Bioorganic & Medicinal Chemistry Letters 18 (2008) 4764–4769

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Aryl sulfones as novel Bradykinin B1 receptor antagonists for treatment of chronic pain

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ARTICLE INFO

Article history:
Received 13 July 2008
Revised 23 July 2008
Accepted 28 July 2008
Available online 31 July 2008

Keywords:
Bradykinin antagonist
Chronic pain
Aryl sulfone

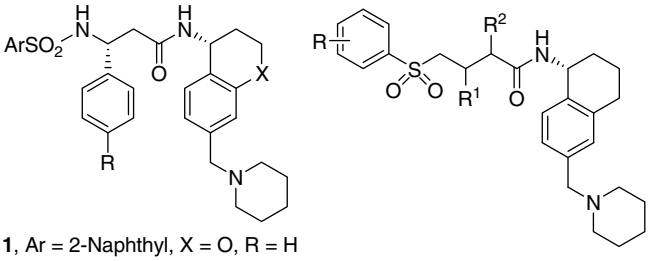
ABSTRACT

We report the development of aryl sulfones as Bradykinin B1 receptor antagonists. Variation of the linker region identified diol **23** as a potent B1 antagonist, while modifications of the aryl moiety led to compound **26**, both of which were efficacious in rabbit biochemical challenge and pain models.

The kinins, bradykinin (BK), kallidin (Lys-BK), and their des-Arg[9/10] metabolites, are vasoactive peptides that are implicated in the propagation of pain and inflammation. They are released in response to tissue injury.[1] They transmit their effects by activating two G-protein coupled receptors termed the B1 and B2 receptors. BK and Lys-BK preferentially bind to the constitutively expressed B2 receptor, which after agonist stimulation is rapidly desensitized and internalized. The B1 receptor, in contrast, is induced following tissue injury and/or inflammation, and is preferentially activated by the longer-lasting des-Arg[9/10] metabolites of BK and Lys-BK.[2] Preclinical studies suggest that the B2 receptor plays a significant role in acute pain processing, while the B1 receptor has been implicated in establishing and maintaining the signaling for chronic pain.[3]

Recently, extensive preclinical research supporting the validity of the B1 receptor as a target for treatment of chronic pain has been published. Peptide antagonists of this receptor have been shown to reverse neurogenic pain induced by capsaicin, and inflammatory pain induced by UV irradiation, carrageenan, complete Freund's adjuvant, or bacterial lipopolysaccharide (LPS).[4] Established hyperalgesia has been shown to be reversed by synthetic peptide B1 antagonists in models of neuropathic pain like streptozotocin-induced diabetes, chronic constriction injury, and partial sciatic nerve lesion.[5]

In addition to peptide antagonists, reports with small-molecule antagonists have also offered corroboration of the role that the B1 receptor plays in chronic pain.[6] These experiments have demonstrated the efficacy of lead compounds in pain and/or biochemical challenge models, such as inflammatory hyperalgesia, neuropathic pain, spinal nociceptive reflex, and B1-mediated hypotension.



1, Ar = 2-Naphthyl, X = O, R = H

2, Ar = 2-Naphthyl, X = CH_2, R = H

3, Ar = 3-CF_3-Ph, X = O, R = F

4, R^1 and R^2 = H/Aryl/OH/alkoxy

Figure 1. Lead arylsulfonamide-based bicyclic amine B1 antagonists and analogous sulfones.

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doi:10.1016/j.bmcl.2008.07.108

These studies support the search for oral small-molecule B1 antagonists as therapy for chronic pain.

Our initial investigations led to arylsulfonamide lead compounds containing bicyclic amine carboxamide moieties (Fig. 1).[7] Structure–activity relationship (SAR) studies on the initial leads **1** and **2** identified compound **3**, which showed modest efficacy in two rabbit in vivo models, a B1-mediated hypotension biochemical challenge model and an efficacy model of inflammatory pain.[8] While these sulfonamides were excellent proof-of-concept molecules, we continued to seek analogs with improved pharmacokinetic and pharmacodynamic properties. In particular, we hoped to address the high human and rat liver microsomal clearance observed with these leads (see compound **2** in Table 1) by making changes to the molecular framework of these compounds.

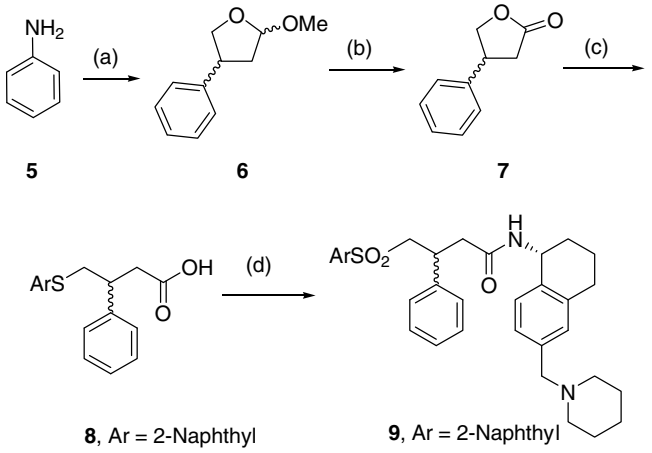
In designing alternative B1 antagonists toward these goals, we sought to introduce small, polar groups in the linker region in combination with searching for replacements for the lipophilic aryl ring of the β-arylglycine core. These investigations, we hoped, would ameliorate the observed oxidative instability in microsomal preparations. Modifying the sulfonamide in compounds **1**–**3** to the corresponding sulfone moiety (substitution of the N–H unit by a CH_2 fragment) would allow the replacement of the core aryl ring with groups like hydroxyl and ether groups, compounds previously unattainable due to unstable aminal-like structures. Hence, as part of this SAR study, we decided to prepare sulfones of the general structure **4** (Fig. 1). Herein, we report on the identification and optimization of aryl sulfone-based B1 antagonists, which led to lead compounds with improved efficacy compared to sulfonamide **3** in animal models for evaluation of in vivo activity.

The compounds that were synthesized as part of this study are shown in Tables 1 and 2, and their preparations are described in Schemes 1–3.[9] Scheme 1 outlines the synthesis of the sulfone analog of sulfonamide **2**, compound **9**. Tetrahydrofuran **6** was obtained from aniline (**5**) via conversion to the diazonium salt, Pd(0)-mediated Heck reaction with dihydrofuran and trapping with methanol.[10] Jones oxidation gave lactone **7**, reaction of which with 2-naphthalenethiolate sodium salt afforded sulfide **8**. Oxidation with Oxone® and amide bond formation with (*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-amine[11] gave the final compound **9**. Compound **10** was synthesized from γ-butyrolactone using a similar protocol.

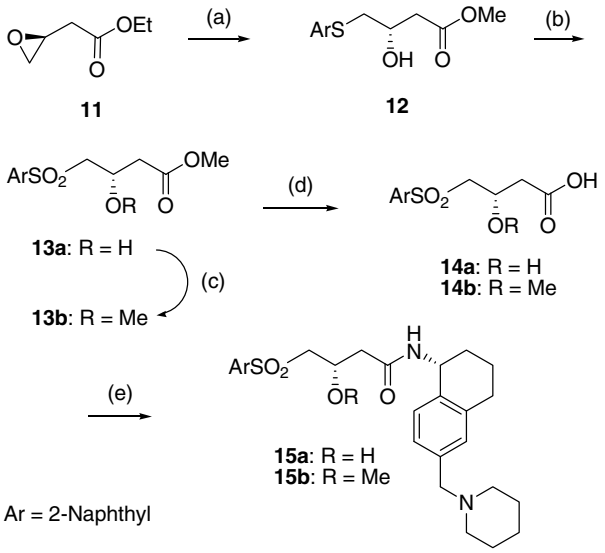
Scheme 2 illustrates the synthesis of the hydroxyl and methyl ether analogs **15a** and **15b**. The commercially available chiral oxirane ethyl ester **11** was treated with sodium 2-naphthalenethiolate in methanol, resulting in ring-opened alcohol **12**. Oxidation afforded sulfone **13a**. The alcohol was converted to the methyl ether with iodomethane for analog **13b**. The corresponding esters were deprotected and individually coupled to (*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-amine in the usual manner, affording the desired final compounds.

The diastereomeric alcohol **16** was prepared from intermediate **13a**. Oxidation of the alcohol to a ketone, reduction to the racemic alcohol with sodium borohydride, and chiral separation with SFC afforded the enantiomer *ent*-**13a**, which was then converted to the final compound in a sequence similar to Scheme 2.

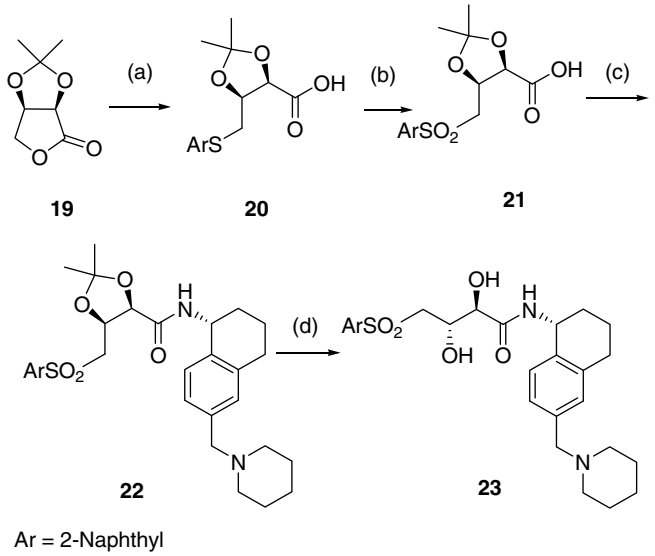
Diastereomeric hydroxyl analogs **17** and **18a** were prepared via the lactone ring-opening procedure outlined in Scheme 1, from corresponding commercially available chiral hydroxy-butyrolac-



Scheme 1. Reagents and conditions: (a) sodium nitrite, 1 M HCl, 0 °C, then dihydrofuran, $Pd(OAc)_2$, MeOH, 71%;[9] (b) Jones reagent, acetone, 91%; (c) 2-naphthalenethiol, NaH, DMF, 0 °C, then **7**, 100 °C, 91%; (d) (i) Oxone®, MeOH, dioxane, water, 88%; (ii) (*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-amine, EDCI, HOBt, DMF, 75%.



Scheme 2. Reagents and conditions: (a) 2-naphthalenethiol, K_2CO_3, MeOH, 82%; (b) Oxone®, methanol, water, 0 °C–rt, 92%; (c) MeI, NaH, DMF, 0 °C, 76%; (d) LiOH, THF, water, 98% for **14a**, 99% for **14b**; (e) (*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-amine, EDCI, HOBt, DMF, 68% for **15a**, 80% for **15b**.



Scheme 3. Reagents and conditions: (a) 2-naphthalenethiol, NaH, DMF, 0 °C, then **19**, 80 °C, 91%; (b) Oxone®, methanol, water, 94%; (c) (*R*)-6-(piperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-1-amine, EDCI, HOBt, DMF, 69%; (d) HCl (4.0 M in dioxane), methanol, 100%.

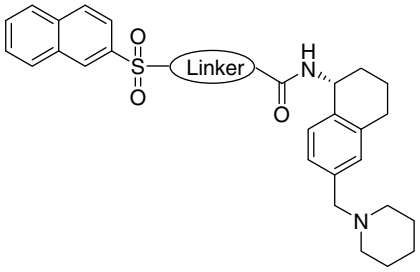
tones. Methyl ether analog **18b** was prepared from iodomethane-mediated alkylation of the corresponding hydroxyl analog intermediate obtained during the synthesis of **18a**.

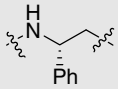
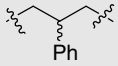
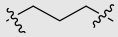
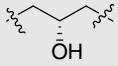
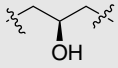
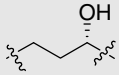
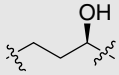
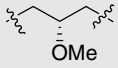
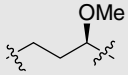
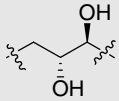
Finally, the synthesis of diol **23** is shown in Scheme 3. Ring opening of the commercially available erythronolactone ketal **19** with 2-naphthalenethiolate anion afforded acid **20**. Oxidation to the sulfone, peptide bond formation, and ketal deprotection with dilute hydrochloric acid afforded the final compound.

The diol compounds shown in Table 2 (compounds **24**–**32**) were prepared by the method outlined in Scheme 3 using corresponding commercially available aryl thiols in the first step.

The compounds synthesized as part of this study were tested in a human B1 receptor binding assay and a human B1 agonist-induced aqueorin-based calcium flux assay in Chinese hamster ovary cells.[7] This discussion is focused on the binding assay data, although similar trends were seen in the functional assay. SAR of the linker region is described in Table 1. Initially, sulfonamide **2** was compared to the corresponding sulfone analog **9**. Encouragingly, the resulting modest sixfold loss in binding affinity showed that the N–H moiety was not an absolute requirement for binding. The high metabolic clearance in human liver microsomal assays, however, remained with the modification to compound **9**. To fur-

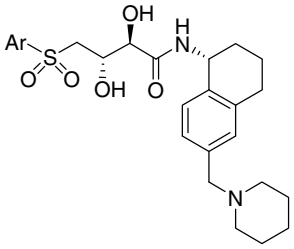
Table 1
SAR of linker region: hB1 binding and functional assay data



Compound	Linker	hB1		HLM (μL/min/mg)	RLM (μL/min/mg)
		Binding K_i[a] (nM)	Aqn IC_{50}[a] (nM)		
2		0.24 ± 0.03	5.5 ± 0.7	919	572
9		1.5	13.7 ± 2.5	744	167
10		59.9	74.8 ± 9.3	50	100
15a		41.4 ± 9.5	48.9 ± 7.9	112	100
16		100	107 ± 21	ND	ND
17		19.1	30.8 ± 2.8	100	143
18a		23.5 ± 5.0	50.6 ± 7.0	100	50
15b		6.4 ± 0.5	16.8 ± 5.6	274	316
18b		169 ± 56	79 ± 21	216	237
23		1.7 ± 0.7	4.0 ± 0.3	100	186

HLM, RLM $n = 1$. ND, not determined.
[a] Values reported are an average of at least 3 determinations with the SEM, unless otherwise noted (values without SEM represent the average of 2 determinations).

Table 2
SAR of aryl region: human and rabbit B1 K_i and IC_{50} data



Compound	Ar	hB1		Rabbit B1 Aqn IC_{50}[a] (nM)	HLM (μL/min/mg)	RLM (μL/min/mg)
		Binding K_i[a] (nM)	Aqn IC_{50}[a] (nM)			
23	2-Naphth	1.7 ± 0.7	4.0 ± 0.3	20.0 ± 1.8	100	186
24	Ph	565 ± 86	977	ND	319	50
25	2-CF_3-Ph	43.8 ± 4.4	297.2	ND	ND	ND
26	3-CF_3-Ph	4.1 ± 0.4	4.3 ± 1.0	11.2 ± 1.9	100	50
27	4-CF_3-Ph	48.4 ± 9.7	44.9	210	50	50
28	3-Cl-Ph	54.4 ± 10.7	39.2 ± 12.2	85.9 ± 7.8	180	139
29	4-Me-Ph	138 ± 26	84.2 ± 9.5	ND	50	50
30	4-*t*Bu-Ph	15.8	4.5 ± 0.8	25.3 ± 6.2	296	50
31	3,4-di-Cl-Ph	16.9	17.1 ± 4.5	20.3 ± 3.8	100	193
32	2,3-di-Cl-Ph	12.7 ± 3.1	9.9	141	214	50

HLM, RLM $n = 1$. ND, not determined.
[a] Values reported are an average of at least 3 determinations with the SEM, unless otherwise noted (values without SEM represent the average of 2 determinations).

ther address this metabolism, we began exploring variations in the linker region. We decided to replace the phenyl moiety with select polar functional groups to test the hypothesis that improving polarity might reduce oxidative metabolism. To establish this SAR, the 2-naphthyl sulfone and the tetralin benzylic amine moieties were kept unchanged.

Compound **10**, with the unsubstituted 3-carbon linker, lost affinity, with $K_i = 59.9$ nM. The (*S*)-hydroxyl analog of **9**, compound **15a**, exhibited a $K_i = 41.4$ nM, while the corresponding (*R*)-hydroxyl analog **16** had a $K_i = 100$ nM. Moving the hydroxyl group one carbon towards the amide carbonyl moiety afforded compounds **17** and **18a**, which had hB1 K_is of 19.0 and 23.5 nM, respectively. The methoxy analog of **15a**, compound **15b**, was only fourfold less potent than **9** ($K_i = 6.4$ nM), while the methylated analog of **18a**, compound **18b**, was less potent ($K_i = 169$ nM). Examination of the liver microsomal assay data showed that while the hydroxyl compounds (**15a**, **17**, and **18a**) possessed improved stability, both methoxy analogs, compounds **15b** and **18b**, were susceptible to greater metabolism. Finally, incorporation of both hydroxyl groups in the same molecule in the *2R, 3S*-configuration afforded compound **23**, which restored binding affinity equivalent to analog **9**. In terms of metabolic profiling of these analogs, a general trend emerged indicating that the hydroxyl group modification conferred the most advantage with regard to stability in liver microsomal assays. This improved metabolic stability, together with the potent binding affinity, directed us toward further optimization of compound **23.**

We established in vivo models in rabbits since these B1 antagonists are not potent at the rodent B1 receptors, but show cross-reactivity with the rabbit.[8] In order to examine the in vivo efficacy of our leads, we sought to optimize the SAR for compounds which show potency at both the human and rabbit B1 receptors. Thus, we also obtained rabbit B1 IC_{50}s from a functional assay to establish the corresponding SAR at the rabbit receptor. Compound **23** was examined initially, and it was shown to be a potent antagonist (rabbit B1 $IC_{50} = 20$ nM). Consequently, we next explored the SAR of the aryl region in compound **23** to identify analogs of the lipophilic naphthyl domain that while maintaining potency might show further improvements in pharmacokinetic or pharmacodynamic parameters (*vide supra*). The B1 binding and functional assay data are shown in Table 2.

The phenyl sulfone **24** lost potency, with hB1 $K_i = 565$ nM. Substitution with lipophilic functional groups on the aryl ring, however, improved the hB1 binding affinity. First, we synthesized the 2-, 3-, and 4-trifluoromethyl substituted phenyl sulfones (compounds **25**–**27**). The 3-trifluoromethylphenyl sulfone **26** was most potent, with hB1 $K_i = 4.1$ nM. The corresponding 3-chlorophenyl analog **28** was 30-fold less potent than **23**, with hB1 $K_i = 54.4$ nM. The 4-tolyl analog **29** lost potency, while the 4-*tert*-butylphenyl sulfone **30** was ninefold less potent than **23** (hB1 $K_i = 15.8$ nM). The di-chlorophenyl substituted analogs **31** and **32** were similar in potencies, with K_is of 16.9 and 12.7 nM, respectively.

The 3-trifluoromethylphenyl sulfone **26** was the most potent on rabbit B1 receptor as well ($IC_{50} = 11.2$ nM). Compounds **23**, **30**, and **31** also had rabbit IC_{50}s in the 20–25 nM range.[12]

Table 3
Pharmacokinetic parameters of compounds **23** and **26**

Compound	Rat in vivo PK				Human PPB (%)	Rabbit PPB (%)
	$t_{1/2}$[a] (h)	Cl[a] (L/h/kg)	V_{ss}[a] (L/kg)	F[b] (%)		
23	2.99	4.6	6.0	14	97.54	95.26
26	4.74	7.3	27.9	18	71.79	78.38

$t_{1/2}$ = half-life, Cl = clearance, V_{ss} = volume of distribution, F = oral bioavailability, PPB = plasma protein binding.
[a] Sprague–Dawley rats dosed i.v. at 3 mg/kg in 100% water/methanesulfonic acid (pH 3.0).
[b] Sprague–Dawley rats dosed p.o. (same dose and formulation).

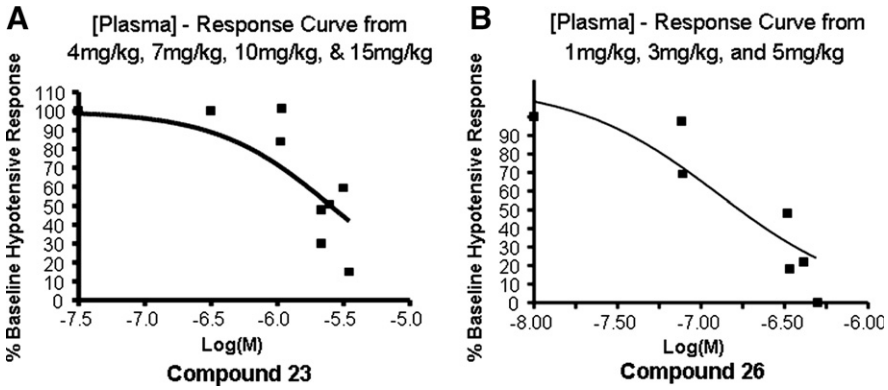


Figure 2. (A) Compound **23** and (B) compound **26** reduce DAK-induced hypotension. For details, see Ref. 8. The *x*-axis shows the measured plasma concentration of the compound. In this study, the plasma IC_{50} for compound **23** is 2500 nM ($CI_{95\%}$ 1277–5010 nM, $R^2 = 0.6616$), while that for compound **26** is 127 nM ($CI_{95\%}$ 34–459 nM, $R^2 = 0.8191$).

Pharmacokinetic parameters of the compounds with highest hB1 binding affinity, compounds **23** and **26**, were profiled next. These data are shown in Table 3. In rats, compound **23** had a half-life of 3 h, high clearance, and low oral bioavailability of 14%. Similarly, compound **26** had a half-life of 4.7 h, high clearance, and oral bioavailability of 18%. As seen in Table 2, both compounds showed lower susceptibility to metabolism in liver microsomes, suggesting other mechanisms for the high rat in vivo clearance. One major difference emerged in plasma protein binding, with the 3-trifluoromethyl analog **26** being less bound in both human and rabbit plasma (in vivo models were developed in rabbits, see below). This encouraging finding was next examined in context of in vivo activity of these compounds.

We tested compounds **23** and **26** in two rabbit pharmacodynamic models described previously.[8] In the first biochemical challenge model, administration of LPS upregulates B1 receptors, and B1 agonists (e.g., DAK: des-Arg[10]-Kallidin) induce a hypotensive response.[13] This effect can be reversed with B1 antagonists.[8] Rabbits were treated with five different doses of compounds, followed by repeat administration of the agonist DAK at two different time points (30 and 75 min). Blood samples were collected prior to the DAK administrations to obtain plasma concentrations of each compound, which were correlated with the hypotensive responses, thus generating two data points for each dose (Fig. 2). As seen in Figure 2, both compounds, injected subcutaneously (s.c.), reversed this hypotension effect in a dose-dependent fashion, with plasma IC_{50}s of 2500 nM (compound **23**) and 127 nM (compound **26**). Interestingly, both compounds are more potent in this model than our previously described lead compound, sulfonamide **3**.[14]

In a model of inflammatory pain, mechanical hyperalgesia was induced in the rabbit hind paw using local injection of carrageenan. Systemic (s.c.) injection of either compound reversed hyperalgesia when administered 2 h after carrageenan (Fig. 3).[15] Compound **26** was more efficacious, with a plasma $EC_{50} = 402$ nM, while compound **23** exhibited a plasma $EC_{50} = 3600$ nM. This rank order of the two compounds parallels the results found in the biochemical challenge model. In addition, both sulfones were also more efficacious than sulfonamide **3**, which showed a maximal reversal of 45.5% at a 10 mg/kg dose. The higher efficacy seen with **26** might perhaps be attributable to the higher free fraction of drug present, compared to **23**.

In summary, we report the identification of aryl sulfone-based B1 antagonists. The replacement of the sulfonamide N–H fragment with a CH_2 unit allowed the introduction of polar replacements of the lipophilic core aryl group in **1–3**, where it was found that incorporation of hydroxyl groups leads to the largest benefit in attenuating metabolic instability. SAR of the linker region led to selection of the (*2R,3S*)-2,3-dihydroxy-butanamide moiety (compound **23**)

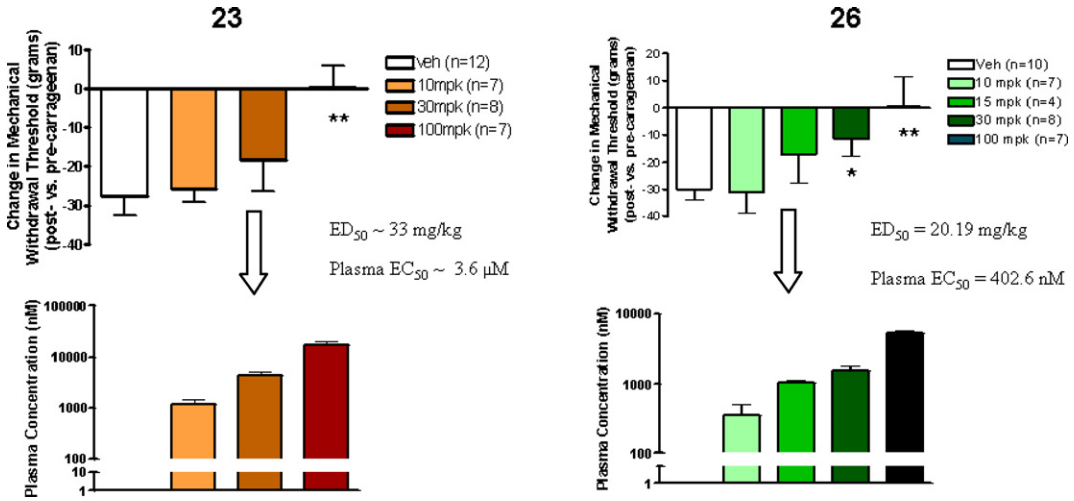


Figure 3. Antinociceptive effects of test compounds **23** and **26** in a rabbit inflammatory pain model (carrageenan-induced mechanical hyperalgesia). Plasma levels of both compounds are also included for each dose. The vehicle was 20% Captisol® in water. $^{*}P < 0.05$, $^{**}P < 0.01$, one-factor ANOVA followed by Dunnett's post hoc multiple comparison test, as compared with the vehicle (s.c.) group.

for further exploration of the aryl region. The 3-trifluoromethylphenyl group (compound **26**) emerged as a potent replacement for the naphthyl moiety, in terms of activity at both the human and rabbit B1 receptors. Both compounds showed activity in two rabbit in vivo models, and are more potent than our previously described lead, sulfonamide **3**. Compound **26** is more efficacious in both the rabbit blood pressure model and the carrageenan-induced mechanical hyperalgesia pain model, suggesting the possible role of greater unbound drug concentration.

Acknowledgment

The authors thank Dr. Jennifer R. Allen and Dr. Christopher Fotsch for critical reading of this letter.

References and notes

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