Synthesis of novel phenyl substituted dibenzonaphthyridines

Manickam Manoj and Karnam Jayaramapillai Rajendra Prasad*

Department of Chemistry, Bharathiar University, Coimbatore 641 046, Tamil Nadu, India

The reaction of 2,4-dichloroquinolines with 2-amino-5-chlorobenzophenone yielded 2-[(2-benzoyl-4-chlorophenyl) amino]-4-chloroquinolines which with sodium methoxide afforded 2-[(2-benzoyl-4-chlorophenyl)amino]-4-methoxyquinolines. These on PPA-catalysed cyclisation gave 2-chloro-12-phenyldibenzo[*b,g*][1,8]naphthyridin-11(6*H*)-ones. Temperature differences for the formation of the final products were due to the *in situ* formation of the 2-[(2-benzoyl-4-chlorophenyl)amino]quinolin-4-ones from the chloro and methoxy intermediates. The dibenzonaphthyridin-11-ones were *N*-methylated at N(6); a methyl group at C(7) was found to hinder the methylation reaction sterically, when a considerably longer reaction time was needed.

Keywords: fused 1,8-naphthyridines, cyclisation, quinolines, methylation, steric effects

Small and structurally interesting compounds that have a readily reactive functional group are new targets of synthetic organic chemists due to the importance of these compounds in the combinatorial approach to drug discovery. In this respect, amino-substituted quinolines have generated from the π-electron deficient quinoline core chemical entities for the synthesis of anti-malarial drugs, *e.g.*, chloroquine, primaquine, active against *Plasmodium falciparum*,[1] Some of the phenylaminoquinolines are also considered as synthetic anti-malarials[2] and have attracted chemists by their utility in deriving various heterocyclic systems such as dibenzonaphthyridines, indoloquinolines, *etc*. A detailed survey of the literature points out the wide utility of chloroquinolines in the preparation of substituted quinolines possessing biological activity,[3,4] in particular, their amino-dechlorination reaction involving aromatic amines, thereby furnishing anilinoquinolines. Research on the chemistry of naphthyridines has expanded considerably in recent years owing to the fact that biologically active compounds have been detected among their derivatives. Numerous reports have claimed that these heterocycles may act as anti-arrhythmic,[5] analgesic,[6] anti-HIV,[7] and anti-cancer agents.[8] In particular, some dibenzonaphthyridines, *i.e.* quinolinoquinolines, act as potent and selective 3-phosphoinositide-dependent kinase-I inhibitors.[9] Many reports present the synthesis of simple dibenzonaphthyridines,[10-15] but only a few accomplish their construction through anilinoquinolines.[14,15]

We report here the synthesis of phenyl substituted dibenzonaphthyridines utilising 2,4-dichloroquinolines (**1**) involving the anilinoquinolines *i.e.* 2-[(2-benzoyl-4-chlorophenyl)amino] -4-chloroquinolines (**2**) and 2-[(2-benzoyl-4-chlorophenyl) amino]-4-methoxyquinolines (**5**) as probable intermediates in the synthesis of phenyl-substituted linear and angular dibenzonaphthyridines.

Results and discussion

In consideration of the above, the 2,4-dichloroquinolines (**1**) were reacted with 2-amino-5-chlorobenzophenone under neat conditions at 160 °C for 30 min. The only products obtained, irrespective of the mole ratio of 2-amino-5-chlorobenzophenone taken for the reaction, were assigned as the 2-substituted products, 2-[(2-benzoyl-4-chlorophenyl)amino]-4-chloroquinolines (**2**) on the basis of the reactivity of the 2- and 4-chloro groups of the 2,4-dichloroquinoline[16] (Scheme 1).

In the ^{1}H NMR spectrum the C2-NH appeared as a broad singlet around δ 11.00 ppm. All the aromatic protons appeared between the region around δ 7.00–8.00 ppm except for a one proton doublet which was shifted abnormally downfield around δ 9.40 ppm. With the help of DEPT-135, H,H-COSY and HMBC correlations the deshielded proton in 2-[(2-benzoyl-4-chlorophenyl)amino]-4-chloro-8-methylquinoline (**2b**) was identified as C6'-H. A one proton doublet at δ 9.39 (J = 8.31 Hz) and a one proton doublet at δ 7.58 (J = 8.31 Hz) have H, H-COSY connection, which are characteristic of C6'- and C5'- protons. The assignment of coupling protons for all the other aromatic protons using H, H-COSY is given in Table.1. The DEPT-135 spectrum displayed 12 CH signals besides the methyl and the carbonyl carbons, the remaining being quaternary carbons. The isolated C6' proton has HMBC connectivity with C1' and C5' carbons. The connectivities of all other protons with the carbons are shown in Fig. 1.

It could be speculated that the reason for the abnormal deshielding of C6'-H is on account of hydrogen bonding between the C2-NH and 2'-carbonyl group fixing the 2-substituent in a particular plane, whereby the C6'-H

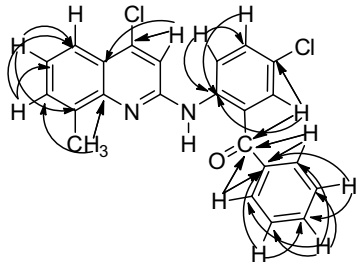
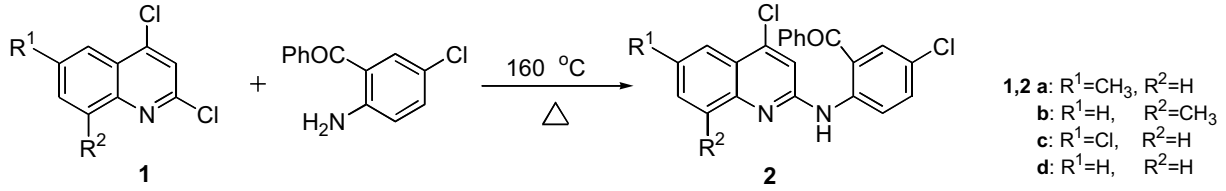


Fig. 1 HMBC connectivity of **2b**.



1,2 a: R^1=CH_3, R^2=H
b: R^1=H, R^2=CH_3
c: R^1=Cl, R^2=H
d: R^1=H, R^2=H

Scheme 1

* Correspondent. E-mail: prasad_125@yahoo.com

Table 1 ^{1}H NMR and their coupling protons of the compound **2b** assigned by H,H-COSY

	^{1}H NMR (δ)	Coupling protons (δ)
1	7.11 (s, 1H, C3-H)	–
2	7.34 (t, 1H, C6-H, *J* = 8.18 Hz)	7.59 (d, 1H, C7-H, *J* = 7.92 Hz), 7.95 (d, 1H, C5-H, *J* = 8.24 Hz)
3	7.53 (m, 1H, C4''-H)	7.54 (m, 2H, C3'', C5''-H)
4	7.54 (m, 2H, C3'', C5''-H)	7.53 (m, 1H, C4''-H), 7.72 (d, 2H C2'', C6''-H, *J* = 7.14 Hz)
5	7.58 (s, 1H, C3'-H)	–
6	7.58 (d, 1H, C5'-H, *J* = 8.31 Hz)	9.39 (d, 1H, C6'-H, *J* = 8.31 Hz)
7	7.59 (d, 1H, C7-H, *J* = 7.92 Hz)	7.34 (t, 1H, C6-H, *J* = 8.18 Hz)
8	7.72 (d, 2H, C2'', C6''-H, *J* = 7.14 Hz)	7.54 (m, 2H, C3'', C5''-H)
9	7.95 (d, 1H, C5-H, *J* = 8.24 Hz)	7.34 (t, 1H, C6-H, *J* = 8.18 Hz)
10	9.39 (d, 1H, C6'-H, *J* = 8.31 Hz)	7.58 (d, 1H, C5'-H, *J* = 8.31 Hz)

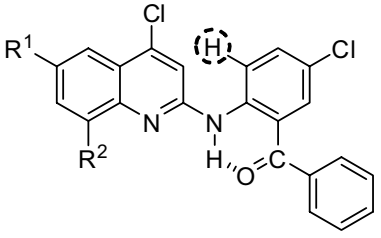


Fig. 2 Preferred orientation of the amines **2**.

(ringed in Fig. 2) becomes situated in the deshielding zone of the quinoline ring current, thus experiencing a reinforced anisotropic effect which shifts the proton to around δ 9.40 ppm. The orientation of the molecule **2** could be assigned as represented. (Fig. 2)

In order to produce the linear dibenzonaphthyridine system by acid-catalysed cyclisation, the 2-[(2-benzoyl-4-chlorophenyl)amino]-4-chloroquinolines (**2**) were heated with PPA. The reaction started only at a temperature of 205–210 °C and was completed in 5 h. Spectral analysis of the product revealed a broad singlet for NH group and the formed products were assigned as 2-chloro-12-phenyldibenzo[*b,g*][1,8]naphthyridin-11(6*H*)-ones (**3**) and not the expected dichloro compounds **4** (Scheme 2). Further, the structure of one of the product, 2-chloro-7-methyl-12-phenyldibenzo[*b,g*][1,8]naphthyridin-11(6*H*)-one (**3b**) was confirmed by a single crystal XRD study, and its ORTEP diagram is shown in Fig. 3.

Here the mechanism for the conversion of **2** to **3** under PPA conditions (Scheme 3) might be the protonation of the ring nitrogen of **2** to give the intermediate **I** followed by *ipso* attack of the $^{-}OP_2O_6HR_2$ ion to the C4-carbon yielding the intermediate **II** which subsequently on intramolecular elimination of a molecule of HCl affords the intermediate **III**. Then **III** on internal electrophilic attack on the positively induced 2'-carbonyl carbon gives the intermediate **IV** which on loss of water yields the product **3**.

It was assumed that the reluctance of the reaction of 2-[(2-benzoyl-4-chlorophenyl)amino]-4-chloroquinolines (**2**) to proceed at lower temperature might be due to the deactivating nature of the chloro group which inhibits the

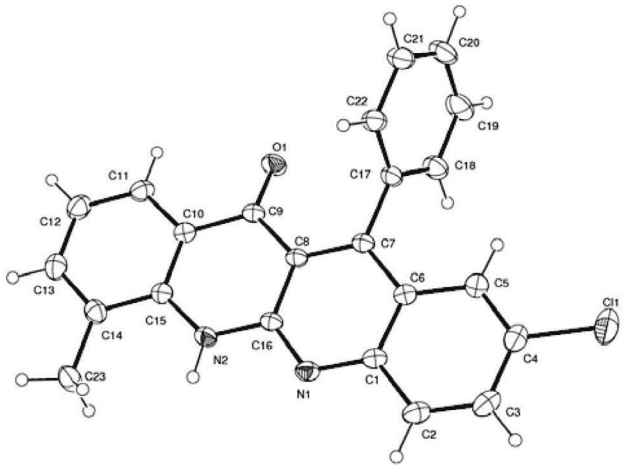
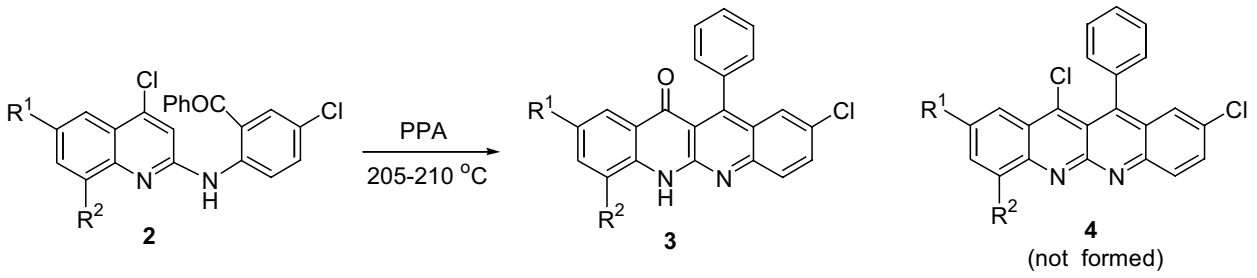


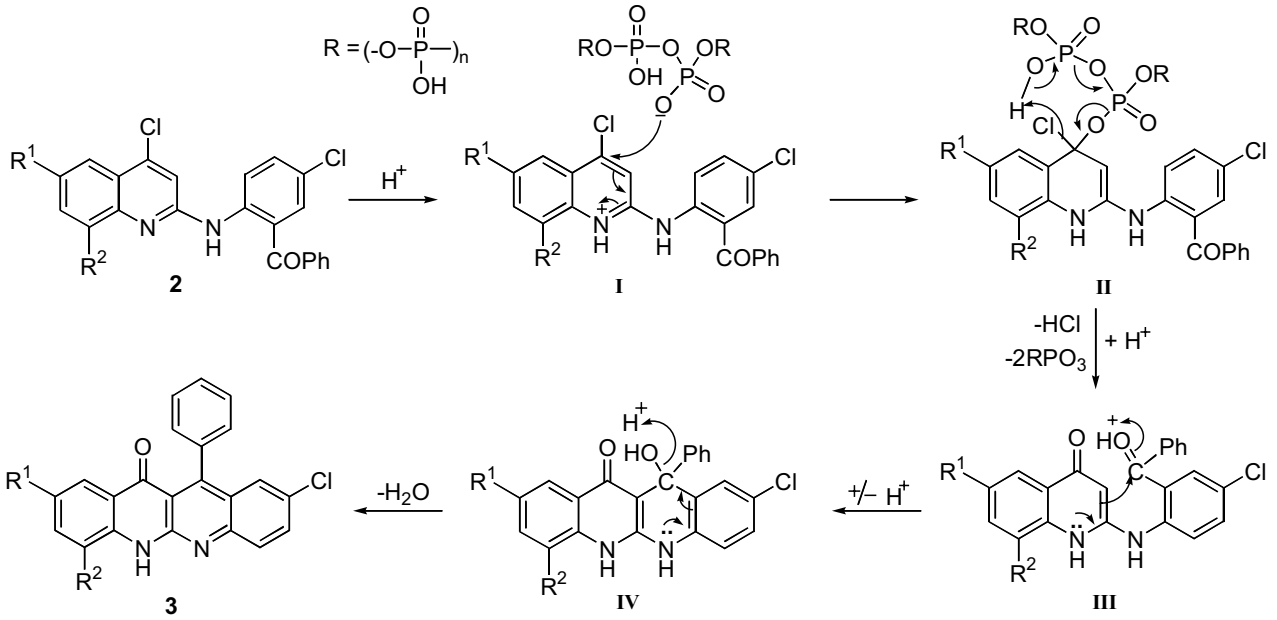
Fig. 3 ORTEP diagram of 2-chloro-7-methyl-12-phenyldibenzo[*b,g*][1,8]naphthyridin-11(6*H*)-one (**3b**).

internal electrophilic substitution at the quinoline C3-position, and the same effect might also explain the rather low yields of the dibenzonaphthyridines **3**. We therefore converted the 4-chloro group in the intermediate **2** into a methoxy group in order to facilitate the reaction. The 2-[(2-benzoyl-4-chlorophenyl)amino]-4-chloroquinolines (**2**) on treatment with sodium methoxide for 10 h afforded the expected 4-methoxyquinolines (**5**) (Scheme 4). In this case also the C6'-H was abnormally deshielded at around δ 9.50 ppm in the ^{1}H NMR, presumably for the same reason as proposed above for compounds **2**.

The 2-[(2-benzoyl-4-chlorophenyl)amino]-4-methoxyquinolines (**5**) was then subjected to PPA and monitored for the initiation of the reaction by gradually increasing the temperature. At a temperature of 130–135 °C, the reaction was found to proceed and was completed in 4 h. Surprisingly, the products proved to be identical with the earlier-formed products **3** from the reaction of **2** in PPA, and not the expected methoxy-products **7** (Scheme 4). A probable explanation for the formation of **3** is that it arises by acid-catalysed ether cleavage[17] of the OCH_3 group of 2-[(2-benzoyl-



Scheme 2 (**a–d**: R^1, R^2 as in Scheme 1).



Scheme 3 (**a–d**: R^1, R^2 as in Scheme 1).

4-chlorophenyl)amino]-4-methoxyquinolines (**5**) to the intermediate 2-[(2-benzoyl-4-chlorophenyl)amino]quinolin-4-ones which further gets cyclised to the final products **3** by the route shown in Scheme 3.

Not only were the temperatures milder, for the formation of the dibenzonaphthyridinones **3** from the methoxy-intermediates **5** (Scheme 4) than from the chloro-compounds **2** (Scheme 2), but the yields were better, on average some 50% improved on the direct method. However, the yields of the methoxy from the chloro compounds were only in the region of 40–50%, so the two-step route cannot be pronounced advantageous over the direct route, in terms of yield.

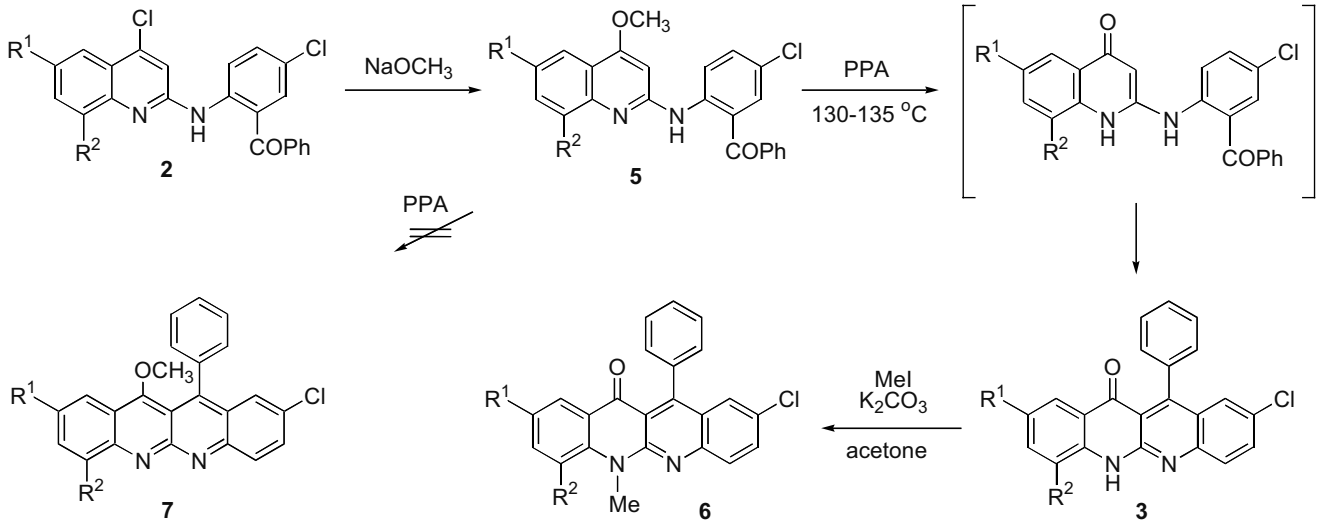
Finally, 2-chloro-12-phenyldibenzo[*b,g*][1,8]naphthyridin-11(6*H*)-one (**3d**) was refluxed with methyl iodide in acetone in the presence of ignited potassium carbonate. The product was formed over 1 h, and was identified as the *N*-methylated product, namely 2-chloro-6-methyl-12-phenyldibenzo[*b,g*][1,8]naphthyridin-11(6*H*)-one (**6d**)**.** The reaction was generalised for the other naphthyridine derivatives, when it was found that the 7-methyl compound (**3b**) took considerably longer (5 h) for the formation of 2-chloro-6,7-dimethyl-12-phenyldibenzo[*b,g*][1,8]naphthyridin-11(6*H*)-one (**6b**). This is readily explained by steric hindrance by the C7-methyl group of the approach of methyl iodide to the N atom at position 6. (Scheme 4)

In summary: (1) the reaction of 2,4-dichloroquinolines (**1**) with 2-amino-5-chloro-benzophenone, whether in excess or not, provided only the monosubstituted products, the 2-[(2-benzoyl-4-chlorophenyl)amino]-4-chloroquinolines (**2**).

(2) Acid-catalysed cyclisation of the compounds **2** using PPA at 205–210 °C yielded the 2-chloro-12-phenyldibenzo [*b,g*][1,8]naphthyridin-11(6*H*)-ones (**3**), probably *via* the quinolinone intermediate **III**.

(3) Treatment of compounds **2** with methanolic sodium methoxide yielded 2-[(2-benzoyl-4-chlorophenyl)amino]-4-methoxyquinolines (**5**) which with PPA at 130–135 °C formed **3**, again *via* the proposed intermediate **III**.

(4) The temperature difference for the formation of **3** from **2** and **5** reflects the relative readiness of the conversion of the Cl and OCH_3 into an OH group (intermediate **III**) under the same acidic conditions. The difference in the yields of the final products **3** from **2** (*ca* 21%) and **5** (*ca* 31%) may have the same explanation.



Scheme 4 (**a–d**: R^1, R^2 as in Scheme 1).

(5) N-Methylation of compounds **3** gave the N(6)-methylated products **6**. The reaction was subject to steric deceleration when a methyl group was present at C7.

Experimental

Melting points were determined on a Mettler FP51 apparatus (Mettler Instruments, Switzerland). IR spectra were recorded on Shimadzu FTIR-8201PC spectrophotometer (Shimadzu, Japan) using KBr discs. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AMX 400 spectrometer at 400 MHz (^{1}H) and 100 MHz (^{13}C) using tetramethylsilane (TMS) as an internal reference; 2D-NMR were recorded on a Bruker AV 300 MHz. The chemical shifts (δ) are expressed in parts per million (ppm). Mass spectra (MS) were recorded on an EI-Shimadzu QP 2010 PLUS GC-MS mass spectrometer. Microanalyses were performed on a Vario EL III model CHNS analyser (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.

2-[(2-Benzoyl-4-chlorophenyl)amino]-4-chloroquinolines (**2a–d**): *general procedure*

The 2,4-dichloroquinoline (**1**, 4 mmol) was heated with 2-amino-5-chlorobenzophenone (4 mmol or excess) under neat conditions at 160 °C for 30 min. The product was washed with water, dried, and purified using silica gel column chromatography eluting with petroleum ether:ethyl acetate mixture (98:2) to obtain **2** which was recrystallised from methanol.

2-[(2-Benzoyl-4-chlorophenyl)amino]-4-chloro-6-methylquinoline (**2a**): Colourless prisms (1.186 g, 73%), m.p. 172–174 °C. IR: ν_{max} 3432 (NH), 1636 (C=O), 1581, 1521, 1148 cm^{-1}. NMR ($CDCl_3$): δ_H 2.54 (s, 3H, C6-CH_3), 7.09 (s, 1H, C3-H), 7.30–7.80 (m, 9H, C7-, C8-, C3'-, C5'-, C2"-, C3"-, C4"-, C5"- and C6"-H), 7.86 (s, 1H, C5-H), 9.22 (d, 1H, C6'-H, J = 8.21 Hz), 10.86 (b s, 1H, NH); δ_C 21.5 (C6-CH_3), 114.3 (C3), 121.4 (C4'), 122.5 (C4a), 124.3 (C2') 127.2 (C6') 128.3 (C5) 129.4 (C2", C6"), 129.7 (C3", C5"), 130.1 (C4"), 130.9 (C3'), 131.3 (C8), 133.2 (C7), 133.9 (C6), 137.1 (C5'), 138.6 (C1"), 142.6 (C1'), 146.0 (C4), 150.3 (C8a), 151.9 (C2), 168.8 (C=O). MS: *m/z* (%) 410/408/406 (M^+, 8/20/35), 391 (15), 378 (47), 377 (65), 343 (27), 105 (38), 77 (79), 44 (100). Anal. Calcd for $C_{23}H_{16}Cl_2N_2O$: C, 67.98; H, 3.94; N, 6.90. Found:C, 67.82; H, 4.14; N, 7.02%.

2-[(2-Benzoyl-4-chlorophenyl)amino]-4-chloro-8-methylquinoline (**2b**): Colourless needles (1.218 g, 75%), m.p. 168–170 °C. IR: ν_{max} 3435 (NH), 1632 (C=O), 1591, 1521, 1152 cm^{-1}. NMR ($CDCl_3$): δ_H 2.75 (s, 3H, C8-CH_3), 7.11 (s, 1H, C3-H), 7.32–7.97 (m, 9H, C6-, C7-, C3'-, C5'-, C2"-, C3"-, C4"-, C5"- and C6"-H), 7.95 (d, 1H, C5-H, J = 8.24 Hz), 9.39 (d, 1H, C6'-H, J = 8.31 Hz), 11.04 (b s, 1H, NH); δ_C 19.8 (C8-CH_3), 114.3 (C3), 121.4 (C4'), 122.5 (C4a), 124.3 (C2') 127.2 (C6') 128.1 (C5) 129.4 (C2", C6"), 129.7 (C3", C5"), 130.1 (C4"), 130.9 (C3'), 131.5 (C6), 132.8 (C7), 133.1 (C8), 137.1 (C5'), 138.6 (C1"), 142.6 (C1'), 146.1 (C4), 150.1 (C8a), 151.8 (C2), 168.8 (C=O). MS: *m/z* (%) 410/408/406 (M^+, 10/23/39), 391 (10), 378 (55), 377 (60), 343 (42), 105 (38), 77 (85), 44 (100). Anal. Calcd for $C_{23}H_{16}Cl_2N_2O$: C, 67.98; H, 3.94; N, 6.90. Found:C, 68.10; H, 4.07; N, 6.88%.

2-[(2-Benzoyl-4-chlorophenyl)amino]-4,6-dichloroquinoline (**2c**): White solid (1.227 g, 72%), m.p. 174–176 °C. IR: ν_{max} 3432 (NH), 1636 (C=O), 1581, 1521, 1148 cm^{-1}. NMR ($CDCl_3$): δ_H 7.13 (s, 1H, C3-H), 7.52–7.82 (m, 9H, C7-, C8-, C3'-, C5'-, C2"-, C3"-, C4"-, C5"- and C6"-H), 8.06 (s, 1H, C5-H), 9.27 (d, 1H, C6'-H, J = 8.19 Hz), 10.89 (b s, 1H, NH); δ_C 114.3 (C3), 121.4 (C4'), 122.3 (C4a), 124.3 (C2') 127.2 (C6') 127.8 (C5) 129.4 (C2", C6"), 129.7 (C3", C5"), 130.1 (C4"), 130.9 (C3'), 130.9 (C8), 131.8 (C6), 133.0 (C7), 137.1 (C5'), 138.6 (C1"), 142.6 (C1'), 145.8 (C4), 150.0 (C8a), 151.7 (C2), 168.8 (C=O). MS: *m/z* (%) 432/430/428/426 (M^+, 1/11/34/35), 398 (35), 397 (55), 391 (21), 321 (30), 105 (55), 77 (71), 44 (100). Anal. Calcd for $C_{22}H_{13}Cl_3N_2O$: C, 61.97; H, 3.05; N, 6.57. Found:C, 62.13; H, 3.12; N, 6.39%.

2-[(2-Benzoyl-4-chlorophenyl)amino]-4-chloroquinoline (**2d**): Colourless prisms (1.16 g, 74%), m.p. 169–171 °C. IR: ν_{max} 3428 (NH), 1632 (C=O), 1589, 1522, 1117 cm^{-1}. NMR ($CDCl_3$): δ_H 7.11 (s, 1H, C3-H), 7.42–7.90 (m, 10H, C6-, C7-, C8-, C3'-, C5'-, C2"-, C3"-, C4"-, C5"- and C6"-H), 8.09 (dd, 1H, C5-H, J = 1.10, 8.28 Hz), 9.23 (d, 1H, C6'-H, J = 8.24 Hz), 10.89 (b s, 1H, NH); δ_C 114.3 (C3), 121.4 (C4'), 123.1 (C4a), 124.3 (C2') 127.2 (C6') 128.5 (C5) 129.4 (C2", C6"), 129.7 (C3", C5"), 130.1 (C4"), 130.9 (C3'), 131.1 (C6), 131.4 (C8), 132.9 (C7), 137.1 (C5'), 138.6 (C1"), 142.6 (C1'), 145.6 (C4), 149.9 (C8a), 151.8 (C2), 168.8 (C=O). MS: *m/z* (%) 396/394/392 (M^+, 15/32/47), 364 (65), 357 (26), 340 (21), 301 (22), 105 (68), 77 (88), 44 (100). Anal. Calcd for $C_{22}H_{14}Cl_2N_2O$: C, 67.35; H, 3.57; N, 7.14. Found: C, 67.26; H, 3.63; N, 7.28%.

2-Chloro-12-phenyldibenzo[b,g][1,8]naphthyridin-11(6H)-ones (**3a–d**) *from 2-[(2-benzoyl-4-chlorophenyl)amino]-4-chloroquinolines* (**2**)

2-[(2-Benzoyl-4-chlorophenyl)amino]-4-chloroquinoline (**2a–d**, 2 mmol) was added to polyphosphoric acid (6 g of P_2O_5 in 3 mL of H_3PO_4) and heated at 205–210 °C for 5 h. The reaction was monitored by using TLC. After the completion of the reaction, the reaction mixture was poured into ice-water and extracted with ethyl acetate, then purified by column chromatography using silica gel, the product eluted with petroleum ether:ethyl acetate (96:4) mixture to get **3** which was recrystallised from methanol.

2-Chloro-9-methyl-12-phenyldibenzo[b,g][1,8]naphthyridin-11(6H)-one (**3a**): Colourless needles (0.170 g, 23%), m.p. 208–210 °C. IR: ν_{max} 3428 (NH), 1647 (C=O), 1608, 1560 and 1471 cm^{-1}. NMR ($CDCl_3$): δ_H 2.38 (s, 3H, C9-CH_3), 7.16-7.87 (m, 10H, C1-, C3-, C4-, C7-, C8-, C2'-, C3'-, C4'-, C5'- and C6'-H), 8.02 (s, 1H, C10-H), 8.66 (b s, 1H, N6-H; δC 18.6 (C9-CH_3), 121.5 (C2), 122.9 (C1), 125.8 (C2', C6'), 126.2 (C3', C4', C5'), 126.8 (C4), 127.8 (C3), 128.0 (C7), 128.1 (C10), 128.3 (C8), 130.0 (C9), 133.4 (C1'), 137.3 (C12), 138.8 (C12a), 147.8 (C10a), 148.3 (C11a), 149.7 (C4a), 150.9 (C6a), 153.4 (C5a), 179.6 (C=O). MS: m/z (%) 372/370 (M^+, 26/80), 369 (100), 355 (15), 354 (10), 335 (15), 334 (10), 184 (10), 77 (42). Anal. Calcd for $C_{23}H_{15}ClN_2O$: C, 74.60; H, 4.05; N, 7.57. Found:C, 74.49; H, 3.95; N, 7.68%.

2-Chloro-7-methyl-12-phenyldibenzo[b,g][1,8]naphthyridin-11(6H)-one (**3b**): Colourless prisms (0.155 g, 21%), m.p. 206–208 °C. IR: ν_{max} 3430 (NH), 1644 (C=O), 1601, 1561 and 1480 cm^{-1}. NMR ($CDCl_3$): δ_H 2.58 (s, 3H, C7-CH_3), 7.08–7.88 (m, 10H, C1-, C3-, C4-, C8-, C9-, C2'-, C3'-, C4'-, C5'- and C6'-H), 8.11 (d, 1H, C10-H, J = 8.10 Hz), 8.51 (b s, 1H, N6-H; δ_C 16.8 (C7-CH_3), 121.5 (C2), 122.9 (C1), 125.8 (C2', C6'), 126.2 (C3', C4', C5'), 126.8 (C4), 127.8 (C3), 127.8 (C9), 128.0 (C10), 128.2 (C8), 130.8 (C7), 133.4 (C1'), 137.3 (C12), 138.8 (C12a), 147.6 (C10a), 148.3 (C11a), 149.7 (C4a), 151.3 (C6a), 153.5 (C5a), 179.6 (C=O). MS: *m/z* (%) 372/370 (M^+, 22/75), 369 (100), 355 (16), 354 (13), 335 (10), 334 (17), 184 (22), 77 (36). Anal. Calcd for $C_{23}H_{15}ClN_2O$: C, 74.60; H, 4.05; N, 7.57. Found:C, 74.71; H, 4.11; N, 7.45%.

2,9-Dichloro-12-phenyldibenzo[b,g][1,8]naphthyridin-11(6H)-one (**3c**): White solid (0.140 g, 18%), m.p. 212–214 °C. IR ν_{max} 3431 (NH), 1642 (C=O), 1605, 1557 and 1473 cm^{-1}. NMR ($CDCl_3$): δ_H 7.19–7.87 (m, 10H, C1-, C3-, C4-,C7-, C8-, C2'-, C3'-, C4'-, C5'- and C6'-H), 8.18 (d, 1H, C10-H, J = 2.40 Hz), 8.96 (b s, 1H, N6-H; δ_C 121.5 (C2), 122.9 (C1), 125.8 (C2', C6'), 126.2 (C3', C4', C5'), 126.8 (C4), 127.8 (C3), 127.9 (C7), 128.0 (C10), 128.1 (C8), 129.4 (C9), 133.4 (C1'), 137.3 (C12), 138.8 (C12a), 147.6 (C10a), 148.3 (C11a), 149.7 (C4a), 150.8 (C6a), 153.4 (C5a), 179.6 (C=O). MS: *m/z* (%) 394/392/390 (M^+, 32/61/100), 389 (82), 375 (18), 355 (16), 354 (10), 328 (25), 184 (27), 75 (15). Anal. Calcd for $C_{22}H_{12}Cl_2N_2O$: C, 67.69; H, 3.08; N, 7.18. Found:C, 67.80; H, 2.99; N, 7.25%.

2-Chloro-12-phenyldibenzo[b,g][1,8]naphthyridin-11(6H)-one (**3d**): Colourless prisms (0.142 g, 20%), m.p. 205–207 °C. IR: ν_{max} 3430 (NH), 1645 (C=O), 1607, 1559 and 1477 cm^{-1}. NMR ($CDCl_3$): δ_H 7.57–7.87 (m, 11H, C1-, C3-, C4-, C7-, C8-, C9-, C2'-, C3'-, C4'-, C5'- and C6'-H), 8.21 (dd, 1H, C10-H, J = 1.30 Hz, 8.08 Hz), 8.86 (b s, 1H, N6-H; δ_C 121.5 (C2), 122.9 (C1), 125.8 (C2', C6'), 126.2 (C3', C4', C5'), 126.8 (C4), 127.8 (C3), 127.9 (C7), 128.2 (C10), 128.9 (C9), 129.4 (C8), 133.4 (C1'), 137.1 (C12), 138.8 (C12a), 147.6 (C10a), 148.3 (C11a), 149.7 (C4a), 151.0 (C6a), 153.4 (C5a), 179.6 (C=O). MS: *m/z* (%) 358/356 (M^+, 30/85), 355 (100), 321 (31), 320 (15), 298 (18), 183 (21), 77 (27), 75 (32). Anal. Calcd for $C_{22}H_{13}ClN_2O$: C, 74.16; H, 3.65; N, 7.87. Found:C, 74.05; H, 3.59; N, 7.94%.

2-[(2-Benzoyl-4-chlorophenyl)amino]-4-methoxyquinolines (**5a–d**): *general procedure*

2-[(2-Benzoyl-4-chlorophenyl)amino]-4-chloroquinoline (**2a–d,** 2 mmol) was added to methanolic sodium methoxide (2 g sodium in 15 mL methanol) and heated on a water bath for 10 h. The reaction was monitored by TLC. After the completion of the reaction, excess of methanol was evaporated, the reaction mixture was poured into ice-water and neutralised with dilute HCl. The resulting precipitate was filtered, dried and purified by column chromatography over silica gel using petroleum ether:ethyl acetate (95 : 5) to give **5**, which was recrystallised from methanol.

2-[(2-Benzoyl-4-chlorophenyl)amino]-4-methoxy-6-methyl-quinoline (**5a**): Colourless prisms (0.346 g, 43%), m.p. 183–185°C IR: ν_{max} 3430 (NH), 1626 (C=O), and 1593, 1522 and 1237 cm^{-1} (OCH_3). NMR ($CDCl_3$): δ_H 2.51 (s, 3H, C6-CH_3), 4.06 (s, 3H, OCH_3), 6.31(s, 1H, C3-H), 7.25–7.81 (m, 9H, C7-, C8-, C3'-, C5'-, C2"-, C3"-, C4"-, C5"- and C6"-H), 7.90 (s, 1H, C5-H), 9.56 (d, 1H, C6'-H, J = 8.53 Hz), 10.91 (b s, 1H, NH); δc: 21.1 (C6-CH_3), 55.8 (O-CH_3), 92.3 (C3), 118.5 (C4'), 119.4 (C4a), 121.5 (C2') 122.0 (C6') 122.8 (C5) 128.4 (C2", C6"), 129.6 (C3", C5"), 130.4 (C4"), 131.6 (C3'), 132.3 (C8), 133.2 (C7), 134.3 (C6), 134.6 (C5'), 138.9 (C1"), 143.1 (C1'), 146.9 (C8a), 152.9 (C4), 163.4 (C2), 199.2 (C=O). MS: *m/z* (%) 404/402 (M^+, 20/55), 401 (14), 387 (18), 386 (27), 374 (44), 371 (32), 105 (50), 77 (100). Anal. Calcd for $C_{24}H_{19}ClN_2O_2$: C, 71.64; H, 4.73; N, 6.97. Found: C, 71.81; H, 4.66; N, 7.03%.

2-[(2-Benzoyl-4-chlorophenyl)amino]-4-methoxy-8-methyl-quinoline (**5b**): Colourless needles (0.370 g, 46%), m.p. 179–181°C. IR ν_{max} 3435 (NH), 1632 (C=O), 1587, 1519, 1231 cm^{-1} (OCH_3). NMR ($CDCl_3$): δ_H 2.74 (s, 3H, C8-CH_3), 4.03 (s, 3H, OCH_3), 6.29 (s, 1H, C3-H), 7.21–7.75 (m, 9H, C6-, C7-, C3'-, C5'-, C2"-, C3"-, C4"-, C5"- and C6"-H), 7.92 (d, 1H, C5-H, J = 8.40 Hz), 9.53 (d, 1H, C6'-H, J = 8.55 Hz), 11.05 (br s, 1H, NH); δ_C 18.7 (C6-CH_3), 55.7 (OCH_3), 92.2 (C3), 118.5 (C4'), 119.4 (C4a), 121.5 (C2') 122.0 (C6') 123.0 (C5) 128.4 (C2", C6"), 129.6 (C3", C5"), 130.4 (C4"), 131.6 (C3'), 131.8 (C6), 133.6 (C7), 134.0 (C8), 134.6 (C5'), 138.9 (C1"), 143.1 (C1'), 146.7 (C8a), 153.1 (C4), 163.4 (C2), 199.2 (C=O). MS: *m/z* (%) 404/402 (M^+, 23/61), 387 (22), 373 (52), 371 (18), 105 (42), 105 (50), 77 (100), 44 (75). Anal. Calcd for $C_{24}H_{19}ClN_2O_2$: C, 71.64; H, 4.73; N, 6.97. Found: C, 71.56; H, 4.80; N, 6.89%.

2-[(2-Benzoyl-4-chlorophenyl)amino]-6-chloro-4-methoxy-quinoline (**5c**): White solid (0.355 g, 42%), m.p. 188–190°C. IR: ν_{max} 3433 (NH), 1634 (C=O), 1587, 1525, 1239 cm^{-1} (OCH_3). NMR ($CDCl_3$): δ_H 4.11 (s, 3H, OCH_3), 6.33 (s, 1H, C3-H), 7.48–7.88 (m, 9H, C7-, C8-, C3'-, C5'-, C2"-, C3"-, C4"-, C5"- and C6"-H), 8.11 (s, 1H, C5-H), 9.49 (d, 1H, C6'-H, J = 8.48 Hz), 10.89 (b s, 1H, NH); δ_C 55.8 (OCH_3), 92.3 (C3), 118.5 (C4'), 119.1 (C4a), 121.5 (C2') 122.0 (C6') 122.1 (C5) 128.4 (C2", C6"), 129.6 (C3", C5"), 130.4 (C4"), 131.6 (C3'), 131.9 (C8), 132.6 (C6), 133.1 (C7), 134.6 (C5'), 138.9 (C1"), 143.1 (C1'), 146.1 (C8a), 152.5 (C4), 163.3 (C2), 199.2 (C=O). MS: *m/z* (%) 426/424/422 (M^+, 8/24/73), 391 (25), 389 (10), 387 (32), 317 (15), 105 (26), 77 (100), 44 (41). Anal. Calcd for $C_{23}H_{16}Cl_2N_2O_2$: C, 65.40; H, 3.79; N, 6.64. Found: C, 65.32; H, 3.86; N, 6.71%

2-[(2-Benzoyl-4-chlorophenyl)amino]-4-methoxyquinoline (**5d**): Colourless prisms (0.349 g 45%), m.p. 177–179°C. IR: ν_{max} 3428 (NH), 1635 (C=O), 1589, 1522, 1233 (OCH_3). ^1H NMR ($CDCl_3$) δ: 4.08 (s, 3H, OCH_3), 6.30 (s, 1H, C3-H), 7.45–7.94 (m, 10H, C6-, C7-, C8-, C3'-, C5'-, C2"-, C3"-, C4"-, C5"- and C6"-H), 8.10 (dd, 1H, C5-H, J = 1.81 Hz, 8.36 Hz), 9.55 (d, 1H, C6'-H, J = 8.62 Hz), 10.99 (b s, 1H, NH); δ_C 55.8 (O-CH_3), 92.3 (C3), 118.5 (C4'), 119.3 (C4a), 121.5 (C2') 122.0 (C6') 122.5 (C5) 128.4 (C2", C6"), 129.6 (C3", C5"), 130.4 (C4"), 131.6 (C3'), 131.6 (C6), 133.4 (C8), 133.7 (C7), 134.6 (C5'), 138.9 (C1"), 143.1 (C1'), 145.9 (C8a), 152.3 (C4), 163.3 (C2), 199.2 (C=O). MS: *m/z* (%) 390/388 (M^+, 25/68), 362 (18), 360 (36), 357 (42), 353 (22), 105 (42), 77 (100), 44 (55). Anal. Calcd for $C_{23}H_{17}ClN_2O_2$: C, 71.13; H, 4.38; N, 7.22. Found:C, 71.01; H, 4.51; N, 7.29%.

2-Chloro-12-phenyldibenzo[b,g][1,8]naphthyridin-11(6H)-ones (**3a–d**) *from 2-[(2-benzoyl-4-chlorophenyl)amino]-4-methoxy-quinolines* (**5**), *general procedure*

2-[(2-Benzoyl-4-chlorophenyl)amino]-4-methoxyquinoline (**5a–d**, 0.002 mol) was added to polyphosphoric acid (6 g of P_2O_5 in 3 mL of H_3PO_4) and heated at 130–135°C for 4 h. The reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured into ice water and extracted with ethyl acetate, purified by column chromatography using silica gel and product eluted with petroleum ether:ethyl acetate (96:4) to provide a white solid. The product was recrystallised from methanol. From the TLC, mixed melting point and superimposible IR spectra, the products were identified as **3**. The yield of the products **3** in this reaction were as follows: **3a,** 31%; **3b,** 33%; **3c,** 29%, **3d,** 30%.

N-Methylation of **3a–d;** *preparation of 2-chloro-6-methyl-12-phenyldibenzo[b,g][1,8]naphthyridin-11(6H)-ones* (**6a–d**), *general procedure*

2-Chloro-12-phenyldibenzo[*b,g*][1,8]naphthyridin-11(6*H*)-one (**3a–d**, 1 mmol) was refluxed with methyl iodide (1 mL) in acetone (10 mL) and in presence of ignited potassium carbonate (2 g) for 1 h (exceptionally, 5 h was required for the conversion of **3b**). The reaction was monitored by TLC. After completion of the reaction the excess of acetone and methyl iodide was evaporated off and the residue treated with ice-water and neutralised with dilute HCl, then extracted with ethyl acetate and purified by column chromatography over silica gel using petroleum ether:ethyl acetate (99:1) as eluant to get **6**. This was recrystallised from ethanol.

2-Chloro-6,9-dimethyl-12-phenyldibenzo[b,g][1,8]naphthyridin-11(6H)-one (**6a**): Pale yellow needles (0.173 g, 45%), m.p. 182–184°C. IR: ν_{max} 1648 (C=O), 1602, 1566, 1482 and 1178 cm^{-1}. NMR ($CDCl_3$): δ_H 2.41 (s, 3H, C9-CH_3), 4.04 (s, 3H, N6-CH_3), 7.21–7.89 (m, 10H, C1-, C3-, C4-, C7-, C8-, C2'-, C3'-, C4'-, C5'- and C6'-H), 7.98 (s, 1H, C10-H); δ_C 18.5 (C9-CH_3), 43.5 (N6-CH_3), 121.5 (C2), 122.9 (C1), 125.8 (C2', C6'), 126.2 (C3', C4', C5'), 126.6 (C7), 126.8 (C4), 127.8 (C3), 127.9 (C10), 128.1 (C8), 129.7 (C9), 133.4 (C1'), 137.3 (C12), 138.8 (C12a), 147.6 (C10a), 148.3 (C11a), 149.7 (C4a), 150.1 (C6a), 151.7 (C5a), 179.6 (C=O). MS: *m/z* (%) 386/384 (M^+, 35/100), 369 (25), 367 (10), 354 (12), 333 (15), 332 (8), 166 (15), 77 (32). Anal. Calcd for $C_{24}H_{17}ClN_2O$: C, 75.00; H, 4.43; N, 7.29. Found:C, 74.88; H, 4.34; N, 7.39%.

2-Chloro-6,7-dimethyl-12-phenyldibenzo[b,g][1,8]naphthyridin-11(6H)-one (**6b**): Pale yellow needles (0.181 g, 47%), m.p. 180–182°C. IR: ν_{max} 1645 (C=O), 1607, 1568, 1484 and 1169 cm^{-1}. NMR ($CDCl_3$): δ_H 2.52 (s, 3H, C7-CH_3), 4.09 (s, 3H, N6-CH_3), 7.17–7.92 (m, 10H, C1-, C3-, C4-, C8-, C9-, C2'-, C3'-, C4'-, C5'- and C6'-H), 8.20 (d, 1H, C10-H, J = 8.21 Hz); δ_C 17.8 (C7-CH_3), 42.7 (N6-CH_3), 121.5 (C2), 122.9 (C1), 125.8 (C2', C6'), 126.2 (C3', C4', C5'), 126.8 (C4), 127.8 (C3), 127.9 (C9), 128.0 (C10), 128.1 (C8), 129.8 (C7), 133.4 (C1'), 137.3 (C12), 138.8 (C12a), 147.4 (C10a), 148.3 (C11a), 149.7 (C4a), 152.0 (C6a), 152.3 (C5a), 179.6 (C=O). MS: *m/z* (%) 386/384 (M^+, 33/100), 369 (38), 367 (15), 354 (23), 333 (10), 332 (19), 166 (36), 77 (54). Anal. Calcd for $C_{24}H_{17}ClN_2O$: C, 75.00; H, 4.43; N, 7.29. Found:C, 75.11; H, 4.38; N, 7.34%.

2,9-Dichloro-6-methyl-12-phenyldibenzo[b,g][1,8]naphthyridin-11(6H)-one (**6c**): Pale yellow solid, m.p. 186–188°C. Yield:(0.170 g, 42%). IR ν_{max} (cm^{-1}):1642 (C=O), 1612, 1560, 1481 and 1175 cm^{-1}. NMR ($CDCl_3$): δ_H 4.23 (s, 3H, N6-CH_3), 7.25–7.98 (m, 10H, C1-, C3-, C4-, C7-, C8-, C2'-, C3'-, C4'-, C5'- and C6'-H), 8.27 (d, 1H, C10-H, J = 2.56 Hz); δ_C 42.9 (N6-CH_3), 121.5 (C2), 122.9 (C1), 125.8 (C2', C6'), 126.2 (C3', C4', C5'), 126.5 (C7), 126.6 (C4), 126.8 (C3), 127.8 (C10), 128.0 (C8), 128.1 (C9), 133.4 (C1'), 137.3 (C12), 138.8 (C12a), 147.5 (C10a), 148.3 (C11a), 149.7 (C4a), 150.3 (C6a), 151.2 (C5a), 179.6 (C=O). MS: *m/z* (%) 408/406/404 (M^+, 19/55/82), 403 (100), 367 (24), 352 (18), 338 (10), 166 (12), 77 (52), 41 (44). Anal. Calcd for $C_{23}H_{14}Cl_2N_2O$: C, 68.32; H, 3.47; N, 6.93. Found:C, 68.40; H, 3.53; N, 6.81%.

2-Chloro-6-methyl-12-phenyldibenzo[b,g][1,8]naphthyridin-11(6H)-one (**6d**): Pale yellow prisms (0.167 g, 45%), m.p. 179–181°C. IR: ν_{max} 1646 (C=O), 1607, 1559, 1477 and 1170 cm^{-1}. NMR ($CDCl_3$): δ_H 4.18 (s, 3H, N6-CH_3), 7.54–7.90 (m, 11H, C1-, C2-, C4-, C7-, C8-, C9-, C2'-, C3'-, C4'-, C5'- and C6'-H), 8.25 (d, 1H, C10-H, J = 8.39 Hz); δ_C 43.3 (N6-CH_3), 121.5 (C2), 122.9 (C1), 125.8 (C2', C6'), 126.2 (C3', C4', C5'), 126.5 (C7), 126.8 (C4), 127.8 (C3), 127.9 (C10), 128.2 (C9), 129.4 (C8), 133.4 (C1'), 137.1 (C12), 138.8 (C12a), 147.4 (C10a), 148.3 (C11a), 149.7 (C4a), 149.9 (C6a), 151.2 (C5a), 179.6 (C=O). MS: *m/z* (%) 372/370 (M^+, 36/100), 355 (35), 353 (12), 335 (15), 333 (8), 166 (16), 77 (52), 41 (42). Anal. Calcd for $C_{23}H_{15}ClN_2O$: C, 74.60; H, 4.05; N, 7.57. Found:C, 74.65; H, 4.00; N, 7.63%.

Supplementary data

The cif file can be obtained as CCDC Deposit no. 751115. These data may be obtained free of charge by emailing: www.ccdc.cam.ac.uk/data_request/cif.

The authors thank IISc, Bangalore, and MKU, Madurai, for NMR, and IICT, Hyderabad, for mass spectral data. The authors acknowledge the financial assistance of UGC, New Delhi, India, under Grant no. F31-122/2005.

Received 13 May 2009; accepted 27 October 2009
Paper 09/0585 doi: 10.3184/030823409X12572441140695
Published online: 8 December 2009

References

1 S. Gemma, G. Kukreja, C. Fattorusso, M. Persica, M.P. Romano, M. Altarelli, L. Savini, G. Campiani, D. Fattorusso, N. Basilico, D. Taramelli, V. Yardley and S. Butini, *Biol. Org. Med. Chem. Lett.*, 2006, **16**, 5384.

2 F.H.S. Curd, C.G. Raison and F.L. Rose, *J. Chem. Soc*., 1947, 898.
3 C.C. Price, E.W. Maynert and V. Boekelheide, *J. Org. Chem*., 1949, **14**, 484.
4 S. Rossiter, J.M. Peron, Philip J. Whitfield and K. Jones, *Bioorg. Med. Chem. Lett.,* 2005, **15,** 4806.
5 E.G. Paronikyan, S.N. Sirakanyan, A.S. Noravyan, T.O. Asatryan, K. Zh. Markaryan and R.A. Aleksanyan, *Khim.-Farm. Zh.,*, 1996, **30**, 365.
6 S.Z. Vatsadze, M.L. Kostochka, V.P. Lezina, V.G. Vinokurov, P.M. Klodt and N.V. Zyk, *Russ. Chem. Bull. Int. Ed*., 2005, **54**, 257.
7 L. Zhuang, J.S. Wai, M.W. Embrey, T.E. Fisher, M.S. Egbertson, L.S. Payne, J.P. Guare, J.P. Vacca, D.J. Hazuda, P.J. Felock, A.L. Wolfe, K.A. Stillmock, M.V. Witmer, G. Moyer, W.A. Schleif, L.J. Gabryelski, Y.M. Leonard, J.J. Lynch, S.R. Michelson and S.D. Young, *J. Med. Chem.,* 2003, **46**, 453.
8 M. Atanasova, S. Ilieva and B. Galabov, *Euro. J. Med. Chem.*, 2007, **42**, 1184.
9 A. Gopalsamy, M. Shi, D.H. Boschelli, R. Williamson, A. Olland, Y. Hu, G. Krishnamurthy, X. Han, K. Arndt and B. Guo, *J. Med. Chem*., 2007, **50**, 5547.
10 A. Gopalsamy, M. Shi and R. Nilakantan, *Org. Proc. Res. Dev.*, 2007, **11**, 450.
11 D. Leslie, R. Thomas, Z. Li, B.C. Bruce and D.A. Williams, *J. Med. Chem*., 2003, **46**, 1049.
12 S.P. Mackay and O. Meth-Cohn, *Synthesis,* 2000, 1121.
13 M. Sekar and K.J. Rajendra Prasad, *Indian J. Chem.*, 1999, **38B**, 969.
14 A. Da Settimo, G. Biaji, G. Primfiore, P.L. Ferrarini, O. Livi and A.M. Marini, *J. Het. Chem*., 1980, **17**, 1225.
15 M. Kidwai and S. Kohli, *Indian J. Chem.*, 2001, **40B**, 248.
16 F.J. Buchman and C.S. Hamilton, *J. Am.Chem. Soc*., 1942, **64**, 1357.
17 M.V. Bhatt and S.U. Kulkarni, *Synthesis*, 1983, 249-282.