© 2017 IJSRST | Volume 3 | Issue 8 | Print ISSN: 2395-6011 | Online ISSN: 2395-602X
Themed Section: Science and Technology

A Simple and Efficient Synthesis of Cynopyridines

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ABSTRACT

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].

Keywords : Cynopyridines, Pyridine Skeleton , NNRTI, GABAA, NMR, TLC

I. INTRODUCTION

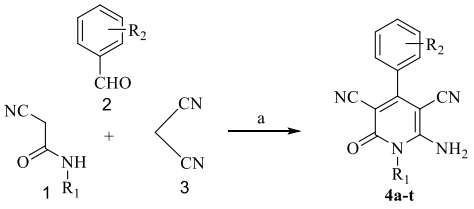
The pyridine skeleton is of great importance to chemists as well as to biologists as it is found in a large variety of naturally occurring compounds and also in clinically useful molecules having diverse biological activities. In association with those, Pyridone and their derivatives play an essential role in several biological processes and have considerable chemical and pharmacological importance [4-6]. 2-Pyridones represent a unique class of pharmacophore, which are observed in various therapeutic agents [7] and antibiotics [8]. 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) [9], as antibacterial [10], antifungal [11], sedative [12] and cardiotonic agents [13]. Moreover, such derivatives have recently become important due to their structural similarity to nucleosides [14]. Also, 2-pyridones were used as ligands for the late 3d-metals [15]. They are also versatile precursors for the construction of complex natural products [16], pyridines [17] and larger pyridone systems such as those found in the nitroguanidine insecticide Imidacloprid [18] and subtype selective GABAA receptor agonists [19]. Consequently, methodologies for the preparation of pyridones have attracted much attention from both industry and academia. 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.

II. EXPERIMENTAL

Materials and Methods

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was routinely checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine. IR spectra were recorded Shimadzu FT-IR-8400 instrument using KBr pellet method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using Direct Injection Probe technique. ^{1}H NMR was determined in DMSO-d_6 solution on a Bruker Ac 400 MHz spectrometer. Elemental analysis of the all the synthesized compounds was carried out on Elemental Vario EL III Carlo Erba 1108 model and the results are in agreements with the structures assigned.

Reaction Scheme



Reagents and conditions: (a) Piperidine, MeOH, reflux, 10-12 h.

Table 1. Physical data of synthesized compounds

Code	R_1	R_2	M.F.	M.W.	M.P. ºC	Yield %	R_{f1}	R_{f2}
4a	pyridin-2-yl	H	$C_{18}H_{11}N_5O$	313	240-242	71	0.52	0.70
4b	pyridin-2-yl	4-F	$C_{18}H_{10}FN_5O$	331	189-191	66	0.50	0.69
4c	pyridin-2-yl	4-Cl	$C_{18}H_{10}ClN_5O$	347	245-247	75	0.48	0.65
4d	pyridin-2-yl	4-NO_2	$C_{18}H_{10}N_6O_3$	358	270-272	74	0.45	0.68
4e	pyridin-2-yl	4-CH_3	$C_{19}H_{13}N_5O$	327	261-263	78	0.53	0.72
4f	pyridin-2-yl	4-OCH_3	$C_{19}H_{13}N_5O_2$	343	204-206	72	0.44	0.64
4g	pyridin-2-yl	3,4-OCH_3	$C_{20}H_{15}N_5O_3$	373	244-246	65	0.55	0.73
4h	pyridin-2-yl	3-NO_2	$C_{18}H_{10}N_6O_3$	358	231-233	61	0.50	0.67
4i	pyridin-2-yl	3-Cl	$C_{18}H_{10}ClN_5O$	347	269-271	70	0.41	0.60
4j	pyridin-2-yl	2-Cl	$C_{18}H_{10}ClN_5O$	347	199-201	72	0.46	0.66
4k	3-Cl-4-F-C_6H_3	H	$C_{19}H_{10}ClFN_4O$	364	219-221	70	0.52	0.69
4l	3-Cl-4-F-C_6H_3	4-F	$C_{19}H_9ClF_2N_4O$	382	227-229	79	0.56	0.74
4m	3-Cl-4-F-C_6H_3	4-Cl	$C_{19}H_9Cl_2FN_4O$	399	190-192	75	0.50	0.66
4n	3-Cl-4-F-C_6H_3	4-NO_2	$C_{19}H_9ClFN_5O_3$	409	247-249	68	0.52	0.69
4o	3-Cl-4-F-C_6H_3	4-CH_3	$C_{20}H_{12}ClFN_4O$	378	239-241	76	0.61	0.77
4p	3-Cl-4-F-C_6H_3	4-OCH_3	$C_{20}H_{12}ClFN_4O_2$	394	215-217	77	0.54	0.68
4q	3-Cl-4-F-C_6H_3	3,4-OCH_3	$C_{21}H_{14}ClFN_4O_3$	424	233-235	69	0.50	0.70
4r	3-Cl-4-F-C_6H_3	3-NO_2	$C_{19}H_9ClFN_5O_3$	409	190-192	66	0.64	0.78
4s	3-Cl-4-F-C_6H_3	3-Cl	$C_{19}H_9Cl_2FN_4O$	399	262-264	70	0.48	0.64
4t	3-Cl-4-F-C_6H_3	2-Cl	$C_{19}H_9Cl_2FN_4O$	399	260-262	75	0.51	0.69

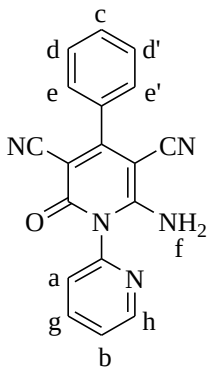
Synthesis of 2-cyano-N-(substituted)acetamides

Synthesis of 2-cyano-N-(substituted)acetamides was achieved using previously published methods [20].

General procedure for the synthesis of 6-amino-1,2-dihydro-4-(aryl)-2-oxo-1-(pyridin-2-yl)pyridine-3,5-dicarbonitriles (4a-t)

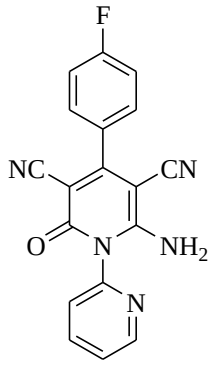
A mixture of 2-cyano-N-(pyridin-2-yl)acetamide (0.01 mol), appropriate aromatic aldehydes (0.01 mol), malononitrile (0.01 mol) and catalytical amount of piperidine in methanol (20 ml) was heated under reflux condition for 10-12 h. The reaction mixture was kept at room temperature for 2-4 h. The solid product obtained was isolated and recrystallized from ethanol.

6-amino-1,2-dihydro-2-oxo-4-phenyl-1-(pyridin-2-yl)pyridine-3,5-dicarbonitrile (4a)



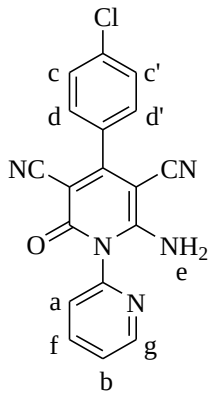
Yield: 71%; mp 240-242 ºC; IR (cm^{-1}): 3466 and 3331 (N-H stretching of primary amine), 3064 (C-H stretching of aromatic ring), 2220 and 2206 (C≡N stretching of nitrile group), 1656 (C=O stretching of pyridone ring), 1606 (N-H deformation of NH_2 group), 1629 (C=N stretching of pyridine ring), 1546 and 1518 (C=C stretching of aromatic ring), 999 (C-H in plane bending for aromatic ring); 802 (C-H out of plane bending for 1,4-disubstituted aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 7.47-7.49 (d, 1H, H_a, J = 7.8 Hz), 7.55 (s, 6H, $H_{b-ee'}$), 7.58 (s, 2H, H_f), 8.02-8.06 (t, 1H, H_g, J = 7.7 Hz), 8.71-8.72 (d, 1H, H_h); MS: m/z 313; Anal. Calcd. for $C_{18}H_{11}N_5O$: C, 69.00; H, 3.54; N, 22.35. Found: C, 68.80; H, 3.50; N, 22.27%.

6-amino-4-(4-fluorophenyl)-1,2-dihydro-2-oxo-1-(pyridin-2-yl)pyridine-3,5-dicarbonitrile (4b)



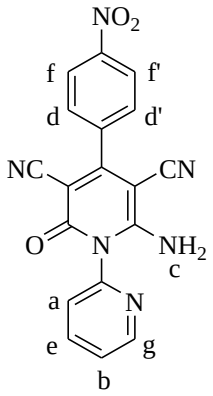
Yield: 66%; mp 189-191 ºC; MS: m/z 331; Anal. Calcd. for $C_{18}H_{10}FN_5O$: C, 65.26; H, 3.04; N, 21.14. Found: C, 65.11; H, 3.00; N, 21.09%.

6-amino-4-(4-chlorophenyl)-1,2-dihydro-2-oxo-1-(pyridin-2-yl)pyridine-3,5-dicarbonitrile (4c)



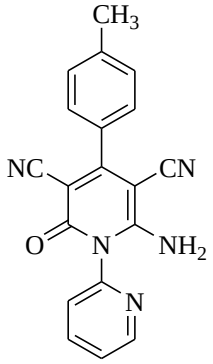
Yield: 75%; mp 245-247 ºC; IR (cm^{-1}): 3485 and 3321 (N-H stretching of primary amine), 3072 (C-H stretching of aromatic ring), 2216 (C≡N stretching of nitrile group), 1672 (C=O stretching of pyridone ring), 1643 (C=N stretching of pyridine ring), 1595 (N-H deformation of NH_2 group), 1531 and 1498 (C=C stretching of aromatic ring), 1352 (C-N stretching for carbon bonded to amino group), 1014 (C-H in plane bending for aromatic ring), 839 (C-H out of plane bending for 1,4-disubstituted aromatic ring), 771 (C-Cl stretching); ^{1}H NMR (DMSO-d_6) δ ppm: 7.39-7.42 (d, 1H, H_a, J = 7.1 Hz), 7.46-7.59 (m, 5H, $H_{b-dd'}$), 7.65 (s, 2H, H_e), 8.03-8.07 (t, 1H, H_f, J = 7.7 Hz), 8.73-8.74 (d, 1H, H_g); MS: m/z 347; Anal. Calcd. for $C_{18}H_{10}ClN_5O$: C, 62.17; H, 2.90; N, 20.14. Found: C, 61.98; H, 2.84; N, 20.11%.

6-amino-1,2-dihydro-4-(4-nitrophenyl)-2-oxo-1-(pyridin-2-yl)pyridine-3,5-dicarbonitrile (4d)



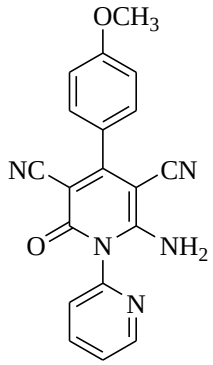
Yield: 74%; mp 270-272 ºC; IR (cm^{-1}): 3296 and 3269 (N-H stretching of primary amine), 3082 (C-H stretching of aromatic ring), 2218 (C≡N stretching of nitrile group), 1664 (C=O stretching of pyridone ring), 1647 (C=N stretching of pyridine ring), 1602 (N-H deformation of NH_2 group), 1552 (NO_2 asymmetrical stretching), 1533 and 1516 (C=C stretching of aromatic ring), 1346 (C-N stretching for carbon bonded to amino group), 1290 (NO_2 symmetrical stretching), 852 (C-H out of plane bending for 1,4-disubstituted aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 7.47-7.49 (d, 1H, H_a, J = 8.0 Hz), 7.56-7.59 (t, 3H, H_{bc}), 7.77-7.79 (d, 2H, $H_{dd'}$, J = 8.6 Hz), 8.03-8.07 (t, 1H, H_e, J = 7.3 Hz), 8.39-8.41 (d, 2H, $H_{ff'}$, J = 8.6 Hz); 8.73-8.74 (d, 1H, H_g); MS: m/z 358; Anal. Calcd. for $C_{18}H_{10}N_6O_3$: C, 60.34; H, 2.81; N, 23.45. Found: C, 60.19; H, 2.75; N, 23.42%.

6-amino-1,2-dihydro-2-oxo-1-(pyridin-2-yl)-4-p-tolylpyridine-3,5-dicarbonitrile (4e)



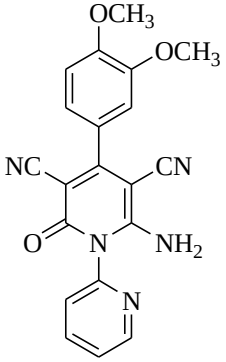
Yield: 78%; mp 261-263 ºC; MS: m/z 327; Anal. Calcd. for $C_{19}H_{13}N_5O$: C, 69.71; H, 4.00; N, 21.39. Found: C, 69.57; H, 3.99; N, 21.31%.

6-amino-1,2-dihydro-4-(4-methoxyphenyl)-2-oxo-1-(pyridin-2-yl)pyridine-3,5-dicarbonitrile (4f)



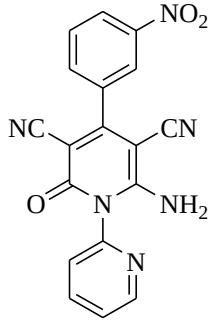
Yield: 72%; mp 204-206 ºC; MS: m/z 343; Anal. Calcd. for $C_{19}H_{13}N_5O_2$: C, 66.47; H, 3.82; N, 20.40. Found: C, 66.31; H, 3.80; N, 20.32%.

6-amino-1,2-dihydro-4-(3,4-dimethoxyphenyl)-2-oxo-1-(pyridin-2-yl)pyridine-3,5-dicarbonitrile (4g)



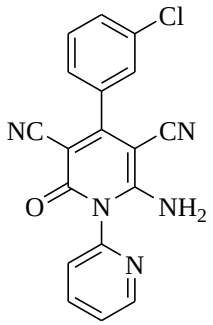
Yield: 65%; mp 244-246 ºC; MS: m/z 373; Anal. Calcd. for $C_{20}H_{15}N_5O_3$: C, 64.34; H, 4.05; N, 18.76. Found: C, 64.20; H, 4.01; N, 18.69%.

6-amino-1,2-dihydro-4-(3-nitrophenyl)-2-oxo-1-(pyridin-2-yl)pyridine-3,5-dicarbonitrile (4h)



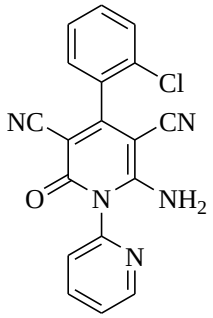
Yield: 61%; mp 231-233 ºC; MS: m/z 358; Anal. Calcd. for $C_{18}H_{10}N_6O_3$: C, 60.34; H, 2.81; N, 23.45. Found: C, 60.16; H, 2.77; N, 23.40%.

6-amino-4-(3-chlorophenyl)-1,2-dihydro-2-oxo-1-(pyridin-2-yl)pyridine-3,5-dicarbonitrile (4i)



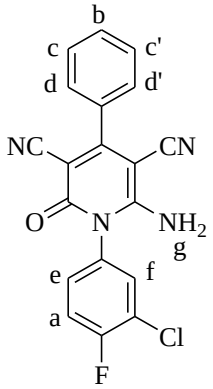
Yield: 70%; mp 269-271 ºC; MS: m/z 347; Anal. Calcd. for $C_{18}H_{10}ClN_5O$: C, 62.17; H, 2.90; N, 20.14. Found: C, 62.01; H, 2.86; N, 20.08%.

6-amino-4-(2-chlorophenyl)-1,2-dihydro-2-oxo-1-(pyridin-2-yl)pyridine-3,5-dicarbonitrile (4j)



Yield: 72%; mp 199-201 ºC; MS: m/z 347; Anal. Calcd. for $C_{18}H_{10}ClN_5O$: C, 62.17; H, 2.90; N, 20.14. Found: C, 62.00; H, 2.87; N, 20.10%.

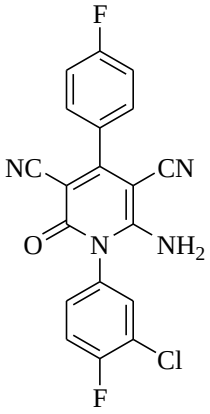
6-amino-1-(3-chloro-4-fluorophenyl)-1,2-dihydro-2-oxo-4-phenylpyridine-3,5-dicarbonitrile (4k)



Yield: 70%; mp 219-221 ºC; IR (cm^{-1}): 3444 and 3304 (N-H stretching of primary amine), 3109 (C-H stretching of aromatic ring), 2224 (C≡N stretching of nitrile group), 1660 (C=O stretching of pyridone ring), 1629 (N-H deformation of NH_2 group), 1527 and 1494 (C=C stretching of aromatic ring), 1300 (C-N stretching for carbon bonded to amino group), 1078 (C-F stretching), 1058 (C-H in plane bending for aromatic ring), 833 (C-H out of plane bending for 1,4-disubstituted aromatic

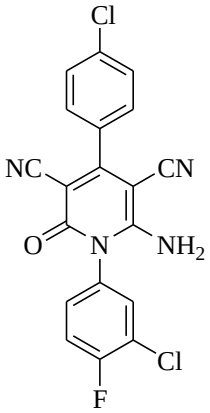
ring), 773 (C-Cl stretching); ^{1}H NMR (DMSO-d_6) δ ppm: 7.27-7.29 (d, 1H, H_a), 7.41-7.45 (t, 1H, H_b), 7.48-7.56 (m, 6H, $H_{cc'-f}$), 7.77 (s, 1H, H_g); MS: m/z 364; Anal. Calcd. for $C_{19}H_{10}ClFN_4O$: C, 62.56; H, 2.76; N, 15.36. Found: C, 62.40; H, 2.73; N, 15.29%.

6-amino-1-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-1,2-dihydro-2-oxo- pyridine-3,5-dicarbonitrile (4l)



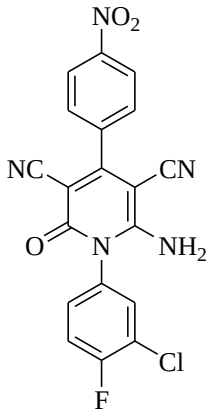
Yield: 79%; mp 227-229 ºC; MS: m/z 382; Anal. Calcd. for $C_{19}H_9ClF_2N_4O$: C, 59.62; H, 2.37; N, 14.64. Found: C, 59.49; H, 2.31; N, 14.54%.

6-amino-1-(3-chloro-4-fluorophenyl)-4-(4-chlorophenyl)-1,2-dihydro-2-oxo- pyridine-3,5-dicarbonitrile (4m)



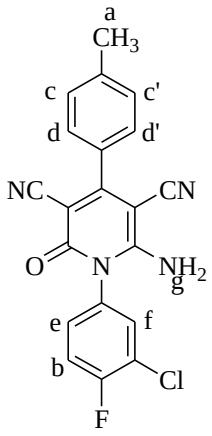
Yield: 75%; mp 190-192 ºC; MS: m/z 399; Anal. Calcd. for $C_{19}H_9Cl_2FN_4O$: C, 57.16; H, 2.27; N, 14.03. Found: C, 57.01; H, 2.21; N, 13.97%.

6-amino-1-(3-chloro-4-fluorophenyl)-1,2-dihydro-4-(4-nitrophenyl)-2-oxo- pyridine-3,5-dicarbonitrile (4n)



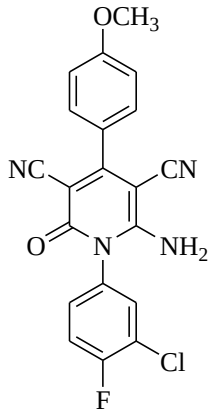
Yield: 68%; mp 247-249 ºC; MS: m/z 409; Anal. Calcd. for C19H9ClFN5O3: C, 55.69; H, 2.21; N, 17.09. Found: C, 55.53; H, 2.20; N, 16.98%.

6-amino-1-(3-chloro-4-fluorophenyl)-1,2-dihydro-2-oxo-4-p-tolylpyridine-3,5-dicarbonitrile (4o)



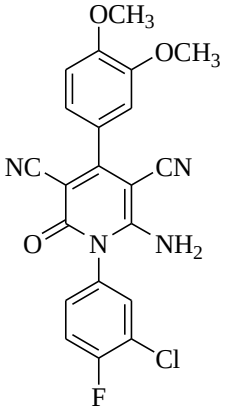
Yield: 76%; mp 239-241 ºC; IR (cm^{-1}): 3423 and 3315 (N-H stretching of primary amine), 3041 (C-H stretching of aromatic ring), 2949 (C-H symmetrical stretching of CH_3 group), 2864 (C-H asymmetrical stretching of CH_3 group), 2224 and 2206 (C≡N stretching of nitrile group), 1662 (C=O stretching of pyridone ring), 1645 (N-H deformation of NH_2 group), 1533 and 1465 (C=C stretching of aromatic ring), 1300 (C-N stretching for carbon bonded to amino group), 1093 (C-F stretching), 1064 (C-H in plane bending for aromatic ring), 817 (C-H out of plane bending for 1,4-disubstituted aromatic ring), 773 (C-Cl stretching); ^{1}H NMR (DMSO-d_6) δ ppm: 2.43 (s, 3H, H_a), 7.23-7.27 (m, 1H, H_b), 7.33-7.35 (d, 2H, $H_{cc'}$), 7.39-7.47 (m, 4H, $H_{dd'-f}$), 7.53 (s, 2H, H_g); MS: m/z 378; Anal. Calcd. for $C_{20}H_{12}ClFN_4O$: C, 63.42; H, 3.19; N, 14.79. Found: C, 63.27; H, 3.15; N, 14.70%.

6-amino-1-(3-chloro-4-fluorophenyl)-1,2-dihydro-4-(4-methoxyphenyl)-2-oxopyridine-3,5-dicarbonitrile (4p)



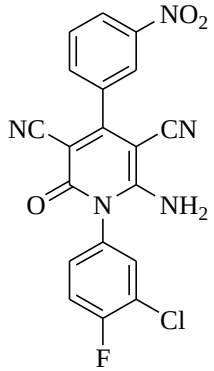
Yield: 77%; mp 215-217 ºC; MS: m/z 394; Anal. Calcd. for $C_{20}H_{12}ClFN_4O_2$: C, 60.85; H, 3.06; N, 14.19. Found: C, 60.69; H, 3.02; N, 14.14%.

6-amino-1-(3-chloro-4-fluorophenyl)-1,2-dihydro-4-(3,4-dimethoxyphenyl)-2-oxopyridine-3,5-dicarbonitrile (4q)



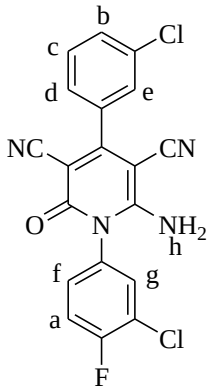
Yield: 69%; mp 233-235 ºC; MS: m/z 424; Anal. Calcd. for $C_{21}H_{14}ClFN_4O_3$: C, 59.37; H, 3.32; N, 13.19. Found: C, 59.21; H, 3.27; N, 13.10%.

6-amino-1-(3-chloro-4-fluorophenyl)-1,2-dihydro-4-(3-nitrophenyl)-2-oxo-pyridine-3,5-dicarbonitrile (4r)



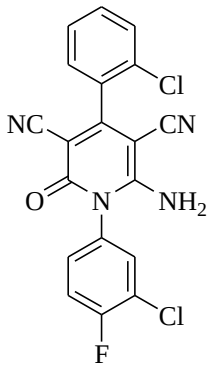
Yield: 66%; mp 190-192 ºC; MS: m/z 409; Anal. Calcd. for $C_{19}H_9ClFN_5O_3$: C, 55.69; H, 2.21; N, 17.09. Found: C, 55.50; H, 2.17; N, 17.03%.

6-amino-1-(3-chloro-4-fluorophenyl)-4-(3-chlorophenyl)-1,2-dihydro-2-oxo-pyridine-3,5-dicarbonitrile (4s)



Yield: 70%; mp 262-264 ºC; IR (cm^{-1}): 3419 and 3331 (N-H stretching of primary amine), 3068 (C-H stretching of aromatic ring), 2218 (C≡N stretching of nitrile group), 1691 (C=O stretching of pyridone ring), 1631 (N-H deformation of NH_2 group), 1531 and 1465 (C=C stretching of aromatic ring), 1300 (C-N stretching for carbon bonded to amino group), 1074 (C-F stretching), 802 (C-H out of plane bending for 1,3-disubstituted aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 7.26-7.30 (m, 1H, H_a), 7.42-7.55 (m, 6H, H_{b-g}), 7.80 (s, 2H, H_h); MS: m/z 399; Anal. Calcd. for $C_{19}H_9Cl_2FN_4O$: C, 57.16; H, 2.27; N, 14.03. Found: C, 57.01; H, 2.21; N, 13.97%.

6-amino-1-(3-chloro-4-fluorophenyl)-4-(2-chlorophenyl)-1,2-dihydro-2-oxo-pyridine-3,5-dicarbonitrile (4t)



Yield: 75%; mp 260-262 ºC; MS: m/z 399; Anal. Calcd. for $C_{19}H_9Cl_2FN_4O$: C, 57.16; H, 2.27; N, 14.03. Found: C, 56.98; H, 2.20; N, 13.99%.

III. RESULTS AND DISCUSSION

The chemistry of pyridine and its derivatives has been studied for over a century due to their diverse biological activities. 3-cyano-2-pyridone derivatives draw a special

attention for their wide spectrum biological activities along with their importance and utility as intermediates in preparing variety of heterocyclic compounds.

Keeping in mind, various biomedical applications and with a view to further assess the pharmacological profile of this class of compounds, four novel series of 3-cyano-2-pyridones (4a-t) have been synthesized.

The synthesis of 3-cyano-2-pyridones was achieved by the reaction of an appropriate aromatic aldehydes, 2-cyano-N-(substituted)acetamides and malononitrile by using methanol as a solvent and piperidine as a catalyst. 2-cyano-N-(substituted) acetamides were prepared by the reaction of substituted anilines with ethyl cyanoacetate. The products were characterized by FT-IR, mass, ^{1}H NMR spectroscopy and elemental analyses.

IV. CONCLUSION

In this paper, synthesis of forty novel 3-cyano-2-pyridone derivatives are reported, which draw a special attention for their wide spectrum biological activities along with their importance and utility as intermediates in preparing variety of heterocyclic compounds. The synthesis was achieved by the reaction of an aromatic aldehydes, 2-cyano-N-(substituted)acetamides and malononitrile by using methanol as a solvent and piperidine as a catalyst.

V. REFERENCES

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