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Note

Synthesis and characterization of some sulfonamide based bis-sydnones and their *in vitro* antimicrobial activity

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4-Sulfonamide substituted novel sydnones have been synthesized. The synthetic strategy utilizes 4,4′-diaminodiphenyl-sulfone as starting material to obtain the 3,3′-(sulfonyldi-4,1-phenylene)bis(4-chlorosulfonyl)sydnone **6** through several steps *viz.* esterification, hydrolysis (saponification), nitrosation, cyclisation and chlorosulfonation, which are then condensed with different secondary amines to get final compounds. All new compounds have been characterized by spectral data as well as elemental analysis and have been tested for their antibacterial activity against gram positive *S. pneumoniae* and *S. aureus*, and gram negative bacteria *E. coli* and *P. aeruginosa*. Some of the synthesized compounds show excellent antimicrobial activity.

Keywords: Synthesis, bis-sydnone, *in vitro*, mesoionic, pharmacological

Ever since their first reported synthesis, sydnones have received much attention and have been reviewed by several authors[1]. Because of their mesoionic character[2], they have been the subject of continual study since their discovery. Many of the substituted sydnones and their derivatives have been proved to possess valuable biological activity[3] and their pharmacological activities in some instance were found high enough for practical purposes[4]. Sydnone compounds are distinct from other aromatic compounds in both reactivity and stability[7]. Interest in sydnone derivatives have increased day by day. Besides, compounds related to 4,4′-diaminodiphenyl sulfone act as antimalarial agents[5] and also the piperazine derivatives are important pharmacophores across a number of different therapeutic areas[6]. Sulfonamides are broad-spectrum antimicrobials inhibiting both gram-positive and gram-negative bacteria, as well as some protozoa, such as coccidians. Piperazine sulfonamides are among the most widely used antibacterial[8] agents in the world, chiefly because of their low cost, low toxicity, and excellent activity against common bacterial disease. In this article is described the further utilization of this strategy for the synthesis of some new 3,3′-(sulfonyldi-4,1-phenylene)bis(4-secondary substituted amino sulfonyl) sydnone **7a-j**.

Results and Discussion

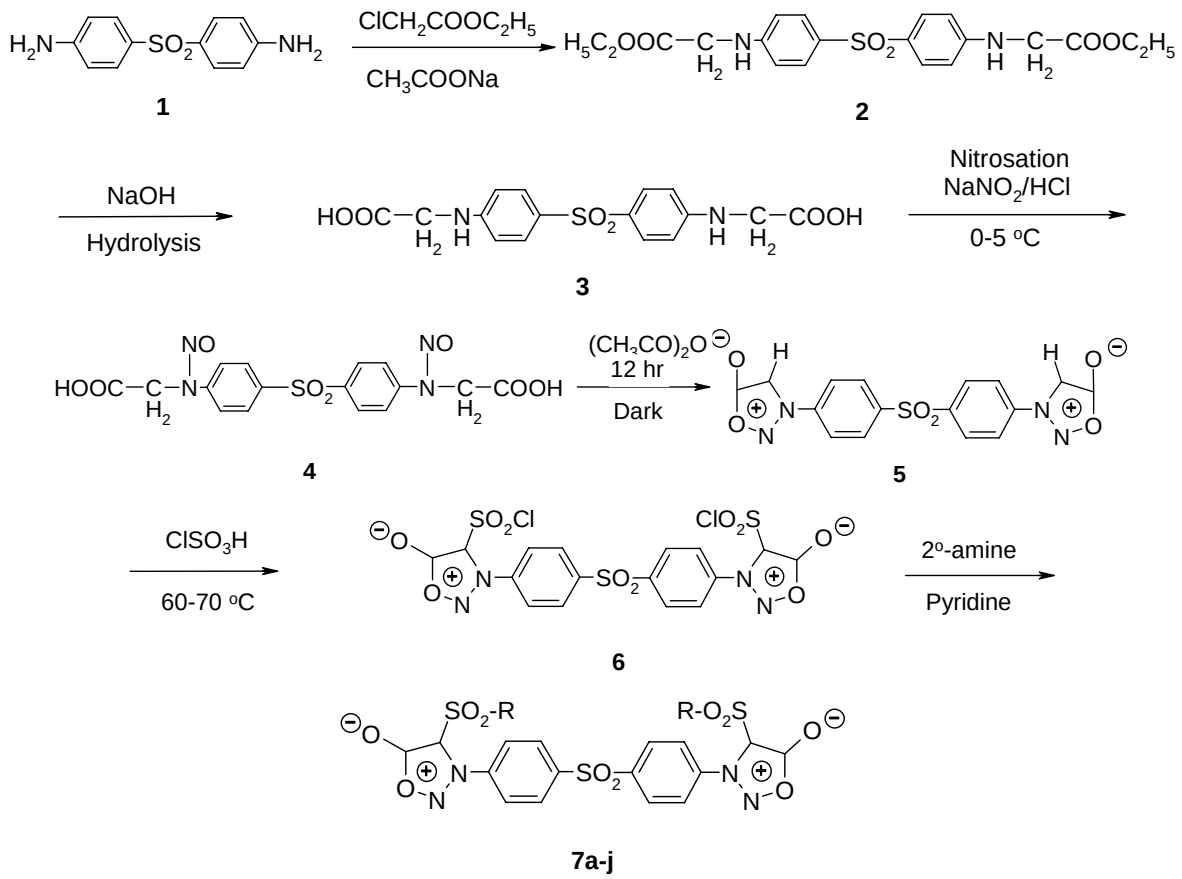
3,3′-(4,4′-Diphenyl)-bissydnonyl sulfone **5** is synthesized by cyclisation of corresponding N-nitro-sophenyl glycine derivative with acetic anhydride. Corresponding bis-sydnone sulfonyl chloride derivative is synthesized by reaction of 1 mole of compound **5** with 2 mole of chlorosulfonic acid in presence of phosphorous pentoxide as catalyst. Sulfonamide derivatives of bis-sydnone **7a-j** are synthesized by condensation of bissydnone sulfony-chloride **6** with different amine derivatives (**Scheme I**). The structure of **7a-j** was confirmed on the basis of their elemental and spectral analysis.

Experimental Section

Melting points were determined by open capillary method and are uncorrected. All compounds were analyzed satisfactorily for C, H, O, N and S. IR spectra (KBr) were recorded on a Shimadzu, Japan FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Advance II 400 MHz NMR spectrometer using DMSO-d_6 as solvent and TMS as internal standard. Mass spectra were recorded on LC/MS instrument operating at 70 eV. C, H, O, N, S analysis was carried out on a Vairo-EL (Elementa) model. Homogeneity of the compounds was checked by TLC on silica gel plates.

General procedure for the synthesis of 3,3′-(sulfonyldi-4,1-phenylene)bis(4-secondary substituted aminosulfonyl)sydnones, 7a-j

4,4′-diaminodiphenyl sulfone (2.48 g, 0.01 mole), ethyl chloro acetate (2.13 mL, 0.02 mole) and anhydrous sodium acetate (3.28 g, 0.04 mole) in dry ethanol (10 mL) together reflux for about 5 hr. The mixture was diluted with water (10 mL). After standing overnight in the refrigerator, crystalline ester **2** was obtained. The compound was purified by recrystallisation from ethanol.



Scheme I

The alkaline solution obtained by boiling **2** (0.01 mole) with sodium hydroxide (0.03 mole) in 36:4 mL (water:ethanol) for 0.5 hr was cooled and acidified with concentrated hydrochloric acid. Pure product **3** was obtained by recrystallisation from ethanol.

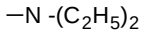
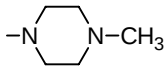
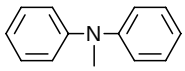
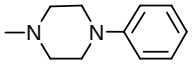
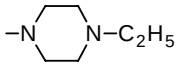
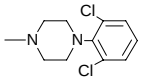
To an ice-cold and well stirred solution of compound **3** (5.82 g, 0.016 mole) in water (40 mL), a freshly prepared sodium nitrate solution (3.32 g, 0.049 mole) in water (10 mL) was added dropwise over a period of 40 min. Concentrated hydrochloric acid was added till complete precipitation and the cold solution allowed to stir for several min. The nitroso compound **4** was filtered off and washed with cold water and dried.

The dried solution of compound **4** in excess of acetic anhydride was stirred for 10 hr. The solution was poured slowly into cold water which was very well stirred. The *p*H of the contents was adjusted to 7.0 with 10% sodium bicarbonate solution. It was then washed well with water and dried. The crude sydnone **5** was purified by recrystallization from benzene-petroleum ether.

Chlorosulfonic acid (2.32 mL, 0.02 mole) was added dropwise into the mixture of compound **5** (3.86 g, 0.01 mole) and catalytic amount of P_2O_5 over 30 min with constant stirring at 0-5°C. The temperature of the well-stirred mixture was not allowed to rise above 5°C. When all the chlorosulphonic acid has been added (about 1 hr), the mixture was refluxed at about 60°C for 1 hr. The solution was then poured into a mixture of crushed ice and water with vigorous stirring. Precipitates of compound **6** were collected by filtration, washed with water and dried.

Compound **6** (0.011 mole) was dissolved in acetone at RT. A solution of amine (0.022 mole) in acetone was added dropwise into the solution of compound **6** over a period of 5 hr with constant stirring. Pyridine (1.0 mL) was added to the well stirred solution after 1 hr and 2 hr respectively during the reaction. The solution was poured into ice with stirring. The precipitate was collected by filtration, washed thrice with water and dried. The synthesized compounds were characterized (**Table I**) after purification by recrystallization from benzene.

Table I — Characterization data of 3,3′-(sulfonyldi-4,1-phenylene)bis(4-secondary substituted amino sulfonyl)sydnones **7a-j**

Compd	R	Mol. Formula (Mol.Wt.)	Yield (% w/w)	m.p. (°C)	Calcd % (Found) C	H	O	N	S
7a		$C_{24}H_{24}N_6O_{12}S_3$ (684.67)	59	178	42.10 (41.95	3.53 3.55	28.04 28.10	12.27 12.21	14.05 13.97)
7b		$C_{24}H_{32}N_6O_8S_3$ (628.75)	64	188	45.85 (45.93	5.13 5.20	20.36 20.40	13.37 13.42	15.30 15.22)
7c		$C_{26}H_{30}N_8O_{10}S_3$ (710.75)	62	170	43.94 (43.98	4.25 4.33	22.51 22.60	15.77 15.72	13.53 13.60)
7d		$C_{40}H_{28}N_6O_{10}S_3$ (848.87)	58	164	56.60 (56.53	3.32 3.28	18.85 18.90	9.90 9.83	11.33 11.27)
7e		$C_{36}H_{34}N_8O_{10}S_3$ (834.89)	63	189	51.79 (51.87	4.10 4.04	19.16 19.13	13.42 13.37	11.52 11.59)
7f		$C_{22}H_{14}N_8O_{10}S_3$ (646.58)	65	147	40.87 (40.83	2.18 2.13	24.74 24.70	17.33 17.28	14.88 14.82)
7g		$C_{28}H_{34}N_8O_{10}S_3$ (738.81)	64	159	45.52 (45.58	4.64 4.69	21.66 21.62	15.17 15.10	13.02 13.10)
7h		$C_{36}H_{30}Cl_4N_8O_{10}S_3$ (972.67)	64	175	44.45 (44.40	3.11 3.18	16.45 16.50	11.52 11.42	9.89 9.96)
7i		$C_{26}H_{30}N_8O_{10}S_3$ (710.75)	58	167	43.94 (43.99	4.25 4.29	22.51 22.59	15.77 15.70	13.53 13.62)
7j		$C_{24}H_{26}N_8O_{10}S_3$ (682.70)	62	187	42.22 (42.28	3.84 3.90	23.44 23.49	16.41 16.38	14.09 14.16)

IR, ^{1}H NMR, ^{13}C NMR and mass spectra of newly synthesized compounds

2: IR (KBr): 3455, 2945, 1339, 1150 cm^{-1}; ^{1}H NMR: δ 1.33 (t, 6H, CH_3), 3.70 (s, 2H, CH_2), 4.00 (s, 2H, NH), 4.35 (q, 4H, COO-CH_2), 6.47-7.70 (m, 8H, Ar-H); ^{13}C NMR: δ 14.46, 61.45, 44.42, 115.08, 128.07, 133.38, 149.12, 171.49; MS: *m/z* 420 consistent with the molecular formula $C_{20}H_{24}N_2O_6S$.

3: IR (KBr): 3459, 2948, 1343, 1350 cm^{-1}; ^{1}H NMR: δ 4.03 (s, 4H, CH_2), 6.37 (s, 2H, NH), 6.40 (s, 2H, COOH), 6.49-7.45 (m, 8H, Ar-H); ^{13}C NMR: δ 44.77, 114.56, 128.64, 133.57, 148.96, 171.79; MS: *m/z* 364 consistent with the molecular formula $C_{16}H_{16}N_2O_6S$.

4: IR (KBr): 2935, 1557, 1355, 1347 cm^{-1}; ^{1}H NMR: δ 4.79 (s, 4H, CH_2), 7.87-8.10 (m, 8H, Ar-H), 11.37 (s, 2H,COOH); ^{13}C NMR: δ 49.24, 121.40, 128.92, 134.77, 141.33, 167.77; MS: *m/z* 422 consistent with the molecular formula $C_{16}H_{14}N_4O_8S$.

5: IR (KBr): 3195, 1745, 1339 cm^{-1}; ^{1}H NMR: δ 7.80 (s, 2H, sydnone), 8.54-8.06 (m, 8H, Ar-H); ^{13}C NMR: δ 95.67, 122.82, 128.70, 131.77, 141.98, 169.13; MS: *m/z* 386 consistent with the molecular formula $C_{16}H_{10}N_4O_6S$.

Table II — *In vitro* activity of compounds **7a-j**

Compd	Gram Positive bacteria				Gram Negative bacteria			
	S. pneumoniae		*S. aureus*		*E. coli*		*P. aeruginosa*	
	IZ	MIC	IZ	MIC	IZ	MIC	IZ	MIC
7a	16	16	19	16	18	16	15	16
7b	14	32	13	64	12	128	13	64
7c	16	32	17	16	17	16	10	-
7d	13	64	14	32	13	64	11	128
7e	10	-	15	32	12	128	10	-
7f	16	32	17	16	17	32	12	64
7g	16	16	18	16	15	32	15	32
7h	13	64	13	128	13	64	10	-
7i	10	-	14	64	12	128	12	128
7j	10	-	13	64	13	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

IZ: Inhibition Zone. MIC: Minimum Inhibitory Concentration

6: IR (KBr): 1745, 1410, 1336 cm^{-1}; ^1H NMR: δ 8.54-8.22 (m, 8H, Ar-H); ^{13}C NMR: δ 168.47, 139.64, 123.18, 126.16, 128.36, 141.66; MS: *m/z* 583 consistent with the molecular formula $C_{16}H_8Cl_2N_4O_{10}S_3$.

7a: IR (KBr): 1732, 1379, 1152 cm^{-1}; ^1H NMR: δ 3.46 (t, 8H, -N-CH_2 morpholine), 3.80 (t, 8H, OCH_2 morpholine), 8.10-8.60 (m, 8H, Ar-H); ^{13}C NMR: δ 42.59, 62.63, 122.72, 129.41, 132.24, 136.30, 142.21, 167.30; MS: *m/z* 684 consistent with the molecular formula $C_{24}H_{24}N_6O_{12}S_3$.

7b: IR (KBr): 2940, 1747, 1460, 1379 cm^{-1}; ^1H NMR: δ 1.06 (t, 12H, CH_3), 3.19 (q, 8H, N-CH_2), 8.10-8.60 (m, 8H, Ar-H); ^{13}C NMR: δ 15.00, 42.10, 122.85, 129.45, 132.75, 137.37, 142.24, 165.33; MS: *m/z* 628 consistent with the molecular formula $C_{24}H_{32}N_6O_8S_3$.

7c: IR (KBr): 2957, 1755, 1379, 1335 cm^{-1}; ^1H NMR: δ 2.36 (s, 6H, CH_3), 2.83 (t, 8H, N-CH_2), 3.56 (t, 8H, SO_2N-CH_2), 8.00-8.60 (m, 8H, Ar-H); ^{13}C NMR: δ 41.35, 44.21, 52.55, 122.84, 129.49, 132.23, 135.42, 142.54, 167.64; MS: *m/z* 710 consistent with the molecular formula $C_{26}H_{30}N_8O_{10}S_3$.

7d: IR (KBr): 1741, 1379, 1160 cm^{-1}; ^1H NMR: δ 7.00-8.65 (m, 28H, Ar-H); ^{13}C NMR: δ 122.95, 127.72, 129.10, 129.43, 130.40, 132.45, 138.54, 142.24, 142.56, 166.97; MS: *m/z* 848 consistent with the molecular formula $C_{40}H_{28}N_6O_{10}S_3$.

7e: IR (KBr): 1740, 1379, 1335 cm^{-1}; ^1H NMR: δ 2.89 (t, 8H, NCH_2 piperazine), 3.69 (t, 8H, N-CH_2), 3.73 (t, 8H, SO_2NCH_2 piperazine), 7.21-8.63 (m, 18H, Ar-H); ^{13}C NMR: δ 45.00, 50.24, 115.96, 119.97, 123.10, 129.23, 129.43, 132.25, 137.21, 142.64, 152.30, 168.46; MS: *m/z* 834 consistent with the molecular formula $C_{36}H_{34}N_8O_{10}S_3$.

7f: IR (KBr): 3375, 1734, 1379 cm^{-1}; ^1H NMR: δ 7.75 (d, CH imidazole), 8.29 (d, 2H, CH imidazole), 8.15-8.72 (m, 8H, Ar-H), 9.27 (s, 2H, N=CH-N imidazole); ^{13}C NMR: δ 119.90, 123.44, 129.45, 132.00, 135.28, 138.26, 138.39, 142.28, 168.94; MS: *m/z* 646 consistent with the molecular formula $C_{22}H_{14}N_8O_{10}S_3$.

7g: IR (KBr): 2960, 1737, 1379, 1335 cm^{-1}; ^1H NMR: δ 1.17 (t, 6H, CH_3), 2.63 (q, 4H, CH_2), 2.81(t, 8H, $C_2H_5NCH_2$ piperazine, 3.63 (t, 8H, SO_2NCH_2 piperazine), 8.21-8.64 (m, 8H, Ar-H); ^{13}C NMR: δ 11.36, 41.70, 44.90, 52.45, 122.75, 129.45, 132.27, 136.74, 142.23, 169.59; MS: *m/z* 738 consistent with the molecular formula $C_{28}H_{34}N_8O_{10}S_3$.

7h: IR (KBr): 1757, 1385, 1331, 743 cm^{-1}; ^1H NMR: δ 3.77 (t, 6H, C-N-CH_2 piperazine), 3.87 (t, 6H, SO_2NCH_2 piperazine), 7.20-7.45 (m, 6H, Ar-H), 8.20-8.59 (m, 8H, Ar-H); ^{13}C NMR: δ 44.73, 50.31, 122.75, 125.70, 128.78, 129.43, 132.26, 136.15, 138.30, 142.25, 144.10, 165.87; MS: *m/z* 980 (M^++8) consistent with the molecular formula $C_{36}H_{30}Cl_4N_8O_{10}S_3$.

7i: IR (KBr): 2960, 1726, 1389, 1329 cm^{-1}; ^1H NMR: δ 1.35 (d, 6H, CH_3), 3.06 (d, 4H, CH_2 piperazine), 3.17 (t, 4H, CH_2 piperazine), 3.68 (t, 4H, NCH_2 piperazine), 4.10 (m, 2H, NCH piperazine), 8.21-8.60 (m, 8H, Ar-H); ^{13}C NMR: δ 17.60, 41.73, 45.70, 47.83, 50.83, 122.81, 129.50, 132.10, 136.60, 142.29, 169.36; MS: *m/z* 710 consistent with the molecular formula $C_{26}H_{30}N_8O_{10}S_3$.

7j: IR (KBr): 1743, 1394, 1325 cm^{-1}; ^1H NMR: δ 2.72 (s, 2H, NH), 3.21 (t, 8H, CH_2NH), 3.59 (t, 8H, NCH_2 piperazine), 8.19-8.58 (m, 8H, Ar-H); ^{13}C NMR: δ 41.73, 45.15, 123.70, 130.43, 132.29, 137.37, 166.96, 142.25; MS: *m/z* 682 consistent with the molecular formula $C_{24}H_{26}N_8O_{10}S_3$.

Antimicrobial activity: The main purpose of the present work is to synthesize new heterocyclic compounds that might be of biological interest. All the synthesized compounds were screened for their antibacterial activity *in vitro* (**Table II**) against gram positive bacteria *Streptococcus pneumoniae* and *Staphylococcus aureus*, and gram negative bacteria *Escherichia coli* and *Pseudomanas aeruginosa*. Preliminary antimicrobial testing has been carried out by the Kirby-Bauer Technique. The reference drugs used were Streptomycin and Penicillin-G respectively. The activity of the samples and the reference drugs was assayed under identical conditions at 200 μg/mL concentration in DMF and the zone of inhibition was measured in mm. In

general all the synthesized 3,3′-(sulfonyldi-4,1-phenylene) bis(4-secondary substituted amino-sulfonyl) sydnone **7a-j** exerted a wide range of modest antibacterial *in vitro* against the tested organisms.

Conclusion

The title compounds were synthesized as new compounds with biological activity and their structures were confirmed successfully by spectral and elemental analyses. The present investigation is centered on the studies of reactions, synthesis, spectral analysis and antimicrobial activity of bis-sydnone sulfonamides.

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