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Synthesis and structural optimization of multiple H-bonding region of diarylalkyl (thio)amides as novel TRPV1 antagonists

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ABSTRACT

Structural optimization of multiple H-bonding region and structure–activity relationship of diarylalkyl amides/thioamides as novel TRPV1 antagonists are described. In particular, we identified amide **34o** and thioamides **35o** and **35r**, of which antagonistic activities were highly enhanced by an incorporation of cyano or vinyl-substituent to the multiple H-bonding region. They exhibited potent $^{45}Ca^{2+}$ uptake inhibitions in rat DRG neuron with IC_{50}s of 25, 32 and 28 nM, respectively.

1. Introduction

Neuropathic pain affects 26 million worldwide patients, and incurs healthcare costs exceeding three billion dollars per year.[1] Despite availability of the powerful drugs for effective pain management the necessity of new non-narcotic analgesics still remains. The nerve damage and analgesic effect of TRPV1 (transient receptor potential vanilloid subfamily 1) agonist are preceded by an intense painful hyperanalgesia caused by TRPV1 activation.[2] Intensive genetic and pharmacological studies on TRPV1 have been conducted since it was cloned in 1997 and these studies have implied that TRPV1 could be a key molecular target for pain management.[3] Thus, much effort has been expended on the excavation of potent and selective antagonists of TRPV1.[4–6]

In this context, we previously reported dibenzyl thioureas (Fig. 1)[7,8] as potent TRPV1 antagonists and their structure–activity relationship (SAR).[9] Recently, we also reported new variants of the lipophilic C-region of diarylalkyl amides.[10] However, our previous studies revealed that amide series exhibited lower antagonistic activities compared to the corresponding thiourea series in spite of optimization of the lipophilic C-region. Thus, our recent work has focused on optimization of the multiple H-bonding part A to improve potency and metabolic and pharmacokinetic profiles of the diarylalkyl amide or thioamide series because they seem to be preferred scaffold in terms of therapeutic application. Fortunately, during our previous studies,[10] we observed that an incorporation of an additional substituent into region A of thiourea enhances antagonistic activity, and this finding encouraged us to execute an extensive investigation in A-region optimization. We herein report potency enhancement by structural optimization of A-region of diarylalkyl amides or thioamides as well as their SAR.

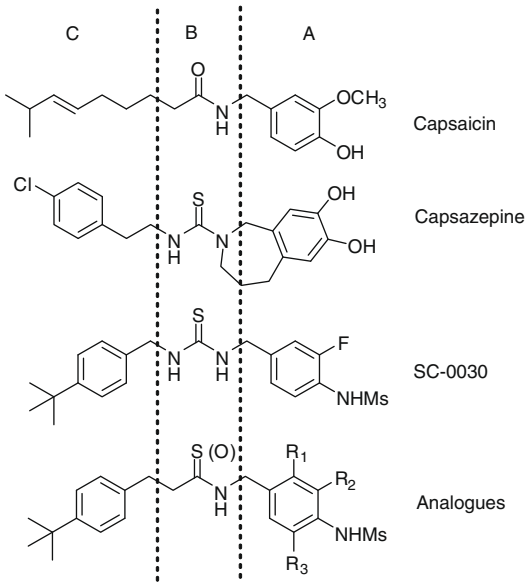

Figure 1. Capsaicin, capsazepine, SC-0030, and potency-enhanced amide analogs.

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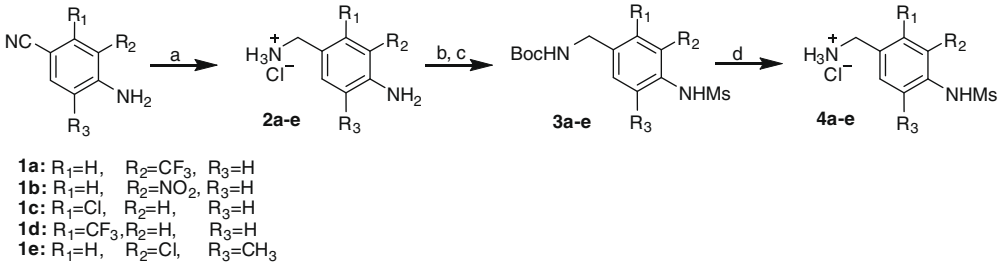
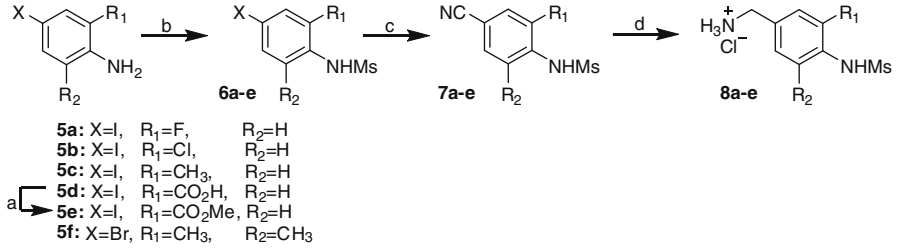
2. Results and discussion

2.1. Chemistry

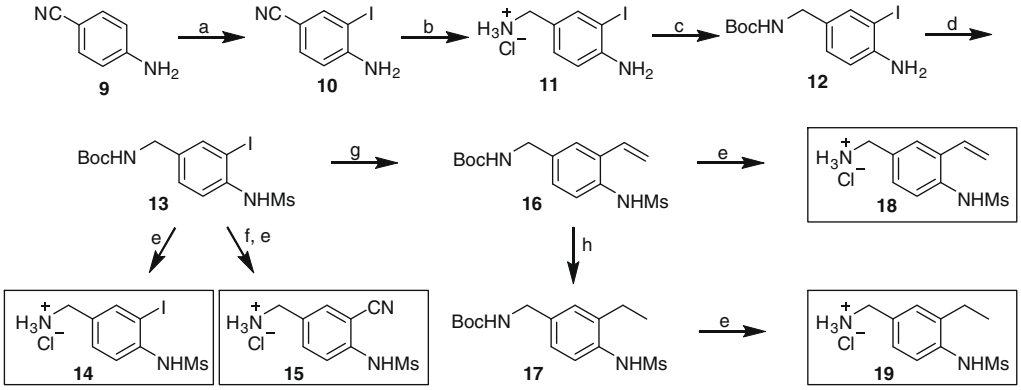
Syntheses of a variety of A-region as benzylamine ammonium salts (**4a–e** and **8a–e**) are described in Schemes 1 and 2. Borane reduction of cyanides **1a–e**, followed by Boc-protection and methanesulfonylation of the resulting benzylamines provided **3a–e**. The benzylamines **3a–e**, were readily converted to the key intermediates **4a–e** via sequential deprotection and salt formation. The commercially available anilines (**5a–f**) were mesylated, and then resulting sulfonamides (**6a–e**) were treated with CuCN to afford **7a–e**. The ammonium salts (**8a–e**) were obtained by BH_3 reduction of **7a–e** followed by treatment with 2 N HCl. The analogues **14, 15, 18** and **19** were also prepared by the procedure described in Scheme 3. Aniline **9** was transformed into **13** by sequential iodination of **9**, nitrile reduction, Boc-protection of the resulting benzylamine followed by methanesulfonylation. The benzylamine **13** was readily converted to the intermediate **14** via sequential deprotection and salt formation. Treatment of **13** with CuCN afforded cyanide, which was readily converted to **15** under acidic condition. Stille coupling[11] of benzylamine **13** with tributylvinyltin gave the vinylbenzylcarbamate **16**, which was treated with 5 N HCl to afford olefin **18**. Pd-catalyzed hydrogenation of **16** followed by Boc-deprotection gave the saturated analogue **19** (Scheme 3). Trisubstituted benzylamines **28–31** were prepared from commercially available aniline **5a** (Scheme 4). Sequential cyanation and iodination of aniline **5a**, reduction of nitrile **21** with borane and Boc-protection followed by methanesulfonylation provided the key intermediate **23**. Treatment of **23** with $Zn(CN)_2$ afforded cyanide **24**, which was readily converted to **28** under acidic condition. Sonogashira coupling[12] of **23** with TMS acetylene gave **25**, which was subjected to the conditions for desilylation and Boc-deprotection to afford **29** in 60% overall yield. Stille coupling of **23** with tributylvinyltin followed by Boc-deprotection gave analogue **30**. Simmons–Smith cyclopropanation[13] of **26** with diethylzinc and CH_2I_2 followed by Boc-deprotection provided cyclopropane **31**.



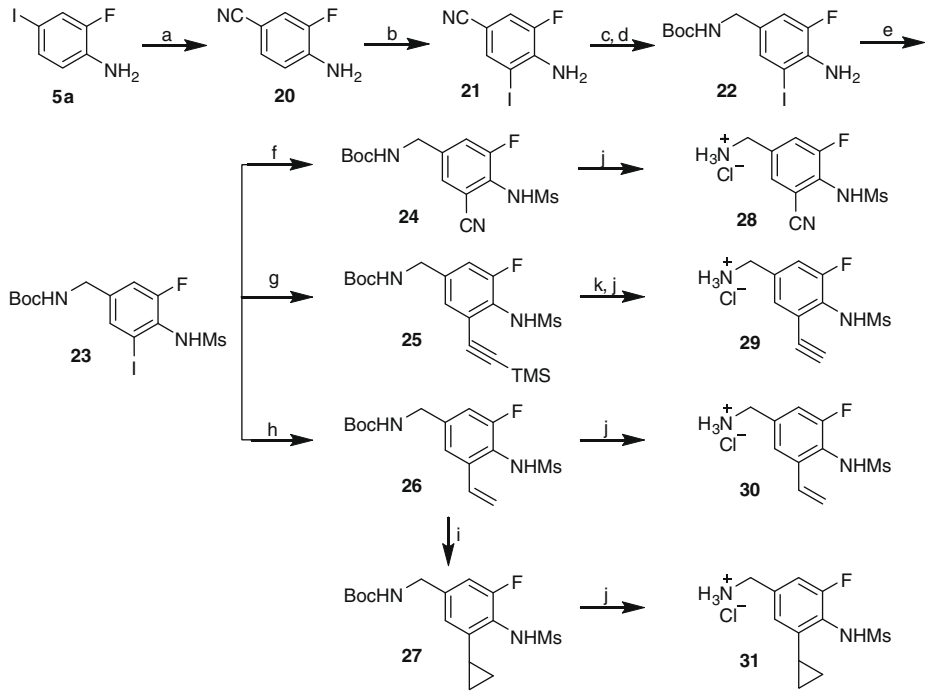
Scheme 1. Reagents and conditions: (a) 1 M BH_3·THF, THF, reflux, then 2 N HCl, 99–100%; (b) $(Boc)_2O$, DMAP, Et_3N, CH_2Cl_2, 69–93%; (c) CH_3SO_2Cl, pyridine, CH_2Cl_2, 36–95%; (d) 5 N HCl, EtOAc, reflux, 100%.



Scheme 2. Reagents and conditions: (a) TMSCl, MeOH, reflux, 49%; (b) CH_3SO_2Cl, pyridine, CH_2Cl_2, 37–93%; (c) CuCN, DMF, 130 °C, 54–98%; (d) 1 M BH_3·THF, THF, reflux, then 2 N HCl, 99–100%.



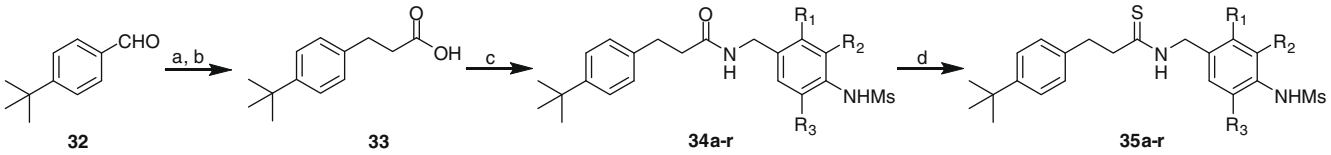
Scheme 3. Reagents and conditions: (a) I_2, H_2O_2, MeOH, 79%; (b) 1 M BH_3·THF, THF, reflux, then 2 N HCl, 99%; (c) $(Boc)_2O$, DMAP, Et_3N, CH_2Cl_2, 83%; (d) CH_3SO_2Cl, pyridine, CH_2Cl_2, 93%; (e) 5 N HCl, EtOAc, reflux, 99–100%; (f) CuCN, DMF, 130 °C, 72%; (g) $Pd(PPh_3)_4$, $CH_2CHSnBu_3$, toluene, reflux, 97%; (h) 10% Pd/C, H_2, THF, 84%.



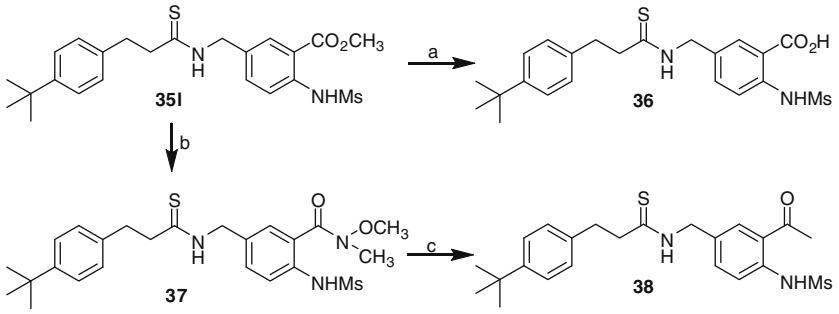
Scheme 4. Reagents and conditions: (a) CuCN, DMF, 130 °C, 80%; (b) 1 M ICl, CH_2Cl_2, 66%; (c) 1 M BH_3·THF, THF, reflux, then 2 N HCl, 99%; (d) $(Boc)_2O$, DMAP, Et_3N, CH_2Cl_2, 81%; (e) CH_3SO_2Cl, pyridine, CH_2Cl_2, 36%; (f) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF, 130 °C, 63%; (g) trimethylsilyl acetylene, $(PPh_3)_2PdCl_2$, CuI, Et_3N, THF, reflux, 84%; (h) $Pd(PPh_3)_4$, $CH_2CHSnBu_3$, toluene, reflux, 69%; (i) Et_2Zn, CH_2I_2, CH_2Cl_2, 40 °C, 99%; (j) 5 N HCl, EtOAc, reflux, 100%; (k) NaOH, THF/H_2O = 2:1, rt, 71%.

Propanoic acid intermediate **33** was prepared by Knoevenagel condensation[14] of aldehyde **32** with malonic acid and hydrogenation of the resulting olefin. Amides **34a–r** were prepared by DMTMM-mediated coupling[15] of various benzylamine ammonium salts (**4a**–**e**, **8a**–**e**, **14**, **15**, **18**, **19**, **28**, **29**, **30** and **31**) with acid **33**. Treatment of amides **34a–r** with Lawesson's reagent gave thioamides **35a–r** (Scheme 5). Hydrolysis of **35l** afforded **36** while treatment of **35l** with *N,O*-dimethylhydroxylamine afforded Weinreb amide **37**, which was then reacted with methyl magnesium iodide to give ketone **38** (Scheme 6).

The in vitro activities of the synthesized analogues are summarized in Table 1. Most of the analogues displayed excellent or considerable TRPV1 antagonistic activities. The thioamide **35a** retained the same antagonistic activity as the parent thiourea SC-0030, which indicates that thioamide moiety could be a useful bioisostere for thiourea scaffold in this series. In addition, the thioamide analogues generally exhibited slightly higher antagonistic activities than the corresponding amides. However, no analogue with the disubstituted A-moiety showed higher potency than the parent thiourea (SC-0030) regardless of substituent or substitution pattern. Move of chloro substituent from R_2 to R_1 position of **35b** resulted in a moderate decrease in $^{45}Ca^{2+}$ uptake inhibitory activity. Analogues with electron-withdrawing groups at R_2-position, such as cyano (**35j**), nitro (**35k**), fluoro (**35a**) and chloro (**35b**) exhibited good antagonistic activities in the range of 40–100 nM. However, introduction of trifluoromethyl (**35e** and **35f**) or carbonyl

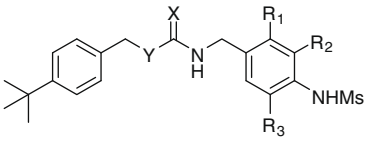


Scheme 5. Reagents and conditions: (a) malonic acid, pyridine, piperidine, reflux, 86%; (b) 10% Pd/C, H_2, THF, 84%; (c) **4a**–**e**, **8a**–**e**, **14**, **15**, **18**, **19**, **28**, **29**, **30** and **31**, DMTMM, NMM, Et_3N, THF, 35–90%; (d) Lawesson's reagent, toluene, reflux, 41–97%.



Scheme 6. Reagents and conditions: (a) LiOH, THF/H_2O = 1:1, rt, 50%; (b) *N*,O-dimethylhydroxylamine, *i*-PrMgCl, THF, 0 °C, 72%; (c) CH_3MgI, THF, 0 °C, 28%.

Table 1
$^{45}Ca^{2+}$ Uptake inhibition by the amide/thioamide analogues



Compound	Y	X	R_1	R_2	R_3	Antagonistic activity, IC_{50} (nM)
SC-0030	NH	S	H	F	H	37
35a	CH_2	S	H	F	H	40
35b	CH_2	S	H	Cl	H	96
35c	CH_2	S	Cl	H	H	3500
35d	CH_2	S	H	I	H	300
35e	CH_2	S	CF_3	H	H	2400
35f	CH_2	S	H	CF_3	H	940
35g	CH_2	S	H	CH_3	H	60
35h	CH_2	S	H	Ethyl	H	240
35i	CH_2	S	H	Vinyl	H	61
35j	CH_2	S	H	CN	H	55
35k	CH_2	S	H	NO_2	H	72
36	CH_2	S	H	CO_2H	H	22,600
35l	CH_2	S	H	CO_2CH_3	H	3700
38	CH_2	S	H	Acetyl	H	1000
35m	CH_2	S	H	CH_3	CH_3	2900
34m	CH_2	O	H	CH_3	CH_3	620
35n	CH_2	S	H	Cl	CH_3	80
34n	CH_2	O	H	Cl	CH_3	100
35o	CH_2	S	H	F	Vinyl	32
34o	CH_2	O	H	F	Vinyl	25
35p	CH_2	S	H	F	Acetylene	75
34p	CH_2	O	H	F	Acetylene	170
35q	CH_2	S	H	F	Cyclopropyl	270
34q	CH_2	O	H	F	Cyclopropyl	360
35r	CH_2	S	H	F	CN	28
34r[10]	CH_2	O	H	F	CN	85

substituent (**36**, **35l** and **38**) led to a significant reduction in antagonistic activity. Interestingly, the methyl-substituted analogue **35g** exhibited more potent activity than the trifluoromethyl-substituted analogue **35f**.

We were very much interested in the R_3-substituent effect on antagonistic effect because we anticipated a potency enhancement by an additional substitution at R_3-position. The substituent effect at R_3-position was quite interesting. Introduction of methyl group (**35n**) at R_3-position of **35b** was tolerable, whereas methyl incorporation at R_3-position of **35g** possessing methyl substituent at R_2-position exhibited a significant decreased antagonistic activity. It is noticeable that introduction of vinyl or nitrile substituent at R_3-position enhance antagonistic activity. In particular, the vinyl-substituted thioamide **35o** and the cyano-substituted thioamide **35r** exhibited higher potency than the parent SC-0030 with IC_{50}s of 32 and 28 nM, respectively. The vinyl-substituted amide **34o** exhibited even better antagonistic activity with IC_{50} of 25 nM than the corresponding thioamide **35o**. However, amide **34r** with a cyano group at R_3-position was threefold less potent than the corresponding thioamide **35r**.

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 three 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 (two 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 two days to kill dividing nonneuronal cells.

2.2.2. Uptake assays

Terasaki plates containing DRG neurons grown for three 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

Our effort for potency enhancement by structural optimization of the multiple H-bonding region has been carried out and this enabled us to identify novel and highly potent TRPV1 antagonists with the therapeutically favorable amide or thioamide scaffolds in B-region. In particular, incorporation of an additional substituent such as cyano or vinyl group at R_3-position of SC-0030 enhanced the antagonistic activity. This obviously provided a valuable compensation for the inevitable potency decrease by replacement of thiourea with the therapeutically preferred amide or thioamide scaffold. Currently, studies on therapeutic application of the analogues **34o**, **35o** and **35r** 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. 4-(Aminomethyl)-2-(trifluoromethyl)aniline ammonium salt (2a)

To a solution of 4-amino-3-(trifluoromethyl)benzo-nitrile **1a** (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-(trifluoromethyl)aniline ammonium salt **2a**, which was directly used for the next step.

4.1.2. 4-(Aminomethyl)-2-nitroaniline ammonium salt (2b)

The compound was prepared from **1b** by the procedure for the synthesis of **2a** in 100% yield; white solid, which was directly used for the next step.

4.1.3. 4-(Aminomethyl)-3-chloroaniline ammonium salt (2c)

The compound was prepared from **1c** by the procedure for the synthesis of **2a** in 100% yield; white solid, which was directly used for the next step.

4.1.4. 4-(Aminomethyl)-3-(trifluoromethyl)aniline ammonium salt (2d)

The compound was prepared from **1d** by the procedure for the synthesis of **2a** in 100% yield; white solid, which was directly used for the next step.

4.1.5. 4-(Aminomethyl)-2-chloro-6-methylaniline ammonium salt (2e)

The compound was prepared from **1e** by the procedure for the synthesis of **2a** in 99% yield; white solid, which was directly used for the next step.

4.1.6. *tert*-Butyl 4-(methylsulfonamido)-3-(trifluoromethyl)-benzylcarbamate (3a)

A solution of 4-(aminomethyl)-2-(trifluoromethyl) aniline ammonium salt **2a** (154 mg, 0.87 mmol) and Et_3N (363 μL, 2.6 mmol) in CH_2Cl_2 was put into the flask and then cooled to 0 °C. To the solution were added DMAP (21 mg, 0.17 mmol) and di-*tert*-butyl-bicarbonate (571 mg, 2.6 mmol) then stirred for 5 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 in vacuo. The obtained liquid was purified by column chromatography (EtOAc/*n*-hexane = 1:2) to give *tert*-butyl 4-amino-3-(trifluoromethyl)benzylcarbamate as a yellow solid (147 mg, 70%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.87 (s, 1H), 7.44 (br s, 1H), 7.23 (d, 1H, J = 8.3 Hz), 4.83 (br s, 1H), 4.22 (br s, 2H), 1.49 (s, 9H).

To the solution of *tert*-butyl 4-amino-3-(trifluoromethyl)benzylcarbamate (73 mg, 0.25 mmol) and pyridine (41 μL, 0.51 mmol) in CH_2Cl_2 (4 mL) was added methanesulfonyl chloride (33 μL, 0.43 mmol) at 0 °C 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, and dried over $MgSO_4$ followed by evaporation. The obtained solid was purified by column chromatography (EtOAc/*n*-hexane = 1:2) to yield a yellow liquid **3a** (47 mg, 51%, two steps). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, 1H, J = 8.4 Hz), 7.53 (s, 1H), 7.47 (d, 1H, J = 8.4 Hz), 6.62 (s, 1H), 4.94 (br s, 1H), 4.32 (d, 2H, J = 5.9 Hz), 2.97 (s, 3H), 1.44 (s, 9H).

4.1.7. *tert*-Butyl 4-(methylsulfonamido)-3-nitrobenzylcarbamate (3b)

The compound was prepared from **2b** by the procedure for the synthesis of **3a** in 57% yield (two steps) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.65 (br s, 1H), 8.48 (d, 1H, J = 2.0 Hz), 7.67 (d, 1H, J = 8.8 Hz), 7.43 (dd, 1H, J = 8.8, 2.0 Hz), 4.97 (br s, 1H), 4.42 (d, 2H, J = 5.9 Hz), 3.10 (s, 3H), 1.46 (s, 9H).

4.1.8. *tert*-Butyl 2-chloro-4-(methylsulfonamido)benzylcarbamate (3c)

The compound was prepared from **2c** by the procedure for the synthesis of **3a** in 78% yield (two steps) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.87 (s, 1H), 7.33–7.45 (m, 2H), 5.11 (br s, 1H), 4.43 (d, 2H, J = 5.2 Hz), 3.02 (s, 3H), 1.45 (s, 9H).

4.1.9. *tert*-Butyl 4-(methylsulfonamido)-2-(trifluoromethyl)-benzylcarbamate (3d)

The compound was prepared from **2d** by the procedure for the synthesis of **3a** in 63% yield (two steps) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.94 (s, 1H), 7.37–7.49 (m, 2H), 5.04 (br s, 1H), 4.41 (d, 2H, J = 5.1 Hz), 2.99 (s, 3H), 1.42 (s, 9H).

4.1.10. *tert*-Butyl 3-chloro-5-methyl-4-(methylsulfonamido)-benzylcarbamate (3e)

The compound was prepared from **2e** by the procedure for the synthesis of **3a** in 86% yield (two steps) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.24 (s, 1H), 7.10 (s, 1H), 4.88 (br s, 1H), 4.24 (d, 2H, J = 5.3 Hz), 3.07 (s, 3H), 2.48 (s, 3H), 1.45 (s, 9H).

4.1.11. *N*-[4-(Aminomethyl)-2-(trifluoromethyl)phenyl]methanesulfonamide ammonium salt (4a)

To a solution of **3a** (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 in vacuo to yield a brown crude solid **4a** (100%).

4.1.12. *N*-[4-(Aminomethyl)-2-nitrophenyl]methanesulfonamide ammonium salt (4b)

The compound was prepared from **3b** by the procedure for the synthesis of **4a** in 100% yield; white solid, which was directly used for the next step.

4.1.13. *N*-[4-(Aminomethyl)-3-chlorophenyl]methanesulfonamide ammonium salt (4c)

The compound was prepared from **3c** by the procedure for the synthesis of **4a** in 100% yield; white solid, which was directly used for the next step.

4.1.14. *N*-[4-(Aminomethyl)-3-(trifluoromethyl)phenyl]methanesulfonamide ammonium salt (4d)

The compound was prepared from **3d** by the procedure for the synthesis of **4a** in 100% yield; white solid, which was directly used for the next step.

4.1.15. *N*-[4-(Aminomethyl)-2-chloro-6-methylphenyl]methanesulfonamide ammonium salt (4e)

The compound was prepared from **3e** by the procedure for the synthesis of **4a** in 100% yield; white solid, which was directly used for the next step.

4.1.16. Methyl 2-amino-5-iodobenzoate (5e)

To a solution of 2-amino-5-iodobenzoic acid **5d** (2.0 g, 7.6 mmol) in MeOH (8.0 mL) was added TMSCl (4.8 mL, 38.0 mmol) dropwise. The reaction mixture was refluxed for 24 h and concentrated in vacuo. The mixture was quenched by aq $NaHCO_3$ and extracted with EtOAc, washed with brine and dried over $MgSO_4$. Purification of the residue by silica gel column chromatography (EtOAc/*n*-hexane = 1:20) was conducted to afford **5e** (1.0 g, 49%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.12 (d, 1H, J = 2.0 Hz), 7.47 (dd, 1H, J = 8.6, 2.2 Hz), 6.45 (d, 1H, J = 8.6 Hz), 5.74 (br s, 2H), 3.84 (s, 3H).

4.1.17. *N*-(2-Fluoro-4-iodophenyl)methanesulfonamide (6a)

The compound was prepared from **5a** by the procedure for the synthesis of **3a** in 87% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.48 (d, 2H, J = 8.5 Hz), 7.30 (t, 1H, J = 8.3 Hz), 6.48 (br s, 1H), 3.01 (s, 3H).

4.1.18. *N*-(2-Chloro-4-iodophenyl)methanesulfonamide (6b)

The compound was prepared from **5b** by the procedure for the synthesis of **3a** in 93% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.74 (d, 1H, J = 2.0 Hz), 7.60 (dd, 1H, J = 2.0, 8.6 Hz), 7.38 (d, 1H, J = 8.6 Hz), 6.73 (br s, 1H), 3.00 (s, 3H); LRMS (FAB+) m/z 332 ($M+H^+$).

4.1.19. *N*-(4-Iodo-2-methylphenyl)methanesulfonamide (6c)

The compound was prepared from **5c** by the procedure for the synthesis of **3a** in 55% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.52–7.56 (m, 2H), 7.21 (d, 1H, J = 8.2 Hz), 6.11 (br s, 1H), 3.00 (s, 3H), 2.25 (s, 3H).

4.1.20. Methyl 5-iodo-2-(methylsulfonamido)benzoate (6d)

The compound was prepared from **5e** by the procedure for the synthesis of **3a** in 37% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.4 (br s, 1H), 8.34 (d, 1H, J = 2.2 Hz), 7.82 (dd, 1H, J = 9.0, 2.2 Hz), 7.52 (d, 1H, J= 9.0 Hz), 3.93 (s, 3H), 3.04 (s, 3H).

4.1.21. *N*-(4-Bromo-2,6-dimethylphenyl)methanesulfonamide (6e)

The compound was prepared from **5f** by the procedure for the synthesis of **3a** in 66% yield as a white solid. ^{1}H NMR (CD_3OD, 300 MHz): δ 7.26 (s, 2H), 3.07 (s, 3H), 2.37 (s, 6H).

4.1.22. *N*-(4-Cyano-2-fluorophenyl)methanesulfonamide (7a)

To a solution of *N*-(2-fluoro-4-iodophenyl)methanesulfonamide **6a** (120 mg, 0.38 mmol) in DMF (5 mL) was added CuCN (41 mg, 0.46 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 over $MgSO_4$. A residue was purified with silica gel column chromatography (EtOAc/*n*-hexane = 1:2) to provide **7a** (65 mg, 80%) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.71 (t, 1H, J = 8.0 Hz), 7.41–7.48 (m, 2H), 6.83 (br s, 1H), 3.11 (s, 3H).

4.1.23. *N*-(2-Chloro-4-cyanophenyl)methanesulfonamide (7b)

The compound was prepared from **6b** by the procedure for the synthesis of **7a** in 81% yield; white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.89 (d, 1H, J = 1.8 Hz), 7.78 (d, 1H, J = 8.5 Hz), 7.69 (dd, 1H, J = 8.5, 1.8 Hz), 3.11 (s, 3H).

4.1.24. *N*-(4-Cyano-2-methylphenyl)methanesulfonamide (7c)

The compound was prepared from **6c** by the procedure for the synthesis of **7a** in 66% yield; white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.49–7.61 (m, 3H), 6.53 (br s, 1H), 3.10 (s, 3H), 2.29 (s, 3H).

4.1.25. Methyl 5-cyano-2-(methylsulfonamido)benzoate (7d)

The compound was prepared from **6d** by the procedure for the synthesis of **7a** in 54% yield; white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.8 (br s, 1H), 8.34 (s, 1H), 7.74–7.82 (m, 2H), 3.95 (s, 3H), 3.13 (s, 3H).

4.1.26. *N*-(4-Cyano-2,6-dimethylphenyl)methanesulfonamide (7e)

The compound was prepared from **6e** by the procedure for the synthesis of **7a** in 98% yield; white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.38 (s, 2H), 3.03 (s, 3H), 2.34 (s, 6H).

4.1.27. *N*-[4-(Aminomethyl)-2-fluorophenyl] methanesulfonamide ammonium salt (8a)

The compound was prepared from **7a** by the procedure for the synthesis of **2a** in 100% yield; white solid, which was directly used for the next step.

4.1.28. *N*-[4-(Aminomethyl)-2-chlorophenyl]methanesulfonamide ammonium salt (8b)

The compound was prepared from **7b** by the procedure for the synthesis of **2a** in 99% yield; white solid, which was directly used for the next step.

4.1.29. *N*-[4-(Aminomethyl)-2-methylphenyl]methanesulfonamide ammonium salt (8c)

The compound was prepared from **7c** by the procedure for the synthesis of **2a** in 100% yield; white solid, which was directly used for the next step.

4.1.30. Methyl 5-(aminomethyl)-2-(methylsulfonamido)benzoate ammonium salt (8d)

The compound was prepared from **7d** by the procedure for the synthesis of **2a** in 100% yield; white solid, which was directly used for the next step.

4.1.31. *N*-[4-(Aminomethyl)-2,6-dimethylphenyl] methanesulfonamide ammonium salt (8e)

The compound was prepared from **7e** by the procedure for the synthesis of **2a** in 100% yield; white solid, which was directly used for the next step.

4.1.32. 4-Amino-3-iodobenzonitrile (10)

To a solution of 4-aminobenzonitrile **9** (1.0 g, 8.5 mmol) in MeOH was added I_2 (1.3 g, 5.1 mmol). The reaction mixture was stirred at room temperature for 30 min, then added a solution of H_2O_2 (0.83 mL) in THF dropwise over 20 min. The reaction mixture was stirred at room temperature for three days. After confirming the completion of the reaction with TLC, the reaction was quenched by aq $Na_2S_2O_3$ and stirred for 20 min, extracted with CH_2Cl_2, washed with brine and dried over $MgSO_4$. Purification of the residue by silica gel column chromatography (EtOAc/*n*-hexane = 1:5) to afford **10** (1.6 g, 79%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.88 (d, 1H, J = 1.8 Hz), 7.37 (dd, 1H, J = 1.8, 8.4 Hz), 6.68 (d, 1H, J= 8.4 Hz), 4.59 (br s, 2H).

4.1.33. 4-(Aminomethyl)-2-iodoaniline ammonium salt (11)

The compound was prepared from **10** by the procedure for the synthesis of **2a** in 99% yield; white solid, which was directly used for the next step.

4.1.34. *tert*-Butyl 4-amino-3-iodobenzylcarbamate (12)

The compound was prepared from **11** by the procedure for the synthesis of **3a** in 83% yield; white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.52 (d, 1H, J = 1.7 Hz), 7.04 (d, 1H, J = 8.0 Hz), 6.67 (d, 1H, J= 8.0 Hz), 4.73 (br s, 1H), 4.12 (d, 2H, J = 5.5 Hz), 4.05 (br s, 2H), 1.43 (s, 9H).

4.1.35. *tert*-Butyl 3-iodo-4-(methylsulfonamido)benzylcarbamate (13)

The compound was prepared from **12** by the procedure for the synthesis of **3a** in 93% yield; white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.72 (d, 1H, J = 1.8 Hz), 7.57 (d, 1H, J = 8.3 Hz), 7.26 (dd, 1H, J = 1.8, 8.3 Hz), 6.57 (br s, 1H), 4.88 (br s, 1H), 4.24 (d, 2H, J = 5.9 Hz), 2.97 (s, 3H), 1.44 (s, 9H).

4.1.36. *N*-[4-(Aminomethyl)-2-iodophenyl]methanesulfonamide ammonium salt (14)

The compound was prepared from **13** by the procedure for the synthesis of **4a** in 100% yield; white solid, which was directly used for the next step.

4.1.37. *N*-[4-(Aminomethyl)-2-cyanophenyl]methanesulfonamide ammonium salt (15)

The compound was prepared from **13** by the procedure for the synthesis of **7a** and **4a** in 72% yield as a white solid, which was directly used for the next step.

4.1.38. *tert*-Butyl 4-(methylsulfonamido)-3-vinylbenzylcarbamate (16)

To a solution of **13** (1.0 g, 2.3 mmol) in toluene (20 mL) were added tributylvinyltin (830 μL, 2.8 mmol) and $Pd(PPh_3)_4$ (140 mg, 0.12 mmol). The mixture was refluxed for 4 h followed by dilution 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 = 1:2) was conducted to afford **16** (740 mg, 97%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.41 (d, 1H, J = 8.2 Hz), 7.38 (d, 1H, J = 2.0 Hz), 7.20 (dd, 1H, J = 1.8, 8.3 Hz), 6.87 (dd, 1H, J = 11.0, 17.0 Hz), 6.32 (br s, 1H), 5.71 (dd, 1H, J = 0.9, 17.0 Hz), 5.46 (dd, 1H, J = 0.9, 11.0 Hz), 4.86 (br s, 1H), 4.29 (d, 2H, J = 5.9 Hz), 2.96 (s, 3H), 1.44 (s, 9H).

4.1.39. *tert*-Butyl 3-ethyl-4-(methylsulfonamido)benzylcarbamate (17)

To a solution of *tert*-butyl 4-(methylsulfonamido)-3-vinylbenzylcarbamate **16** (350 mg, 1.1 mmol) in THF was added catalytic amount of 10% palladium on activated carbon under H_2 gas, followed by stirring for 8 h at room temperature. The resulting mixture was diluted with Et_2O, filtered through Celite pad, and then concentrated in vacuo to give **17** (310 mg, 84%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.40 (d, 1H, J = 8.1 Hz), 7.11–7.15 (m, 2H), 6.15 (s, 1H), 4.82 (br s, 1H), 4.26 (d, 2H, J = 5.5 Hz), 2.99 (s, 3H), 2.63 (q, 2H, J= 7.5 Hz), 1.44 (s, 9H), 1.22 (t, 3H, J = 7.5 Hz).

4.1.40. *N*-[4-(Aminomethyl)-2-vinylphenyl]methane sulfonamide ammonium salt (18)

The compound was prepared from **16** by the procedure for the synthesis of **4a** in 99% yield; white solid, which was directly used for the next step.

4.1.41. *N*-[4-(Aminomethyl)-2-ethylphenyl]methane sulfonamide ammonium salt (19)

The compound was prepared from **17** by the procedure for the synthesis of **4a** in 100% yield; white solid, which was directly used for the next step.

4.1.42. 4-Amino-3-fluorobenzonitrile (20)

The compound was prepared from **5a** by the procedure for the synthesis of **7a** in 80% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.21–7.26 (m, 2H), 6.74 (t, 1H, J = 8.3 Hz), 4.20 (br s, 2H).

4.1.43. 4-Amino-3-fluoro-5-iodobenzonitrile (21)

To a solution of benzonitrile **20** (4.1 g, 30.0 mmol) in CH_2Cl_2 (100 mL) was added ICl (1 M solution in CH_2Cl_2, 40 mL, 40.0 mmol) dropwise. The reaction mixture was stirred at room temperature for 20 h, then quenched by addition of saturated aq $Na_2S_2O_3$ followed by dilution 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 = 1:5) to afford **21** (3.4 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).

4.1.44. *tert*-Butyl 4-amino-3-fluoro-5-iodobenzylcarbamate (22)

The compound was prepared from **21** by the procedure for the synthesis of **2a** and **3a** in 80% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.30 (s, 1H), 6.91 (d, 1H, J = 11.0 Hz), 4.76 (br s, 1H), 4.13 (d, 2H, J = 4.6 Hz), 1.44 (s, 9H).

4.1.45. *tert*-Butyl 3-fluoro-5-iodo-4-(methylsulfonamido)-benzylcarbamate (23)

The compound was prepared from **22** by the procedure for the synthesis of **3a** in 36% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.56 (s, 1H), 7.08 (d, 1H, J = 10.0 Hz), 6.12 (s, 1H), 4.92 (br s, 1H), 4.24 (d, 2H, J = 5.9 Hz), 3.23 (s, 3H), 1.44 (s, 9H).

4.1.46. *tert*-Butyl 3-cyano-5-fluoro-4-(methylsulfonamido)-benzylcarbamate (24)

To a solution of benzylcarbamate **23** (156 mg, 0.35 mmol) in DMF (3 mL) were 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 diluted with EtOAc. A diluted solution was washed with water (2×) and brine, and then dried over MgSO4. The residue was purified by silica gel column chromatography (EtOAc/*n*-hexane = 1:3) to afford **24** as a solid (76 mg, 63%).^{1}H NMR ($CDCl_3$, 300 MHz): 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).

4.1.47. *tert*-Butyl 3-fluoro-4-(methylsulfonamido)-5-[(trimethylsilyl)ethynyl]benzylcarbamate (25)

To a solution of benzylcarbamate **23** (130 mg, 0.29 mmol) in THF (10 mL) were added CuI (2.8 mg, 0.01 mmol), $(PPh_3)_2PdCl_2$ (10 mg, 0.01 mmol), trimethylsilyl acetylene (62 μL, 0.44 mmol) and Et_3N (122 μL, 0.88 mmol). A reaction mixture was heated to 70 °C, stirred for 3 h, cooled to room temperature, and was diluted with EtOAc. A diluted solution was washed with water and brine, and then dried over $MgSO_4$. The residue was purified by column chromatography (EtOAc/*n*-hexane = 1:2) to afford **25** as a solid (102 mg, 84%).^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.18 (s, 1H), 7.08 (d, 1H, J = 10.8 Hz), 6.40 (s, 1H), 4.90 (br s, 1H), 4.23 (d, 2H, J = 5.9 Hz), 3.21 (s, 3H), 1.44 (s, 9H), 0.25 (s, 9H).

4.1.48. *tert*-Butyl 3-fluoro-4-(methylsulfonamido)-5-vinylbenzylcarbamate (26)

The compound was prepared from **23** by the procedure for the synthesis of **16** in 69% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.29 (s, 1H), 7.13 (dd, 1H, J = 18.0, 11.0 Hz), 6.98 (dd, 1H, J = 1.8, 10.0 Hz), 6.34 (br s, 1H), 5.75 (d, 1H, J = 18.0 Hz), 5.41 (d, 1H, J = 11.0 Hz), 4.99 (br s, 1H), 4.27 (d, 2H, J = 6.1 Hz), 3.03 (d, 3H, J = 1.1 Hz), 1.44 (s, 9H).

4.1.49. *tert*-Butyl 3-cyclopropyl-5-fluoro-4-(methylsulfonamido) benzylcarbamate (27)

To a solution of vinylbenzylcarbamate **26** (50 mg, 0.15 mmol) in CH_2Cl_2 (2 mL) were added diethylzinc (440 μL, 0.44 mmol) and diiodomethane (60 μL, 0.73 mmol) at 0 °C. The reaction mixture was stirred for 48 h at 40 °C, cooled to room temperature, then quenched by addition of saturated aqueous $NaHCO_3$ followed by dilution with EtOAc. A diluted solution was washed with water and brine, and then dried with $MgSO_4$. The residue was purified by column chromatography (EtOAc/*n*-hexane = 1:2) to afford benzylcarbamate **27** (52 mg, 99%).^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.89 (d, 1H, J = 13.0 Hz), 6.63 (s, 1H), 6.00 (s, 1H), 4.85 (br s, 1H), 4.22 (d, 2H, J = 6.2 Hz), 3.14 (d, 3H, J = 1.1 Hz), 2.26 (m, 1H), 1.44 (s, 9H), 1.03–1.07 (m, 2H), 0.65–0.69 (m, 2H).

4.1.50. *N*-[4-(Aminomethyl)-2-cyano-6-fluorophenyl]methanesulfonamide ammonium salt (28)

The compound was prepared from **24** by the procedure for the synthesis of **4a** in 100% yield; white solid, which was directly used for the next step.

4.1.51. *N*-[4-(Aminomethyl)-2-ethynyl-6-fluorophenyl]methanesulfonamide ammonium salt (29)

To a solution of benzylcarbamate **25** (102 mg, 0.25 mmol) in THF/H_2O (2:1, 10 mL) was added NaOH (49 mg, 1.2 mmol). The reaction mixture was stirred at room temperature for 2.5 h, then diluted with EtOAc. 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 = 1:1) to afford *tert*-butyl 3-ethynyl-5-fluoro-4-(methylsulfonamido) benzylcarbamate (60 mg, 71%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.23 (br s, 1H), 7.10 (d, 1H, J = 10.8 Hz), 6.37 (s, 1H), 4.90 (br s, 1H), 4.24 (d, 2H, J = 6.2 Hz), 3.45 (s, 1H), 3.23 (s, 3H), 1.44 (s, 9H).

The compound **29** was prepared from *tert*-butyl 3-ethynyl-5-fluoro-4-(methylsulfonamido)benzylcarbamate by the procedure for the synthesis of **4a** in 100% yield; white solid, which was directly used for the next step.

4.1.52. *N*-[4-(Aminomethyl)-2-fluoro-6-vinylphenyl]methanesulfonamide ammonium salt (30)

The compound was prepared from **26** by the procedure for the synthesis of **4a** in 100% yield; white solid, which was directly used for the next step.

4.1.53. *N*-[4-(Aminomethyl)-2-cyclopropyl-6-fluorophenyl]methanesulfonamide ammonium salt (31)

The compound was prepared from **27** by the procedure for the synthesis of **4a** in 100% yield; white solid, which was directly used for the next step.

4.2. General procedure for coupling to amides (34a–35r)

To a solution of 4-*tert*-butylbenzaldehyde **32** (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 resulting 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 in vacuo to give (*E*)-3-(4-*tert*-butylphenyl)acrylic acid 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).

To a solution of (*E*)-3-(4-*tert*-butylphenyl)acrylic acid in THF was added a catalytic amount of 10% palladium on activated carbon under H_2 gas followed by stirring for 1 h at room temperature. The resulting mixture was diluted with Et_2O, filtered through Celite pad, and then concentrated in vacuo to give 3-(4-*tert*-butylphenyl) propanoic acid **33**, which was directly used for the next step. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.31 (d, 2H, J = 8.3 Hz), 7.14 (d, 2H, J = 8.3 Hz), 2.95 (t, 2H, J = 7.9 Hz), 2.69 (t, 2H, J = 7.9 Hz), 1.29 (s, 9H).

To a solution of acid **33** (1.0 mmol) in the THF were added 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium 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 benzylammonium salt (1.2 mmol) was added. 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 $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using CH_2Cl_2/MeOH as eluent.

To a solution of amide (1.0 mmol) in toluene was added Lawesson's reagent (2.0 mmol). The reaction mixture was refluxed for 5 h. After cooling to ambient temperature followed by dilution with EtOAc, the organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using EtOAC/*n*-hexane as eluent.

4.2.1. 3-(4-*tert*-Butylphenyl)-*N*-[3-fluoro-4-(methylsulfonamido) benzyl]propanamide (34a)

The compound was prepared from **8a** 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), 1.29 (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; LRMS (FAB+): *m/z* 407 ($M+H^+$); HRMS (FAB+) calcd for $C_{21}H_{28}FN_2O_3S$ ($M+H^+$): 407.1805, found 407.1802.

4.2.2. 3-(4-*tert*-Butylphenyl)-*N*-[3-chloro-4-(methylsulfonamido) benzyl]propanamide (34b)

The compound was prepared from **8b** by the general procedure for the synthesis of amides in 90% yield as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.53 (d, 1H, J = 8.4 Hz), 7.28–7.29 (m, 3H), 7.10 (d, 2H, J = 8.2 Hz), 7.07 (dd, 1H, J = 1.7, 1.7 Hz), 6.74 (br s, 1H), 4.34 (d, 2H, J = 6.0 Hz), 2.97 (s, 3H), 2.94 (t, 2H, J = 7.6 Hz),

2.51 (t, 2H, J = 7.6 Hz), 1.28 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.3, 149.2, 137.4, 137.1, 132.6, 128.8, 128.0, 127.4, 125.5, 125.2, 122.6, 42.4, 39.9, 38.3, 34.4, 31.3, 31.0; IR (neat) cm^{-1}: 3264, 2955, 1649, 1515, 1452, 1332, 1154; LRMS (FAB+): m/z 423 (M+H$^+$); HRMS (FAB+) calcd for $C_{21}H_{28}ClN_2O_3S$ (M+H$^+$): 423.1509, found 423.1512.

4.2.3. 3-(4-*tert*-Butylphenyl)-*N*-[2-chloro-4-(methylsulfonamido) benzyl]propanamide (34c)

The compound was prepared from **4c** by the general procedure for the synthesis of amides in 83% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.20–7.29 (m, 4H), 7.09 (d, 2H, J = 8.2 Hz), 6.98 (dd, 1H, J = 8.2, 2.2 Hz), 6.81 (br s, 1H), 5.82 (br s, 1H), 4.42 (d, 2H, J = 6.0 Hz), 2.99 (s, 3H), 2.92 (t, 2H, J = 7.6 Hz), 2.51 (t, 2H, J = 7.6 Hz), 1.28 (s, 9H); IR (neat) cm^{-1}: 3357, 2958, 1667, 1550, 1484, 1314, 1146, 617; LRMS (FAB+): m/z 423 (M+H$^+$).

4.2.4. 3-(4-*tert*-Butylphenyl)-*N*-[3-iodo-4-(methylsulfonamido) benzyl]propanamide (34d)

The compound was prepared from **14** by the general procedure for the synthesis of amides in 58% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.65 (d, 1H, J = 1.8 Hz), 7.46 (d, 1H, J = 8.4 Hz), 7.17–7.28 (m, 2H), 7.06–7.12 (m, 3H), 6.63 (s, 1H), 5.98 (br s, 1H), 4.28 (d, 2H, J = 5.9 Hz), 2.92 (s, 3H), 2.90 (t, 2H, J = 7.9 Hz), 2.48 (t, 2H, J = 7.7 Hz), 1.29 (s, 9H); IR (neat) cm^{-1}: 3300, 2960, 1650, 1542, 1485, 1366, 1155; LRMS (FAB+): m/z 515 (M+H$^+$).

4.2.5. 3-(4-*tert*-Butylphenyl)-*N*-[4-(methylsulfonamido)-2-(trifluoromethyl)benzyl]propanamide (34e)

The compound was prepared from **4d** by the general procedure for the synthesis of amides in 80% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.42–7.43 (m, 2H), 7.25–7.32 (m, 3H), 7.18 (d, 2H, J = 8.3 Hz), 6.63 (s, 1H), 5.68 (br s, 1H), 4.51 (d, 2H, J = 5.9 Hz), 3.02 (s, 1H), 2.93 (t, 2H, J = 7.6 Hz), 2.50 (t, 2H, J = 7.6 Hz), 1.28 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.6, 149.3, 137.3, 136.5, 133.1, 132.2, 127.9, 125.5, 123.6, 117.8, 55.9, 39.9, 38.3, 34.4, 31.3, 31.0; IR (neat) cm^{-1}: 2961, 1651, 1543, 1473, 1367, 1316, 1156, 1054, 972, 759; LRMS (FAB+): m/z 457 (M+H$^+$).

4.2.6. 3-(4-*tert*-Butylphenyl)-*N*-[4-(methylsulfonamido)-3-(trifluoromethyl)benzyl]propanamide (34f)

The compound was prepared from **4a** by the general procedure for the synthesis of amides in 54% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.73 (m, 1H), 7.53 (m, 1H), 7.35 (m, 1H), 7.26–7.30 (m, 2H), 7.10 (d, 2H, J = 6.6 Hz), 6.65 (br s, 1H), 5.83 (br s, 1H), 4.40 (d, 2H, J = 6.1 Hz), 2.96 (s, 3H), 2.94 (d, 2H, J = 5.9 Hz), 2.54 (t, 2H, J = 3.9 Hz), 1.27 (s, 9H); IR (neat) cm^{-1}: 2959, 1541, 1471, 1366, 1316, 1133, 753; LRMS (EI): m/z 456 (M).

4.2.7. 3-(4-*tert*-Butylphenyl)-*N*-[3-methyl-4-(methylsulfonamido) benzyl]propanamide (34g)

The compound was prepared from **8c** by the general procedure for the synthesis of amides in 44% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.36 (d, 1H, J = 8.0 Hz), 7.30 (d, 2H, J = 8.3 Hz), 7.08–7.13 (m, 3H), 7.03 (d, 1H, J = 8.3 Hz), 6.20 (br s, 1H), 5.62 (br s, 1H), 4.35 (d, 2H, J = 5.7 Hz), 2.98 (s, 3H), 2.97 (t, 2H, J = 7.7 Hz), 2.52 (t, 2H, J = 7.7 Hz), 2.27 (s, 3H), 1.28 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.1, 149.2, 137.6, 136.3, 133.9, 130.8, 130.7, 128.0, 126.6, 125.4, 123.1, 43.0, 40.0, 38.4, 34.4, 31.4, 31.1; IR (neat) cm^{-1}: 2961, 1644, 1322, 1153; LRMS (FAB+): m/z 403 (M+H$^+$); HRMS (FAB+) calcd for $C_{22}H_{31}N_2O_3S$ (M+H$^+$): 403.2055, found 403.2056.

4.2.8. 3-(4-*tert*-Butylphenyl)-*N*-[3-ethyl-4-(methylsulfonamido) benzyl]propanamide (34h)

The compound was prepared from **19** by the general procedure for the synthesis of amides in 51% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.36 (d, 1H, J = 8.0 Hz), 7.28 (d, 2H, J = 7.9 Hz), 7.11 (d, 3H, J = 7.9 Hz), 7.01 (d, 1H, J = 8.1 Hz), 6.34 (s, 1H), 5.71 (br s, 1H), 4.35 (d, 2H, J = 5.7 Hz), 2.98 (s, 3H), 2.94 (t, 2H, J = 8.1 Hz), 2.62 (t, 2H, J = 7.5 Hz), 2.50 (t, 2H, J = 7.8 Hz), 1.28 (s, 9H), 1.20 (t, 3H, J = 7.5 Hz); IR (neat) cm^{-1}: 3296, 2962, 1649, 1541, 1489, 1323, 1153; LRMS (FAB+): m/z 417 (M+H$^+$).

4.2.9. 3-(4-*tert*-Butylphenyl)-*N*-[4-(methylsulfonamido)-3-vinylbenzyl]propanamide (34i)

The compound was prepared from **18** by the general procedure for the synthesis of amides in 73% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.25–7.41 (m, 4H), 7.09–7.14 (m, 3H), 6.84 (dd, 1H, J = 17.0, 11.0 Hz), 6.23 (br s, 1H), 5.69 (d, 1H, J = 18.0 Hz), 5.62 (br s, 1H), 5.47 (d, 1H, J = 11.0 Hz), 4.38 (d, 2H, J = 5.9 Hz), 2.99 (s, 3H), 2.92–2.97 (m, 2H), 2.51 (t, 2H, J = 7.6 Hz), 1.28 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.1, 137.6, 136.8, 132.4, 131.3, 128.3, 128.0, 126.8, 125.8, 125.4, 118.8, 64.0, 43.0, 40.1, 38.4, 34.4, 31.3, 31.1; IR (neat) cm^{-1}: 3295, 2960, 1648, 1541, 1324, 1152; LRMS (FAB+): m/z 415 (M+H$^+$); HRMS (FAB+) calcd for $C_{23}H_{31}N_2O_3S$ (M+H$^+$): 415.2055, found 415.2048.

4.2.10. 3-(4-*tert*-Butylphenyl)-*N*-[3-cyano-4-(methylsulfonamido) benzyl]propanamide (34j)

The compound was prepared from **15** by the general procedure for the synthesis of amides in 80% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.62 (d, 1H, J = 8.6 Hz), 7.47 (d, 1H, J = 2.0 Hz), 7.40 (d, 1H, J = 8.6 Hz), 7.30 (d, 2H, J = 8.3 Hz), 7.11 (d, 2H, J = 8.3 Hz), 6.85 (s, 1H), 5.72 (br s, 1H), 4.37 (d, 2H, J = 6.0 Hz), 3.08 (s, 3H), 2.95 (t, 2H, J = 7.5 Hz), 2.53 (t, 2H, J = 7.5 Hz), 1.29 (s, 9H); IR (neat) cm^{-1}: 3397, 2960, 2222, 1649, 1539, 1334, 1155; LRMS (FAB+): m/z 414 (M+H$^+$).

4.2.11. 3-(4-*tert*-Butylphenyl)-*N*-[4-(methylsulfonamido)-3-nitrobenzyl]propanamide (34k)

The compound was prepared from **4b** by the general procedure for the synthesis of amides in 38% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.65 (br s, 1H), 8.08 (s, 1H), 7.80 (d, 1H, J = 8.5 Hz), 7.47 (d, 1H, J = 8.5 Hz), 7.28 (d, 2H, J = 8.3 Hz), 7.10 (d, 2H, J = 8.3 Hz), 5.74 (br s, 1H), 4.40 (d, 2H, J = 6.1 Hz), 3.10 (s, 3H), 2.94 (t, 2H, J = 7.6 Hz), 2.53 (t, 2H, J = 7.3 Hz), 1.28 (s, 9H); IR (neat) cm^{-1}: 3288, 2961, 1649, 1536, 1345; LRMS (EI): m/z 433 (M+).

4.2.12. Methyl 5-{[3-(4-*tert*-butylphenyl)propanamido]methyl}-2-(methylsulfonamido)benzoate (34l)

The compound was prepared from **8d** by the general procedure for the synthesis of amides in 43% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.93 (d, 1H, J = 2.2 Hz), 7.67 (d, 1H, J = 8.6 Hz), 7.37 (dd, 1H, J = 8.6, 2.2 Hz), 7.29 (d, 2H, J = 8.4 Hz), 7.37 (d, 2H, J = 8.3 Hz), 5.67 (br s, 1H), 4.37 (d, 2H, J = 5.9 Hz), 3.91 (s, 3H), 3.02 (s, 3H), 2.98 (t, 2H, J = 7.3 Hz), 2.53 (t, 2H, J = 8.1 Hz), 1.29 (s, 9H); IR (neat) cm^{-1}: 2926, 1687, 1264, 1157, 794; LRMS (EI): m/z 446 (M+).

4.2.13. 3-(4-*tert*-Butylphenyl)-*N*-[3,5-dimethyl-4-(methylsulfonamido)benzyl]propanamide (34m)

The compound was prepared from **8e** by the general procedure for the synthesis of amides in 51% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.29 (d, 2H, J = 8.3 Hz), 7.10 (d, 2H, J = 8.3 Hz), 6.91 (s, 2H), 5.88 (br s, 1H), 5.65 (br s, 1H), 4.28 (d, 2H, J = 5.7 Hz), 3.03 (s, 3H), 2.94 (t, 2H, J = 7.7 Hz), 2.49 (t, 2H, J = 7.7 Hz), 2.33 (s, 6H), 1.25 (s, 9H); IR (neat) cm^{-1}: 3272, 2961, 1648, 1539, 1316, 1145; LRMS (EI): m/z 416 (M+).

4.2.14. 3-(4-*tert*-Butylphenyl)-*N*-[3-chloro-5-methyl-4-(methylsulfonamido)benzyl]propanamide (34n)

The compound was prepared from **4e** by the general procedure for the synthesis of amides in 35% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.28–7.31 (m, 2H), 7.11–7.16 (m, 3H), 7.04 (s, 1H), 6.07 (s, 1H), 5.68 (br s, 1H), 4.33 (d, 2H, J = 6.1 Hz), 3.06 (s, 3H), 2.95 (t, 2H, J = 7.6 Hz), 2.52 (t, 2H, J = 7.6 Hz), 2.46 (s, 3H), 1.28 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.2, 149.2, 141.2, 139.5, 137.5, 130.5, 129.6, 128.0, 126.4, 125.5, 41.5, 38.3, 34.4, 31.4, 31.0, 20.0; IR (neat) cm^{-1}: 3296, 2960, 1650, 1540, 1472, 1153, 794; LRMS (FAB+): *m/z* 437 (M+); HRMS (FAB+) calcd for $C_{22}H_{30}ClN_2O_3S$ (M+H$^+$): 437.1666, found 437.1662.

4.2.15. 3-(4-*tert*-Butylphenyl)-*N*-[3-fluoro-4-(methylsulfonamido)-5-vinylbenzyl]propanamide (34o)

The compound was prepared from **30** by the general procedure for the synthesis of amides in 63% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.22–7.32 (m, 3H), 7.08–7.18 (m, 3H), 6.92 (d, 1H, J = 10.0 Hz), 5.92 (br s, 1H), 5.76 (d, 1H, J = 17.0 Hz), 5.69 (br s, 1H), 5.44 (d, 1H, J = 11.0 Hz), 4.39 (d, 2H, J = 6.0 Hz), 3.05 (s, 3H), 2.96 (t, 2H, J = 7.6 Hz), 2.52 (t, 2H, J = 7.6 Hz), 1.28 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.1, 149.2, 139.4, 137.5, 131.6, 128.0, 125.5, 121.0, 118.0, 114.2, 114.0, 42.9, 40.9, 40.8, 38.3, 34.8, 31.3, 31.0; IR (neat) cm^{-1}: 3233, 2922, 1646, 1540, 1317, 1151; LRMS (FAB+): *m/z* 433 (M+); HRMS (FAB+) calcd for $C_{23}H_{30}FN_2O_3S$ (M+H$^+$): 433.1961, found 433.1954.

4.2.16. 3-(4-*tert*-Butylphenyl)-*N*-[3-acetylene -5-fluoro-4-(methylsulfonamido)benzyl]propanamide (34p)

The compound was prepared from **29** by the general procedure for the synthesis of amides in 90% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.31 (d, 1H, J = 8.2 Hz), 7.18 (s, 1H), 7.12 (d, 1H, J = 8.0 Hz), 7.02 (br s, 1H), 6.39 (s, 1H), 5.68 (br s, 1H), 4.34 (d, 2H, J = 6.1 Hz), 3.46 (s, 1H), 3.23 (s, 3H), 2.95 (t, 2H, J = 7.5 Hz), 2.51 (t, 2H, J = 7.5 Hz), 1.28 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.4, 149.2, 138.9, 139.8, 137.4, 128.0, 127.6, 127.5, 125.4, 120.5, 120.4, 117.0, 116.9, 84.9, 42.5, 42.4, 42.3, 38.2, 34.4, 31.3, 31.0; IR (neat) cm^{-1}: 3269, 2959, 1581, 1482, 1332, 1154, 762; LRMS (FAB+): *m/z* 431 (M+); HRMS (FAB+) calcd for $C_{23}H_{28}FN_2O_3S$ (M+H$^+$): 431.1805, found 431.1797.

4.2.17. 3-(4-*tert*-Butylphenyl)-*N*-[3-cyclopropyl-5-fluoro-4-(methylsulfonamido)benzyl]propanamide (34q)

The compound was prepared from **31** by the general procedure for the synthesis of amides in 87% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.30 (d, 2H, J = 8.4 Hz), 7.12 (d, 2H, J = 8.4 Hz), 6.80 (d, 1H, J = 10.0 Hz), 6.06 (s, 1H), 6.01 (s, 1H), 5.61 (br s, 1H), 4.32 (d, 2H, J = 5.9 Hz), 3.14 (d, 3H, J = 1.1 Hz), 3.02 (s, 3H), 2.95 (t, 2H, J = 7.7 Hz), 2.50 (t, 2H, J = 7.6 Hz), 2.24 (m, 1H), 1.28 (s, 9H), 1.02–1.08 (m, 2H), 0.62–0.68 (m, 2H); IR (neat) cm^{-1}: 3432, 2961, 1645, 1371, 1318, 1151; LRMS (FAB+): *m/z* 447 (M+).

4.2.18. 3-(4-*tert*-Butylphenyl)-*N*-[3-cyano-5-fluoro-4-(methylsulfonamido)benzyl]propanamide (34r)

The compound was prepared from **28** by the general procedure for the synthesis of amides in 39% yield 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; LRMS (FAB+): *m/z* 432 (M+); HRMS (FAB+) calcd for $C_{22}H_{27}FN_3O_3S$ (M+H$^+$): 432.1757, found 432.1762.

4.2.19. 3-(4-*tert*-Butylphenyl)-*N*-[3-fluoro-4-(methylsulfonamido)benzyl]propanethioamide (35a)

The compound was prepared from **34a** by the general procedure for the synthesis of thioamides in 80% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.48 (t, 1H, J = 8.1 Hz), 7.30 (d, 2H, J = 8.2 Hz), 7.13 (d, 2H, J = 8.3 Hz), 6.90–6.97 (m, 2H), 6.57 (br s, 1H), 4.71 (d, 2H, J = 5.3 Hz), 3.11 (t, 2H, J = 7.1 Hz), 2.99 (s, 3H), 2.97 (t, 2H, J = 7.1 Hz), 1.27 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 205.1, 154.9, 153.0, 149.4, 136.9, 135.3, 135.2, 128.1, 125.4, 123.6, 115.6, 115.4, 48.8, 48.6, 39.9, 34.8, 34.3, 31.3; IR (neat) cm^{-1}: 3255, 2961, 1590, 1513, 1445, 1402; LRMS (FAB+): *m/z* 423 (M+); HRMS (FAB+) calcd for $C_{21}H_{28}FN_2O_2S_2$ (M+H$^+$): 423.1576, found 423.1574.

4.2.20. 3-(4-*tert*-Butylphenyl)-*N*-[3-chloro-4-(methylsulfonamido)benzyl]propanethioamide (35b)

The compound was prepared from **34b** by the general procedure for the synthesis of thioamides in 70% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.57 (d, 1H, J = 8.4 Hz), 7.26–7.30 (m, 3H), 7.12 (d, 2H, J = 8.3 Hz), 7.06 (dd, 1H, J = 8.4, 2.0 Hz), 6.75 (br s, 1H), 4.71 (d, 2H, J = 5.3 Hz), 3.11 (t, 2H, J = 6.6 Hz), 2.99 (s, 3H), 2.98 (t, 2H, J = 6.8 Hz), 1.27 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 205.1, 149.5, 136.9, 134.5, 133.2, 129.4, 128.1, 128.0, 125.5, 125.0, 122.3, 48.9, 48.7, 40.0, 34.9, 34.4, 31.4; IR (neat) cm^{-1}: 3307, 2960, 1499, 1390, 1329, 1158; LRMS (FAB+): *m/z* 439 (M+H$^+$); HRMS (FAB+) calcd for $C_{21}H_{28}ClN_2O_2S_2$ (M+H$^+$): 439.1281, found 439.1269.

4.2.21. 3-(4-*tert*-Butylphenyl)-*N*-[2-chloro-4-(methylsulfonamido)benzyl]propanethioamide (35c)

The compound was prepared from **34c** by the general procedure for the synthesis of thioamides in 83% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.25–7.29 (m, 4H), 7.10 (d, 2H, J = 8.2 Hz), 7.01 (dd, 1H, J = 2.4, 8.2 Hz), 6.87 (br s, 1H), 4.80 (d, 2H, J = 5.5 Hz), 3.06 (t, 2H, J = 6.9 Hz), 3.02 (s, 3H), 2.94 (t, 2H, J = 6.9 Hz), 1.28 (s, 9H); IR (neat) cm^{-1}: 3433, 3218, 2957, 1667, 1525, 1318, 1153, 979; LRMS (FAB+): *m/z* 439 (M+H$^+$).

4.2.22. 3-(4-*tert*-Butylphenyl)-*N*-[3-iodo-4-(methylsulfonamido)benzyl]propanethioamide (35d)

The compound was prepared from **34d** by the general procedure for the synthesis of thioamides in 71% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.70 (d, 1H, J = 1.8 Hz), 7.52 (d, 1H, J = 8.4 Hz), 7.28 (d, 2H, J = 8.2 Hz), 7.09–7.20 (m, 4H), 6.60 (s, 1H), 4.68 (d, 2H, J = 5.3 Hz), 3.08 (t, 2H, J = 7.0 Hz), 2.98 (s, 3H), 2.95 (t, 2H, J = 7.0 Hz), 1.28 (s, 9H); IR (neat) cm^{-1}: 3322, 2960, 1533, 1488, 1386, 1329; LRMS (FAB+): *m/z* 531 (M+H$^+$).

4.2.23. 3-(4-*tert*-Butylphenyl)-*N*-[4-(methylsulfonamido)-2-(trifluoromethyl)benzyl]propanethioamide (35e)

The compound was prepared from **34e** by the general procedure for the synthesis of thioamides in 80% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.42–7.43 (m, 2H), 7.25–7.32 (m, 3H), 7.18 (d, 2H, J = 8.3 Hz), 6.63 (s, 1H), 5.68 (br s, 1H), 4.51 (d, 2H, J = 5.9 Hz), 3.02 (s, 3H), 2.93 (t, 2H, J = 7.6 Hz), 2.50 (t, 2H, J = 7.6 Hz), 1.28 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.6, 149.3, 137.3, 136.5, 133.1, 132.2, 127.9, 125.5, 123.6, 117.8, 55.9, 39.9, 38.3, 34.4, 31.3, 31.0; IR (neat) cm^{-1}: 2961, 1651, 1543, 1473, 1367, 1316, 1156, 1054, 972, 759; LRMS (FAB+): *m/z* 457 (M+H$^+$).

4.2.24. 3-(4-*tert*-Butylphenyl)-*N*-[4-(methylsulfon amido)-3-(trifluoromethyl)benzyl]propanethioamide (35f)

The compound was prepared from **34f** by the general procedure for the synthesis of thioamides in 54% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.73 (m, 1H), 7.55 (m, 1H), 7.35 (m, 1H), 7.26–7.30 (m, 2H), 7.10 (d, 2H, J = 6.6 Hz), 6.66 (br s, 1H), 5.83 (br s, 1H), 4.40 (d, 2H, J = 6.1 Hz), 2.96 (s, 3H), 2.93 (t, 2H,

J = 5.9 Hz), 2.54 (t, 2H, J = 5.9 Hz), 1.27 (s, 9H); IR (neat) cm^{-1}: 2959, 1541, 1471, 1366, 1316, 1133, 753; LRMS (EI): *m/z* 456 (M).

4.2.25. 3-(4-*tert*-Butylphenyl)-*N*-[3-methyl-4-(methylsulfonamido)benzyl]propanethioamide (35g)

The compound was prepared from **34g** by the general procedure for the synthesis of thioamides in 77% yield as a white solid. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.37 (d, 1H, J = 8.3 Hz), 7.30 (d, 2H, J = 8.3 Hz), 7.09–7.13 (m, 3H), 6.99 (dd, 1H, J = 8.1, 1.9 Hz), 6.23 (br s, 1H), 4.67 (d, 2H, J = 5.1 Hz), 3.10 (t, 2H, J = 7.2 Hz), 3.00 (s, 3H), 2.95 (t, 2H, J = 7.1 Hz), 2.27 (s, 3H), 1.28 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 204.6, 149.4, 137.1, 134.5, 133.9, 131.2, 130.8, 128.1, 127.1, 125.5, 123.0, 49.6, 48.9, 40.2, 34.9, 34.4, 31.4, 18.0; IR (neat) cm^{-1}: 3293, 2960, 1505, 1396, 1322, 1153; LRMS (FAB+): *m/z* 419 ($M+H^+$); HRMS (FAB+) calcd for $C_{22}H_{31}N_2O_2S_2$ ($M+H^+$): 419.1827, found 419.1830.

4.2.26. 3-(4-*tert*-Butylphenyl)-*N*-[3-ethyl-4-(methylsulfonamido)benzyl]propanethioamide (35h)

The compound was prepared from **34h** by the general procedure for the synthesis of thioamides in 74% yield as a white solid. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.32 (d, 1H, J = 8.2 Hz), 7.23 (d, 2H, J = 8.2 Hz), 7.05–7.08 (m, 4H), 6.93 (dd, 1H, J = 2.0, 8.3 Hz), 6.26 (s, 1H), 4.64 (d, 2H, J = 5.0 Hz), 3.03 (t, 2H, J = 7.4 Hz), 2.94 (s, 3H), 2.78 (t, 2H, J = 7.3 Hz), 2.57 (q, 2H, J = 7.5 Hz), 1.23 (s, 9H), 1.16 (t, 3H, J = 7.5 Hz); IR (neat) cm^{-1}: 3301, 2962, 1504, 1489, 1397, 1323, 1153; LRMS (FAB+): *m/z* 433 ($M+H^+$).

4.2.27. 3-(4-*tert*-Butylphenyl)-*N*-[4-(methylsulfonamido)-3-vinylbenzyl]propanethioamide (35i)

The compound was prepared from **34i** by the general procedure for the synthesis of thioamides in 63% yield as a white solid. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.38 (d, 1H, J = 8.3 Hz), 7.36 (d, 1H, J = 2.0 Hz), 7.27 (d, 2H, J = 8.3 Hz), 7.14 (br s, 1H), 7.11 (d, 2H, J = 8.3 Hz), 7.05 (dd, 1H, J = 2.0, 8.2 Hz), 6.84 (dd, 1H, J = 11.0, 17.4 Hz), 6.36 (s, 1H), 5.70 (d, 1H, J = 18.1 Hz), 5.48 (d, 1H, J = 11.7 Hz), 4.72 (d, 2H, J = 5.1 Hz), 3.08 (t, 2H, J = 7.2 Hz), 2.98 (s, 3H), 2.94 (t, 2H, J = 7.1 Hz), 1.27 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 204.8, 149.4, 137.0, 134.5, 133.0, 132.4, 131.1, 128.7, 128.1, 127.4, 125.5, 124.4, 119.6, 49.6, 48.9, 40.2, 34.9, 34.4, 31.4, 29.7; IR (neat) cm^{-1}: 3299, 3020, 2962, 2920, 1497, 1397, 1326; LRMS (EI): *m/z* 430 (M+); HRMS (FAB+) calcd for $C_{23}H_{31}N_2O_2S_2$ ($M+H^+$): 431.1827, found 431.1820.

4.2.28. 3-(4-*tert*-Butylphenyl)-*N*-[3-cyano-4-(methylsulfonamido)benzyl]propanethioamide (35j)

The compound was prepared from **34j** by the general procedure for the synthesis of thioamides in 65% yield as a white solid. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.62 (d, 1H, J = 8.6 Hz), 7.47 (d, 1H, J = 2.2 Hz), 7.35 (dd, 1H, J = 2.2, 8.6 Hz), 7.29 (d, 2H, J = 8.4 Hz), 7.20 (br s, 1H), 7.11 (d, 2H, J = 8.4 Hz), 6.92 (s, 1H), 4.75 (d, 2H, J = 5.7 Hz), 3.09 (s, 3H), 3.06–3.11 (m, 2H), 2.94–2.99 (m, 2H), 1.28 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 205.8, 149.6, 138.8, 136.9, 134.1, 132.3, 128.1, 125.6, 121.6, 115.6, 104.4, 64.0, 48.8, 48.1, 40.8, 38.4, 34.8, 34.4, 31.4; IR (neat) cm^{-1}: 3311, 2959, 2222, 1534, 1500, 1418, 1336, 1158; LRMS (FAB+): *m/z* 430 ($M+H^+$); HRMS (FAB+) calcd for $C_{22}H_{28}N_3O_2S_2$ ($M+H^+$): 430.1623, found 430.1631.

4.2.29. 3-(4-*tert*-Butylphenyl)-*N*-[4-(methylsulfonamido)-3-nitrobenzyl]propanethioamide (35k)

The compound was prepared from **34k** by the general procedure for the synthesis of thioamides in 58% yield as a white solid. ^1H NMR ($CDCl_3$, 300 MHz): δ 9.69 (br s, 1H), 8.11 (d, 1H, J = 2.0 Hz), 7.81 (d, 1H, J = 8.8 Hz), 7.47 (dd, 1H, J = 8.4, 2.0 Hz), 7.29 (d, 2H, J = 8.4 Hz), 7.12 (d, 2H, J = 8.3 Hz), 4.80 (d, 2H, J = 5.9 Hz), 3.12 (s, 3H), 3.11 (t, 2H, J = 7.1 Hz), 2.98 (t, 2H, J = 6.6 Hz), 1.27 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 205.9, 149.6, 136.9, 135.9, 133.7, 132.3, 128.1, 125.8, 125.5, 119.8, 48.7, 47.9, 40.9, 34.9, 34.4, 31.3; IR (neat) cm^{-1}: 3293, 2960, 1623, 1534, 1389, 1344; LRMS (FAB+): *m/z* 450 (M+); HRMS (FAB+) calcd for $C_{21}H_{28}N_3O_4S_2$ ($M+H^+$): 450.1521, found 450.1532.

4.2.30. Methyl 5-{[3-(4-*tert*-butylphenyl)propanethioamido]-methyl}-2-(methylsulfonamido)benzoate (35l)

The compound was prepared from **34l** by the general procedure for the synthesis of thioamides in 91% yield as a white solid. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.95 (d, 1H, J = 2.0 Hz), 7.67 (d, 1H, J = 8.4 Hz), 7.33 (dd, 1H, J = 8.6, 2.2 Hz), 7.28 (d, 2H, J = 8.2 Hz), 7.12 (d, 2H, J = 8.2 Hz), 4.73 (d, 2H, J = 5.1 Hz), 3.92 (s, 3H), 3.10 (t, 2H, J = 7.0 Hz), 3.03 (s, 3H), 2.97 (t, 2H, J = 7.5 Hz), 1.27 (s, 9H); IR (neat) cm^{-1}: 3211, 2959, 1689, 1585, 1503, 1398; LRMS (FAB+): *m/z* 463 (M+).

4.2.31. 3-(4-*tert*-Butylphenyl)-*N*-[3,5-dimethyl-4-(methylsulfonamido)benzyl]propanethioamide (35m)

The compound was prepared from **34m** by the general procedure for the synthesis of thioamides in 75% yield as a white solid. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.29 (d, 2H, J = 8.2 Hz), 7.13 (d, 2H, J = 8.4 Hz), 6.96 (s, 2H), 5.75 (br s, 1H), 4.65 (d, 2H, J = 5.1 Hz), 3.10 (t, 2H, J = 7.3 Hz), 3.09 (s, 3H), 2.95 (t, 2H, J = 7.3 Hz), 2.38 (s, 6H), 1.27 (s, 9H); IR (neat) cm^{-1}: 3182, 2920, 1646, 1517, 1401, 1306; LRMS (FAB+): *m/z* 433 (M+).

4.2.32. 3-(4-*tert*-Butylphenyl)-*N*-[3-chloro-5-methyl-4-(methylsulfonamido)benzyl]propanethioamide (35n)

The compound was prepared from **34n** by the general procedure for the synthesis of thioamides in 56% yield as a white solid. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.27–7.32 (m, 2H), 7.11–7.16 (m, 3H), 7.05 (br s, 1H), 6.03 (br s, 1H), 4.73 (d, 2H, J = 5.1 Hz), 3.08 (s, 3H), 2.96 (t, 2H, J = 7.3 Hz), 2.49 (t, 2H, J = 7.3 Hz), 2.03 (s, 3H), 1.29 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 205.6, 181.9, 135.7, 134.5, 130.1, 128.1, 128.0, 126.9, 126.4, 125.5, 110.0, 48.6, 41.7, 41.5, 34.9, 34.4, 31.4, 30.9; IR (neat) cm^{-1}: 3248, 2960, 1650, 1536, 1323, 1153; LRMS (FAB+): *m/z* 453 (M+); HRMS (FAB+) calcd for $C_{22}H_{30}ClN_2O_2S_2$ ($M+H^+$): 453.1437, found 453.1441.

4.2.33. 3-(4-*tert*-Butylphenyl)-*N*-[3-fluoro-4-(methylsulfonamido)-5-vinylbenzyl]propanethioamide (35o)

The compound was prepared from **34o** by the general procedure for the synthesis of thioamides in 83% yield as a white solid. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.26–7.28 (m, 4H), 7.07–7.16 (m, 3H), 6.89 (dd, 1H, J = 6.0, 9.9 Hz), 5.99 (s, 1H), 5.76 (d, 1H, J = 17.5 Hz), 5.45 (d, 1H, J = 11.1 Hz), 4.74 (d, 2H, J = 5.4 Hz), 3.09 (t, 2H, J = 7.4 Hz), 3.06 (s, 3H), 2.95 (t, 2H, J = 7.4 Hz), 1.27 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 205.3, 149.5, 139.5, 137.0, 131.4, 131.3, 128.1, 125.5, 121.7, 118.5, 114.7, 49.2, 48.8, 48.1, 41.1, 41.0, 34.9, 34.4, 31.3; IR (neat) cm^{-1}: 3305, 2961, 1578, 1533, 1445, 1398; LRMS (FAB+): *m/z* 449 (M+); HRMS (FAB+) calcd for $C_{23}H_{30}FN_2O_2S_2$ ($M+H^+$): 449.1733, found 449.1726.

4.2.34. 3-(4-*tert*-Butylphenyl)-*N*-[3-acetylene-5-fluoro-4-(methylsulfonamido)benzyl]propanethioamide (35p)

The compound was prepared from **34p** by the general procedure for the synthesis of thioamides in 41% yield as a white solid. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.30 (d, 1H, J = 8.2 Hz), 7.18 (s, 1H), 7.12 (d, 1H, J = 8.1 Hz), 7.00 (br s, 1H), 6.41 (s, 1H), 4.71 (d, 2H, J = 5.3 Hz), 3.48 (s, 1H), 3.24 (s, 3H), 3.08 (t, 2H, J = 7.3 Hz), 2.95 (t, 2H, J = 6.9 Hz), 1.28 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 205.5, 149.4, 136.9, 136.3, 136.2, 126.1, 125.5, 120.3, 117.5, 117.3, 85.4, 48.8, 48.5, 42.6, 42.5, 34.9, 34.4, 31.3; IR (neat) cm^{-1}: 3270, 2959, 1581, 1482, 1332, 1154, 763; LRMS (FAB+): *m/z* 447 (M +);

HRMS (FAB+) calcd for $C_{23}H_{28}FN_2O_2S_2$ (M+H$^+$): 447.1576, found 447.1587.

4.2.35. 3-(4-*tert*-Butylphenyl)-*N*-[3-cyclopropyl-5-fluoro-4-(methylsulfonamido)benzyl]propanethioamide (35q)

The compound was prepared from **34q** by the general procedure for the synthesis of thioamides in 97% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.28 (d, 2H, J = 8.3 Hz), 7.17 (br s, 1H), 7.11 (d, 2H, J = 8.1 Hz), 6.75 (d, 1H, J = 10.1 Hz), 6.64 (s, 1H), 6.09 (s, 1H), 4.66 (d, 2H, J = 5.3 Hz), 3.15 (s, 3H), 3.08 (t, 2H, J = 7.4 Hz), 2.29 (t, 2H, J = 7.2 Hz), 2.21 (m, 1H), 1.27 (s, 9H), 1.02–1.09 (m, 2H), 0.62–0.67 (m, 2H); IR (neat) cm^{-1}: 3302, 2961, 1535, 1446, 1324, 1152; LRMS (FAB+): *m/z* 463 (M+).

4.2.36. 3-(4-*tert*-Butylphenyl)-*N*-[3-cyano-5-fluoro-4-(methylsulfonamido)benzyl]propanethioamide (35r)

The compound was prepared from **34r** by the general procedure for the synthesis of thioamides in 96% yield as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.20–7.32 (m, 4H), 7.12 (d, 2H, J = 8.4 Hz), 6.35 (s, 1H), 4.78 (d, 2H, J = 5.7 Hz), 3.30 (s, 3H), 3.09 (t, 2H, J = 6.6 Hz), 2.99 (t, 2H, J = 6.6 Hz), 1.28 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 205.6, 149.7, 138.5, 136.8, 134.2, 132.3, 128.1, 125.6, 121.7, 115.5, 48.9, 47.8, 40.8, 38.4, 34.8, 34.3, 31.3; IR (neat) cm^{-1}: 3200, 2954, 2224, 1726, 1531, 1326, 1159; LRMS (FAB+): *m/z* 448 (M+); HRMS (FAB+) calcd for $C_{22}H_{27}FN_3O_2S_2$ (M+H$^+$): 448.1529, found 448.1520.

4.2.37. 5-{[3-(4-*tert*-Butylphenyl)propanethioamido]methyl}-2-(methylsulfonamido)benzoic acid (36)

To a solution of thioamide **35l** (100 mg, 0.22 mmol) in THF/H_2O = 1:1 (2 mL) was added LiOH–H_2O (27 mg, 0.65 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 in vacuo to give the acid **36** (48 mg, 50%) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.05 (d, 1H, J = 1.7 Hz), 7.58 (d, 1H, J = 8.6 Hz), 7.33 (dd, 1H, J = 8.4, 2.2 Hz), 7.27 (d, 2H, J = 8.0 Hz), 7.13 (d, 2H, J = 8.2 Hz), 4.74 (s, 2H), 3.06 (t, 2H, J = 7.3 Hz), 2.98 (s, 3H), 2.91 (t, 2H, J = 7.7 Hz), 1.25 (s, 9H); IR (neat) cm^{-1}: 3229, 2958, 1682, 1502, 1393, 1327; LRMS (FAB+): *m/z* 449 (M+).

4.2.38. *N*-[3-Acetyl-4-(methylsulfonamido)benzyl]-3-(4-*tert*-butylphenyl)propanethioamide (38)

To a solution of thioamide **35l** (60 mg, 0.14 mmol) in THF (4 mL) was added NHMe(OMe) (20 mg, 0.20 mmol). The reaction mixture was added dropwise of *i*-PrMgCl (2.0 M in THF, 0.28 mL, 0.56 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h, then diluted with EtOAc. 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 = 3:2) to afford **37** (46 mg, 72%).

To a solution of benzamide **37** (46 mg, 0.09 mmol) in THF (4 mL) was added methyl magnesium iodide (1.0 M in ether, 0.12 mL, 0.12 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h, then diluted with EtOAc. 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 = 1:1) was conducted to afford **38** (12 mg, 28%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.85 (d, 1H, J = 2.2 Hz), 7.60 (d, 1H, J = 8.6 Hz), 7.24–7.26 (m, 3H), 7.06 (d, 2H, J = 8.3 Hz), 4.71 (d, 2H, J = 5.7 Hz), 3.04 (t, 2H, J = 7.2 Hz), 2.99 (s, 3H), 2.94 (t, 2H, J = 7.1 Hz), 2.58 (s, 3H), 1.22 (s, 9H); IR (neat) cm^{-1}: 3762, 2960, 1651, 1505, 1394, 1335, 1156; LRMS (EI): *m/z* 446 (M+).

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