ISSN 1984-6428
ONLINE
www.orbital.ufms.br

Orbital 2009, *1* (3), 296-305

Full Paper

Synthesis and studies of bissydnone sulfonamides based on 4,4'-diaminodiphenyl methane

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Received: 02 October 2009; accepted: 30 December 2009. Available online: 16 January 2010.

ABSTRACT: *3,3'-(4,4'-Diphenyl)bissydnonyl methane* ***(5)*** *was synthesized and subjected to chlorosulfonation followed by amination resulted in to formation of 3,3'-(methylenedi-1,4-phenylene)bis[4-{(4-substituted-amino)sulfonyl} sydnone* ***(7a-j)****. The structure of the newly synthesized compounds was checked by spectral data and purity of the compounds was checked by elemental analysis as well as thin layer chromatography. Some compounds showed excellent activity against gram positive and gram negative bacterial strain.*

Keywords*: sulfonamide, mesoionic, sydnone, NMR spectroscopy, IR spectroscopy, elemental analysis*

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Introduction

During past years many interesting data have been obtained on the structures [1, 2], reactivities [3, 4], physicochemical properties [5, 6] and biological actions [7-10] of sydnone compounds. In recent years much attention has been devoted to the synthesis of sydnone and their biological activities. Carbon atom at 4th position of sydnone ring bears a partial negative charge, accordingly electrophilic substitution for instance halogenation [11], nitration [12], acylation [13], and sulfonation [14] occurs at 4th position.

Sydnone derivatives derived from 4,4'-bis(aminophenyl)sulfone (Figure 1) were found to possess antimalarial activity [15].

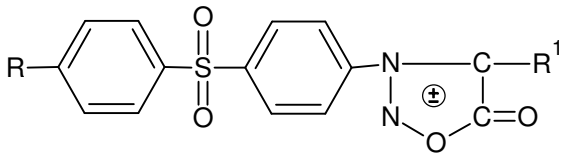


Figure 1. 4,4'-bis(aminophenyl)sulfones. Where R=Cl, NO_2 and R^1= H, Br.

3,3'-(4,4'-Diphenyl)bissydnonyl methane (Figure 2) showed strong effect on coronary dilation and inhibition of platelet aggregation. 3,3'-(4,4'-Diphenyl)bissydnonyl ether also showed cardiotropic and inhibition of platelet aggregation [16].

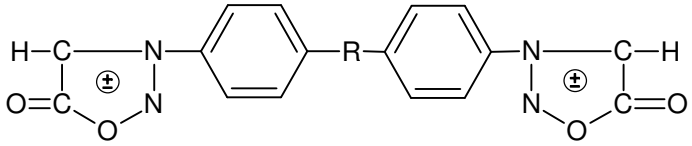


Figure 2. 3,3'-(4,4'-Diphenyl)bissydnonyl methane (R = CH_2) and 3,3'-(4,4'-Diphenyl)bissydnonyl ether (R = O).

Sulfonamide derivatives have proved fruitful area of research and subject of much interest due to their importance for various applications, and their widespread potential and proven biological and pharmacological activities. Sydnones have played a crucial role in the development of theory in heterocyclic chemistry and occupy a unique place in heterocycles. Badami et al [17-19] have synthesized various 3-arylsydnone-4-sulfonamide derivatives having potent biological properties.

These observations encouraged us to continue our current work to synthesize new

heterocyclic containing bissydnone sulfonamides based on 4,4′-diamino diphenyl methane.

Material and Methods

General

The starting material 4,4′-diaminodiphenyl methane was received from Atul Limited, Valsad. All other the reagents were of AR grade. All the melting points were uncorrected and were determined by open tube capillary method. CHN analysis was carried Carlo Erba 1108. IR spectra (KBr) were recorded on Shimadzu, Japan FTIR spectrophotometer. ^{1}H NMR spectra were recorded on Bruker Advance II 400 MHz NMR spectrometer and ^{13}C NMR spectra were recorded on Bruker Advance II 40 MHz NMR spectrometer using deuterated dimethylsulphoxide (DMSO-d_6) as a solvent and TMS as an internal standard. Purity of the compounds was checked by TLC on silica gel plates.

Chemistry

*2,2′-[Methylenebis(1,4-phenyleneimino)]diethyl acetate (**2**)*

4,4′-Diaminodiphenyl methane (1.98 g, 0.01 mol), ethylchloroacetate (2.13 mL, 0.02 mol) in dry ethanol (10 mL) and anhydrous sodium acetate (3.28 g, 0.04 mol) were refluxed for 5 hours. The mixture was diluted with water (10 mL). After standing overnight in the refrigerator, crystalline ester was obtained. The crude solid was purified by recrystallization from ethanol. Yield: 3.01 g, 80 %., m.p. 110-112 ^{0}C. I.R. (KBr): 2959, 2928, 2875, 2854, 1756, 1521,1307 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.34 (t, 6H, CH_3), 3.95 (s, 2H, NH), 4.05 (s, 6H, CH_2), 4.35 (q, 4H, OCH_2), 6.50-7.00 (m, 8H, Ar-H),. ^{13}C NMR (40 MHz, DMSO-d_6): δ 14.64, 40.50, 44.26, 61.24, 112.65, 128.95, 129.01, 145.87,170.97. Anal (%) for $C_{21}H_{26}N_2O_4$, Calcd. C, 68.09; H, 7.07; N, 7.56. Found: C, 68.13; H, 7.11; N, 7.58.

*2,2'-[Methylenebis(1,4-phenyleneimino)]diacetic acid (**3**)*

Compound **2** (3.70 g, 0.01 mol) and sodium hydroxide (1.2 g, 0.03 mol) were dissolved in a solution of distilled water and ehanol (36:4mL). The mixture was stirred at reflux temperature for 30 minutes. The resultant mixture was cooled and acidified with hydrochloric acid. White crystalline product was obtained, it was recrystallized from ethanol. Yield: 2.23 g, 70 %, m.p. 130-135 ^{0}C. I.R. (KBr): 2925, 2856, 2570-3209, 1719, 1518,1297 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.05 (s, 2H, CH_2), 4.10 (s, 4H, CH_2), 6.35 (s, 2H, NH), 6.40 (s, 2H, OH), 6.50-7.10 (m, 8H, Ar-H). ^{13}C NMR (40 MHz, DMSO-d_6): δ 40.82, 44.75, 112.28, 129.22, 129.47, 145.63, 171.54. Anal (%) for

$C_{17}H_{18}N_2O_4$. Calcd. C, 64.96; H, 5.77; N, 8.91. Found: C, 64.94; H, 5.79; N, 8.96.

*2,2'-{Methylenebis[1,4 -phenylene (nitrosoimino)]}diacetic acid (**4**)*[20]

To an ice-cold and well stirred solution of compound **3** (5.02 g, 0.016 mol) in water (40 mL), a freshly prepared sodium nitrate solution (3.32 g, 0.049 mol) was added drop wise over a period of 40 minutes. Concentrated hydrochloric acid was added till complete precipitation and allowed to stir cold solution for several minutes. The solid nitroso compound was filtered off and washed with cold water and dried. Yield: 3.80 g, 64 %. m.p. 130-135 ^{0}C. I.R. (KBr): 2925, 2853, 2570-3200, 1719, 1554, 1325 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.12 (s, 2H, CH_2), 4.84 (s, 2H, N-CH_2), 7.25-7.54 (m, 8H, Ar-H), 11.36 (s, 2H, COOH). ^{13}C NMR (40 MHz, DMSO-d_6): δ 40.61, 48.94, 122.88, 129.54, 137.20, 138.63, 167.61. Anal (%) for $C_{17}H_{16}N_4O_6$ Calcd. C, 54.84; H, 4.33; N, 15.05. Found: C, 54.81; H, 4.37; N, 14.98.

*3,3'-(4,4'-Diphenyl)bissydnonyl methane (**5**)*

The dried compound **4** (4.00 g, 0.0107 mol) was stirred for 12 hours in 40 mL acetic anhydride. The solution was poured slowly into cold water which was very well stirred. The pH of the content was adjusted to 7.0 with 10 % sodium bicarbonate solution. The solid crude product was washed well with water and dried. The crude sydnone was recrystallized from benzene-petroleum ether. The product obtained was orange solid.Yield: 2.52 g, 70 %. m.p. 120-123 ^{0}C. I.R. (KBr): 3157, 2925, 2853 1745 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.26 (s, 2H, CH_2), 7.76 (s, 2H, sydnone), 7.14-8.13 (m, 8H, Ar-H). ^{13}C NMR (40 MHz, DMSO-d_6): δ 39.43, 121.89, 128.26, 129.20, 139.36, 141.15, 168.20. Anal (%) for $C_{17}H_{12}N_4O_4$. Calcd. C, 60.71; H, 3.60; N, 16.66. Found: C, 60.68; H, 3.65; N, 16.63.

*3,3'-(Methylenedi-1,4-phenylene)bis(4-chlorosulfonyl) sydnone (**6**)*

Chlorosulfonic acid (2.32 mL, 0.02 mol) was added drop wise into the mixture of compound **5** (3.36 g, 0.01 mol) and catalytic amount of P_2O_5 over 30 minutes with constant stirring at 0-5 ^{0}C. The temperature of the well-stirred mixture does not rise above 5 ^{0}C. When all the chlorosulphonic acid has been added, reflux the mixture at about 60 ^{0}C for about 1 hour. The solution was then poured into a mixture of crushed ice and water with vigorous stirring. Precipitation was collected by filtration, washed three times with water and dried. Yield: 3.94 g, 74 %. m.p. 239-241 ^{0}C. I.R. (KBr): 2928, 1745, 1395, 1180 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.25 (s, 2H, CH_2), 7.29-8.12 (m, 8H, Ar-H). ^{13}C NMR (40 MHz, DMSO-d_6): δ 39.65, 121.76, 122.97, 128.58, 138.86, 140.85, 169.64. Anal (%) for $C_{17}H_{10}Cl_2N_4O_8S_2$. Calcd. C, 38.29; H, 1.89; N, 10.51. Found: C, 38.12; H, 2.01; N, 10.43.

General procedure for the synthesis of 3,3'-(Methylenedi-1,4-phenylene)bis[4-{(4-

*substituted-amino)sulfonyl} sydnone (**7a-j**)*

3,3'-(Methylenedi-1,4-phenylene)bis(4-chlorosulfonyl)sydnone (**6)** (5.86 g, 0.011 mol) was dissolved in acetone at room temperature. A solution of amine (0.022 mol) in acetone was added drop wise in to the solution of 3,3'-(Methylenedi-1,4-phenylene)bis(4-chlorosulfonyl)sydnone (**6)** over a period of 5 hours with constant stirring. Add 1.0 mL of pyridine to the well stirred solution after 1 hour and 2 hour 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.

*I.R., ^{1}H NMR and ^{13}C NMR of newly synthesized compounds **(7a-j)***

*3,3'-(Methylenedi-1,4-phenylene)bis[4-{(4-methylpiperazin-1-yl) sulfonyl} sydnone] (**7a**)*

Yield: 4.64 g, 64 %., m.p. 187-189 ^{0}C. IR (KBr): 1143, 1370, 1737, 2869, 2930, 2967, 3378 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.28-8.22 (m, 8H, Ar-H), 4.28(s, 2H, CH_2), 3.66 (t, 4H, SO_2NCH_2), 2.75 (t, 4H, NCH_2), 2.46 (s, 6H, CH_3); ^{13}C NMR (40 MHz, DMSO-d_6): δ 160.86, 141.76, 129.43, 128.96, 121.34, 89.76, 52.59, 44.50, 41.23, 39.53. Anal.(%) for $C_{27}H_{32}N_8O_8S_2$. Calcd. C, 49.08; H, 4.88; N, 16.96. Found: C, 49.12; H, 4.85; N, 16.93.

*3,3'-(Methylenedi-1,4-phenylene)bis[4-{(4-morpholin-4-yl)sulfonyl} sydnone] (**7b**)*

Yield: 4.19 g, 60 %., m.p. 170-172 ^{0}C. IR (KBr): 1143, 1158, 1372, 1734, 2933 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.23-8.18 (m, 8H, Ar-H), 4.27 (s, 2H, CH_2), 3.47-3.73 (m, 16H, morpholine); ^{13}C NMR (40 MHz, DMSO-d_6): δ 160.49, 141.62, 129.85, 129.11, 121.17, 89.70, 62.72, 42.56, 39.30. Anal.(%) for $C_{25}H_{26}N_6O_{10}S_2$. Calcd. C, 47.31; H, 4.13; N, 13.24. Found: C, 47.36; H, 4.05; N, 13.29.

*3,3'-(Methylenedi-1,4-phenylene)bis[4-{(diethylamino)sulfonyl} sydnone] (**7c**)*

Yield: 4.26 g, 64 %, m.p. 178-180 ^{0}C. IR (KBr): 954, 1143, 1375, 1735, 2931, 2884, 2849 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.23-8.18 (m, 8H, Ar-H), 1.18 (t, 12H, CH_3), 3.15 (q, 8H, CH_2), 4.23 (s, 2H, CH_2); ^{13}C NMR (40 MHz, DMSO-d_6): δ 160.96, 141.24, 129.92, 129.10, 121.23, 89.36, 42.15, 39.54, 14.96. Anal.(%) for $C_{25}H_{30}N_6O_8S_2$. Calcd. C, 49.49; H, 4.98; N, 13.85. Found: C, 49.41; H, 4.95; N, 13.79.

*3,3'-(Methylenedi-1,4-phenylene)bis[4-{(diphenylamino)sulfonyl} sydnone] (**7d**)*

Yield: 5.01 g, 57 %, m.p. 173-175 ^{0}C. IR (KBr): 1148, 1364, 1742, 2936 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.32-8.38 (m, 28H, Ar-H), 4.23 (s, 2H, CH_2); ^{13}C NMR (40 MHz, DMSO-d_6): δ 160.59, 142.69, 141.52, 130.32, 129.91, 129.15, 128.95, 127.73, 121.54, 89.43. Anal. (%) for $C_{41}H_{30}N_6O_8S_2$. Calcd. C, 61.64; H, 3.79; N, 10.52. Found: C,

61.69; H, 3.85; N, 10.59.

*3,3'-(Methylenedi-1,4-phenylene)bis[4-{(4-phenylpiperazin-1-yl) sulfonyl} sydnone] (**7e**)*

Yield: 5.10 g, 59 %, m.p. 184-186 ^{0}C. IR (KBr): 1145, 1372, 1738, 2930, 3372 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.80-8.33 (m, 18H, Ar-H), 4.31 (s, 2H, CH_2), 3.75-3.68 (m, 16H, piperazine); ^{13}C NMR (40 MHz, DMSO-d_6): δ 160.64, 152.54, 141.63, 129.70, 129.15, 129.04, 121.08, 119.86, 116.45, 89.71, 50.55, 44.48, 39.30. Anal.(%) for $C_{37}H_{36}N_8O_8S_2$. Calcd. C, 56.62; H, 4.62; N, 14.28. Found: C, 56.68; H, 4.68; N, 14.33.

*3,3'-(Methylenedi-1,4-phenylene)bis[4-{(imidazol-1-yl)sulfonyl} sydnone] (**7f**)*

Yield: 4.06 g, 62 %, m.p. 171-173 ^{0}C. IR (KBr): 1151, 1365, 1740, 2937, 3157-2830 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.35 (s, 2H, N=CH-N), 7.31-8.42 (m, 8H, Ar-H), 8.32 (d, 2H, NCH), 7.75 (d, 2H, NCH), 4.25 (s, 2H, CH_2); ^{13}C NMR (40 MHz, DMSO-d_6): δ 160.75, 141.52, 138.12, 135.73, 121.80, 129.78, 129.21, 119.78, 89.55, 39.30 Anal.(%) for $C_{23}H_{16}N_8O_8S_2$. Calcd. C, 46.31; H, 2.70; N, 18.78. Found: C, 46.36; H, 2.64; N, 18.84.

*3,3'-(Methylenedi-1,4-phenylene)bis[4-{(4-ethylpiperazin-1-yl)sulfonyl} sydnone] (**7g**)*

Yield: 4.39 g, 58 %, m.p. 166-168 ^{0}C. IR (KBr): 1145, 1363, 1743, 2864, 2879, 2932, 2968, 3374 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.31-8.27 (m, 8H, Ar-H), 4.25 (s, 2H, CH_2), 2.92 (t, 8H, N-CH_2), 2.73 (q, 4H, CH_2), 2.60 (t, 8H, SO_2NCH_2), 1.25 (t, 6H, CH_3); ^{13}C NMR (40 MHz, DMSO-d_6): δ 160.54, 141.43, 129.95, 129.13, 121.19, 89.37, 51.10, 50.64, 40.23, 39.32, 11.12. Anal. (%) for $C_{29}H_{36}N_8O_8S_2$. Calcd. C, 50.57; H, 5.27; N, 16.27. Found: C, 50.52; H, 5.23; N, 16.33.

*3,3'-(Methylenedi-1,4-phenylene)bis[4-{(4-[2,6-dichlorophenyl]piperazin-1-yl) sulfonyl}sydnone] (**7h**)*

Yield: 6.59 g, 65 %, m.p. 169-171 ^{0}C. IR (KBr): 1092, 1146, 1361, 1744, 2933, 3381 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.19-8.25 (m, 14H, Ar-H), 4.25 (s, 2H, CH_2), 3.87-3.79 (m, 16H, piperazine); ^{13}C NMR (40 MHz, DMSO-d_6): δ 160.64, 143.88, 136.65, 129.97, 129.11, 128.62, 125.75, 121.32, 89.66, 50.21, 44.62, 39.30. Anal.(%) for $C_{37}H_{32}Cl_4N_8O_8S_2$. Calcd. C, 48.17; H, 3.50; N, 12.14. Found: C, 48.23; H, 3.54; N, 12.18.

*3,3'-(Methylenedi-1,4-phenylene)bis[4-{(2-methylpiperazin-1-yl)sulfonyl} sydnone] (**7i**)*

Yield: 3.99 g, 55 %, m.p. 158-160 ^{0}C. IR (KBr): 1157, 1367, 1729, 2878, 2945, 2963, 3378 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.30-8.22 (m, 8H, Ar-H), 4.53 (q, 2H, N-CH piperazine), 4.26 (s, 2H, CH_2), 3.67 (t, 4H, NCH_2 piperazine), 3.21 (t, 4H, CH_2

piperazine), 2.80 (d, 4H, CH_2 piperazine), 1.78 (s, 2H, NH), 1.39 (d, 6H, CH_3); ^{13}C NMR (40 MHz, DMSO-d_6): δ 160.34, 141.67, 129.67, 128.54, 121.32, 89.86, 50.94, 47.32, 45.70, 41.64, 39.26, 17.44. Anal.(%) for $C_{27}H_{32}N_8O_8S_2$. Calcd. C, 49.08; H, 4.88; N, 16.96. Found: C, 49.12; H, 4.94; N, 16.93.

*3,3'-(Methylenedi-1,4-phenylene)bis[4-{(piperazin-1-yl)sulfonyl} sydnone] (**7j**)*

Yield: 5.01 g, 57 %, m.p. 163-165 ^{0}C. IR (KBr): 1163, 1364, 1737, 2945, 3370 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.25-8.17 (m, 8H, Ar-H), 4.28 (s, 2H, CH_2), 3.67-3.26 (m, 16H, $NHCH_2$), 2.80 (s, 2H, NH); ^{13}C NMR (40 MHz, DMSO-d_6): δ 160.64, 141.56, 129.89, 129.11, 121.12, 89.46, 45.12, 41.81, 39.30. Anal. (%) for $C_{25}H_{28}N_8O_8S_2$. Calcd. C, 47.46;H, 4.46; N, 17.71. Found: C, 47.54; H, 4.53; N, 17.65.

Antibacterial Activity

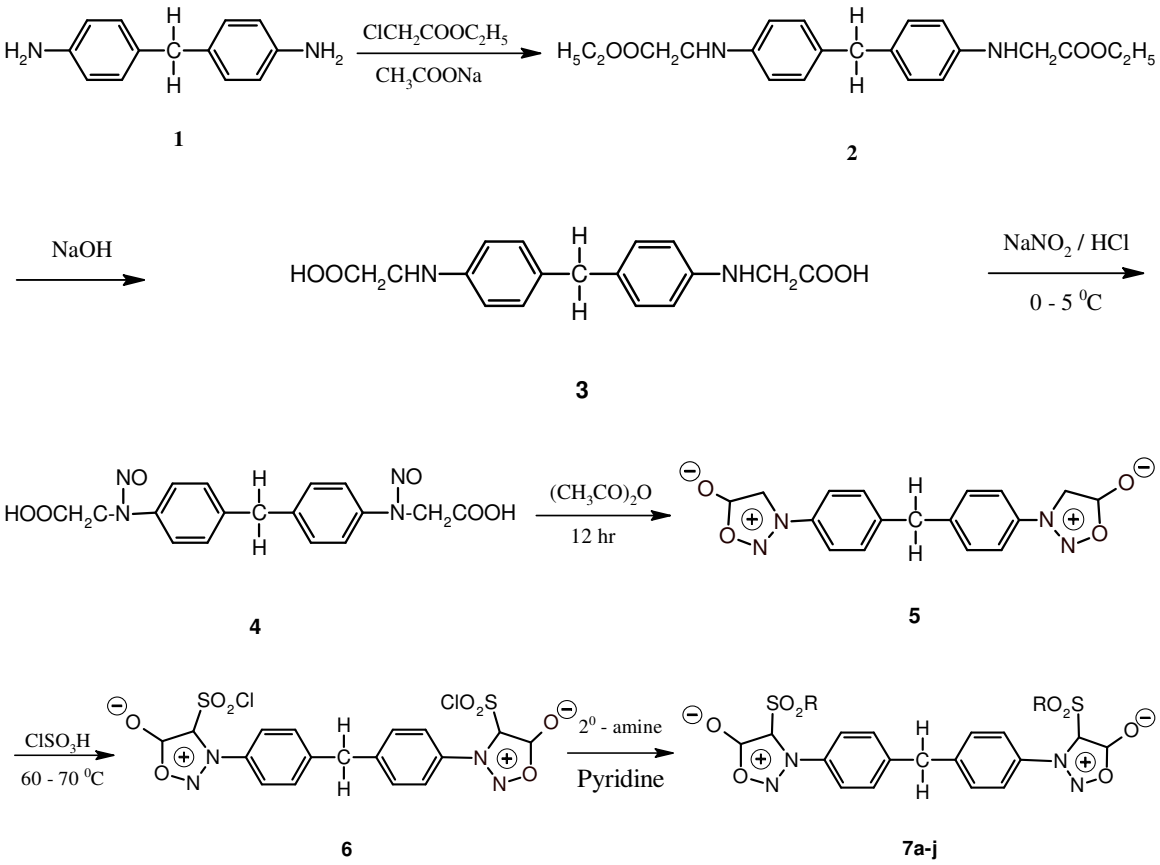
Newly synthesized compounds were also screened for their antibacterial activity against four species of bacterial strain in which two are gram positive bacteria, they are *Streptococcus pneumoniae*, *Staphylococcus aureus* and rest of two are gram negative bacteria, they are *Escherichia coli*, *Pseudomonas aeruginosa* and compare with standard drugs Penicillin and Streptomycin. Minimum Inhibitory Concentration (MIC) was determined by Broth Dilution Method [21] and Zone of Inhibition was determined by Agar Cup Method (Kirby-Bauer Technique) [22].

The sample compounds were screened at 200 µg/mL under identical conditions and the zone of inhibition was measured in mm. A reading of 10 mm indicates no zone.

Results and Discussion

Herein we have described the synthesis, characterization and biological evaluation of novel 3,3'-(methylenedi-1,4-phenylene)bis(4-substituted amino sulfonyl)sydnone (**7a-j**). The reaction of 3,3'-(methylenedi-1,4-phenylene)bis(4-chlorosulfonyl)sydnone (**6**) with substituted amine derivatives led to the formation of 3,3'-(Methylenedi-1,4-phenylene)bis[4-{(substituted amino)sulfonyl}sydnone (**7a-j,** Scheme 1). All compounds were analyzed satisfactorily by CHN elemental analysis. The I.R spectrum of the compounds displayed absorption band between 1729-1744 cm^{-1} which is the characteristics of carbonyl group of sydnone and also showed 1361-1375, 1143-1157 and 2930-2945 cm^{-1}, characteristic of $SO_{2asy,}$ SO_{2sym} and CH_2 group. All the IR spectral characteristics of different sulfonamide samples are in good agreement with proposed structure and are shown in experimental section. The IR spectrum of compound **5** showed absorption bands at 1745 cm^{-1} characteristic to the C=O group. The ^1H NMR

spectra of compound **5** showed a singlet at δ 7.76 ppm characteristic to the proton at C_4 of the sydnone. The ^{1}H NMR of compounds (**7a-j**) displayed the chemical shift value near δ 7.19-8.42 ppm is due to the presence of aromatic protons. ^{13}C NMR of carbon at four position of sydnone ring resonance at near δ 90.00 and carbonyl carbon of sydnone ring near δ 161.00. The other proton shift values of (**7a-j**) are indicating in experimental section. The antibacterial activity of all the synthesized compounds is shown in Table 1. Compound **7e** is found most active against *S. pneumoniae* and *P. aeruginosa*. Phenyl substitution at 4th position of phenyl ring increase activity against these two micro organism species while **7a** bearing methyl group at fourth position of piperazine ring shows highest activity against *S. aureus*. Compound **7i** bearing methyl group at second position of piperazine ring shows highest activity against *E. coli* while compound **7e** found most active against *P. Aeruginosa*. The yield of the compounds **7a-j** varies from 55-65 %, depending upon nature of amine component used.



Scheme 1: Synthesis of 3,3'-(methylenedi-1,4-phenylene)bis[4-{(4-substituted-amino) sulfonyl} sydnone (**7a-j**) from 4,4'-diaminodiphenyl methane. R = 7a: N-methyl piperazine; 7b: morpholine; 7c: diethylamine; 7d: diphenylamine; 7e: N-phenyl piperazine; 7f: imidazole; 7g: N-ethyl piperazine; 7h: *N*-(2,6-dichlorophenyl)piperazine; 7i: 2-methyl piperazine; 7j: piperazine.

Conclusion

The new sulfonamide derivatives of sydnone were synthesized and evaluated their antibacterial activity. The activity varies with the different substituent on sulfonamide linkage. It is noted that the potential of the compounds increase, minimum inhibitory concentration decreases. Most of the compounds found to possess antibacterial activity.

Table 1. Antibacterial activity of 3,3'-(Methylenedi-1,4-phenylene)bis(4-substituted-amino sulfonyl)sydnone (**7a-j**).

Compd. No.	**Gram Positive Organism**				**Gram Negative Organism**			
	S.pneumoniae		***S.aureus***		***E.Coli***		***P. aeruginosa***	
	IZ	**MIC**	**IZ**	**MIC**	**IZ**	**MIC**	**IZ**	**MIC**
7a	14	64	18	32	13	64	10	-
7b	12	128	13	128	16	32	12	128
7c	10	-	14	64	14	32	13	64
7d	14	32	16	32	18	16	12	128
7e	17	32	15	32	16	32	13	32
7f	14	32	15	32	16	16	10	-
7g	10	-	13	64	14	64	10	-
7h	12	64	10	-	15	32	13	64
7i	13	64	14	64	17	32	12	128
7j	13	64	10	-	14	64	13	64
Streptomycin	40	0.25	40	0.125	28	1.0	34	0.5
Penicillin-G	35	0.25	45	0.125	30	0.5	38	0.25

Acknowledgements

We are grateful to Atul Limited, Valsad for providing some useful chemicals. We also thank to Head of the Department of Chemistry, Veer Narmad South Gujarat University, Surat for providing necessary research facilities.

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