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Transition-Metal-Free Regioselective One-Pot Synthesis of Aryl Sulfones from Sodium Sulfinates via Quinone Imine Ketal

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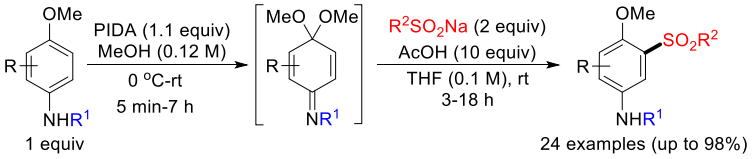
ABSTRACT: A novel, efficient and regioselective transition-metal-free one-pot synthesis of aryl sulfones via the reactive quinone imine ketal intermediate is demonstrated using easily accessible bench-stable sulfinate salts. A broad range of functionality on *p*-anisidine substrates as well as sulfinate salts was tolerated under the mild reaction condition to provide the corresponding aryl sulfones in good to excellent yields.



INTRODUCTION

Organosulfones are recognized as privileged functional groups having an immense application in agrochemicals,[1] pharmaceuticals[2] and material chemistry.[3] Among them, aryl sulfones are known to be antifungal,[4] antibacterial[5] and antitumoral[6] agents as well as the inhibitors of HIV-1 reverse transcriptase.[7] Figure 1 shows selected biologically active molecules featuring

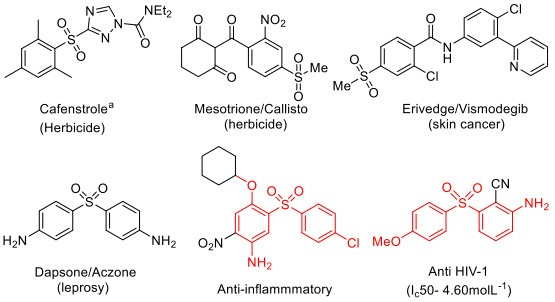
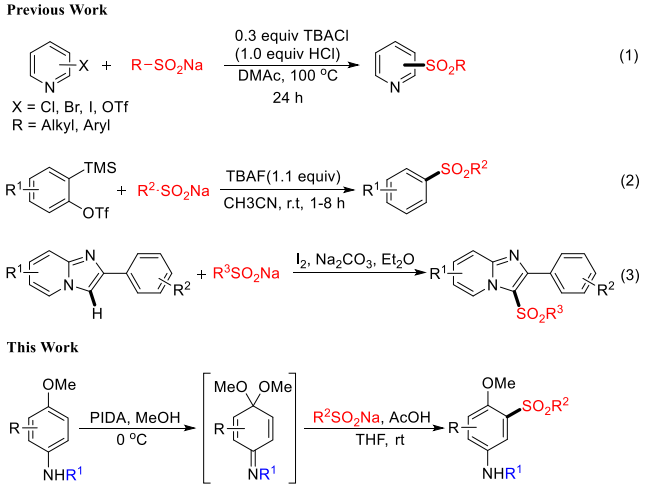


Figure 1. Bioactive compounds containing sulfone[1,2,7]
[a]*J. Agric. Food Chem.* **2006**, *54*, 7724. Copyright [2006] American Chemical Society.

aryl sulfone pharmacophore.[1,2,7] In addition to their medicinal importance, aryl sulfones are also versatile reactive intermediates in organic synthesis and used in well-known organic transformations such as the Ramberg–Backlund reaction and the Julia olefination.[8] In the past decades, tremendous efforts have been devoted to the development of novel methodologies for the incorporation of sulfone-containing substituents into organic frameworks.[9] Due to their compelling synthetic utility[8] and substantial biological[1,2,4-7] as well as material applications,[3] the development of facile methods for aryl sulfones has stimulated considerable interest.

The most common method utilizes the reaction of pre-functionalized aromatic/heteroaromatic halides and sulfinate salts in the presence of a transition-metal catalyst.[9c,g,i] Recently, Peddinti et al reported catalyst-free sulfonylation of 2-methoxyphenols via masked *o*-benzoquinone using sulfonyl hydrazides at 70 °C.[9f] Zeng et al developed electrochemical oxidation of aminophenols in the presence of benzenesulfinate.[9j] Previously, Kolesnikov and co-workers reported sulfonylation of *N*-(arylthio)-1,4-benzoquinonimines with benzenesulfininate to obtain various aryl sulfones.[9k] In 2011, Maloney and co-workers developed the transition-metal-free sulfonylation of pyridines using sulfinate salts (Scheme 1, eq. 1).[10] In 2014, we reported the method for the synthesis of aryl sulfones using *in situ* generated arynes (eq. 2).[11] Very recently, Shao and co-workers reported the difunctionalization of imidazo[1,2-a]-pyridine to access sulfones using sulfinate salts (eq.

Scheme 1. Selected Transition-Metal-Free approaches to Aryl Sulfones using Sodium Sulfinates



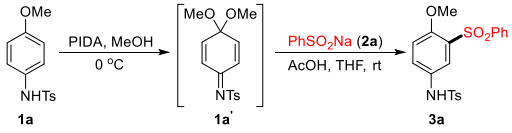
3).[12] In addition to these advancements few other transition-metal-free methods using sodium sulfinate salts had been developed for the synthesis of organosulfones,[13] but to the best of our knowledge quinone imine ketal (QIK) has not been utilized for the synthesis of aryl sulfones.

QIK has emerged as the powerful synthetic intermediate for the development of novel methodologies[14] and total synthesis of natural products.[15] Their remarkable electrophilicity addresses a variety of organic transformation such as cycloaddition reaction,[14h] nucleophilic addition reaction,[14a,b,d-g] multicomponent reaction,[14c] among others. We hypothesized that the QIK formed *in situ* in the reaction mixture could be utilized as a latent sulfone functionalized aromatic ring employing acid-mediated activation. This design will ultimately enrich the chemistry of quinone-related compounds. Herein, we report the mild and efficient protocol for the synthesis of aryl sulfones utilizing QIK as a potent intermediate.

RESULTS AND DISCUSSION

The optimization of the protocol was achieved by changing various reaction parameters. Initially, *N*-tosyl QIK **1a'** generated *in situ* from *N*-tosyl *p*-anisidine (**1a**) in methanol was treated with sulfinate salt (1.1 equiv) and AcOH (10 equiv) at rt. The expected product **3a** was obtained in 32% yield in 12 h (Table 1, entry 1). To our delight, the yield improved substantially and the reaction time also reduced to 6 h when THF was used as the solvent for the second step (entry 2). The addition of less or more equivalents of AcOH resulted into low yields (entries 3-7). For further improvement in the yield, more equivalents of sulfinate salt was used, however, the yield did not improve (entry 8). Hence, the addition sequence of the second step was modified. The solution of QIK **1a'** and sulfinate salt **2a** in THF was stirred for 1 h followed by the addition of acetic acid, which resulted in the enhancement of the yield (entry 9). When 2 equiv of **2a** was used, the desired

Table 1: Optimization of Reaction Condition[a]



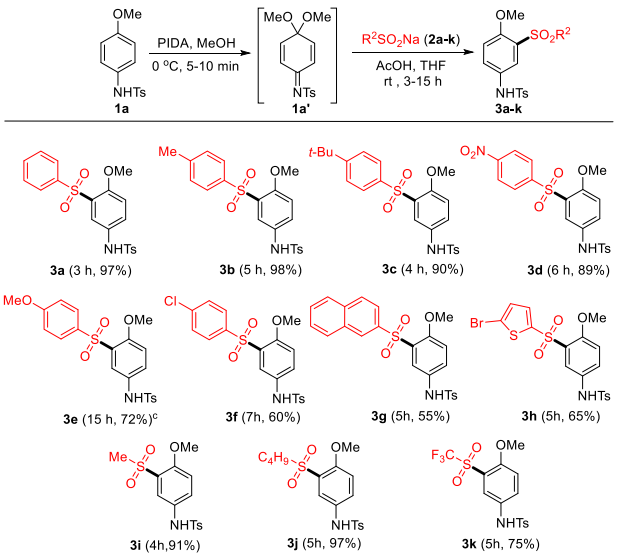
entry	solvent[b]	AcOH (equiv)	**2a** (equiv)	time (h)	yield (%)[c]
1	MeOH	10	1.1	12	32
2	THF	10	1.1	06	83
3	THF	01	1.1	12	52
4	THF	02	1.1	12	55
5	THF	08	1.1	12	60
6	THF	15	1.1	06	50
7	THF	20	1.1	06	48
8	THF	10	2.0	03	84
9[d]	THF	10	1.5	06	90
10[d]	THF	10	2.0	03	97

[a]All the reactions were performed on 20 mg scale of **1a**, [b]Solvent for the second step, [c]Isolated yield, [d]Acetic acid was added after 1 h to the reaction mixture containing sulfinate salt.

product **3a** was obtained in excellent yield (entry 10).

With the optimized reaction condition (Table 1, entry 10) in hand, we investigated the substrate scope of this newly developed protocol by reacting different sulfinate salts **2a-k** with **1a** (Scheme 2). The optimized condition worked well for a variety of aryl, alkyl and heteroaryl sulfinate salts. Unsubstituted as well as alkyl substituted aryl sulfone moiety-containing compounds **3a**, **3b** and **3c** were formed in excellent yields. The aryl sulfinate containing an electron withdrawing substituent furnished the corresponding sulfone **3d** in excellent

Scheme 2: Synthesis of Sulfones from Various Sodium Sulfinates[a,b]



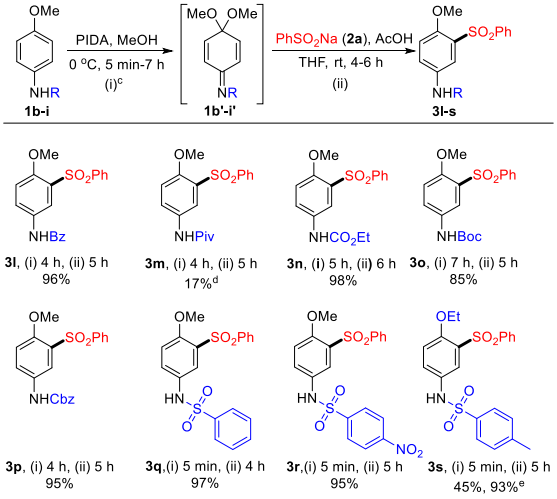
[a]Reaction was performed on 50 mg scale of **1a**, [b]Isolated yield, [c]Reaction carried out at 60 °C.

yield under the optimized condition. On the other hand, probably due to the electron releasing effect of the methoxy group, aryl sulfinate **2e** needed little extra time and temperature than anticipated to obtain the product **3e** in better yield. The halo substituted sulfinate salt showed similar effect on the reaction and the desired product **3f** was formed in moderate yield. The polyaromatic sulfinate salt reacted well and conceded the product **3g** in moderate yield. The sulfinate salt having the heteroaromatic ring also underwent the reaction smoothly to provide the product **3h** in good yield. Overall, the reaction of sulfinate salts having electron rich aromatic ring (**2e-h**) was slower and provided lower yields as compared to the aryl sulfinate salts having electron neutral/deficient aromatic ring (**2a-d**). Pleasingly, aliphatic sulfinate salts also reacted well under the developed protocol and the corresponding sulfones **3i** and **3j** were synthesized in excellent yields. Trifluoromethyl substituted sulfone **3k** was synthesized in very good yield under these conditions.

After exploring the reactivity pattern of various sulfinate salts, we further planned to explore the scope of the reaction using variously substituted *p*-anisidines (Scheme 3 and 4). Various *N*-substituents, as well as *O*-substituents on *p*-anisidines (**1b-i**) were tested under the developed protocol.

The *in situ* formation of QIKs (**1b'-f'**) from the corresponding amide and carbamate containing substrates (**1b-f**) required addition of triethylamine and more time as compared to the sulfonamide containing substrates (**1g-i**). The benzoate protected *p*-anisidine **1b** provided the product **3l** in an excellent

Scheme 3: Synthesis of Sulfones from Various *N, O*-Substituted *p*-Anisidines[a,b]

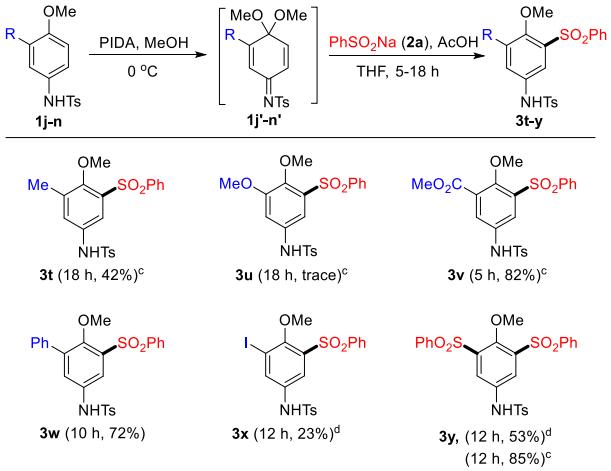


[a]Reaction was performed on 50 mg scale of **1b**,**d-i**, [b]Isolated yield, [c]Triethylamine (3 eqiv) was used for the preparation of QIK **1b'-f'**, [d]Reaction was performed on 100 mg scale of **1c**, [e]Reaction carried out at 60 °C.

yield. Whereas, pivaloyl protected *p*-anisidine **1c** furnished sulfone **3m** in low yield. It can be reasoned that the steric hindrance of the bulkier pivaloyl moiety present in the close proximity of the amide nitrogen resists the reaction with PIDA. the The carbamate group-containing substrates **1d**, **1e**, and **1f** provided the desired products **3n**, **3o,** and **3p** respectively in very good yields. Various sulfonamide containing sulfones **3q** and **3r** were synthesized in excellent yields. The scope of the protocol was also tested using ethoxy substituted sulfonamide substrate **1i** and the expected product **3s** was formed in a moderate yield under the optimized protocol. The steric hindrance of the ethyl group might be inhibiting the nucleophilic attack of the sulfinate salt at rt. However, the yield of **3s** was significantly increased to 93% by elevating the reaction temperature.

The scope of the reaction using various substituents on the aryl ring of *p*-anisidines was also studied (Scheme 4). It has been observed that higher temperature was necessary for the reaction with methyl substituted *p*-anisidine to obtain the sulfone **3t** in moderate yield. Unfortunately, electron donating substituents on *p*-anisidine did not afford the sulfone **3u** under the developed protocol. Hence, we isolated the corresponding QIK **1k'** and performed the next reaction, but the product **3u** was formed in only trace amount. We were unable to isolate sufficient quantity of the product **3u** by usual flash column chromatography, but HRMS analysis showed the product formation. Electron withdrawing group on *p*-anisidine moiety was well tolerated and the product **3v** was obtained in very good yield at little higher temperature. The phenyl substituted compound **3w** was formed in a good yield. Interestingly, from the substrate **1n** containing iodine group, two different products **3x** and **3y** were formed under the optimized conditions, but at high temperature exclusively disulfone **3y** was formed

Scheme 4: Synthesis of Sulfones using Various Aryl Ring-Substituted *p*-Anisidines[a,b]



[a]Reaction was performed on 50 mg scale of **1j-m**, [b]Isolated yield, [c]Reaction at 60 °C, [d]Reaction was performed on 100 mg scale of **1n**.

in good yield. The product **3y** may be formed by the displacement of iodine group. In general, substituted *p*-anisidines resulted in inferior yields (Scheme 4) than that of the unsubstitued *p*-anisidnes (Scheme 2 and 3) because the reaction leads to more substituted aromatic ring. Furthermore, the presence of electron rich substituents on *p*-anisidines (**1j**, **1k**) provided lower yields (**3t**, **3u**) due to less electrophilic QIK intermediates, whereas *p*-anisidines having electron withdrawing substituents (**1l**, **1m and 1n**) provided better yields (**3v**, **3w** and **3x,y**) because of the more electrophilic QIK intermeidates.

The regioselectivity of the interesting protocol was confirmed by the 2D NMR analysis of the substrates **3a**, **3v**, **3x** and **3y**. The scalability of the reaction was also investigated. We performed the reaction of **1a** on 1 mmol scale, and the expected product **3a** was obtained in 88% yield.

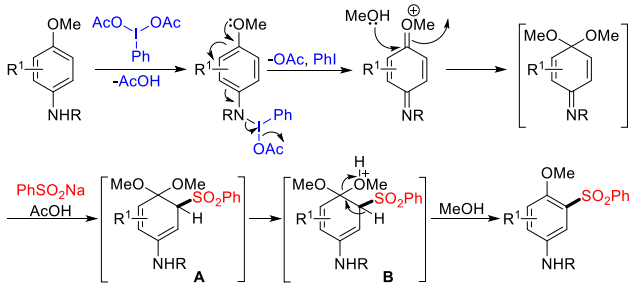


Figure 2. Plausible Reaction Mechanism

A plausible mechanism of the reaction based on the above observations and literature report[16] is depicted in Figure 2. First, the QIK was formed in the presence of PIDA by the usual mechanism.[17] Phenyl sulfinate attacks QIK to form the intermediate **[A]** by Michael addition. The rearomatization occurs by the removal of methanol in the presence of acetic acid to get the desired sulfone product.

CONCLUSION

In conclusion, a convenient one-pot transition-metal-free protocol has been developed for the preparation of aryl sulfones regioselectively via the formation of QIKs in good to excellent yields. This developed protocol is operationally simple, high yielding and does not require excess reagent and additives. Various types of sulfones such as diaryl sulfones, aryl-alkyl sulfones, and aryl-heteroaryl sulfones can be prepared easily by following this method. We are in the process of applying this method for the synthesis of bioactive molecules, natural products, drugs, and drug intermediates.

EXPERIMENTAL SECTION

General Considerations. All reagents and solvents were used as received from commercial sources unless and otherwise noted. All experiments were carried out in a round bottom flask equipped with a stirring bar. Aluminium plates precoated with silica gel 60 PF254, 0.25 mm or 0.5 mm, were utilized for thin-layer chromatography (TLC) to monitor the progress of a reaction. Visualization of the developed TLC plate was performed by irradiation with UV light. Column chromatographic purifications were carried out on flash silica gel (240−400 mesh) using ethyl acetate and petroleum ether as eluents. The ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded on 200/400/500 MHz and 100/125 MHz NMR spectrometers respectively, in $CDCl_3$ or DMSO-d_6. Chemical shifts were reported as δ values from standard peaks. The melting points were recorded on a Buchi instrument, and are uncorrected. High-resolution mass spectrometry (HRMS) was performed on a TOF/Q-TOF mass spectrometer. All the N-substituted *p*-anisidines were prepared using known literature procedures.[14f, 18] The quinone imine ketals were prepared in situ as per the literature procedures.[14f, 17a] Sodium sulfinates **2a**, **2i** and **2k** were purchased from commercial sources and rest of the sodium sulfinates were prepared using known literature procedures.[13e, 19]

Experimental Procedures:

I] General Experimental Procedure for the Synthesis of Sulfones:

A] Synthesis of Sulfones 3a-k:

To a solution of tosylated *p*-anisidine **1a** (50 mg, 1 equiv) in methanol (0.12 M) was added (diacetoxyiodo)benzene (PIDA, 64 mg, 1.1 equiv) at 0 ^{o}C. The resulting mixture was stirred at 0 ^{o}C and the reaction progress was monitored by TLC (approx. 5 min). After complete consumption of **1a**, MeOH was evaporated on a rotatory evaporator and the residue was dissolved in THF (0.1 M). To this solution was added the corresponding sulfinate salt **2a-k** (2 equiv) and the reaction mixture was stirred for 1 h at room temperature followed by the addition of AcOH (10 equiv). After stirring for 3-15 h at room temperature, THF was evaporated in *vacuo* and the residue was purified by flash silica gel column chromatography using a gradient of ethyl acetate-petroleum ether to afford the corresponding sulfones **3a-k** in good to excellent yields.

B] Synthesis of Sulfones 3l-p:

To a solution of *N*-substituted *p*-anisidine **1b-f** (50 mg, 1 equiv) and NEt_3 (3 equiv) in MeOH (0.34 M), a solution of PIDA (2 equiv) in MeOH (0.34 M) was added dropwise at 0 °C under an argon atmosphere. The reaction mixture was stirred at 0 °C for 1 h and gradually warmed to rt. After complete consumption of **1b-f**, MeOH was evaporated on a rotatory evaporator and the residue was dissolved in THF (0.1 M). To the resulting solution was added sulfinate salt **2a** (2 equiv) and the reaction mixture was stirred for 1 h at room temperature followed by the addition of AcOH (10 equiv). After being stirred for 4-6 h at room temperature, THF was evaporated on a rotatory evaporator and the residue was purified by flash silica gel column chromatography using a gradient of ethyl acetate-petroleum ether to afford the corresponding sulfones **3l-p** in good to excellent yields.

C] Synthesis of Sulfones 3q-y:

To a solution of *N*-substituted *p*-anisidine **1g-n** (50 mg, 1 equiv) in methanol (0.12 M) was added PIDA (1.1 equiv) at 0 ^{o}C. The resulting mixture was stirred at 0 ^{o}C and the reaction progress was monitored by TLC (approx. 5 min). After complete consumption of **1g-n**, MeOH was evaporated on a rotatory evaporator and the residue was dissolved in THF (0.1 M). To this solution was added sulfinate salt **2a** (2 equiv) and the reaction mixture was stirred for 1 h at room temperature followed by the addition of AcOH (10 equiv). After stirring for 4-18 h at room temperature, THF was evaporated in *vacuo* and the residue was purified by flash silica gel column chromatography using a gradient of ethyl acetate-petroleum ether to afford the corresponding sulfones **3q-y** in good to excellent yields.

II] Typical Experimental Procedure for the Preparation of 3a on 0.18 mmol scale:

To a solution of **1a** (50 mg, 1 equiv) in methanol (1.5 mL, 0.12 M) was added PIDA (64 mg, 1.1 equiv) at 0 ^{o}C. The resulting mixture was stirred at 0 ^{o}C and the reaction progress was monitored by TLC (approx. 5 min). After complete consumption of **1a**, MeOH was evaporated on a rotatory evaporator and the residue was dissolved in THF (1.8 mL, 0.1 M). To this solution was added **2a** (59 mg, 2 equiv) and the reaction mixture was stirred for 1 h at room temperature followed by the addition of AcOH (108 μL, 10 equiv). After stirring for 3 h at room temperature, THF was evaporated in *vacuo* and the residue was purified by flash silica gel column chromatography using a gradient of ethyl acetate-petroleum ether (2:3) to afford the sulfone **3a** in 97% yield (73 mg).

III] Experimental Procedure for the Preparation of 3a on 1 mmol scale:

To a solution of **1a** (277 mg, 1 mmol) in methanol (8.3 mL, 0.12 M) was added PIDA (354 mg, 1.1 mmol) at 0 ^{o}C. The resulting mixture was stirred at 0 ^{o}C and the reaction progress was monitored by TLC (approx. 5 min). After complete consumption of **1a**, MeOH was evaporated on a rotatory evaporator and the residue was dissolved in THF (10 mL, 0.1 M). To this solution was added **2a** (328 mg, 2 mmol) and the reaction mixture was stirred for 1 h at room temperature followed by the addition of AcOH (600 μL, 10 mmol). After stirring for 3 h at room temperature, THF was evaporated in *vacuo* and the residue was purified by flash silica gel column chromatography using a gradient of ethyl acetate-petroleum ether (2:3) to afford the sulfone **3a** in 88% yield (367 mg).

*N-(4-Methoxy-3-(phenylsulfonyl)phenyl)-4-methylbenzenesulfonamide (**3a**).* Obtained as an off white solid, (73 mg, 97% yield); Mp = 190-192 ^{o}C; **Reaction time:** 3 h;

Rf: 0.5 (2:3 EtOAc:Pet. Ether); **^{1}H NMR (400 MHz, DMSO-d_6)** δ 10.21 (s, 1H), 7.76-7.66 (m, 4H), 7.59 (d, J = 7.9 Hz, 4H), 7.41-7.30 (m, 3H), 7.06 (d, J = 9.2 Hz, 1H), 3.64 (s, 3H), 2.37 (s, 3H); **^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6)** δ 153.6, 143.4, 140.5, 136.0, 133.5, 130.4, 129.7, 129.2, 129.0, 128.2, 127.7, 126.8, 121.9, 114.4, 56.2, 20.9; **HRMS** (ESI-TOF) m/z: [M+Na]+ calcd for $C_{20}H_{19}NO_5S_2Na$ 440.0597, found 440.0594.

*N-(4-Methoxy-3-tosylphenyl)-4-methylbenzenesulfonamide (**3b**)*. Obtained as a white solid, (76 mg, 98% yield); Mp = 191-193 ^{o}C; **Reaction time:** 5 h; Rf: 0.7 (2:3 EtOAc:Pet. Ether); **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.73 (d, J = 7.9 Hz, 2H), 7.63-7.55 (m, 3H), 7.51 (dd, J = 8.6 and 2.4 Hz, 1H), 7.31-7.23 (m, 4H), 6.84 (d, J = 9.2 Hz, 1H), 6.71 (s, 1H), 3.74 (s, 3H), 2.43 (s, 6H); **^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$)** δ 155.0, 144.2 (2C), 137.8, 135.5, 131.0, 129.8, 129.5, 129.2 (2C), 128.5, 127.3, 124.6, 113.4, 56.2, 21.6; **HRMS** (ESI-TOF) m/z: [M+Na]+ calcd for $C_{21}H_{21}NO_5S_2Na$ 454.0753, found 454.0751.

*N-(3-((4-(tert-Butyl)phenyl)sulfonyl)-4-methoxyphenyl)-4-methylbenzenesulfonamide (**3c**)*. Obtained as a white solid, (77 mg, 90% yield); Mp = 176-178 ^{o}C; **Reaction time:** 4 h; Rf: 0.6 (2:3 EtOAc:Pet. Ether); **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.77 (d, J = 8.6 Hz, 2H), 7.64-7.57 (m, 3H), 7.53-7.45 (m, 3H), 7.25 (d, J = 8.5 Hz, 2H), 6.87 (s, 1H), 6.84 (d, J = 9.2 Hz, 1H), 3.76 (s, 3H), 2.42 (s, 3H), 1.33 (s, 9H); **^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$)** δ 157.1, 155.0, 144.1, 137.7, 135.5, 130.8, 129.8, 129.4, 129.2, 128.3, 127.3, 125.5, 124.6, 113.4, 56.2, 35.2, 31.0, 21.6; **HRMS** (ESI-TOF) m/z: [M+Na]+ calcd for $C_{24}H_{27}NO_5S_2Na$ 496.1223, found 496.1222.

*N-(4-Methoxy-3-((4-nitrophenyl)sulfonyl)phenyl)-4-methylbenzenesulfonamide (**3d**)*. Obtained as a pale yellow solid, (74 mg, 89% yield); Mp = 171-173 ^{o}C; **Reaction time:** 6 h; Rf: 0.5 (2:3 EtOAc:Pet. Ether); **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.32 (d, J = 6.7 Hz, 2H), 8.05 (d, J = 7.3 Hz, 2H), 7.72 (s, 1H), 7.65 (d, J = 7.3 Hz, 2H), 7.52 (d, J = 8.6 Hz, 1H), 7.28 (d, J = 6.1 Hz, 2H), 7.19 (s, 1H), 6.87 (d, J = 8.6 Hz, 1H), 3.76 (s, 3H), 2.44 (s, 3H); **^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$)** δ 154.8, 150.4, 146.4, 144.4, 135.4, 131.4, 129.8, 129.7 (2C), 127.6, 127.3, 124.4, 123.8, 113.5, 56.3, 21.6; **HRMS** (ESI-TOF) m/z: [M+Na]+ calcd for $C_{20}H_{18}N_2O_7S_2Na$ 485.0448, found 485.0445.

*N-(4-Methoxy-3-((4-methoxyphenyl)sulfonyl)phenyl)-4-methylbenzenesulfonamide (**3e**)*. Obtained as a white solid, (58 mg, 72% yield (at 60 ^{o}C); Mp = 178-180 ^{o}C; **Reaction time:** 15 h; Rf: 0.4 (1:1 EtOAc:Pet. Ether); **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.79 (d, J = 8.5 Hz, 2H), 7.64-7.56 (m, 3H), 7.50 (dd, J = 8.5 and 2.4 Hz, 1H), 7.25 (d, J = 7.9 Hz, 2H), 6.94 (d, J = 8.5 Hz, 2H), 6.83 (d, J = 8.6 Hz, 1H), 6.75 (s, 1H), 3.87 (s, 3H), 3.76 (s, 3H), 2.43 (s, 3H); **^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$)** δ 163.4, 154.9, 144.1, 135.6, 132.3, 130.7 (2C), 129.9, 129.8, 129.2, 127.3, 124.4, 113.7, 113.4, 56.2, 55.6, 21.6; **HRMS** (ESI-TOF) m/z: [M+Na]+ calcd for $C_{21}H_{21}NO_6S_2Na$ 470.0702, found 470.0699.

*N-(3-((4-Chlorophenyl)sulfonyl)-4-methoxyphenyl)-4-methylbenzenesulfonamide (**3f**)*. Obtained as a white solid, (49 mg, 60% yield); Mp = 186-188 ^{o}C; **Reaction time:** 7 h; Rf: 0.4 (2:3 EtOAc:Pet. Ether); **^{1}H NMR (500 MHz, CDCl$_3$)** δ 7.81 (d, J = 8.8 Hz, 2H), 7.66-7.61 (m, 3H), 7.54 (dd, J = 8.8 and 2.3 Hz, 1H), 7.47 (d, J = 8.4 Hz, 2H), 7.32-7.25 (m, 2H), 6.90 (s, 1H), 6.87 (d, J = 8.8 Hz, 1H), 3.77 (s, 3H), 2.45 (s, 3H); **^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$)** δ 154.9, 144.2, 139.9, 139.2, 135.6, 131.1, 129.9, 129.8, 129.4, 128.9, 128.8, 127.3, 124.5, 113.4, 56.2, 21.6; **HRMS** (ESI-TOF) m/z: [M+H]+ calcd for $C_{20}H_{19}ClNO_5S_2$ 452.0388, found 452.0383.

*N-(4-Methoxy-3-(naphthalen-2-ylsulfonyl)phenyl)-4-methylbenzenesulfonamide (**3g**)*. Obtained as a white solid, (46 mg, 55% yield); Mp = 168-170 ^{o}C; **Reaction time:** 5 h; Rf: 0.5 (2:3 EtOAc:Pet. Ether); **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.55 (s, 1H), 7.99 (d, J = 7.9 Hz, 1H), 7.91 (d, J = 6.1 Hz, 2H), 7.81-7.74 (m, 2H), 7.71-7.60 (m, 4H), 7.52 (dd, J = 9.2 and 3.1 Hz, 1H), 7.27 (t, J = 8.2 Hz, 2H), 7.14 (s, 1H), 6.82 (d, J = 8.5 Hz, 1H), 3.71 (s, 3H), 2.43 (s, 3H); **^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$)** δ 154.9, 144.1, 137.6, 135.5, 135.0, 131.9, 130.8, 130.2, 129.7, 129.4, 129.3, 129.1, 129.0, 128.6, 127.8, 127.4, 127.3, 124.5, 123.2, 113.4, 56.2, 21.6; **HRMS** (ESI-TOF) m/z: [M+Na]+ calcd for $C_{24}H_{21}NO_5S_2Na$: 490.0753, found: 490.0751.

*N-(3-((5-Bromothiophen-2-yl)sulfonyl)-4-methoxyphenyl)-4-methylbenzenesulfonamide (**3h**)*. Obtained as an off white solid, (59 mg, 65% yield); Mp = 177-179 ^{o}C; **Reaction time:** 5 h; Rf: 0.5 (1:1 EtOAc:Pet. Ether); **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.61-7.51 (m, 4H), 7.46 (s, 1H), 7.26 (d, J = 7.9 Hz, 2H), 7.05 (s, 1H), 6.93 (d, J = 8.5 Hz, 1H), 6.64 (s, 1H), 3.92 (s, 3H), 2.43 (s, 3H); **^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$)** δ 155.1, 144.3, 142.5, 135.4, 134.5, 131.4, 130.2, 129.9, 129.4, 129.1, 127.3, 124.3, 122.0, 113.5, 56.3, 21.6; **HRMS** (ESI-TOF) m/z: [M+Na]+ calcd for $C_{18}H_{16}{}^{81}BrNO_5S_3Na$ 525.9246, found 525.9241.

*N-(4-Methoxy-3-(methylsulfonyl)phenyl)-4-methylbenzenesulfonamide (**3i**)*. Obtained as a white solid, (58 mg, 91% yield); Mp = 206-208 ^{o}C; **Reaction time:** 4 h; Rf: 0.5 (1:1 EtOAc:Pet. Ether); **^{1}H NMR (400 MHz, DMSO-d_6)** δ 10.24 (s, 1H), 7.59 (d, J = 7.9 Hz, 2H), 7.54 (d, J = 2.4 Hz, 1H), 7.37-7.32 (m, 3H), 7.19 (d, J = 8.5 Hz, 1H), 3.86 (s, 3H), 3.18 (s, 3H), 2.33 (s, 3H); **^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6)** δ 153.6, 143.4, 136.2, 130.4, 129.8, 128.5, 128.0, 126.7, 121.3, 114.1, 56.5, 42.5, 21.0; **HRMS** (ESI-TOF) m/z: [M+Na]+ calcd for $C_{15}H_{17}NO_5S_2Na$ 378.0440, found 378.0439.

*N-(3-(Butylsulfonyl)-4-methoxyphenyl)-4-methylbenzenesulfonamide (**3j**)*. Obtained as a white solid, (69 mg, 97% yield); Mp = 134-136 ^{o}C; **Reaction time:** 5 h; Rf: 0.5 (2:3 EtOAc:Pet. Ether); **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.65-7.57 (m, 3H), 7.43 (d, J = 3.1 Hz, 1H), 7.22 (d, J = 7.9 Hz, 2H), 7.03 (s, 1H), 6.98 (d, J = 8.5 Hz, 1H), 3.94 (s, 3H), 3.29 (t, J = 7.9 Hz, 2H), 2.38 (s, 3H), 1.54 (m, 2H), 1.37 (m, 2H), 0.88 (t, J = 7.3 Hz, 3H); **^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$)** δ 155.0, 144.1, 135.6, 130.3, 129.8, 129.7, 127.3, 127.0, 124.8, 113.3, 56.6, 53.9, 24.4, 21.5, 21.4, 13.5; **HRMS** (ESI-TOF) m/z: [M+H]+ calcd for $C_{18}H_{24}NO_5S_2$ 398.1090, found 398.1085.

*N-(4-Methoxy-3-((trifluoromethyl)sulfonyl)phenyl)-4-methylbenzenesulfonamide (**3k**)*. Obtained as a white solid, (55 mg, 75% yield); Mp = 112-114 ^{o}C; **Reaction time:** 5 h; Rf: 0.5 (2:3 EtOAc:Pet. Ether); **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.61 (s, 1H), 7.87 (d, J = 9.8 Hz, 1H), 7.75 (d, J = 8.3 Hz, 2H), 7.28 (m, 4H), 3.81 (s, 3H), 2.40 (s, 3H); **^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$)** δ 155.7, 144.8, 135.6, 133.1, 129.9, 127.4, 125.6, 122.3, 119.6 (q, J = 326.0 Hz, CF3), 117.4, 115.7, 56.0,

21.6; **HRMS** (ESI-TOF) m/z: [M+H]+ calcd for $C_{15}H_{15}F_3NO_5S_2$ 410.0338, found 410.0334.

*N-(4-Methoxy-3-(phenylsulfonyl)phenyl)benzamide (**3l**)*. Obtained as a white solid, (78 mg, 96% yield); Mp = 176-178 °C; **Reaction time**: 5 h; R*f*: 0.5 (2:3 EtOAc:Pet. Ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.85 (s, 1H), 8.37 (dd, *J* = 8.5 and 1.8 Hz, 1H), 8.26 (d, *J* = 2.4 Hz, 1H), 7.94 (d, *J* = 7.9 Hz, 2H), 7.87 (d, *J* = 7.3 Hz, 2H), 7.56 (t, *J* = 7.3 Hz, 1H), 7.50-7.40 (m, 3H), 7.31 (t, *J* = 7.6 Hz, 2H), 6.91 (d, *J* = 9.2 Hz, 1H), 3.72 (s, 3H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ (one aromatic carbon overlaps): 166.1, 153.4, 140.9, 134.2, 133.1, 131.8, 131.7, 128.5, 128.5, 128.4, 128.3, 127.2, 121.7, 113.2, 56.2; **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{20}H_{18}NO_4S$ 368.0951, found 368.0946.

*N-(4-Methoxy-3-(phenylsulfonyl)phenyl)pivalamide (**3m**)*. Obtained as a white solid, (28 mg, 17% yield); Mp = 129-131 °C; **Reaction time**: 5 h; R*f*: 0.6 (2:3 EtOAc:Pet. Ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.14 (dd, *J* = 8.3 and 2.3 Hz, 1H), 8.00 (d, *J* = 2.3 Hz, 1H), 7.96 (d, *J* = 7.5 Hz, 2H), 7.65 (s, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 1H), 3.72 (s, 3H), 1.30 (s, 9H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 177.0, 153.5, 141.1, 133.1, 131.4, 128.6, 128.5, 128.3, 128.2, 121.7, 113.2, 56.2, 39.5, 27.5; **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{18}H_{22}NO_4S$ 348.1264, found 348.1260.

*Ethyl (4-methoxy-3-(phenylsulfonyl)phenyl)carbamate (**3n**)*. Obtained as a white solid, (84 mg, 98% yield); Mp = 141-143 °C; **Reaction time**: 6 h; R*f*: 0.4 (2:3 EtOAc:Pet. Ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.98-7.95 (m, 3H), 7.84 (bs, 1H), 7.60-7.55 (m, 1H), 7.51-7.45 (m, 2H), 6.93 (s, 1H), 6.87 (d, *J* = 9.2 Hz, 1H), 4.22 (q, *J* = 7.6 Hz, 2H), 3.72 (s, 3H), 1.29 (t, *J* = 7.6 Hz, 3H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 153.9, 153.0, 141.1, 133.0, 131.3, 128.9, 128.5, 128.4, 126.4, 120.5, 113.4, 61.4, 56.2, 14.5; **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{16}H_{18}NO_5S$ 336.0900, found 336.0897.

*tert-Butyl (4-methoxy-3-(phenylsulfonyl)phenyl)carbamate (**3o**)*. Obtained as a white solid, (69 mg, 85% yield); Mp = 182-184 °C; **Reaction time**: 5 h; R*f*: 0.6 (2:3 EtOAc:Pet. Ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.97 (d, *J* = 7.3 Hz, 3H), 7.81 (bs, 1H), 7.57 (t, *J* = 7.3 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 1H), 6.74 (s, 1H), 3.71 (s, 3H), 1.51 (s, 9H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 152.9, 152.8, 141.3, 133.0, 131.8, 129.1, 128.5, 128.4, 126.2, 120.5, 113.4, 80.9, 56.2, 28.3; **HRMS** (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{18}H_{21}NO_5SNa$ 386.1033, found 386.1031.

*Benzyl (4-methoxy-3-(phenylsulfonyl)phenyl)carbamate (**3p**)*. Obtained as a white solid, (73 mg, 95% yield); Mp = 170-172 °C; **Reaction time**: 5 h; R*f*: 0.6 (2:3 EtOAc:Pet. Ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.00-7.91 (m, 3H), 7.85 (bs, 1H), 7.57 (t, *J* = 7.3 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 2H), 7.41-7.29 (m, 5H), 7.00 (s, 1H), 6.86 (d, 9.2 Hz, 1H), 5.20 (s, 2H), 3.72 (s, 3H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 153.6, 153.1, 141.0, 135.9, 133.0, 131.1, 129.0, 128.6, 128.5, 128.4, 128.3, 128.2, 126.4, 120.6, 113.4, 67.1, 56.2; **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{21}H_{20}NO_5S$ 398.1057, found 398.1053.

*N-(4-Methoxy-3-(phenylsulfonyl)phenyl)benzenesulfonamide (**3q**)*. Obtained as a white solid, (74 mg, 97% yield); Mp = 173-175 °C; **Reaction time**: 4 h; R*f*: 0.5 (2:3 EtOAc:Pet. Ether); **^{1}H NMR (400 MHz, DMSO-d_6)** δ 10.28 (s, 1H), 7.72-7.62 (m, 7H), 7.61-7.52 (m, 4H), 7.35 (dd, *J* = 8.5 and 1.8 Hz, 1H), 7.06 (d, *J* = 9.2 Hz, 1H), 3.64 (s, 3H); **^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6)** δ 153.8, 140.5, 138.8, 133.6, 133.1, 130.2, 129.6, 129.3, 129.0, 128.3, 127.8, 126.8, 122.3, 114.4, 56.2; **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{19}H_{18}NO_5S_2$ 404.0621, found 404.0616.

*N-(4-Methoxy-3-(phenylsulfonyl)phenyl)-4-nitrobenzenesulfonamide (**3r**)*. Obtained as a pale yellow solid, (69 mg, 95% yield); Mp = 183-185 °C; **Reaction time**: 5 h; R*f*: 0.5 (1:1 EtOAc:Pet. Ether); **^{1}H NMR (400 MHz, DMSO-d_6)** δ 10.64 (s, 1H), 8.41 (d, *J* = 9.2 Hz, 2H), 7.95 (d, *J* = 8.4 Hz, 2H), 7.75 (d, *J* = 6.9 Hz, 2H), 7.72-7.63 (m, 2H), 7.56 (t, *J* = 7.6 Hz, 2H), 7.37 (dd, *J* = 9.2 and 3.1 Hz, 1H), 7.10 (d, *J* = 9.2 Hz, 1H), 3.66 (s, 3H); **^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6)** δ 154.2, 150.0, 144.2, 140.4, 133.7, 130.0, 129.4, 129.0, 128.5, 128.4, 127.9, 124.7, 122.7, 114.6, 56.3; **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{19}H_{17}N_2O_7S_2$ 449.0472, found 449.0466.

*N-(4-Ethoxy-3-(phenylsulfonyl)phenyl)-4-methylbenzenesulfonamide (**3s**)*. Obtained as a white solid, [33 mg, 45% yield (at rt); 69 mg, 93% yield (at 60 °C)]; Mp = 168-170 °C; **Reaction time**: 5 h; R*f*: 0.5 (2:3 EtOAc:Pet. Ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.84 (d, *J* = 7.3 Hz, 2H), 7.66-7.56 (m, 4H), 7.53-7.43 (m, 3H), 7.25 (d, *J* = 7.9 Hz, 2H), 6.94 (s, 1H), 6.80 (d, *J* = 9.2 Hz, 1H), 3.94 (q, *J* = 7.3 Hz, 2H), 2.42 (s, 3H), 1.28 (t, *J* = 7.3 Hz, 3H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 154.4, 144.1, 140.8, 135.5, 133.1, 131.1, 129.7, 129.0, 128.8, 128.6, 128.4, 127.3, 124.6, 113.9, 65.0, 21.6, 14.2; **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{21}H_{22}NO_5S_2$ 432.0934, found 432.0928.

*N-(4-Methoxy-3-methyl-5-(phenylsulfonyl)phenyl)-4-methylbenzenesulfonamide (**3t**)*. Obtained as a white solid, [31 mg, 42% yield (at 60 °C)]; Mp = 169-171 °C; **Reaction time**: 18 h; R*f*: 0.6 (2:3 EtOAc:Pet. Ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.83 (d, *J* = 7.6 Hz, 2H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.53 (d, *J* = 3.1 Hz, 1H), 7.47 (t, *J* = 8.1 Hz, 2H), 7.35 (d, *J* = 2.3 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 3H), 3.78 (s, 3H), 2.42 (s, 3H), 2.20 (s, 3H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 153.8, 144.2, 141.2, 135.7, 135.1, 134.9, 133.2, 132.5, 130.7, 129.8, 128.7, 127.9, 127.3, 120.2, 61.8, 21.6, 16.2; **HRMS** (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{21}H_{21}NO_5S_2Na$ 454.0753, found 454.0754.

*N-(3,4-Dimethoxy-5-(phenylsulfonyl)phenyl)-4-methylbenzenesulfonamide (**3u**)*. **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{21}H_{21}NO_6S_2Na$ 470.0702, found 470.0697.

*Methyl 2-methoxy-5-(4-methylphenylsulfonamido)-3-(phenylsulfonyl)benzoate (**3v**)*. Obtained as a white solid, [58 mg, 82% yield (at 60 °C)]; Mp = 172-174 °C; **Reaction time**: 5 h; R*f*: 0.4 (1:49 Acetone:DCM); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.96 (s, 2H), 7.84 (d, *J* = 7.6 Hz, 2H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.62-7.55 (m, 2H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.26 (d, *J* = 7.6 Hz, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 2.41 (s, 3H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 164.3, 155.5, 144.5, 140.6, 136.9, 135.4, 133.6, 132.6, 130.1, 129.9, 128.9, 128.1, 127.4, 126.6, 125.9, 64.1, 52.8, 21.6; **HRMS** (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{22}H_{21}NO_7S_2Na$ 498.0652, found 498.0655.

*N-(6-Methoxy-5-(phenylsulfonyl)-[1,1'-biphenyl]-3-yl)-4-methylbenzenesulfonamide (**3w**)*. Obtained as a white solid, (50 mg, 72% yield); Mp = 128-130 °C; **Reaction time**: 10 h;

R*f*: 0.4 (2:3 EtOAc:Pet. Ether); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.82 (d, *J* = 7.6 Hz, 2H), 7.64 (d, *J* = 7.6 Hz, 3H), 7.52 (t, *J* = 7.3 Hz, 1H), 7.44-7.39 (m, 3H), 7.28 (s, 6H), 7.19 (d, *J* = 8.4 Hz, 2H), 3.09 (s, 3H), 2.34 (s, 3H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 152.9, 144.3, 141.2, 137.4, 136.0, 135.7, 135.6, 133.3, 132.6, 130.3, 129.8, 128.8, 128.6, 128.6, 128.3, 128.1, 127.4, 121.2, 61.2, 21.6; **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{26}H_{24}NO_5S_2$ 494.1090, found 494.1085.

*N-(3-Iodo-4-methoxy-5-(phenylsulfonyl)phenyl)-4-methylbenzenesulfonamide (**3x**).* Obtained as a white solid, (31 mg, 23% yield); Mp = 185-187 ^{o}C; **Reaction time**: 12 h; R*f*: 0.4 (1:4 EtOAc:Pet. Ether); **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.89 (d, *J* = 2.7 Hz, 1H), 7.84 (d, *J* = 7.3 Hz, 2H), 7.73-7.68 (m, 3H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.36 (s, 1H), 7.29 (d, *J* = 8.4 Hz, 2H), 3.94 (s, 3H), 2.43 (s, 3H); **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 154.8, 144.6, 140.5, 137.6, 136.0, 135.5, 134.2, 133.7, 130.0, 128.9, 128.1, 127.4, 122.4, 93.7, 63.1, 21.6; **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{20}H_{19}INO_5S_2$ 543.9744, found 543.9751.

*N-(4-Methoxy-3,5-bis(phenylsulfonyl)phenyl)-4-methylbenzenesulfonamide (**3y**).* Obtained as a white solid (73 mg, 53% yield (at rt); 59 mg, 85% yield (at 60 ^{o}C from 50 mg **1n**)); Mp = 223-225 ^{o}C; **Reaction time**: 12 h; R*f*: 0.2 (1:4 EtOAc:Pet. Ether); **^{1}H NMR (500 MHz, DMSO-d_6)** δ 10.98 (s, 1H), 7.98 (s, 2H), 7.64 (t, *J* = 7.6 Hz, 4H), 7.57 (d, *J* = 8.0 Hz, 4H), 7.47 (t, *J* = 7.6 Hz, 4H), 7.40 (d, *J* = 8.0 Hz, 2H), 3.89 (s, 3H), 2.36 (s, 3H); **^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6)** δ 151.5, 144.2, 139.8, 137.7, 135.4, 135.0, 134.1, 130.0, 129.2, 127.1, 126.8, 125.4, 66.6, 21.0; **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{26}H_{24}NO_7S_3$ 558.0709, found 558.0707.

*4-Methyl-N-(3,4,4-trimethoxycyclohexa-2,5-dien-1-ylidene)benzenesulfonamide (**1k'**)*[20]. Obtained as a pale yellow solid (54 mg, 98% yield) as a mixture of trans and cis-isomer in 1.8:1 ratio; Mp = 115-117 ^{o}C; **Reaction time**: 5 min; R*f*: 0.3 (2:3 EtOAc:Pet. Ether); **^{1}H NMR (200 MHz, DMSO-d_6)** δ 7.81 (d, *J* = 7.83 Hz, 2H), 7.43 (d, *J* = 8.2 Hz, 2.4H), 6.91 (d, *J* = 10.5 Hz, 0.4H), 6.81 (d, *J* = 10.1 Hz, 0.6H), 6.63 (s, 0.6H), 6.37 (dd, *J* = 8.8 and 1.4 Hz, 0.6 H), 5.78 (s, 0.3H), 3.86 (s, 1.9H), 3.81 (s, 1H), 3.21 (s, 6H), 2.4 (s, 3H); **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{16}H_{20}NO_5S$ 338.1057, found 338.1055.

ASSOCIATED CONTENT

Supporting Information

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Notes

The authors declare no competing financial interest

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