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# Synthesis, characterization and biological importance of aminocyanopyridines

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**Abstract:** Synthesis of 4, 6–bis[2′-amino-3′-cyano-4′-(substituted phenyl)-6′-pyridyl] resorcinol derivatives were achieved from the mixture of bichalcones, malononitrile and ammonium acetate following Knoevenagel reaction and Michael addition. The structures of the synthesized compounds were characterized by IR, $^{1}$HNMR, $^{13}$CNMR, mass spectral data and elemental analysis. The compounds **($III_{a-h}$)** were screened for their *in vitro* activity against ***Psedomonas, Bacillus sp., Streptococcus, Staphylococcus, E.coli, C.albicans, and A.niger.*** All the compounds were found to possess significant activities against the bacteria and fungi chosen at optimum concentration. The antifeedant activity of the compounds **IIIb, IIIe** and **IIIg** has been found to possess very high.
**Keywords:** Bichalcones, malononitrile, aminocyanopyridines, antimicrobial, antifeedant activity.

## Introduction

Pyridine derivatives have occupied a unique position in the field of medicinal chemistry. Many naturally occurring compounds having pyridine moiety show interesting biological and pharmacological activities. Pyridine derivatives have been used as herbicides[1], for enrichment of cereals[2], for regulation of arterial pressure[3] and cholesterol levels in blood[4]. Some of them constitute an important class of antitumor compounds[5, 6]. 2-Amino-3-cyanopyridines have been identified to possess antibacterial[7], antimicrobial[8, 9], antifungal[10], cardiotonic[11], analgesic[12], antiinflammatory[13] and anti lung cancer[14] activities. They have also been found to be selective IKK - β serine - threonine protein kinase inhibitors[15]. Recently, many synthetic methods have been used for the preparation of 2-amino-3-cyano pyridine derivatives[16-18]. This prompted us to synthesise a series of 4, 6-bis [2′-amino-3′-cyano-4′-(substituted phenyl)- 6′- pyridyl] resorcinol ($III_{a-h}$) starting from 4,6-diacetylresocinol.

## Experimental

All the chemicals used were purchased from Merck AnalaR Grade and purified wherever necessary following the standard methods. The purity of the compounds was checked by TLC using silica gel G plates. Melting points were recorded in open capillary tubes and were uncorrected. FT-IR spectra were recorded on Perkin Elmer spectrometer using KBr pellets. $^{1}$H-NMR and $^{13}$C-NMR spectra were taken in DMSO-$d_6$ on a 400 MHz and 300MHz Bruker spectrometer respectively with TMS as an internal standard. Mass spectra were obtained on SHIMADZU GC-MS Spectrometer. Column chromatography was carried out on silica gel 60-120 mesh. Elemental analysis were taken using an elementer analysiser model Vario EL III.

**Synthesis of 4, 6-diacetylresorcinol (I)**

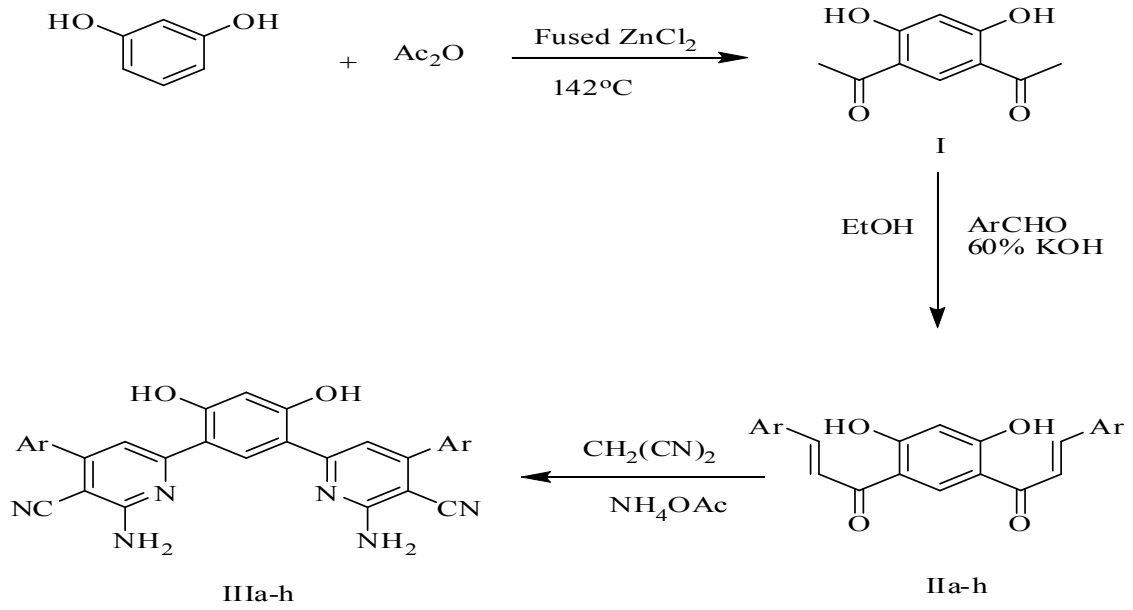
To a mixture of freshly fused zinc chloride (100 g) and dry acetic anhydride (140 ml) in a conical flask, powdered resorcinol (100 g) was added with constant stirring. The mixture was gently heated on a flame to 142 ºC for about 15 min. The viscous red solution was allowed to cool to room temperature and 1:1 hydrochloric acid (800 ml) was then added to the syrupy mass with constant stirring. After a few minutes, an orange red crystalline solid separated out. It was then filtered and dried in air. The dried sample was recrystallized from methanol to give colorless needles. Mp.177-179 ºC (Lit[19] 178-180). The yield of the product was found to be 70%.

**Synthesis of bichalcones (IIa-h)**

The synthesis of bichalcones was carried out by the method given in the literature[20]. A homogeneous mixture of 4,6-diacetyl resorcinol **(I)** (3.88 g, 0.02 mol), substituted benzaldehyde (0.04 mol) in ethanol (80 ml) and aqueous potassium hydroxide (60%) were kept at room temperature for 24 h. The reaction mixture was then treated with 1:1 hydrochloric acid and poured into ice with stirring. The solid thus obtained was filtered, washed with water and dried. It was then recrystallized from methanol and chloroform mixture (1:1).

**Synthesis of 4,6-bis[2′- amino-3′-cyano-4′-(substituted phenyl)-6′-pyridyl] resorcinol(IIIa-h)**

A mixture of compound **(IIa-h)** (0.01 mol) dissolved in 50 ml of dry ethanol, malononitrile (0.60 g, 0.02 mol) and ammonium acetate (6.18 g, 0.08 mol) was refluxed on water bath for 24 h. The formation of the product was monitored by TLC. The reaction mixture was then poured into crushed ice and kept overnight in a refrigerator. The solid thus obtained was filtered, washed with water and dried in air. The dried sample was recrystallized from ethanol. Finally the product was subjected to column chromatography for further purification using silica gel (60-120 mesh) and $CHCl_3$-MeOH mixture (3:1) as eluent.




**Scheme-I**

Ar = IIIa - phenyl
IIIb - 4 - methoxyphenyl
IIIc - 4- chlorophenyl
IIId - 4- methylphenyl
IIIe - 3, 4 - dimethoxyphenyl
IIIf - 4 -N,N – dimethylphenyl
IIIg - 3,4,5 - trimethoxyphenyl
IIIh - 3 - methylphenyl

**Table-1: IR and analytical data of Compounds IIIa-h**

| Code No. | Ar | Molecular weight | Molecular Formula | M.P °C | Yield % | OH υ $cm^{-1}$ | N-H υ $cm^{-1}$ | C≡N υ $cm^{-1}$ |
|---|---|---|---|---|---|---|---|---|
| IIIa | phenyl | 496 | $C_{30}H_{20}N_6O_2$ | 228 | 65 | 3351 | 3235 | 2209 |
| IIIb | 4 - methoxyphenyl | 556 | $C_{32}H_{24}N_6O_4$ | 210 | 70 | 3343 | 3223 | 2208 |
| IIIc | 4- chlorophenyl | 564 | $C_{30}H_{18}Cl_2N_6O_2$ | 188 | 63 | 3357 | 3198 | 2210 |
| IIId | 4- methylphenyl | 524 | $C_{32}H_{24}N_6O_2$ | 256 | 59 | 3347 | 3241 | 2212 |
| IIIe | 3, 4 -dimethoxyphenyl | 616 | $C_{34}H_{28}N_6O_6$ | 146 | 62 | 3342 | 3222 | 2207 |
| IIIf | 4-N,N-dimethylphenyl | 582 | $C_{34}H_{30}N_8O_2$ | 210 | 66 | 3354 | 3227 | 2213 |
| IIIg | 3, 4, 5-trimethoxyphenyl | 676 | $C_{36}H_{32}N_6O_8$ | 278 | 54 | 3356 | 3242 | 2216 |
| IIIh | 3- methylphenyl | 524 | $C_{32}H_{24}N_6O_2$ | 194 | 50 | 3352 | 3235 | 2215 |

All the compounds gave satisfactory elemental analysis.

**Table-2: Antimicrobial and antifeedant activities**

| Sample code | Conc. | Antibacterial activity | | | | | Antifungal activity | | % of Antifeedant activity |
|---|---|---|---|---|---|---|---|---|---|
| | | Diameter zone of inhibition (mm) | | | | | | | |
| | | *Psedomonas* | *Bacillus sp.* | *Streptococcus* | *Staphylococcus* | *E.coli* | *C. albicans* | *A. niger* | |
| **Std.** | **5µg** | **25** | **29** | **32** | **25** | **30** | **29** | **40** | |
| IIIa | 50µg | 11 | 15 | 12 | 15 | 15 | 12 | 12 | 91.41 |
| | 100µg | 14 | 16 | 14 | 16 | 17 | 15 | 18 | |
| | 250µg | 18 | 19 | 21 | 19 | 21 | 18 | 18 | |
| IIIb | 50µg | 10 | - | 11 | - | - | 12 | 12 | 92.76 |
| | 100µg | 13 | - | 16 | - | 13 | 18 | 15 | |
| | 250µg | 18 | 11 | 18 | 12 | 20 | 18 | 16 | |
| IIIc | 50µg | - | 14 | 22 | 18 | 15 | 15 | 15 | 88.93 |
| | 100µg | - | 18 | 19 | 21 | 20 | 15 | 18 | |
| | 250µg | 17 | 19 | 23 | 22 | 20 | 20 | 25 | |
| IIId | 50µg | 12 | 14 | - | 13 | 15 | 15 | 15 | 92.48 |
| | 100µg | 15 | 16 | 17 | 16 | 17 | 15 | 18 | |
| | 250µg | 18 | 17 | 21 | 19 | 18 | 18 | 20 | |
| IIIe | 50µg | 13 | 12 | 12 | 11 | - | 12 | 12 | 95.87 |
| | 100µg | 14 | 15 | 16 | 15 | 13 | 15 | 15 | |
| | 250µg | 18 | 16 | 20 | 16 | 20 | 15 | 25 | |
| IIIf | 50µg | - | 11 | 12 | 15 | 15 | 13 | 14 | 87.65 |
| | 100µg | 14 | 16 | 14 | 16 | 17 | 15 | 16 | |
| | 250µg | 18 | 19 | 21 | 19 | 21 | 16 | 19 | |
| IIIg | 50µg | 12 | 13 | 14 | 13 | - | - | 12 | 96.79 |
| | 100µg | 16 | 14 | 15 | 18 | 13 | 12 | 14 | |
| | 250µg | 18 | 19 | 21 | 19 | 20 | 20 | 18 | |
| IIIh | 50µg | - | 12 | 11 | 13 | 12 | 12 | 14 | 87.42 |
| | 100µg | 14 | 16 | 13 | 16 | 15 | 15 | 16 | |
| | 250µg | 19 | 19 | 21 | 17 | 18 | 17 | 18 | |

Solvent- DMSO

## Results and Discussion

The physical constants and IR data were summarized in Table-1. The compound **IIIa** is considered as a representative compound. The IR spectrum of the compound shows bands at 3351 and 3235 $cm^{-1}$ due to -OH and $-NH_2$ groups respectively. Another band at 2209 $cm^{-1}$ is due the stretching frequency of -C≡N group. In $^1$HNMR spectrum, two singlets at δ 6.74 and 8.38 are assigned for $C_2$-H and $C_5$-H of resorcinol moiety. Another broad singlet at δ 6.69 is due to the $NH_2$ protons. In $^{13}$CNMR, the C≡N carbon appears at δ 115.7 and ipso carbon at δ 140.4. The mass spectrum shows an intense peak at m/z 496 (41%) consistent with its molecular formula $C_{30}H_{20}N_6O_2$.

**Antibacterial activity**

All the synthesized compounds were screened for their *in vitro* antibacterial activity in various concentrations by Disc Diffusion method against ***Psedomonas, Bacillus, Streptococcus, Staphylococcus*** and ***E.coli*** using Chloromphenic(5µg/disc) as standard antibiotic drug. Compound **IIIc** is found to possess appreciable activity against four of the above organisms and poor activity against ***Psedomonas***. The other compounds are active at optimum concentrations (Table-2).

**Antifungal activity**

All the compounds were tested for their *in vitro* antifungal activity against ***C. albicans and A. niger*** using Co-trimazole (25µg/disc) as standard drug. From the results, an appreciable activity has been found for compounds **IIIb, IIIc, IIId** and **IIIe** against ***C. albicans*** *and* ***A. niger*** at optimum concentrations (Table-2).

**Antifeedant Activity**

All the compounds synthesized were tested for their antifeedant activity by non-choice test method using 6 h prestarved fifth instar larvae of *Bombyx mori L*. Compounds **IIIb, IIIe** and **IIIg** exhibited highest antifeedant activity. The present study indicated that an increase of methoxy group in the phenyl moiety found to increase the antifeedant activity of aminocyanopyridine compounds (Table-2).

**4, 6-Bis[2′- amino-3′-cyano-4′- phenyl-6′-pyridyl] resorcinol (IIIa)**

$^1$H NMR (DMSO $d_6$): δ 6.74(1H, s, $C_2$-H), 8.38(1H, s, $C_5$-H), 8.10 (2H, s, $C_{5'}$), 6.69 (4H, s, -$NH_2$), 7.5-7.41 (10H, m, Ar-H), 11.19(2H, s, - OH). $^{13}$C NMR (DMSO $d_6$): δ 156.3($C_1$, $C_3$), 105.4($C_2$), 118.4($C_4$, $C_6$), 127.2($C_5$), 158.3($C_{6'}$), 109.1($C_{5'}$), 154.4($C_{4'}$), 85.6($C_{3'}$), 163.1($C_{2'}$), 115.7 (C≡N), 140.4($C_{1''}$), 129.6($C_{2''}$, $C_{6''}$), 132.2($C_{3''}$, $C_{5''}$, $C_{6''}$).

**4, 6-Bis[2′- amino-3′-cyano-4′(4′′-methoxyphenyl)-6′-pyridyl] resorcinol (IIIb)**

$^1$H NMR (DMSO $d_6$): δ 6.68 (1H, s, $C_2$-H), 8.27(1H, s, $C_5$-H), 7.91(2H, s, $C_{5'}$), 6.78 (4H, s, -$NH_2$), 7.73-7.55(8H, m, Ar-H), 11.25(2H, s, - OH), 3.83(3H, s, -OMe). $^{13}$C NMR (DMSO $d_6$): δ 155.8($C_1$, $C_3$), 104.4($C_2$), 116.8($C_4$, $C_6$), 128.4($C_5$), 157.7($C_{6'}$), 111.6($C_{5'}$), 153.4($C_{4'}$), 85.6($C_{3'}$), 162.6($C_{2'}$), 114.2(C≡N), 135.6($C_{1''}$), 130.4($C_{2''}$, $C_{6''}$), 120.3($C_{3''}$, $C_{5''}$), 164.1($C_{4''}$), 55.8(-$OCH_3$).

**4, 6-Bis[2′- amino-3′-cyano-4′(4′′-chlorophenyl)-6′-pyridyl]resorcinol (IIIc)**

$^1$H NMR (DMSO $d_6$) : δ 6.62 (1H, s, $C_2$-H), 8.42(1H, s, $C_5$-H), 7.83(2H, s, $C_{5'}$), 6. 87 (4H, s, -$NH_2$), 7.63-7.22 (8H, m, Ar-H), 11.49(2H, s, - OH). $^{13}$C NMR (DMSO $d_6$): δ 156.5($C_1$, $C_3$), 104.9($C_2$), 120.1($C_4$, $C_6$), 127.2($C_5$), 159.2($C_{6'}$), 110.7($C_{5'}$), 154.6($C_{4'}$), 88.2($C_{3'}$), 165.1($C_{2'}$), 113.2(C≡N), 140.8($C_{1''}$), 128.6($C_{2''}$, $C_{6''}$), 129.5($C_{3''}$, $C_{5''}$), 134.8($C_{4''}$).

**4, 6-Bis[2′- amino-3′-cyano-4′(4′′-methylphenyl)-6′-pyridyl]resorcinol (IIId)**

$^1$H NMR (DMSO $d_6$): δ 6.65(1H, s, $C_2$-H), 8.34(1H, s, $C_5$-H), 8.01(2H, s, $C_{5'}$), 6.83(4H, s, -$NH_2$), 7.65-7.34 (8H, m, Ar-H), 11.36(2H, s, - OH), 3.04(3H, s, - Me). $^{13}$C NMR (DMSO $d_6$) : δ 153.3($C_1$, $C_3$), 104.9($C_2$), 118.8($C_4$, $C_6$), 126.2($C_5$), 157.2($C_{6'}$), 112.1($C_{5'}$), 155.6 ($C_{4'}$), 87.6($C_{3'}$), 164.1($C_{2'}$), 115.7(C≡N), 140.4($C_{1''}$), 129.6($C_{2''}$, $C_{6''}$), 129.5($C_{3''}$, $C_{5''}$), 132.8($C_{4''}$), 24.6 (-$CH_3$).

**4, 6-Bis[2′- amino-3′-cyano-4′(3′′,4′′-dimethoxy phenyl)-6′-pyridyl] resorcinol (IIIe)**

$^1$H NMR (DMSO $d_6$): δ 6.71 (1H, s, $C_2$-H), 8.37(1H, s, $C_5$-H), 7.97(2H, s, $C_{5'}$), 6.89 (4H, s, -$NH_2$), 7.59-7.45(6H, m, Ar-H), 11.10(2H, s, - OH), 3.81(12H, s, -OMe). $^{13}$C NMR (DMSO $d_6$): δ 156.2($C_1$, $C_3$), 104.4($C_2$), 116.2($C_4$, $C_6$), 128.6($C_5$), 158.7($C_{6'}$), 111.4($C_{5'}$), 154.0($C_{4'}$), 85.6($C_{3'}$), 163.2($C_{2'}$), 114.5 (C≡N), 135.6($C_{1''}$), 113.4($C_{2''}$), 152.3($C_{3''}$, $C_{4''}$), 117.1($C_{5''}$), 122.4($C_{6''}$), 56.1(-$OCH_3$).

**4, 6-Bis[2′- amino-3′-cyano-4′(4′′-N,N-dimethyl phenyl)-6′-pyridyl] resorcinol (IIIf)**

$^1$H NMR (DMSO $d_6$): δ 6.81 (1H, s, $C_2$-H), 8.29(1H, s, $C_5$-H), 8.12 (2H, s, $C_{5'}$), 6.74 (4H, s, -$NH_2$), 7.76-7.55(6H, m, Ar-H), 11.21(2H, s, - OH), 3.01 (12H, s, -Me). $^{13}$C NMR (DMSO $d_6$): δ 157.3($C_1$, $C_3$), 105.4($C_2$), 118.4($C_4$, $C_6$), 127.2($C_5$), 158.3($C_{6'}$), 109.1($C_{5'}$), 154.4($C_{4'}$), 85.6($C_{3'}$), 163.1($C_{2'}$), 115.7 (C≡N), 125.5($C_{1''}$), 128.3($C_{2''}$, $C_{6''}$), 113.2($C_{3''}$, $C_{5''}$) 155.2 ($C_{4''}$), 44.6 ($CH_3$).

**4, 6-Bis[2′- amino-3′-cyano-4′(3′′,4′′,5′′-trimethoxy phenyl)-6′-pyridyl] resorcinol (IIIg)**

$^1$H NMR(DMSO $d_6$) : δ 6.61 (1H, s, $C_2$-H), 8.29(1H, s, $C_5$-H), 8.07(2H, s, $C_{5'}$), 6.79 (4H, s, -$NH_2$), 7.69-7.52(4H, m, Ar-H), 11.28(2H, s, - OH), 3.88(18H, s, -OMe). $^{13}$C NMR (DMSO $d_6$): δ 154.8 ($C_1$, $C_3$), 105.1($C_2$), 116.8($C_4$, $C_6$), 128.4($C_5$), 157.7($C_{6'}$), 112.6($C_{5'}$), 152.1($C_{4'}$), 85.6($C_{3'}$), 162.6($C_{2'}$), 114.2 (C≡N), 135.6($C_{1''}$), 130.4($C_{2''}$, $C_{6''}$), 153.5($C_{3''}$, $C_{5''}$), 139.1($C_{4''}$), 56.4($C_{3''}$, $C_{5''}$-$OCH_3$) 60.2($C_{4''}$-$OCH_3$).

**4, 6-Bis[2′- amino-3′-cyano-4′(3′′-methylphenyl)-6′-pyridyl] resorcinol (IIIh)**

$^1$H NMR (DMSO $d_6$): δ 6.54(1H, s, $C_2$-H), 8.24(1H, s, $C_5$-H), 8.12(2H, s, $C_{5'}$), 6.79(4H, s, -$NH_2$), 7.61-7.43 (8H, m, Ar-H), 11.19(2H, s, - OH), 3.21(3H, s, - Me). $^{13}$C NMR (DMSO $d_6$) : δ 155.7($C_1$, $C_3$), 106.3($C_2$), 117.9($C_4$,$C_6$), 126.8($C_5$), 157.8($C_{6'}$), 109.9($C_{5'}$), 154.4($C_{4'}$), 85.9($C_{3'}$), 163.7($C_{2'}$), 116.1(C≡N),

137.4($C_{1''}$), 129.0($C_{2''}$), 124.6 ($C_{6''}$), 138.2($C_{3''}$), 129.7($C_{5''}$), 129.1($C_{6''}$), 40.4($CH_3$).

## Conclusion

Synthesis of 4, 6–bis[2′-amino-3′-cyano-4′-(substituted phenyl)-6′-pyridyl] resorcinol derivatives **IIIa-h** were achieved by adopting Knoevenagel and Michael addition reactions. All the compounds were found to possess appreciable activity against the bacteria and fungi at optimum concentrations. The antifeedant activity of the synthesized compounds **IIIb, IIIe** and **IIIg** has found to possess very high activity.

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