A SYNTHESIS OF 1,2,3,4-TETRAHYDRO-1,6-NAPHTHYRIDINES

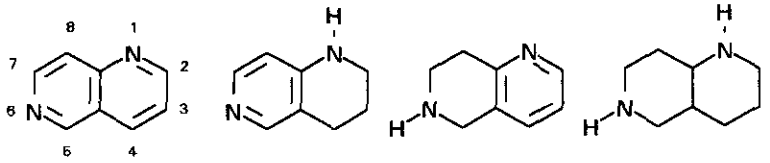
Pedro J. Victory*, Jordi Teixidó, and José I. Borrell

CETS Institut Químic de Sarrià (Universitat Ramon Llull), Departament de Química Orgànica, E-08017 Barcelona, Spain

Abstract- 8-Cyano-3,4-dihydro-1,6-naphthyridin-2(1*H*)-ones were obtained by nucleophilic substitution of the methoxyl group of 5-cyano-3,4-dihydro-6-methoxy-2(1*H*)-pyridones (**5a-d**) by malononitrile or cyanoacetamide followed by cyclization in acidic or basic medium.

INTRODUCTION

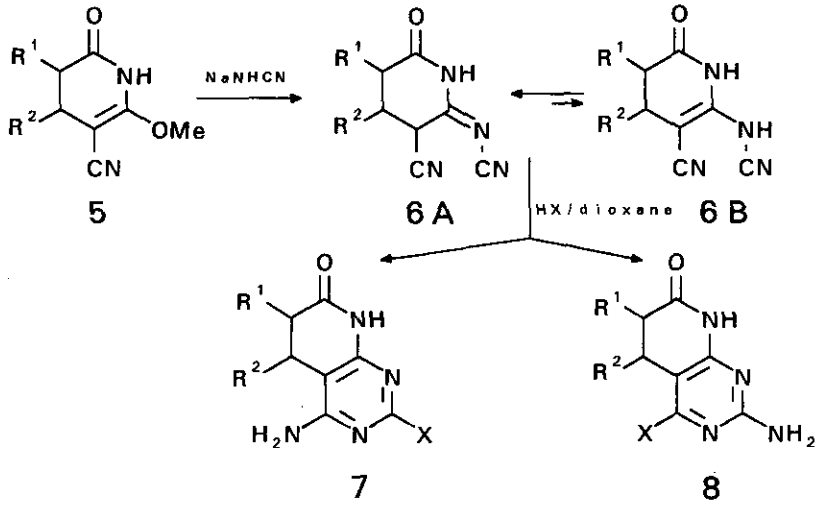
1,6-Naphthyridines (pyrido[4,3-*b*]pyridines) have received relatively little attention although they show a wide range of biological activities.[1] According to the degree of unsaturation of the rings, they can be classified in four groups; totally aromatic 1,6-naphthyridines (**1**), 1,2,3,4-tetrahydro-1,6-naphthyridines (**2**), 5,6,7,8-tetrahydro-1,6-naphthyridines (**3**), and decahydro-1,6-naphthyridines (**4**).



1 2 3 4

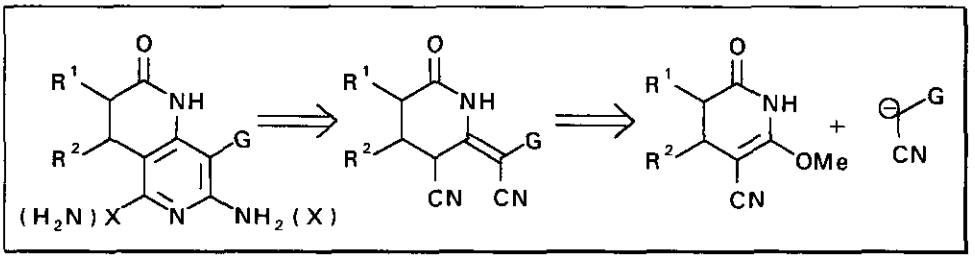
The first group collects the largest number of reported compounds,[2] the rest of them being very scarce and generally appearing fused to other rings. In particular, three different strategies have been used for the synthesis of 1,2,3,4-tetrahydro-1,6-naphthyridines (**2**); the most employed one involves the construction of the saturated ring starting from a pyridine ring.[3] The partial hydrogenation[4] of **1**, and the formation of the pyridine ring starting from a functionalized piperidine[5] have also been described.

During the past years our group has developed[6] a synthesis of 5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidines based on the cyclization of dinitriles in acid medium[7] (*Scheme* **1**).Thus, the substitution of the enol methoxy group of **5** yields the dinitrile system (**6**), which only appears as the tautomer form (**6A**). The treatment of **6** with hydrogen halide in dioxane affords the 4-amino-2-halo- or the 2-halo-4-aminopyrido[2,3-*d*]pyrimidine, (**7**) or (**8**), depending on the halide and the thermal level employed. These results are independent of the nature of the substituents R^1 and R^2.



Scheme 1

The versatility of this procedure and the retro-synthetic analysis of the 1,2,3,4-tetrahydro-1,6-naphthyridine skeleton depicted in Scheme 2 prompted us to consider the pyridones (**5**) as starting materials for the synthesis of 3,4-dihydro-1,6-naphthyridin-2(1*H*)-ones.

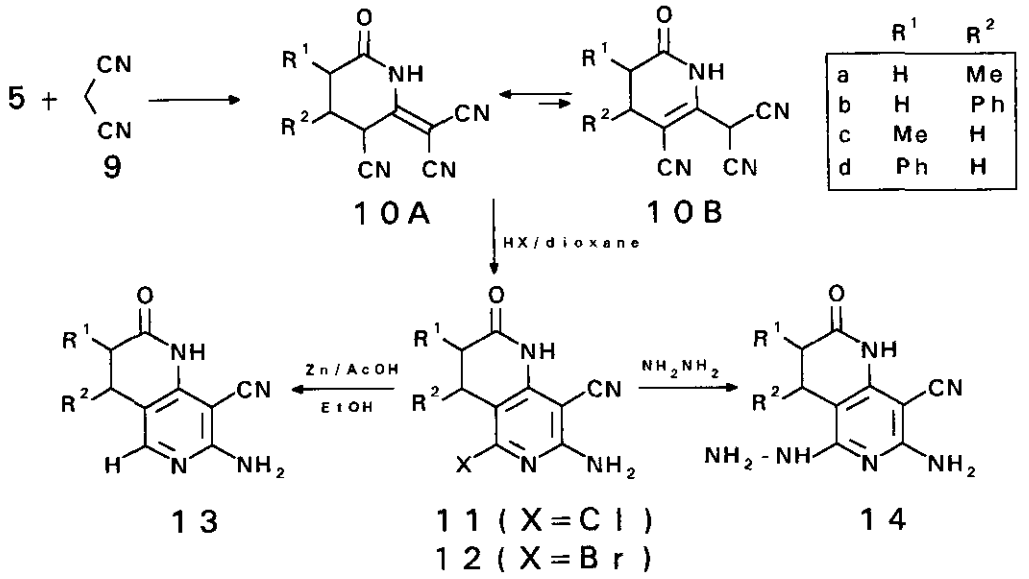


Scheme 2

RESULTS AND DISCUSSION

Now we wish to report that the treatment of the pyridones (**5a-d**) with malononitrile (**9**) yielded the corresponding substitution products as the sole tautomer form (**10A**). Cyclization of **10a-d** in acidic medium (HCl, HBr / dioxane or dioxane/benzene) afforded the corresponding 7-amino-5-halo-8-cyano-3,4-dihydro-1,6-naphthyridin-2(1*H*)-ones, (**11a-d**) or (**12a-d**), in high yield (Scheme 3). The direction of the cyclization is independent of the hydrogen halide, the thermal level employed and the nature of the substituents R^1 and R^2. This behavior, examined in the light of our previous findings,[6] suggests that the reaction proceeds through the tautomer (**10B**). The structures (**11**) and (**12**) have been confirmed both chemically and spectroscopically. Thus, the dehalogenation of **11a-d** and **12a-d** yielded the same product, (**13a-d**), confirming that the halogens are at the same position. Furthermore, the substitution by hydrazine afforded **14a-d** which confirms that the halogen is not in the neighborhood of the cyano group at C-8

(otherwise, the cyclization of the hydrazine substituent and the cyano group would have taken place). On the other hand, the ^{13}C nmr chemical shifts of the pyridine ring carbons (C-4a, C-5, C-7, C-8, and C-8a) are very similar for both structures (Table 1). Finally, the X-ray diffraction study[8] of **12a** has confirmed the 7-amino-5-halo structure of the cyclization products.



Scheme 3

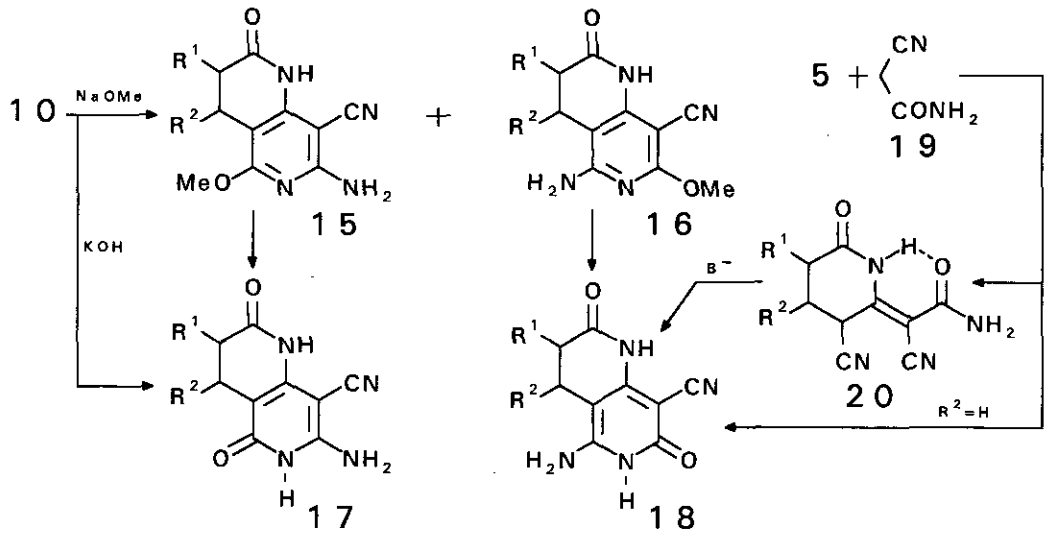
It is interesting to point out that the cyclization of **10a-d** in basic medium (NaOMe/MeOH) yielded the two possible positional isomers (**15a-d**) and (**16a-d**) (Scheme 4). **15b,d** were also accessible by substitution of the bromine of **12b,d** by sodium methoxide . The yields of **16a,b** were higher than those of **15a,b** probably due to the steric hindrance that implies the presence of R^2 for the attack of the nucleophile. Surprisingly , while the cyclizations of **10a,c** (R=Me) proceed without difficulties, **10b,d** (R=Ph) afforded the dipyridones (**17b,d**) and (**18b,d**) due to the hydrolysis or transetherification[9] of **15b,d** and **16b,d.**

Several assays were carried out in order to minimize the formation of **17b,d** and **18b,d.** Thus, when the NaOMe was generated "in situ" (0.1 mol of Na in 50 ml of MeOH), **10b** gave **18b** in 85% yield using MeOH dried with sodium, or in 75% yield when it was distilled over dimethyl phthalate. Its formation was avoided to a large extent only when commercial NaOMe in anhydrous MeOH was used.

The structure of the dipyridones **17** and **18** were ensured chemically. Thus, the treatment of **10a-d** with aqueous KOH afforded **17a-d.** On the other hand, while the treatment of **5a,b** with cyanoacetamide (**19**) gave **20a,b** (R^1=H, R^2=Me, Ph), **5c,d** directly afforded the naphthyridines (**18c,d**; R^1=Me, Ph, R^2=H). As it can be seen, a substituent R^2 causes the reaction to stop at the open intermediate **20** in normal reaction conditions. Nevertheless, the ulterior treatment of **20a,b** in basic medium (OH^-/H_2O, RO^-/ROH) gave **18a,b** quantitatively by

intramolecular cyclization of the amide group and the cyano group.

Once the intermediates (**20**) were obtained, the treatment with hydrogen halide was assayed in order to obtain the corresponding naphthyridines.



Scheme 4

Surprisingly, whatever it may be the hydrogen halide, the solvent or the thermal level employed, **20** was recovered unaltered in all the cases. We consider the presence of a strong intramolecular hydrogen bond between the amide carbonyl group and the cyclic N-H group (δ N-H = 8.7 for **10** and δ N-H = 12.5 for **20**) as a possible reason for this anomalous behavior. This hydrogen bridge would lead to a greater rigidity of the molecule which would preclude the short lived imidoyl halide of the α-amide nitrile to reach the non coplanar cyano group.

ACKNOWLEDGEMENT

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EXPERIMENTAL

Melting points were taken on a Büchi-Tottoli apparatus and are uncorrected. Ir spectra (KBr) were measured on a Perkin-Elmer 683 or on a Bomem Michelson-100 FTIR. ^{1}H and ^{13}C nmr spectra were recorded on a Bruker AC-80 and on a Varian XL-200/F19 (*Universitat de Barcelona*) in DMSO-d_6 (or TFA-d whenever reported). Chemical shifts are expressed as δ (ppm) values relative to tetramethylsilane (TMS) as the internal reference standard; coupling constants (J) are given in Hz. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quadriplet, m = multiplet, bs = broad signal. Mass spectra were obtained on a Hewlett-Packard 5995 A spectrometer with an electron beam of 70 eV. Microanalyses were performed at the *Institut de Química Bio-Orgànica del C.S.I.C.*

(Barcelona).

5-Cyano-3,4-dihydro-6-methoxy-2(1H)-pyridones **(5a-d).** The starting pyridones (**5a-d**) were obtained as previously described by our group.[6a]

5-Cyano-6-dicyanomethylene-2-piperidones **(10a-d). General Procedure:** A mixture of 0.050 mol of the corresponding pyridone (**5a-d**), 0.050 mol of malononitrile (**9**) and 0.050 mol of sodium in 300 ml of anhydrous dioxane and 5 drops of methanol, was heated under reflux for the time (t) indicated in each case. Then, the dark solid obtained was filtered off, suspended in 60 ml of ethanol and neutralized with an equimolar amount of ethanolic HCl. The solid obtained was filtered and the mother liquor was concentrated *in vacuo* to give an extra crop of solid. The combined solids were washed with water, ethanol, and ether, and dried *in vacuo* over phosphorous pentoxide. The crude piperidones (**10a-d**) were recrystallized from AcOEt/EtOH or AcOEt/hexane.

5-Cyano-6-dicyanomethylene-4-methyl-2-piperidone **(10a).**- t = 19 h, yield: 8.40 g (84 %), as a mixture of diastereoisomers *cis:trans* 2:5 (^{1}H nmr), mp 177-179 ^{o}C. Ir ν: 3235, and 3170 (N-H), 2250, 2240, and 2225 (CN), 1750, and 1735 (C=O), and 1595 cm^{-1} (C=C). ^{1}H Nmr δ: 1.08 and 1.15 (3H, 2d, J= 6 Hz, Me), 2.1-2.9 (3H, m, H-3 and H-4), 4.5 and 4.7 (1H, 2d, J= 6 Hz, C<u>H</u>-CN, deuterable), and 8.8 (1H, bs, N-H, deuterable). ^{13}C Nmr δ: 186.6 (C-2), 35.5 (C-3), 27.0 (C-4), 34.5 (C-5), 161.5 (C-6), 61.9 [<u>C</u>(CN)$_2$], 113.8, 112.8, and 111.1 (CN), 17.2 (Me). Ms, m/z (%): 200 (M$^+$, 7), 69 (100). *Anal.* Calcd for $C_{10}H_8N_4O$: C , 60.00; H, 4.03; N, 27.98. Found: C, 59.74; H, 3.97; N, 28.07.

5-Cyano-6-dicyanomethylene-4-phenyl-2-piperidone **(10b).**- t = 1.5 h, yield: 12.18 g (93 %), mp 251-253 ^{o}C. Ir ν: 3230, and 3150 (N-H), 2250, 2235, and 2225 (CN), 1750, and 1725 (C=O), and 1605 cm^{-1} (C=C). ^{1}H Nmr δ: 3.0 (1H, m, H-3), 3.5 and 4.0 (2H, 2m, H-4), 4.6-5.0 (1H, m, C<u>H</u>-CN, deuterable), 7.5 (5H, m, Ph), and 8.7 (1H, bs, N-H, deuterable). ^{13}C Nmr δ: 169.0 (C-2), 32.6 (C-3), 35.7 (C-4), 36.3 (C-5), 160.1 (C-6), 68.1 [<u>C</u>(CN)$_2$], 114.0, 113.0, and 111.2 (CN), 136.7, 127.6, 127.3, and 126.8 (Ph). Ms, m/z (%): 262 (M$^+$, 10), 220 (38), 131 (100), 103 (30).

5-Cyano-6-dicyanomethylene-3-methyl-2-piperidone **(10c).**- t = 13 h, yield: 6.00 g (60 %), mp 160-163 ^{o}C. Ir ν: 3250, and 3150 (N-H), 2230 (CN), 1725 (C=O), and 1600 cm^{-1} (C=C). ^{1}H Nmr δ: 1.18 (3H, d, J=6 Hz, Me), 2.3 (2H, m, H-4), 2.6 (1H, m, H-3), 4.8 (1H, bs, C<u>H</u>-CN, deuterable), and 8.5 (1H, bs, N-H, deuterable). ^{13}C Nmr δ: 171.8 (C-2), 32.9 (C-3), 28.3 (C-4), 28.9 (C-5), 162.2 (C-6), 60.7 [<u>C</u>(CN)$_2$], 116.1, 113.1, and 111.2 (CN), 14.4 (Me). Ms, m/z (%): 200 (M$^+$, 9), 69 (100). *Anal.* Calcd for $C_{10}H_8N_4O$: C , 60.00; H, 4.03; N, 27.98. Found: C, 60.32; H, 3.85; N, 28.25.

5-Cyano-6-dicyanomethylene-3-phenyl-2-piperidone **(10d).**- t = 2 h, yield: 9.85 g (75 %), mp 199-201 ^{o}C. Ir ν: 3250, and 3165 (N-H), 2230 (CN), 1745 (C=O), and 1600 cm^{-1} (C=C). ^{1}H Nmr δ: 2.7 (2H, m, H-4), 4.1 (1H, m, H-3), 4.9 (1H, bs, C<u>H</u>-CN, deuterable), 7.4 (5H, bs, Ph), and 9.0 (1H, bs, N-H, deuterable). ^{13}C Nmr δ: 170.5 (C-2), 44.4 (C-3), 28.4 (C-4), 29.1 (C-5), 162.3 (C-6), 64.0 [<u>C</u>(CN)$_2$], 116.2, 113.5, and 111.5 (CN), 137.2, 129.2, 129.0, and 128.0 (Ph). Ms, m/z (%): 262 (M$^+$, 83), 233 (100), 131 (24), 103 (52). *Anal.* Calcd for $C_{15}H_{10}N_4O$: C , 68.70; H, 3.84; N, 21.36. Found: C, 68.31; H, 3.91; N, 21.36.

7-Amino-8-cyano-5-halo-3,4-dihydro-1,6-naphthyridin-2(1H)-ones **(11a-d, X=Cl) and (12a-d, X=Br). General Procedure:** A stream of anhydrous hydrogen chloride or hydrogen bromide was bubbled through a suspension of 0.01 mol of the corresponding piperidone **10a-d** in 150 ml of the solvent "S" at the temperature "T" until

saturation (1-2 h). The stream was maintained for 0.5-1 h, then was stopped and the mixture was stirred at room temperature for 1 h and for 24 h in a closed vessel. The hydrochloride or hydrobromide of the cyclization product was filtered and the solution was concentrated *in vacuo* to give a crude solid. Both solids were treated separately as follows. The solid is suspended in methanol and neutralized with methanolic ammonia solution. The solid obtained was filtered, washed with water, cold ethanol, and ether, and dried *in vacuo* over phosphorous pentoxide. The crude naphthyridines **11a-d** (X=Cl) and **12a-d** (X=Br) were recrystallized from ethanol.

7-Amino-5-chloro-8-cyano-3,4-dihydro-4-methyl-1,6-naphthyridin-2(1H)-one **(11a).**- S =dioxane/benzene 4:3, T =room temperature, yield: 2.08 g (88 %), mp 236-238 °C. Ir ν: 3405, 3340, 3320, and 3225 (N-H), 2220 (CN), 1690 (C=O), 1645, 1615, and 1555 cm^{-1}. ^1H Nmr δ: 1.1 (3H, d, J=7 Hz, Me), 2.5-3.5 (3H, m, H-3 and H-4), 7.0 (2H, bs, NH_2, deuterable), and 10.4 (1H, bs, N-H, deuterable). ^{13}C Nmr see Table 1. Ms, m/z (%): 238 (M^++2, 10), 236 (M^+, 28), 223 (35), 221 (100), 186 (10). *Anal.* Calcd for $C_{10}H_9N_4OCl$: C , 50.75; H, 3.83; N, 23.67; Cl, 14.98. Found: C, 50.70; H, 3.80; N, 23.80; Cl, 14.95.

7-Amino-5-chloro-8-cyano-3,4-dihydro-4-phenyl-1,6-naphthyridin-2(1H)-one **(11b).**- S =dioxane/benzene 1:1, T =5 °C, yield: 2.44 g (82 %), mp 284-286 °C. Ir ν: 3415, 3380, 3300, and 3180 (N-H), 2215 (CN), 1710 (C=O), 1640, 1600, and 1565 cm^{-1}. ^1H Nmr δ: 2.7 (1H, m, H-3), 3.2 (1H, m, H-3), 4.6 (1H, m, H-4), 6.7 (2H, bs, NH_2, deuterable), 7.2 (5H, m, Ph), and 10.6 (1H, bs, N-H, deuterable). ^{13}C Nmr see Table 1. Ms, m/z (%): 300 (M^++2, 8), 298 (M^+, 24), 223 (35), 221 (100). *Anal.* Calcd for $C_{15}H_{11}N_4OCl$: C , 60.31; H, 3.71; N, 18.75; Cl, 11.87. Found: C, 60.15; H, 3.69; N, 18.85; Cl, 11.75.

7-Amino-5-chloro-8-cyano-3,4-dihydro-3-methyl-1,6-naphthyridin-2(1H)-one **(11c).**- S =dioxane, T =5°C, yield: 2.19 g (93 %), mp 302-305 °C. Ir ν: 3480, 3390, 3290, and 3150 (N-H), 2215 (CN), 1700 (C=O), 1640, 1600, and 1565 cm^{-1}. ^1H Nmr δ: 1.15 (3H, d, J=7 Hz, Me), 2.3-3.2 (3H, m, H-3 and H-4), 6.8 (2H, bs, NH_2, deuterable), and 10.4 (1H, bs, N-H, deuterable). ^{13}C Nmr see Table 1. Ms, m/z (%): 238 (M^++2, 31), 236 (M^+, 99), 210 (11), 208 (32), 173 (68), 145 (100). *Anal.* Calcd for $C_{10}H_9N_4OCl$: C , 50.75; H, 3.83; N, 23.67; Cl, 14.98. Found: C, 50.67; H, 3.68; N, 23.86; Cl, 14.99.

7-Amino-5-chloro-8-cyano-3,4-dihydro--3-phenyl-1,6-naphthyridin-2(1H)-one **(11d).**- S =dioxane/benzene 1:1, T =5 °C, yield: 2.80 g (94 %), mp >300 °C. Ir ν: 3445, 3380, 3310, and 3205 (N-H), 2210 (CN), 1695 (C=O), 1625, 1600, and 1555 cm^{-1}. ^1H Nmr δ: 3.1 (2H, m, H-4), 4.0 (1H, m, H-3), 6.9 (2H, bs, NH_2, deuterable), and 7.25 (5H, m, Ph). ^{13}C Nmr see Table 1. Ms, m/z (%): 300 (M^++2, 32), 298 (M^+, 100), 223 (16), 221 (45), 118 (52). *Anal.* Calcd for $C_{15}H_{11}N_4OCl$: C , 60.31; H, 3.71; N, 18.75; Cl, 11.87. Found: C, 60.13; H, 3.67; N, 18.67; Cl, 11.80.

7-Amino-5-bromo-8-cyano-3,4-dihydro-4-methyl-1,6-naphthyridin-2(1H)-one **(12a).**- S =dioxane/benzene 1:1, T =5°C, yield: 2.53 g (90 %), mp >300 °C. Ir ν: 3480, 3430, 3300, and 3180 (N-H), 2220 (CN), 1710 (C=O), 1630, 1595, and 1555 cm^{-1}. ^1H Nmr δ: 1.1 (3H, d, J=7 Hz, Me), 2.0-3.0 (3H, m, H-3 and H-4), 7.0 (2H, bs, NH_2, deuterable), and 10.2 (1H, bs, N-H, deuterable). ^{13}C Nmr see Table 1. Ms, m/z (%): 282 (M^++2, 25), 280 (M^+, 27), 267 (100), 265 (99), 186 (93). *Anal.* Calcd for $C_{10}H_9N_4OBr$: C , 42.73; H, 3.23; N, 19.93; Br, 28.43. Found: C, 42.70; H, 3.11; N, 20.18; Br, 28.31.

7-Amino-5-bromo-8-cyano-3,4-dihydro-4-phenyl-1,6-naphthyridin-2(1H)-one **(12b).**- S =dioxane/benzene 1:1, T =5 °C, yield: 3.29 g (96 %), mp >300 °C. Ir ν: 3410, 3380, 3300, and 3180 (N-H), 2215 (CN), 1710 (C=O), 1635, 1595, and 1560 cm^{-1}. ^1H Nmr δ: 2.7 (1H, m, H-3), 3.2 (1H, m, H-3), 4.4 (1H, m, H-4), 7.2 (2H, bs, NH_2, deuterable), 7.2 (5H, m, Ph), and 10.5 (1H, bs, N-H, deuterable). ^{13}C Nmr see Table 1. Ms, m/z (%): 344

($M^+ + 2$, 77), 342 (M^+, 76), 267 (100), 265 (93). *Anal.* Calcd for $C_{15}H_{11}N_4OBr$: C , 52.50; H, 3.23; N, 16.32; Br, 23.28. Found: C, 52.60; H, 3.26; N, 16.30; Br, 23.12.

***7-Amino-5-bromo-8-cyano-3,4-dihydro-3-methyl-1,6-naphthyridin-2(1H)-one* (12c).**- S =dioxane/benzene 1:1, T =5°C, yield: 2.19 g (78 %), mp 290-292 °C. Ir ν: 3480, 3370, 3315, and 3175 (N-H), 2220 (CN), 1715 (C=O), 1645, 1595, and 1555 cm^{-1}. ^1H Nmr δ: 1.15 (3H, d, J=7 Hz, Me), 2.6 (2H, m, H-4), 2.95 (1H, m, H-3), 7.0 (2H, bs, NH_2, deuterable), and 10.2 (1H, bs, N-H, deuterable). ^{13}C Nmr see Table 1. Ms, m/z (%): 282 ($M^+ + 2$, 68), 280 (M^+, 71), 254 (10), 252 (11), 145 (100). *Anal.* Calcd for $C_{10}H_9N_4OBr$: C , 42.73; H, 3.23; N, 19.93; Br, 28.43. Found: C, 42.85; H, 3.10; N, 20.15; Br, 28.15.

***7-Amino-5-bromo-8-cyano-3,4-dihydro--3-phenyl-1,6-naphthyridin-2(1H)-one* (12d).**- S =dioxane/benzene 1:1, T =5 °C, yield: 3.40 g (99 %), mp >300 °C. Ir ν: 3445, 3385, 3305, and 3205 (N-H), 2215 (CN), 1695 (C=O), 1625, 1600, and 1550 cm^{-1}. ^1H Nmr δ: 3.1 (2H, d, J=8 Hz, H-4), 4.1 (1H, q, J=8 Hz, H-3), 7.1 (2H, bs, NH_2, deuterable), and 7.3 (5H, s, Ph). ^{13}C Nmr (TFA-d) see Table 1. Ms, m/z (%): 344 ($M^+ + 2$, 99), 342 (M^+, 100), 267 (50), 265 (51), 118 (52). *Anal.* Calcd for $C_{15}H_{11}N_4OBr$: C , 52.50; H, 3.23; N, 16.32; Br, 23.28. Found: C, 52.47; H, 3.20; N, 16.24; Br, 23.17.

	11a	11b	11c	11d	12a	12b	12c	12d
C-2	170.3	169.3	173.4	171.5	169.9	169.0	173.4	177.2
C-3	37.3	38.7	33.9	45.2	37.3	39.9	33.9	46.9
C-4	27.7	37.7	29.0	28.9	29.9	38.7	31.3	31.8
C-4a	110.2	107.6	105.4	105.5	112.4	110.0	108.0	111.4
C-5	151.5	152.5	151.0	151.6	144.7	146.1	144.6	138.0
C-7	159.6	159.6	159.1	159.6	158.9	159.2	158.9	157.7
C-8	76.4	76.5	76.0	76.1	76.6	76.8	76.3	80.0
C-8a	150.2	151.1	151.2	150.8	148.9	150.2	150.4	158.9
CN	114.2	114.0	114.2	114.2	113.8	113.8	114.1	114.4
R	18.3	140.9 128.9 127.1 126.6	14.8	138.2 128.7 128.5 127.4	18.3	140.7 128.5 126.9 126.6	14.7	133.4 130.9 130.3 129.3

Table 1: ^{13}C Nmr spectral data of naphthyridines 11a-d and 12a-d

Dehalogenation of 11a-d and 12a-d. General Procedure: A mixture of 0.002 mol of the corresponding 5-halonaphthyridine (**11a-d** *or* **12a-d**), 1.3 g (0.02 mol) of zinc powder, 2 ml of acetic acid, 7 ml of 2 M sulfuric acid and 40 ml of ethanol was heated at reflux for "t" h. The solution was filtered and the ethanol was eliminated *in vacuo*. The remaining liquid was neutralized carefully with concentrated sodium hydroxide solution. The precipitate was filtered, washed with water and dried *in vacuo* over phosphorous pentoxide. The crude solid was recrystallized from ethanol to give pure **13a-d**.

***7-Amino-8-cyano-3,4-dihydro-4-methyl-1,6-naphthyridin-2(1H)-one* (13a).**- a) Starting from **11a**: t = 10 h, yield: 94 %, mp 225-227 °C. Ir ν: 3385, 3330, 3205, and 3145 (N-H), 2225 (CN), 1700 (C=O), 1655, 1620, and 1570 cm^{-1}. ^1H Nmr δ: 1.15 (3H, d, J=7 Hz, Me), 2.0-3.3 (3H, m, H-3 and H-4), 6.6 (2H, bs, NH_2, deuterable), and 7.9 (1H, s, H-5). ^{13}C Nmr δ: 170.7 (C-2), 38.3 (C-3), 26.9 (C-4), 113.4 (C-4a), 150.1 (C-5), 160.5 (C-7),

76.6 (C-8), 148.4 (C-8a), 114.8 (CN), and 19.6 (Me). Ms, m/z (%): 202 (M^+, 35), 187 (100). *Anal.* Calcd for $C_{10}H_{10}N_4O$: C , 59.40; H, 4.98; N, 27.71. Found: C, 59.50; H, 4.96; N, 27.83. b) Starting from **12a**: t = 1 h, yield: 97 %.

***7-Amino-8-cyano-3,4-dihydro-4-phenyl-1,6-naphthyridin-2(1H)-one* (13b).**- a) Starting from **11b**: t = 4 h, yield: 93 %, mp 254-256 °C. Ir ν: 3430, 3340, 3240, and 3160 (N-H), 2230 (CN), 1705 (C=O), 1655, 1625, and 1580 cm^{-1}. ^1H Nmr δ: 2.5-3.0 (2H, m, H-3), 4.3 (1H, m, H-4), 6.7 (2H, bs, NH_2, deuterable), 7.3 (5H, bs, Ph), and 7.7 (1H, s, H-5). ^{13}C Nmr δ: 169.8 (C-2), 38.2 (C-3), 37.2 (C-4), 111.2 (C-4a), 151.3 (C-5), 160.4 (C-7), 76.6 (C-8), 148.6 (C-8a), 114.5 (CN), 141.9, 128.7, 127.1, and 127.0 (Ph). Ms, m/z (%): 264 (M^+, 100), 187 (81). *Anal.* Calcd for $C_{15}H_{12}N_4O$: C , 68.17; H, 4.58; N, 21.20. Found: C, 68.32; H, 4.56; N, 21.40. b) Starting from **12b**: t = 1 h, yield: 67 %.

***7-Amino-8-cyano-3,4-dihydro-3-methyl-1,6-naphthyridin-2(1H)-one* (13c).**- a) Starting from **11c**: t = 16 h, yield: 52 %, mp 265-266 °C. Ir ν: 3480, 3310, and 3150 (N-H), 2215 (CN), 1695 (C=O), 1640, 1615, and 1575 cm^{-1}. ^1H Nmr δ: 1.1 (3H, d, J=6 Hz, Me), 2.0-2.9 (3H, m, H-3 and H-4), 6.4 (2H, bs, NH_2, deuterable), 7.8 (1H, s, H-5), and 10.3 (1H, bs, N-H, deuterable). ^{13}C Nmr δ: 173.3 (C-2), 34.5 (C-3), 28.5 (C-4), 108.2 (C-4a), 150.1 (C-5), 159.9 (C-7), 76.2 (C-8), 148.6 (C-8a), 114.4 (CN), and 14.8 (Me). Ms, m/z (%): 202 (M^+, 100), 187 (10). *Anal.* Calcd for $C_{10}H_{10}N_4O$: C , 59.40; H, 4.98; N, 27.71. Found: C, 59.33; H, 5.05; N, 27.34. b) Starting from **12c**: t = 16 h, afforded a mixture of **12c** and **13c**.

***7-Amino-8-cyano-3,4-dihydro-3-phenyl-1,6-naphthyridin-2(1H)-one* (13d).**- a) Starting from **11d**: t = 16 h, yield: 46 %, mp 285-286 °C. Ir ν: 3480, 3410, 3310, and 3200 (N-H), 2220 (CN), 1700 (C=O), 1640, 1615, and 1575 cm^{-1}. ^1H Nmr δ: 3.1 (2H, d, J=8 Hz, H-4), 3.9 (1H, t, J=8 Hz, H-4), 6.6 (2H, bs, NH_2, deuterable), 7.3 (5H, s, Ph), and 8.0 (1H, s, H-5). ^{13}C Nmr δ: 171.4 (C-2), 45.9 (C-3), 28.5 (C-4), 108.2 (C-4a), 150.5 (C-5), 160.0 (C-7), 76.6 (C-8), 148.6 (C-8a), 114.6 (CN), 138.2, 128.4, 128.1, and 127.0 (Ph). Ms, m/z (%): 264 (M^+, 100), 187 (34). *Anal.* Calcd for $C_{15}H_{12}N_4O$: C , 68.17; H, 4.58; N, 21.20. Found: C, 68.48; H, 4.68; N, 21.11. b) Starting from **12d**: t = 16 h, yield: 74 %.

Reaction of 11a-d and 12a-d with hydrazine. General Procedure: A mixture of 0.002 mol of the corresponding 5-halonaphthyridine (**11a-d** or **12a-d**), 10 g (0.2 mol) of 100% hydrazine hydrate and 20 ml of ethanol or dioxane was heated at reflux for "t" h. The solution was cooled and 15 ml of water were added. The precipitate was filtered, washed, with water, cool etanol and ether, and dried *in vacuo* over phosphorous pentoxide to give **14a-d**.

***7-Amino-8-cyano-5-hydrazino-3,4-dihydro-4-methyl-1,6-naphthyridin-2(1H)-one* (14a).**- a) Starting from **11a**: t = 20 h, yield: 40 %, mp 242-244 °C. Ir ν: 3425, 3360, 3325, and 3250 (N-H), 2205 (CN), 1695 (C=O), 1635, 1620, and 1580 cm^{-1}. ^1H Nmr δ: 0.95 (3H, d, J=6 Hz, Me), 2.1-3.1 (3H, m, H-3 and H-4), 6.3 (3H, bs, NH, deuterable), 7.1 (1H, bs, NH, deuterable), and 8.0 (2H, bs, NH, deuterable). ^{13}C Nmr δ: 169.7 (C-2), 37.4 (C-3), 23.3 (C-4), 94.5 (C-4a), 157.2 (C-5), 160.0 (C-7), 66.1 (C-8), 145.1 (C-8a), 116.5 (CN), and 18.1 (Me). Ms, m/z (%): 232 (M^+, 61), 217 (100). b) Starting from **12a**: t = 20 h, yield: 61 %.

***7-Amino-8-cyano-5-hydrazino-3,4-dihydro-4-phenyl-1,6-naphthyridin-2(1H)-one* (14b).**- a) Starting from **11b**: t = 1.5 h, yield: 41 %, mp 282-285 °C. Ir ν: 3490, 3390, and 3300 (N-H), 2195 (CN), 1705 (C=O), 1610, and 1560 cm^{-1}. ^1H Nmr δ: 2.5-3.3 (2H, m, H-3), 4.3 (1H, d, J=6 Hz, H-4), 6.4 (3H, bs, NH, deuterable), 7.1 (2H, NH, deuterable), 7.25 (5H, bs, Ph), and 7.9 (1H, bs, NH, deuterable). ^{13}C Nmr δ: 168.8 (C-2), 38.9 (C-3), 33.3 (C-4), 91.7 (C-4a), 157.5 (C-5), 160.3 (C-7), 66.2 (C-8), 146.6 (C-8a), 116.3 (CN), 141.5, 128.2, 126.7, and 126.5 (Ph). Ms, m/z (%): 294 (M^+, 50), 217 (100). b) Starting from **12b**: t = 1 h, yield: 68 %.

***7-Amino-8-cyano-5-hydrazino-3,4-dihydro-3-methyl-1,6-naphthyridin-2(1H)-one* (14c).**- a) Starting from **11c**: t = 17 h, yield: 30 %, mp 293-295 °C. Ir ν: 3440, 3375, 3330, and 3200 (N-H), 2200 (CN), 1700 (C=O), 1645, 1620, and 1575 cm^{-1}. ^1H Nmr δ: 1.15 (3H, d, J=7 Hz, Me), 2.2-2.9 (3H, m, H-3 and H-4), 6.3 (3H, bs, NH, deuterable), 6.5 (2H, bs, NH, deuterable), and 7.9 (1H, bs, NH, deuterable). ^{13}C Nmr δ: 168.6 (C-2), 34.1 (C-3), 24.3 (C-4), 89.4 (C-4a), 159.3 (C-5), 159.7 (C-7), 69.3 (C-8), 154.6 (C-8a), 116.9 (CN), and 15.9 (Me). Ms, m/z (%): 232 (M^+, 100), 215 (47). b) Starting from **12c**: t = 16 h, yield: 64 %.

***7-Amino-8-cyano-5-hydrazino-3,4-dihydro-3-phenyl-1,6-naphthyridin-2(1H)-one* (14d).**- a) Starting from **11d**: t = 2 h, yield: 75 %, mp 225-229 °C. Ir ν: 3480, 3360, 3320, and 3240 (N-H), 2195 (CN), 1635, 1610, and 1580 cm^{-1}. ^1H Nmr δ: 3.0-4.2 (3H, m, H-3 and H-4), 5.6 (3H, bs, NH, deuterable), 6.0 (2H, bs, NH, deuterable), 7.4 (5H, bs, Ph), and 9.3 (1H, bs, NH, deuterable). ^{13}C Nmr δ: 172.7 (C-2), 47.8 (C-3), 26.3 (C-4), 88.7 (C-4a), 159.4 (C-5), 160.1 (C-7), 66.5 (C-8), 154.3 (C-8a), 118.3 (CN), 141.0, 128.0, 127.7, and 126.6 (Ph). Ms, m/z (%): 294 (M^+, 53), 175 (100). b) Starting from **12d**: t = 1 h, yield: 85 %.

Cyclization of 10a-d in NaMeO/MeOH. General Procedure: A mixture of 0.005 mol of **10a-d** and 0.015 mol of NaMeO in 100 ml of methanol was heated at reflux for "t" h. Then the solvent was removed *in vacuo*, the solid obtained was solved in water and neutralized with 6 M HCl. The precipitate was filtered, washed with water, cold ethanol and ether, and was dried *in vacuo* over phosphorous pentoxide. The crude material was chromatographed (*AcOEt/ hexane, 2:3*) to separate **15a-d** and **16a-d.**

***7-Amino-8-cyano-3,4-dihydro-5-methoxy-4-methyl-1,6-naphthyridin-2(1H)-one* (15a) *and* *5-Amino-8-cyano-3,4-dihydro-7-methoxy-4-methyl-1,6-naphthyridin-2(1H)-one* (16a).**- t = 24 h, yields: 23 % (**15a**), 63 % (**16a**), mp 210-211 °C (**15a**), 240-241 °C (**16a**). *Anal.* Calcd for $C_{11}H_{12}N_4O_2$: C , 56.89; H, 5.21; N, 24.12. Found: C, 56.91; H, 5.35; N, 23.85. Ir (**15a**) ν: 3460, 3340, 3240, and 3180 (N-H), 2220 (CN), 1705 (C=O), 1630, and 1585 cm^{-1}. ^1H Nmr (**15a**) δ: 1.0 (3H, d, J=7 Hz, Me), 2.2-3.2 (3H, m, H-3 and H-4), 3.85 (3H, s, OMe), and 6.8 (2H, bs, NH, deuterable). ^{13}C Nmr (**15a**) δ: 170.5 (C-2), 37.8 (C-3), 23.8 (C-4), 97.9 (C-4a), 162.4 (C-5), 160.1 (C-7), 70.3 (C-8), 148.8 (C-8a), 115.5 (CN), 53.7 (OMe), and 18.9 (Me). Ms (**15a**), m/z (%): 232 (M^+, 25), 217 (100). Ir (**16a**) ν: 3420, 3340, and 3235 (N-H), 2220 (CN), 1700 (C=O), 1645, 1620, and 1575 cm^{-1}. ^1H Nmr (**16a**) δ: 1.0 (3H, d, J=7 Hz, Me), 2.2-3.2 (3H, m, H-3 and H-4), 3.85 (3H, s, OMe), and 6.7 (2H, bs, NH, deuterable). ^{13}C Nmr (**16a**) δ: 169.7 (C-2), 37.6 (C-3), 24.3 (C-4), 97.7 (C-4a), 157.0 (C-5), 163.9 (C-7), 70.0 (C-8), 147.6 (C-8a), 114.8 (CN), 53.5 (OMe), and 17.7 (Me). Ms (**16a**), m/z (%): 232 (M^+, 34), 217 (100).

***7-Amino-8-cyano-3,4-dihydro-5-methoxy-4-phenyl-1,6-naphthyridin-2(1H)-one* (15b) *and* *5-Amino-8-cyano-3,4-dihydro-7-methoxy-4-phenyl-1,6-naphthyridin-2(1H)-one* (16b).**- t = 190 h, commercial NaMeO in absolute methanol, yields: <5 % (**15b**), 30 % (**16b**), mp >300 °C (**15b**), 242-244 °C (**16b**). Ir (**15b**) ν: 3490, 3410, and 3250 (N-H), 2220 (CN), 1705 (C=O), 1630, and 1575 cm^{-1}. ^1H Nmr (**15b**) δ: 2.6-4.4 (3H, m, H-3 and H-4), 3.8 (3H, s, OMe), 6.8 (2H, bs, NH, deuterable), 7.1-7.4 (5H, m, Ph), and 10.0 (1H, bs, NH, deuterable). ^{13}C Nmr (**15b**) δ: 169.7 (C-2), 38.4 (C-3), 33.9 (C-4), 95.3 (C-4a), 162.5 (C-5), 159.8 (C-7), 70.5 (C-8), 149.4 (C-8a), 115.0 (CN), 53.7 (OMe), 142.1, 128.4, and 126.8 (Ph). Ms (**15b**), m/z (%): 294 (M^+, 26), 217 (100). Ir (**16b**) ν: 3420, 3350, and 3240 (N-H), 2225 (CN), 1705 (C=O), 1645, 1620, and 1575 cm^{-1}. ^1H Nmr (**16b**) δ: 2.6-4.4 (3H, m, H-3 and H-4), 3.9 (3H, s, OMe), 6.8 (2H, bs, NH, deuterable), 7.1-7.4 (5H, m, Ph), and 10.1 (1H, bs, NH, deuterable). ^{13}C Nmr (**16b**) δ: 169.3 (C-2), 38.7 (C-3), 34.2 (C-4), 95.3 (C-4a), 157.7 (C-5), 164.4 (C-7), 70.3 (C-8), 149.2 (C-8a), 114.8 (CN), 53.7 (OMe), 140.9, 128.5, and 126.9 (Ph). Ms (**16b**), m/z (%): 294 (M^+, 31), 217 (100). **15b** was also obtained starting from 0.5 g (1.5 mmol) of **12b** when refluxed for 150 h with 0.5 g (22

mmol) of Na in 30 ml of methanol, yield: 0.13 g (29 %).

***7-Amino-8-cyano-3,4-dihydro-5-methoxy-3-methyl-1,6-naphthyridin-2(1H)-one* (15c) *and* *5-Amino-8-cyano-3,4-dihydro-7-methoxy-3-methyl-1,6-naphthyridin-2(1H)-one* (16c).**- t = 55 h, yields: 35 % (**15c**), 35 % (**16c**), mp 215-216 °C (**15c**), 240-242 °C (**16c**). *Anal.* Calcd for $C_{11}H_{12}N_4O_2$: C , 56.89; H, 5.21; N, 24.12. Found: C, 56.58; H, 5.09; N, 23.91. Ir (**15c**) ν: 3450, 3350, and 3240 (N-H), 2205 (CN), 1695 (C=O), 1635, and 1575 cm^{-1}. ^1H Nmr (**15c**) δ: 1.15 (3H, d, J=6 Hz, Me), 2.3-3.0 (3H, m, H-3 and H-4), 3.9 (3H, s, OMe), and 6.7 (2H, bs, NH, deuterable). ^{13}C Nmr (**15c**) δ: 173.4 (C-2), 34.1 (C-3), 25.1 (C-4), 92.4 (C-4a), 162.2 (C-5), 159.5 (C-7), 70.2 (C-8), 149.4 (C-8a), 115.2 (CN), 53.4 (OMe), and 14.9 (Me). Ms (**15c**), m/z (%): 232 (M^+, 100), 217 (64). Ir (**16c**) ν: 3420, 3350, and 3240 (N-H), 2225 (CN), 1700 (C=O), 1645, 1625, and 1575 cm^{-1}. ^1H Nmr (**16c**) δ: 1.18 (3H, d, J=6 Hz, Me), 2.0-3.0 (3H, m, H-3 and H-4), 3.9 (3H, s, OMe), 6.8 (2H, bs, NH, deuterable), and 10.2 (1H, bs, NH, deuterable). ^{13}C Nmr (**16c**) δ: 172.9 (C-2), 33.9 (C-3), 26.2 (C-4), 92.5 (C-4a), 157.5 (C-5), 163.9 (C-7), 70.0 (C-8), 148.5 (C-8a), 114.8 (CN), 53.4 (OMe), and 15.0 (Me). Ms (**16c**), m/z (%): 232 (M^+, 100), 217 (62).

***7-Amino-8-cyano-3,4-dihydro-5-methoxy-3-phenyl-1,6-naphthyridin-2(1H)-one* (15d) *and* *5-Amino-8-cyano-3,4-dihydro-7-methoxy-3-phenyl-1,6-naphthyridin-2(1H)-one* (16d).**- t = 6 h, yields: 20 % (**15d**), 5 % (**16d**), mp 268-275 °C (**15d**), 224-225 °C (**16d**). *Anal.* Calcd for $C_{16}H_{14}N_4O_2$: C , 65.30; H, 4.79; N, 19.04. Found: C, 65.38; H, 4.93; N, 18.80. Ir (**15d**) ν: 3450, 3390, 3320, and 3210 (N-H), 2215 (CN), 1695 (C=O), 1670, 1625, and 1575 cm^{-1}. ^1H Nmr (**15d**) δ: 2.6-3.5 (3H, m, H-3 and H-4), 3.85 (3H, s, OMe), 6.7 (2H, bs, NH, deuterable), and 7.3 (5H, m, Ph). ^{13}C Nmr (**15d**) δ: 170.9 (C-2), 45.5 (C-3), 25.1 (C-4), 92.3 (C-4a), 162.3 (C-5), 159.6 (C-7), 70.2 (C-8), 149.0 (C-8a), 115.0 (CN), 53.4 (OMe), 138.5, 128.2, 128.0, and 126.8 (Ph). Ms (**15d**), m/z (%): 294 (M^+, 100), 217 (48). Ir (**16d**) ν: 3410, 3335, and 3230 (N-H), 2220 (CN), 1700 (C=O), 1645, 1620, and 1575 cm^{-1}. ^1H Nmr (**16d**) δ: 2.6-3.5 (3H, m, H-3 and H-4), 3.8 (3H, s, OMe), 6.7 (2H, bs, NH, deuterable), and 7.3 (5H, m, Ph). Ms (**16d**), m/z (%): 294 (M^+, 100), 217 (29). **15d** was also obtained starting from 0.5 g (1.5 mmol) of **12d** when refluxed for 150 h with 0.5 g (22 mmol) of Na in 30 ml of methanol, yield: 0.27 g (61 %).

Cyclization of 10a-d in aqueous KOH. General Procedure: 1 to 2 g of potassium hydroxide were added to a mixture of 0.005 mol of **10a-d** and 20 ml of water until a clear solution was obtained. Then, 2 extra KOH pellets and 10 ml of water were added and the mixture was heated at reflux for 5 h. After 24 h of stirring at room temperature, the solution was acidified with 6 M HCl and stirred for 3 h. The precipitate was filtered, washed with water, cold ethanol and ether, and dried *in vacuo* over phosphorous pentoxide to yield **17a-d.**

***7-Amino-8-cyano-3,4-dihydro-4-methyl-1,6-naphthyridine-2,5(1H,6H)-dione* (17a).**- Yield: 50 %, mp >300 °C. Ir ν: 3480, 3450, 3240, and 3180 (N-H), 2220 (CN), 1710 (C=O), 1655, 1635, and 1560 cm^{-1}. ^1H Nmr δ: 0.95 (3H, d, J=6 Hz, Me), 2.2-3.3 (3H, m, H-3 and H-4), 6.6 (2H, bs, NH, deuterable), 10.2 (1H, bs, NH, deuterable), and 10.5 (1H, bs, NH, deuterable). ^{13}C Nmr δ: 170.7 (C-2), 37.6 (C-3), 22.9 (C-4), 99.0 (C-4a), 165.8 (C-5), 159.4 (C-7), 74.5 (C-8), 151.6 (C-8a), 116.1 (CN), and 19.4 (Me). Ms m/z (%): 218 (M^+, 24), 203 (100).

***7-Amino-8-cyano-3,4-dihydro-4-phenyl-1,6-naphthyridine-2,5(1H,6H)-dione* (17b).**- Yield: 50 %, mp >300 °C. Ir ν: 3380, 3340, and 3210 (N-H), 2225 (CN), 1705 (C=O), 1665, 1645, 1620, and 1590 cm^{-1}. ^1H Nmr δ: 2.6-4.6 (3H, m, H-3 and H-4), 6.6 (2H, bs, NH, deuterable), 7.2 (5H, m, Ph), 10.2 (1H, bs, NH, deuterable), and 11.0 (1H, bs, NH, deuterable). ^{13}C Nmr δ: 173.8 (C-2), 36.4 (C-3), 35.3 (C-4), 102.0 (C-4a), 163.1 (C-5), 161.6 (C-7), 74.8 (C-8), 154.4 (C-8a), 116.0 (CN), 142.3, 128.5, 127.4, and 126.6 (Ph). Ms m/z (%): 280 (M^+, 30), 203 (100).

7-Amino-8-cyano-3,4-dihydro-3-methyl-1,6-naphthyridine-2,5(1H,6H)-dione **(17c)**.- Yield: 28 %, mp >300 °C. Ir ν: 3420, 3360, 3250, and 3150 (N-H), 2220 (CN), 1720 (C=O), 1660, and 1565 cm^{-1}. Ms m/z (%): 218 (M^+, 100), 203 (17).

7-Amino-8-cyano-3,4-dihydro-3-phenyl-1,6-naphthyridine-2,5(1H,6H)-dione **(17d)**.- Yield: 20 %, mp >300 °C. Ir ν: 3410, 3350, 3240, and 3170 (N-H), 2210 (CN), 1720 (C=O), 1660, 1645, 1630, and 1555 cm^{-1}. Ms m/z (%): 280 (M^+, 100), 203 (31).

Treatment of (5a-d) with cyanoacetamide. General procedure: A mixture of 0.050 mol of the corresponding pyridone **(5a-d)**, 0.050 mol of cyanoacetamide **(19)** and 0.050 mol of sodium in 300 ml of anhydrous dioxane and 5 drops of methanol, was heated under reflux for the time (t) indicated in each case. Then, the dark solid obtained was filtered off, suspended in 60 ml of ethanol and neutralized with an equimolar ammount of ethanolic HCl. The solid obtained was filtered and the mother liquor was concentrated *in vacuo* to give an extra crop of solid. The combined solids were washed with water, ethanol, and ether, and dried *in vacuo* over phosphorous pentoxide.

(Z)-6-Carbamoylcyanomethylene-5-cyano-3-methyl-2-piperidone **(20a)**.- t = 22 h, yield: 75 %, mp 213-215 °C. Ir ν: 3430, 3210, and 3140 (N-H), 2225, and 2220 (CN), 1715, and 1665 (C=O), and 1595 cm^{-1} (C=C). ^{1}H Nmr δ: 1.0 and 1.2 (3H, 2d, J=6 Hz, Me), 2.1-3.5 (3H, m, H-3 and H-4), 4.4-4.6 (1H, 2d, C<u>H</u>-CN, deuterable), 7.8 (2H, bs, NH_2, deuterable), and 12.4 (1H, bs, N-H, deuterable). ^{13}C Nmr δ: 169.6 (C-2), 35.3 (C-3), 27.3 (C-4), 34.6 (C-5), 156.5 (C-6), 82.5 [<u>C</u>(CN)($CONH_2$)], 115.1, and 114.4 (CN), 165.6 ($CONH_2$), and 17.3 (Me). Ms, m/z (%): 218 (M^+, 22), 69 (100). *Anal.* Calcd for $C_{10}H_{10}N_4O_2$: C , 55.04; H, 4.62; N, 25.67. Found: C, 55.20; H, 4.47; N, 25.67. When 0.5 g of **20a** were heated at reflux with 0.23 g of Na in 100 ml of methanol, *5-amino-8-cyano-3,4-dihydro-4-methyl-1,6-naphthyridine-2,7-(1H,6H)-dione* **(18a)** was obtained in 90 % yield, mp >300. Ir ν: 3410, 3330, and 3210 (N-H), 2220 (CN), 1700 (C=O), 1650, 1630, and 1590 cm^{-1}. ^{1}H Nmr δ: 1.0 (3H, d, J=7 Hz, Me), 2.1-3.3 (3H, m, H-3 and H-4), 6.8 (2H, bs, NH, deuterable), and 9.6 (2H, bs, NH, deuterable). ^{13}C Nmr δ: 170.3 (C-2), 37.6 (C-3), 23.4 (C-4), 89.1 (C-4a), 152.2 (C-5), 161.3 (C-7), 72.0 (C-8), 151.2 (C-8a), 116.6 (CN), and 18.5 (Me). Ms m/z (%): 218 (M^+, 32), 203 (100). *Anal.* Calcd for $C_{10}H_{10}N_4O_2$: C , 55.04; H, 4.62; N, 25.67. Found: C, 55.06; H, 4.64; N, 25.68.

(Z)-6-Carbamoylcyanomethylene-5-cyano-4-phenyl-2-piperidone **(20b)**.- t = 7 h, yield: 82 %, mp 208-210 °C. Ir ν: 3470, 3340, and 3210 (N-H), 2220, and 2210 (CN), 1715, and 1665 (C=O), and 1590 cm^{-1} (C=C). ^{1}H Nmr δ: 2.9-4.0 (3H, m, H-3 and H-4), 4.7 (1H, m, C<u>H</u>-CN, deuterable), 7.5 (5H, m, Ph), 7.2 (2H, bs, NH_2, deuterable), and 12.5 (1H, bs, N-H, deuterable). ^{13}C Nmr δ: 168.3 (C-2), 33.8 (C-3), 37.0 (C-4), 38.1 (C-5), 157.5 (C-6), 83.5 [<u>C</u>(CN)($CONH_2$)], 116.1, and 114.9 (CN), 167.0 ($CONH_2$), 138.5, 130.0, 129.1, and 128.5 (Ph). Ms, m/z (%): 280 (M^+, 22), 69 (100). When 0.5 g of **20b** were heated at reflux with 0.23 g of Na in 100 ml of methanol, *5-amino-8-cyano-3,4-dihydro-4-phenyl-1,6-naphthyridine-2,7-(1H,6H)-dione* **(18b)** was obtained in 95 % yield, mp >300. Ir ν: 3410, 3330, 3220, and 3190 (N-H), 2220 (CN), 1695 (C=O), 1670, 1640, and 1590 cm^{-1}. ^{1}H Nmr δ: 2.6-4.4 (3H, m, H-3 and H-4), 6.8 (2H, bs, NH, deuterable), 7.25 (5H, m, Ph), 9.9 (1H, bs, NH, deuterable), and 11.1 (1H, bs, NH, deuterable). ^{13}C Nmr (DMSO) δ: 169.3 (C-2), 38.8 (C-3), 33.3 (C-4), 86.4 (C-4a), 153.1 (C-5), 161.3 (C-7), 72.2 (C-8), 151.7 (C-8a), 116.4 (CN), 141.2, 128.6, 126.9, and 126.8 (Ph). Ms m/z (%): 280 (M^+, 35), 203 (100).

5-Amino-8-cyano-3,4-dihydro-3-methyl-1,6-naphthyridine-2,7-(1H,6H)-dione **(18c)**.- t = 24 h, yield: 70 %, mp >300 °C. Ir ν: 3410, 3340, 3250, and 3190 (N-H), 2215 (CN), 1700 (C=O), 1670, and 1640 cm^{-1}. ^{1}H Nmr δ: 1.15 (3H, d, J=7 Hz, Me), 2.0-3.0 (3H, m, H-3 and H-4), 6.8 (2H, bs, NH, deuterable), 9.7 (1H, bs, NH,

deuterable), and 10.8 (1H, bs, NH, deuterable). ^{13}C Nmr δ: 173.2 (C-2), 34.1 (C-3), 25.1 (C-4), 83.8 (C-4a), 152.8 (C-5), 161.0 (C-7), 72.0 (C-8), 151.3 (C-8a), 116.2 (CN), and 15.0 (Me). Ms m/z (%): 218 (M^+, 100), 203 (95).

5-Amino-8-cyano-3,4-dihydro-3-phenyl-1,6-naphthyridine-2,7-(1H,6H)-dione **(18d).**- t = 7 h, yield: 60 %, mp >300 °C. Ir ν: 3440, 3350, and 3230 (N-H), 2210 (CN), 1695 (C=O), 1645, and 1630 cm^{-1}. ^{1}H Nmr δ: 2.7-4.2 (3H, m, H-3 and H-4), 6.8 (2H, bs, NH, deuterable), 7.4 (5H, m, Ph), and 9.9 (2H, bs, NH, deuterable). ^{13}C Nmr (TFA-d) δ: 178.6 (C-2), 47.6 (C-3), 27.3 (C-4), 93.1 (C-4a), 154.0 (C-5), 165.4 (C-7), 74.8 (C-8), 153.8 (C-8a), 113.0 (CN), 136.7, 131.4, 130.9, and 129.8 (Ph). Ms m/z (%): 280 (M^+, 56), 203 (37), 118 (100).

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