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# Selectivity in the Thermal Cyclization of 2-Piperidino-3-vinylpyridines

**Vicente Ojea, Miguel A. Maestro, José Mª Quintela***

Departamento de Química Fundamental e Industrial, Universidade da Coruña. Campus da Zapateira, E-15071 A Coruña. Spain.

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***Abstract:*** New achiral 2-(4-substituted-piperidino)-3-vinylpyridines undergo stereoselective isomerization to pyrido [1,2-*a*][1,8]naphthyridines. The stereoselectivity of this reaction was found dependent on the experimental conditions (temperature and solvent polarity) and the stereoelectronic features of the piperidino substituent. NMR spectroscopy allowed the determination of the compound conformation in solution and the relative configuration of the cyclized products. A mechanistic approximation to the diastereoselectivity based on molecular mechanics is put foward.

In 1972, Meth-Cohn and Suschitzky reviewed the formation of heterocycles by ring closure of ortho-substituted tertiary anilines (the '*tert*-amino' effect).[1] Reinhoudt *et al* extended this type of reaction to dialkylanilines having an *ortho*-vinyl substituent, thus developing a novel procedure for obtaining carbon-carbon bonds by insertion into a virtually non-activated $NCH_2$ group.[2] Their research into the synthesis of optically pure quinoline derivatives resulted in the description of a unique example of 'self-reproduction of chirality'[3] in which no chiral auxiliary reagents were required.[4] In pursuance of extending the applicability of the '*tert*-amino effect' over 2-amino-3-vinylpyridines, we recently reported the synthesis of several heterotri- and heterotetracyclic compounds,[5,6] and introduced the electrocyclization of 3-aza-hexatriene systems in the '*tert*-amino chemistry'.[7] This paper reports the synthesis of new achiral 2-(4-substituted-piperidino)-3-vinylpyridines and the stereoselective thermal isomerization to pyrido[1,2-*a*][1,8]naphthyridine derivative.[8,9] An explanation for the selectivity is suggested on the basis of molecular mechanic analysis and an NMR conformational study of the cyclized products.

The starting compounds for the thermal isomerization, **3a-f**, were readily prepared in two steps from 2-chloro-3-formylpyridine derivative **1**.[5] Nucleophylic substitution of the α-chlorine atom by the 4-substituted piperidines was accomplished by refluxing in THF. The desired aldehydes **2a-e** were obtained in good yields (86-96%) and their structures were confirmed by $^{13}C$ NMR [δ = 46.8-50.4 ($PyNCH_2$), δ = 185.7-185.9 (CHO)]. Knoevenagel condensation of the carbonyl group of **2a-f** with malononitrile was carried out in refluxing toluene containing of *n*-butylamine and ammonium acetate.[10] In this manner, 2-piperidino-3-vinylpyridine derivatives **3a-f** were obtained as dark-yellow solids in excellent yields (90-97 %).[11] Compounds **3a-f** present a characteristic singlet (δ = 7.41-7.47) corresponding to the vinyl hydrogen in the $^1H$ NMR spectrum and a resonance (δ = 156.8-156.9) for the α-vinylic carbons in the $^{13}C$ NMR spectrum (Scheme 1). Heating **3a-f** in a polar solvent (DMSO, pyridine, butanol, pentanol or heptanol) converted them into the corresponding cyclized products (Scheme 1). After column chromathography, mixtures of *cis*-3,4a-dihydro **4a-f** and *trans*-3,4a-dihydro **5a-f** pyrido[1,2-*a*][1,8]naphthyridine derivatives were obtained, as shown by their $^1H$ NMR spectra, which included a characteristic set of signals for each diastereomer. Thus the double doublet assigned to the bridgehead hydrogen atom (H-4a) appeared between 3.85 and 4.16 ppm for the major isomers **4a-f**, and at 3.63-3.84 ppm for the minor ones **5a-f**. Integration of these pair of signals revealed the thermal cyclization to proceed with diasteroselectivity. The **4a-f/5a-f** ratio was found to be

dependent on the reaction conditions (temperature and solvent polarity) and on the stereoelectronic effects of the piperidino substituent (Table 1 and 2).

**Scheme 1**

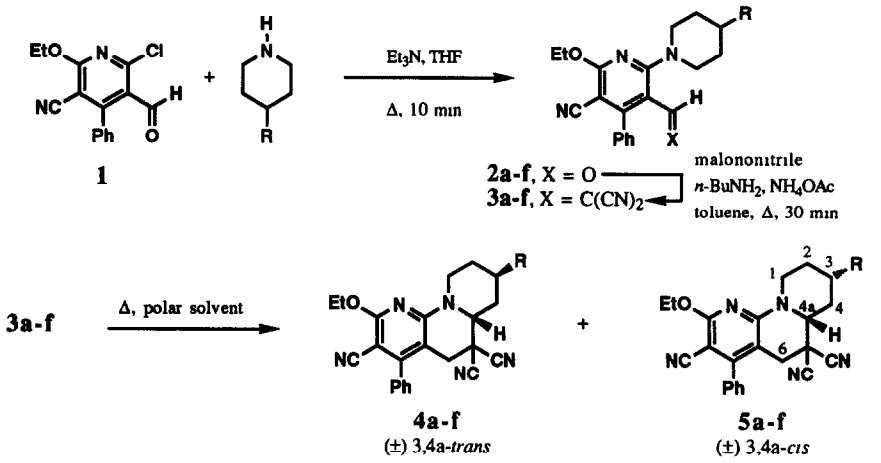



**Table 1:** Selectivity in *tert*-amyl alcohol at 110° C and correlation of characteristic $^1$H NMR signals for Compounds **4,5a-f**.

| | R | ratio 4:5 | reaction time (yield, %) | H-4a | | $H_{eq}$-1 | |
|---|---|---|---|---|---|---|---|
| | | | | 4a-f | 5a-f | 4a-f | 5a-f |
| a | Me | 71:29 | 12 d (90) | 3.85 | 3.68 | 4.66 | 5.05 |
| b | *t*-Bu | 82:18 | 12 d (85) | 3.96 | 3.63 | 4.27 | 5.08 |
| c | Bzl | 65:35 | 14 d (92) | 3.96 | 3.65 | 4.64 | 5.04 |
| d | Ph | 77:23 | 15 d (91) | 3.92 | 3.84 | 4.60 | 5 22 |
| e | OH | 60:40 | 15 d (80) | 4.16 | 3.72 | 4.82 | 5.06 |
| f | Pi | 59:41 | 10 d (75) | 4.05 | 3.70 | 4.50 | 5.09 |

**Table 2:** Temperature and solvent polarity dependence of the selectivity in the thermal isomerization of **3a**.

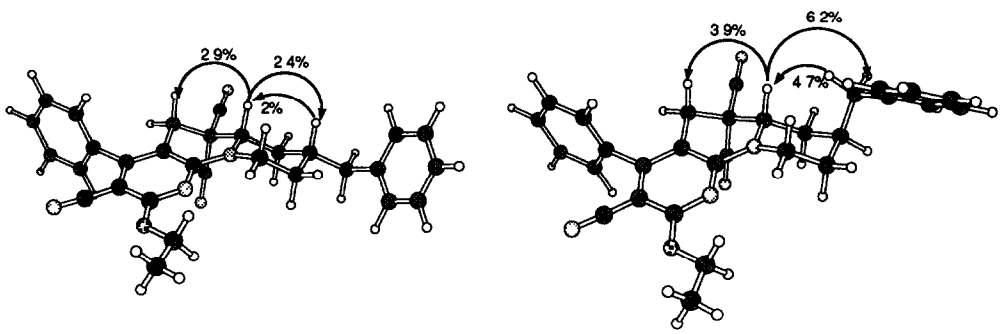
| temperature (DMSO) | 4a:5a ratio | reaction time (yield, %) |
|---|---|---|
| 80 °C | 67:33 | 17 d (81) |
| 100 °C | 64:36 | 4 d (87) |
| 120 °C | 62:38 | 10 h (93) |
| 140 °C | 61:39 | 3.5 h (92) |
| 160 °C | 59:41 | 1 h (86) |

| solvent (120 °C) | 4a:5a ratio | reaction time (yield, %) |
|---|---|---|
| acetonitrile | 63:37 | 1 d (98) |
| pyridine | 64:36 | 2 d (94) |
| *n*-BuOH | 67:33 | 3 5 d (97) |
| pentanol | 69:31 | 5 d (85) |
| *t*-amylalcohol | 70:30 | 6 d (87) |

The **4+5a-f** mixtures were sucessfully resolved by using reversed-phase HPLC (case **a**), repeated fractional crystallization (**b**, **c** and **d**) or medium-pressure column chromathography (**e** and **f**). The pure compounds were used to confirm the $^1$H NMR assignments by COSY experiments. Then the conformations of the cyclized products were determined, as were the relative configuration of H-3 and H-4a for all the **4/5** pairs using $^1$H NOE difference spectroscopy.[12] The NOE results obtained for **4c** and **5c** are given by way of representative example, in figure 1: irradiation of the benzylic hydrogen atoms (H-1′) of **4d** produced 4.7% NOE at H-4a; conversely, irradiation of the bridgehead hydrogen atom (H-4a) resulted in an enhancement of 6.2% at H-1′; irradiation of H-3 of **5c** gave rise to a NOE of 2% at H-4a, irradiation of which yielded an enhancement of 2.4% at H-3. On the basis of the complete set of $^1$H NOE results[13] we can concluded that the major isomers **4a-f** have their R group on the same side of the molecule where H-4a is located (i.e. a *trans*-arrangement between H-3 and H-4a); on the other hand, in the minor isomers **5a-f**, H-3 and H-4a should be arranged in *cis*. Good correlation between H-4a and the Heq-1 absorptions of each pair of isomers **4a-f** and **5a-f** (Table 1) was found.

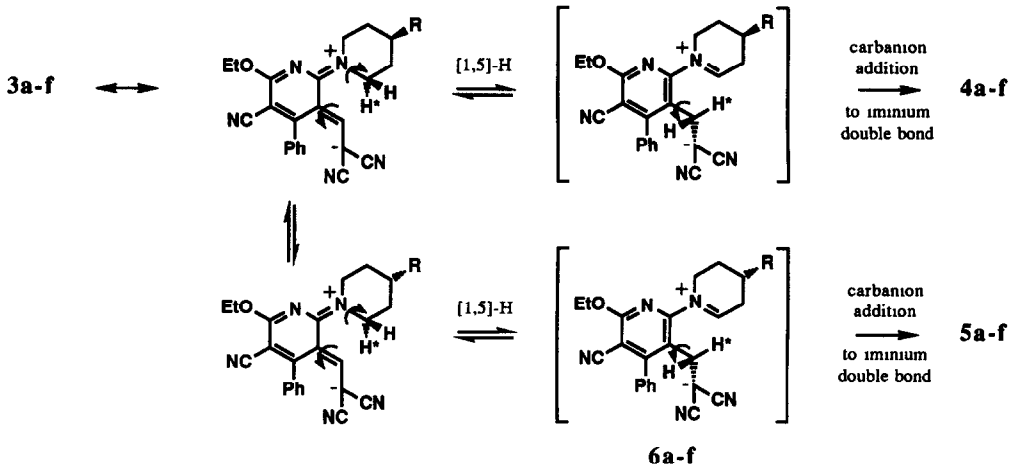
The minimum energy conformation for **4a-f** and **5a-f** were determined using the MMX force field[14] (Figure 1). They were quite consistent with the $^1$H NOE results. In addition, molecular mechanics calculations confirmed that the major products were not thermodynamic, so the selectivity should be kinetically control, as shown by its moderate, though regular, observed dependence on the reaction temperature (Table 2).

**Fig. 1.** Minimum Energy Conformations for **4/5c** showing characteristic NOEs.



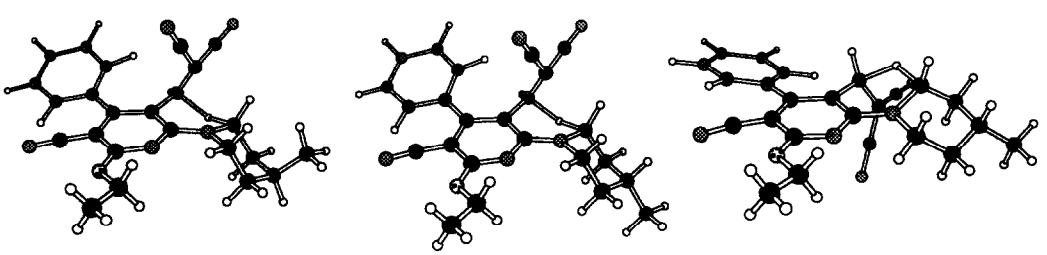

The thermal isomerization can be assumed to occur in two consecutive reactions (Scheme 2).[15] The first, which is the rate-determining step, involves a thermal suprafacial [1,5] hydrogen shift of one of the α-methylene protons adjacent to the piperidine nitrogen of **3a-f** to yield the 1,5-dipolar intermediate **6a-f**. The 'negative end' of **6** is stabilized by the presence of two electron-withdrawing groups. Subsequently, intramolecular addition of the carbanion to the iminium double bond affords the cyclized products **4a-f** and **5a-f**. Also, as the hydrogen shift causes a disrotatory twist of the ends involved, further rotation in the same direction enables a face-selective carbanion addition. This closure process is driven in the initial rotation direction by the electrostatic attraction between the opposite charges (a change in the rotation direction of the carbanion would force a disfavored charge separation). Thus, the lack of equilibration of the helical dipolar intermediates makes the cyclized products completely dependent on the relative configuration of the sigmatropic transition states.

**Scheme 2:** Mechanism of the Thermal Cyclization




We consider the different transition states to be 'pro-*cis*' or 'pro-*trans*', and ascribe the observed selectivity to the greater relative stability of the 'pro-*trans*' ones. There are one equatorial proton and one axial proton over the α-methylene groups adjacent to the piperidine nitrogen atom liable to undergo the sigmatropic shift over or under the plane of the π system, and the R substituent can be in an equatorial or axial disposition arrangement, so we initially considered eight different transition states. Two of them were antarafacial, so they were discarded. The resulting six posible starting geometries for the transition states were optimized by molecular mechanics, their relative minimum energies beind assessed in parallel. The 'pro-trans' transition state with the migrating hydrogen atom and the R substituent in an equatorial arrangement over the same side of the molecule (type $H_{eq}$-$Me_{eq}$ pro-**4a**) proved to be the most stable. The same conformation with the R substituent in an axial arrangement was also found to be the most stable 'pro-cis' transition state (type $Me_{ax}$-$H_{eq}$ pro-**5a**), since 'pro-cis' transition states with an R substituent in an equatorial arrangement were more crowed (type $Me_{eq}$-$H_{eq}$ pro-**5a**). From these results we can conclude that the selectivity can be determined by the population diference between the conformers of **3** with R in an axial or equatorial arrangement at the reaction temperature.

**Fig. 2:** Minimum Energy conformations predicted by the MMX force field for the proposed transition states to **6a**.



$Me_{ax}$-$H_{eq}$ pro-5a
E(MMX) = 12 76 Kcal/mol

$Me_{eq}$-$H_{eq}$ pro-4a
E(MMX) = 11 18 Kcal/mol

$Me_{eq}$-$H_{eq}$ pro-5a
E(MMX) = 16 01 Kcal/mol

In conclusion, a new stereoselective synthesis of pyrido[1,2-*a*][1,8]naphthyridine derivatives has been achieved by thermal isomerization of 2-(4-substituted piperidino)-3-vinylpyridines. This constitutes a novel example of the selective posibilities of the "*tert*-amino effect" in heterocyclic chemistry. A rational mechanistic explanation of the selectivity is given.

## EXPERIMENTAL PART

All reagents used were commercial grade chemicals from freshly opened containers, except for 4-*tert*-butylpiperidine, which was synthesized by following the literature procedure.[16] Silica gel 60 HF $_{254+366}$ for thin-layer chromatography and Silica gel 60 (230-400 mesh) for medium-pressure chromatography were purchased from Merck. Melting points were measured using a Büchi 510 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 383 IR spectrophotometer on KBr slides, $^1$H and $^{13}$C NMR (200 and 50 MHz respectively) were measured on a Bruker AC200F spectrometer at using $DCCl_3$ as solvent. MS were recorded on a Kratos MS-50 spectrometer using electron impact mode at 70 eV. HPLC separation was performed using a $\mu$-Bondapak C-18 column (300 x 7.8 mm).

***5-Formyl-6-(4-substituted piperidino)pyridines 2a-f; General Procedure:***

A solution of 2-chloro-5-cyano-6-ethoxy-3-formyl-4-phenylpyridine (**1**, 0.5 g, 1.75 mmol), a suitable substituted piperidine (1.75 mmol) and $Et_3N$ (0.27 mL, 1.95 mmol) in THF (10 mL) is refluxed for 10 min. Upon cooling, the $Et_3NHCl$ precipitated is filtered off, washed with THF (2 mL), and discarded. The solvent is removed under reduced pressure and the residue is purified by medium-pressure chromatography on a silica gel column (22 x 1.5 cm) to obtain **2a-f** as colorless solids.

All compounds **2a-f** exhibit typical absorption signals for the pyridine nucleus and its subtituents in the $^1$H and $^{13}$C NMR. $^1$H NMR: 1.44-1.48 (3H, t, $J$ = 7.1 Hz, $OCH_2C\underline{H}_3$); 4.47-4.48 (2H, q, $J$ = 7.1 Hz, $OCH_2$); 7.41-7.54 (m, $5H_{arom}$). $^{13}$C NMR: 14.2 ($OCH_2\underline{C}H_3$); 63.5-63.8 ($OCH_2$); 85.4-86.0, 109.1-109.3, 158.8-159.1, 164.1-164.2, 165.3-165.6 ($C_{pyridyl}$); 115.4-115.6 (CN); 128.6-128.7, 129.7, 130.0-130.2, 134.2-134.3 ($C_{phenyl}$).

*3-Cyano-2-ethoxy-5-formyl-6-(4-methylpiperidino)-4-phenylpyridine* ***2a***: General procedure was followed; medium-pressure chromatography was performed by using $CH_2Cl_2$:hexane (4:1) as eluent; yield: 0.52 g (86%); mp 110 - 112 °C (EtOH:hexane 1:5). $^1$H NMR: 0.98 (3H, d, $J$ = 6.0 Hz, $CHC\underline{H}_3$); 1.30-1.36 (1H, m, $\underline{H}CCH_3$); 1.70-1.79 (4H, m, $NCH_2CH_2$); 3.15 (2H, td, $J$ = 13.3, 2.5 Hz, $NCH_{ax}$); 4.13 (2H, br d, $J$ = 13.3 Hz, $NCH_{eq}$); 9.17 (s, 1H, CHO). $^{13}$C NMR: 21.5 ($HC\underline{C}H_3$); 30.5 ($H\underline{C}CH_3$); 34.3 ($NCH_2\underline{C}H_2$); 50.0 ($NCH_2$); 185.7 (CHO). MS: 350 ($M^+$+1, 23); 349 ($M^+$, 100); 348 ($M^+$-1, 19); 332 (96); 320 (22); 304 (42); 279 (10); 262 (8); 250 (10); 238 (6); 224 (12); 195 (10); 140 (20). High Resolution MS: $C_{21}H_{23}N_3O_2$, calc: 349.1790, found: 349.1783. IR: 2980, 2940, 2920, 2860, 2750 (CH); 2220 (CN); 1650 (CO); 1580, 1560, 1530 ($CC_{arom}$) cm$^{-1}$.

*3-Cyano-2-ethoxy-5-formyl-4-phenyl-6-(4-tert-butylpiperidino)pyridine* ***2b***: General procedure was followed; medium-pressure chromatography was performed by using $CH_2Cl_2$:hexane (3:2) as eluent; yield: 0.68 g (96%); mp 155 - 159 °C (EtOH:hexane 1:5). $^1$H NMR: 0.89 [9H, s, $CH(C\underline{H}_3)_3$]; 1.33-1.44 (3H, m, $\underline{H}_{ax}C\underline{H}C(CH_3)_3$); 1.82 (2H, br d, $J$ = 9.6 Hz, $NCH_2CH_{eq}$); 3.12 (2H, br t, $J$ = 12, 2.5 Hz, $NCH_{ax}$); 4.23 (br 2H, d, $J$ = 13 Hz, $NCH_{eq}$); 9.18 (1H, s, CHO). $^{13}$C NMR: 27.1 ($C(\underline{C}H_3)_3$); 27.2 ($NCH_2\underline{C}H_2$); 32.1 ($\underline{C}(CH_3)_3$); 46.3 ($H\underline{C}$-*t*-Bu); 50.4 ($NCH_2$); 185.7 (CHO). MS: 392 ($M^+$+1, 24); 391 ($M^+$, 89); 390 ($M^+$-1, 17); 374 (100); 346 (25); 140 (30). High Resolution MS: $C_{24}H_{29}N_3O_2$, calc: 391.2270, found: 391.2280. IR: 3060, 2980, 2880, 2780 (CH); 2220 (CN); 1670 (CO); 1585, 1570, 1540, 1520 ($CC_{arom}$) cm$^{-1}$.

*2-(4-Benzylpiperidino)-5-cyano-6-ethoxy-3-formyl-4-phenylpyridine* ***2c***: General procedure was followed; medium-pressure chromatography was performed by using $CH_2Cl_2$:hexane (2:1) as eluent; yield: 0.70 g (95%); mp 138 - 140 °C (EtOH:hexane 1:6). $^1$H NMR: 1.35-1.55 (2H, m, $NCH_2CH_{ax}$); 1.80 (2H, br d, $J$ = 13.0 Hz, $NCH_2CH_{eq}$); 1.80-1.98 (1H, m, HCBzl); 2.61 (2H, d, $J$ = 7.0 Hz, $HCC\underline{H}_2Ph$); 3.17 (2H, td, $J$ = 13.0, 2.0 Hz, $NCH_{ax}$); 4.15 (2H, br d, $J$ = 13.0 Hz, $NCH_{eq}$); 7.16-7.34 ($5H_{benzyl}$, m); 9.19 (1H, s, CHO). $^{13}$C NMR: 32.2 ($NCH_2\underline{C}H_2$); 37.7 (HCBzl); 42.7 ($HC\underline{C}H_2Ph$); 49.9 ($NCH_2$); 126.0, 128.3, 129.0, 139.9 ($C_{benzyl}$); 185.7 (CHO). MS: 427 ($M^+$+2, 4); 426 ($M^+$+1, 30); 425 ($M^+$, 100); 424 ($M^+$-1, 24); 408 (56); 396 (12); 380 (14); 306 (3); 288 (4); 264 (5); 252 (5); 236 (5); 224 (7); 140 (8). High Resolution MS:

$C_{27}H_{27}N_3O_2$, calc: 425.2103, found: 425.2094. IR: 3060, 3040, 2980, 2930, 2850 (CH); 2220 (CN); 1660 (CO); 1580, 1560, 1515 ($CC_{arom}$) $cm^{-1}$.

*3-Cyano-2-ethoxy-5-formyl-4-phenyl-6-(4-phenylpiperidino)pyridine* ***2d:*** General procedure was followed; medium-pressure chromatography was performed by using $CH_2Cl_2$:hexane (2:1) as eluent; yield: 0.67 g (93%); mp 174 - 176 °C (EtOH). $^1H$ NMR: 1.82-2.10 (4H, m, $NCH_2C\underline{H}_2$); 2.61 (1H, m, HCPh); 3.33 (2H, td, $J$ = 13.3, 3.1 Hz, $NCH_{ax}$); 4.33 (2H, br d, $J$ = 13.3 Hz, $NCH_{eq}$); 7.20-7.38 ($5H_{phenyl}$, m); 9.24 (1H, s, CHO). $^{13}C$ NMR: 33.4 ($NCH_2\underline{C}H_2$); 42.3 (HCPh); 50.4 ($NCH_2$); 126.5, 126.8, 128.5, 145.0 ($C_{phenyl}$); 185.8 (CHO). MS: 413 ($M^+$+2, 4); 412 ($M^+$+1, 29); 411 ($M^+$, 100); 410 ($M^+$-1, 22); 394 (44); 382 (12); 366 (6); 290 (12); 262 (12); 250 (7); 236 (4); 224 (6). High Resolution MS: $C_{26}H_{25}N_3O_2$, calc: 411.1947, found: 411.1950. IR: 3020, 2980, 2940, 2920, 2850 (CH); 2220 (CN); 1670 (CO); 1580, 1560, 1520 ($CC_{arom}$) $cm^{-1}$.

*3-Cyano-2-ethoxy-5-formyl-6-(4-hydroxypiperidino)-4-phenylpyridine* ***2e:*** General procedure was followed; medium-pressure chromatography was performed by using $CH_2Cl_2$:EtOH (30:1) as eluent; yield: 0.55 g (94%); mp 154 - 156 °C ($CH_2Cl_2$:EtOH). $^1H$ NMR: 1.68-1.73 (2H, m, $NCH_2CH_{ax}$); 1.98-2.15 (3H, m, $HCO\underline{H}$ + $NCH_2CH_{eq}$); 3.46 (2H, ddd, $J$ = 13.0, 8.8, 3.4 Hz, $NCH_{ax}$); 3.90-4.02 (3H, m, $\underline{H}COH$ + $NCH_{eq}$); 9.17 (1H, s, CHO). $^{13}C$ NMR: 34.2 ($NCH_2\underline{C}H_2$); 46.8 ($NCH_2$); 66.6 (HCOH); 185.9 (CHO). MS: 352 ($M^+$+1, 26); 351 ($M^+$, 100); 350 ($M^+$-1, 12); 334 (61); 316 (20); 288 (84). High Resolution MS: $C_{20}H_{21}N_3O_3$, calc: 351.1583, found: 351.1561. IR: 3420 (OH); 3050, 2980, 2930, 2860 (CH); 2220 (CN); 1670 (CO); 1580, 1560, 1515 ($CC_{arom}$) $cm^{-1}$.

*3-Cyano-2-ethoxy-5-formyl-4-phenyl-6-(4-piperidinopiperidino)pyridine* ***2f:*** General procedure was followed; medium-pressure chromatography was performed by using $CH_2Cl_2$:EtOH (10:1) as eluent; yield: 0.67 g (92%); mp 169 - 171 °C (EtOH:hexane 1:4). $^1H$ NMR: 1.50-1.60 (6H, m, $HCNCH_2C\underline{H}_2C\underline{H}_2$); 1.70 (2H, qd, $J$ = 12, 3.5 Hz, $PyNCH_2CH_{ax}$); 1.93 (2H, br d, $NCH_2CH_{eq}$); 2.50-2.54 (4H, m, $HCNC\underline{H}_2$); 2.59 (1H, tt, J = 11.2, 3.3 Hz, HCPy); 3.16 (2H, td, $J$ = 13.4, 2.1 Hz, $PyNCH_{ax}$); 4.19 (2H, br d, $PyNCH_{eq}$); 9.17 (1H, s, CHO). $^{13}C$ NMR: 24.6 ($HCNCH_2CH_2\underline{C}H_2$); 26.3 ($HCNCH_2\underline{C}H_2$); 28.2 ($PyNCH_2\underline{C}H_2$); 49.3 ($HCN\underline{C}H_2$); 50.2 ($PyNCH_2$); 61.9 (HCPi); 185.8 (CHO). MS: 419 ($M^+$+1, 1); 418 ($M^+$, 4); 417 ($M^+$-1, 2); 401 (14); 124 (100). High Resolution MS: $C_{25}H_{30}N_4O_2$, calc: 418.2369, found: 418.2374. IR (KBr): 3060, 3030, 2940, 2850, 2800 (CH); 2220 (CN); 1670 (CO); 1580, 1560, 1520 ($CC_{arom}$) $cm^{-1}$.

***3-(2,2,-Dicyanovinyl)-2-(4-substituted piperidino)pyridines 3a-f; General Procedure:***

A solution of 5-cyano-6-ethoxy-3-formyl-4-phenyl-2-(4-substituted piperidino)pyridine **2a-f**, 1.4 mmol), malononitrile (0.185 g, 2.8 mmol), *n*-butylamine (0.14 mL, 1.4 mmol) and $NH_4OAc$ (0.11 g, 1.4 mmol) in toluene is refluxed for 20 min. Upon cooling, the solvent is removed under reduced pressure and the resulting solid is purified by medium-pressure chromatography on a silica gel column (15 x 1.5 cm) to obtain **3a-f** as dark yellow solids.

All compounds **3a-f** exhibit typical absorption signals for the pyridine nucleus and its subtituents in the $^1H$ and $^{13}C$ NMR. $^1H$ NMR: 1.46-1.49 (3H, t, $J$ = 7.1 Hz, $OCH_2C\underline{H}_3$); 4.50-4.54 (2H, q, $J$ = 7.1 Hz, $OCH_2$); 7.24-7.45 ($2H_{arom}$, m); 7.49-7.66 ($3H_{arom}$, m). $^{13}C$ NMR: 14.1-14.3 ($OCH_2\underline{C}H_3$); 64.0-64.2 ($OCH_2$); 87.7-88.5, 102.9-103.4, 159.5-159.9, 161.5-161.6, 163.8-164.0 ($C_{pyridyl}$); 112.2-112.4 (CN); 128.5, 129.1-129.3, 130.2-130.4, 133.6-133.7 ($C_{phenyl}$).

*3-Cyano-5-(2,2-dicyanovinyl)-2-ethoxy-6-(4-methylpiperidino)-4-phenylpyridine* ***3a:*** General procedure was followed; medium-pressure chromatography was performed by using $CH_2Cl_2$ as eluent; yield: 0.50 g (90%); mp 198 - 200 °C (EtOH). $^1H$ NMR: 1.00 (3H, d, $J$ = 6.1 Hz, $CHC\underline{H}_3$); 1.23-1.34 (1H, m, $\underline{H}CCH_3$); 1.75-1.83 (4H, m, $NCH_2C\underline{H}_2$); 3.31 (2H, td, $J$ = 12.6, 2.1 Hz, $NCH_{ax}$); 4.00 (2H, br d, $NCH_{eq}$); 7.42 (1H, s, =CH). $^{13}C$ NMR: 21.4 ($HC\underline{C}H_3$); 30.3 ($H\underline{C}CH_3$); 34.0 ($NCH_2\underline{C}H_2$); 48.6 ($NCH_2$); 77.2 [=$\underline{C}(CN)_2$]; 114.7 (CN); 156.8 (=CH). MS: 398 ($M^+$+1, 27); 397 ($M^+$, 100); 382 (10); 368 (60); 357 (10); 341 (6); 332 (35); 329 (38); 304 (31); 288 (7); 273 (11); 262 (11); 248 (18); High Resolution MS: $C_{24}H_{23}N_5O$, calc: 397.19025, found: 397.1907. IR: 2980, 2940, 2920, 2860, 2750 (CH); 2220 (CN); 1650 (CO); 1580, 1560, 1530 ($CC_{arom}$) $cm^{-1}$.

*3-Cyano-5-(2,2-dicyanovinyl)-2-ethoxy-4-phenyl-6-(4-tert-butylpiperidino)pyridine* ***3b:*** General procedure was followed; medium-pressure chromatography was performed by using $CH_2Cl_2$:hexane 3:2 as eluent; yield: 0.60 g (97%); mp 210 - 212 °C (EtOH). $^1H$ NMR: 0.89 [9H, s, $CH(C\underline{H}_3)_3$]; 1.25-1.43 (3H, m, $\underline{H}_{ax}C\underline{H}C(CH_3)_3$); 1.83 (2H, br d, $NCH_2CH_{eq}$); 3.28 (2H, br t, $NCH_{ax}$); 4.05 (2H, br d, $NCH_{eq}$); 7.43 (1H,

s, =CH). $^{13}$C NMR: 27.0 [C(<u>C</u>H$_3$)$_3$ + NCH$_2$<u>C</u>H$_2$]; 32.2 [<u>C</u>(CH$_3$)$_3$]; 45.8 (H<u>C</u>-*t*-Bu); 48.9 (NCH$_2$); 77.2 [=C(CN)$_2$]; 114.6 (CN); 156.8 (=CH). MS: 440 (M$^+$+1, 31); 439 (M$^+$, 100); 438 (M$^+$-1, 9); 410 (50); 382 (46); 374 (48); 354 (67); 288 (46). High Resolution MS: $C_{27}H_{29}N_5O$, calc: 439.2372, found: 439.2391. IR: 3060, 2960, 2880 (CH); 2220 (CN); 1570, 1530, 1510 (CC$_{arom}$) cm$^{-1}$.

*2-(4-Benzylpiperidino)-5-Cyano-3-(2,2-dicyanovinyl)-6-ethoxy-4-phenylpyridine 3c:* General procedure was followed; medium-pressure chromatography was performed by using $CH_2Cl_2$:hexane (3:2) as eluent; yield: 0.63 g (95%); mp 182 - 184 °C (EtOH). $^1$H NMR: 1.33 (2H, qd, *J* = 12.0, 3.8 Hz, NCH$_2$CH$_{ax}$); 1.80 (br d, 2H, *J* = 12 Hz, NCH$_2$CH$_{eq}$); 1.93-1.97 (1H, m, HCBzl); 2.60 (2H, d, *J* = 7.1 Hz, HCC<u>H</u>$_2$Ph); 3.28 (2H, td, *J* = 12.4, 2.2 Hz, NCH$_{ax}$); 4.15 (2H, br d, *J* = 12.4 Hz, NCH$_{eq}$); 7.14-7.20 (2H$_{benzyl}$, m); 7.21-7.30 (3H$_{benzyl}$, m); 7.41 (1H, s, =CH). $^{13}$C NMR: 31.9 (NCH$_2$<u>C</u>H$_2$); 37.4 (HCBzl); 42.6 (H<u>C</u>CH$_2$Ph); 48.5 (NCH$_2$); 77.5 [=C(CN)$_2$]; 114.6 (CN); 126.2, 128.4, 129.0, 139.5 (C$_{benzyl}$); 156.8 (=CH). MS: 475 (M$^+$+2, 5); 474 (M$^+$+1, 33); 473 (M$^+$, 100); 472 (M$^+$-1, 5); 445 (5); 444 (9); 408 (12); 380 (6); 354 (6); 288 (4). High Resolution MS: $C_{30}H_{27}N_5O$, calc: 473.2216, found: 473.2135. IR: 3060, 3030, 3000, 2940, 2850 (CH); 2220 (CN); 1565, 1510, 1485 (CC$_{arom}$) cm$^{-1}$.

*3-Cyano-5-(2,2-dicyanovinyl)-2-ethoxy-4-phenyl-6-(4-phenylpiperidino)pyridine 3d:* General procedure was followed; medium-pressure chromatography was performed by using $CH_2Cl_2$:hexane (3:2) as eluent; yield: 0.58 g (90%); mp 218 - 220 °C (EtOH). $^1$H NMR: 1.81 (2H, qd, *J* = 12.6, 3.8 Hz, NCH$_2$CH$_{ax}$); 2.93 (1H, tt, *J* = 12.0, 3.6 Hz, HCPh); 3.50 (2H, td, *J* = 12.6, 2.0 Hz, NCH$_{ax}$); 4.16 (2H, br d, *J* = 12.6 Hz, NCH$_{eq}$); 7.22-7.35 (5H$_{phenyl}$, m); 7.47 (1H, s, =CH). $^{13}$C NMR: 33.2 (NCH$_2$<u>C</u>H$_2$); 42.0 (HCPh); 48.9 (NCH$_2$); 77.9 [=C(CN)$_2$]; 114.5 [=C(<u>C</u>N)$_2$]; 126.7, 126.8, 128.7, 144.5 (C$_{phenyl}$); 156.9 (=CH). MS: 459 (M$^+$, 13); 398 (15); 368 (6); 265 (9); 250 (17); 231 (8); 219 (13); 193 (3); 181 (18); 178 (21); 169 (24); 119 (29). High Resolution MS: $C_{29}H_{25}N_5O$, calc: 459.2059, found: 459.2055. IR: 3080, 3060, 3040, 2980, 2950, 2860 (CH); 2220 (CN); 1580, 1565, 1515 (CC$_{arom}$) cm$^{-1}$.

*3-Cyano-5-(2,2-dicianovinyl)-2-ethoxy-6-(4-hydroxypiperidino)-4-phenylpyridine 3e:* General procedure was followed; medium-pressure chromatography was performed by using $CH_2Cl_2$:EtOH (40:1) as eluent; yield: 0.52 g (97%); mp 98 - 100 °C ($CH_2Cl_2$:EtOH). $^1$H NMR: 1.64-1.75 (2H, m, NCH$_2$CH$_{ax}$); 1.98 (1H, br s, HCO<u>H</u>); 1.97-2.10 (2H, m, NCH$_2$CH$_{eq}$); 3.50 (2H, ddd, *J* = 12.6, 8.5, 3.3 Hz, NCH$_{ax}$); 3.90 (2H, dt, NCH$_{eq}$); 4.05-4.15 (1H, m, <u>H</u>COH); 7.45 (1H, s, =CH). $^{13}$C NMR: 33.9 (NCH$_2$<u>C</u>H$_2$); 45.5 (NCH$_2$); 65.9 (HCOH); 78.3 [=C(CN)$_2$]; 114.5 (CN); 156.9 (=CH). MS: 400 (M$^+$+1, 28); 399 (M$^+$, 100); 398 (M$^+$-1, 10); 370 (41); 331 (34); 288 (77); 248 (48); 189 (52). High Resolution MS: $C_{23}H_{21}N_5O$, calc: 399.1695, found: 39.1676. IR: 3450 (OH); 3060, 2980, 2935, 2860 (CH); 2220 (CN); 1580, 1565, 1510 (CC$_{arom}$) cm$^{-1}$.

*3-Cyano-5-(2,2-dicyanovinyl)-2-ethoxy-4-phenyl-6-(4-piperidinopiperidino)pyridine 3f:* General procedure was followed; medium-pressure chromatography was performed by using $CH_2Cl_2$:EtOH (20:1) as eluent; yield: 0.59 g (91%); mp 182 - 185°C (EtOH). $^1$H NMR: 1.44-1.50 (2H, m, HCNCH$_2$CH$_2$C<u>H</u>$_2$); 1.60-1.80 (6H, m, HCNCH$_2$C<u>H</u>$_2$ + PyNCH$_2$C<u>H</u>$_{ax}$); 2.03 (2H, br d, NCH$_2$CH$_{eq}$); 2.58-2 65 (4H, m, HCNC<u>H</u>$_2$); 2.75 (1H, tt, *J* = 11.0, 3.9 Hz, HCPi); 3.29 (2H, td, *J* = 13.4, 2.1 Hz, PyNCH$_{ax}$); 4.05 (2H, br d, PyNCH$_{eq}$); 7.45 (1H, s, =CH). $^{13}$C NMR: 24.2 (HCNCH$_2$CH$_2$<u>C</u>H$_2$); 25.6 (HCNCH$_2$<u>C</u>H$_2$); 27.7 (PyNCH$_2$<u>C</u>H$_2$); 47.8 (HCN<u>C</u>H$_2$); 50.2 (PyNCH$_2$); 61.6 (HCPi); 78.2 [=C(CN)$_2$]; 114.4, 114.5 (CN); 156.9 (=CH). MS: 467 (M$^+$+1, 1); 466 (M$^+$, 10); 465 (M$^+$-1, 1); 439 (15); 354 (20); 124 (100). High Resolution MS: $C_{28}H_{30}N_6O$, calc: 466.2481, found: 466.2489. IR: 3050, 2930, 2850, 2800 (CH); 2220 (CN); 1565, 1515 (CC$_{arom}$) cm$^{-1}$.

***Hexahydro-1H-pyrido[1,2-a][1,8]naphthyridine derivatives 4a-f and 5a-f;***

Method A: A solution of 3-cyano-5-(2,2,-dicyanovinyl)-2-ethoxy-4-phenyl-6-(4-substituted piperidino)pyridine (**3a-i**, 0.1 g) in DMSO (5 mL) is heated for until all starting material had disappeared as checked by TLC (see Tables 1 and 2). Upon cooling, reaction crude is poured into water (50 mL) and extracted with ethyl acetate (2 x 10 mL). The combined organic layers are dried with $Na_2SO_4$ and the solvent is removed under reduced pressure. The resulting solid is purified by medium-pressure chromatography on a silica gel column (12 x 1 cm) to obtain **4+5a-f** as colorless solids.

Method B: A solution of 3-cyano-5-(2,2,-dicyanovinyl)-2-ethoxy-4-phenyl-6-(4-substituted piperidino)pyridine (**3a-i**, 0.1 g) in a polar solvent (5 mL) is heated for until all starting material had disappeared as checked by TLC (see Tables 1 and 2). Upon cooling, the solvent is removed under reduced pressure. The resulting solid is purified by medium-pressure chromatography on a silica gel column (12 x 1 cm) to obtain **4+5a-f** as colorless solids

All compounds **4a-f** and **5a-f** exhibit typical absorption signals for the pyridine nucleus and its subtituents in the $^1H$ and $^{13}C$ NMR. $^1H$ NMR: 1.42-1.46 (3H, t, $J$ = 7.1 Hz, $OCH_2\underline{C}H_3$); 4.42-4.47 (2H, q, $J$ = 7.1 Hz, $OCH_2$); 7.15-7.22 ($1H_{arom}$, m); 7.25-7.36 ($1H_{arom}$, m); 7.45-7.60 ($3H_{arom}$, m). $^{13}C$ NMR: 14.2-14.4 ($OCH_2\underline{C}H_3$); 62.9-63.1 ($OCH_2$); 84.5-86.0, 99.2-100.2, 153.9-154.7, 155.4-158.5, 163.7-164.1 ($C_{pyridyl}$); 112.3-112.8 (CN); 127.8-129.5 (four or five signals, $C_{phenyl}$), 134.2-134.3 ($C_{phenyl}$).

*9-Ethoxy-7-phenyl-3-methyl-2,3,4,4a,5,6-hexahydro-1H-pyrido[1,2-a][1,8]naphthyridin-5,5,8-tricarbonitrile* ***4,5a***: General procedure was followed; medium-pressure chromatography was performed by using $CH_2Cl_2$:hexane (2:1) as eluent; yield: 60-97 mg (60-97%). The resolution of the mixture was performed by means of HPLC using a mixture $CH_3CN$:$H_2O$ (1:1) as eluent. MS: 398 ($M^+$+1, 16); 397 ($M^+$, 61); 396 ($M^+$-1, 5); 368 (10); 332 (10); 304 (5); 276 (4); 236 (2); 149 (3). High Resolution MS: $C_{24}H_{23}N_5O$, calc: 397.1902, found: 397.1895.

*trans-3,4a-Dihydro* ***4a***: mp 175 - 176 °C (MeOH/hexane). $^1H$ NMR: 1.17 (3H, d, $J$ = 7.2 Hz, $HCC\underline{H}_3$); 1.58-1.67 (2H, m, $H_{ax}$-2,4); 1.87-2.06 (2H, m, $H_{eq}$-2 and $H_{eq}$-4); 2.33-2.37 (1H, m, H-3); 3.07 and 3.17 (2H, AB system, $J$ = 16.0 Hz, H-6); 3.20 (1H, ddd, $J$ = 13.4, 2.1 Hz, $H_{ax}$-1); 3.85 (1H, dd, $J$ = 11.4, 4.0 Hz, H-4a); 4.66 (1H, ddd, $J$ = 13.7, 4.7, 3.7 Hz, $H_{eq}$-1). $^{13}C$ NMR: 16.7 ($H\underline{C}CH_3$); 24.4 (C-3); 29.4, 33.1 (C-2,4); 34.4 (C-6); 36.2 (C-5); 39.8 (C-1); 54.5 (C-4a); 113.9, 115.6 [$C(CN)_2$]. IR: 3050, 2960, 2940, 2870 (CH); 2220 (CN); 1585, 1570, 1550, 1500 ($CC_{arom}$) $cm^{-1}$.

*cis-3,4a-Dihydro* ***5a***: mp 190 - 194 °C (EtOH/hexane). $^1H$ NMR: 1.10 (3H, d, $J$ = 6.3 Hz, $HCC\underline{H}_3$); 1.70-1.89 (2H, m, $H_{ax}$-3, $H_{eq}$-2 or $H_{eq}$-4), 2.26 (1H, ddd, $J$ = 12.5, 5.3, 3.0 Hz, $H_{eq}$-2 or $H_{eq}$-4); 2.83 (1H, td, $J$ = 13.4, 2.1 Hz, $H_{ax}$-1); 3.05 and 3.17 (2H, AB system, $J$ = 15.9 Hz, H-6); 3.68 (1H, dd, $J$ = 11.7, 2.9 Hz, H-4a); 5.05 (1H, ddd, $J$ = 13.5, 4.5, 2.1 Hz, $H_{eq}$-1). $^{13}C$ NMR: 21.6 ($H\underline{C}CH_3$); 30.3 (C-3); 32.6, 32.9 (C-2,4); 36.0 (C-5); 37.1 (C-6); 45.4 (C-1); 58.9 (C-4a); 113.9, 115.6 [$C(CN)_2$]. IR: 3050, 2960, 2940, 2870 (CH); 2220 (CN); 1585, 1570, 1550, 1500 ($CC_{arom}$) $cm^{-1}$.

*9-Ethoxy-7-phenyl-3-tert-butyl-2,3,4,4a,5,6-hexahydro-1H-pyrido[1,2-a][1,8]naphthyridin-5,5,8-tricarbonitrile* ***4,5b***: General procedure was followed; medium-pressure chromatography was performed by using $CH_2Cl_2$:hexane (3:2) as eluent; yield: 70-95 mg (70-95 %). MeOH was used for fractional crystallization. MS: 440 ($M^+$+1, 29 ); 439 ($M^+$, 100); 438 ($M^+$-1, 7); 424 (13); 410 (18); 382 (19); 374 (29); 354 (31). High Resolution MS: $C_{27}H_{29}N_5O$, calc: 439.2372, found: 439.2386.

*trans-3,4a-Dihydro* ***4b***: mp 152-155 °C (MeOH). $^1H$ NMR: 0.95 [9H, s, $C(C\underline{H}_3)_3$]; 1.50-2.30 (5H, m); 3.07 and 3.17 (2H, AB system, $J$ = 15.8 Hz, H-6); 3.49 (1H, td, $J$ = 12.9, 3.2 Hz, $H_{ax}$-1); 3.95 (1H, dd, $J$ = 11.0, 4.0 Hz, H-4a); 4.27 (1H, dt, $J$ = 13.0, 4.0 Hz, $H_{eq}$-1). $^{13}C$ NMR: 23.0 (C-2 or 4); 26.6 [$C(\underline{C}H_3)_3$]; 28.1 (C-2 or 4); 33.4[$\underline{C}(CH_3)_3$]; 34.0 (C-6); 35.8 (C-5); 39.5 (C-1); 42.5 (C-3); 56.5 (C-4a); 114.1 [$C(CN)_2$]. IR: 3060, 2960, 2860 (CH); 2210 (CN); 1590, 1570, 1550, 1485 ($CC_{arom}$) $cm^{-1}$.

*cis-3,4a-Dihydro* ***5b***: mp 229-231 °C (MeOH). $^1H$ NMR: 0.94 [9H, s, $C(C\underline{H}_3)_3$]; 1.32-1.50 (3H, m, $H_{eq}$-2, $H_{ax}$-2 and $H_{ax}$-4); 1.85-1.95 (1H, m, $H_{eq}$-2); 2.25-2.35 (1H, m, $H_{eq}$-4); 2.74-2.90 (1H, td, $H_{ax}$-1); 3.05 and 3.18 (2H, AB system, $J$ = 15.9, H-6); 3.63 (1H, dd, $J$ = 10.7, 2.8 Hz, H-4a); 5.04- 5.18 (1H, dt, $H_{eq}$-1). $^{13}C$ NMR: 25.6 (C-2 or 4); 27.0 [$C(\underline{C}H_3)_3$]; 30.6 (C-2 or 4); 32.3 [$\underline{C}(CH_3)_3$]; 33.2 (C-6); 36.5 (C-5); 45.4 (C-1, 3); 59.4 (C-4a); 114.1 [$C(CN)_2$]. IR: 3060, 2960, 2860 (CH); 2220 (CN); 1585, 1570, 1550, 1485 ($CC_{arom}$) $cm^{-1}$.

*3-Benzyl-9-ethoxy-7-phenyl-2,3,4,4a,5,6-hexahydro-1H-pyrido[1,2-a][1,8]naphthyridin-5,5,8-tricarbonitrile* ***4,5c***: General procedure was followed; medium-pressure chromatography was performed by using $CH_2Cl_2$:hexane 3:2 as eluent; yield: 75-93 mg (75-93 %). EtOH was used for fractional crystallization. MS: 474 ($M^+$+1, 34); 473($M^+$, 100); 472 ($M^+$-1, 9); 443 (8); 420(4); 417 (4); 408 (11); 394 (5); 354 (7); 300 (4). High Resolution MS: $C_{30}H_{27}N_5O$, calc: 473.2215, found: 473.2227.

*trans-3,4a-Dihydro* ***4c***: mp 224 - 226 °C (EtOH). $^1H$ NMR: 1.68-1.77 (1H, m, $H_{eq}$-2); 1.83-2.04 (2H, m, $H_{ax}$-2 and $H_{ax}$-4); 2.21 (1H, ddd, $J$ = 13.3, 4.5, 3.1 Hz, $H_{eq}$-4); 2.40-2.50 (1H, br s, $H_{eq}$-3); 2.84 (2H, d, $J$ = 8.1 Hz, $CH_2C_6H_5$); 3.10 and 3.19 (2H, AB system, $J$ = 16.0 Hz, H-6); 3.36 (1H, ddd, $J$ = 13.8, 11.7, 3.6 Hz, $H_{ax}$-1); 3.96 (1H, dd, $J$ = 12.1, 3.2 Hz, H-4a); 4.64 (1H, dt, $J$ = 13.7, 4.5 Hz, $H_{eq}$-1); 7.18-7.38 ($5H_{benzyl}$, m). $^{13}C$ NMR: 27.2 (C-2); 32.1 (C-3); 32.2 (C-4); 33.5 (C-6); 36.4 (C-5); 37.4 ($CH_2C_6H_5$); 40.3 (C-1); 55.1 (C-4a); 113.9, 115.5 [$C(CN)_2$]; 126.5, 126.6, 128.6, 128.8, 128.9, 139.3 ($C_{benzyl}$). IR: 3060, 3030, 2950, 2880 (CH); 2220 (CN); 1590, 1575, 1550, 1500 ($CC_{arom}$) $cm^{-1}$.

*cis-3,4a-Dihydro* ***5c***: mp 254 - 256 °C (EtOH). $^1H$ NMR: 1.20-1.35 (1H, m, $H_{ax}$-2); 1.35-1.50 (1H, m, $H_{ax}$-4); 1.78-2.00 (2H, m, $H_{eq}$-2 and $H_{ax}$-3); 2.30 (1H, ddd, $J$ = 12.6, 5.2, 2.9 Hz, $H_{eq}$-4); 2.50-2.85 (3H, m, $H_{ax}$-1 and $H_2CC_6H_5$); 3.04 and 3.17 (2H, AB system, $J$ = 16.0 Hz, H-6); 3.65 (1H, dd, $J$ = 11.7, 2.9

Hz, H-4a); 5.04 (1H, ddd, $J$ = 13.5, 4.5, 2.2 Hz, $H_{eq}$-1); 7.27-7.35 ($5H_{benzyl}$, m). $^{13}C$ NMR: 30.2 (C-2); 32.8 (C-4); 35.3 (C-6); 36.1 (C-5); 37.2 (C-3); 42.5 ($CH_2C_6H_5$); 45.1 (C-1); 58.7 (C-4a); 113.8, 115.5 [$C(CN)_2$]; 126.5, 128.5, 128.7, 128.8, 129.0, 138.8 ($C_{benzyl}$). IR: 3060, 2980, 2940, 2920, 2860 (CH); 2220 (CN); 1590, 1570, 1550, 1485 ($CC_{arom}$) $cm^{-1}$.

*9-Ethoxy-3,7-diphenyl-2,3,4,4a,5,6-hexahydro-1H-pyrido[1,2-a][1,8]naphthyridin-5,5,8-tricarbonitrile* ***4,5d***: General procedure was followed; medium-pressure chromatography was performed by using $CH_2Cl_2$:hexane (2:1) as eluent; yield: 80-96 mg (80-96 %). EtOH was used for fractional crystallization. MS: 460 ($M^+$+1, 33); 459 ($M^+$, 100); 129 (20). High Resolution MS: $C_{29}H_{25}N_5O$, calc: 459.2059, found: 459.2052.

*trans-3,4a-Dihydro* ***4d***: mp 205 - 207 °C (EtOH). $^1H$ NMR: 2.13-2.44 (3H, m, $H_{ax}$-2 and $H_{ax}$-4 and $H_{eq}$-2); 2.81 (1H, dtd, $J$ = 13.8, 3.3, 1.6 Hz, $H_{eq}$-4); 3.05 and 3.17 (2H, AB system, $J$ = 16.0 Hz, H-6); 3.33 (1H, ddd, $J$ = 13.6, 11.1, 3.6 Hz, $H_{ax}$-1); 3.44-3.52 (1H, m, $H_{eq}$-3); 3.92 (1H, dd, $J$ = 11.7, 3.3 Hz, H-4a); 4.60 (1H, dt, $J$ = 13.6, 4.7 Hz, $H_{eq}$-1); 7.30-7.50 ($5H_{phenyl}$, m). $^{13}C$ NMR: 28.1 (C-2); 32.9 (C-4); 33.4 (C-6); 33.8 (C-3); 36.2 (C-5); 40.9 (C-1); 55.3 (C-4a); 113.9, 115.6 [$C(CN)_2$]; 126.8, 127.1, 129.0, ,141.0 ($C_{phenyl}$). IR: 3040, 3020, 2980, 2940, 2860 (CH); 2220 (CN); 1580, 1570, 1550, 1490($CC_{arom}$) $cm^{-1}$.

*cis-3,4a-Dihydro* ***5d***: mp 245 - 248 °C (EtOH). $^1H$ NMR: 1.86 (1H, q, $J$ = 12.2 Hz, $H_{ax}$-4); 1.77-1.93 (1H, qd, $J$ = 12.3, 4.0 Hz, $H_{ax}$-2); 2.06-2.13 (1H, br d, $H_{eq}$-2); 2.49 (1H, ddd, $J$ = 12.8 , 5.1, 3.2 Hz, $H_{eq}$-4); 2.91 (1H, tt, $J$ = 12.3, 3.2 Hz, $H_{ax}$-3); 3.10 and 3.20 (2H, AB system, $J$ = 16.0 Hz, H-6); 2.99 (1H, td, $J$ = 13.5, 3.1 Hz, $H_{ax}$-1); 3.84 (1H, dd, $J$ = 11.7, 2.9 Hz, H-4a); 5.22 (1H, ddd, $J$ = 13.5, 4.4, 2.4 Hz, $H_{eq}$-1); 7.25-7.45 ($5H_{phenyl}$, m). $^{13}C$ NMR: 31.5 (C-2); 32.9 (C-4); 36.1 (C-5); 41.2 (C-3); 45.4 (C-1); 59.0 (C-4a); 113.8, 115.4 [$C(CN)_2$]; 126.6, 127.2, 128.9, 143.2 ($C_{phenyl}$). IR: 3040, 3010, 2980, 2940, 2860 (CH); 2210 (CN); 1580, 1570, 1550, 1490 ($CC_{arom}$) $cm^{-1}$.

*9-Ethoxy-3-hydroxy-7-phenyl-2,3,4,4a,5,6-hexahydro-1H-pyrido[1,2-a][1,8]naphthyridin-5,5,8-tricarbonitrile* ***4,5e***: General procedure was followed; medium-pressure chromatography allowed the resolution of the mixture by using a gradient of eluents (AcOEt:hexane: from 1:1 to 3:2); yield: 65-93 mg (65-93 %). MS: 400 ($M^+$+1, 26); 399 ($M^+$, 100); 398 ($M^+$-1, 14); 370 (19); 288 (23). High Resolution MS: $C_{23}H_{21}N_5O_2$, calc: 399.1695, found: 399.1678.

*trans-3,4a-Dihydro* ***4e***: mp 128 - 130 °C ($CH_2Cl_2$/EtOH). $^1H$ NMR: 1.80-.90 (3H, m, $H_{ax}$-2 and $H_{ax}$-4 and $H_{eq}$-4); 1.95-2.20 (1H, br s, HCOH); 2.27-2.36 (1H, br d, $H_{eq}$-2); 3.07 and 3.15 (2H, AB system, $J$ = 16.0 Hz, H-6); 3.30 (1H, ddd, $J$ = 13.4, 11.1, 5.3 Hz, $H_{ax}$-1); 4.16 (1H, dd, $J$ = 12.0, 2.9 Hz, H-4a); 4.37 (1H, br s, $H_{ax}$-3); 4.79 (1H, ddd, $J$ = 13.4, 4.8, 2.7 Hz, $H_{eq}$-1). $^{13}C$ NMR: 31.4 (C-4); 32.8 (C-2); 35.7 (C-6); 35.8 (C-5); 39.3 (C-1); 34.2 (C-4a); 62.8 (C-3); 113.8, 115.7 [$C(CN)_2$]. IR: 3460 (OH); 3060, 2940, 2880 (CH); 2220 (CN); 1590, 1575, 1555, 1505 ($CC_{arom}$) $cm^{-1}$.

*cis-3,4a-Dihydro* ***5e***: mp 163 - 164 °C ($CH_2Cl_2$/EtOH). $^1H$ NMR: 1.60-1.75 (3H, m, $H_{ax}$-2, $H_{ax}$-4 and HCOH); 2.11-2.20 (1H, m, $H_{eq}$-4); 2.51-2.60 (1H, m, $H_{eq}$-2); 2.87 (1H, td, $J$ = 13.5, 3.0 Hz, $H_{ax}$-1); 3.07 and 3.18 (2H, AB system, $J$ = 16.0 Hz, H-6); 3.72 (1H, dd, $J$ = 12.0, 2.8 Hz, H-4a); 3.90-4.02 (1H, m, $H_{ax}$-3); 5.11 (1H, ddd, $J$ = 13.7, 4.7, 2.7 Hz, $H_{eq}$-1). $^{13}C$ NMR· 32.7 (C-4); 33.3 (C-2); 35.7 (C-5); 37.5 (C-6); 43.3 (C-1); 57.3 (C-4a); 67.1 (C-3); 113.6, 115.4 [$C(CN)_2$]. IR: 3470 (OH); 3065, 2955, 2860 (CH); 2220 (CN); 1575, 1565, 1545, 1505 ($CC_{arom}$) $cm^{-1}$.

*9-Ethoxy-7-phenyl-3-piperidino-2,3,4,4a,5,6-hexahydro-1H-pyrido[1,2-a][1,8]naphthyridin-5,5,8-tricarbonitrile* ***4,5f***: General procedure was followed; medium-pressure chromatography allowed the resolution of the mixture by using a gradient of eluents (AcOEt:hexane: from 2:3 to 4:1); yield: 71-94 mg (71-94 %). MS: 467 ($M^+$+1, 2); 466 ($M^+$, 5); 354 (4); 124 (100). High Resolution MS: $C_{28}H_{30}N_6O$, calc: 466.2481, found: 466.2475.

*trans-3,4a-Dihydro* ***4f***: mp 210 - 215 °C (EtOH). $^1H$ NMR: 1.40-1.69 (6H, m, $HCNCH_2C\underline{H}_2C\underline{H}_2$); 1.70-1.87 (2H, m, $H_{ax}$-2 and $H_{ax}$-4); 2.20-2.27 (1H, m, $H_{eq}$-2); 2.45-2.57 (4H, m, $HCNCH_2$); 2.57-2.70 (2H, m, $H_{eq}$-3 and $H_{eq}$-4); 3.09 and 3.17 (2H, AB system, $J$ = 16.0 Hz, H-6); 3.33 (1H, td, $J$ = 12.4, 2.2 Hz, $H_{ax}$-1); 4.06 (1H, dd, $J$ = 11.5, 2.2 Hz, H-4a); 4.50 (1H, dt, $J$ = 12.5, 4.1 Hz, $H_{eq}$-1). $^{13}C$ NMR: 24.1 ($HCNCH_2CH_2\underline{C}H_2$); 25.9 ($HCNCH_2\underline{C}H_2$); 26.7, 31.6 (C-2,4); 33.8 (C-6); 36.4 (C-5); 39.6 (C-1); 51.1 ($HCN\underline{C}H_2$); 54.5 (C-3); 55.3 (C-4a); 114.0, 115.7 [$C(CN)_2$]. IR: 3070, 2990, 2940, 2860, 2820, 2780 (CH); 2220 (CN); 159, 1575, 1555, 1505 ($CC_{arom}$) $cm^{-1}$.

*cis-3,4a-Dihydro* ***5f***: mp 245 - 248 °C (EtOH). $^1H$ NMR: 1.44-1.55 (2H, m, $HCNCH_2CH_2C\underline{H}_2$); 1.54-1.79 (6H, m, $H_{ax}$-2, $H_{ax}$-4 and $HCNCH_2C\underline{H}_2$); 2.04-2 16 (1H, m, $H_{eq}$-2); 2.42 (1H, dq, $H_{eq}$-4); 2.50-2.58 (4H, m, $HCNC\underline{H}_2$); 2.65 (1H, tt, $J$ = 11.7, 3.2 Hz, $H_{ax}$-3); 2.84 (1H, td, $J$ = 13.5, 2.8 Hz, $H_{ax}$-1); 3.06 and 3.17 (2H, AB system, $J$ = 16.0 Hz, H-6); 3.75 (1H, dd, $J$ = 11.7, 2.8 Hz, H-4a); 5.11 (1H, ddd, $J$ = 13.6,

4.3, 2.7 Hz, $H_{eq}$-1). $^{13}C$ NMR: 24.2 ($HCNCH_2CH_2CH_2$); 25.6 ($HCNCH_2CH_2$); 26.5, 30.9 (C-2,4); 32.9 (C-6); 36.0 (C-5); 44.4 (C-1); 50.1 ($NCH_2$); 58.4 (C-3); 61.2 (C-4a); 113.7, 115.4 [$C(CN)_2$]. IR: 3060, 2940, 2860, 2810 (CH); 2220 (CN); 1590, 1575, 1555, 1505 ($CC_{arom}$) $cm^{-1}$.

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