Asian Journal of Chemistry; Vol. 28, No. 1 (2016), 138-142

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2016.19279

Synthesis and Antibacterial Studies of 1-[3-(Trifluoromethoxy)-phenylmethanone]piperidine-4-carboxylic Acid Derivatives

V.B. REDDY[1], V.K. PRASAD[2] and P. VENKATARAMANA[1,*]

[1]Department of Chemistry, Sri Krishnadevaraya University, Anantapur-515 003, India
[2]Denisco Chemicals Pvt. Ltd., Hyderabad-500 855, India

*Corresponding author: E-mail: ramanapv2013@yahoo.com; ramanapv2013@gmail.com

Received: 27 April 2015; *Accepted*: 25 June 2015; *Published online*: 5 October 2015; AJC-17562

Synthesis of novel piperidine-4-carboxamide derivatives as antibacterial agents has elevated impact on medicinal field. In the present work, ten new compounds were synthesized and screened toward their antibacterial studies. The structures of these compounds were characterized and analyzed by spectral studies such as IR, mass and ^{1}H NMR and compounds **6a** and **6c-6h**, were observed to possess potent antimicrobial activity.

Keywords: Derivatives of piperidine-4-carboxamide, Synthesis, Antibacterial screening.

INTRODUCTION

The piperidine structure is the important scaffold for several significant bioactive molecules [1]. Piperidine occurs naturally and can be obtained from *Pipernigrum* L [2] and several other synthetic methods have also been presented for its synthesis [3]. Previous researchers have identified the importance of piperidine scaffolds, which possessed an extensive range of pharmacological applications. The scaffolds and the synthetic derivatives of piperidine were observed to be active against various bacterial and fungal strains [4,5]. In the present decade, synthesis of many of the piperidine scaffolds and their derivatives have been reported by our research scientists with various biological activities display biological significance such as CC Chemokine Receptor [6] antioxidant activities [7], microbial activity [8], antidepressant and antioxidant activity [9,10], p38α MAP kinase inhibitors [11], anti-HIV [12,13], antihypertensive [14] and antitumor agents [15]. Encouraged by the various biological activities related with the piperidine scaffolds and in continuation of our work [16]. We report here the synthesis, characterization and antibacterial activity of new piperidine 4-carboxamide scaffold and its derivatives (**6a-6j**).

EXPERIMENTAL

Purification of solvents was carried out according to standard procedures 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 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.

Methyl 1-[3-(trifluoromethoxy)phenylmethanone]-piperidine-4-carboxylate (2): To the solution of methyl piperidine-4-carboxylate (**1**) (500 mg, 3.4 mmol) in THF (5 mL) was added triethylamine (0.99 mL, 6.8 mmol) and 3-trifluoromethoxy benzoyl chloride (1.2 g, 5.2 mmol). The reaction contents were allowed to stir at room temperature for 12 h to obtain the white solid. The precipitated solids were filtered, washed with *n*-hexane and dried at the pump to afford compound **2**. Colourless liquid; Yield: 510 mg, 48 %; b.p.: 185-190 °C; IR (KBr, ν_{max}, cm^{-1}): 3457, 2955, 1734, 1635, 1583, 1448, 1375, 1317, 1260, 1217, 1171, 1039, 962, 902, 798, 74; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42 (t, *J* = 12.0 Hz, 1H), 7.32 (d, *J* = 12.0 Hz, 1H), 7.29 (br, 1H), 7.24 (br, 1H) 4.5 (br, 1H), 3.7 (s, 3 H), 3.72 (t, 1H), 3.2 (m, 2H), 2.52 (m 1H), 2.0 (m, 2H), 1.58 (m, 2 H); ESI- MS: *m/z* (rel. abund. %): 332.10 (M^+, 100).

1-[3-(Trifluoromethoxy)phenylmethanone]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 2 N HCl, diluted with dichloromethane (20 mL) followed by water (7 mL). The organic layer was separated, washed with brine solution to obtain the compound **3**. White solid; Yield: 370 mg, 68 %; m.p.: 175-180 °C; IR (KBr, ν_{max}, cm^{-1}): 3444, 2932, 1727, 1603, 1451, 1374, 1259, 1216, 1172, 1018, 750; ^{1}H NMR (400 $CDCl_3$, 400 MHz): δ 11.7 (br.s,1H) 7.49 (s,1H), 7.43 (d, *J* = 8 Hz, 1H), 7.32 (d, *J* = 8 Hz, 1H),7.29 (s, 1H), 4.45 (br, 1H), 3.82 (br, 1H), 3.11 (m, 2 H), 2.64 (m, 1H), 2.04 (m, 2H), 1.760 (m, 2 H); ESI- MS: *m/z* (rel. abund. %): 318.27 (M^+, 100).

Methyl-5-[3-(trifluoromethoxy)phenylmethanone-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 (2 × 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 30 % EtOAc/Hexane to afford compound **4.** Pale white solid; Yield: 280 mg, 66 %; m.p.: 160-162 °C; IR (neat, ν_{max}): 3431, 2925, 2858, 1620, 1442, 1255, 1219, 1170, 1079, 954; ^{1}H NMR: ($CDCl_3$, 400 MHz): δ 7.96 (br.s, 1H-NH), 7.66 (d, *J* = 6.4 Hz, 1H), 7.46 (t, *J* = 7.2 Hz, 1H), 7.34 (d, *J* = 7.6Hz, 1H), 7.22 - 7.33 (d, 4 H), 4.68 (br.p, 1H), 3.90 (s, 3H), 3.8(t,1H),3.06 (br.t, 2H) 2.55 (s, 3 H)2.47(q, 1H) 1.87-2.03 (m, 4 H). ESI MS: *m/z* (rel. abund. %): 465.37 (M^+,100).

5-[3-(Trifluoromethoxy)phenylmethanone 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 2 N HCl, diluted with DCM (30 mL) followed by water (7 mL), the organic layer was separated and washed with brine solution to afford compound **5**. Light brown solid; Yield: 200 mg, 75 %; m.p.: 256-258 °C; IR (neat): ν_{max} 3301, 2932, 2560, 1704, 1654, 1524, 1403, 1350, 1326, 1147, 1063, 948, 1147,, 828, 726, 893; ^{1}H NMR: (DMSO, 300 MHz): δ 12.60 (br.s, 1H), 10.0 (s, 1H,NH), 8.2 (s, *J* = 3.2 Hz, 1H), 7.69 (d, *J* = 2.8 Hz, 1H), 7.66 (t, *J* = 2.8 Hz, 1H), 7.33 (d, 3 H), 7.19 (d, *J* = 11.2 Hz, 1H), 4.50 (br, 1H), 3.50 (br, 1H), 3.12 (br, 1H), 2.89 (br, 1H), 2.59 (br, 1H), 2.45 (s, 3 H),1.63-1.91 (br,4H). ESI MS: *m/z* (rel. abund. %): 448.9 (M^-, 100).

General experimental procedure for the synthesis of piperidine 4-carboxamide derivatives (6a-6j): To a stirred solution of THF (2 mL) containing compound **5** (100 mg, 0.212 mmol) were added sequentially, HATU (120 mg, 0.318 mmol), EDC.HCl (61 mg, 0.318 mmol), TEA (0.6 mL,0.42 mmol) and various amines (0.318 mmol). The resulting mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with dichloromethane (10 mL) followed by water (10 mL), the organic layer was separated and washed with 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-[3-(trifluoromethoxy)phenylmethanone]piperidine-4-carboxamide (6a): White solid; Yield: 50 mg, 45 %; m.p.: 137 °C; IR (KBr, ν_{max}, cm^{-1}): 3478, 3278, 3061, 2926, 2861, 1658, 1621, 1539, 1497, 1450, 1411, 1260, 1219, 1162, 1044, 954, 830, 749, 700, 635; ^{1}H NMR: ($CDCl_3$, 400 MHz):): δ 7.66 (s, 1H,NH), 7.48 (s, *J* = 10.0 Hz, 1H), 7.45 (d, *J* = 10.20 Hz, 1H), 7.37 (d, 2 H), 7.33 (t, 2 H), 7.18 (d, *J* = 10.8 Hz, 1H), 5.84 (t, 1H, NH), 4.54 (br, 1H), 4.08(m, 2H), 3.75 (br, 1H), 2.99 (br, 2H), 2.52 (m, 1H), 2.40 (s, 3H), 2.04 (br.q, 4 H); ESI MS: *m/z* (rel. abund. %): 531.8 (M^+, 100).

N-[3-(Cyclopropylmethylcarbamoyl)-4-methylphenyl]-1-[3-(trifluoromethoxy)phenylmethanone]piperidine-4-carboxamide (6b): Brown solid; Yield: 55 mg, 50 %; m.p.: 172-176 °C; IR (neat, ν_{max}, cm^{-1}): 3403, 2927, 2852, 1633, 1417, 1252, 1217, 1157, 668, 531; ^{1}H NMR: ($CDCl_3$, 300 MHz): δ 7.60 (d, *J* = 10.8 Hz, 2H), 7.48 (t, *J* = 10.4 Hz, 1H), 7.34 (m, 3 H), 7.15 (d, *J* = 10.8 Hz, 1H), 6.02 (br, 1H), 4.52 (br,1H), 3.75 (br,1H), 2.99 (m, 1H), 2.88 (m, 2H), 2.56 (m, 1H), 2.49 (s, 3H), 2.04 (m, 4H), 0.895 (q, *J* = 8.8 Hz, 2H), 0.65 (q, 2H); ESI MS: *m/z* (rel. abund. %): 489.9 (M^+, 100).

N-[3-(2-Methyl-neopentylcarbamoyl)-4-methylphenyl]-1-[3-(trifluoromethoxy)phenylmethanone]piperidine-4-carboxamide (6c): Light Brown solid; Yield: 75 mg, 65 %; m.p.: 190-192 °C; IR (KBr, ν_{max}, cm^{-1}): 3453, 3299, 3064, 2957, 2863, 2109, 1624, 1542, 1497, 1448, 1410, 1254, 1218, 1176, 1033, 952, 827, 749, 699, 634; ^{1}H NMR: ($CDCl_3$, 300 MHz): δ 7.66 (s, 1H,NH), 7.48 (t, *J* = 10.0 Hz, 1H), 7.33-7.37 (dd, 3H), 7.29 (d, 2H), 7.17 (d, *J* = 10.8 Hz, 1H), 5.84 (t, 1H, NH), 4.54 (br,1H), 3.75 (br, 1H), 3.26 (d, *J* = 8.8 Hz, 2H), 3.01 (br, 2H), 2.52 (m, 1H), 2.40 (s, 3H), 2.04 (br, 4H), 0.98 (s, 9H); ^{13}C NMR: ($CDCl_3$, 400 MHz): δ 19.18, 27.31, 28.66, 32.19, 41.74, 43.52, 47.03,51.00, 118.50, 119.52, 121.68, 122.11,125.15, 130.24, 131.31, 135.86, 137.20, 137.72, 149.14, 168.60, 170.22, 172.65. ESI MS: *m/z* (rel. abund. %): 520.28 (M^+, 100)

N-[3-(*t*-Butylcarbamoyl)-4-methylphenyl]-1-[3-(trifluoromethoxy)phenylmethanone]piperidine-4-carboxamide (6d): Yellow solid; Yield: 70 mg, 63 %; m.p.: 187-189 °C; IR (neat, ν_{max}, cm^{-1}): 3439, 3302, 3063, 2958, 2924, 2860, 1641, 1542, 1495, 1449, 1410, 1366, 1326, 1254, 1218, 1169, 1036, 960, 823, 797, 633; ^{1}H NMR: ($CDCl_3$, 400 MHz): δ, 7.48 (br,d, *J* = 8.4 Hz, 3H), 7.35 (t, *J* = 7.2 Hz, 2H), 7.29 (d, *J* = 7.2 Hz, 2 H), 7.13 (d, *J* = 8.4 Hz, 1H), 5.56 (s, 1H, NH), 4.54 (br, 1H), 3.75 (br, 1H), 2.96 (br, 2 H), 2.52 (m,1H) 2.36 (s, 3H), 1.86 (br, 4H), 1.35 (s, 9 H); ESI MS: *m/z* (rel. abund. %): 506.50 (M^+, 100).

N-[3-(Pentan-3yl-carbamoyl)-4-methylphenyl]-1-[3-(trifluoromethoxy)phenylmethanone]piperidine-4-carboxamide (6e): Pale yellow solid; Yield: 80 mg, 70 %;

m.p.: 162-165 °C; IR (KBr, ν_{max}, cm^{-1}): 3292, 3067, 2965, 2932, 2876, 1630, 1543, 1496, 1448, 1411, 1375, 1325, 1255, 1218, 1710, 1095, 1036, 956, 888, 825, 794, 699, 634; ^{1}H NMR: ($CDCl_3$, 400 MHz): δ, 7.65 (br, 1H, NH), 7.50 (br, 1H), 7.43 (m, 2H), 7.41 (m, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.33 (d, *J* = 7.6 Hz, 1H), 7.15 (d, *J* = 8.0 Hz, 1H), 5.50 (d, *J* = 8.0 Hz, 1H, NH), 4.54 (br, 1H), 3.98 (br, 1H), 3.88 (br, 1H), 3.00 (br, 2 H), 2.52 (m, 1H), 2.39 (s, 3H), 1.86 (br, 4 H), 1.66 (p, 2 H), 1.50 (p, 2 H), 0.99 (t, 6H); ^{13}C NMR: ($CDCl_3$, 400 MHz): δ 10.42, 19.05, 27.44, 28.64, 40.74, 43.42, 47.03, 52.69, 117.31, 118.57, 119.04, 119.50, 121.10, 122.10, 125.14, 130.21, 131.18, 135.83, 137.37, 149.13, 168.60, 170.06, 172.79; ESI MS: *m/z* (rel. abund. %): 520.0 (M^+, 100).

N-[(Isopropyl-2-methyl carbamoyl)-4-methylphenyl]-1-[3-(trifluoromethoxy)phenylmethanone]piperidine-4-carboxamide (6f): Brown solid; Yield: 75 mg, 69 %; m.p.: 185-188 °C; IR (KBr, ν_{max}, cm^{-1}): 3444,, 3301, 3064, 2971, 2927, 2861, 1633, 1542, 1496, 1449, 1411, 1369, 1328, 1258, 1218, 1170, 1034, 953, 888, 825, 803, 750, 699, 634,543; ^{1}H NMR: ($CDCl_3$, 400 MHz): δ 7.54 (br, 1H, NH), 7.44 (d, 2 H), 7.34 (t, 2H), 7.29 (dt, 2H), 7.14 (d, *J* = 8.0 Hz, 1H), 5.52 (d, *J* = 8.0 Hz, 1H, NH), 4.7 (br,1H), 4.25 (m, 1H), 3.79 (br, 1H), 3.0 (br, 2H), 2.52 (br, 1H), 2.38 (s, 3H), 1.86 (br, 4H), 1.17 (d, 6 H); ESI MS: *m/z* (rel. abund. %): 492.5 (M^+, 100).

N-[(Ethyl-2-methyl carbamoyl)-4-methylphenyl]-1-[3-(trifluoromethoxy)phenylmethanone]piperidine-4-carboxamide (6g): White solid; Yield: 65 mg, 62 %; m.p.: 130-132 °C; IR (KBr, ν_{max}, cm^{-1}): 3256, 3073, 2969, 2929, 2871, 1632, 1590, 1563, 1492, 1433, 1411, 1377, 1347, 1338, 1318, 1251, 1205, 1171, 1078, 1040, 959, 909, 890, 805, 793, 830, 750, 697, 718, 629, 602; ^{1}H NMR: ($CDCl_3$, 400 MHz): δ 7.64 (br, 1H, NH), 7.44 (t, *J* = 8.0 Hz, 1H), 7.34 (m, 5 H), 7.18 (d, *J* = 8.4 Hz, 1H), 5.80 (m, 1H), 4.54 (br, 1H), 3.88 (br, 1H), 3.5 (p, *J* = 7.2 Hz, 2H), 3.0 (br, 3H), 2.40 (s, 3H), 2.20 (br, 2H), 1.86 (br, 2H), 1.22 (t, *J* = 7.4 Hz, 3H);^{13}C NMR: ($CDCl_3$, 300 MHz): δ 14.80, 17.69, 19.08, 28.67, 34.80, 35.08, 43.54, 109.97, 118.69,119.53, 121.61, 122.13, 125.16, 130.23, 131.33, 135.76, 136.91, 137.73, 149.15, 168.65, 169.81, 172.67; ESI MS: *m/z* (rel. abund. %): 478.54 (M^+, 100).

N-[(Prop-2ynylcarbamoyl)-4-methylphenyl]-1-[3-(trifluoromethoxy)phenylmethanone]piperidine-4-carboxamide (6h): White solid; Yield: 85 mg, 79 %; m.p.: 215-220 °C; IR (KBr, ν_{max}, cm^{-1}): 3437, 3289, 3057, 2924, 2857, 1614, 1541, 1496, 1448, 1409, 1384, 1340, 1323, 1253, 1218, 1171, 1033, 956, 893, 828, 751, 634; ^{1}H NMR: ($CDCl_3$, 300 MHz): δ 7.67 (br, 1H,NH), 7.46 (t, *J* = 10.4 Hz, 1H), 7.38 (m, 4H), 7.29 (d, *J* = 10.4 Hz, 1H), 7.19 (d, *J* = 10.4 Hz, 1H), 6.12 (m, 1H,NH), 4.75 (br, 1H), 4.25 (m, 2H), 3.8 (br, 1H), 3.03 (br, 3H), 2.41 (s, 3H), 2.27 (s, 1H), 1.87 (br, 4H); ^{13}C NMR: ($CDCl_3$, 300 MHz): δ 19.12, 28.62, 29.49, 41.63, 43.48, 71.810, 79.258, 109.99, 118.62, 118.78, 119.52, 122.02, 122.16, 125.15, 130.25, 131.48, 131.83, 135.75, 137.64, 149.15, 168.68, 169.48, 172.75; ESI MS: *m/z* (rel. abund. %): 488.1 (M^+, 100).

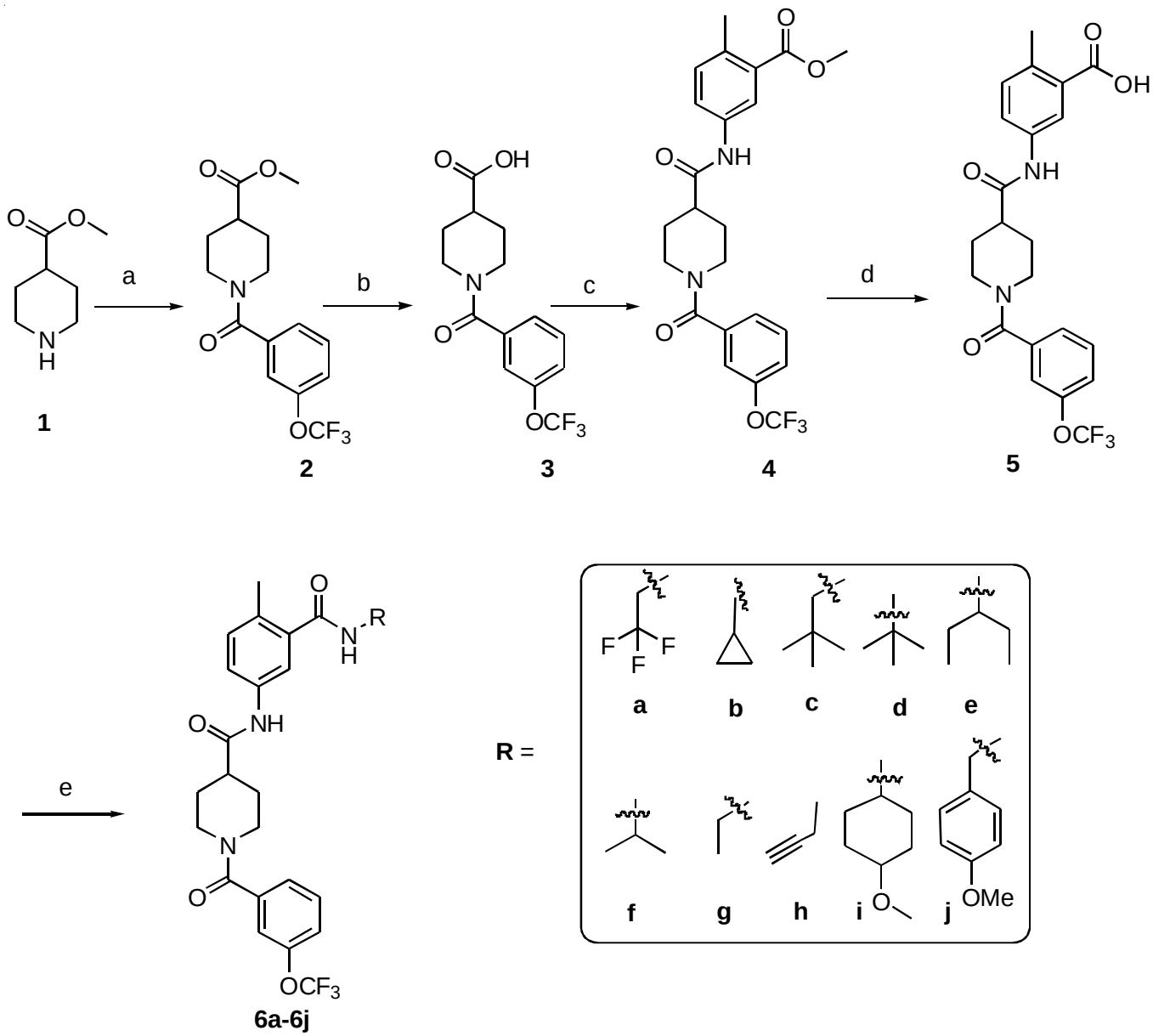
N-[(Cyclohexyl-2-methyl carbamoyl)-4-methylphenyl]-1-[3-(trifluoromethoxy)phenylmethanone]piperidine-4-carboxamide (6i): White solid; Yield: 70 mg, 56 %; m.p.:115-118 °C; IR (KBr, ν_{max}, cm^{-1}): 3428, 3292, 2925, 2856, 2731, 1634, 1596, 1548, 1504, 1490, 1448, 1378, 1338, 1259, 1219, 1173, 1137, 1100, 1033, 958, 928, 902, 803, 784, 754, 702; ^{1}H NMR: ($CDCl_3$, 400 MHz): δ 7.56 (d, *J* = 1.6 Hz, 1H,NH), 7.46 (t, *J* = 8.0 Hz, 1H), 7.35 (m, 5H), 7.17 (d, *J* = 8.4 Hz, 1H), 5.56 (d, *J* = 8.0 Hz, 1H), 4.54 (br, 1H), 3.97 (m, 1H), 3.87 (m, 1H), 3.39 (s, 3H), 3.14 (m, 1H), 3.12 (br, 2 H), 2.49 (m, 1H), 2.38 (s, 3 H), 2.07 (m, 6H), 1.86 (br, 2H), 1.35 (m, 2H), 1.31 (m, 2H); ^{13}C NMR: ($CDCl_3$, 300 MHz): δ 19.01, 28.61, 30.08, 30.50, 41.59, 43.51, 48.32, 55.85, 109.99, 118.62, 118.78, 119.50, 121.73, 122.04, 122.16, 125.13, 130.25, 131.26, 135.63, 137.02, 137.65, 149.15, 168.65, 169.37, 172.70; ESI MS: *m/z* (rel. abund. %): 562.6 (M^+, 100).

N-[(4-Methoxybenzyl)-2-methylcarbamoyl]-4-methylphenyl-1-(3-trifluoromethoxy)phenylmethanone)piperidine-4-carboxamide (6j): Yellow solid; Yield: 85 mg, 68 %; m.p.: 152 °C; IR (KBr, ν_{max}, cm^{-1}): 3289, 3063, 2925, 2858, 1614, 1541, 1513, 1448, 1322, 1251, 1218, 1175, 1033, 954, 895, 824, 750, 635; ^{1}H NMR: ($CDCl_3$, 300 MHz): δ 7.58 (br, 1H, NH), 7.45 (m, 5H), 7.35 (m, 3 H), 7.16 (d, *J* = 11.2 Hz, 1H), 6.88 (d, 2H, *J* = 9.2 Hz), 6.09 (m, 1H), 4.70 (m, 1H), 4.54 (d, *J* = 8.0 Hz, 2H), 3.80 (s, 3 H), 3.80 (br, 1H), 3.0 (m, 2 H), 2.50 (m, 1H), 2.47 (s, 3 H), 1.85 (m, 4 H); ESI MS: *m/z* (rel. abund. %): 570.31 (M^+, 100).

RESULTS AND DISCUSSION

The present research work describes the synthesis of piperidine 4-carboxylic acid derivatives **6a-6j** as represented in **Scheme-I**. The alkylation of ethyl piperidine-4-carboxylate (**1**) with 4-trifluoromethylsulfonyl chloride was performed in the presence of triethylamine to obtain methyl 1-(4-(trifluoromethyl)phenylsulfonyl)piperidine-4-carboxylate (**2**). The carboxylic acid derivative (**3**) was obtained by hydrolysis of compound **2** with NaOH in methanol. The amide coupling of carboxylic acid derivative (**3**) with methyl-5-amino-2-methylbenzoate was carried out utilizing HOBt and EDC.HCl to afford methyl-5-(4-(trifluoromethyl)phenylsulfonyl)piperidine-4-carboxamido)-2-methylbenzoate (**4**). Hydrolysis of compound **4** with NaOH in methanol at room temperature resulted in the formation of carboxylic acid derivative **5**. Compound **5** upon treatment with various 2° amines in presence of HATU and EDC.HCl and triethylamine at room temperature furnished novel piperidine-4-carboxamide derivatives (**6a-6j**).

Antibacterial activity: The results of antimicrobial studies of the ten new piperidine-4-carboxamide derivatives **6a-6j** (Table-1) have shown some exciting structure-activity relationships. Compounds **6a** and **6c-6h,** exhibited excellent activity against all the tested bacterial strains when compared with the standard drug norfloxacin, while the compounds **6b** and **6i** showed good activity and compound **6j** displayed least activity against all the tested bacterial strains. From the above interpretation, it shows 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. The above observations concludes 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 stains such as *Escherichia coli*, *Pseudomonas aeruginosa,*



Scheme-I: Experimental conditions: a) 3-trifluoromethoxylbenzoyl 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**), HATU, EDC. HCl, triethylamine, THF, r.t, 12 h

TABLE-1
RESULTS OF ANTIBACTERIAL ACTIVITY OF COMPOUNDS **6a-6j** (CONCENTRATION USED 25 µg/mL OF DMSO)

Compound No.	Zone of inhibition (mm)			
	Gram-negative bacteria		Gram-positive bacteria	
	Escherichia coli	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	*Staphylococcus pyogenes*
6a	18	13	20	12
6b	16	14	18	13
6c	18	13	20	13
6d	18	14	19	15
6e	18	13	20	12
6f	18	13	20	12
6g	18	13	20	12
6h	18	13	20	12
6i	17	12	19	11
6j	12	9	11	8
Standard drug*	22	20	21	19

*Norfloxacin (25 µg/mL of DMSO)

Streptococcus pyogenes and *Staphylococcus aureus* bacterial strains.

Conclusion

New piperidine-4-carboxamide derivatives (**6a-6j**) were prepared and tested against *Escherichia coli*, *Pseudomonas aeruginosa, Streptococcus pyogenes* and *Staphylococcus aureus* bacterial strains with reference to the standard drug norfloxacin at the concentration 25 µg/mL. From the findings, it can be concluded 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, that is by altering the suitable 'R' in the piperidine-4-caboxamide derivative may lead to a promising antibacterial agent.

ACKNOWLEDGEMENTS

The authors are thankful to the Head of Department of Chemistry, Sri Krishnadevaraya University, Anantapur, India for his constant encouragement.

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