Design of Potent, Orally Available Antagonists of the Transient Receptor Potential Vanilloid 1. Structure−Activity Relationships of 2-Piperazin-1-yl-1*H*-benzimidazoles

Vassil I. Ognyanov,*[,†] Chenera Balan,[†] Anthony W. Bannon,[‡] Yunxin Bo,[†] Celia Dominguez,[†] Christopher Fotsch,[†] Vijay K. Gore,[†] Lana Klionsky,[‡] Vu V. Ma,[†] Yi-Xin Qian,[†] Rami Tamir,[‡] Xianghong Wang,[†] Ning Xi,[†] Shimin Xu,[†] Dawn Zhu,[‡] Narender R. Gavva,[‡] James J. S. Treanor,[‡] and Mark H. Norman[†]

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

Received January 19, 2006

The vanilloid receptor-1 (VR1 or TRPV1) is a membrane-bound, nonselective cation channel that is predominantly expressed by peripheral neurons sensing painful stimuli. TRPV1 antagonists produce antihyperalgesic effects in animal models of inflammatory and neuropathic pain. Herein, we describe the synthesis and the structure−activity relationships of a series of 2-(4-pyridin-2-ylpiperazin-1-yl)-1*H*-benzo-[*d*]imidazoles as novel TRPV1 antagonists. Compound **46ad** was among the most potent analogues in this series. This compound was orally bioavailable in rats and was efficacious in blocking capsaicin-induced flinch in rats in a dose-dependent manner. Compound **46ad** also reversed thermal hyperalgesia in a model of inflammatory pain, which was induced by complete Freund's adjuvant (CFA).

Introduction

The vanilloid receptor-1 (VR1 or TRPV1)[1] is a polymodal nociceptor that belongs to the family of the transient receptor potential (TRP) ion channels. The highly Ca^{2+} permeable TRPV1 receptor is predominantly expressed in sensory neurons[2−4] and is involved in the detection of painful stimuli. The endogenous activators of TRPV1 are generated as a result of tissue injury and inflammatory conditions in research animals[5−7] and in humans[8,9] and include heat (>42 °C), protons (pH 5),[10] and ligands such as the endocannabinoid anandamide[11] and lipoxygenase metabolites.[12] TRPV1 is also activated by exogenous ligands such as the vanilloid capsaicin (**1**)[2] and its ultrapotent analogue resiniferatoxin (RTX, **2**) (Figure 1).[13]

TRPV1 hyperstimulation by capsaicin has an analgesic effect, since it leads to long-term desensitization of the sensory neurons to additional agonist challenges, including noxious stimuli such as heat and acid. Capsaicin is the active component of various topical muscle pain relievers, and both capsaicin and RTX have been used to treat the pain associated with diabetic neuropathy and arthritis.[2,4] The clinical uses of TRPV1 agonists such as capsaicin, however, are limited due to side effects of a burning sensation, irritation and neurotoxicity[3] resulting from the continuous influx of Ca^{2+} ions into the cells. On the other hand, blockade of the pain-signaling pathway with a TRPV1 antagonist represents a promising strategy for the development of novel analgesics[14] with potentially fewer side effects. This rationale is also supported by the observation that thermal hyperalgesia is reduced in inflammatory pain models in knockout mice lacking the TRPV1 gene.[15,16]

Capsazepine (**3**)[17] (Figure 1), the first reported competitive antagonist of TRPV1, emerged as a result of structure−activity relationship (SAR) studies of capsaicin. It was demonstrated that capsazepine blocks the capsaicin-induced uptake of Ca^{2+} in neonatal rat dorsal root ganglia and shows species-dependent efficacies in various in vivo models of inflammatory hyperalgesia and chronic pain.[18−20] However, it was also found that capsazepine blocks receptors other than TRPV1, such as voltage-gated Ca^{2+} channels[21] and nicotinic acetylcholine receptors,[22] and does not act as an antagonist when the TRPV1 channel is activated by heat or acid.

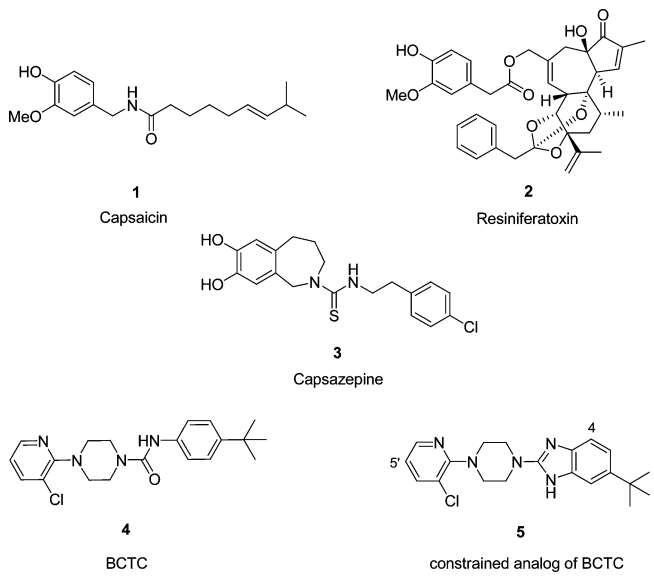


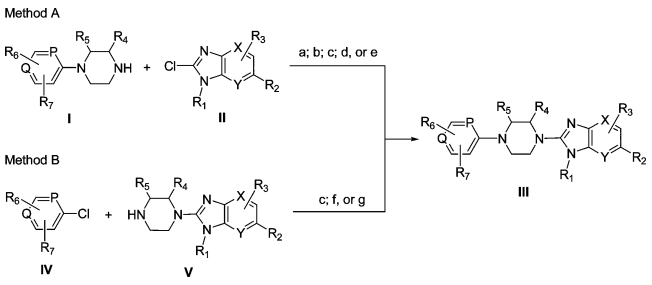
Figure 1. The TRPV1 agonists capsaicin and resiniferatoxin and selected examples of TRPV1 antagonists.

During the past few years, several classes of TRPV1 antagonists, either structurally related or not to the exogenous agonists capsaicin and RTX, have been described, and their chemistry and pharmacology have been reviewed.[23−26] One extensively studied class of TRPV1 antagonists is based on urea templates.[23,24,27−29] For example, the potent TRPV1 antagonist *N*-(4-*tert*-butylphenyl)-4-(3-chloropyridin-2-yl)piperazine-1-carboxamide (BCTC) (**4**)[30] (Figure 1) is a member of a well-studied chemical series of urea-based TRPV1 antagonists that contains a piperazine-1-carboxamide template. The BCTC template was disclosed for the first time by Neurogen[31] and more recently by Johnson & Johnson,[32] Bayer,[33] GlaxoSmithKline,[34] Abbott,[35] and Purdue Pharma.[36] While BCTC was found to be efficacious

* To whom correspondence should be addressed. Tel: 805-447-1509. Fax: 805-480-1337. E-mail: vassilo@amgen.com.
† Department of Chemistry Research and Discovery.
‡ Department of Neuroscience.

10.1021/jm060065y CCC: $33.50
Published on Web 05/19/2006

Scheme 1[a,b]



[a] R_1 = H; X, Y, P, and Q = C or N. [b]Conditions: (a) *N*,*N*-diisopropylethylamine, CH_3CN, 180 °C, microwave; (b) *N*,*N*-diisopropylethylamine, DMSO, 80 °C; (c) Et_3N, CuI, 3-methyl-1-butanol, 220 °C, microwave; (d) *N*,*N*-diisopropylethylamine, dioxane, 190 °C, microwave; (e) $NaHCO_3$, 3-methyl-1-butanol, 150 °C, microwave; (f) *N*,*N*-diisopropylethylamine, 250 °C, microwave; (g) K_2CO_3, Cu powder, DMF, 120 °C.

in animal models of chronic pain, it has shown poor metabolic stability, a short half-life, poor aqueous solubility, and moderate oral bioavailability.[36]

As a continuation of our efforts to identify novel TRPV1 antagonists with improved bioavailability, we have investigated conformationally constrained analogues of BCTC. We have found that the rigidified analogue **5** (Figure 1), designed by the isosteric replacement of the amide bond of BCTC (**4**) with an imidazole ring,[37] behaved as a relatively potent TRPV1 antagonist. Herein, we describe the synthesis and biological activity of a series of 2-(4-pyridin-2-ylpiperazin-1-yl)-1*H*-benzo[*d*]-imidazoles of type **5** as novel TRPV1 class of antagonists based on constrained analogues of BCTC (Figure 1). Recently, we were the first to disclose this novel 2-piperazin-1-yl-1*H*-benzimidazole template in a patent application.[38,39] In this paper, we include an extensive SAR data set, which provides insights into the binding mode of this novel class of TRPV1 antagonists.

For the purposes of our study, we employed rat TRPV1 channel recombinantly expressed in Chinese hamster ovary (CHO) cells. The ability of compounds to inhibit both the capsaicin- and pH-mediated influx of $^{45}Ca^{2+}$ was examined. This investigation provided an understanding of the SAR of this class of compounds, resulting in the discovery of a potent new TRPV1 antagonist (e.g., compound **46ad**) with good oral bioavailability and in vivo activity in animal models of pain.

Chemistry

The majority of the compounds required for our SAR study, represented by structure **III**, were prepared by two general routes (methods A and B, Scheme 1). In method A, *N*-aryl- and *N*-heteroarylpiperazines of type **I** were coupled with 2-chloro-1*H*-benzimidazoles and related heterocycles of type **II** by heating under conventional or microwave-assisted conditions in the presence of a base. A similar type of *N*-arylation reaction is utilized in method B, where chloro-heteroaromatic compounds of type **IV** were coupled with 2-piperazinyl-1*H*-benzimidazoles of type **V**.

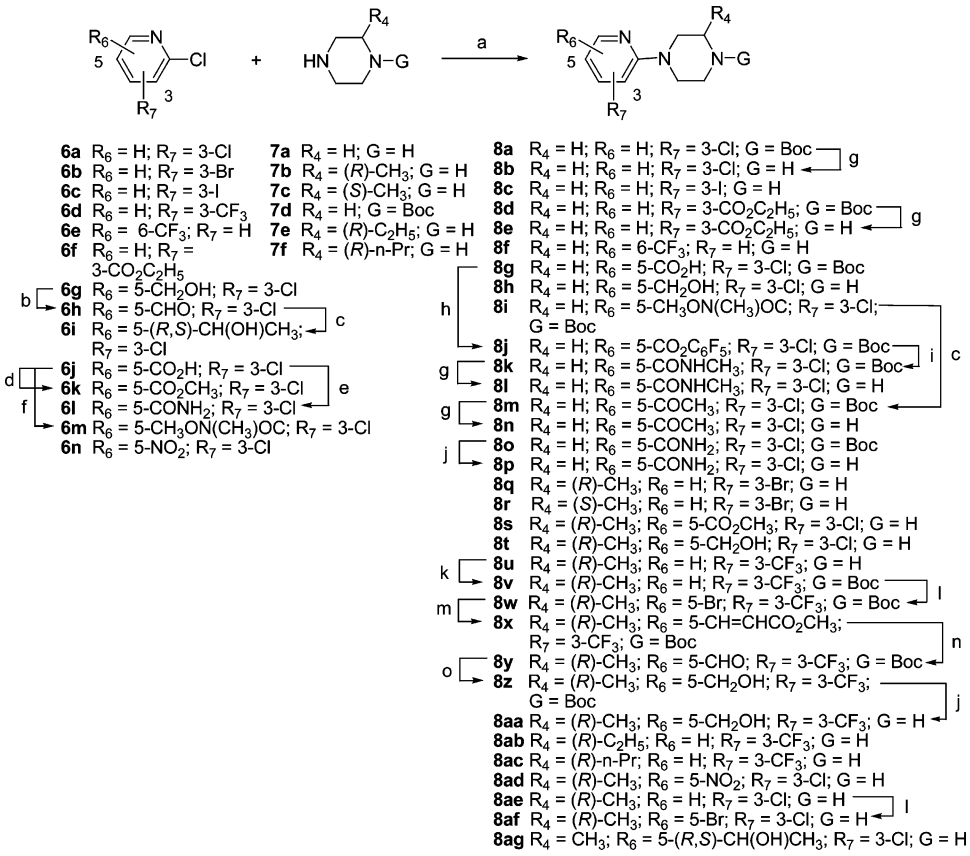
Schemes 2 and 3 detail the synthesis of the piperazine building blocks of type **I** that were employed in general method A. For example, the mono- and disubstituted 2-chloropyridines **6a**−**n** were coupled with unprotected and Boc-protected piperazines **7a**−**f** in the presence of a tertiary amine and K_2CO_3 or $NaHCO_3$ to give 1-pyridin-2-ylpiperazines **8a**, **8c,d**, **8f**−**i**, **8o**, **8q**−**u**, **8ab**−**8ae**, and **8ag**, respectively. The 2-chloropyridines **6a**−**g** and **6j** were obtained from commercial sources, and **6n** was prepared according to the method of Koch and Schnatterer,[40] while the aldehyde **6h** and the alcohol **6i** were prepared from the hydroxymethyl derivative **6g**. Ester **6k** and amides **6l** and **6m** were prepared from the carboxylic acid **6j** as illustrated in Scheme 2. The Boc protecting group of the 4-pyridin-2-ylpiperazines **8a**, **8d**, **8k**, and **8m** and was removed with a saturated solution of HCl gas in ethyl acetate, while trifluoroacetic acid was used for the deprotection of **8o** and **8z**. Carbodiimide-assisted esterification of the 5-carboxylic acid **8g** with 2,3,4,5,6-pentafluorophenol gave the ester **8j**, which upon treatment with methylamine yielded the *N*-methylamide **8k**. Ketone **8m** was prepared by treatment of the Weinreb amide **8i** with methylmagnesium bromide. The Boc protecting group of **8v** was introduced by treating the piperazine derivative **8u** with Boc anhydride in the presence of 1 N NaOH. Treatment of the 4-pyridin-2-ylpiperazines **8v** and **8ae** with bromine in dichloromethane afforded the corresponding 5-bromo-substituted derivatives **8w** and **8af**, respectively. Heck olefination of the Boc-protected 5-bromo derivative **8w** with methyl acrylate gave alkene **8x**. Dihydroxylation of the alkene **8x** with catalytic osmium tetroxide and stoichiometric *N*-methylmorpholine *N*-oxide[41] gave a glycol intermediate, which subsequently underwent oxidative C−C cleavage with lead tetraacetate to produce aldehyde **8y**. Reduction of the aldehyde **8y** with sodium borohydride afforded the 5-hydroxymethyl derivative **8z**.

Additional piperazine building blocks of type **I** were prepared as shown in Scheme 3. Under microwave irradiation, (*R*)-2-methylpiperazine (**7b**) was coupled with the 2-chloropyridine **6b** to give the corresponding mixture of products of *N*-arylation **9** and **8q** (Scheme 3). Separation of the mixture by column chromatography gave access to pure **9**, which was formed by arylation of the more hindered nitrogen atom of the piperazine **7b**. The 4-chloro-substituted pyridines **10a** and **10b** were coupled with *N*-Boc-protected piperazine (**7d**) in the presence of base to give the 1-pyridin-4-ylpiperazines **11a** and **11c**, respectively. The 6-chloropyrimidine **10c**[42] was reacted with **7d** in an analogous manner to produce 4-piperazin-1-ylpyrimidine **11e**. The Boc protecting group of 4-pyridin-4-ylpiperazine **11a** was cleaved with trifluoroacetic acid, while in the case of **11c** and **11e** the deprotection was achieved with a saturated solution of HCl gas in ethyl acetate. Finally, condensing the aniline **12** with bis(2-chloroethyl)amine hydrochloride (**13**) under microwave irradiation without any solvent[43] gave rise to the 1-phenylpiperazine **14**.

The piperazines used in the preparation of the *N*-aryl- and *N*-heteroarylpiperazines of type **I** (Schemes 1−3) and 2-piperazinyl-1*H*-benzimidazoles of type **V** (Schemes 1 and 7) were commercially available or were synthesized according to the methods shown in Scheme 4. Coupling of the *N*-Fmoc protected amino acids **15a** and **15b** with glycine methyl ester in the presence of PS-carbodiimide furnished amides **16a** and **16b**, which underwent intramolecular cyclization after treatment with piperidine to give the corresponding diketopiperazines **17a** and **17b**. Subsequent reduction of **17a** and **17b** with $LiAlH_4$ gave the target 2-alkyl-substituted piperazines **7e** and **7f**, respectively.

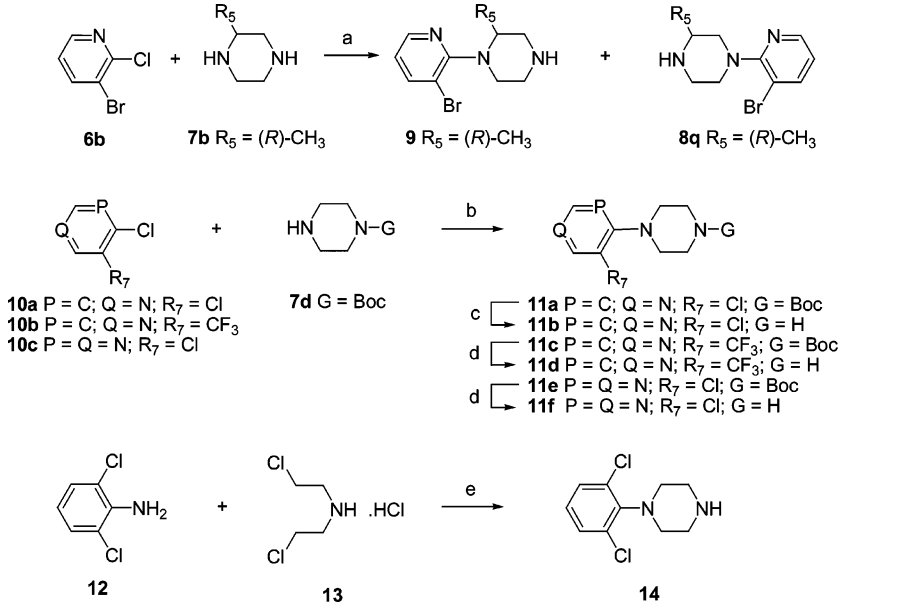
Scheme 5 describes the preparation of 2-chloro-1*H*-benzimidazoles of type **II** required for the synthesis of the TRPV1 antagonists by general method A, Scheme 1. The 1,2-diaminoarenes **18a**−**n** were converted into the 2-chloro-1*H*-benzimidazoles **20a**−**o** via the imidazolones **19a**−**o**. 1,1′-Carbonyldiimidazole was used as carbonylating reagent for the preparation of imidazolones **19a**−**d**, **19f**−**h**, and **19j**−**o**, while in the case of **19e** *N*,*N*-disuccinimidyl carbonate was employed. The 4-aryl-substituted imidazolone **19i** was prepared by microwave-assisted Suzuki arylation of the 4-bromobenzimidazolone **19f**.

Scheme 2[a]



[a] Conditions: (a) for **8a**, **8g**, **8h**, **8i**, **8o**, **8s**−**u**, and **8ag**, Cu-powder, K_2CO_3, DMF, 120 °C; for **8c**, **8d**, **8f**, **8q**, **8r, 8ad,** and **8ae**, *N*,*N*-diisopropylethylamine, NMP, 240 °C, microwave; for **8ab** and **8ac**, $NaHCO_3$, 3-methylbutan-1-ol, 170 °C, microwave; (b) MnO_2, 1:1 CH_2Cl_2/hexane, 20 °C; (c) 3 M MeMgBr in Et_2O, THF, 20 °C; (d) *p*-TsOH, MeOH, reflux; (e) (1) $(COCl)_2$, DMF, 20 °C; (2) 28% NH_4OH, 20 °C; (f) (1) $(COCl)_2$, DMF, 20 °C; (2) CH_3ONHCH_3·HCl, 10% K_2CO_3, CH_2Cl_2, 20 °C; (g) sat. solution of HCl in EtOAc, 20 °C; (h) 2,3,4,5,6-pentafluorophenol, 1,3-dicyclohexylcarbodiimide, EtOAc, 20 °C; (i) 2 M $MeNH_2$ in THF, 20 °C; (j) TFA, CH_2Cl_2, 20 °C; (k) O(COO-*t*-Bu)$_2$, 1 N NaOH, THF, 20 °C; (l) Br_2, CH_2Cl_2, 20 °C; (m) CH_2═$CHCO_2Me$, $Pd(OAc)_2$, benzyltriethylammonium chloride, DMF, 40 °C; (n) (1) 4% OsO_4 in H_2O, *N*-methylmorpholine *N*-oxide, acetone, 20 °C; (2) $Pb(OAc)_4$, CH_2Cl_2, 20 °C; (o) $NaBH_4$, MeOH, 0 °C;

Scheme 3[a]

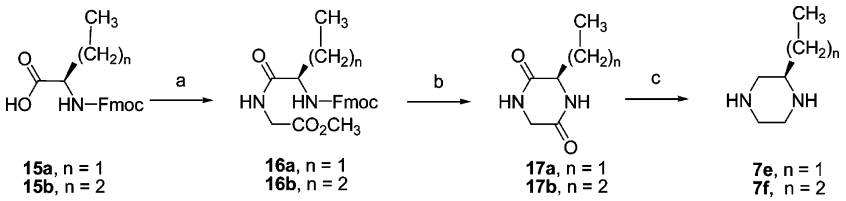


[a] Conditions: (a) *N*,*N*-diisopropylethylamine, NMP, 240 °C, microwave; (b) Cu-powder, K_2CO_3, DMF, 120 °C; (c) TFA, CH_2Cl_2, 20 °C; (d) sat. solution of HCl in EtOAc, 20 °C; (e) (1) 200 °C, microwave; (2) 1 N NaOH.

Finally, chlorination of the benzimidazolones **19a**−**o** with phosphorus oxychloride provided the necessary 2-chloro-1*H*-benzimidazole intermediates **20a**−**o**.

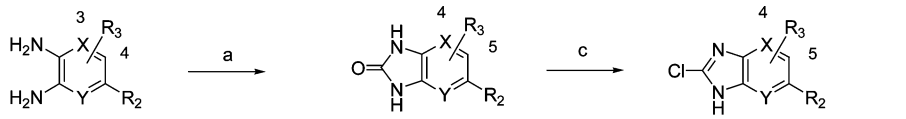
The 1,2-diaminoarenes **18b**−**e** used in the preparation of the 2-chloro-1*H*-benzimidazoles **20b**−**e** were synthesized according to the reactions illustrated in Scheme 6. Acetylation of aniline

Scheme 4[a]



[a] Conditions: (a) $MeO_2CCH_2NH_2 \cdot HCl$, 1-hydroxy-7-azabenzotriazole, *N*,*N*-diisopropylethylamine, PS-carbodiimide, CH_2Cl_2, 20 °C; (b) piperidine, CH_2Cl_2, 20 °C; (c) $LiAlH_4$, THF, reflux.

Scheme 5[a,b]



18a R_2 = *t*-Bu; R_3 = H; X = Y = C
18b R_2 = CF_3; R_3 = 4-Br; X = Y = C
18c R_2 = CF_3; R_3 = 3-NO_2; X = Y = C
18d R_2 = CF_3; R_3 = H; X = N; Y = C
18e R_2 = CF_3; R_3 = H; X = C; Y = N
18f R_2 = CF_3; R_3 = 3-Br; X = Y = C
18g R_2 = F; R_3 = H; X = Y = C
18h R_2 = CN; R_3 = H; X = Y = C
18i R_2 = Cl; R_3 = H; X = Y = C
18j R_2 = CH_3; R_3 = H; X = Y = C
18k R_2 = CO_2CH_3; R_3 = H; X = Y = C
18l R_2 = CF_3; R_3 = 3-CF_3; X = Y = C
18m R_2 = CF_3; R_3 = H; X = Y = C
18n R_2 = Br; R_3 = H; X = Y = C

19a R_2 = *t*-Bu; R_3 = H; X = Y = C
19b R_2 = CF_3; R_3 = 5-Br; X = Y = C
19c R_2 = CF_3; R_3 = 4-NO_2; X = Y = C
19d R_2 = CF_3; R_3 = H; X = N; Y = C
19e R_2 = CF_3; R_3 = H; X = C; Y = N
19f R_2 = CF_3; R_3 = 4-Br; X = Y = C
19g R_2 = F; R_3 = H;; X = Y = C
19h R_2 = CN; R_3 = H; X = Y = C
19i R_2 = CF_3; R_3 = 4-(3,4,5-trifluorophenyl); X = Y = C
19j R_2 = Cl; R_3 = H; X = Y = C
19k R_2 = CH_3; R_3 = H; X = Y = C
19l R_2 = CO_2CH_3; R_3 = H; X = Y = C
19m R_2 = CF_3; R_3 = 4-CF_3; X = Y = C
19n R_2 = CF_3; R_3 = H; X = Y = C
19o R_2 = Br; R_3 = H; X = Y = C

20a R_2 = *t*-Bu; R_3 = H; X = Y = C
20b R_2 = CF_3; R_3 = 5-Br; X = Y = C
20c R_2 = CF_3; R_3 = 4-NO_2; X = Y = C
20d R_2 = CF_3; R_3 = H; X = N; Y = C
20e R_2 = CF_3; R_3 = H; X = C; Y = N
20f R_2 = CF_3; R_3 = 4-Br; X = Y = C
20g R_2 = F; R_3 = H; X = Y = C
20h R_2 = CN; R_3 = H; X = Y = C
20i R_2 = CF_3; R_3 = 4-(3,4,5-trifluorophenyl); X = Y = C
20j R_2 = Cl; R_3 = H; X = Y = C
20k R_2 = CH_3; R_3 = H; X = Y = C
20l R_2 = CO_2CH_3; R_3 = H; X = Y = C
20m R_2 = CF_3; R_3 = 4-CF_3; X = Y = C
20n R_2 = CF_3; R_3 = H; X = Y = C
20o R_2 = Br; R_3 = H; X = Y = C

[a] X and Y = C or N. [b]Conditions: (a) for **19a**−**d**, **19f**−**h, 19j**−**o**, 1,1′-carbonyldiimidazole, THF, 20 °C; for **19e**, *N*,*N*-disuccinimidyl carbonate, MeCN, 75 °C; (b) 3,4,5-trifluorophenylboronic acid, $PdCl_2(PPh_3)_2$, Na_2CO_3, $MeO(CH_2)_2OMe$, H_2O, EtOH, 120 °C, microwave; (c) $POCl_3$, 95 °C.

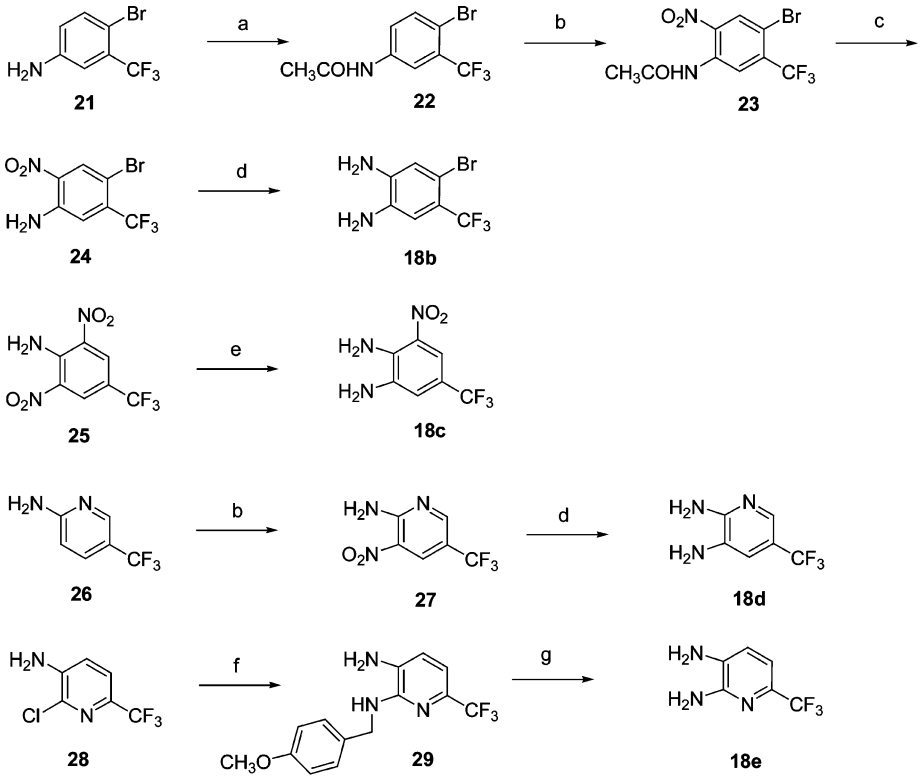
21 gave the *N*-acetylaniline **22**, which was nitrated at the less hindered ortho-position with a mixture of concentrated nitric acid and concentrated sulfuric acid to give nitro derivative **23**. Subsequent hydrolysis of the *N*-acetyl group and reduction of the nitro group of **23** with tin(II) chloride dihydrate afforded the desired 1,2-diaminobenzene **18b**. Partial palladium-catalyzed hydrogenation of the symmetrical 2,6-dinitroaniline derivative **25** gave the nitro-substituted 1,2-diaminobenzene **18c**. Nitration of 2-aminopyridine **26** ortho to the amino group gave **27**, which was then reduced with tin(II) chloride dihydrate to form the 2,3-diaminopyridine **18d**. The amino group at position 2 of the regioisomeric 2,3-diaminopyridine **18e** was introduced by amination of the 2-chloropyridine **28** with 4-methoxybenzylamine under microwave irradiation, followed by debenzylation using trifluoroacetic acid.

Scheme 7 shows the preparation of 2-piperazinyl-1*H*-benzimidazoles building blocks of type **V** used in the synthesis of TRPV1 antagonists via general method B (Scheme 1). Compounds **30a** and **30b** were prepared by microwave-assisted coupling of the piperazines **7a** and **7c** with the 2-chlorobenzimidazoles **20n** and **20i**, respectively.

Schemes 8−11 illustrate the synthesis of the TRPV1 antagonists that were prepared by modification of the substituents of 2-piperazin-1-yl-1*H*-benzimidazoles of type **III**. The starting benzimidazoles used in Schemes 8−11 (**31a**,**b**, **33**, **35**, **37a**,**b**, **39**, **42**, **43a**, **44a,c**, and **45**) were synthesized by method A or method B described in Scheme 1. Scheme 8 describes modification of the substituents of 2-piperazin-1-yl-1*H*-benzimidazoles by reactions involving nitro group transformations. The nitro groups of **31a** and **31b** were reduced by palladium-catalyzed hydrogenation to give the corresponding amines **32a** and **32b**, while the nitro group of the bromo derivative **33** was reduced with tin(II) chloride dihydrate to afford amine **34**. Several additional 2-piperazin-1-yl-1*H*-benzimidazoles were prepared by reactions involving the amino group of **32a** and **32b**. For example, reductive alkylation of **32a** and **32b** with aldehydes was utilized to produce **32c**, **32f**, and **32g**, while acylation of **32b** with cyclohexanecarboxylic acid and di-*tert*-butyl dicarbonate afforded **32d** and **32e**, respectively.

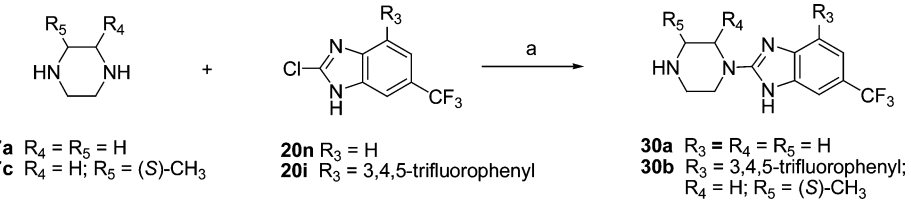
Scheme 9 lists modifications based on reactions involving a carbonyl group on the 5′-position of the pyridine ring. The aldehyde **36** was obtained by oxidation of the hydroxymethyl derivative **35** with activated manganese(IV) oxide. The carboxylic acid **38a** was prepared by saponification of the ester **37a**. Grignard addition of methylmagnesium bromide and phenylmagnesium bromide to the carbonyl group of the aldehyde **36** gave the secondary alcohols **38c** and **38d**, respectively. Alternatively, reduction of the ketone **37b** with sodium borohydride in methanol gave the corresponding secondary alcohol **38b**.

Scheme 6[a]



[a] Conditions: (a) Ac_2O, 20 °C; (b) concd HNO_3, concd H_2SO_4, 0−20 °C; (c) 3 N NaOH, MeOH, 90 °C; (d) $SnCl_2 \cdot H_2O$, EtOAc, EtOH, 70 °C; (e) H_2, 10% Pd/C, EtOH, 20 °C; (f) 4-methoxybenzylamine, $NaHCO_3$, 3-methyl-1-butanol, 220 °C, microwave; (g) TFA, CH_2Cl_2, 20 °C.

Scheme 7[a]



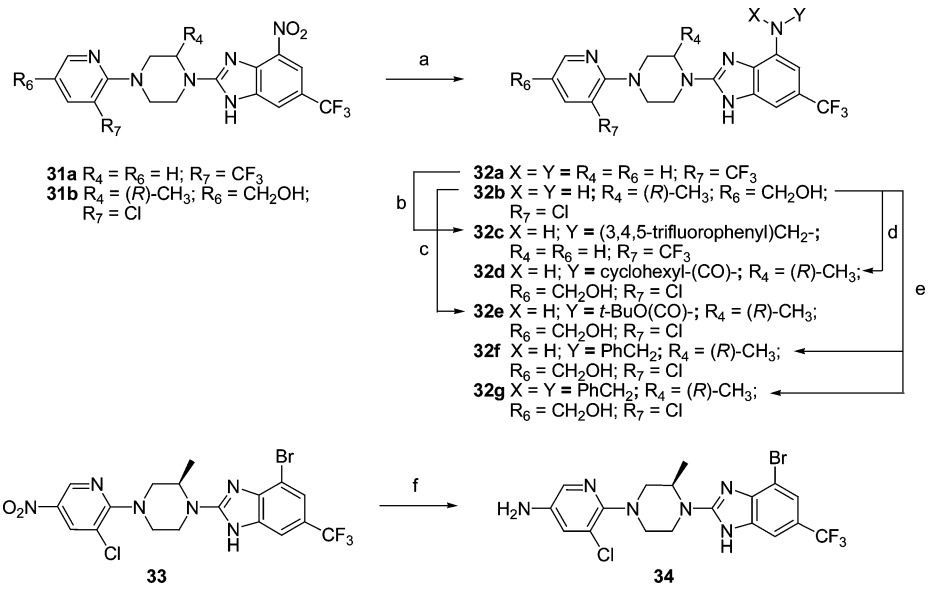
[a] Conditions: (a) for **30a**, DMSO, 80 °C; for **30b**, *N*,*N*-diisopropylethylamine, MeCN, 180 °C, microwave.

N-substituted benzimidazole derivatives were also prepared (Scheme 10). For instance, treatment of the sodium salt of the benzimidazole **39** with benzyl bromide gave the isomeric mixture of **40** and **41**, which was separated by column chromatography. The regiochemical assignment for compounds **40** and **41** was confirmed on the basis of 2D-NOESY NMR analysis.

Scheme 11 describes the preparation of 2-piperazin-1-yl-1*H*-benzimidazoles by reactions involving bromo-functionalized analogues. For example, Suzuki coupling of the aryl bromides **42**, **34**, and **43a** with various arylboronic acids under conventional heating or microwave irradiation gave the arylated analogues **46a**, **46e**, and **46m**, respectively. Analogously, Suzuki coupling of **44a** with various arylboronic acids gave the arylated analogues **46b**, **46q**−**v**, and **46x-ab**. Amine **46e** was acylated with acetoxyacetic acid in the presence of benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate and *N*,*N*-diisopropylethylamine and subsequently hydrolyzed with potassium carbonate in methanol to give the hydroxyacetylamino derivative **46f**. Arylation of the bromo-functionalized diastereomeric mixture of secondary alcohols **44c** with 3,4,5-trifluorophenylboronic acid gave the mixture of the diastereoisomers **46k** and **46l**, which were next separated by preparative HPLC. The configuration of each isomer at the chiral center of the 1-hydroxyethyl substituent was assigned at random. To prepare the 4-trifluoromethylcyclohexyl analogue **46p**, the aryl bromide **44a** was treated with 4,4,5,5-tetramethyl-2-(4-trifluoromethylcyclohex-1-enyl)[1,3,2]dioxaborolane to give 4-trifluoromethylcyclohex-1-enyl intermediate, which was reduced by palladium-catalyzed hydrogenation.

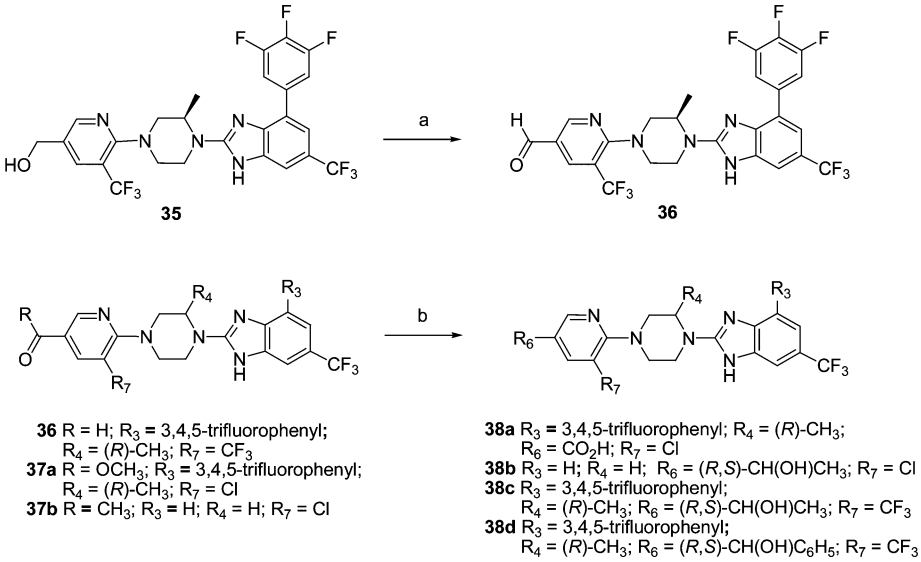
Several other derivatives were prepared by using organotin and organozinc cross-coupling reactions. For example, Stille coupling of the aryl bromides **44a** and **45** with 2-tributylstannylthiazole and tributylvinyltin in the presence of tetrakis(triphenylphosphine)palladium(0) as catalyst provided the thiazolyl analogue **46n** and the vinyl analogue **46ac**, respectively. Further dihydroxylation of the vinyl analogue **46ac** with catalytic osmium tetraoxide and stoichiometric *N*-methylmorpholine *N*-oxide[41] gave glycol **46ad** as a mixture of diastereoisomers. Analogously, Stille coupling of **44a** with 2-tributylstannylpyrazine gave the pyrazine analogue **46w**. Negishi coupling of **44a** with 3,4-difluorobenzylzinc bromide furnished the 3,4-difluorobenzyl analogue **46o**. Selected bromo-substituted 2-piperazin-1-yl-1*H*-benzimidazoles of type **III** were also employed in Buchwald amination reactions. For example, *N*-alkylation of **43a** with 2-(trimethylsilyl)ethoxymethyl chloride in the presence of base provided the *N*-protected benzimidazole **43b**. Subsequent microwave irradiation of **43b** with 4-(trifluoromethyl)benzyl-

Scheme 8[a]



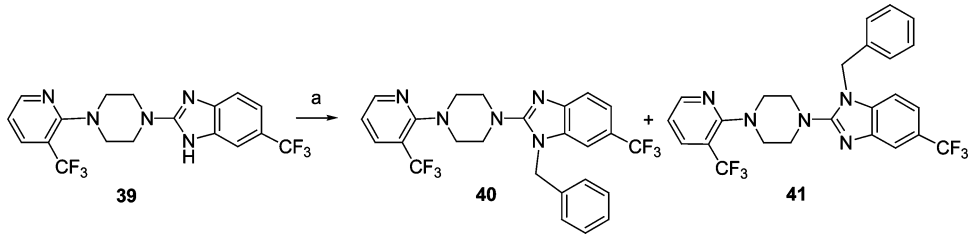
[a] Conditions: (a) H_2, 10% Pd/C, EtOH, 20 °C; (b) 3,4,5-trifluorobenzaldehyde, $NaBH(OAc)_3$, $CHCl_3$, 20 °C; (c) $O(COO\text{-}t\text{-}Bu)_2$, 1 N NaOH, THF, 20 °C; (d) cyclohexanecarboxylic acid, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide·HCl, CH_2Cl_2, 20 °C; (e) $PhCH_2CHO$, $NaBH(OAc)_3$, $CHCl_3$, 20 °C; (f) $SnCl_2 \cdot H_2O$, DMF, 80 °C.

Scheme 9[a]



[a] Conditions: (a) MnO_2, CH_2Cl_2, 20 °C; (b) for **38a**, (1) 1 N NaOH, THF, 50 °C; (2) 1 N HCl, 20 °C; for **38b**, $NaBH_4$, MeOH, 0 °C; for **38c**, CH_3MgBr, THF, 0 °C; for **38d**, C_6H_5MgBr, THF, 0 °C.

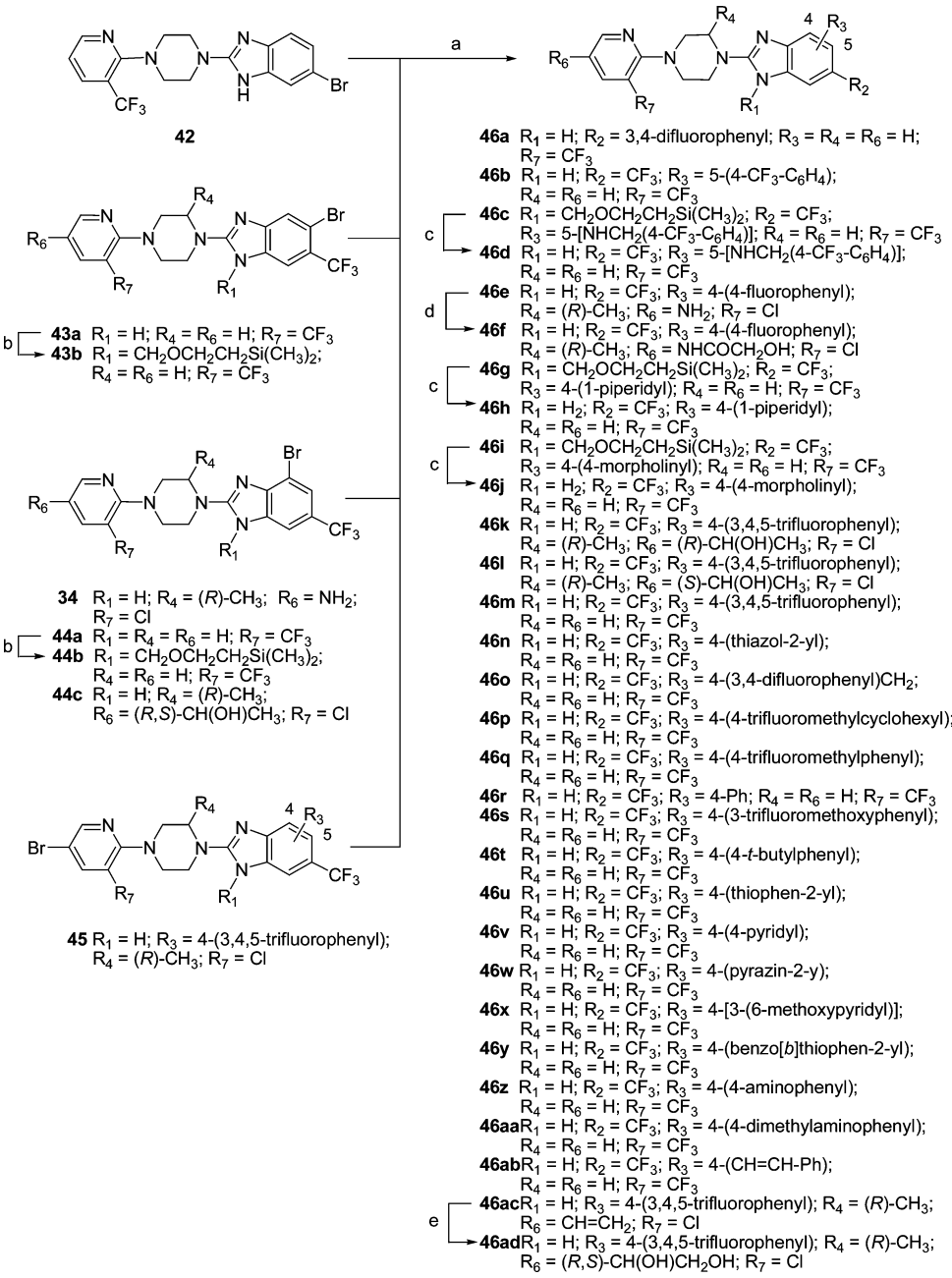
Scheme 10[a]



[a] Conditions: (a) (1) 50% NaH in mineral oil, DMF, 0−20 °C; (2) $C_6H_5CH_2Br$, 0 to 20 °C; (3) separation by column chromatography.

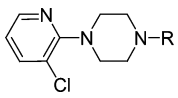
amine in the presence of sodium *tert*-butoxide, tris(dibenzylideneacetone)dipalladium(0) as catalyst and 2-(di-*tert*-butylphosphino)biphenyl as phosphine ligand gave the benzylamine derivative **46c**. The target compound **46d** was obtained after cleavage of the 2-(trimethylsilyl)ethoxymethyl protective groups of **46g** with trifluoroacetic acid. The analogous Buchwald amination reaction of the *N*-protected **44b** with piperidine and morpholine gave the corresponding piperidine derivative **46g** and the morpholine derivative **46i**. Next, cleavage of the protective group gave the target compounds **46h** and **46j**.

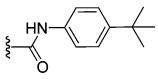
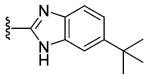
Scheme 11[a]



[a] Conditions: (a) for **46a**, **42**, 3,4-difluorophenylboronic acid, $Pd(PPh_3)_4$, 2 M Na_2CO_3, LiCl, $MeO(CH_2)_2OMe$, H_2O, EtOH, 80 °C; for **46b**, **43a**, 4-trifluoromethylphenylboronic acid, $Pd(PPh_3)_4$, 2 M Na_2CO_3, dioxane, 170 °C, microwave; for **46c**, **43b**, 4-$CF_3C_6H_4CH_2NH_2$, tris(dibenzylideneacetone)-dipalladium(0), 2-(di-*tert*-butylphosphino)biphenyl, *t*-BuONa, toluene, 150 °C, microwave; for **46e**, **34**, 4-fluorophenylboronic acid, $Pd(PPh_3)_2Cl_2$, Na_2CO_3, dimethoxyethane, H_2O, EtOH, 82 °C; for **46g**, **44b**, piperidine, tris(dibenzylideneacetone)dipalladium(0), 2-(di-*tert*-butylphosphino)biphenyl, *t*-BuONa, toluene, 150 °C, microwave; for **46i**, **44b**, morpholine, tris(dibenzylideneacetone)dipalladium(0), 2-(di-*tert*-butylphosphino)biphenyl, *t*-BuONa, toluene, 150 °C, microwave; for **46k** and **46l**, **44c**, (1) 3,4,5-trifluorophenylboronic acid, $Pd(PPh_3)_4$, 0.4 M Na_2CO_3, MeCN, 90 °C, (2) separation of diastereoisomers by prep. HPLC; for **46m**, **44a**, 3,4,5-trifluorophenylboronic acid, $Pd(PPh_3)_4$, 2 M Na_2CO_3, dioxane, 170 °C, microwave; for **46n**, **44a**, 2-tributylstannylthiazole, $Pd(PPh_3)_4$, dioxane, 140 °C, microwave; for **46o**, **44a**, 0.5 M 3,4-difluorobenzylzinc bromide, $Pd(PPh_3)_4$, THF, reflux; for **46p**, **44a**, (1) 4,4,5,5-tetramethyl-2-(4-trifluoromethylcyclohex-1-enyl)[1,3,2]dioxaborolane, $Pd(PPh_3)_4$, Na_2CO_3, $MeO(CH_2)_2OMe$, 200 °C, microwave; (2) H_2, 10% Pd/C, EtOH, 20 °C; for **46q**, **44a**, 4-trifluoromethylphenylboronic acid, $Pd(PPh_3)_4$, 2 M Na_2CO_3, LiCl, $MeO(CH_2)_2OMe$, H_2O, EtOH, 80 °C; for 46r, **44a**, phenylboronic acid, $Pd(PPh_3)_4$, 2 M Na_2CO_3, LiCl, $MeO(CH_2)_2OMe$, H_2O, EtOH, 80 °C; for **46s**, **44a**, 3-trifluoromethoxyphenylboronic acid, $Pd(PPh_3)_2Cl_2$, Na_2CO_3, dimethoxyethane, H_2O, EtOH, 82 °C; for **46t**, **44a**, 4-*tert*-butylphenylboronic acid, $Pd(PPh_3)_2Cl_2$, Na_2CO_3, dimethoxyethane, H_2O, EtOH, 82 °C; for **46u**, **44a**, thiophen-2-ylboronic acid, $Pd(PPh_3)_2Cl_2$, Na_2CO_3, dimethoxyethane, H_2O, EtOH, 82 °C; for **46v**, **44a**, pyridin-4-ylboronic acid, $Pd(PPh_3)_2Cl_2$, Na_2CO_3, dimethoxyethane, H_2O, EtOH, 82 °C; for **46w**, **44a**, 2-tributylstannylpyrazine, $Pd(PPh_3)_4$, dioxane, 140 °C, microwave; for **46x**, **44a**, 3-(6-methoxypyridyl)boronic acid, $Pd(PPh_3)_2Cl_2$, Na_2CO_3, dimethoxyethane, H_2O, EtOH, 82 °C; for **46y**, **44a**, benzo[*b*]thiophen-2-ylboronic acid, $Pd(PPh_3)_2Cl_2$, Na_2CO_3, dimethoxyethane, H_2O, EtOH, 82 °C; for **46z**, **44a**, 4-aminophenylboronic acid, $Pd(PPh_3)_2Cl_2$, Na_2CO_3, dimethoxyethane, H_2O, EtOH, 82 °C; for **46aa**, **44a**, 4-dimethylamino-phenylboronic acid, $Pd(PPh_3)_2Cl_2$, Na_2CO_3, dimethoxyethane, H_2O, EtOH, 82 °C; for **46ab**, **44a**, *trans*-2-phenylvinylboronic acid, $Pd(PPh_3)_2Cl_2$, Na_2CO_3, dimethoxyethane, H_2O, EtOH, 82 °C; for **46ac**, **45**, $CH_2{=}CHSnBu_3$, $Pd(Ph_3P)_4$, 3,5-di-*tert*-butylphenol, LiCl, dioxane, 95 °C; (b) 2-(trimethylsilyl)ethoxy-methyl chloride, *N*,*N*-diisopropylethylamine, CH_2Cl_2, 20 °C; (c) TFA, CH_2Cl_2, 20 °C; (d) (1) $CH_3CO_2CH_2CO_2H$, benzotriazol-1-yloxytris(dimethyl-amino)phosphonium hexafluorophosphate, *N*,*N*-diisopropylethylamine, CH_2Cl_2, 20 °C; (2) K_2CO_3, MeOH, 20 °C; (e) 4-methylmorpholine *N*-oxide, OsO_4, acetone, 20 °C.

Table 1. Inhibition of $^{45}Ca^{2+}$ Influx: BCTC (**4**) and Its Constrained Analogue (**5**)



Entry	R	capsaicin stimulus IC_{50} (nM)	pH stimulus IC_{50} (nM)
4		0.4 ± 0.3	0.5 ± 0.6
5		87 ± 18	310 ± 117

Results and Discussion

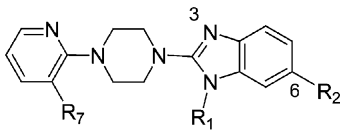
The compounds were tested for their ability to block the capsaicin- or acid-induced (pH 5) uptake of $^{45}Ca^{2+}$ in CHO cells expressing rat TRPV1. Functional activity is reported as IC_{50} (nM) in Tables 1−7. All compounds reported herein behaved as antagonists.[44] Results are the average of at least two independent experiments with three replicates at each concentration.

Conformationaly constrained analogues of BCTC (**4**) could be generated by incorporating the carboxanilide function into a five-membered heterocyclic ring fused with the adjacent aromatic ring. For example, our initial results showed that isosteric replacement of the carboxanilide function of BCTC (**4**) with a benzimidazole ring system gave the constrained analogue **5** with an IC_{50} value of 87 nM in the capsaicin-mediated assay and 310 nM in the pH-mediated assay (Table 1).

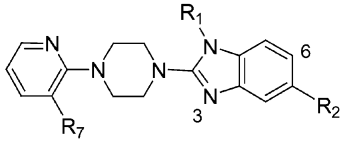
Since the constrained analogue **5** displayed reasonable potency as TRPV1 antagonist, we decided to do a detailed structure−activity relationship (SAR) investigation of **5** in order to provide an understanding of the structural features that influence the functional activity of this novel template. Our initial strategy was to prepare analogues of **5** by stepwise introduction of various substituents on the benzimidazole (Tables 2 and 3), the piperazine (Table 5), and the pyridine (Table 6) rings of the 2-(4-pyridin-2-ylpiperazin-1-yl)-1*H*-benzo[*d*]imidazole template of **5**. In addition, several analogues of **5** having modified benzimidazole and pyridine rings were also prepared (Tables 4 and 7, respectively). The results from this initial SAR were used next in the design of a set of analogues by combining the optimum substituents on all preferred sites of the template of **5** (Table 8).

As exemplified by compound **47a** in Table 2, replacement of the chlorine substituent of the pyridine ring of **5** with a trifluoromethyl group led to 2-fold potency decrease (IC_{50} = 183 nM) in the capsaicin-activated uptake assay and almost unchanged potency (IC_{50} = 282 nM) in the pH-mediated assay. Due to the relatively similar potencies of the chloro analogue **5** and the trifluoromethyl analogue **47a**, the remaining compounds listed in Table 2 retained the trifluoromethyl substituent on the pyridine ring ($R_7 = CF_3$) and differed by the nature of the substituents R_1 and R_2 on the benzimidazole ring. The potency in the capsaicin-induced Ca^{2+} uptake assay was nearly restored (IC_{50} = 110 nM) when the *tert*-butyl substituent of the benzimidazole ring of **47a** was replaced with the strongly electron-withdrawing trifluoromethyl group to provide the analogue **39**. Replacement of the trifluoromethyl group of the

Table 2. Inhibition of $^{45}Ca^{2+}$ Influx: Substituents on the Benzimidazole Ring



5, 39, 40, 42, 46a, 47a-f



41

entry	R_1	R_2	R_7	IC_{50} (nM) capsaicin stimulus	IC_{50} (nM) pH stimulus
5	H	t-Bu	Cl	87 ± 18	310 ± 117
47a	H	t-Bu	CF_3	183 ± 24	282 ± 53
39	H	CF_3	CF_3	110 ± 22	301 ± 84
47b	H	CH_3	CF_3	3350 ± 330	>4000
47e	H	CN	CF_3	3300 ± 160	>4000
47f	H	CO_2CH_3	CF_3	1230 ± 380	>4000
46a	H	3,4-difluoro-Ph	CF_3	1140 ± 260	351 ± 34
47c	H	F	CF_3	>4000	>4000
47d	H	Cl	CF_3	1130 ± 96	17250 ± 830
42	H	Br	CF_3	123 ± 13	194 ± 58
40	CH_2Ph	CF_3	CF_3	577 ± 65	157 ± 11
41	CH_2Ph	CF_3	CF_3	6480 ± 1180	151 ± 6

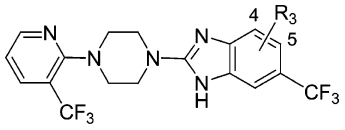
benzimidazole ring of **39** with the electron-donating methyl group resulted in dramatic reduction of potency in both assays (compound **47b**). A similar decrease of antagonistic activity in both assays was observed for the nitrile **47e**, while ester **47f** was 11-fold less active in the caspsaicin-mediated assay but remained inactive in the pH-mediated assay. In contrast, the potency of the 3,4-difluorophenyl substituted **46a** was similar to that of **47f** in the capsaicin assay but retained the activity of **39** in the pH assay. When the substituent R_2 of the benzimidazole ring was halogen, the potency in the capsaicin-mediated assay improved upon increasing of the size of the halogen atom (i.e., F (**47c**) ≪ Cl (**47d**) < Br (**42**)). The activity of the bromo-substituted derivative **42** was comparable to that of the trifluoromethyl derivative **39**.

The effect of substituting the nitrogen atom of the benzimidazole ring was also investigated. *N*-Alkylation of the analogue **39** with benzyl bromide gave the corresponding isomeric products **40** and **41**. The *N*-benzyl isomer **40** was 5-fold less potent (IC_{50} = 577 nM) in the capsaicin-mediated assay in comparison with **39**. In the case of the isomer **41**, the decrease of the potency in the capsaicin-mediated assay was more pronounced (IC_{50} = 6480 nM). In contrast, a 2-fold potency increase was observed for both isomers in the pH-mediated assay.

In summary, the influence of the steric effects of the substituents R_2 on the potency of the TRPV1 antagonists in Table 2 was more pronounced than the electronic effects, with trifluoromethyl, bromo, and *tert*-butyl groups being the optimal substituents. *N*-Alkylation of the benzimidazole ring was detrimental to activity in the capsaicin-mediated assay, suggesting certain steric limitations and/or specific requirement for hydrogen-bond-donor interactions with binding site of the receptor.

The compounds shown in Table 3 were prepared to investigate the influence of introducing additional substituents at the

Table 3. Inhibition of $^{45}Ca^{2+}$ Influx: Substituents on the Phenyl Ring of the Benzimidazole Ring



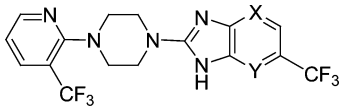
entry	R_3	IC_{50} (nM) capsaicin stimulus	IC_{50} (nM) pH stimulus
39	H	110 ± 22	301 ± 14
43a	5-Br	166 ± 16	43 ± 2
46b	5-(4-CF_3-Ph)	8240 ± 13	201 ± 41
46d	5-[$NHCH_2$(4-CF_3-Ph)]	94 ± 9	141 ± 26
44a	4-Br	131 ± 12	74 ± 13
31a	4-NO_2	1660 ± 120	878 ± 35
32a	4-NH_2	3380 ± NA	>4000
48	4-CF_3	325 ± 21	120 ± 11
46q	4-(4-CF_3-Ph)	51 ± 6	37 ± 3
46m	4-(3,4,5-trifluoro-Ph)	33 ± 8	26 ± 12
46s	4-(3-CF_3O-Ph)	26 ± 14	21 ± 20
46t	4-(4-*tert*-butyl-Ph)	13 ± 5	4 ± 1
46r	4-Ph	141 ± 11	68 ± 27
46u	4-thiophen-2-yl	373 ± 92	221 ± 44
46n	4-thiazol-2-yl	688 ± 78	454 ± 63
46v	4-pyrid-4-yl	267 ± 23	188 ± 138
46w	4-pyrazin-2-yl	129 ± 32	51 ± 20
46x	4-[3-(6-methoxypyridyl)]	111 ± 15	99 ± 19
46y	4-benzo[*b*]thiophen-2-yl	26 ± 4	22 ± 0.6
46h	4-piperid-1-yl	29 ± 7	21 ± 1
46j	4-morpholinyl	50 ± 2	95 ± 11
46p	4-[4-(trifluoromethyl)cyclohex-1-yl]	10 ± 3	9 ± 0.2
46z	4-(4-amino-Ph)	1900 ± 1	308 ± 14
46aa	4-(4-(dimethylamino)-Ph)	108 ± 8	69 ± 19
46o	4-[CH_2(3,4-difluoro-Ph)]	71 ± 11	52 ± 10
46ab	4-(CH═CH-Ph)	185 ± 81	140 ± 12
32c	4-[$NHCH_2$(3,4,5-trifluoro-Ph)	132 ± 9	81 ± 8

4- and 5-positions of the benzimidazole ring of the trifluoromethyl analogue **39**. We found that the introduction of additional substituents at position 5 of the benzimidazole ring seemed to provide limited benefits. For example, substitution of position 5 of **39** with a bromine atom gave the analogue **43a**. This substitution led to a 1.5-fold decrease of potency in the capsaicin-mediated assay and a 7-fold increase in the pH-mediated assay. Introduction of the bulkier (4-trifluoromethyl)-phenyl group (i.e., **46b**) resulted in additional loss of potency in the capsaicin-mediated assay, relative to **43a**; however, the potency was restored to that of **39** when the (4-trifluoromethyl)-phenyl group was attached to position 5 via a $-NHCH_2-$ linker (i.e., **46d**).

The introduction of substituents at position 4 of the trifluoromethyl analogue **39** initially did not look promising. For example, the 4-bromo derivative **44a** was nearly equipotent with the 5-bromo derivative **43a**. The 4-nitro derivative **31a** was approximately 13-fold less potent, and the 4-amino derivative **32a** was 26-fold less potent than the corresponding bromo derivative **44a** in the capsaicin-mediated assay, while the trifluoromethyl analogue **48** was approximately 2-fold less potent. We observed dramatic increase in potency (161-fold, IC_{50} = 51 nM) in the capsaicin-mediated assay, and a 5-fold increase (IC_{50} = 37 nM) in the pH-mediated assay when the (4-trifluoromethyl)phenyl group was transferred from position 5 (i.e., **46b**) to position 4 (i.e., **46q**) of the benzimidazole ring. This promising result prompted us to prepare an additional number of analogues substituted at position 4.

Further improvement of the potency in the capsaicin-mediated assay was observed for the 3,4,5-trifluorophenyl analogue **46m** (IC_{50} = 33 nM), the (3-trifluoromethoxy)phenyl analogue **46s** (IC_{50} = 26 nM), and the 4-*tert*-butylphenyl analogue **46t** (IC_{50} = 13 nM). In the case of **46r**, the lack of substitution of the phenyl ring resulted in a decrease of potency (IC_{50} = 141 nM) in the capsaicin-mediated assay, in comparison with the substituted phenyl analogues (**46q**, **46m**, **46s**, and **46t**). Various five-membered aromatic heterocycles (i.e., thiophene derivative **46u** and thiazol derivative **46n**) and six-membered aromatic heterocycles (i.e., pyridine and pyrazine derivatives **46v**−**x**) were also tolerated at position 4 of the benzimidazole ring; however, their potencies in the capsaicin-mediated assay were almost equal or up to 5-fold lower than the potency of the corresponding phenyl analogue **46r**. The addition of a fused benzene ring to the thiophene heterocycle of **46u** (IC_{50} = 373 nM) resulted in the fused bicyclic analogue **46y** (IC_{50} = 26 nM) and a 14-fold increase of potency in the capsaicin-mediated assay. We found that saturated six-membered heterocycles such as the 1-piperidyl group of analogue **46h** and the morpholin-4-yl group of analogue **46j** were well-tolerated. Saturation of the phenyl ring of the 4-(trifluoromethyl)phenyl analogue **46q** (IC_{50} = 51 nM) gave the 4-(trifluoromethyl)cyclohex-1-yl derivative **46p**, which was the most potent 4-substituted compound shown in Table 3 with IC_{50}'s of 10 and 9 nM in the capsaicin-mediated and the pH-mediated assays, respectively. Introduction of amino group at para-position of the phenyl ring of **46r** gave the 12-fold less potent derivative **46z** (IC_{50} = 1900 nM) in the capsaicin-mediated assay; however, the potency was almost restored in the case of the bulkier dimethylaminophenyl derivative **46aa**.

Table 4. Inhibition of $^{45}Ca^{2+}$ Influx: Variations to the Benzimidazole Ring

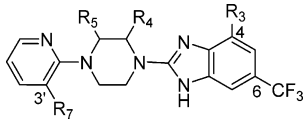


entry	X	Y	IC_{50} (nM) capsaicin stimulus	IC_{50} (nM) pH stimulus
39	C	C	110 ± 22	301 ± 14
49a	N	C	1,550 ± 65	884 ± 560
49b	C	N	1,090 ± 580	1410 ± 58

Several analogues having aryl substituents linked via a linker group to position 4 of the benzimidazole ring were prepared. For example, the analogue **46o** having a $-CH_2-$ linker blocked the uptake of $^{45}Ca^{2+}$ with an IC_{50} of 71 nM in the capsaicin-mediated assay and with IC_{50} of 52 nM in the pH-mediated assay. In the case of the styryl analogue **46ab**, the potency in the capsaicin-mediated assay was almost unchanged (IC_{50} = 185 nM) in comparison with the potency of the phenyl analogue **46r** (IC_{50} = 141 nM). However, introduction of a $-NHCH_2-$ linker between the 3,4,5-trifluorophenyl group and the benzimidazole ring of **46m** (IC_{50} = 33 nM) gave the analogue **32c**, which was found to be 4-fold less potent (IC_{50} = 132 nM) in the capsaicin-mediated assay.

In summary, the preliminary SAR observed for the compounds listed in Table 3 revealed the existence of a relatively large hydrophobic pocket in the TRPV1 receptor, since introduction of bulky lipophilic groups at position 4 of the benzimidazole ring gave TRPV1 antagonists with improved or retained potency, compared to compound **39**. Attachment of similar hydrophobic substituents at position 5 was less favorable (i.e., compound **46b**). However the potency could be improved when the bulky hydrophobic group was attached via a $-NHCH_2-$ linker (i.e., analogue **46d**). Presumably, the addition of this linker

Table 5. Inhibition of $^{45}Ca^{2+}$ Influx: Substituents on the Piperazine Ring



entry	R_3	R_4	R_5	R_7	IC_{50} (nM) capsaicin stimulus	IC_{50} (nM) pH stimulus
39	H	H	H	CF_3	110 ± 22	301 ± 14
50a	H	(*R*)-CH_3	H	CF_3	48 ± 8	35 ± 9
50b	H	(*R*)-CH_2CH_3	H	CF_3	648 ± 39	>4000
50c	H	(*R*)-$CH_2CH_2CH_3$	H	CF_3	3230 ± 130	>4000
51a	4-(3,4,5-trifluoro-Ph)	(*R*)-CH_3	H	Br	6.7 ± 5	2.6 ± 2
51b	4-(3,4,5-trifluoro-Ph)	(*S*)-CH_3	H	Br	104 ± 11	75 ± 5
51c	4-(3,4,5-trifluoro-Ph)	H	(*R*)-CH_3	Br	4.3 ± 2	1.8 ± 0.3
51d	4-(3,4,5-trifluoro-Ph)	H	(*S*)-CH_3	Br	767 ± 693	254 ± 17

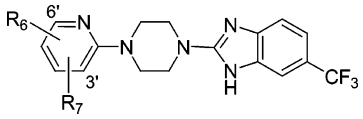
allows the hydrophobic group of **46d** to reach the space occupied by the substituents at position 4.

Next we examined modifications to the benzimidazole ring. As shown in Table 4, replacement of the phenyl ring of the benzimidazole analogue **39** with a pyridine ring was detrimental to activity. For example, the analogue **49a** (X = N; Y = C) was 14-fold less potent (IC_{50} = 1550 nM), and its isomer **49b** (X = C; Y = N) was 10-fold less potent (IC_{50} = 1090 nM) than the parent compound **39** (IC_{50} = 110 nM) in the capsaicin-mediated assay. Similar reductions of potencies in the pH-mediated assay were also noted.

Table 5 reports the results of substituted piperazine ring analogues of type **III**, which carry trifluoromethyl, chloro, or bromo substituents on the pyridine ring. Analogue **50a**, which was formed by introduction of (*R*)-methyl group at the carbon atom of the piperazine ring adjacent to the nitrogen atom attached to the benzimidazole ring, was 2-fold more potent (IC_{50} = 48 nM) than the unsubstituted analogue **39** (IC_{50} = 110 nM) in the capsaicin-induced $^{45}Ca^{2+}$ uptake assay. The potency of **50a** in the pH-mediated assay increased 9-fold (IC_{50} = 35 nM) in comparison to that of the parent compound **39**. However, stepwise elongation of the alkyl substituent of the piperazine ring (e.g. compounds **50b** and **50c**) resulted in dramatic decrease of the activity in the capsaicin-induced $^{45}Ca^{2+}$ uptake assay and loss of potency in the pH-mediated assay, suggesting that methyl is optimal in terms of length and size. Replacement of the trifluoromethyl group of the pyridine ring with bromine atom (R_7 = Br) together with the simultaneous introduction of a (*R*)- or (*S*)-methyl group onto the piperazine ring and the well-tolerated (3,4,5-trifluoromethyl)phenyl group at position 4 of the benzimidazole ring gave rise to the potent enantiomers **51a** and **51b**, respectively. The (*R*)-methyl enantiomer **51a** (IC_{50} = 6.7 nM) was approximately 15-fold more potent than the (*S*)-methyl enantiomer **51b** (IC_{50} = 104 nM) in the capsaicin-mediated assay and 30-fold more potent in the pH-mediated assay. This result indicates that *R*-configuration of the R_4 substituent of the piperazine ring is preferred. This stereochemical effect was more pronounced for the enantiomers **51c** and **51d**, having a methyl group attached to the carbon atom of the piperazine ring adjacent to the nitrogen atom linked to the pyridine ring. For example, the (*R*)-methyl enantiomer **51c** (IC_{50} = 4.3 nM) was found to be 178-fold more potent than the corresponding (*S*)-methyl enantiomer **51d** (IC_{50} = 767 nM) in the capsaicin-mediated assay.

Several analogues were prepared to explore alternative substitutions on the pyridine ring attached to the core piperazine ring of the 2-piperazin-1-yl-1*H*-benzimidazole template (Table 6). The 3′-trifluoromethyl substituted analogue **39** blocked the uptake of $^{45}Ca^{2+}$ with an IC_{50} of 110 nM in the capsaicin-mediated assay and with an IC_{50} of 301 nM in the pH-mediated assay, while the unsubstituted at the pyridine ring analogue **52a** was significantly less potent in both assays. The transfer of the trifluoromethyl group from the 3′-position to the 4′-, 5′-, and 6′-positions of the pyridine ring also gave substantially less active analogues (i.e., **52b**, **52c**, and **52d**, respectively). These results indicate that substitution of the pyridine ring is essential for the potency, and that position 3′ is the optimum site. Therefore, we focused our attention to 3-substituted analogues. Unfortunately, modifications of the trifluoromethyl group of the 3′-substituted analogue **39** did not lead to an increase of potency, as exemplified by the analogues **52e**−**i**.[46] The chloro analogue **52e** was 3-fold less potent (IC_{50} = 309 nM), and the bulkier iodo-substituted analogue **52f** was 2-fold less potent (IC_{50} = 221 nM) than **39** (IC_{50} = 110 nM) in the capsaicin-mediated assay. The methyl analogue **52g** (IC_{50} = 402 nM) was also significantly less potent than **39**, while a more dramatic reduction of potency was observed for the cyano- and the ethoxycarbonyl analogues **52h** and **52i**, respectively.

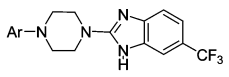
Table 6. Inhibition of $^{45}Ca^{2+}$ Influx: Substituents on the Pyridine Ring

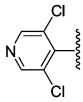
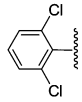


entry	R_6	R_7	IC_{50} (nM) capsaicin stimulus	IC_{50} (nM) pH stimulus
39	H	3-CF_3	110 ± 22	301 ± 14
52a	H	H	5790 ± 4290	>40000
52b	H	4-CF_3	>5640 ± 58	11930 ± 14660
52c	5-CF_3	H	11290 ± 270	>40000
52d	6-CF_3	H	>40000	>40000
52e	H	3-Cl	309 ± 25	705 ± 165
52f	H	3-I	221 ± 15	310 ± 50
52g	H	3-CH_3	402 ± 117	1140 ± 580
52h	H	3-CN	6290 ± 500	7080 ± 280
52i	H	3-$CO_2C_2H_5$	23780 ± 6800	>40000
37b	5-C(=O)CH_3	3-Cl	581 ± 13	832 ± 75
38b	(*R*,*S*)-5-CH(OH)CH_3	3-Cl	461 ± 43	652 ± 92
52j	5-CH_2OH	3-Cl	64 ± 10	98 ± 14
52k	5-C(=O)NH_2	3-Cl	430 ± 23	1000 ± 200
52l	5-C(=O)NHCH_3	3-Cl	493 ± 58	>40000

The second set of compounds shown in Table 6 was prepared to study the influence of a second substituent on the pyridine ring. The 3′-chloro-5′-acetyl derivative **37b** was prepared as the first compound of this series, since we had access to its synthetic

Table 7. Inhibition of $^{45}Ca^{2+}$ Influx: Variations to the Aromatic Ring



Entry	Ar	capsaicin stimulus IC_{50} (nM)	pH stimulus IC_{50} (nM)
39		110 ± 22	301 ± 14
53a		2,060 ± 250	406 ± 84
53b		2,380 ± 150	2,850 ± 250
53c		3,910 ± 140	8,030 ± 640
53d		1,370 ± 100	1,990 ± 120
53e		>40,000	1,270 ± 20
53f		2,110 ± 590	>40,000

precursor, the 1-(3-chloro-5-acetylpyridin-2-yl)piperazine (**8n**) (Scheme 2). Compound **37b** was found to be almost 2-fold less potent (IC_{50} = 581 nM) in the capsaicin-mediated assay and nearly equipotent (IC_{50} = 831 nM) to the 5′-unsubstituted analogue **52e** in the pH-mediated assay. This result suggested that introduction of a second substituent at position 5′ of the pyridine ring might be tolerated to some extent. Therefore, the remaining compounds shown in Table 6 were prepared to probe the influence of additional substituents at position 5′ of the pyridine ring on the functional activity of the 3′-chloro-substituted analogue **52e**. For example, the potency of the hydroxyethyl analogue **38b** (IC_{50} = 461 nM) was about the same as that of **52e** (IC_{50} = 309 nM) in the capsaicin-mediated assay. However, a substantial improvement of the activity of the 3′-chloro analogue **52e** was observed when a hydroxymethyl group was introduced at position 5′ of the pyridine ring. Compound **52j** was 5-fold more potent than **52e** in the capsaicin-mediated assay (IC_{50} = 64 nM) and 7-fold more potent in the pH-mediated assay (IC_{50} = 98 nM). On the other hand, the potency of the chloro analogue **52e** was not improved in the case of the 5′-amides **52k** and **52l**.

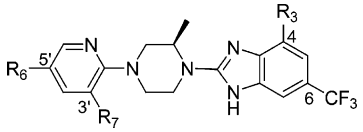
In summary, the SAR for the compounds included in Table 6 showed that position 3′ of the pyridine moiety is the optimum site for substitution and that a trifluoromethyl group or chlorine or iodine atoms are the most preferable substituents. Introduction of a second substituent, preferably a hydroxymethyl group, at position 5′ of the pyridine ring led to an increase in potency.

Table 7 displays the results of compounds **53a**−**f**, which were designed to explore the influence of an alternative type of aromatic group attached to the piperazine ring on the functional TRPV1 activity. The 2-trifluoromethyl-substituted phenyl analogue **53a** (IC_{50} = 2060 nM) was 20-fold less potent than the parent 2-(3-trifluoromethyl)pyridinyl analogue **39** (IC_{50} = 110 nM) in the capsaicin-mediated assay but nearly equipotent in the pH-mediated assay. Moving the nitrogen atom from the ortho- to the para-position of the pyridine ring was detrimental to activity (i.e., the 4-(3-trifluoromethyl)pyridinyl analogue **53b**). This result suggests that the presence of a hydrogen-bond-accepting nitrogen atom at the ortho-position is important for the binding with the TRPV1 receptor. This observation is in agreement with the SAR of the pyridine fragment of the BCTC series of TRPV1 antagonists reported previously.[36] Replacement of the trifluoromethyl group of **53b** with a chlorine atom gave the slightly less active analogue **53c**. However, subsequent addition of a second chlorine atom to **53c** gave the analogue **53d**, which showed about a 3-fold increase of potency (IC_{50} = 1370 nM) in the capsaicin-mediated assay. As exemplified by the dichlorophenyl analogue **53e**, removal of the nitrogen atom of **53d** led to a dramatic loss of potency in the capsaicin-mediated assay, while the potency in the pH-mediated assay was increased 2-fold. As might be expected, the pyrimidine analogue **53f** showed 2-fold potency improvement relative to the pyridine analogue **53c** in the capsaicin-mediated assay; however, this trend did not extend to the pH-mediated assay, in which **53f** showed a dramatic loss of activity.

Finally, the analogues included in Table 8 were prepared to study the influence of combining the best substituents (see Tables 2−6) on the core and the flanking moieties of the novel template of TRPV1 antagonists. The analogues were designed by maintaining the optimum trifluoromethyl and (*R*)-methyl groups for the substituent R_2 of the benzimidazole ring and for the substituent R_4 of the piperazine ring, respectively, while the substituents R_3, R_6, and R_7 were varied. This effort led to the identification of TRPV1 antagonists with substantially improved potency. For example, the introduction of the 3,4,5-trifluorophenyl group at the 4-position of the benzimidazole ring and the hydroxymethyl group at the 5′-position of the pyridine ring gave the potent analogue **35**. This compound was 34-fold more potent (IC_{50} = 1.4 nM) then the parent 2-(3-trifluoromethyl)pyridinyl analogue **50** (IC_{50} = 48 nM) in the capsaicin-mediated assay and 50-fold more potent (IC_{50} = 0.7 nM) in the pH-mediated assay. Similar increases in potencies were also observed for the analogues **32d**−**g** that retained the hydroxymethyl group at R_6 and have various bulky hydrophobic groups as R_3. It is worth noting that the bulkier *N*,*N*-dibenzylamino-substituted analogue **32g** (IC_{50} = 1.9 nM) was approximately 4-fold more potent than the benzylamino analogue **32f** (IC_{50} = 7 nM), which provides an additional insight on the size of the hydrophobic pocket of the TRPV1 receptor. Also well-tolerated was the replacement of the hydroxymethyl group of **35** with the bulkier (*R*,*S*)-[1-(1-hydroxyethyl)] and (*R*,*S*)-1-hydroxy-1-phenylmethyl groups (i.e., **38c** and **38d**). The diastereoisomers **46k** and **46l** were prepared and separated to probe the influence of the configuration of the chiral [1-(1-hydroxyethyl)] substituent on the antagonistic activity. The isomer **46k** was 4-fold more potent (IC_{50} = 0.6 nM) than the isomer **46l** (IC_{50} = 2.6 nM) in the capsaicin-mediated assay and almost equipotent in the pH-mediated assay. Addition of a second hydroxyl group to the (*R*,*S*)-[1-(1-hydroxyethyl)] substituent of **38c** gave the (*R*,*S*)-1,2-dihydroxyethyl-substituted diastereomeric mixture **46ad**, which was approximately equipotent with **38c** in both assays. Replacement of the amino group of the analogue **46e** (IC_{50} = 98 nM) with the bulkier hydroxyacetylamino group gave the analogue **46f** (IC_{50} = 30 nM) and resulted in 3-fold increase of the potency in the capsaicin-mediated assay.

These results indicate that relatively large, heteroatom-

Table 8. Inhibition of $^{45}Ca^{2+}$ Influx: Substituents on the Benzimidazole, Piperazine and Pyridine Rings



				IC_{50} (nM)	
entry	R_3	R_6	R_7	capsaicin stimulus	pH stimulus
50	H	H	CF_3	48 ± 8	35 ± 9
35	4-(3,4,5-trifluoro-Ph)	CH_2OH	CF_3	1.4 ± 0.6	0.7 ± 0.3
32d	NHCO-cyclohexyl	CH_2OH	Cl	1.6 ± 0.3	1.2 ± 0.2
32e	4-$NHCO_2$-t-Bu	CH_2OH	Cl	2.1 ± 0.6	1.1 ± 0.6
32f	$NHCH_2$-Ph	CH_2OH	Cl	7.0 ± 0.4	6.7 ± 1
32g	$N(CH_2\text{-Ph})_2$	CH_2OH	Cl	1.9 ± 0.3	0.9 ± 0.1
38c	4-(3,4,5-trifluoro-Ph)	(*R*,*S*)-CH(OH)CH_3	CF_3	1.5 ± 0.5	1.0 ± 0.2
38d	4-(3,4,5-trifluoro-Ph)	(*R*,*S*)-CH(OH)Ph	CF_3	2.8 ± 0.3	3.7 ± 0.3
46k	4-(3,4,5-trifluoro-Ph)	(*R*)-CH(OH)CH_3[a]	Cl	0.6 ± 0.4	2.3 ± 0.2
46l	4-(3,4,5-trifluoro-Ph)	(*S*)-CH(OH)CH_3[a]	Cl	2.6 ± 0.4	3.0 ± 0.3
46ad	4-(3,4,5-trifluoro-Ph)	(*R*,*S*)-CH(OH)CH_2OH	Cl	0.9 ± 0.7	0.9 ± 0.7
46e	4-(4-F-Ph)	NH_2	Cl	98 ± 3.2	33 ± 3.2
46f	4-(4-F-Ph)	$NHCOCH_2OH$	Cl	30 ± 2.1	9.2 ± 1.2
37a	4-(3,4,5-trifluoro-Ph)	CO_2CH_3	Cl	0.3 ± 0.0	0.3 ± 0.1
38a	4-(3,4,5-trifluoro-Ph)	CO_2H	Cl	46 ± 19	27 ± 2
45	4-(3,4,5-trifluoro-Ph)	Br	Cl	3.4 ± 1.1	3.3 ± 0.2
46ac	4-(3,4,5-trifluoro-Ph)	$CH{=}CH_2$	Cl	1.3 ± 0.1	1.7 ± 0.1

[a] The configuration was assigned at random.

containing substituents are well-tolerated at position 5′ of the pyridine ring. We also found that the receptor-binding site is even able to tolerate charged substituents at position 5′ of the pyridine ring. For example, the substituted with a carboxylic group analogue **38a** maintained significant activity at the TRPV1 receptor. Nonpolar substituents, as exemplified with the bromide **45** and the vinyl-substituted analogue **46ac**, were also well-tolerated at position 5′ of the pyridine ring.

Pharmacokinetic Profile. Compound **46ad** was selected for in vivo pharmacokinetic (PK) study with intravenous (iv) and oral (po) dosing in Sprague−Dawley rats, since it was one of the most potent in vitro analogues in the capsaicin-mediated assay (IC_{50} = 0.9 nM) and in the pH-mediated assay (IC_{50} = 0.9 nM). Following iv administration of 1 mg/kg, **46ad** demonstrated a low rate of clearance (CL = 270 mL/h/kg), a relatively low volume of distribution (V_{ss} = 1893 mL/kg), and an elimination half-life ($t_{1/2}$) of 5.6 h. Compound **46ad** was relatively well-absorbed (t_{max} = 4 h, C_{max} = 617 ng/mL) following oral administration of 5 mg/kg and was found to be orally bioavailable (F = 17%).

In Vivo Profile. Compound **46ad** was evaluated in two animal models of nociception. The first model examined the ability of **46ad** to block the capsaicin-induced paw flinching in rats, while the second investigated the effect of **46ad** on complete Freund's adjuvant (CFA)-induced thermal hyperalgesia.

When dosed orally, the potent TRPV1 antagonist **46ad** was efficacious in vivo by blocking capsaicin-induced flinching in rats (capsaicin 0.5 μg/0.25 mL per paw, eight animals per group) with ED_{50} of 8.8 mg/kg (Figure 2).

In the CFA-induced thermal hyperalgesia model, **46ad** significantly reversed thermal hyperlgesia produced by administration of CFA at a dose of 30 mg/kg, po (Figure 3).

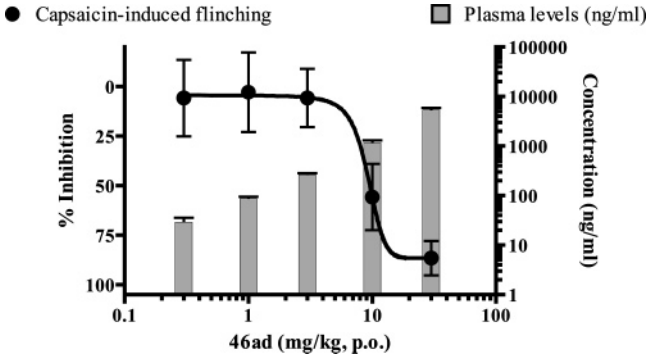


Figure 2. Effect of compound **46ad** on capsaicin-induced flinching in rats.

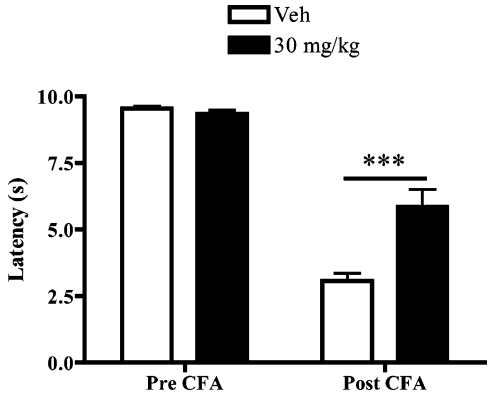


Figure 3. Effect of compound **46ad** on CFA-induced thermal hyperalgesia in rats.

Conclusions

A novel class of TRPV1 antagonists was identified by constraining analogues of BCTC (**4**) into a 2-(4-pyridin-2-ylpiperazin-1-yl)-1*H*-benzo[*d*]imidazole template. A series of compounds was prepared, first, by stepwise introduction of various substituents on the benzimidazole, the piperazine, and the pyridine rings of the template and, second, by combining the optimum substituents on all preferred sites of the template. A summary of the SAR obtained in this study is illustrated in Figure 4.

We found that *N*-benzylation of the benzimidazole ring was detrimental to activity, suggesting certain steric limitations and/or specific requirement for hydrogen-bond-donor interactions with binding site at the receptor. On the other hand, substitution at position 6 of the benzimidazole ring was well-tolerated, and

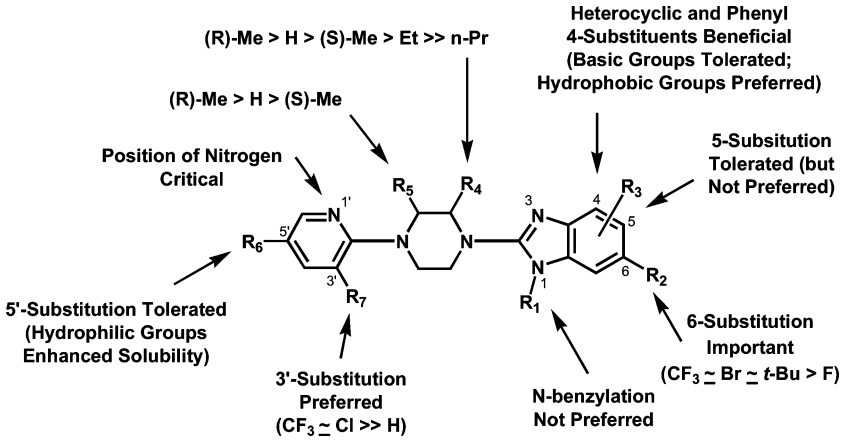


Figure 4. Summary of SAR.

trifluoromethyl, bromo, and *tert*-butyl groups were identified as the optimal substituents. The introduction of an additional substituent at position 5 of the benzimidazole ring seemed to provide limited benefit, due to steric limitations. On the other hand, the introduction of an additional substituent at position 4 of the benzimidazole ring led to significant enhancement of the activity. For example, bulky hydrophobic groups were found to be the preferred substituents at position 4, which revealed the existence of a new, relatively large hydrophobic pocket in the TRPV1 receptor.

We found that substitution of the piperazine ring with a methyl group resulted in enhancement of potency and that the preferred configuration of the substituents R_4 and R_5 was *R*. A methyl group was found as the optimal R_4 substituent, since increase of the size and length of this substituent to ethyl and *n*-propyl led to substantial decrease of activity.

Next we studied the structural features of the pyridine ring that influence the functional activity of the novel template of TRPV1 antagonists. The presence of substituents on the pyridine ring and ortho-attachment of the pyridine ring to the piperazine core were critical for potency. We found that position 3′ of the pyridine ring was the most tolerated site for substitution, and a trifluoromethyl group or chlorine or iodine atoms were the most preferred substituents. Additional substitution of the pyridine ring at position 5′ with various polar, charged, or hydrophobic groups maintained or increased the potency.

Finally, the simultaneous introduction of bulky lipophilic substituents at position 4 of the benzimidazole ring, a methyl group as the substituent R_4 of the piperazine core, and polar or charged groups at position 5′ of the pyridine ring gave rise to the most potent compounds in the series.

As a result of this SAR investigation, we identified the potent analogue **46ad**, which showed good pharmacokinetic profile and was found to be orally bioavailable. In vivo, compound **46ad** was found to be effective at preventing capsaicin-induced flinching in rats in a dose-dependent manner, and it reversed thermal hyperalgesia in a model of inflammatory pain, which was induced by complete Freund's adjuvant (CFA).

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. Purity of the compounds was determined on an Agilent 1100 spectrometer by method A [Phenomenex Luna C_8 column (100 × 4.6 mm) at a 1.0 mL/min flow rate using a gradient of 5−100% 5 mM ammonium acetate (pH 5.5) in acetonitrile and 20 mM ammonium acetate (pH 5.5) in water] and method B [Phenomenex Luna C_8 column (100 × 4.6 mm) at a 1.0 mL/min flow rate using a gradient of 10−100% 0.1% formic acid in acetonitrile and 0.1% formic acid in water]. The purity of the compounds was determined on an HP 1100 spectrometer by method C [Gemini C_{18} column (150 × 4.6 mm) at a 1.25 mL/min flow rate using a gradient of 10−95% 5 mM ammonium acetate (pH 5.5) in acetonitrile and 20 mM ammonium acetate (pH 5.5) in water] and method D [Synergi Max-RP column (150 × 4.6 mm) at a 1.0 mL/min flow rate using a gradient of 10−90% 0.1% formic acid in acetonitrile and 0.1% formic acid in water]. Silica gel chromatography was performed using either glass columns packed with silica gel (200−400 mesh, Aldrich Chemical) or prepacked silica gel cartridges (Biotage). Melting points were determined on a Buchi-545 melting point apparatus and are uncorrected. ^{1}H NMR spectra were determined with a Bruker 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 analysis was 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 water or organic solvents were tenaciously retained in some analytical samples, even after prolonged drying under reduced pressure.

6-*tert*-Butyl-2-(4-(3-chloropyridin-4-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole (5). A mixture of the 2-chlorobenzoimidazole **20a** (209 mg, 1 mmol), piperazine **8b** (305 mg, 1.5 mmol), and *N*,*N*-diisopropylethylamine (0.7 mL, 4 mmol) in DMSO (5 mL) was stirred at 80 °C for 24 h. The mixture was then cooled to room temperature, diluted with water (10 mL), and extracted with EtOAc (2 × 20 mL). The combined organic phases were washed with water (2 × 10 mL) and brine (5 mL), dried over Na_2SO_4, and filtered. The filtrate was evaporated in vacuo and the residue was purified by silica gel chromatography, eluting with 20% EtOAc/hexane to give 0.17 g (46%) of the title compound as a yellow amorphous solid. MS (ESI, pos. ion) *m*/*z*: 370 (M + 1). ^{1}H NMR (DMSO-d_6): δ 1.31 (s, 9 H), 3.36−3.42 (m, 4 H), 3.60−3.80 (m, 4 H), 7.00 (dd, J = 8.2, 2.0 Hz, 1 H), 7.04 (dd, J = 7.8, 4.7 Hz, 1 H), 7.14 (d, J = 8.2 Hz, 1 H), 7.23 (d, J = 1.6 Hz, 1 H), 7.84 (dd, J = 7.8, 1.6 Hz, 1 H), 8.25 (dd, J = 4.7, 2.0 Hz, 1 H). LC/MS retention time: A, 9.60 min; B, 6.77 min.

4-Nitro-6-(trifluoromethyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole (31a). A mixture of 2-chlorobenzoimidazole **20c** (1.5 g, 5.7 mmol), 1-(3-trifluoromethylpyridin-2-yl)piperazine (1.8 g, 7.8 mmol), and *N*,*N*-diisopropylethylamine (1 mL, 5.7 mmol) in 1,4-dioxane (1 mL) was

heated in a microwave synthesizer at 200 °C for 40 min. The mixture was evaporated in vacuo and the residue was purified by silica gel column chromatography, eluting with 30% EtOAc/hexane to give 2.1 g (80%) of the title compound as an orange solid. Mp: 192.9−193 °C. MS (ESI, pos. ion) *m*/*z*: 461 (M + 1). ^{1}H NMR (CD_3OD): δ 3.26−3.38 (m, 4 H), 3.76−3.88 (m, 4 H), 7.13 (dd, J = 6.0, 5.6 Hz, 1 H), 7.68 (br s, 1 H), 7.97 (d, J = 8.0 Hz, 1 H), 8.02 (s, 1 H), 8.42 (d, J = 4.0 Hz, 1 H). Anal. ($C_{18}H_{14}F_6N_6O_2$): C, H, N.

(*R*)-(5-Chloro-6-(3-methyl-4-(4-nitro-6-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-2-yl)piperazin-1-yl)pyridin-3-yl)methanol (31b). A mixture of 2-chlorobenzoimidazole **20c** (1.33 g, 5 mmol), piperazine **8t** (1.21 g, 5 mmol), and *N*,*N*-diisopropylethylamine (1.75 mL, 10 mmol) in EtOH (4 mL) was heated in a microwave synthesizer at 175 °C for 60 min. The mixture was evaporated in vacuo and the residue was purified by silica gel column chromatography, eluting with 60% EtOAc/hexane to give 1.81 g (77%) of the title compound as a yellow solid. MS (ESI, pos. ion) *m*/*z*: 471 (M + 1). ^{1}H NMR (CD_3OD): δ 1.51 (d, J = 6.7 Hz, 3 H), 3.07 (dt, J = 12.1, 2.7 Hz, 1 H), 3.17 (dd, J = 12.5, 2.7 Hz, 1 H), 3.70 (dt, J = 12.1, 2.7 Hz, 1 H), 3.83 (t, J = 11.5 Hz, 2 H), 4.19 (d, J = 12.9 Hz, 1 H), 4.56 (s, 2 H), 4.65 (br s, 1 H), 7.69−7.80 (m, 2 H), 8.10 (br s, 1 H), 8.17 (br s, 1 H).

6-(Trifluoromethyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)-piperazin-1-yl)-1*H*-benzo[*d*]imidazol-4-amine (32a). Compound **31a** (1.8 g, 3.9 mmol) was added to a suspension of 10% Pd/C (0.16 g) in EtOH (50 mL) under a hydrogen atmosphere. The reaction mixture was stirred at room temperature for 4 h and filtered through a pad of Celite. The filtrate was evaporated under reduced pressure and the residue was purified by silica gel column chromatography, eluting with 45% EtOAc/hexane to give 1.1 g (66%) of the title compound as a off-white amorphous solid. MS (ESI, pos. ion) *m*/*z*: 431 (M + 1). ^{1}H NMR (CD_3OD): δ 3.58−3.66 (m, 4 H), 3.90−4.00 (m, 4 H), 6.90 (s, 1 H), 7.13 (s, 1 H), 7.45 (dd, J = 7.6, 5.0 Hz, 1 H), 8.28 (dd, J = 7.6, 1.4 Hz, 1 H), 8.74 (d, J = 3.6 Hz, 1 H). Anal. ($C_{18}H_{16}F_6N_6$): C, H, N.

(*R*)-(6-(4-(4-Amino-6-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-2-yl)-3-methylpiperazin-1-yl)-5-chloropyridin-3-yl)methanol (32b). Following the procedure described for compound **32a**, compound **31b** provided the title compound (96%) as a yellow gum. MS (ESI, pos. ion) *m*/*e*: 441 (M + 1).

***N*-(3,4,5-Trifluorobenzyl)-6-(trifluoromethyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazol-4-amine (32c).** $NaBH(OAc)_3$ (211 mg, 1 mmol) was added to a mixture of compound **32a** (215 mg, 0.5 mmol) and 3,4,5-trifluorobenzaldehyde (88 mg, 0.55 mmol) in chloroform (2 mL) in one portion. The reaction mixture was stirred at room temperature for 2 h and concentrated in vacuo. The residue was dissolved in EtOAc (30 mL), washed successively with 1 N NaOH (15 mL) and brine (15 mL), dried over $MgSO_4$, and filtered. The filtrate was evaporated in vacuo and the residue was purified by silica gel chromatography, eluting with 25% EtOAc/hexane to give 175 mg (61%) of the title compound as a white solid. MS (ESI, pos. ion) *m*/*z*: 575 (M + 1). ^{1}H NMR (CD_3OD): δ 3.36−3.42 (m, 4 H), 3.60−4.72 (m, 4 H), 6.39 (s, 1 H), 6.92 (s, 1 H), 7.10−7.30 (m, 3 H), 8.06 (dd, J = 7.8 Hz, 1.5 Hz, 1 H), 8.51 (d, J = 3.7 Hz, 1 H). Anal. ($C_{25}H_{19}F_9N_6$) C, H, N.

(*R*)-*N*-(2-(4-(3-Chloro-5-(hydroxymethyl)pyridin-2-yl)-2-methylpiperazin-1-yl)-6-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-4-yl)cyclohexanecarboxamide (32d). A mixture of compound **32b** (221 mg, 0.5 mmol), cyclohexanecarboxylic acid (71 mg, 0.55 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (76 mg, 0.4 mmol) in dichloromethane (5 mL) was stirred at room temperature for 36 h. Water (20 mL) was added and the mixture was extracted with EtOAc (2 × 40 mL). The combined organic phases were washed with brine (20 mL), dried over Na_2SO_4, and filtered. The solvent was removed in vacuo and the residue was purified by silica gel chromatography, eluting with 80% EtOAc/hexanes to give 94 mg (34%) of the title compound as a white solid. MS (ESI, pos. ion) *m*/*z*: 551 (M + 1). ^{1}H NMR (CD_3OD): δ 1.26−1.75 (m, 8 H), 1.78−1.88 (m, 1 H), 1.90−2.00 (m, 2 H), 2.00−2.10 (m, 2 H), 2.59 (t, J = 12.1 Hz, 1 H), 3.17 (dt, J = 12.1, 3.1 Hz, 1 H), 3.27 (dd, J = 12.1, 2.9 Hz, 1H), 3.75 (dt, J = 12.1, 3.1 Hz, 1 H), 3.83 (t, J = 12.5 Hz, 2 H), 3.95 (d, J = 11.3 Hz, 1 H), 4.49 (br s, 1 H), 4.65 (s, 2 H), 7.35 (br s, 1 H), 7.87 (d, J = 2.9 Hz, 1 H), 8.27 (s, 1 H), 8.34 (br s, 1 H). LC/MS retention time: A, 10.32 min; B, 8.42 min.

(*R*)-*tert*-Butyl 2-(4-(3-Chloro-5-(hydroxymethyl)pyridin-2-yl)-2-methylpiperazin-1-yl)-6-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-4-ylcarbamate (32e). To a mixture of compound **32b** (221 mg, 1.0 mmol) and 1 N NaOH (1 mL) in THF (5 mL) was added di-*tert*-butyl dicarbonate (131 mg, 0.6 mmol) in one portion with stirring at room temperature. The mixture was stirred at room temperature for 30 min, diluted with water (20 mL), and extracted with EtOAc (2 × 40 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, and filtered. The filtrate was evaporated in vacuo and the residue was purified by silica gel column chromatography, eluting with 60% EtOAc/hexane to give 110 mg (41%) of the title compound as a light-yellow solid. MS (ESI, pos. ion) *m*/*e*: 541 (M + 1). ^{1}H NMR (CD_3OD): δ 1.47 (d, J = 6.6 Hz, 3 H), 1.55 (s, 9 H), 3.06 (dt, J = 12.1, 3.1 Hz, 1 H), 3.17 (dd, J = 12.3, 3.3 Hz, 1 H), 3.63 (dt, J = 12.1, 3.5 Hz, 1 H), 3.82 (t, J = 12.3 Hz, 2 H), 3.92 (d, J = 12.7 Hz, 1 H), 4.37 (br s, 1 H), 4.56 (s, 2 H), 7.20 (br s, 1 H), 7.77 (s, 1 H), 7.91 (br s, 1 H), 8.17 (s, 1 H). LC/MS retention time: A, 10.59 min; B, 8.51 min.

(*R*)-(5-Chloro-6-(4-(4-(dibenzylamino)-6-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-2-yl)-3-methylpiperazin-1-yl)pyridin-3-yl)-methanol (32g). To a solution of compound **32b** (221 mg, 0.5 mmol) in MeCN (2 mL) was added benzaldehyde (0.085 mL, 0.55 mmol) dropwise with stirring at room temperature. After the addition, the mixture was stirred at room temperature for 20 min and then $NaBH(OAc)_3$ (127 mg, 0.6 mmol) was added in one portion. The mixture was stirred for 4 h at room temperature, 1 N NaOH (5 mL) was added, and the mixture was extracted with EtOAc (2 × 40 mL). The combined organic phases were washed with brine (20 mL), dried over Na_2SO_4, and filtered. The filtrate was evaporated in vacuo and the residue was purified by silica gel chromatography, eluting with 60% EtOAc/hexane to give 112 mg (42%) of the title compound as a light-yellow solid. MS (ESI, pos. ion) *m*/*z*: 621 (M + 1). ^{1}H NMR (CD_3OD): δ 1.44 (d, J = 6.3 Hz, 3 H), 3.06 (dt, 12.1, 3.1 Hz, 1 H), 3.16 (dd, J = 12.5, 2.4 Hz, 1 H), 3.58 (dt, J = 12.1, 2.4 Hz, 1 H), 3.79 (t, J = 10.6, Hz, 2 H), 3.99 (d, J = 12.9, Hz, 1 H), 4.44 (br s, 1 H), 4.55 (s, 2 H), 4.55−4.70 (m, 2 H), 6.49 (br s, 2 H), 6.89 (br s, 1 H), 7.10−7.30 (m, 10 H), 7.76 (s, 1 H), 8.16 (s, 1 H). LC/MS retention time: A, 12.03 min; B, 9.81 min.

(*R*)-(6-(4-(4-(Benzylamino)-6-(trifluoromethyl)-1*H*-benzo[*d*]-imidazol-2-yl)-3-methylpiperazin-1-yl)-5-chloropyridin-3-yl)-methanol (32f). Compound **32f** was formed as a second product of the reaction described for compound **32g** and was isolated as a light-yellow solid (yield 98 mg, 36%). MS (ESI, pos. ion) *m*/*z*: 531 (M + 1).^{1}H NMR (CD_3OD): δ 1.44 (d, J = 6.3 Hz, 3 H), 3.06 (dt, 12.1, 3.1 Hz, 1 H), 3.16 (dd, J = 12.5, 2.4 Hz, 1 H), 3.58 (dt, J = 12.1, 2.4 Hz, 1 H), 3.73−3.93 (m, 3 H), 4.33 (br s, 1 H), 4.45 (s, 2 H), 4.55 (s, 2 H), 6.49 (s, 1 H), 6.89 (br s, 1 H), 7.25 (t, J = 7.1 Hz, 1 H), 7.33 (t, J = 7.4 Hz, 2 H), 7.45 (d, J = 7.4 Hz, 2 H), 7.76 (s, 1 H), 8.16 (s, 1 H). LC/MS retention time: A, 10.36 min; B, 7.86 min.

(*R*)-4-Bromo-2-(4-(3-chloro-5-nitropyridin-2-yl)-2-methyl-piperazin-1-yl)-6-(trifluoromethyl)-1*H*-benzo[*d*]imidazole (33). A mixture of piperazine **8ad** (970 mg, 3.79 mmol), 2-chlorobenzoimidazole **20f** (1.1 g, 3.79 mmol), *N*,*N*-diisopropylethylamine (0.79 mL, 4.55 mmol), and copper(I) iodide (1 mg) in 3-methylbutan-1-ol (5 mL) was heated in a microwave synthesizer at 200 °C for 60 min. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (gradient 5−100% EtOAc/CH_2Cl_2) to give 1.1 g (58%) of the title compound as a brown solid. MS (ESI, pos. ion) *m*/*z*: 519, 521 (M + 1).

(*R*)-6-(4-(4-Bromo-6-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-2-yl)-3-methylpiperazin-1-yl)-5-chloropyridin-3-amine (34). A

mixture of compound **33** (1.1 g, 2.12 mmol) and tin(II) chloride dihydrate (0.957 g, 4.24 mmol) in DMF (7 mL) was heated to 80 °C with stirring for 3 h. The reaction mixture was allowed to cool to room temperature and was diluted with EtOAc (100 mL). To the stirred mixture was added slowly a saturated aqueous solution of $NaHCO_3$ (200 mL) and Celite (10 g). The mixture was stirred at room temperature for 18 h and was filtered. The organic layer was separated from the filtrate and the aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated. The residue was purified by flash silica gel column chromatography (gradient 0−20% MeOH/CH_2Cl_2) to give 0.444 g (44%) of the title compound as a brown solid. MS (ESI, pos. ion) *m*/*z*: 489, 491 (M + 1).

(*R*)-(6-(3-Methyl-4-(6-(trifluoromethyl)-4-(3,4,5-trifluorophenyl)-1*H*-benzo[*d*]imidazol-2-yl)piperazin-1-yl)-5-(trifluoromethyl)pyridin-3-yl)methanol (35). A mixture of piperazine **8aa** (825 mg, 3.0 mmol), 2-chlorobenzoimidazole **20i** (1.05 g, 3.0 mmol), and *N*,*N*-diisopropylethylamine (1.05 mL, 6 mmol) in EtOH (5 mL) was heated in a microwave synthesizer at 175 °C for 4 h. The mixture was evaporated in vacuo and the residue was purified by silica gel column chromatography, eluting with 60% EtOAc/hexane to give 1.45 g (41%) of the title compound as a white solid. MS (ESI, pos. ion) *m*/*e*: 590 (M + 1). ^{1}H NMR (CD_3OD): δ 1.43 (d, J = 6.6 Hz, 3 H), 3.14 (dt, J = 12.5, 3.1 Hz, 1 H), 3.32−3.42 (m, 3 H), 3.48 (d, J = 11.7 Hz, 1 H), 3.62 (dt, J = 12.1, 3.1 Hz, 1 H), 4.05 (dd, J = 13.1, 2.1 Hz, 1 H), 4.46 (br s, 1 H), 4.65 (s, 2 H), 7.45 (s, 1 H), 7.49 (s, 1 H), 7.82−7.94 (m, 2 H), 8.06 (s, 1 H), 8.50 (s, 1 H). LC/MS retention time: A, 12.01 min; B, 11.86 min.

(*R*)-6-(3-Methyl-4-(6-(trifluoromethyl)-4-(3,4,5-trifluorophenyl)-1*H*-benzo[*d*]imidazol-2-yl)piperazin-1-yl)-5-(trifluoromethyl)nicotinaldehyde (36). A suspension of compound **35** (1.18 g, 2 mmol) and MnO_2 (3.48 g, 40 mmol) in CH_2Cl_2 (50 mL) was stirred at room temperature for 4 h. The reaction mixture was filtered though a pad of Celite and the filter cake was washed with EtOAc. The filtrate was evaporated in vacuo to give 1.01 g (86%) of the title compound as a white solid. MS (ESI, pos. ion) *m*/*z*: 588 (M + 1).

(*R*)-Methyl 5-Chloro-6-(3-methyl-4-(6-(trifluoromethyl)-4-(3,4,5-trifluorophenyl)-1*H*-benzo[*d*]imidazol-2-yl)piperazin-1-yl)nicotinate (37a). A mixture of piperazine **8s** (271 mg, 1.0 mmol), 2-chlorobenzoimidazole **20i** (350 mg, 1.0 mmol), *N*,*N*-diisopropylethylamine (0.35 mL, 2 mmol) in EtOH (1 mL) was heated in a microwave synthesizer at 175 °C for 1 h. The reaction mixture was evaporated in vacuo and the residue was purified by silica gel column chromatography (60% EtOAc/hexane) to give 163 mg (28%) of the title compound as a white solid. MS ESI, pos. ion) *m*/*e*: 584 (M + 1). ^{1}H NMR (CD_3OD): δ 1.42 (d, J = 6.3 Hz, 3 H), 3.21 (dt, J = 12.5, 3.1 Hz, 1 H), 3.31−3.38 (m, 1 H), 3.70 (dt, J = 12.5, 3.1 Hz, 1 H), 3.89 (s, 3 H), 4.08 (d, J = 12.1 Hz, 1 H), 4.18 (t, J = 14.0 Hz, 2 H), 4.50 (br s, 1 H), 7.47 (s, 2 H), 7.85 (br s, 2 H), 8.19 (d, J = 2.0 Hz, 1 H), 8.73 (d, J = 2.0 Hz, 1 H). LC/MS retention time: A, 12.85 min; B, 13.28 min.

1-(5-Chloro-6-(4-(5-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-2-yl)piperazin-1-yl)pyridin-3-yl)ethanone (37b). A mixture of piperazine **8n** (0.6 g, 1.92 mmol), 2-chlorobenzoimidazole **20n** (0.423 g, 1.92 mmol), and *N*,*N*-diisopropylethylamine (1 mL, 6 mmol) in dioxane (1 mL) was heated in a microwave synthesizer at 190 °C for 45 min. The reaction mixture was diluted with EtOAc (100 mL), washed with saturated aqueous solution of $NaHCO_3$ (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (30% EtOAc in hexane) to give 0.67 g (82%) of the title compound as a white amorphous solid. MS (ESI, pos. ion) *m*/*z*: 424 (M + 1). ^{1}H NMR (DMSO-d_6): δ 2.62 (s, 3 H), 3.70−3.81 (m, 8 H), 7.33−7.37 (m, 1 H), 7.41−7.45 (m, 1 H), 7.55 (s, 1 H), 8.25 (s, 1 H), 8.85 (s, 1 H). Anal. ($C_{19}H_{17}ClF_3N_5O\cdot H_2O$): C, H, N.

(*R*)-5-Chloro-6-(3-methyl-4-(6-(trifluoromethyl)-4-(3,4,5-trifluorophenyl)-1*H*-benzo[*d*]imidazol-2-yl)piperazin-1-yl)nicotinic Acid (38a). A mixture of ester **37a** (58 mg, 0.1 mmol) and 1 N NaOH (0.11 mL) in THF (1 mL) was stirred at 50 °C for 16 h. HCl (1 N, 0.11 mL) was added and the mixture was extracted with EtOAc (2 × 20 mL). The combined organic phases were washed with brine (5 mL), dried over Na_2SO_4, and filtered. The filtrate was evaporated in vacuo and the residue was purified by silica gel chromatography (10% MeOH/EtOAc) to give 38 mg (57%) of the title compound as a white amorphous solid. MS (ESI, pos. ion) *m*/*z*: 570 (M + 1). ^{1}H NMR (CD_3OD): δ 1.43 (d, J = 6.7 Hz, 3 H), 3.16 (dt, J = 12.1, 3.1 Hz, 1 H), 3.24−3.34 (m, 1 H), 3.65 (dt, J = 12.6, 3.1 Hz, 1 H), 4.02−4.22 (m, 3 H), 4.49 (br s, 1 H), 7.46 (br s, 2 H), 7.76−7.87 (m, 2 H), 8.18 (br s, 1 H), 8.73 (br s, 1 H). LC/MS retention time: A, 9.89 min; B, 11.74 min.

1-(5-Chloro-6-(4-(6-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-2-yl)piperazin-1-yl)pyridin-3-yl)ethanol (38b). To a solution of ketone **37b** (0.3 g, 0.71 mmol) in MeOH (20 mL) was added portionwise $NaBH_4$ (0.037 g, 1.0 mmol) with stirring at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, quenched with 20 mL of saturated aqueous solution of $NaHCO_3$, and diluted with EtOAc (50 mL). The organic phase was separated, washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was crystallized from 1:1 EtOAc/hexane mixture to give 0.27 g (90%) of the title compound. MS (ESI, pos. ion) *m*/*z*: 426 (M + 1). ^{1}H NMR (DMSO-d_6): δ 1.26−1.37 (m, 3 H), 3.28−3.42 (m, 4 H), 3.62−3.74 (m, 4 H), 4.74 (dt, J = 11.0, 6.3 Hz, 1 H), 5.34 (d, J = 4.7 Hz, 1 H), 7.27 (d, J = 7.8 Hz, 1 H), 7.31−7.39 (m, 1 H), 7.47 (s, 1 H), 7.79 (s, 1 H), 8.21 (s, 1 H), 11.89 (br s, 1 H). LC/MS retention time: A, 8.81 min; B, 4.47 min.

(*R*)-1-(6-((*R*)-3-Methyl-4-(6-(trifluoromethyl)-4-(3,4,5-trifluorophenyl)-1*H*-benzo[*d*]imidazol-2-yl)piperazin-1-yl)-5-(trifluoromethyl)pyridin-3-yl)ethanol and (*S*)-1-(6-((*R*)-3-Methyl-4-(6-(trifluoromethyl)-4-(3,4,5-trifluorophenyl)-1*H*-benzo[*d*]imidazol-2-yl)piperazin-1-yl)-5-(trifluoromethyl)pyridin-3-yl)ethanol (38c). To a solution of aldehyde **36** (88 mg, 0.15 mmol) in THF (2 mL) was added CH_3MgBr (0.063 mL, 0.19 mmol, 3.0 M in ether) at 0 °C, and the mixture was stirred at 0 °C for 10 min. After the addition of a saturated aqueous solution of NH_4Cl (5 mL), the mixture was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, and filtered. The filtrate was evaporated in vacuo and the residue was purified by silica gel chromatography, eluting with 60% EtOAc/hexane to give 78 mg (86%) of the title compound as a mixture of diastereomers. MS (ESI, pos. ion) *m*/*e*: 604 (M + 1). ^{1}H NMR (CD_3OD): δ 1.45 (d, J = 6.6 Hz, 3 H), 1.46 (d, J = 6.6 Hz, 3 H), 3.13 (dt, J = 12.2, 2.8 Hz, 1 H), 3.30−3.40 (m, 2 H), 3.48 (d, J = 12.7 Hz, 1 H), 3.63 (dt, J = 12.5, 3.1 Hz, 1 H), 4.04 (d, J = 12.1 Hz, 1 H), 4.46 (br s, 1 H), 4.92 (q, J = 6.6 Hz, 1 H), 7.45 (s, 1 H), 7.50 (s, 1 H), 7.82−7.96 (m, 2 H), 8.07 (s, 1 H), 8.52 (s, 1 H). LC/MS retention time: A, 12.28 min; B, 12.22 min.

(*R*)-(6-((*R*)-3-Methyl-4-(6-(trifluoromethyl)-4-(3,4,5-trifluorophenyl)-1*H*-benzo[*d*]imidazol-2-yl)piperazin-1-yl)-5-(trifluoromethyl)pyridin-3-yl)phenylmethanol and (*S*)-(6-((*R*)-3-Methyl-4-(6-(trifluoromethyl)-4-(3,4,5-trifluorophenyl)-1*H*-benzo[*d*]imidazol-2-yl)piperazin-1-yl)-5-(trifluoromethyl)pyridin-3-yl)phenylmethanol (38d). To a solution of the aldehyde **36** (88 mg, 0.15 mmol) in THF (2 mL) was added C_6H_5MgBr (0.19 mL, 0.19 mmol, 1.0 M solution in THF) at 0 °C. After the addition, the mixture was stirred at 0 °C for 10 min. A saturated aqueous solution of NH_4Cl (5 mL) was added, and the mixture was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, and filtered. The fitrate was removed in vacuo and the residue was purified by silica gel column chromatography (60% EtOAc/hexane) to give 81 mg (89%) of the title compound as a mixture of diastereoisomers. MS (ESI, pos. ion) *m*/*z*: 666 (M + 1). ^{1}H NMR (CD_3OD): δ 1.33 (d, J = 6.7 Hz, 3 H), 3.13 (dt, J = 12.1, 3.5 Hz, 1 H), 3.20−3.30 (m, 2 H), 3.48 (d, J = 11.3 Hz, 1 H), 3.52 (dt, J = 12.1, 3.1 Hz, 1 H), 3.95 (d, J = 12.5 Hz, 1 H), 4.36 (br s, 1 H), 5.78 (s, 1 H), 7.27 (t, J = 6.7 Hz, 1 H), 7.20−7.45 (m, 4 H), 7.80 (br s, 2 H), 7.93 (s, 2 H), 8.40 (s, 2 H). LC/MS retention time: A, 12.81 min; B, 13.20 min.

6-(Trifluoromethyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole (39). A solution of 1-(3-trifluoromethylpyridin-2-yl)piperazine (0.38 g, 1.6 mmol), 2-chlorobenzoimidazole **20n** (0.3 g, 1.36 mmol), and *N*,*N*-diisopropylethylamine (0.28 mL, 1.6 mmol) in DMSO (10 mL) was heated to 80 °C for 16 h. The reaction mixture was left to reach room temperature and was diluted with EtOAc (50 mL), washed with brine (2 × 20 mL), dried over Na_2SO_4, and filtered. The filtrate was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (30% EtOAc/hexane) to afford 0.18 g (30%) of the title compound as a solid. Mp: 221−224 °C. MS (ESI, pos. ion) *m*/*z*: 416 (M + 1). ^{1}H NMR (DMSO-d_6): δ 3.26−3.45 (m, 4 H), 3.67−3.74 (m, 4 H), 7.27 (d, J = 7.0 Hz, 2 H), 7.34−7.38 (m, 1 H), 7.48 (s, 1 H), 8.12 (d, J = 7.8 Hz, 1 H), 8.57 (d, J = 4.3 Hz, 1 H), 11.94 (br s, 1 H). Anal. ($C_{18}H_{15}F_6N_5$): C, H, N.

1-Benzyl-6-(trifluoromethyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole (40). To a solution of compound **39** (415 mg, 1.0 mmol) in anhydrous DMF (5 mL) was added sodium hydride (72 mg, 50% in mineral oil, 1.5 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 0.5 h and cooled to 0 °C. Benzyl bromide (171 mg, 1.0 mmol) was added, and the mixture was stirred at room temperature for 16 h. The reaction mixture was then quenched with saturated aqueous solution of $NaHCO_3$ (30 mL) and extracted with EtOAc (2 × 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (25% EtOAc/hexane) to give 84 mg (17%) of the title compound as a white solid. Mp: 154−157 °C. MS (ESI, pos. ion) *m*/*z*: 506 (M + 1). ^{1}H NMR ($CDCl_3$): δ 3.30−3.40 (m, 4 H), 3.40−3.50 (m, 4 H), 5.30 (s, 2 H), 7.05 (dd, J = 8.0, 4.8 Hz, 1 H), 7.18 (d, J = 7.0 Hz, 2 H), 7.26−7.40 (m, 5 H), 7.47 (d, J = 8.2 Hz, 1 H), 7.70 (d, J = 8.2 Hz, 1 H), 7.89 (dd, J = 7.6, 1.8 Hz, 1 H), 8.45 (dd, J = 4.8, 1.2 Hz, 1 H), LC/MS retention time: A, 12.05 min; B, 11.93 min.

1-Benzyl-5-(trifluoromethyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole (41). The title compound was obtained as a second product of the reaction described for the preparation of compound **40** and isolated as a white solid (yield 11 mg, 2%). MS (ESI, pos. ion) *m*/*z*: 506 (M + 1). ^{1}H NMR ($CDCl_3$): δ 3.36−3.48 (m, 8 H), 5.29 (s, 2 H), 7.03 (dd, J = 7.6, 4.5 Hz, 1 H), 7.08 (d, J = 8.2 Hz, 1 H), 7.17 (d, J = 7.0 Hz, 2 H), 7.27−7.44 (m, 4H), 7.87 (dd, J = 7.8, 2.0 Hz, 1 H), 7.92 (s, 1 H), 8.45 (dd, J = 4.8, 1.2 Hz, 1 H). Anal. ($C_{25}H_{21}F_6N_5$·0.2EtOAc): C, H, N.

6-Bromo-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole (42). Following the procedure described for compound **39**, 1-(3-trifluoromethylpyridin-2-yl)piperazine and 2-chlorobenzoimidazole **20o** provided the title compound (66%) as a white amorphous solid. MS (ESI, pos. ion) *m*/*z*: 428 (M + 1). ^{1}H NMR (DMSO-d_6): δ 3.28−3.38 (m, 4 H), 3.60−3.70 (m, 4 H), 7.06 (s, 1 H), 7.14 (m, 1 H), 7.19−7.30 (m, 1 H), 7.36 (s, 1 H), 8.10 (d, J = 7.4 Hz, 1 H), 8.56 (d, J = 3.5 Hz, 1 H), 11.66 (s, 1 H). Anal. ($C_{17}H_{15}BrF_3N_5$): C, H, N.

5-Bromo-6-(trifluoromethyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole (43a). Following the procedure described for compound **39**, 1-(3-trifluoromethylpyridin-2-yl)piperazine and 2-chlorobenzoimidazole **20b** provided the title compound (83%) as a white solid. MS (ESI, pos. ion) *m*/*z*: 496 (M + 1). ^{1}H NMR (DMSO-d_6): δ 3.35−3.46 (m, 4 H), 3.67−3.74 (m, 4 H), 7.27 (dd, J = 7.8, 4.7 Hz, 1 H), 7.56 (s, 1 H), 7.59 (s, 1 H), 8.13 (dd, J = 7.8, 2.0 Hz, 1 H), 8.57 (d, J = 3.5 Hz, 1 H). LC/MS retention time: A, 10.75 min; B, 9.05 min.

5-Bromo-6-(trifluoromethyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazole (43b). To a solution of compound **43a** (203 mg, 0.41 mmol) in dichloromethane (6 mL) were added *N*,*N*-diisopropylethylamine (148 mg, 1.15 mmol) and 2-(trimethylsilyl)-ethoxymethyl chloride (94 mg, 0.57 mmol). The reaction mixture was stirred at room temperature for 16 h. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography (30% EtOAc/hexane) to afford 176 mg (69%) of the title compound as an amorphous solid. MS (ESI, pos. ion) *m*/*z*: 624 (M + 1).

4-Bromo-6-(trifluoromethyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole (44a). Following the procedure described for compound **39**, 1-(3-trifluoromethylpyridin-2-yl)piperazine and 2-chlorobenzoimidazole **20f** provided the title compound (90%) as a white solid. Mp: 196 °C. MS (ESI, pos. ion) *m*/*z*: 494 (M + 1). ^{1}H NMR ($CDCl_3$): δ 3.40−3.50 (m, 4 H), 3.70−3.80 (m, 4 H), 7.09 (dd, J = 8.0, 4.0 Hz, 1 H), 7.48 (s, 1 H), 7.53 (s, 1 H), 7.93 (d, J = 8.0 Hz, 1 H), 8.48 (d, J = 4.0 Hz, 1 H). Anal. ($C_{18}H_{14}BrF_6N_5$): C, H, N.

4-Bromo-6-(trifluoromethyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazole (44b). Following the procedure described for compound **43b**, compound **44a** and 2-(trimethylsilyl)ethoxymethyl chloride provided the title compound (34%) as a light-brown oil. MS (ESI, pos. ion) *m*/*z*: 564 (M + 1). **(*R*)-1-(6-((*R*)-4-(4-Bromo-6-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-2-yl)-3-methylpiperazin-1-yl)-5-chloropyridin-3-yl)ethanol and (*S*)-1-(6-((*R*)-4-(4-Bromo-6-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-2-yl)-3-methylpiperazin-1-yl)-5-chloropyridin-3-yl)ethanol (44c).** A mixture of the piperazines **8ag** (766 mg, 3 mmol), 2-chlorobenzoimidazole **20f** (902 mg, 3 mmol), and *N*,*N*-diisopropylethylamine (1.05 mL, 6 mmol) in EtOH (2 mL) was heated in a microwave synthesizer at 175 °C for 1 h. The reaction mixture was evaporated in vacuo and the residue was purified by silica gel chromatography (60% EtOAc/hexane) to give 638 mg (41%) of the title compound as a mixture of diastereoisomers. MS (ESI, pos. ion) *m*/*z*: 518 (M + 1). ^{1}H NMR (CD_3OD): δ 1.44 (d, J = 6.3 Hz, 3 H), 1.48 (d, J = 6.7 Hz, 3 H), 3.05 (dt, J = 12.5, 3.1 Hz, 1 H), 3.15 (dd, J = 12.6, 3.8 Hz, 1 H), 3.64 (dt, J = 12.5, 3.1 Hz, 1 H), 3.80 (t, J = 12.5 Hz, 2 H), 4.49 (br s, 1 H), 4.78−4.85 (m, 1 H), 7.43 (br s, 1 H), 7.44 (br s, 1 H), 7.78 (d, J = 2.0 Hz, 1 H), 8.18 (d, J = 2.0 Hz, 1 H).

(*R*)-2-(4-(5-Bromo-3-chloropyridin-2-yl)-2-methylpiperazin-1-yl)-6-(trifluoromethyl)-4-(3,4,5-trifluorophenyl)-1*H*-benzo[*d*]-imidazole (45). A mixture of piperazine **8af** (875 mg, 3 mmol), 2-chlorobenzoimidazole **20i** (1.05 g, 3 mmol), and *N*,*N*-diisopropylethylamine (1.05 mL, 6 mmol) in EtOH (5 mL) was heated in a microwave synthesizer at 180 °C for 4 h. The reaction mixture was evaporated in vacuo and the residue was purified by silica gel chromatography (40% EtOAc/hexane) to give 3.09 g (34%) of the title compound as a white solid. MS (ESI, pos. ion) *m*/*z*: 606 (M + 1). ^{1}H NMR ($CDCl_3$): δ 1.50 (d, J = 6.6 Hz, 3 H), 3.10 (dt, J = 12.1, 3.1 Hz, 1 H), 3.21 (dd, J = 12.5, 3.5 Hz, 1 H), 3.68 (dt, J = 12.1, 3.1 Hz, 1 H), 3.80−4.00 (m, 2 H), 4.05 (br s, 1 H), 4.35 (br s, 1 H), 7.40−7.55 (m, 2 H), 7.70−7.90 (m, 1 H), 7.79 (d, J = 2.3 Hz, 1 H), 8.25 (d, J = 2.0 Hz, 1 H), 8.25−8.40 (m, 1 H). LC/MS retention time: A, 13.39 min; B, 14.06 min.

6-(3,4-Difluorophenyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)-piperazin-1-yl)-1*H*-benzo[*d*]imidazole (46a). To a mixture of 3,4-difluorophenylboronic acid (111 mg, 0.7 mmol) and 6-bromobenzoimidazole **42** (213 mg, 0.5 mmol) in ethylene glycol dimethyl ether (2 mL) were added lithium chloride (63 mg, 1.5 mmol) and 2 M aqueous solution of sodium carbonate (0.75 mL, 1.5 mmol). Nitrogen gas was bubbled through the mixture for 10 min and tetrakis(triphenylphosphine)palladium (58 mg, 0.05 mmol) was added. The reaction mixture was stirred at 80 °C under nitrogen atmosphere for 16 h, cooled to room temperature, diluted with EtOAc (50 mL), and filtered through Celite pad. The filtrate was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (55% EtOAc/hexane) to give 96 mg (42%) of the title compound as a white solid. MS (ESI, pos. ion) *m*/*z*: 460 (M + 1). ^{1}H NMR (DMSO-d_6): δ 3.28−3.38 (m, 4 H), 3.60−3.70 (m, 4 H), 7.18−7.34 (m, 3 H), 7.40−7.51 (m, 3 H), 7.68−7.60 (m, 1 H), 8.09 (dd, J = 7.8, 1.6 Hz, 1 H), 8.55 (dd, J = 4.8, 1.2 Hz, 1 H). LC/MS retention time: A, 10.42 min; B, 7.54 min.

6-(Trifluoromethyl)-5-(4-(trifluoromethyl)phenyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole, Trifluoroacetic Acid Salt (46b). A mixture of 5-bromobenzo-

imidazole **43a** (120 mg, 0.24 mmol), 4-(trifluoromethyl)phenylboronic acid (60 mg, 0.32 mmol), tetrakis(triphenylphosphine)-palladium(0) (28 mg, 0.02 mmol), and sodium carbonate (0.25 mL, 2 M solution in water) in dioxane (1.75 mL) was heated to 170 °C in a microwave synthesizer for 20 min. The reaction mixture was cooled to room temperature, diluted with EtOAc (10 mL), and filtered through a Varian Chem-Elut (3 mL) diatomaceous earth cartridge, and the filtrate was evaporated in vacuo. The residue was purified by preparative HPLC (gradient 0.1% trifluoroacetic acid in acetonitrile) to give 98 mg (72%) of the title compound as an amorphous solid. MS (ESI, pos. ion) *m*/*z*: 560 (M + 1). ^{1}H NMR (CD_3OD): δ 3.47−3.51 (m, 4 H), 3.85−3.89 (m, 4 H), 7.29 (dd, J = 7.6, 4.5 Hz, 1 H), 7.34 (s, 1 H), 7.55 (d, J = 7.8 Hz, 2 H), 7.73−7.81 (m, 3 H), 8.11 (d, J = 7.8 Hz, 1 H), 8.56 (d, J = 3.9 Hz, 1 H). Anal. ($C_{25}H_{18}F_9N_5 \cdot CF_3CO_2H$): C, H, N.

***N*-(4-(Trifluoromethyl)benzyl)-6-(trifluoromethyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1-((2-(trimethylsilyl)-ethoxy)methyl)-1*H*-benzo[*d*]imidazol-5-amine, Trifluoroacetic Acid Salt (46c).** A mixture of 5-bromobenzoimidazole **43b** (88 mg, 0.14 mmol), 4-(trifluoromethyl)benzylamine (37 mg, 0.21 mmol), tris(dibenzylideneacetone)dipalladium(0) (8 mg, 0.01 mmol), 2-(di-*tert*-butylphosphino)biphenyl (8 mg, 0.03 mmol), and sodium-*tert*-butoxide (31 mg, 0.33 mmol) in toluene (2 mL) was heated at 150 °C in a microwave synthesizer for 14 min. The reaction mixture was cooled to room temperature, diluted with EtOAc (5 mL), and filtered through a Celite pad. The filtrate was concentrated in vacuo, and the residue was dissolved in MeOH (4 mL) and purified by preparative HPLC (gradient 0.1% trifluoroacetic acid in acetonitrile) to give the title compound as pale-yellow oil. MS (ESI, pos. ion) *m*/*z*: 719 (M + 1).

***N*-(4-(Trifluoromethyl)benzyl)-6-(trifluoromethyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazol-5-amine, Trifluoroacetic Acid Salt (46d).** Compound **46c** was treated with 1:1 mixture of CF_3CO_2H/CH_2Cl_2 (3 mL) and stirred at room temperature for 12 h. The reaction mixture was concentrated to yield a gummy residue, which was dissolved in MeOH (4 mL) and purified by preparative HPLC (gradient 0.1% trifluoroacetic acid in acetonitrile) to give 7 mg (8%) of the title compound as a yellow amorphous solid. MS (ESI, pos. ion) *m*/*z*: 589 (M + 1). ^{1}H NMR (CD_3OD): δ 3.43−3.49 (m, 4 H), 3.75−3.82 (m, 4 H), 4.67 (s, 2 H), 6.49 (s, 1 H), 7.32 (dd, J = 7.6, 4.9 Hz, 1 H), 7.53 (s, 1 H), 7.61 (d, J = 8.0 Hz, 2 H), 7.67 (d, J = 8.0 Hz, 2 H), 8.13 (d, J = 8.0 Hz, 1 H), 8.58 (d, J = 4.3 Hz, 1 H). LC/MS retention time: A, 11.21 min; B, 8.27 min.

(*R*)-5-Chloro-6-(4-(4-(4-fluorophenyl)-6-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-2-yl)-3-methylpiperazin-1-yl)pyridin-3-amine (46e). A mixture of compound **34** (444 mg, 0.909 mmol), 4-fluorophenylboronic acid (191 mg, 1.36 mmol), dichloro-bis-(triphenylphosphine)palladium(II) (128 mg, 0.181 mmol), and Na_2CO_3 (385 mg, 3.64 mmol) in a solution of 7:3:2 1,2-dimethoxyethane/H_2O/EtOH (4.5 mL) was heated to 82 °C for 3 h. The reaction mixture was cooled to room temperature and filtered. The filter cake was washed with MeOH (20 mL), and the combined filtrates were concentrated in vacuo. The residue was purified by silica gel column chromatography (gradient 15−100% EtOAc/hexane) to give 301 mg (66%) of the title compound as a brown solid. MS (ESI, pos. ion) *m*/*z*: 505, 507 (M + 1). ^{1}H NMR (CD_3OD): δ 1.39 (d, J = 6.3 Hz, 3 H), 2.84−2.96 (m, 2 H), 3.30−3.50 (m, 3 H), 3.80−4.00 (m, 1 H), 4.30−4.70 (m, 1 H), 7.08−7.60 (m, 7 H), 7.9 (br s, 1 H). Anal. ($C_{24}H_{21}ClF_4N_6 \cdot 0.5EtOAc \cdot 0.05H_2O$): C, H, N.

(*R*)-*N*-(5-Chloro-6-(4-(4-(4-fluorophenyl)-6-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-2-yl)-3-methylpiperazin-1-yl)pyridin-3-yl)-2-hydroxyacetamide (46f). A mixture of compound **46e** (117 mg, 0.232 mmol), acetoxyacetic acid (27 mg, 0.232 mmol), benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (154 mg, 0.348 mmol), and *N*,*N*-diisopropylethylamine (0.08 mL, 0.464 mmol) in CH_2Cl_2 (1.5 mL) was stirred at room temperature for 18 h. The reaction mixture was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (gradient 0−100% EtOAc/hexane) to give 139 mg (99%) of (*R*)-2-(5-chloro-6-(4-(4-(4-fluorophenyl)-6-(trifluoromethyl)-1*H*-benzo-[*d*]imidazol-2-yl)-3-methylpiperazin-1-yl)pyridin-3-ylamino)-2-oxoethyl acetate as a brown solid. MS (ESI, pos. ion) *m*/*z*: 605 (M + 1).

A mixture of the acetate from the previous step (139 mg, 0.23 mmol) and potassium carbonate (63 mg, 0.46 mmol) in MeOH (1.5 mL) was stirred at room temperature for 30 min. The reaction mixture was filtered and the filter cake was washed with MeOH (2 mL). The combined filtrates were concentrated in vacuo, and the residue was purified by silica gel column chromatography (gradient 40−60% EtOAc/hexane) to give 45 mg (35%) of the title compound as an orange solid. MS (ESI, pos. ion) *m*/*z*: 563 (M + 1). ^{1}H NMR (CD_3OD): δ 1.56 (d, J = 6.4 Hz, 3 H), 3.05−3.3 (m, 2 H), 3.60−3.90 (m, 3 H), 4.05−4.30 (m, 3 H), 4.55 (br s, 1 H), 7.20−7.60 (m, 5 H), 8.0−8.17 (m, 2 H) 8.29 (d, J = 2.4 Hz, 1 H), 8.53 (d, J = 2.4 Hz, 1 H). LC/MS retention time: A, 10.54 min; B, 5.81 min.

4-Piperidin-1-yl-6-(trifluoromethyl)-2-(4-(3-(trifluoromethyl)-pyridin-2-yl)piperazin-1-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazole (46g). Following the procedure described for compound **46c**, compound **44b** and piperidine provided the title compound (19%) as an oil. MS (ESI, pos. ion) *m*/*z*: 629 (M + 1).

4-Piperidin-1-yl-6-(trifluoromethyl)-2-(4-(3-(trifluoromethyl)-pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole, Trifluoroacetic Acid Salt (46h). Following the procedure described for compound **46d**, compound **46g** and trifluoroacetic acid provided the crude product, which was purified by preparative HPLC (gradient 0.1% trifluoroacetic acid in acetonitrile) to give the title compound (20%) as a colorless film. MS (ESI, pos. ion) *m*/*z*: 499 (M + 1). ^{1}H NMR (CD_3OD): δ 1.69 (s, 2 H), 1.89 (s, 4 H), 3.30−3.50 (m, 8 H), 3.87 (s, 4 H), 7.16−7.30 (m, 2 H), 7.3 (s, 1H), 8.05 (s, 1 H), 8.50 (s, 1 H). LC/MS retention time: A, 12.22 min; B, 8.61 min.

4-Morpholino-6-(trifluoromethyl)-2-(4-(3-(trifluoromethyl)-pyridin-2-yl)piperazin-1-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazole (46i). Following the procedure described for compound **46c**, compound **44b** and morpholine provided the title compound (34%) as an amorphous solid.

4-Morpholino-6-(trifluoromethyl)-2-(4-(3-(trifluoromethyl)-pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole (46j). Following the procedure described for compound **46d**, compound **46i** and trifluoroacetic acid provided the title compound (8%) as an amorphous solid. MS (ESI, pos. ion) *m*/*z*: 501 (M + 1). ^{1}H NMR (CD_3OD): δ 3.11−3.17 (m, 4 H), 3.43−3.50 (m, 4 H), 3.92 (dd, J = 11.7, 5.1 Hz, 8 H), 7.20 (s, 1 H), 7.28 (dd, J = 7.4, 5.1 Hz, 1 H), 7.36 (s, 1 H), 8.04−8.12 (m, 1 H), 8.55 (d, J = 3.9 Hz, 1 H). LC/MS retention time: C, 16.61 min; D, 11.86 min.

(*R*)-1-(5-Chloro-6-((*R*)-3-methyl-4-(6-(trifluoromethyl)-4-(3,4,5-trifluorophenyl)-1*H*-benzo[*d*]imidazol-2-yl)piperazin-1-yl)pyridin-3-yl)ethanol (46k). The title compound was isolated by preparative HPLC separation of the diastereoisomeric mixture of products of the reaction for the preparation of compound **46l**. The *R*-configuration of the chiral secondary alcohol was assigned at random. MS (ESI, neg ion) *m*/*z*: 570 (M − 1). ^{1}H NMR (CD_3OD): δ 1.44 (d, J = 6.7 Hz, 3 H), 1.49 (d, J = 6.6 Hz, 3 H), 3.06 (dt, J = 12.5, 3.2 Hz, 1 H), 3.15 (dd, J = 12.1, 3.3 Hz, 1 H), 3.64 (dt, J = 12.5, 3.1 Hz, 1 H), 3.80 (t, J = 12.5 Hz, 2 H), 4.06 (d, J = 12.9 Hz, 1 H), 4.40−4.52 (m, 1 H), 4.82 (q, J = 6.4 Hz, 1 H), 7.46 (s, 2 H), 7.78 (d, J = 1.9 Hz, 1 H), 7.86 (br s, 2 H), 8.18 (d, J = 1.6 Hz, 1 H). LC/MS retention time: A, 12.04 min; B, 11.58 min.

(*S*)-1-(5-Chloro-6-((*R*)-3-methyl-4-(6-(trifluoromethyl)-4-(3,4,5-trifluorophenyl)-1*H*-benzo[*d*]imidazol-2-yl)piperazin-1-yl)pyridin-3-yl)ethanol (46l). To a solution of the diastereomeric mixture **44c** (416 mg, 0.8 mmol) in MeCN (3 mL) was added 3,4,5-trifluorophenylboronic acid (282 mg, 1.6 mmol), $Pd(PPh_3)_4$ (84 mg, 0.08 mmol), and Na_2CO_3 (4 mL, 0.4 M in water, 1.6 mmol). The mixture was stirred at 90 °C under N_2 atmosphere for 20 h, cooled to room temperature, and diluted with water (20 mL). The reaction mixture was extracted with EtOAc (2 × 40 mL). The combined organic extracts were washed with brine (20 mL), dried over

Na_2SO_4, and filtered. The filtrate was evaporated in vacuo and the residue was purified by silica gel column chromatography (50% EtOAc/hexane) to give 277 mg (61%) of the product of the reaction as a mixture of diastereoisomers. Separation of the mixture by preparative HPLC on a Chiralcel OD column (10% EtOH/hexane) afforded the fast-running diastereoisomer **46l**. The *S*-configuration of the chiral secondary alcohol of the isomer **46l** was assigned at random. MS (ESI, neg ion) *m*/*z*: 570 (M-1). ^{1}H NMR (CD_3OD): δ 1.44 (d, J = 6.6 Hz, 3 H), 1.49 (d, J = 6.6 Hz, 3 H), 3.06 (dt, J = 12.5, 3.1 Hz, 1 H), 3.15 (dd, J = 12.1, 3.3 Hz, 1 H), 3.64 (dt, J = 12.5, 3.1 Hz, 1 H), 3.80 (t, J = 12.5 Hz, 2 H), 4.06 (d, J = 12.9 Hz, 1 H), 4.40−4.52 (m, 1 H), 4.82 (q, J = 6.4 Hz, 1 H), 7.46 (s, 2 H), 7.78 (d, J = 1.9 Hz, 1 H), 7.86 (br s, 2 H), 8.18 (d, J = 1.6 Hz, 1 H). LC/MS retention time: A, 12.05 min; B, 11.57 min.

6-(Trifluoromethyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)-piperazin-1-yl)-4-(3,4,5-trifluorophenyl)-1*H*-benzo[*d*]imidazole (46m). A mixture of compound **44a** (2.22 g, 4.5 mmol), 3,4,5-trifluorophenylboronic acid (1.1 g, 6 mmol), $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol), Na_2CO_3 monohydrate (1 g, 8 mmol), dimethoxyethane (7 mL), H_2O (3 mL), and EtOH (2 mL) was subjected to microwave irradiation at 120 °C with stirring for 10 min. The mixture was diluted with water (10 mL) and extracted with EtOAc (2 × 20 mL). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo and the residue was purified by silica gel chromatography, eluting with 35% EtOAc/hexane to give 1.7 g (69%) of the title compound as a white amorphous solid. MS (ESI, pos. ion) *m*/*z*: 546 (M + 1). ^{1}H NMR (CD_3OD): δ 3.34−3.42 (m, 4 H), 3.74−3.84 (m, 4 H), 7.22 (dd, J = 7.4, 4.9 Hz, 1 H), 7.47 (br s, 2 H), 7.88 (br s, 2 H), 8.06 (dd, J = 7.8, 1.5 Hz, 1 H), 8.51 (d, J = 3.7 Hz, 1 H). Anal. ($C_{24}H_{16}F_9N_5$): C, H, N.

4-Thiazol-2-yl-6-(trifluoromethyl)-2-(4-(3-(trifluoromethyl)-pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole, Trifluoroacetic Acid Salt (46n). A mixture of compound **44a** (148 mg, 0.3 mmol), 2-tributylstannylthiazole (187 mg, 0.5 mmol), $Pd(PPh_3)_4$ (46 mg, 0.04 mmol), and 1,4-dioxane (1 mL) was subjected to microwave irradiation at 140 °C with stirring for 60 min. The solvent was removed in vacuo and the residue was purified by preparative HPLC (gradient 0.1% trifluoroacetic acid in acetonitrile) to give 120 mg (80%) of the title compound as a white amorphous solid. MS (ESI, pos. ion) *m*/*z*: 499 (M + 1). ^{1}H NMR ($CDCl_3$): δ 3.40−3.52 (m, 4 H), 3.84 (br s, 4 H), 7.10 (dd, J = 8.0, 4.0 Hz, 1 H), 7.60−7.80 (m, 2 H), 7.81 (s, 1 H), 7.93 (dd, J = 8.0, 4.0 Hz, 1 H), 8.49 (d, J = 4.0 Hz, 1 H), 9.00 (d, J = 4.0 Hz, 1 H), 10.55 (br s, 1 H). Anal. ($C_{21}H_{16}F_6N_6S\cdot0.11TFA\cdot0.22H_2O$): C, H, N.

4-(3,4-Difluorobenzyl)-6-(trifluoromethyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole, Trifluoroacetic Acid Salt (46o). A mixture of 4-bromobenzoimidazole **44a** (148 mg, 0.3 mmol), a 0.5 M solution of 3,4-difluorobenzylzinc bromide in THF (2 mL, 1 mmol), and $Pd(PPh_3)_4$ (35 mg, 0.03 mmol) was heated at reflux for 12 h. The solvent was removed in vacuo and the residue was purified by preparative HPLC (gradient 0.1% trifluoroacetic acid in acetonitrile) to give 25 mg (13%) of the title compound as a white amorphous solid. MS (ESI, pos. ion) *m*/*z*: 542 (M + 1). ^{1}H NMR ($CDCl_3$): δ 3.20−3.30 (m, 4 H), 3.60−3.70 (m, 4 H), 4.15 (s, 2 H), 7.01−7.13 (m, 5 H), 7.26 (s, 1 H), 7.93 (d, J = 8.0 Hz, 1 H), 8.45 (d, J = 4.4 Hz, 1 H). LC/MS retention time: A, 11.93 min; B, 6.42 min.

6-(Trifluoromethyl)-4-(4-(trifluoromethyl)cyclohexyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]-imidazole (46p). To 4-trifluoromethylcyclohexanone (4.98 g, 30 mmol) in THF (100 mL) was added lithium bistrimethylsilylamide (30 mL, 1 M solution in THF) over a period of 30 min with stirring at −78 °C. After stirring for 1 h at −78 °C, a solution of *N*-phenyltrifluoromethanesulfonimide (10.71 g, 30 mmol) in THF (100 mL) was added over a period of 30 min. The reaction mixture was stirred at −78 °C for 2 h and slowly warmed to room temperature over a period of 6 h. The reaction mixture was extracted with EtOAc, and the combined organic extracts were washed with water, dried over Na_2SO_4, and filtered. The filtrate was evaporated and the residue was purified by silica gel column chromatography (10% ethyl acetate/hexane) to give 5.6 g (63%) of 4-(trifluoromethyl)cyclohex-1-enyl trifluoromethanesulfonate as an oil. MS (ESI, pos. ion) *m*/*z*: 299 (M + 1).

To a solution of the triflate from the previous step (5.6 g, 18.8 mmol) in dioxane (100 mL) were added bisboronpinacolate (5.6 g, 22 mmol), potassium acetate (6 g, 61 mmol), $PdCl_2$(dppf) (315 mg, 0.6 mml), and dppf (332 mg, 0.6 mmol), and the contents were flushed with nitrogen. The reaction mixture was heated at 80 °C overnight. The solvents were removed in vacuo, and the residue was extracted with EtOAc and washed with water. The organic layer was separated, dried over Na_2SO_4, and filtered. The filtrate was evaporated and the residue was purified by silica gel column chromatography (10% ethyl acetate/hexane) to give 4.23 g (81%) of 4,4,5,5-tetramethyl-2-(4-trifluoromethyl-cyclohex-1-enyl)[1,3,2]-dioxaborolane as white amorphous solid. MS (ESI, pos. ion) *m*/*z*: 277 (M + 1).

A mixture of 4-bromobenzoimidazole **44a** (100 mg, 0.5 mmol), 4,4,5,5-tetramethyl-2-(4-trifluoromethyl-cyclohex-1-enyl)[1,3,2]-dioxaborolane from the previous step (200 mg, 0.72 mmol), $Pd(PPh_3)_4$ (58 mg, 0.05 mmol), and Na_2CO_3 (80 mg, 0.75 mmol) in dimethoxyethane (1 mL) was subjected to microwave irradiation at 200 °C with stirring for 40 min. The solvent was removed in vacuo and the residue purified by silica gel chromatography (60% EtOAc/hexane) to give 58 mg (52%) of 6-(trifluoromethyl)-4-(4-(trifluoromethyl)cyclohex-1-enyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole, trifluoroacetic acid salt, as a white solid. MS (ESI, pos. ion) *m*/*z*: 564 (M + 1). Mp: 214−217 °C.

6-(Trifluoromethyl)-4-(4-(trifluoromethyl)cyclohex-1-enyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole, trifluoroacetic acid salt, from the previous step (10 mg) was subjected to catalytic hydrogenation in EtOH (1 mL) using 10% Pd/C (10 mg) as catalyst. The reaction was conducted at room temperature under 1 atm of hydrogen for 2 days. The catalyst was filtered through a Celite pad and the filter cake was washed with methanol. The combined filtrates were evaporated in vacuo to give 10 mg (100%) of the title compound as a film. MS (ESI, pos. ion) *m*/*z*: 565 (M + 1). ^{1}H NMR (CD_3OD): δ 1.50−2.10 (m, 10 H), 3.31 (s, 4 H), 3.67 (s, 4 H), 7.00−7.20 (m, 2 H), 7.27 (s, 1 H), 7.97 (d, J = 7.8 Hz, 1 H), 8.42 (s, 1 H). LC/MS retention time: A, 12.28 min; B, 3.21 min.

6-(Trifluoromethyl)-4-(4-(trifluoromethyl)phenyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]-imidazole (46q). Following the procedure described for compound **46m**, compound **44a** and 4-trifluoromethylphenylboronic acid provided the title compound (83%) as a white solid. MS (ESI, pos. ion) *m*/*z*: 548 (M + 1). ^{1}H NMR (CD_3OD): δ 3.32−3.40 (m, 4 H), 3.76−3.82 (m, 4 H), 7.22 (dd, J = 7.7, 2.8 Hz, 1 H), 7.47 (s, 1 H), 7.51 (s, 1 H), 7.77 (s, 1 H), 7.79 (s, 1 H), 8.08−8.04 (m, 3 H), 8.51 (d, J = 3.9 Hz, 1 H). Anal. ($C_{25}H_{18}F_9N_5$): C, H, N.

4-Phenyl-6-(trifluoromethyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole (46r). Following the procedure described for compound **46m**, compound **44a** and phenylboronic acid provided the title compound (65%) as an amorphous solid. MS (ESI, pos. ion) *m*/*z*: 492 (M + 1). ^{1}H NMR (CD_3OD): δ 3.34−3.42 (m, 4 H), 3.72−3.80 (m, 4 H), 7.21 (dd, J = 7.5, 2.5 Hz, 1 H), 8.00−7.39 (m, 7 H), 8.04 (d, J = 6.8 Hz, 1 H), 8.50 (d, J = 4.5 Hz, 1 H). Anal. ($C_{24}H_{19}F_6N_5$): C, H, N.

4-(3-(Trifluoromethoxy)phenyl)-6-(trifluoromethyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]-imidazole, Trifluoroacetic Acid Salt (46s). Following the procedure described for compound **46m**, compound **44a** and 3-(trifluoromethoxy)phenylboronic acid provided the crude product which was purified by preparative HPLC (gradient 0.1% trifluoroacetic acid in acetonitrile) to give the title compound (60%) as an off-white amorphous solid. MS (ESI, pos. ion) *m*/*z*: 576 (M + 1). ^{1}H NMR ($CDCl_3$): δ 3.40−3.50 (m, 4 H), 3.68−3.80 (m, 4 H), 7.08 (dd, J = 8.0, 4.0 Hz, 1 H), 7.12−8.40 (m, 7 H), 8.50 (d, J = 4.0 Hz, 1 H). Anal. ($C_{25}H_{18}F_9N_5O\cdot0.15TFA$): C, H, N.

4-(4-*tert*-Butylphenyl)-6-(trifluoromethyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole (46t). Following the procedure described for compound **46m**, compound **44a** and 4-*tert*-butylphenylboronic acid provided the title compound (76%) as a white solid. Mp: 214 °C. MS (ESI, pos. ion) *m*/*z*: 548 (M + 1). ^{1}H NMR ($CDCl_3$): δ 1.37 (s, 9 H), 3.43 (br s, 4 H), 3.70−3.82 (m, 4 H), 7.08 (br s, 1 H), 7.33 (s, 1 H), 7.50−7.60 (m, 3 H), 7.68 (s, 1 H), 7.92 (d, J = 7.6 Hz, 1 H), 8.30 (s, 1 H), 8.47 (d, J = 3.6 Hz, 1 H). Anal. ($C_{28}H_{27}F_6N_5$): C, H, N.

4-Thiophen-2-yl-6-(trifluoromethyl)-2-(4-(3-(trifluoromethyl)-pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole, Trifluoroacetic Acid Salt (46u). Following the procedure described for compound **46m**, compound **44a** and (thiophen-2-yl)boronic acid provided the crude product, which was purified by preparative HPLC (gradient 0.1% trifluoroacetic acid in acetonitrile) to give the title compound (57%) as a white amorphous solid. MS (ESI, pos. ion) *m*/*z*: 498 (M + 1). ^{1}H NMR (CD_3OD): δ 3.40−3.50 (m, 4 H), 3.80−3.90 (m, 4 H), 7.20−7.25 (m, 2 H), 7.58 (d, J = 10.5 Hz, 2 H), 7.61 (dd, J = 5.2, 1.0 Hz, 1 H), 7.65 (dd, J = 7.8, 1.5 Hz, 1 H), 8.54 (d, J = 4.7 Hz, 1 H). Anal. ($C_{22}H_{16}F_6N_6S$·1.5TFA): C, H, N.

4-Pyridin-4-yl-6-(trifluoromethyl)-2-(4-(3-(trifluoromethyl)-pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole (46v). Following the procedure described for compound **46m**, compound **44a** and pyridin-4-ylboronic acid provided the title compound (50%) as a white solid. Mp: 293 °C. MS (ESI, pos. ion) *m*/*z*: 493 (M + 1). ^{1}H NMR (CD_3OD): δ 3.32−3.42 (m, 4 H), 3.74−3.86 (m, 4 H), 7.22 (dd, J = 7.7, 4.9 Hz, 1 H), 7.51 (br s, 1 H), 7.65 (br s, 1 H), 8.06 (d, J = 7.8 Hz, 1 H), 8.18 (br s, 2 H), 8.51 (d, J = 4.2 Hz, 1 H), 8.61 (br s, 2 H). Anal. ($C_{23}H_{18}F_5N_6$): C, H, N.

4-Pyrazin-2-yl-6-(trifluoromethyl)-2-(4-(3-(trifluoromethyl)-pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole (46w). Following the procedure described for compound **46n**, compound **44a** and 2-tributylstannylpyrazine provided the title compound (51%) as a yellow amorphous solid. MS (ESI, pos. ion) *m*/*z*: 494 (M + 1). ^{1}H NMR ($CDCl_3$): δ 3.40−3.52 (m, 4 H), 3.78−3.86 (m, 4 H), 7.08−7.14 (m, 1 H), 7.80 (s, 1 H), 7.90−7.96 (m, 2 H), 8.46−8.52 (m, 1 H), 8.58 (s, 1 H), 8.68 (s, 1 H), 9.36 (br s, 1 H), 10.75 (br s, 1 H). Anal. ($C_{22}H_{17}F_6N_7$): C, H, N.

4-(6-Methoxypyridin-3-yl)-6-(trifluoromethyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole, Trifluoroacetic Acid Salt (46x). Following the procedure described for compound **46m**, compound **44a** and 3-(6-methoxypyridyl)-boronic acid provided the crude product, which was purified by preparative HPLC (gradient 0.1% trifluoroacetic acid in acetonitrile) to give the title compound (32%) as a white amorphous solid. MS (ESI, pos. ion) *m*/*z*: 523 (M + 1). ^{1}H NMR (CD_3OD): δ 3.40−3.50 (m, 4 H), 3.80−3.90 (m, 4 H), 3.99 (s, 3 H), 6.82 (d, J = 8.6 Hz, 1 H), 7.26 (dd, J = 8.1, 5.3 Hz, 1 H), 7.53 (s, 1 H), 7.62 (s, 1 H), 8.00 (dd, J = 8.4, 2.2 Hz, 1 H), 8.08 (d, J = 7.7 Hz, 1 H), 8.49 (d, J = 1.9 Hz, 1 H), 8.53 (d, J = 4.6 Hz, 1 H). Anal. ($C_{24}H_{20}F_6N_6O$·0.95TFA·0.2H_2O): C, H, N.

4-Benzo[*b*]thiophen-2-yl-6-(trifluoromethyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole (46y). Following the procedure described for compound **46m**, compound **44a** and benzo[*b*]thiophen-2-ylboronic acid provided the title compound (61%) as an off-white amorphous solid. MS (ESI, pos. ion) *m*/*z*: 548 (M + 1). ^{1}H NMR (CD_3OD): δ 3.24−3.34 (m, 4 H), 3.70−3.80 (m, 4 H), 7.13 (dd, J = 8.0, 1.2 Hz, 1 H), 7.20−7.34 (m, 3 H), 7.56 (s, 1 H), 7.72−7.80 (m, 2 H), 7.98 (d, J = 7.6 Hz, 1 H), 8.32 (s, 1 H), 8.42 (d, J = 4.0 Hz, 1 H). Anal. ($C_{26}H_{19}F_6N_5S$): C, H, N.

4-(6-(Trifluoromethyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)-piperazin-1-yl)-1*H*-benzo[*d*]imidazol-4-yl)benzenamine (46z). Following the procedure described for compound **46m**, compound **44a** and 4-aminophenylboronic acid provided the title compound (48%) as amorphous solid. MS (ESI, pos. ion) *m*/*z*: 507 (M + 1). ^{1}H NMR (CD_3OD): δ 3.61−3.65 (m, 4 H), 4.01−4.03 (m, 4 H), 4.03 (s, 6 H), 7.11 (d, J = 8.6 Hz, 2 H), 7.48 (dd, J = 7.6, 4.5 Hz, 1 H), 7.54 (s, 1 H), 7.67 (s, 1 H), 7.81 (d, J = 7.2 Hz, 2 H), 8.31 (d, J = 7.4 Hz, 1 H), 8.77 (d, J = 5.5 Hz, 1 H). Anal. ($C_{24}H_{20}F_6N_6$·0.12TFA) C, H, N.

***N*,*N*-Dimethyl-4-(6-(trifluoromethyl)-2-(4-(3-(trifluoromethyl)-pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazol-4-yl)benzenamine (46aa).** Following the procedure described for compound **46m**, compound **44a** and 4-dimethylaminophenylboronic acid provided the title compound (45%) as a tan amorphous solid. MS (ESI, pos. ion) *m*/*z*: 535 (M + 1). ^{1}H NMR ($CDCl_3$): δ 3.07 (s, 6 H), 3.10−3.20 (m, 4 H), 3.44−3.54 (m, 4 H), 6.98 (d, J = 8.0 Hz, 2 H), 7.18−7.24 (m, 1 H), 7.28 (br s, 1 H), 7.41 (br s, 1 H), 7.50−7.60 (m, 2 H), 8.05 (d, J = 8.0 Hz, 1 H), 8.50 (d, J = 4.8 Hz, 1 H).

(*E*)-4-Styryl-6-(trifluoromethyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole (46ab). Following the procedure described for compound **46m**, compound **44a** and *trans*-2-phenylvinylboronic acid provided the title compound (53%) as a solid. Mp: 117.9−118 °C. MS (ESI, pos. ion) *m*/*z*: 518 (M + 1). ^{1}H NMR ($CDCl_3$): δ 3.18 (s, 4 H), 3.63 (s, 4 H), 7.10−7.20 (m, 2H), 7.25−7.35 (m, 3 H), 7.50−7.60 (m, 5 H), 7.92 (s, 1 H), 8.43 (s, 1 H). Anal. ($C_{26}H_{21}F_6N_5$·0.1H_2O·0.3EtOAc): C, H, N.

(*R*)-2-(4-(3-Chloro-5-vinylpyridin-2-yl)-2-methylpiperazin-1-yl)-6-(trifluoromethyl)-4-(3,4,5-trifluorophenyl)-1*H*-benzo[*d*]-imidazole (46ac). A mixture of compound **45** (2.73 g, 4.5 mmol), tributylvinylstannane (1.5 mL, 5.0 mmol), $Pd(Ph_3P)_4$ (255 mg, 0.23 mmol), LiCl (570 mg, 13.5 mmol), and a few crystals of 2,6-di-*tert*-butylphenol in dioxane (40 mL) was stirred at 95 °C for 5 h. The reaction mixture was cooled to room temperature, diluted with EtOAc (200 mL), washed with water (50 mL) and brine (50 mL), dried over Na_2SO_4, and filtered. The filtrate was evaporated in vacuo and the residue was purified by silica gel chromatography (20% EtOAc/hexane) to give 1.75 g (72%) of the title compound as a gum. MS (ESI, pos. ion) *m*/*z*: 552 (M + 1). ^{1}H NMR ($CDCl_3$): δ 1.51 (d, J = 6.6 Hz, 3 H), 3.11 (dt, J = 12.5, 3.1 Hz, 1 H), 3.22 (dd, J = 12.5, 4.0 Hz, 1 H), 3.69 (dt, J = 12.5, 3.1 Hz, 1 H), 3.72 (s, 1 H), 3.60−4.08 (m, 3 H), 4.38 (br s, 1 H), 5.32 (d, J = 11.0 Hz, 1 H), 5.71 (d, J = 17.6 Hz, 1 H), 6.63 (dd, J = 17.6, 11.0 Hz, 1 H), 7.44 (br s, 1 H), 7.50 (br s, 1 H), 7.74 (d, J = 2.0 Hz, 1 H), 7.84 (br s, 1 H), 8.18 (d, J = 1.6 Hz, 1 H), 8.37 (br s, 1 H).

(*R*)-1-(5-Chloro-6-((*R*)-3-methyl-4-(6-(trifluoromethyl)-4-(3,4,5-trifluorophenyl)-1*H*-benzo[*d*]imidazol-2-yl)piperazin-1-yl)pyridin-3-yl)ethane-1,2-diol and (*S*)-1-(5-Chloro-6-((*R*)-3-methyl-4-(6-(trifluoromethyl)-4-(3,4,5-trifluorophenyl)-1*H*-benzo[*d*]imidazol-2-yl)piperazin-1-yl)pyridin-3-yl)ethane-1,2-diol (46ad). A mixture of compound **46ac** (1.65 g, 3 mmol), OsO_4 (0.95 mL, 0.15 mmol, 4% in water), and *N*-methylmorpholine *N*-oxide (421 mg, 3.6 mmol) in acetone (20 mL) was stirred at room temperature for 5 h. The reaction mixture was treated with saturated $NaHSO_3$ (20 mL) and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4, and filtered. The filtrate was evaporated in vacuo and the residue was purified by silica gel column chromatography (EtOAc) to give 1.09 g (62%) of the desired product as a mixture of diastereoisomers. MS (ESI, pos. ion) *m*/*z*: 586 (M + 1). ^{1}H NMR (CD_3OD): δ 1.49 (d, J = 6.3 Hz, 3 H), 3.06 (dt, J = 12.5, 3.5 Hz, 1 H), 3.15 (dd, J = 12.5, 3.3 Hz, 1 H), 3.56−3.70 (m, 3 H), 3.81 (t, J = 11.7 Hz, 2 H), 4.07 (d, J = 11.7 Hz, 1 H), 4.47 (br s, 1 H), 4.66 (t, J = 5.5 Hz, 1 H), 7.40−7.52 (m, 2 H), 7.79 (s, 1 H), 7.88 (br s, 2 H), 8.19 (s, 1 H). Anal. ($C_{26}H_{22}ClN_5F_6O_2$·0.8H_2O): C, H, N.

6-*tert*-Butyl-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole (47a). A mixture of 2-chlorobenzoimidazole **20a** (0.209 g, 1 mmol), 1-(3-trifluoromethylpyridin-2-yl)piperazine (0.346 g, 1.65 mmol), and *N*,*N*-diisopropylethylamine (0.28 mL, 1.6 mmol) in MeCN (1 mL) was heated in a microwave synthesizer at 180 °C for 30 min. The reaction mixture was evaporated under vacuo and the residue was purified by silica gel column chromatography (30% EtOAc/hexane) to give 0.137 g (34%) of the title compound as a white solid. Mp: 247−249 °C. MS (ESI, pos. ion) *m*/*z*: 404 (M + 1). ^{1}H NMR (DMSO-d_6): δ 1.31 (s, 9 H), 3.25−3.35 (m, 4 H), 3.57−3.65 (m, 4 H), 7.01 (d, J = 8.2 Hz, 1 H), 7.13 (d, J = 8.2 Hz, 1 H), 7.22 (s, 1 H), 7.26 (dd, J = 7.8, 4.7 Hz, 1 H), 8.12 (d, J = 7.8 Hz, 1 H), 8.57 (d, J = 4.3 Hz, 1 H). LC/MS retention time: A, 9.91 min; B, 6.83 min.

6-Methyl-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole Hydrochloride (47b). Following the procedure described for compound **47a**, 2-chlorobenzoimidazole **20k** and 1-(3-trifluoromethylpyridin-2-yl)piperazine provided the crude reaction product. A solution of the product in EtOAc was treated with a 1 M solution of hydrogen chloride in Et_2O and the mixture was evaporated under reduced pressure. The residue was dried in vacuo to give the title compound (39%) as a white solid. MS (ESI, pos. ion) *m*/*z*: 362 (M + 1). ^{1}H NMR (DMSO-d_6): δ 2.33 (s, 3 H), 3.20−3.30 (m, 4 H), 3.50−3.64 (m, 4 H), 6.76 (d, J = 7.4 Hz, 1 H), 7.02 (s, 1 H), 7.09 (d, J = 7.4 Hz, 1 H), 7.20−7.30 (m, 1 H), 8.12 (d, J = 7.4 Hz, 1 H), 8.57 (d, J = 3.5 Hz, 1 H), 11.33 (br s, 1 H). Anal. ($C_{18}H_{18}F_3N_5$·HCl): C, H, N.

6-Fluoro-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole, Trifluoroacetic Acid Salt (47c). A mixture of the 2-chlorobenzimidazole **20g** (170 mg, 1.0 mmol), 1-(3-trifluoromethylpyridin-2-yl)piperazine (347 mg, 1.5 mmol), and sodium bicarbonate (250 mg, 2.9 mmol) in isoamyl alcohol (2 mL) was heated at 150 °C in a microwave synthesizer for 10 min. The reaction mixture was cooled to room temperature, diluted with MeOH (3 mL), and filtered. The filtrate was evaporated under reduced pressure and the residue was purified by preparative HPLC (gradient 0.1% trifluoroacetic acid in acetonitrile) to give 90 mg (25%) of the title compound as an amorphous solid. MS (ESI, pos. ion) *m*/*z*: 366 (M + 1). ^{1}H NMR (CD_3OD): δ 3.43−3.49 (m, 4 H), 3.79−3.85 (m, 4 H), 7.07−7.14 (m, 1 H), 7.20 (dd, J = 8.2, 2.3 Hz, 1 H), 7.28 (dd, J = 7.8, 5.1 Hz, 1 H), 7.40 (dd, J = 9.0, 4.3 Hz, 1 H), 8.10 (d, J = 8.0 Hz, 1 H), 8.55 (d, J = 4.0 Hz, 1 H). Anal. ($C_{17}H_{15}F_4N_5$·1.3CF_3COOH): C, H, N.

6-Chloro-2-[4-(3-trifluoromethylpyridin-2-yl)piperazin-1-yl]-1*H*-benzo[*d*]imidazole (47d). Following the procedure described for compound **47a**, 2-chlorobenzoimidazole **20j** and 1-(3-trifluoromethylpyridin-2-yl)piperazine provided the title compound (47%) as a white solid. Mp: 228−231 °C. MS (ESI, pos. ion) *m*/*z*: 382 (M + 1).). ^{1}H NMR (DMSO-d_6): δ 3.18−3.28 (m, 4 H), 3.58−3.68 (m, 4 H), 6.85−7.00 (m, 1 H), 7.10−7.30 (m, 3 H), 8.15 (d, J = 6.7 Hz, 1 H), 8.57 (d, J = 3.9 Hz, 1 H), 11.65 (br s, 1 H). Anal. ($C_{17}H_{15}ClF_3N_5$): C, H, N.

2-(4-(3-(Trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-3*H*-benzo[*d*]imidazole-5-carbonitrile, Trifluoroacetic Acid Salt (47e). Following the procedure described for compound **47c**, 2-chlorobenzoimidazole **20h** and 1-(3-trifluoromethylpyridin-2-yl)piperazine provided the title compound (4%) as an amorphous solid. MS (ESI, pos. ion) *m*/*z*: 373 (M + 1). ^{1}H NMR (CD_3OD): δ 3.46−3.54 (m, 4 H), 3.86−3.93 (m, 4 H), 7.31 (dd, J = 7.8, 4.7 Hz, 1 H), 7.57 (d, J = 8.2 Hz, 1 H), 7.71 (dd, J = 8.2, 1.6 Hz, 1 H), 7.78 (s, 1 H), 8.10−8.14 (m, 1 H), 8.58 (d, J = 3.5 Hz, 1 H). Anal. ($C_{18}H_{15}F_3N_6$·1.4CF_3CO_2H): C, H, N.

Methyl 2-(4-(3-(Trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-3*H*-benzo[*d*]imidazole-5-carboxylate, Trifluoroacetic Acid Salt (47f). Following the procedure described for compound **47c**, 2-chlorobenzoimidazole **20l** and 1-(3-trifluoromethylpyridin-2-yl)-piperazine provided the title compound (33%) as an amorphous solid. MS (ESI, pos. ion) *m*/*z*: 406 (M + 1). ^{1}H NMR (CD_3OD): δ 3.48−3.51 (m, 4 H), 3.86−3.90 (m, 4 H), 3.96 (s, 3 H), 7.30 (dd, J = 7.4, 5.1 Hz, 1 H), 7.50 (d, J = 8.2 Hz, 1 H), 8.01−8.06 (m, 2 H), 8.09−8.14 (m, 1 H), 8.57 (d, J = 3.5 Hz, 1 H). LC/MS retention time: C, 14.25 min, D, 8.14 min.

4,6-Bis(trifluoromethyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole (48). Following the procedure described for compound **47a**, 2-chlorobenzoimidazole **20m** and 1-(3-trifluoromethylpyridin-2-yl)piperazine provided the title compound (47%) as a white solid. Mp: 142 °C. MS (ESI, pos. ion) *m*/*z*: 484 (M + 1). ^{1}H NMR (CD_3OD): δ 3.34−3.44 (m, 4 H), 3.78−3.88 (m, 4 H), 7.22 (dd, J = 7.8, 4.9 Hz, 1 H), 7.52 (s, 1 H), 7.65 (br s, 1 H), 8.06 (dd, J = 7.9, 1.5 Hz, 1 H), 8.51 (d, J = 3.7 Hz, 1 H). Anal. ($C_{18}H_{15}F_6N_5$): C, H, N.

6-(Trifluoromethyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)-piperazin-1-yl)-1*H*-imidazo[4,5-*b*]pyridine, Trifluoroacetic Acid Salt (49a). A mixture of 2-chloroimidazopyridine **20d** (45 mg, 0.203 mmol), 1-(3-trifluoromethyl-pyridin-2-yl)piperazine (47 mg, 0.203 mmol), triethylamine (59 μL, 0.406 mmol), and copper(I) iodide (1 mg, 0.005 mmol) in 3-methyl-butan-1-ol (0.5 mL) was heated in a microwave synthesizer at 220 °C for 0.5 h. The reaction mixture was cooled to room temperature and was filtered. The filtrate was evaporated in vacuo and the residue was purified by preparative HPLC (gradient 0.1% CF_3CO_2H/MeCN) to give 55 mg (65%) of the title compound as a colorless solid. MS (ESI, positive ion) *m*/*z*: 417 (M + 1). ^{1}H NMR (CD_3OD): δ 3.40−3.50 (m, 4 H), 3.90−4.00 (m, 4 H), 7.26−7.31 (m, 1 H), 7.91 (s, 1 H), 8.11 (d, J = 7.8 Hz, 1 H), 8.40−8.60 (m, 2 H). LC/MS retention time: A, 9.22 min; B, 5.93 min.

5-(Trifluoromethyl)-2-(4-(3-(trifluoromethyl)pyridin-2-yl)-piperazin-1-yl)-3*H*-imidazo[4,5-*b*]pyridine, Trifluoroacetic Acid Salt (49b). Following the procedure described for compound **47c**, 2-chlorobenzoimidazole **20e** and 1-(3-trifluoromethylpyridin-2-yl)-piperazine provided the title compound (2%) as an amorphous solid. MS (ESI, pos. ion) *m*/*z*: 417 (M + 1). ^{1}H NMR (DMSO-d_6): δ 3.32−3.36 (m, 4 H), 3.76−3.79 (m, 4 H), 7.28 (dd, J = 7.7, 4.8 Hz, 1 H), 7.47 (d, J = 8.0 Hz, 1 H), 7.68 (d, J = 7.8 Hz, 1 H), 8.13 (dd, J = 7.8, 1.6 Hz, 1 H), 8.57 (d, J = 4.0 Hz, 1 H). LC/MS retention time: A, 9.39 min; B, 8.75 min.

(*R*)-2-(2-Methyl-4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-6-(trifluoromethyl)-1*H*-benzo[*d*]imidazole (50a). A mixture of piperazine **8u** (245 mg, 1 mmol), 2-chlorobenzoimidazole **20n** (176 mg, 0.8 mmol), *N*,*N*-diisopropylethylamine (0.34 mL, 2 mmol), and copper iodide (19 mg, 0.1 mmol) in dioxane (2 mL) was heated in a microwave synthesizer at 200 °C for 1.5 h. The reaction mixture was evaporated in vacuo and the residue was purified by silica gel column chromatography (EtOAc) to give 163 mg (38%) of the title compound as a solid. Mp: 216.3-218.7 °C. MS (ESI, pos. ion) *m*/*z*: 430 (M + 1). ^{1}H NMR ($CDCl_3$): δ 1.44 (d, J = 6.6 Hz, 3 H), 3.13−3.25 (dt, J = 12.1, 3.5 Hz, 1 H), 3.35−3.52 (m, 2 H), 3.55−3.75 (m, 2 H), 3.83−3.97 (m, 1 H), 4.35 (br s, 1 H), 7.12 (dd, J = 7.9, 4.9 Hz, 1 H), 7.20−7.30 (m, 2 H), 7.36−7.53 (m, 2 H), 7.71 (s, 1 H), 7.95 (dd, J = 7.8, 2.0 Hz, 1 H), 8.25 (br s, 1 H) 8.51 (dd, J = 4.9, 1.4 Hz, 1 H). LC/MS retention time: A, 10.39 min; B, 7.36 min.

(*R*)-2-(2-Ethyl-4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-6-(trifluoromethyl)-1*H*-benzo[*d*]imidazole (50b). A mixture of 2-chlorobenzoimidazole **20n** (0.082 g, 0.37 mmol) and piperazine **8ab** (0.096 g, 0.37 mmol) in ethanol (2 mL) was heated at 170 °C in a microwave sythesizer for 2 h. The reaction mixture was evaporated in vacuo and the residue was purified by by preparative HPLC (gradient 0.1% CF_3CO_2H/MeCN) to give 10 mg of a colorless film. The film was dissolved in dichloromethane (2 mL) and the solution was washed with a saturated aqueous solution of $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (gradient 0−15% MeOH/CH_2Cl_2) to give 5 mg (3%) of the title compound as a white amorphous solid. MS (ESI, pos. ion) *m*/*z*: 444 (M + 1). ^{1}H NMR (CD_3OD): δ 0.93 (t, J = 7.1 Hz, 3 H), 1.80−2.00 (m, 2 H), 3.17 (dt, J = 12.1, 3.3 Hz, 1 H), 3.30−3.40 (m, 1 H), 3.52 (t, J = 12.3 Hz, 2 H), 3.64 (dt, J = 12.5, 3.2 Hz, 1 H), 3.96 (d, J = 12.8 Hz, 1 H), 4.10 (br s, 1 H), 7.24 (dd, J = 7.7, 5.0 Hz, 1 H), 7.25−7.37 (m, 2 H), 7.46 (br s, 1 H), 8.06 (d, J = 7.8 Hz, 1 H), 8.52 (d, J = 3.8 Hz, 1 H). LC/MS retention time: A, 10.63 min; B, 7.37 min.

(*R*)-2-(2-Propyl-4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-6-(trifluoromethyl)-1*H*-benzo[*d*]imidazole (50c). Following the procedure described for compound **50b**, 2-chlorobenzoimidazole **20i** and piperazine **8ac** provided the title compound (2%) as a white amorphous solid. MS (ESI, pos. ion) *m*/*z*: 458 (M + 1). ^{1}H NMR (CD_3OD): δ 0.92 (t, J = 7.3 Hz, 3 H), 1.20−1.40 (m, 2 H), 1.76−2.00 (m, 2 H), 3.10−3.16 (m, 1 H), 3.28−3.32 (m, 1 H), 3.47 (br s, 1 H), 3.52 (br s, 1 H), 3.62 (dt, J = 12.3, 2.6 Hz, 1 H), 3.96 (d, J = 12.7 Hz, 1 H), 4.26 (br s, 1 H), 7.25 (dd, J = 7.8, 4.8 Hz, 1 H), 7.26−7.36 (m, 2 H), 7.47 (br s, 1 H), 8.07 (d, J = 7.9 Hz, 1 H), 8.52 (d, J = 3.9 Hz, 1 H). LC/MS retention time: A, 11.31 min; B, 8.20 min.

(*R*)-2-(4-(3-Bromopyridin-2-yl)-2-methylpiperazin-1-yl)-6-(trifluoromethyl)-4-(3,4,5-trifluorophenyl)-1*H*-benzo[*d*]imidazole (51a). Following the procedure described for compound **47a**, 2-chlorobenzoimidazole **20n** and piperazine **8q** provided the title compound (73%) as a white amorphous solid. MS (ESI, pos. ion) *m*/*z*: 570 (M + 1). ^{1}H NMR (CD_3OD): δ 1.53 (d, J = 6.8 Hz, 3 H), 3.09 (dt, J = 12.4, 3.6 Hz, 1 H), 3.21 (dd, J = 12.8, 3.4 Hz, 1 H), 3.60−3.98 (m, 3 H), 4.10 (d, J = 11.2 Hz, 1 H), 4.51 (br s, 1 H), 6.97 (dd, J = 8.0, 4.8 Hz, 1 H), 7.47 (br s, 2 H), 7.92 (br s, 2 H), 7.98 (dd, J = 8.0, 1.2 Hz, 1 H) 8.28 (d, J = 4.8 Hz, 1 H). Anal. ($C_{24}H_{18}BrF_6N_5$): C, H, N.

(*S*)-2-(4-(3-Bromopyridin-2-yl)-2-methylpiperazin-1-yl)-6-(trifluoromethyl)-4-(3,4,5-trifluorophenyl)-1*H*-benzo[*d*]imidazole (51b). Following the procedure described for compound **47a**, 2-chlorobenzoimidazole **20i** and piperazine **8r** provided the title compound (84%) as a white amorphous solid. MS (ESI, pos. ion) *m*/*z*: 570 (M + 1). ^{1}H NMR (CD_3OD): δ 1.51 (d, J = 6.4 Hz, 3 H), 3.00−3.05 (m, 1 H), 3.19 (dd, J = 12.0, 3.2 Hz, 1 H), 3.60−3.86 (m, 3 H), 4.07 (d, J = 11.2 Hz, 1 H), 4.49 (br s, 1 H), 6.94 (dd, J = 8.0, 4.8 Hz, 1 H), 7.36−7.60 (m, 2 H), 7.80−7.90 (m, 2 H), 7.96 (d, J = 8.0 Hz, 1 H), 8.25 (dd, J = 4.8, 1.6 Hz, 1 H). MS *m*/*z*: 571 (M + 1). Anal. ($C_{24}H_{18}BrF_6N_5$): C, H, N.

(*R*)-2-(4-(3-Bromopyridin-2-yl)-3-methylpiperazin-1-yl)-6-(trifluoromethyl)-4-(3,4,5-trifluorophenyl)-1*H*-benzo[*d*]imidazole (51c). Following the procedure described for compound **47a**, 2-chlorobenzoimidazole **20i** and piperazine **9** provided the title compound (64%) as white amorphous solid. MS (ESI, pos. ion) *m*/*z*: 570 (M + 1). ^{1}H NMR (CD_3OD): δ 1.12 (d, J = 6.0 Hz, 3 H), 3.10−3.30 (m, 1 H), 3.50−3.65 (m, 2 H), 3.70−3.90 (m, 3 H), 4.05 (br s, 1H), 6.98 (dd, J = 8.0, 4.8 Hz, 1 H), 7.47 (s, 2 H), 7.86 (br s, 2 H), 7.99 (dd, J = 7.6, 1.6 Hz, 1 H), 8.29 (dd, J = 4.4, 1.6 Hz, 1 H). LC/MS retention time: A, 12.89 min; B, 6.82 min.

(*S*)-2-(4-(3-Bromopyridin-2-yl)-3-methylpiperazin-1-yl)-6-(trifluoromethyl)-4-(3,4,5-trifluorophenyl)-1*H*-benzo[*d*]imidazole (51d). Following the procedure described for compound **47a**, piperazine **30b** and 2-chloropyridine **6b** provided the title compound (18%) as a white amorphous solid. MS (ESI, pos. ion) *m*/*z*: 570 (M + 1). ^{1}H NMR (CD_3OD): δ 1.12 (d, J = 6.0 Hz, 3 H), 3.10−3.30 (m, 1 H), 3.50−3.65 (m, 2 H), 3.70−3.90 (m, 3 H), 4.05 (br s, 1H), 6.98 (dd, J = 8.0, 4.8 Hz, 1 H), 7.47 (s, 2 H), 7.86 (br s, 2 H), 7.98 (dd, J = 7.6, 1.6 Hz, 1 H), 8.28 (dd, J = 4.4, 1.6 Hz, 1 H). LC/MS retention time: A, 12.81 min; B, 7.86 min.

2-(4-Pyridin-2-ylpiperazin-1-yl)-6-(trifluoromethyl)-1*H*-benzo[*d*]imidazole (52a). Following the procedure described for compound **5**, 2-chlorobenzimidazole **20n** and 1-(pyridin-2-yl)-piperazine provided the title compound (19%) as amorphous solid. MS (ESI, pos. ion) *m*/*z*: 570 (M + 1).^{1}H NMR (DMSO-d_6): δ 3.52−3.86 (m, 8 H), 6.62−6.72 (m, 1 H), 6.93 (d, J = 8.6 Hz, 1 H), 7.28 (s, 1 H), 7.36 (d, J = 8.2 Hz, 1 H), 7.47 (br s, 1 H), 7.58 (t, J = 7.2 Hz, 1 H), 8.15 (d, J = 3.5 Hz, 1 H), 11.89 (br s, 1 H). Anal. ($C_{17}H_{16}F_3N_5$): C, H, N.

6-(Trifluoromethyl)-2-(4-(4-(trifluoromethyl)pyridin-2-yl)-piperazin-1-yl)-1*H*-benzo[*d*]imidazole (52b). Following the procedure described for compound **31a**, 2-chloro-4-(trifluoromethyl)-pyridine and piperazine **30a** provided the title compound (66%) as a white amorphous solid. MS (ESI, pos. ion) *m*/*z*: 416 (M + 1). ^{1}H NMR (CD_3OD): δ 3.66−3.76 (m, 4 H), 3.78−3.88 (m, 4 H), 6.88 (d, J = 5.2 Hz, 1 H), 7.10 (s, 1 H), 7.30 (d, J = 8.2 Hz, 1 H), 7.36 (d, J = 8.2 Hz, 1 H), 7.50 (s, 1 H), 8.32 (d, J = 5.2 Hz, 1 H). Anal. ($C_{18}H_{15}F_6N_5$): C, H, N.

6-(Trifluoromethyl)-2-(4-(5-(trifluoromethyl)pyridin-2-yl)-piperazin-1-yl)-1 *H*-benzo[*d*]imidazole (52c). Following the procedure described for compound **47a**, 1-(5-(trifluoromethyl)pyridin-2-yl)piperazine and 2-chlorobenzimidazole **20n** provided the title compound (98%) as a white solid. Mp: 214 °C. MS (ESI, pos. ion) *m*/*z*: 416 (M + 1). ^{1}H NMR ($CDCl_3$): δ 3.74 (d, J = 7.2 Hz, 2 H), 3.76−3.86 (m, 4 H), 3.86−3.96 (m, 4 H), 6.74 (d, J = 9.2 Hz, 2 H), 7.39 (br s, 1 H), 7.66 (br s, 1 H), 7.72 (dd, J = 8.8, 2.0 Hz, 1 H), 8.45 (s, 1 H). Anal. ($C_{18}H_{15}F_6N_5$): C, H, N.

6-(Trifluoromethyl)-2-(4-(6-(trifluoromethyl)pyridin-2-yl)-piperazin-1-yl)-1*H*-benzo[*d*]imidazole (52d). Following the procedure described for compound **47a**, piperazine **8f** and 2-chlorobenzimidazole **20n** provided the title compound (68%) as a white amorphous solid. MS (ESI, pos. ion) *m*/*z*: 416 (M + 1). ^{1}H NMR ($CDCl_3$): δ 3.64−3.74 (m, 4 H), 3.78−3.88 (m, 4 H), 6.85 (d, J = 8.0 Hz, 1 H), 7.02 (d, J = 8.0 Hz, 1 H), 7.37 (br s, 2 H), 7.58 (br s, 1 H), 7.64 (t, J = 8.0 Hz, 1 H). Anal. ($C_{18}H_{15}F_6N_5$): C, H, N.

2-(4-(3-Chloropyridin-2-yl)piperazin-1-yl)-6-(trifluoromethyl)-1*H*-benzo[*d*]imidazole (52e). Following the procedure described for compound **47a**, piperazine **8b** and 2-chlorobenzimidazole **20n** provided the title compound (41%) as a white solid. Mp: 208−210 °C. MS (ESI, pos. ion) *m*/*z*: 382 (M + 1). ^{1}H NMR (DMSO-d_6): δ 3.37−3.43 (m, 4 H), 3.65−3.75 (m, 4 H), 7.06 (dd, J = 7.8, 4.7 Hz, 1 H), 7.28 (br s, 1 H), 7.32−7.42 (m, 1 H), 7.48 (br s, 1 H), 7.86 (d, J = 7.8 Hz, 1 H), 8.26 (d, J = 4.7 Hz, 1 H), 11.89 (br s, 1 H). Anal. ($C_{17}H_{15}ClF_3N_5 \cdot 0.25H_2O$): C, H, N.

2-(4-(3-Iodopyridin-2-yl)piperazin-1-yl)-6-(trifluoromethyl)-1*H*-benzo[*d*]imidazole (52f). Following the procedure described for compound **47a**, piperazine **8c** and 2-chlorobenzimidazole **20n** provided the title compound (58%) as a white amorphous solid. MS (ESI, pos. ion) *m*/*z*: 474 (M + 1). ^{1}H NMR ($CDCl_3$): δ 3.00−3.10 (m, 4 H), 3.18−3.28 (m, 4 H), 6.64 (d, J = 7.6 Hz, 1 H), 6.66 (d, J = 7.6 Hz, 1 H), 8.06 (d, J = 7.6 Hz, 1 H), 8.07 (d, J = 7.6 Hz, 1 H), 8.27 (d, J = 4.4 Hz, 1 H), 8.28 (d, J = 4.8 Hz, 1 H). Anal. ($C_{17}H_{15}F_3IN_5 \cdot 0.2H_2O$): C, H, N.

2-(4-(3-Methylpyridin-2-yl)piperazin-1-yl)-6-(trifluoromethyl)-1*H*-benzo[*d*]imidazole, Trifluoroacetic Acid Salt (52g). Following the procedure described for compound **47a**, piperazine **30a** and 2-chloro-3-methylpyridine provided the crude product, which was purified by preparative HPLC (gradient 0.1% trifluoroacetic acid in acetonitrile) to give the title compound (73%) as a white amorphous solid. MS (ESI, pos. ion) *m*/*z*: 362 (M + 1). ^{1}H NMR ($CDCl_3$): δ 3.48−3.52 (m, 4 H), 3.94 (br s, 4 H), 7.19 (dd, J = 8.0 Hz, 4.0 Hz, 1 H), 7.40−7.48 (m, 2 H), 7.60 (s, 1 H), 7.84 (d, J = 8.0 Hz, 1 H), 8.11 (d, J = 4.0 Hz, 1 H). Anal. ($C_{18}H_{18}F_3N_5 \cdot 2.3TFA \cdot 1.4H_2O$): C, H, N.

2-(4-(6-(Trifluoromethyl)-1*H*-benzo[*d*]imidazol-2-yl)piperazin-1-yl)nicotinonitrile (52h). Following the procedure described for compound **47a**, 2-piperazin-1-ylnicotinonitrile and 2-chlorobenzimidazole **20n** provided the title compound (56%) as a white amorphous solid. MS (ESI, pos. ion) *m*/*z*: 373 (M + 1). ^{1}H NMR (DMSO-d_6): δ 3.75 (m, 8 H), 6.98 (dd, J = 7.4, 4.7 Hz, 1 H), 7.20−7.60 (m, 3 H), 8.12 (d, J = 7.8 Hz, 1 H), 8.45 (d, J = 4.0 Hz, 1 H), 11.90 (s, 1 H). LC/MS retention time: A, 8.87 min; B, 5.71 min.

Ethyl 2-(4-(6-(Trifluoromethyl)-1*H*-benzo[*d*]imidazol-2-yl)-piperazin-1-yl)nicotinate Hydrochloride (52i). Following the procedure described for compound **47a**, piperazine **8e** and 2-chlorobenzimidazole **20n** provided the crude reaction product. A solution of the product in EtOAc was treated with a 1 M solution of hydrogen chloride in Et_2O and the mixture was evaporated under reduced pressure. The residue was dried in vacuo to give the title compound title compound (71%) as a white amorphous solid. MS (ESI, pos. ion) *m*/*z*: 420 (M + 1). ^{1}H NMR ($CDCl_3$): δ 1.34 (t, J = 7.2 Hz, 3 H), 3.45−3−55 (m, 4 H), 3.69−3.81 (m, 4 H), 4.32 (q, J = 7.0 Hz, 2 H), 6.83 (dd, J = 7.6, 4.9 Hz, 1 H), 7.26−7.36 (m, 2 H), 7.49 (br s, 1 H), 8.06 (dd, J = 7.8, 2.0 Hz, 1 H), 8.28 (dd, J = 4.7, 2.0 Hz, 1 H). Anal. ($C_{20}H_{20}N_5F_3O_2$): C, H, N.

(5-Chloro-6-(4-(6-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-2-yl)piperazin-1-yl)pyridin-3-yl)methanol (52j). Following the procedure described for compound **31a**, piperazine **8h** and 2-chlorobenzimidazole **20n** provided the title compound (42%) as a solid. Mp: 162−165 °C. MS (ESI, pos. ion) *m*/*z*: 412 (M + 1). ^{1}H NMR (DMSO-d_6): δ 3.30−3.40 (m, 4 H), 3.65−3.75 (m, 4 H), 4.47 (d, J = 5.8 Hz, 2 H), 5.30 (t, J = 5.5 Hz, 1 H), 7.20−7.50 (m, 3 H), 7.78 (d, J = 2.0 Hz, 1 H), 8.19 (d, J = 2.0 Hz, 1 H). Anal. ($C_{18}H_{17}ClN_5F_3O$): C, H, N.

5-Chloro-6-(4-(6-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-2-yl)-piperazin-1-yl)nicotinamide (52k). Following the procedure described for compound **31a**, piperazine **8p** and 2-chlorobenzimidazole **20n** provided the title compound (81%) as a white amorphous solid. MS (ESI, pos. ion) *m*/*z*: 425 (M + 1). ^{1}H NMR (DMSO-

d_6): δ 3.70−3.80 (m, 4 H), 3.80−4.00 (m, 4 H), 7.49−7.54 (m, 1 H), 7.58−7.62 (m, 1 H), 7.71 (s, 1 H), 7.76 (s, 1 H), 8.28 (br s, 1 H), 8.45 (s, 1 H), 8.93 (br s, 1 H). Anal. ($C_{18}H_{16}ClN_6F_3O\cdot 0.4H_2O$): C, H, N.

5-Chloro-*N*-methyl-6-(4-(6-(trifluoromethyl)-1*H*-benzo[*d*]-imidazol-2-yl)piperazin-1-yl)nicotinamide (52l). Following the procedure described for compound **31a**, piperazine **8l** and 2-chlorobenzimidazole **20n** provided the title compound (62%) as a white amorphous solid. MS (ESI, pos. ion) *m*/*z*: 439 (M + 1). ^{1}H NMR (DMSO-d_6): δ 2.85 (d, J = 3.9 Hz, 3 H), 3.60−3.70 (m, 4 H), 3.72−3.82 (m, 4 H), 7.34 (br s, 1 H), 7.38−7.59 (m, 2 H), 8.25 (s, 1 H), 8.59 (br s, 1 H), 8.72 (s, 1 H), 11.95 (br s, 1 H). Anal. ($C_{19}H_{18}ClN_6F_3O\cdot 0.1EtOAc$): C, H, N.

6-(Trifluoromethyl)-2-(4-(2-(trifluoromethyl)phenyl)piperazin-1-yl)-1*H*-benzo[*d*]imidazole (53a). Following the procedure described for compound **31a**, 1-(2-(trifluoromethyl)phenyl)piperazine and 2-chlorobenzimidazole **20n** provided the title compound (37%) as a white solid. Mp: 268−269 °C. MS (ESI, pos. ion) *m*/*z*: 415 (M + 1). ^{1}H NMR (DMSO-d_6): δ 3.01 (br s, 4 H), 3.69 (br s, 4 H), 7.20−7.80 (m, 7 H), 11.86 (d, J = 12.0 Hz, 1 H). Anal. ($C_{19}H_{16}N_4F_6$): C, H, N.

6-(Trifluoromethyl)-2-(4-(3-(trifluoromethyl)pyridin-4-yl)-piperazin-1-yl)-1*H*-benzo[*d*]imidazole (53b). Following the procedure described for compound **47a**, piperazine **11d** and 2-chlorobenzimidazole **20n** provided the title compound (20%) as a light-yellow solid. Mp: 220−224 °C. MS (ESI, pos. ion) *m*/*z*: 416 (M + 1). ^{1}H NMR (DMSO-d_6): δ 2.46−2.56 (m, 4 H), 2.83−2.93 (m, 4 H), 6.30−6.50 (m, 3 H), 6.61 (br s, 1 H), 7.66 (d, J = 5.9 Hz, 1 H), 7.78 (s, 1 H). Anal. ($C_{18}H_{15}F_6N_5$): C, H, N.

2-(4-(3-Chloropyridin-4-yl)piperazin-1-yl)-6-(trifluoromethyl)-1*H*-benzo[*d*]imidazole, Trifluoroacetic Acid Salt (53c). Following the procedure described for compound **47a**, piperazine **11b** and 2-chlorobenzimidazole **20n** provided the title compound (63%) as trifluoroacetic acid salt after purification by preparative HPLC (gradient 0.1% trifluoroacetic acid in acetonitrile). Mp: 159−161 °C. MS (ESI, pos. ion) *m*/*z*: 382 (M + 1). ^{1}H NMR (DMSO-d_6): δ 3.60−3.80 (m, 4 H), 3.86−3.96 (m, 4 H), 7.33 (d, J = 5.9 Hz, 1 H), 7.54−7.63 (m, 2 H), 7.70 (s, 1 H), 8.45 (d, J = 5.9 Hz, 1 H), 8.63 (s, 1 H). LC/MS retention time: A, 8.70 min; B, 3.74 min.

2-(4-(3,5-Dichloropyridin-4-yl)piperazin-1-yl)-6-(trifluoromethyl)-1*H*-benzo[*d*]imidazole (53d). Following the procedure described for compound **5**, 1-(3,5-dichloropyridin-4-yl)piperazine and 2-chlorobenzimidazole **20n** provided the title compound (33%) as amorphous solid. MS (ESI, pos. ion) *m*/*z*: 416 (M + 1). ^{1}H NMR (CD_3OD): δ 3.60−3.64 (m, 4 H), 3.83−3.88 (m, 4 H), 7.52−7.62 (m, 2 H), 7.65 (s, 1 H), 8.44 (s, 2 H). LC/MS retention time: A, 9.76 min; B, 6.47 min.

2-(4-(2,6-Dichlorophenyl)piperazin-1-yl)-6-(trifluoromethyl)-1*H*-benzo[*d*]imidazole (53e). Following the procedure described for compound **5**, piperazine **14** and 2-chlorobenzimidazole **20n** provided the title compound (63%) as a white solid. Mp: 263−265 °C. MS (ESI, pos. ion) *m*/*z*: 415 (M + 1). ^{1}H NMR ($CDCl_3$): δ 3.36−3.46 (m, 4 H), 3.72−3.82 (m, 4 H), 7.00−7.09 (m, 1 H), 7.20−7.56 (m, 3 H), 7.72 (s, 1 H), 8.28 (br s, 1 H). LC/MS retention time: A, 10.98 min; B, 7.66 min.

2-(4-(5-Chloropyrimidin-4-yl)piperazin-1-yl)-6-(trifluoromethyl)-1*H*-benzo[*d*]imidazole (53f). Following the procedure described for compound **5**, piperazine **11f** and 2-chlorobenzimidazole **20n** provided the title compound (69%) as white solid. Mp: 66.6−66.7 °C. MS (ESI, pos. ion) *m*/*z*: 383 (M + 1). ^{1}H NMR (DMSO-d_6): δ 3.01 (br s, 4 H), 3.17 (br s, 4 H), 6.59 (d, J = 8.0 Hz, 1 H), 6.67 (d, J = 8.0 Hz, 1 H), 6.78 (s, 1 H), 7.68 (s, 1 H), 7.86 (s, 1 H). Anal. ($C_{16}H_{14}ClF_3N_6\cdot 0.75H_2O$): C, H, N.

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

Pharmacokinetic Studies. Male Sprague−Dawley rats (weight range 225−280 g) with surgically implanted femoral vein and jugular vein cannulae were obtained from Hilltop Lab Animals Inc. (Scottsdale, PA). Animals were fasted overnight and the following day compounds were administered either by oral gavage or by intravenous bolus injection. Oral formulations were made 24−48 h prior to dosing, while intravenous formulations were made on the day of dosing. Blood samples were collected over 8 h via jugular cannula into a heparinized tube. Following centrifugation, plasma samples were stored in a freezer to maintain −70 °C until analysis. Lithium heparinized plasma samples (40 μL) were precipitated with acetonitrile containing the internal standard (IS). The supernatant was transferred into a 96-well plate, and an aliquot of 20 μL was injected onto an LC−MS/MS system. The analytes were separated by a reversed-phase on a C-18 analytical column. The analyte ions were generated by an atmospheric pressure chemical ionization (APCI) source and detected by a Sciex API3000 triple quadrupole mass spectrometer operated in the multiple reaction monitoring (MRM) mode. Study sample concentrations were determined from a weighted ($1/x^2$) linear regression of peak area ratios (analyte peak area/IS peak area) versus the theoretical concentrations of the calibration standards. Pharmacokinetic parameters were calculated by noncompartmental methods using WinNonLin (Pharsight Corp., Mountainview, CA).

Method for Capsaicin-Induced Flinching Model. Male rats (Sprague−Dawley; Charles River Laboratories, Wilmington, MA) were allowed 5−7 days acclimation to the LAR prior to use in the experiment. The day prior to the experiment, animals were numbered sequentially by marking the tail with a permanent marker. For the dose response study, the combined data from three separate studies was used for analysis. The treatment groups are listed below.

The first treatment was either vehicle or **46ad** administered via oral gavage using a dose volume of 5 mL/kg in an Ora-Plus/5% Tween 80 vehicle solution. Following the first treatment, rats were placed into acclimation cages (12 cm × 26 cm × 12 cm front height/15 cm rear height) that were identical to those to be used for the behavioral scoring. Animals acclimated for 2 h prior to the second treatment.

The second treatment for all groups was an intraplantar injection of capsaicin, except in the vehicle/vehicle group, which received an intraplantar injection of the vehicle [5% EtOH in phosphate-buffered saline (PBS) without Ca^{2+}, Mg^{2+}] used for capsaicin. The dose of capsaicin utilized was 0.5 μg administered in a volume of 25 μL. This dose of capsaicin was based on earlier characterization work and found to be a minimally effective reproducible dose. The intraplantar injection was made with a 3/10 cm^3 insulin syringe fitted with a 28.5-gauge needle. For the intraplantar injection, rats were placed headfirst into a rat restrainer and the right foot was marked (top and bottom) with a permanent marker to make a clear identification of the injected foot. Next, with the foot extended, the injection was made into the center of the bottom of the foot (i.e., intraplantar). The rat was then immediately placed into an

observation chamber for flinch counting. At all times, animals were treated gently as to minimize stress.

The behavioral measure scored was number of flinches. Flinches were recorded for 1 min by observers (2) who were blinded to the treatment conditions. A flinch was defined as a "flick" of the paw either when the animal lifts it from the floor or when the paw was held-up. If the paw was just held up, the counting continued at a constant pace until the paw was placed again on the chamber's surface. If the paw was held up and biting occurred, it was counted as a response. Immediately following the 1-min test period, the animals were transferred to another person who took blood for determination of plasma levels of compound. Blood was taken via a cardiac stick in animals anesthetized with CO_2. Blood was collected in heparinized tubes and kept on ice until centrifugation at 14 000*g* for 5 min. Plasma (200 μL) was removed, kept at 4 °C during experiment, and frozen at − 80 °C until submission for blood level determinations. Percent maximal possible effect (%MPE) was computed as ((Veh/Cap − Veh/Veh) − (Drug/Cap-Veh/Veh))/(Veh/Cap − Veh/Veh).

Method for CFA-Induced Thermal Hyperalgesia. Prior to being tested, male rats (Harlan Sprague−Dawley, Harlan Industries, Indianapolis, IN) were allowed at least a 4-day acclimation period to the testing environment, followed by a 2-day habituation to the testing equipment and paradigm. The paw withdrawal latencies were tested using a commercially available paw thermal stimulator (Yaksh hot box, Anesthesiology Research Laboratory, Department of Anesthesiology, University of California at San Diego). The device consists of rat compartments (plexiglass cubicles) over a glass surface maintained at a constant temperature of 30 °C; underneath the glass lays a radiant heat source consisting of a high intensity projector lamp bulb (EIKO CXL/CXR, 8V 50W). An attached, angled mirror facilitates visualization of the footpad and positioning of the radiant heat to the plantar surface of the paw. Nociception was measured as the latency for the rat to remove its paw when the radiant light is activated (current set at 4.75 A). A daily calibration of the hot box's settings was done in order to produce a consistent paw withdrawal latency (PWL) of approximately 8−10 s as the baseline response. A 20-s cutoff was imposed on the stimulus duration to prevent tissue damage. On the day of testing, after 45 min of additional acclimation in the plexiglass cubicles, thermal stimuli were delivered four times to each hind paw in an alternating manner at a 5-min interstimulus interval. The first PWL measurement was discarded (it tended to be unusually high and variable), and the three subsequent measurements were averaged to obtain baseline PWL.

After PWL baseline testing, inflammation was induced by subplantar injection of CFA into the left hind paw using a 1-mL syringe with a 27-gauge $^1/_2$ in. needle. Care was taken to avoid a backflow of injected solution after needle withdrawal. CFA injection produces an intense inflammation; behavioral hyperalgesia develops 3−5 h after the injection, peaks at 6−24 h, and lasts for more than 5 days. For this study, animals were dosed (po) with **46ad** at a dosing volume of 5 mL/kg 21 h after CFA injection. The vehicle for **46ad** was OraPlus/5% Tween 80. Rats were tested 2 h following treatment, and investigators conducting PWL testing were blinded to the treatment conditions.

Acknowledgment. We thank our colleagues Sekhar Surapaneni, Annette Bak. and their co-workers in the PKDM and pharmaceutics departments and Duncan Smith for providing the 2D-NOESY NMR analyses. We also acknowledge Randy Hungate and Jean-Claude Louis for their support.

Note Added after ASAP Publication. This manuscript was released ASAP on May 19, 2006, with an incorrect structure for Table 5. The correct version was posted on May 24, 2006.

Supporting Information Available: Combustion analysis results for all final compounds and synthetic procedures for intermediates that were not included in the Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org.

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JM060065Y