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Synthesis and Characterization of Novel Pyridine and Pyrimidine Based 1,2,4-Triazoles with Nematicidal Activity

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A series of new 2-phenyl-pyrido[2,3-*e*]-[1,2,4]triazolo[1,5-*c*]pyrimidine and its derivatives (**5a-f**) have been synthesized conveniently by cyclization of *N*-(4-imino-4*H*-pyrido[2,3-*d*]pyrimidin-3-yl)-benzamide and its derivatives (**4a-f**). The synthesis of title compounds commenced from commercially obtainable 2-amino-3-cyanopyridine (**1**) and by including *N*-(3-cyano-pyridin-2-yl)-formimidic acid ethyl ester (**2**) and benzoic acid *N*'-[(3-cyano-pyridin-2-ylimino)-methyl]hydrazide and its derivatives (**3a-f**) as intermediates. The chemical structures of all newly discovered compounds were established by IR, ^{1}H NMR and ^{13}C NMR, mass spectral data and elemental analysis. Further, the target compounds have been used to find their nematicidal activity towards two well known nematicides such as *Ditylenchus myceliophagus* and *Caenorhabditis elegans*.

Keywords: Pyridine, Pyrimidine, 1,2,4-Triazoles, Nematicidal activity.

INTRODUCTION

1,2,4-Triazole ring systems have been well studied and so far a variety of biological activities have been reported for a large number of their derivatives, such as antibacterial [1], antifungal [2], antitubercular [3], antimycobacterial [4], anticancer [5], diuretic [6] and hypoglycemic [7] properties. Thiazole and its derivatives have attracted continuing interest over the years because of their varied biological activities like antibacterial [8] and antifungal [9], anti-HIV [10], hypertension [11]], anti-inflammatory [12], anticancer [13], anti-convulsant [14], anti-inflammation [15], antidepressant and tubercular activities [16]. Pyrimidines represent an important class of heterocycles and their structural framework is not only a key constituent of nucleic bases, alkaloids and numerous pharmacophores with variety of potent biological activities. Pyrimidines occupy a distinct and unique place in medicine, large array of pyrimidine non-nucleoside derivatives possess a variety of pharmacological properties. These properties include anticancer [17], antiviral [18], antibacterial [19], antifungal [20], antiprotozoal [21], antihypertensive [22], antihistaminic [23], anti-inflammatory [24] and central nervous activities [25].

EXPERIMENTAL

All reagents and solvents were used as purchased without further purification. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Crude products were purified by column chromatography on silica gel of 60-120 mesh. IR spectra were obtained on a Perkin-Elmer BX serried FTIR 5000 spectrometer using KBr pellet. NMR spectra were recorded on a Varian 300 MHz spectrometer for ^{1}H NMR and 100 MHz spectrometer ^{13}C NMR. The chemical shifts were reported as ppm down field using TMS as an internal standard. Mass spectra were recorded on a VG-Micromass 7070H spectrometer operating at 70 eV.

Synthesis of *N*-(3-cyano-pyridin-2-yl)-formimidic acid ethyl ester (2): A mixture of 2-amino-3-cyanopyridine (**1**) (0.01 mol) and triethyl orthoformate (5 mL) was boiled under reflux for 7 h with constant stirring. After completion of the reaction (monitored by TLC), cooled the reaction mixture, the solvent was removed under reduced pressure and the residue obtained was triturated with ethanol. The solid product obtained was collected by filtration and recrystallized from ethanol to give compound *N*-(3-cyano-pyridin-2-yl)-formimidic acid ethyl ester (**2**) in pure form.

Synthesis of benzoic acid *N*'-[(3-cyano-pyridin-2-ylimino)-methyl]hydrazides (3a-f): A solution of *N*-(3-cyano-pyridin-2-yl)-formimidic acid ethyl ester (**2**) (0.01 mol) in ethanol (5 mL) was added to a solution of aryl hydrazide (0.01 mL) in ethanol (5 mL). The reaction mixture was stirred constantly for 3-4 h. After realization of the reaction (examined

by TLC), the resulted solution was poured in ice-cold water (20 mL) and the obtained precipitate was filtered off, washed and recrystallized with ethanol to get pure *N*'-[(3-cyano-pyridin-2-ylimino)-methyl]hydrazides (**3a-f**).

Synthesis of *N*-(4-imino-4*H*-pyrido[2,3-*d*]pyrimidin-3-yl)-benzamides (4a-f): A suspension of *N*'-[(3-cyano-pyridin-2-ylimino)methyl]hydrazides (**3a-f**) (0.01 mol) in DMF (5 mL) was refluxed for 2-3 h with constant stirring. After accomplishment of the reaction (examined by TLC), the mixture was poured into ice-cold water. Crude product was collected by filtration, washed, dried and recrystallized from ethyl alcohol to get pure corresponding *N*-(4-imino-4*H*-pyrido[2,3-*d*]pyrimidin-3-yl)-benzamides (**4a-f**).

Synthesis of 2-phenyl-pyrido[2,3-*e*]-[1,2,4]triazolo[1,5-*c*]pyrimidines (5a-f): A suspension of *N*-(4-imino-4*H*-pyrido[2,3-*d*]pyrimidin-3-yl)-benzamides (**4a-f**) in chloroform (5 mL) was heated at reflux temperature on uniform stirring for 12-14 h. After achievement of the reaction (examined by TLC), the mixture is precipitated after poured in ice-cold water. The crude product was filtered off and washed with hexane and recrystallized with ethyl acetate to get corresponding pure 2-phenyl-pyrido[2,3-*e*]-[1,2,4]triazolo[1,5-*c*]pyrimidines **(5a-f)**.

Physical and spectral data

***N*-(3-Cyano-pyridin-2-yl)-formimidic acid ethyl ester (2):** Yield: 71 %, m.p.: 157-159 °C, IR (KBr, ν_{max}, cm^{-1}): 3066 (C-H, Ar), 2948 (C-H, CH_3), 2244 (C≡N), 1584 (C=C), 1442 (C=N), 1138 (C-O); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.35-7.12 (m, 3H pyridine), 4.16 (q, 2H, *J* = 5.4 Hz, CH_2), 2.89 (s, 1H, N=CH), 1.27 (t, 3H, *J* = 5.4 Hz, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.5, 158.7, 152.6, 139.6, 121.5, 115.6, 106.3, 54.6, 16.5; MS: 175 *m/z* (M^+); Elemental analysis (%): Calculated for $C_9H_9N_3O$: C-61.70, H-5.18, N-23.99. Found: C-59.89, H-4.98, N-22.56.

Benzoic acid *N*'-[(3-cyano-pyridin-2-ylimino)-methyl]hydrazide (3a): Yield: 73 %, m.p.: 121-123 °C, IR (KBr, ν_{max}, cm^{-1}): 3339 (N-H), 3045 (C-H, Ar), 2228 (C≡N), 1669 (C=O), 1584 (C=C, Ar), 1462 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.71 (s, 1H, NH), 7.62-7.40 (m, 5H, Ar-H), 7.42-7.21 (m, 3H, pyridine), 4.45 (s, 1H, NH), 2.69 (s, 1H, N=CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.6, 164.5, 161.6, 153.6, 139.4, 131.7, 129.6, 126.9 (2), 124.6 (2), 122.3, 119..2 106.3; MS: 265 *m/z* (M^+); Elemental analysis (%): Calculated for $C_{14}H_{11}N_5O$: C-63.39, H-4.18, N-26.40. Found: C-61.26, H-4.06, N-25.16.

4-Methyl-benzoic acid *N*'-[(3-cyano-pyridin-2-ylimino)-methyl]hydrazide (3b): Yield: 76 %, m.p.: 140-142 °C, IR (KBr, ν_{max}, cm^{-1}): 3344 (N-H), 3055 (C-H, Ar), 2948 (C-H, CH_3), 2229 (C≡N), 1674 (C=O), 1569 (C=C, Ar), 1432 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.48 (s, 1H, NH), 7.42 (d, 2H, *J* = 7.4 Hz, Ar-H), 7.39-7.23 (m, 3H, pyridine), 7.32 (d, 2H, *J* = 7.4 Hz, Ar-H), 4.58 (s, 1H, NH), 2.64 (s, 1H, N=CH), 2.36 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.4, 165.3, 161.8, 153.4, 141.0, 138.6, 132.6, 130.2 (2), 125.4 (2), 120.3, 116.3, 105.6, 22.6; MS: 279 *m/z* (M^+); Elemental analysis (%): Calculated for $C_{15}H_{13}N_5O$: C-64.51, H-4.69, N-25.07. Found: C-63.62, H-4.46, N-24.02.

4-Methoxy-benzoic acid *N*'-[(3-cyano-pyridin-2-ylimino)-methyl]hydrazide (3c): Yield: 70 %, m.p.: 123-125 °C, IR (KBr, ν_{max}, cm^{-1}): 3352 (N-H), 3046 (C-H, Ar), 2942 (C-H, CH_3), 2233 (C≡N), 1666 (C=O), 1558 (C=C, Ar), 1438 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.52 (s, 1H, NH), 7.46 (d, 2H, *J* = 7.0 Hz, Ar-H), 7.42-7.20 (m, 3H, pyridine), 7.38 (d, 2H, *J* = 7.0 Hz, Ar-H), 4.62 (s, 1H, NH), 2.74 (s, 1H, N=CH), 2.65 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.6, 166.5, 163.2, 160.2, 153.6, 140.3, 130.2 (2), 123.6, 120.5, 116.5, 112.3 (2), 102.3, 54.3; MS: 295 *m/z* (M^+); Elemental analysis (%): Calculated for $C_{15}H_{13}N_5O_2$: C-61.01, H-4.44, N-23.72. Found: C-59.65, H-4.12, N-22.14.

4-Fluoro-benzoic acid *N*'-[(3-cyano-pyridin-2-ylimino)-methyl]hydrazide (3d): Yield: 68 %, m.p.: 130-132 °C, IR (KBr, ν_{max}, cm^{-1}): 3362 (N-H), 3048 (C-H, Ar), 2241 (C≡N), 1670 (C=O), 1565 (C=C, Ar), 1442 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.61 (s, 1H, NH), 7.52 (d, 2H, *J* = 7.2 Hz, Ar-H), 7.47-7.36 (m, 3H, pyridine), 7.41 (d, 2H, *J* = 7.2 Hz, Ar-H), 4.70 (s, 1H, NH), 2.69 (s, 1H, N=CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.3, 165.8, 163.4, 160.2, 153.6, 140.5, 130.2 (2), 127.4, 120.7, 117.5, 114.6 (2), 100.3; MS: 283 *m/z* (M^+); Elemental analysis (%): Calculated for $C_{14}H_{10}N_5OF$: C-59.36, H-3.56, F-6.71, N-24.72. Found: C-57.95, H-3.42, F-5.98, N-23.69.

4-Bromo-benzoic acid *N*'-[(3-cyano-pyridin-2-ylimino)-methyl]hydrazide (3e): Yield: 70 %, m.p.: 152-154 °C, IR (KBr, ν_{max}, cm^{-1}): 3355 (N-H), 3050 (C-H, Ar), 2248 (C≡N), 1675 (C=O), 1584 (C=C, Ar), 1454 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.56 (s, 1H, NH), 7.48 (d, 2H, *J* = 7.4 Hz, Ar-H), 7.40-7.28 (m, 3H, pyridine), 7.36 (d, 2H, *J* = 7.4 Hz, Ar-H), 4.65 (s, 1H, NH), 2.72 (s, 1H, N=CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.3, 165.3, 161.5, 156.4, 142.3, 133.2 (2), 131.0, 129.5 (2), 125.3, 120.6, 116.8, 102.4; MS: 344 *m/z* (M^+); Elemental analysis (%): Calculated for $C_{14}H_{10}N_5OBr$: C-48.86, H-2.93, Br-23.22, N-20.35. Found: C-46.98, H-2.67, Br-22.36, N-19.84.

4-Nitro-benzoic acid *N*'-[(3-cyano-pyridin-2-ylimino)-methyl]hydrazide (3f): Yield: 66 %, m.p.: 119-121 °C, IR (KBr, ν_{max}, cm^{-1}): 3350 (N-H), 3044 (C-H, Ar), 2248 (C≡N), 1671 (C=O), 1580 (C=C, Ar), 1518 (N=O), 1465 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.62 (s, 1H, NH), 7.54 (d, 2H, *J* = 7.6 Hz, Ar-H), 7.58-7.36 (m, 3H, pyridine), 7.46 (d, 2H, *J* = 7.6 Hz, Ar-H), 4.72 (s, 1H, NH), 2.81 (s, 1H, N=CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.6, 168.5, 166.3, 153.2, 150.2, 140.3, 138.6, 128.8 (2), 124.6 (2), 122.7, 118.6, 103.2; MS: 310 *m/z* (M^+); Elemental analysis (%): Calculated for $C_{14}H_{10}N_6O$: C-54.20, H-3.25, N-27.09. Found: C-52.69, H-3.12, N-26.14.

***N*-(4-Imino-4*H*-pyrido[2,3-*d*]pyrimidin-3-yl)-benzamide (4a):** Yield: 68 %, m.p.: 155-157 °C, IR (KBr, ν_{max}, cm^{-1}): 3357 (N-H), 3052 (C-H, Ar), 1664 (C=O), 1568 (C=C, Ar), 1463 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.65-7.32 (m, 5H, Ar-H), 7.51-7.28 (m, 3H, pyridine), 7.25 (s, 1H, NH), 3.92 (s, 1H, =NH), 2.54 (s, 1H, N=CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.5, 165.3, 162.5, 160.2, 1506, 135.2, 131.8, 130.2, 128.6 (2), 125.4 (2), 120.4, 119.5; MS: 265 *m/z* (M^+); Elemental analysis (%): Calculated for $C_{14}H_{11}N_5O$: C-63.39, H-4.18, N-26.40. Found: C-61.65, H-4.06, N-25.14.

***N*-(4-Imino-4*H*-pyrido[2,3-*d*]pyrimidin-3-yl)-4-methyl-benzamide (4b):** Yield: 77 %, m.p.: 115-117 °C, IR (KBr, ν_{max}, cm^{-1}): 3347 (N-H), 3048 (C-H, Ar), 2944 (C-H, CH_3),

1671 (C=O), 1584 (C=C, Ar), 1468 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.61 (d, 2H, *J* = 7.4 Hz, Ar-H), 7.47-7.30 (m, 3H, pyridine), 7.42 (d, 2H, *J* = 7.4 Hz, Ar-H), 7.34 (s, 1H, NH), 3.85 (s, 1H, =NH), 2.69 (s, 1H, N=CH), 2.58 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.5, 166.3, 164.8, 162.8, 153.2, 140.2, 135.6, 131.5, 130..2 (2), 128.6 (2), 123.7, 121.5, 21.0; MS: 279 *m/z* (M^+); Elemental analysis (%): Calculated for $C_{15}H_{13}N_5O$: C-64.51, H-4.69, N-25.07 Found: C-62.68, H-4.46, N-24.58.

***N*-(4-Imino-4*H*-pyrido[2,3-*d*]pyrimidin-3-yl)-4-methoxy-benzamide (4c):** Yield: 68 %, m.p.: 130-132 °C, IR (KBr, ν_{max}, cm^{-1}): 3355 (N-H), 3039 (C-H, Ar), 2937 (C-H, CH_3), 1665 (C=O), 1588 (C=C, Ar), 1471 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.58 (d, 2H, *J* = 7.5 Hz, Ar-H), 7.52-7.36 (m, 3H, pyridine), 7.46 (d, 2H, *J* = 7.5 Hz, Ar-H), 7.38 (s, 1H, NH), 3.92 (s, 1H, =NH), 2.72 (s, 1H, N=CH), 2.65 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.5, 166.4, 165.3, 163.4, 162.5, 155.6, 136.5, 130.2 (2), 126.5, 124.8, 120.4, 116.2 (2), 58.4; MS: 295 *m/z* (M^+); Elemental analysis (%): Calculated for $C_{15}H_{13}N_5O_2$: C-61.01, H-4.44, N-23.72. Found: C-59.69, H-4.23, N-22.84.

***N*-(4-Imino-4*H*-pyrido[2,3-*d*]pyrimidin-3-yl)-4-fluoro-benzamide (4d):** Yield: 74 %, m.p.: 145-147 °C, IR (KBr, ν_{max}, cm^{-1}): 3348 (N-H), 3041 (C-H, Ar), 1670 (C=O), 1578 (C=C, Ar), 1468 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.65 (d, 2H, *J* = 7.3 Hz, Ar-H), 7.60-7.32 (m, 3H, pyridine), 7.41 (d, 2H, *J* = 7.3 Hz, Ar-H), 7.33 (s, 1H, NH), 3.84 (s, 1H, =NH), 2.77 (s, 1H, N=CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.5, 166.4, 165.6, 162.3, 160.2, 154.2, 136.4, 128.6, 126.3 (2), 124.6, 122.0, 116.3 (2); MS: 283 *m/z* (M^+); Elemental analysis (%): Calculated for $C_{14}H_{10}N_5OF$: C-59.36, H-3.56, F-6.71, N-24.72. Found: C-57.98, H-3.36, F-6.12, N-23.65.

***N*-(4-Imino-4*H*-pyrido[2,3-*d*]pyrimidin-3-yl)-4-bromo-benzamide (4e):** Yield: 72 %, m.p.: 153-155 °C, IR (KBr, ν_{max}, cm^{-1}): 3356 (N-H), 3049 (C-H, Ar), 1667 (C=O), 1569 (C=C, Ar), 1474 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.59 (d, 2H, *J* = 7.4 Hz, Ar-H), 7.52-7.30 (m, 3H, pyridine), 7.39 (d, 2H, *J* = 7.4 Hz, Ar-H), 7.36 (s, 1H, NH), 3.79 (s, 1H, =NH), 2.81 (s, 1H, N=CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.5, 167.8, 165.3, 162.8, 152.3, 134.5, 132.8 (2), 130.2, 128.6 (2), 125.3, 122.3, 120.5; MS: 344 *m/z* (M^+); Elemental analysis (%): Calculated for $C_{14}H_{10}N_5OBr$: C-48.86, H-2.95, Br-23.22, N-20.35. Found: C-46.98, H-2.78, Br-22.23, N-19.86.

***N*-(4-Imino-4*H*-pyrido[2,3-*d*]pyrimidin-3-yl)-4-nitro-benzamide (4f):** Yield: 70 %, m.p.: 133-135 °C, IR (KBr, ν_{max}, cm^{-1}): 3362 (N-H), 3051 (C-H, Ar), 1670 (C=O), 1575 (C=C, Ar), 1510 (N=O), 1481 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.56 (d, 2H, *J* = 7.2 Hz, Ar-H), 7.49-7.33 (m, 3H, pyridine), 7.36 (d, 2H, *J* = 7.2 Hz, Ar-H), 7.28 (s, 1H, NH), 3.84 (s, 1H, =NH), 2.86 (s, 1H, N=CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.4, 167.5, 163.2, 160.2, 153.4, 150.3, 141.0, 135.7, 129.5 (2), 124.6, 122.3 (2), 119.4; MS: 310 *m/z* (M^+); Elemental analysis (%): Calculated for $C_{14}H_{10}N_6O_3$: C-54.20, H-3.25, N-27.09. Found: C-52.69, H-3.09, N-26.23.

2-Phenyl-pyrido[2,3-*e*]-[1,2,4]triazolo[1,5-*c*]pyrimidine (5a): Yield: 66 %, m.p.: 148-150 °C, IR (KBr, ν_{max}, cm^{-1}): 3070 (C-H, Ar), 1574 (C=C, Ar), 1466 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.48-7.20 (m, 5H, Ar-H), 7.39-7.21 (m, 3H, pyridine), 3.68 (s, 1H, =NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.4, 156.3, 148.2, 146.8, 143.2, 137.5, 134.7, 130.2, 128.6 (2), 126.3 (2), 122.3, 120.3; MS: 247 *m/z* (M^+); Elemental analysis (%): Calculated for $C_{14}H_9N_5$: C-68.01, H-3.67, N-28.32. Found: C-66.23, H-3.36, N-27.48.

2-(4-Methyl-phenyl)-pyrido[2,3-*e*]-[1,2,4]triazolo[1,5-*c*]pyrimidine (5b): Yield: 76 %, m.p.: 158-160 °C, IR (KBr, ν_{max}, cm^{-1}): 3060 (C-H, Ar), 2962 (C-H, CH_3), 1574 (C=C, Ar), 1475 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.68 (d, 2H, *J* = 7.0 Hz, Ar-H), 7.52 (d, 2H, *J* = 7.0 Hz, Ar-H), 7.42-7.28 (m, 3H, pyridine), 3.86 (s, 1H, =NH), 2.70 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.6, 155.3, 150.2, 148.7, 146.5, 138.5, 136.2, 134.2, 130.2 (2), 124.0 (2), 122.3, 119.2, 22.6; MS: 261 *m/z* (M^+); Elemental analysis (%): Calculated for $C_{15}H_{11}N_5$: C-68.95, H-4.24, N-26.80. Found: C-66.36, H-4.12, N-25.62.

2-(4-Methoxy-phenyl)-pyrido[2,3-*e*]-[1,2,4]triazolo[1,5-*c*]pyrimidine (5c): Yield: 73 %, m.p.: 133-135 °C, IR (KBr, ν_{max}, cm^{-1}): 3066 (C-H, Ar), 2948 (C-H, CH_3), 1582 (C=C, Ar), 1484 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.59 (d, 2H, *J* = 7.1 Hz, Ar-H), 7.58 (d, 2H, *J* = 7.1 Hz, Ar-H), 7.48-7.33 (m, 3H, pyridine), 3.81 (s, 1H, =NH), 2.75 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.3, 159.8, 157.4, 154.8, 148.6, 147.6, 133.6, 128.4, 126.4 (2), 121.0, 118.6, 113.5 (2), 55.3; MS: 277 *m/z* (M^+); Elemental analysis (%): Calculated for $C_{15}H_{11}N_5O$: C-64.97, H-4.00, N-25.26. Found: C-63.12, H-3.89, N-24.69.

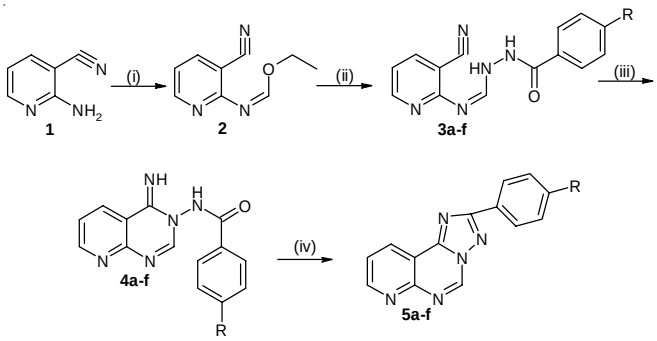
2-(4-Fluoro-phenyl)-pyrido[2,3-*e*]-[1,2,4]triazolo[1,5-*c*]pyrimidine (5d): Yield: 68 %, m.p.: 140-142 °C, IR (KBr, ν_{max}, cm^{-1}): 3074 (C-H, Ar), 1575 (C=C, Ar), 1488 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.56 (d, 2H, *J* = 7.5 Hz, Ar-H), 7.52 (d, 2H, *J* = 7.5 Hz, Ar-H), 7.43-7.28 (m, 3H, pyridine), 3.77 (s, 1H, =NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.2, 157.4, 154.3, 149.5, 148.6, 147.5, 136.2, 133.2, 127.6 (2), 122.0, 120.4, 114.7 (2); MS: 265 *m/z* (M^+); Elemental analysis (%): Calculated for $C_{14}H_8N_5F$: C-63.39, H-3.04, F-7.16, N-26.40. Found: C-62.12, H-2.84, F-6.87, N-25.23.

2-(4-Bromo-phenyl)-pyrido[2,3-*e*]-[1,2,4]triazolo[1,5-*c*]pyrimidine (5e): Yield: 77 %, m.p.: 159-161 °C, IR (KBr, ν_{max}, cm^{-1}): 3078 (C-H, Ar), 1584 (C=C, Ar), 1477 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.60 (d, 2H, *J* = 7.1 Hz, Ar-H), 7.49 (d, 2H, *J* = 7.1 Hz, Ar-H), 7.40-7.26 (m, 3H, pyridine), 3.69 (s, 1H, =NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.8, 156.4, 155.1, 147.8, 146.1, 145.2, 135.6, 134.1, 129.7 (2), 124.1, 122.5, 116.4 (2); MS: 326 *m/z* (M^+); Elemental analysis (%): Calculated for $C_{14}H_8N_5Br$: C-51.56, H-2.47, Br-24.50, N-21.47. Found: C-50.12, H-2.36, Br-23.45, N-20.12.

2-(4-Nitro-phenyl)-pyrido[2,3-*e*]-[1,2,4]triazolo[1,5-*c*]pyrimidine (5f): Yield: 74 %, m.p.: 133-135 °C, IR (KBr, ν_{max}, cm^{-1}): 3071 (C-H, Ar), 1590 (C=C, Ar), 1521 (N=O), 1474 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.54 (d, 2H, *J* = 7.3 Hz, Ar-H), 7.46 (d, 2H, *J* = 7.3 Hz, Ar-H), 7.45-7.32 (m, 3H, pyridine), 3.71 (s, 1H, =NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 157.4, 155.2, 150.4, 149.8, 148.7, 146.5, 143.2, 137.4, 127.9 (2), 125.7 (2), 123.3, 121.2; MS: 292 *m/z* (M^+); Elemental analysis (%): Calculated for $C_{14}H_8N_6O_2$: C-57.57, H-2.76, N-28.76. Found: C-56.39, H-2.56, N-27.41.

RESULTS AND DISCUSSION

In continuation of our study on the synthesis of biologically active heterocycles, we have reported the synthetic route to a novel series of 2-phenyl-pyrido[2,3-*e*]-[1,2,4]triazolo[1,5-*c*]pyrimidine and its derivatives **(5a-f)**. The synthesis of title compounds commenced from commercially available 2-amino-3-cyanopyridine (**1**) and by including *N*-(3-cyano-pyridin-2-yl)formimidic acid ethyl ester (**2**), benzoic acid *N*'-[(3-cyano-pyridin-2-ylimino)methyl]hydrazide and its derivatives (**3a**) and *N*-(4-imino-4*H*-pyrido[2,3-*d*]pyrimidin-3-yl)benzamide and its derivatives (**4a-f**) as intermediates (**Scheme-I**). Thus the initial intermediate **2** was prepared from the reaction between compound **1** and triethyl orthoformate under reflux for 7 h with constant stirring. Formation of the compound **2** is confirmed by IR, ^{1}H NMR and ^{13}C NMR and mass spectral analysis. The IR spectrum of compound **2** showed the bands at 3066 (C-H, Ar), 2948 (C-H, CH_3), 2244 (C≡N), 1584 (C=C), 1442 (C=N), 1138 (C-O) cm^{-1}. In the ^{1}H NMR spectrum, the precessional frequency between δ 7.35-7.12 ppm as multiplet for three protons are associated with pyridine ring. The quartet signal for two protons of CH_2 group linked with δ 4.16 ppm. The resonance frequency at δ 2.89 ppm as singlet for one proton is related to N=CH group. Three protons of CH_3 group as triplet is appeared at δ 1.27 ppm. The ^{13}C NMR spectrum of this compound exhibited the signals at various δ-chemical shifts such as 169.5, 158.7, 152.6, 139.6, 121.5, 115.6, 106.3, 54.6 and 16.5 ppm. The mass spectrum of the compound **93** displayed a molecular ion peak at *m/z* 175 (M^+).



(i) $CH(OEt)_3$, reflux, 7 h; (ii) Aryl hydrazide, EtOH, RT, 3-4 h; (iii) DMF, reflux, 2-3 h; (iv) $CHCl_3$, reflux, 12-14 h. **3-5 R** a) = -H; b) = -CH_3; c) = -OCH_3; d) = -F; e) = -Br; f) = -NO_2

Scheme-I

Then compound **2** is turned into the next intermediate **3a-f** when reacts with aryl hydrazide in ethanol at room temperature on uniform stirring for 3-4 h. Emergence of the compound **3a** is established by its different spectral study. The IR spectrum of compound **3a** display the bands 3339 (N-H), 3045 (C-H, Ar), 2228 (C≡N), 1669 (C=O), 1584 (C=C, Ar) and 1462 (C=N) cm^{-1}. In the ^{1}H NMR spectrum, the singlet signal for one proton of NH group linked with δ 7.71 ppm. The precessional frequency between δ 7.62-7.40 ppm as multiplet for five protons are associated with aromatic ring. Three protons of pyridine ring as multipley are appeared at δ 7.42-7.21 ppm. The resonance frequency at δ 4.45 ppm as singlet for ne proton is related to NH group. The signal appeared at δ 2.69 ppm as singlet for one proton connected with N=CH group. The ^{13}C NMR spectrum of this compound displayed the signals at various δ-chemical shifts such as 171.6, 164.5, 161.6, 153.6, 139.4, 131.7, 129.6, 126.9, 124.6, 122.3, 119.2 and 106.3 ppm. The mass spectrum of the compound **3a** exhibited a molecular ion peak at *m/z* 265 (M^+).

Then compound **4a-f** is achieved from compound **3** in dimethyl formamide solvent on steady stirring under reflux for 2-3 h. The compound **4a** is identified by IR, ^{1}H NMR and ^{13}C NMR and mass spectral examination. The IR spectrum of compound **4a** disclose the bands at 3357 (N-H), 3052 (C-H, Ar), 1664 (C=O), 1568 (C=C, Ar) and 1463 (C=N) cm^{-1}. In the ^{1}H NMR spectrum, the precessional frequency between δ 7.65-7.32 ppm as multiplet for five protons are associated with aromatic ring. The resonance frequency between δ 7.51-7.28 ppm as multiplet for three protons is related to pyridine ring. The δ-chemical shift at 7.25 ppm as singlet for one proton is corresponding to NH group. The singlet signal for one proton of =NH group linked with δ 3.92 ppm. One proton of N=CH group as singlet is appeared at 2.54 ppm. The ^{13}C NMR spectrum of this compound showed the signals at various δ-chemical shifts such as 167.5, 165.3, 162.5, 160.2, 1506, 135.2, 131.8, 130.2, 128.6, 125.4, 120.4 and 119.5 ppm. The mass spectrum of the compound **4a** performed a molecular ion peak at *m/z* 265 (M^+). The chemical structures of the other compounds of this chain are judged with same method.

Finally, compound **4a-f** on cyclization in chloroform at reflux temperature on stable stirring for 12-14 h is converted into the title compounds **5a-f**. Evolution of the compound **5a** is confirmed by IR, ^{1}H NMR and ^{13}C NMR and mass spectral investigation. The IR spectrum of compound **5a** exhibited the bands at 3070 (C-H, Ar), 1574 (C=C, Ar) and 1466 (C=N) cm^{-1}. In the ^{1}H NMR spectrum, the signal appeared at δ 7.48-7.20 ppm as multiplet for five protons connected with aromatic ring. Three protons of pyridine ring as multiplet are appeared between δ 7.39-7.21 ppm. The singlet signal for one proton of =NH group linked with δ 3.68 ppm. The ^{13}C NMR spectrum of this compound disclosed the signals at various δ-chemical shifts such as 159.4, 156.3, 148.2, 146.8, 143.2, 137.5, 134.7, 130.2, 128.6, 126.3, 122.3 and 120.3 ppm. The mass spectrum of the compound **5a** showed a molecular ion peak at *m/z* 247 (M^+). The chemical structures of the different compounds of this order are evaluated with same strategy. Further, the target compounds were used to find their nematicidal activity towards two well known nematicides namely *Ditylenchus myceliophagus* and *Caenorhabditis elegans*.

Nematicidal activity: All the newly prepared 2-phenyl-pyrido[2,3-*e*]-[1,2,4]triazolo[1,5-*c*]pyrimidine and its derivatives **(5a-f)** have been examined for their nematicidal activity towards two well known nematicides namely *Ditylenchus myceliophagus* and *Caenorhabditis elegans* by aqueous *in vitro* screening technique [26] at various concentrations. *D. myceliophagus* was extracted form the cultivated mushrooms (*Agaricus bisporus*) infected with the nematode. *C. elegans* was grown on 10 cm 8P plates on a Na22 bacteria diet; they grow in a very thick layer and constitute an abundant food source for large quantities of nematode. The nematode water suspension was collected in petri dishes. Suspension of adult worms from 5 day old culture was diluted with approximately 100 to 250 nematodes/mL of water, 100 µL of the nematode

TABLE-1
MEDIAN LETHAL DOSE (LD_{50}, ppm) OF COMPOUNDS **5a-f**

Entry	**5a**	**5b**	**5c**	**5d**	**5e**	**5f**	Levamisole
D. myceliophagus	155	270	950	430	570	170	150
C. elegans	170	220	850	200	590	750	180

suspension was introduced into a solution of each test compound at various concentrations in a well of 24-well plates and incubated at 25 °C. The percentage of immobile nematodes was recorded after 2 days. The nematicidal activity of each compound tested was compared with the standard drug levamisole.

The results are expressed in terms of LD_{50} *i.e.* median lethal dose at which 50 % of nematodes became immobile (dead). The nematicidal screening data (Table-1) reveal that the compound **5e** is the most effective against *D. myceliophagus* and *C. elegans* with LD_{50} of 160 and 180 ppm, respectively and is almost equally active as the standard levamisole. Compounds **5h** and **5j** are also most active against *C. elegans* with LD_{50} of 190 ppm and *D. myceliophagus* with LD_{50} of 180 ppm, respectively. The other tested compounds tested showed moderate activity. The comparison of LD_{50} values (in ppm) of the selected compounds **5e**, **5f**, **5h** and **5j** and the standard drug levamisole against nematodes is presented in Fig. 1.

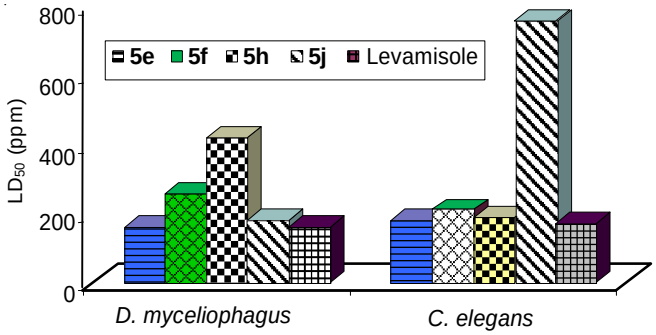


Fig. 1. Comparison of LD_{50} values of selected compounds and standard drug

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