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Original article

2-(3-Fluoro-4-methylsulfonylaminophenyl)propanamides as potent TRPV1 antagonists: Structure activity relationships of the 2-oxy pyridine C-region

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ABSTRACT

The structure activity relationships of 2-oxy pyridine derivatives in the C-region of *N*-(6-trifluoromethyl-pyridin-3-ylmethyl) 2-(3-fluoro-4-methylsulfonylaminophenyl)propanamides as *h*TRPV1 antagonists were investigated. The analysis indicated that the lipophilicity of the 2-oxy substituents was critical for potent antagonism and 4 or 5 carbons appeared to be optimal for activity. Multiple compounds proved to have comparable activity to **1**, which had been reported as the most potent antagonist for capsaicin activity among the previous series of compounds. Further analysis of compounds **22** (2-isobutyloxy) and **53** (2-benzyloxy) in the formalin test in mice demonstrated strong analgesic activity with full efficacy. Docking analysis of ***53S*** using our hTRPV1 homology model indicated that the A- and B-region 2-(3-fluoro-4-methylsulfonylaminophenyl)propanamide made important hydrophobic and hydrogen bonding interactions with Tyr511 and that the C-region 6-trifluoromethyl and 2-benzyloxy groups of pyridine occupied the two hydrophobic binding pockets, respectively.

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1. Introduction

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 [1]. The receptor is activated by endogenous agonists including protons [2], noxious heat [3], and inflammatory lipid mediators [4,5] as well as by natural products such as capsaicin (CAP) [6] and resiniferatoxin (RTX) [7]. The increase in intracellular Ca^{2+} upon TRPV1 activation causes excitation of the primary sensory neurons and the consequent central perception of pain. TRPV1 antagonists, by inhibiting this transmission of nociceptive signaling from the periphery to the CNS, have thus attracted much attention as potential analgesics. In recent years a number of TRPV1 antagonists have been developed as novel analgesic and anti-inflammatory agents, particularly for the treatment of neuropathic pains [8]. The clinical development and therapeutic potential of TRPV1 antagonists have been extensively reviewed [9–15].

Recently, we investigated a series of *N*-(2-amino-6-trifluoro methyl-pyridin-3-ylmethyl) 2-(3-fluoro-4-methylsulfonylaminoph enyl)propanamides, designed by combining previously identified pharmacophoric elements, as *h*TRPV1 antagonists [16]. Among them, compound **1** showed the most potent antagonism with $K_{i(CAP)} = 0.3$ nM and $IC_{50(pH)} = 8.4$ nM, being thus 150-fold and 230-fold better than precedent lead **2** [17] for CAP and pH antagonism, respectively (Fig. 1). In addition, the compound **1*S***, the S-form of **1**, was found to be highly selective for TRPV1 with $K_{i(CAP)} = 0.2$ nM and

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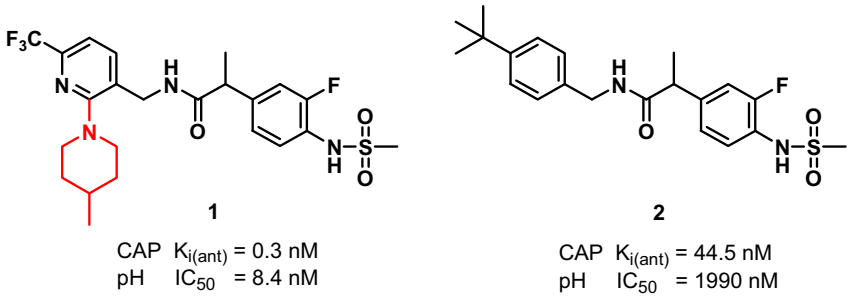


Fig. 1. Lead TRPV1 antagonists.

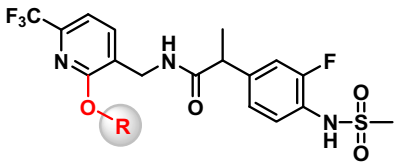


Fig. 2. General structure of the designed compounds.

displayed strong analgesic activity in a neuropathic pain model with almost no side effects. Consistent with its mechanism of action *in vivo* being through TRPV1, compound **1*S*** blocked capsaicin-induced hypothermia but caused modest TRPV1-related hyperthermia in mice.

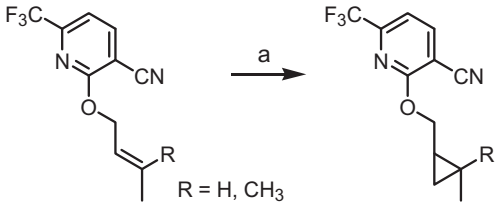
Our structural analysis indicated that the enhanced potency of **1** compared to **2** was attributable to a new hydrophobic interaction with the receptor, afforded by the additional 4-methylpiperidine moiety in **1**. Specifically, docking analysis using the hTRPV1 homology model which we developed indicated that the 4-methylpiperidinyl group in the C-region of **1** interacted with a hydrophobic region on the receptor composed of Met514 and Leu515 [16].

As a continuation of our SAR analysis of the 2-substituent in the *N*-(6-trifluoromethyl-pyridin-3-ylmethyl) C-region, we have investigated its 2-oxy derivatives (Fig. 2) as *h*TRPV1 antagonists. For a selected potent antagonist in the series, we further characterized analgesic activity in the formalin pain model and performed molecular modeling with our *h*TRPV1 homology model.

2. Results and discussion

2.1. Chemistry

The syntheses of the final compounds are represented in Scheme 1. 2-Oxy substituted pyridines **5** were synthesized either by



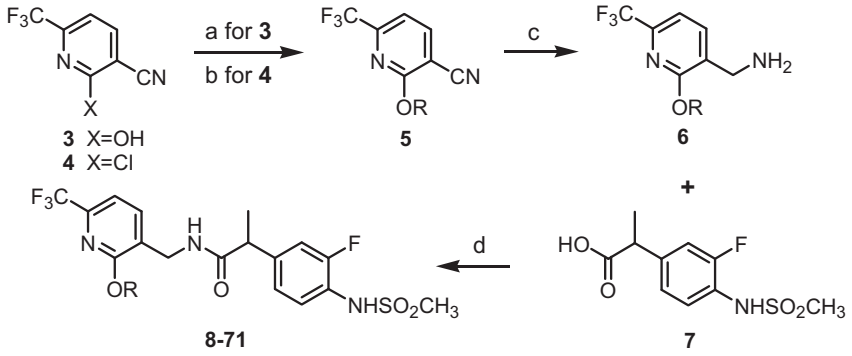
Scheme 2. Syntheses of the 2-cyclopropylmethyloxy pyridine C-region. Reagents and conditions: (a) diiodomethane, diethylzinc, CH_2Cl_2.

O-alkylation of pyridone **3** [16] or by the nucleophilic substitution of various alcohols with 2-chloropyridine **4** [16]. Pyridines **5** containing cyclopropyl substituents were prepared from the corresponding alkenes by the Simmons–Smith reaction, as shown in Scheme 2. The nitrile groups of **5** were reduced to yield the corresponding primary amines **6**. The amines were coupled with 2-(3-fluoro-4-methylsulfonylaminophenyl)propionic acid 7 [17] to provide the final compounds **8**–**71**.

2.2. Structure–activity relationship (SAR) analysis

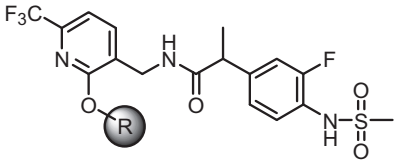
The synthesized TRPV1 ligands were evaluated *in vitro* for antagonism as measured by inhibition of activation by capsaicin (CAP) and pH as indicated. The assays were conducted using a fluorometric imaging plate reader (FLIPR) with human TRPV1 heterologously expressed in Chinese hamster ovary (CHO) cells [16]. The results are summarized in Tables 1–5, together with the potencies of the previously reported parent antagonist **1**.

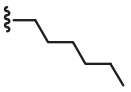
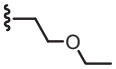
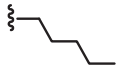
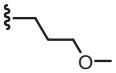
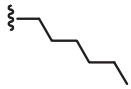
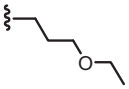
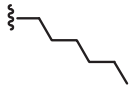
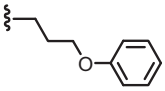
To investigate the SAR for 2-oxy derivatives of the pyridine C-region we began with the straight 2-alkyloxy derivatives (Table 1). Starting from the 2-methoxy derivative **8**, the antagonistic activity was enhanced sharply as the number of carbons in the chain increased until reaching a maximum with the 2-butoxy derivative **11**,



Scheme 1. Syntheses of 2-(3-fluoro-4-methylsulfonylaminophenyl)propanamide analogs. Reagents and conditions: (a) [Method A] RBr, K_2CO_3, 18-crown-6, DMF, heat; (b) [Method B] ROH, DBU, 1,4-dioxane or CH_3CN, reflux: [Method C] ROH, NaH, THF, reflux: [Method D] ROH, Cs_2CO_3, DMF, heat: [Method E] ROH, KF, DMF, heat; (c) [Method F] 2 M BH_3–SMe_2 in THF: [Method G] H_2, 10% Pd–C, AcOH, MeOH: [Method H] LAH, diethylether: [Method I] $NaBH_4$, $NiCl_2$–$6H_2O$, MeOH; (d) EDC, HOBt, DMF.

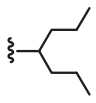
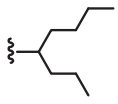
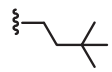
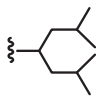
Table 1
*In vitro h*TRPV1 antagonistic activities for straight 2-alkyloxy derivatives.



	R	K_i [CAP] (nM)	IC_{50} [pH] (nM)		R	K_i [CAP] (nM)	IC_{50} [pH] (nM)
1		0.3	8.4	**13*R***		WE	WE
8		68.8	WE	**14**		1.6	183
9		12.7	277	**15**		1	43
10		0.9	90.1	**16**		49	WE
11		0.3	30.5	**17**		50	WE
12		0.7	27.3	**18**		15.3	WE
13		0.5	29.9	**19**		9.7	462
13*S*		0.4	12.3	**20**		1.5	161

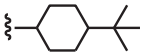
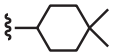
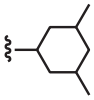
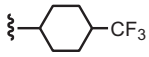
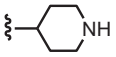
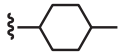
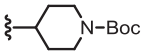
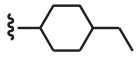
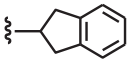
WE: weakly effective (1 μM < K_i or IC_{50} < 10 μM).
NE: not effective (K_i or IC_{50} > 10 μM).

Table 2
In vitro hTRPV1 antagonistic activities for branched 2-alkyloxy derivatives.

	R	K_i [CAP] (nM)	IC_{50} [pH] (nM)		R	K_i [CAP] (nM)	IC_{50} [pH] (nM)
21		2.1	93.4	**25**		1.1	NE
22		0.5	52.6	**26**		0.7	WE
23		0.8	15.1	**27**		0.5	WE
24		0.9	23.8	**28**		0.7	WE

WE: weakly effective (1 μM < K_i or IC_{50} < 10 μM).
NE: not effective (K_i or IC_{50} > 10 μM).

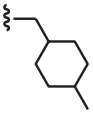
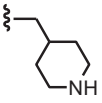
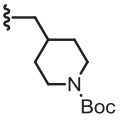
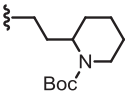
Table 3
In vitro hTRPV1 antagonistic activities for 2-cycloalkyloxy derivatives.

	R	K_i [CAP] (nM)	IC_{50} [pH] (nM)		R	K_i [CAP] (nM)	IC_{50} [pH] (nM)
29		1.4	69.8	**35**		7.7	242
30		0.9	28.7	**36**		0.9	140
31		1.3	43.4	**37**		3	174
32		0.3	14	**38**		WE	NE
33		2.9	43.1	**39**		1.3	293
34		4.8	125	**40**		2.7	WE

WE: weakly effective (1 μM < K_i or IC_{50} < 10 μM).
NE: not effective (K_i or IC_{50} > 10 μM).

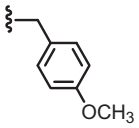
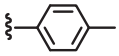
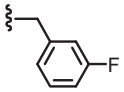
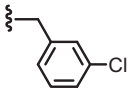
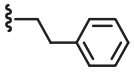
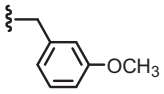
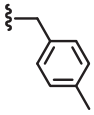
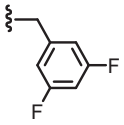
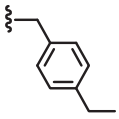
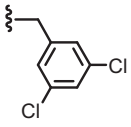
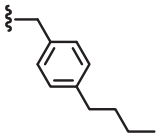
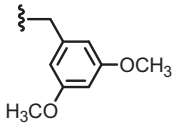
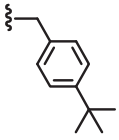
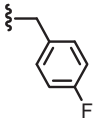
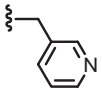
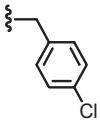
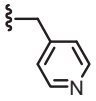
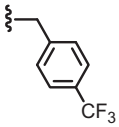
which was as potent as **1** with $K_{i(CAP)} = 0.3$ nM. The activity stayed constant upon further chain lengthening through the hexyloxy derivative **13**, with all showing highly potent antagonism (**11**–**13**). The two stereoisomers of **13** showed stereospecificity for their antagonistic activity. **13*S*** was the eutomer and **13*R*** was the distomer, consistent with previous findings [16,18]. Unsaturation of the alkyl chain led to a decrease in activity. For example, the *Z*-alkene isomers **14** and **15** were ca. 5-fold and 1.5-fold less potent than the alkyl surrogates **11** and **12**, respectively, for CAP antagonism. Introduction of oxygen to the alkyl chain caused a dramatic loss of activity. For example, the oxygenated analogs **16** and **19** exhibited 160-fold and 20-fold less potent CAP antagonism than did the parents **11** and **13**, respectively. Similarly, **17** and **18**, analogs of **12** oxygenated at different positions along the alkyl chain, were 70-fold and 22-fold less potent than the parent, respectively. However, addition of a lipophilic phenyl group to **18** to yield compound **20** led to potent antagonism. The SAR analysis for this series of straight 2-alkyloxy group thus indicated that the lipophilicity of side chain was critical for antagonism, probably due to its hydrophobic interaction with the receptor, and the optimal number of carbons appeared to be four.

Table 4
In vitro hTRPV1 antagonistic activities for 2-cycloalkylmethyloxy derivatives.

	R	K_i [CAP] (nM)	IC_{50} [pH] (nM)		R	K_i [CAP] (nM)	IC_{50} [pH] (nM)
41		1.1	115	**46**		0.7	19.7
42		0.3	5.1	**47**		1.0	44.4
43		1.1	161	**48**		WE	NE
44		0.3	40.5	**49**		3.4	342
45		0.4	11.6	**50**		0.3	16.6

WE: weakly effective (1 μM < K_i or IC_{50} < 10 μM).
NE: not effective (K_i or IC_{50} > 10 μM).

Table 5
In vitro hTRPV1 antagonistic activities for 2-aryloxy and arylmethyloxy derivatives.

	R	K_i [CAP] (nM)	IC_{50} [pH] (nM)		R	K_i [CAP] (nM)	IC_{50} [pH] (nM)
51		6.4	WE	**62**		2.6	653
52		2.8	WE	**63**		0.8	69
53		0.5	18.6	**64**		4.9	95
54		0.5	27.6	**65**		0.8	43.7
55		1.5	53	**66**		1.0	93
56		3.7	165	**67**		2.6	114
57		16	337	**68**		0.7	76
58		2.1	182	**69**		29.5	WE
59		2.5	25	**70**		142	WE
60		2.5	132	**71**		51	WE
61		3.2	66.1				

WE: weakly effective (1 μM < K_i or IC_{50} < 10 μM).
NE: not effective (K_i or IC_{50} > 10 μM).

Next, the SAR of branched 2-alkyloxy derivatives was investigated (Table 2). Similar to the findings for the derivatives with straight alkyl chains, the branched 4 carbon derivative **22** showed the most potent antagonism, but with high potency being retained with longer substituents up to the 9-carbon derivative **28**. The comparison of activity between straight and branched alkyl derivatives indicated that the straight alkyl derivatives generally showed slightly better antagonism than did the corresponding branched ones (for example, **10** *vs* **21**, **11** *vs* **22**, **12** *vs* **23**/**25** and **13** *vs* **24**). Interestingly, compounds **25**–**28** were found to have a unique profile in which they highly antagonized the activation by capsaicin but not by pH. This is an important distinction. Hyperthermia

associated with antagonism is a side effect of concern. SAR studies have shown that antagonists may differ in their relative activities against agonism by capsaicin, by low pH, and by elevated temperature. Antagonism of the response to low pH is the predominant predictor of whether an antagonist may induce hyperthermia as a side effect, so antagonists blocking the response to capsaicin but not low pH may be of particular interest for further evaluation [19].

The SAR of 2-cycloalkyloxy derivatives was investigated next (Table 3). The analysis indicated that the SAR pattern was similar to that of the above series, and compound **30** with 5 carbons was optimal for antagonism. To examine the effect of substitution on the cyclic ring, the cyclohexyl derivatives of **31** were further investigated. Whereas the 4-trifluoromethyl group in **32** enhanced antagonism compared to **31**, the 4-methyl group in **33** reduced activity, suggesting that lipophilicity is a contributor to the activity. The 4-ethyl and 4-*t*-butyl derivatives, **34** and **35**, reduced the antagonism, probably due to steric repulsion with the receptor. However, the 4,4-dimethyl and 3,5-dimethyl analogs, **36** and **37**, retained good antagonism. The results indicated that lipophilicity at the 4-position of the cyclohexyl ring was important for potent antagonism, but there were steric constraints such that size bigger than methyl led to the reduction of activity. A similar SAR pattern was found for the 4-position of piperidine ring in the C-region previously [16]. Introduction of nitrogen at the 4-position in **38** led to dramatic loss of activity. However, its activity was recovered by adding the lipophilic Boc group to the nitrogen, as in **39**. Compound **40**, the phenyl-fused analog of **30**, still displayed good CAP antagonism, indicating that the phenyl group was tolerated.

Next, the SAR of 2-cycloalkylmethyloxy derivatives was investigated. This series was designed by inserting a methyl group into the compounds of the 2-cycloalkyloxy series of Table 3. Generally the insertion led to a 2- to 5-fold enhancement in antagonism compared to that of the corresponding parent compounds (for example, **29** *vs* **44**, **30** *vs* **45**, **31** *vs* **46**, and **33** *vs* **47**). Of particular interest, compounds **4**2, **44**–**46** and **50** displayed high potency in the sub-nanomolar range. Compounds **48**–**50** demonstrated a similar SAR pattern to that shown in Table 3 in which the introduction of a nitrogen at the 4-position abolished the activity. Conversely, compound **50** exhibited excellent antagonism, suggesting that the *N*-Boc moiety made an appropriate hydrophobic interaction with the receptor.

Finally, we sought to evaluate the SAR of 2-aryloxy and 2-arylmethyloxy derivatives. In the 2-aryloxy series, the 2-phenyloxy derivative **51** exhibited reasonable antagonism and its 4-methylation, providing **52**, further increased activity. The 2-arylmethyloxy derivatives showed better antagonism compared to the corresponding 2-aryloxy ones (**51** *vs* **54**, **52** *vs* **55**), as described above for the 2-cycloalkyloxy and 2-cycloalkylmethyloxy series. The 2-phenylethyloxy derivative **54** was found to be as potent as **53**. Further optimization was conducted with the 2-benzyloxy derivative **53** to examine the effect of substitution. Introduction of 4-substituents on the benzyl group, including alkyls (**55**–**58**), halogens (**59**–**60**), trifluoromethyl (**61**) and methoxy (**62**), decrease the antagonism slightly. In the other hand, 3-substituted benzyl derivatives showed better antagonism compared to the corresponding 4-substituted surrogates (for example, **59** *vs* **63** for F, **60** *vs* **64** for Cl, **62** *vs* **65** for OCH_3). 3,5-Disubstituted derivatives displayed activity similar to that of the corresponding 3-substituted ones (for example, **63** *vs* **66** for F, **64** *vs* **67** for Cl, **65** *vs* **68** for OCH_3). 2-Pyridinylmethyloxy derivatives (**69**–**71**) were much less potent than the 2-benzyloxy derivative **53**, confirming that incorporation of nitrogen into the ring was detrimental to antagonism.

Detailed *in vitro* activity of **22** and **53**, the two selected antagonists in this study, was investigated for multiple TRPV1 activators including capsaicin, pH, heat (45 °C) and *N*-arachidonoyl dopamine (NADA), and compared to the activity of lead **1** (Table 6). Both showed excellent antagonism of all four TRPV1 activators and comparable activities to **1**. Particularly, compound **53** exhibited excellent potency toward NADA activation.

Table 6
In vitro hTRPV1 antagonistic activities for **1**, **22** and **53** to multiple activators.

Activators	**1** (nM)	**22** (nM)	**53** (nM)
CAP (f) K_i	0.3	0.5	0.5
pH (IC_{50})	8.4	52.6	18.6
Heat 45 °C (IC_{50})	4.5	67.5	52.3
NADA (f) K_i	0.23	0.29	0.001

2.3. Analgesic activity

We evaluated the *in vivo* analgesic activities of two selected antagonists, **22** and **53**, in the formalin test [20] in mice upon oral administration. Compound **22** showed a significant antinociceptive effect, with 63.4 ± 11.5% and 60.8 ± 9.9% (mean ± SEM) inhibition of response at the doses of 0.1 and 0.3 mg/kg, respectively ($p < 0.05$). Compound **53** inhibited the nociceptive response by 41.8 ± 17.3% and 54.1 ± 26.3% at the doses of 0.1 and 0.3 mg/kg, respectively ($p < 0.05$). Since we had observed that TRPV1 knockout mice showed approximately 50% of the magnitude of response in the formalin test as was seen in wild-type mice (unpublished observations), the inhibition of the formalin response that we found for the two antagonists would correspond to the expected result for full TRPV1 blockade.

2.4. Molecular modeling

Using our human TRPV1 (hTRPV1) model [16], built based on our rat TRPV1 (rTRPV1) model [21], we performed a flexible docking study of compound **53*S***, the active isomer of **53**. As shown in Fig. 3, a binding mode generally similar to that of **1*S*** [16] was obtained with the *S* form of compound **53**. The sulfonylaminobenzyl group (A-region) occupied the deep bottom hole and was involved in a hydrophobic interaction with Tyr511. A fluorine atom of the A-region participated in hydrogen bonding with Ser512 and Tyr555 and NH of the sulfonamide group made hydrogen bonds with Ser512. The amide group (B region) made a hydrogen bond with Tyr511 and also contributed to the appropriate positioning of the C-region for the hydrophobic interaction. In addition, the 3-trifluoromethyl group (C-region) extended toward the upper hydrophobic areas composed of Leu547 and Thr550, forming hydrophobic interactions. Furthermore, the 2-benzyloxy group in the C-region made an additional hydrophobic interaction with the hydrophobic region composed of Met514 and Leu515.

3. Conclusion

The structure activity relationship of 2-oxy pyridine derivatives in the C-region of *N*-(6-trifluoromethyl-pyridin-3-ylmethyl) 2-(3-fluoro-4-methylsulfonylaminophenyl)propanamides as hTRPV1 antagonists was investigated. The analysis indicated that the lipophilicity of the 2-oxy substituents was a key determinant of antagonism. Generally, as the lipophilicity of the 2-oxy substituents increased, the antagonism was enhanced until it reached a maximal value, after which it remained constant. The number of 4 or 5 carbons appeared to be optimal for activity. Numerous compounds (**11**, **13**, **22**, **27**, **32**, **42**, **44**, **45**, **50**, **53** and **54**) were found to have comparable potency to **1**, which had recently been reported as the most potent antagonist of a previous series, with a range of $K_{i(CAP)} = 0.3–0.5$ nM. Among the compounds, **22** (2-isobutyloxy) and **53** (2-benzyloxy) demonstrated strong analgesic activity in the

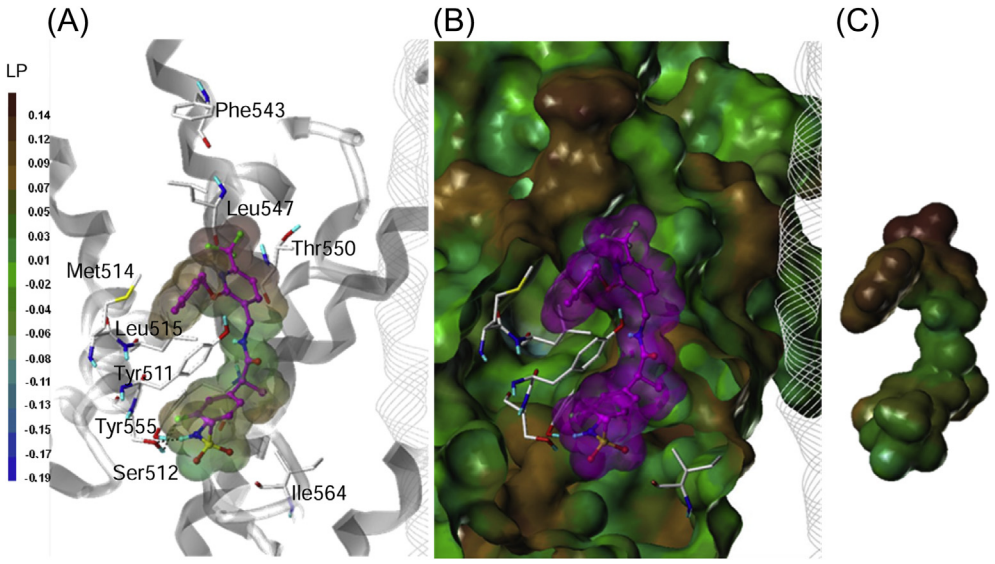


Fig. 3. Flexible docking result of **53*S*** in the hTRPV1 model. (A) Binding mode of **53S**, the *S* isomer of **53**. The key interacting residues are marked and displayed as capped-stick with carbon atoms in white. The helices are colored by gray and the helices of the adjacent monomer are displayed in line ribbon. Compound **53*S*** is depicted as ball-and-stick with carbon atoms in magenta. 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 representations of the docked ligand and hTRPV1. The Fast Connolly surface of hTRPV1 was generated by MOLCAD and colored by the lipophilic potential property. The surface of hTRPV1 is *Z*-clipped and that of the ligand is in its carbon color for clarity. (C) Van der Waals surface of the ligand colored by its lipophilic potential property.

formalin test in mice with full efficacy. Docking analysis of **53*S*** with our hTRPV1 homology model indicated that the 2-(3-fluoro-4-methylsulfonylaminophenyl)propanamide (A and B-regions) made critical hydrophobic and hydrogen bonding interactions with Tyr511, and the 6-trifluoromethyl and 2-benzyloxy groups of pyridine (C-region) interacted the two hydrophobic regions composed of Leu547/Thr550 and Met514/Leu515, respectively.

4. Experimental

4.1. Chemistry

All chemical reagents were commercially available. Melting points were determined on a Büchi Melting Point B-540 apparatus and are uncorrected. Silica gel column chromatography was performed on silica gel 60, 230–400 mesh, Merck. Nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a JEOL JNM-LA 300 and Bruker Avance 400 MHz FT-NMR spectrometer. 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. Elemental analyses were performed with an EA 1110 Automatic Elemental Analyzer, CE Instruments.

4.1.1. General procedure for the synthesis of ***5***

4.1.1.1. Method A (for ***29*****–*****40****).* To a stirred solution of **3** (1.0 mmol) in *N*,*N*-dimethylformamide (6 mL) at 0 °C was added 18-crown-6 ether (cat.), potassium carbonate (2 mmol) followed by bromide compound (1.2 mmol). The reaction mixture was heated at 60–90 °C for overnight 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 EtOAc:hexane (1:2) as eluant.

4.1.1.2. Method B (for ***8*****–*****13****,* ***21*****–*****28*** *and* ***51*****–*****58****).* To a stirred solution of **4** (1.0 mmol) in 1,4-dioxane or acetonitrile (5 mL) at 0 °C was added 1,8-diazabicyclo[5.4.0]undec-7-ene (2 mmol) followed by alcohol compound (1.2 mmol). The reaction mixture was stirred at 50 °C for overnight, and extracted with EtOAc for 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 EtOAc:hexane (1:2) as eluant.

4.1.1.3. Method C (for ***16*****–*****20*** *and* ***41*****–*****43****).* To a stirred solution of **4** (1.0 mmol) in anhydrous THF (5 mL) at 0 °C was added sodium hydride (2.5 mmol) followed by alcohol compound (1.2 mmol). The reaction mixture was stirred at 50 °C for 5 h, 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 EtOAc:hexane (1:2) as eluant.

4.1.1.4. Method D (for ***14*****–*****15****,* ***48*****–*****50*** *and* ***59*****–*****71****).* To a stirred solution of **4** (1.0 mmol) in *N*,*N*-dimethylformamide (5 mL) at 0 °C was added cesium carbonate (3.0 mmol) followed by alcohol compound (1.2 mmol). The reaction mixture was stirred at 60–90 °C for overnight, 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 EtOAc:hexane (1:2) as eluant.

4.1.1.5. Method E (for ***44*****–*****47****).* To a stirred solution of **4** (1.0 mmol) in *N*,*N*-dimethylformamide (5 mL) was added potassium fluoride (2.0 mmol) followed by alcohol compound (1.2 mmol). The reaction mixture was stirred at 60–90 °C for overnight 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 EtOAc:hexane (1:2) as eluant.

4.1.2. General procedure for nitrile reduction

4.1.2.1. Method F (for ***16*****–*****20****,* ***29*****–*****37*** *and* ***59*****–*****68****).* To a stirred solution of nitrile (2.0 mmol) in anhydrous THF (1 mL) was added 2 M

$BH_3 \cdot SMe_2$ in THF (3 mL, 3 equiv) at room temperature. After being refluxed for 8 h, the reaction mixture was cooled to room temperature and 2 M HCl solution was added. Then the mixture was refluxed for 30 min, cooled to room temperature, neutralized by 2 M NaOH solution 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 CH_2Cl_2:MeOH (10:1) as eluant.

*4.1.2.2. Method G (for **8**–**13**, **21**–**28** and **51**–**58**).* A suspension of nitrile (5.0 mmol) and 10% Pd/C (500 mg) and concentrated HCl (3 mL) in MeOH (30 mL) was hydrogenated under a balloon of hydrogen for 6 h at room temperature and filtered through Celite. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel using EtOAc eluant.

*4.1.2.3. Method H (for **14**–**15**, **41**–**47** and **69**–**71**).* To a cooled solution of nitrile (1.0 mmol) in anhydrous THF at 0 °C (5 mL) was added slowly lithium aluminum hydride (3.0 mmol) in portion wise. The mixture was refluxed for overnight, cooled to room temperature and quenched by dropwise addition of water. The solution was filtered through Celite and dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using CH_2Cl_2:MeOH (10:1) as eluant.

*4.1.2.4. Method I (for **38**–**40** and **48**–**50**).* To a stirred solution of nitrile (1.0 mmol) and $NiCl_2 \cdot 6H_2O$ (2.0 mmol) in MeOH (8 mL) was added sodium borohydride (4.0 mmol) slowly. The mixture was refluxed for 12 h and then cooled to room temperature. The solution was filtered through Celite and dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using CH_2Cl_2:MeOH (10:1) as eluant.

4.1.3. General procedure for amide coupling

A mixture of acid (5.0 mmol), amine (5.5 mmol), *N*-(3-dimethylaminopropyl)-*N*′-ethyl-carbodiimide hydrochloride (6.0 mmol), and 1-hydrxybenzotriazole hydrate in *N*,*N*-dimethylformamide (20 mL) was stirred for 12 h at room temperature. The reaction mixture was extracted with EtOAc several times. The combined organic extracts were washed with 1 M HCl (25 mL) and brine (25 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using EtOAc:hexane (1:2) as eluant.

*4.1.3.1. N-((2-Methoxy-6-(trifluoromethyl)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**8**).* Yield 81%, white solid, mp 122–124 °C; ^{1}H NMR ($CDCl_3$) δ 7.60 (d, J = 7.3 Hz, 1H), 7.52 (dd, J = 8.3, 8.3 Hz, 1H), 7.21 (d, J = 7.3 Hz, 1H), 7.12–7.06 (m, 2H), 6.50 (bs, NH), 6.00 (bt, NH), 4.37 (d, J = 6.1 Hz, 2H), 3.95 (s, 3H), 3.52 (q, J = 7.1 Hz, 1H), 3.04 (s, 3H), 1.49 (d, J = 7.0 Hz, 3H); MS (FAB) m/z 450 (M + H). Anal. Calcd for $C_{18}H_{19}F_4N_3O_4S$: C, 48.10; H, 4.26; N, 9.35. Found: C, 48.27; H, 4.24; N, 9.33.

*4.1.3.2. N-((2-Ethoxy-6-(trifluoromethyl)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**9**).* Yield 68%, white solid, mp 138–140 °C; ^{1}H NMR ($CDCl_3$) δ 7.58 (d, J = 7.3 Hz, 1H), 7.51 (dd, J = 8.2, 8.2 Hz, 1H), 7.19 (d, J = 7.3 Hz, 1H), 7.12–7.05 (m, 2H), 6.58 (bs, NH), 6.02 (bt, NH), 4.44–4.36 (m, 4H), 3.53 (q, J = 7.0 Hz, 1H), 3.03 (s, 3H), 1.49 (d, J = 7.1 Hz, 3H), 1.34 (t, 3H, J = 7.1 Hz); MS (FAB) m/z 464 (M + H). Anal. Calcd for $C_{19}H_{21}F_4N_3O_4S$: C, 49.24; H, 4.57; N, 9.07. Found: C, 49.40; H, 4.56; N, 9.04.

*4.1.3.3. N-((2-Propoxy-6-(trifluoromethyl)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**10**).* Yield 78%, white solid, mp 88–90 °C; ^{1}H NMR ($CDCl_3$) δ 7.58 (d, J = 7.5 Hz, 1H), 7.52 (dd, J = 8.2, 8.2 Hz, 1H), 7.19 (d, J = 7.3 Hz, 1H), 7.12–7.05 (m, 2H), 6.50 (bs, NH), 5.97 (bt, NH), 4.39–4.23 (m, 4H), 3.52 (q, J = 7.1 Hz, 1H), 3.03 (s, 3H), 1.74 (m, 2H), 0.99 (t, J = 7.3 Hz, 3H); MS (FAB) m/z 478 (M + H). Anal. Calcd for $C_{20}H_{23}F_4N_3O_4S$: C, 50.31; H, 4.86; N, 8.80. Found: C, 50.14; H, 4.88; N, 8.83.

*4.1.3.4. N-((2-Butoxy-6-(trifluoromethyl)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**11**).* Yield 77%, white solid, mp 77–79 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, J = 7.3 Hz, 1H), 7.52 (dd, J = 8.1, 8.1 Hz, 1H), 7.19 (d, J = 7.5 Hz, 1H), 7.12–7.05 (m, 2H), 6.46 (bs, NH), 5.96 (bt, NH), 4.39–4.28 (m, 4H), 3.51 (q, J = 7.1 Hz, 1H), 3.03 (s, 3H), 1.75–1.66 (m, 2H), 1.49 (d, J = 7.1 Hz, 3H), 1.49–1.37 (m, 2H), 0.98 (t, J = 9.5 Hz, 3H); MS (FAB) m/z 492 (M + H). Anal. Calcd for $C_{21}H_{25}F_4N_3O_4S$: C, 51.32; H, 5.13; N, 8.55. Found: C, 51.49; H, 5.11; N, 8.52.

*4.1.3.5. N-((2-Pentyloxy-6-(trifluoromethyl)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**12**).* Yield 71%, white solid, mp 58–60 °C; ^{1}H NMR ($CDCl_3$) δ 7.57 (d, J = 7.5 Hz, 1H), 7.52 (dd, J = 8.2, 8.2 Hz, 1H), 7.19 (d, J = 7.4 Hz, 1H), 7.12–7.05 (m, 2H), 6.45 (bs, NH), 5.98 (bt, NH), 4.38–4.29 (m, 4H), 3.51 (q, J = 7.0 Hz, 1H), 3.03 (s, 3H), 1.77–1.67 (m, 2H), 1.49 (d, J = 7.1 Hz, 3H), 1.43–1.35 (m, 4H), 0.93 (t, J = 7.1 Hz, 3H); MS (FAB) m/z 506 (M + H). Anal. Calcd for $C_{22}H_{27}F_4N_3O_4S$: C, 52.27; H, 5.38; N, 8.31. Found: C, 52.41; H, 5.36; N, 8.28.

*4.1.3.6. N-((2-Hexyloxy-6-(trifluoromethyl)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**13**).* Yield 90%, white solid, mp 84–86 °C; ^{1}H NMR ($CDCl_3$) δ 7.60 (d, J = 7.3 Hz, 1H), 7.52 (dd, J = 8.3, 8.3 Hz, 1H), 7.21 (d, J = 7.3 Hz, 1H), 7.12–7.06 (m, 2H), 6.50 (bs, NH), 6.00 (bt, NH), 4.37 (d, J = 6.1 Hz, 2H), 3.95 (s, 3H), 3.52 (q, J = 7.1 Hz, 1H), 3.04 (s, 3H), 1.49 (d, J = 7.0 Hz, 3H); MS (FAB) m/z 520 (M + H). Anal. Calcd for $C_{23}H_{29}F_4N_3O_4S$: C, 53.17; H, 5.63; N, 8.09. Found: C, 53.00; H, 5.64; N, 8.13.

*4.1.3.7. (Z)-N-((2-(But-2-en-1-yloxy)-6-(trifluoromethyl)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**14**).* Yield 72%, white solid, mp 110 °C; ^{1}H NMR ($CDCl_3$) δ 7.59 (d, J = 8.2 Hz, 1H), 7.52 (dd, J = 8.3 Hz, 1H), 7.20 (d, J = 7.5 Hz, 1H), 7.09 (dd, J = 11.5, 1.8 Hz, 1H), 7.06 (d, J = 9.1 Hz, 1H), 6.48 (bs, 1H), 6.01 (bt, 1H), 5.76 (m, 1H), 5.58 (m, 1H), 4.94 (d, J = 6.8 Hz, 2H), 4.37 (d, J = 6.0 Hz, 2H), 3.50 (q, J = 7.0 Hz, 1H), 3.02 (s, 3H), 1.77 (d, J = 7.0 Hz, 3H), 1.48 (d, J = 7.1 Hz, 3H); MS (FAB) m/z 490 (M + H). Anal. Calcd for $C_{21}H_{23}F_4N_3O_4S$: C, 51.53; H, 4.74; N, 8.58. Found: C, 51.36; H, 4.75; N, 8.61.

*4.1.3.8. (Z)-N-((2-(Pent-2-en-1-yloxy)-6-(trifluoromethyl)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**15**).* Yield 66%, white solid, mp 107 °C; ^{1}H NMR ($CDCl_3$) δ 7.59 (d, J = 7.4 Hz, 1H), 7.51 (dd, J = 8.4 Hz, 1H), 7.20 (d, J = 8.4 Hz, 1H), 7.09 (dd, J = 11.5, 1.8 Hz, 1H), 7.06 (d, J = 9.2 Hz, 1H), 6.49 (s, 1H), 6.01 (bt, 1H), 5.67 (m, 1H), 5.52 (m, 1H), 4.92 (d, J = 4.7 Hz, 2H), 4.37 (d, J = 6.4 Hz, 2H), 3.50 (q, J = 6.8 Hz, 1H), 3.03 (s, 3H), 2.20 (m, 2H), 1.48 (d, J = 7.1 Hz, 3H), 1.02 (t, J = 7.5 Hz, 3H); MS (FAB) m/z 504 (M + H). Anal. Calcd for $C_{22}H_{25}F_4N_3O_4S$: C, 52.48; H, 5.00; N, 8.35. Found: C, 52.69; H, 4.99; N, 8.33.

*4.1.3.9. N-((2-(2-Methoxyethoxy)-6-(trifluoromethyl)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**16**).* Yield 68%, white solid, mp 109 °C; ^{1}H NMR ($CDCl_3$) δ 7.65 (d, J = 7.5 Hz, 1H), 7.51 (t, J = 8.4 Hz, 1H), 7.23 (d, J = 7.2 Hz, 1H), 7.12 (m, 2H), 6.54 (bt, 1H), 6.45 (bs, 1H), 4.56 (m, 2H), 4.41 (t, J = 3.6 Hz, 2H),

3.74 (t, J = 4.5 Hz, 2H), 3.48 (q, J = 7.2 Hz, 1H), 3.43 (s, 3H), 3.01 (s, 3H), 1.47 (d, J = 6.9 Hz, 3H); MS (FAB) m/z 494 (M + H). Anal. Calcd for $C_{20}H_{23}F_4N_3O_5S$: C, 48.68; H, 4.70; N, 8.52. Found: C, 48.49; H, 4.71; N, 8.55.

*4.1.3.10. N-((2-(2-Ethoxyethoxy)-6-(trifluoromethyl)pyridin-3-yl) methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**17**).* Yield 70% white solid, mp 118 °C; ^{1}H NMR ($CDCl_3$) δ 7.63 (d, J = 7.6 Hz, 1H), 7.52 (t, J = 8.3 Hz, 1H), 7.24 (d, J = 7.4 Hz, 1H), 7.11 (m, 2H), 6.55 (bt, 1H), 6.46 (bs, 1H), 4.55 (m, 2H), 4.40 (t, J = 3.6 Hz, 2H), 3.73 (t, J = 4.5 Hz, 2H), 3.63 (q, J = 7.2 Hz, 2H), 3.47 (q, J = 7.2 Hz, 1H), 3.44 (s, 3H), 3.01 (s, 3H), 1.42 (d, J = 6.8 Hz, 3H); MS (FAB) m/z 508 (M + H). Anal. Calcd for $C_{21}H_{25}F_4N_3O_5S$: C, 49.70; H, 4.97; N, 8.28. Found: C, 49.51; H, 4.99; N, 8.31.

*4.1.3.11. N-((2-(3-Methoxypropoxy)-6-(trifluoromethyl)pyridin-3-yl) methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**18**).* Yield 77%, white solid, mp 112 °C; ^{1}H NMR ($CDCl_3$) δ 7.61 (d, J = 7.3 Hz, 1H), 7.49 (dd, J = 8.1 Hz, 1H), 7.20 (d, J = 7.3 Hz, 1H), 7.02–7.11 (m, 2H), 6.44 (bt, 1H), 4.47–4.50 (m, 2H), 4.34 (d, J = 6.0 Hz, 2H), 3.42–3.61 (m, 3H), 3.36 (s, 3H), 3.03 (s, 3H), 1.89–2.01 (m, 2H), 1.47 (d, J = 7.1 Hz, 3H); MS (FAB) m/z 508 (M + H). Anal. Calcd for $C_{21}H_{25}F_4N_3O_5S$: C, 49.70; H, 4.97; N, 8.28. Found: C, 49.88; H, 4.96; N, 8.24.

*4.1.3.12. N-((2-(3-Ethoxypropoxy)-6-(trifluoromethyl)pyridin-3-yl) methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**19**).* Yield 60%, white solid, mp 113 °C; ^{1}H NMR ($CDCl_3$) δ 7.61 (d, J = 7.5 Hz, 1H), 7.50 (dd, J = 8.3 Hz, 1H), 7.20 (d, J = 7.5 Hz, 1H), 7.01–7.12 (m, 2H), 6.35 (bt, H), 4.37–4.50 (m, 2H), 4.35 (d, J = 6.0 Hz, 2H), 3.47–3.60 (m, 5H), 3.03 (s, 3H), 1.90–2.01 (m, 2H), 1.47 (d, J = 7.0 Hz, 3H), 1.20 (t, J = 7.1 Hz, 3H); MS (FAB) m/z 522 (M + H). Anal. Calcd for $C_{22}H_{27}F_4N_3O_5S$: C, 50.67; H, 5.22; N, 8.06. Found: C, 50.49; H, 5.24; N, 8.09.

*4.1.3.13. N-((2-(2-Phenoxyethoxy)-6-(trifluoromethyl)pyridin-3-yl) methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**20**).* Yield 68%, white solid, mp 70 °C; ^{1}H NMR ($CDCl_3$) δ 7.66 (d, J = 7.3 Hz, 1H), 7.41 (dd, J = 8.4, 8.4 Hz, 1H), 7.22–7.35 (m, 3H), 6.88–7.05 (m, 5H), 6.42 (bs, 1H), 6.21 (bt, 1H), 4.63–4.82 (m, 2H), 4.27–4.42 (m, 4H), 3.34 (q, J = 7.1 Hz, 1H), 2.99 (s, 3H), 1.38 (d, J = 7.0 Hz, 3H); MS (FAB) m/z 556 (M + H). Anal. Calcd for $C_{25}H_{25}F_4N_3O_5S$: C, 54.05; H, 4.54; N, 7.56. Found: C, 54.23; H, 4.52; N, 7.53.

*4.1.3.14. N-((2-Isopropoxy-6-(trifluoromethyl)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**21**).* Yield 81%, white solid, mp 66–68 °C; ^{1}H NMR ($CDCl_3$) δ 7.56 (d, J = 7.5 Hz, 1H), 7.50 (dd, J = 8.1 Hz, 1H), 7.16 (d, J = 7.5 Hz, 1H), 7.12–7.05 (m, 2H), 6.70 (bs, NH), 6.05 (bt, NH), 5.36 (m, 1H), 3.53 (q, J = 7.1 Hz, 1H), 3.03 (s, 3H), 1.49 (d, J = 7.1 Hz, 3H), 1.30 (t, 6H); MS (FAB) m/z 478 (M + H). Anal. Calcd for $C_{20}H_{23}F_4N_3O_4S$: C, 50.31; H, 4.86; N, 8.80. Found: C, 50.49; H, 4.84; N, 8.77.

*4.1.3.15. N-((2-Isobutoxy-6-(trifluoromethyl)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**22**).* Yield 84%, white solid, mp 62–64 °C; ^{1}H NMR ($CDCl_3$) δ 7.60 (d, J = 7.3 Hz, 1H), 7.52 (dd, J = 8.3, 8.3 Hz, 1H), 7.21 (d, J = 7.3 Hz, 1H), 7.12–7.06 (m, 2H), 6.50 (bs, NH), 6.00 (bt, NH), 4.37 (d, J = 6.1 Hz, 2H), 3.95 (s, 3H), 3.52 (q, J = 7.1 Hz, 1H), 3.04 (s, 3H), 1.49 (d, J = 7.0 Hz, 3H); MS (FAB) m/z 492 (M + H). Anal. Calcd for $C_{21}H_{25}F_4N_3O_4S$: C, 51.32; H, 5.13; N, 8.55. Found: C, 51.15; H, 5.15; N, 8.58.

*4.1.3.16. N-((2-Isopentyloxy-6-(trifluoromethyl)pyridin-3-yl) methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**23**).* Yield 68%, white solid, mp 136–139 °C; ^{1}H NMR (CD_3OD) δ 7.40–7.49 (m, 2H), 7.14–7.23 (m, 3H), 4.38 (t, J = 7.2 Hz, 2H), 4.31 (d, J = 7.5 Hz, 2H), 3.71 (q, J = 6.9 Hz, 1H), 2.97 (s, 3H), 1.76 (m, 1H), 1.64 (q, J = 6.6 Hz, 2H), 1.45 (d, J = 6.9 Hz, 3H), 0.95 (d, J = 6.6 Hz, 6H); MS (FAB) m/z 506 (M + H). Anal. Calcd for $C_{22}H_{27}F_4N_3O_4S$: C, 52.27; H, 5.38; N, 8.31. Found: C, 52.06; H, 5.40; N, 8.35.

*4.1.3.17. N-((2-(3,3-Dimethylbutoxy)-6-(trifluoromethyl)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**24**).* Yield 70%, white solid, mp 64–66 °C; ^{1}H NMR (CD_3OD) δ 7.40–7.48 (m, 2H), 7.13–7.22 (m, 3H), 4.42 (t, J = 7.5 Hz, 2H), 4.31 (d, J = 7.2 Hz, 2H), 3.72 (q, J = 6.9 Hz, 1H), 2.97 (s, 3H), 1.68 (t, J = 7.2 Hz, 2H), 1.45 (d, J = 6.9 Hz, 3H), 0.97 (s, 9H); MS (FAB) m/z 520 (M + H). Anal. Calcd for $C_{23}H_{29}F_4N_3O_4S$: C, 53.17; H, 5.63; N, 8.09. Found: C, 53.30; H, 5.62; N, 8.06.

*4.1.3.18. N-((2-(Pentan-3-yloxy)-6-(trifluoromethyl)pyridin-3-yl) methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**25**).* Yield 65%, colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.55 (d, J = 7.5 Hz, 1H), 7.49 (t, J = 8.4 Hz, 1H), 7.12 (m, 3H), 6.25 (t, J = 5.7 Hz, 1H), 5.20 (m, 1H), 4.42 (m, 2H), 3.58 (q, J = 6.9 Hz, 1H), 3.01 (s, 3H), 1.70 (m, 4H), 1.49 (d, J = 6.9 Hz, 3H), 0.90 (m, 6H); MS (FAB) m/z 506 (M + H). Anal. Calcd for $C_{22}H_{27}F_4N_3O_4S$: C, 52.27; H, 5.38; N, 8.31. Found: C, 52.09; H, 5.40; N, 8.34.

*4.1.3.19. N-((2-(Heptan-4-yloxy)-6-(trifluoromethyl)pyridin-3-yl) methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**26**).* Yield 68%, colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.56 (d, J = 7.4 Hz, 1H), 7.48 (t, J = 8.5 Hz, 1H), 7.11 (m, 3H), 6.24 (t, J = 5.8 Hz, 1H), 5.21 (m, 1H), 4.43 (m, 2H), 3.59 (q, J = 6.8 Hz, 1H), 3.02 (s, 3H), 1.71 (m, 4H), 1.48 (d, J = 6.9 Hz, 3H), 1.25 (m, 4H), 0.92 (m, 6H); MS (FAB) m/z 534 (M + H). Anal. Calcd for $C_{24}H_{31}F_4N_3O_4S$: C, 54.02; H, 5.86; N, 7.88. Found: C, 54.22; H, 5.85; N, 7.85.

*4.1.3.20. N-((2-(Nonan-5-yloxy)-6-(trifluoromethyl)pyridin-3-yl) methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**27**).* Yield 57%, pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.49–7.56 (m, 2H), 7.15 (d, J = 7.7 Hz, 1H), 7.08 (t, J = 5.9 Hz, 1H), 6.47 (bs, 1H), 5.98 (bt, 1H), 5.29 (m, 1H), 4.37 (m, 2H), 3.49 (q, J = 7.0 Hz, 1H), 3.03 (s, 3H), 1.57 (m, 2H), 1.49 (d, J = 7.0 Hz, 3H), 1.24–1.31 (m, 8H), 0.88–0.90 (m, 6H); MS (FAB) m/z 562 (M + H). Anal. Calcd for $C_{26}H_{35}F_4N_3O_4S$: C, 55.60; H, 6.28; N, 7.48. Found: C, 55.78; H, 6.27; N, 7.45.

*4.1.3.21. N-((2-(2,6-Dimethylheptan-4-yloxy)-6-(trifluoromethyl) pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl) propanamide (**28**).* Yield 67%, colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.57 (d, J = 7.5 Hz, 1H), 7.49 (t, J = 8.6 Hz, 1H), 7.12 (m, 3H), 6.25 (t, J = 5.8 Hz, 1H), 5.22 (m, 1H), 4.44 (m, 2H), 3.57 (q, J = 6.9 Hz, 1H), 3.03 (s, 3H), 1.71 (m, 4H), 1.49 (d, J = 6.8 Hz, 3H), 1.24 (m, 2H), 0.92 (m, 12H); MS (FAB) m/z 562 (M + H). Anal. Calcd for $C_{26}H_{35}F_4N_3O_4S$: C, 55.60; H, 6.28; N, 7.48. Found: C, 55.78; H, 6.26; N, 7.44.

*4.1.3.22. N-((2-Cyclobutoxy-6-(trifluoromethyl)pyridin-3-yl) methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**29**).* Yield 80%, white solid, mp 76–78 °C; ^{1}H NMR ($CDCl_3$) δ 7.58–7.51 (m, 2H), 7.18 (d, J = 7.3 Hz, 1H), 7.13–7.07 (m, 2H), 6.50 (bs, NH), 6.00 (bt, NH), 5.20 (m, 1H), 4.37 (d, J = 6.2 Hz, 2H), 3.56 (q, J = 7.0 Hz, 1H), 3.03 (s, 3H), 2.50–2.40 (m, 2H), 2.05–1.65 (m, 4H), 1.50 (d, J = 7.1 Hz, 3H); MS (FAB) m/z 490 (M + H). Anal. Calcd for $C_{21}H_{23}F_4N_3O_4S$: C, 51.53; H, 4.74; N, 8.58. Found: C, 51.35; H, 4.76; N, 8.61.

*4.1.3.23. N-((2-Cyclopentyloxy-6-(trifluoromethyl)pyridin-3-yl) methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**30**).* Yield 79%, white solid, mp 67–69 °C; ^{1}H NMR ($CDCl_3$) δ 7.56 (d, J = 7.5 Hz, 1H), 7.50 (dd, J = 8.1, 8.1 Hz, 1H), 7.16 (d, J = 7.5 Hz, 1H), 7.12–7.05 (m, 2H), 6.70 (bs, NH), 6.05 (bt, NH), 5.36 (m, 1H), 3.53 (q,

J = 7.1 Hz, 1H), 3.03 (s, 3H), 1.49 (d, J = 7.1 Hz, 3H), 1.30 (t, 6H); MS (FAB) m/z 504 (M + H). Anal. Calcd for $C_{22}H_{25}F_4N_3O_4S$: C, 52.48; H, 5.00; N, 8.35. Found: C, 52.67; H, 4.98; N, 8.33.

*4.1.3.24. N-((2-Cyclohexyloxy-6-(trifluoromethyl)pyridin-3-yl) methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**31**).* Yield 80%, white solid, mp 81–83 °C; ^{1}H NMR ($CDCl_3$) δ 7.56 (d, J = 7.5 Hz, 1H), 7.50 (dd, J = 8.1 Hz, 1H), 7.16 (d, J = 7.5 Hz, 1H), 7.12–7.05 (m, 2H), 6.70 (bs, NH), 6.05 (bt, NH), 5.36 (m, 1H), 3.53 (q, J = 7.1 Hz, 1H), 3.03 (s, 3H), 1.49 (d, J = 7.1 Hz, 3H), 1.30 (t, 6H); MS (FAB) m/z 518 (M + H). Anal. Calcd for $C_{23}H_{27}F_4N_3O_4S$: C, 53.38; H, 5.26; N, 8.12. Found: C, 53.59; H, 5.23; N, 8.07.

*4.1.3.25. N-((6-Trifluoromethyl-2-(4-(trifluoromethyl)cyclohexyloxy) pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl) propanamide (**32**).* Yield 30%, white solid, mp 66–68 °C; ^{1}H NMR ($CDCl_3$) δ 7.59 (d, J = 7.0 Hz, 1H), 7.51 (dd, J = 8.2 Hz, 1H), 7.20 (d, J = 7.5 Hz, 1H), 7.13–7.05 (m, 2H), 6.50 (bs, NH), 5.91 (bt, NH), 5.43 (m, 1H), 4.39 (m, 2H), 3.51 (q, J = 6.6 Hz, 1H), 3.03 (s, 3H), 2.20–2.08 (m, 3H), 1.85–1.77 (m, 2H), 1.63–1.50 (m, 4H), 1.49 (d, J = 7.1 Hz, 3H); MS (FAB) m/z 586 (M + H). Anal. Calcd for $C_{24}H_{26}F_7N_3O_4S$: C, 49.23; H, 4.48; N, 7.18. Found: C, 49.50; H, 4.51; N, 7.14.

*4.1.3.26. N-((2-(4-Methylcyclohexyloxy)-6-(trifluoromethyl)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**33**).* Yield 78%, white solid, mp 107–109 °C; ^{1}H NMR ($CDCl_3$) δ 7.57–7.49 (m, 2H), 7.16 (d, J = 7.3 Hz, 1H), 7.12–7.05 (m, 2H), 6.48 (bs, NH), 5.99 (bt, NH), 5.00 (m, 1H), 4.34 (d, J = 5.8 Hz, 2H), 3.51 (q, J = 6.8 Hz, 1H), 3.03 (s, 3H), 2.12–2.00 (m, 2H), 1.80–1.72 (m, 2H), 1.50–1.10 (m, 5H), 1.48 (d, J = 7.1 Hz, 3H), 0.94 (d, J = 6.6 Hz, 3H); MS (FAB) m/z 532 (M + H). Anal. Calcd for $C_{24}H_{29}F_4N_3O_4S$: C, 54.23; H, 5.50; N, 7.91. Found: C, 54.40; H, 5.51; N, 7.95.

*4.1.3.27. N-((2-(4-Ethylcyclohexyloxy)-6-(trifluoromethyl)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**34**).* Yield 65%, white solid, mp 123–125 °C; ^{1}H NMR ($CDCl_3$) δ 7.57–7.50 (m, 2H), 7.16 (d, J = 7.3 Hz, 1H), 7.12–7.05 (m, 2H), 6.47 (bs, NH), 5.99 (bt, NH), 5.00 (m, 1H), 4.34 (m, 2H), 3.52 (q, J = 7.5 Hz, 1H), 3.03 (s, 3H), 2.13–2.03 (m, 2H), 1.87–1.80 (m, 2H), 1.49 (d, J = 7.1 Hz, 3H), 1.32–1.04 (m, 7H), 0.91 (t, J = 7.1 Hz, 3H); MS (FAB) m/z 546 (M + H). Anal. Calcd for $C_{25}H_{31}F_4N_3O_4S$: C, 55.04; H, 5.73; N, 7.70. Found: C, 55.20; H, 5.72; N, 7.68.

*4.1.3.28. N-((2-(4-tert-Butylcyclohexyloxy)-6-(trifluoromethyl)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**35**).* Yield 69%, white solid, mp 83–85 °C; ^{1}H NMR ($CDCl_3$) δ 7.57–7.50 (m, 2H), 7.16 (d, J = 7.3 Hz, 1H), 7.12–7.05 (m, 2H), 6.46 (bs, NH), 5.98 (bt, NH), 4.96 (m, 1H), 4.34 (m, 2H), 3.51 (q, J = 7.1 Hz, 1H), 3.03 (s, 3H), 2.20–2.10 (m, 2H), 1.88–1.80 (m, 2H), 1.49 (d, J = 7.1 Hz, 3H), 1.30–1.00 (m, 5H), 0.89 (s, 9H); MS (FAB) m/z 574 (M + H). Anal. Calcd for $C_{27}H_{35}F_4N_3O_4S$: C, 56.53; H, 6.15; N, 7.33. Found: C, 56.38; H, 6.17; N, 7.35.

*4.1.3.29. N-((2-(4,4-Dimethylcyclohexyloxy)-6-(trifluoromethyl)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**36**).* Yield 63%, white solid, mp 86 °C; ^{1}H NMR ($CDCl_3$) δ 7.56–7.50 (m, 2H), 7.17 (d, J = 7.2 Hz, 1H), 7.11–7.05 (m, 2H), 6.44 (bs, NH), 5.97 (bt, NH), 4.96 (m, 1H), 4.33 (m, 2H), 3.52 (q, J = 7.2 Hz, 1H), 3.03 (s, 3H), 2.20–2.10 (m, 2H), 1.88–1.80 (m, 2H), 1.49 (d, J = 7.1 Hz, 3H), 1.30–1.00 (m, 4H), 0.96 (d, J = 6.3 Hz, 6H); MS (FAB) m/z 546 (M + H). Anal. Calcd for $C_{25}H_{31}F_4N_3O_4S$: C, 55.04; H, 5.73; N, 7.70. Found: C, 54.90; H, 5.74; N, 7.73.

*4.1.3.30. N-((2-(3,5-Dimethylcyclohexyloxy)-6-(trifluoromethyl)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl) propanamide (**37**).* Yield 66%, white solid, mp 84 °C; ^{1}H NMR ($CDCl_3$) δ 7.55–7.51 (m, 2H), 7.18 (d, J = 7.4 Hz, 1H), 7.10–7.06 (m, 2H), 6.42 (bs, NH), 5.98 (bt, NH), 4.95 (m, 1H), 4.34 (m, 2H), 3.53 (q, J = 7.2 Hz, 1H), 3.03 (s, 3H), 2.22–2.10 (m, 2H), 1.88–1.80 (m, 2H), 1.48 (d, J = 7.1 Hz, 3H), 1.29 (m, 1H), 1.28–1.00 (m, 3H), 0.96 (d, J = 6.3 Hz, 6H); MS (FAB) m/z 546 (M + H). Anal. Calcd for $C_{25}H_{31}F_4N_3O_4S$: C, 55.04; H, 5.73; N, 7.70. Found: C, 54.89; H, 5.74; N, 7.73.

*4.1.3.31. N-((2-(Piperidin-4-yloxy)-6-(trifluoromethyl)pyridin-3-yl) methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**38**).* Yield 69%, white solid, mp 80–82 °C; ^{1}H NMR ($CDCl_3$) δ 7.58 (d, J = 7.5 Hz, 1H), 7.41 (dd, J = 8.3 Hz, 1H), 7.27 (d, J = 7.5 Hz, 1H), 7.19–7.11 (m, 2H), 5.29 (m, 1H), 4.36 (m, 2H), 3.71 (q, J = 7.0 Hz, 1H), 3.20 (m, 2H), 3.01–2.90 (m, 2H), 2.97 (s, 3H), 2.06 (m, 2H), 1.81 (m, 2H), 1.45 (d, J = 7.1 Hz, 3H); MS (FAB) m/z 519 (M + H). Anal. Calcd for $C_{22}H_{26}F_4N_4O_4S$: C, 50.96; H, 5.05; N, 10.81. Found: C, 50.78; H, 5.07; N, 10.84.

*4.1.3.32. tert-Butyl 4-(3-((2-(3-fluoro-4-(methylsulfonamido)phenyl) propanamido)methyl)-6-(trifluoromethyl)pyridin-2-yloxy)piperidine-1-carboxylate (**39**).* Yield 75%, white solid, mp 82–84 °C; ^{1}H NMR ($CDCl_3$) δ 7.60 (d, J = 7.3 Hz, 1H), 7.50 (dd, J = 8.2 Hz, 1H), 7.20 (d, J = 7.3 Hz, 1H), 7.13–7.04 (m, 2H), 5.87 (bt, NH), 5.24 (m, 1H), 4.36 (d, 2H), 3.70–3.62 (m, 2H), 3.54 (q, J = 7.7 Hz, 1H), 3.28–3.17 (m, 2H), 3.04 (s, 3H), 1.98–1.88 (m, 2H), 1.54–1.40 (m, 2H), 1.51 (d, 3H), 1.50 (s, 9H); MS (FAB) m/z 619 (M + H). Anal. Calcd for $C_{27}H_{34}F_4N_4O_6S$: C, 52.42; H, 5.54; N, 9.06. Found: C, 52.59; H, 5.52; N, 9.03.

*4.1.3.33. N-((2-(2,3-Dihydro-1H-inden-2-yloxy)-6-(trifluoromethyl) pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl) propanamide (**40**).* Yield 83%, white solid, mp 135 °C; ^{1}H NMR ($CDCl_3$) δ 7.59 (d, J = 7.3 Hz, 1H), 7.46 (dd, J = 8.2 Hz, 1H), 7.29–7.24 (m, 5H), 6.99 (dd, J = 2.0 Hz, 1H), 6.91 (d, J = 8.8 Hz, 1H), 6.35 (bs, 1H), 5.89 (m, 1H), 5.79 (bt, 1H), 4.27 (m, 2H), 3.43 (dd, J = 5.5 Hz, 2H), 3.08–3.04 (m, 3H), 3.00 (s, 3H), 1.31 (d, J = 7.1 Hz, 3H); MS (FAB) m/z 552 (M + H). Anal. Calcd for $C_{26}H_{25}F_4N_3O_4S$: C, 56.62; H, 4.57; N, 7.62. Found: C, 56.79; H, 4.56; N, 7.59.

*4.1.3.34. N-((2-(Cyclopropylmethoxy)-6-(trifluoromethyl)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**41**).* Yield 81%, white solid, mp 89–91 °C; ^{1}H NMR ($CDCl_3$) δ 7.60 (d, J = 7.3 Hz, 1H), 7.52 (dd, J = 8.3 Hz, 1H), 7.21 (d, J = 7.3 Hz, 1H), 7.12–7.06 (m, 2H), 6.50 (bs, NH), 6.00 (bt, NH), 4.37 (d, J = 6.1 Hz, 2H), 3.95 (s, 3H), 3.52 (q, J = 7.1 Hz, 1H), 3.04 (s, 3H), 1.49 (d, J = 7.0 Hz, 3H); MS (FAB) m/z 490 (M + H). Anal. Calcd for $C_{21}H_{23}F_4N_3O_4S$: C, 51.53; H, 4.74; N, 8.58. Found: C, 51.70; H, 4.73; N, 8.55.

*4.1.3.35. N-((2-((2-Methylcyclopropyl)methoxy)-6-(trifluoromethyl) pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl) propanamide (**42**).* Yield 75%, white solid, mp 96–97 °C; ^{1}H NMR (CD_3OD) δ 7.48 (d, J = 7.5 Hz, 1H), 7.43 (dd, J = 8.1 Hz, 1H), 7.15–7.23 (m, 3H), 4.34 (d, J = 5.1 Hz, 2H), 4.20 (d, J = 7.1 Hz, 2H), 3.73 (q, J = 6.9 Hz, 1H), 2.98 (s, 3H), 1.46 (d, J = 7.1 Hz, 3H), 1.04 (d, J = 6.0 Hz, 3H), 0.95 (m, 1H), 0.78 (m, 1H), 0.51 (m, 1H), 0.31 (m, 1H); MS (FAB) m/z 504 (M + H). Anal. Calcd for $C_{22}H_{25}F_4N_3O_4S$: C, 52.48; H, 5.00; N, 8.35. Found: C, 52.63; H, 5.01; N, 8.37.

*4.1.3.36. N-((2-((2,2-Dimethylcyclopropyl)methoxy)-6-(trifluoromethyl)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**43**).* Yield 72%, white solid, mp 63–65 °C; ^{1}H NMR ($CDCl_3$) δ 7.58 (d, J = 7.3 Hz, 1H), 7.51 (dd, J = 8.4 Hz, 1H), 7.19 (d, J = 7.3 Hz, 1H), 7.14–7.05 (m, 2H), 6.54 (bs,

NH), 6.07 (bt, NH), 4.57–4.33 (m, 3H), 4.24–4.15 (m, 1H), 3.51 (q, J = 7.1 Hz, 1H), 3.03 (s, 3H), 1.49 (dd, J = 1.7 Hz, 3H), 1.13 (d, J = 1.5 Hz, 3H), 1.09 (s, 3H), 1.06–0.95 (m, 1H), 0.57 (dd, J = 8.4, 4.4 Hz, 1H), 0.28 (m, 1H); MS (FAB) m/z 518 (M + H). Anal. Calcd for $C_{23}H_{27}F_4N_3O_4S$: C, 53.38; H, 5.26; N, 8.12. Found: C, 53.55; H, 5.24; N, 8.10.

*4.1.3.37. N-((2-(Cyclobutylmethoxy)-6-(trifluoromethyl)pyridin-3-yl) methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**44**).* Yield 79%, white solid, mp 100–102 °C; ^{1}H NMR ($CDCl_3$) δ 7.57 (d, J = 7.5 Hz, 1H), 7.50 (dd, J = 8.2, 8.2 Hz, 1H), 7.19 (d, J = 7.3 Hz, 1H), 7.12–7.04 (m, 2H), 6.64 (bs, NH), 6.02 (bt, NH), 4.45–4.26 (m, 4H), 3.51 (q, J = 7.1 Hz, 1H), 3.03 (s, 3H), 2.71 (m, 1H), 2.13–1.79 (m, 6H), 1.48 (d, J = 7.1 Hz, 3H); MS (FAB) m/z 504 (M + H). Anal. Calcd for $C_{22}H_{25}F_4N_3O_4S$: C, 52.48; H, 5.00; N, 8.35. Found: C, 52.67; H, 4.99; N, 8.32.

*4.1.3.38. N-((2-(Cyclopentylmethoxy)-6-(trifluoromethyl)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**45**).* Yield 70%, white solid, mp 112–114 °C; ^{1}H NMR ($CDCl_3$) δ 7.58–7.51 (m, 2H), 7.18 (d, J = 7.3 Hz, 1H), 7.13–7.07 (m, 2H), 6.50 (bs, NH), 6.00 (bt, NH), 5.20 (m, 1H), 4.37 (d, J = 6.2 Hz, 2H), 3.56 (q, J = 7.0 Hz, 1H), 3.03 (s, 3H), 2.50–2.40 (m, 2H), 2.05–1.65 (m, 4H), 1.50 (d, J = 7.1 Hz, 3H); MS (FAB) m/z 518 (M + H). Anal. Calcd for $C_{23}H_{27}F_4N_3O_4S$: C, 53.38; H, 5.26; N, 8.12. Found: C, 53.55; H, 5.24; N, 8.09.

*4.1.3.39. N-((2-(Cyclohexylmethoxy)-6-(trifluoromethyl)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**46**).* Yield 73%, white solid, mp 108–110 °C; ^{1}H NMR ($CDCl_3$) δ 7.56 (d, J = 7.3 Hz, 1H), 7.51 (dd, J = 8.3, 8.3 Hz, 1H), 7.18 (d, J = 7.3 Hz, 1H), 7.12–7.04 (m, 2H), 6.57 (bs, NH), 5.99 (bt, NH), 4.38 (m, 2H), 4.16 (m, 2H), 3.51 (q, J = 7.1 Hz, 1H), 3.03 (s, 3H), 1.82–1.67 (m, 5H), 1.49 (d, J = 7.1 Hz, 3H), 1.32–1.00 (m, 6H); MS (FAB) m/z 532 (M + H). Anal. Calcd for $C_{24}H_{29}F_4N_3O_4S$: C, 54.23; H, 5.50; N, 7.91. Found: C, 54.05; H, 5.51; N, 7.94.

*4.1.3.40. N-((2-((4-Methylcyclohexyl)methoxy)-6-(trifluoromethyl) pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl) propanamide (**47**).* Yield 73%, white solid, mp 71–73 °C; ^{1}H NMR ($CDCl_3$) δ 7.56 (d, J = 7.3 Hz, 1H), 7.50 (dd, J = 8.2, 8.2 Hz, 1H), 7.18 (d, J = 7.5 Hz, 1H), 7.12–7.04 (m, 2H), 6.59 (bs, NH), 6.00 (bt, NH), 4.45–4.11 (m, 4H), 3.51 (q, J = 7.1 Hz, 1H), 3.03 (s, 3H), 1.95–1.25 (m, 12H), 1.10–0.90 (m, 4H); MS (FAB) m/z 546 (M + H). Anal. Calcd for $C_{25}H_{31}F_4N_3O_4S$: C, 55.04; H, 5.73; N, 7.70. Found: C, 54.89; H, 5.75; N, 7.74.

*4.1.3.41. N-((2-(Piperidin-4-ylmethoxy)-6-(trifluoromethyl)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**48**).* Yield 66%, white solid, mp 52–54 °C; ^{1}H NMR (CD_3OD) δ 7.58 (d, J = 7.9 Hz, 1H), 7.43 (dd, J = 8.3, 8.3 Hz, 1H), 7.29 (d, J = 7.4 Hz, 1H), 7.22–7.15 (m, 2H), 4.47–4.23 (m, 4H), 3.73 (q, J = 7.1 Hz, 1H), 3.43–3.36 (m, 2H), 3.05–2.93 (m, 2H), 3.00 (s, 3H), 2.04–1.96 (m, 3H), 1.53–1.45 (m, 2H), 1.46 (d, J = 7.1 Hz, 3H); MS (FAB) m/z 533 (M + H). Anal. Calcd for $C_{23}H_{28}F_4N_4O_4S$: C, 51.87; H, 5.30; N, 10.52. Found: C, 51.69; H, 5.32; N, 10.55.

*4.1.3.42. tert-Butyl 4-((3-((2-(3-fluoro-4-(methylsulfonamido) phenyl)propanamido)methyl)-6-(trifluoromethyl)pyridin-2-yloxy) methyl)piperidine-1-carboxylate (**49**).* Yield 52%, white solid, mp 59–61 °C; ^{1}H NMR ($CDCl_3$) δ 7.60 (d, J = 7.5 Hz, 1H), 7.52 (dd, J = 8.4, 8.4 Hz, 1H), 7.21 (d, J = 7.5 Hz, 1H), 7.12–7.05 (m, 2H), 5.83 (bs, NH), 4.37 (d, J = 5.9 Hz, 2H), 4.25–4.07 (m, 4H), 3.53 (q, J = 6.4 Hz, 1H), 3.04 (s, 3H), 2.78–2.63 (m, 2H), 1.90 (m, 1H), 1.68–1.55 (m, 2H), 1.48 (s, 9H), 1.25–1.05 (m, 2H); MS (FAB) m/z 633 (M + H). Anal. Calcd for $C_{28}H_{36}F_4N_4O_6S$: C, 53.16; H, 5.74; N, 8.86. Found: C, 52.96; H, 5.76; N, 8.90.

*4.1.3.43. tert-Butyl 2-(2-(3-((2-(3-fluoro-4-(methylsulfonamido) phenyl)propanamido)methyl)-6-(trifluoromethyl)pyridin-2-yloxy) ethyl)piperidine-1-carboxylate (**50**).* Yield 64%, white solid, mp 60 °C; ^{1}H NMR ($CDCl_3$) δ 7.62 (d, J = 7.9 Hz, 1H), 7.50 (dd, J = 8.3, 8.4 Hz, 1H), 7.21 (d, J = 7.7 Hz, 1H), 7.15–7.05 (m, 2H), 5.85 (bs, NH), 4.36 (d, J = 5.6 Hz, 2H), 4.22–4.05 (m, 4H), 3.50 (q, J = 6.4 Hz, 1H), 3.03 (s, 3H), 2.79–2.63 (m, 2H), 1.92 (m, 2H), 1.65–1.55 (m, 2H), 1.44 (s, 9H), 1.22–1.05 (m, 2H); MS (FAB) m/z 647 (M + H). Anal. Calcd for $C_{29}H_{38}F_4N_4O_6S$: C, 53.86; H, 5.92; N, 8.66. Found: C, 53.69; H, 5.94; N, 8.69.

*4.1.3.44. N-((2-Phenoxy-6-(trifluoromethyl)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**51**).* Yield 80%, white solid, mp 95–97 °C; ^{1}H NMR (CD_3OD) δ 7.75 (d, J = 7.2 Hz, 1H), 7.00–7.49 (m, J = 7.8 Hz, 9H), 6.26 (bt, 1H), 4.51 (d, J = 5.7 Hz, 2H), 3.56 (q, J = 6.9 Hz, 1H), 3.01 (s, 3H), 1.48 (d, J = 6.9 Hz, 3H); MS (FAB) m/z 512 (M + H). Anal. Calcd for $C_{23}H_{21}F_4N_3O_4S$: C, 54.01; H, 4.14; N, 8.22. Found: C, 53.83; H, 4.16; N, 8.25.

*4.1.3.45. N-((2-(p-Tolyloxy)-6-(trifluoromethyl)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**52**).* Yield 78%, white solid, mp 167 °C; ^{1}H NMR ($CDCl_3$) δ 7.74 (d, J = 7.5 Hz, 1H), 7.47 (dd, J = 8.4, 8.4 Hz, 1H), 7.31 (d, J = 7.9 Hz, 1H), 7.18 (d, J = 8.8 Hz, 2H), 7.01 (m, 2H), 6.91 (m, 2H), 4.49 (m, 2H), 3.58 (q, J = 7.0 Hz, 1H), 2.94 (s, 3H), 1.49 (d, J = 7.1 Hz, 3H); MS (FAB) m/z 526 (M + H). Anal. Calcd for $C_{24}H_{23}F_4N_3O_4S$: C, 54.85; H, 4.41; N, 8.00. Found: C, 54.67; H, 4.43; N, 8.03.

*4.1.3.46. N-((2-Benzyloxy-6-(trifluoromethyl)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**53**).* Yield 71%, white solid, mp 115 °C; ^{1}H NMR ($CDCl_3$) δ 7.62 (d, J = 7.1 Hz, 1H), 7.47 (dd, J = 8.4, 8.4 Hz, 1H), 7.44–7.36 (m, 5H), 7.24 (d, J = 7.5 Hz, 1H), 7.04 (dd, J = 11.2, 1.8 Hz, 1H), 6.97 (d, J = 8.4 Hz, 1H), 6.42 (bs, 1H), 5.96 (bt, 1H), 5.41 (m, 2H), 4.39 (m, 2H), 3.41 (q, J = 7.1 Hz, 1H), 3.01 (s, 3H), 1.42 (d, J = 7.1 Hz, 3H); MS (FAB) m/z 526 (M + H). Anal. Calcd for $C_{24}H_{23}F_4N_3O_4S$: C, 54.85; H, 4.41; N, 8.00. Found: C, 54.66; H, 4.43; N, 8.03.

*4.1.3.47. N-((2-Phenethoxy-6-(trifluoromethyl)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**54**).* Yield 78%, white solid, mp 98 °C; ^{1}H NMR ($CDCl_3$) δ 7.60 (d, J = 7.4 Hz, 1H), 7.46 (dd, J = 8.3, 8.3 Hz, 1H), 7.33 (m, 5H), 7.19 (d, J = 7.3 Hz, 1H), 6.97 (dd, J = 11.3, 1.8 Hz, 1H), 6.89 (d, J = 8.9 Hz, 1H), 6.43 (bs, 1H), 5.70 (bt, 1H), 4.66 (m, 1H), 4.50 (m, 1H), 4.28 (d, J = 6.2 Hz, 2H), 3.14–3.05 (m, 3H), 2.99 (s, 3H), 1.36 (d, J = 7.1 Hz, 3H); MS (FAB) m/z 540 (M + H). Anal. Calcd for $C_{25}H_{25}F_4N_3O_4S$: C, 55.65; H, 4.67; N, 7.79. Found: C, 55.83; H, 4.65; N, 7.75.

*4.1.3.48. N-((2-(4-Methylbenzyloxy)-6-(trifluoromethyl)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**55**).* Yield 68%, white solid, mp 117–119 °C; ^{1}H NMR ($CDCl_3$) δ 7.61 (d, J = 7.4 Hz, 1H), 7.47 (dd, J = 8.1, 8.1 Hz, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 7.2 Hz, 1H), 7.20 (d, J = 7.9 Hz, 2H), 7.03 (dd, J = 11.5, 1.9 Hz, 1H), 6.96 (d, J = 8.6 Hz, 1H), 6.46 (bs, 1H), 5.98 (bt, 1H), 5.36 (m, 2H), 4.37 (m, 2H), 3.40 (q, J = 7.1 Hz, 1H), 3.01 (s, 3H), 2.28 (s, 3H), 1.42 (d, J = 7.0 Hz, 3H); MS (FAB) m/z 540 (M + H). Anal. Calcd for $C_{25}H_{25}F_4N_3O_4S$: C, 55.65; H, 4.67; N, 7.79. Found: C, 55.84; H, 4.65; N, 7.76.

4.1.3.49. N-((2-(4-Ethylbenzyloxy)-6-(trifluoromethyl)pyridin-3-yl) methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide

(**56**). Yield 78%, white solid, mp 137 °C; ^{1}H NMR ($CDCl_3$) δ 7.61 (d, J = 7.7 Hz, 1H), 7.47 (dd, J = 8.3, 8.3 Hz, 1H), 7.34 (d, J = 8.1 Hz, 2H), 7.23 (d, J = 7.7 Hz, 3H), 7.03 (dd, J = 11.2, 2.1 Hz, 1H), 6.84 (d, J = 8.6 Hz, 1H), 6.40 (bs, 1H), 5.96 (bt, 1H), 5.38 (m, 2H), 4.37 (m, 2H), 3.41 (q, J = 7.1 Hz, 1H), 3.01 (s, 3H), 2.68 (q, J = 7.5 Hz, 2H), 1.41 (d, J = 7.1 Hz, 3H), 1.25 (t, J = 7.6 Hz, 3H); MS (FAB) m/z 554 (M + H). Anal. Calcd for $C_{26}H_{27}F_4N_3O_4S$: C, 56.41; H, 4.92; N, 7.59. Found: C, 56.61; H, 4.90; N, 7.55.

*4.1.3.50. N-((2-(4-Butylbenzyloxy)-6-(trifluoromethyl)pyridin-3-yl) methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**57**).* Yield 72%, white solid, mp 131 °C; ^{1}H NMR ($CDCl_3$) δ 7.61 (d, J = 7.5 Hz, 1H), 7.48 (dd, J = 8.2, 8.2 Hz, 1H), 7.33 (d, J = 8.1 Hz, 2H), 7.23 (d, J = 7.3 Hz, 1H), 7.10 (d, J = 7.9 Hz, 2H), 7.04 (dd, J = 11.2, 2.0 Hz, 1H), 6.97 (d, J = 8.6 Hz, 1H), 6.41 (bs, 1H), 5.94 (bt, 1H), 5.38 (m, 2H), 4.37 (m, 2H), 3.39 (q, J = 7.0 Hz, 1H), 3.01 (s, 3H), 2.63 (t, J = 7.8 Hz, 2H), 1.61 (m, 2H), 1.41 (d, J = 7.1 Hz, 3H), 1.38 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H); MS (FAB) m/z 582 (M + H). Anal. Calcd for $C_{28}H_{31}F_4N_3O_4S$: C, 57.82; H, 5.37; N, 7.22. Found: C, 57.98; H, 5.38; N, 7.20.

*4.1.3.51. N-((2-(4-tert-Butylbenzyloxy)-6-(trifluoromethyl)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**58**).* Yield 78%, white solid, mp 105–107 °C; ^{1}H NMR ($CDCl_3$) δ 7.61 (d, J = 7.1 Hz, 1H), 7.48 (dd, J = 8.3, 8.3 Hz, 1H), 7.45–7.37 (m, 4H), 7.23 (d, J = 7.3 Hz, 1H), 7.04 (dd, J = 11.2, 1.9 Hz, 1H), 6.97 (d, J = 8.1 Hz, 1H), 6.42 (bs, 1H), 5.98 (bt, 1H), 5.39 (m, 2H), 4.38 (m, 2H), 3.40 (q, J = 7.3 Hz), 3.00 (s, 3H), 1.41 (d, J = 7.1 Hz, 1H), 1.34 (s, 9H); MS (FAB) m/z 582 (M + H). Anal. Calcd for $C_{28}H_{31}F_4N_3O_4S$: C, 57.82; H, 5.37; N, 7.22. Found: C, 57.99; H, 5.38; N, 7.19.

*4.1.3.52. N-((2-(4-Fluorobenzyloxy)-6-(trifluoromethyl)pyridin-3-yl) methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**59**).* Yield 68%, white solid, mp 142 °C; ^{1}H NMR ($CDCl_3$) δ 7.59 (d, J = 7.3 Hz, 1H), 7.48 (dd, J = 8.3, 8.3 Hz, 1H), 7.41 (m, 2H), 7.23 (d, J = 7.5 Hz, 1H), 7.06 (m, 3H), 6.99 (d, J = 8.0 Hz, 1H), 6.51 (bs, 1H), 5.93 (bt, 1H), 5.37 (m, 2H), 4.38 (m, 2H), 3.45 (q, J = 7.1 Hz, 1H), 3.02 (s, 3H), 1.44 (d, J = 7.1 Hz, 3H); MS (FAB) m/z 544 (M + H). Anal. Calcd for $C_{24}H_{22}F_5N_3O_4S$: C, 53.04; H, 4.08; N, 7.73. Found: C, 53.20; H, 4.06; N, 7.70.

*4.1.3.53. N-((2-(4-Chlorobenzyloxy)-6-(trifluoromethyl)pyridin-3-yl) methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**60**).* Yield 74%, white solid, mp 154 °C; ^{1}H NMR ($CDCl_3$) δ 7.60 (d, J = 7.5 Hz, 1H), 7.48 (dd, J = 8.3, 8.3 Hz, 1H), 7.39–7.28 (m, 4H), 7.24 (d, J = 7.5 Hz, 1H), 7.05 (dd, J = 11.2, 2.0 Hz, 1H), 7.00 (d, J = 8.3 Hz, 1H), 6.48 (bs, 1H), 5.91 (bt, 1H), 5.37 (d, J = 4.7 Hz, 2H), 4.39 (m, 2H), 3.45 (q, J = 7.1 Hz, 1H), 3.02 (s, 3H), 1.44 (d, J = 7.0 Hz, 3H); MS (FAB) m/z 560 (M + H). Anal. Calcd for $C_{24}H_{22}ClF_4N_3O_4S$: C, 51.48; H, 3.96; N, 7.50. Found: C, 51.67; H, 3.95; N, 7.47.

*4.1.3.54. N-((6-(Trifluoromethyl)-2-(4-(trifluoromethyl)benzyloxy) pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl) propanamide (**61**).* Yield 63%, white solid, mp 167 °C; ^{1}H NMR ($CDCl_3$) δ 7.64 (d, J = 8.4 Hz, 1H), 7.61 (d, J = 8.6 Hz, 2H), 7.55 (d, J = 8.1 Hz, 2H), 7.49 (dd, J = 8.2, 8.2 Hz, 1H), 7.25 (d, J = 8.3 Hz, 1H), 7.07 (dd, J = 11.2, 2.0 Hz, 1H), 7.01 (d, J = 7.9 Hz, 1H), 6.43 (bs, 1H), 5.89 (bt, 1H), 5.46 (m, 2H), 4.42 (d, J = 6.0 Hz, 2H), 3.48 (q, J = 7.1 Hz, 1H), 3.02 (s, 3H), 1.45 (d, J = 7.1 Hz, 3H); MS (FAB) m/z 594 (M + H). Anal. Calcd for $C_{25}H_{22}F_7N_3O_4S$: C, 50.59; H, 3.74; N, 7.08. Found: C, 50.77; H, 3.72; N, 7.05.

*4.1.3.55. N-((2-(4-Methoxybenzyloxy)-6-(trifluoromethyl)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**62**).* Yield 67%, white solid, mp 138 °C; ^{1}H NMR ($CDCl_3$) δ 7.62 (d, J = 7.2 Hz, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.37 (d, J = 8.7 Hz, 2H), 7.23 (d, J = 7.2 Hz, 1H), 7.00 (m, 4H), 6.45 (bs, 1H), 5.94 (bt, 1H), 5.43 (m, 2H), 4.37 (m, 2H), 3.83 (s, 3H), 3.41 (m, 1H), 3.01 (s, 3H), 1.42 (d, J = 7.2 Hz, 3H); MS (FAB) m/z 556 (M + H). Anal. Calcd for $C_{25}H_{25}F_4N_3O_5S$: C, 54.05; H, 4.54; N, 7.56. Found: C, 54.22; H, 4.52; N, 7.53.

*4.1.3.56. N-((2-(3-Fluorobenzyloxy)-6-(trifluoromethyl)pyridin-3-yl) methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**63**).* Yield 68%, white solid, mp 140 °C; ^{1}H NMR ($CDCl_3$) δ 7.63 (d, J = 7.5 Hz, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.36 (d, J = 6 Hz, 1H), 7.23 (m, 6H), 6.55 (bs, 1H), 5.97 (bt, 1H), 5.41 (d, J = 5.4 Hz, 2H), 4.40 (s, 2H), 3.48 (q, J = 6.9 Hz, 1H), 3.01 (s, 3H), 1.45 (d, J = 7.2 Hz, 3H); MS (FAB) m/z 544 (M + H). Anal. Calcd for $C_{24}H_{22}F_5N_3O_4S$: C, 53.04; H, 4.08; N, 7.73. Found: C, 52.91; H, 4.07; N, 7.70.

*4.1.3.57. N-((2-(3-Chlorobenzyloxy)-6-(trifluoromethyl)pyridin-3-yl) methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**64**).* Yield 66%, white solid, mp 155 °C; ^{1}H NMR ($CDCl_3$) δ 7.63 (d, J = 7.5 Hz, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.31 (m, 7H), 5.93 (bt, 1H), 5.97 (bt, 1H), 5.39 (d, J = 7.2 Hz, 2H), 4.42 (s, 2H), 3.47 (q, J = 6.9 Hz, 1H), 3.01 (s, 3H), 1.46 (d, J = 6.9 Hz, 3H); MS (FAB) m/z 560 (M + H). Anal. Calcd for $C_{24}H_{22}ClF_4N_3O_4S$: C, 51.48; H, 3.96; N, 7.50. Found: C, 51.38; H, 3.95; N, 7.48.

*4.1.3.58. N-((2-(3-Methoxybenzyloxy)-6-(trifluoromethyl)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**65**).* Yield 68%, white solid, mp 128 °C; ^{1}H NMR ($CDCl_3$) δ 7.62 (d, J = 7.7 Hz, 1H), 7.46 (dd, J = 8.3, 8.3 Hz, 1H), 7.31 (dd, J = 8.1 Hz, 1H), 7.23 (d, J = 7.4 Hz, 1H), 7.06–6.88 (m, 4H), 6.90 (m, 1H), 6.49 (bs, 1H), 5.99 (bt, 1H), 5.39 (m, 2H), 4.39 (m, 2H), 3.83 (s, 3H), 3.42 (q, J = 7.1 Hz, 1H), 3.01 (s, 3H), 1.42 (d, J = 7.1 Hz, 3H); MS (FAB) m/z 556 (M + H). Anal. Calcd for $C_{25}H_{25}F_4N_3O_5S$: C, 54.05; H, 4.54; N, 7.56. Found: C, 54.19; H, 4.52; N, 7.53.

*4.1.3.59. N-((2-(3,5-Difluorobenzyloxy)-6-(trifluoromethyl)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**66**).* Yield 66%, white solid, mp 145–148 °C; ^{1}H NMR ($CDCl_3$) δ 7.63 (d, J = 7.5 Hz, 1H), 7.52 (t, J = 8.4 Hz, 1H), 7.27 (d, J = 3 Hz, 1H), 7.10 (m, 2H), 6.94 (m, 2H), 6.79 (t, J = 2.1 Hz, 1H), 6.47 (bs, 1H), 5.91 (bt, 1H), 5.39 (m, 2H), 4.43 (q, J = 3.3 Hz, 2H), 3.51 (q, J = 6.9 Hz, 1H), 3.02 (s, 3H), 1.48 (d, J = 6.9 Hz, 3H); MS (FAB) m/z 562 (M + H). Anal. Calcd for $C_{24}H_{21}F_6N_3O_4S$: C, 51.34; H, 3.77; N, 7.48. Found: C, 51.52; H, 3.75; N, 7.45.

*4.1.3.60. N-((2-(3,5-Dichlorobenzyloxy)-6-(trifluoromethyl)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**67**).* Yield 72%, white solid, mp 156–160 °C; ^{1}H NMR ($CDCl_3$) δ 7.63 (d, J = 7.5 Hz, 1H), 7.63 (t, J = 7.5 Hz, 1H), 7.51 (t, J = 8.1 Hz, 1H), 7.33 (bs, 3H), 7.26 (m, 1H), 7.10 (m, 2H), 6.50 (bs, 1H), 5.92 (bt, 1H), 5.36 (m, 2H), 4.43 (m, 2H), 3.53 (q, J = 6.6 Hz, 1H), 3.02 (s, 3H), 1.45 (d, J = 9.6 Hz, 3H); MS (FAB) m/z 595 (M + H). Anal. Calcd for $C_{24}H_{21}Cl_2F_4N_3O_4S$: C, 48.49; H, 3.56; N, 7.07. Found: C, 48.65; H, 3.54; N, 7.03.

*4.1.3.61. N-((2-(3,5-Dimethoxybenzyloxy)-6-(trifluoromethyl)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**68**).* Yield 65%, white solid, mp 148 °C; ^{1}H NMR ($CDCl_3$) δ 7.63 (d, J = 7.3 Hz, 1H), 7.45 (dd, J = 8.3, 8.3 Hz, 1H), 7.24 (d, J = 7.5 Hz, 1H), 7.04 (dd, J = 11.2, 2.0 Hz, 1H), 6.98 (d, J = 8.8 Hz, 1H), 6.59 (d, J = 2.2 Hz, 2H), 6.45 (t, J = 2.4 Hz, 1H), 6.00 (bt, 1H), 5.26–5.41 (m, 2H), 4.30–4.48 (m, 2H), 3.81 (s, 6H), 3.43 (q, J = 7.3 Hz, 1H), 3.01 (s, 3H), 1.43 (d, J = 7.1 Hz, 3H); MS (FAB) m/z 586 (M + H). Anal. Calcd for $C_{26}H_{27}F_4N_3O_6S$: C, 53.33; H, 4.65; N, 7.18. Found: C, 53.50; H, 4.63; N, 7.15.

*4.1.3.62. N-((2-(Pyridin-2-ylmethoxy)-6-(trifluoromethyl)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**69**).* Yield 67%, white solid, mp 105 °C; ^{1}H NMR ($CDCl_3$) δ 8.61 (d, J = 4.7 Hz, 1H), 7.74 (dd, J = 7.6, 1.7 Hz, 1H), 7.67 (d, J = 7.3 Hz, 1H), 7.42 (dd, J = 8.2, 8.2 Hz, 1H), 7.43 (d, J = 7.7 Hz, 1H), 7.33 (m, 1H), 7.24 (d, J = 7.5 Hz, 1H), 7.09 (dd, J = 11.4, 2.0 Hz, 1H), 7.01 (d, J = 8.2 Hz, 1H), 6.54 (bs, 1H), 5.51 (m, 2H), 4.45 (d, J = 5.7 Hz, 2H), 3.58 (q, J = 7.0 Hz, 1H), 3.01 (s, 3H), 1.46 (d, J = 7.0 Hz, 3H); MS (FAB) m/z 527 (M + H). Anal. Calcd for $C_{23}H_{22}F_4N_4O_4S$: C, 52.47; H, 4.21; N, 10.64. Found: C, 52.66; H, 4.19; N, 10.62.

*4.1.3.63. N-((2-(Pyridin-3-ylmethoxy)-6-(trifluoromethyl)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**70**).* Yield 68%, white solid, mp 95–97 °C; ^{1}H NMR ($CDCl_3$) δ 8.69 (m, 2H), 7.79 (d, J = 7.7 Hz, 1H), 7.64 (d, J = 7.5 Hz, 1H), 7.48 (dd, J = 8.1 Hz, 1H), 7.34 (m, 1H), 7.25 (d, J = 7.5 Hz, 1H), 7.05 (dd, J = 11.4, 1.9 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 5.87 (bt, 1H), 5.41 (s, 2H), 4.38 (d, J = 6.2 Hz, 2H), 3.49 (q, J = 7.3 Hz, 1H), 3.04 (s, 3H), 1.46 (d, J = 7.1 Hz, 3H); MS (FAB) m/z 527 (M + H). Anal. Calcd for $C_{23}H_{22}F_4N_4O_4S$: C, 52.47; H, 4.21; N, 10.64. Found: C, 52.63; H, 4.19; N, 10.60.

*4.1.3.64. N-((2-(Pyridin-4-ylmethoxy)-6-(trifluoromethyl)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (**71**).* Yield 75%, white solid, mp 103–105 °C; ^{1}H NMR ($CDCl_3$) δ 8.49 (d, J = 6.2 Hz, 2H), 7.61 (d, J = 7.4 Hz, 1H), 7.49 (d, J = 6.2 Hz, 2H), 7.40 (dd, J = 8.3, 8.3 Hz, 1H), 7.32 (d, J = 7.4 Hz, 1H), 7.19 (dd, J = 11.5, 2.0 Hz, 1H), 7.14 (d, J = 8.4 Hz, 1H), 5.49 (s, 2H), 4.35 (m, 2H), 3.72 (q, J = 6.9 Hz, 1H), 2.96 (s, 3H), 1.45 (d, J = 7.0 Hz, 3H); MS (FAB) m/z 527 (M + H). Anal. Calcd for $C_{23}H_{22}F_4N_4O_4S$: C, 52.47; H, 4.21; N, 10.64. Found: C, 52.65; H, 4.20; N, 10.61.

4.2. Animal test

4.2.1. Animals

The studies were conducted with male NMRI mice (20–35 g) and male Sprague Dawley rats (130–180 g), supplied by commercial breeders (Charles River, Sulzfeld, Germany; Iffa Credo, Brussels, Belgium; Janvier, Genest St. Isle, France). Animals were housed under a 12:12 h light–dark cycle (lights on at 06:00 a.m.), and with room temperature 20–24 °C, relative air humidity 35–70%, 15 air changes per hour, and air movement <0.2 m/s. The animals had free access to standard laboratory food (Ssniff R/M-Haltung, Ssniff Spezialdiäten GmbH, Soest, Germany) and tap water. All animals were used only once in all pain models. There were at least five days between delivery of the animals and the start of experiment. Animal testing was performed in accordance with the recommendations and policies of the International Association for the Study of Pain [22] and the German Animal Welfare Law. All study protocols were approved by the local government committee for animal research, which is also an ethics committee. Animals were assigned randomly to treatment groups. Different doses and vehicle were tested in a randomized fashion. Although the operators performing the behavioral tests were not formally 'blinded' with respect to the treatment, they were not aware of the study hypothesis or the nature of differences between drugs.

4.2.2. Formalin test

The formalin test is a broadly used model of chemically-induced persistent pain [20]. Generally two phases of the nociceptive response can be observed in this model: a first phase starting immediately after injection, and a second phase starting around 15 min after formalin injection. In the first phase nociceptors are activated directly by the chemical stimulation of formalin and therefore this period is considered as a model of acute pain. The second phase reflects a spinal and peripheral hypersensitization (chronic phase) and is considered as a model for chronic pain. In this study, a period within the second phase was analyzed. The test was carried out in a plexiglass box with a mirror placed behind to allow an unobstructed view of the animals. Each animal was injected with 20 μl of 1% formalin in 0.9% NaCl subcutaneously into the dorsal surface of the right hind paw. After placing the mice back into the chamber the nociceptive behavior was measured by observation during the time interval of 21–24 min post-formalin and the amount of time spent licking and biting the injected paw was counted [20]. A vehicle control group was included for each investigation. Statistical significance is tested by Kruskal–Wallis-Test. Group size was 10 animals.

4.3. Molecular modeling

The 3D structure of the ligand was generated with Concord and energy minimized using MMFF94s force field and MMFF94 charge until the rms of Powell gradient was 0.05 kcal mol^{-1} A^{-1} in SYBYL-X 1.2 (Tripos Int., St. Louis, MO, USA). The flexible docking study on our hTRPV1 model [16] was performed by GOLD v.5.0.1 (Cambridge Crystallographic Data Centre, Cambridge, UK), which uses 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 hTRPV1 model. The side chains of the nine residues, which are important for ligand binding, (i.e., Tyr511, Ser512, Met514, Leu515, Leu518, Phe543, Leu547, Thr550, and Asn551) were set to be flexible with 'crystal mode' in GOLD. The ligand was docked using the GoldScore scoring function with 30 GA runs. Other parameters were set as default. All computation calculations were undertaken on Intel® Xeon™ Quad-core 2.5 GHz workstation with Linux Cent OS release 5.5.

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