Synthesis, Characterization and Antibacterial Activity of Halogenated Aryl Sulfonamides Derived from 2-Amino-4-chloroanisole

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Summary: In the current work, a number of new *N*-(5-chloro-2-methoxyphenyl)aryl sulfonamides (**3a-e**) and *N*-ethyl/benzyl-*N*-(5-chloro-2-methoxyphenyl)aryl sulfonamides (**6a-e** and **7a-e**) were synthesized and evaluated for their biological activities. The synthesis was carried out by coupling 2-amino-4-chloroanisole (**1**) with different aryl sulfonyl chlorides, **2a-e**, under dynamic pH control in aqueous medium to form aryl sulfonamides, **3a-e**. Further, *N*-ethyl/benzyl-*N*-(5-chloro-2-methoxyphenyl)aryl sulfonamides (**6a-e** and **7a-e**) were synthesized by stirring **3a-e** with the electrophiles, **4** and **5**, in the presence of sodium hydride and *N,N*-dimethylformamide. The structures of the synthesized compounds were characterized from their spectral data. In addition, the *in vitro* antibacterial activity of all the target compounds was investigated against Gram-negative and Gram-positive bacteria using ciprofloxacin as a reference drug. Many of these compounds exhibited moderate to good activity and subtle structural changes in the substituents altered the inhibitory properties significantly.

Keywords: 2-Amino-4-chloroanisole, Aryl sulfonyl chloride, Biological evaluation, ^{1}H-NMR, IR, EI-MS.

Introduction

The basic part of sulfonamides is the sulfamoyl group i.e. -SO_2NH-. This class of compounds has been gaining interest because of their various biological activities such as anti-microbial, anti-thyroid, anti-inflammatory, anti-tumor, anti-cancer, anti-viral etc; and also inhibition ability of various enzymes like carbonic anhydrase, cystein protease, cyclohydrogenase and HIV protease [1-7]. These compounds have shown activity against Gram-positive and Gram-negative bacteria and also anti-fungal activity along with the inhibition ability of acetyl cholinesterase, butyryl cholinesterase and lipoxygenase enzymes etc [8-10]. PABA required by the bacteria for the production of folic acid is analoguous to sulfonamides and so sulfonamides suppress the formation of folic acid and finally purine and DNA [11].

The researchers are interested to introduce new compounds with much potential against various microbes and so a number of compounds are being synthesized including heterocyclic moieties bearing sulfamoyl group for the control of diseases. In continuation of our previous research work on sulfonamides [8-13], this was a fruitful attempt to synthesize a new series of *N*-(5-chloro-2-methoxyphenyl)aryl sulfonamides (**3a-e**) and also *N*-ethyl/benzyl-*N*-(5-chloro-2-methoxyphenyl)aryl sulfonamides (**6a-e** and **7a-e**) showing significant activity against the Gram-negative and Gram-positive bacteria using ciprofloxacin as reference standard. The compounds with relatively high potential against bacteria may contribute in the field of medicinal chemistry and also helpful in the drug discovery and drug development program.

Results and Discussion

The *N*-(5-chloro-2-methoxyphenyl)aryl sulfonamides (**3a-e**) and *N*-ethyl/benzyl-*N*-(5-chloro-2-methoxyphenyl)aryl sulfonamides (**6a-e** and **7a-e**) were synthesized according to the protocol sketched in Scheme-1. The general reaction conditions and the structural characterization are described in experimental section.

Our objective was to synthesize some new *N*-(un)substituted aryl sulfonamides and to find out their biological activities. We synthesized different sulfonamides in excellent yields having good biological activities. The synthesis was geared up by the reaction of 2-amino-4-chloroanisole (**1**) with different halogenated aryl sulfonyl chlorides (**2a-e**) in an aqueous medium with pH of 9-10. The basic medium is essential to keep the lone pair of amino group active otherwise it is captured by the HCl produced during the reaction. The precipitates of final product were acquired by the addition of dilute HCl. The products, **3a-e**, were further substituted at nitrogen atom bearing acidic proton by stirring with ethyl/benzyl halides in the presence of sodium

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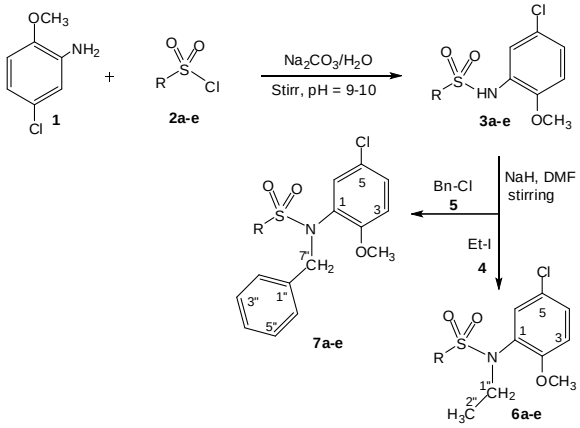
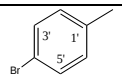
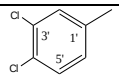
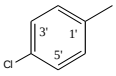
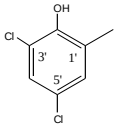
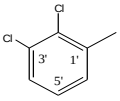
hydride and *N*,*N*-dimethylformamide (DMF). These derived products were obtained after the addition of cold distilled water and were filtered off or extracted by solvent, depending upon the nature of product. All the compounds were evaluated for the antibacterial activity against Gram-negative and Gram-positive bacteria. The structures of all the synthesized compounds were corroborated by spectral data.



Compd. No.	-R	Compd. No.	-R
3a,6a,7a		**3d,6d,7d**	
3b,6b,7b		**3e,6e,7e**	
3c,6c,7c			

Scheme-1: Outline for the synthesis of *N*-ethyl/benzyl derivatives of halogenated aryl sulfonamides derived from 2-amino-4-chloroanisole.

The compound **3a** was synthesized as light black amorphous solid, in a yield of 87% and melting point of 146-148 °C. The molecular formula $C_{13}H_{11}BrClNO_3S$ was elucidated by EIMS having molecular ion peak at *m/z* 376 and also by counting the number of protons in ^{1}H-NMR spectrum. The IR spectrum showed the absorption bands at 3206 (N-H stretching), 3075 (Ar C-H stretching), 1607 (Ar C=C stretching) and 1369 (S=O stretching) cm^{-1}. The EI-MS presented a distinguishable peak at *m/z* 312 after the separation of sulfonyl group (SO_2). The two distinct peaks at *m/z* 220 for 4-bromophenylsulfonyl group and at 156 for 2-methoxy-5-chloroaniline group supported well the structure of synthesized compound. The other prominent peaks are mentioned in the spectral data. In the aromatic section of ^{1}H–NMR spectrum, the two doublets at δ 7.62 (d, J = 8.4 Hz, 2H, H-2' and H-6') and 7.55 (d, J = 8.8 Hz, 2H, H-3' and H-5') were allocated to the four protons of *para* substituted phenyl ring linked to sulfamoyl group. The doublet at δ 7.51 (d, J = 2.0 Hz, 1H, H-6), doublet of doublet at 7.00 (dd, J = 8.8, 2.4 Hz, 1H, H-4), doublet at 6.65 (d, J = 8.4 Hz, 1H, H-3) and a singlet at 3.64 (s, 3H, CH_3O-2) were allotted to three protons of other tri-substituted aniline ring and one methoxy group in the molecule at second position. On the basis of all these evidences, the structure of compound **3a** was named as *N*-(5-chloro-2-methoxyphenyl)-4-bromobenzenesulfonamide. The mass fragmentation pattern of *N*-(5-chloro-2-methoxyphenyl)-4-bromobenzenesulfonamide (**3a**) is clearly described in Fig. 1. Similarly, the structures of other compounds **3b-e**, **6a-e** and **7a-e** were characterized by ^{1}H-NMR, IR and EI-MS as described in spectral data section.

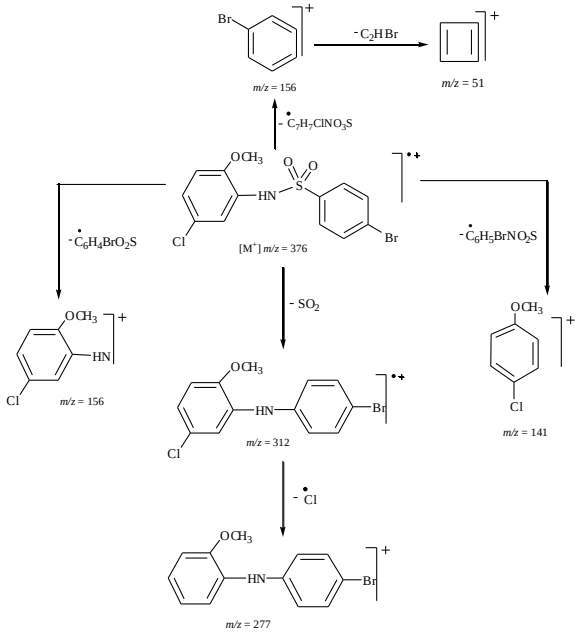


Fig. 1: Mass Fragmentation pattern of *N*-(5-chloro-2-methoxyphenyl)-4-bromobenzenesulfonamide (**3a**)

Antibacterial Activity

The results of % age inhibition and MIC (minimum inhibitory concentration) values for antibacterial activity of the synthesized compounds against Gram-negative and Gram-positive bacteria are presented in Table-1 and Table-2. The two synthesized compounds, *N*-(5-chloro-2-methoxyphenyl)-2-hydroxy-3,5-dichlorobenzene sulfonamide (**3e**) and *N*-(5-chloro-2-methoxyphenyl)-*N*-benzyl-4-chlorobenzenesulfonamide (**7b**), showed activity against all the bacterial strains with good %

age inhibition and MIC values with respect to the reference standard drug ciprofloxacin. The good activity of these compounds is probably due to the slight structural changes in the substituents which altered the inhibitory properties significantly. The compounds **3b**, **3c**, **3d**, **6c** and **7b** were active against the both bacterial strains of Gram-positive bacteria relative to ciprofloxacin, the reference standard. The compounds **3a** and **7d** were active against all the bacterial strains of Gram-negative bacteria. These compounds can further be exploited and their derivatives could be synthesized to get closer to MIC values of the standard. In this way, the compounds could be potential target in the drug discovery and drug development program. The compounds **6a**, **6d**, **6e**, **7c** and **7e** remained inactive against all the bacterial strains.

Experimental

General

2-Amino-4-chloroanisole and halogenated aryl sulfonyl chlorides were purchased from Merck, Alfa Aesar and Sigma Aldrich through local suppliers along with analytical grade solvents and utilized without purification. Purity of synthesized compounds was confirmed by thin layer chromatography (TLC) applying ethyl acetate and *n*-hexane as solvent systems. TLC plates were purchased from local supplier. TLC plates were visualized under UV at 254 nm and also by spraying with ceric sulfate solution. Melting points of solid synthesized compounds were recorded by open capillary tube, on a Griffin-George melting point apparatus with uncorrection. The I.R. spectra were recorded in KBr pellet method on a Jasco-320-A spectrophotometer with wave number in cm^{-1}. ^{1}H-NMR spectra were recorded in $CDCl_3$ on a Bruker spectrometers operating at 400 MHz. The chemical shift values are given in ppm (δ) units with TMS as reference and the coupling constants (J) are in Hz. Mass spectra (EI-MS) were recorded on a JMS-HX-110 spectrometer.

Table-1: %age Inhibition results of antibacterial activity of synthesized compounds

Compound	%age inhibition					
	Salmonella typhi (-)	*E.coli (-)*	*K. pneumonae (-)*	*P. aeruginosa (-)*	*B. subtilis (+)*	*S.aureus(+)*
3a	**60.00±2.54**	**56.23±2.67**	**59.93±1.97**	**22.15±3.67**	**55.54±2.22**	**23.1±1.35**
3b	**76.50±1.31**	**44.41±2.34**	**53.67±2.11**	**66.10±2.34**	**53.96±1.45**	**66.03±4.23**
3c	**60.01±0.99**	**12.34±3.45**	**44.51±2.34**	**64.05±2.12**	**69.04±2.12**	**37.31±2.34**
3d	**51.09±2.67**	**7.77±1.34**	**46.83±2.56**	**60.55±3.21**	**63.64±2.45**	**19.32±1.12**
3e	**58.43±1.14**	**86.05±2.43**	**88.23±3.31**	**86.15±2.98**	**87.21±1.56**	**78.12±2.32**
6a	**45.01±2.16**	**13.56±3.45**	**48.01±1.30**	**56.01±2.48**	**62.19±1.16**	**39.65±1.45**
6b	**45.56±3.09**	**51.34±1.34**	**38.91±2.31**	**53.21±1.56**	**64.43±1.56**	**44.46±1.23**
6c	**78.23±1.45**	**76.32±1.78**	**53.41±2.67**	**54.34±2.31**	**47.98±0.33**	**54.45±1.91**
6d	**48.69±1.68**	**31.54±4.51**	**40.18±3.13**	**61.67±3.19**	**64.18±2.85**	**39.22±2.10**
6e	**52.31±2.93**	**48.35±3.45**	**37.91±2.47**	**56.59±2.40**	**36.78±4.06**	**33.12±3.17**
7a	**49.23±2.17**	**4.41±2.11**	**53.41±1.89**	**83.41±1.38**	**80.46±3.66**	**51.23±0.22**
7b	**54.21±2.12**	**55.09±2.78**	**44.34±1.78**	**78.91±2.56**	**77.36±2.87**	**51.23±1.56**
7c	**51.03±1.34**	**35.67±3.27**	**46.76±2.34**	**51.82±4.02**	**65.14±3.48**	**53.73±1.19**
7d	**90.29±2.01**	**57.09±1.34**	**63.41±2.55**	**63.11±3.45**	**79.91±2.41**	**61.32±2.31**
7e	**52.39±2.13**	**23.24±1.98**	**65.02±2.17**	**59.25±3.14**	**56.37±1.63**	**42.18±2.01**
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 compounds

Compound	MIC values					
	S. typhi (-)	*E.coli (-)*	*K. pneumonae (-)*	*P. aeruginosa (-)*	*B. subtilis (+)*	*S. aureus(+)*
3a	**16.92±0.24**	**7.42±0.16**	**15.21±0.10**	**16.93±0.18**	**15.91±0.27**	-
3b	**16.72±0.42**	**15.31 ± 0.17**	-	**19.15±0.27**	**12.66±0.22**	**16.12±0.12**
3c	**16.23±1.61**	-	-	-	**14.13±0.99**	**14.52±2.34**
3d	**14.12±0.95**	-	-	-	**20.95±1.11**	**15.82±3.11**
3e	**12.31±0.39**	**13.06±0.88**	**12.01±2.03**	**12.74±0.27**	**15.42±1.09**	**12.29±0.61**
6a	-	-	-	-	-	-
6b	**15.31±0.22**	-	**19.62±1.54**	-	-	**16.52±0.71**
6c	-	**17.81±0.24**	**13.45±0.49**	**17.34±0.52**	**13.06±0.73**	**17.88±0.62**
6d	-	-	-	-	-	-
6e	-	-	-	-	-	-
7a	**11.40±0.02**	**20.14±0.45**	-	**17.55±2.33**	-	**13.11±1.22**
7b	**13.41±0.11**	**20.14±0.52**	**16.67±0.71**	**17.31±0.73**	**17.99±0.33**	**13.33±0.02**
7c	-	-	-	-	-	-
7d	**12.94±0.98**	**14.20±0.56**	**15.23±0.72**	**14.94±0.61**	**12.17±0.04**	-
7e	-	-	-	-	-	-
Ciprofloxacin	**8.32±0.25**	**8.98±0.78**	**8.91±0.13**	**8.12±0.36**	**8.47±0.44**	**8.99±0.28**

Note: MIC = Minimum inhibitory concentration.

General procedure for the synthesis of different chlorinated sulfonamides **(3a-e)**

2-Amino-4-chloroanisole (0.001 mol; **1**) was suspended in 100 mL RB flask containing 25 mL distilled water. The pH of reaction mixture was kept 9-10 during the whole reaction by aqueous Na_2CO_3 solution. The halogenated aryl sulfonyl chlorides (0.001 mol; **2a-e**) were added to the suspension gradually over 10-15 min keeping the pH of solution 9-10. The reaction contents were stirred for 3-5 h. The reaction completion was monitored by TLC. Concentrated HCl (2-3 mL) was added to make the pH of 2-3. The reaction mixture was kept at RT for 5-10 min and the formed solid precipitates were filtered off, washed with distilled water and dried to yield the corresponding products (**3a-e**). Recrystallization was carried out from methanol.

N-(5-Chloro-2-methoxyphenyl)-4-bromobenzene sulfonamide **(3a)**

Light black amorphous solid; Yield: 87%; M.P. 146-148 °C; Molecular formula: $C_{13}H_{11}BrClNO_3S$; Molecular weight: 376; IR (KBr): λ_{max} (cm^{-1}): 3206 (N-H stretching), 3075 (Ar C-H stretching), 1607 (Ar C=C stretching), 1369 (S=O stretching); ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ 7.62 (d, *J* = 8.4 Hz, 2H, H-2' and H-6'), 7.55 (d, *J* = 8.8 Hz, 2H, H-3' and H-5'), 7.51 (d, *J* = 2.0 Hz, 1H, H-6), 7.00 (dd, *J* = 8.8, 2.4 Hz, 1H, H-4), 6.65 (d, *J* = 8.4 Hz, 1H, H-3), 3.64 (s, 3H, CH_3O-2); EI-MS: *m/z* 380 $[M+4]^+$, 378 $[M+2]^+$, 376 $[M]^+$, 361 $[M-CH_3]^+$, 345 $[M-OCH_3]^+$, 312 $[M-SO_2]^+$, 220 $[C_6H_4BrSO_2]^+$, 156 $[C_7H_7ClNO]^+$.

N-(5-Chloro-2-methoxyphenyl)-4-chlorobenzene sulfonamide **(3b)**

Greyish black amorphous solid; Yield: 77%; M.P. 144-146 °C; Molecular formula: $C_{13}H_{11}Cl_2NO_3S$; Molecular weight: 332; IR (KBr): λ_{max} (cm^{-1}): 3210 (N-H stretching), 3080 (Ar C-H stretching), 1610 (Ar C=C stretching), 1360 (S=O stretching); ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ 7.69 (d, *J* = 8.8 Hz, 2H, H-2' and H-6'), 7.52 (d, *J* = 2.0 Hz, 1H, H-6), 7.38 (d, *J* = 8.8 Hz, 2H, H-3' and H-5'), 7.00 (dd, *J* = 8.8, 2.4 Hz, 1H, H-4), 6.65 (d, *J* = 8.8 Hz, 1H, H-3), 3.64 (s, 3H, CH_3O-2); EI-MS: *m/z* 336 $[M+4]^+$, 334 $[M+2]^+$, 332 $[M]^+$, 317 $[M-CH_3]^+$, 301 $[M-OCH_3]^+$, 268 $[M-SO_2]^+$, 175 $[C_6H_4ClSO_2]^+$, 156 $[C_7H_7ClNO]^+$.

N-(5-Chloro-2-methoxyphenyl)-2,3-dichlorobenzene sulfonamide **(3c)**

Grey amorphous solid; Yield: 67%; M.P. 166-168 °C; Molecular formula: $C_{13}H_{10}Cl_3NO_3S$; Molecular weight: 366; IR (KBr): υ_{max} (cm^{-1}): 3209 (N-H stretching), 3083 (Ar C-H stretching), 1617 (Ar C=C stretching), 1354 (S=O stretching); ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ 7.98 (dd, *J* = 8.0, 1.2 Hz, 1H, H-6'), 7.62 (dd, *J* = 7.6, 1.2 Hz, 1H, H-4'), 7.43 (d, *J* = 2.4 Hz, 1H, H-6), 7.29 (t, *J* = 8.4 Hz, 1H, H-5'), 6.95 (dd, *J* = 8.8, 2.4 Hz, 1H, H-4), 6.67 (d, *J* = 8.8 Hz, 1H, H-3), 3.73 (s, 3H, CH_3O-2); EI-MS: *m/z* 372 $[M+6]^+$, 370 $[M+4]^+$, 368 $[M+2]^+$, 366 $[M]^+$, 351 $[M-CH_3]^+$, 335 $[M-OCH_3]^+$, 302 $[M-SO_2]^+$, 210 $[C_6H_3Cl_2SO_2]^+$, 156 $[C_7H_7ClNO]^+$.

N-(5-Chloro-2-methoxyphenyl)-3,4-dichlorobenzene sulfonamide **(3d)**

Light grey amorphous solid; Yield: 70%; M.P. 164-166 °C; Molecular formula: $C_{13}H_{10}Cl_3NO_3S$; Molecular weight: 366; IR (KBr): λ_{max} (cm^{-1}): 3207 (N-H stretching), 3061 (Ar C-H stretching), 1619 (Ar C=C stretching), 1358 (S=O stretching); ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ 7.86 (d, *J* = 1.2 Hz, 1H, H-2'), 7.56 (dd, *J* = 8.4, 1.6 Hz, 1H, H-6'), 7.51 (d, *J* = 2.4 Hz, 1H, H-6), 7.48 (d, *J* = 8.4 Hz, 1H, H-5'), 7.02 (dd, *J* = 8.4, 2.4 Hz, 1H, H-4), 6.67 (d, *J* = 8.8 Hz, 1H, H-3), 3.67 (s, 3H, CH_3O-2); EI-MS: *m/z* 372 $[M+6]^+$, 370 $[M+4]^+$, 368 $[M+2]^+$, 366 $[M]^+$, 351 $[M-CH_3]^+$, 335 $[M-OCH_3]^+$, 302 $[M-SO_2]^+$, 210 $[C_6H_3Cl_2SO_2]^+$, 156 $[C_7H_7ClNO]^+$.

N-(5-Chloro-2-methoxyphenyl)-2-hydroxy-3,5-dichlorobenzenesulfonamide **(3e)**

Light purple amorphous solid; Yield: 81%; M.P. 178-180 °C; Molecular formula: $C_{13}H_{10}Cl_3NO_4S$; Molecular weight: 382; IR (KBr): λ_{max} (cm^{-1}): 3220 (N-H stretching), 3084 (Ar C-H stretching), 1611 (Ar C=C stretching), 1340 (S=O stretching); ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ 7.49 (s, 1H, H-6'), 7.48 (d, *J* = 2.4 Hz, 1H, H-4'), 7.46 (d, *J* = 2.4 Hz, 1H, H-6), 7.09 (dd, *J* = 8.8, 2.4 Hz, 1H, H-4), 6.69 (d, *J* = 8.8 Hz, 1H, H-3), 3.66 (s, 3H, CH_3O-2); EI-MS: *m/z* 388 $[M+6]^+$, 386 $[M+4]^+$, 384 $[M+2]^+$, 382 $[M]^+$, 367 $[M-CH_3]^+$, 351 $[M-OCH_3]^+$, 318 $[M-SO_2]^+$, 226 $[C_6H_3Cl_2OSO_2]^+$, 156 $[C_7H_7ClNO]^+$.

General procedure for the synthesis of N-ethyl/benzyl substituted sulfonamides **(6a-e and 7a-e)**

The compounds **3a-e** (0.001 mol) were dissolved in 5-10 mL dimethylformamide (DMF) and then NaH (0.001 mol) was added to the homogeneous solution. The reaction mixture was stirred for 20-25 min at RT and then ethyl/benzyl halides (0.001 mol) were poured to the reaction mixture followed by

further stirring for 3-4 h. The completion of reaction was monitored by TLC. The product was obtained by filtration or solvent extraction after the addition of cold distilled water.

N-(5-Chloro-2-methoxyphenyl)-N-ethyl-4-bromo benzenesulfonamide **(6a)**

Light purple amorphous solid; Yield: 79%; M.P. 82-84 °C; Molecular formula: $C_{15}H_{16}BrClNO_3S$; Molecular weight: 404; IR (KBr): λ_{max} (cm^{-1}): 3074 (Ar C-H stretching), 1606 (Ar C=C stretching), 1370 (S=O stretching); ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ 7.58 (d, J = 8.8 Hz, 2H, H-2' and H-6'), 7.49 (d, J = 8.8 Hz, 2H, H-3' and H-5'), 7.36 (d, J = 2.4 Hz, 1H, H-6), 7.05 (dd, J = 8.8, 2.4 Hz, 1H, H-4), 6.63 (d, J = 8.8 Hz, 1H, H-3), 3.44 (s, 3H, CH_3O-2), 3.41 (q, J = 7.2 Hz, 2H, CH_2-1"), 0.99 (t, J = 7.2 Hz, 3H, CH_3-2"); EI-MS: *m/z* 408 $[M+4]^+$, 406 $[M+2]^+$, 404 $[M]^+$, 389 $[M-CH_3]^+$, 373 $[M-OCH_3]^+$, 340 $[M-SO_2]^+$, 220 $[C_6H_4BrSO_2]^+$, 156 $[C_7H_7ClNO]^+$.

N-(5-Chloro-2-methoxyphenyl)-N-ethyl-4-chloro benzenesulfonamide **(6b)**

Purple amorphous solid; Yield: 83%; M.P. 84-86 °C; Molecular formula: $C_{15}H_{16}Cl_2NO_3S$; Molecular weight: 360; IR (KBr): λ_{max} (cm^{-1}): 3076 (Ar C-H stretching), 1609 (Ar C=C stretching), 1354 (S=O stretching); ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ 7.68 (d, J = 8.4 Hz, 2H, H-2' and H-6'), 7.53 (d, J = 2.0 Hz, 1H, H-6), 7.36 (d, J = 8.4 Hz, 2H, H-3' and H-5'), 7.10 (dd, J = 8.8, 2.4 Hz, 1H, H-4), 6.63 (d, J = 8.8 Hz, 1H, H-3), 3.64 (s, 3H, CH_3O-2), 3.35 (q, J = 7.6 Hz, 2H, CH_2-1"), 1.01 (t, J = 7.6 Hz, 3H, CH_3-2"); EI-MS: *m/z* 364 $[M+4]^+$, 362 $[M+2]^+$, 360 $[M]^+$, 345 $[M-CH_3]^+$, 329 $[M-OCH_3]^+$, 296 $[M-SO_2]^+$, 175 $[C_6H_4ClSO_2]^+$, 156 $[C_7H_7ClNO]^+$.

N-(5-Chloro-2-methoxyphenyl)-N-ethyl-2,3-dichloro benzenesulfonamide **(6c)**

Brownish grey amorphous solid; Yield: 69%; M.P. 106-108 °C; Molecular formula: $C_{15}H_{15}Cl_3NO_3S$; Molecular weight: 394; IR (KBr): λ_{max} (cm^{-1}): 3084 (Ar C-H stretching), 1620 (Ar C=C stretching), 1353 (S=O stretching); ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ 7.95 (dd, J = 8.4, 1.6 Hz, 1H, H-6'), 7.62 (dd, J = 8.4, 1.6 Hz, 1H, H-4'), 7.53 (d, J = 2.0 Hz, 1H, H-6), 7.31 (t, J = 8.4 Hz, 1H, H-5'), 7.05 (dd, J = 8.4, 2.4 Hz, 1H, H-4), 6.63 (d, J = 8.4 Hz, 1H, H-3), 3.67 (s, 3H, CH_3O-2), 3.32 (q, J = 7.6 Hz, 2H, CH_2-1"), 1.02 (t, J = 7.6 Hz, 3H, CH_3-2"); EI-MS: *m/z* 400 $[M+6]^+$, 398 $[M+4]^+$, 396 $[M+2]^+$, 394 $[M]^+$, 379 $[M-CH_3]^+$, 363 $[M-OCH_3]^+$, 330 $[M-SO_2]^+$, 210 $[C_6H_3Cl_2SO_2]^+$, 156 $[C_7H_7ClNO]^+$.

N-(5-Chloro-2-methoxyphenyl)-N-ethyl-3,4-dichloro benzenesulfonamide **(6d)**

Greyish brown amorphous solid; Yield: 73%; M.P. 104-106 °C; Molecular formula: $C_{15}H_{15}Cl_3NO_3S$; Molecular weight: 394; IR (KBr): λ_{max} (cm^{-1}): 3064 (Ar C-H stretching), 1616 (Ar C=C stretching), 1356 (S=O stretching); ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ 7.81 (d, J = 1.6 Hz, 1H, H-2'), 7.59 (dd, J = 8.4, 1.6 Hz, 1H, H-6'), 7.47 (d, J = 2.4 Hz, 1H, H-6), 7.39 (d, J = 8.4 Hz, 1H, H-5'), 6.97 (dd, J = 8.8, 2.4 Hz, 1H, H-4), 6.65 (d, J = 8.8 Hz, 1H, H-3), 3.61 (s, 3H, CH_3O-2), 3.29 (q, J = 7.6 Hz, 2H, CH_2-1"), 1.07 (t, J = 7.6 Hz, 3H, CH_3-2"); EI-MS: *m/z* 400 $[M+6]^+$, 398 $[M+4]^+$, 396 $[M+2]^+$, 394 $[M]^+$, 379 $[M-CH_3]^+$, 363 $[M-OCH_3]^+$, 330 $[M-SO_2]^+$, 210 $[C_6H_3Cl_2SO_2]^+$, 156 $[C_7H_7ClNO]^+$.

N-(5-Chloro-2-methoxyphenyl)-N-ethyl-2-hydroxy-3,5-dichlorobenzenesulfonamide **(6e)**

Dark brown amorphous solid; Yield: 89%; M.P. 126-128 °C; Molecular formula: $C_{15}H_{15}Cl_3NO_4S$; Molecular weight: 410; IR (KBr): λ_{max} (cm^{-1}): 3081 (Ar C-H stretching), 1612 (Ar C=C stretching), 1339 (S=O stretching); ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ 7.57 (s, 1H, H-6'), 7.43 (d, J = 2.4 Hz, 1H, H-4'), 7.36 (d, J = 2.4 Hz, 1H, H-6), 7.08 (dd, J = 8.8, 2.4 Hz, 1H, H-4), 6.70 (d, J = 8.8 Hz, 1H, H-3), 3.49 (s, 3H, CH_3O-2), 3.41 (q, J = 7.2 Hz, 2H, CH_2-1"), 1.05 (t, J = 7.2 Hz, 3H, CH_3-2"); EI-MS: *m/z* 416 $[M+6]^+$, 414 $[M+4]^+$, 412 $[M+2]^+$, 410 $[M]^+$, 395 $[M-CH_3]^+$, 379 $[M-OCH_3]^+$, 346 $[M-SO_2]^+$, 226 $[C_6H_3Cl_2OSO_2]^+$, 156 $[C_7H_7ClNO]^+$.

N-(5-Chloro-2-methoxyphenyl)-N-benzyl-4-bromo benzenesulfonamide **(7a)**

Purple amorphous solid; Yield: 89%; M.P. 86-88 °C; Molecular formula: $C_{20}H_{17}BrClNO_3S$; Molecular weight: 466; IR (KBr): λ_{max} (cm^{-1}): 3073 (Ar C-H stretching), 1605 (Ar C=C stretching), 1362 (S=O stretching); ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ 7.61 (d, J = 8.4 Hz, 2H, H-2' and H-6'), 7.58 (d, J = 8.4 Hz, 2H, H-3' and H-5'), 7.49-7.47 (m, 5H, H-2" to H-6"), 7.41 (d, J = 2.0 Hz, 1H, H-6), 7.15 (dd, J = 8.4, 2.0 Hz, 1H, H-4), 6.66 (d, J = 8.4 Hz, 1H, H-3), 3.61 (s, 2H, CH_2-7"), 3.54 (s, 3H, CH_3O-2); EI-MS: *m/z* 470 $[M+4]^+$, 468 $[M+2]^+$, 466 $[M]^+$, 451 $[M-CH_3]^+$, 435 $[M-OCH_3]^+$, 402 $[M-SO_2]^+$, 220 $[C_6H_4BrSO_2]^+$, 156 $[C_7H_7ClNO]^+$.

N-(5-Chloro-2-methoxyphenyl)-N-benzyl-4-chloro benzenesulfonamide **(7b)**

Light purple amorphous solid; Yield: 82%; M.P. 84-86 °C; Molecular formula: $C_{20}H_{17}Cl_2NO_3S$;

Molecular weight: 422; IR (KBr): λ_{max} (cm^{-1}): 3087 (Ar C-H stretching), 1609 (Ar C=C stretching), 1357 (S=O stretching); ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ 7.67 (d, *J* = 8.4 Hz, 2H, H-2' and H-6'), 7.50 (d, *J* = 2.0 Hz, 1H, H-6), 7.35 (d, *J* = 8.4 Hz, 2H, H-3' and H-5'), 7.18-7.13 (m, 5H, H-2" to H-6"), 7.03 (dd, *J* = 8.8, 2.4 Hz, 1H, H-4), 6.66 (d, *J* = 8.8 Hz, 1H, H-3), 3.43 (s, 2H, CH_2-7"), 3.30 (s, 3H, CH_3O-2); EI-MS: *m/z* 426 $[M+4]^+$, 424 $[M+2]^+$, 422 $[M]^+$, 407 $[M-CH_3]^+$, 391 $[M-OCH_3]^+$, 358 $[M-SO_2]^+$, 175 $[C_6H_4ClSO_2]^+$, 156 $[C_7H_7ClNO]^+$.

N-(5-Chloro-2-methoxyphenyl)-N-benzyl-2,3-dichloro benzenesulfonamide **(7c)**

Grey black amorphous solid; Yield: 74%; M.P. 112-114 °C; Molecular formula: $C_{20}H_{16}Cl_3NO_3S$; Molecular weight: 456; IR (KBr): λ_{max} (cm^{-1}): 3081 (Ar C-H stretching), 1619 (Ar C=C stretching), 1351 (S=O stretching); ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ 8.05 (dd, *J* = 8.0, 1.2 Hz, 1H, H-6'), 7.62 (dd, *J* = 8.0, 1.2 Hz, 1H, H-4'), 7.53 (d, *J* = 2.4 Hz, 1H, H-6), 7.35 (t, *J* = 8.0 Hz, 1H, H-5'), 7.31-7.28 (m, 5H, H-2" to H-6"), 6.97 (dd, *J* = 8.8, 2.4 Hz, 1H, H-4), 6.62 (d, *J* = 8.8 Hz, 1H, H-3), 3.62 (s, 2H, CH_2-7"), 3.53 (s, 3H, CH_3O-2); EI-MS: *m/z* 462 $[M+6]^+$, 460 $[M+4]^+$, 458 $[M+2]^+$, 456 $[M]^+$, 441 $[M-CH_3]^+$, 425 $[M-OCH_3]^+$, 392 $[M-SO_2]^+$, 210 $[C_6H_3Cl_2SO_2]^+$, 156 $[C_7H_7ClNO]^+$.

N-(5-Chloro-2-methoxyphenyl)-N-benzyl-3,4-dichloro benzenesulfonamide **(7d)**

Grey brown amorphous solid; Yield: 71%; M.P. 110-112 °C; Molecular formula: $C_{20}H_{16}Cl_3NO_3S$; Molecular weight: 456; IR (KBr): λ_{max} (cm^{-1}): 3057 (Ar C-H stretching), 1620 (Ar C=C stretching), 1375 (S=O stretching); ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ 7.79 (d, *J* = 1.2 Hz, 1H, H-2'), 7.61 (dd, *J* = 8.4, 1.2 Hz, 1H, H-6'), 7.57 (d, *J* = 2.4 Hz, 1H, H-6), 7.45 (d, *J* = 8.4 Hz, 1H, H-5'), 7.33-7.28 (m, 5H, H-2" to H-6"), 7.12 (dd, *J* = 8.4, 2.4 Hz, 1H, H-4), 6.64 (d, *J* = 8.4 Hz, 1H, H-3), 3.71 (s, 2H, CH_2-7"), 3.48 (s, 3H, CH_3O-2); EI-MS: *m/z* 462 $[M+6]^+$, 460 $[M+4]^+$, 458 $[M+2]^+$, 456 $[M]^+$, 441 $[M-CH_3]^+$, 425 $[M-OCH_3]^+$, 392 $[M-SO_2]^+$, 210 $[C_6H_3Cl_2SO_2]^+$, 156 $[C_7H_7ClNO]^+$.

N-(5-Chloro-2-methoxyphenyl)-N-benzyl-2-hydroxy-3,5-dichlorobenzenesulfonamide **(7e)**

Brown amorphous solid; Yield: 64%; M.P. 130-132 °C; Molecular formula: $C_{20}H_{16}Cl_3NO_4S$; Molecular weight: 472; IR (KBr): λ_{max} (cm^{-1}): 3087 (Ar C-H stretching), 1615 (Ar C=C stretching), 1342 (S=O stretching); ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ 7.50 (s, 1H, H-6'), 7.46 (d, *J* = 2.0 Hz, 1H, H-4'), 7.36-7.33 (m, 5H, H-2" to H-6"), 7.24 (d, *J* = 2.0 Hz, 1H, H-6), 7.12 (dd, *J* = 8.4, 2.0 Hz, 1H, H-4), 6.72 (d, *J* = 8.4 Hz, 1H, H-3), 3.45 (s, 2H, CH_2-7"), 3.39 (s, 3H, CH_3O-2); EI-MS: *m/z* 478 $[M+6]^+$, 476 $[M+4]^+$, 474 $[M+2]^+$, 472 $[M]^+$, 457 $[M-CH_3]^+$, 441 $[M-OCH_3]^+$, 408 $[M-SO_2]^+$, 226 $[C_6H_3Cl_2OSO_2]^+$, 156 $[C_7H_7ClNO]^+$.

Antibacterial Activity Assay

The antibacterial activity assay includes sterile 96-wells microplates under aseptic conditions. This method works on the directly related microbial cell number to the microbial growth (log phase of growth) and so incremented absorbance of broth medium [14-15]. Four Gram-negative (*Salmonella typhi*, *Escherichia coli*, *Klebsiella pneumonae* and *Pseudomonas aeruginosa*) and two Gram-positive bacterika (*Bacillus subtilis* and *Staphylococcus aureus*) were used after maintaining on stock culture agar medium. The 200 µL of each well was filled with 20 µg of test samples (after dilution with suitable solvents) and 180 µL fresh bacterial culture (overnight maintained after suitable dilution with fresh nutrient broth). The initial absorbance was kept between 0.12-0.19 at 540 nm and the incubation was processed at 37 °C for 16-24 h with lid on the microplate. The difference in the absorbance before and after incubation at 540 nm using microplate reader was an index for bacterial growth. The percent inhibition was calculated as:

$$\text{Inhibition (\%)} = \frac{X - Y}{X} \times 100$$

Where

X = absorbance in control with bacterial culture

Y = absorbance in test sample

Results are mean of triplicate (n=3, ± SEM). Ciprofloxacin was taken as reference standard. Minimum inhibitory concentration was also computed with suitable dilutions (5-30 µg/well) and results were calculated using EZ-Fitz Perrella Scientific Inc. Amherst USA software.

Statistical Analysis

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

Conclusion

The projected structures of the synthesized compounds are well supported by spectroscopic data. Also from the antibacterial activity results (Table-1),

it is obvious that the compounds were found to possess significant inhibitory action for the different bacterial strains. In short, we have inaugurated a series of compounds with significant biological activity and these may be assistive for the pharmaceutical industries in designing of medicines. Synthesis of some new analogues of similar sort, exploring of their biological activities and assessment of their SAR is under investigation.

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