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Synthesis and Antibacterial Activity of *N*-Substituted Derivatives of *N*-(Oxolan-2-ylmethyl)-4-Chlorobenzenesulfonamide

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A series of new *N*-substituted derivatives of *N*-(oxolan-2-ylmethyl)-4-chlorobenzenesulfonamide (**3**) have been synthesized and further evaluated for antibacterial activity. The molecule *N*-(oxolan-2-ylmethyl)-4-chlorobenzenesulfonamide (**3**), was prepared in an aqueous basic medium by the reaction of 2-oxolanemethylamine (**1**) and 4-chlorobenzenesulfonyl chloride (**2**) under dynamic pH control. It was further stepped up to yield *N*-alkyl/aralkyl-*N*-(oxolan-2-ylmethyl)-4-chlorobenzenesulfonamides (**5a-f**) by its reaction with alkyl/aralkyl halides (**4a-f**) in a polar aprotic medium in the presence of lithium hydride. The proposed structures of the synthesized molecules were corroborated by IR, ^{1}H NMR and EI-MS spectral data. The resulted MIC values of these compounds showed their good activity against *S. aureus*, the Gram-positive bacteria.

Keywords: 2-Oxolanemethylamine, 4-Chlorobenzenesulfonyl chloride, Antibacterial activity, Sulfonamides.

INTRODUCTION

Sulfonamides, an important class for pharmacists, have been part of anticancer, anti-inflammatory and antiviral agents[1] and used as animal husbandry, food additives[2] and veterinary medicines to treat infections in livestock herds[3]. These molecules are widely employed credibly because of low cost, low toxicity and astonishing activity against bacterial infections[4]. Although, other antibiotics have minimized the usage of this class yet it is in practice because of their broad spectrum activity[5] such as for gastrointestinal and urinary tract infections owing to their ease of administration and non-interaction with defense mechanism of host[6]. The mechanism of sulfonamidic action involves the inhibition of *p*-amino benzoic acid into folic acid[7-9]. A simple and facile method of synthesis of sulfonamides involves the nucleophilic attack of alkyl/aralkyl/aryl amines on sulfonyl halides[10] or the reduction of aryl sulfonyl azides to aryl sulfonamides[11]. They are also used as protecting groups of -OH and -NH in organic synthesis[12].

A series of *N*-substituted molecules have been synthesized using 2-oxolanemethylamine (**1**) as precursor. The literature review on biological activities of sulfonamides[1-5] and our last synthetic work[13,14] on this class prompted us to evaluate the antibacterial activity of the synthesized compounds derived from 2-oxolanemethylamine. The synthesized molecules depicted the moderate antibacterial activity.

EXPERIMENTAL

Thin layer chromatography (TLC) was employed to evaluate the progress of reactions and purity of compounds using different concentrations of ethyl acetate and *n*-hexane mixtures as solvent system. The pre-coated silica gel G-25-UV$_{254}$ plates were utilized for TLC and visualized under 254 nm and by ceric sulphate reagent. The melting points were recorded on a Gallonkamp apparatus by open capillary tube and were uncorrected. The IR spectra were recorded in KBr pellet on a Jasco-320-A spectrophotometer. ^{1}H NMR spectra were recorded at 400 MHz on a Bruker spectrometer using $CHCl_3$-d_1. Chemical shifts are depicted in ppm with TMS as internal reference. Mass spectra (EIMS) were recorded on a JMS-HX-110 spectrometer, with a data system.

Synthesis of *N*-(oxolan-2-ylmethyl)-4-chlorobenzenesulfonamide (3): 2-Oxolanemethylamine (1; 1.33 mL) was poured into 50 mL distilled water in a 250 mL round bottom flask followed by the addition of solid Na_2CO_3 (0.2 g). The mixture was stirred for 5-10 min and after that equimolar 4-chlorobenzenesulfonyl chloride (**2**; 2.72 g) was added. The basicity of the reaction mixture was maintained at pH 8-10 by solid Na_2CO_3 till the single spot on TLC plate. The contents were continuously stirred for 2-3 h. After complete reaction, few drops of concentrated HCl were added gradually till the pH 2-3. The solid product was precipitated and separated by

filtration as white amorphous powder; yield: 84 %; m.p. 76 °C; m.f.: $C_{11}H_{14}NO_3SCl$; m.w.: 275 g mol^{-1}; ^1H 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_{ax}-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).

General procedure for the synthesis of *N*-substituted derivatives of 3 (5a-f): The molecule **3** (0.2 g, 0.07 mmol) was completely dissolved in DMF (12 mL) in a 50 mL RB flask and was activated by LiH (0.004 g) on stirring for 15-20 minutes. Then alkyl/aralkyl halides (**4a-f**, 0.07 mmol) were added and stirring was continued for further 3-4 h till the single spot by TLC. Ice cold distilled water was added to the reaction mixture and reaction mixture was kept at 25 °C for 5-10 min. The reaction contents were basified up to pH 9 to 10. Liquid products were collected through solvent extraction using $CHCl_3$ and solid products through filtration.

***N*-Ethyl-N-(oxolan-2-ylmethyl)-4-chlorobenzenesulfonamide (5a):** Dark sticky solid; Yield: 78 %; m.f: $C_{13}H_{18}NO_3SCl$; m.w.: 303 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 2948 (Ar C-H), 1617 (Ar C=C), 1412 (S=O), 1173 (C-O-C), 695 (C-Cl); ^1H NMR ($CDCl_3$, 400 MHz, δ/ppm): 7.74 (d, *J* = 8.4 Hz, 2H, H-2', H-6'), 7.44 (d, *J* = 8.4 Hz, 2H, H-3', H-5'), 4.04-3.97 (m, 1H, H-2), 3.82-3.79 (m, 1H, H_{eq}-5), 3.72-3.68 (m, 1H, H_{ax}-5), 3.37-3.32 (m, 2H, H-1''), 3.25 (dd, *J* = 14.4, 7.2 Hz, 1H, H_a-6), 3.09 (dd, *J* = 14.8, 7.2 Hz, 1H, H_b-6), 2.00-1.94 (m, 1H, H_{eq}-4), 1.91-1.84 (m, 1H, H_{eq}-3), 1.68-1.60 (m, 2H, H_{ax}-3, H_{ax}-4), 1.10 (t, *J* = 7.2 Hz, 3H, CH_3-2''); EIMS (*m/z*): 305 $[M + 2]^+$, 303 $[M]^+$, 175 $[C_6H_4ClO_2S]^+$, 111 $[C_6H_4Cl]^+$, 99 $[C_5H_9NO]^+$, 85 $[C_5H_9O]^+$, 76 $[C_6H_4]^+$, 71 $[C_4H_7O]^+$.

***N*-(1-Methylethyl)-*N*-(oxolan-2-ylmethyl)-4-chlorobenzenesulfonamide (5b):** Light yellow sticky liquid; yield: 73 %; m.f.: $C_{14}H_{20}NO_3SCl$; m.w.: 317 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 2940 (Ar C-H), 1625 (Ar C=C), 1430 (S=O), 1170 (C-O-C), 705 (C-Cl); ^1H NMR ($CDCl_3$, 400 MHz, δ/ppm): 7.77 (d, *J* = 8.4 Hz, 2H, H-2', H-6'), 7.43 (d, *J* = 8.8 Hz, 2H, H-3', H-5'), 4.15-4.09 (m, 1H, H-2), 3.96-3.89 (m, 1H, H-1''), 3.84-3.80 (m, 1H, H_{eq}-5), 3.75-3.73 (m, 1H, H_{ax}-5), 3.26 (dd, *J* = 15.2, 5.2 Hz, 1H, H_a-6), 3.12 (dd, *J* = 11.2, 6.8 Hz, 1H, H_b-6), 2.13-2.00 (m, 2H, H_{eq}-3, H_{eq}-4), 1.93-1.83 (m, 2H, H_{ax}-3, H_{ax}-4), 1.12 (d, *J* = 6.8 Hz, 6H, CH_3-2'', CH_3-3''); EIMS (*m/z*): 319 $[M + 2]^+$, 317 $[M]^+$, 175 $[C_6H_4ClO_2S]^+$, 111 $[C_6H_4Cl]^+$, 99 $[C_5H_9NO]^+$, 85 $[C_5H_9O]^+$, 76 $[C_6H_4]^+$, 71 $[C_4H_7O]^+$.

***N*-(1-Methylbutyl)-*N*-(Oxolan-2-ylmethyl)-4-chlorobenzenesulfonamide (5c):** Light grey sticky liquid; yield: 75 %; m.f.: $C_{16}H_{24}NO_3SCl$; m.w.: 345 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 2965 (Ar C-H), 1624 Ar (C=C), 1422 (S=O), 1200 (C-O-C), 690 (C-Cl); ^1H NMR ($CDCl_3$, 400 MHz, δ/ppm): 7.77 (d, *J* = 8.4 Hz, 2H, H-2', H-6'), 7.44 (d, *J* = 8.0 Hz, 2H, H-3', H-5'), 4.12-4.04 (m, 1H, H-2), 3.83-3.78 (m, 1H, H_{eq}-5), 3.75-3.71 (m, 1H, H_{ax}-5), 3.26-3.18 (m, 1H, H-1''), 3.12 (dd, *J* = 14.8, 8.4 Hz, 1H, H_a-6), 3.05 (dd, *J* = 15.2, 8.4 Hz, 1H, H_b-6), 2.03-1.95 (m, 1H, H_{eq}-4), 1.88-1.81 (m, 1H, H_{eq}-3), 1.75-1.70 (m, 2H, H-2''), 1.35-1.23 (m, 2H, H_{ax}-3, H_{ax}-4), 1.12 (sec, *J* = 7.6 Hz, 2H, H-3''), 0.90 (d, *J* = 6.8 Hz, 3H, CH_3-5''), 0.77 (t, *J* = 7.2 Hz, 3H, CH_3-4''); 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 $[C_4H_2]^+$.

***N*-(2-Chlorobenzyl)-*N*-(oxolan-2-ylmethyl)-4-chlorobenzenesulfonamide (5d):** Light grey sticky liquid; yield: 83 %; m.f.: $C_{18}H_{19}NO_3SCl_2$; m.w.: 399 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 2966 (Ar C-H), 1620 (Ar C=C), 1415 (S=O), 1165 (C-O-C), 708 (C-Cl); ^1H NMR ($CDCl_3$, 400 MHz, δ/ppm): 7.76 (d, *J* = 8.4 Hz, 2H, H-2', H-6'), 7.49 (d, *J* = 7.6 Hz, 1H, H-3''), 7.45 (d, *J* = 8.4 Hz, 2H, H-3', H-5'), 7.27 (ddd, *J* = 7.6, 1.2 Hz, 1H, H-4''), 7.22 (d, *J* = 7.6 Hz, 1H, H-6''), 7.18 (ddd, *J* = 7.6, 1.2 Hz, 1H, H-5''), 4.50 (s, 2H, H-7''), 3.92-3.85 (m, 1H, H-2), 3.69-3.46 (m, 2H, H-5), 3.35 (dd, *J* = 14.8, 4.4 Hz, 1H, H_a-6), 3.18 (dd, *J* = 14.8, 8.0 Hz, 1H, H_b-6), 2.93-2.85 (m, 2H, H_{eq}-3, H_{eq}-4), 1.58-1.51 (m, 2H, H_{ax}-3, H_{ax}-4); EIMS (*m/z*): 403 $[M + 4]^+$, 401 $[M + 2]^+$, 399 $[M]^+$, 175 $[C_6H_4ClO_2S]^+$, 125 $[C_7H_6Cl]^+$, 111 $[C_6H_4Cl]^+$, 99 $[C_5H_9NO]^+$.

***N*-(4-Chlorobenzyl)-*N*-(oxolan-2-ylmethyl)-4-chlorobenzenesulfonamide (5e):** White amorphous solid; yield: 79 %; m.p. 77 °C; m.f.: $C_{18}H_{19}NO_3SCl_2$; m.w.: 399 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 2968 (Ar C-H), 1625 (Ar C=C), 1395 (S=O), 1205 (C-O-C), 698 (C-Cl); ^1H NMR ($CDCl_3$, 400 MHz, δ/ppm): 7.74 (d, *J* = 8.4 Hz, 2H, H-2', H-6'), 7.44 (d, *J* = 8.4 Hz, 2H, H-3', H-5'), 7.25 (d, *J* = 8.0 Hz, 2H, H-3'', H-5''), 7.21 (d, *J* = 8.0 Hz, 2H, H-2'', H-6''), 4.48 (s, 2H, H-7''), 3.86-3.79 (m, 1H, H-2), 3.67-3.57 (m, 2H, H-5), 3.30 (dd, *J* = 14.4, 4.0 Hz, 1H, H_a-6), 3.03 (dd, *J* = 14.8, 8.0 Hz, 1H, H_b-6), 2.03-1.96 (m, 1H, H_{eq}-4), 1.79-1.71 (m, 1H, H_{eq}-3), 1.47-1.39 (m, 2H, H_{ax}-3, H_{ax}-4); EIMS (*m/z*): 403 $[M + 4]^+$, 401 $[M + 2]^+$, 399 $[M]^+$, 175 $[C_6H_4ClO_2S]^+$, 125 $[C_7H_6Cl]^+$, 111 $[C_6H_4Cl]^+$, 99 $[C_5H_9NO]^+$, 90 $[C_7H_6]^+$.

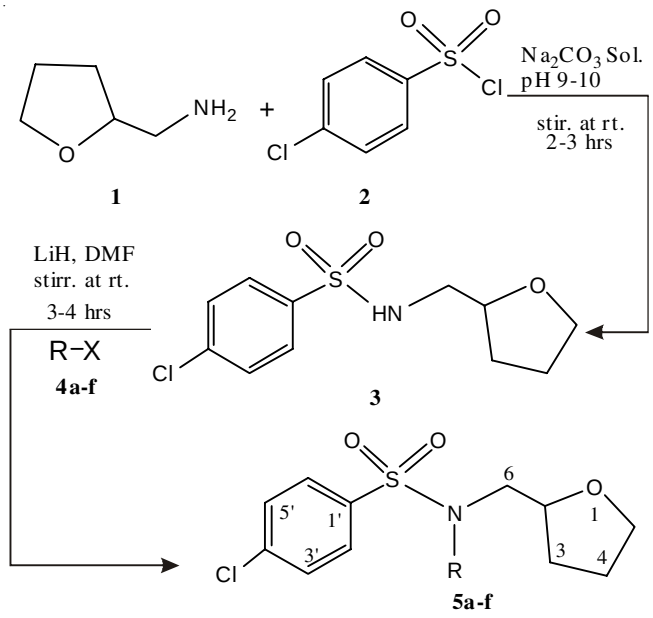
***N*-(4-Bromobenzyl)-*N*-(oxolan-2-ylmethyl)-4-chlorobenzenesulfonamide (5f):** Light grey amorphous solid; yield: 81 %; m.p. 110 °C; m.f.: $C_{18}H_{19}NO_3SBrCl$; m.w: 443 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 2960 (Ar C-H), 1590 (Ar C=C), 1415 (S=O), 1175 (C-O-C), 702 (C-Cl); ^1H NMR ($CDCl_3$, 400 MHz, δ/ppm): 7.75 (d, *J* = 8.4 Hz, 2H, H-2', H-6'), 7.45 (d, *J* = 8.4 Hz, 2H, H-3', H-5'), 7.41 (d, *J* = 8.4 Hz, 2H, H-3'', H-5''), 7.14 (d, *J* = 8.4 Hz, 2H, H-2'', H-6''), 4.46 (s, 1H, H-7''), 3.86-3.78 (m, 1H, H-2), 3.69-3.54 (m, 2H, H-5), 3.31 (dd, *J* = 14.8, 4.0 Hz, 1H, H_a-6), 3.03 (dd, *J* = 14.8, 8.0 Hz, 1H, H_b-6), 1.82-1.73 (m, 2H, H_{eq}-3, H_{eq}-4), 1.49-1.43 (m, 2H, H_{ax}-3, H_{ax}-4); EIMS (*m/z*): 447 $[M + 4]^+$, 445 $[M + 2]^+$, 443 $[M]^+$, 175 $[C_6H_4ClO_2S]^+$, 169 $[C_7H_6Br]^+$, 111 $[C_6H_4Cl]^+$, 99 $[C_5H_9NO]^+$, 90 $[C_7H_6]^+$.

Antibacterial activity: The antimicrobial activity was determined following the principle that increased absorbance of broth medium is directly related to log phase of growth and was performed in sterile 96-wells microplates under aseptic conditions[15,16].

Statistical analysis: All the measurements were accounted in triplicate and statistical analysis was performed by Microsoft Excel 2010. Results are presented as mean ± sem.

RESULTS AND DISCUSSION

2-Oxolanemethylamine (**1**) was converted into *N*-(oxolan-2-ylmethyl)-4-chlorobenzenesulfonamide (**3**) in one step and further into *N*-substituted derivatives, **5a-f**, in second step by the protocol given in **Scheme-I**. The synthesized molecules



Compound	-R	Compound	-R
5a	—CH$_2$—CH$_3$ (1", 2")	**5d**	7", H$_2$C, Cl, 1", 3", 5"
5b	3"CH$_3$, CH—CH$_3$ (1", 2")	**5e**	7", H$_2$C, 1", 3", 5", Cl
5c	CH$_3$ 5", CH—CH$_2$—CH$_2$—CH$_3$ (1", 2", 3", 4")	**5f**	7", H$_2$C, 1", 3", 5", Br

Scheme-I

were further evaluated for their antibacterial activity. All the reaction conditions and reagents are explained in experimental section.

N-(Oxolan-2-ylmethyl)-4-chlorobenzenesulfonamide (**3**) was synthesized by the reaction of 2-oxolanemethylamine (**1**) and 4-chlorobenzenesulfonyl chloride (**2**) at room temperature in an aqueous weak basic medium after stirring for 2-3 h. To accomplish better yield, the reaction mixture was weakly acidified by concentrated HCl and then the precipitated product was filtered. The acidic medium is necessary for good yield but high acidity has negative effect. A series of *N*-alkyl/aralkyl-*N*-(oxolan-2-ylmethyl)-4-chlorobenzenesulfonamide derivatives, **5a-f**, were synthesized from molecule **3** by its reaction with various alkyl/aralkyl halides, **4a-f**, in a polar aprotic solvent such as DMF and in the presence of LiH as activator. The target molecules were obtained from a weak basic medium through solvent extraction or filtration. The sulfonamide **3** was obtained as white amorphous powder in 84 % yield and with melting point of 76 °C. The EIMS spectrum showed the $[M]^+$ ion peak at *m/z* 275 corresponding to the molecular formula $C_{11}H_{14}NO_3SCl$. The molecular formula was established from molecular ion peak in EIMS and by counting the number of protons in its ^{1}H NMR spectrum. Two *ortho* coupled doublets appeared the most downfield in the aromatic region of ^{1}H NMR at δ 7.73 (d, *J* = 8.0 Hz, 2H, H-2', H-6') and 7.43 (d, *J* = 8.8 Hz, 2H, H-3', H-5') and were assigned to protons of 1,4-disubstituted 4-chlorobenzenesulfonyl ring. The six multiplets in the range of δ 4.05-3.98 (for H-2), 3.84-3.82 (for H_{eq}-5), 3.71-3.67 (for H_{ax}-5), 2.03-1.95 (for H_{eq}-4), 1.90-1.84 (for H_{eq}-3) and 1.69-1.59 ppm (for H_{ax}-3 and H_{ax}-4); and two doublets of doublet at δ 3.21 and δ 3.11 ppm (for H_a-6 and H_b-6) affirmed the presence of 2-oxolanemethyl group. The absorption bands of IR and cationic peaks of EIMS spectrum, as depicted in experimental section, well supported the structure of compound **3**. Thus the structure of compound **3** was assigned the name of *N*-(oxolan-2-ylmethyl)-4-chlorobenzene-sulfonamide. The proposed structures of the synthesized molecules, compounds **5a-f**, were corroborated on the same lines as depicted above.

Antibacterial activity (*in vitro*): The percentage inhibition and MIC values of all the synthesized molecules relative to ciprofloxacin are shown in Tables 1 and 2, respectively. The screening of all the synthesized molecules against Gram-negative and Gram-positive bacteria demonstrated that all the molecules executed moderate activity against *S. aureus*. The molecules, compounds **5d** and **5f** remained better inhibitors of with MIC values of 11.22 ± 3.13 and 11.72 ± 3.76 μ mol/L, respectively, relative to that of ciprofloxacin, the reference standard, 9.06 ± 1.76 μ mol/L. Among all the compounds, **5c** showed no activity against any bacterial strain. The molecule, compound **5b**, executed the most activity against *S. typhi* with MIC value of 9.29 ± 1.25 μ mol/L comparable to that of ciprofloxacin as 8.09 ± 2.13 μ mol/L. The better activity of compound **5b** was probably because of small branched aliphatic group attached to nitrogen of sulfamoyl group. The only molecule, compound **5d** showed moderate activity against *P. aeroginosa* and all remained inactive against *E. coli* and *B. subtilis*. The order of inhibition activity of all the active molecules against *S. typhi* was compounds **5b** > **5d** > **5a** and that against *S. aureus* was compound **5d** > **5f** > **5e** > **5a** > **5b**.

TABLE-1
PERCENTAGE INHIBITION VALUES OF ANTIBACTERIAL ACTIVITY

	% Inhibition				
Compounds	*S. typhi (-)*	*E. coli (-)*	*P. aeroginosa (-)*	*B. subtilis (+)*	*S. aureus (+)*
5a	51.03 ± 2.86	38.25 ± 2.00	42.13 ± 2.17	46.45 ± 2.98	51.14 ± 2.04
5b	62.94 ± 4.03	43.04 ± 4.32	47.13 ± 3.63	47.90 ± 1.56	65.76 ± 2.97
5c	25.29 ± 3.09	25.63 ± 3.21	8.50 ± 2.54	38.44 ± 1.56	48.42 ± 3.52
5d	52.79 ± 5.00	32.13 ± 3.79	51.38 ± 3.88	33.66 ± 2.47	64.37 ± 2.42
5e	34.19 ± 1.10	23.58 ± 5.00	35.00 ± 2.72	31.77 ± 4.32	59.18 ± 3.43
5f	49.04 ± 1.40	45.42 ± 2.42	41.25 ± 4.00	26.08 ± 1.13	63.29 ± 4.94
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

	Minimum inhibitory concentration				
Compounds	*S. typhi* (-)	*E. coli* (-)	*P. aeroginosa* (-)	*B. subtilis* (+)	*S. aureus* (+)
5a	17.33 ± 1.15	–	–	–	15.26 ± 1.46
5b	9.29 ± 1.25	–	–	–	15.87 ± 4.18
5c	–	–	–	–	–
5d	14.93 ± 1.59	–	18.29 ± 3.69	–	11.22 ± 3.13
5e	–	–	–	–	14.92 ± 2.34
5f	–	–	–	–	11.72 ± 3.76
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

Conclusion

The series of synthesized molecules was obtained in better yields by a simple method. All the molecules were evaluated for their antibacterial activity and their MIC values rendered them moderate inhibitors relative to ciprofloxacin. The compound, **5b** showed better activity against *S. typhi* and compound **5d** against *S. aureus*. The whole series was active against *S. aureus* except compound **5c**. Thus these molecules might be employed in drug industries for further evaluation of toxicity and affectivity to other bugs.

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