An efficient approach for the synthesis of novel methyl sulfones in acetic acid medium and evaluation of antimicrobial activity

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Abstract: A series of nine methyl sulphones (3a–3i) starting from the aldehydes (1a–1i) were synthesized in two consecutive steps. In the first step, preparation of allyl alcohols (2a–2i) from their corresponding aldehydes by the reaction of sodium borohydride in methanol at room temperature is reported. Finally, methyl sulphones are synthesized by condensing sodium methyl sulfinites with allyl alcohols in the presence of BF₃·OEt₂ in acetic acid medium at room temperature for about 2–3 h. The reaction conditions are simple, yields are high (85%–95%), and the products were obtained with good purity. All the synthesized compounds were characterized by their ¹H, ¹³C NMR, and mass spectral analysis. All the title compounds were screened for antimicrobial activity. Among the compounds tested, the compound 3f has inhibited both Gram positive and Gram negative bacteria effectively and compound 3i has shown potent antifungal activity. These promising components may help to develop more potent drugs in the near future for the treatment of bacterial and fungal infections.

Keywords: BF₃·OEt₂, allyl alcohols, methyl sulphones, antibacterial, antifungal

1. Introduction

The alcohol functional group is one of the more important groups for the synthesis of many drugs which are being used widely throughout the world [1–5]. As the alcohol functional group is not a good leaving group, it becomes the main obstacle for producing versatile novel drugs in organic synthesis. The nucleophilic substitution in the alcohol group is very difficult under mild conditions [6–12]. For the replacement of the OH group, one has to convert this alcohol group into a Cl group which is a better leaving group. In the previous studies, it was revealed that the conversion of the OH group into a mesylate group took place [13]. Direct conversion of alcohols into ethers, diaryl alkanes, and sulphonamides was successful [14–16]. So, we have decided to optimize the convenient route for the conversion of alcohols into sulfones under mild conditions. Earlier works revealed that direct conversion of alcohols into sulfones using brønsted acids like formic acids, acetic acid, and HCl [17–20], could be generated from sodium sulfide, sodium sulfinates, sulfoinic acids, potassium meta bisulfitite, sulfonyl chloride, and arenesulfonyl cyanide [21–27]. Among these reagents, sodium sulfinate is the best reagent due to ease of handling, and from a stability point of view.

Reddy and co-workers [28–29] reported that the reaction between p-toluenesulfonyl cyanide, and allylic alcohols leads to the formation of p-toluenesulfonyl cyanide, in the presence of diisopropylethylamine, later the adduct gets converted into a sulfonyl rearrangement product. Direct substitution of the allylic amine with sodium sulfinites in the presence of boronic acid [30] and the use of FeCl₃ as a catalyst and chlorotrimethylsilane as an additive [31], were also reported. Direct substitution of alcohols in the presence of boron trifluoride etherate with sodium sulfinites was prepared in which dichloromethane as a solvent was used under optimized parameters at 50 °C with 82% yield [32]. Oxidation of the methylthio derivative to the corresponding sulfones using m-CPBA was reported by Pujol et al [33]. Cu-catalyzed aerobic oxidation to synthesize from aryl halides and DMSO is described by Yuan et al. [34]. Fe(OH)₃-catalyzed synthesis of aryl

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sulfones using aryl sulfonyl chloride with arenes is also reported [35]. The L-Proline sodium salt/CuI-mediated coupling reaction of aryl halides with sulfonic acids is also documented by Ma and Zhu [36]. Yuan et al. have recently synthesized aryl ethyl sulfones from sodium sulfinate and di-tert-butyl peroxide in the H₂O medium [37]. Very recently, an eco-friendly approach to the construction of aryl methyl sulfone from SO₂ and methyl reagents is exemplified by Jiang et al. [38]. An excellent review on sulfones was presented very recently by Trost et al. [39]. In view of this and as an extension to our search for novel antimicrobial agents [40–44], the authors herein made an attempt to synthesize the titled sulfones and screen their antimicrobial properties.

2. Present work

We synthesized allyl alcohols, which were derived from respective aldehydes by reduction with sodium borohydride. A total of 9 aryl methyl sulfones were synthesized using BF₃·OEt₂ as a catalyst and AcOH as a solvent in the present methodology shown in Scheme 1.

Huang et al. [32] reported on the synthesis of sulfinates using BF₃·OEt₂ in CH₂Cl₂ solvent medium optimized at 45–50 °C moderate temperatures via the more favourable SN¹ mechanism through the conversion of sodium p-toluenesulfinate into corresponding nucleophile sulfinic acid, i.e. O-attack. Surprisingly, when acetic acid was used as a solvent, we could observe the formation of sulfones possibly via S-attack following the SN² mechanism, thereby indicating the significant role of solvent in product formation. The aim was achieved with various benzyl alcohols and sodium methyl sulfinates. Shorter reaction times and direct isolation of products were the added advantages in using the previous method.

Baidya et al. [45] explained about the thermal stability of the sulfones over the sulfinates. According to their studies, PhSO₂⁻ reacts with highly stabilized benzyldihyridium ions to give sulfone derivatives exclusively, but in the case of highly reactive benzyldihyridium ions it gives mixtures of sulfinates Ar₂CH-OS(O)Ph and sulfones Ar₂CH-SO₂Ph; the latter rearranges to the thermodynamically more stable sulfones through an ionization recombination sequence.

In the given Scheme 2, the reaction mechanism was explained schematically. Using acetic acid as a solvent instead of dichloromethane favors reaction at room temperature. Initially, BF₃·OEt₂ activates the hydroxyl group to become protonated and subsequent elimination of water molecule occurs. As a result carbonium ion formation took place at room temperature itself. The formed carbonium ion was attacked by nucleophile of the sodium methyl sulfinates leading to the formation of sulfinate derivatives. Later, the product rearranged into thermodynamically more stable sulfones.

We chose the benzyl alcohol, and sodium methyl sulfinates as substrates for optimization of the reaction initially in the presence of BF₃·OEt₂. The authors carried out a couple of reactions by changing the concentration of BF₃·OEt₂, varying from 0.2 equivalents to 2.0 equivalents. Finally, we could achieve the yields of the target molecule variables from 15 to 92% as shown in Table 1.

![Scheme 1: Synthesis of aryl methylsulfones.](image1)

![Scheme 2: Possible reaction mechanism for conversion of alcohol into sulfones.](image2)
The highest yields of the compound were obtained with 1.8 equivalents of BF$_3$OEt$_2$. A couple of reactions were conducted with 1.8 equivalents of BF$_3$OEt$_2$ at various time periods ranging from 1 to 8 h. During the time period from 1 to 3 h, the yields found increased, and when the time period was prolonged from 3 to 8 h, the yields decreased. This reaction conversion was tremendously effective on the solvent which was used. For this reason, several trial reactions were carried out with both the polar solvents and nonpolar solvents. Lesser yields were reported with the nonpolar solvent cyclohexane (Table 1, entry 10). Next to cyclohexane, polar solvents like DMSO, and THF gave the yields of 25%, and 20% respectively. With the exception of acetic acid other solvents got the yields of the desired product below 50%. The best yields ranging from 80% to 92% (Table 1, entries 2–6) were obtained with the acetic acid. So, finally, we have concluded that the reaction is more favorable with the protic solvents.

The above optimized reaction conditions were verified and or generalized with structurally different types of alcohols. The obtained yields of desired products were mentioned in Table 2, entries 1–9.

The best yield (95%) of the desired molecule was obtained with the nitro alcohol derivatives (3i), under the optimized reaction condition. The lowest yields were obtained with the electron donating groups, which existed in the substrates. Electron withdrawing groups, which were present in the substrate molecules favor the conversion with excellent yields. The alcohol 1a having three donation groups present in the ortho and para position gave less yield (Table 2, entry 1). Due to the presence of orthosteric effect, alcohol derivatives 3a and 3e gave less yields (Table 2, entries 1, 5). The fewer number of donating groups present in the alcohol substrates increase the yields from 85% to 88%. The phenyl ring has a lesser withdrawing effect than the nitro group results and yields almost the highest yields.

### Table 1. Reaction conditions for optimization.

| Entry | BF$_3$Et$_2$O | Solvent | T °C | Time (h) | Yield (%) |
|-------|----------------|---------|------|----------|-----------|
| 1     | 0.2            | CH$_2$Cl$_2$ | 50   | 3        | 40        |
| 2     | 1.0            | CH$_3$COOH  | 28   | 3        | 80        |
| 3     | 1.4            | CH$_3$COOH  | 28   | 3        | 82        |
| 4     | 1.6            | CH$_3$COOH  | 28   | 3        | 86        |
| 5     | 1.8            | CH$_3$COOH  | 28   | 3        | 92        |
| 6     | 2.0            | CH$_3$COOH  | 28   | 3        | 90        |
| 7     | 1.8            | DMSO       | 30   | 3        | 25        |
| 8     | 1.8            | THF        | 28   | 3        | 20        |
| 9     | 1.8            | CHCl$_3$   | 28   | 3        | 37        |
| 10    | 1.8            | Cyclohexane | 28   | 3        | 15        |
| 11    | 1.8            | CH$_3$NO$_2$ | 28   | 3        | 39        |
| 12    | 1.8            | C$_6$H$_4$NO$_2$ | 28   | 3        | 40        |
| 13    | 1.8            | 1,4-Dioxane | 28   | 3        | 42        |
| 14    | 1.8            | CH$_3$CN    | 28   | 3        | 25        |
| 15    | 1.8            | DMF        | 28   | 3        | 38        |
| 16    | 1.8            | Acetone    | 28   | 3        | 30        |

3. Biological activity

All the synthesized compounds were screened for antimicrobial activity and results were depicted in Table 3. Among the screened compounds (3a–3i), compound 3f with dimethoxy, hydroxyl benzyl group showed the highest inhibition zone followed by compounds 3a, 3c, and 3h. Further, the compound 3i was found to be effective on fungal strains. The remaining compounds showed moderate activity.

4. Conclusion

This method is a modified method for methyl sulfones and reaction yields of 85% to 95% were obtained. In this method, the solvent acetic acid was used, which is inexpensive when compared with the solvent dichloromethane solvent, and this reaction is carried out at room temperature. We have applied this method for the synthesis of 9 compounds of which 7 are novel (3a–3i).
The compounds bearing dimethoxy, hydroxyl benzyl group have shown prominent antibacterial activity when compared to compounds without these groups. It was also confirmed that the compounds bearing nitro group have shown prominent antifungal activity when compared to other compounds. Further investigation in this area may help to create more potent drugs for the treatment of bacterial and fungal infections.

Table 2. Sulfonation of various alcohols with sodium methyl sulfinates.

| Entry | Compound structure | Number | Yield (%) |
|-------|-------------------|--------|-----------|
| 1     | ![Structure 1]    | 3a     | 85        |
| 2     | ![Structure 2]    | 3b     | 88        |
| 3     | ![Structure 3]    | 3c     | 90        |
| 4     | ![Structure 4]    | 3d     | 91        |
| 5     | ![Structure 5]    | 3e     | 88        |
| 6     | ![Structure 6]    | 3f     | 86        |
| 7     | ![Structure 7]    | 3g     | 88        |
| 8     | ![Structure 8]    | 3h     | 92        |
| 9     | ![Structure 9]    | 3i     | 95        |

*Yields refer to pure products after column chromatography.*

**Reaction conditions:** 1a–1i (1.96 μmol), 2 (1.96 μmol), BF₃·OEt₂ (3.5 mL), Acetic acid (3 mL), at rt for 3h.
## 5. Experimental section

### 5.1. General preparation of compounds (1a–1i)

NaBH₄ (4.76 µmol) was added to the ethyl alcohol (3 mL) and the reaction mixture was stirred at room temperature for 5 min. Respectively, aldehyde compound (4.76 µmol) was added to the reaction mixture and stirred continuously for 1 h. Reaction mixture completion was confirmed by the TLC. After completion of the reaction, the mixture was quenched with 10% HCl (3 mL) and ethanol was evaporated under reduced pressure. After the complete removal of ethanol, saturated sodium bisulphite (1 × 5 mL) was added. The organic compound was extracted with dichloromethane (20 mL) and water (10 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure; to give 1a–1i compounds.

Yield, ¹H NMR, ESI-MS (M⁺H) data of all compounds, and CHNS/O elemental analysis (Perkin-Elmer 2400, PerkinElmer Inc., Waltham, MA, USA) composition data of each product are given below.

### 5.1.1. (2,4,6-trimethoxyphenyl)methanol (1a)

Brown solid, yield 91.2%; ¹H NMR (CDCl₃, 400 MHz): δ 6.12 (s, 2H), 4.69 (s, 2H), 3.81 (s, 6H), 3.80 (s, 3H), 2.16 (s, 3H); ESI MS (M⁺H): m/z 199.01.

### 5.1.2. 4-(hydroxymethyl)-2-methoxyphenol (1b)

White solid, ²H NMR (CD₂OD, 400 MHz): δ 6.95 (s, 1H), 6.79 (s, 2H), 4.52 (s, 2H), 3.85 (s, 3H); ¹³C NMR (CD₂OD, 100 MHz): δ 147.54, 145.47, 132.86, 119.75, 114.66, 110.79, 63.98, 55.04; ESI MS (M⁺H): m/z 155.26.

### 5.1.3. 1,8-dihydroxy-3-(hydroxymethyl)anthracene-9,10-dione (1c)

Pale white solid, ¹H NMR (DMSO-d₆, 100 MHz): δ 11.90 (s, 2H), 7.79–7.64 (m, 3H), 7.35–7.24 (m, 2H), 5.57 (t, J = 5.8 Hz, 1H), 4.57 (d, J = 5.8 Hz, 2H); ESI MS (M⁺H): m/z 135.19.

### 5.1.4. 3-phenylprop-2-en-1-ol (1d)

Light yellow solid, ¹H NMR (CDCl₃, 500 MHz): δ 7.36–7.32 (m, 2H), 7.27–7.24 (m, 2H), 7.23–7.19 (m, 1H), 6.59 (s, 1H), 6.55 (s, 1H), 4.44–4.42 (m, 2H); ESI MS (M⁺H): m/z 135.19.

### 5.1.5. 2-(1-hydroxyethyl)-3,5-dimethoxyphenol (1e)

Yellow solid, ¹H NMR (CDCl₃, 400 MHz): δ 5.85 (s, 1H), 5.82 (s, 1H), 4.61 (s, 1H), 4.0 (s, 1H), 3.82 (s, 1H), 3.65 (s, 6H), 1.55 (s, 3H); ESI MS (M⁺H): m/z 199.06.

### 5.1.6. 1-(3,4-Dimethoxyphenyl)-1-propanol (1f)

Brown solid, ¹H NMR (CDCl₃, 400 MHz): δ 7.05 (d, 1H), 6.94–6.85 (dd, J = 8.1 Hz, 2H), 4.85 (m, 1H), 3.88 (ds, 6H), 2.45 (bs, OH), 1.84–1.78 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H); ESI MS (M⁺H): m/z 197.29.

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### Table 3. Antimicrobial activity of the synthesized compounds (3a–3i).

| Compound Code | S. aureus (ATCC 25923) | B. Cereus (ATCC H) | P. Aeruginosa (ATCC 27853) | E. coli (ATCC 35218) | C. Albicans (ATCC 90028) | A. Niger (NCCS 1196) |
|---------------|-----------------------|--------------------|-----------------------------|-----------------------|--------------------------|---------------------|
|               | 50 (mg/mL) | 100 (mg/mL) | 150 (mg/mL) | 50 (mg/mL) | 100 (mg/mL) | 150 (mg/mL) | 50 (mg/mL) | 100 (mg/mL) | 150 (mg/mL) | 50 (mg/mL) | 100 (mg/mL) | 150 (mg/mL) |
| 3a            | -         | 11        | 18        | -        | -         | -         | 08        | 17        | 23        | 08        | 12        | 18        |
| 3b            | 08        | 12        | 17        | -        | -         | -         | 07        | 15        | 21        | 09        | 13        | 17        |
| 3c            | 07        | 12        | 18        | -        | -         | -         | 08        | 16        | 23        | 10        | 12        | 18        |
| 3d            | 06        | 13        | 17        | -        | -         | -         | 07        | 13        | 16        | 08        | 12        | 15        |
| 3e            | 07        | 14        | 18        | -        | -         | -         | 08        | 16        | 20        | 09        | 13        | 18        |
| 3f            | 08        | 16        | 19        | -        | -         | -         | 10        | 17        | 24        | 09        | 14        | 17        |
| 3g            | 07        | 14        | 16        | -        | -         | -         | 08        | 12        | 15        | 08        | 14        | 17        |
| 3h            | 07        | 13        | 18        | -        | -         | -         | 07        | 18        | 23        | 08        | 15        | 18        |
| 3i            | 06        | 14        | 17        | -        | -         | -         | 06        | 12        | 16        | 08        | 14        | 17        |

Ciproflaxacin (30 mg/disc) | 24 | 18 | 24 | 23 | NA | NA |

Fluconazole (25 µg/disc) | NA | NA | NA | 22 | 20 | 20 |
1. General preparation of compounds (3a–i)

The respective benzyl alcohol (1.96 μmol) was dissolved in acetic acid (3 mL). BF₃·OEt₂ (3.5 mL, 3.528 μmol) was added to the reaction mixture at room temperature. Sodium methyl sulfinate (200 mg, 1.96 μmol) was added to the reaction mixture and stirred for 30 min. Reaction mixture completion was confirmed by the TLC. After completion of the reaction, the reaction mixture was quenched with NaHCO₃ solution (10 mL). The organic compound was extracted with dichloromethane (20 mL) and water (10 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude material was purified by the silica gel chromatography to give the compounds 3a–3i.

2. General preparation of compounds (3a–i)

2.1. 1,3,5-trimethoxy-2-((methylsulfonyl)methyl)benzene (3a)

Brown solid, yield 85%; IR (υ,KBr): 3033 (Aromatic C=C), 2988, 2976 (CH₃), 1024(SO₂) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 6.16 (s, 2H), 4.38 (s, 2H), 3.85 (s, 6H), 3.82 (s, 3H), 2.77 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): 162.23, 159.72, 98.86, 91.03, 90.44, 56.04, 55.94, 55.45, 50.26, 40.31; ESI MS: m/z 181 (M-SO₂Me).CHNS: Anal. calcd. for C₁₁H₁₀O₂S; C, 50.75; H, 6.20; S, 12.32. Found: C, 50.61; H, 6.11; S, 12.49.

2.2. 2-methoxy-4-((methylsulfonyl)methyl)phenol (3b)

Brown solid, yield 88%; IR (υ,KBr): 3323 (phenolic OH), 2888, 2785 (CH₃), 1020 (SO₂) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 6.70–6.67 (m, 3H), 4.41 (s, 2H), 3.83 (s, 3H), 3.46 (s, 1H), 2.96 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 192.69, 181.48, 170.38, 162.82, 146.52, 137.29, 133.93, 133.60, 124.76, 122.39, 120.15, 115.85, 115.32, 64.70, 20.77; ESI MS (M+2H): m/z 333.CHNS: Anal. calcd. for C₁₆H₁₂O₃S; C, 57.83; H, 3.64; S, 9.65. Found: C, 57.91; H, 3.49; S, 9.81.

2.3. 1,8-dihydroxy-3-((methylsulfonyl)methyl)anthracene-9,10-dione (3c)

Brown solid, yield 91%; IR (υ,KBr): 3321 (phenolic OH), 3040 (Aromatic C=C), 1020 (SO₂) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 12.06 (s, 1H), 12.04 (s, 1H), 7.85–7.83 (m, 1H), 7.78 (s, 1H), 7.71–7.67 (t, J = 16 Hz, 1H), 7.52–7.30 (d, 1H), 7.26 (s, 1H), 5.19 (s, 2H), 2.19 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 192.69, 181.48, 170.38, 162.82, 146.52, 137.29, 133.93, 133.60, 124.76, 122.39, 120.15, 115.85, 115.32, 64.70, 20.77; ESI MS (M+2H): m/z 333.CHNS: Anal. calcd. for C₁₆H₁₂O₅S; C, 57.83; H, 3.64; S, 9.65. Found: C, 57.91; H, 3.49; S, 9.81.

2.4. 1.-(E)-3-(methylsulfonyl)prop-1-ylbenzene (3d)

Brown solid, yield 91%; IR (υ,KBr): 3033 (Aromatic C=C), 2970, 2965 (CH₃), 1024 (SO₂) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.31–7.29 (m, 2H), 7.25–7.22 (m, 2H), 7.19–7.17 (m, 1H), 6.56–6.53 (m, 1H), 6.22–6.16 (m, 1H), 4.09–4.07 (d, J = 8, 2H), 3.00 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 137.67, 136.33, 129.19, 128.08, 127.08, 122.13, 58.35, 40.25; ESI MS: m/z 118 (M+SO₂).CHNS: Anal. calcd. for C₁₆H₁₁O₂S; C, 61.20; H, 6.16; S, 16.34. Found: C, 61.09; H, 6.03; S, 16.47.

2.5. 3.5-dimethoxy-2-((methylsulfonyl)methyl)phenol (3e)

Brown solid, yield 86%; IR (υ,KBr): 3041 (Aromatic C=C), 2980, 2889 (CH₃), 1024 (SO₂) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 6.20–6.15 (m, 2H), 4.40–4.36 (m, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 2.97 (s, 3H), 1.79 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 167.49, 164.44, 162.99, 113.34, 93.61, 91.47, 62.29, 56.79, 56.04, 37.80, 17.52; ESI MS (M+H): m/z 258(M+).CHNS: Anal. calcd. for C₁₆H₁₀O₃S; C, 50.75; H, 6.20; S, 12.32. Found: C, 50.60; H, 6.11; S, 12.47.

2.6. 1,2-dimethoxy-4-((methylsulfonyl)propyl)benzene (3f)

Brown solid, yield 88%; IR (υ,KBr): 3033 (Aromatic C=C), 2988, 2972, 1024 (SO₂) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 6.91 (s, 1H), 6.84–6.82 (m, 2H), 4.13–4.11 (m, 1H), 3.82 (s, 6H), 3.03(s, 3H), 2.25–2.20 (m, 2H), 1.04-1.01 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 149.53, 147.02, 135.91, 117.05, 116.41, 113.45, 69.90, 56.78, 39.66, 23.95, 11.02; ESI MS (M+H): m/z 215(M+).CHNS: Anal. calcd. for C₁₆H₁₀O₃S; C, 55.79; H, 7.02; S, 12.42. Found: C, 55.65; H, 6.89; S, 12.54.

2.7. (Z)-1,4-bis(methylsulfonyl)but-2-ene, (Z)-4-(methylsulfonyl)but-2-en-1-ol (3g)

Brown solid, yield 88%; IR (υ,KBr): 3323 (OH), 1020 (SO₂) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 5.83–5.82 (m, 1H), 5.72–5.70 (m, 3H), 4.67–4.63 (m, 4H), 4.55–4.54 (m, 2H), 2.04 (s, 3H), 2.03 (s, 6H); ESI-MS (M+H): m/z 261(M+).
5.2.8. (methylsulfonyl)diphenylmethane(3h) [31]
Brown solid, yield 92%; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.65–7.57 (m, 4H), 7.43–7.33 (m, 6H), 5.32 (s, 1H), 2.77 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$132.80, 129.73, 129.66, 128.50, 74.84, 40.02; ESI MS (M$^+$H)$: m/z$247. CHNS: Anal. calcd. for C$_{14}$H$_{14}$O$_2$S; C, 68.26; H, 5.73; S, 13.02. Found: C, 68.17; H, 5.61; S, 13.16.

5.2.9. 1-((methylsulfonyl)methyl)-4-nitrobenzene (3i) [46]
Brown solid, yield 95%; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.44 (d, $J$ = 8.8 Hz, 2H), 8.16 (d, $J$ = 8.8 Hz, 2H), 3.12 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$150.9, 145.86, 129.25, 124.36, 44.29; ESI MS (M$^+$H)$: m/z$198. CHNS: Anal. calcd. for C$_8$H$_9$NO$_4$S; C, 44.64; H, 4.21; N, 6.51; S, 14.90. Found: C, 44.51; H, 4.12; N, 6.51; S, 14.99.

5.3. Antibacterial activity [47]
The antibacterial activity of the compounds was determined by means of the disc diffusion method. Cultures of each bacterium (E.coli, Bacillus cereus, Staphylococcus aureus, and Pseudomonas aeruginosa) were inoculated to the nutrient broth and incubated at 37°C for 16 h., respective bacterial culture was inoculated in the MHA plate by using the spread plate method. Discs (6 mm in diameter) were impregnated with 25, 50, and 75 µg/mL concentrations in DMSO solution of the compounds (3a–3i) and placed on the surface of the MHA inoculated with bacteria, which were incubated at 37°C for 24 h. The inhibition zones were measured with a caliper considering the total diameters. Similarly, each plate carried a blank disc, the disk with DMSO, and ciprofloxacin disc (30 µg/mL) as standard.

5.4 Antifungal activity
The antifungal activity of the compounds was determined by means of the disc diffusion method. Cultures of each fungal (C.Albicans, and A. niger) were inoculated to the nutrient broth and incubated at 37°C for 16 h. Respective fungal culture was inoculated in the SDA plate by using the spread plate method. Discs (6 mm in diameter) were impregnated with 25, 50, and 75 µg/mL concentrations in DMSO solution of the compounds (3a–3i) and placed on the surface of the MHA inoculated with bacteria, which were incubated at 37°C for 24 h. The inhibition zones were measured with a caliper considering the total diameters. Similarly, each plate carried a blank disc, disc with DMSO, and fluconazole disc (30 µg/mL) as standard.

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Conflict of interest
The authors declare no conflict of interest.

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