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Practical Synthesis of a Vanilloid Receptor-1 Antagonist

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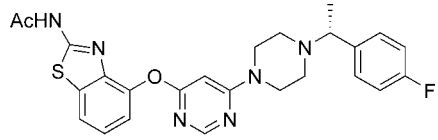

Small molecule TRPV1 antagonists have been a recent focus in the search for pain treatment agents. We herein describe a practical and scalable synthesis of AMG 628 (**1**), a bis-substituted pyrimidine derivative that was identified as a highly efficacious agent, suitable for clinical development. Highlights of our approach include a practical route to a substituted benzothiazole, a scalable synthesis of an enantiopure piperazine fragment, and identification of conditions for selective coupling reactions on 2,6-dichloropyrimidine, to access the active pharmaceutical ingredient in high purity and overall yield.

Introduction

Vanilloid receptor-1 (TRPV1 or VR1) is a nonselective cation channel that is a member of the transient receptor potential (TRP) super family and is expressed on nociceptive C and Aδ fibers. TRPV1 is activated by heat, protons (H^+), and several endogenous and exogenous ligands. Activation of TRPV1 by capsaicin, an active constituent of hot peppers, induces localized release from the activated nerve terminals of substance P (neurokinin 1), calcitonin gene-related peptide (CGRP), and other molecules, resulting in localized hyperemia (flare) accompanied by pain, hyperalgesia, and allodynia. Pharmacological inhibition of TRPV1 receptors in rats and molecular disruption of the TRPV1 gene in mice reduces the response to painful stimuli associated with inflammatory activity. Therefore, the in vivo pharmacological effects of small molecule antagonists of TRPV1 have been a recent focus in the search for agents designed for treatment of chronic pain.[1,2]

Efforts of our Medicinal Chemistry team led to the recent discovery of novel 4-oxopyrimidine-based TRPV1 antagonists.[3] On the basis of in vivo efficacy and pharmacokinetic profile AMG 628 was selected for further evaluation and pursued as a clinical development candidate.[3c] The original approach toward AMG 628 (**1**) is outlined in Scheme 1. Hydroxybenzothiazole **2** was coupled with 4,6-dichloropyrimidine (**3**) to afford intermediate **4**. The piperazine was accessed via reductive amination of *N*-Boc piperazine **5** with 1-(4-fluorophenyl)ethanone. Subsequently the enantiomers were separated by reverse-phase HPLC on a chiral phase and the Boc protecting group was removed under standard conditions to afford the piperazine building block **6**. AMG 628 (**1**) was obtained by using a base-mediated coupling reaction of the two fragments. Overall this approach allowed access to the target molecule in sufficient quantities for initial biological testing. To develop a robust large-scale synthesis of AMG 628, we needed to secure scaleable routes to key building blocks **2** and **6**, and define a route that would allow access to the target molecule without relying on time-consuming and costly purification steps.

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(1) For a general overview see: (a) Szallasi, A.; Appendino, G. *J. Med. Chem.* **2004**, *47*, 2717. (b) Rami, K. H.; Gunthorpe, M. J. *Drug Discovery Today: Ther. Strategies* **2004**, *1*, 97–104.

(2) For disclosure of clinical development candidates see: (a) Lukin, K.; Hsu, M. C.; Chambournier, G.; Kotecki, B.; Venkatramani, C. J.; Leanna, M. R. *Org. Process Res. Dev.* **2007**, *11*, 578. (b) Rami, H. K.; Thompson, M.; Stemp, G.; Fell, S.; Jerman, J. C.; Stevens, A. J.; Smart, D.; Sargent, B.; Sanderson, D.; Randall, A. D.; Gunthorpe, M. J.; Davis, J. B. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3287.

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(4) $424 for 25 g.

(5) (a) Erlenmeyer, H.; Ueberwasser, H. *Helv. Chim. Acta* **1942**, *25*, 515. (b) Feng, P. K.; Fernando, Q. *J. Am. Chem. Soc.* **1960**, *82*, 2115. (c) Gupta, R. R.; Ojha, K. G.; Kalwania, G. S.; Kumar, M. *Heterocycles* **1980**, *14*, 1145.

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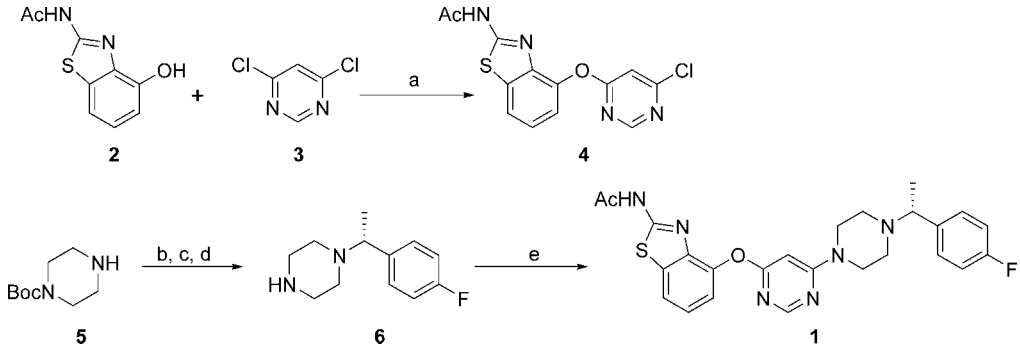
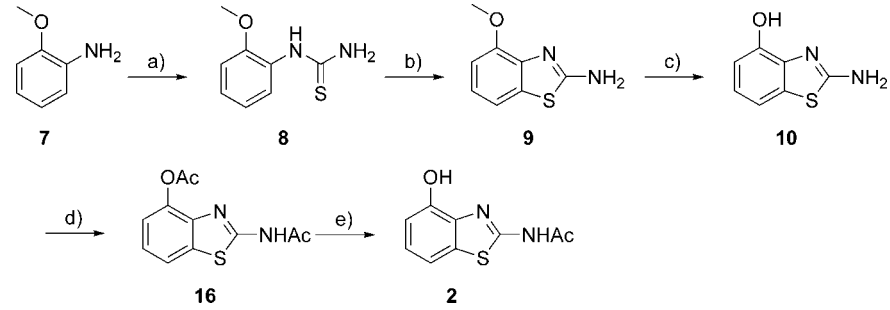
SCHEME 1. Discovery Route to AMG 628[a]



[a] Reagents and conditions: (a) K_2CO_3, acetone, reflux; (b) 1-(4-fluorophenyl)ethanone, Ti(O*i*Pr)$_4$, THF, 75 °C; $NaBH(OAc)_3$, MeOH, −48 °C to room temperature; (c) RP-HPLC Chirobiotic TAG column (4.6 × 250 mm); (d) trifluoroacetic acid, CH_2Cl_2, room temperature; (e) **4**, K_2CO_3, DMF, 85 °C.

SCHEME 2. Benzothiazole Synthesis[a]



[a] Original conditions: (a) 2 M HCl, NH_4Cl, KSCN, reflux, 65%; (b) Br_2, CH_2Cl_2, 60%; (c) 48% aq HBr, reflux, 95%. Optimized procedure: (a) trifluoroacetic acid, KSCN, IPAc, 80 °C, 74%;(b) LiBr, Br_2, acetic acid, 40 °C, 72%; (c) 48% aq HBr, catechol, reflux, 93%. (d) Ac_2O, triethylamine, EtOAc, reflux, 82%. (e) KOH, DMSO, 85 °C, 90%.

Results and Discussion

Scaleable Route to *N*-(4-Hydroxybenzothiazol-2-yl)acetamide. 4-Methoxybenzothiazol-2-ylamine **9** is commercially available, but the price is prohibitive for large-scale supplies of this intermediate.[4] We therefore investigated the development of a scaleable synthesis of 4-hydroxybenzothiazol-2-ylamine **10**. The initial conditions employed for the scale-up of this intermediate (Scheme 2) relied upon literature procedures.[5] To overcome some of the difficulties encountered with the scale-up of these first-generation reaction conditions an extensive optimization of each individual step of this synthetic sequence was performed.

Reaction of *o*-anisidine with potassium isothiocyanate under aqueous acidic conditions afforded thiourea **8**. We observed incomplete conversion of the starting material in this reaction even when an excess of potassium isothiocyanate (6 equiv) was employed. The isolation of the material was plagued by the formation of the dimeric thiourea **11** requiring a recrystallization to purify **9**. Overall the reaction under standard conditions afforded the desired product in only a moderate yield of 65%. We postulated that the use of water as solvent and the presence of ammonium chloride leads to significant decomposition of potassium isothiocyanate,[6] thereby making a large excess of this reagent necessary to achieve acceptable conversions. We investigated alternative solvents for this conversion and the reaction proceeds well in isopropyl acetate or 2-butyl acetate in the presence of potassium isothiocyanate (1.5 equiv) and trifluoroacetic acid (2.5 equiv). At 80 °C the reaction is completed within 6–7 h. The product crystallizes out of the reaction mixture and can be isolated in 74% yield (>99% HPLC purity). The symmetric thiourea impurity **11** is formed at lower levels (<5%) and it is well rejected in the mother liqours.

The Hugerschoff reaction is the classical method for the transformation of arylthioureas into aminobenzothiazoles under oxidative conditions.[7] Treatment of arylthiourea **8** with bromine provided access to 4-methoxybenzothiazol-2-ylamine **9** in 60% yield. Closer examination of the reaction profile by HPLC revealed the formation of several impurities during this reaction. Bromination of the aromatic core results in the formation of brominated impurities **12** and **13**.[8] A recrystallization of the material is necessary to reject those impurities at this stage, otherwise carryover of related impurities into later stages of the synthetic sequence is observed. Another noteworthy byproduct of this reaction is the thiadiazole **14** (10–15%). To the best of our knowledge this byproduct has not been reported before as a result of a Hugerschoff benzothiazole synthesis. A plausible mechanism for the formation of this impurity is shown in Scheme 3. Oxidation of the sulfur with bromine, followed by reaction with another molecule of **8** and subsequent intermolecular cyclization could explain the generation of this impurity.[9] The formation of the corresponding parent compound, named Hector's base,[10] has been observed upon treatment of phenylthiourea with oxidizing agents like hydrogen peroxide. The original reaction conditions for the Hugerschoff reaction

(6) Zil'berman, E. N.; Lazaris, A. Y. *J. Gen. Chem. USSR.* **1963**, *33*, 1012.

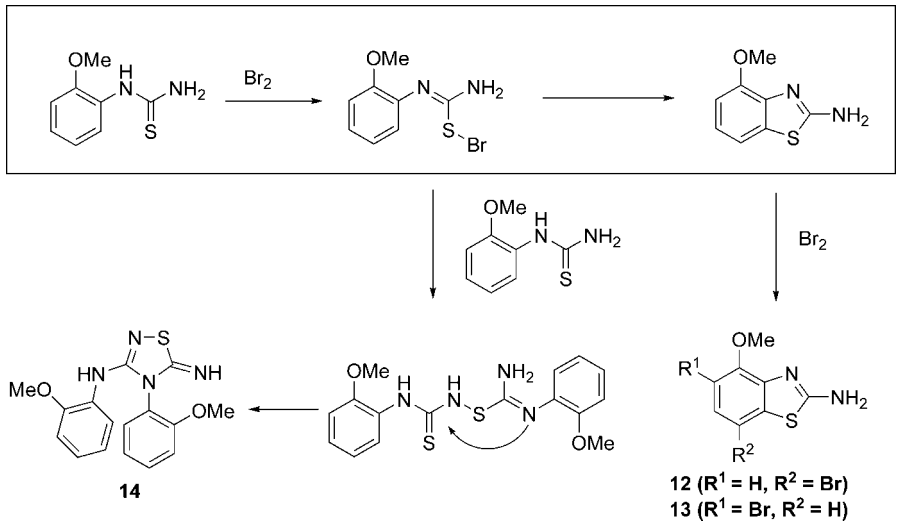
(7) (a) Hugerschoff, A. *Chem. Ber.* **1901**, *34*, 3130. (b) Hugerschoff, A. *Chem. Ber.* **1903**, *36*, 3121.

(8) Identified by LC/MS analysis.

(9) The intermediates in this proposed mechanism were not observed directly.

(10) (a) Mamaeva, E. A.; Bakibaev, A. A. *Tetrahedron* **2003**, *59*, 7521. (b) Hector, D. S. *Chem. Ber.* **1889**, *22*, 1176. (c) Butler, A. R.; Glidewell, C.; Liles, D. S. *Acta Crystallogr., Sect. B* **1978**, *34*, 3241.

SCHEME 3. Mechanism for Impurity Formation during the Hugerschoff Reaction



(bromine in dichloromethane) also presented a significant engineering challenge upon scale-up. After addition of bromine the suspension of the starting material is converted into an insoluble oil, which solidifies over time leading to large chunks of material. Stirring of the reaction mixture was difficult making recovery of the material from the reactor cumbersome. Therefore the Hugerschoff reaction was investigated by using a broad range of halogenating agents, such as Br_2, NBS, I_2, ICl, HBr, trichloroisocyanuric acid, and dibromodimethylhydantoin, in a variety of media, consisting of typical organic solvents (ethyl acetate, acetic acid, acetonitrile, dichloromethane, and THF) and inorganic and organic acids (isobutyric acid, sulfuric acid, hydrochloric acid, methanesulfonic acid, trifluoromethanesulfonic acid, trifluoroacetic acid).

This survey of conditions failed to identify major improvements over the originally used conditions. Application of recently published conditions with benzyltrimethylammonium tribromide in acetic acid[11] led to a clean reaction and isolation of the product in 80% yield. Applying considerations of atom economy and cost of goods we did not pursue the use of this reagent on scale, and instead investigated the in situ generation of tribromide ion. Reaction of thiourea **8** with 1.5 equiv of lithium bromide and 1.0 equiv of bromine in acetic acid led to a clean reaction with >95% conversion. Only 2–3% brominated impurities **12** and **13** and <1% of thiadiazole **14** was formed. The product was crystallized directly from the reaction mixture and was obtained in good yield (72%) and high purity (>99%).

Deprotection of the methyl ether **9** was initially accomplished by using hydrobromic acid under forcing conditions.[12] Although the reaction was relatively clean up to a 50 kg scale, the formation of the ring methylated impurity **15** (~2.5%, identified my LC/MS) was problematic at 200 kg scale Figure 1. This byproduct probably arises through Friedel–Crafts alkylation with either the generated bromomethane or in situ formed methanol, which could serve as precursors to methyl cation under the strongly acidic reaction conditions. The optimization of this deprotection reaction required only a minor change. The Friedel–Crafts alkylation of the product can be avoided by using a suitable trapping agent for the generated methyl species. Addition of catechol (0.3 equiv) to the reaction mixture leads to a cleaner reaction profile reducing the impurity **15** to <0.3%. The catechol is completely rejected in the isolation, and the product is still obtained in very high yield (93%). With these improvements a scaleable process for the preparation of 4-hydroxybenzothiazol-2-ylamine (**10**) was in hand.

Direct conversion of **10** into the *N*-acetylated derivative **2** failed, and preferential *O*-acetylation was observed under standard conditions.[13] Alternatively, after bisacetylation a selective cleavage of the more labile *O*-acetyl group was exploited. Standard acetylation with excess acetic anhydride in the presence of triethylamine in ethyl acetate afforded the desired bisacetylated compound in good yield (80–90%). The reaction could also be performed in THF. The selective monodeprotection was carried out with potassium hydroxide in DMSO at elevated temperature. NMP or dioxane perform equally well as solvents for this reaction. Close monitoring of the reaction by HPLC is necessary to achieve the desired conversion (<1% **16**) and to avoid overhydrolysis of the *N*-acetyl group. Even under optimized conditions (3–5 h reaction time) some overhydrolysis cannot be avoided, leading to 5–10% **10** in the crude reaction mixture. The final product **2** was isolated in good yield (80–90%) and purity (~99%, <0.5% of **10** and **16**) after addition of water to the cooled reaction mixture.

Development of the Synthesis of 1-[(*R*)-1-(4-Fluorophenyl)-ethyl]piperazine. Different routes were considered for the synthesis for the chiral piperazine fragment **6** (Scheme 4).[14] Route A involves the reductive amination of 1-(4-fluorophenyl)ethanone with a protected piperazine derivative. This

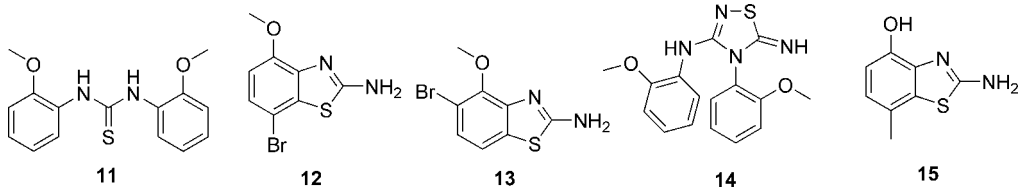
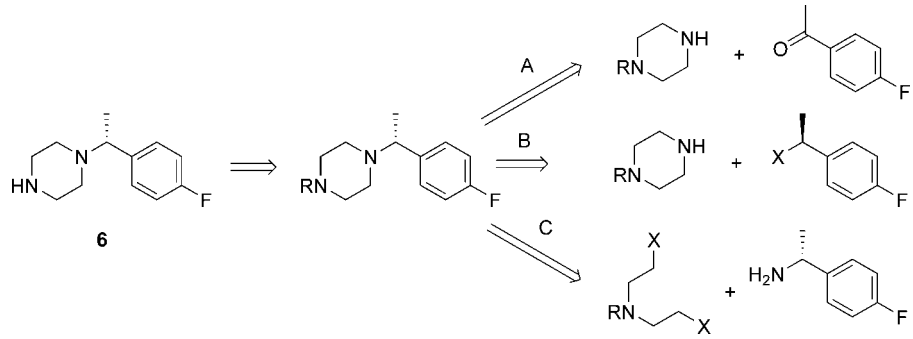
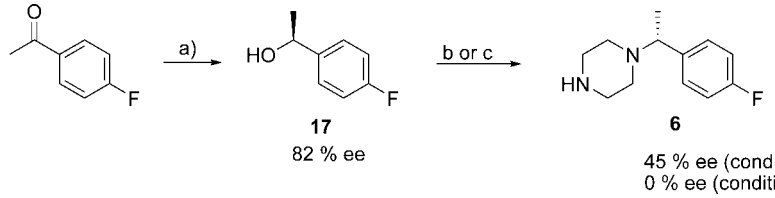


FIGURE 1. Major impurites in benzothiazole synthesis.

SCHEME 4. Retrosynthetic Analysis of Piperazine



SCHEME 5. S_N2 Approach to Piperazine[a]



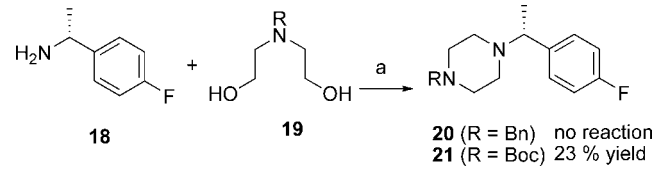
[a] Reagents and conditions: (a) (*R*)-Me-CBS-catalyst (5 mol %), BH_3-dimethylsulfide, CH_2Cl_2, 75%, 82% ee; (b) (i) MsCl, tetramethylpiperidine, acetonitrile, 0 °C, (ii) *N*-Boc-piperazine, rt, 70%, (iii) trifluoroacetic acid, CH_2Cl_2, 74%; (c) (i) HBr, heptane, (ii) piperazine, IPAc, 75%.

procedure was used in discovery, but required chiral chromatography to separate the enantiomers. Although optical resolution of *rac*-**6** was an option, the relatively late-stage resolution would make this approach inefficient.

Route B involves a stereospecific S_N2 displacement of an activated benzylic alcohol (Scheme 5).[15] Enantioselective reduction of 1-(4-fluorophenyl)ethanone afforded chiral alcohol **17** in good yield and acceptable enantiomeric excess (ee 82%).[16] Attempted isolation of the corresponding mesylate led to complete decomposition. Under optimized conditions the benzylic alcohol was transformed in situ at 0 °C to the mesylate, which was then reacted with *N*-Boc piperazine. This activation of the benzylic alcohol as the mesylate led to significant epimerization (45% ee). Complete epimerization was observed through the benzylic bromide.[17]

As chiral phenethylamines are generally readily available by enzymatic or classical resolution of the corresponding racemates,[18] as well as by enantioselective hydrogenation, the alternative formation of the piperazine ring (route C) was developed. Indeed, (*R*)-1-(4-fluorophenyl)ethylamine **18** is commercially available, providing a suitable starting material for the synthesis of AMG 628. The metal-catalyzed cyclization of diols with primary amines has been reported, occurring through a catalytic cycle involving alcohol oxidation, imine formation, and imine reduction. Most catalyst systems are ruthenium based; however, relatively high reaction temperatures are required (>150 °C).[19,20] A recently reported iridium-catalyzed version of this reaction is run at lower temperatures prompting us to investigate the potential of this method (Scheme 6).[21] The published examples include the formation of pyrrolidines, piperidines, azepanes, and morpholines, but did not include piperazines.[22] Two different derivatives of diethanolamine were prepared and subjected to the *N*-heterocyclization. The reaction was investigated with use of the conditions reported in the literature ($(Cp^*IrCl_2)_2$, K_2CO_3, toluene, 90 °C). No product could be detected when the reaction was performed with *N*-benzyl-protected diethanolamine. Gratifyingly, the reaction with the Boc-protected derivative led to the formation of the desired product, albeit in relatively low yield. On the basis of the catalytic cycle of the reaction, alternative metal catalysts that promote reversible oxidation and reduction of alcohols were investigated.[23] Several catalysts (Shvo's catalyst,[24] Park's

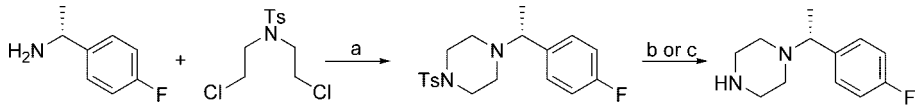
SCHEME 6. Metal-Catalyzed Piperazine Formation[a]



[a] Reagents and conditions: (a) $[Cp^*IrCl_2]_2$, K_2CO_3, toluene, 90 °C.

(11) Jordan, A. D.; Lou, C.; Reitz, A. B. *J. Org. Chem.* **2003**, *68*, 8693.
(12) Lane, T. J.; Sam, A. *J. Am. Chem. Soc.* **1961**, *83*, 2223.
(13) The following conditions were used: acetic anhydride, triethylamine, ethyl acetate, rt.
(14) An enantioselective hydroamination (for a leading reference see: Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 9546. of 4-fluorostyrene with piperazine also appears feasible, but this option was not explored due to the relatively high price of the starting material.
(15) For examples on related substrates see: (a) Arink, A. M.; Kronenburg, C. M. P.; Jastrzebski, J. T. B. H.; Lutz, M.; Spek, A. W.; Gossage, R. A.; van Koten, G. *J. Am. Chem. Soc.* **2004**, *126*, 16249. (b) Tagat, J. R.; Steensma, R. W.; McCombie, S. T. W.; Nazareno, D. V.; Lin, S.-I.; Neustadt, B. R.; Cox, K.; Xu, S.; Wojcik, L.; Murray, M. G.; Vantuno, N.; Baroudy, B. M.; Strizki, J. M. *J. Med. Chem.* **2001**, *44*, 3343.
(16) The obtained result was slightly inferior to results reported in the literature but no detailed optimization of this reaction was carried out at this point. For a reference see: Mathre, D. J.; Thompson, A. S.; Douglas, A. W.; Hoogsten, K.; Carroll, J. D.; Gorley, E. Q.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 2880.
(17) Barnett, C. J.; Huff, B.; Kobierski, M. E.; Letourneau, M.; Wilson, T. M. *J. Org. Chem.* **2004**, *69*, 7653.
(18) Ault, A. *Org. Synth.* **1969**, *49*, 93.
(19) Murahashi, S.-I.; Kondo, K.; Hakata, T. *Tetrahedron Lett.* **1982**, *23*, 229.
(20) Abbenhuis, R. A.T.M.; Boersma, J.; van Koten, G. *J. Org. Chem.* **1998**, *63*, 4282.
(21) Fujita, K.; Fujii, T.; Yamguchi, R. *Org. Lett.* **2004**, *6*, 3525.
(22) A ruthenium-catalyzed synthesis of piperazines was reported earlier (Abbenhuis, R. A. T. M.; Boersma, J.; van Koten, G. *J. Org. Chem.* **1998**, *63*, 4282.) but elevated temperatures of 180 °C were necessary. The successful examples (yields 7–34%) were limited to cyclization with anilines. No products were obtained when primary aliphatic amines were used in the reaction.

SCHEME 7. Scaleable Route to Chiral Piperazine[a]

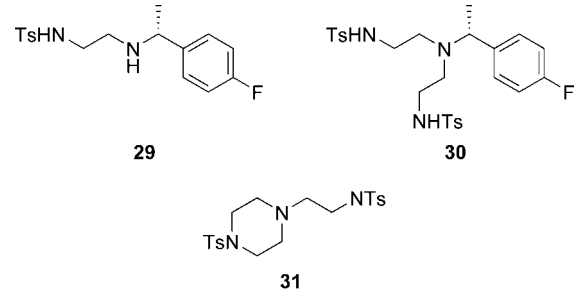


18 22 23 6

[a] (Reagents and conditions: (a) diisopropylethylamine, 125 °C, 86%; (b) HBr, AcOH, 4-hydroxybenzoic acid, rt, 2 d, 90%; (c) H_2SO_4, trifluoroacetic acid, 75 °C, 5 h, 70%, 97.4% purity, >99.0% ee.

catalyst,[25] Wilkinson's catalyst, $[Ir(COD)Cl]_2$/dppp, $(Cp^*IrCl_2)_2$, $[Cp^*RhCl_2]_2$, (indenyl)$(PPh_3)_2RuCl_2$) were screened in toluene and THF in the presence and the absence of base (KOAc, KO*t*Bu, K_2CO_3, $NaHCO_3$). Product formation was only detected when $(Cp^*IrCl_2)_2$ was used as catalyst, and no improvement over the initial result was obtained.

The synthesis of piperazines by cyclization of primary amines with bisalkylating agents has been previously reported.[26] The success of the reaction is dependent on the nature of the nitrogen-protecting group. Alkyl protecting groups on the nitrogen atom have only been used scarcely, since the nucleophilicity of the nitrogen atom would presumably lead to the formation of aziridinium intermediates that could engage in undesired side reactions. Similarly carbamate protecting groups only afford the desired products in low yields.[27] The Ts-protecting group has been used most successfully for this type of reaction.[26] Several different protecting groups on the nitrogen atom were briefly investigated, in an attempt to circumvent the Ts-protecting group. The direct cyclization of (*R*)-1-(4-fluorophenyl)ethylamine **18** with bis(2-chloroethyl)amine hydrochloride provided the desired product **5** along with unconsumed starting material **18**. Two different amide and carbamate protecting groups on the nitrogen were also investigated. Cyclization with the formyl-protected bisalkylating agent led only to trace amounts of product. Similar results were obtained with the Boc-protected bisalkylating agent; only minor amounts of the desired product were formed, instead the formation of an unidentified different product was observed. On the basis of the disappointing results with alternative protecting groups it was decided to concentrate further studies on sulfonamide protecting groups (Scheme 7). The reaction with commercially available **22** as the bisalkylating agent was performed under the conditions reported in the literature. Reaction of **18** with 1.1 equiv of **22** in diisopropylethylamine at 125 °C for 12–16 h led to complete conversion of the starting material. The isolation procedure for Ts-piperazine **23** was optimized and the product isolated by precipitation with an ethanol/water mixture. The product was obtained in 86% yield (45 g scale). A resuspension of the crude material in ethanol/water mixtures leads to improvement in the impurity profile. The impurities **29–31** were usually present in batches of **23** (Figure 2). These impurities were identified by LC/MS and their structure was confirmed by independent synthesis. All these



29 30 31

FIGURE 2. Impurities in piperazine formation.

impurities are rejected, and in the subsequent deprotection step the intermediate **6** is obtained in high purity (>99% purity).

The cleavage of *N*-toluenesulfonamides is generally difficult and often involves harsh reaction conditions. The deprotection conditions described in the literature[26a] with use of 3 equiv of 4-hydroxybenzoic acid in 10 volumes of HBr (33 wt % solution in acetic acid) afforded the desired compound in high yield. Complete conversion was obtained after 2 d at room temperature. The reaction mixture was diluted with water and the aqueous phase was washed with toluene to remove side products. After adjustment of the pH with potassium hydroxide (pH >10) the product **6** could be obtained by extraction with ethyl acetate (91% yield on 10 g scale). No racemization of the benzylic stereocenter was observed throughout this synthetic sequence. Scale-up of this sequence allowed access to multikilogram quantities of intermediate **6**. However, there were limitations to this approach. The deprotection step was sluggish upon scale-up (3–4 d at room temperature) leading to 3–5% of unreacted starting material **23** remaining. An increase in reaction temperature was not deemed appropriate, due to the volatile nature of hydrobromic acid. On the basis of literature precedent reductive conditions (RedAl and Super-Hydride)[28] were investigated but no significant conversion was observed. Further screening of the reaction conditions focused on acidic conditions, specifically sulfuric acid.[29] Various aqueous dilutions of sulfuric acid were tested, but only concentrated sulfuric acid afforded complete conversion for reactions at 75 °C. While these reaction conditions were a significant improvement over the original conditions, the workup and isolation protocol was inefficient. The large excess of sulfuric acid had to be neutralized with sodium hydroxide leading to a strongly exothermic reaction and large workup volumes. Trifluoroacetic acid was tested as an acidic cosolvent to reduce the equivalents of sulfuric acid. Under optimized conditions the reaction was performed in a mixture of trifluoroacetic acid and concentrated sulfuric acid at 75 °C. Complete conversion was observed after 5–6 h. After workup the product was isolated by crystallization from heptane (70%, 97–98% purity). The relatively low isolated yield is a reflection of the high solubility of this compound in all organic solvents;

(23) Pàmies, O.; Bäckvall, J. E. *Chem. Eur. J.* **2001**, *7*, 5052.
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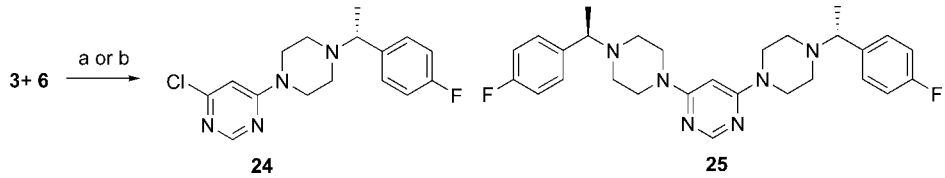
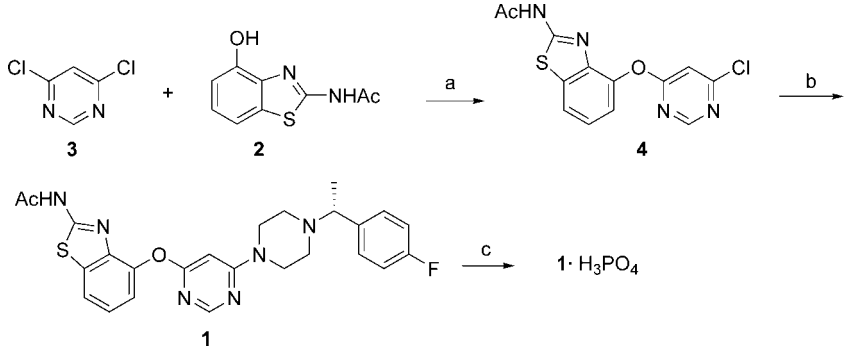
SCHEME 8. Displacements with Piperazine Nucleophile[a]



[a] Reagents and conditions: (a) DMSO or EtOH, heat, unselective reaction leading to mixtures; (b) **6** (1.1 equiv), triethylamine (1.2 equiv), DMF, 70 °C, 6 h, 100% conversion to desired product **24**.

SCHEME 9. Completion of AMG 628 Synthesis[a]



[a] Reagents and conditions: (a) **3** (1.05 equiv), potassium carbonate (1.1 equiv), dimethylacetamide, 55 °C, 90%, 98.5% purity, (b) 6 (1.1 equiv), triethylamine (1.2 equiv), dimethylformamide, 75 °C, 86%, 99.0% purity, (c) phosphoric acid (1.2 equiv), isopropyl alcohol, water, 94%, 99.6% purity.

the deprotection reaction itself is very clean. Although the crude reaction mixture containing piperazine **6** could be used directly in a coupling reaction with **4** to produce AMG 628, the piperazine was isolated to install an additional control point. Indeed, the isolation also offered the additional advantage that an upgrade in enantiomeric excess could be realized whereby Ts-piperazine **23** with 98.0% ee afforded **6** with >99.0% ee.

Coupling of the Key Building Blocks. Having established scaleable routes to both **2** and **6**, the order of the coupling steps leading to AMG 628 was evaluated. Direct reaction of 4,6-dichlorpyrimidine (**3**) with piperazine **6** in the absence of base leads to mixtures of mono- and disubstituted products **24** and **25** (Scheme 8). Conditions that allow selective monodisplacement were developed where the reaction of **3** with **6** (1.1 equiv) in the presence of triethylamine (1.2 equiv) or potassium carbonate (1.2 equiv) allows selective synthesis of intermediate **24** (<0.5% of **25**). Unfortunately this compound is a low-melting solid (mp 79 °C), therefore making its isolation as a crystalline material more difficult.

The addition of the hydroxybenzothiazole followed by the piperazine was used in the original synthesis from the discovery team and we decided to reinvestigate this strategy. Early lots of **4** were produced by coupling of **2** with 4,6-dichloropyrimidine (**3**) in refluxing acetone in the presence of K_2CO_3 (Scheme 9). The product was obtained in high yield (94–96%) and purity (97–99%). The selectivity of the reaction was usually high with only small amounts (<1.0%) of the disubstituted product **26** (Figure 2) observed, even when using equimolar amounts of the starting materials.[30] Another side product that is generated during the reaction is the deacetylated material **27**. In acetone the reaction mixture is heterogeneous throughout the reaction, since both **2** and **3** are only partially soluble, leading to relatively

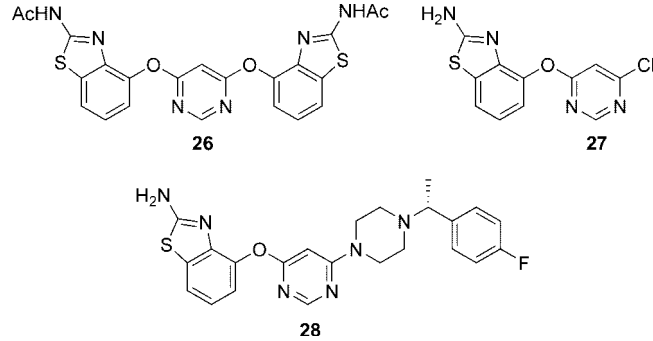


FIGURE 3. Impurities in the final coupling step.

long reaction times (15 h at 70 g scale). Concerns about the scalability of the acetone process led us to reinvestigate the conditions for the coupling reaction. Initially, the reaction was screened at room temperature in eight different solvents (DMAc, acetone, DMSO, acetonitrile, 2-methyltetrahydrofuran, butanone, ethyl acetate, isopropyl alcohol) by using a slight excess of 4,6-dichloropyrimidine (1.05 equiv) and potassium carbonate (1.1 equiv) as base. Good conversions (>90%) were observed in polar aprotic solvents like DMSO and DMAc. A similar solvent screen was conducted with triethylamine as base. Only low conversions were observed with the organic base, even when the reaction temperature was raised to 80 °C. On the basis of the initial screen the reaction in DMAc was further optimized and transformed into a scalable process. To minimize the formation of **26**, an excess of 4,6-dichloropyrimidine was used (1.05 equiv). Complete conversion was observed after 2 h (<0.5% **1**) at 55 °C. The product **4** was isolated at the end of the reaction by a simple filtration after the addition of water as the antisolvent. This procedure could be scaled up to multiple kilograms and the product was routinely obtained in good yield (85–90%) and acceptable purity (>98.0% **4**, < 0.5% **26** and <1.0% **27**) (Figure 3).

The final transformation en route to AMG 628 was the coupling of intermediate **4** with piperazine **6**. The Medicinal

(30) The equimolar amounts for the starting materials are based on stoichiometry calculation not accounting for the potency of the starting materials. It was later discovered that the starting material **2** often only has potency (wt/wt %) of 90–95%, which then de facto leads to use of excess 4,6-dichloropyrimidine in the coupling reaction.

Chemistry synthesis utilized potassium carbonate as base in DMF (80–90 °C). The reaction is fairly sluggish (incomplete conversion of **4** after 5 h), which leads to the formation of a significant amount of byproducts. Purification of the crude mixture had to be performed via column chromatography. The major byproduct is formed in as much as 28% (HPLC). The structure was identified as the bispiperazine adduct **25**. This byproduct formation highlighted the labile nature of the pyrimidine−oxygen bond toward strong nucleophiles, therefore, milder reaction conditions were screened to obtain material of higher purity. Inorganic bases, such as sodium bicarbonate and sodium carbonate, led to cleaner reaction profiles. Sodium bicarbonate was used as base in the initial scale-up. The reaction was performed in DMF at 90 °C with sodium bicarbonate (3 equiv) as base. The reaction was complete after 2.5 h and the product could be isolated by simple addition of water. Some shortcomings were observed with this procedure. Large volumes of water had to be used to ensure a good recovery and rejection of the inorganic salts, making the procedure inherently inefficient.[31]

Interestingly, the reaction could be performed in the absence of any external base, although it stalled at approximately 60% conversion. We speculated that an organic base might be sufficient to trap the liberated hydrochloric acid allowing the reaction to reach completion. Triethylamine, diisopropylethylamine, and tetramethylpiperidine were demonstrated to be suitable bases, but ultimately the first was chosen. The reaction is best performed with use of a slight excess of **6** (1.05 equiv) and triethylamine (1.2 equiv) in DMF providing complete conversion after 3 h at 75 °C. The product is isolated from a DMF/isopropyl alcohol/water mixture in high yield (86%) and purity with less than <0.5% of the deacetylated impurity **28**. The triethylammonium chloride salts that are formed during the reaction are fully rejected in the mother liqours. The phosphate salt of AMG 628 was chosen as a suitable pharmaceutical form for development due to its desirable properties. This salt is obtained in high yield (91–94%) and purity (>99.0%) by treatment of the free base with phosphoric acid in a mixture of isopropyl alcohol and water.

Summary

A concise synthesis of the TRPV1 antagonist AMG 628 was developed. In the course of our studies a scaleable process for the synthesis of hydroxybenzothiazole **2** in five steps and 36% overall yield from *o*-anisidine was developed. In these studies valuable insights into the Hugerschoff reaction were gained and a new reagent mixture consisting of LiBr/Br_2 was identified. A scaleable route to piperazine **6** was also established. In the course of these studies optimized reaction conditions for the deprotection of toluenesulfonamides were developed which should be applicable to related systems. The key building blocks were assembled in two highly efficient and selective coupling steps to afford the desired target compound AMG 628 phosphate in three steps and 73% overall yield. Especially noteworthy is the use of a mild organic base to promote the final coupling reaction, thus avoiding reaction at the labile C−O bond.

Experimental Section

1-[(*R*)-1-(4-Fluorophenyl)ethyl]-4-(toluene-4-sulfonyl)piperazine (23). (*R*)-1-(4-Fluorophenyl)ethylamine (**18**, 1.00 kg, 7.18 mol), *N*,*N*-bis(2-chloroethyl)-4-toluenesulfonamide (**22**, 2.13 kg, 7.18 mol), and diisopropylethylamine (2.495 L, 14.32 mol) were charged to a glass-lined reactor. The reaction mixture was heated to reflux (∼130 °C) for 36 h. The progress of the reaction is monitored by GC; the reaction is complete once **18** is <1%. The reaction mixture is transferred into a mixture of deionized water (6 L), ice (20 kg), potassium carbonate (7 kg), and dichloromethane (25 L). The layers are separated and the aqueous layer is extracted with dichloromethane (3 × 5 L). The combined organic layers are treated with activated charcoal, dried over magnesium sulfate, and then evaporated to dryness under vacuum. The resulting residue is triturated with hexane (10 L), and the mixture is aged at 0 °C for 30 min. The solids were isolated by vacuum filtration. The reactor was rinsed with cold hexane (3 × 4 L) and the rinse was transferred to the filter as a cake wash. The material was dried on the filter under a stream of nitrogen. The product is obtained as an off-white crystalline solid (2.50 kg, 96% yield). Mp 129 °C. IR 1343, 1221, 1162, 1116, 956, 839, 819, 732, 655, 646, 629, 582, 546, 514 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.63 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 7.16–7.23 (m, 2H), 6.92–7.00 (m, 2H), 3.36 (q, J = 6.9 Hz, 1H), 2.89–3.03 (m, 4H), 2.50–2.62 (m, 2H), 2.40–2.47 (m, 5H), 1.29 (d, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 161.8 ($^1J_{CF}$ = 245 Hz), 143.5, 139.1, 132.4, 129.6, 128.9 ($^3J_{CF}$ = 8 Hz), 127.9, 115.0 ($^2J_{CF}$ = 21 Hz), 63.6, 49.4, 46.3, 21.5, 19.4. HRMS *m/e* calcd for $C_{19}H_{24}FN_2O_2S$ (M + H) 363.1537, found 363.1533.

1-[(*R*)-1-(4-Fluorophenyl)ethyl]piperazine (6). Trifluoroacetic acid (8.4 L) was charged to a glass-lined reactor, efficient stirring was established, and the reaction mixture was cooled to 5 °C. 1-[(*R*)-1-(4-Fluorophenyl)ethyl]-4-(toluene-4-sulfonyl)piperazine (**23**, 4.18 kg, 11.5 mol) was charged in portions, while keeping the internal temperature <20 °C. Concentrated sulfuric acid (4.18 L) was added slowly, controlling the exothermic acid–base reaction. The reaction mixture is heated to 75 °C and the reaction progress was monitored by HPLC. Complete consumption of **23** (<0.5%) was observed after 6 h. The reaction mixture was cooled to 5 °C and deionized water (33.0 L) was charged while maintaining a temperature of <20 °C. The pH of the solution was adjusted to 8.0 ± 0.5 by addition of 10 N aqueous sodium hydroxide while maintaining a temperature of <20 °C. The aqueous layer was extracted with isopropyl acetate (4 × 10.5 L). The combined organic phases were washed with 1 N NaOH (2 × 10.5 L). The organic phase was returned to the reactor and the solvent was removed by distillation under reduced pressure, until 12–13 L remained. Heptane (12.6 L) was added and the solvent was removed by distillation under reduced pressure until 12–13 L remained. Heptane (12.6 L) was added and the solvent was removed by distillation under reduced pressure until 7 L remained. The mixture was cooled to –10 °C and then aged at this temperature for 2 h. The solids were isolated by vacuum filtration. The reactor was rinsed with cold heptane (2 L) and the rinse was transferred to the filter as a cake wash. The material was dried on the filter under a stream of nitrogen for 1 h and then transferred to a vacuum oven. The material was dried at 45 °C for 15 h. The product is obtained as an off-white crystalline solid (1.68 kg, 70% yield, 97.74% purity by HPLC). Mp 70 °C. IR 3263, 2942, 2805, 1600, 1506, 1449, 1378, 1216, 1154, 1123, 1097, 933, 846, 824, 773, 741, 646, 576, 544, 480 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.26–7.30 (m, 2H), 6.95–7.06 (m, 2H), 3.33 (q, J = 6.8 Hz, 1H), 2.82–2.88 (m, 4H), 2.40–2.50 (m, 1H), 2.28–2.37 (m, 2H), 2.01–2.09 (m, 2H), 1.33 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 161.7 ($^1J_{CF}$ = 245 Hz), 139.5, 129.0 ($^3J_{CF}$ = 8 Hz), 114.8 ($^2J_{CF}$ = 21 Hz), 64.5, 51.7, 46.2, 19.5. Anal. Calcd for $C_{12}H_{19}FN_2O$ (**5** monohydrate): C, 63.69; H, 8.46; N, 12.38. Found: C, 63.81; H, 8.35; N, 12.31. HRMS *m/e* calcd for $C_{12}H_{18}FN_2$ (M + H) 209.1449, found 209.1450.

***N*-[4-(6-Chloropyrimidin-4-yloxy)benzothiazol-2-yl]acetamide (4).** Dimethylacetamide (8.8 L), 4,6-dichloropyrimidine (**3**, 1.377 kg, 9.24 mol), *N*-(4-hydroxy-benzothiazol-2-yl)-acetamide (**2**, 1.832 kg, 8.80 mol), and potassium carbonate (1.338 kg, 9.68 mol) were

(31) An additional suspension in ethanol/water, followed by filtration was needed to reduce the content of DMF in the API (∼4000 ppm in the crude material).

charged to a glass-lined reactor and the reaction mixture was heated to 55 °C; the reaction progress was monitored by HPLC. Complete consumption of **2** (<0.5%) was observed after 2 h. The reaction mixture was cooled to 10 °C. Deionized water (8.8 L) was charged while maintaining a temperature of <20 °C. The product appeared as crystalline material during this addition. The contents of the reactor were cooled to 10 °C and aged at this temperature for 2 h. The solids were isolated by vacuum filtration. The reactor as rinsed with deionized water (1 × 4.4 L and 4 × 2.2 L) and the rinse was transferred to the filter as a cake wash. The material was dried on the filter under a stream of nitrogen for 1 h and then transferred to a vacuum oven. The material was dried at 60 °C for 36 h. The product is obtained as an off-white crystalline solid (2.54 kg, 90% yield, 98.47% purity by HPLC). The isolated solids contained <0.5% of *N*-{4-[6-(2-acetylaminobenzothiazol-4-yloxy)pyrimidin-4-yloxy]benzothiazol-2-yl}acetamide (**26**) and 4-(6-chloropyrimidin-4-yloxy)benzothiazol-2-ylamine (**27**). Mp 260 °C. IR 1541, 1446, 1419, 1339, 1294, 1268, 1251, 1227, 1177, 1096, 984, 957, 894, 865, 845, 792, 754, 745, 721 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.43 (s, 1H), 8.59 (s, 1H), 7.93 (dd, J = 7.4, 1.4 Hz, 1H), 7.49 (s, 1H), 7.37 (dd, J = 8.0, 7.6 Hz, 1H), 7.32 (dd, J = 8.0, 1.4 Hz, 1H), 2.14 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 169.9, 169.7, 160.9, 158.9, 158.6, 143.0, 141.1, 133.7, 124.0, 119.9, 118.8, 107.7, 22.7. Anal. Calcd for $C_{13}H_9ClN_4O_2S$: C, 48.68; H, 2.83; N, 17.47. Found: C, 48.39; H, 2.91; N, 17.24.

***N*-[4-(6-{4-[(*R*)-1-(4-Fluorophenyl)ethyl]piperazin-1-yl}pyrimidin-4-yloxy)benzothiazol-2-yl]acetamide (1).** Dimethylformamide (9.47 L), *N*-[4-(6-chloro-pyrimidin-4-yloxy)benzothiazol-2-yl]acetamide (**4**, 2.374 kg, 7.40 mol), and 1-[(*R*)-1-(4-fluorophenyl)ethyl]piperazine (**6**, 1.695 kg, 8.14 mol) were charged to a glass-lined reactor. Efficient stirring was established and triethylamine (1.240 L, 8.89 mol) was added at room temperature. The reaction mixture was heated to 75 °C, and the reaction progress was monitored by HPLC. Complete consumption of **4** (<0.5%) was observed after 3 h. The reaction mixture was cooled to rt and a polish filtration through a glass frit (porosity M) was performed, then the reactor and the filter were rinsed with dimethylformamide (1.2 L). The crude reaction mixture was transferred back into the reactor and 3.6 L of solvent was removed by vacuum distillation. Isopropyl alcohol (19.0 L) was charged to the reactor while maintaining a temperature of >60 °C. The product appeared as crystalline material during this addition. Subsequently, deionized water (13.1 L) was charged while maintaining the temperature at >60 °C. The contents of the reactor were cooled to 10 °C and aged at this temperature for 30 min. The solids were isolated by vacuum filtration. The reactor was rinsed with isopropyl alcohol (2 × 4.8 L) and the rinse was transferred to the filter as a cake wash. The material was dried on the filter under a stream of nitrogen for 14 h and then transferred to a vacuum oven. The material was dried at 60 °C for 48 h. The product is obtained as an off-white crystalline solid (3.15 kg, 86% yield, 98.98% purity by HPLC). Mp 249 °C. IR 1695, 1600, 1566, 1540, 1506, 1452, 1287, 1274, 1264, 1219, 1201, 1185, 1154, 1014, 1002, 836, 820, 746, 552 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.42 (s, 1H), 8.06 (s, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.30–7.40 (m, 3H), 7.12–7.22 (m, 3H), 6.32 (s, 1H), 3.57 (m, 4H), 3.50 (q, J = 6.8 Hz, 1H), 2.41–2.49 (m, 2H), 2.32–2.39 (m, 2H), 2.15 (s, 3H), 1.31 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 169.8, 169.4, 163.6, 161.0 ($^1J_{CF}$ = 242 Hz), 157.9, 157.3, 144.1, 141.7, 139.1 ($^4J_{CF}$ = 3 Hz), 133.3,129.2 ($^3J_{CF}$ = 8 Hz), 124.0, 119.2, 118.9, 114.8 ($^2J_{CF}$ = 20 Hz), 85.7, 62.7, 49.4, 43.9, 22.6, 19.1. HRMS *m/e* calcd for $C_{25}H_{26}FN_6O_2S$ (M + H) 493.1817, found 493.1803.

***N*-[4-(6-{4-[(*R*)-1-(4-Fluorophenyl)ethyl]piperazin-1-yl}pyrimidin-4-yloxy)benzothiazol-2-yl]acetamide Phosphate (1·H_3PO_4).** *N*-[4-(6-{4-[(*R*)-1-(4-fluorophenyl)ethyl]piperazin-1-yl}pyrimidin-4-yloxy)-benzothiazol-2-yl]acetamide (**1**, 2900 g, 5.88 mol), isopropyl alcohol (25.6 L), and deionized water (4.4 L) were charged to a glass-lined reactor. Efficient stirring was established. The reaction mixture was heated to 65 °C and a solution of phosphoric acid (410.3 mL, 7.05 mol) in isopropyl alcohol (1.5 L) was charged at this temperature. The solids dissolved completely and after approximately 30 min the salt precipitated as a crystalline solid. The mixture was held at 65 °C for 2 h and then cooled to 20 °C. The solids were isolated by vacuum filtration after aging for 2 h. The reactor was rinsed with isopropyl alcohol (2 × 5.8 L) and the rinse was transferred to the filter as a cake wash. The material was dried on the filter for 1 h and transferred to a vacuum oven. The material was dried at 60 °C for 19 h. The product is obtained as a white crystalline solid (3.28 kg, 94% yield, 99.56% pruity by HPLC, ee 99.5%, 3800 ppm isopropyl alcohol). Mp 243 °C. IR 1596, 1566, 1548, 1292, 1227, 1197, 1180, 1110, 1095, 1069, 1014, 994, 976, 952, 845, 808, 741, 523, 515, 487, 447, 416 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.44 (s, 1H), 8.08 (s, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.35–7.42 (m, 2H), 7.29–7.33 (m, 1H), 7.13–7.20 (m, 3H), 6.34 (s, 1H), 3.61 (m, 5H), 2.49–2.58 (m, 2H), 2.34–2.47 (m, 2H), 2.16 (s, 3H), 1.36 (d, J = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 169.9, 169.5, 163.6, 161.3 ($^1J_{CF}$ = 244 Hz), 158.0, 157.3, 144.1, 141.7, 138.3, 133.4,129.5 ($^3J_{CF}$ = 8 Hz), 124.0, 119.2, 118.9, 115.0 ($^2J_{CF}$ = 20 Hz), 85.8, 62.9, 49.3, 43.5, 22.6, 18.8. Anal. Calcd for $C_{25}H_{28}FN_6O_6PS$: C, 50.84; H, 4.78; N, 14.23. Found: C, 50.55; H, 4.81; N, 13.98. HRMS *m/e* calcd for $C_{25}H_{26}FN_6O_2S$ (M + H) 493.1817, found 493.1807.

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Supporting Information Available: Copies of ^1H NMR and ^{13}C NMR spectra for compounds **1**, **1**·H_3PO_4, **2**, **4**, **6**, **10**, **14**, **16**, **23**–**29**, and **31**, copies of ^1H NMR for compounds **8**, **9** and **17**, experimental procedures and characterization data for compounds **2**, **8**–**10**, **14**, and **16**, and characterization data for compounds **24**–**31**. This material is available free of charge via the Internet at http://pubs.acs.org.

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