Studies on Synthesis of Some New Sydnone Containing Compounds and their Biological Activities

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Abstract: Some new sydnone derivatives 3-[4-(morpholin-4-yl)phenyl]-4-(secondary substituted amino-4-yl methyl) sydnone 6(a-j), 3-[4-(morpholin-4-yl) phenyl]-4-(secondary substituted amino-4-yl sulfonyl) sydnone 8(a-j) were synthesized starting from 4-chloroaniline (1). The characterization of the newly synthesized compounds was established by IR, $^1$H NMR, $^{13}$C NMR and Elemental analysis. The final compounds were tested for their antimicrobial activity against several microbes.

Keywords: Sydnone, Mesoionic, Antimicrobial activity

Introduction

Mesoionic compounds are of special interest among heterocycles due to their unusual structure, chemical properties and synthetic utility. Sydnones are the most important representatives of mesoionic compounds having the 1, 2, 3-oxadiazole skeleton bearing an oxygen atom attached to the 5 position. Various electrophilic substitution reactions such as halogenation, nitration, acylation, sulphonation occur at the fourth position of the sydnone ring containing a hydrogen atom. Sydnone derivatives have been the focus of great interest because of their remarkable biological properties, such as antibacterial, antitumor, antifungal, antimalarial, antiparasitic, analgesic, antioxidant, anti inflammatory. Sydnones show liquid crystalline properties. The N-methyl sydnones having a high dielectric constant was used as a solvent for lithium battery electrolyte. We planned to undertake the synthesis and characterization of some new sydnone derivatives containing some heterocyclic system at position-4 linked through methylene and sulphonyl bridge with the hope to achieve enhanced biological activity.

Experimental

Melting points were determined by open capillary method and are uncorrected. The structures of the compounds were confirmed by $^1$H and $^{13}$C nuclear magnetic resonance and
Fourier transform infrared. $^1$H NMR spectra were recorded with Bruker Avance II 400 MHz NMR spectrometer at SAIF, Chandigarh, in CDCl$_3$ or DMSO-d$_6$ using TMS as internal standard and chemical shifts are expressed in $\delta$ ppm. $^{13}$C NMR spectra of the compounds were recorded with a Bruker Avance II 400 MHz NMR spectrometer at SAIF (Sophisticated Analytical Instrument Facilities), Chandigarh. The IR spectra were recorded with a Thermo Scientific Nicolet iS10 FTIR specrophotometer at the Department of Chemistry, Veer Narmad South Gujarat University. Elemental analysis (C, H, N) were performed on Thermo Finnigan EA 1112 Flash Elemental Analyzer at G.N.F.C. (Gujarat Narmada Valley Fertilizer Company Ltd., Bharuch). The progress of reactions and the purity of synthesized compounds were checked by TLC on E-Merck precoated 60 F$_{254}$ plates and the spots were examined under short-wave UV light. The synthesis of $3$-[4-(morpholin-4-yl) phenyl]-4-(secondary substituted amino-4-yl methyl)-sydnone $6(a-j)$ and $3$-[4-(morpholin-4-yl) phenyl]-4-(secondary substituted amino-4-yl sulfonyl) sydnone $8(a-j)$ are shown in Scheme 1.

![Scheme 1](image)

General synthesis of intermediates and product

$N$-(4-Chlorophenyl) glycine (2)

4-Chloroaniline (0.011 mol) was added to an ice-cooled solution of chloroacetic acid (0.01 mol) and 2 mL of water which was neutralized by 10% sodium hydroxide solution. The reaction mixture was refluxed for 20 minutes after cooling to room temperature in an ice bath, 0.5 g of sodium hydroxide pellet was added and the mixture was extracted with methylene dichloride
to remove the unreacted aniline. Acidifying the aqueous solution with concentrated HCl till complete precipitation and recrystallization with ethanol to give compound 2. Yield 80.00%; mp 145-147 °C; IR spectrum (KBr, ν cm⁻¹): 3323-3278 (OH, NH), 2937, 2937 (CH₂), 1705 (CO); ¹H NMR spectrum (DMSO-d₆, δ ppm): 4.31 (s, 2H, CH₂), 6.45 (s, 1H, COOH), 6.56 (s, 1H, NH), 6.90-7.23 (m, 4H, Ar-H); ¹³C NMR spectrum (DMSO-d₆, δ ppm): 44.98, 114.32, 123.26, 129.10, 146.07, 172.18. Anal. calcd. for C₆H₅N₃S: C, 47.66; H, 3.33; N, 27.79; S, 21.21; found: C, 47.55; H, 3.42; N, 27.70; S, 21.32.

N- Nitroso N-(4-chlorophenyl) glycine (3)
A cold solution of sodium nitrite (0.01 mol) in 5 mL of water was added drop wise to the suspension of N-(4-chlorophenyl) glycine (0.01 mole) in 40 mL of water at 0-5 °C with stirring. After complete addition stirring was continued for 2 h and keeps it overnight, the reaction mixture was filtered off and the nitroso compound was precipitated by adding concentrated HCl. The product was collected, dried and recrystallised from methanol to furnish compound 3. Yield 78.00%; mp 104-106 °C; IR spectrum (KBr, ν cm⁻¹): 3258-2530 (OH), 2925, 2857 (CH₂), 1715 (CO), 1571 (NO); ¹H NMR spectrum (DMSO-d₆, δ ppm): 5.02 (s, 2H, CH₂), 6.93-7.48 (m, 4H, Ar-H), 11.56 (s, 1H, COOH); ¹³C NMR spectrum (DMSO-d₆, δ ppm): 49.43, 120.78, 128.31, 130.46, 138.89, 168.24. Anal. calcd. For C₈H₆ClN₃OS: C, 42.20; H, 2.66; N, 18.46; S, 14.08; found: C, 42.11; H, 2.75; N, 18.34; S, 14.19.

3-(4-Chlorophenyl) sydnone (4)
The dried N-nitroso-N-(4-chlorophenyl) glycine and acetic anhydride were taken in ratio of 1: 5 by weight and stirred for 10 h. The solution was poured slowly in to cold water which was very well stirred. The pH of the content was neutralized with 10% sodium bicarbonate solution and washed with water and dried. The crude sydnones was recrystallized from benzene-petroleum ether to give compound 4. Yield 98.00%; mp 140-145 °C; IR spectrum (KBr, ν cm⁻¹): 3178 (CH), 1750 (CO); ¹H NMR (DMSO-d₆, δ ppm): 7.22 (s, 1H, sydnone), 7.55-8.18 (m, 4H, Ar-H); ¹³C NMR (DMSO-d₆, δ ppm): 124.12, 128.55, 130.63, 135.2 2, 140.92, 169.19. Anal. calcd. For C₈H₉N₅OS: C, 43.04; H, 4.06; N, 31.37; S, 14.36; found: C, 43.16; H, 4.18; N, 31.25; S, 14.24.

3-[4-(Morpholin-4-yl) phenyl] sydnone (5)
3-(4-Chlorophenyl) Sydnone (0.01 mol) and morpholine (0.01 mol) were refluxed for 24 h. The solution was poured over the crushed ice. The resulting crystals were filtered, rinsed with cold hexane and recrystallized from ethanol to give compound 5. Yield 78.00%; mp 177-179 °C. IR spectrum (KBr, ν cm⁻¹): 1754 (CO), 3150 (CH); ¹H NMR (CDCl₃, δ ppm): 3.17 (t, 4H, -N-CH₂), 3.64 (t, 4H, -O-CH₂), 6.76-7.73 (m, 5H, Ar-H); ¹³C NMR (DMSO-d₆, δ ppm): 53.51, 66.53, 114.12, 123.19, 123.42, 126.35, 149.58, 169.19. Anal. calcd. For C₁₂H₁₅N₃O₃: C, 57.84; H, 6.06; N, 16.87; found: C, 57.73; H, 6.12; N, 16.82.

Synthesis of compounds (6a-j)
The mixture of various secondary amine (0.009 mol), 0.25 g paraformaldehyde and 3-[4-(morpholin-4-yl) phenyl] sydnone (0.003 mol) were added to 10 mL of acetic acid and 10 mL ethanol and whole the mixture was heated at 70 °C for 3 h. After complete the reaction cool it and ethanol was distilled off, 20 mL of water was added and neutralized with aqueous sodium bicarbonate to afford the crude product. Recrystallization from 95% ethanol to give compounds 6(a-j).
3-[4-(Morpholin-4-yl) phenyl]-4-(piperazin-4-yl methyl)sydnone (6a)
Yield: 65%; mp 149-151 °C; IR spectrum (KBr, ν, cm⁻¹): 3233 (NH), 2933, 2866 (CH₂), 1740 (CO); \(^1^H\) NMR (DMSO-d₆, δ ppm): 1.93 (s, 1H, NH), 2.42 (t, 4H, -N-CH₂), 2.63 (t, 4H, -N-CH₂), 3.23 (t, 4H, -N-CH₂), 3.54 (s, 2H, -CH₂), 3.65 (t, 4H, -O-CH₂), 6.89-7.78 (m, 4H, Ar-H); \(^1^C\) NMR (DMSO-d₆, δ ppm): 44.56, 51.07, 53.01, 54.46, 66.34, 63.14, 114.33, 126.35, 128.06, 142.48, 149.67, 168.25. Anal. calcd. for C₁₇H₂₃N₅O₃: C, 59.12; H, 6.71; N, 20.28; found: C, 59.07; H, 6.76; N, 20.21.

3-[4-(Morpholin-4-yl) phenyl]-4-(morpholin-4-yl methyl)sydnone (6b)
Yield: 69%; mp 110-112 °C; IR spectrum (KBr, ν, cm⁻¹): 2918, 2840 (CH₂), 1747 (CO); \(^1^H\) NMR (DMSO-d₆, δ ppm): 2.55 (t, 4H, -N-CH₂), 3.25 (t, 4H, -N-CH₂), 3.56 (s, 2H, -CH₂), 3.65 (t, 8H, -O-CH₂), 6.90-7.79 (m, 4H, Ar-H); \(^1^C\) NMR (DMSO-d₆, δ ppm): 47.58, 53.02, 54.49, 66.32, 114.38, 126.42, 128.09, 142.34, 149.63, 168.15. Anal. calcd. for C₁₇H₂₂N₄O₄: C, 58.95; H, 6.40; N, 16.17; found: C, 58.87; H, 6.45; N, 16.23.

3-[4-(Morpholin-4-yl) phenyl]-4-(1-methylpiperazin-4-yl methyl)sydnone (6c)
Yield: 55%; mp 113-115 °C; IR spectrum (KBr, ν, cm⁻¹): 2986-2853 (CH₂, CH₃), 1760 (CO); \(^1^H\) NMR (DMSO-d₆, δ ppm): 2.23 (s, 3H, CH₃), 2.34 (t, 4H, -N-CH₂), 2.46 (t, 4H, -N-CH₂), 3.22 (t, 4H, -N-CH₂), 3.54 (s, 2H, -CH₂), 3.63 (t, 4H, -O-CH₂), 6.92-7.84 (m, 4H, Ar-H); \(^1^C\) NMR (DMSO-d₆, δ ppm): 46.91, 48.42, 53.01, 54.39, 56.28, 66.32, 114.12, 126.45, 128.14, 142.39, 149.73, 168.18. Anal. calcd. for C₁₈H₂₅N₅O₃: C, 60.15; H, 7.01; N, 19.48; found: C, 60.07; H, 6.93; N, 19.43.

3-[4-(Morpholin-4-yl) phenyl]-4-(piperidin-4-yl methyl)sydnone (6d)
Yield: 59%; mp 123-125 °C; IR spectrum (KBr, ν, cm⁻¹): 2921, 2853 (CH₂, CH₃), 1760 (CO); \(^1^H\) NMR (DMSO-d₆, δ ppm): 1.51-1.59 (m, 6H, 3CH₂), 2.43 (t, 4H, -N-CH₂), 3.21 (t, 4H, -N-CH₂), 3.54 (s, 2H, -CH₂), 3.65 (t, 4H, -O-CH₂), 6.93-7.87 (m, 4H, Ar-H); \(^1^C\) NMR (DMSO-d₆, δ ppm): 24.29, 24.89, 49.33, 53.00, 54.35, 66.30, 114.27, 126.35, 128.33, 142.32, 149.88, 168.23. Anal. calcd. for C₁₈H₂₄N₄O₃: C, 62.77; H, 7.02; N, 16.27; found: C, 62.69; H, 6.96; N, 16.33.

3-[4-(Morpholin-4-yl) phenyl]-4-(1-acetylpiperazin-4-yl methyl)sydnone (6e)
Yield: 61%; mp 151-154 °C; IR spectrum (KBr, ν, cm⁻¹): 2936, 2854 (CH₂), 1745 (CO); \(^1^H\) NMR (DMSO-d₆, δ ppm): 2.23 (s, 3H, CH₃), 2.49 (t, 4H, -N-CH₂), 3.19 (t, 4H, -N-CH₂), 3.42 (t, 4H, -N-CH₂), 3.55 (s, 2H, -CH₂), 3.63 (t, 4H, -O-CH₂), 6.92-7.84 (m, 4H, Ar-H); \(^1^C\) NMR (DMSO-d₆, δ ppm): 24.29, 24.89, 49.33, 53.00, 54.35, 66.30, 114.27, 126.35, 128.33, 142.32, 149.88, 168.23. Anal. calcd. for C₁₉H₂₅N₅O₄: C, 58.90; H, 6.50; N, 18.08; found: C, 59.01; H, 6.58; N, 18.14.

3-[4-(Morpholin-4-yl) phenyl]-4-(1-phenylpiperazin-4-yl methyl)sydnone (6f)
Yield: 65%; mp 139-141 °C; IR spectrum (KBr, ν, cm⁻¹): 2936, 2854 (CH₂), 1745 (CO); \(^1^H\) NMR (DMSO-d₆, δ ppm): 2.55 (t, 4H, -N-CH₂), 3.22 (t, 8H, -N-CH₂), 3.53 (s, 2H, -CH₂), 3.61 (t, 4H, -O-CH₂), 6.79-7.72 (m, 9H, Ar-H); \(^1^C\) NMR (DMSO-d₆, δ ppm): 21.22, 48.06, 49.92, 53.04, 54.27, 66.26, 114.34, 126.45, 128.21, 142.36, 149.62, 168.77, 168.20. Anal. calcd. for C₁₉H₂₅N₅O₃: C, 60.15; H, 7.02; N, 16.27; found: C, 62.69; H, 6.96; N, 16.33.

3-[4-(Morpholin-4-yl) phenyl]-4-(1-ethylpiperazin-4-yl methyl)sydnone (6g)
Yield: 54%; mp 118-120 °C; IR spectrum (KBr, ν, cm⁻¹): 2987-2864 (CH₂, CH₃), 1742 (CO); \(^1^H\) NMR (DMSO-d₆, δ ppm): 1.09 (t, 3H, CH₃), 2.39 (q, 2H, CH₂CH₃), 2.38 (t, 4H, -N-CH₂),
2.54 (t, 4H, -N-CH2), 3.21 (t, 4H, -N-CH2), 3.54 (s, 2H, -CH2), 3.60 (t, 4H, -O-CH2), 6.71-7.59 (m, 4H, Ar-H); 13C NMR (DMSO-d6, δ ppm): 13.76, 48.14, 49.66, 53.03, 54.28, 55.94, 66.36, 109.57, 114.39, 126.31, 128.25, 142.33, 149.79, 168.19. Anal. calcd. for C19H27N5O3: C, 60.78; H, 7.79; N, 18.65; found: C, 60.69; H, 7.71; N, 18.73.

3-[4-(Morpholin-4-yl) phenyl]-4-[1-(4-methoxyphenyl)piperazin-4-yl methyl] sydnone (6h)

Yield: 62%; mp 156-158 °C; IR spectrum (KBr, ν, cm⁻¹): 2988-2855 (CH2, CH3), 1753 (CO); 1H NMR (DMSO-d6, δ ppm): 2.51 (t, 4H, -N-CH2), 2.67 (t, 4H, -N-CH2), 3.20 (t, 4H, -N-CH2), 3.52 (s, 2H, -CH2), 3.61 (t, 4H, O-CH2), 3.65 (s, 3H, CH3), 6.67-7.53 (m, 4H, Ar-H); 13C NMR (DMSO-d6, δ ppm): 45.21, 53.00, 54.41, 57.39, 60.39, 66.32, 114.35, 126.45, 128.32, 142.46, 149.83, 168.26. Anal. calcd. for C24H29N5O4: C, 63.84; H, 6.47; N, 15.51; found: C, 63.78; H, 6.52; N, 15.69.

3-[4-(Morpholin-4-yl) phenyl]-4-(1-methyl-3-phenylpiperazin-4-yl methyl) sydnone (6i)

Yield: 58%; mp 167-169 °C; IR spectrum (KBr, ν, cm⁻¹): 2965-2854 (CH2, CH3), 1760 (CO); 1H NMR (DMSO-d6, δ ppm): 2.23 (s, 3H, CH3), 2.71 (t, 2H, -N-CH2), 2.78 (t, 2H, -N-CH2), 3.17 (t, 4H, -N-CH2), 3.50 (s, 2H, CH2), 3.64 (t, 4H, -O-CH2), 4.07 (t, 1H, -N-CH), 6.71-7.66 (m, 9H, Ar-H); 13C NMR (DMSO-d6, δ ppm): 45.82, 46.89, 53.02, 54.45, 56.45, 61.26, 66.12, 67.51, 114.28, 126.39, 127.07, 127.99, 128.23, 128.92, 134.85, 142.34, 149.53, 168.15. Anal. calcd. for C24H29N5O3: C, 66.19; H, 6.71; N, 15.51; found: C, 63.78; H, 6.52; N, 15.69.

3-[4-(Morpholin-4-yl) phenyl]-4-[1-(2,3-dichlorophenyl)piperazin-4-yl methyl] sydnone (6j)

Yield: 63%; mp 144-146 °C; IR spectrum (KBr, ν, cm⁻¹): 3292, 2863 (CH2), 1752 (CO), 1H NMR (DMSO-d6, δ ppm): 2.61 (t, 4H, -N-CH2), 3.21 (t, 4H, -N-CH2), 3.42 (t, 4H, -N-CH2), 3.53 (s, 2H, CH2), 3.63 (t, 4H, -O-CH2), 6.65-7.09 (m, 4H, Ar-H); 13C NMR (DMSO-d6, δ ppm): 48.42, 52.29, 53.01, 54.55, 66.21, 114.24, 117.61, 123.98, 126.46, 127.27, 128.22, 129.29, 133.34, 142.39, 149.51, 150.68, 168.11. Anal. calcd. for C23H25Cl2N5O3: C, 56.33; H, 5.14; N, 14.46; found: C, 56.28; H, 5.09; N, 14.33.

3-[4-(Morpholin-4-yl) phenyl]sydnone sulphonyl chloride (7)

Chlorosulphonic acid (0.03 mol) was added drop wise in to the mixture of 3-[4-(morpholin-4-yl) phenyl] sydnone (0.01 mol) and catalytic amount of P2O5 over 30 min with constant stirring at 0-5 °C. When all the chlorosulphonic acid has been added (about 1 h), stir the reaction mixture for 2 h and keep it overnight at room temperature or heat the reaction mixture on a water bath for 1 hour to complete the reaction. Allow to cool and pour the oily mixture into crushed ice with stirring. Break up any lumps of solid material and stir the mixture for several minutes in order to obtain greenish-yellow solid product. Filter of the product and wash with cold water and dry to give compound 7. Yield 87.00%; mp 205-207 °C. IR spectrum (KBr, ν, cm⁻¹): 1755 (CO), 1396, 1178 (SO2); 1H NMR (CDCl3, δ ppm): 3.18. (t, 4H, -N-CH2), 3.63 (t, 4H, -O-CH2), 6.77-7.69 (m, 4H, Ar-H). Anal. calcd. for C19H18N2O2S2Cl: C, 41.42; H, 4.06; N, 12.07; S, 9.23; found: C, 41.41; H, 4.18; N, 12.15; S, 9.14.

Synthesis of compounds (8a-j)

3-[4-(Morpholin-4-yl) phenyl] sydnone sulphonyl chloride (0.01 mol) was dissolved in acetone. A solution of various secondary amine (0.022 mol) in acetone was added drop wise in to 3-[4-(morpholin-4-yl) phenyl] sydnone sulphonyl chloride solution over a period of 5 h.
with constant stirring. Add 1.0 mL of pyridine to the well stirred solution after 1 h and 2 h respectively during the reaction. The solution was poured in to ice with stirring. Precipitation was collected by filtration, washed thrice with water and dried. recrystallization from benzene to give compounds 8(a-j).

3-[4-(Moropholin-4-yl) phenyl]- 4-(piperazin-4-yl sulfonyl)sydnone (8a)
Yield: 2.39 g (64%); mp 192-194 °C; IR spectrum (KBr, v, cm⁻¹): 3225 (NH), 1760 (CO), 1351, 1185 (SO₂); ¹H NMR (DMSO-d₆, δ ppm): 1.91 (s, 1H, NH), 2.46 (t, 4H, -N-CH₂), 2.65 (t, 4H, -N-CH₂), 3.19 (t, 4H, -N-CH₂), 3.64 (t, 4H, -O-CH₂), 6.79-7.72 (m, 4H, Ar-H); ¹³C NMR (DMSO-d₆, δ ppm): 44.51, 51.03, 53.43, 66.29, 109.36, 114.35, 126.35, 128.03, 149.61, 169.19. Anal. calcd. for C₁₆H₂₁N₅O₅S: C, 48.29; H, 5.61; N, 17.63; found: C, 48.35; H, 5.70; N, 17.55.

3-[4-(Moropholin-4-yl) phenyl]-4-(morpholin-4-yl sulfonyl)sydnone (8b)
Yield: 2.39 g (70%); mp 247-249 °C; IR spectrum (KBr, ν, cm⁻¹): 1755 (CO), 1370, 1182 (SO₂); ¹H NMR (DMSO-d₆, δ ppm): 2.93 (t, 4H, -N-CH₂), 3.22 (t, 4H, -N-CH₂), 3.65 (t, 8H, -O-CH₂), 6.86-7.70 (m, 4H, Ar- H); ¹³C NMR (DMSO-d₆, δ ppm): 47.51, 53.28, 66.29, 109.36, 114.31, 126.35, 128.08, 149.61, 169.19. Anal. calcd. for C₁₆H₂₀N₄O₆S: C, 48.35; H, 5.37; N, 13.88; found: C, 48.25; H, 5.45; N, 13.95.

3-[4-(Moropholin-4-yl) phenyl]-4-(1-methylpiperazin-4-yl sulfonyl)sydnone (8c)
Yield: 2.39 g (72%); mp 218-220 °C; IR spectrum (KBr, ν, cm⁻¹): 2989, 2875 (CH₃), 1758 (CO), 1386, 1177 (SO₂); ¹H NMR (DMSO-d₆, δ ppm): 2.25 (s, 3H, CH₃), 2.36 (t, 4H, -N-CH₂), 2.45 (t, 4H, -N-CH₂), 3.19 (t, 4H, -N-CH₂), 3.66 (t, 4H, -O-CH₂), 6.79-7.73 (m, 4H, Ar-H); ¹³C NMR (DMSO-d₆, δ ppm): 24.81, 48.47, 53.27, 56.23, 66.34, 109.43, 114.23, 126.38, 128.12, 149.78, 169.12. Anal. calcd. for C₁₇H₂₃N₅O₅S: C, 49.42; H, 6.12; N, 16.87; found: C, 49.55; H, 6.05; N, 16.95.

3-[4-(Moropholin-4-yl) phenyl]-4-(piperidin-4-yl sulfonyl)sydnone (8d)
Yield: 2.39 g (80%); mp 206-208 °C; IR spectrum (KBr, ν, cm⁻¹): 1752 (CO), 1370, 1179 (SO₂); ¹H NMR (DMSO-d₆, δ ppm): 1.53-1.59 (m, 6H, 3CH₂), 3.04 (t, 4H, -N-CH₂), 3.20 (t, 4H, -N-CH₂), 3.63 (t, 4H, -O-CH₂), 6.76-7.67 (m, 4H, Ar-H); ¹³C NMR (DMSO-d₆, δ ppm): 24.01, 24.87, 49.23, 53.35, 66.29, 109.29, 114.25, 126.46, 128.23, 149.87, 169.24. Anal. calcd. for C₁₇H₂₂N₄O₅S: C, 51.32; H, 5.61; N, 14.20; found: C, 51.42; H, 5.95; N, 14.12.

3-[4-(Moropholin-4-yl) phenyl]-4-(1-acetylpiraperazin-4-yl sulfonyl)sydnone (8e)
Yield: 2.39 g (68%); mp 212-214 °C; IR spectrum (KBr, ν, cm⁻¹): 2987, 2860 (CH₃), 1750 (CO), 1680 (CO), 1382, 1174 (SO₂); ¹H NMR (DMSO-d₆, δ ppm): 2.13 (s, 3H, CH₃), 2.61 (t, 4H, -N-CH₂), 3.19 (t, 4H, -N-CH₂), 3.45 (t, 4H, -N-CH₂), 3.64 (t, 4H, -O-CH₂), 6.89-7.74 (m, 4H, Ar-H); ¹³C NMR (DMSO-d₆, δ ppm): 21.18, 48.03, 49.89, 53.37, 66.21, 109.45, 114.27, 126.41, 128.19, 149.65, 168.78, 169.22. Anal. calcd. for C₁₈H₂₃N₅O₆S: C, 49.07; H, 5.59; N, 16.06; found: C, 49.15; H, 5.65; N, 15.95.

3-[4-(Moropholin-4-yl) phenyl]-4-(1-phenylpiperazin-4-yl sulfonyl)sydnone (8f)
Yield: 2.39 g (82%); mp 218-220 °C; IR spectrum (KBr, ν, cm⁻¹): 2987, 2860 (CH₃), 1750 (CO), 1680 (CO), 1382, 1174 (SO₂); ¹H NMR (DMSO-d₆, δ ppm): 2.13 (s, 3H, CH₃), 2.61 (t, 4H, -N-CH₂), 3.19 (t, 4H, -N-CH₂), 3.45 (t, 4H, -N-CH₂), 3.64 (t, 4H, -O-CH₂), 6.89-7.74 (m, 4H, Ar-H); ¹³C NMR (DMSO-d₆, δ ppm): 48.12, 53.15, 53.39, 66.45, 109.42, 114.28, 121.87, 126.43, 128.19, 129.63, 149.78, 169.12. Anal. calcd. for C₂₂H₂₅N₅O₆S: C, 55.79; H, 5.61; N, 14.72; found: C, 55.85; H, 5.65; N, 14.65.
3-[4-(Morpholin-4-yl) phenyl]-4-(1-ethylpiperazin-4-yl sulfonoyl)sydnone (8g)
Yield: 2.39 g (75%); mp 195-197 °C; IR spectrum (KBr, ν, cm⁻¹): 2964, 2870 (CH₃), 1747 (CO), 1388, 1177 (SO₂); ¹H NMR (DMSO-d₆, δ ppm): 1.23 (t, 3H, CH₃), 2.39 (q, 2H, CH₂CH₃), 2.36 (t, 4H, -N-CH₂), 2.51 (t, 4H, -N-CH₂), 3.19 (t, 4H, -O-CH₂), 6.74-7.69 (m, 4H, Ar-H); ¹³C NMR (DMSO-d₆, δ ppm): 13.79, 48.10, 49.63, 53.22, 53.93, 66.33, 109.54, 114.38, 126.35, 128.25, 149.69, 169.09. Anal. calcd. for C₁₈H₂₅N₅O₅S: C, 50.78; H, 6.32; N, 16.29; found: C, 50.85; H, 6.25; N, 16.38.

3-[4-(Morpholin-4-yl) phenyl]-4-[1-(4-methoxyphenyl)piperazin-4-yl sulfonoyl]sydnone (8h)
Yield: 2.39 g (85%); mp 187-189 °C; IR spectrum (KBr, ν, cm⁻¹): 2980, 2858 (CH₃), 1749 (CO), 1364, 1174 (SO₂); ¹H NMR (DMSO-d₆, δ ppm): 2.59 (t, 4H, -N-CH₂), 2.66 (t, 4H, -N-CH₂), 3.20 (t, 4H, -O-CH₂), 3.68 (s, 3H, CH₃), 6.77-7.63 (m, 4H, Ar-H); ¹³C NMR (DMSO-d₆, δ ppm): 45.14, 53.41, 57.33, 60.40, 66.25, 109.36, 114.21, 126.42, 128.32, 149.85, 169.25. Anal. calcd. for C₂₃H₂₇N₅O₆S: C, 54.82; H, 5.73; N, 13.80; found: C, 54.90; H, 5.68; N, 13.88.

3-[4-(Morpholin-4-yl) phenyl]-4-(1-methyl-3-phenylpiperazin-4-yl sulfonoyl)sydnone (8i)
Yield: 2.39 g (82%); mp 237-239 °C; IR spectrum (KBr, ν, cm⁻¹): 2968, 2852 (CH₃), 1755 (CO), 1380, 1181 (SO₂); ¹H NMR (DMSO-d₆, δ ppm): 2.25 (s, 3H, CH₃), 2.71 (t, 2H, -N-CH₂), 2.78 (t, 2H, -N-CH₂), 3.18 (t, 4H, -O-CH₂), 3.65 (t, 4H, -N-CH₂), 4.10 (t, 1H, -N-CH), 6.75-7.67 (m, 9H, Ar-H); ¹³C NMR (DMSO-d₆, δ ppm): 45.83, 46.91, 53.45, 56.53, 61.24, 66.07, 66.52, 109.26, 114.22, 126.35, 127.00, 127.98, 128.22, 128.95, 134.84, 149.58, 169.17. Anal. calcd. for C₂₃H₂₇N₅O₅S: C, 56.45; H, 6.06; N, 14.32; found: C, 56.55; H, 5.97; N, 14.28.

3-[4-(Morpholin-4-yl) phenyl]-4-[1-(2,3-dichlorophenyl)piperazin-4-yl sulfonoyl]sydnone (8j)
Yield: 2.39 g (74%); mp 217-219 °C; IR spectrum (KBr, ν, cm⁻¹): 1760 (CO), 1374, 1172 (SO₂); ¹H NMR (DMSO-d₆, δ ppm): 2.56(t, 4H, -N-CH₂), 3.20 (t, 8H, -N-CH₂), 3.63 (t, 4H, -O-CH₂), 6.58-7.11 (m, 7H, Ar-H); ¹³C NMR (DMSO-d₆, δ ppm): 48.44, 52.26, 53.55, 66.23, 109.16, 114.29, 117.62, 123.96, 126.43, 127.25, 128.20, 129.23, 133.33, 149.50, 150.63, 169.10. Anal. calcd. for C₂₂H₂₃Cl₂N₅O₅S: C, 48.59; H, 4.61; N, 12.88; found: C, 48.65; H, 4.58; N, 12.96.

Results and Discussion

Biological evaluation (Antimicrobial activity)

All the newly synthesized compounds were screened in vitro for their antibacterial and antifungal activities by broth dilution method (Table 1). The antibacterial activity of the compounds was tested against S.aureus and B.subtilis as Gram positive and P.aeruginosa and E.coli as Gram negative bacterial strains. Antifungal activity of the compound was tested against C.albicans as fungal strain. Ciprofloxacin was used as standard antibacterial drug and Flucanazole was used as standard antifungal drug. Standard strains were procured from Institute of Microbial Technology, Chandigarh.

The lowest concentration inhibiting growth of the organism is recorded as the MIC. DMSO was used as diluent. The stock 1000 μg/mL was prepared. Serial dilutions were prepared in primary and secondary screening. Mueller Hinton Broth was used as nutrient
medium to grow and dilute the drug suspension for the test bacteria, and sabaouraus dextrose broth used for fungal nutrition. Inoculum size for test strain was adjusted to $10^8$ CFU [Colony Forming Unit] per milliliter by comparing the turbidity. The control tube containing no antibiotic is immediately sub cultured (before inoculation) by spreading a loopful evenly over a quarter of plate of medium suitable for the growth of the test organism and put for incubation at 37 °C overnight. The tubes are then incubated overnight. The MIC of the control organism is read to check the accuracy of the drug concentrations. The amount of growth from the control tube before incubation (which represents the original inoculum) is compared.

**Table 1.** Antimicrobial activity (MIC μg/mL) of synthesized compounds 6(a-j) and 8(a-j)

<table>
<thead>
<tr>
<th>Compd.</th>
<th>Minimum inhibitory concentration, μg/mL</th>
<th>Gram +ve</th>
<th>Gram -ve</th>
<th>Antifungal</th>
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<tr>
<td></td>
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<td><em>S.aureus</em></td>
<td><em>B. subtilis</em></td>
<td><em>P.aeruginosa</em></td>
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<tr>
<td>6a</td>
<td></td>
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<td>500</td>
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<td>1000</td>
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<tr>
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<td>250</td>
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<tr>
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<tr>
<td>Flucanazole</td>
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</table>

From the screening results, it can be seen that compound 6d showed good activity against gram +ve bacteria. Compound 8e showed excellent activity against all bacteria, whereas Compound 8a displayed good activity against both of the Gram positive bacteria. Compound 6i was found significantly active against Gram positive bacteria *S.aureus* compared with Ciprofloxacin. Compound 8d showed good activity against Gram positive bacteria *S.aureus* and Gram negative bacteria *E.coli*. The tested compound 6d and 8a demonstrated good antifungal activity against *C.albicans*. Rest of the compounds showed moderate to weak activity against other bacteria and fungi compared with the standard drugs.

**Conclusion**

In this work, we have synthesized a series of new sydnone derivatives 6(a-j) and 8(a-j) which were tested for their antimicrobial activity and their structures are confirmed successfully by IR, $^1$H NMR, $^{13}$C NMR spectra and elemental analysis. Antibacterial activity
of title compounds showed that methyl group present at 4th position of piperazine ring in compound 8c could be responsible for increase activity against *S.aureus*, *B.subtilis*, *P.aeruginosa* and *E.coli*. Compound 6i has phenyl group at 2nd position and methyl group at 4th position to show highest activity against *S.aureus*. The activity varies with the different substituents on methylene and sulphonyl linkages.

**Acknowledgment**
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**References**