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Synthesis, Antibacterial and Lipoxygenase Activities of *N*-[(Dimethyl substituted)phenyl]-*N*-(4-chlorophenyl)-4-chlorobenzenesulfonamides

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In present research work, a new series of *N*-[(dimethyl substituted)phenyl]-*N*-(4-chlorophenyl)-4-chlorobenzenesulfonamides (**5a-f**) was synthesized and also evaluated for their biological activities. The reaction of 4-chlorobenzenesulfonyl chloride (**1**) with dimethyl substituted aniline (**2a-f**) in aqueous alkaline medium yielded *N*-[(dimethyl substituted)phenyl]-4-chlorobenzenesulfonamides (**3a-f**). The target compounds **5a-f** were synthesized by reacting the compounds **3a-f** with electrophile, 4-chlorobenzyl chloride (**4**) in aprotic solvent, DMF and NaH. All the synthesized compounds were characterized by IR, ^{1}H NMR and EIMS. All the synthesized derivatives were screened for antibacterial potential and were also subjected for lipoxygenase enzyme inhibition activity.

Keywords: Dimethyl substituted aniline, Sulfonamides, Antibacterial activity, Lipoxygenase activity, Spectral analysis.

INTRODUCTION

Sulfonamides is a class of organic compounds that exhibit sulfamoyl group (-NSO_2) as a functional group. Sulfonamides are known for their high biological potential and medicinal importance. Due to excellent biological activities, sulfonamides are widely used as antimicrobial, anticancer, anti-inflammatory and antiviral agents[1-5]. Sulfonamides have been subjected to a number of biological evaluations like antifungal and enzyme inhibitory potential[6,7].

In continuation of our interest[8-11], we have described herein the synthesis of various *N*-substituted sulfonamides derived from dimethyl substituted aniline and reported their biological activities. The newly synthesized compounds showed varying degree of antibacterial and lipoxygenase activities.

EXPERIMENTAL

Thin layer chromatography (TLC) was utilized to detect the purity of the synthesized compounds using EtOAc and *n*-hexane as mobile phase and visualized by UV lamp at 254 nm. Griffin-George melting point apparatus was used to record the melting points of all derivatives by open capillary tube method and were found uncorrected. Jasco-320-A spectrophotometer was utilized for IR spectra by KBr pellet method. ^{1}H NMR spectra were recorded in CD_3OD on a Bruker spectrometers at 500 MHz using tetramethylsilane as reference standard and chemical shift mentioned in δ-values while the coupling constants (J) are mentioned in Hz. JMS-HX-110 spectrometer was used to record the mass spectra (EIMS).

Procedure for the synthesis of *N*-[(dimethyl substituted) phenyl]-4-chlorobenzene-sulfonamides (3a-f): Dimethyl substituted aniline (**2a-f**, 0.01 mol) was suspended in 30 mL distilled water in a 100 mL round bottom flask and then added Na_2CO_3 solution (20 %) to maintained the pH 9-10. Afterward, 4-chlorobenzenesulfonyl chlorides (1, 0.01 mol) was introduced into the flask slowly with continuous stirring. The reaction contents were allowed to stir for 2-3 h and reaction progress was monitored by TLC till the single spot. On reaction completion dilute HCl was added along with continuous shaking to bring the pH to 3-4. The precipitates of compounds **3a-f** formed were then filtered, washed, dried and followed the further reaction.

Synthesis of *N*-[(dimethyl substitu-ted)phenyl]-*N*-(4-chlorophenyl)-4-chlorobenzene-sulfonamides (5a-f): Compounds **3a-f** (0.01 mol) was dissolved in 10 mL *N*,*N*-dimethyl formamide (DMF) in a 100 mL round bottom flask. Sodium hydride (0.01 mol) was added to reaction flask and set to stir for 0.5 h at room temperature. The electrophile, 4-chlorobenzyl chloride (**4**, 0.01 mol) were added to reaction contents and set to stir for 4-5 h. to synthesize the target compounds **5a-f**. On

reaction completion, the reaction mixture was quenched with ice cold distilled water. The precipitates formed were then filtered, washed with distilled water and dried to yield the target compounds **5a-f**.

***N*-(2,3-Dimethylphenyl)-*N*-[(4-chlorophenyl)methyl]-4-chlorobenzenesulfonamide (5a):** White amorphous solid; yield: 81 %; m.p. 122-124 °C; mol. formula: $C_{21}H_{19}C_{l2}NSO_2$; mol. wt.: 420; IR (KBr, ν_{max}, cm^{-1}): 3057 (Ar-H), 1533 (Ar C=C), 1413 (-SO_2-), 1142 (C-N), 563 (C-Cl); ^{1}H NMR (500 MHz, CD_3OD, ppm): δ 7.63 (d, *J* = 9.0 Hz, 2H, H-2', H-6'), 7.48 (d, *J* = 8.5 Hz, 2H, H-3', H-5'), 7.18 (d, *J* = 8.5 Hz, 2H, H-2", H-6"), 7.03 (d, *J* = 8.5 Hz, 2H, H-3", H-5"), 7.04 (d, *J* = 7.5 Hz, 1H, H-6), 6.94 (t, *J* = 7.5 Hz, 1H, H-5), 6.77 (d, *J* = 8.0 Hz, 1H, H-4), 4.25 (s, 2H, H-7"), 2.21 (s, 3H, CH_3-2), 1.98 (s, 3H, CH_3-3); EIMS (*m/z*): 420 $[M]^{\bullet+}$, 356 $[M\text{-}SO_2]^{\bullet+}$, 175 $[C_6H_4ClSO_2]^+$, 245 $[M\text{-}C_6H_4ClSO_2]^+$, 120 $[M\text{-}C_{13}H_9Cl_2SO_2]^+$, 111 $[C_6H_4Cl]^+$, 105 $[M\text{-}C1_3H_{10}Cl_2NSO_2]^{\bullet+}$, 90 $[M\text{-}C_{14}H_{13}ClNSO_2]^+$, 76 $[C_6H_4]^{\bullet+}$, 75$[M\text{-}C_{15}H_{16}ClNSO_2]$ $^{\bullet+}$.

***N*-(2,4-Dimethylphenyl)-*N*-[(4-chlorophenyl)methyl]-4-chlorobenzenesulfonamide (5b):** Light grey amorphous solid; yield: 83 %; m.p. 120-122 °C; mol. formula: $C_{21}H_{19}Cl_2N\text{-}SO_2$; mol. wt.: 420; IR (KBr, ν_{max}, cm^{-1}): 3056 (Ar-H), 1527 (Ar C=C), 1412 (-SO_2-), 1142 (C-N), 557 (C-Cl); ^{1}H NMR (500 MHz, CD_3OD, ppm): δ 7.63 (d, *J* = 8.5 Hz, 2H, H-2', H-6'), 7.46 (d, *J* = 9.0 Hz, 2H, H-3', H-5'), 7.17 (d, *J* = 8.5 Hz, 2H, H-2", H-6"), 7.07 (d, *J* = 8.5 Hz, 2H, H-3", H-5"), 6.93 (br. s, 1H, H-6), 6.89(dd, *J* = 6.0,1.5 Hz, 1H, H-5), 6.85 (s, 1H, H-3), 4.23 (s, 2H, H-7"), 2.24 (s, 3H, CH_3-2), 1.98 (s, 3H, CH_3-4); EIMS (*m/z*): 420 $[M]^{\bullet+}$, 356 $[M\text{-}SO_2]^{\bullet+}$, 175 $[C_6H_4ClSO_2]^+$, 245 $[M\text{-}C_6H_4ClSO_2]^+$, 120 $[M\text{-}C_{13}H_9Cl_2SO_2]^+$, 111 $[C_6H_4Cl]^+$, 105 $[M\text{-}C_{13}H_{10}Cl_2NSO_2]^{\bullet+}$, 90 $[M\text{-}C_{14}H_{13}ClN\text{-}SO_2]^+$, 76 $[C_6H_4]^{\bullet+}$, 75 $[M\text{-}C_{15}H_{16}ClNSO_2]^{\bullet+}$.

***N*-(2,5-Dimethylphenyl)-*N*-[(4-chlorophenyl)methyl]-4-chlorobenzenesulfonamide (5c):** White amorphous solid; yield: 86 %; m.p. 110-112 °C; mol. formula: $C_{21}H_{19}Cl_2NSO_2$; mol. wt.: 420; IR (KBr, ν_{max}, cm^{-1}): 3058 (Ar-H), 1532 (Ar C=C), 1410 (-SO_2-), 1139 (C-N), 557 (C-Cl); ^{1}H NMR (500 MHz, CD_3OD, ppm): δ 7.63 (d, *J* = 9.0 Hz, 2H, H-2', H-6'), 7.45 (d, *J* = 8.5 Hz, 2H, H-3', H-5'), 7.13 (d, *J* = 8.5 Hz, 2H, H-2", H-6"), 7.09 (d, *J* = 8.5 Hz, 2H, H-3", H-5"),6.95 (d, *J* = 7.5 Hz, 1H, H-3), 6.91 (d, *J* = 8.0 Hz, 1H, H-4), 6.84 (s, 1H, H-6), 4.21 (s, 2H, H-7"), 2.17 (s, 3H, CH_3-2), 1.91 (s, 3H, CH_3-5); EIMS (*m/z*): 420 $[M]^{\bullet+}$, 356 $[M\text{-}SO_2]^{\bullet+}$, 175 $[C_6H_4ClSO_2]^+$, 245 $[M\text{-}C_6H_4ClSO_2]^+$, 120 $[M\text{-}C_{13}H_9Cl_2SO_2]^+$, 111 $[C_6H_4Cl]^+$, 105 $[M\text{-}C_{13}H_{10}Cl_2NSO_2]^{\bullet+}$, 90 $[M\text{-}C_{14}H_{13}ClN\text{-}SO_2]^+$, 76 $[C_6H_4]^{\bullet+}$, 75 $[M\text{-}C_{15}H_{16}ClNSO_2]^{\bullet+}$.

***N*-(2,6-Dimethylphenyl)-*N*-[(4-chlorophenyl)methyl]-4-chlorobenzenesulfonamide (5d):** Cream white amorphous solid; yield: 87%; m.p. 128-130 °C; mol. formula: $C_{21}H_{19}Cl_2NSO_2$; mol. wt.: 420; IR (KBr, ν_{max}, cm^{-1}): 3054 (Ar-H), 1532 (Ar C=C), 1407 (-SO_2-), 1139 (C-N), 553 (C-Cl); ^{1}H NMR (500 MHz, CD_3OD, ppm): δ 7.68 (d, *J* = 9.0 Hz, 2H, H-2', H-6'), 7.51 (d, *J* = 8.5 Hz, 2H, H-3', H-5'), 7.15 (d, *J* = 8.5 Hz, 2H, H-2", H-6"), 7.11 (d, *J* = 8.5 Hz, 2H, H-3", H-5"), 7.06-6.96 (m, 3H, H-3 to H-5), 4.19 (s, 2H, H-7"), 2.02 (s, 6H, CH_3-2, CH_3-6); EIMS (*m/z*): 420 $[M]^{\bullet+}$, 356 $[M\text{-}SO_2]^{\bullet+}$, 175 $[C_6H_4ClSO_2]^+$, 245 $[M\text{-}C_6H_4ClSO_2]^+$, 120 $[M\text{-}C_{13}H_9Cl_2SO_2]^+$, 111 $[C_6H_4Cl]^+$, 105 $[M\text{-}C_{13}H_{10}Cl_2NSO_2]^{\bullet+}$, 90 $[M\text{-}C_{14}H_{13}ClNSO_2]^+$.

***N*-(3,4-Dimethylphenyl)-*N*-[(4-chlorophenyl)methyl]-4-chlorobenzenesulfonamide (5e):** Yellow amorphous solid; yield: 86 %; m.p. 120-122 °C; mol. formula: $C_{21}H_{19}Cl_2NSO_2$; mol. wt.: 420; IR (KBr, ν_{max}, cm^{-1}): 3058 (Ar-H), 1534 (Ar C=C), 1415 (-SO_2-), 1146 (C-N), 567 (C-Cl); ^{1}H NMR (500 MHz, CD_3OD, ppm): δ 7.65 (d, *J* = 9.0 Hz, 2H, H-2', H-6'), 7.46 (d, *J* = 8.5 Hz, 2H, H-3', H-5'), 7.21 (d, *J* = 8.5 Hz, 2H, H-2", H-6"), 7.05 (d, *J* = 8.5 Hz, 2H, H-3", H-5"), 6.96 (d, *J* = 13.0 Hz, 1H, H-6), 6.84 (br. s, 1H, H-2), 6.79 (dd, *J* = 10.0, 1.0 Hz, 1H, H-5), 4.17 (s, 2H, H-7"), 2.16 (s, 6H, CH_3-3, CH_3-4); EIMS (*m/z*): 420 $[M]^{\bullet+}$, 356 $[M\text{-}SO_2]^{\bullet+}$, 175 $[C_6H_4ClSO_2]^+$, 245 $[M\text{-}C_6H_4ClSO_2]^+$, 120 $[M\text{-}C_{13}H_9Cl_2SO_2]^+$, 111 $[C_6H_4Cl]^+$, 105 $[M\text{-}C_{13}H_{10}Cl_2NSO_2]^{\bullet+}$, 90 $[M\text{-}C_{14}H_{13}ClNSO_2]^+$, 76 $[C_6H_4]^{\bullet+}$, 75 $[M\text{-}C_{15}H_{16}ClNSO_2]^{\bullet+}$.

***N*-(3,5-Dimethylphenyl)-*N*-[(4-chlorophenyl)methyl]-4-chlorobenzenesulfonamide (5f):** Light yellow amorphous solid; yield: 84 %; m.p. 122-124 °C; mol. formula: $C_{21}H_{19}Cl_2N\text{-}SO_2$; mol. wt.: 420; IR (KBr, ν_{max}, cm^{-1}): 3055 (Ar-H), 1532 (Ar C=C), 1414 (-SO_2-), 1139 (C-N), 564 (C-Cl); ^{1}H NMR (500 MHz, CD_3OD, ppm): δ 7.63 (d, *J* = 9.0 Hz, 2H, H-2', H-6'), 7.43 (d, *J* = 8.5 Hz, 2H, H-3', H-5'), 7.23 (d, *J* = 8.5 Hz, 2H, H-2", H-6"), 7.16 (d, *J* = 8.5 Hz, 2H, H-3", H-5"), 6.73 (s, 2H, H-2, H-6), 6.66 (s, 1H, H-4), 4.18 (s, 2H, H-7"), 2.19 (s, 6H, CH_3-3, CH_3-5); EIMS (*m/z*): 420 $[M]^{\bullet+}$, 356 $[M\text{-}SO_2]^{\bullet+}$, 175 $[C_6H_4ClSO_2]^+$, 245 $[M\text{-}C_6H_4ClSO_2]^+$, 120 $[M\text{-}C_{13}H_9Cl_2SO_2]^+$, 111 $[C_6H_4Cl]^+$, 105 $[M\text{-}C_{13}H_{10}Cl_2NSO_2]^{\bullet+}$, 90 $[M\text{-}C_{14}H_{13}ClNSO_2]^+$, 76 $[C_6H_4]^{\bullet+}$, 75 $[M\text{-}C_{15}H_{16}ClNSO_2]^{\bullet+}$.

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[12,13].

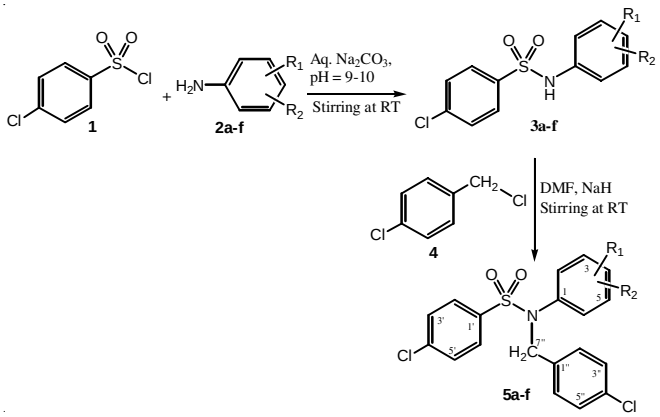
Lipoxygenase assay: Lipoxygenase activity was assayed according to the reported method[14-16] but with slight modifications.

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

The undertaken research work was an effort to synthesize a new series of biological active compounds which may be helpful in drug development program. The parent molecules, *N*-[(dimethyl substituted)phenyl]-4-chlorobenzene-sulfonamide (**3a-f**) were synthesized by coupling dimethyl substituted aniline (**2a-f**) with 4-chlorobenzenesulfonyl chlorides (**1**) in basic aqueous medium under dynamic pH control. The products were obtained on acidification by dil. HCl drop by drop but avoid excess of acid that can decrement the yield. The parent molecules were derivatized by gearing up with electrophile, 4-chlorobenzyl chloride (**4**) to synthesize the target compounds **5a-f** (**Scheme-I**) in the presence of NaH as activator in a polar aprotic solvent. The structures of all the synthesized derivatives were corroborated by spectral data.

Compound **5a** was precipitated as white amorphous solid with 81 % yield and having melting point 122-124 °C. The EI-MS spectrum showed the molecular ion peak at *m/z* 248-$[M]^{+\bullet}$ owing to molecular formula as $C_{21}H_{19}NSO_2Cl_2$. In the aromatic region of ^{1}H NMR spectrum, the downfield signals appeared at δ 7.63 (d, *J* = 9.0 Hz, 2H, H-2', H-6') and 7.48



Compound	5a	5b	5c	5d	5e	5f
R_1	2-CH_3	2-CH_3	2-CH_3	2-CH_3	3-CH_3	3-CH_3
R_2	3-CH_3	4-CH_3	5-CH_3	6-CH_3	4-CH_3	5-CH_3

Scheme-I: Outline for the synthesis of *N*-[(dimethyl substituted)phenyl]-*N*-(4-chlorophenyl)-4-chlorobenzenesulfonamides

(d, *J* = 8.5 Hz, 2H, H-3', H-5'), due to double integration and higher coupling constant, these signals were assigned to the protons of 2-chlorobenzenesulfonyl group and the signals at δ 7.18 (d, *J* = 8.5 Hz, 2H, H-2", H-6"), 7.03 (d, *J* = 8.5 Hz, 2H, H-3", H-5") and 4.25 (s, 2H, H-7") affirmed the presence of 4-chlorobenzyl moiety. The other three signals of aromatic region resonating at 7.04 (d, *J* = 7.5 Hz, 1H, H-6), 6.94 (t, *J* = 7.5 Hz, 1H, H-5), 6.77 (d, *J* = 8.0 Hz, 1H, H-4) which indicated the presence of tri-substituted aromatic ring. In the aliphatic region the signals of two methyl group were appeared at δ 2.21 (s, 3H, CH_3-2) and 1.98 (s, 3H, CH_3-3). All the functional groups in the molecule were supported by IR and the EI-MS spectral data. All these evidences assigned the structure of **5a** as *N*-(2,3-dimethylphenyl)-*N*-[(4-chloro-phenyl)-methyl]-4-chlorobenzene sulfonamide. Similarly the structures of other synthesized molecules were corroborated on the basis of spectral evidences of IR, ^{1}H NMR and EI-MS.

Antibacterial activity (*in vitro*): The percentage inhibition and MIC values of the synthesized molecules relative to ciprofloxacin are shown in Tables 1 and 2, respectively. Among the synthesized compounds, the compound **5f** was the most active inhibitor against *P. aeruginosa* with MIC value of 13.11 ± 0.96 μM relative to the reference standard having MIC value of 8.48 ± 1.91 μM, probably due to the presence of 3,5-disubstituted phenyl group present in the molecule. Against *E. coli* and *S. typhi*, the compound **5f** showed promising activity with MIC value 13.76 ± 0.49 and 19.04 ± 0.79 μM relative to the reference standard drug having MIC value 8.06 ± 1.07 and 9.27 ± 1.58 μM, respectively. In general the activity expressed by the synthesized compounds was good as supported by their MIC values.

Enzyme inhibition activity: The screening against lipoxygenase (LOX) enzyme revealed that these molecules exhibited good inhibitory potential as it was evident from their IC_{50} values (Table-3). The compounds, **5a** and **5b** were the relatively good inhibitor having IC_{50} values of 87.92 ± 1.38 and 95.57 ± 1.35 μmol, respectively, relative to Baicalein, a reference standard with IC_{50} value of 22.4 ± 1.3 μmol. The inhibitory results showed that the compounds could be potential target in the drug discovery and drug development program.

Conclusion

All the structures were elucidated through spectral analysis and were supported by the biological screening. The results

TABLE-1
ANTIBACTERIAL ACTIVITY (%) INHIBITION) OF TESTED COMPOUNDS

Compdound	(%) Inhibition					
	Gram-negative bacteria				Gram-positive bacteria	
	S. typhi (-)	*E. coli* (-)	*K. pneumoniae* (-)	*P. aeroginosa* (-)	*B. subtilis* (+)	*S. aerus* (+)
5a	44.33 ± 1.21	44.54 ± 3.61	30.64 ± 1.09	49.79 ± 2.04	49.75 ± 3.45	44.35 ± 1.19
5b	30.13 ± 2.67	28.01 ± 3.63	32.70 ± 2.41	36.23 ± 0.59	33.46 ± 4.84	34.87 ± 4.13
5c	41.10 ± 1.31	33.97 ± 3.30	47.10 ± 1.81	55.27 ± 2.27	50.97 ± 4.91	44.63 ± 4.22
5d	38.75 ± 2.01	56.86 ± 1.52	40.23 ± 1.68	62.25 ± 3.42	51.05 ± 3.15	47.35 ± 0.88
5e	42.52 ± 3.08	31.81 ± 4.48	42.80 ± 3.11	58.55 ± 3.27	39.89 ± 2.27	43.95 ± 2.51
5f	51.25 ± 1.50	66.81 ± 1.52	34.14 ± 1.95	61.38 ± 1.04	55.10 ± 0.20	48.42 ± 0.96
Ciprofloxacin	91.21 ± 0.22	92.00 ± 0.23	90.63 ± 0.12	91.38 ± 0.01	90.35 ± 0.21	91.98 ± 0.04

TABLE-2
ANTIBACTERIAL ACTIVITY (MIC) OF THE TESTED COMPOUNDS

Compdound	MIC					
	Gram-negative bacteria				Gram-positive bacteria	
	S. typhi (-)	*E. coli* (-)	*K. pneumoniae* (-)	*P. aeroginosa* (-)	*B. subtilis* (+)	*S. aerus* (+)
5a	-	-	-	-	-	-
5b	-	-	-	-	-	-
5c	-	-	-	15.62 ± 1.27	19.48 ± 1.91	-
5d	-	17.67 ± 1.31	-	15.35 ± 2.21	19.07 ± 0.65	-
5e	-	-	-	18.07 ± 0.62	-	-
5f	19.04 ± 0.79	13.76 ± 0.49	-	13.11 ± 0.96	17.04 ± 0.80	-
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

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

TABLE-3
LIPOXYGENASE ACTIVITY OF TESTED COMPOUNDS

Compound	LOX		
	Conc. (mM)	(%) Inhibition	IC_{50}
5a	0.25	97.87 ± 1.21	87.92 ± 1.38
5b	0.25	96.98 ± 1.25	95.57 ± 1.35
5c	0.25	33.45 ± 1.19	-
5d	0.25	52.36 ± 1.14	196.21 ± 1.16
5e	0.25	45.36 ± 1.21	-
5f	0.25	80.09 ± 1.11	113.95 ± 1.29
Baicalein	0.5	93.79 ± 1.27	22.4 ± 1.3

of biological analysis, obtained as MIC and IC_{50} values rendered the synthesized compounds as moderate inhibitors for enzymes but relatively better antibacterial agents.

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