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A new class of bradykinin 1 receptor antagonists containing the piperidine acetic acid tetralin core

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Abstract—The bradykinin 1 (B1) receptor is upregulated during times of inflammation and is important for maintaining inflamed and chronic pain states. Blocking this receptor has been shown to reverse and/or ameliorate pain and inflammation in animal models. In this report, we describe a new class of B1 receptor antagonists that contain the piperidine acetic acid tetralin core. A structure–activity relationship for these analogs is described in this paper. The most potent compounds from this class have IC_{50}s < 20 nM in a B1 receptor functional assay. One of these compounds, **13g**, shows modest oral bioavailability in rats.

The kinins and their cognate receptors play a prominent role in pain and inflammation. The bradykinin subtype 2 (B2) receptor is constitutively expressed in the central and peripheral nervous system, vascular and tissue endothelium, and on a number of inflammatory cells.[1,2] In contrast, the bradykinin subtype 1 (B1) receptor is only expressed at very low levels or not at all under basal conditions, but it is rapidly upregulated following tissue injury and during inflammation.[3–5] Although the B1 and B2 receptors have similar signaling cascades, they have very different patterns of regulation. When the B2 receptor is activated by its ligands, bradykinin (BK) or kallidin, it is rapidly desensitized and internalized.[6] The B1 receptor, on the other hand, is thought to maintain chronic inflammation and pain, since the receptor is not desensitized and internalized when activated by its ligands, des-Arg(9)-BK or des-Arg(10)-kallidin.[1] The B1 receptor, therefore, is an attractive drug target since it is important for maintaining inflammation and chronic pain states.

Several groups have demonstrated that peptide antagonists to the B1 receptor inhibit inflammation and pain in animal models. In rats for example, B1 receptor peptide antagonists reversed or prevented the development of hyperalgesia induced by Freund's adjuvant, UV light,[7] and zymosan.[8] In the mouse streptozotocin-induced diabetic model, a B1 receptor peptide antagonist attenuated thermal hyperalgesia.[9] A systemically administered B1 receptor peptide antagonist also inhibited nociceptive spinal reflex [10] in hyperalgesic rabbits induced with Freund's adjuvant. More recently, in a carrageenan-induced hyperalgesia model, a subcutaneous injection of a B1 peptide antagonist (des-Arg10-[Leu9]-kallidin) reversed mechanical hyperalgesia.[11]

In the past few years, non-peptide, small molecule antagonists to the B1 receptor have appeared in the literature. Compounds from these reports inhibited nociceptive spinal reflex in rabbits,[12] hyperalgesia in mice,[13] and prevented neuropathic pain in rats.[14] This last study used a compound named SSR-240612 (Sanofi), which is

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reported to be in Phase I clinical trials for the treatment of chronic pain.

Given the evidence supporting the involvement of B1 in inflammation and pain, we launched an effort to identify orally available non-peptide B1 antagonists. In this report, we describe the discovery and SAR of a new class of non-peptide antagonists exemplified by compound **2**.

A pharmacophore found on many non-peptide B1 receptor antagonists contains an aryl sulfonamide, a linker group, and a basic group.[15] A compound identified early in our research program has a similar motif (see Fig. 1). Compound **1** contains a naphthyl sulfonamide attached to a β-phenylalanine (linker group) that is appended to a benzyl amine (basic group). This compound had an IC_{50} = 4.8 μM in our human B1 functional assay (calcium influx). To improve the potency of this compound, we added conformational constraints to the structure hoping to bias a bioactive conformation. To that end, we replaced the β-phenylalanine with a piperidine-2-acetic acid group and the benzyl amine group with a tetralin ring system, which resulted in a compound with two less rotatable bonds. Besides adding conformational constraints, we removed two of the phenyl rings and alkylated the terminal amine. The result was compound **2**, which was threefold more potent (IC_{50} = 1.5 μM) than compound **1**. Encouraged by these results, we prepared additional analogs in this series, which we describe in this publication.[16]

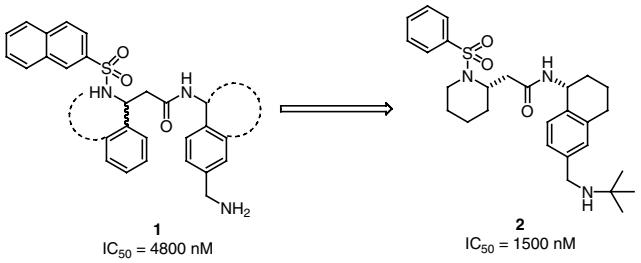
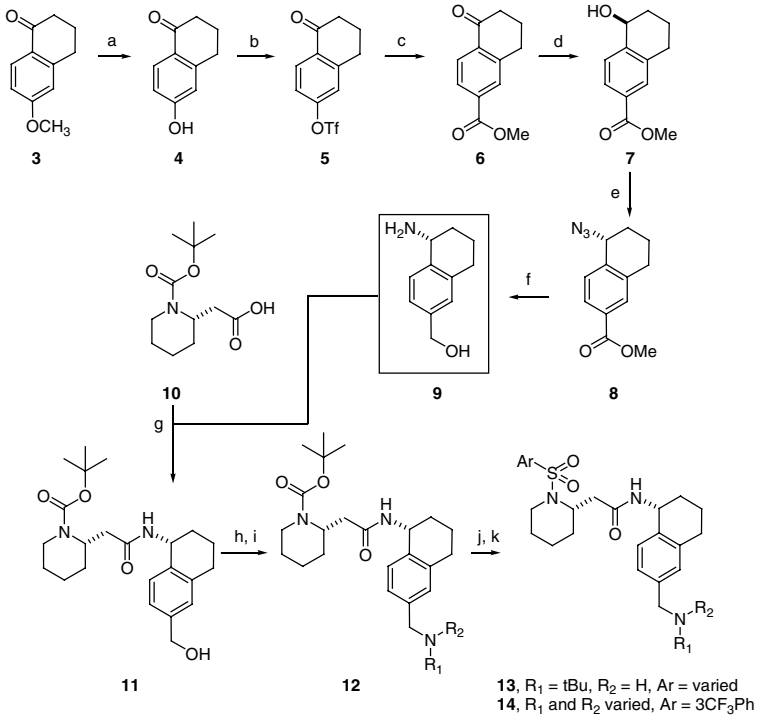


Figure 1. Design of a conformationally constrained analog.

A synthetic approach that provided analogs of **2** is outlined in Scheme 1. The tetralin portion was constructed from commercially available 6-methoxy tetralone (**3**). Demethylation of **3** using HBr provided phenol **4**, which was converted to the corresponding triflate **5**. Carbonylation of **5** with carbon monoxide in the presence of methanol gave methyl ester **6**. CBS reduction[17] of **6** gave the *S*-alcohol **7** in >99% ee. Treating alcohol **7** with diphenylphosphoryl azide and diazobicycloundecene gave the *R*-azide **8** with inversion.[18] Exhaustive reduction of **8** with $LiAlH_4$ gave the amino alcohol **9**. This product was coupled with the commercially available Boc-protected *R*-piperidine acetic acid (**10**) to give **11**. Benzylic oxidation of **11** with manganese dioxide followed by reductive amination gave compound **12**. Deprotection of **12** gave an intermediate that was sulfonylated in the last step to give an arylsulfonamide. Compounds **13a**–**q** all have the *tert*-butyl amine on the tetralin, but the arylsulfonamide group is varied. Compounds **14a**–**j** hold



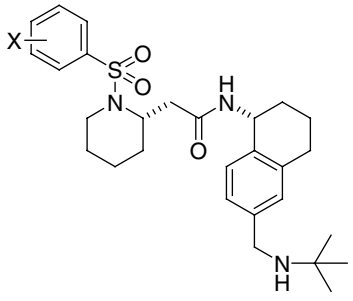
Scheme 1. Reagents and conditions: (a) 48% HBr (88%); (b) Tf_2O, Et_3N, CH_2Cl_2 (quant.); (c) 2 mol% $Pd(OAc)_2$, 2 mol% dppp, CO, DMF, MeOH, 65 °C (65%); (d) 5 mol% (*R*)-methyl CBS reagent, 1.2 equiv BH_3·DMS, toluene, −20 °C (81%); (e) 1.2 equiv. DPPA, DBU, toluene 0 °C (92%); (f) 2.1 equiv $LiAlH_4$, THF (73%); (g) HOBT, EDC, DMF; (h) MnO_2, THF; (i) $NaBH(OAc)_3$, amine, DCE; (j) HCl, EtOAc; (k) $ArSO_2Cl$, Et_3N, CH_2Cl_2.

constant the *meta*-trifluoromethylphenylsulfonamide while the amine groups are varied.

Our first step was to explore the structure–activity relationship (SAR) of the aryl group on the sulfonamide (see Table 1).[19] Analogs were prepared that contained substituents at the 4-position of the aryl ring (**13a**–**f**). The most potent compound in this set contained the 4-methyl group, compound **13a** (IC_{50} = 130 nM). Analogs with larger groups at the 4-position were tolerated, but none were as potent as **13a** (see analogs **13b**–**d**). Compounds with smaller groups at the 4-position had even higher IC_{50}s. The 4-chloro analog, **13e**, was sixfold less potent than **13a**, which suggests that potency was more affected by electronics than by size since the methyl group and chloro group have similar van der Waals radii. Even the analog with the 4-methoxy group, **13f**, was 10-fold less potent than **13a**, which was surprising since the 4-butoxy analog, **13d**, was only fivefold less potent than **13a**.

Exploring substitutions on the 3-position we found that the 3-chloro analog, **13h**, had an IC_{50} = 73 nM, and the 3-trifluoromethyl analog, **13g**, had an IC_{50} = 13 nM, which was more than 180-fold more potent than compound **2**. To see if potency could be improved by adding the 4-methyl group to these two analogs, we prepared compounds **13i** and **13k**. No improvement in potency was seen for the 3-trifluoromethyl-4-methyl analog, compound **13k** (IC_{50} = 16 nM vs 13 nM for **13a**). However, the 3-chloro-4-methyl analog, **13i**, was threefold more potent (IC_{50} = 22 nM) than the 3-chloro analog **13h**.

Table 1.



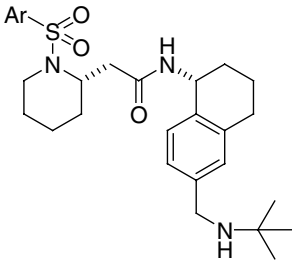
Compound	X	hB1 binding IC_{50}[a] (nM)	hB1 functional IC_{50}[a] (nM)
2	H	1700 ± 220	2400 ± 1200
13a	4-Me	93 ± 27	130 ± 50
13b	4-CF_2CF_3	360 ± 30	210 ± 30
13c	4-Ph	690 ± 80[b]	540 ± 140[c]
13d	4-$O(CH_2)_3CH_3$	1200 ± 260[b]	590 ± 70
13e	4-Cl	560 ± 70	810 ± 150
13f	4-OMe	780 ± 170[b]	1400 ± 300[b]
13g	3-CF_3	23 ± 8[b]	13 ± 8[b]
13h	3-Cl	120 ± 30	73 ± 10
13i	3-Cl, 4-Me	15 ± 5[b]	22 ± 9[b]
13k	3-CF_3, 4-Me	11 ± 3	16 ± 7

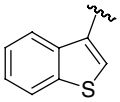
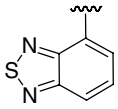
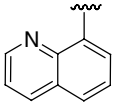
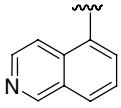
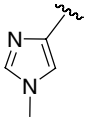
[a] Values reported represent an average of two determinations for each compound unless otherwise noted.
[b] n = 4.
[c] n = 3.

We also replaced the aryl ring with a set of heteroaryl compounds (see Table 2). The benzothiophene analog, **13m**, was the most potent compound in this set with an IC_{50} = 66 nM, while the benzthiadiazole analog, **13n**, was threefold less potent than **13m**. The potency of the quinoline and isoquinoline analogs, **13o** and **13p**, was affected by the position of nitrogen. The quinoline analog had an IC_{50} = 440 nM. However, the isoquinoline analog, **13p**, which differs from **13o** only by a small change in the position of the ring nitrogen, was 10-fold less potent than **13o**. The *N*-methylimidazole analog, **13q**, had significantly reduced activity (IC_{50} > 40 μM).

We then explored alternatives to the NH-*tert*-butyl group on **13g** by preparing a group of analogs with various other amines on the tetralin ring (see Table 3). Analogs containing branched alkyl groups were 3- to 18-fold less potent than **13g** (see compounds **14a**–**c**). Compounds that either had an amine with an electron-withdrawing or an electron-donating group were also prepared. The trifluoroethyl analog, **14d**, was 54-fold less potent than **13g**, but the methoxyethyl analog, **14e**, was only fourfold less potent than **13g**. Compounds containing amines with small cycloalkyl groups (**14f**–**14h**) all had similar potencies (IC_{50} = 30–50 nM).

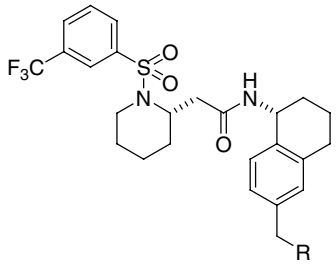
Table 2.



Compound	Ar	hB1 binding IC_{50}[a] (nM)	hB1 functional IC_{50}[a] (nM)
13m		14 ± 1	66 ± 8
13n		150 ± 20	180 ± 70[b]
13o		220 ± 50	440 ± 250[c]
13p		610 ± 130	4300 ± 110
13q		>100,000	>40,000

[a] Values reported represent an average of two determinations for each compound unless otherwise noted.
[b] n = 4.
[c] n = 3.

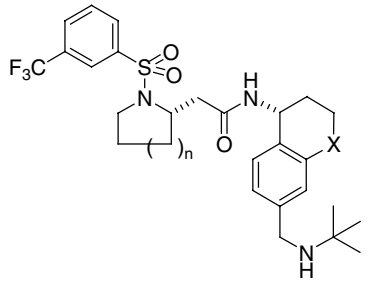
Table 3.



Compound	R	hB1 binding IC_{50}[a] (nM)	hB1 functional IC_{50}[a] (nM)
13g	NH-*tert*-butyl	23 ± 8[b]	13 ± 8[b]
14a	NH-*iso*-propyl	72 ± 1	110 ± 30
14b	$NHCH_2$-*tert*-Butyl	59 ± 12	230 ± 70
14c	NH-*iso*-butyl	13 ± 2[b]	42 ± 18[b]
14d	NH–CH_2CF_3	1900 ± 1500[c]	700 ± 480[d]
14e	NH–$CH_2CH_2OCH_3$	21 ± 5[b]	46 ± 12
14f	NH–CH_2-*cyclo*-propyl	16 ± 1	31 ± 5
14g	NH-*cyclo*-propyl	48 ± 2	47 ± 18
14h	NH-*cyclo*-butyl	58 ± 14	54 ± 4
14i	$N(CH_3)_2$	62 ± 13	160 ± 43
14j	Azetidine	1100 ± 230	4300 ± 340

[a] Values reported represent an average of two determinations for each compound unless otherwise noted.
[b] $n = 4$.
[c] $n = 32$.
[d] $n = 188$.

Table 4.



Compound	*n*	X	hB1 binding IC_{50}[a] (nM)	hB1 functional IC_{50}[a] (nM)
13g	2	CH_2	23 ± 8	13 ± 8
15a	2	O	160 ± 30[c]	95 ± 40
15b	1	O	1500 ± 10[b]	960 ± 90

[a] Values reported represent an average of four determinations for each compound unless otherwise noted.
[b] $n = 2$.
[c] $n = 6$.

Finally, two analogs containing smaller tertiary amines were tested. Dimethylamine derivative, **14i**, was 12-fold less potent than **13g**, and the analog with the azetidine group, **14j**, was 330-fold less potent than **13g**.

Derivatives containing alternatives to the piperidine and tetralin were also investigated (see Table 4). Replacing the tetralin ring on **13g** with a chroman ring[20] gave compound **15a**. This single modification from a methylene to an oxygen in the right-hand ring system resulted in a compound that was ca. sevenfold less potent than **13g**. Contracting the ring size from a piperidine to pyrrolidine ring resulted in compound **15b**, which was 10-fold less potent than **15a**.

Table 5. In vitro potency and rat pharmacokinetics of compounds **13g**[21]

hB1 binding IC_{50} (nM)	hB1 functional IC_{50} (nM)	$t_{1/2}$[a] (h)	Cl[a] (mL h^{-1} kg^{-1})	*Vss*[a] (mL kg^{-1})	Oral %*F*[b]
23 ± 8	13 ± 8	2	2200	5400	19%

[a] Dosed iv (1 mg kg^{-1}) in DMSO.
[b] Dosed po (10 mg kg^{-1}) in 2% HPMC/1% Tween 80 in water.

In summary, we have prepared several compounds with low-nanomolar IC_{50}s in the human B1 receptor functional assay. In addition, all compounds were selective for the B1 receptor since the human B2 receptor IC_{50}s were all >20,000 nM. In this series of compounds, a bulky electron-withdrawing group on the 3-position on the arylsulfonamide is preferred. Small alkyl and halo groups are tolerated at the 4-position, but larger groups are less potent. On the amine portion of this series, the groups preferred were secondary amines with branched alkyl groups. Less preferred were those amines with three carbons or fewer. Changes to the tetralin also resulted in less potent compounds.

Finally, we examined the pharmacokinetics of **13g** in rats (see Table 5) to determine how this compound might perform in vivo. This compound had a half-life of 2 h and oral bioavailability of 19%. The large volume of distribution (>5 L kg^{-1}) suggests that the compound may reach the peripheral tissue where the B1 receptor would be expressed during times of inflammation. Our efforts to modify this compound to improve the potency and pharmacokinetic profile will be reported in future publications.

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20. Compounds containing a chroman ring system were prepared by procedures that are analogous to those found in Scheme 1.
21. Analytical data for compound **13g**: ^{1}H NMR (CD_3OD) δ = 8.15 (m, 2H), 7.96 (d, 1H, J = 7.6), 7.81 (t, 1H, J = 9), 7.1–7.2 (m, 3H), 4.99 (t, 1H, J = 4), 4.66 (q, 1H, J = 5), 3.80 (dd, 1H, J = 4, 14), 3.64 (s, 2H), 3.12 (dt, 1H, J = 2, 14), 2.78 (m, 2H), 2.51 (d, 2H, J = 8), 1.2–1.9 (m, 10 H), 1.19 (s, 9 H); LC–MS 100% pure at 220 and 254 nm; *m/z* (+ion) = 566.2 (MH+); *m/z* (−ion) = 610.2 ($M+HCO_2^-$).