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Synthesis, Characterization and Antibacterial Activity of Some New 3-{[4-(2-Methoxyphenyl)piperazin-1-yl]sulfonyl}benzohydrazide-hydrazone Derivatives

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In this article, a series of novel derivatives of 3-{[4-(2-methoxyphenyl)piperazin-1-yl]sulfonyl}benzohydrazide have been reported. The structures of all compounds have been evaluated by elemental analysis and spectral analysis (IR, MS and ^{1}H NMR). All the compounds have been screened for antimicrobial activity against two Gram-positive bacteria *viz*., *Staphylococcus aureus* and *Staphylococcus pyogenes,* two Gram-negative bacteria *viz*., *Escherichia coli* and *Pseudomonas aeruginosa.* Compounds **6g** (R = 4-NO_2) and **6h** (R = 2-OH, 3-OMe) exhibited excellent antibacterial activity, while the compounds **6a** (R = H), **6b** (R = 2-OMe), **6f** (R = 4-OMe), **6i** (R = 3,4-diethoxy) and **6j** (R = 3-OMe, 4-OEt) displayed good antibacterial activity.

Keywords: 1-(2-Methoxyphenyl)piperazine, 3-(Chlorosulfonyl)benzoic acid, Hydrazones, Antibacterial activity, Synthesis, Ciprofloxacin.

INTRODUCTION

Development of novel chemotherapeutic agents is an important and challenging task for the medicinal chemists and many research programs are directed towards the design and synthesis of new drugs for their chemotherapeutic usage. The emergence of old and new antibiotic-resistant bacterial strains in the last decades constitutes a substantial need for new classes of antibacterial agents[1]. The rapid rise in bacterial resistance to the traditional antibiotics such as penicillins[2] and tetracycline[3] has encouraged a continuing search for new classes of compounds with novel modes of antibacterial activity.

Hydrazone compounds constitute an important class for new drug development in order to discover an effective compound against multidrug resistant microbial infection. Hydrazones represent a resourceful compound of organic class having the basic structure $R_1R_2C{=}NNR_3R_4$[4,5]. Hydrazones and their derivatives are known to exhibit interesting diverse biological activities like anti-HIV[6], antitubercular[7,8], antioxidant[9], anti-inflammatory[10,11], antimicrobial[12,13], anticonvulsant[14,15], analgesic[16,17], anticancer[18,19], antiprotozoal[20], antiparasitic[21] and cardioprotective[22].

These reports prompted us to synthesize the novel derivatives of 3-{[4-(2-methoxyphenyl)piperazin-1-yl]sulfonyl}-benzohydrazide. The structures of all compounds have been evaluated by elemental analysis and spectral analysis (IR, MS and ^{1}H NMR). All the compounds have been screened for antimicrobial activity against two Gram-positive bacteria *viz*., *Staphylococcus aureus* and *Staphylococcus pyogenes,* two Gram-negative bacteria *viz*., *Escherichia coli* and *Pseudomonas aeruginosa.* Most of the newly synthesized compounds showed excellent to good antimicrobial activity against these strains.

EXPERIMENTAL

Solvents and reagents were obtained from commercial source and used without purification. The IR spectra (ν_{max}, cm^{-1}) were recorded in solid state KBr dispersion using Perkin Elmer FT-IR spectrometer. The ^{1}H-NMR spectra was recorded on Varian 500 MHz spectrometer. The chemical shifts were reported in δ (ppm) relative to TMS. The mass spectra were recorded on API 2000 Perkin Elmer PE-Sciex mass spectrometer. The reactions were monitored by Thin-layer chromatography (TLC). Melting points were determined on polman melting point apparatus (Model No MP96) by open capillary method and are uncorrected. All the reactions were carried out under nitrogen atmosphere.

Synthesis of 3-{[4-(2-methoxyphenyl)piperazin-1-yl]sulfonyl}benzoic acid (3) and methyl 3-{[4-(2-methoxyphenyl)piperazin-1-yl]sulfonyl}benzoate (4): To a stirred solution of 1-(2-methoxyphenyl)piperazine (**1**) (104 g, 0.544

mol) in methanol (500 mL), cooled to 0-5 °C, was added slowly 3-chlorosulfonylbenzoic acid (100 g, 0.454 mol) and stirred at room temperature for 8 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to 0-5 °C and slowly added conc. sulfuric acid (8.88 g, 0.0905 mol). The reaction contents were heated to reflux for 12 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in dichloromethane (500 mL). The organic layer was washed with water (250 mL), 10 % sodium bicarbonate (2 × 250 mL) and further washed with water (250 mL). The organic layer was separated and dried over Na_2SO_4, filtered and concentrated to obtain methylester **4**. White solid; Yield: 90 %; m.p.: 110-113 °C; IR (KBr, ν_{max}, cm^{-1}): 3444, 3068, 2989, 2961, 2902, 2859, 2831, 2756, 2684, 2558, 2328, 2037, 1731, 1722, 1595, 1504, 1461, 1450, 1438, 1389, 1354, 1332, 1299, 1284, 1269, 1241, 1225, 1189, 1171, 1132, 1125, 1089, 1078, 1067, 1042, 1026, 999, 963, 943, 911, 855, 818, 792, 749, 717, 685, 659; ^{1}H NMR (500 MHz, DMSO-d_6): 8.32-8.26 (m, 1H), 8.10 (d, *J* = 7.2 Hz, 1H), 7.86 (t, *J* = 7.6 Hz, 1H), 7.04-6.88 (m, 4H), 3.92 (s, 3H), 3.75 (s, 3H), 3.05-3.03 (m, 8H); ESI-MS: *m/z*, 391.2 $(M+H)^+$.

3-{[4-(2-Methoxyphenyl)piperazin-1-yl]sulfonyl}-benzohydrazide (5): To a stirred solution of methylester **4** (120 g, 0.308 mol) in methanol (600 mL) was added 80 % aqueous hydrazine hydride (28.8 g, 0.461 mol) at room temperature and heated to 45-50 °C for 15 h. The completion of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature and the precipitated solids was filtered and washed with methanol (50 mL) to afford compound **5**. White solid; Yield: 80 %; m.p.: 190-192 °C; IR (KBr, ν_{max}, cm^{-1}): 3351, 3333, 3280, 3110, 3070, 2999, 2990, 2947, 2927, 2907, 2897, 2887, 2865, 2850, 1715, 1705, 1670, 1637, 1594, 1576, 1572, 1561, 1544, 1512, 1498, 1491, 1487, 1476, 1464, 1454, 1449, 1400, 1388, 1380, 1351, 1336, 1331, 1299, 1299, 1279, 1270, 1253, 1211, 659; ^{1}H NMR (500 MHz, DMSO-d_6): 10.12 (s, 1H), 8.17 (d, *J* = 1.5 Hz, 2H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.78 (t, *J* = 8.5 Hz, 1H), 6.95 (dd, *J* = 1.5, 6.0 Hz, 1H), 6.91-6.85 (m, 3H), 4.60 (s, 2H), 3.70 (s, 3H), 3.02 (m, 8H); ESI-MS: *m/z*, 391.4 $(M+H)^+$.

Synthesis of hydrazones derivatives (6a-j): To a stirred solution of compound **5** (1g, 2.56 mmol) in methanol (10 mL) was added corresponding substituted benzaldehydes **a-j** (3.80 mmol) and heated to 50 °C for 12 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to 0 -5 °C and the precipitated solids were filtered. Yields of the product varied between 88 and 96 %.

3-{[4-(2-Methoxyphenyl)piperazin-1-yl]sulfonyl}-*N*'-[(*E*)-phenylmethylidene]benzohydrazide (6a): Off-white solid; Yield: 92 %; m.p.: 194-196 °C; IR (KBr, ν_{max}, cm^{-1}): 3436, 3350, 3187, 3116, 3060, 3047, 3005, 2986, 2981, 2972, 2964, 2955, 2949, 2922, 2888, 2831, 2776, 2761, 2692, 2682, 2192, 2041, 1652, 1616, 1603, 1600, 1592, 1582, 1567, 1519, 1501, 1480, 1448, 1427, 1420, 1402, 1388, 1381, 1356, 1338, 1332, 1324, 1306, 1281, 1276, 1270, 1264, 1257, 1245, 1231, 1225, 1199, 1179, 1172, 168, 1153; ^{1}H NMR (500 MHz, DMSO-d_6): 12.12 (s, 1H), 8.50 (s, 1H), 8.28 (d, *J* = 7.5 Hz, 2H), 8.01 (d, *J* = 8.5 Hz, 1H), 7.87 (t, *J* = 8.0 Hz, 1H), 7.77 (t, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 2.5 Hz, 3H), 6.98-6.95 (m, 1H), 6.90-6.84 (m, 3H), 3.82 (s, 3H), 3.06-3.03 (m, 8H); ESI-MS: *m/z*, 479.3 $(M+H)^+$.

3-{[4-(2-Methoxyphenyl)piperazin-1-yl]sulfonyl}-*N*'-[(*E*)-(2-methoxyphenyl)methylidene]benzohydrazide (6b): White solid; Yield: 95 %; m.p.: 194-200 °C; IR (KBr, ν_{max}, cm^{-1}): 3342, 3190, 3117, 3060, 3032, 3006, 2984, 2952, 2982, 2913, 2820, 1725, 1717, 1658, 1619, 1601, 1581, 1553, 1519, 1501, 1479, 1464, 1458, 1450, 1443, 1439, 1426, 1418, 1402, 1389, 1384, 1353, 1337, 1331, 1324, 1306, 1285, 1277, 1269, 1243, 1228, 1223, 1196, 1173, 1153, 1148, 1126, 1115, 1090, 1081, 1075, 1068, 1051, 1046, 1037, 1025; ^{1}H NMR (500 MHz, DMSO-d_6): 12.11 (s, 1H), 8.86 (s, 1H), 8.32 (d, *J* = 7.5 Hz, 2H), 7.90 (dd, *J* = 1.5, 6.0 Hz, 1H), 7.85 (t, *J* = 8.0 Hz, 2H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.98 (t, *J* = 8.0 Hz, 1H), 6.96-6.84 (m, 4H), 3.88 (s, 3H), 3.70 (s, 3H), 3.05-3.04 (m, 8H); ESI-MS: *m/z*, 531.4 $(M+H)^+$.

***N*'-[(*E*)-(2-Chlorophenyl)methylidene]-3-{[4-(2-methoxyphenyl)piperazin-1-yl]sulfonyl}benzohydrazide (6c):** White solid; Yield: 95 %; m.p.: 146-148 °C; IR (KBr, ν_{max}, cm^{-1}): 3608, 3499, 3411, 3320, 3207, 3112, 3077, 3001, 2991, 2985, 2979, 2974, 2965, 2948, 2940, 2927, 2896, 2883, 2876, 2847, 2828, 2774, 2753, 1761, 1734, 1659, 1635, 1627, 1613, 1597, 1586, 1560, 1518, 1499, 1480, 1467, 1460, 1457, 1453, 1447, 1441, 1434, 1399, 1389, 1383, 1375, 1331, 1321; ^{1}H NMR (500 MHz, DMSO-d_6): 12.25 (s, 1H), 8.48 (s, 1H), 8.28 (d, *J* = 6.5 Hz, 2H), 8.00 (d, *J* = 7.5 Hz, 1H), 7.87 (t, *J* = 8.0 Hz, 1H), 7.82 (s, 1H), 7.72 (t, *J* = 5.0 Hz, 2H), 6.98-6.95 (m, 1H), 6.91-6.85 (m, 3H), 3.70 (s, 3H), 3.06-3.03 (m, 8H); ESI-MS: *m/z*, 513.5 $(M+H)^+$.

***N*'-[(*E*)-(3-Chlorophenyl)methylidene]-3-{[4-(2-methoxyphenyl)piperazin-1-yl]sulfonyl}benzohydrazide (6d):** White solid; Yield: 92 %; m.p.: 134-136 °C; IR (KBr, ν_{max}, cm^{-1}): 3564, 3473, 3377, 3294, 3209, 3120, 3066, 2974, 2950, 2930, 2907, 2872, 2852, 2844, 2833, 2775, 2754, 2419, 2033, 2007, 1751, 1661, 1621, 1596, 1588, 1566, 1517, 1499, 1491, 1488, 1475, 1465, 1455, 1449, 1441, 1437, 1426, 1415, 1400, 1388, 1382, 1344, 1335, 1327, 1319, 1297, 1278, 1267, 1254, 1239, 1229, 1225, 1196, 1173, 1154, 1145, 1127, 1117, 1105, 1098, 1089, 1081, 1076, 1068, 1041; ^{1}H NMR (500 MHz, DMSO-d_6): 12.34 (s, 1H), 8.90 (s, 1H), 8.32 (d, *J* = 6.5 Hz, 2H), 8.06 (dd, *J* = 1.5, 6.5 Hz, 2H), 7.86 (t, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 9.0 Hz, 1H), 6.89-6.85 (m, 3H), 3.70 (s, 3H), 3.07-3.03 (m, 8H); ESI-MS: *m/z*, 513.5 $(M+H)^+$.

***N*'-[(*E*)-(2-Bromophenyl)methylidene]-3-{[4-(2-methoxyphenyl)piperazin-1-yl]sulfonyl}benzohydrazide (6e):** White solid; Yield: 94 %; m.p.: 134-136 °C; IR (KBr, ν_{max}, cm^{-1}): 3444, 3342, 3184, 3108, 3046, 2966, 2952, 2943, 2921, 2894, 2886, 2848, 2840, 2830, 1732, 1660, 1654, 1651, 1616, 1592, 1582, 1563, 1560, 1557, 1518, 1504, 1482, 1468, 1461, 1453, 1431, 1422, 1401, 1388, 1373, 1368, 1346, 1335, 1331, 1327; ^{1}H NMR (500 MHz, DMSO-d_6): 12.25 (s, 1H), 8.46 (s, 1H), 8.28 (d, *J* = 8.0 Hz, 2H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.96 (s, 1H), 7.86 (t, *J* = 7.5 Hz, 1H), 7.75 (d, *J* = 7.5 Hz, 1H), 7.66 (d, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 1H), 6.98-6.95 (m, 1H), 6.90-6.85 (m, 3H), 3.70 (s, 3H), 3.06-3.02 (m, 8H); ESI-MS: *m/z*, 557.3 $(M+H)^+$.

3-{[4-(2-Methoxyphenyl)piperazin-1-yl]sulfonyl}-*N*'-[(*E*)-(4-methoxyphenyl)methylidene]benzohydrazide (6f):

White solid; Yield: 94 %; m.p.: 110-115 °C; IR (KBr, ν_{max}, cm^{-1}): 3443, 3309, 3250, 3120, 3062, 3019, 3000, 2975, 2956, 2835, 2778, 2652, 2560, 2401, 2034, 2001, 1659, 1624, 1606, 1624, 1606, 1585, 1572, 1530, 1513, 1508, 1501, 1483, 1451, 1430, 1422, 1402, 1388, 1384, 1348, 1338, 1332, 1324, 1310, 1282, 1245, 1199, 1173, 1156, 1145, 1127, 1114, 1099, 1083, 1076, 1067, 1046, 1027, 1003, 997, 987, 948, 920, 910, 875, 862, 854, 834, 823; ^{1}H NMR (500 MHz, DMSO-d_6): 11.99 (s, 1H), 8.44 (s, 1H), 8.27 (s, 2H), 7.98 (d, *J* = 7.0 Hz, 1H), 7.86 (t, *J* = 7.5 Hz, 1H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.03 (d, *J* = 9.0 Hz, 2H), 6.98-6.91 (m, 1H), 6.89-6.84 (m, 3H), 3.82 (s, 3H), 3.70 (s, 3H), 3.06-3.02 (m, 8H); ESI-MS: *m/z*, 509.5 $(M+H)^+$.

3-{[4-(2-Methoxyphenyl)piperazin-1-yl]sulfonyl}-*N*'-[(*E*)-(4-nitrophenyl)methylidene]benzohydrazide (6g): Yellow solid; Yield: 96 %; m.p.: 153-155 °C; IR (KBr, ν_{max}, cm^{-1}): 3497, 3443, 3371, 3282, 3188, 3117, 3077, 3057, 3017, 2966, 2948, 2909, 2870, 2830, 2777, 1769, 1662, 1618, 1596, 1591, 1586, 1580, 1561, 1537, 1519, 1507, 1501, 1479, 1464, 1459, 1449, 1417, 1411, 1401, 1391, 1385, 1377, 1343, 1336, 1331, 1322, 1315, 1307, 1291, 1271, 1255, 1246, 1229, 1224, 1196, 1166, 1150, 1140, 1115, 1097, 1068, 1015, 980; ^{1}H NMR (500 MHz, DMSO-d_6): 12.41 (s, 1H), 8.60 (s, 1H), 8.32 (d, *J* = 9.0 Hz, 3H), 8.02 (d, *J* = 8.5 Hz, 3H), 7.88 (t, *J* = 8.5 Hz, 1H), 6.98-6.95 (m, 1H), 6.91-6.85 (m, 3H), 3.70 (s, 3H), 3.07-3.03 (m, 8H); ESI-MS: *m/z*, 524.6 $(M+H)^+$.

***N*'-[(*E*)-(2-Hydroxy-3-methoxyphenyl)methylidene]-3-{[4-(2-methoxyphenyl)piperazin-1-yl]sulfonyl}benzohydrazide (6h):** White solid; Yield: 92 %; m.p.: 124-128 °C; IR (KBr, ν_{max}, cm^{-1}): 3368, 3278, 3123, 3065, 3024, 2999, 2940, 2922, 2872, 2834, 2761, 2187, 1675, 1624, 1607, 1588, 1578, 1570, 1553, 1519, 1509, 1487, 1464, 1428, 1390, 1382, 1353, 1330, 1324, 1312, 1305, 1290, 1285, 1245, 1171, 1155, 1150, 1127, 1115, 1102, 1080, 1073, 1070, 1040, 1026, 1080, 1073, 950, 926, 913, 863, 837, 826, 813, 804, 777, 765; ^{1}H NMR (500 MHz, DMSO-d_6): 12.31 (s, 1H), 10.80 (s, 1H), 8.72 (s, 1H), 8.30 (dd, *J* = 2.5 Hz, 2H), 8.00 (d, *J* = 7.5 Hz, 1H), 7.88 (t, *J* = 8.5 Hz, 1H), 7.20 (dd, *J* = 1.0, 8.5 Hz, 1H), 7.05 (dd, *J* = 1.2, 8.5 Hz, 1H), 6.98-6.91 (m, 1H), 6.89-6.84 (m, 4H), 3.82 (s, 3H), 3.70 (s, 3H), 3.07-3.03 (m, 8H); ESI-MS: *m/z*, 525.5 $(M+H)^+$.

***N*'-[(*E*)-(3,4-Diethoxyphenyl)methylidene]-3-{[4-(2-methoxyphenyl)piperazin-1-yl]sulfonyl}benzohydrazide (6i):** White solid; Yield: 90 %; m.p.: 127-130 °C; IR (KBr, ν_{max}, cm^{-1}): 3448, 3349, 3324, 3129, 3079, 3021, 2987, 2848, 2833, 2777, 2645, 2595, 2102, 2030, 2000, 1685, 1627, 1598, 1583, 1575, 1564, 1538, 1527, 1511, 1506, 1564, 1538, 1527, 1511, 1506, 1501, 1484, 1474, 1461, 1449, 1444, 1436, 1392, 1382, 1372, 1363, 1339, 1335, 1328, 1321, 1311, 1287, 1252, 1245, 1201, 1171, 1156, 1142, 1125, 1116, 1092, 1084, 1076, 1069, 1061, 1039, 1032, 1028, 1003, 999, 980, 952, 935; ^{1}H NMR (500 MHz, DMSO-d_6): 11.98 (s, 1H), 8.40 (s, 1H), 8.26 (dd, *J* = 6.5 Hz, 2H), 7.98 (d, *J* = 8.5 Hz, 1H), 7.86 (t, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 1.5 Hz, 1H), 7.21 (dd, *J* = 2.0, 8.5 Hz, 1H), 7.02 (d, *J* = 8.5 Hz, 1H), 6.98-6.95 (m, 1H), 6.91-6.85 (m, 3H), 4.09 (q, *J* = 6.5 Hz, 4H), 3.70 (s, 3H), 3.07-3.03 (m, 8H), 1.35 (t, *J* = 6.5 Hz, 6H); ESI-MS: *m/z*, 565.7 $(M + H)^+$.

***N*'-[(*E*)-(3-Ethoxy-4-methoxyphenyl)methylidene]-3-{[4-(2-methoxyphenyl)piperazin-1-yl]sulfonyl}benzohydrazide (6j):** White solid; Yield: 88 %; m.p.: 194-195 °C; IR (KBr, ν_{max}, cm^{-1}): 3336, 3216, 3117, 3065, 3022, 2982, 2964, 2944, 2915, 2905, 2869, 2833, 2101, 2033, 1642, 1621, 1599, 1509, 1505, 1500, 1483, 1466, 1459, 1454, 1430, 1418, 1402, 1392, 1383, 1373, 1369, 1298, 1263, 1251, 1242, 1202, 1200, 1193, 1175, 1151, 1138, 1084, 1076, 1068, 1050, 1031, 1004, 998, 988, 964, 961; ^{1}H NMR (500 MHz, DMSO-d_6): 11.99 (s, 1H), 8.42 (s, 1H), 8.28 (d, *J* = 8.0 Hz, 2H), 7.98 (d, *J* = 7.5 Hz, 1H), 7.86 (t, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 5.8 Hz, 1H), 7.21 (dd, *J* = 1.5, 8.5 Hz, 1H), 7.40 (d, *J* = 6.5 Hz, 1H), 6.98-6.94 (m, 1H), 6.92-6.85 (m, 3H), 4.06 (q, *J* = 7.5 Hz, 2H), 3.83 (s, 3H), 3.68 (s, 3H), 3.05-3.03 (m, 8H), 1.35 (t, *J* = 7.5 Hz, 3H); ESI-MS: *m/z*, 573.3 $(M+H)^+$.

Antibacterial screening: The antimicrobial activity was determined using disc diffusion method by measuring zone of inhibition in mm [23]. All the compounds, **6a-6j** were screened *in vitro* at a concentration of 250 g/mL for antibacterial activity against two Gram-positive pathogenic organisms: *Staphylococcus aureus* and *Staphylococcus pyogenes,* two Gram-negative organisms: *Escherichia coli* and *Pseudomonas aeruginosa* (Table-1). Standard antibacterial drug ciprofloxacin (250 g/disc) was also tested under similar conditions against these organisms. Each experiment was done in triplicate and the average reading was taken. Growth inhibition was calculated with reference to positive control. Hydrazide-hydrazone **(6a-6j)** was dissolved in dimethyl sulphoxide at 250 µg/mL concentration. The inhibition zones were measured in millimeters at the end of an incubation period of 48 h at 35 ± 2 °C. DMSO alone showed no inhibition.

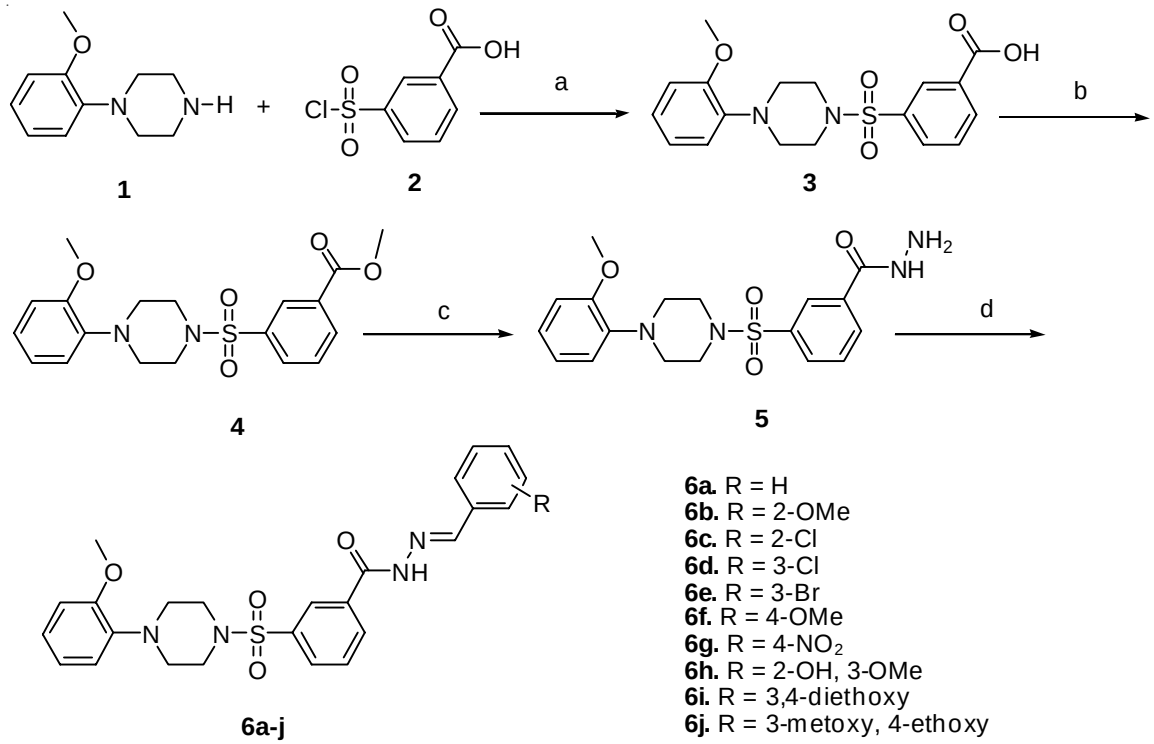
RESULTS AND DISCUSSION

The reaction scheme for the synthesis of 3-{[4-(2-methoxyphenyl)piperazin-1-yl]sulfonyl}benzohydrazides (**6a-j**) is represented in **Scheme-I**. The methylester derivative (**4**) was prepared by the condensation of 1-(2-methoxyphenyl)piperazine (**1**) and 3-chlorosulfonylbenzoic acid (**2**). The reaction of methyl 3-{[4-(2-methoxyphenyl)piperazin-1-yl]sulfonyl}benzoate (**4**) with hydrazine hydrate in methanol at 50 °C for 15 h resulted in the formation of 3-{[4-(2-methoxyphenyl)piperazin-1-yl]sulfonyl}benzohydrazide (**5**). Coupling of compound **5** with aromatic benzaldehydes **a-j** in methanol at 50 °C for 12 h resulted in the formation of hydrazone derivatives **6a-j**. The structural elucidation of the newly synthesized compounds **6a-j** was done on the basis of their ^{1}HNMR, IR and mass analysis. In general the IR spectra of the hydrazohydrazide derivatives **6a-j** had a strong, characteristic band in the region 1700-1647 cm^{-1} due to the C=O stretching vibration. The N-H stretching vibration of the compounds **6a-j** gave rise to a band at 3473-3180 cm^{-1}. The stretching bands for C=C and C=N groups were observed at 1609-1496 cm^{-1}. (ESI) MS analysis was performed in the positive ion mode, showing peaks at *m/z*, corresponding to the expected monoisotopic mass of the $[M+H]^+$ ion. As a representative example the ^{1}H NMR spectra of compound **6f** is explained as follows, a singlet signal with one proton integration resonating at 11.99 ppm and 8.44 ppm corresponds to Ar–CONH and –N=**CH**-Ar respectively.

TABLE-1
ANTIBACTERIAL ACTIVITY OF INTERMEDIATES AND COMPOUNDS **6a-j**

Compound No.	R	Gram-negative bacteria		Gram-positive bacteria	
		E. coli MTCC 443	*P. aeruginosa* MTCC 424	*S. aureus* MTCC 96	*S. pyogenes* MTCC 442
		Zone of inhibition (mm)			
6a	H	25	25	17	18
6b	2-OMe	26	24	17	18
6c	2-Cl	18	16	13	11
6d	3-Cl	18	16	11	12
6e	3-Br	16	14	12	14
6f	4-OMe	25	23	19	19
6g	4-NO_2	31	29	25	25
6h	2-OH, 3-OMe	30	28	26	25
6i	3,4-Diethoxy	26	27	18	19
6j	3-OMe, 4-OEt	27	25	18	17
[a]Ciprofloxacin	–	28	27	22	22

[a]Concentration: 250 µg/mL



Experimental conditions: a,b): methanol, 0-5 °C, 8 h; catalytic; conc; H_2SO_4, methanol, reflux, 12 h; c) hydrazine-hydrate, methanol, 45-50 °C, 15 h; c) Aromatic benzaldehydes **a-j,** methanol, 50 °C, 12 h.

Scheme-I: Synthesis of novel benzohydrazides (**6a-6j**)

The protons resonating at 8.27 ppm (singlet with two proton integration), 7.98 ppm and 7.86 ppm (doublet with two proton integration) corresponds to the aromatic ring flanked to -SO_2 group. The protons resonating at 7.70 ppm and 7.03 ppm as doublets with two proton integration corresponds to *p*-methoxy aromatic ring while the protons resonating at 6.98-6.84 ppm as multiplets corresponds to the 2-methoxy aryl ring. The remaining protons corresponding to methoxy and piperazine group are found to be resonating in the expected regions.

Antibacterial activity: The antibacterial activity of the 3-{[4-(2-methoxyphenyl)piperazin-1-yl]sulfonyl}benzohydrazide derivatives (**6a-j**) is summarized in Table-1. It is observed that compounds **6g** (R = 4-NO_2) and **6h** (R = 2-OH, 3-OMe) exhibited excellent antibacterial activity, while the compounds **6a** (R = H), 6b (R = 2-OMe), **6f** (R = 4-OMe), **6i** (R = 3,4-diethoxy) and **6j** (R = 3-OMe, 4-OEt) displayed good antibacterial activity and the remaining compounds **6c** (R = 2-Cl, **6d** (R = 3-Cl) and **6e** (R = 3-Br) showed moderate antibacterial activity.

Conclusion

The present paper described the coupling of 3-{[4-(2-methoxyphenyl)piperazin-1-yl]sulfonyl}benzohydrazide (**5**) with aromatic benzaldehydes **a-j** which resulted in the formation of benzohydrazides **6a-j**. They were characterized by ^{1}HNMR, IR and mass analysis and were further evaluated for antibacterial activity against *Staphylococcus aureus, Staphylococcus pyogenes, Escherichia coli* and *Pseudomonas*

aeruginosa (utilizing ciprofloxacin as the standard antibacterial drug). Compounds **6g** (R = 4-NO_2) and **6h** (R = 2-OH, 3-OMe) exhibited excellent antibacterial activity, while the compounds **6a** (R = H), **6b** (R = 2-OMe), **6f** (R = 4-OMe), **6i** (R = 3,4-diethoxy) and **6j** (R = 3-OMe, 4-OEt) displayed good antibacterial activity.

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