2-Aminobenzophenones as a Novel Class of Bradykinin B_1 Receptor Antagonists

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Selective bradykinin (BK) B_1 receptor antagonists could be novel therapeutic agents for the treatment of pain and inflammation. Elucidation of the structure activity relationships of the structurally novel HTS lead compound **1** provided potent hBK B_1 receptor antagonists with excellent receptor occupancy in the CNS of hBK B_1 transgenic rats.

Introduction

Bradykinin (BK[a]), an autacoid peptide, plays a variety of roles in the pathophysiological processes accompanying pain and inflammation. Its biological actions are mediated by two known G-protein coupled receptors named B_1 and B_2. The BK B_2 receptor is constitutively expressed in most cell types and evokes acute pain responses following tissue injury, whereas the BK B_1 receptor is induced during inflammatory insults or painful stimuli.[1] In animal models, BK B_1 receptor agonists, such as des-Arg^9-bradykinin (DABK) and des-Arg^{10}-kallidin (DAK), produce hyperalgesia, an effect that can be blocked by peptide BK B_1 receptor antagonists such as des-Arg^9-Leu^8-bradykinin (DALBK) and des-Arg^{10}-Leu^9-kallidin (DALK).[2] A study result from the BK B_1 receptor knockout mouse has implicated a role for the BK B_1 receptor in inflammation, algesia, and neuropathic pain.[3] In addition to the accepted peripheral mode of action of the BK B_1 receptor, the BK B_1 receptor has also been accorded a central role on the basis of recent results that demonstrate that the BK B_1 receptor is constitutively expressed in the central nervous system (CNS) of mice and rats.[4] Accordingly, selective and effective BK B_1 receptor antagonists hold promise as novel therapeutic agents for the treatment of pain and inflammation.[5]

The current study was initiated with a high-throughput screen (HTS) lead, compound **1**, a 2-aminobenzophenone derivative (Figure 1). This paper reports the SAR study results of this novel structural class of compounds that exhibit excellent binding affinity, good pharmacokinetic profile, and excellent receptor occupancy in an ex vivo receptor occupancy assay.

Chemistry. Compounds described in this paper were prepared straightforwardly according to the route depicted in Scheme 1. From the commercially available benzophenone, sulfonamide formation followed by the reduction of the nitro group afforded the aniline derivative (**1a**). Treatment of the aniline with triphosgene followed by an amine or an alcohol gave the desired compounds **20** and **26**, respectively. The amide derivatives were prepared by coupling of intermediate **1a** with either acids (EDC/HOBT) or acid chlorides. The (2-aminophenyl)(5-fluoropyridin-2-yl)methanone (**1b**) was synthesized by the metal halogen exchange of bromopyridine and addition to 2-amino-benzoacetonitrile. The other benzophenones were prepared in an analogous fashion.

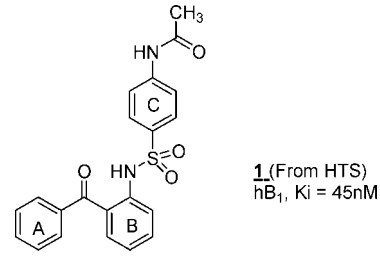
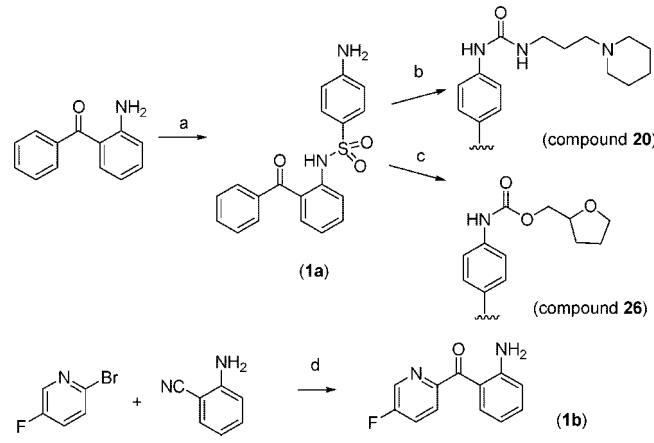


Figure 1. HTS lead.

Scheme 1[a]



[a] (a) (i) 4-Nitrobenzene sulfonyl chloride, pyridine, DCM, 31%; (ii) Fe, EtOH/HOAc/H_2O, 100 °C, 90%. (b) Triphosgene, 3-piperidin-1-ylpropan-1-amine, TEA,THF, 0 °C to rt, 69%. (c) Triphogene, tetrohydrofurfuryl alcohol, TEA, THF, 0 °C to rt. (d) nBuLi, 0 °C THF, 58%.

Biological Results and Discussion. Compound **1** was considered a good starting point in terms of binding affinity for hB_1 receptor (Table 1). However, several potential issues of this compound were revealed after detailed triage. While compound **1** is not a substrate for P-glycoprotein (P-gp) mediated efflux[6,7] and not a potassium channel blocker (human

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[a] Abbreviations: BK, bradykinin; DABK, des-Arg^9-bradykinin; DAK, des-Arg^{10}-kallidin; DALBK, des-Arg^9-Leu^8-bradykinin; DALK, des-Arg^{10}-Leu^9-kallidin; HTS, high-throughput screen; hERG, human ether-a-go-go-related gene; P-gp, P-glycoprotein; PXR, pregnane X-receptor; HLM, human liver microsomes; RLM, rat liver microsomes; DLM, dog liver microsomes; MLM, monkey liver microsomes; GSH, glutathione.

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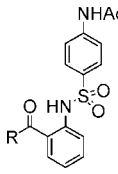
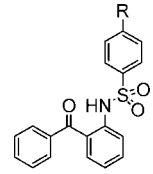
Table 1. A-Ring SAR: Binding Affinities of hB_1 Receptor Antagonists[a]

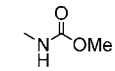
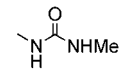
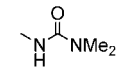
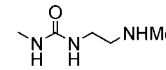
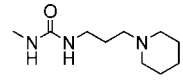
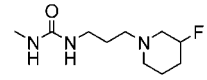
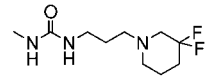
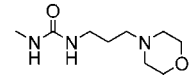


comp. #	R	Ki[a]	comp. #	R	Ki[a]
1		45	**8**		56
2		251	**9**		331
3		65	**10**		28
4		23	**11**		202
5		>10000	**12**		72
6		108	**13**		431
7		70	**14**		24
			15		43

[a] Values represent the numerical average of at least two experiments. Interassay variability was ±25%.

Table 2. Amide SAR: Binding Affinities of hB_1 Receptor Antagonists



comp. #	R	Ki[a]
16		>10uM
17		217
18		215
19		19
20		0.25
21		1.2
22		5.6
23		2.1

ether-a-go-go-related gene (hERG): $IC_{50} > 10\ \mu M$),[8] it is a pregnane X-receptor (PXR) agonist[9] (Table 4). Compound **1** has modest clearance, short half-life, and poor bioavailablity in rats and short half-life in dogs (Table 4). The poor PK profile could be attributed in part to its rapid metabolism in liver microsomes (Table 5). After incubation of compound **1** in liver microsomes in the presence of NADPH for 30 min, the remaining amount of parent compound is less than 10% in all species examined (humans, dogs, rats, and monkeys).

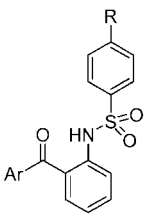
Initial SAR study results revealed that the benzophenone motif can be replaced with a biaryl ether but with less potency than benzophenone. The ketone linker otherwise is intolerant to replacement with other functionalities. Likewise, replacement of the sulfonamide moiety with amide, urea, carbamate, alkyl, and aryl linkers led to inactive compounds. B-ring substitution and replacement with heterocycle were similarly unfruitful.

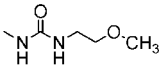
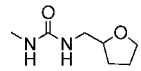
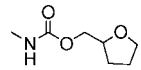
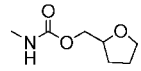
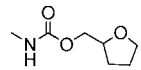
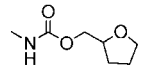
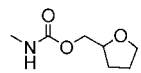
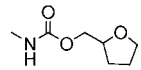
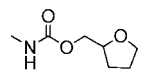
To explore A-ring substitution, the fluorine atom was used as a probe. Among the three positions on the phenyl A-ring (compound **2** to **4**), the *para*-fluoro compound **4** showed a 2-fold improvement in potency versus the lead compound **1** (Table 1). A similar trend was observed for the chlorine analogues (compounds **5** to **7**), which were less potent than the corresponding fluorine analogues. Other substituents, such as methyl, methoxyl, cyano, hydroxyl, and trifluoromethyl, at the *para*-position of the A-ring decreased binding affinity significantly. Difluorosubstitution was tolerated but offered no significant advantage (compounds **8**−**10**). Replacement of the A-ring phenyl with pyridines was examined (compounds **11**−**13**). Although the potency of pyridine derivative **11** was decreased by 5-fold, compound **11** reduced PXR activation (Table 4) and attenuated the rate of metabolism in liver microsomes (stability: d > h > r > m) (Table 5). Compound **11** shows modest clearance similar to **1** (24 mL/min/kg), but improved half-life (1.2 h), measurable bioavailability (11%) in rats, and low clearance (1.2 mL/min/kg) in dogs (Table 4). Combining this finding with the potency enhancing *para*-F led to compounds **14** and **15**. Fluoro pyridine compound **14** was 8-fold more potent than compound **11**. Gratifyingly, the microsomal stability of compound **14** was good (Table 5).

C-ring substitution and replacement with a variety of different heterocycles proved to be poorly tolerated. The amide side chain, on the other hand, was much more amendable to modification. While the replacement of amide with carbamate (compound **16**) caused a significant loss of binding affinity, the urea analogues **17** and **18** were only 4-fold less potent than compound **1** (Table 2). Appending a basic amine group at the side chain improved the binding affinity 11-fold (Compound **19**). The potency could be improved to subnanomolar by increasing chain length and appending a piperidine ring in the amide chain (compound **20**). Compound **20** has an excellent binding affinity for the hB_1 receptor and exhibits a good PXR, PK profiles (Table 4). However, compound **20** is susceptible to Pgp mediated efflux (MDR1, (B/A)/(A/B): 14) and has increased affinity for hERG: $IC_{50} = 1\ \mu M$. We speculated that the basicity of amine could be the culprit for the undesired ancillary activities. Therefore, the importance of the basicity of compound **20** was investigated. Introduction of β-fluorine at the piperidine ring to reduce the pK_a of compound[10] gave compound **21** with about 5-fold loss of potency and no significant improvement for hERG activity ($IC_{50} = 1.6\ \mu M$). Multiple fluorine substitution further debilitated the binding affinity of analogue by 5-fold and improved potassium channel activity ($IC_{50} = 6.2\ \mu M$) (compound **22**). Replacement of piperidine ring with less basic morpholine ring (compound **23**) impaired potency 10-fold relative to parent compound **20**. As anticipated, compound **23** shows improvement in terms of P-gp susceptibility (MDR1, (B/A)/(A/B): 4.8, Papp: 21.4×10^{-6}cm/s) and hERG blockade ($IC_{50} = 6.5\ \mu M$).

The study was then focused on replacing the basic amine with other neutral group. Replacement of methyl amine in compound **19** with a methoxyl group yielded an equally potent compound **24** (Table 3). Introduction of ring constraint tetrahydrofuran (analogue **25**, racemic) was also tolerated. Although the carbamate analogue, **16**, was not active, replacement of urea linker in compound **25** with carbamate led to a compound, **26**

Table 3. Binding Affinities of hB_1 Receptor Antagonists[a]



comp. #	Ar	R	Ki[a]
24	Ph		24
25	Ph		15
26	Ph		0.7
27		 racemic	2.6
28		 1st eluted	1.3
29		 2nd eluted	0.6
30		 racemic	0.2
31		 1st eluted	2.1
32		 2nd eluted	0.7

[a] Values represent the numerical average of at least two experiments. Interassay variability was ± 25%.

Table 4. Ancillary Activities and Pharmacokinetics of Selected hB_1 Receptor Antagonists

	Pgp[a]				rat PK[d]			dog PK[e]	
compound	MDR1	Papp	hERG[b]	PXR[c]	*F* (%)	CL	$t_{1/2}$	CL	$t_{1/2}$
1	2.5	27	>10	81	3	26	0.3	7.5	0.5
4			>10	70	16	18	3.7	11	1.4
11				37	11	24	1.2	1.2	1.2
14				24				3.6	0.9
20	14	34	1.0	13	41	29	14	17	1.5
26	2.3	26	8.2	88	3	43	9.7	17	1.9
27	2.6	31	>10	40	17	40	1.4	3.4	1.4
28			>10	39				3.1	2.6
29	4.2	33	>30	39	3	40	1.7	2.9	2.2
30	3.1	26	>10	56				14	1.8
32			>30	63	<1	26	1.1	6.2	2.8

[a] MDR1 directional transport ratio (B/A)/(A/B). Values represent the average of three experiments and interassay variability was ±20%. Papp: $\times 10^{-6}$cm/s. [b] IC_{50} in μm. Inhibition of MK-499 binding to hERG in HEK293 cells. [c] % activation relative to rifampicin @ 10 μm. [d] Sprague−Dawley rats ($n = 3$). *F*: % oral bioavailability; $t_{1/2}$: hours; CL: mL/min/kg. Oral dose: 10 mg/kg; iv dose: 2 mg/kg. Interanimal variability was less than 20%. [e] Mongrel dogs ($n = 2$). iv coadministration with other analogues; $t_{1/2}$: hours; CL: mL/min/kg; iv dose: 0.25 mg/kg. Interanimal variability was less than 20%.

(racemic), which displays subnanomolar binding affinity for the hB_1 receptor. Lacking the basic amine group, compound **26** now possessed a good profile for P-gp efflux and improved IKr activity (Table 4). However, compound **26** is a PXR activator and has high clearance and poor bioavailablity in rats (Table 4), which is in accordance with the finding that it is rapidly metabolized in liver microsomes (Table 5).

To ameliorate the microsomal stability of compound, the stable A-ring moieties (ref compounds **11** and **14**) were incorporated into **26** to afford compounds **27** and **30**, respectively. Compound **27** (racemic) has a binding affinity of 2.6 nM (about 3-fold less potent than compound **26**) and is neither P-gp substrate nor an ion channel blocker and has an improved PXR profile vs **1** (Table 4). The microsomal stability of **27** was improved marginally versus compound **1** (Table 5). However, the bioavailabilty of **27** was improved although it had high clearance in rats (Table 4). Resolution of **27** by chiral chromatography yielded compounds **28**, the first eluted compound, and **29**, the second eluted compound.

As anticipated, receptor binding affinity and the configuration of the asymmetric center were linked. Compound **29** with a subnanomaolar K_i is 2-fold more potent than compound **28**. Unexpectedly, the stability of compound **28** was poor (data not shown), and the PK profile of compound **29** was not improved vs **27**. A similar SAR result was observed for the 4-fluro-2-pyrido analogue. Compound **30**, in a racemic form, has a K_i of 0.2 nM, which is more potent than compound **27**. However, compound **30** was microsomal unstable (Table 5). Chiral separation of **30** delivered the two enantiomers, **31** and **32**. Once again, the second eluted isomer (**32**) was more potent than the first eluted isomer (compound **31**) but showed poor rat PK and PXR profiles.

To assess the selectivity of this series compounds, compound **29** was screened in a panel of assays[11] representing 170 enzymes, receptors, and transporters. Compound **29** showed a no-hit in the screen (except BK B_1 receptor inhibition) and demonstrated an excellent selectivity.

The in vitro liver microsomes stability study results showed that the metabolism of compounds in this series was both NADPH and species dependent (Table 5). A similar trend of stability across species was observed (liver microsomal stability: dog > human > rat > monkey). Further study of compound **26** revealed that it underwent extensive mono- and dioxidation in both human liver microsomes (HLM) and rat liver microsomes (RLM). In the presence of glutathione (GSH), significant GS-adduct were formed.

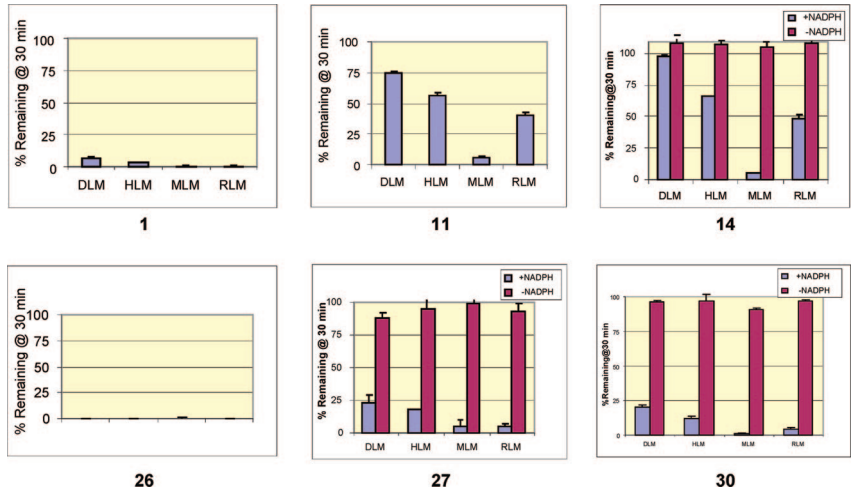
To determine the extent to which the compounds in this series occupy the human BK B_1 receptor in vivo, **26** was examined in an ex vivo receptor occupancy study in transgenic rats in which the human BK B_1 receptor is constitutively overexpressed.[12] In this study, **26** showed dose dependent occupancy following iv infusion over 30 min (Table 6). At a dose of 12 mg/kg, compound **26** shows 74 and 80% of receptor occupancy in both brain and spinal cord at concentrations of 5837 and 9427 nM, respectively. These data suggest that compound **26** penetrates the blood−brain barrier and occupies the receptor in the CNS which is in accordance with the finding that compound **26** is not a substrate for P-gp mediated efflux (Table 4).

Conclusion. In summary, the compounds disclosed in this paper represent a new structural class of BK B_1 receptor antagonists. Several compounds possess excellent binding affinities for the hB_1 receptor. Modification of HTS lead, compound **1**, led to **26** which exhibited promising ex vivo receptor occupancy in transgenic rats. Compound **27** showed a balanced profile in terms of potency, P-gp susceptibility, hERG blockade, and pharmacokinetics.

Experimental Procedures

General Procedures. ^1H and ^{13}C (300, 400, or 600 MHz) NMR spectra were recorded on a Varian VXR 300, Unity Inova 400, or Unity Inova 600 spectrometer. The chemical shifts are reported in δ (ppm) using the δ 0.00 signal of Me_4Si as an internal standard. LC/MS data were obtained on a Waters 2690 separations module and Micromass ZM. High resolution MS (HRMS) data were obtained on a Bruker 3T or 7T FTICR MS with either electrospray ionization or APCI. HPLC spectra were

Table 5. In Vitro Liver Microsomes Stability Study of Selected Compounds[a]



[a] Compound was incubated in liver microsomes for 30mins. For compound **1**, **11**, and **26**, the stabilities of compounds were examined only in the presence of NADPH.

Table 6. Ex Vivo Receptor Occupancy Study Results of Compound **26**

dose (mg/kg)	compartment	occupancy (%)	conc (nM)
0.12	plasma		80
	brain	22	70
	spinal cord	28	97
1.2	plasma		995
	brain	49	438
	spinal cord	62	597
12	plasma		13245
	brain	74	5837
	spinal cord	80	9427

recorded on a Hewlett-Packard 1100 with a YMC-Pack Pro C-18 column or Atlantis dC_{18} column with a 5−95% CH_3CN/H_2O gradient at 215 nm. Chiral HPLC spectra were recorded on a Hewlett-Packard 1100 with a ChiralPak AD column utilizing 40% hexanes (containing 0.1% diethylamine) and 60% EtOH as eluent at 230 nm.

4-Amino-*N*-(2-benzoylphenyl)benzenesulfonamide (I). 2-Aminobenzophenone (20 mg) was dissolved in 1 mL of methylene chloride and 4-nitrobenzenesulfonyl chloride (34 mg, 1.5 equiv) was added thereto followed by pyridine ($\varphi.\varphi$16 mL, 2 equiv). After 10 min, the reaction mixture was concentrated in vacuo and subjected to flash chromatography (eluting with 0−25% EtOAc/hexane) to provide *N*-(2-benzoylphenyl)-4-nitrobenzenesulfonamide (12 mg, 31%). LC/MS, M + H^+ found: 383.1. This reaction was also carried out in multi-gram scale. The crude material was carried on to the next reaction without further purification.

The above nitrobenzenesulfonamide (500 mg) was dissolved in 10 mL of 2:2:1 EtOH/HOAc/water and elemental iron (508 mg, 7.4 equiv) was added thereto followed by 5 μL of concentrated HCl. The reaction mixture was heated to 100 °C for 10 min and then cooled to rt and diluted with 35 mL of water. The layers were separated, and the aqueous layer was extracted three times with methylene chloride. The organic layer was washed twice with saturated sodium bicarbonate and twice with water, back extracted once with methylene chloride, and dried over sodium sulfate, filtered, and concentrated in vacuo. Crude 4-amino-*N*-(2-benzoylphenyl)benzenesulfonamide (416 mg, 90%), which was used without further purification. Purity was determined by LC/MS (M + H^+ found: 353.1).

(2-Aminophenyl)(5-fluoropyridin-2-yl)methanone (II). 2-Bromo-5-fluoropyridine (10 g, 56.8 mmol) and 2-aminobenzonitrile (5.6 g, 47.4 mmol) were dissolved in 100 mL of toluene and cooled to −30 °C. To the resulting solution was added nBuLi (1.6 M in hexanes, 65 mL, 104 mmol, 2.2 equv) dropwise and warmed to 0 °C for 90 min. The reaction was then poured into 100 mL of cooled (0 °C) 3N HCl and stirred for 15 min. Then 5N NaOH was added until basic and then extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layer was washed with brine (1 × 100 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. Flash chromatography of crude residue (0−30% EtOAc/hexanes) gave 6 g (58%) of (2-aminophenyl)(5-fluoropyridin-2-yl)methanone as a solid (LC/MS found: 217.2).

1-[3-({[(4-{[(2-Benzoylphenyl)amino]sulfonyl}phenyl)amino]-carbonyl}amino)propyl]piperidinium trifluoroacetate (20). Triphosgene (28 mg, 1/3 equiv) was dissolved in 1 mL of THF and the solution was cooled to 0 °C. A solution of 4-amino-*N*-(2-benzoylphenyl)benzenesulfonamide (100 mg) in 3 mL of THF and 0.15 mL of triethylamine was added to the triphosgene solution. The reaction mixture was warmed to rt and stirred for 30 min. A solution of 3-(piperidin-1-yl)propan-1-amine (60 mg, 1.5 equiv) in 3 mL of THF and 0.15 mL of triethylamine was added and the reaction mixture was stirred at room temperature overnight. The reaction was quenched with water and diluted with EtOAc. The organic layer was washed once each with water and brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The title product was obtained as the TFA salt (130 mg) following reverse phase chromatography (5−95% acetonitrile/water/0.1% TFA). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 1.25 (s, 1H), 1.45 (m, 1H), 1.97 (m, 4H), 2.50 (m, 2H), 2.65 (m, 2H), 3.05 (m, 2H), 3.38 (t, J = 5 Hz, 2H), 3.47 (d, J = 12 Hz, 2H), 7.08 (t, J = 7 Hz, 1H), 7.40 (m, 6H), 7.52 (m, 3H), 7.77 (d, J = 8 Hz, 1H), 9.22 (s, 1H), 10.05 (s, 1H) and 10.55 (m, 1H). ESMS, M + H^+ found: 521.2. High resolution MS: m/z found 521.2229 (M + 1), calculated 521.2217 (M + 1).

Tetrahydrofuran-2-ylmethyl 4-{[(2-benzoylphenyl)amino]sulfonyl}phenylcarbamate (26). Triphosgene (28 mg, 1/3 equiv) was dissolved in 1 mL of THF and the solution was cooled to 0 °C. A solution of 4-amino-*N*-(2-benzoylphenyl)benzenesulfonamide (100 mg) in 3 mL of THF and 0.15 mL of triethylamine was added to the triphosgene solution.The reaction mixture was warmed to room temperature and stirred for 30 min. A solution of tetrahyhdrofurfuryl alcohol (44 mg, 1.5 equiv) in 3 mL of THF and 0.15 mL of triethylamine was added to the reaction mixture and the mixture was stirred overnight. The reaction was quenched with water and diluted with EtOAc. The organic layer was washed once each with water and brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The title product was obtained following flash chromatography (10−95% EtOAc/hex). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 1.95 (m, 2H), 2.06 (m, 1H), 2.67 (d, J = 9.5, 1H), 3.88 (m, 2H), 4.06 (m, 1H), 4.14 (m, 1H), 4.29 (dd, J = 3, 11, 1H), 6.71 (s, 1H), 7.10 (m, 1H), 7.40 (m, 6H), 7.56 (m, 2H), 7.64 (m, 2H), 7.79 (d, J = 8 hz, 1H) and 10.50 (s, 1H). ESMS, M + H^+ found 481.8.

High resolution MS: *m/z* found 481.1441 (M + 1), calculated 481.1428 (M + 1).

***N*-[4-({[2-(2-Fluorobenzoyl)phenyl]amino}sulfonyl)phenyl]-acetamide (2).** ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.19 (s, 3H), 7.09 (m, 3H), 7.20 (m, 1H), 7.38 (m, 1H), 7.50 (m, 4H), 7.80 (m, 3H), and 10.82 (s, 1H). High Resolution MS: *m/z* found 413.0966 (M + 1), calculated 413.0966 (M + 1).

***N*-[4-({[2-(3-Fluorobenzoyl)phenyl]amino}sulfonyl)phenyl]-acetamide (3).** ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.19 (s, 3H), 4.12 (d, J = 7 Hz, 1H), 7.04 (d, J = 8.5 Hz, 1H), 7.12 (m, 1H), 7.25 (m, 2H), 7.40 (m, 4H), 7.54 (m, 1H), 7.62 (d, J = 7.7 Hz, 2H), 7.89 (d, J = 7.7 Hz, 1H), and 9.90 (s, 1H). High resolution MS: *m/z* found 413.0970 (M + 1), calculated 413.0966 (M + 1).

***N*-[4-({[2-(4-Fluorobenzoyl)phenyl]amino}sulfonyl)phenyl]-acetamide (4).** ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.19 (s, 3H), 7.06 (td, J = 2, 9 Hz, 2H), 7.15 (m, 2H), 7.26 (d, J = 2 Hz, 1H), 7.35 (m, 1H), 7.46 (td, J = 2, 5 Hz, 2H), 7.56 (m, 3H), 7.79 (d, J = 8 Hz, 1H), and 9.70 (s, 1H). High resolution MS: *m/z* found 413.0983 (M + 1), calculated 413.0966 (M + 1).

***N*-[4-({[2-(2-Chlorobenzoyl)phenyl]amino}sulfonyl)phenyl]-acetamide (5).** ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.19 (s, 3H), 6.99 (t, J = 7 Hz, 1H), 7.18 (d, J = 7 Hz, 1H), 7.33 (m, 2H), 7.42 (m, 2H), 7.50 (t, J = 8.8 Hz, 1H), 7.58 (d, J = 8.6 Hz, 2H), 7.82 (m, 3H), and 11.10 (s, 1H). High resolution MS: *m/z* found 429.0669 (M + 1), calculated 429.0671 (M + 1).

***N*-[4-({[2-(3-Chlorobenzoyl)phenyl]amino}sulfonyl)phenyl]-acetamide (6).** ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.19 (s, 3H), 7.14 (m, 2H), 7.35 (m, 3H), 7.42 (d, J = 8.7 Hz, 2H), 7.31 (m, 1H), 7.57 (m, 3H), 7.80 (d, J = 8.1 Hz, 1H), and 9.80 (s, 1H). High resolution MS: *m/z* found 429.0669 (M + 1), calculated 429.0671 (M + 1).

***N*-[4-({[2-(4-Chlorobenzoyl)phenyl]amino}sulfonyl)phenyl]-acetamide (7).** ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.09 (s, 3H), 7.15 (d, J = 7.8 Hz, 1H), 7.30 (m, 1H), 7.40 (m, 1H), 7.75 (m, 9H), and 9.78 (s, 1H). High resolution MS: *m/z* found 429.0666 (M + 1), calculated 429.0671 (M + 1).

***N*-[4-({[2-(2,4-Difluorobenzoyl)phenyl]amino}sulfonyl)phenyl]-acetamide (8).** ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.19 (s, 3H), 6.86 (t, J = 7.4 Hz, 1H), 6.95 (t, J = 8.5 Hz, 1H), 7.05 (t, J = 8 Hz, 1H), 7.33 (m, 2H), 7.53 (m, 3H), 7.76 (m, 3H) and 10.60 (s, 1H). High resolution MS: *m/z* found 431.0886 (M + 1), calculated 431.0872 (M + 1).

***N*-[4-({[2-(3,4-Difluorobenzoyl)phenyl]amino}sulfonyl) phenyl]acetamide (9).** ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.19 (s, 3H), 7.06 (m, 2H), 7.18 (m, 1H), 7.34 (m, 2H), 7.54 (m, 3H), 7.78 (m, 3H), and 10.70 (s, 1H). LC/MS: *m/z* = 431.2 (M + 1).

***N*-[4-({[2-(2,3-Difluorobenzoyl)phenyl]amino}sulfonyl) phenyl]acetamide (10).** ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.19 (s, 3H), 7.18 (m, 4H), 7.34 (dd, J = 7.7, 1.4 Hz, 1H), 7.38 (d, J = 8.8 Hz, 2H), 7.58 (d, J = 8.8 Hz, 3H), 7.80 (d, J = 8.2 Hz, 1H), and 9.60 (s, 1H). High resolution MS: *m/z* found 431.0883 (M + 1), calculated 431.0872 (M + 1).

***N*-[4-({[2-(Pyridin-2-ylcarbonyl)phenyl]amino}sulfonyl)phenyl]acetamide (11).** ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.19 (s, 3H), 7.08 (t, J = 8.3, 1H), 7.50 (m, 4H), 7.76 (m, 2H), 7.83 (m, 1H), 7.89 (td, J = 2, 8 Hz, 1H), 8.65 (d, J = 1 Hz, 1H) and 10.70 (s, 1H). High resolution MS: *m/z* found 396.1009 (M + 1), calculated 396.1013 (M + 1).

***N*-[4-({[2-(Pyridin-3-ylcarbonyl)phenyl]amino}sulfonyl)phenyl]acetamide (12).** ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.17 (s, 3H), 7.16 (t, J = 7.8 Hz, 1H), 7.26 (m, 1H), 7.40 (m, 4H), 7.60 (m, 3H), 7.82 (d, J = 8.3 Hz, 1H), 7.88 (d, J = 7.8 Hz, 1H), 8.50 (s, 1H), 8.76 (s, 1H) and 9.92 (s, 1H). High resolution MS: *m/z* found 396.1019 (m + 1), calculated 396.1013 (M + 1).

***N*-(4-{[(2-Isonicotinoylphenyl)amino]sulfonyl}phenyl) acetamide (13).** ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.19 (s, 3H), 7.13 (t, J = 7.7, 1H), 7.25 (m, 3H), 7.35 (d, J = 8 Hz, 1H), 7.48 (d, J = 8.8 Hz, 2H), 7.61 (t, J = 8.6 Hz, 1H), 7.69 (d, J = 8.7 Hz, 2H), 7.81 (d, J = 8.6 Hz, 1H) 8.74 (s, 2H) and 10.16 (s, 1H). High resolution MS: *m/z* found 396.1008 (M + 1), calculated 396.1013 (M + 1).

***N*-{4-[({2-[(5-Fluoropyridin-2-yl)carbonyl]phenyl}amino)sulfonyl]phenyl}acetamide (14).** ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.17 (s, 3H), 7.13 (m, 2H), 7.45 (d, J = 8.7 Hz, 2H), 7.55 (m, 2H), 7.69 (d, J = 8.9 Hz, 2H), 7.76 (t, J = 7.2 Hz, 2H), 7.95 (q, J = 4.5 Hz, 1H), 8.46 (d, J = 2.8 Hz, 1H) and 10.27 (s, 1H). High resolution MS: *m/z* found 414.0917 (M + 1), calculated 414.0919 (M + 1).

***N*-{4-[({2-[(6-Fluoropyridin-3-yl)carbonyl]phenyl}amino)sulfonyl]phenyl}acetamide (15).** ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.19 (s, 3H), 7.01 (dd, J = 8.5, 3 Hz, 1H), 7.20 (t, J = 7.5 Hz, 1H), 7.35 (s, 1H), 7.37 (m, 3H), 7.81 (d, J = 8.3 Hz, 1H), 8.02 (td, J = 7.5, 6 Hz, 1H) and 8.10 (d, J = 2 Hz, 1H). High resolution MS: *m/z* found 414.0930 (M + 1), calculated 414.0919 (M + 1).

Methyl (4-{[(2-Benzoylphenyl)amino]sulfonyl}phenyl)carbamate (16). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 3.63 (m, 3H), 6.44 (m, 2H), 7.48 (m, 5H), 7.58 (m, 2H), 7.64 (m, 2H) and 7.76 (m, 2H). ES MS: *m/z* = 411.2 (M + 1).

***N*-(2-Benzoylphenyl)-4-{[(methylamino)carbonyl]amino}benzenesulfonamide (17).** LC/MS: *m/z* = 410.3 (M + 1).

***N*-(2-Benzoylphenyl)-4-{[(dimethylamino)carbonyl]amino}-benzenesulfonamide (18).** ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 3.02 (s, 6H), 6.32 (s, 1H), 7.08 (t, J = 6.6 Hz, 1H), 7.39 (m, 2H), 7.40 (m, 3H), 7.53 (m, 2H), 7.62 (m, 2H), 7.78 (d, J = 8 Hz, 1H) and 10.12 (s, 1H). High resolution MS: *m/z* found 424.1329 (M + 1), calculated 424.1326 (M + 1).

2-({[(4-{[(2-Benzoylphenyl)amino]sulfonyl}phenyl)amino]carbonyl} amino)-*N*-methylethanaminium Chloride (19). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.57 (t, J = 5 Hz, 3H), 3.00 (m, 2H), 3.37 (d, J = 6 Hz, 2H), 6.64 (m, 1H), 7.18 (d, J = 8 Hz, 1H), 7.26 (t, J = 7 Hz, 1H), 7.38 (d, J = 6 Hz, 1H), 7.50 (m, 8H), 7.64 (t, J = 7 Hz, 1H), 8.45 (m, 2H), 9.36 (s, 1H) and 9.88 (s, 1H). High resolution MS: *m/z* found 453.1590 (M + 1), calculated 453.1591 (M + 1).

1-[3-({[(4-{[(2-Benzoylphenyl)amino]sulfonyl}phenyl)amino]-carbonyl}amino)propyl]piperidinium trifluoroacetate (20). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 1.25 (s, 1H), 1.45 (m, 1H), 1.97 (m, 4H), 2.50 (m, 2H), 2.65 (m, 2H), 3.05 (m, 2H), 3.38 (t, J = 5 Hz, 2H), 3.47 (d, J = 12 Hz, 2H), 7.08 (t, J = 7 Hz, 1H), 7.40 (m, 6H), 7.52 (m, 3H), 7.77 (d, J = 8 Hz, 1H), 9.22 (s, 1H), 10.05 (s, 1H) and 10.55 (m, 1H). High resolution MS: *m/z* found 521.2229 (M + 1), calculated 521.2217 (M + 1).

***N*-(2-Benzoylphenyl)-4-[({[3-(3-fluoropiperidin-1-yl)propyl]-amino}carbonyl)amino]benzenesulfonamide (21).** ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 1.47 (m, 1H), 1.63 (m, 3H), 1.90 (m, 1H), 2.14 (m, 2H), 2.52 (m, 1H), 2.66 (m, 1H), 2.95 (m, 1H), 3.22 (m, 2H), 3.63 (m, 1H), 4.87 (s, 1H), 5.03 (s, 1H), 6.72 (d, J = 8.6 Hz, 1H), 7.06 (t, J = 7.6 Hz, 1H), 7.33 (m, 3H), 7.43 (m, 4H). 7.58 (m, 3H), 7.77 (d, J = 8 Hz, 1H) and 10.05 (s, 1H). High resolution MS: *m/z* found 539.2123 (M + 1), calculated 539.2123 (M + 1).

1-[3-({[(4-{[(2-Benzoylphenyl)amino]sulfonyl}phenyl)amino]-carbonyl}amino)propyl]-3,3-difluoropiperidinium trifluoroacetate (22). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.02 (s, 2H), 2.15 (s, 4H), 3.18 (s, 4H), 3.38 (s, 4H), 7.09 (t, J = 7.6 Hz, 1H), 7.37 (m, 7H), 7.56 (m, 4H), 7.75 (d, J = 8 Hz, 1H), 9.03 (s, 1H) and 10.08 (s, 1H). High resolution MS: *m/z* found 557.2025 (M + 1), calculated 557.2029 (M + 1).

4-[3-({[(4-{[(2-Benzoylphenyl)amino]sulfonyl}phenyl)amino]-carbonyl}amino)propyl]morpholin-4-ium Trifluoroacetate (23). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.06 (m, 2H), 2.88 (m, 2H), 3.14 (m, 2H), 3.38 (m, 4H), 3.91 (t, J = 12 Hz, 2H), 4.48 (m, 2H), 7.08 (t, J = 8.5 Hz, 1H), 7.40 (m, 7H), 7.51 (m, 2H), 7.57 (d, J = 8 Hz, 2H), 7.77 (d, J = 8 Hz, 1H), 8.75 (s, 1H) and 10.08 (s, 1H). High resolution MS: *m/z* found 523.2009 (M + 1), calculated 523.2010 (M + 1).

***N*-(2-Benzoylphenyl)-4-({[(2-methoxyethyl)amino]carbonyl}-amino)benzenesulfonamide (24).** ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 3.42 (m, 5H), 3.52 (m, 2H), 4.92 (m, 1H), 7.80 (t, J = 7 Hz, 2H), 7.23 (m, 2H), 7.40 (m, 4H), 7.50 (m, 2H), 7.60 (d, J = 9 Hz, 2H), 7.78 (d, J = 8 Hz, 1H) and 10.05 (s, 1H). High resolution MS: *m/z* found 454.1426 (M + 1), calculated 454.1431 (M + 1).

***N*-(2-Benzoylphenyl)-4-({[(tetrahydrofuran-2-ylmethyl)amino]carbonyl}amino)benzenesulfonamide (25).** ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 1.64 (m, 1H), 1.98 (m, 3H), 3.12 (m, 1H), 3.55 (m, 1H), 3.83 (m, 2H), 4.03 (m, 1H), 4.90 (m, 1H), 7.10 (m, 1H), 7.26 (m, 2H), 7.40 (m, 5H), 7.50 (m, 2H), 7.58 (m, 2H), 7.78 (d, J = 8 Hz, 1H) and 10.06 (s, 1H). High resolution MS: *m*/*z* found 480.1556 (M + 1), calculated 480.1588 (M + 1).

Tetrahydrofuran-2-ylmethyl[4-({[2-(pyridin-2-ylcarbonyl)phenyl}amino}sulfonyl)phenyl]carbamate (27). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 1.97 (m, 1H), 2.03 (m, 1H), 2.65 (d, J = 9.2 Hz, 2H), 3.83 (m, 1H), 3.87 (m, 1H), 4.05 (m, 1H), 4.14 (m, 1H), 4.27 (dd, J = 11, 3 Hz, 1H), 6.80 (s, 1H), 7.09 (t, J = 8 Hz, 1H), 7.33 (d, J = 9 Hz, 2H), 7.47 (m, 2H), 7.70 (d, J = 9 Hz, 2H), 7.76 (t, J = 8 Hz, 2H), 7.86 (m, 2H), 7.87 (d, J = 6 Hz, 1H) and 10.56 (s, 1H). High resolution MS: *m*/*z* found 482.1417 (M + 1), calculated 482.1381 (M + 1).

Tetrahydrofuran-2-ylmethyl[4-({[2-(pyridin-2-ylcarbonyl)phenyl}amino}sulfonyl)phenyl]carbamate (1st Eluting) (28). LC/MS: *m*/*z* = 482.2 (M + 1).

Tetrahydrofuran-2-ylmethyl[4-({[2-(pyridin-2-ylcarbonyl)phenyl}amino}sulfonyl)phenyl]carbamate (2nd Eluting) (29). LC/MS: *m*/*z* = 482.2 (M + 1).

Tetrahydrofuran-2-ylmethyl{4-[({2-[(5-fluoropyridin-2-yl)carbonyl]phenyl}amino)sulfonyl]phenyl}carbamate (30). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 1.93 (m, 2H), 2.06 (m, 1H), 3.84 (q, J = 8 Hz, 1H), 3.90 (q, J = 8 Hz, 1H), 4.05 (m, 1H), 4.14 (m, 1H), 4.28 (dd, J = 3, 11 Hz, 1H), 6.78 (s, 1H), 7.10 (t, J = 6 Hz, 1H), 7.29 (d, J = 9 Hz, 2H), 7.75 (m, 2H), 7.94 (m, 2H), 8.46 (d, J = 3 Hz, 1H), and 10.24 (s, 1H). High resolution MS: *m*/*z* found 500.1290 (M + 1), calculated 500.1286 (M + 1).

Tetrahydrofuran-2-ylmethyl{4-[({2-[(5-fluoropyridin-2-yl)carbonyl]phenyl}amino)sulfonyl]phenyl}carbamate (1st Eluting) (31). LC/MS: *m*/*z* = 500.2 (M + 1).

Tetrahydrofuran-2-ylmethyl{4-[({2-[(5-fluoropyridin-2-yl)carbonyl]phenyl}amino)sulfonyl]phenyl}carbamate (2nd Eluting) (32). LC/MS: *m*/*z* = 500.2 (M + 1).

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Supporting Information Available: PK procedures and metabolite ID data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Bock, M. G.; Hess, J. F.; Pettibone, D. J. Bradykinin-1 receptor antagonists. In *Annual Reports in Medicinal Chemistry*; Doherty, A. M., Ed.; Elsevier Inc.: New York, 2003; Vol. 38, pp 111−120. (b) Couture, R.; Harrisson, M.; Vianna, R. M.; Cloutier, F. Kinin receptors in pain and inflammation. *Eur. J. Pharmacol.* **2001**, *429*, 161–176. (c) Bock, M. G.; Longmore, J. Bradykinin antagonists: new opportunities. *Curr. Opin. Chem. Biol.* **2000**, *4*, 401–406. (d) Marceau, F. Kinin B_1 receptors: a review. *Immunopharmacology* **1995**, *30*, 1–26. (e) Regoli, D.; Barabe, J. Pharmacology of bradykinin and related kinins. *Pharmacol. Rev.* **1980**, *32*, 1–46.

(2) Rupniak, N. M. J.; Longmore, J.; Hill, R. G. Elucidation of the role of bradykinin B_1 and B_2 receptors in nociception and inflammation using selective antagonists and transgenic mice. In *Molecular Basis of Pain Induction*; Wood, J., Ed.; John Wiley Press: New York; 2000, pp 149−174.

(3) (a) Pesquero, J. B.; Araujo, R. C.; Heppenstall, P. A.; Stucky, C. L.; Silva, J. A., Jr.; Walther, T.; Oliveira, S. M.; Pesquero, J. L.; Paiva, A. C. M.; Calixto, J. B.; Lewin, G. R.; Bader, M. Hypoalgesia and altered inflammatory responses in mice lacking kinin B_1 receptors. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 8140–8145. (b) Ferreira, J.; Campos, M. M.; Araujo, R.; Bader, M.; Pesquero, J. B.; Calixto, J. B. The use of kinin B_1 and B_2 receptor knockout mice and selective antagonists to characterize the nociceptive responses caused by kinins at spinal level. *Neuropharmacology* **2002**, *43*, 1188–1197. (c) Ferreira, J.; Beirith, A.; Mori, M. A. S.; Araujo, R. C.; Bader, M.; Pesquero, J. B.; Calixto, J. B. Reduced nerve injury-induced neuropathic pain in kinin B_1 receptor knock-out mice. *J. Neurosci.* **2005**, *25* (9), 2405–2412.

(4) (a) Seabrook, G. R.; Bowery, B. J.; Heavens, R.; Brown, N.; Ford, H.; Sirinathsinghi, D. J. S.; Borkowski, J. A.; Hes, J. F.; Strader, C. D.; Hill, R. G. Expression of B_1 and B_2 bradykinin receptor mRNA and their functional roles in sympathetic ganglia and sensory dorsal root ganglia neurons from wild type and B_2 receptor knockout mice. *Neuropharmacology* **1997**, *36*, 1009–1017. (b) Ma, Q.-P.; Hill, R. G.; Sirinathsinghi, D. J. S. Basal expression of bradykinin B_1 receptor in peripheral sensory aganglia in the rat. *Neuroreport* **2000**, *11*, 4003–4005. (c) Wotherspoon, G.; Winter, J. Bradykinin B_1 receptor is constitutively expressed in the rat sensory nervous system. *Neurosci. Lett.* **2000**, *294*, 175–178.

(5) (a) Su, D.-S.; Markowitz, M. K.; Dipardo, R. M.; Murphy, K. L.; Harrell, C. M.; O'Malley, S. S.; Ransom, R. W.; Chang, R. S. L.; Ha, S.; Hess, F. J.; Pettibone, D. J.; Mason, G. S.; Boyce, S.; Freidinger, R. M.; Bock, M. G. Discovery of a potent, non-peptide bradykinin B_1 receptor antagonist. *J. Am. Chem. Soc.* **2003**, *125*, 7516–7517. (b) Kuduk, S. D.; Ng, C.; Feng, D.-M.; Wai, J. M.-C.; Chang, R. S. L.; Harrell, C. M.; Murphy, K. L.; Ransom, R. W.; Reiss, D. R.; Ivarsson, M.; Mason, G.; Boyce, S.; Tang, C.; Prueksaritanont, T.; Freidinger, R. M.; Pettibone, D. J.; Bock, M. G. 2,3-Diaminopyridine bradykinin B1 receptor antagonists. *J. Med. Chem.* **2004**, *47*, 6439–6442. (c) Wood, M. R.; Books, K. M.; Kim, J. J.; Wan, B.-L.; Murphy, K. L.; Chang, R. S. L.; Tang, C.; Prueksaritanont, T.; Detwiler, T. J.; Hettrick, L. A.; Landis, E. R.; Leonard, Y. M.; Krueger, J. A.; Lewis, S. D.; Pettibone, D. J.; Freidinger, R. M.; Bock, M. G. Novel bradykinin B1 receptor antagonists. Cyclopropylamino acid amide as a pharmacophoric replacement fro 2,3-diaminopyridine. *J. Med. Chem.* **2006**, *48*, 1231–1234. (d) Kuduk, S. D.; Di Marco, C. N.; Chang, R. K.; Wood, M. R.; Schirripa, K. M.; Kim, J. J.; Wai, J. M. C.; DiPardo, R. M.; Murphy, K. L.; Ransom, R. W.; Harrell, C. M.; Reiss, D. R.; Holahan, M. A.; Cook, J.; Hess, J. F.; Sain, N.; Urban, M. O.; Tang, C.; Prueksaritanont, T.; Pettibone, D. J.; Bock, M. G. Development of orally bioavailable and CNS penetrant biphenylaminocyclopropane carboxamide bradykinin B_1 receptor antagonists. *J. Med. Chem.* **2007**, *50*, 272–282. (e) Su, D.-S.; Lim, J. J.; Markowitz, M. K.; Wan, B.-L.; Murphy, K. L.; Reiss, D. R.; Harrell, C. M.; O'Malley, S. S.; Ransom, R. W.; Chang, R. S. L.; Pettibone, D. J.; Tang, C.; Prueksaritanont, T.; Freidinger, R. M.; Bock, M. G. Potent Bradykinin B_1 Receptor Antagonists: 4-Substituted Phenyl Cyclohexanes. *Bioorg. Chem. Lett.* **2007**, *14*, 6045–6048.

(6) Hochman, J. H.; Yamazaki, M.; Ohe, T.; Lin, J. H. Evaluation of drug interaction with P-glycoprotein in drug discovery: in vitro assessment of the potential for drug−drug interactions with P-glycoprotein. *Curr. Drug Metab.* **2002**, *3*, 257–273.

(7) P-gp mediated directional transport were performed in LLC-PK1 cells expressing genes for human P-gp (MDR1), and the ratio of transport from basalateral to apical (B to A) direction to the ratio of transport from apical to basalateral (A to B) direction was measured. for the assay protocols, please see ref 5d.

(8) For hERG binding assay protocol, see the following, Butcher, J. W.; Claremon, D. A.; Connolly, T. M.; Dean, D. C.; Karczewski, J.; Koblan, K. S.; Kostura, M. J.; Liverton, N. J.; Melillo, D. G. Radioligand and binding assay. PCT International Patent Appl. WO0205860A1, 2002.

(9) (a) Wilson, T. M.; Kliewer, S. A. PXR, CAR and drug metabolism. *Nat. Rev.* **2002**, *1*, 259–266. (b) Xie, W.; Uppal, H.; Saini, S. P. S.; Mu, Y.; Little, J. M.; Radominska-Pandya, A.; Zemaitis, M. A. Orphan nuclear receptor-mediated xenobiotic regulation in drug metabolism. *Drug Discovery Today* **2004**, *9* (10), 442–449.

(10) van Niel, M. B.; Collins, I.; Beer, M. S.; Broughton, H. B.; Cheng, S. K. F.; Goodacre, S. C.; Heald, A.; Locker, K. L.; Macleod, A. M.; Morrison, D.; Moyes, C. R.; O'Connor, D.; Pike, A.; Rowley, M.; Russell, M. G. N.; Sohal, B.; Stanton, J. A.; Thomas, S.; Verrier, H.; Watt, A. P.; Castro, J. L. Fluorination of 3-(3-(piperidin-1-yl)propyl)indoles and 3-(3-(piperazin-1-yl)propyl)indoles gives selective human 5-HT1D receptor ligands with improved pharmacokinetic profiles. *J. Med. Chem.* **1999**, *42*, 2087–2104.

(11) Panlabs (MDS Pharma Services, Bothell, WA).

(12) (a) Su, D.-S.; Markowitz, M. K.; Murphy, K. L.; Wan, B.-L.; Zrada, M. M.; Harrell, C. M.; O'Malley, S. S.; Hess, J. F.; Ransom, R. W.; Chang, R. S.; Wallace, M. A.; Raab, C. E.; Dean, D. C.; Pettibone, D. J.; Freidinger, R. M.; Bock, M. G. Development of an efficient and selective radioligand for bradykinin B1 receptor occupancy studies. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 6045–6048. (b) Hess, J.; F.; Ransom, R. W.; Zeng, Z.; Chang, R. S. L.; Hey, P. J.; Warren, L.; Harrell, C. M.; Murphy, K. L.; Chen, T. B.; Miller, P. J.; Lis, E.; Reiss, D.; Gibson, R. E.; Markowitz, M. K.; DiPardo, R. M.; Su, D.-S.; Bock, M. G.; Gould, R. J.; Pettibone, D. J. Generation and

characterization of a human bradykinin receptor B_1 transgenic rat as a pharmacodynamic model. *J. Pharmacol. Exp. Ther.* **2004**, *310* (2), 488–497. (c) Ransom, R. W.; Harrell, C. M.; Reiss, D. R.; Murphy, K. L.; Chang, R. S. L.; Hess, J. F.; Miller, P. J.; O'Malley, S. S.; Hey, P. J.; Kunapuli, P.; Su, D.-S.; Markowitz, M. K.; Wallace, M. A.; Raab, C. E.; Jones, A. N.; Dean, D. C.; Pettibone, D. J.; Freidinger, R. M.; Bock, M. G. Pharmacological characterization and radioligand binding properties of a high-affinity, non-peptide, bradykinin B1 receptor antagonist. *Eur. J. Pharmacol.* **2004**, *499*, 77–84.

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