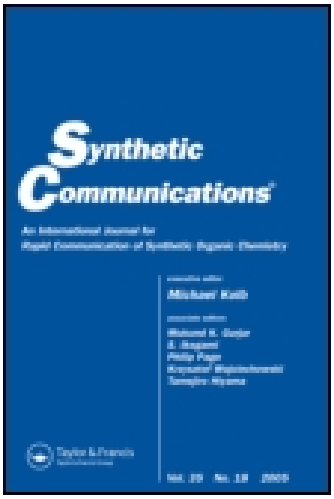


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis of Novel Alkyl and Aryl Substituted Dibenzo[b,h][1,6]naphthyridines

M. Manoj [a] & K. J. Rajendra Prasad [a]

[a] Department of Chemistry , Bharathiar University , Coimbatore , Tamil Nadu , India

Accepted author version posted online: 29 Jul 2011.Published online: 06 Oct 2011.

To cite this article: M. Manoj & K. J. Rajendra Prasad (2012) Synthesis of Novel Alkyl and Aryl Substituted Dibenzo[b,h][1,6]naphthyridines, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 42:3, 434-446, DOI: 10.1080/00397911.2010.525336

To link to this article: http://dx.doi.org/10.1080/00397911.2010.525336

Synthetic Communications®, 42: 434–446, 2012

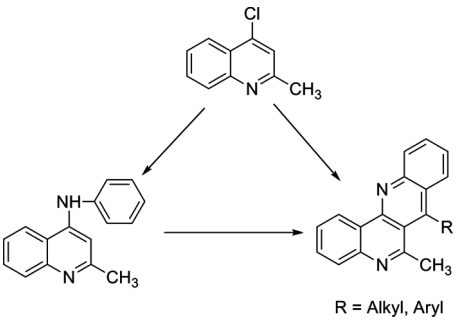
ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2010.525336

Taylor & Francis
Taylor & Francis Group

SYNTHESIS OF NOVEL ALKYL AND ARYL SUBSTITUTED DIBENZO[*b,h*][1,6]NAPHTHYRIDINES

M. Manoj and K. J. Rajendra Prasad
Department of Chemistry, Bharathiar University, Coimbatore, Tamil Nadu, India

GRAPHICAL ABSTRACT



Abstract *A one-pot synthesis of 7-alkyl and aryl substituted dibenzo[*b,h*][1,6]naphthyridines is reported from the reaction of 4-chloro-2-methylquinolines and alkyl/aryl substituted aminoketones. Because the yield of the dibenzonaphthyridines was poor, in an alternative method the title compounds were prepared from the 4-chloro-2-methylquinolines via anilinoquinolines as intermediates employing alkyl and aryl carboxylic acids, which improved yields.*

Keywords Aminoketones; anilinoquinolines; 4-chloro-2-methylquinolines; substituted dibenzo[*b,h*][1,6]naphthyridines

INTRODUCTION

There are a vast number of pharmacologically active heterocyclic compounds, of which many are in regular therapeutic usage. The heterocyclic system containing a quinoline nucleus has found broad application in drug development for the treatment of MCH (melanin concentrating hormone) receptor-related disorders,[1] cell proliferative diseases,[2] transmissible spongiform encephalopathies,[3] malignant tumors (such as stomach cancer, brain tumor, and large intestine cancer),[4] and bacterial infections in mammals.[5] Since the discovery of cinchona alkaloids as

Received August 16, 2010.
Address correspondence to K. J. Rajendra Prasad, Department of Chemistry, Bharathiar University, Coimbatore, Tamil Nadu, India. E-mail: prasad_125@yahoo.com

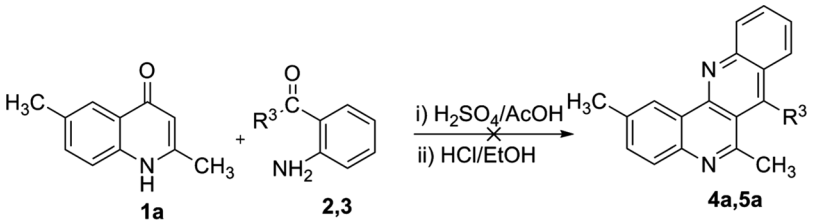
antimalarial agents, quinoline alkaloids in general and amino substituted quinolines in particular, research has focused on turning the quinoline (π-electron deficient heterocycle) core into active chemical entities for the synthesis of antimalarial drugs active against *Plasmodium falciparum*[6] (e.g., chloroquine, primaquine, etc.). Some of the phenylaminoquinolines are also considered as synthetic, antimalarials,[7] and chemists have utilized them in deriving various heterocycles such as dibenzonaphthyridines and indoloquinolines. A detailed survey of the literature shows that the reaction of chloroquinolines has been aimed at getting substituted quinolines that possessed biological activity.[8,9] One among them is the amination reaction involving aromatic amines, which derives the respective anilinoquinolines [i.e., (*N*-phenylamino)quinolines].

Research on the chemistry of naphthyridines has expanded considerably in recent years because biologically active compounds have been detected among the derivatives of these heterocycles. Numerous reports have pertained to these heterocycles as anti-arrhythmic,[10] anti-alalgesic,[11] anti-HIV,[12] and anticancer agents.[13] Particularly, some of the dibenzonaphthyridines (i.e., quinoline dimers) act as potent and selective 3-phosphoinostide-dependent kinase-I inhibitors.[14] Since the discovery of first naphthyridine by Reissert in 1893,[15] many procedures have evolved for the synthesis of simple benzo and dibenzonaphthridines,[16–19] and only very few accomplish their construction through anilinoquinolines.[20,21]

Recently in our laboratory dibenzonaphthyridines have been synthesized via anilinoquinolines as potential intermediates.[22–24] In continuation, herein we report the synthesis of alkyl and aryl substituted dibenzo[*b,h*][1,6]naphthyridines utilizing 4-chloro-2-methylquinolines in two different ways. One of the methods employs one-pot synthesis while the other exploits (*N*-phenylamino)quinolines as intermediates.

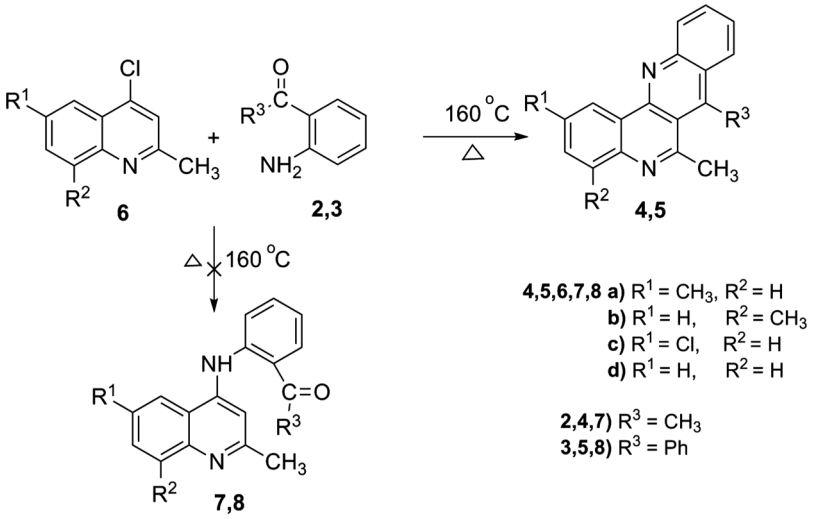
RESULTS AND DISCUSSION

Because the approach to 7-alkyl and aryl-substituted-2,6-dimethyl dibenzo[*b,h*][1,6]naphthyridines (**4a**, **5a**) from the reaction of 2,6-dimethylquinolin-4(1*H*)-one (**1**) and *o*-aminoacetophenone (**2**)/*o*-aminobenzophenone (**3**) under acidic condition was not successful (Scheme 1), similar to our earlier report,[25] we considered an alternative approach[22] in which 4-chloro-2,8-dimethylquinoline (**6b**)



2,4a) $R^3 = CH_3$
3,5a) $R^3 = Ph$

Scheme 1. Attempted synthesis of dibenzonaphthyridines.



Scheme 2. One-pot synthesis of dibenzonaphthyridines.

was treated with *o*-aminoacetophenone **2** under neat conditions at 160 °C for half an hour in the hope of obtaining the respective ketones **7**, **8**, which may be suitable intermediates to the target molecule **4**, **5** (Scheme 2). The reaction yielded a single product.

Its infrared (IR) spectrum showed stretching vibrations at 1627 cm^{-1} and 1596 cm^{-1} due to the presence of C=N groups. Its ^1H NMR spectrum showed the presence of three methyl protons at δ 2.83, 3.23, and 3.31 due to C_4-CH_3, C_7-CH_3, and C_6-CH_3 respectively. All the aromatic protons appeared between δ 7.51 and 8.19, while C_1-H appeared at δ 9.10 as a doublet ($J = 7.59$ Hz). The absence of a C=O group in the IR and ^{13}C NMR spectra revealed that the expected uncyclized compound **7b** was not formed. Further, the absence of C_3-H of a quinoline moiety in its ^1H NMR spectrum confirmed this view. Its mass spectrum showed the molecular ion peak at m/z 272 and elemental analysis supported the molecular formula as $C_{19}H_{16}N_2$. All the spectral and analytical data were in agreement with the cyclized structure, namely 4,6,7-trimethyldibenzo[*b,h*][1,6]naphthyridine (**4b**). The reaction was generalized for other quinoline derivatives **6a**, **c**, **d** to yield the respective dibenzonaphthyridines **4a**, **c**, **d**.

A similar set of reactions was extended to *o*-aminobenzophenone to afford 6-methyl-7-phenyldibenzo[*b,h*][1,6]naphthyridines **5** and not the uncyclized product **8**. The structure of the obtained product **5** was confirmed by spectral and analytical data. The structure of one of the compounds [namely, 2-chloro-6-methyl-7-phenyl-dibenzo[*b,h*][1,6]naphthyridine (**5c**)] has been solved through single-crystal x-ray diffraction (XRD) studies and its ORTEP diagram is shown in Fig. 1.

The mechanism for the formation of the products **4** and **5** from **6** and amino-ketones **2** and **3** can be interpreted via the formation of the intermediate **I** by the elimination of HCl from **6**, which further catalyzes the cyclization by the protonation of the 2′-carbonyl group to form the oxonium ion intermediate **II**. Its reaction at the quinoline C_3-position by intramolecular electrophilic cyclisation gives the

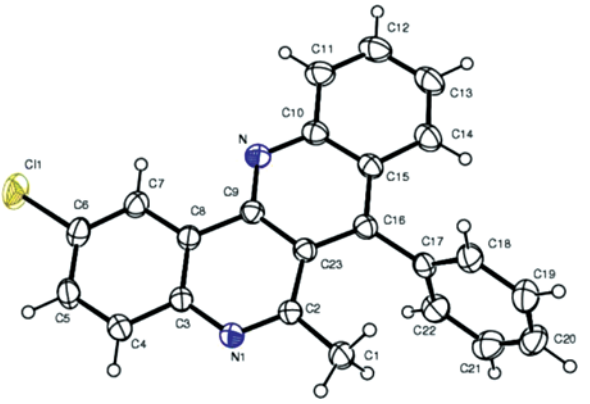
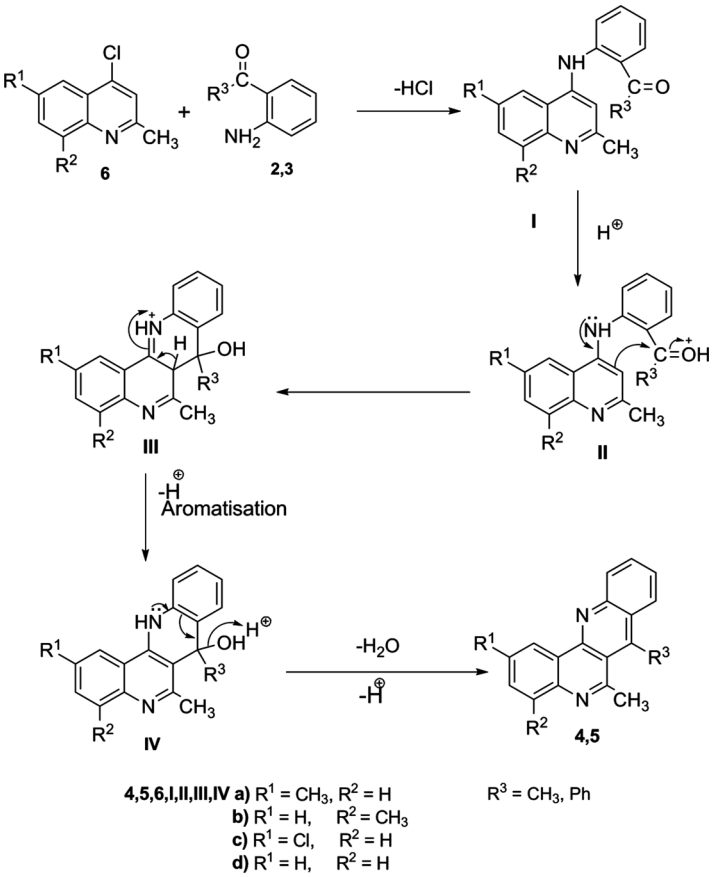
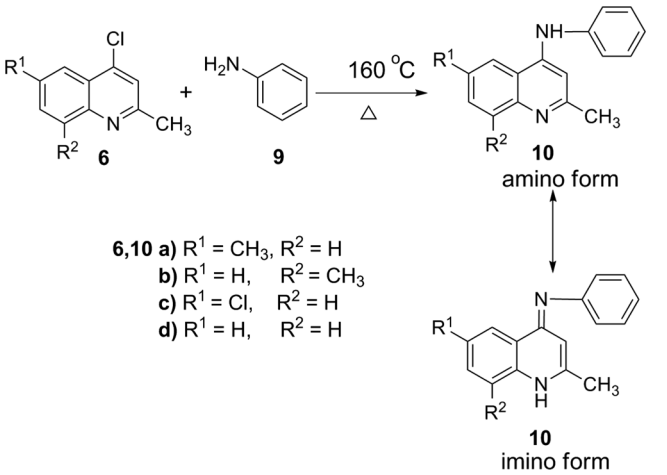


Figure 1. ORTEP diagram of 2-chloro-6-methyl-7-phenyldibenzo[*b,h*][1,6]naphthyridine (**5c**). (Figure is provided in color online.)



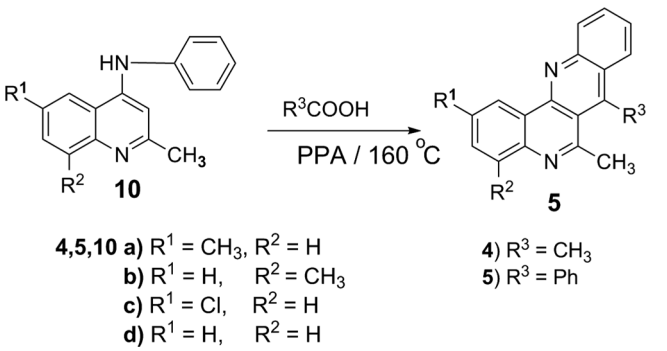
Scheme 3. Mechanism for the formation of 6-methyl-7-substituted dibenzo[*b,h*][1,6]naphthyridines from 4-chloro-2-methylquinolines.



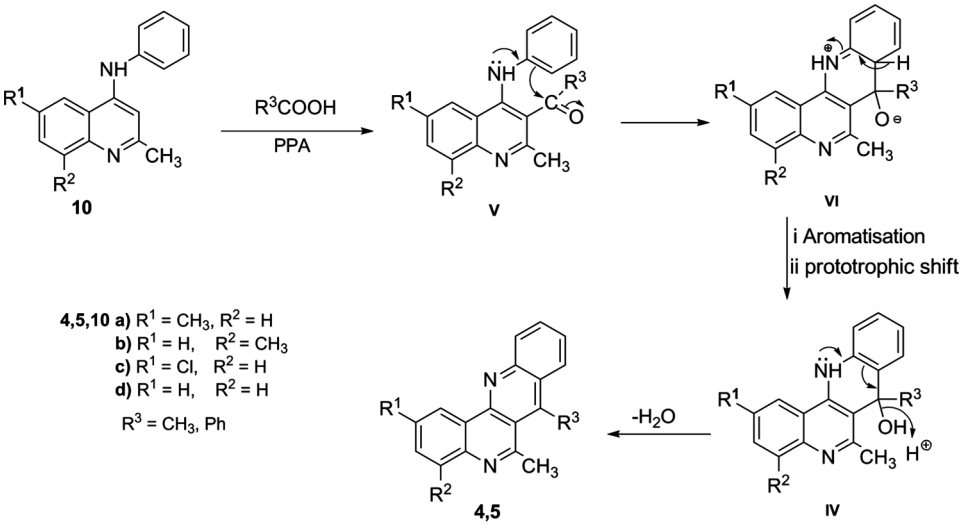
Scheme 4. Preparation of anilinoquinolines.

intermediate **III**, which on aromatization to **IV** and subsequent loss of a water molecule under the influence of acid yields the final products (**4** and **5**) (Scheme 3).

The yield of the one-pot synthesis of 6-methyl-7-substituted dibenzo[*b,h*][1,6] naphthyridine (**4**, **5**) as outlined in Scheme 2 was only moderate (~27%), so we devised an alternative route in which 4-chloro-2,8-dimethylquinoline (**6b**) was heated with aniline (**9**) under neat conditions at 160 °C for half an hour (Scheme 4). Its IR spectrum showed stretching at 3378 cm^{-1} due to the presence of the NH group. In its ^1H NMR spectrum, the two methyl protons appeared at δ 2.76 and δ 2.95 due to C_8-CH_3 and C_2-CH_3 respectively. The peculiar C_3-H emerged as a singlet at δ 6.71. The rest of the aromatic protons were found between δ 7.31 and δ 8.80. Two one-proton-broad singlets at δ 10.50 and δ 12.41 were due to C_4-NH of amino form and N_1-H of imino form respectively. The ratio of amino and imino forms was 1:1. Its ^{13}C NMR spectrum showed the presence of 17 carbons. Hence, the structure of the product obtained was assigned as 2,8-dimethyl-4-(*N*-phenylamino)quinoline (**10b**), which was found to be in tautomeric equilibrium with its imino form. The generality of



Scheme 5. Cyclization of anilinoquinolines to dibenzonaphthyridines.



Scheme 6. Mechanism for the formation of 6-methyl-7-substituted dibenzo[*b,h*][1,6]naphthyridines from anilinoquinolines.

the reaction was tested with other quinoline derivatives **6a**, **c**, **d** to accomplish the respective anilinoquinolines **10a**, **c**, **d**.

Next, the anilinoquinoline **10b** was heated with acetic acid in the presence of polyphosphoric acid to 160 °C for 5 h to give the product (Scheme 5). From thin-layer chromatography (TLC), mixed melting point, and superimposible IR spectra, the compound was identified as the same one (**4b**) obtained earlier from 4-chloro-2,8-dimethylquinoline (**6b**) and *o*-aminoacetophenone (**2**) in the one-pot synthesis under neat condition. Similarly **10a**, **c**, **d** afforded the respective **4a**, **c**, **d**. In another set of experiments, **10** was reacted with benzoic acid in the presence of PPA to furnish the respective dibenzonaphthyridines **5**.

Table 1. Comparison of yield: Method 1 and Method 2

Final compounds				Yield (%)			
				Method 1	Method 2		
Compound	R^1	R^2	R^3	One pot **6**→**4** or **6**→**5**	**6**→**10**	**10**→**4** or **10**→**5**	Overall
4a	CH_3	H	CH_3	30	70	52	36
4b	H	CH_3	CH_3	30	75	45	36
4c	Cl	H	CH_3	29	65	52	34
4d	H	H	CH_3	30	72	50	38
5a	CH_3	H	Ph	23	70	43	32
5b	H	CH_3	Ph	25	75	40	28
5c	Cl	H	Ph	22	65	43	30
5d	H	H	Ph	25	72	40	30

A plausible mechanism to the product, through the intermediate **V** via acylation of **10** at the quinoline 3 position and acid-catalyzed cyclization to the aniline ring through the intermediates **VI** and **IV**, is shown in Scheme 6.

Even though the synthesis involves two steps to the product, the overall yield was somewhat better (~33%) than that of the one-pot synthesis. The yield of the products obtained from the two methods are compared in Table 1.

CONCLUSION

The one-pot synthesis (method 1) of the final products from the reaction of 4-chloro-2-methylquinolines and aminoketones under neat conditions takes the least time but gives poor yield. Even though the alternate method (Method 2) involves two steps, the overall yield is comparatively better, but the time consumption is large.

EXPERIMENTAL

Melting points (mp) were determined on Mettler FP 51 apparatus (Mettler Instruments, Switzerland) and are uncorrected. They are expressed in degree centigrade (°C). IR spectra were recorded on Schimadzu FTIR-8201PC spectrophotometer (Schimadzu, Japan) using KBr disc. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AMX 400 [400 MHz (^{1}H) and 100 MHz (^{13}C)] spectrometer, and 2D-NMR were recorded on Bruker AV (30-MHz) instrument using tetramethylsilane (TMS) as an internal reference. The chemical shifts are expressed in parts per million (ppm). Mass spectra (MS) were recorded on AutoSpec EI+ Shimadzu QP 2010 Plus gas chromatography–mass spectrometry (GC-MS) instrument. Microanalyses were performed on a Vario EL III model CHNS analyzer (Vario, Germany) at the Department of Chemistry, Bharathiar University. The purity of the products was tested by TLC with plates coated with silica gel G, with petroleum ether and ethyl acetate as developing solvents.

6,7-Dimethyldibenzo[*b,h*][1,6]naphthyridines (4) from 4-Chloro-2-methyl-quinolines (6)

General procedure. The appropriate 4-chloro-2-methylquinoline (**6**, 0.001 mol) was heated with *o*-aminoacetophenone (**2**, 0.13 mL, 0.001 mol) under neat conditions at 160 °C for half an hour. The crude product was washed with water, adsorbed, and purified by column chromatography over silica gel, eluting with a petroleum ether/Ethyl acetate (97:3) mixture to get **4**, which was then recrystallized from methanol.

Compound 4a. Colorless needles; mp 200–202 °C; yield: 0.092 g (30%); IR ν_{max} (cm^{-1}): 1621 and 1590 (C=N), 1532, 1450; ^{1}H NMR ($CDCl_3$) δ: 2.71 (s, 3H, C_2-CH_3), 3.04 (s, 3H, C_7-CH_3), 3.14 (s, 3H, C_6-CH_3), 7.59–8.12 (m, 5H, C_3-, C_4-, C_8-, C_9-, C_{10}-H), 8.16 (d, 1H, C_{11}-H, $J = 8.22$ Hz), 9.09 (s, 1H, C_1-H); ^{13}C NMR ($CDCl_3$) δ: 20.14 (C_2-CH_3), 25.51 (C_7-CH_3), 28.92 (C_6-CH_3), 117.11 (C_{7a}), 122.04 (C_{6a}), 122.90 (C_8), 126.18 (C_1), 126.51 (C_9), 126.79 (C_7), 127.89 (C_4), 128.86 (C_3),

129.56 (C_{10}), 130.13 (C_{11}), 132.66 (C_2), 134.91 (C_{12b}), 136.60 (C_{11a}), 145.75 (C_{4a}), 147.50 (C_{12a}), 158.90 (C_6); MS: *m/z* (%) 272 (100, M^+), 271 (11), 257 (12), 242 (7), 230 (8), 136 (14), 128 (6), 115 (8), 89 (12). 77 (10). Anal. calcd. for $C_{19}H_{16}N_2$: C, 83.83; H, 5.88; N, 10.29. Found: C, 83.70; H, 6.11; N, 10.19%.

Compound 4b. Colorless needles; mp 203–205 °C; yield: 0.086 g (30%); IR ν_{max} (cm^{-1}) 1627, 1596 (C=N), 1533, 1455; ^1H NMR ($CDCl_3$) δ: 2.83 (s, 3 H, C_4-CH_3), 3.23 (s, 3H, C_7-CH_3), 3.31 (s, 3H, C_6-CH_3), 7.51–8.02 (m, 5H, C_2-, C_3-, C_8-, C_9-, C_{10}-H), 8.19 (d, 1H, C_{11}-H, $J = 8.52$ Hz), 9.10 (d, 1H, C_1-H, $J = 7.59$ Hz); ^{13}C NMR ($CDCl_3$) δ: 22.66 (C_4-CH_3), 25.51 (C_7-CH_3), 28.92 (C_6-CH_3), 117.11 (C_{7a}), 122.04 (C_{6a}), 122.90 (C_8), 126.16 (C_1), 126.51 (C_9), 126.79 (C_7), 127.15 (C_2), 128.14 (C_3), 129.56 (C_{10}), 130.13 (C_{11}), 132.66 (C_4), 134.91 (C_{12b}), 136.60 (C_{11a}), 147.09 (C_{4a}), 147.50 (C_{12a}), 158.90 (C_6). MS: *m/z* (%) 272 (100, M^+), 271 (12), 257 (8), 242 (6), 230 (5), 136 (10), 128 (7), 115 (12), 89 (14). 77 (10). Anal. calcd. for $C_{19}H_{16}N_2$: C, 83.83; H, 5.88; N, 10.29. Found: C, 83.92; H 6.01; N, 10.07%.

Compound 4c. White solid; mp 207–209 °C; yield : 0.089 g (29%); IR ν_{max} (cm^{-1}) : 1632, 1601 (C=N), 1537, 1452; ^1H NMR ($CDCl_3$) δ: 3.12 (s, 3H, C_7-CH_3), 3.18 (s, 3H, C_6-CH_3) 7.51–8.13 (m, 5H, C_3-, C_4-, C_8-, C_9-, C_{10}-H), 8.15 (d, 1H, C_{11}-H, $J = 8.50$ Hz), 9.14 (s, 1H, C_1-H); ^{13}C NMR ($CDCl_3$) δ: 25.51 (C_7-CH_3), 28.92 (C_6-CH_3), 117.11 (C_{7a}), 122.04 (C_{6a}), 122.90 (C_8), 126.01 (C_1), 126.51 (C_9), 126.79 (C_7), 127.76 (C_4), 128.80 (C_3), 129.56 (C_{10}), 130.13 (C_{11}), 131.45 (C_2), 134.91 (C_{12b}), 136.60 (C_{11a}), 145.09 (C_{4a}), 147.50 (C_{12a}), 158.90 (C_6); MS: *m/z* (%) 294/292 (30/95) ($M+2/M^+$), 277 (8), 262 (12), 257 (7), 256 (15), 136 (12), 128 (10), 115 (6), 77(18). Anal. calcd. for $C_{18}H_{13}N_2Cl$: C, 73.97; H, 4.45; N, 9.58. Found: C, 74.35; H, 4.79; N, 9.20%.

Compound 4d. Colorless prisms; mp 198–200 °C; yield : 0.082 g (30%); IR ν_{max} (cm^{-1}): 1625, 1596 (C=N), 1524, 1451; ^1H NMR ($CDCl_3$) δ: 3.10 (s, 3 H, C_7-CH_3), 3.18 (s, 3H, C_6-CH_3) 7.49–8.07 (m, 6H, C_2-, C_3-, C_4-, C_8-, C_9-, C_{10}-H), 8.13 (d, 1H, C_{11}-H, $J = 8.49$ Hz), 9.07 (d, 1H, C_1-H, $J = 7.99$ Hz); ^{13}C NMR ($CDCl_3$) δ: 25.51 (C_7-CH_3), 28.92 (C_6-CH_3), 117.11 (C_{7a}), 122.04 (C_{6a}), 122.90 (C_8), 126.16 (C_1), 126.51 (C_9), 126.79 (C_7), 127.15 (C_2), 127.66 (C_4), 128.14 (C_3), 129.56 (C_{10}), 130.13 (C_{11}), 134.91 (C_{12b}), 136.60 (C_{11a}), 147.09 (C_{4a}), 147.50 (C_{12a}), 158.90 (C_6).; MS: *m/z* (%) 258 (93, M^+), 257 (14), 243 (8), 232 (6), 228 (10), 141 (8), 126 (6), 115 (12), 77 (15). Anal. calcd. for $C_{18}H_{14}N_2$: C, 83.72; H, 5. 43; N, 10.85. Found: C, 83.70; H, 5.81; N, 10.49%.

6-Methyl-7-phenyldibenzo[*b,h*][1,6]naphthyridines (5) from 4-Chloro-2-methylquinolines (6)

General procedure. The appropriate 4-chloro-2-methylquinoline (**6**, 0.001 mol) was heated with *o*-aminobenzophenone (**3**, 0.20 g, 0.001 mol) under neat conditions at 160 °C for half an hour. The product was washed with water, adsorbed, and purified by chromatography on silica gel, eluting with petroleum ether/ethyl acetate (98:2) mixture to get **5**, which was then recrystallized from methanol.

Compound 5a. Colorless prisms; mp 250–252 °C; yield: 0.083 g (23%); IR ν_{max} (cm^{-1}): 1625 and 1609 cm^{-1} (C=N); ^1H NMR ($CDCl_3$) δ: 2.33 (s, 3H,

C_6-CH_3), 2.70 (s, 3H, C_2-CH_3), 7.41–7.92 (m, 10H, C_3-, C_4-, C_8-, C_9-, C_{10}-, C'_2-, C'_3-, C'_4-, C'_5-, C'_6-H), 8.30 (d, 1H, C_{11}−H, $J = 8.51$ Hz), 9.06 (s, 1H, C_1-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 19.7 (C_2-CH_3), 28.4 (C_6-CH_3), 117.6 (C_8), 124.1 (C_1), 125.0 (C_9), 125.9 (C'_2, C'_6), 126.5 (C'_3, C'_4, C'_5), 127.5 (C'_1), 128.5 (C_7), 128.7 (C_4), 128.9 (C_{7a}), 129.0 (C_{10}), 131.2 (C_{11}), 131.3 (C_3), 135.0 (C_2), 138.3 (C_{12b}), 143.1 (C_{6a}), 146.9 (C_{11a}), 147.7 (C_{12a}), 148.1 (C_{4a}), 157.2 (C_6); MS: m/z (%) 334 (M^+ 100), 333 (25), 319 (10), 293 (15), 257 (32), 166 (23), 77 (32), 43 (48). Anal. calcd. for $C_{24}H_{18}N_2$: C, 86.23; H, 5.39; N, 8.38. Found: C, 85.97; H, 5.59; N, 8.44%.

Compound 5b. Colorless needles; mp 245–247 °C; yield: 0.092 g (25%); IR ν_{max} (cm^{-1}): 1635 and 1605 (C=N); ^{1}H NMR ($CDCl_3$) δ: 2.35 (s, 3H, C_6-CH_3) 2.85 (s, 3H, C_4-CH_3), 7.39–7.84 (m, 10H, C_2-, C_3-, C_8-, C_9-, C_{10}-, C'_2-, C'_3-, C'_4-, C'_5-, C'_6-H), 8.33 (d, 1H, C_{11}-H, $J = 8.53$ Hz), 9.10 (d, 1H, C_1-H, $J = 7.92$ Hz); ^{13}C NMR ($CDCl_3$) δ: 20.2 (C_4-CH_3), 28.6 (C_6-CH_3), 117.6 (C_8), 124.4 (C_1), 125.0 (C_9), 125.9 (C'_2, C'_6), 126.5 (C'_3, C'_4, C'_5), 127.5 (C'_1), 128.5 (C_7), 128.7 (C_2), 128.9 (C_{7a}), 129.0 (C_{10}), 131.2 (C_{11}), 131.7 (C_3), 136.2 (C_4), 138.3 (C_{12b}), 143.1 (C_{6a}), 146.9 (C_{11a}), 147.7 (C_{12a}), 148.8 (C_{4a}), 157.2 (C_6); MS: m/z (%) 334 (M^+ 100), 333 (35), 319 (15), 293 (10), 257 (10), 166 (42), 77 (55), 43 (55). Anal. calcd. for $C_{24}H_{18}N_2$: C, 86.23; H, 5.39; N, 8.38. Found: C, 86.01; H, 5.50; N, 8.49%.

Compound 5c. White solid; mp 255–257 °C; Yield: 0.081 g (22%); IR ν_{max} (cm^{-1}): 1633 and 1610 (C=N); ^{1}H NMR ($CDCl_3$) δ: 2.36 (s, 3H, C_6-CH_3), 7.37–7.96 (m, 10H, C_3-, C_4-, C_8-, C_9-, C_{10}-, C'_2-, C'_3-, C'_4-, C'_5-, C'_6-H), 8.34 (d, 1H, C_{11}-H, $J = 8.41$ Hz), 9.19 (s, 1H, C_1-H); ^{13}C NMR ($CDCl_3$) δ: 28.8 (C_6-CH_3), 117.6 (C_8), 123.8 (C_1), 125.0 (C_9), 125.9 (C'_2, C'_6), 126.5 (C'_3, C'_4, C'_5), 127.5 (C'_1), 128.5 (C_7), 128.5 (C_4), 128.9 (C_{7a}), 129.0 (C_{10}), 131.2 (C_{11}), 131.2 (C_3), 134.5 (C_2), 138.3 (C_{12b}), 143.1 (C_{6a}), 146.9 (C_{11a}), 147.7 (C_{12a}), 148.1 (C_{4a}), 157.2 (C_6); MS: m/z (%) 356/354 (M^+, 31/100), 341 (55) 339 (19), 319 (350), 292 (25), 177 (18), 165 (23), 77 (12), 43 (22). Anal. calcd. for $C_{23}H_{15}ClN_2$: C, 77. 97; H, 4.24; N, 7.91. Found: C, 77.89; H, 4.33; N, 7.87%.

Compound 5d. Colorless prisms; mp 242–244 °C; yield: 0.088 g (25%); IR ν_{max} (cm^{-1}): 1623 and 1607 (C=N); ^{1}H NMR ($CDCl_3$) δ 2.34 (s, 3H, C_6-CH_3), 7.40–7.99 (m, 11H, C_2-, C_3-, C_4-, C_8-, C_9-, C_{10}-, C'_2-, C'_3-, C'_4-, C'_5-, C'_6-H), 8.41 (d, 1H, C_{11}-H, $J = 8.96$ Hz), 9.14 (d, 1H, C_1-H, $J = 8.10$ Hz); ^{13}C NMR ($CDCl_3$) δ: 28.6 (C_6-CH_3), 117.6 (C_8), 124.1 (C_1), 125.0 (C_9), 125.9 (C'_2, C'_6), 126.5 (C'_3, C'_4, C'_5), 127.5 (C'_1), 128.5 (C_7), 128.5 (C_2), 128.9 (C_{7a}), 129.0 (C_{10}), 131.2 (C_{11}), 131.3 (C_3), 133.0 (C_4), 138.3 (C_{12b}), 143.1 (C_{6a}), 146.9 (C_{11a}), 147.7 (C_{12a}), 148.0 (C_{4a}), 157.2 (C_6); MS: m/z (%) 320 (M^+, 100), 319 (75), 315 (20), 168 (23), 121 (43), 68 (54), 44 (42). Anal. calcd. for $C_{23}H_{16}N_2$: C, 86.25; H, 5.00; N, 8.75. Found: C, 86.49; H, 5.20; N, 8.31%.

6-Methyldibenzo[*b,h*][1,6]naphthyridines (4 and 5) from 2-Methyl-4-(*N*-phenylamino)quinolines (10)

Preparation of 2-methyl-4-(N-phenylamino)quinolines (10) from 4-chloro-2-methyl quinolines (6): General procedure. 4-Chloro-2-methylquinoline (**6**, 0.002 mol) was heated with aniline (**9**, 0.002 g, 0.002 mol) under neat

condition at 160 °C for half an hour. The product was washed with water, adsorbed and purified by chromatography on silica gel, and eluted with an ethyl acetate/ Methanol (95:5) mixture to get the anilinoquinoline **10**, which was then recrystallized from methanol.

Compound 10a. Colorless needles; mp > 300 °C; yield: 0.399 g (70%); IR ν_{max} (cm^{-1}): 3367 (NH); ^{1}H NMR (DMSO-d_6) δ: 2.54 (s, 3H, C_2-CH_3), 2.59 (s, 3H, C_6-CH_3), 6.75 (s, 1H, C_3-H), 7.48–7.94 (m, 7H, C_7-, C_8-, C'_2-, C'_3-, C'_4, C'_5-, C'_6-H), 8.51 (s, 1H, C_5-H), 10.58 (b s, 1H, C_4-NH amino form), 14.31 (b s, 1H, N_1-H imino form). The ratio of amino form to imino form is 1:1. ^{13}C NMR (DMSO-d_6) δ: 18.9 (C_2-CH_3), 24.8 (C_6-CH_3), 100.5 (C_3), 117.4 (C_{4a}), 118.9 (C'_2, C'_6), 123.5 (C'_3, C'_5), 125.2 (C_5), 125.6 (C'_4), 132.6 (C_7), 135.1 (C_8), 136.9 (C_6), 137.8 (C'_1), 137.8 (C_{8a}), 151.9 (C_4), 153.7 (C_2); MS: m/z (%) 248 (M^+ 100), 247 (40), 232 (20), 218 (15), 191 (35), 130 (19), 123 (15), 77 (42). Anal. calcd. for $C_{17}H_{16}N_2$: C, 82.25; H, 6.46; N, 11.29. Found: C, 82.05; H, 6.60; N, 11.35%.

Compound 10b. White solid; mp > 300 °C; yield: 0.423 g (75%); IR (KBr) ν_{max} (cm^{-1}): 3378 (NH); ^{1}H NMR (DMSO-d_6) δ: 2.76 (s, 3H, C_8-CH_3), 2.95 (s, 3H, C_2-CH_3), 6.71 (s, 1H, C_3-H), 7.31–7.65 (m, 7H, C_6-, C_7-, C'_2-, C'_3-, C'_4-, C'_5-, C'_6-H), 8.80 (d, 1H, C_5-H, $J = 7.12$ Hz), 10.50 (b s, 1H, C_4-NH amino form), 12.41 (b s, 1H, N_1-H imino form). The ratio of amino form to imino form is 1:1). ^{13}C NMR (DMSO-d_6) δ; 19.2 (C_2-CH_3), 25.1 (C_8-CH_3), 100.8 (C_3), 117.4 (C_{4a}), 118.9 (C'_2, C'_6), 123.5 (C'_3, C'_5), 124.8 (C_5), 125.6 (C'_4), 131.5 (C_6), 136.1 (C_7), 137.4 (C_8), 137.8 (C'_1), 138.2 (C_{8a}), 151.9 (C_4), 153.7 (C_2); MS: m/z (%) 248 (M^+ 100), 247 (25), 232 (15), 218 (20), 191 (31), 130 (18), 77 (42), 44(35). Anal. calcd. for $C_{17}H_{16}N_2$: C, 82.25; H, 6.46; N, 11.29. Found: C, 82.15; H, 6.30; N, 11.55%.

Compound 10c. White solid; mp > 300 °C; yield: 0.416 g (65%); IR ν_{max} (cm^{-1}): 3368 (NH); ^{1}H NMR (DMSO-d_6) δ: 2.61 (s, 3H, C_2-CH_3), 6.81 (s, 1H, C_3-H), 7.48–8.13 (m, 7H, C_7, C_8, C'_2-, C'_3-, C'_4-, C'_5, C'_6-H), 8.89 (s, 1H, C_5-H), 10.74 (b s, 1H, C_4-NH amino form), 14.71 (b s 1H, N_1-H imino form). The ratio of amino form to imino form is 1:1). ^{13}C NMR (DMSO-d_6) δ: 19.4 (C_2-CH_3), 100.4 (C_3), 117.2 (C_{4a}), 118.9 (C'_2, C'_6), 123.5 (C'_3, C'_5), 125.0 (C_5), 125.6 (C'_4), 132.5 (C_7), 134.8 (C_8), 136.2 (C_6), 137.8 (C'_1), 137.8 (C_{8a}), 151.9 (C_4), 153.7 (C_2); MS: m/z (%) 268 (M^+ 100), 267 (50), 253 (15) 232 (18), 122 (28), 77 (52), 65 (36), 44 (60). Anal. calcd. for $C_{16}H_{13}ClN_2$: C, 71.64; H, 4.85; N, 10.44. Found: C, 71.25; H, 4.68; N, 10.65%.

Compound 10d. White solid; mp > 300 °C; yield: 0.386 g (72%); IR ν_{max} (cm^{-1}): 3365 (NH); ^{1}H NMR (DMSO-d_6) δ: 2.60 (3H, s, C_2-CH_3), 6.69 (s, 1H, C_3-H), 7.46–8.08 (m, 8H, C_6-, C_7-, C_8-, C'_2-, C'_3-, C'_4-, C'_5-, C'_6-H), 8.51 (d, 1H, C_5-H, $J = 7.20$ Hz), 10.61 (b s, 1H, C_4-NH amino form), 13.91 (b s, 1H, N_1-H imino form). The ratio of amino form to imino form is 1:1). ^{13}C NMR (DMSO-d_6) δ: 19.0 (C_2-CH_3), 100.6 (C_3), 117.3 (C_{4a}), 118.9 (C'_2, C'_6), 123.5 (C'_3, C'_5), 124.7 (C_5), 125.6 (C'_4), 131.4 (C_6), 136.1 (C_8), 136.4 (C_7), 137.8 (C'_1), 138.2 (C_{8a}), 151.9 (C_4), 153.7 (C_2); MS: m/z (%) 234 (M^+ 100), 233 (20), 191 (25), 124 (10), 90(8), 77 (52) 76 (30), 44 (25). Anal. calcd. for $C_{16}H_{14}N_2$: C, 82.06; H, 5.98; N, 11.96. Found: C, 82.52; H, 6.05; N, 11.43%.

Cyclization of 2-methyl-4-(N-phenylamino)quinoline (10) with acetic acid. A mixture of 2-methyl-4-(*N*-phenylamino)quinoline (**10**, 0.001 mol) and acetic acid (0.122 mg, 0.0011 mmol) was added to polyphosphoric acid (P_2O_5, 1 g, and H_3PO_4, 0.5 mL) and heated at 160 °C for 5 h. The reaction mixture was poured into ice water and extracted with ethyl acetate. The crude product obtained was purified by column chromatography over silica gel using a petroleum ether/ethyl acetate (97:3) mixture to get a pale yellow solid. The product 6,7-dimethyldibenzo[*b,h*][1,6]-naphthyridine **(4)** was recrystallized using methanol as prisms. From the TLC and superimposible IR spectra, the compound was identified as the same one obtained from the earlier one-pot synthesis of 4-chloro-2-methylquinoline (**6**) with *o*-amino-acetophenone under neat conditions. Further, the mixed melting points of this compound and the compound obtained earlier from the one-pot synthesis were undepressed. The yields of the products obtained by the two methods are compared in Table 1.

Cyclization of 2-methyl-4-(N-phenylamino)quinoline (10) with benzoic acid. A mixture of 2-methyl-4-(*N*-phenylamino)quinoline (**10**, 0.001 mmol) and benzoic acid (0.122 mg, 0.0011 mmol) was added to polyphosphoric acid (P_2O_5, 1 g, and H_3PO_4, 0.5 mL) and heated at 160 °C for 5 h. The reaction mixture was poured into ice water, neutralized with saturated sodium bicarbonate solution, and extracted with ethyl acetate. The crude product obtained was purified by column chromatography over silica gel using a petroleum ether/ethyl acetate (98:2) mixture to get a pale yellow solid. The product 6-methyl-7-phenyldibenzo[*b,h*][1,6]naphthyridines (**5**) was recrystallized using methanol as prisms. From the TLC and superimposible IR spectra, the compound was identified as the same one obtained from the earlier one-pot synthesis of 4-chloro-2-methylquinoline (**6**) with *o*-aminobenzophenone under neat conditions. Further, the mixed melting points of this compound and the compound obtained earlier from the one-pot synthesis were undepressed. The yield of the products obtained by the two methods are compared in Table 1.

X-Ray Crystallographic Data

Crystallographic data of the structure **5c** (obtained from method 2) in this article have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC No. 750053. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, or via e-mail to deposit@ccdc.cam.ac.uk.

ACKNOWLEDGMENTS

The authors thank IISc, Bangalore, and MKU, Madurai for NMR spectra; the Indian Institute for Chemical Technology, Hyderabad, for mass spectral data; and IIT, Madras, Chennai, for single-crystal XRD data.

REFERENCES

1. Frimurer, T. M.; Ulven, T.; Hoegberg, T. P.; Norregaard, K.; Little, P. B.; Receveur, J. M. Int. Patent WO 2004052371 A2, June 24, 2004.

2. Leblond, B.; Petit, S.; Picard, V.; Taverne, T.; Schweighoffer, F. Int. Patent WO 2004076445 A2, September 10, 2004.
3. Murakami-Kubo, I.; Doh-ura, K.; Ishikawa, K.; Kawatake, S.; Sasaki, K.; Kira, J.-I.; Ohta, S.; Iwaki, T. Quinoline derivatives are therapeutic candidates for transmissible spongiform encephalopathies. *J. Virol.* **2004**, *78*, 1281–1288.
4. Miwa, A.; Yoshino, T.; Osawa, T.; Sakai, T.; Shimizu, T.; Fujiwara, Y. Int. Patent WO 2003033472 A1, April 24, 2003.
5. Davies, D. T.; Jones, G. E.; Lightfoot, A. P.; Markwell, R. E.; Pearson, N. D. Int. Patent WO 2002008224 A1, January 31, 2002.
6. Gemma, S.; Kukreja, G.; Fottorusso, C.; Persico, M.; Romano, M. P.; Altarelli, M.; Savini, L.; Campiani, G.; Fattorusso, D.; Basiliico, N.; Taramelli, D.; Yardley, V.; Butini, S. Synthesis of N_1-arylidene-N_2-quinolyl- and N_2-acrydinylhydrazones as potent antimalarial agents active against CQ-resistant *P. falciparum* strains. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5384–5388.
7. Curd, F. H. S.; Raison, C. G.; Rose, F. L. Synthetic antimalarials: Some arylamino-aminoalkyl quinoline derivatives. *J. Chem. Soc.* **1947**, 899.
8. Price, C. C.; Maynert, E. W.; Boekelheide, V. Some 4,8-diaminoquinolines. *J. Org. Chem.* **1949**, 484–487.
9. Rossiter, S.; Peron, J. M.; Whitfield, P. J.; Jones, K. Synthesis and anthelmintic properties of arylquinolines with activity against drug-resistant nematodes. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4806–4808.
10. Paronikyan, E. G.; Sirakanyan, S. N.; Noravyan, A. S.; Asatryan, T. O.; Markaryan, K.; Aleksanyan, R. A. Synthesis and antiarrhythmic activity of 7-benzyl(ethyl)-1-hydroxy-4-carbamoyl-3-oxo-5,6-dihydro-8*H*-2,7-naphthyridines. *Phar. Chem. J.* **1996**, *30*(6), 365–367.
11. Vatsadze, S. Z.; Kostochka, M. L.; Lezina, V. P.; Vinokurov, V. G.; Klodt, P. M.; Zyk, N. V. Synthesis of new derivatives of 5,6,7,8 tetrahydro[1,6]naphthyridines and their pharmacological properties. *Russ. Chem. Bull. Int. Ed.* **2005**, *54*, 257–258.
12. Zhuang, L.; Wai, J. S.; Embrey, M. W.; Fisher, T. E.; Egbertson, M. S.; Payne, L. S.; Guare, J. P.; Vacca, J. P.; Hazuda, D. J.; Felock, P. J.; Wolfe, A. L.; Stillmock, K. A.; Witmer, M. V.; Moyer, G.; Schleif, W. A.; Gabryelski, L. J.; Leonard, Y. M.; Lynch, J. J.; Michelson, S. R.; Young, S. D. Design and synthesis of 8-hydroxy-[1,6]-naphthyridines as novel inhibitors of HIV-1 integrase in vitro and in infected cells. *J. Med. Chem.* **2003**, *46*, 453–456.
13. Atanasova, M.; Ilieva, S.; Galabov, B.; QSAR analysis of 1,4-dihydro-4-oxo-1-(2-thiazolyl)-1,8-naphthyridines with anticancer activity. *Eur. J. Med. Chem.* **2007**, *42*, 1184–1192.
14. Gopalsamy, A.; Shi, M.; Boschelli, D. H.; Williamson, R.; Olland, A.; Hu, Y.; Krishnamurthy, G.; Han, X.; Arndt, K.; Guo, B. Discovery of dibenzo[*c,f*][2,7]naphthyridines as potent and selective 3-phosphoinositide-dependent kinase-1 inhibitors. *J. Med. Chem.* **2007**, *50*, 5547–5549.
15. Reissert, A. Ueber Di-(γ-amidopropyl) essigsäure (Diamino.1.7.heptanmethylsäure.4) und ihr inneres Condensations product, das Octohydro.1.8.naphtyridin. *Ber. Dtsch. Chem. Ges.* **1893**, *26*, **2137**.
16. Sekar, M.; Rajendra Prasad, K. J. Synthesis of dibenzo[*b,h*][1,6]naphthyridin-5,6-diones. *Indian J. Chem.* **1999**, *38B*, 969–970.
17. Gopalsamy, A.; Shi, M.; Nilakantan, R. An efficient synthesis of dibenzo[*c,f*]-2, 7-naphthyridine ring system through design of experiments. *Org. Process Res. Dev.* **2007**, *11*, 450–454.
18. Leslie, D. W.; Thomas, R.; Li, Z.; Bruce, B. C.; Williams, D. A. Synthesis and cytotoxic activity of carboxamide derivatives of benzo[*b*][1,6]naphthyridines. *J. Med. Chem.* **2003**, *46*, 1049–1054.

19. Hutton, M. S.; Mackay, P. S.; Meth-Cohn, O. Synthesis of benzo[*i*]phenanthridine and dibenzo[*c,h*][1,6]naphthyridine analogues of the antitumour benzo[*c*]phenanthridines. *Synthesis* **2000**, *8*, 1121–1124.
20. Da; Settimo, A.; Biaji, G.; Primfiore, G.; Ferrarini, P. L.; Livi, O.; Marini, A. M. Synthesis of some 3,7-disubstituted quino[3,2-*c*][1,8]naphthyridines. *J. Heterocycl. Chem.* **1980**, *17*, 1225–1229.
21. Kidwai, M.; Kohli, S. Synthesis of dibenzo[*b,g*]-5-methyl-[1,8]naphthyridines. *Indian J. Chem.* **2001**, *40B*, 248–249.
22. Manoj, M.; Rajendra Prasad, K. J. An efficient synthesis of phenyl substituted dibenzonaphthyridines. *J. Chem. Res.* **2009**, 485–488.
23. Manoj, M.; Rajendra Prasad, K. J. Synthesis of novel substituted dibenzonaphthyridines. *Z. Naturforsch.* **2009**, *64B*, 851–857.
24. Manoj, M.; Rajendra Prasad, K. J. A facile synthesis of alkyl and aryl substituted dibenzo[*b,g*][1,8]naphthyridin-5-ones. *Synth. Commun.* **2010**, *40*, 3290–3308.
25. Sridharan, M.; Rajendra Prasad, K. J. Novel 13*H*-indolo[3,2-*c*]acridines and their methyl derivatives. *J. Chem. Res.* **2007**, 164–169.