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Synthesis and Antimicrobial screening of Some New Piperidine Derivatives

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ABSTRACT

Piperidine and its derivatives have high impact on medical field due to its wide variety of pharmacological action. In the present investigation, an attempt to synthesize some novel biologically active piperidine derivatives was made. The structures of the newly synthesized compounds were characterized by spectral data and were screened for anti-microbial activity. Compounds ***6b****,* ***6d****,* ***6e****,* ***6f*** *and* ***6g*** *were found to possess potent anti-bacterial activity.*

Keywords: Piperidine derivatives, antimicrobial activity, synthesis, ethylpiperidine-4-carboxylate.

INTRODUCTION

Due to the increasing number of multidrug resistant developed by the microbes, currently used antimicrobial agent are futile and antibacterial diseases are very widespread, therefore, the design and synthesis of new antimicrobial molecules has been of vast interest in recent year. Various strategies are currently being engaged to develop new antibiotics and to advance the effectiveness of established antimicrobial compounds. An additional attractive approach for the growth of antibacterial agents is the research of compounds that target bacterial membranes. Bacterial membrane is highly preserved among most species of Gram-negative and Gram-positive bacteria. Having an exceptional importance in heterocyclic compounds and due to its wide range of therapeutic activities, piperidine exhibit biological importance such as CCR5 antagonist-based HIV-1 entry inhibitors [1], GABA uptake inhibitors [2], anti-influenza virus [3],antibacterial activity [4-5], antidepressant and antioxidant activity [6-7], p38α MAP kinase inhibitors [8], anti-HIV [9-10], antihypertensive [11] and antitumor agents [12]. The synthesis of piperidine is easy, economic and less time consuming. According to recent reports on pharmacological effects of substituted piperidines, there is still an increasing interest in synthesizing and bio testing of new pharmacophores based on piperidine derivatives [13-17]. Encouraged by the various biological activities associated with the piperidine scaffolds, we report here in the synthesis, characterization and antibacterial activity of new piperidine 4-carboxamide derivatives (**6a–6j**).

MATERIALS AND METHODS

The solvents were purified according to standard procedures prior to use, and all commercial chemicals were used as received. For thin-layer chromatography (TLC) analysis, Merck pre-coated Plates (silica gel 60 F254) were used and eluting solvents are indicated in the procedures. Merck silica gel 60 (230-400 mesh) was used for flash column chromatography. Melting point (M.p) determinations were performed by using Mel-temp apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Unity instrument at room temperature at 400 MHz. Chemical shifts are reported in δ parts per million (ppm) downfield from tetramethylsilane (TMS) with reference to internal solvent and coupling constants 'J' in Hz. The mass spectra were recorded on Agilent ion trap MS. Infrared (IR) spectra were recorded on a Perkin Elmer FT-IR spectrometer. All the amines used for the preparation of **6a-6j** were purchased from commercial sources.

Ethyl 1-(4-(trifluoromethyl)phenylsulfonyl)piperidine-4-carboxylate 2: To a stirred solution of ethyl piperidine-4-carboxylate **1** (500 mg, 3.4 mmol) in THF (5 mL) was added triethylamine (0.99 mL, 6.8 mmol) and 4-trifluoromethylsulfonyl chloride (1.2g , 5.2 mmol). The reaction mixture was allowed to stir at room temperature for 2 h to obtain the white solid. The precipitated solids were filtered, washed with n-Hexane and dried at the pump to afford compound **2**. Colorless liquid; Yield: 500 mg, 40%; ^{1}H NMR (400 MHz, DMSO-D_6): δ 7.90 (d, 2 H, *J* = 7.0 Hz), 7.82 (d, 2 H, *J* = 6.8 Hz), 4.15 (q, 2 H, *J* = 6.9 Hz), 3.62 (m, 2 H), 2.60 (m 2 H), 2.30 (m,1 H), 2.01 (m, 2 H), 1.90 (m, 2 H), 1.20 (t, 3 H, *J* = 7.2 Hz); EI- MS: m/z (rel.abund. %): 351 (M^+, 100).

Synthesis of 1-(4-(trifluoromethyl)phenylsulfonyl)piperidine-4-carboxylic acid 3: To a stirred solution of MeOH (5 mL) containing compound **2** (500 mg, 1.4 mmol), was added NaOH (227 mg, 5.6 mmol) and water (1 mL). The resulting mixture was stirred at room temperature for 6 h. The reaction mixture was poured into ice cold water, acidified with 2N HCl, diluted with diethyl ether (50 mL) followed by water (7 mL). The organic layer was separated, washed with water (4 x 50 mL) followed by brine solution to obtain the compound **3**. White solid; Yield: 350 mg, 72%; IR (KBr): υ_{max} 3415, 2924, 2854, 1698, 1404, 1384, 1404, 1367, 1334, 1324, 1284, 1252, 1163, 1145, 1110, 1062, 1016, 958, 946, 923, 842, 747, 728, 699, 605, 591, 567, 532 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.90 (d, 2 H, *J* = 7.8 Hz), 7.82 (d, 2 H, *J* = 7.6 Hz), 3.62 (m, 2 H), 2.60 (m, 2 H), 2.30 (m, 1 H), 2.01 (m, 2 H), 1.90 (m, 2 H); ESI MS: m/z (rel.abund. %): 335.94 (M^+, 100).

Synthesis of Methyl 5-(4-(trifluoromethyl) phenylsulfonyl) piperidine-4-carboxamido)-2-methylbenzoate 4: To a stirred solution of THF (5 mL) containing compound **3** (350 mg, 1.03 mmol) were added sequentially, HOBT (224 mg, 1.6 mmol), EDC.HCl (306 mg, 1.6 mmol),TEA (0.28 mL, 2.0 mmol) and methyl 5-amino-2-methylbenzoate **3a** (198 mg, 1.2 mmol). The resulting mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with dichloromethane (10 mL) followed by water (15 mL), the organic layer was separated, washed with water (4 x 15 mL) followed by brine solution to obtain the crude compound **4**.The crude compound was purified by column chromatography using 60-120 silica gel and eluted with 20% EtOAC / Hexane to afford compound **4.** Pale white solid ;Yield: 300 mg, 69%; M.p: 165-167 ^oC; IR (neat): υ_{max} 3290, 2954, 1721, 1653, 1583, 1520, 1438, 1404, 1358, 1319, 1259, 1159, 942, 823, 723, 594 cm^{-1}; ^{1}H NMR: ($CDCl_3$, 400MHz): δ 10.0 (br.s, 1 H), 8.0 (m, 5 H), 7.70 (br.s, 1 H), 7.2 (br.s, 1 H), 3.80 (s, 3 H), 3.70 (m, 2 H), 2.50 (s, 3 H) , 2.40 (m, 3 H), 1.85 (m, 2 H), 1.70 (m, 2 H). ESI MS: m/z (rel.abund. %): 485.10 (M^+,100).

5-(4-(trifluoromethyl)phenylsulfonyl)piperidine-4-carboxamido)-2-methylbenzoic acid (5)*:* To a stirred solution of MeOH (5 mL) containing compound **4** (300 mg, 0.619 mmol), were added NaOH (99 mg, 2.47 mmol) and water (0.6 mL). The resulting mixture was stirred at room temperature for 6 h. The reaction mixture was poured into ice cold water and acidified with 2N HCl, diluted with diethyl ether (50 mL) followed by water (7 mL), the organic layer was separated and washed with water (4 x 5mL) followed

by brine solution to afford compound **5**. Light brown solid; Yield: 250 mg, 85%; M.p: 264-266 ^{o}C; IR (neat): υ_{max} 3301, 2932, 2560, 1704, 1654, 1524, 1403, 1350, 1326, 1147, 1063, 948, 1147, ,828, 726, 893 cm^{-1}; ^{1} H NMR: ($CDCl_3$, 400MHz): δ 12.90 (m, 1 H), 9.80 (s, 1 H), 8.0 (m, 5 H), 7.65 (dd, 1 H, *J* = 1.6 Hz, 2.4 Hz), 7.20 (d, 1 H, *J* = 8.4 Hz), 3.70 (m, 2 H), 2.50 (s, 3 H), 2.50 (m, 2 H), 2.40 (m, 1 H), 1.90 (m, 2 H), 1.70 (m, 2 H). ESI MS: m/z (rel.abund. %): 471.10 (M^+, 100).

General Procedure for piperidine 4-carboxamide derivatives: To a stirred solution of THF (2 mL) containing compound **5** (100 mg, 0.212 mmol) were added sequentially, propylphosphonic anhydrate (PPA) (101 mg, 0.319 mmol), TEA (0.6 mL,0.042 mmol) and various amines **a-j** (0.01 mmol). The resulting mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with dichloromethane (10 mL) followed by water (15 mL), the organic layer was separated and washed with water (4 x 15 mL) followed by brine solution to obtain the crude compound **6a-6j**. The crude compound was purified by preparative-TLC and eluted with 25% EtOAC/Hexane to afford compounds **6a – 6j.**

N-(3-(2,2,2-trifluoroethylcarbamoyl)-4-methylphenyl)-1-(4 -(trifluoromethyl)phenylsulfonyl)piperidine-4-carboxamide 6a: White solid; Yield: 110 mg, 47%; M.p: 202-206 ^{o}C; IR (KBr): υ_{max} 3341, 3258, 3103, 2959, 2932, 2854, 1693, 1658, 1542, 1405, 1326, 1261, 1163, 1063, 934, 844, 725, 594 cm^{-1}; ^{1} H NMR: ($CDCl_3$, 400 MHz): δ 7.90 (d, 2 H, *J* = 7.6 Hz), 7.82 (d, 2 H, *J* =7.8 Hz), 7.64 (m, 1 H), 7.32 (dd, 1 H, *J* =1.4, 2.4 Hz),7.24 (m, 1 H), 7.18 (d, 1 H, *J* = 7.6 Hz), 6.20 (m, 1 H), 4.15 (m, 2 H), 3.82 (m, 2 H), 2.56 (m, 2 H), 2.40 (s, 3 H), 2.24 (m, 1 H), 1.96 (m, 4 H); ^{13} C NMR: ($CDCl_3$, 100 MHz): 13.18, 19.19, 22.21, 38.06, 57.86, 115.51, 115.30, 120.88, 123.93, 124.01, 127.28, 132.30, 136.80, 152.04, 159.11; ESI MS: m/z (rel.abund. %): 551.91 (M^+, 100).

N-(3-(cyclopropylmethylcarbamoyl)-4-methylphenyl)-1-(4-(trifluoromethyl) phenylsulfonyl) piperidine-4-carboxamide 6b: Brown solid; Yield: 115 mg, 51%; M.p: 110-113 ^{o}C; IR (neat): υ_{max} 3351, 3299, 3081, 2927, 1642, 1540, 1404, 1323, 1168, 1134, 1108, 1062, 1016, 933, 844, 787, 739, 725, 607, 595, 571 cm^{-1}; ^{1} H NMR: ($CDCl_3$, 400 MHz): δ 7.92 (m, 4 H), 7.58 (d, 1 H, *J* = 4.4 Hz), 7.40 (dd, 1 H, *J* = 4.4 , 6.2 Hz), 7.19 (d, 1 H, *J* = 7.2 Hz), 3.85 (m, 2 H), 3.40 (d, 2 H, *J* =7.4 Hz), 3.0 (d, 1 H, *J* = 7 .2 Hz), 2.45 (m, 2 H, *J* = 7.2 Hz), 2.35 (s, 3 H), 1.85 (m, 4 H), 0.5 (m, 2 H); ESI MS: m/z (rel.abund. %): 523.97 (M^+, 100).

N-(3-(2-methyl-neopentylcarbamoyl)-4-methylphenyl)-1-(4-(trifluoromethyl) phenylsulfonyl) piperidine -4-carboxamide (6c) : Light Brown solid ;Yield: 100 mg, 69%; M.p: 194-196 ^{o}C; IR (KBr): υ_{max} 3286, 3236, 3072, 2961, 2866, 1665, 1648, 1611, 1543, 1467, 1450, 1404, 1366, 1323, 1249, 1209, 1171, 1137, 1108, 1062, 928, 897, 880, 856, 845, 740, 724, 740, 724, 698,609, 594,521 cm^{-1}; ^{1}H NMR: ($CDCl_3$, 400 MHz): δ 8.25 (m, 1 H), 8.02 (d, 2 H, *J* =7.6 Hz), 7.98 3.40 (d, 2 H, *J* =7.4 Hz), 7.52 (d, 1 H, *J* = 6.6 Hz), 7.4 (dd, 1 H, *J* =6.6 Hz,6.4 Hz), 7.18 (d, 1 H, *J* =7.6 Hz), 3.95 (m, 2 H), 3.2 (m, 2 H), 2.45 (m, 2 H), 2.35 (s, 3 H), 2.34 (m, 1 H), 1.95 (m, 2 H), 1.85 (m, 2 H), 0.9 (s, 9 H). ^{13}C NMR: ($CDCl_3$, 100 MHz): δ 18.17, 18.36, 19.89, 24.03, 34.07, 37.28, 42.30, 110.49, 112.88, 114.06, 116.06, 116.67, 117.99, 118.03, 120.12, 122.57, 122.75, 125.73, 126.05, 127.91, 129.24, 132.16, 163.47, 165.84. ESI MS: m/z (rel.abund. %): 540.25 (M^+, 100)

N-(3-(cyclopropylcarbamoyl)-4-methylphenyl)-1-(4-(trifluoromethyl)phenylsulfonyl)piperidine-4-carboxamide 6d: White solid ;Yield: 105 mg, 48%; M.p: 149-151 ^{o}C; ^{1}H NMR: ($CDCl_3$, 400 MHz): δ 7.92 (d, 2 H, *J* = 6.6 Hz), 7.80 (d, 2 H, *J* = 6.8 Hz), 7.45 (m, 1H), 7.30 (m, 1H), 7.1 (d, 1H, *J* = 6.6 Hz), 6.40 (m, 1 H), 5.50 (m,1 H), 3.80 (d, 2 H, J = 6.8 Hz), 2.85 (br, 1 H), 2.50 (br, 2 H), 2.32 (s, 3 H), 2.30 (m, 1 H), 2.0 (m, 4 H), 1.32 (m, 1 H), 0.9 (m, 2 H), 0.6 (m, 2 H); ^{13}C NMR: ($CDCl_3$, 100 MHz): δ 18.24, 22.05, 27.23, 41.14, 44.69, 117.92, 120.34, 125.54, 127.35, 130.08, 135.59, 136.35, 139.37,170.47, 171.94; EI MS: m/z (rel.abund. %): 510.2 (M^+, 100).

N-(3-(t-butylcarbamoyl)-4-methylphenyl)-1-(4-(trifluoromethyl)phenylsulfonyl)piperidine-4-carboxamide 6e: Yellow solid; Yield: 110 mg, 49%; M.p: 194-196 ^{o}C; IR (neat): υ_{max} 3434, 3384, 3297, 3056, 2929, 2968, 2855, 1650, 1595, 1531, 1451, 1405, 1355, 1323, 1230, 1225, 1168, 1138, 1108, 1094, 1062, 1017, 929, 887, 842, 786, 739, 725, 697 595, 573. ^{1}H NMR: ($CDCl_3$, 400 MHz): δ 7.92 (d, 2 H, *J* = 7.4 Hz), 7.82 (d, 2 H, *J* = 7.6 Hz), 7.32 (m, 3 H), 7.06 (m, 1 H), 6.40 (m, 1 H), 5.50 (m,1 H), 3.80 (m, 2 H),), 2.50 (m, 2 H), 2.30 (s, 3 H), 2.28 (m, 1 H), 1.85 (m, 4 H), 1.41 (s, 9 H)**;** ^{13}C NMR: ($CDCl_3$, 100 MHz): δ 17.90, 27.09, 27.87, 40.96, 44.55, 50.51, 117.44, 119.76, 125.37, 127.20, 129.21, 129.76, 135.49, 137.59, 139.32, 168.46, 171.74, 172.47; ESI MS: m/z (rel.abund. %): 526.18 (M^+, 100) .

N-(3-(pentan-3yl)carbamoyl)-4-methylphenyl)-1-(4-(trifluoromethyl)phenylsulfonyl)piperidine-4-carboxamide 6f: Pale yellow solid ;Yield: 100 mg, 43%; M.p:160-162 ^{o}C; IR (KBr): υ_{max} 3375, 3307, 3059, 2965, 2932, 2876, 1638, 1613, 1538, 1459, 1404, 1355, 1323, 1251, 1169, 1136, 1108, 1062, 1017, 932, 844, 786, 739, 725, 697, 595, 573; ^{1}H NMR: ($CDCl_3$, 400 MHz): δ 7.94 (d, 2 H, *J* = 7.4 Hz), 7.82 (d, 2 H, *J* = 7.6 Hz), 7.40 (m, 2 H), 7.10 (m, 1 H), 6.40 (m, 1 H), 5.5 (m,1 H), 3.9 (m, 1 H), 3.8 (d, 1 H, *J* = 6.8 Hz), 2.50 (m, 2 H), 2.35 (s, 3 H), 2.30 (m, 1 H), 1.99 (m, 4 H), 1.72 (m, 4 H), 1.48 (m, 3 H), 1.32 (m, 1 H), 0.9 (t, 3 H, J = 6.2 Hz)**;** ^{13}C NMR: ($CDCl_3$, 100 MHz): δ 10.10, 18.50, 27.87, 40.96, 46.50, 52.10, 118.40, 120.76, 125.40, 127.20, 129.21, 130.26, 136.49, 138.50, 140.0, 169.20, 172.52; ESI MS: m/z (rel.abund. %): 540.17 (M^+, 100).

N-(isopropyl-2-methyl)carbamoyl)-4-methylphenyl)-1-(4-(trifluoromethyl) phenylsulfonyl) piperidine-4-carboxamide 6g: Brown solid ;Yield: 105 mg, 53%; M.p: 193-195 ^{o}C; IR (KBr): υ_{max} 3371, 3287, 3060, 2972, 2928, 2854, 1639, 1612, 1595, 1539, 1456, 1404, 1323, 1251, 1169, 1135, 1108, 1094, 1016, 933, 845, 787, 739, 725, 697, 595, 572; ^{1}H NMR: ($CDCl_3$, 400MHz): δ 7.94 (d, 2 H, *J* = 8.4 Hz), 7.82 (d, 2 H, *J* = 8.4 Hz), 7.45 (m, 2 H), 7.35 (dd, 1 H, *J* = 1.2, 1.2 Hz), 7.20 (d, 1 H, *J* = 7.6 Hz), 5.65 (m, 1 H), 4.2 (m, 1 H), 3.8 (m, 1 H), 2.5 (t, 2 H, *J* = 10.8 Hz), 2.35 (s, 3 H), 2.25 (m, 1 H), 1.99 (m, 4 H), 1.25 (d, 6 H, *J* = 6.4 Hz) **;** ^{13}C NMR: ($CDCl_3$, 100 MHz): δ 18.20, 22.09, 27.07, 40.96, 45.40, 118.80, 120.20, 125.20, 127.22, 130.20, 136.10, 137.60, 140.20, 168.40, 172.40; ESI MS: m/z (rel.abund. %): 512.02 (M^+, 100).

N-(Ethyl-2-methyl)carbamoyl)-4-methylphenyl)-1-(4-(trifluoromethyl)phenylsulfonyl)piperidine-4-carboxamide 6h: White solid ;Yield: 100 mg, 47%; M.p: 134-136 ^{o}C; IR (KBr): υ_{max} 3380, 3302, 3071, 2928, 2853, 1639, 1613, 1594, 1538, 1448, 1404, 1323, 1275, 1168, 1135, 1108, 1094, 1016, 932, 844, 786, 739, 725, 595; ^{1}H NMR: ($CDCl_3$, 400 MHz): δ 7.92 (d, 2 H, *J* = 8.4 Hz), 7.82 (d, 2 H, *J* = 8.4 Hz), 7.52 (m, 1 H), 7.45 (m, 1 H), 7.31 (dd, 1 H, *J* = 2.0, 2.4 Hz), 7.12 (d, 1 H, *J* = 8.4 Hz), 5.65 (m, 1 H), 3.80 (m, 2 H), 3.48 (q, 2 H, *J* = 6.8 Hz), 2.5 (m, 2 H), 2.35 (s, 3 H), 2.25 (m, 1 H), 1.99 (m, 4 H), 1.24 (t, 3 H, *J* = 7.2 Hz) **;** EI MS: m/z (rel.abund. %): 498.1(M^+, 100).

N-(cyclohexyl-2-methyl)carbamoyl)-4-methylphenyl)-1-(4-(trifluoromethyl) phenylsulfonyl) piperidine-4-carboxamide 6i: White solid ;Yield: 110 mg, 46%; M.p:221-223 ^{o}C; IR (KBr): υ_{max} 3373, 3292, 3058, 2932, 2856, 1640, 1594, 1541, 1497, 1450, 1404, 1323, 1251, 1168, 1135, 1109, 1094, 1016, 933, 891, 844, 786, 738, 725, 595; ^{1}H NMR: ($CDCl_3$, 400 MHz): δ 9.80 (s, 1 H), 8.06 (d, 2 H, *J* = 8.8 Hz), 8.02 (d, 2 H, *J* = 8.4 Hz), 7.52 (dd, 1 H, *J* = 2.0, 2.4 Hz), 7.42 (d, 1 H, *J* = 2.0 Hz), 7.12 (d, 1 H, *J* = 8.0 Hz), 3.8 (m, 2 H), 2.5 (m, 2 H), 2.3 (m, 1 H), 2.25 (s, 3 H), 1.62-1.80 (m, 9 H), 1.2-1.4 (m, 6 H) **;** ^{13}C NMR: ($CDCl_3$, 100 MHz): δ 18.10, 26.10, 27.80, 34.50, 42.40, 45.10, 50.10, 118.44, 120.46, 125.37, 127.20, 130.21, 135.66, 137.59, 140.30, 168.40, 172.47; EI MS: m/z (rel.abund. %): 552.24 (M^+, 100).

N-(4-methoxybenzyl)-2-methyl)carbamoyl)-4-methylphenyl)-1-(4-(trifluoromethyl) phenylsulfonyl) piperidine-4-carboxamide 6j: Yellow solid ;Yield: 120 mg, 49%; M.p:159-162 ^{o}C; IR (KBr): υ_{max} 3332, 3280, 3054, 2926, 2839, 1672, 1641, 1612, 1532, 1514, 1403, 1349, 1327, 1250, 1164, 1137, 1062, 1036, 1017, 928, 839, 740, 727, 595; ^{1}H NMR: ($CDCl_3$, 400MHz): δ 7.92 (d, 2 H, *J* = 8.0 Hz), 7.82 (d, 2 H, *J* = 8.2 Hz), 7.52 (m, 1 H), 7.34 (d, 1 H, *J* = 6.0 Hz), 7.20 (m,3 H), 7.14 (d, 1 H, *J* = 8.0 Hz), 6.84 (d, 2 H, *J* =

8.2 Hz),6.0 (m, 1 H), 4.5 (d, 2 H, *J* = 7.0 Hz), 3.82 (s, 3 H), 3.85 (m,1 H), 2.50 (m, 2 H), 2.40 (s, 3 H), 2.20 (m, 1H), 2.0 (m, 4 H)**;** EI MS: m/z (rel.abund. %): 590.12 (M^+, 100).

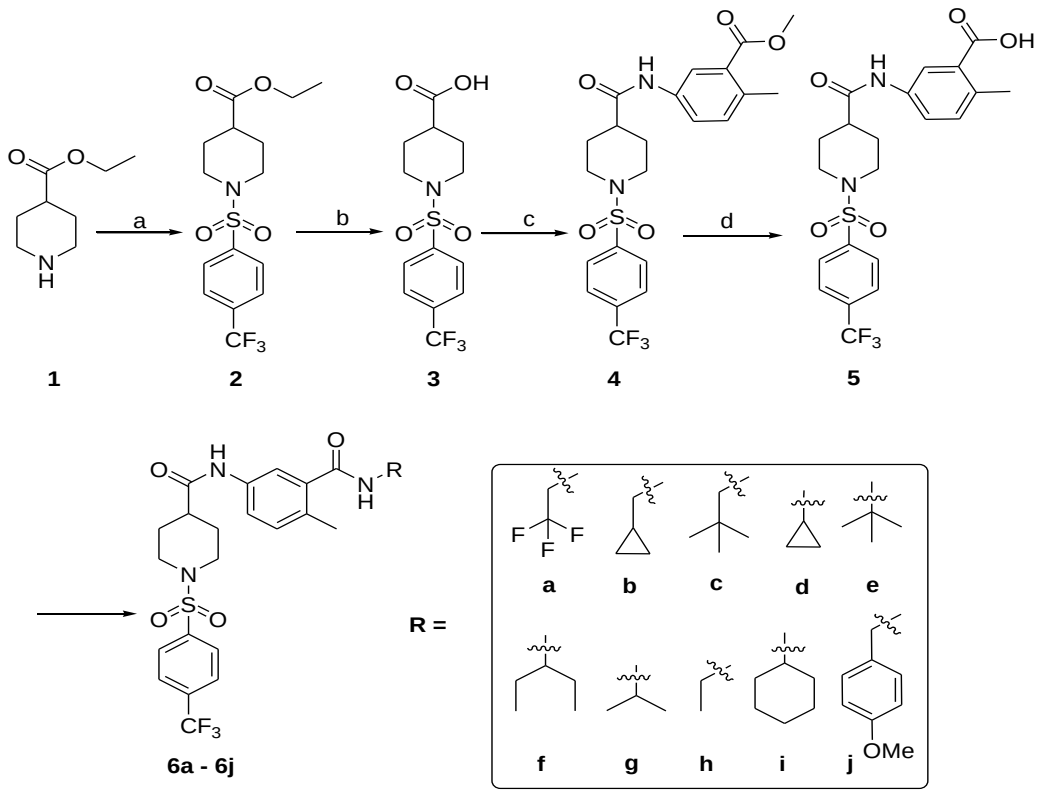
ANTIMICROBIAL BIOASSAY

Piperidine 4-carboxamide derivatives (**6a–6j**) were dissolved in dimethyl sulphoxide at 25 µg/mL concentration. The composition of nutrient agar medium was Yeast extract (5 g), NaCl (10 g), Bactotryptone (10 g), final pH 7.4. The piperidine 4-carboxamide derivatives were tested against two Gram negative strains viz., i) *Escherichia coli* (MTCC 443), *(ii) Pseudomonas aeruginosa* (MTCC 424) and two Gram positive strains viz., (iii) *Staphylococcus aureus* (MTCC96) *iv) Streptococcus pyogenes* (MTCC442) using agar well diffusion method according to the literature protocol [21-23]. After 18 h, the exponentially growing cultures of the six bacteria in nutrient broth at 37 ^oC were diluted in sterile broth. From each of these diluted cultures, 1mL was added to 100 mL sterilized and cooled nutrient agar media to give a final bacterial count of 1 x 10^6 cell/ml. The plates were set at room temperature and later dried at 37 ^oC for 20h. Paper discs (6mm, punched from whatmann no 41 paper) were ultraviolet sterilized and used for the assays. Discs were soaked in different concentration of the test solution and placed on the inoculated agar media at regular intervals of 6-7 cm, care was taken to ensure that excess solution was not on the discs. The plates were incubated at 37 ^oC in an inverted fashion. 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

Synthesis: The piperidine 4-carboxamide derivatives **6a-6j** described in this paper were prepared according to the synthetic **Scheme 1**. The reaction of ethyl piperidine-4-carboxylate **1** with 4-trifluoromethylsulfonyl chloride was carried out in the presence of triethylamine to obtain methyl 1-(4-(trifluoromethyl)phenylsulfonyl)piperidine-4-carboxylate **2.** The hydrolysis of compound **2** with NaOH in methanol resulted in the formation of carboxylic acid derivative **3**. The amide coupling of carboxylic acid derivative **3** with methyl-5-amino-2-methylbenzoate in presence of HOBt and EDC.HCl furnished methyl-5-(4-(trifluoromethyl)phenylsulfonyl)piperidine-4-carboxamido)-2-methylbenzoate **4.** The hydrolysis of compound **4** with NaOH in methanol at room temperature leads to the formation of carboxylic acid derivative **5**. Compound **5** upon treatment with various amines **a-j** in presence of propylphsophonic anhydrate (PPA) and triethylamine at room temperature produced acid amide derivatives **6a-6j**.

Antibacterial evaluation: Preliminary anti-microbial evaluation with ten new piperidine-4-carboxamide derivatives **6a-6j** (**Table 1**) has established some interesting structure-activity relationships. Compounds **6a, 6c, 6e 6f, 6g** and **6h** exhibited excellent activity against all the tested bacterial strains when compared with the standard drug Norfloxacin, while the compounds **6b, 6d and 6i** showed good activity and compound **6j** displayed moderate activity against all the tested bacterial strains. In general, it is observed that the compounds incorporated with the alkyl substituent exhibited excellent activity when compared to the standard drug Norfloxacin and the compounds having the cyclic substituent in the series displayed good to moderate activity. From the above observations it can be concluded that by altering the suitable alkyl chain in the piperidine 4-carboxamide scaffold may lead to a promising antibacterial agent for all the tested bacterial strains such as *Escherichia coli*, *Pseudomonas aeruginosa*, *Streptococcus pyogenes* and *Staphylococcus aureus* bacterial strains.



Scheme 1. Synthesis of piperidine 4-carboxamide derivatives **(6a – 6j)**

Table-1 Results of Antibacterial Activity of Compounds **6a-6j** (Concentration Used 25 µg/mL of DMSO).

Compound No.	*Gram negative*		*Gram positive*	
	E.Coli ***MTCC 443***	*P.aeruginosa* ***MTCC 424***	*S.Aureus* ***MTCC 96***	*S.Pyogenes* ***MTCC 442***
	Zones of Inhibition of compounds 6a –6f in mm			
6a	22	17	24	16
6b	20	18	21	17
6c	22	17	24	16
6d	20	15	19	14
6e	22	17	24	16
6f	22	17	24	16
6g	22	17	24	16
6h	22	17	24	16
6i	21	16	23	15
6j	16	13	15	12
Standard Drug Norfloxacin (25 µg/mL of DMSO)	25	19	25	19

Experimental Conditions: a) 4-trifluoromethylsulfonyl chloride, triethyl amine, DCM, r.t., 2 h; b) NaOH, MeOH, H_2O, r.t, 6 h; c) HOBT, EDC. HCl, triethylamine, methyl-5-amino-2-methylbenzoate,THF, r.t, 12 h; d) NaOH, MeOH, H_2O, r.t, 6 h; e) Amines **(a – j),** Propylphosphoric acid, triethylamine, THF, r.t, 12 h.

APPLICATIONS

In the present study the synthesized derivatives have been screened for their antibacterial activity and were found to be promising as active pharmacophore. Further studies are undergoing to explore the scope of the various biological activities.

CONCLUSIONS

Ten new piperidine-4-carboxamide derivatives **6a-6j** were prepared and tested against: *Escherichia coli*, *Pseudomonas aeruginosa*, *Streptococcus pyogenes* and *Staphylococcus aureus* bacterial strain with reference to the standard drug Norfloxacin at the concentration 25 µg/mL. It is observed that the compounds incorporated with substituent's such as aliphatic alkyl chains exhibited excellent activity, while the compounds having the cyclic ring substituent in the series displayed good to moderate activity. From these findings it can be concluded that by altering the suitable 'R' in the piperidine-4-caboxamide derivative may lead to a promising antibacterial agent.

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REFERENCES

[1] Ming-xin Dong, Lu Lu, Haitao Li, Xiaohua Wang, Hong Lu, Shibo Jiang, Qiu-yun Dai. *Bioorg.Med.Chem.Lett*., **2012,** 22, 3284-3286.
[2] Jiange Zhang, Pei Zhang, Xianbo Liu, Kai Fang, Guoqiang Lin. *Bioorg.Med.Chem.Lett.*, **2007,** 17, 3769-3773.
[3] Antonios Kolocouris, Dimitrios Tataridis, George Fytas, Thomas Mavromoustakos, George B. Foscolos, Nicolas Kolocouris, Erik De Clercq. *Bioorg.Med.Chem.Lett*., **1999,** 9, 3465-3470.
[4] Zhao Dang, Yushe Yang, Ruyun Ji, Shuhua Zhang. *Bioorg.Med.Chem.Lett*., **2007,** 17, 4523-4526.
[5] Hyo-Nim Shin, Seon Hee Seo, Hyunah Choo, Gyochang Kuem, Kyung Il Choi, Ghilsoo Nam. *Bioorg.Med.Chem.Lett*., **2013,** 23,1193-1196.
[6] M.K. Prashanth, D. Hosakere, K.M. Revanasiddappa, B. Lokanatha Rai, *Bioorg.Med.Chem.Lett*., **2012,** 22, 7065-7070.
[7] Yong-Yong Zheng, Lin Guo, Xue-Chu Zhen, Jian-Qi Li. *Eur.J.Med. Chem.*, **2012,** 54**,** *123-136.*
[8] J. Babu Mavunkel, J. John Perumattam, Xuefei Tan; R. Gregory Luedtke, Qing Lu, Don Lim, Darin Kizer, Sundeep Dugar, Sarvajit Chakravarty, Yong-jin Xu, Joon Jung, Albert Liclican, E. Daniel Levy, Jocelyn Tabora. *Bioorg.Med.Chem.Lett*., **2010**, 20, 1059-1062.
[9] Xuwang Chen, Peng Zhan, Xin Liu, Ziheng Cheng, Caicai Meng, Siyuan Shao, Christophe Pannecouque, Erik De Clercq, Xinyong Liu. *Bioorg.Med.Chem.*, **2012,** 20, 3856-3864.
[10] Xuwang Chen, Peng Zhan, Christophe Pannecouque, Jan Balzarini, Erik De Clercq, Xinyong Liu. *Eur.J.Med. Chem.*, **2012**, 51, 60-66.
[11] Susumu Watanuki, Keisuke Matsuura, Yuichi Tomura, Minoru Okada, Toshio Okazaki, Mitsuaki Ohta, Shin-ichi Tsukamoto. *Bioorg.Med.Chem.*, **2011,** 19, 5628-5638.
[12] Xin-Hua Liu, Jun Li, Jing Bo Shi, Bao-An Song, Xing-Bao Qi. *Eur.J.Med. Chem.*, **2012,** 51, 294-299.

[13] J.A. Colapret, G. Diamantidis, H.K. Spencer, T.C. Spaulding, F.G. Rudo, *J Med Chem.,* **1989**, 32, 968.
[14] H. Khalid, Aziz-UR-Rehman, M.A. Abbasi, M. Khan. *Int., J. Pharmacy and Pharmaceutical Sciences*, **2002**, 4, 443-448.
[15] S. Kalpesh, Parikh, P. Sandip Vyas., *Der Chemica Sinica.,* **2012**, 3, 430-434.
[16] Manish Mittal, M. Suraj Sarode, M. Ramesh, G. Shingare, Vidyasagar, S. Birendra. *J. Chem. Pharm. Res.*, **2011**, 3, 766-774.
[17] Hemendra Pratap Singh**.**, sayan D Gupta2., Moorthy, N.S.H.N., Int., J. Pharm. Tech Research., **2009,** 1, 282-287.