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One Pot Synthesis of Bioactive Novel Cyanopyridones

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ABSTRACT. Cyanopyridone was prepared by the condensation of cyanoacetamide, substituted arylaldehydes and malononitrile in presence of pipyridine. The structure of the synthesized compound **CP 1–20** was assigned on the basis of elemental analysis, IR, ^{1}H-NMR and mass spectroscopy. These compounds were also screened for antimicrobial activity. The Minimum Inhibitory Concentration (MIC) of all the synthesized compounds was compared with standard drugs.

Key words: Cyanopyrimidones, Cyanoacetamide, Antimicrobial activity, Malononitrile, Pipyridine

INTRODUCTION

Pyridone and their derivatives play an essential role in several biological processes and have considerable chemical and pharmacological importance.[1–3] The 2-pyridones represent a unique class of pharmacophore, which are observed in various therapeutic agents[4] and antibiotics.[5] The 3-cyanopyridin-2-one nucleus is the structural basis of the alkaloid ricinine (**I**), the first known alkaloid containing a cyano-group. Cheney et al. reported 4,6-diaryl-2-oxo-1,2-dihydropyridine-3-carbonitriles (**II**), as inhibitors of the oncogenic serine/threonine kinas PIM-1, which plays a role in cancer cell survival, differentiation and proliferation.[6] Wendt et al. showed that several compounds with the same general formula as above (**II**) but with higher lipophilic properties (**III**) can inhibit surviving which is a member of the inhibitor of apoptosis family (IAP).[7]

The thienopyridone agonist (**IV**) showed modest AMPK (adenosine monophosphate-activated protein kinase) activity[8] (*Fig*. 1). 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] andcardiotonic agent.[13] Moreover, such derivatives have recently become important due to their structural similarity to nucleosides.[14]

They are also versatile precursors for the construction of complex natural products[15] pyridines[16] and larger pyridone systems such as those found in the nitro guanidine insecticide Imidacloprid[17] and subtype selective GABA receptor agonists. Consequently, methodologies for the preparation of pyridones have attracted much attention from both industrial and academic areas.

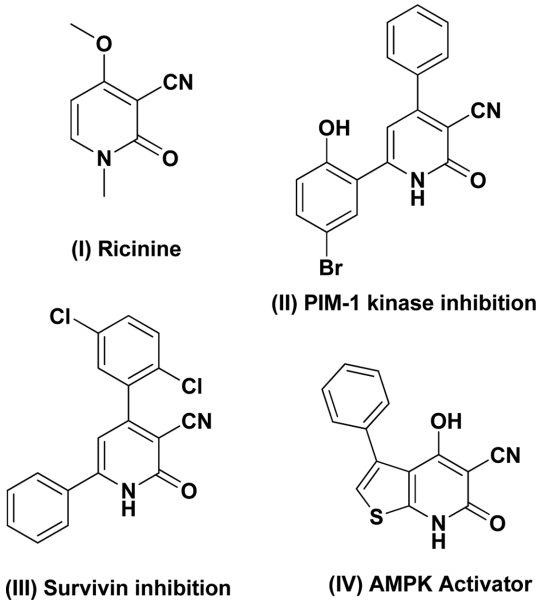
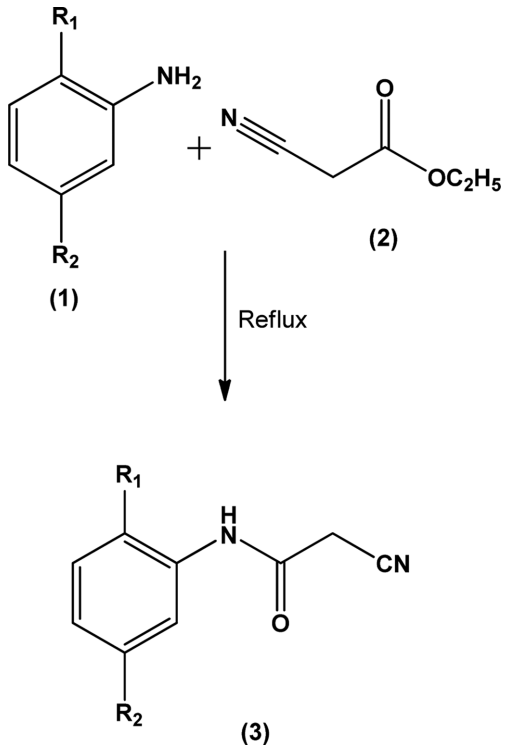


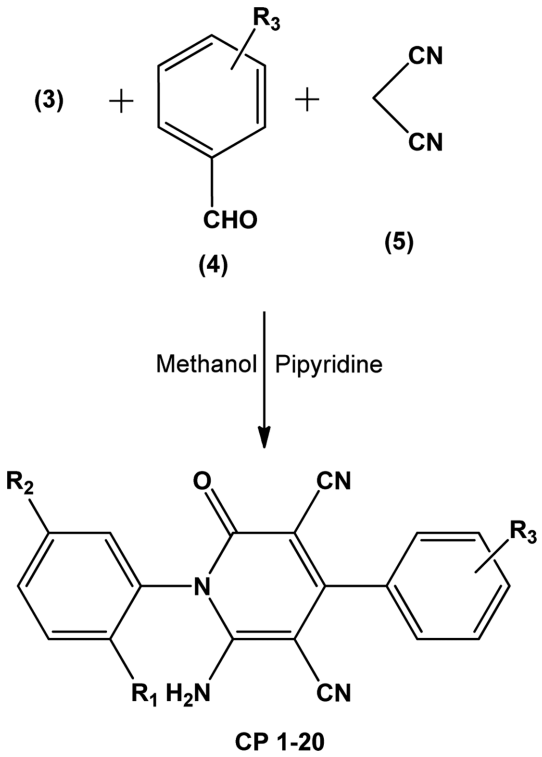
***Figure* 1.** Some reported potent cynopyridones.

EXPERIMENTAL

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



Scheme **1.** Synthesis of 2-cyano-N-(substituted) acetamides.



Scheme **2.** One spot synthesis of **CP 1–20**.

technique. ^{1}H-NMR was determined using DMSO-d_6 as asolvent 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.

Preparations of Cyanoacetamide Derivatives

The disubstituted aniline (10 mmol) and ethyl 2-cyanoacetate (10 mmol) were refluxed on sand bath for 3–4 hours to yield 2-cyano-N-(substituted) acetamides[18] (**3**) in good yields (*Scheme* 1).

General Procedure for Synthesis of Cyanopyridones (CP 1–20)

A mixture of substituted 10 mmol of cyanoacetamide (**3**), 10 mmol substituted aldehyde (**4**) and 10 mmol of malononitrile (**5**) were dissolve in 30 ml of methanol, catalytic amount of pipyridine was added. The reaction mixture was heated under reflux on water bath for 20–22 h (under TLC analysis). After completion of the reaction, filtered product was washed with methanol and recrystalized from ethanol (*Scheme* 2).

6-Amino-1-(2,5-dichlorophenyl)-2-oxo-4-phenyl-1,2-dihydro pyridine-3,5-dicarbonitrile (CP-1):

MP: 272–274 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 7.01–7.11 (t, 1H, Ar–H), 7.10–7.12 (t, 2H, Ar–H, J = 11.6 Hz), 7.52–7.55 (t, 2H, Ar–H, J = 11.6 Hz), 7.68–7.69 (d, 1H, Ar–diCl), 7.75–7.78 (d, 1H, Ar–diCl), 7.85 (s, 1H, Ar–diCl), 8.20 (s, 2H, NH_2); IR (KBr, υ/cm^{-1}): 3665 and 3522 (NH_2), 3194 (Ar–H), 2218 (C≡N), 1639 (C=O), 774 (C–Cl); MS m/z (%): 380 (M^+), 364 (100), 329 (6), 304 (14), 288 (31), 210 (16), 187 (23), 152 (8), 77 (32). Elemental Analysis for $C_{19}H_{10}Cl_2N_4O$: Calculated: C, 59.86; H, 2.64; N, 14.70. Found: C, 59.40; H, 2.30; N, 14.35%.

6-Amino-1-(2,5-dichlorophenyl)-4-(4-methoxyphenyl)-2-oxo-1,2-dihydro pyridine-3,5-dicarbonitrile (CP-2):

MP: 280–284 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 3.85 (s, 3H, OCH_3), 7.12–7.15 (d, 2H, 4-OCH_3–Ar–H, J = 11.6 Hz), 7.52–7.55 (d, 2H, 4-OCH_3–Ar–H, J = 11.6 Hz), 7.68–7.69 (d, 1H, diCl–Ar–H), 7.75–7.78 (d, 1H, diCl–Ar–H), 7.85 (s, 1H, diCl–Ar–H), 8.28 (s, 2H, NH_2); IR (KBr, υ/cm^{-1}): 3665 and 3522 (NH_2), 3194 (Ar–H), 2218 (C≡N), 1639 (C=O), 1173 (C–O–C), 774 (C–Cl); MS m/z (%): 410 (M^+), 394 (16), 375 (100), 360 (4), 332 (6), 196 (4), 187 (16), 152 (8), 109 (7), 75 (4). Elemental Analysis for $C_{20}H_{12}Cl_2N_4O_2$: Calculated: C, 58.41; H, 2.94; N, 13.62. Found: C, 58.21; H, 2.45; N, 13.33%.

6-Amino-1-(2,5-dichlorophenyl)-4-(2-methoxyphenyl)-2-oxo-1,2-dihydro pyridine-3,5-dicarbonitrile (CP-3):

MP: 280–284 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ

ppm: 3.87 (s, 3H, OCH_3), 7.10–7.13 (d, 2H, 4-OCH_3–Ar–H, J = 11.6 Hz), 7.54–7.57 (d, 2H, 4-OCH_3–Ar–H, J = 11.6 Hz), 7.22–7.28 (t, 2H, 4-OCH_3–Ar–H,), 7.65–7.67 (d, 1H, diCl–Ar–H), 7.71–7.74 (d, 1H, diCl–Ar–H), 7.84 (s, 1H, diCl–Ar–H), 8.28 (s, 2H, NH_2); IR (KBr, υ/cm^{-1}): 3665 and 3522 (NH_2), 3194 (Ar–C–H), 2218 (C≡N), 1639 (C=O), 1173 (C–O–C), 774 (C–Cl); MS m/z (%): 410 (M^+), 394 (45), 375 (100), 360 (6), 332 (9), 196 (8), 187 (21), 152 (6), 109 (11), 75 (8). Elemental Analysis for $C_{20}H_{12}Cl_2N_4O_2$: Calculated: C, 58.41; H, 2.94; N, 13.62. Found: C, 58.26; H, 2.54; N, 13.46%.

6-Amino-1-(2,5-dichlorophenyl)-4-(4-nitrophenyl)-2-oxo-1,2-dihydro pyridine-3,5-dicarbonitrile (CP-4):

MP: 245–250 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 8.12–8.15 (d, 2H, 4-NO_2–Ar–H, J = 11.6 Hz), 7.52–7.55 (d, 2H, 4-NO_2–Ar–H, J = 11.6 Hz), 7.68–7.69 (d, 1H, diCl–Ar–H), 7.75–7.78 (d, 1H, diCl–Ar–H), 7.85 (s, 1H, diCl–Ar–H), 8.38 (s, 2H, NH_2); IR (KBr, υ/cm^{-1}): 3665 and 3522 (NH_2), 3194 (Ar–C–H), 2218 (C≡N), 1639 (C=O), 1355–1315 (NO_2), 774 (C–Cl); MS m/z (%): 425 (M^+), 304 (25), 288 (100), 237 (15), 210 (12), 187 (5), 152 (7), 126 (13), Elemental Analysis for $C_{19}H_9Cl_2N_5O_3$: Calculated: C, 53.54; H, 2.13; N, 16.43. Found: C, 53.22; H, 2.04; N, 16.18%.

6-Amino-1-(2,5-dichlorophenyl)-4-(2-nitrophenyl)-2-oxo-1,2-dihydro pyridine-3,5-dicarbonitrile (CP-5):

MP: 234–236 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 8.10–8.13 (d, 2H, 2-NO_2–Ar–H, J = 11.6 Hz), 7.22–7.25 (d, 2H, 2-NO_2–Ar–H, J = 11.6 Hz), 7.54–7.57 (t, 2H, 2-NO_2–Ar–H), 7.65–7.67 (d, 1H, diCl–Ar–H), 7.71–7.74 (d, 1H, diCl–Ar–H), 7.84 (s, 1H, diCl–Ar–H), 8.28 (s, 2H, NH_2); IR (KBr, υ/cm^{-1}): 3665 and 3522 (NH_2), 3194 (Ar–H), 2218 (C≡N), 1639 (C=O), 1355–1315 (NO_2), 774 (C–Cl); MS m/z (%): 425(M^+), 304 (25), 288 (100), 237 (15), 210 (12), 187 (5), 152 (7), 126 (13). Elemental Analysis for $C_{19}H_9Cl_2N_5O_3$: Calculated: C, 53.54; H, 2.13; N, 16.43. Found: C, 53.20; H, 2.08; N, 16.26%.

6-Amino-1-(2,5-dichlorophenyl)-2-oxo-4-(p-tolyl)-1,2-dihydro pyridine-3,5-dicarbonitrile (CP-6):

MP: 284–286 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 2.05 (s, 3H, CH_3), 7.10–7.13 (d, 2H, CH_3–Ar–H, J = 11.6 Hz), 7.42–7.45 (d, 2H, OCH_3–Ar–H, J = 11.6 Hz), 7.68–7.69 (d, 1H, diCl–Ar–H), 7.75–7.78 (d, 1H, diCl–Ar–H), 7.85 (s, 1H, diCl–Ar–H), 8.28 (s, 2H, NH_2); IR (KBr, υ/cm^{-1}): 3665 and 3522 (NH_2), 2870 (CH_3), 3194 (Ar–C–H), 2218 (C≡N), 1639 (C=O), 774 (C–Cl); MS m/z (%): 394 (M^+), 380 (10), 359 (95), 282 (5), 254 (8), 233 (9), 202 (12), 142 (18), 91 (13), 77 (27). Elemental Analysis for$C_{20}H_{12}Cl_2N_4O$: Calculated: C, 60.78; H, 3.06; N, 14.18. Found: C, 60.68; H, 3.00; N, 14.10%.

6-Amino-1-(2,5-dichlorophenyl)-4-(4-bromophenyl)-2-oxo-1,2-dihydro pyridine-3,5-dicarbonitrile (CP-7):

MP: 298–300 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 7.53–7.56 (d, 2H, 4-Br–Ar–H, J = 11.6 Hz), 7.79–7.82 (d, 2H, 4-Br–Ar–H, J = 11.6 Hz), 7.68–7.69 (d, 1H, diCl–Ar–H), 7.75–7.78 (d, 1H, diCl–Ar–H), 7.85 (s, 1H, diCl–Ar–H), 8.28 (s, 2H, NH_2); IR (KBr, υ/cm^{-1}): 3665 and 3522 (NH_2), 3194 (Ar–H), 2218 (C≡N), 1639 (C=O), 774 (C–Cl), 642 (C–Br); MS m/z (%): 460 (M^+), 425 (95), 401 (23), 323 (18), 293 (10), 205 (12), 218 (8), 164 (9), 77 (65). Elemental Analysis for $C_{19}H_9BrCl_2N_4O$: Calculated: C, 49.60; H, 1.97; N, 12.18. Found: C, 49.37; H, 1.85; N, 12.07%.

6-Amino-1-(2,5-dichlorophenyl)-4-(3-bromophenyl)-2-oxo-1,2-dihydro pyridine-3,5-dicarbonitrile (CP-8):

MP: 305–308 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 7.38–7.41 (m, 3H, 3-Cl–Ar–H), 7.49 (s, 1H, 3-Cl–Ar–H), 7.68–7.69 (d, 1H, diCl–Ar–H), 7.75–7.78 (d, 1H, diCl–Ar–H), 7.85 (s, 1H, diCl–Ar–H), 8.28 (s, 2H, NH_2); IR (KBr, υ/cm^{-1}): 3665 and 3522 (NH_2), 3194 (Ar–C–H), 2218 (C≡N), 1639 (C=O), 774 (C–Cl), 642 (C–Br); MS m/z (%): 460 (M^+), 425 (95), 401 (23), 323 (18), 293 (10), 205 (12), 218 (8), 164 (9), 77 (65). Elemental Analysis for $C_{19}H_9BrCl_2N_4O$: Calculated: C, 49.60; H, 1.97; N, 12.18. Found: C, 49.27; H, 1.90; N, 12.11%.

6-Amino-1-(2,5-dichlorophenyl)-4-(4-chlorophenyl)-2-oxo-1,2-dihydro pyridine-3,5-dicarbonitrile (CP-9):

MP: 278–282 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 7.50–7.53 (d, 2H, 4-Cl–Ar–H, J = 11.6 Hz), 7.75–7.78 (d, 2H, 4-Cl–Ar–H, J = 11.6 Hz), 7.68–7.69 (d, 1H, diCl–Ar–H), 7.75–7.78 (d, 1H, diCl–Ar–H), 7.85 (s, 1H, diCl–Ar–H), 8.28 (s, 2H, NH_2); IR (KBr, υ/cm^{-1}): 3665 and 3522 (NH_2), 3194 (Ar–H), 2218 (C≡N), 1639 (C=O), 774 (C–Cl); MS m/z (%): 414 (M^+), 379 (90), 304 (21), 288 (25), 254 (5), 210 (15), 142 (8), 77 (29). Elemental Analysis for $C_{19}H_9Cl_3N_4O$: Calculated: C, 54.90; H, 2.18 N, 13.48. Found: C, 54.70; H, 2.10 N, 13.25%.

6-Amino-1-(2,5-dichlorophenyl)-4-(3-chlorophenyl)-2-oxo-1,2-dihydro pyridine-3,5-dicarbonitrile (CP-10):

MP: 285–288 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 7.28–7.31 (m, 3H, 3-Cl–Ar–H), 7.45 (s, 1H, 3-Cl–Ar–H), 7.68–7.69 (d, 1H, diCl–Ar–H), 7.75–7.78 (d, 1H, diCl–Ar–H), 7.85 (s, 1H, diCl–Ar–H), 8.28 (s, 2H, NH_2); IR (KBr, υ/cm^{-1}): 3665 and 3522 (NH_2), 3194 (Ar–H), 2218 (C≡N), 1639 (C=O), 774 (C–Cl); MS m/z (%): 414 (M^+), 379 (90), 304 (21), 288 (25), 254 (5), 210 (15), 142 (8), 77 (29). Elemental Analysis for $C_{19}H_9Cl_3N_4O$: Calculated: C, 54.90; H, 2.18 N, 13.48. Found: C, 54.55; H, 2.08N, 13.14%.

6-Amino-1-(2,5-dimethylphenyl)-2-oxo-4-phenyl-1,2-dihydro pyridine-3,5-dicarbonitrile (CP-11):

MP: 283–285 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 2.02 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 7.55 (s, 5H, Ar–H), 7.25–7.35 (d, 2H, diCH_3–Ar–H), 7.12–7.15 (d, 2H, 4-OCH_3–Ar–H, J = 11.6 Hz), 7.52–7.55 (d, 2H, 4-OCH_3–Ar–H, J = 11.6 Hz), 7.10 (s, 1H, diCH_3–Ar–H), 7.90 (s, 2H, NH_2), IR (KBr, υ/cm^{-1}): 3641 and 3447 (N–H), 3206 (Ar–H), 2870 (CH_3), 2215 (C≡N), 1631 (C=O), 774 (C–Cl); MS m/z (%): 340 (M^+, 24), 325 (100), 309 (20), 164 (24), 107 (18), 103 (28), 91 (45), 77 (36). Elemental Analysis for $C_{21}H_{16}N_4O$: Calculated: C, 74.10; H, 4.74; N, 16.46. Found: C, 74.06; H, 4.64; N, 16.56%.

6-Amino-1-(2,5-dimethylphenyl)-4-(4-methoxyphenyl)-2-oxo-1,2-dihydro pyridine-3,5-dicarbonitrile (CP-12):

MP: 255–260 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 2.02 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 7.25–7.35 (d, 2H, diCH_3–Ar–H), 7.12–7.15 (d, 2H, 4-OCH_3–Ar–H, J = 11.6 Hz), 7.52–7.55 (d, 2H, 4-OCH_3–Ar–H, J = 11.6 Hz), 7.10 (s, 1H, diCH_3–Ar–H), 7.90 (s, 2H, NH_2); IR (KBr, υ/cm^{-1}): 3651 and 3457 (N–H), 3206 (Ar–H), 2870 (CH_3), 2215 (C≡N), 1631 (C=O), 1172 (C–O–C symmetrical stretching OCH_3 group); MS m/z (%): 370(M^+, 20), 355 (95), 324 (17), 205 (20), 164 (17), 107 (15), 103 (24), 91 (40), 77 (30). Elemental Analysis for $C_{22}H_{18}N_4O_2$: Calculated: C, 71.34; H, 4.90; N, 15.13.Found: C, 71.30; H, 4.87; N, 15.08%.

6-Amino-1-(2,5-dimethylphenyl)-4-(2-methoxyphenyl)-2-oxo-1,2-dihydro pyridine-3,5-dicarbonitrile (CP-13):

MP: 225–228 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 2.02 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 7.10–7.13 (d, 2H, 4-OCH_3–Ar–H, J = 11.6 Hz), 7.54–7.57 (d, 2H, 4-OCH_3–Ar–H, J = 11.6 Hz), 7.22–7.28 (t, 2H, 4-OCH_3–Ar–H), 7.25–7.35 (d, 2H, diCH_3–Ar–H), 7.10 (s, 1H, diCH_3–Ar–H), 7.90 (s, 2H, NH_2); IR (KBr, υ/cm^{-1}): 3650 and 3440 (N–H), 3206 (C–H aromatic), 2870 (CH_3), 2215 (C≡N), 1631 (C=O), 1172 (C–O–C symmetrical stretching OCH_3 group); MS m/z (%): 370 (M^+, 22), 355 (96), 324 (14), 205 (19), 164 (5), 107 (10), 103 (32), 91 (30), 77 (35). Elemental Analysis for $C_{22}H_{18}N_4O_2$: Calculated: C, 71.34; H, 4.90; N, 15.13. Found: C, 71.31; H, 4.85; N, 15.10%.

6-Amino-1-(2,5-dimethylphenyl)-4-(4-nitrophenyl)-2-oxo-1,2-dihydro pyridine-3,5-dicarbonitrile (CP-14):

MP: 195–198 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 2.02 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 7.11 (s, 1H, diCH_3–Ar–H), 7.25–7.35 (d, 2H, diCH_3–Ar–H), 7.58–7.61 (d, 2H, 4Br–Ar–H, J = 11.2 Hz), 7.79–7.82 (d, 2H, 4Br–Ar–H, J = 11.6 Hz), 7.91 (s, 2H, NH_2); IR (KBr, υ/cm^{-1}): 3644 and 3446 (N–H), 3200 (C–H aromatic), 2855 (CH_3), 2250 (C≡N), 1631 (C=O), 1350–1310 (NO_2); MS m/z (%): 385 (M^+, 31), 370 (100), 339 (28), 205 (15), 164 (8), 122 (30), 103 (30), 77 (30). Elemental Analysis for $C_{21}H_{15}N_5O_3$: Calculated: C, 65.45; H, 3.92; N, 18.17.Found: C, 65.40; H, 3.91; N, 18.15%.

6-Amino-1-(2,5-dimethylphenyl)-4-(2-nitrophenyl)-2-oxo-1,2-dihydro pyridine-3,5-dicarbonitrile (CP-15):

MP: 228–230 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 1.90 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 7.25–7.35 (d, 2H, diCH_3–Ar–H), 7.10 (s, 1H, diCH_3–Ar–H), 7.90 (s, 2H, NH_2), 8.10–8.13 (d, 2H, 2-NO_2–Ar–H, J = 11.6 Hz), 7.22–7.25 (d, 2H, 2-NO_2–Ar–H, J = 11.6 Hz), 7.54–7.57 (t, 2H, 2-NO_2–Ar–H); IR (KBr, υ/cm^{-1}): 3351 and 3457 (N–H), 3206 (C–H aromatic), 2870 (CH_3), 2215 (C≡N), 1631 (C=O), 1355–1315 (NO_2); MS m/z (%): 385 (M^+, 29), 370 (98), 339 (30), 205 (14), 164 (6), 122 (21), 91 (8), 77 (45). Elemental Analysis for $C_{21}H_{15}N_5O_3$: Calculated: C, 65.45; H, 3.92; N, 18.17. Found: C, 65.35; H, 3.88; N, 18.10%.

6-Amino-1-(2,5-dimethylphenyl)-2-oxo-4-(p-tolyl)-1,2-dihydro pyridine-3,5-dicarbonitrile (CP-16):

MP: 220–222 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 1.90 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 7.25–7.35 (d, 2H, diCH_3–Ar–H), 7.12–7.15 (d, 2H, 4-OCH_3–Ar–H, J = 11.6 Hz), 7.52–7.55 (d, 2H, 4-OCH_3–Ar–H, J = 11.6 Hz), 7.10 (s, 1H, diCH_3–Ar–H), 7.90 (s, 2H, NH_2); IR (KBr, υ/cm^{-1}): 3650 and 3450 (N–H), 3205 (C–H aromatic), 2868 (CH_3), 2340 (C≡N), 1629 (C=O); MS m/z (%): 354 (M^+, 36), 339 (92), 308 (26), 205 (13), 164 (11), 103 (22), 91 (10), 77 (42). Elemental Analysis for $C_{22}H_{18}N_4O$: Calculated: C, 74.56; H, 5.12; N, 15.81. Found: C, 74.50; H, 5.11; N, 15.71%.

6-Amino-1-(2,5-dimethylphenyl)-4-(4-bromophenyl)-2-oxo-1,2-dihydro pyridine-3,5-dicarbonitrile (CP-17):

MP: 275–279 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 2.02 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 7.11 (s, 1H, diCH_3–Ar–H), 7.25–7.35 (d, 2H, diCH_3–Ar–H), 7.53–7.56 (d, 2H, 4Br–Ar–H J = 11.2 Hz), 7.79–7.82 (d, 2H, 4Br–Ar–H, J = 11.6 Hz), 7.93 (s, 2H, NH_2); IR (KBr, υ/cm^{-1}): 3640 and 3438 (N–H), 3206 (C–H aromatic), 2870 (CH_3), 2215 (C≡N), 1631 (C=O), 642 (C–Br); MS m/z (%): 418 (M^+, 61), 403 (100), 323 (18), 309 (10), 205 (12), 164 (14), 103 (32), 91 (20), 77 (65). Elemental Analysis for $C_{21}H_{15}BrN_4O$: Calculated: C, 60.16; H, 3.61; N, 13.36. Found: C, 60.11; H, 3.51; N, 13.31%.

6-Amino-1-(2,5-dimethylphenyl)-4-(3-bromophenyl)-2-oxo-1,2-dihydro pyridine-3,5-dicarbonitrile (CP-18):

MP: 290–292 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 2.02 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 7.11 (s, 1H, diCH_3–Ar–H), 7.25–7.35 (d, 2H, diCH_3–Ar–H), 7.42–7.55 (m, 4H, 3Br–Ar–H), 7.93 (s, 2H, NH_2); IR (KBr, υ/cm^{-1}): 3635 and 3420 (N–H), 3206 (C–H aromatic), 2872 (CH_3), 2215

(C≡N), 1631 (C=O), 642 (C–Br); MS m/z (%): 418 (M^+, 57), 403 (100), 323 (20), 309 (10), 205 (9), 164 (14), 103 (30), 91 (18), 77 (65). Elemental Analysis for $C_{21}H_{15}BrN_4O$: Calculated: C, 60.16; H, 3.61; N, 13.36. Found: C, 60.13; H, 3.57; N, 13.31%.

6-Amino-1-(2,5-dimethylphenyl)-4-(4-chlorophenyl)-2-oxo-1,2-dihydro pyridine-3,5-dicarbonitrile (CP-19):

MP: 235–238 ºC; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 2.02 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 7.11 (s, 1H, diCH_3–Ar–H), 7.25–7.35 (d, 2H, diCH_3–Ar–H), 7.50–7.53 (d, 2H, 4Br–Ar–H, J = 11.2Hz), 7.77–7.80 (d, 2H, 4Br–Ar–H, J = 11.6Hz), 7.91 (s, 2H, NH_2); IR (KBr, υ/cm^{-1}): 3635 and 3440 (N–H), 3202 (C–H aromatic), 2870 (CH_3), 2211 (C≡N), 1641 (C=O), 772 (C–Cl); MS m/z (%): 374 (M^+, 52), 359 (100), 276 (21), 309 (8), 205 (11), 164 (15), 103 (25), 91 (15), 77 (60). Elemental Analysis for $C_{21}H_{15}ClN_4O$: Calculated: C, 67.29; H, 4.03; N, 14.95. Found: C, 67.25; H, 3.95; N, 14.89%.

6-Amino-1-(2,5-dimethylphenyl)-4-(3-chlorophenyl)-2-oxo-1,2-dihydro pyridine-3,5-dicarbonitrile (CP-20):

MP: 258–260 ºC; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 2.02 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 7.11 (s, 1H, diCH_3–Ar–H), 7.25–7.35 (d, 2H, diCH_3–Ar–H), 7.42–7.55 (m, 4H, 3Br–Ar–H), 7.93 (s, 2H, NH_2); IR (KBr, υ/cm^{-1}): 3590 and 3457 (N–H), 3200 (C–H aromatic), 2860 (CH_3), 2210 (C≡N), 1621 (C=O), 774 (C–Cl); MS m/z (%): 374 (M^+, 55), 359 (98), 276 (16), 309 (6), 205 (10), 164 (12), 103 (28), 91 (18), 77 (58). Elemental Analysis for $C_{21}H_{15}ClN_4O$: Calculated: C, 67.29; H, 4.03; N, 14.95. Found: C, 67.25; H, 4.00; N, 14.92%.

Antimicrobial Screening

The synthesized compound were tested for their antibacterial and antifungal activity (MIC) in vitro by broth dilution method[19–21] with two Gram-positive bacteria *Staphylococcus aureus (S.a.)* MTCC 96, *Streptococcus pyogenes (S.p.)* MTCC 443, two Gram-negative bacteria *Escherichia coli (E.c.)* MTCC 442, *Pseudomonas aeruginosa (P.a.)* MTCC 441 and three fungal strains *Candida albicans (C.a.)* MTCC 227, *Aspergillus niger (A.n.)* MTCC 282, *Aspergillus clavatus (A.c.)* MTCC 1323 taking ampicillin, chloramphenicol, ciprofloxacin, norfloxacin, nystatin, and griseofulvin as standard drugs.

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 of 1.56, 3.12, 6.25, 10, 12.5, 25, 50, 62.5, 100, 125, 250, 500 and 1000 μg mL^{-1}. The tubes were inoculated with 10^8 cfu mL^{-1} (colony forming unit mL^{-1}) 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.

RESULTS AND DISCUSSION

The compound **1** and **2** reacted in a solvent free condition to provide the starting materials **(3)** in good yields for the synthesis of desired product **(CP 1–20)**.

As shown in the reaction (*Scheme* 2) the synthesis of the target molecules **CP 1–20** was carried out. The compound **3** was reacted with the various substituted **4** and **5** compounds to give different target molecules. All the molecules have been synthesized under the conventional method using methanol as a solvent and pipyridine as a catalyst.

The physical data like molecular formula, molecular weight, melting point, and percentage of yield of all the synthesized target molecules are shown in *Table* 1.

The purity of all the synthesized compound was checked by TLC (8:2:n-hexane:ethylacetate). The target molecules were conformed on the basis of ^{1}H-NMR, IR, Mass Spectrometry. The ^{1}H-NMR spectra showed the broad peak in between 7.5–8.0 ppm which showed the presence of an –NH_2 functional group. The aromatic ring protons and J values were found to be in accordance with substitution pattern on phenyl ring. The sharp band near 2250 cm^{-1} in IR spectra indicates the presence of –CN group. Systematic fragmentation pattern was observed in mass spectral analysis for all the synthesized compounds. Molecular ion peak was observed in agreement with molecular weight of respective compound. All the synthesized target molecules showed screening in vitro studies on the selected microorganism and fungal species. Among the tested compounds **CP-1**, **CP-2**, **CP-7** and **CP-15** exhibited more antimicrobial activity against gram positive and gram negative bacteria and **CP-9**, **CP-10** and **CP-17** exhibited comparatively moderate anti fungal activity (*Table* 2).

CONCLUSION

In summary we have developed a simple, one pot method for the preparation of a series of 6-amino-1-(2,5-disub-

***Table* 1.** Physical data of all the synthesized compounds

Code	R_1, R_2	R_3	M.F.	M.W. (gm/mole)	M.P. (°C)	% of yield
CP-1	Cl	H	$C_{19}H_{10}Cl_2N_4O$	380	272–274	71
CP-2	Cl	4-OCH_3	$C_{20}H_{12}Cl_2N_4O_2$	410	280–284	66
CP-3	Cl	2-OCH_3	$C_{20}H_{12}Cl_2N_4O_2$	410	254–258	75
CP-4	Cl	4-NO_2	$C_{19}H_9Cl_2N_5O_3$	425	245–250	74
CP-5	Cl	2-NO_2	$C_{19}H_9Cl_2N_5O_3$	425	234–236	78
CP-6	Cl	4-CH_3	$C_{20}H_{12}Cl_2N_4O$	394	284–286	72
CP-7	Cl	4-Br	$C_{19}H_9BrCl_2N_4O$	458	298–300	65
CP-8	Cl	3-Br	$C_{19}H_9BrCl_2N_4O$	458	305–308	61
CP-9	Cl	4-Cl	$C_{19}H_9Cl_3N_4O$	414	278–282	70
CP-10	Cl	3-Cl	$C_{19}H_9Cl_3N_4O$	414	285–288	72
CP-11	CH_3	H	$C_{21}H_{16}N_4O$	340	283–285	68
CP-12	CH_3	4-OCH_3	$C_{22}H_{18}N_4O_2$	370	255–260	71
CP-13	CH_3	2-OCH_3	$C_{22}H_{18}N_4O_2$	370	225–228	74
CP-14	CH_3	4-NO_2	$C_{21}H_{15}N_5O_3$	385	195–198	65
CP-15	CH_3	2-NO_2	$C_{21}H_{15}N_5O_3$	385	228–230	69
CP-16	CH_3	4-CH_3	$C_{22}H_{18}N_4O$	354	220–222	74
CP-17	CH_3	4-Br	$C_{21}H_{15}BrN_4O$	418	275–279	70
CP-18	CH_3	3-Br	$C_{21}H_{15}BrN_4O$	418	290–292	75
CP-19	CH_3	4-Cl	$C_{21}H_{15}ClN_4O$	374	235–238	68
CP-20	CH_3	3-Cl	$C_{21}H_{15}ClN_4O$	374	258–260	72

***Table* 2.** Minimal inhibitory concentration (MIC) of all synthesized compounds

Code	S.a.	S.p.	E.c.	P.a.	C.a.	A.n.	A.c.
CP-1	100	62.5	250	250	>1000	500	100
CP-2	100	500	62.5	250	500	>1000	1000
CP-3	200	250	200	100	500	1000	1000
CP-4	100	500	125	1000	500	1000	1000
CP-5	250	1000	250	500	500	250	250
CP-6	1000	500	1000	1000	500	500	1000
CP-7	100	62.5	125	100	500	500	500
CP-8	100	1000	250	1000	1000	500	1000
CP-9	250	250	100	500	100	500	500
CP-10	125	100	100	500	500	100	1000
CP-11	500	500	250	200	>1000	>1000	>1000
CP-12	250	200	150	100	500	500	250
CP-13	200	500	250	500	250	500	>1000
CP-14	100	500	250	200	>1000	>1000	>1000
CP-15	250	250	62.5	250	1000	1000	500
CP-16	500	500	250	500	250	>1000	>1000
CP-17	100	500	250	200	500	100	250
CP-18	250	250	500	250	1000	500	>1000
CP-19	200	250	500	500	500	250	500
CP-20	500	100	500	500	>1000	>1000	>1000
Ampicillin	250	100	100	100	–	–	–
Chloramphenicol	50	50	50	50	–	–	–
Ciprofloxacin	50	50	25	25	–	–	–
Nystatin	–	–	–	–	100	100	100
Greseofulvin	–	–	–	–	500	100	100

stituted phenyl)-2-oxo-4-substituted phenyl-1,2-dihydropyridine-3,5-dicarbonitrile. All the synthesized compounds were characterized by FT-IR, ^{1}H-NMR, mass spectroscopy and elemental analysis. The compounds were subjected for different biological activities and all the synthesized compounds showed good to moderate antimicrobial activity, results of other activities are awaiting. Further efforts toward this end will be reported in due course.

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