Novel Vanilloid Receptor-1 Antagonists: 3. The Identification of a Second-Generation Clinical Candidate with Improved Physicochemical and Pharmacokinetic Properties

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Based on the previously reported clinical candidate, AMG 517 (compound **1**), a series of related piperazinylpyrimidine analogues were synthesized and evaluated as antagonists of the vanilloid 1 receptor (VR1 or TRPV1). Optimization of in vitro potency and physicochemical and pharmacokinetic properties led to the discovery of (*R*)-*N*-(4-(6-(4-(1-(4-fluorophenyl)ethyl)piperazin-1-yl)pyrimidin-4-yloxy)benzo[*d*]-thiazol-2-yl)acetamide (**16p**), a potent TRPV1 antagonist [rTRPV1(CAP) IC_{50} = 3.7 nM] with excellent aqueous solubility (≥200 μg/mL in 0.01 N HCl) and a reduced half-life (rat $t_{1/2}$ = 3.8 h, dog $t_{1/2}$ = 2.7 h, monkey $t_{1/2}$ = 3.2 h) as compared to AMG 517. In addition, compound **16p** was shown to be efficacious at blocking a TRPV1-mediated physiological response in vivo (ED_{50} = 1.9 mg/kg, p.o. in the capsaicin-induced flinch model in rats) and was also effective at reducing thermal hyperalgesia induced by complete Freund's adjuvant in rats (MED = 1 mg/kg, p.o). Based on its improved overall profile, compound **16p** (AMG 628) was selected as a second-generation candidate for further evaluation in human clinical trials as a potential new treatment for chronic pain.

Introduction

The vanilloid receptor-1 (VR1 or TRPV1) is a nonselective cation channel belonging to the transient receptor potential (TRP) super family that plays a role as an integrator of multiple pain-producing stimuli.[1] Over the past several years, TRPV1 has emerged as an exciting target for the treatment of chronic pain,[2] and we have reported the identification and SAR development of several novel classes of TRPV1 antagonists, including cinnamides,[3] thiazoles,[4] benzimidazoles,[5] and pyrimidines.[6,7] Investigations into the latter class of compounds have been particularly fruitful and have provided us with a rich supply of TRPV1 antagonists for further study.

In parts 1 and 2 of this series, we described the structure−activity relationship (SAR) investigations leading to the discovery of the pyrimidine class of TRPV1 antagonists.[6,7] These studies led to the identification of our first TRPV1 clinical candidate AMG 517 (**1**, Figure 1). AMG 517 was chosen for evaluation in human clinical trials based on its potent efficacy in pharmacological models and its excellent safety profile. As this promising candidate progressed into clinical development, we sought to identify a second-generation TRPV1 antagonist with an improved profile. The two areas that we felt AMG 517 could be improved upon were its half-life and solubility. In preclinical studies, AMG 517 was found to be extremely stable in vitro and in vivo and was shown to have very long half-lives in multiple species (rat $t_{1/2}$ = 31 h, dog $t_{1/2}$ = 41 h, monkey $t_{1/2}$ = 62 h).[7] Based on this preclinical pharmacokinetic data, allometric projections predicted a human half-life of 60−120 h and significant accumulation upon multiple-dose administration. In addition, AMG 517 was found to have low aqueous solubility (<1 μg/mL in PBS or 0.01 N HCl).[8] These two factors, although not critical for further progression of AMG 517, presented challenges to the development of this candidate. Therefore, our goal was to identify a novel second-generation clinical candidate with a similar pharmacological profile to AMG 517, but with increased aqueous solubility and a reduced half-life that would make the compound suitable for QD or BID dosing.

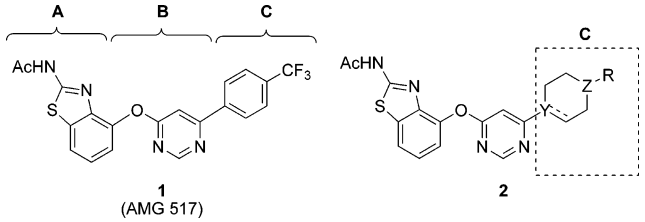

Figure 1. AMG 517 (**1**) and generic structure (**2**) used for SAR investigations of region **C**.

In the previous two reports, we described our SAR investigations leading to the optimization of the central core, **B** (oxopyrimidine),[6] and the heteroaryl moiety, **A** (*N*-acetyl benzothiazole,[7] **1**; Figure 1). With these two groups optimized to provide analogues with exquisite TRPV1 potency, we then turned our attention to region **C** of the molecule in attempts to modulate the physicochemical properties of these antagonists (**2**; Figure 1). We envisaged that we could effect both half-life and solubility through modification of the metabolically stable 4-(trifluoromethyl)phenyl moiety. Our strategy was 2-fold: (1) introduction of saturation into the 4-(trifluoromethyl)phenyl ring to reduce structural planarity and disrupt crystal-stacking capability (e.g., compound **2**; where Y, Z = C); and (2) replacement of the 4-(trifluoromethyl)phenyl group with various saturated aza-heterocycles (e.g., compound **2**; where Y = N and Z = CH, O, or N) to create the potential for salt formation. Herein, we describe the synthesis and biological evaluation of a novel series of TRPV1 antagonists based on generic structure **2**, which led to the discovery of the second-generation TRPV1 clinical candidate, AMG 628.

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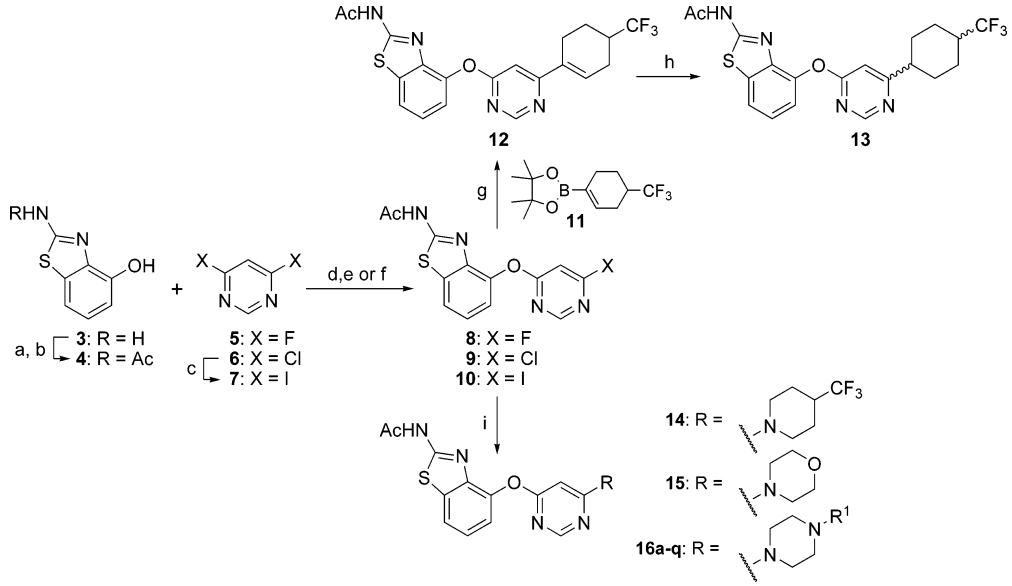
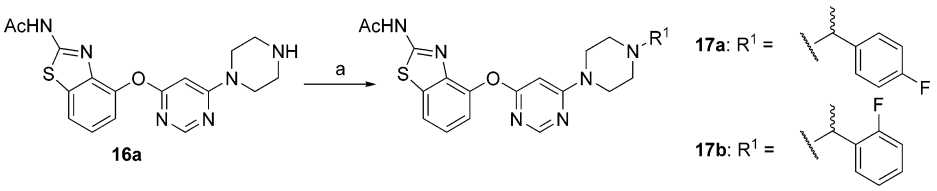
Scheme 1[a]



[a] Reagents and conditions: (a) Ac_2O, toluene, reflux; (b) K_2CO_3, MeOH, room temperature; (c) NaI, 47% HI, 40 °C; (d) 4,6-difluoropyrimidine (**5**), DMSO, room temperature; (e) 4,6-dichloropyrimidine (**6**), K_2CO_3, acetone, reflux; (f) 4,6-diiodopyrimidine (**7**), K_2CO_3, DMSO, 80 °C; (g) $PdCl_2(PPh_3)_2$, Na_2CO_3, DME/EtOH/H_2O (2:1:1), 120 °C, microwave; (h) ammonium formate, $Pd(OH)_2$, *n*-butanol, 120 °C; (i) 4-(trifluoromethyl)piperidine, morpholine or piperazines, K_2CO_3, DMF or DMSO.

Scheme 2[a]



[a] Reagents and conditions: (a) 4′-fluoroacetylphenone or 2′-fluoroacetylphenone, Ti(O*i*-Pr)$_4$, THF, 75 °C; $NaBH_4$, MeOH, −48 °C to room temperature.

Chemistry

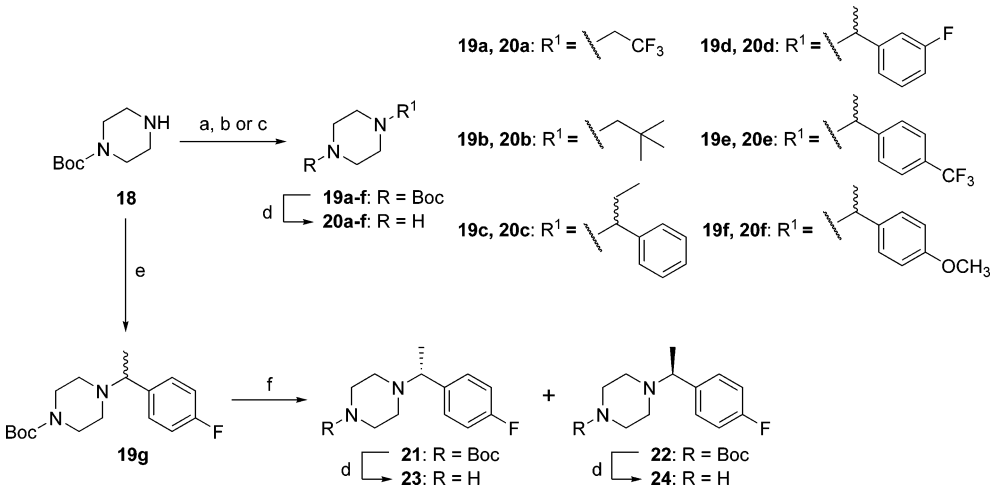
The synthetic routes employed to prepare the saturated analogues (**12** and **13**) as well as a majority of the aza-heterocyclic derivatives (**14**, **15**, **16a**−**q**) are outlined in Scheme 1. Diacetylation of compound **3** with excess acetic anhydride, followed by selective hydrolysis of the acetate group under basic conditions, provided acetamide **4**. Condensation of acetamide **4** with 4,6-difluoropyrimidine (**5**) proceeded smoothly at room temperature in DMSO to give fluoropyrimidine **8** in good yield. Similarly, coupling of acetamide **4** with 4,6-dichloropyrimidine (**6**) or 4,6-diiodopyrimidine (**7**)[9] in the presence of potassium carbonate generated chloropyrimidine **9** and iodopyrimidine **10**, respectively. Suzuki coupling of boronate **11**[10] with iodopyrimidine **10** afforded the desired trifluoromethylcyclohexenyl analogue **12**. Subsequent hydrogenation at high temperature in the presence of ammonium formate and a catalytic amount of palladium hydroxide provided the fully saturated analogue **13** as an inseparable mixture of *trans*- and *cis*-isomers (1.6:1).[11] Direct nucleophilic displacement of the fluorine or chlorine atoms in intermediates **8** or **9** with a variety of six-membered cyclic amines provided compounds **14**, **15**, and **16a**−**q** in good yields.

In some cases, additional modifications to piperazine derivative **16a** (R^1 = H) were required. For example, compounds **17a** and **17b** were prepared by the condensation of 2′- or 4′-fluoroacetophenones with compound **16a** using Ti(O*i*-Pr)$_4$ followed by reduction of the resulting imine with $NaBH_4$ (Scheme 2). Unfortunately, this method did not prove to be very general, and we found that reductive aminations of **16a** with other acetophenones resulted in low yields. Therefore, we investigated an alternative synthetic route wherein the requisite *N*-alkylated piperazines (**20a**−**f**, **23**, **24**, and **26**) were prepared according to Schemes 3 and 4 prior to the condensation with the pyrimidinyl chloride **9**. We found that the yield of final product could be improved by reversing the sequence in this manner.

The syntheses of piperazine intermediates **20a**−**f**, **23**, and **24** are outlined in Scheme 3. *N*-Boc-piperazine (**18**) was converted to *N*-trifluoroethylpiperazine (**20a**) by alkylation with 2,2,2-trifluoroethyl trifluoromethanesulfonate, followed by removal of the Boc-group under acidic conditions. Alternatively, reductive amination of *N*-Boc-piperazine (**18**) with trimethylacetaldehyde and $NaBH(OAc)_3$, followed by Boc-deprotection provided *N*-neopentylpiperazine (**20b**). Due to the poor reactivity of alkyl aryl ketones with compound **18**, imine formation was conducted in refluxing THF in the presence of Ti(O*i*-Pr)$_4$. The resulting imines were readily reduced with $NaBH(OAc)_3$ to provide the desired alkylated piperazines **19c**−**g**. The racemic mixture of Boc-protected piperazine **19g** was resolved by chiral HPLC chromatography with a Chirobiotic TAG column (4.6 × 250 mm) to provide the antipodes **21** and **22**. Subsequent removal of the Boc-groups under acidic conditions gave the enantiopure piperazines **23** and **24**.

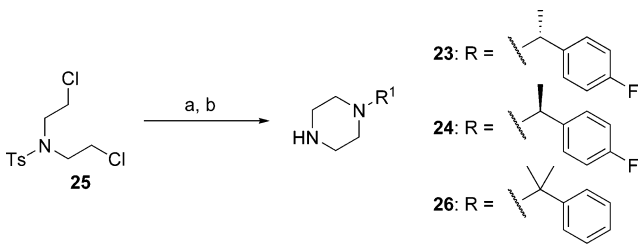
To eliminate the tedious chiral separation step, an alternate route to the enantiopure piperazines **23** and **24** starting from commercially available nonracemic amines was developed (Scheme 4). In addition to providing larger amounts of the chiral derivatives, this alternate route also allowed us to unambiguously

Scheme 3[a]



[a] Reagents and conditions: (a) CF_3CH_2OTf, *i*-Pr_2NEt, THF, reflux; (b) trimethylacetaldehyde, AcOH, $NaBH(OAc)_3$, 1,2-dichloroethane, 50 °C; (c) propiophenone, 3′-fluoroacetophenone, 4′-trifluoromethylacetophenone or 4′-methoxyacetophenone, Ti(O*i*-Pr)$_4$, THF, 75 °C; $NaBH(OAc)_3$, MeOH, −48 °C to room temperature; (d) TFA, CH_2Cl_2, room temperature; (e) 4′-fluoroacetophenone, Ti(O*i*-Pr)$_4$, THF, 75 °C; $NaBH(OAc)_3$, MeOH, −48 °C to room temperature; (f) rp-HPLC Chirobiotic TAG column (4.6 × 250 mm).

Scheme 4[a]



[a] Reagents and conditions; (a) (*R*)-1-(4-fluorophenyl)ethanamine, (*S*)-1-(4-fluorophenyl)ethanamine or 2-phenylpropan-2-amine, *i*-Pr_2NEt, 125 °C; (b) HBr, 4-hydroxybenzoic acid, room temperature.

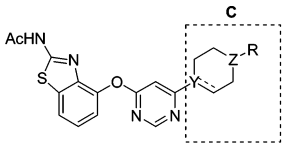
assign the absolute stereochemistries for intermediates **23** and **24** and, by extension, the final analogues **16p** and **16q**. Cyclization of bis(2-chloroethyl)-4-methylbenzenesulfonamide (**25**) with (*R*)-1-(4-fluorophenyl)ethylamine or (*S*)-1-(4-fluorophenyl)ethylamine, followed by removal of the *p*-toluenesulfonyl groups using HBr and 4-hydroxybenzoic acid, provided the enantiopure piperazines **23** and **24**, respectively.[12] In a similar manner, 1-(2-phenylpropan-2-yl)piperazine (**26**) was prepared from *N*,*N*-bis(2-chloroethyl)-4-methylbenzenesulfonamide (**25**) and 2-phenylpropan-2-amine.

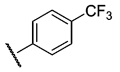
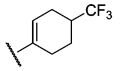
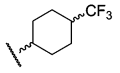
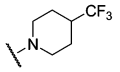
Results and Discussion

The compounds prepared in this paper were tested for their ability to block the capsaicin- (500 nM) or acid- (pH 5) induced influx of $^{45}Ca^{2+}$ into rat TRPV1-expressing Chinese hamster ovary (CHO) cells. Functional activity is reported as IC_{50} values in Tables 1 and 2. All compounds reported herein behaved as antagonists, as confirmed by separate assays designed to measure agonist activity.

TRPV1 antagonist activities for the initial set of compounds examined the effect of ring saturation (compounds **12** and **13**) as well as replacement of the 4-(trifluoromethyl)phenyl group with simple heterocycles, such as 4-(trifluoromethyl)piperidinyl (**14**), morpholine (**15**), and piperidine (**16a**; Table 1). For comparison, the data for AMG 517 (compound **1**) is also included in Table 1. Partial ring saturation of the C-ring of AMG 517 (i.e., 4-(trifluoromethyl)cyclohexenyl analogue **12**), resulted in an approximately 30-fold decrease of potency in the capsaicin-mediated assay and a 4-fold decrease in the acid-mediated assay.

Table 1. In Vitro TRPV1 Activities and Aqueous Solubility for Saturated **C**-Rings (**12** and **13**) and Simple Heterocycles (**14**, **15**, and **16a**)



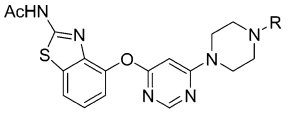
Compound No.	C	rTRPV1 (CAP)[a] IC_{50} (nM)	rTRPV1 (acid)[a] IC_{50} (nM)	Solubility[b] (0.01 N HCl, μg/mL)
1		0.9 ± 0.8	0.5 ± 0.2	< 1
12		27 ± 7	2.4 ± 0.7	13
13		350 ± 199	10 ± 5	5
14		330 ± 45	19 ± 1	9
15		>4000	>4000	32
16a		>4000	>4000	173

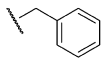
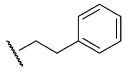
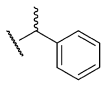
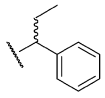
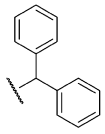
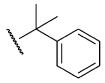
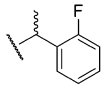
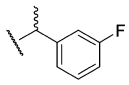
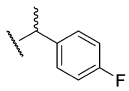
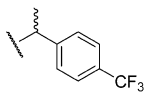
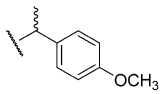
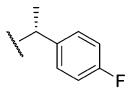
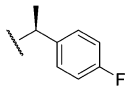
[a] IC_{50} values based on inhibition of capsaicin- (500 nM) or acid- (pH 5) induced influx of $^{45}Ca^{2+}$ into rat TRPV1- expressing CHO cells. (Each IC_{50} value reported represents an average of at least two independent experiments with three replicates at each concentration (±SEM).) [b] Thermodynamic solubility measured in a high-throughput automated format.[8]

Further reduction of the planarity to the fully saturated cyclohexyl analogue **13** gave an additional reduction in potency in both assays. These results suggest that the antagonist with a planar aromatic C-ring affords optimum binding affinity to the receptor. Nevertheless, we were encouraged by the fact that the partially saturated and fully saturated analogues **12** and **13** maintained moderate inhibitory activity and showed the anticipated improvement in solubility (13 μg/mL and 5 μg/mL in 0.01 N HCl, respectively).

Consequently, we replaced the 4-(trifluoromethyl)phenyl group of AMG 517 (compound **1**) with heterocyclic moieties, such as piperidines, morpholines, and piperazines (i.e., **14**, **15**, and **16a**−**q**), to find a more potent antagonist with better

Table 2. In Vitro TRPV1 Activities, Aqueous Solubility and In Vivo Clearance for 4-Substituted Piperazinyl Analogues (**16a**−**q**, **17a**, and **17b**)



Compound No.	R	rTRPV1 (CAP)[a] IC_{50} (nM)	rTRPV1 (acid)[a] IC_{50} (nM)	Solubility[b] (0.01 N HCl, μg/mL)	CL (L/h/kg) (i.v.)[c]
16a	H	>4000	>4000	173	---
16b		1300 ± 25	>4000	≥ 200	---
16c		1500 ± 200	>4000	≥ 200	---
16d		3.0 ± 0.2	5.0 ± 1.0	≥ 200	1.5
16e		380 ± 80	120 ± 35	≥ 200	---
16f		43 ± 3	7.5 ± 1.0	1.5	1.0
16g		39 ± 5	93 ± 3	≥ 200	---
16h		3700 ± 200	>4000	≥ 200	---
16i		4.8 ± 0.4	6 ± 1	≥ 200	3.9
16j		20 ± 12	30 ± 2	≥ 200	---
16k		1400 ± 700	20 ± 6	46	---
16l		45 ± 6	29 ± 3	≥ 200	---
17b		2.7 ± 0.8	2.5 ± 0.7	≥ 200	3.0
16m		16 ± 2	7 ± 1	≥ 200	3.2
17a		4.9 ± 0.6	3.1 ± 0.5	≥ 200	1.1
16n		5 ± 1	1.8 ± 0.3	≥ 200	1.4
16o		39 ± 4	20 ± 2	≥ 200	---
16p		3.7 ± 0.8	2 ± 0.3	≥ 200	0.8
16q		7 ± 3	5 ± 0.4	≥ 200	1.8

[a] 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).) [b] Thermodynamic solubility measured in a high-throughput automated format.[8] [c] Study in fed male Sprague−Dawley rats dosed at 1 mg/kg in DMSO with sampling time up to 6 h. $n = 2$ animals per study. Interanimal variability was less than or equal to 30%.

Table 3. Pharmacokinetic Profile and Solubility for Compounds **1**, **17a**, **16n**, **16p**, and **16q**

cmpd	$AUC_{0-\infty}$ (ng·h/mL) (iv)[a]	CL (L/h/kg) (iv)[a]	V_{ss} (L/kg) (iv)[a]	$t_{1/2}$ (h) (iv)[a]	$AUC_{0-\infty}$ (ng·h/mL) (po)	F (%)	solubility[e] (μg/mL) HCl (0.01 N)	PBS	SIF
1	5400	0.19	1.6	6.3[b]	12 500[c]	32	<1	<1	6.6
17a	1000	1.0	2.9	2.4	1800[d]	35	≥200	5	34
16n	720	1.4	4.5	2.7	120[d]	3	≥200	5	121
16p	1200	0.8	2.8	2.7	3100[d]	51	≥200	7	64
16q	550	1.8	5.7	2.5	2550[d]	93	≥200	31	121

[a] Study in fed male Sprague−Dawley rats dosed at 1 mg/kg in DMSO with sampling time up to 6 h. $n = 2$ animals per study. Interanimal variability was less than or equal to 30%. [b] Underestimation of the true half-life of compound **1** due to limited sampling time. [c] Study in fasted male Sprague−Dawley rats dosed at 3 mg/kg as a suspension in 5% Tween 80/Oraplus with sampling time up to 8 h. [d] Study in fasted male Sprague−Dawley rats dosed at 5 mg/kg as a suspension in 5% Tween 80/Oraplus with sampling time up to 8 h. [e] Thermodynamic solubility measured in a high-throughput automated format.[8]

aqueous solubility. The 4-(trifluoromethyl)piperidinyl analogue **14** displayed reasonable potency with an IC_{50} value of 330 nM in the capsaicin-mediated assay and 19 nM in the acid-mediated assay. However, the IC_{50} values for morpholine analogue **15** and piperazine analogue **16a** were greater than 4000 nM in both assays. This significant reduction in potency was presumably due to the lack of a lipophilic group in the 4-position of these analogues. This result is consistent with the SAR established in the cinnamide series, where we found that a lipophilic group in this region was important for activity.[3]

To improve the potency of **16a**, a variety of lipophilic groups were installed in the 4-position of the piperazine **C**-ring. A comparison of in vitro potency, aqueous solubility, and clearance data for these 4-substituted piperazinyl analogues is shown in Table 2. Initially, the *N*-isopropyl and *N*-*t*-butyl analogues **16b** and **16c** were examined based on the similarity in size to the trifluoromethyl group. A slight improvement in activity was observed for these compounds as compared to **16a**, along with a significant improvement in solubility as compared to AMG 517. By extending the *t*-butyl group one carbon atom further from piperazine ring, a dramatic improvement in potency was observed. The neopentyl analogue **16d** had an IC_{50} value of 3 nM in the capsaicin assay and an IC_{50} value of 5 nM in the acid-mediated assay. Replacement of the neopentyl group with 2,2,2-trifluoroethyl (i.e., **16e**) led to a 100-fold decrease of potency in the capsaicin-mediated assay and a 20-fold decrease of potency in the acid-mediated assay relative to **16d**.

Although the potency and solubility properties of compound **16d** were encouraging, the compound exhibited moderate in vivo clearance in rats ($CL_{in\ vivo} = 1.5$ L/h/kg) and poor oral bioavailability ($F_{oral} = 14\%$). Subsequent metabolite identification studies of compound **16d** in rat liver microsomes indicated that the major site of metabolism was oxidation on the neopentyl group. Therefore, we turned our attention to exploring different lipophilic groups at the 4-position of piperazine ring with the goal of maintaining potency and improving clearance. Based on size and lipophilicity, the phenyl group was initially chosen to replace the neopentyl moiety. 4-Phenylpiperazine **16f** exhibited reasonable potency in the capsaicin- and acid-mediated assays, with IC_{50} values of 43 nM and 7.5 nM, respectively.

The influence of adding a linker between the piperazine and phenyl group was examined. For example, a carbon atom was inserted between the piperazine and phenyl group to generate benzylpiperazine analogue **16g**. The methylene linker did not improve on activities in the capsaicin- and acid-mediated assays in comparison to **16f**, however, a significant increase in aqueous solubility (≥200 μg/mL in 0.01 N HCl) was obtained. Extending the linking group one atom longer (phenethylpiperazine analogue **16h**) was not tolerated (IC_{50} values ≥4000 nM in both the capsaicin- and acid-mediated assays). Next we examined the effect of an additional substituent on the benzylic position of **16g** (i.e., **16i**−**l**). The addition of a methyl group at this position led to a 10-fold increase in potency (**16i** vs **16g**); however, as the size of the group increased to ethyl (**16j**) and phenyl (**16k**), potency decreased. The geminal dimethyl analogue **16l** also showed a significant reduction in potency relative to the monomethyl analogue **16i**.

While the 1-(1-phenylethyl)piperazine analogue **16i** showed excellent potency in both assays ($IC_{50} = 4.8$ nM and 6 nM in the capsaicin- and acid-mediated assays, respectively) and good solubility (≥200 μg/mL in 0.01 N HCl), the compound suffered from high in vivo clearance ($CL_{in\ vivo} = 3.9$ L/h/kg). Therefore, we prepared a series of substituted phenyl analogues of compound **16i** with the intention of blocking metabolism on the aromatic ring, thus reducing clearance (i.e., **16m**−**q** and **17a**,**b**).

The 2-fluorophenyl analogue **17b** showed a 2-fold improvement in potency over compound **16i** in both assays. The activity of the 3-fluorophenyl analogue **16m** was 3-fold less than compound **16i** in the capsaicin-mediated assay but was comparable to **16i** in the acid-mediated assay. Unfortunately, both **17b** and **16m** exhibited unacceptable in vivo clearance ($CL_{in\ vivo} > 3$ L/h/kg) and offered no advantage over **16i**. On the other hand, the results for the 4-fluorophenyl analogue **17a** were more promising. Compound **17a** was equipotent to **16i** in the capsaicin-mediated assay and 2-fold more potent than **16i** in the acid-mediated assay. Moreover, **17a** demonstrated a significantly lower in vivo clearance ($CL_{in\ vivo} = 1.1$ L/h/kg) relative to **16i**. The potency of the 4-trifluoromethylphenyl analogue **16n** was similar to **17a** and showed improved in vivo clearance in the rat ($CL_{in\ vivo} = 1.4$ L/h/kg) as well. Analogue **16o**, with an electronic-donating methoxy group at the *para*-position of the phenyl ring, was less potent than either the unsubstituted analogue **16i** or the analogues with electron-deficient aromatic rings such as **17b**, **16m**, **17a**, and **16n**.

Because of the excellent potency and low clearance demonstrated by racemate **17a**, each of the antipodes were synthesized for further evaluation (*R*, **16p**, and *S*, **16q**). While both enantiomers showed comparable in vitro potency, the *R*-isomer (**16p**) was superior in terms of pharmacokinetic profile with over a 2-fold lower rate of clearance in comparison to the *S*-isomer (**16q**; 0.8 vs 1.8 L/h/kg, respectively).

Pharmacokinetic and Solubility Profiles. Due to the excellent in vitro activities and aqueous solubilities of compounds **17a**, **16n**, **16p**, and **16q**, the pharmacokinetic and solubility profiles of these compounds were evaluated further. A comparison with the clinical candidate AMG 517 is shown in Table 3. The data from the preliminary pharmacokinetic studies using the 6-hour time point are reported for comparison purposes. The higher rate of clearance translated into a shorter half-life, $t_{1/2} =$ 2.7 h for **17a** versus 6.4 h for **1**. Compound **17a** also showed

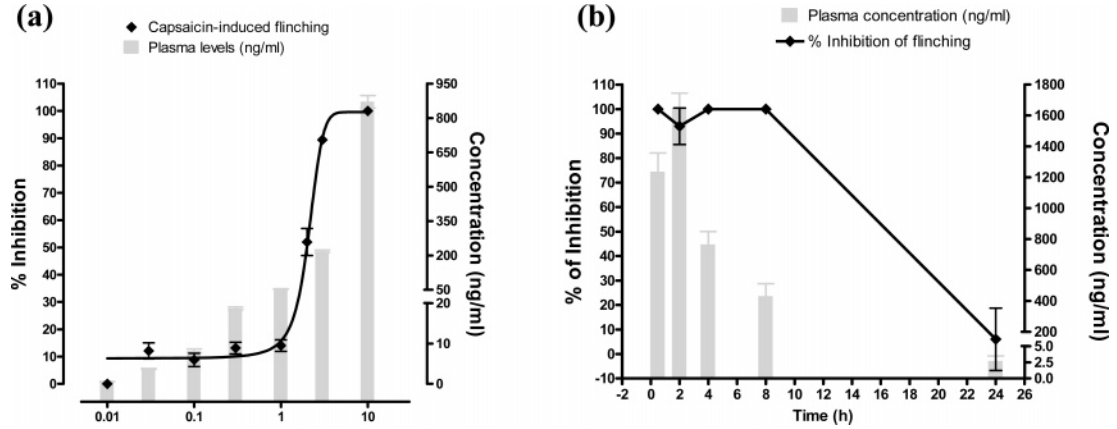


Figure 2. (a) Effects of compound **16p** on capsaicin-induced flinching in rats and corresponding plasma levels (ED_{50} = 1.9 mg/kg; n = 8/group). (b) Time course of **16p** inhibition of capsaicin-induced flinching in rats (10 mg/kg (p.o.); n = 8/group).

Table 4. Mean Pharmacokinetic Parameters for Compound **16p** in Preclinical Species and Predicted Human Pharmacokinetic Parameters Based on Allometric Scaling[a]

species	CL (mL/h/kg) (iv)	V_{ss} (mL/kg) (iv)	$t_{1/2}$ (h) (iv)	F_{oral} (%)
rat	830[b]	2600[b]	3.8[b]	51[c]
dog	2400[d]	4000[d]	2.7[d]	83[e]
monkey	400[d]	900[d]	3.2[d]	12[f]
human (projected)	1500−5000	3000	3−15	

[a] Variability for $AUC_{0-\infty}$, CL ,and V_{ss} values ranged from 3 to 19%, and variability for F_{oral} ranged from 13 to 43% for all species. [b] Study in fed male Sprague−Dawley rats dosed at 1 mg/kg in DMSO with sampling time up to 72 h. [c] Study in fasted male Sprague−Dawley rats dosed at 5 mg/kg as a suspension in 5% Tween 80/Oraplus. [d] Study in fed male animal dosed at 1 mg/kg in 80% PEG-400/H_2O. [e] Study in fasted male animal dosed at 3 mg/kg in 10% Pluronic F108/ Oraplus. [f] Study in fasted male animal dosed at 3 mg/kg in 10% Pluronic F108/H_2O.

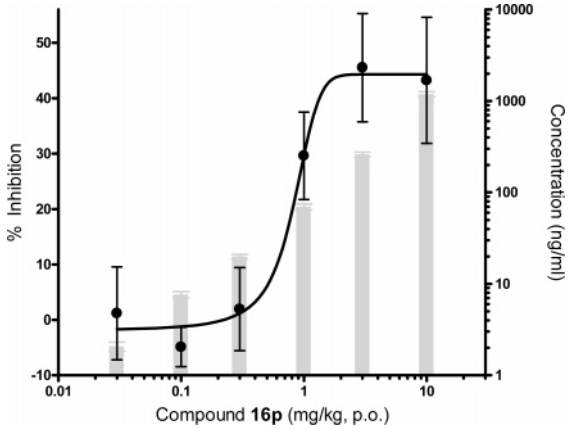


Figure 3. Dose−response curve with compound **16p** in CFA-induced thermal hyperalgesia.

good absorption upon oral dosing ($AUC_{0-\infty}$ = 1800 ng·h/mL; F_{oral} = 35%). In contrast, the trifluoromethyl analogue **16n** showed a reasonable half-life (2.7 h), but it had poor oral bioavailability (F_{oral} = 3%) presumably due to high first-pass metabolism. Compound **16p** exhibited low clearance ($CL_{in\ vivo}$ = 0.8 L/h/kg), good systemic exposure ($AUC_{0-\infty}$ = 1200 ng·h/mL), and a reasonable half-life ($t_{1/2}$ = 2.7 h) when delivered intravenously. Upon oral administration, compound **16p** showed excellent bioavailability ($AUC_{0-\infty}$ = 3100 ng·h/mL, F_{oral} = 51%).

Because half-life was a key parameter that we sought to optimize in the second-generation compound, the pharmacokinetic studies in rats were repeated with an extended sampling time (72 h) to get a more accurate $t_{1/2}$ measurement (Table 4). Unlike AMG 517, where a substantial difference was observed in the extended pharmacokinetic studies, the half-life for compound **16p** did not change significantly when the sampling time was extended to 72 h ($t_{1/2}$ = 2.7 h vs 3.8 h). In addition to examining compound **16p** in rats, the pharmacokinetics was also examined in dogs and monkeys. Compound **16p** exhibited moderate to high clearance and moderate to high volumes of distribution in all preclinical species examined. The oral bioavailability ranged from 12 to 83% among the three species. The human pharmacokinetic parameters projected based upon allometric scaling of rat and monkey data are also presented in Table 4. Based on this analysis, compound **16p** is projected to have a significantly shorter half-life than AMG 517 in humans (3−15 h vs 60−120 h) and would be suitable for QD or BID dosing. This reduction in predicted human half-life, as well as the enhanced solubility profile of compound **16p**, represented a significant improvement over AMG 517.

In Vivo Efficacy. On the basis of its excellent in vitro potency, selectivity,[13] and pharmacokinetic profile, compound **16p** was chosen for further in vivo evaluation. The compound was first tested in an agonist challenge model (capsaicin-induced flinching in rats) and the results are illustrated in Figure 2. Compound **16p** potently suppressed capsaicin-evoked paw flinching in rats in a dose-dependent manner with an ED_{50} of 1.9 mg/kg, p.o. (corresponding to **16p** plasma level of approximately 128 ng/mL; Figure 2a). Because of the significantly shorter half-life of compound **16p** as compared to AMG 517, we were interested in evaluating the duration of this flinch effect. For this reason, a time-course experiment was conducted. At a 10 mg/kg (p.o.) dose, compound **16p** blocked capsaicin-induced flinching (Figure 2b) up to 8 h.

As we demonstrated for AMG 517, we found that compound **16p** was efficacious at reversing thermal hyperalgesia in the complete Freund's adjuvant (CFA) model of inflammation-induced pain in rats in a dose−dependent manner (Figure 3). The minimum effect dose (MED) for compound **16p** was approximately 1 mg/kg, corresponding to a plasma level of ∼70 ng/mL.

Summary

In this investigation we examined a variety of replacements for the **C**-ring of AMG 517 in attempts to modulate the physicochemical properties of our first generation TRPV1 clinical candidate. The SAR of this series of TRPV1 antagonists demonstrated that replacement of the 4-(trifluoromethyl)phenyl

moiety with saturated rings or heterocycles was effective in increasing aqueous solubility and modifying the pharmacokinetic properties. While potency was reduced with the saturated carbocyclic rings, activity was maintained with substituted piperazines as the **C**-ring replacements. Furthermore, we found that hydrophobic groups in the 4-position of the piperazine ring gave the best results. This investigation culminated in the discovery of compound **16p**, (*R*)-*N*-(4-(6-(4-(1-(4-fluorophenyl)-ethyl)piperazin-1-yl)pyrimidin-4-yloxy)benzo[*d*]thiazol-2-yl)acetamide. Compound **16p** demonstrated excellent in vitro potency, in vivo efficacy, and pharmacokinetic profile with increased solubility (≥200 μg/mL in 0.01 N HCl) and a reduced half-life (rat $t_{1/2}$ = 3.8 h, dog $t_{1/2}$ = 2.7 h, monkey $t_{1/2}$ = 3.2 h) as compared to AMG 517. Based on its enhanced overall profile, compound **16p** ((*R*)-*N*-(4-(6-(4-(1-(4-fluorophenyl)ethyl)piperazin-1-yl)pyrimidin-4-yloxy)benzo[*d*]thiazol-2-yl)acetamide; AMG 628) was chosen as our second-generation TRPV1 clinical candidate for further evaluation as a potential new treatment for inflammatory pain.[14]

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 specrometers. 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. ^{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). Low-resolution mass spectral (MS) data were determined on a Perkin-Elmer-SCIEX API 165 mass spectrometer using ES ionization modes (positive or negative). Combustion analyses were performed by Atlantic Microlab, Inc., Norcross, GA, and were within ±0.4% of calculated values, unless otherwise noted. Combustion analysis 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-Hydroxybenzo[*d*]thiazol-2-yl)acetamide (4).** To a suspension of 2-aminobenzo[*d*]thiazol-4-ol (40 g, 240 mmol) in toluene (400 mL) was added acetic anhydride (220 mL, 2400 mmol) at room temperature. The reaction mixture was stirred at 115 °C for 22 h. The solvents were evaporated and the residue was azeotroped with EtOAc to give 2-acetamidobenzo[*d*]thiazol-4-yl acetate (47 g, 78%) as a tan solid. MS (ESI, pos. ion) *m*/*z*: 251 (M + 1). The suspension of the above solid (47 g) in MeOH (500 mL) was treated with K_2CO_3 (52 g, 380 mmol) and stirred at room temperature for 6 h. MeOH was evaporated and the residue was diluted with H_2O. The resulting mixture was neutralized with concd HCl to pH = 7 and extracted with EtOAc (3×). The combined organic phases were dried over sodium sulfate, filtered, and concentrated in vacuo to provide *N*-(4-hydroxybenzo[*d*]thiazol-2-yl)acetamide (38 g, 98%) as a tan solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.32 (br s, 1 H), 9.80 (br s, 1 H), 7.33 (d, *J* = 7.4 Hz, 1H), 7.09 (dd, *J* = 7.4, 7.4 Hz, 1H), 6.82 (d, *J* = 7.4 Hz, 1H), 2.18 (s, 3H). MS (ESI, pos. ion) *m*/*z*: 209 (M + 1).

4,6-Diiodo-pyrimidine (7). A mixture of 4,6-dichloropyrimidine (**6**; 1.00 g, 6.70 mmol), NaI (1.36 g, 9.00 mmol), and hydriodic acid (57 wt % in H_2O, 20 mL, 151.0 mmol) was heated at 40 °C with stirring for 1 h. The reaction mixture was stirred at room temperature for 20 h and basified with 10 N NaOH to pH = 10. The resulting precipitate was filtered, washed with H_2O, and dried in vacuo to give the title compound as a light-yellow solid (1.86 g, 84%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.61 (s, 2 H). MS (ESI, pos. ion) *m*/*z*: 332 (M + 1).

***N*-(4-(6-Fluoropyrimidin-4-yloxy)benzo[*d*]thiazol-2-yl)acetamide (8).** A mixture of *N*-(4-hydroxybenzo[*d*]thiazol-2-yl)acetamide (**4**; 300 mg, 1.4 mmol) and 4,6-difluoropyrimidine (**5**; 0.17 mL, 1.4 mmol) in DMF (3 mL) was stirred at room temperature for 18 h. The reaction mixture was then diluted with H_2O (20 mL), and the resulting off-white precipitate was collected by filtration and dried under vacuum to give the title compound (360 mg, 84%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.44 (s, 1 H), 8.54 (s, 1 H), 7.94 (d, *J* = 7.8 Hz, 1 H), 7.32−7. 40 (m, 2 H), 7.09 (s, 1 H), 2.15 (s, 3 H). MS (ESI, pos. ion) *m*/*z*: 305 (M + 1).

***N*-(4-(6-Chloropyrimidin-4-yloxy)benzo[*d*]thiazol-2-yl)acetamide (9).** 2,6-Dichloropyrimidine (**6**; 50.4 g, 340 mmol), K_2CO_3 (51.4 g, 370 mmol), and benzothiazole (**4**; 70.4 g, 340 mmol) were weighed into a 2 L flask equipped with a reflux condenser and a mechanical stirrer. Acetone (700 mL) was added and the mixture was heated to reflux while stirring at 450 rpm. HPLC indicated complete conversion after 15 h. The mixture was cooled to room temperature and H_2O (700 mL) was added. The product precipitated and the suspension was stirred for 2 h. The solids were isolated by vacuum filtration. The filter cake was dried in the vacuum oven (65 °C, 48 h) to obtain the title compound as an off-white solid (104 g, 96%). Mp: 268−275 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.43 (s, 1 H), 8.59 (d, *J* = 0.8 Hz, 1 H), 7.94 (dd, *J* = 7.6, 1.4 Hz, 1 H), 7.51 (d, *J* = 0.8 Hz, 1 H), 7.28−7.43 (m, 2 H), 2.15 (s, 3 H). MS (ESI, pos. ion.) *m*/*z*: 321 (M + 1).

***N*-(4-(6-Iodopyrimidin-4-yloxy)benzo[*d*]thiazol-2-yl)acetamide (10).** A mixture of 4,6-diiodopyrimidine (**7**; 0.72 g, 2.2 mmol), *N*-(4-hydroxybenzo[d]thiazol-2-yl)acetamide (**4**; 0.43 g, 2.0 mmol), and K_2CO_3 (0.43 g, 3.0 mmol) in DMSO (3.0 mL) was heated at 80 °C for 1 h. The reaction mixture was cooled to room temperature, diluted with H_2O, and stirred for 18 h. The resulting precipitate was filtered, washed with H_2O, and dried in vacuo to give the title compound as a light-yellow solid (0.85 g, 95%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.43 (s, 1 H), 8.42 (s, 1 H), 7.93 (d, *J* = 7.8 Hz, 1 H), 7.82 (s, 1 H), 7.23−7.47 (m, 2 H), 2.15 (s, 3 H). MS (ESI, pos. ion) *m*/*z*: 413 (M + 1).

4,4,5,5-Tetramethyl-2-(4-trifluoromethyl-cyclohex-1-enyl)-[1,3,2]dioxaborolane (11). To a solution of 4-(trifluoromethyl)-cyclohex-1-enyl trifluoromethanesulfonate (6.1 g, 20 mmol) in dioxane (100 mL) was added bis(pinacolato)diboron (5.6 g, 22 mmol), potassium acetate (5.9 g, 60 mmol), $PdCl_2$(dppf) (320 mg, 0.6 mmol), and dppf (330 mg, 0.6 mmol) under a nitrogen atmosphere. The reaction mixture was heated at 80 °C with stirring for 18 h, cooled to room temperature, and filtered through Celite. The filtrate was evaporated in vacuo and the residue was purified by silica gel column chromatography (10% EtOAc/hexane) to give 4.2 g (75%) of the title compound as a white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.52 (d, *J* = 2.4 Hz, 1 H), 2.05−2.45 (m, 5 H), 1.93−2.05 (m, 1 H), 1.38−1.51 (m, 1 H), 1.26 (s, 12 H). MS (ESI, pos. ion) *m*/*z*: 277 (M + 1).

***N*-{4-[6-(4-Trifluoromethyl-cyclohex-1-enyl)-pyrimidin-4-yloxy]-benzothiazol-2-yl}-acetamide (12).** A mixture of *N*-(4-(6-iodopyrimidin-4-yloxy)benzo[d]thiazol-2-yl)acetamide (**10**; 220 mg, 0.54 mmol), 4,4,5,5-tetramethyl-2-(4-trifluoromethyl-cyclohex-1-enyl)-[1,3,2]dioxaborolane (**11**; 220 mg, 0.81 mmol), $PdCl_2(PPh_3)_2$ (38 mg, 0.05 mmol), and Na_2CO_3 (86 mg, 0.81 mmol) in DME/EtOH/H_2O (2:1:1, 3.2 mL) was heated at 120 °C in a microwave reactor for 15 min. The reaction mixture was cooled to room temperature and solvents were removed in vacuo. The residue was purified by silica gel chromatography (gradient: 0−1.0% 2 M NH_3 in MeOH/CH_2Cl_2) to give the title compound as a white solid (120 mg, 52%). Mp: 130−131 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.42 (s, 1 H), 8.58 (s, 1 H), 7.91 (d, *J* = 8.0 Hz, 1 H), 7.37 (t, *J* = 8.0 Hz, 1 H), 7.29 (d, *J* = 8.0 Hz, 1 H), 7.23 (s, 1 H), 7.07 (s, 1 H), 2.56−2.67 (m, 2 H), 2.46−2.51 (m, 2 H), 2.33 (m, 1 H), 2.14 (s, 3 H), 2.04 (m, 1 H), 1.59 (m, 1 H). MS (ESI, pos. ion) *m*/*z*: 435 (M + 1). Anal. ($C_{20}H_{17}F_3N_4O_2S$): C, H, N.

***trans*-*N*-{4-[6-(4-Trifluoromethyl-cyclohexyl)-pyrimidin-4-yloxy]-benzothiazol-2-yl}-acetamide and *cis*-*N*-{4-[6-(4-Trifluoromethyl-cyclohexyl)-pyrimidin-4-yloxy]-benzothiazol-2-yl}-acetamide (13).** To a mixture of *N*-{4-[6-(4-trifluoromethyl-cyclohex-1-enyl)-pyrimidin-4-yloxy]-benzothiazol-2-yl}-acetamide (**12**; 94 mg, 0.22 mmol) and ammonium formate (270 mg, 4.3 mmol) in *n*-butanol (4 mL) was added palladium hydroxide (23 mg, 20 wt % Pd on carbon, wet, Aldrich) at room temperature under a nitrogen atmosphere. The reaction mixture was heated at 120 °C with stirring for 17 h, cooled to room temperature, filtered through Celite, and washed with MeOH. The filtrates were combined and evaporated in vacuo. The residue was purified by silica gel chromatography (gradient: 0−4.0% MeOH/CH_2Cl_2) to give the title compound as a 1:1.6 mixture of *cis*- and *trans*-isomers (45 mg, 48%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.44 (s, 1 H), 8.62 (s, 1 H), 7.92 (d, J = 8.0 Hz, 1 H), 7.37 (t, J = 8.0 Hz, 1 H), 7.29 (t, J = 7.2 Hz, 1 H), 7.12 (s, 1 H), 2.98 (m, 1 H), 2.33 (m, 1 H), 2.14 (s, 3 H), 2.11 (m, 1 H), 1.98 (m, 3 H), 1.75 (m, 1 H), 1.62 (m, 2 H), 1.41 (m, 1 H) and ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.46 (s, 1 H), 8.58 (s, 1 H), 7.92 (d, J = 8.0 Hz, 1 H), 7.37 (t, J = 8.0 Hz, 1 H), 7.29 (t, J = 7.2 Hz, 1 H), 7.05 (s, 1 H), 2.71 (m, 1 H), 2.33 (m, 1 H), 2.14 (s, 3 H), 2.11 (m, 1 H), 1.98 (m, 3 H), 1.75 (m, 1 H), 1.62 (m, 2 H), 1.41 (m, 1 H). MS (ESI, pos. ion) *m*/*z*: 437 (M + 1). Anal. ($C_{20}H_{19}F_3N_4O_2S\cdot0.5\ H_2O$): C, H, N.

***N*-(4-(6-(4-(Trifluoromethyl)piperidin-1-yl)pyrimidin-4-yloxy-)benzo[*d*]thiazol-2-yl)acetamide (14).** To a mixture of *N*-(4-(6-chloropyrimidin-4-yloxy)benzo[*d*]thiazol-2-yl)acetamide (**9**; 300 mg, 0.9 mmol) and K_2CO_3 (500 mg, 3.6 mmol) in DMF (3.0 mL) was added 4-(trifluoromethyl)piperidine (400 mg, 1.9 mmol), and the mixture was heated at 80 °C for 3.5 h. The reaction was then allowed to cool to room temperature and H_2O (1.0 mL) was added. The resulting precipitates were collected by filtration and washed with H_2O. The resulting solid was suspended in MeOH, collected by filtration, and dried in vacuo to provide the title compound as an off-white solid (160 mg, 39%). Mp: 327−328 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.42 (s, 1 H), 8.09 (s, 1 H), 7.86 (dd, J = 7.9, 1.1 Hz, 1 H), 7.33 (t, J = 7.9 Hz, 1 H), 7.21 (dd, J = 7.9, 1.1 Hz, 1 H), 6.41 (s, 1 H), 4.48 (d, J = 11.7 Hz, 2 H), 2.88−2.99 (m, 2 H), 2.61−2.76 (m, 1 H), 2.15 (s, 3 H), 1.88 (d, J = 11.0 Hz, 2 H), 1.30−1.44 (m, 2 H). MS (ESI, pos. ion) *m*/*z*: 438 (M + 1). Anal. ($C_{19}H_{18}F_3N_5O_2S$): C, H, N.

***N*-(4-(6-Morpholinopyrimidin-4-yloxy)benzo[*d*]thiazol-2-yl)-acetamide (15).** This material was prepared according to the procedure described for compound **14** from morpholine (0.11 mL, 1.2 mmol) and *N*-(4-(6-chloro-pyrimidin-4-yloxy)-benzothiazol-2-yl)-acetamide (**9**; 200 mg, 0.62 mmol). The title compound was obtained as a white solid (150 mg, 66%). Mp: 308−311 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.44 (s, 1 H), 8.11 (s, 1 H), 7.86 (d, J = 7.8 Hz, 1 H), 7.34 (t, J = 7.8 Hz, 1 H), 7.21 (d, J = 7.8 Hz, 1 H), 6.38 (s, 1 H), 3.63−3.70 (m, 4 H), 3.54−3.60 (m, 4 H), 2.16 (s, 3 H). MS (ESI, pos. ion) *m*/*z*: 372 (M + 1). Anal. ($C_{17}H_{17}N_5O_3S\cdot0.2\ H_2O$): C, H, N.

***N*-(4-(6-(Piperazin-1-yl)pyrimidin-4-yloxy)benzo[*d*]thiazol-2-yl)acetamide (16a).** A mixture of *N*-(4-(6-chloropyrimidin-4-yloxy)benzo[*d*]thiazol-2-yl)acetamide (**9**; 320 mg, 1.0 mmol) and piperazine (860 mg, 1.0 mmol) in DMF (2.0 mL) was heated at 80 °C for 15 min. The reaction was then allowed to cool to room temperature and H_2O (1.0 mL) was added. The resulting precipitates were collected by filtration and washed with H_2O. The resulting solid was suspended in MeOH, collected by filtration, and dried in vacuo to provide the title compound as a light-yellow solid (330 mg, 89% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.07 (s, 1 H), 7.86 (dd, J = 8.0, 1.0 Hz, 1 H), 7.33 (t, J = 7.8 Hz, 1 H), 7.20 (dd, J = 7.8, 0.8 Hz, 1 H), 6.31 (s, 1 H), 3.48−3.55 (m, 4 H), 2.70−2.77 (m, 4 H), 2.16 (s, 3 H). MS (ESI, pos. ion) *m*/*z*: 371 (M + 1). Anal. ($C_{17}H_{18}N_6O_2S\cdot0.2\ H_2O$): C, H, N.

***N*-(4-(6-(4-Isopropylpiperazin-1-yl)pyrimidin-4-yloxy)benzo-[*d*]thiazol-2-yl)acetamide (16b).** This material was prepared according to the procedure described for compound **14** from *N*-(4-(6-chloropyrimidin-4-yloxy)benzo[*d*]thiazol-2-yl)acetamide (**9**; 320 mg, 1.0 mmol) and 1-isopropylpiperazine (260 mg, 2.0 mmol). The title compound (260 mg, 63%) was obtained as light-yellow crystals. Mp: 264−265 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.47 (s, 1 H), 8.11 (s, 1 H), 7.89 (d, J = 7.8 Hz, 1 H), 7.37 (t, J = 8.0 Hz, 1 H), 7.24 (d, J = 7.0 Hz, 1 H), 6.38 (s, 1 H), 3.61 (br s, 4 H), 2.73 (dt, J = 12.9, 6.5 Hz, 1 H), 2.49−2.53 (m, 4 H), 2.19 (s, 3 H), 1.03 (d, J = 6.6 Hz, 6 H). MS (ESI, pos. ion) *m*/*z*: 413 (M + 1). Anal. ($C_{20}H_{24}N_6O_2S\cdot0.2\ H_2O$): C, H, N.

***N*-(4-(6-(4-*tert*-Butylpiperazin-1-yl)pyrimidin-4-yloxy)benzo-[*d*]thiazol-2-yl)acetamide (16c).** To a suspension of *N*-(4-(6-fluoropyrimidin-4-yloxy)benzo[*d*]thiazo-2-yl]acetamide (**8**; 100 mg, 0.33 mmol) in EtOH (2 mL) was added 1-*tert*-butylpiperazine[15] (72 mg, 0.32 mmol). The reaction mixture was heated at 150 °C for 5 min using a microwave reactor. The reaction mixture was cooled, the solvents were removed in vacuo, and the residue was washed with MeOH to give *N*-(4-(4-*tert*-butylpiperazinyl)pyrimidine-4-yloxy)benzo[*d*]thiazo-2-yl]acetamide (65 mg, 46%) as a white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.99 (br s, 1 H), 8.20 (s, 1 H), 7.68 (d, J = 7.8 Hz, 1 H), 7.33 (t, J = 7.8 Hz, 1 H), 7.22 (d, J = 7.0 Hz, 1 H), 6.02 (s, 1 H), 3.61 (br s, 4 H), 2.65 (br s, 4 H), 2.24 (s, 3 H), 1.11 (s, 9 H). MS (ESI, pos. ion) *m*/*z*: 427 (M + 1). Anal. Calcd for $C_{21}H_{26}N_6O_2S\cdot1.3H_2O$: C, 56.06; H, 6.41; N, 18.68; S, 7.13. Found: C, 56.37; H, 6.10; N, 18.17; S, 7.29.

***N*-(4-(6-(4-Neopentylpiperazin-1-yl)pyrimidin-4-yloxy)benzo-[*d*]thiazol-2-yl)acetamide (16d).** To a solution of *tert*-butyl piperazine-1-carboxylate **18** (8.4 g, 45 mmol) in 1,2-dichloroethane (100 mL) was added acetic acid (2.7 mL, 47 mmol) at 50 °C, and the reaction mixture was stirred for 20 min. Trimethylacetaldehyde (9.5 mL, 70 mmol) was added into the solution, immediately followed by sodium triacetoxyborohydride (19.2 g, 90 mmol). After 1.5 h, the mixture was allowed to cool to room temperature and saturated $NaHCO_3$ (300 mL) was added. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic phases were dried over sodium sulfate, filtered, and concentrated in vacuo to provide *tert*-butyl 4-neopentylpiperazine-1-carboxylate (**19b**; 12.6 g, 100%) as a pale-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.33−3.44 (m, 4 H) 2.40−2.51 (m, 4 H), 2.06 (s, 2 H), 1.46 (s, 9 H), 0.87 (s, 9 H). MS (ESI, pos. ion) *m*/*z*: 257 (M + 1).

To a stirred solution of *tert*-butyl 4-neopentylpiperazine-1-carboxylate (**19b**; 11.6 g, 45 mmol) in 70 mL of CH_2Cl_2 was added 2,2,2-trifluoroacetic acid (30.0 mL, 390 mmol) at room temperature and the solution was stirred for 18 h. The solvent was evaporated, and the oily residue was dissolved in CH_2Cl_2 (100 mL) and treated with saturated $NaHCO_3$ aqueous solution. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). The combined extracts were washed with brine (200 mL), dried over Na_2SO_4, and concentrated in vacuo to afford 1-neopentylpiperazine (**20b**) as a white solid (7.8 g, 60%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.49 (br s, 1 H), 3.02−3.34 (m, 4 H), 2.60−2.95 (m, 4 H), 2.15 (s, 2 H), 0.86 (s, 9 H). MS (ESI, pos. ion) *m*/*z*: 157 (M + 1).

To a 5 mL microwave reaction tube was added *N*-(4-(6-fluoropyrimidin-4-yloxy)benzo[*d*]thiazol-2-yl)acetamide (**8**; 320 mg, 1.0 mmol) and 1-neopentylpiperazine (**20b**; 210 mg, 1.34 mmol) in DMSO (4.0 mL). The reaction was heated at 150 °C for 70 min in a microwave reactor. The reaction mixture was partitioned between H_2O (50 mL) and EtOAc (30 mL). The aqueous phase was extracted with EtOAc (2 × 30 mL). The combined organic phases were washed with H_2O (2 × 50 mL) and saturated aqueous NaCl (50 mL). The organic phase was dried over sodium sulfate, filtered, and concentrated in vacuo to afford a light-yellow solid (406 mg). The crude product was purified by silica gel chromatography (10%−80% EtOAc in hexanes) to afford the title compound **16d** (230 mg, 51%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.76 (s, 1 H), 8.20 (s, 1 H), 7.68 (d, J = 7.9 Hz, 1 H), 7.34 (t, J = 8.0 Hz, 1 H), 7.16−7.24 (m, 1 H), 6.02 (s, 1 H), 3.56 (br s, 4 H), 2.57 (br s, 4 H), 2.24 (s, 3 H), 2.10 (s, 2 H), 0.90 (s, 9 H). MS (ESI, pos. ion) *m*/*z*: 441 (M + 1). Anal. ($C_{22}H_{28}N_6O_2S$): C, H, N.

***N*-(4-(6-(4-(2,2,2-Trifluoroethyl)piperazin-1-yl)pyrimidin-4-yloxy)benzo[*d*] thiazol-2-yl)acetamide (16e).** To a solution of *tert*-butyl piperazine-1-carboxylate (**18**; 500 mg, 2.7 mmol) in THF (20 mL) was added diisopropylethylamine (0.50 mL, 2.7 mmol) followed by 2,2,2-trifluoroethyl trifluoromethanesulfonate (620 mg, 2.7 mmol), and the reaction mixture was stirred at reflux for 4 h. The resulting mixture was allowed to cool to room temperature, concentrated in vacuo, and purified by silica gel column chromatography (gradient: 5−10% MeOH in CH_2Cl_2) to afford *tert*-butyl 4-(2,2,2-trifluoroethyl)piperazine-1-carboxylate (**19a**; 670 mg, 97%) as a white crystalline solid. To a solution of **19a** in CH_2Cl_2 (50 mL) was added trifluoroacetic acid (5 mL, 65 mmol). The reaction mixture was stirred at room temperature for 2 h. The solvent was removed in vacuo. The crude material was dissolved in CH_2Cl_2 (100 mL) and washed with saturated aqueous $NaHCO_3$ (2 × 100 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to give 1-(2,2,2-trifluoroethyl)piperazine (**20a**) as a clear oil (0.40 mg, 91%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.80 (br s, 1 H), 3.83 (br s, 4 H), 3.31 (br s, 2 H), 3.09 (q, J = 9.2 Hz, 2 H), 2.91−3.03 (m, 2 H). MS (ESI, pos. ion) *m*/*z*: 169 (M + 1).

To a 2.5 mL microwave vial was added 1-(2,2,2-trifluoroethyl)-piperazine (**20a**; 0.40 g, 2.9 mmol) and *N*-(4-(6-fluoropyrimidin-4-yloxy)benzo[*d*]thiazol-2-yl)acetamide (**8**; 0.80 g, 2.6 mmol) in DMSO (4 mL). The vial was sealed and the solution was stirred at 110 °C for 17 h. The reaction mixture was allowed to reach room temperature. Water (20 mL) was added to the reaction mixture and the aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL). The combined CH_2Cl_2 layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by silica gel column chromatography (gradient: 20−80% EtOAc in hexanes) to give the title compound **16e** as an off-white solid (0.68 g, 63%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.44 (s, 1 H), 8.09 (s, 1 H), 7.86 (d, J = 7.2 Hz, 1 H), 7.33 (t, J = 7.9 Hz, 1 H), 7.20 (d, J = 7.2 Hz, 1 H), 6.38 (s, 1 H), 3.62 (s, 4 H), 3.26 (q, J = 10 Hz, 2 H), 2.68 (s, 4 H), 2.16 (s, 3 H). MS (ESI, pos. ion) *m*/*z*: 453 (M + 1). Anal. ($C_{19}H_{19}F_3N_6O_2S$): C, H, N.

***N*-(4-(6-(4-Phenylpiperazin-1-yl)pyrimidin-4-yloxy)benzo[*d*]-thiazol-2-yl)acetamide (16f).** This material was prepared according to the procedure described for compound **14** from 1-phenylpiperazine (0.20 mL, 1.3 mmol) and *N*-(4-(6-chloro-pyrimidin-4-yloxy)-benzothiazol-2-yl)-acetamide (**9**; 200 mg, 0.62 mmol). The title compound was obtained as an off-white solid (200 mg, 73%). Mp: 292.0−292.3 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.12 (s, 1 H), 7.86 (d, J = 7.8 Hz, 1 H), 7.33 (t, J = 7.9 Hz, 1 H), 7.19−7.28 (m, 3 H), 6.99 (d, J = 8.2 Hz, 2 H), 6.82 (t, J = 7.2 Hz, 1 H), 6.43 (s, 1 H), 3.76 (br s, 4 H), 3.19−3.25 (m, 4 H), 2.15 (s, 3 H). MS (ESI, pos. ion) *m*/*z*: 447 (M + 1). Anal. ($C_{23}H_{22}N_6O_2S$·0.2 H_2O): C, H, N.

***N*-(4-(6-(4-Benzylpiperazin-1-yl)pyrimidin-4-yloxy)benzo[*d*]-thiazol-2-yl)acetamide (16g).** This material was prepared according to the procedure described for compound **14** from 1-benzylpiperazine (0.20 mL, 1.2 mmol) and *N*-(4-(6-chloro-pyrimidin-4-yloxy)-benzothiazol-2-yl)-acetamide (**9**; 200 mg, 0.62 mmol). The title compound was obtained as a tan solid (150 mg, 52%). Mp: 217−218 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.42 (s, 1 H), 8.07 (s, 1 H), 7.85 (dd, J = 7.9, 0.9 Hz, 1 H), 7.25−7.37 (m, 6 H), 7.20 (dd, J = 7.8, 0.8 Hz, 1 H), 6.35 (s, 1 H), 3.60 (br s, 4 H), 3.53 (s, 2 H), 2.40−2.45 (m, 4 H), 2.15 (s, 3 H). MS (ESI, pos. ion) *m*/*z*: 461 (M + 1). Anal. ($C_{24}H_{24}N_6O_2S$): C, H, N.

***N*-(4-(6-(4-Phenethylpiperazin-1-yl)pyrimidin-4-yloxy)benzo-[*d*]thiazol-2-yl)acetamide (16h).** This material was prepared according to the procedure described for compound **14** from 1-phenethylpiperazine (360 mg, 1.90 mmol) and *N*-(4-(6-chloro-pyrimidin-4-yloxy)-benzothiazol-2-yl)-acetamide (**9**; 300 mg, 0.94 mmol). The title compound was obtained as a white solid (21 mg, 5%). Mp: 128−133 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.43 (s, 1 H), 8.08 (s, 1 H), 7.85 (d, J = 7.8 Hz, 1 H), 7.15−7.36 (m, 7 H), 6.37 (s, 1 H), 3.60 (br s, 4 H), 2.72−2.81 (m, 2 H), 2.54−2.61 (m, 2 H), 2.50 (s, 4 H), 2.15 (s, 3 H). MS (ESI, pos. ion) *m*/*z*: 475 (M + 1). Anal. ($C_{25}H_{26}N_6O_2S$·1.5 H_2O): C, H, N.

***N*-(4-(6-(4-(1-Phenylethyl)piperazin-1-yl)pyrimidin-4-yloxy)-benzo[*d*]thiazol-2-yl)acetamide (16i).** This material was prepared according to the procedure described for compound **14** from 1-(1-phenylethyl)piperazine (0.24 mL, 1.2 mmol) and *N*-(4-(6-chloro-pyrimidin-4-yloxy)-benzothiazol-2-yl)-acetamide (**9**; 200 mg, 0.62 mmol). The title compound was obtained as a solid (92 mg, 31%). Mp: 132−135 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.42 (s, 1 H), 8.05 (s, 1 H), 7.84 (dd, J = 8.0, 1.0 Hz, 1 H), 7.22−7.38 (m, 6 H), 7.19 (dd, J = 7.8, 1.0 Hz, 1 H), 6.32 (s, 1 H), 3.57 (br s, 4 H), 3.46 (q, J = 6.6 Hz, 1 H), 2.41−2.48 (m, 2 H), 2.31−2.40 (m, 2 H), 2.15 (s, 3 H), 1.33 (d, J = 6.7 Hz, 3 H). MS (ESI, pos. ion) *m*/*z*: 475 (M + 1). Anal. ($C_{25}H_{26}N_6O_2S$·0.5 H_2O): C, H, N.

***N*-(4-(6-(4-(1-Phenylpropyl)piperazin-1-yl)pyrimidin-4-yloxy)-benzo[*d*]thiazol-2-yl)acetamide (16j).** A mixture of piperazine-1-carboxylic acid *tert*-butyl ester (**18**; 500 mg, 2.7 mmol), propiophenone (0.54 mL, 4.0 mmol) in THF (2.5 mL) at room temperature was treated with titanium tetra-isopropoxide (2.4 mL, 8.1 mmol) under nitrogen and then stirred at 75 °C for 16 h. The reaction mixture was cooled to −48 °C and then treated with sodium triacetoxyborohydride (1720 mg, 8.10 mmol) followed by MeOH (1.3 mL). The resulting mixture was allowed to warm to room temperature over 1.5 h. The reaction mixture was diluted with EtOAc (20 mL) and washed with aqueous 1 N NaOH (2 × 30 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The crude material was purified by silica gel chromatography (gradient: 0−5% MeOH/CH_2Cl_2) to obtain *tert*-butyl 4-(1-phenylpropyl)piperazine-1-carboxylate (**19c**) as a yellow oil (510 mg, 62%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.60−7.57 (m, 2 H), 7.53−7.46 (m, 3 H), 3.54−3.51 (m, 5 H), 2.76 (m, 2 H), 2.50 (m, 2 H), 2.10 (m, 1 H), 1.95 (m, 1 H), 1.60 (s, 9 H), 0.96 (t, J = 7.6 Hz, 3 H). MS (ESI, pos. ion) *m*/*z*: 305 (M + 1).

A solution of *tert*-butyl 4-(1-phenylpropyl)piperazine-1-carboxylate (**19c**; 510 mg, 1.71 mmol) in CH_2Cl_2 (3.5 mL) was treated with TFA (0.8 mL) at room temperature and stirred for 16 h. The solvent and excess TFA were removed under vacuum to give 1-(1-phenylpropyl)piperazine (**20c**) as a TFA salt. Following the procedure described for compound **14**, the above 1-(1-phenylpropyl)piperazine (**20c**), *N*-(4-(6-chloro-pyrimidin-4-yloxy)-benzothiazol-2-yl)-acetamide (**9**; 550 mg, 1.7 mmol), and K_2CO_3 (940 mg, 6.6 mmol) provided the title compound **16j** as an off-white solid (376 mg, 29% over three steps). Mp: 213−215 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.41 (s, 1 H), 8.03 (s, 1 H), 7.84 (d, J = 8.0 Hz, 1 H), 7.29−7.38 (m, 3 H), 7.22−7.29 (m, 3 H), 7.17 (d, J = 7.2 Hz, 1 H), 6.29 (s, 1 H), 3.56 (s, 4 H), 3.56 (m, 1 H), 2.30−2.42 (m, 4 H), 2.14 (s, 3 H), 1.87−1.99 (m, 1 H), 1.66−1.79 (m, 1 H), 0.73 (t, J = 7.2 Hz, 3 H). MS (ESI, pos. ion) *m*/*z*: 489 (M + 1). Anal. ($C_{26}H_{28}N_6O_2S$·0.2 H_2O): C, H, N.

***N*-(4-(6-(4-Benzhydrylpiperazin-1-yl)pyrimidin-4-yloxy)benzo[*d*]thiazol-2-yl)acetamide (16k).** This material was prepared according to the procedure described for compound **14** from 1-benzhydrylpiperazine (310 mg, 1.2 mmol) and *N*-(4-(6-chloro-pyrimidin-4-yloxy)-benzothiazol-2-yl)-acetamide (**9**; 200 mg, 0.62 mmol). The title compound was obtained as an off-white solid (150 mg, 46%). Mp: 156.0−156.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.43 (s, 1 H), 8.06 (s, 1 H), 7.84 (dd, J = 8.2, 0.8 Hz, 1 H), 7.47 (d, J = 7.4 Hz, 4 H), 7.27−7.35 (m, 5 H), 7.16−7.24 (m, 3 H), 6.32 (s, 1 H), 4.35 (s, 1 H), 3.61 (s, 4 H), 2.37 (s, 4 H), 2.15 (s, 3 H). MS (ESI, pos. ion) *m*/*z*: 537 (M + 1). Anal. ($C_{30}H_{28}N_6O_2S$·2H_2O): C, H, N.

***N*-(4-(6-(4-(2-Phenylpropan-2-yl)piperazin-1-yl)pyrimidin-4-yloxy)benzo[*d*]thiazol-2-yl)acetamide (16l).** A mixture of *N*,*N*-bis(2-chloroethyl)-4-methylbenzenesulfonamide (**25**; 860 mg, 2.9 mmol), 2-phenylpropan-2-amine (780 mg, 5.8 mmol) in *N*,*N*-diisopropylpropylethylamine (2.0 mL) was heated at 125 °C for 3 d. The reaction was then allowed to cool to room temperature and partitioned between H_2O (20 mL) and CH_2Cl_2 (20 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were washed with H_2O (50 mL) and saturated aqueous NaCl (50 mL). The organic phase was dried over sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by silica gel chromatography (50−100% CH_2-

Cl_2 in hexanes) to afford 1-(2-phenylpropan-2-yl)-4-tosylpiperazine (790 mg, 76%) as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (d, J = 6.8 Hz, 2 H), 7.40 (d, J = 8.0 Hz, 2 H), 7.34 (d, J = 8.0 Hz, 2 H), 7.25 (m, 2 H), 7.18 (m, 1 H), 2.95 (br s, 4 H), 2.55 (t, J = 4.6 Hz, 4 H), 2.46 (s, 3 H), 1.30 (s, 6 H). MS (ESI, pos. ion) m/z: 359 (M + 1).

To a mixture of 1-(2-phenylpropan-2-yl)-4-tosylpiperazine (790 mg, 2.2 mmol) and 4-hydroxybenzoic acid was added hydrogen bromide solution (33 wt % in acetic acid, 8.0 mL) at room temperature. The reaction mixture was stirred for 4 d at room temperature. The resulting mixture was cooled to 0 °C followed by addition of H_2O (20 mL) and CH_2Cl_2 (20 mL). A white precipitate was formed and removed by filtration. The filter cake was washed with H_2O (3×). The combined aqueous layers were extracted with CH_2Cl_2 (2×) and toluene (2×). The aqueous phase was then cooled to 0 °C, basified with 10 M NaOH aqueous solution to pH = 12, and extracted with CH_2Cl_2 (3×). The combined organic phases were washed with H_2O and brine, dried over sodium sulfate, filtered, and concentrated in vacuo to afford 1-(2-phenylpropan-2-yl)piperazine (**26**; 390 mg, 86%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (m, 2 H), 7.30 (m, 2 H), 7.19 (m, 1 H), 2.85 (t, J = 4.8 Hz, 4 H), 2.45 (t, J = 4.8 Hz, 4 H), 1.82 (br s, 3 H), 1.33 (s, 6 H). MS (ESI, pos. ion) m/z: 205 (M + 1).

Following the procedure described for compound **14**, 1-(2-phenylpropan-2-yl)piperazine (**26**; 470 mg, 2.3 mmol) and *N*-(4-(6-chloropyrimidin-4-yloxy)benzo[*d*]thiazol-2-yl)acetamide (**9**; 490 mg, 1.5 mmol) provided the title product **16l** (450 mg, 92%) as a light-yellow solid. Mp: 223−224 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.43 (s, 1 H), 8.06 (s, 1 H), 7.85 (d, J = 7.8 Hz, 1 H), 7.54 (d, J = 7.8 Hz, 2 H), 7.33 (q, J = 7.7 Hz, 3 H), 7.16−7.26 (m, 2 H), 6.32 (s, 1 H), 3.56 (br s, 4 H), 2.45 (s, 4 H), 2.15 (s, 3 H), 1.32 (s, 6 H). MS (ESI, pos. ion) m/z: 489 (M + 1). Anal. ($C_{25}H_{28}N_6O_2S$·0.3 H_2O): C, H, N.

***N*-(4-(6-(4-(1-(3-Fluorophenyl)ethyl)piperazin-1-yl)pyrimidin-4-yloxy)benzo[*d*]thiazol-2-yl)acetamide (16m).** Analogous to the procedure in the preparation of compound **16j**, 3′-fluoroacetophenone (0.49 mL, 4.00 mmol), piperazine-1-carboxylic acid *tert*-butyl ester (**18**; 500 mg, 2.7 mmol), and *N*-(4-(6-chloro-pyrimidin-4-yloxy)-benzothiazol-2-yl)-acetamide (**9**; 630 mg, 1.9 mmol) provided the title compound as a white solid (680 mg, 51% over three steps). Mp: 204 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.42 (s, 1 H), 8.05 (s, 1 H), 7.84 (d, J = 7.8 Hz, 1 H), 7.34−7.43 (m, 1 H), 7.31 (t, J = 7.8 Hz, 1 H), 7.13−7.22 (m, 3 H), 7.02−7.12 (m, 1 H), 6.32 (s, 1 H), 3.57 (br s, 4 H), 3.52 (q, J = 6.8 Hz, 1 H), 2.42−2.48 (m, 2 H), 2.30−2.41 (m, 2 H), 2.14 (s, 3 H), 1.32 (d, J = 6.7 Hz, 3 H). MS (ESI, pos. ion) m/z: 493 (M + 1). Anal. ($C_{25}H_{25}FN_6O_2S$·0.5 H_2O): C, H, N.

***N*-(4-(6-(4-(1-(4-(Trifluoromethyl)phenyl)ethyl)piperazin-1-yl)pyrimidin-4-yloxy)benzo[*d*]thiazol-2-yl)acetamide (16n).** Analogous to the procedure for the preparation of compound **16j**, 4′-trifluoromethyl-acetophenone (750 mg, 4.0 mmol), piperazine-1-carboxylic acid *tert*-butyl ester (**18**; 500 mg, 2.7 mmol), and *N*-(4-(6-chloro-pyrimidin-4-yloxy)-benzothiazol-2-yl)-acetamide (**9**; 610 mg, 1.9 mmol) provided the title compound as a white solid (730 mg, 50% over three steps). Mp: 153−155 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.42 (s, 1 H), 8.06 (s, 1 H), 7.85 (dd, J = 8.0, 1.0 Hz, 1 H), 7.71 (d, J = 8.2 Hz, 2 H), 7.58 (d, J = 8.2 Hz, 2 H), 7.32 (t, J = 7.9 Hz, 1 H), 7.19 (dd, J = 7.8, 0.8 Hz, 1 H), 6.32 (s, 1 H), 3.52−3.64 (m, 5 H), 2.44−2.48 (m, 2 H), 2.30−2.41 (m, 2 H), 2.15 (s, 3 H), 1.34 (d, J = 6.7 Hz, 3 H). MS (ESI, pos. ion) m/z: 543 (M + 1). Anal. ($C_{26}H_{25}F_3N_6O_2S$·0.5 H_2O): C, H, N.

***N*-(4-(6-(4-(1-(4-Methoxyphenyl)ethyl)piperazin-1-yl)pyrimidin-4-yloxy)benzo[*d*]thiazol-2-yl)acetamide (16o).** Analogous to the procedure in the preparation of compound **16j**, 1-(4-methoxyphenyl)ethanone (600 mg, 4.0 mmol), piperazine-1-carboxylic acid *tert*-butyl ester (**18**; 500 mg, 2.7 mmol), and *N*-(4-(6-chloro-pyrimidin-4-yloxy)-benzothiazol-2-yl)-acetamide (**9**; 590 mg, 1.8 mmol) provided the title compound as a white solid (300 mg, 22% in three steps). Mp: 150−151 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.43 (s, 1 H), 8.05 (s, 1 H), 7.85 (d, J = 7.8 Hz, 1 H), 7.32 (t, J = 7.8 Hz, 1 H), 7.16−7.26 (m, 3 H), 6.90 (d, J = 8.6 Hz, 2 H), 6.32 (s, 1 H), 3.75 (s, 3 H), 3.56 (br s, 4 H), 3.43 (q, J = 6.5 Hz, 1 H), 2.39−2.48 (m, 2 H), 2.30−2.39 (m, 2 H), 2.15 (s, 3 H), 1.31 (d, J = 6.7 Hz, 3 H). MS (ESI, pos. ion) m/z: 505 (M + 1). Anal. Calcd for $C_{26}H_{28}N_6O_3S$·H_2O: C, 59.75; H, 5.79; N, 16.08; S, 6.14. Found: C, 59.38; H, 5.48; N, 16.66; S, 6.62.

***(S)*-*tert*-Butyl 4-(1-(4-Fluorophenyl)ethyl)piperazine-1-carboxylate (21) and (*R*)-*tert*-Butyl 4-(1-(4-Fluorophenyl)ethyl)-piperazine-1-carboxylate (22).** A mixture of 4′-fluoroacetophenone (1.0 mL, 8.0 mmol) and piperazine-1-carboxylic acid *tert*-butyl ester (**18**; 1.00 g, 5.0 mmol) in THF (3.0 mL) at room temperature was treated with titanium tetra-isopropoxide (5.0 mL, 16.00 mmol) under nitrogen and then stirred at 75 °C for 18 h. The reaction mixture was cooled to −48 °C and then treated with sodium triacetoxyborohydride (3.00 g, 16.0 mmol) followed by MeOH (2.0 mL). The resulting mixture was allowed to warm to room temperature over 1.5 h. The reaction mixture was diluted with EtOAc (100 mL) and washed with aqueous 5 N NaOH (4 × 30 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude material was purified by silica gel chromatography (gradient: 0−5% MeOH/ CH_2Cl_2) to obtain *tert*-butyl 4-(1-(4-fluorophenyl)ethyl)piperazine-1-carboxylate (**19g**) as a yellow oil (0.74 g, 44%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.29−7.35 (m, 2 H), 7.10−7.17 (m, 2 H), 3.46 (q, J = 6.7 Hz, 1 H), 3.27 (br s, 4 H), 2.26−2.36 (m, 2 H), 2.17−2.26 (m, 2 H), 1.37 (s, 9 H), 1.27 (d, J = 6.7 Hz, 3 H). MS (ESI, pos. ion) m/z: 309 (M + 1).

Chiral separation of *tert*-butyl 4-(1-(4-fluorophenyl)ethyl)piperazine-1-carboxylate (**19g**; 1.29 g) was performed on an Agilent 1100 specrometer by Chirobiotic TAG column (4.6 × 250 mm) at a 1.0 mL/min flow rate using isocratic MeOH/acetic acid/triethyamine (100:0.08:0.02). (*R*)-*tert*-Butyl 4-(1-(4-fluorophenyl)-ethyl)piperazine-1-carboxylate (**21**; 0.49 g, t_r = 13.16 min, 93% ee) and (*S*)-*tert*-butyl 4-(1-(4-fluorophenyl)ethyl)piperazine-1-carboxylate (**22**; 0.42 g, t_r = 8.88 min, 96% ee) were obtained.

***(R)*-1-(1-(4-Fluorophenyl)ethyl)piperazine (23).** Method A: A solution of (*R*)-*tert*-butyl 4-(1-(4-fluorophenyl)ethyl)piperazine-1-carboxylate (**21**; 480 mg, 1.5 mmol) in CH_2Cl_2 (2.0 mL) was treated with TFA (0.5 mL) at room temperature and stirred for 18 h. The solvents and excess TFA were removed under vacuum to give (*R*)-1-(1-(4-fluorophenyl)ethyl)piperazine (**23**) as a TFA salt. MS (ESI, pos. ion) m/z: 209 (M + 1).

Method B: A mixture of *N*,*N*-bis(2-chloroethyl)-4-methylbenzenesulfonamide (39.2 g, 134 mmol; **25**), (*R*)-1-(4-fluorophenyl)-ethanamine (17.0 g, 122 mmol), and *N*,*N*-diisopropylpropylethylamine (42.5 mL) under a nitrogen atmosphere was heated at 125 °C for 20 h. The reaction was then allowed to cool to room temperature. A mixture of EtOH/H_2O (70/30, 100 mL) was added slowly to the reaction mixture and stirred overnight. The resulting solid was filtered off and washed with H_2O (3 × 50 mL) and hexanes (2 × 50 mL). The filter cake was suspended in a mixture of EtOH/H_2O (1:1; 120 mL) for 3.5 h. The resulting solid was collected by filtration, washed with EtOH/H_2O (1:1, 2 × 40 mL), EtOH/H_2O (70:30, 30 mL) and hexanes (2 × 40 mL). The solid was dried in a vacuum oven at 50 °C for 17 h to provide (*R*)-1-(1-(4-fluorophenyl)ethyl)-4-tosylpiperazine (35.4 g, 80%). Mp: 129 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, J = 8.2 Hz, 2 H), 7.33 (d, J = 8.2 Hz, 2 H), 7.16−7.23 (m, 2 H), 6.92−7.00 (m, 2 H), 3.36 (q, J = 6.9 Hz, 1 H), 2.89−3.03 (m, 4 H), 2.50−2.62 (m, 2 H), 2.40−2.47 (m, 5 H), 1.29 (d, J = 6.9 Hz, 3 H). MS (ESI, pos. ion) m/z: 363 (M + 1).

To a mixture of (*R*)-1-(1-(4-fluorophenyl)ethyl)-4-tosylpiperazine (20.0 g, 55.2 mmol) and 4-hydroxybenzoic acid (22.9 g, 165 mmol) was added hydrogen bromide solution (33 wt. % in acetic acid, 220 mL) at room temperature. The reaction mixture was stirred under nitrogen atmosphere for 2 d with a mechanical stirrer at room temperature. Water (200 mL) was slowly added to the reaction mixture (mildly exothermic), and the reaction mixture was continually stirred for 2 h. A white precipitate was formed and removed by filtration. The filter cake was washed with H_2O (2 × 50 mL). The combined acidic aqueous washes were washed with toluene (4 × 50 mL). The aqueous phase was then cooled to 0 °C, basified with KOH pellets portionwise until pH > 10, and extracted with

toluene (3 × 50 mL) and EtOAc (50 mL). The combined organic phases were washed with brine (100 mL), dried over sodium sulfate, filtered, and concentrated in vacuo to afford (*R*)-1-(1-(4-fluorophenyl)ethyl)piperazine (**23**; 10.4 g, 91%) as a pale brown solid. Mp: 70−71 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26−7.30 (m, 2 H), 6.95−7.06 (m, 2 H), 3.33 (q, J = 6.8 Hz, 1 H), 2.82−2.88 (m, 4 H), 2.40−2.50 (m, 1 H), 2.28−2.37 (m, 2 H), 2.01−2.09 (m, 2 H), 1.33 (d, J = 6.8 Hz, 3 H). MS (ESI, pos. ion) *m*/*z*: 209 (M + 1).

(*S*)-1-(1-(4-Fluorophenyl)ethyl)piperazine (24). Method A: Analogous to the method A in the preparation of compound **23**, (*S*)-*tert*-butyl 4-(1-(4-fluorophenyl)ethyl)piperazine-1-carboxylate (**22**; 420 mg, 1.4 mmol) provided (*S*)-1-(1-(4-fluorophenyl)ethyl)-piperazine (**24**) as a TFA salt. MS (ESI, pos. ion) *m*/*z*: 209 (M + 1).

Method B: Analogous to the method B in the preparation of compound **23**, *N*,*N*-bis(2-chloroethyl)-4-methylbenzenesulfonamide **25** (21.0 g, 134 mmol), (*S*)-1-(4-fluorophenyl)ethanamine (9.0 g, 120 mmol) provided (*S*)-1-(1-(4-fluorophenyl)ethyl)piperazine (**24**; 7.4 g, 56% over two steps) as a pale-yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26−7.30 (m, 2 H), 6.95−7.06 (m, 2 H), 3.33 (q, J = 6.8 Hz, 1 H), 2.82−2.88 (m, 4 H), 2.40−2.50 (m, 1 H), 2.28−2.37 (m, 2 H), 2.01−2.09 (m, 2 H), 1.33 (d, J = 6.8 Hz, 3 H). MS (ESI, pos. ion) *m*/*z*: 209 (M + 1).

(*R*)-*N*-(4-(6-(4-(1-(4-Fluorophenyl)ethyl)piperazin-1-yl)pyrimidin-4-yloxy)benzo[*d*]thiazol-2-yl)acetamide (16p). A mixture of *N*-(4-(6-chloropyrimidin-4-yloxy)benzo[*d*]thiazol-2-yl)acetamide (**9**; 3.0 g, 9.4 mmol), (*R*)-1-(1-(4-fluorophenyl)ethyl)piperazine (**23**; 2.0 g, 9.8 mmol, from the procedure described for compound **23**, method B), and Na_2CO_3 (2.4 g, 9.4 mmol) in DMF (30.0 mL) was heated at 90 °C for 5.5 h. The reaction mixture was transferred dropwise to a flask containing H_2O (240 mL) and stirred vigorously for 30 min. The resulting precipitate was collected by filtration and washed with H_2O (1 × 50 mL and 2 × 25 mL) followed by hexanes (3 × 50 mL). The resulting solid was dried under vacuum to provide the title compound as an off-white solid (4.1 g, 88%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.41 (s, 1 H), 8.06 (s, 1 H), 7.84 (dd, J = 7.8, 0.8 Hz, 1 H), 7.27−7.40 (m, 3 H), 7.11−7.22 (m, 3 H), 6.32 (s, 1 H), 3.57 (br s, 4 H), 3.50 (q, J = 6.8 Hz, 1 H), 2.40−2.48 (m, 2 H), 2.30−2.38 (m, 2 H), 2.15 (s, 3 H), 1.31 (d, J = 6.7 Hz, 3 H). MS (ESI, pos. ion) *m*/*z*: 493 (M + 1). Anal. ($C_{25}H_{25}FN_6O_2S$): C, H, N.

(*S*)-*N*-(4-(6-(4-(1-(4-Fluorophenyl)ethyl)piperazin-1-yl)pyrimidin-4-yloxy)benzo[*d*]thiazol-2-yl)acetamide (16q). This material was prepared according to the procedure described for compound **16p** from *N*-(4-(6-chloropyrimidin-4-yloxy)benzo[*d*]-thiazol-2-yl)acetamide (**9**; 430 mg, 1.4 mmol) and (*S*)-1-(1-(4-fluorophenyl)ethyl)piperazine (**24**; 280 mg, 1.4 mmol, from the procedure described for compound **24**, method A). The title compound was obtained as an off-white solid (271 mg, 41%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.41 (s, 1 H), 8.06 (s, 1 H), 7.84 (dd, J = 7.8, 0.8 Hz, 1 H), 7.27−7.40 (m, 3 H), 7.11−7.22 (m, 3 H), 6.32 (s, 1 H), 3.57 (br s, 4 H), 3.50 (q, J = 6.8 Hz, 1 H), 2.40−2.48 (m, 2 H), 2.30−2.38 (m, 2 H), 2.15 (s, 3 H), 1.31 (d, J = 6.7 Hz, 3 H). MS (ESI, pos. ion) *m*/*z*: 493 (M + 1). Anal. ($C_{25}H_{25}FN_6O_2S$): C, H, N.

***N*-(4-(6-(4-(1-(4-Fluorophenyl)ethyl)piperazin-1-yl)pyrimidin-4-yloxy)benzo[*d*]thiazol-2-yl)acetamide (17a).** A mixture of *N*-(4-(6-(piperazin-1-yl)pyrimidin-4-yloxy)benzo[*d*]thiazol-2-yl)acetamide (**16a**; 200 mg, 0.54 mmol) and 4′-fluoro-acetophenone (0.1 mL, 0.81 mmol) in THF (2 mL) at room temperature was treated with titanium tetra-isopropoxide (0.47 mL, 1.6 mmol) under nitrogen and then stirred at 75 °C for 16 h. The reaction mixture was cooled to −48 °C and then treated with sodium borohydride (60 mg, 1.6 mmol) followed by MeOH (1.0 mL). The resulting mixture was allowed to warm to room temperature over 3.5 h. The reaction mixture was diluted with EtOAc (50 mL) and washed with aqueous 1 N NaOH (2 × 50 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude material was purified by silica gel chromatography (gradient: 0−5% MeOH/CH_2Cl_2) to provide the title compound as a white solid (5 mg, 2%). Mp: 241−242 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.41 (s, 1 H), 8.06 (s, 1 H), 7.84 (dd, J = 7.8, 0.8 Hz, 1 H), 7.27−7.40 (m, 3 H), 7.11−7.22 (m, 3 H), 6.32 (s, 1 H), 3.57 (br s, 4 H), 3.50 (q, J = 6.8 Hz, 1 H), 2.40−2.48 (m, 2 H), 2.30−2.38 (m, 2 H), 2.15 (s, 3 H), 1.31 (d, J = 6.7 Hz, 3 H). MS (ESI, pos. ion) *m*/*z*: 493 (M + 1). Anal. ($C_{25}H_{25}FN_6O_2S$): C, H, N.

***N*-(4-(6-(4-(1-(2-Fluorophenyl)ethyl)piperazin-1-yl)pyrimidin-4-yloxy)benzo[*d*]thiazol-2-yl)acetamide (17b).** This material was prepared according to the procedure described for compound **17a** from *N*-(4-(6-(piperazin-1-yl)pyrimidin-4-yloxy)benzo[*d*]thiazol-2-yl)acetamide (**16a**; 60 mg, 0.16 mmol) and 2′-fluoro-acetylphenone (0.03 mL, 0.24 mmol). The title compound (29 mg, 37%) was obtained as a pale-yellow solid. Mp: 203−204 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.43 (s, 1 H), 8.06 (s, 1 H), 7.85 (d, J = 7.8 Hz, 1 H), 7.48 (t, J = 7.4 Hz, 1 H), 7.32 (t, J = 8.0 Hz, 2 H), 7.14−7.26 (m, 3 H), 6.33 (s, 1 H), 3.86 (q, J = 7.0 Hz, 1 H), 3.58 (br s, 4 H), 2.42−2.48 (m, 2 H), 2.35−2.42 (m, 2 H), 2.15 (s, 3 H), 1.36 (d, J = 6.7 Hz, 3 H). MS (ESI, pos. ion) *m*/*z*: 493 (M + 1). Anal. ($C_{25}H_{25}FN_6O_2S$): C, H, N.

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Supporting Information Available: Elemental analysis data for final compounds **12**−**15**, **16a**−**q**, and **17a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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