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N-(Furan-2-ylmethyl)-cyanoacetamide in heterocyclic synthesis: Synthesis of novel antimicrobial agents encompassing furan, pyridine, chromene, and chromenopyridine moieties

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ABSTRACT

The key intermediate 2-cyano-N-(furan-2-ylmethyl)acetamide was obtained by the solvent free reaction of ethyl cyanoacetate and furfurylamine. Cyclocondensation of cyanoacetamide with acetylacetone, benzoylacetone or ethyl acetoacetates furnished the corresponding pyridinone derivatives. Aminopyridone derivatives were obtained by treatment cyanoacetamide with arylidenemalononitrile, arylmethylidene-cyanoacetate or 2-(2-oxoindolin-3-ylidene)-malononitrile. Reaction the cyanoacetamide with salicyaldehyde afforded 2H-chromene-3-carboxamide derivatives depends on the reaction conditions. Reaction the resulting of chromone with malononitrile, ethyl cyanoacetate or cyanoacetamide afforded the chromenopyridine derivatives. Evaluation of antibacterial and antifungal activities for the synthesized compounds was carried out to probe their activities. Most of the tested compounds showed significant activities.

Keywords: Cyanoacetamide; Furan; Pyridine; Chromene; Chromenopyridine; Antimicrobial activity

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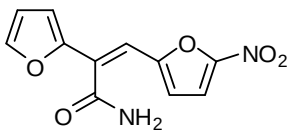
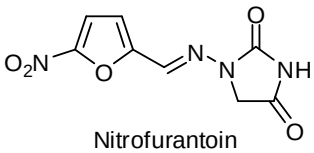
INTRODUCTION

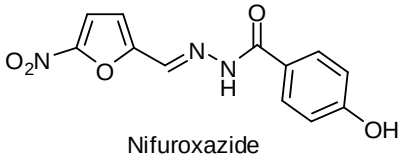
Disease causing microbes that have become resistant to drug therapy are an increasing public health problem nowadays. Infectious diseases have been serious and growing threatens to human health during the past few decades. As pathogenic bacteria continuously evolve mechanisms of resistance to currently used antibacterial, so the discovery of novel and potent antibacterial drugs is the best way to overcome bacterial resistance and develop effective therapies [1-7]. The furan ring is a very important bioactive structure that is considered to be a basic building block in the design and synthesis of new drugs. Furan rings are electron-rich systems that are amenable to act as good ligands for metal ions. Furan derivatives that are substituted at the 2- and 5- positions are frequently found in nature. These derivatives show broad-spectrum pharmacological properties [8-10]. 5-Nitrofurans have been widely used as antibacterial and anti-parasitic agents, as well as food and feed additives. The fact that most of them are mutagens and some are carcinogens has reduced their usage. For example, furylfuramide (AF2) which was found to be mutagenic in bacterial tests and carcinogenic in animals was banned as a food additive in Japan in the 1970s. However, some compounds of the series, such as nitrofurantoin and nifuroxazide, are still used as antibacterial agents in human [11, 12].



Furylfuramide



Nitrofurantoin



Nifuroxazide

Cyanoacetanilide derivatives are important and versatile reagents, which have especially been used for the synthesis of polyfunctionalized five- and six-membered rings and condensed heterocycles. Cyanoacetanilides are

polyfunctional compounds that possess both electrophilic and nucleophilic properties. Furthermore, cyanoaetanilide derivatives were exploited as a key precursor for the synthesis of polycondensed heterocyclic compounds as pyrazolo- quinazoline, pyridoquinazoline, chromenopyridoquinazoline [13-23]. As a part of our continuing study on the synthesis of biologically active compounds and on the basis of the fact that more efficacious antibacterial compounds can be designed by joining two or more biologically active heterocyclic systems together in a single molecular framework, this paper presents the synthesis of new furan derivatives carrying two or more heterocyclic rings as hybrid molecules possessing antimicrobial activity utilizing inexpensive cyanoacetamide intermediate as the starting material.

MATERIALS AND METHODS

Experimental

Melting points were determined on a digital Gallen-Kamp MFB-595 instrument and are uncorrected. IR spectra (KBr) were measured on a Shimadzu 440 spectrometer. ^{1}HNMR and ^{13}C spectra were recorded in DMSO-d_6 on a Brucker (500 MHz) spectrometer using TMS as an internal standard; chemical shifts are reported as δ_{ppm} units. Mass spectra were performed on a Shimadzu GSMS-QP 1000 Ex mass spectrometer at 70eV. The elemental analyses were carried out at the Microanalytical Center, Cairo University, Cairo, Egypt.

2-Cyano-N-(furan-2-ylmethyl)acetamide (1):

Furfural amine was fused with excess ethyl cyanoacetate at ~210 °C in an oil-bath for 20 min. Excess ethyl cyanoacetate was evaporated under vacuum. The solid product remained was triturated with methanol. The solid product obtained was filtered and crystallized from toluene to give **1** as yellow brownish crystals. Yield: 80%. FT-IR (ν, cm^{-1}): 3210 (NH), 2264 (C≡N); ^{1}H-NMR in DMSO-d_6 : δppm = 3.65 (s, 2H, $\underline{CH_2}CO$), 4.30 (s, 2H, NH$\underline{CH_2}$), 6.3, 6.4, 7.6 (m, 3H, Fur-H), 8.8 (s, 1H, NH; cancelled with D_2O). ^{13}C-NMR (DMSO-d_6): δ_{ppm} = 25.19, 35.88 (2CH_2), 116.04 (CN), 107.0, 110.46, (2$C_{3,4}$-furan), 142.34, 151.33 (2$C_{2,5}$-furan), and 162.04 C=O).

***N*-(Furan-ylmethyl)-2-oxo-2*H*-furo[2,3-*b*]indole-3-carboxamide (2):**

To a solution of cyanoacetamide (0.01 mol) in ethanol (30 mL), isatin (0.01 mol) and piperidine (0.5 mL) were added. The reaction mixture was refluxed fo 4h. The product that obtained was collected and crystallized from ethanol. Reddish brown powder, Yield (72 %) ; mp 162-164^{o}C; IR (KBr) νmax /cm^{-1} : 3140 (NH), 3053 (CH-Ar), 2938 (CH-sp^3), 1722 (C=O-lactone); ^{1}H-NMR (DMSO-d_6): δ_{ppm} = 4.83 (s, 2H, CH_2), 6.28 (d, J 3.41 Hz, 1H, CH-furfuryl), 6.59 (d, J 3.41 Hz, 1H, CH-furfuryl), 6.85-7.76 (m, 5H, 4-isatin+CH-Ofurfuryl), 10.75 (s, 1H, NH; cancelled with D_2O); Anal. Calcd for $C_{16}H_{10}N_2O_4$ (294.26.49): C, 65.31; H, 5.43; N, 9.52. Found: C, 65.54; H, 5.35; N, 9.71%.

6`-Amino-1`-(furan-2-ylmethyl)-2,2`-dioxo-2`,3`-dihydro-1`*H*-spiro[indoline-3,4`-pyrid-ine]-3`,5`-dicarbonitrile (3)

A mixture of compound 1 (0.01 mol), 2-(2-oxoindolin-3-ylidene)malononitrile (0.01 mol), piperidine (0.5 mL) in ethanol (30 mL) was heated under reflux for 4 h. The resultant solid product was collected and crystallized from ethanol/DMF. Yield (67%) as brown crystals; mp 110–112°C; IR: 3347, 3213, 3118 (NH/NH_2), 2884 (CH-sp3), 2190 (C ≡ N), 1720, 1646 cm-1(2C= O); ^{1}H-NMR: δ ^{1}H-NMR (DMSO-d_6): δ_{ppm} = 4.21 (s, 1H, CH-pyridine), 4.77 (s, 2H, CH_2), 6.29 (d, J 3.41 Hz, 1H, CH-furfuryl), 6.46 (d, J 3.41 Hz, 1H, CH-furfuryl), 6.82-7.75 (m, 5H, 4-isatin+CH-Ofurfuryl), 10.68, 11.00 (2s, 3H, NH_2+NH; cancelled with D_2O); Anal. Calcd for $C_{19}H_{13}N_5O_3$: C, 63.51; H, 3.65; N, 19.49. Found: C, 63.77; H, 3.53; N, 19.82.

1-(Furan-2-ylmethyl)-2-oxo-1,2-dihydropyridine-3-carbonitriles (4a, b):

A mixture of compound **1** (0.01 mol), acetylacetone or benzoylacetone (0.01 mol) and piperidine (0.5 mL) in ethanol (30 mL) was heated under reflux for 4 h; the solid product thus formed was filtered off, dried and recrystallized from ethanol to give **4a,b**.

1-(Furan-2-ylmethyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (4a): yellow crystals, Yield (74%), mp 180-182^{o}C, IR (KBr) ν max /cm^{-1}: 3024 (CH-Ar), 2976, 2948 (CH-sp3), 2218 (CN), 1654 (C=O); ^{1}H NMR (DMSO-d_6): δ_{ppm} = 2.26, 2.47 (2s, 6H, 2CH_3), 5.21 (s, 2H, CH_2), 6.31 (s, 1H, CH-pyridine), 6.34 (d, J 3.41 Hz, 1H, CH-furfuryl), 6.40 (d, J 3.41 Hz, 1H, CH-furfuryl), 7.58 (s, 1H, CH-Ofurfuryl); ^{13}C-NMR (DMSO-d_6): δ_{ppm} = 20.78, 20.86 (2CH_3), 40.97 (CH_2), 116.04 (CN), 99.79. 109.45, 109.80, 111.14, 143.35 149.34, 152.82, 159.36 (8C) and 160.53 (C=O); Anal. Calcd for $C_{13}H_{12}N_2O_3$ (228.25): C, 68.41; H, 5.30; N, 12.27. Found: C, 68.22; H, 5.58; N, 12.15%.

1-(Furan-2-ylmethyl)-4-methyl-2-oxo-6-phenyl-1,2-dihydropyridine-3-carbonitrile (4b): yellow crystals, Yield (72%), mp 156-158^{o}C, IR (KBr) ν max /cm^{-1}: 3018 (CH-Ar), 2876 (CH-sp3), 2216 (CN), 1658 (C=O); ^{1}H NMR

(DMSO-d_6): δ_{ppm} = 2.37 (s, 3H, CH_3), 5.03 (s, 2H, CH_2), 5.94 (s, 1H, CH-pyridine), 6.28 (d, J 3.41 Hz, 1H, CH-furfuryl), 6.33 (d, J 3.41 Hz, 1H, CH-furfuryl), 7.39-7.58 (m, 6H, Ph+CH-O furfuryl); ^{13}C-NMR (DMSO-d_6): δ_{ppm} = 20.99 (CH_3), 42.55 (CH_2), 116.04 (CN), 101.77, 108.12, 108.46, 111.06, 111.13, 127.54, 127.9, 128.69, 129.07, 130.48, 134.17, 142.94, 149.15, 153.74 (14C) and 160.23(C=O); Anal. Calcd for $C_{18}H_{14}N_2O_2$ (290.11): C, 74.47; H, 4.86; N, 9.65. Found: C, 74.32; H, 4.57; N, 9.55%.

1-(Furan-2-ylmethyl)-4-methyl-2,6-dioxo-1,2,5,6-tetrahydropyridine-3-carbonitriles (5a,b):
To a solution of the cyanoactamide **1** (0.01 mol) in ethanol (30 mL), ethyl acetoacetate derivatives (0.01 mol) and piperidine (0.5 mL) were added, and the reaction mixture was heated under reflux for 4 h. The reaction mixture was allowed to cool and then treated with ice cold water and the formed product was collected by filtration, dried and recrystallized from ethanol.

1-(Furan-2-ylmethyl)-4-methyl-2,6-dioxo-1,2,5,6-tetrahydropyridine-3-carbonitrile (5a):
Brown powder, Yield (64%), mp 184-186^{o}C; IR (KBr) νmax /cm^{-1}: 3421, (OH), 3032 (CH-Ar), 2974, 2842 (CH-sp^3), 2216 (CN), (1662 (C=O), 1623 (C=N); ^{1}H NMR (DMSO-d_6): δ_{ppm} = 2.47 (s, 3H, CH_3), 4.25 (s, 2H, CH_2), 4.99 (s, 1H, CH-pyridine), 6.26 (d, J 3.41 Hz, 1H, CH-furfuryl), 6.37 (d, J 3.41 Hz, 1H, CH-furfuryl), 7.54 (s, 1H, CH-O furfuryl), 8.66 (s, 1H, OH; cancelled with D_2O); ^{13}C-NMR (DMSO-d_6): δ_{ppm} = 20.32 (CH_3), 43.34 (CH_2), 116.53 (CN), 101.77, 107.80, 110.00, 110.93, 134.17, 142.82, 151.80, 159.78 (8C) and 162.91(C=O); Anal. Calcd for $C_{12}H_{10}N_2O_3$ (230.22): C, 62.60; H, 4.38; N, 12.17. Found: C, 62.82; H, 4.58; N, 12.35%.

1-(Furan-2-ylmethyl)-4,5-dimethyl-2,6-dioxo-1,2,5,6-tetrahydropyridine-3-carbonitrile (5b):
Brown powder, Yield (62%), mp 194-196^{o}C; IR (KBr) νmax /cm^{-1}: 3436, (OH), 3063 (CH-Ar), 2973-2935 (CH-sp^3), 2215 (CN), 1674 (C=O), 1612 (C=N); ^{1}H NMR (DMSO-d_6): δ_{ppm} = 2.47, 3.28 (2s, 6H, 2CH_3), 4.24 (s, 2H, CH_2), 6.24 (d, J 3.41 Hz, 1H, CH-furfuryl), 6.38 (d, J 3.41 Hz, 1H, CH-furfuryl), 7.54 (s, 1H, CH-O furfuryl), 8.65 (s, 1H, OH; cancelled with D_2O); Anal. Calcd for $C_{13}H_{12}N_2O_3$ (244.25): C, 63.93; H, 4.95; N, 11.47. Found: C, 63.68; H, 4.80; N, 11.69%.

3-(aryl)-2-cyano-N-(furan-2-ylmethyl)acrylamides (6a-e):
To a solution of cyanoacetamide **1** (0.01 mol) and the appropriate aromatic aldehyde (0.01 mol) in ethanol (30 mL) was added a few drops of piperidine, and the reaction mixture was refluxed for 4 h and then allowed to cool. The precipitate that formed was filtered, washed with ethanol, dried and crystallized from ethanol.

3-(2-Bromophenyl)-2-cyano-*N*-(furan-2-ylmethyl)acrylamide (6a): Yellow crystals, Yield (78%), mp 145-147^{o}C; IR (KBr) νmax /cm^{-1}: 3354 (NH), 3006 (CH-Ar), 2925 (CH-sp^3), 2216 (CN), 1675 (C=O); ^{1}H NMR (DMSO-d_6): δ_{ppm} = 4.42 (s, 2H, CH_2), 6.29 (d, J 3.41 Hz, 1H, CH-furfuryl), 6.40 (d, J 3.41 Hz, 1H, CH-furfuryl), 7.45-7.81 (m, 5H, 4Ar-H+ CH-O furfuryl), 8.30 (s, 1H, CH=), 9.07 (s, 1H, NH; cancelled with D_2O); ^{13}C-NMR (DMSO-d_6): δ_{ppm} = 36.96 (CH_2), 115.68 (CN), 107.91, 110.85, 110.98, 124.84, 128.75, 130.46, 132.74, 133.69, 133.75, 142.73, 150.28, 151.88 (12C) and 160.52 (C=O); Anal. Calcd for $C_{15}H_{11}BrN_2O_2$ (330.16): C, 54.40; H, 3.53; N, 8.46. Found: C, 54.62; H, 3.12; N, 8.27%.

3-(2-Chlorophenyl)-2-cyano-*N*-(furan-2-ylmethyl)acrylamide (6b): Yellow crystals, Yield (73%), mp 125-127^{o}C; IR (KBr) νmax /cm^{-1}: 3261 (NH), 3003 (CH-Ar), 2903 (CH-sp^3), 2210 (CN), 1662 (C=O); ^{1}H NMR (DMSO-d_6): δ_{ppm} = 4.40 (s, 2H, CH_2), 6.29 (d, J 3.41 Hz, 1H, CH-furfuryl), 6.40 (d, J 3.41 Hz, 1H, CH-furfuryl), 7.49-7.99 (m, 5H, 4Ar-H+ CH-O furfuryl), 8.35 (s, 1H, CH=), 9.04 (s, 1H, NH; cancelled with D_2O); ^{13}C-NMR (DMSO-d_6): δ_{ppm} = 36.94 (CH_2), 115.79 (CN), 107.91, 110.86, 110.97, 128.26, 130.20, 130.52, 130.84, 133.75, 134.50, 142.71, 147.66, 151.88 (12C) and 160.50 (C=O); Anal. Calcd for $C_{15}H_{11}ClN_2O_2$ (286.71): C, 62.84; H, 3.87; N, 9.77. Found: C, 62.63; H, 3.64; N, 9.56%.

2-Cyano-*N*-(furan-2-ylmethyl)-3-(4-methylphenyl)acrylamide (6c): Yellow powder, Yield (70%), mp 135-137^{o}C; IR (KBr) νmax /cm^{-1}: 3380 (NH), 3032 (CH-Ar), 2932 (CH-sp^3), 2211 (CN), 1676 (C=O); ^{1}H NMR (DMSO-d_6): δ_{ppm} = 2.23 (s, 3H, CH_3), 4.27 (s, 2H, CH_2), 6.29 (d, J 3.41 Hz, 1H, CH-furfuryl), 6.38 (d, J 3.41 Hz, 1H, CH-furfuryl), 7.35, 7.84 (2d, 4H, Ar-H), 7.57(s, 1H, CH-O furfuryl), 8.12 (s, 1H, CH=), 8.93 (s, 1H, NH; cancelled with D_2O); Anal. Calcd for $C_{16}H_{14}N_2O_2$ (266.29): C, 72.16; H, 5.30; N, 10.52. Found: C, 72.34; H, 5.35; N, 10.71%.

2-Cyano-*N*-(furan-2-ylmethyl)-3-(4-methoxyphenyl)acrylamide (6d): Yellow powder, Yield (72%), mp 124-126^{o}C; IR (KBr) νmax /cm^{-1}: 3369 (NH), 3032 (CH-Ar), 2931 (CH-sp^3), 2208 (CN), 1670 (C=O); ^{1}H NMR (DMSO-d_6): δ_{ppm} = 3.85 (s, 3H, OCH_3), 4.27 (s, 2H, CH_2), 6.26 (d, J 3.41 Hz, 1H, CH-furfuryl), 6.39 (d, J 3.41 Hz, 1H, CH-furfuryl), 7.12, 7.95 (2d, 4H, Ar-H), 7.56(s, 1H, CH-O furfuryl), 8.10 (s, 1H, CH=), 8.84 (s, 1H, NH; cancelled with D_2O); ^{13}C-NMR (DMSO-d_6): δ_{ppm} = 36.89 (CH_2), 56.08 (OCH_3), 115.28 (CN), 102.86, 107.68,

110.95, 117.32, 124.23, 124.82, 132.43, 132.74, 142.61, 150.72, 152.20, 161.87 (12C) and 163.10 (C=O); Anal. Calcd for $C_{16}H_{14}N_2O_3$ (282.29): C, 68.07; H, 5.00; N, 9.92. Found: C, 68.30; H, 5.24; N, 9.70%.

3-(furan-2-yl)-2-Cyano-*N*-(furan-2-ylmethyl)acrylamide (6e): Brown powder, Yield (69%), mp 140-142^{o}C; IR (KBr) νmax /cm^{-1}: 3361 (NH), 3041 (CH-Ar), 2931 (CH-sp^3), 2212 (CN), 1674 (C=O); ^{1}H NMR (DMSO-d$_6$): δ_{ppm} = 4.35 (s, 2H, CH_2), 6.25 (d, J 3.41 Hz, 1H, CH-furfuryl), 6.37 (d, J 3.41 Hz, 1H, CH-furfuryl), 6.76 (d, J 3.41 Hz, 1H, CH-furyl), 7.34 (d, J 3.41 Hz, 1H, CH-furyl), 7.57(s, 1H, CH-O furfuryl), 7.97(s, 1H, CH-O furyl), 8.11 (s, 1H, CH=), 8.84 (s, 1H, NH; cancelled with D_2O); Anal. Calcd for $C_{13}H_{10}N_2O_3$ (242.23): C, 64.46; H, 4.16; N, 11.56. Found: C, 64.35; H, 4.33; N, 11.43%.

6-Amino-1-(Furan-2-ylmethyl)-2-oxo-4-aryl-1,2-dihydropyridine-3,5-dicarbonitriles (7a-e):
Method A: A solution of the appropriate arylidene nitrile **6** (0.01 mol) in ethanol (30 mL) containing piperidine (0.5 mL) was treated with malononitrile (0.01 mol). The reaction was refluxed for 4h.

Method B: A mixture of compound **1** (0.01 mol), the requisite arylidene malononitrile (0.01 mol) and piperidine (0.01 mol) in ethanol (30 mL) was heated under reflux for 4 h; the solid product which was collected, recrystallized from ethanol.

6-Amino-1-(Furan-2-ylmethyl)-4-(4-methylphenyl)-2-oxo-1,2-dihydropyridine-3,5-di- carbonitriles (7a): Yellow crystals, Yield (76%), mp 235-237^{o}C; IR (KBr) νmax /cm^{-1}: 3313, 3233 (NH_2), 2960, 2930 (CH-sp^3), 2211 (CN), 1670 (C=O); ^{1}H NMR (DMSO-d$_6$): δ_{ppm} = 2.46 (s, 3H, CH_3), 5.25 (s, 2H, CH_2), 6.40 (d, J 3.41 Hz, 1H, CH-furfuryl), 6.45 (d, J 3.41 Hz, 1H, CH-furfuryl), 7.31, 7.33 (2d, 4H, Ar-H), 7.62 (s, 1H, CH-O furfuryl), 8.82 (s, 2H, NH_2; cancelled with D_2O); ^{13}C-NMR (DMSO-d$_6$): δ_{ppm} = 21.39 (CH_3), 40.53 (CH_2), 116.18 (CN), 75.90, 87.70, 107.71, 110.99, 116.85, 128.39, 129.53, 132.01, 132.65, 140.58, 143.85, 148.18, 156.76, 159.42 (14C) and 160.52 (C=O);Anal. Calcd for $C_{19}H_{14}N_4O_2$ (330.34): C, 69.08; H, 4.27; N, 16.96. Found: C, 69.31; H, 4.04; N, 16.71%.

6-Amino-1-(Furan-2-ylmethyl)-4-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles (7b): Yellow powder, Yield (75%), mp 215-217^{o}C; IR (KBr) νmax /cm^{-1}: 3324, 3238 (NH_2), 2962, 2937 (CH-sp^3), 2218 (CN), 1665 (C=O);^{1}H NMR (DMSO-d$_6$): δ_{ppm} = 3.81 (s, 3H, OCH_3), 5.29 (s, 2H, CH_2), 6.40 (d, J 3.41 Hz, 1H, CH-furfuryl), 6.52 (d, J 3.41 Hz, 1H, CH-furfuryl), 7.08, 7.41 (2d, 4H, Ar-H), 7.66 (s, 1H, CH-O furfuryl), 8.48 (s, 2H, NH_2; cancelled with D_2O); Anal. Calcd for $C_{19}H_{14}N_4O_3$ (346.11): C, 65.89; H, 4.07; N, 16.18. Found: C, 65.62; H, 4.14; N, 16.26%.

6-Amino-4-(furan-2-yl)-1-(Furan-2-ylmethyl)-2-oxo-1,2-dihydropyridine-3,5-dica- rbonitriles (7c): Brown powder, Yield (71%), mp 250-252^{o}C; IR (KBr) νmax /cm^{-1}: 3313, 3233 (NH_2), 2960, 2930 (CH-sp^3), 2211 (CN), 1670 (C=O); ^{1}H NMR (DMSO-d$_6$): δ_{ppm} = 4.32 (s, 2H, CH_2), 6.22 (d, J 3.41 Hz, 1H, CH-furfuryl), 6.36 (d, J 3.41 Hz, 1H, CH-furfuryl), 6.22 (d, J 3.41 Hz, 1H, CH-furfuryl), 7.10 (d, J 3.41 Hz, 1H, CH-furfuryl), 7.54 (s, 1H, CH-O furfuryl), 7.96 (s, 1H, CH-O furyl), 8.41 (s, 2H, NH_2); Anal. Calcd for $C_{16}H_{10}N_4O_3$ (306.28): C, 62.74; H, 3.29; N, 18.29. Found: C, 62.63; H, 3.13; N, 18.28%.

Ethyl 2-amino-5-cyano -4-aryl-1-(Furan-2-ylmethyl)-6-oxo-1,6-dihydropyridine-3-carb- oxylates (8a,b):
Method A: A mixture of compound **1** (0.01 mol), ethyl 2-cyano-3-arylacrylate (0.01 mol) and piperidine (0.01 mol) in ethanol (30 mL) was heated under reflux for 6 h; the solid product which was produced on heating was collected and recrystallized from ethanol.

Ethyl 2-amino-4-(2-Bromophenyl)-5-cyano-1-(furan-2-ylmethyl)-6-oxo-1,6-dihydro pyridine-3-carboxylate (8a): Yellow powder, Yield (65%), mp 242-244^{o}C; IR (KBr) νmax /cm^{-1}: 3354, 3212 (NH_2), 3026 (CH-Ar), 2925, 2854 (CH-sp^3), 2217 (CN), 1712, 1655 (2C=O); ^{1}H NMR (DMSO-d$_6$): δ_{ppm} = 1.23 (t, J 7.5, 3H, CH_3), 3.76 (q, J 7.5, 2H, CH_2), 5.34 (s, 2H, CH_2), 6.42 (d, J 3.41 Hz, 1H, CH-furfuryl), 6.47 (d, J 3.41 Hz, 1H, CH-furfuryl), 7.25-7.67 (m, 5H, 4Ar-H+ CH-O furfuryl), 9.07 (s, 2H, NH_2; cancelled with D_2O); Anal. Calcd for $C_{20}H_{16}BrN_3O_4$ (442.26): C, 54.31; H, 3.65; N, 9.50. Found: C, 54.42; H, 3.42; N, 9.37%.

Ethyl 2-amino-4-5-cyano-4-(furan-yl)-1-(furan-2-ylmethyl)-6-oxo-1,6-dihydro- pyridine-3-carboxylate (8b): Yellow powder, Yield (65%), mp 242-244^{o}C; IR (KBr) νmax /cm^{-1}: 3343, 3228 (NH_2), 3043 (CH-Ar), 2928, 2865 (CH-sp^3), 2214 (CN), 1708, 1653 (2C=O); ^{1}H-NMR (DMSO-d$_6$): δ_{ppm} = 1.21 (t, J 7.5, 3H, CH_3), 4.16 (q, J 7.5, 2H, CH_2), 4.21 (s, 2H, CH_2), 6.22 (d, J 3.4 Hz, 1H, CH-furfuryl), 6.53 (d, J 3.4 Hz, 1H, CH-furfuryl), 7.02 (d, J 3.4 Hz, 1H, CH-furyl), 7.83 (d, J 3.41 Hz, 1H, CH-furyl), 7.54 (s, 1H, CH-O furfuryl), 7.98 (s, 1H, CH-O furyl), 8.58 (s, 2H, NH_2; cancelled with D_2O); Anal. Calcd for $C_{20}H_{16}BrN_3O_4$ (442.26): C, 54.31; H, 3.65; N, 9.50. Found: C, 54.42; H, 3.42; N, 9.37%.

***N*-(Furan-2-ylmethyl)-2-imino-2*H*-chromene-3-carboxamide (10):**
A mixture of equimolar amount of **1** (0.01 mol), salicyaldehyde (0.01 mol) and amm. acetate (0.015 mol) was refluxed in ethanol (30 mL) for 3 h. The solid product formed was collected by filtration and recrystallized from ethanol: Yellow powder, Yield (68%), mp 168-170^{o}C; IR (KBr) νmax /cm^{-1}: 3405, 3361 (2NH), 3064 (CH-Ar), 2918 (CH-sp^{3}), 1674 (C=O); ^{1}H-NMR (DMSO-d$_6$): δ_{ppm} 4.53 (s, 2H, CH$_2$), 6.25 (d, J 3.4 Hz, 1H, CH-furfuryl), 6.35 (d, J 3.4 Hz, 1H, CH-furfuryl), 7.25-7.34 (m, 4H, Ar-H), 7.56 (s, 1H, CH-O furfuryl), 8.42 (s, 1H, chromen-H-4), 8.92, 9.02 (2s, 2H, 2NH; cancelled with D$_2$O); ^{13}C-NMR (DMSO-d$_6$): δ_{ppm} = 36.64 (CH$_2$), 116.61 (CN), 107.66, 110.00, 110.87, 118.90, 119.88, 125.60, 130.39, 134.62, 143.01, 148.16, 152.06, 154.35, (12C), 160.81 (C=N) and 161.52 (C=O); Anal. Calcd for $C_{15}H_{12}N_2O_3$ (268.27): C, 67.16; H, 4.51; N, 10.44. Found: C, 67.35; H, 4.36; N, 10.28%.

***N*-(Furan-2ylmethyl)-2-oxo-2*H*-chromene-3-carboxamide (11)**
Method A: To a solution of 1 (0.01mol) in acetic anhydride (20 mL), salicylaldehyde (0.01 mol) and sod.acetate (0.5g) were added. The mixture was refluxed for 1hr, the solid product after cooling was collected by filtration and recrystallized from ethanol.

Method B: A solution of the corresponding iminochromene **10** (0.01 mol) in ethanol (30 mL), hydrochloric acid or acetic acid (5mL) was refluxed for 1h: Yellow powder, Yield (64%), mp 175-177^{o}C; IR (KBr) νmax /cm^{-1}: 3367 (NH), 3054 (CH-Ar), 2920 (CH-sp^{3}), 1700, 1675 (2C=O); ^{1}H-NMR (DMSO-d$_6$): δ_{ppm} 4.48 (s, 2H, CH$_2$), 6.10 (d, J 3.4 Hz, 1H, CH-furfuryl), 6.39 (d, J 3.4 Hz, 1H, CH-furfuryl), 7.25-7.57 (m, 4H, Ar-H), 7.75 (s, 1H, CH-O furfuryl), 8.42 (s, 1H, chromen-H-4), 10.55 (s, H, NH; cancelled with D$_2$O); Anal. Calcd for $C_{15}H_{11}NO_4$ (269.25): C, 66.91; H, 4.12; N, 5.20. Found: C, 66.75; H, 4.35; N, 5.27%.

Synthesis of chromeno[3,4-c]pyridine 12-14
A mixture of **10** (0.01 mol) and malononitrile, ethyl cyanoacetate or compound **1** (0.01 mol) and piperidine (0.5 mL) in ethanol (30 mL) was heated under reflux for 3h. The solid product was collected by filtration and recrystallized from ethanol.

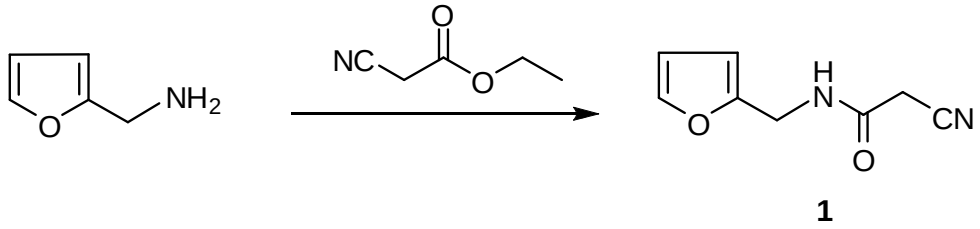
2-Amino-3-(furan-2-ylmethyl)-5-imino-4-oxo-4,5-dihydro-3*H*-chromeno[3,4-c]pyridine-1-carbo nitrile (12): Yellow powder, Yield (61%), mp 204-206^{o}C; IR (KBr) νmax /cm^{-1}: 3439, 3348 (NH$_2$, NH), 3058 (CH-Ar), 2945 (CH-sp^{3}), 2207 (C≡N), 1665 (C=O); ^{1}H-NMR (DMSO-d$_6$): δ_{ppm} 4.53 (s, 2H, CH$_2$), 6.35 (d, J 3.4 Hz, 1H, CH-furfuryl), 6.39 (d, J 3.4 Hz, 1H, CH-furfuryl), 7.40-7.97 (m, 4H, Ar-H), 7.78 (s, 1H, CH-O furfuryl), 8.84, 9.01 (2s, 3H, NH$_2$, NH; cancelled with D$_2$O); Mass spectrum showed a molecular ion peak at m/z 332 (3.2%), M+1(3.2%) with a base peak at m/z=300, other significant peak were observed at 272(34.0), 256(3.5) and 230(4.36); Anal. Calcd for $C_{18}H_{12}N_4O_3$ (332.31): C, 65.06; H, 3.64; N, 16.86. Found: C, 65.23; H, 3.35; N, 16.27%.

3-(furan-2-ylmethyl)-2-hydroxy-5-imino-4-oxo-4,5-dihydro-3*H*-chromeno[3,4-c]pyridine-1-carbonitrile (13), Yellow powder, Yield (59%), mp 224-226^{o}C; IR (KBr) νmax /cm^{-1}: 3446, 3234 (OH, NH), 3057 (CH-Ar), 2940 (CH-sp^{3}), 2210 (C≡N), 1663 (C=O); ^{1}H-NMR (DMSO-d$_6$): δ_{ppm} 4.58 (s, 2H, CH$_2$), 6.25 (d, J 3.4 Hz, 1H, CH-furfuryl), 6.38 (d, J 3.4 Hz, 1H, CH-furfuryl), 7.24-7.82 (m, 4H, Ar-H), 7.79 (s, 1H, CH-O furfuryl), 9.012, 11.45 (2s, 2H, NH, OH; cancelled with D$_2$O); Anal. Calcd for $C_{18}H_{11}N_3O_4$ (333.30): C, 64.86; H, 3.33; N, 12.61. Found: C, 64.63; H, 3.65; N, 12.47%.

2-amino-N,3-bis(furan-2ylmethyl)-5-imino-4-oxo-4,5-dihydro-3H-chromeno[3,4-c]pyrid ine-1-carbonitrile (14) Yellow powder, Yield (61%), mp 204-206^{o}C; IR (KBr) νmax /cm^{-1}: 3425, 3332, 3245 (NH$_2$, NH), 3043 (CH-Ar), 2934 (CH-sp^{3}), 1675, 1654 (C=O); ^{1}H-NMR (DMSO-d$_6$): δ_{ppm} 4.43, 4.66 (2s, 4H, 2CH$_2$), 6.25 (d, J 3.4 Hz, 2H, 2CH-furfuryl), 6.36 (d, J 3.4 Hz, 1H, CH-furfuryl), 6.38 (d, J 3.4 Hz, 1H, CH-furfuryl),7.25-7.78 (m, 4H, Ar-H), 7.58, 7.58 (2s, 2H, 2CH-O furfuryl), 8.42, 10.55 (2s, 3H, NH$_2$, NH; cancelled with D$_2$O); ^{13}C-NMR (DMSO-d$_6$): δ_{ppm} = 36.64, 43.31 (2CH$_2$), 115.65 (CN), 106.60, 107.64, 110.86, 110.95, 118.77, 120.74, 124.91, 130.36, 133.32, 140.17, 142.68, 143.00, 150.75, 151.62, (18C), 153.53 (C=N) and 159.12, 161.25 (2C=O); Anal. Calcd for $C_{23}H_{18}N_4O_5$ (430.41): C, 64.18; H, 4.22; N, 13.02. Found: C, 64.28; H, 4.16; N, 13.28%.

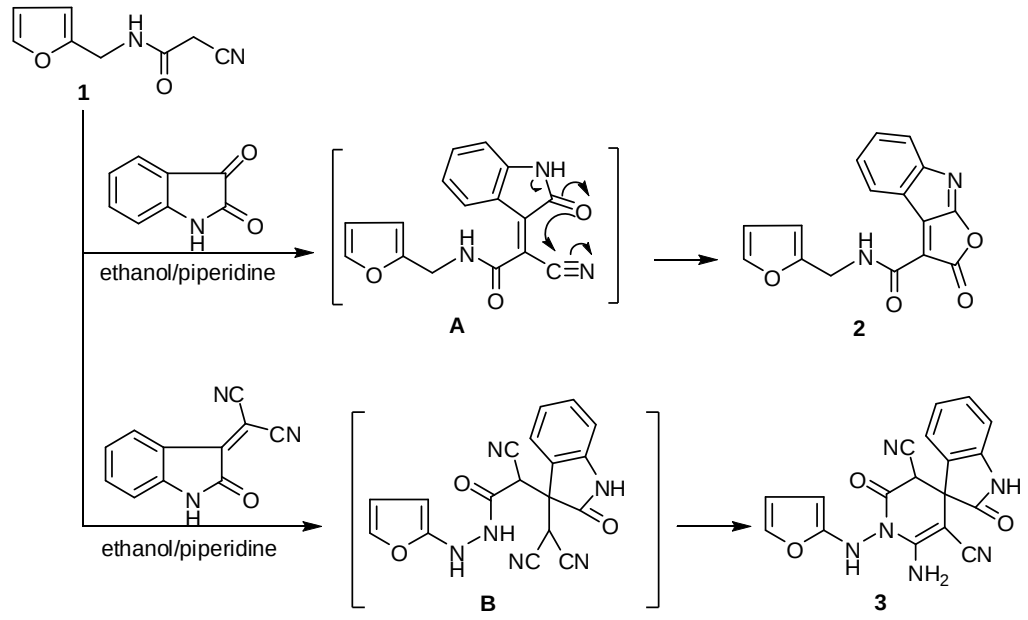
RESULTS AND DISCUSSION

The key intermediate 2-cyano-*N*-(furan-2-ylmethyl)acetamide **(1)** was obtained by the solvent free reaction of ethyl cyanoacetate and furfurylamine (Scheme 1). ^{1}H NMR spectrum of **1** exhibited two sharp singlet signals at: δ = 3.65 ppm and 4.30 ppm assignable to $\underline{CH_2}$CO and $\underline{CH_2}$NH protons, two doublet signals at: δ = 6.30 and 6.40 ppm specific for furfuryl protons-3, 4 and CH-O furfuryl-5 at δ 7.60 ppm, and a singlet signal at δ 8.8 ppm due to NH proton. ^{13}C NMR: 25.19, 35.88 (2CH$_2$), 116.04 (CN), 107.0, 110.46 (2C-furfuryl-3,4), 142.34, 151.33 (2C-furfuryl-2,5), and 162.04(C=O)



Scheme 1

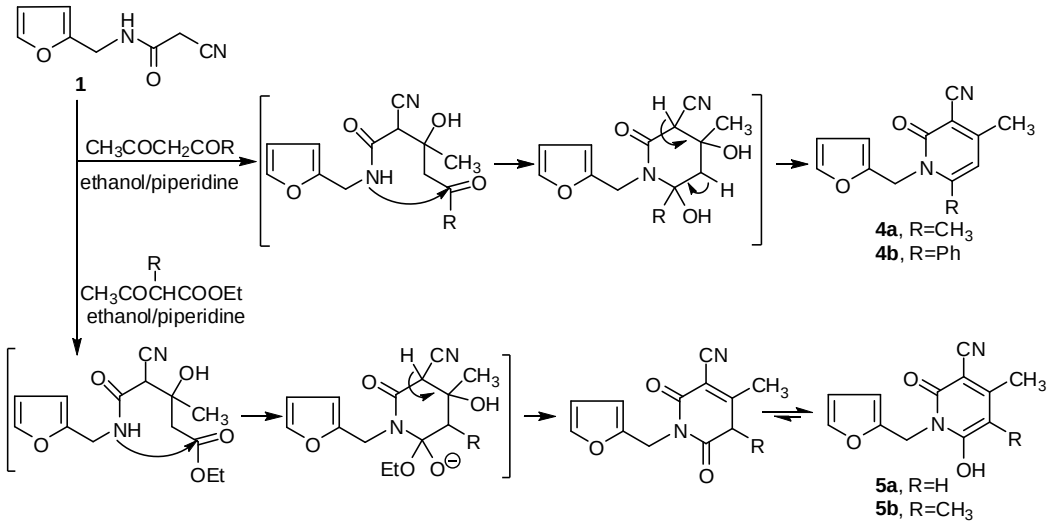
The reactivity of compound **1** toward some carbonyl reagents was studied. Thus, the Knoevenagel condensation of cyanoacetamide **1** with isatin as dicarbonyl compound in ethanolic piperidine solution at reflux temperature afforded *N*-(furan-ylmethyl)-2-oxo-2*H*-furo[2,3-*b*]indole-3-carboxamide **(2)** as a sole product (Scheme 2). The structure was assigned for the reaction product on the basis of its elemental analysis and spectral data. The IR spectrum lacked an absorption band due to a nitrile function and revealed absorption bands at 3140 and1722 characteristic to NH and lactone C=O group respectively. ^{1}H NMR spectrum exhibited no signal due to CO$\underline{CH_2}$ and displayed signals for furfuryl in addition to isatin protons and singlet signal at 10.75 specific for NH. The formation of compound **2** is assumed to proceed via the condensation of the active methylene group with isatin carbonyl which underwent in situ intramolecular cyclization through the nucleophillic attack of the hydroxyl group to the nitile function and imine hydrolysis. In addition, the reaction of **1** with 2-(2-oxoindolin-3-ylidene)- malononitrile in refluxing ethanol in the presence of catalytic amounts of piperidine yielded the spiro[indoline-3,4′-pyridine] derivative **3**. Evidence of the structure of compound **3** includes the infrared spectrum which reveals strong absorption bands at: δ = 3347, 3213 and 3118 cm^{-1} for the NH_2, NH group and contains the characteristic absorption band at 2224 cm^{-1} for the cyano group. The ^{1}H NMR spectrum shows a singlet at: δ = 4.77 ppm assigned for the CH_2 protons, two doublets at 6.29, 6.46 ppm assigned for furfuryl-3,4, two downfield singlet at: δ = 10.86, 11.00 ppm for the NH_2 and NH proton (D_2O exchangeable). The formation of spiro derivative **3** is assumed to proceed via Michael addition of the ionized methylene group of **1** to the activated double bond to give the intermediate Michael adduct followed by intramolecular cyclization through nucleophilic addition of the amino group to the cyano group and tautomerization.



Scheme 2

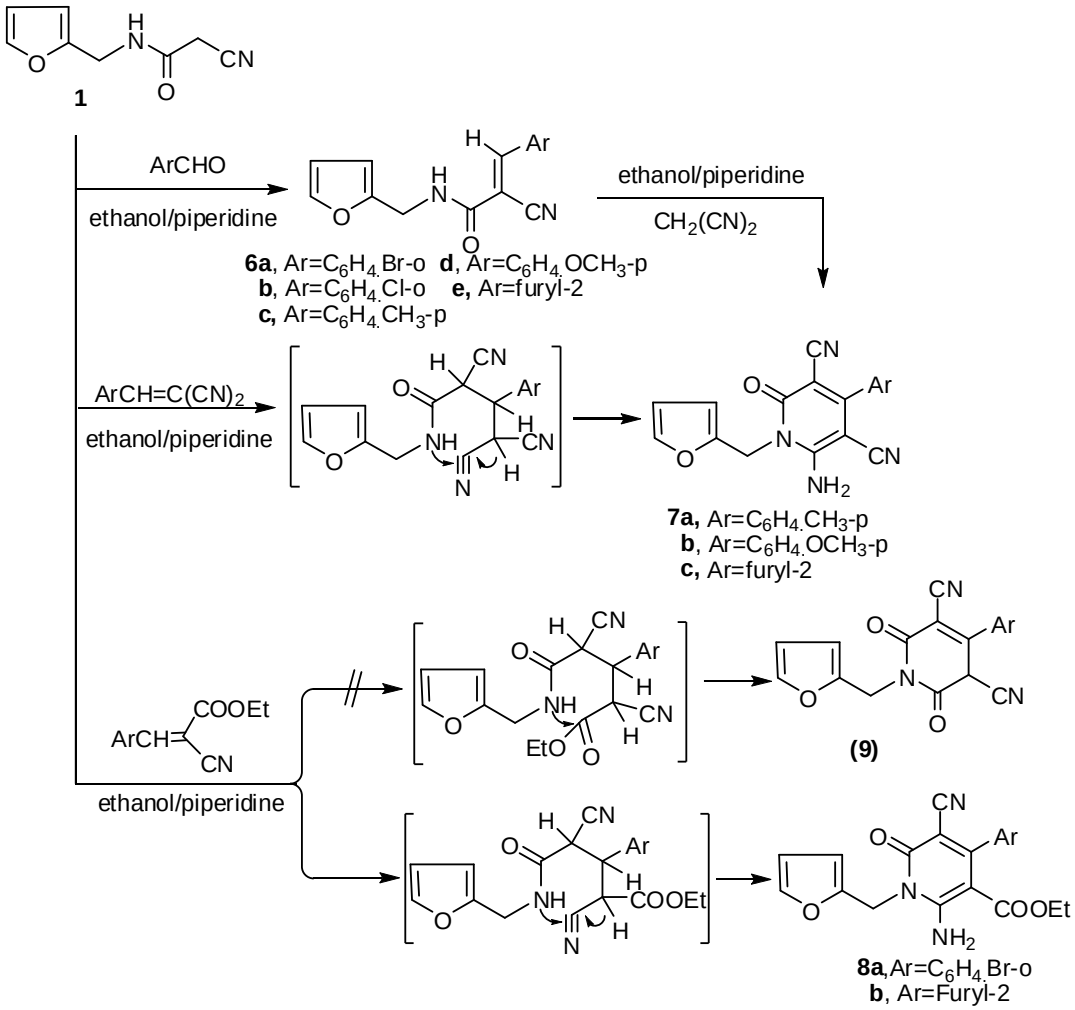
Pyridone and their fused derivatives play an essential role in several biological processes and have considerable chemical and pharmacological importance. To explore the synthetic potentiality of cyanoacetanilide **1** in pyridones synthesis, it was of interest to investigate the reactivity of compound **1** toward some dicarbonyl compounds reagents. Thus, cyclocondensation of compound **1** with acetylacetone or benzoylacetone furnished the corresponding pyridinone derivatives **4a, b**, *via* intramolecular heterocyclization of the non-isolable intermediate by loss of water (Scheme 3). The structure of **4** was inferred from its spectral data. The IR spectrum of compound **4a** showed absorption bands at 2206 and 1654 cm^{-1} correspond to CN, and C=O functions, respectively. Its ^{1}H NMR spectrum showed three singlet signals at: δ = 2.26, 2.47 and 5.21 ppm corresponding for $2CH_3$ and CH_2, where the furfuryl and pyridine-protons were observed at: δ = 6.31, 6.34, 6.40 and 7.58. In a similar, pyridinones derivatives

5a, b were obtained through cyclocondensation of compound **1** with ethyl acetoacetates in refluxing ethanol containing piperidine as catalyst. The structure of the newly synthesized was corroborated on the basis of spectral and analytical data. The IR spectra of compounds of **5a** as an example exhibited strong absorptions in the region 3421, 2216, 1662 cm^{-1} due to OH, CN and C=O respectively. ^{1}H NMR spectra of **5a** three singlets at: δ = 2.47, 4.25 and 4.99 corresponding for CH_3, CH_2 and CH-pyridin respectively and two doublets were observed at: δ = 6.26 and 6.37 ppm each integrating for one proton, while the OH group was appeared as a singlet at 8.66 ppm.



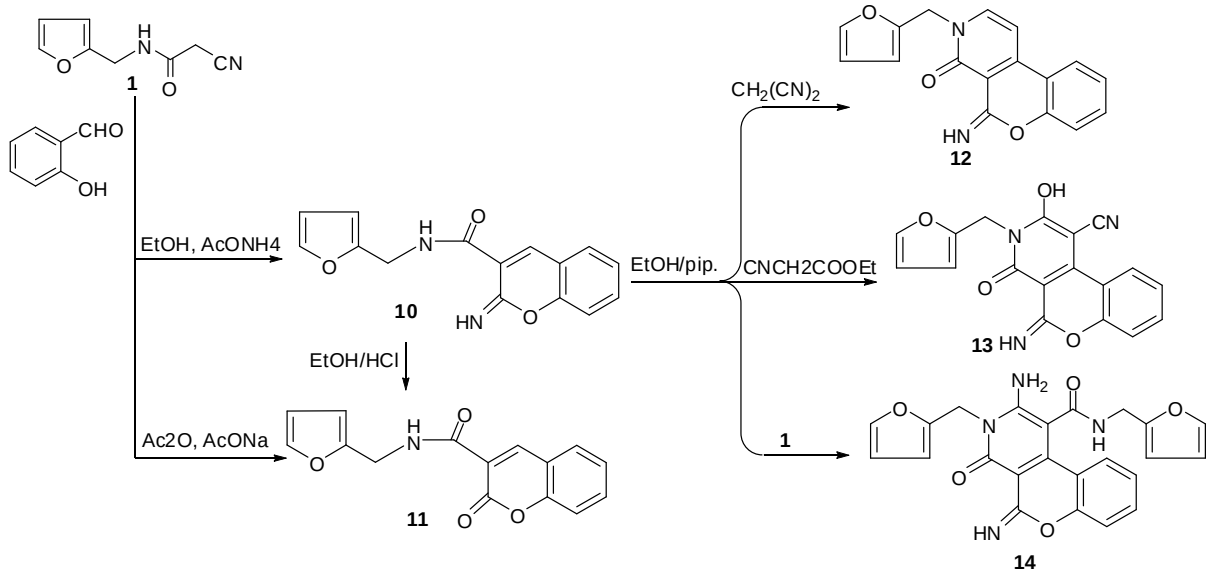
Scheme 3

Knoevenagel Condensation of compound **1** with some aldehydes in ethanolic piperidine at reflux temperature furnished the arylidene derivatives **6a-e** in high yield (Scheme 4). The structures of compounds **6** were assigned on the basis of their elemental analyses and spectral data. For example, ^{1}H NMR spectrum of **6d** revealed **3** singlet signals at: δ = 3.85, 4.27 and 8.10 ppm assignable to the methoxy, CH_2 and CH olefinic protons, respectively, besides the aromatic and NH protons. Compounds **6** contains two reactive sites, a cyano group, adjacent to the α-position of the α,β-unsaturated ketonegroup itself. These groups render it susceptible to react via a nucleophilic cycloaddition reaction onto the cyano function. When compound **6** was reacted with malononitrile in boiling ethanol containing a catalytic amount of piperidine caused nulceophilic addition followed by cyclization to afford amino-pyridone derivatives **7a-c.** Compound **7** was also obtained by refluxing **1** with arylidenemalononitrile in ethanol. The structure of isolated product was elucidated on the basis of its elemental analysis and spectral data. IR spectrum of **7c** exhibited strong stretching frequencies in the region of 3424 and 3238 cm^{-1}, attributable to the amino group, in addition to the presence of a strong absorption band at 2218 cm^{-1} due to a CN group. Its ^{1}H NMR spectrum displayed a singlet signal at: δ = 3.81 ppm assigned to the methoxy rotons in addition to the presence of a singlet signal at: δ = 8.48 ppm exchangeable with D_2O assignable to the NH_2 protons. In a similar manner, the reaction of compound **1** with ethyl arylmethylidene-cyanoacetate under reflux condition in ethanol in the presence of catalytic amounts of piperidine gave ethyl aminopyridone carboxylate derivatives **8a, b** rather than the cyanopyridone derivatives **9** on the basis of spectral data. The infrared spectrum of the reaction product revealed absorption bands at 3354, 3212, 2217 and 1655 cm^{-1}corresponding to NH_2, CN and C=O groups, respectively. The ^{1}H NMR spectrum showed a triplet at: δ = 1.23 ppm and a quartet at: δ = 3.76 ppm assigned to the ethyl group in addition to the presence of a singlet at: δ = 9.07 due to NH_2 group. The formation of compound **8** is assumed to proceed via nucleophilic addition of the active methylene to the double bond followed by addition to the cyano group.



Scheme 4

It has been reported that compounds with a chromene backbone have a wide range of biological properties. Reaction of cyanoacetamide **1** with salicyaldehyde depends on the reaction conditions. Thus, cyclocondensation of **1** with salicylaldehyde in ethanol using amm.acetate as a catalyst, where *N*-(furan-2-ylmethyl)-2-imino-2*H*-chromene-3-carboxamide **(10)** was obtained (Scheme 5). On the other hand, upon repeating the same reaction in the presence of acetic anhydride/sod.acetate *N*-(furan-2-ylmethyl)-2-oxo-2*H*-chromene-3-carboxamide **(11)** was obtained. The structure of **10, 11** was inferred from their spectral data. The IR spectrum of **10** showed absorption bands at 3405, 3361 and 1674 cm^{-1} corresponding to 2NH and amidic C=O functions, respectively. Its ^1H NMR spectrum showed a multiplet signal integrated for 8 protons 2 singlet signals at: δ = 4.35 and 8.42 corresponding for CH_2 and chromene-H-4 and two singlet at: δ = 8.92 and 9.02 ppm for 2NH which were exchangeable with D_2O. Moreover, the resulting chromone derivatives have latent functional constituents, which have the potential for further chemical transformations that give new routes for the preparation of substituted chromenopyridine derivatives. Thus, Reaction of chromone **10** with malononitrile in refluxing ethanol containing a catalytic amount of piperidine afforded a product with analytical and spectral data in good agreement with chromeno[3,4-c]pyridine derivative **(12)**. The structure of **12** has been confirmed on the basis of elemental analysis and spectral data. IR spectrum of **12** showed NH_2 NH at 3439, 3348, C≡N at 2207 and C=O (amide) at 1650 cm^{-1}. Mass spectrum of **12** showed a molecular ion peak at m/z 332 (3.2%) with a base peak at m/z 300. Based on the foregoing data, structure 12 was assigned to this product. The formation of **12** was assumed to proceed via the addition of an active methylene group to the double bond of chromene giving Michael adduct that spontaneously cyclized, aromatizes to yield iminochromenopyridine derivative scheme **3**. In continuation to our interest in the synthesis of chromone derivatives containing nitrogen heterocyclic systems, compound **10** was allowed to react with other active methylene derivatives. Thus, cyclocondensation of **10** with ethyl cyanoacetate or compound **1** in ethanol under reflux containing few drops of piperidine afforded the chromenopyridine derivatives **13** and **15**. The analytical and spectral data of **13** and **15** are in agreement with the proposed structures. Thus, IR spectrum of **13** showed a band due to the cyano group at 2210 cm^{-1}, also, its ^1H NMR spectrum exhibited two singlet signals at: δ = 9.01 and 11.45 ppm corresponding NH and OH groups.



Scheme 5

Table 1: Antimicrobial activity of the synthesized compounds against the Gram +ve bacteria expressed as inhibition diameter zones in millimeters (mm) based on well diffusion assay

Compd. No.	*S. epidermidis*	*S. aureus*	*E. faecalis*	*B. subtilis*
St.	25.4±0.18	28.9±0.14	22.6±0.31	34.6±0.35
1	12.4±0.43	10.3±0.32	NA	10.2±0.41
2	16.9±0.54	16.1±0.14	NA	17.2±0.33
3	24.6±0.28	23.3±0.35	19.2±0.52	23.4±0.63
4a	17.8±0.67	17.3±0.56	12.4±0.34	18.4±0.38
4b	14.8±0.44	13.9±0.15	12.1±0.42	15.4±0.58
5a	21.9±0.63	21.6±0.52	17.3±0.34	23.7±0.24
5b	21.3±0.52	20.6±0.55	16.4±0.43	21.7±0.58
6a	15.6±0.53	14.3±0.44	14.3±0.37	16.4±0.23
6b	17.0±0.42	15.3±0.36	9.6±0.52	15.8±0.68
6c	13.7±0.58	13.1±0.53	12.3±0.33	14.5±0.28
6d	15.7±0.45	14.2±0.29	NA	16.4±0.63
6e	22.3±0.58	21.9±0.25	18.1±0.39	23.9±0.44
7a	19.3±0.36	17.9±0.52	12.6±0.34	19.4±0.54
7b	21.3±0.25	20.3±0.37	16.9±0.32	20.6±0.37
7c	23.0±0.35	21.4±0.61	15.4±0.19	24.6±0.36
8a	17.3±0.37	16.4±0.52	10.8±0.24	17.9±0.18
8b	16.9±0.31	15.2±0.27	10.0±0.52	17.1±0.21
10	18.8±0.17	19.9±0.38	13.7±0.56	19.6±0.42
11	14.4±0.38	13.9±0.29	13.6±0.37	15.0±0.25
12	26.0±0.37	25.8±0.19	20.3±0.27	28.7±0.24
13	14.9±0.31	14.5±0.44	13.9±0.25	15.6±0.19
15	12.9±0.44	10.3±0.58	NA	14.2±0.25

Evaluation of antimicrobial evaluation

The antibacterial activity was screened against four Gram-positive bacteria; *Staphylococcus epidermidis* (RCMB 010024), Staphylococcus aureus (RCMB 010027), *Enterococcus faecalis* (RCMB 010068) and *Bacillis subtilis* (RCMB 010063)] and four Gram-negative bacteria; *Proteous vulgaris* (RCMB 010085), *Klebsiella pneumonia* (RCMB 010093), *Shigella flexneri* (RCMB 0100542) and *Neisseria gonorrhoeae* (RCMB 010076)] using ampicillin and gentamycin as standard antibacterial drugs. Antifungal activity was screened against four fungal species *Aspergillus fumigates* (RCMB 02564), *Aspergillus clavatus* (RCMB 02593), *Candida albicans* (RCMB 05035) and *Geotricum candidum* (RCMB 05096)] where amphotricin was used as the standard antifungal drug. Agar diffusion method was used for the determination of the preliminary screening of antibacterial and antifungal activities. Antimicrobial tests were carried out by the agar well diffusion method [3] using 100 µL of tested compound solution prepared by dissolving 5 mg of the chemical compound in 1 mL of dimethyl sulfoxide (DMSO). The inoculated plates were then incubated for 24 h at 37 ^{o}C. After incubation time, antimicrobial activity was evaluated by measuring the nihbition zone diameters against the test organisms and compared with standard zone size ranges that determine susceptibility. Visual bacteria growth is observed only in areas in which the drug concentrations are below those required for growth inhibition. The experiment was carried out in triplicate and the average zone of

inhibition was calculated. The antimicrobial activity of the synthesized compounds was determined by the broth dilution method as described by NCCLS. The minimal inhibitory concentrations (MICs) for compounds that showed significant growth inhibition zones (>10 mm) were determined using twofold serial dilution method [3]. The inhibition zone diameters, attributed to the tested original concentration (5 mg/mL) as a preliminary test are shown in Tables 1-4.

Table 2: Antimicrobial activity of the synthesized compounds against the Gram -ve bacteria expressed as inhibition diameter zones in millimeters (mm) based on well diffusion assay

Compd. No.	*P. vulgaris*	*K.pneumonia*	*S. flexneri*	*N. gonorrhoeae*
St.	23.4±0.3	26.3±0.15	24.8±0.24	19.9±0.18
1	11.3±0.37	12.4±0.28	10.8±0.43	NA
2	15.6±0.64	17.3±0.64	NA	NA
3	24.6±0.28	21.7±0.67	23.4±0.63	19.3±0.35
4a	16.6±0.28	17.8±0.63	NA	NA
4b	NA	NA	NA	NA
5a	19.9±0.29	21.3±0.63	19.9±0.34	17.9±0.25
5b	20.3±0.76	21.6±0.34	23.6±0.44	17.4±0.53
6a	NA	NA	NA	NA
6b	14.3±0.37	16.4±0.28	15.8±0.43	NA
6c	NA	NA	NA	NA
6d	13.4±0.63	14.5±0.51	NA	NA
6e	20.9±0.63	21.9±0.36	24.8±0.31	18.1±0.28
7a	19.3±0.19	20.4±0.25	22.8±0.38	18.8±0.14
7b	20.2±0.16	23.6±0.34	20.4±0.52	17.3±0.20
7c	15.7±0.56	15.9±0.77	13.6±0.35	NA
8a	17.1±0.73	16.3±0.81	15.4±0.43	11.4±0.42
8b	14.6±0.63	14.9±0.42	10.2±0.66	NA
10	19.8±0.32	21.4±0.34	23.8±0.34	19.32±0.23
11	14.3±0.32	15.2±0.58	NA	NA
12	24.9±0.43	22.6±0.43	24.7±0.54	19.32±0.54
13	12.6±0.23	13.6±0.12	15.7±0.31	16.7±0.58
15	NA	NA	NA	NA

Table 3: Antifungal activity of the synthesized compounds against the pathological fungi expressed as inhibition diameter zones in millimeters (mm) based on well diffusion assay

Compd. No.	*A. fumigatus*	*A. clavatus*	*C. albicans*	*G. candidum*
St.	23.7±0.10	21.9±0.12	26.4±0.20	25.4±0.16
1	12.3±0.21	11.5±0.11	10.6±0.51	14.7±0.32
2	15.7±0.23	14.7±0.14	12.8±0.53	16.7±0.33
3	20.3±0.35	20.6±0.29	23.8±0.33	23.6±0.19
4a	15.6±0.63	13.9±0.54	12.2±0.36	16.4±0.77
4b	13.6±0.36	12.6±0.19	NA	13.6±0.25
5a	20.6±0.36	18.3±0.35	19.5±0.44	20.6±0.58
5b	21.6±0.62	19.4±0.34	19.6±0.64	20.3±0.53
6a	14.6±0.53	15.2±0.36	NA	15.8±0.54
6b	13.4±0.25	12.7±0.42	10.6±0.58	13.6±0.36
6c	17.0±0.36	15.2±0.25	15.8±0.44	16.9±0.73
6d	12.3±0.25	12.6±0.37	NA	13.4±0.34
6e	19.3±0.58	20.7±0.22	19.8±0.44	22.4±0.34
7a	19.9±0.52	17.6±0.67	19.9±0.43	20.3±0.58
7b	19.4±0.46	18.0±0.25	17.5±0.41	19.0±0.19
7c	20.4±0.35	19.4±0.67	22.3±0.24	21.5±0.66
8a	14.6±0.53	13.5±0.42	11.6±0.31	15.9±0.77
8b	11.8±0.36	12.3±0.35	14.9±0.58	16.4±0.44
10	18.8±0.36	19.3±0.35	22.9±0.58	21.4±0.44
11	16.7±0.23	14.8±0.28	13.6±0.55	18.3±0.27
12	23.4±0.32	20.9±0.25	20.6±0.19	24.9±0.58
13	14.2±0.63	14.8±0.58	NA	14.0±0.19
15	11.0±0.63	12.1±0.43	NA	12.9±0.58

Table 4: Minimum inhibitory concentration (µg/mL) of the more potent synthesized compounds against the pathological organisms

Organisms	Comd. No.									
	St	**3**	**5a**	**5b**	**6e**	**7a**	**7b**	**7c**	**10**	**12**
S. epidermidis	0.48	0.97	3.9	0.24	1.95	3.9	1.95	3.9	1.95	3.9
S. aureus	0.06	0.97	3.9	0.24	3.9	7.81	3.9	3.9	1.95	0.24
E. faecalis	1.95	31.25	62.5	7.81	125	62.5	15.63	31.25	7.81	1.95
B. subtilis	0.007	1.95	1.95	0.06	0.97	3.9	0.97	0.97	7.81	0.06
P. vulgaris	1.95	3.9	7.81	3.9	7.81	15.63	7.81	7.81	7.81	1.95
K. pneumonia	0.24	1.95	3.9	0.48	1.95	7.81	1.95	3.9	15.63	0.97
S. flexneri	0.48	3.9	7.81	3.9	7.81	1.95	0.48	1.95	3.9	0.97
N. gonorrhoeae	7.81	62.5	125	15.63	500	62.5	31.25	31.25	62.5	15.63
A. fumigatus	1.95	15.63	31.25	3.9	15.63	15.63	7.81	15.63	15.63	3.9
A.clavatus	0.48	3.9	1.95	0.12	0.98	0.98	1.95	7.81	7.81	1.95
C. albicans	0.24	31.25	62.5	7.81	31.25	125	31.25	62.5	0.48	0.24
G. candidum	0.48	1.95	7.81	0.48	7.81	15.63	3.9	7.81	3.9	0.97

The tabulated antimicrobial screening results of the tested compounds revealed that:

1-Compound **12** (MIC = 3.9 µg mL^{-1}) exhibit higher activity than the standard ampiclin against *S. epidermidis*, compounds **3** and **7c** (MIC = 0.97, 3.9 µg mL^{-1}) showed equipotent activity, compounds **5a, b, 7b** and **6e** (MIC = 3.9, 0.24, 1.95, 1.95 µg mL^{-1}) exhibits high inhibitory effect, while compounds **2, 4a, 6a, b, d, 8a, b** and **10** exhibit moderate inhibitory effect.

2-Compounds **3 (**MIC = **0.97, 1.95** µg mL^{-1}) and **12** (MIC = 0.24, 1.95 µg mL^{-1}) exhibit excellent inhibitory effects against *S. aureus*, *E. faecalic* and compounds **5a** (MIC = 3.9, 62.5 µg mL^{-1})**, 5b** (MIC = 0.24, 7.81 µg mL^{-1})**, 6e** (MIC = 3.9, 125 µg mL^{-1})**, 7b** (MIC = 0.24, 1.95 µg mL^{-1}) **and 7c** (MIC = 3.9, 31.25 µg mL^{-1}) have high activity, on the other hand the remaining compounds showed wek to moderate effects.

3-Compounds **3** and **12** (MIC = 3.9, 1.95 µg mL^{-1}) demonstrated higher activity than the standard against *P. vulgaris*, compounds **5a** (MIC = 7.81 µg mL^{-1})**, 5b** (MIC = 3.9 µg mL^{-1})**, 6e** (MIC = 7.81 µg mL^{-1})**, 7a** (MIC = 15.63 µg mL^{-1})**, 7b** (MIC = 7.81 µg mL^{-1}) and **10** (MIC = 7.81 µg mL^{-1}) exhibit high inhibitory effects, while compounds **2, 4a, 7c** and **8a** have moderate effects.

4- Compounds **3** (MIC = 1.95, 3.9, 62.5 µg mL^{-1}) **5a** (MIC = 3.9, 7.81, 125 µg mL^{-1})**, 5b** (MIC = 0.48, 3.9, 15.63 µg mL^{-1})**, 6e** (MIC = 1.95, 7.81, 500 µg mL^{-1}) **7a** (MIC = 7.81, 1.95, 62.5 µg mL^{-1})**, 7b** (MIC = 1.95, 0.48, 31.25 µg mL^{-1}), **7c** (MIC = 3.9, 1.95, 31.25 µg mL^{-1}), **10** (MIC = 15.63, 3.9, 62.5 µg mL^{-1}) and **12** (MIC =0.97, 0.97, 15.63 µg mL^{-1}) depicted high effects towards *K. pneumonia*, *S. flexneri* and *N. gonorrhveae*, while no activity was showed for compounds **4b, 6a** and **15** towards the tested (–ve) strains.

5-Compounds **3** (MIC = 15.63, 3.9, 31.25, 1.95 µg mL^{-1})**, 5a** (MIC = 31.25, 1.95, 62.5, 7.81 µg mL^{-1})**, 5b** (MIC = 3.9, 0.12, 7.81, 0.48 µg mL^{-1})**, 6e** (MIC = 15.63, 0.98, 31.25, 7.81 µg mL^{-1})**, 7a** (MIC = 15.63, 0.98, 125, 15.63 µg mL^{-1}), **7b** (MIC = 7.81, 1.95, 31.25, 3.9 µg mL^{-1}), **7c** (MIC = 15.63, 7.81, 62.5, 7.81 µg mL^{-1})**, 10** (MIC = 15.63, 7.81, 0.48, 3.9 µg mL^{-1}) and **12** (MIC = 3.9, 1.95, 0.24, 0.97 µg mL^{-1}) showed high effects against the fungi under tests. On the other hand, compounds **2, 4a, 8a** and **11** exhibited moderate activity.

A close look at the SAR (structure-activity relationship) of these compounds clearly indicated the influence of peripheral substituent on the antimicrobial potency. It interesting to note that while, the indole derivative **2** showed weak effects, the spiroindoline derivative **3** exhibited excellent activity against the screened strains. In the case of compounds **4a, b** and **5a, b,** while compounds **4a, b** which bearing 2-oxodihydropyridine demonstrated moderate activity, compounds **5a, b** which bearing 2,4-dioxodihydropyridine exhibited high effects against most of the strains under screened. In spite of the arylidene derivatives **6a-d** which joined to aryl moiety exhibited moderate effects against the screened organisms, the arylidene derivative **6e** which containing two furan groups showed high effects. The modification for some of the arylidene derivatives into aminonitrilepyridone derivatives **7a-c** depicted better antimicrobial and antifungal effects, in fact compound **7c** emerged as the most potent of the series may be due to the presence two furan nucleus. On the other hand, the conversion of the arylidene into aminoesterpyridine **8a, b** there is no change in the microbial effects. In fact, compound **12** which contain iminochromenopyridine emerged as the most potent derivative against the screened strains.

CONCLUSION

In conclusion, a series of modified furan and pyridone, which emerged as a new and important class of antimicrobial agents, was successfully designed and synthesized. The results revealed that chromenopyridene bearing the furan moiety showed the most potent activity.

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