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Synthesis of *N*-(Un)Substituted-*N*-(2-Methoxyphenyl/Phenyl)-4-Chlorobenzenesulfonamides as Potent Antibacterial Derivatives

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Sulfonamides belong to a biologically dynamic class of compounds with considerable importance for organic synthetic chemists. In the presented work, a benign series of chlorinated sulfonamides, **3a-b**, was synthesized by coupling alkoxy (un) substituted anilines, **2a-b**, with 4-chlorobenzenesulfonyl chloride (**1**) under basic pH control in an aqueous medium. The sulfonamides, **3a-b**, were geared up with alkyl/aralkyl halides, **4-6**, in a basic aprotic solvent to yield the target molecules, **7a-b**, **8a-b** and **9a-b**. The structures of all the derivatives were furnished by ^{1}H NMR, IR and EI-MS spectral analysis. All the synthesized compounds were screened for α-chemotrypsin and antibacterial activities.

Keywords: Substituted anilines, 4-Chlorobenzenesulfonyl chloride, Enzyme inhibition study.

INTRODUCTION

Sulfonamides bear sulfamoyl (-SO_2NH-) group and are pharmacologically significant class of compounds. Sulfamoyl group is considered crucial for drugs being used extensively as anticancer, antimicrobial, antiviral, antihydrod, antiinflammatory and antitumor agents along with carbonic anhydrase inhibitors[1]. Because of less toxicity, increased activity and less cost, sulfonamides are widely used as antibacterial agents[2-6]. The *p*-aminobenzoic acid (PABA) is involved in synthesis of folic acid in bacterial cell. Sulfonamides are related to *p*-aminobenzoic acid in structure and so inhibit *p*-aminobenzoic acid conversion to folic acid. Finally the synthesis of purine and DNA is inhibited[1]. Sulfonamide synthesis generally takes place by nucleophilic substitution reactions. Amine, the nucleophile, attacks on sulfonyl chloride[7] while electrophilic substitution reaction takes place during *N*-substitution of these resulted molecules. Sulfonamides have been reported in more than 30 drugs of vast clinical applications[8]. These molecules also find their applications in animal husbandry and food additives[9].

Literature survey revealed that small variations in the structure of sulfonamides can cause significant changes in biological activity. These results insisted scientists to focus on synthesis of variety of *N*-substituted derivatives of sulfonamides to introduce new drug candidates with enhanced biological potential. The demonstrated research work was a successful attempt to synthesize pharmacologically potent compounds. In sequence of our prior research work on chlorinated sulfonamide[10-12], the further synthesis was brought about to prepare new competent that might work as a remedy of several diseases owing to their splendid therapeutic potential.

EXPERIMENTAL

All the chemical reagents were purchased through local suppliers, Merck and Alfa Aeser branded and did not processed for further purification. All solvents used were of analytical grade. Thin layer chromatography (TLC) was applied to confirm the purity of the synthesized compounds with solvent systems consisting of different percentages of ethyl acetate and *n*-hexane. Developed TLC plates were visualized by UV lamp at wavelength of 254 nm and UV inactive reagents were identified by spraying with ceric sulfate solution. Infrared spectra were recorded on a Jasco-320-A spectrophotometer by KBr pellet method. Melting points were recorded by the help of Griffin-George melting point apparatus using open capillary tube and uncorrected. ^{1}H NMR spectra were recorded in CD_3OD on a Bruker spectrometers operating at 500 MHz. The chemical shift values are given in ppm scale while TMS was used as reference and the coupling constants (J) are mentioned in Hz. Mass spectra (EI-MS) were taken on a JMS-HX-110 spectrometer.

General procedure for synthesis of different chlorinated sulfonamides (3a-b): Alkoxy (un)substituted anilines (0.001

mol; **2a-b**) were dispersed in 100 mL round bottom flask containing 50 mL distilled water. 10 % aqueous Na_2CO_3 solution was used to maintain the pH = 9-10. 4-Chlorobenzenesulfonyl chloride (0.001 mol; **1**) was introduced to reaction flask gradually in 10-15 min sustaining the pH at 9-10. Reaction contents were allowed to stir for 3-5 h at room temperature. The reaction coordinates were checked by TLC (*n*-hexane: ethyl acetate; 70:30) time by time till completion. Reaction mixture was acidified by adding 3-4 mL concentrated HCl slowly to bring the pH to 2-3. The solid precipitates were filtered and washed with distilled water to obtain the products **3a-b** on drying. Precipitates were recrystallized by methanol.

Procedure for the synthesis of *N*-[alkoxy (un)substituted phenyl]-*N*-alkyl/aralkyl-4-chlorobenzenesulfonamide (7a-b, 8a-b, 9a-b): Compounds, **3a-b** (0.01 mol) were dissolved in 10 mL polar aprotic solvent DMF in a 100 mL round bottom flask. Sodium hydride (0.01 mol) was introduced to reaction contents to activate the reaction and set to stir for 0.5 h at room temperature. The electrophiles ethyl iodide, benzyl chloride and 4-chlorobenzyl chloride (**4-6**; 0.01 mol) were added to reaction contents and stirred for 4-5 h to yield the target compounds, **7a-b**, **8a-b** and **9a-b**. On completion ice cold distilled water was added to the reaction mixture along with vigorous shaking to yield the precipitates. The precipitates formed were left for 10-15 min undisturbed and then filtered, washed with water and dried to yield the target compounds, **7a-b**, **8a-b** and **9a-b**.

Antibacterial activity: The antibacterial activity method was based on the principle that microbial cell number or microbial growth was directly related to the log phase of growth with increase in absorbance of broth medium[10,13].

Lipoxygenase assay: Lipoxygenase activity was assayed according to the reported method[14,15] but with slight modifications.

α-Chymotrypsin assay: α-Chymotrypsin inhibition assay was carried out according to the reported method[16,17].

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

Spectral characterization of all the synthesized derivatives

***N*-Phenyl-*N*-ethyl-4-chlorobenzenesulfonamide (7a):** White amorphous solid; Yield: 79 %; m.p. 116-118 °C; m.f.: $C_{14}H_{14}NSO_2Cl$; m.w.: 295; IR (KBr, ν_{max}, cm^{-1}): 3056 (Ar-H), 1537 (Ar C=C), 1421 (-SO_2-), 1151 (C-N), 561 (C-Cl); ^{1}H NMR (500 MHz, CD_3OD, ppm): δ 7.68 (d, *J* = 9 Hz, 2H, H-2', H-6'), 7.45 (d, *J* = 8.5 Hz, 2H, H-3', H-5'), 7.21 (d, *J* = 10 Hz, 2H, H-2, H-6), 7.09-7.04 (m, 3H, H-3 to H-5), 3.56 (q, *J* = 7.5 Hz, 2H, H-1"), 1.03 (t, *J* = 7.5 Hz, 2H, H-2"); EIMS (*m/z*): 297 $[M + 2]^{\bullet+}$, 295 $[M]^{\bullet+}$, 231 $[M\text{-}SO_2]^{\bullet+}$, 175 $[C_6H_4ClSO_2]^+$, 120 $[M\text{-}C_6H_4ClSO_2]^+$, 92 $[M\text{-}C_8H_8ClSO_2]^+$, 111 $[C_6H_4Cl]^+$, 77 $[M\text{-}C_8H_9ClNSO_2]^{\bullet+}$, 76 $[C_6H_4]^{\bullet+}$.

***N*-(2-Methoxyphenyl)-*N*-ethyl-4-chlorobenzenesulfonamide (7b):** White amorphous solid; Yield: 78 %; m.p. 106-108 °C; m.f.: $C_{15}H_{16}NSO_3Cl$; m.w.: 325; IR (KBr, ν_{max}, cm^{-1}): 3062 (Ar-H), 1532 (Ar C=C), 1422 (-SO_2-), 1153 (C-N), 563 (C-Cl); ^{1}H NMR (500 MHz, CD_3OD, ppm): δ 7.65 (d, *J* = 9 Hz, 2H, H-2', H-6'), 7.44 (d, *J* = 8.5 Hz, 2H, H-3', H-5'), 7.40 (d, *J* = 8 Hz, 1H, H-6), 7.11 (dt, *J* = 8.5, 1.5 Hz, 1H, H-4), 6.88 (dt, *J* = 9, 1.5 Hz, 1H, H-5), 6.81 (d, *J* = 8.5 Hz, 1H, H-3), 3.61 (q, *J* = 7.5 Hz, 2H, H-1"), 3.50 (s, 3H, CH_3O-2), 1.04 (t, *J* = 7.5 Hz, 2H, H-2"); EIMS (*m/z*): 327 $[M + 2]^{\bullet+}$, 325 $[M]^{\bullet+}$, 261 $[M\text{-}SO_2]^{\bullet+}$, 175 $[C_6H_4ClSO_2]^+$, 150 $[M\text{-}C_6H_4ClSO_2]^+$, 122 $[M\text{-}C_8H_8ClSO_2]^+$, 111 $[C_6H_4Cl]^+$, 107 $[M\text{-}C_8H_9ClNSO_2]^{\bullet+}$, 76 $[C_6H_4]^{\bullet+}$.

***N*-Phenyl-*N*-benzyl-4-chlorobenzenesulfonamide (8a):** White amorphous solid; Yield: 83 %; m.p. 112-114 °C; m.f.: $C_{19}H_{16}NSO_2Cl$; m.w.: 357; IR (KBr, ν_{max}, cm^{-1}): 3053 (Ar-H), 1532 (Ar C=C), 1416 (-SO_2-), 1144 (C-N), 557 (C-Cl); ^{1}H NMR (500 MHz, CD_3OD, ppm): δ 7.68 (d, *J* = 9 Hz, 2H, H-2', H-6'), 7.47 (d, *J* = 8.5 Hz, 2H, H-3', H-5'), 7.23 (d, *J* = 10 Hz, 2H, H-2, H-6), 7.18-7.14 (m, 5H, H-2" to H-6"), 7.10-7.05 (m, 3H, H-3 to H-5), 4.71 (s, 2H, H-7"); EIMS (*m/z*): 359 $[M + 2]^{\bullet+}$, 357 $[M]^{\bullet+}$, 293 $[M\text{-}SO_2]^{\bullet+}$, 175 $[C_6H_4ClSO_2]^+$, 182 $[M\text{-}C_6H_4ClSO_2]^+$, 111 $[C_6H_4Cl]^+$, 92 $[M\text{-}C_{13}H_{10}ClSO_2]^+$, 76 $[C_6H_4]^{\bullet+}$.

***N*-(2-Methoxyphenyl)-*N*-benzyl-4-chlorobenzenesulfonamide (8b):** Light pink amorphous solid; Yield: 87 %; m.p. 110-112 °C; m.f.: $C_{20}H_{18}NSO_3Cl$; m.w.: 387; IR (KBr, ν_{max}, cm^{-1}): 3057 (Ar-H), 1535 (Ar C=C), 1413 (-SO_2-), 1143 (C-N), 565 (C-Cl); ^{1}H NMR (500 MHz, CD_3OD, ppm): δ 7.66 (d, *J* = 9 Hz, 2H, H-2', H-6'), 7.45 (d, *J* = 8.5 Hz, 2H, H-3', H-5'), 7.41 (d, *J* = 8.5, 2.5 Hz, 1H, H-6), 7.18-7.12 (m, 5H, H-2" to H-6"), 7.12 (dt, *J* = 8.5, 2 Hz, 1H, H-4), 6.87 (dt, *J* = 9.5, 2.5 Hz, 1H, H-5), 6.81 (d, *J* = 9.5 Hz, 1H, H-3), 4.68 (s, 2H, H-7"), 3.50 (s, 3H, CH_3O-2); EIMS (*m/z*): 389 $[M + 2]^{\bullet+}$, 387 $[M]^{\bullet+}$, 323 $[M\text{-}SO_2]^{\bullet+}$, 175 $[C_6H_4ClSO_2]^+$, 212 $[M\text{-}C_6H_4ClSO_2]^+$, 122 $[M\text{-}C_{13}H_{10}ClSO_2]^+$, 111 $[C_6H_4Cl]^+$, 107 $[M\text{-}C_{13}H_{11}ClNSO_2]^{\bullet+}$, 76 $[C_6H_4]^{\bullet+}$.

***N*-Phenyl-*N*-[(4-chlorophenyl)methyl]-4-chlorobenzenesulfonamide (9a):** White amorphous solid; Yield: 82 %; m.p. 118-120 °C; m.f.: $C_{19}H_{15}NSO_2Cl_2$; m.w.: 392; IR (KBr, ν_{max}, cm^{-1}): 3055 (Ar-H), 1534 (Ar C=C), 1414 (-SO_2-), 1143 (C-N), 557 (C-Cl); ^{1}H NMR (500 MHz, CD_3OD, ppm): δ 7.69 (d, *J* = 9 Hz, 2H, H-2', H-6'), 7.47 (d, *J* = 8.5 Hz, 2H, H-2", H-6"), 7.45 (d, *J* = 8.5 Hz, 2H, H-3', H-5'), 7.22 (d, *J* = 10 Hz, 2H, H-2, H-6), 7.31 (d, *J* = 8.5 Hz, 2H, H-3", H-5"), 7.08-7.04 (m, 3H, H-3 to H-5), 4.61 (d, *J* = 13.5 Hz, 1H, Ha-7"), 4.17 (d, *J* = 13.5 Hz, 1H, Hb-7"); EIMS (*m/z*): 394 $[M + 2]^{\bullet+}$, 392 $[M]^{\bullet+}$, 328 $[M\text{-}SO_2]^{\bullet+}$, 175 $[C_6H_4ClSO_2]^+$, 217 $[M\text{-}C_6H_4ClSO_2]^+$, 92 $[M\text{-}C_{13}H_9Cl_2SO_2]^+$, 111 $[C_6H_4Cl]^+$, 76 $[C_6H_4]^{\bullet+}$.

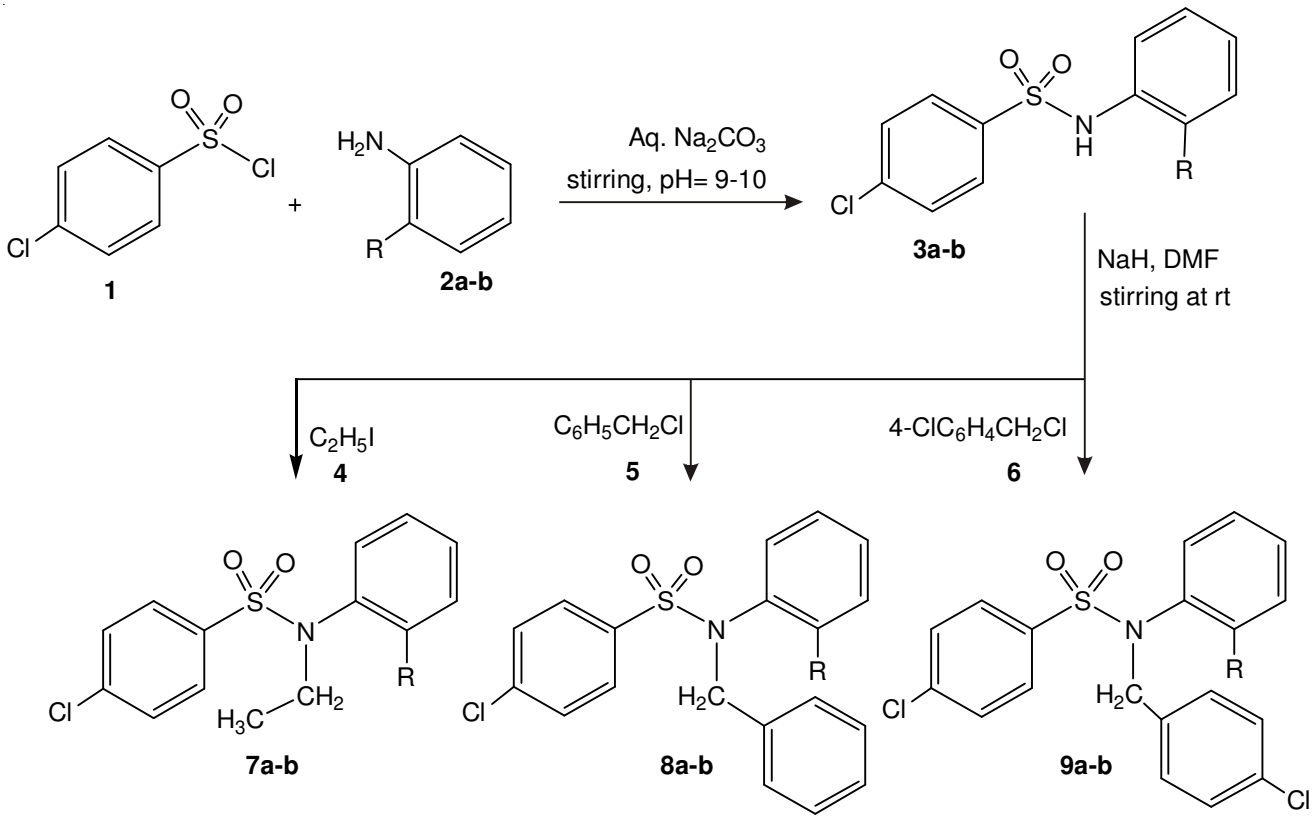
***N*-(2-Methoxyphenyl)-*N*-[(4-chlorophenyl)methyl]-4-chlorobenzenesulfonamide (9b):** White amorphous solid; Yield: 83 %; m.p. 112-114 °C; m.f.: $C_{20}H_{17}NSO_3Cl_2$; m.w.: 422; IR (KBr, ν_{max}, cm^{-1}): 3055 (Ar-H), 1531 (Ar C=C), 1411 (-SO_2-), 1141 (C-N), 561 (C-Cl); ^{1}H NMR (500 MHz, CD_3OD, ppm): δ 7.65 (d, *J* = 9 Hz, 2H, H-2', H-6'), 7.48 (d, *J* = 8.5 Hz, 2H, H-2", H-6"), 7.44 (d, *J* = 8.5 Hz, 2H, H-3', H-5'), 7.40 (dd, *J* = 13.5, 2.5 Hz, 1H, H-6), 7.27 (d, *J* = 8.5 Hz, 2H, H-3", H-5"), 7.11 (ddd, *J* = 13.5, 3 Hz, 1H, H-4), 6.88 (ddd, *J* = 10.5, 2.5 Hz, 1H, H-5), 6.81 (dd, *J* = 13.5, 1.5 Hz, 1H, H-3), 4.63 (d, *J* = 13.5 Hz, 1H, Ha-7"), 4.13 (d, *J* = 13.5 Hz, 1H, Hb-7"), 3.50 (s, 3H, CH_3O-2); EIMS (*m/z*): 424 $[M + 2]^{\bullet+}$, 422 $[M]^{\bullet+}$, 358 $[M\text{-}SO_2]^{\bullet+}$, 175 $[C_6H_4ClSO_2]^+$, 247 $[M\text{-}C_6H_4ClSO_2]^+$, 122 $[M\text{-}C_{13}H_9Cl_2SO_2]^+$, 111 $[C_6H_4Cl]^+$, 107 $[M\text{-}C_{13}H_{10}Cl_2NSO_2]^{\bullet+}$, 76 $[C_6H_4]^{\bullet+}$.

RESULTS AND DISCUSSION

A series of chlorinated sulfonamides have been synthesized as outlined in **Scheme-I**. All derivatives were subjected for antibacterial activity against four Gram-negative (*K. pneumonae*, *E. coli*, *P. aeroginosa* and *S. typhi*) and two Gram-positive (*B. subtilis* and *S. aureus*) bacteria. The aim to synthesize these compounds was to introduce new potent drug candidates that might find applications in the drug development.

The parent sulfonamides, *N*-alkoxy (un)substituted 4-chlorobenzenesulfonamide (**3a-b**) were yielded by coupling of alkoxy (un)substituted aniline (**2a-b**) with 4-chlorobenzenesulfonyl chloride (**1**) in the presence of sodium carbonate solution at pH 9-10. The products were produced after addition of dilute hydrochloric acid drop by drop. Excess use of acid was avoided to retain the yield. Compound (**3a-b**) on reaction with different alkyl halides such as ethyl iodide (**4**), benzyl chloride (**5**) and 4-chlorobenzyl chloride (**6**) yielded the *N*-substituted derivatives of sulfonamides, **7a-b**, **8a-b** and **9a-b**, respectively. Sodium hydride was used to provide basic medium in DMF as solvent. All the products were obtained by treating with cold distilled water. Spectral data affirmed the structures of all the derivatives. Compound **9a** was produced as white amorphous solid in 82 % yield having melting point 118-120 °C with molecular formula $C_{19}H_{15}NSO_2Cl_2$ and molar mass 392. The structure and mass were established by different spectroscopic techniques. In EI-MS molecular ion peak appeared at *m/z* 392. Other characteristic peaks appeared at *m/z* 328, 217 and 175 after the loss of SO_2, loss of phenylsulfonyl group and due to chlorinated phenylsulfonyl cation respectively. IR spectrum revealed characteristics peaks at 1414 for sulfonyl stretching, 1534 for carbon to carbon double bond stretching and 3055 for aromatic proton stretching. In the ^{1}H NMR spectrum the *p*-chlorophenyl sulfonyl group revealed signals at δ 7.69 and 7.45 each as doublet with integration of two protons each and coupling constant of 9 & 8.5 Hz, respectively. Signals of *N*-phenyl group resonated at δ 7.22 (d, *J* = 10 Hz, 2H, H-2, H-6) and 7.08-7.04 (m, 3H, H-3 to H-5), while *N*-(4-chlorophenyl)methyl group showed signals at δ 7.47 and as multiplet integrated for five protons indicated the presence of benzyl group, the methylene of benzyl group revealed at d 4.84. Signals appeared at δ 1.69-1.53 (m, 4H, H-2, H-6) and 7.31 each as doublet having integration of two protons and *J* value of 8.5 Hz. All these spectral data affirmed the structure of **9a** as *N*-phenyl-*N*-[(4-chlorophenyl) methyl]-4-chlorobenzenesulfonamide. Similarly the structures of all other compounds were elaborated by the help of these spectroscopic techniques.

Antibacterial and enzyme inhibition activity: All the compounds were screened for antibacterial activity and enzyme inhibition potential and results are depicted in Tables 1 to 3. It was observed that most of the compounds were active as antibacterial agents while enzyme inhibition potential was not appreciable.



Compd.	R
7a,8a,9a	H
7b,8b,9b	2-OCH_3

Scheme-I: Synthesis of *N*-((alkoxy (un)substituted)phenyl)-4-chloro-benzenesulfonamide

TABLE-1
PERCENTAGE INHIBITION VALUES OF ANTIBACTERIAL ACTIVITY OF SYNTHESIZED DERIVATIVES

Compound	Percentage inhibition					
	S. typhi (-)	*E. coli* (-)	*K. pneumonae* (-)	*B. subtilis* (+)	*S. aureus* (+)	*P. aeroginosa* (-)
7a	48.46 ± 1.46	78.88 ± 2.79	51.09 ± 1.74	69.15 ± 1.95	66.65 ± 2.12	73.67 ± 1.42
7b	73.66 ± 0.46	73.67 ± 0.11	64.85 ± 0.15	72.22 ± 2.05	82.08 ± 2.51	78.64 ± 0.82
8a	-	-	-	-	-	-
8b	52.68 ± 0.65	43.17 ± 2.13	50.31 ± 0.61	56.43 ± 4.52	55.19 ± 4.42	66.23 ± 1.4
9a	47.67 ± 3.12	53.74 ± 2.34	42.51 ± 1.61	54.59 ± 1.19	66.22 ± 2.57	47.68 ± 2.50
9b	37.61 ± 2.86	20.42 ± 1.90	37.10 ± 2.31	34.22 ± 1.35	37.04 ± 2.80	47.82 ± 4.82
Ciprofloxacin	91.21 ± 0.22	92.00 ± 0.23	90.63 ± 0.12	90.35 ± 0.21	91.98 ± 0.04	91.38 ± 0.01

TABLE-2
MIC VALUES OF ANTIBACTERIAL ACTIVITY OF SYNTHESIZED DERIVATIVES

	MIC values					
Compound	*S. typhi* (-)	*E. coli* (-)	*K. pneumonae* (-)	*P. aeroginosa* (-)	*B. subtilis* (+)	*S. aureus* (+)
7a	-	10.33 ± 2.98	19.45 ± 1.95	10.45 ± 0.63	13.51 ± 1.99	12.01 ± 2.34
7b	12.55 ± 1.00	11.78 ± 1.34	13.26 ± 0.89	9.8 ± 0.65	12.63 ± 1.48	12.28 ± 1.44
8a	-	-	-	-	-	-
8b	18.34 ± 1.60	-	19.82 ± 0.32	13.66 ± 1.11	16.05 ± 1.21	13.66 ± 1.99
9a	-	17.88 ± 1.34	-	-	17.89 ± 1.41	13.27 ± 1.77
9b	-	-	-	-	-	-
Ciprofloxacin	9.27 ± 1.58	8.06 ± 1.07	8.51 ± 0.14	8.48 ± 1.91	9.04 ± 1.86	8.95 ± 1.33

TABLE-3
α-CHEMOTRYPSIN ENZYME INHIBITION ACTIVITY OF SYNTHESIZED DERIVATIVES

Compound	Concentration (mM)	Chemotrypsin	
		% Inhibition	IC_{50}
7a	0.5	52.56 ± 0.06	> 400
7b	0.5	74.74 ± 0.11	330 ± 0.08
8a	0.25	40.35 ± 0.05	-
8b	0.25	68.08 ± 0.05	345.27 ± 0.01
9a	0.25	50.23 ± 0.08	> 400
9b	0.25	78.99 ± 0.09	210.11 ± 0.02
Chymostatin	0.25	93.50 ± 0.91	8.24 ± 0.11

Compound **7a** showed potential against *E. coli* and *P. aeroginosa* with MIC values of 10.33 ± 2.98 and 10.45 ± 0.63, respectively relative to that of standard, 8.06 ± 1.07 and 8.48 ± 1.91, respectively. Compound **7b** was active against all the bacterial strains (*S. typhi*, *E.coli*, *K. pneumonae*, *P. aeroginosa*, *B. subtilis* and *S. aureus*) with MIC values of 12.55 ± 1, 11.78 ± 1.34, 13.26 ± 0.89, 9.8 ± 0.65 12.63 ± 1.48 and 12.28 ± 1.44, respectively, as compared to ciprofloxacin with MIC values of 9.27 ± 1.58, 8.06 ± 1.07, 8.51 ± 0.14, 8.48 ± 1.91, 9.04 ± 1.86 and 8.95 ± 1.33, respectively. All these results showed that **7b** was most active against *P. aeroginosa*. The results of enzyme inhibition analysis of these compounds were not too much significant against α-chemotrypsin enzyme.

Conclusion

The molecules were synthesized in awesome amounts and their structures were corroborated through ^{1}H NMR with sufficient support of IR and EIMS spectral data. It was noted that the most of the derivatives were moderately good antibacterial agents with no activity against α-chymotrypsin enzyme. Furthermore, these molecules can be analyzed for *in vivo* activity by the pharmacological industries to evaluate their toxicity and hence as new drug candidate.

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