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Practical synthesis of 8-acyl-7-alkyl-1,6-naphthyridin-5(6*H*)-ones

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Abstract—Reaction of a set of enaminones with 2-chloronicotinoyl chloride or 2,6-dichloro-5-fluoronicotinoyl chloride mainly leads to *N*-acylation products which cyclize directly or reacting with sodium hydride to give 8-acyl-7-alkyl-1,6-naphthyridin-5(6*H*)-ones. Due to their easy availability these compounds are attractive precursors for synthesis of polycondensed heterocycles like naphtho[2,3-*h*][1,6]naphthyridin-5-ones and pyrido[3,2-*c*][1,6]naphthyridin-6-ones.

1. Introduction

1,6-Naphthyridin-5(6*H*)-ones are an important class of azaheterocycles regarding their various biological activity.[1–4] On the other hand, these compounds can be used as synthons for the building of enlarged heterocyclic systems when they are conveniently substituted.[5,6]

The preparation of 1,6-naphthyridin-5(6*H*)-ones is relatively well documented[1,2,7–9] but few methods allow the functionalisation with keto groups like acetyl or benzoyl.[10,11]

We published recently[12] a synthetic approach of benzoyl substituted quinolin-4-ones and isoquinolin-4-ones based on the acylation reaction of enaminones. In the present work are reported results showing the possible application of this method to the preparation of 8-acyl-7-alkyl-1,6-naphthyridin-5(6*H*)-ones.

2. Results and discussion

2.1. Synthesis of 8-acyl-7-alkyl-1,6-naphthyridin-5(6*H*)-ones

The reaction of 2-chloronicotinoyl chloride **1a** or 2,6-dichloro-5-fluoronicotinoyl chloride **1b** with a series of enaminones **2** was investigated according to the experimental procedure described previously.[12]

Using these conditions, three kinds of compounds were isolated: 3-acyl-2-alkyl-1,8-naphthyridin-4-ones (**3**), 8-acyl-7-alkyl-1,6-naphthyridin-5-ones (**4**) and *N*-acylated enaminones (**5**) (Scheme 1).

Nevertheless, it can be noticed that the formation of whole these compounds during a single reaction is not observed as shown in Table 1. In half of the cases, a single product is isolated (entries 1–3, 6, 9 and 10); in the others cases, a mixture of two compounds, easily separated, is obtained (entries 4, 5, 8, 9, 11, 12). Total yield in the different products depends on the substitution of the nicotinoyl chloride: it is low with **1b**, but moderate to good with **1a**. The structure of compounds **3**–**5** have been established by ^{1}H and ^{13}C NMR and elemental analysis. Moreover, X-ray crystallography data have confirmed the structure of **4bg** (Fig. 1).

Data reported in Table 1 need some comments. Contrary to enaminoesters which led exclusively to an α *C*-acylation,[13,14] enaminones **2** used in this work give mainly *N*-acylated compounds (**5**). The cyclisation reaction of these ones in the experimental conditions chosen depends on the structure of the acid chloride. Compared to our previous results, changing aromatic acid chlorides (i.e. 2,4,5-trifluorobenzoylchloride and 2-chloro-5-nitrobenzoylchloride)[12] by pyridinic acid chlorides **1a** or **1b** undergoes a complete modification of the ratio between the three products of the reaction. *N*-acylated enaminones **5** become the main product here, while they were observed only once in the previous work.

The experimental procedure has been tentatively modified for experiments leading exclusively to compounds **5** (entries 1–3, 9, 10, Table 1). Indeed, one can reasonably assume that the lack of cyclisation did not justify the use of two kinds of bases. Curiously, when only one base (triethylamine or DBU) was used, the yield in compound **5** was lower. On the other hand, the classical acylation reaction in pyridine led to the expected compounds like **5** only when primary

Keywords: acylation; enamines; naphthyridines; cyclisation.

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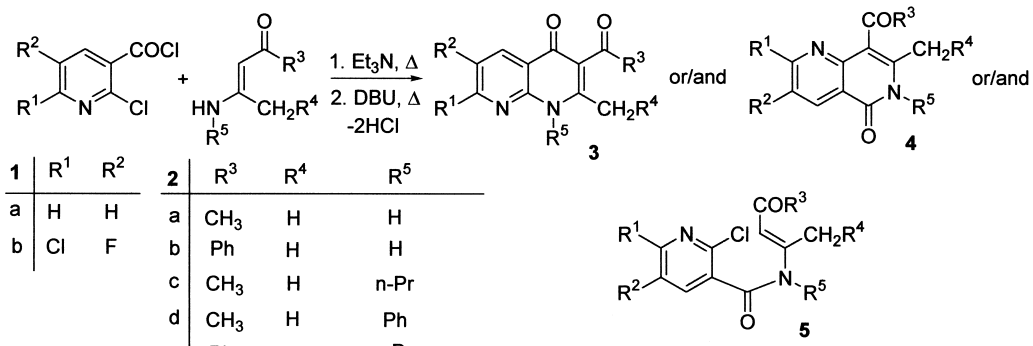


1	R^1	R^2
a	H	H
b	Cl	F

2	R^3	R^4	R^5
a	CH_3	H	H
b	Ph	H	H
c	CH_3	H	n-Pr
d	CH_3	H	Ph
e	Ph	H	n-Pr
f	Ph	Ph	n-Pr
g	Ph	Ph	Ph
h	Ph	Ph	CH_2Ph
i	Ph	Ph	$CH_2(p\text{-}OCH_3Ph)$

Scheme 1.

Table 1. Yield for products obtained from the reaction of **1** with **2**

Entry	Precursors		Products (yield, %)[a]		
1	**1a**	**2a**	–[b]	–	**5aa** (48)
2	**1a**	**2b**	–	–	**5ab** (59)
3	**1a**	**2c**	–	–	**5ac** (84)
4	**1a**	**2d**	**3ad** (7)	–	**5ad** (78)
5	**1a**	**2e**	**3ae** (26)	–	**5ae** (71)
6	**1a**	**2f**	–	**4af** (52)	–
7	**1a**	**2h**	**3ah** (10)	**4ah** (39)	–
8	**1a**	**2i**	**3ai** (13)	**4ai** (47)	–
9	**1b**	**2c**	–	–	**5bc** (42)
10	**1b**	**2d**	–	–	**5bd** (37)
11	**1b**	**2g**	**3bg** (11)	**4bg** (14)	–
12	**1b**	**2h**	**3bh** (22)	**4bh** (27)	–

[a] Yield for isolated products.
[b] Not observed.

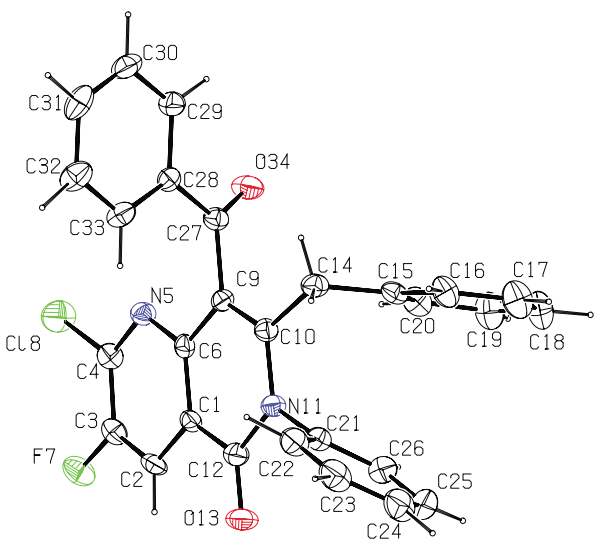


Figure 1. The ORTEP diagram of **4bg**.

enaminones (**2a**, **2b**, **2j**) are used and in low yield (Scheme 2). Nevertheless, this latest approach could be interesting to prepare **5aj** which cannot be obtained using the general method.

All the enaminones (**5**) can be cyclised into naphthyridinones **4** in presence of NaH in THF as solvent (Scheme 3) (yield: 30–80%). Lower yield is observed for compounds for which R^5=H despite an excess of sodium hydride. Taking into account this result, the best efficient way for preparing this kind of compound would consist in a deprotection of the N-6 nitrogen atom. The preparation of **4aj** (Scheme 4) confirms the feasibility of this approach.

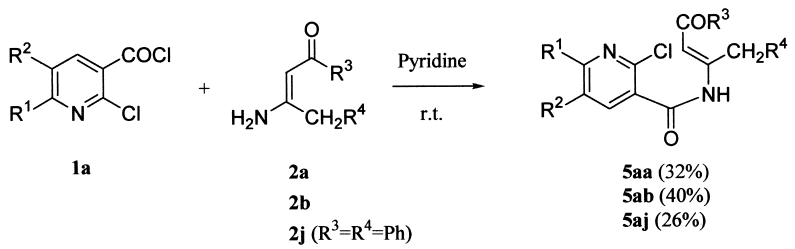
In summary, the methods proposed in this work allow the preparation of 8-acyl-7-alkylnaphthyridin-5(6*H*)-ones **4** in one or two steps from simple precursors. The easy obtention of precursors and the simplicity of the experimental procedure compensate for the relatively low yield observed.

2.2. Reaction of 8-acyl-7-alkyl-1,6-naphthyridin-5(6*H*)-ones (4)

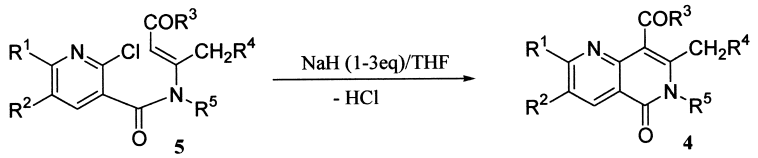
The various substitutions of the prepared naphthyridinones **4** allow different chemical transformations. Few examples are given below (Schemes 5–8).

Then the chlorine atom of the compounds prepared from the acid chlorides **1b** (compound **4bh** is taken as example) can be easily substituted by different nucleophiles (Scheme 5). This kind of reaction is often used in the chemistry of antibacterial quinolones.[15,16] Moreover, a classical method based on the application of a mixture of phosphorus oxychloride and phosphorus pentachloride[5] allows the conversion (in moderate yield) of 1,6-naphthyridin-5-ones (R^5=H) to 1,6-naphthyridines (Scheme 6).

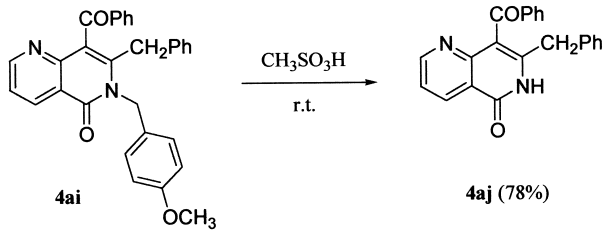
All the naphthyridinones **4** obtained bear acyl and alkyl substituents placed in *o*-position (this is specific of the proposed synthetic method). Then, different cyclisation reactions implying these groups can occur. Two examples of this kind of transformations (based on known methods)[17–19] are given in Schemes 7 and 8. The polycyclic systems built, especially naphtho[2,3-*h*][1,6]naphthyridin-5-ones (**9** and **10**) and pyrido[2,3-*c*][1,6]naphthyridin-6-ones (**13** and **14**) are to the best of our knowledge not described in the literature.



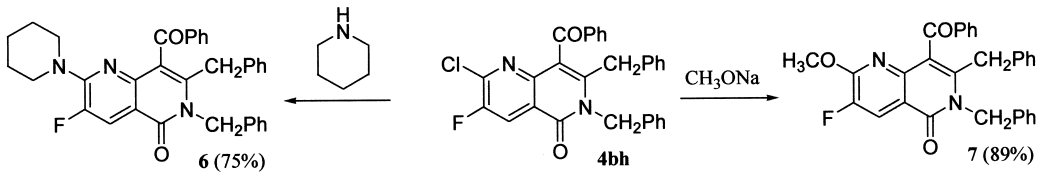
Scheme 2.



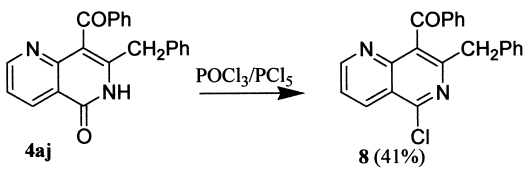
Scheme 3.



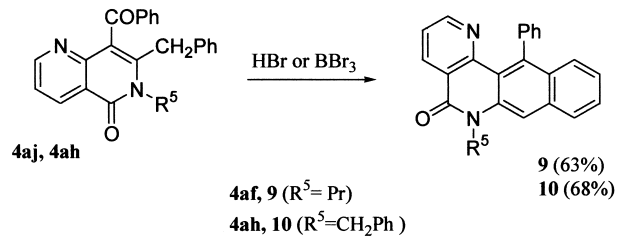
Scheme 4.



Scheme 5.



Scheme 6.



Scheme 7.

The biological activity of these compounds is now under investigation.

3. Experimental

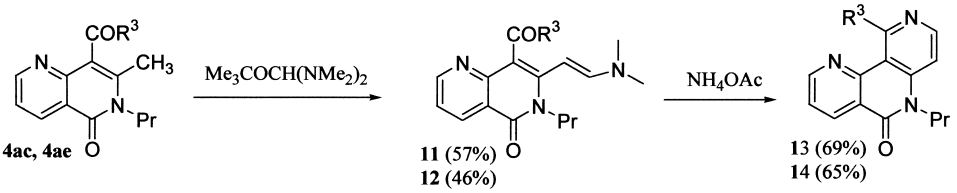
3.1. Materials and methods

^{1}H and ^{13}C NMR spectra were recorded on a Bruker BM 250 spectrometer (250 and 62.5 MHz, respectively, for ^{1}H and ^{13}C) using tetramethylsilane as internal standard. Chemical shifts are given in ppm and coupling constants in Hz. Melting points (°C), measured in capillary tubes on a Buchi 510 apparatus, are uncorrected. Column chromatography was performed on silica gel Merck (70–230 mesh). Elemental analysis was performed by the Microanalytical Center of the University of Aix-Marseille III. The identification of previously reported compounds were made by ^{1}H NMR and melting points comparison with literature data.

3.2. Starting materials

Acid chloride **1a** (Avocado), **1b** (Aldrich), enaminone **2a** (Lancaster) and *tert*-butoxy-bis(dimethylamino)methane (Bredereck's reagent) (Aldrich) are commercially available.

Enaminones **2h–2j** were prepared from corresponding 1,3-diketones and primary amines according to a standard procedure.[20] Compounds **2b**,[21] **2c**,[22] **2d**,[23] **2e**,[24] **2f**[12] and **2g**[25] were synthesised by the described methods.



4ac, **11**, **13** (R^3 =CH_3) ; **4ae**, **12**, **14** (R^3 = Ph)

Scheme 8.

3.2.1. 3-Benzylamino-1,4-diphenylbut-2-en-1-one (2h). White solid (79%). Mp 98°C. ^{1}H NMR ($CDCl_3$): 3.69 (2H, s, CH_2), 4.41 (2H, s, NCH_2), 5.80 (1H, s, CH), 7.18–7.31 (10H, m, H arom), 7.43 (3H, m, H arom), 7.83 (2H, m, H arom), 11.70 (1H, s, NH).

3.2.2. 1,4-Diphenyl-3-(4-methoxybenzyl)aminobut-2-en-1one (2i). Yellow solid (96%). Mp 111°C. ^{1}H NMR ($CDCl_3$): 3.70 (2H, s, CH_2), 3.82 (3H, s, OCH_3), 4.31 (2H, s, NCH_2), 5.69 (1H, s, CH), 6.79 (2H, d, J=8.7 Hz, H arom), 7.12 (2H, d, J=8.7 Hz, H arom), 7.22–7.43 (8H, m, H arom), 7.84 (2H, m, H arom), 11.71 (1H, s, NH).

3.2.3. 3-Amino-1,4-diphenylbut-2-en-1-one (2j). Yellow oil (96%). ^{1}H NMR ($CDCl_3$): 3.69 (2H, s, CH_2), 6.10 (1H, s, CH), 7.28–7.49 (8H, m, H arom), 7.79 (2H, m, H arom), 10.21 (2H, s, NH_2).

3.3. General method for the synthesis of compounds 3–5

A solution of acid chloride **1** (5 mmol) in dry toluene (8 ml) was added to a mixture of enaminone **2** (3.2 mmol) and dry Et_3N (10 mmol) in dry toluene (7 ml). The resulting mixture was refluxed for 3 h, then DBU (10 mmol) was added and refluxing was maintained for 3 h more. The solvent was evaporated to dryness and the residue was dissolved in 25 ml CH_2Cl_2. The organic phase was washed with a saturated solution of NH_4Cl and then with brine, dried ($MgSO_4$) and evaporated. The crude product was purified by column chromatography on silica gel.

3.3.1. 4-(2-Chloronicotinoyl)aminopent-2-en-1-one (5aa). R_f=0.38 (cyclohexane/EtOAc 7:3), 48% yield, white solid, mp 86–87°C (from methanol). ^{1}H NMR ($CDCl_3$): 1.90 (3H, s, CH_3), 2.24 (3H, s, $COCH_3$), 5.24 (1H, s, CH), 7.10 (1H, dd, J=7.5, 4.8 Hz, H-5′), 7.67 (1H, dd, J=7.5, 1.8 Hz, H-4′), 8.24 (1H, dd, J=4.8, 1.8 Hz, H-6′), 12.59 (1H, s, NH). ^{13}C NMR ($CDCl_3$): 22.6 (q), 31.3 (q), 107.9 (d), 123.3 (d), 132.5 (s), 139.0 (d), 148.7 (s), 152.1 (d), 154.9 (s), 165.1 (s), 200.8 (s). Anal. calcd for $C_{11}H_{11}ClN_2O_2$: C, 55.36; H, 4.65; N, 11.74; found: C, 55.33; H, 4.61; N, 11.76.

3.3.2. 3-(2-Chloronicotinoyl)amino-1-phenylbut-2-en-1-one (5ab). R_f=0.62 (cyclohexane/EtOAc 7:3), 59% yield, white solid, mp 128–129°C (from methanol). ^{1}H NMR ($CDCl_3$): 2.44 (3H, s, CH_3), 6.00 (1H, s, CH), 7.16 (1H, dd, J=7.5, 4.8 Hz, H-5′), 7.22 (2H, m, H arom), 7.33 (1H, m, H arom), 7.69 (2H, m, H arom), 7.78 (1H, dd, J=7.5, 1.8 Hz, H-4′), 8.31 (1H, dd, J=4.8, 1.8 Hz, H-6′), 13.12 (1H, s, NH). ^{13}C NMR ($CDCl_3$): 23.4 (q), 104.2 (d), 123.4 (d), 128.6 (d), 129.4 (d), 132.6 (s), 133.6 (d), 139.0 (s), 139.1 (d), 148.9 (s), 152.1 (d), 157.2 (s), 165.3 (s), 192.4 (s). Anal. calcd for $C_{16}H_{13}ClN_2O_2$: C, 63.90; H, 4.36; N, 9.31; found C, 63.92; H, 4.34; N, 9.30.

3.3.3. 4-[*N*-Propyl-*N*-(2-chloronicotinoyl)amino]-pent-3-en-2-one (5ac). R_f=0.48 (cyclohexane/EtOAc 8:2), 84% yield, yellow oil. ^{1}H NMR ($CDCl_3$): 0.91 (3H, t, J=7.5 Hz, $CH_2CH_2CH_3$), 1.50 (2H, m, $CH_2CH_2CH_3$), 2.00 (3H, s, CH_3), 2.21 (3H, s, $COCH_3$), 3.52 (2H, m, $CH_2CH_2CH_3$), 6.93 (1H, s, CH), 7.12 (1H, m, H-5′), 7.61 (1H, dd, J=7.8, 1.8 Hz, H-4′), 8.27 (1H, dd, J=4.5, 1.8 Hz, H-6′). ^{13}C NMR ($CDCl_3$): 11.2 (q), 18.5 (q), 21.2 (t), 31.7 (q), 47.6 (t), 122.5 (d), 125.3 (d), 133.1 (s), 136.8 (d), 147.2 (s), 150.0 (d), 151.2 (s), 165.2 (s), 196.2 (s). Anal. calcd for $C_{14}H_{17}ClN_2O_2$: C, 59.89; H, 6.10; N, 9.98; found C, 59.90; H, 6.11; N, 9.96.

3.3.4. 4-[*N*-Phenyl-*N*-(2-chloronicotinoyl)amino]-pent-3-en-2-one (5ad). R_f=0.43 (cyclohexane/EtOAc 8:2), 78% yield, yellow oil. ^{1}H NMR ($CDCl_3$): 1.68 (3H, s, CH_3), 1.98 (3H, s, $COCH_3$) 5.7 (1H, s, CH), 6.72–6.85 (5H, m, H arom), 7.24 (1H, m, H-5′), 7.39 (1H, dd, J=7.9, 1.7 Hz, H-4′), 7.78 (1H, dd, J=4.4, 1.7 Hz, H-6′). ^{13}C NMR ($CDCl_3$): 18.7 (q), 31.8 (q), 121.8 (d), 122.1 (d), 123.4 (s), 127.7 (d), 128.2 (d), 129.3 (d), 137.8 (d), 139.4 (s), 146.5 (s), 150.0 (d), 152.9 (s), 165.8 (s), 197.2 (s). Anal. calcd for $C_{17}H_{15}ClN_2O_2$: C, 64.87; H, 4.80; N, 8.90; found: C, 64.85; H, 4.82; N, 8.93.

3.3.5. 3-Acetyl-2-methyl-1-phenyl-1,8-naphthyridin-4(1*H*)-one (3ad). R_f=0.27 (cyclohexane/EtOAc 8:2), 7% yield, white solid, mp 142–143°C (from methanol). ^{1}H NMR ($CDCl_3$): 2.11 (3H, s, CH_3), 2.72 (3H, s, $COCH_3$), 7.21 (2H, m, H arom), 7.34 (1H, m, H-6), 7.67 (3H, m, H arom), 8.51 (1H, dd, J=4.5, 1.9 Hz, H-7), 8.72 (1H, dd, J=7.8, 1.9 Hz, H-5). ^{13}C NMR ($CDCl_3$): 20.3 (q), 32.5 (q), 120.6 (d), 121.1 (s), 125.0 (s), 129.1 (d), 129.6 (d), 130.2 (d), 136.7 (d), 138.9 (s), 151.8 (s), 152.7 (s), 152.9 (d), 176.3 (s), 203.7 (s). Anal. calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07; found C, 73.26; H, 5.01; N, 10.04.

3.3.6. 4-[*N*-Propyl-*N*-(2-chloronicotinoyl)amino]-1-phenylbut-2-en-1-one (5ae). R_f=0.44 (cyclohexane/EtOAc 8:2), 71% yield, white solid, mp 80–81°C (from methanol). ^{1}H NMR ($CDCl_3$): 1.02 (3H, t, J=7.5 Hz, $CH_2CH_2CH_3$), 1.71 (2H, m, $CH_2CH_2CH_3$), 2.34 (3H, s, CH_3), 3.76 (2H, m, $CH_2CH_2CH_3$), 6.61 (1H, s, CH), 7.32 (1H, m, H-5′), 7.41 (2H, m, H arom), 7.52 (1H, m, H arom), 7.61 (2H, m, H arom), 7.69 (1H, dd, J=7.6, 1.7 Hz, H-6′), 8.34 (1H, m, H-4′). ^{13}C NMR ($CDCl_3$): 11.4 (q), 19.3 (q), 21.7 (t), 47.6 (t), 122.6 (d), 123.4 (s), 128.7 (d), 128.8 (d), 133.2 (d), 133.3 (d), 136.5 (d), 138.1 (s), 147.8 (s), 150.2 (d),

152.4 (s), 165.3 (s), 190.1 (s). Anal. calcd for $C_{19}H_{19}ClN_2O_2$: C, 66.57; H, 5.59; N, 8.17; found C, 66.55; H, 5.60; N, 8.19.

3.3.7. 3-Benzoyl-2-methyl-1-propyl-1,8-naphthyridin-4(1*H*)-one (3ae). R_f=0.32 (cyclohexane/EtOAc 8:2), 26% yield, white solid, mp 177–178°C (from methanol). ^{1}H NMR ($CDCl_3$): 1.02 (3H, t, J=7.3 Hz, $CH_2CH_2CH_3$), 1.81 (2H, m, $CH_2CH_2CH_3$), 2.44 (3H, s, CH_3), 4.50 (2H, t, J=7.2 Hz, $CH_2CH_2CH_3$), 7.21 (1H, dd, J=7.4, 4.5 Hz, H-6), 7.41 (2H, m, H arom), 7.54 (1H, m, H arom), 7.92 (2H, m, H arom), 8.62 (1H, dd, J=7.4, 1.7 Hz, H-5), 8.75 (1H, dd, J=4.4, 1.8 Hz, H-7). ^{13}C NMR ($CDCl_3$): 11.4 (q), 18.4 (q), 22.8 (t), 47.0 (t), 120.1 (d), 121.2 (s), 123.6 (s), 128.8 (d), 129.5 (d), 133.6 (d), 135.9 (d), 137.7 (s), 150.3 (s), 150.4 (s), 152.6 (d), 175.6 (s), 197.0 (s). Anal. calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14; found C, 74.40; H, 5.89; N, 9.09.

3.3.8. 8-Benzoyl-7-benzyl-6-propyl-1,6-naphthyridin-5(6*H*)-one (4af). R_f=0.35 (cyclohexane/EtOAc 8:2), 52% yield, white solid, mp 167–168°C (from methanol). ^{1}H NMR ($CDCl_3$): 0.92 (3H, t, J=7.4 Hz, $CH_2CH_2CH_3$), 1.61 (2H, m, $CH_2CH_2CH_3$), 3.88 (2H, t, J=7.8 Hz, $CH_2CH_2CH_3$), 4.01 (2H, s, CH_2), 7.25 (5H, m, H arom), 7.40 (3H, m, H arom and H-3), 7.54 (1H, m, H arom), 7.89 (2H, m, H arom), 8.68 (1H, dd, J=8.0, 1.5 Hz, H-4), 8.77 (1H, dd, J=3.8, 1.5 Hz, H-2). ^{13}C NMR ($CDCl_3$): 11.3 (q), 22.0 (t), 37.0 (t), 46.4 (t), 120.1 (s), 120.2 (s), 121.9 (d), 127.2 (d), 128.0 (d), 128.7 (d), 129.0 (d), 129.7 (d), 133.7 (d), 135.9 (s), 136.2 (d), 137.7 (s), 142.4 (s), 151.8 (s), 154.6 (d), 162.7 (s), 196.1 (s). Anal. calcd for $C_{25}H_{22}N_2O_2$: C, 78.51; H, 5.80; N, 7.32; found C, 78.42; H, 5.71; N, 7.38.

3.3.9. 8-Benzoyl-6,7-dibenzyl-1,6-naphthyridin-5(6*H*)-one (4ah). R_f=0.53 (cyclohexane/EtOAc 8:2), 39% yield, white solid, mp 134–135°C (from methanol). ^{1}H NMR ($CDCl_3$): 3.81 (2H, s, CH_2), 5.22 (2H, s, NCH_2), 7.09–7.44 (13H, m, H arom and H-3), 7.52 (1H, m, H arom), 7.89 (2H, m, H arom), 8.74 (1H, dd, J=8.0, 1.8 Hz, H-4), 8.79 (1H, dd, J=4.5, 1.8 Hz, H-2). ^{13}C NMR ($CDCl_3$): 37.0 (t), 47.0 (t), 120.3 (s), 120.9 (s), 122.3 (d), 126.0 (d), 127.5 (d), 127.7 (d), 128.0 (d), 129.2 (d), 129.3 (d), 129.9 (d), 133.9 (d), 135.7 (s), 135.9 (s), 136.8 (d), 137.8 (s), 142.9 (s), 152.2 (s), 155.1 (d), 163.3 (s), 195.7 (s). Anal. calcd for $C_{29}H_{22}N_2O_2$: C, 80.91; H, 5.15; N, 6.51; found C, 80.82; H, 5.09; N, 6.43.

3.3.10. 3-Benzoyl-1,2-dibenzyl-1,8-naphthyridin-4(1*H*)-one (3ah). R_f=0.35 (cyclohexane/EtOAc 8:2), 10% yield, white solid, mp 154–155°C (from methanol). ^{1}H NMR ($CDCl_3$): 3.96 (2H, s, CH_2), 5.70 (2H, s, NCH_2), 7.00 (2H, m, H arom), 7.21–7.49 (13H, m, H arom, H-6 and H-7), 7.91 (2H, m, H arom), 8.70 (1H, dd, J=8.1, 1.7 Hz, H-5). ^{13}C NMR ($CDCl_3$): 37.1 (t), 47.5 (t), 120.6 (d), 121.1 (s), 125.5 (s), 127.4 (d), 127.7 (d), 128.1 (d), 128.7 (d), 129.2 (d), 129.5 (d), 133.6 (d), 135.5 (s), 136.3 (d), 136.9 (s), 137.5 (s), 151.0 (s), 151.9 (s), 153.0 (d), 176.2 (s), 195.9 (s). Anal. calcd for $C_{29}H_{22}N_2O_2$: C, 80.91; H, 5.15; N, 6.51; found C, 80.83; H, 5.10; N, 6.49.

3.3.11. 8-Benzoyl-7-benzyl-6-(4-methoxybenzyl)-1,6-naphthyridin-5(6*H*)-one (4ai). R_f=0.27 (cyclohexane/EtOAc 8:2), 47% yield, white solid, mp 105–106°C (from methanol). ^{1}H NMR ($CDCl_3$): 3.84 (3H, s, OCH_3), 3.92 (2H, s, CH_2), 5.19 (2H, s, NCH_2), 6.91 (2H, dd, J=8.7, 1.5 Hz, H arom), 7.09 (2H, dd, J=8.7, 1.5 Hz, H arom), 7.21–7.39 (8H, m, H arom and H-3), 7.49 (1H, m, H arom), 7.88 (2H, m, H arom), 8.74 (1H, dd, J=8.1, 1.8 Hz, H-4), 8.80 (1H, dd, J=4.6, 1.8 Hz, H-2). ^{13}C NMR ($CDCl_3$): 36.7 (t), 46.3 (t), 55.3 (q), 114.4 (d), 120.1 (s), 120.7 (s), 122.1 (d), 126.8 (d), 127.3 (d), 127.8 (d), 129.1 (d), 129.7 (d), 133.7 (d), 135.7 (s), 135.8 (s), 136.6 (d), 137.6 (s), 142.8 (s), 152.0 (s), 154.8 (d), 159.0 (s), 163.2 (s), 195.7 (s). Anal. calcd for $C_{30}H_{24}N_2O_3$: C, 78.24; H, 5.25; N, 6.08; found C, 78.19; H, 5.20; N, 6.02.

3.3.12. 3-Benzoyl-2-benzyl-1-(4-methoxybenzyl)-1,8-naphthyridin-4(1*H*)-one (3ai). R_f=0.12 (cyclohexane/EtOAc 8:2), 13% yield, white solid, mp 98–99°C (from methanol). ^{1}H NMR ($CDCl_3$): 3.81 (5H, s, OCH_3 and CH_2), 4.01 (2H, s, NCH_2), 6.81 (2H, dd, J=8.7, 2.1 Hz, H arom), 6.92 (2H, dd, J=8.7, 2.1 Hz, H arom), 7.19–7.49 (9H, m, H arom and H-6), 7.88 (2H, m, H arom), 8.70 (2H, m, H-5 and H-7). ^{13}C NMR ($CDCl_3$): 37.0 (t), 47.1 (t), 55.4 (q), 114.6 (d), 120.6 (d), 121.1 (s), 125.5 (s), 126.9 (d), 127.4 (d), 128.1 (d), 128.8 (d), 129.2 (d), 129.5 (d), 133.5 (d), 135.6 (s), 135.7 (s), 136.2 (d), 137.5 (s), 151.0 (s), 152.0 (s), 153.0 (d), 159.2 (s), 176.2 (s), 196.0 (s). Anal. calcd for $C_{30}H_{24}N_2O_3$: C, 78.24; H, 5.25; N, 6.08; found C, 78.18; H, 5.19; N, 5.99.

3.3.13. 4-[*N*-Propyl-*N*-(2,5-dichloro-4-fluoronicotinoyl)amino]-pent-3-en-2-one (5bc). R_f=0.50 (cyclohexane/EtOAc 7:3), 42% yield, yellow oil. ^{1}H NMR ($CDCl_3$): 0.87 (3H, t, J=7.3 Hz, $CH_2CH_2CH_3$), 1.57 (2H, m, $CH_2CH_2CH_3$), 1.99 (3H, s, CH_3), 2.18 (3H, s, $COCH_3$), 3.52 (2H, t, J=7.1 Hz, $CH_2CH_2CH_3$), 5.99 (1H, s, CH), 7.43 (1H, d, J_{HF}=6.9 Hz, H-4′). ^{13}C NMR ($CDCl_3$): 10.9 (q), 18.2 (t), 20.9 (t), 31.6 (q), 47.6 (t), 125.0 (d, $^2J_{CF}$=24.8 Hz), 125.4 (d), 133.1 (s), 137.7 (s, $^2J_{CF}$=21.4 Hz), 140.3 (s, $^3J_{CF}$=3.7 Hz), 150.7 (s), 153.5 (s, $^1J_{CF}$=263.4 Hz), 162.7 (s), 196.5 (s). Anal. calcd for $C_{14}H_{15}Cl_2FN_2O_2$: C, 50.47; H, 4.54; N, 8.41; found C, 50.49; H, 4.55; N, 8.44.

3.3.14. 4-[*N*-Phenyl-*N*-(2,5-dichloro-4-fluoronicotinoyl)amino]-pent-3-en-2-one (5bd). R_f=0.51 (cyclohexane/EtOAc 7:3), 37% yield, yellow oil. ^{1}H NMR ($CDCl_3$): 2.04 (3H, s, CH_3), 2.31 (3H, s, $COCH_3$), 6.11 (1H, s, CH), 7.12–7.26 (5H, m, H arom), 7.50 (1H, d, J_{HF}=7.0 Hz, H-4′). ^{13}C NMR ($CDCl_3$): 19.0 (q), 32.3 (q), 126.5 (d, $^2J_{CF}$=22.3 Hz), 127.3 (d), 128.0 (d), 129.0 (d), 129.9 (d), 133.1 (s), 138.7 (s, $^2J_{CF}$=16.0 Hz), 139.4 (s), 140.4 (s, $^3J_{CF}$=3.8 Hz), 153.2 (s), 153.6 (s, $^1J_{CF}$=264.1 Hz), 163.8 (s), 197.5 (s). Anal. calcd for $C_{17}H_{13}Cl_2FN_2O_2$: C, 55.60; H, 3.57; N, 7.63; found C, 55.62; H, 3.59; N, 7.60.

3.3.15. 8-Benzoyl-7-benzyl-2-chloro-3-fluoro-6-phenyl-1,6-naphthyridin-5(6*H*)-one (4bg). R_f=0.75 (CH_2Cl_2/pentane 9:1), 14% yield, white solid, mp 157–158°C (from methanol). ^{1}H NMR ($CDCl_3$): 3.70 (2H, s, CH_2), 6.69 (2H, m, H arom), 6.82 (2H, m, H arom), 7.00 (3H, m, H arom), 7.29 (3H, m, H arom), 7.42 (2H, m, H arom), 7.59 (1H, m, H arom), 7.91 (2H, m, H arom), 8.29 (1H, d, J_{HF}=7.6 Hz, H-4). ^{13}C NMR ($CDCl_3$): 37.6 (t), 118.8 (s), 121.0 (s, $^3J_{CF}$=3.3 Hz), 122.7 (d, $^2J_{CF}$=20.5 Hz), 126.9 (d),

128.3 (d), 128.4 (d), 128.8 (d), 129.1 (d), 129.3 (d), 129.8 (d), 134.0 (d), 135.5 (s), 136.8 (s), 137.6 (s), 144.4 (s, $^4J_{CF}$=2.1 Hz), 145.4 (s, $^2J_{CF}$=20.9 Hz), 148.1 (s), 153.1 (s, $^1J_{CF}$=263.1 Hz), 161.9 (s), 194.6 (s). Anal. calcd for $C_{28}H_{18}ClFN_2O_2$: C, 71.72; H, 3.87; N, 5.97; found C, 71.69; H, 3.84; N, 5.93.

Crystal data for **4bg**. ($C_{28}H_{18}ClFN_2O_2$) M_r=468.89, orthorhombic, a=9.485(2) Å, b=19.397(4) Å, c=25.298(5) Å, V=4654.3(17) Å^3, space group *Pcab*, Z=8, D_c=1.338 mg m^{-3}, $F(000)$=1936, μ=0.201 mm^{-1}, T=293 K, θ_{max}=26.97°, $0<h<12$, $0<k<24$, $0<l<32$, reflections collected 3806, independent reflection 3806 (full-matrix least-squares on F^2). Atomic coordinates, thermal parameters and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Center as supplementary publication number CCDC 186741.

3.3.16. 3-Benzoyl-2-benzyl-7-chloro-6-fluoro-1-phenyl-1,8-naphthyridin-4(1*H*)-one (3bg). R_f=0.50 (CH_2Cl_2/pentane 9:1), 11% yield, white solid, mp 132–133°C (from methanol). ^{1}H NMR ($CDCl_3$): 3.81 (2H, s, CH_2), 6.72 (2H, m, H arom), 6.89 (2H, m, H arom), 7.03 (3H, m, H arom), 7.29 (2H, m, H arom), 7.44 (3H, m, H arom), 7.52 (1H, m, H arom), 7.89 (2H, m, H arom), 8.40 (1H, d, J_{HF}=7.1 Hz, H-5). ^{13}C NMR ($CDCl_3$): 37.8 (t), 120.8 (s, $^3J_{CF}$=2.9 Hz), 121.9 (d, $^2J_{CF}$=20.5 Hz), 124.8 (s), 127.0 (d), 128.5 (d), 128.6 (d), 128.8 (d), 129.4 (d), 129.5 (d), 129.6 (d), 133.8 (d), 135.5 (s), 137.0 (s), 137.2 (s), 142.6 (s, $^2J_{CF}$=20.1 Hz), 147.2 (s, $^4J_{CF}$=2.6 Hz), 152.8 (s), 156.1 (s, $^1J_{CF}$=261.1 Hz), 175.3 (s), 195.4 (s). Anal. calcd for $C_{28}H_{18}ClFN_2O_2$: C, 71.72; H, 3.87; N, 5.97; found C, 71.69; H, 3.81; N, 5.93.

3.3.17. 8-Benzoyl-2-chloro-6,7-dibenzyl-3-fluoro-1,6-naphthyridin-5(6*H*)-one (4bh). R_f=0.41 (cyclohexane/EtOAc 8:2), 27% yield, white solid, mp 160–161°C (from methanol). ^{1}H NMR ($CDCl_3$): 3.81 (2H, s, CH_2), 5.21 (2H, s, NCH_2), 7.09–7.41 (12H, m, H arom), 7.49 (1H, m, H arom), 7.82 (2H, m, H arom), 8.40 (1H, d, J_{HF}=7.6 Hz, H-4). ^{13}C NMR ($CDCl_3$): 36.9 (t), 47.2 (t), 119.5 (s), 120.5 (s, $^3J_{CF}$=3.3 Hz), 122.9 (d, $^2J_{CF}$=20.4 Hz), 126.0 (d), 127.6 (d), 127.9 (d), 128.0 (d), 128.8 (d), 129.3 (d), 129.4 (d), 129.7 (d), 134.0 (d), 135.5 (s), 136.3 (s), 137.6 (s), 143.7 (s), 145.5 (s, $^2J_{CF}$=20.9 Hz), 147.8 (s, $^4J_{CF}$=4.4 Hz), 153.1 (s, $^1J_{CF}$=263.2 Hz), 162.0 (s), 194.4 (s). Anal. calcd for $C_{29}H_{20}ClFN_2O_2$: C, 72.12; H, 4.17; N, 5.80; found C, 72.13; H, 4.15; N, 5.82.

3.3.18. 3-Benzoyl-7-chloro-1,2-dibenzyl-6-fluoro-1,8-naphthyridin-4(1*H*)-one (3bh). R_f=0.37 (cyclohexane/EtOAc 8:2), 22% yield, white solid, mp 153–154°C (from methanol). ^{1}H NMR ($CDCl_3$): 3.95 (2H, s, CH_2), 5.60 (2H, s, NCH_2), 7.01 (2H, m, H arom), 7.09–7.42 (10H, m, H arom), 7.51 (1H, m, H arom), 7.75 (2H, m, H arom), 8.10 (1H, d, J_{HF}=6.0 Hz, H-5). ^{13}C NMR ($CDCl_3$): 37.0 (t), 48.5 (t), 121.1 (s, $^3J_{CF}$=6.0 Hz), 122.1 (d, $^2J_{CF}$=20.1 Hz), 125.6 (s), 127.8 (d), 128.0 (d), 128.1 (d), 128.2 (d), 129.0 (d), 129.5 (d), 129.6 (d), 129.7 (d), 134.0 (d), 135.0 (s), 136.0 (s), 136.9 (s), 142.7 (s, $^2J_{CF}$=22.3 Hz), 146.0 (s, $^4J_{CF}$=4.0 Hz), 152.1 (s), 152.2 (s, $^1J_{CF}$=260.5 Hz), 174.7 (s), 195.3 (s). Anal. calcd for $C_{29}H_{20}ClFN_2O_2$: C, 72.12; H, 4.17; N, 5.80; found C, 72.07; H, 4.11; N, 5.79.

3.4. General method for primary enaminones acylation in pyridine

A mixture of **1a** (880 mg, 5 mmol) and **2** (**2a**, **2b**, **2j**) (2.5 mmol) in dry pyridine (5 ml) was stirred at room temperature for 5 h. The resulting solution was poured into cold water (10 ml). The aqueous phase was acidified with 10% HCl to pH 5–6 and extracted with CH_2Cl_2 (2×20 ml). The organic phase was washed with water (2×20 ml) and brine (2×20 ml), dried ($MgSO_4$) and evaporated. The crude product was purified by column chromatography on silica gel (cyclohexane/EtOAc 8:2).

3.4.1. Compound 5aa. 32% yield. The obtained compound has the same characteristics as those obtained by the method discussed in Section 3.3 (cf. Section 3.3.1).

3.4.2. Compound 5ab. 40% yield. The obtained compound has the same characteristics as those obtained by the method discussed in Section 3.3 (cf. Section 3.3.2).

3.4.3. 3-(2-Chloronicotinoyl)amino-1,4-diphenylbut-3-en-2-one (5aj). R_f=0.43 (cyclohexane/EtOAc 8:2), 26% yield, yellow oil. ^{1}H NMR ($CDCl_3$): 4.14 (2H, s, CH_2), 6.16 (1H, s, CH), 6.99–7.37 (8H, m, H arom and H-5′), 7.41 (1H, m, H arom), 7.90 (1H, m, H arom), 8.09 (1H, dd, J=7.7, 1.9 Hz, H-4′), 8.39 (1H, dd, J=4.8, 1.9 Hz, H-6′), 13.20 (1H, s, NH). ^{13}C NMR ($CDCl_3$): 44.0 (t), 121.6 (d), 122.6 (d), 125.9 (s), 128.1 (d), 128.9 (d), 129.0 (d), 129.1 (d), 129.8 (d), 133.5 (s), 133.9 (d), 136.4 (s), 141.0 (d), 142.8 (s), 150.6 (s), 152.7 (d), 162.0 (s), 195.6 (s). Anal. calcd for $C_{22}H_{17}ClN_2O_2$: C, 70.12; H, 4.55; N, 7.43; found: C, 70.10; H, 4.58; N, 7.45.

3.5. General method for cyclisation of 5 in 4

To a stirred suspension of NaH (3 mmol, 9 mmol for **5aa**, **5ab** and **5aj**) in dry THF (5 ml) a solution of compound **5** (3 mmol) in dry THF (5 ml) was slowly added. The mixture was refluxed for 4 h and the solvent was evaporated in vacuo. The resulting oil was dissolved in cooled water. The aqueous phase was acidified with 10% HCl to pH 5–6 and extracted with CH_2Cl_2 (2×20 ml). The combined organic phases were washed with water (30 ml) and brine (2×30 ml), dried ($MgSO_4$) and evaporated. The crude product was purified by column chromatography on silica gel.

3.5.1. 8-Acetyl-7-methyl-1,6-naphthyridin-5(6*H*)-one (4aa). R_f=0.32 (EtOAc/cyclohexane 8:2), 30% yield, white solid, mp >250°C. ^{1}H NMR (DMSO-d^6): 2.04 (3H, s, CH_3), 2.37 (3H, s, $COCH_3$), 7.29 (1H, dd, J=8.1, 4.8 Hz, H-3), 8.28 (1H, dd, J=8.1, 1.8 Hz, H-4), 8.71 (1H, dd, J=4.8, 1.8 Hz, H-2), 11.57 (1H, s, NH). ^{13}C NMR (DMSO-d^6): 18.3 (q), 30.1 (q), 119.3 (s), 120.6 (s), 122.6 (d), 136.5 (d), 143.6 (s), 153.4 (s), 155.5 (d), 163.0 (s), 203.2 (s). Anal. calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85; found C, 65.30; H, 4.95; N, 13.82.

3.5.2. 8-Benzoyl-7-methyl-1,6-naphthyridin-5(6*H*)-one

(4ab). R_f=0.38 (EtOAc/cyclohexane 8:2), 35% yield, white solid, mp >250°C. ^{1}H NMR (DMSO-d^6): 1.93 (3H, s, CH_3), 7.21 (1H, dd, *J*=8.1, 4.5 Hz, H-3), 7.29 (2H, m, H arom), 7.41 (1H, m, H arom), 7.59 (2H, m, H arom), 8.30 (1H, dd, *J*=8.1, 1.8 Hz, H-4), 8.48 (1H, dd, *J*=4.5, 1.8 Hz, H-2), 11.68 (1H, s, NH). ^{13}C NMR (DMSO-d^6): 18.1 (q), 116.9 (s), 120.7 (s), 122.6 (d), 130.0 (d), 130.4 (d), 134.7 (d), 136.4 (d), 139.1 (s), 142.7 (s), 154.3 (s), 155.5 (d), 163.3 (s), 196.8 (s). Anal. calcd for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60; found C, 72.69; H, 4.59; N, 10.62.

3.5.3. 8-Acetyl-7-methyl-6-propyl-1,6-naphthyridin-5(6*H*)-one (4ac). R_f=0.22 (cyclohexane/EtOAc 8:2), 51% yield, white solid, mp 59–61°C. ^{1}H NMR ($CDCl_3$): 0.92 (3H, t, *J*=7.4 Hz, $CH_2CH_2CH_3$), 1.61 (2H, m, CH_2CH_2-CH_3), 2.31 (3H, s, CH_3), 2.54 (3H, s, $COCH_3$), 3.91 (2H, t, *J*=8.0 Hz, $CH_2CH_2CH_3$), 7.25 (1H, dd, *J*=8.1, 4.5 Hz, H-3), 8.52 (1H, dd, *J*=8.1, 2.1 Hz, H-4), 8.74 (1H, dd, *J*=4.5, 2.2 Hz, H-2). ^{13}C NMR ($CDCl_3$): 11.1 (q), 16.9 (q), 21.8 (t), 33.1 (q), 45.8 (t), 119.3 (s), 121.0 (s), 121.2 (d), 135.9 (d), 140.7 (s), 150.7 (s), 153.9 (d), 161.8 (s), 203.9 (s). Anal. calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47; found C, 68.79; H, 6.62; N, 11.41.

3.5.4. 8-Acetyl-7-methyl-6-phenyl-1,6-naphthyridin-5(6*H*)-one (4ad). R_f=0.45 (cyclohexane/EtOAc 8:2), 46% yield, white solid, mp 91–92°C. ^{1}H NMR ($CDCl_3$): 1.70 (3H, s, CH_3), 2.40 (3H, s, $COCH_3$), 6.93 (2H, m, H arom), 7.00 (1H, dd, *J*=8.0, 4.6 Hz, H-3), 7.19 (3H, m, H arom), 8.22 (1H, dd, *J*=8.0, 1.7 Hz, H-4), 8.62 (1H, dd, *J*=4.5, 1.7 Hz, H-2). ^{13}C NMR ($CDCl_3$): 18.8 (q), 33.2 (q), 119.8 (s), 120.9 (s), 121.7 (d), 128.2 (d), 129.0 (d), 129.8 (d), 136.2 (d), 137.9 (s), 141.5 (s), 151.3 (s), 154.4 (d), 162.5 (s), 203.7 (s). Anal. calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07; found C, 73.32; H, 5.05; N, 10.04.

3.5.5. 8-Benzoyl-7-methyl-6-propyl-1,6-naphthyridin-5(6*H*)-one (4ae). R_f=0.32 (cyclohexane/EtOAc 6:4), 80% yield, white solid, mp 156–157°C. ^{1}H NMR ($CDCl_3$): 1.00 (3H, t, *J*=7.3 Hz, $CH_2CH_2CH_3$), 1.79 (2H, m, CH_2CH_2-CH_3), 2.40 (3H, s, CH_3), 4.14 (2H, t, *J*=7.3 Hz, CH_2CH_2-CH_3), 7.32 (1H, m, H3), 7.39 (2H, m, H arom), 7.52 (1H, m, H arom), 7.95 (2H, m, H arom), 8.65 (1H, dd, *J*=7.9, 1.6 Hz, H-4), 8.69 (1H, dd, *J*=4.6, 1.6 Hz, H-2). ^{13}C NMR ($CDCl_3$): 11.4 (q), 17.8 (q), 22.1 (t), 46.0 (t), 118.5 (s), 119.6 (s), 121.5 (d), 128.8 (d), 129.7 (d), 133.7 (d), 136.2 (d), 137.8 (s), 141.8 (s), 151.8 (s), 154.5 (d), 162.4 (s), 196.6 (s). Anal. calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14; found C, 74.46; H, 5.90; N, 9.11.

3.5.6. 8-Benzoyl-7-benzyl-1,6-naphthyridin-5(6*H*)-one (4aj). 42% yield, white solid, mp >250°C. ^{1}H NMR (DMSO-d^6): 4.22 (2H, s, CH_2), 7.18–7.26 (5H, m, H arom), 7.31 (3H, m, H arom and H-3), 7.45 (1H, m, H arom), 7.75 (2H, m, H arom), 8.50 (1H, dd, *J*=7.8, 1.8 Hz, H-4), 8.55 (1H, dd, *J*=4.4, 1.8 Hz, H-2), 10.60 (1H, s, NH). ^{13}C NMR (DMSO-d^6): 43.3 (t), 118.5 (s), 122.3 (d), 126.7 (s), 128.4 (d), 128.6 (d), 128.8 (d), 128.9 (d), 130.1 (d), 132.0 (s), 134.0 (d), 136.0 (s), 137.2 (d), 153.3 (d), 160.5 (s), 160.9 (s), 177.5 (s), 193.7 (s). Anal. calcd for $C_{22}H_{16}N_2O_2$: C, 77.63; H, 4.74; N, 8.23; found C, 77.64; H, 4.70; N, 8.19.

3.5.7. 8-Acetyl-2-chloro-3-fluoro-7-methyl-6-propyl-1,6-naphthyridin-5(6*H*)-one (4bc). R_f=0.43 (cyclohexane/EtOAc 7:3), 41% yield, white solid, mp 110–112°C. ^{1}H NMR ($CDCl_3$): 0.94 (3H, t, *J*=6.3 Hz, $CH_2CH_2CH_3$), 1.62 (2H, m, $CH_2CH_2CH_3$), 2.37 (3H, s, CH_3), 2.56 (3H, s, $COCH_3$), 3.97 (2H, t, *J*=7.6 Hz, $CH_2CH_2CH_3$), 8.18 (1H, d, J_{HF}=7.8 Hz, H-4). ^{13}C NMR ($CDCl_3$): 11.2 (q), 17.1 (q), 21.9 (t), 33.1 (q), 46.3 (t), 119.7 (s, ^3J=3.4 Hz), 119.8 (s), 122.5 (d, $^2J_{CF}$=20.1 Hz), 142.4 (s), 144.4 (s, $^2J_{CF}$=20.6 Hz), 146.6 (s, $^2J_{CF}$=4.8 Hz), 152.3 (s, $^1J_{CF}$=267.2 Hz), 160.8 (s), 202.6 (s). Anal. calcd for $C_{14}H_{14}ClFN_2O_2$: C, 56.67; H, 4.76; Cl, 11.95; F, 6.40; N, 9.44; found C, 56.65; H, 4.77; Cl, 11.92; F, 6.39; N, 9.45.

3.5.8. 8-Acetyl-2-chloro-3-fluoro-7-methyl-6-phenyl-1,6-naphthyridin-5(6*H*)-one (4bd). R_f=0.46 (cyclohexane/EtOAc 7:3), 54% yield, white solid, mp 119–120°C. ^{1}H NMR ($CDCl_3$): 1.95 (3H, s, CH_3), 2.63 (3H, s, $COCH_3$), 7.16 (2H, m, H arom), 7.40 (3H, m, H arom), 8.22 (1H, d, J_{HF}=7.7 Hz, H-4). ^{13}C NMR ($CDCl_3$): 19.1 (q), 33.1 (q), 119.7 (s), 120.3 (s, $^3J_{CF}$=3.4 Hz), 122.8 (d, $^2J_{CF}$=20.2 Hz), 128.1 (d), 129.5 (d), 130.1 (d), 137.7 (s), 143.3 (s), 144.9 (s, $^2J_{CF}$=25.8 Hz), 147.6 (s, $^4J_{CF}$=4.3 Hz), 153.0 (s, $^1J_{CF}$=258.5 Hz), 161.1 (s), 202.2 (s). Anal. calcd for $C_{17}H_{12}ClFN_2O_2$: C, 61.73; H, 3.66; N, 8.47; found C, 61.72; H, 3.63; N, 8.49.

3.6. 8-Benzoyl-7-benzyl-1,6-naphthyridin-5(6*H*)-one (4aj) (by deprotection reaction)

A solution of **4ai** (120 mg, 0.26 mmol) in methanesulfonic acid (4 ml) was stirred at room temperature for 4 h. The resulting mixture was poured into cold water. The aqueous phase was basified with a concentrated NaOH solution. The precipitate formed was filtered, washed with water, dried and purified by column chromatography on silica gel (cyclohexane/EtOAc 1:1, R_f=0.57 (cyclohexane/EtOAc 2:8)) to afford compound **4aj** (70 mg, 78%) as a white solid.

The obtained compound has the same characteristics as those obtained by the method discussed in Section 3.5. (cf. Section 3.5.6).

3.6.1. 8-Benzoyl-6,7-dibenzyl-3-fluoro-2-piperidino-1,6-naphthyridin-5(6*H*)-one (6). A solution of **4bf** (120 mg, 0.25 mmol) and piperidine (85 mg, 1 mmol) in acetonitrile (30 ml) was refluxed for 7 h and the solvent was evaporated. The resulting oil was dissolved in CH_2Cl_2 (20 ml), washed with water (2×30 ml), brine (2×30 ml), dried ($MgSO_4$) and evaporated. The crude product was purified by column chromatography on silica gel (CH_2Cl_2/pentane 9:1, R_f=0.48) to afford compound **6** (100 mg, 75%) as a white solid.

Mp 100–101°C. ^{1}H NMR ($CDCl_3$): 1.21 (6H, m, CH_2 of piperido), 3.19 (4H, m, CH_2 of piperido), 3.84 (2H, s, CH_2), 5.20 (2H, s, NCH_2), 7.02–7.29 (12H, m, H arom), 7.41 (1H, m, H arom), 7.72 (2H, m, H arom), 7.91 (1H, d, J_{HF}=14.2 Hz, H-4). ^{13}C NMR ($CDCl_3$): 24.9 (t), 25.9 (t), 36.7 (t), 48.4 (t), 53.7 (t), 112.7 (s, $^3J_{CF}$=3.6 Hz), 120.0 (s), 120.8 (d, $^2J_{CF}$=21.4 Hz), 126.1 (d), 127.4 (d), 127.6 (d), 128.2 (d), 128.6 (d), 129.2 (d), 129.3 (d), 129.5 (d), 133.1 (d), 136.7 (s), 137.4 (s), 139.0 (s), 143.2 (s), 148.2 (s), 148.4

(s, $^1J_{CF}$=257.8 Hz), 151.3 (s, $^2J_{CF}$=7.3 Hz), 162.5 (s), 196.7 (s). Anal. calcd for $C_{34}H_{30}FN_3O_2$: C, 76.82; H, 5.69; N, 7.90; found C, 76.85; H, 5.65; N, 7.92.

3.6.2. 8-Benzoyl-6,7-dibenzyl-3-fluoro-2-methoxy-1,6-naphthyridin-5(6*H*)-one (7). To a stirred solution of **4bf** (120 mg, 0.25 mmol) in dry DME (10 ml) was added slowly a 1.0 M solution of MeONa (2.5 ml, 2.5 mmol). The mixture was stirred at room temperature for 16 h and poured into cold water. The aqueous phase was acidified with 10% HCl to pH 6–7 and extracted with CH_2Cl_2 (2×20 ml). The organic phase was washed with water (1×20 ml), brine (2×20 ml), dried ($MgSO_4$) and evaporated. The crude product was purified by column chromatography on silica gel (CH_2Cl_2) to afford compound **7** (110 mg, 89%) as a white solid.

R_f=0.70 (CH_2Cl_2/pentane 8:2), mp 163–164°C. ^{1}H NMR ($CDCl_3$): 3.40 (3H, s, OCH_3), 3.81 (2H, s, CH_2), 5.24 (2H, s, NCH_2), 7.02–7.32 (12H, m, H arom), 7.39 (1H, m, H arom), 7.72 (2H, m, H arom), 8.1 (1H, d, J_{HF}=9.9 Hz, H-4). ^{13}C NMR ($CDCl_3$): 36.4 (t), 46.8 (t), 54.2 (q), 115.4 (s, $^3J_{CF}$=3.1 Hz), 119.4 (s), 120.9 (d, $^2J_{CF}$=17.2 Hz), 125.8 (d), 127.2 (d), 127.5 (d), 127.8 (d), 128.4 (d), 129.0 (d), 129.1 (d), 129.2 (d), 133.1 (d), 135.9 (s), 136.5 (s), 138.4 (s), 143.6 (s), 146.3 (s, $^4J_{CF}$=5.0 Hz), 146.6 (s, $^1J_{CF}$=261.3 Hz), 156.2 (s, $^2J_{CF}$=14.5 Hz), 162.1 (s), 195.4 (s). Anal. calcd for $C_{30}H_{23}FN_2O_3$: C, 75.30; H, 4.84; N, 5.85; found C, 75.28; H, 4.82; N, 5.89.

3.6.3. 8-Benzoyl-7-benzyl-5-chloro-1,6-naphthyridine (8). A mixture of **4aj** (125 mg, 0.33 mmol) and PCl_5 (100 mg, 0.47 mmol) in $POCl_3$ (1 ml) was refluxed for one day and the solvent was evaporated. The resulting oil was dissolved in cold water. The aqueous phase was basified with a saturated Na_2CO_3 solution to pH 7–8 and extracted with CH_2Cl_2 (3×10 ml). The organic phase was washed with water (1×20 ml), brine (2×20 ml), dried ($MgSO_4$) and evaporated. The crude product was purified by column chromatography on silica gel (cyclohexane/EtOAc 8:2, R_f=0.41) to afford compound **8** (48 mg, 41%) as a white solid.

Mp 158–159°C. ^{1}H NMR ($CDCl_3$): 4.10 (2H, s, CH_2), 7.00–7.24 (5H, m, H arom), 7.32 (2H, m, H arom), 7.45 (2H, m, H arom and H-3), 7.69 (2H, m, H arom), 8.49 (1H, dd, J=8.5, 1.7 Hz, H-4), 8.80 (1H, dd, J=4.4, 1.8 Hz, H-2). ^{13}C NMR ($CDCl_3$): 41.6 (t), 120.7 (s), 123.3 (d), 126.5 (d), 128.3 (d), 128.6 (d), 129.3 (d), 129.7 (d), 130.9 (s), 133.9 (d), 134.5 (d), 137.3 (s), 137.7 (s), 150.9 (s), 151.1 (s), 153.6 (s), 155.4 (d), 196.3 (s). Anal. calcd for $C_{22}H_{15}ClN_2O$: C, 73.64; H, 4.21; N, 7.81; found C, 73.67; H, 4.18; N, 7.80.

3.6.4. 12-Phenyl-6-propylnaphto[2,3-*h*][1,6]naphthyridin-5(6*H*)-one (9). A 1.0 M solution of boron tribromide in CH_2Cl_2 (3 ml, 3 mmol) was added slowly to a stirred solution of **4af** (289 mg, 0.75 mmol) in CH_2Cl_2 (20 ml) at −78°C under a dry argon atmosphere. The solution was allowed to warm to ambient temperature and was stirred overnight. The resulting solution was poured into water (30 ml). The organic phase was washed with water (30 ml) and then with brine (30 ml), dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, CH_2Cl_2, R_f=0.8) to afford compound **9** as a white solid (170 mg, 63%).

Mp 159°C. ^{1}H NMR ($CDCl_3$): 1.10 (3H, t, J=7.5 Hz, $CH_2CH_2CH_3$), 1.93 (2H, m, $CH_2CH_2CH_3$), 4.39 (2H, t, J=7.7 Hz, $CH_2CH_2CH_3$), 7.15 (3H, m, H arom), 7.25 (1H, m, H arom), 7.41–7.52 (5H, m, H arom), 7.80 (1H, m, H arom), 7.94 (1H, m, H arom), 8.32 (1H, dd, J=4.4, 1.9 Hz, H-2), 8.61 (1H, dd, J=7.9, 1.9 Hz, H4). ^{13}C NMR ($CDCl_3$): 11.6 (q), 20.5 (t), 44.8 (t), 111.4 (d), 118.5 (s), 121.9 (s), 122.1 (d), 124.9 (d), 126.2 (d), 127.3 (d), 127.5 (d), 127.8 (d), 127.9 (d), 129.4 (d), 130.1 (s), 133.9 (s), 136.0 (d), 136.1 (s), 140.9 (s), 142.3 (s), 150.9 (s), 151.6 (d), 161.3 (s). Anal. calcd for $C_{25}H_{20}N_2O$: C, 82.39; H, 5.53; N, 7.69; found C, 82.42; H, 5.50; N, 7.67.

3.6.5. 6-Benzyl-12-phenylnaphto[2,3-*h*][1,6]naphthyridin-5(6*H*)-one (10). A solution of **4ah** (108 mg, 0.25 mmol) in aqueous HBr (2 ml) was heated at 100°C for 4 h. The resulting mixture was poured into water with ice. The aqueous phase was basified with a concentrated NaOH solution. The precipitate formed is filtered, washed with water, dried and purified by column chromatography on silica gel (CH_2Cl_2, R_f=0.75) to provide compound **10** (70 mg, 68%) as a white solid.

Mp 180–181°C. ^{1}H NMR ($CDCl_3$): 5.70 (2H, s, CH_2), 7.09–7.43 (14H, m, H arom), 7.62 (2H, m, H arom), 8.32 (1H, dd, J=4.4, 1.9 Hz, H-2), 8.65 (1H, dd, J=8.0, 1.9 Hz, H-4). ^{13}C NMR ($CDCl_3$): 47.4 (t), 112.8 (d), 118.6 (s), 121.9 (s), 122.4 (d), 125.2 (d), 126.4 (d), 126.7 (d), 127.5 (d), 127.55 (d), 127.6 (d), 127.9 (d), 128.1 (d), 129.2 (d), 129.5 (d), 130.4 (s), 133.9 (s), 136.4 (s), 136.5 (d), 136.6 (s), 141.0 (s), 142.4 (s), 151.4 (s), 152.1 (d), 162.1 (s). Anal. calcd for $C_{29}H_{20}N_2O$: C, 84.44; H, 4.89; N, 6.79; found C, 84.40; H, 4.86; N, 6.75.

3.7. Reaction of compounds 4 with Bredereck's reagent. General procedure

To a stirred solution of compound **4ac** or **4ae** (0.5 mmol) in 1,4-dioxane (5 ml), Bredereck's reagent (0.55 mmol) was added. The resulting mixture was heated under reflux for 5 h. After cooling to ambient temperature, the solution was poured into water (5 ml). The red precipitate was filtered, washed with water, dried and purified by column chromatography on silica gel to provide compound **11** or **12**.

3.7.1. 8-Acetyl-7-(2-dimethylaminovinyl)-6-propyl-1,6-naphthyridin-5(6*H*)-one (11). 54% yield, red solid, mp 129°C. ^{1}H NMR ($CDCl_3$): 0.78 (3H, t, J=7.2 Hz, $CH_2CH_2CH_3$), 1.52 (2H, m, $CH_2CH_2CH_3$), 2.22 (3H, s, CH_3), 2.66 (6H, s, $N(CH_3)_2$), 3.88 (2H, t, J=7.2 Hz, $CH_2CH_2CH_3$), 4.57 (1H, d, J=12.6 Hz, $CHN(CH_3)_2$), 6.37 (1H, d, J=12.6 Hz, CH), 7.02 (1H, dd, J=8.1, 4.5 Hz, H-3), 8.35 (1H, dd, J=8.1, 1.8 Hz, H-4), 8.60 (1H, dd, J=4.5, 1.8 Hz, H-2). ^{13}C NMR ($CDCl_3$): 11.5 (q), 21.1 (t), 33.1 ($COCH_3$), 41.1 (q), 46.5 (t), 87.8 (d), 114.2 (s), 118.8 (s), 121.5 (C3), 136.9 (C4), 146.1 (s), 149.0 (d), 154.5 (s), 163.2 (s), 196.1 (s). Anal. calcd for $C_{17}H_{21}N_3O_2$: C, 68.20; H, 7.07; N, 14.04; found C, 68.24; H, 7.05; N, 14.01.

3.7.2. 8-Benzoyl-7-(2-dimethylaminovinyl)-6-propyl-1,6-

naphthyridin-5(6*H*)-one (12). 46% yield, red solid, mp160°C. ^{1}H NMR ($CDCl_3$): 0.90 (3H, t, J=7.4 Hz, $CH_2CH_2CH_3$), 1.70 (2H, m, $CH_2CH_2CH_3$), 2.50 (6H, s, $N(CH_3)_2$), 4.00 (2H, t, J=7.4 Hz, $CH_2CH_2CH_3$), 4.40 (1H, d, J=12.9 Hz, $CHN(CH_3)_2$), 6.39 (1H, d, J=12.9 Hz, CH), 7.10 (1H, dd, J=8.0, 4.5 Hz, H-3), 7.26 (2H, m, H arom), 7.39 (1H, m, H arom), 7.72 (2H, m, H arom), 8.55 (1H, dd, J=8.0, 1.8 Hz, H-4), 8.68 (1H, dd, J=4.5, 1.8 Hz, H-2). ^{13}C NMR ($CDCl_3$): 11.5 (q), 22.1 (t), 40.3 (q), 46.1 (t), 87.6 (d), 115.7 (s), 118.9 (s), 120.5 (C3), 128.4 (d), 129.2 (d), 132.7 (d), 136.4 (C4), 139.3 (s), 146.0 (s), 148.6 (d), 152.5 (s), 154.6 (C2), 162.7 (s), 196.4 (s). Anal. calcd for $C_{22}H_{23}N_3O_2$: C, 73.11; H, 6.41; N, 11.63; found C, 73.14; H, 6.45; N, 11.62.

3.8. Synthesis of pyrido[3,2-*c*][1,6]naphthyridin-6(5*H*)-ones. General procedure

0.5 mmol of **11** or **12** in DMF (5 ml) was added to a stirred solution of ammonium acetate (70 mg, 1 mmol) in DMF (5 ml). The reaction mixture was heated at 95–100°C for 5 h. The resulting solution was allowed to cool to ambient temperature and then was poured into water (5 ml). The precipitate formed was filtered off, washed with water and dried to provide compounds **13** and **14**.

3.8.1. 1-Methyl-5-propylpyrido[3,2-*c*][1,6]naphthyridin-6(5*H*)-one (13). 69% yield, yellow solid, mp 135–136°C. ^{1}H NMR ($CDCl_3$): 0.88 (3H, t, J=7.2 Hz, $CH_2CH_2CH_3$), 1.62 (2H, m, $CH_2CH_2CH_3$), 3.13 (3H, s, CH_3), 4.10 (2H, t, J=7.8 Hz, $CH_2CH_2CH_3$), 6.95 (1H, d, J=5.7 Hz, H-7), 7.31 (1H, dd, J=8.1, 4.5 Hz, H-3), 8.34 (1H, d, J=6.0 Hz, H-8), 8.58 (1H, dd, J=8.1, 2.1 Hz, H-4), 8.86 (1H, dd, J=4.5, 2.1 Hz, H-2). ^{13}C NMR ($CDCl_3$): 12.1 (q), 21.4 (t), 30.4 (t), 45.4 (t), 108.2 (d), 115.5 (s), 122.5 (s), 123.2 (d), 137.2 (d), 145.8 (s), 149.2 (d), 151.9 (s), 153.6 (d), 161.2 (s), 162.3 (s). Anal. calcd for $C_{15}H_{15}N_3O$: C, 71.13; H, 5.97; N, 16.59; found C, 71.11; H, 5.99; N, 16.56.

3.8.2. 1-Phenyl-5-propylpyrido[3,2-*c*][1,6]naphthyridin-6(5*H*)-one (14). 65% yield, white solid, mp 181°C. ^{1}H NMR ($CDCl_3$): 1.10 (3H, t, J=7.5 Hz, $CH_2CH_2CH_3$), 1.90 (2H, m, $CH_2CH_2CH_3$), 4.41 (2H, t, J=7.8 Hz, $CH_2CH_2CH_3$), 7.21 (1H, d, J=5.0 Hz, H-7), 7.32–7.43 (6H, m, H arom and H-3), 8.50 (1H, dd, J=4.4, 2.6 Hz, H-2), 8.67 (1H, dd, J=7.1, 1.9 Hz, H4), 8.71 (1H, d, J=4.8 Hz, H-8). ^{13}C NMR ($CDCl_3$): 11.5 (q), 20.8 (t), 44.7 (t), 107.8 (d), 114.4 (s), 121.6 (s), 123.1 (d), 127.6 (d), 127.8 (d), 128.6 (d), 136.1 (d), 143.9 (s), 145.5 (s), 148.7 (d), 149.7 (s), 152.4 (d), 160.5 (s), 161.6 (s). Anal. calcd for $C_{20}H_{17}N_3O$: C, 76.17; H, 5.43; N, 13.32; found C, 76.14; H, 5.40; N, 13.29.

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