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SYNTHESIS AND CYTOKININ ACTIVITY OF *N*-ACYLAMINODEAZAPURINES

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Key Word Index—7-Aminoimidazo[4,5-*b*]pyridine, 4-aminoimidazo[4,5-*c*]pyridine, 7-aminoimidazo [4,5-*c*]-pyridine, cytokinin activity, tobacco callus

Abstract—Three 7-acylaminoimidazo[4,5-*b*]pyridines, namely 7-pentanoylaminoimidazo[4,5-*b*]pyridine (**1**), 7-benzoylaminoimidazo[4,5-*b*]pyridine(**2**), and 7-(2-furoylamino)imidazo[4,5-*b*]pyridine(**3**), six 4-acylaminoimidazo[4,5-*c*]pyridines, namely 4-propionylaminoimidazo[4,5-*c*]pyridine(**4**), 4-butyrylaminoimidazo[4,5-*c*]pyridine(**5**), 4-pentanoylaminoimidazo[4,5-*c*]pyridine(**6**), 4-hexanoylaminoimidazo[4,5-*c*]pyridine(**7**), 4-benzoylaminoimidazo[4,5-*c*]pyridine(**8**), and 4-(2-furoylamino)imidazo[4,5-*c*]-pyridine(**9**), and seven 7-acylaminoimidazo[4,5-*c*]pyridines, namely 7-propionylaminoimidazo[4,5-*c*]-pyridine(**10**), 7-butyrylaminoimidazo[4,5-c]pyridine(**11**), 7-pentanoylaminoimidazo[4,5-*c*]pyridine(**12**), 7-hexanoylaminoimidazo[4,5-*c*]pyridine(**13**),7-benzoylaminoimidazo[4,5-*c*]pyridine(**14**),7-phenylacetylaminoimidazo[4,5-*c*]pyridine(**15**), and 7-(2-furoylamino)imidazo[4,5-*c*]pyridine(**16**) were synthesized and tested for their cytokinin activity with the tobacco callus bioassay. **2** showed a cytokinin activity at 1×10^{-8} M and gave a callus yield about 72% of that produced by kinetin at 1×10^{-6} M. **1**, **3** and **8** showed the optimum growth responses in the range of 10^{-7}–10^{-6} M. **4**, **5**, **7**, **9**–**16** were slightly active These results support previous reports that a nitrogen atom at the 3-position in the purine ring plays an important role in conferring high cytokinin activity.

INTRODUCTION

It is well known that the structure of cytokinins possessing a high activity includes an intact adenine ring with a N^6-substituent of specific alkyl [1] or acyl [2–4] groups. The following exceptions have, however, been reported [5, 6]. 8-azakinetin and 6-benzylamino-8-azapurine [7]; 1-deaza- and 3-deaza- analogs of kinetin and 6-(3-methyl-2-butenylamino)purine [8]; 8-benzylamino-2-methyl-*s*-triazolo[1,5-*a*]pyrazine and 8-benzylamino-2-methyl-*s*-triazolo[1,5-*a*]pyridine, and 4(7)-benzylaminoimidazole [9]. These compounds show cytokinin activity on tobacco callus and contain a common structural moiety, namely either an imidazole or a triazole ring and an amino group at position-6 of the heterocyclic ring corresponding to the purine ring.

On the other hand, cytokinin activity of N^6-acyl derivatives of adenine has been described [4, 10]. For example, 6-benzoylaminopurine shows almost the same cytokinin activity as 6-benzylaminopurine at its optimum concentration.

In this connection it seemed interesting to examine the cytokinin activity of kinetin analogs modified both in the purine ring and in the side chain of the same molecule. We have now synthesized

three 7-acylaminoimidazo[4,5-*b*]pyridines, six 4-acylaminoimidazo[4,5-*c*]pyridines and seven 7-acylaminoimidazo[4,5-*c*]pyridines, and tested them for cytokinin activity with the tobacco callus assay The results are reported in this paper.

RESULTS AND DISCUSSION

Sixteen acyl derivatives (Table 1) were prepared by condensation of several acyl chlorides with 7-aminoimidazo[4,5-*b*]pyridine [11–13], 4-aminoimidazo[4,5-*c*]pyridine and 7-aminoimidazo [4,5-*c*]pyridine[11,12,14], respectively All the compounds gave satisfactory elemental analysis and their structures were verified by spectrophotometric determinations. Their physicochemical characterizations are described in the experimental section The cytokinin activity of these compounds (**1**–**16**) was determined by the fresh weight yield of the callus obtained with the optimum concentrations of the compounds used in the tobacco callus bioassay

Three 7-acylaminoimidazo[4,5-*b*]pyridines were as active as kinetin and 6-benzylaminopurine on the tobacco callus as shown in Fig. 1. 7-Benzoylaminoimidazo[4,5-b]pyridine showed cytokinin activity at 1×10^{-8} M and gave a callus yield of about 72% of that produced by kinetin at 1×10^{-6} M. 7-Pentanoylaminoimidazo[4-5-*b*]pyridine and 7-(2-furoylamino)imidazo[4,5-*b*]pyridine showed optimum growth responses at 1×10^{-7} M and 1×10^{-6} M, respectively

Table 1 List of compounds tested for cytokinin activity

1	7-Pentanoylaminoimidazo[4 5-*b*]pyridine
2,	7-Benzoylaminoimidazo[4,5-*b*]pyridine
3,	7-(2-Furoylamino)imidazo[4 5-*b*]pyridine
4,	4-Propionylaminoimidazo[4 5-*c*]pyridine
5,	4-Butyrylaminoimidazo[4,5-*c*]pyridine
6,	4-Pentanoylaminoimidazo[4,5-*c*]pyridine
7	4-Hexanoylaminoimidazo[4,5-*c*]pyridine
8,	4-Benzoylaminoimidazo[4,5-*c*]pyridine
9	4-(2-Furoylamino)imidazo[4,5-*c*]pyridine
10,	7-Propionylaminoimidazo[4,5-*c*]pyridine
11,	7-Butyrylaminoimidazo[4,5-*c*]pyridine
12,	7-Pentanoylaminoimidazo[4,5-*c*]pyridine
13,	7-Hexanoylaminoimidazo[4,5-*c*]pyridine
14,	7-Benzoylaminoimidazo[4,5-*c*]pyridine
15,	7-Phenylacetylaminoimidazo[4,5-*c*]pyridine
16,	7-(2-Furoylamino)imidazo[4,5-*c*]pyridine

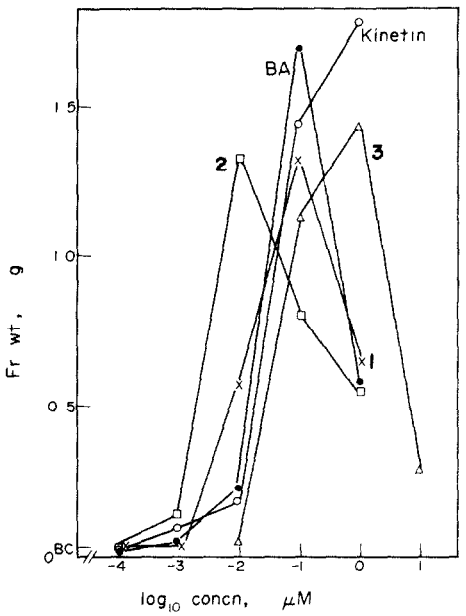

Fig 1 Effect of **1**, **2**, **3** BA and kinetin on fr wt yield of tobacco callus BC Basal medium control, BA 6-Benzylaminopurine

However, 4-acylaminoimidazo[4,5-*c*]pyridines, except for 4-benzoylaminoimidazo[4,5-*c*]pyridine, showed lower activity (Fig 2) 4-Pentanoylaminoimidazo[4,5-*c*]pyridine and 4-(2-furoyl-

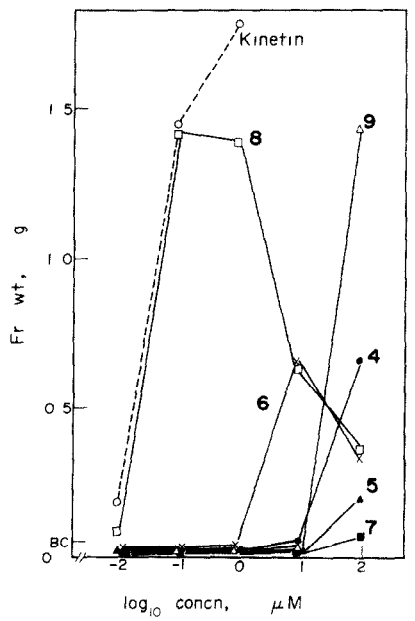

Fig 2 Effect of **4**, **5**, **6**, **7**, **8**, **9** and kinetin on fr wt yield of tobacco callus BC Basal medium control

amino)imidazo[4,5-*c*]pyridine showed the optimum growth response at 1×10^{-5} M and 1×10^{-4} M, respectively. 4-Benzoylaminoimidazo[4,5-*c*]pyridine showed unexpectedly high cytokinin activity [8] and its optimum concentration was in the range of 10^{-7}–10^{-6} M.

It can be concluded that the nitrogen atom at the 3-position of the purine ring plays an important role in the exhibition of cytokinin activity when the cytokinin activities of 4-acylaminoimidazo[4,5-*c*]pyridines are compared with those of 7-acylaminoimidazo[4,5-*b*]pyridines. In order to examine whether the nitrogen atom at the 3-position of the purine ring is necessary for a high cytokinin activity or not, seven acyl derivatives of 7-aminoimidazo[4,5-*c*]pyridine(1-deaza-2-aza-3-deazaadenine) were synthesized and tested for their cytokinin activity. As shown in Fig 3, 7-acylaminoimidazo[4,5-*c*]pyridines gave the optimum growth response in the range 10^{-5}–10^{-4} M. 7-Phenylacetylaminoimidazo[4,5-*c*]pyridine showed cytokinin activity at 1×10^{-5} M and gave a callus yield about 70% that produced by kinetin at 1×10^{-6} M. Therefore none of these compounds showed such high cytokinin activity as that found for the 7-acylaminoimidazo[4,5-*b*]-pyridines. In addition it is known that 4(7)-benzylaminoimidazole, 8-benzylamino-2-methyl-s-triazolo[1,5-*a*]pyrazine and 4-(3-methyl-2-butenylamino)imidazo[4,5-*c*]pyridine show the optimum growth response at about 10^{-5} M, whereas 7-(3-methyl-2-butenylamino)imidazo[4,5-*b*]pyridine shows cytokinin activity at 10^{-8} M.

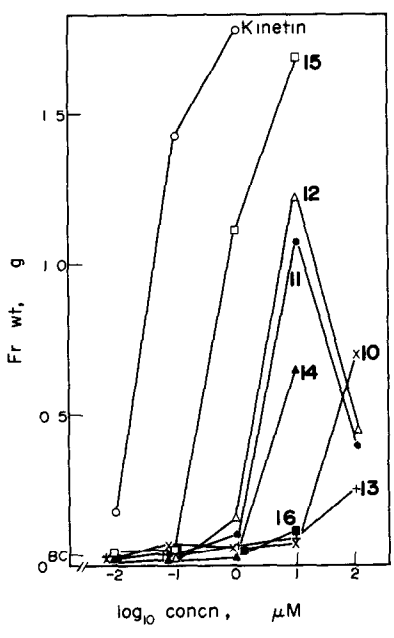

Fig 3 Effect of **10**, **11**, **12**, **13**, **14**, **15**, **16** and kinetin on fr wt yield of tobacco callus BC Basal medium control

It is consequently evident that the nitrogen atom at the 3-position of the purine ring plays an important role in the exhibition of a high cytokinin activity as shown by Rogozinska *et al.* [8]. On the other hand, 4-benzoylaminoimidazo[4,5-*c*]pyridine showed a higher cytokinin activity than that given by other 4-acylaminoimidazo[4,5-*c*]pyridines Generally the substitution of aromatic acyl groups as the side chain appeared to increase the cytokinin activity when compared with that found with aliphatic acyl groups. However, *n*-pentanoyl derivatives showed exceptionally good activity. The relationship between the length of the acyl group side chain and the cytokinin activity corresponds to that found in the case of alkyl group side chains [1]. It is thus inferred that the size of the side chain acyl group influences the cytokinin activity.

All new compounds described here which were modified in both the pyrimidine moiety of the purine ring and with alkyl side chain showed cytokinin activity in the concentration range 10^{-8}–10^{-4} M Among them, 7-benzoylaminoimidazo[4,5-*b*]pyridine, 7-pentanoylaminoimidazo-[4,5-*b*]pyridine and 4-benzoylaminoimidazo-[4,5-*c*]pyridine were found to show excellent cytokinin activity.

EXPERIMENTAL

Bioassay procedure Cytokinin activity of the compounds was assayed by the method of Linsmaier and Skoog [15] Tests were carried out in Erlenmeyer flasks containing 20 ml of culture medium and various concentrations of the test compounds Each flask was sterilized and inoculated with 3 pieces (8 mg) each of the tobacco pith callus The flask was kept in the dark for 30 days Fresh wt of the callus was measured and the average wt of 12 calluses was compared with the wts of basal and kinetin treated controls

Synthesis of test compounds All UV spectra were determined in 95% EtOH, and all mp's were measured on a micro-melting point apparatus

7-Pentanoylaminoimidazo[4,5-b]*pyridine*(**1**) 7-Aminoimidazo[4,5-*b*]pyridine sulfate (0 7 g, 4 mmol) was suspended in 10 ml dry Py to which 0 5 ml (5 mmol) pentanoyl chloride was added and the reaction mixture was refluxed for 2 hr After cooling, excess Py was removed under red pres and residue was neutralized with an aq soln of $NaHCO_3$ The soln was conc under red pres The resulting ppt was filtered,

washed with iced H_2O, and purified by recrystallization from EtOH–H_2O to give colourless needles. Yield 47%, mp 210–211° (Found: C, 60.66; H, 6.50; N, 25.52. $C_{11}H_{13}ON_4$ requires: C, 60.53; H, 6.47; N, 25.67%). IR (KBr) cm^{-1}: 1665, 1540 (–CONH–). NMR(D_2O–NaOD) δ: 0.97 (3H, *t*, –Me), 1.57 [4H, *m*, $-(CH_2)_2-$], 2.50 (2H, *t*, $-COCH_2-$), 7.38 (1H, *d*, *J* 6Hz, C-6), 8.10 (1H, *d*, *J* 6Hz, C-5), 8.10 (1H, s, C-2). UV λ_{max} nm (log ϵ): 273 (4.30). Compounds **2**–**16** were prepared in a similar manner. Their yields and physicochemical characterizations are described below.

7-*Benzoylaminoimidazo*[4,5-b]*pyridine*(**2**). Yield, 62%, mp 271–272° (Found: C, 64.81; H, 4.26; N, 23.12. $C_{13}H_{10}ON_4$ requires: C, 65.53; H, 4.23; N, 23.52%). IR (KBr) cm^{-1}: 1686, 1530 (–CONH–). NMR(D_2O–NaOD) δ: 7.50 (3H, *m*, C_6H_5 ring protons), 8.02 (2H, *m*, C_6H_5 ring protons), 6.83 (1H, *d*, *J* 6Hz, C-6), 8.02 (1H, *d*, *J* 6Hz, C-5), 8.02 (1H, s, C-2). UV λ_{max} nm (log ϵ): 284 (4.37).

7-(2-*Furoylamino*)*imidazo*[4,5-b]*pyridine*(**3**). Yield, 58%, mp >300. (Found: C, 58.06; H, 3.66; N, 24.48. $C_{11}H_8O_2N_4$ requires: C, 57.89; H, 3.53; N, 24.55%). IR (KBr) cm^{-1}: 1680, 1520 (–CONH–). NMR(D_2O–NaOD) δ: 6.60 (1H, *q*, furan ring proton), 7.00 (1H, *d*, furan ring proton), 7.60 (1H, *d*, furan ring proton), 6.85 (1H, *d*, *J* 5Hz, C-6), 8.05 (1H, *d*, *J* 5Hz, C-5), 8.02 (1H, s, C-2). UV λ_{max} nm (log ϵ): 292 (4.49).

4-*Propionylaminoimidazo*[4,5-c]*pyridine hydrochloride*(**4**). Yield, 30%, mp 230–232° (Found: C, 46.91; H, 4.71; N, 24.59. $C_9H_9ON_4$ HCl requires: C, 47.68; H, 4.86; N, 24.72%). IR (KBr) cm^{-1}: 1705, 1565 (–CONH–). NMR(D_2O–NaOD) δ: 1.15 (3H, *t*, –Me), 2.67 (2H, *q*, $-COCH_2-$), 7.56 (1H, *d*, *J* 7Hz, C-7), 7.92 (1H, *d*, *J* 7Hz, C-6), 8.38 (1H, s, C-2). UV λ_{max} nm (log ϵ): 283 (3.98).

4-*Butyrylaminoimidazo*[4,5-c]*pyridine hydrochloride*(**5**). Yield, 17%, mp 295–297° (Found: C, 49.21; H, 5.48; N, 22.72. $C_{10}H_{11}ON_4$ HCl requires: C, 49.89; H, 5.48; N, 23.28%). IR (KBr) cm^{-1}: 1705, 1580 (–CONH–). NMR(D_2O–NaOD) δ: 0.97 (3H, *t*, –Me), 1.70 (2H, *m*, $-CH_2-$), 2.66 (2H, *t*, $-COCH_2-$), 7.66 (1H, *d*, *J* 6Hz, C-7), 7.96 (1H, *d*, *J* 6Hz, C-6), 8.40 (1H, s, C-2). UV λ_{max} nm (log ϵ): 283 (3.96).

4-*Pentanoylaminoimidazo*[4,5-c]*pyridine*(**6**). Yield, 61%, mp 163–164° (Found: C, 60.78; H, 6.48; N, 25.60. $C_{11}H_{13}ON_4$ requires: C, 60.53; H, 6.47; N, 25.67%). IR (KBr) cm^{-1}: 1665, 1552 (–CONH–). NMR(D_2O–NaOD) δ: 0.90 (3H, *t*, –Me), 1.56 [4H, *m*, $-(CH_2)_2-$], 2.47 (2H, *t*, $-COCH_2-$), 7.40 (1H, *d*, *J* 6Hz, C-7), 7.85 (1H, *d*, *J* 6Hz, C-6), 8.03 (1H, s, C-2). UV λ_{max} nm (log ϵ): 282 (4.004).

4-*Hexanoylaminoimidazo*[4,5-c]*pyridine*(**7**). Yield, 43%, mp 162–162.5° (Found: C, 61.96; H, 6.91; N, 24.06. $C_{12}H_{15}ON_4$ requires: C, 62.05; H, 6.94; N, 24.12%). IR (KBr) cm^{-1}: 1670, 1560 (–CONH–). NMR(D_2O–NaOD) δ: 0.92 (3H, *t*, –Me), 1.40 [6H, *m*, $-(CH_2)_3-$], 2.55 (2H, *t*, $-COCH_2-$), 7.50 (1H, *d*, *J* 6Hz, C-7), 7.95 (1H, *d*, *J* 6Hz, C-6), 8.10 (1H, s, C-2). UV λ_{max} nm (log ϵ): 282 (4.017).

4-*Benzoylaminoimidazo*[4,5-c]*pyridine*(**8**). Yield, 70%, mp 97–99° (Found: C, 65.65; H, 4.36; N, 23.55. $C_{13}H_{10}ON_4$ requires: C, 65.53; H, 4.23; N, 23.52%). IR (KBr) cm^{-1}: 1680, 1535 (–CONH–). NMR(D_2O–NaOD) δ: 7.60 (3H, *m*, C_6H_5 ring protons), 8.15 (2H, *m*, C_6H_5 ring protons), 7.63 (1H, *d*, *J* 6Hz, C-7), 8.17 (1H, *d*, *J* 6Hz, C-6), 8.35 (1H, s, C-2). UV λ_{max} nm (log ϵ): 292 (4.14).

4-(2-*Furoylamino*)*imidazo*[4,5-c]*pyridine*(**9**). Yield, 43%, mp 101–103° (Found: C, 57.87; H, 3.56; N, 24.43. $C_{11}H_8O_2N_4$ requires: C, 57.89; H, 3.53; N, 24.55%). IR (KBr) cm^{-1}: 1680, 1530 (–CONH–). NMR(D_2O–NaOD) δ: 6.65 (1H, *q*, furan ring proton), 7.05 (1H, *d*, furan ring proton), 7.68 (1H, *d*, furan ring proton), 7.36 (1H, *d*, *J* 6Hz, C-7), 7.88 (1H, *d*, *J* 6Hz, C-6), 8.03 (1H, s, C-2). UV λ_{max} nm (log ϵ): 297 (4.13).

7-*Propionylaminoimidazo*[4,5-c]*pyridine*(**10**). Yield, 37%, mp 253–255° (Found: C, 56.08; H, 5.31; N, 28.96. $C_9H_{10}ON_4$ requires: C, 56.83; H, 5.30; N, 29.46%). IR (KBr) cm^{-1}: 1655, 1545 (–CONH–). NMR(D_2O–NaOD) δ: 1.73 (3H, *t*, –Me), 2.49 (2H, *q*, $-CH_2-$), 8.19 (1H, s, C-6), 8.26 (1H, s, C-4), 8.67 (1H, s, C-2). UV λ_{max} nm (log ϵ): 265 (3.99).

7-*Butyrylaminoimidazo*[4,5-c]*pyridine*(**11**). Yield, 33%, mp 267–268° (Found: C, 58.53; H, 5.89; N, 27.05. $C_{10}H_{12}ON_4$ requires: C, 58.81; H, 5.92; N, 27.44%). IR (KBr) cm^{-1}: 1640, 1530 (–CONH–). NMR(D_2O–NaOD) δ: 1.00 (3H, *t*, Me), 1.64 (2H, *m*, $-CH_2-$), 2.50 (2H, *t*, $-COCH_2-$), 8.09 (1H, s, C-6), 8.13 (1H, s, C-4), 8.67 (1H, s, C-2). UV λ_{max} nm (log ϵ): 265 (3.99).

7-*Pentanoylaminoimidazo*[4,5-c]*pyridine*(**12**). Yield, 95%, mp 266–267° (Found: C, 60.52; H, 6.46; N, 25.58. $C_{11}H_{14}ON_4$ requires: C, 60.53; H, 6.47; N, 25.67%). IR (KBr) cm^{-1}: 1650, 1535 (–CONH–). NMR(D_2O–NaOD) δ: 0.87 (3H, *t*, Me), 1.60 [4H, *m*, $-(CH_2)_2-$], 2.47 (2H, *t*, $-COCH_2-$), 8.06 (1H, s, C-6), 8.13 (1H, s, C-4), 8.67 (1H, s, C-2). UV λ_{max} nm (log ϵ): 265 (4.00).

7-*Hexanoylaminoimidazo*[4,5-c]*pyridine*(**13**). Yield, 58%, mp 262–263° (Found: C, 61.86; H, 6.88; N, 23.93. $C_{12}H_{16}ON_4$ requires: C, 62.05; H, 6.94; N, 24.12%). IR (KBr) cm^{-1}: 1645, 1535 (–CONH–). NMR(D_2O–NaOD) δ: 0.83 (3H, *t*, –Me), 1.33 [6H, *m*, $-(CH_2)_3-$], 2.67 (2H, *t*, $-COCH_2-$), 8.09 (1H, s, C-6), 8.16 (1H, s, C-4), 8.67 (1H, s, C-2). UV λ_{max} nm (log ϵ): 265 (4.017).

7-*Benzoylaminoimidazo*[4,5-c]*pyridine*(**14**). Yield, 77%, mp 275.5° (Found: C, 65.29; H, 4.26; N, 23.36. $C_{13}H_{10}ON_4$ requires: C, 65.53; H, 4.23; N, 23.52%). IR (KBr) cm^{-1}: 1650, 1535 (–CONH–). NMR(D_2O–NaOD) δ: 7.67 (3H, *m*, C_6H_5 ring protons), 8.03 (2H, *m*, C_6H_5 ring protons), 8.33 (1H, s, C-6), 8.60 (1H, s, C-4), 8.83 (1H, s, C-2). UV λ_{max} nm (log ϵ): 280 (4.066).

7-*Phenylacetylaminoimidazo*[4,5-c]*pyridine*(**15**). Yield, 67%, mp 259–260° (Found: C, 66.39; H, 4.89; N, 22.09. $C_{14}H_{12}ON_4$ requires: C, 66.65; H, 4.79; N, 22.21%). IR (KBr) cm^{-1}: 1650, 1550 (–CONH–). NMR(D_2O–NaOD) δ: 3.80 (2H, s, CH_2), 7.30 (5H, s, C_6H_5 ring protons), 8.17 (1H, s, C-6), 8.63 (1H, s, C-4), 8.67 (1H, s, C-2). UV λ_{max} nm (log ϵ): 267 (3.92).

7-(2-*Furoylamino*)*imidazo*[4,5-c]*pyridine*(**16**). Yield, 51%, mp 257–258° (Found: C, 57.71; H, 3.58; N, 24.71. $C_{11}H_8O_2N_4$ requires: C, 57.89; H, 3.53; N, 24.55%). IR (KBr) cm^{-1}: 1680, 1535 (–CONH–). NMR(D_2O–NaOD) δ: 6.70 (1H, *q*, furan ring proton), 7.37 (1H, *d*, furan ring proton), 7.92 (1H, *q*, furan ring proton), 8.33 (1H, s, C-6), 8.63 (1H, s, C-4), 8.80 (1H, s, C-2). UV λ_{max} nm (log ϵ): 293 (4.18).

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