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Chemoselective synthesis of aryl carboxamido sulfonic acid derivatives

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ABSTRACT

A one-pot two-step synthetic strategy for the preparation of aryl carboxamido sulfonic acid derivatives was developed. The synthesis started from *m*-(chlorosulfonyl)benzoyl chloride, which was reacted with amines, alcohols, thiols, or sodium azide and catalytic activator at rt to give the corresponding sulfonic acid derivatives in good yields. The short reaction times and the one-pot chemoselective nature of the procedure diminished undesired side reactions and enhanced the efficiency of the reaction. In cases of electron-donor and electron-deficient substituted carboxanilides, piperidine was successfully incorporated at sulfur to obtain the corresponding sulfonamides in yields of 46% (4-nitroaniline) to nearly quantitative (4-methoxyaniline). The optimized conditions were applied to the preparation of diarylsulfonamides, sulfonic esters, thiosulfonates, and a sulfonyl azide, which are very important and key structures in modern organic synthesis. Furthermore, the method has been successfully used in the preparation of inhibitors of isocitrate dehydrogenase mutants, which are closely related to tumorigenesis.

1. Introduction

Sulfonic acid derivatives are very useful pharmaceutical compounds, exhibiting a wide range of biological activities such as antimicrobial, anti-cancer, anti-inflammatory, and antiviral functions.[1–3] The sulfonamide group is considered a transition-state mimic of peptide hydrolysis and is therefore used in the design of potent and irreversible protease inhibitors.[4] A large number of structurally novel sulfonamide derivatives showed remarkable inhibitory activities against quite significant proteases such as matrix metalloproteases, tumor necrosis factor-α converting enzyme (TACE), and HIV protease, and the resulting loss of protease activity invited research into small molecule treatments for cancer, arthritis, and acquired immunodeficiency syndrome (AIDS).[5] Recently, Hamachi and co-workers described an application of sulfonic esters in site-specific protein labeling and biofunctional imaging.[6–9] The tremendous utility of sulfonylated molecules necessitates their rapid and effective synthesis, particularly with a view to synthesize molecular libraries.

Numerous sulfonamide syntheses have been developed. A one-pot reaction of sulfinic acid salts (prepared by reacting organometallic reagents and sulfur dioxide) with *N*-chlorobenzotriazole can be used to synthesize sulfonamides.[10] Ruano et al. recently reported a one-pot two-step oxidative method to convert methyl sulfinates and a range of amines into the corresponding sulfonamides, using *m*-CPBA.[11] Caddick and co-workers reported a synthesis of sulfonamides from various pyridinium sulfonates using the activating reagent triphenylphosphine ditriflate.[12] The last method provided high yields and tolerated a variety of functional groups.

The sulfonylation of amines with sulfonyl chlorides in the presence of base is one of the most important methods of sulfonamide preparation because of its high efficiency and simplicity.[2,13] However, this method is limited by the formation of undesired disulfonamides and by the hydrolytic decomposition of highly active sulfonyl chlorides.[14] Recently, the direct conversion of a sulfonic acid to a sulfonamide was achieved using 2,4,6-trichloro-1,3,5-triazine to form the reactive sulfonyl chloride intermediate.[15,16] Mersharm and co-workers used copper(II) oxide to efficiently catalyze the transformation of sulfonyl chlorides to sulfonamides and sulfonic esters in the absence of base in good yields.[17] Although the moisture sensitivity, harsh preparative conditions, and disulfonamide side reactions of sulfonyl chlorides considerably restrict their use in sulfonamide syntheses, their high reactivity with primary amines makes them attractive for the development of new, mild, and straightforward synthetic methods.

m-(Chlorosulfonyl)benzoyl chloride (CSBC) bears two highly reactive functional groups, an acyl chloride, and a sulfonyl chloride. It is an ideal building block for the simple bi-directional expansion of the

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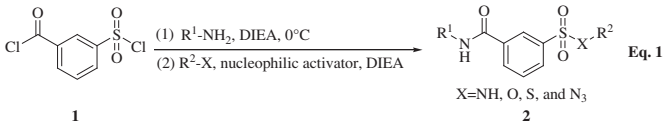
structural complexity of substituted arylsulfonyl compounds (Scheme 1). Owing to the differential reactivities of its acyl and sulfonyl chlorides, CSBC chemoselectively reacts at the more reactive acyl chloride, followed by sulfonyl coupling to give diverse carboxamido sulfonic acid derivatives in two distinct steps.[18] Even though the acyl and sulfonyl chloride groups participate in two sequential coupling reactions for the introduction of different substituents, the high reactivity of each functional group can easily lead to decomposition in the presence of base during the reaction. In addition, the subsequent flash column chromatography leads to the decomposition of unreacted sulfonyl chloride intermediates, and thereby, reduces the reaction yield and contaminates the desired product with byproducts such as sulfonic acids. Furthermore, the reactivity of CSBC with other nucleophiles such as alcohols, thiols, and azides has rarely been assessed. Therefore, a concise synthetic strategy is needed to facilitate the construction of structurally related molecular libraries. This report describes the development of a one-pot two-step strategy for the synthesis of aryl carboxamido sulfonic acid derivatives that is shorter and more efficient than currently known procedures.



1 2

Scheme 1. General scheme for the one-pot synthesis of carboxamido sulfonic acid derivatives.

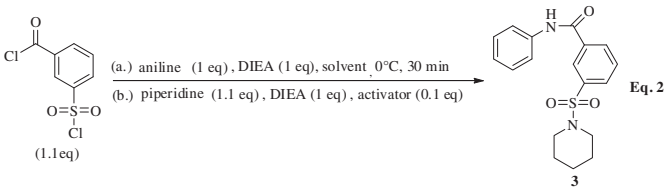
2. Results and discussion

2.1. Optimization of a one-pot, two-step synthesis of carboxamido sulfonamides

Making use of the well-known difference in reactivity between acyl chlorides and sulfonyl chlorides,[18] CSBC **1** was reacted with two different nucleophiles in a one-pot strategy to give the desired, disubstituted products **2** (Scheme 1). In the presence of *N*,*N*-diisopropylethylamine (DIEA), primary amines reacted chemoselectively with the more reactive acid chloride, leaving the sulfonyl chloride untouched. Subsequently, without quenching or work-up processes, the second nucleophile was added, along with a catalytic amount of nucleophilic activator (4-dimethylaminopyridine (DMAP), trimethylamine, or pyridine) and 1 equiv of DIEA. Compared to the one-pot synthesis, disubstituted sulfonamides could also be obtained in two individual steps; however, the average yield of the two-step procedure was generally about 60%.[18] Carboxamido sulfonamides, sulfonic esters, thiosulfonates, and sulfonic azides could also be synthesized using this one-pot strategy.

A variety of solvent/nucleophilic activator combinations were screened to optimize the reaction conditions (Scheme 1 and Table 1). In the model study, aniline (1 equiv) was used as the initial nucleophile to form the amide bond with the highly reactive acid chloride; then, the resulting intermediate was treated with piperidine (1.1 equiv) in the presence of a nucleophilic activator (0.1 equiv) to give the disubstituted product (Eq. 2 in Table 1). Using *N*,*N*-dimethylformamide (DMF) as the reaction solvent resulted in the decomposition of *m*-(chlorosulfonyl)benzoyl chloride (entries 1 and 2).[19] The use of solvents such as dichloromethane (DCM), acetonitrile (ACN), or tetrahydrofuran (THF) overcame this problem. In the preparation of sulfonic esters, the absence of catalytic activator resulted in no distinguishable product formation after 24 h. Referring to Table 1, DMAP in DCM as well as TMA·HCl in THF showed good catalytic ability in the formation of sulfonamide **2**. By contrast, the use of ACN instead of DCM or THF in the presence of different catalysts resulted in lower yields and prolonged reaction times (entries 5 and 6). Therefore, considering organic solubility and reaction efficiency, the use of a catalytic amount of DMAP in dichloromethane promised general applicability in the synthesis of diverse sulfonic acid derivatives.

Table 1
Optimization of reaction conditions for the one-pot synthesis of sulfonamides



3

Entries	Solvent	Activator	Time[a] (h)	Isolated yield (%)
1	DMF	DMAP	—	Decomposed
2	DMF	TMA·HCl	—	Decomposed
3	DCM	DMAP	1	87
4	DCM	TMA·HCl	24	20
5	ACN	DMAP	24	48
6	ACN	TMA·HCl	24	43
7	THF	DMAP	24	67
8	THF	TMA·HCl	1	87

TMA·HCl:trimethylamine hydrochloride.
DIEA: *N*,*N*-diispropylethylamine.
[a] Reaction time in the second step.

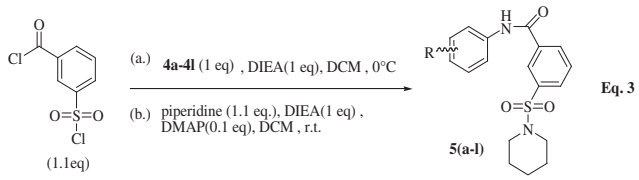
2.2. R^1-group substituent effects in the syntheses of sulfonamides

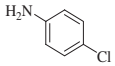
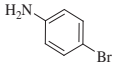
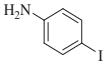
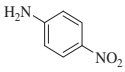
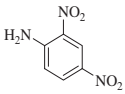
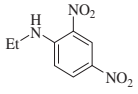
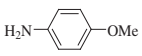
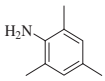
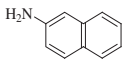
A series of substituted anilines bearing electron-withdrawing and electron-donating groups (**4a**–**4l**, Table 2) were used to examine the reactivity in the first coupling step, after which the corresponding sulfonamides were formed using piperidine. Anilines substituted with chlorine, bromine, or iodine (at the *ortho*, *meta*, and *para* positions in **4a**–**4e**) did not obviously affect the production of the desired products **5a**–**5e**. Despite the presence of electron-withdrawing nitro group, a moderate yield (77%) was obtained with *m*-nitroaniline (**4f**), in which the amino group is apparently less affected by resonance effect. However, in the case of 4-nitroaniline (**4g**), nitro substitution at the *para* position considerably diminished the nucleophilicity of the amino group and thereby lowered the reaction yield (46%, entry 7). In the case of 2,4-dinitroaniline (**4h**), the yield of **5h** after 20 h was 5%. The reaction yield improved to 40% after the addition of a half equivalent of pyridine (entry 8). The secondary amine *N*-ethyl-2,4-dinitroaniline (**4i**) was expected to be more reactive than dinitroaniline **4h** because of the electron-donating nature of the *N*-ethyl group; however, the steric hinderance due to the ethyl group diminished the reactivity of the amine and resulted in no product formation (entry 9). As expected, the yields of 4-methoxyl (**4j**) and 2,4,6-trimethyl (**4k**) substituted anilines were almost quantitative; these findings are rationalized by consideration of the strongly electron-donating group(s) (entries 10 and 11). The fused 2-aminonaphthalene could also serve as a nucleophile in the reaction with **1**, giving a moderate yield (72%, entry 12). The applicability of diverse R^1 substituents in the developed one-pot synthetic strategy greatly expands the structural variability possible in the synthesis of sulfonamides.

2.3. Applicability of the one-pot, two-step preparation for carboxamido sulfonamides, sulfonic esters, thiosulfonates, and a sulfonyl azide

To expand the utility of this method in organic synthesis, the preparation of sulfonamides, sulfonic esters, thiosulfonates, and sulfonyl azides was attempted. In addition to piperidine, primary aliphatic amine **6a** and pyrrolidine **6b** were successfully employed

Table 2
Diversely substituted anilines in the synthesis of sulfonamides **5a**–**5l**



Entries	Substrate (**4a**–**4l**)	Product (**5a**–**5l**)	Isolated yield (%)
1		**5a**	69
2		**5b**	73
3		**5c**	72
4		**5d**	70
5		**5e**	78
6		**5f**	77
7		**5g**	46
8		**5h**	40[a]
9		**5i**	—[b]
10		**5j**	Quant
11		**5k**	90
12		**5l**	72

[a] Pyridine of 0.5 equiv instead of DMAP in the reaction.
[b] No desired product obtained.

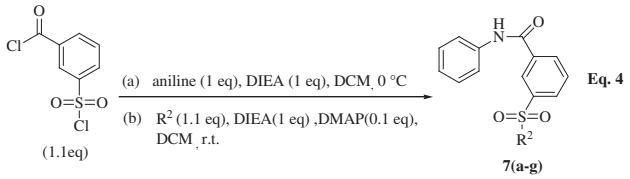
in the preparation of substituted sulfonamides, providing the corresponding sulfonylbenzanilides **7a** and **7b** in excellent yields over two steps (85–90%, entries 1 and 2). Considering the importance of sulfonyl azides as building blocks in organic synthesis,[20–22] the weakly nucleophilic azido group was also successfully employed in the formation of a substituted sulfonyl azide. Sodium azide smoothly produced the benzanilido sulfonyl azide **7c** in 80% yield in the absence of a nucleophilic activator (entry 3).

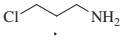
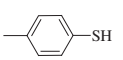
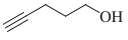
When highly nucleophilic thiols participated in the one-pot synthesis, complete conversion to the newly formed thiosulfonates was observed. But, in the case of thiocresol, the product **7d** was obtained in 48% yield owing to the decomposition during column chromatography (entry 4). When *tert*-butyl thiol **6e** was employed in thiosulfonate formation, the desired product **7e** was obtained in good yield (72%). Oxygen nucleophiles result in sulfonic esters that are valuable intermediates in organic synthesis and show important pharmacological properties.[23] However, the reaction of sulfonyl chlorides with alcohols may result in β-elimination byproducts instead of the sulfonic esters.[24] In order to expand the scope of our method to the synthesis of sulfonic esters from sulfonyl chlorides and alcohols, we investigated the reaction of the sulfonyl chloride with an aliphatic alcohol tether bearing an alkyne functional group. A moderate yield of the product **7f** in the one-pot reaction was obtained (65%). In the presence of 4 Å molecular sieves, the yield of compound **7f** was improved to 80% (entry 6), and similarly, a quantitative yield was obtained for sulfonyl isopropyl ester **7g** (entry 7).

2.4. Preparation of sulfonamide-type inhibitors for isocitrate dehydrogenase mutants

The developed one-pot synthetic strategy provides a new method for the preparation of the sulfonamide-type inhibitors of isocitrate dehydrogenase isoform (IDH) mutants (IDH1m and IDH2m). The association of IDH mutants and their abnormal product D-2-hydroxyglutarate is known to be closely related to tumorigenesis.[25] Sulfonamide analogues **10a**–**10d** (Table 4) were synthesized and their inhibition of IDH1m and IDH2m was further evaluated via in vitro and ex vivo assays. Compounds **10a** and **10b** are known to show the best inhibition activity against IDH1m, giving IC_{50} values below 1 μM[26]

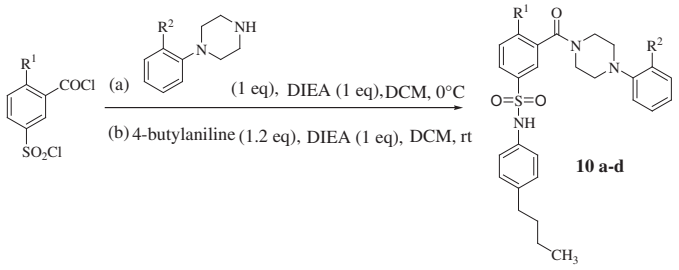
Table 3
One-pot synthesis of diverse benzanilido sulfonic acid derivatives



Entries	Substrate (R^2)	Product (**7a**–**7g**)	Isolated yield (%)
1		**7a**	85
2		**7b**	90
3	NaN_3	**7c**	80[a]
4		**7d**	48[a]
5	$(CH_3)_3C-SH$	**7e**	72[a]
6		**7f**	80[b]
7		**7g**	99[b]

[a] No addition of DMAP.
[b] Addition of 3 equiv in weight of 4 Å molecular sieves at step (b).

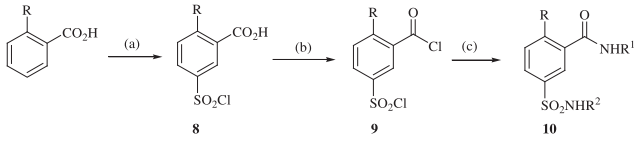
Table 4
Preparation of various sulfonamide inhibitors of IDH mutants



Entries	Substrate (R^1)	Substrate (R^2)	Product (**10a**–**10d**)	Isolated yield (%)
1	Me	OMe	**10a**	66[a]
2	Me	Cl	**10b**	64[a]
3	H	OMe	**10c**	71
4	H	Cl	**10d**	72

[a] Overall yield for the four steps from 2-methyl benzoic acid.

Here, an efficient and concise strategy for the preparation of compound **10** analogues was proposed, as shown in Scheme 2. 5-(Chlorosulfonyl)-2-methylbenzoyl chloride (**9**) can be prepared by the chlorosulfonation of 2-methyl benzoic acid with chlorosulfuric acid and subsequent treatment with $SOCl_2$. Compound **9** was obtained without further purification beyond the removal of excess $SOCl_2$ under reduced pressure. Then, compounds **10a** and **10b** were synthesized conveniently using the developed one-pot method, by sequentially adding the first amine (NH_2R^1) with the second one (NH_2R^2). The one-pot strategy described here afforded increased overall yields (66% (**10a**) and 64% (**10b**) over four steps, Table 4) with a reduced number of steps and reaction times compared to the original sequence for the preparation of these anti-cancer agents.[26] Further, CSBC without methyl substitution was also used to successfully prepare **10c** and **10d** in 71% and 72% yields; these compounds are known to exhibit moderate IDH1m inhibition activity at IC_{50} between 1 and 50 μM[26]



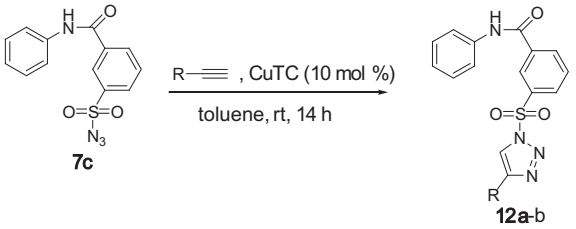
Scheme 2. Preparation of sulfonamide inhibitors. (a) HSO_3Cl, 50 °C, 2 h, 93%; (b) $SOCl_2$, rt, 16 h, 100%; (c) R^1NH_2, R^2NH_2, DIPEA 0 °C to rt for 3 h, 68–70%.

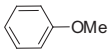
The method proposed here can be easily used to prepare scaffolds that may be utilized in combinatorial chemistry approaches for the preparation of derivatives and chemical libraries of compounds. Such derivatives and compound libraries may display biological activities and be useful for identifying and designing compounds that possess particular activities. It is noteworthy that this strategy can be extended to substituted chlorosulfonyl benzoyl chlorides; no significant change in the reactivity or yield was observed in these transformations.

2.5. Substituted sulfonyl azides in the preparation of sulfonyl triazole derivatives via Cu(I)-catalyzed cycloaddition

To evaluate the utility of the sulfonic acid derivatives obtained by our one-pot strategy in advanced chemical reactions, azido compound **7c** provided a unique opportunity for the preparation of 1,4-sulfonyl triazoles using Cu(I)-catalyzed cycloaddition reactions. These 1,4-sulfonyl triazoles have received significant attention in click chemistry owing to their synthetic versatility. A wide range of functionalized sulfonyl azides can be easily prepared in one-pot using our strategy by employing different nucleophiles in the initial acyl chloride substitution stage, followed by sodium azide in the sulfonyl chloride substitution stage. As shown in Table 5, the sulfonyl azide **7c** (Table 3, entry 3), prepared by the one-pot method, was treated with alkynes to afford the corresponding 1,4-sulfonyl triazoles **12a** and **12b** via Cu(I)-catalyzed cycloaddition in the presence of copper(I) thiophene-2-carboxylate (CuTC) catalyst.[27] The reaction was carefully optimized and gave moderate yields (78% and 87%). The 1,4-sulfonyl triazole products were relatively unstable compared to their nonsulfonylated 1,4-triazole counterparts because of the presence of the strongly electron-withdrawing sulfonyl group. Upon further treatment with Cu catalysts, these sulfonyl triazoles could be converted into various synthetically important compounds such as amides,[21] amidines,[28] and imidates,[29] via nucleophilic attacks on the resultant ketenimine intermediates. Here, the one-pot procedure could provide, with high efficiency, variously substituted sulfonyl azides, which could subsequently be converted to reactive sulfonyl triazoles from different alkynes for advanced chemical transformations.

Table 5
Cu(I)-catalyzed cycloadditions of a benzanilido sulfonyl azide derivative



Entries	Substrate (R)	Product (**12a**–**12c**)	Isolated yield (%)
1		**12a**	78
2		**12b**	87

CuTC: copper(I) thiophene-2-carboxylate.

3. Conclusion

An efficient and convenient one-pot two-step procedure for the synthesis of carboxamido sulfonic acid derivatives was developed. The procedure tolerated various functional groups and obviated purification of highly moisture-sensitive sulfonyl chloride intermediates. Although the electronic and steric characteristics of the participating nucleophiles R^1 and R^2 affected the coupling efficiency, the desired coupling products were obtained in moderate to high yields by using base and a nucleophilic activator. In this study, nucleophilic substitution occurred selectively at the carbonyl group; no products from bis-addition were observed. Furthermore, alcohols, thiols, and sodium azide were also used as nucleophiles to give the corresponding sulfonic esters, thiosulfonates, and sulfonyl azide in good to excellent yields. The developed one-pot method has been demonstrated as a concise and efficient route to prepare bioactive inhibitors of IDH mutants. To evaluate the applicability of this method in expanding the structural complexity of resultant disubstituted sulfonic derivatives, via Cu(I)-catalyzed cycloaddition, the substituted sulfonyl azide **7c** has been used to give important compound **12**, which can be further converted into various

organic compounds. The one-pot synthetic strategy developed here successfully prevented undesired decomposition and side reactions (such as β-elimination) during the synthesis of sulfonic acid derivatives and is expected to be applied in the construction of sulfonic acid-based molecular libraries.

4. Experimental section

4.1. General methods

^{1}H and ^{13}C NMR spectra were acquired at 300 MHz and 75 MHz, respectively (unless other indicated), related to $CDCl_3$ (calibrated at 7.26 ppm in ^{1}H NMR and at 77.0 ppm in ^{13}C NMR) and methanol-d_4 (calibrated at 4.87, 3.31 ppm in ^{1}H NMR and at 49.15 ppm in ^{13}C NMR). Melting points were determined in open capillary tubes. Flash chromatography was performed using silica gel (43–60 μm, Merck).

4.2. Representative procedure for the one-pot synthesis of sulfonamides

The procedure for the preparation of compound **3** is representative for all sulfonamides prepared from *m*-(chlorosulfonyl)benzoyl chloride. Aniline (62.9 mg, 0.675 mmol) was dissolved in CH_2Cl_2 (1 mL), followed by addition of DIEA (117 μL, 0.675 mmol) at 0 °C. Then, *m*-(chlorosulfonyl)benzoyl chloride (113.36 μL, 0.743 mmol) in a solution of CH_2Cl_2 (1 mL) was added to the reaction mixture by syringe, drop-wise. After reacting for 30 min, the ice bath was removed. DIEA (117 μL, 0.675 mmol), DMAP (6.81 mg, 0.0675 mmol), piperidine (66 μL, 0.675 mmol) were added to the solution at 25 °C. The reaction was checked by TLC until the starting material was completely converted to product (1 h). After removal of CH_2Cl_2 under reduced pressure, the crude mixture was purified by column chromatography to obtain the desired product.

4.2.1. Compound ***3***. White solid; mp: 150–151 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.52 (s, 1H), 8.29 (d, *J*=6 Hz, 2H), 7.93 (d, *J*=9 Hz), 7.84–7.77 (m, 3H), 7.38 (t, *J*=6 Hz, 2H), 7.13 (t, *J*=6 Hz, 1H), 2.93 (t, *J*=6 Hz, 4H), 1.58–1.50 (m, 4H), 1.37–1.32 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 164.0, 138.7, 136.0, 135.9, 132.0, 130.1, 129.6, 128.6, 126.4, 124.0, 120.6, 46.6, 24.6, 22.8; HRMS (ESI): calcd for $C_{18}H_{20}N_2O_3S$ $[M-H]^-$: 343.1116, found: 343.1108; IR (neat): 2941, 2853, 1654, 1599, 1541, 1442, 1324, 1668, 932, 579.

4.2.2. Compound ***5a***. White solid; mp: 152 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.49 (dd, *J*=8.1, 0.9 Hz, 1H), 8.43 (s, 1H), 8.28 (s, 1H), 8.12 (d, *J*=7.8 Hz, 1H), 7.96 (d, *J*=8.1 Hz, 1H), 7.70 (t, *J*=7.8 Hz, 1H), 7.43 (dd, *J*=7.9, 0.9 Hz, 1H), 7.35 (td, *J*=8.1, 0.9 Hz, 1H), 7.12 (td, *J*=7.8, 0.9 Hz, 1H), 3.05 (t, *J*=5.4 Hz, 4H), 1.70–1.62 (m, 4H), 1.48–1.40 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.9, 138.1, 135.9, 134.4, 131.1, 130.0, 129.4, 128.2, 126.4, 125.6, 123.6, 122.0, 47.2, 25.4, 23.6; HRMS (ESI): calcd for $C_{18}H_{18}N_2O_3SCl$ $[M-H]^-$: 377.0727, found: 377.0721; IR (CH_2Cl_2): 2941, 2853, 1668, 1480, 1440, 1341, 1313, 1170.

4.2.3. Compound ***5b***. White solid; mp: 150 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.42 (s, 1H), 8.20 (s, 1H), 8.14 (d, *J*=7.8 Hz, 1H), 7.87 (dt, *J*=6, 1.2 Hz, 1H), 7.82 (t, *J*=1.8 Hz, 1H), 7.65 (t, *J*=7.8 Hz, 1H), 7.55 (t, *J*=7.8 Hz, 1H), 7.30 (t, *J*=8.1 Hz, 1H), 7.15 (dd, *J*=7.8, 1.2 Hz, 1H), 2.99 (t, *J*=5.4 Hz, 4H), 1.64–1.56 (m, 4H), 1.45–1.37 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.7, 139.1, 137.3, 136.1, 135.0, 132.3, 130.9, 130.3, 130.1, 125.9, 125.3, 121.0, 118.9, 47.3, 25.3, 23.6; HRMS (ESI): calcd for $C_{18}H_{18}N_2O_3SCl$ $[M-H]^-$: 377.0727, found: 377.0725; IR (CH_2Cl_2): 2924, 2852, 1659, 1482, 1423, 1339, 1314, 1169.

4.2.4. Compound ***5c***. White solid; mp: 142–143 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18 (s, 1H), 8.14 (d, *J*=8.1 Hz, 1H), 8.05 (s, 1H), 7.92 (d, *J*=7.8 Hz, 1H), 7.69 (d, *J*=7.8 Hz, 1H), 7.64 (d, *J*=9 Hz, 3H), 7.36 (d, *J*=9 Hz, 2H), 3.02 (t, *J*=5.4 Hz, 4H), 1.68–1.60 (m, 4H),1.47–1.43 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.6, 137.1, 136.5, 136.1, 132.3, 130.7, 130.2, 129.9, 129.3, 125.9, 122.2, 47.2, 25.3, 23.5; HRMS (ESI): calcd for $C_{18}H_{18}N_2O_3SCl$ $[M]^+$: 377.0727, found: 377.0733.

4.2.5. Compound ***5d***. White solid; mp: 204 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.17 (s, 1H), 8.14 (d, *J*=7.8 Hz, 1H), 8.04 (s, 1H), 7.92 (d, *J*=7.8 Hz, 1H), 7.68 (t, *J*=7.8 Hz, 1H), 7.59 (d, *J*=8.7 Hz, 2H), 7.50 (d, *J*=8.7 Hz, 2H), 3.02 (t, *J*=5.4 Hz, 4H), 1.64 (quin, *J*=5.4 Hz, 1H), 1.43 (quin, *J*=5.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.6, 137.2, 137.0, 136.1, 132.3, 130.7, 130.0, 125.9, 122.4, 117.9, 47.2, 25.3, 23.6; HRMS (ESI): calcd for $[M-H]^-$: 421.0222, found: 421.0215; IR (CH_2Cl_2): 1655, 1591, 1529, 578, 507.

4.2.6. Compound ***5e***. White solid; mp: 206.4 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.58 (s, 1H), 8.27 (d, *J*=9.0 Hz, 2H), 7.94 (d, *J*=7.8 Hz, 1H), 7.80 (t, *J*=7.8 Hz, 1H), 7.72 (d, *J*=8.7 Hz, 2H), 7.62 (d, *J*=8.7 Hz, 2H), 2.93 (t, *J*=5.4 Hz, 4H), 1.55–1.53 (m, 4H), 1.37–1.36 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 164.1, 138.6, 137.3, 136.1, 135.6, 132.0, 130.2, 129.7, 126.3, 122.7, 46.6, 24.6, 22.8; HRMS (ESI): calcd for $[M-H]^-$: 469.0083, found: 469.0083; IR (CH_2Cl_2): 1652, 1601, 1527, 499.

4.2.7. Compound ***5f***. White solid; mp: 143–144 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.93 (s, 1H), 8.78–8.77 (m, 1H), 8.33–8.31 (m, 2H), 8.21 (dd, 1H, *J*=3.0, 6.0 Hz), 8.01–7.96 (m, 2H), 7.87–7.82 (m, 1H), 7.71–8.66 (m, 1H), 2.96–2.92 (t, 4H, *J*=6.0 Hz), 1.59–1.52 (m, 4H), 1.40–1.32 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 164.6, 147.9, 140.0, 136.2, 135.2, 132.2, 130.6, 130.1, 129.8, 126.5, 118.5, 114.7, 47.3, 25.3, 23.6; HRMS (ESI): calcd for $C_{18}H_{19}N_3O_5S$ $[M-H]^-$: 388.0967, found: 388.0958; IR (neat): 3273, 3084, 2922, 2839, 1658, 1598, 1523, 1341, 1168, 576.

4.2.8. Compound ***5g***. Yellow solid; mp: 227–228 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.78 (s, 1H), 8.29–8.18 (m, 4H), 7.96–7.88 (m, 3H), 7.69 (t, 1H, *J*=9 Hz), 2.99 (t, 4H, *J*=6 Hz), 1.66–1.58 (m, 4H), 1.45–1.42 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.8, 144.3, 143.9, 137.4, 135.6, 132.6, 131.2, 130.2, 125.9, 125.3, 120.7; HRMS (ESI): calcd for $C_{18}H_{19}N_3O_5S$ $[M-H]^-$: 388.0967, found: 388.0958; IR (neat): 2923, 2853, 1660, 1531, 1342, 1168, 577.

4.2.9. Compound ***5h***. Yellow solid; mixture, product; ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.71 (s, 1H), 9.277 (d, *J*=9.6 Hz, 1H), 9.22 (d, *J*=2.7 Hz, 1H), 8.58 (dd, *J*=9.3, 2.7 Hz, 1H), 8.56 (d, *J*=2.7 Hz, 1H), 8.38 (s, 1H), 8.05 (d, *J*=7.8 Hz, 1H), 7.776 (t, *J*=7.8 Hz, 1H), 3.085 (t, *J*=5.4 Hz, 4H), 1.685–1.499 (m, 4H), 1.478–1.421 (m, 2H); 2,4-dinitroaniline: ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.115 (d, *J*=2.4 Hz, 1H), 8.22 (dd, *J*=2.7 Hz, 1H), 6.9 (d, *J*=9.3 Hz, 1H): ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.9, 149.7, 149.6, 141.6, 136.4, 132.4, 130.9, 130.0, 129.2, 126.6, 125.9, 121.0, 119.7, 46.6, 24.7, 22.8; 2,4-dinitroaniline: ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.8, 135.1, 128.6, 128.2, 123.3, 119.8; HRMS (ESI): calcd for $C_{18}H_{17}N_4O_7S$ $[M]^+$: 433.0818, found: 433.0813.

4.2.10. Compound ***5j***. White solid; mp: 178.9 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18 (s, 1H), 8.13 (d, *J*=7.8 Hz, 1H), 8.10 (s, 1H), 7.88 (d, *J*=7.8 Hz, 1H), 7.65 (t, *J*=7.8 Hz, 1H), 7.57 (d, *J*=8.6 Hz, 2H), 6.91 (d, *J*=8.9 Hz, 2H), 3.82 (s, 3H), 3.00 (t, *J*=5.3 Hz, 4H), 1.62 (quintet, *J*=5.6 Hz, 4H), 1.47–1.35 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 164.3, 157.1, 137.3, 136.5, 132.0, 130.8, 130.5, 129.8, 125.8, 122.6, 114.5, 55.7, 47.2, 25.3, 23.6; HRMS (ESI): calcd for $C_{19}H_{22}N_2O_4S$ $[M+Na]^+$: 397.1198, found: 397.1181; IR (CH_2Cl_2): 2936, 1633, 1604, 1543, 1508, 1447, 1409, 1339, 1166.

4.2.11. Compound ***5k***. White solid; mp: 153 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.27 (s, 1H), 8.12 (d, *J*=7.8 Hz, 1H), 7.86 (d, *J*=7.8 Hz, 2H),

7.60 (t, *J*=7.8 Hz, 1H), 6.90 (s, 2H), 2.99 (t, *J*=5.1 Hz, 4H), 2.28 (s, 3H), 2.20 (s, 6H), 1.63–1.56 (m, 4H), 1.45–1.38 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.8, 137.2, 137.1, 135.8, 135.4, 131.8, 131.1, 130.2, 129.5, 129.0, 126.3, 47.0, 25.2, 23.4, 21.1, 18.3; HRMS (ESI): calcd for $C_{21}H_{26}N_2O_3S$ $[M-H]^-$: 385.1586, found: 385.1579; IR (CH_2Cl_2): 1574, 1610, 1651.

4.2.12. Compound ***5l***. White solid; mp: 124–126 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.78 (s, 1H, NH), 8.46 (d, *J*=5.7 Hz, 2H), 8.06–7.97 (m, 3H), 7.91–7.83 (m, 2H), 7.66 (d, *J*=6.9 Hz, 1H), 7.61–7.54 (m, 3H), 2.98 (s, 4H), 1.62–1.52 (m, 4H), 1.44–1.34 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 164.8, 136.2, 135.4, 133.8, 133.5, 132.2, 130.3, 129.8, 129.2, 128.1, 126.6, 126.1, 126.1, 125.5, 124.1, 123.3, 46.6, 24.7, 22.8; HRMS (ESI): calcd for $C_{22}H_{21}N_2O_3S$ $[M-H]^-$: 393.1273, found: 393.1274; IR (CH_2Cl_2): 1652, 1599, 1526, 851, 754, 725, 701.

4.3. General procedure for the synthesis of sulfonyl azide, sulfonic esters and thiosulfonates

The procedure for the preparation of compound **7g** is representative for sulfonic acid derivatives prepared from *m*-(chlorosulfonyl)benzoyl chloride. Aniline (244 mg, 2.62 mmol) was dissolved in CH_2Cl_2 (2 mL), followed by addition of DIEA (456 μL, 2.62 mmol) and 4 Å molecular sieves (786 mg) at 0 °C. Then, *m*-(chlorosulfonyl)benzoyl chloride (440 μL, 2.88 mmol) in a solution of CH_2Cl_2 (1 mL) was added to the reaction mixture by syringe, drop-wise. After reacting for 30 min, the ice bath was removed. DIEA (456 μL, 2.62 mmol), DMAP (160 mg, 1.31 mmol), and distillated isopropanol (1000 μL, 13.078 mmol) were added to the solution at 25 °C. The reaction was checked by TLC until the starting material was completely converted to product (12 h). After removal of CH_2Cl_2 under reduced pressure, the crude mixture was purified by column chromatography to obtain the desired product.

4.3.1. Compound ***7a***. White solid; mp: 140–141 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.50 (s, 1H), 8.36 (s, 1H), 8.23 (d, *J*=7.8 Hz, 1H), 7.99 (d, *J*=8.1 Hz, 1H), 7.84 (t, *J*=6 Hz, 1H), 7.78 (m, 3H), 7.37 (t, *J*=7.8 Hz, 2H), 7.12 (t, *J*=7.5 Hz, 1H), 3.62 (t, *J*=6.3 Hz, 2H), 2.91 (q, *J*=6.6 Hz, 2H), 1.83 (q, *J*=6.6 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 164.2, 140.7, 138.8, 135.9, 131.4, 129.6, 129.3, 128.7, 125.9, 124.0, 120.6, 42.3, 32.0; HRMS (ESI): calcd for $C_{16}H_{17}N_2O_3NaSCl$ $[M+Na]^+$: 375.0546, found: 375.0529; IR (neat): 3286, 2924, 1656, 1598, 1496, 1442, 1323.

4.3.2. Compound ***7b***. White solid; mp: 135–136 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.51 (s, 1H), 8.33 (s, 1H), 8.27 (d, *J*=7.8 Hz, 1H), 8.01 (d, *J*=8.1 Hz, 1H), 7.83–7.75 (m, 3H), 7.38 (t, *J*=7.5 Hz, 2H), 7.13 (t, *J*=7.5, 1H), 3.19 (t, *J*=6.6 Hz, 4H), 1.69–1.64 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 164.0, 138.7, 136.7, 135.8, 131.9, 129.9, 129.7, 128.6, 126.2, 124.0, 120.6, 47.8, 24.7. HRMS (ESI): calcd for $C_{17}H_{18}N_2O_3NaS$ $[M+Na]^+$: 353.0936, found: 353.0920; IR (MeOH): 3333, 2958, 1650, 1600, 1538, 1443, 1328, 1198.

4.3.3. Compound ***7c***. White solid; mp: 157–158 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.61 (s, 1H), 8.56 (s, 1H), 8.44 (d, *J*=7.8 Hz, 1H), 8.24 (d, *J*=8.1 Hz, 1H), 7.92 (t, *J*=7.8 Hz, 1H), 7.78 (d, *J*=8.1 Hz, 2H), 7.38 (t, *J*=7.8 Hz, 2H), 7.14 (t, *J*=7.5 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 163.3, 138.6, 137.9, 136.5, 134.5, 130.6, 130.0, 128.7, 126.2, 124.2, 120.7; HRMS (ESI): calcd for $C_{13}H_{10}N_4O_3S$ $[M-H]^-$: 301.0395, found: 301.0396; IR (neat): 2142, 1643, 1440, 1375, 1168.

4.3.4. Compound ***7d***. Syrup; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (s, 1H), 7.79 (s, 1H), 7.67 (d, *J*=7.6 Hz, 1H), 7.64 (d, *J*=7.6 Hz, 1H), 7.58 (d, *J*=8.0 Hz, 2H), 7.38 (t, *J*=7.6 Hz, 2H), 7.36 (d, *J*=8.2 Hz, 2H), 7.34 (t, *J*=8.0 Hz, 1H), 2.30 (s, 3H), 7.09 (d, *J*=8.2 Hz, 2H), 7.14 (t, *J*=7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.93, 138.59, 138.01, 137.86, 135.84, 132.96, 130.56, 129.98, 129.45, 129.07, 128.79, 125.83, 125.72, 124.71, 120.21, 21.04; HRMS (ESI) calcd for $C_{20}H_{17}NO_3S_2$ $[M+H]^+$: 384.0728, found: 383.1179; IR (neat): 3302, 3064, 2925, 2855, 1652, 1601, 1541, 1489, 1445, 1325, 1261, 805, 752, 691.

4.3.5. Compound ***7e***. Syrup; ^{1}H NMR (400 MHz, $CDCl_3$): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H, –NH), 8.37 (s, 1H, Ha), 8.08 (d, *J*=7.7 Hz, 1H, Hd), 8.00 (d, *J*=7.7 Hz, 1H, Hd), 7.63 (d, *J*=7.9 Hz, 2H, Hb), 7.55 (t, *J*=7.9 Hz, 1H, Hc), 7.30 (t, *J*=7.7 Hz, 2H, He), 7.12 (t, *J*=7.7 Hz, 1H, Hf), 1.38 (s, 9H, Hg), ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.97, 147.13, 137.46, 136.18, 132.14, 129.66, 30.74, 129.57, 129.00, 125.10, 124.97, 120.64, 56.02; HRMS (ESI) calcd $C_{17}H_{19}NO_3S_2$ for $[M-H]^-$: 348.0728, found: 348.0720; IR (neat): 3340, 3074, 2971, 1656, 1601, 1546, 1445, 1332, 1264, 1147, 914, 761, 693, 613.

4.3.6. Compound ***7f***. White solid; mp: 121–123 °C; ^{1}H NMR (300 MHz, MeOD): δ 8.42 (s, 1H), 8.23 (d, *J*=7.8 Hz, 1H), 8.06 (d, *J*=7.5 Hz, 1H), 7.74 (t, *J*=8.4, 7.5 Hz, 1H), 7.65 (d, *J*=8.1 Hz, 2H), 7.32 (t, *J*=7.5 Hz, 1H), 7.12 (t, *J*=7.5 Hz, 1H), 4.18 (t, *J*=6.0 Hz, 2H), 2.19 (dt, *J*=2.4, 4.5 Hz, 2H), 2.12 (d, *J*=5.1 Hz, 1H), 1.84–1.74 (m, 2H). ^{13}C NMR (75 MHz, MeOD): δ 166.7, 139.7, 138.2, 137.9, 134.1, 131.9, 131.2, 130.0, 128.4, 126.1, 122.6, 83.1, 71.1, 70.8, 29.1, 15.4; HRMS (ESI): calcd for $C_{18}H_{18}NO_4S$ $[M+H]^+$: 344.0957, found: 344.0948; IR (CH_2Cl_2): 2123, 1652, 1600, 1539, 787, 858, 755, 692.

4.3.7. Compound ***7g***. White solid; mp: 137–138 °C. ^{1}H NMR (300 MHz, CDCl3): δ 8.77 (s, 1H), 8.38 (s, 1H), 8.14 (d, *J*=7.8 Hz, 1H), 8.00 (d, *J*=7.5 Hz, 1H), 7.65 (d, *J*=7.8 Hz, 2H), 7.57 (t, *J*=7.8 Hz, 1H), 7.31 (t, *J*=7.5 Hz, 2H), 7.14 (t, *J*=7.2 Hz, 1H), 4.79–4.70 (m, 4H), 1.23 (d, *J*=6.3 Hz, 6H); ^{13}C NMR (75 MHz, CDCl3): δ 164.4, 138.0, 137.7, 136.3, 132.8, 130.3, 129.8, 129.1, 126.3, 125.1, 121.0, 78.5, 22.8 HRMS (ESI): calcd for $C_{16}H_{17}NO_4S$ $[M-H]^-$: 318.0800, found: 318.0795; IR (CH_2Cl_2): 3301, 2986, 1656, 1540, 1443, 1182, 913.

4.4. General procedure for the synthesis of sulfonamide-type inhibitors

The procedure for the preparation of compound **10a**: to a stirred solution of 5-chlorosulfonyl-2-methyl-benzoylchloride (65 mg; 0.258 mmol) in DCM (1.3 mL) was added DIEA (0.045 mL; 0.258 mmol) followed by 1-(2-methylphenyl) piperazine (49.56 mg) and stirred at 0 °C for 30 min and at rt for 30 min under nitrogen atmosphere. To the reaction mixture was added 4-butylaniline (46.16 mg; 0.309 mmol) followed by DIEA (0.045 mL; 0.258 mmol) and stirred for 2 h at rt under nitrogen atmosphere. TLC indicated completion of the reaction. The reaction mixture was diluted with DCM (20 mL), washed with H_2O (2×5 mL), dried over $MgSO_4$, filtered, and concentrated to afford the crude compound, which was purified by silica gel flash column chromatography using 20–25% ethyl acetate in hexane as an eluent to afford the desired product as a syrup (95.16 mg; 70.8%).

4.4.1. Compound ***10a***. Syrup; ^{1}H NMR (300 MHz, MeOD): δ 7.73 (d, *J*=8.1 Hz, 1H), 7.49 (s, 1H), 7.41 (d, *J*=8.1 Hz, 1H), 7.18–6.88 (m, 8H), 3.91–3.85 (m, 5H), 3.31–3.04 (m, 4H), 2.79–2.75 (m, 2H), 2.42 (t, *J*=36, 2H), 2.32 (s, 3H), 1.51–1.41 (m, 2H), 1.30–1.20 (m, 2H), 0.84 (t, *J*=14.7, 3H); ^{13}C NMR (75 MHz, MeOD): δ 170.09, 153.91, 141.69, 141.25, 141.02, 138.72, 137.39, 136.23, 132.56, 130.11, 128.93, 125.88, 125.14, 122.99, 122.22, 119.95, 112.93, 56.10, 52.40, 51.69, 43.01, 35.88, 34.71, 23.28, 19.24, 14.24; HRMS (ESI) calcd for $C_{29}H_{36}N_3O_4S$ $[M+H]^+$: 522.2431, found: 522.2427.

4.4.2. Compound ***10b***. Syrup; ^{1}H NMR (300 MHz, MeOD): δ 7.78 (d, *J*=6.6 Hz, 1H), 7.77 (s, 1H), 7.52–7.39 (m, 2H), 7.30 (t, *J*=14.4, 1H), 7.15–7.02 (m, 6H), 3.94–3.92 (m, 2H), 3.14–3.09 (m, 4H),

2.80 (m, 2H), 2.44 (t, J=29.7, 2H), 2.37 (s, 3H), 1.54–1.43 (m, 2H), 1.33–1.23 (m, 2H), 0.87 (t, J=14.4, 3H); ^{13}C NMR (75 MHz, MeOD): δ 170.17, 149.88, 141.24, 140.99, 138.74, 137.36, 136.26, 132.59, 131.63, 130.08, 129.05, 128.91, 125.90, 125.70, 122.97, 122.14, 52.91, 49.59, 43.12, 35.89, 34.69, 23.33, 19.25, 14.22; HRMS (ESI) calcd for $C_{30}H_{31}N_3O_3SCl$ $[M+Na]^+$: 548.1775, found: 548.1712.

4.4.3. Compound ***10c****.* Syrup; ^{1}H NMR (300 MHz, MeOD): δ 7.91 (d, J=7.5 Hz, 1H), 7.74 (s, 1H), 7.67–7.59 (m, 2H), 7.09–6.91 (m, 8H), 3.88 (m, 5H), 3.31 (m, 2H), 3.08 (m, 2H), 2.88–2.86 (m, 2H), 2.48 (t, J=15.3, 2H), 1.55–1.48 (m, 2H), 1.34–1.24 (m, 2H), 0.88 (t, J=14.4, 3H); ^{13}C NMR (75 MHz, MeOD): δ 170.37, 153.88, 141.62, 141.35, 141.15, 137.44, 136.14, 132.45, 130.88, 130.15, 129.56, 126.65, 125.14, 123.14, 122.23, 119.92, 112.95, 56.11, 52.26, 51.67, 43.55, 35.90, 34.71, 23.29, 14.26; HRMS (ESI) calcd for $C_{28}H_{34}N_3O_4S$ $[M+H]^+$: 508.2270, found: 508.2276.

4.4.4. Compound ***10d****.* Syrup; ^{1}H NMR (300 MHz, MeOD): δ 7.93 (d, J=1.8 Hz, 1H), 7.90 (s, 1H), 7.71–7.64 (m, 2H), 7.41 (d, J=7.8 Hz, 1H), 7.34 (t, J=14.4, 1H), 7.30–6.99 (m, 5H), 3.91 (br, 2H), 3.34–3.33 (m, 4H), 3.01 (br, 2H), 2.85 (b, 2H), 2.47 (t, J=15.6 Hz, 2H), 1.54–1.34 (m, 2H), 1.31–1.21 (m, 2H), 0.87 (t, J=14.7 Hz, 3H); ^{13}C NMR (75 MHz, MeOD): δ 170.52, 149.92, 141.33, 141.17, 137.41, 136.14, 132.43, 131.61, 130.91, 130.10, 130.02, 129.54, 129.02, 126.59, 125.66, 123.13, 122.12, 52.68, 51.98, 43.70, 35.89, 34.68, 23.30, 14.17; HRMS (ESI) calcd for $C_{27}H_{29}N_3O_3SCl$ $[M-H]^+$: 510.1618, found: 510.1626.

4.5. General procedure for the synthesis of 1,4-triazoles

The procedure for the preparation of compound **11a**: to a stirred solution of phenyl acetylene (25.33 mg; 0.248 mmol) in toluene (0.82 mL) was added CuTC (3.14 mg; 0.0165 mmol) and stirred for 10 min at rt. To the resultant mixture was added compound **7c** (50 mg, 0.165 mmol) and stirred for 14 h at rt. The progress of the reaction was monitored by TLC. The reaction mixture was diluted with ethyl acetate (25 mL), stirred with cuprisorb resin (100 mg) for 30 min to remove Cu, filtered, washed with H_2O (2×5 mL), dried over anhyd $MgSO_4$, filtered, and concentrated to afford the desired product as a syrup (53 mg; 79.3%).

4.5.1. Compound ***12a****.* Syrup; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.63 (s, 1H), 8.36 (s, 1H), 8.31–8.26 (m, 2H), 8.13 (s, 1H), 7.82 (d, J=4.2 Hz, 2H), 7.75 (t, J=9.6 Hz, 1H), 7.64 (d, J=4.8 Hz, 2H), 7.46–7.38 (m, 5H), 7.20 (t, J=9.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.97, 147.69, 137.17, 136.99, 136.80, 134.62, 131.37, 130.61, 129.35, 129.21, 129.06, 128.43, 126.89, 126.12, 125.32, 120.60, 119.10 HRMS (ESI) calcd for $C_{21}H_{16}N4O_3S$ $[M+Na]^+$: 427.0841, found: 427.0835.

4.5.2. Compound ***12b****.* Syrup; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.62 (s, 1H), 8.31–8.27 (m, 3H), 8.08 (s, 1H), 7.76–7.73 (m, 3H), 7.64 (d, J=4.5 Hz, 2H), 7.40 (t, J=9.0 Hz, 2H), 7.20 (t, J=8.7 Hz, 1H), 6.96 (d, J=5.1 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 162.97, 160.46, 137.17, 136.96, 136.93, 134.56, 131.33, 130.59, 129.21, 127.51, 126.81, 125.31, 121.01, 120.58, 118.10, 114.47, 55.35 HRMS (ESI) calcd for $C_{22}H_{18}N_4O_4S$ $[M+Na]^+$: 457.0946, found: 457.0941.

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Supplementary data

^{1}H NMR and ^{13}C NMR of compounds. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.01.028.

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