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Synthesis, characterization and antimicrobial activity of new aliphatic sulfonamide

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Abstract—A series of novel aliphatic sulfonamide derivatives (**1**–**7**) were synthesized and characterized by elemental analyses, FT-IR, ^{1}H NMR, ^{13}C NMR and LC–MS techniques. All the synthesized compounds were evaluated in vitro as antimicrobial agents against representative strains of Gram-positive (*Staphylococcus aureus* ATCC 25953, *Bacillus cereus* ATCC 6633 and *Listeria monocytogenes* ATCC Li6 (isolate), Gram-negative bacteria (*Escherichia coli* ATCC 11230) and antifungal agent against *Candida albicans* (clinical isolate) by both disc diffusion and minimal inhibition concentration (MIC) methods. All these bacteria and fungus studied were screened against some antibiotics to compare with our chemicals' zone diameters. Our aliphatic sulfonamides have highest powerful antibacterial activity for Gram-negative bacteria than Gram-positive bacteria and antibacterial activity decreases as the length of the carbon chain increases.
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1. Introduction

The sulfonamide –SO_2NH– group occurs in numerous biologically active compounds, which include antimicrobial drugs, saluretics, carbonic anhydrase inhibitors, insulin-releasing sulfonamides, antithyroid agents, antitumour drugs and number of other biological activities.[1–9]

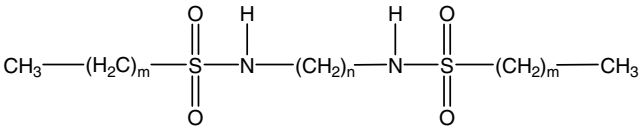
Sulfonamides are among the most widely used antibacterial agents in the world, chiefly because of their low cost, low toxicity and excellent activity against common bacterial diseases. The synergetic action of sulfonamides with trimethoprim has brought about enormous resurgence of sulfonamide usage everywhere over the last decade.

This prompted us to synthesize a series of novel symmetric aliphatic sulfonamides. So, we obtained a series of new symmetric sulfonamides (**1**–**7**) and characterized their structure by FT-IR, ^{1}H NMR, ^{13}C NMR and LC/MS techniques. We have investigated their antibacterial activities against Gram-positive *Staphylococcus aureus* ATCC 25953, *Bacillus cereus* ATCC 6633 and *Listeria monocytogenes* ATCC Li6 (isolate), Gram-negative bacteria (*Escherichia coli* ATCC 11230) and antifungal activity against *Candida albicans* (clinical isolate) by both disc diffusion and minimal inhibition concentration (MIC) methods. All these bacteria and fungus studied were screened against proper antibiotics to compare with our chemicals' zone diameters.

2. Results and discussion

Structural formula of a series of aliphatic sulfonamides (1–7) is given below.

Illustrated in Scheme 1 is the general synthetic route used to prepare our compounds. The exothermic nucle-



(1) psen (m = 2, n = 2)
(2) pspr (m = 2, n = 3)
(3) psbut (m = 2, n = 4)
(4) bsen (m = 3, n = 2)
(5) bspr (m = 3, n = 3)
(6) bsbut (m = 3, n = 4)
(7) bspen (m = 3, n = 5)

Keywords: Antimicrobial activity; Sulfonamides; Aliphatic sulfonamide; MIC.

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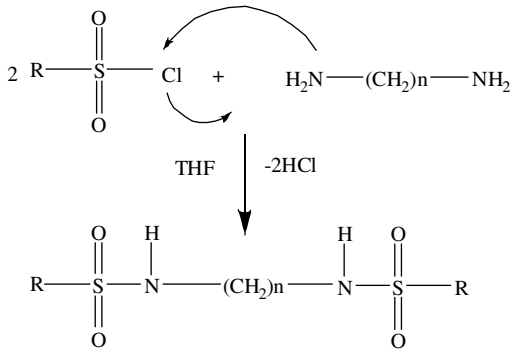

Scheme 1. Preparation of symmetric aliphatic sulfonamide.

ophilic substitution reaction of the aliphatic diamines with different alkyl sulfonyl chlorides was carried out in different solvents (acetonitrile, *N*,*N*-dimethylformamide, THF, dichloromethane, and ethylacetate) to improve the yield. Among the different solvents used, THF helps a better nucleophilic substitution reaction for the series of compounds (**1**–**7**).

Synthesis, ^{1}H NMR and ^{13}C NMR data of compound (4) have already been reported in the literature,[10] and synthesis of compound (**5**) has also been described but there is no detailed knowledge of these compounds.[11,12]

2.1. NMR spectra

NMR spectra of compounds were recorded in DMSO-d_6 taking using TMS as an internal standard. ^{1}H NMR and ^{13}C NMR data for half of the compounds are given in Tables 1 and 2, respectively. It is known that rotation around single bonds brings about the mixture of conformers in the solution. As seen in Tables 1 and 2, symmetric CH_3– and symmetric –CH_2– groups have same chemical shift, indicating that they have same chemical environment. Then, the most stable conformer of the molecules in the solution has C_2 symmetry axis.

NMR chemical shift calculations for most stable conformers were performed using GIAO approach in order to make correct assignment of proton and carbon peaks, which are now widely used in efficient assignment. All calculated data will be submitted later. Proton peak at $\delta \sim 6.9$ ppm and $\delta \sim 3$ ppm corresponds to proton chemical shifting of the SO_2–NH and CH_2–NH moiety of the compounds (**1**–**7**), respectively.

2.2. FT-IR spectra

Wave number of the selected vibration of IR spectra of the compounds is listed in Table 3. The absence of NH_2 vibrations which are observed between 3300 and 3350 cm^{-1} as double bonds and presence of single and strong NH band at ~3280 cm^{-1} confirms the presence of secondary amine groups in our compounds (**1**–**7**).[13] The IR spectra of the compounds were found to be very similar to each other. More characteristic vibrations of the compounds are as follows: asymmetric (ν_{as}) and symmetric (ν_{as}) stretching vibrations of SO_2 groups are observed at ~1115 and ~1135 cm^{-1}, respectively. Terminal methyl group stretching vibration band is found between 2970 and 1875 cm^{-1}.

Table 1. The ^{1}H NMR data of the compounds (for half of molecules)

m	*n*	Assignment	Psen	Pspr	Psbut	Bsen	Bspr	Bsbut	Bspen
2		<CH_3>CH_2	0.98 (t, 3H)	1.06 (t, 3H)	0.98 (t, 3H)				
2		CH_3<CH_2>	1.67 (m, 2H)	1.80 (m, 2H)	1.47 (m, 2H)				
3		<CH_3>CH_2CH_2				0.97 (t, 2H)	0.98 (t, 2H)	0.89 (t, 2H)	0.89 (t, 2H)
3		CH_3<CH_2>CH_2				1.48 (m, 2H)	1.49 (m, 2H)	1.41 (m, 2H)	1.37 (m, 2H)
3		CH_3CH_2<CH_2>				1.55 (m, 2H)	1.78 (m, 2H)	1.48 (m, 2H)	1.45 (m,2H)
2,3		<CH_2>SO_2	2.99 (t, 2H)	3.24 (t, 2H)	2.95 (t, 2H)	3.01 (t, 2H)	3.28 (t, 2H)	2.98 (t, 2H)	2.94 (t, 2H)
	2–5	NH<CH_2>	3.02 (t, 2H)	2.99 (t, 2H)	2.93 (t, 2H)	3.05 (t, 2H)	3.02 (t, 2H)	2.94 (t, 2H)	2.89 (t, 2H)
	3–5	$NHCH_2$<CH_2>	—	1.84 (m, 2H)	1.66 (m, 2H)	—	1.80 (m, 2H)	1.62 (m, 2H)	1.62 (m, 2H)
	5	$NHCH_2CH_2$<CH_2>	—	—	—	—	—	—	1.39 (m, 2H)
All	All	SO_2<NH>	7.10	6.99	6.95	6.99	6.93	6.94	6.92

Table 2. The ^{13}C NMR data of the compounds

m	*n*	Assignment	Psen	Pspr	Psbut	Bsen	Bspr	Bsbut	Bspen
2		<CH_3>CH_2	13.15	12.95	13.20				
2		CH_3<CH_2>	17.36	17.32	17.38				
3		<CH_3>CH_2CH_2	—	—	—	13.59	13.59	13.98	13.98
3		CH_3<CH_2>CH_2				21.53	21.53	21.34	21.34
3		CH_3CH_2<CH_2>				25.62	25.62	25.75	25.76
2.3		<CH_2>SO_2	43.12	54.17	53.08	39.50	52.45	1.07	51.07
	2–5	NH<CH_2>	53.40	39.81	42.38	52.30	39.53	39.41	39.41
	3–5	$NHCH_2$<CH_2>	—	31.05	27.35	—	31.43	27.35	29.69
	5	$NHCH_2CH_2$<CH_2>	—	—	—	—	—	—	23.69

Table 3. Wave number (cm^{-1}) of selected vibration of the compounds

Compound	υ_{NH}	δ_{NH}	$\upsilon_{as}(SO_2)$	$\upsilon_{s}(SO_2)$
Psen (**1**)	3226(sh)	1459(sh)	1317(w)	1133(m)
Pspr (**2**)	3252(sh)	1463(sh)	1315(w)	1133(m)
Psbut (**3**)	3274(sh)	1429(sh)	1317(w)	1135(m)
Bsen (**4**)	3282(sh)	1480(sh)	1320(w)	1136(m)
Bspr (**5**)	3293(sh)	1429(sh)	1314(w)	1135(m)
Bsbut (**6**)	3275(sh)	1461(sh)	1316(w)	1135(m)
Bspen (**7**)	3290(sh)	1480(sh)	1321(w)	1136(m)

υ, stretching vibration; δ, bending vibration; sh, sharp; *m*, medium.

2.3. Biological activity

In the present study, the antimicrobial activities of compounds were screened against various pathogens in vitro by disc diffusion and microdilution methods. Penicillin G, ampicillin, oxacillin and ketoconazole were used as positive controls against both bacteria and yeast in disc diffusion method. The results of our antibacterial and antifungal studies of all the synthesized compounds are depicted in Tables 4 and 5. As seen in Table 4, compound (**5**) is the most potent sulfonamide among this series. It showed good antibacterial activity against both Gram-negative bacteria (*E. coli* at 225 μg/mL, *L. monocytogenes* at 225 μg/mL) and Gram-positive bacteria (*B. cereus* at 180 μg/mL, *S. aureus* at 216 μg/mL), and also antifungal activity against *C. albicans* at 315 μg/mL. Similarly, other sulfonamide (**1**) showed observable activity against Gram-negative bacteria (*E. coli* at 150 μg/mL, *L. monocytogenes* at 300 μg/mL) and Gram-positive bacteria (*S. aureus* at 350 μg/mL).

As seen in Table 5, the longest sulfonamide (**7**) shows the highest antifungal activity against *C. albicans* and its sensitivity compares to that of reference antibiotic (ketoconazole). The compound (**1**, **2**, **5** and **7**) exhibits more activity against both *S. aureus* and *B. cereus*. Their sensitivity was compatible with reference disc of ampicillin, however, reference disc of penicillin shows the highest activity only against *S. aureus*. Compound (**5**) displays more activity against all test microorganisms except*S. aureus* by disc diffusion method.

This is probably due to the lipophilic alkyl chain that helps the molecule to penetrate through the lipid cell membrane of Gram-negative bacteria. From the results obtained, it comes out that the antibacterial activity decreases as the length of the carbon chain increases. This could be due to bulkiness of the carbon chain, which renders the molecule unable to penetrate through the cell wall of the bacteria.

3. Conclusion

In conclusion, a series of novel symmetric aliphatic sulfonamides (**1**–**7**) were synthesized and their antimicrobial activities have been evaluated. All compounds demonstrated potent inhibition against all the strains tested. Further research in this area is in progress in our laboratory. Consequently, these compounds may be suggested for industrial application.

Table 4. The MIC's of the tested compounds

Compound	MIC (μg/mL)				
	S. aureus ATCC 25923	*B. cereus* ATCC 6633	*L. monocytogenes* Li6 (isolate)	*E. coli* ATCC 11230	*C. albicans* (clinical isolate)
Psen (**1**)	300	250	300	150	300
Pspr (**2**)	456	380	532	228	532
Psbut (**3**)	336	336	228	240	336
Bsen (**4**)	216	243	216	243	324
Bspr (**5**)	270	180	225	225	315
Bsbut (**6**)	648	463	648	555	555
Bspen (**7**)	432	540	432	486	540

Table 5. Inhibition zones (diameter) in mm of compound and reference antibiotic discs against tested microorganisms by disc diffusion method

Compound	*S. aureus* ATCC 25923	*B. cereus* ATCC 6633	*L. monocytogenes* Li6	*E. coli* ATCC 11230	*C. albicans* (clinical isolate)
Psen (**1**)	12	—	16	11	—
Pspr (**2**)	11	—	11	12	12
Psbut (**3**)	—	—	—	12	11
Bsen (**4**)	—	—	—	10	—
Bspr (**5**)	—	10	11	10	10
Bsbut (**6**)	10	—	—	11	12
Bspen (**7**)	—	—	—	12	13
Penicillin	19	—	—	—	—
Ampicillin	—			9	
Oxacillin	—	9	—	—	—
Ketoconazole	—	—	—	—	16

4. Experimental

The elemental analyses (C, H, N and S) were performed on a LECO–CHSNO-9320 type elemental analyzer. The IR spectra (4000–400 cm^{-1}) were recorded on a Mattson-1000 FT-IR spectrophotometer with samples prepared as KBr pellets. NMR spectra were recorded on a Bruker-Spectrospin Avance DPX-400 Ultra-Shield (400 MHz) using DMSO-d_6 and $CDCl_3$ as a solvent and TMS as an internal standard. LC/MS-APCl were recorded on AGILENT 1100. The melting point was recorded on a Opti MELT 3 hot stage apparatus. TLC was conducted on 0.25 mm silica gel plates (60F254, Merck). Visualization was made with ultraviolet light. All extracted solvents (all from Merck) were dried over anhydrous Na_2SO_4 and evaporated with a BUCHI rotary evaporator. Reagents were obtained commercially from Aldrich (ACS grade) and used as received.

4.1. General procedure for the synthesis

The nucleophilic substitution reaction of the aliphatic diamines with different alkyl sulfonyl chlorides was carried out as follows: to the THF solution of aliphatic diamines was added by slowly dropwise THF solution of alkylsulfonyl chlorides (R-SO_2Cl) (1:2 equiv), maintaining the temperature between −5 and −10 °C. Then, the reaction mixture was stirred for 24 h at room temperature (completion of the reaction was monitored by TLC). After the completion of the reaction, solvent was evaporated in vacuum. The solid residue was purified by column chromatography.

4.1.1. Synthesis of 1-propanesulfonamide-*N*,*N*′-1,2-ethanediylbis (1). The general synthetic method described above affords as white solid from ethylendiamine (3.5 mL, 52.0 mmol) and propanesulfonyl chloride (3.0 mL, 25.9 mmol). The product was crystallized from tetrahydrofurane/*n*-hexane mixture (2:1). Yield 75%; mp 94–95 °C; MS (70 eV, APCl): 273.1 ($M+1^{+\cdot}$, 100%), 274.1 ($M+2^{+}$, 11.5%), 275.1 ($M+3^{+}$, 10.5%), 167.1 ($M+2^{+\cdot}-C_3H_7SO_2^{\cdot}$, 47.5%), 150.1 ($M^{+}-C_3H_7SO_2NH^{\cdot}$, 6.7%); Anal. Calcd for $C_8H_{20}N_2O_4S_2$: C, 35.29; H, 7.35; N, 10.29; S, 23.52. Found: C, 35.72; H, 7.42; N, 10.29; S, 22.99.

4.1.2. Synthesis of 1-propanesulfonamide-*N*,*N*′-1,3-propanediylbis (2). The general synthetic method described above affords as white solid from 1.3-diaminopropane (4.3 mL, 52.0 mmol) and 1-propanesulfonyl chloride (3.0 mL, 25.9 mmol). The product was crystallized from tetrahydrofurane/*n*-hexane mixture (3:1). Yield 88%; mp 127–128 °C; MS (70 eV, APCl): 287.1 ($M+1^{+\cdot}$, 100%), 288.1 ($M+2^{+\cdot}$, 13.1%), 289.1 ($M+3^{+\cdot}$, 7.5%), 136.1 ($M^{+\cdot}-C_3H_7SO_2NH(CH_2)_2^{\cdot}$, 21.7%), 164.2 ($M^{+\cdot}-C_3H_7SO_2NH^{\cdot}$, 61.2%); Anal. Calcd for $C_9H_{22}N_2O_4S_2$: C, 37.76; H, 7.69; N, 9.79; S, 22.38. Found: C, 38.09; H, 7.77; N, 9.97; S, 22.31.

4.1.3. Synthesis of 1-propanesulfonamide-*N*,*N*′-1,4-butanediylbis (3). The general synthetic method described above affords as white solid from 1.4-diaminobutane (4.2 mL, 47.2 mmol) and 1-propanesulfonyl chloride (3.0 mL, 26.0 mmol). The product was crystallized from tetrahydrofurane/*n*-hexane mixture (3:1). Yield 84%; mp 121–122 °C; MS (70 eV, APCl): 301.1 ($M+1^{+\cdot}$, 100%), 302.1 ($M+2^{+}$, 13.2%), 303.1 ($M+3^{+\cdot}$, 10.2%), 195.1 ($M+2^{+\cdot}-C_3H_7SO_2^{\cdot}$, 43.9%), 178.1 ($M^{+}-C_3H_7SO_2NH^{\cdot}$, 13.3%); Anal. Calcd for $_{10}H_{24}N_2O_4S_2$: C, 40.00; H, 8.00; N, 9.3; S, 21.33. Found: C, 40.7; H, 7.86; N, 9.13; S, 21.35.

4.1.4. Synthesis of 1-butanesulfonamid-*N*,*N*′-1,2-ethanediylbis (4). The general synthetic method described above affords as white solid from ethylendiamine (3.1 mL, 46.0 mmol) and 1-butanesulfonyl chloride (3 mL, 23.0 mmol). The product was crystallized from ethanol/*n*-hexane mixture (3:1). Yield 82%; mp 112–113 °C; MS (70 eV, APCl): 301.1 ($M+1^{+}$, 62.8%), 302.1 ($M+2^{+}$, 9.0%), 303.1 ($M+3^{+}$, 7.1%), 134.1 ($M-2^{+}-C_3H_7SO_2NH(CH_2)_2^{\cdot}$, 21.7%), 164.1 ($M^{+\cdot}-C_4H_9SO_2NH^{\cdot}$, 37.9%), 181.1 ($M+2^{+\cdot}-C_4H_9SO_2^{\cdot}$, 100%); Anal. Calcd for $C_{10}H_{24}N_2O_4S_2$: C, 40.0; H, 8.0; N, 9.33.; S, 21.3. Found: C, 40.23; H, 7.94; N, 9.10; S, 21.51.

4.1.5. Synthesis of 1-butanesulfonamide-*N*,*N*′-1,3-propanediylbis (5). The general synthetic method described above affords as white solid from 1,3-diaminopropane (3.95 mL, 47.5 mmol) and 1-butanesulfonyl chloride (3.0 mL, 23.7 mmol). The product was crystallized from ethanol/*n*-hexane mixture (2:1). Yield 88%; mp 116–117 °C; MS (70 eV, APCl): 315.1 ($M+1^{+\cdot}$, 100%), 316.1 ($M+2^{+\cdot}$, 14.5%), 317.1 ($M+3^{+}$, 10.4%), 195.1 ($M+2^{+\cdot}-C_4H_9SO_2^{\cdot}$, 31.5%); Anal. Calcd for $C_{11}H_{26}N_2O_4S_2$: C, 42.04; H, 8.28; N, 8.92; S, 20.38. Found: C, 42.17; H, 8.45; N, 9.32; S, 19.98.

4.1.6. Synthesis of 1-butanesulfonamide-*N*,*N*′-1,4-butanediylbis (6). The general synthetic method described above affords as white solid from 1,4-diaminobutane (4.7 mL, 47.4 mmol) and 1-butanesulfonyl chloride (3.0 mL, 23.7 mmol). Product was recrystallized from ethanol/benzene mixture (2:1). Yield 88%; mp 117–118 °C; MS (70 eV, APCl): 329.1 ($M+1^{+\cdot}$, 100%), 330.1 ($M+2^{+}$, 16.1%), 331.1 ($M+3^{+\cdot}$, 11.1%), 209.1 ($M+2^{+\cdot}-C_4H_9SO_2^{\cdot}$, 28.9%), 192.1 ($M^{+\cdot}-C_4H_9SO_2NH^{\cdot}$, 9.2%); Anal. Calcd for $C_{12}H_{28}N_2O_4S_2$: C, 43.9; H, 8.5; N, 8.5; S, 19.5. Found: C, 44.33; H, 8.37; N, 8.61; S, 19.52.

4.1.7. Synthesis of 1-butanesulfonamide-*N*,*N*′-1,5-pentanediylbis (7). The general synthetic method described above affords as white solid from 1,5-diaminopentane (2.0 mL, 16.0 mmol) and 1-butanesulfonyl chloride (1.06 mL, 8.1 mmol). The product was crystallized from methanol/*n*-hexane mixture (2:1). Yield 80%; mp 123–124 °C; MS (70 eV, APCl): 343.5 ($M+1^{+\cdot}$, 100%), 344.15 ($M+2^{+}$, 16.1%), 345.1 ($M+3^{+}$, 10.1%), 223.1 ($M+2^{+}-C_4H_9SO_2^{\cdot}$, 3.9%); Anal. Calcd for $C_{13}H_{30}N_2O_4S_2$: C, 45.6; H, 8.77; N, 8.18; S, 18.71. Found: C, 45.87; H, 8.20; N, 8.16; S, 18.94.

4.2. Biological activity: in vitro evaluation of antimicrobial activity

Staphylococcus aureus ATCC 25923, *B. cereus* ATCC 6633, *L. monocytogenes* Li6 (isolate), *E. coli* ATCC 11230 and *C. albicans* (clinical isolate) cultures were

obtained from Gazi University, Biology Department. Bacterial strains were cultured overnight at 37 °C in Nutrient Broth. The yeast was cultured overnight at 30 °C in YEPD Broth. These stock cultures were stored in the dark at 4 °C during the survey.

4.3. Minimal inhibitory concentration

Minimal inhibitory concentrations (MIC) were determined by microdilution broth method following the procedures recommended by the National Committee for Clinical Laboratory Standards.[14,15] MIC's were defined as the lowest concentrations of the antimicrobial agents that inhibited visible growth of the microorganism. All tests were performed in Mueller–Hinton Broth (MHB) and YEPD Broth. The compounds under the test were dissolved in analytically pure dimethylsulfoxide (DMSO) and geometric dilutions ranging from 100 to 1000 μg/mL of the compounds.[16–18]

4.4. Determination of inhibition zones

Inhibition zones of compounds were determined by the disc diffusion method.[19] The antimicrobial screening was performed using Mueller–Hinton Agar and YEPD Agar for a yeast. The culture suspensions were prepared and adjusted by comparing against 0.3 Mc Farland turbidity tubes. Mueller–Hinton and YEPD agar (20 mL) were poured into each sterile Petri dish after injecting cultures (100 μL) of microorganisms and distributing medium in Petri dish homogeneously. Compounds were filtered with a pore size of 0.45 μm. All of the compounds were dissolved in DMSO of 5 mg/mL. Empty sterilized discs of 6 mm (Schlieicher and Schule. No.2668. Germany) were each impregnated with 50 μL of compounds. Discs were placed on agar plates and the cultures were incubated at 37 °C for 24 h for bacteria and 48 h for *C. albicans*. Inhibition zones formed on the medium were evaluated in mm. The solvent control (DMSO) did not show any antimicrobial activity. Studies were performed in duplicate. Inhibition zones were compared with those of reference discs. Reference discs used for control are as follows: ketoconazole (50 μg), ampicillin (10 μg), tetracycline (30 μg), penicillin (10 U), chloramphenicol (30 μg) and oxacillin (1 μg).

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