# Design and Synthesis of Novel Sulfonamide-Containing Bradykinin $hB_2$ Receptor Antagonists. 1. Synthesis and SAR of α,α-Dimethylglycine Sulfonamides

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We recently published the extensive in vivo pharmacological characterization of MEN 16132 (*J. Pharmacol. Exp. Ther.* **2005**, 616−623; *Eur. J. Pharmacol.* **2005**, *528*, 7), a member of the sulfonamide-containing human $B_2$ receptor ($hB_2R$) antagonists. Here we report, in detail, how this family of compounds was designed, synthesized, and optimized to provide a group of products with subnanomolar affinity for the $hB_2R$ and high in vivo potency after topical administration to the respiratory tract. The series was designed on the basis of indications from the X-ray structures of the key structural motifs **A** and **B** present in known antagonists and is characterized by the presence of an α,α-dialkyl amino acid. The first lead (**17**) of the series was submitted to extensive chemical work to elucidate the structural requirements to increase $hB_2$ receptor affinity and antagonist potency in bioassays expressing the human $B_2$ receptor ($hB_2R$). The following structural features were selected: a 2,4-dimethylquinoline moiety and a piperazine linker acylated with a basic amino acid. The representative lead compound **68** inhibited the specific binding of [$^3$H]BK to $hB_2R$ with a p*K*i of 9.4 and antagonized the BK-induced inositolphosphate (IP) accumulation in recombinant cell systems expressing the $hB_2R$ with a p$A_2$ of 9.1. Moreover, compound **68** when administered (300 nmol/kg) intratracheally in the anesthetized guinea pig, was able to significantly inhibit BK-induced bronchoconstriction for up to 120 min after its administration, while having a lower and shorter lasting effect on hypotension.

## Introduction

Bradykinin (BK) is an endogenous nonapeptide (Arg$^1$-Pro$^2$-Pro$^3$-Gly$^4$-Phe$^5$-Ser$^6$-Pro$^7$-Phe$^8$-Arg$^9$) that has been shown to be involved in a variety of pathophysiological responses such as inflammation, rhinitis, asthma, and tissue injury and remodeling. Together with kallidin (KD, [Lys$^0$]BK), BK is the major mammalian representative of the kinin family of oligopeptide hormones. These two linear peptides are predominantly released by the action of tissue and plasma kallikrein enzymes on large inactive precursors (kininogens), thus acting as local hormones.

In mammals, the biological effect of kinins are mediated through activation of two distinct cell surface receptors, designated $B_1$ and $B_2$.[2] These membrane-bound receptors are members of the type 1 G protein coupled receptors (GPCR) superfamily.[3] Whereas $B_1$ receptors are inducible, or poorly expressed, under physiological conditions,[4] $B_2$ receptors are constitutively expressed in several cell types and mediate most of the known effects of BK and KD.[5] Inhaled BK induces potent bronchoconstriction and cough in asthmatic patients[6] and rhinitis-like symptoms when instilled into the nose.[7] Furthermore, BK is generated in human nasal secretions during rhinovirus infections[8] and allergic rhinitis.[9] On the basis of these findings, a potential therapeutic role for kinin $B_2$ receptor antagonists has been hypothesized in the treatment of airway inflammatory pathologies associated with hyper-responsiveness to BK, such as chronic bronchial asthma,[10] or with the release of BK, such as perennial and seasonal allergic rhinitis.[11] On the other hand, kinins also exert effects on the cardiovascular system: several studies suggest that BK contributes to the antihypertensive and cardioprotective effects of ACE inhibitors,[12] and acute changes in cardiovascular parameters produced by kinin $B_2$ receptor antagonists have been observed.[13] This indicates that in targeting airway inflammatory pathologies it is important to avoid interfering at the cardiovascular level.

A number of studies have been carried out on peptide[14] and non-peptide BK antagonists.[15] One series of non-peptide antagonists (FR-173657, Chart 1) was derived by Fujisawa researchers from extensive medicinal chemistry modifications on a lead discovered by screening a series of angiotensin II receptor antagonists.[16]

Further work has been carried out by Fournier researchers, by substituting the 2,4-dichloro-phenyl-*N*-methylamide moiety with a 2,4-dichlorophenyl prolinyl sulfonamide (LF16-0687, Chart 1).[17] This paper describes our work on the 2,4-dichloro-3-(2,4-methyl-8-quinolyloxymethyl) phenyl framework undertaken with the aim of developing new, selective $hB_2R$ antagonists suitable for local administration (aerosol, intratracheal, or intranasal routes), free from cardiovascular side effects.

The *N*-methylamide moiety attached to the dichlorobenzene ring of FR-173657 and its analogues plays a key role in receptor recognition;[18] in fact, this kind of system tends to adopt a *cis*-conformation, with the amide and the phenyl plane almost perpendicular to one another.[19] Data on the conformation of LF16-0687 and its analogues have not been reported in the literature, but it can intuitively be anticipated that the system should be relatively rigid.

An analysis of the Cambridge Crystallographic Database (CCDB) indicated that the turn induced by the sulfonamide moiety mimics quite well that of the *N*-methyl aryl amide. Moreover, the introduction of a proline moiety in the place of the glycine unit increases the rigidity of the system which then finds some release for optimal phenylamidino interaction with the receptor, via the flexible propylendiamine linker. In fact,

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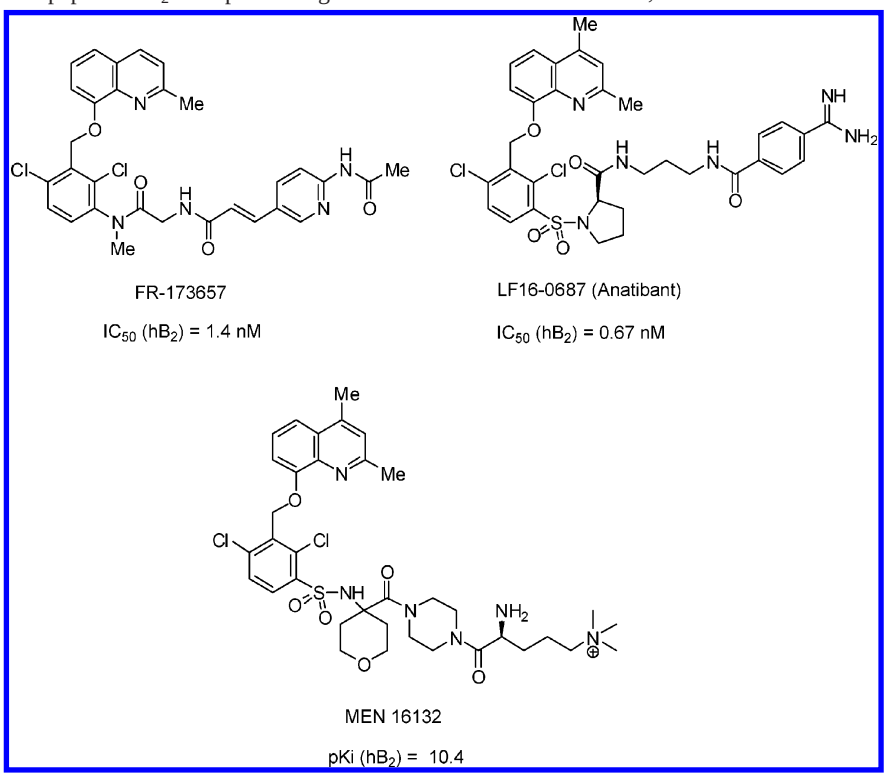
**Chart 1.** Competitive, Nonpeptidic $hB_2$ Receptor Antagonists FR-173657 and Anatibant, and MEN 16132




the substitution of the proline unit with a glycine or an α-alkyl amino acid causes a large drop in binding affinity,[20] probably due to excessive flexibility. We wondered if the known propensity of α,α-dialkyl amino acids to induce turns[21] could be exploited to introduce the necessary rigidity into the system, while at the same time leaving chemical space for pharmacodynamic (PD) and pharmacokinetic (PK) property optimization. Indeed, a comparison of the X-ray structures[22] of *N*-(2,4-dichloro-3-methylphenyl)-*N*-methylacetamide (**A**), (*R*)-1-(2,4-dichloro-3-methyl benzenesulfonyl)-pyrrolidine-2-carboxylic acid methyl ester (**B**), and 2,4-dichlorosulfonylamide of α,α-dimethyl glycine methyl ester (**C**) (Figure 1), prepared in our labs as model compounds, showed that the induced turn was quite similar and that the terminal carboxylate was pointing in the same direction, albeit at a different angle.

Following these positive indications, extensive chemical work was undertaken to explore the SARs for a series of 2,4-dichlorosulfonamides of α,α-dimethylglycine. Compounds were first evaluated for their ability to inhibit the binding of tritiated BK to $hB_2R$. Whenever the p*K*i value was greater than 8.4, the molecules were evaluated using a functional assay in CHO cells expressing the $hB_2R$. The receptor selectivity of the compounds was also assessed by measuring their ability to inhibit the binding of [$^3$H][desArg$^9$]Lys-BK to the $hB_1R$.

## Chemistry

The compounds described in this study are shown in Tables 1 and 2, and the synthetic methods for their preparation are outlined in Schemes 1−3.

Commercially available 2,6-dichlorotoluene **1** was converted into the 3-sulfonyl chloride derivative **2** by treatment with chlorosulfonic acid. Coupling of **2** with the *tert*-butyl ester of α,α-dimethyl glycine afforded the corresponding sulfonamide **3**, which was then brominated with NBS to give benzyl bromide **4**. Nucleophilic substitution with hydroxyquinolines **8a** or **8b**, mediated by sodium hydride in DMF, gave ether **5**. Acid cleavage of the *tert*-butyl ester and coupling with amines $NHR_1R_2$ produced products **7a**,**b**.

Hydroxyquinoline **8a** is commercially available, while **8b** was prepared according to the synthetic sequence shown in Scheme 2. Condensation of 3-hydroxybenzaldehyde with acetone to give the α,*β*-unsaturated ketone **10** was followed by *β*-methylation with lithium dimethyl cuprate.[23] The oxime **12**, obtained via condensation of ketone **11** with 2,4-dinitrohydroxylamine,[24] was submitted to intramolecular cyclization under Narasaka[25] conditions to obtain **8b** in high yield and in good purity.

When $R_1$ or $R_2$ contained a BOC-protected amino group, this was used to further functionalize the molecules, as shown in Scheme 3.

The BOC group was removed with 4 N HCl in dioxane, and the resulting free amine was coupled with a carboxylic acid to obtain amides **14**, converted into a guanidino group (**15**) with Goodman's reagent,[26] or submitted to reductive amination with an aldehyde or ketone to obtain amines **16**.

## Results and Discussion

When we started our research program, the reported nonpeptidic $hB_2R$ antagonists had been developed for oral delivery. Since we were optimizing molecules for airway delivery, the optimization pathway we followed was quite different. In fact, in contrast to the intestinal mucosa, the pulmonary epithelium has been shown to be highly permeable to compounds with high molecular polar surface areas (e.g., PSA = 479 Å),[27] and this allowed us to fully exploit the receptor's extremely high affinity for positively charged compounds.[28] The initial insertion of our scaffold into the structure LF16-0687 (**18**, Table 1) confirmed that the conformation induced by the α,α-dimethylglycine was slightly different from that of the parent compound: the p*K*i of amidine **18** was 7.7, compared to 9.1 for LF16-0687. These data were interesting anyway, and using α,α-dimethylglycine as a starting point, we undertook a systematic modification of the chain linked to the carboxylate function to define primary SARs for our system (Table 1).

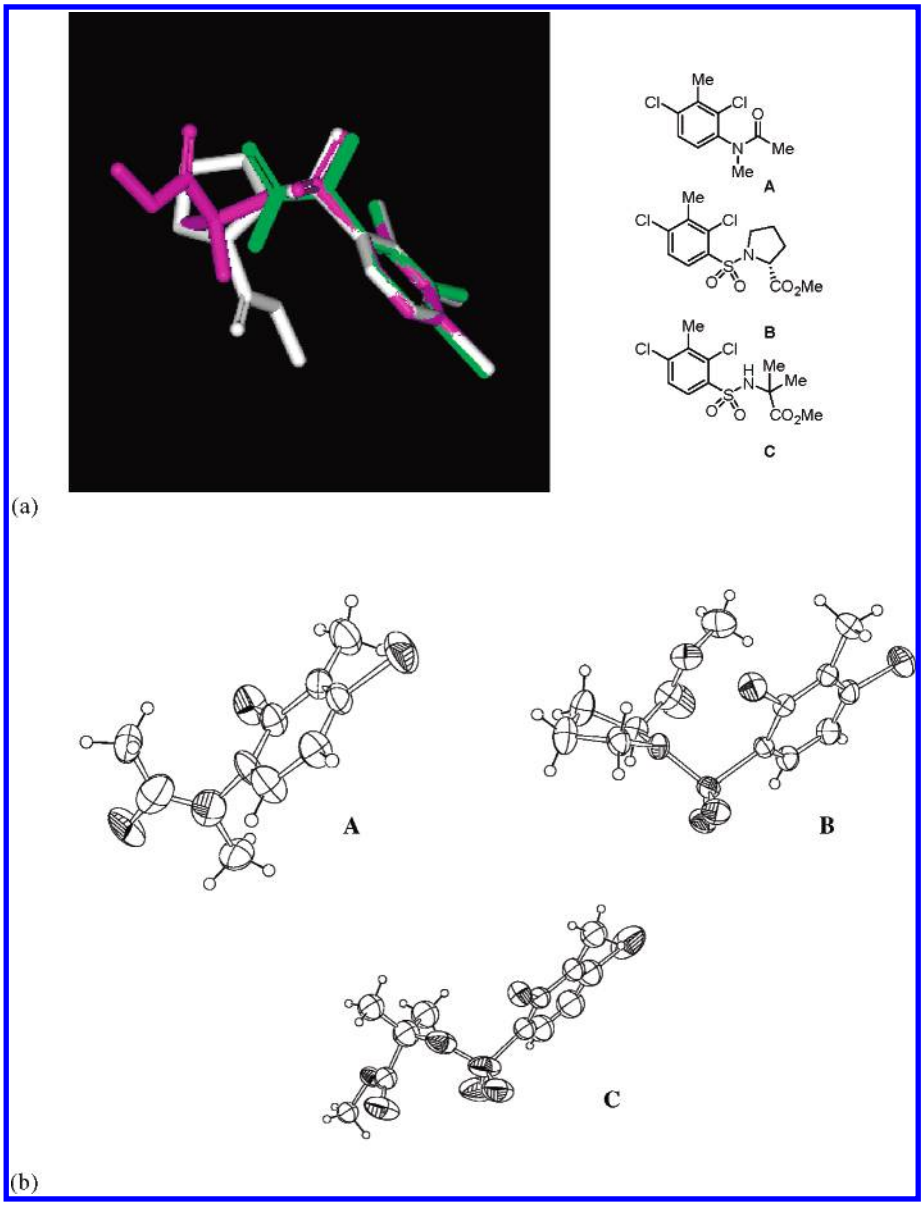



**Figure 1.** (a) Superposition of the X-ray structures obtained for test compounds **A** (green), **B** (white), and **C** (magenta). The figure was made with WebLab ViewerLite 4.0. (b) ORTEP representation for fragments **A**, **B**, and **C**.

A short neutral chain containing a phenyl ring (**19**−**22**) or solubilizing methoxy groups (**23**, **24**) were of no use in improving affinity. A slightly better result was obtained with the introduction of a basic moiety, either as an amino group (**25**−**29**) or a guanidino group (**30**−**32**). It is interesting to note that compounds **31** and **32** show almost the same affinity as **18**, despite their simpler structure. The inclusion of the terminal amino group into a piperidine, piperazine, or morpholine ring (**33**-**38**) was detrimental to binding.

Reductive amination on the propylendiamine linker was undertaken with the idea of maintaining the basic amino group and the hope of gaining some binding energy from the interaction of an aromatic group, with a flexible linker, with the surrounding portion of the receptor (**39**−**50**) through generic aromatic interactions (we had no receptor model to guide our work). However, despite all the substituents introduced, the affinity for the $hB_2R$ was always lower or equal to that of the simpler aliphatic amines and guanidines.

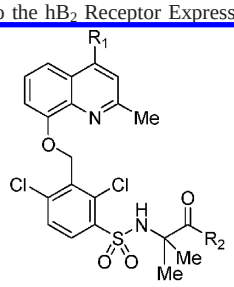
We then decided to try to gain some binding energy by modifying the entropy of the molecule through constraint of the linker/basic group into a ring (Table 2).

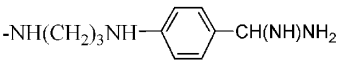
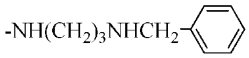
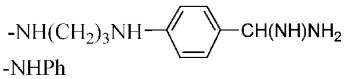
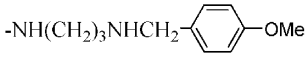
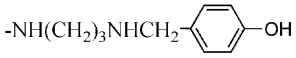
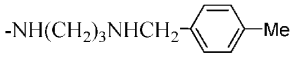
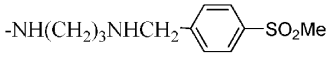
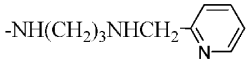
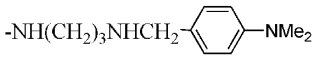
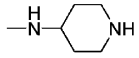
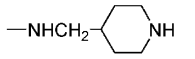
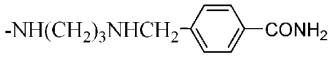
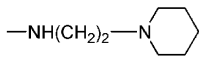
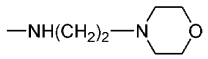
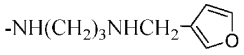
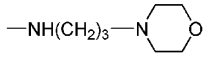
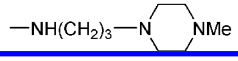
Indeed, rigidification of the linker, via the use of piperazine, gave compound **53**, which showed a net improvement in binding affinity over its flexible analogue **25**. Furthermore, its guanidine derivative, **54**, had a $pK_i > 8$. Elongation of the terminal chain and introduction of a second positively charged group was also beneficial for binding (**55**−**61**).

The best results were obtained with the insertion of the charged group into a chiral amino terminal amino acid moiety; both α- and *β*-amino acids gave compounds with excellent affinity, while the acylation of the primary amino group (**71**) was detrimental, supporting the critical role of basic groups. Only the optimal enantiomers are shown in Table 2 (**62**−**71**); the other enantiomers were less active (results not reported).

As mentioned previously, compounds having a p*K*i value higher than 8.4 were assessed for their ability to antagonize BK-induced functional responses, i.e., inositolphosphate (IP) accumulation as an index of receptor-activated phospholipase C, coupled to the $hB_2R$ expressed in CHO cells. These data were considered critical not only for the evaluation of the antagonist activity but also to explore the effect of our

**Table 1.** Binding of LF16-0687 and Compounds **17**−**50** to the $hB_2$ Receptor Expressed in CHO Cells



| Compd | $R_1$ | $R_2$ | pKi[a] | Compd | $R_1$ | $R_2$ | pKi[a] |
|---|---|---|---|---|---|---|---|
| **LF16-0687** | | | 9.1 | | | | |
| **17** | Me |  | 8.1 | **39** | H |  | 6.7 |
| **18** | H |  | 7.7 | **40** | H |  | 6.4 |
| **19** | H | -NHPh | 5.1 | | | | |
| **20** | H | $-NHCH_2Ph$ | <5.0 | **41** | H |  | 6.1 |
| **21** | H | $-NH(CH_2)_2Ph$ | <5.0 | | | | |
| **22** | H | $-NH(CH_2)_3Ph$ | <5.0 | **42** | H |  | 6.7 |
| **23** | H | $-NH(CH_2)_2OMe$ | 5.1 | | | | |
| **24** | H | $-NH(CH_2)_3OMe$ | 6.4 | **43** | H |  | 7.1 |
| **25** | H | $-NH(CH_2)_2NH_2$ | 7.0 | | | | |
| **26** | H | $-NH(CH_2)_3NH_2$ | 6.8 | **44** | H |  | 6.7 |
| **27** | Me | $-NH(CH_2)_3NH_2$ | 7.6 | | | | |
| **28** | H | $-NH(CH_2)_4NH_2$ | 6.7 | **45** | H |  | 7.1 |
| **29** | H | $-NH(CH_2)_3NMe_2$ | 6.7 | | | | |
| **30** | H | $-NHC(NH)NH_2$ | 7.2 | **46** | H |  | 7.4 |
| **31** | H | $-NH(CH_2)_2NHC(NH)NH_2$ | 7.7 | | | | |
| **32** | H | $-NH(CH_2)_3NHC(NH)NH_2$ | 7.4 | **47** | H |  | 6.8 |
| **33** | H |  | 7.1 | | | | |
| **34** | H |  | 6.8 | **48** | H |  | 6.9 |
| **35** | H |  | 6.5 | | | | |
| **36** | H |  | 5.6 | **49** | H |  | 6.5 |
| **37** | H |  | 6.2 | **50** | H |  | 6.8 |
| **38** | H |  | 6.6 | | | | |

[a] p*K*i for inhibition of specific binding of [$^3$H]BK to $hB_2$ receptor in stably transfected CHO cells membrane preparations. For details see the Experimental Section.

compounds on living cells. Generally, the functional values roughly correlated with the p$K_i$ values.

Remarkable data came from the compounds where the dimethylquinoline was introduced in place of the monomethylquinoline (**55**/**56**, **62**/**63**, **64**/**65**, **67**/**68**, **69**/**70**). In fact, the dimethyl derivatives, while maintaining almost the same binding affinity, displayed higher antagonist potency. The reasons for this phenomenon were not clear. A partial agonist behavior for the monomethyl derivatives was excluded, since the compounds did not show agonist responses at the concentration used. None of the compounds showed a p$K_i$ > 5.5 on the $hB_1R$ binding test.

Compound **68**, which had both excellent affinity and potency, was first evaluated in a GPI bioassay, where it showed a p$A_2$ = 10, and was subsequently tested in the guinea pig for its ability to reduce the BK-induced bronchoconstriction. After intratracheal administration at 300 nmol/kg, it was able to significantly inhibit (ca. 80%) BK-induced bronchoconstriction for at least 210 min, while only showing a weak and transient reduction (ca. 30% for 60 min) in the hypotensive effect.

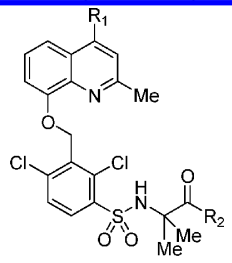
## Conclusions

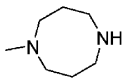
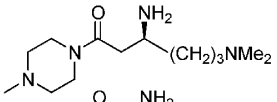
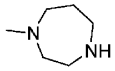
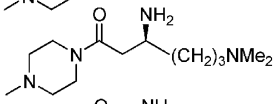
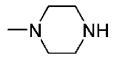
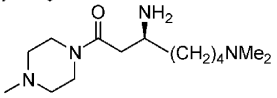
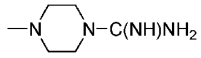
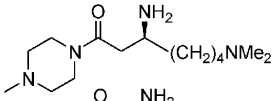
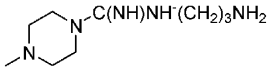
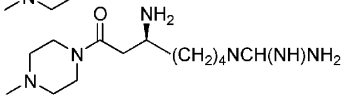
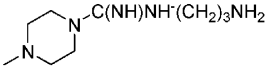
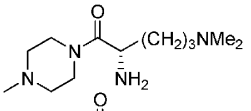
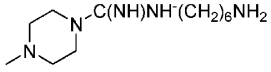
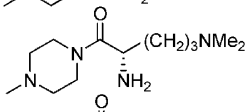
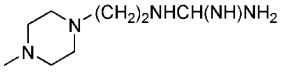
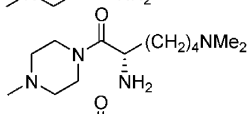
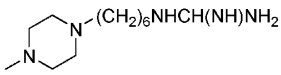
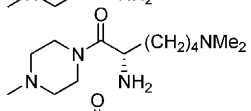
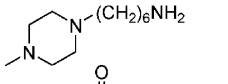
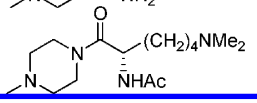
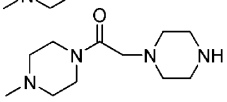
The α,α-dimethylsulfonamide described in this paper represent a novel class of $hB_2R$ antagonists that may be used to design agents to treat local airway diseases involving kinin $B_2$ receptor stimulation. The highly promising result showed by compound **68** was used as a starting point for further PK and PD improvements, eventually leading to MEN 16132,[1] a compound able to significantly inhibit BK-induced bronchoconstriction for at least 210 min at a dose of 0.1 μmol/kg after intratracheal administration, with minimal systemic side effects. Details of this work will be published shortly.

## Experimental Section

**(A) Chemistry.** Commercial chemicals and solvents were of reagent grade and used without further purification. The following abbreviations are used for reagents and solvents: AcOH, acetic

**Table 2.** Binding and in Vitro Functional Activity on the $hB_2$ Receptor of Compounds **51**−**71**



| Compd | $R_1$ | $R_2$ | pKi[a] | $pA_2$[b] | Compd | $R_1$ | $R_2$ | pKi[a] | $pA_2$[b] |
|---|---|---|---|---|---|---|---|---|---|
| **51** | H |  | 7.0 | NT | **62** | H |  | 9.1 | 7.40 |
| **52** | H |  | 7.6 | NT | **63** | Me |  | 9.2 | 8.60 |
| **53** | H |  | 7.6 | NT | **64** | H |  | 9.2 | 7.40 |
| **54** | H |  | 8.4 | 7.40 | **65** | Me |  | 9.3 | 8.60 |
| **55** | H |  | 8.8 | 7.96 | **66** | H |  | 8.9 | 8.10 |
| **56** | Me |  | 9.0 | 8.60 | **67** | H |  | 9.4 | 7.60 |
| **57** | H |  | 9.0 | 8.10 | **68** | Me |  | 9.4 | 9.10 |
| **58** | H |  | 8.0 | 7.40 | **69** | H |  | 8.7 | 7.95 |
| **59** | H |  | 8.8 | 8.10 | **70** | Me |  | 9.2 | 8.50 |
| **60** | H |  | 8.6 | 7.70 | **71** | H |  | 8.0 | 7.70 |
| **61** | H |  | 8.4 | 7.60 | | | | | |

[a] See Table 1. [b] $pA_2$ for the $hB_2$ mediated accumulation of inositol monophosphate in stably transfected CHOdhfr-/$hB_2$R cells. For details see the Experimental Section.

acid; AcCN, acetonitrile; DCM, dichloromethane; DDQ, dichlorodimethylquinone; DMF, dimethylformamide; DMSO, dimethyl sulfoxide; EDAC, *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide; EtOAc, ethyl acetate; $Et_2O$, diethyl ether; EtOH, ethanol; HOAt, 7-aza-1-hydroxybenzotriazole; MeOH, methanol; NBS, *N*-bromosuccinimide; TES, triethylsilane; TFA, trifluoroacetic acid.

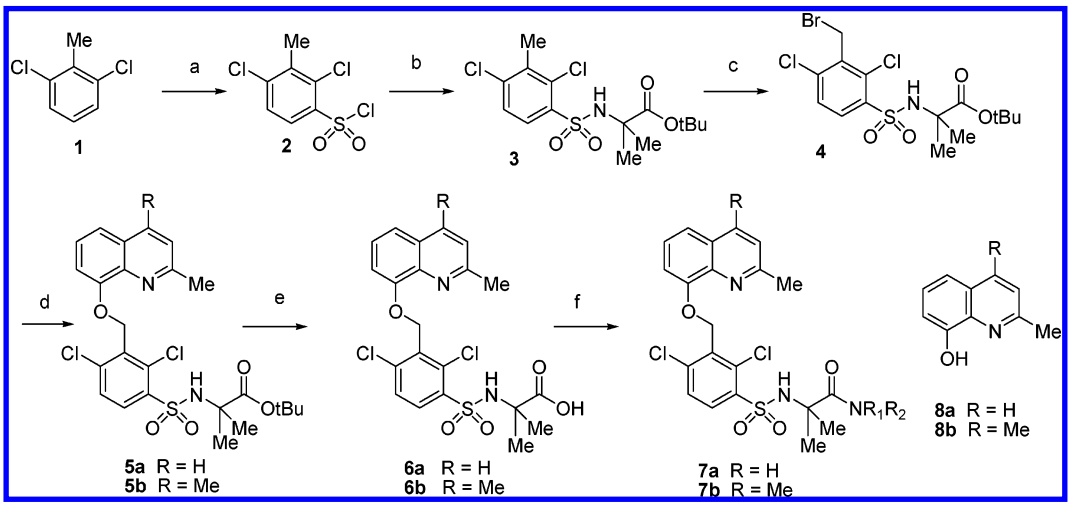
Merck silica gel (Kieselgel 60) was used for analytical thin-layer chromatography (TLC, $F_{254}$ plates) and flash chromatography (230−400 mesh).

Purity evaluation was performed through analytical HPLC using either a 600 E Waters pump, coupled to a Jasco 875 UV detector, and a Merck-Hitachi D-2500 integrator, a system comprising a Jasco PU-980 pump, LG-980-02 gradient unit, UV-975 UV/vis detector, and a Merck-Hitachi D-2500 integrator, or a Beckman System Gold apparatus. Solvents were (A) water 0.1% TFA and (B) AcCN 0.1% TFA, flow 1 mL/min. HPLC systems were as follows: system A, Vydac RP-18 column, 5 $\mu$m, 250 × 4.6 mm, $\lambda$ = 220 nm; from 80% to 8% solvent (A) in 24 min; system B, Symmetry 300 RP-18 column, 250 × 4.6 mm, $\lambda$ = 220 nm; from 80% to 20% solvent (A) in 20 min; and system C, Jupiter RP-18 column, 5$\mu$m, 150 × 4.6 mm, $\lambda$ = 210, 240 nm; from 80% to 20% solvent (A) in 20 min.

Preparative reverse phase HPLC was performed on a Waters600E apparatus with a Jasco 874 UV detector or on a Waters Delta-Prep 3000 apparatus. The mobile phases were the same as for the analytical systems. Gradient elution was employed. The columns used were either a SymmetryPrep C18, 7 $\mu$m, 19 × 300 mm, a Hibar Lichrosorb RP-18, 7 $\mu$m, 25 × 250 mm, or a Vydac C18, 10 $\mu$m, 22 × 250 mm. Peak detection was at 220 and 254 nm. Chemical yields are not optimized.

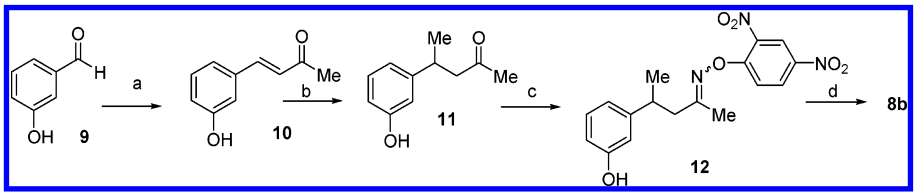
NMR experiments were recorded on a Varian Gemini 200 model J200 HC, a Varian 300 MHz spectrometer (equipped with a 5 mm inverse probe), or a Bruker Avance 400 MHz and are referenced to residual solvent signals: $CDCl_3$ ($\delta$ 7.26) or DMSO-$d_6$ ($\delta$ 2.49). Chemical shifts are reported in $\delta$ units (parts per million) and are assigned as singlets (s), doublets (d), doublets of doublets (dd), triplets (t), quartet (q), quintet (quin), multiplets (m), broad signals (br), or very broad signals (vbr). Coupling constants (*J*) are reported in hertz (Hz).

**Scheme 1**[a]



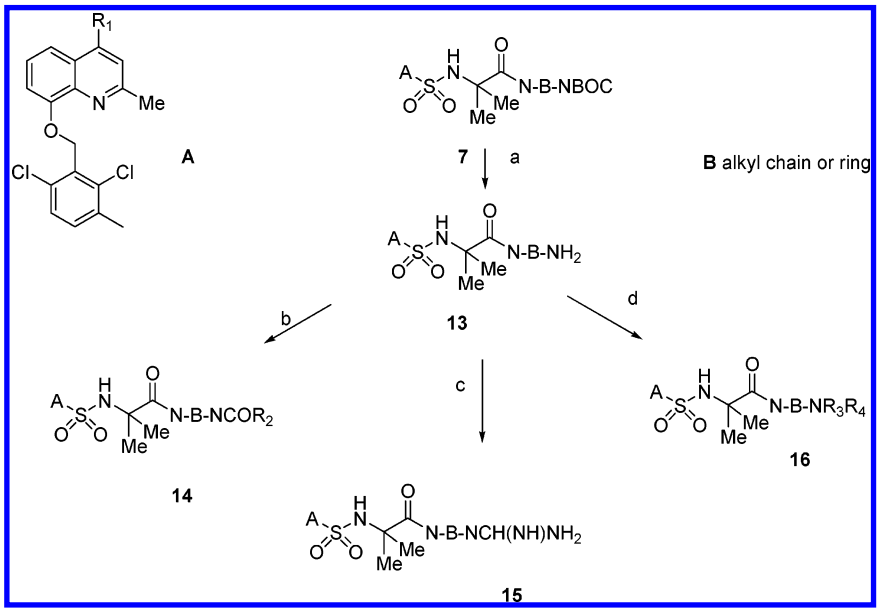

[a] Reagents: (a) chlorosulfonic acid; (b) 1,1-dimethylglycine *tert*-butyl ester, $NaHCO_3$, $H_2O$/AcCN; (c) NBS, benzoyl peroxide, $CCl_4$; (d) NaH, DMF, **8a** or **8b**; (e) TFA, TES, DCM; (f) HOAt, EDAC, $NHR_1R_2$.

**Scheme 2**[a]




[a] Reagents: (a) acetone, NaOH; (b) CuCl, MeMgBr, THF; (c) *O*-(2,4-dinitrophenyl)hydroxylamine, HCl; (d) NaH, DDQ, dioxane.

**Scheme 3**[a]




[a] Reagents: (a) 4 N HCl, dioxane; (b) HOAt, EDAC, DMF; (c) Goodman's reagent, DIPEA; (d) $NHR_3R_4$, (polystyrylmethyl)trimethyl cyanoborohydride resin, DCM/AcOH.

Mass spectra were recorded using a Waters Alliance 2795 HPLC system fitted with a UV-PDS 996 diode array detector, a ZMD mass spectrometer, and a GL Science Inertsil ODS-3 column (50 × 3 mm, 3 $\mu$m) or a ThermoFinnigan LCQ equipped with APCI or ESI source.

**2,4-Dichloro-3-methylbenzenesulfonyl Chloride (2).** 2,6-Dichlorotoluene **1** (4.8 mL, 37.3 mmol) was added dropwise over 2 h to chlorosulfonic acid (10 mL, 151 mmol). At the end of the addition, the resulting mixture was heated at 40 °C for 2 h. The solution turned violet. Then it was cooled to room temperature and poured with caution onto a water/ice mixture (0.5 L) under vigorous stirring. A white solid separated that was filtered off, washed with water, and dried in vacuo in the presence of KOH. The resulting solid was treated with hexane (200 mL) with vigorous stirring. Filtration and concentration of the organic layer afforded the desired product (8.23 g, 85% yield). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.96 (1H, d, $J$ = 8.5 Hz), 7.51 (1H, d, $J$ = 8.5 Hz), 2.66 (3H, s). MS $m/z$ calcd for $C_7H_5Cl_3O_2S$: 259.54. Found: 260.2 $[M + H]^+$.

**2-(2,4-Dichloro-3-methylbenzenesulfonylamino)-2-methylpropionic Acid *tert*-Butyl Ester (3).** A solution of the sulfonyl chloride **2** (569 mg, 2.18 mmol) in acetonitrile (10 mL) was added dropwise to a solution of the 1,1-dimethylglycine *tert*-butyl ester (512 mg,

2.62 mmol) in aq $NaHCO_3$ (224 mg in 5 mL water). At the end of the addition, a second identical portion of $NaHCO_3$ solution was added and stirring continued at room temperature. At the end of the reaction (HPLC control), the solvent was distilled off in vacuo and the residue partitioned between EtOAc (75 mL) and 1 N HCl (75 mL). The two layers were separated, and the organic phase was further washed with 1 N HCl (75 mL), water (2 × 75 mL), 5% $NaHCO_3$ (2 × 75 mL), and brine (75 mL); dried over $Na_2SO_4$; filtered; and concentrated in vacuo to afford **3** (682 mg, 82%) as a pale orange solid. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.35 (1H, s), 7.85 (1H, d, $J$ = 8.6 Hz), 7.65 (1H, d, $J$ = 8.6 Hz), 2.37 (3H, s), 1.38 (9H, s), 1.26 (6H, s). MS $m/z$ calcd for $C_{15}H_{21}Cl_2NO_4S$: 382.0. Found: 383.0 $[M + H]^+$.

**2-(3-Bromomethyl-2,4-dichlorobenzenesulfonylamino)-2-methylpropionic Acid *tert*-Butyl Ester (4).** A solution of **3** (1.00 g, 2.6 mmol), NBS (2.50 g, 13.0 mmol), and benzoyl peroxide (100 mg, 0.41 mmol) in $CCl_4$ (40 mL) was heated at 95 °C under nitrogen. After 4 h an additional portion (100 mg, 0.41 mmol) of benzoylperoxide was added. At the end of the reaction (HPLC control, RP-C18), the mixture was cooled to room temperature, the insoluble succinimide filtered off, and the solvent distilled off in vacuo. Flash chromatographic purification (silica, hexane/EtOAc 18:1) afforded 1.03 g (86% yield) of bromo derivative **4**. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.04 (1H, d, $J$ = 8.6 Hz), 7.50 (1H, d, $J$ = 8.6 Hz), 6.13 (1H, s), 4.82 (2H, s), 1.50 (9H, s), 1.42 (6H, s). MS $m/z$ calcd for $C_{15}H_{20}BrCl_2NO_4S$: 459.0. Found: 460.0 $[M + H]^+$.

**2-[2,4-Dichloro-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonylamino]-2-methylpropionic Acid *tert*-Butyl Ester (5a) and 2-[2,4-Dichloro-3-(2,4-dimethylquinolin-8-yloxymethyl)benzenesulfonylamino]-2-methylpropionic Acid *tert*-Butyl Ester (5b).** A solution of quinoline (**8a** or **8b**, 5.46 mmol) in DMF (10 mL) was cooled in an ice bath. Sodium hydride (80% in mineral oil, 180 mg, 6.00 mmol) was added portionwise and the mixture was left to reach room temperature. When gas production ceased, a solution of benzyl bromide **4** (2.10 g, 4.55 mmol) in DMF (10 mL) was added dropwise. At the end of the reaction (TLC or HPLC control) the mixture was poured over water/ice (400 mL). A precipitate formed, which was filtered off, washed with cold water, and dried in vacuo to give the desired product in quantitative yield. (**5a**) $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.47 (1H, br s), 8.21 (1H, d, $J$ = 8.4 Hz), 8.01 (1H, d, $J$ = 8.7 Hz), 7.76 (1H, d, $J$ = 8.7 Hz), 7.56−7.32 (4H, m), 5.53 (2H, s), 2.62 (3H, s), 1.41 (9H, s), 1.26 (6H, s). MS $m/z$ calcd for $C_{25}H_{28}Cl_2N_2O_5S$: 538.1. Found: 539.1 $[M + H]^+$. (**5b**) $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.07 (1H, d, $J$ = 8.6 Hz), 7.62 (1H, d, $J$ = 8.4 Hz), 7.46 (1H, d, $J$ = 8.6 Hz), 7.38 (1H, dd, $J$ = 8.4, 8.4 Hz), 7.22 (1H, d, $J$ = 8.4 Hz), 7.15 (1H, s), 6.11 (1H, s), 5.67 (2H, s), 2.65 (3H, s), 2.62 (3H, s), 1.46 (9H, s), 1.54 (6H, s). MS $m/z$ calcd for $C_{26}H_{30}Cl_2N_2O_5S$: 552.1. Found: 553.1 $[M + H]^+$.

**2-[2,4-Dichloro-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonylamino]-2-methylpropionic Acid (6a) and 2-[2,4-Dichloro-3-(2,4-dimethylquinolin-8-yloxymethyl)benzenesulfonylamino]-2-methylpropionic Acid (6b).** A solution of *tert*-butyl ester (**5a** or **5b**, 2.50 g, 4.64 mmol), TES (1.83 mL, 11.6 mmol), and TFA (17 mL, 232 mmol) in DCM (100 mL) was stirred at room temperature. At the end of the reaction (HPLC control), $Et_2O$ was added (150 mL). After 15 min of stirring a white precipitate was formed, which was filtered off, washed with $Et_2O$, and dried in vacuo to obtain the desired acid in quantitative yield. (**6a**) $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.67 (1H, d, $J$ = 8.6 Hz), 8.15 (1H, d, $J$ = 8.6 Hz), 7.83 (1H, t), 7.70−7.50 (4H, m), 6.37 (1H, vbr s), 5.63 (2H, s), 2.93 (3H, s), 1.53 (6H, s). (**6b**) $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.40 (1H, s), 8.05 (1H, d, $J$ = 8.5 Hz), 7.85−7.30 (5H, m), 5.50 (2H, s), 2.75 (3H, br s), 2.65 (3H, br s), 1.30 (6H, s).

**General Method for the Preparation of Amides 7a and 7b.** A solution of the carboxylic acid **6a** or **6b** (11.4 mmol), HOAt (1.510 g, 11.09 mmol), and EDAC (2.47 g, 11.7 mmol) in DCM (20 mL) was stirred in an ice bath for 30 min. A solution of the desired, neutral amine (15.68 mmol) in DCM (3 mL) was added and stirring continued at 0° for 30 min and then at room temperature till the end of the reaction (HPLC control).

In some cases, the crude reaction mixture was poured directly onto a silica gel flash column and eluted with hexane/EtOAc mixtures. In others, the DCM solution was washed with 1 N HCl, 5% $Na_2CO_3$, water, and brine; dried over $Na_2SO_4$, and concentrated in vacuo.

**(*E*)-4-(3-Hydroxyphenyl)but-3-en-2-one (10).** To an ethanol solution (150 mL) of 3-hydroxybenzaldehyde **9** (25.5 g, 0.209 mol) and acetone (60.6 g, 1.05 mol) was added 10% aqueous sodium hydroxide (150 mL) at 0 °C. The mixture was stirred for 2 h at 0 °C (TLC, silica, petroleum ether/EtOAc 2:1) and then neutralized by adding 1 N aq HCl. The organic material was extracted with EtOAc, and the combined extracts were washed with saturated NaCl and dried over $Na_2SO_4$. The solvent was removed in vacuo and the crude material was treated with $Et_2O$ (200 mL), stirred for 3 h, filtered, washed with $Et_2O$, and dried to give 17 g of pure 4-(3-hydroxyphenyl)but-3-en-2-one. Concentration of the ethereal layers resulted in a batch of crude **10** (19 g) which was purified by flash column chromatography (petroleum ether/EtOAc 2:1) to give an additional 12 g of **10** (86%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.50 (1H, d, $J$ = 16 Hz), 7.30 (1H, dd, $J$ = 7.7 Hz), 7.15 (1H, dd, $J$ = 7.2 Hz), 7.10 (1H, s), 6.96 (1H, dd, $J$ = 7.2 Hz), 6.70 (1H, d, $J$ = 16 Hz), 6.45 (1H, s), 2.45 (3H, s). MS $m/z$ calcd for $C_{10}H_{10}O_2$: 162.0. Found: 163.0 $[M + H]^+$.

**4-(3-Hydroxyphenyl)pentan-2-one (11).** Anhydrous CuCl (1.00 g, 10.1 mmol) was added with stirring to a 3 N ethereal solution of MeMgBr (48 mL, 140 mmol) at 0 °C. 4-(3-Hydroxyphenyl)-but-3-en-2-one (**10**) (9.35 g, 57.6 mmol) in dry tetrahydrofuran (200 mL) was slowly added to the reaction mixture at 0 °C. Along with the addition of the ketone, more CuCl (1.00 g) was added portionwise. The reaction mixture was stirred at room temperature for 1 h (TLC, silica, petroleum ether/EtOAc 4:1) and then quenched under cooling (ice/salt) by the slow addition of 6 N HCl under vigorous stirring. The organic material was extracted with ethyl acetate, and the combined extracts were washed with water, saturated aqueous $Na_2S_2O_3$, and again with water and dried over $Na_2SO_4$. After the solvent was removed in vacuo, the crude material was purified by flash column chromatography (petroleum ether/EtOAc 4:1) to give 4-(3-hydroxyphenyl)pentan-2-one **11** (7.0 g, 67%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.20 (1H, t, $J$ = 7.5 Hz), 6.80 (1H, d, $J$ = 8 Hz), 6.70 (1H, s), 6.65 (1H, d, $J$ = 7 Hz), 5.25 (1H, br s), 3.25 (1H, m), 2.80 (1H, dd, $J$ = 17, 7.0 Hz), 2.55 (1H, dd, $J$ = 17, 7.5 Hz), 2.10 (3H, s), 1.30 (3H, d, $J$ = 6 Hz). MS $m/z$ calcd for $C_{11}H_{14}O_2$: 178.2. Found: 179 $[M + H]^+$.

**4-(3-Hydroxyphenyl)pentan-2-one *O*-(2,4-Dinitrophenyl)-oxime (12).** *O*-(2,4-Dinitrophenyl)hydroxylamine (10.22 g, 51.33 mmol) was dissolved in EtOH (500 mL) by warming on a steam bath. 4-(3-Hydroxyphenyl)pentan-2-one **11** (9.15 g, 51.3 mmol) was added, and the solution was swirled until it was homogeneous. Concentrated HCl (20 drops) was added and the mixture stirred at room temperature. After 1 h (TLC, silica, petroleum ether/EtOAc 4:1) the mixture was concentrated to half volume and diluted with EtOAc (1.5 L). The organic solution was washed with saturated $NaHCO_3$, water, and saturated NaCl; dried ($Na_2SO_4$); and concentrated under reduced pressure to give 20 g of crude **12** (2:1 mixture of E/Z isomers, 80% HPLC purity, 87% yield) which was used in the next step without purification. MS $m/z$ calcd for $C_{17}H_{17}N_3O_6$: 359.1. Found: 360 $[M + H]^+$.

**2,4-Dimethylquinolin-8-ol (8b).** To a 1,4-dioxane (200 mL) suspension of sodium hydride (17.45 g, 55% in mineral oil, previously washed with hexane, 0.400 mol) was added a 1,4-dioxane solution (500 mL) of 4-(3-hydroxyphenyl)pentan-2-one *O*-2,4-dinitrophenyloxime **12** (18 g, 80%, 0.04 mol) and the mixture heated to 50 °C. After 20 h, the reaction mixture was acidified with AcOH (40 mL) and then a 1,4-dioxane solution (200 mL) of DDQ (4.54 g, 0.02 mmol) was added. The resulting mixture was immediately heated to reflux. After 2 h (TLC, silica, petroleum ether/EtOAc 4:1) the reaction mixture was diluted with water (300 mL) and neutralized with saturated aqueous $NaHCO_3$, and the organic material was extracted with EtOAc. The organic phase was washed with saturated NaCl and dried over $Na_2SO_4$. After evaporation of the solvent the crude material was purified by flash

chromatography (petroleum ether/EtOAc 4:1) to afford 2,4-dimethyl-8-hydroxyquinoline **8b**, which was recrystallized from ethanol (4.86 g, 70%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.40 (2H, m), 7.25 (1H, s), 7.05 (1H, d, $J = 7$ Hz), 2.65 (3H, s), 2.60 (3H, s). MS *m*/*z* calcd for $C_{11}H_{11}NO$: 173.1. Found: 174 $[M + H]^+$.

**General Synthesis of Amides 14.** A solution of the carboxylic acid (0.09 mmol) and HOAt (14 mg, 0.09 mmol) in DMF (2.5 mL) was cooled in an ice bath and EDAC (17 mg, 0.09 mmol) was added. Stirring was continued at 0 °C for 0.5−1.0 h, a solution of the amine (0.06 mmol) was added, and stirring continued for an additional 30 min at 0 °C and then at room temperature overnight. The solvent was distilled off in vacuo and the resulting crude mixture was purified by RP chromatography to obtain the desired product.

**General Synthesis of Guanidines 15.** A solution of the amine (2.34 mmol), Goodman's reagent (1.06 g, 2.72 mmol), and DIPEA (2.81 mmol) in DCM (4 mL) was stirred at room temperature for 2 days. At the end of the reaction (HPLC control) the solvent was distilled off in vacuo and the crude product purified by flash chromatography (silica) with the opportune eluant. The Boc protecting group was removed via treatment with TFA/DCM (1:1) to obtain the desired guanidines as their trifluoroacetate salts.

**General Synthesis of Amines 16.** A solution of the amine (0.065 mmol) and the opportune aldehyde (0.067 mmol) in DCM−AcOH (10:1) (2 mL) was stirred at room temperature for 30 min. The (polystyrylmethyl)trimethyl cyanoborohydride resin (22 mg, 0.09 mmol) was added and stirring was continued at room temperature overnight. At the end of the reaction (HPLC control), the mixture was filtered and the resin was washed with DCM (2 × 4 mL). The resulting solution was concentrated in vacuo and the residue was purified by preparative HPLC (RP-C18) to obtain the desired products as the corresponding trifluoroacetate salts.

***N*-[3-(4-Carbamimidoylphenylamino)propyl]-2-[2,4-dichloro-3-(2,4-dimethylquinolin-8-yloxymethyl)benzenesulfonylamino]-2-methylpropionamide Trifluoroacetate Salt (17).** $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 9.40 (2H, s), 9.19 (2H, s), 8.85 (1H, t), 8.10 (2H, m), 8.00 (2H, m), 7.90 (2H, m), 7.85−7.40 (6H, m), 5.55 (2H, s), 3.30 (2H, m), 3.10 (2H, m), 2.70 (3H, s), 2.60 (3H, s), 1.70 (2H, m), 1.30 (6H, s). MS *m*/*z* calcd for $C_{33}H_{36}Cl_2N_6O_4S$: 698.1. Found: 699 $[M + H]^+$. HPLC purity: system A, 95.8%, $t_R$ = 13.9 min.

***N*-[3-(4-Carbamimidoylphenylamino)propyl]-2-[2,4-dichloro-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonylamino]-2-methylpropionamide Trifluoroacetate Salt (18).** $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 9.37 (2H, br s), 9.00 (2H, br s), 8.68 (1H, t), 8.30 (1H, br s), 8.10 (1H, d), 8.00 (2H, d), 7.87 (2H, d), 7.77 (1H, d), 7.70 (1H, t), 7.60−7.33 (4H, m), 5.53 (2H, s), 3.30 (2H, m), 3.13 (2H, m), 2.63 (3H, s), 1.70 (2H, m), 1.28 (6H, s). MS *m*/*z* calcd for $C_{32}H_{34}Cl_2N_6O_5S$: 684.2. Found: 685.1 $[M + H]^+$. HPLC purity: system B, 94.1%, $t_R$ = 10.07 min.

**2-[2,4-Dichloro-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonylamino]-2-methyl-*N*-phenylpropionamide Trifluoroacetate Salt (19).** $^1$H NMR (600 MHz, DMSO-$d_6$): $\delta$ 9.28 (1H, s), 8.30 (1H, br s), 8.16 (1H, s), 8.06 (1H, d), 7.73 (1H, d), 7.64−7.42 (4H, m), 7.50 (1H, d), 7.42−7.25 (3H, m), 7.08 (1H, t), 5.43 (2H, s), 2.62 (3H, s): 1.39 (6H, s). MS *m*/*z* calcd for $C_{27}H_{25}Cl_2N_3O_4S$: 557.0. Found: 558.2 $[M + H]^+$. HPLC purity: system C, 95.72%, $t_R$ = 12.42 min.

***N*-Benzyl-2-[2,4-dichloro-3-(2-methylquinolin-8-yloxymethyl)-benzenesulfonylamino]-2-methylpropionamide Trifluoroacetate Salt (20).** $^1$H NMR (600 MHz, DMSO-$d_6$): $\delta$ 8.39 (1H, br s), 8.14−8.09 (2H, m), 8.09 (1H, d), 7.76 (1H, d), 7.67−7.34 (4H, m), 4.34−7.21 (5H, m), 5.33 (2H, s), 4.28 (2H, d): 2.67 (3H, br s), 1.33 (6H, s). MS *m*/*z* calcd for $C_{28}H_{27}Cl_2N_3O_4S$: 571.1. Found: 572.1 $[M + H]^+$. HPLC purity: system C, 96.1%, $t_R$ = 12.40 min.

**2-[2,4-Dichloro-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonylamino]-2-methyl-*N*-phenethylpropionamide Trifluoroacetate Salt (21).** $^1$H NMR (600 MHz, DMSO-$d_6$): $\delta$ 9.35 (1H, br s), 8.44 (1H, br s), 8.07 (1H, d), 8.00 (1H, s), 7.77 (1H, d), 7.71−7.42 (5H, m), 7.31−7.15 (4H, m), 5.55 (2H, s), 3.27 (4H, m), 2.68 (5H, m), 1.22 (6H, s). MS *m*/*z* calcd for $C_{29}H_{29}Cl_2N_3O_4S$: 585.1. Found: 586.1 $[M + H]^+$. HPLC purity: system C, 97.1%, $t_R$ = 13.15 min.

**2-[2,4-Dichloro-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonylamino]-2-methyl-*N*-(3-phenylpropyl)propionamide Trifluoroacetate Salt (22).** $^1$H NMR (600 MHz, DMSO-$d_6$): $\delta$ 8.32 (1H, br s), 8.08 (1H, d), 8.06 (1H, s), 7.78 (1H, d), 7.39−7.33 (5H, m), 7.28−7.12 (4H, m), 5.53 (2H, s), 3.07 (2H, m), 2.39 (3H, s), 2.56 (2H, m), 1.69 (2H, m), 1.30 (3H, s), 1.25 (3H, s). MS *m*/*z* calcd for $C_{30}H_{31}Cl_2N_3O_4S$: 599.1. Found: 600.1 $[M + H]^+$. HPLC purity: system C, 96.6%, $t_R$ = 13.92 min.

**2-[2,4-Dichloro-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonylamino]-*N*-(2-methoxyethyl)-2-methylpropionamide Trifluoroacetate Salt (23).** $^1$H NMR (600 MHz, DMSO-$d_6$): $\delta$ 8.51 (1H, br s), 8.15 (1H, s), 8.07 (1H, d), 7.78 (1H, d), 7.73−7.46 (4H, m), 5.58 (2H, s), 3.32 (2H, t), 3.23 (3H, s), 3.21 (2H, t), 2.73 (3H, br s), 1.28 (6H, s). MS *m*/*z* calcd for $C_{24}H_{27}Cl_2N_3O_4S$: 539.1. Found: 540.1 $[M + H]^+$. HPLC purity: system C, >99%, $t_R$ = 9.13 min.

**2-[2,4-Dichloro-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonylamino]-*N*-(3-methoxypropyl)-2-methylpropionamide Trifluoroacetate Salt (24).** $^1$H NMR (600 MHz, DMSO-$d_6$): $\delta$ 8.49 (1H, br s), 8.07 (1H, d), 8.02 (1H, s), 7.77 (1H, d), 7.71−7.48 (4H, m), 5.58 (2H, s), 3.31 (2H, t), 3.19 (3H, s), 3.09 (2H, t), 2.71 (3H, br s), 1.64 (2H, tt), 1.25 (6H, s). MS *m*/*z* calcd for $C_{25}H_{29}Cl_2N_3O_4S$: 553.1. Found: 554.1 $[M + H]^+$. HPLC purity: system D, 99%, $t_R$ = 9.13 min.

***N*-(2-Aminoethyl)-2-[2,4-dichloro-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonylamino]-2-methylpropionamide Hydrochloride Salt (25).** $^1$H NMR (600 MHz, DMSO-$d_6$): $\delta$ 8.65 (1H, br s), 8.14 (1H, s), 8.08 (1H, d), 7.83−7.56 (4H, m), 7.79 (1H, d), 5.58 (2H, s), 3.29 (2H, m), 2.83 (2H, m), 2.78 (3H, br s), 1.31 (3H, s). MS *m*/*z* calcd for $C_{23}H_{26}Cl_2N_4O_4S$: 524.1. Found: 525.1 $[M + H]^+$. HPLC purity: system A, >99%, $t_R$ = 5.90 min.

***N*-(3-Aminopropyl)-2-[2,4-dichloro-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonylamino]-2-methylpropionamide Trifluoroacetate Salt (26).** $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.05 (2H, m), 7.85 (1H, t), 7.55 (1H, d), 7.50 (1H, d), 7.40 (1H, t), 7.3 (3H, m), 5.80 (2H, s), 3.43 (2H, m), 2.95 (2H, m), 2.82 (3H, s), 1.73 (2H, m), 1.40 (6H, s). MS *m*/*z* calcd for $C_{24}H_{28}Cl_2N_4O_4S$: 538.1. Found: 539.1 $[M + H]^+$. HPLC purity: system B, 99.0%, $t_R$ = 8.88 min.

***N*-(3-Aminopropyl)-2-[2,4-dichloro-3-(2,4-dimethylquinolin-8-yloxymethyl)benzenesulfonylamino]-2-methylpropionamide Trifluoroacetate Salt (27).** $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.15 (1H, s), 8.05 (1H, d), 7.81 (1H, d), 7.81−7.30 (8H, m), 5.58 (2H, s), 3.19 (2H, m), 2.85 (2H, m), 2.69 (3H, s), 2.61 (3H, s), 1.73 (2H, m), 1.31 (6H, s). MS *m*/*z* calcd for $C_{25}H_{30}Cl_2N_4O_4S$: 552.1. Found: 553.1 $[M + H]^+$. HPLC purity: system A, 99.0%, $t_R$ = 6.38 min.

***N*-(4-Aminobutyl)-2-[2,4-dichloro-3-(2,4-dimethylquinolin-8-yloxymethyl)benzenesulfonylamino]-2-methylpropionamide Trifluoroacetate Salt (28).** $^1$H NMR (600 MHz, DMSO-$d_6$): $\delta$ 8.31 (1H, br s), 8.07 (1H, d), 8.02 (1H, s), 7.70−7.36 (7H, m), 5.68 (2H, s), 3.07 (2H, m), 2.77 (2H, m), 2.63 (3H, br s), 1.48 (4H, m), 1.26 (6H, s). MS *m*/*z* calcd for $C_{25}H_{30}Cl_2N_4O_4S$: 552.1. Found: 553.1 $[M + H]^+$. HPLC purity: system C, 97.6%, $t_R$ = 6.36 min.

**2-[2,4-Dichloro-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonylamino]-*N*-(3-(dimethylamino)propyl)-2-methylpropionamide Trifluoroacetate Salt (29).** $^1$H NMR (600 MHz, DMSO-$d_6$): $\delta$ 9.24 (1H, br s), 8.32 (1H, br s), 8.17 (1H, s), 8.07 (1H, d), 7.82 (1H, m), 7.78 (1H, d), 7.65−7.38 (4H, m), 5.54 (2H, s), 3.16 (2H, m), 3.04 (2H, m), 2.77 (6H, s), 2.65 (3H, br s), 1.78 (2H, m), 1.27 (6H, s). MS *m*/*z* calcd for $C_{26}H_{32}Cl_2N_4O_4S$: 566.1. Found: 567.3 $[M + H]^+$. HPLC purity: system C, 97.6%, $t_R$ = 5.98 min.

**2,4-Dichloro-*N*-(2-guanidino-1,1-dimethyl-2-oxoethyl)-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonamide Trifluoroacetate Salt (30).** $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 10.5 (1H, s), 8.71 (1H, s), 8.50 (2H, br s), 8.29 (3H, br s), 8.08 (1H, d), 7.83 (1H, d), 7.63−7.37 (4H, m), 5.54 (2H, s), 2.62 (3H, s), 1.37 (6H,

s). MS *m/z* calcd for $C_{22}H_{23}Cl_2N_5O_4S$: 523.1. Found: 524.0 [M + H]$^+$. HPLC purity: system A, 97.0%, $t_R$ = 7.32 min.

**2-[2,4-Dichloro-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonylamino]-*N*-(2-guanidinoethyl)-2-methylpropionamide (31).** $^1$H NMR (600 MHz, DMSO-$d_6$): $\delta$ 8.34 (1H, br s), 8.14 (1H, s), 8.06 (1H, d), 7.70 (2H, m), 7.77−7.31 (4H, m), 6.97 (4H, vbr s), 5.56 (2H, s), 3.17 (4H, m), 2.66 (3H, br s), 1.29 (6H, s). MS *m/z* calcd for $C_{24}H_{28}Cl_2N_6O_4S$: 566.1. Found: 567.3 [M + H]$^+$. HPLC purity: system C, 94.3%, $t_R$ = 6.51 min.

**2-[2,4-Dichloro-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonylamino]-*N*-(3-guanidinopropyl)-2-methylpropionamide Trifluoroacetate Salt (32).** $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.38 (1H, br s), 8.08 (2H, m), 7.79 (1H, d), 7.67 (1H, m), 7.54 (4H, m), 5.58 (2H, s), 3.12 (4H, m), 2.71 (3H, s), 1.62 (2H, m), 1.33 (6H, s). MS *m/z* calcd for $C_{25}H_{30}Cl_2N_6O_4S$: 580.1. Found: 581.1 [M + H]$^+$. HPLC purity: system A, 98.3%, $t_R$ = 13.06 min.

**2-[2,4-Dichloro-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonylamino]-2-methyl-*N*-piperidin-4-ylpropionamide Trifluoroacetate Salt (33).** $^1$H NMR (600 MHz, DMSO-$d_6$): $\delta$ 8.48 (1H, br m), 8.24 (2H, br m), 8.08 (1H, d), 8.00 (1H, s), 7.79 (1H, d), 7.61−7.36 (5H, m), 5.56 (2H, s), 3.26 (3H, m), 2.98 (2H, m), 2.64 (3H, s), 1.86 (2H, m), 1.60 (2H, m), 1.26 (6H, s). MS *m/z* calcd for $C_{26}H_{30}Cl_2N_4O_4S$: 564.1. Found: 565.1 [M + H]$^+$. HPLC purity: system A, 99%, $t_R$ = 6.18 min.

**2-[2,4-Dichloro-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonylamino]-2-methyl-*N*-piperidin-4-ylmethyl-ropionamide Trifluoroacetate Salt (34).** $^1$H NMR (600 MHz, DMSO-$d_6$): $\delta$ 8.43 (1H, m), 8.28 (1H, br s), 8.10 (1H, m), 8.07 (1H, s), 8.10 (1H, d), 7.78 (1H, d), 7.69 (1H, t), 7.64−7.36 (4H, m), 5.58 (2H, s), 3.26 (2H, m), 3.00 (2H, m), 2.88 (2H, m), 2.62 (3H, br s), 1.74 (2H, m), 1.72 (1H, m), 1.27 (6H, s), 1.25 (2H, m). MS *m/z* calcd for $C_{27}H_{32}Cl_2N_4O_4S$: 578.1. Found: 579.2 [M + H]$^+$. HPLC purity: system A, 99%, $t_R$ = 6.15 min.

**2-[2,4-Dichloro-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonylamino]-2-methyl-*N*-(2-piperidin-1-yl-ethyl)propionamide Trifluoroacetate Salt (35).** $^1$H NMR (600 MHz, DMSO-$d_6$): $\delta$ 9.04 (1H, br s), 8.36 (1H, br s), 8.24 (1H, s), 8.06 (1H, d), 8.00 (1H, t), 7.79 (1H, d), 7.65−7.37 (4H, m), 5.55 (2H, s), 3.45 (4H, m), 3.10 (2H, m), 2.95 (2H, m), 2.65 (3H, s), 1.81 (2H, m), 1.63 (3H, m), 1.37 (1H, m), 1.27 (6H, s). MS *m/z* calcd for $C_{28}H_{34}Cl_2N_4O_4S$: 592.1. Found: 593.3 [M + H]$^+$. HPLC purity: system C, 90.2%, $t_R$ = 7.27 min.

**2-[2,4-Dichloro-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonylamino]-2-methyl-*N*-(2-morpholin-4-ylethyl)propionamide Trifluoroacetate Salt (36).** $^1$H NMR (600 MHz, DMSO-$d_6$): $\delta$ 9.62 (1H, br s), 8.32 (1H, br s), 8.25 (1H, s), 8.05 (1H, d), 7.96 (1H, t), 7.80 (1H, d), 7.67−7.37 (4H, m), 5.55 (2H, s), 3.98 (2H, m), 3.62 (2H, m), 3.44 (4H, m), 3.15 (4H, m), 2.64 (3H, s), 1.28 (6H, s). MS *m/z* calcd for $C_{27}H_{32}Cl_2N_4O_5S$: 594.1. Found: 595.1 [M + H]$^+$. HPLC purity: system A, 99%, $t_R$ = 6.32 min.

**2-[2,4-Dichloro-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonylamino]-2-methyl-*N*-(3-morpholin-4-yl-propyl)propionamide Trifluoroacetamide (37).** $^1$H NMR (600 MHz, DMSO-$d_6$): $\delta$ 9.53 (1H, br s), 8.33 (1H, br s), 8.18 (1H, s), 8.08 (1H, d), 7.84 (1H, t), 7.81 (1H, d), 7.68−7.35 (4H, m), 5.54 (2H, s), 3.95 (2H, m), 3.63 (2H, m), 3.39 (2H, m), 3.16 (2H, m), 3.07 (4H, m), 2.64 (3H, s), 1.82 (2H, m), 1.29 (6H, s). MS *m/z* calcd for $C_{28}H_{34}Cl_2N_4O_5S$: 608.1. Found: 609.1 [M + H]$^+$. HPLC purity: system A, 99%, $t_R$ = 6.27 min.

**2-[2,4-Dichloro-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonylamino]-2-methyl-*N*-[3-(4-methylpiperazin-1-yl)propyl]-propionamide Trfluoroacetate Salt (38).** $^1$H NMR (600 MHz, DMSO-$d_6$): $\delta$ 8.34 (1H, br s), 8.14 (1H, s), 8.07 (1H, d), 7.79 (1H, d), 7.72 (1H, br s), 7.65−7.60 (4H, m), 5.56 (2H, s), 3.37 (8H, br m), 3.12 (4H, m), 2.74 (3H, s), 2.65 (3H, s), 1.70 (2H, m), 1.23 (6H, s). MS *m/z* calcd for $C_{29}H_{37}Cl_2N_5O_4S$: 621.2. Found: 622.2 [M + H]$^+$. HPLC purity: system A, 99%, $t_R$ = 5.45 min.

***N*-(3-Benzylaminopropyl)-2-[2,4-dichloro-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonylamino]-2-methylpropionamide Trifluoroacetate Salt (39).** $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.74 (2H, br s), 8.29 (1H, s), 8.16 (1H, br s), 8.06 (1H, d), 7.84 (1H, m), 7.77 (1H, d), 7.55−7.40 (9H, m), 5.55 (2H, s), 2.21 (2H, m), 3.16 (2H, m), 2.90 (2H, m), 2.64 (3H, s), 1.81 (2H, m), 1.55 (6H, s). MS *m/z* calcd for $C_{31}H_{34}Cl_2N_4O_4S$: 528.1 Found: 529.1 [M + H]$^+$. HRMS calcd for $C_{31}H_{35}Cl_2N_4O_4S$ [M + H]$^+$: 629.1756. Found: 629.1712. HPLC purity: system A, 99%, $t_R$ = 8.40 min.

**2-[2,4-Dichloro-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonylamino]-*N*-[3-(4-fluorobenzylamino)propyl]-2-methylpropionamide Trifluoroacetate Salt (40).** $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.67 (2H, br s), 8.32 (1H, br s), 8.16 (1H, s), 8.06 (1H, d), 7.85 (1H, m), 7.75 (1H, d), 7.62−7.41 (6H, m), 7.29 (2H, m), 5.56 (2H, s), 4.12 (2H, m), 3.18 (2H, m), 2.91 (2H, m), 2.65 (3H, s), 1.76 (2H, m), 1.26 (6H, s). MS *m/z* calcd for $C_{31}H_{33}Cl_2FN_4O_4S$: 546.1. Found: 547.0 [M + H]$^+$. HRMS calcd for $C_{31}H_{34}Cl_2FN_4O_4S$ [M + H]$^+$: 647.1662. Found: 647.1680. HPLC purity: system B 98.2%, $t_R$ = 11.86 min.

**2*N*-[3-(4-Chlorobenzylamino)propyl]-2-[2,4-dichloro-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonylamino]-2-methylpropionamide Trifluoroacetate Salt (41).** $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.71 (2H, br s), 8.26 (1H, br s), 8.15 (1H, s), 8.06 (1H, d), 7.82 (1H, t), 7.80 (1H, d), 7.62−7.35 (8H, m), 5.53 (2H, s), 4.15 (2H, m), 3.18 (2H, m), 2.91 (2H, m), 2.62 (3H, s), 1.79 (2H, m), 1.26 (6H, s). MS *m/z* calcd for $C_{31}H_{33}Cl_3N_4O_4S$: 662.1. Found: 663.0 [M + H]$^+$. HRMS calcd for $C_{31}H_{34}Cl_3N_4O_4S$ [M + H]: 665.1337. Found: 665.1301. HPLC purity: system A, > 99%, $t_R$ = 9.38 min.

**2-[2,4-Dichloro-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonylamino]-*N*-[3-(4-methoxybenzylamino)propyl]-2-methylpropionamide Trifluoroacetate Salt (42).** $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.63 (2H, br s), 8.28 (1H, br s), 8.17 (1H, s), 8.01 (1H, d), 7.83 (1H, m), 7.79 (1H, d), 7.60−7.50 (4H, m), 7.50 (2H, d), 7.00 (2H, d), 5.54 (2H, d), 4.01 (2H, m), 3.75 (3H, s), 3.17 (2H, m), 2.87 (2H, m), 2.67 (3H, s), 1.75 (2H. m), 1.25 (6H, s). MS *m/z* calcd for $C_{32}H_{36}Cl_2N_4O_5S$: 658.1. Found: 659.0 [M + H]$^+$. HRMS calcd for $C_{32}H_{37}Cl_2N_4O_5S$ [M + H]$^+$: 659.1862. Found: 659.1864. HPLC purity: system A, >99%, $t_R$ = 8.49 min.

**2-[2,4-Dichloro-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonylamino]-*N*-[3-(4-hydroxybenzylamino)propyl]-2-methylpropionamide Trifluoroacetate Salt (43).** $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 9.68 (1H, s), 8.55 (2H, br s), 8.27 (1H, br s), 8.18 (1H, s), 8.10 (1H, d), 7.86 (1H, m), 7.82 (1H, d), 7.64−7.36 (4H, m), 7.27 (2H, d), 6.82 (2H, d), 5.52 (2H, s), 4.00 (2H, s), 3.14 (2H, m), 2.82 (2H, m), 2.59 (3H, s), 1.73 (2H, m), 1.23 (6H, s). MS *m/z* calcd for $C_{32}H_{34}Cl_2N_4O_5S$: 644.1. Found: 645.0 [M + H]$^+$. HRMS calcd for $C_{32}H_{35}Cl_2N_4O_5S$ [M + H]: 645.1705. Found: 645.1710. HPLC purity: system A, >99%, $t_R$ = 7.30 min.

**2-[2,4-Dichloro-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonylamino]-2-methyl-*N*-[3-(4-methylbenzylamino)propyl]-propionamide Trifluoroacetate Salt (44).** $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.62 (2H, br s), 8.25 (1H, br s), 8.14 (1H, s), 8.01 (1H, d), 7.83 (2H, m), 7.79 (1H, s), 7.62−7.37 (4H, m), 7.37 (2H, d), 7.25 (2H, d), 5.50 (2H, s), 4.10 (2H, m), 3.12 (2H, m), 2.85 (2H, m), 2.62 (3H, s), 2.30 (3H, s), 1.75 (2H, m), 1.25 (6H, s). MS *m/z* calcd for $C_{32}H_{36}Cl_2N_4O_4S$: 642.1. Found: 643.1 [M + H]$^+$. HRMS calcd for $C_{32}H_{37}Cl_2N_4O_4S$ [M + H]: 643.1913. Found: 643.1897. HPLC purity: system A, 98.4%, $t_R$ = 9.61 min.

**2-[2,4-Dichloro-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonylamino]-*N*-[3-(4-methanesulfonylbenzylamino)propyl]-2-methylpropionamide Trifluoroacetate Salt (45).** $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.87 (2H, br s), 8.30 (1H, br s), 8.17 (1H, s), 8.09 (1H, d), 8.00 (2H, d), 7.91 (1H, m), 7.89 (1H, d), 7.85 (2H, d), 7.65−7.39 (4H, m), 5.57 (2H, s), 4.30 (2H, s), 3.22 (3H, s), 3.13 (2H, m), 2.96 (2H, m), 2.61 (3H, s), 1.83 (2H, m), 1.26 (6H, s). MS *m/z* calcd for $C_{32}H_{36}Cl_2N_4O_6S_2$ : 706.1. Found: 706.9 [M + H]$^+$. HRMS calcd for $C_{32}H_{37}Cl_2N_4O_6S_2$ [M + H]$^+$: 707.1532. Found: 707.1524. HPLC purity: system A, >99%, $t_R$ = 7.54 min.

**2-[2,4-Dichloro-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonylamino]-2-methyl-*N*-{3-[(pyridin-2-ylmethyl)amino]-propyl}propionamide Trifluoroacetate Salt (46).** $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 9.00 (2H, br s), 8.65 (1H, m), 8.40 (1H, br s), 8.15 (1H, s), 8.05 (1H, d), 7.90 (1H, m), 7.80 (2H, m), 7.90−7.40

(6H, m), 5.55 (2H, s), 4.30 (2H, m), 3.15 (2H, m), 3.00 (2H, m), 2.65 (3H, s), 1.83 (2H, m), 1.30 (6H, s). MS *m*/*z* calcd for $C_{30}H_{33}Cl_2N_5O_4S$: 629.1. Found: 630.0 $[M + H]^+$. HRMS calcd for $C_{30}H_{34}Cl_2N_5O_4S$ [M + H]: 630.1719. Found: 630.1697. HPLC purity: system A, 98.1%, $t_R$ = 7.30 min.

**2-[2,4-Dichloro-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonylamino]-*N*-[3-(4-(dimethylamino)benzylamino)propyl]-2-methylpropionamide Trifluoroacetate Salt (47).** $^1$H NMR (400 MHz, DMSO-$d_6$): δ 8.52 (2H, br s), 8.32 (1H, br s), 8.16 (1H, s), 8.08 (1H, d), 7.84 (1H, m), 7.76 (1H, d), 7.62−7.40 (4H, m), 7.24 (2H, d), 6.72 (2H, d), 5.56 (2H, s), 4.00 (2H, m), 3.16 (2H, m), 2.88 (6H, s), 2.84 (2H, m), 2.64 (3H, s), 1.80 (2H, m), 1.28 (6H, s). MS *m*/*z* calcd for $C_{33}H_{39}Cl_2N_5O_4S$: 671.2. Found: 672.1 $[M + H]^+$. HPLC purity: system A, 99.2%, $t_R$ = 6.53 min.

**4-[(3-{2-[2,4-Dichloro-3-(2-methylquinolin-8-yloxymethyl)-benzenesulfonylamino]-2-methylpropionylamino}propylamino)-methyl]benzamide Trifluoroacetate Salt (48).** $^1$H NMR (400 MHz, DMSO-$d_6$): δ 8.83 (2H, br s), 8.39 (1H, br s), 8.22 (1H, s), 8.11 (1H, d), 8.11 (1H, m), 7.93 (2H, d), 7.85 (2H, m), 7.83−7.43 (6H, m), 5.56 (2H, s), 4.22 (2H, br s), 3.22 (2H, m), 3.00 (2H, m), 2.65 (3H, s), 1.83 (2H, m), 1.26 (6H, s). MS *m*/*z* calcd for $C_{32}H_{35}Cl_2N_5O_5S$: 671.1. Found: 672.1 $[M + H]^+$. HPLC purity: system A, 95.3%, $t_R$ = 6.29 min.

**2-[2,4-Dichloro-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonylamino]-*N*-{3-[(furan-3-ylmethyl)amino]propyl}-2-methylpropionamide Trifluoroacetate Salt (49).** $^1$H NMR (400 MHz, DMSO-$d_6$): δ 8.65 (2H, br s), 8.35 (1H, br s), 8.18 (1H, s), 8.01 (1H, d), 7.83 (4H, m), 7.76−7.41 (4H, m), 6.61 (1H, s), 5.59 (2H, s), 4.0 (2H, br s), 3.15 (2H, m), 2.91 (2H, m), 2.63 (3H, s), 1.78 (2H, m), 1.30 (6H, s). MS *m*/*z* calcd for $C_{29}H_{32}Cl_2N_4O_5S$: 618.1. Found: 619.1 $[M + H]^+$. HPLC purity: system A, 98.0%, $t_R$ = 7.95 min.

**2-[2,4-Dichloro-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonylamino]-*N*-{3-[(1*H*-imidazol-4-ylmethyl)amino]propyl}-2-methylpropionamide Trifluoroacetate Salt (50).** $^1$H NMR (400 MHz, DMSO-$d_6$): δ 8.93 (2H, br s), 8.64 (1H, br s), 8.32 (1H, m), 8.18 (1H, s), 8.04 (1H, d), 8.04 (1H, m), 7.82 (2H, m), 7.68−7.42 (7H, m), 5.75 (1H, s), 5.55 (2H, s), 4.18 (2H, br s), 3.18 (2H, m), 2.95 (2H, m), 2.66 (3H, s), 1.77 (2H, m), 1.25 (6H, s). MS *m*/*z* calcd for $C_{28}H_{32}Cl_2N_6O_4S$: 618.1. Found: 619.0 $[M + H]^+$. HPLC purity: system A, >99%, $t_R$ = 5.75 min.

***N*-(2-Azepan-1-yl-1,1-dimethyl-2-oxoethyl)-2,4-dichloro-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonamide Trifluoroacetate Salt (51).** $^1$H NMR (600 MHz, DMSO-$d_6$): δ 8.76 (1H, s), 8.20 (2H, br s), 8.13 (1H, m), 8.01 (1H, d), 7.84 (1H, d), 7.61−7.35 (4H, m), 5.56 (2H, s), 3.85−3.17 (8H, vbr m), 2.62 (3H, s), 2.12 (2H, m), 1.93 (2H, m), 1.23 (6H, s). MS *m*/*z* calcd for $C_{27}H_{32}Cl_2N_4O_4S$: 578.1. Found: 579.2 $[M + H]^+$. HPLC purity: system A, 99%, $t_R$ = 7.47 min.

**2,4-Dichloro-*N*-(2-[1,4]diazepan-1-yl-1,1-dimethyl-2-oxoethyl)-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonamide Trifluoroacetate Salt (52).** $^1$H NMR (600 MHz, DMSO-$d_6$): δ 8.74 (1H, s), 8.63 (2H, br s), 8.29 (1H, m), 8.08 (1H, d), 7.83 (1H, d), 7.62−7.36 (4H, m), 5.58 (2H, s), 3.89−3.17 (8H, vbr m), 2.63 (3H, s), 2.07 (2H, m), 1.25 (6H, s). MS *m*/*z* calcd for $C_{26}H_{30}Cl_2N_4O_4S$: 564.1. Found: 565.1 $[M + H]^+$. HPLC purity: system C, 95.9%, $t_R$ = 6.20 min.

**2,4-Dichloro-*N*-[1,1-dimethyl-2-(4-methylpiperazin-1-yl)-2-oxoethyl]-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonamide (53).** $^1$H NMR (600 MHz, DMSO-$d_6$): δ 9.83 (1H, m), 8.68 (1H, s), 8.34 (1H, br s), 8.06 (1H, d), 7.82 (1H, d), 7.66−7.38 (4H, m), 5.58 (2H, s), 4.58 (2H, m), 3.51 (2H, m), 3.17 (2H, m), 3.00 (2H, m), 2.60 (3H, s), 1.22 (6H, s). MS *m*/*z* calcd for $C_{26}H_{30}Cl_2N_4O_4S$: 564.1. Found: 565.2 $[M + H]^+$. HPLC purity: system C, 99%, $t_R$ = 6.09 min.

**4-{2-[2,4-Dichloro-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonylamino]-2-methylpropionyl}piperazine-1-carboxamidine Trifluoroacetate Salt (54).** $^1$H NMR (600 MHz, DMSO-$d_6$): δ 8.70 (1H, s), 8.26 (1H, br s), 8.05 (1H, d), 7.81 (1H, d), 7.36 (1H, m), 7.48−7.41 (6H, m), 5.57 (2H, s), 3.50 (8H, m), 3.63 (3H, s), 1.23 (6H, s). MS *m*/*z* calcd for $C_{26}H_{30}Cl_2N_6O_4S$: 592.1. Found: 593.3 $[M + H]^+$. HPLC purity: system A, 97.6%, $t_R$ = 6.34 min.

***N*-(3-Aminopropyl)-4-{2-[2,4-dichloro-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonylamino]-2-methylpropionyl}-piperazine-1-carboxamidine Trifluoroacetate Salt (55).** $^1$H NMR (400 MHz, DMSO-$d_6$): δ 8.72 (1H, s), 8.32 (1H, br s), 8.08 (1H, d), 7.98−7.72 (7H, m), 7.64−7.40 (4H, m), 5.62 (2H, s), 3.75−3.52 (8H, m), 3.26 (2H, m), 2.88 (2H, m), 2.66 (3H, s), 1.80 (2H, m), 1.22 (6H, s). MS *m*/*z* calcd for $C_{29}H_{37}Cl_2N_7O_4S$: 649.2. Found: 650.2 $[M + H]^+$. HPLC purity: system A, >99%, $t_R$ = 8.50 min.

***N*-(3-Aminopropyl)-4-{2-[2,4-dichloro-3-(2,4-dimethylquinolin-8-yloxymethyl)benzenesulfonylamino]-2-methylpropionyl}-piperazine-1-carboxamidine Trifluoroacetate Salt (56).** $^1$H NMR (400 MHz, DMSO-$d_6$): δ 8.58 (1H, s), 8.08 (1H, d), 7.80 (8H, m), 7.62−7.36 (3H, m), 5.62 (2H, s), 3.75−3.45 (8H, m), 3.28 (2H, m), 2.86 (2H, m), 2.68 (3H, s), 2.64 (3H, s), 1.80 (2H, m), 1.66 (6H, s). MS *m*/*z* calcd for $C_{30}H_{39}Cl_2N_7O_4S$: 663.2. Found: 664.3 $[M + H]^+$. HRMS calcd for $C_{30}H_{40}Cl_2N_7O_4S$ $[M + H]^+$: 664.2224. Found: 664.2239. HPLC purity: system B, 99.8%, $t_R$ = 9.36 min.

***N*-(6-Aminohexyl)-4-{2-[2,4-dichloro-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonylamino]-2-methylpropionyl}-piperazine-1-carboxamidine Trifluoroacetate Salt (57).** $^1$H NMR (400 MHz, DMSO-$d_6$): δ 8.71 (1H, s), 8.33 (1H, br s), 8.08 (1H, d), 7.79 (1H, d), 7.67 (7H, m), 7.64−7.40 (4H, m), 5.60 (2H, s), 3.70−3.45 (8H, m), 3.19 (2H, m), 2.77 (2H, m), 2.64 (3H, s), 1.52 (4H, m), 1.25 (4H, m), 1.21 (6H, s). MS *m*/*z* calcd for $C_{32}H_{43}Cl_2N_7O_4S$: 691.2. Found: 692.1 $[M + H]^+$. HPLC purity: system B, 99.8%, $t_R$ = 9.16 min.

**2,4-Dichloro-*N*-{2-[4-(2-guanidinoethyl)piperazin-1-yl]-1,1-dimethyl-2-oxoethyl}-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonamide Trifluoroacetate Salt (58).** $^1$H NMR (600 MHz, DMSO-$d_6$): δ 10.05 (1H, vbr s), 8.71 (1H, s), 8.32 (1H, br s), 8.05 (1H, d), 7.82 (1H, d), 7.77−7.16 (8H, m), 5.55 (2H, s), 4.71−2.84 (8H, vbr m), 2.64 (3H, s), 1.56 (6H, s). MS *m*/*z* calcd for $C_{28}H_{35}Cl_2N_7O_4S$: 635.3. Found: 636.2 $[M + H]^+$. HPLC purity: system A, 99%, $t_R$ = 5.68 min.

**2,4-Dichloro-*N*-{2-[4-(6-guanidinohexyl)piperazin-1-yl]-1,1-dimethyl-2-oxoethyl}-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonamide Trifluoroacetate Salt (59).** $^1$H NMR (400 MHz, DMSO-$d_6$): δ 9.83 (1H, br s), 8.93(1H, br s), 8.76 (1H, s), 8.31 (1H, br s), 8.05 (1H, d), 7.81 (1H, d), 7.64−7.38 (5H, m), 5.57 (2H, s), 4.57 (2H, m), 3.62 (2H, m), 3.09 (6H, m), 3.00 (2H, m), 2.62 (3H, s), 1.67 (2H, m), 1.48 (2H, m), 1.35 (4H, m), 1.26 (6H, s). MS *m*/*z* calcd for $C_{32}H_{43}Cl_2N_7O_4S$: 691.2. Found: 692.2 $[M + H]^+$. HPLC purity: system A, 99.4%, $t_R$ = 6.46 min.

***N*-{2-[4-(6-Aminohexyl)piperazin-1-yl]-1,1-dimethyl-2-oxoethyl}-2,4-dichloro-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonamide Trifluoroacetate Salt (60).** $^1$H NMR (400 MHz, DMSO-$d_6$): δ 8.73 (1H, s), 8.25 (1H, br s), 8.00 (1H, d), 7.79 (1H, d), 7.71 (4H, br s), 7.60−7.30 (5H, m), 5.54 (2H, s), 4.58 (2H, br s), 3.56 (4H, m), 3.15 (4H, m), 2.94 (2H, m), 2.75 (2H, m), 2.58 (3H, s), 1.67 (2H, m), 1.50 (2H, m), 1.33 (6H, m), 1.25 (4H, m). calcd for $C_{31}H_{41}Cl_2N_5O_4S$: 649.2. Found: 650.2 $[M + H]^+$. HPLC purity: system A, 99.0%, $t_R$ = 6.26 min.

**2,4-Dichloro-*N*-{1,1-dimethyl-2-oxo-2-[4-(2-piperazin-1-ylacetyl)piperazin-1-yl]ethyl}-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonamide Trifluoroacetate Salt (61).** $^1$H NMR (400 MHz, DMSO-$d_6$): δ 8.85 (1H, br s), 8.71 (1H, s), 8.31 (2H, br s), 8.08 (1H, d), 7.81 (1H, d), 7.64−7.40 (4H, m), 5.56 (2H, s), 3.54 (8H, m), 3.25 (6H, m), 3.06 (4H, m), 2.67 (3H, s), 1.60 (4H, m), 1.25 (6H, s). MS *m*/*z* calcd for $C_{31}H_{38}Cl_2N_6O_5S$: 676.2. Found: 677.1 $[M + H]^+$. HPLC purity: system B, 99.4%, $t_R$ = 7.67 min.

***N*-{2-[4-((*S*)-3-Amino-6-(dimethylamino)hexanoyl)piperazin-1-yl]-1,1-dimethyl-2-oxoethyl}-2,4-dichloro-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonamide Trifluoroacetate Salt (62).** $^1$H NMR (400 MHz, DMSO-$d_6$): δ 9.50 (1H, br s), 8.67 (1H, s), 8.24 (1H, d), 8.05 (1H, d), 7.81 (4H, m), 7.57−7.45 (4H, m), 5.57 (2H, s), 3.65−345 (8H, m), 3.03 (2H, m), 2.76 (6H, s),

2.76 (2H, m), 2.62 (3H, s), 2.62 (1H, m), 1.69 (2H, m), 1.59 (2H, m), 1.24 (6H s). MS *m*/*z* calcd for $C_{33}H_{44}Cl_2N_6O_5S$: 706.2. Found: 707.3 $[M + H]^+$. HPLC purity: system B, >99%, $t_R$ = 7.64 min.

***N*-{2-[4-((*S*)-3-Amino-6-(dimethylamino)hexanoyl)piperazin-1-yl]-1,1-dimethyl-2-oxoethyl}-2,4-dichloro-3-(2,4-dimethylquinolin-8-yloxymethyl)benzenesulfonamide Trifluoroacetate Salt (63).** $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 9.50 (1H, br s), 8.70 (1H, s), 8.05 (1H, d), 7.77 (4H, m), 7.77−7.25 (4H, m), 5.55 (2H, s), 3.65−3.20 (8H, m), 3.05 (2H, m), 2.75 (6H, s), 2.85−2.55 (10H, m), 1.70 (2H, m), 1.57 (2H, m), 1.23 (6H, s). MS *m*/*z* calcd for $C_{34}H_{46}Cl_2N_6O_5S$: 720.2. Found: 721.2 $[M + H]^+$. HPLC purity: system B, 98.9%, $t_R$ = 13.56 min.

***N*-{2-[4-((*S*)-3-Amino-7-(dimethylamino)heptanoyl)piperazin-1-yl]-1,1-dimethyl-2-oxoethyl}-2,4-dichloro-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonamide Trifluoroacetate Salt (64).** $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 9.43 (1H, br s), 8.69 (1H, s), 8.29 (1H, br s), 8.07 (1H, d), 7.81 (1H, d), 7.76 (3H, m), 7.62−7.28 (4H, m), 5.57 (2H, s), 3.83−3.29 (8H, m), 3.00 (2H, m), 2.78 (6H, s), 2.78−2.57 (4H, m), 2.62 (3H, s), 1.59 (4H, m), 1.36 (2H, m), 1.24 (6H, s). MS *m*/*z* calcd for $C_{34}H_{46}Cl_2N_6O_5S$: 720.2. Found: 721.2 $[M + H]^+$. HPLC purity: system B, 99.32%, $t_R$ = 7.59 min.

***N*-{2-[4-((*S*)-3-Amino-7-(dimethylamino)heptanoyl)piperazin-1-yl]-1,1-dimethyl-2-oxoethyl}-2,4-dichloro-3-(2,4-dimethylquinolin-8-yloxymethyl)benzenesulfonamide (65).** $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 9.43 (1H, br s), 8.68 (1H, s), 8.07 (1H, d), 7.79 (1H, d), 7.75 (3H, m), 7.61−7.23 (3H, m), 5.59 (2H, s), 3.73−3.20 (8H, m), 3.00 (2H, m), 2.77−2.55 (10H, m), 1.61 (4H, m), 1.36 (2H, m), 1.25 (6H, s). MS *m*/ *z* calcd for $C_{35}H_{48}Cl_2N_6O_5S$: 734.2. Found: 735.2 $[M + H]^+$. HPLC purity: system B, 99.8%, $t_R$ = 13.56 min.

***N*-{2-[4-((*S*)-3-Amino-7-guanidinoheptanoyl)piperazin-1-yl]-1,1-dimethyl-2-oxoethyl}-2,4-dichloro-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonamide Trifluoroacetate Salt (66).** $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.98 (2H, br s), 8.69 (1H, s), 8.32 (1H, br s), 8.09 (1H, d), 7.82 (1H, d), 7.71 (3H, br s), 7.64−7.33 (4H, m), 7.09 (5H, br s), 5.58 (2H, s), 3.73−3.20 (8H, m), 3.09 (3H, m), 2.82 (1H, d), 2.66 (3H, s), 2.60 (1H, m), 1.60 (2H, m), 1.47 (2H, m), 1.35 (2H, m), 1.27 (6H, s). MS *m*/*z* calcd for $C_{33}H_{44}Cl_2N_8O_5S$: 734.3. Found: 735.0 $[M + H]^+$. HPLC purity: system B, 93.6%, $t_R$ = 7.90 min.

***N*-{2-[4-((*S*)-2-Amino-5-(dimethylamino)pentanoyl)piperazin-1-yl]-1,1-dimethyl-2-oxoethyl}-2,4-dichloro-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonamide Trifluoroacetate Salt (67).** $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 9.57 (1H, br s), 8.52 (1H, s), 8.20 (4H, br s), 8.05 (1H, d), 7.82 (1H, d), 7.59−7.32 (4H, m), 5.54 (2H, s), 4.55 (1H, m), 3.55 (8H, m), 3.04 (2H, m), 2.77 (6H, s), 2.64 (3H, s), 1.73 (4H, m), 1.27 (3H, s), 1.23 (3H, s). MS *m*/*z* calcd for $C_{32}H_{42}Cl_2N_6O_5S$: 692.2. Found: 693.1 $[M + H]^+$. HPLC purity: system B, 99.2%, $t_R$ = 7.28 min.

***N*-{2-[4-((*S*)-2-Amino-5-(dimethylamino)pentanoyl)piperazin-1-yl]-1,1-dimethyl-2-oxoethyl}-2,4-dichloro-3-(2,4-dimethylquinolin-8-yloxymethyl)benzenesulfonamide Trifluoroacetate Salt (68).** $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 9.48 (1H, br s), 8.76 (1H, s), 8.19 (3H, br s), 8.04 (1H, d), 7.86 (1H, d), 7.76−7.24 (4H, m), 6.59 (2H, s), 4.57 (1H, m), 3.50 (8H, m), 3.07 (2H, m), 2.81 (6H, s), 2.66 (3H, s), 2.62 (3H, s), 1.71 (4H, m), 1.28 (3H, s), 1.21 (3H, s). MS *m*/*z* calcd for $C_{33}H_{44}Cl_2N_6O_5S$: 706.2. Found: 706.9 $[M + H]^+$. HPLC purity: system B, 99.8%, $t_R$ = 13.44 min.

***N*-{2-[4-((*S*)-2-Amino-6-(dimethylamino)hexanoyl)piperazin-1-yl]-1,1-dimethyl-2-oxoethyl}-2,4-dichloro-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonamide Trifluoroacetate Salt (69).** $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 9.32 (1H, br s), 8.72 (1H, s), 8.30 (1H, br s), 8.15 (3H, br s), 8.10 (1H, d), 7.85 (1H, d), 7.65−7.40 (4H, m), 5.55 (2H, s), 4.50 (1H, m), 3.50 (8H, br s), 3.00 (2H, m), 2.80 (6H, s), 2.67 (3H, s), 1.73 (2H, m), 1.60 (2H, m), 1.37 (2H, m), 1.25 (3H, s). MS *m*/*z* calcd for $C_{33}H_{44}Cl_2N_6O_5S$: 706.2. Found: 707.2 $[M + H]^+$. HPLC purity: system B, 99.9%, $t_R$ = 8.16 min.

***N*-{2-[4-((*S*)-2-Amino-6-(dimethylamino)hexanoyl)piperazin-1-yl]-1,1-dimethyl-2-oxoethyl}-2,4-dichloro-3-(2,4-dimethylquinolin-8-yloxymethyl)benzenesulfonamide Trifluoroacetate Salt (70).** $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 9.50 (1H, br s), 8.65 (1H, s), 8.15 (3H, br s), 8.08 (1H, d), 7.85 (1H, d), 7.85−7.47 (4H, m), 5.60 (2H, s), 4.50 (1H, m), 3.77 (8H, m), 3.06 (2H, m), 2.77 (6H, s), 2.73 (3H, s), 2.67 (3H, s), 1.72 (2H, m), 1.62 (2H, m), 1.33 (2H, m), 1.25 (6H, s). MS *m*/*z* calcd for $C_{34}H_{46}Cl_2N_6O_5S$: 720.2. Found: 721.2 $[M + H]^+$. HPLC purity: system B, 99.6%, $t_R$ = 13.34 min.

***N*-[(*S*)-1-(4-{2-[2,4-Dichloro-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonylamino]-2-methylpropionyl}piperazine-1-carbonyl)-5-(dimethylamino)pentyl]acetamide Trifluoroacetate Salt (71).** $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 9.30 (1H, br s), 8.71 (1H, s), 8.47 (1H, br s), 8.25 (1H, d), 8.07 (1H, d), 7.82 (1H, d), 7.82 (1H, d), 7.69−7.44 (4H, m), 5.62 (2H, s), 4.75 (1H, m), 3.58 (8H, m), 3.02 (2H, m), 2.75 (6H, s), 2.71 (3H, s), 1.89 (3H, s), 1.62 (4H, m), 1.29 (2H, m), 1.29 (6H, s). MS *m*/*z* calcd for $C_{35}H_{46}Cl_2N_6O_6S$: 748.2. Found: 749.1 $[M + H]^+$. HPLC purity: system B, <99%, $t_R$ = 8.12 min.

**(B) Biology. Receptor Binding Assays.** Binding assays were performed using membranes of CHO cells expressing the $hB_2R$ as previously described.[29] The buffer used for binding experiments was *N*-tris(hydroxymethyl)methyl-2-aminoethanesulfonic acid (10 mM, pH 7.4) containing 1,10-phenanthroline (1 mM), bacitracin (140 $\mu$g/mL), and bovine serum albumin (1 g/L). Binding assays were performed at room temperature in a final volume of 0.5 mL, and an incubation time of 60 min was used. The [$^3$H]BK concentration was comparable with its calculated $K_d$ value (0.1−0.2 nM), and the membrane concentration was 100−150 $\mu$g/mL. Competing ligands were tested under a wide range of concentrations (1 pM−10 $\mu$M). Nonspecific binding was defined as the amount of labeled ligand bound in the presence of 1 $\mu$M BK. The final concentration of DMSO in the binding assay was 1% and did not affect binding parameters. Reactions were stopped by filtration with UniFilter-96 plates GF/B (Packard Instrument Company), presoaked for at least 2 h in polyethylenimine 0.6%, and using a MicroMate 96 cell harvester (Packard Instrument Co.). The tubes and filters were then washed five times with 0.5-mL aliquots of Tris buffer (50mM, pH 7.4, 4 °C). The filters were dried and soaked in Microscint 40 (50 $\mu$L/well, Packard Instrument Co.), and the bound radioactivity was counted using a TopCount Microplate Scintillation Counter (Packard Instrument Co.). Binding parameters were evaluated using GraphPad Prism 4.0 (GraphPad, San Diego, CA) to determine the ligand concentration inhibiting the radioligand binding of the 50% ($IC_{50}$). The −log of $K_i$ values ($pK_i$) were calculated from the Cheng−Prusoff equation $K_i = IC_{50}/(1 + [\text{radioligand}]/K_d)$.

**Measurement of Inositol Monophosphate Accumulation.** The assay was performed according to the method of Berridge.[30] CHO cells stably transfected with the $hB_2R$ were plated in 24-well plates ($1.8 \times 10^5$ cells/well) and incubated at 37 °C overnight. Cells were labeled in the presence of a labeling medium (Ham's F-12/MEM$\alpha$ = 1/1, 1% dyalized FCS, 2 mM glutamine and 50 IU/mL penicillin/streptomycin) by adding 1 $\mu$Ci/well [1,2-$^3$H(N)]-*myo*-inositol for 24 h. The labeled culture medium was aspirated, and the cells were preincubated in the absence (control) or presence of an opportune nanomolar concentration of the chosen compound for 20 min and then incubated in the absence or the presence of $1 \times 10^{-11}$ up to $1 \times 10^{-5}$ M BK for 40 min at 37 °C in IP1 modified buffer (135 mM PBS, 20 mM Na/Hepes pH 7.4, 2 mM $CaCl_2$, 1.2 mM $MgSO_4$, 1mM EGTA, 11.1 mM glucose, 25 mM LiCl, 0.05% BSA, 1mM 1,10-phenantroline, and 140 $\mu$g/mL bacitracin). At the end of the incubation period, 1 mL of ice-cold methanol/0.1 N HCl (2:1 v/v) was added to liberate the inositol phosphate formed. The aqueous phase was applied to an anion exchange column (AG 1-X8 Bio-Rad, Hercules, CA) and the inositol monophosphate eluted with 0.2 M ammonium formate/0.1 M formic acid. In the IP1 fraction, the radioactivity was determined by liquid scintillation spectrometry. Agonist concentration−response curves in the absence and presence of antagonists were fitted by sigmoidal nonlinear regression

(GraphPad Prism 4.0) to determine the concentration producing 50% ($EC_{50}$) of the agonist control maximal response ($E_{max}$). The affinity of competitive antagonism was expressed in terms of $pA_2$ calculated from the equation $pA_2 = \log [CR - 1] - \log [\text{antagonist concentration}]$, where CR is the concentration-ratio of equieffective concentrations of agonist ($EC_{50}$) obtained in the presence and in absence of antagonist.

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**Supporting Information Available:** Experimental details of the X-ray data collections and crystallographic parameters. This material is available free of charge via the Internet at http://pubs.acs.org.

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