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RESEARCH ARTICLE

SYNTHESIS, CHARACTERIZATION AND *IN VITRO* ANTIMICROBIAL ACTIVITY OF NOVEL 4,4′-BIS[3-CHLORO-4-ARYL-AZETIDIN-2-ONE-1-YL]DIPHENYL SULPHONES

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A novel series of 4,4′-bis[3-chloro-4-aryl-azetidin-2-one-1-yl]diphenyl sulphones 3(a-t) have been synthesized by appropriate synthetic route. Cyclocondensation of 4,4′-diaminodiphenylsulphone with various aromatic or heterocyclic aldehyde yield the schiff bases 2(a-t). These schiff's bases on condensation with chloroacetyl chloride in presence of triethylamine gave substituted 2-azetidinones 3(a-t). The structure of the newly synthesized compounds were confirmed by analytical and spectral (IR, ^{1}H-NMR and Mass) data. The entire test compounds (3a-t) were assayed *in vitro* for their antibacterial activity against two different strains of Gram-negative (*E. coli* and *P. aeruginosa*) and Gram-positive (*S. aureus* and *B. subtilis*) bacteria. The minimum inhibitory concentration (MIC) was determined for test compounds and for reference standards. The test compounds showed significant antibacterial activity against the microbial strains used, when tested *in vitro*.

Key words: 2-Azetidinone, Schiff base, Dapsone, Antibacterial activity.

INTRODUCTION

The synthesis of natural and heterocyclic compounds has always drawn the attention of chemist over the years mainly because of their important biological properties (Dahiya and Gautam, 2011). Particularly, the role of *β*-lactam which are endowed with unique structure and potent antibacterial activity. The 2-azetidinone (*β*-lactam) ring system is the common structural feature of a number of broad spectrum *β*-lactam antibiotics, including penicillins, cephalosporins, carbapenems, nocardicins, monobactams, clavulanic acid, sulbactams and tazobactams, which have been widely used as chemotherapeutic agents to treat bacterial infections and microbial diseases (Morin and Gorman, 1982; George, 1993; Delpiccolo *et al* 2003; Gootz, 1990; Maiti *et al* 2006; Singh, 2004; Risi *et al* 2001; Durckheimer *et al* 1985).

Most of the researches up to early 90s focused on synthesis of 2-azetidinones and study of their antibacterial property. In recent years, renewed interest has been focused on the synthesis and modification of *β*-lactam ring to obtain compounds with diverse pharmacological activities like cholesterol absorption inhibitory activity (Burnett *et al* 1994), human tryptase (Slusarchyk *et al* 2002), thrombin (Han *et al* 1995) and chymase inhibitory activity (Aoyama *et al* 2001), vasopressin V1a antagonist activity (Guillon *et al* 2007), antidiabetic (Goel *et al* 2004), anti-inflammatory (Kumar and Rajput, 2009), antiparkinsonian (Srivastava *et al* 1999) and anti-HIV activity (Sperka *et al* 2005). They are also found to be a potent inhibitor of serine protease, human leukocyte elastase and human cytomegalovirus protease enzyme (Vergely *et al* 1996; Knight *et al* 1992; Firestone *et al* 1990; Singh and Micetich, 2000) and are effective on central nervous system. These derivatives are also found to be moderately active against several types of cancer (Veinberg *et al* 1998). Recently, reports have been received which focus on the diverse pharmacological properties

associated with the monocyclic 2-azetidinone moiety (Mehta *et al* 2010).

Diphenylsulfone derivatives were also found to possess antibacterial activity (Elslager *et al* 1969; Wolf *et al* 2002). In addition, antibacterial (El-Gaby *et al* 2000), antifungal (El-Gaby *et al* 2002), insulin releasing (Maren, 1976) and carbonic anhydrase inhibitory (Supuran *et al* 1998) activities of sulfonamides were reported. The incorporation of diphenylsulfone moiety into various heterocyclic systems was found to increase their pharmacological activity.

Therefore, it was envisaged that chemical entities with dapsone and 2-azetidinone moieties would result in compounds of interesting biological activities. In view of these findings, we have attempted to incorporate these two biologically active components together to give a confined structure like the titled compounds for evaluating its antimicrobial activity. In this study, we have reported the synthesis of some new 2-azetidinone derivatives from dapsone and their antibacterial activity.

MATERIALS AND METHODS

General

Laboratory chemicals were supplied by Himedia chemicals, National chemical laboratory and Fischer Scientific Ltd. Melting points of the synthesized compounds were determined in open-glass capillaries using microprocessor-based melting point apparatus and were uncorrected. The purity of the compounds was checked by thin layer chromatography (TLC). Silica gel plates 0.20 mm, 60G, precoated sheets obtained from Merck, Darmstadt (Germany) were used for TLC. Developing solvent system of chloroform: acetone (9:1) was used and the spots were visualized by iodine vapour as visualizing agent.

IR spectra (KBr disc) were recorded on Shimadzu Perkin-Elmer 8201 PC, I.R. spectrometer, using KBr pellets in the range of 4000–400 cm^{-1}. ^{1}H-NMR spectra were scanned on Bruker DRX 300 NMR spectrometer at 300 MHz. All spectra were obtained in dimethyl sulphoxide and chemical shift values are reported as values in ppm relative to TMS ($\delta = 0$) as internal standard. Mass spectra were recorded on THERMO Finnigan LCQ Advantage max ion trap mass spectrometer. Elemental analyses of the newly synthesized compounds were performed on Carlo Erba 1108 analyzer. Elemental analyses of all the compounds were in agreement with the calculated values.

Chemistry

4,4′-Bis(substituted arylideneamino) diphenyl sulphones **2(a-t)** and 4,4′-bis[3-chloro-4-aryl-azetidin-2-one-1-yl]diphenyl sulphone. **3(a-t)** were prepared according to reported method (Staudinger, 1907; Singh, 2003).

*General procedure for the synthesis of 4,4'-Bis(substituted arylideneamino) diphenyl sulphones **2(a-t)***

To a solution of 4,4′diamino diphenyl sulphone (**1**) (0.01 mol) in 30 ml of ethanol:appropriate aldehydes (**a-t**) (0.025 mol) and 2-3 drops of concentrated sulphuric acid were added. The reaction mixture was refluxed for 6 h. The reaction mixture was cooled and poured onto crushed ice. The reaction was monitored by TLC on silica gel using chloroform:acetone (9:1). The separated solid was isolated, washed with water and recrystallized by suitable solvent to give title compounds (**Table 1**).

*4,4'-Bis(benzylideneamino)diphenyl sulphone (**2a**):*

Yellow crystals (dioxane), yield: 75%, m.p. 201-203°C; IR (KBr, cm^{-1}): 1612.4 (C=N), 1141.9 (SO_2, sym), 1242.6 (SO_2, asym), 699 (C-S-C); ^{1}H-NMR (DMSO) δ in ppm: 4.6 (s, 2H, 2×N=CH-Ar), 6.2-8.5 (m, 16H, 4×4 Ar-H); MS: *m/z* 424 (M^+), 347, 270, 256, 228, 200, 154, 108. Anal. Calcd. for $C_{26}H_{20}N_2O_2S$: C, 73.49; H, 4.71; N, 6.59; O, 7.53; S, 7.53. Found: C, 73.47; H, 4.69; N, 6.65; O, 7.51; S, 7.50.

*4,4'-Bis(4-methylbenzylideneamino)diphenyl sulphone (**2b**):*

Cream powder (dioxane), yield: 65%, m.p. 205-206°C; IR (KBr, cm^{-1}): 1598.9 (C=N), 1143.8 (SO_2, sym), 1244.3 (SO_2, asym), 711 (C-S-C); ^{1}H-NMR (DMSO) δ in ppm: 4.5 (s, 2H, 2×N=CH-Ar), 3.4 (s, 6H, 2×Ar-CH_3) 6.0-8.4 (m, 16H, 4×4 Ar-H); MS: *m/z* 452 (M^+), 437, 422, 348, 271, 257, 227, 201. Anal. Calcd. for $C_{28}H_{24}N_2O_2S$: C, 74.24; H, 5.30; N, 6.18; O, 7.07; S, 7.07. Found: C, 74.23; H, 5.28; N, 6.15; O, 7.05; S, 7.06.

*4,4'-Bis(2-chlorobenzylideneamino)diphenyl sulphone (**2c**):*

Yellow crystals (dioxane), yield: 62%, m.p. 195-196°C; IR (KBr, cm^{-1}): 1605.3 (C=N), 1140.9 (SO_2, sym), 1249.1 (SO_2, asym), 705.3 (C-S-C), 815.1 (C-Cl); ^{1}H-NMR (DMSO) δ in ppm: 4.3 (s, 2H, 2×N=CH-Ar), 6.3-8.7 (m, 16H, 4×4 Ar-H); MS: *m/z* 493 (M^+), 458, 423, 347, 269, 255, 228, 200. Anal. Calcd. for $C_{26}H_{18}Cl_2N_2O_2S$: C, 63.23; H, 3.64;

N, 5.67; O, 6.48; S, 6.48. Found: C, 63.21; H, 3.62; N, 5.64; O, 6.46; S, 6.47.

*4,4'-Bis(3-chlorobenzylideneamino)diphenyl sulphone (**2d**):*
Yellow crystals (dioxane), yield: 59%, m.p. 186-187°C; IR (KBr, cm^{-1}): 1598.5 (C=N), 1145.6 (SO_2, sym), 1251.2 (SO_2, asym), 710.3 (C-S-C), 814.9 (C-Cl); ^{1}H-NMR (DMSO) δ in ppm: 4.5 (s, 2H, 2×N=CH-Ar), 6.1-8.6 (m, 16H, 4×4 Ar-H); MS: *m/z* 493 (M^+), 459, 424, 347, 270, 256, 228, 200. Anal. Calcd. for $C_{26}H_{18}Cl_2N_2O_2S$: C, 63.23; H, 3.64; N, 5.67; O, 6.48; S, 6.48. Found: C, 63.20; H, 3.61; N, 5.65; O, 6.47; S, 6.46.

*4,4'-Bis(4-chlorobenzylideneamino)diphenyl sulphone (**2e**):*
Yellow crystals (dioxane), yield: 58%, m.p. 184-185°C; IR (KBr, cm^{-1}): 1608.5 (C=N), 1152.7 (SO_2, sym), 1253.8 (SO_2, asym), 712.3 (C-S-C), 820.2 (C-Cl); ^{1}H-NMR (DMSO) δ in ppm: 4.3 (s, 2H, 2×N=CH-Ar), 6.0-8.5 (m, 16H, 4×4 Ar-H); MS: *m/z* 493 (M^+), 457, 423, 348, 269, 254, 227, 201. Anal. Calcd. for $C_{26}H_{18}Cl_2N_2O_2S$: C, 63.23; H, 3.64; N, 5.67; O, 6.48; S, 6.48. Found: C, 63.21; H, 3.62; N, 5.65; O, 6.45; S, 6.45.

*4,4'-Bis(2-hydroxybenzylideneamino)diphenyl sulphone (**2f**):*
Orange crystals (dioxane), yield: 67%, m.p. 194-195°C; IR (KBr, cm^{-1}): 1610.3 (C=N), 1153.4 (SO_2, sym), 1249.8 (SO_2, asym), 721.3 (C-S-C), 3414.1 (O-H); ^{1}H-NMR (DMSO) δ in ppm: 4.3 (s, 2H, 2×N=CH-Ar), 5.2 (s, 2H, 2×Ar-OH), 6.2-8.7 (m, 16H, 4×4 Ar-H); MS: *m/z* 456 (M^+), 439, 422, 363, 346, 270, 255, 229, 201. Anal. Calcd. for $C_{26}H_{20}N_2O_4S$: C, 68.34; H, 4.38; N, 6.13; O, 14.01; S, 7.00. Found: C, 68.33; H, 4.37; N, 6.11; O, 14.00; S, 6.99.

*4,4'-Bis(3-hydroxybenzylideneamino)diphenyl sulphone (**2g**):*
Orange crystals (dioxane), yield: 63%, m.p. 190-191°C; IR (KBr, cm^{-1}): 1609.8 (C=N), 1146.2 (SO_2, sym), 1252.2 (SO_2, asym), 718.2 (C-S-C), 3417.3 (O-H); ^{1}H-NMR (DMSO) δ in ppm: 4.1 (s, 2H, 2×N=CH-Ar), 4.9 (s, 2H, 2×Ar-OH), 6.1-8.5 (m, 16H, 4×4 Ar-H); MS: *m/z* 456 (M^+), 438, 423, 362, 348, 271, 256, 227, 202. Anal. Calcd. for $C_{26}H_{20}N_2O_4S$: C, 68.34; H, 4.38; N, 6.13; O, 14.01; S, 7.00. Found: C, 68.32; H, 4.36; N, 6.10; O, 13.99; S, 6.98.

*4,4'-Bis(4-hydroxybenzylideneamino)diphenyl sulphone (**2h**):*
Orange crystals (dioxane), yield: 65%, m.p. 185-186°C; IR (KBr, cm^{-1}): 1608.5 (C=N), 1147.3 (SO_2, sym), 1253.4 (SO_2, asym), 720.1 (C-S-C), 3420.2 (O-H); ^{1}H-NMR (DMSO) δ in ppm: 4.3 (s, 2H, 2×N=CH-Ar), 5.1 (s, 2H, 2×Ar-OH), 6.3-8.7 (m, 16H, 4×4 Ar-H); MS: *m/z* 456 (M^+), 440, 424, 363, 346, 271, 254, 228, 200. Anal. Calcd. for $C_{26}H_{20}N_2O_4S$: C, 68.34; H, 4.38; N, 6.13; O, 14.01; S, 7.00. Found: C, 68.31; H, 4.35; N, 6.11; O, 13.98; S, 6.97.

*4,4'-Bis(2-nitrobenzylideneamino)diphenyl sulphone (**2i**):*
Yellow crystals (dioxane), yield: 74%, m.p. 213-214°C; IR (KBr, cm^{-1}): 1615.3 (C=N), 1142.2 (SO_2, sym), 1255.2 (SO_2, asym), 1344.1 (NO_2, sym), 1514.2 (NO_2, asym), 710.9 (C-S-C); ^{1}H-NMR (DMSO) δ in ppm: 4.0 (s, 2H, 2×N=CH-Ar), 6.1-8.5 (m, 16H, 4×4 Ar-H); MS: *m/z* 514 (M^+), 468, 422, 392 361, 347, 270, 255, 226, 201. Anal. Calcd. for $C_{26}H_{18}N_4O_6S$: C, 60.64; H, 3.49; N, 10.88; O, 18.65; S, 6.21. Found: C, 60.62; H, 3.46; N, 10.86; O, 18.62; S, 6.19.

*4,4'-Bis(3-nitrobenzylideneamino)diphenyl sulphone (**2j**):*
Yellow crystals (dioxane), yield: 72%, m.p. 218-219°C; IR (KBr, cm^{-1}): 1613.4 (C=N), 1141.5 (SO_2, sym), 1254.4 (SO_2, asym), 1346.3 (NO_2, sym), 1512.6 (NO_2, asym), 718.2 (C-S-C); ^{1}H-NMR (DMSO) δ in ppm: 4.3 (s, 2H, 2×N=CH-Ar), 6.3-8.7 (m, 16H, 4×4 Ar-H); MS: *m/z* 514 (M^+), 467, 421, 393 362, 349, 271, 256, 228, 200. Anal. Calcd. for $C_{26}H_{18}N_4O_6S$: C, 60.64; H, 3.49; N, 10.88; O, 18.65; S, 6.21. Found: C, 60.63; H, 3.47; N, 10.85; O, 18.64; S, 6.20.

*4,4'-Bis(4-nitrobenzylideneamino)diphenyl sulphone (**2k**):*
Yellow crystals (dioxane), yield: 76%, m.p. 215-216°C; IR (KBr, cm^{-1}): 1617.8 (C=N), 1148.2 (SO_2, symmetry), 1256.2 (SO_2, asymmetry), 1349.4 (NO_2, symmetry), 1510.9 (NO_2, asymmetry), 721.1 (C-S-C); ^{1}H-NMR (DMSO) δ in ppm: 4.1 (s, 2H, 2×N=CH-Ar), 6.0-8.5 (m, 16H, 4×4 Ar-H); MS: *m/z* 514 (M^+), 467, 421, 393 362, 349, 271, 256, 228, 200. Anal. Calcd. For $C_{26}H_{18}N_4O_6S$: C, 60.64; H, 3.49; N, 10.88; O, 18.65; S, 6.21. Found: C, 60.62; H, 3.48; N, 10.86; O, 18.63; S, 6.19.

*4,4'-Bis(3-bromobenzylideneamino) diphenyl sulphone (**2l**):*
Yellow powder (dioxane), yield: 64%, m.p. 208-209°C; IR (KBr, cm^{-1}): 1610.3 (C=N), 1142.3 (SO_2,

sym), 1244.2 (SO_2, asym), 713.4 (C-S-C), 632.2 (C-Br); ^{1}H-NMR (DMSO) δ in ppm: 4.2 (s, 2H, 2×N=CH-Ar), 6.1-8.5 (m, 16H, 4×4 Ar-H); MS: *m/z* 582 (M^+), 503, 424, 348, 268, 256, 227, 202. Anal. Calcd. For $C_{26}H_{18}Br_2N_2O_2S$: C, 53.58; H, 3.09; N, 4.80; O, 5.49; S, 5.49. Found: C, 53.56; H, 3.07; N, 4.78; O, 5.48; S, 5.47.

*4,4'-Bis(4-methoxybenzylideneamino) diphenyl sulphone (**2m**):*
yellow powder (dioxane), yield: 69%, m.p. 176-177°C; IR (KBr, cm^{-1}): 1613.4 (C=N), 1149.4 (SO_2, sym), 1250.3 (SO_2, asym), 726.2 (C-S-C), 1032.4 (C-O); ^{1}H-NMR (DMSO) δ in ppm: 4.3 (s, 2H, 2×N=CH-Ar), 3.6 (s, 6H, 2×Ar-OCH_3) 6.4-8.8 (m, 16H, 4×4 Ar-H); MS: *m/z* 484 (M^+), 469,454, 422, 347, 269, 254, 228, 200. Anal. Calcd. for $C_{28}H_{24}N_2O_4S$: C, 69.34; H, 4.95; N, 5.77; O, 13.20; S, 6.60. Found: C, 69.32; H, 4.92; N, 5.75; O, 13.18; S, 6.58.

*4,4'-Bis(3,4-di methoxybenzylideneamino) diphenyl sulphone (**2n**)*
yellow powder (dioxane), yield: 62%, m.p. 181-182°C; IR (KBr, cm^{-1}): 1617.1 (C=N), 1144.6 (SO_2, sym), 1242.8 (SO_2, asym), 728.1 (C-S-C), 1036.3 (C-O); ^{1}H-NMR (DMSO) δ in ppm: 4.2 (s, 2H, 2×N=CH-Ar), 3.4 (s, 6H, 2×Ar-OCH_3) 6.3-8.7 (m, 16H, 4×4 Ar-H); MS: *m/z* 544 (M^+), 529, 514, 499, 484, 451, 201. Anal. Calcd. for $C_{30}H_{28}N_2O_6S$: C, 66.10; H, 5.14; N, 5.14; O, 17.62; S, 5.87. Found: C, 66.08; H, 5.12; N, 5.13; O, 17.60; S, 5.85.

*4,4'-Bis(3,4,5-trimethoxybenzylideneamino) diphenyl sulphone (**2o**):*
yellow powder (dioxane), yield: 55%, m.p. 184-185°C; IR (KBr, cm^{-1}): 1614.9 (C=N), 1147.2 (SO_2, sym), 1251.2 (SO_2, asym), 723.6 (C-S-C), 1040.2 (C-O); ^{1}H-NMR (DMSO) δ in ppm: 4.4 (s, 2H, 2×N=CH-Ar), 3.6 (s, 6H, 2×Ar-OCH_3) 6.1-8.5 (m, 16H, 4×4 Ar-H); MS: *m/z* 604 (M^+), 589, 573, 558, 542, 511, 480, 449, 418, 200. Anal. Calcd. for $C_{32}H_{32}N_2O_8S$: C, 63.50; H, 5.29; N, 4.63; O, 21.16; S, 5.29. Found: C, 63.48; H, 5.26; N, 4.61; O, 21.15; S, 5.27.

*4,4'-Bis(3-methoxy-4-hydroxybenzylideneamino) diphenyl sulphone (**2p**):*
yellow powder (dioxane), yield: 57%, m.p. 191-192°C; IR (KBr, cm^{-1}): 1610.7 (C=N), 1149.3 (SO_2, sym), 1255.3 (SO_2, asym), 729.5 (C-S-C), 3418.1 (O-H), 1043.2 (C-O); ^{1}H-NMR (DMSO) δ in ppm: 4.1 (s, 2H, 2×N=CH-Ar), 3.3 (s, 6H, 2×Ar-OCH_3), 4.9 (s, 2H, 2×Ar-OH), 6.3-8.6 (m, 16H, 4×4 Ar-H); MS: *m/z* 516(M^+), 499, 482, 454, 437, 420, 201. Anal. Calcd. for $C_{28}H_{24}N_2O_6S$: C, 65.04; H, 4.64; N, 5.42; O, 18.58; S, 6.19. Found: C, 65.02; H, 4.62; N, 5.40; O, 18.57; S, 5.38.

*4,4'-Bis(4-dimethylaminobenzylideneamino) diphenyl sulphone (**2q**):*
yellow powder (dioxane), yield: 61%, m.p. 169-170°C; IR (KBr, cm^{-1}): 1613.2 (C=N), 1258.2 (SO_2, asym), 1151.4 (SO_2, sym), 730.5 (C-S-C), 1340.8 (C-N); ^{1}H-NMR (DMSO) δ: 4.3 (s, 2H, 2×N=CH-Ar), 3.2 (s, 6H, 2×Ar-NMe_2), 6.0-8.5 (m, 16H, 4×4 Ar-H); MS: *m/z* 510(M^+), 480, 450, 466, 436, 422, 435, 200. Anal. Calcd. for $C_{30}H_{30}N_4O_2S$: C, 70.49; H, 5.87; N, 10.96; O, 6.26; S, 6.26. Found: C, 70.47; H, 5.85; N, 10.94; O, 6.24; S, 6.23.

*4,4'-Bis(3,5-dibromo-2-hydroxybenzylidene amino)diphenyl sulphone (**2r**):*
yellow powder (dioxane), yield: 58%, m.p. 180-181°C; IR (KBr, cm^{-1}): 1613.3 (C=N), 1146.2 (SO_2, sym), 1246.4 (SO_2, asym), 716.8 (C-S-C), 636.5 (C-Br), 3420.2 (O-H); ^{1}H-NMR (DMSO) δ in ppm: 4.3 (s, 2H, 2×N=CH-Ar), 5.0 (s, 2H, 2×Ar-OH), 6.3-8.7 (m, 16H, 4×4 Ar-H); MS: *m/z* 772 (M^+), 755, 738, 693, 659, 614, 535, 580, 501, 456, 422, 200. Anal. Calcd. for $C_{26}H_{16}Br_4N_2O_4S$: C, 40.40; H, 2.07; N, 3.62; O, 8.28; S, 4.14. Found: C, 40.38; H, 2.05; N, 3.60; O, 8.26; S, 4.12.

*4,4'-Bis(2-furfuralideneamino)diphenyl sulphone (**2s**):*
yellow crystals (dioxane), yield: 49%, m.p. 220-221°C; IR (KBr, cm^{-1}): 1614.6 (C=N), 1142.8 (SO_2, sym), 1249.1 (SO_2, asym), 705.9 (C-S-C); ^{1}H-NMR (DMSO) δ in ppm: 4.5 (s, 2H, 2×N=CH-Ar), 6.2-8.5 (m, 16H, 4×4 Ar-H); MS: *m/z* 404 (M^+), 336, 268, 257, 230, 200, 155, 109. Anal. Calcd. for $C_{22}H_{16}N_2O_4S$: C, 65.27; H, 3.95; N, 6.92; O, 15.82; S, 7.91. Found: C, 65.25; H, 3.93; N, 6.90; O, 15.80; S, 7.89.

*4,4'-Bis(2-thienylideneamino)diphenyl sulphone (**2t**):*
Brown crystals (dioxane), yield: 45%, m.p. 195-196°C; IR (KBr, cm^{-1}): 1618.2 (C=N), 1144.5 (SO_2, sym), 1252.2 (SO_2, asym), 710.2 (C-S-C); ^{1}H-NMR (DMSO) δ in ppm: 4.3 (s, 2H, 2×N=CH-Ar), 6.4-8.9 (m, 16H, 4×4 Ar-H); MS: *m/z* 436 (M^+), 352, 270, 258, 231, 201, 151, 108. Anal. Calcd. for $C_{22}H_{16}N_2O_2S_3$: C, 60.47; H, 3.66; N, 6.41; O, 7.33; S, 21.99. Found: C, 60.45; H, 3.64; N, 6.39; O, 7.30; S, 21.97.

*General procedure for the synthesis of 4,4'-bis[3-chloro-4-aryl-azetidin-2-one-1-yl]diphenyl sulphone **3(a-t)***

To mixture of appropriate shiff's bases **2(a-t)** (0.01 mol) and triethylamine (0.025 mol) in dry 1,4-dioxane, chloracetyl chloride (0.025 mol) was added drop wise at 5-10°C. The mixture was stirred for 6 h. and left at RT for three days. The separated solid was filtered, washed with water and recrystallized from suitable solvent to give title compounds (**Table 1**).

*4,4'-Bis[3-chloro-4-phenyl-azetidin-2-one-1-yl] diphenyl sulphone (**3a**):*

Cream crystals (ethanol), yield: 86%, m.p. 169-170°C; IR (KBr, cm^{-1}): 1680.4 (C=O), 1146.2 (SO_2, symmetry), 1258 (SO_2, asymmetry), 695 (C-S-C); ^{1}H-NMR (DMSO) δ in ppm: 4.3-4.5 (d, 2H, 2×CH-Cl of Azetidinone), 2.8-2.9 (d, 2H, 2×CH-Ar of Azetidinone), 7.2-8.5 (m, 16H, 4×4 Ar-H); MS: *m/z* 577 (M^+), 542, 507, 500, 423, 408, 365, 353, 299, 154, 108. Anal. Calcd. for $C_{30}H_{22}Cl_2N_2O_4S$: C, 62.34; H, 3.80; N, 4.84; O, 11.08; S, 5.54. Found: C, 62.32; H, 3.78; N, 4.83; O, 11.05; S, 5.52.

*4,4'-Bis[3-chloro-4-(4-methylphenyl)-azetidin-2-one-1-yl]diphenyl sulphone (**3b**):*

Cream powder (ethanol), yield: 77%, m.p. 173-174°C; IR (KBr, cm^{-1}): 1692.6 (C=O), 1143.3 (SO_2, sym), 1304.4 (SO_2, asym), 720.3 (C-S-C), 1593 (C=C); ^{1}H-NMR (DMSO) δ in ppm: 4.4-4.7 (d, 2H, 2×CH-Cl of Azetidinone), 3.0-3.1 (d, 2H, 2×CH-Ar of Azetidinone), 2.4-2.6 (s, 6H, 2×Ar-CH_3) 7.5-8.3 (m, 16H, 4×4 Ar-H); MS: *m/z* 605 (M^+), 590, 575, 570, 535, 507, 500, 423, 408, 365, 353, 299, 154, 108. Anal. Calcd. for $C_{32}H_{26}Cl_2N_2O_4S$: C, 63.41; H, 4.29; N, 4.62; O, 10.56; S, 5.28. Found: C, 63.39; H, 4.27; N, 4.60; O, 10.53; S, 5.26.

*4,4'-Bis[3-chloro-4-(2-chlorophenyl)-azetidin-2-one-1-yl]diphenyl sulphone (**3c**):*

Off white crystals (ethanol), yield: 83%, m.p. 186-187°C; IR (KBr, cm^{-1}): 1680.2 (C=O), 1147.8 (SO_2, symmetry), 1303.7 (SO_2, asymmetry), 744.0 (C-S-C), 833.2 (C-Cl); ^{1}H-NMR (DMSO) δ in ppm: 4.2-4.5 [2H, d, 2×CH-Cl of Azetidinone], 2.7-3.0 [2H, d, 2×CH-Ar of Azetidinone], 7.5-8.5 [16H, m, 4×4Ar-H]; MS: *m/z* 646.5 (M^+), 610, 576, 541, 475, 410, 302, 258, 152, 108. Anal. Calcd. for $C_{30}H_{20}Cl_4N_2O_4S$: C, 55.69; H, 3.09; N, 4.33; O, 9.90; S, 4.95. Found: C, 55.67; H, 3.07; N, 4.30; O, 9.88; S, 4.93.

*4, 4'-Bis[3-chloro-4-(3-chlorophenyl)-azetidin-2-one-1-yl]diphenyl sulphone (**3d**):*

Off white crystals (ethanol), yield: 66%, m.p. 210-212°C; IR (KBr, cm^{-1}): 1683.2 (C=O), 1147.2 (SO_2, symmetry), 1256.7 (SO_2, asymmetry), 695.4 (C-S-C), 830.2 (C-Cl); ^{1}H-NMR (DMSO) δ in ppm: 4.0-4.3 [2H, d, 2×CH-Cl of Azetidinone], 2.5-2.7 [2H, d, 2×CH-Ar of Azetidinone], 7.2-8.1 [16H, m, 4×4Ar-H]; MS: *m/z* 646 (M^+), 608, 575, 540, 473, 408, 300, 257, 151, 106. Anal. Calcd. for $C_{30}H_{20}Cl_4N_2O_4S$: C, 55.69; H, 3.09; N, 4.33; O, 9.90; S, 4.95. Found: C, 55.66; H, 3.08; N, 4.31; O, 9.89; S, 4.92.

*4,4'-Bis[3-chloro-4-(4-chlorophenyl)-azetidin-2-one-1-yl]diphenyl sulphone (**3e**):*

Off white crystals (ethanol), yield: 72%, m.p. 214-215°C; IR (KBr, cm^{-1}): 1693.3 (C=O), 1148.4 (SO_2, symmetry), 1260.5 (SO_2, asymmetry), 694.6 (C-S-C), 836.0 (C-Cl); ^{1}H-NMR (DMSO) δ in ppm: 4.3-4.5 [2H, d, 2×CH-Cl of Azetidinone], 2.4-2.6 [2H, d, 2×CH-Ar of Azetidinone], 7.3-8.3 [16H, m, 4×4Ar-H]; MS: *m/z* 646 (M^+), 609, 574, 538, 472, 409, 301, 256, 150, 107. Anal. Calcd. for $C_{30}H_{20}Cl_4N_2O_4S$: C, 55.69; H, 3.09; N, 4.33; O, 9.90; S, 4.95. Found: C, 55.68; H, 3.07; N, 4.32; O, 9.87; S, 4.92.

*4,4'-Bis[3-chloro-4-(2-hydroxyphenyl)-azetidin-2-one-1-yl]diphenyl sulphone (**3f**):*

Cream crystals (ethanol), yield: 78%, m.p. 156-157°C; IR (KBr, cm^{-1}): 1689.8 (C=O), 1151.4 (SO_2, symmetry), 1259.5 (SO_2, asymmetry), 696.2 (C-S-C), 3414.1 (O-H); ^{1}H-NMR (DMSO) δ in ppm: 4.5-4.6 [2H, d, 2×CH-Cl of Azetidinone], 3.4-3.6 [2H, d, 2×CH-Ar of Azetidinone], 4.0 (s, 2H, 2×Ar-OH), 7.3-8.3 [16H, m, 4×4Ar-H]; MS: *m/z* 609 (M^+), 592, 575, 539, 515, 498, 421, 386, 351, 256, 150, 107. Anal. Calcd. for $C_{30}H_{22}Cl_2N_2O_6S$: C, 59.06; H, 3.60; N, 4.59; O, 15.75; S, 5.25. Found: C, 59.03; H, 3.58; N, 4.56; O, 15.73; S, 5.22.

*4,4'-Bis[3-chloro-4-(3-hydroxyphenyl)-azetidin-2-one-1-yl]diphenyl sulphone (**3g**):*

Cream crystals (ethanol), yield: 67%, m.p. 189-190°C; IR (KBr, cm^{-1}): 1683.7 (C=O), 1154.1 (SO_2, symmetry), 1260.4 (SO_2, asymmetry), 3416.1 (O-H), 693.8 (C-S-C); ^{1}H-NMR (DMSO) δ in ppm: 4.3-4.4 [2H, d, 2×CH-Cl of Azetidinone], 3.2-3.4 [2H, d, 2×CH-Ar of Azetidinone], 3.9 (s, 2H, 2×Ar-OH), 7.0-8.1 [16H, m, 4×4Ar-H]; MS: *m/z* 609 (M^+), 591, 573, 538, 514, 496, 420, 384, 350, 257, 152, 107. Anal. Calcd. for $C_{30}H_{22}Cl_2N_2O_6S$: C, 59.06; H, 3.60; N, 4.59; O, 15.75; S, 5.25. Found: C, 59.04; H, 3.57; N, 4.57; O, 15.74; S, 5.23.

*4,4'-Bis[3-chloro-4-(4-hydroxyphenyl)-azetidin-2-one-1-yl]diphenyl sulphone (**3h**):*
Cream crystals (ethanol), yield: 84%, m.p. 165-166°C; IR (KBr, cm^{-1}): 1685.2 (C=O), 1144.4 (SO_2, symmetry), 1259.3 (SO_2, asymmetry), 3417 (O-H), 699.2 (C-S-C); ^{1}H-NMR (DMSO) δ in ppm: 4.2-4.4 [2H, d, 2×CH-Cl of Azetidinone], 3.1-3.2 [2H, d, 2×CH-Ar of Azetidinone], 3.8 (s, 2H, 2×Ar-OH), 6.8-8.0 [16H, m, 4×4Ar-H]; MS: *m/z* 609 (M^+), 590, 572, 538, 513, 495, 419, 384, 349, 256, 151, 108. Anal. Calcd. for $C_{30}H_{22}Cl_2N_2O_6S$: C, 59.06; H, 3.60; N, 4.59; O, 15.75; S, 5.25. Found: C, 59.05; H, 3.58; N, 4.58; O, 15.73; S, 5.23.

*4,4'-Bis[3-chloro-4-(2-nitrophenyl)-azetidin-2-one-1-yl]diphenyl sulphone (**3i**):*
Yellow crystals (ethanol), yield: 79%, m.p. 178-179°C; IR (KBr, cm^{-1}): 1690.3 (C=O), 1147.2 (SO_2, symmetry), 1348.6 (SO_2, asymmetry), 1343.5 (NO_2, symmetry), 1513.2 (NO_2, asymmetry), 721.4 (C-S-C), 1589.9 (C=C); ^{1}H-NMR (DMSO) δ in ppm: 4.2-4.4 [2H, d, 2×CH-Cl of Azetidinone], 2.5-2.7 [2H, d, 2×CH-Ar of Azetidinone], 7.1-8.0 [16H, m, 4×4Ar-H]; MS: *m/z* 667 (M^+), 574, 501, 405, 409, 299, 241, 153, 106. Anal. Calcd. for $C_{30}H_{20}Cl_2N_4O_8S$: C, 53.93; H, 2.99; N, 8.38; O, 19.17; S, 4.79. Found: C, 53.91; H, 2.97; N, 8.36; O, 19.15; S, 4.76.

*4,4'-Bis[3-chloro-4-(3-nitrophenyl)-azetidin-2-one-1-yl]diphenyl sulphone (**3j**):*
Yellow crystals (ethanol), yield: 78%, m.p. 195-196°C; IR (KBr, cm^{-1}): 1682.3 (C=O), 1149.4 (SO_2, symmetry), 1343.5 (SO_2, asymmetry), 1343.2 (NO_2, symmetry), 1517.3 (NO_2, Asymmetry), 724.5 (C-S-C), 1589.3 (C=C); ^{1}H-NMR (DMSO) δ in ppm: 4.3-4.5 [2H, d, 2×CH-Cl of Azetidinone], 2.6-2.8 [2H, d, 2×CH-Ar of Azetidinone], 7.3-8.3 [16H, m, 4×4Ar-H]; MS: *m/z* 667 (M^+), 575, 499, 406, 298, 240, 154, 105. Anal. Calcd. for $C_{30}H_{20}Cl_2N_4O_8S$: C, 53.93; H, 2.99; N, 8.38; O, 19.17; S, 4.79. Found: C, 53.90; H, 2.96; N, 8.35; O, 19.15; S, 4.77.

*4,4'-Bis[3-chloro-4-(4-nitrophenyl)-azetidin-2-one-1-yl]diphenyl sulphone (**3k**):*
Yellow crystals (ethanol), yield: 82%, m.p. 201-202°C; IR (KBr, cm^{-1}): 1694.3 (C=O), 1142.6 (SO_2, symmetry), 1344.1 (SO_2, asymmetry), 1345.3 (NO_2, symmetry), 1522.3 (NO_2, Asymmetry), 722.9 (C-S-C), 1593.0 (C=C); ^{1}H-NMR (DMSO) δ in ppm: 4.1-4.3 [2H, d, 2×CH-Cl of Azetidinone], 2.4-2.6 [2H, d, 2×CH-Ar of Azetidinone], 7.4-8.6 [16H, m, 4×4Ar-H]; MS: *m/z* 667.5 (M^+), 576, 500, 408, 299, 242, 155, 108. Anal. Calcd. for $C_{30}H_{20}Cl_2N_4O_8S$: C, 53.93; H, 2.99; N, 8.38; O, 19.17; S, 4.79. Found: C, 53.92; H, 2.96; N, 8.35; O, 19.14; S, 4.77.

*4,4'-Bis[3-chloro-4-(3-bromophenyl)-azetidin-2-one-1-yl]diphenyl sulphone (**3l**):*
Yellow powder (ethanol), yield: 63%, m.p. 206-207°C; IR (KBr, cm^{-1}): 1692.6 (C=O), 1141.9 (SO_2, symmetry), 1320.8 (SO_2, asymmetry), 725.3 (C-S-C), 621.3 (C-Br); ^{1}H-NMR (DMSO) δ in ppm: 4.6-4.7 [2H, d, 2×CH-Cl of Azetidinone], 3.2-3.3 [2H, d, 2×CH-Ar of Azetidinone], 7.5-7.7 [16H, m, 4×4Ar-H]; MS: *m/z* 735 (M^+), 700, 665, 655, 575, 540, 501, 410, 300, 241, 156, 109. Anal. Calcd. for $C_{30}H_{20}Br_2Cl_2N_2O_4S$: C, 48.96; H, 2.72; N, 3.80; O, 8.70; S, 4.35. Found: C, 48.94; H, 2.70; N, 3.78; O, 8.68; S, 4.33.

*4,4'-Bis[3-chloro-4-(4-methoxyphenyl)-azetidin-2-one-1-yl]diphenyl sulphone (**3m**):*
Cream powder (ethanol), yield: 79%, m.p. 248-249°C; IR (KBr, cm^{-1}): 1692.8 (C=O), 1155.2 (SO_2, symmetry), 1319.3 (SO_2, asymmetry), 720.4 (C-S-C), 1038.5 (C-O); ^{1}H-NMR (DMSO) δ in ppm: 4.2-4.3 [2H, d, 2×CH-Cl of Azetidinone], 2.4-2.6 [2H, d, 2×CH-Ar of Azetidinone], 3.9 (s, 6H, 2×Ar-OCH_3), 7.5-8.4 [16H, m, 4×4Ar-H]; MS: *m/z* 637.5 (M^+), 622, 607, 575, 567, 541, 299, 155, 107. Anal. Calcd. for $C_{32}H_{26}Cl_2N_2O_6S$: C, 60.23; H, 4.07; N, 4.39; O, 15.05; S, 5.01. Found: C, 60.21; H, 4.05; N, 4.37; O, 15.03; S, 5.00.

*4,4'-Bis[3-chloro-4-(3,4-dimethoxyphenyl)-azetidin-2-one-1-yl]diphenyl sulphone (**3n**):*
Cream powder (ethanol), yield: 82%, m.p. 211-212°C; IR (KBr, cm^{-1}): 1688.7 (C=O), 1151.3 (SO_2, symmetry), 1297.8 (SO_2, asymmetry), 717.2 (C-S-C), 1036.3 (C-O); ^{1}H-NMR (DMSO) δ in ppm: 4.5-4.6 [2H, d, 2×CH-Cl of Azetidinone], 2.9-3.1 [2H, d, 2×CH-Ar of Azetidinone], 4.1 (s, 6H, 2×Ar-OCH_3), 7.6-8.4 [16H, m, 4×4Ar-H]; MS: *m/z* 697.5 (M^+), 682, 666, 651, 635, 604, 573, 540, 301, 108. Anal. Calcd. for $C_{34}H_{30}Cl_2N_2O_8S$: C, 58.48; H, 4.30; N, 4.01; O, 18.34; S, 4.58. Found: C, 58.46; H, 4.27; N, 3.99; O, 18.32; S, 4.56.

*4,4'-Bis[3-chloro-4-(3,4,5-trimethoxyphenyl)-azetidin-2-one-1-yl]diphenyl sulphone (**3o**):*
Yellow powder (ethanol), yield: 65%, m.p. 217-218°C; IR (KBr, cm^{-1}): 1691.4 (C=O), 1152.3 (SO_2, symmetry), 1293.8 (SO_2, asymmetry), 719.9 (C-S-C), 1042.4 (C-O); ^{1}H-NMR (DMSO) δ in ppm: 4.4-4.6 [2H, d, 2×CH-Cl of Azetidinone], 2.5-2.7 [2H, d, 2×CH-Ar of Azetidinone], 4.2 (s, 6H, 2×Ar-OCH_3), 7.6-8.5 [16H, m, 4×4Ar-H]; MS: *m/z* 757.6

(M^+), 726, 695, 664, 633, 602, 571, 542, 300, 107. Anal. Calcd. for $C_{36}H_{34}Cl_2N_2O_{10}S$: C, 57.01; H, 4.48; N, 3.69; O, 21.11; S, 4.22. Found: C, 56.99; H, 4.46; N, 3.67; O, 21.09; S, 4.20.

*4,4'-Bis[3-chloro-4-(3-methoxy-4-hydroxyphenyl)-azetidin-2-one-1-yl]diphenyl sulphone (**3p**):*
Yellow powder (ethanol), yield: 58%, m.p. 182-183°C; IR (KBr, cm^{-1}): 1694.2 (C=O), 1153.5 (SO_2, symmetry), 1305.3 (SO_2, asymmetry), 728.3 (C-S-C), 1040.2 (C-O), 3423.1 (O-H); ^{1}H-NMR (DMSO) δ in ppm: 4.4-4.5 [2H, d, 2×CH-Cl of Azetidinone], 3.1-3.2 [2H, d, 2×CH-Ar of Azetidinone], 3.8 (s, 2H, 2×Ar-OH), 4.1 (s, 6H, 2×Ar-OCH_3), 7.4-8.3 [16H, m, 4×4Ar-H]; MS: *m/z* 669.5 (M^+), 652, 635, 619, 604, 574, 541, 299, 107. Anal. Calcd. for $C_{32}H_{26}Cl_2N_2O_8S$: C, 57.35; H, 3.88; N, 4.18; O, 19.11; S, 4.77. Found: C, 57.33; H, 3.86; N, 4.16; O, 19.09; S, 4.75.

*4,4'-Bis[3-chloro-4-(4-dimethylaminophenyl)-azetidin-2-one-1-yl]diphenyl sulphone (**3q**):*
Yellow powder (ethanol), yield: 74%, m.p. 195-196°C; IR (KBr, cm^{-1}): 1697.3 (C=O), 1152.7 (SO_2, sym), 1308.6 (SO_2, asym), 722.5 (C-S-C), 1346.5 (C-N); ^{1}H-NMR (DMSO) δ in ppm: 4.4-4.5 [2H, d, 2×CH-Cl of Azetidinone], 3.5-3.6 [2H, d, 2×CH-Ar of Azetidinone], 3.0 (s, 6H, 2×Ar-$N(CH_3)_2$), 6.4-8.2 (m, 16H, 4×4 Ar-H); MS: *m/z* 663.6 (M^+), 648, 633, 618, 603, 589, 575, 542, 300, 108. Anal. Calcd. for $C_{34}H_{32}Cl_2N_4O_4S$: C, 61.48; H, 4.82; N, 8.43; O, 9.64; S, 4.82. Found: C, 61.46; H, 4.80; N, 8.41; O, 9.62; S, 4.80.

*4,4'-Bis[3-chloro-4-(3,5-dibromo-2-hydroxy phenyl)-azetidin-2-one-1-yl]diphenyl sulphone (**3r**):*
Yellow powder (ethanol), yield: 73%, m.p. 214-215°C; IR (KBr, cm^{-1}): 1694.4 (C=O), 1156.2 (SO_2, symmetry), 1312.5 (SO_2, asymmetry), 723.2 (C-S-C), 3425.0 (O-H), 622.3 (C-Br); ^{1}H-NMR (DMSO) δ in ppm: 4.4-4.6 [2H, d, 2×CH-Cl of Azetidinone], 3.2-3.3 [2H, d, 2×CH-Ar of Azetidinone], 4.0 (s, 2H, 2×Ar-OH), 7.5-7.7 [16H, m, 4×4Ar-H]; MS: *m/z* 925 (M^+), 908, 891, 811, 731, 651, 571, 541, 299, 107. Anal. Calcd. for $C_{30}H_{18}Br_4Cl_2N_2O_6S$: C, 38.91; H, 1.94; N, 3.02; O, 10.37; S, 3.45. Found: C, 38.89; H, 1.92; N, 3.00; O, 10.35; S, 3.42.

*4,4'-Bis[3-chloro-4-(2-furfuralidene)-azetidin-2-one-1-yl]diphenyl sulphone (**3s**):*
Brown crystals (ethanol), yield: 57%, m.p. 205206°C; IR (KBr, cm^{-1}): 1689.7 (C=O), 1143.6 (SO_2, symmetry), 1315.3 (SO_2, asymmetry), 723.5 (C-S-C), 1592.7 (C=C); ^{1}H-NMR (DMSO) δ in ppm: 4.3-4.5 [2H, d, 2×CH-Cl of Azetidinone], 2.8-3.0 [2H, d, 2×CH-Ar of Azetidinone], 6.5-7.1 [16H, m, 4×4Ar-H]; MS: *m/z* 557.4 (M^+), 489, 421, 408, 300, 241, 156, 138, 109. Anal. Calcd. for $C_{26}H_{18}Cl_2N_2O_6S$: C, 55.97; H, 3.22; N, 5.02; O, 17.22; S, 5.74. Found: C, 55.95; H, 3.20; N, 5.00; O, 17.20; S, 5.72.

*4,4'-Bis[3-chloro-4-(2-thynalidene)-azetidin-2-one-1-yl]diphenyl sulphone (**3t**):*
Brown crystals (ethanol), yield: 56%, m.p. 189-190°C; IR (KBr, cm^{-1}): 1695.2 (C=O), 1148.4 (SO_2, sym), 1291.9 (SO_2, asym), 718.3 (C-S-C), 1596.3 (C=C); ^{1}H-NMR (DMSO) δ in ppm: 4.2-4.4 [2H, d, 2×CH-Cl of Azetidinone], 2.6-2.8 [2H, d, 2×CH-Ar of Azetidinone], 6.4-7.1 [16H, m, 4×4Ar-H]; MS: *m/z* 589.5 (M^+), 505, 422, 409, 299, 240, 155, 137, 108. Anal. Calcd. for $C_{26}H_{18}Cl_2N_2O_4S_3$: C, 52.92; H, 3.05; N, 4.74; O, 10.85; S, 16.28. Found: C, 52.90; H, 3.02; N, 4.72; O, 10.83; S, 16.26.

Antibacterial screening

In the present study, liquid broth tube dilution method was used for the determination of minimum inhibitory concentration of the synthesized compounds. The MIC was taken as the lowest concentration (highest dilution) without visible growth. Bacterial strain of *S. aureus* (ATCC-6538P), *B. subtilis* (ATCC-6633), *E. coli* (ATCC-8739) and *P. aeruginosa* (ATCC-9027) obtained from the National collection of industrial microorganism (NCIM), India were used for the study. Nutrient broth was used as a growth medium and incubation was done in electrically heated incubator at 37°C for 24 h. A stock solution of each synthesized compound (1 mg/ml) was prepared in dimethylformamide. Required concentrations were prepared by appropriate dilution of stock solution with distilled water. In the same way, solution of standard drug was prepared. A loop full of original lyophilized microbial strain was transferred into required medium aseptically and incubated at 37°C for 48 h. These were used as stock culture. The stock cultures were diluted appropriately to produce the final inoculum concentration 1×10^6 bacterial cell/ml. Ampicillin was used as reference drug for the antibacterial activity.

Serial dilutions were prepared in a primary and secondary screening. In primary screening serial dilution of test compounds was carried out and the following concentration was used: 1000, 500, 250, 125, 62, 32, 16, 8, 4 and 1 μg/ml.

Table 1. Structural and physicochemical data of the synthesized compounds

Compd.	R	Molecular formula	Molecular weight	Melting point	% Yield	R_f	MS
2a	-C_6H_5	$C_{26}H_{20}N_2O_2S$	424.51	201-203	75	0.68	424
2b	4-CH_3-C_6H_5-	$C_{28}H_{24}N_2O_2S$	452.56	205-206	65	0.65	452
2c	2-Cl-C_6H_5-	$C_{26}H_{18}Cl_2N_2O_2S$	493.40	195-196	62	0.62	493
2d	3-Cl-C_6H_5-	$C_{26}H_{18}Cl_2N_2O_2S$	493.40	186-187	59	0.54	493
2e	4-Cl-C_6H_5-	$C_{26}H_{18}Cl_2N_2O_2S$	493.40	184-185	58	0.63	493
2f	2-OH-C_6H_5-	$C_{26}H_{20}N_2O_4S$	456.51	194-195	67	0.56	456
2g	3-OH-C_6H_5-	$C_{26}H_{20}N_2O_4S$	456.51	190-191	63	0.60	456
2h	4-OH-C_6H_5-	$C_{26}H_{20}N_2O_4S$	456.51	185-186	65	0.68	456
2i	2-NO_2-C_6H_5-	$C_{26}H_{18}N_4O_6S$	514.50	213-214	74	0.61	514
2j	3-NO_2-C_6H_5-	$C_{26}H_{18}N_4O_6S$	514.50	218-219	72	0.72	514
2k	4-NO_2-C_6H_5-	$C_{26}H_{18}N_4O_6S$	514.50	215-216	76	0.58	514
2l	3-Br-C_6H_5-	$C_{26}H_{18}Br_2N_2O_2S$	582.30	208-209	64	0.62	582
2m	4-OCH_3-C_6H_5-	$C_{28}H_{24}N_2O_4S$	484.56	176-177	69	0.65	484
2n	3,4-Di-OCH_3-C_6H_4-	$C_{30}H_{28}N_2O_6S$	544.61	181-182	62	0.56	544
2o	3,4,5-Tri-OCH_3-C_6H_3-	$C_{32}H_{32}N_2O_8S$	604.67	184-185	55	0.67	604
2p	3-OCH_3,4-OH-C_6H_4-	$C_{28}H_{24}N_2O_6S$	516.56	191-192	57	0.58	516
2q	4-$N(CH_3)_2$-C_6H_5-	$C_{30}H_{30}N_4O_2S$	510.64	169-170	61	0.59	510
2r	3,5-Di-Br, 2-OH-C_6H_3-	$C_{26}H_{16}Br_4N_2O_4S$	772.09	180-181	58	0.69	772
2s	-C_4H_4O	$C_{22}H_{16}N_2O_4S$	404.43	220-221	49	0.77	404
2t	-C_4H_4S	$C_{22}H_{16}N_2O_2S_3$	436.56	195-196	45	0.67	436
3a	-C_6H_5	$C_{30}H_{22}Cl_2N_2O_4S$	577.47	169-170	86	0.73	577
3b	4-CH_3-C_6H_5-	$C_{32}H_{26}Cl_2N_2O_4S$	605.53	173-174	77	0.63	605
3c	2-Cl-C_6H_5-	$C_{30}H_{20}Cl_4N_2O_4S$	646.36	186-187	83	0.75	646
3d	3-Cl-C_6H_5-	$C_{30}H_{20}Cl_4N_2O_4S$	646.36	210-212	66	0.78	646
3e	4-Cl-C_6H_5-	$C_{30}H_{20}Cl_4N_2O_4S$	646.36	214-215	72	0.80	646
3f	2-OH-C_6H_5-	$C_{30}H_{22}Cl_2N_2O_6S$	609.47	156-157	78	0.64	609
3g	3-OH-C_6H_5-	$C_{30}H_{22}Cl_2N_2O_6S$	609.47	189-190	67	0.77	609
3h	4-OH-C_6H_5-	$C_{30}H_{22}Cl_2N_2O_6S$	609.47	165-166	84	0.72	609
3i	2-NO_2-C_6H_5-	$C_{30}H_{20}Cl_2N_4O_8S$	667.47	178-179	79	0.67	667
3j	3-NO_2-C_6H_5-	$C_{30}H_{20}Cl_2N_4O_8S$	667.47	195-196	78	0.76	667
3k	4-NO_2-C_6H_5-	$C_{30}H_{20}Cl_2N_4O_8S$	667.47	201-202	82	0.63	667
3l	3-Br-C_6H_5-	$C_{30}H_{20}Br_2Cl_2N_2O_4S$	735.26	206-207	63	0.59	735
3m	4-OCH_3-C_6H_5-	$C_{32}H_{26}Cl_2N_2O_6S$	637.52	248-249	79	0.75	637
3n	3,4-Di-OCH_3-C_6H_4-	$C_{34}H_{30}Cl_2N_2O_8S$	697.58	211-212	82	0.67	697
3o	3,4,5-Tri-OCH_3-C_6H_3-	$C_{36}H_{34}Cl_2N_2O_{10}S$	757.63	217-218	65	0.63	757
3p	3-OCH_3,4-OH-C_6H_4-	$C_{32}H_{26}Cl_2N_2O_8S$	669.52	182-183	58	0.56	669
3q	4-$N(CH_3)_2$-C_6H_5-	$C_{34}H_{32}Cl_2N_4O_4S$	663.61	195-196	74	0.69	663
3r	3,5-Di-Br, 2-OH-C_6H_3-	$C_{30}H_{18}Br_4Cl_2N_2O_6S$	925.06	214-215	73	0.58	925
3s	-C_4H_4O	$C_{26}H_{18}Cl_2N_2O_6S$	557.40	205-206	57	0.71	557
3t	-C_4H_4S	$C_{26}H_{18}Cl_2N_2O_4S_3$	589.53	189-190	56	0.68	589

Test compounds at various concentrations were added to culture medium in a sterilized borosilicate test tube and different bacterial strains were inoculated at 10^6 bacilli/ml concentration. The tubes were incubated at 37°C for 24 h for antibacterial activity and then examined for the presence or absence of growth of the test organisms. All experiments were performed in triplicate. The MIC of the test compound was between the lowest concentration inhibiting the growth and highest concentration allowing the growth. These two concentrations for each compound were noted. The exact MIC of the each compound was determined by repeating the experiment, using a range of concentration between these two concentrations by secondary screening. The MIC values were obtained from the lowest concentration of the test compound where the tubes remained clear, indicated that the bacterial growth was completely inhibited at this concentration. The MIC values were expressed in μg/ml and the results are given in the **Table 2**.

Table 2. *In vitro* antibacterial activity of the 2-azetidinone compounds **3(a-t)**

Compound	Gram-positive bacteria		Gram-negative bacteria	
	S. aureus (ATCC-6538P)	*B. subtilis* (ATCC-6633)	*E. coli* (ATCC-8739)	*P. aeruginosa* (ATCC-9027)
3a	48*	49	52	54
3b	45	47	49	50
3c	03	04	06	07
3d	08	09	11	13
3e	06	6.5	08	10
3f	18	20	22	25
3g	25	27	29	32
3h	20	21	23	25
3i	2.0	2.5	04	05
3j	1.0	1.5	03	04
3k	0.5	1.0	02	03
3l	11	13	15	16
3m	29	31	33	35
3n	33	36	38	40
3o	39	41	43	45
3p	29	32	35	37
3q	40	42	44	46
3r	10	12	15	17
3s	13	16	18	21
3t	12	14	16	19
Ampicillin	10.5	0.5	25	30

*MIC in μg/ml

RESULTS AND DISCUSSION

Chemistry

4,4′-diamino diphenyl sulphone (dapsone) (**1**) was condensed with various aromatic and heterocyclic aldehyde in ethanol in the presence of concentrated sulphuric acid as a catalyst to yield the 4,4′-Bis(substituted-arylideneamino) diphenyl sulphones **2(a-t)**. This Schiff's bases on cyclocondensation with chloracetyl chloride in presence of triethylamine yielded substituted 2-azetidinone derivatives **3(a-t)** (**Scheme 1**).

The structures of synthesized compounds **2(a-t)** were confirmed by elemental analysis and IR absorption bands at 1594 (-N=CH-), 1150 (SO_2, sym), 1252 (SO_2, asym), 694 (-C-S-C-). Some additional peaks appear due to substitution in aromatic ring showing absorption band at 3414 (O-H), 1348 (NO_2, symmetry), 1516 (NO_2, asymmetry), 765 (C-Cl). In ^{1}H-NMR spectra, common signals that appear include a singlet at δ 4.6 for (-N=CH-), a multiplet at δ 6.5-8.8 corresponds to aromatic proton. Due to substitution on aromatic ring, a singlet appeared at δ 3.5 for (–OCH_3), a singlet at 4.9 for (-OH), a singlet at δ 2.6 for (–CH_3) and a singlet at δ 3.9 for -NMe_2. The structure of the synthesized compounds **3(a-t)** were supported by elemental analysis and IR spectra as observed in **2(a-t)** with disappearance of 1594 cm^{-1} for (-N=CH-) band with 1695 cm^{-1} for (-C=O) of azetidinone. The ^{1}H-NMR signals of cyclized azetidinone was observed as doublet at δ 4.2-4.5, corresponding

to (-CH-Cl), doublet at δ 2.7-3.0, corresponding to (-CH-Ar) of azetidinone and multiplet at δ 7.5-8.5, corresponding to aromatic proton. The other signals observed were same as **2(a-t)**. The structural and physicochemical data of the synthesized compounds are given in **Table 1**.

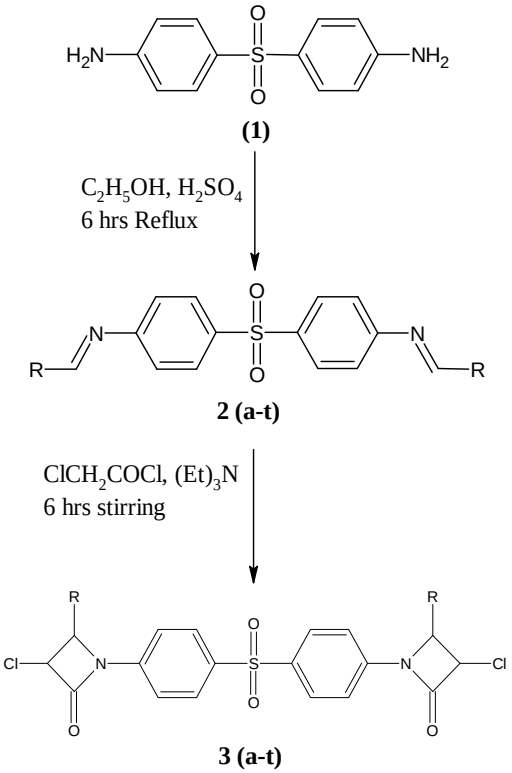

Fig. 1. Synthesis of 4, 4′-bis[3-chloro-4-aryl-azetidin-2-one-1-yl]diphenylsulphones **3(a-t)** (R=Heterocyclic or aryl ring)

Antimicrobial activity

Antibacterial activity of the synthesized compounds **3(a-t)** in form of the minimum inhibitory concentrations (MICs) was evaluated against various pathogenic bacterial strains of *S. aureus* (ATCC-6538P), *B. subtilis* (ATCC-6633), *E. coli* (ATCC-8739) and *P. aeruginosa* (ATCC-9027). The antimicrobial activities were carried out by broth tube dilution method as described by standard protocol. The minimum inhibitory concentrations (MICs) of the tested compounds and results of antibacterial screening of the synthesized compounds are presented in the **Table 2**. Modest antibacterial activity is observed with most of the tested compounds. All the synthesized compounds showed good to moderate activity with MIC value in the range of 0.5–54 μg/ml. particularly, compound **3i**, **3j**, **3k** and **3c** showed good activity (MIC value 0.5-7.0 μg/ml) against different strain of micro-organism. Moreover, **3d**, **3e**, **3l**, **3r**, **3s** and **3t** displayed comparable activity against *S. aureus*, *E. coli* and *P. aeruginosa* to the reference drug ampicillin. However, no compound showed comparable activity against *B. subtilis* relative to reference drug.

CONCLUSION

Novel schiff bases and 2-azetidinones derivatives from dapsone were synthesized. The newly synthesized 4,4′-Bis[3-chloro-4-aryl-azetidin-2-one-1-yl]diphenyl sulphones **3(a-t)** exhibit a remarkable inhibition of the growth of a wide spectrum of gram-positive and gram-negative bacteria. All the compounds **3(a-t)** showed excellent antibacterial activity. Overall observation from the results of the antimicrobial activity of the synthesized compounds revealed that compounds containing -Cl, -NO_2 group are more active than the remaining compounds.

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