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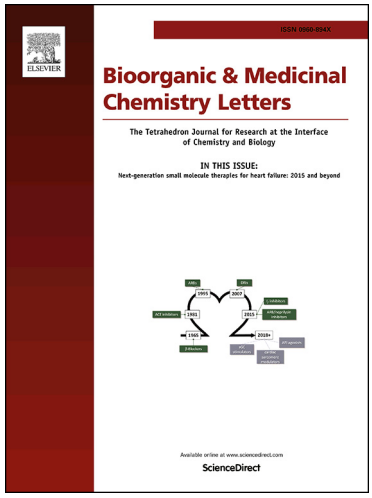

Discovery of 2-(3,5-Difluoro-4-methylsulfonaminophenyl)propanamides as Potent TRPV1 Antagonists

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Graphical Abstract

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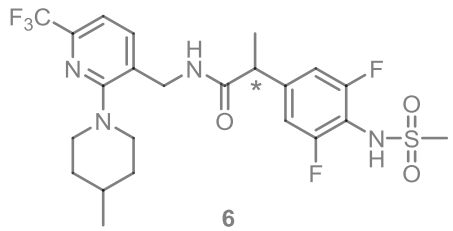

6

Activators, parameter	6
***h*TRPV1**	
CAP (f)K_i (nM)	0.2
pH, IC_{50} (nM)	8.7
heat 45°C, IC_{50} (nM)	8.1
***r*TRPV1**	
CAP (f)K_i (nM)	0.1

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Discovery of 2-(3,5-Difluoro-4-methylsulfonaminophenyl)propanamides as Potent TRPV1 Antagonists

Changhoon Kim [a], Jihyae Ann [a], Sunho Lee [a], Wei Sun [b], Peter M. Blumberg [c], Robert Frank-Foltyn [d], Gregor Bahrenberg [d], Hannelore Stockhausen [d], Thomas Christoph [d], Jeewoo Lee [a,*]

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ABSTRACT

A series of A-region analogues of 2-(3-fluoro-4-methylsufonamidophenyl) propanamide **1** were investigated as TRPV1 antagonists. The analysis of structure-activity relationship indicated that a fluoro group at the 3- (or/and) 5-position and a methylsulfonamido group at the 4-position were optimal for antagonism of TRPV1 activation by capsaicin. The most potent antagonist **6** not only exhibited potent antagonism of activation of *h*TRPV1 by capsaicin, low pH and elevated temperature but also displayed highly potent antagonism of activation of *r*TRPV1 by capsaicin. Further studies demonstrated that antagonist **6** blocked the hypothermic effect of capsaicin *in vivo*, consistent with its *in vitro* mechanism, and it showed promising analgesic activity in the formalin animal model.

The transient receptor potential vanilloid 1 (TRPV1), a key nociceptor triggering C-fiber sensory neurons, represents a promising therapeutic target for the treatment of neuropathic pain and a wide range of other conditions in which C-fiber sensory neurons are involved.[1-3] The TRPV1 nociceptor is activated by elevated temperature, by low pH, and by both endogenous endovanilloids and exogenous agents such as capsaicin, as well as being responsive to the state of the signaling pathways in the cells.[4-7] Although intense efforts has been directed at the development of potent TRPV1 antagonists,[8] side effects such as hyperthermia or loss of sensitivity to heat pain represent an on-going challenge. Recognition that different modes of TRPV1 activation are differentially associated with some side effects and are differentially manipulable by ligands provides powerful motivation for detailed understanding of TRPV1 structure-activity relations.[3,9]

Previously, we have investigated an extensive series of 2-(3-fluoro-4-methylsulfonamidophenyl)propanamides as human TRPV1 antagonist.[10-21] Among them, antagonist **1** (R_1=F, R_2=H, R_3=H, R_4=Me in **Figure 1**) showed highly potent antagonism for multiple activators including capsaicin ($K_{i(CAP)}$ = 0.2 nM, activity of the *S*-isomer), *N*-arachidonoyl dopamine (NADA), low pH and heat (45 ^{o}C). This antagonism was stereospecific to the *S*-configuration in the propanamide. Consistent with the *in vitro* mechanism of action, compound **1** antagonized capsaicin-induced hypothermia in mice and demonstrated a strong antiallodynic effect in neuropathic pain models. The basis for its high potency was shown by molecular docking studies using our established *h*TRPV1 homology model,[10] indicating that the 6-trifluoromethyl group and the 2-substituent in the pyridine C-region made hydrophobic interactions with pockets composed of Leu547/Thr550 and Met514/Leu515, respectively, regions that have been identified as critical for potent antagonism.[10-14]

The pharmacophoric region of antagonist **1** can be divided into so-called A, B and C-regions, as previously described for capsaicin (**Figure 1)**. The analysis of the structure activity relationships (SAR) of **1** have initially focused on the C-region, in which a variety of functional groups including the amino[10], oxy[11], thio[12], alkyl[13], aryl[14] and sulfonamido[15] groups were incorporated at the 2-position of 6-trifluorophenylpyridine along with substitution at the 6-position with a *tert*-butyl group[16] as well as with the pyridine core modified by its isomers[17] or replaced by phenyl[18] and pyrazole[19] surrogates. In addition, the SAR of the B-region propanamide group was also explored by the substitution with alpha-substituted acetamide[20] and urea[21] surrogates.

As part of our continuing effort to optimize TRPV1 antagonists as clinical candidates for neuropathic pain, we herein have investigated the SAR of the A-region corresponding to the

3-fluoro-4-methylsulfonylaminophenyl group in **1**. In this study, we modified the 3-position (R_1) and 5-position (R_2) on the phenyl ring, and incorporated various substituents on the nitrogen (R_3) and sulfur (R_4) of the sulfonamide group (**Figure 1**).

We describe the synthesis of a series of 3,5-substituted 4-sulfonamidophenyl derivatives and characterize their antagonism toward activation of *h*TRPV1 by capsaicin. With a selected potent antagonist in the series, we further characterized in detail its *in vitro* activities and mode of action *in vivo*.

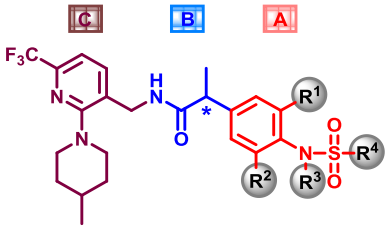
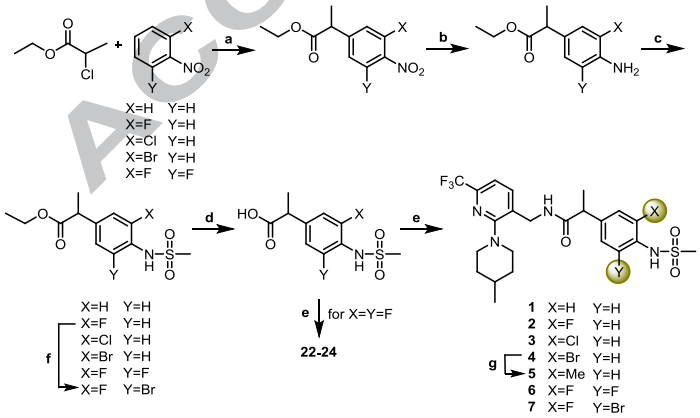


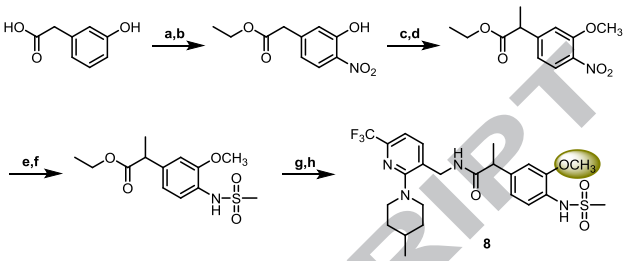
Figure 1. Modification on the 4-methylsulfonamidophenyl A-region

The syntheses of 3,5-substituted 4-methylsulfonamido phenyl analogues are described in **Schemes 1-3**. For the synthesis of 3 (or/and 5)-halo analogues (**Scheme 1**), Makosza's vicarious nucleophilic substitution[22] of 2-halonitrobenzenes with ethyl 2-chloropropanoate provided the corresponding ethyl 2-(4-nitrophenyl)propionates in good yields. The nitro groups were reduced to the corresponding amines by either hydrogenation or tin(II) chloride reduction and were then converted to the 4-methylsulfonamino groups. Their esters were hydrolyzed to the corresponding acids, which were coupled with the C-region amine, (2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methanamine, to afford the final 3,5-halo analogues (**1**-**4**, **6**). The bromination of ethyl 2-(3-fluoro-4-methylsulfonamido phenyl)propionate at the 5-position by oxybromination followed by the preceding method, including hydrolysis and the coupling reaction, gave the 3-fluoro-5-bromo analogue (**7**). The 3-methyl analogue (**5**) was synthesized from the corresponding 3-bromo analogue (**4**) by Migita-Kosugi-Stille coupling[23]. The C-region derivatives (**22**-**24**) of the 3,5-difluoro analogue (**6**) were synthesized using the corresponding C-regions previously reported.[12,19]



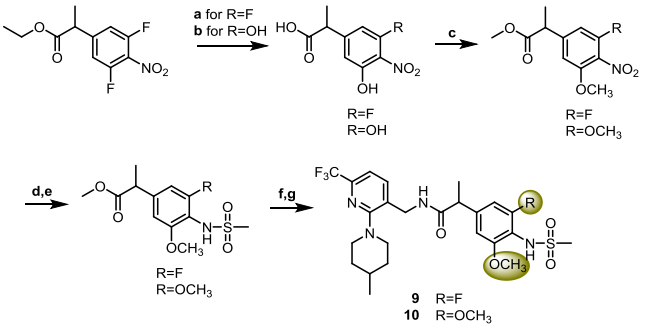
Scheme 1. Synthesis of 3 (or/and 5)-halo analogues
Reagents and conditions: (a) t-BuOK, DMF, 30 ˚C; (b) Pd/C, H_2, EtOH, r.t. or $SnCl_2.2H_2O$, EtOH, reflux; (c) MsCl, pyridine, 0 ºC to r.t.; (d) LiOH·H_2O, THF/H_2O (1:1), r.t.; (e) RNH_2, EDC, HOBt, TEA, CH_3CN (or DMF) (f) oxone, NaBr, acetone/water; (g) $Pd(PPh_3)_4$, $SnMe_4$, toluene, reflux.

For the synthesis of the 3-methoxy analogue (**8**), ethyl 2-(3-hydroxyphenyl)acetate was nitrated and then *O*-methylated to give the nitro intermediate. By following the preceding method, the final **8** was readily obtained (**Scheme 2**).



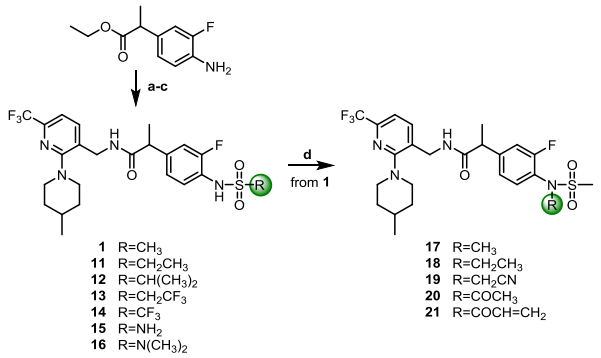
Scheme 2. Synthesis of the 3-methoxy analogues
Reagents and conditions: (a) cH_2SO_4, EtOH, reflux; (b) HNO_3, AcOH, 0 ºC; (c) K_2CO_3, MeI, acetone, r.t.; (d) NaH, MeI, 0 ºC to r.t.; (e) Pd/C, H_2, THF/EtOH, rt; (f) MsCl, pyridine, 0 ºC to r.t.; (g) LiOH·H_2O, THF/H_2O (1:1), r.t.; (h) RNH_2, EDC, HOBt, TEA, CH_3CN

For the syntheses of the 3-fluoro-5-methoxy (**9**) and 3,5-dimethoxy (**10**) analogues, ethyl 2-(3,5-difluoro-4-nitrophenyl)propionate was selectively converted to either monohydroxy or dihydroxy analogues under appropriate hydrolysis and were then *O*-methylated to afford the 4-nitro propionate intermediates. By following the preceding method, **9** and **10** were readily obtained (**Scheme 3**).



Scheme 3. Syntheses of the 3-fluoro-5-methoxy and 3,5-dimethoxy analogues
Reagents and conditions: (a) LiOH, THF/H_2O, reflux, 12 h; (b) NaOH, DMSO, reflux, 12 h; (c) MeI, NaH, DMF, 0 ˚C to r.t.; (d) Pd/C, H_2, EtOH, r.t.; (e) MsCl, pyridine, 0 ºC to r.t.; (f) LiOH·H_2O, THF/H_2O (1:1), r.t.; (e) RNH_2, EDC, HOBt, TEA, CH_3CN

The syntheses of 3-fluoro-4-(substituted)sulfonamido analogues are described in **Scheme 4**. Starting from ethyl 2-(4-amino-3-fluorophenyl)propanoate prepared in Scheme 1, the *N*-sulfonylation with various sulfonyl chlorides followed by the preceding method provided the final 4-sulfonamido/sulfamoylaminophenyl analogues (**11**-**16**). Meanwhile, the 4-methylsulfonamidophenyl analogue (**1**) was alkylated or acylated on the nitrogen of the sulfonamido group to afford the final *N*-substituted sulfonamidophenyl analogues (**17**-**21**).

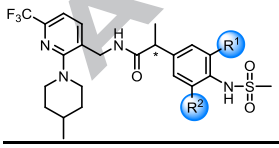


Scheme 4. Syntheses of 3-fluoro-4-(substituted)sulfonamido analogues
Reagents and conditions: (a) RSO_2Cl, pyridine, 0 °C to r.t.; (b) $LiOH{\cdot}H_2O$, THF/H_2O (1:1), r.t.; (c) RNH_2, EDC, HOBt, TEA, CH_3CN; (d) MeI, K_2CO_3, ACN, 18-C-6, reflux, 8 h for **17**; EtI, K_2CO_3, ACN, 18-C-6, reflux for **18**; 2-iodoacetonitrile, K_2CO_3, ACN, 18-C-6, reflux for **19**; Ac_2O, pyridine/THF (1:1), reflux, 12 h for **20**; 3-bromopropanoyl chloride, K_2CO_3, ACN, 18-C-6, reflux for **21**.

The *in vitro* assay was conducted using a fluorometric imaging plate reader (FLIPR) with *h*TRPV1 heterologously expressed in Chinese hamster ovary (CHO) cells.[10] The antagonistic activity of the synthesized compounds was measured by inhibition of TRPV1 activation by capsaicin (100 nM) and expressed as binding affinity ($K_{i(CAP)}$). The results are summarized in **Tables 1-3** and the activities are compared to that of the potent antagonist **1** ($K_{i(CAP)}$ = 0.3 nM) previously reported.[10]

First, we investigated the SAR of 3,5-substituted A-region analogues (**Table 1**). The unsubstituted analogue (**2**) was 4-fold less active than **1**. In the SAR of 3-substituted analogues, the substitution of the 3-fluoro group with other halogens, including chloride (**3**) and bromide (**4**), decreased the antagonism progressively as the size increased. On the other hand, the substitution with electron-donating groups, including methyl (**5**) and methoxy (**8**) groups, led to relatively little reduction in antagonistic potency. In the SAR of 3,5-disubstituted analogues, incorporation of an additional fluoro group at the 5-position in **1** further enhanced the antagonism to afford the highly potent antagonist **6** with a $K_{i(CAP)}$ = 0.2 nM. On the other hand, incorporation of bromo (**7**) and methoxy (**9**) groups caused a slight reduction in antagonism. The 3,5-dimethoxy analogue (**10**) exhibited a 2-fold reduction in antagonism compared to that of the 3-methoxy analogue (**8**).

Table 1. *In vitro h*TRPV1 antagonistic activities for 3,5-substituted 4-methylsulfonamidophenyl derivatives



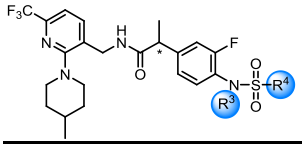
	R_1	R_2	$K_{i(CAP)}$ (nM)
1	F	H	0.3[a]
2	H	H	1.2 (±0.17)
3	Cl	H	2.3 (±0.38)
4	Br	H	3.2 (±0.82)
5	Me	H	0.6 (±0.13)
8	OMe	H	0.8 (±0.04)
6	F	F	0.2 (±0.07)
7	F	Br	0.7 (±0.19)
9	F	OMe	0.3 (±0.02)
10	OMe	OMe	1.6 (±0.17)

[a] refer 10

Overall, the SAR analysis of ring substitution in **1** indicated that the fluoro group at the 3- and 5- positions was the optimal substituent for potent antagonism.

Next, we explored the SAR of the 4-methylsulfonamido moiety in **1** (**Table 2**). The increase in the size of alkyl group, providing **11** and **12**, led to a progressive decrease in antagonism. The substitution of the terminal methyl group in **11** with the electron-withdrawing trifluoromethyl group (**13**) led to a further reduction in antagonism. Meanwhile, while the replacement of the methyl group of **1** by the electron-withdrawing trifluoromethyl group (**14**) almost abolished the antagonism, the substitution with an electron-donating amino group (**15**) led to only a 9-fold reduction in antagonism. The *N*-dimethylsulfamoyl analogue (**16**) showed further reduction in antagonism compared to **15** due to its increased size, in line with the SAR of alkyl groups. The nitrogen of the 4-methylsulfonamido group was also modified by adding different substituents. The incorporation of alkyl groups, such as the methyl (**17**), ethyl (**18**) and cyanomethyl (**19**) groups, led to dramatic loss in antagonism. In addition, the incorporation of an acyl group, such as the acetyl (**20**) and acryl (**21**) groups, also caused a decrease in antagonism, but with less extent compared to those of the alkyl groups. Overall, the SAR of the methylsulfonamido group in **1** indicated that any modification led to the reduction in antagonism, suggesting that the methylsulfonamido group was the optimal group at the 4-position for antagonism.

Table 2. *In vitro h*TRPV1 antagonistic activities for *N*-substituted 3-fluoro-4-sulfonamidophenyl derivatives

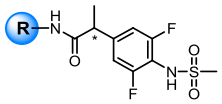


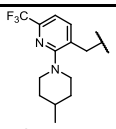
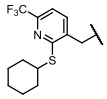
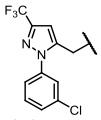
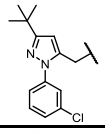
	R_3	R_4	$K_{i(CAP)}$ (nM)
1	H	CH_3	0.3
11	H	CH_2CH_3	4.4 (±0.89)
12	H	$CH(CH_3)_2$	8.7 (±1.34)
13	H	CH_2CF_3	43.7 (±6.8)
14	H	CF_3	WE
15	H	NH_2	2.7 (±0.73)
16	H	$N(CH_3)_2$	42 (±5.6)
17	CH_3	CH_3	55.5 (±8.3)
18	CH_2CH_3	CH_3	22.7 (±4.1)
19	CH_2CN	CH_3	WE
20	$C(=O)CH_3$	CH_3	11.9 (±2.2)
21	$C(=O)CH=CH_2$	CH_3	2.4 (±0.64)

Finally, since the 3,5-difluoro analogue (**6**) was found to be the most potent antagonist in this series, we further investigated its representative C-region analogues (**Table 3**). As anticipated, all of the pyridine and pyrazole C-region analogues displayed potent antagonism with a range of $K_{i(CAP)}$ = 0.2 -1.2 nM.

Detailed *in vitro* activities of **6**, the most potent antagonist in this series, were investigated for the different TRPV1 activators, *viz*. capsaicin, low pH and heat (45°C) (**Table 4**). Antagonist **6** showed excellent antagonism of *h*TRPV1 activation toward pH and heat with IC_{50} = 8.7 and 8.1 nM, respectively. In addition, antagonist **6** also proved to be a highly potent antagonist of capsaicin action against rat TRPV1 (*r*TRPV1) with $K_{i(CAP)}$ = 0.1 nM.

Table 3. *In vitro h*TRPV1 antagonistic activities for the C-region analogues of **6**



	R[a]	$K_{i[CAP]}$ (nM)
6		0.2
22		0.9 (±0.17)
23		0.8 (±0.12)
24		1.2 (±0.29)

[a] ref. 12 for **22**, ref. 19 for **23**, **24**

Consistent with its *in vitro* mechanism of action, it was able to block *in vivo* the acute hypothermic response to capsaicin (3 mg/kg) injected intraperitoneally (ip). The oral administration (po) of 3 and 10 mg/kg **6** antagonized the effect of capsaicin on body temperature with 57% and 100% inhibition, respectively, of the hypothermia induced by capsaicin. The *in vivo* analgesic activity of **6** was evaluated employing the formalin test[24] in mice (**Table 4**). It demonstrated a reasonable antinociceptive effect in the second period (20–30 min after injection), with 43% inhibition of response at the dose of 3 mg/kg by intravenous injection (iv). However, it showed hyperthermia at 10 mg/kg po as side effect probably due to strong antagonism to all activators as shown in Table 4.[9]

Table 4. Antagonistic activities of **6** for multiple activators in *h*TRPV1 and *r*TRPV1.

Activators, parameter	**6**
***h*TRPV1**	
CAP (f)K_i (nM)	0.2
pH, IC_{50} (nM)	8.7
heat 45°C, IC_{50} (nM)	8.1
***r*TRPV1**	
CAP (f)K_i (nM)	0.1
Anti-hypothermia[a]	57% (3 mg/kg, po)
	100% (10 mg/kg, po)
Formalin test	43% (3 mg/kg, iv)

[a] Inhibition percent to hypothermic response by 3 mg/kg ip capsaicin

In summary, a series of 3-fluoro-4-methylsufonamidophenyl A-region analogues of potent antagonist **1** were investigated. The analysis of SAR indicated that a fluoro group at the 3- (or/and) 5-position and a 4-methylsulfonamido group at the 4-position were optimal for TRPV1 antagonism to capsaicin activation, and any modification in the A-region led to a reduction in antagonism except for incorporation of an additional fluoro group into the 5-position. The most potent antagonist **6** exhibited potent antagonism toward capsaicin, low pH and elevated temperature for *h*TRPV1 and also displayed highly potent antagonism to capsaicin for *r*TRPV1. Further studies indicated that antagonist **6** blocked the hypothermic effect of capsaicin *in vivo*, consistent with its *in vitro* mechanism, and showed promising analgesic activity in the formalin mouse pain model.

Acknowledgments

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- A series of A-region analogues of 2-(3-fluoro-4-methylsufonamidophenyl)propanamide were investigated as TRPV1 antagonists.
- Compound **6** showed highly potent antagonism toward capsaicin activation.
- Compound **6** displayed anti-hypothermic effect and promising analgesic activity in vivo.