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PII: S0960-894X(14)00583-6
DOI: http://dx.doi.org/10.1016/j.bmcl.2014.05.074
Reference: BMCL 21688

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 18 April 2014
Revised Date: 16 May 2014
Accepted Date: 21 May 2014

Please cite this article as: Ryu, H., Seo, S., Cho, S-H., Kim, H.S., Jung, A., Kang, D.W., Son, K., Cui, M., Hong, S-h., Sharma, P.K., Choi, S., Blumberg, P.M., Frank-Foltyn, R., Bahrenberg, G., Stockhausen, H., Schiene, K., Christoph, T., Frormann, S., Lee, J., 2-Alkyl/Alkenyl Substituted Pyridine C-region Analogues of 2-(3-Fluoro-4-methylsulfonylaminophenyl)propanamides as Highly Potent TRPV1 Antagonists, *Bioorganic & Medicinal Chemistry Letters* (2014), doi: http://dx.doi.org/10.1016/j.bmcl.2014.05.074

Bioorganic & Medicinal Chemistry Letters
journal homepage: www.elsevier.com

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ARTICLE INFO

Article history:
Received
Revised
Accepted
Available online

Keywords:
Vanilloid Receptor 1
TRPV1 Antagonist
Capsaicin
Resiniferatoxin
Molecular modeling

ABSTRACT

A series of 2-alkyl/alkenyl pyridine C-region derivatives of 2-(3-fluoro-4-methylsulfonylaminophenyl)propanamides were investigated as *h*TRPV1 antagonists. Multiple compounds showed excellent and stereospecific TRPV1 antagonism with better potency than previous lead **2**. Among them, compound **15f** demonstrated a strong analgesic profile in a rat neuropathic pain model and blocked capsaicin-induced hypothermia in a dose-dependent manner. Docking analysis of **(*S*)-15f** with our *h*TRPV1 homology model provided insight into its specific binding mode.

The transient receptor potential V1 (TRPV1) receptor is a non-selective cation channel with high Ca^{2+} permeability which functions as a molecular integrator of nociceptive stimuli predominantly expressed on sensory neurons.[1] The receptor is activated by a diverse range of stimuli including protons,[2] noxious heat,[3] endogenous mediators[4,5] and natural products such as capsaicin (CAP)[6] and resiniferatoxin (RTX)[7]. Since the increase in intracellular Ca^{2+} upon TRPV1 activation causes excitation of the primary sensory neurons and the consequent central perception of pain, the blocking of TRPV1 provides a promising strategy for the development of novel analgesics, particularly for neuropathic pain.[8] In consequence, an intense effort has been made to identify potent and selective TRPV1 antagonists, with numerous reviews summarizing their therapeutic development and documenting their clinical development.[9-15]

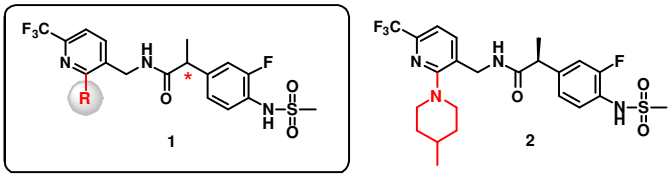

Figure 1. Structural series of TRPV1 antagonists (**1**) and lead antagonist (**2**)

Recently, we reported that compound **2,** the lead structure from series **1**, showed highly potent antagonism to multiple TRPV1 activators including capsaicin, pH, heat (45 °C) and NADA (for example, $K_{i(CAP)}$ = 0.2 nM, $IC_{50(pH)}$ = 6.3 nM) (**Figure 1**). In addition, compound **2** demonstrated strong analgesic activity in the rat neuropathic pain model with almost no off-target effects and it blocked capsacin-induced hypothermia, consistent with its *in vitro* mechanism of action.[16] The modeling analysis of **2** using our hTRPV1 homology model suggested that its high potency could be attributed to a new hydrophobic interaction provided by the 4-methylpiperidine moiety in addition to that by the 6-trifluoromethyl group in the

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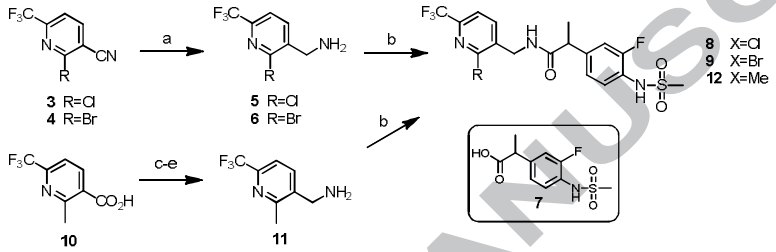
C-region. Consistent with the modeling, the SAR analysis with other 2-substituents in the pyridine C-region, 2-oxy[17] and 2-thio[18] derivatives, indicated that a hydrophobic interaction by the 2-substituents with the receptor was critical for its potent antagonism.

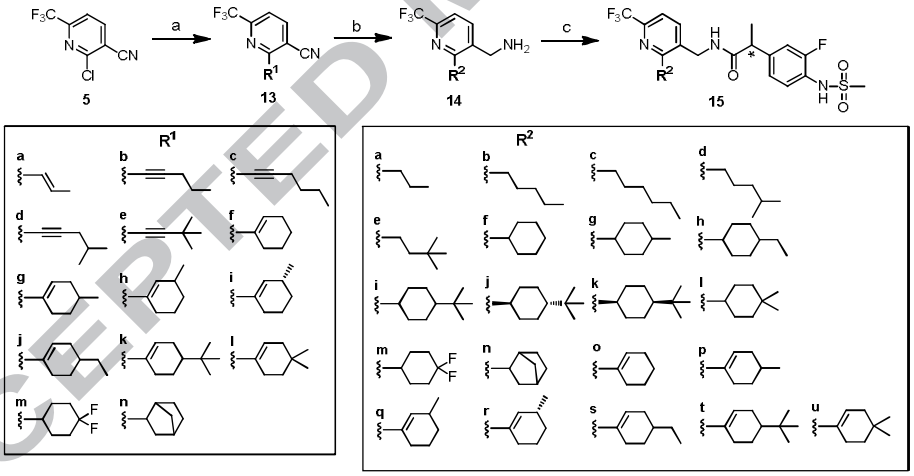
In order to further optimize the 2-substitutent in the *N*-(6-trifluoromethyl-pyridin-3-ylmethyl) C-region, here we have investigated the structure activity relationships of 2-alkyl type derivatives as *h*TRPV1 antagonists. With a selected potent antagonist in the series, we have further characterized its analgesic activity and its inhibition of capsaicin-induced hypothermia in animal models and we have performed molecular modeling with our *h*TRPV1 homology model.

The key intermediates of the C-region, 2-chloropyridine **3** and 2-bromopyridine **4,** were prepared from the corresponding pyridone using $POCl_3$ or PBr_3, respectively, using the procedure in our previous report. The nitrile reduction of **3** and **4** followed by coupling with propanoic acid **7**[19] provided the final compounds **8** and **9**. The 2-methyl derivative **12** was synthesized starting from commercially available nicotinic acid **10** in conventional 4 steps (**Scheme 1**).

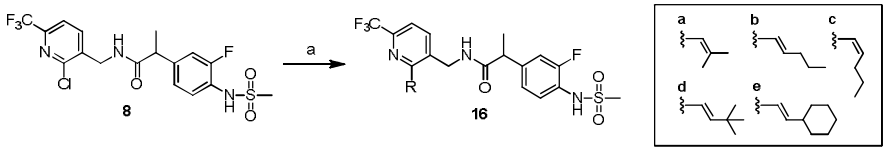
A library of alkynyl, alkenyl and alkyl groups were reacted with 2-chloropyridine **5** to afford 2-substituted pyridines **13** using a palladium-catalyzed coupling reaction (Suzuki reaction for **13a** and **13f**-**13n** and Sonogashira reaction for **13b**-**13e**). Nitriles **13** were either fully reduced to yield the corresponding primary amines **14a**-**14n** with 2-alkyl substituents or chemoselectively reduced to give the amines **14o**-**14u** with 2-alkenyl substituents. The amines of **14** were coupled with racemic or chiral propanoic acid **7** to provide the corresponding final compounds **15a**-**15u**, (**Scheme 2**). Alternatively, the 2-alkenyl analogues (**16a**-**e**) were synthesized directly from the 2-chloro substituted compound **8** by Suzuki coupling (**Scheme 3**).



Scheme 1. Synthesis of 2-halo and 2-methyl derivatives
Reagents and conditions: (a) BH_3-SMe_2 in THF, 80-90%; (b) Compoud **7**, EDC, HOBt, TEA, CH_3CN, 70-80% (c) $LiAlH_4$, THF, 75%; (d) DPPA, NEt_3, toluene, 72%; (e) PPh_3, H_2O, 85%



Scheme 2. Synthesis of 2-alkyl, 2-cycloakyl, and 2-cycloalkenyl derivatives
Reagents and conditions: (a) **13a**: CH_3CH=CH-$B(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, toluene/1,4-dioxane, reflux, overnight, 63%, **13b-13e**: $Pd(PPh_3)_4$, CuI, NEt_3 or DIPEA, toluene or NMP, 90 °C, overnight, 50-75%, **13f-13n**: R-$B(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, toluene/EtOH, 45-80%; (b) **14a-14n**: H_2, Pd-C, c-HCl, MeOH, RT, overnight, 40-92%, **14o**-**14u**: Raney Ni, NH_3 in MeOH, 50-75%; (c) Compound **7**, EDC, HOBt, TEA (or DIEA), CH_3CN (or DMF), 70-90%



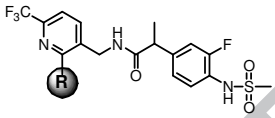
Scheme 3. Synthesis of 2-alkenyl derivatives
Reagents and conditions: (a) R-$B(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, toluene-EtOH, 100 °C, 1 h, microwave, 62-72%

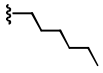
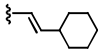
The synthesized TRPV1 ligands were evaluated *in vitro* for antagonism as measured by inhibition of activation by capsaicin (100 nM). The assays were conducted using a fluorometric imaging plate reader (FLIPR) with human TRPV1 heterologously expressed in Chinese hamster ovary (CHO) cells.[16] The results are summarized in Tables 1 and 2, together with the potencies of the previously reported racemate of **2** ($K_{i(CAP)}$ = 0.3 nM) as a reference.[16]

First, we examined the 2-chloro (**8**) and 2-bromo (**9**) derivatives which were the synthetic precursors for the synthesis of the 2-alkenyl derivatives. They were found to be weak antagonists, probably due to low lipophilicity or insufficient size to make hydrophobic interactions with the receptor.

To investigate the SAR for 2-alkyl/alkenyl derivatives of the pyridine C-region, we began by examining the effect of linear alkyl chains on the antagonism of capsaicin response. Antagonistic activity increased with the number of carbons in the chain up to 5 carbons as seen with **12**, **15a**, **15b**. However, as seen with **15c**, the antagonism decreased after that, indicating that the number of carbons in this series which appeared to be optimal for antagonism was five. A similar pattern was observed in our previous SAR analysis with the series of the corresponding linear 2-alkyloxy[17] and 2-alkylthio[18] derivatives, for which once again the 2-butyloxy and 2-butylthio derivatives, corresponding to 5 carbons, were optimal with low lipophilicity and potent antagonism. The branched derivatives **15d** and **15e** showed better antagonism than the corresponding straight derivative **15c** by ca. 2-fold, suggesting that the hydrophobic pocket for the 2-alkyl chain could be better filled by the branched group.

Table 1. *In vitro h*TRPV1 antagonistic activities for acyclic 2-alkyl and 2-alkenyl derivatives

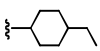
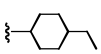
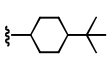
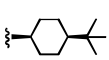
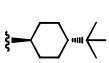
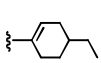
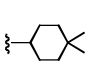
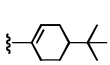
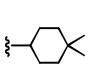
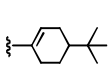
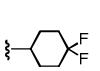


	R	K_i [CAP] (nM)		R	K_i [CAP] (nM)
rac-2		0.3	**15d**		0.9
8		WE	**15e**		0.6
9		169	**16a**		11.5
12		387	**16b**		0.9
15a		22.7	**16c**		2.1
15b		1	**16d**		0.7
15c		1.6	**16e**		0.7

The SAR of 2-alkenyl derivatives was also investigated. The isobutenyl derivative **16a** exhibited moderate antagonistic activity intermediate between the activities of **15a** (3 carbons) and **15b** (5 carbons). Whereas the *trans*-pentenyl derivative **16b** showed potency comparable to the corresponding saturated derivative **15b**, the *cis*-pentenyl derivative **16c** was 2-fold less potent than **15b**. Compounds **16d** and **16e** exhibited similar, potent antagonism comparable to the corresponding saturated derivative **15e**.

Next, we sought to evaluate the SAR of 2-cyclohexyl derivatives because previous reports indicated that the 2-cyclohexyl analogues in a series of 2-oxy and 2-thio derivatives provided potent antagonism (**Table 2**).[17,18] The cyclohexyl derivative **15f** showed potent antagonism with $K_{i(CAP)}$ = 0.6 nM, which was a 2.5-fold improvement over that of the corresponding linear derivative **15c**. A further 2-fold improvement in potency, with $K_{i(CAP)}$ = 0.3 nM, was obtained with (***S*)-15f**, the eutomer of **15f**.

Table 2. *In vitro h*TRPV1 antagonistic activities for 2-cyclohexyl derivatives

	R	K_i [CAP] (nM)		R	K_i [CAP] (nM)
15f		0.6	**15n**		1.5
(*S*)-15f		0.3	**(*S*)-15n**		0.8
15g		0.4	**15o**		0.7
15h		0.3	**15p**		0.3
(*S*)-15h		0.2	**(*S*)-15p**		0.2
15i		0.3	**15q**		0.2
15j		1.3	**15r**		0.1
15k		0.3	**15s**		0.1
15l		0.4	**15t**		0.2
(*S*)-15l		0.3	**(*S*)-15t**		0.1
15m		1.5	**15u**		0.2
			(*S*)-15u		0.1

We next explored 4-alkyl cyclohexyl derivatives based on the previous SAR results from the series of 2-piperidinyl, 2-cyclohexyloxy and 2-cyclohexylthio derivatives,[16-18] which indicated that alkyl substituents at the 4 position further improved potency. The 4-methyl cyclohexyl derivative **15g** showed better antagonism than the parent **15f** and the 4-ethyl derivative **15h** exhibited further enhanced potency with a 2-fold increase compared to **15f**. The 4-*t*-butyl cyclohexyl derivative **15i** was found to be as potent as the 4-ethyl derivative **15h** and its trans isomer **15k** was found to be the preferred geometric isomer. The 4,4-dimethyl cyclohexyl derivative **15l** also exhibited potent antagonism comparable to the 4-monoalkyl derivatives. However, the 4,4-difluoro cyclohexyl derivative displayed reduced potency, presumably due to its polarity. The bicyclic derivative **15n** was 2.5-fold less potent than the corresponding monocycle **15f**. We conclude from this SAR analysis of our series of cyclohexyl derivatives that 4-alkyl groups further improved the potency, providing better hydrophobic interaction with the receptor as found in **15h**, **15i** and **15l**.

Finally, we examined 2-cyclohexenyl derivatives as rigid analogues of the corresponding cyclohexyl derivatives. Generally, the cyclohexenyl derivatives exhibited better potency compared to the corresponding cyclohexyl derivatives. The cyclohexenyl derivative **15o** showed similar potency compared to the parent cyclohexyl derivative **15f**. Impressively, the introduction of alkyl groups on the cyclohexene such as 4-methyl (**15p**), 3-methyl (**15q** and **15r**), 4-ethyl (**15s**), 4-t-butyl (**15t**), and 4,4-dimethyl (**15u**) led to extremely potent antagonists with a range of $K_{i(CAP)}$ = 0.1-0.3 nM. As eutomers, the (*S*)-isomers of **15h**, **15l**, **15n**, **15p**, **15t** and **15u** were synthesized independently and found to be ca. 2-fold more potent than the corresponding racemates as expected.

Overall SAR analysis indicated that the antagonism in a series of 2-alkyl/alkenyl pyridine C-regions showed the following order of potency: cycloalkenyl > cycloalkyl > branched alkyl > linear alkyl. 4-Alkyl groups on the ring improved the potency further.

Next, the *in vitro* activity of compound **15f,** taken as a representative antagonist in this series, was investigated by using other TRPV1 activators (**Table 3**). We found that compound **15f** also showed excellent antagonism toward activators other than capsaicin such as pH, heat (45°C) and *N*-arachidonoyl dopamine (NADA), with potencies in the low nanomolar range.

Consistent with its *in vitro* mechanism of action as an *h*TRPV1 antagonist, *in vivo* **15f** also blocked response to capsaicin (**Table 4**). **15f** was administered orally at doses of 0.1 and 0.3 mg/kg 15 min before intraperitoneal injection of 3 mg/Kg capsaicin, following the procedure described previously.[16] These doses of **15f** inhibited the hypothermic response to capsaicin, assayed 30 min after capsaicin injection, by 24% and 78%, respectively. We further evaluated the analgesic activity of compound **15f** administered orally in the rat Bennett model[20] for neuropathic pain (**Table 4**). We found that the **15f** showed dose-dependent anti-allodynic activity with ED_{50} = 1.6 mg/Kg po (max 60% at 10 mg/Kg). It was thus more potent than pregabalin (ED_{50} = 42.2 mg/Kg, max 69% at 100 mg/Kg) and showed approximately comparable maximal effect.

Table 3. *In vitro* antagonism of **15f** for various activators of human TRPV1

Activators, parameter	**15f**
CAP, K_i (nM)	0.6
pH, IC_{50} (nM)	43.4
heat 45°C, IC_{50} (nM)	14.1
NADA, K_i (nM)	0.2

Table 4. Inhibition of capsaicin-induced hypothermia and analgesic activity of compound **15f** on CCI-induced cold allodynia after oral administration in mouse. Data, n = 10, mean ± SEM, * p<0.05 vs vehicle. MPE, maximal possible effect.

	0.1 mg/kg	0.3 mg/kg	1 mg/kg	10 mg/kg
CAP-induced Hypothermia	24% inh.	78% inh.		
Bennett Model	25 MPE		53 MPE	60 MPE

Using our human TRPV1 (hTRPV1) model[16] built based on our rat TRPV1 (rTRPV1) model[21], we performed a flexible docking study of **(*S*)-15f.** As illustrated in **Figure 2**, **(*S*)-15f** displayed a binding mode generally similar to that of **2**[16]. The sulfonylaminobenzyl group (A-region) occupied the deep bottom hole and was involved in the hydrophobic interactions with Val508, Tyr511, Ile564, Tyr565, and Ile569. A fluorine atom of the A-region participated in hydrogen bonding with Ser512 and the NH of the sulfonamide group made hydrogen bonds with Tyr565. The amide group (B region) made a hydrogen bond with Tyr511 and also contributed to the appropriate positioning of the C-region for its hydrophobic interactions. In addition, the 3-trifluoromethyl group (C-region) extended toward Thr550 in the hydrophobic area. The pyridine ring (C-region) made hydrophobic interactions with Tyr554 and the adjacent monomer Phe587. Furthermore, the cyclohexyl group in the C-region made an additional hydrophobic interaction with Leu515.

In summary, we investigated the structure activity relationships of 2-alkyl/alkenyl pyridine C-region derivatives of the previous lead **2** as *h*TRPV1 antagonists. Multiple compounds in the series, particularly cyclohexenyl derivatives, showed excellent and stereospecific TRPV1 antagonism with better potencies than reference **2**. Compound **15f** was selected for further study and was shown to antagonize capsaicin-induced hypothermia in a dose-dependent manner, consistent with its action *in vivo* being through TRPV1, and it demonstrated strong analgesic activity in a rat neuropathic pain model. Docking analysis of **(*S*)-15f** with our *h*TRPV1 homology model indicated that **(*S*)-15f** showed a binding mode similar to that previously reported[16] for compound **2**.

Acknowledgements

This research was supported by Research Grants from Grunenthal, Grants from the National Research Foundation of Korea (NRF) (R11-2007-107-02001-0), Grants from the National Leading Research Lab (NLRL) program (2011-0028885), and in part by the Intramural Research Program of NIH, Center for Cancer Research, NCI (Project Z1A BC 005270).

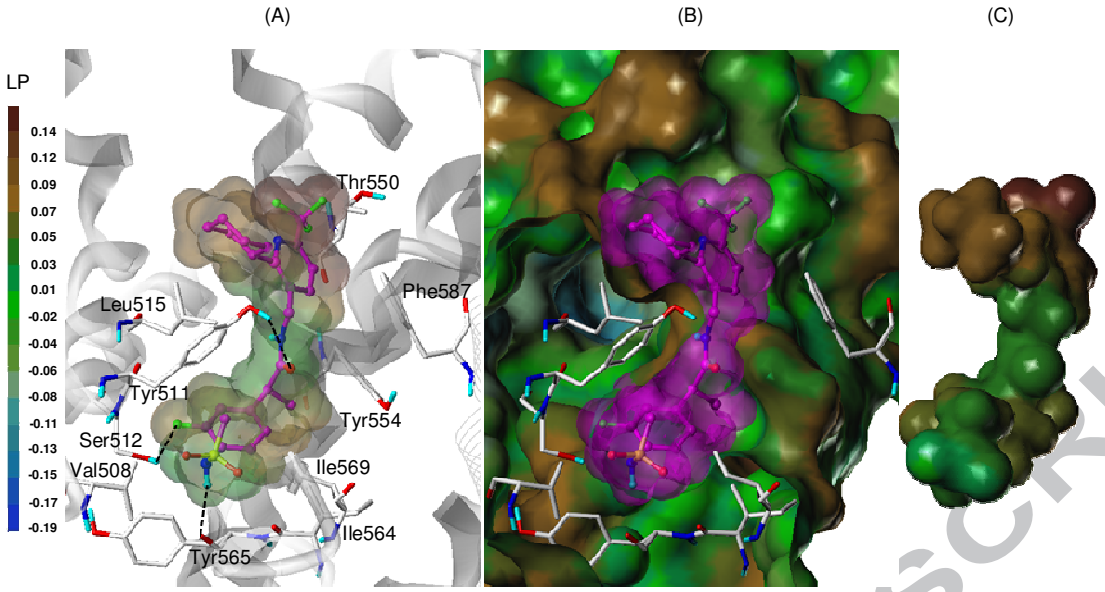


Figure 2. Flexible docking result of **(*S*)-15f** in the hTRPV1 model.
(A) Predicted binding mode of the **(*S*)-15f.** The key interacting residues are marked and displayed as capped-stick with carbon atoms in white. The helices are colored by gray and the helices of the neighboring monomer are displayed in line ribbon. **(*S*)-15f** is depicted as a ball-and-stick with carbon atoms in magenta and the van der Waals surface of the ligand is presented with its lipophilic potential property. Hydrogen bonds are shown as black dashed lines and non-polar hydrogens are undisplayed for clarity. (B) Surface of hTRPV1 and the docked ligand. The Fast Connolly surface of hTRPV1 was generated by MOLCAD and colored by the lipophilic potential property. For clarity, the surface of hTRPV1 is Z-clipped and that of the ligand is in its carbon color. (C) Van dar Waals surface of the ligand colored by its lipophilic potential property.

References and Notes

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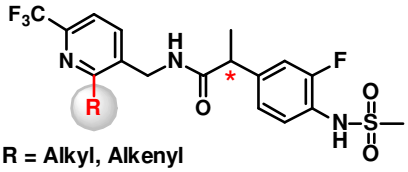

R = Alkyl, Alkenyl