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A convenient way to dibenzo[c,h]-1,5-naphthyridines (11-aza-benzo[c] phenanthridines).

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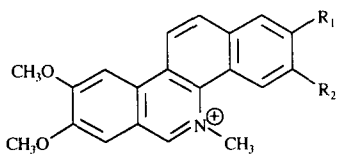
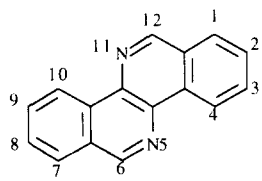
Abstract : Whereas thermal cyclisation of variously substituted 2,3-diarylacrylazides easily provided a new way to 3-aryl-isoquinolones, nitration of these compounds mainly led to corresponding 3-aryl-4-nitro-isoquinolones. After reduction into 4-amino-3-aryl-isoquinolones, amidification and subsequent cyclization gave the yet unknown title compounds. Copyright © 1996 Elsevier Science Ltd

Among the naturally occurring benzo[c]phenanthridine alkaloids and other "azachrysene" derivatives which have been reviewed repeatedly[1-5], several compounds display various biological properties[6]. Especially, Fagaronine **1** and Nitidine **2** retained a persistent attention and these compounds and analogues continue to be the matter of new and detailed investigations for their potential interest in the areas of anticancer and even antiviral drugs[7-10].



1 : R_1 = OH ; R_2 = OCH_3
2 : R_1 + R_2 = OCH_2O



3
Dibenzo[c,h]-1,5-naphthyridines or 11-aza-benzo[c]phenanthridines

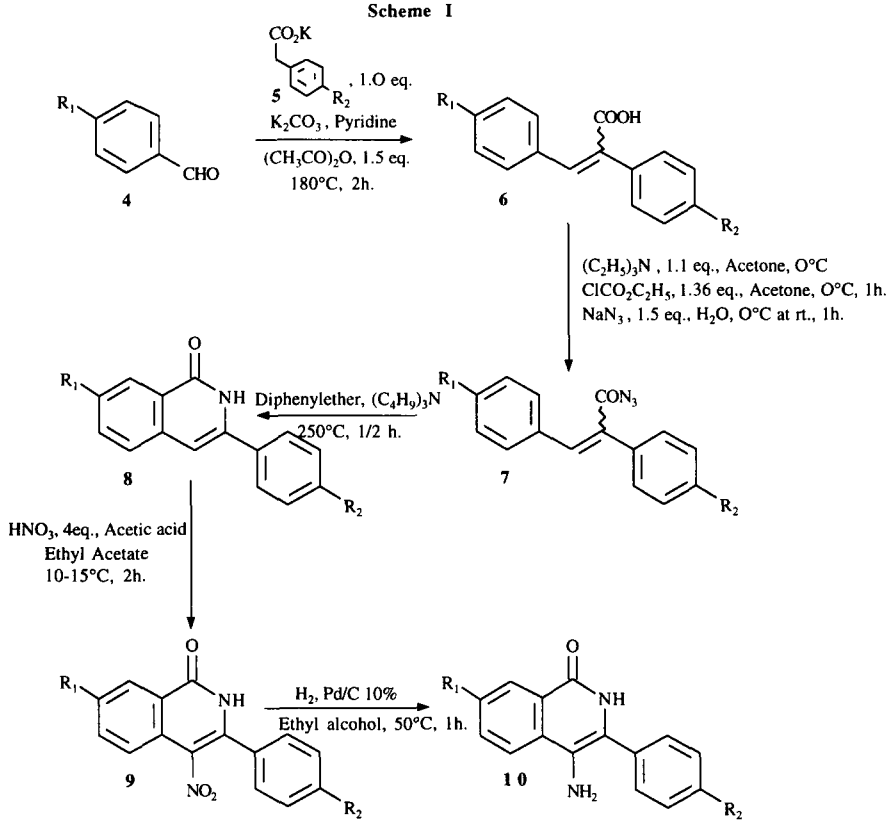
It was thus surprising to state that "aza"-benzo[c]phenanthridines, whose numerous possible isomers (eleven if 5-N is maintained) can be drawn, remained nearly unexplored, at least to the best of our knowledge.

As our continuing interest in the field of potential antitumor agents led us to put forward a first synthetic study in these series, we wish now to report the convenient way to polysubstituted dibenzo[c,h]-1,5-naphthyridines **3** that we have worked out.

Different 3-aryl-isoquinolines and isoquinolones have recently been synthesized and studied in various ways and conditions[11-14]. In all cases, however, 2-N-alkyl[11-12] or 1-C-aryl[13-14] substituted derivatives were concerned. Since 3-aryl 2-N-unsubstituted isoquinolin-1-ones were desired, an appropriate way to these key

intermediates must be thus devised. Application to 2,3-diarylacrylic acids of the old Eloy and Deryckere method to isoquinolones[15] proved to be successfull for this purpose. Starting from easily available substituted benzaldehydes **4** and arylacetic acids **5**, 2,3-diarylacrylic acids **6**, corresponding azides **7** and 3-aryl-isoquinolin-1-(*2H*)-ones **8** (**a,b,c,d**) were obtained in good yields.

Scheme I



a) $R_1 = R_2 = H$; b) $R_1 = OCH_3$; $R_2 = H$; c) $R_1 = H$; $R_2 = OCH_3$; d) $R_1 = R_2 = OCH_3$

In order to build up dibenzo[c,h]-1,5-naphthyridines **3**, a nitrogen atom at the 4-position of compounds **8** was required. It was introduced by nitration of isoquinolones **8** with concentrated nitric acid in acetic acid at temperature below 15°C. In these conditions, 3-aryl-4-nitro-isoquinolin-1-(*2H*)-ones **9** were obtained, occasionally beside some traces of other nitrated derivatives which were not fully characterized. Catalytic reduction of nitro-isoquinolones **9** over 10 % palladized charcoal obviously gave the expected 4-amino-3-aryl-isoquinolin-1-(*2H*)-ones **10** (Scheme I).

Whereas reaction of these 4-amino-isoquinolones **10** with ethyl chlorocarbonate led to carbamates **11**,

thermal cyclisation of compounds **11** (**a,b,c**) provided dibenzo[c,h]-1,5-naphthyridin-6,12-(*5H,11H*)-diones **12** (**a,b**).

In order to perform the dichlorination of **12a**, various attempts were carried out with boiling phosphorous oxychloride, phenylphosphonic acid dichloride at 150°C and with the mixture phosphorous oxychloride, benzyltriethylammonium chloride and diethylaniline in boiling acetonitrile. Probably due to the very low solubility of **12a**, dichlorination was incomplete and the expected compound was obtained in low yield. On the contrary, dichlorination of the more soluble compound **12b**, with phenylphosphonic acid dichloride at 150°C, easily provided 70 % of the dichloro derivative **13b**.

However, in an attempt to transform compound **11b** into **14b** with phenylphosphonic acid dichloride at 150°C, we ascertained that lengthening these reaction conditions directly led to dichloro derivative **13b** with 45-50 % yield. The same transformation also succeeded from **11a** and **11d**, thereby providing compound **13a** in better yield than in preceding conditions, and **13c** as well.

On the other hand, the carbamates **11**(**a,b,d**) heated in phenylphosphonic acid dichloride at 160°C for a period limited to 45 min, afforded chloro-isoquinoline carbamates **14**(**a,b,c**) which have been reduced over 10 % palladized charcoal to corresponding carbamates **14** (**d,e,f**). As recently described for 2-phenyl-1-naphthylamine carbamate analogs[16,17], these 3-aryl-4-amino-isoquinoline carbamates **14** were thermally cyclized in boiling diphenylether to give dibenzo[c,h]-1,5-naphthyridin-12-(*11H*)-ones **15**(**a,b,c**).

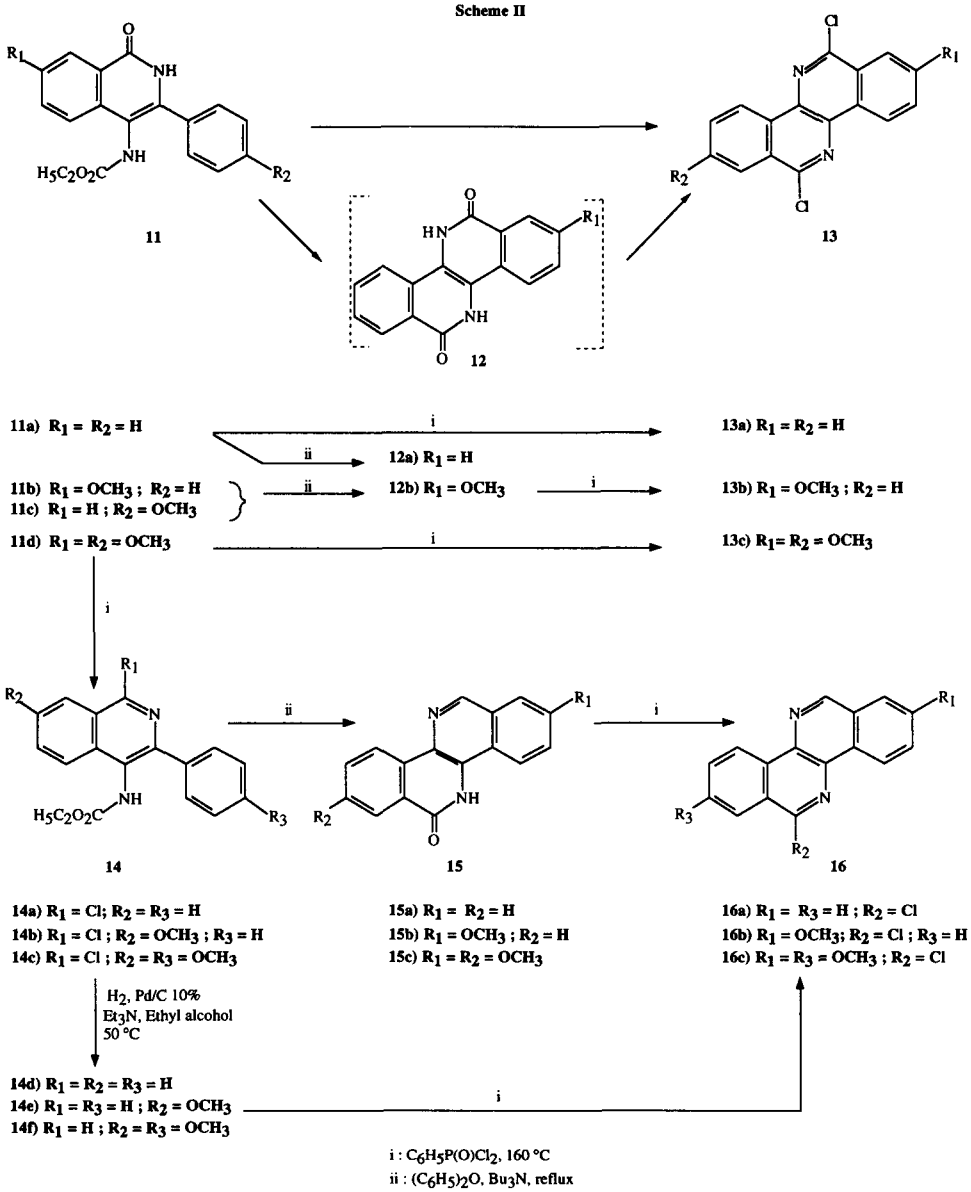
These last compounds were then easily chlorinated in usual conditions giving the yet unknown polysubstituted dibenzo[c,h]-1,5-naphthyridine derivatives **16** (**a,b,c**) which correspond to 11-aza-benzo[c] phenanthridines (scheme II).

Moreover, as observed for direct transformation of compounds **11** to **13**, boiling phenylphosphonic acid dichloride also react with carbamate **14e** to give 6-chloro-2,8-dimethoxy-dibenzo[c,h]-1,5-naphthyridine **16b** (20 % yield). This stepwise synthesis to mono chloro derivatives was however arduous and another possibility to obtain other derivatives of these new series was envisaged. Acetamides **17** were obviously obtained in nearly quantitative yield from amines **10** and acetic anhydride. Reaction with boiling phosphorous oxychloride then directly led to 6-chloro-12-methyl-dibenzo[c,h]-1,5-naphthyridines **18**, although in yields which did not exceed 40 % (scheme III). However, our attempts to perform the same reaction from corresponding formamides totally failed.

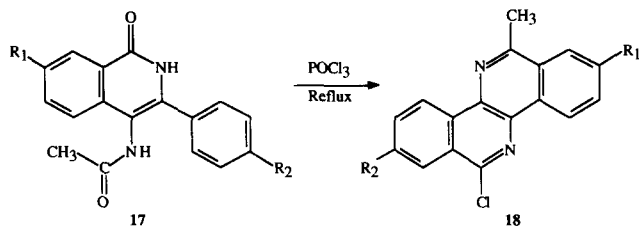
The different amino substituted derivatives **19a-g** were obtained from the chloro derivatives (**13**, **16** and **18**) by heating at reflux in an excess of the required diamines for a 24h period.

In conclusion, this paper describes a convenient and general route to 3-aryl-isoquinolin-1-(*2H*)-ones and to variously polysubstituted dibenzo[c,h]-1,5-naphthyridine derivatives. Biological and physicochemical properties of these compounds will be compared to those of related naturally occurring benzo[c]phenanthridin alkaloids and to recently reported 6-(dialkylaminoalkyl)amino substituted benzo[c]phenanthridin which inhibited topoisomerase II and/or I. Corresponding results will be reported in forthcoming papers.

Scheme II

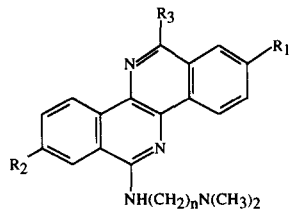

11
12
13
11a) R1 = R2 = H
11b) R1 = OCH3 ; R2 = H
11c) R1 = H ; R2 = OCH3
11d) R1 = R2 = OCH3
12a) R1 = H
12b) R1 = OCH3
13a) R1 = R2 = H
13b) R1 = OCH3 ; R2 = H
13c) R1= R2 = OCH3
14
15
16
14a) R1 = Cl; R2 = R3 = H
14b) R1 = Cl ; R2 = OCH3 ; R3 = H
14c) R1 = Cl ; R2 = R3 = OCH3
14d) R1 = R2 = R3 = H
14e) R1 = R3 = H ; R2 = OCH3
14f) R1 = H ; R2 = R3 = OCH3
15a) R1 = R2 = H
15b) R1 = OCH3 ; R2 = H
15c) R1 = R2 = OCH3
16a) R1 = R3 = H ; R2 = Cl
16b) R1 = OCH3; R2 = Cl ; R3 = H
16c) R1 = R3 = OCH3 ; R2 = Cl
H2, Pd/C 10%
Et3N, Ethyl alcohol
50 °C
i : C6H5P(O)Cl2, 160 °C
ii : (C6H5)2O, Bu3N, reflux

Scheme III



17a) $R_1 = R_2 = H$
17b) $R_1 = OCH_3$; $R_2 = H$
17c) $R_1 = H$; $R_2 = OCH_3$
17d) $R_1 = R_2 = OCH_3$

18a) $R_1 = R_2 = H$
18b) $R_1 = OCH_3$; $R_2 = H$
18c) $R_1 = H$; $R_2 = OCH_3$
18d) $R_1 = R_2 = OCH_3$



19

19a) $R_1 = R_2 = R_3 = H$; n = 2
19b) $R_1 = R_2 = H$; $R_3 = CH_3$; n = 2
19c) $R_1 = R_2 = H$; $R_3 = CH_3$; n = 3
19d) $R_1 = R_2 = OCH_3$; $R_3 = H$; n = 2
19e) $R_1 = R_2 = OCH_3$; $R_3 = CH_3$; n = 2
19f) $R_1 = R_2 = OCH_3$; $R_3 = CH_3$; n = 3
19g) $R_1 = OCH_3$; $R_2 = R_3 = H$; n = 2

Experimental

The melting points were taken on a Kofler hot stage apparatus and were uncorrected. Elemental analyses were performed by the "Service Central de microanalyse", CNRS, ICSN, 91198, Gif sur Yvette, France. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded at 200 MHz for all the described compounds on a Bruker AC200 spectrometer and all the spectra are consistent with the assigned structures. Chemical shifts (δ) are reported in ppm units with tetramethylsilane as an internal standard and coupling constants (J) are given in hertz (Hz). ^{13}C NMR spectra were recorded on a 400 MHz VARIAN. The chemical shifts were expressed in ppm. The assigments of signals were fully performed by the 2D ^1H-^{13}C correlation experiments (Reverse detection for HMQC and HMBC). Mass spectra (MS) were obtained on a NERMAG R10-10-C by direct introduction. Ionization was obtained by chemical ionization with ammonia (C.I., NH_3). Mass spectral data were reported as m/z.

E-2,3-diarylacrylic acids 6 (a,b,c,d) : These compounds have been prepared as already described.

6a : mp 172°C ; lit. mp 174°C[18a].

6b : mp 194°C ; lit. mp 189°C[18b].

6c : mp 155°C.

6d : mp 216°C ; lit. mp 217-218°C[19].

3-Aryl-isoquinolin-1-(*2H*)-ones 8 (a,b,c,d). General technique. The solution of the required 2,3-diarylacrylic acid **6** (0.1 mol) and triethylamine (0.11 mol) in acetone (250 ml) was cooled to 0°C. A solution of ethyl chlorocarbonate (0.136 mol) in acetone (80 ml) was added dropwise under stirring, while maintaining the temperature at 0°C for a 1 h period after complete addition. A solution of sodium azide **7** (0.15 mol) in water (25 ml) was progressively added at 0°C and the mixture was allowed to reach room temperature for 1 h. It was poured in ice water (1 l) and the resulting precipitate was collected, washed with water and air dried for a 15 h period. The resulting crude azide **7** was dissolved in diphenylether (50 ml at 30°C) and added dropwise to a mixture of diphenylether (180 ml) and tributylamine (14.1 ml) heated and maintained at 250°C. After 30 min. at the same temperature, diphenylether was evaporated under reduced pressure and the cooled residue was taken up in toluene (150 ml). The solid was collected and recrystallized from ethyl acetate to provide the expected 3-aryl-isoquinolin-1-(*2H*)-one as colourless needles.

8a : Yield : 80.5 % ; mp 205°C. Anal. Calcd for $C_{15}H_{11}NO$: C, 81.43 ; H, 5.01 ; N, 6.33 ; found : C, 81.30 ; H, 5.04 ; N, 6.10. ^{1}H NMR ($CDCl_3$) δ : 6.80 (s, 1H, 4-H), 7.49-7.78 (m, 8H, 5-H + 6-H + 7-H + 2'-H + 3'-H + 4'-H + 5'-H + 6'-H), 8.40 (d, 1H, 8-H, J_{7-8}= 7.5 Hz), 10.54 (s, 1H, 2-NH).

8b : Yield : 86 % ; mp 236°C. Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.47 ; H, 5.22 ; N, 5.57 ; found : C, 76.17 ; H, 5.26 ; N, 5.56. ^{1}H NMR (DMSO-d_6) δ : 3.92 (s, 3H, 7-OCH_3), 6.93 (s, 1H, 4-H), 7.63 (m, 8H, 5-H + 6-H + 8-H + 2'-H + 3'-H + 4'-H + 5'-H + 6'-H), 11.47 (s, 1H, 2-NH).

8c : Yield : 77 % ; mp 242°C. Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.47 ; H, 5.22 ; N, 5.57 ; found : C, 76.27 ; H, 4.99 ; N, 5.43. ^{1}H NMR ($CDCl_3$) δ : 3.86 (s, 3H, 4'-OCH_3), 6.72 (s, 1H, 4-H), 7.02 (d, 2H, 3'-H + 5'-H, $J_{2'-3'} = J_{5'-6'}$ = 8.0 Hz), 7.47 (d, 1H, 6'-H, $J_{5'-6'}$ = 7.9 Hz), 7.63 (m, 4H, 5-H + 6-H + 7-H + 8-H), 8.37 (d, 1H, 2'-H, $J_{2'-3'}$ = 7.9 Hz), 9.75 (s, 1H, 2-NH).

8d : Yield : 85 % ; mp 238-240°C. Anal. Calcd $C_{17}H_{15}NO_3$: C, 72.58 ; H, 5.37 ; N, 4.98 ; found : C, 72.51 ; H, 5.33 ; N, 4.91 . ^{1}H NMR (DMSO-d_6) δ : 3.85 (1, 3H, 7-OCH_3), 3.91 (s, 3H, 4'-OCH_3), 6.86 (s, 1H, 4-H), 7.06 (d, 2H, 3'-H + 5'-H, $J_{2'-3'} = J_{5'-6'}$ = 7.9 Hz), 7.36 (dd, 1H, 6-H, J_{6-8} = 2.6 Hz and J_{5-6} = 8.0 Hz), 7.67 (m, 2H, 5-H + 8-H), 7.76 (d, 2H, 2'-H + 6'-H, $J_{2'-3'} = J_{5'-6'}$=7.9 Hz), 11.45 (s, 1H, 2-NH).

3-Aryl-4-nitro-isoquinolin-1-(*2H*)-ones 9 (a,b,c,d). General technique. The solution of the required 3-arylisoquinolone (50 mmol) in acetic acid (100 to 200 ml) and ethyl acetate (20 to 40 ml) was cooled to 10-15°C under stirring and a cooled solution of nitric acid (200 mmol, d = 1.52), in acetic acid (40 ml) was added dropwise while maintaining the temperature below 15°C. Stirring was pursued 2 h further and the mixture was poured in water (500 ml). The solid was collected, air dried and recrystallized from toluene or ethyl acetate to provide pale yellow microcrystals.

9a : Yield : 75 % ; mp 248°C. Anal. Calcd for $C_{15}H_{10}N_2O_3$: C, 67.66 ; H, 3.79 ; N, 10.52 ; found : C, 67.57 ; H, 3.72 ; N, 10.52. Beside this compound which corresponded to the expected one (^{1}H NMR), traces of a less soluble one in toluene, mp > 270°C was also isolated. Its elemental analysis : found % C, 67.48-67.7 ; H, 3.59-3.65 ; N, 10.55-10.40, corresponded to an isomer of **9a** which was not further studied. ^{1}H NMR (DMSO-d_6) δ : 7.57-7.76 (m, 7H, 5-H + 6-H + 2'-H + 3'-H + 4'-H + 5'-H + 6'-H), 7.95 (m, 1H, 7-H), 8.36 (d, 1H, 8-H, J_{7-8} = 7.8 Hz), 12.24 (s, 1H, 2-NH).

9b : Yield : 90 % ; mp 251°C. Anal. Calcd for $C_{16}H_{12}N_2O_4$: C, 64.86 ; H, 4.08 ; N, 9.46 ; found : C, 65.07 ; H, 4.33 ; N, 9.18. ^{1}H NMR (DMSO-d_6) δ : 3.96 (s, 3H, 7-OCH_3), 7.66 (m, 8H, 5-H + 6-H + 8-H + 2'-H + 3'-H + 4'-H + 5'-H + 6'-H), 11.90 (s, 1H, 2-NH).

9c : Yield : 66 % ; mp 270°C. Anal. Calcd for $C_{16}H_{12}N_2O_4$: C, 64.86 ; H, 4.08 ; N, 9.46 ; found : C, 64.57 ; H, 3.76 ; N, 9.55. Remark : This compound was purified by column chromatography over silica gel, with methylene chloride as eluant. ^{1}H NMR (DMSO-d_6) δ : 3.85 (s, 3H, 4'-OCH_3), 7.50 (m, 7H, 5-H + 6-H + 7-H + 2'-H + 3'-H + 5'-H + 6'-H), 8.32 (d, 1H, 8-H, $J_{7\text{-}8}$ = 2.9 Hz), 12.07 (s, 1H, 2-NH).

9d : Yield : 89 % ; mp 280°C. Anal. Calcd for $C_{17}H_{14}N_2O_5$: C, 62.57 ; H, 4.32 ; N, 8.59 ; found : C, 62.31 ; H, 4.44 ; N, 8.83. Remark : in this case, the initial mixture was heterogeneous and nitration was performed below 10°C ; ^{1}H NMR (DMSO-d_6) δ : 3.86 (s, 3H, 7-OCH_3), 3.96 (s, 3H, 4'-OCH_3), 7.09 (d, 2H, 3'-H + 5'-H, $J_{2'\text{-}3'}$=$J_{5'\text{-}6'}$= 8.7 Hz), 7.50 (m, 3H, 6-H + 2'-H + 6'-H), 7.64 (d, 1H, 5-H, $J_{5\text{-}6}$ = 9.0 Hz), 7.75 (d, 1H, 8-H, $J_{6\text{-}8}$= 2.4 Hz), 12.11 (s, 1H, 2-NH).

4-Amino-3-aryl-isoquinolin-1-(*2H*)-ones 10 (a,b,c,d). The mixture of 3-aryl-4-nitro-isoquinolone **9** (10 mmol) and 10 % palladized charcoal (1 g) in ethyl alcohol (200 ml) was placed under hydrogen atmosphere and heated to 50°C. It was then stirred till absorption of the theoretical volume of hydrogen (672 ml) and stirring was pursued 1 h further. After cooling, filtration and evaporation under reduced pressure, the resulting solid was recrystallized from toluene to give colourless microcrystals or needles.

10a : Yield : 78 % ; mp 212-214°C. Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25 ; H, 5.12 ; N, 11.86 ; found : C, 76.32 ; H, 4.89 ; N, 11.59. ^{1}H NMR (DMSO-d_6) δ : 4.19 (s, 2H, 4-NH_2), 7.57 (m, 5H, 3'-H + 4'-H + 5'-H + 6'-H), 7.81-7.98 (m, 3H, 5-H + 6-H + 7-H), 8.29 (d, 1H, 8-H, $J_{7\text{-}8}$ = 6.6 Hz), 10.93 (s, 1H, 2-NH).

10b : Yield : 72 % ; mp 206°C. Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16 ; H, 5.30 ; N, 10.52 ; found : C, 72.30 ; H, 5.18 ; N, 10.51. ^{1}H NMR (DMSO-d_6) δ : 3.93 (s, 3H, 7-OCH_3), 4.21 (s, 2H, 4-NH_2), 7.49 (m, 6H, 6-H + 2'-H + 3'-H + 4'-H + 5'-H + 6'-H), 7.72 (s, 1H, 8-H), 7.96 (d, 1H, 5-H, $J_{5\text{-}6}$ = 8.6 Hz), 10.90 (s, 1H, 2-NH).

10c : Yield : 53 % ; mp 219°C. Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.14 ; H, 5.30 ; N, 10.52 ; found : C, 72.10 ; H, 5.52 ; N, 10.41. ^{1}H NMR ($CDCl_3$) δ : 3.41 (s, 2H, 4-NH_2), 3.87 (s, 3H, 4'-OCH_3), 7.04 (d, 2H, 3'-H + 5'-H, $J_{2'\text{-}3'}$ = $J_{5'\text{-}6'}$ = 8.7 Hz), 7.46-7.54 (m, 4H, 5-H + 6-H + 2'-H + 6'-H), 7.73-7.83 (m, 2H, 7-H + 2-NH), 8.46 (d, 1H, 8-H, $J_{7\text{-}8}$ = 7.1 Hz).

10d : Yield : 95 % ; mp 234°C (dec.). Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.90 ; H, 5.44 ; N, 9.45 ; found : C, 68.85 ; H, 5.41 ; N, 9.28. ^{1}H NMR (DMSO d-6) δ : 3.85 (s, 3H, 7-OCH_3), 3.92 (s, 3H, 4'-OCH_3), 4.11 (s, 2H, 4-NH_2), 7.08 (d, 2H, 3'-H + 5'-H, $J_{2'\text{-}3'}$ = $J_{5'\text{-}6'}$ = 8.7 Hz), 7.44 (m, 3H, 6-H + 2'-H + 6'-H), 7.70 (d, 1H, 8-H, $J_{6\text{-}8}$ = 2.7 Hz), 7.92 (d, 1H, 5-H, $J_{5\text{-}6}$= 9.0 Hz), 10.84 (s, 1H, 2-NH).

Ethyl-[N-(3-aryl-isoquinolin-1-(*2H*)-one)-4-yl] carbamates 11 (a,b,c,d). Amino derivative **10** (2 mmol) was dissolved in pyridine (10 ml) and ethyl chloroformate (4 mmol) was added under stirring. The mixture was stirred at room temperature for a further 15 h period, poured in water (150 ml) filtered, washed with water, then with ethyl acetate and air dried to provide colourless crystals.

11a : Yield : 89 % ; mp 191°C. Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.12 ; H, 5.23 ; N, 9.08 ; found : C, 70.08

; H, 5.24 ; N, 8.91. ^{1}H NMR (DMSO-d_6) δ : 1.16 (t, 3H, -$CH_2\underline{CH_3}$), 4.18 (q, 2H, -$\underline{CH_2}CH_3$), 5.96 (s, 1H, 4-NH), 7.47-7.82 (m, 8H, 5-H + 6-H + 7-H + 2'-H + 3'-H + 4'-H + 5'-H + 6'-H), 8.42 (d, 1H, 8-H, $J_{7\text{-}8}$ = 8.2 Hz), 9.24 (s, 1H, 2-NH).

11b : Yield : 93 % ; mp 275-280°C. Anal. Calcd for $C_{19}H_{18}N_2O_4$, 0.25 H_2O : C, 66.56 ; H, 5.40 ; N, 8.17 ; O, 19.85 ; found : C, 66.43 ; H, 5.46 ; N, 8.13 ; O, 18.96. ^{1}H NMR ($CDCl_3$) δ : 1.26 (t, 3H, -$CH_2\underline{CH_3}$), 3.93 (s, 3H, 7-OCH_3), 4.00 (q, 2H, -$\underline{CH_2}CH_3$), 7.49 (m, 7H, 5H + 6-H + 2'-H + 3'-H + 4'-H + 5'-H + 6'-H), 7.69 (d, 1H, 8-H, $J_{6\text{-}8}$ = 2.4 Hz), 8.65 (s, 1H, 4-NH), 11.51 (s, 1H, 2-NH). MS (C.I., NH_3) 339 (MH^+).

11c : Yield : 83 % ; mp 220°C. Anal. Calcd for $C_{19}H_{18}N_2O_4$: C, 67.45 ; H, 5.36 ; N, 8.28 ; found : C, 67.55 ; H, 5.45 ; N, 8.47. ^{1}H NMR ($CDCl_3$) δ : 1.25 (t, 3H, -$CH_2\underline{CH_3}$), 3.85 (s, 3H, 4'-OCH_3), 4.16 (q, 2H, -$\underline{CH_2}CH_3$), 5.93 (s, 1H, 4-NH), 6.98 (d, 2H, 3'-H + 5'-H, $J_{2'\text{-}3'} = J_{5'\text{-}6'}$ = 7.5 Hz), 7.43-7.57 (m, 3H, 6-H + 2'-H + 6'-H), 7.71-7.75 (m, 2H, 5-H + 7-H), 8.38 (d, 1H, 8-H, $J_{7\text{-}8}$ = 7.3 Hz), 9.22 (s, 1H, 2-NH).

11d : Yield : 90 % ; mp 183°C. Anal. Calcd for $C_{20}H_{20}N_2O_5$: C, 65.21 ; H, 5.47 ; N, 7.61 ; found : C, 65.28 ; H, 5.62 ; N, 7.39. ^{1}H NMR (DMSO-d_6) δ : 1.18 (t, 3H, -$CH_2\underline{CH_3}$), 3.84 (s, 3H, 7-OCH_3), 3.92 (s, 3H, 4'-OCH_3), 4.03 (q, 2H, -$\underline{CH_2}CH_3$), 7.04 (d, 2H, 3'-H + 5'-H, $J_{2'\text{-}3'} = J_{5'\text{-}6'}$ = 8.6 Hz), 7.36-7.55 (m, 4H, 5-H + 6-H + 2'-H + 6'-H), 7.68 (d, 1H, 8-H, $J_{6\text{-}8}$ = 2.2 Hz), 8.61 (s, 1H, 4-NH), 11.43 (s, 1H, 2-NH).

Dibenzo[c,h]1,5-naphthyridin-6,12-(*5H,11H*)-dione 12(a,b). The mixture of carbamate **11(a,b,c)** (1 mmol), tributyl amine (0.4 ml) and diphenylether (10 ml) was heated at reflux till disappearance of the starting material (TLC monitoring). Achievement of the cyclisation required about 4 h and to the cooled mixture, xylene (30 ml) was added. The resulting solid was collected, taken up in boiling xylene (where it was insoluble) and filtered to provide the pure expected compound.

12a : Yield : 78 % ; mp > 280°C. Anal. Calcd for $C_{16}H_{10}N_2O_2$: C, 73.27 ; H, 3.84 ; N, 10.68 ; found : C, 73.30 ; H, 4.23 ; N, 10.73.

12b : Yield : 74 % from **11b** ; 76 % from **11c** ; mp > 280°C. Anal. Calcd for $C_{17}H_{12}N_2O_3$: C, 69.86 ; H, 4.14 ; N, 9.58 ; found : C, 69.97 ; H, 4.31 ; N, 9.75.

Remark : Due to the insolubility of these compounds in the common NMR solvents these spectra could not be obtained.

6,12-Dichlorodibenzo[c,h]-1,5-naphthyridin 13(a,c). The mixture of compound **11(a,d)** (1 mmol) and phenylphosphonic acid dichloride (9 ml) was heated in an oil bath at 160°C under argon. The initial heterogeneous mixture progressively turned grey and transformation of **11a** was complete after 9 h (24h for **11c**) (TLC monitoring) under stirring at this temperature. To the cooled mixture, ice water (100 ml) was added and stirring was pursued for 15 h. After neutralization with concentrated aqueous ammonia, the resulting precipitate was collected, air dried and chromatographed over a silica gel column, eluting with pure dichloromethane. The fraction (rf = 0.9) corresponding to the dichloro derivative **13a**, was recrystallized from toluene to give pale yellow needles.

13a : Yield : 44 % ; mp > 270°C. Anal. Calcd for $C_{16}H_8Cl_2N_2$: C, 64.24 ; H, 2.70 ; N, 9.36 ; Cl, 23.71 ; found : C, 64.15 ; H, 2.89 ; N, 9.42 ; Cl, 23.70. (same remark as for compounds **12a** and **b**).

13c : Yield : 77 % ; mp 274°C. Anal. Calcd for $C_{18}H_{12}Cl_2N_2O_2$: C, 60.19 ; H, 3.37 ; N, 7.80 ; Cl, 19.74 ; found : C, 59.57 ; H, 3.59 ; N, 7.54 ; Cl, 20.21. ^{1}H NMR ($CDCl_3$) δ : 4.04 (s, 6H, 2-OCH_3 and 8-OCH_3), 7.58 (dd, 2H, 3-H + 9-H, $J_{1-3} = J_{7-9} = 2.4$ Hz and $J_{3-4} = J_{9-10} = 8.8$ Hz), 7.72 (d, 2H, 1-H + 7-H, J_{7-9} = 2.4 Hz), 9.05 (d, 2H, 4-H + 10-H, $J_{3-4} = J_{9-10} = 9.2$ Hz). ^{13}C NMR ($CDCl_3$) δ : 54.9 (OCH_3), 104.8 (C-1), 122.8 (C-3), 124.9 (C-4), 127.0 (C-6a), 129.0 (C-4a), 132.3 (C-4b), 148.9 (C-6), 159.3 (C-2).

6,12-Dichloro-2-methoxy dibenzo[c,h]-1,5-naphthyridin 13b. The mixture of compound **12b** (1 mmol) and phenylphosphonic acid dichloride (5 ml) was heated under stirring in an oil bath at 160°C for 1 h and treated as for **13a**. The crude precipitate was collected, air dried and recrystallized from toluene.

13b : Yield : 71 % ; mp 242°C. Anal. Calcd for $C_{17}H_{10}Cl_2N_2O$: C, 62.03 ; H, 3.06 ; N, 8.51 ; O, 4.86 ; Cl, 21.54 ; found : C, 61.87 ; H, 3.40 ; N, 8.40 ; O, 4.95 ; Cl, 21.32. ^{1}H NMR (DMSO-d_6) δ : 4.04 (s, 3H, 2-OCH_3), 7.56 (dd, 1H, 3-H, $J_{1-3} = 2.4$ Hz and $J_{3-4} = 8.1$ Hz), 7.69 (d, 1H, 1-H, $J_{1-3} = 2.4$ Hz), 7.80 (dd, 1H, 8-H, $J_{8-10} = 2.5$ Hz and $J_{7-8} = J_{8-9} = 8.0$ Hz), 7.95 (dd, 1H, 9-H, $J_{7-9} = 2.5$ Hz and $J_{8-9} = J_{9-10} = 8.0$ Hz), 8.43 (d, 1H, 7-H, $J_{7-9} = 8.1$ Hz), 9.03 (d, 1H, 4-H, $J_{3-4} = 9.0$ Hz), 9.11(d, 1H, 10-H, $J_{9-10} = 8.3$ Hz). ^{13}C NMR ($CDCl_3$) δ : 104.7 (C-1), 122.8 (C-3), 123.0 (C-10), 125.2 (C-4), 125.5 (C-6a), 125.9 (C-7), 127.5 (C-12a), 128.0 (C-8), 128.8 (C-4a), 131.0 (C-9), 132.0 (C-10b), 133.4 (C-4b), 134.1 (C-10a), 148.8 (C-12), 150.0 (C-6), 159.5 (C-2).

Ethyl-N-[(3-aryl-1-chloro-isoquinolin)-4-yl]carbamates 14 (a,b,c). The mixture of carbamate **11** (**a,b,d**) (1.5 mmol) and phenylphosphonic acid dichloride (10 ml) was stirred and heated in an oil bath at 160°C under nitrogen for 45 min and cooled to room temperature. It was cautiously poured in ice water (100 ml), stirred for a 2 h period, neutralized with concentrated aqueous ammonia and the resulting precipitate was collected, air dried and either chromatographed over a silica gel column eluting with dichloromethane (**14a**) or directly recrystallized from heptane (**14b**) and ethyl alcohol (**14c**).

14a : Yield : 75 % ; mp 145°C. Anal. Calcd for $C_{18}H_{15}ClN_2O_2$: C, 66.16 ; H, 4.63 ; N, 8.57 ; Cl, 10.89 ; found : C, 66.18 ; H, 4.92 ; N, 8.27 ; Cl, 11.09. ^{1}H NMR ($CDCl_3$) δ : 1.20 (t, 3H, -$CH_2\underline{CH_3}$), 4.20 (q, 2H, -$\underline{CH_2}CH_3$), 6.45 (s, 1H, 4-NH), 7.36-7.48 (m, 3'-H + 4'-H + 5'-H), 7.62-7.82 (m, 4H, 6-H + 7-H + 2'-H + 6'-H), 7.98 (d, 1H, 5-H, $J_{5-6} = 8.0$ Hz), 8.33 (d, 1H, 8-H, $J_{7-8} = 7.9$ Hz).

14b : Yield : 76 % ; mp 159°C. Anal. Calcd for $C_{17}H_{19}ClN_2O_3$: C, 63.95 ; H, 4.77 ; N, 7.85 ; Cl, 9.46 ; found : C, 63.84 ; H, 4.86 ; N, 7.68 ; Cl, 9.68. ^{1}H NMR (DMSO-d_6) δ : 1.18 (t, 3H, -$CH_2\underline{CH_3}$), 4.04 (m, 5H, 7-OCH_3 + -$\underline{CH_2}CH_3$), 7.48-7.70 (m, 7H, 6-H + 8-H + 2'-H + 3'-H + 4'-H + 5'-H + 6'-H), 8.02 (d, 1H, 5-H, $J_{5-6} = 9.1$ Hz), 9.50 (s, 1H, 4-NH).

14c : Yield : 76 % ; mp 198°C. Anal. Calcd for $C_{20}H_{19}ClN_2O_4$: C, 62.09 ; H, 4.91 ; N, 7.24 ; found : C, 61.76 ; H, 5.07 ; N, 7.02. ^{1}H NMR (DMSO-d_6) δ : 1.22 (t, 3H, -$CH_2\underline{CH_3}$), 3.85 (s, 3H, 4'-OCH_3), 4.03 (d, d + q, 5H, 7-OCH_3 + -$\underline{CH_2}CH_3$), 7.07 (d, 2H, 3'-H + 5'-H, $J_{2'-3'} = J_{5'-6'} = 8.8$ Hz), 7.56 (d, 1H, 8-H, J_{6-8} = 2.1 Hz), 7.61-7.73 (m, 3H, 6-H + 2'-H + 6'-H), 7.96 (d, 1H, 5-H, $J_{5-6} = 9.2$ Hz), 9.43 (s, 1H, 4-NH).

Ethyl-N-[(3-arylisoquinolin)4-yl] carbamates 14 (d,e,f). The mixture of the preceding compound **14** (**a, b** or **c**) (1.5 mmol), 10 % palladized charcoal (150 mg), triethylamine (0.22 ml) in absolute ethyl alcohol (20 ml) was heated in an oil bath at 50°C and stirred under hydrogen atmosphere till absorption of the theoretical

volume of hydrogen and filtered when cooled. After evaporation of solvent, the solid residue was recrystallized from ethyl alcohol to provide colourless crystals.

14d : Yield : 76 % ; mp 202°C. Anal. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.96 ; H, 5.52 ; N, 9.58 ; found : C, 73.71 ; H, 5.46 ; N, 9.49. ^{1}H NMR ($CDCl_3$) δ : 1.22 (t, 3H, -$CH_2\underline{CH_3}$), 4.16 (q, 2H, -$\underline{CH_2}CH_3$), 6.37 (s, 1H, 4-NH), 7.44-7.77 (m, 7H, 5-H + 6-H + 7-H + 8-H + 3'-H + 4'-H + 5'-H), 8.01 (m, 2H, 2'-H + 6'-H), 9.27 (s, 1H, 1-H).

14e : Yield : 81 % ; mp 133°C. Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.81 ; H, 5.59 ; N, 8.70 ; found : C, 70.53 ; H, 5.51 ; N, 8.57. ^{1}H NMR (DMSO-d_6) δ : 1.20 (t, 3H, -$OCH_2\underline{CH_3}$), 3.37 (s, 3H, 7-OCH_3), 4.04 (q, 2H, -$O\underline{CH_2}CH_3$), 7.41-7.57 (m, 5H, 5-H + 6-H + 3'-H + 4'-H + 5'-H), 7.64 (s, 1H, 8-H), 7.73 (m, 2H, 2'-H + 6'-H), 7.90 (d, 1H, 5-H, $J_{5\text{-}6}$ = 8.0 Hz), 9.28 (s, 1H, 1-H), 9.34 (s, 1H, 4-NH).

14f : Yield : 85 % ; mp 182 °C. Anal. Calcd for $C_{20}H_{20}N_2O_4$, 0.5 H_2O : C, 66.48 ; H, 5.81 ; N, 7.75 ; found : C, 66.65 ; H, 8.82 ; N, 7.79. ^{1}H NMR (DMSO-d_6) δ : 1.28 (t, 3H, -$CH_2\underline{CH_3}$), 3.84 (s, 3H, 7-OCH_3), 3.97 (s, 3H, 4'-OCH_3), 4.08 (q, 2H, -$\underline{CH_2}CH_3$), 7.05 (d, 2H, 3'-H + 5'-H, $J_{2'\text{-}3'} = J_{5'\text{-}6'}$ = 8.8 Hz), 7.52 (dd, 1H, 6-H, $J_{6\text{-}8}$= 2.5 Hz and $J_{5\text{-}6}$ = 9.1 Hz), 7.62 (d, 1H, 8-H, $J_{6\text{-}8}$ = 2.5 Hz), 7.71 (d, 2H, 2'-H + 6'-H, $J_{2'\text{-}3'} = J_{5'\text{-}6'}$ = 8.8 Hz), 7.87 (d, 1H, 5-H, $J_{5\text{-}6}$ = 9.1 Hz), 9.25 (s, 1H, 1-H), 9.29 (s, 1H, 4-NH). MS (C.I., NH_3) : m/z 353 (MH^+).

Dibenzo[c,h]-1,5-naphthyridin-6-(*5H*)-ones 15 (a,b,c). The mixture of ethyl-[N-(3-aryl-isoquinolin)4-yl] carbamate **14** (**d,e** or **f**) (1.5 mmol), tributylamine (0.4 ml) and diphenylether (10 ml) was heated at reflux under stirring till disappearance of the starting compound **14** (3 h for **15a**, 50 min for **15b** and **15c**). After cooling, toluene (50 ml) was added and the resulting solid was collected. It was taken up in boiling toluene (50 ml), cooled and filtered to provide the pure tetracyclic compound as pale yellow microcrystals.

15a : Yield : 71 % ; mp (dec) 188°C. Anal. Calcd for $C_{16}H_{10}N_2O$: C, 78.04 ; H, 4.03 ; N, 11.38 ; found : C, 77.72 ; H, 3.91 ; N, 11.03. ^{1}H NMR (DMSO-d_6) δ : 7.73-7.88 (m, 2H, 2-H + 3-H), 7.91-8.03 (m, 2H, 8-H + 9-H), 8.28 (dd, 1H, 1-H, $J_{1\text{-}3}$ = 1.2 Hz and $J_{1\text{-}2}$ = 8.2 Hz), 8.40 (dd, 1H, 10-H, $J_{7\text{-}9}$ = 1.1 Hz and $J_{9\text{-}10}$ = 8.0 Hz), 8.94 (m, 2H, 4-H + 7-H), 9.27 (s, 1H, 12-H), 12.12 (s, 1H, 5-NH).

15b : Yield : 68 % ; mp > 280°C. Anal. Calcd for $C_{17}H_{12}N_2O_2$: C, 73.90 ; H, 4.38 ; N, 10.14 ; found : C, 73.59 ; H, 4.36 ; N, 10.06. ^{1}H NMR (DMSO-d_6) δ : 4.01 (s, 3H, 2-OCH_3), 7.60 (s, 1H, 1-H), 7.73 (m, 2H, 8-H + 9-H), 7.97 (m, 1H, 3-H), 8.37 (m, 1H, 10-H), 8.87 (d, 2H, 4-H + 7-H), 9.19 (s, 1H, 12-H), 12.08 (s, 1H, 5-NH).

15c : Yield : 30 % ; mp > 300°C. Anal. Calcd for $C_{18}H_{14}N_2O_3$: C, 70.58 ; H, 4.61 ; N, 9.15 ; found : C, 70.60 ; H, 4.45 ; N, 9.24. ^{1}H NMR (DMSO-d_6) δ : 3.98 (s, 3H, 2-OCH_3), 4.00 (s, 3H, 8-OCH_3), 7.56 (m, 2H, 3-H + 9-H), 7.70 (d, 1H, 1-H, $J_{1\text{-}3}$ = 2.6 Hz), 7.80 (d, 1H, 7-H, $J_{7\text{-}9}$ = 2.7 Hz), 8.80 (d, 1H, 10-H, $J_{9\text{-}10}$ = 9.3 Hz), 8.87 (d, 1H, 4-H, $J_{3\text{-}4}$ = 8.9 Hz), 9.16 (s, 1H, 12-H), 12.10 (s, 1H, 5-NH).

6-Chloro-dibenzo[c,h]-1,5-naphthyridins 16 (a,b,c). The mixture of the preceding dibenzonaphthyridinone **15** (**a**, **b** or **c**) (1 mmol) and phenylphosphonic acid dichloride (10 ml) was placed under nitrogen and heated in an oil bath at 160°C for a 3 h period. The cooled mixture was cautiously poured in ice water, stirred for 2 h and neuralized with concentrated aqueous ammonia. The precipitate was collected, air

dried and recrystallized from toluene to give yellow crystals.

16a : Yield : 53 % ; mp > 260°C. Anal. calcd for $C_{16}H_9ClN_2$, 0.5 H_2O : C, 70.20 ; H, 3.66 ; N, 10.24 ; found : C, 69.80 ; H, 3.58 ; N, 10.06. ^1H NMR ($CDCl_3$) δ : 7.83-7.91 (m, 2H, 2-H + 3-H), 7.91-8.04 (m, 2H, 8-H + 9-H), 8.18 (d, 1H, 1-H, J_{1-2} = 7.9 Hz), 8.53 (d, 1H, 10-H, J_{8-10} = 1.4 Hz and J_{9-10} = 9.1 Hz), 9.20 (d, 1H, 4-H, J_{3-4} = 7.8Hz), 9.35 (d, 1H, 7-H, J_{7-8} = 7.9 Hz), 9.52 (s, 1H, 12-H). MS (C.I., NH_3) : m/z 265 (MH^+).

16b : Yield : 66 % ; mp 222 °C. Anal. Calcd for $C_{17}H_{11}ClN_2O$: C, 69.28 ; H, 3.76 ; N, 9.5 ; Cl, 12.03 ; O, 5.43 ; found : C, 69.15 ; H, 4.03 ; N, 9.47 ; Cl, 11.64 ; O, 5.53. ^1H NMR ($CDCl_3$) δ : 4.02 (s, 3H, 2-OCH_3), 7.42 (s, 1H, 1-H), 7.56 (dd, 1H, 3-H, J_{1-3} = 2.5 Hz and J_{3-4} = 9.0 Hz), 7.81 (m, 1H, 8-H), 7.97 (m, 1H, 9-H), 8.47 (d, 1H, 7-H, J_{7-8} = 8.5 Hz), 9.05 (d, 1H, 4-H, J_{3-4} = 9.0 Hz), 9.23 (d, 1H, 10-H, J_{9-10} = 9.2 Hz), 9.37 (s, 1H, 12-H). ^{13}C NMR (DMSO d-$_6$) δ : 106.0 (C-1), 123.0 (C-3), 123.7 (C-10), 125.4 (C-4), 126.1 (C-6a), 126.7 (C-7), 127.9 (C-4a), 128.4 (C-8), 130.0 (C-12a), 131.1 (C-9), 133.7 (C-10b), 134.6 (C-4b), 136.0 (C-10a), 150.7 (C-6), 151.6 (C-12), 155.5 (CH_3), 159.7 (C-2).

16c : Yield : 54 % ; mp 212°C. Anal. calcd for $C_{18}H_{13}ClN_2O_2$: C, 66.56 ; H, 4.00 ; N, 8.63 ; O, 9.86 ; Cl, 10.94 ; found : C, 66.31 ; H, 4.28 ; N, 8.78 ; O, 10.39 ; Cl, 10.73. ^1H NMR (DMSO-d_6) δ : 4.04 (s, 3H, 2-OCH_3), 4.07 (s, 3H, 8-OCH_3), 7.66 (d, 1H, 3-H, J_{3-4} = 9.0 Hz), 7.69 (d, 1H, 7-H, J_{7-9} = 2.5 Hz), 7.74 (dd, 1H, 9-H, J_{7-9} = 2.5 Hz and J_{9-10} = 9.0 Hz), 7.78 (d, 1H, 1-H, J_{1-3} = 2.0 Hz), 8.79 (d, 1H, 4-H, J_{3-4} =9.0Hz), 9.05 (d, 1H, 10-H, J_{9-10} = 9.0 Hz), 9.50 (s, 1H, 12-H). ^{13}C NMR (DMSO d-$_6$) δ : 105.5 (C-7), 107.3 (C-1), 123.4 (C-3), 123.7 (C-9), 124.3 (C-4), 125.6 (C-10), 126.9 (C-4a+C-6a), 129.6 (C-12a), 130.2 (C-10a), 132.5 (C-4b), 133.1 (C-10b), 148.5 (C-6), 152.6 (C-12), 159.3 (C-2), 159.7 (C-8).

4-Acetamido-3-aryl-isoquinolin-1-(*2H*)-ones 17 (a,b,c,d). The amino-isoquinolone **10** (**a**,**b**,**c** or **d**) (10 mmol) was dissolved in boiling pyridine (10 ml) and acetic anhydride (2.5 g, 25 mmol) was added. The mixture was refluxed for 15 min, cooled and water, then 6N hydrochloric acid, were added. The solid was filtered, air dried and recrystallized from ethyl alcohol to provide colourless or pale yellow crystals.

17a : Yield : 85.5 % ; mp > 280°C. Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.36 ; H, 5.07 ; N, 10.07 ; found : C, 73.24 ; H, 5.23 ; N, 10.15. ^1H NMR (DMSO-d_6) δ : 1.96 (s, 3H, -$COCH_3$), 7.51-7.61 (m, 7H, 5-H + 6-H + 2'-H + 3'-H + 4'-H + 5'-H + 6'-H), 7.79 (m, 1H, 7-H), 8.25 (m, 1H, 8-H), 9.27 (s, 1H, 4-NH), 11.49 (s, 1H, 2-NH).

17b : Yield : 56 % ; mp > 270°C ; Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.12 ; H, 5.23 ; N, 9.09 ; found : C, 70.08 ; H, 5.44 ; N, 8.89. ^1H NMR (DMSO-d_6) δ : 1.95 (s, 3H, -$COCH_3$), 3.93 (s, 3H, 7-OCH_3), 7.49 (m, 7H, 5-H + 6-H + 2'-H + 3'-H + 4'-H + 5'-H + 6'-H), 7.69 (s, 1H, 8-H), 9.27 (s, 1H, 4-NH), 11.50 (s, 1H, 2-NH).

17c : Yield : 76 % ; mp > 270°C. Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.12 ; H, 5.23 ; N, 9.09 ; found : C, 70.08 ; H, 5.44 ; N, 8.89. ^1H NMR ($CDCl_3$) δ : 2.15 (s, 3H, -$COCH_3$), 3.85 (s, 3H, 4'-OCH_3), 6.58 (s, 1H, 4-NH), 7.00 (m, 3H, 5-H + 3'-H + 5'-H), 7.36-7.76 (m, 4H, 5-H + 7-H + 2'-H + 6'-H), 8.39 (d, 1H, 8-H, J_{7-8} = 7.1 Hz), 8.77 (s, 1H, 2-NH).

17d : Yield : 91 % ; mp > 300°C. Anal. Calcd for $C_{19}H_{18}N_2O_4$: C, 67.44 ; H, 5.36 ; N, 8.28 ; found : C,

67.24 ; H, 5.28 ; N, 8.28. ^{1}H NMR (DMSO-d_6) δ : 1.97 (s, 3H, -$COCH_3$), 3.84 (s, 3H, 7-OCH_3), 3.92 (s, 3H, 4'-OCH_3), 7.04 (d, 2H, 3'-H + 5'-H, $J_{2'-3'} = J_{5'-6'} = 8.7$ Hz), 7.37-7.53 (m, 4H, 5-H + 6-H + 2'-H + 6'-H), 7.67 (d, 1H, 8-H, J_{6-8}= 2.5 Hz), 9.23 (s, 1H, 4-NH), 11.41 (s, 1H, 2-NH).

6-Chloro-12-methyl-dibenzo[c,h]-1,5-naphthyridines 18 (a,b,c,d). The mixture of 4-acetamido-3-aryl-2*H*-isoquinoline-1-one **17** (**a,b,c,d**) (10 mmol) in phosphorous oxychloride (50 ml) was quickly heated at reflux under stirring and maintained at reflux for 3 h. Excess phosphorous oxychloride was evaporated, the residue was poured in ice water (100 ml) and basified with concentrated aqueous ammonia. The solid was collected, air dried and chromatographed over a silica gel column, eluting with pure dichloromethane. The more mobile pure fraction (rf 0.95) was evaporated and the residue was recrystallized from xylene to provide yellow needles.

18a : Yield : 38 % ; mp 285°C. Anal. Calcd for $C_{17}H_{11}ClN_2$: C, 73.24 ; H, 3.94 ; N, 10.05 ; Cl, 12.74 ; found : C, 73.13 ; H, 3.81 ; N, 9.97 ; Cl, 13.04. ^{1}H NMR ($CDCl_3$) δ : 3.23 (s, 3H, 12-CH_3), 7.81-8.01 (m, 4H, 2-H + 3-H + 8-H + 9-H), 8.28 (d, 1H, 1-H, J_{1-2} = 8.2 Hz), 8.50 (d, 1H, 10-H, J_{9-10} = 7.9 Hz), 9.23 (d, 1H, 4-H, J_{3-4} = 7.9 Hz), 9.42 (d, 1H, 7-H, J_{7-8} = 7.8 Hz).

18b : Yield : 73 % ; mp : 213°C. Anal. Calcd for $C_{18}H_{13}ClN_2O$, 0.5 H_2O : C, 68.03 ; H, 4.41 ; N, 8.82 ; found : C, 67.86 ; H, 4.15 ; N, 8.80. ^{1}H NMR ($CDCl_3$) δ : 3.08 (s, 3H, 12-CH_3), 4.00 (s, 3H, 2-OCH_3), 7.41 (d, 1H, 1-H, J_{1-3} = 2.4 Hz), 7.49 (dd, 1H, 3-H, J_{1-3} = 2.4 Hz and J_{3-4} = 9.2 Hz), 7.75 (dd, 1H, 8-H, J_{8-10} = 2.8 Hz and J_{7-8} =J_{8-9} = 8.6 Hz), 7.91 (dd, 1H, 9-H, J_{7-9} = 2.5 Hz and J_{8-9} = J_{9-10} = 8.0 Hz), 8.40 (dd, 1H, 7-H, J_{7-9} = 2.4 Hz and J_{7-8} = 8.0 Hz), 9.03 (d, 1H, 4-H, J_{3-4} = 8.0 Hz), 9.22 (d, 1H, 10-H, J_{9-10} = 8.0 Hz). ^{13}C NMR ($CDCl_3$) δ : 23.4 (CH_3), 55.4 (OCH_3), 105.1 (C-1), 121.6 (C-3), 123.8 (C-10), 125.9 (C-4), 126.1 (C-6a), 126.6 (C-7), 127.6 (C-4a), 128.2 (C-8), 129.0 (C-12a), 131.3 (C-9), 132.4 (C-10b), 133.9 (C-4b), 135.8 (C-10 a), 149.6 (C-6), 157.7 (C-12), 159.4 (C-2). MS (C.I., NH_3) : m/z 309 (MH^+).

18c : Yield : 48 % ; mp 187°C. Anal. Calcd for $C_{18}H_{13}ClN_2O$: C, 70.02 ; H, 4.25 ; N, 9.07 ; Cl, 11.48. found : C, 69.83 ; H, 4.15 ; N, 8.82 ; Cl, 11.37. ^{1}H NMR ($CDCl_3$) δ : 3.17 (s, 3H, 6-CH_3), 4.08 (s, 3H, 2-OCH_3), 7.76-8.16 (m, 4H, 1-H + 3-H + 8-H + 9-H), 8.45 (d, 1H, 10-H, J_{9-10} = 7.0 Hz), 9.04 (d, 1H, 4-H, J_{3-4} = 7.0 Hz), 9.19 (d, 1H, 7-H, J_{7-8} = 10 Hz).

18d : Yield : 31 % ; mp 252°C. Anal. Calcd for $C_{19}H_{15}ClN_2O_2$: C, 67.36 ; H, 4.43 ; N, 8.27 ; Cl, 10.49 ; found : C, 67.17 ; H, 4.55 ; N, 8.05 ; Cl, 10.38. ^{1}H NMR ($CDCl_3$) δ : 3.09 (s, 3H, 12-CH_3), 4.01 (s, 3H, 2-OCH_3), 4.03 (s, 3H, 8-OCH_3), 7.45 (d, 1H, 1-H, J_{1-3}=2.5 Hz), 7.52 (dd, 1H, 3-H, J_{1-3}= 2.5 Hz and J_{3-4}= 9.0 Hz), 7.56 (d, 1H, 9-H, J_{9-10} = 9.0 Hz), 7.70 (s, 1H, 7-H), 9.06 (d, 1H, 4-H, J_{3-4} = 8.9 Hz), 9.16 (d, 1H, 10-H, J_{9-10} = 9.0 Hz). ^{13}C NMR ($CDCl_3$) δ : 105.2 (C-7), 105.3 (C-1), 121.6 (C-3), 123.1 (C-9), 125.6 (C-10), 127.5 (C-6a), 127.7 (C-4a), 128.6 (C-12a), 130.7 (C-10a), 132.7 (C-10b), 132.8 (C-4b), 148.4 (C-6), 157.8 (C-12), 159.1 (C-2), 159.6 (C-8).

6-dimethylaminealkylamino-dibenzo[c,h]-1,5-naphthyridines 19 (a-f). The required 6-chloro-dibenzo[c,h]-1,5-naphthyridine (1 mmol) was heated in 2-dimethylaminoethylamine or 3-dimethylaminopropylamine (5 ml) at reflux till disappearance of the starting compound and excess of the diamine was evaporated under reduced pressure. The residue was taken up in water and the solid was collected,

air dried and recrystallized from cyclohexane or hexane to give pale yellow crystals. In the case of compound **19a**, purification was performed by column chromatography over alumina and the pure solid residue was taken up in hexane. Compounds **19** (**d**,**e**,**f**) were directly transformed into their bis maleate salts by boiling in the presence of an excess (3.3 equivalents) of maleic acid in acetone as solvent. These bis maleates were obtained as monohydrates.

19a : Yield : 61 % ; mp 128°C. Anal. Calcd for $C_{20}H_{20}N_4$: C, 75.94 ; H, 6.30 ; N, 17.10 ; found : C, 75.64 ; H, 6.42 ; N, 17.40. ^{1}H NMR ($CDCl_3$) δ : 2.40 (s, 6H, -N(CH_3)$_2$), 2.75 (t, 2H, β-CH_2), 3.95 (q, 2H, α-CH_2), 6.45 (m, 1H, 6-NH), 7.63-7.73 (m, 2H, 2-H + 3-H), 7.78-7.90 (m, 2H, 8-H + 9-H), 7.98 (d, 1H, 1-H, J_{1-2} = 8.2 Hz), 8.05 (d, 1H, 10-H, J_{9-10} = 7.9 Hz), 9.10 (d, 1H, 4-H, J_{3-4} = 7.8 Hz), 9.17 (d, 1H, 7-H, J_{7-8} = 7.9 Hz), 9.20 (s, 1H, 12-H).

19b : Yield : 94 % ; mp 154°C. Anal. Calcd for $C_{21}H_{22}N_4$: C, 76,33 ; H, 6.71 ; N, 16.96 ; found : C,75.96 ; H, 6.60 ; N, 16.95. ^{1}H NMR (DMSO-d_6) δ : 2.32 (s, 6H, -N(CH_3)$_2$), 2.73 (t, 2H, β-CH_2), 3.05 (s, 3H, 12-CH_3), 3.35 (s, 1H, 6-NH), 3.92 (q, 2H, α-CH_2), 7.70-8.00 (m, 5H, 1-H + 2-H + 3-H + 8-H + 9-H), 8.30 (d, 1H, 10-H, J_{9-10} = 8.0 Hz), 8.40 (d, 1H, 4-H, J_{3-4} = 8.0 Hz), 9.07 (d, 1H, 7-H, J_{7-8} = 8.0 Hz).

19c : Yield : 85 % ; mp 108-110°C, became solid and mp 118°C. Anal. Calcd for $C_{22}H_{24}N_4$: C, 76.71 ; H, 7.02 ; N, 16.27 ; found : C, 76.57 ; H, 7.06 ; N, 16.28.^{1}H NMR (DMSO-d_6) δ : 1.99 (t, 2H, β-CH_2), 2.24 (s, 6H, -N(CH_3)$_2$), 2.47 (t, 2H, γ-CH_2), 3.05 (s, 3H, 12-CH_3), 3.37 (s, 1H, 6-NH), 3.82 (q, 2H, α-CH_2), 7.76-8.01 (m, 5H, 1-H + 2-H + 3-H + 8-H + 9-H), 8.28 (d, 1H, 10-H, J_{9-10} = 8.0 Hz), 8.40 (d, 1H, 4-H, J_{3-4} = 7.9 Hz), 9.08 (d, 1H, 7-H, J_{7-8} = 8.0 Hz).

19d : Yield : 60 % ; mp 138°C ; Anal. Calcd for $C_{22}H_{24}N_4O_2$, H_2O : C, 67.00 ; H, 6.59 ; N, 14.29 ; found : C, 67.31 ; H, 6.33 ; N, 14.26. ^{1}H NMR (DMSO-d_6) δ : 2.35 (s, 6H, -N(CH_3)$_2$), 2.76 (t, 2H, β-CH_2), 3.92 (q, 2H, α-CH_2), 3.99 (s, 3H, 8-OCH_3), 4.00 (s, 3H, 2-OCH_3), 7.54 (dd, 2H, 9-H + 3-H, J_{1-3} = J_{7-9} = 2.0 Hz and J_{3-4} = J_{9-10} = 9.0 Hz), 7.63 (d, 1H, 1-H, J_{1-3} = 2.2 Hz), 7.85 (d, 1H, 7-H, J_{7-9} = 1.9 Hz), 7.89 (t, 1H, 6-NH), 8.89 (d, 1H, 4-H, J_{3-4} = 9.0 Hz), 8.95 (d, 1H, 10-H, J_{9-10} = 9.0 Hz), 9.12 (s, 1H, 12-H). MS (C.I., NH_3) : m/z 377 (MH^+).

19e : Yield : 71 % ; mp 205°C ; Anal. Calcd for $C_{23}H_{26}N_4O_2$, $2C_4H_4O_4$, H_2O : C, 58.12 ; H, 5.93 ; N, 8.73 ; found : C, 58.11 ; H, 5.56 ; N, 8.39. ^{1}H NMR (DMSO-d_6) δ : 2.33 (s, 6H, -N(CH_3)$_2$), 2.73 (t, 2H, β-CH_2), 3.00 (s, 3H, 12-CH_3), 3.90 (q, 2H, α-CH_2), 4.00 (s, 3H, 8-OCH_3), 4.01 (s, 3H, 2-OCH_3), 7.48-7.56 (m, 3H, 1-H + 3-H + 9-H), 7.75 (t, 1H, 6-NH), 7.81 (d, 1H, 7-H, J_{7-9} = 2.0 Hz), 8.95 (d, 2H, 4-H + 10-H, J_{3-4} = J_{9-10} = 9.2 Hz).

19f : Yield : 70 % ; mp 195°C ; Anal. Calcd for $C_{24}H_{28}N_4O_2$, $2C_4H_4O_4$, H_2O : C, 58.71 ; H, 5.81 ; N, 8.56 ; found : C, 58.99 ; H, 5.83 ; N, 8.23. ^{1}H NMR (DMSO-d_6) δ : 1.98 (q, 2H, β-CH_2), 2.23 (s, 6H, -N(CH_3)$_2$), 2.46 (t, 2H, γ-CH_2), 3.00 (s, 3H, 12-CH_3), 3.80 (q, 2H, α-CH_2), 3.99 (s, 3H, 8-OCH_3), 4.01 (s, 3H, 2-OCH_3), 7.48-7.56 (m, 3H, 1-H + 3-H + 9-H), 7.78 (d, 1H, 10-H, J_{9-10} = 9.0 Hz), 7.89 (t, 1H, 6-NH), 8.96 (m, 2H, 4-H+ 7-H).

19g : Yield : 50 % ; mp 154°C ; Anal. Calcd for $C_{21}H_{21}N_4O$, H_2O : C, 69.42 ; H, 6.33 ; N, 15.43 ; found : C, 69.26 ; H, 6.29 ; N, 15.51. ^{1}H NMR ($CDCl_3$) δ : 2.39 (s, 6H, -N(CH_3)$_2$), 2.79 (t, 2H, β-CH_2), 3.91 (t,

2H, α-CH_2), 4.00 (s, 3H, 2-OCH_3), 6.50 (s, 1H, 6-NH), 7.33 (s, 1H, 1-H), 7.45 (dd, 1H, 3-H, J_{1-3} = 2.5 Hz and J_{3-4} = 8.4 Hz), 7.63 (t, 1H, 8-H, J_{8-10} = 2.4 Hz and J_{7-8} = J_{8-9} = 8.2 Hz), 7.82 (t, 1H, 9-H, J_{7-9} = 2.4 Hz and J_{8-9} = J_{9-10} = 8.1 Hz), 7.95 (d, 1H, 7-H, J_{7-8} = 8.2 Hz), 9.00 (d, 1H, 4-H, J_{3-4} = 8.1 Hz), 9.10 (s, 1H, 12-H, J_{1-12} = 8.2 Hz), 9.13 (d, 1H, 10-H, J_{9-10} = 8.2 Hz). ^{13}C NMR δ : 38.7 (C-α), 45.2 ($N(CH_3)_2$), 57.9 (C-β), 105.4 (C-1), 119.5 (C-6a), 121.7 (C-3 + C-7), 123.8 (C-10), 125.4 (C-4), 126.9 (C-8), 127.9 (C-4a), 130.4 (C-9 + C-10b + C-4b), 135.2 (C-10a), 135.23 (C-12a), 145.9 (C-12), 153.3 (C-6), 158.9 (-OCH_3). MS (C.I., NH_3) : m/z 347 ($M2H^+$).

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