An Efficient Synthesis of Benzo[*b*][1,8]naphthyridine-3-carboxylic Methyl Esters

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Methyl-3-(2-chloroquinolin-3-yl)acrylates **5a-i** on reaction with methyl amine in acetonitrile yielded methyl-3-[2-(methylamino)quinolin-3-yl]acrylates **6a-i**. When, these were followed by the reaction with the Vilsmeier reagent, they afforded methyl benzo[*b*][1,8]naphthyridin-3-carboxylate **7a-i** in good yields.

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Several [1,8]naphthyridines and its derivatives are documented for their pharmacological properties exhibiting antibacterial, anti-fungal [1], anti-malarial, anti-hypertensive [2], anti-mycobacterial [3], anti-thrombic [4] activities.

Earlier, workers from our laboratory have reported the synthesis of 1,2,3,4-tetrahydrodibenzo[*b*,*g*][1,8]naphthyridine [5] and 6-phenyl-1,2,3,4-tetrahydrodibenzo[*b*,*g*]-[1,8]naphthyridine [6] in good yields from 2-chloro-3-formyl quinolines and 2-chloro-3-formyl-4-phenylquinolines respectively. Herein, we report a convenient method for the synthesis of hitherto unreported compounds methyl benzo[*b*][1,8]naphthyridin-3-carboxylates **7a-i** in good yields from methyl-3-(2-chloroquinolin-3-yl)acrylates **5a-i**.

With the aim at the synthesis of benzo fused [1,8]naphthyridines, we utilized 2-chloro-3-formyl quinolines **1a-i** as the starting compounds, which were prepared by following O. Meth cohn procedure [7]. These were converted to the oxo compounds **2a-i** by refluxing with 4 *M* HCl. They were then condensed with malonic acid under the conditions of Knoevenagel reaction to furnish the acrylic acids [8] **3a-i**.

Esterification of **3a-i** in absolute methanol and concentrated sulphuric acid at reflux temperature for 5-6 hrs furnished methyl-3-(2-oxo-1,2-dihydroquinolin-3-yl)acrylates [9] **4a-I** (Figure 1). The compound **4a** upon dehydroxy chlorination with freshly distilled phosphorus oxychloride resulted in a creamy white compound. This was followed by recrystallisation from pet.ether: benzene (4:1 v/v) giving rise to needle shaped crystals.

The IR spectrum of the compound displayed bands for CO at 1709 cm^{-1}, (–C–Cl) at 1062 cm^{-1}. Its ^{1}H-NMR spectra showed singlets at 8.16 δ and 3.23 δ for C_4-H and CH_3 of ester respectively, doublets for vinyl protons at 6.56 δ, 7.82 δ with J=16 Hz typical of the *trans* configuration and multiplet for C_5, C_6, C_7, C_8-H at 7.61 δ -7.88 δ ppm. Its mass spectra with the m/e value at 247 (M^+) and 249 (M+2) (one third the intensity of the parent peak), confirmed the structure of the compound as methyl-3-(2-chloroquinolin-3-yl)acrylate **5a** [10] (Table 1). The procedure was extended to synthesize **5b-i**.

The chloro esters **5a-i** were then subjected to the sequencial steps involved in the synthesis of benzopyrano[4,3-*b*]-pyridine-5-ones by Heber *et a*l [11].

Methyl-3-(2-chloroquinolin-3-yl)acrylates **5a-i** were further converted into the dienamines **6a-i** by a very slow treatment with two equivalents of the methyl amine in acetonitrile. For the vinyl protons, ^{1}H NMR spectroscopy showed doublets at δ =6.38-6.61 ppm and 8.05-8.29 ppm typical of *trans* configuration of the double bonds. The IR spectra of **6a-i** displayed the absorption bands for a conjugated ester carbonyl at (ν = 1705-1725 cm^{-1}) and –NH group (ν = 3345-3371 cm^{-1}). The heterocyclisation of **6a-i** occurred smoothly with an excess of Vilsmeier reagent (mole ratio 1:6), on a steam bath to give benzo fused [1,8]naphthyridines in good yields. The structures of **7a-i** were unambiguously deduced from IR, proton nmr, mass spectra and elemental analysis.

The mechanism for the heterocyclisation of **6a-i** probably involves N-formylation of **6** to give the dimethyliminium salt (**A**), followed by the nucleophilic attack of the chloride ion on the N-alkyl moiety provoking simultaneous electrocyclic ring closure. The aromatization occurs by the elimination of dimethylamine, to give methyl benzo-[*b*][1,8]naphthyridin-3-carboxylates **7a-i** (Figure- 2).

EXPERIMENTAL

Melting points were determined using Raaga mp apparatus and are uncorrected. The IR spectra were recorded on an FTIR 8201(PC)S spectrometer as KBr pellets and the absorption frequencies are expressed in reciprocal centimeter (cm^{-1}). Proton NMR spectra were recorded on a Gemini-200 MHz or on a Varian AMX 400 spectrometer in $CDCl_3$. The chemical shifts

were expressed in δ (PPM) downfield from tetramethylsilane as an internal standard. Elemental analysis was performed by Elementar Analyser Vario EL III and the values are within the permissible limits (±0.4). The Mass spectra were recorded by EIMS technique on an Autospec mass spectrometer. The crude products were checked by thin layer chromatography and purified by column chromatography using silica gel (60-120 mesh).

Preparation of Methyl-3-(2-chloroquinolin-3-yl)acrylate **5a-i**.

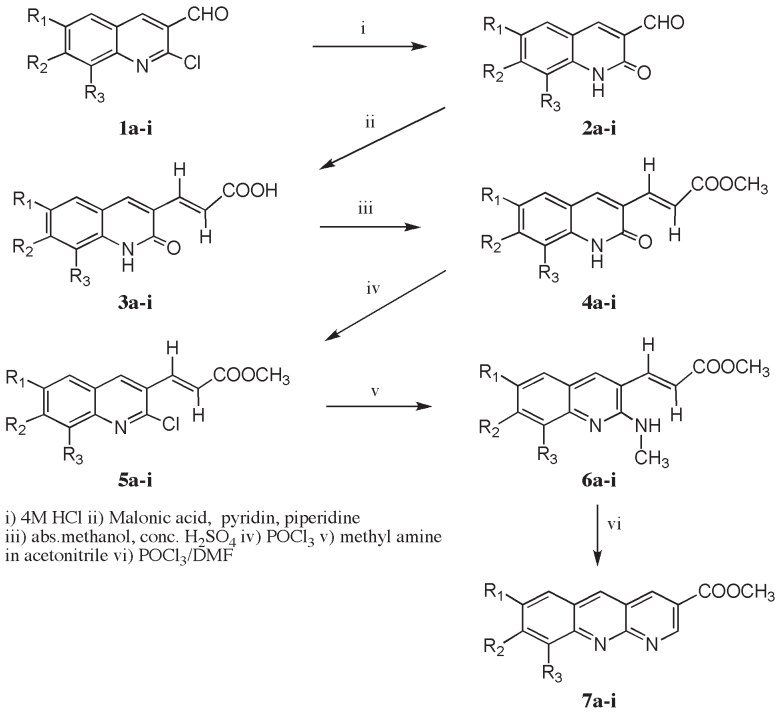
General Procudure.

The methyl ester **4** (0.0228 mole) was treated with freshly distilled phosphorus oxychloride (13.6 ml, 0.148 mole) and kept on a steam bath for 5-6 hrs. On cooling and pouring into crushed ice, the compound separated as a creamy white solid. It was then recrystallized from pet. ether:benzene (4:1v/v) and obtained as yellow coloured needles.

Preparation of methyl-3-[2-(methylamino)quinolin-3-yl]acrylates **6a-i**.

General Procedure.

To a stirred mixture of methyl-3-(2-chloroquinolin-3-yl)acrylate **5** (1 mmole) in acetonitrile (5ml) at 0 °C, a solution of the methyl amine (2.1mmole) in acetonitrile was added slowly in drops over a period of one hour, followed by stirring, for about 3 hrs. The reaction was then suspended on a steam bath for 10 hrs. On cooling, the crystalline product was collected by filtration, washed successively with acetonitrile. An additional product was obtained by concentrating the fil-



a) R_1= R_2= R_3= H; **b**) R_1= CH_3, R_2= R_3= H; **c**) R_1= R_3= H , R_2= CH_3; **d**) R_1= R_2= H, R_3= CH_3; **e**) R_1= OCH_3, R_2= R_3= H; **f**) R_1= R_3= H, R_2= OCH_3; **g**) R_1= R_2= H, R_3= OCH_3; **h**) R_1= R_2= CH_3, R_3=H; **i**) R_1= H, R_2= R_3= -CH=CH-CH=CH-

Figure 1

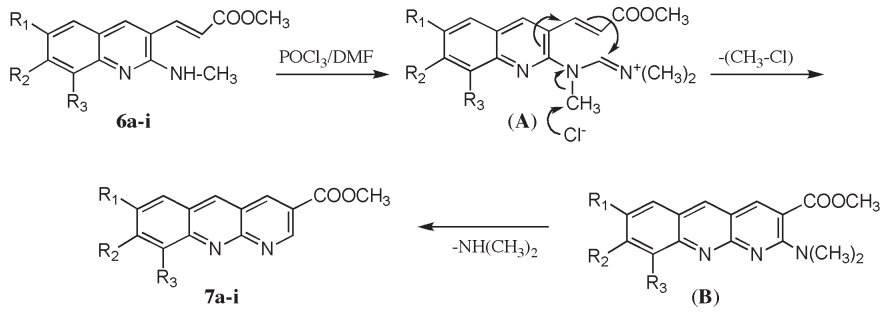


Figure 2

trates under reduced pressure and recrystallised from absolute ethanol.

Table 1

Physical and Spectral Data of **5a-i**

Compound	Yield (%)	Mp (°C)	IR(cm^{-1})	Mass (m/z)
5a	85	220-221	1709, 1263, 1051	247, 249
5b	87	120-121	1701, 1262, 1050	261, 263
5c	89	144-145	1708, 1261, 1049	261, 263
5d	92	130-131	1709, 1260, 1052	261, 263
5e	80	170-171	1709, 1265, 1059	277, 279
5f	85	165-166	1712, 1267, 1061	277, 279
5g	89	159-160	1718, 1269, 1062	277, 279
5h	83	260-261	1708, 1260, 1041	275, 277
5i	80	205-206	1718, 1266, 1048	297, 299

Physical and Spectral Data of **6a-i**.

Methyl-3-[2-(methylamino)quinolin-3-yl]acrylate (**6a**).

This compound was obtained as light yellowish crystals (ethanol); yield=65%; mp= 292-293 ºC; IR: CO 1715, 1251 cm^{-1}, NH 3345 cm^{-1}, ^{1}H NMR ($CDCl_3$): δ 3.32 (d, J=5Hz, 3H, -NCH_3), 3.41 (s, 3H, CH_3 of ester), 6.41 (d, J=16Hz, -CH=C*H*$_{trans}$), 7.51-7.91 (m, 4H, C_5, C_6, C_7, C_8-H), 7.98 (d, J=16Hz -C*H*=CH_{trans}), 8.13 (s, 1H, C_4-H), 8.21 (s, br, -NH); ms: m/z 242 (M^+)

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.82; N, 11.57. Found: C, 69.10; H, 5.72; N, 11.47.

Methyl-3-[6-methyl-2-(methylamino)quinolin-3-yl] acrylate (**6b**).

This compound was obtained as light yellowish crystals (ethanol); yield=63%; mp= 273-274 ºC; IR: CO 1719, 1256cm^{-1}, NH 3351cm^{-1}, ^{1}H NMR ($CDCl_3$): δ 2.46 (s, 3H, -CH_3), 3.23 (d, J=5.1Hz, 3H, -NCH_3), 3.33 (s, 3H, CH_3 of ester), 6.46 (d, J=15.8Hz, -CH=C*H*$_{trans}$), 7.53-8.12 (m, 3H, C_5, C_7, C_8-H), 8.06 (d, J=15.8Hz, -C*H*=CH_{trans}), 8.11 (s, 1H, C_4-H), 8.21 (s, br, -NH), ms: m/z 256 (M^+).

Anal. Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.20; H, 6.25; N, 10.90.

Methyl-3-[7-methyl-2-(methylamino)quinolin-3-yl] acrylate (**6c**).

This compound was obtained as light yellowish crystals (ethanol); yield=67%; mp= 284-285 ºC; IR: CO 1716, 1258cm^{-1}, NH 3349cm^{-1}, ^{1}H NMR ($CDCl_3$): δ 2.34 (s, 3H, -CH_3), 3.19(d, J=5.1Hz, 3H, -NCH_3), δ3.29 (s, 3H, CH_3 of ester), 6.43(d, J=15.8Hz, -CH=C*H*$_{trans}$), 7.47-8.13(m, 4H, C_4, C_5, C_6, C_8-H), 8.05(d, J=15.8Hz, -C*H*=CH_{trans}), 8.20(s, br, -NH), ms: m/z 256 (M^+).

Anal. Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.20; H, 6.25; N, 10.90.

Methyl-3-[8-methyl-2-(methylamino)quinolin-3-yl] acrylate (**6d**)

This compound was obtained as light yellowish crystals (ethanol); yield=69%; mp= 289-290 ºC; IR: CO 1714, 1257cm^{-1}, NH 3351cm^{-1}, ^{1}H NMR ($CDCl_3$): δ 2.39 (s, 3H, -CH_3), 3.19 (d, J=6Hz, 3H, -NCH_3), 3.31 (s, 3H, CH_3 of ester), 6.40 (d, J=15.8Hz, -CH=C*H*$_{trans}$), 7.43-8.11 (m, 4H, C_4, C_5, C_6, C_7-H), 8.06 (d, J=15.8Hz, -C*H*=CH_{trans}), 8.20 (s, br, -NH), ms: m/z 256 (M^+).

Anal. Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.22; H, 6.21; N, 10.90.

Methyl-3-[6-methoxy-2-(methylamino)quinolin-3-yl] acrylate (**6e**).

This compound was obtained as light yellowish crystals (ethanol); yield=63%; mp= 278-279 ºC; IR: CO 1705, 1252cm^{-1}, NH 3345cm^{-1}, ^{1}H NMR ($CDCl_3$): δ 3.25 (d, J=6Hz, 3H, -NCH_3), 3.41 (s, 3H, CH_3 of ester), 3.61 (s, 3H, -CH_3), 6.47 (d, J=16Hz, -CH=C*H*$_{trans}$), 7.49-8.19 (m, 4H, C_4, C_5, C_7, C_8-H), 8.16 (d, J=16Hz, -C*H*=CH_{trans}), 8.49 (s, br, -NH), ms: m/z 272 (M^+).

Anal. Calcd. for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.12; H, 5.85; N, 10.20.

Methyl-3-[7-methoxy-2-(methylamino)quinolin-3-yl] acrylate (**6f**).

This compound was obtained as light yellowish crystals (ethanol); yield= 65%; mp= 281-282 ºC; IR: CO 1706, 1250cm^{-1}, NH 3342cm^{-1}, ^{1}H NMR ($CDCl_3$)= 3.27 (d, J=6Hz, 3H, -NCH_3), 3.43 (s, 3H, CH_3 of ester), 3.64 (s, 3H, -CH_3), 6.48 (d, J=16Hz, -CH=C*H*$_{trans}$), 7.51-8.23 (m, 4H, C_4, C_5, C_6, C_8-H), 8.19 (d, J= 16Hz, -C*H*=CH_{trans}), 8.51 (s, br, -NH), ms: m/z 272 (M^+).

Anal. Calcd. for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.13; H, 5.91; N, 10.22.

Methyl-3-[8-methoxy-2-(methylamino)quinolin-3-yl] acrylate (**6g**).

This compound was obtained as light yellowish crystals (ethanol); yield=65%; mp= 295-296 ºC; IR: CO 1701, 1240cm^{-1}, NH 3341cm^{-1}, ^{1}H NMR ($CDCl_3$): δ 3.30 (d, J=6Hz, 3H, -NCH_3), 3.46 (s, 3H, CH_3 of ester), 3.67 (s, 3H, -CH_3), 6.52 (d, J=15.8Hz, -CH=C*H*$_{trans}$), 7.59-8.30 (m, 4H, C_4, C_5, C_6, C_7 -H), 8.21 (s, br, -NH), 8.22 (d, J=15.8Hz, -C*H*=CH_{trans}), ms: m/z 272 (M^+).

Anal. Calcd. for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.14; H, 5.92; N, 10.26.

Methyl-3-[6,8-dimethyl-2-(methylamino)quinolin-3-yl] acrylate (**6h**).

This compound was obtained as light yellowish crystals (ethanol); yield=65%; mp= 301-302 ºC; IR: CO 1713, 1246cm^{-1}, NH 3353cm^{-1}, ^{1}H NMR ($CDCl_3$): δ 2.35, 2.43 (s each, 3H, -CH_3), 3.23 (s, 3H, CH_3 of ester), 3.09 (d, J=6Hz, 3H, -NCH_3), 6.38 (d, J=16Hz, CH=C*H*$_{trans}$), 7.41-8.03 (m, 3H, C_4, C_5, C_7 -H), 8.07 (s, br, -NH), 8.12 (d, J=16Hz, -C*H*=CH_{trans}-), ms: m/z 270 (M^+).

Anal. Calcd. for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.37. Found: C, 71.01; H, 6.68; N, 10.30.

Methyl-3-[2-(methylamino)benzo[*h*]quinolin-3-yl] acrylate (**6i**).

This compound was obtained as yellow crystals (ethanol); yield=60%; mp= 309-310 ºC; IR: CO 1725, 1260cm^{-1}, NH 3371cm^{-1}, ^{1}H NMR ($CDCl_3$): δ 3.26 (d, J=6Hz, 3H, -NCH_3), 3.33 (s, 3H, CH_3 of ester), 6.61 (d, J=16Hz, -CH=C*H*$_{trans}$), 8.29 (d, J=16Hz, -C*H*=CH_{trans}), 7.56-9.31 (m, 3H, C_4, C_5, C_6, C_7,C_8, C_9, C_{10} -H), 8.62 (s, br, -NH), ms: m/z 292 (M^+).

Anal. Calcd. for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.51; N, 9.59. Found: C, 73.91; H, 5.49; N, 9.52.

Preparation of Methyl benzo[*b*][1,8]naphthyridin-3-carboxylates **7a-i**.

General Procedure.

To a stirred mixture of anhydrous DMF at 0 °C (1.85 ml), $POCl_3$ (0.46 ml) (4.9 mmole) was added in drops for about half an hour. Stirring was continued for another hour, followed by the addition of **6** (200 mg). The reaction was then carried out on a steam bath, till its completion over a period of 16 hrs. After cooling, the mixture was poured into ice water and the precipitate thus obtained was collected by filtration, washed with water, dried and recrystallised from ethanol.

Methyl benzo[*b*][1,8]naphthyridin-3-carboxylate (**7a**).

This compound was obtained as yellow crystals (ethanol); yield=62%; mp= 260-261 ºC; IR: CO 1730, ^{1}H NMR ($CDCl_3$): δ 3.10 (s, 3H, CH_3 of ester), 7.57-8.05 (m, 4H, C_6, C_7, C_8, C_9-H), 8.32 (s, 1H, C_4-H), 8.62 (s, 1H, C_5-H), 8.96 (s, 1H, C_2-H), ms: m/z 238 (M^+).

Anal. Calcd. for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.50 H, 4.19; N, 11.72.

Methyl-7-methylbenzo[*b*][1,8]naphthyridin-3-carboxylate (**7b**).

This compound was obtained as yellow crystals (ethanol); yield=62%; mp= 248-249 ºC; IR: CO 1729, ^{1}H NMR ($CDCl_3$): δ 2.51 (s, 3H, -CH_3), 3.09 (s, 3H, CH_3 of ester), 7.63 (d, J=8.2Hz, C_8-H), 7.83 (d, J=8.2Hz, C_9-H), 8.35 (s, 1H, C_4-H), 8.43 (s, 1H, C_6-H), 8.63 (s, 1H, C_5-H), 9.02 (s, IH, C_2-H), ms: m/z 252 (M^+).

Anal. Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.41; H, 4.79; N, 11.11. Found: C, 71.38; H, 4.73; N, 11.10.

Methyl-8-methylbenzo[*b*][1,8]naphthyridin-3-carboxylate (**7c**).

This compound was obtained as yellow crystals (ethanol); yield=64%; mp= 254-255 ºC; IR: CO 1727, ^{1}H NMR ($CDCl_3$): δ 2.49 (s, 3H, -CH_3), 3.08 (s, 3H, CH_3 of ester), 7.53-8.78 (m, 3H, C_6, C_7 , C_9-H), 8.45 (s, 1H, C_4-H), 8.52 (s, 1H, C_9-H), 8.67 (s, 1H, C_5-H), 9.01 (s, 1H, C_2-H), ms: m/z 252 (M^+).

Anal. Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.41; H, 4.79; N, 11.11. Found: C, 71.37; H, 4.72; N, 11.09.

Methyl-9-methylbenzo[*b*][1,8]naphthyridin-3-carboxylate (**7d**).

This compound was obtained as yellow crystals (ethanol); yield=66%; mp= 263-264 ºC; IR: CO 1719, ^{1}H NMR ($CDCl_3$): δ 2.52 (s, 3H, -CH_3), 3.08 (s, 3H, CH_3 of ester), 7.54-8.83 (m, 3H, C_6, C_7, C_8-H) 8.52 (s, 1H, C_9-H), 8.53 (s, 1H, C_4-H), 8.55 (s, 1H, C_5-H), 9.01 (s, 1H, C_2-H), ms: m/z 252 (M^+).

Anal. Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.41; H, 4.79; N, 11.11. Found: C, 71.33; H, 4.70; N, 11.06.

Methyl-7-methoxybenzo[*b*][1,8]naphthyridin-3-carboxylate (**7e**).

This compound was obtained as yellow crystals (ethanol); yield=62%; mp= 251-252 ºC; IR:CO 1732, ^{1}H NMR ($CDCl_3$): δ 3.16(s, 3H, -CH_3 of ester), 3.96 (s, 3H, -OCH_3), 7.70-8.78 (m, C_5, C_6, C_8,C_9-H), 8.51 (s, 1H, C_4-H), 9.05 (s, 1H, C_2-H), ms: m/z 268 (M^+).

Anal. Calcd. for $C_{15}H_{12}N_2O_3$: C, 67.15; H, 4.51; N, 10.44. Found: C, 67.10; H, 4.49; N, 10.40

Methyl- 8-methoxybenzo[*b*][1,8]naphthyridin-3-carboxylate (**7f**).

This compound was obtained as yellow crystals (ethanol); yield=62%; mp= 258-259 ºC; IR: CO 1720, ^{1}H NMR ($CDCl_3$): δ 3.19 (s, 3H, -CH_3 of ester), 3.86 (s, 3H, -OCH_3), 7.59-8.91 (m, 5H, C_4, C_5, C_6, C_8, C_9-H), 9.09 (s, 1H, C_2-H), ms: m/z 268 (M^+).

Anal. Calcd. for $C_{15}H_{12}N_2O_3$: C, 67.15; H, 4.51; N, 10.44. Found: C, 67.14; H, 4.49; N, 10.41

Methyl-9-methoxybenzo[*b*][1,8]naphthyridin-3-carboxylate (**7g**).

This compound was obtained as yellow crystals (ethanol); yield=60%; mp= 264-265 ºC; IR: CO 1720, ^{1}H NMR ($CDCl_3$): δ 3.21 (s, 3H, -CH_3 of ester), 3.80 (s, 3H, -OCH_3), 7.59-8.95 (m, 5H, C_4, C_5, C_6, C_7, C_8-H), 9.05 (s, 1H, C_2-H), ms: m/z 268 (M^+).

Anal. Calcd. for $C_{15}H_{12}N_2O_3$: C, 67.15; H, 4.51; N, 10.44. Found: C, 67.10; H, 4.49; N, 10.40

Methyl-6,8-dimethylbenzo[*b*][1,8]naphthyridin-3-carboxylate (**7h**).

This compound was obtained as yellow crystals (ethanol); yield=60%; mp= 270-271 ºC; IR: CO 1728, ^{1}H NMR ($CDCl_3$): δ 2.40, 2.51 (s each, 3H, -CH_3), 3.11 (s, 3H, -CH_3 of ester), 7.41-8.82 (m, 5H, C_4, C_5, C_6, C_8-H), 8.3(s, 1H, C_2-H), ms: m/z 266 (M^+).

Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.11; H, 5.28; N, 10.49.

Methyl Benzo[g]naphtho[*b*][1,8]naphthyridin-3-carboxylate (**7i**).

This compound was obtained as yellow crystals (ethanol); yield=60%; mp= 309-310 ºC; IR:CO 1735, ^{1}H NMR($CDCl_3$): δ 3.21 (s, 3H, -CH_3 of ester), 7.62-9.16 (m, 8H, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}-H), ms: m/z 288 (M^+).

Anal. Calcd. for $C_{18}H_{12}N_2O_2$: C, 74.99; H, 4.20; N, 9.72. Found: C, 74.90; H, 4.19; N, 9.69.

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