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Synthesis of novel amide derivatives of furo[3,2-c]pyridin-4-amine as potential antibacterial agents

N. Sree Lakshmana Rao[a], K. R. S. Prasad[a], Mandava V. Basaveswara Rao*[b]

[a]*Deprtement of Chemistry , K L University, Vaddeswaram, Guntur, AP, India.*
[b]*Deprtement of Chemistry , Krishna University, Machilipatnam, AP, India.*

ABSTRACT

*The biological activities associated with furo[3,2-c]pyridine, the synthesis, spectroscopic identification and antibacterial activity of amide analogues (**6a-6k**) derived from 4-aminofuro[3,2-c]pyridine **5** in a few high yielding steps from commercially available 2-Furanldehyde (**Scheme 1**) is described. Amide derivatives of 4-aminofuro [3, 2-c] pyridine (**6a-6k**) was tested for antibacterial activity against Gram positive and Gram negative bacterial strains. The 1-methyl-pyrrole **6i**, 1-methyl indole **6j** and quinoline **6k** moieties showed highest activity (inhibitory zone 19-23 mm) against both the Gram-negative bacteria and Gram-positive bacteria On the other hand, compounds **6e - 6h** showed moderate activity (inhibitory zone 13-18 mm) and **6a - 6d** showed weak activity (inhibitory zone 9 – 12 mm).*

Key words: 2-Furanldehyde, furo [3,2-c]pyridine, amide derivatives, antibacterial activities

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INTRODUCTION

The treatment of bacterial infections remains a challenging therapeutic problem because of emerging infectious diseases and the increasing number of multidrug-resistant microbial pathogens. Therefore, there is an urgent need for development of new antibacterial agents with divergent and unique structure and with a mechanism of action possibly different from that of existing antimicrobial agents [1, 2]. A variety of fused pyridines have been studied for a long time in the field of the chemistry of heterocyclic compounds [3, 4] and play a significant role in bioactive molecules [5, 6]. In recent years many number of articles have been reported on the synthesis and reactivity of various furo [3, 2-*c*] pyridines [7-15]. The furo[3,2-c]pyridine derivatives are emerging as a useful pharmacophore in several therapeutic areas such as, as protease kinase inhibitor [16], antipsychotic activity [17], antihypertension [18], diutetic property [19], treatment of skin diseases [20] and in treating depression and cerebral ischemia [21]. Encouraged by these interesting biological activities associated with furo [3,2-c]pyridine, we report here in the synthesis, spectroscopic identification and antibacterial activity of amide analogues (**6a-6k**) derived from 4-aminofuro[3,2-c]pyridine **5** in a few high yielding steps from commercially available 2-Furaldehyde (**Scheme 1**). The synthesized targets were screened for their antibacterial activity against *Escheria.Coli*, *Pseudomonas .aeruginosa*, *Staphylococcus.aureus* and *Streptococus .pyogenes*, while using Chloramphenicol, as the standard drug.

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 precoated 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 (mp) 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 400MHz. Chemical shifts are reported in δ parts per million (ppm) downfield from tetramethylsilane (TMS) with reference to internal solvent and coupling constants 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 carboxylic acids used for the preparation of **6a-6k** were purchased from commercial sources.

(E)-3-(furan-2-yl) acrylic acid (1)

To a mixture of furan-2-carbaldehyde (5 g, 52.03 mmol), malonic acid (5.95 g, 57.23 mmol), TBAB (26.0 mmol), K_2CO_3 (26.0 mmol) and distilled water (25 mL) was irradiated in a microwave oven at 900 W for 5 min at 100 ^oC. After complete conversion as indicated by TLC, the reaction mass was poured into the ice cold water (50 mL) and the precipitated solid was filtered and dried under vacuum to afford compound **2a,** 6.1 g (yield 85%), m.p. 152-153 ^oC; IR (KBr): ν_{max} 1691 (-C=O), 1666 (-CH=CH-CO, α,β-unsaturated str.), 1410 (C=C str.);cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): ð 7.54 (d, 1H, -CH=CH-C=O, J = 16.2 Hz), 7.50 (d, 1H, furan-H, J = 5.2 Hz), 6.68 (d, 1H, furan-H, J = 5.2 Hz), 6.50 (m, 1H, furan-H), 6.34 (d, 1H, -CH=CH-C=O, J = 16.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$), δ: 111.4, 112.7, 121.6, 134.3, 145.9, 151.6, 170.6; EI MS: m/z (rel.abund.%) 139.1 (M^+, 100).

(E)-3-(furan-2-yl)acrylic acid (2)

To a solution of cyanuric chloride (2.27 g, 5 mmol) in dichloromethane (60 mL), N-methylmorpholine (4.05 mL, 36.90 mmol) was added at 0-5 ^oC with continuous stirring. A white suspension was formed to which a solution of the carboxylic acid **1** (5.0 g, 36.90 mmol) in dichloromethane (10 mL) was added and the stirring was continued for 3 h. The mixture was filtered through and to this filtrate, NaN_3 (2.40 g, 36.90 mmol) added and the stirring was continued for 3 h at room temperature. After completion of the reaction (TLC), the mixture was washed with a saturated solution of $NaHCO_3$ (3 x 10 mL) and then with water (3 x 10 mL). The organic layer was dried with anhydrous Na_2SO_4, passed through a short silica-gel column, and the solvent removed under reduced pressure to afford **2,** 4.1 g (yield 70%), m.p. 58-60 ^oC; IR (KBr): ν_{max} 2146 (-N_3), 1685 (-CH=CH-CO, α,β-unsaturated str.), 1428 (C=C str.) cm^{-1}; ^{1}H- NMR (400 MHz, $CDCl_3$): ð 7.52 (d, 1H, -CH=CH-C=O, J = 16.0 Hz), 7.46 (s, 1H, furan-H), 6.70 (d, 1H, furan-H, J = 8.0 Hz), 6.50 (m, 1H, furan-H), 6.30 (d, 1H, -CH=CH-C=O, J = 16.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 110.6, 116.5, 120.6, 132.3, 144.9, 149.6, 169.1; EI MS: m/z (rel.abund.%) 164.2 (M^+, 100).

Furo [3, 2-c] pyridin-4(5H)-one (3)

To a solution of tributyl amine (4.0 mL, 16.86 mmol) in diphenyl ether (30 mL) heated at 230 °C was added, a pre-mixed solution of azide **2** (5 g, 30.67 mmol) in dichloromethane (15 mL) over a period of 30 min. The reaction mixture was continued to stir at the same temperature for another 30 min. The reaction mixture was cooled to room temperature and diluted with 150 mL of hexane. After stirring for 15 min, the precipitated solid was filtered, washed with hexane (2 x 100 mL) and dried under vacuum to afford **3,** 3.31g (yield 80%), m.p. 186-188 ^oC; IR (KBr): ν_{max} 1664 (-C=ONH str); cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): ð 12.5 (br.s, 1H, NH), 7.56 (d, 1H, furan-H, J = 4.4 Hz), 7.32 (d, 1H, pyridone-H, J = 9.4 Hz), 7.02 (d, 1H, furan-H, J = 4.0 Hz), 6.60 (d, 1H, pyridone-H, J = 9.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$), δ: 110.0, 110.7, 113.4, 129.4, 147.9, 155.4, 163.2; EI MS: m/z (rel.abund.%) 136.2 (M^+, 100).

4-chlorofuro [3, 2-c] pyridine (4)

To a solution of trichloroisocyanuric acid (8.60 g, 37.0 mmol) in toluene (25 mL) was added triphenylphosphine (29.11 g, 111 mmol), at 0-5^{o}C with continuous stirring for 15 min. To the above reaction mixture, compound **3** (5 g, 37 mmol) was added and refluxed for 5.5 h. After completion of the reaction (TLC), the solvent was evaporated to obtain the crude compound. The crude compound was purified by flash column chromatography using 3-5% of MeOH/$CHCl_3$ as an eluent to afford **4**, 3.39g (yield 60%), m.p. 88-89 ^oC; IR (KBr): ν_{max} 3432, 3098, 1571, 1465, 1432, 1330, 1272, 1201, 1053, 1019, 936, 898, 784, 746, 642, 589 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): ð 6.90 (d, 1H, *J* = 4.0 Hz), 7.42 (d, 1H , *J* = 16.0 Hz), 7.70 (d, 1H , *J* = 4.0 Hz),8.28 (d, 1H , *J* = 16.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 104.9, 109.9, 122.4, 142.0, 143.6, 149.7, 160.9; EI MS: m/z (rel.abund.%) 154.2 (M^+, 100).

Furo[3,2-c]pyridin-4-amine (5)

To a stainless steel reactor was added compound **4** (5 g, 29.41 mmol), followed by 1, 4-dioxane (30 mL) and 28% aqueous ammonia (50 mL). The mixture was heated to 150 ^{o}C and developed about 250 psi of pressure. After 17 h, the reaction mixture was cooled to rt and concentrated *in vacuum*. The residue was dissolved in chloroform, washed with brine solution, dried over *anhydrous* Na_2SO_4 and concentrated. The crude compound was purified by flash column chromatography using 3-5% of MeOH/$CHCl_3$ as an eluent to afford amine **5** (Yield: 1.78 g, 45%, brown solid); M.p: 118-120 ^{o}C; IR (KBr): ν_{max} 3452, 3330, 3194, 2958, 2924, 1625, 1596, 1537, 1468, 1440, 1383, 1258, 1209, 1118, 1058, 998, 903, 854 cm^{-1}; ^{1}H NMR (00 MHz, CDCl3): ð 4.90 (br.s, 2H), 6.65 (s, 1H), 6.96 (d, 1H , *J* = 6.0 Hz), 7.58 (s, 1H), 7.98 (d, 1H *J* = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 104.9, 109.9, 113.0, 143.6, 148.2, 157.1, 160.9; EI MS: m/z (rel.abund.%) 135.2 (M^+, 100).

General Experimental Procedure for the Synthesis of amides (6a-6k)

To a stirred solution of furo [3, 2-c] pyridin-4-amine (2.23 mmol) in DMF (25 vol) and triethyl amine (4.46 mmol) was added carboxylic acids (2.23 mmol) followed by HOBT (2.68 mmol) and HBTU (2.68 mmol) and stirred at r.t for 12 h to 16 h. Upon completion, the reaction mixture was concentrated and the residue was extracted with EtOAc. The combined organic layer was washed with water, brine solution, dried and concentrated to afford the crude amide compounds. The crude products are either recrystalliszed or purified by column chromatography to afford the title compounds (**6a-6k**) in yields ranging from 62 to 84%.

N-(furo [3, 2-c] pyridin-4-yl) benzamide (6a)

White solid; Yield: 420 mg, 80%; m.p. 144-146 °C; IR (KBr): ν_{max} 3411, 3248, 3121, 1688, 1607, 1586, 1532, 1492, 1452, 1434, 1362, 1314, 1278, 1254, 1144, 1098, 852, 789, 757, 703, 684 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): ð 7.28 (d, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 16.0 Hz, 1H), 7.64 - 7.50 (m, 3H), 7.69 (d, *J* = 8.0 Hz, 1H), 8.02 (d, *J* = 16.0 Hz , 2H), 8.18 (d, 1H ,*J* = 8.0 Hz), 9.20 (br.s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): ð 104.9, 109.9, 113.0, 127.5 (2C), 128.9 (2C), 132.2, 134.2, 143.6, 148.2, 160.9, 161.1, 164.8; EI-MS: m/z (rel.abund.%) 239.3 (M^+, 100).

N-(furo [3,2-c]pyridin-4-yl)-4-methylbenzamide (6b)

Brown viscous liquid, Yield: 473 mg, 84% ; IR (neat): ν_{max} 3408, 3242, 3119, 1682, 1601, 1581, 1528, 1488, 1449, 1421, 1352, 1309, 1268, 1251, 1139, 1088, 848, 782, 751, 702, 679 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): ð 2.35 (s, 3H), 6.30 (d, *J* = 16.0 Hz, 1H), 6.60 (d, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 2.0 Hz, 2H), 7.38 (d, *J* = 16.0 Hz, 1H), 7.83 (d, *J* = 2.0 Hz, 2H), 8.12 (d, *J* = 8.0 Hz, 1H), 9.05 (br.s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): ð 24.3, 104.9, 109.9, 113.0, 127.4 (2C), 129.2 (2C),131.2, 141.8, 143.6, 148.2, 160.9, 161.1, 164.83; EI-MS: m/z (rel.abund.%) 253.0 (M^+, 100).

N-(furo[3,2-c]pyridin-4-yl)-4-methoxybenzamide (6c)

Pale yellow viscous liquid, Yield: 450 mg, 75% ; IR (neat): ν_{max} 3339, 3223, 3011, 1680, 1592, 1569, 1510, 1488, 1435, 1412, 1338, 1308, 1256, 1239, 1126, 1078, 842, 784, 742, 669 cm^{-1}; ^{1}H NMR (400 MHz, dmso-d_6): ð 3.83 (s, 3H) , 6.60 (d, *J* = 8.4 Hz, 1H), 7.17 (d, *J* = 2.0 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.92 (d, *J* = 2.0 Hz, 2H), 8.13 (d, *J* = 8.0 Hz, 1H), 9.12 (br.s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): ð 55.8, 104.8, 109.9, 113.0, 114.4 (2C), 126.5, 128.5 (2C), 146.6, 148.1, 160.9, 161.1, 164.0, 164.7; EI- MS: m/z (rel.abund.%) 268.2 (M^+, 100).

N-(furo [3, 2-c] pyridin-4-yl)-2-(p-tolyl) acetamide (6d)

Pale yellow solid, Yield: 365 mg, 62% ; m.p. 114-115 °C; IR (KBr): ν_{max} 3412, 3233, 3100, 1679, 1607, 1584, 1533, 1479, 1452, 1427, 1359, 1315, 1271, 1254, 1138, 1115, 864, 787, 748, 685 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): ð 2.34 (s, 2H), 3.85 (s, 2H), 7.11 (s, 4H), 7.18 (d, *J* = 8.6 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 8.13 (d, *J* = 7.8 Hz, 1H), 8.31 (d, *J* = 8.6 Hz, 1H), 9.15 (br.s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): ð 21.3, 44.5, 104.8, 109.9, 119.5, 129.5 (2C), 129.9 (2C), 132.6, 137.3, 146.6, 146.7, 152.5, 160.9, 171.0; EI- MS: m/z (rel.abund.%) 266.1 (M^+, 100).

N-(furo [3, 2-c] pyridin-4-yl) cyclohexanecarboxamide (6e)

Yellow oily liquid, Yield: 382 mg, 70% ; IR (neat): ν_{max} 3338, 3100, 1646, 1612, 1564, 1528, 1466, 1437, 1417, 1351, 1309, 1267, 1247, 1131, 1120, 859, 772, 736, 677 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): ð 1.43-1.53 (m, 6 H), 1.55-1.80 (m, 4 H), 2.30-2.38 (m, 1H), 7.18 (d, *J* = 8.6 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 8.13 (d, *J* = 7.8 Hz,

1H), 8.31 (d, *J* = 8.6 Hz, 1H), 9.15 (br.s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): ð 24.8 (2C), 25.3, 29.4 (2C), 43.22, 104.8, 109.9, 119.5, 146.6, 146.7, 152.5, 160.9, 172.9; EI-MS: m/z (rel.abund.%) 244.2 (M^+, 100).

N-(furo[3,2-c]pyridin-4-yl)-4-methylcyclohexanecarboxamide (6f)
Brown viscous liquid, Yield: 415 mg, 72% ; IR (neat): ν_{max} 3327, 3093, 1638, 1610, 1557, 1532, 1468, 1432, 1410, 1348, 1300, 1260, 1241, 1129, 1116, 852, 768, 733, 672 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): ð 0.96 (d, *J* = 6.0 Hz, 3 H), 1.27-1.80 (m, 9 H), 2.28-2.38 (m, 1H), 7.30 (d, *J* = 2.0 Hz, 1H), 7.62 (d, *J* = 5.6 Hz, 1H), 7.89 (d, *J* = 1.6 Hz, 1H), 8.18 (d, *J* = 5.6 Hz, 1H), 10.44 (br.s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): ð 20.7, 26.9 (2C), 30.9, 32.6 (2C), 43.5, 104.8, 109.9, 119.5, 146.6, 146.7, 152.5, 160.9, 172.96 ; EI-MS: m/z (rel.abund.%) 258.1 (M^+, 100).

N-(furo[3,2-c]pyridin-4-yl)-4-methoxycyclohexanecarboxamide (6g)
Yellow oily liquid, Yield: 382 mg, 62% ; ^{1}H NMR (400 MHz, DMSO-d_6): 1.27-2.45 (m, 9 H) , 3.10 (m, 1H), 3.35 (d, *J* = 4.2 Hz, 3 H), 7.18 (d, *J* = 2.2 Hz, 1H), 7.29 (d, *J* = 5.6 Hz, 1H), 7.60 (d, *J* = 1.6 Hz, 1H), 8.13 (d, *J* = 6.0 Hz, 1H), 9.02 (br.s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): ð 23.5 (2C), 30.8 (2C), 43.5, 5.1, 81.3, 104.8, 109.9, 119.5, 146.6, 146.7, 152.5, 160.9, 172.9; EI-MS: m/z (rel.abund.%) 275.0 (M^+, 100).

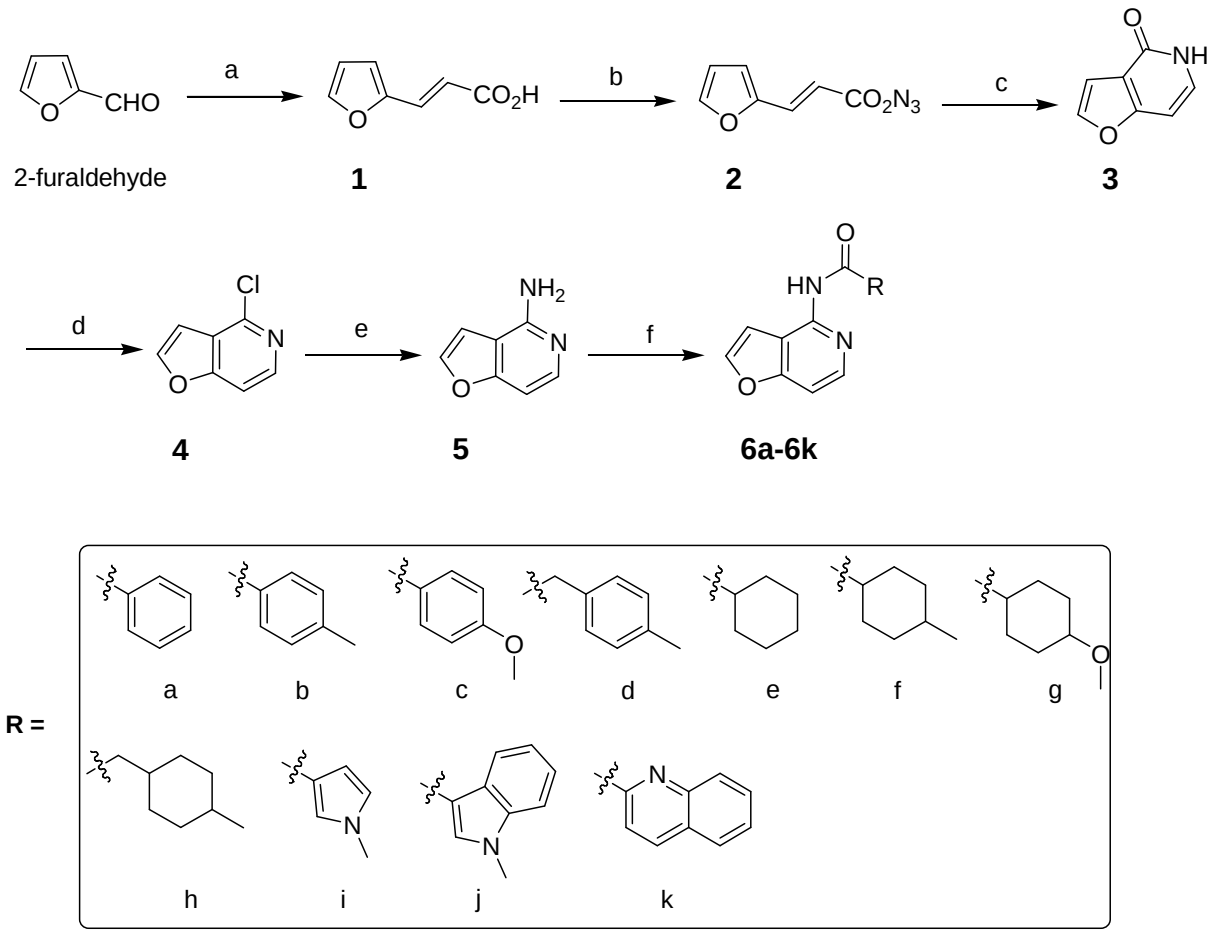
N-(furo[3,2-c]pyridin-4-yl)-2-(4-methylcyclohexyl)acetamide (6h)
Brown viscous liquid, Yield: 401 mg, 66% ; ^{1}H NMR (400 MHz, DMSO-d_6): ð 0.96 (d, *J* = 6.0 Hz, 3H), 1.27-1.66 (m, 10 H), 2.14 (d, *J* = 7.2 Hz, 2 H), 6.92 (d, *J* = 2.0 Hz, 1H), 7.46 (d, *J* = 5.6 Hz, 1 H), 7.98 (d, *J* = 1.6 Hz, 1H), 8.18 (d, *J* = 5.6 Hz, 1H), 10.54 (br.s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): ð 20.7, 26.9 (2C), 30.9, 32.6 (2C), 43.5, 104.8, 109.9, 119.5, 146.6, 146.7, 152.5, 160.9, 172.9 ; EI-MS: m/z (rel.abund.%) 273.0 (M^+, 100).

N-(furo[3,2-c]pyridin-4-yl)-1-methyl-1H-pyrrole-3-carboxamide (i)
Brown solid, Yield: 442 mg, 82% ; m.p. 94-95 °C; ^{1}H NMR (400 MHz, DMSO-d_6): ð 41.0 (s, 3 H), 6.20 (d, *J* = 7.8 Hz, 1H), 6.60 (d, *J* = 8.0 Hz, 1H), 6.98 (s, 1H), 7.24 (d, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 8.82 (br.s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): ð 37.1, 102.5,104.8, 109.9, 110.2, 113.0, 122.8, 123.6, 146.6, 148.1, 161.1, 164.7, 169.9; EI-MS: m/z (rel.abund.%) 242.0 (M^+, 100).

N-(furo[3,2-c]pyridin-4-yl)-1-methyl-1H-indole-3-carboxamide (6j)
Yellow solid, Yield: 510 mg, 78% ; m.p. 121-122 °C; ^{1}H NMR (400 MHz, dmso-d_6): ð 4.0 (s,3H), 7.44 - 7.33 (m, 2H), 7.54 (t, 1H, *J* = 8.0 Hz), 7.66 (t, 1H, *J* = 7.2 Hz), 7.74 (d, 1H, *J* = 8.0 Hz), 7.82 (d,1H, *J* = 8.0 Hz), 7.98 (d,1H, *J* = 8.0 Hz), 8.18 (d, 1H, *J* = 8.4 Hz), 8.80 (br.s, 1H); ^{13}C NMR (100 MHz, dmso-d_6): ð33.36, 104.82, 109.96, 109.63, 112.38, 113.03, 119.86, 121.76, 121.80, 126.65, 135.13, 136.53, 146.60, 148.23, 160.92, 161.31, 164.74; EI MS: m/z (rel.abund.%) 293.0 (M^+, 100).

N-(furo[3,2-c]pyridin-4-yl)quinoline-2-carboxamide (6k)
Pale yellow solid, Yield: 447 mg, 69% ; m.p. 168-169 °C; ^{1}H NMR (400 MHz, DMSO-d_6): ð 7.30 (d, *J* = 1.2 Hz, 1H), 7.60 (d, *J* = 6.0 Hz, 1H), 7.81 (t, *J* = 7.2 Hz, 1H), 7.89 (t, *J* = 7.2 Hz, 1H), 8.14-8.12 (m, 3H), 8.28 (d, *J* = 5.2 Hz, 1H), 8.66 (d, *J* = 5.6 Hz, 1H), 9.02 (d, *J* = 8.4 Hz, 1H), 10.23 (br.s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): ð 104.8, 109.9, 113.0, 119.5, 127.3, 127.9, 129.3, 130.3, 130.6, 136.6, 146.6, 148.1, 150.2, 158.3, 160.9, 161.1, 119.4; EI-MS: m/z (rel.abund.%) 290.0 (M^+, 100).

Antibacterial Bioassay:
Amide derivatives (**6a – 6k**) were dissolved in dimethyl sulphoxide at 300 µg/mL concentration. The composition of nutrient agar medium was Bactotryptone (10 g), yeast extract (5 g), NaCl (10 g), final pH 7.4. After 18 h the exponentially growing cultures of the six bacteria in nutrient broth at 37 ^{o}C 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 ^{o}C 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. All the samples were taken in triplicates. The plates were incubated at 37 ^{o}C in an inverted fashion. Activity was determined by zones showing complete inhibition (mm). Growth inhibition was calculated with reference to positive control



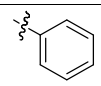
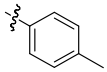
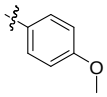
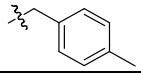
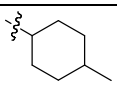
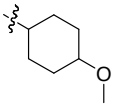
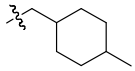
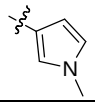
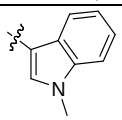
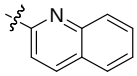
Scheme 1. Synthesis of Furo[3,2-*c*] amide derivatives 6a-6k; ***Experimental conditions: a) malonic acid, TBAB, water, microwave, 100 °C, 5 min; b) Cyanuric chloride, N-methylmorpholine, NaN_3, 0-5 °C, 3h; c) tributyl amine, diphenyl ether, 230 °C, 30 min; (d) trichloroisocyanuric acid, triphenylphosphine, toluene, reflux, 5.5 h; (e) aqueous;28% ammonia, 1,4-dioxane, 150 °C, 17 h; (f) RCOOH,HOBT,HBTU,DMF, rt,16 h.***

RESULTS AND DISCUSSION

Synthesis

The synthesis of amide derivatives of Furo[3,2-c]pyridin-4-amine **5** is described in **Scheme-1**. Knoevenagel condensation between furan-2-carbaldehyde and malonic acid in the presence of tetra butyl ammonium bromide (TBAB) and K_2CO_3 under microwave irradiation for 5 min at 100 ^oC using water as an energy transfer medium resulted in the acrylic acid intermediate **1,** shorter reaction time and water as the solvent medium makes this reaction a greener protocol. Transformation of acrylic acid intermediate **1** to acyl azide **2** was accomplished using NaN_3 in presence of cyanuric chloride, N-methylmorpholine in dichloromethane at room temperature for 3 h. It is important to note that cyanuric chloride is a safe and inexpensive reagent in comparison to the reported use of hazardous and expensive triphosgene [22]. Curtius rearrangement of azide **2** to compounds **3** was facilitated by heating respective azide at 230 ^oC in presence of diphenyl ether. Treatment of compounds **3** with trichloroisocyanuric acid in presence of triphenyl phosphine in refluxing toluene afforded chloride intermediate **4** [23]. The chlorination of the hydroxyheteroaromatics is usually done using $POCl_3$, $POCl_3/PCl_5$, $POCl_3/R_3N$, or NCS/PPh_3. One main drawback of using $POCl_3$ is the aqueous workup where the chloro compound can go back to the starting hydroxyhetero aromatic compound because of the heat generated in the quenching of $POCl_3$, these problems was circumvented by using a combination of PPh_3 and trichloroisocyanuric acid to afford the corresponding chloro compound in moderate to good yields. The synthesis of Furo[3,2-c]pyridine-4-amine **5** was achieved by heating chlorides **4** in steel reactor with 28% aqueous ammonia at 150 ^oC for 17 h. Amine **5** was coupled with various carboxylic acids in presence of HOBT, HBTU and triethyl amine in DMF to obtain amide derivatives **(6a-6k)** as depicted in Scheme **1**.

Table-1 Results of Antibacterial Bioassay of Compounds 6a-6k (Concentration Used 300 µg/mL of DMSO). *Zones of Inhibition of Compounds 6a-6k in mm*

Compound No.	R	*Gram negative*		*Gram positive*	
		E.Coli ***MTCC 443***	*P.aeruginosa* ***MTCC 424***	*S.Aureus* ***MTCC 96***	*S.Pyogenes* ***MTCC 442***
6a		11	12	11	10
6b		12	9	10	8
6c		12	10	10	9
6d		10	12	9	10
6e		13	17	14	16
6f		16	17	18	15
6g		17	16	18	17
6h		18	17	16	18
6i		23	21	21	20
6j		22	20	21	19
6k		23	21	20	22
Standard Drug	Chloramphenicol (300 µg/mL of DMSO)	22	20	21	19

Antibacterial Activity

Compounds **6a – 6k** were tested against two Gram negative strains viz., i) *Escherichia coli* (MTCC443), *(ii) Pseudomonas aeruginosa* (MTCC424), and two Gram positive *Staphylococcus aureus* strains *viz. i). Streptococcus pyogenes* (MTCC442), *and ii)* (MTCC96) using agar well diffusion method according to the literature protocol [24-29].The antibacterial activity of the analogues (300 µg/mL concentration) was compared with standard drug chloramphenicol and the results of investigation have been presented in Table **1**. Based on the test results it is evident that several of synthesized amide derivatives possess moderate to good activity against the Gram +ve and Gram –ve bacteria. The 1-methyl-pyrrole **6i**, 1-methyl indole **6j** and quinoline **6k** moieties showed highest activity (inhibitory zone 19-23 mm) against both the Gram-negative bacteria and Gram-positive bacteria. On the other hand, compounds **6e - 6h** showed moderate activity (inhibitory zone 13-18 mm) and **6a - 6d** showed weak activity (inhibitory zone 9 – 12 mm) against both Gram-positive and Gram negative bacterial strains. According to structure–activity relationships (SAR), it can be concluded that 1-methyl-pyrrole, 1-methyl indole, and quinoline moieties are essential for the antimicrobial activity. Compounds **6a-6k**, showed weak antibacterial activity when tested at 25, 50, and 100 µg/mL concentrations against *Escherichia coli*, *Pseudomonas aeruginosa*, *Streptococcus*

pyogenes and *Staphylococcus aureus* bacterial strains. Anti-bacterial activity for these compounds **(6a-6k)** were not tested at higher concentrations (>300 μg/mL).

CONCLUSION

In conclusion, we have synthesized Amide derivatives of 4-aminofuro [3, 2-*c*] pyridine (**6a-6k**) and tested for their antibacterial activity against Gram positive and Gram negative bacterial strains with chloramphenicol standard drug. Based on the test results it can be concluded that 1-methyl-pyrrole, 1-methyl indole, and quinoline moieties are essential for the antimicrobial activity, it indicates that the basic moiety can be a potential scaffold for antibacterial drugs. Thus further lead optimization is required to get wide spectrum of activity.

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