Design and Synthesis of Peripherally Restricted Transient Receptor Potential Vanilloid 1 (TRPV1) Antagonists

Nuria Tamayo,*[,†] Hongyu Liao,[†] Markian M. Stec,[†] Xianghong Wang,[†] Partha Chakrabarti,[†] Dan Retz,[†] Elizabeth M. Doherty,[†] Sekhar Surapaneni,[§] Rami Tamir,[#] Anthony W. Bannon,[#] Narender R. Gavva,[#] and Mark H. Norman[†]

Department of Chemistry Research and Discovery, Department of Neuroscience, and Department of Pharmacokinetics and Drug Metabolism, Amgen, Inc., One Amgen Center Drive, Thousand Oaks, California 91320-1799

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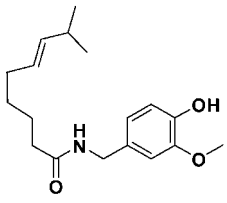
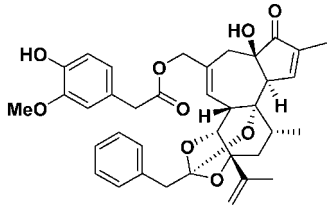
Transient receptor potential vanilloid 1 (TRPV1) channel antagonists may have clinical utility for the treatment of chronic nociceptive and neuropathic pain. We recently advanced a TRPV1 antagonist, **3** (AMG 517), into clinical trials as a new therapy for the treatment of pain. However, in addition to the desired analgesic effects, this TRPV1 antagonist significantly increased body core temperature following oral administration in rodents. Here, we report one of our approaches to eliminate or minimize the on-target hyperthermic effect observed with this and other TRPV1 antagonists. Through modifications of our clinical candidate, **3** a series of potent and peripherally restricted TRPV1 antagonists have been prepared. These analogues demonstrated on-target coverage in vivo but caused increases in body core temperature, suggesting that peripheral restriction was not sufficient to separate antagonism mediated antihyperalgesia from hyperthermia. Furthermore, these studies demonstrate that the site of action for TRPV1 blockade elicited hyperthermia is outside the blood−brain barrier.

Introduction

Capsaicin (**1**), the pungent component of hot chili peppers, and related irritants are activators of the transient receptor potential vanilloid 1 channel (TRPV1[a]).[1] TRPV1 is a ligand-gated nonselective cation channel primarily expressed by a subset of nociceptive neurons in the dorsal root and trigeminal ganglia.[2] Activation of TRPV1 by extracellular acidity, noxious heat, other vanilloids, including the ultrapotent diterpenoid resiniferatoxin (RTX, **2**), or certain endogenous lipids leads to an influx of calcium and sodium ions through the channel. This activation causes a depolarization of the cell membrane and eventually leads to the sensation of pain. The activators, often associated with tissue injury or inflammation, appear to operate by reducing the heat threshold of the receptor. Evidence suggests that TRPV1 is a key integrator of the pain response because it is up-regulated following inflammation and nerve damage.[3,4]



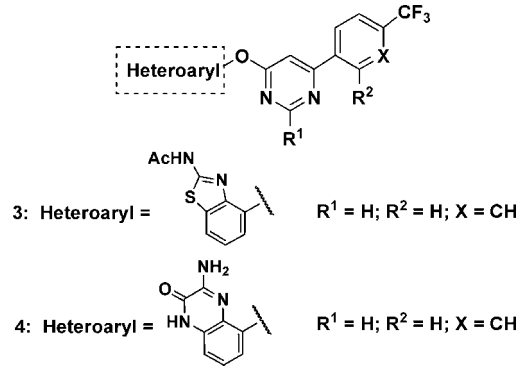
1 (Capsaicin)



2 (RTX)

Hyperstimulation of TRPV1 by capsaicin and related agonists has an analgesic effect resulting from desensitization of a subset of primary neurons involved in nociception and neurogenic inflammation. Capsaicin is used in many topical preparations as a pain reliever; however, the small therapeutic window between the analgesic effects and the excitatory side effects has limited the development of TRPV1 agonists as systemic agents.[5] On the other hand, TRPV1 antagonists may offer a rapid onset of analgesic action by blockade of the pain-signaling pathway with potentially fewer side effects.[6]

Following the cloning of TRPV1,[7] numerous pharmaceutical companies began the search for novel antagonists of this receptor as potential therapeutics for pain.[8] From our own investigations, we recently reported a series of substituted pyrimidines as novel and potent TRPV1 antagonists for the treatment of hyperalgesia.[9] From this series, we advanced compound **3** (AMG 517) into clinical trials.[10]



Compound **3** inhibited the Ca^{2+} influx evoked by capsaicin in vitro in both human ($IC_{50} = 0.8 \pm 0.4$ nM) and rat ($IC_{50} = 0.9 \pm 0.8$ nM) TRPV1-expressing cells and was able to block low pH-mediated responses of human ($IC_{50} = 0.6 \pm 0.3$ nM) and rat ($IC_{50} = 0.5 \pm 0.2$ nM) TRPV1. In rats, compound **3** blocked capsaicin-induced flinching ($EC_{50} = 0.33$ mg/kg, po), thus demonstrating on-target in vivo efficacy. Compound **3** was also efficacious in models of inflammatory pain. However, in addition to the desired analgesic effects, we observed a small

* To whom correspondence should be addressed. Phone: 805-447-8814. Fax: 805-480-1337. E-mail: ntamayo@amgen.com.
† Department of Chemistry Research and Discovery.
§ Department of Pharmacokinetics and Drug Metabolism.
# Department of Neuroscience.
[a] Abbreviations: TRPV1, transient receptor potential vanilloid 1; RTX, resiniferatoxin; *B*/*P*, brain-to-plasma ratio; PSA, polar surface area; HBD, hydrogen bond donor; Rot, rotatable bonds; Het, heterocycle.

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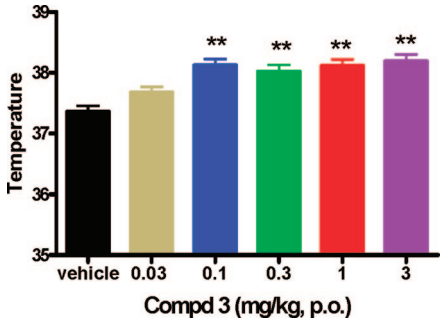


Figure 1. Effect of compound **3** on body core temperature in male Sprague–Dawley rats implanted with radiotelemetry probes, 60 min after treatment (n = 6–12/group): (**) $p < 0.01$.

but significant increase in core body temperature after oral administration in rodents (Figure 1).[11]

The hyperthermic side effect we observed for compound **3**, as well as for other TRPV1 antagonists, prompted us to closely examine the effect of TRPV1 on body temperature regulation.[12] In one aspect of these studies, we examined the effect of peripherally restricted TRPV1 antagonists. Because the hypothalamus is the key area of the brain known to be involved in thermoregulation,[13] we postulated that we may be able to separate the analgesic effect of our TRPV1 antagonists from their hyperthermic effect if they were excluded from the central nervous system. Unfortunately, all of the initial derivatives of compound **3** we had prepared and evaluated at that time had significant brain penetration. For example, compound **3** had exhibited significant CNS penetration with a brain-to-plasma ratio (*B*/*P*) of 1. Therefore, to test our hypothesis, we needed to prepare and evaluate novel derivatives of compound **3** that had low brain-to-plasma ratios while at the same time maintaining potent TRPV1 activities. In this paper we report the details of the design and synthesis of peripherally restricted TRPV1 antagonists based on derivatives of compound **3**.

As we modified the compounds in this series to minimize CNS penetration, it was important to make specific structural changes that would be likely to maintain excellent TRPV1 antagonism. Therefore, as a basis for the design of new peripherally restricted derivatives, we were guided by the results obtained from our previous structure–activity relationship (SAR) investigations.[9b,14] For example, in this study we chose to employ two heterocyclic groups that had previously demonstrated superior TRPV1 antagonism, the 2-NHAc benzothiazole ring (as contained in compound **3**) and the 2-aminoquinoxalinone ring system (as contained in compound **4**). Our earlier studies also revealed that substituents at the 2-position of the central pyrimidine ring (R^1) were, in general, well tolerated for TRPV1 potency. Additionally, we found that we could introduce substituents at the ortho position (R^2) of the phenyl ring (X = CH) or pyridine ring (X = N) and maintain good TRPV1 activities. Therefore, we prepared a series of derivatives with additional heteroatoms and polar groups at R^1, R^2, and X and examined their effect on potency, CNS penetration, efficacy (as determined by inhibition of in vivo capsaicin-induced flinching), and body core temperature.

Chemistry

The synthetic routes employed to prepare the 2-substituted pyrimidine analogues (R^1 substitutions) are outlined in Schemes 1 and 2. Commercially available 2-amino-4,6-dichloropyrimidine (**5**) was reacted with either *N*-(4-hydroxybenzo[*d*]thiazol-2-yl)acetamide[9b] or 3-amino-5-hydroxyquinoxalin-2(1*H*)-one[9b] to give aminopyrimidines **6** and **8**, respectively. Subsequent Suzuki coupling with 4-(trifluoromethyl)phenylboronic acid afforded the desired 2-substituted pyrimidines **7** and **9** (Scheme 1).

In the cases where primary amines were used at the R^1 position (**13a–f**), a more convergent synthetic route was used (Scheme 2). Suzuki coupling between 2,4,6-tricholoropyrimidine (**10**) and 4-(trifluoromethyl)phenylboronic acid afforded the dichloropyrimidine intermediate **11**. This compound was then coupled with 3-amino-5-hydroxyquinoxalin-2(1*H*)-one to give the key 2-chloropyrimidine intermediate **12**. Direct nucleophilic displacement of the chloro group of **12** with a variety of primary amines provided compounds **13a–f** in moderate yields.

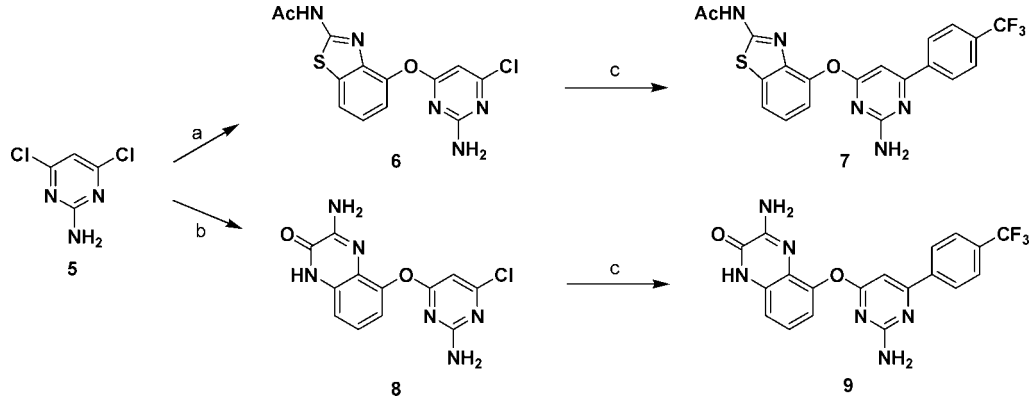
Scheme 3 outlines the synthesis of the R^2 substituted derivatives, **18a**,**b** and **19a–d**. Protection of 3-trifluoromethyl aniline (**14**) with di-*tert*-butyl dicarbonate followed by ortho-lithiation and treatment with trimethylborate provided 2-(*tert*-butoxycarbonylamino)-4-(trifluoromethyl)phenylboronic acid (**15**). Suzuki coupling of **15** with 2,4-dichloropyrimidine (**16**) gave the chloropyrimidine **17a** in moderate yield. Intermediate **17a** was reacted with either *N*-(4-hydroxybenzo[*d*]thiazol-2-yl)acetamide[9b] or 3-amino-5-hydroxyquinoxalin-2(1*H*)-one,[9b] and subsequent cleavage of the Boc protecting group with trifluoroacetic acid led to the disubstituted pyrimidines **18a** and **19a**, respectively. Alternatively, derivatization at the ortho position was accomplished prior to the introduction of the heterocyclic ring. In these cases, the Boc group of **17a** was cleaved with trifluoroacetic acid and the anilino group was derivatized by treatment with isobutylisocyanate, picolinoyl chloride, or isonicotinoyl chloride to give intermediates **17b–d**. The chloropyrimidines **17b–d** were then treated with either *N*-(4-hydroxybenzo[*d*]thiazol-2-yl)acetamide or 3-amino-5-hydroxyquinoxalin-2(1*H*)-one to give the desired disubstituted pyrimidine targets **18b** and **19b–d**.

To increase the number of heteroatoms and also to facilitate the synthesis of analogues, a series of ortho-substituted (R^2) pyridine derivatives were prepared (**24a–e**, Scheme 4). The pyridinyl ring was introduced by a Stille coupling reaction between 2-chloro-3-(tributylstannyl)-6-(trifluoromethyl)pyridine (**22**) and the iodopyrimidine intermediate **20**. Stannane **22** was prepared by treatment of 2-chloro-6-(trifluoromethyl)pyridine (**21**) with LDA, followed by quenching with tributyltin chloride. The chloropyridine **23** was reacted with a variety of primary amines to afford the target compounds **24a–e**.

Finally, R^1 and R^2-phenyl/pyridine disubstituted analogues **28a–c** and **31** were prepared according to Scheme 5. Reaction of 2,4,6-trichloropyrimidine (**10**) with 2-methoxyethylamine or (*S*)-1-methoxy-2-propylamine afforded substituted dichloropyrimidines **25a** and **25b**. Coupling between dichloropyrimidines **25a**,**b** or 2-amino-4,6-dichloropyrimidine (**5**) and 3-amino-5-hydroxyquinoxalin-2(1*H*)-one gave the trisubstituted pyrimidines **26a**,**b**, and **8**, respectively. Subsequent Suzuki coupling of 2-(*tert*-butoxycarbonylamino)-4-(trifluoromethyl)phenylboronic acid (**15**) with chloropyrimidines **26a**,**b** and **8** afforded a mixture of *N*-Boc derivatives **27a–c** and deprotected analogues **28a–c**. The Boc protecting group was completely removed by treatment with trifluoroacetic acid in dichloromethane, leading to the target pyrimidines **28a–c**.

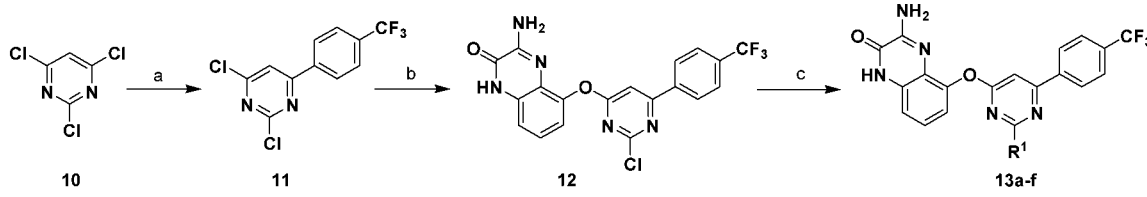
The synthesis of the final pyridylpyrimidine derivative **31** started with the halogen exchange of chloroaminopyrimidine **25b** with sodium iodide in a solution of hydriodic acid to yield iodopyrimidine **29** in good yield. Stille coupling between iodopyrimidine **29** and 2-chloro-3-(tributylstannyl)-6-(trifluoromethyl)pyridine (**22**) furnished chloropyridine **30**. Treat-

Scheme 1. Synthesis of Aminopyrimidines **7** and **9**[a]



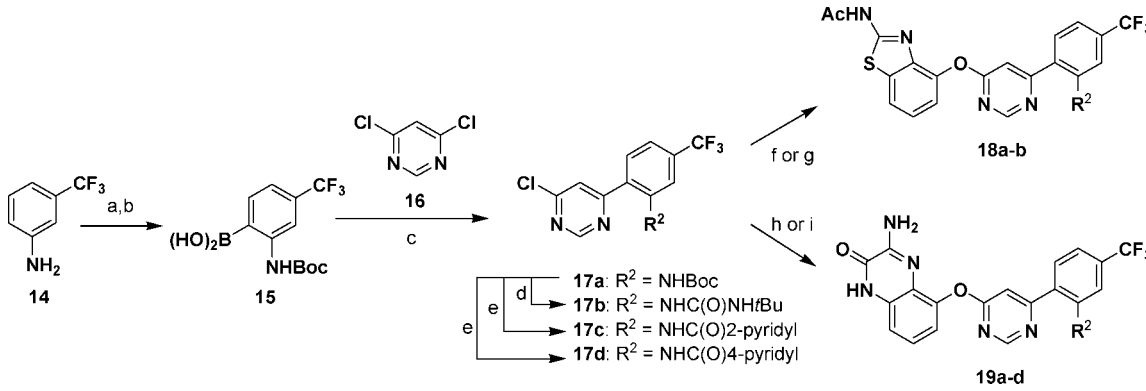
[a] Reagents and conditions: (a) *N*-(4-hydroxybenzo[*d*]thiazol-2-yl)acetamide, K_2CO_3, DMF, 60 °C, 77%; (b) 3-amino-5-hydroxyquinoxalin-2(1*H*)-one, Cs_2CO_3, DMF, 100 °C, 77%; (c) 4-(trifluoromethyl)phenylboronic acid, $Pd(PPh_3)_2Cl_2$, 2 M Na_2CO_3, DME, EtOH, microwave; **7**, 125 °C, 90%; **9**, 120 °C, 17%.

Scheme 2. Preparation of Substituted Aminopyrimidines **13a–f**[a]



[a] Reagents and conditions: (a) 4-(trifluoromethyl)phenylboronic acid, $Pd(OAc)_2$, PPh_3, Na_2CO_3, DME, microwave, 140 °C, 49%; (b) 3-amino-5-hydroxyquinoxalin-2(1*H*)-one, Cs_2CO_3, DMF, 70 °C, 78%; (c) amine, EtOH, microwave, 140 °C, 33−72%.

Scheme 3. Synthesis of Ortho-Substituted Pyrimidines **18a**,**b** and **19a–d**[a]



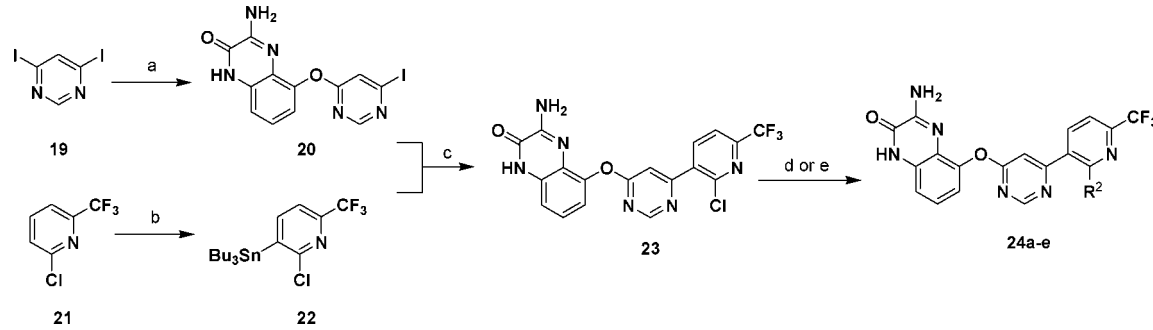
[a] Reagents and conditions: (a) di-*tert*-butyl dicarbonate, toluene, 100 °C, 90%; (b) (i) *sec*-BuLi, trimethyl borate, THF, −70 to −10 °C; (ii) HCl (1 M), 98% (two steps); (c) **16**, $Pd(PPh_3)_4$, K_2CO_3, DME/H_2O, 70 °C, 35%; (d) (i) TFA, CH_2Cl_2, 25 °C, 84%; (ii) 2-isocyanato-2-methylpropane, $MgCl_2$, DCE, 65 °C, 60%; (e) (i) TFA, CH_2Cl_2, 25 °C, 84%; (ii) picolinoyl chloride or isonicotinoyl chloride, $^iPr_2NEt$, CH_2Cl_2, 25 °C, 57−82%; (f) (i) *N*-(4-hydroxybenzo[*d*]thiazol-2-yl)acetamide, NaH, DMF, 25 °C, 54%; %; (ii) TFA, CH_2Cl_2, 25 °C, 100%; (g) *N*-(4-hydroxybenzo[*d*]thiazol-2-yl)acetamide, Cs_2CO_3, DMF, 60 °C, 26%; (h) (i) 3-amino-5-hydroxyquinoxalin-2(1*H*)-one, Cs_2CO_3, DMF, 45 °C, 74%; (ii) TFA, CH_2Cl_2, 25 °C, 66%; (i) 3-amino-5-hydroxyquinoxalin-2(1*H*)-one, Cs_2CO_3, DMF; **19b**, 65 °C, 51%; **19c**,**d**, 50 °C, 77–80%.

ment of intermediate **30** with 3,4-dimethoxybenzylamine followed by deprotection with trifluoroacetic acid afforded the aminopyridine analogue **31**.

Results and Discussion

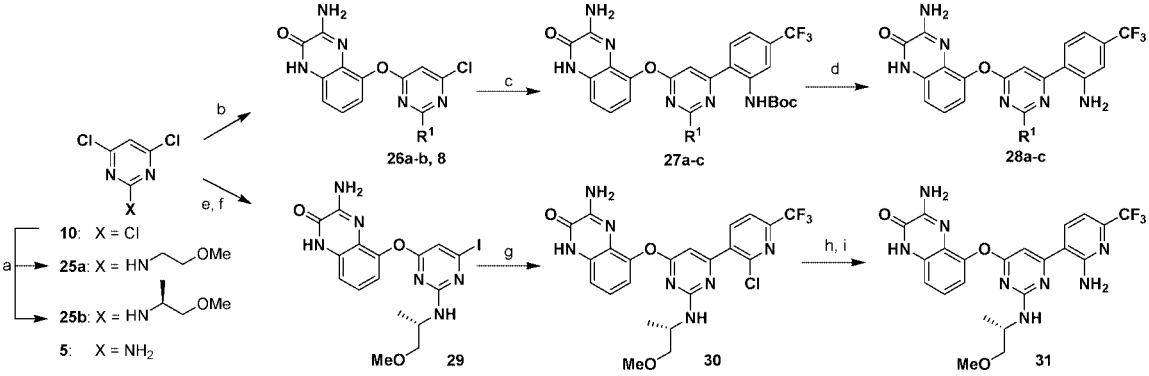
Our approach to the discovery of peripherally restricted pyrimidine TRPV1 antagonists was based on the premise that passive diffusion is the primary process for translocation of these compounds from the bloodstream to the brain. Central nervous system (CNS) permeability (and in general transcellular permeability) is a complex function of physicochemical properties of molecules such as size, lipophilicity, hydrogen-bonding potential, charge, and conformation.[15] In general, CNS-penetrant compounds are somewhat smaller than other biologically active molecules (90% of them have molecular weights of less than 500). They also have 2−7 hydrogen-bonding groups, while the range for non-CNS-penetrant agents is 2−9. In addition, over 90% of the CNS-active drugs have seven or fewer rotatable bonds, while this number is 10 for peripherally restricted compounds. Finally, compounds that access the CNS are in general more lipophilic (larger log *P*) than non-CNS targeted compounds,[16] and they generally have polar surface area (PSA) values less than 90.[17] Therefore, with these guiding principles in mind, we sought to restrict the CNS penetration of our TRPV1

Scheme 4. Synthesis of Ortho-Substituted Pyrimidines **24a–e**[a]



[a] Reagents and conditions: (a) 3-amino-5-hydroxyquinoxalin-2(1*H*)-one, K_2CO_3, DMSO, 80 °C, 72%; (b) LDA, tributyltin chloride, −78 °C, THF, 43%; (c) $Pd(PPh_3)_4$, CuI, DMF, 60 °C, 60%; (d) (i) (3,4-dimethoxyphenyl)methanamine, DMSO, 125 °C, 37%; (ii) TFA, 25 °C, 59%; (e) amine, DMSO, 25−100 °C, 21−55%.

Scheme 5. Synthesis of Disubstituted Pyrimidines **28a–c** and **31**[a]



[a] Reagents and conditions: (a) 2-methoxyethanamine or (*S*)-1-methoxy-2-propylamine; **25a**, dioxane, 60 °C, 28%; **25b**, EtOH, microwave, 140 °C, 12%; (b) 3-amino-5-hydroxyquinoxalin-2(1*H*)-one, Cs_2CO_3, DMF, 80−100 °C, 75−80%; (c) 2-(*tert*-butoxycarbonylamino)-4-(trifluoromethyl)phenylboronic acid (**15**), $Pd(PPh_3)_2Cl_2$, 2 M Na_2CO_3, DME, EtOH, microwave, 120 °C; (d) TFA, CH_2Cl_2, 25 °C, 41−73% (combined yield steps c and d); (e) **25b**, 57% HI solution, NaI, CH_2Cl_2, 25 °C, 74%; (f) 3-amino-5-hydroxyquinoxalin-2(1*H*)-one, Cs_2CO_3, DMF, 90 °C, 57%; (g) **22**, $Pd(PPh_3)_4$, CuI, DMF, 100 °C, 63%; (h) (3,4-dimethoxyphenyl)methanamine, DMSO, microwave, 120 °C, 77%; (i) TFA, CH_2Cl_2, 25 °C, 87%.

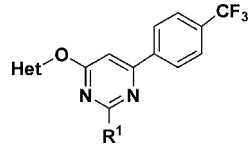
antagonists by (1) increasing molecular weight, (2) increasing the number of hydrogen bond donors (HBD), (3) increasing the number of rotatable bonds, (4) decreasing lipopholicity, and (5) increasing the polar surface area.[18]

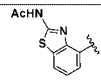
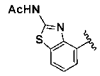
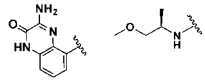
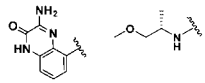
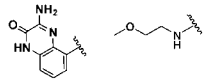
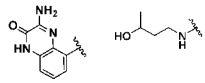
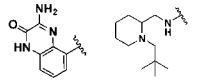
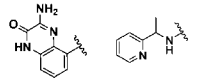
The compounds prepared were tested for their ability to inhibit capsaicin (Cap) or acid (pH 5) induced uptake of $^{45}Ca^{2+}$ in CHO cells expressing rat TRPV1. Functional activity is reported in the Tables as $IC_{50} \pm$ SEM (nM) and is the average of at least three separate experiments run in triplicate. Compounds that were potent in vitro ($IC_{50} < 10$ nM) were evaluated for their ability to penetrate the CNS by determining brain-to-plasma ratios (*B*/*P*) in rats following a single iv administration (5 mg/kg). Plasma and brains were collected 30 min after dosing, and total concentration of compound was determined by HPLC. For the purpose of this study we measured compound concentrations in nonperfused whole-brain samples. Taking into account the residual concentration of drug present as a consequence of brain capillary blood volume, we considered compounds having a brain-to-plasma ratio of less than or equal to 0.1 as peripherally restricted.[19]

Compounds meeting the above criteria were then assayed for on-target activity in vivo in the capsaicin-induced flinch model.[20] In vivo on-target activity was measured by the inhibition of capsaicin-induced flinching, after oral dosing of the TRPV1 antagonist. Compounds that were found to be both efficacious in the flinch model (>95% inhibition) and peripherally restricted ($B/P \leq 0.1$) were then evaluated for their effect on body core temperature.

We began our investigation by examining several 2-substituted pyrimidine derivatives (Table 1). In this series the effect of the heteroaryl ether group on potency and brain-to-plasma ratio was determined initially, that is, 2-NHAc benzothiazole vs 2-aminoquinoxalinone (**3** vs **4** and **7** vs **9**). In both cases, the analogues containing the 2-aminoquinoxalinone group (**4** and **9**) had better in vitro potencies as well as lower brain-to-plasma ratios compared to their corresponding benzothiazole counterparts (**3** and **7**). The 2-aminoquinoxalinone group serves to increase the PSA value, decrease the log *P*, and introduce two additional hydrogen bond donors. Therefore, we continued our investigations by maintaining the 2-aminoquinoxalinone group and introducing a variety of primary amines at the 2-position of the pyrimidine ring (R^1). The substituents, on the basis of our previously established SAR,[13] were anticipated to maximize potency while also increasing the overall PSA values, number of hydrogen bond donors, and number of rotatable bonds. This exercise provided a series of potent TRPV1 antagonists ($IC_{50} < 16$ nM) with significantly lower brain levels than compound **3**. Several of these new derivatives met our criteria of brain-to-plasma ratios (≤0.1) and were selected for further in vivo evaluation (**9** and **13c**,**d**,**f**), while in some cases, the plasma ratios obtained were considered too high for advancement (compounds **13a**,**b**,**e**). The higher brain-to-plasma ratios of compounds **3**, **4**, and **7** compared to the other compounds in the table can be attributed in part to each of these possessing three or fewer hydrogen bond donating groups. In

Table 1. In Vitro Rat TRPV1 Activities and Calculated Physicochemical Properties for 2-Substitued Pyrimidines (R^1)



Comp	Het	R^1	rTRPV1[a] (Cap)	rTRPV1[a] (H+)	MW[b]	PSA	clogP	HBD	Rot	B/P[c]
3		H	0.9 ± 0.8	0.5 ± 0.2	430	77	5.1	1	5	0.73 ± 0.05
4		H	0.64 ± 0.04	0.57 ± 0.06	399	107	3.4	3	4	0.40 ± 0.13
7		NH_2	11.9 ± 1.4	4.8 ± 0.9	445	103	5.2	3	5	0.44 ± 0.08
9		NH_2	3.7 ± 0.7	2.6 ± 0.4	414	133	2.8	5	4	0.07 ± 0.01
13a			0.3 ± 0.1	0.3 ± 0.1	486	128	3.3	4	8	0.15 ± 0.09
13b			0.8 ± 0.1	1.0 ± 0.2	486	128	3.3	4	8	0.19 ± 0.04
13c			0.6 ± 0.2	0.8 ± 0.1	472	128	2.9	4	8	0.05 ± 0.00
13d			16.1 ± 3.0	8.7 ± 2.4	486	139	2.9	5	8	0.03 ± 0.01
13e			2.0 ± 0.3	2.1 ± 0.3	582	122	5.7	4	9	0.24 ± 0.01
13f			2.8 ± 0.6	5.7 ± 0.7	519	132	3.6	4	7	0.04 ± 0.02

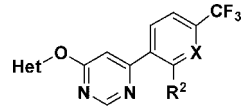
[a] IC_{50} values based inhibition of capsaicin- (500 nM) or acid- (pH 5) induced influx of $^{45}Ca^{2+}$ into rat TRPV1 expressing CHO cells. Each IC_{50} value reported represented an average of at least two experiments with three replicates at each concentration (±SEM). [b] Physicochemical properties were calculated using Amgen proprietary software (ADAAPT).[17] [c] Study in male Sprague−Dawley rats dosed at 5 mg/kg solution in DMSO with sampling at 0.5 h ($n = 3$).

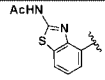
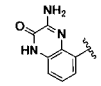
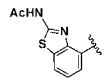
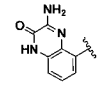
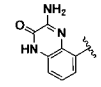
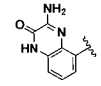
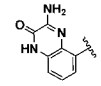
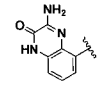
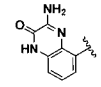
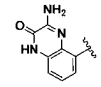
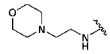
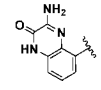
addition, these three analogues have the lowest PSA values in the set. Compound **13e**, with the highest clogP, also ranks among the higher brain-to-plasma ratios. The most effective combination of properties is represented by compounds **9**, **13c**, **13d**, and **13f**. For these analogues, the relatively high PSA values (>128), low clogP (<3.6), and increased number of HBD (4–5) and rotatable bonds (4–7) translated into the lowest brain-to-plasma ratios (<0.1).

Next, we examined the impact of substitution at the ortho position (R^2) of the phenyl/pyridine ring on potency and brain penetration (Table 2). For comparison the representative amino analogues **18a**, having a NHAc benzothiazole as the heterocyclic group, and **19a**, containing the 2-aminoquinoxalinone group, were prepared. Compound **19a** displayed over 10-fold increased potency in the Cap-induced TRPV1 assay and had a significantly lower brain-to-plasma ratio compared to that of **18a**. However, both analogues had brain-to-plasma ratios larger than 0.1. To further decrease brain penetration, an analogue having a urea functionality at the ortho position on the phenyl ring was prepared. The urea not only increased the polar surface area of the compound but also served to increase the molecular weight and add additional hydrogen bond donors. The urea derivative **19b** displayed good potencies (IC_{50}(Cap) = 4.1 nM; $IC_{50}(H^+)$ = 5.2 nM) and a significantly lower brain-to-plasma ratio (0.04) than **19a**. Since the urea group was well tolerated and because we knew that certain basic amides were also well tolerated, on the basis of previous SAR studies,[21] two amide analogues **19c** and **19d**, both having very large molecular weights and polar surface areas, were synthesized. Both amides showed good TRPV1 potencies; however, the brain-to-plasma ratio of the 4-pyridylamide **19d** was lower compared to the corresponding 2-pyridyl isomer **19c**.

Similar to the pyrimidine series (R^1), we kept the 2-aminoquinoxalinone ring constant and introduced a variety of amines at the R^2 position. To simplify the synthesis and also increase the number of heteroatoms, a series of ortho-substituted pyridines were prepared. Initially, we examined the analogue with an amino group as the R^2 substituent (**24a**). This analogue was an extremely potent TRPV1 antagonist and had a brain-to-

Table 2. In Vitro Rat TRPV1 Activities and Calculated Physicochemical Properties for Ortho-Substituted Derivatives (R^2)



Comp	Het	R^1	X	rTRPV1 [a] (Cap)	rTRPV1 [a] (H+)	MW[b]	PSA	clogP	HBD	Rot	B/P[c]
18a		NH_2	CH	15.9 ± 1.6	3.6 ± 0.3	445	103	4.7	3	5	0.93 ± 0.15
19a		NH_2	CH	1.5 ± 0.1	3.9 ± 0.8	414	133	3.0	5	4	0.23 ± 0.05
18b			CH	2.4 ± 0.4	6.0 ± 0.6	545	118	6.3	3	7	0.19 ± 0.12
19b			CH	4.1 ± 1.1	5.2 ± 0.4	513	148	4.7	5	6	0.04 ± 0.01
19c			CH	0.7 ± 0.1	0.7 ± 0.1	519	149	3.9	4	6	0.21 ± 0.09
19d			CH	3.3 ± 0.6	2.1 ± 0.2	519	149	3.7	4	6	0.07 ± 0.02
24a		NH_2	N	0.8 ± 0.3	2.7 ± 0.8	415	146	3.6	5	4	0.11 ± 0.02
24b			N	0.7 ± 0.2	1.3 ± 0.1	473	141	3.6	4	8	0.04 ± 0.01
24c			N	1.1 ± 0.3	1.8 ± 0.1	485	141	3.5	4	6	0.09 ± 0.03
24d			N	2.2 ± 0.2	18.8 ± 1.2	528	144	3.4	4	8	0.04 ± 0.02
24e			N	0.9 ± 0.3	1.7 ± 0.7	568	135	6.2	4	9	0.25 ± 0.10

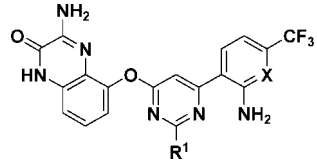
[a] IC_{50} values based inhibition of capsaicin- (500 nM) or acid- (pH 5) induced influx of $^{45}Ca^{2+}$ into rat TRPV1 expressing CHO cells. Each IC_{50} value reported represented an average of at least two experiments with three replicates at each concentration (±SEM). [b] Physicochemical properties were calculated using Amgen proprietary software (ADAAPT).[17] [c] Study in male Sprague−Dawley rats dosed at 5 mg/kg solution in DMSO with sampling at 0.5 h ($n = 3$).

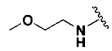
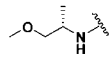
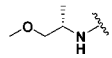
plasma ratio of approximately 0.1. On the basis of our knowledge of the SAR in this series, we selected primary amines that would increase or maintain potency and minimize brain penetration. With this selection, a series of very potent TRPV1 antagonists **24b–e** with very low brain-to-plasma ratios were prepared. The only analogues from this set that failed to meet our criteria ($B/P \leq 0.1$) were **19c** ($B/P = 0.2$) and **24e** ($B/P = 0.25$). The high lipophilicity of the latter analogue (clogP = 6.2) may account for the higher brain penetration observed.

In addition to the monosubstituted derivatives described above, we examined compounds with substituents at both R^1 and R^2 (Table 3). In this series the 2-aminoquinoxalinone ring system was used as the heteroaryl ether to maximize polar surface area, molecular weight, and number of hydrogen bond donors. Primary amines or an amino group at the R^1 position of the pyrimidine core were used while keeping an amino substituent at the R^2 position constant (**28a–c** and **31**). All of the disubstituted analogues prepared had very large PSA values (over 150), several hydrogen bond donors (6–7), and low clogP values (<3.1), resulting in very low brain penetrations ($B/P \leq 0.1$). However, the aminopyrimidine analogue **28c** was 10-fold less potent than the other members of this series.

From the three sets of TRPV1 antagonists prepared (2-pyrimidines, ortho-substituted, and disubstituted derivatives), 12 compounds were identified that were potent in vitro ($IC_{50} < 10$ nM) and had brain-to-plasma ratios of 0.1 or lower (**13c**,**d**,**f**, **19b**,**d**, **24a–d**, **28a**,**b**, and **31**).[22] The on-target in vivo efficacy of these analogues was determined in the capsaicin-induced flinching model in rats, and the results are shown in Figure 2. In this model the compounds were administered orally at a single dose (1, 3, or 10 mg/kg as a suspension in 5% Tween-80 in OraPlus) 1 h prior to the capsaicin challenge.[23] Although several compounds significantly inhibited capsaicin-induced flinching (>50%) at the dose used,[24] only those that completely (>95%) blocked on-target in vivo activity were advanced to telemetry studies.

Table 3. In Vitro Rat TRPV1 Activities and Calculated Physicochemical Properties for Disubstituted Analogues



Comp	R^1	X	rTRPV1[a] (Cap)	rTRPV1[a] (H+)	MW[b]	PSA	clogP	HBD	Rot	B/P[c]
28a		CH	4.3 ± 0.6	5.9 ± 0.4	487	154	2.5	6	7	0.10 ± 0.02
28b		CH	3.8 ± 0.4	2.7 ± 0.6	501	154	2.9	6	7	0.07 ± 0.02
28c	NH_2	CH	34.5 ± 8.6	61.9 ± 3.5	429	159	3.1	7	4	0.04 ± 0.01
31		N	4.4 ± 0.2	6.4 ± 0.3	502	167	3.1	6	6	0.04 ± 0.00

[a] IC_{50} values based 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 represented an average of at least two experiments with three replicates at each concentration (±SEM). [b] Physicochemical properties were calculated using Amgen proprietary software (ADAAPT).[17] [c] Study in male Sprague−Dawley rats dosed at 5 mg/kg solution in DMSO with sampling at 0.5 h ($n = 3$).

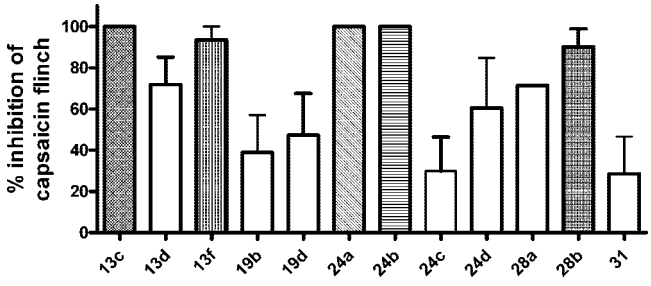


Figure 2. Inhibition of capsaicin-induced flinching. Compounds were dosed orally at 1 mg/kg (**13c**, **24b**), 3 mg/kg (**24a**,**c**,**d**), or 10 mg/kg (**13d**,**f**, **19b**,**d**, **28a**,**b**, **31**) in 5% Tween-80/OraPlus 1 h prior to capsaicin challenge; $n = 8$ per group of male Sprague–Dawley rats.

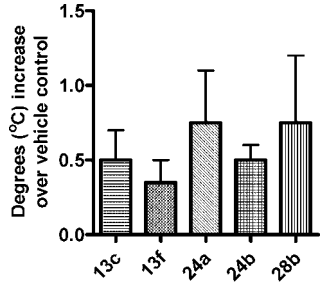


Figure 3. Effect of TRPV1 antagonists on body core temperature. Compounds were dosed orally at 1 mg/kg (**13c**), 3 mg/kg (**24b**), or 10 mg/kg (**13f**, **24a**, **28b**) in 5% Tween-80/OraPlus to male Sprague–Dawley rats ($n = 6$ per group) implanted with radiotelemetry probes. Body core temperature baselines were recorded 30 min before dosing, and temperature recordings were continued for 2 h.

The five most efficacious and peripherally restricted TRPV1 antagonists (**13c**, **13f**, **24a**, **24b**, and **28b**) were then tested in a telemetry model to examine their effects on body core temperature. Rats implanted with radiotelemetry probes were dosed orally with a single dose of the TRPV1 antagonists (**13c**, **13f**, **24a**, **24b**, and **28b**). Body core temperatures were recorded 30 min prior to drug administration and continued for 2 h postdose. Figure 3 shows the increase in body core temperature over control animals at the 60-min time point, which usually corresponds with the maximum increase in body core temperature.

Unfortunately, all five TRPV1 antagonists showed a significant increase in body core temperature (>0.5 °C) compared to vehicle control. These results suggest that peripheral restriction alone is not sufficient to eliminate TRPV1 antagonist-induced hyperthermia and the site of action for the hyperthermic effect is predominantly outside the blood−brain barrier. This is consistent with findings recently reported by Steiner indicating that (a) TRPV1 antagonists cause hyperthermia through vasoconstriction and increased thermogenesis and (b) TRPV1 antagonist-induced hyperthermia results from blockade of tonically active visceral TRPV1 channels, confirming the site of action outside the blood−brain barrier.[25]

Summary

We recently advanced compound **3** into clinical trials as a new therapy for the treatment of pain. However, in addition to its analgesic effect, this TRPV1 antagonist significantly increased body core temperature when dosed in rodents. In this investigation, we sought to examine whether peripheral restriction could minimize or eliminate the on-target increase on body core temperature. A series of potent and low brain penetrant TRPV1 antagonists were designed and prepared. Compounds having IC_{50} values of less than 10 nM and brain-to-plasma ratios of 0.1 or less were evaluated in the capsaicin-induced rat flinching model. Those that completely inhibited flinching were tested in telemetry rats, but all increased body core temperature. Peripheral restriction of TRPV1 antagonists did not eliminate hyperthermia, suggesting that the site of action is predominantly outside the blood−brain barrier. Minimizing brain penetration was not sufficient to separate the analgesic properties of TRPV1 antagonists from the on-target hyperthermia observed in rodents.

Experimental Section

Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Anhydrous solvents were obtained from Aldrich or EM Science and used directly. All reactions involving air- or moisture-sensitive reagents were performed under a nitrogen or argon atmosphere. All 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 Agilent 1100 and HP 1100 spectrometers. 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 with a Buchi-545 melting point apparatus and are uncorrected. ^{1}H 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). High-resolution mass spectral (HRMS) data were determined on a Agilent LC/MSD TOF mass spectrometer. Combustion analyses were performed by Atlantic Microlabs, Inc., Norcross, GA, and were within ±0.4% of calculated values, unless otherwise noted. Combustion analyses and ^{1}H NMR spectra showed that fractional molar amounts of H_2O or organic solvents were tenaciously retained in some analytical samples, even after prolonged drying under reduced pressure.

***N*-(4-(2-Amino-6-chloropyrimidin-4-yloxy)benzo[*d*]thiazol-2-yl)acetamide (6).** A 250 mL round-bottomed flask was charged with 2-amino-4,6-dichloropyrimidine (**5**) (0.98 g, 6.0 mmol), *N*-(4-hydroxybenzo[*d*]thiazol-2-yl)acetamide (1.25 g, 6.0 mmol), K_2CO_3 (0.97 g, 7.0 mmol), and DMF (20 mL). The reaction mixture was heated at 60 °C for 16 h and then allowed to reach room temperature. The mixture was partitioned between H_2O 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 (60% EtOAc/hexanes) to give the title compound as an off-white solid (1.54 g, 77%). MS (ESI, positive ion) *m*/*z*: 336 (M + 1).

***N*-(4-(2-Amino-6-(4-(trifluoromethyl)phenyl)pyrimidin-4-yloxy)benzo[*d*]thiazol-2-yl)acetamide (7).** A 10 mL microwave reaction tube was charged with 4-(trifluoromethyl)phenylboronic acid (0.30 g, 1.6 mmol), *N*-(4-(2-amino-6-chloropyrimidin-4-yloxy)benzo[*d*]thiazol-2-yl)acetamide (**6**; 0.37 g, 1.1 mmol), $Pd(PPh_3)_2Cl_2$ (0.11 g, 0.15 mmol), Na_2CO_3 (0.25 g, 2.0 mmol), and DME/EtOH/H_2O (2.1/0.6/0.9 mL). The reaction tube was sealed and heated at 125 °C for 30 min and allowed to cool to room temperature. The mixture was diluted with EtOAc and filtered through a pad of Celite. The filtrate was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (40% EtOAc/hexanes) to give the title compound as a white solid (0.44 g, 90%). Mp: 232.5–234.3 °C. ^{1}H NMR (400 MHz, CD_3OD): δ 8.26 (d, J = 8.2 Hz, 2H), 7.86–7.83 (m, 3H), 7.41 (t, J = 7.9 Hz, 1H), 7.31 (dd, J = 7.8 Hz, 1.0 Hz, 1H), 6.86 (s, 1H), 2.22 (s, 3H). MS (ESI positive ion) *m*/*z*: 446 (M + 1). HRMS calculated for $C_{20}H_{14}F_3N_5O_2S$ $(M + H)^+$ 446.08931, found 446.08994.

3-Amino-5-(2-amino-6-chloropyrimidin-4-yloxy)quinoxalin-2(1*H*)-one (8). A 25 mL round-bottomed flask was charged with 4,6-dichloropyrimidin-2-amine (0.30 g, 1.83 mmol), 3-amino-5-hydroxyquinoxalin-2(1*H*)-one (0.32 g, 1.83 mmol), Cs_2CO_3 (1.79 g, 5.49 mmol), and DMF (5 mL). The reaction mixture was heated at 100 °C for 16 h and allowed to reach room temperature. The mixture was partitioned between H_2O and EtOAc. The organic phase was separated, washed successively with H_2O and saturated aqueous NaCl, dried over Na_2SO_4, and filtered. Purification by recrystallization from EtOAc provided **8** as a white solid (0.43 g, 77%). MS (ESI positive ion) *m*/*z*: 305 (M + 1).

4-(3-Amino-2-oxo-1,2-dihydroquinoxalin-5-yloxy)-6-(4-(trifluoromethyl)phenyl)pyrimidin-2-aminium trifluoroacetate (9). A 10 mL microwave reaction tube was charged with 3-amino-5-(2-amino-6-chloropyrimidin-4-yloxy)quinoxalin-2(1*H*)-one (**8**; 0.15 g, 0.49 mmol), 4-(trifluoromethyl)phenylboronic acid (0.14 g, 0.74 mmol), $Pd(PPh_3)_2Cl_2$ (35 mg, 0.05 mmol), Na_2CO_3 (78 mg, 0.74 mmol), and DME/EtOH/H_2O (1.4/0.4/0.6 mL). The reaction mixture was heated at 120 °C for 20 min using a microwave reactor and then concentrated under reduced pressure. Purification, first by silica gel column chromatography (75% EtOAc/hexanes) followed by preparative HPLC (10–90% CH_3CN/H_2O, 0.1% TFA), provided the title compound as a TFA salt (35 mg, 17%). ^{1}H NMR (400 MHz, CD_3OD): δ 8.27 (d, J = 8.0 Hz, 2H), 7.86 (d, J = 8.2 Hz, 2H), 7.26 (t, J = 8.0 Hz, 1H), 7.17 (dd, J = 8.2 Hz, 1.2 Hz, 1H), 7.09 (dd, J = 7.9 Hz, 1.3 Hz, 1H), 6.86 (s, 1H). MS (ESI positive ion) *m*/*z*: 415 (M + 1). HRMS calculated for $C_{19}H_{13}F_3N_6O_2$ $(M + H)^+$ 415.11248, found 415.11271.

2,4-Dichloro-6-(4-(trifluoromethyl)phenyl)pyrimidine (11). A 20 mL microwave tube was charged with 2,4,6-trichloropyrimidine (4.0 g, 22 mmol), 4-(trifluoromethyl)phenylboronic acid (4.2 g, 22 mmol), $Pd(OAc)_2$ (0.25 g, 1.1 mmol), PPh_3 (0.58 g, 2.2 mmol), Na_2CO_3 (6.3 g, 60 mmol), and DME (5 mL). The reaction mixture was sealed, heated in the microwave at 140 °C for 30 min, and allowed to cool to room temperature. The mixture was diluted with EtOAc and filtered through a pad of Celite, and the filtrate was evaporated under reduced pressure. Purification by silica gel column chromatography (5% EtOAc/hexanes) followed by recrystallization from MeOH provided the title compound as a white solid (2.9 g, 49%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, J = 8.2 Hz, 2H), 7.80 (d, J = 8.4 Hz, 2H), 7.73 (s, 1H). MS (ESI positive ion) *m*/*z*: 293, 295 (M + 1).

3-Amino-5-(2-chloro-6-(4-(trifluoromethyl)phenyl)pyrimidin-4-yloxy)quinoxalin-2(1*H*)-one (12). A 25 mL round-bottomed flask was charged with 3-amino-5-hydroxyquinoxalin-2(1*H*)-one (0.89 g, 5.0 mmol), 2,4-dichloro-6-(4-(trifluoromethyl)phenyl)pyrimidine (1.46 g, 5.0 mmol), Cs_2CO_3 (1.63 g, 5.0 mmol), and DMF (5 mL). The reaction mixture was heated at 70 °C for 3 h and then allowed to reach room temperature. The mixture was partitioned between H_2O 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 recrystallization from CH_2Cl_2 to provide the title compound as a white solid (1.89 g, 78%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.34 (s, 1H), 8.40 (d, J = 7.9 Hz, 2H), 7.93 (d, J = 8.8 Hz, 2H), 7.89 (s, 1H), 7.21–7.07 (m, 2H). MS (ESI positive ion) *m*/*z*: 434 (M + 1).

(*R*)-3-Amino-5-(2-(1-methoxypropan-2-ylamino)-6-(4-(trifluoromethyl)phenyl)pyrimidin-4-yloxy)quinoxalin-2(1*H*)-one (13a).[26] A 10 mL microwave reaction tube was charged with 3-amino-5-(2-chloro-6-(4-(trifluoromethyl)phenyl)pyrimidin-4-yloxy)quinoxalin-2(1*H*)-one (**12**; 0.20 g, 0.46 mmol), 1-methoxypropan-2-amine (82 mg, 0.92 mmol), and EtOH (2 mL). The reaction mixture was stirred and heated in a microwave at 140 °C for 40 min, and then the solvent was evaporated under reduced pressure. Purification by silica gel column chromatography (40% EtOAc/hexanes) provided 3-amino-5-(2-(1-methoxypropan-2-ylamino)-6-(4-(trifluoromethyl)-phenyl)pyrimidin-4-yloxy)quinoxalin-2(1*H*)-one (0.15 g, 66%). MS (ESI positive ion) *m*/*z*: 487 (M + 1).

Purification of racemic 3-amino-5-(2-(1-methoxypropan-2-ylamino)-6-(4-(trifluoromethyl)phenyl)pyrimidin-4-yloxy)quinoxalin-2(1*H*)-one using chiral SFC (under the following conditions, Chiralcel ODH (250 mm × 21 mm), 30% methanol/CO_2 (100 bar), 65 mL/min, 220 nm) provided (*R*)-3-amino-5-(2-(1-methoxypropan-2-ylamino)-6-(4-(trifluoromethyl)phenyl)pyrimidin-4-yloxy)quinoxalin-2(1*H*)-one as a white solid (**13a**, 46 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 8.29 (d, J = 8.0 Hz, 2H), 7.84 (d, J = 8.2 Hz, 2H), 7.24 (t, J = 8.0 Hz, 1H), 7.15 (dd, J = 8.2 Hz, 1.4 Hz, 1H), 7.06 (dd, J = 7.8 Hz, 1.4 Hz, 1H), 6.82 (s, 1H), 3.34–3.20 (m, 6H), 1.14 (br s, 3H). MS (ESI positive ion) *m*/*z*: 487 (M + 1). Anal. ($C_{23}H_{21}F_3N_6O_3$) C, H, N.

(*S*)-3-Amino-5-(2-(1-methoxypropan-2-ylamino)-6-(4-(trifluoromethyl)phenyl)pyrimidin-4-yloxy)quinoxalin-2(1*H*)-one (13b). Purification of racemic 3-amino-5-(2-(1-methoxypropan-2-ylamino)-6-(4-(trifluoromethyl)phenyl)pyrimidin-4-yloxy)quinoxalin-2(1*H*)-one using chiral SFC (under the following conditions Chiralcel ODH (250 × 21 mm), 30% methanol/CO_2 (100 bar), 65 mL/min, 220 nm) provided (*S*)-3-amino-5-(2-(1-methoxypropan-2-ylamino)-6-(4-(trifluoromethyl)phenyl)pyrimidin-4-yloxy)quinoxalin-2(1*H*)-one (**13b**, 45 mg). ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.29 (d, J = 8.0 Hz, 2H), 7.84 (d, J = 8.2 Hz, 2H), 7.24 (t, J = 8.0 Hz, 1H), 7.15 (dd, J = 8.2 Hz, 1.4 Hz, 1H), 7.06 (dd, J = 7.8 Hz, 1.4 Hz, 1H), 6.82 (s, 1H), 3.34–3.20 (m, 6H), 1.14 (br s, 3H). MS (ESI positive ion) *m*/*z*: 487 (M + 1). Anal. ($C_{23}H_{21}F_3N_6O_3$) C, H, N.

3-Amino-5-(2-(2-methoxyethylamino)-6-(4-(trifluoromethyl)-phenyl)pyrimidin-4-yloxy)quinoxalin-2(1*H*)-one (13c). This material was prepared according to the procedure described for compound **13a** from 3-amino-5-(2-chloro-6-(4-(trifluoromethyl)phenyl)pyrimidin-4-yloxy)quinoxalin-2(1*H*)-one (**12**; 0.10 g, 0.23 mmol), 2-methoxyethanamine (35 mg, 0.46 mmol), and EtOH (2 mL). The title compound was obtained as a white solid (65 mg, 60%). ^{1}H NMR (400 MHz, CD_3OD): δ 8.28 (d, $J = 7.7$ Hz, 2H), 7.83 (d, $J = 8.2$ Hz, 2H), 7.24 (t, $J = 8.0$ Hz, 1H), 7.15 (dd, $J = 8.3$ Hz, 1.4 Hz, 1H), 7.07 (dd, $J = 7.8$ Hz, 1.4 Hz, 1H), 6.82 (s, 1H), 3.75–3.23 (m, 7H). MS (ESI positive ion) *m/z*: 473 (M + 1). Anal. ($C_{22}H_{19}F_3N_6O_3 \cdot 0.5H_2O$) C, H, N.

4-(3-Amino-2-oxo-1,2-dihydroquinoxalin-5-yloxy)-*N*-(3-hydroxybutyl)-6-(4-(trifluoromethyl)phenyl)pyrimidin-2-aminium trifluoroacetate (13d). This material was prepared according to the procedure described for compound **13a** from 3-amino-5-(2-chloro-6-(4-(trifluoromethyl)phenyl)pyrimidin-4-yloxy)quinoxalin-2(1*H*)-one (**12**; 80 mg, 0.18 mmol), 4-amino-4-butanol (33 mg, 0.37 mmol), and EtOH (2 mL). After purification by preparative HPLC (10–90% CH_3CN/H_2O, 0.1% TFA) the title compound was obtained as a TFA salt (65 mg, 72%). ^{1}H NMR (400 MHz, CD_3OD): δ 8.19 (d, $J = 8.0$ Hz, 2H), 7.77 (d, $J = 8.4$ Hz, 2H), 7.21 (t, $J = 8.0$ Hz, 1H), 7.10 (dd, $J = 8.2$ Hz, 1.4 Hz, 1H), 7.03 (dd, $J = 7.8$ Hz, 1.2 Hz, 1H), 6.72 (s, 1H), 3.71 (br s, 1H), 3.30–3.15 (m, 3H), 1.60–1.47 (m, 2H), 1.09–1.07 (m, 3H). MS (ESI positive ion) *m/z*: 487 (M + 1). HRMS calculated for $C_{23}H_{21}F_3N_6O_3$ $(M + H)^+$ 487.17000, found 487.17028.

3-Amino-5-(2-((1-neopentylpiperidin-2-yl) methylaminoamino)-6-(4-(trifluoromethyl)phenyl)pyrimidin-4-yloxy)quinoxalin-2(1*H*)-one trifluoroacetate (13e). This material was prepared according to the method described for compound **13a** from 3-amino-5-(2-chloro-6-(4-(trifluoromethyl)phenyl)pyrimidin-4-yloxy)quinoxalin-2(1*H*)-one (**12**; 87 mg, 0.20 mmol), (1-neopentylpiperidin-2-yl)methanamine (74 mg, 0.40 mmol), and EtOH (2 mL). Purification by preparative HPLC (10–90% CH_3CN/H_2O, 0.1% TFA) provided the title compound as a TFA salt (40 mg, 33%). ^{1}H NMR (400 MHz, CD_3OD): δ 8.25–8.21 (m, 2H), 7.83–7.79 (m, 2H), 7.29–7.25 (m, 1H), 7.13–7.07 (m, 2H), 6.96 (br s, 1H), 3.57–3.35 (m, 2H), 3.12–2.94 (m, 5H), 1.98–1.51 (m, 9H), 1.02 (br s, 9H). MS (ESI positive ion) *m/z*: 582 (M + 1). HRMS calculated for $C_{30}H_{34}F_3N_7O_2$ $(M + H)^+$ 582.27988, found 582.27941.

3-Amino-5-(2-(1-(pyridin-2-yl)ethylamino)-6-(4-(trifluoromethyl)-phenyl)pyrimidin-4-yloxy)quinoxalin-2(1*H*)-one (13f). This material was prepared according to the method described for compound **13a** from 3-amino-5-(2-chloro-6-(4-(trifluoromethyl)phenyl)pyrimidin-4-yloxy)quinoxalin-2(1*H*)-one (**12**; 87 mg, 0.20 mmol), 1-(pyridin-2-yl)ethanamine (49 mg, 0.40 mmol), and EtOH (2 mL). Purification by silica gel column chromatography (10–90% EtOAc/hexanes) afforded the title compound as a white solid (70 mg, 67%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.26 (s, 1H), 8.39–8.13 (m, 3H), 7.87–7.32 (m, 3H), 7.19–6.82 (m, 7H), 4.45 (m, 1H), 1.49 (br s, 3H). MS (ESI positive ion) *m/z*: 520 (M + 1). Anal. ($C_{26}H_{20}F_3N_7O_2$) C, H, N.

2-(*tert*-Butoxycarbonylamino)-4-(trifluoromethyl)phenylboronic acid (15). A 500 mL round-bottomed flask was charged with 3-(trifluoromethyl)aniline (21.2 mL, 0.17 mol), di-*tert*-butyl dicarbonate (45.0 g, 0.21 mol), and toluene (300 mL). The reaction mixture was heated at 100 °C for 18 h and then allowed to cool to room temperature. The solvent was removed under reduced pressure, and the residue was diluted with heptanes. After removal of most of the heptanes under reduced pressure, a precipitate was obtained and it was collected by filtration. *tert*-Butyl 3-(trifluoromethyl)phenylcarbamate (40.3 g, 90%) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.73 (s, 1H), 7.92 (s, 1H), 7.64 (d, $J = 8.2$ Hz, 1H), 7.48 (t, $J = 7.9$ Hz, 1H), 7.30 (d, $J = 7.6$ Hz, 1H), 1.48 (s, 9H).

A 500 mL round-bottomed flask was charged with *tert*-butyl 3-(trifluoromethyl)phenylcarbamate (20.0 g, 0.08 mol) and THF (150 mL). The solution was cooled to −35 °C, and *sec*-butyllithium (1.4 M solution in cyclohexane, 120 mL, 0.17 mol) was added. The resulting solution was stirred at −30 °C for 1 h and then cooled to −70 °C. At this temperature, trimethyl borate (34 mL, 0.31 mol) was added, and the reaction mixture was warmed to −10 °C and stirred for 2 h. Then it was diluted with 1 M HCl and the pH was adjusted to 4.5. The phases were separated, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with saturated aqueous NaCl, dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure to afford 2-(*tert*-butoxycarbonylamino)-4-(trifluoromethyl)phenylboronic acid (**15**) as a yellow foam (22.9 g, 98%). The product was taken to the next step without purification.

***tert*-Butyl 2-(6-chloropyrimidin-4-yl)-5-(trifluoromethyl)phenylcarbamate (17a).** A 500 mL round-bottomed flask was charged with 4,6-dichloropyrimidine (22.2 g, 0.15 mol), 2-(*tert*-butoxycarbonylamino)-4-(trifluoromethyl)phenylboronic acid (23.0 g, 0.07 mol), and $Pd(PPh_3)_4$ (2.6 g, 2.3 mmol), K_2CO_3 (21.1 g, 0.15 mol), and DME/H_2O (10:1, 250 mL). The reaction mixture was heated at 70 °C under a nitrogen atmosphere for 14 h and then allowed to cool to room temperature. The reaction mixture was filtered through a pad of Celite, and the filter pad was washed with DME (50 mL). The solvent was partially removed under reduced pressure, and the resulting mixture was extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and filtered, and the filtrate was concentrated under reduced pressure. Purification by silica gel flash chromatography (0–50% EtOAc/hexanes) afforded the title compound as a white solid (10.1 g, 35%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.91 (s, 1H), 9.11 (s, 1H), 8.75 (s, 1H), 7.76–7.74 (m, 2H), 7.36 (d, $J = 8.2$ Hz, 1H), 1.54 (s, 9H). MS (ESI positive ion) *m/z*: 374 (M + 1).

***N*-(4-(6-(2-Amino-4-(trifluoromethyl)phenyl)pyrimidin-4-yloxy)benzo[*d*]thiazol-2-yl)acetamide (18a).** A 250 mL round-bottomed flask was charged with *N*-(4-hydroxybenzo[*d*]thiazol-2-yl)acetamide (4.90 g, 24 mmol) and DMF (75 mL) and cooled to 0 °C. To the reaction mixture NaH (0.94 g, 24 mmol, 60% dispersion in oil) was added, and the suspension was stirred for 5 min at 0 °C and then 15 min at room temperature. *tert*-Butyl 2-(6-chloropyrimidin-4-yl)-5-(trifluoromethyl)phenylcarbamate (**17a**, 7.85 g, 21 mmol) was added, and the solution was stirred at room temperature for 24 h. The mixture was diluted with 1% aqueous NaOH (500 mL) and then extracted with 1:1 EtOAc/hexanes. The organic phase was washed with H_2O and saturated aqueous NaCl, dried over Na_2SO_4, and filtered. The crude material was purified by silica gel chromatography (18–50% EtOAc/hexanes) followed by recrystallization from toluene to afford the title compound as a white solid (4.24 g, 54%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.43 (s, 1H), 10.98 (s, 1H), 8.86 (s, 1H), 8.46 (s, 1H), 8.14 (d, $J = 8.3$ Hz, 1H), 7.95 (d, $J = 7.8$ Hz, 1H), 7.81 (s, 1H), 7.54 (d, $J = 8.3$ Hz, 1H), 7.36 (t, $J = 7.8$ Hz, 1H), 7.35–7.32 (m, 1H), 2.14 (s, 3H), 1.45 (s, 9H). MS (ESI positive ion) *m/z*: 546 (M + 1).

A 25 mL round-bottomed flask was charged with *tert*-butyl 2-(6-(2-acetamidobenzo[*d*]thiazol-4-yloxy)pyrimidin-4-yl)-5-(trifluoromethyl)phenylcarbamate (0.22 g, 0.41 mmol), TFA (2.5 mL), and CH_2Cl_2 (2.5 mL). The solution was stirred at room temperature for 1 h, and the solvent was removed under reduced pressure. The resulting pale-yellow residue was taken into saturated aqueous $NaHCO_3$ and sonicated. The precipitate was collected by filtration, and the filter cake was washed with H_2O and air-dried to afford the title compound as a light-yellow solid (0.19 g, 100%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.42 (s, 1H), 8.75 (s, 1H), 7.93 (d, $J = 6.2$ Hz, 2H), 7.60 (s, 1H), 7.28–7.27 (m, 2H), 7.09 (s, 1H), 6.90–6.89 (m, 1H), 4.03 (br s, 2H), 2.14 (s, 3H). MS (ESI positive ion) *m/z*: 446 (M + 1). Anal. ($C_{20}H_{14}F_3N_5O_2S \cdot 0.4H_2O$) C, H, N.

1-*tert*-Butyl-3-(2-(6-chloropyrimidin-4-yl)-5-(trifluoromethyl)phenyl)urea (17b). A 250 mL round-bottomed flask was charged with *tert*-butyl 2-(6-chloropyrimidin-4-yl)-5-(trifluoromethyl)phenylcarbamate (**17a**, 10.0 g, 17 mmol) and CH_2Cl_2 (100 mL). The solution was cooled to 0 °C, and TFA (25 mL) was added. The reaction mixture was stirred for 10 min at 0 °C and 2 h at room temperature. After removal of the solvent under reduced pressure, the residue was taken into EtOAc and saturated aqueous $NaHCO_3$.

The organic phase was separated, washed with saturated aqueous $NaHCO_3$, H_2O, saturated aqueous NaCl, and dried over Na_2SO_4. The residue was purified by silica gel chromatography (5–20% EtOAc/hexanes) to afford 2-(6-chloropyrimidin-4-yl)-5-(trifluoromethyl)benzenamine as a yellow solid (6.2 g, 84%). MS (ESI positive ion) *m/z*: 274 (M + 1).

A 50 mL round-bottomed flask was charged with 2-(6-chloropyrimidin-4-yl)-5-(trifluoromethyl)benzenamine (0.11 g, 0.4 mmol), 2-isocyanato-2-methylpropane (0.05 g, 0.5 mmol), and DCE (5 mL). The reaction mixture was heated at 40 °C for 1 h, and an additional amount of 2-isocyanato-2-methylpropane (0.39 g, 4.0 mmol) was added followed by $MgCl_2$ (0.38 g, 4.0 mmol). The mixture was heated at 65 °C for 18 h and allowed to cool to room temperature. The reaction mixture was diluted with $CHCl_3$, washed with H_2O, dried over Na_2SO_4, and filtered. The filtrate was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (10–20% EtOAc/hexanes) to afford the title compound as a white solid (90 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.80 (s, 1H), 9.09 (s, 1H), 8.75 (s, 1H), 7.78 (s, 1H), 7.73 (d, J = 8.2 Hz, 1H), 7.30 (d, J = 8.2 Hz, 1H), 1.42 (s, 9H). MS (ESI positive ion) *m/z*: 373 (M + 1).

1-(2-(6-(2-Acetamidobenzo[*d*]thiazol-4-yloxy)pyrimidin-4-yl)-5-(trifluoromethyl)phenyl)-3-*tert*-butylurea (18b). A 50 mL round-bottomed flask was charged with 1-*tert*-butyl-3-(2-(6-chloropyrimidin-4-yl)-5-(trifluoromethyl)phenyl)urea (**17b**; 0.19 g, 0.51 mmol), *N*-(4-hydroxybenzo[*d*]thiazol-2-yl)acetamide (0.21 g, 1.0 mmol), Cs_2CO_3 (0.32 g, 1.0 mmol), and DMF (5 mL). The reaction mixture was heated at 60 °C for 18 h and cooled to room temperature. After removal of the solvents under reduced pressure, the residue was diluted with $CHCl_3$ and then 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 preparative HPLC (30–100% CH_3CN/H_2O, 0.1% TFA). The fractions were concentrated, dissolved in $CHCl_3$, washed with 10% aqueous Na_2CO_3, dried over Na_2SO_4, and concentrated to give the title compound as a white solid (70 mg, 26%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.42 (s, 1H), 9.87 (s, 1H), 8.83 (s, 1H), 8.69 (s, 1H), 7.94 (dd, J = 11.0 Hz, 8.4 Hz, 2H), 7.68 (s, 1H), 7.40–7.35 (m, 3H), 7.06 (s, 1H), 2.14 (s, 3H), 1.29 (s, 9H). MS (ESI positive ion) *m/z*: 545 (M + 1). HRMS calculated for $C_{25}H_{23}F_3N_6O_3S$ $(M + H)^+$ 545.15772, found 545.15755.

3-Amino-5-(6-(2-amino-4-(trifluoromethyl)phenyl)pyrimidin-4-yloxy)quinoxalin-2(1*H*)-one (19a). A 150 mL round-bottomed flask was charged with *tert*-butyl 2-(6-chloropyrimidin-4-yl)-5-(trifluoromethyl)phenylcarbamate (**17a**; 2.0 g, 5.4 mmol), 3-amino-5-hydroxyquinoxalin-2(1*H*)-one hydrobromide (1.4 g, 5.4 mmol), Cs_2CO_3 (3.52 g, 10.8 mmol), and DMF (25 mL). The mixture was stirred at 25 °C for 16 h and heated at 45 °C for 18 h. After cooling to room temperature, the reaction mixture was diluted with H_2O (200 mL). The precipitate was collected by filtration, and the filter cake was washed with H_2O and EtOAc/hexanes (5%) and then air-dried. The crude material was purified by silica gel chromatography (30–100% EtOAc/hexanes) to give *tert*-butyl 2-(6-(3-amino-2-oxo-1,2-dihydroquinoxalin-5-yloxy)pyrimidin-4-yl)-5-(trifluoromethyl)phenylcarbamate as a white solid (2.03 g, 74%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.31 (s, 1H), 11.08 (s, 1H), 8.85 (s, 1H), 8.48 (s, 1H), 8.12 (d, J = 8.2 Hz, 1H), 7.69 (s, 1H), 7.54 (d, J = 7.4 Hz, 1H), 7.19–7.01 (m, 5H), 1.45 (s, 9H). MS (ESI positive ion) *m/z*: 515 (M + 1).

A 250 mL round-bottomed flask was charged with *tert*-butyl 2-(6-(3-amino-2-oxo-1,2-dihydroquinoxalin-5-yloxy)pyrimidin-4-yl)-5-(trifluoromethyl)phenylcarbamate (1.88 g, 3.7 mmol) and CH_2Cl_2 (100 mL). The mixture was cooled to 0 °C, and then TFA (25 mL) was added and the mixture was allowed to warm to 25 °C. After being stirred for 2 h, the reaction was quenched by saturated aqueous $NaHCO_3$ and EtOAc was added. The organic phase was separated, washed with H_2O and saturated aqueous NaCl, and dried over Na_2SO_4. The solvents were removed under vacuum to provide the title compound as a pale-yellow solid (1.01 g, 66%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.30 (s, 1H), 8.73 (s, 1H), 7.89 (d, J = 8.2 Hz, 1H), 7.55 (d, J = 0.8 Hz, 1H), 7.18–7.09 (m, 5H), 7.02 (dd, J = 7.6 Hz, 1.6 Hz, 1H), 6.87 (dd, J = 8.3 Hz, 1.3 Hz, 1H). MS (ESI positive ion) *m/z*: 415 (M + 1). Anal. ($C_{19}H_{13}F_3N_6O_2 \cdot H_2O$) C, H, N.

1-(2-(6-(3-Amino-2-oxo-1,2-dihydroquinoxalin-5-yloxy)pyrimidin-4-yl)-5-(trifluoromethyl)phenyl)-3-*tert*-butylurea (19b). A 50 mL round-bottomed flask was charged with 1-*tert*-butyl-3-(2-(6-chloropyrimidin-4-yl)-5-(trifluoromethyl)phenyl)urea (**17b**; 0.30 g, 0.80 mmol), 3-amino-5-hydroxyquinoxalin-2(1*H*)-one (0.29 g, 1.6 mmol), Cs_2CO_3 (0.52 g, 1.6 mmol), and DMF (5 mL). The reaction mixture was heated at 65 °C for 18 h and allowed to cool to room temperature. Then it was diluted with $CHCl_3$, washed with H_2O, dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure and purified by silica gel chromatography (2:2:1 hexanes/EtOAc/$CHCl_3$). The product obtained was treated with hot ^{i}PrOAc, filtered, and dried to give the title compound as a white solid (0.21 g, 51%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.29 (s, 1H), 9.88 (s, 1H), 8.82 (s, 1H), 8.72 (s, 1H), 7.89 (d, J = 8.2 Hz, 1H), 7.55 (s, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.19–7.02 (m, 6H), 1.29 (s, 9H). MS (ESI positive ion) *m/z*: 514 (M + 1). Anal. ($C_{24}H_{22}F_3N_7O_3$) C, H, N.

***N*-(2-(6-chloropyrimidin-4-yl)-5-(trifluoromethyl)phenyl)picolinamide (17c).** A solution of 2-(6-chloropyrimidin-4-yl)-5-(trifluoromethyl)benzenamine (see **17b**; 0.40 g, 1.46 mmol), *N,N*-diisopropylethylamine (1.00 mL, 5.85 mmol), and picolinoyl chloride hydrochloride (0.39 g, 2.19 mmol) in CH_2Cl_2 (10 mL) was stirred at 25 °C for 24 h. The reaction mixture was partitioned between EtOAc/hexanes (1:1) and saturated aqueous $NaHCO_3$. The phases were separated and the organic phase was washed successively with saturated aqueous $NaHCO_3$, H_2O, saturated aqueous NaCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. Purification by silica gel chromatography (10–50% EtOAc/hexanes) afforded the title compound as a white solid (0.45 g, 82%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.81 (s, 1H), 9.38 (s, 1H), 9.09 (s, 1H), 8.85 (d, J = 4.7 Hz, 1H), 8.38 (s, 1H), 8.28 (d, J = 8.2 Hz, 1H), 8.15–8.05 (m, 2H), 7.71–7.68 (m, 1H), 7.60 (d, J = 8.2 Hz, 1H). MS (ESI positive ion) *m/z*: 379 (M + 1).

***N*-(2-(6-(3-Amino-2-oxo-1,2-dihydroquinoxalin-5-yloxy)pyrimidin-4-yl)-5-(trifluoromethyl)phenyl)picolinamide (19c).** A solution of *N*-(2-(6-chloropyrimidin-4-yl)-5-(trifluoromethyl)phenyl)picolinamide (**17c**; 0.10 g, 0.26 mmol), 3-amino-5-hydroxyquinoxalin-2(1*H*)-one (69 mg, 0.39 mmol), and Cs_2CO_3 (0.19 g, 0.57 mmol) in DMF (4 mL) was stirred at 50 °C for 19 h. The reaction was quenched with an aqueous buffer (3.0 M NaCl/0.3 M sodium citrate, pH 7). The precipitate was collected by filtration and the filter cake was washed with H_2O and EtOAc/hexanes (1:1) and dried under vacuum to afford the title compound as a tan solid (10 mg, 80%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.31 (s, 1H), 9.16 (s, 1H), 9.07 (s, 1H), 8.81 (d, J = 4.5 Hz, 1H), 8.25 (d, J = 8.2 Hz, 1H), 8.18 (d, J = 7.6 Hz, 1H), 8.10–8.06 (m, 1H), 7.79 (s, 1H), 7.70–7.64 (m, 2H), 7.19–7.04 (m, 4H). MS (ESI positive ion) *m/z*: 520 (M + 1). Anal. ($C_{25}H_{16}F_3N_7O_3 \cdot 0.5H_2O$) C, H, N.

***N*-(2-(6-Chloropyrimidin-4-yl)-5-(trifluoromethyl)phenyl)isonicotinamide (17d).** Following the procedure described for compound **17c**, 2-(6-chloropyrimidin-4-yl)-5-(trifluoromethyl)benzenamine (0.40 g, 1.46 mmol) was reacted with isonicotinoyl chloride hydrochloride (0.39 g, 2.2 mmol) to provide the title compound as a yellow solid (0.31 g, 57%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.07 (s, 1H), 9.28 (s, 1H), 8.84 (d, J = 5.5 Hz, 2H), 8.65 (s, 1H), 8.33 (s, 1H), 8.22 (d, J = 8.2 Hz, 1H), 7.82 (d, J = 5.7 Hz, 2H), 7.74 (d, J = 8.2 Hz, 1H). MS (ESI positive ion) *m/z*: 379 (M + 1).

***N*-(2-(6-(3-Amino-2-oxo-1,2-dihydroquinoxalin-5-yloxy)pyrimidin-4-yl)-5-(trifluoromethyl)phenyl)isonicotinamide (19d).** Following the procedure described for compound **19c**, *N*-(2-(6-chloropyrimidin-4-yl)-5-(trifluoromethyl)phenyl)isonicotinamide (**17d**; 0.10 g, 0.26 mmol) was reacted with 3-amino-5-hydroxyquinoxalin-2(1*H*)-one (70 mg, 0.40 mmol) and Cs_2CO_3 (0.17 g, 0.53 mmol) to afford the title compound as a tan solid (0.11 g, 77%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.90 (s, 1H), 12.30 (s, 1H), 8.99 (s, 1H), 8.84–8.82 (m, 3H), 8.28 (d, J = 8.3 Hz, 1H), 7.84 (d, J = 6.1 Hz, 2H), 7.77 (s,

1H), 7.71 (d, $J = 8.1$ Hz, 1H), 7.16–7.09 (m, 2H), 7.00 (dd, $J = 7.6$ Hz, 1.7 Hz, 1H). MS (ESI positive ion) *m/z*: 520 (M + 1). Anal. ($C_{25}H_{16}F_3N_7O_3 \cdot 0.5H_2O$) C, H, N.

3-Amino-5-(6-iodopyrimidin-4-yloxy)quinoxalin-2(1*H*)-one (20). A 25 mL round-bottomed flask was charged with 4,6-diiodopyrimidine (2.57 g, 7.74 mmol), K_2CO_3 (1.61 g, 11.6 mmol), 3-amino-5-hydroxyquinoxalin-2(1*H*)-one (1.37 g, 7.74 mmol), and DMSO (5 mL). The reaction mixture was heated at 80 °C for 1 h, allowed to cool to room temperature, and then quenched with saturated aqueous $NaHCO_3$ (5 mL). The resulting precipitate was collected by filtration, and the solid was washed with H_2O and MeOH, and then dried under vacuum to afford **20** as a light-yellow solid (2.11 g, 72%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.29 (s, 1H), 8.41 (s, 1H), 7.66 (s, 1H), 7.16–7.08 (m, 2H), 6.99 (dd, $J = 7.6$ Hz, 1.6 Hz, 1H). MS (ESI positive ion) *m/z*: 382 (M + 1).

2-Chloro-3-(tributylstannyl)-6-(trifluoromethyl)pyridine (22). A 250 mL round-bottomed flask was charged with *N,N*-diisopropylamine (4.25 g, 42 mmol) and THF (70 mL). The reaction mixture was cooled to −78 °C, and *n*-butyllithium (2.5 M in hexanes, 14 mL, 36 mmol) was added. The solution was stirred at 0 °C for 15 min before being cooled to −78 °C. To the reaction mixture was added 2-chloro-6-(trifluoromethyl)pyridine (5.45 g, 30 mmol), and the solution was stirred at −78 °C for 1 h. Tributyltin chloride (11.72 g, 36 mmol) was added, and the mixture was stirred for an additional 1 h before being allowed to warm to 0 °C. The reaction was quenched by the addition of saturated NH_4Cl, and the organic layer was separated. The aqueous layer was extracted with ether, and the combined organic layers were washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (0.5% EtOAc/hexanes) to give **22** as a clear oil (6.07 g, 43%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, $J = 7.2$ Hz, 1H), 7.51 (d, $J = 7.4$ Hz, 1H), 1.57–1.51 (m, 6H), 1.37–1.19 (m, 12H), 0.92–0.88 (m, 9H).

3-Amino-5-(6-(2-chloro-6-(trifluoromethyl)pyridin-3-yl)pyrimidin-4-yloxy)quinoxalin-2(1*H*)-one (23). A 250 mL round-bottomed flask was charged with 3-amino-5-(6-iodopyrimidin-4-yloxy)quinoxalin-2(1*H*)-one (**20**; 14.1 g, 37 mmol), CuI (1.4 g, 7.3 mmol), $Pd(PPh_3)_4$ (3.5 g, 3.0 mmol), 2-chloro-3-(tributylstannyl)-6-(trifluoromethyl)pyridine (18.8 g, 40 mmol), and DMF (100 mL). The reaction mixture was heated at 60 °C for 18 h and allowed to cool to room temperature. Then it was diluted with H_2O (300 mL), and the resulting precipitate was collected by filtration. Recrystallization from EtOH afforded the title compound as a white solid (9.6 g, 60%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.31 (s, 1H), 8.87 (s, 1H), 8.38–8.37 (m, 1H), 8.15–8.14 (m, 1H), 7.50 (s, 1H), 7.16–7.05 (m, 3H). MS (ESI positive ion) *m/z*: 435 (M + 1).

3-Amino-5-(6-(2-amino-6-(trifluoromethyl)pyridin-3-yl)pyrimidin-4-yloxy)quinoxalin-2(1*H*)-one (24a). A 5 mL microwave tube was charged with 3-amino-5-(6-(2-chloro-6-(trifluoromethyl)pyridin-3-yl)pyrimidin-4-yloxy)quinoxalin-2(1*H*)-one (**23**; 0.22 g, 0.52 mmol), (3,4-dimethoxyphenyl)methanamine (0.16 mL, 1.04 mmol), and DMSO (1 mL). The reaction mixture was heated and stirred in a microwave at 125 °C for 25 min and then allowed to cool to room temperature. The mixture was diluted with EtOAc and washed with H_2O. The organic layer was dried over $MgSO_4$ and filtered. Purification by silica gel chromatography (0–2% MeOH (2 M NH_3) in CH_2Cl_2) afforded 5-(6-(2-(3,4-dimethoxybenzylamino)-6-(trifluoromethyl)pyridin-3-yl)pyrimidin-4-yloxy)-3-aminoquinoxalin-2(1*H*)-one as a yellow solid (0.11 g, 37%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.28 (s, 1H), 9.66 (s, 1H), 8.78 (s, 1H), 8.43 (d, $J = 8.4$ Hz, 1H), 7.76 (s, 1H), 7.18–7.00 (m, 4H), 6.94–6.87 (m, 2H), 6.61–6.58 (m, 1H), 4.62 (d, $J = 5.8$ Hz, 2H), 3.71 (s, 6H). MS (ESI positive ion) *m/z*: 566 (M + 1).

A 25 mL round-bottomed flask was charged with 5-(6-(2-(3,4-dimethoxybenzylamino)-6-(trifluoromethyl)pyridin-3-yl)pyrimidin-4-yloxy)-3-aminoquinoxalin-2(1*H*)-one (0.10 g, 0.18 mmol) and TFA (3 mL). The mixture was stirred at room temperature for 18 h, and the solvent was removed under reduced pressure. The residue was diluted with EtOAc and washed successively with saturated aqueous $NaHCO_3$, H_2O, saturated aqueous NaCl, dried over Na_2SO_4, and filtered. Removal of the solvent under vacuum provided the title compound as a light-yellow solid (44 mg, 59%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.28 (s, 1H), 8.78 (s, 1H), 8.39 (d, $J = 7.8$ Hz, 1H), 7.97 (br s, 2H), 7.71 (s, 1H), 7.16 (t, $J = 7.9$ Hz, 1H), 7.11–7.07 (m, 2H), 7.02 (dd, $J = 7.7$ Hz, 1.3 Hz, 1H). MS (ESI positive ion) *m/z*: 416 (M + 1). HRMS calculated for $C_{18}H_{12}F_3N_7O_2$ $(M + H)^+$ 416.10773, found 416.10813.

3-Amino-5-(6-(2-(2-methoxyethylamino)-6-(trifluoromethyl)-pyridin-3-yl)pyrimidin-4-yloxy)quinoxalin-2(1*H*)-one (24b). A 5 mL microwave tube was charged with 3-amino-5-(6-(2-chloro-6-(trifluoromethyl)pyridin-3-yl)pyrimidin-4-yloxy)quinoxalin-2(1*H*)-one (0.40 g, 0.92 mmol), 2-methoxyethanamine (0.35 g, 4.60 mmol), and DMSO (2 mL). The reaction mixture was heated and stirred in a microwave at 100 °C for 15 min and then allowed to cool to room temperature. The mixture was diluted with EtOAc, washed with H_2O and saturated aqueous NaCl, and dried over $MgSO_4$. The crude product was first purified by silica gel chromatography (5% MeOH (2 M NH_3) in CH_2Cl_2) and then by reverse-phase HPLC (5–95% CH_3CN/H_2O, 0.1% TFA) to afford the title compound as a TFA salt. This material was partitioned between EtOAc and saturated aqueous $NaHCO_3$. The organic layer was separated, washed with saturated aqueous $NaHCO_3$ and H_2O, and dried over Na_2SO_4. Removal of the solvent under vacuum provided the title compound as a pale-yellow solid (0.25 g, 55%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.30 (s, 1H), 9.47 (t, $J = 5.1$ Hz, 1H), 8.79 (s, 1H), 8.45 (d, $J = 7.8$ Hz, 1H), 7.78 (s, 1H), 7.16 (t, $J = 8.0$ Hz, 1H), 7.11–7.07 (m, 2H), 7.03 (dd, $J = 7.6$ Hz, 1.4 Hz, 1H), 3.64 (q, $J = 5.4$ Hz, 2H), 3.54 (t, $J = 5.4$ Hz, 2H), 3.29 (s, 3H). MS (ESI positive ion) *m/z*: 474 (M + 1). Anal. ($C_{21}H_{18}F_3N_7O_3$) C, H, N.

3-Amino-5-(6-(2-((*R*)-tetrahydrofuran-3-ylamino)-6-(trifluoromethyl)pyridin-3-yl)pyrimidin-4-yloxy)quinoxalin-2(1*H*)-one (24c). This material was prepared according to the method described for compound **24b** from 3-amino-5-(6-(2-chloro-6-(trifluoromethyl)pyridin-3-yl)pyrimidin-4-yloxy)quinoxalin-2(1*H*)-one (0.40 g, 0.92 mmol) and (*R*)-tetrahydrofuran-3-amine (0.12 g, 1.3 mmol). Purification by reverse-phase HPLC (5–95% CH_3CN/H_2O, 0.1% TFA) provided the title compound as a TFA salt. This salt was partitioned between EtOAc and saturated aqueous $NaHCO_3$. The organic layer was separated, washed with saturated aqueous $NaHCO_3$ and H_2O, and dried over Na_2SO_4. Removal of the solvent under vacuum provided the title compound as an off-white solid (0.19 g, 43%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.30 (s, 1H), 9.57–9.56 (m, 1H), 8.79 (s, 1H), 8.82 (s, 1H), 8.49–8.48 (m, 1H), 7.80 (s, 1H), 7.14–6.99 (m, 6H), 4.58–4.55 (m, 1H), 3.98–3.94 (m, 1H), 3.87–3.85 (m, 1H), 3.78–3.72 (m, 1H), 3.62–3.57 (m, 1H), 2.34–2.30 (m, 1H), 1.90–1.85 (m, 1H). MS (ESI positive ion) *m/z*: 486 (M + 1). HRMS calculated for $C_{22}H_{18}F_3N_7O_3$ $(M + H)^+$ 486.14960, found 486.14970.

3-Amino-5-(6-(2-(2-morpholinoethylamino)-6-(trifluoromethyl)pyridin-3-yl)pyrimidin-4-yloxy)quinoxalin-2(1*H*)-one (24d). A 10 mL round-bottomed flask was charged with 3-amino-5-(6-(2-chloro-6-(trifluoromethyl)pyridin-3-yl)pyrimidin-4-yloxy)quinoxalin-2(1*H*)-one (0.15 g, 0.35 mmol), 2-morpholinoethanamine (0.14 mL, 1.05 mmol), and DMSO (3 mL). The mixture was stirred at 25 °C for 2.5 days and then partitioned between saturated aqueous $NaHCO_3$ and EtOAc. The phases were separated, and the organic phase was washed with H_2O and saturated aqueous NaCl, dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure and purified by silica gel chromatography (0.5–5% MeOH (2 M NH_3) in CH_2Cl_2). Further purification by reverse-phase HPLC (2–100% CH_3CN/H_2O, 0.1% TFA) afforded the title compound as a TFA salt. This material was partitioned between saturated aqueous $NaHCO_3$ and EtOAc. The phases were separated, and the organic phase was washed with H_2O and saturated aqueous NaCl, dried over Na_2SO_4, and filtered. Removal of the solvent under vacuum provided the title compound as yellow solid (38 mg, 21%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.30 (s, 1H), 9.54 (br s, 1H), 8.81 (s, 1H), 8.42 (d, $J = 8.0$ Hz, 1H), 7.77 (s, 1H), 7.18–7.02 (m, 4H), 3.58–3.55 (m, 6H), 2.56–2.54 (m, 2H), 2.44 (br s, 4H). MS

(ESI positive ion) *m/z*: 529 (M + 1). HRMS calculated for $C_{24}H_{23}F_3N_8O_3$ $(M + H)^+$ 529.19180, found 529.19282.

3-Amino-5-(6-(2-((1-isobutylpiperidin-2-yl)methylamino)-6-(trifluoromethyl)pyridin-3-yl)pyrimidin-4-yloxy)quinoxalin-2(1*H*)-one (24e). This material was prepared according to the method described for compound **24b** from 3-amino-5-(6-(2-chloro-6-(trifluoromethyl)pyridin-3-yl)pyrimidin-4-yloxy)quinoxalin-2(1*H*)-one (0.31 g, 0.71 mmol), (1-isobutylpiperidin-2-yl)ethanamine (0.26 g, 1.4 mmol), and DMSO (2 mL). Purification by silica gel chromatography (0–5% MeOH (2 M NH_3) in CH_2Cl_2) provided the title compound as a yellow solid (0.13 g, 33%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.27 (s, 1H), 9.44 (br s, 1H), 8.75 (s, 1H), 8.40 (d, J = 7.8 Hz, 1H), 7.74 (s, 1H), 7.18–6.99 (m, 4H), 3.61–3.52 (m, 2H), 2.88–2.87 (m, 1H), 2.44–2.42 (m, 1H), 2.05–1.96 (m, 2H), 1.76–1.41 (m, 6H), 1.26–1.25 (m, 2H), 0.78 (d, J = 6.5 Hz, 3H), 0.73 (d, J = 6.5 Hz, 3H). MS (ESI positive ion) *m/z*: 569 (M + 1). Anal. ($C_{28}H_{31}F_3N_8O_2$) C, H, N.

4,6-Dichloro-*N*-(2-methoxyethyl)pyrimidin-2-amine (25a). A 100 mL round-bottomed flask was charged with 2,4,6-trichloropyrimidine (2.93 g, 16 mmol), 2-methoxyethanamine (1.20 g, 16 mmol), and dioxane (5 mL). The reaction mixture was stirred at 60 °C for 3 h and then concentrated under reduced pressure. Purification by silica gel chromatography (10–20% EtOAc/hexanes) afforded **25a** as a white solid (0.99 g, 28%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.60 (s, 1H), 5.72 (br s, 1H), 3.62 (q, J = 5.3 Hz, 2H), 3.55 (t, J = 4.8 Hz, 2H), 3.37 (s, 3H). MS (ESI positive ion) *m/z*: 222 (M + 1).

3-Amino-5-(6-chloro-2-(2-methoxyethylamino)pyrimidin-4-yloxy)quinoxalin-2(1*H*)-one (26a). A 25 mL round-bottomed flask was charged with 4,6-dichloro-*N*-(2-methoxyethyl)pyrimid-2-amine (0.50 g, 2.3 mmol), 3-amino-5-hydroxyquinoxalin-2(1*H*)-one (0.39 g, 2.3 mmol), Cs_2CO_3 (1.47 g, 4.50 mmol), and DMF (5 mL). The reaction mixture was heated at 80 °C for 16 h and allowed to cool to room temperature. To the reaction mixture was added H_2O and EtOAc, and the phases were separated. The organic phase was washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by silica gel chromatography (65% EtOAc/hexanes) provided the title compound (0.61 g, 75%). MS (ESI positive ion) *m/z*: 363 (M + 1).

3-Amino-5-(6-(2-amino-4-(trifluoromethyl)phenyl)-2-(2-methoxyethylamino)pyrimidin-4-yloxy)quinoxalin-2(1*H*)-one (28a). A 5 mL microwave tube was charged with 2-(*tert*-butoxycarbonylamino)-4-(trifluoromethyl)phenylboronic acid (0.25 g, 0.83 mmol), 3-amino-5-(6-chloro-2-(2-methoxyethylamino)pyrimidin-4-yloxy)-quinoxalin-2(1*H*)-one (0.20 g, 0.55 mmol), $Pd(PPh_3)_2Cl_2$ (38 mg, 0.05 mmol), Na_2CO_3 (87 mg, 0.83 mmol), and DME/EtOH/H_2O (1.4/0.4/0.6, 2.4 mL). The reaction mixture was stirred and heated in a microwave at 120 °C for 20 min. The Boc protective group was completely removed by treatment with TFA/CH_2Cl_2 (1/1, 5 mL) for 1 h at room temperature. After removal of the solvents under reduced pressure, the reaction mixture was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$, H_2O, and saturated aqueous NaCl. Purification by silica gel chromatography (55% EtOAc/hexanes) afforded the title compound as a white solid (0.17 g, 73%). ^{1}H NMR (400 MHz, MeOH-d_4): δ 7.65 (d, J = 8.2 Hz, 1H), 7.21 (t, J = 8.1 Hz, 1H), 7.09 (dd, J = 8.1 Hz, 1.3 Hz, 1H), 7.04–7.01 (m, 2H), 6.87 (dd, J = 8.2 Hz, 1.2 Hz, 1H), 6.54 (s, 1H), 3.47–3.31 (m, 4H), 3.24 (br s, 3H). MS (ESI positive ion) *m/z*: 488 (M + 1). Anal. ($C_{22}H_{20}F_3N_7O_3$) C, H, N.

(*S*)-4,6-Dichloro-*N*-(1-methoxypropan-2-yl)pyrimidin-2-amine (25b). A 20 mL microwave tube was charged with 2,4,6-trichloropyrimidine (4.58 g, 25 mmol), (*S*)-1-methoxypropan-2-amine (2.22 g, 25 mmol), and EtOH (5 mL). The reaction mixture was stirred and heated in a microwave at 140 °C for 15 min. After cooling to room temperature, the reaction mixture was concentrated in vacuo and the residue purified by silica gel chromatography (10–20% EtOAc in hexanes) to afford **25b** (0.68 g, 12%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.58 (s, 1H), 5.58 (br s, 1H), 4.26–4.21 (m, 1H), 3.45–3.40 (m, 2H), 3.37 (s, 3H), 1.25 (d, J = 6.8 Hz, 3H). MS (ESI positive ion) *m/z*: 237 (M + 1).

(*S*)-3-Amino-5-(6-chloro-2-(1-methoxypropan-2-ylamino)pyrimidin-4-yloxy)quinoxalin-2(1*H*)-one (26b). This material was prepared according to the method described for compound **26a** from (*S*)-4,6-dichloro-*N*-(1-methoxypropan-2-yl)pyrimidin-2-amine (0.62 g, 2.63 mmol), 3-amino-5-hydroxyquinoxalin-2(1*H*)-one (0.51 g, 2.89 mmol), Cs_2CO_3 (1.71 g, 5.25 mmol), and DMF (5 mL). Purification by silica gel chromatography (65% EtOAc/hexanes) afforded the title compound as a white solid (0.80 g, 80%). MS (ESI positive ion) *m/z*: 377 (M + 1).

3-Amino-5-(6-(2-amino-4-(trifluoromethyl)phenyl)-2-((*S*)-1-methoxypropan-2-ylamino)pyrimidin-4-yloxy)quinoxalin-2(1*H*)-one (28b). This material was prepared according to the method described for compound **28a** from 2-(*tert*-butoxycarbonylamino)-4-(trifluoromethyl)phenylboronic acid (0.41 g, 1.4 mmol), (*S*)-3-amino-5-(6-chloro-2-(1-methoxypropan-2-ylamino)pyrimidin-4-yloxy)quinoxalin-2(1*H*)-one (0.34 g, 0.90 mmol), $Pd(PPh_3)_2Cl_2$ (63 mg, 0.09 mmol), Na_2CO_3 (0.14 g, 1.4 mmol), and DME/EtOH/H_2O (1.4/0.4/0.6, 2.4 mL). The Boc protective group was completely removed by treatment with TFA/CH_2Cl_2 (1/1, 5 mL) for 1 h at room temperature. The crude material was purified by silica gel chromatography (45% EtOAc/hexanes) to give the title compound as a light-yellow solid (0.22 g, 49%). ^{1}H NMR (400 MHz, MeOH-d_4): δ 7.69 (d, J = 8.2 Hz, 1H), 7.23 (t, J = 8.1 Hz, 1H), 7.11 (dd, J = 8.2 Hz, 1.2 Hz, 1H), 7.06–7.03 (m, 2H), 6.90 (d, J = 8.0 Hz, 1H), 6.58 (s, 1H), 3.32 (br s, 6H), 1.09 (br s, 3H). MS (ESI positive ion) *m/z*: 502 (M + 1). Anal. ($C_{23}H_{22}F_3N_7O_3$) C, H, N.

3-Amino-5-(2-amino-6-(2-amino-4-(trifluoromethyl)phenyl)pyrimidin-4-yloxy)quinoxalin-2(1*H*)-one (28c). This material was prepared according to the method described for compound **28a** from 2-(*tert*-butoxycarbonylamino)-4-(trifluoromethyl)phenylboronic acid (0.18 g, 0.59 mmol), $Pd(PPh_3)_2Cl_2$ (28 mg, 0.04 mmol), 3-amino-5-(2-amino-6-chloropyrimidin-4-yloxy)quinoxalin-2(1*H*)-one (**8**; 0.12 g, 0.39 mmol), Na_2CO_3 (63 mg, 0.59 mmol), and DME/EtOH/H_2O (1.4/0.4/0.6, 2.4 mL). The Boc protective group was removed by treatment with TFA/CH_2Cl_2 (1/1, 5 mL) for 1 h at room temperature. The reaction mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, H_2O, and saturated aqueous NaCl. Purification by silica gel chromatography (55% EtOAc/hexanes) afforded the title compound as an off-white solid (70 mg, 41%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.24 (s, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.30 (br s, 2H), 7.15–7.03 (m, 3H), 6.96 (dd, J = 7.8 Hz, 1.2 Hz 1H), 6.80–6.75 (m, 3H), 6.55 (s, 1H). MS (ESI positive ion) *m/z*: 430 (M + 1). Anal. ($C_{19}H_{14}F_3N_7O_2$) C, H, N.

(*S*)-3-Amino-5-(6-iodo-2-(1-methoxypropan-2-ylamino)pyrimidin-4-yloxy)quinoxalin-2(1*H*)-one (29). A 100 mL round-bottomed flask was charged with 4,6-dichloro-*N*-(2-methoxyethyl)pyrimidin-2-amine (**25b**, 0.26 g, 1.17 mmol), hydriodic acid (57% HI solution, 0.04 mL, 1.65 mmol), NaI (0.25 g, 1.65 mmol), and CH_2Cl_2 (5 mL), and the mixture was then stirred at room temperature for 2 h. The reaction mixture was diluted with EtOAc (50 mL), washed successively with 1 N NaOH and saturated aqueous NaCl, and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure and purified by silica gel chromatography (7% EtOAc/hexanes) to afford (*S*)-4,6-diiodo-*N*-(1-methoxypropan-2-yl)pyrimidin-2-amine (0.34 g, 74%). MS (ESI positive ion) *m/z*: 420 (M + 1).

A solution of (*S*)-4,6-diiodo-*N*-(1-methoxypropan-2-yl)pyrimidin-2-amine (0.34 g, 0.78 mmol), 3-amino-5-hydroxyquinoxalin-2(1*H*)-one (0.14 g, 0.78 mmol), and Cs_2CO_3 (0.51 g, 1.56 mmol) in DMF (5 mL) was stirred at 90 °C for 16 h. After the mixture was cooled to room temperature, water was added and the reaction mixture was extracted twice with EtOAc. The combined extracts were dried over Na_2SO_4, and the filtrate was concentrated under reduced pressure. Purification by silica gel chromatography (65% EtOAc/hexanes) afforded the title compound as an off-white solid (0.21 g, 57%).

3-Amino-5-(6-(2-chloro-6-(trifluoromethyl)pyridin-3-yl)-2-((*S*)-1-methoxypropan-2-ylamino)pyrimidin-4-yloxy)quinoxalin-2(1*H*)-one (30). A 25 mL round-bottomed flask was charged with 2-chloro-3-(tributylstannyl)-6-(trifluoromethyl)pyridine (**22**; 0.30 g,

0.64 mmol), (*S*)-3-amino-5-(6-iodo-2-(1-methoxypropan-2-ylamino)pyrimidin-4-yloxy)quinoxalin-2(1*H*)-one (**29**; 0.20 g, 0.43 mmol), CuI (33 mg, 0.13 mmol), $Pd(PPh_3)_4$ (50 mg, 0.06 mmol), and DMF (5 mL). The reaction mixture was heated at 100 °C for 3 h and then allowed to cool to room temperature. The mixture was diluted with EtOAc, washed with 10% aqueous Na_2CO_3 (20 mL) and saturated aqueous NaCl, and dried over $MgSO_4$. Purification by silica gel chromatography (20–60% EtOAc/hexanes) afforded **30** (0.14 g, 63%). MS (ESI positive ion) *m*/*z*: 522 (M + 1).

3-(6-(3-Amino-2-oxo-1,2-dihydroquinoxalin-5-yloxy)-2-((*S*)-1-methoxypropan-2-ylamino)pyrimidin-4-yl)-6-(trifluoromethyl)-pyridin-2-aminium trifluoroacetate (31). A 5 mL microwave tube was charged with 3-amino-5-(6-(2-chloro-6-(trifluoromethyl)pyridin-3-yl)-2-((*S*)-1-methoxypropan-2-ylamino)pyrimidin-4-yloxy)quinoxalin-2(1*H*)-one (0.13 g, 0.25 mmol), (3,4-dimethoxyphenyl)methanamine (83 mg, 0.50 mmol), and DMSO (2 mL). The reaction mixture was stirred and heated at 120 °C for 40 min in a microwave. Purification by preparative HPLC (10–100% CH_3CN/H_2O, 0.1% TFA) afforded 5-(6-(2-(3,4-dimethoxybenzylamino)-6-(trifluoromethyl)pyridin-3-yl)-2-((*S*)-1-methoxypropan-2-ylamino)pyrimidin-4-yloxy)-3-aminoquinoxalin-2(1*H*)-one (0.12 g, 77%) as a TFA salt. MS (ESI positive ion) *m*/*z*: 653 (M + 1).

A 25 mL round-bottomed flask was charged with 5-(6-(2-(3,4-dimethoxybenzylamino)-6-(trifluoromethyl)pyridin-3-yl)-2-(*S*)-1-methoxypropan-2-ylamino)pyrimidin-4-yloxy)-3-aminoquinoxalin-2(1*H*)-one (0.12 g, 0.18 mmol) and 80% TFA in CH_2Cl_2 (5 mL). The reaction mixture was stirred at room temperature for 6 h and concentrated under reduced pressure. Purification by preparative HPLC (10–100% CH_3CN/H_2O, 0.1% TFA) afforded the title compound as a TFA salt (80 mg, 87%). ^{1}H NMR (400 MHz, MeOH-d_6): δ 8.17 (d, J = 8.0 Hz, 1H), 8.12 (t, J = 8.1 Hz, 1H), 7.15–7.09 (m, 2H), 7.03 (d, J = 7.8 Hz, 1H), 6.75 (s, 1H), 3.33–3.30 (m, 2H), 3.20 (br s, 4H), 1.07 (br s, 3H). MS (ESI positive ion) *m*/*z*: 503 (M + 1). HRMS calculated for $C_{22}H_{21}F_3N_8O_3$ $(M + H)^+$ 503.17615, found 503.17759.

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Supporting Information Available: Elemental analysis and compound purity data for all the final compounds **7**, **9**, **13a–f**, **18a**,**b**, **19a**,**b**, **24a–d**, **28a–c**, and **31**; information on biological assays and in vivo studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Quantitative brain microdialysis would allow a more accurate determination of compound free fraction in the brain.

(20) We determined on-target in vivo efficacy by measuring inhibition of capsaicin-induced flinching in rats. The compounds were dosed orally (see ref 9b).

(21) Unpublished results.

(22) Compound **9** was not progressed forward because of unavailability of material at the time of the study.

(23) Oral doses were selected on the basis of potency and PKDM properties.
(24) Very low plasma concentrations (<50 ng/mL) were obtained for those compounds that did not show at least 50% inhibition of flinching.
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(26) The absolute stereochemistries of **13a** and **13b** were assigned by co-injecting the racemic mixture on a chiral column with enantiomerically pure (*S*)-3-amino-5-(2-(1-methoxypropan-2-ylamino)-6-(4-(trifluoromethyl)phenyl)pyrimidin-4-yloxy)quinoxalin-2(1*H*)-one (**13b**) prepared from commercially available 1-(*S*)-methoxypropan-2-amine.

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