Synthesis of 3- cyano-2-pyridone derivative and its utility in the synthesis of some heterocyclic compounds with expecting antimicrobial activity

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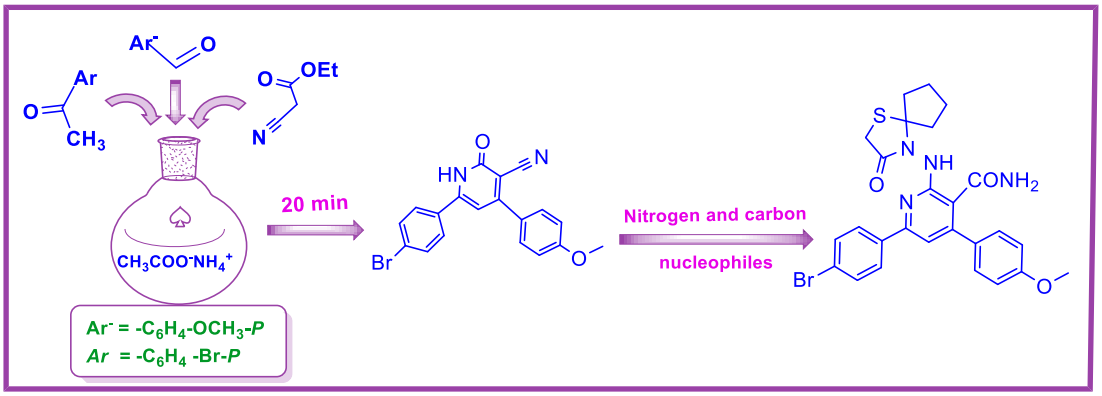

Abstract:

New 2-pyridone derivatives bearing *p*-methoxyphenyl and *p*-bromophenyl substituents at C-4 and C-6, were prepared smoothly by the one-pot reaction in high yield, and in a comparatively short time, it reacted with phosphorous oxychloride to produce the corresponding chloro compound. The latter was reacted with several nitrogen nucleophiles such as sodium azide, hydrazine, acetohydrazide, and benzohydrazide to give tetrazolo, hydrazino, and triazolo derivatives respectively. The reaction of hydrazino derivative with cyclopentanone, furan-2-carbaldehyde afforded the corresponding hydrazone derivatives. Cyclocondensation of the latter compounds with thioglycolic acid afforded the nicotinamide derivatives. 2-Pyridone reacted with ethyl chloroacetate to afford chloroacetate and ethyl acetate derivatives. Ethyl acetate derivative reacted with hydrazine hydrate and gave the acetohydrazide derivative, it was condensed with *p*-anisaldehyde and gave the 4-methoxybenzylidene acetohydrazide derivative. Also, 2-pyridone reacted with chloroacetic acid and or benzoyl chloride, afforded the benzoate derivative and 2-((6-(4-bromophenyl)-3-cyano-4-(4-methoxyphenyl) pyridin-2-yl) oxy) acetic acid respectively. Structures of the products were confirmed using spectroscopic data and elemental analyses. Antibacterial activity of the synthesized compounds was evaluated against E.coli and S. aureus.

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Keywords: Chloropyridine, tetrazole, triazole, thiazolidine.

Introduction:

The pyridine nucleus exists in a lot of products like food, vitamins, plants, dyes, adhesives, pesticides, and drugs [1]. Figure 1. It is oftentimes utilized in drugs because it capable of forming hydrogen bonds, solubility in water, and its basicity. In recent years, various substituted heterocycles containing pyridine moiety have shown significant activity as antibacterial[2], antiviral[3],anti-inflammatory agents[4], antihypertensive[4,5], analgesic[6], antipyretics[7], divretic[8], antiasthmatic[9,10], antioxidant[11], antifungal[12], cardiovascular agents[13] , treatment of Alzheimer's disease[14], and HIV-1 specific reverse transcriptase inhibitors[15].. It was worth mentioning that different pyridine and pyrazole were noticed to have a significantly broad range of applications particularly as anticancer agents [16, 17]. The sake of the current study is to construct a novel group of pyridine derivatives that might have biological activity as the continuation of our efforts [18-24] conducted in the direction of preparation of novel heterocyclic compounds with expected biological activity.

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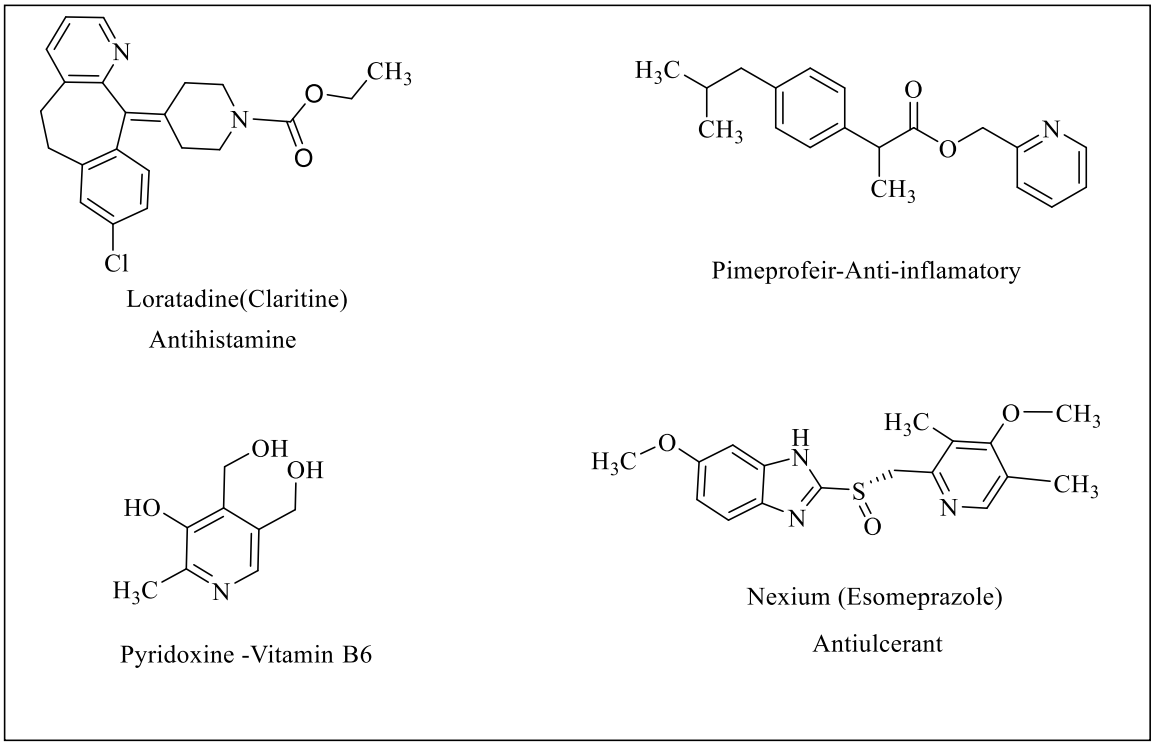
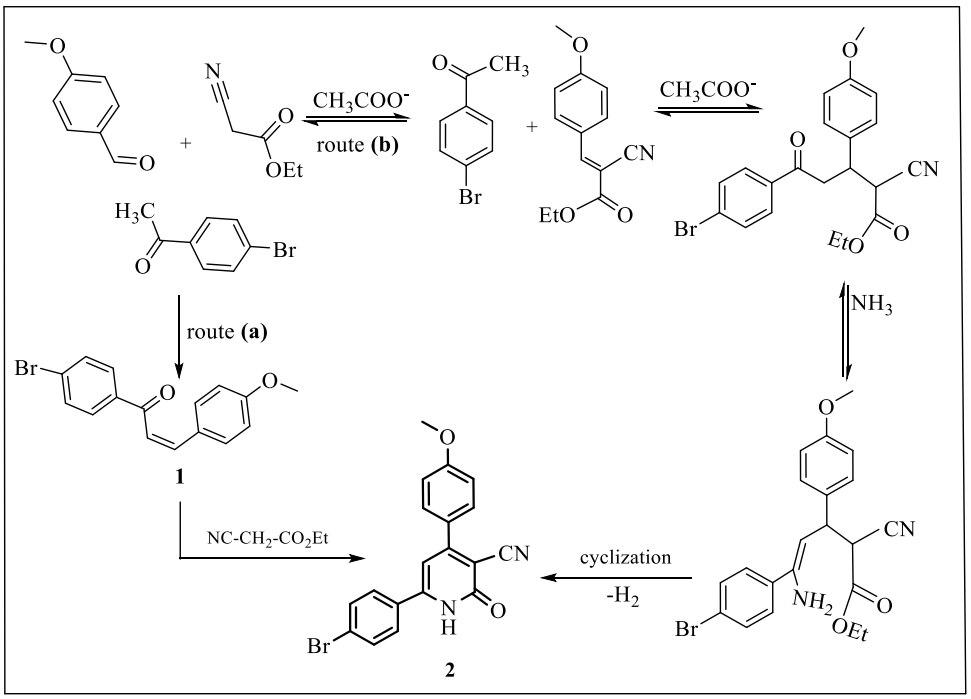


Fig 1 structure of some pyridine drugs

Results and Discussion:

Condensation of 4-bromo acetophenone and 4-methoxy benzaldehyde (Claisen–Schmidt, base-catalyzed) afforded (1-(4-bromophenyl)-3-(4-methoxyphenyl) prop-2-en-1-one (**1).** This procedure involves longer reaction time and lower yield (yield: 68%, reaction time: 5 hours and m.p: 170–172 °C). [25] The reaction proceeds *via the* production of the enone **1** accompanied by Michael's reaction through the addition of ethyl cyanoacetate, then cyclization to give the desired pyridone **2** (route **a**). A particular kind of organic synthetic protocol characterized by mixing three reactants or more, allowing them to interact together to yield the requested compound in a one-pot procedure is known as multi-component reactions. Facile one-pot, four-component condensation of 4-methoxy benzaldehyde, 4-bromo acetophenone, ethyl cyanoacetate, and ammonium acetate proceed smoothly [19], to afford new 2-pyridone derivative **2** (route **b**), in high yield and in a relatively short time (**Scheme 1)**.

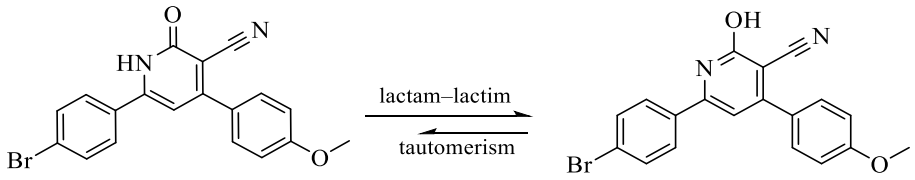
Scheme 1. One pot formation of 2- pyridone derivative 2 *via* **multicomponent approach.**



The reaction proceeds *via* condensation of 4-methoxybenzaldehyde with the reactive CH_2 group in ethyl cyanoacetate, rather than the less active methyl group in 4-bromoacetophenone. Then the resulted cyanoacrylate undergoes Michael addition with 4-bromo acetophenone, with subsequent substitution of enolic OH by NH_2, then cyclization with the removal of ethyl alcohol then dehydrogenation to give the desired product **2**.

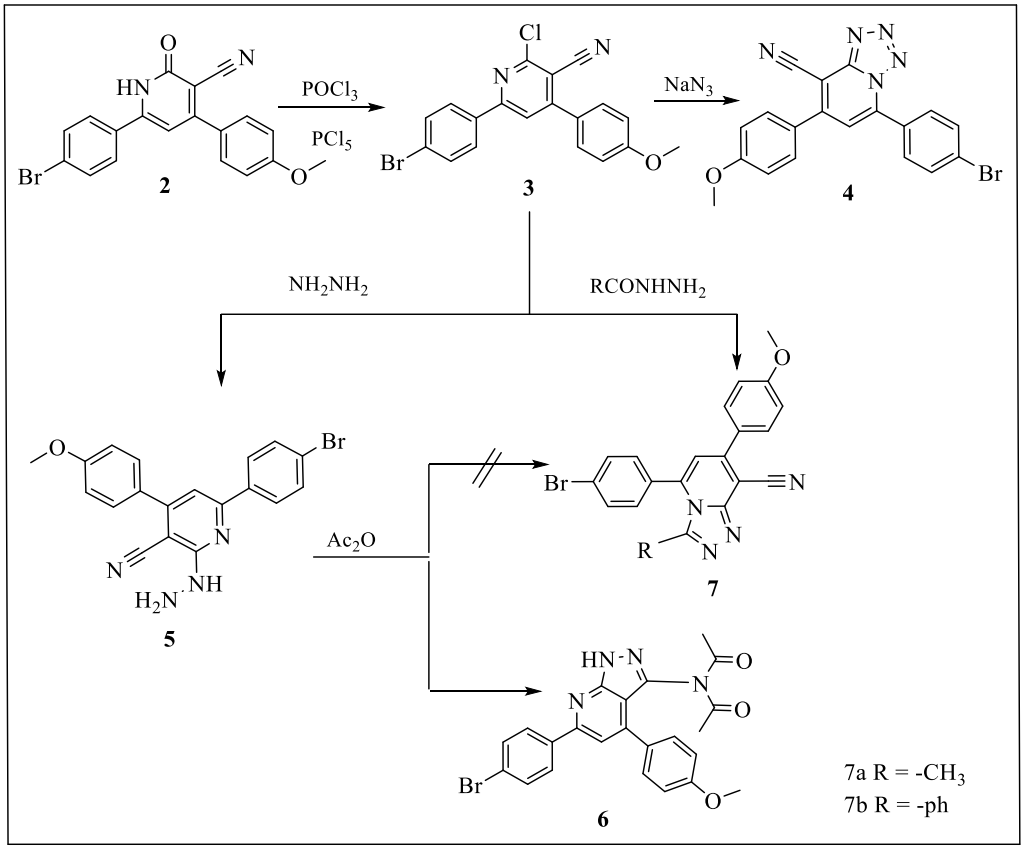
The chemical structure of pyridone **2** was proved by spectral data, since its infrared exhibited bands at 3267, 2221, and 1659 cm^{-1} for NH, CN, and CO groups, respectively. The ^{1} H-NMR spectrum showed singlet signals at δ 4.57 and 12.52 ppm, due to NH and OH proton, respectively. The above-mentioned spectroscopic data indicate the presence of lactam–lactim dynamic equilibrium. From the intensity of the ^{1}HNMR spectrum, the ratio of NH signals to OH signals was (36:100) or ca (1:3). This means that the lactim form is more predominate in solution [21, 23] (**Scheme 2)**.

Scheme 2. Lactam–lactim Tautomerism.



The latter compound was utilized as a start for the formation of diversified new heterocyclic products (**Scheme 3)**, thus pyridone derivative **2** reacted with phosphorous oxychloride , phosphorous pentachloride, and yield the chloro compound[19] **3**. The chemical structure of the chloro derivative **3** was elucidated using its micro elemental analytical and spectroscopic information. The infrared spectrum presented the disappearance of the NH, CO bands, along with the appearance of strong, sharp bands at 2220, 650 cm^{-1} for CN and C–Cl aryl. ^{1}H NMR spectrum displayed singlet, multiplet peaks at 3.84 together with 7.16 – 8.23 ppm, for methyl and aromatic protons.

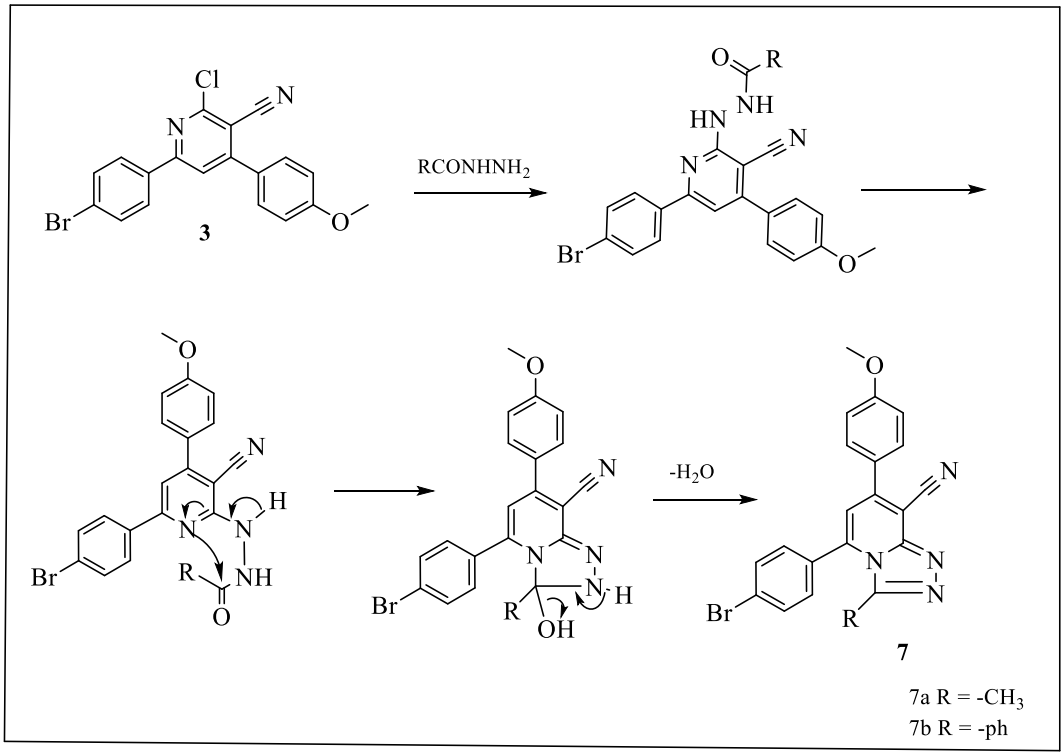
Scheme 3. Reaction of chloro derivative 3 with different nitrogen nucleophiles.



The behavior of chloro derivative **3** towards different nitrogen nucleophiles has been investigated with the aim to get new heterocyclic compounds. Chloro compound **3** reacted with sodium azide and gave the corresponding tetrazolo derivative [20, 26] **4**. Tetrazolo derivative **4** was proved from the infrared spectrum which presents bands at 2220, 1100 cm^{-1} for CN, tetrazole ring mode. As well, MS clarifies a peak due to its molecular weight. The reaction of hydrazine hydrate and chloro derivative **3**, afforded hydrazino derivative **5**. The infrared spectrum of the hydrazino derivative **5** exhibited strong bands at 3430, 3343 cm^{-1} for NH_2, and NH. ^1H NMR spectrum offered singlet signals at 4.62 together with 9.51 ppm due to NH_2 and NH protons, respectively (D_2O exchangeable). The reaction of acetic anhydride with hydrazino derivative **5** afforded the pyrazole derivative **6**, and not the expected triazole derivative **7**. Here authors offer speculation that the addition of NH_2 moiety of hydrazino derivative on the cyano group takes place easier than acylation followed by cyclization to produce the triazolo derivative **7**. This was proved by spectroscopic information, where the infrared data of pyrazole derivative **6** was devoid of any absorption concerning to cyano group and revealed strong absorption bands at 3435, 1729 cm^{-1} due to NH, CO groups respectively. ^1H NMR spectrum presents three singlet signals at 2.16, 3.85 in addition to 10.84 ppm assigned to 2 ($NCOCH_3$), OCH_3 plus NH protons.

It was worth mentioning that treatment of the chloro compound **3** with acetohydrazide and/or benzohydrazide in refluxing n-butanol afforded the triazolo derivatives **7a-b** [27] **(Scheme 4)**.

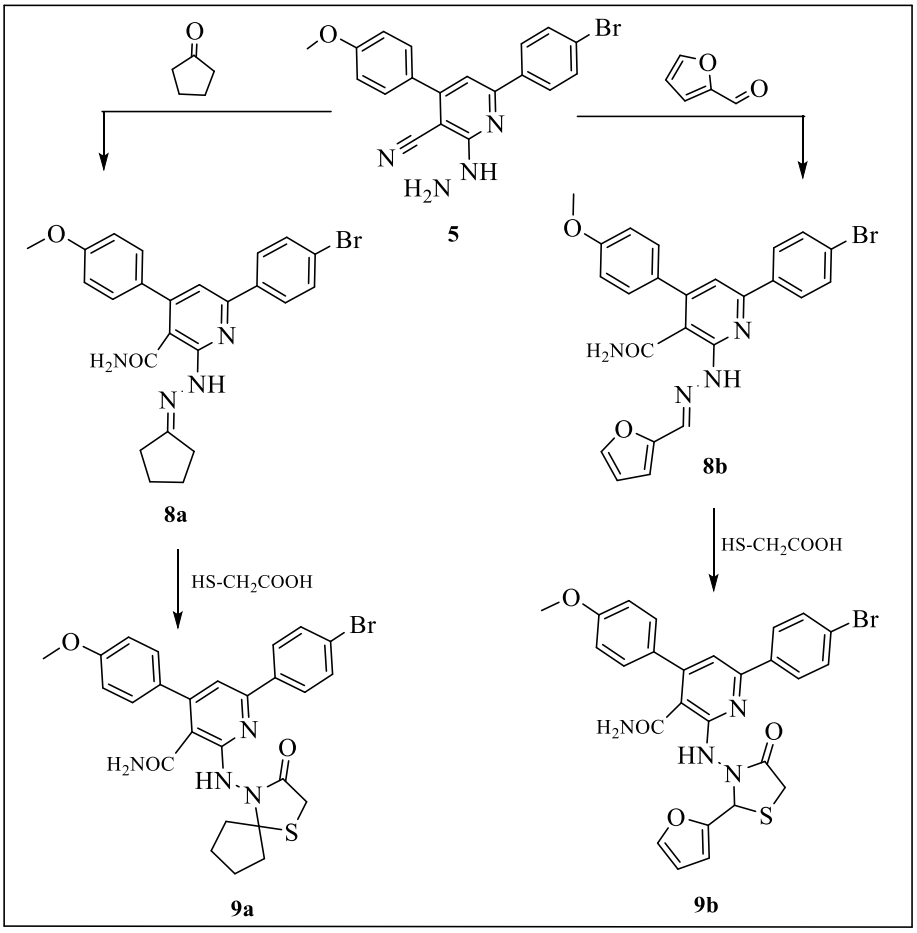
Scheme 4. Suggested mechanism for the formation of 7a–b.



The infrared and ^{1}H NMR spectra of **7a**, **7b** were void of any signal related to the proton of the NH group. Treatment of the hydrazino derivative **5** with cyclopentanone and/or furan-2-carbaldehyde in refluxing DMF and drops of acetic acid yielded the pyridine derivatives [27] **8a** and **8b**, respectively. Compounds **8a, 8b** got support from their spectroscopic information, where the infrared spectra were devoid of any absorption bands for the CN group, and exhibited strong absorption bands around 3197, 3146, 1657, and 1663 cm^{-1} attributed to NH_2 and carbonyl of amide**.** (The amide moiety produced from acid hydrolysis of the nitrile group). ^{1}H NMR spectra showed singlet signals near δ 8.98–9.20 besides 11.52–11.80 ppm, for NH_2 amide along with NH, (D_2O exchangeable). The reaction between compounds **8a**, **8b** and thioglycolic acid [27] takes place *via* thia Micheal addition (cyclocondensation) and gave spiro, thiazolidine derivatives **9a** and **9b**, respectively (**Scheme 5).**

The infrared spectra of nicotinamide derivatives **9a**, **9b** displayed absorption bands at 3205, 1665, 1671, 1673, and 1637 cm^{-1} assigned to NH and carbonyl group.

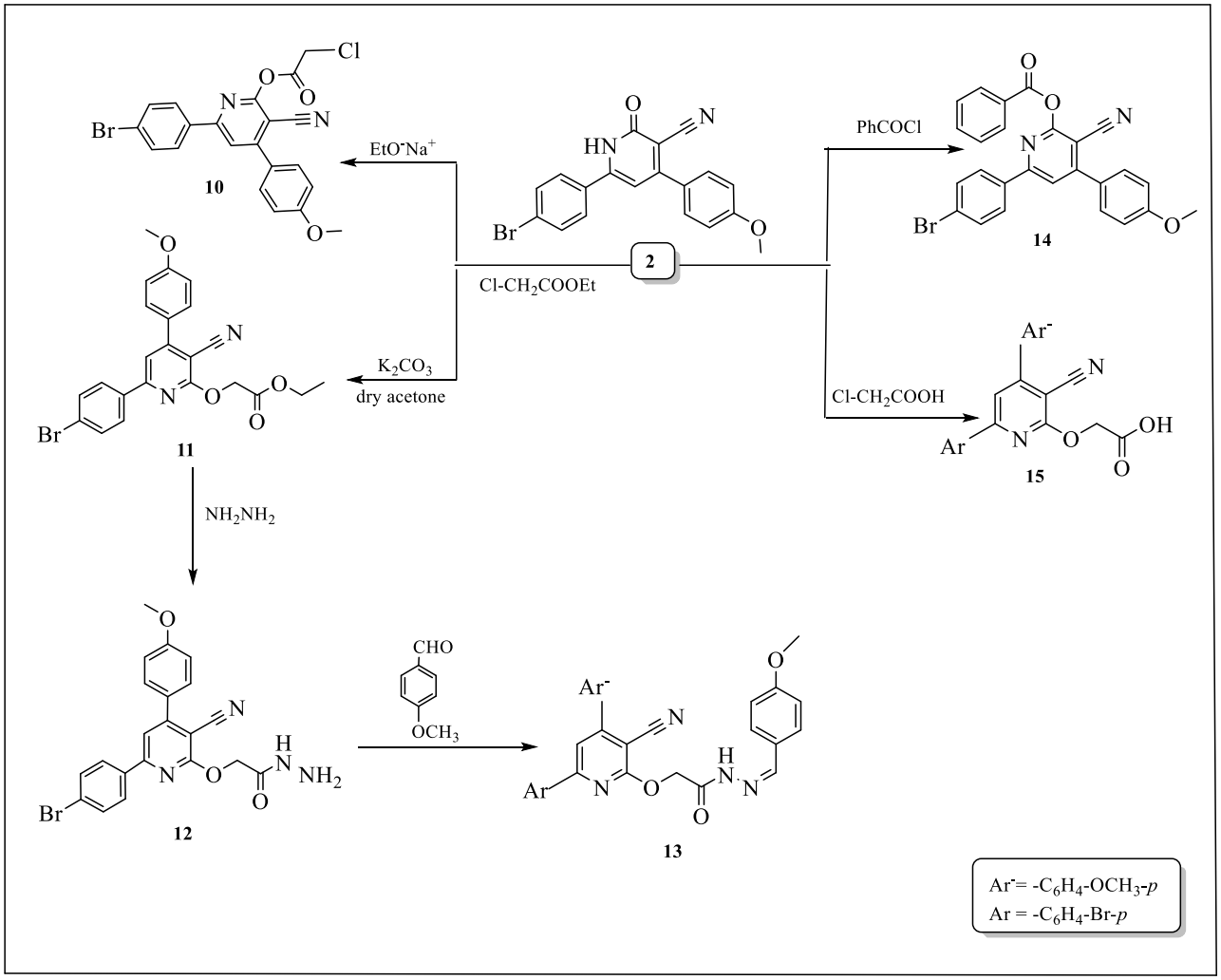
Scheme 5. Formation of derivatives 8a- b and 9a-b.



Pyridine chloroacetate derivative **10** was obtained by refluxing dihydropyridine **2**, ethyl chloroacetate together with sodium ethoxide in absolute ethanol. The infrared spectrum of compound **10** presented a band near 1750 cm^{-1} accounts for CO (chloroester). While pyridine derivative **11** was obtained when the reaction was carried out in dry acetone plus anhydrous potassium carbonate. The infrared spectrum of acetate derivative **11** displayed a strong absorption band near 1733 cm^{-1} attributed to the carbonyl of ester. The ^{1}H NMR spectrum displayed signals near 4.24, 1.12, along with 5.04 ppm as a quartet, triplet, and singlet, respectively for (CH_2CH_3) and (CH_2CO) protons (**Scheme 6).** Whereas the reaction of acetate derivative **11**, hydrazine hydrate gave the corresponding acetohydrazide **12**. The infrared spectrum of **12** detected bands at 3439, 3341 as well as 1644 cm^{-1} for NH_2, NH and carbonyl groups, respectively. Whilst its ^{1}H - NMR presented two broad singlet signals near 9.01 - 9.21 together with 9.50 ppm assigned to NH_2 and NH protons. Moreover, acetohydrazide **12** was reacted with *p*- anisaldehyde and gave the corresponding benzylidene derivative **13**. infrared spectrum of **13** display absorption bands near 3062 , 2221,1660 besides 1620 for NH, CN, CO in addition to C=N groups, respectively.

Benzoate derivative **14** was achieved by refluxing dihydropyridine **2** together with benzoyl chloride in boiling pyridine. The infrared spectrum of the benzoate derivative **14** did not present any signal for NH but gave a signal for C=O near 1761 cm^{-1}. Analogously, pyridine acetic acid derivative **15** was prepared by refluxing dihydropyridine **2** with chloroacetic acid, fused sodium acetate in absolute ethanol [28]. This compound was produced *via* the *O*-alkylation reaction for the hydroxyl group of compound **2**, using chloroacetic acid as an alkylating agent. The infrared spectrum of derivative **15** evidenced strong absorption bands near 3437, 1715 cm^{-1} for hydroxyl plus carbonyl groups, respectively. Its ^{1} H NMR spectrum did not offer any signal due to the NH proton but showed a singlet signal near12.48 ppm for OH proton (D_2O exchangeable).

Scheme 6. Formation of compounds 10 – 15.



The Antimicrobial activity of some prepared derivatives has been evaluated [29, 30]. The results obtained are tabulated in Table 1.

Table 1: The Response of various types of the tested microorganisms to some of the prepared derivatives in vitro culture

No.	Compound	*Escherichia Coli* Gm(-) bacteria		*Staphylococcus aureus* Gm(+) bacteria	
		inhibition zone diameter (mm)	% Activity index	inhibition zone diameter (mm)	% Activity index
1	**2**	12	48.0	13	52.0
2	**3**	12	48.0	14	56.0
3	**4**	21	84.0	18	72.0
4	**5**	16	64.0	16	64.0
5	**6**	18	72.0	18	72.0
6	**8a**	NE	0.00	10	40.0
7	**8b**	12	48.0	14	56.0
8	**9a**	22	88.0	20	80.0
9	**11**	NE	00.0	NE	00.0
10	**12**	NE	00.0	12	48.0
11	**13**	NE	00.0	8	32.0
12	**14**	8	32.0	10	40

13	**15**	18	72.0	19	76.0
Cefoxitin		25	100	25	100

NE → Not Effective

The results of the antibacterial screening as listed in Table (1) indicate that derivatives **4**, **5**, **6**, **9a**, **15** showed the largest activities against Gram negative bacteria *Escherichia Coli*, (derivative **9a** has the maximum activity), and compounds **2**, **3**, **8b** showed moderate activities. While derivatives **14** showed weak activity. Derivatives **8a**, **11**, **12**, **13** were inactive compounds against *Escherichia Coli*. Derivatives **4**, **5**, **6**, **9a**, **15** exhibited intensive activities against Gram positive bacteria (*Staphylococcus aureus*). Likewise (compound 9a has the highest activity), derivatives **2**, **3**, **8a**, **8b**, **12**, **14** have moderate activities .While compound **13** showed weak activity. Derivative **11** was an inactive compound against *Staphylococcus aureus*.

Experimental:

All melting points were determined on a Gallenkamp electric melting point device (Shimadzu, Japan) and uncorrected. The IR spectra were carried out on a Pye Unicam SP-3-300 Infrared spectrophotometer, characterized as Thermoscintific Nitolet is in Waltham, MA02451, USA, using potassium bromide disks. Proton NMR and ^{13}C-NMR spectra were recorded on 300 spectrophotometers (Rheinstetten, Germany), 300 and125 MHz, respectively. TMS as internal standard, and in DMSO-d6 solvents. Chemical shifts are documented in ppm. All mass spectra were done at 70 eV, carried out on Shimadzu GCMS-QP1000EX mass Spectrophotometer (Shimadzu Corp., Kyoto, Japan). All the spectroscopic measurements were done at the NMR laboratory at the Faculty of Pharmacy; the Chemical Laboratories Ministry of Defense, Egypt, the Microanalytical CHN data were run at, and Ain Shams University, Egypt (the Micro Analytical Center). All the chemical reactions were monitored by TLC on silica gel coated aluminum sheets (Silica Gel 60 F254, Merck, and Kenilworth, NJ).

6-(4-Bromophenyl)-4-(4-methoxyphenyl)-2-oxo-1, 2-dihydropyridine-3-carbonitrile (2)

A multicomponent reaction, containing (1.99 g , 0.01 mol) of 4-bromo acetophenone , (1.37g , 0.01 mol) 4- methoxy benzaldehyde, ethyl cyanoacetate (1.13g , 0.01 mol) ,and ammonium acetate (0.06 mol) in absolute ethanol (40 mL) was refluxed as a one-pot reaction for 20 min. The separated solid while hot was filtered, dried, and recrystallized from methanol, Yellow crystals, yield 89%, m.p 281-283 ^{0}C. IR (cm^{-1}) ν: 3267, 2221, 1659 (NH, CN, CO). ^{1}H-NMR (DMSO-*d6*), δ (ppm): 3.37 (s, 3H, OCH_3); 4.57 (br.s, 1H, NH, D_2O exchangeable), 6. 80 (d ,2H,ortho -OCH3) ; 7.53-7.82 (m,5H, Ar-H + pyridine H5) ; 8.17 (d,2H ,ortho bromophenyl moiety) ; 12.52 (br.s,1H,OH , exchangeable with D_2O). ^{13}C-NMR (DMSO): 54.97, 114.08(2), 105.98, 115.01, 116.81, 120.29, 121.73, 128.67(2), 130.95(2), 132.03(2), 139.19, 150.60, 155.51, 157.46, 160.98. MS m/z (%):380,[M-1]$^{\cdot+}$(19);381, [M]$^{\cdot+}$,(23), 364(32),338 (100),342 (12) 156(43),158(7),111(13), 75 (56). Anal. Calcd for $C_{19}H_{13}BrN_2O_2$ (381): C, 59.86; H, 3.44; Br, 20.96; N, 7.35; Found: C, 60.00; H, 3.27; Br, 21.06; N, 7.19%.

6-(4-Bromophenyl)-2-chloro-4-(4-methoxyphenyl) nicotinonitrile (3)

Dihydropyridine **2** (3.81 g, 0.01 mol), PCl_5 (2.08 g, 0.01 mol), and $POCl_3$ (5 mL) were refluxed on a water bath for 4 h. Then the reaction mixture was cooled and poured gradually into crushed ice-cold water. The precipitate formed was filtered off and recrystallized from methanol and gave 2-chloro-3-nicotinonitrile derivative **3** as Yellowish crystals, yield 89 %, m.p 176-178 ^{0}C. IR (cm^{-1}) ν: 2220, 650 (CN, C-Cl). ^{1}H-NMR ($CDCl_3$), δ (ppm) : 3.84 (s ,3H , OCH_3) ; 7.16 – 8.23 (m,9H, 8Ar-H + pyridine -H5) .^{13}C-NMR (DMSO): 55.92,103.88,113.54(2),116.11,119.02, 121.54 ,127.33, 128.90(2), 131.0(2) ,131.09(2),137.82, 151.42,158.2,160,163.40. MS m/z (%):401, [M]$^{\cdot+}$, Cl^{37}, 30), 399, [M]$^{\cdot+}$,Cl^{35},100) 365(44), 158(11), 156(34), 111(7), 75(50.8). Anal. Calcd for $C_{19}H_{12}BrClN_2O$ (400): C, 57.10; H, 3.03; Br, 19.99; Cl, 8.87; N, 7.01**.** Found: C, 57.23; H, 2.98; Br, 20.02; Cl, 8.79; N, 6.98%.

5-(4-Bromophenyl)-7-(4-methoxyphenyl) tetrazolo [1, 5-a] pyridine-8-carbonitrile (4)

A mixture of compound **3** (4 g; 0.01 mol) and NaN_3 (0.65 g, 0.01 mol) in acetic acid (30 mL) refluxed for 5 h. ,cooled then added to 200 mL cold water ,the formed precipitate was decanted, dried, and purified from dioxane, yield 76%, m.p. 246–248 ^{0}C. IR (cm^{-1}) ν: 2220 (CN). ^{1}H-NMR (DMSO-*d6*), δ (ppm): 3.79 (s, 3H,-OCH_3), 7.12-8.37 (m, 9H, 8 Ar-H + pyridine H 5). ^{13}C-NMR (DMSO): 55.89, 103.4, 113.7(2), 116.2, 120.8, 121.1, 128.8(2), 129.2(2), 130.9 132(2), 134.8, 136.2, 152.4, 155.3, 160.8. MS m/z (%): 408 [M+2] $^{\cdot+}$ 5 ; 407 [M+1] $^{\cdot+}$ 8 ; 406 [M]$^{\cdot+}$ 12, 375(4.2) ,380(1.1),349 (42), 244(33),193(100) ,154(43.5),137(26) ,117(23),78(48), 61(19).Anal. Calcd for $C_{19}H_{12}BrN_5O$ (406): C, 56.18; H, 2.98; N, 17.24. Found: C, 55.99; H, 3.00; N, 17.05%.

6-(4-Bromophenyl)-2-hydrazinyl-4-(4-methoxyphenyl) nicotinonitrile (5)

A mixture of chloro derivative **3** (4 g, 0.01 mol) in ethanol (20 mL) , hydrazine hydrate (.0.64 mL,50-60% , 0.02 mol) was heated under reflux for 7 h. , after cooling ,solid material was collected by filtration and recrystallized from (2:1) DMF-dioxane, yellow crystals, yield: 79%, m.p. 189-191^{0}C. IR (cm^{-1}) ν: 3430, 3343, 2205 (NH_2, NH, CN).^{1}H NMR (DMSO- *d6*), δ (ppm): 3.84 (s, 3H, OCH_3), 4.62 (br.s, 2H, NH_2, D_2O exchangeable), 7.22-8.23 (m, 9H, 8Ar-H+pyridine-H5), 9.51 (br.s, 1H, NH, D_2O exchangeable). ^{13}C-NMR (DMSO): 54.87, 84.1, 114.8(2), 116.9, 119.2, 128.9 (2), 129.8(2), 131.1, 132.8(2), 137.8, 154.8 (2), 158.1, 159.4. MS m/z(%): 395 $[M]^{\cdot+}$, 38.2 ; 379 (8.6),363(100),340(22), 308(3) ,229(11),186(10.7), 156(23), 75(48). Anal. Calcd for $C_{19}H_{15}BrN_4O$ (395): C, 57.74; H, 3.83; N, 14.17**;** Found, 57.86; H, 3.78; N, 14.10 %.

N-acetyl-N-(6-(4-bromophenyl)-4-(4-methoxyphenyl)-1*H*-pyrazolo [3, 4-b] pyridin-3-yl) acetamide (6):

A mixture of hydrazino derivative **5** of (3.95g, 0.01 mol), acetic anhydride (20 mL) was heated under reflux for 7 h. The excess acetic anhydride and acetic acid were removed in vacuo, treated with crushed ice, the formed precipitate was collected by filtration and purified from ethyl alcohol, yield 78%, m.p 259-260 ^{0}C. IR (cm^{-1}) ν: 3435, 1729 (NH, CO). ^{1}H NMR (DMSO-*d6*), δ (ppm): 2.16 (s, 6H, –N $(COCH_3)_2$), 3.85 (s, 3H,-OCH_3), 7.14-8.22(m, 9H, 8Ar-H+pyridine-H5), 10.84 (br.s, 1H, NH). ^{13}C-NMR (DMSO): 24.8(2),55.79, 90.2,114.8(2),121.2,128.5(2),129.8(2), 132.4(2),136, ,137.7,149.7, 150.4 153.9,154,154.7,158.8,172.2(2). MS m/z (%): 478$[M-1]^{\cdot+}$, 8.7; 479$[M]^{\cdot+}$, 12, 384(100), 363(34), 339(11.3), 325(7), 216(19),118(42), 75(51). Anal. Calcd for $C_{23}H_{19}BrN_4O_3$ (479): C, 57.63; H, 4.00; Br, 16.67; N, 11.69. Found: C, 57.80; H, 3.94; Br, 16.61; N, 11.72 %.

Triazolo derivatives 7 a, b

General method: A mixture of 2-chloro nicotinonitrile derivative **3** (4.79 g, 0.01 mol) in n -butanol (20 mL), acetohydrazide, and or benzohydrazide (0.01 mol) was heated under reflux condition for 20 h., cooled. The separated solid was recrystallized from the appropriate solvent to give compounds **7 a, b.**

5-(4-Bromophenyl)-7-(4-methoxyphenyl)-3-methyl-[1, 2, 4] triazolo [4, 3-a] pyridine-8-carbonitrile (7a)

Dark -Yellow powder (dioxane), yield: 58%, m.p 221-223 ^{0}C. IR (cm^{-1}) ν: 2220 (CN). ^{1}H NMR (DMSO-*d6*), δ (ppm): 2.41 (s, 3H,-CH_3, triazole)**,** 3.79 (s, 3H, OCH_3), 7.22 - 8.74 (m, 9H, 8 Ar-H + pyridine – H5). ^{13}C-NMR (DMSO): 12.2,55.54,103.7,114.8(2),116.9,121.2,126.8,128.9(2),,130.1(2),,132.7(2),,141.2,146.9,149.3,153.8,161,161.7.162.1.MS m/z (%): 423 $[M+4]^{\cdot+}$ (4), 421 $[M+2]^{\cdot+}$,(32); 419 $[M]^{\cdot+}$ (74) ; 404 $[M-CH_3]^{+}$,(100); 378(8), 332(9), 223(11), 158(7),78(48). Anal. Calcd for $C_{21}H_{15}BrN_4O$ (419): C, 60.16; H, 3.61; Br, 19.06; N, 13.36: Found: C, 60.30; H, 3.50; Br, 19.00; N, 13.40%.

5-(4-Bromophenyl)-7-(4-methoxyphenyl)-3-phenyl-[1, 2, 4] triazolo [4, 3-a] pyridine-8-carbonitrile (7b)

Dark-yellow powder (DMF), yield 59%, m.p. 169-170 ^{0}C. IR (cm^{-1}) ν: 2220 (CN). ^{1}H NMR (DMSO-*d6*), δ (ppm): 3.08 (s, 3H, OCH_3), 6.84-8.36 (m, 14H, 13Ar-H+ pyridine -H5). ^{13}C-NMR (DMSO): 54.9, 103.4,114.2(2),116.1,121.9,127.1 (2), 128.9(2),129.3(2),129.8(2),131.7,132.3(2),134.1,141.5,151.3,152.7,152.3,154.8,160.7,162.8 . MS m/z (%):483 $[M+2]^{\cdot+}$,33;481$[M]^{\cdot+}$ (71), 325(24),299(10), 225(7),156(9.1) ,75(52) Anal. Calcd for $C_{26}H_{17}BrN_4O$ (481): C, 64.88; H, 3.56; Br, 16.60; N, 11.64. Found: C, 65.05; H, 3.51; Br, 16.62; N, 11.56%.

Hydrazone derivatives 8 a, b

General method: A reaction mixture containing (3.95 g, 0.01 mol) of compound **5**, (0.01mol) cyclopentanone, and or furan-2-carbaldehyde in 25 mL DMF, drops of acetic acid was refluxed for 8 h. After concentration, the residues were purified from ethanol to leave products **8a, b.**

6-(4-Bromophenyl)-2-(2-cyclopentylidenehydrazinyl)-4-(4-methoxyphenyl) nicotinamide (8a):

Reddish-brown crystals (MeOH), Yield 74%, m.p 216–218°C. IR (cm^{-1}) ν: 3425, 3146, 1657, 1608(NH_2, NH, CO, C=N). ^{1}H NMR (DMSO-*d6*), δ (ppm): 1.74 -2.08 (m, 8H, cyclopentylidene)**,** 3.72 (s, 3H, OCH_3), 7.07 - 8.22 (m, 9H, 8 Ar-H + pyridine – H5), 8.98 (br.s, 2H, NH_2, amide), 11.52 (br.s, 1H, NH, D_2O exchangeable). ^{13}C-NMR (DMSO): 23.5 (2),29.4(2),55.86,109.1,111.3,114.2(2),121.4,128.6(2),129.3(2),132.1(2),133.7,138.2,150.1,153.2,160.8,163.2,167.8, 181.4 . MS m/z (%):479 $[M^{+\cdot}]$, 25; 463(4.8), 435(100), 382(12), 184(18) 156(41), 75(62).Anal.Calcd for $C_{24}H_{23}BrN_4O_2$ (479): C, 60.13; H, 4.84; Br, 16.67 N, 11.69**.** Found, 60.28; H, 4.80; Br, 16.61; N, 11.7%.

6-(4-Bromophenyl)-2-(2-(furan-2-ylmethylene) hydrazinyl)-4-(4-methoxyphenyl) nicotinamide (8b)

Off-white crystals (EtOH), yield 52%, m.p 204–206°C.IR (cm^{-1}) ν: 3423, 3197 1663, and 1615 (NH_2, NH, CO amide, C═N). ^{1}H NMR (DMSO-*d6*), δ (ppm): 3.78 (s, 3H, OCH_3), 6.59-6.72 (m, 2H, Furan ring), 7.18 – 8.14(m, 1H , furan ring, 9H, 8 Ar-H + pyridine – H5), 8.21 (s, 1H, N=C-H), 9.20 (s ,2H,NH_2 amide) ,11.80 (s, 1H, NH, D_2O exchangeable). ^{13}C- NMR (DMSO): 54.94,109.4,111.3,112.8,114.2(2),118.7,121.3,128.2(2) , 130.1(2),131.7, 132.8(2), 134.2,136.8,138.3,144.8,148.6,151,153.8,160.8,164.6,168.9. MS m/z (%):491[$M^{+\cdot}$], 1.2.Anal. Calcd for $C_{24}H_{19}BrN_4O_3$ (491): C, 58.67; H, 3.90; Br, 16.26; N, 11.40.Found: C, 58.86; H, 3.78; Br, 16.20; N, 11.30%.

General method: (9a and b)

A mixture of derivatives **8a**, or **8b** (0.01 mol), thioglycolic acid (0.7 mL, 0.01 mol) in dry benzene (25 mL) was refluxed for 10 hours. The solid obtained after evaporation of the solvent was filtered off and purified from the suitable solvent to leave compounds **9a** and **b**

6-(4-Bromophenyl)-4-(4-methoxyphenyl)-2-((3-oxo-1-thia-4- aza spiro [4.4] nonan-4-yl) amino) nicotinamide (9a)

Dark- yellow crystals (dioxane), Yield 69%, m.p 244-246 ^{0}C. IR (cm^{-1}) ν: 3208 (NH), 1665 (C=O), 1671 (C=O) cm^{-1}. ^{1}H NMR (DMSO-*d6*), δ, ppm: 1.76 (m, 4H, $2CH_2$ cyclopent), 2.04 (m, 4H, $2CH_2$ cyclopent), 2.98 (d, 2H, CH_2S), 3.70 (s, 3H, OCH_3), 7.38 (s, 2H, NH_2, D_2O exchangeable), 6.98 - 8.02 (m, 9H, 8Ar-H + pyridine- H5), 9.80 (s, 1H, NH, D_2O exchangeable).^{13}C-NMR(DMSO):21.2(2),33.4,36.2(2),54.90,64.1,107.1,114.6(2),116.2,121.2,128.1(2),129.3(2),132.3 (2), 133.8,138.6,148.6,152.4,158.9,161.3,166.3,167.8 MS m/z (%):553 [$M^{+\cdot}$], 32.Anal. Calcd for $C_{26}H_{25}BrN_4O_3S$ (553): C, 56.42; H, 4.55; Br, 14.44; N, 10.12; S, 5.79. Found C, 56.55; H, 4.42; Br, 14.41; N, 10.14; S, 5.80%.

6-(4-Bromophenyl)-2-((2-(furan-2-yl)-4-oxothiazolidin-3-yl) amino)-4-(4-methoxyphenyl) nicotinamide (9b):

Dark yellow powder (dioxane), Yield 68%, m.p 302–304 °C. IR (cm^{-1}) ν: 3205 (NH), 1637 (C=O), 1673 (C=O). ^{1} H NMR (DMSO-*d6*) δ 3.78(s,3H,OCH_3), 4.20 (d, 2H, CH_2-thiazolidine), 5.18 (s, 1H, thiazolidine), 6.52-6.64 (m, 2H, Furan moiety), 7.02– 8.20 (m, 10H ,1H,furan moiety , 8 Ar-H , pyridine H-5), 8.02 (s, 2H, NH_2 amide), 9.80 (br.s, 1H, NH, D_2O exchangeable.^{13}C-NMR (DMSO): 32.7,54.90 ,64.4, 106.3,107.7 ,110.2, 114.9(2), 116.1, 120.4, 128.1(2), 129.4(2),132.8(2),133.6,138.1,142.1,147.3,150.8,153.2, 158.8,160.8,168.1,168.6.MS m/z (%):556 [$M^{+\cdot}$], 5.5 .Anal. Calcd for $C_{26}H_{21}BrN_4O_4S$ (565): C, 55.23; H, 3.74; Br, 14.13; N, 9.91; S, 5.67. Found: C, 55.38; H, 3.68; Br, 14.15; N, 9.88; S, 5.72%.

6-(4-Bromophenyl)-3-cyano-4-(4-methoxyphenyl) pyridin-2-yl-2-chloroacetate (10)

A reaction mixture of dihydropyridine derivative **2** (3.81g, 0.01mol) and ethyl chloroacetate (4, 26 mL, 0.04 mol) in absolute ethanol (15 mL) /sodium ethoxide (0.68 gm., 0.01mol) refluxed 6 hrs. After cooling, neutralization with dil-HCl; the separated product was purified from benzene to afford **10.** Yield 48%, yellow crystals, m.p. 288-290 ^{0} C. IR (cm^{-1}) ν: 2217, 1750 (CN, CO). ^{1}H NMR (DMSO-*d6*), δ (ppm): 3.78(s, 3H,-OCH_3), 4.54 (s, 2H, $ClCH_2CO$-), 6.96-8.02 (m, 9H, 8Ar-H + pyridine- H5).^{13}C-NMR (DMSO): 41.2,54.9, 92.1,114.2(2),116.2,120.8,121.7,128.1(2),129.8(2), 131.2,132.1(2),138.6, 157.4,157.9,160.6,162.1,164.1. MS m/z (%):458[$M^{+\cdot}$], 65. Anal.Calcd for $C_{21}H_{14}BrClN_2O_3$ (458) C, 55.11; H, 3.08; Br, 17.46; Cl, 7.75; N, 6.12. Found: C, 55.26; H, 3.02; Br, 17.42; Cl, 7.73; N, 6.06%.

Ethyl 2-((6-(4-bromophenyl)-3-cyano-4-(4-methoxyphenyl) pyridin-2-yl) oxy) acetate (11)

A mixture of dihydropyridine-3-carbonitrile **2** (3.81 g, 0.01 mol) / dry acetone (25 mL), ethyl chloroacetate (4.9 g, 0.04 mol), K_2CO_3 -anhydrous (5.5 g, 0.04 mol) was refluxed in a water bath for 12 hrs. After evaporation of the excess solvent, the solid obtained was washed with H_2O (to eliminate excess K_2CO_3), then purified from ethyl alcohol, yellow crystals, yield 79%, m.p 166-167^{0}C. IR (cm^{-1}) ν: 2223.1733 (CN, CO, ester). ^{1}H NMR (DMSO-*d6*), δ (ppm): δ (ppm): 1.12(t, 3H, -$CH_2\underline{CH_3}$ ester), 3.30 (s,3H,-OCH_3),4.24 (q,2H,-$\underline{CH_2}CH_3$ester),5.04 (s,2H,-OCH_2CO) ,6.64-8.02 (m,9H,8Ar-H+pyridineH5).^{13}C-NMR(DMSO):14.8,55.9,60.8,62.9,90.8,110.2,114.1(2),116.1,120.2,128.3(2),129.4(2),131,132.6(2), 138.4,155.8,157.3,161.8,164.5,169.8.MSm/z(%):467[M]$^{+}$(1),393(100),384(3),369(22),371(14) 156(34), 158(13),111(6) 75 (44).Anal. Calcd for $C_{23}H_{19}BrN_2O_4$ (467): C, 59.11; H, 4.10; Br, 17.10; N, 5.99. Found C, 59.23; H, 4.06; Br, 17.08; N, 6.00%.

2-((6-(4-Bromophenyl)-3-cyano-4-(4-methoxyphenyl) pyridin-2-yl) oxy) acetohydrazide (12)

A mixture of acetate derivative **11 (**4.67 g , 0.01 mol) in ethyl alcohol (35 mL) , hydrazine hydrate (1 mL, 0.02 mol, 98%) was boiled under refluxed for 7 hrs., the separated solid after cooling was filtered, purified using DMF, dark-

yellow crystals, yield 72%, m.p 197-199 ^{0}C. IR (cm^{-1}) ν: 3439 , 3341 ,2221, 1644 (NH_2, NH, CN).^{1}H NMR (DMSO-*d6*), δ (ppm): 3.36 (s ,3H , OCH_3) ; 4.68 (s,2H, OCH_2CO) ; 6.74-8.16 (m,9H, 8Ar-H + pyridine H5); 9. 01 - 9.21 (s, 2H, NH_2); 9.50 (br.s, 1H, NH) with D_2O exchangeable). ^{13}C-NMR(DMSO):55.89,66.8,92.4,106.4,114.5(2),116.1,121.3, 126.4,128.2,(2)129.8,(2),,132.2(2)133.1,136.2,156.1,157.8,162.2,163.8,168.1,MS m/z (%):453 [M] $^{\cdot+}$ (5); 455 [M+2] $^{\cdot+}$ (2.3), 365(22),232(12), 156(33), ,158(14),109 (10.8),111(8.4),75(50). Anal. Calcd for $C_{21}H_{17}BrN_4O_3$ (453): C, 55.64; H, 3.78; Br, 17.63; N, 12.36. Found: C, 55.70; H, 3.73; Br, 17.59; N, 12.42%.

2-((6-(4-Bromophenyl)-3-cyano-4-(4-methoxyphenyl) pyridin-2-yl) oxy)-N'-(4-methoxybenzylidene) acetohydrazide (13)

A mixture of the hydrazide derivative **12** (4.53 g, 0.01 mol), (1.36g, 0.01mol) *p*-methoxy benzaldehyde / DMF (30 mL) was boiled under reflux 9 hrs. The precipitate formed was purified from ethanol to produce acetohydrazide derivative **13**, orange needles crystals, yield 72%, m.p 181-183 ^{0}C. IR (cm^{-1}) ν: 3062, 2221, 1660 1620 (NH, CN, CO, C=N). ^{1}H NMR (DMSO-*d6*), the chemical) shift δ (ppm): 2.99 (s, 6H, 2 OCH_3), 4.60 (s, 2H, OCH_2CO), 6.76-7.73 (m, 13H, Ar-H + pyridine -H5), 8.60 (s, 1H, N=C-H)**,** 11.20 (br.s,1H, NH,D_2O exchangeable).^{13}C-NMR(DMSO):54.89(2),66.4, 93.8, 114.4(2),114.8(2),116.1,121.9,128.8(2),129.2(2),130.4(2)131.6,132.2(2),138.8, 144.2,154.6, 159.8,162.2, 163.1,170.8. MS m/z (%):571 [M] $^{\cdot+}$ (3.8) , 388(14.6),335 (12.7), 156 (44),75 (38) .Anal. Calcd for $C_{29}H_{23}BrN_4O_4$ (571): C, 60.96; H, 4.06; Br, 13.98; N, 9.80. Found: C, 61.00; H, 3.94; Br, 14.00; N, 9.76%.

6-(4-Bromophenyl)-3-cyano-4-(4-methoxyphenyl) pyridin-2-yl benzoate (14)

A reaction mixture of 2-oxo-1, 2-dihydropyridine-3-carbonitrile derivative **2** (3.81 g, 0.01 mol), benzoyl chloride (1.4 g, 0.01 mol) / pyridine (25 mL) was refluxed 5 hrs. Then cooled, poured in cold water-crushed ice/dil- HCl, the precipitate formed was purified from methanol, brown crystals, yield 64%, m.p 162-163 ^{o}C. IR (cm^{-1}) ν: 2222, 1761 (CN, CO) .^{1}H NMR (DMSO-*d6*): 3.79 (s, 3H, OCH_3); 6.98 (d, 2H, ortho –OCH_3),7.60-7.88(m, 8H, 7Ar-H + pyridine-H5),8,12(d,2H, ,ortho bromophenyl),8.20(d,2H,ortho benzoate).^{13}C-NMR(DMSO):55.89,101.03,114.94(2),116.90,122.17(2),127.01, 129.33,130.28(2),131.96(2),134.81,139.78, 146.88, 158.52, 164.50,165.43. MS m/z (%):485[M]$^{\cdot+}$(3.3) ,459(100),367 (18), 303(12),192(8),158(7), 75(52).Anal. Calcd for $C_{26}H_{17}BrN_2O_3$ (485): C, 64.34; H, 3.53; Br, 16.46; N, 5.77.Found: C, 64.50; H, 3.50; Br, 16.42; N, 5.71%.

2-((6-(4-Bromophenyl)-3-cyano-4-(4-methoxyphenyl) pyridin-2-yl) oxy) acetic acid (15)

A mixture of 3- cyano-2-oxo-1, 2-dihydropyridine derivative **2** (3.81 g, 0.01mol), chloro acetic acid (0.94 g, 0.01 mol), CH_3COONa (0.82g, 0.01mol) /absolute ethyl alcohol (30 mL) was refluxed for 5 hrs. Then cooled, diluted with H_2O for removal of excess CH_3COONa, acidified with dil-HCl to (pH=2.5). The solid formed was recrystallized from (EtOH), yellow crystals; yield 82%, m.p. 290-292^{0}C. IR (cm^{-1}) ν: 3437, 1715 (broad OH, CO acid). ^{1}H NMR (DMSO-*d6*), δ (ppm) : 3.80 (s, 3H , OCH3),3.98 (s,2H,OCH_2CO), 6.91-8.10 (m,9H, 8Ar-H + pyridine H5); 12.48 (s,1H,OH , D_2O exchangeable).^{13}CNMR(DMSO):55.87,64.76,93.81,114.82(2),116.03,128.63(2),129,6(2),131.92(2),155.8,157.6,161.14, 164.9. MS m/z (%):438 [M-1]$^{\cdot+}$(10),422(34),394(100),368(19), 214(7),158(29),75 (44). Anal. Calcd for $C_{21}H_{15}BrN_2O_4$ (439): C, 57.42; H, 3.44; Br, 18.19; N, 6.38. Found: C, 57.50; H, 3.38; Br, 18.20; N, 6.35%.

Antimicrobial activity:

The antibacterial screening was carried out at the Lab of Microbiology, Ain Shams University, Science Faculty, Cairo, Egypt. The codes of the strains were Staph.aureus ATCC 6538 and E.coli ATCC25922.Compounds **2**, **3**,**4**,**5**,**6**, **8a**, **8b**, **9a**, **11**, **12**, **13**, **14** and **15** were examined in vitro for antibacterial activity against Staphylococcus *aureus* (Gram-positive bacteria) and *Escherichia coli* (Gram-negative bacteria) by make use of disc diffusion technique [29, 30] at disc concentration of 1 mg/mL. Cefoxitin was used as a standard antibacterial agent. DMSO was used as a solvent. The zone of inhibition of bacterial growth rate was detected.

Conclusion:

This study introduces a facile, one-pot reaction for the synthesis of new 3- cyano-2-pyridione derivative and its utility in the synthesis of new heterocyclic compounds. Some of the synthesized derivatives were checked against Gram-negative bacteria *(Escherichia Coli*) and Gram-positive bacteria (*Staphylococcus aureus*). In general, these compounds showed good to moderate antibacterial activity. Compound **9a** possesses the maximum activity towards Gram negative bacteria *(Escherichia Coli),* Gram positive bacteria (*Staphylococcus aureus*).

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