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Original Article

Synthesis, spectral analysis and biological screening of some new N-(un)substituted N-(5-chloro-2-methoxyphenyl)-aryl sulfonamides

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ABSTRACT

Objectives: Due to various biological activities of sulfonamides, a series of new N-(5-chloro-2-methoxyphenyl)-aryl sulfonamides (**3a–e**) and their N-benzyl/ethyl substituted derivatives (**6a–e** & **7a–e**) were synthesized followed by antibacterial activity evaluation.
Methods: A facile and environmentally benign series of N-(5-chloro-2-methoxyphenyl)-aryl sulfonamide (**3a–e**) was synthesized in basic aq. medium by coupling of 5-chloro-2-methoxyaniline (**1**) and various aryl sulfonyl chlorides (**2a–e**). Further N-benzyl/ethyl substituted derivatives (**6a–e** & **7a–e**) were synthesized by stirring **3a–e** with the electrophiles **4** & **5** at room temperature (RT). The structure elucidation of the synthesized compounds was processed through spectral data.
Results: All the newer synthesized aryl sulfonamide derivatives were obtained in moderate to good yields in the range of 74–85%. Out of fifteen synthesized derivatives, six compounds **3b**, **3c**, **3e**, **6a**, **7d** & **7e** were active against the both bacterial strains of Gram-positive bacteria relative to ciprofloxacin, the reference standard. The significant activity of compound **6a** against all bacterial strains might be due to ethyl and *ter*-butyl groups in the molecule.
Conclusion: The synthesized compounds exhibited moderate to good activity against the applied bacterial strains and so the structural changes in the substituents altered the inhibitory properties significantly.

1. Introduction

Sulfonamides bears SO_2NH – moiety and are increasingly used as anti-microbial, anti-inflammatory & anti-viral agents; against different infections; inhibitor of a series of enzymes like carbonic anhydrase etc.[1–6] Sulfonamides are analogous to PABA (required by the bacteria for the production of folic acid) and suppress the synthesis of folic acid & finally DNA.[7]

The exploration of new drug candidates is going on in the world to inaugurate new compounds exhibiting high potential

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against the different microbes relating to various diseases. In extension of our previous work on sulfonamides,[4–7] the current research work was an attempt to synthesize pharmacologically important compounds having potential against the different Gram-negative & Gram-positive bacteria. The synthesized compounds having prominent activity may be helpful in drug designing for pharmaceutical industries for the remedy of numerous diseases.

2. Experimental

2.1. General

All the aryl sulfonyl chlorides and 2-amino-4-chloroanisole were purchased from Merck, Alfa Aeser & Sigma Aldrich through local suppliers and used without further purification. Purity of synthesized compounds was assured by thin layer chromatography (TLC), ethyl acetate & *n*-hexane was utilized as solvent systems; and visualized under UV at 254 nm and also by spraying with ceric sulphate solution. Melting points of all the synthesized compounds were recorded by open capillary tube, on a Griffin–George melting point apparatus and were also uncorrected. The I.R. spectra were recorded by potassium bromide pellet method on a Jasco-320-A spectrophotometer with wave number in cm^{-1}. ^1H NMR spectra were recorded in $CDCl_3$ on a Bruker spectrometers operating at 400 MHz. The chemical shift values are reported in ppm (δ) units taking TMS as reference, and the coupling constants (J) are in Hz. Mass spectra (EI-MS) were recorded on a JMS-HX-110 spectrometer.

2.2. General procedure for the synthesis of different chlorinated sulfonamides (3a–e)

2-Amino-4-chloroanisole (0.01 mol; **1**) was dispersed in 30 mL distilled water in 100 mL RB flask. The pH of the reaction mixture was maintained 9–10 during the reaction by aq. Na_2CO_3 solution. Different aryl sulfonyl chlorides (0.01 mol; **2a–e**) were added to the basic solution gradually over 10–15 min keeping the pH of solution 9–10. The reaction contents were kept on stirring for 3–5 h. After the reaction completion, monitored by TLC (*n*-hexane:EtOAc; 70:30), 3–4 mL dil. HCl was poured till the pH of 2–3. The reaction mixture was kept at RT for 10–15 min; the solid precipitates were filtered off, washed by distilled water, dried and recrystallized to yield the products (**3a–e**).

2.2.1. N-(5-Chloro-2-methoxyphenyl)-4-ter-butylbenzenesulfonamide (3a)

Brownish black amorphous solid; Yield: 78%; M.P. 144–146 °C; Molecular formula: $C_{17}H_{20}ClNO_3S$; Molecular weight: 353; IR (KBr, ν_{max}/cm^{-1}): 3203 (N–H stretching), 3076 (Ar C–H stretching), 1612 (Ar C=C stretching), 1365 (S=O stretching); ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.69 (d, J = 8.4 Hz, 2H, H-2′ & H-6′), 7.52 (d, J = 2.4 Hz, 1H, H-6), 7.42 (d, J = 8.4 Hz, 2H, H-3′ & H-5′), 6.96 (dd, J = 8.8, 2.4 Hz, 1H, H-4), 6.63 (d, J = 8.8 Hz, 1H, H-3), 3.62 (s, 3H, $\underline{CH_3}$O-2), 1.28 (s, 9H, $(\underline{CH_3})_3$C-4′); EI-MS: *m/z* 355 $[M+2]^+$, 353 $[M]^+$, 338 $[M\text{-}CH_3]^+$, 322 $[M\text{-}OCH_3]^+$, 289 $[M\text{-}SO_2]^+$, 197 $[C_{10}H_{13}SO_2]^+$, 156 $[C_7H_7ClNO]^+$.

2.2.2. N-(5-Chloro-2-methoxyphenyl)-2,4,6-trimethylbenzenesulfonamide (3b)

Grey amorphous solid; Yield: 85%; M.P. 146–148 °C; Molecular formula: $C_{16}H_{18}ClNO_3S$; Molecular weight: 339; IR (KBr, ν_{max}/cm^{-1}): 3208 (N–H stretching), 3079 (Ar C–H stretching), 1609 (Ar C=C stretching), 1363 (S=O stretching);^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.27 (d, J = 2.8 Hz, 1H, H-6), 6.91 (dd, J = 8.8, 2.4 Hz, 1H, H-4), 6.89 (s, 2H, H-3′ & H-5′), 6.66 (d, J = 8.4 Hz, 1H, H-3), 3.72 (s, 3H, $\underline{CH_3}$O-2), 2.62 (s, 6H, $\underline{CH_3}$-2′ & $\underline{CH_3}$-6′), 2.24 (s, 3H, $\underline{CH_3}$-4′); EI-MS: *m/z* 341 $[M+2]^+$, 339 $[M]^+$, 324 $[M\text{-}CH_3]^+$, 308 $[M\text{-}OCH_3]^+$, 275 $[M\text{-}SO_2]^+$, 183 $[C_9H_{11}SO_2]^+$, 156 $[C_7H_7ClNO]^+$.

2.2.3. N-(5-Chloro-2-methoxyphenyl)-4-methoxybenzenesulfonamide (3c)

Light purple amorphous solid; Yield: 65%; M.P. 136–138 °C; Molecular formula: $C_{14}H_{14}ClNO_4S$; Molecular weight: 327; IR (KBr, ν_{max}/cm^{-1}): 3190 (N–H stretching), 3057 (Ar C–H stretching), 1601 (Ar C=C stretching), 1359 (S=O stretching); ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.64 (d, J = 8.8 Hz, 2H, H-2′ & H-6′), 7.12 (dd, J = 8.8, 2.8 Hz, 1H, H-4), 7.04 (d, J = 2.4 Hz, 1H, H-6), 6.92 (d, J = 8.8 Hz, 2H, H-3′ & H-5′), 6.63 (d, J = 8.8 Hz, 1H, H-3), 3.85 (s, 3H, $\underline{CH_3}$O-4′), 3.40 (s, 3H, $\underline{CH_3}$O-2); EI-MS: *m/z* 329 $[M+2]^+$, 327 $[M]^+$, 312 $[M\text{-}CH_3]^+$, 296 $[M\text{-}OCH_3]^+$, 263 $[M\text{-}SO_2]^+$, 171 $[C_7H_7OSO_2]^+$, 156 $[C_7H_7ClNO]^+$.

2.2.4. N-(5-Chloro-2-methoxyphenyl)-4-acetylbenzenesulfonamide (3d)

Grey amorphous solid; Yield: 71%; M.P. 156–158 °C; Molecular formula: $C_{15}H_{14}ClNO_4S$; Molecular weight: 339; IR (KBr, ν_{max}/cm^{-1}): 3218 (N–H stretching), 3081 (Ar C–H stretching), 1612 (Ar C=C stretching), 1356 (S=O stretching), 1720 (C=O stretching); ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.97 (d, J = 8.0 Hz, 2H, H-2′ & H-6′), 7.86 (d, J = 8.4 Hz, 2H, H-3′ & H-5′), 7.54 (d, J = 2.0 Hz, 1H, H-6), 6.99 (dd, J = 8.4, 2.4 Hz, 1H, H-4), 6.63 (d, J = 8.8 Hz, 1H, H-3), 3.63 (s, 3H, $\underline{CH_3}$O-2), 2.59 (s, 3H, $\underline{CH_3}$CO); EI-MS: *m/z* 341 $[M+2]^+$, 339 $[M]^+$, 324 $[M\text{-}CH_3]^+$, 208 $[M\text{-}OCH_3]^+$, 275 $[M\text{-}SO_2]^+$, 183 $[C_8H_7OSO_2]^+$, 156 $[C_7H_7ClNO]^+$.

2.2.5. N-(5-Chloro-2-methoxyphenyl)naphthalene-2-ylsulfonamide (3e)

Cream grey amorphous solid; Yield: 69%; M.P. 156–158 °C; Molecular formula: $C_{17}H_{14}ClNO_3S$; Molecular weight: 347; IR (KBr, ν_{max}/cm^{-1}): 3215 (N–H stretching), 3085 (Ar C–H stretching), 1615 (Ar C=C stretching), 1365 (S=O stretching); ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 8.36 (brd s, 1H, H-7′), 7.90 (d, J = 7.6 Hz, 1H, H-4′), 7.86 (d, J = 8.8 Hz, 1H, H-3′), 7.84 (d, J = 2.4 Hz, 1H, H-8′), 7.73 (dd, J = 8.4, 2.0 Hz, 1H, H-2′), 7.60 (ddd, J = 9.6, 1.2 Hz, 1H, H-6′), 7.58 (ddd, J = 9.6, 2.4 Hz, 1H, H-5′), 7.09 (br. s, 1H, H-6), 6.93 (dd, J = 8.8, 2.4 Hz, 1H, H-4), 6.57 (d, J = 8.8 Hz, 1H, H-3), 3.56 (s, 3H, $\underline{CH_3}$O-2); EI-MS: *m/z* 349 $[M+2]^+$, 347 $[M]^+$, 332 $[M\text{-}CH_3]^+$, 316 $[M\text{-}OCH_3]^+$, 283 $[M\text{-}SO_2]^+$, 191 $[C_{10}H_7SO_2]^+$, 156 $[C_7H_7ClNO]^+$.

2.3. General procedure for the synthesis of different N-ethyl/benzyl aryl sulfonamides (6a–e & 7a–e)

The calculated amount of **3a–e** (0.01 mol) was dissolved in 10 mL dimethylformamide (DMF) followed by the addition of sodium hydride (0.01 mol) to the mixture. The mixture was stirred for 0.5 h at RT and then ethyl/benzyl halides (0.01 mol)

was added to the mixture and the solution was further stirred for 3–4 h. After the reaction completion, verified by TLC, the product was precipitated after the addition of cold distilled water. 2–3 mL aq. Na_2CO_3 was added to make basic pH of 9. The product was filtered off, washed with distilled water and recrystallized from methanol.

2.3.1. N-(5-Chloro-2-methoxyphenyl)-N-ethyl-4-ter-butylbenzenesulfonamide (6a)

Light brown amorphous solid; Yield: 79%; M.P. 84–86 °C; Molecular formula: $C_{19}H_{24}ClNO_3S$; Molecular weight: 381; IR (KBr, v_{max}/cm^{-1}): 3078 (Ar C–H stretching), 1621 (Ar C=C stretching), 1369 (S=O stretching); ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.76 (d, J = 8.8 Hz, 2H, H-2′ & H-6′), 7.60 (d, J = 2.0 Hz, 1H, H-6), 7.49 (d, J = 8.8 Hz, 2H, H-3′ & H-5′), 6.99 (dd, J = 8.8, 2.0 Hz, 1H, H-4), 6.64 (d, J = 8.8 Hz, 1H, H-3), 3.57 (s, 3H, $\underline{CH_3}$O-2), 3.60 (q, J = 7.2 Hz, 2H, H-1′′), 1.19 (s, 9H, $(\underline{CH_3})_3$C-4′), 0.99 (t, J = 7.2 Hz, 3H, H-2′′); EI-MS: m/z 383 $[M+2]^+$, 381 $[M]^+$, 366 $[M\text{-}CH_3]^+$, 350 $[M\text{-}OCH_3]^+$, 317 $[M\text{-}SO_2]^+$, 197 $[C_{10}H_{13}SO_2]^+$, 156 $[C_7H_7ClNO]^+$.

2.3.2. N-(5-Chloro-2-methoxyphenyl)-N-ethyl-2,4,6-trimethylbenzenesulfonamide (6b)

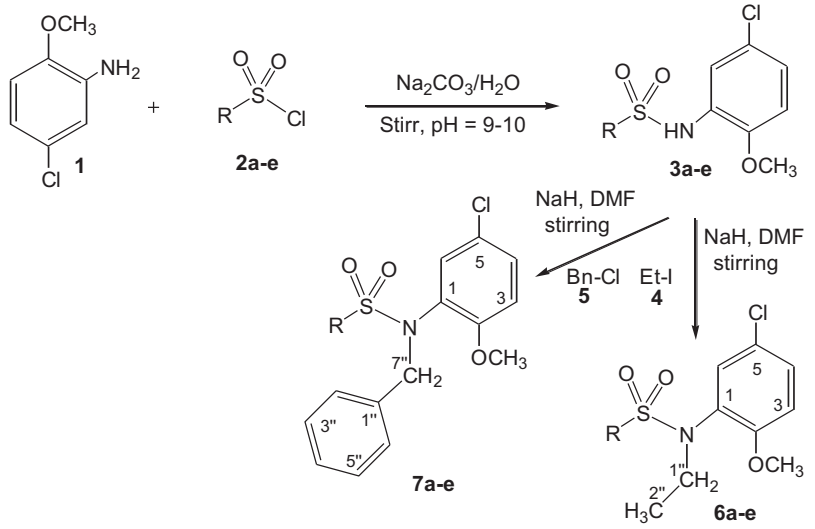
Light grey amorphous solid; Yield: 81%; M.P. 118–120 °C; Molecular formula: $C_{18}H_{22}ClNO_3S$; Molecular weight: 367; IR (KBr, v_{max}/cm^{-1}): 3080 (Ar C–H stretching), 1614 (Ar C=C stretching), 1367 (S=O stretching); ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.35 (d, J = 2.8 Hz, 1H, H-6), 6.95 (dd, J = 8.8, 2.8 Hz, 1H, H-4), 6.79 (s, 2H, H-3′ & H-5′), 6.66 (d, J = 8.8 Hz, 1H, H-3), 3.76 (s, 3H, $\underline{CH_3}$O-2), 3.39 (q, J = 7.2 Hz, 2H, H-1′′), 2.57 (s, 6H, $\underline{CH_3}$-2′ & $\underline{CH_3}$-6′), 2.28 (s, 3H, $\underline{CH_3}$-4′), 0.99 (t, J = 7.2 Hz, 3H, H-2′′); EI-MS: m/z 369 $[M+2]^+$, 367 $[M]^+$, 352 $[M\text{-}CH_3]^+$, 336 $[M\text{-}OCH_3]^+$, 303 $[M\text{-}SO_2]^+$, 183 $[C_9H_{11}SO_2]^+$, 156 $[C_7H_7ClNO]^+$.

2.3.3. N-(5-Chloro-2-methoxyphenyl)-N-ethyl-4-methoxybenzenesulfonamide (6c)

Dark grey amorphous solid; Yield: 89%; M.P. 102–104 °C; Molecular formula: $C_{16}H_{18}ClNO_4S$; Molecular weight: 355; IR (KBr, v_{max}/cm^{-1}): 3056 (Ar C–H stretching), 1603 (Ar C=C stretching), 1369 (S=O stretching); ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.62 (d, J = 8.8 Hz, 2H, H-2′ & H-6′), 7.18–7.22 (m, 2H, H-4 & H-6), 6.90 (d, J = 8.8 Hz, 2H, H-3′ & H-5′), 6.71 (d, J = 8.4 Hz, 1H, H-3), 3.84 (s, 3H, $\underline{CH_3}$O-4′), 3.56 (q, J = 7.2 Hz, 2H, H-1′′), 3.45 (s, 3H, $\underline{CH_3}$O-2), 1.02 (t, J = 7.2 Hz, 3H, H-2′′); EI-MS: m/z 357 $[M+2]^+$, 355 $[M]^+$, 340 $[M\text{-}CH_3]^+$, 324 $[M\text{-}OCH_3]^+$, 291 $[M\text{-}SO_2]^+$, 171 $[C_7H_7OSO_2]^+$, 156 $[C_7H_7ClNO]^+$.

2.3.4. N-(5-Chloro-2-methoxyphenyl)-N-ethyl-4-acetylbenzenesulfonamide (6d)

Blackish grey amorphous solid; Yield: 66%; M.P. 86–88 °C; Molecular formula: $C_{17}H_{19}ClNO_4S$; Molecular weight: 367; IR (KBr, v_{max}/cm^{-1}): 3084 (Ar C–H stretching), 1607 (Ar C=C



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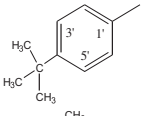
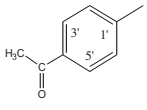
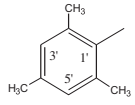
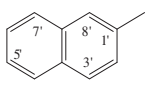
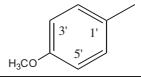
3a,6a,7a		3d,6d,7d	
3b,6b,7b		3e,6e,7e	
3c,6c,7c			

Scheme 1 – Outline for the synthesis of various N-substituted N-(5-chloro-2-methoxyphenyl)-aryl sulfonamides.

stretching), 1351 (S=O stretching), 1719 (C=O stretching); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.99 (d, J = 8.0 Hz, 2H, H-2′ & H-6′), 7.78 (d, J = 8.0 Hz, 2H, H-3′ & H-5′), 7.48 (d, J = 2.4 Hz, 1H, H-6), 7.03 (dd, J = 8.0, 2.4 Hz, 1H, H-4), 6.71 (d, J = 8.0 Hz, 1H, H-3), 3.41 (s, 3H, CH_3O-2), 3.30 (q, J = 7.2 Hz, 2H, H-1′′), 2.50 (s, 3H, CH_3CO-4′), 1.00 (t, J = 7.2 Hz, 3H, H-2′′); EI-MS: m/z 369 $[M+2]^+$, 367 $[M]^+$, 352 $[M\text{-}CH_3]^+$, 336 $[M\text{-}OCH_3]^+$, 303 $[M\text{-}SO_2]^+$, 183 $[C_8H_7OSO_2]^+$, 156 $[C_7H_7ClNO]^+$.

2.3.5. *N-(5-Chloro-2-methoxyphenyl)-N-ethylnaphthalen-2-ylsulfonamide (6e)*

Grey amorphous solid; Yield: 81%; M.P. 116–118 °C; Molecular formula: $C_{19}H_{19}ClNO_3S$; Molecular weight: 375; IR IR (KBr, ν_{max}/cm^{-1}): 3081 (Ar C–H stretching), 1619 (Ar C=C stretching), 1363 (S=O stretching); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.38 (brd s, 1H, H-7′), 7.88 (d, J = 8.0 Hz, 1H, H-4′), 7.85 (d, J = 8.4 Hz, 1H, H-3′), 7.80 (d, J = 2.4 Hz, 1H, H-8′), 7.71 (dd, J = 8.4, 2.0 Hz, 1H, H-2′), 7.64 (ddd, J = 9.2, 1.2 Hz, 1H, H-6′), 7.55 (ddd, J = 9.2, 2.0 Hz, 1H, H-5′), 7.13 (brd s, 1H, H-6), 6.89 (dd, J = 8.4, 2.0 Hz, 1H, H-4), 6.64 (d, J = 8.4 Hz, 1H, H-3), 3.52 (s, 3H, CH_3O-2), 3.46 (q, J = 7.2 Hz, 2H, H-1′′), 0.96 (t, J = 7.2 Hz, 3H, H-2′′); EI-MS: m/z 377 $[M+2]^+$, 375 $[M]^+$, 360 $[M\text{-}CH_3]^+$, 344 $[M\text{-}OCH_3]^+$, 311 $[M\text{-}SO_2]^+$, 191 $[C_{10}H_7SO_2]^+$, 156 $[C_7H_7ClNO]^+$.

2.3.6. *N-(5-Chloro-2-methoxyphenyl)-N-benzyl-4-ter-butylbenzenesulfonamide (7a)*

Blackish brown amorphous solid; Yield: 75%; M.P. 108–110 °C; Molecular formula: $C_{24}H_{16}ClNO_3S$; Molecular weight: 443; IR (KBr, ν_{max}/cm^{-1}): 3086 (Ar C–H stretching), 1613 (Ar C=C stretching), 1356 (S=O stretching); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.89 (d, J = 8.4 Hz, 2H, H-2′ & H-6′), 7.70–7.66 (m, 5H, H-2′′ to H-6′′), 7.59 (d, J = 2.4 Hz, 1H, H-6), 7.41 (d, J = 8.4 Hz, 2H, H-3′ & H-5′), 7.19 (dd, J = 8.4, 2.4 Hz, 1H, H-4), 6.63 (d, J = 8.4 Hz, 1H, H-3), 4.49 (s, 2H, H-7′′), 3.51 (s, 3H, CH_3O-2), 1.20 (s, 9H, $(CH_3)_3$C-4′); EI-MS: m/z 445 $[M+2]^+$, 443 $[M]^+$, 428 $[M\text{-}CH_3]^+$, 412 $[M\text{-}OCH_3]^+$, 379 $[M\text{-}SO_2]^+$, 197 $[C_{10}H_{13}SO_2]^+$, 156 $[C_7H_7ClNO]^+$.

2.3.7. *N-(5-Chloro-2-methoxyphenyl)-N-benzyl-2,4,6-trimethylbenzenesulfonamide (7b)*

Light pink amorphous solid; Yield: 73%; M.P. 128–130 °C; Molecular formula: $C_{23}H_{24}ClNO_3S$; Molecular weight: 429; IR (KBr, ν_{max}/cm^{-1}): 3077 (Ar C–H stretching), 1606 (Ar C=C stretching), 1361 (S=O stretching); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.52–7.47 (m, 5H, H-2′′ to H-6′′), 7.29 (d, J = 2.4 Hz, 1H, H-6), 6.85 (dd, J = 8.4, 2.4 Hz, 1H, H-4), 6.75 (s, 2H, H-3′ & H-5′), 6.63 (d, J = 8.4 Hz, 1H, H-3), 3.69 (s, 2H, H-7′′), 3.49 (s, 3H, CH_3O-2), 2.55 (s, 6H, CH_3-2′ & CH_3-6′), 2.15 (s, 3H, CH_3-4′); EI-MS: m/z 431

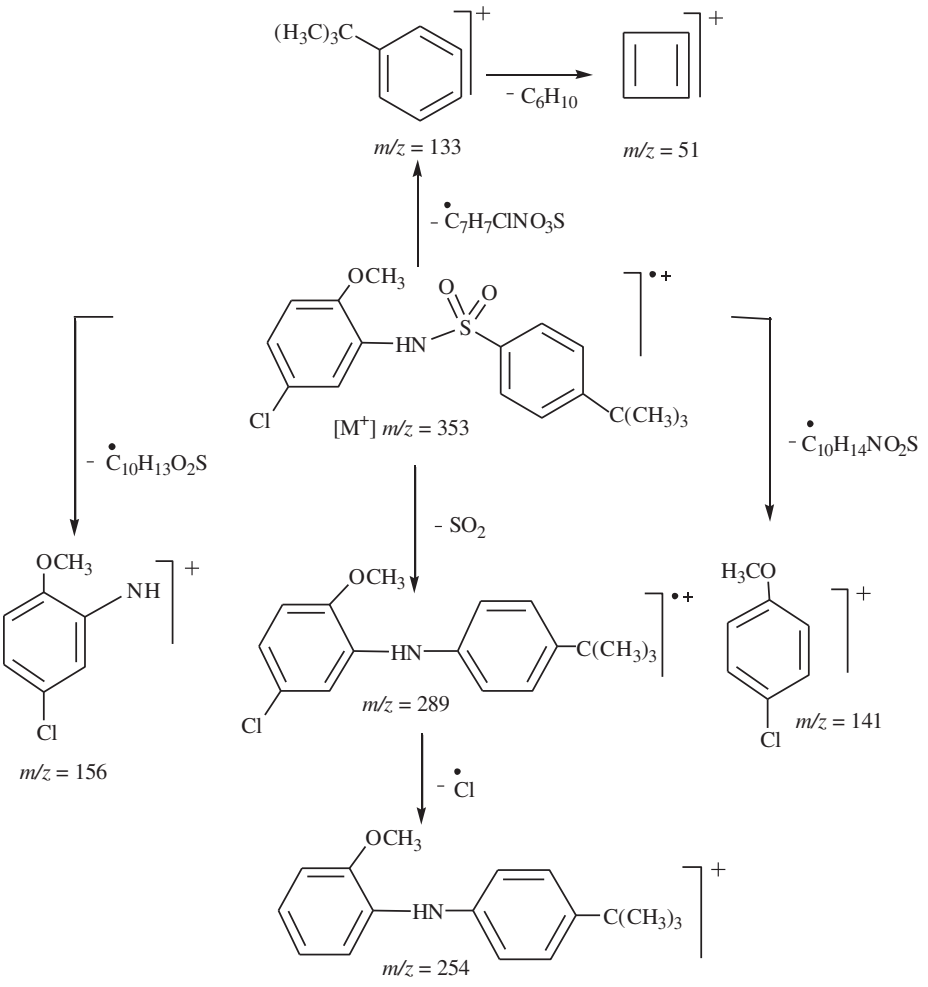


Fig. 1 – Mass fragmentation pattern of *N*-(5-Chloro-2-methoxyphenyl)-4-*ter*-butylbenzenesulfonamide (3a).

$[M + 2]^+$, 429 $[M]^+$, 414 $[M\text{-}CH_3]^+$, 398 $[M\text{-}OCH_3]^+$, 365 $[M\text{-}SO_2]^+$, 183 $[C_9H_{11}SO_2]^+$, 156 $[C_7H_7ClNO]^+$.

2.3.8. *N-(5-Chloro-2-methoxyphenyl)-N-benzyl-4-methoxybenzenesulfonamide (7c)*

Light grey amorphous solid; Yield: 72%; M.P. 108–110 °C; Molecular formula: $C_{21}H_{20}ClNO_4S$; Molecular weight: 417; IR (KBr, ν_{max}/cm^{-1}): 3067 (Ar C–H stretching), 1599 (Ar C=C stretching), 1365 (S=O stretching); ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.64 (d, $J = 8.8$ Hz, 2H, H-2′ & H-6′), 7.20–7.16 (m, 5H, H-2′′–H-6′′), 7.12 (dd, $J = 8.8$, 2.8 Hz, 1H, H-4), 7.04 (d, $J = 2.4$ Hz, 1H, H-6), 6.92 (d, $J = 8.8$ Hz, 2H, H-3′ & H-5′), 6.63 (d, $J = 8.8$ Hz, 1H, H-3), 4.70 (s, 2H, H-7′′), 3.85 (s, 3H, $\underline{CH_3}$O-4′), 3.40 (s, 3H, $\underline{CH_3}$O-2); EI-MS: *m/z* 419 $[M + 2]^+$, 417 $[M]^+$, 402 $[M\text{-}CH_3]^+$, 386 $[M\text{-}OCH_3]^+$, 353 $[M\text{-}SO_2]^+$, 171 $[C_7H_7OSO_2]^+$, 156 $[C_7H_7ClNO]^+$.

2.3.9. *N-(5-Chloro-2-methoxyphenyl)-N-benzyl-4-acetylbenzenesulfonamide (7d)*

Greyish black amorphous solid; Yield: 88%; M.P. 92–94 °C; Molecular formula: $C_{22}H_{20}ClNO_4S$; Molecular weight: 429; IR (KBr, ν_{max}/cm^{-1}): 3079 (Ar C–H stretching), 1611 (Ar C=C stretching), 1354 (S=O stretching), 1723 (C=O stretching); ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.95 (d, $J = 8.4$ Hz, 2H, H-2′ & H-6′), 7.82 (d, $J = 8.4$ Hz, 2H, H-3′ & H-5′), 7.52–7.47 (m, 5H, H-2′′ to H-6′′), 7.41 (d, $J = 2.0$ Hz, 1H, H-6), 6.90 (dd, $J = 8.4$, 2.0 Hz, 1H, H-4), 6.64 (d, $J = 8.4$ Hz, 1H, H-3), 3.49 (s, 2H, H-7′′), 3.40 (s, 3H, $\underline{CH_3}$O-2), 2.55 (s, 3H, $\underline{CH_3}$CO); EI-MS: *m/z* 431 $[M + 2]^+$, 429 $[M]^+$, 414 $[M\text{-}CH_3]^+$, 398 $[M\text{-}OCH_3]^+$, 365 $[M\text{-}SO_2]^+$, 183 $[C_8H_7OSO_2]^+$, 156 $[C_7H_7ClNO]^+$.

2.3.10. *N-(5-Chloro-2-methoxyphenyl)-N-benzyl naphthalen-2-ylsulfonamide (7e)*

Light grey amorphous solid; Yield: 74%; M.P. 112–114 °C; Molecular formula: $C_{24}H_{20}ClNO_3S$; Molecular weight: 437; IR (KBr, ν_{max}/cm^{-1}): 3087 (Ar C–H stretching), 1618 (Ar C=C stretching), 1366 (S=O stretching); ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 8.32 (brd s, 1H, H-7′), 7.94 (d, $J = 8.0$ Hz, 1H, H-4′), 7.83 (d, $J = 8.4$ Hz, 1H, H-3′), 7.82 (d, $J = 2.4$ Hz, 1H, H-8′), 7.71 (dd, $J = 8.4$, 2.0 Hz, 1H, H-2′), 7.58 (ddd, $J = 9.6$, 1.2 Hz, 1H, H-6′), 7.54 (ddd, $J = 9.6$, 2.4 Hz, 1H, H-5′), 7.25–7.21 (m, 5H, H-2′′ to H-6′′), 7.10 (brd s, 1H, H-6), 6.95 (dd, $J = 8.4$, 2.4 Hz, 1H, H-4), 6.55 (d, $J = 8.4$ Hz, 1H, H-3), 3.39 (s, 2H, H-7′′), 3.32 (s, 3H, $\underline{CH_3}$O-2); EI-MS: *m/z* 439 $[M + 2]^+$, 437 $[M]^+$, 422 $[M\text{-}CH_3]^+$, 406 $[M\text{-}OCH_3]^+$, 373 $[M\text{-}SO_2]^+$, 191 $[C_{10}H_7SO_2]^+$, 156 $[C_7H_7ClNO]^+$.

2.4. *Antibacterial activity assay*

The antibacterial activity was processed using a reported method.[8,9] Four Gram-negative and two Gram-positive bacteria were maintained on stock culture agar medium. The total volume of each well was 200 μL with 20 μg of the test samples diluted by solvents and 180 μL of overnight maintained fresh bacterial culture after suitable dilution with fresh nutrient broth. The initial absorbance was maintained between 0.12 and 0.19 at 540 nm and the incubation was processed at 37 °C for 16–24 h with lid on the microplate. The absorbance was observed before and after incubation at 540 nm using microplate reader; and the difference was an indicant of bacterial growth. The percent inhibition was calculated using the formula,

Table 1 – Antibacterial activity of synthesized compounds.

Compound	% Age inhibition/MIC					
	S. typhi (–)	*E. coli* (–)	*K. pneumoniae* (–)	*P. aeruginosa* (–)	*B. subtilis* (+)	*S. aureus* (+)
3a	47.21 ± 2.56/15.92 ± 0.02	13.86 ± 2.45/9.12 ± 0.21	38.31 ± 1.34/8.22 ± 0.12	51.61 ± 2.98/–	68.89 ± 2.86/–	38.45 ± 0.35/20.24 ± 0.11
3b	75.36 ± 1.26/15.13 ± 0.18	30.32 ± 3.12/–	24.57 ± 2.11/–	75.35 ± 1.11/–	66.04 ± 3.45/13.69 ± 0.31	38.21 ± 2.67/13.93 ± 0.17
3c	58.39 ± 1.98/16.41 ± 0.29	38.34 ± 2.41/11.44 ± 0.01	31.98 ± 2.34/11.32 ± 0.13	73.75 ± 3.87/–	69.68 ± 1.65/16.71 ± 0.21	31.42 ± 2.33/13.44 ± 0.31
3d	59.04 ± 3.01/–	32.42 ± 0.25/–	47.31 ± 1.05/–	62.25 ± 0.65/–	52.33 ± 0.81/–	38.03 ± 0.45/–
3e	76.04 ± 3.22/16.32 ± 3.65	25.64 ± 4.02/14.91 ± 0.72	66.37 ± 3.26/–	63.41 ± 1.67/15.24 ± 0.79	67.07 ± 2.41/12.84 ± 0.84	65.91 ± 1.46/14.33 ± 0.72
6a	88.79 ± 2.31/13.51 ± 0.19	79.55 ± 2.98/13.69 ± 0.97	72.20 ± 1.78/13.43 ± 0.44	87.21 ± 1.54/13.41 ± 0.52	88.36 ± 1.67/12.01 ± 1.91	74.89 ± 3.12/15.01 ± 0.41
6b	68.34 ± 2.54/–	17.07 ± 1.87/-	48.27 ± 2.91/–	41.73 ± 0.66/–	67.02 ± 1.09/–	49.06 ± 3.01/–
6c	37.23 ± 2.13/–	34.45 ± 0.56/-	45.39 ± 1.34/–	45.98 ± 3.21/–	45.67 ± 1.76/–	48.98 ± 2.31/–
6d	64.37 ± 2.91/–	52.12 ± 2.15/-	43.36 ± 1.03/–	52.15 ± 3.05/–	61.47 ± 1.01/–	43.13 ± 1.65/–
6e	65.17 ± 2.64/–	37.28 ± 3.89/-	59.21 ± 2.83/–	71.31 ± 1.07/–	32.19 ± 3.06/–	53.85 ± 4.37/–
7a	63.80 ± 3.19/–	51.72 ± 4.19/–	82.18 ± 2.09/–	60.34 ± 3.53/–	52.17 ± 3.04/–	51.07 ± 1.68/–
7b	61.64 ± 3.34/16.39 ± 0.94	11.27 ± 3.67/–	45.67 ± 2.61/–	45.23 ± 1.66/–	57.82 ± 2.09/14.51 ± 1.22	47.56 ± 2.31/–
7c	44.26 ± 2.61/–	43.61 ± 3.89/–	53.72 ± 3.05/–	62.16 ± 2.91/–	59.49 ± 2.71/–	42.02 ± 1.03/–
7d	79.14 ± 4.11/12.13 ± 0.31	39.92 ± 1.45/17.31 ± 2.11	48.37 ± 1.45/–	74.55 ± 3.55/–	80.54 ± 1.87/11.93 ± 0.14	53.23 ± 1.35/14.51 ± 0.18
7e	58.39 ± 2.23/16.23 ± 1.34	6.64 ± 2.78/–	43.32 ± 2.67/–	51.15 ± 2.94/–	68.07 ± 1.23/15.16 ± 0.29	47.78 ± 2.11/17.02 ± 0.27
Ciprofloxacin	**91.21 ± 0.22/8.32 ± 0.25**	**92.00 ± 0.23/8.98 ± 0.78**	**90.63 ± 0.12/8.91 ± 0.13**	**90.35 ± 0.21/8.12 ± 0.36**	**91.98 ± 0.04/8.47 ± 0.44**	**91.38 ± 0.01/8.99 ± 0.28**

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

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

where X is absorbance in control with bacterial culture and Y is absorbance in test sample. Ciprofloxacin was used as reference standard. Minimum inhibitory concentration (MIC) was also computed with suitable dilutions (5–30 μg/well) and results were calculated using EZ-Fit5 Perrella Scientific Inc. Amherst USA software.

3. Results and discussion

3.1. Chemistry

Due to high curiosity for the new compounds having much potential against the different microbes, the attempt was made to contribute in this regard. Our objective was to synthesize some new *N*-(un)substituted aryl sulfonamides and to find out their antibacterial activities. The *N*-(5-chloro-2-methoxyphenyl)-aryl sulfonamides (**3a–e**) and *N*-benzyl/ethyl substituted *N*-(5-chloro-2-methoxyphenyl)-aryl sulfonamides (**6a–e** & **7a–e**) were synthesized according to the protocol sketched in Scheme 1, in excellent yields having good antibacterial activities.

The compound **3a** was synthesized as brownish black amorphous solid with 78% yield and 144–146 °C melting point. The molecular formula $C_{17}H_{20}ClNO_3S$ was supported by EI-MS with $[M]^+$ at *m/z* 353 (also a distinguishable peak at *m/z* 289 after the removal of sulfonyl group) and number of protons in ^1H NMR spectrum. The IR spectrum affirmed the sulfonyl group at 1365 cm^{-1} and –NH– group at 3203 cm^{-1}. In aromatic section of ^1H NMR spectrum, the signals of *p*-substituted phenyl ring linked to sulfonyl group appeared as two doublets integrated for two protons each with coupling constant of 8.4 Hz, one at δ 7.69 (*ortho* to the sulfonyl group) while other at δ 7.42 (*meta* to the sulfonyl group). The signals appearing at δ 7.52 (d, $J = 2.4$ Hz, 1H, H-6), 6.96 (dd, $J = 8.8, 2.4$ Hz, 1H, H-4) and 6.63 (d, $J = 8.8$ Hz, 1H, H-3) were allotted to three protons of tri-substituted aniline ring. In the aliphatic section of ^1H NMR spectrum, the signals revealed at δ 3.62 (s, 3H, CH_3O-2) for methoxy group at 2nd position of substituted aniline & 1.28 (s, 9H, $(CH_3)_3C$-4′) for tertiary butyl group at 4th position of other benzene ring. Thus the structure of compound **(3a)** was corroborated and named as *N*-(5-Chloro-2-methoxyphenyl)-4-*ter*-butylbenzenesulfonamide. The mass fragmentation pattern of **3a** is clearly sketched in Fig. 1. Similarly, the structures of other synthesized compounds were characterized by ^1H NMR, IR and EI-MS as described in experimental section.

3.2. Antibacterial activity

The results of % age inhibition & MIC values for antibacterial activity of the synthesized compounds against Gram-negative & Gram-positive bacteria are described in Table 1.

The compounds *N*-(5-Chloro-2-methoxyphenyl)-*N*-ethyl-4-*ter*-butylbenzenesulfonamide **(6a)** expressed activity against all the bacterial strains with good % age inhibition & MIC values relative to the reference standard ciprofloxacin, probably due to presence of N-substitution of ethyl and *ter*-butyl groups in the molecule. The compounds **3b**, **3c**, **3e**, **6a**, **7d** & **7e** were active against the both bacterial strains of Gram-positive. The compounds **6b**, **6c**, **6d**, **6e**, **7a** & **7c** were inactive against all the bacterial strains of Gram-negative & Gram-positive bacteria. These compounds can further be exploited and their derivatives could be synthesized to get MIC values near to standard. So these compounds might be potential target in the drug discovery and development programme.

4. Conclusion

The synthesized compounds are well supported by spectroscopic data. From the antibacterial activity data (Table 1), it is concluded that the series of compounds depicted remarkable inhibitory action against different bacterial strains. Synthesis, biological activity evaluation and estimation of SAR of some more analogues are under investigation. In this way, the compounds could be potential target in the discovery of medicine and drug development programme.

Conflicts of interest

All authors have none to declare.

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