.	Core	rTRPV1 (CAP)[b] IC_{50} (nM)	rTRPV1 (acid)[b] IC_{50} (nM)
12		> 4000	> 4000
13		230 ± 70	1300 ± 140
14		1210 ± 60	> 4000
15		> 4000	> 4000
16		> 4000	> 4000
17		120 ± 50	680 ± 120
18		> 4000	> 4000
19		> 4000	> 4000
20		780 ± 110	> 4000
21		840 ± 540	> 4000
22		> 4000	> 4000
23		760 ± 90	> 4000

[a] NH-linked derivatives resulting from cyclization route **B**, Figure 2. [b] IC_{50} values based on inhibition of capsaicin- (500 nM) or acid- (pH 5) induced influx of $^{45}Ca^{2+}$ into rat TRPV1-expressing CHO cells. (Each IC_{50} value reported represents an average of at least two independent experiments with three replicates at each concentration (±SEM).)

Table 3. In Vitro TRPV1 Activities for Pyrimidines **24**−**27**[a]



cmpd	V	rTRPV1 (CAP)[b] IC_{50} (nM)	rTRPV1 (acid)[b] IC_{50} (nM)
17	NH	120 ± 50	680 ± 120
24	NMe	>4000	2200 ± 260
25	O	290 ± 100	670 ± 3
26	S	>4000	>4000
27	CH_2	914 ± 173	>4000

[a] Alternative linking groups (V) from cyclization route **A**, Figure 2. [b] IC_{50} values based on inhibition of capsaicin- (500 nM) or acid- (pH 5) induced influx of $^{45}Ca^{2+}$ into rat TRPV1-expressing CHO cells. (Each IC_{50} value reported represents an average of at least two independent experiments with three replicates at each concentration (±SEM).)

in this region of the molecule, exhibited poor inhibitory activity in the TRPV1 assays.

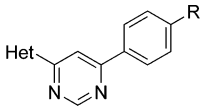
To further test the hypothesis that a heteroatom is required in this position of the molecule, we prepared the 2-aminopyridine analogue (compound **13**) to mimic the hydrogen-bond acceptor of cinnamide **9**. Incorporation of a nitrogen into the W position of the ring led to a dramatic increase in potency as compared to compound **12**. Although pyridine **13** was 3−4-fold less active than cinnamide **9** in both the capsaicin- and the acid-mediated assays, this result demonstrated that an *N*-substituted heterocyclic ring could serve as an isosteric replacement to the acrylamide core. The remaining three isomeric pyridine analogues, **14**, **15**, and **16**, were prepared to determine the optimal placement of the nitrogen atom within the heterocyclic core. As the nitrogen atom was moved counterclockwise around the ring, TRPV1 activity decreased. The inhibition of $^{45}Ca^{2+}$ influx for the pyridine analogues ranked in the following order: **13** > **14** ≫ **15**, **16**. The results obtained for the pyridyl isomers indicated that the position adjacent to the aminobenzodioxane moiety was the optimal position of the nitrogen (i.e., W = N), and that the nitrogen in pyridine **13** could serve as an adequate replacement for the cinnamide carbonyl oxygen of compound **9**.

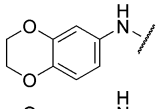
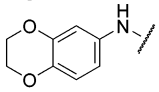
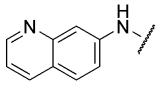
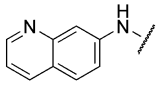
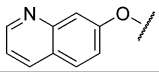
The next set of derivatives contained two nitrogens within the heterocyclic core and consisted of the three isomeric pyrimidines (**17**−**19**), the two isomeric pyridazines (**20**−**21**), and the 2,6-disubsituted pyrazine analogue (**22**). The inhibition for these analogues ranked in the following order: **17** > **20**, **21** > **18**, **19**, **22**. The 4,6-disubstituted pyrimidine (**17**) was the most potent pyrimidine isomer and had an IC_{50} = 120 nM in the capsaicin-mediated assay. The two pyridazine isomers (**20** and **21**) showed comparable potencies, while the pyrazine derivative (**22**) was significantly less active than either of the pyridazines. The general trends observed for these diazaheterocycles are consistent with results obtained in the pyridine series (**13**−**16**). For example, the results suggest that (1) the nitrogen in the position that mimics the cinnamide carbonyl is preferred (i.e., W = N in compounds **17** and **20**), and (2) the nitrogen between the *t*-butylphenyl and benzodioxane groups is detrimental to activity (i.e., Z = N in compounds **18**, **19**, and **22**).

The final constrained derivative evaluated in this study was the 1,3,5-triazine derivative, **23**. This analogue had an IC_{50} of 760 nM in the capsaicin-mediated assay, but was less active at blocking $^{45}Ca^{2+}$ influx when the channel was activated by low pH. The results obtained for compound **23** are consistent with the SAR results observed for the pyridine and pyrimidine derivatives, wherein the contribution of adding the third nitrogen into the ring appears to be additive. For example, triazine **23** can be viewed as the result of adding the key nitrogen (at position W) to the 2,6-disubstituted pyrimidine isomer **19**. Adding the nitrogen to this position leads to a compound with significantly increased activity (i.e., **23** vs **19**). Similarly, the addition of a nitrogen at the "nonpreferred" position (at position Z) to the potent 4,6-disubstituted pyrimidine derivative resulted in a significant decrease in activity (i.e., **17** vs **23**).

The SAR results outlined above demonstrate that the 4-aminopyrimidine core of compound **17** is a suitable isosteric replacement for the acrylamide moiety of compound **9**. To see how the pharmacophores of these two compounds compared, we calculated the low-energy conformations of cinnamide **9** and pyrimidine **17** and superimposed the resulting structures (Figure 3). In both cases, a flat conformation is preferred wherein the benzodioxane, the core (acrylamide or 4-aminopyrimidine), and the *t*-butylphenyl groups are coplanar. The two low-energy conformations superimpose well and the alignment of the cinnamide carbonyl of **9** and the pyrimidine nitrogen of compound **17** are clearly favorable (the structures are off-set slightly for illustrative purposes).

Table 4. In Vitro TRPV1 Activities for Pyrimidines **17**, **73**, **74**, **78**, and **79**



Compound No.	Het	R	rTRPV1 (CAP)[a] IC_{50} (nM)	rTRPV1 (acid)[a] IC_{50} (nM)	hTRPV1 (CAP)[a] IC_{50} (nM)	hTRPV1 (acid)[a] IC_{50} (nM)
17		*t*-Bu	120 ± 50	680 ± 120	51 ± 27	270 ± 160
73		CF_3	430 ± 10	1200 ± 550	120 ± 60	250 ± 30
78		*t*-Bu	2.0 ± 0.2	22 ± 2.5	1.9 ± 0.1	6.9 ± 0.7
79		CF_3	4.5 ± 0.2	6.6 ± 1.5	0.6 ± 0.2	0.3 ± 0.1
74		CF_3	7.4 ± 1.0	8.0 ± 6.0	3.7 ± 1.0	4.2 ± 0.6

[a] IC_{50} values based on inhibition of capsaicin- (500 nM) or acid- (pH 5) induced influx of $^{45}Ca^{2+}$ into rat or human TRPV1-expressing CHO cells. (Each IC_{50} value reported represents an average of at least two independent experiments with three replicates at each concentration (±SEM).)

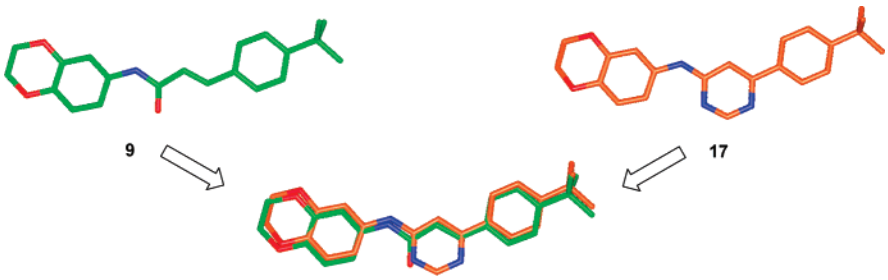


Figure 3. Minimum-energy conformations of compounds **9** (green) and **17** (orange) and their aligned structures.

In the second phase of our investigation, we made changes to the linking group between the pyrimidine heterocycle and the benzodioxane moiety (Table 3). As we observed in the cinnamide series, *N*-methylation resulted in a loss of activity (**24** vs **17**).[22a] However, the O-linked derivative (4-oxopyrimidine **25**) maintained significant TRPV1 inhibitory activity, with IC_{50} values of 290 and 670 nM in the capsaicin- and acid-mediated assays, respectively. This result is in contrast to the substantial decrease in activity that we observed for the corresponding ester analogue of cinnamide **9** and demonstrates that a hydrogen bond donating linker at this position is not an absolute requirement for TRPV1 antagonism.[22a] Taken together, these results also suggest that the loss in activity observed upon *N*-methylation is likely due to an unfavorable conformational change that results between the 4-aminopyrimidine core and the benzodioxane group rather than due to the loss of the NH hydrogen-bond donor in compound **17**. The S- and CH_2-linked analogues (**26** and **27**) were significantly less active than the O- or NH-linked pyrimidines, **25** and **17**.

With the pyrimidine ring identified as an acceptable alternative to the acrylamide core, we were interested in examining the effect of incorporating some of the optimum pharmacophoric elements identified from our cinnamide SAR investigations into this new class of TRPV1 antagonists. The results of both the rat and the human receptors are reported in Table 4. For example, we knew from our previous studies that replacing the aminobenzodioxane group of cinnamide **9** with a 7-aminoquinoline group led to enhanced TRPV1 inhibitory activity in our in vitro assays.[22a] In addition, we found that we could reduce metabolism within the cinnamide series by using a trifluoromethylphenyl in place of the *t*-butylphenyl group while at the same time maintaining comparable potency. Therefore, we prepared and evaluated the corresponding derivatives with the new 4-aminopyrimidine core and found that the SAR was consistent with the cinnamides series (compounds **73**, **78**, and **79**; Table 4). For example, replacement of the *t*-butylphenyl with the trifluoromethylphenyl group resulted in a slight decrease in activity (compound **73** vs **17**); however, potency was increased 25−60-fold by the replacement of the benzodioxane with the 7-aminoquinoline group (compound **78** vs **17**). The effect of combining both the aminoquinoline and the trifluoromethylphenyl substituents on the 4-aminopyrimidine core was also examined. This combination gave an additional 3- to 20-fold increase in potency over compound **78** at the human TRPV1 receptor. Finally, the effect of these two modifications were evaluated within the *O*-linked series, as exemplified by 4-oxopyrimidine **74**. As was observed for the corresponding 4-aminopyrimidine analogue, **79**, the 4-oxopyrimidine derivative, **74**, was a potent TRPV1 antagonist in both the capsaicin- and acid-mediated assays.

Due to the excellent in vitro activities of pyrimidines **74**, **78**, and **79**, the pharmacokinetic profiles of these compounds were

Table 5. Mean Pharmacokinetic Parameters of Compounds **9**, **74**, **78**, and **79** Following Intravenous Administration in Sprague−Dawley Rats

	dose[c] (mg/kg)	$AUC_{0-\infty}$ (ng·h/mL)	CL (L/h/kg)	V_{ss} (L/kg)	$t_{1/2}$ (h)
9[a]	3	680	4.4	2.1	1.1
78[a]	2	340	2.9	3.1	1.6
79[a]	2	320	3.1	3.0	1.7
74[b]	2	1590	1.2	3.0	2.8

[a] $n = 2$ animals per study. Interanimal variability was less than or equal to 30%. [b] Data is the mean of four studies. Variability for CL, V_{ss} and $t_{1/2}$ values ranged from 29 to 40%, and variability for $AUC_{0-\infty}$ was 77%. [c] Dosed as a solution in DMSO.

Table 6. Mean Pharmacokinetic Parameters of Compounds **9**, **74**, **78**, and **79** Following Oral Administration[a] in Sprague−Dawley Rats

	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0-\infty}$ (ng·h/mL)	bioavailability, F_{oral} (%)
9[b]	25	0.5	24	3
78[b]	34	0.5	79	5
79[b]	26	5.0	94	6
74[c]	300	1.2	2040	31

[a] Dosed at 5 mg/kg as a suspension in 5% Tween 80 in Oraplus. [b] $n = 2$ animals per study. Interanimal variability was less than or equal to 30%. [c] Data is the mean of five studies. Variability for C_{max}, t_{max}, and F_{oral} values ranged from 39 to 50% and variability for $AUC_{0-\infty}$ was 84%.

evaluated in Sprague−Dawley rats (Tables 5 and 6; the pharmacokinetic data for compound **9** is also included for comparison). Both of the 4-aminopyrimidine derivatives (**78** and **79**) showed similar pharmacokinetic profiles, exhibiting high clearances that approached liver blood flow following an intravenous dose. This resulted in low exposures ($AUC_{0-\infty}$ = 340 and 320 ng·h/mL, respectively) and modest half-lives ($t_{1/2}$ = 1.6−1.7 h). When administered orally compounds **78** and **79** showed low bioavailability possibly due to high first-pass metabolism. On the other hand, changing the NH-linking group to an oxygen significantly improved the i.v. pharmacokinetic profile. The 4-oxopyrimidine derivative, **74**, had a low to moderate clearance ($CL_{in\ vivo}$ = 1.2 L/h/kg) and a longer half-life ($t_{1/2}$ = 2.8 h), which resulted in five times the exposure in plasma as compared to its corresponding NH-linked derivative, **79**. Similarly, the pharmacokinetic profile of compound **74** was significantly better than either of the 4-aminopyrimidines, **78** or **79**, or cinnamide **9** when administered orally. Upon oral dosing, compound **74** showed approximately 10-fold improvement in C_{max}, a 5-fold improvement in $AUC_{0-\infty}$, and good bioavailability (F_{oral} = 31%) as compared to that of pyrimidines **78** and **79**.

On the basis of its potent in vitro activity at TRPV1 and its good pharmacokinetic profile, 4-oxopyrimidine **74** was evaluated in two in vivo models; one designed to access its "on-target" activity (antagonism of TRPV1 in vivo) and the second one to determine its potential analgesic activity (Figure 4). Initially, compound **74** was evaluated for its ability to reverse capsaicin-induced hypothermia in rats,[15] an on-target biochemical challenge model. The results are illustrated in Figure 4a. In this model, compound **74** or vehicle was administered orally to Sprague−Dawley rats (treatment 1) and temperature was monitored by radiotelemetry. After 90 min, 10 mg/kg of capsaicin or vehicle was injected into the peritoneal cavity (treatment 2). In the vehicle/capsaicin group, a significant drop in core body temperature (~1.5 °C) was observed. Pretreatment of compound **74** completely blocked this capsaicin-induced hypothermic response when dosed at 40 mg/kg, p.o. With this encouraging result, 4-oxopyrimidine **74** was also evaluated for its ability to block thermal hyperalgesia in the CFA model in rats (Figure 4b). In this model, CFA was injected into the plantar

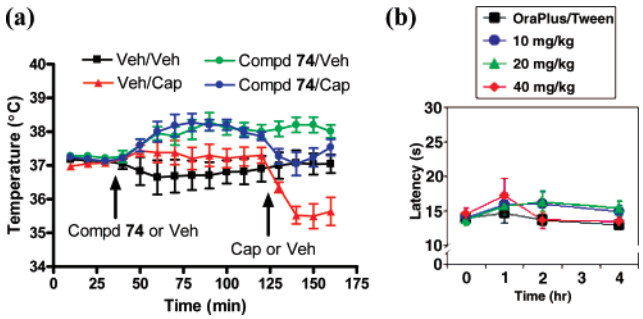


Figure 4. (a) Effect of compound **74** in the reversal of capsaicin-induced hypothermia model in rats (40 mg/kg, p.o.). (b) Effect of compound **74** in the CFA-induced thermal hyperalgesia model in rats 10, 20, and 40 mg/kg, p.o.

surface of the hind paw of Sprague−Dawley rats, producing an intense inflammatory response.[26] After 21 h, compound **74** was administered orally at 10, 20, or 40 mg/kg. Three hours after dosing, a thermal stimulation was applied to the inflamed paw and withdrawal latencies were measured. Although a slight increase in the paw withdrawal latencies were observed at the 1 h time point with the highest dose, the effect of compound **74** was not significant in this pain model.

Summary

We have described the synthesis and biological evaluation of a series of conformationally constrained analogues of the s-*cis* conformer of cinnamide **9** and have demonstrated that the 2-aminopyridine and 4-aminopyrimidine cores are suitable isosteric replacements for the acrylamide moiety (compounds **13**, **17**, and **73**, **78**, and **79**). These conformational constraints allowed for a favorable planar alignment of the key pharmacophoric elements found in cinnamide **9** (e.g., the benzodioxane and *t*-butylphenyl) and also established that the nitrogen in pyridine **13** and the nitrogen adjacent to the aminobenzodioxane group in pyrimidine **17** (i.e., W = N) could serve as replacements for the cinnamide carbonyl oxygen. Additionally, we determined that the NH-linker is not required for activity in this new series of TRPV1 antagonists and found that it can be replaced with an oxygen and still maintain potency (compound **25**). Finally, we demonstrated that potent, orally available TRPV1 antagonists could be prepared by combining the 7-substituted quinoline and the trifluoromethylphenyl groups with the 4-amino- and 4-oxopyrimidine cores (compounds **79** and **74**). In fact, the new 4-oxopyrimidine derivative **74** was not only 10-fold more potent than the original lead, cinnamide **9** (e.g., rTRPV1, IC_{50} = 7.4 nM vs 79 nM, respectively), but also had significantly improved pharmacokinetic properties (e.g., lower clearance, $CL_{in\ vivo}$ = 1.2 vs 4.4 L/h/kg, and higher oral bioavailability, F_{oral} = 31% vs 3%, respectively). Compound **74** was also shown to be efficacious in vivo at blocking capsaicin-induced hypothermia in rats; however, it did not show significant activity in the CFA-induced pain model. This investigation has provided us with novel scaffolds for the further study of related TRPV1 antagonists. Additional SAR analysis, as well as in vivo efficacy of related compounds, will be reported in parts 2 and 3 of this series.

Experimental Section

Functional $^{45}Ca^{2+}$ Uptake Assays. Chinese hamster ovary (CHO) cells stably expressing human or rat TRPV1 channels were generated by transfecting pcDNA3.1 expression vector containing human or rat TRPV1 cDNAs. CHO cells were maintained in Dulbecco's modified Eagle's medium supplemented with 10%

dialyzed fetal bovine serum, penicillin, streptomycin, l-glutamine, and nonessential amino acids. A calcium phosphate method was used for stable transfection (5 μg of DNA per 2×10^6 cells in 60 mm dishes), and 800 μg/mL geneticin was used as a selection agent. After 2 weeks of selection, single colonies were picked and screened for expression of TRPV1 in the agonist-induced $^{45}Ca^{2+}$ uptake assay. Positive clones were expanded and used in studies described here.

Two days prior to the assay, cells were seeded in Cytostar 96-well plates (Amersham) at a density of 20 000 cells/well. The activation of TRPV1 is followed as a function of cellular uptake of radioactive calcium ($^{45}Ca^{2+}$, ICN). All the $^{45}Ca^{2+}$ uptake assays had a final $^{45}Ca^{2+}$ at 10 μCi/mL. These assays were conducted as follows: (1) agonist assay, compounds were incubated with TRPV1-expressing CHO cells in 1:1 ratio of F-12 and HBSS (Hanks' buffered saline solution) supplemented with BSA 0.1 mg/mL and 1 mM HEPES (pH 7.4) at room temperature for 2 min in the presence of $^{45}Ca^{2+}$ prior to compound washout; (2) capsaicin antagonist assay, compounds were preincubated with TRPV1 expressing CHO cells in HBSS (Hanks' buffered saline solution) supplemented with BSA 0.1 mg/mL and 1 mM HEPES (pH 7.4) at room temperature for 2 min prior to addition of $^{45}Ca^{2+}$ and capsaicin (final concentration, 0.5 μM) in F-12 and then left for an additional 2 min prior to compound washout; (3) proton antagonist assay, compounds were preincubated with TRPV1 expressing CHO cells at room temperature for 2 min prior to addition of $^{45}Ca^{2+}$ in 30 mM Hepes/Mes buffer (final pH 5) and then left for an additional 2 min prior to compound washout; (4) compound washout and analysis, assay plates were washed two times with PBS and 0.1 mg/mL BSA using an ELX405 plate washer (Bio-Tek Instruments, Inc.) immediately after the functional assay. Radioactivity in the 96-well plates was measured using a MicroBeta Jet (Perkin-Elmer, Inc.). IC_{50} values were calculated by generating antagonist inhibition curves using Xlfit version 2.0.6 (ID Business Solutions, Ltd). The reported results were the average of at least two independent experiments with three replicates at each concentration (±SEM).

Radiotelemetry in Rats. Male Sprague−Dawley rats (CRL, Wilmington, MA) weighing 175−250 g (6−8 weeks of age) were single-housed and allowed to acclimate for 1 week in the animal care facility prior to start of the experiment. The temperature in the room used for radiotelemetry experiments was maintained at 20 ± 2 °C. To implant the radiotelemetry probe (model ER-4000 PDT; Mini Mitter, Brend, OR), rats were lightly anesthetized using isoflourane (IsoFlo, Abbott Laboratories, Chicago, IL) at a concentration of 2% isoflourane at 2 L/min oxygen flow. In right lateral recumbence, the left, lateral abdominal wall was clipped and cleaned with Betadine solution (Purdue Frederick Company, Stamford, CT) followed by 70% alcohol in water. A 3−4 mm incision was made through the skin and abdominal wall into which a sterilized probe was inserted. The surgical site was closed with absorbable suture material (4-0 Vicryl, Ethicon Inc, Somerville, NJ) and black silk suture material (4-0, Ethicon, Inc. Somerville, NJ), and the animals were returned to home caging for recovery and allowed 3 days of recovery prior to the drug experiment.

On the day of the experiment, single-housed animals were placed on radiotelemetry receivers. A baseline of body core temperature was recorded for 30 min prior to the drug administration. Rats (eight per group) were either treated with vehicle or single to various doses of TRPV1 antagonists in a dose volume of 5 mL/kg in an Ora-Plus/5% Tween-80 (oral gavage), and the body core temperature recordings were continued for two more hours.

Molecular Modeling. The molecular modeling studies were carried out using molecular dynamics/mechanics[45] and ab initio quantum mechanics.[46] The conformational search was carried out with high-temperature molecular dynamics, and simulations were conducted using the MacroModel.[45] Energy calculations were performed using the Merck molecular (MMFF94) force field[47] in aqueous medium using the GB/SA water model.[48] The 10 lowest-energy conformations of compounds **9** and **17** were chosen for further optimization by quantum mechanics. Calculations were performed using density functional theory, as implemented in Gaussian98 software,[46] utilizing the B3LYP hybrid density functional and the 6-31G* basis set. The lowest-energy conformers from these 10 calculations for both compound **9** and compound **17** were used for the final assessment for the results that are as shown in Figure 3.

Chemistry. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. All reactions involving air- or moisture-sensitive reagents were performed under a nitrogen or argon atmosphere. All microwave-assisted reactions were conducted with a Smith Synthesizer from Personal Chemistry, Uppsala, Sweden. All final compounds were purified to >95% purity as determined by LC/MS obtained on an Agilent 1100 or HP 1100 spectrometer. Purity was determined on an Agilent 1100 spectrometer by method A, Phenomenex Luna C_8 column (100 × 4.6 mm, 5μ) at 40 °C with a 1.0 mL/min flow rate using a gradient of 5−100% 5 mM ammonium acetate in acetonitrile in 5 mM ammonium acetate in water, pH 6.5, over 15 min, or by method B, Phenomenex Luna C_8 column (100 × 4.6 mm, 5 μ) at 40 °C with a 1.0 mL/min flow rate using a gradient of 50−100% 0.1% formic acid in acetonitrile in 0.1% formic acid in water over 10 min. Alternatively, purity was determined on an HP 1100 spectrometer by method C, YMC-AQ-C18 column (150 × 4.6 mm, 5 μ) at room temperature with a 1.0 mL/min flow rate using a gradient of 10−100% 0.1% HCOOH in acetonitrile in 0.1% HCOOH in water over 14 min; method D, Phenomenex Luna C_8 column (100 × 4.6 mm, 5 μ) at 40 °C with a 1 mL/min flow rate using a gradient of 5−100% 0.1% TFA in acetonitrile in 0.1% TFA in water over 15 min; method E, YMC−ODS-AM C18 column (100 × 2.1 mm, 5 μ) at 40 °C with a 0.5 mL/min flow rate using a gradient of 10−100% 0.1% TFA in acetonitrile in 0.1% TFA in water over 15 min; method F, DS-AM C18 column (100 × 2.1 mm, 5 μ) at 40 °C with a 0.5 mL/min flow rate using a gradient of 10−100% 0.1% HCOOH in acetonitrile in 0.1% HCOOH in water over 15 min; or by method G, Synergi MAX-RP C12 column (50 × 2.0 mm, 4 μ) at 40 °C with a 0.8 mL/min flow rate using a gradient of 10−100% 0.1% TFA in acetonitrile in 0.1% TFA in water over 5 min. Silica gel chromatography was performed using either glass columns packed with silica gel (200−400 mesh, Aldrich Chemical) or prepacked silica gel cartridges (Biotage or Redisep). Melting points were determined on a Buchi-545 melting point apparatus and are uncorrected. NMR spectra were determined with a Bruker 300 MHz or DRX 400 MHz spectrometer. Chemical shifts are reported in parts per million (ppm, δ units). Low-resolution mass spectral (MS) data were determined on a Perkin-Elmer-SCIEX API 165 mass spectrometer using electrospray (ES) ionization modes (positive or negative). High-resolution mass spectral (HRMS) data were determined on a 7T Bruker FTICR mass spectrometer using ES ionization mode (positive). Combustion analyses were performed by Atlantic Microlab, Inc., Norcross, GA, and were within 0.4% of calculated values, unless otherwise noted.

(*E*)-3-(4-*tert*-Butylbenzylidene)-1-(2,3-dihydrobenzo[*b*][1,4]-dioxin-6-yl)piperidin-2-one (10). To a solution of δ-valerolactam (**29**; 0.79 g, 8.0 mmol) in 1,4-dioxane (7.0 mL) was added 3,4-ethylenedioxyiodobenzene (**28**; 1.8 g, 6.7 mmol), potassium phosphate tribasic (2.8 g, 13 mmol), and *N*,*N*′-dimethylethylenediamine (0.071 mL, 0.67 mmol). The reaction vessel was carefully evacuated and refilled with N_2 (3×). Copper(I) iodide (0.064 g, 0.33 mmol) was added, and the reaction vessel was carefully evacuated and refilled again with N_2 (3×). The reaction mixture was stirred at 85 °C for 20 h and allowed to cool to room temperature. The mixture was filtered and the filtrate was passed through a plug of silica gel, and the filter cake was washed with EtOAc. The combined filtrates were evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (gradient: 60−100% EtOAc/hexanes) to give 0.87 g (56%) of 1-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)piperidin-2-one (**30**) as an off-white solid. MS (ESI, pos. ion) *m*/*z*: 378 (M + 1). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.75−1.85 (m, 4 H), 2.33 (t, J = 6.3 Hz, 2 H), 3.51 (t, J = 5.6 Hz, 2 H), 4.23 (s, 4 H), 6.69 (dd, J = 8.6, 2.3 Hz, 1 H), 6.75 (d, J = 2.3 Hz, 1 H), 6.82 (d, J = 8.6 Hz, 1 H).

To a flame-dried, N_2-purged, 15 mL, round-bottomed flask was added 1-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)piperidin-2-one (**30**; 0.30 g, 1.3 mmol) and THF (5.0 mL). The mixture was cooled to −78 °C and then lithium diisopropylamide (1.8 M solution in heptane/THF/ethylbenzene, 0.79 mL, 1.4 mmol) was added. The reaction mixture was stirred for 10 min at −78 °C and then warmed to 0 °C. After stirring for 30 min at 0 °C, the solution was again cooled to −78 °C. 4-*tert*-Butylbenzaldehyde (0.26 mL, 1.5 mmol) was added, and the mixture was stirred at −78 °C for 30 min. The reaction mixture was allowed to warm to 0 °C, stirred at 0 °C for 15 min, and then poured into a saturated aqueous solution of NH_4Cl. The solution was extracted with EtOAc, and the combined organic extracts were successively washed with H_2O and saturated aqueous NaCl, dried over Na_2SO_4, and filtered. The filtrate was evaporated under reduced pressure, and the residue was dissolved in CH_2Cl_2 (10 mL) and treated with triethylamine (0.54 mL, 3.9 mmol). The mixture was cooled to 0 °C, treated with methanesulfonyl chloride (0.20 mL, 2.6 mmol), and stirred at 0 °C for 2 h and at 25 °C for 1 h. The reaction mixture was poured into a saturated aqueous solution of NH_4Cl and extracted with EtOAc. The combined organic extracts were washed successively with H_2O and saturated aqueous NaCl, dried over Na_2SO_4, and filtered. The filtrate was evaporated under reduced pressure, and the residue was dissolved in THF (10 mL) and treated with 1,8-diazabicyclo(5.4.0)-undec-7-ene (0.58 mL, 3.9 mmol) at 25 °C. The reaction mixture was stirred for 24 h at 25 °C and then poured into a mixture of 0.1 N HCl and EtOAc/hexanes (1:1). The organic phase was separated and washed successively with H_2O, saturated aqueous solution of $NaHCO_3$, H_2O, and saturated aqueous NaCl, then dried over Na_2SO_4, and filtered. The filtrate was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (gradient: 10−45% EtOAc/hexanes) to give 0.15 g (31%) of the title compound as a white solid. MS (ESI, pos. ion) *m*/*z*: 378 (M + 1). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.30 (s, 9 H), 1.86−1.93 (m, 2 H), 2.81−2.87 (m, 2 H), 3.64−3.69 (m, 2 H), 4.25 (s, 4 H), 6.77 (dd, J = 8.3, 2.2 Hz, 1 H), 6.84−6.87 (m, 2 H), 7.39 (d, J = 8.6 Hz, 2 H), 7.45 (d, J = 8.3 Hz, 2 H), 7.60 (s, 1 H). Anal. ($C_{24}H_{27}NO_3$): C, H, N.

3-(4-*tert*-Butylbenzyl)-1-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-pyridin-2(1*H*)-one (11). A mixture of 2-hydroxypyridine (**31**; 2.5 g, 26 mmol) and 4-(*tert*-butyl)benzyl bromide (**32**; 1.6 mL, 8.8 mmol) was heated in a microwave at 190 °C for 5 min. The reaction mixture was partitioned between a mixture of saturated aqueous solution of $NaHCO_3$ and EtOAc. The organic phase was separated, washed successively with H_2O and saturated aqueous NaCl, dried over Na_2SO_4, and filtered. The filtrate was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (gradient: 50−100% EtOAc/hexanes, then 100% EtOAc) to give 0.23 g (11%) of 3-(4-*tert*-butylbenzyl)pyridin-2(1*H*)-one (**33**) as a yellow solid, which was used in the next step without additional purification. Analytically pure material was obtained through second purification by silica gel chromatography (gradient: 75−100% EtOAc/hexanes) to afford a white solid. MS (ESI, pos. ion) *m*/*z*: 242 (M + 1). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.25 (s, 9 H), 3.64 (s, 2 H), 6.10 (dd, J = 6.5, 6.7 Hz, 1 H), 7.15 (d, J = 8.2 Hz, 2 H), 7.18 (dd, J = 6.7, 2.1 Hz, 1 H), 7.22 (dd, J = 6.5, 2.0 Hz, 1 H), 7.28 (d, J = 8.2 Hz, 2 H), 11.52 (s, 1 H).

Following the procedure described for compound **30**, 3-(4-*tert*-butylbenzyl)pyridin-2(1*H*)-one (**33**; 0.10 g, 0.41 mmol) was reacted with 3,4-ethylenedioxyiodobenzene (**28**; 0.13 g, 0.50 mmol) to provide 0.13 g (80%) of the title compound as a white solid. MS (ESI, pos. ion) *m*/*z*: 376 (M + 1). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.25 (s, 9 H), 3.70 (s, 2 H), 4.28 (s, 4 H), 6.21 (dd, J = 6.7, 6.8 Hz, 1 H), 6.81 (dd, J = 8.5, 2.4 Hz, 1 H), 6.90 (d, J = 2.3 Hz, 1 H), 6.94 (d, J = 8.6 Hz, 1 H), 7.18 (d, J = 8.2 Hz, 2 H), 7.22 (dd, J = 6.7, 1.5 Hz, 1 H), 7.30 (d, J = 8.2 Hz, 2 H), 7.46 (dd, J = 6.8, 1.8 Hz, 1 H). Anal. ($C_{24}H_{25}NO_3$): C, H, N.

3-(4-*tert*-Butylphenyl)-*N*-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)phenyl-1-amine (12). An aqueous solution of K_2CO_3 (3.0 mL, 6 mmol, 2 M) was added to a slurry of 1-chloro-3-iodobenzene (**35**; 0.50 g, 2.1 mmol), 4-*tert*-butylphenylboronic acid (**34**; 0.41 g, 2.3 mmol), polystyrene triphenylphosphine palladium(0) (0.50 g, 0.11 mmol/g, 0.055 mmol), and 1:1 DME/EtOH (20 mL). The solution was heated at 75 °C for 18 h. The reaction mixture was allowed to cool to room temperature, filtered, and evaporated to give 3-(4-*tert*-butylphenyl)chlorobenzene (**42**). MS (ESI, pos. ion) *m*/*z*: 245 (M + 1). This material was used without further purification.

The crude 3-(4-*tert*-butylphenyl)chlorobenzene (**42**) was dissolved in toluene (4 mL) and 1,4-benzodioxan-6-amine (**52**; 300 mg, 1.99 mmol), Pd_2dba_3 (25 mg, 0.027 mmol), 1,1′-bis(diphenylphosphino)ferrocine (dppf; 25 mg, 0.045 mmol), and sodium *tert*-butoxide (230 mg, 2.4 mmol) were added. The mixture was heated at 150 °C for 10 min in a microwave and then evaporated under reduced pressure. The residue was purified by silica gel column chromatography (gradient: 5−20% EtOAc/hexanes). The material was purified further by preparative HPLC (gradient: 10−90% CH_3CN/H_2O, 0.1% TFA) to give 8 mg (1% overall yield based on 1-chloro-3-iodobenzene (**35**)) of the title compound as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (s, 9 H), 4.25 (m, 4 H), 6.71 (m, 2 H), 6.80 (m, 1 H), 6.92 (m, 1 H), 7.07 (m, 1 H), 7.16 (m, 1 H), 7.27 (m, 1 H), 7.44 (d, J = 8.5 Hz, 2 H), 7.50 (d, J = 8.5 Hz, 2 H). HRMS calcd for $(C_{24}H_{25}NO_2)H^+$, 360.19581; found, 360.19619. LC/MS retention time: [E] 10.96 min; [G] 3.06 min.

[4-(4-*tert*-Butyl-phenyl)-pyridin-2-yl]-(2,3-dihydro-benzo[1,4]-dioxin-6-yl)-amine (13). To 4-bromopyridine hydrochloride (**39**; 8.9 g, 46 mmol) and tetrakis(triphenylphosphine)palladium(0) (1.6 g, 1.4 mmol) in a round-bottomed flask was added 1,2-dimethoxyethane (250 mL) with stirring under N_2. After 20 min, a solution of aqueous sodium carbonate (9.7 g in 70 mL of H_2O) and 4-*tert*-butylbenzeneboronic acid (**34**; 9.8 g, 55 mmol) were added sequentially to the mixture, and the mixture was stirred at reflux overnight. The reaction mixture was allowed to reach room temperature and the 1,2-dimethoxyethane was evaporated under reduced pressure. To the residue was added EtOAc, and the aqueous phase was separated and extracted with EtOAc (2 × 100 mL). The organic layers were combined, washed with saturated aqueous NaCl, dried over Na_2SO_4, and filtered. The filtrate was evaporated under reduced pressure, and the residue was purified by silica gel flash chromatography (20% EtOAc/hexanes) to give 8.7 g (75%) of 4-(4-*tert*-butyl-phenyl)pyridine (**46**) as a white solid. MS (ESI, pos. ion) *m*/*z*: 212 (M + 1). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.31 (s, 9 H), 7.54 (d, J = 8.3 Hz, 2 H), 7.69 (d, J = 4.7 Hz, 2 H), 7.73 (d, J = 8.3 Hz, 2 H), 8.62 (d, J = 4.1 Hz, 2 H).

To a mixture of 4-(4-*tert*-butyl-phenyl)pyridine (**46**; 8.7 g, 41.3 mmol) and methyltrioxorhenium(VII) (170 mg, 0.7 mmol) in CH_2Cl_2 (18 mL) was added hydrogen peroxide (12 mL) dropwise with stirring at room temperature under N_2. The reaction mixture was stirred at room temperature for 18 h then partitioned between CH_2Cl_2 and saturated aqueous NaCl. The aqueous layer was extracted with CH_2Cl_2 (40 mL) and the combined organic layers were dried over Na_2SO_4 and filtered. The filtrate was evaporated, and the resulting residue was dried in vacuo to give 8.9 g (95%) of 4-(4-*tert*-butyl-phenyl)-pyridine 1-oxide as an off-white solid. MS (ESI, pos. ion) *m*/*z*: 228 (M + 1). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.31 (s, 9 H), 7.51 (d, J = 7.3 Hz, 2 H), 7.71 (d, J = 8.2 Hz, 2 H), 7.75 (d, J = 5.8 Hz, 2 H), 8.25 (d, J = 5.6 Hz, 2 H). To a solution of triphenylphosphine (2.4 g, 9.1 mmol) in CH_2Cl_2 (10 mL) was added bromine (0.43 mL, 8.5 mmol) with stirring at 0 °C. The mixture was stirred at 0 °C for 10 min, and 4-(4-*tert*-butyl-phenyl)-pyridine 1-oxide (1.5 g, 6.5 mmol) was added, followed by Et_3N (1.2 mL). The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 18 h. The reaction mixture was then partitioned between CH_2Cl_2 and saturated aqueous NaCl. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4 and filtered. The filtrate was evaporated under reduced pressure, and the resulting residue was purified by silica gel flash chromatography (10% EtOAc/hexanes) to give 0.25 g (13%) of 2-bromo-4-(4-*tert*-butyl-phenyl)-pyridine (**47**) as a light-yellow oil. MS (ESI, pos. ion) *m*/*z*: 293 (M + 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (s, 9 H), 7.42−7.58 (m, 6 H), 7.71 (s, 1 H), 8.39−8.42 (m, 1 H).

To an oven-dried, 50 mL, round-bottomed flask was added 2-bromo-4-(4-*tert*-butyl-phenyl)-pyridine (**47**; 183 mg, 0.63 mmol) and 1,4-benzodioxan-6-amine (**52**; 191 mg, 1.3 mmol), followed by anhydrous toluene (60 mL) and DMF (6 mL). Nitrogen was bubbled through the solution via a needle for 1 h. Palladium acetate (21 mg, 0.01 mmol) and BINAP (59 mg, 0.01 mmol) were then added to the mixture, followed by sodium *tert*-butoxide (170 mg, 1.8 mmol). The reaction mixture was heated in a 90 °C oil bath for 18 h. After cooling to room temperature, the reaction mixture was dissolved in ether, washed with saturated aqueous NaCl, dried over Na_2SO_4, and filtered. The filtrate was evaporated under reduced pressure, and the residue was purified by silica gel flash chromatography (25% EtOAc/hexanes) to give 0.13 g (53%) of the title compound as a light-tan solid. Mp 162.1−163.1 °C. MS (ESI, pos. ion) *m*/*z*: 361 (M + 1). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.32 (s, 9 H), 4.19 (d, J = 5.1 Hz, 2 H), 4.22 (d, J = 5.1 Hz, 2 H), 6.76 (d, J = 8.7 Hz, 1 H), 6.97−7.02 (m, 3 H), 7.39 (s, 1 H), 7.53 (d, J = 8.4 Hz, 2 H), 7.61 (d, J = 8.4 Hz, 1 H), 8.15 (d, J = 5.9 Hz, 1 H), 8.90 (br s, 1 H). Anal. ($C_{23}H_{24}N_2O_2$): C, H, N.

5-(4-*tert*-Butylphenyl)-*N*-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)pyridin-3-amine (14). A mixture of 3-bromo-5-iodopyridine (**54**; 340 mg, 1.19 mmol), 1,4-benzodioxane-6-amine (**52**; 300 mg, 2 mmol), Pd_2dba_3 (20 mg, 0.022 mmol), dppf (20 mg, 0.036 mmol), sodium *tert*-butoxide (140 mg, 1.44 mmol), and toluene (4 mL) was heated at 150 °C for 10 min in a microwave. The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography (gradient: 1−3% MeOH/CH_2Cl_2) to give 362 mg (99%) of 5-bromo-*N*-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)pyridin-3-amine (**58**) as a light-yellow solid. MS (ESI, pos. ion) *m*/*z*: 307, 309 (M + 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.27 (m, 4 H), 5.54 (s, 1 H), 6.63 (d, J = 8.0 Hz, 1 H), 6.68 (s, 1 H), 6.85 (d, J = 8.0 Hz, 1 H), 7.36 (s, 1 H), 8.09 (s, 1 H), 8.14 (s, 1 H).

A mixture of 5-bromo-*N*-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-pyridin-3-amine (**58**; 154 mg, 0.502 mmol), 4-*tert*-butylphenylboronic acid (**34**; 107 mg, 0.60 mmol), polystyrene triphenylphosphine palladium(0) (45 mg, 0.11 mmol/g, 0.005 mmol), 2 M aqueous solution of Na_2CO_3 (0.75 mL), and a 1:1 mixture of DME/EtOH (4 mL) was heated at 120 °C for 5 min in a microwave. The resulting slurry was filtered. The filtrate was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (gradient: 10−40% EtOAc/hexanes) to give 106 mg (59%) of the title compound as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (s, 9 H), 4.26 (m, 4 H), 5.63 (s, 1 H), 6.65 (d, J = 8.5 Hz, 1 H), 6.71 (s, 1 H), 6.83 (d, J = 8.5 Hz, 1 H), 7.43 (s, 1 H), 7.48 (m, 4 H), 8.22 (s, 1 H), 8.31 (s, 1 H). HRMS calcd for $(C_{23}H_{24}N_2O_2)H^+$, 361.19105; found, 361.19077. LC/MS retention time: [E] 7.88 min; [F] 8.13 min.

2-(4-*tert*-Butylphenyl)-*N*-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)pyridin-4-amine (15). To a 50 mL, round-bottomed flask was added 2-chloro-4-iodopyridine (**53**; 0.29 g, 1.2 mmol), 1,4-benzodioxane-6-amine (**52**; 0.18 g, 1.2 mmol), $Pd(OAc)_2$ (13 mg, 0.06 mmol), 1,1,4,7,7-pentakis(1*H*-benzimidazol-2-ylmethyl)-1,4,7-triazaheptane (DTPB; 18 mg, 0.060 mmol), K_3PO_3 (0.51 g, 2.4 mmol), and toluene (8 mL). The mixture was heated to reflux for 10 h. The reaction mixture was allowed to reach room temperature, and the solvent was removed under reduced pressure. Purification of the residue by silica gel column chromatography (1:1 EtOAc/hexanes) afforded 0.17 g (54%) of 2-chloro-*N*-(2,3-dihydrobenzo-[*b*][1,4]dioxin-6-yl)pyridin-4-amine (**57**). MS (ESI, pos. ion) *m*/*z*: 264 (M + 1).

To a 100 mL, round-bottomed flask containing 2-chloro-*N*-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)pyridin-4-amine (**57**; 0.26 g, 1.0 mmol), was added 4-*tert*-butylphenylboronic acid (**34**; 0.55 g, 3.0 mmol), acetonitrile (6 mL), and 10% aqueous solution of Na_2CO_3 (6 mL). $Pd(PPh_3)_4$ (0.058 g, 0.050 mmol) was added, and the mixture was heated at 90 °C for 8 h. The mixture was allowed to reach room temperature, diluted with 5% aqueous solution of NaCl (10 mL), and then extracted with EtOAc (35 mL). The organic layer was dried over Na_2SO_4 and filtered. The filtrate was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (33% EtOAc/hexanes) to provide 0.56 g (52%) of the title product as a yellow oil. MS (ESI, pos. ion) *m*/*z*: 361 (M + 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (s, 9 H), 4.27 (s, 4 H), 5.94 (s, 1 H), 6.71 (m, 3 H), 6.86 (d, J = 8.5 Hz, 1 H), 7.10 (d, J = 1.8 Hz, 1 H), 7.44 (d, J = 8.3 Hz, 2 H), 7.81 (d, J = 7.3 Hz, 2 H), 8.31 (d, J = 5.6 Hz, 1 H). Anal. ($C_{23}H_{24}N_2O_2 \cdot 0.5H_2O$): C, H, N.

6-(4-*tert*-Butylphenyl)-*N*-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)pyridin-2-amine (16). The intermediate 2-bromo-6-(4-*tert*-butylphenyl)pyridine (**43**) was prepared by the method described for the preparation of compound **46** from 2,6-dibromopyridine (**36**; 2.4 g, 10 mmol), tetrakis(triphenylphosphine)palladium(0) (0.36 g, 0.3 mmol), aqueous sodium carbonate(1.1 g, 10 mmol in 15 mL of H_2O), and 4-*tert*-butylbenzeneboronic acid (**34**; 1.8 g, 10 mmol) in 1,2-dimethoxyethane (50 mL). The solvent was evaporated, and the residue was extracted with EtOAc (2×). The organic layers were combined, dried over Na_2SO_4, filtered, and evaporated to give 2.98 g of **43** as a crude yellow solid. A portion of this crude material (1.0 g, 3.4 mmol), and 1,4-benzodioxan-6-amine (**52**; 1.0 g, 6.8 mmol) were added to an oven-dried, 50 mL, round bottomed flask followed by toluene (170 mL) and DMF (17 mL). The reaction was stirred at room temperature for 1 h as N_2 was bubbled though the solution. Palladium acetate (76 mg, 0.34 mmol) and BINAP (212 mg, 0.34 mmol) were then added to the mixture, followed by sodium *tert*-butoxide (915 mg, 9.5 mmol). The reaction mixture was heated in a 90 °C oil bath for 18 h. After cooling to room temperature, the crude reaction mixture was dissolved in ether and washed with saturated aqueous NaCl. The organic layer was separated, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by column chromatography (1:8 to 1:4 EtOAc/hexanes) to give 0.29 g (24%) of the title compound as a yellow foam. MS (ESI, pos. ion) *m*/*z*: 361 (M + 1). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.32 (s, 9 H), 4.19−4.24 (m, 4 H), 6.69 (d, J = 8.2 Hz, 1 H), 6.78 (d, J = 8.7 Hz, 1 H), 7.08−7.10 (m, 1 H), 7.22 (d, J = 7.4 Hz, 1 H), 7.49 (d, J = 8.4 Hz, 2 H), 7.52−7.60 (m, 2 H), 7.94 (d, J = 8.4 Hz, 2 H), 8.89 (br s, 1 H). Anal. ($C_{23}H_{24}N_2O_2 \cdot 0.25$ H_2O): C, H, N.

6-(4-*tert*-Butylphenyl)-*N*-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)pyrimidin-4-amine (17). To a 500 mL, round-bottomed flask containing 4,6-dichloropyrimidine (**37**; 5.20 g, 34.9 mmol) in 1,4-dioxane (100 mL) was added 4-*tert*-butylphenylboronic acid (**34**; 4.31 g, 24.2 mmol) and $Pd(PPh_3)_4$ (1.01 g, 0.87 mmol). A solution of 2 M K_2CO_3 (44 mL) was added, and the mixture was stirred under N_2 at 90 °C for 5 h. The reaction mixture was allowed to cool to room temperature and concentrated in vacuo to reduce the volume to ∼50 mL. The residue was partitioned between EtOAc (100 mL) and H_2O (200 mL). The aqueous phase was extracted with EtOAc (2 × 100 mL). The combined organic phases were washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered, and concentrated in vacuo to yield 9.67 g of thick magenta colored oil. The crude material was purified by silica gel chromatography (gradient: 0−30% EtOAc/hexanes), followed by a second silica gel chromatography (gradient: 50−100% $CHCl_3$/hexanes) to give 5.42 g (63%) of 6-[4-(*tert*-butyl)phenyl]-4-chloropyrimidine (**44**) as a white solid. MS (ESI, pos. ion.) *m*/*z*: 247 (M + 1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (s, 9 H), 7.55 (d, J = 8.7 Hz, 2 H), 7.73 (s, 1 H), 8.02 (d, J = 8.7 Hz, 2 H), 9.02 (s, 1 H).

A mixture of 6-[4-(*tert*-butyl)phenyl]-4-chloropyrimidine (**44**; 0.25 g, 1.0 mmol) and 1,4-benzodioxane-6-amine (**52**; 0.15 g, 1.0 mmol) in 1,4-dioxane (5 mL) was heated at reflux under N_2 for 3 h. The reaction mixture was allowed to reach room temperature and then was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (1:2 EtOAc/hexanes) to provide the title product as an off-white solid, yield 0.185 g (51%). Mp 199−202 °C. MS (ESI, pos. ion) *m*/*z*: 362 (M + 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (s, 9 H), 4.28 (s, 4 H), 6.82 (m, 3 H), 6.97 (s, 1 H), 7.48 (d, J = 8.5 Hz, 2 H), 7.88 (d, J = 8.5 Hz, 2 H), 8.61 (s, 1 H). Anal. ($C_{22}H_{23}N_3O_2 \cdot 0.25$ H_2O): C, H, N.

4-(4-*tert*-Butylphenyl)-*N*-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)pyrimidin-2-amine (18). To a 100 mL, round-bottomed flask

was added 4-chloro-2-(methylthio)pyrimidine (**40**; 0.32 g, 2.0 mmol, Aldrich), 4-*tert*-butylphenylboronic acid (**34**; 0.35 g, 2.0 mmol), CH_3CN (15 mL), and 10% aqueous Na_2CO_3 (10 mL). $Pd(PPh_3)_4$ (0.45 g, 0.39 mmol) was added, and the mixture was heated at 90 °C for 6 h. The product was extracted with EtOAc (15 mL). The combined organic extracts were washed with 5% aqueous NaCl, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel chromatography (20% EtOAc/hexanes) afforded 0.45 g (89%) 4-(4-*tert*-butylphenyl)-2-(methylthio)pyrimidine (**48**) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (s, 9 H), 2.65 (s, 3 H), 7.34 (d, J = 4.0 Hz, 1 H), 7.52 (d, J = 8.0 Hz, 2 H), 8.03 (d, J = 8.0 Hz, 2 H), 8.51 (d, J = 4.0 Hz, 1 H). MS (ESI, pos. ion) m/z: 259 (M + 1).

To a 100 mL, round-bottomed flask was added 4-(4-*tert*-butylphenyl)-2-(methylthio)pyrimidine (**48**; 0.11 g, 0.43 mmol), *m*-CPBA (0.15 g, 0.85 mmol), and CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temperature for 1 h. The solution was concentrated with a rotary evaporator, and the residue was purified by silica gel chromatography with 1:2 EtOAc/hexanes to afford 0.10 g (86%) of 4-(4-*tert*-butylphenyl)-2-(methylsulfinyl)pyrimidine (**49**) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (s, 9 H), 3.43 (s, 3 H), 7.57 (d, J = 8.0 Hz, 2 H), 7.88 (d, J = 8.00 Hz, 1 H), 8.10 (d, J = 12.0 Hz, 2 H), 8.89 (d, J = 4.0 Hz, 1 H). MS (ESI, pos. ion) m/z: 275 (M + 1).

A mixture of 4-(4-*tert*-butylphenyl)-2-(methylsulfinyl)pyrimidine (**49**; 0.47 g, 1.7 mmol) and 1,4-benzodioxane-6-amine (**52**; 0.26 g, 1.7 mmol) in 1,4-dioxane (8 mL) and EtOH (8 mL) was heated at reflux under N_2 for 22 h. The reaction mixture was allowed to reach room temperature and evaporated under reduced pressure. The residue was purified by silica gel chromatography (1:5 EtOAc/hexanes) to provide 0.31 mg (51%) of the title product as a yellow solid. Mp 199−202 °C. MS (ESI, pos. ion) m/z: 362 (M + 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (s, 9 H), 4.27 (m, 4 H), 6.85 (d, J = 8.7 Hz, 1 H), 7.06 (m, 3 H), 7.39 (d, J = 2.5 Hz, 1 H), 7.52 (dd, J = 6.7, 1.7 Hz, 2 H), 7.99 (dd, J = 6.7, 1.7 Hz, 2 H), 8.41 (d, J = 5.2 Hz, 1 H). Anal. ($C_{22}H_{23}N_3O_2 \cdot 0.25\ H_2O$): C, H, N.

(2-(4-*tert*-Butylphenyl)-*N*-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)pyrimidin-4-amine (19). A mixture of 2,4-dichloropyrimidine (**55**; 1.0 g, 6.7 mmol) and 1,4-benzodioxane-6-amine (**52**; 1.0 g, 6.7 mmol) in EtOH (30 mL) was stirred at room temperature for 12 h. The solvent was removed in vacuo, and the residue was taken in CH_2Cl_2/MeOH (2:1 v/v, 8 mL). The insoluble material was filtered through a fritted glass funnel, and the filtrate was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (1:3 ethyl acetate/hexanes) to give 0.40 g (23%) of 2-chloro-*N*-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)pyrimidin-4-amine (**59**) as a yellow oil. MS (ESI, pos. ion) m/z: 264 (M + 1).

To a 100 mL, round-bottomed flask containing 2-chloro-*N*-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)pyrimidin-4-amine (**59**; 0.12 g, 0.46 mmol) was added 4-*tert*-butylphenylboronic acid (**34**; 0.16 g, 0.91 mmol), acetonitrile (10 mL), and 10% aqueous solution of Na_2CO_3 (6 mL). $Pd(PPh_3)_4$ (0.036 g, 0.023 mmol) was added, and the mixture was heated at 90 °C for 14 h. After cooling to 25 °C, the mixture was diluted with 5% aqueous NaCl (10 mL) and the product was extracted with EtOAc (35 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The product was purified by silica gel chromatography (1:3 EtOAc/hexanes) to provide 0.10 g (60%) of the title compound as an off-white solid. Mp 68−71 °C. MS (ESI, pos. ion) m/z: 362 (M + 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (s, 9 H), 4.28 (s, 4 H), 6.50 (d, J = 5.9 Hz, 1 H), 6.76 (s, 1 H), 6.85 (m, 2 H), 6.95 (d, J = 2.4 Hz, 1 H), 7.48 (dd, J = 6.7, 1.8 Hz, 2 H), 8.29 (dd, J = 6.7, 1.8 Hz, 2 H), 8.34 (d, J = 5.9 Hz, 1 H). Anal. ($C_{22}H_{23}N_3O_2 \cdot 0.1H_2O$): C, H, N.

5-(4-*tert*-Butylphenyl)-*N*-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)pyridazin-3-amine (20). A mixture of 2-(4-*tert*-butylphenyl)-acetonitrile (**61**; 13.01 g, 75.08 mmol), glyoxylic acid hydrate (10.43 g, 113.3 mmol), and potassium carbonate (26.34 g, 190.6 mmol) was suspended in MeOH (250 mL) and heated at reflux for 1 h. The reaction mixture was allowed to reach room temperature, and the resulting thick solid precipitate was collected by filtration. The filter cake was washed with MeOH and CH_2Cl_2 and then dissolved in H_2O (500 mL). The aqueous solution was cooled with an ice−water bath, and the crystalline precipitate was collected by filtration. The mother liquor was concentrated, and the resulting residue was redissolved into H_2O (250 mL). Subsequent cooling afforded additional product. The crops were combined and dried in the air to afford 8.85 g (44%) of (*Z*)-3-(4-*tert*-butylphenyl)-3-cyanoacrylate (**62**). MS (ESI, pos. ion) m/z: 230 (M + 1). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.28 (s, 9 H), 7.03 (s, 1 H), 7.42−7.55 (m, 4 H).

A solution of (*Z*)-3-(4-*tert*-butylphenyl)-3-cyanoacrylate (**62**; 8.65 g, 32.35 mmol) in 88% formic acid (80 mL) containing concentrated H_2SO_4 (6 mL) was stirred at reflux for 3 h. The reaction mixture was allowed to cool to room temperature and then cooled further in an ice bath. The resulting solid precipitate was filtered, washed with H_2O, and air-dried to afford 6.25 g (84%) of 3-(4-*tert*-butylphenyl)furan-2,5-dione (**63**). MS (ESI, pos. ion) m/z: 231 (M + 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (s, 9 H), 6.95 (s, 1 H), 7.54 (dt, J = 8.8, 2.1 Hz, 2 H), 7.93 (dt, J = 8.8, 2.1 Hz, 2 H).

To a solution of 3-(4-*tert*-butylphenyl)furan-2,5-dione (**63**; 6.05 g, 26.3 mmol) in acetic acid (50 mL) was added hydrazine hydrate (1.4 mL) dropwise with stirring at room temperature. The reaction mixture was stirred at room temperature for 1.5 h and heated at reflux for 4.5 h. The reaction mixture was allowed to cool to room temperature, and the resulting precipitate was collected via filtration through a filter funnel to afford 3.57 g of 4-(4-*tert*-butylphenyl)-1,2-dihydropyridazine-3,6-dione (**64**). The filtrate was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (10% MeOH/CH_2Cl_2) to give 0.367 g of additional product. The combine yield was 3.94 g (61%). MS (ESI, pos. ion) m/z: 245 (M+1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (s, 9 H), 7.24 (s, 1 H), 7.51 (d, J = 8.5 Hz, 2 H), 7.77 (d, J = 8.5 Hz, 2 H).

A mixture of 4-(4-*tert*-butylphenyl)-1,2-dihydropyridazine-3,6-dione (**64**) (3.38 g, 13.8 mmol) and $POCl_3$ (20 mL) was stirred at 72 °C for 5 h under N_2. The reaction mixture was cooled to room temperature and the excess of $POCl_3$ was evaporated under reduced pressure. The residue was quenched with crushed ice, and the mixture was neutralized by the addition of a saturated aqueous solution of $NaHCO_3$. The solid precipitate was collected by filtration, and the filter cake was washed with H_2O and dried in vacuo to afford 3.1 g (93%) of 4-(4-*tert*-butylphenyl)-3,6-dichloropyridazine (**65**) as a tan solid. MS (ESI, pos. ion) m/z: 245 (M+1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (s, 9 H), 7.44−7.51 (m, 3 H), 7.52−7.58 (m, 2 H).

A mixture of 4-(4-*tert*-butylphenyl)-3,6-dichloropyridazine (**65**) (0.150 g, 0.53 mmol) and 1,4-benzodioxan-6-amine (**52**) (0.080 g, 0.53 mmol) in EtOH (3 mL) was stirred at 180 °C for 20 min in a microwave. The reaction mixture was evaporated under reduced pressure, and the residue was purified by silica gel flash column chromatography (3:1 EtOAc/hexanes) to afford 0.14 g (65%) of 5-(4-*tert*-butylphenyl)-6-chloro-*N*-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)pyridazin-3-amine (**66**). MS (ESI, pos. ion) m/z: 396 (M+1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (s, 9 H), 4.27 (s, 4 H), 6.71−6.80 (m, 1 H), 6.81−6.90 (m, 2 H), 6.94 (s, 1 H), 7.06 (s, 1 H), 7.34−7.43 (m, 2 H), 7.45−7.56 (m, 2 H). MS (ESI, pos. ion) m/z: 396 (M+1).

A mixture of 5-(4-*tert*-butylphenyl)-6-chloro-*N*-(2,3-dihydrobenzo-[*b*][1,4]dioxin-6-yl)pyridazin-3-amine (**66**) (0.053 g, 0.134 mmol), EtOH (8 mL) and Zn (highly reactive Rieke metal, suspension in THF, 2 mL, 0.1 g/mL) was heated at 72 °C for 48 h under N_2. The reaction mixture was allowed to cool to room temperature and was filtered through a pad of Celite. The filtrate was evaporated under reduced pressure and the residue was purified by reverse phase HPLC (Phenomenex, Luna 10 μM C18(2), 100 Å, 150 × 30 mm; 1−99% CH_3CN(0.1% TFA)/H_2O (0.1%TFA)) followed by preparative TLC (Whatman Silica Gel 60 Å (20 × 20 cm, 1000 μm); 5% MeOH/ CH_2Cl_2 + 1% NH_4OH) to afford 0.015 g (30%) of the title compound. MS (ESI, pos. ion) m/z: 362 (M+1). ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 9 H), 4.25−4.32 (m, 4 H,) 6.78−6.84 (m, 1 H), 6.86−6.92 (m, 2 H), 7.12 (d, J = 1.9 Hz, 1 H), 7.22 (br s, 1 H),

7.49−7.56 (m, 4 H), 8.88 (d, J = 1.9 Hz, 1 H). Anal. ($C_{22}H_{23}N_3O_2 \cdot 0.75H_2O$): C, H, N.

6-(4-*tert*-Butylphenyl)-*N*-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)pyridazin-4-amine (21). A 2 N aqueous solution of K_2CO_3 (3.0 mL) and $Pd(PPh_3)_4$ (0.295 g, 0.26 mmol) were added to a solution of 3-chloro-5-methoxypyridazine (**41**)[38] (0.330 g, 2.28 mmol) and 4-*tert*-butylphenylboronic acid (**34**) (0.616 g, 3.46 mmol) in diethylene glycol dimethyl ether (4.0 mL). The yellow suspension was stirred at 90 °C for 18 h under N_2. The reaction mixture was allowed to cool to room temperature and was filtered through a pad of Celite. The filtrate was evaporated under reduced pressure and the residue was diluted with EtOAc. The organic phase was separated, washed successively with H_2O and saturated aqueous NaCl, dried over Na_2SO_4, and filtered. The filtrate was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (70% EtOAc/hexanes) to afford 0.52 g (88%) of 3-(4-*tert*-butylphenyl)-5-methoxypyridazine (**50**). MS (ESI, pos. ion) *m*/*z*: 243 (M+1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 (s, 9 H), 4.00 (s, 3 H), 7.25 (d, J = 2.8 Hz, 1 H), 7.51−7.60 (m, 2 H), 7.96−8.03 (m, 2 H), 8.88 (d, J = 2.8 Hz, 1 H).

A mixture of 3-(4-*tert*-butylphenyl)-5-methoxypyridazine (**50**) (0.24 g, 1.00 mmol) and 47% HI (3.0 mL) was stirred at 150 °C for 90 min in a microwave. The reaction mixture was filtered, and the filter cake was washed successively with H_2O then CH_2Cl_2. The material was allowed to air-dry to give 0.20 g (88%) of 6-(4-*tert*-butylphenyl)pyridazin-4-ol as pale-yellow crystals. MS (ESI, pos. ion) *m*/*z*: 229 (M+1). ^{1}H NMR (CD_3OD): δ 1.40 (s, 9 H), 7.70 (d, J = 2.8 Hz, 1 H), 7.73−7.79 (m, 2 H), 7.83−7.90 (m, 2 H), 8.78 (d, J = 2.8 Hz, 1 H). 6-(4-*tert*-Butylphenyl)pyridazin-4-ol (0.248 g, 1.0 mmol) was reacted with $POCl_3$ (3.0 mL) under the conditions described for compound **65** to give 0.13 g (51%) of the title compound as a crystalline solid. MS (ESI, pos. ion) *m*/*z*: 247 (M+1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 (s, 9 H), 7.54−7.60 (m, 2 H), 7.87 (d, J = 2.3 Hz, 1 H), 8.02 (d, J = 8.7 Hz, 2 H), 9.13 (d, J = 2.1 Hz, 1 H).

Reaction of 3-(4-*tert*-butylphenyl)-5-chloropyridazine (**51**) (0.063 g, 0.256 mmol) with 1,4-benzodioxan-6-amine (**52**) (0.050 g, 0.327 mmol), under the conditions described for compound **66**, gave 0.074 g (80%) of the title compound as tan solid. MS (ESI, pos. ion) *m*/*z*: 362 (M+1). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.32 (s, 9 H), 4.25 (s, 4 H), 6.72−6.95 (m, 3 H), 7.21 (d, J = 2.6 Hz, 1 H), 7.52 (d, J = 8.3 Hz, 2 H), 7.87 (d, J = 8.3 Hz, 2 H), 8.70 (d, J = 2.6 Hz, 1 H), 8.97 (s, 1 H). Anal. ($C_{22}H_{23}N_3O_2 \cdot 0.25H_2O$): C, H, N.

6-(4-*tert*-Butylphenyl)-*N*-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)pyrazin-2-amine (22). To a 20 mL microwave reaction tube was added 2,6-dichloropyrazine (**38**; 0.516 g, 3.46 mmol), 4-*tert*-butylbenzeneboronic acid (**34**; 0.558 g, 3.13 mmol), $Pd(PPh_3)_4$ (0.402 g, 0.348 mmol), and 1,4-dioxane (8 mL). The mixture was deoxygenated by bubbling argon through the solution for 5 min. Potassium carbonate (1.80 mL of a 2.0 M solution, 3.60 mmol) was added. The solution was heated at 140 °C for 20 min in a microwave. The reaction mixture was partitioned between H_2O and EtOAc. The aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic phases were washed successively with H_2O and saturated aqueous NaCl. The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo to afford 1.34 g of pale yellow oil. The crude product was purified by silica gel chromatography (EtOAc/hexanes 0−20%), followed by additional silica gel chromatography (0−60% CH_2Cl_2/hexanes) to afford 412 mg (48%) of 2-(4-*tert*-butylphenyl)-6-chloropyrazine (**45**) as a clear oil. MS (ESI, pos. ion.) *m*/*z*: 247 (M + 1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (s, 9 H), 7.54 (d, J = 8.5 Hz, 2 H), 7.97 (d, J = 8.5 Hz, 2 H), 8.49 (s, 1 H), 8.92 (s, 1 H).

To a 5 mL microwave reaction tube was added 2-(4-*tert*-butylphenyl)-6-chloropyrazine (**45**; 0.315 g, 1.28 mmol), 2,3-dihydrobenzo[*b*][1,4]dioxin-6-amine (**52**; 0.203 g, 1.34 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.0333 g, 0.0364 mmol), 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl (0.0320 g, 0.0813 mmol), and sodium *tert*-butoxide (0.1487 g, 1.55 mmol) in toluene (3 mL). The mixture was deoxygenated by bubbling Ar through the solution for 5 min and then stirred at 120 °C for 20 min in a microwave. The reaction mixture was partitioned between H_2O (50 mL) and EtOAc (50 mL). The aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic phases were washed with saturated aqueous NaCl. The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo to afford 0.53 g of a light brown solid. The solid was washed with CH_2Cl_2 and purified by silica gel chromatography (gradient: 30−70% EtOAc/hexanes) to afford 265 mg (57%) of the title compound as a light-yellow solid. MS (ESI, pos. ion.) *m*/*z*: 362 (M + 1). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.33 (s, 9 H), 4.13−4.33 (m, 4 H), 6.83 (d, J = 8.9 Hz, 1 H), 7.13 (dd, J = 8.8, 2.5 Hz, 1 H), 7.46−7.62 (m, 3 H), 7.98 (d, J = 8.5 Hz, 2 H), 8.09 (s, 1 H), 8.43 (s, 1 H), 9.39 (s, 1 H). Anal. ($C_{22}H_{23}N_3O_2 \cdot 0.25H_2O$): C, H, N.

4-(4-*tert*-Butylphenyl)-*N*-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-1,3,5-triazin-2-amine (23). To a 5 mL reaction vial was added 2,4-dichloro-1,3,5-triazine (**56**; 0.407 g, 2.72 mmol), 1,4-benzodioxane-6-amine (**52**; 0.412 g, 2.73 mmol), and *t*-BuOH (3 mL). The gray mixture was stirred at room temperature for 20 min. The reaction mixture was poured into 50 mL of saturated aqueous $NaHCO_3$. The aqueous phase was extracted with EtOAc (50 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by silica gel chromatography (gradient: 0−100% EtOAc/hexanes) to provide 0.376 g (52%) of 4-chloro-*N*-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-1,3,5-triazin-2-amine (**60**) as a tan solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.25−4.33 (m, 4 H) 6.85−6.97 (m, 2 H) 7.18 (s, 1 H) 7.35 (s, 1 H), 8.44−8.56 (m, 1 H). MS (ESI, pos. ion) *m*/*z*: 265 (M + 1).

To a 5 mL microwave reaction vial was added 4-chloro-*N*-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-1,3,5-triazin-2-amine (**60**; 0.190 g, 0.716 mmol), 4-*tert*-butylphenylboronic acid (**34**; 0.156 g, 0.878 mmol), tetrakis(triphenylphosphine) palladium(0) (0.049 g, 0.042 mmol) and 1,4-dioxane (3 mL). Ar was bubbled through the solution for 5 min. A 2 M aqueous solution of K_2CO_3 (2.0 M, 0.900 mL, 1.80 mmol) was added to the solution as the Ar bubbling was continued. The reaction mixture was stirred at 130 °C for 10 min in microwave. The reaction mixture was partitioned between H_2O and EtOAc. The aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting brown residue was purified by silica gel chromatography to afford 0.048 g (19%) of the title compound as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (s, 9 H), 4.25−4.35 (m, 4 H,) 6.89 (d, J = 8.67 Hz, 1 H), 7.03 (br s, 1 H), 7.19 (br s, 1 H), 7.35 (br s, 1 H), 7.53 (d, J = 8.7 Hz, 2 H), 8.36 (d, J = 8.3 Hz, 2 H), 8.75 (br s, 1 H). MS (ESI, pos. ion) *m*/*z*: 363 (M + 1). Anal. ($C_{21}H_{22}N_4O_2$): C, H, N.

6-(4-*tert*-Butylphenyl)-N-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-N-methylpyrimidin-4-amine (24). To a glass vial was added 4-(4-*tert*-butylphenyl)-6-chloropyrimidine (**44**; 0.10 g, 0.4 mmol), 2,3-dihydrobenzo[*b*][1,4]dioxin-6-amine (**52**; 0.06 g, 0.4 mmol), and EtOH (1.5 mL). The reaction mixture was stirred in a microwave at 170 °C for 15 min. The solution was concentrated in vacuo and the crude product was dissolved in acetone (5 mL). Iodomethane (0.1 mL, 3.2 mmol) and MP-carbonate (0.25 g, 0.8 mmol) were added, and the reaction mixture was shaken at room temperature for 16 h. The reaction mixture was concentrated in vacuo, and the crude residue was purified by silica gel chromatography (1:1 ethyl acetate/hexanes) to afford 3.53 g (71%) of the title compound as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 9 H), 3.54 (s, 3 H), 4.28 (s, 4 H), 6.42 (dd, J = 2.4, 8.4 Hz, 1 H), 6.46 (d, J = 2.4 Hz, 1 H), 6.71(s, 1 H), 6.83 (d, J = 8.4 Hz, 1 H), 7.41 (d, J = 8.4 Hz, 2 H), 7.70 (d, J = 8.4 Hz, 2 H), 7.98 (s, 1 H). HRMS calcd for $(C_{23}H_{25}N_3O_2)H^+$, 376.20250; found, 376.20240. LC/MS retention time: [A] 11.16 min; [C] 6.29 min.

4-(4-*tert*-Butylphenyl)-6-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yloxy)pyrimidine (25). To a 50 mL, round-bottomed flask was added 3,4-(ethylenedioxy)phenol (**67**;[41] 46 mg, 302 μmol), 4-(4-*tert*-butylphenyl)-6-chloropyrimidine (**44**; 75 mg, 302 μmol), cesium carbonate (99 mg, 302 μmol), and DMF (2 mL). The reaction mixture was stirred at 65 °C for 30 min and then allowed to cool

to room temperature. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (2 × 40 mL). The combined organic extracts were washed successively with H_2O, saturated aqueous NaCl, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography, eluting with 40% EtOAc/hexanes to give 48 mg (44%) of the title compound as a white solid. Mp 137−138 °C. ^{1}H NMR (400 MHz,-$CDCl_3$): δ ppm 1.36 (s, 9 H), 4.29 (s, 4 H), 6.67 (dd, J = 8.80, 2.74 Hz, 1 H), 6.74 (d, J = 2.74 Hz, 1 H), 6.92 (d, J = 8.80 Hz, 1 H), 7.21 (s, 1 H), 7.52 (d, J = 8.61 Hz, 2 H), 7.98 (d, J = 8.61 Hz, 2 H), 8.84 (s, 3 H). (ESI, pos. ion) *m*/*e*: 363 (M^+ + 1). Anal. ($C_{22}H_{22}N_2O$): C, H, N.

4-(4-*tert*-Butylphenyl)-6-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-ylthio)pyrimidine (26). This material was prepared according to the method describe for compound **25** from 4-(4-*tert*-butylphenyl)-6-chloropyrimidine (**44**; 123 mg, 499 μmol), 3,4-(ethylenedioxy)-thiophenol (**68**; 84 μL, 499 μmol), and cesium carbonate (325 mg, 997 μmol) in DMF (1 mL). The crude product was purified by silica gel chromatography (40% EtOAc/hexanes) to afford 123 mg (65%) of the title compound as a white solid. Mp: 132−133 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.34 (s, 9 H), 4.29 − 4.38 (m, 4 H), 6.99 (d, J = 8.22 Hz, 1 H), 7.09 − 7.14 (m, 1 H), 7.17 (d, J = 2.93 Hz, 2 H), 7.47 (d, J = 8.61 Hz, 2 H), 7.82 (d, J = 8.80 Hz, 2 H), 8.94 (s, 1 H). MS (ESI, pos. ion) *m*/*e*: 379 (M^+ + 1). Anal. ($C_{22}H_{22}N_2O_2S$): C, H, N.

4-(4-*tert*-Butylphenyl)-6-((2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)methyl)pyrimidine (27). Sodium hydride (60% dispersion in mineral oil, 10 mg, 0.3 mmol) was added to a stirred solution of 4-(4-*tert*-butylphenyl)-6-chloropyrimidine (**44**; 50 mg, 0.2 mmol), 2,3-dihydrobenzo[*b*][1,4]dioxine-6-carbaldehyde (36 mg, 0.3 mmol), and 1,3-dimethylimidazolium iodide (5 mg, 0.1 mmol) in dioxane (20 mL). The mixture was stirred at reflux for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was partitioned between EtOAc (100 mL) and H_2O (70 mL). The organic extract was dried over Na_2SO_4, filtered, and concentrated. Purification by silica gel chromatography (2:3 ethyl acetate/hexanes) afforded 44 mg (58%) of (6-(4-*tert*-butylphenyl)pyrimidin-4-yl)-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)methanone (**69**) as a tan oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (s, 9 H), 4.28 (m, 4 H), 6.96 (d, J = 8.4 Hz, 1 H), 7.55 (d, J = 8.4 Hz, 1 H), 7.72 (m, 2 H), 8.11 (d, J = 8.4 Hz, 2 H), 8.34 (s, 1 H), 9.35 (s, 1 H). MS (ESI, pos. ion) *m*/*z*: 375 (M + 1).

Sodium borohydride (20 mg, 0.5 mmol) was added to a stirred solution of (6-(4-*tert*-butylphenyl)pyrimidin-4-yl)(2,3-dihydrobenzo-[*b*][1,4]dioxin-6-yl)methanone (**69**; 0.10 g, 1 mmol) in MeOH (5 mL), and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was partitioned between EtOAc (10 mL) and H_2O (20 mL). The organic extract was dried over Na_2SO_4, filtered, and concentrated. Purification by silica gel chromatography (1:1 ethyl acetate/hexanes) afforded 74 mg (74%) of the title compound as a tan oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.33 (s, 9 H), 4.19 (s, 4 H), 5.59 (s, 1 H), 6.27 (s, 1 H), 6.78 (d, J = 8.8 Hz, 1 H), 6.91 (m, 2 H), 7.59 (d, J = 8.8 Hz, 2 H), 8.13 (d, J = 8.8 Hz, 2 H), 9.07 (s, 1 H). MS (ESI, pos. ion) *m*/*z*: 377 (M + 1).

Benzoyl chloride (45 mg, 0.3 mmol) was added to a stirred solution of (6-(4-*tert*-butylphenyl)pyrimidin-4-yl)(2,3-dihydrobenzo-[*b*][1,4]dioxin-6-yl)methanol (**70**) (100 mg, 0.3 mmol) and pyridine (1.0 mL, 12.3 mmol) in anhydrous THF (7 mL). The mixture was stirred at room temperature for 16 h. The solution was concentrated under reduced pressure and the residue was dissolved in EtOAc (20 mL) and washed with H_2O (2 × 20 mL). The organic extract was dried over $MgSO_4$ and passed through a silica gel plug to afford 96 mg of crude (6-(4-*tert*-butylphenyl)pyrimidin-4-yl)(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)methyl benzoate. A solution of this crude material (50 mg, 1 mmol) and 10% palladium-carbon (200 mg) in MeOH (5 mL) was stirred under H_2 (balloon) for 20 h. The reaction mixture was filtered through a layer of Celite and the filtrate was concentrated in vacuo. Purification by silica gel chromatography (1:4 ethyl acetate/hexanes) afforded 11 mg (10%) of the title compound as a tan oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (s, 9 H), 4.07 (s, 2 H), 4.26 (s, 4 H), 6.82 (m, 3 H), 7.51 (m, 3 H), 7.98 (d, J = 8.8 Hz, 2 H), 9.19 (s, 1 H). HRMS: Calcd for ($C_{23}H_{25}N_3O_2$)-H^+: 361.19160; Found: 361.19011. LC/MS retention time: [B] 8.66 min; [D] 9.70 min.

***N*-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-6-(4-(trifluoromethyl)phenyl) pyrimidin-4-amine (73).** To a 500 mL, round-bottomed flask was added 4,6-dichloropyrimidine (**37**) (14 g, 95 mmol), 4-(trifluoromethyl)phenylboronic acid (**71**) (6.0 g, 32 mmol), acetonitrile (95 mL) and 1 M aqueous solution of sodium carbonate (95 mL). The mixture was deoxygenated by sparging the solution with N_2 for 15 min. The catalyst, $Pd(PPh_3)_4$ (1.9 g, 1.6 mmol), was added and the resulting yellow mixture was stirred at 80 °C for 15 h. After cooling to 25 °C, the reaction mixture was concentrated under reduced pressure to remove the acetonitrile. The residue was diluted with an aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3×). The combined extracts were dried over Na_2SO_4 and filtered. The filtrate was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (gradient: 1.5−10% EtOAc/hexanes) to afford 3.4 g (41%) of 4-chloro-6-(4-(trifluoromethyl)phenyl)pyrimidine (**72**) as a white solid. MS (ESI, pos. ion) *m*/*z*: 259 (M + 1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78−7.81 (m, 3 H), 8.20 (d, J = 8.1 Hz, 2 H), 9.09 (s, 1 H).

To a 5-mL microwave vial was added 4-chloro-6-(4-(trifluoromethyl)phenyl)pyrimidine (**72**; 0.10 g, 0.39 mmol), 2,3-dihydrobenzo[*b*][1,4]dioxin-6-amine (**52**; 0.089 g, 0.59 mmol), and EtOH (4.0 mL). The reaction mixture was stirred at 180 °C for 30 min in a microwave. After cooling to room temperature, the reaction mixture was concentrated in vacuo, and the residue was dissolved in CH_2Cl_2. The solution was washed successively with 10% aqueous Na_2CO_3, H_2O, and saturated aqueous NaCl. The organic layer was dried over Na_2SO_4 and filtered. Silica gel was added to the filtrate, and the solvent was removed with a rotary evaporator. The crude material was purified by silica gel chromatography (gradient, 10−40% EtOAc/hexanes) to afford 0.064 g (46%) of the title compound as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.21−4.28 (m, 4 H), 6.85 (d, J = 8.6 Hz, 1 H), 7.06 (dd, J = 8.7, 2.4 Hz, 1 H), 7.22 (d, J = 1.0 Hz, 1 H), 7.35 (d, J = 1.8 Hz, 1 H), 7.91 (d, J = 8.2 Hz, 2 H), 8.22 (d, J = 8.0 Hz, 2 H), 8.71 (d, J = 0.6 Hz, 1 H), 9.61 (s, 1 H). MS (ESI, pos. ion) *m*/*z*: 374 (M + 1). Anal. ($C_{19}H_{14}F_3N_3O_2$): C, H, N.

7-(6-(4-(Trifluoromethyl)phenyl)pyrimidin-4-yloxy)quinoline (74). To a 100 mL, round-bottomed flask containing 6-(4-trifluoromethylphenyl)-4-chloropyrimidine (**72**; 2.5 g, 9.7 mmol) and 7-hydroxyquinoline (2.0 g, 14 mmol) in DMF (30 mL), was added sodium hydride (0.54 g, 60%, 14 mmol) in portions. The mixture was stirred at room temperature for 4 h, and the reaction was quenched carefully with ice−water. The mixture was diluted with EtOAc (100 mL), and the organic layer was washed with H_2O (50 mL). The insoluble material was filtered and collected, and the organic phase was dried with Na_2SO_4, filtered, and concentrated. The insoluble material and the residue were combined and purified by silica gel chromatography (50% EtOAc/hexanes) to provide 2.4 g (67%) of the title product as a white solid. Mp 178−180 °C. MS (ESI, pos. ion) *m*/*z*: 368 (M + 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (m, 3 H), 7.78 (d, J = 8.0 Hz, 2 H), 7.93 (d, J = 8.0 Hz, 2 H), 8.22 (m, 3 H), 8.88 (s, 1 H), 8.96 (dd, J = 4.4, 1.6 Hz, 1 H). Anal. ($C_{20}H_{12}F_3N_3O$): C, H, N.

***N*-(6-(4-*tert*-Butylphenyl)pyrimidin-4-yl)quinolin-7-amine (78).** A solution of 7-nitro-1,2,3,4-tetrahydro-quinoline (**74**;[43] 4.0 g, 22 mmol) in dichloromethane (500 mL) was stirred at 25 °C and treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (10 g, 44 mmol) in portions. The reaction mixture was stirred at 25 °C for 1 h and filtered, and the filter cake was washed with CH_2Cl_2. The combined filtrate was evaporated under reduced pressure to give the crude product as a brown solid (4.4 g). The solid was dissolved in hot EtOAc (200 mL), and the solution was treated with decolorizing carbon (1 g) and filtered though Celite. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (25% EtOAc/hexanes) to give 3.2 g (81%) of 7-nitroquinoline (**75**) as an off-white solid. MS (ESI, pos. ion)

m/*z*: 175 (M + 1). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.77−7.80 (m, 1 H), 8.29 (d, J = 9.0 Hz, 1 H), 8.35 (dd, J = 9.0, 2.3 Hz, 1 H), 8.60 (d, J = 8.3 Hz, 1 H), 8.82 (d, J = 2.0 Hz, 1 H), 9.13 (dd, J = 4.2, 1.6 Hz, 1 H).

The solution of 7-nitroquinoline (**75**; 3.2 g, 18 mmol) in MeOH (200 mL) was purged with N_2 and treated with 10% palladium on carbon (1.0 g). The suspension was purged with H_2 and stirred under 1 atm H_2 for 16 h. The mixture was purged with N_2 and filtered through Celite. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (gradient: 5−10% MeOH/ CH_2Cl_2) to give 710 mg (27%) of quinolin-7-amine (**76**) as a brown solid. MS (ESI, pos. ion) *m*/*z*: 145 (M + 1). ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.75 (br s, 2 H), 6.93 (s, 1 H), 6.98 (d, J = 8.6 Hz, 1 H), 7.07 (dd, J = 7.8, 4.2 Hz, 1 H), 7.60 (d, J = 8.6 Hz, 1 H), 8.00 (d, J = 7.8 Hz, 1 H), 8.58 (d, J = 2.9 Hz, 1 H).

To a 5 mL microwave reaction tube was added 4-(4-*tert*-butylphenyl)-6-chloropyrimidine (**44**; 0.200 g, 0.811 mmol), quinolin-7-amine (**76**; 0.124 g, 0.861 mmol), tris(dibenzylideneacetone)-dipalladium(0) (0.022 g, 0.024 mmol), 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl (0.0202 g, 0.0513 mmol), and sodium *tert*-butoxide (0.117 g, 1.22 mmol) in toluene (2.5 mL). The solution was stirred in a microwave at 120 °C for 20 min. The resulting precipitate was collected via filtration through a filtered funnel and washed with EtOAc and H_2O. The crude material was purified by preparative reverse phase HPLC (Phenomenex, Luna 10 μM C18(2), 100 Å, 150 × 30 mm; 1−99% MeCN (0.1% TFA)/ H_2O (0.1% TFA)). The acetonitrile was removed with a rotary evaporator to provide an aqueous suspension. The solid was collected by filtration and dissolved in EtOAc. The resulting solution was washed with a saturated aqueous solution of $NaHCO_3$. The organic phase was dried over Na_2SO_4, filtered, and concentrated. The residue was purified further by silica gel chromatography (0−10% IPA/$CHCl_3$ w/ 1% NH_3OH) to afford 0.042 g (15%) of the title compound as a white solid. Mp 260.5−262.3 °C. MS (ESI, pos. ion.) *m*/*z*: 355 (M + 1). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.33 (s, 9 H), 7.31−7.45 (m, 2 H), 7.58 (d, J = 8.6 Hz, 2 H), 7.77−7.87 (m, 1 H), 7.88−7.97 (m, 1 H), 8.01 (d, J = 8.5 Hz, 2 H), 8.26 (d, J = 7.2 Hz, 1 H), 8.66 (d, J = 1.8 Hz, 1 H), 8.75−8.93 (m, 2 H), 10.10 (s, 1 H). Anal. ($C_{23}H_{22}N_4 \cdot 0.3H_2O$): C, H, N.

***N*-(6-(4-(Trifluoromethyl)phenyl)pyrimidin-4-yl)quinolin-7-amine (79).** A mixture of 4-chloro-6-(4-trifluoromethylphenyl)-pyrimidine (**72**; 0.30 g, 1.2 mmol) and 7-quinolylamine (**76**; 0.17 g, 1.2 mmol) was stirred at 200 °C for 10 min in a microwave. The resulting solid was partitioned between saturated aqueous solution of $NaHCO_3$ (100 mL) and EtOAc (200 mL). The organic phase was washed with saturated aqueous NaCl, dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (60% EtOAc/hexanes) to give the crude reaction product. The crude material was recrystallized from CH_2Cl_2/EtOAc/hexanes and purified further by silica gel chromatography (50% EtOAc/CH_2Cl_2) to give a solid that was triturated with 1:1 CH_2Cl_2/hexanes (50 mL). The solid was collected by suction filtration and dried in vacuo at 60 °C overnight to afford 135 mg (32%) of the title product as a pale-tan solid. Mp 259.6−260.3 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.41 (dd, J = 8.2, 4.2 Hz, 1 H), 7.46 (s, 1 H), 7.83 (dd, J = 8.9, 2.1 Hz, 1 H), 7.93−7.97 (m, 3 H), 8.27−8.29 (m, 3 H), 8.68 (d, J = 1.5, 1 H), 8.85 (dd, J = 4.2, 1.6 Hz, 1 H), 8.91 (s, 1 H), 10.22 (s, 1 H). MS (ESI, pos. ion) *m*/*z*: 367 (M + 1). Anal. ($C_{24}H_{27}NO_3$): C, H, N): C, H, N.

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Supporting Information Available: Elemental analysis or HRMS and HPLC data for final compounds **10**−**27**, **73**, **74**, **78**, and **79**. This material is available free of charge via the Internet at http://pubs.acs.org.

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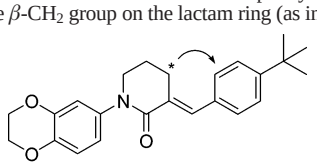

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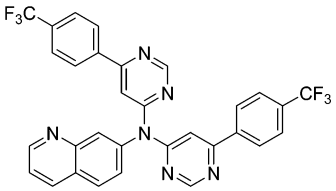

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