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Synthesis and Antibacterial Activity of Hydrazone Derivatives Bearing 3-(6,7-Dihydrothieno[3,2-*c*]pyridin-5(4*H*)-ylsulfonyl)benzoicacid Scaffold

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The present work describes the synthesis and antibacterial activity of 3-(6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-ylsulfonyl)benzohydrazide derivatives (**7a-p**) prepared from commercially available 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (**1**). They were characterized by ^{1}H NMR, IR and mass spectral analysis. The synthesized compounds **7a-p**, were tested against Gram negative and Gram positive bacterial strains *viz*; (i) *Escherichia coli* (MTCC 443), (ii) *Pseudomonas aeruginosa* (MTCC 424) (iii) *Staphylococcus aureus* (MTCC 96) and (iv) *Streptococcus pyogenes* (MTCC 442) using agar well diffusion method. Compounds **7g** (R = 2-OH, 4-OCHF$_2$), **7h** (R = 2-NO$_2$), **7i** (R = 3-NO$_2$), **7j** (R = 4-NO$_2$) and **7n** (4-OH) displayed excellent antibacterial activity (zone of inhibition: 25-32 mm) against both the Gram positive and Gram negative bacterial strains. Compounds **7f** (R = 2-F, 3-Cl), **7k** (R = 2-OMe), **7l** (R = 4-OMe), **7m** (R = 4-OEt), **7o** (R = 3-OMe), **7p** (R = 3,4-OEt) showed good antibacterial activity (zone of inhibition: 19-26 mm).

Keywords: 4,5,6,7-Tetrahydrothieno[3,2-*c*]pyridine, 3-(Chlorosulfonyl)benzoicacid, Hydrazones, Antibacterial activity, Norfloxacin.

INTRODUCTION

4,5,6,7-Tetrahydrothieno[3,2-*c*]pyridine and its derivatives, *e.g*. clopidogrel[1] and ticlopidine[2], are well recognized for their non-cytotoxic and complement inhibition properties. A series of 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine have been evaluated for their human phenylethanolamine-N-methyltransferase inhibitory potency and affinity for the α2-adrenoceptor[3]. 4,5,6,7-Tetrahydrothieno[3,2-*c*]pyridine derivatives are known as bioactive molecules since very long time and are well known for anti-inflammatory and analgesic agents[4-8]. They are used in medicine as allosteric adenosine receptor modulators for uses including protection against hypoxia and ischemia induced injury and treatment of adenosine-sensitive cardiac arrhythmias[9-11].

Even though there has been a steadfast increase in resistance to antimicrobial agents between important bacterial pathogens throughout the world. It is well known that the number of new antimicrobial agents being brought to the market had a steady turn down in the past decades. The lack of interest by pharmaceutical industry in antibacterial agents is related to number of factors, including many generic antimicrobial agents currently on the market that still have varying degrees of usefulness and that are considered first lines of therapy by many public health authorities[12,13]. The worldwide rise of antimicrobial resistance, combined with the rapid rate of microbial evolution and the slower development of novel antibiotics, accents the crucial need for novel therapeutics. Development of new antimicrobial or antipathogenic agents that act upon new microbial targets is a necessity[14].

Hydrazones possess an important class of biologically active drug molecules[15]. Hydrazones[16,17] having an azomethine -NHN=CH- portion are synthesized by heating the appropriate substituted hydrazides with aldehydes in solvent. Hydrazone derivatives possess anti-inflammatory[18], anticonvulsant, analgesic, anti-HIV, antimicrobial[19-21], antibacterial[22,23] and antitumor properties[24].

Inspired by the various biological activities associated with hydrazone and 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine derivative, the present work is focused towards the synthesis and antibacterial activity of 3-(6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-ylsulfonyl)benzohydrazide derivatives (**7a-p**) prepared from commercially available 4,5,6,7-tetrahydrothieno[3,2-c]pyridine.

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 Bruker-Avance 500 MHz spectrometer. The chemical shifts were reported in δ/ppm relative to TMS. The mass spectra were recorded on using a Perkin Elmer PE-SCIEX-API 2000 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-(6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-ylsulfonyl)benzoic acid (3): To a solution of compound **1** (12.5 g, 71.42 mmol) in methanol (90 mL) was added triethylamine (10.5 g, 103.78 mmol) followed by 3-(chlorosulfonyl)benzoic acid (15 g, 68.181 mmol) at 20-25 °C and stirred for 4 h. After completion of the reaction, the precipitated solid was filtered at the pump and dried. The crude compound was recrystallized from ethanol to obtain the pure compound **3**. White solid, Yield: 18 g, 81 %; m.p.: 220-223 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.54 (s, 1H), 8.26 (t, *J* = 1.5 Hz, 1H), 8.22 (d, *J* = 1.5 Hz, 1H), 8.02 (d, *J* = 6.5 Hz, 1H), 7.76 (t, *J* = 8.5 Hz, 1H), 7.32 (d, *J* = 4.5 Hz, 1H), 6.86 (d, *J* = 5.5 Hz, 1H), 4.20 (brs, 2H), 3.42 (brs, 2H), 2.42 (brs, 2H).

Synthesis of methyl 3-(6,7-dihydrothieno[3,2-c]pyridin-5(4*H*)-ylsulfonyl)benzoate (4): To a solution of compound **3** (15 g, 46.38 mmol) in methanol (100 mL) was added sulphuric acid (1.66 mL) and refluxed for 5 h. After completion of the reaction, methanol was evaporated under reduced pressure and the obtained residue was taken in ethyl acetate (100 mL) and washed with 10 % aquous $NaHCO_3$ solution (2 × 35 mL) followed by water and brine solution. The organic layer was separated, dried over Na_2SO_4, filtered and evaporated to afford compound **4**. Off white solid, Yield: 14 g, 92 %; m.p.: 140-143 °C.

Synthesis of 3-(6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-ylsulfonyl)benzohydrazide (5): To a solution of compound **4** (12 g, 35.56 mmol) in methanol (90 mL) was added hydrazine hydrate (6.24 g, 124.86 mmol) and heated to 50 °C for 15 h. After completion of the reaction, methanol was evaporated under reduced pressure to obtain crude compound. The crude compound was recrystallized from ethanol to obtain the pure compound **5**. Offwhite solid, Yield: 10 g, 83 %; m.p.: 175-178 °C; IR (KBr, ν_{max}, cm^{-1}): 3478, 3389, 3346, 3331, 3245, 3216, 3155, 3093, 3077, 3062, 2974, 2858, 1725, 1712, 1679, 1636, 1624, 1603, 1596, 1582, 1572, 1556, 1505, 1482, 1470, 1467, 1461, 1438, 1430, 1425, 1421, 1407, 1399, 1385, 1365, 1362, 1336, 1326, 1320, 1312, 1300, 1282, 1277, 1250, 1237, 1224, 1191, 1181, 1157, 1135, 1127, 1104, 1086, 1046, 1022, 1014, 991, 982, 968, 959, 943, 921, 917, 907, 856, 804, 754, 732, 659, cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.07 (s, 1H), 8.22 (t, *J* = 2.0 Hz, 1H), 8.09 (d, *J* = 8.0 Hz, 1H), 7.93 (t, *J* = 6.5 Hz, 1H), 7.70 (t, *J* = 8.5 Hz, 1H), 7.32 (d, *J* = 4.5 Hz, 1H), 6.84 (d, *J* = 5.5 Hz, 1H), 4.58 (brs, 2H), 4.20 (brs, 2H), 3.40 (brs, 2H), 2.84 (brs, 2H).

General experimental procedure for the synthesis of hydrazones derivatives (7a-p): To a stirred solution of compound **5** (500 mg, 148.18 mmol) in ethanol (15 mL) was added corresponding aromatic aldehydes **6a-p** (1.03 mmol) and heated to reflux for 12 h. After completion of the reaction, the reaction mixture was cooled to 10 °C, filtered and washed with cold ethanol followed by *n*-hexane to obtain the pure compounds. Yields of the product varied between 80 and 90 %.

3-(6,7-Dihydrothieno[3,2-*c*]pyridin-5(4*H*)-ylsulfonyl)-*N*'-[(*E*)-phenylmethylidene]benzohydrazide (7a): Offwhite solid; m.p.: 220-221 °C; IR (KBr, ν_{max}, cm^{-1}): 3436, 3223, 3067, 2908, 2841, 1643, 1603, 1557, 1490, 1476, 1466, 1449, 1426, 1399, 1366, 1348, 1322, 1311, 1296, 1272, 1240, 1203, 1172, 1146, 1086, 1061, 1035, 1023, 991, 968, 942, 891, 871, 851, 831, 807, 756, 743, 715, 691, 657; ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.05 (s, 1H), 8.48 (s, 1H), 8.32 (s, 1H), 8.20 (d, *J* = 9.0 Hz, 1H), 8.0 (d, *J* = 9.0 Hz, 1H), 7.79-7.73 (m, 3H), 7.47-7.43 (m, 3H), 7.30 (d, *J* = 7.0 Hz, 1H), 6.84 (d, *J* = 6.5 Hz, 1H), 4.21 (brs, 2H), 3.43 (brt, *J* = 7.5 Hz, 2H), 2.82 (brt, *J* = 7.0 Hz, 2H); ESI-MS: *m/z*, 426.4 (M + H)$^+$.

***N*'-[(*E*)-(2-Chlorophenyl)methylidene]-3-(6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-ylsulfonyl)benzohydrazide (7b):** Pale yellow solid; m.p.: 229-231 °C; IR (KBr, ν_{max}, cm^{-1}): 3449, 3186, 3068, 2919, 2845, 1658, 1594, 1551, 1463, 1442, 1431, 1413, 1400, 1367, 1348, 1312, 1298, 1281, 1239, 1218, 1200, 1175, 1166, 1145, 1125, 1086, 1068, 1046, 1030, 992, 975, 944, 896, 864, 851, 824, 775, 754, 738, 718, 701, 688, 664, ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.28 (s, 1H), 8.88 (s, 1H), 8.34 (s, 1H), 8.22 (d, *J* = 9.5 Hz, 1H), 8.08-8.00 (m, 2H), 7.78 (t, *J* = 9.5 Hz, 1H), 7.54 (t, *J* = 9.5 Hz, 1H), 7.50-7.46 (m, 2H), 7.29 (d, *J* = 6.5 Hz, 1H), 6.84 (d, *J* = 6.5 Hz, 1H), 4.22 (brs, 2H), 3.43 (t, *J* = 7.5 Hz, 2H), 2.82 (brt, *J* = 7.0 Hz, 2H); ESI-MS: *m/z*, 460.4 (M + H)$^+$.

***N*'-[(*E*)-(3-Chlorophenyl)methylidene]-3-(6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-ylsulfonyl)benzohydrazide (7c):** Pale yellow solid; m.p.: 238-240 °C; IR (KBr, ν_{max}, cm^{-1}): 3443, 3216, 3059, 2908, 2856, 2323, 1656, 1614, 1601, 1558, 1475, 1458, 1431, 1415, 1402, 1363, 1352, 1324, 1312, 1299, 1278, 1240, 1223, 1202, 1299, 1278, 1240, 1223, 1202, 1176, 1151, 1131, 1099, 1083, 1024, 990, 975, 948, 920, 896, 880, 866, 828, 812, 791, 779, 754, 739, 728, 715, 688, 662; ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.19 (s, 1H), 8.46 (s, 1H), 8.32 (s, 1H), 8.20 (d, *J* = 9.5 Hz, 1H), 8.0 (d, *J* = 10.0 Hz, 1H), 7.80-7.75 (m, 3H), 7.70 (brt, *J* = 3.5 Hz, 1H), 7.50 (brt, *J* = 5.5 Hz, 1H), 7.30 (d, *J* = 6.5 Hz, 1H), 6.84 (d, *J* = 6.5 Hz, 1H), 4.20 (brs, 2H), 3.43 (t, *J* = 7.5 Hz, 2H), 2.82 (brs, 2H); ESI-MS: *m/z*, 460.4 (M + H)$^+$.

***N*'-[(*E*)-(4-Chlorophenyl)methylidene]-3-(6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-ylsulfonyl)benzohydrazide (7d):** Pale yellow solid; m.p.: 210-212 °C; IR (KBr, ν_{max}, cm^{-1}): 3212, 3182, 3076, 3050, 2918, 2856, 1654, 1605, 1596, 1571, 1543, 1490, 1469, 1459, 1429, 1403, 1363, 1351, 1322, 1290, 1278, 1238, 1219, 1201, 1176, 1166, 1140, 1112, 1086, 1065, 1024, 1012, 990, 974, 955, 942, 894, 866, 851, 819, 774, 748, 738, 716, 695, 684, 663; ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.13 (s, 1H), 8.40 (s, 1H), 8.32 (s, 1H), 8.20 (d, *J* = 10.0 Hz, 1H), 8.0 (d, *J* = 10.0 Hz, 1H), 7.79-7.76 (m, 3H), 7.52 (d, *J* = 11.0 Hz, 2H), 7.30 (d, *J* = 6.5 Hz, 1H), 6.84 (d, *J* = 6.5 Hz, 1H), 4.20 (brs, 2H), 3.43 (t, *J* = 7.5 Hz, 2H), 2.82 (brs, 2H); ESI-MS: *m/z*, 460.4 (M + H)$^+$.

***N*'-[(*E*)-(3-Bromophenyl)methylidene]-3-(6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-ylsulfonyl)benzohydrazide (7e):** Yellow solid; m.p.: 235-236 °C; IR (KBr, ν_{max}, cm^{-1}): 3108, 3092, 3086, 3055, 2975, 2968, 2947, 2908, 2879, 2855, 2409, 2346, 2003, 1656, 1604, 1600, 1587, 1556, 1496, 1475, 1464,

1458, 1442, 1431, 1425, 1416, 1391, 1319, 1311, 1305, 1299, 1286, 1277, 1249, 1240, 1233, 1225, 1209, 1203, 1195, 1175, 1166, 1150, 1134, 1131, 1117, 1103, 1096, 1083, 1068, 1036, 962, 954, 940, 873, 775, 660; ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.19 (s, 1H), 8.44 (s, 1H), 8.32 (s, 1H), 8.21 (d, *J* = 9.0 Hz, 1H), 8.02 (d, *J* = 10.0 Hz, 1H), 7.94 (s, 1H), 7.79-7.54 (m, 2H), 7.62 (d, *J* = 10.0 Hz, 1H), 7.41 (t, *J* = 10.0 Hz, 1H), 7.30 (d, *J* = 6.5 Hz, 1H), 6.84 (d, *J* = 6.5 Hz, 1H), 4.20 (brs, 2H), 3.43 (t, *J* = 7.5 Hz, 2H), 2.82 (brs, 2H); ESI-MS: *m/z*, 504.2 $(M + H)^+$.

***N*'-[(*E*)-(3-Chloro-2-fluorophenyl)methylidene]-3-(6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-ylsulfonyl)benzohydrazide (7f):** Pale yellow solid; m.p.: 235-236 °C; IR (KBr, ν_{max}, cm^{-1}): 3075, 3054, 2920, 2859, 2345, 1656, 1601, 1544, 1450, 1428, 1408, 1367, 1351, 1321, 1310, 1297, 1231, 120, 1173, 1148, 1137, 1110, 1085, 1065, 1024, 990, 974, 950, 941, 895, 882, 868, 822, 775, 747, 738, 731, 717, 704, 684, 663; ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.28 (s, 1H), 8.71 (s, 1H), 8.34 (s, 1H), 8.22 (d, *J* = 9.5 Hz, 1H), 8.0 (d, *J* = 9.5 Hz, 1H), 7.91 (t, *J* = 8.5 Hz, 1H), 7.78 (t, *J* = 10.0 Hz, 1H), 7.70 (t, *J* = 9.5 Hz, 1H), 7.35-7.31 (m, 2H), 6.84 (d, *J* = 6.0 Hz, 1H), 4.22 (brs, 2H), 3.42 (brs, 2H), 2.82 (brs, 2H); ESI-MS: *m/z*, 478.2 $(M-H)^+$.

3-(6,7-Dihydrothieno[3,2-*c*]pyridin-5(4*H*)-ylsulfonyl)-*N*'-[(*E*)-(4-difluoromethoxy-2-hydroxyphenyl)methylidene]benzohydrazide (7g): Pale yellow solid; m.p.: 170-172 °C; IR (KBr, ν_{max}, cm^{-1}): 3125, 3067, 2943, 2917, 28880, 2851, 2408, 2325, 1663, 1622, 1601, 1591, 1585, 1580, 1560, 1535, 1522, 1516, 1509, 1485, 1475, 1470, 1458, 1454, 1434, 1408, 1376, 1369, 1349 1331, 1312, 1293, 1284, 1260, 1240, 1220, 1168, 1155, 1130, 1068, 1052, 1004, 990, 968, 945, 903, 895, 886, 881, 855, 844, 839, 830, 825, 804, 787, 781, 740, 707, 662; ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.02 (s, 1H), 10.20 (s, 1H), 8.34 (s, 1H), 8.32 (s, 1H), 8.20 (d, *J* = 10.0 Hz, 1H), 8.0 (d, *J* = 10.0 Hz, 1H), 7.76 (t, *J* = 9.0 Hz, 1H), 7.44 (d, *J* = 2.0 Hz, 1H), 7.23 (d, *J* = 6.5 Hz, 1H), 7.19-7.14 (m, 2H), 6.84 (d, *J* = 6.5 Hz, 1H), 4.20 (brs, 2H), 3.42 (t, *J* = 7.0 Hz, 2H), 2.48 (t, *J* = 7.0 Hz, 2H); ESI-MS: *m/z*, 508.0 $(M + H)^+$.

3-(6,7-Dihydrothieno[3,2-*c*]pyridin-5(4*H*)-ylsulfonyl)-*N'*-[(*E*)-(2-nitrophenyl)methylidene]benzohydrazide (7h): Yellow solid; m.p.: 233-234 °C; IR (KBr, ν_{max}, cm^{-1}): 3125, 3068, 2945, 2920, 2879, 2846, 2458, 2332, 2097, 2003, 1660, 1615, 1600, 1591, 1552, 1538, 1526, 1485, 1463, 1447, 1440, 1423, 1414, 1406, 1400, 1395, 1367, 1360, 1346, 1340, 1334, 1327, 1315, 1307, 1300, 1282, 1272, 1247, 1238, 1228, 1217, 1206, 1199, 1192, 1174, 1168, 1164, 1155, 1150, 1142, 1138, 1114, 1087, 1072, 1068, 1037, 1029, 1011, 993, 971, 946, 908, 897, 874, 862, 850, 770, 752, 711, 655; ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.40 (s, 1H), 8.90 (s, 1H), 8.33 (s, 1H), 8.22 (d, *J* = 9.5 Hz, 1H), 8.14-8.08 (m, 2H), 8.01 (d, *J* = 10.0 Hz, 1H), 7.85-7.76 (m, 2H), 7.72-7.60 (m, 1H), 7.30 (d, *J* = 6.0 Hz, 1H), 6.84 (d, *J* = 6.5 Hz, 1H), 4.22 (brs, 2H), 3.44 (brt, *J* = 7.0 Hz, 2H), 2.82 (brs, 2H); ESI-MS: *m/z*, 469.5 $(M-H)^+$.

3-(6,7-Dihydrothieno[3,2-*c*]pyridin-5(4*H*)-ylsulfonyl)-*N*'-[(*E*)-(3-nitrophenyl)methylidene]benzohydrazide (7i): Yellow solid; m.p.: 190-192 °C; IR (KBr, ν_{max}, cm^{-1}): 3124, 3070, 3062, 3041, 2971, 2961, 2939, 2923, 2881, 2856, 2039, 1661, 1622, 1607, 1588, 1537, 1487, 1463, 1445, 1438, 1421, 1414, 1406, 1400, 1394, 1349, 1329, 1313, 1306, 1300, 1285, 1276, 1246, 1238, 1212, 1199, 1194, 1165, 1153, 1145, 1114, 1087, 1073, 1069, 1037, 1027, 1015, 991, 980, 976, 971, 960, 954, 943, 920, 914, 905, 897, 873, 867, 859, 827, 817, 810, 720, 650; ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.32 (s, 1H), 8.60 (s, 1H), 8.33 (s, 1H), 8.28 (d, *J* = 8.5 Hz, 1H), 8.24 (d, *J* = 9.0 Hz, 2H), 8.20 (d, *J* = 9.5 Hz, 1H), 8.01 (d, *J* = 10.0 Hz, 1H), 7.80-7.74 (m, 2H), 7.30 (d, *J* = 6.0 Hz, 1H), 6.84 (d, *J* = 6.5 Hz, 1H), 4.22 (brs, 2H), 3.44 (brt, *J* = 7.0 Hz, 2H), 2.82 (brs, 2H); ESI-MS: *m/z*, 469.5 $(M-H)^+$.

3-(6,7-Dihydrothieno[3,2-*c*]pyridin-5(4*H*)-ylsulfonyl)-*N*'-[(*E*)-(4-nitrophenyl)methylidene]benzohydrazide (7j): Pale yellow solid; m.p.: 239-240 °C; IR (KBr, ν_{max}, cm^{-1}): 3113, 3086, 3068, 3055, 2985, 2898, 2844, 2443, 1694, 1598, 1589, 1539, 1511, 1471, 1458, 1448, 1422, 1402, 1393, 1345, 1323, 1305, 1288, 1263, 1205, 1160, 1139, 1094, 1076, 1032, 1010, 989, 967, 945, 937, 896, 860, 833, 806, 771, 752, 741, 716, 707, 694, 680, 661; ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.35 (s, 1H), 8.58 (s, 1H), 8.34-8.29 (m, 3H), 8.20 (d, *J* = 9.5 Hz, 1H), 8.03-8.0 (m, 3H), 7.78 (t, *J* = 10.0 Hz, 1H), 7.30 (d, *J* = 6.0 Hz, 1H), 6.84 (d, *J* = 6.0 Hz, 1H), 4.20 (brs, 2H), 3.43 (brt, *J* = 7.0 Hz, 2H), 2.82 (brs, 2H); ESI-MS: *m/z*, 469.5 $(M-H)^+$.

3-(6,7-Dihydrothieno[3,2-*c*]pyridin-5(4*H*)-ylsulfonyl)-*N*'-[(*E*)-(2-methoxyphenyl)methylidene]benzohydrazide (7k): White solid; m.p.: 194-195 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.05 (s, 1H), 8.84 (s, 1H), 8.35 (s, 1H), 8.24 (d, *J* = 9.0 Hz, 1H), 7.98-7.94 (m, 1H), 7.88 (dd, *J* = 8.0, 10.0 Hz, 1H), 7.56 (t, *J* = 10.0 Hz, 1H), 7.40 (t, *J* = 10.0 Hz, 1H), 7.30 (d, *J* = 6.5 Hz, 1H), 7.10 (t, *J* = 10.5 Hz, 1H), 7.02 (t, *J* = 6.5 Hz, 1H), 6.84 (d, *J* = 6.5 Hz, 1H), 4.20 (brs, 2H), 3.86 (s, 3H), 3.42 (t, *J* = 7.5 Hz, 2H), 2.82 (brs, 2H); IR (KBr, ν_{max}, cm^{-1}): 3323, 3209, 3196, 3185, 3116, 3108, 3101, 3070, 3061, 3053, 2938, 2925, 2890, 2882, 2858, 2843, 2627, 2601, 2097, 1646, 1621, 1600, 1585, 1574, 1565, 1551, 1528, 1509, 1482, 1467, 1461, 1459, 1437, 1419, 1403, 1388, 1381, 1363, 1359, 1350, 1340, 1335, 1328, 1311, 1304, 1301, 1289, 1267, 1248, 1239, 1224, 12116, 1207, 1201, 1191, 1167, 1151, 1142, 11145, ESI-MS: *m/z*, 456.0 $(M + H)^+$.

3-(6,7-Dihydrothieno[3,2-*c*]pyridin-5(4*H*)-ylsulfonyl)-*N*'-[(*E*)-(4-methoxyphenyl)methylidene]benzohydrazide (7l): White solid; m.p.: 225-227 °C; IR (KBr, ν_{max}, cm^{-1}): 3324, 3222, 3127, 3066, 3016, 3007, 2980, 2930, 2920, 2908, 2877, 2834, 2576, 2555, 2182, 2024, 1643, 1622, 1605, 1583, 1557, 1528, 1512, 1484, 1466, 1445, 1442, 1434, 1420, 1407, 1401, 1391, 1347, 1331, 1322, 1317, 1298, 1282, 1259, 1195, 1171, 1154, 1146, 1118, 1087, 1078, 1068, 1045, 1027, 1005, 990, 977, 969, 959, 942, 903, 891, 878, 863, 852, 829, 820, 807, 792.^{1}H NMR (500 MHz, DMSO-d_6): δ 11.92 (s, 1H), 8.42 (s, 1H), 8.31 (s, 1H), 8.20 (d, *J* = 9.5 Hz, 1H), 8.04-7.94 (m, 1H), 7.76 (d, *J* = 10.0 Hz, 1H), 7.68 (d, *J* = 10.5 Hz, 2H), 7.30 (t, *J* = 6.5 Hz, 1H), 7.03 (d, *J* = 11.0 Hz, 2H), 6.84 (d, *J* = 6.5 Hz, 1H), 4.20 (brs, 2H), 3.80 (s, 3H), 3.42 (t, *J* = 7.5 Hz, 2H), 2.82 (t, *J* = 6.5 Hz, 2H); ESI-MS: *m/z*, 456.0 $(M + H)^+$.

3-(6,7-Dihydrothieno[3,2-*c*]pyridin-5(4*H*)-ylsulfonyl)-*N*'-[(*E*)-(4-ethoxyphenyl)methylidene]benzohydrazide (7m): Off white solid; m.p.: 240-243 °C; IR (KBr, ν_{max}, cm^{-1}): 3221, 3066, 2980, 2908, 1641, 1603, 1557, 1510, 1475, 1424, 1392, 1349, 1323, 1298, 1272, 1252, 1171, 1146, 1113, 1089, 1068, 1044, 991, 968, 942, 892, 862, 834, 808, 768, 743, 716, 686, 665; ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.92 (s, 1H),

8.42 (s, 1H), 8.32 (s, 1H), 8.20 (d, *J* = 9.5 Hz, 1H), 8.04 (d, *J* = 9.5 Hz, 1H), 7.76 (t, *J* = 9.5 Hz, 1H), 7.66 (d, *J* = 11.0 Hz, 2H), 7.30 (d, *J* = 6.5 Hz, 1H), 7.00 (d, *J* = 10.5 Hz, 2H), 6.84 (d, *J* = 6.5 Hz, 1H), 4.20 (brs, 2H), 4.08 (q, *J* = 8.0 Hz, 2H), 3.44 (t, *J* = 7.0 Hz, 2H), 2.82 (brt, *J* = 6.5 Hz, 2H), 1.34 (t, *J* = 8.0 Hz, 3H); ESI-MS: *m/z*, 470.4 $(M + H)^+$.

3-(6,7-Dihydrothieno[3,2-*c*]pyridin-5(4*H*)-ylsulfonyl)-*N*'-[(*E*)-(4-hydroxyphenyl)methylidene]benzohydrazide (7n): White solid; m.p.: 197-198 °C; IR (KBr, ν_{max}, cm^{-1}): 3228, 3066, 2931, 2906, 2845, 2693, 1642, 1604, 1584, 1562, 1514, 1452, 1426, 1400, 1367, 1347, 1322, 1298, 1240, 1172, 1146, 1087, 1064, 1031, 991, 973, 941, 894, 864, 833, 807, 768, 738, 713, 685, 666; ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.85 (s, 1H), 9.94 (brs, 1H), 8.37 (s, 1H), 8.30 (s, 1H), 8.20 (d, *J* = 10 Hz, 1H), 7.98 (d, *J* = 10.0 Hz, 1H), 7.75 (t, *J* = 10.0 Hz, 1H), 7.56 (d, *J* = 10.0 Hz, 2H), 7.30 (d, *J* = 6.5 Hz, 1H), 6.84 (t, *J* = 6.0 Hz, 1H), 4.20 (brs, 2H), 3.42 (t, *J* = 7.0 Hz, 2H), 2.82 (t, *J* = 7.0 Hz, 2H); ESI-MS: *m/z*, 442.5 $(M + H)^+$.

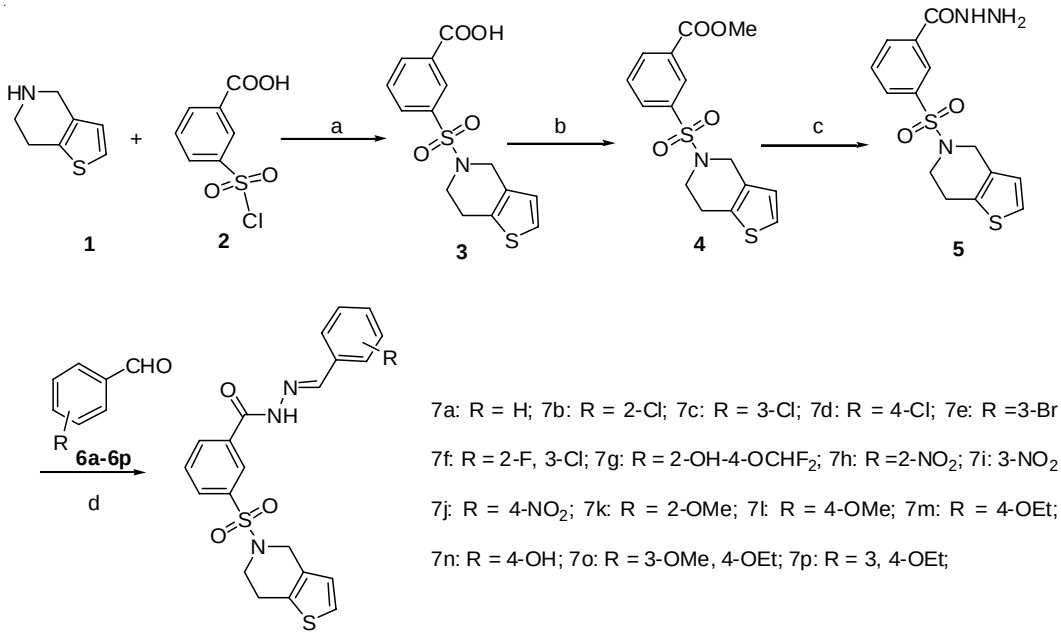
3-(6,7-Dihydrothieno[3,2-*c*]pyridin-5(4*H*)-ylsulfonyl)-*N*'-[(*E*)-(4-ethoxy-3-methoxyphenyl)methylidene]benzohydrazide (7o): White solid; m.p.: 220-221 °C; IR (KBr, ν_{max}, cm^{-1}): 3304, 3198, 3105, 3065, 3035, 3018, 3009, 2959, 2945, 2870, 2837, 2030, 1644, 1619, 1603, 1583, 1571, 1562, 1542, 1520, 1512, 1505, 1488, 1477, 1460, 1442, 1434, 1418, 1412, 1405, 1400, 1392, 1347, 1329, 1321, 1317, 1368, 1303, 1296, 1282, 1276, 1265, 1249, 1212, 1202, 1192, 1164, 1150, 1141, 1119, 1113, 1106, 1088, 1072, 1063, 1054, 1049, 1036, 1024, 1006, 990, 968. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.95 (s, 1H), 8.40 (s, 1H), 8.31 (s, 1H), 8.20 (d, *J* = 10.0 Hz, 1H), 7.98-7.94 (m, 1H), 7.76 (t, *J* = 10.0 Hz, 1H), 7.34 (d, *J* = 1.5 Hz, 1H), 7.30 (t, *J* = 6.0 Hz, 1H), 7.18 (dd, *J* = 2.5, 10.5 Hz, 1H), 7.02 (d, *J* = 10.5 Hz, 1H), 6.84 (d, *J* = 6.0 Hz, 1H), 4.20 (brs, 2H), 4.06 (q, *J* = 9.0 Hz, 2H), 3.82 (s, 3H), 3.40 (brt, *J* = 7.0 Hz, 2H), 2.82 (brs, 2H), 1.34 (t, *J* = 9.0 Hz, 3H); ESI-MS: *m/z*, 500.1 $(M + H)^+$.

***N*'-[(*E*)-(3,4-diethoxyphenyl)methylidene]-3-(6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-ylsulfonyl)benzohydrazide (7p):** Off white solid; m.p.: 178-179 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.92 (s, 1H), 8.38 (s, 1H), 8.30 (s, 1H), 8.18 (d, *J* = 10.0 Hz, 1H), 7.98 (dd, *J* = 9.5 Hz, 1H), 7.76 (t, *J* = 10.0 Hz, 1H), 7.31 (dd, *J* = 2.0, 11.5 Hz, 1H), 7.20 (dd, *J* = 2.5, 10.0 Hz, 1H), 7.03 (d, *J* = 10.5 Hz, 1H), 6.84 (d, *J* = 6.0 Hz, 1H), 4.20 (brs, 2H), 4.08 (q, *J* = 9.0 Hz, 4H), 3.42 (brt, *J* = 7.0 Hz, 2H), 2.82 (t, *J* = 7.0 Hz, 2H), 1.35 (t, *J* = 9.0 Hz, 6H); ESI-MS: *m/z*, 513.63 $(M + H)^+$.

Biological assay: The synthesized compounds **7a-p**, were tested against Gram negative and Gram positive bacterial strains *viz*; (i) *Escherichia coli* (MTCC 443), (ii) *Pseudomonas aeruginosa* (MTCC 424) (iii) *Staphylococcus aureus* (MTCC 96) and (iv) *Streptococcus pyogenes* (MTCC 442). The antibacterial activity of the compounds was carried out using agar well diffusion method according to the literature protocol[25,26]. The compounds were dissolved in dimethylsulphoxide at 100 µg/mL concentrations and the standard antibacterial drug, Norfloxacin was used as the reference antibiotic. The antibacterial activity was determined by zones showing complete inhibition (mm). Growth inhibition was calculated with reference to positive control. All the samples were taken in triplicates.

RESULTS AND DISCUSSION

The synthetic sequence for the preparation of hydrazide-hydrazone derivatives (**7a-p**) is shown in **Scheme-I**. The starting material 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (**1**) is utilized as one of the key intermediate for the synthesis of clopidogrel an antiplatelet drug[27]. Condensation of 4,5,6,7-tetrahydrothieno[3,2-c]pyridine (**1**) with 3-(chlorosulfonyl)-benzoic acid (**2**) in presence of triethylamine in methanol resulted in the formation of 3-(6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-ylsulfonyl)benzoic acid (**3**). The benzoic acid



Scheme-I: Synthesis of novel hydrazone derivatives (**7a-p**)

(**3**) was converted to corresponding methyl ester derivative 3-(6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-ylsulfonyl)benzoate (**4**), which upon reaction with hydrazine hydrate in ethanol at reflux led to the formation of the key intermediate 3-(6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-ylsulfonyl)benzohydrazide (**5**). Coupling of benzohydrazide (**5**) with aromatic aldehydes (**6a-p**) yielded hydrazo-hydrazide derivatives (**7a-p**). They were characterized by ^{1}H NMR, IR and mass spectral analysis. The mass spectra of compounds showed (M + H) peaks, in agreement with their molecular formula.

Experimental conditions: (a) Triethylamine, MeOH, 20-25 °C, 4 h; (b) Conc; H_2SO_4, MeOH, reflux, 5 h; (c) $NH_2NH_2.H_2O$, methanol, 50 °C, 15 h; (d) benzaldehydes (**6a-p**), ethanol, reflux, 12 h.

Antimicrobial testing: Table-1 depicts the antibacterial activity results. It is observed from the table that most of the compounds (**7a-p**) showed significant antibacterial activity against all the tested bacterial strains. Compounds **7g** (R = 2-OH, 4-$OCHF_2$), **7h** (R = 2-NO_2), **7i** (R = 3-NO_2), **7j** (R = 4-NO_2) and **7n** (4-OH) displayed excellent antibacterial activity (zone of inhibition: 25-32 mm) against both the Gram positive and Gram negative bacterial strains. Compounds **7f** (R = 2-F, 3-Cl), **7k** (R = 2-OMe), **7l** (R = 4-OMe), **7m** (R = 4-OEt), **7o** (R = 3-OMe), **7p** (R = 3,4-OEt) showed good antibacterial activity (zone of inhibition: 19-26 mm) while the remaining compounds **7a** (R = H), **7b** (R = 2-Cl), **7c** (R = 3-Cl), **7d** (R = 4-Cl), **7e** (R = 3-Br) showed moderate antibacterial activity (zone of inhibition: 14-22 mm). From the Table-1, it can be generalized that the compounds incorporated with R = 2-OH, 4-CHF_2, 2-NO_2, 3-NO_2, 4-NO_2 and 4-OH, exhibited excellent antibacterial activity while the compounds with R = 2-F, 3-Cl, 2-OMe, 4-OMe, 4-OEt, 3-OMe, 3,4-OEt showed good antibacterial activity, from the above observations it can be stated that, by further varying R substituent's in the main scaffold may lead to promising antibacterial agents.

TABLE-1
ANTIBACTERIAL ACTIVITY OF COMPOUNDS **7a-p**

Compound No.	*E. coli* MTCC 443	*P. aeruginosa* MTCC 424	*S. aureus* MTCC 96	*S. pyogenes* MTCC 442
	Zone of inhibition in (mm)[b]			
7a	20	16	19	15
7b	22	18	20	16
7c	21	17	19	14
7d	20	19	18	26
7e	20	17	17	15
7f	25	22	24	20
7g	30	28	30	25
7h	31	27	29	26
7i	32	29	29	25
7j	31	28	30	27
7k	24	21	24	19
7l	26	20	24	20
7m	26	22	23	20
7n	30	27	29	25
7o	26	21	25	20
7p	25	21	25	19
Norfloxacin[a]	27	23	26	21

[a]Concentration: 100 µg/mL^{-1} of DMSO; [b]Values, including diameter of the well (8 mm), are means of three replicates; [c]No activity

Conclusion

The present paper describes the synthesis and antibacterial activity of 3-(6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-ylsulfonyl)benzohydrazide derivatives (**7a-p**). The antibacterial activity data revealed that the hydrazone derivatives with R = 2-OH, 4-CHF_2, 2-NO_2, 3-NO_2, 4-NO_2 and 4-OH, exhibited excellent antibacterial activity while the compounds with R = 2-F, 3-Cl, 2-OMe, 4-OMe, 4-OEt, 3-OMe, 3,4-OEt showed good antibacterial activity.

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