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A Study on Cyanopyridones Synthesis and Biological Evaluation

Mrs. Azra Begam Afridi*

Assistant Professor, Department of Chemistry, K. K. P. G College, Etawah, Uttar Pradesh

Abstract – Cyanopyridone derivatives are generated by both microwave assisted and conventional methods. The condensation of chalcones with ethylcyanoacetate in the presence of ammonium acetate in ethanol leads to cyanopyridones. In microwave synthesis, the reactions are considerably faster and the yields are significantly higher. The rapid assembly of molecular diversity is an important goal of synthetic organic chemistry and is one of the key paradigms of modern drug discovery. On the other hand, cyanopyridone and cyanopyridine derivatives have shown to posses promising antimicrobial and anticancer activities. we have designed and synthesized a series of 4,6-disubstituted-3- cyano-2-pyridone derivatives (4a-o) via one-pot multicomponent reaction using 3-substituted- 1H-pyrazole-4-carbaldehydes (1a-e), various acetyl compounds (2a-c), ethyl cyanoacetate (3) and ammonium acetate. All the target molecules were screened for their antimicrobial activity against various microorganisms.

Keywords: Cyanopyridone, Bipyridine, Antimicrobial Activity

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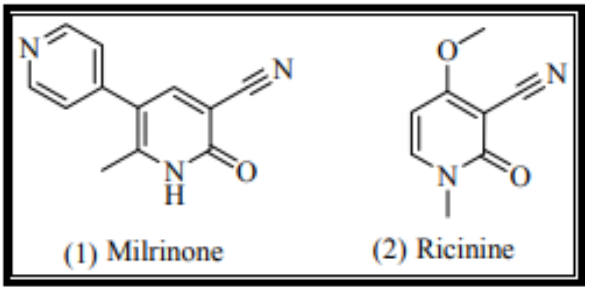
1. INTRODUCTION

The pyridine skeleton is of great importance to chemists as well as to biologists as it is found in a large variety of naturally occurring compounds and also in clinically useful molecules having diverse biological activities. The pyridine ring systems have emerged as integral backbones of over 7000 existing drugs [1,2]. The pyridine ring is also an integral part of anticancer and anti-inflammatory agents[3].

In association with those, Pyridone and their derivatives play an essential role in several biological processes and have considerable chemical and pharmacological importance. 2-Pyridones represent a unique class of pharmacophore, which are observed in various therapeutic agents and antibiotics[4]. These heterocycles attracted attention because of their applications as bioactive compounds for example as a promising class of HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs) ,as antibacterial , antifungal , sedative , and cardiotonic agents[5] . Moreover, such derivatives have recently become important due to their structural similarity to nucleosides. Also, 2-pyridones were used as ligands for the late 3d-metals.

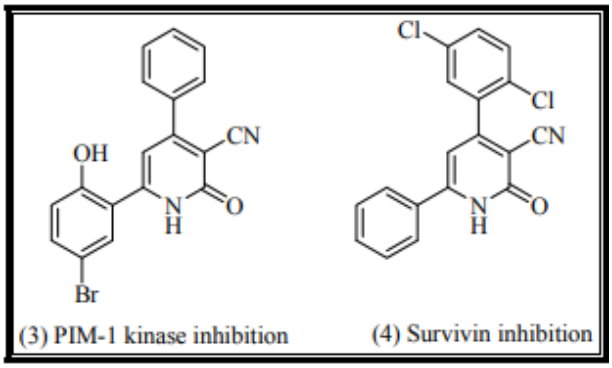
They are also versatile precursors for the construction of complex natural products,pyridines ,and larger pyridone systems such as those found in the nitroguanidine insecticide Imidacloprid and subtype selective GABAA receptor agonists[6]. Consequently, methodologies for the preparation of pyridones have attracted much attention from both industry and academia[7]. 3-Cyano-2-Pyridones are much interest in the anticancer activity of these compounds owing to different types of biological targets they might interfere with for this effect to occur e.g. PDE3, PIM1 Kinase, and Survivin protein. The 3-cyanopyridin-2-one nucleus is the structural basis of the alkaloid ricinine (2), the first known alkaloid containing a cyano-group.



Milrinone (1) is a 3-cyano-2-oxopyridine derivative that has been introduced to the clinic for the treatment of congestive heart failure. Its mechanism of action involves PDE3 inhibition, leading to high levels of cAMP and consequent inotropic effect. Recent studies showed that PDE3, PDE4 and PDE5 are over expressed in cancerous cells compared with normal cells. In addition, cross inhibition of PDE3 together with other PDEs may lead to inhibition of tumor cell growth and angiogenesis [8]. The inhibition of PDE3 was able to inhibit the growth and proliferation of the squamous cell carcinoma cell line HeLa, and in

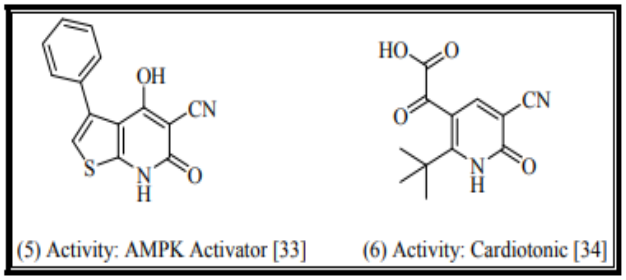
HSG cells and further studies revealed that the pyridone derivative, cilostamide- a selective PDE3 inhibitor- has synergism action to the anti-apoptotic action of PDE4 inhibitors in leukemia cells [9-10].

Cheney et al. reported 4,6-diaryl-2-oxo-1,2-dihydropyridine-3-carbonitriles (3), as inhibitors of the oncogenic serine/threonine kinase PIM-1, which plays a role in cancer cell survival, differentiation and proliferation. PIM-1 kinase has been shown to be over expressed in a variety of cancer cell lines . Wendt et al. showed that several compounds with the same general formula as above but with higher lipophilic properties (4) can inhibit survivin which is a member of the inhibitor of apoptosis family (IAP)[11]. The level of expression of surviving in tumor cells is often associated with poor prognosis and shorter patient survival rates[12]. Survivin is highly expressed in most human tumors and fetal tissue but undetectable in most terminally differentiated adult tissues. This fact therefore makes survivin an ideal target for cancer therapy [13]



(3) PIM-1 kinase inhibition (4) Survivin inhibition

The thienopyridone agonist is showed modest AMPK activity. AMPK (adenosine monophosphate-activated protein kinase), a heterotrimeric serine/ threonine kinase, is well established as a key sensor and regulator of intracellular and whole-body energy metabolism [14]. Activation of AMPK alters carbohydrate and lipid metabolism to increase fatty acid oxidation and glucose uptake and decrease fatty acid and cholesterol synthesis. Through its central role in the regulation of glucose and lipid metabolism, AMPK is emerging as an attractive molecular target for the treatment of diabetes, metabolic syndrome, and obesity [15].



(5) Activity: AMPK Activator [33] (6) Activity: Cardiotonic [34]

2. MATERIALS AND METHODS

2.1. Chemistry

Melting points were determined by open capillary method and are uncorrected. The IR spectra (in KBr pellets) were recorded on a Thermo Nicolet avatar 330-FT-IR spectrophotometer. 1H NMR spectra were recorded (DMSO-d6) on a Varian (400 MHz) spectrometer. Chemical shift values are given in δ scales. The mass spectra were recorded on API 2000 LC/MS system. Elemental analyses were performed on a Flash EA 1112 series CHNS-O analyzer. The completion of the reaction was checked by thin layer chromatography (TLC) on silica gel coated aluminium sheets (silica gel 60 F254). Commercial grade solvents and reagents were used without further purification[16].

2.2. General procedure for the synthesis of 4,6-disubstituted-3-cyano-2-pyridones (4a-o)

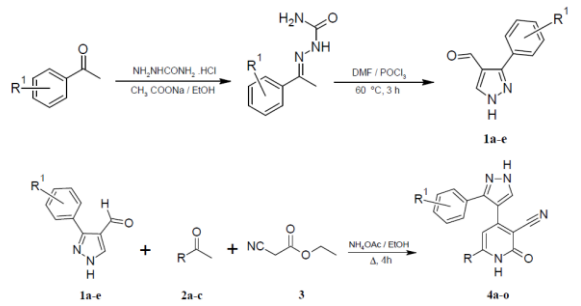
A mixture of 3-substituted-1H-pyrazole-4-carbaldehydes 1a-e (0.001 mol), corresponding acetyl compounds 2a-c (0.001 mol), ethyl cyanoacetate (0.0012 mol) and ammonium acetate (0.008 mol) were refluxed in ethanol for 4 h. The reaction mixture was cooled to obtain precipitate which was filtered, washed with ethanol and recrystallized from suitable solvent to get pure product.

2.2.1. 2-oxo-4-(3-phenyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)-1,2-dihydropyridine-3-carbonitrile (4a)

Yield 53 % ; M.p. >300 oC; IR (KBr, umax cm-1): 3229, 3090 (N-H), 2211 (C≡N), 1635 (C=O), 1594 (C=N); 1H NMR (DMSO-d6): δ 13.53 (bs,1H, pyrazole-NH), 12.66 (s, 1H, pyridone ring NH), 8.32 (s, 1H, pyrazole-5H), 7.18-7.89 (m, 8H, Ar-H), 6.23 (s, 1H, pyridone-5H); MS: m/z = 345 (M+1). Anal. calcd. for C19H12N4OS: C, 66.26; H, 3.51; N, 16.27. Found: C, 66.20; H, 3.55; N, 16.24%.

2.2.2. 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-oxo-6-(thiophen-2-yl)-1,2-dihydropyridine-3-carbonitrile (4b)

Yield 56 %; M.p. >300 oC; IR (KBr, umax cm-1): 3245, 3088 (N-H), 2205 (C≡N), 1637 (C=O), 1594 (C=N); MS: m/z = 363 (M+1). 13C NMR: 163.7, 163.4, 161.3, 152.0, 134.7, 131.5, 130.48, 130.4, 129.3, 117.1, 116.2, 116.0, 114.3, 106.6; Anal. calcd. for C19H11FN4OS: C, 62.97; H, 3.06; N, 15.46. Found: C, 62.91; H, 3.02; N, 15.41 %.



4a: R= Thienyl, R¹=H; 4b: R= Thienyl, R²= 4-F; 4c: R= Thienyl, R²= 4-Cl; 4d: R= Thienyl, R²= 2,4-Cl₂; 4e: R= Thienyl, R²= 4-CH₃; 4f: R= 1-napthyl, R¹= H; 4g: R= 1-napthyl, R²= 4-OCH₃; 4h: R=1-napthyl, R²= 4-F; 4i: R= 1-napthyl, R²= 4-Cl; 4j: R= 1-napthyl, R²= 2,4-Cl₂; 4k: R=1-napthyl, R²= 4-CH₃; 4l: R= 5-Cl-thienyl, R²= H; 4m: R= 5-Cl-thienyl, R²= 4-F; 4n: R= 5-Cl-thienyl, R²= 4-Cl; 4o: R= 5-Cl-thienyl, R²= 4-CH₃

Scheme 1: Synthetic route for 4,6-disubstituted-3-cyano-2-pyridone derivatives

2.2.3. 4-[3-(4-chlorophenyl)-1H-pyrazol-4-yl]-2-oxo-6-(thiophen-2-yl)-1,2-dihydropyridine-3-carbonitrile (4c)

Yield 51 %; M.p. >300 oC; IR (KBr, umax cm-1): 3224, 3080 (N-H), 2216 (C≡N), 1638 (C=O), 1594 (C=N); 1H NMR (DMSO-d6): δ 13.56 (bs,1H, pyrazole-NH), 12.67 (s, 1H, pyridone ring NH), 8.24 (s, 1H, pyrazole-5H), 7.20-7.92 (m, 7H, Ar-H), 6.30 (s, 1H, pyridone-5H); MS: m/z = 379 (M+1). Anal. calcd. for C19H11ClN4OS: C, 60.24; H, 2.93; N, 14.79. Found: C, 60.19; H, 2.89; N, 14.75 %.

2.2.4 4-[3-(2,4-dichlorophenyl)-1H-pyrazol-4-yl]-2-oxo-6-(thiophen-2-yl)-1,2-dihydropyridine-3-carbonitrile (4d)

Yield 49 %; M.p. >300 oC; IR (KBr, umax cm-1): 3199, 3088 (N-H), 2214 (C≡N), 1649 (C=O), 1606 (C=N); 1H NMR (DMSO-d6): δ 13.54 (bs,1H, pyrazole-NH), 12.65 (s, 1H, pyridone ring NH), 8.38 (s, 1H, pyrazole-5H), 7.17-7.82 (m, 6H, Ar-H), 6.15 (s, 1H, pyridone-5H); MS: m/z = 412 (M+). Anal. calcd. for C19H10Cl2N4OS: C, 55.22; H, 2.44; N, 13.56. Found: C, 55.18; H, 2.39; N, 13.51 %.

2.2.5. 4-[3-(4-methylphenyl)-1H-pyrazol-4-yl]-2-oxo-6-(thiophen-2-yl)-1,2-dihydropyridine-3-carbonitrile (4e)

Yield 56 %; M.p. >300 oC; IR (KBr, umax cm-1): 3321, 3088 (N-H), 2807 (Aliphatic C-H), 2213 (C≡N), 1632 (C=O), 1596 (C=N); 1H NMR (DMSO-d6): δ 13.56 (bs,1H, pyrazole-NH), 12.67 (s, 1H, pyridone ring NH), 8.11 (s, 1H, pyrazole-5H), 7.17-7.85 (m, 7H, Ar-H), 6.42 (s, 1H, pyridone-5H), 2.32 (s, 3H, -CH3); 13C NMR: 163.2, 152.4, 145.9, 138.2, 136.9, 135.7, 131.5, 129.7, 129.3, 128.1, 117.1, 114.0, 106.7, 96.7, 21.0; MS: m/z = 359 (M+1). Anal. calcd. for C20H14N4OS: C, 67.02; H, 3.94; N, 15.63. Found: C, 67.06; H, 3.91; N, 15.59 %.

2.2.6. 6-(naphthalen-1-yl)-2-oxo-4-(3-phenyl-1H-pyrazol-4-yl)-1,2-dihydropyridine-3-carbonitrile (4f)

Yield 58 %; M.p. >300 oC; IR (KBr, umax cm-1): 3121, 3088 (N-H), 2221 (C≡N), 1634 (C=O), 1594 (C=N); 13C NMR: 162.1, 153.2, 150.3, 133.4, 131.1, 130.9, 130.2, 129.3, 128.8, 128.6, 128.0, 127.7, 126.9, 117.7, 114.2, 109.7, 100.05; MS: m/z = 389 (M+1). Anal. calcd. for C25H16N4O: C, 77.30; H, 4.15; N, 14.42. Found: C, 77.26; H, 4.12; N, 14.38 %.

2.2.7. 4-[3-(4-methoxyphenyl)-1H-pyrazol-4-yl]-6-(naphthalen-1-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (4g)

Yield 60 %; M.p. >300 oC; IR (KBr, umax cm-1): 3217, 3088 (N-H), 2220 (C≡N), 1638 (C=O), 1586 (C=N); 1H NMR (DMSO-d6): δ 13.55 (bs,1H, pyrazole-NH), 12.65 (s, 1H, pyridone ring NH), 8.15 (s, 1H, pyrazole-5H), 7.02-8.05 (m, 11H, Ar-H), 6.0 (s, 1H, pyridone-5H) 3.79 (s, 3H, -OCH3). MS: m/z = 419 (M+1). Anal. calcd. for C26H18N4O2: C, 74.63; H, 4.34; N, 13.39. Found: C, 74.59; H, 4.31; N, 13.34 %.

2.2.8. 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-6-(naphthalen-1-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (4h)

Yield 57 %; M.p. >300 oC; IR (KBr, umax cm-1): 3291, 3066 (N-H), 2211 (C≡N), 1657 (C=O), 1599 (C=N); 1H NMR (DMSO-d6): δ 13.56 (bs,1H, pyrazole-NH), 12.78 (s, 1H, pyridone ring NH), 8.36 (s, 1H, pyrazole-5H), 7.31-8.06 (m, 11H, Ar-H), 6.02 (s, 1H, pyridone-5H). 13C NMR: 163.8, 162.0, 153.1, 150.5, 133.4, 130.8, 130.3, 128.9, 128.0, 127.5, 126.9, 125.5, 125.0, 117.1, 116.3, 116.1, 114.3, 109.6; MS: m/z = 407 (M+1). Anal. calcd. for C25H15FN4O: C, 73.88; H, 3.72; N, 13.79. Found: C, 73.81; H, 3.65; N, 13.74 %.

2.2.9. 4-[3-(4-chlorophenyl)-1H-pyrazol-4-yl]-6-(naphthalen-1-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (4i)

Yield 50 %; M.p. >300 oC; IR (KBr, umax cm-1): 3217, 3058 (N-H), 2207 (C≡N), 1655 (C=O), 1600 (C=N); 1H NMR (DMSO-d6): δ 13.53 (bs,1H, pyrazole-NH), 12.76 (s, 1H, pyridone ring NH), 8.26 (s, 1H, pyrazole-5H), 7.47-8.06 (m, 11H, Ar-H), 6.03 (s, 1H, pyridone-5H). 13C NMR: 162.1, 152.9, 150.6, 133.4, 130.9, 130.3, 129.3, 128.9, 128.0, 127.5, 126.9, 125.6, 125.0, 117.1, 114.5, 109.7, 100.1; MS: m/z = 423 (M+1). Anal. calcd. for C25H15ClN4O: C, 71.01; H, 3.58; N, 13.25. Found: C, 71.05; H, 3.53; N, 13.20 %.

2.2.10. 4-[3-(2,4-dichlorophenyl)-1H-pyrazol-4-yl]-6-(naphthalen-1-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (4j)

Yield 48 %; M.p. >300 oC; IR (KBr, umax cm-1): 3145, 3058 (N-H), 2215 (C≡N), 1647 (C=O), 1592 (C=N); 1H NMR (DMSO-d6): δ 13.55 (bs,1H, pyrazole-NH), 12.66 (s, 1H, pyridone ring NH), 8.40 (s, 1H, pyrazole-5H), 7.44-8.06 (m, 11H, Ar-H), 5.87 (s, 1H, pyridone-5H). MS: m/z = 457 (M+).

Anal. calcd. for C25H14Cl2N4O: C, 65.66; H, 3.09; N, 12.25. Found: C, 65.61; H, 3.01; N, 12.19 %.

2.2.11. 4-[3-(4-methylphenyl)-1H-pyrazol-4-yl]-6-(naphthalen-1-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (4k)

Yield 56 %; M.p. >300 oC; IR (KBr, umax cm-1): 3215, 3069 (N-H), 2221 (C≡N), 1653 (C=O), 1612 (C=N); MS: m/z = 403 (M+1). Anal. calcd. for C26H18N4O: C, 77.59; H, 4.51; N, 13.92. Found: C, 77.53; H, 4.45; N, 13.88 %.

2.2.12. 6-(5-chlorothiophen-2-yl)-2-oxo-4-(3-phenyl-1H-pyrazol-4-yl)-1,2-dihydropyridine-3-carbonitrile (4l)

Yield 45 %; M.p. >300 oC; IR (KBr, umax cm-1): 3217, 3088 (N-H), 2210 (C≡N), 1646 (C=O), 1602 (C=N); 1H NMR (DMSO-d6): 1H NMR (DMSO-d6): δ 13.52 (bs,1H, pyrazole-NH), 12.72 (s, 1H, pyridone ring NH), 8.26 (s, 1H, pyrazole-5H), 7.23-7.98 (m, 7H, Ar-H), 6.24 (s, 1H, pyridone-5H). MS: m/z = 379 (M+1). Anal. calcd. for C19H11ClN4OS: C, 60.24; H, 2.93; N, 14.79. Found: C, 60.21; H, 2.97; N, 14.74 %.

2.2.13. 6-(5-chlorothiophen-2-yl)-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-oxo-1,2-dihydropyridine -3-carbonitrile (4m)

Yield 48 %; M.p. >300 oC; IR (KBr, umax cm-1): 3224, 3089 (N-H), 2213 (C≡N), 1646 (C=O), 1602 (C=N); 1H NMR (DMSO-d6): 1H NMR (DMSO-d6): δ 13.55 (bs,1H, pyrazole-NH), 12.72 (s, 1H, pyridone ring NH), 8.18 (s, 1H, pyrazole-5H), 7.18-7.87 (m, 6H, Ar-H), 6.47 (s, 1H, pyridone-5H). MS: m/z = 397 (M+1). Anal. calcd. for C19H10ClFN4OS: C, 57.51; H, 2.54; N, 14.12. Found: C, 57.47; H, 2.50; N, 14.08 %.

2.2.14. 4-[3-(4-chlorophenyl)-1H-pyrazol-4-yl]-6-(5-chlorothiophen-2-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (4n)

Yield 51 %; M.p. >300 oC; IR (KBr, umax cm-1): 3254, 3085 (N-H), 2212 (C≡N), 1630 (C=O), 1583 (C=N); 1H NMR (DMSO-d6): 1H NMR (DMSO-d6): δ 13.53 (bs,1H, pyrazole-NH), 12.72 (s, 1H, pyridone ring NH), 8.18 (s, 1H, pyrazole-5H), 7.09-7.75 (m, 6H, Ar-H), 6.24 (s, 1H, pyridone-5H). MS: m/z = 412 (M+). Anal. calcd. for C19H10Cl2N4OS: C, 55.22; H, 2.44; N, 13.56. Found: C, 55.17; H, 2.39; N, 13.50 %.

2.2.15. 6-(5-chlorothiophen-2-yl)-4-[3-(4-methylphenyl)-1H-pyrazol-4-yl]-2-oxo-1,2-dihydropyri - dine-3-carbonitrile (4o)

Yield 53 %; M.p. >300 oC; IR (KBr, umax cm-1): 3257, 3083 (N-H), 2213 (C≡N), 1627 (C=O), 1585 (C=N); 1H NMR (DMSO-d6): 1H NMR (DMSO-d6): δ 13.55 (bs,1H, pyrazole-NH), 12.66 (s, 1H, pyridone ring NH), 8.07 (s, 1H, pyrazole-5H), 7.21-7.66 (m, 6H, Ar-H), 6.72 (s, 1H, pyridone-5H) 2.32 (s, 3H, -CH3). MS: m/z = 393 (M+1). Anal. calcd. for C20H13ClN4OS: C,61.14; H, 3.34; N, 14.26. Found: C, 61.11; H, 3.29; N, 14.20 %.

3. BIOLOGICAL EVALUATION

3.1 Antimicrobial evaluation

All the synthesized compounds (BHD-101 to BHD-140) were tested for their antibacterial and antifungal activity (MIC) in vitro by broth dilution method [102, 103] with two Gram-positive bacteria Staphylococcus aureus MTCC-96, Streptococcus pyogenes MTCC 443, two Gram-negative bacteria Escherichia coli MTCC 442, Pseudomonas aeruginosa MTCC 441 and three fungal strains Candida albicans MTCC 227, Aspergillus Niger MTCC 282, Aspergillus clavatus MTCC 1323 taking ampicillin, chloramphenicol, ciprofloxacin, norfloxacin, nystatin, and greseofulvin as standard drugs. The standard strains were procured from the Microbial Type Culture Collection (MTCC) and Gene Bank, Institute of Microbial Technology, Chandigarh, India. The minimal inhibitory concentration (MIC) values for all the newly synthesized compounds, defined as the lowest concentration of the compound preventing the visible growth, were determined by using microdilution broth method according to NCCLS standards [18]. Serial dilutions of the test compounds and reference drugs were prepared in Muellere-Hinton agar. Drugs (10 mg) were dissolved in dimethylsulfoxide (DMSO, 1 mL). Further progressive dilutions with melted Muellere-Hinton agar were performed to obtain the required concentrations[19]. In primary screening 1000 µg mL-1, 500 µg mL-1 and 250 µg mL-1 concentrations of the synthesized drugs were taken. The active synthesized drugs found in this primary screening were further tested in a second set of dilution at 200 µg mL-1, 100 µg mL-1, 50 µg mL-1, 25 µg mL-1, 12.5 µg mL-1, and 6.25 µg mL-1 concentration against all microorganisms. The tubes were inoculated with 108 cfu mL-1 (colony forming unit/mL) and incubated at 37 ºC for 24 h. The MIC was the lowest concentration of the tested compound that yields no visible growth (turbidity) on the plate. To ensure that the solvent had no effect on the bacterial growth, a control was performed with the test medium supplemented with DMSO at the same dilutions as used in the experiments and it was observed that DMSO had no effect on the microorganisms in the concentrations studied.

3.2 Antibacterial activity

The antibacterial activity of newly synthesized compounds (**4a-o**) were determined by well plate method in Mueller-Hinton Agar. The compounds were tested against a panel of pathogenic microorganisms, including *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas*

aeruginosa. Microorganism strains were maintained on nutrient agar medium at 37°C. The cultures were inoculated in fresh 10 mL Nutrient Broth to yield an initial suspension of approximately 10–100 cfu/mL. All broths were then incubated statically at the aforementioned temperatures for microorganisms, for 18-24 h so that all cells were in the stationary phase. Susceptibility of the test organism to the compounds was determined by employing in the well plate technique.The bacterial suspensions were diluted tenfold in distilled water, and 0.1 mL from the appropriate dilution was spread plated on nutrient agar in order to give a population of approximately 106 cfu/plate. The wells were dug in each Petri plate by sterilized cork borer. The compounds were dissolved in DMSO and appropriate dilutions were made (1mg/mL and 0.5mg/mL). The same procedure was repeated for different micro-organisms. Each experiment was carried out in triplicate. After the inoculation of organism and compound, the Petri plates were incubated for 24 hrs at 37oC. After the incubation, the inhibition zone was measured and the values for Dimethylsulphoxide (DMSO) were subtracted to get the actual values. Streptomycin was used as standard drug.

3.3 Antifungal activity

The fungal strains used in this study were *Aspergillus flavus*, *Chrysosporium Keratinophilum* and *Candida albicans*. The required amounts of each fungal strain were removed from the stock and suspended in 5mL of distilled water with 2 drops of Tween 80. This suspension was uniformly spread on Petri plates containing Potato dextrose agar media using sterile swabs[20]. After applying the samples into the wells formed by using the same technique for tests on bacteria, the plates were incubated at 25 °C for 3 days. The plates were then examined for the presence of zones of inhibition and the results were recorded. Fluconazole was used as a standard drug [21].

4. LITERATURE SURVEY

Shridhar Malladi (2012) et al. A series of new 4,6-disubstituted-3-cyano-2-pyridone derivatives (4a-o) were synthesized. The structures of all target molecules (4a-o) have been confirmed by various spectral techniques and elemental analyses. The newly synthesized compounds were screened for antibacterial and antifungal activity and most of the compounds showed significant activity comparable with that of the standard drug. The results revealed that 4b, 4c, 4d, 4g, 4m, 4n and 4o showed good antibacterial activity towards all bacterial strains (Escherichia coli, Staphylococcus aureus and Pseudomonas aeruginosa) when compared to standard drug streptomycin. Amongst all the compounds, 4c showed moderate antifungal activity against Aspergillus flavus. The acute toxicity study has also been carried out for biologically active compounds and the experimental studies revealed that compounds were safe up to 2000 mg/kg and no deaths of animals were recorded.[22]

Taslimahemad T. Khatri, (2014) et al. Synthesis, structural characterization, and biological activity studies of novel pyrido[2,3-d]pyrimidines (10a−h, 11a−h) are described. Cyclization of cynoacetamides (4, 5) with malonitrile (7) and aldehyde (6a−h) via Hantzsch pyridine synthesis afforded cyanopyridones (8a−h, 9a−h), which on cyclization with formic acid under microwave conditions led to the final product. All the reactions are significantly faster and the isolated yields are remarkably higher in microwave conditions compared to the conventionally heated reactions. The compounds were tested in vitro for their antibacterial activity against Escherichia coli, Pseudomonas aeruginosa, Bacillus subtillus, Staphylococcus aureus, and Micrococcus luteus and antifungal activity against Trichphyton longifusus, Candida albicans, Microsporum canis, Fusarium solani. Compounds 10b, 10e, 11b and 11e exhibited good antibacterial and antifungal activities compared with standards.[23]

Hend M. El-Sehrawi (2016) et al. In this study twenty six novel derivatives of 6-oxo-pyridine-3-carboxamide were synthesized and evaluated as antibacterial and antifungal agents. Synthesis of the 2-amino-4-methyl-6-oxo-N,1-diphenyl-1,6-dihydropyridine-3-carboxamide 1 was carried out by reacting equimolar quantities of acetoacetanilide and cyanoacetanilide in ethanol using triethylamine as a catalyst. The results of the in vitro antimicrobial evaluation showed that, the 6-oxo-N,1-diphenyl-5-(p-tolyldiazenyl)-1,6-dihydropyridine-3-carboxamide, 5c displayed broad-spectrum antibacterial activity which was equipotent to both Ampicillin and Gentamicin against the tested bacteria. Moreover, compounds 3a, 5c and 9b were equipotent to the reference drug, Amphotericin B, against Aspergillus fumigatus (MIC = 1.95µg/ml). 2D QSAR studies were carried out in order to correlate the observed activity to the binding mode of these compounds, in addition to their molecular properties that might be controlling their activities.[24]

K. A. Parmar (2011) et al. Heterocyclic compounds have been indispensable in the recent far reaching developments in science and technology embracing a vast spectrum of advances of both theoretical and practical relevance. Endowed with unique properties, they are well recognized for their multifaceted pharmacological, medicinal and biochemical behaviors. Heterocyclic compounds offer many opportunities for synthetic organic chemists. Cyanopyridone and Isoxazole derivatives have been prepared from condensation of chalcones (I) with acetate and hydroxylamine hydrochloride respectively. The structural assignments of the products have been made on the basis of their elemental analyses, spectral analyses and other physico-chemical

investigations, antimicrobial activities of the synthesized compounds have been determined qualitatively against different pathogenic bacteria.[245

Talent Raymond Makhanya (2019) et al. Nine novel fused indolo [1,8] naphthyridine derivatives were synthesized using the Povarov reaction, in a one-pot system, and were fully characterized by spectroscopic techniques such as FT-IR, NMR, TOF-MS, and elemental analysis. Furthermore, their antibacterial activities against six bacterial strains were assessed. The results of the bioassay demonstrated that compounds 4a, 4c, and 4i showed good inhibitory effect with a MIC value ranging from 0.04687 to 0.09375 mM against Bacillus cereus and Staphylococcus aureus. The toxicity of 4a–i, evaluated through mutagenicity test against Salmonella typhimurium TA 98 and TA100 strains, revealed that there was no significant increase in the number of revertant colonies in comparison with the control, sodiumazide.[26]

Abouzid KAM (2017) et al. Targeting Pim-1 kinase recently proved to be profitable for conquering cancer proliferation. In the current study, we report the design, synthesis and biological evaluation of two novel series of 2-amino cyanopyridine series (5a-g) and 2-oxocyanopyridine series (6a-g) targeting Pim-1 kinase. All of the newly synthesized compounds were evaluated for their in vitro anticancer activity against a panel of three cell lines, namely, the liver cancer cell line (HepG2), the colon cancer cell line (HCT-116) and the breast cancer cell line (MCF-7). Most of the compounds showed good to moderate anti-proliferative activity against HepG2 and HCT-116 cell lines while only few compounds showed significant cytotoxic activity against MCF-7 cell line. Further, the Pim-1 kinase inhibitory activity for the two series was evaluated where most of the tested compounds showed marked Pim-1 kinase inhibitory activity (26%-89%). Moreover, determination of the IC_{50} values unraveled very potent molecules in the submicromolar range where compound 6c possessed an IC_{50} value of 0.94 µM. Moreover, apoptosis studies were conducted on the most potent compound 6c to evaluate the proapoptotic potential of our compounds. Interestingly, it induced the level of active caspase 3 and boosted the Bax/Bcl2 ratio 22704 folds in comparison to the control. Finally, a molecular docking study was conducted to reveal the probable interaction with the Pim-1 kinase active site.[27]

5. CONCLUSIONS

The synthesis of some new pyridine and bipyridine synthesized a series of 4,6-disubstituted-3- cyano-2-pyridone derivatives **(4a-o)** via one-pot multicomponent reaction using 3-substituted- 1*H*-pyrazole-4-carbaldehydes **(1a-e)**, various acetyl compounds **(2a-c),** ethyl cyanoacetate **(3)** and ammonium acetate. All the compounds were screened for its antimicrobial activity. Moreover, some of the biological activities showed that compound exhibits significant tumor and antioxidant activities.

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Corresponding Author

Mrs. Azra Begam Afridi*

Assistant Professor, Department of Chemistry, K. K. P. G College, Etawah, Uttar Pradesh