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t-Butyl pyridine and phenyl C-region analogues of 2-(3-fluoro-4-methylsulfonylaminophenyl)propanamides as potent TRPV1 antagonists

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ABSTRACT

A series of 2-substituted 6-*t*-butylpyridine and 4-*t*-butylphenyl C-region analogues of 2-(3-fluoro-4-methylsulfonamidophenyl)propanamides were investigated for *h*TRPV1 antagonism. The analysis of structure activity relationships indicated that the pyridine derivatives generally exhibited a little better antagonism than did the corresponding phenyl surrogates for most of the series. Among the compounds, compound **7** showed excellent antagonism toward capsaicin activation with K_i = 0.1 nM and compound **60*S*** demonstrated a strong antiallodynic effect with 83% MPE at 10 mg/kg in the neuropathic pain model. The docking study of **7*S*** in our *h*TRPV1 homology model indicated that the interactions between the A/B-regions of **7*S*** with Tyr511 and the interactions between the *t*-butyl and ethyl groups in the C-region of **7*S*** with the two hydrophobic binding pockets of *h*TRPV1 contributed to the high potency.

1. Introduction

TRP family members represent critical nociceptors, responding both directly to chemical and thermal insults as well as indirectly in response to signaling pathways activated in response to inflammation and cellular injury.[1–3] Among TRP family members, TRPV1, the receptor for capsaicin, has become a target of particular therapeutic interest for a broad range of conditions including inflammatory and neuropathic pain. While complementary therapeutic strategies are directed at TRPV1 agonists and antagonists, antagonists have received the greatest attention. Intense medicinal chemical efforts, coupled with insights from structural analysis of TRPV1 and computer modeling,[4–7] are yielding potent lead compounds.[8] The current paper describes our on-going efforts to refine our understanding of the structure–activity relations of antagonists targeting human TRPV1.

Recently, we demonstrated that a series of *N*-((6-trifluoromethyl-pyridin-3-yl)methyl) 2-(3-fluoro-4-methylsulfonamidophenyl)propanamides (**Template I**) were potent and stereoselective *h*TRPV1 antagonists for multiple activators (Fig. 1).[9–18] Like capsaicin, our antagonistic template can be divided into three pharmacophoric parts, designated the A, B and C-regions as shown in Fig. 1. The structure activity relationships of the template have been investigated for the B-region, including the evaluation of α-substituted acetamide[15] and urea[18] groups. Likewise, the structure activity relationships have been investigated for the C-region, in which a variety of functional groups including the amino,[9] oxy,[10] thio,[11] alkyl[12], aryl[13] and sulfonamido[17] groups were incorporated at the 2-position of pyridine and the pyridine core was modified by its isomers[14] or by a phenyl group.[16] In these series, numerous compounds exhibited highly potent antagonism toward TRPV1 activators including capsaicin (CAP), *N*-arachidonoyl dopamine (NADA), low pH, and heat (45 °C) and antagonism was stereospecific to the *S*-configuation. Additionally, *in vivo* studies of selected antagonists demonstrated

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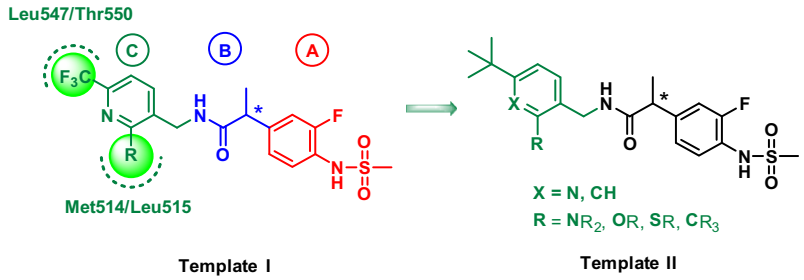


Fig. 1. Design of *t*-butylpyridine and phenyl C-region TRPV1 antagonists.

that these compounds blocked capsaicin-induced hypothermia, consistent with their *in vitro* mechanism of action as *h*TRPV1 antagonists, and that they produced strong antiallodynic effects in neuropathic pain models.

Docking studies using our established *h*TRPV1 homology model indicated that the 2-substituent and the 6-trifluoromethyl groups in the pyridine C-region made hydrophobic interactions with the pockets composed of Met514/Leu515 and Leu547/Thr550, respectively, that were critical for their potent antagonism.[9–13]

As part of our continuing effort to advance TRPV1 antagonists as clinical candidates for neuropathic pain, we have investigated the *t*-butylpyridine and phenyl surrogates of the 6-trifluoromethylpyridine C-region derivatives previously reported as potent antagonists. The motivation was that our modeling suggested that the *t*-butyl group in this series might provide a fit superior to that of the trifluoromethyl group for the hydrophobic pocket composed of Leu547/Thr550 (Fig. 1). In this paper, we synthesized a series of 2-substituted 6-*t*-butylpyridin-3-ylmethyl and 4-*t*-butylbenzyl C-region derivatives (**Template II**) and evaluated their antagonism toward activation of *h*TRPV1 by capsaicin. With selected potent antagonists in the series, we characterized their analgesic activities in a neuropathic pain model. Finally, we carried out a docking study using our *h*TRPV1 homology model to identify their mode of binding to the receptor.

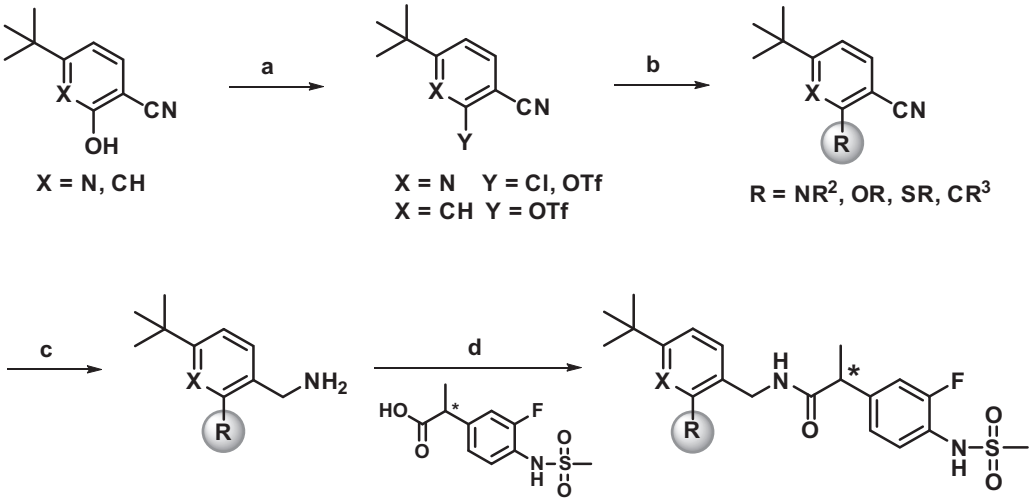
2. Result and discussion

2.1. Chemistry

The general synthesis of target compounds was described in Scheme 1. Starting from 6-*t*-butyl-2-hydroxynicotinonitrile[19,20] and 4-*t*-butyl-2-hydroxybenzonitrile[21], the 2-hydroxy groups were converted to the corresponding chloride (Y = Cl, Method A) or triflate (Y = OTf, Method B), respectively. The 2-hydroxy, chloride, or triflate groups in the *t*-butylpyridine and phenyl C-region were transformed to a variety of substituents including amino, oxy, thio and alkyl/aryl groups employing 3 different methods (Methods C-E) as appropriate. The nitrile group was reduced into the corresponding amine by catalytic hydrogenation or with borane/$LiAlH_4$. Finally, the synthesized C-region amines were coupled with the propionic acid A-region[14] previously reported to afford the final compounds **1**–**62**.

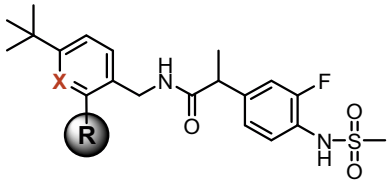
2.2. In vitro TRPV1 antagonism

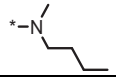
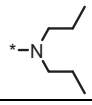
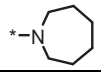
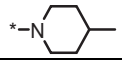
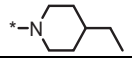
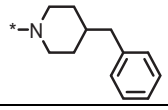
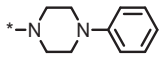
The synthesized compounds were evaluated *in vitro* for TRPV1 antagonism as measured by inhibition of activation by capsaicin (100 nM). The assays were conducted using a fluorometric imaging plate reader (FLIPR) with *h*TRPV1 heterologously expressed in Chinese hamster ovary (CHO) cells.[9] The results are summarized in Tables 1–4.



Scheme 1. The synthesis of *t*-butylpyridine and phenyl C-region antagonists. Reaction and conditions: (a) [*Method A*] phenylphosphonic dichloride, sealed tube, 170 °C, 10 h (Y = Cl); [*Method B*] trifluoromethanesulfonic anhydride, TEA, MC, 0 °C, 1 h (Y = OTf); (b) [*Method C*] neat R-X (X = NH, OH, SH), r.t, 12 h, for **1**–**8**, **12***, **18***, **19***, **27***, **28***, **33***, **34*** (Y = Cl), **42**–**47**, **59**–**62** (Y = OTf) (* added DBU as a base and reflux); [*Method D*] R-X (X = I, Br, SH, OH), K_2CO_3, 18-crown-6 ether, CH_3CN (or DMF), reflux, 14 h for **9**–**11**, **13**–**17**, **20**–**24**, **48**–**58** (Y = OH), **25**, **26**, **29**–**32**, **35**–**38** (Y = Cl); [*Method E*] $Pd(PPh_3)_4$, 2 M Na_2CO_3, RB$(OH)_2$, toluene/1,4-dioxane (2:1 v/v), reflux, 12 h, for **39**, **40**, **41**, **63**, **64** (Y = OTf); [*Method F*] R^1NH, EDC, HOBt, TEA, DMF or 1,4-dioxane, r.t, 12 h for **30**–**32** (for the conversion of R = $S(CH_2)_2CO_2H$ to R = $S(CH_2)_2CONR^1$); (c) [*Method G*] 2 M $BH_3{\cdot}SMe_2$ in THF, reflux, 16 h for **1**–**38**, **41**–**48**, **51**, **54**, **57**–**62**; [*Method H*] $LiAlH_4$, ether, reflux, 12 h for **49**, **50**, **52**, **53**, **55**, **56**; [*Method I*] H_2, Pd/C, MeOH/AcOH (10:3 v/v), 40 °C, 12 h for **39**, **40**, **63**, **64**; (d) EDC, HOBt, TEA, DMF (or CH_3CN, 1,4-dioxane, CH_2Cl_2), r.t, 12 h.

Table 1
*In vitro h*TRPV1 antagonistic activities for 2-amino derivatives.



R	X = N	K_i [CAP] (nM)	X = CH	K_i [CAP] (nM)
	**1**	1.2	**42**	1.0
	**2**	2.5		
	**3**	1.2	**43**	8.1
	**4**	1.1	**44**	1.9
	**5**	0.9	**45**	6.2
	**6**	1.9	**46**	0.7
	**7**	0.1		
	**8**	0.3		
			**47**	0.8

First, we investigated the SAR for 2-amino derivatives of the 6-*t*-butylpyridine C-region (Table 1). The acyclic and cyclic amine derivatives with 4–6 carbons (**1**–**5**) in this study exhibited similar and potent antagonism with a range of K_i = 0.9–2.5 nM. It was previously reported that 4-substituted piperidinyl derivatives of the 6-trifluoromethylpyridine C-region demonstrated excellent antagonism.[14] This was in line with 6-*t*-butylpyridine surrogates (**6**–**8**), which also proved to be very potent antagonists. In particular, the 4-ethyl (**7**) and 4-benzyl piperidinyl (**8**) derivatives displayed exceptional antagonism with K_i = 0.1 and 0.3 nM, respectively.

We also examined the 2-amino derivatives of the 4-*t*-butylphenyl C-region. They showed similar or less potent antagonism compared to the corresponding 6-*t*-butylpyridine surrogates. Among them, 4-methyl (**46**) and 4-phenyl (**47**) piperidinyl derivatives displayed potent antagonism with K_i = 0.7 and 0.8 nM, respectively.

We next explored the SAR for 2-oxy derivatives of the 6-*t*-butylpyridine C-region (Table 2). In the straight 2-alkyloxy derivatives (**9**–**14**), the antagonism was enhanced as the number of carbons in the chain increased up to 4–5 carbons. The butyloxy (**12**) and pentyloxy (**13**) derivatives showed similar and potent antagonism with a range of K_i = 0.8–0.9 nM. The SAR of branched 2-alkoxy and 2-cycloalkoxy derivatives was also studied. The comparison of activity between straight and branched alkoxy derivatives indicated that the branched derivatives exhibited slightly better antagonism than did the corresponding straight alkoxy derivatives (*e.g.* **12** *vs.* **16**, **13** *vs.* **17**). However, in the comparison between straight and cyclic alkoxy derivatives (*e.g.* **13** *vs.* **18**, **14** *vs.* **19**) the straight alkoxy derivatives were more potent. The insertion of an oxygen into the pentyl chain of compound **13**, providing **20** and **21**, led to a clear reduction in potency. The 2-benzyloxy derivatives were also investigated and the 4-fluorobenzyloxy derivative (**23**) showed good antagonism.

We also investigated the 2-oxy derivatives of the 4-*t*-butylphenyl C-region. As in the 2-amino series, they exhibited similar or less potent antagonism compared to the corresponding 6-*t*-butylpyridine surrogates. Among them, the 2-hexyloxy (**51**) and 2-isopentyloxy (**54**) derivatives displayed potent antagonism with K_i = 0.5 and 0.6 nM, respectively.

We next explored the SAR for 2-thio derivatives of the 6-*t*-butylpyridine C-region (Table 3). Generally, the antagonistic activities of the 2-thio derivatives were slightly less potent than those of the corresponding 2-oxy derivatives. Moreover, the incorporation of a polar group at the terminus of the 2-alkylthio group (**30**–**32**) led to a dramatic reduction in antagonism. For the cyclohexylthio derivative (**34**), the two stereoisomers in the propanamide B-region revealed a marked stereospecific preference for the *S*-isomer (**34*S***), consistent with our previous findings.[9] The 4-*t*-butylphenyl C-region surrogates (**60**, **60*S***, **60*R***) exhibited similar stereospecific antagonism. The 2-benzylthio derivatives (**35**–**38**) exhibited moderate antagonism regardless of substituent.

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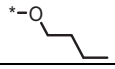
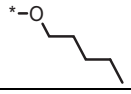
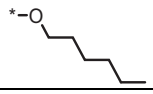
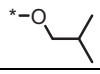
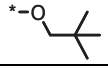
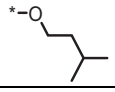
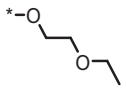
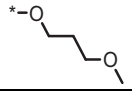
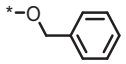
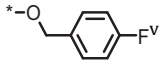
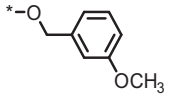
Table 2
*In vitro h*TRPV1 antagonistic activities for 2-oxy derivatives.

R	X = N	K_i [CAP] (nM)	X = CH	K_i [CAP] (nM)
	**9**	14.3		
	**10**	14.8		
	**11**	1.7	**48**	4.4
	**12**	0.9	**49**	1.4
	**13**	0.8	**50**	2.2
	**14**	2.7	**51**	0.5
	**15**	2.3		
	**16**	0.6	**52**	2.1
			**53**	3.8
	**17**	0.8	**54**	0.6
	**18**	1.5	**55**	1.8
	**19**	2.5	**56**	8.1
	**20**	23.9		
	**21**	5.6		
	**22**	4.4	**57**	2.9
	**23**	0.8	**58**	3.8
	**24**	6.0		

Finally, we investigated representative 2-alkyl, 2-cycloalkyl and aryl derivatives of the 6-*t*-butylpyridine and 4-*t*-butylphenyl C-regions (Table 4). As was the case with other substituents, the 6-*t*-butylpyridine C-region derivatives displayed more potent antagonism than did those of the 4-*t*-butylphenyl C-region. In particular, the 4-fluorophenyl derivative (**41**) displayed excellent antagonism with K_i = 0.3 nM.

2.3. Analgesic activity

Previously, we reported that the 2-cyclohexylthio-6-trifluoromethylpyridine C-region derivative exhibited dose-dependent and anti-allodynic activity with high potency and efficacy in a neuropathic pain model and proved to be superior to previous leads.[11] Thus, we evaluated the *in vivo* analgesic activities of its *t*-butylpyridine and phenyl surrogates, **34*S*** and **60*S***, upon oral administration in the Bennett mouse model[22] (CCI: Chronic Constriction Injury model) of neuropathic pain (Fig. 2). Compound **60*S*** demonstrated a dose-dependent antiallodynic effect on cold allodynia with max 83% MPE at 10 mg/kg. The pattern for compound **34*S*** was more complicated, with it affording greater than 50% MPE at 3 mg/kg but then yielding decreased antiallodynic activity as the dose was increased from 3 mg/kg to 10 mg/kg. Analysis of capsaicin-induced hypothermia by **34*S*** revealed the same pattern (46% and

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Table 3
In vitro hTRPV1 antagonistic activities for 2-thio derivatives.

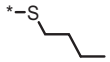
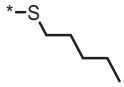
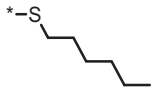
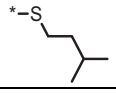
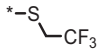
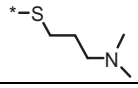
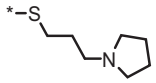
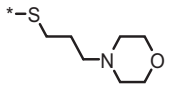
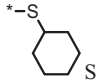
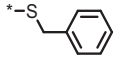
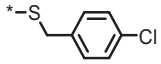
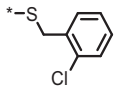
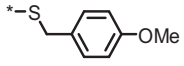
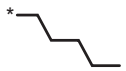
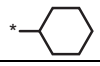
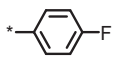
R	X = N	K_i [CAP] (nM)	X = CH	K_i [CAP] (nM)
	**25**	3.2	**59**	6.7
	**26**	3.1		
	**27**	1.5		
	**28**	5.9		
	**29**	4.1		
	**30**	51.8		
	**31**	17.1		
	**32**	112		
	**33**	2.5		
	**34**	8.5	**60**	7.4
	**34*S***	3.4	**60*S***	6.0
	**34*R***	36.4	**60*R***	89.2
	**35**	4.0		
	**36**	3.4		
	**37**	3.8		
	**38**	3.5		

Table 4
In vitro hTRPV1 antagonistic activities for 2-alkyl/aryl derivatives.

R	X = N	K_i [CAP] (nM)	X = CH	K_i [CAP] (nM)
	**39**	1.9	**61**	2.8
	**40**	3.1	**62**	9.8
	**41**	0.3		

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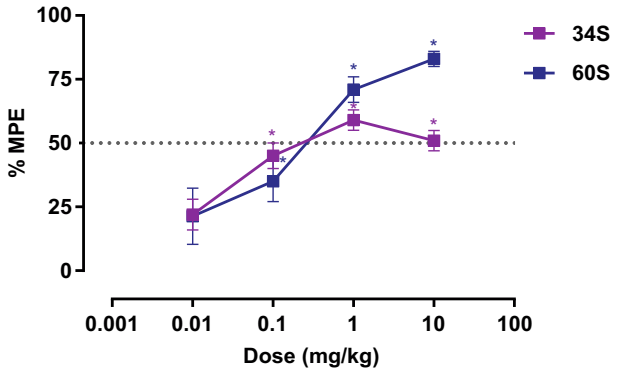

Fig. 2. Analgesic activity of compounds **34*S***, **60*S*** on CCI-induced cold allodynia (Bennett model) after oral administration in the mouse. Data, n = 10, mean ± SEM, $^{*}p < 0.05$ vs vehicle. MPE, maximal possible effect.

15% MPE at 3 and 10 mg/kg po, respectively, data not shown), suggesting that **34*S*** might be a partial agonist at 10 mg/kg under these conditions.

2.4. Molecular modeling

To analyse the binding interactions of *t*-butylpyridine C-region antagonists, we performed a flexible docking study of the *S*-isomer of compound **7** (**7*S***), the most potent antagonist in this series, with our *h*TRPV1 model[9] constructed on the basis of our rat TRPV1 model.[4] Structurally, compare to the previously reported GRT12360[9], **7*S*** has *t*-butyl and ethyl groups in the C-region pyridine and piperidine rings, repectively.

As shown in Fig. 3, the binding modes of **7*S*** and GRT12360 appeared to be similar. The 4-methylsulfonaminophenyl group in the A-region occupied the deep bottom hole and was involved in the hydrophobic interactions with Tyr511, Ile564, and Ile569. The fluorine atom in the A-region showed a hydrogen bonding interaction with Ser512 and hydrophobic interactions with Val508, Tyr555, and Tyr565. The amide group in the B-region was able to form hydrogen bonding with Tyr511 and contributed to the proper positioning of the C-region. The *t*-butyl group in the C-region oriented toward the hydrophobic pocket composed of Leu547 and Thr550, along with Phe587 from the adjacent monomer. Moreover, the 4-ethylpiperidine ring in the C-region participated in the hydrophobic interactions with Tyr511, Leu515 and Met514. It

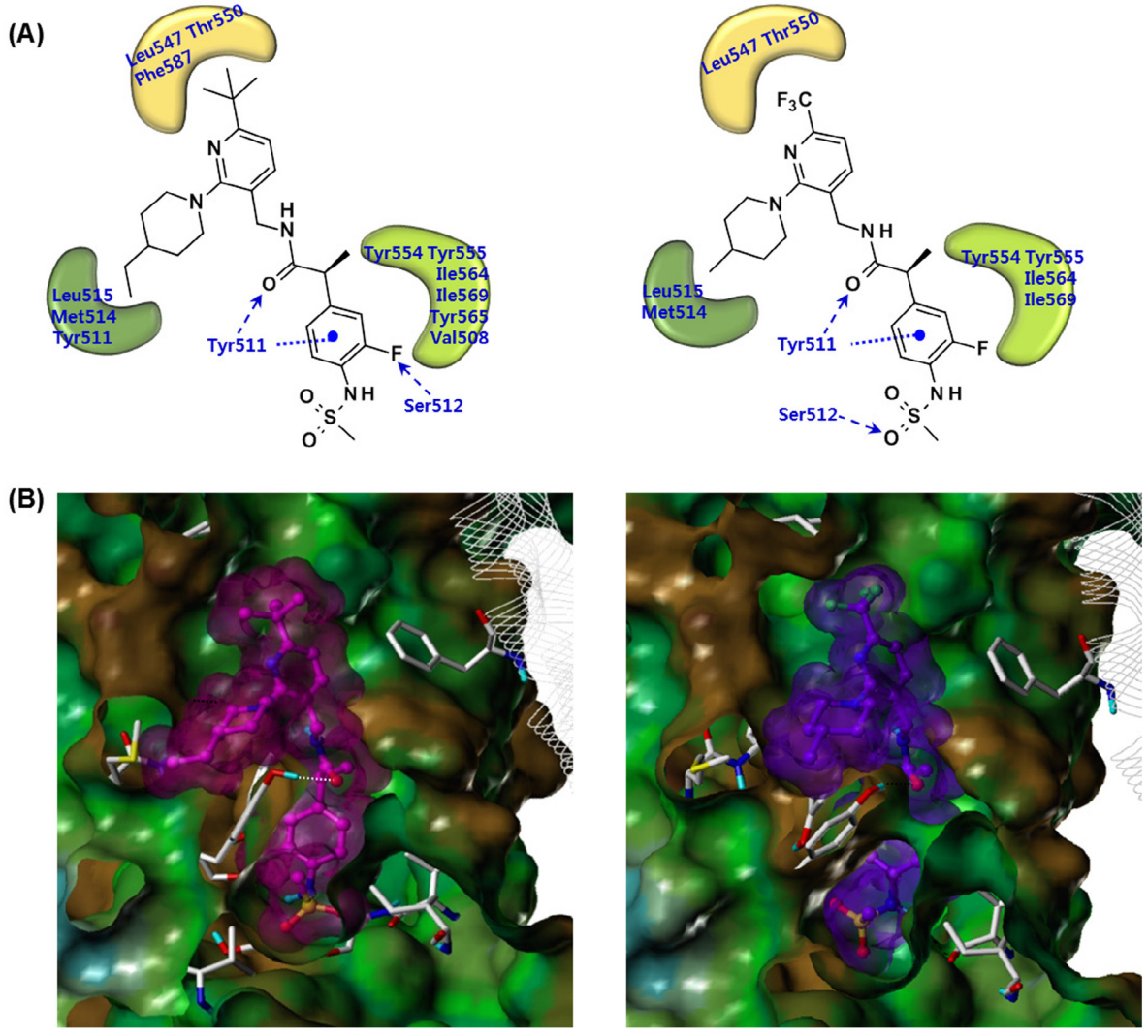

Fig. 3. Docking results of **7*S*** and GRT12360 in the *h*TRPV1 model. (A) 2-D representation of the binding interactions of **7*S*** (left) and **GRT12360** (right) in *h*TRPV1. Hydrogen bonding interactions are illustrated with in blue dashed line arrows, and hydrophobic interactions are displayed with curved patches. (B) The Fast Connolly surface of *h*TRPV1 and the van der Waals surface of docked ligands. MOLCAD was used to create the molecular surface of *h*TRPV1 and the surface is displayed with the lipophilic potential property. For clarity, the surface of *h*TRPV1 is Z-clipped and that of ligands are colored in magenta and purple, repectively.

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was noted that Tyr511 was involved in interactions with all three of the A, B and C-regions of **7*S***.

3. Conclusion

The structure activity relationship of 2-substituted 6-*t*-butylpyridine and 4-*t*-butylphenyl C-region derivatives of 2-(3-fluoro-4-methylsulfonamidophenyl)propanamides for antagonism of *h*TRPV1 was investigated. The analysis indicated that the pyridine C-region derivatives generally exhibited a little better antagonism than did the corresponding phenyl surrogates for most of the series. A number of compounds showed excellent antagonism toward capsaicin activation with subnanomolar potencies. Among them, the analgesic activity of the two chiral 2-cyclohexylthiopyridine (**34*S***) and phenyl (**60*S***) analogues were evaluated orally in the CCI neuropathic mouse model. Compound **60*S*** demonstrated strong anti-allodynia activity with 83% MPE at 10 mg/kg in the neuropathic pain model whereas **34*S*** displayed partial agonism at 10 mg/kg. The docking study of *S*-isomer of compound **7** (**7*S***), an exceptionally potent antagonist with K_i = 0.1 nM, in our *h*TRPV1 homology model indicated that Tyr511 engaged in hydrogen bonding with the carbonyl of the B-region and a charge-transfer interaction with the phenyl in the A-region, while the *t*-butyl and ethyl groups in the C-region interacted with the hydrophobic pockets of the binding site.

4. Experimental

4.1. General

All chemical reagents were commercially available. Silica gel column chromatography was performed on silica gel 60, 230–400 mesh, Merck. Nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra were recorded on JEOL JNM-LA 300 [300 MHz (^{1}H), 75 MHz (^{13}C)] and Bruker Avance 400 MHz FT-NMR [400 MHz (^{1}H), 100 MHz (^{13}C)] spectrometers. Chemical shifts are reported in ppm units with Me_4Si as a reference standard. Mass spectra were recorded on a VG Trio-2 GC–MS and 6460 Triple Quad LC/MS. All final compounds were purified to >95% purity, as determined by high-performance liquid chromatography (HPLC). HPLC was performed on an Agilent 1120 Compact LC (G4288A) instrument using an Agilent Eclipse Plus C18 column (4.6 × 250 mm, 5 μm) and a Daicel Chiralcel OD-H column (4.6 × 250 mm, 5 μm).

4.2. General procedure

4.2.1. Method A

A mixture of *t*-butyl starting material (1.00 mmol) and phenylphosphonic dichloride (1.3 mL) was refluxed for 10 h in a sealed tube. The reaction mixture was cooled to ambient temperature and filtered through a silica gel pad. Water (15 mL) was added to the filtrate, after which the filtrate was extracted with EtOAc (15 mL × 2). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using EtOAc/hexanes (1:10) as eluant.

4.2.2. Method B

To a mixture of *t*-butyl starting material (1.00 mmol) in CH_2Cl_2 was added triethylamine (3.00 mmol), trifluoromethanesulfonic anhydride (1.10 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h. The reaction mixture was extracted with EtOAc (15 mL × 2). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using EtOAc/hexanes (1:4) as eluant.

4.2.3. Method C

A mixture of *t*-butyl starting material (1.00 mmol) and amine (or alcohol, thiol) (1.20 mmol) was stirred for 12 h at room temperature. The reaction mixture was extracted with EtOAc (10 mL). The aqueous phase was saturated with aq. NaCl and extracted again with EtOAc (15 mL). The combined organic extracts were washed with 1 N HCl (5 mL) and brine (5 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using EtOAc/hexanes (1:10) as eluant.

4.2.4. Method D

A mixture of *t*-butyl starting material (1.00 mmol), alkyl halide (or alcohol, thiol) (2.00 mmol), K_2CO_3 (2.00 mmol), and 18-crown-6 ether (1.50 mmol) in DMF (or CH_3CN) was refluxed for 14 h. The reaction mixture was cooled to ambient temperature and extracted with EtOAc (10 mL). The aqueous phase was saturated with aq NaCl and extracted again with EtOAc (15 mL). The combined organic extracts were washed with 1 N HCl (5 mL) and brine (5 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using EtOAc/hexanes (1:10) as eluant.

4.2.5. Method E

A mixture of *t*-butyl starting material (1.00 mmol), $Pd(PPh_3)_4$ (0.10 mmol), and 2 M Na_2CO_3 (7.30 mmol) in toluene was refluxed for 30 min. After 30 min, to the reaction mixture was added boronic acid (2.00 mmol) in 1,4-dioxane. The reaction mixture was refluxed for 14 h. The reaction mixture was cooled to ambient temperature and extracted with EtOAc (10 mL). The aqueous phase was saturated with aq NaCl and extracted again with EtOAc (15 mL). The combined organic extracts were washed with 1 N HCl (5 mL) and brine (5 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using EtOAc/hexanes (1:30) as eluant.

4.2.6. Method F

A mixture of carboxylic acid compound (1.00 mmol), amine (1.00 mmol), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (1.00 mmol) and 1-hydroxybenzotriazole hydrate (1.00 mmol) in DMF (5 mL) was stirred for 12 h at room temperature. The reaction mixture was extracted with EtOAc (10 mL). The aqueous phase was saturated with aq NaCl and extracted again with EtOAc (15 mL). The combined organic extracts were washed with 1 N HCl (5 mL) and brine (5 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using EtOAc/hexanes (1:4 to 1:1) as eluant.

4.2.7. Method G

To a stirred solution of nitrile (1.00 mmol) in anhydrous THF (10 mL) was added 2 M $BH_3{\cdot}SMe_2$ in THF (1.10 mmol) at room temperature. After being refluxed for 16 h, the mixture was cooled to ambient temperature, 2 N HCl was added dropwise, and the solution was then refluxed for 30 min. After cooling to ambient temperature, the mixture was neutralized with 1 N NaOH and extracted with EtOAc several times. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using MeOH/CH_2Cl_2 (1:10) as eluant.

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4.2.8. Method H

To a stirred solution of nitrile (1.00 mmol) in anhydrous ether (10 mL) was added $LiAlH_4$ (2.00 mmol) at 0 °C. After being refluxed for 12 h, the mixture was cooled to 0 °C, H_2O (10 mL) was slowly added dropwise, followed by 15% aqueous NaOH solution (10 mL) and H_2O (30 mL). After addition, the mixture was allowed to warm to ambient temperature with stirring for 30 min. The mixture was then filtered over Celite and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using MeOH/CH_2Cl_2 (1:10) as eluant.

4.2.9. Method I

The mixture of nitrile (1.00 mmol) and Pd/C in MeOH/AcOH (10:3 v/v) was stirred at 40 °C under H_2 (1 atm). After stirring, the mixture was filtered over Celite and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using MeOH/ CH_2Cl_2 (1:10) as eluant.

4.2.10. General procedure for amide coupling

A mixture of 2-(3-fluoro-4-(methylsulfonamido)phenyl) propanoic acid (1.00 mmol), amine (1.00 mmol), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (1.50 mmol) and 1-hydroxybenzotriazole hydrate (1.50 mmol) in DMF (5 mL) was stirred for 12 h at room temperature. The reaction mixture was extracted with EtOAc (10 mL). The aqueous phase was saturated with aq NaCl and extracted again with EtOAc (15 mL). The combined organic extracts were washed with 1 N HCl (5 mL) and brine (5 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using EtOAc/hexanes (1:2 to 1:1) as eluant.

4.3. Chemical spectra

*4.3.1. N-((6-(tert-Butyl)-2-(butyl(methyl)amino)pyridin-3-yl) methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**1**)*

Yield 55%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (dd, J = 8.3, 8.3 Hz, 1H), 7.45 (d, J = 7.9 Hz, 1H), 7.19–7.05 (m, 3H), 6.52 (bs, 1H), 6.13 (bt, 1H), 4.46 (d, J = 5.9 Hz, 2H), 3.50 (q, J = 7.1 Hz, 1H), 3.12–3.05 (m, 2H), 3.04 (s, 3H), 2.80 (s, 3H), 1.42–1.58 (m, 5H), 1.38–1.20 (m, 11H), 0.90 (t, J = 7.3 Hz, 3H), MS (FAB) m/z 493 (MH^+).

*4.3.2. N-((6-(tert-Butyl)-2-(dipropylamino)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**2**)*

Yield 52%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (t, J = 8.2 Hz, 1H), 7.29 (d, J = 7.7 Hz, 1H), 7.17 (dd, J = 11.3, 1.8 Hz, 1H), 7.08 (d, J = 8.4 Hz, 1H), 6.85 (d, J = 7.7 Hz, 1H), 6.74 (bs, 1H), 6.47 (bt, 1H), 4.47–4.33 (m, 2H), 3.49 (q, J = 7.0 Hz, 1H), 3.07–2.96 (m, 7H), 1.52–1.34 (m, 7H), 1.29 (s, 9H), 0.82 (t, J = 7.3 Hz, 6H), MS (FAB) m/z 507 (MH^+)

*4.3.3. N-((6-(tert-Butyl)-2-(pyrrolidin-1-yl)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**3**)*

Yield 55%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (t, J = 8.2 Hz, 1H), 7.24 (d, J = 7.7 Hz, 1H), 7.20 (dd, J = 11.0, 2.0 Hz, 1H), 7.08 (d, J = 8.8 Hz, 1H), 6.50 (bs, 1H), 5.90 (bs, 1H), 4.40 (d, J = 4.6 Hz, 2H), 3.50 (q, J = 7.0 Hz, 1H), 3.39 (m, 4H), 3.02 (s, 3H), 1.83 (m, 4H), 1.50 (d, J = 7.1 Hz, 3H), 1.29 (s, 9H), MS (FAB) m/z 477 (MH^+).

*4.3.4. N-((6-(tert-Butyl)-2-(piperidin-1-yl)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**4**)*

Yield 43%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (t, J = 8.2 Hz, 1H), 7.30 (d, J = 7.9 Hz, 1H), 7.20 (dd, J = 11.2, 2.0 Hz, 1H), 7.09 (d, J = 8.2 Hz, 1H), 6.90 (m, 1H), 6.89 (d, J = 7.8 Hz, 1H), 4.40 (m, 2H), 3.50 (q, J = 7.1 Hz, 1H), 3.00 (m, 7H), 1.60 (m, 6H), 1.50 (d, J = 7.1 Hz, 3H), 1.30 (s, 9H), MS (FAB) m/z 491 (MH^+).

*4.3.5. N-((2-(Azepan-1-yl)-6-(tert-butyl)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**5**)*

Yield 63%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (t, J = 8.4 Hz, 1H), 7.24 (d, J = 7.7 Hz, 1H), 7.16 (dd, J = 11.3, 2.0 Hz, 1H), 7.08 (d, J = 8.7 Hz, 1H), 6.74 (d, J = 7.7 Hz, 1H), 6.16 (bs, 1H), 4.37 (m, 2H), 3.51 (q, J = 7.1 Hz, 1H), 3.34–3.30 (m, 4H), 3.02 (s, 3H), 1.73 (m, 4H), 1.58–1.49 (m, 4H), 1.51 (d, J = 7.1 Hz, 3H), 1.29 (s, 9H), MS (FAB) m/z 505 (MH^+).

*4.3.6. N-((6-(tert-Butyl)-2-(4-methylpiperidin-1-yl)pyridin-3-yl) methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**6**)*

Yield 63%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (t, J = 8.2 Hz, 1H), 7.30 (d, J = 7.7 Hz, 1H), 7.19–7.05 (m, 2H), 6.89 (d, J = 7.7 Hz, 1H), 4.45–4.39 (m, 2H), 3.52 (q, J = 7.0, 1H), 3.25 (m, 2H), 3.02 (s, 3H), 2.78 (m, 2H), 1.71–1.50 (m, 5H), 1.51 (d, J = 7.1 Hz, 3H), 1.30 (s, 9H), 0.97 (d, J = 6.6 Hz, 3H), MS (FAB) m/z 505 (MH^+).

*4.3.7. N-((6-(tert-Butyl)-2-(4-ethylpiperidin-1-yl)pyridin-3-yl) methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**7**)*

Yield 60%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (t, J = 8.4 Hz, 1H), 7.30 (d, J = 7.9 Hz, 1H), 7.16 (d, J = 11.3 Hz, 1H), 7.09 (d, J = 7.7 Hz, 2H), 6.89 (d, J = 7.7 Hz, 1H), 6.45 (s, 1H), 4.50–4.36 (m, 2H), 3.51 (q, J = 7,1 Hz, 1H), 3.31–3.23 (m, 2H), 3.01 (s, 3H), 2.83–2.71 (m, 2H), 1.81–1.73 (m, 2H), 1.51 (d, J = 6.9 Hz, 3H), 1.29–1.02 (m, 14H), 0.92 (t, J = 7.1 Hz, 3H), MS (FAB) m/z 519 (MH^+).

*4.3.8. N-((2-(4-Benzylpiperidin-1-yl)-6-(tert-butyl)pyridin-3-yl) methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**8**)*

Yield 75%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (m, 1H), 7.32–7.07 (m, 8H), 6.89 (d, J = 7.7 Hz, 1H), 6.80 (bt, 1H), 6.56 (bs, 1H), 4.41 (m, 2H), 3.50 (q, J = 7.1 Hz, 1H), 3.25 (m, 2H), 3.00 (s, 3H), 2.75 (m, 2H), 2.58 (d, J = 6.6 Hz, 3H), 1.75–1.65 (m, 3H), 1.50 (d, J = 7.1 Hz, 3H), 1.28 (m, 11H), MS (FAB) m/z 581 (MH^+).

*4.3.9. N-((6-(tert-Butyl)-2-methoxypyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**9**)*

Yield 58%, pale yellow solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (dd, J = 8.1, 8.1 Hz, 1H), 7.37 (d, J = 7.5 Hz, 1H), 7.15–7.06 (m, 2H), 6.80 (d, J = 7.2 Hz, 1H), 6.01 (bt, 1H), 4.30 (m, 2H), 3.89 (s, 3H), 3.49 (q, J = 6.9 Hz, 1H), 3.02 (s, 3H), 1.48 (d, J = 6.9 Hz, 2H), 1.30 (s, 9H), MS (FAB) m/z 438 (MH^+).

*4.3.10. N-((6-(tert-Butyl)-2-ethoxypyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**10**)*

Yield 55%, pale yellow solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (dd, J = 8.1, 8.1 Hz, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.17–7.05 (m, 2H), 6.78 (d, J = 7.5 Hz, 1H), 6.54 (bs, 1H), 6.05 (bt, 1H), 4.40–4.28 (m, 4H), 3.48 (q, J = 6.9 Hz, 1H), 3.03 (s, 3H), 1.33 (d, J = 6.9 Hz, 1H), 1.32–1.25 (m, 12H), MS (FAB) m/z 452 (MH^+).

*4.3.11. N-((6-(tert-Butyl)-2-propoxypyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**11**)*

Yield 48%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (dd, J = 8.4, 8.4 Hz, 1H), 7.37 (d, J = 7.2 Hz, 1H), 7.13 (dd, J = 11.1, 2.0 Hz, 1H), 7.06 (d, J = 8.2 Hz, 1H), 6.79 (d, J = 7.5 Hz, 1H), 6.03 (bt, 1H), 4.40–4.21 (m, 4H), 3.48 (q, J = 7.1 Hz, 1H), 3.02 (s, 3H), 1.78–1.65 (m, 2H), 1.48 (d, J = 7.1 Hz, 3H), 1.29 (s, 9H), 0.98 (t, J = 7.5 Hz, 3H), MS (FAB) m/z 466 (MH^+).

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*4.3.12. N-((2-Butoxy-6-(tert-butyl)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**12**)*

Yield 77%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (dd, J = 8.4, 8.4 Hz, 1H), 7.36 (d, J = 7.5 Hz, 1H), 7.15–7.05 (m, 2H), 6.79 (d, J = 7.5 Hz, 1H), 6.59 (bs, 1H), 6.06 (bt, 1H), 4.39–4.23 (m, 4H), 3.48 (q, J = 7.3 Hz, 1H), 3.02 (s, 3H), 1.69 (m, 2H), 1.48 (d, J = 7.1 Hz, 3H), 1.43 (m, 2H), 1.29 (s, 9H), 0.97 (t, J = 7.3 Hz, 3H), MS (FAB) m/z 480 (MH^+).

*4.3.13. N-((6-(tert-Butyl)-2-(pentyloxy)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**13**)*

Yield 54%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (dd, J = 8.1, 8.1 Hz, 1H), 7.33 (d, J = 7.5 Hz, 1H), 7.11 (dd, J = 11.4, 1.8 Hz, 1H), 7.03 (d, J = 8.4 Hz, 1H), 6.76 (d, J = 7.5 Hz, 1H), 6.51 (bs, 1H), 6.03 (bt, 1H), 4.38 (m, 4 H), 3.48 (q, J = 6.9 Hz, 1H), 3.01 (s, 3H), 1.70 (m, 2 H), 1.47 (d, J = 6.9 Hz, 3H), 1.40–1.36 (m, 4H), 1.39 (s, 9H), 0.92 (t, J = 6.9 Hz, 3H), MS (FAB) m/z 494 (MH^+).

*4.3.14. N-((6-(tert-Butyl)-2-(hexyloxy)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**14**)*

Yield 83%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (dd, J = 8.4, 8.4 Hz, 1H), 7.36 (d, J = 7.5 Hz, 1H), 7.15–7.05 (m, 2H), 6.79 (d, J = 7.5 Hz, 1H), 6.58 (bs, 1H), 6.07 (bt, 1H), 4.39–4.24 (m, 4H), 3.48 (q, J = 7.0 Hz, 1H), 3.02 (s, 3H), 1.71 (m, 2H), 1.48 (d, J = 7.1 Hz, 3H), 1.45–1.25 (m, 6H), 1.29 (s, 9H), 0.91 (m, 3H), MS (FAB) m/z 508 (MH^+).

*4.3.15. N-((6-(tert-Butyl)-2-isopropoxypyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**15**)*

Yield 80%, pale yellow solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (dd, J = 8.1, 8.1 Hz, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.14–7.05 (m, 2H), 6.77 (d, 7.8 Hz, 1H), 6.05 (bt, 1H), 5.33 (m, 1H), 4.28 (m, 2H), 3.48 (q, J = 6.9 Hz, 1H), 3.02 (s, 3H), 1.49 (d, J = 6.9 Hz, 3H), 1.29–1.25 (m, 15H), MS (FAB) m/z 466 (MH^+).

*4.3.16. N-((6-(tert-Butyl)-2-isobutoxypyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**16**)*

Yield 25%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ δ 7.34 (d, J = 7.5 Hz, 1H), 6.86 (d, J = 7.9 Hz, 1H), 6.74 (m, 3H), 6.00 (bs, 1H), 5.65 (s, 1H), 4.27 (m, 4H), 6.80 (s, 3H), 3.48 (q, J = 7.0 Hz, 1H), 1.68 (m, 2H), 1.51 (m, 6H), 1.29 (s, 9H), 0.93 (d, J = 6.6 Hz, 6H), MS (FAB) m/z 494 (MH^+).

*4.3.17. N-((6-(tert-Butyl)-2-(isopentyloxy)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**17**)*

Yield 60%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (dd, J = 8.1, 8.1 Hz, 1H), 7.30 (d, J = 7.5 Hz, 1H), 7.20 (dd, J = 11.4, 1.8 Hz, 1H), 7.09 (d, J = 8.4 Hz, 1H), 6.74 (d, J = 7.5 Hz, 1H), 6.25 (bt, 1H), 4.35–4.24 (m, 4H), 3.49 (q, J = 6.9 Hz, 1H), 2.97 (s, 3H), 1.74 (m, 1H), 1.58 (q, J = 6.9 Hz, 2H), 1.44 (d, J = 6.9 Hz, 2H), 1.25 (s, 9H), 0.89 (d, J = 6.6 Hz, 6H), MS (FAB) m/z 494 (MH^+).

*4.3.18. N-((6-(tert-Butyl)-2-(2-ethoxyethoxy)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**18**)*

Yield 68%, yellow solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (dd, J = 8.4, 8.4 Hz, 1H), 7.40 (d, J = 3.8 Hz, 1H), 6.81 (d, J = 3.8 Hz, 1H), 6.51–6.47 (m, 2H), 4.58–4.25 (m, 4H), 3.76 (t, J = 4.8 Hz, 2H), 3.58 (q, J = 7.1 Hz, 1H), 3.48 (q, J = 7.0 Hz, 1H), 3.01 (s, 3H), 1.46 (d, J = 7.1 Hz, 3H), 1.29 (s, 9H), 1.22 (t, d = 7.0 Hz, 3H), MS (FAB) m/z 495 (MH^+).

*4.3.19. N-((6-(tert-Butyl)-2-(3-methoxypropoxy)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**19**)*

Yield 52%, yellow solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (dd, J = 8.2, 8.2 Hz, 1H), 7.38 (d, J = 7.5 Hz, 1H), 7.12 (dd, J = 11.2, 2.0 Hz, 1H), 7.06 (d, J = 8.0 Hz, 1H), 6.79 (d, J = 7.5 Hz, 1H), 6.66 (bs, 1H), 6.28 (bt, 1H), 4.45–4.34 (m, 2H), 4.34–4.20 (m, 2H), 3.57–3.42 (m, 3H), 3.35 (s, 3H), 3.02 (s, 3H), 2.00–1.87 (m, 2H), 1.48 (d, J = 7.1 Hz, 3H), 1.29 (s, 9H), MS (FAB) m/z 496 (MH^+).

*4.3.20. N-((6-(tert-Butyl)-2-(cyclopentyloxy)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**20**)*

Yield 76%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (dd, J = 8.3, 8.3 Hz, 1H), 7.35 (d, J = 7.7 Hz, 1H), 7.14–7.05 (m, 2H), 6.77 (d, J = 7.5 Hz, 1H), 6.59 (bs, 1H), 6.03 (bt, 1H), 5.44 (m, 1H), 4.36–4.21 (m, 1H), 3.48 (q, J = 6.8 Hz, 1H), 3.02 (s, 3H), 1.96 (m, 2H), 1.75–1.60 (m, 6H), 1.48 (d, J = 7.1 Hz, 3H), 1.29 (s, 9H), MS (FAB) m/z 492 (MH^+).

*4.3.21. N-((6-(tert-Butyl)-2-(cyclohexyloxy)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**21**)*

Yield 74%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (dd, J = 8.3, 8.3 Hz, 1H), 7.36 (d, J = 7.3 Hz, 1H), 7.14–7.05 (m, 2H), 6.77 (d, J = 7.5 Hz, 1H), 6.70 (bs, 1H), 6.14 (bt, 1H), 5.10 (m, 1H), 4.39–4.23 (m, 2H), 3.49 (q, J = 7.1 Hz, 1H), 3.02 (s, 3H), 1.92 (m, 2H), 1.71 (m, 2H), 1.60–1.25 (m, 6H), 1.48 (d, J = 7.1 Hz, 1H), 1.28 (s, 9H), MS (FAB) m/z 506 (MH^+).

*4.3.22. N-((2-(Benzyloxy)-6-(tert-butyl)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**22**)*

Yield 86%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46–7.30 (m, 7H), 7.06 (dd, J = 11.2, 1.8 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 6.84 (d, J = 7.5 Hz, 1H), 6.53 (bs, 1H), 6.06 (bt, 1H), 5.42 (m, 2H), 4.42–4.26 (m, 2H), 3.38 (q, J = 7.1 Hz, 1H), 2.98 (s, 3H), 1.41 (d, J = 7.1 Hz, 3H), 1.30 (s, 9H), MS (FAB) m/z 514 (MH^+).

*4.3.23. N-((6-(tert-Butyl)-2-((4-fluorobenzyl)oxy)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**23**)*

Yield 63%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.35 (m, 4H), 7.09–6.97 (m, 4H), 6.84 (d, J = 7.5 Hz, 1H), 6.58 (bs, 1H), 6.00 (bt, 1H), 5.37 (m, 2H), 4.34 (m, 2H), 3.41 (q, J = 7.1 Hz, 1H), 3.00 (s, 3H), 1.42 (d, J = 7.1 Hz, 3H), 1.30 (s, 9H), MS (FAB) m/z 532 (MH^+).

*4.3.24. N-((6-(tert-Butyl)-2-((3-methoxybenzyl)oxy)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**24**)*

Yield 51%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46–7.29 (m, 3H), 7.09–6.82 (m, 6H), 6.07 (bt, 1H), 5.39 (s, 2H), 4.34 (m, 2H), 3.82 (s, 3H), 3.39 (q, J = 7.1 Hz, 1H), 2.99 (s, 3H), 1.41 (d, J = 7.1 Hz, 3H), 1.31 (s, 9H), MS (FAB) m/z 544 (MH^+).

*4.3.25. N-((6-(tert-Butyl)-2-(butylthio)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**25**)*

Yield 64%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (t, J = 8.3 Hz, 1H), 7.32 (d, J = 7.9 Hz, 1H), 7.15 (dd, J = 11.4, 1.8 Hz, 1H), 7.08 (d, J = 8.3 Hz, 1H), 6.94 (d, J = 7.9 Hz, 1H), 6.67 (bs, 1H), 6.00 (bt, 1H), 4.41–4.25 (m, 2H), 3.70 (s, 2H), 3.52 (q, J = 7.0 Hz, 1H), 3.22 (t, J = 7.4 Hz, 2H), 3.02 (s, 2H), 1.72–1.62 (m, 2H), 1.50–1.47 (m, 12H), 0.94 (t, J = 7.3 Hz, 3H), MS (FAB) m/z 496 (MH^+).

*4.3.26. N-((6-(tert-Butyl)-2-(pentylthio)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**26**)*

Yield 28%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (t, J = 8.2 Hz, 1H), 7.32 (d, J = 7.9 Hz, 1H), 7.15 (dd, J = 11.3, 2.0 Hz, 1H), 7.08 (d, J = 8.2 Hz, 1H), 6.94 (d, J = 7.7 Hz, 1H), 5.95 (bt, 1H), 4.41–4.26 (m, 2H), 3.51 (q, J = 7.0 Hz, 1H), 3.21 (t, J = 7.3 Hz, 2H), 3.02 (s, 3H), 1.74–1.64 (m, 2H), 1.49 (d, J = 7.3 Hz, 3H), 1.44–1.24 (m, 11H), 0.90 (t, J = 7.1 Hz, 3H), MS (FAB) m/z 510 (MH^+).

*4.3.27. N-((6-(tert-Butyl)-2-(hexylthio)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**27**)*

Yield 91%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (dd, J = 8.4, 8.2 Hz, 1H), 7.33 (d, J = 7.7 Hz, 1H), 7.15 (dd, J = 11.3, 1.8 Hz, 1H), 7.08 (m, 1H), 6.95 (d, J = 7.9 Hz, 1H), 6.48 (bs, 1H), 5.91 (bt, 1H), 4.33 (m, 2H), 3.51 (q, J = 7.0 Hz, 1H), 3.21 (t, J = 7.5 Hz, 2H), 3.02 (s, 3H), 1.74–1.25 (m, 10H), 0.89 (t, J = 6.8 Hz, 3H), MS (FAB) m/z 524 (MH^+).

*4.3.28. N-((6-(tert-Butyl)-2-(isopentylthio)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**28**)*

Yield 21%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (t, J = 8.4 Hz, 1H), 7.33 (d, J = 7.9 Hz, 1H), 7.17–7.07 (m, 2H), 6.95 (d, J = 7.9 Hz, 1H), 6.43 (bs, 1H), 5.90 (bs, 1H), 4.36–4.30 (m, 2H), 3.51 (q, J = 7.3 Hz, 1H), 3.25–3.20 (m, 2H), 3.02 (s, 3H), 1.73–1.71 (m, 1H), 1.49 (d, J = 7.1 Hz, 3H), 1.32 (s, 9H), 0.94 (d, J = 6.6 Hz, 6H), MS (FAB) m/z 510 (MH^+).

*4.3.29. N-((6-(tert-Butyl)-2-((2,2,2-trifluoroethyl)thio)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**29**)*

Yield 50%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (t, J = 8.3 Hz, 1H), 7.41 (d, J = 7. 9 Hz, 1H), 7.15–7.04 (m, 3H), 6.59 (bs, 1H), 5.91 (bt, 1H), 4.36 (t, J = 5.7 Hz, 2H), 4.12 (q, J = 9.8 Hz, 2H), 3.52 (q, 1H), 3.01 (s, 3H), 1.49 (d, J = 6.9 Hz, 3H), 1.32 (s, 9H), MS (FAB) m/z 522 (MH^+).

*4.3.30. N-((6-(tert-Butyl)-2-((3-(dimethylamino)propyl)thio)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**30**)*

Yield 20%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (t, J = 8.2 Hz, 1H), 7.35 (d, J = 7.7 Hz, 1H), 7.18–7.08 (m, 2H), 6.99 (d, J = 7.9 Hz, 1H), 6.60 (bs, 1H), 5.95 (bt, 1H), 4.37–4.31 (m, 2H), 3.54 (q, J = 7.1 Hz, 1H), 3.22 (t, J = 7.1 Hz, 2H), 3.03 (s, 3H), 2.92–2.86 (m, 2H), 2.57 (s, 6H), 1.50 (d, J = 7.1 Hz, 3H), 1.33 (s, 9H), MS (FAB) m/z 525 (MH^+).

*4.3.31. N-((6-(tert-Butyl)-2-((3-(pyrrolidin-1-yl)propyl)thio)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**31**)*

Yield 28%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (t, J = 8.3 Hz, 1H), 7.35 (d, J = 7.9 Hz, 1H), 7.15 (dd, J = 11.3, 1.8 Hz, 1H), 7.09 (d, J = 9.4 Hz, 1H), 6.98 (d, J = 7.9 Hz, 1H), 6.51 (bs, 1H), 5.92 (bt, 1H), 4.42–4.26 (m, 2H), 3.53 (q, J = 7.1 Hz, 1H), 3.30–3.19 (m, 4H), 3.04 (s, 3H), 2.91–2.82 (m, 2H), 2.73–2.65 (m, 2H), 2.28–2.14 (m, 4H), 1.87–1.85 (m, 2H), 1.49 (d, J = 7.3 Hz, 3H), 1.34 (s, 9H), MS (FAB) m/z 551 (MH^+).

*4.3.32. N-((6-(tert-Butyl)-2-((3-morpholinopropyl)thio)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**32**)*

Yield 32%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (t, J = 8.4 Hz, 1H), 7.36 (d, J = 7.5 Hz, 1H), 7.10 (m, 2H), 6.96 (d, J = 8.1 Hz, 1H), 5.92 (bt, 1H), 4.03 (m, 2H), 3.76 (m, 4H), 3.54 (m, 1H), 3.17 (m, 2H), 3.00 (s, 3H), 2.44 (m, 6H), 1.74 (m, 2H), 1.50 (d, J = 7.1 Hz, 3H), 1.32 (s, 9H), MS (FAB) m/z 567 (MH^+).

*4.3.33. N-((6-(tert-Butyl)-2-(cyclopentylthio)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**33**)*

Yield 59%, yellow solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (t, J = 8.2 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.14 (d, J = 11.3 Hz, 1H), 7.08 (d, J = 7.8 Hz, 1H), 6.94 (d, J = 7.6 Hz, 1H), 6.43 (s, 1H), 5.90 (bt, 1H), 4.33–4.14 (m, 2H), 4.17 (m, 1H), 3.50 (q, J = 6.9 Hz, 1H), 3.02 (s, 3H), 2.17 (m, 2H), 1.80–1.63 (m, 6H), 1.49 (d, J = 7.1 Hz, 3H), 1.32 (s, 9H), MS (FAB) m/z 508 (MH^+).

*4.3.34. N-((6-(tert-Butyl)-2-(cyclohexylthio)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**34**)*

Yield 92%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (t, J = 8.2 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.14 (d, J = 11.3 Hz, 1H), 7.08 (d, J = 7.8 Hz, 1H), 6.94 (d, J = 7.6 Hz, 1H), 6.43 (bs, 1H), 5.90 (bt, 1H), 4.33–4.14 (m, 2H), 4.17 (m, 1H), 3.50 (q, J = 6.9 Hz, 1H), 3.02 (m, 4H), 1.89 (m, 2H), 1.75 (m, 2H), 1.60 (m, 1H), 1.49 (d, J = 7.1 Hz, 3H), 1.36–1.24 (m, 14H), MS (FAB) m/z 522 (MH^+).

*4.3.35. N-((2-(Benzylthio)-6-(tert-butyl)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**35**)*

Yield 40%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (t, J = 8.2 Hz, 1H), 7.38–7.21 (m, 6H), 7.11 (dd, J = 11.4, 2.0 Hz, 1H), 7.05–6.99 (m, 2H), 6.52 (s, 1H), 5.89 (bt, 1H), 4.53 (d, J = 1.8 Hz, 2H), 4.40–4.24 (m, 2H), 3.46 (q, J = 7.1 Hz, 1H), 2.99 (s, 3H), 1.45 (d, J = 7.1 Hz, 3H), 1.34 (s, 9H), MS (FAB) m/z 530 (MH^+).

*4.3.36. N-((6-(tert-Butyl)-2-((4-chlorobenzyl)thio)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**36**)*

Yield 53%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (t, J = 8.3 Hz, 1H), 7.37 (d, J = 7.8 Hz, 1H), 7.32–7.21 (m, 4H), 7.12 (dd, J = 11.3, 2.0 Hz, 1H), 7.05 (d, J = 8.6 Hz, 1H), 7.01 (d, J = 7.9 Hz, 1H), 4.49 (s, 1H), 3.47 (q, J = 7.3 Hz, 1H), 3.01 (s, 1H), 1.58 (s, 2H), 1.47 (d, J = 7.1 Hz, 3H), 1.32 (s, 9H), MS (FAB) m/z 564 (M^+).

*4.3.37. N-((6-(tert-Butyl)-2-((2-chlorobenzyl)thio)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**37**)*

Yield 60%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (t, J = 8.4 Hz, 1H), 7.36 (d, J = 7.9 Hz, 1H), 7.31–7.25 (m, 2H), 7.11 (dd, J = 11.2, 2.0 Hz, 1H), 7.05–6.98 (m, 2H), 6.91–6.80 (m, 2H), 6.61 (bs, 1H), 5.04 (bt, 1H), 4.48 (d, J = 1.7 Hz, 2H), 4.38–4.23 (m, 2H), 3.45 (q, J = 7.1 Hz, 1H), 2.99 (s, 3H), 1.45 (d, J = 7.1 Hz, 3H), 1.34 (s, 9H), MS (FAB) m/z 564 (MH^+).

*4.3.38. N-((6-(tert-Butyl)-2-((4-methoxybenzyl)thio)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**38**)*

Yield 62%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (t, J = 8.4 Hz, 1H), 7.37 (d, J = 7.9 Hz, 1H), 7.31–7.29 (m, 2H), 7.10 (dd, J = 11.3, 2.0 Hz, 1H), 7.05–6.98 (m, 2H), 6.86–6.82 (m, 2H), 6.48 (bs, 1H), 5.88 (bt, 1H), 4.48 (d, J = 1.8 Hz, 2H), 4.39–4.23 (m, 2H), 3.79 (s, 3H), 3.45 (q, J = 7.3 Hz, 1H), 2.99 (s, 3H), 1.45 (d, J = 7.1 Hz, 3H), 1.35 (s, 9H), MS (FAB) m/z 560 (MH^+).

*4.3.39. N-((6-(tert-Butyl)-2-pentylpyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**39**)*

Yield 37%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (dd, J = 7.8 Hz, 1H), 7.30 (d, J = 8.1 HZ, 1H), 7.17 (m, 1H), 7.08 (m, 1H), 7.02 (d, J = 7.8 H, 1H), 4.39 (m, 2H), 3.50 (q, J = 6.9 Hz, 1H), 3.01 (s, 3H), 2.06 (t, J = 8.25 Hz, 2H), 1.54 (m, 5H), 1.33 (m, 4H), 1.30 (s, 9H), 0.89 (m, 3H), MS (FAB) m/z 478 (MH^+).

*4.3.40. N-((6-(tert-Butyl)-2-cyclohexylpyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**40**)*

Yield 42%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (dd, J = 7.8 Hz, 1H), 7.30 (d, J = 8.1 HZ, 1H), 7.17 (m, 1H), 7.08 (m, 1H), 7.02 (d, J = 7.8 H, 1H), 4.39 (m, 2H), 3.50 (q, J = 6.9 Hz, 1H), 3.01 (s, 3H), 1.75 (m, 5H), 1.58–1.44(m, 5H), 1.33–1.23 (m, 13H), MS (FAB) m/z 490 (MH^+).

*4.3.41. N-((6-(tert-Butyl)-2-(4-fluorophenyl)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**41**)*

Yield 64%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51–7.42 (m, 4H), 7.26 (d, J = 8.0 Hz, 1H), 7.11–6.98 (m, 4H), 6.53 (bs, 1H), 5.48 (bt, 1H), 4.45 (d, J = 5.3 Hz, 2H), 3.43 (q, J = 7.1 Hz, 1H), 3.02

(s, 3H), 1.44 (d, J = 7.1 Hz, 3H), 1.35 (s, 9H), MS (FAB) m/z 502 (MH^+).

*4.3.42. N-(4-(tert-Butyl)-2-(butyl(methyl)amino)benzyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**42**)*

Yield 15%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (t, J = 8.2 Hz, 1H), 7.29 (s, 1H), 7.12 (m, 2H), 6.47 (m, 2H), 4.52 (m, 2H), 3.52 (d, J = 7.1 Hz, 1H), 3.01 (s, 3H), 2.08 (m, 2H), 2.60 (s, 3H), 1.50 (d, J = 7.1 Hz, 3H), 1.41 (m, 2H), 1.29 (m, 11H), 0.90 (t, J = 7.2 Hz, 3H), MS (FAB) m/z 492 (MH^+).

*4.3.43. N-(4-(tert-Butyl)-2-(pyrrolidin-1-yl)benzyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**43**)*

Yield 44%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (dd, J = 8.2, 8.2 Hz, 1H), 7.16 (dd, J = 11.2, 1.8 Hz, 1H), 7.08–7.02 (m, 2H), 7.00 (d, J = 1.8 Hz, 1H), 6.93 (dd, J = 8.1, 2.0 Hz, 1H), 6.49 (bs, 1H), 4.45 (m, 2H), 3.49 (q, J = 7.0 Hz, 1H), 3.06 (m, 4H), 3.02 (s, 3H), 1.86–1.81 (m, 4H), 1.49 (d, J = 7.1 Hz, 3H), 1.30 (s, 9H), MS (FAB) m/z 476 (MH^+).

*4.3.44. N-(4-(tert-Butyl)-2-(piperidin-1-yl)benzyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**44**)*

Yield 94%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (dd, J = 8.3, 8.3 Hz, 1H), 7.17 (dd, J = 11.4, 1.8 Hz, 1H), 7.12–7.03 (m, 4H), 7.01 (bt, 1H), 6.49 (bs, 1H), 4.54–4.39 (m, 2H), 3.50 (q, J = 7.1 Hz, 1H), 3.01 (s, 3H), 2.84–2.75 (m, 4H), 1.64–1.54 (m, 6H), 1.50 (d, J = 7.1 Hz, 3H), 1.29 (s, 9H), MS (FAB) m/z 490 (MH^+).

*4.3.45. N-(2-(Azepan-1-yl)-4-(tert-butyl)benzyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**45**)*

Yield 48%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (dd, J = 8.2, 8.2 Hz, 1H), 7.32 (s, 1H), 7.23 (s, 2H), 7.14 (dd, J = 11.2, 1.8 Hz, 1H),7.08 (d, J = 8.2 Hz, 1H), 6.52 (bs, 1H), 6.43 (bt, 1H), 4.53 (m, 2H), 3.50 (q, J = 7.0 Hz, 1H), 3.04–3.00 (m, 7H), 1.72–1.64 (m, 8H), 1.50 (d, J = 7.0 Hz, 3H), 1.29 (s, 9H), MS (FAB) m/z 504 (MH^+).

*4.3.46. N-(4-(tert-Butyl)-2-(4-methylpiperidin-1-yl)benzyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**46**)*

Yield 88%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (dd, J = 8.3, 8.3 Hz, 1H), 7.17 (dd, J = 11.2, 1.8 Hz, 1H), 7.13–7.05 (m, 4H), 6.95 (bt, 1H), 6.47 (bs, 1H), 4.54–4.39 (m, 2H), 3.49 (q, J = 7.1 Hz, 1H), 3.01 (s, 3H), 3.00–2.92 (m, 2H), 2.72–2.60 (m, 2H), 1.79–1.65 (m, 2H), 1.50 (d, J = 7.0 Hz, 3H), 1.29 (s, 9H), 1.26–1.18 (m, 3H), 0.98 (d, J = 6.4 Hz, 3H), MS (FAB) m/z 504 (MH^+).

*4.3.47. N-(4-(tert-Butyl)-2-(4-phenylpiperazin-1-yl)benzyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**47**)*

Yield 87%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (dd, J = 8.3, 8.3 Hz, 1H), 7.28–7.35 (m, 5H), 7.13 (m, 1H), 7.07 (d, J = 8.4 Hz, 1H), 6.89–6.99 (m, 3H), 6.32 (bt, 1H), 4.53–4.67 (m, 2H), 3.55 (q, J = 7.1 Hz, 1H), 3.20–3.28 (m, 4H), 3.00–3.08 (m, 4H), 2.94 (s, 3H), 1.49 (d, J = 6.9 Hz, 3H), 1.30 (s, 9H), MS (FAB) m/z 567 (MH^+).

*4.3.48. N-(4-(tert-Butyl)-2-propoxybenzyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**48**)*

Yield 74%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (t, J = 8.2 Hz, 1H), 7.16–7.04 (m, 3H), 6.91 (d, J = 7.7 Hz, 1H), 6.85 (s, 1H), 6.44 (s, 1H), 5.95 (bt, 1H), 4.41–4.35 (m, 2H), 3.92 (t, J = 4.0 Hz, 2H), 3.46 (q, J = 7.5 Hz, 1H), 3.01 (s, 3H), 1.77–1.70 (m, 2H), 1.48 (d, J = 6.9 Hz, 3H), 1.30 (s, 9H), 1.00 (t, J = 7.3 Hz, 3H), MS (FAB) m/z 465 (MH^+).

*4.3.49. N-(2-Butoxy-4-(tert-butyl)benzyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**49**)*

Yield 61%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (t, J = 8.2 Hz, 1H), 7.16–7.04 (m, 3H), 6.90 (dd, J = 7.8, 1.8 Hz, 1H), 6.80 (d, J = 1.6 Hz, 1H), 6.59 (bs, 1H), 5.98 (bt, 1H), 4.45–4.29 (m, 2H), 4.01–3.90 (m, 2H), 3.46 (q, J = 7.1 Hz, 1H), 3.01 (s, 3H), 1.75–1.65 (m, 2H), 1.51–1.39 (m, 5H), 1.30 (s, 9H), 0.97 (t, J = 7.3 Hz, 3H), MS (FAB) m/z 479 (MH^+).

*4.3.50. N-(4-(tert-Butyl)-2-(pentyloxy)benzyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**50**)*

Yield 64%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (t, J = 8.2 Hz, 1H), 7.16–7.04 (m, 3H), 6.90 (m, 2H), 6.52 (bs, 1H), 5.99 (bt, 1H), 4.45–4.29 (m, 2H), 4.01–3.89 (m, 2H), 3.46 (q, J = 7.1 Hz, 1H), 3.01 (s, 3H), 1.77–1.68 (m, 2H), 1.48 (d, J = 7.1 Hz, 3H), 1.46–1.34 (m, 4H), 1.30 (s, 9H), 0.93 (t, J = 7.1 Hz, 3H), MS (FAB) m/z 493 (MH^+).

*4.3.51. N-(4-(tert-Butyl)-2-(hexyloxy)benzyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**51**)*

Yield 70%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16–7.04 (m, 3H), 6.90 (m, 2H), 6.52 (bs, 1H), 5.99 (bt, 1H), 4.45–4.29 (m, 2H), 4.01–3.89 (m, 2H), 3.46 (q, J = 7.1 Hz, 1H), 3.01 (s, 3H), 1.77–1.68 (m, 2H), 1.48 (d, J = 7.1 Hz, 3H), 1.46–1.25 (m, 6H), 1.30 (s, 9H), 0.93 (t, J = 7.1 Hz, 3H), MS (FAB) m/z 507 (MH^+).

*4.3.52. N-(4-(tert-Butyl)-2-isobutoxybenzyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**52**)*

Yield 60%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (t, J = 8.4 Hz, 1H), 7.16–7.10 (m, 2H), 7.05 (d, J = 8.0 Hz, 1H), 6.90 (dd, J = 7.6, 1.6 Hz, 1H), 6.84 (d, J = 1.6 Hz, 1H), 6.54 (bs, 1H), 5.94 (bt, 1H), 4.99–4.30 (m, 2H), 3.77–3.68 (m, 2H), 3.45 (q, J = 6.9 Hz, 1H), 3.01 (s, 3H), 2.00 (heptet, J = 6.6 Hz, 1H), 1.47 (d, J = 7.1 Hz, 3H), 1.30 (s, 9H), 0.99 (d, J = 6.6 Hz, 6H), MS (FAB) m/z 479 (MH^+).

*4.3.53. N-(4-(tert-Butyl)-2-(neopentyloxy)benzyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**53**)*

Yield 59%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (t, J = 8.2 Hz, 1H), 7.16–7.11 (m, 2H), 7.04 (d, J = 8.2 Hz, 1H), 6.91 (dd, J = 7.7, 1.8 Hz, 1H), 6.84 (d, J = 1.6 Hz, 1H), 6.52 (bs, 1H), 5.90 (bt, 1H), 4.50–4.31 (m, 2H), 3.63–3.57 (m, 2H), 3.44 (q, J = 7.1 Hz, 1H), 3.01 (s, 3H), 1.47 (d, J = 6.9 Hz, 3H), 1.31 (s, 9H), 1.00 (s, 9H), MS (FAB) m/z 493 (MH^+).

*4.3.54. N-(4-(tert-Butyl)-2-(isopentyloxy)benzyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**54**)*

Yield 54%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (t, J = 8.4 Hz, 1H), 7.16–7.10 (m, 2H), 7.05 (d, J = 8.0 Hz, 1H), 6.90 (dd, J = 7.6, 1.6 Hz, 1H), 6.84 (d, J = 1.6 Hz, 1H), 6.54 (bs, 1H), 5.94 (bt, 1H), 4.99–4.30 (m, 2H), 3.77–3.68 (m, 2H), 3.45 (q, J = 6.9 Hz, 1H), 3.01 (s, 3H) 1.74 (heptet, J = 6.6 Hz, 1H), 1.58 (q, J = 6.9 Hz, 2H), 1.47 (d, J = 7.1 Hz, 3H), 1.30 (s, 9H), 0.90 (d, J = 6.6 Hz, 6H), MS (FAB) m/z 493 (MH^+).

*4.3.55. N-(4-(tert-Butyl)-2-(cyclopentyloxy)benzyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**55**)*

Yield 60%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (t, J = 8.2 Hz, 1H), 7.16–7.04 (m, 3H), 6.90–6.86 (m, 2H), 6.51 (bs, 1H), 5.94 (bt, 1H), 4.78 (m, 1H), 4.41–4.25 (m, 2H), 3.45 (q, J = 7.1 Hz, 1H), 3.01 (s, 3H), 1.90–1.61 (m, 8H), 1.47 (d, J = 7.1 Hz, 3H), 1.29 (s, 9H), MS (FAB) m/z 491 (MH^+).

*4.3.56. N-(4-(tert-Butyl)-2-(cyclohexyloxy)benzyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**56**)*

Yield 63%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (t, J = 8.4 Hz, 1 h), 7.17–6.86 (m, 5H), 6.44 (bs, 1H), 6.01 (bt, 1 h),

4.45–4.30 (m, 3H), 3.46 (q, J = 6.9 Hz, 1H), 3.01 (s, 3H), 1.86 (m, 2H), 1.71 (m, 2H), 1.60–1.29 (m, 18H), MS (FAB) m/z 505 (MH^+).

*4.3.57. N-(2-(Benzyloxy)-4-(tert-butyl)benzyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**57**)*

Yield 65%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (m, 6H), 7.15 (d, J = 7.7 Hz, 1H), 7.07 (d, J = 11.2 Hz, 1H), 6.94 (m, 3H), 6.47 (bs, 1H), 6.00 (bt, 1H), 5.06 (s, 2H), 4.49–4.33 (m, 2H), 3.37 (q, J = 7.0 Hz, 1H), 2.97 (s, 3H), 1.41 (d, J = 7.1 Hz, 3H), 1.29 (s, 9H), MS (FAB) m/z 513 (MH^+).

*4.3.58. N-(4-(tert-Butyl)-2-((4-fluorobenzyl)oxy)benzyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**58**)*

Yield 70%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (t, J = 8.1 Hz, 1H), 7.36–7.21 (m, 4H), 7.12–7.03 (m, 4H), 6.98 (m, 1H), 6.43 (s, 1H), 4.45 (bs, 1H), 3.40 (q, J = 7.1 Hz, 1H), 3.00 (s, 3H), 1.42 (d, J = 7.1 Hz, 3H), 1.29 (s, 9H), MS (FAB) m/z 531 (MH^+).

*4.3.59. N-(4-(tert-Butyl)-2-(butylthio)benzyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**59**)*

Yield 50%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (t, J = 8.2 Hz, 1H), 7.35 (s, 1H), 7.13 (m, 4H), 6.47 (bs, 1H), 5.90 (bt, 1H), 4.47 (m, 2H), 3.50 (q, J = 7.0 Hz, 1H), 3.02 (s, 3H), 2.87 (t, J = 7.2 Hz, 2H), 1.58 (m, 2H), 1.49 (d, J = 7.1 Hz, 3H), 1.18 (m, 2H), 1.30 (s, 9H), 0.92 (t, J = 7.2 Hz, 3H), MS (FAB) m/z 495 (MH^+).

*4.3.60. N-(4-(tert-Butyl)-2-(cyclohexylthio)benzyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**60**)*

Yield 85%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (dd, J = 8.3, 8.3 Hz, 1H), 7.43 (s, 1H), 7.21 (m, 2H), 7.14 (dd, J = 11.3, 1.8 Hz, 1H), 7.08 (d, J = 8.4 Hz, 1H), 6.44 (bs, 1H), 5.94 (bt, 1H), 4.50 (m, 2H), 3.49 (q, J = 7.1 Hz, 1H), 3.02 (m, 4H), 1.89 (m, 2H), 1.75 (m, 2H), 1.60 (m, 1H), 1.49 (d, J = 7.1 Hz, 3H), 1.36–1.24 (m, 14H), MS (FAB) m/z 521 (MH^+).

*4.3.61. N-(4-(tert-Butyl)-2-pentylbenzyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**61**)*

Yield 75%, pale yellow oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (t, J = 8.22 Hz, 1H), 7.52 (m, 1H), 7.22–7.09 (m, 3H), 6.47 (s, 1H), 5.59 (bs, 1H), 4.45 (m, 2H), 3.55 (q, J = 7.14 Hz, 1H), 3.02 (s, 3H), 2.06 (t, J = 8.25 Hz, 2H), 1.54 (m, 5H), 1.33 (m, 4H), 1.30 (s, 9H), 0.89 (m, 3H), MS (FAB) m/z 477 (MH^+).

*4.3.62. N-(4-(tert-Butyl)-2-cyclohexylbenzyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**62**)*

Yield 75%, pale yellow oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53–7.46 (m, 2H), 7.35 (m, 1H), 7.21 (d, J = 7.80 Hz, 1H), 7.14 (dd, J = 8.1, 1.8 Hz, 1H), 7.04 (d, J = 8.40 Hz, 1H), 6.53 (s, 1H), 5.57 (bs, 1H), 4.50 (m, 2H), 3.50 (q, J = 6.90 Hz, 1H), 3.01 (s, 3H), 2.65 (m, 1H), 1.82–1.23 (m, 22H), MS (FAB) m/z 489 (MH^+)

4.4. Molecular modeling

The 3D structures of the molecules were generated using Concord and energy minimized with an MMFF94s force field and MMFF94 charge until the rms of the Powell gradient was 0.05 kcal mol^{-1} A^{-1} in SYBYL-X 2.0 (Tripos Int., St. Louis, MO, USA). The flexible docking study on our *h*TRPV1 model[9] was carried out using GOLD v.5.2 (Cambridge Crystallographic Data Centre, Cambridge, UK), which employees a genetic algorithm (GA) and allows for full ligand flexibility and partial protein flexibility. The binding site was defined as 8 Å around the capsaicin docked in the *h*TRPV1 model. The side chains of the nine residues (i.e., Tyr511, Ser512, Met514, Leu515, Leu518, Phe543, Leu547, Thr550, and Asn551) were set to be flexible with 'crystal mode' in GOLD. Compound **7*S*** was docked using the GoldScore scoring function with 30 GA runs, and the other parameters were set as the default values. All the computation calculations were undertaken on an Intel® Xeon™ Quad-core 2.5 GHz workstation with Linux Cent OS release 5.5.

4.5. Biological assay

The methods for *in vitro* and *in vivo* assays were reported previously. All animal protocols were approved by the institutional review committee at Grünenthal Innovations.

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