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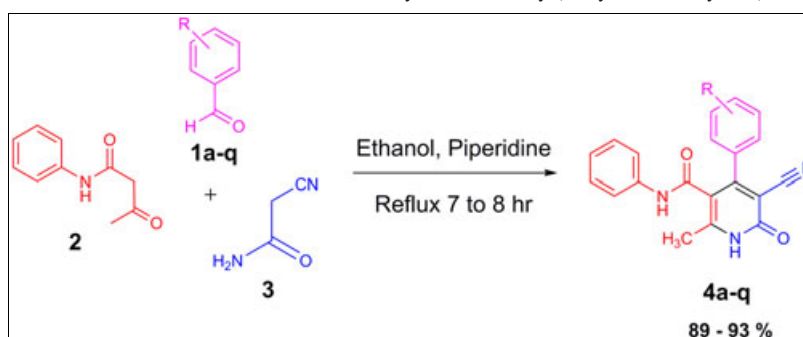
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A series of carboxamide and cyano functionalized pyridone derivatives **4a–q** have been synthesized *via* one-pot synthesis of various aldehydes **1a–q**, acetoacetanilide **2**, and cyanoacetamide **3**. The reaction was simple and afforded pyridone derivatives in good yield, 89 to 93%. The novel pyridone derivatives were achieved by Hantzsch one-pot synthesis. Moreover, the synthesized compounds were screened against Gram-positive and Gram-negative bacteria and fungi for their activity. Among them, compound **4c** shows highest inhibition at 4.25 mm against *Staphylococcus aureus* and 3.75 mm against *Escherichia coli* Gram-positive and Gram-negative bacteria, respectively.

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## INTRODUCTION

Pyridone scaffold is present in a huge number of natural and synthetic biologically active compounds. 2-Pyridone derivatives and their analogues have attracted considerable interest recently because of their antimicrobial, anxiety, antitumor, antiviral, anticancer, antituberculosis, and anti-inflammatory properties [1–8]. Well-known drugs amrinone (a) [9] and milrinone (b) [10] used for the treatment of heart failure contains 2-pyridone moiety in their structure. Recently, pyridone derivative having carboxamide substitution (c) [11] has been synthesized and identified as most potent active against the replication of Hepatitis B virus DNA with  $IC_{50}$  value of 3.4 mM.

Moreover, pyridone derivative (d) has been known as a specific non-nucleoside reverse transcriptase inhibitor of human immune deficiency virus-1 [12]. 2-Pyridones are important intermediates in some synthetic approaches for the synthesis of camptothecin family of antitumor agents. Arnold *et al.* have synthesized novel pyridone derivatives (e) and observed potent antibacterial agent [13]. Cyano containing pyridone (f) [14] derivatives have been synthesized by novel route and found as potent antiproliferative agents (Fig. 1). Many pyridone derivatives containing cyano and carboxamide derivatives

have been synthesized using novel methods and screened for their potent biological activity [15–18]. Hence, synthesis of carboxamide and cyano functionalized pyridones has gained much chemical and pharmaceutical importance in recent years.

Literature survey reveals that only a few methods have been reported for one-pot synthesis of pyridones by condensation of three components, an aldehyde, a  $\beta$ -ketoester, and cyanoacetate or cyanoacetamide under acidic or basic conditions such as  $HNO_3$ ,  $H_2SO_4$ , Piperidine,  $NH_4OAc$ ,  $ZnO$ ,  $SOCl_2$ , and so on [19–23]. However, these methods suffer from very low yields and harsh reaction conditions. Thus, there is a need for simple and efficient procedure to synthesize functionalized pyridones under mild conditions. Earlier, we have demonstrated the application of acetoacetanilide for the synthesis of novel heterocycles [24,25]. Herein, we wish to report the simple and multicomponent one-pot reaction of carboxamide and cyano functionalized pyridone derivatives and their antimicrobial and antifungal screening.

## RESULTS AND DISCUSSION

The tremendous biological potential of pyridone derivatives bearing carboxamide and cyano

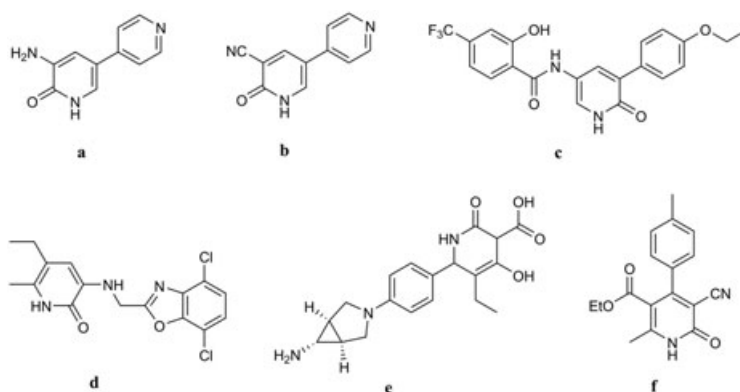


Figure 1. Compounds containing pyridone scaffold for medicinal interest.

Table 1

Comparative study of base and solvent for the synthesis of **4a**.

Sr. no.	Solvent	Base	Yield in %	Time in h
1	MeOH	K <sub>2</sub> CO <sub>3</sub>	75	10
2	EtOH	K <sub>2</sub> CO <sub>3</sub>	78	10
3	THF	K <sub>2</sub> CO <sub>3</sub>	70	9
4	MeOH	Morpholine	83	9
5	EtOH	Morpholine	85	7
6	THF	Morpholine	87	8
7	MeOH	Piperidine	89	8
8	EtOH	Piperidine	93	8
9	THF	Piperidine	87	9

groups motivated us to synthesize some novel pyridones. Thus, we have selected acetoacetanilide as a precursor for carboxamide group and cyanoacetamide for cyano group. Initially, the reaction of benzaldehyde **1a**, acetoacetanilide **2**, and cyanoacetamide **3** was examined using various solvent and base. We found that good yield of compound **4a** was obtained using ethanol as solvent and piperidine as base at reflux temperature Table 1.

Using the aforementioned standard process, we have synthesized all pyridone derivatives in good to excellent yields Scheme 1. The data are depicted in Table 2.

The structures of compounds were established on the basis of spectral studies. The <sup>1</sup>H NMR of compound **4a** showed a singlet of *NH* proton of pyridine ring at 12.93  $\delta$

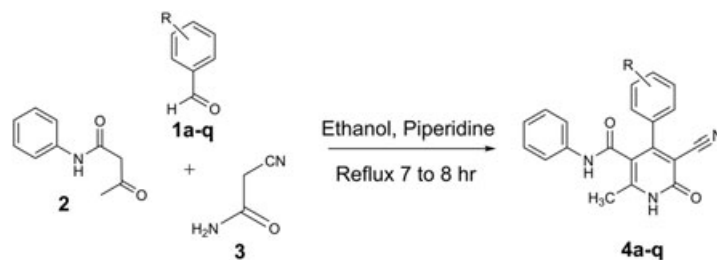
Table 2

Physical properties of pyridones **4a–q**.

Entry	R	Yield in %	Time in h	Melting range
<b>4a</b>	H	93	8	170–172
<b>4b</b>	2-F	92	7	225–227
<b>4c</b>	2-Br	93	8	211–213
<b>4d</b>	4-OCH <sub>3</sub>	92	8	121–123
<b>4e</b>	4-N(CH <sub>3</sub> ) <sub>2</sub>	91	7	172–174
<b>4f</b>	2-OH	92	7	198–200
<b>4g</b>	2-Cl	93	7	208–210
<b>4h</b>	4-Cl	91	8	200–202
<b>4i</b>	4-Br	93	7	228–230
<b>4j</b>	4-F	89	8	231–233
<b>4k</b>	3-NO <sub>2</sub>	91	8	236–238
<b>4l</b>	4-OH	92	8	162–164
<b>4m</b>	4-OH-3-OCH <sub>3</sub>	92	7	222–224
<b>4n</b>	2-NO <sub>2</sub>	91	8	200–202
<b>4o</b>	3-Cl	90	7	198–200
<b>4p</b>	4-CH <sub>3</sub>	93	7	182–184
<b>4q</b>	Furfural	91	8	225–227

ppm due to deshielding effect of adjacent groups. The proton of amide group appeared at 10.22  $\delta$  ppm. The  $-CH_3$  protons appeared as singlet at 2.37  $\delta$  ppm. Aromatic protons showed at 7.0 to 7.4  $\delta$  ppm. The IR signal appeared at 2232  $cm^{-1}$  and at 1715, 1723  $cm^{-1}$  due to the presence of cyano and keto group, respectively. The data suggest the formation of pyridone ring system. The present method may give library of

Scheme 1. Synthesis of carboxamide and cyano bearing pyridone derivatives **4a–q**.



**Table 3**  
Antimicrobial activity of selected compounds.

Entry	Gram positive		Gram negative		Fungi
	<i>Bacillus subtilis</i>	<i>Staphylococcus aureus</i>	<i>Escherichia coli</i>	<i>Pseudomonas aeruginosa</i>	<i>Aspergillus niger</i>
4a	3.00	NILL	4.00	NILL	3.75
4b	3.25	NILL	3.00	NILL	3.75
4c	3.50	4.25	3.75	3.00	3.00
4d	3.50	NILL	NILL	NILL	3.00
4e	3.25	NILL	3.50	NILL	3.25
4q	NILL	3.50	3.25	1.50	3.75

Zone of inhibition in mm; Concentration: 1000 microgram per mL.

pyridone derivatives with high diversity. The physical properties of newly synthesized compounds are given in Table 2.

**Biological activity.** In these experiments, five microorganisms were used. This group included two Gram-positive bacteria: *Bacillus subtilis* and *Staphylococcus aureus*; two Gram-negative bacteria: *Escherichia coli* and *Pseudomonas aeruginosa* for antibacterial activity; and Fungi *Aspergillus niger* was used for antifungal activity.

Nutrient agar or broths (Himedia PVT Ltd., India) were used for bacterial cultivation. Before the experiments, all bacteria were subcultured on fresh media and then incubated for 24 h in temperature 30°C (*P. aeruginosa* and *S. aureus*) and 37°C (remaining bacteria). *A. niger* culture was inoculated in Potatoe dextrose Agar, and then, spore suspension was made by using tween 80 surfactant. Next, suspensions of microorganisms in saline/Tween 80 water were prepared, and their density was established at a level of 0.5 according to McFarland Standard.

Antimicrobial activity of aqueous solutions of substrates and products of chemical synthesis was determined by well diffusion assay. Suspensions of microorganisms were overlaid with agar media and after medium solidification; the wells (10 mm in diameter) were cut with sterile cork borer. To the wells, 100 µL of substrates and surfactants solutions were introduced. The plates were incubated for 24 h at the temperature of 30°C or 37°C depending on the indicator microorganism.

After incubation, the diameter of inhibition zones were measured in millimeters. Tests were performed in triplicate, and the mean values are presented. The results are shown in Table 3.

## CONCLUSION

In summary, we have developed an efficient and simple method for the synthesis of cyano and carboxamide bearing pyridone derivatives using one-pot system. The yields were good to excellent of all compounds. Among

the synthesized compounds, selected compounds were screened against Gram-positive and Gram-negative bacteria and fungi and examined zone of inhibition. Out of six compounds, 4c has shown inhibition against Gram-positive and Gram-negative bacteria. However, all compounds have shown inhibition at 3 to 3.75 mm against fungi *A. niger*.

## EXPERIMENTAL

**General synthesis of 5-cyano-2-methyl-6-oxo-N-phenyl-4-aryl-1,6-dihydropyridine-3-carboxamide 4a-q.** To a solution of various aldehydes (5.6 mmol) (1a-q) in ethanol (10 mL), piperidine was added in catalytical amount and stirred for 5 min at room temperature. Then, cyanoacetamide (5.6 mmol) and acetoacetanilide (5.6 mmol) was added and refluxed on boiling water bath at 78°C for appropriate time. The reaction was being monitored by thin-layer chromatography using Hexane : EtOAc (8:2). After completion of the reaction, the reaction was cooled in refrigerator for overnight. The separated product was filtered off and air dried to obtain the desired products 4a-q in high yields.

**5-Cyano-2-methyl-6-oxo-N,4-diphenyl-1,6-dihydropyridine-3-carboxamide 4a.** Cream color solid.  $R_f$ : 0.24.  $^1\text{H NMR}$  (400 MHz;  $\text{DMSO-}d_6$ ):  $\delta$  2.37 (s, 3H), 7.00 to 7.48 (m, 10H), 10.22 (s, 1H), 12.93 (s, 1H);  $^{13}\text{C NMR}$  (100 MHz;  $\text{DMSO-}d_6$ ): 17, 99, 110, 115, 117, 119, 123, 126, 127, 128, 129, 134, 136, 138, 141, 150, 159, 160, 162, 166, 169. ms:  $m/z$  329. Anal. Calcd for  $\text{C}_{20}\text{H}_{15}\text{N}_3\text{O}_2$ : C, 72.94; H, 4.59; N, 12.76. Found: C, 72.90; H, 4.60; N, 12.69.

**5-Cyano-4-(2-fluorophenyl)-2-methyl-6-oxo-N-phenyl-1,6-dihydropyridine-3-carboxamide 4b.** Cream color solid.  $R_f$ : 0.23.  $^1\text{H NMR}$  (400 MHz;  $\text{DMSO-}d_6$ ):  $\delta$  2.36 (s, 3H), 7.12 to 7.62 (m, 9H), 10.31 (s, 1H), 12.89 (s, 1H); ms:  $m/z$  348. Anal. Calcd for  $\text{C}_{20}\text{H}_{14}\text{FN}_3\text{O}_2$ : C, 69.16; H, 4.06; N, 12.10. Found: C, 69.11; H, 4.02; N, 12.09.

**4-(2-Bromophenyl)-5-cyano-2-methyl-6-oxo-N-phenyl-1,6-dihydropyridine-3-carboxamide 4c.** Cream color solid.  $R_f$ : 0.23.  $^1\text{H NMR}$  (400 MHz;  $\text{DMSO-}d_6$ ):  $\delta$  2.50 (d, 3H),

$J = 1.6$ ), 7.00 to 7.61 (m, 9H), 9.86 (s, 1H), 12.85 (s, 1H); ms:  $m/z$  409. *Anal.* Calcd for  $C_{20}H_{14}BrN_3O_2$ : C, 58.84; H, 3.46; N, 10.29. Found: C, 58.81; H, 3.42; N, 10.29.

**5-Cyano-4-(4-methoxyphenyl)-2-methyl-6-oxo-N-phenyl-1,6-dihydropyridine-3-carboxamide 4d.** Yellow color solid.  $R_f$ : 0.24.  $^1H$  NMR (400 MHz; DMSO- $d_6$ ):  $\delta$  2.35 (s, 3H), 3.74 (s, 3H), 6.97 to 7.44 (m, 9H), 10.34 (s, 1H), 12.87 (s, 1H); ms:  $m/z$  359. *Anal.* Calcd for  $C_{21}H_{17}N_3O_3$ : C, 70.18; H, 4.77; N, 11.69. Found: C, 70.15; H, 4.75; N, 11.69.

**5-Cyano-4-(4-(dimethylamino)phenyl)-2-methyl-6-oxo-N-phenyl-1,6-dihydropyridine-3-carboxamide 4e.** Reddish brown color solid.  $R_f$ : 0.21.  $^1H$  NMR (400 MHz; DMSO- $d_6$ ):  $\delta$  2.51 (s, 3H), 3.05 (s, 6H), 6.80 to 8.01 (m, 9H), 10.32 (s, 1H), 13.23 (s, 1H);  $^{13}C$  NMR (100 MHz; DMSO- $d_6$ ): 20, 97, 108, 111(d), 113, 118 (d), 119, 128, 129, 132, 142, 150 (d), 152, 160, 163. ms:  $m/z$  372. *Anal.* Calcd for  $C_{22}H_{20}N_4O_2$ : C, 70.95; H, 5.41; N, 15.04. Found: C, 70.92; H, 5.42; N, 15.01.

**5-Cyano-4-(2-hydroxyphenyl)-2-methyl-6-oxo-N-phenyl-1,6-dihydropyridine-3-carboxamide 4f.** Yellow color solid.  $R_f$ : 0.24.  $^1H$  NMR (400 MHz; DMSO- $d_6$ ):  $\delta$  2.36 (s, 3H), 6.74 to 7.81 (m, 9H), 10.22 (s, 1H), 10.36 (s, 1H), 13.21 (s, 1H). ms:  $m/z$  345. *Anal.* Calcd for  $C_{20}H_{15}N_3O_3$ : C, 69.56; H, 4.38; N, 12.17. Found: C, 69.52; H, 4.36; N, 12.15.

**4-(2-Chlorophenyl)-5-cyano-2-methyl-6-oxo-N-phenyl-1,6-dihydropyridine-3-carboxamide 4g.** Yellow color solid.  $R_f$ : 0.23.  $^1H$  NMR (400 MHz; DMSO- $d_6$ ):  $\delta$  2.35 (s, 3H), 7.01 to 7.86 (m, 9H), 10.31 (s, 1H), 12.82 (s, 1H). ms:  $m/z$  369. *Anal.* Calcd for  $C_{20}H_{14}ClN_3O_2$ : C, 66.03; H, 3.88; N, 11.55. Found: C, 66.05; H, 3.86; N, 11.52.

**4-(4-Chlorophenyl)-5-cyano-2-methyl-6-oxo-N-phenyl-1,6-dihydropyridine-3-carboxamide 4h.** Cream color solid.  $R_f$ : 0.23.  $^1H$  NMR (400 MHz; DMSO- $d_6$ ):  $\delta$  2.34 (s, 3H), 7.00 to 7.86 (m, 9H), 10.33 (s, 1H), 12.85 (s, 1H). ms:  $m/z$  369. *Anal.* Calcd for  $C_{20}H_{14}ClN_3O_2$ : C, 66.03; H, 3.88; N, 11.55. Found: C, 66.05; H, 3.86; N, 11.52.

**4-(4-Bromophenyl)-5-cyano-2-methyl-6-oxo-N-phenyl-1,6-dihydropyridine-3-carboxamide 4i.** Cream color solid.  $R_f$ : 0.24.  $^1H$  NMR (400 MHz; DMSO- $d_6$ ):  $\delta$  2.36 (d, 3H), 7.02 to 7.67 (m, 9H), 9.92 (s, 1H), 12.89 (s, 1H); ms:  $m/z$  409. *Anal.* Calcd for  $C_{20}H_{14}BrN_3O_2$ : C, 58.84; H, 3.46; N, 10.29. Found: C, 58.82; H, 3.43; N, 10.27.

**5-Cyano-4-(4-fluorophenyl)-2-methyl-6-oxo-N-phenyl-1,6-dihydropyridine-3-carboxamide 4j.** Orange color solid.  $R_f$ : 0.23.  $^1H$  NMR (400 MHz; DMSO- $d_6$ ):  $\delta$  2.38 (s, 3H), 7.11 to 7.62 (m, 9H), 10.32 (s, 1H), 12.85 (s, 1H); ms:  $m/z$  348. *Anal.* Calcd for  $C_{20}H_{14}FN_3O_2$ : C, 69.16; H, 4.06; N, 12.10. Found: C, 69.15; H, 4.04; N, 12.08.

**5-Cyano-2-methyl-4-(3-nitrophenyl)-6-oxo-N-phenyl-1,6-dihydropyridine-3-carboxamide 4k.** Yellow color solid.  $R_f$ : 0.21.  $^1H$  NMR (400 MHz; DMSO- $d_6$ ):  $\delta$  2.36 (s, 3H), 7.12 to 8.02 (m, 9H), 10.36 (s, 1H), 13.12 (s, 1H); ms:  $m/z$  374. *Anal.* Calcd for  $C_{20}H_{14}N_4O_4$ : C, 64.17; H, 3.77; N, 14.97. Found: C, 64.15; H, 3.75; N, 14.98.

**5-Cyano-4-(4-hydroxyphenyl)-2-methyl-6-oxo-N-phenyl-1,6-dihydropyridine-3-carboxamide 4l.** Reddish color solid.  $R_f$ : 0.24.  $^1H$  NMR (400 MHz; DMSO- $d_6$ ):  $\delta$  2.35 (s, 3H), 6.65 to 7.61 (m, 9H), 10.23 (s, 1H), 10.35 (s, 1H), 12.89 (s, 1H). ms:  $m/z$  345. *Anal.* Calcd for  $C_{20}H_{15}N_3O_3$ : C, 69.56; H, 4.38; N, 12.17. Found: C, 69.55; H, 4.35; N, 12.17.

**5-Cyano-4-(4-hydroxy-3-methoxyphenyl)-2-methyl-6-oxo-N-phenyl-1,6-dihydropyridine-3-carboxamide 4m.** Yellow color solid.  $R_f$ : 0.22.  $^1H$  NMR (400 MHz; DMSO- $d_6$ ):  $\delta$  2.34 (s, 3H), 3.81 (s, 3H), 6.71 to 7.75 (m, 8H), 9.81 (s, 1H), 10.32 (s, 1H), 12.87 (s, 1H). ms:  $m/z$  376. *Anal.* Calcd for  $C_{21}H_{17}N_3O_4$ : C, 67.19; H, 4.56; N, 11.19. Found: C, 67.15; H, 4.55; N, 11.17.

**5-Cyano-2-methyl-4-(2-nitrophenyl)-6-oxo-N-phenyl-1,6-dihydropyridine-3-carboxamide 4n.** Reddish color solid.  $R_f$ : 0.21.  $^1H$  NMR (400 MHz; DMSO- $d_6$ ):  $\delta$  2.33 (s, 3H), 7.11 to 8.02 (m, 9H), 10.35 (s, 1H), 13.11 (s, 1H); ms:  $m/z$  374. *Anal.* Calcd for  $C_{20}H_{14}N_4O_4$ : C, 64.17; H, 3.77; N, 14.97. Found: C, 64.14; H, 3.77; N, 14.96.

**4-(3-Chlorophenyl)-5-cyano-2-methyl-6-oxo-N-phenyl-1,6-dihydropyridine-3-carboxamide 4o.** Cream color solid.  $R_f$ : 0.24.  $^1H$  NMR (400 MHz; DMSO- $d_6$ ):  $\delta$  2.34 (s, 3H), 7.01 to 7.82 (m, 9H), 10.32 (s, 1H), 12.89 (s, 1H). ms:  $m/z$  369. *Anal.* Calcd for  $C_{20}H_{14}ClN_3O_2$ : C, 66.03; H, 3.88; N, 11.55. Found: C, 66.01; H, 3.85; N, 11.53.

**5-Cyano-2-methyl-6-oxo-N-phenyl-4-(p-tolyl)-1,6-dihydropyridine-3-carboxamide 4p.** Cream color solid.  $R_f$ : 0.26.  $^1H$  NMR (400 MHz; DMSO- $d_6$ ):  $\delta$  2.34 (s, 3H), 2.32 (s, 3H), 7.02 to 7.72 (m, 9H), 10.23 (s, 1H), 12.85 (s, 1H). ms:  $m/z$  343. *Anal.* Calcd for  $C_{21}H_{17}N_3O_2$ : C, 73.45; H, 4.99; N, 12.24. Found: C, 73.44; H, 4.95; N, 12.23.

**5-Cyano-4-(furan-2-yl)-2-methyl-6-oxo-N-phenyl-1,6-dihydropyridine-3-carboxamide 4q.** Reddish brown color solid.  $R_f$ : 0.24.  $^1H$  NMR (400 MHz; DMSO- $d_6$ ):  $\delta$  2.35 (s, 3H), 6.91 to 8.12 (m, 8H), 10.32 (s, 1H), 12.91 (s, 1H). ms:  $m/z$  319. *Anal.* Calcd for  $C_{18}H_{13}N_3O_3$ : C, 67.71; H, 4.10; N, 13.16. Found: C, 67.70; H, 4.05; N, 13.13.

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