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Design, synthesis, and biological evaluation of novel diarylalkyl amides as TRPV1 antagonists

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ABSTRACT

We have developed a new class of diarylalkyl amides as novel TRPV1 antagonists. They exhibited potent $^{45}Ca^{2+}$ uptake inhibitions in rat DRG neuron. In particular, the amide **59** was identified as a potent antagonist with IC_{50} of 57 nM. The synthesis and structure–activity relationship of the diarylalkyl amides are also described.

1. Introduction

TRPV1 (transient receptor potential vanilloid subfamily 1),[1] as a ligand-gated non-selective cation channel with high $^{45}Ca^{2+}$ permeability, is predominantly expressed on primary sensory neurons. TRPV1 has evoked great interest since it was clearly demonstrated as a new target for treatment of various pain states, by molecular cloning and various in vivo pain models.[2–5] In particular, recent extensive findings have implied that direct blockade of TRPV1 by its antagonists could be a promising way for the discovery of novel analgesics.[6]

Over the recent years, a number of new TRPV1 antagonists have been reported.[7] We have also reported the dibenzyl thiourea analogs including SC-0030 **(1)**,[8] which exhibit highly potent competitive TRPV1 antagonistic effects, as well as their structure–activity relationship (SAR).[9] More recently, we have extended our work for structural optimization of our thiourea series via incorporation of new scaffolds, which are expected to improve metabolic and pharmacokinetic profiles of the thiourea series. We herein report novel diarylalkyl amides as a new class of TRPV1 antagonists with excellent $^{45}Ca^{2+}$ uptake inhibitions in rat DRG neuron as well as their structure–activity relationship.

2. Results and discussion

2.1. Chemistry

Our work commenced with an introduction of amide moiety in the B region of **1**, known as a dipolar interaction part[8,9] for the exclusion of thiourea moiety because sulfur atom is known to be easily oxidized by the endogenous metabolic enzymes.[10] We initially attempted to replace the thiourea moiety with other pharmacologically useful isosteric moieties such as urea and amide (Fig. 1).

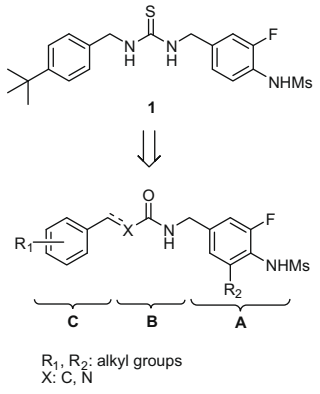

Figure 1. Amide and urea analogs based on thiourea **1**.

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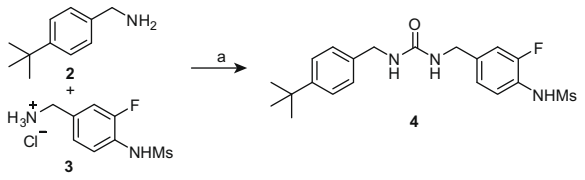
The urea analog **4** (Scheme 1) was synthesized by an assembly of the benzylamines **3**[9] and **2**.[11] The corresponding amides **7** and **26b** were also prepared to simplify the urea moiety by eliminating one of the nitrogen of urea moiety.

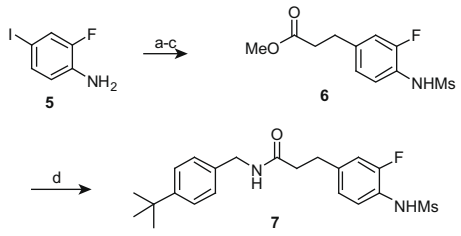
The amide **7** (Scheme 2) was synthesized by coupling of 4-*tert*-butylbenzylamine **2** with the ester **6**, which was prepared by methanesulfonylation of **5** and Heck reaction of the resulting sulfonamide with methylacrylate[12] followed by olefin reduction.

For further optimization of C region of the amide series, the analogs **23–34b** with a variety of C regions were prepared by a unified synthetic procedure (Scheme 4). The acids **10** and **11** (Scheme 3) instead of the corresponding aldehydes bearing methylcyclopropyl or *iso*-butyl substituents were separately synthesized for the amide analogs **27** and **28** (Scheme 4). Wittig olefination of **8** followed by cyclopropanation of the resulting olefin and then Heck reaction with methylacrylate afforded the α,β-unsaturated ester **9,** which were readily converted to the acids **10** and **11** by sequential hydrogenation and ester hydrolysis.

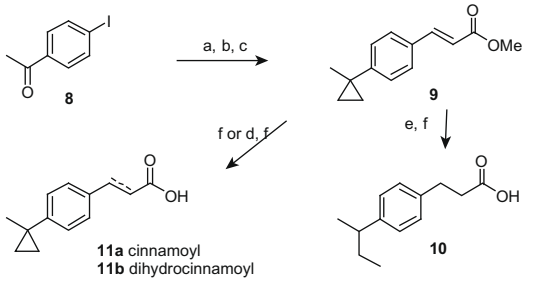
Other acids **22** of Scheme 4 were prepared by Knoevenagel condensation of the corresponding benzaldehydes **12–21** with malonic acid, followed by hydrogenation of the resulting olefin. All amides **23–34b** were prepared by DMTMM-mediated coupling of **3** with the corresponding acids. The di-*tert*-butyl analog **32** and the tetrahydronaphthalene analog **34b** have been prepared for an investigation of steric effect of the substituted aromatic moiety.



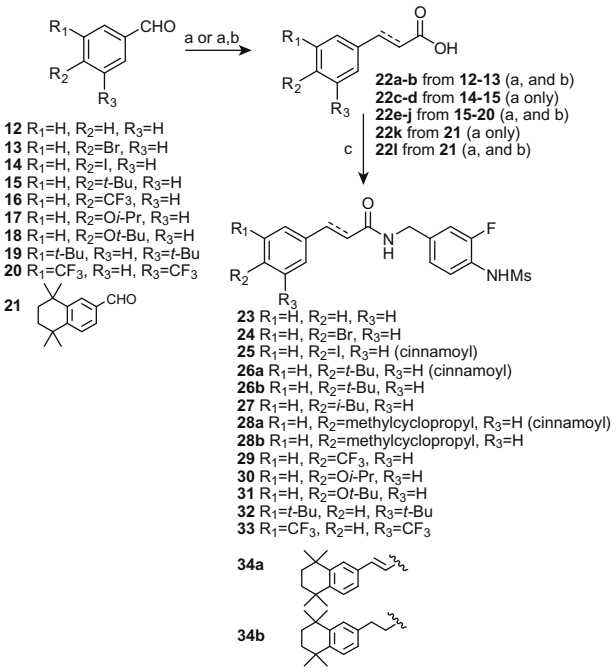
Scheme 1. Reagents and conditions: (a) $(Boc)_2O$, DMAP, Et_3N, CH_2Cl_2, 53%.



Scheme 2. Reagents and conditions: (a) CH_3SO_2Cl, pyridine, CH_2Cl_2, 95%; (b) $Pd(OAc)_2$, DPPF, methylacrylate, Et_3N, DMF, 80 °C, 91%; (c) 10% Pd/C, H_2, MeOH, 86%; (d) **2**, toluene, reflux, 63%.



Scheme 3. Reagents and conditions: (a) CH_3PPh_3Br, *n*-BuLi, THF, 73%; (b) CH_2I_2, Et_2Zn, toluene, 99%; (c) methylacrylate, $Pd(OAc)_2$, DPPF, Et_3N, DMF, 80 °C, 84%; (d) 10% Pd/C, H_2, THF, 2 h, 94%; (e) 10% Pd/C, H_2, THF, 8 h, 77%; (f) LiOH, THF/H_2O, 91–100%.

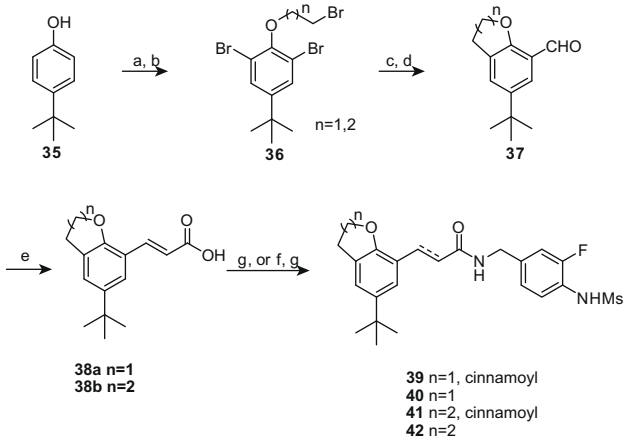


Scheme 4. Reagents and conditions: (a) malonic acid, pyridine, piperidine, reflux, 82–99%; (b) 10% Pd/C, H_2, THF, 72–96%; (c) **3**, DMTMM, NMM, Et_3N, THF, 62–88%.

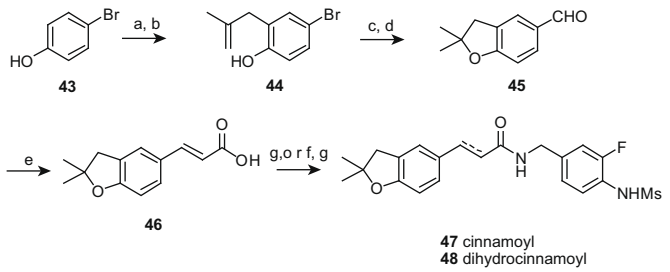
The selected cinnamoyl analogs were prepared to examine the rigidity effect of the linker between the B and C regions.

The dihydrobenzofuranyl and the dihydrochromanyl amide analogs **39–42** were synthesized as described in Scheme 5. The key intermediates **38a** and **38b** were prepared by bromination and O-alkylation of **35**, followed by sequential cyclization[13] and formylation. The amide coupling of **38a–b** with **3** provided the cinnamoyl amide **39** and **41** while coupling of the saturated acid of **38a–b** with **3** afforded the dihydrocinnamoyl analogs **40** and **42**.

The cinnamoyl amide **47** was prepared by coupling of the acid **46** with the amine **3** in the presence of DMTMM. The cinnamoic acid intermediate **46** was prepared by sequential O-alkylation of **43**, Claisen rearrangement of the resulting allyl ether, intramolecular etherification and then formylation, followed by condensation of the resulting aldehyde with malonic acid (Scheme 6). The dihy-



Scheme 5. Reagents and conditions: (a) $BTMABr_3$, CH_2Cl_2/MeOH = 5:2, 96%; (b) $BrCH_2CH_2CH_2Br$ or $BrCH_2CH_2Br$, NaOH, H_2O, reflux, 48–77%; (c) *n*-BuLi, THF, −78 °C, 59–69%; (d) *t*-BuLi, DMF, THF, 56–93%; (e) malonic acid, pyridine, piperidine, reflux, 86–90%; (f) 10% Pd/C, H_2, THF, 92–99%; (g) **3**, DMTMM, NMM, Et_3N, THF, 49–81%.

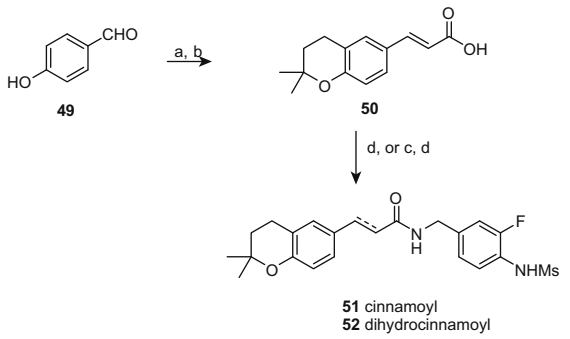


Scheme 6. Reagents and conditions: (a) 3-bromo-2-methylpropene, K_2CO_3, acetone, reflux, 99%; (b) DMF, 190 °C, 87%; (c) I_2, CH_2Cl_2, 80%; (d) *t*-BuLi, DMF, THF, 86%; (e) malonic acid, pyridine, piperidine, reflux, 72%; (f) 10% Pd/C, H_2, THF, 72%; (g) **3**, DMTMM, NMM, Et_3N, THF, 91%.

drocinnamoyl analog **48** was prepared by Pd-catalyzed hydrogenation of **46**, followed by amidation of the resulting acid with the amine **3**.

The 2,2-dimethylchromanyl analogs **51** and **52** were also prepared from the acid **50** by the same procedure described in Scheme 6. The acid **50** was derived from **49** via benzopyran ring formation[14] and Knoevenagel condensation (Scheme 7).

Finally, the A region optimized analogs **57–59**, which possess the C regions of the representative potent amides **26b**, **28b** and **34b**, were synthesized by coupling the ammonium salt **56** with the corresponding phenylpropanoic acid (Scheme 8). The



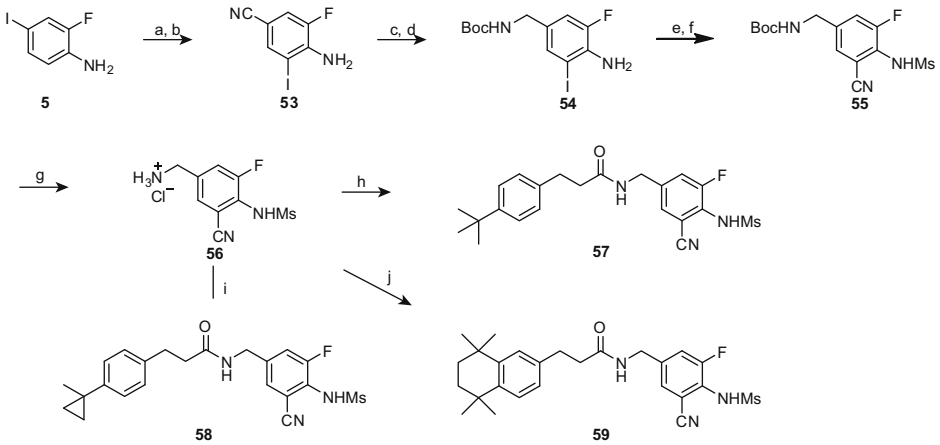
Scheme 7. Reagents and conditions : (a) 1-bromo-3-methyl-2-butene, K_{10}, CCl_4, 8.4%; (b) malonic acid, pyridine, piperidine, reflux, 86%; (c) 10% Pd/C, H_2, THF, 93%; (d) **3**, DMTMM, NMM, Et_3N, THF, 77–92%.

iodobenzonitrile **53** was prepared from the commercially available 2-fluoro-4-iodoaniline **5** via sequential cyanation and iodination. Reduction of the nitrile **53** with borane and protection of the resulting benzylamine provided **54**. Methanesulfonylation of the aniline **54** and subsequent $Zn(CN)_2$ treatment afforded the cyanide **55**, which was readily converted to the key intermediate **56**. Finally amide coupling of **56** with the corresponding arylpropanoic acids afforded the desired amide analogs**.**

The in vitro activities of the synthesized analogs are summarized in Table 1. The urea analog **4** exhibited lower antagonistic activity than the thiourea **1** as reported in our previous papers.[9] As we anticipated, the amide **7** exhibited threefold lower antagonistic activities than the parent urea **4** in $^{45}Ca^{2+}$ uptake inhibition. In contrast, the amide **26b** is more active than the urea, which implies that the amide possessing the nitrogen at the A region site could be an alternative scaffold for the thiourea.

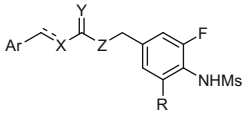
We also examined the antagonistic activity of the C region modified amide analogs. Our previous work revealed that the thiourea analogs consisting of the 4-*tert*-butylbenzyl groups in the C region are more active than any other C region modified analogs. The amide series also exhibited the similar trend as shown in Table 1. The analogs **24** and **25** possessing *para*-halogen substituent showed a significant loss of antagonistic activity. The analogs **28**, which possess methylcyclopropyl substituent known as an isostere of *tert*-butyl group, exhibited slightly lower potency than the 4-*tert*-butyl analog **26b**. However, the 4-trifluoromethyl analog **29** exhibited moderate activity. Replacement of 4-*tert*-butyl group by *iso*-propoxy (**30**) or *tert*-butoxy (**31**) led to a complete loss of antagonistic activity.

On the basis of our previous studies,[15] the substituent effect of the C region were also confirmed. Interestingly, the analog **32**, which possesses 2,4-di-*tert*-butylphenyl group was almost equipotent to the amide **26b** having 4-*tert*-butylphenyl group. The similar trend was observed in the trifluoromethyl series of **29** and **33** although they exhibited much lower antagonistic activities compared to those of the 4-*tert*-butyl series. The bulkier tetramethyl–tetrahydronaphthyl analogs exhibited good or excellent antagonistic activities. Thus, the electronic and steric effects of the C region on antagonistic activity were further examined by introduction of a variety of heterobicyclic systems. The dihydrobenzofuranyl analogs **39**, **40**, **47** and **48** exhibited weak activity. However, the analogs consisting of benzopyranyl moieties **41**, **42**, **51** and **52** exhibited higher activities compared to those of the corresponding benzofuranyl analogs although their potencies were still not satis-



Scheme 8. Reagents and conditions: (a) CuCN, DMF, 130 °C, 80%; (b) 1 M ICl, CH_2Cl_2, 66%; (c) 1 M BH_3·THF, THF, reflux, then 2 N HCl, 99%; (d) $(Boc)_2O$, DMAP, Et_3N, CH_2Cl_2, 81%; (e) CH_3SO_2Cl, pyridine, CH_2Cl_2, 36%; (f) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF, 130 °C, 63%; (g) 5 N HCl, EtOAc, reflux, 100%; (h) **22e**, DMTMM, NMM, Et_3N, THF, 39%; (i) **11b**, DMTMM, NMM, Et_3N, THF, 69%; (j) **22l**, DMTMM, NMM, Et_3N, THF, 59%.

Table 1
$^{45}Ca^{2+}$ Uptake inhibition by the amide analogs



Compound	Ar=	X	Y	Z	R	Antagonistic activity, IC_{50} (nM)
1	4-*tert*-Butylphenyl	NH	S	NH	H	37
4	4-*tert*-Butylphenyl	NH	O	NH	H	710
7	4-*tert*-Butylphenyl	NH	O	CH_2	H	2800
23	Phenyl	CH_2	O	NH	H	>10,000
24	4-Bromophenyl	CH_2	O	NH	H	>10,000
25	4-Iodophenyl	CH	O	NH	H	>10,000
26a	4-*tert*-Butylphenyl	CH	O	NH	H	490
26b	4-*tert*-Butylphenyl	CH_2	O	NH	H	170
27	4-*iso*-Butylphenyl	CH_2	O	NH	H	640
28a	4-Methylcyclopropylphenyl	CH	O	NH	H	390
28b	4-Methylcyclopropylphenyl	CH_2	O	NH	H	360
29	4-Trifluoromethylphenyl	CH_2	O	NH	H	4600
30	4-*iso*-Propoxyphenyl	CH_2	O	NH	H	>10,000
31	4-*tert*-Butoxyphenyl	CH_2	O	NH	H	>10,000
32	3,5-Di-*tert*-butylphenyl	CH_2	O	NH	H	200
33	3,5-Ditrifluoromethylphenyl	CH_2	O	NH	H	2500
34a	5,5,8,8-Tetramethyl-5,6,7,8-tetrahydronaphthyl	CH	O	NH	H	340
34b	5,5,8,8-Tetramethyl-5,6,7,8-tetrahydronaphthyl	CH_2	O	NH	H	180
39	5-*tert*-Butyl-2,3-dihydrobenzofuranyl	CH	O	NH	H	1500
40	5-*tert*-Butyl-2,3-dihydrobenzofuranyl	CH_2	O	NH	H	5000
41	6-*tert*-Butylchroman	CH	O	NH	H	920
42	6-*tert*-Butylchroman	CH_2	O	NH	H	280
47	2,2-Dimethyl-2,3-dihydrobenzofuranyl	CH	O	NH	H	4300
48	2,2-Dimethyl-2,3-dihydrobenzofuranyl	CH_2	O	NH	H	>10,000
51	2,2-Dimethylchroman	CH	O	NH	H	1400
52	2,2-Dimethylchroman	CH_2	O	NH	H	7200
57	4-*tert*-Butylphenyl	CH_2	O	NH	CN	85
58	4-Methylcyclopropylphenyl	CH_2	O	NH	CN	210
59	5,5,8,8-Tetramethyl-5,6,7,8-tetrahydronaphthyl	CH_2	O	NH	CN	57

factory. It is noticeable that the analog **42** was 17-fold potent compared to the analog **40**. Olefin effect in the B region seems not consistent because the cinnamoyl analogs (**25**, **26a**, **28a, 34a**, **39**, **41**, **47** and **51**) exhibited a variety of potencies compared to those of the corresponding arylpropanoyl analogs.

Finally, the antagonistic activities of **57**–**59**, obtained via further A region-optimization of **26b**, **28b** and **34b** on the basis of our preliminary studies,[16] were examined. These analogs possessing cyanide at the R_2 position of the A region exhibited two to fourfold increases in TRPV1 antagonistic activity.

2.2. Biological evaluation

2.2.1. $^{45}Ca^{2+}$ Uptake assays. Culture of DRG neurons

DRG neurons were prepared from neonatal Sprague-Dawley rats. DRGs of all spinal levels were dissected aseptically and collected. Ganglia were incubated sequentially for 30 min at 37 °C in 200 U/mL collagenase and 2.5 mg/mL trypsin. The digestion was halted by an addition of an equal volume of DME/F12 medium supplemented with 10% horse serum. The ganglia were then triturated through a fire-polished pasteur pipet, filtered through nylon membrane, and spun down. Dissociated cells were plated onto Terasaki plates previously coated with 10 μg/mL poly-D-ornithine at a density of 1500–1700 neurons/well. The cells were then cultured for 3 days in DME/F12 medium containing 1.2 g/L sodium bicarbonate, 15 mM HEPES, 50 mg/L gentamycin, and 10% horse serum, diluted 1:1 with identical medium conditioned by C6 glioma cells (2 days on a confluent monolayer) in a humidified atmosphere at 37 °C containing 5% CO_2. Medium was supplemented with 200 ng/mL nerve growth factor. Cytosine arabinoside (100 μM) was added for the first 2 days to kill dividing nonneuronal cells.

2.2.2. Uptake assays

Terasaki plates containing DRG neurons grown for 3 days were equilibrated with four washes of HEPES (10 mM, pH 7.4)-buffered calcium- and magnesium-free Hank's balanced salt solution. The solution in each well was removed from the individual wells. For antagonistic studies, medium (10 μL) containing 10 μCi/mL $^{45}Ca^{2+}$ and 0.5 M capsaicin together with the test concentration of the compound was added to each well. The neurons were incubated at room temperature for 10 min, and then the Terasaki plates were washed six times in HEPES (10 mM, pH 7.4)-buffered calcium and magnesium-free Hank's balanced salt solution and dried in an oven. Sodium dodecyl sulfate (0.3%, 10 μL) was then added to dissolve the cells and extract the $^{45}Ca^{2+}$. The contents of each well were transferred to scintillation vials and counted in 3 mL of aquasol-2 scintillant. Antagonistic activities of test compounds were given as IC_{50} (the concentration of the compound necessary to reduce the response to 0.5 μM capsaicin by 50%). The IC_{50} values were estimated at least three replicates at each concentrated. Each compound was tested at least in two independent experiments.

3. Conclusion

We have developed a number of novel amide series of TRPV1 antagonists with a variety of lipophilic moieties, which enable the replacement of the representative *tert*-butylbenzyl moiety. Moreover, we have identified new and potent TRPV1 antagonists of diarylalkyl amide via further optimization of A, B regions. Combination of cyano, fluoro and sulfonamido groups in A-region with 4-*tert*-butylbenzyl, 4-methylcyclopropylphenyl or tetrahydronaphthylmethyl groups in C-region provided the best activi-

ties. In particular, the amides **57** and **59** were identified as the highly potent TRPV1 antagonists with IC_{50}s of 85 and 57 nM, respectively. They are 12-fold potent than the parent amide **26b**, which was a variant of the urea **4**. We have also established the structure–activity relationship of the synthesized amide analogs through the structural optimization. Currently, systematic studies on the therapeutic application including pharmacokinetic profiles of the potent amide analogs are in progress.

4. Experimental

4.1. General methods

All reagents including starting materials and solvents were purchased from Aldrich Chemical Co. or TCI and used without further purification. Silica gel column chromatography was performed on Silica Gel 60, 230–400 mesh, Merck. NMR spectra were recorded on a JEOL LNM-LA 300 (300 MHz), Bruker, FT NMR AVANCE 400 (400 MHz), Bruker, FT-NMR AVANCE 500 (500 MHz) and TMS (tetramethylsilane) was used as an internal standard. Chemical shifts (δ) were recorded in ppm and coupling constants (J) in hertz (Hz). IR (infrared) spectra were recorded on a Jasco FT/IR-4200 and Perkin–Elmer 1710 FT spectrometer. Low resolution mass spectra were obtained on a VG Trio-2 GC–MS. High resolution mass spectra were obtained on a JEOL JMS-AX 505wA and JEOL JMS-HX/HX 110A spectrometer.

4.1.1. *N*-(4-[({4-*tert*-Butylbenzyl}aminocarboyl)-amino]methyl-2-fluorophenyl)methanesulfonamide (4)

A mixture of amine **2** (100 μL, 0.57 mmol), DMAP (21 mg, 0.17 mmol), $(Boc)_2O$ (149 mg, 0.68 mmol) and Et_3N (236 μL, 1.70 mmol) in CH_2Cl_2 (5 mL) was stirred at room temperature for 4 h. 3-Fluoro-4-methylsulfonamidobenzylamine salt **3** (159 mg, 0.62 mmol) was added into the reaction mixture. The mixture was then stirred at room temperature for 10 h and extracted with CH_2Cl_2. The combined organic phases were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by silica gel column chromatography (EtOAc/*n*-hexane = 2:1) to give **4** as a white solid (123 mg, 53%). ^{1}H NMR ($CDCl_3$+CD_3OD, 300 MHz) δ 7.35 (t, 1H, J = 8.1 Hz), 7.29 (d, 2H, J = 8.4 Hz), 7.15 (d, 2H, J = 8.6 Hz), 7.00–6.93 (m, 2H), 4.24 (s, 2H); 4.22 (s, 2H), 2.91 (s, 3H), 1.24 (s, 9H); LRMS (FAB+): m/z 408 ($M+H^+$).

4.1.2. Methyl 3-3-fluoro-4-[(methanesulfony)-amino]phenylpropanoate (6)

To a solution of 2-fluoro-4-iodoaniline **5** (1.50 g, 6.33 mmol) in CH_2Cl_2 (40 mL) were added pyridine (1.02 mL) and methanesulfonyl chloride (700 μL, 9.50 mmol). The mixture was stirred at room temperature for 1.5 h and then diluted with water, and extracted with CH_2Cl_2 several times. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by silica gel column chromatography (EtOAc/*n*-hexane = 1:3) afforded 1.89 g (95%) of *N*-(2-fluoro-4-iodophenyl)methanesulfonamide.

To a solution of *N*-(2-fluoro-4-iodophenyl)methane- sulfonamide (100 mg, 0.32 mmol) in DMF (10 mL) were added $Pd(OAc)_2$ (3.6 mg, 0.016 mmol), 1,1′-bis(diphenylphosphino)ferrocene (10 mg, 0.018 mmol), Et_3N (90 μL, 0.64 mmol) and methylacrylate (276 mg, 3.20 mmol). The mixture was stirred at 60 °C for 24 h, and was then diluted with water, and extracted with CH_2Cl_2 several times. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by silica gel column chromatography (EtOAc/*n*-hexane = 1:1) to afford 78 mg (91%) of (*E*)-methyl 3-[3-fluoro-4-(methylsulfonamido)phenyl]acrylate.

A solution of (*E*)-methyl 3-[3-fluoro-4-(methylsulfonamido)phenyl]acrylate (78 mg, 0.29 mmol) and 10% palladium on carbon (10 mg) in MeOH (10 mL) were hydrogenated under a balloon of hydrogen for 3 h (TLC check). The reaction mixture was filtered through a pad of Celite, then rinsed with Et_2O. The filtrate was concentrated and dried under vacuum to give **6** (68 mg, 86%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45 (t, 1H, J = 8.2 Hz), 6.98 (d, 1H, J = 8.3 Hz), 6.46 (s, 1H), 3.66 (s, 3H), 3.00 (s, 3H), 2.91 (t, 2H, J = 7.6 Hz), 2.60 (t, 2H, J = 7.6 Hz).

4.1.3. *N*-(4-*tert*-Butylbenzyl)-3-[3-fluoro-4-(methyl-sulfonamido)phenyl]propanamide (7)

To a solution of **6** (30 mg, 0.11 mmol) in toluene (4 mL) was added 4-*tert*-butylbenzylamine **2** (150 μL, 0.92 mmol). The mixture was refluxed for 3 h and diluted with water, and extracted with CH_2Cl_2 several times. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by silica gel column chromatography (EtOAc/*n*-hexane = 1:1) to afford **7** (28 mg, 63%) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39 (t, 1H, J = 8.2 Hz), 7.29 (d, 2H, J = 8.3 Hz), 7.07 (d, 2H, J = 8.3 Hz), 6.92–6.95 (m, 2H), 6.33 (s, 1H), 5.54 (s, 1H), 4.31 (d, 2H, J = 5.6 Hz), 2.93 (s, 3H), 2.92 (t, 2H, J = 7.4 Hz), 2.41 (t, 2H, J = 7.6 Hz), 1.24 (s, 9H); IR (neat) cm^{-1}: 3234, 2960, 1639, 1513, 1401, 1325, 1155; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.1, 155.4, 153.0, 150.7, 140.5, 134.9, 127.6, 125.6, 125.0, 124.9, 124.0, 122.5, 122.4, 115.9, 115.7, 43.4, 39.7, 37.7, 34.5, 31.3, 30.8; HR-MS (FAB+) calcd for $C_{21}H_{28}FN_2O_3S$ ($M+H^+$): 407.1805, found 407.1808.

4.1.4. (*E*)-Methyl 3-(4-(1-methylcyclopropyl) phenyl)acrylate (9)

To a solution of CH_3PPh_3Br (2.2 g, 6.1 mmol) in THF were added *n*-BuLi (1.6 M solution in THF, 3.3 mL, 5.3 mmol) at 0 °C. The reaction mixture was stirred at same temperature for 2 h, then a solution of 1-(4-iodophenyl)ethanone **8** (1.0 g, 4.1 mmol) in THF was added. The reaction mixture was warmed to room temperature. After confirming the completion of the reaction with TLC, the reaction was quenched by aq NH_4Cl and stirred for 20 min. The resulting solution was concentrated, extracted with EtOAc, washed with brine and dried over $MgSO_4$. Purification of the residue by silica gel column chromatography (EtOAc/*n*-hexane = 1:5) to yield colorless oil 724 mg (73%) of 1-iodo-4-(prop-1-en-2-yl)benzene.

To a solution of 1-iodo-4-(prop-1-en-2-yl)benzene (500 mg, 2.0 mmol) in toluene at 0 °C were added CH_2I_2 (825 μL, 10 mmol) and Et_2Zn (1.0 M solution in THF, 10 mL, 10 mmol.). The temperature of reaction mixture was raised to room temperature. After confirming the completion of the reaction with TLC, the solution mixture was quenched by aq NH_4Cl and stirred for 20 min. The resulting solution was concentrated, extracted with EtOAc, washed with brine and dried over $MgSO_4$. The obtained liquid was concentrated under reduced pressure to yield a pale yellow oil 523 mg (99%) of 1-iodo-4-(1-methylcyclopropyl)benzene.

To a solution of 1-iodo-4-(1-methylcyclopropyl) benzene (285 mg, 1.1 mmol) in DMF (5 mL) were added $Pd(OAc)_2$ (12 mg, 0.06 mmol), DPPF (37 mg, 0.07 mmol), Et_3N (306 μL, 2.2 mmol) and methylacrylate (300 μL, 3.3 mmol). The reaction mixture was stirred at 80 °C for 12 h, cooled to room temperature and then diluted with Et_2O. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by silica gel column chromatography (EtOAc/*n*-hexane = 1:5) to afford **9** (201 mg, 84%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.69 (d, 1H, J = 15.9 Hz), 7.44 (d, 2H, J = 8.3 Hz), 7.24 (d, 2H, J = 8.3 Hz), 6.41 (d, 1H, J = 15.9 Hz), 3.79 (s, 3H), 1.40 (s, 3H), 0.84 (m, 2H, J = 5.2 Hz), 0.76–0.82 (m, 2H).

4.1.5. 3-(4-*sec*-Butylphenyl)propanoic acid (10)

To a solution of (*E*)-methyl 3-(4-(1-methylcyclopropyl) phenyl) acrylate **9** (100 mg, 0.46 mmol) was dissolved in anhydrous THF (10 mL), and added a catalytic amount of 10% palladium on activated carbon to carry out hydrogenation, followed by stirring at room temperature for 8 h. The resulting mixture was diluted with Et_2O, filtered through Celite pad, and then concentrated under reduced pressure to yield 78 mg (77%) of methyl 3-(4-*sec*-butylphenyl)propanoate.

To a solution of methyl 3-(4-*sec*-butylphenyl)- propanoate (78 mg, 0.35 mmol) in THF/H_2O = 1:1 (2 mL) was added LiOH–H_2O (19 mg, 0.46 mmol). The reaction mixture was stirred at room temperature for 1 h, acidified with 1 N HCl and then extracted with EtOAc. The combined organic phases were washed with water and brine, dried over $MgSO_4$, concentrated and dried on a vacuum to give the acid **10** (73 mg, 100%) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.11 (d, 4H, J = 1.5 Hz), 2.93 (t, 2H, J = 7.9 Hz), 2.67 (t, 2H, J = 7.9 Hz), 2.55 (m, 1H); 1.51–1.61 (m, 2H), 1.22 (d, 3H, J = 7.0 Hz), 0.80 (t, 3H, J = 7.4 Hz).

4.1.6. (*E*)-3-(4-(1-Methylcyclopropyl)phenyl) acrylic acid (11a)

The compound was prepared from **9** by the procedure for the synthesis of **10** in 91% yield; white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.72 (d, 1H, J = 15.9 Hz), 7.41 (d, 2H, J = 8.4 Hz), 7.19 (d, 2H, J = 8.2 Hz), 6.36 (d, 1H, J = 15.9 Hz), 1.35 (s, 3H), 0.83 (t, 2H, J = 5.2 Hz), 0.71–0.77 (m, 2H).

4.1.7. 3-(4-(1-Methylcyclopropyl)phenyl)propanoic acid (11b)

The compound was prepared from **9** by the procedure for the synthesis of **10** in 86% (2 steps) yield; white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.11 (d, 2H, J = 8.3 Hz), 7.04 (d, 2H, J = 8.3 Hz), 2.84 (t, 2H, J = 7.9 Hz), 2.56 (t, 2H, J = 7.9 Hz), 1.31 (s, 3H), 0.75 (t, 2H, J = 5.2 Hz), 0.61–0.64 (m, 2H).

4.2. General procedure for coupling to amides (23–34b)

To a solution of substituted benzaldehyde (1.0 mmol) in pyridine (5 mL) were added malonic acid (1.5 mmol) and piperidine (dropwise 0.3 mmol). The reaction mixture was refluxed for 2 h as confirming CO_2 generation. After the completion of the reaction, the resultant mixture was acidified with 2 N HCl and then extracted with EtOAc. The combined organic phases were washed with water and brine, dried over $MgSO_4$, concentrated and dried on a vacuum to give the acid as a white solid.

To a solution of acid in THF was added a catalytic amount of 10% palladium on activated carbon to carry out hydrogenation, followed by stirring for 0.5–2 h at room temperature. The resulting mixture was diluted with Et_2O, filtered through Celite pad, and then concentrated in vacuo to give the crude acid, which was directly used for the next step.

To a solution of acid (1.0 mmol) in the THF were added 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methyl- morpholinium chloride (DMTMM) (1.5 mmol), NNM (1.0 mmol) and Et_3N (2.0 mmol). The reaction mixture was stirred for 4 h, and then methanesulfonamide HCl salt (1.2 mmol) was added into the reaction mixture. The mixture was stirred for 10 h at room temperature. The reaction mixture was concentrated in vacuo. The residue was extracted with CH_2Cl_2. A combined organic layer was washed with water and brine, dried over MgSO4, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using CH_2Cl_2/MeOH as eluant.

4.2.1. 3-Phenylpropanoic acid (22a)

The compound was prepared from **12** by the general procedure for the synthesis of acids in 95% yield (2 steps) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29 (t, 2H, J = 7.6 Hz), 7.18–7.22 (m, 3H), 2.97 (t, 2H, J = 7.6 Hz), 2.66 (t, 2H, J = 7.6 Hz).

4.2.2. 3-(4-Bromophenyl)propanoic acid (22b)

The compound was prepared from **13** by the general procedure for the synthesis of acids in 83% yield (2 steps) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25 (d, 2H, J = 8.4 Hz), 7.13 (d, 2H, J = 8.4 Hz), 2.92 (t, 2H, J = 7.5 Hz), 2.65 (t, 2H, J = 7.5 Hz).

4.2.3. (*E*)-3-(4-Iodophenyl)acrylic acid (22c)

The compound was prepared from **14** by the general procedure for the synthesis of acids in 90% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.76 (d, 2H, J = 8.3 Hz), 7.58 (d, 1H, J = 16.1 Hz), 7.36 (d, 2H, J = 8.3 Hz), 6.51 (d, 1H, J = 16.1 Hz).

4.2.4. (*E*)-3-(4-*tert*-Butylphenyl)acrylic acid (22d)

The compound was prepared from **15** by the general procedure for the synthesis of acids in 88% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.78 (d, 1H, J = 16.0 Hz), 7.50 (d, 2H, J = 8.4 Hz), 7.42 (d, 2H, J = 8.6 Hz), 6.43 (d, 1H, J = 16.0 Hz), 1.32 (s, 9H).

4.2.5. 3-[4-(*tert*-Butyl)phenyl]propanoic acid (22e)

The compound was prepared from **15** by the general procedure for the synthesis of acids in 74% yield (2 steps) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31 (d, 2H, J = 8.4 Hz), 7.14 (d, 2H, J = 8.2 Hz), 2.95 (t, 2H, J = 7.9 Hz), 2.69 (t, 2H, J = 7.9 Hz), 1.29 (s, 9H).

4.2.6. 3-(4-(Trifluoromethyl)phenyl)propanoic acid (22f)

The compound was prepared from **16** by the general procedure for the synthesis of acids in 93% yield (2 steps) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.53 (d, 2H, J = 8.1 Hz), 7.31 (d, 2H, J = 8.1 Hz), 3.00 (t, 2H, J = 7.6 Hz), 2.68 (t, 2H, J = 7.6 Hz).

4.2.7. 3-(4-Isopropoxyphenyl)propanoic acid (22g)

The compound was prepared from **17** by the general procedure for the synthesis of acids in 90% yield (2 steps) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.08 (d, 2H, J = 8.4 Hz), 6.80 (d, 2H, J = 8.4 Hz), 4.49 (m, 1H), 2.87 (t, 2H, J = 7.8 Hz), 2.63 (t, 2H, J = 7.7 Hz), 1.26–1.30 (m, 6H).

4.2.8. 3-(4-*tert*-Butoxyphenyl)propanoic acid (22h)

The compound was prepared from **18** by the general procedure for the synthesis of acids in 96% yield (2 steps) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.52 (d, 2H, J = 8.4 Hz), 7.01 (d, 2H, J = 8.6 Hz), 2.98 (t, 2H, J = 7.6 Hz), 2.71 (t, 2H, J = 7.6 Hz), 1.37 (s, 9H).

4.2.9. 3-(3,5-Di-*tert*-butylphenyl)propanoic acid (22i)

The compound was prepared from **19** by the general procedure for the synthesis of acids in 82% yield (2 steps) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.21 (t, 1H, J = 1.7 Hz), 6.98 (d, 2H, J = 1.6 Hz), 2.92 (t, 2H, J = 7.3 Hz), 2.65 (t, 2H, J = 7.3 Hz), 1.27 (s, 18H).

4.2.10. 3-(3,5-Bis(trifluoromethyl)phenyl)propanoic acid (22j)

The compound was prepared from **20** by the general procedure for the synthesis of acids in 83% yield (2 steps) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.71 (s, 1H), 7.62 (s, 2H), 3.02 (t, 2H, J = 6.8 Hz), 2.66 (t, 2H, J = 6.8 Hz).

4.2.11. (*E*)-3-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)acrylic acid (22k)

The compound was prepared from **21** by the general procedure for the synthesis of acids in 94% yield as a yellow solid. ^{1}H NMR

($CDCl_3$, 300 MHz): δ 7.78 (d, 1H, J = 15.9 Hz), 7.45 (s, 1H), 7.33 (d, 2H, J = 0.9 Hz), 6.41 (d, 1H, J = 15.9 Hz), 1.68 (s, 4H), 1.28 (s, 6H), 1.27 (s, 6H).

4.2.12. 3-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)propanoic acid (22l)

The compound was prepared from **21** by the general procedure for the synthesis of acids in 83% yield (2 steps) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.23 (d, 1H, J = 8.1 Hz), 7.12 (d, 1H, J = 2.0 Hz), 6.97 (dd, 1H, J = 2.0, 2.0 Hz), 2.90 (t, 2H, J = 7.9 Hz), 2.65 (t, 2H, J = 7.8 Hz), 1.65 (s, 4H), 1.25 (s, 12H).

4.2.13. *N*-(3-Fluoro-4-(methylsulfonamido)benzyl)-3-phenylpropanamide (23)

The compound was prepared from **22a** by the general procedure for the synthesis of amides in 83% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.45 (t, 1H, J = 8.4 Hz), 7.17–7.27 (m, 5H), 6.89–6.92 (m, 2H), 6.41 (br s, 1H), 5.62 (br s, 1H), 4.35 (d, 2H, J = 6.2 Hz), 2.99 (s, 3H), 2.96 (t, 2H, J = 7.5 Hz), 2.52 (t, 2H, J = 7.5 Hz); IR (neat) cm^{-1}: 2925, 1649, 1515, 1452, 1332, 1156, 972, 758; LRMS (FAB+): *m/z* 351 (M+H$^+$).

4.2.14. 3-(4-Bromophenyl)-*N*-(3-fluoro-4-(methylsulfonamido)benzyl)propanamide (24)

The compound was prepared from **22b** by the general procedure for the synthesis of amides in 64% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.47 (t, 1H, J = 8.3 Hz), 7.38 (d, 2H, J = 8.1 Hz), 7.06 (d, 2H, J = 8.1 Hz), 6.90–6.93 (m, 2H), 6.43 (br s, 1H), 5.63 (br s, 1H), 4.34 (d, 2H, J = 6.0 Hz), 3.00 (s, 3H), 2.94 (t, 2H, J = 7.3 Hz), 2.49 (t, 2H, J = 7.3 Hz); IR (neat) cm^{-1}: 2925, 1650, 1515, 1452, 1332, 1155, 1111, 973, 816; LRMS (FAB+): *m/z* 429 (M+H$^+$).

4.2.15. (*E*)-*N*-(3-Fluoro-4-(methylsulfonamido) benzyl)-3-(4-iodophenyl)acrylmide (25)

The compound was prepared from **22c** by the general procedure for the synthesis of amides in 87% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.75 (d, 2H, J = 8.3 Hz), 7.58 (d, 1H, J = 15.9 Hz), 7.46 (m, 1H), 7.33 (d, 2H, J = 8.3 Hz), 7.14 (t, 2H, J = 8.1 Hz), 6.66 (d, 1H, J = 15.9 Hz), 4.46 (s, 2H), 2.96 (s, 3H); IR (neat) cm^{-1}: 2921, 2397, 1647, 1611, 1512, 1324, 1146, 1111, 971, 814; LRMS (EI+): *m/z* 474 (M).

4.2.16. (*E*)-3-(4-*tert*-Butylphenyl)-*N*-(3-fluoro-4-(methylsulfonamido)benzyl)acrylamide (26a)

The compound was prepared from **22d** by the general procedure for the synthesis of amides in 88% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.66 (d, 1H, J = 15.6 Hz), 7.50 (t, 1H, J = 8.3 Hz), 7.35–7.44 (q, 4H, J = 16.8 Hz), 7.08–7.14 (t, 2H, J = 8.3 Hz), 6.47 (s, 1H); 6.36 (d, 1H, J = 15.6 Hz), 5.96 (br s, 1H), 4.52 (d, 2H, J = 6.1 Hz), 2.99 (s, 3H), 1.30 (s, 9H); HR-MS (FAB+) calcd for $C_{21}H_{26}FN_2O_3S$ (M+H$^+$): 405.1648, found 405.1637.

4.2.17. 3-(4-*tert*-Butylphenyl)-*N*-(3-fluoro-4-(methylsulfonamido)benzyl)propanamide (26b)

The compound was prepared from **22e** by the general procedure for the synthesis of amides in 71% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40 (t, 1H, J = 8.2 Hz), 7.23 (d, 2H, J = 8.3 Hz), 7.06 (d, 2H, J = 8.3 Hz), 6.88–6.91 (m, 2H), 6.49 (s, 1H), 5.68 (br s, 1H), 4.30 (d, 2H, J = 5.6 Hz), 2.93 (s, 3H), 2.89 (t, 2H, J = 7.6 Hz), 2.54 (t, 2H, J = 7.4 Hz), 1.19 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.3, 155.2, 152.8, 149.2, 137.7, 137.6, 137.4, 127.9, 125.4, 124.0, 123.6, 115.0, 114.8, 42.5, 39.7, 38.3, 34.3, 31.3, 31.0; HR-MS (FAB+) calcd for $C_{21}H_{28}FN_2O_3S$ (M+H$^+$): 407.1805, found 407.1802.

4.2.18. 3-(4-*sec*-Butylphenyl)-*N*-(3-fluoro-4-(methylsulfonamido)benzyl)propanamide (27)

The compound was prepared from **10** by the general procedure for the synthesis of amides in 62% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45 (t, 1H, J = 8.2 Hz), 7.06–7.12 (m, 4H), 6.94 (t, 2H, J = 9.2 Hz), 6.51 (s, 1H), 5.69 (s, 1H), 4.34 (d, 2H, J = 6.0 Hz), 2.98 (s, 3H), 2.94 (t, 2H, J = 7.5 Hz), 2.51 (t, 2H, J = 7.5 Hz), 2.53–2.56 (m, 1H); 1.55 (t, 2H, J = 7.2 Hz), 1.19 (d, 3H, J = 7.0 Hz), 0.78 (t, 3H, J = 7.3 Hz); IR (neat) cm^{-1}: 3289, 2960, 2925, 1650, 1514, 1335, 1158, 1112, 973, 823; LRMS (FAB+): *m/z* 407 (M+H$^+$).

4.2.19. (*E*)-*N*-(3-Fluoro-4-(methylsulfonamido)benzyl)-3-(4-(1-methylcyclopropyl)phenyl)acrylamide (28a)

The compound was prepared from **11a** by the general procedure for the synthesis of amides in 87% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.66 (d, 1H, J = 15.6 Hz), 7.51 (t, 1H, J = 8.2 Hz), 7.40 (d, 2H, J = 8.4 Hz), 7.21 (d, 2H, J = 8.4 Hz), 7.07–7.14 (m, 2H), 6.59 (s, 1H), 6.39 (d, 1H, J = 15.6 Hz), 6.08 (br s, 1H), 4.52 (d, 1H, J = 6.0 Hz), 2.99 (s, 3H), 1.39 (s, 3H), 0.84 (t, 2H, J = 5.2 Hz), 0.74–0.80 (m, 2H); IR (neat) cm^{-1}: 3270, 1655, 1617, 1514, 1330, 1155, 1111, 977, 757; HR-MS (FAB+) calcd for $C_{21}H_{24}FN_2O_3S$ (M+H$^+$): 403.1492, found 403.1494.

4.2.20. *N*-(3-Fluoro-4-(methylsulfonamido)benzyl)-3-(4-(1-methylcyclopropyl)phenyl)propanamide (28b)

The compound was prepared from **11b** by the general procedure for the synthesis of amides in 67% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.47 (m, 1H), 7.07–7.16 (m, 4H), 6.93 (t, 2H, J = 9.3 Hz), 6.45 (s, 1H), 5.63 (s, 1H), 4.36 (d, 2H, J = 6.0 Hz), 2.99 (s, 3H), 2.94 (t, 2H, J = 7.5 Hz), 2.50 (t, 2H, J = 7.5 Hz), 1.37 (s, 3H), 0.79 (t, 2H, J = 5.9 Hz), 0.68–0.72 (m, 2H); IR (neat) cm^{-1}: 3269, 1651, 1585, 1514, 1334, 1157, 1111, 757; HR-MS (FAB+) calcd for $C_{21}H_{26}FN_2O_3S$ (M+H$^+$): 405.1648, found 405.1654.

4.2.21. *N*-(3-Fluoro-4-(methylsulfonamido)benzyl)-3-(4-(trifluoromethyl)phenyl)propanamide (29)

The compound was prepared from **22f** by the general procedure for the synthesis of amides in 75% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.51 (d, 2H, J = 7.9 Hz), 7.45 (t, 1H, J = 8.2 Hz), 7.29 (d, 2H, J = 7.9 Hz), 6.90–6.93 (m, 2H), 6.45 (s, 1H), 5.68 (br s, 1H), 4.35 (d, 2H, J = 6.1 Hz), 3.05 (t, 2H, J = 7.5 Hz), 2.99 (s, 3H), 2.53 (t, 2H, J = 7.5 Hz); IR (neat) cm^{-1}: 3226, 2921, 1643, 1540, 1324, 1154, 1110, 827; LRMS (FAB+): *m/z* 419 (M+H$^+$).

4.2.22. *N*-(3-Fluoro-4-(methylsulfonamido)benzyl)-3-(4-isopropoxyphenyl)propanamide (30)

The compound was prepared from **22g** by the general procedure for the synthesis of amides in 66% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.46 (t, 1H, J = 8.2 Hz), 7.07 (d, 2H, J = 8.4 Hz), 6.92 (t, 2H, J = 9.9 Hz), 6.78 (d, 2H, J = 8.6 Hz), 6.44 (br s, 1H), 5.59 (br s, 1H), 4.48 (m, 1H), 4.34 (d, 2H, J = 6.2 Hz), 2.99 (s, 3H), 2.91 (t, 2H, J = 6.9 Hz), 2.49 (t, 2H, J = 6.9 Hz), 1.30 (d, 6H, J = 6.0 Hz); IR (neat) cm^{-1}: 3273, 2976, 1651, 1586, 1512, 1366, 1333, 1240, 1157, 1115, 766; LRMS (FAB+): *m/z* 409 (M+H$^+$).

4.2.23. 3-(4-*tert*-Butoxyphenyl)-*N*-(3-fluoro-4-(methylsulfonamido)benzyl)propanamide (31)

The compound was prepared from **22h** by the general procedure for the synthesis of amides in 71% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.43 (t, 1H, J = 8.2 Hz), 7.05 (d, 2H, J = 8.6 Hz), 6.86 (d, 2H, J = 8.4 Hz), 6.82–6.84 (m, 2H), 5.77 (br s, 1H), 4.32 (d, 2H, J = 5.9 Hz), 2.98 (s, 3H), 2.92 (t, 2H, J = 7.4 Hz), 2.49 (t, 2H, J = 7.4 Hz), 1.29 (s, 9H); IR (neat) cm^{-1}: 3289, 2977, 1651, 1510, 1334, 1159, 1111, 763; LRMS (FAB+): *m/z* 423 (M+H$^+$).

4.2.24. 3-(3,5-Di-*tert*-butylphenyl)-*N*-(3-fluoro-4-(methylsulfonamido)benzyl)propanamide (32)

The compound was prepared from **22i** by the general procedure for the synthesis of amides in 88% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34 (t, 1H, J = 5.4 Hz), 7.28 (s, 1H), 7.06 (s, 2H), 6.82–6.85 (m, 2H), 6.42 (br s, 1H), 5.66 (br s, 1H), 4.36 (d, 2H, J = 5.9 Hz), 2.98 (s, 3H), 2.95 (t, 2H, J = 7.3 Hz), 2.55 (t, 2H, J = 7.3 Hz), 1.28 (s, 18H); IR (neat) cm^{-1}: 2960, 1650, 1597, 1543, 1366, 1311, 1157, 758; HR-MS (FAB+) calcd for $C_{25}H_{36}FN_2O_3S$ (M+H$^+$): 463.2431, found 463.2426.

4.2.25. 3-(3,5-Bis(trifluoromethyl)phenyl)-*N*-(3-fluoro-4-(methylsulfonamido)benzyl)propanamide (33)

The compound was prepared from **22j** by the general procedure for the synthesis of amides in 82% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.72 (s, 1H), 7.66 (s, 2H), 7.47 (t, 1H, J = 8.6 Hz), 6.94 (t, 2H, J = 9.7 Hz), 6.43 (br s, 1H), 5.63 (br s, 1H), 4.37 (d, 2H, J = 6.0 Hz), 3.13 (t, 2H, J = 7.1 Hz), 2.99 (s, 3H), 2.56 (t, 2H, J = 7.4 Hz); IR (neat) cm^{-1}: 3296, 1654, 1589, 1544, 1371, 1313, 1281, 1133, 974, 683; LRMS (FAB+): m/z 487 (M+H$^+$).

4.2.26. (*E*)-*N*-(3-Fluoro-4-(methylsulfonamido) benzyl)-3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro- naphthalen-2-yl)acrylamide (34a)

The compound was prepared from **22k** by the general procedure for the synthesis of amides in 68% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.59 (d, 1H, J = 15.5 Hz), 7.44 (d, 1H, J = 8.3 Hz), 7.39 (d, 1H, J = 4.8 Hz), 7.24 (d, 2H, J = 1.1 Hz), 7.02–7.09 (m, 2H), 6.40 (d, 1H, J = 15.5 Hz), 4.45 (s, 2H), 2.94 (s, 3H), 1.63 (s, 4H), 1.23 (s, 6H),1.22 (s, 6H); IR (neat) cm^{-1}: 2925, 1658, 1619, 1514, 1333, 1156, 977; HR-MS (FAB+) calcd for $C_{25}H_{32}FN_2O_3S$ (M+H$^+$): 459.2118, found 459.2115.

4.2.27. *N*-(3-Fluoro-4-(methylsulfonamido)benzyl)-3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphtha-alene-2-yl)propanamide (34b)

The compound was prepared from **22l** by the general procedure for the synthesis of amides in 80% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.47 (m, 1H), 7.22 (d, 1H, J = 7.9 Hz), 6.92–7.12 (m, 4H), 6.56 (s, 1H), 5.74 (br s, 1H), 4.37 (d, 2H, J = 5.9 Hz), 2.99 (s, 3H), 2.92 (t, 2H, J = 7.8 Hz), 2.52 (t, 2H, J = 7.8 Hz), 1.64 (s, 4H), 1.24 (s, 6H), 1.23 (s, 6H); IR (neat) cm^{-1}: 3271, 2959, 1650; 1586, 1514, 1335, 1157, 974, 758; HR-MS (FAB+) calcd for $C_{25}H_{34}FN_2O_3S$ (M+H$^+$): 461.2274, found 461.2258.

4.3. 5-tert-Butyl-2,3-dihydrobenzofuranyl/6-tert-Butylchroman analogues are prepared by below methods

4.3.1. 1,3-Dibromo-2-(2-bromoethoxy)-5-*tert*-butylbenzene (36a)

To a solution of 4-*tert*-butyl- phenol **35** (1.2 g, 8.2 mmol) in CH_2Cl_2/MeOH = 5:2 (35 mL) were added benzyltrimethylammonium tribromide (6.4 g, 16 mmol). The reaction mixture was stirred at room temperature for 1 h and diluted with CH_2Cl_2. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/*n*-hexane = 1:3) to afford 2,6-dibromo-4-*tert*-butylphenol (2.5 g, 96%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.42 (s, 2H), 5.71 (s, 1H), 1.26 (s, 9H).

1,2-Dibromoethane (420 μL, 4.9 mmol) was added to a stirred solution of sodium hydroxide (156 mg, 3.9 mmol) and 2,6-dibromo-4-*tert*-butylphenol (1.0 g, 3.3 mmol) in water (15 mL). The stirred mixture was refluxed 12 h, cooled and the product was extracted into Et_2O (2 × 100 mL). The combined extracts were washed with 2 N HCl and brine (100 mL), dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/*n*-hexane = 1:3) to afford **36** (333 mg, 48%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.47 (s, 2H), 4.27 (t, 2H, J = 6.9 Hz), 3.71 (t, 2H, J = 6.9 Hz), 1.26 (s, 9H).

4.3.2. 1,3-Dibromo-2-(3-bromopropoxy)-5-*tert*-butylbenzene (36b)

The reaction was performed by same preparation method of **36a**, then the crude product was purified by silica gel chromatography (EtOAc/*n*-hexane = 1:10) to provide **36b** (77%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.47 (s, 2H), 4.09 (t, 2H, J = 5.7 Hz), 3.71 (t, 2H, J = 6.6 Hz), 2.30–2.40 (m, 2H), 1.26 (s, 9H).

4.3.3. 5-*tert*-Butyl-2,3-dihydrobenzofuran-7-carbaldehyde (37a)

n-BuLi (1.0 mL, 1.6 M in hexanes, 1.6 mmol) was added to a solution of 1,3-dibromo-2-(2-bromoethoxy)-5-*tert*-butylbenzene **36a** (647 mg, 1.6 mmol) in THF (6 mL) at −78 °C under argon. The mixture was stirred at this temperature for 30 min, allowed to warm to 0 °C, and poured into water (20 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined extracts were dried over $MgSO_4$ and concentrated in vacuo to give a residue which was purified by flash chromatography over silica using (EtOAc/*n*-hexane = 1:10) as the eluant to give 7-bromo-5-*tert*-butyl-2,3-dihydrobenzofuran (235 mg, 59%) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.23 (br s, 1H), 7.13 (br s, 1H), 4.62 (t, 2H, J = 8.7 Hz), 3.28 (t, 2H, J = 8.7 Hz), 1.27 (s, 9H).

To a solution of 7-bromo-5-*tert*-butyl-2,3-dihydrobenzofuran (235 mg, 0.92 mmol) in THF (5 mL) was added dropwise of *t*-BuLi (1.7 M in hexanes, 1.1 mL, 1.9 mmol) at −78 °C, then warmed to 0 °C. To the reaction mixture was added DMF (78 μL, 1.0 mmol), then stirred at 0 °C for 30 min followed by dilution with Et_2O. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/*n*-hexane = 1:10) to afford **37a** (176 mg, 93%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.16 (s, 1H), 7.55 (br s, 1H), 7.46 (br s, 1H), 4.70 (t, 2H, J = 8.7 Hz), 3.21 (t, 2H, J = 8.7 Hz), 1.29 (s, 9H).

4.3.4. 6-*tert*-Butylchroman-8-carbaldehyde (37b)

The compound was prepared from **36b** by the procedure for the synthesis of **37a** in 39% yield (2 steps) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.38 (s, 1H), 7.64 (d, 1H, J = 2.6 Hz), 7.27 (t, 1H, J = 1.3 Hz), 4.26 (t, 2H, J = 5.2 Hz), 2.81 (t, 2H, J = 6.5 Hz), 2.00–2.07 (m, 2H), 1.27 (s, 9H).

4.3.5. (*E*)-3-(5-*tert*-Butyl-2,3-dihydrobenzofuran-7-yl)acrylic acid (38a)

The compound was prepared from **37a** by the general procedure for the synthesis of acids in 90% yield as a yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.79 (d, 1H, J = 15.9 Hz), 7.26 (br s, 1H), 7.20 (br s, 1H), 6.75 (d, 1H, J = 15.9 Hz), 4.65 (t, 2H, J = 8.7 Hz), 3.20 (t, 2H, J = 8.6 Hz), 1.28 (s, 9H).

4.3.6. (*E*)-3-(6-*tert*-Butylchroman-8-yl)acrylic acid (38b)

The compound was prepared from **37b** by the general procedure for the synthesis of acids in 86% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.05 (d, 1H, J = 16.3 Hz), 7.33 (d, 1H, J = 2.4 Hz), 7.09 (d, 1H, J = 2.4 Hz), 6.58 (d, 1H, J = 15.9 Hz), 4.24 (t, 2H, J = 5.1 Hz), 2.78 (t, 2H, J = 6.5 Hz), 1.93–2.01 (m, 2H), 1.28 (s, 9H).

4.3.7. (*E*)-3-(5-*tert*-Butyl-2,3-dihydrobenzofuran-7-yl)-*N*-(3-fluoro-4-(methylsulfonamido)benzyl)acrylamide (39)

The compound was prepared from **38a** by the general procedure for the synthesis of amides in 63% yield as a white solid. ^{1}H

NMR ($CDCl_3$, 300 MHz): δ 7.62 (d, 1H, J = 15.5 Hz), 7.49 (t, 2H, J = 8.0 Hz), 7.07–7.21 (m, 3H), 6.78 (d, 1H, J = 15.5 Hz), 6.53 (br s, 1H), 5.98 (br s, 1H), 4.62 (t, 2H, J = 8.7 Hz), 4.53 (d, 2H, J = 6.1 Hz), 3.19 (t, 2H, J = 8.7 Hz), 2.99 (s, 3H), 1.27 (s, 9H); IR (neat) cm^{-1}: 2960, 1653, 1592, 1513, 1451, 1333, 1280, 1157, 977, 821, 733; LRMS (FAB+): m/z 447 ($M+H^+$).

4.3.8. 3-(5-*tert*-Butyl-2,3-dihydrobenzofuran-7-yl)-*N*-(3-fluoro-4-(methylsulfonamido)benzyl)propanamide (40)

The compound was prepared from **38a** by the general procedure for the synthesis of amides in 75% yield (2 steps) as a white solid. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.46 (m, 1H), 7.10 (m, 1H), 6.89–6.96 (m, 2H), 6.58 (d, 1H, J = 6.4 Hz), 6.11 (br s, 1H), 5.96 (br s, 1H), 4.56 (t, 2H, J = 8.7 Hz), 4.37 (d, 2H, J = 5.9 Hz), 3.13 (t, 2H, J = 8.6 Hz), 2.99 (s, 3H), 2.90 (t, 2H, J = 7.6 Hz), 2.58 (t, 2H, J = 7.7 Hz), 1.25 (s, 9H); IR (neat) cm^{-1}: 3267, 2959, 1585, 1514, 1480, 1335, 1281, 1157, 975, 819, 757; LRMS (FAB+): m/z 449 ($M+H^+$).

4.3.9. (*E*)-3-(6-*tert*-Butylchroman-8-yl)-*N*-(3-fluoro-4-(methylsulfonamido)benzyl)acrylamide (41)

The compound was prepared from **38b** by the general procedure for the synthesis of amides in 60% yield as a white solid. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.83 (d, 1H, J = 15.8 Hz), 7.47 (t, 2H, J = 8.1 Hz), 7.27 (d, 1H, J = 2.4 Hz), 7.03–7.14 (m, 2H), 6.61 (d, 1H, J = 15.8 Hz), 6.09 (br s, 1H), 4.52 (d, 2H, J = 6.0 Hz), 4.20 (t, 2H, J = 5.1 Hz), 2.98 (s, 3H), 2.77 (t, 2H, J = 6.4 Hz), 1.94–2.02 (m, 2H), 1.25 (s, 9H); IR (neat) cm^{-1}: 3269, 2958, 1655, 1615, 1515, 1451, 1333, 1223, 1157, 977; 757; LRMS (FAB+): m/z 461 ($M+H^+$).

4.3.10. 3-(6-*tert*-Butylchroman-8-yl)-*N*-(3-fluoro-4-(methylsulfonamido)benzyl)propanamide (42)

The compound was prepared from **38b** by the general procedure for the synthesis of amides in 49% yield (2 steps) as a white solid. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.44 (t, 1H, J = 8.3 Hz), 6.91–6.99 (m, 4H), 6.65 (s, 1H), 6.03 (br s, 1H), 4.37 (d, 2H, J = 5.9 Hz), 4.10 (t, 2H, J = 5.1 Hz), 2.99 (s, 3H), 2.89 (t, 2H, J = 7.7 Hz), 2.74 (t, 2H, J = 6.5 Hz), 2.55 (t, 2H, J = 7.7 Hz), 1.87–1.95 (m, 2H), 1.26 (s, 9H); IR (neat) cm^{-1}: 2957, 1648, 1516, 1480, 1333, 1157, 974, 757; HR-MS (FAB+) calcd for $C_{24}H_{31}FN_2O_4S$ ($M+H^+$): 462.1989, found 462.1985.

4.4. 2,2-dimethyl-2,3-dihydrobenzofuran analogues are prepared by below methods

4.4.1. 4-Bromo-2-(2-methylallyl) phenol (44)

To a solution of 4-bromophenol **43** (300 mg, 1.73 mmol) in acetone (7 mL) was added K_2CO_3 (1.2 g, 8.67 mmol) and 3-bromo-2-methypropene (192 μL, 1.91 mmol). The reaction mixture was refluxed for overnight. The resulting mixture was cooled to ambient temperature and then diluted with CH_2Cl_2. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo to give 1-bromo-4-(2-methyl- allyloxy)benzene (392 mg, 99%) which was directly used for the next step. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.36 (t, 1H, J = 2.7 Hz), 7.33 (t, 1H, J = 2.8 Hz), 6.80 (t, 1H, J = 2.8 Hz), 6.77 (t, 1H, J = 2.7 Hz), 5.06 (br s, 1H), 4.98 (br s, 1H), 4.38 (s, 2H), 1.80 (s, 3H).

To a solution of 1-bromo-4-(2-methylallyloxy) benzene (259 mg, 1.1 mmol) in DMF (7 mL) was refluxed for overnight. After cooling to ambient temperature and dilution with Et_2O, the organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/*n*-hexane = 1:3) to afford **44** (221 mg, 87%). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.08–7.18 (m, 2H), 6.63(d, 1H, J = 9.2 Hz), 5.79 (s, 1H), 4.82 (s, 1H), 4.72 (s, 1H), 3.23(s, 2H), 1.64 (s, 3H).

4.4.2. 2,2-Dimethyl-2,3-dihydrobenzofuran-5-carbaldehyde (45)

To a solution of phenol **44** (120 mg, 0.53 mmol) in CH_2Cl_2 (5 mL) was added I_2 (27 mg, 0.11 mmol). The reaction mixture was stirred at room temperature for 12 h, then quenched by addition of saturated aqueous $Na_2S_2O_3$ and diluted with CH_2Cl_2. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromate-graphy (EtOAc/*n*-hexane = 1:3) to afford 5-bromo-2,2-dimethyl-2,3-dihydrobenzofuran (96 mg, 80%). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.18–7.27 (m, 2H), 6.63 (d, 1H, J = 8.4 Hz), 3.00 (s, 2H), 1.48 (s, 6H).

To a solution of 5-bromo-2,2-dimethyl-2,3-dihydrobenzofuran (171 mg, 0.75 mmol) in THF (4 mL) was added dropwise of *t*-BuLi (1.7 M in hexanes, 885 μL) at −78 °C, then warmed to 0 °C. To the reaction mixture was added DMF (64 μL, 0.83 mmol), then reaction mixture were stirred at 0 °C for 30 min followed by dilution with Et_2O. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/*n*-hexane = 1:3) to afford **45** (114 mg, 86%). ^1H NMR ($CDCl_3$, 300 MHz) δ 9.77 (s, 1H), 7.67 (s, 1H), 7.64 (d, 1H, J = 8.3 Hz), 6.80 (d, 1H, J = 8.3 Hz), 3.02 (s, 2H), 1.48 (s, 6H).

4.4.3. (*E*)-3-(2,2-Dimethyl-2,3-dihydrobenzofuran-5-yl)acrylic acid (46)

The compound was prepared from **45** by the general procedure for the synthesis of acids in 72% yield as a yellow solid. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.74 (d, 1H, J = 15.7 Hz), 7.36 (s, 1H), 7.32 (d, 1H, J = 8.3 Hz), 6.73 (d, 1H, J = 8.3 Hz), 6.28 (d, 1H, J = 15.7 Hz), 3.01 (s, 2H), 1.47 (s, 6H).

4.4.4. (*E*)-3-(2,2-Dimethyl-2,3-dihydrobenzofuran-5-yl)-*N*-(3-fluoro-4-(methylsulfonamido)benzyl) acrylamide (47)

The compound was prepared from **46** by the general procedure for the synthesis of amides in 91% yield as a white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.62 (d, 1H, J = 15.4 Hz), 7.50 (m, 1H), 7.29 (s, 1H), 7.09–7.15 (m, 2H), 6.70 (d, 1H, J = 8.1 Hz), 6.51 (m, 1H), 6.25 (d, 1H, J = 15.4 Hz), 5.91 (br s, 1H), 4.53 (d, 2H, J = 6.1 Hz), 2.99 (s, 3H), 2.98 (s, 2H), 1.46 (s, 6H); IR (neat) cm^{-1}: 3269, 1655, 1588, 1514, 1484, 1335, 1156, 1111, 974, 820, 757; LRMS (FAB+): m/z 419 ($M+H^+$).

4.4.5. 3-(2,2-Dimethyl-2,3-dihydrobenzofuran-5-yl)-*N*-(3-fluoro-4-(methylsulfonamido)benzyl)propanamide (48)

The compound was prepared from **46** by the general procedure for the synthesis of amides in 91% yield (2 steps) as a white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.46 (m, 1H), 7.10 (m, 1H), 6.88–6.95 (m, 2H), 6.69 (s, 1H), 6.61 (d, 1H, J = 8.0 Hz), 6.31 (br s, 1H), 5.77 (br s, 1H), 4.35 (d, 2H, J = 5.9 Hz), 2.99 (s, 3H), 2.98 (s, 2H), 2.88 (t, 2H, J = 7.5 Hz), 2.48 (t, 2H, J = 7.4 Hz), 1.43 (s, 6H); IR (neat) cm^{-1}: 3273, 2928, 1651, 1584, 1514, 1486, 1335, 1156, 1112, 973, 818, 757; LRMS (FAB+): m/z 421 ($M+H^+$).

4.5. 2,2-dimethyl-chromane analogues are prepared by below methods

4.5.1. (*E*)-3-(2,2-Dimethylchroman-6-yl)acrylic acid (50)

To a solution of 4-hydroxybenzaldehyde **49** (300 mg, 2.5 mmol) in anhydrous CCl_4 (15 mL) was added montmorillonite K10 Clay (1313 mg, 20 equiv) and 1-bromo-3-methyl-2-butene (317 μL, 2.7 mmol). The reaction mixture was stirred at room temperature for 16 h. The solid was removed by filtering over Celite and washed with CH_2Cl_2. The combined filtrate and washes were concentrated in vacuo to give a colorless oil. Purification of the residue by silica gel chromatography (EtOAc/*n*-hexane = 1:3) provided 2,2-di-

methyl chroman-6-carbaldehyde (39 mg, 8.4%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.80 (s, 1H), 7.58–7.61(m, 2H), 6.85 (d, 1H, J = 9.0 Hz), 2.82 (t, 2H, J = 6.7 Hz), 1.81–1.85 (m, 2H), 1.35 (s, 6H).

The reaction was performed by same general preparation procedure, then purification of the crude product by silica gel chromatography (CH_2Cl_2/MeOH = 20:1) provided **50** (55 mg, 86%) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.71 (d, 1H, J = 15.9 Hz), 7.26–7.31 (m, 2H), 6.78 (d, 1H, J = 8.4 Hz), 6.29 (d, 1H, J = 15.9 Hz), 2.78 (t, 2H, J = 6.8 Hz), 1.81 (t, 2H, J = 6.8 Hz), 1.33 (s, 6H).

4.5.2. (*E*)-3-(2,2-Dimethylchroman-6-yl)-*N*-(3-fluoro-4-(methylsulfonamido)benzyl)acrylamide (51)

The compound was prepared from **50** by the general procedure for the synthesis of amides in 77% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.61 (d, 1H, J = 15.4 Hz), 7.50 (m, 1H), 7.19 (br s, 1H), 7.07–7.14 (m, 2H), 7.75 (d, 1H, J = 8.4 Hz), 6.51 (s, 1H), 6.27 (d, 1H, J = 15.4 Hz), 5.93 (br s, 1H), 4.53 (d, 2H, J = 6.1 Hz), 2.99 (s, 3H), 2.75 (t, 2H, J = 6.8 Hz), 1.79 (t, 2H, J = 6.8 Hz), 1.32 (s, 6H); IR (neat) cm^{-1}: 3269, 1582, 1514, 1336, 1271, 1156, 975, 819, 757; LRMS (FAB+): m/z 433 (M +H$^+$).

4.5.3. 3-(2,2-Dimethylchroman-6-yl)-*N*-(3-fluoro-4-(methylsulfonamido)benzyl)propanamide (52)

The compound was prepared from **50** by the general procedure for the synthesis of amides in 92% yield (2 steps) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45 (m, 1H), 7.09 (m, 1H), 6.86–6.96 (m, 2H), 6.71 (s, 1H), 6.66 (d, 1H, J = 9.0 Hz), 6.28 (br s, 1H), 5.79 (br s, 1H), 4.33 (d, 2H, J = 5.9 Hz), 2.99 (s, 3H), 2.86 (t, 2H, J = 7.5 Hz), 2.69 (t, 2H, J = 6.8 Hz), 2.48 (t, 2H, J = 7.5 Hz), 1.75 (t, 2H, J = 6.8 Hz), 1.29 (s, 6H); IR (neat) cm^{-1}: 3271, 2931, 1650, 1584, 1512, 1336, 1157, 974, 819, 758; LRMS (FAB+): m/z 435 (M+H$^+$).

4.6. A part-modified analogues are prepared by below methods

4.6.1. 4-Amino-3-fluoro-5-iodobenzonitrile (53)

To a solution 2-fluoro-4-iodoaniline **5** (2.0 g, 8.4 mmol) in DMF (30 mL) was added CuCN (982 mg, 11 mmol). The reaction mixture was stirred at 130 °C for 8 h. After cooling to room temperature, the mixture was poured into water and extracted with EtOAc. A diluted solution was washed water (2×) and brine, and then dried with $MgSO_4$. A residue was purified with column chromatography (EtOAc/*n*-hexane = 1:2) to provide 4-amino-3-fluorobenzonitrile (914 mg, 80%) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.21–7.26 (m, 2H), 6.74 (t, 1H, J = 8.4 Hz), 4.20 (br s, 2H).

To a solution of 4-amino-3-fluorobenzonitrile (2.6 g, 19 mmol) in CH_2Cl_2 (20 mL) was added ICl (1.0 M CH_2Cl_2, 38 mL, 38 mmol). The reaction mixture was stirred for 20 h, then quenched by adding $Na_2S_2O_3$ solution. The aqueous solution was extracted with CH_2Cl_2 then the combined organic solution was washed with water and brine, dried with $MgSO_4$, concentrated in vacuo. The residue was purified with column chromatography (EtOAc/*n*-hexane = 1:2) to give **53** as a white solid (3.3 g, 66%). ^{1}H NMR ($CDCl_3$, 300 MHz), δ 7.69 (t, 1H, J = 1.5 Hz), 7.23 (dd, 1H, J = 1.7, 10.0 Hz), 4.68 (br s, 2H).

4.6.2. *tert*-Butyl 4-amino-3-fluoro-5-iodobenzylcarbamate (54)

To a solution of **53** (842 mg, 3.2 mmol) in THF (8 mL) was added BH_3–THF (1 M solution in THF, 9.6 mL, 9.6 mmol) dropwise. The reaction mixture was refluxed for 3 h and 2 *N* HCl (1.0 mL) was added. The resulting mixture was refluxed for an additional 1 h and then concentrated in vacuo to give 971 mg (99%) of the crude 4-(aminomethyl)-2-fluoro-6-iodoaniline HCl salt, which was directly used for the next step.

A solution of 4-(aminomethyl)-2-fluoro-6-iodoaniline (971 mg, 3.2 mmol,) and Et_3N (1.3 mL, 9.6 mmol) in CH_2Cl_2 was put into the flask and then cooled to 0 °C. To the solution were added 4-dimethylaminopyridine (78 mg, 0.64 mmol) and di-*tert*-butyldicarbonate (2.1 g, 9.6 mmol) then stirred for 12 h. After confirming the completion of the reaction with TLC, the resulting solution was extracted with CH_2Cl_2, washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The obtained liquid was purified by column chromatography (EtOAc/*n*-hexane = 1:2) to give **54** as a yellow solid (940 mg, 80%, 2 steps). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29 (s, 1H), 6.91 (dd, 1H, J = 1.3, 1.5 Hz), 4.85 (s, 1H), 4.12 (d, 2H, J = 7.0 Hz), 1.42 (s, 9H).

4.6.3. *tert*-Butyl 3-cyano-5-fluoro-4-(methylsulfonamido)benzylcarbamate (55)

To a solution of *tert*-butyl 4-amino-3-fluoro-5-iodobenzylcarbamate **54** (300 mg, 0.82 mmol) and pyridine (200 μL, 2.5 mmol) in CH_2Cl_2 (20 mL) was put into the flask and then cooled to 0 °C. To the solution was added methanesulfonyl chloride (76 μL, 0.98 mmol) and heated to reflux for overnight. After confirming the completion of the reaction with TLC, the reaction solution was acidified by 10% HCl, extracted with EtOAc, washed with water and brine, dried over $MgSO_4$ and evaporated. The obtained solid was purified by column chromatography (EtOAc/*n*-hexane = 1:2) to yield a yellow liquid *tert*-butyl 3-fluoro-5-iodo-4-(methylsulfonamido)benzylcarbamate (130 mg, 36%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56 (s, 1H), 7.09 (dd, 1H, J = 1.8, 1.7 Hz), 6.32 (s, 1H), 4.99 (br s, 1H), 4.24 (d, 2H, J = 5.7 Hz), 3.22 (s, 3H), 1.44 (s, 9H).

To a solution of *tert*-butyl 3-fluoro-5-iodo-4-(methylsulfonamido)benzylcarbamate (156 mg, 0.35 mmol) in DMF (3 mL) was added $Zn(CN)_2$ (82 mg, 0.70 mmol) and $Pd(PPh_3)_4$ (81 mg, 0.07 mmol). A reaction mixture was heated to 130 °C, stirred for 3 h, cooled to room temperature, and was diluted with EtOAc. A diluted solution was washed water (2×) and brine, and then dried with $MgSO_4$. The residue was purified by column chromatography (EtOAc/*n*-hexane = 1:3) to yield solid **55** (76 mg, 63%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.40 (m, 2H), 6.48 (s, 1H), 5.01 (br s, 1H), 4.31 (d, 2H, J = 6.4 Hz), 3.28 (s, 3H), 1.44 (s, 9H).

4.6.4. *N*-(4-Aminomethyl-2-cyano-6-fluorophenyl) methanesulfonamide (56)

To a solution **55** (160 mg, 0.47 mmol) in EtOAc (6 mL) was added 5 N HCl (583 μL) and stirred for 1 h. After confirming the completion of the reaction with TLC, the reaction solution was concentrated under reduced pressure to yield a brown crude solid **56** (crude 100%).

4.6.5. 3-(4-*tert*-Butylphenyl)-*N*-(3-cyano-5-fluoro-4-(methylsulfonamido)benzyl)propanamide (57)

The reaction was performed by same general preparation procedure, then purification of the crude product by silica gel chromatography (CH_2Cl_2/MeOH = 20:1) to afford **57** (39%) as a white solid. ^{1}H NMR (CD_3OD, 500 MHz) δ 7.46 (s, 1H), 7.33 (d, 1H, J = 10.4 Hz), 7.31 (d, 2H, J = 8.2 Hz), 7.11 (d, 2H, J = 8.2 Hz), 4.34 (s, 2H), 3.12 (s, 3H), 2.90 (t, 2H, J = 7.4 Hz), 2.54 (t, 2H, J = 7.4 Hz), 1.28 (s, 9H); ^{13}C NMR (CD_3OD, 125 MHz) δ 176.4, 161.5, 159.5, 151.1, 144.1, 139.7, 130.1, 130.0, 129.8, 127.2, 122.1, 121.9, 117.8, 117.0, 43.6, 43.0, 39.6, 36.0, 33.0, 32.6; IR (neat) cm^{-1}: 3432, 2960, 2499, 2222, 1641, 1429, 1328, 1278; HR-MS (FAB+) calcd for $C_{22}H_{27}FN_3O_3S$ (M+H$^+$): 432.1757, found 432.1762.

4.6.6. *N*-(3-Cyano-5-fluoro-4-(methylsulfonamido)benzyl)-3-(4-(1-methylcyclopropyl)phenyl)propanamide (58)

The reaction was performed by the general preparation procedure, then purification of the crude product by silica gel chromatography (CH_2Cl_2/MeOH = 20:1) to afford **58** (69%) as a white solid. ^{1}H NMR (CD_3OD, 300 MHz) δ 7.35 (s, 1H), 7.20 (dd, 1H, J = 1.8, 2.0 Hz), 7.04 (m, 1H), 6.96–6.99 (m, 3H), 4.23 (s, 2H), 3.19 (s, 3H), 2.79 (t, 2H, J = 7.4 Hz), 2.43 (t, 2H, J = 7.4 Hz), 1.26 (s, 3H),

0.65–0.71 (m, 2H), 0.57–0.60 (m, 2H); ^{13}C NMR (CD_3OD, 125 MHz) δ 176.3, 161.5, 159.5, 147.1, 144.2, 140.1, 139.8, 130.1, 130.0, 129.0, 128.6, 122.1, 121.9, 117.7, 117.1, 43.6, 43.0, 39.6, 33.0, 26.9, 21.0, 16.9; IR (neat) cm^{-1}: 3363, 2959, 2222, 1644, 1546, 1424, 1323, 1148, 980, 770; HR-MS (FAB+) calcd for $C_{22}H_{25}FN_3O_3S$ ($M+H^+$): 430.1601, found 430.1602.

4.6.7. *N*-(3-Cyano-5-fluoro-4-(methylsulfonamido)benzyl)-3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)propanamide (59)

The reaction was performed by the general preparation procedure, then purification of the crude product by silica gel chromatography (CH_2Cl_2/MeOH = 20:1) to afford **59** (59%) as a white solid. ^{1}H NMR (CD_3OD, 300 MHz): δ 7.49(s, 1H), 7.37 (dd, 1H, J = 1.8, 2.0 Hz), 7.20 (d, 1H, J = 8.0 Hz), 7.14 (d, 1H, J = 1.8 Hz), 6.91 (dd, 1H, J = 2.0, 2.0 Hz), 4.36 (s, 2H), 3.12 (s, 3H), 2.87 (t, 2H, J = 7.5 Hz), 2.52 (t, 2H, J = 7.5 Hz), 1.67 (s, 4H), 1.23 (s, 12H); ^{13}C NMR (CD_3OD, 125 MHz) δ 176.5, 146.7, 144.6, 139.7, 130.1, 130.0, 128.5, 128.1, 127.8, 127.4, 122.1, 122.0, 117.1, 43.7, 43.0, 39.6, 37.1, 37.0, 35.9, 35.7, 33.2, 33.1, 33.0; IR (neat) cm^{-1}: 2959, 2224, 1707, 1654, 1585, 1540, 1492, 1337, 1157, 974, 771; HR-MS (FAB+) calcd for $C_{26}H_{33}FN_3O_3S$ ($M+H^+$): 486.2227, found 486.2218.

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