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Synthesis and biological screening of *N*-Substituted derivatives of *N*-benzyl-4-chlorobenzenesulfonamide

Aziz-ur-Rehman[1,*], Awais-ur-Rehman[2], Muhammad Athar Abbasi[1], Hira Khalid[1], Parsa Dar[1], Khalid Mohammad Khan[3]

1 Department of Chemistry, Government College University, Lahore-54000, Pakistan.
2 Department of Chemistry, Minhaj University, Lahore, Pakistan.
3 HEJ Research Institute of Chemistry, International Center for Chemical and Biological Sciences, University of Karachi, Karachi-75270, Pakistan.

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***Corresponding author:**

Email : azizryk@yahoo.com
Tel : (+92)-42-111000010. Ext.449

ABSTRACT

In the present study, a series of *N*-substituted derivatives of *N*-benzyl-4-chlorobenzenesulfonamide has been synthesized. The reaction of benzylamine (1) with 4-chlorobenzenesulfonyl chloride (2) yielded the parent compound *N*-benzyl-4-chlorobenzenesulfonamide (3), which further on treatment with different electrophiles (4a-i) in the presence of sodium hydride furnished into *N*-substituted sulfonamides (5a-i). The structure of synthesized compounds has been established by IR, ^{1}H-NMR and EI-MS. All the compounds have been screened for their antimicrobial activity.

INTRODUCTION

The basic sulfonamide group SO_2NH- occurs in various biological active compounds including antimicrobial drugs, antithyroid agents, antitumor antibiotics and inhibitors of carbonic anhydrase [1,2]. Sulfonamides are widely used to treat microbial infections by inhibiting the growth of gram negative and gram positive bacteria, some protozoa and fungi [3]. Clinically sulfonamides are used to treat several urinary tract infections and gastrointestinal infections [4]. Sulfonamides that are aromatic or hetroaromatic are responsible for the inhibition of the growth of tumor cells. They act as antitumor agents by inhibiting the carbonic anhydrase. Sulfonamides are structurally similar to p-aminobenenzoic acid (PABA) which is a cofactor that is needed by the bacteria for the synthesis of folic acid. Sulfonamides antibiotics inhibit the conversion of PABA into folic acid and thus ultimately inhibit the synthesis of purine and DNA. Sulfonamide antibiotics are used as veterinary medicines to treat infections in livestock herds [5,6].

Literature survey revealed that minor modification in the structure of sulfonamide can lead to quantitative as well as qualitative changes in the biological activity. It prompted us to synthesize the various N-substituted derivatives of sulfonamides derived from benzylamine with an objective to search new contenders of drug having significant enhanced activity and could be helpful in controlling many degenerative diseases. For this, the parent sulfonamide N-benzyl-4-chlorobenzenesulfonamide (3) was first prepared by reacting 4-chlorobenzenesulfonyl chloride with benzylamine at room temperature in basic medium. Simple stirring gave the desired compound in excellent yield. Then it was further processed to obtain different new N-alkyl substituted sulfonamides.

Experimental Protocol Chemistry

Procedure for the synthesis of N-benzyl-4-chlorobenzenesulfonamide in aqueous medium

The nucleophilic substitution reaction of amine with 4-chlorobenzenesulfonyl chloride was carried out as follows: a mixture of 4-chlorobenzenesulfonyl chloride (10.0 mmol; 4.22 g) and benzylamine (10.0 mmol; 2.18 mL) was suspended in 50 mL water. The suspension pH was maintained at 9.0 to 10.0 by adding aqueous solution of a base (Na_2CO_3) at ambient temp. The solution was stirred and monitored by using analytical technique TLC for the completion of reaction. Then concentrated HCl was added gradually to adjust the pH to 2.0. The precipitates were collected by filtration, washed with distilled H_2O and dried to afford the title compound 3. CH_3OH was used to dissolve the product and then it was re-crystallized by slow evaporation of the solvent, to generate off white crystalline solid of N-benzyl-4-chlorobenzenesulfonamide (3). Yield 92%.

General procedure for the synthesis of N-alkyl substituted sulfonamides in DMF

The calculated amount of N-benzyl-4-chlorobenzenesulfonamide (0.1 mmol; 3) was taken in a round bottomed flask (50 mL), then N,N-dimethyl formamide (DMF) (10 mL) was added to dissolve it followed by the addition of sodium hydride (0.1 mmol) to the mixture. The mixture was stirred for 30 minutes at room temperature and then slowly added the alkyl halide to the mixture and the solution was further stirred for three hours. The progress of reaction was monitored via TLC till single spot. After completion of reaction, mixture was quenched with cold water (50 mL). The acquired precipitation was filtered, washed with water and dried to acquire the resultant derivatives. In some cases, the solid precipitation was not formed in the flask then compound was extracted through solvent extraction method by chloroform/ ethyl acetate to yield the corresponding N-substituted N-benzyl-4-chlorobenzenesulfonamide (5ai) derivatives.

METHODOLOGY

Melting points of the synthesized compounds were recorded on a Griffin and George melting point apparatus by open capillary tube and were uncorrected. Purity was checked on thin layer chromatography (TLC) on pre-coated silica gel G-25-UV_{254} plates with different solvent systems using ethyl acetate and n-hexane giving single spot. Detection was carried out at 254 nm, and by ceric sulphate reagent. The I.R. spectra were recorded in KBr pellet method on a Jasco-320-A spectrophotometer (wave number in cm^{-1}). Nuclear magnetic resonance spectra were recorded in $CDCl_3$ on a Bruker spectrometers operating at 300 MHz. Chemical shifts are given in ppm. Mass spectra (EIMS) were recorded on a JMS-HX-110 spectrometer, with a data system.

PHYSICAL CHARACTERIZATION AND SPECTRAL DATA

N-Benzyl-4-chlorobenzenesulfonamide (3)

Off white crystalline solid, Yield-92%; m.p. 135-137°C. IR (KBr, cm^{-1}): v_{max}: 3441 (N-H stretching), 3033 (C-H stretching of aromatic ring), 2942 (-CH_2- stretching), 1521 (C=C stretching of aromatic ring), 1319 (-SO_2- stretching), ^{1}H-NMR (300 MHz, MeOD δ / ppm): 7.76 (d, J = 8.7 Hz, 2H, H-3′ & H-5′), 7.50 (d, 2H, J = 8.7 Hz, H-2′ & H-6′), 7.40-7.31 (m, 5H, H-2 to H-6), 4.07 (s, 2H, CH_2-7). Mol. formula: $C_{13}H_{12}ClNO_2S$, EIMS m/z: 281 (23%) $[M]^+$, 217 (45%), 175 (23%), 91 (100%).

N-Benzyl-N-methyl-4-chlorobenzenesulfonamide (5a)

Buff coloured solid, Yield-69%; IR (KBr, cm^{-1}): v_{max}: 3038 (C-H stretching of aromatic ring), 2940 (-CH_2- stretching), 1525 (C=C stretching of aromatic ring), 1316 (-SO_2- stretching), ^{1}H-NMR (300 MHz, MeOD δ / ppm): 7.78 (d, J = 8.7 Hz, 2H, H-3′ & H-5′), 7.51 (d, 2H, J = 8.7 Hz, H-2′ & H-6′), 7.38-7.30 (m, 5H, H-2 to H-6), 4.09 (s, 2H, CH_2-7), 0.91 (t, J = 6.5 Hz, 3H, -CH_3). Mol. formula: $C_{14}H_{14}ClNO_2S$, EIMS m/z: 295 (16%) $[M]^+$, 231 (34%), 204 (42%), 91 (100%).

N-Benzyl-N-ethyl -4-chlorobenzenesulfonamide (5b)

Brown gammy liquid, Yield-58%; IR (KBr, cm^{-1}): v_{max}: 3031 (C-H stretching of aromatic ring), 2938 (-CH_2- stretching), 1519 (C=C stretching of aromatic ring), 1321 (-SO_2- stretching), ^{1}H-NMR (300 MHz, MeOD δ / ppm): 7.83 (d, J = 8.7 Hz, 2H, H-3′ & H-5′), 7.52 (d, 2H, J = 8.7 Hz, H-2′ & H-6′), 7.35-7.28 (m, 5H, H-2 to H-6), 4.36 (s, 2H, CH_2-7), 3.19 (q, 2H, CH_2-1"), 0.91 (t, J = 6.5 Hz, 3H, - CH_2-2"). Mol. formula: $C_{15}H_{16}ClNO_2S$, EIMS m/z: 309 (14%) $[M]^+$, 245 (39%), 218 (62%), 91 (100%).

N-Benzyl-N-(propan-2-yl)-4-chlorobenzenesulfonamide (5c)

White sticky solid; Yield-77%; IR (KBr, cm^{-1}): v_{max}: 3041 (C-H stretching of aromatic ring), 2934 (-CH_2- stretching), 1523 (C=C stretching of aromatic ring), 1318 (-SO_2- stretching), ^{1}H-NMR (300 MHz, MeOD δ / ppm): 7.80 (d, J = 8.7 Hz, 2H, H-3′ & H-5′), 7.56 (d, 2H, J = 8.7 Hz, H-2′ & H-6′), 7.36-7.28 (m, 5H, H-2 to H-6), 4.42 (s, 2H, CH_2-7), 4.13 (m, 1H, CH-1"), 0.94 (d, J = 6.5 Hz, 6H, - CH_2-2" & 3"). Mol. formula: $C_{16}H_{18}ClNO_2S$, EIMS m/z: 323 (16%) $[M]^+$, 259 (32%), 232 (47%), 91 (100%).

N-Benzyl-N-butyl-4-chlorobenzenesulfonamide (5d)

Gammy liquid, Yield-63%; IR (KBr, cm^{-1}): v_{max}: 3034 (C-H stretching of aromatic ring), 2930 (-CH_2- stretching), 1529 (C=C stretching of aromatic ring), 1323 (-SO_2- stretching), ^{1}H-NMR (300 MHz, MeOD δ / ppm): 7.83 (d, J = 8.7 Hz, 2H, H-3′ & H-5′), 7.59 (d, 2H, J = 8.7 Hz, H-2′ & H-6′), 7.37-7.29 (m, 5H, H-2 to H-6), 4.34 (s, 2H, CH_2-7), 3.19 (br. t, 2H, CH_2-1"), 1.27 (m, 2H, CH_2-3"), 1.11 (m, 2H, CH_2-2"), 0.73 (t, J = 6.5 Hz, 3H, -CH_3-4"). Mol. formula: $C_{17}H_{20}ClNO_2S$, EIMS m/z: 337 (23%) $[M]^+$, 273 (41%), 246 (35%), 91 (100%).

N-Benzyl- N-pentyl-4-chlorobenzenesulfonamide (5e)

White amorphous solid, Yield-68%; IR (KBr, cm^{-1}): v_{max}: 3041 (C-H stretching of aromatic ring), 2937 (-CH_2- stretching), 1525 (C=C stretching of aromatic ring), 1327 (-SO_2- stretching), ^{1}H-NMR (300 MHz, MeOD δ / ppm): 7.82 (d, J = 8.7 Hz, 2H, H-3′ & H-5′), 7.59 (d, 2H, J = 8.7 Hz, H-2′ & H-6′), 7.33-7.24 (m, 5H, H-2 to H-6), 4.34 (s, 2H, CH_2-7), 3.09 (br. t, 2H, CH_2-1"), 1.28 (m, 2H, CH_2-2"), 1.08 (m, 4H, CH_2-3" & 4"), 0.77 (t, J = 6.5 Hz, 3H, -CH_3-5"). Mol. formula: $C_{18}H_{22}ClNO_2S$, EIMS m/z: 351 (15%) $[M]^+$, 287 (35%), 260 (61%), 91 (100%)

N-Allyl- N-benzyl-4-chlorobenzenesulfonamide (5f)

Transparent sticky solid, Yield-72%; IR (KBr, cm^{-1}): v_{max}: 3045 (C-H stretching of aromatic ring), 2931 (-CH_2- stretching), 1521 (C=C stretching of aromatic ring), 1322 (-SO_2- stretching), ^{1}H-NMR (300 MHz, MeOD δ / ppm): 7.80 (d, J = 8.7 Hz, 2H, H-3′ & H-5′), 7.57 (d, 2H, J = 8.7 Hz, H-2′ & H-6′), 7.35-7.27 (m, 5H, H-2 to H-6), 4.37 (s, 2H, CH_2-7), 5.78 (m, 1H, H-2"), 5.03 (dd, J =1.6, 17.3 Hz, 1H, H_b-3"), 4.96 (dd, J =1.2, 10 Hz, 1H, H_a-3′), 4.47 (s, 2H, CH_2-1′). Mol. formula: $C_{16}H_{16}ClNO_2S$, EIMS m/z: 321 (12%) $[M]^+$, 257 (47%), 230 (64%), 91 (100%)

N-Benzyl-N-(2-bromoethyl)-4-chlorobenzenesulfonamide (5g)

Gray coloured solid, Yield-58%; IR (KBr, cm^{-1}): v_{max}: 3047 (C-H stretching of aromatic ring), 2933 (-CH_2- stretching), 1523 (C=C stretching of aromatic ring), 1322 (-SO_2- stretching), ^{1}H-NMR (300 MHz, MeOD δ / ppm): 7.85 (d, J = 8.7 Hz, 2H, H-3′ & H-5′), 7.60 (d, 2H, J = 8.7 Hz, H-2′ & H-6′), 7.36-7.30 (m, 5H, H-2 to H-6), 4.39 (s, 2H, CH_2-7), 3.29 (t, J = 5.4 Hz, 2H, CH_2-1"), 3.20 (t, J = 5.4 Hz, 2H, CH_2-2"). Mol. formula: $C_{15}H_{15}BrClNO_2S$, EIMS m/z: 388 (21%) $[M]^+$, 324 (41%), 297 (61%), 91 (100%)

N, N-Dibenzyl-4-chlorobenzenesulfonamide (5h)

Gammy solid, Yield-76%; IR (KBr, cm^{-1}): v_{max}: 3039 (C-H stretching of aromatic ring), 2948 (-CH_2- stretching), 1531 (C=C stretching of aromatic ring), 1338 (-SO_2- stretching), ^{1}H-NMR (300 MHz, MeOD δ / ppm): 7.81 (d, J = 8.7 Hz, 2H, H-3′ & H-5′), 7.54 (d, 2H, J = 8.7 Hz, H-2′ & H-6′), 7.23-7.01 (m, 10H, H-2 to H-6 & H-2" to H-6"), 4.31 (s, 4H, CH_2-7 & CH_2-7"). Mol. formula: $C_{20}H_{18}ClNO_2S$, EIMS m/z: 371 (19%) $[M]^+$, 307 (38%), 175 (48%), 91 (100%).

N-benzyl-N-(2-phenylethyl)-4-chlorobenzenesulfonamide (5i)

Light pink coloured solid, Yield-81%; IR (KBr, cm^{-1}): v_{max}: 3041 (C-H stretching of aromatic ring), 2939 (-CH_2- stretching), 1520 (C=C stretching of aromatic ring), 1321 (-SO_2- stretching), ^{1}H-NMR (300 MHz, MeOD δ / ppm): 7.80 (d, J = 8.7 Hz, 2H, H-3′ & H-5′), 7.57 (d, 2H, J = 8.7 Hz, H-2′ & H-6′), 7.18-6.99 (m, 10H, H-2 to H-6 & H-2" to H-6"), 4.37 (s, 2H, CH_2-7), 4.01 (br.s, 2H, CH_2-1"), 3.59 (t, J = 5.4 Hz, 2H, CH_2-2"). Mol. formula: $C_{21}H_{20}ClNO_2S$, EIMS m/z: 385 (12%) $[M]^+$, 321 (34%), 294 (53%), 91 (100%).

Biological screening antimicrobial activity

Antibacterial assay

Microbial strains: The extracted oils of both cultivars were individually tested against a set of microorganisms, including two Gram-positive bacteria: Staphylococcus aureus (S. aureus), API Staph TAC 6736152, Bacillus subtilis (B. subtilis) JS 2004, two Gram-negative bacteria: Escherichia coli (E. coli) ATCC 25922, and Pasteurella multocida (P. multocida) (local isolate) The pure bacterial strains were obtained from Department of Clinical Medicine and Surgery, University of Agriculture, Faisalabad, Pakistan. Purity and identity were verified by the Institute of Microbiology, University of Agriculture, Faisalabad, Pakistan. Bacterial strains were cultured overnight at 37 ºC in Nutrient agar (NA, Oxoid).

Disc diffusion method: The antibacterial activity of the compounds was determined by disc diffusion method. Briefly, 100 µL of suspension of tested microorganisms, containing 10^7 colony-forming units (CFU)/mL of bacteria cells on **NA** medium. The filter discs (6 mm in diameter) were individually impregnated with compound solution, placed on the agar plates which had previously been inoculated with the tested microorganisms. Discs without samples were used as a negative control. Streptomycin sulphate (30 µg/dish) (Oxoid, UK) were used as positive reference for bacteria to compare sensitivity of strain/isolate in analyzed microbial species. Plates, after 2 h at 4 ºC, were incubated at 37ºC for 18 h for bacteria strains. Antibacterial activity was evaluated by measuring the diameter of the growth inhibition zones (zone reader) in millimeters for the organisms and comparing to the controls [7]. The results were presented in Table-1.

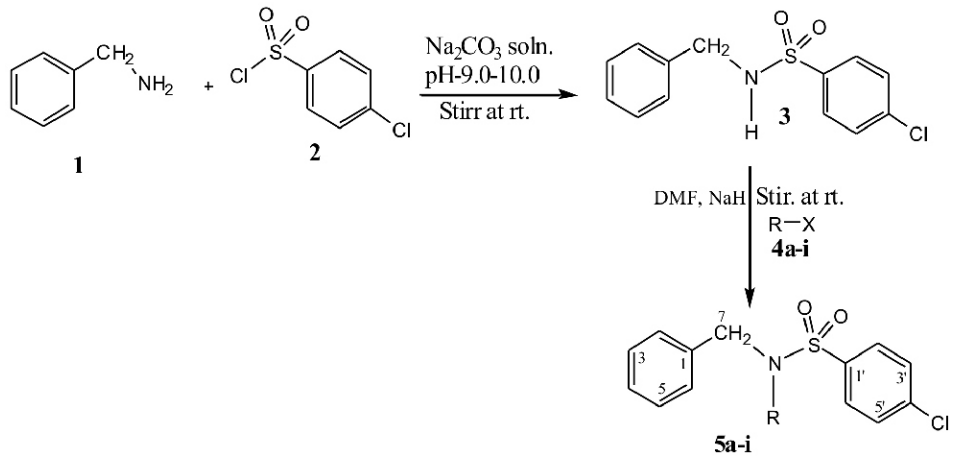
Antifungal activity

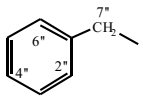
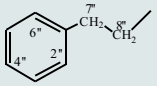
In vitro antifungal assays of all the synthesized compounds were performed against fungal strains Aspergillus niger, Aspergillus flavus, F. Solani and A. Fusarium using agar well diffusion method [8]. The fungal cultures were raised by growing on potato dextrose agar media at pH 7.4 for six days at 25°C. The spores were harvested in sterilized normal saline (0.9% NaCl in distilled water) and its concentration was adjusted to 1x10 /mL with a Haemometer. The autoclaved molten media (20 mL) was poured in each 90 mm sterilized Petri plate and allowed to solidify. To study the growth response of fungi species, 0.4 mL of the synthesized compound solution (5mg/ml) was poured into each plate and spread over the agar media. 10 µL spore suspension was poured in to small depression made at the center of the plate and kept for 6 days at 25°C. After six days of incubation, the fungal growth were measured and compared with the control. The control plates contained only DMSO for which fungal growth is taken as 100% (without inhibition). The fungal activity of all the synthesized compounds was assessed by comparing the zone of fungal growth in treated plates with that of control plates in mm. The results were presented in table-2. The MIC values of the bioactive compounds were determined by the micro-dilution method reported by Sarker et al. (2007). The results are shown in Table-3.

RESULTS AND DISCUSSION

In the undertaken research, a series of N-substituted sulfonamide were synthesized. The parent compound N-benzyl-4-chlorobenzenesulfonamide (3) was prepared by a process similar to the known literature procedure [9,10] using benzylamine (1) and 4-chlorobenzenesulfonyl chloride (2). Reaction of (3) with different electrophiles 4a-i yielded a series of N-substituted N-benzyl-4-chlorobenzenesulfonamide (5a-i) as represented in Scheme 1. Synthesis of all derivatives 5a-i was performed in DMF (N,N-dimethylformamide) using sodium hydride (NaH) as the base. Complete conversion was achieved within 30 to 70 min by stirring. The products were isolated by adding cold water in the reaction mixture and filtering off the precipitated solid. In some cases, compound was taken out through solvent extraction method by chloroform/ ethyl acetate. Parent compound 3 was synthesized as off white crystalline solid. The molecular formula $C_{13}H_{12}ClNO_2S$ was established by HR-MS showing molecular ion peak at m/z 281.7590. The IR spectrum showed absorption bands at 3441 cm^1, 3033 cm^1, 2942 cm^1, 1521 cm^1 and 1521 cm^{-1} which were assigned to, SO_2-N-H (stretching of sulfonamide), C-H (aromatic stretching), -CH_2- (stretching of methylene group), C=C (stretching of aromatic ring) and -SO_2- (stretching of sulfonyl group) respectively. The EI-MS gave characteristic peaks at m/z 217, 175 and 91 which were attributed to the loss of SO_2 (sulfonyl), 4-chlorobenzene sulfonyl and loss of tropylium ion fragments respectively. In the aromatic region of the ^{1}H-NMR spectrum signals appeared at δ 7.76 (d, J = 8.7 Hz, 2H, H-3□ & H-5□) and 7.50 (d, 2H, J = 8.7 Hz, H-2□ & H-6□) which were assigned to the para disubstituted benzenesulfonyl ring. The signals resonated at δ 7.40-7.31 (m, 5H, H-2 to H-6) which showed the presence of mono substituted aromatic ring. In the aliphatic region of the ^{1}H-NMR spectrum, a singlet signal appeared at 4.07 (s, 2H, CH_2-7) which indicated the presence of methylene group in the molecule. On the basis of above cumulative evidences, the structure of 3 was assigned as N-benzyl-4-chlorobenzenesulfonamide. Similarly, the structure of other compounds was characterized by ^{1}H-NMR, IR and mass spectral data as described in experimental section.

In vitro antibacterial activities were performed against Staphylococcus aureus, Bacillus subtilis, Pasturella multocida and Escherichia coli keeping Chloramphenicol as standard and in vitro antifungal activity was performed against Aspergillus niger, Aspergillus flavus, F. Solani and A. Fusarium keeping Miconazole as standard. All the synthesized compounds showed good and moderate activity against the gram positive bacteria



Compound	R	Compound	R
5a	$-CH_3$ (1")	**5f**	$-CH_2-CH=CH_2$ (1", 2", 3", H_a, H_b)
5b	$-CH_2-CH_3$ (1", 2")	**5g**	$-CH_2-CH_2-Br$ (1", 2")
5c	$-CH(CH_3)_2$ (1", 2", 3")	**5h**	
5d	$-CH_2-CH_2-CH_2-CH_3$ (1", 2", 3", 4")	**5i**	
5e	$-CH_2-CH_2-CH_2-CH_2-CH_3$ (1", 2", 3", 4", 5")		

Scheme 1: Synthesis of *N*-substituted sulfonamides derived from benzylamine.

Table 1: Antibacterial activity of *N*-benzyl-4-chlorobenzenesulfonamide and its derivatives.

S. NO.	[a]Zone of inhibition (diameter) mm Gram positive bacteria		Gram negative bacteria	
	Staphylococcus aureus	*Bacillus subtilis*	*Pasturella multocida*	*Escherichia coli*
3	11	09	07	-
5a	10	10	-	-
5b	06	07	06	-
5c	07	07	-	-
5d	09	08	-	-
5e	10	10	06	08
5f	07	07		-
5g	15	14	12	15
5h	06	07	-	-
5i	16	15	12	12
loramphenicol	22	20	18	21

[a]Values are means of three determinations, the ranges of which are less than 5% of the mean in all cases.

Table 2: Antifungal activity of *N*-benzyl-4-chlorobenzenesulfonamide and its derivatives.

S. NO.	[a]Zone of inhibition (diameter) mm			
	Aspergillus Niger	*Aspergillus Flavus*	*F. Solani*	*A. Fusarium*
3	05	07	-	-
5a	10	-	-	-
5b	07	09	-	-
5c	07	08	-	-
5d	08	-	-	-
5e	10	-	-	-
5f	10	-		-
5g	11	13	-	-
5h	08	10	-	
5i	12	11	-	-
Miconazole	17	18	14	17

[a]Values are means of three determinations, the ranges of which are less than 5% of the mean in all cases.

Table 3: Minimal inhibitory concentration values (μg/mL) of *N*-benzyl-4-chlorobenzene sulfonamide and its derivatives.

S. NO.	Gram positive bacteria		Gram negative bacteria		Fungal strain	
	S. aureus	*B. subtilis*	*P. multocida*	*E. coli*	*A. Niger*	*A. Flavus*
	MIC	MIC	MIC	MIC	MIC	MIC
3	196	186	178	-	198	201
5a	322	169	-	-	287	-
5b	273	311	189	-	267	259
5c	273	349	-	-	318	287
5d	309	327	-	-	282	-
5e	221	315	316	198	298	-
5f	248	156		-	308	-
5g	187	314	347	237	311	277
5h	265	297	-	-	312	365
5i	187	324	326	314	355	267
Chloramphenicol	127	148	122	149	-	-
Miconazole	-	-	-	-	157	187

[a]Values are means of three determinations, the ranges of which are less than 5% of the mean in all cases.

than the standard compounds used in the assay. In the case of gram negative bacteria, the following compounds 3, 5b, 5e, 5g and 5i showed moderate activity against Pasturella multocida and in case of Escherichia coli only 5e, 5g and 5i compounds only showed activity but remaining compounds acquire no activity. All the synthesized compounds showed moderate fungal activity against the A. niger and A. flavus except four compounds 5a, 5d, 5e & 5f which remained inactive against A. flavus. Similarly, all the compounds showed no activity against F. Solani and A. Fusarium fungus. The data of the MIC depicted the similar trend as observed in the antibacterial activity. Higher the value of zone of inhibition lower will be the MIC (Table-3). The is reciprocal relationship in the zone of inhibition and MIC.

CONCLUSION

The proposed structure of the synthesized compound is well supported by spectroscopic data. From the antimicrobial activity data (Table-1 to 3), it may be concluded that many synthesized compounds showed good to moderate activity and few remained inactive against the antimicrobials.

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