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# Synthesis, Characterization and Antimicrobial activity Studies of Bis-sulfonamide Derivatives

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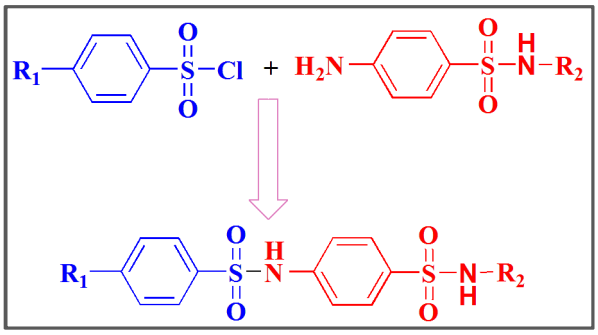
## ABSTRACT

*A series of thiazole, oxazole and isoxazole derivatives containing sulfonamide moieties were synthesized and the structure of the new derivatives was confirmed using FT-IR, $^1$H NMR, LCMS and elemental analysis. The antimicrobial activities of these compounds were evaluated against two Gram-positive, two Gram-negative and two fungal strains by disc diffusion method. Thiazole derivative containing 4-methoxy phenyl group has observed as a potent antimicrobial agent.*

### Graphical Abstract




**Keywords:** Chlorosulfonic acid, Bis-sulfonamide, Antibacterial, Antifungal, Disc diffusion.

## INTRODUCTION

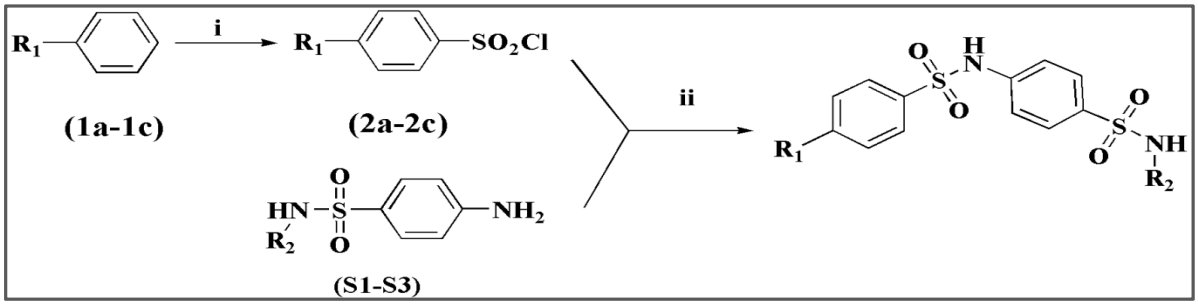
The sulfa drugs and their derivatives have a significant position among the class of organic compounds, which have broad applications in many biological aspects [1]. The sulfonamides were the first drugs wildly employed and systematically applied as preventive against various diseases. These compounds display biological activities such as antibacterial, antifungal, antimycobacterial, antiviral and antitumor agents because of their specific structure [2-8]. Prontosil was the first antibiotic sulfa drug successfully used to treat bacterial as well as fungal infections [9]. After sulfanilamide discovery, a number of chemical variations were evaluated and the best therapeutic results were selected from the compounds in which one hydrogen atom of the $SO_2$-$NH_2$ group was replaced by heterocyclic ring [10]. More advanced studies exposed that modified sulfonamides showed moderate

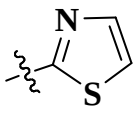
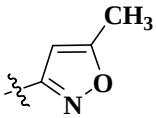
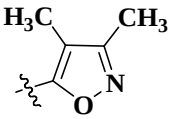
to high antibacterial activity [11] and new macrocyclic bis-sulfonamides have identified as antimicrobial agents [12]. Many sulfanilamide derivatives were used as Sulfa drugs, such as Sulfadiazine (against intestinal tract infections), Sulfamethazine (against urinary tract infections) and Sulfathiazole (against bacterial infections). Sulfonamides act as inhibitors of folic acid synthesis in the living system which assists in the flourishing condition for bacteria. Sulfa drugs are being synthesized to act according to the mode of action from past to present day, which is to compete with the essential metabolite of the bacteria in its reproduction. A large number of structurally novel *N*-substituted sulfanilamide derivatives have been reported to possess antitumor activity. Some of the candidates such as E7010, ER-34410 or E7070 are examples in advanced clinical trials [13].

## MATERIALS AND METHODS

The starting materials and reagents used for the synthesis of targeted derivatives were procured from commercial sources and used without further purification. All the reactions were monitored by Thin Layer Chromatography (TLC) using a mixture of EtOAc: Hexane (1:1) as eluent. It was performed in Aluminium sheets pre-coated with silica gel (Merk KGaA). The melting points (uncorrected) of final compounds were determined with Digital Melting Point Apparatus EQ 730 (Equiptronics) using an open capillary tube with the heating rate of 10 °C/min. $^1$H NMR spectra were recorded on a Bruker+ 400 MHz spectrometer using DMSO-$d_6$ as a solvent. FT-IR spectra were recorded in the region from 400 cm$^{-1}$ to 4000 cm$^{-1}$ by using Shimadzu IR spectrometer in solid phase KBr. LCMS were recorded on an Agilent 1100 LC/MSD-Trap-XCT instrument in the positive mode.

**General Procedure for the synthesis of compounds 2a-2c:** Synthesis of arylbenzene-1-sulfonyl chlorides, **2a-2c** was carried out by chlorosulfonation reaction of benzene, chlorobenzene and anisole (**1a-1c**) with chlorosulfonic acid in chloroform at 0-5ºC and the reaction was maintained at room temperature for 12 h [14, 15]. The product was isolated by quenching in crushed ice to remove the excess of chlorosulfonic acid and other byproducts. The compound **2a** was colourless viscous liquid, **2b** was pale yellow crystals and **2c** was off-white crystals. The synthetic strategy for the target molecules is depicted in Scheme 1.




| Comp. No | 3a | 3b | 3c | 4a | 4b | 4c | 5a | 5b | 5c |
|---|---|---|---|---|---|---|---|---|---|
| $R_1$ | H | Cl | $OCH_3$ | H | Cl | $OCH_3$ | H | Cl | $OCH_3$ |
| | | S1 | | | S2 | | | S3 | |
| $R_2$ | |  | | |  | | |  | |

**Scheme 1**. Synthesis of sulfonamide derivatives

Reaction conditions**.** i). $ClSO_3H/CHCl_3$, RT, 12 h; ii). Pyridine/$CHCl_3$, RT, 8-10 h

**General procedure for the synthesis of compounds 3a-3c, 4a-4c and 5a-5c:** The final compounds **3a-3c, 4a-4c** and **5a-5c** were synthesized by condensing the above intermediates with different sulfa drugs (**S1**, **S2** and **S3**). The reaction was carried out in chloroform in presence of pyridine at RT for 8-10 h. The excess of the base was removed by adjusting the pH to neutral (pH 7) by dil. HCl and the precipitated product were separated by filtration (Scheme 1).

**4-[(Benzenesulfonyl)amino]-N-(1,3-thiazol-2-yl)benzene-1-sulfonamide (3a):** Yield 86 %; mp 154-156 ºC; IR (KBr, $cm^{-1}$): 3371, 3251 (N-H stretch), 3113 (C-H stretch), 1629 (C=N), 1595 (N-H bend), 1313, 1180 ($SO_2$). $^1$H NMR (DMSO-$d_6$) δ/ppm: 6.82(s, 1H, thiazole), 7.25(s, 1H, thiazole), 7.52-7.54 (d, 2H, Ar-H), 7.59-7.63(m, 3H, Ar-H), 7.82-7.84(d, 2H, Ar-H), 7.88-7.90(d, 2H, Ar-H), 11.09 (s, 1H, N-H), 12.61 (s, 1H, N-H); MS-ESI (m/z) calcd. ($[M+H]^+$), 396.0; Found 395.9; Anal. calcd. for C, 45.56; H, 3.31; N, 10.63; S, 24.32; Found C, 45.64; H, 3.27; N, 10.58; S, 24.37.

**4-Chloro-N-{4-[(1,3-thiazol-2-yl)sulfamoyl]phenyl}benzene-1-sulfonamide (3b):** Yield 84 %; mp 182-184 ºC; IR (KBr, $cm^{-1}$): 3351, 3185 (N-H stretch), 3117 (C-H stretch), 1632 (C=N), 1595 (N-H bend), 1326, 1154 ($SO_2$). $^1$H NMR (DMSO-$d_6$) δ/ppm: 6.81(s, 1H, thiazole), 7.23(s, 1H,thiazole proton), 7.52-7.54 (d, 2H, Ar-H), 7.58-7.60(d, 2H, Ar-H), 7.68-7.70(d, 2H, Ar-H), 7.77-7.79(d, 2H, Ar-H), 11.02 (s, 1H, N-H), 12.63 (s, 1H, N-H); MS-ESI (m/z) calcd. ($[M+H]^+$), 429.9; Found 429.8; Anal. calcd. for $C_{15}H_{12}N_3S_3O_4Cl$: C, 41.91; H, 2.81; Cl, 8.25; N, 9.77; S, 22.38; Found C, 41.87; H, 2.78; Cl, 8.19; N, 9.81; S, 22.43.

**4-Methoxy-N-{4-[(1,3-thiazol-2-yl)sulfamoyl]phenyl}benzene-1-sulfonamide(3c):** Yield 82 %; mp 196-198 ºC; IR (KBr, $cm^{-1}$): 3367, 3178 (N-H stretch), 2978 (C-H stretch), 1634 (C=N), 1592 (N-H bend), 1313, 1144 ($SO_2$). $^1$H NMR (DMSO-$d_6$) δ/ppm: 6.75(s, 1H, thiazole), 7.45(s, 1H, thiazole), 7.08-7.10 (d, 2H, Ar-H), 7.62-7.64(d, 2H, Ar-H), 7.77-7.79(d, 2H, Ar-H), 7.83-7.85(d, 2H, Ar-H), 10.71(s, 1H, N-H), 12.59 (s, 1H, N-H); MS-ESI (m/z) calcd. ($[M+H]^+$), 426.0; Found 426.1; Anal. calcd. for $C_{16}H_{15}N_3S_3O_5$: C, 45.16; H, 3.55; N, 9.88; S, 22.61; Found C, 45.20; H, 3.60; N, 9.93; S, 22.57.

**4-[(Benzenesulfonyl)amino]-N-(5-methyl-1,2-oxazol-3-yl)benzene-1-sulfonamide (4a):** Yield 83 %; mp 157-159 ºC; IR (KBr, $cm^{-1}$): 3361, 3125 (N-H stretch), 2988 (C-H stretch), 1631 (C=N), 1598 (N-H bend), 1334, 1164 ($SO_2$). $^1$H NMR (DMSO-$d_6$) δ/ppm: 2.31(s, 3H, $CH_3$), 6.09(s, 1H, oxazole proton), 7.28-7.30 (d, 2H, Ar-H), 7.58-7.63 (m, 3H, Ar-H), 7.87-7.89(d, 2H, Ar-H), 7.90-7.92(d, 2H, Ar-H), 11.17 (s, 1H, N-H), 11.31 (s, 1H, N-H); MS-ESI (m/z) calcd. ($[M+H]^+$), 394.0; Found 393.9; Anal. calcd. for $C_{16}H_{15}N_3S_2O_5$: C, 48.84; H, 3.84; N, 10.68; S, 16.30; Found C, , 48.93; H, 3.92; N, 10.71; S, 16.37.

**4-Chloro-N-{4-[(5-methyl-1,2-oxazol-3-yl)sulfamoyl]phenyl}benzene-1-sulfonamide (4b):** Yield 81 %; mp 162-164ºC; IR (KBr, $cm^{-1}$): 3236, 3120 (N-H stretch), 3068 (C-H stretch), 1620 (C=N), 1593 (N-H bend), 1327, 1172 ($SO_2$). $^1$H NMR (DMSO-$d_6$) δ/ppm: 2.28(s, 3H, $CH_3$), 6.08(s, 1H, oxazole proton), 7.26-7.28 (d, 2H, Ar-H), 7.64-7.66 (d, 2H, Ar-H), 7.73-7.75 (d, 2H, Ar-H), 7.82-7.84(d, 2H, Ar-H), 11.10 (s, 1H, N-H), 11.33 (s, 1H, N-H); MS-ESI (m/z) calcd. ($[M+H]^+$), 428.0; Found 427.9; Anal. calcd. for $C_{16}H_{14}N_3S_2O_5Cl$: C, 44.91; H, 3.30; Cl, 8.29; N, 9.82; S, 14.99; Found C, 44.87; H, 3.35; Cl, 8.24; N, 9.77; S, 14.94.

**4-Methoxy-N-{4-[(5-methyl-1,2-oxazol-3-yl)sulfamoyl]phenyl}benzene-1-sulfonamide (4c):** Yield 79 %; mp 197-199ºC; IR (KBr, $cm^{-1}$): 3287, 3176 (N-H stretch), 3010 (C-H stretch), 1638 (C=N), 1591 (N-H bend), 1320, 1164 ($SO_2$). $^1$H NMR (DMSO-$d_6$) δ/ppm: 2.30(s, 3H, $CH_3$), 3.85(s, 3H, $OCH_3$), 6.09(s, 1H,oxazole proton), 7.08-7.10(d, 2H, Ar-H), 7.24-7.26(d, 2H, Ar-H), 7.86-7.88(d, 2H, Ar-H), 7.91-7.93(d, 2H, Ar-H), 10.78 (s, 1H, N-H), 11.29 (s, 1H, N-H); MS-ESI (m/z) calcd. ($[M+H]^+$), 424.0; Found 423.9; Anal. calcd. for $C_{17}H_{17}N_3S_2O_6$: C, 48.22; H, 4.05; N, 9.92; S, 15.14; Found C, 48.18; H, 4.09; N, 9.97; S, 15.19.

**4-[(Benzenesulfonyl)amino]-N-(3,4-dimethyl-1,2-oxazol-5-yl)benzene-1-sulfonamide (5a):** Yield 79 %; mp 188-190 ºC; IR (KBr, $cm^{-1}$): 3292, 3181(N-H stretch), 2998 (C-H stretch), 1639 (C=N), 1598 (N-H bend), 1323, 1184 ($SO_2$). $^1$H NMR (DMSO-$d_6$) δ/ppm: 1.65(s, 3H, $CH_3$), 2.08(s, 3H, $CH_3$), 7.58-7.60(d, 2H, Ar-H), 7.62-7.66 (m, 3H, Ar-H), 7.92-7.94(d, 2H, Ar-H), 8.08-8.10(d, 2H, Ar-H), 10.62(s, 1H, N-H), 10.93 (s, 1H, N-H); MS-ESI (m/z) calcd. ($[M+H]^+$), 408.0; Found 407.9; Anal. calcd. for $C_{17}H_{17}N_3S_2O_5$: C, 50.11; H, 4.21; N, 10.31; S, 15.74; Found C, 50.16; H, 4.27; N, 10.26; S, 15.69.

**4-Chloro-N-{4-[(3,4-dimethyl-1,2-oxazol-5-yl)sulfamoyl]phenyl}benzene-1-sulfonamide(5b):** Yield 76 %; mp 193-195ºC; IR (KBr, $cm^{-1}$): 3234 3152 (N-H stretch), 3056 (C-H stretch), 1640 (C=N), 1595 (N-H bend), 1332, 1170 ($SO_2$). $^1$H NMR (DMSO-$d_6$) δ/ppm: 1.65(s, 3H, $CH_3$), 2.08(s, 3H, $CH_3$), 7.60-7.62(d, 2H, Ar-H), 7.65-7.676(m, 2H, Ar-H), 7.92-7.94(d, 2H, Ar-H), 8.07-8.9(d, 2H, Ar-H), 10.69(s, 1H, N-H), 10.96 (s, 1H, N-H); MS-ESI (m/z) calcd. ($[M+H]^+$), 442.0; Found 441.9; Anal. calcd. for $C_{17}H_{16}N_3S_2O_5Cl$: C, 46.20; H, 3.65; Cl, 8.02; N, 9.51; S, 14.51; Found C, 46.16; H, 3.60; Cl, 8.07; N, 9.57; S, 14.47.

**N-{4-[(3,4-dimethyl-1,2-oxazol-5-yl)sulfamoyl]phenyl}-4-methoxybenzene-1-sulfonamide(5c):** Yield 75 %; mp 197-199ºC; IR (KBr, $cm^{-1}$): 3361, 3275 (N-H stretch), 3047 (C-H stretch), 1664 (C=N), 1593 (N-H bend), 1336, 1159 ($SO_2$). $^1$H NMR (DMSO-$d_6$) δ/ppm: 1.65(s, 3H, $CH_3$), 2.08(s, 3H, $CH_3$), 3.84(s, 1H, $OCH_3$), 7.12-7.14(d, 2H, Ar-H), 7.61-7.63(d, 2H, Ar-H), 7.92-7.94(d, 2H, Ar-H), 8.00-7.98(d, 2H, Ar-H), 10.45(s, 1H, N-H), 10.92(s, 1H, N-H); MS-ESI (m/z) calcd. ($[M+H]^+$), 438.0; Found 437.9; Anal. calcd. for $C_{18}H_{19}N_3S_2O_6$: C, 49.42; H, 4.38; N, 9.60; S, 14.66; Found C, 49.48; H, 4.42; N, 9.64; S, 14.70.

## RESULTS AND DISCUSSION

The intermediate compounds (**2a-2c**) were synthesized by chlorosulfonation reaction. The starting materials (**1a-1c**) were reacted with the chlorosulfonic acid in chloroform and the product was precipitated while pouring into ice. The final compounds were prepared by a nucleophilic substitution reaction of sulfa drugs with the intermediates (**2a-2c**). The reaction was carried out by condensing the above intermediates with different sulfa drugs (**S1**, **S2** and **S3**) in pyridine/chloroform at RT for 10 h.

**Spectral analysis:** The newly synthesized compounds were initially characterized by checking the melting points, elemental analysis and LCMS and further confirmation was done by recording the FT-IR and $^1$H NMR spectroscopy. The IR spectra of final compounds observed two medium intensity absorption frequencies in the range 3120-3371 $cm^{-1}$ corresponding tothe NH stretching vibrations. The high intense peaks in the ranges 1313-1336 $cm^{-1}$and 1154-1180 $cm^{-1}$ are due to the asymmetric and symmetric S=O stretching modes respectively and the peaks at 1620-1664 $cm^{-1}$ for C=N stretching confirm the assigned structures [**16, 17**].

The $^1$H NMR spectra of compounds have shown the aromatic protons in the range 7.08-8.12 ppm. The electronegative chloro group shifted the aromatic protons, *ortho* to chloro group to the deshielded area and the replacement of chloro with methoxy group further increased the chemical shift values. The thiazole ring protons observed at δ 6.75-7.25 ppm and oxazole ring proton observed at 6.08-6.09 ppm. The N-H protons are observed in the most deshielded region due to the presence of the neighbouring S=O group. Among the two N-H protons observed, the proton bonded to the heterocyclic ring has exhibited the higher chemical shift values [**18, 19**] compared to N-H bonded to a phenyl ring. This may be due to the possibility of charge transfer between the nitrogen atoms for resonance stabilization.

## APPLICATION

**Antibacterial analysis:** The antibacterial activity of synthesized compounds was evaluated against two Gram-positive bacterial strains (*B. subtilis* and *S. aureus*) and two Gram-negative bacterial strains (*E. coli* and *P. aeruginosa*) by disc diffusion method [**20**]. Brain Heart Infusion agar was used as medium and the samples were tested at 100 µg $mL^{-1}$ concentrations. Ciprofloxacin was used as reference standard drug and DMSO as a solvent control. The bacterial colonies were transferred to the plates and the inoculums were prepared by adjusting the turbidity to a McFarland 0.5 turbidity standard. The wells were prepared by pressing a heated hollow tube of diameter 5 mm on an inoculated agar plate. The compounds were tested with 100 µg $mL^{-1}$ concentration. 50 µL of each compound is applied to the respective wells and incubated for 18-24 h at 37ºC. The inhibition zone was measured in mm by holding the measuring device. The mean zone inhibition values are summarized in Table 1.

Among the 5-membered heterocyclic substitutions, thiazole derivatives have observed as potent compounds and among the functional groups, methoxy containing derivatives have shown significant antimicrobial activity. The thiazole sulfonamide derivative containing methoxy functional group (compound **3c**) has identified as very good antimicrobial agents. The unsubstituted, as well as chloro substituted compounds, were less active against the bacterial strains.

**Table 1**. The antibacterial and antifungal activity of compounds by disc diffusion method

| Comp. No. | $R_1$ | $R_2$ | Antibacterial activity (mm) | | | | Antifungal activity (mm) | |
|---|---|---|---|---|---|---|---|---|
| | | | *BS* | *SA* | *EC* | *PA* | *CA* | *AN* |
| **3a** | H | thiazol-2-yl | 7 | 11 | 12 | 8 | 6 | 7 |
| **3b** | Cl | thiazol-2-yl | 16 | 9 | 12 | 10 | **24** | **26** |
| **3c** | $OCH_3$ | thiazol-2-yl | **22** | **19** | **18** | **25** | 16 | 12 |
| **4a** | H | methyl-1,2-oxazol-3-yl | 9 | 11 | 10 | 8 | 11 | 10 |
| **4b** | Cl | methyl-1,2-oxazol-3-yl | 13 | 12 | 14 | 12 | 8 | 11 |
| **4c** | $OCH_3$ | methyl-1,2-oxazol-3-yl | 17 | 15 | 13 | 15 | 13 | 15 |
| **5a** | H | dimethyl-1,2-oxazol-5-yl | 10 | 10 | 8 | 9 | 7 | 7 |
| **5b** | Cl | dimethyl-1,2-oxazol-5-yl | 11 | 13 | 11 | 10 | 8 | 15 |
| **5c** | $OCH_3$ | dimethyl-1,2-oxazol-5-yl | 14 | 17 | 15 | 11 | 18 | 16 |
| Ciprofloxacin | -- | -- | 20 | 23 | 21 | 22 | NT | NT |
| Fluconazole | -- | -- | NT | NT | NT | NT | 23 | 23 |

**Values are mean (n=2). Ciprofloxacin (100 µg $mL^{-1}$) and Fluconazole (100 µg $mL^{-1}$) were used asa reference. Bold font indicates the considerable activity of compounds against the respective organisms. 'NT' indicates not tested.* ***BS****: B. subtilis,* ***SA****: S. aureus,* ***EC****: E. coli,* ***PA****: P. aeruginosa,* ***CA****: C. albicans, and* ***AN****: A. niger.*

**Antifungal analysis:** The Compounds were tested against two fungal species *C.albicans* and *A. niger* by disc diffusion method at 100 µg $mL^{-1}$ concentrations as described above. In this method, sabouraud agar was used as a medium instead of Brain heart infusion agar and fluconazole as a reference drug. The compounds were tested with 100 µg $mL^{-1}$ concentration and the mean zone inhibition values are summarized in table 1.

Thiazole and dimethyl oxazole derivatives were displayed as good antifungal agents. The *p*-chloro derivative containing thiazole moiety in compound **3b** has exhibited highest activity against both fungal strains. The compound with dimethyl oxazole derivative containing a *p*-methoxy group (**5c**) has considerable antifungal activity compared to other compounds. A graphical representation of the antimicrobial activity of tested compounds has shown in figure 1.

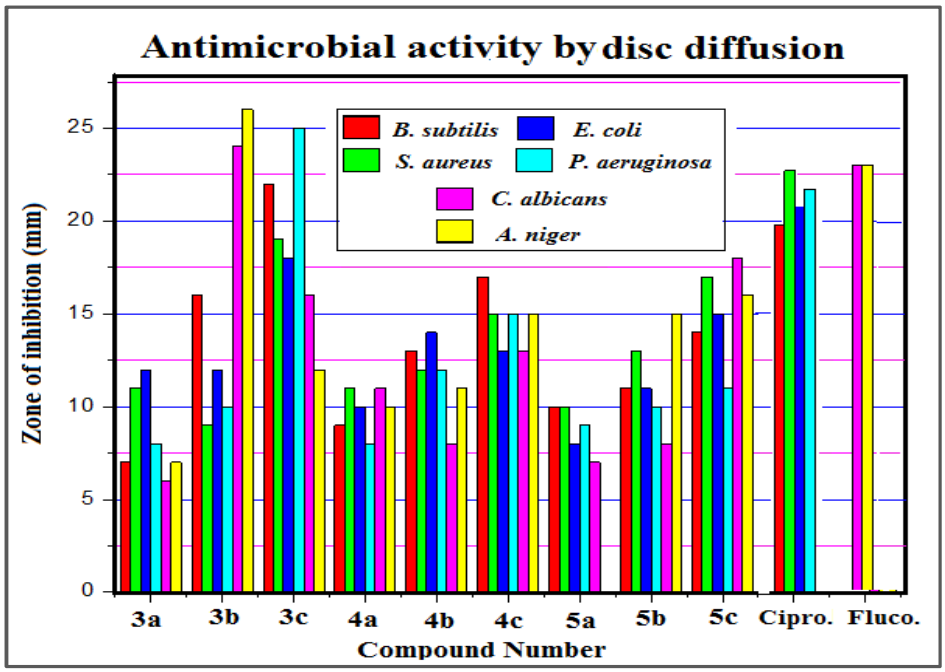



**Figure 1**.Graphical representation of the antimicrobial activity of tested compounds.

## CONCLUSION

A series of nine bis-sulfonamide derivatives were synthesized and characterized by different spectroscopic techniques. The compounds were evaluated for their *in vitro* antimicrobial studies. Among the different derivatives, compounds with thiazole heterocyclic ring have exhibited more toxicity compared to oxazole ring. Similarly, methoxy substituted phenyl ring has shown higher activity compared to chloro or unsubstituted rings. The thiazole ring compound with a *p*-methoxy group (**3c**) has shown the highest activity against the bacterial strains and thiazole ring with a *p*-chloro group (**3b**) was more toxic against the tested fungal strains.

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