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Structure–activity relationship of the cinnamamide family of antibiotic potentiators for methicillin-resistant *Staphylococcus aureus* (MRSA)†

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Methicillin-resistant *Staphylococcus aureus* (MRSA) is a global public health threat. MRSA has evolved a complex set of biochemical processes that mobilize the organism for inducible resistance on challenge by β-lactam antibiotics. Interfering pharmacologically with this machinery has the potential to reverse the β-lactam-resistance phenotype, whereby susceptibility to obsolete antibiotics would be restored. We describe herein our discovery of one class of such agents, the cinnamamide family of antibiotic potentiators. A hit compound of the class (compound **1**) showed modest potentiation of the activity of oxacillin, a penicillin antibiotic, against an MRSA strain. A total of 50 analogues of compound **1** were prepared and screened. Seven of these compounds showed more dramatic potentiation of the antibacterial activity, which lowered the minimal-inhibitory concentrations (MICs) for the antibiotic by as much as 64- to 128-fold.

1. Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) has evolved an elaborate scheme for manifestation of resistance to β-lactam antibiotics. A key component of this process involves sensing of the presence of the antibiotic by either the BlaR1 or MecR1 antibiotic sensor/signal transducers, integral membrane proteins, which then transduce the signal to the cytoplasmic side of the membrane.[1–4] During this process, a cytoplasmic protease domain is activated, which degrades the gene repressors BlaI or MecI, which leads to transcription of genes *blaZ* and *mecA* for the resistance determinants β-lactamase and penicillin-binding protein 2A, respectively.[5–7] Furthermore, there are other contributors to the resistance response, such as two-component systems.[8,9] All in all, exposure of the organism to the antibiotic creates a state of mobilization, the outcome of which is broad resistance to virtually the entire class of β-lactam antibiotics. These subjects have been reviewed.[10–12] The complexity of the system implies the potential for interference by small molecules at many steps of this elaborate process that could reverse the antibiotic-resistance phenotype.[13] We describe one such class of compounds in the present report.

Screening of compounds within our labs for potentiators of activity of oxacillin (OXA), a penicillin antibiotic (a β-lactam), recently identified compound **1** as a modest potentiator. Compound **1** was able to reduce the minimal-inhibitory concentration (MIC) of oxacillin for strain MRSA252 (also known as strain USA200) from 256 μg mL^{-1} to 128 μg mL^{-1} consistently, when it was present at 20 μM. MRSA252 is a strain derived from the hospital-acquired MRSA-16 (EMRSA-16) epidemic.[14,15] Furthermore, **1** did not show any antibacterial activity of its own, indicating that the lowering of the MIC value for oxacillin likely involved interference with a step in the aforementioned elaborate process of response by the organism to the antibiotic challenge. The reduction in the MIC was a mere two-fold, but it was reproducible, alerting us to explore further. We undertook to carry out a structure–activity relationship (SAR) study for this compound class, as we outline herein, with the intention of identifying more potent compounds.

We dissected the compound into four segments, referred to as SAR1–4 (coloured boxes; Fig. 1), to evaluate the structural contributions of each segment of the template toward the activity. As the actual target is presently unknown, the search would be guided by generating structural diversity at

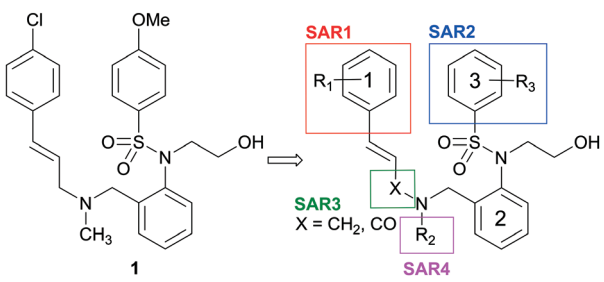

Fig. 1 Compound **1** and the four sites for structural diversification: SAR1 (red), SAR2 (blue), SAR3 (green), and SAR4 (purple).

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each of these SAR sites and screening for the potentiation activity.

2. Results and discussion

Synthesis

Compound **1** was synthesized as reported in the literature.[16] For synthetic expediency, we explored the possibility of substituting the tertiary amine at the core of the molecule with an amide. The SAR1 diversified the structure at the site that is boxed in red. Scheme 1 outlines the synthetic route to compound **6**, but the strategy is general for other cinnamic derivatives within the red box.

Briefly, the aniline amine of 2-aminobenzyl alcohol was sulfonylated to give the sulfonamide **2**. The alcohol in **2** was oxidized to the aldehyde **3** and this underwent reductive amination to the appropriate amine (in this case a methylated amine) to produce the intermediate **4**. Compound **4** was allowed to react with *p*-(trifluoromethyl)cinnamic acid using the coupling reagent 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU)[18–20] to give **5**. Compound **5** was *N*-alkylated with 2-iodoethanol[21] to produce the final compound **6**. By variation of the corresponding cinnamic derivatives in the red box, we transformed compound **4** into a series of structures diversified at this specific site.

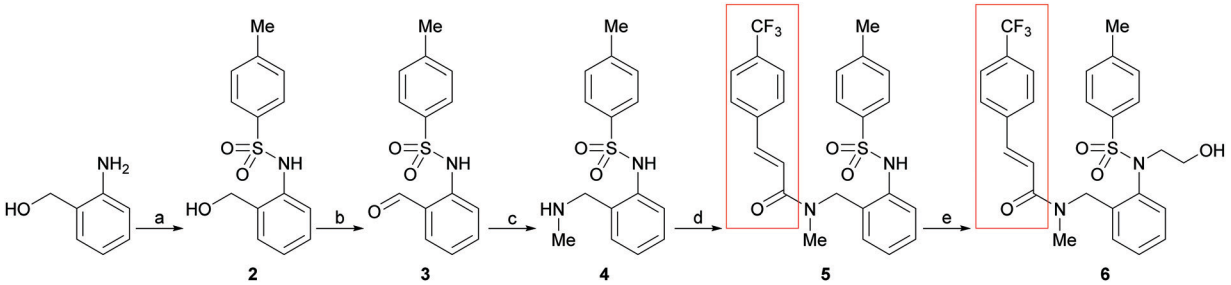
Diversification at the SAR2 site took place as shown in Scheme 2. The starting point was 2-nitrobenzyl alcohol. The alcohol was activated with methanesulfonyl chloride, which was in turn displaced by methylamine.[22] The appropriate cinnamyl derivative was introduced (intermediate **9**) and the nitro functionality was then reduced using zinc to intermediate **10**. The SAR2 variable (boxed in blue) was introduced using the desired sulfonyl chloride, in this case 4-fluorosulfonyl chloride, to produce compound **11**. *N*-Alkylation[21] of **11** completed the synthesis, giving compound **12**.

SAR3 and SAR4 variables, boxed in green and purple in Fig. 1, respectively, used the synthetic routes in either Scheme 1 or Scheme 2 to achieve diversification at both sites. To achieve the diversification in SAR3 as amines (SAR3-a) and amides (SAR3-b), suitable cinnamyl methanesulfonate (in an S_N2 reaction) or cinnamic acid (in a HATU-mediated coupling reaction) were used, respectively (Fig. 2). Lastly, diversification in SAR4 was achieved using different alkylated amines. A total of 50 compounds were synthesized in the diversification of the four SAR regions.

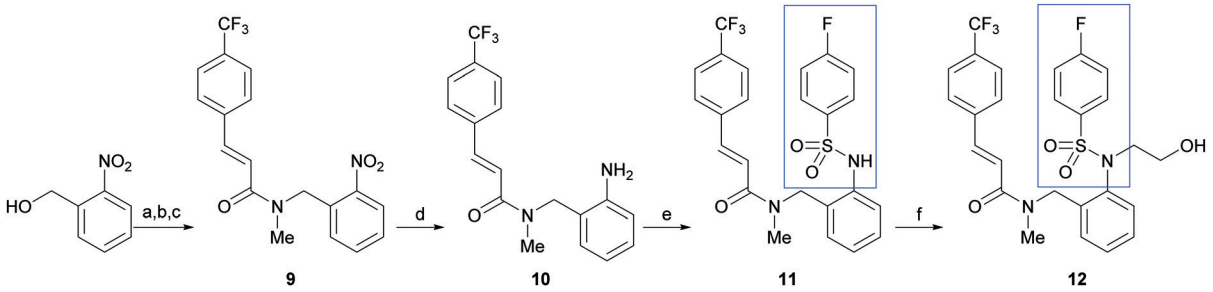
Evaluation of the compounds

Each synthetic compound was tested alone to explore if it would exhibit antibacterial activity of its own. None of the compounds did, so we evaluated them as potentiators of MRSA next. The activity of each compound was evaluated by assessment of the minimal-inhibitory concentration (MIC) for oxacillin (OXA) with strain MRSA252 in the presence of the given synthetic sample with a fixed 20 μM concentration. The MIC of OXA against strain MRSA252 in the absence of any potentiator was 256 μg mL^{-1}. These assessments are given in Table 1. The compounds that lowered the MIC from 256 μg mL^{-1} to <8 μg mL^{-1} were deemed as active potentiators (Table 1; given in blue). The values ≥8 μg mL^{-1} are in red for less active compounds.

The results of SAR1 (on ring 1) indicated that the presence of an electron-withdrawing group (EWG) at the *para* position of the ring is beneficial. All of the seven most active compounds (**6** and **12–17**) had a chloro atom or a trichloromethyl moiety at the *para* position. When another chloro atom (**26**, **27** and **45**) was introduced into the structure, either at the *ortho* or *meta* position, the potentiation activity was lost. A hydrogen atom or an electron-donating group (EDG), such as methoxy or acetamide (**35–37**, **40**, and **41**), showed loss of potentiation activity. SAR2 was explored as well with either EWG or EDG substitutions. Compounds containing EWGs and/or apolar groups preferred the *para* positions. 4-Fluoro (**12** and **17**), 4-methyl (**6** and **16**), and 3-fluoro-4-methyl (**14**) were well tolerated, all lowering the MIC for OXA to below 8 μg mL^{-1}. The introduction of an isopropyl (**28**), nitro (**29**), trifluoromethoxy (**30**), cyano (**32**), or trifluoromethyl (**39**) group at the *para* position resulted in abrogation of the activity. When EDGs 4-methoxy (**37**) or 3,4-ethylenedioxy (**31**) were introduced, the compounds did not show any potentiation. While a simple mono-substituted phenyl ring (**15**) lowered the MIC to 4 μg mL^{-1}, the compounds with the benzene



Scheme 1 Synthetic route for SAR1 derivatives. (a) *p*-Toluenesulfonyl chloride, pyridine, DCM, reflux, overnight, yield 94%; (b) manganese(IV) oxide,[17] DCM, rt, 72 h, yield 85%; (c) methylamine 40 wt% in H_2O, MeOH, 30 min, then $NaBH_4$, 0 °C, 1 h, yield 98%; (d) 4-(trifluoromethyl)cinnamic acid, HATU, DIPEA, DMF, rt, overnight, yield 71%; (e) 2-iodoethanol, K_2CO_3, DMF, 60 °C, 24 h, yield 62%.



Scheme 2 Synthetic route for SAR2 derivatives. (a) Methanesulfonyl chloride, THF, rt, 2 h, yield 99%; (b) methylamine 40 wt% in H_2O, 30 min, then $NaBH_4$, THF, rt, 1 h, yield 98%; (c) 4-(trifluoromethyl)cinnamic acid, HATU, DIPEA, DMF, rt, 24 h, yield 67%; (d) zinc, NH_4Cl, acetone, reflux, 5 h, yield 69%; (e) 4-fluorobenzenesulfonyl chloride, pyridine, DCM, 0 °C to rt, 24 h, yield 65%; (f) 2-iodoethanol, K_2CO_3, DMF, 60 °C, 24 h yield 61%.

bioisostere thiophene (**33** and **34**) did not show any activity. SAR3 identified which X linker was more active between amide and amine. Amines **1** and **37** to **45** showed modest to no potentiation activity of OXA, although the MIC never went below 8 μg mL^{-1}. Amides **6** and **12** to **17** produced MIC values in the range of 2–4 μg mL^{-1}, indicating that a hydrogen-bond acceptor might be beneficial. The SAR4 exploration aimed to study the effect of different alkyl groups such as methyl (**6** and **12** to **17**), ethyl (**20**), cyclopropyl (**21**), isopropyl (**22**), and isoamyl (**23** and **24**) or merely hydrogen (**25**) at the amide position. Only the methyl substitution resulted in potentiation of the OXA activity. Interestingly, the ethyl alcohol chain introduced during the last step of the synthesis in both Schemes 1 and 2 was essential for the activity. Compound **11**, related to compound **12** minus the ethyl chain, was devoid of activity.

Table 2 expands on the study at the R_1 group (red box). The explored chemical space involved the synthesis of a cinnamyl bioisostere such as (4-chlorophenoxy)methyl (**46**) or a reduced double bond in the cinnamyl moiety (**47**). The introduction of heterocycles (**48**–**51**), naphthyl (**52**), phenyl (**53** and **54**), and ethenyl (**55**–**57**) moieties, an inverted amide (**58**) and a *meta* instead of *ortho* connected compound (**59**) was also explored, however all of these modifications were not tolerated.

Notwithstanding the fact that there are no stereogenic centers in these compounds, they appear to exhibit three-dimensional attributes, as discerned from their NMR spectra. The introduction of the *N*-ethyl alcohol chain, critical for the biological function, in the last step of both the synthetic schemes (red oval in Fig. 3) produced rigidity and particularly slow rotation at the amide (blue oval in Fig. 3). This produced a higher-than-expected number of signals in the ^{1}H-NMR spectra. To demonstrate that this observation was due to slow bond rotation, hence a conformational phenomenon, multiple ^{1}H-NMR spectra were acquired at increasing temperatures (starting at 25 °C with temperature increments of 10 °C) with a representative of the class (compound **16**). Fig. 3 shows 8 different NMR spectra superposed between 2.8 ppm and 3.3 ppm, the region where the methyl of the amide (circled in blue) is present. As shown in the spectrum at 25 °C,

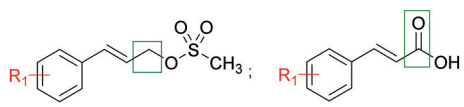
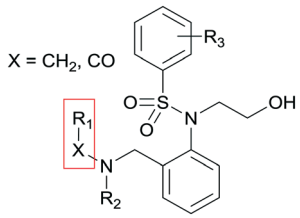


Fig. 2 Precursors for SAR3 exploration.

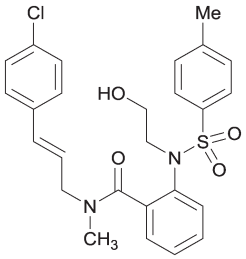
Table 1 Minimal-inhibitory concentration (MIC) for oxacillin (OXA) against strain MRSA252 in the presence of 20 μM potentiator. MIC values of 8 μg mL^{-1} and above are given in red and those below in blue

	SAR1	SAR2	SAR3	SAR4	MIC OXA
1	4-Cl	4-OMe	X = CH_2	-Me	128
6	4-CF_3	4-Me	X = CO	-Me	2
11	Same as **12** but without the lateral ethyl alcohol chain				≥256
12	4-CF_3	4-F	X = CO	-Me	2
13	4-CF_3	4-Et	X = CO	-Me	4
14	4-CF_3	3-F-4-Me	X = CO	-Me	4
15	4-CF_3	H	X = CO	-Me	4
16	4-Cl	4-Me	X = CO	-Me	2
17	4-Cl	4-F	X = CO	-Me	4
18	4-F	4-Me	X = CO	-Me	≥256
19	4-Me	4-Me	X = CO	-Me	64
20	4-CF_3	4-Me	X = CO	-Et	≥256
21	4-CF_3	4-Me	X = CO	-C_3H_6	≥256
22	4-CF_3	4-Me	X = CO	-*i*Pr	≥256
23	4-Cl	4-OMe	X = CH_2	-isobutyl	128
24	4-Cl	4-Me	X = CH_2	-isobutyl	128
25	4-CF_3	4-Me	X = CO	-H	≥256
26	2,4-Cl	4-Me	X = CO	-Me	≥256
27	3,4-Cl	4-Me	X = CO	-Me	16
28	4-CF_3	4-*i*Pr	X = CO	-Me	32
29	4-CF_3	4-NO_2	X = CO	-Me	≥256
30	4-CF_3	4-OCF_3	X = CO	-Me	32
31	4-CF_3	3,4-Ethylenedioxy	X = CO	-Me	64
32	4-CF_3	4-CN	X = CO	-Me	32
33	4-Cl	2-Thiophene	X = CO	-Me	256
34	4-Cl	3-Thiophene	X = CO	-Me	≥256
35	4-OMe	4-Me	X = CO	-Me	≥256
36	4-NHAc	4-Me	X = CO	-Me	≥256
37	H	4-OMe	X = CH_2	-Me	≥256
38	4-Cl	4-Me	X = CH_2	-Me	32
39	4-Cl	4-CF_3	X = CH_2	-Me	64
40	H	4-CF_3	X = CH_2	-Me	32
41	H	4-Me	X = CH_2	-Me	≥256
42	4-Cl	4-NHAc	X = CH_2	-Me	≥256
43	4-Cl	-Benzyl	X = CH_2	-Me	≥256
44	4-Cl	4-Cl	X = CH_2	-Me	16
45	3,4-Cl	4-Me	X = CH_2	-Me	32

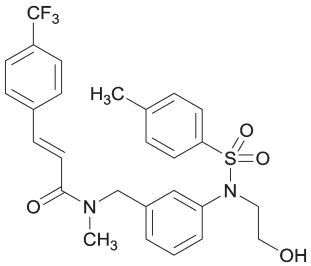
Table 2 Additional structures with more broad modification at the R_1 position. MICs are given for oxacillin against strain MRSA252 in the presence of 20 μM potentiator



	SAR1	SAR2	SAR3	SAR4	MIC OXA
46	(4-Chlorophenoxy)methyl	-Me	4-Me	X = CO	≥256
47	2-(4-Chlorophenyl)ethyl	-Me	4-Me	X = CO	≥256
48	(*E*)-5-(4-Chlorophenyl)-furan-2-ylethenyl	-Me	4-Me	X = CO	≥256
49	(*E*)-2-(3-Pyridinyl)ethenyl	-Me	4-Me	X = CO	≥256
50	(*E*)-2-(2-Furanyl)ethenyl	-Me	4-Me	X = CO	≥256
51	(*E*)-2-(5-Bromothiophenyl)ethenyl	-Me	4-Me	X = CO	≥256
52	6-Bromo-2-naphthyl	-Me	4-Me	X = CO	≥256
53	4-Chlorophenyl	-Me	4-Me	X = CO	≥256
54	Phenyl	-Me	4-CF_3	X = CH_2	≥256
55	Ethenyl	-Me	4-Cl	X = CH_2	≥256
56	Ethenyl	-*i*Pr	4-OMe	X = CH_2	≥256
57	Ethenyl	-Me	4-Me	X = CH_2	≥256



58 MIC = ≥256

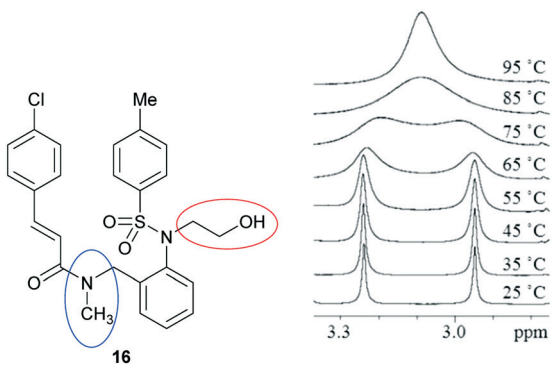


59 MIC = ≥256

the methyl resonance is split into two peaks of roughly equal intensity, which merge into one at 95 °C.

The breadth of the potentiation

The potentiation activity of compounds **6** and **12–17** was studied with three additional MRSA strains: NRS100, a *mecA*-positive strain resistant to methicillin, oxacillin, and tetracycline; NRS386 (also known as strain USA700) a strain associated with both community and healthcare infections,[23] and NRS70 a resistant strain isolated in 1982.[24] We maintained a fixed 20 μM concentration of the synthetic compound throughout these studies. Compounds **6**, **12** and **16** showed an OXA MIC of 2 μg mL^{-1} and compounds **13–15** and **17** exhibited an OXA MIC of 4 μg mL^{-1} against MRSA252; 128-fold and 64-fold lowering of MIC, respectively (Table 3). Among the additional three strains, only NRS70 did not show pronounced potentiation. In fact, the range of the MIC values against NRS100 and NRS386 was essentially the same with a handful of exceptions.



16

Fig. 3 Compound **16** and its ^{1}H-NMR signals between 2.8 and 3.3 ppm. Introduction of the hydroxyethyl moiety (red oval) introduced conformational rigidity into the molecule, documented by the merger of the methyl signals for the *N*-methylamide only at 95 °C.

3. Conclusion

We disclose here a class of cinnamamide potentiators of β-lactam antibiotic activity against MRSA. The active

Table 3 MIC values of oxacillin (OXA) in the presence or absence of synthetic compounds (given at 20 μM)

MIC OXA μg mL^{-1}								
Strain	No compd	**6**	**12**	**13**	**14**	**15**	**16**	**17**
MRSA252	256	2	2	4	4	4	2	4
NRS100	256	4	2	16	2	2	2	1
NRS386	256	4	8	8	8	2	4	1
NRS70	32	16	16	16	16	16	8	8

potentiators that we have discovered lack antibacterial activity of their own. This study encompassed evaluation of 50 analogues of the original hit molecule, which lowered the MIC for oxacillin with strain MRSA252 from 256 μg mL^{-1} to 2 to 4 μg mL^{-1} for molecules **6** and **12** to **17**. The target(s) for this class of compounds need(s) to be elucidated, the identification of which should stimulate further investigation of their biological function.

4. Experimental methods

Minimal-inhibitory concentration (MIC) determination

MICs were determined with the broth microdilution method following the Clinical & Laboratory Standards Institute (CLSI) guidelines with slight modifications. Determination of MICs was performed by two-fold serial dilution of each compound in cation-adjusted Mueller-Hinton II broth (CAMHB II) with a DMSO concentration of 2.4%. Experiments were carried out in triplicate in 96-well plates with an inoculum of 5×10^5 CFU mL^{-1}, followed by incubation at 36 °C for 16–20 h. The MIC was recorded as the lowest concentration that inhibited bacterial growth.

Syntheses

A detailed procedure for the synthesis of **6** (Scheme 1), **12** (Scheme 2), and **13** to **17** is given. The following procedures are representative for all the 51 compounds (compound **1** plus 50 analogues; NMR and MS data for the complete set is given in the ESI†). The purity of all the final compounds was found to be ≥95% and it was determined by LC/MS using a Bruker-Q II TOF electrospray mass spectrometer coupled with a Dionex UltiMate 3000 ultra-high pressure liquid chromatograph. The solvents used were 0.1% formic acid in H_2O (A) and 0.1% formic acid in acetonitrile (B). Each sample run was 10 min as follows: 1 min of 10% B, 8 min of gradient to 100% B, and 1 min of gradient back to 10% B. The flow rate was 0.4 mL min^{-1} and UV/vis detection was carried out at 240 nm. Purification of products was accomplished by silica-gel column chromatography using a Teledyne ISCO CombiFlash Rf 200i.

N-(2-(Hydroxymethyl)phenyl)-4-methylbenzenesulfonamide (2)

To a solution of 2-aminobenzyl alcohol (6.50 g, 52.8 mmol) and pyridine (5.50 mL, 68.6 mmol) in dichloromethane (DCM, 50 mL), *p*-toluenesulfonyl chloride (12.08 g, 58.1 mmol) was slowly added in small portions. The solution was stirred overnight under reflux. Water (25 mL) was added to the reaction mixture. The aqueous layer was separated and the organic solution was washed with brine and then dried over anhydrous Na_2SO_4. The filtered solution was evaporated to afford an off-white solid (13.82 g, 94%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.89 (s, 1 H), 7.60–7.68 (m, 2 H), 7.43 (d, J = 8.1 Hz, 1 H), 7.23–7.28 (m, 2 H), 7.21 (dd, J = 8.6, 0.5 Hz, 2 H), 7.05–7.11 (m, 2 H), 2.38 (s, 3 H) 4.39 (s, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 144.01, 137.18, 136.63, 131.83, 129.58, 129.50, 129.25, 127.28, 125.57, 123.69, 64.15, 21.76. HRMS (m/z): $[M + Na]^+$, calcd for $C_{14}H_{15}NNaO_3S$, 300.0665; found, 300.0638.

N-(2-Formylphenyl)-4-methylbenzenesulfonamide (3)

Compound **2** (13.5 g, 48.7 mmol) was dissolved in dichloromethane (DCM, 500 mL). Manganese dioxide (52.9 g, 608.5 mmol) is added in one portion to the solution. The reaction mixture was stirred for 72 hours at room temperature and the suspension was filtered through a pad of celite. The filtrate was concentrated under reduced pressure to produce a yellowish solid (11.40 g, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 10.79 (br. s., 1 H), 9.83 (s, 1 H), 7.78 (d, J = 8.3 Hz, 2 H), 7.69 (d, J = 8.3 Hz, 1 H), 7.59 (dd, J = 7.6, 1.5 Hz, 1 H), 7.51 (ddd, J = 8.6, 7.2, 1.6 Hz, 1 H), 7.20–7.30 (m, 2 H), 7.16 (td, J = 7.6, 1.0 Hz, 1 H), 2.37 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 195.19, 144.38, 140.18, 136.64, 136.31, 136.02, 129.97, 127.49, 123.13, 122.09, 117.99, 21.75. HRMS (m/z): $[M + Na]^+$, calcd for $C_{14}H_{13}NNaO_3S$, 298.0508; found, 298.0526.

4-Methyl-*N*-(2-((methylamino)methyl)phenyl)-benzenesulfonamide (4)

Compound **3** (6 g, 21.8 mmol) was dissolved in methanol (600 mL). A 40% solution of methylamine in water (2.5 mL, 28.3 mmol) was added to the methanol solution. The reaction was stirred for 30 min at room temperature and was then chilled to ice–water temperature. Powdered sodium borohydride was added (412 mg, 10.9 mmol) in small portions to the solution over 5 min. After 1 h the excess of borohydride was neutralized with 250 mL of water and the methanol was evaporated under reduced pressure. The remaining water was washed with DCM and the layers were separated. The organic layer was dried over anhydrous Na_2SO_4, the suspension was filtered and the filtrate was evaporated to give an off-white solid (6.22 g, 98%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.63–7.69 (m, 2 H), 7.50 (d, J = 7.8 Hz, 1 H), 7.17–7.25 (m, 3 H), 6.94–7.01 (m, 2 H), 3.47 (s, 2 H), 2.37 (s, 3 H), 2.35 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 143.51, 138.38, 138.12, 129.77, 129.67, 128.70, 128.07, 127.02, 124.14, 121.47, 55.04, 35.62, 21.76. HRMS (m/z): $[M + H]^+$, calcd for $C_{15}H_{19}N_2O_2S$, 291.1162; found, 291.1161.

(*E*)-*N*-Methyl-*N*-(2-((4-methylphenyl)sulfonamido)benzyl)-3-(4-(trifluoromethyl)phenyl)acrylamide (5)

To a solution of 4-(trifluoromethyl)cinnamic acid (162 mg, 0.8 mmol) in anhydrous *N*,*N*-dimethylformamide (DMF, 6 mL), 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]-pyridinium 3-oxid hexafluorophosphate (HATU, 316 mg, 0.8 mmol) was added and the solution was stirred for 10 min at room temperature. Compound **4** (435 mg, 1.5 mmol) was added and the solution was allowed to stir for an additional 20 min, at which point *N*,*N*-diisopropylethylamine (DIPEA, 0.39 mL, 2.3 mmol) was added and the solution was stirred at room temperature overnight. The solution was diluted with 30 mL of diethyl ether and was washed once with water. The organic layer was dried over anhydrous Na_2SO_4, the mixture

was filtered and the filtrate was evaporated to dryness. The solid material was purified on silica gel using a gradient of 3 : 7 EtOAc/hexane to 1 : 1 EtOAc/hexane, producing a white solid (260 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.23 (s, 1 H), 7.86 (d, J = 15.3 Hz, 1 H), 7.50–7.77 (m, 7 H), 7.30 (t, J = 7.1 Hz, 1 H), 7.16 (d, J = 7.5 Hz, 3 H), 7.06 (t, J = 7.5 Hz, 1 H), 6.86 (d, J = 15.3 Hz, 1 H), 4.21 (s, 2 H), 3.08 (s, 3 H), 2.33 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 167.33, 143.51, 143.32, 138.46, 137.57, 136.95, 131.82, 131.58, 129.88, 129.69, 128.43, 128.13, 127.52, 127.33, 126.07, 125.46, 124.71, 123.41, 122.77, 120.04, 118.79, 49.56, 35.24, 21.76. HRMS (m/z): $[M + H]^+$, calcd for $C_{25}H_{24}F_3N_2O_3S$, 489.1454; found, 489.1440.

(*E*)-*N*-(2-((*N*-(2-Hydroxyethyl)-4-methylphenyl)sulfonamido)benzyl)-*N*-methyl-3-(4-(trifluoromethyl)phenyl)acrylamide (6)

2-Iodoethanol (24 μL, 0.3 mmol) and potassium carbonate (70 mg, 0.5 mmol) were added to a solution of compound 5 (100 mg, 0.2 mmol) in *N*,*N*-dimethylformamide (DMF, 2 mL). The solution was heated at 60 °C for 24 h. The mixture was then diluted with 5 mL water and was washed with diethyl ether two times. The organic layer was dried over anhydrous Na_2SO_4, the mixture was filtered and the filtrate was evaporated to dryness. The crude product was purified by silica-gel column chromatography in a gradient of 7 : 3 EtOAc/hexane to 1 : 0 EtOAc/hexane, affording a white solid (66 mg, 62%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.00 (d, J = 8.1 Hz, 1 H), 7.80 (t, J = 8.4 Hz, 2 H), 7.69 (d, J = 8.3 Hz, 1 H), 7.66 (d, J = 7.1 Hz, 0.5 H), 7.63 (d, J = 7.1 Hz, 0.5 H), 7.50–7.58 (m, 2.5 H), 7.41–7.48 (m, 2 H), 7.29–7.39 (m, 1 H), 7.13–7.23 (m, 1.5 H), 7.03–7.13 (m, 1 H), 6.55 (dd, J = 4.2, 7.3 1 H), 5.13–5.19 (m, 0.5 H), 5.04–5.10 (m, 0.5 H), 4.92–5.01 (m, 1 H), 4.80–4.87 (m, 1 H), 3.82–3.96 (m, 1 H), 3.40–3.54 (m, 1 H), 3.26–3.34 (m, 1 H), 3.19–3.26 (m, 1 H), 3.15 (s, 1.5 H), 3.00 (s, 1.5 H) 2.42 (s, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 165.92, 165.89, 143.81, 143.63, 139.92, 139.82, 139.23, 139.00, 137.80, 137.57, 134.68, 134.35, 129.75, 129.70, 128.90, 128.68, 128.41, 127.79, 127.72, 127.67, 127.43, 127.37, 126.68, 125.95, 125.59, 125.56, 121.45, 120.89, 58.76, 58.56, 53.95, 53.76, 49.66, 47.19, 35.28, 34.51, 21.02. HRMS (m/z): $[M + H]^+$, calcd for $C_{27}H_{28}F_3N_2O_4S$, 533.1716; found, 533.1749.

2-Nitrobenzyl methanesulfonate (7)

Methanesulfonyl chloride (12.64 mL, 163.3 mmol) was added to a solution of 2-nitrobenzyl alcohol (20 g, 130.6 mmol) and triethylamine (10 mL, 143.7 mmol) in tetrahydrofuran (THF, 50 mL). The reaction was stirred at room temperature for 2 h, at which time, the solvent was removed by evaporation under reduced pressure. The residue was dissolved in dichloromethane and was washed with water. The organic layer was dried over Na_2SO_4, the mixture was filtered and the filtrate was evaporated to dryness to give a pale-yellow solid (30.08 g, 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.17 (d, J = 8.1 Hz, 1 H), 7.68–7.79 (m, 2 H), 7.53–7.59 (m, 1 H), 5.65 (s, 2 H), 3.12 (d, J = 0.5 Hz, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 147.20, 134.57, 130.37, 129.92, 129.62, 125.53, 68.28, 37.98. HRMS (m/z): $[M + H]^+$, calcd for $C_8H_{13}N_2O_5S$, 249.0540; found, 249.0534.

N-Methyl-1-(2-nitrophenyl)methanamine (8)

Methylamine 40 wt% in water (112 mL, 1294.5 mmol) was added dropwise over half an hour to a solution of compound 7 (30 g, 129.8 mmol) in tetrahydrofuran (THF, 140 mL) at room temperature. TLC analysis showed that the reaction was completed within 2 h. The solvent was evaporated under reduced pressure and the remaining oil was taken up in 100 mL dichloromethane. To this solution were added water (100 mL) and 37% hydrochloric acid until pH 4 was reached. The aqueous fraction was separated and washed with DCM and the organic portion was discarded. Fresh DCM was added to the aqueous solution. The mixture was treated with 10% NaOH until pH 11 was reached. The organic fraction was separated and saved. The water fraction was then washed again with DCM. The combined organic solution was dried over anhydrous Na_2SO_4, the mixture was filtered and the filtrate was evaporated to dryness to give a yellow oil (21.00 g, 98%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.93 (dt, J = 8.1, 1.6 Hz, 1 H), 7.53–7.63 (m, 2 H), 7.36–7.43 (m, 1 H), 3.98 (d, J = 1.5 Hz, 2 H), 2.40–2.48 (m, 3 H), 1.60 (br. s., 1 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 147.28, 135.64, 135.35, 131.46, 128.15, 124.95, 52.99, 36.36. HRMS (m/z): $[M + H]^+$, calcd for $C_8H_{11}N_2O_2$, 167.0815; found, 167.0804.

(*E*)-*N*-Methyl-*N*-(2-nitrobenzyl)-3-(4-(trifluoromethyl)phenyl)acrylamide (9)

To a solution of compound 8 (3.07 g, 23.1 mmol), 4-trifluoromethylcinnamic acid (4.00 g, 23.1 mmol) and HOBt wetted with 14% water (3.75 g, 22.2 mmol) in *N*,*N*-dimethylformamide (100 mL), were added *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC HCl, 4.26 g, 27.8 mmol) and subsequently *N*,*N*-diisopropylethylamine (DIPEA, 8.1 mL, 46.5 mmol). The reaction mixture was allowed to stir at room temperature for 24 h. The *N*,*N*-dimethylformamide was removed *in vacuo* and DCM was added to the residue. The DCM was washed with water, 5% aqueous HCl solution, 5% aqueous NaOH solution and brine. The organic solution was dried over anhydrous Na_2SO_4, the mixture was filtered and the filtrate was evaporated to dryness. The crude was purified by column chromatography on silica gel with elution in 1 : 1 EtOAc/hexane to give a yellowish solid (5.62 g, 67%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.19 (d, J = 7.8 Hz, 0.5 H), 8.05 (d, J = 7.8 Hz, 0.5 H), 7.78 (d, J = 15.2 Hz, 1 H), 7.57–7.74 (m, 3 H), 7.48–7.57 (m, 2 H), 7.43 (t, J = 7.7 Hz, 1 H), 7.36 (d, J = 7.3 Hz, 1 H), 7.07 (d, J = 15.4 Hz, 0.5 H), 6.74 (d, J = 15.4 Hz, 0.5 H), 5.11 (s, 1 H), 5.07 (s, 1 H), 3.22 (s, 1.5 H), 3.11 (s, 1.5 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 167.23, 166.80, 148.82, 147.95, 142.56, 142.31, 138.65, 138.45, 134.80, 134.00, 133.12, 132.92, 131.73, 131.14, 129.30, 129.02, 128.98, 128.74, 128.37, 127.77, 126.06, 125.95, 125.42, 120.85, 119.36, 119.04, 51.74, 49.48, 36.37, 35.27. HRMS (m/z): $[M + H]^+$, calcd for $C_{18}H_{16}F_3N_2O_3$, 365.1108; found, 365.1125.

(*E*)-*N*-(2-Aminobenzyl)-*N*-methyl-3-(4-(trifluoromethyl)phenyl)acrylamide (10)

A 5 M solution of NH_4Cl in water (6.97 mL, 34.9 mmol) was added to a solution of compound **9** (4.00 g, 11.0 mmol) in acetone (75 mL) in a two-neck round-bottom flask. The solution was heated to reflux, and then zinc (3.23 g, 49.4 mmol) was added in small portions through the side neck to maintain a moderate rate of reaction. The reaction mixture was refluxed for 5 h. The solution was brought to room temperature. The solid that formed during the reaction was filtered and discarded. The filtrate was washed with water, and the organic fraction was dried over anhydrous Na_2SO_4. The mixture was filtered and the filtrate was evaporated to give a yellow/orange liquid (2.90 g, 69%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.73 (d, J = 15.4 Hz, 1 H), 7.57–7.67 (m, 4 H), 7.12 (td, J = 7.6, 1.50 Hz, 1 H), 7.08 (dd, J = 7.3, 1.2 Hz, 1 H), 6.96 (m, 1 H), 6.58–6.72 (m, 2 H), 4.63 (s, 4 H), 3.08 (s, 3 H). ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 166.45, 146.47, 141.83, 138.77, 132.11, 131.56, 131.31, 129.73, 128.21, 127.42, 126.05, 126.02, 125.98, 125.95, 125.18, 123.07, 120.91, 119.96, 119.54, 117.24, 115.65, 49.24, 34.53. HRMS (m/z): $[M + H]^+$, calcd for $C_{18}H_{18}F_3N_2O_2$, 335.1366; found, 533.1364.

(*E*)-*N*-(2-((4-Fluorophenyl)sulfonamido)benzyl)-*N*-methyl-3-(4-(trifluoromethyl)phenyl)acrylamide (11)

Pyridine (0.44 ml, 5.4 mmol) was added to a solution of compound **10** (300 mg, 0.9 mmol) in anhydrous DCM (6 mL) under an argon atmosphere. The solution was chilled to ice–water temperature and a solution of *p*-fluorobenzenesulfonyl chloride (350 mg, 1.8 mmol) in anhydrous DCM (3 mL) was added. Another equivalent of the sulfonyl chloride (175 mg, 0.9 mmol) in anhydrous DCM (1.5 mL) was added after 3 h and the reaction was aged for an additional 24 hours. The solution was washed with water, 5% HCl and brine. The organic layer was dried over anhydrous $NaSO_4$, the suspension was filtered and the filtrate was concentrated under reduced pressure to dryness. The residue was purified on silica gel in a gradient of 3 : 7 EtOAc/hexane to 1 : 1 EtOAc/hexane to afford the title compound as a white solid (282 mg, 65%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 10.31 (s, 1 H), 7.88 (s, 1 H), 7.77–7.86 (m, 2 H), 7.57–7.70 (m, 5 H), 7.29–7.38 (m, 1 H), 7.16 (dd, J = 7.4, 1.3 Hz, 1 H), 7.01–7.14 (m, 3 H), 6.75–6.90 (m, 1 H), 3.10 (s, 3 H), 4.18 (s, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 167.42, 166.19, 164.17, 143.55, 138.30, 136.58, 136.54, 136.52, 131.81, 130.03, 129.99, 129.91, 128.40, 127.67, 127.28, 126.11, 126.09, 126.07, 125.11, 125.07, 123.81, 122.95, 120.79, 118.53, 116.35, 116.17, 49.50, 35.27. HRMS (m/z): $[M + H]^+$, calcd for $C_{24}H_{21}F_4N_2O_3S$, 493.1204; found, 493.1219.

(*E*)-*N*-(2-((4-Fluoro-*N*-(2-hydroxyethyl)phenyl)sulfonamido)benzyl)-*N*-methyl-3-(4-(trifluoromethyl)phenyl)acrylamide (12)

2-Iodoethanol (24 μL, 0.3 mmol) and potassium carbonate (70 mg, 0.5 mmol) were added to a solution of compound **11** (100 mg, 0.2 mmol) in *N*,*N*-dimethylformamide (DMF, 2 mL). The solution was stirred at 60 °C for 24 h. The mixture was then diluted with 5 mL water and was washed with diethyl ether (2×). The combined organic layer was dried over anhydrous Na_2SO_4, the mixture was filtered and the filtrate was evaporated to dryness. The crude product was purified by silica-gel column chromatography in a gradient of 7 : 3 EtOAc/hexane to 1 : 0 EtOAc/hexane, affording a white solid (65 mg, 61%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.00 (d, J = 8.1 Hz, 1 H), 7.61–7.85 (m, 6 H), 7.42–7.55 (m, 2.5 H), 7.29–7.42 (m, 1 H), 7.03–7.25 (m, 2.5 H), 6.60 (dd, J = 7.3, 5.1 Hz, 1 H), 5.06–5.24 (m, 1 H), 4.95–5.05 (m, 1 H), 4.79–4.94 (m, 1 H), 3.83–3.99 (m, 1 H), 3.40–3.58 (m, 1 H), 3.23–3.40 (m, 1 H), 3.17 (s, 1.5 H), 3.02 (s, 1.5 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 165.93, 165.89, 163.49, 163.40, 139.98, 139.86, 139.25, 139.18, 139.03, 138.98, 137.51, 137.27, 133.86, 133.83, 133.52, 133.49, 130.93, 130.84, 130.77, 130.67, 129.46, 129.32, 129.11, 129.07, 129.07, 128.70, 128.63, 128.42, 127.89, 127.80, 127.53, 127.49, 126.78, 126.05, 125.61, 125.59, 121.43, 120.84, 116.67, 116.60, 116.43, 116.37, 58.66, 58.47, 54.01, 53.82, 49.63, 47.17, 35.29, 34.52. HRMS (m/z): $[M + H]^+$, calcd for $C_{26}H_{25}F_4N_2O_4S$, 537.1466; found, 537.1444.

(*E*)-*N*-(2-((4-Ethyl-*N*-(2-hydroxyethyl)phenyl)sulfonamido)benzyl)-*N*-methyl-3-(4-(trifluoromethyl)phenyl)acrylamide (13)

This compound was prepared by the same procedure as for **12** and was purified with gradient silica gel column chromatography from 7 : 3 EtOAc/hexane to 1 : 0 EtOAc/hexane, affording a white solid (138 mg, 38%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.99 (d, J = 8.07 Hz, 1 H), 7.79 (t, J = 8.3 Hz, 2 H), 7.69 (d, J = 8.1 Hz, 1 H), 7.60–7.68 (m, 1 H), 7.55 (d, J = 8.31 Hz, 1 H), 7.58 (d, J = 8.1 Hz, 1 H), 7.42–7.52 (m, 2.5 H), 7.29–7.41 (m, 1 H), 7.13–7.25 (m, 2.5 H), 7.03–7.13 (m, 1 H), 6.57 (dd, J = 7.6, 4.1 Hz, 1 H), 5.11–5.24 (m, 0.5 H), 5.01–5.11 (m, 0.5 H), 4.89–5.01 (m, 1 H), 4.72–4.88 (m, 1 H), 3.79–3.95 (m, 1 H), 3.40–3.58 (m, 1 H), 3.19–3.28 (m, 1 H), 3.14 (s, 1.5 H), 2.99 (s, 1.5 H), 2.64–2.78 (m, 2 H), 1.13–1.30 (m, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 165.93, 165.90, 149.79, 149.62, 140.01, 139.87, 139.26, 139.22, 139.20, 139.02, 137.81, 137.58, 134.88, 134.58, 128.95, 128.74, 128.66, 128.60, 128.51, 128.46, 127.96, 127.82, 127.76, 127.43, 126.68, 125.97, 125.65, 125.62, 121.45, 120.85, 58.78, 58.58, 53.96, 53.76, 49.67, 47.20, 35.30, 34.57, 28.03, 15.03. HRMS (m/z): $[M + H]^+$, calcd for $C_{28}H_{30}F_3N_2O_4S$, 547.1873; found, 547.1873.

(*E*)-*N*-(2-((3-Fluoro-*N*-(2-hydroxyethyl)-4-methylphenyl)sulfonamido)benzyl)-*N*-methyl-3-(4-(trifluoromethyl)phenyl)acrylamide (14)

This compound was prepared by the same procedure as for **12** and was purified with gradient silica gel column chromatography from 7 : 3 EtOAc/hexane to 1 : 0 EtOAc/hexane, giving a white solid (78 mg, 56%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.98 (d, J = 7.8 Hz, 1 H), 7.77 (t, J = 8.9 Hz, 2 H), 7.67 (d, J = 8.1 Hz, 1.5 H), 7.63 (m, 1 H), 7.51–7.59 (m, 1 H), 7.45–7.51 (m, 1 H), 7.29–7.45 (m, 3 H), 7.02–7.25 (m, 2.5 H), 6.62 (d, J =

7.6 Hz, 1 H), 5.11–5.22 (m, 0.5 H), 5.02–5.11 (m, 0.5 H), 4.92–5.02 (m, 1 H), 4.71–4.91 (m, 1 H), 3.80–4.03 (m, 1 H), 3.49 (br. s., 1 H), 3.43 (br. s., 1 H), 3.22–3.38 (m, 3 H), 3.15 (s, 1.5 H), 2.99 (s, 1.5 H), 2.33 (s, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 165.95, 165.91, 140.00, 139.90, 139.25, 139.21, 139.01, 137.45, 137.22, 136.76, 136.70, 132.61, 132.55, 130.85, 130.68, 130.51, 129.47, 129.12, 128.74, 128.70, 128.46, 127.89, 127.85, 127.55, 127.51, 126.78, 126.06, 125.65, 125.61, 123.91, 123.88, 123.76, 123.72, 121.43, 120.87, 114.50, 114.37, 114.25, 114.11, 58.69, 58.49, 54.08, 53.88, 49.63, 47.18, 35.30, 34.56, 14.37. HRMS (*m*/*z*): [M + H]$^+$, calcd for $C_{27}H_{27}F_4N_2O_4S$, 511.1622; found, 511.1606.

(*E*)-*N*-(2-(*N*-(2-Hydroxyethyl)phenylsulfonamido)benzyl)-*N*-methyl-3-(4-(trifluoromethyl)phenyl)acrylamide (15)

This compound was prepared by the same procedure as for **12** and was purified with gradient silica gel column chromatography from 7 : 3 EtOAc/hexane to 1 : 0 EtOAc/hexane, affording a white solid (80 mg, 73%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.00 (d, J = 7.6 Hz, 1 H), 7.72–7.87 (m, 3 H), 7.58–7.72 (m, 6 H), 7.44–7.56 (m, 0.5 H), 7.27–7.42 (m, 1 H), 7.02–7.25 (m, 2.5 H), 6.53 (t, J = 6.8 Hz, 1 H), 5.05–5.25 (m, 1 H), 4.93–5.04 (m, 1 H), 4.76–4.92 (m, 1 H), 3.80–4.04 (m, 1 H), 3.52 (br. s., 0.5 H), 3.46 (br. s., 0.5 H), 3.20–3.30 (m, 1.5 H), 3.16 (s, 1 H), 3.01 (s, 1.5 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 165.92, 165.89, 139.95, 139.84, 139.25, 139.02, 138.99, 137.64, 137.46, 137.40, 137.13, 133.40, 133.26, 129.45, 129.32, 129.26, 129.14, 128.96, 128.67, 128.53, 128.40, 127.73, 127.60, 127.45, 127.37, 126.71, 125.98, 125.59, 125.55, 125.51, 125.46, 125.36, 122.75, 122.65, 121.42, 120.85, 58.72, 58.52, 54.04, 53.84, 49.64, 47.18, 35.28, 34.50. HRMS (*m*/*z*): [M + H]$^+$, calcd for $C_{26}H_{26}F_3N_2O_4S$, 519.1560; found, 519.1544.

(*E*)-3-(4-Chlorophenyl)-*N*-(2-((*N*-(2-hydroxyethyl)-4-methylphenyl)sulfonamido)benzyl)-*N*-methylacrylamide (16)

This compound was prepared by the same procedure as for **12** and was purified with gradient silica gel column chromatography from 7 : 3 EtOAc/hexane to 1 : 0 EtOAc/hexane, producing a white solid (190 mg, 69%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.80 (d, J = 8.5 Hz, 1 H), 7.61 (d, J = 8.3 Hz, 1 H), 7.58 (d, J = 6.6 Hz, 0.5 H), 7.55 (d, J = 7.3 Hz, 1.5 H), 7.52 (d, J = 8.3 Hz, 1 H), 7.49 (d, J = 8.6 Hz, 1 H), 7.44 (t, J = 7.7 Hz, 2 H), 7.35–7.41 (m, 1.5 H), 7.29–7.35 (m, 1 H), 7.13–7.23 (m, 1 H), 6.98–7.13 (m, 1.5 H), 6.56 (dd, J = 7.7, 3.1 Hz, 1 H), 5.01–5.16 (m, 1 H), 4.89–5.00 (m, 1 H), 4.73–4.89 (m, 1 H), 3.78–3.96 (m, 1 H), 3.40–3.55 (m, 1 H), 3.19–3.26 (m, 1 H), 3.14 (s, 1.5 H), 2.99 (s, 1.5 H), 2.42 (s, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 166.13, 166.11, 143.84, 143.67, 140.39, 140.32, 139.35, 139.15, 137.77, 137.53, 134.64, 134.35, 134.11, 134.07, 134.03, 133.92, 129.86, 129.81, 129.74, 129.56, 128.93, 128.81, 128.49, 127.82, 127.77, 127.70, 127.38, 126.68, 125.94, 119.26, 118.73, 58.76, 58.55, 53.96, 53.76, 49.63, 47.18, 35.28, 34.55, 21.08. HRMS (*m*/*z*): [M + H]$^+$, calcd for $C_{26}H_{32}N_2O_3S$, 451.2050; found, 451.2068.

(*E*)-3-(4-Chlorophenyl)-*N*-(2-((4-fluoro-*N*-(2-hydroxyethyl)phenyl)sulfonamido)benzyl)-*N*-methylacrylamide (17)

This compound was prepared by the same procedure as for **12** and was purified with gradient silica gel column chromatography from 7 : 3 EtOAc/hexane to 1 : 0 EtOAc/hexane, affording a white solid (142 mg, 39%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.80 (d, J = 7.9 Hz, 1 H), 7.66–7.77 (m, 2 H), 7.53–7.66 (m, 2 H), 7.43–7.53 (m, 3 H), 7.29–7.43 (m, 2.5 H), 7.20 (q, J = 7.5 Hz, 1 H), 6.95–7.15 (m, 1.5 H), 6.48–6.66 (m, 1 H), 5.02–5.22 (m, 1 H), 4.91–5.02 (m, 1 H), 4.74–4.91 (m, 1 H), 3.75–3.99 (m, 1 H), 3.40–3.59 (m, 1 H), 3.21–3.40 (m, 2 H), 3.14 (s, 1.5 H), 3.00 (s, 1.5 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 166.12, 166.09, 140.36, 140.29, 139.31, 139.11, 137.46, 137.22, 134.07, 134.04, 133.89, 133.83, 130.90, 130.81, 130.74, 130.65, 129.80, 129.50, 129.04, 128.78, 128.60, 127.84, 127.44, 126.76, 126.00, 119.24, 118.70, 116.65, 116.58, 116.43, 116.36, 58.64, 58.45, 53.98, 53.81, 49.58, 47.13, 35.26, 34.49. HRMS (*m*/*z*): [M + H]$^+$, calcd for $C_{25}H_{25}ClN_2O_4S$, 503.1202; found, 503.1205.

Conflicts of interest

The authors declare no conflicts of interest.

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