Synthesis of 5-Amino-1,2,3,4-tetrahydrobenzo[*b*][1,7]naphthyridines and 2,3,4,4a,5,6-Hexahydrobenzo[*c*][2,6]naphthyridines

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This paper describes the synthesis of some 5-amino-1,2,3,4-tetrahydrobenzo[*b*][1,7]naphthyridines and 2,3,4,4a,5,6-hexahydrobenzo[*c*][2,6] naphthyridines starting from anilines and 1-benzyl-4-ethoxycarbonylpiperidin-3-one. The compounds were prepared in order to study their potential acetylcholinesterase inhibitory activity.

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According to "cholinergic hypothesis", senile dementia of the Alzheimer type has been associated with a loss of cholinergic neurotransmission [1,2], which compromises some cognitive functions. One of the most interesting approaches to therapy is based on the treatment of patients with cholinesterase inhibitors, in order to increase the level of brain acetylcholine, consequently enhancing chemical transmission at cholinergic synapses.

In the last years several analogues and homologues of Tacrine **1** [3-6], a cholinesterase inhibitor approved by the Food and Drug Administration in the United States for treating patients with mild to moderate Alzheimer's disease, have been synthesized and studied in order to increase biological potency and selectivity towards acetylcholinesterase with the aim to diminish the harmful side effects which greatly limit a long-term clinical treatment [7].

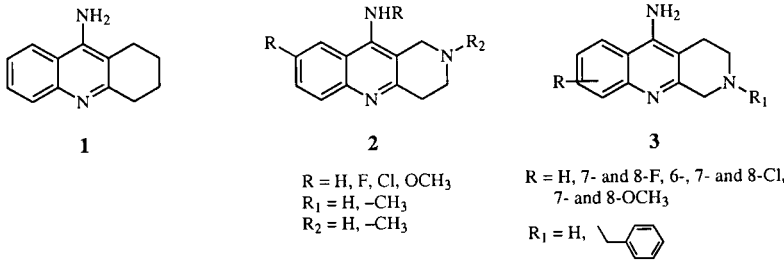


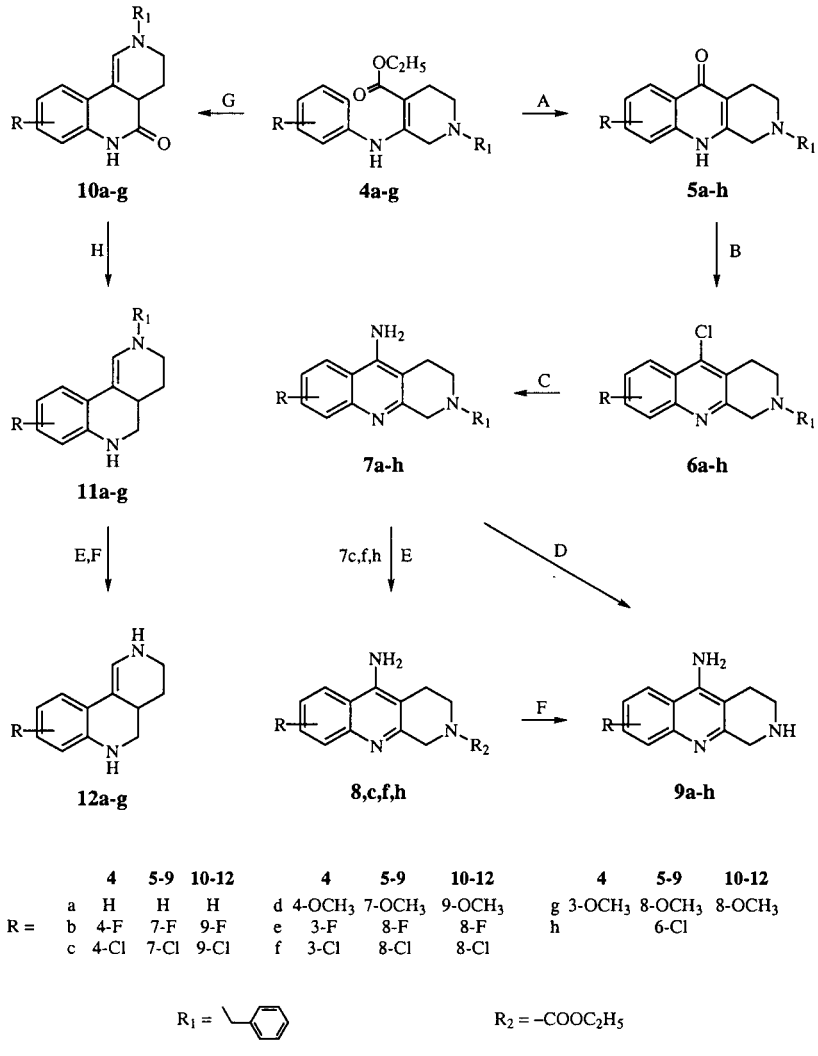
Figure 1.

As a part of our studies directed towards the search of new cholinesterase agents, we have recently performed the synthesis of some 10-amino-1,2,3,4-tetrahydrobenzo-[*b*][1,6]naphthyridines **2** [8], structurally related to Tacrine, which unfortunately displayed a reduced enzyme affinity as compared to the target drug. On the basis of the well known concept of bioisosterism, as a rationale approach to the selection of synthetic goals for trying an improvement of biologically active drugs [9], it seemed to be suitable to undertake the preparation of the isomeric 5-amino-1,2,3,4-tetrahydrobenzo[*b*][1,7]naphthyridines **3** which appear hitherto not to have been extensively studied as only two patents reported their preparation, but no chemical data were given [10,11].

The synthetical pathways to the benzo[*b*][1,7]naphthyridines **3** are summarized in Scheme 1. The synthetic route we have previously described for the preparation of benzo[*b*][1,6]naphthyridines, starting from isatins and 1-benzyl- or 1-ethoxycarbonylpiperidin-3-one, could not be followed because of poor yields of the Pfitzinger reaction and the rather troublesome preparation of some substituted isatins. Starting enaminoesters **4**, obtained by condensation of the appropriate anilines with 1-benzyl-4-ethoxycarbonylpiperidin-3-one [12] in refluxing toluene and in the presence of a catalytic amount of *p*-toluenesulfonic acid, were cyclized in boiling diphenyl ether to give the 1,2,3,4-tetrahydrobenzo[*b*][1,7]naphthyridin-5(10*H*)-ones **5**.

It is noteworthy that *N*-(3-fluoro- and 3-methoxyphenyl)-1-benzyl-4-ethoxycarbonyl-3-pyridinamines **4e** and **4g** afforded only the 8-fluoro- and 8-methoxybenzo-[*b*][1,7]naphthyridinones **5e** and **5g**, while the corresponding chloro derivative **4f** provided an isomeric 1:1 mixture of 6- and 8-chlorobenzo[*b*][1,7]naphthyridinones **5h** and **5f**. Reaction of **5** with phosphorus oxychloride at 25-50° provided the 5-chloroderivatives **6**, in yields ranging from 60 to 95%. The 5-amino-2-benzyl-1,2,3,4-tetrahydrobenzo[*b*][1,7]naphthyridines **7** were obtained, according to a previously described procedure [5], by bubbling

Scheme 1



R =	4	5-9	10-12		4	5-9	10-12		4	5-9	10-12
a	H	H	H	d	4-OCH_3	7-OCH_3	9-OCH_3	g	3-OCH_3	8-OCH_3	8-OCH_3
b	4-F	7-F	9-F	e	3-F	8-F	8-F				
c	4-Cl	7-Cl	9-Cl	f	3-Cl	8-Cl	8-Cl	h		6-Cl	

R_1 = $R_2 = -COOC_2H_5$

Reagents: A: Ph_2O, reflux; B: $POCl_3$, 25°-50°; C: NH_3/phenol, 170°; D: H_2, Pd/C, 3 atmospheres, E: ClCOOEt, toluene, 100°; F: 20% KOH, reflux; G: Ph_2O, *p*-toluenesulfonic acid reflux; H: $LiAlH_4$/diethyl ether, rt.

anhydrous ammonia into a phenolic solution of compounds **6** at 170° for 2 hours.

Catalytic hydrogenolysis of benzyl derivatives **7** over palladium on charcoal in a Parr apparatus afforded the expected 5-amino-1,2,3,4-tetrahydrobenzo[*b*][1,7]naphthyridines **9a,b,d,e,g**. The chloro derivatives **7c,f,h**, under the same conditions, gave instead a complex mixture of several compounds; so their benzyl groups were cleaved by reaction with ethyl chloroformate followed by hydrolysis of the ethoxycarbonyl derivatives **8c,f,h** in a 20% (1:1) hydroalcoholic solution of potassium hydroxide.

Finally, cyclization of enaminoesters **4** in refluxing diphenyl ether and in the presence of catalytic amounts of *p*-toluenesulfonic acid led, by a hydrolytic rearrangement, to the formation of 2-benzyl-2,3,4,4a-tetrahydrobenzo-[*c*][2,6]naphthyridin-5-(6*H*)-ones **10**, hitherto not reported in the chemical literature. Their structure was confirmed by ^1H mono and bidimensional nmr and NOE experiments; the presence of an asymmetric carbon atom was pointed out by chiral high pressure liquid chromatography analysis.

Reduction of compounds **10** with lithium aluminium hydride in diethyl ether, followed by *N*-debenzylation of the intermediates **11**, by reaction with ethyl chloroformate followed by alkaline hydrolysis, provided the expected 2,3,4,4a,5,6-hexahydrobenzo[*c*][2,6]naphthyridines **12**. Derivatives **9** and **12** were evaluated for enzymatic inhibitory activity *versus* acetylcholinesterase from rat cerebral cortex, according to the procedure of Ellman [13]. While compounds **12** did not show to possess activity, benzonaphthyridines **9** displayed interesting behavior depending either on the chemical feature, or on the position of R substituent.

As previously noticed for Tacrine and its derivatives [14], substitution at the 8-position, corresponding to the 6 position of Tacrine, led to a good enhancement of inhibitory activity in comparison with other positions and the different substituents produced changes in potency in the following increasing order: methoxy, fluoro and hydrogen, chloro. The inhibitory activity of compounds **9a-h** showed as IC_{50} values, ranging from 0.06 μ*M* for the chloro derivative **9f** to 0.5 μ*M* for the methoxy derivative **9g** (IC_{50} of Tacrine = 0.19 μ*M*). The presence of a fluorine atom in **9e** did not induce any activity enhancement in respect to that of the unsubstituted compound **9a**, IC_{50} being 0.25 μ*M* for both compounds.

In conclusion, replacement of the tetrahydroquinoline moiety of Tacrine by a tetrahydro[1,7]naphthyridine unit proved to be unimportant in *in vitro* cholinesterase inhibitory activity.

EXPERIMENTAL

Melting points were taken on a Kofler hot stage apparatus and are uncorrected. The ^{1}H-nmr spectra were obtained on a Varian Gemini 200 MHz instrument; all values were reported in ppm (δ) and standard abbreviations were used (a = apparent; b = broad; d = doublet; dd = doublet of doublets; m = multiplet; q = quadruplet; s = singlet; t = triplet); assignments were also based on ^{1}H-COSY and NOE experiments; electron ionization mass spectra were recorded on a HP 59980 B spectrometer operating at 70 eV. Column chromatographic separations were accomplished on Merck silica gel (70-230 mesh) or on Merck aluminium oxide 90. Chiral high pressure liquid chromatographic analysis of compounds **10** was performed on a Daicel stainless-steel Chiralcel OD (250 x 4.6 mm I.D.) column at 20°, mobile phase consisting of *n*-hexane/2-propanol/diethylamine 90:10:0.1 v/v/v, flux 0.6 ml/minute, uv detector operating at λ = 254 nm. The purity of each compound was checked on silica gel C. Erba 60 F_{254} or Merck aluminium oxide 60 F_{254} (type E) plates and spots were located by uv light. Sodium sulfate was used to dry organic solutions.

General Procedure for the Preparation of *N*-Aryl-1-benzyl-4-ethoxycarbonyl-1,2,5,6-tetrahydro-3-pyridinamines **4a-g**.

A mixture of the appropriate aniline (0.1 mole), *N*-benzyl-4-ethoxycarbonylpiperidin-3-one (28.7 g, 0.11 mole) [12] and *p*-toluenesulfonic acid monohydrate (0.3 g), in toluene (150 ml) was stirred and refluxed in an oil bath for 8 hours with a Dean-Stark trap to remove water. Evaporation of the solvent to dryness gave a crude mixture which was chromatographed on an aluminium oxide column, by eluting with a 30:70 v/v ethyl acetate/*n*-hexane mixture.

Compounds **4** were used without further purification. Analytical samples were obtained by crystallization from appropriate solvent.

N-Phenyl-1-benzyl-4-ethoxycarbonyl-1,2,5,6-tetrahydro-3-pyridinamine **4a**.

This compound was obtained from aniline in 55% yield, mp 59-61° (*n*-hexane); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 10.47 (s, 1H, NH), 7.28-7.01 (m, 10 H, aromatic protons), 4.10 (q, 2H, OCH_2), 3.51 (s, 2H, benzyl CH_2), 3.22 (s, 2H, H-2), 2.52 (at, 2H, H-6), 2.32 (at, 2H, H-5), 1.20 (t, 3H, CH_3); ms: (m/z) 336 (M^+), 245, 231, 217, 142.

Anal. Calcd. for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 74.82; H, 7.41; N, 8.39.

N-(4-Fluorophenyl)-1-benzyl-4-ethoxycarbonyl-1,2,5,6-tetrahydro-3-pyridinamine **4b**.

This compound was obtained from 4-fluoroaniline in 62% yield, mp 90-91° (methanol); ms: (m/z) 354 (M^+), 263, 249, 235.

Anal. Calcd. for $C_{21}H_{23}FN_2O_2$: C, 71.17; H, 6.54; N, 7.90. Found: C, 71.20; H, 6.70; N, 7.94.

N-(4-Chlorophenyl)-1-benzyl-4-ethoxycarbonyl-1,2,5,6-tetrahydro-3-pyridinamine **4c**.

This compound was obtained from 4-chloroaniline in 62% yield, mp 134-135° (methanol); ms: m/z 370 (M^+), 279, 251.

Anal. Calcd. for $C_{21}H_{23}ClN_2O_2$: C, 68.01; H, 6.25; N, 7.55. Found: C, 68.00; H, 6.28; N, 7.56.

N-(4-Methoxyphenyl)-1-benzyl-4-ethoxycarbonyl-1,2,5,6-tetrahydro-3-pyridinamine **4d**.

This compound was obtained from 4-methoxyaniline in 52% yield, mp 115-116° (ethanol); ms: m/z 366 (M^+), 261, 247.

Anal. Calcd. for $C_{22}H_{26}N_2O_3$: C, 72.11; H, 7.15; N, 7.64. Found: C, 72.22; H, 7.41; N, 7.60.

N-(3-Fluorophenyl)-1-benzyl-4-ethoxycarbonyl-1,2,5,6-tetrahydro-3-pyridinamine **4e**.

This compound was obtained from 3-fluoroaniline in 60% yield, mp 58-59° (methanol); ms: (m/z) 354 (M^+), 263, 249, 235, 162.

Anal. Calcd. for $C_{21}H_{23}FN_2O_2$: C, 71.17; H, 6.54; N, 7.90. Found: C, 71.11; H, 6.83; N, 7.97.

N-(3-Chlorophenyl)-1-benzyl-4-ethoxycarbonyl-1,2,5,6-tetrahydro-3-pyridinamine **4f**.

This compound was obtained from 3-chloroaniline in 70% yield, mp 89-91° (methanol); ms: (m/z) 370 (M^+), 279, 265, 251.

Anal. Calcd. for $C_{21}H_{23}ClN_2O_2$: C, 68.01; H, 6.25; N, 7.55. Found: C, 68.03; H, 6.26; N, 7.58.

N-(3-Methoxyphenyl)-1-benzyl-4-ethoxycarbonyl-1,2,5,6-tetrahydro-3-pyridinamine **4g**.

This compound was obtained from 3-methoxyaniline in 53% yield, mp 48-50° (methanol); ms: (m/z) 366 (M^+), 320, 275, 247, 229.

Anal. Calcd. for $C_{22}H_{26}N_2O_3$: C, 72.11; H, 7.15; N, 7.64. Found: C, 72.23; H, 7.25; N, 7.60.

General Procedure for the Preparation of 2-Benzyl-1,2,3,4-tetrahydrobenzo[*b*][1,7]naphthyridin-5(10*H*)-ones **5a-h**.

Each compound **4** (15 g) was dissolved in warm diphenyl ether (80 ml). The flask was fitted with a Dean-Stark trap to remove ethanol and the mixture was heated to reflux temperature under stirring for 10-15 minutes. After cooling, *n*-hexane (200 ml) was added to the mixture and the precipitate solid was collected by filtration, washed thoroughly with *n*-hexane, then crystallized. Isomeric compounds **5f** and **5h** were separated by column chromatography on aluminium oxide, eluting with a 2:1 v/v ethyl acetate/*n*-hexane mixture, then crystallized.

2-Benzyl-1,2,3,4-tetrahydrobenzo[*b*][1,7]naphthyridin-5(10*H*)-one **5a**.

This compound was obtained from **4a** in 50% yield, mp 238-240° (ethyl acetate); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 11.39 (s, 1H, NH), 8.05 (d, 1H, H-6), 7.55 (at, 1H, H-8), 7.40-7.18 (m, 7H, H-7, H-9 and phenyl protons), 3.67 (s, 2H, benzyl CH_2), 3.43 (s, 2H, H-1), 2.70 (at, 2H, H-4), 2.52 (at, 2H, H-3); ms: (m/z) 290 (M^+), 199, 171.

Anal. Calcd. for $C_{19}H_{18}N_2O \cdot 0.5H_2O$: C, 76.23; H, 6.40; N, 9.36. Found: C, 77.79; H, 6.31; N, 9.60.

2-Benzyl-7-fluoro-1,2,3,4-tetrahydrobenzo[*b*][1,7]naphthyridin-5(10*H*)-one **5b**.

This compound was obtained from **4b** in 55% yield, mp 245-247° (methanol); ms: (m/z) 308 (M^+), 217, 189, 161.

Anal. Calcd. for $C_{19}H_{17}FN_2O$: C, 74.01; H, 5.56; N, 9.08. Found: C, 73.73; H, 5.84; N, 9.20.

2-Benzyl-7-chloro-1,2,3,4-tetrahydrobenzo[*b*][1,7]naphthyridin-5(10*H*)-one **5c**.

This compound was obtained from **4c** in 58% yield, mp 249-251° (methanol); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 11.58 (s, 1H, NH), 7.98 (d, 1H, H-6, $J_{6,8}$ = 2.5 Hz), 7.60 (dd, 1H, H-8, $J_{8,9}$ = 8.9 Hz, $J_{6,8}$ = 2.5 Hz), 7.42 (d, 1H, H-9, $J_{8,9}$ = 8.9 Hz), 7.35 (m, 5H, phenyl protons), 3.68 (s, 2H, benzyl CH_2), 3.43 (s, 2H, H-1), 2.73 (at, 2H, H-4), 2.51 (at, partially under the dimethyl-d_6 sulfoxide signal, 2H, H-3); ms: (m/z) 324 (M^+), 233, 205, 120.

Anal. Calcd. for $C_{19}H_{17}ClN_2O$: C, 70.26; H, 5.28; N, 8.62. Found: C, 70.30; H, 5.07; N, 8.52.

2-Benzyl-7-methoxy-1,2,3,4-tetrahydrobenzo[*b*][1,7]naphthyridin-5(10*H*)-one **5d**.

This compound was obtained from **4d** in 41% yield, mp 249-250° (ethyl acetate); ms: (m/z) 320 (M^+), 229, 201, 186.

Anal. Calcd. for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74. Found: C, 75.76; H, 6.34; N, 8.71.

2-Benzyl-8-fluoro-1,2,3,4-tetrahydrobenzo[*b*][1,7]naphthyridin-5(10*H*)-one **5e**.

This compound was obtained from **4e** in 40% yield, mp 240-241° (methanol/ethyl acetate); ms: (m/z) 308 (M^+), 217, 189, 161, 120.

Anal. Calcd. for $C_{19}H_{17}FN_2O \cdot 0.2H_2O$: C, 73.15; H, 5.62; N, 8.98. Found: C, 73.40; H, 5.50; N, 9.14.

2-Benzyl-8-chloro-1,2,3,4-tetrahydrobenzo[*b*][1,7]naphthyridin-5(10*H*)-one **5f**.

This compound was obtained from **4f** in 53% yield, mp 212-214° (ethyl acetate); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 11.47 (s, 1H, NH), 8.04 (d, 1H, H-6), 7.50-7.15 (m, 7H, H-7, H-9 and phenyl protons), 3.69 (s, 2H, benzyl CH_2), 3.42 (s, 2H, H-1), 2.73 (at, 2H, H-4), 2.50 (at, partially under the dimethyl-d_6 sulfoxide signal, 2H, H-3); ms: (m/z) 324 (M^+), 233, 205, 120.

Anal. Calcd. for $C_{19}H_{17}ClN_2O \cdot 0.2H_2O$: C, 69.49; H, 5.34; N, 8.53. Found: C, 69.20; H, 5.06; N, 8.39.

2-Benzyl-8-methoxy-1,2,3,4-tetrahydrobenzo[*b*][1,7]naphthyridin-5(10*H*)-one **5g**.

This compound was obtained from **4g** in 54% yield, mp 248-250° (ethanol); ms: (m/z) 320 (M^+), 229, 201, 173.

Anal. Calcd. for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74. Found: C, 74.75; H, 6.57; N, 8.87.

2-Benzyl-6-chloro-1,2,3,4-tetrahydrobenzo[*b*][1,7]naphthyridin-5(10*H*)-one **5h**.

This compound was obtained from **4h** in 45% yield, mp 238-240° (ethyl acetate); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 7.44 (t, 1H, H-8), 7.35 (m, 6H, phenyl protons and H-7), 7.17 (d, 1H, H-9), 3.68 (s, 2H, benzyl CH_2), 3.39 (s, 2H, H-1), 2.72 (at, 2H, H-4), 2.49 (at, partially under the dimethyl-d_6 sulfoxide signal, 2H, H-3); ms: (m/z) 324 (M^+), 233, 205, 170, 120.

Anal. Calcd. for $C_{19}H_{17}ClN_2O$: C, 70.26; H, 5.28; N, 8.62. Found: C, 70.28; H, 5.36; N, 8.53.

General Procedure for the Preparation of 2-Benzyl-5-chloro-1,2,3,4-tetrahydrobenzo[*b*][1,7]naphthyridines **6a-h**.

Each compound **5** (10 g) was added portionwise with stirring, to phosphorus oxychloride (60 ml). The mixture was allowed to react for 30 minutes at room temperature in the case of **5a,b** and at 50° when **5c-g** were used. After cooling, the reaction mixture was diluted with diethyl ether. The precipitate solid was rapidly collected by filtration, washed with ether and treated with diluted aqueous ammonium hydroxide. Extraction with ethyl acetate followed by removal of the solvent under reduced pressure gave the 5-chloro derivatives **6** which were used without further purification. Analytical samples of compounds **6** were obtained by crystallization from appropriate solvent.

2-Benzyl-5-chloro-1,2,3,4-tetrahydrobenzo[*b*][1,7]naphthyridine **6a**.

This compound was obtained from **5a** in 94% yield, mp 98-100° (*n*-hexane); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 8.13 (dd, 1H, H-6), 7.92 (dd, 1H, H-9), 7.76 (t, 1H, H-8), 7.66 (t, 1H, H-7), 7.37 (m, 5H, phenyl protons), 3.75 (s, 2H, H-1), 3.74 (s, 2H benzyl CH_2), 3.03 (at, 2H, H-4), 2.84 (at, 2H, H-3); ms: (m/z) 308 (M^+), 231, 217, 189.

Anal. Calcd. for $C_{19}H_{17}ClN_2$: C, 73.90; H, 5.55; N, 9.07. Found: C, 73.88; H, 5.37; N, 9.21.

2-Benzyl-5-chloro-7-fluoro-1,2,3,4-tetrahydrobenzo[*b*]-[1,7]naphthyridine **6b**.

This compound was obtained from **5b** in 90% yield, mp 107-108° (*n*-hexane); ms: (m/z) 326 (M^+), 235, 208, 172.

Anal. Calcd. for $C_{19}H_{16}FClN_2$: C, 69.83; H, 4.93; N, 8.57. Found: C, 69.75; H, 4.82; N, 8.48.

2-Benzyl-5,7-dichloro-1,2,3,4-tetrahydrobenzo[*b*][1,7]naphthyridine **6c**.

This compound was obtained from **5c** in 95% yield, mp 133-135° (ethyl acetate); ms: (m/z) 342 (M^+), 265, 251, 188.

Anal. Calcd. for $C_{19}H_{16}Cl_2N_2$: C, 66.48; H, 4.70; N, 8.16. Found: C, 66.35; H, 4.42; N, 8.01.

2-Benzyl-5-chloro-7-methoxy-1,2,3,4-tetrahydrobenzo[*b*][1,7]-naphthyridine **6d**.

This compound was obtained from **5d** in 60% yield, mp 89-91° (*n*-hexane); ms: (m/z) 338 (M^+), 261, 247, 219, 184.

Anal. Calcd. for $C_{20}H_{19}ClN_2O$: C, 70.90; H, 5.65; N, 8.27. Found: C, 70.75; H, 5.78; N, 8.28.

2-Benzyl-5-chloro-8-fluoro-1,2,3,4-tetrahydrobenzo[*b*]-[1,7]naphthyridine **6e**.

This compound was obtained from **5e** in 70% yield, mp 95-97° (cyclohexane); ms: (m/z) 326 (M^+), 249, 235, 208.

Anal. Calcd. for $C_{19}H_{16}FClN_2 \cdot 0.5H_2O$: C, 67.96; H, 5.10; N, 8.34. Found: C, 68.15; H, 4.91; N, 8.26.

2-Benzyl-5,8-dichloro-1,2,3,4-tetrahydrobenzo[*b*][1,7]naphthyridine **6f.**

This compound was obtained from **5f** in 80% yield, mp 109-110° (cyclohexane); ms: (m/z) 342 (M^+), 265, 251, 188.

Anal. Calcd. for $C_{19}H_{16}Cl_2N_2$: C, 66.48; H, 4.70; N, 8.16. Found: C, 66.32; H, 4.56; N, 8.04.

2-Benzyl-5-chloro-8-methoxy-1,2,3,4-tetrahydrobenzo[*b*][1,7]-naphthyridine **6g**.

This compound was obtained from **5g** in 90% yield, mp 90-92° (ethyl acetate); ms: (m/z) 338 (M^+), 261, 247, 219.

Anal. Calcd. for $C_{20}H_{19}ClN_2O$: C, 70.90; H, 5.65; N, 8.27. Found: C, 70.84; H, 5.75; N, 8.35.

2-Benzyl-5,6-dichloro-1,2,3,4-tetrahydrobenzo[*b*][1,7]naphthyridine **6h.**

This compound was obtained from **5h** in 80% yield, mp 115-118° (cyclohexane); ms: (m/z) 342 (M^+), 265, 251, 188.

Anal. Calcd. for $C_{19}H_{16}Cl_2N_2$: C, 66.48; H, 4.70; N, 8.16. Found: C, 66.19; H, 4.9; N, 8.09.

General Procedure for the Preparation of 5-Amino-2-benzyl-1,2,3,4-tetrahydrobenzo[*b*][1,7]naphthyridines **7a-h**.

A mixture of each compound **6** (10 g) and phenol (50 g) was heated at 170° in an oil bath and anhydrous ammonia was bubbled into the mixture for 2.5 hours. After cooling, 10% sodium hydroxide (300 ml) was added to the mixture and the resulting suspension was vigorously stirred for 15 minutes. The precipitate was collected by filtration, washed with water and dried at 60° under reduced pressure. Further purification was achieved by chromatography on aluminium oxide by eluting with a 1:1 v/v ethyl acetate/*n*-hexane mixture, followed by crystallization.

5-Amino-2-benzyl-1,2,3,4-tetrahydrobenzo[*b*][1,7]naphthyridine **7a.**

This compound was obtained from **6a** in 51% yield, mp 150-155° (ethyl acetate/*n*-hexane); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 8.15 (d, 1H, H-6), 7.58 (d, 1H, H-9), 7.48 (t, 1H, H-8), 7.35 (m, 6H, H-7 and phenyl protons), 6.45 (bs, 2H, NH_2), 3.65 (s, 2H, benzyl CH_2), 3.53 (s, 2H, H-1), 2.76 (at, 2H, H-4), 2.64 (at, 2H, H-3); ms: (m/z) 289 (M^+), 198, 170, 94.

Anal. Calcd. for $C_{19}H_{19}N_3$: C, 78.86; H, 6.62; N, 14.52. Found: C, 78.52; H, 6.32; N, 14.57.

5-Amino-2-benzyl-7-fluoro-1,2,3,4-tetrahydrobenzo[*b*][1,7]-naphthyridine **7b**.

This compound was obtained from **6b** in 35% yield, mp 188-190° (ethyl acetate/*n*-hexane); ms: (m/z) 307 (M^+), 216, 188.

Anal. Calcd. for $C_{19}H_{18}FN_3$: C, 74.25; H, 5.90; N, 13.67. Found: C, 74.40; H, 5.85; N, 13.63.

5-Amino-2-benzyl-7-chloro-1,2,3,4-tetrahydrobenzo[*b*]-[1,7]naphthyridine **7c**.

This compound was obtained from **6c** in 38% yield, mp 160-162° (ethyl acetate/*n*-hexane); ms: (m/z) 323 (M^+), 246, 232, 204.

Anal. Calcd. for $C_{19}H_{18}ClN_3$: C, 70.47; H, 5.60; N, 12.98. Found: C, 70.23; H, 5.87; N, 12.80.

5-Amino-2-benzyl-7-methoxy-1,2,3,4-tetrahydrobenzo[*b*][1,7]-naphthyridine **7d**.

This compound was obtained from **6d** in 58% yield, mp 221-223° (ethyl acetate); ms: (m/z) 319 (M^+), 228, 200.

Anal. Calcd. for $C_{20}H_{21}N_3O$: C, 75.21; H, 6.63; N, 13.16. Found: C, 74.97; H, 6.80; N, 12.98.

5-Amino-2-benzyl-8-fluoro-1,2,3,4-tetrahydrobenzo[*b*][1,7]-naphthyridine **7e**.

This compound was obtained from **6e** in 49% yield, mp 150-152° (ethyl acetate); ms: (m/z) 307 (M^+), 230, 216, 188.

Anal. Calcd. for $C_{19}H_{18}FN_3$: C, 74.25; H, 5.90; N, 13.67. Found: C, 73.98; H, 6.17; N, 13.47.

5-Amino-2-benzyl-8-chloro-1,2,3,4-tetrahydrobenzo[*b*][1,7]-naphthyridine **7f**.

This compound was obtained from **6f** in 60% yield, mp 190-192° (ethyl acetate/*n*-hexane); ms: (m/z) 323 (M^+), 232, 169.

Anal. Calcd. for $C_{19}H_{18}ClN_3$: C, 70.47; H, 5.60; N, 12.98. Found: C, 70.30; H, 5.38; N, 12.81.

5-Amino-2-benzyl-8-methoxy-1,2,3,4-tetrahydrobenzo[*b*][1,7]-naphthyridine **7g**.

This compound was obtained from **6g** in 51% yield, mp 175-177° (ethyl acetate); ms: (m/z) 319 (M^+), 228, 200, 185.

Anal. Calcd. for $C_{20}H_{21}N_3O \cdot 0.75H_2O$: C, 72.16; H, 6.81; N, 12.62. Found: C, 72.48; H, 6.49; N, 12.53.

5-Amino-2-benzyl-6-chloro-1,2,3,4-tetrahydrobenzo[*b*][1,7]-naphthyridine **7h**.

This compound was obtained from **6h** in 58% yield, mp 170-172° (ethyl acetate); ms: (m/z) 323 (M^+), 232, 204, 169.

Anal. Calcd. for $C_{19}H_{18}ClN_3 \cdot 0.2H_2O$: C, 69.70; H, 5.66; N, 12.83. Found: C, 69.69; H, 5.87; N, 12.80.

General Procedure for the Preparation of 5-Amino-1,2,3,4-tetrahydrobenzo[*b*][1,7]naphthyridines **9a,b,d,e,g**.

Compounds **7a,b,d,e,g** (1 g) were hydrogenated in ethanol containing a few drops of concentrated hydrochloric acid (100 ml), over 5% palladium charcoal (0.2 g) at 3 atmospheres and room temperature for 24 hours. The suspension was filtered and the resulting solution was concentrated under reduced pressure. The residue was dissolved in water (10 ml) and made alkaline with 10 *N* potassium hydroxide. The precipitate which had formed was collected by filtration, washed with cold water, dried at 60° under reduced pressure, then crystallized.

5-Amino-1,2,3,4-tetrahydrobenzo[*b*][1,7]naphthyridine **9a**.

This compound was obtained from **7a** in 44% yield, mp 198-200° (ethyl acetate/*n*-hexane); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 8.13 (d, 1H, H-6), 7.61 (d, 1H, H-9), 7.48 (t, 1H, H-8), 7.27 (t, 1H, H-7), 6.34 (bs, 2H, NH_2), 3.83 (s, 2H, H-1), 3.02 (t, 2H, H-4), 2.54 (t, partially under dimethyl-d_6 sulfoxide signal, 2H, H-3), 1.69 (m, 1H, NH); ms: (m/z) 199 (M^+), 184, 171, 144.

Anal. Calcd. for $C_{12}H_{13}N_3 \cdot H_2O$: C, 66.34; H, 6.96; N, 19.34. Found: C, 66.30; H, 6.85; N, 19.02.

5-Amino-7-fluoro-1,2,3,4-tetrahydrobenzo[*b*][1,7]naphthyridine **9b.**

This compound was obtained from **7b** in 40% yield, mp 200-202° (water); ms: (m/z) 217 (M^+), 190, 147.

Anal. Calcd. for $C_{12}H_{12}FN_3 \cdot 0.25H_2O$: C, 65.00; H, 5.68; N, 18.95. Found: C, 65.27; H, 5.48; N, 18.63.

5-Amino-7-methoxy-1,2,3,4-tetrahydrobenzo[*b*][1,7]naphthyridine **9d**.

This compound was obtained from **7d** in 50% yield, mp 236-238° (water); ms: m/z 229 (M^+), 214, 201, 185.

Anal. Calcd. for $C_{13}H_{15}N_3O$: C, 68.10; H, 6.59; N, 18.33. Found: C, 68.15; H, 6.48; N, 18.19.

5-Amino-8-fluoro-1,2,3,4-tetrahydrobenzo[*b*][1,7]naphthyridine **9e**.

This compound was obtained from **7e** in 70% yield, mp 165-167° (ethanol/ethyl acetate); ms: (m/z) 217 (M^+), 189, 147.

Anal. Calcd. for $C_{12}H_{12}FN_3 \cdot H_2O$: C, 61.26; H, 6.00; N, 17.86. Found: C, 61.40; H, 5.96; N, 17.59.

5-Amino-8-methoxy-1,2,3,4-tetrahydrobenzo[*b*][1,7]naphthyridine **9g**.

This compound was obtained from **7g** in 35% yield, mp 228-230° (water); ms: (m/z) 229 (M^+), 214, 201, 185.

Anal. Calcd. for $C_{13}H_{15}N_3O$: C, 68.10; H, 6.59; N, 18.33. Found: C, 68.12; H, 6.46; N, 18.06.

General Procedure for the Preparation of 5-Amino-2-ethoxycarbonyl-1,2,3,4-tetrahydrobenzo[*b*][1,7]naphthyridines **8c,f,h**.

A mixture of each compound **7c,f,h** (1 g, 6.2 mmoles) and ethyl chloroformate (0.91 ml, 9.4 mmoles) in anhydrous toluene (50 ml) was stirred at 100° for 4-5 hours. The solvent was removed *in vacuo* and the residue, treated with diluted ammonium hydroxide, was extracted with ethyl acetate. The organic layer was evaporated to dryness and the solid obtained crystallized.

5-Amino-7-chloro-2-ethoxycarbonyl-1,2,3,4-tetrahydrobenzo-[*b*][1,7]naphthyridine **8c**.

This compound was obtained from **7c** in 60% yield, mp 170-172° (ethyl acetate); ms: (m/z) 305 (M^+), 276, 232.

Anal. Calcd. for $C_{15}H_{16}ClN_3O_2 \cdot H_2O$: C, 55.64; H, 5.60; N, 12.98. Found: C, 55.93; H, 5.60; N, 12.98.

5-Amino-8-chloro-2-ethoxycarbonyl-1,2,3,4-tetrahydrobenzo-[*b*][1,7]naphthyridine **8f**.

This compound was obtained from **7f** in 65% yield, mp 222-224° (ethyl acetate); ms: (m/z) 305 (M^+), 276, 232, 204.

Anal. Calcd. for $C_{15}H_{16}ClN_3O_2 \cdot 0.25H_2O$: C, 58.07; H, 5.36; N, 13.54. Found: C, 58.15; H, 5.40; N, 13.31.

5-Amino-6-chloro-2-ethoxycarbonyl-1,2,3,4-tetrahydrobenzo-[*b*][1,7]naphthyridine **8h**.

This compound was obtained from **7h** in 53% yield, mp 164-166° (ethyl acetate); ms: (m/z) 305 (M^+), 276, 232, 204.

Anal. Calcd. for $C_{15}H_{16}ClN_3O_2 \cdot 0.25H_2O$: C, 58.07; H, 5.36; N, 13.54. Found: C, 58.25; H, 5.33; N, 13.41.

General Procedure for the Preparation of 5-Amino-1,2,3,4-tetrahydrobenzo[*b*][1,7]naphthyridines **9c,f,h**.

A suspension of each compound **8c,f,h** (1 g) in a 15% (1:1) hydroalcoholic solution of potassium hydroxide (30 ml) was refluxed for 2 hours. After cooling, ethanol was removed under reduced pressure; the precipitated solid was collected by filtration, washed thoroughly with water, dried at 60° *in vacuo*, then crystallized.

5-Amino-7-chloro-1,2,3,4-tetrahydrobenzo[*b*][1,7]naphthyridine **9c**.

This compound was obtained from **8c** in 73% yield, mp 268-270° (water); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 8.27 (dd, 1H, H-6, $J_{6,8}$ = 2.1 Hz), 7.62 (d, 1H, H-9, $J_{8,9}$ = 8.9 Hz), 7.47 (dd, 1H, H-8, $J_{8,9}$ = 8.9 Hz $J_{6,8}$ = 2.1 Hz), 6.48 (bs, 2H, NH_2), 3.82 (s, 2H, H-1), 3.01 (at, 2H, H-4), 2.49 (aq, under dimethyl-d_6 sulfoxide signal, 2H, H-3), 1.86 (m, 1H, NH); ms: (m/z) 233 (M^+), 206, 178, 169, 140.

Anal. Calcd. for $C_{12}H_{12}ClN_3 \cdot 0.25H_2O$: C, 60.51; H, 5.29; N, 17.64. Found: C, 60.69; H, 4.95; N, 17.78.

5-Amino-8-chloro-1,2,3,4-tetrahydrobenzo[*b*][1,7]naphthyridine **9f**.

This compound was obtained from **8f** in 70% yield, mp 240-242° (ethyl acetate); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 8.17 (d, 1H, H-6, $J_{6,7}$ = 8.9 Hz), 7.62 (dd, 1H, H-9, $J_{7,9}$ = 2.0 Hz), 7.28 (dd, 1H, H-7, $J_{6,7}$ = 8.9 Hz, $J_{7,9}$ = 2.0 Hz), 6.53 (bs, 2H, NH_2), 3.81 (s, 2H, H-1), 3.01 (at, 2H, H-4), 2.49 (aq, under the dimethyl-d_6 sulfoxide signal, 2H, H-3), 1.63 (m, 1H, NH); ms: (m/z) 233 (M^+), 230, 196, 140.

Anal. Calcd. for $C_{12}H_{12}ClN_3$: C, 61.67; H, 5.18; N, 17.98. Found: C, 61.60; H, 5.15; N, 17.82.

5-Amino-6-chloro-1,2,3,4-tetrahydrobenzo[*b*][1,7]naphthyridine **9h**.

This compound was obtained from **8h** in 78% yield, mp 220-222° (water); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 7.61 (d, 1H, H-9), 7.41 (t, 1H, H-8), 7.32 (d, 1H, H-7), 6.54 (bs, 2H, NH_2), 3.82 (s, 2H, H-1), 3.03 (at, 2H, H-4), 2.45 (at, 2H, H-3), 1.20 (m, 1H, NH); ms: (m/z) 233 (M^+), 218, 206, 169.

Anal. Calcd. for $C_{12}H_{12}ClN_3$: C, 61.67; H, 5.18; N, 17.98. Found: C, 61.53; H, 5.20; N, 17.91.

General Procedure for the Preparation of 2-Benzyl-2,3,4,4a-tetrahydrobenzo[*c*][2,6]naphthyridin-5(6*H*)-ones **10a-g.**

Each compound **4** (10 g) was dissolved in warm diphenyl ether (60 ml) and a catalytic amount of *p*-toluenesulfonic acid monohydrate (0.2 g) was added. The flask was fitted with a Dean-Stark trap to remove ethanol and the mixture was heated to reflux temperature with stirring for 10-15 minutes. After cooling, *n*-hexane (200 ml) was added and the precipitate was collected by filtration, washed thorougly with *n*-hexane, then crystallized.

2-Benzyl-2,3,4,4a-tetrahydrobenzo[*c*][2,6]naphthyridin-5(6*H*)-one **10a.**

This compound was obtained from **4a** in 58% yield, mp 132-134°(ethanol); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 11.03 (s, 1H, NH), 7.42 (d, 1H, H-10), 7.32 (m, 6H, H-7 and phenyl protons), 7.01 (t, 1H, H-8), 6.92 (t, 1H, H-9), 6.26 (t, 1H, H-1), 4.43 (as, 2H, benzyl CH_2), 3.90 (t, 1H, H-4a), 3.30 (m, 2H, H-3), 2.44 (m, partially under the dimethyl-d_6 sulfoxide signal, 1H, H-4eq), 2.25 (m, 1H, H-4ax); ms: (m/z) 290 (M^+), 199, 156, 143. Chiral high pressure liquid chromathography analysis showed an enatiomeric resolution with two peaks at 33.4 and 38.4 minutes retention times.

Anal. Calcd. for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65. Found: C, 78.43; H, 6.13; N, 9.72.

2-Benzyl-9-fluoro-2,3,4,4a-tetrahydrobenzo[*c*][2,6]naphthyridin-5(6*H*)-one **10b.**

This compound was obtained from **4b** in 30% yield, mp 135-136° (ethyl acetate); ms: (m/z) 308 (M^+), 217, 174, 161.

Anal. Calcd. for $C_{19}H_{17}FN_2O \cdot 0.5H_2O$: C, 71.91; H, 5.72; N, 8.83. Found: C, 71.90; H, 5.71; N, 8.66.

2-Benzyl-9-chloro-2,3,4,4a-tetrahydrobenzo[*c*][2,6]naphthyridin-5(6*H*)-one **10c.**

This compound was obtained from **4c** in 36% yield, mp 144-145° (methanol); ms: (m/z) 324 (M^+), 233, 177, 133.

Anal. Calcd. for $C_{19}H_{17}ClN_2O$: C, 70.26; H, 5.28; N, 8.62. Found: C, 70.28; H, 4.94; N, 8.48.

2-Benzyl-9-methoxy-2,3,4,4a-tetrahydrobenzo[*c*][2,6]naphthyridin-5(6*H*)-one **10d.**

This compound was obtained from **4d** in 49% yield, mp 131-133° (ethanol); ms: (m/z) 320 (M^+), 229, 187, 173.

Anal. Calcd. for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74. Found: C, 74.82; H, 6.39; N, 8.76.

2-Benzyl-8-fluoro-2,3,4,4a-tetrahydrobenzo[*c*][2,6]naphthyridin-5(6*H*)-one **10e.**

This compound was obtained from **4e** in 35% yield, mp 125-127° (ethanol); ms: (m/z) 308 (M^+), 289, 217, 175.

Anal. Calcd. for $C_{19}H_{17}FN_2O$: C, 74.01; H, 5.56; N, 9.08. Found: C, 74.03; H, 5.27; N, 9.10.

2-Benzyl-8-chloro-2,3,4,4a-tetrahydrobenzo[*c*][2,6]naphthyridin-5(6*H*)-one **10f.**

This compound was obtained from **4f** in 34% yield, mp 127-129° (methanol); ms: (m/z) 324 (M^+).

Anal. Calcd. for $C_{19}H_{17}ClN_2O$: C, 70.26; H, 5.28; N, 8.62. Found: C, 70.37; H, 5.11; N, 8.74.

2-Benzyl-8-methoxy-2,3,4,4a-tetrahydrobenzo[*c*][2,6]naphthyridin-5(6*H*)-one **10g.**

This compound was obtained from **4g** in 33% yield, mp 116-118° (ethyl acetate); ms: (m/z) 320 (M^+), 305, 229, 187, 173, 158.

Anal. Calcd. for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74. Found: C, 75.17; H, 6.42; N, 8.87.

General Procedure for the Preparation of 2-Benzyl-2,3,4,4a,5,6-hexahydrobenzo[*c*][2,6]naphthyridines **11a-g.**

To a stirred suspension of lithium aluminium hydride (1 g, 26 mmoles) in anhydrous diethyl ether (20 ml), a suspension of each compound **10** (6.5 mmoles) in anhydrous diethyl ether (100 ml) was added slowly at room temperature. The mixture was allowed to react overnight under stirring, then cooled in an ice bath and treated with water (5 ml). The precipitated hydroxides were removed by filtration and rinsed thoroughly with diethyl ether. The solvent was evaporated to dryness and crude products **11** were purified by chromatography on an aluminium oxide column by eluting with an 1:1 ethyl acetate/*n*-hexane mixture.

2-Benzyl-2,3,4,4a,5,6-hexahydrobenzo[*c*][2,6]naphthyridine **11a.**

This compound was obtained from **10a** in 40% yield, mp 112-114° (methanol); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 10.84 (s, 1H, NH), 7.39 (d, 1H, H-10), 7.31 (ad, 5H, phenyl protons), 7.26 (d, 1H, H-7), 6.98 (t, 1H, H-8), 6.89 (t, 1H, H-9), 6.16 (s, 1H, H-1), 3.62 (s, 2H, benzyl CH_2), 3.46 (m, 1H, H-4a), 2.99 (t, 1H, H-3eq), 2.72 (q, 1H, H-5eq), 2.57 (q, 1H, H-5ax), 2.49 (m, partially under the dimethyl-d_6 sulfoxide signal, 1H, H-4eq), 2.23 (m, 1H, H-3ax), 1.96 (m, 1H, H-4ax); ms: (m/z) 276 (M^+), 185, 156, 143, 133.

Anal. Calcd. for $C_{19}H_{20}N_2$: C, 82.57; H, 7.29; N, 10.14. Found: C, 82.37; H, 7.17; N, 10.11.

2-Benzyl-9-fluoro-2,3,4,4a,5,6-hexahydrobenzo[*c*][2,6]naphthyridine **11b.**

This compound was obtained from **10b** in 73% yield, mp 125-127° (methanol); ms: m/z 294 (M^+), 203, 174, 161, 148, 133.

Anal. Calcd. for $C_{19}H_{19}FN_2$: C, 77.52; H, 6.51; N, 9.52. Found: C, 77.40; H, 6.63; N, 9.45.

2-Benzyl-9-chloro-2,3,4,4a,5,6-hexahydrobenzo[*c*][2,6]naphthyridine **11c.**

This compound was obtained from **10c** as an oil in 80% yield, hydrochloride mp 203-205° (ethanol/diethyl ether); ms: m/z 310 (M^+), 190, 177, 133.

Anal. Calcd. for $C_{19}H_{19}ClN_2 \cdot HCl$: C, 65.71; H, 5.80; N, 8.07. Found: C, 65.47; H, 5.83; N, 7.95.

2-Benzyl-9-methoxy-2,3,4,4a,5,6-hexahydrobenzo[*c*][2,6]naphthyridine **11d.**

This compound was obtained from **10d** in 35% yield, mp 38-40° (cyclohexane); ms: m/z 306 (M^+), 215, 186, 173, 159, 132.

Anal. Calcd. for $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.14. Found: C, 78.31; H, 7.27; N, 9.10.

2-Benzyl-8-fluoro-2,3,4,4a,5,6-hexahydrobenzo[*c*][2,6]naphthyridine **11e.**

This compound was obtained from **10e** in 60% yield, mp 122-124° (methanol); ms: (m/z) 294 (M^+), 203, 199, 174,161, 133.

Anal. Calcd. for $C_{19}H_{19}FN_2$: C, 77.52; H, 6.51; N, 9.52. Found: C, 77.83; H, 6.69; N, 9.70.

2-Benzyl-8-chloro-2,3,4,4a,5,6-hexahydrobenzo[*c*][2,6]naphthyridine **11f.**

This compound was obtained from **10f** in 73% yield, mp 70-72° (*n*-hexane); ms: (m/z) 310 (M^+), 276, 219, 177, 159, 133.

Anal. Calcd. for $C_{19}H_{19}ClN_2$: C, 73.42; H, 6.16; N, 9.01. Found: C, 73.25; H, 6.21; N, 8.98.

2-Benzyl-8-methoxy-2,3,4,4a,5,6-hexahydrobenzo[*c*][2,6]naphthyridine **11g.**

This compound was obtained from **10g** as a viscous oil in 63% yield, hydrochloride mp 102-104° (methanol/diethyl ether); ms: (m/z) 306 (M^+), 187, 173, 158, 133.

Anal. Calcd. for $C_{20}H_{22}N_2O \cdot HCl$: C, 70.06; H, 6.76; N, 8.17. Found: C, 70.18; H, 6.58; N, 8.20.

General Procedure for the Preparation of 2,3,4,4a,5,6-Hexahydrobenzo[*c*][2,6]naphthyridines **12a-g.**

A mixture of each compound **11** (6 mmoles) and ethyl chloroformate (1.3 g, 12 mmoles) in toluene (50 ml) was heated at 90-100° for 4-5 hours. The solution was evaporated to dryness under reduced pressure and the obtained 2-ethoxycarbonyl-2,3,4,4a,5,6-hexahydrobenzo[*c*][2,6]naphthyridines were purified by chromatography on a silica gel column by eluting with a 1:1 ethyl acetate/*n*-hexane mixture. Analytical samples were obtained by crystallization. A suspension of each 2-ethoxycarbonyl derivative (1 g) in a 15% (1:1) hydroalcoholic solution of potassium hydroxide (40 ml) was refluxed for 5 hours. After cooling, ethanol was evaporated under reduced pressure and the suspension was extracted with ethyl acetate. Removal of the solvent afforded crude compounds **12** which were directly crystallized.

2,3,4,4a,5,6-Hexahydrobenzo[*c*][2,6]naphthyridine **12a.**

This compound was obtained from **11a** in 64% yield, mp 128-130° (toluene); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 11.08 (s, 1H, 6-NH), 7.38 (d, 1H, H-10), 7.26 (d, 1H, H-7), 6.97 (t, 1H, H-8), 6.89 (t, 1H, H-9), 6.14 (s, 1H, H-1), 3.23 (m, 2H, H-4a and H-5eq), 2.88 (m, 2H, H-3eq and H-4eq), 2.74 (q, 1H, H-5ax), 2.12 (m,1H, H-3ax), 1.81 (m, 1H, H-4ax); ms: (m/z) 186 (M^+), 156, 144, 130.

Anal. Calcd. for $C_{12}H_{14}N_2$: C, 77.38; H, 7.58; N, 15.04. Found: C, 77.40; H, 7.53; N, 15.06.

The 2-ethoxycarbonyl derivative had mp 138-140° (toluene), ms: (m/z) 258 (M^+), 243, 156, 143, 130.

Anal. Calcd. for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 70.01; H, 6.73; N, 10.60.

9-Fluoro-2,3,4,4a,5,6-hexahydrobenzo[*c*][2,6]naphthyridine **12b.**

This compound was obtained from **11b** in 51% yield, mp 152-154° (toluene); ms: (m/z) 204 (M^+), 190, 185, 162.

Anal. Calcd. for $C_{12}H_{13}FN_2$: C, 70.57; H, 6.42; N, 13.72. Found: C, 70.61; H, 6.38; N, 13.81.

The 2-ethoxycarbonyl derivative had mp 168-170° (methanol), ms: (m/z) 276 (M^+), 259, 231.

Anal. Calcd. for $C_{15}H_{17}FN_2O_2$: C, 65.20; H, 6.20; N, 10.14. Found: C, 65.27; H, 6.16; N, 10.14.

9-Chloro-2,3,4,4a,5,6-hexahydrobenzo[*c*][2,6]naphthyridine **12c.**

This compound was obtained from **11c** in 87% yield, mp 125-127° (toluene); ms: (m/z) 220 (M^+), 190, 178, 164, 143.

Anal. Calcd. for $C_{12}H_{13}ClN_2$: C, 65.31; H, 5.94; N, 12.69. Found: C, 65.22; H, 6.09; N, 12.67.

The 2-ethoxycarbonyl derivative had mp 136-138° (toluene); ms: (m/z) 292 (M^+), 277, 263, 247, 190, 177, 156.

Anal. Calcd. for $C_{15}H_{17}ClN_2O_2$: C, 61.54; H, 5.85; N, 9.57. Found: C, 61.73; H, 5.68; N, 9.17.

9-Methoxy-2,3,4,4a,5,6-hexahydrobenzo[*c*][2,6]naphthyridine **12d.**

This compound was obtained from **11d** in 30% yield, mp 79-81° (ethyl acetate); ms: (m/z) 216 (M^+), 174, 160, 130.

Anal. Calcd. for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.01; H, 7.53; N, 12.88.

The 2-ethoxycarbonyl derivative had mp 134-135° (ethyl acetate); ms: (m/z) 288 (M^+), 273, 243, 186, 173.

Anal. Calcd. for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72. Found: C, 66.70; H, 7.30; N, 9.73.

8-Fluoro-2,3,4,4a,5,6-hexahydrobenzo[*c*][2,6]naphthyridine **12e.**

This compound was obtained from **11e** in 54% yield, mp 105-107° (toluene/diethyl ether); ms: (m/z) 204 (M^+), 186, 174, 161, 148.

Anal. Calcd. for $C_{12}H_{13}FN_2$: C, 70.57; H, 6.42; N, 13.72. Found: C, 70.48; H, 6.30; N, 13.51.

The 2-ethoxycarbonyl derivative had mp 155-157° (toluene), ms: (m/z) 276 (M^+), 247, 202, 187, 174, 161, 148, 133.

Anal. Calcd. for $C_{15}H_{17}FN_2O_2$: C, 65.20; H, 6.20; N, 10.14. Found: C, 65.12; H, 6.28; N, 10.09.

8-Chloro-2,3,4,4a,5,6-hexahydrobenzo[*c*][2,6]naphthyridine **12f.**

This compound was obtained from **11f** in 85% yield, mp 133-135° (toluene); ms: (m/z) 220 (M^+), 190, 178, 164, 143.

Anal. Calcd. for $C_{12}H_{13}ClN_2$: C, 65.31; H, 5.94; N, 12.69. Found: C, 65.56; H, 6.16; N, 12.58.

The 2-ethoxycarbonyl derivative had mp 162-164° (toluene); ms: (m/z) 292 (M^+), 277, 263, 246, 203, 190, 177.

Anal. Calcd. for $C_{15}H_{17}ClN_2O_2$: C, 61.54; H, 5.85; N, 9.57. Found: C, 61.41; H, 6.00; N, 9.32.

8-Methoxy-2,3,4,4a,5,6-hexahydrobenzo[*c*][2,6]naphthyridine **12g.**

This compound was obtained from **11g** in 30% yield, mp 107-109° dec (diethyl ether); ms: (m/z) 216 (M^+), 186, 174, 158.

Anal. Calcd. for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.01; H, 7.51; N, 12.80.

The 2-ethoxycarbonyl derivative had mp 108-109° (ethyl acetate/*n*-hexane), ms: (m/z) 288 (M^+), 259, 242, 227, 186, 173.

Anal. Calcd. for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72. Found: C, 66.60; H, 6.90; N, 9.88.

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