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Graphical Abstract





2-(3-Fluoro-4-methylsulfonylaminophenyl) Propanamides as Potent TRPV1 Antagonists: Structure Activity Relationships of the 2-Oxy Pyridine C-region

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Key Words: TRPV1 antagonists, analgesic, molecular modeling, capsaicin

Abstract

The structure activity relationships of 2-oxy pyridine derivatives in the C-region of N-(6trifluoromethyl-pyridin-3-ylmethyl) 2-(3-fluoro-4-methylsulfonylaminophenyl) propanamides as hTRPV1 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 **53**S using our hTRPV1 homology indicated that the and B-region 2-(3-fluoro-4model Amethylsulfonylaminophenyl)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.

1. Introduction

The transient receptor potential V1 (TRPV1) receptor is a non-selective cation ch annel with high Ca²⁺ permeability which functions as a molecular integrator of nociceptiv e 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 capsaici n (CAP)⁶ and resiniferatoxin (RTX)⁷. The increase in intracellular Ca²⁺ upon TRPV1 acti vation causes excitation of the primary sensory neurons and the consequent central perce ption of pain. TRPV1 antagonists, by inhibiting this transmission of nociceptive signaling from the periphery to the CNS, have thus attracted much attention as potential analgesic s. In recent years a number of TRPV1 antagonists have been developed as novel analges ic and anti-inflammatory agents, particularly for the treatment of neuropathic pains.⁸ The clinical development and therapeutic potential of TRPV1 antagonists have been extensivel y reviewed.⁹⁻¹⁵

Recently, we investigated a series of *N*-(2-amino-6-trifluoromethyl-pyridin-3-ylmeth yl) 2-(3-fluoro-4-methylsulfonylaminophenyl)propanamides, designed by combining previous ly 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, be ing thus 150-fold and 230-fold better than precedent lead 2^{17} for CAP and pH antagonism m, respectively (**Figure 1**). In addition, the compound **1***S*, the S-form of **1**, was found t o be highly selective for TRPV1 with $K_{i(CAP)} = 0.2$ nM and displayed strong analgesic a ctivity in a neuropathic pain model with almost no side effects. Consistent with its mech anism of action *in vivo* being through TRPV1, compound **1***S* blocked capsaicin-induced h ypothermia 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 addit ional 4-methylpiperidine moiety in 1. Specifically, docking analysis using the hTRPV1 ho mology 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-substitutent in the N-(6-trifluoro methyl-pyridin-3-ylmethyl) C-region, we have investigated its 2-oxy derivatives (**Figure 2**) as *h*TRPV1 antagonists. For a selected potent antagonist in the series, we further charac terized analgesic activity in the formalin pain model and performed molecular modeling with our *h*TRPV1 homology model.

Figure 2. General structure of the designed compounds



2. Results and Discussion

2.1. Chemistry

The syntheses of the final compounds are represented in Scheme 1. 2-Oxy substit uted pyridines **5** were synthesized either by O-alkylation of pyridone 3^{16} or by the nucle ophilic substitution of various alcohols with 2-chloropyridine 4^{16} . Pyridines **5** containing c yclopropyl substituents were prepared from the corresponding alkenes by the Simmons–S mith 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-methylsulf onylaminophenyl)propionic acid 7^{17} to provide the final compounds **8-71**.



Scheme 1. Syntheses of 2-(3-fluoro-4-methylsulfonylaminophenyl) propanamide analogues Reagents and conditions: (a) [Method A] RBr, K₂CO₃, 18-crown-6, DMF, heat; (b) [Method B] ROH, DBU, 1,4-dioxane or CH₃CN, reflux: [Method C] ROH, NaH, THF, reflux: [Method D] ROH, Cs₂CO₃, DMF, heat: [Method E] ROH, KF, DMF, heat; (c) [Method F] 2M BH₃-SMe₂ in THF: [Method G] H₂, 10% Pd-C, AcOH, MeOH: [Method H] LAH, diethylether: [Method I] NaBH₄, NiCl₂-6H₂O, MeOH; (d) EDC, HOBt, DMF



Scheme 2. Syntheses of the 2-cyclopropylmethyloxy pyridine C-region
Reagents and conditions: (a) Diiodomethane, Diethylzinc, CH₂Cl₂
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**, which was as pote nt as **1** with $K_{i(CAP)} = 0.3$ nM. The activity stayed constant upon further chain lengtheni ng 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} Uns aturation of the alkyl chain led to a decrease in activity. For example, the Z-alkene isom ers **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 analogues **16** and **19** exhibited 1 60-fold and 20-fold less potent CAP antagonism than did the parents **11** and **13**, respectively. Similarly, **17** and **18**, analogues of **12** oxygenated at different positions along the al kyl chain, were 70-fold and 22-fold less potent than the parent, respectively. However, a

ddition of a lipophilic phenyl group to **18** to yield compound **20** led to potent antagonis m. The SAR analysis for this series of straight 2-alkyloxy group thus indicated that the 1 ipophilicity of side chain was critical for antagonism, probably due to its hydrophobic int eraction with the receptor, and the optimal number of carbons appeared to be four.

Table 1. In vitro hTRPV1 Antagonistic Activities for Straight 2-Alkyloxy Derivatives

F₃C

	R	K _i [CAP] (nM)	IC ₅₀ [pH] (nM)	Å	R	K _i [CAP] (nM)	IC ₅₀ [pH] (nM)
1		0.3	8.4	13R		WE	WE
8	* —	68.8	WE	14	[≹] ∕	1.6	183
9	≹	12.7	277	15	[€]	1	43
10	≹	0.9	90.1	16	[§] -∕- ₀ ∕	49	WE
11	\$	0.3	30.5	17	[§] ₀	50	WE
12	\$	0.7	27.3	18	§ −	15.3	WE
13	*	0.5	29.9	19	\$ 	9.7	462
135	*	0.4	12.3	20	\$	1.5	161

WE: weakly effective $(1 \ \mu M < K_i \text{ or } IC_{50} < 10 \ \mu M)$ NE: not effective $(K_i \text{ or } IC_{50} > 10 \ \mu M)$

Next, the SAR of branched 2-alkyloxy derivatives was investigated (Table 2). Si

milar 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 be tween straight and branched alkyl derivatives indicated that the straight alkyl derivatives generally showed slightly better antagonism than did the corresponding branched ones (for r 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 elevate d temperature. Antagonism of the response to low pH is the predominant predictor of w hether an antagonist may induce hyperthermia as a side effect, so antagonists blocking th e response to capsaicin but not low pH may be of particular interest for further evaluati on.¹⁹

	R	K _i [CAP] (nM)	IC ₅₀ [pH] (nM)		R	K _i [CAP] (nM)	IC ₅₀ [pH] (nM)
21	ş<	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

Table 2. In vitro hTRPV1 Antagonistic Activities for Branched 2-Alkyloxy Derivatives

WE: weakly effective (1 μ M<K_i or IC₅₀<10 μ M) NE: not effective (K_i or IC₅₀>10 μ M)

The SAR of 2-cycloalkyloxy derivatives was investigated next (Table 3). The ana

lysis indicated that the SAR pattern was similar to that of the above series, and compou nd **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 th e 4-trifluoromethyl group in **32** enhanced antagonism compared to **31**, the 4-methyl grou p 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 st eric repulsion with the receptor. However, the 4,4-dimethyl and 3,5-dimethyl analogues, **3 6** and **37**, retained good antagonism. The results indicated that lipophilicity at the 4-posit ion of the cyclohexyl ring was important for potent antagonism, but there were steric co nstraints such that size bigger than methyl led to the reduction of activity. A similar SA R pattern was found for the 4-position of piperidine ring in the C-region previously.¹⁶ In troduction of nitrogen at the 4-position in **38** led to dramatic loss of activity. However, i ts activity was recovered by adding the lipophilic Boc group to the nitrogen, as in **39**. Compound **40**, the phenyl-fused analogue of **30**, still displayed good CAP antagonism, in dicating that the phenyl group was tolerated.

	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	ξ ∕NH	WE	NE
33	≹ − ∕ −	2.9	43.1	39	ξ −√N−Вос	1.3	293

 Table 3. In vitro hTRPV1 Antagonistic Activities for 2-Cycloalkyloxy Derivatives

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34	₹ − <u></u> <u></u>	4.8	125	40		2.7	WE
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WE: weakly effective $(1 \ \mu M < K_i \text{ or } IC_{50} < 10 \ \mu M)$ NE: not effective $(K_i \text{ or } IC_{50} > 10 \ \mu M)$

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 **42**, **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.

	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	₹NH	WE	NE
44	*	0.3	40.5	49	€ N Boc	3.4	342
45	*	0.4	11.6	50	€ N Boc′	0.3	16.6

Table 4. In vitro hTRPV1 Antagonistic Activities for 2-Cycloalkylmethyloxy Derivatives

WE: weakly effective (1 μ M<K_i or IC₅₀<10 μ M) NE: not effective (K_i or IC₅₀>10 μ M)

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 OCH₃). 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 OCH₃). 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.

	R	K _i [CAP] (nM)	IC ₅₀ [pH] (nM)		R	K _i [CAP] (nM)	IC ₅₀ [pH] (nM)
51		6.4	WE	62	₹ OCH3	2.6	653
52	∞ −	2.8	WE	63	ξF	0.8	69

Table 5. In vitro hTRPV1 Antagonistic Activities for 2-Aryloxy and Arylmethyloxy Derivatives

53		0.5	18.6	64	₹CI	4.9	95
54		0.5	27.6	65	₹OCH3	0.8	43.7
55		1.5	53	66	₹F	1.0	93
56		3.7	165	67	₹	2.6	114
57		16	337	68	H ₃ CO	0.7	76
58		2.1	182	69		29.5	WE
59		2.5	25	70	₹N	142	WE
60		2.5	132	71	₹ _N	51	WE
61	CF3	3.2	66.1				

WE: weakly effective $(1 \ \mu M < K_i \text{ or } IC_{50} < 10 \ \mu M)$ NE: not effective $(K_i \text{ or } IC_{50} > 10 \ \mu M)$

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 $(45^{\circ}C)$ and *N*-arachidonoyl dopamine (NADA), and compared to the activity of lead **1** (**Table 6**). B oth showed excellent antagonism of all four TRPV1 activators and comparable activities

to 1. Particularly, compound 53 exhibited excellent potency toward NADA activation.

I (nM)	22 (nM)	53 (nM)
0.3	0.5	0.5
8.4	52.6	18.6
4.5	67.5	52.3
0.23	0.29	0.001
	1 (nM) 0.3 8.4 4.5 0.23	I 22 (nM)0.30.58.452.64.567.50.230.29

Table 6. In vitro hTRPV1 Antagonistic Activities for 1, 22 and 53 to multiple activators

2.3. Analgesic Activity

We evaluated the *in vivo* analgesic activities of two selected antagonists, 22 and 53, in the formalin test²⁰ in mice upon oral administration. Compound 22 showed a signi ficant antinociceptive effect, with 63.4 ± 11.5 % and 60.8 ± 9.9 % (mean \pm SEM) inhibitio n of response at the doses of 0.1 and 0.3 mg/kg, respectively (p < 0.05). Compound 53 inh ibited the nociceptive response by 41.8 \pm 17.3 % and 54.1 \pm 26.3 % at the doses of 0.1 and 0.3 mg/kg, respectively that TRPV1 knock-out mice showed approximately 50% of the magnitude of response in the formalin test as was se en in wild-type mice (unpublished observations), the inhibition of the formalin response t hat we found for the two antagonists would correspond to the expected result for full T RPV1 blockade.

2.4. Molecular Modeling

Using our human TRPV1 (hTRPV1) model¹⁶, built based on our rat TRPV1 (rTRPV1) model²¹, we performed a flexible docking study of compound **53***S*, the active isomer of **53**. As

shown in Figure 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.





(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-polor 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 dar Waals surface of the ligand colored by its lipophilic potential property.

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 formalin test in mice with full efficacy. Docking analysis of **53S** 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 (¹H-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 Me₄Si 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 $^{\circ}$ C was added 18crown-6 ether (cat.), potassium carbonate (2 mmol) followed by bromide compound (1.2 mmol). The reaction mixture was heated at 60-90 $^{\circ}$ C for overnight and extracted with EtOAc several times. The combined organic layers were washed with brine, dried over MgSO₄, 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 $^{\circ}$ C was added 1,8diazabicyclo[5.4.0]undec-7-ene (2 mmol) followed by alcohol compound (1.2 mmol). The reaction mixture was stirred at 50 $^{\circ}$ C for overnight, and extracted with EtOAc for several times. The combined organic layers were washed with brine, dried over MgSO₄, 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 $^{\circ}$ C was added sodium hydride (2.5 mmol) followed by alcohol compound (1.2 mmol). The reacton mixture was stirred at 50 $^{\circ}$ C for 5 h, and extracted with EtOAc several times. The combined organic layers were washed with brine, dried over MgSO₄, 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 $^{\circ}$ C was added cesium carbonate (3.0 mmol) followed by alcohol compound (1.2 mmol). The reaction mixture was stirred at 60-90 $^{\circ}$ C for overnight, and extracted with EtOAc several times. The combined organic layers were washed with brine, dried over MgSO₄, 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 $^{\circ}$ C for overnight and extracted with EtOAc several times. The combined organic layers were washed with brine, dried over MgSO₄, 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 BH₃·SMe₂ 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 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 MgSO₄, and concentrated *in vacuo*. The residue was purified by flash column

chromatography on silica gel using CH₂Cl₂: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 vac*uo 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 $^{\circ}$ C (5 mL) was added slowly lithium aluminium 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 MgSO₄, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using CH₂Cl₂: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 NiCl₂·6H₂O (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 MgSO₄, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using CH₂Cl₂: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*'-ethylcarbodiimide 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 MgSO₄, 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; ¹H NMR (CDCl₃) 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 C₁₈H₁₉F₄N₃O₄S: 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; ¹H NMR (CDCl₃) 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 C₁₉H₂₁F₄N₃O₄S: 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; ¹H NMR (CDCl₃) 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 C₂₀H₂₃F₄N₃O₄S: 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; ¹H NMR (300 MHz, CDCl₃) 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, 3 H), 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 C₂₁H₂₅F₄N₃O₄S: 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; ¹H NMR (CDCl₃) 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 C₂₂H₂₇F₄N₃O₄S: 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; ¹H NMR (CDCl₃) 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 C₂₃H₂₉F₄N₃O₄S: 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; ¹H NMR (CDCl₃) 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 C₂₁H₂₃F₄N₃O₄S: 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; ¹H NMR (CDCl₃) 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, 1 H), 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 C₂₂H₂₅F₄N₃O₄S: 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-Methoxy)-6-(trifluoromethyl)pyridin-3-yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (16)

Yield 68%, white solid, mp 109 °C; ¹H NMR (CDCl₃) 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 C₂₀H₂₃F₄N₃O₅S: 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; ¹H NMR (CDCl₃) 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; ¹H NMR (CDCl₃) 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 C₂₁H₂₅F₄N₃O₅S: 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; ¹H NMR (CDCl₃) 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 C₂₂H₂₇F₄N₃O₅S: 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; ¹H NMR (CDCl₃) 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 C₂₅H₂₅F₄N₃O₅S: 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; ¹H NMR (CDCl₃) 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 C₂₀H₂₃F₄N₃O₄S: 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; ¹H NMR (CDCl₃) 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 C₂₁H₂₅F₄N₃O₄S: 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; ¹H NMR (CD₃OD) 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 C₂₂H₂₇F₄N₃O₄S: 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; ¹H NMR (CD₃OD) 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 C₂₃H₂₉F₄N₃O₄S: 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; ¹H NMR (CDCl₃) 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 C₂₂H₂₇F₄N₃O₄S: 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; ¹H NMR (CDCl₃) 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 C₂₄H₃₁F₄N₃O₄S: C, 54.02; H, 5.86; N, 7.88. Found: C, 54.22; H, 5.85; N,

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; ¹H NMR (CDCl₃) 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 C₂₆H₃₅F₄N₃O₄S: 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; ¹H NMR (CDCl₃) 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 C₂₆H₃₅F₄N₃O₄S: 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; ¹H NMR (CDCl₃) 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 C₂₁H₂₃F₄N₃O₄S: 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; ¹H NMR (CDCl₃) 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 C₂₂H₂₅F₄N₃O₄S: 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; ¹H NMR (CDCl₃) 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 C₂₃H₂₇F₄N₃O₄S: 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; ¹H NMR (CDCl₃) 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 C₂₄H₂₆F₇N₃O₄S: 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-(3fluoro-4-(methylsulfonamido)phenyl)propanamide (33)

Yield 78%, white solid, mp 107-109 °C; ¹H NMR (CDCl₃) 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 C₂₄H₂₉F₄N₃O₄S: 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; ¹H NMR (CDCl₃) 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 C₂₅H₃₁F₄N₃O₄S: 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-(3fluoro-4-(methylsulfonamido)phenyl)propanamide (35)

Yield 69%, white solid, mp 83-85 °C; ¹H NMR (CDCl₃) 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 C₂₇H₃₅F₄N₃O₄S: 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-(3fluoro-4-(methylsulfonamido)phenyl)propanamide (36)

Yield 63%, white solid, mp 86 °C; ¹H NMR (CDCl₃) 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; ¹H NMR (CDCl₃) 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 C₂₅H₃₁F₄N₃O₄S: 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; ¹H NMR (CDCl₃) 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 C₂₂H₂₆F₄N₄O₄S: 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; ¹H NMR (CDCl₃) 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

C₂₇H₃₄F₄N₄O₆S: 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; ¹H NMR (CDCl₃) 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 C₂₆H₂₅F₄N₃O₄S: 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; ¹H NMR (CDCl₃) 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 C₂₁H₂₃F₄N₃O₄S: 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; ¹H NMR (CD₃OD) 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 C₂₂H₂₅F₄N₃O₄S: 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-3yl)methyl)-2-(3-fluoro-4-(methylsulfonamido)phenyl)propanamide (43)

Yield 72%, white solid, mp 63-65 °C; ¹H NMR (CDCl₃) 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 C₂₃H₂₇F₄N₃O₄S: 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; ¹H NMR (CDCl₃) 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 C₂₂H₂₅F₄N₃O₄S: 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; ¹H NMR (CDCl₃) 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* = 7.1Hz, 3H); MS (FAB) *m*/*z* 518 (M+H). Anal. Calcd for C₂₃H₂₇F₄N₃O₄S: C, 53.38; H, 5.26; N, 8.12. Found: C, 53.55; H, 5.24; N, 8.09.



(methylsulfonamido)phenyl)propanamide (46)

Yield 73%, white solid, mp 108-110 °C; ¹H NMR (CDCl₃) 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 C₂₄H₂₉F₄N₃O₄S: 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; ¹H NMR (CDCl₃) 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 C₂₅H₃₁F₄N₃O₄S: 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; ¹H NMR (CD₃OD) 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 C₂₃H₂₈F₄N₄O₄S: 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; ¹H NMR (CDCl₃) 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; ¹H NMR (CDCl₃) 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 C₂₉H₃₈F₄N₄O₆S: 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; ¹H NMR (CD₃OD) 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 C₂₃H₂₁F₄N₃O₄S: 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; ¹H NMR (CDCl₃) 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 C₂₄H₂₃F₄N₃O₄S: 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; ¹H NMR (CDCl₃) 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 C₂₄H₂₃F₄N₃O₄S: 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; ¹H NMR (CDCl₃) 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 C₂₅H₂₅F₄N₃O₄S: 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; ¹H NMR (CDCl₃) 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 C₂₅H₂₅F₄N₃O₄S: 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; ¹H NMR (CDCl₃) 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 C₂₆H₂₇F₄N₃O₄S: 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; ¹H NMR (CDCl₃) 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 C₂₈H₃₁F₄N₃O₄S: 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; ¹H NMR (CDCl₃) 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 C₂₈H₃₁F₄N₃O₄S: 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; ¹H NMR (CDCl₃) 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 C₂₄H₂₂F₅N₃O₄S: 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; ¹H NMR (CDCl₃) 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, 2.0Hz, 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 C₂₄H₂₂ClF₄N₃O₄S: 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; ¹H NMR (CDCl₃) 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 C₂₅H₂₂F₇N₃O₄S: 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; ¹H NMR (CDCl₃) 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 C₂₅H₂₅F₄N₃O₅S: 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; ¹H NMR (CDCl₃) 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, 3 H), 1.45 (d, *J* = 7.2 Hz, 3H); MS (FAB) *m*/*z* 544 (M+H). Anal. Calcd for C₂₄H₂₂F₅N₃O₄S: 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; ¹H NMR (CDCl₃) 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 C₂₄H₂₂ClF₄N₃O₄S: 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; ¹H NMR (CDCl₃) 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; ¹H NMR (CDCl₃) 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 C₂₄H₂₁F₆N₃O₄S: 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; ¹H NMR (CDCl₃) 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 C₂₄H₂₁Cl₂F₄N₃O₄S: 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-(3fluoro-4-(methylsulfonamido)phenyl)propanamide (68)

Yield 65%, white solid, mp 148 °C; ¹H NMR (CDCl₃) 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 C₂₆H₂₇F₄N₃O₆S: 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; ¹H NMR (CDCl₃) 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 C₂₃H₂₂F₄N₄O₄S: 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; ¹H NMR (CDCl₃) 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 C₂₃H₂₂F₄N₄O₄S: 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; ¹H NMR (CDCl₃) 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 Pain²² 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 randomised fashion. Although the operators performing the behavioural 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 plexiglas box with a mirror placed behind to allow an unobstructed view of the animals. Each animal was injected with 20 μ l of 1 % formalin in 0.9 % NaCl subcutaneously into the dorsal surface of the right hindpaw. After placing the mice back into the chamber the nociceptive behaviour was measured by observation during the time interval of 21 to 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⁻¹A⁻¹ in SYBYL-X 1.2 (Tripos Int., St. Louis, MO, USA). The flexible docking study on our hTRPV1 model¹⁶ 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[®] XeonTM Quad-core 2.5 GHz workstation with Linux Cent OS release 5.5.

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- A series of 2-(3-fluoro-4-methylsulfonylaminophenyl) propanamides were investigated as *h*TRPV1 antagonists.
- Multiple compounds proved to be potent TRPV1 antagonists.
- The binding mode of representive antagonist was proposed using our hTRPV1 homology model.