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Synthesis, Spectral Characterization and biological activity of *N*-Substituted Derivatives of Tetrahydrofuran-2-ylmethylamine

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ABSTRACT
Tetrahydrofuran-2-ylmethylamine (1) was subjected to condensation reaction with 4-chlorobenzenesulfonyl chloride (2) in a mild basic medium to synthesize *N*-(tetrahydrofuran-2-ylmethyl)-4-chlorobenzenesulfonamide (3). A series of *N*-substituted derivatives, 5a-f, were synthesized by condensing alkyl/aralkyl halides, 4a-f, with 3 under polar aprotic conditions using sodium hydride activator. The spectral characterization of all the molecules included IR, ^{1}H-NMR and EI-MS data. The biological activity evaluation rendered 5c as moderate inhibitor of all the bacterial strains.

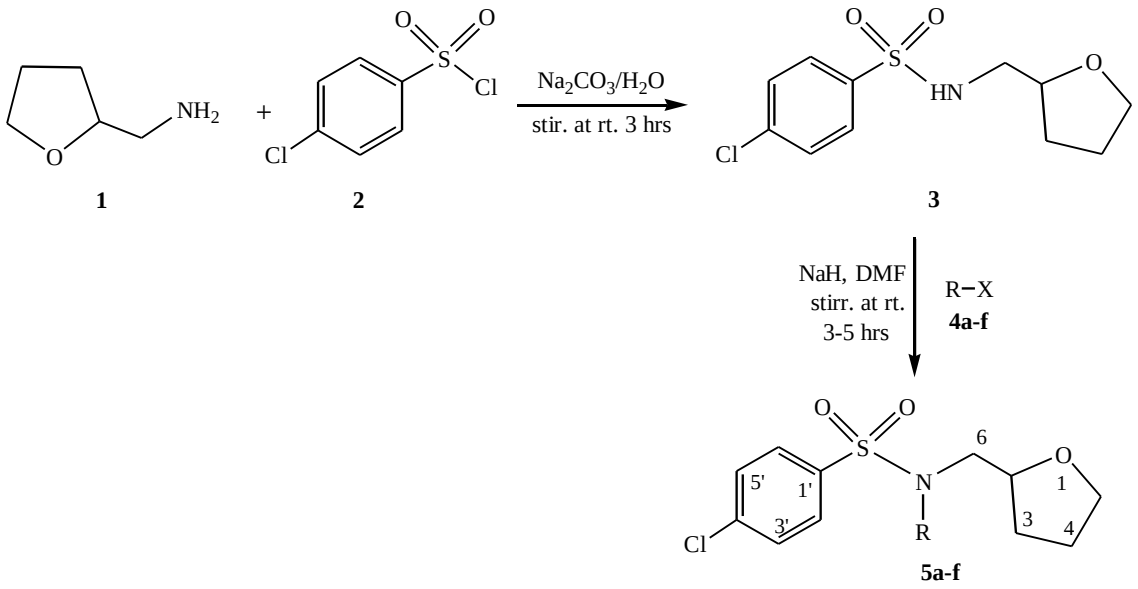
Key words: 4-Chlorobenzenesulfonyl chloride, Antibacterial activity, Sulfonamide, Tetrahydrofuran-2-ylmethylamine.

1. INTRODUCTION
Anticancer, anti-inflammatory and antiviral agents include sulfamoyl group[1], the basic functional group of sulfonamides. The food additives[2] and veterinary medicines[3] involve such compounds. The broad use of such compounds owes to their less cost and less toxicity[4]. Besides arise of drugs of other functionalities, sulfonamides are under synthesis on account of broad spectrum activities[5,6]. Such molecules are known to have compatibility with *p*-aminobenzoic acid and so block their conversion to folic acid[7-9]. The simple sulfonamide synthesis can be propagated by condensation reaction of substituted amines and substituted sulfonyl halides[10] or by reduction of substituted sulfonyl azides[11]. Organic synthesis makes use of this class as protective group for hydroxyl and amino groups[12].

The heterocyclic compounds are known to possess promising biological activities[13-15]. The tetrahydrofuran-2-ylmethylamine derivatives have been known to possess antidepressant[16], antibacterial[17], anti-HCV[18] and anti-inflammatory[19] activities.

The attracting microbial activities[1-5,13,20] instigated us to synthesize *N*-substituted derivatives of tetrahydrofuran-2-ylmethylamine (**1**) for antibacterial activity evaluation. The synthesized molecule, **5c**, executed the moderate antibacterial activity against all the bacterial strains taken into account.

2. RESULTS AND DISCUSSION
The *N*-substituted derivatives of tetrahydrofuran-2-ylmethylamine (**1**) were synthesized according to scheme 1 and evaluated for antibacterial activity against certain bacterial strains of gram-bacteria. The reaction conditions with proper procedures are mentioned explanatory in experimental section.



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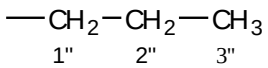
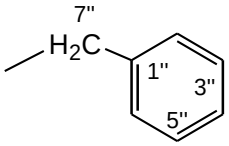
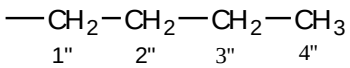
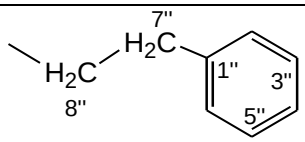
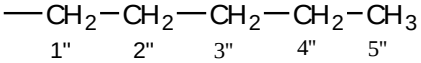
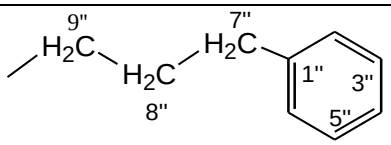
Scheme.1: *N*-Substituted-*N*-(tetrahydrofuran-2-ylmethyl)-4-chlorobenzenesulfonamide (**5a-f**)

Compound	-R	Compound	-R
5a		**5d**	
5b		**5e**	
5c		**5f**	

2.1 *Chemistry*

Tetrahydrofuran-2-ylmethylamine (**1**) was made to react with 4-chlorobenzenesulfonyl chloride (**2**) in water under definite pH control by stirring for 3 hours. *N*-(Tetrahydrofuran-2-ylmethyl)-4-chlorobenzenesulfonamide (**3**) was collected by filtration from slightly acidic medium to ensure better yield. *N*-Substituted-*N*-(tetrahydrofuran-2-ylmethyl)-4-chlorobenzenesulfonamide (**5a-f**) were synthesized by stirring **3** and alkyl/aralkyl halides, **4a-f**, in DMF after activation by NaH. The synthesized molecules were collected either by solvent extraction or filtration. The molecule, **3**, was precipitated as white amorphous solid with 84% yield and purity was checked by melting point noted as 76 ^{o}C. The mol. formula, $C_{11}H_{14}ClNO_3S$, was composed on the basis of mol. ion peak in EIMS at *m/z* 275 and proton integration in proton NMR spectrum. The wave number values in IR and *m/z* values in EIMS spectra are explicated in experimental section. In ^{1}H-NMR spectrum, a doublet at δ 7.73 (d, J = 8.0 Hz, 2H, H-2', H-6') was assigned to two de-shielded protons in the vicinity of sulfonyl group and other doublet at δ 7.43 (d, J = 8.8 Hz, 2H, H-3', H-5') was nominated for relatively less de-shielded two protons in the vicinity of chloro group. The saturated five member ring of tetrahydrofuran was furnished by six multiplets as 4.05-3.98 (m, 1H, H-2), 3.84-3.82 (m, 1H, H_{eq}-5), 3.71-3.67 (m, 1H, H_{ax}-5), 2.03-1.95 (m, 1H, H_{eq}-4), 1.90-1.84 (m, 1H, H_{eq}-3) and 1.69-1.59 (m, 2H, H_{ax}-3, H_{ax}-4). The two methylene protons linked to second position of tetrahydrofuran resonated at δ 3.21 (dd, J = 14.0, 6.8 Hz, 1H, H_a-6) and 3.11 (dd, J = 14.8, 7.2 Hz, 1H, H_b-6). The above discussion named **3** as *N*-(tetrahydrofuran-2-ylmethyl)-4-chlorobenzenesulfonamide. The structures of all the synthesized molecules were corroborated and named through spectral analysis.

2.2 *Biological activity*

The synthesized molecules were subjected to biological activity evaluation regarding antibacterial activity for gram-bacteria using ciprofloxacin as reference standard. The activity results are presented as %age inhibition and MIC values in tables 1 and 2. The molecule, **5c** bearing long aliphatic chain, demonstrated moderate activity against all the bacterial strains. *S. aureus* was inhibited by all the molecules with MIC values comparable to that of ciprofloxacin. The inhibitory action of the molecules against this strain was in the order of **5f>5c>5e>5b>5d>5a**. The better activity of **5f**, with MIC of 10.21±4.43 µmoles/L with respect to 9.29±1.25 µmoles/L, may be attributed to the presence of aralkyl group with long aliphatic chain which extends the π-π interaction of aromatic ring. *S. typhi* was moderately inhibited by all the molecules except **5a** which remained inactive at all and **5b** which was the best inhibitor with MIC value of 11.36±1.66 µmoles/L relative to 8.09±2.13 µmoles/L. Only **5c** was active against *E. coli* with very moderate MIC value of 12.69±1.54 µmoles/L relative to 8.93±1.09 µmoles/L. *P. aeroginosa* and *B. subtilis* were moderately inhibited by **5a**, **5b**, **5c** and **5d** only.

Table.1: %age inhibition values of antibacterial activity

	%AGE INHIBITION				
Compound	***S. typhi (-)***	***E. coli (-)***	***P. aeroginosa (-)***	***B. subtilis (+)***	***S. aureus (+)***
5a	40.81±4.78	22.75±2.42	54.01±1.68	52.15±2.82	59.37±1.88
5b	56.69±0.37	44.46±3.46	54.06±2.19	53.06±4.35	76.71±3.54
5c	53.60±4.34	55.08±4.42	52.63±4.15	51.88±4.86	74.94±4.68
5d	53.90±2.28	25.04±1.88	61.31±3.81	56.83±2.53	64.81±2.82
5e	53.24±4.59	36.29±4.46	35.81±5.00	33.98±3.87	70.01±3.20
5f	50.22±2.57	40.71±3.96	45.75±2.95	23.12±3.44	78.10±0.38
Ciprofloxacin	90.56±1.34	89.95±2.04	87.99±1.13	88.06±0.81	88.92±0.06

Table.2: MIC values of antibacterial activity

	MIC				
Compound	**S. typhi (-)**	**E. coli (-)**	**P. aeroginosa (-)**	**B. subtilis (+)**	**S. aureus (+)**
5a	-	-	17.84±4.81	15.74±3.85	13.56±2.41
5b	11.36±1.66	-	19.03±3.19	13.59±3.32	11.49±3.92
5c	16.75±3.50	12.69±1.54	17.58±2.50	17.03±1.98	10.45±1.87
5d	12.12±1.32	-	11.43±1.62	10.65±4.57	11.88±3.20
5e	12.15±2.50	-	-	-	10.68±1.41
5f	18.95±2.57	-	-	-	10.21±4.43
Ciprofloxacin	8.09±2.13	8.93±1.09	8.87±2.54	9.12±2.32	9.06±1.76

NOTE: Minimum inhibitory concentration (MIC) was measured with suitable dilutions (5-30 µg/ well) and results were calculated using EZ-Fit Perrella Scientific Inc. Amherst USA software.

3. EXPERIMENTAL WORK

3.1 *General*

The chemicals employed for synthesis were Alfa Aesar and Sigma Aldrich branded obtained through local suppliers. The synthesis of compounds was partially confirmed through TLC using EtOAc and *n*-C_6H_{14} mixture as solvent system; by SiO_2 gel with nomination of G-25-UV_{254} pre-coated Al-plates. Compounds were supported by melting points, recorded by Gallonkamp through uncorrection. The compounds were finally confirmed by spectral data of IR, scanned by pellet procedure of potassium bromide on spectrophotometer-Jasco-320-A; of ^{1}H-NMR, recorded at 400 MHz on Bruker spectrometer in $CDCl_3$; of EIMS, scanned on spectrometer-JMS-HX-110.

3.2 *Procedure for synthesis of N-(Tetrahydrofuran-2-ylmethyl)-4-chlorobenzenesulfonamide (3)*

Tetrahydrofuran-2-ylmethylamine (**1**; 0.012 mol) was taken in 250 mL RB flask followed by 50 mL distilled water and stirred for 15 minutes. 5 mL 10% aqueous Na_2CO_3 solution was added followed by 4-chlorobenzenesulfonyl chloride (**2**; 0.012 mol). The system was kept on stirring for 3 hours with pH control, 8-10, by 10% Na_2CO_3 solution till single spot by TLC. For separation of product, 2 mL concentrated HCl was used to acidify reaction mixture for pH 5-6. The settled solid was separated *via* filtration followed by washing through distil. water. White amorphous powder; Yield: 84%; M.P: 76 ^{o}C; Mol. formula: $C_{11}H_{14}ClNO_3S$; Mol. mass: 275 gmol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 2951 (Ar C-H), 1602 (Ar C=C), 1419 (S=O), 1183 (C-O-C), 703 (C-Cl); ^{1}H-NMR ($CDCl_3$, 400 MHz, δ/ppm): 7.73 (d, J = 8.0 Hz, 2H, H-2', H-6'), 7.43 (d, J = 8.8 Hz, 2H, H-3', H-5'), 4.05-3.98 (m, 1H, H-2), 3.84-3.82 (m, 1H, H_{eq}-5), 3.71-3.67 (m, 1H, H_{ax}-5), 3.21 (dd, J = 14.0, 6.8 Hz, 1H, H_a-6), 3.11 (dd, J = 14.8, 7.2 Hz, 1H, H_b-6), 2.03-1.95 (m, 1H, H_{eq}-4), 1.90-1.84 (m, 1H, H_{eq}-3), 1.69-1.59 (m, 2H, H_{ax}-3, H_{ax}-4); EIMS (*m/z*): 277 $[M+2]^+$, 275 $[M]^+$, 175 $[C_6H_4ClO_2S]^+$, 111 $[C_6H_4Cl]^+$, 100 $[C_5H_{10}NO]^+$, 85 $[C_5H_9O]^+$, 76 $[C_6H_4]^+$, 71 $[C_4H_7O]^+$, 50 $[C_4H_2]^+$.

3.3 *General procedure for synthesis of N-Substituted-N-(tetrahydrofuran-2-ylmethyl)-4-chlorobenzenesulfonamide (5a-f)*

The parent compound, **3** (0.002 mol) was dissolved in 13 mL DMF in 100 mL RB flask. Sodium hydride (0.002 mol) was added followed up stirring of 0.5 hour. Alkyl/aralkyl halides (0.002 mol) were poured and stirred for 3-4 hours till single spot through TLC. The title compounds were filtered or extracted and dried for further analysis.

3.3.1 *N-Propyl-N-(tetrahydrofuran-2-ylmethyl)-4-chlorobenzenesulfonamide (5a)*

Light brown liquid; Yield: 84%; Mol. formula: $C_{14}H_{20}ClNO_3S$; Mol. mass: 317 gmol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 2970 (Ar C-H), 1580 (Ar C=C), 1420 (S=O), 1190 (C-O-C), 680 (C-Cl); ^{1}H-NMR ($CDCl_3$, 400 MHz, δ/ppm): 7.73 (d, J = 8.8 Hz, 2H, H-2', H-6'), 7.44 (d, J = 8.4 Hz, 2H, H-3', H-5'), 4.02-3.95 (m, 1H, H-2), 3.81-3.76 (m, 1H, H_{eq}-5), 3.73-3.67 (m, 1H, H_{ax}-5), 3.42 (t, J = 6.8 Hz, 2H, H-1"), 3.24-3.17 (m, 1H, H_a-6), 3.11-3.05 (m, 1H, H_b-6), 2.04-1.95 (m, 1H, H_{eq}-4), 1.89-1.81 (m, 1H, H_{eq}-3), 1.68-1.53 (m, 2H, H_{ax}-3, H_{ax}-4), 0.97-0.88 (m, 2H, H-2"), 0.82 (t, J = 7.2 Hz, 3H, CH_3-3"); EIMS (*m/z*): 319 $[M+2]^+$, 317 $[M]^+$, 175 $[C_6H_4ClO_2S]^+$, 111 $[C_6H_4Cl]^+$, 99 $[C_5H_9NO]^+$, 91 $[C_7H_7]^+$, 85 $[C_5H_9O]^+$, 76 $[C_6H_4]^+$, 71 $[C_4H_7O]^+$, 50 $[C_4H_2]^+$.

3.3.2 *N-Butyl-N-(tetrahydrofuran-2-ylmethyl)-4-chlorobenzenesulfonamide (5b)*

Yellow sticky liquid; Yield: 69%; Mol. formula: $C_{15}H_{22}ClNO_3S$; Mol. mass: 331 gmol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 2935 (Ar C-H), 1608 (Ar C=C), 1412 (S=O), 1180 (C-O-C), 710 (C-Cl); ^{1}H-NMR ($CDCl_3$, 400 MHz, δ/ppm): 7.73 (d, J =

8.4 Hz, 2H, H-2', H-6'), 7.43 (d, J = 8.4 Hz, 2H, H-3', H-5'), 4.01-3.95 (m, 1H, H-2), 3.79-3.74 (m, 1H, H_{eq}-5), 3.70-3.65 (m, 1H, H_{ax}-5), 3.29 (dd, J = 14.8, 6.8 Hz, 1H, H_a-6), 3.27-3.19 (m, 2H, H-1"), 3.10 (dd, J = 14.4, 7.2 Hz, 1H, H_b-6), 2.01-1.95 (m, 1H, H_{eq}-4), 1.87-1.81 (m, 1H, H_{eq}-3), 1.66-1.60 (m, 2H, H_{ax}-3, H_{ax}-4), 1.50 (qui, J = 6.8 Hz, 2H, H-2"), 1.23 (sex, J = 7.2 Hz, 2H, H-3"), 0.85 (t, J = 7.2 Hz, 3H, CH_3-4"); EIMS (*m/z*): 333 $[M+2]^+$, 331 $[M]^+$, 175 $[C_6H_4ClO_2S]^+$, 111 $[C_6H_4Cl]^+$, 99 $[C_5H_9NO]^+$, 85 $[C_5H_9O]^+$, 76 $[C_6H_4]^+$, 71 $[C_4H_7O]^+$, 57 $[C_4H_9]^+$, 50 $[C_4H_2]^+$.

3.3.3 *N-Pentyl-N-(tetrahydrofuran-2-ylmethyl)-4-chlorobenzenesulfonamide (5c)*

Light yellow sticky liquid; Yield: 71%; Mol. formula: $C_{16}H_{24}ClNO_3S$; Mol. mass: 345 gmol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 2945 (Ar C-H), 1580 (Ar C=C), 1390 (S=O), 1190 (C-O-C), 705 (C-Cl); ^{1}H-NMR ($CDCl_3$, 400 MHz, δ/ppm): 7.73 (d, J = 8.8 Hz, 2H, H-2', H-6'), 7.44 (d, J = 8.4 Hz, 2H, H-3', H-5'), 4.01-3.96 (m, 1H, H-2), 3.79-3.74 (m, 1H, H_{eq}-5), 3.70-3.66 (m, 1H, H_{ax}-5), 3.31 (dd J = 14.8, 6.8 Hz, 1H, H_a-6), 3.25-3.19 (m, 2H, H-1"), 3.10 (dd, J = 14.4, 7.2 Hz, 1H, H_b-6), 2.02-1.96 (m, 1H, H_{eq}-4), 1.88-1.82 (m, 1H, H_{eq}-3), 1.63-1.56 (m, 2H, H_{ax}-3, H_{ax}-4), 1.52 (qui, J = 8.4 Hz, 2H, H-2"), 1.27-1.15 (m, 4H, H-3", H-4"), 0.84 (t, J = 6.8 Hz, 3H, CH_3-5"); EIMS (m/z): 347 $[M+2]^+$, 345 $[M]^+$, 175 $[C_6H_4ClO_2S]^+$, 111 $[C_6H_4Cl]^+$, 99 $[C_5H_9NO]^+$, 85 $[C_5H_9O]^+$, 76 $[C_6H_4]^+$, 71 $[C_5H_{11}]^+$, 71 $[C_4H_7O]^+$, 50 $[C_4H_2]^+$.

3.3.4 *N-Benzyl-N-(tetrahydrofuran-2-ylmethyl)-4-chlorobenzenesulfonamide (5d)*

White solid amorphous; Yield: 80%; M.P: 91 ^{o}C; Mol. formula: $C_{18}H_{20}ClNO_3S$; Mol. mass: 365 gmol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 2956 (Ar C-H), 1605 (Ar C=C), 1410 (S=O), 1170 (C-O-C), 706 (C-Cl); ^{1}H-NMR ($CDCl_3$, 400 MHz, δ/ppm): 7.76 (d, J = 8.4 Hz, 2H, H-2', H-6'), 7.44 (d, J = 8.8 Hz, 2H, H-3', H-5'), 7.29-7.25 (m, 5H, H-2" to H-6"), 4.54 (s, 2H, H-7"), 3.89-3.82 (m, 1H, H-2), 3.71-3.66 (m, 1H, H_{eq}-5), 3.62-3.57 (m, 1H, H_{ax}-5), 3.28 (dd, J = 10.4, 6.4, 1H, H_a-6), 3.08 (dd, J = 14.4, 7.6 Hz, 1H, H_b-6), 1.81-1.73 (m, 2H, H_{eq}-3, H_{eq}-4), 1.52-1.41 (m, 2H, H_{ax}-3, H_{ax}-4); EIMS (m/z): 367 $[M+2]^+$, 365 $[M]^+$, 175 $[C_6H_4ClO_2S]^+$, 111 $[C_6H_4Cl]^+$, 99 $[C_5H_9NO]^+$, 91 $[C_7H_7]^+$, 85 $[C_5H_9O]^+$, 76 $[C_6H_4]^+$, 71 $[C_4H_7O]^+$, 65 $[C_5H_5]^+$, 50 $[C_4H_2]^+$.

3.3.5 *N-(2-Phenylethyl)-N-(tetrahydrofuran-2-ylmethyl)-4-chlorobenzenesulfonamide (5e)*

White crystalline solid; Yield: 76%; M.P: 85 ^{o}C; Mol. formula: $C_{19}H_{22}ClNO_3S$; Mol. mass: 379 gmol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 2945 (Ar C-H), 1612 (Ar C=C), 1390 (S=O), 1182 (C-O-C), 704 (C-Cl); ^{1}H-NMR ($CDCl_3$, 400 MHz, δ/ppm): 7.77 (d, J = 8.4 Hz, 2H, H-2', H-6'), 7.47 (d, J = 8.4 Hz, 2H, H-3', H-5'), 7.26-7.15 (m, 5H, H-2" to H-6"), 4.77 (t, J = 6.8 Hz, 2H, H-8"), 3.94-3.88 (m, 1H, H-2), 3.77-3.71 (m, 1H, H_{eq}-5), 3.68-3.64 (m, 1H, H_{ax}-5), 3.17-3.07 (m, 2H, H-6), 2.91-2.85 (t, J = 6.8 Hz, 2H, H-7"), 1.94-1.81 (m, 2H, H_{eq}-3, H_{eq}-4), 1.60-1.53 (m, 2H, H_{ax}-3, H_{ax}-4); EIMS (m/z): 381 $[M+2]^+$, 379 $[M]^+$, 175 $[C_6H_4ClO_2S]^+$, 111 $[C_6H_4Cl]^+$, 105 $[C_8H_9]^+$, 99 $[C_5H_9NO]^+$, 91 $[C_7H_7]^+$, 85 $[C_5H_9O]^+$, 76 $[C_6H_4]^+$, 71 $[C_4H_7O]^+$, 65 $[C_5H_5]^+$, 50 $[C_4H_2]^+$.

3.3.6 *N-(3-Phenylpropyl)-N-(tetrahydrofuran-2-ylmethyl)-4-chlorobenzenesulfonamide (5f)*

Light green liquid; Yield: 75%; Mol. formula: $C_{20}H_{24}ClNO_3S$; Mol. mass: 393 gmol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 2940 (Ar C-H), 1610 (Ar C=C), 1420 (S=O), 1190 (C-O-C), 701 (C-Cl); ^{1}H-NMR ($CDCl_3$, 400 MHz, δ/ppm): 7.66 (d, J = 8.4 Hz, 2H, H-2', H-6'), 7.43 (d, J = 8.4 Hz, 2H, H-3', H-5'), 7.26 (t, J = 7.2 Hz, 2H, H-3", H-5"), 7.16 (t, J = 7.2 Hz, 1H, H-4"), 7.13 (d, J = 7.2, 2H, H-2", H-6"), 4.86 (t, J =7.2 Hz, 2H, H-9"), 3.99-3.92 (m, 1H, H-2), 3.76-3.72 (m, 1H, H_{eq}-5), 3.69-3.64 (m, 1H, H_{ax}-5), 3.30 (dd, J = 8.4, 5.2 Hz, 1H, H_a-6), 3.27-3.21 (m, 1H, H_{eq}-4), 3.19-3.12 (m, 1H, H_{eq}-3), 3.12 (dd, J = 9.2, 6.0 Hz, 1H, H_b-6), 1.64 (t, J =7.2 Hz, 2H, H-7"), 1.85 (qui, J = 7.2, 5H, H-8"); EIMS (m/z): 395 $[M+2]^+$, 393 $[M]^+$, 175 $[C_6H_4ClO_2S]^+$, 119 $[C_9H_{11}]^+$, 111 $[C_6H_4Cl]^+$, 105 $[C_8H_9]^+$, 99 $[C_5H_9NO]^+$, 91 $[C_7H_7]^+$, 85 $[C_5H_9O]^+$, 76 $[C_6H_4]^+$, 71 $[C_4H_7O]^+$, 65 $[C_5H_5]^+$, 50 $[C_4H_2]^+$.

3.4 *Antibacterial activity*

The antimicrobial activity was assayed by the reported method[21,22] according to the principle of increased absorbance of broth medium is directly related to log phase of growth.

3.5 *Statistical analysis*

The results, presented as mean±SEM after statistical analysis by Microsoft Excel 2010, were built from the measurements accounted in triplicate.

4. CONCLUSION

The molecules with long aliphatic chain are found to possess better inhibition activity than the smaller or branched aliphatic chain. The synthesized compounds have been found to be better inhibitor of *S. aureus*, a strain of gram-positive bacteria. These molecules were corroborated structurally by spectral evidences of IR, ^{1}H-NMR and EIMS. The better yields convinced the validation and precision of adopted procedures. The compound, **5c** was moderate inhibitor of all the bacterial strains taken into account. The series of molecules can be investigated for the activity against *S. aureus*, known to be cause of respiratory diseases.

5. REFERENCES

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