Journal of Molecular Structure 1358 (2026) 145406

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: www.elsevier.com/locate/molstr

Regioselectivity and steric effects in the phosphorus oxychloride–mediated synthesis of methyl-substituted dibenzo-naphthyridines

M. Sangeetha [a,*], S. Packiaraj [b,*], M. Manoj [c], J. Anitha [d], K. Banupriya [e]

[a] Science and Humanities (Chemistry), Dhanalakshmi Srinivasan College of Engineering, Coimbatore, 641105, Tamil Nadu, India
[b] Science and Humanities (Chemistry), Kangeyam Institute of Technology, Tirupur, 638108, Tamilnadu, India
[c] Department of Chemistry, Bharathiar University, Coimbatore, 641046, Tamilnadu, India
[d] Vedantaa Institute of Medical Science, Vedanta Hospital and Research Center, Dahanu, Maharashtra, 401606, India
[e] Science and Humanities (Chemistry), Sri Krishna College of Engineering and Technology, Coimbatore, 641008, Tamil Nadu, India

ARTICLE INFO

Keywords:
m-Toluidine
Malonic acid
Phosphorus oxychloride
Regioselectivity
DFT calculations
Dibenzo-naphthyridines

ABSTRACT

The reaction of *m*-toluidine with malonic acid in the presence of phosphorus oxychloride predominantly yielded the 5-methyl isomer (**1a**), with minor formation of the 7-methyl isomer (**1b**). Density functional theory (DFT) calculations at the B3LYP/6-311++G(d,p) level showed that the 7-methyl isomer is thermodynamically more stable by 6.59 kcal mol^{-1}, indicating that the experimentally favored 5-methyl isomer forms under kinetic control. The preferential formation of **1a** is attributed to steric and kinetic effects during cyclization. Owing to the inseparability of the two isomers, subsequent reactions afforded mixtures of angular and linear dibenzo-naphthyridines, characterized by ^{1}H NMR and confirmed by GC–MS analysis. Overall, this study provides insight into the regioselectivity and steric effects governing dibenzo-naphthyridine formation, highlighting a case where kinetic control overrides thermodynamic stability.

1. Introduction

Cyclic polyaza compounds such as quinolines, naphthyridines, and phenanthridines represent essential structural motifs in many naturally occurring alkaloids and their synthetic analogues, exhibit a wide range of biological activities [1]. Among these, the quinoline nucleus serves as a central pharmacophore in the design of medicinally important compounds, particularly those possessing potent antimalarial properties [2], as well as diverse biological activities including antimicrobial, antiviral, and anticancer effects [3–5]. Quinoline derivatives have been widely investigated as inhibitors of tyrosine kinases, proteasome, topoisomerase, tubulin polymerization, and are also recognized for their involvement in DNA repair processes [6]. Natural alkaloids such as camptothecin, containing the quinoline nucleus, exhibit notable antitumor activity [7,8]. In addition, synthetic anilinoquinoline derivatives have substantiated significant antimalarial efficacy [9] and have extensively utilized as valuable intermediates in the synthesis of complex heterocyclic frameworks such as indoloquinolines [10] and dibenzonaphthyridines [11].

In recent years, naphthyridines and their functional derivatives have attracted substantial interest from synthetic organic chemists owing to their diverse pharmacological properties, including antiarrhythmic [12], analgesic [13], anti-HIV [14,15], and anticancer [16] activities. To construct isomeric forms of angular and linear dibenzonaphthyridines, our earlier studies [17,18] employed chloroquinolines as precursors and anilinoquinolines as key intermediates. One such approach utilized the Bernthsen reaction, involving the condensation of anilinoquinolines with benzoic acid in the presence of polyphosphoric acid (PPA) as a catalyst. In a modified procedure, Eaton's reagent was adopted as an alternative for PPA to improve the product yield [19]. In both cases, the formation of angular dibenzonaphthyridines was thermodynamically favored over the linear isomers when 2,4-dichloroquinoline was employed as starting material and 2,4-bisanilinoquinoline was employed as intermediate.

The preparation of 2,4-dichloroquinoline generally involves the reaction of substituted anilines with malonic acid in the presence of phosphorus oxychloride at elevated temperatures (~100°C). In our previous reports, para- and ortho-toluidines were effectively utilized as starting materials, yielding a single isomer of 2,4-dichloroquinolines. However, meta-toluidine has not been previously explored, primarily due to the anticipated formation of a mixture of positional isomers. In the present work, we report the first synthesis of isomeric 5-methyl- and

* Correspond authors.
E-mail addresses: sangeethachem17@gmail.com (M. Sangeetha), srajguru1987@gmail.com (S. Packiaraj).

https://doi.org/10.1016/j.molstruc.2026.145406
Received 16 November 2025; Received in revised form 13 January 2026; Accepted 17 January 2026
Available online 17 January 2026

7-methyl-2,4-dichloroquinolines derived from m-toluidine and malonic acid under phosphorus oxychloride-mediated conditions. A literature precedent [20] indicates that when *m*-chloroaniline is employed as a substrate for quinoline synthesis, 7-chloroquinoline forms as the major product (67%) along with 5-chloroquinoline (33%). In contrast, our results reveal the formation of sterically hindered 2,4-dichloro-5-methylquinoline as the major product, while the sterically favored 2,4-dichloro-7-methylquinoline yielded as the minor component.

The two isomeric products were unambiguously characterized and differentiated using ^{1}H NMR and GC–MS analyses, providing distinct spectral signatures for each positional isomer. Furthermore, these chloroquinoline derivatives were utilized to synthesize the corresponding anilinoquinolines, which were subsequently employed in the formation of angular and linear dibenzonaphthyridines. This study is novel in its demonstration of *m*-toluidine as an effective substrate for dichloroquinoline formation, leading to an unexpected product distribution pattern. The work also establishes clear ^{1}H NMR-based differentiation criteria for methyl-substituted 2,4-dichloroquinoline isomers, thereby offering valuable structural insight for future synthetic and mechanistic studies involving substituted quinoline derivatives.

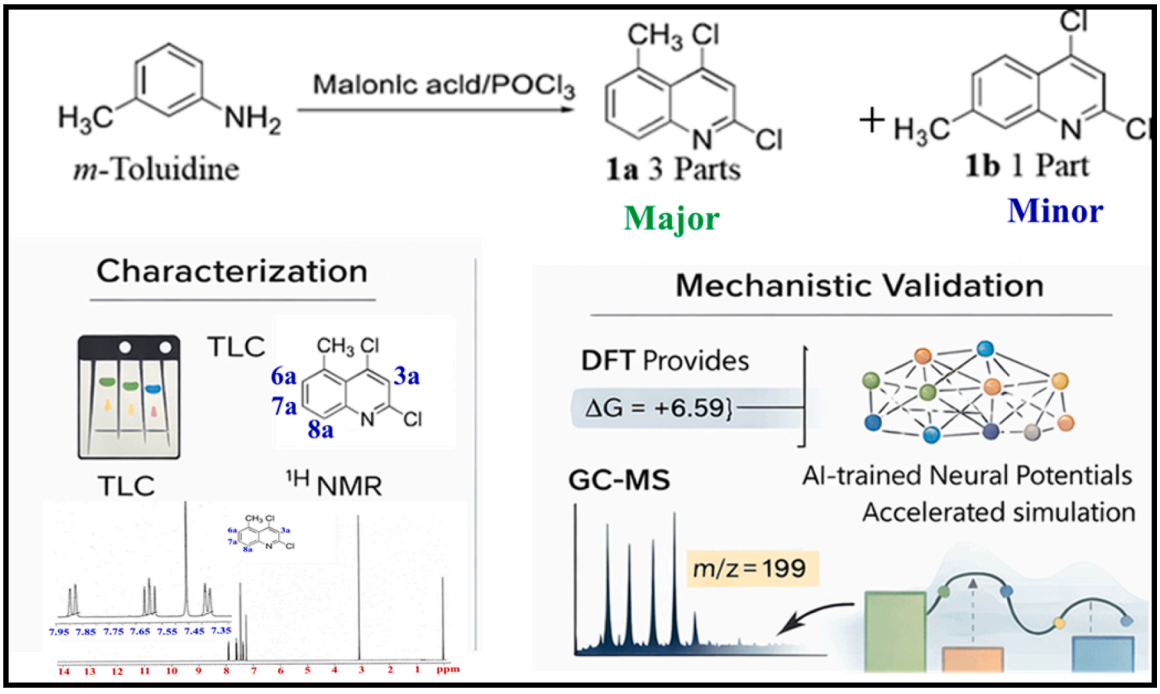
2. Results and discussion

The reaction of *m*-toluidine with malonic acid in the presence of phosphorus oxychloride afforded a mixture of 2,4-dichloro-5-methylquinoline and 2,4-dichloro-7-methylquinoline (Scheme 1). Although the crude product exhibited a single spot on TLC and a characteristic C=N stretching band at 1585 cm^{-1} in the IR spectrum (Fig. 1), detailed ^{1}H NMR analysis (Fig. 2) revealed the coexistence of two positional isomers in an approximate 3:1 ratio (5-methyl:7-methyl). Two singlets integrating to three protons each appeared at δ 3.03 and δ 2.58 in the ratio 3:1, corresponding to the methyl groups at C5 and C7, respectively. The downfield signal at δ 3.03 was assigned to C5–CH_3, deshielded by the adjacent 4-chloro substituent. The aromatic region further supported this assignment: a one-proton triplet at δ 7.60 (J = 7.82 Hz) and a one-proton singlet at δ 7.81 corresponded to the C7–H of the 5-methyl isomer and the C8–H of the 7-methyl isomer, respectively, also maintaining a 3:1 ratio. The C3–H protons of both isomers appeared as singlets at δ 7.47 and δ 7.44 in the same proportion, while the remaining aromatic protons resonated between δ 7.36 and 8.09.

The GC–MS spectrum (Fig. 3) exhibited two retention peaks of identical molecular ion (m/z = 199) in a 3:1 area ratio, confirming the presence of two isomeric products. The combined spectroscopic data thus confirm the formation of 2,4-dichloro-5-methylquinoline (major) and 2,4-dichloro-7-methylquinoline (minor). Interestingly, the formation of the sterically hindered 5-methyl isomer as the major product is contrary to conventional steric expectations. This unusual regioselectivity may arise from electronic effects during cyclization or kinetic control of the annulation step, where resonance stabilization near the 4-chloro substituent favours bond formation at C5. Further mechanistic studies, including computational modeling under variable reaction conditions, are underway to clarify the origin of this unanticipated regioselectivity. In parallel, extended mechanistic validation through multivariate thermal and electronic modeling is in progress to rationalize this unexpected selectivity, bridging experimental observations with theoretical insights as shown in Scheme 1.

Attempts to separate the two isomers by column chromatography were unsuccessful; hence, the crude mixture was subjected to crystallization using an ethyl acetate–ethanol solvent system. This process yielded two fractions-one as colourless prisms and the other as a spongy residue. The colourless prisms were manually separated and analysed by ^{1}H NMR spectroscopy (Fig. 4). The spectrum exhibited a three-proton singlet at δ 3.03 (C5–CH_3), a one-proton doublet at δ 7.38 (J = 7.16 Hz, C6–H), a one-proton singlet at δ 7.47 (C3–H), a one-proton triplet at δ 7.60 (J = 7.82 Hz, C7–H), and a one-proton doublet at δ 7.89 (J = 8.44 Hz, C8–H). Based on these resonances, the colourless crystalline compound was identified as 2,4-dichloro-5-methylquinoline (**1a**), while the 7-methyl isomer (**1b**) remained un-isolated in pure form.

To understand the predominance of the sterically hindered 5-methyl isomer, density functional theory (DFT) calculations were performed using the B3LYP/6-311++G(d,p) level of theory [21]. The computed total energies of **1a** and **1b** were −853787.9772 and −853794.5709 kcal mol^{-1}, respectively, indicating that the 7-methyl isomer is thermodynamically more stable by 6.59 kcal mol^{-1} (Table 1). Despite its lower



Scheme 1. Regioselective synthesis of chlorinated methyl-substituted quinoline derivatives *via* $POCl_3$-mediated, with observed product distribution ratios. Product identification was confirmed by TLC, ^{1}H NMR, and GC–MS (m/z = 199), while DFT calculations supported the observed regioselectivity (ΔG = +6.59).

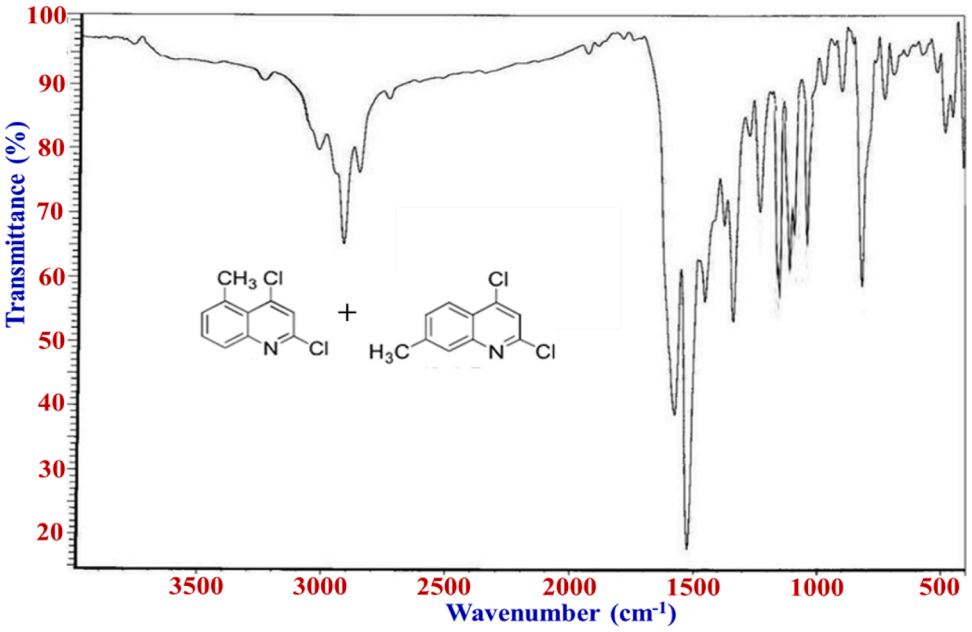


Fig. 1. IR Spectrum of mixture of 2,4-dichloro-5-methylquinoline (**1a**) and 2,4-dichloro-7- methylquinoline (**1b**).

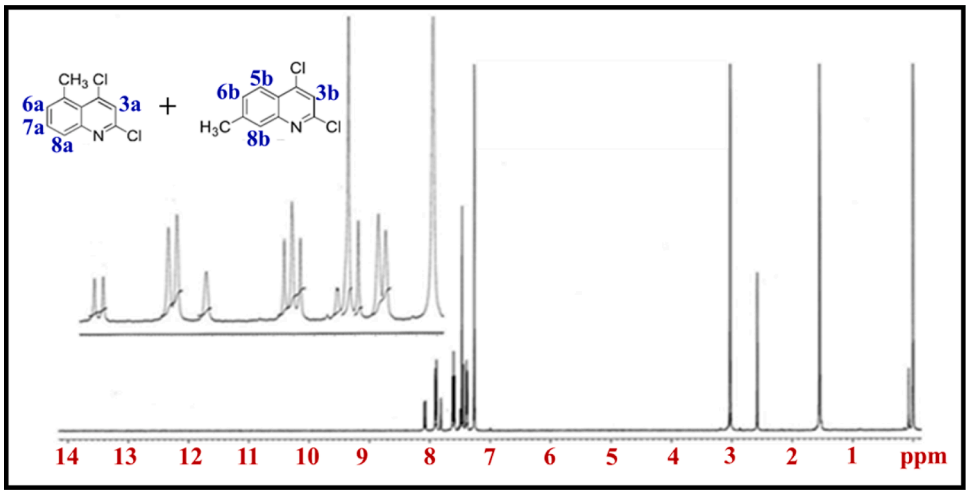


Fig. 2. ^{1}H NMR of mixture of 2,4-dichloro-5-methylquinoline (**1a**) and 2,4-dichloro-7- methylquinoline (**1b**).

energy, the 7-methyl isomer formed only in minor proportion experimentally, suggesting that the reaction proceeds under kinetic control rather than favouring thermodynamic equilibrium. The dominance of **1a** may thus arise from electronic effects during the annulation step, where resonance stabilization near the 4-chloro substituent favours cyclization at the C5 position. Additionally, solubility and crystallization factors may contribute to enrichment of the 5-methyl product. The combination of experimental and computational findings underscores an unusual regioselectivity, in which the sterically less favoured 5-methyl isomer predominates, offering valuable insight into the mechanistic behavior of phosphorus oxychloride–mediated quinoline ring formation.

Therefore, the mixture of the two isomers was utilized to prepare dibenzonaphthyridines through potential intermediates, anilinoquinolines, as shown in Schemes 2, 3, and 4. Although the starting compounds, 5- and 7-methyl isomers of 2,4-dichloroquinoline, were present in a ratio of 3:1, the ratio of the isomeric products obtained from the reactions in Schemes 2, 3, and 4 varied from 1:1 to 10:1, as confirmed by ^{1}H NMR spectra and, in some cases, GC-MS spectra. Since the 5-methyl isomer predominates over the 7-methyl isomer in the starting 2,4-dichloroquinoline, their corresponding isomeric products generally showed higher ratios in most cases. However, the ratios of the two isomers obtained in the final products varied unpredictably, and the reason for this remains ambiguous. The different isomer ratios of the final products are listed in Table 2, with ^{1}H NMR and GC-MS spectra provided in the Electronic Supplementary Information (ESI; Figures S1–S31).

3. Conclusions

In this study, we report the first successful utilization of *m*-toluidine in the phosphorus oxychloride afforded a mixture of kinetically favoured 2,4-dichloro-5-methylquinoline as major entity and thermodynamically favoured 2,4-dichloro-7-methylquinoline as minor one. The preferential formation of the sterically hindered 5-methyl isomer is attributed to electronic effects near the 4-chloro substituent that favor cyclization at C5. Subsequent conversion of the inseparable isomeric mixture into anilinoquinolines and dibenzonaphthyridines produced products with varying isomeric ratios, reflecting the combined influence

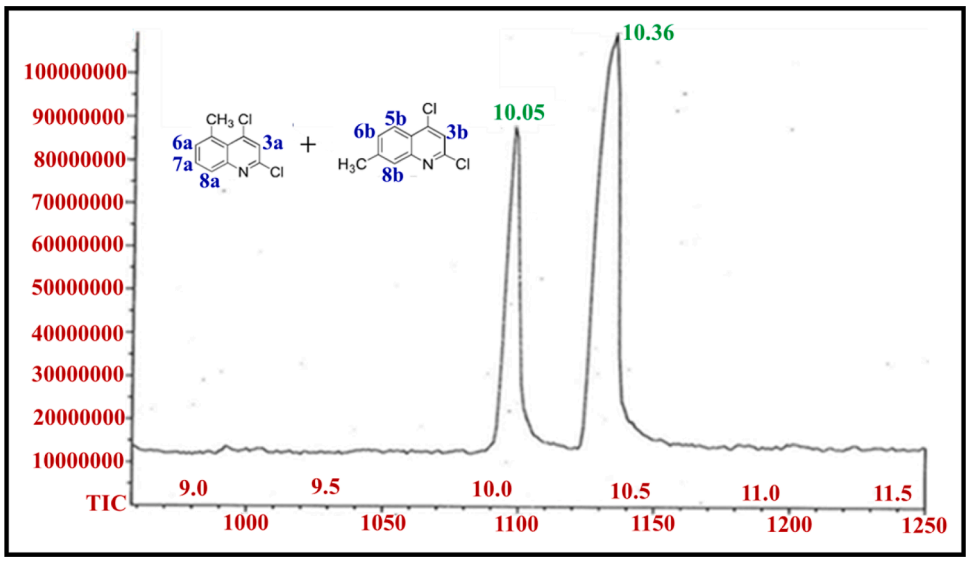


Fig. 3. GC-Mass spectrum of mixture of 2,4-dichloro-5-methylquinoline (**1a**) and 2,4-dichloro-7- methylquinoline (**1b**).

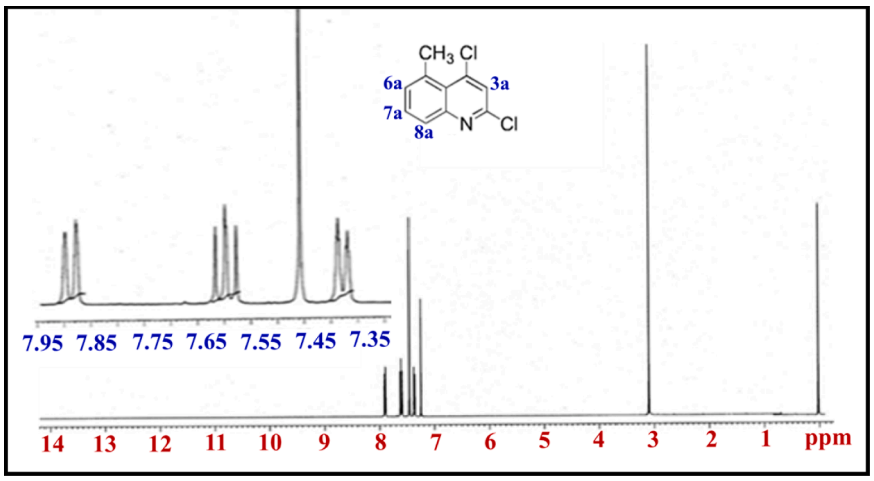


Fig. 4. ^{1}H NMR of mixture of 2,4-dichloro-5-methylquinoline (**1a**).

of steric, electronic, and solubility effects. Overall, this work highlights a rare case where kinetic control overrides thermodynamic stability, offering new insight into regioselective quinoline-based heterocyclic framework formation from *m*-toluidine.

Experimental Section

Preparation of 2,4-dichloro-5-methylquinoline (1a) and 2,4-dichloro-7-methylquinoline (1b): General Procedure

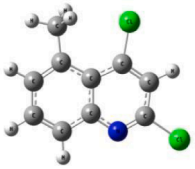
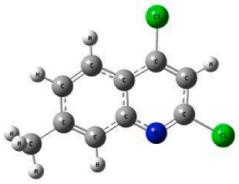
An appropriate mixture of m-toluidine (0.1 mol) and malonic acid (0.1 mol) was heated with phosphorus oxychloride (100 mL) over a water bath for 16 hours. The resulting crude product was poured into crushed ice. The filtrate was subjected to column chromatography, and the product was eluted with petroleum ether. Although the product showed a single spot on TLC, ^{1}H NMR revealed the presence of two isomers. Crystallization from an ethyl acetate:ethanol mixture afforded one of the isomers (C5-isomer) as colorless prisms, while the other remained spongy as a white solid.

Colorless prisms ($C_{10}H_7Cl_2N$): m.p.: 82–86 °C; Yield: 15.40 g (73%); IR (KBr) νmax, cm^{-1} (Fig. 1): 1585, 1521, 1148, 1047, 1039; ^{1}H NMR (400 MHz, $CDCl_3$, Fig. 2) δ, ppm: 2.58 (s, 3H, C7-CH_3), 3.03 (s, 3H, C5-CH_3; ratio of C5-CH_3 to C7-CH_3 = 3:1), 7.44 (s, 1H, C3-H for C7-isomer), 7.47 (s, 1H, C3-H for C5-isomer; ratio of C3-H for C5 to C7 isomer = 3:1), 7.36–8.09 (m, 4H, C6-, C8-H for C5-isomer and C5-, C6-H for C7-isomer), 7.60 (t, 1H, C7-H, J = 7.82 Hz for C5-isomer), 7.81 (s, 1H, C8-H for C7-isomer). GC-MS (Fig. 3) exhibited two retention peaks with a peak area ratio of 3:1. Molecular formula of the isomers: $C_{10}H_7Cl_2N$.

Preparation of: 4-chloro-5,4′-dimethyl-2-(N-phenylamino) quinoline (2a), 4-chloro-7,4′-dimethyl-2-(N-phenylamino)quinoline (2b), 2-chloro-5,4′-dimethyl-4-(N-phenylamino)quinoline (3a), 2-chloro-7,4′-dimethyl-4-(N-phenylamino)quinoline (3b), 5,4′,4″-trimethyl-2,4-bis-(N-phenylamino)quinoline (4a), and 7,4′,4″-trimethyl-2,4-bis-(N-phenylamino)quinoline (4b).

A mixture of the appropriate 2,4-dichloroquinolines (1a and 1b, 0.01 mol) and *p*-toluidine (0.01 mol) was heated under neat conditions at 160°C for 30 minutes. The crude product was washed with water, dried, and analyzed by TLC, which indicated the presence of three products. These were separated by column chromatography over silica gel, using petroleum ether:ethyl acetate (99:1 and 98:2) to afford 4-chloro-5,4′-dimethyl-2-(N-phenylamino)quinoline (**2a**) and 4-chloro-7,4′-dimethyl-2-(N-phenylamino)quinoline (**2b**), which were recrystallized from ethanol, and 2-chloro-5,4′-dimethyl-4-(N-phenylamino)quinoline (**3a**) and 2-chloro-7,4′-dimethyl-4-(N-phenylamino)quinoline (**3b**), also recrystallized from ethanol. The third fraction was eluted with ethyl acetate:methanol (95:5) to give 5,4′,4″-trimethyl-2,4-bis-(N-phenylamino)quinoline (**4a**) and 7,4′,4″-trimethyl-2,4-bis-(N-phenylamino)

Table 1
Calculated energies and energy differences of possible conformers of 5-methyl 2,4- dichloroquinoline (**1a**) and 7-methyl 2,4-dichloroquinoline (**1b**) by DFT/B3lyp/6-311++g (d,p) method with their optimized geometry.

Compounds	Energy		Optimised geometry
	Hartree	kcal/mol	
5-methyl 2,4-dichloroquinoline (**1a**)	-1360.596608	-853787.9772	
7-methyl 2,4-dichloroquinoline (**1b**)	-1360.607115	-853794.5709	

quinoline (**4b**), which were recrystallized from methanol.

Yellow solid ($C_{17}H_{15}ClN_2$); m.p.: 118–122 °C; Yield: 0.620 g (22%); IR (KBr) νmax, cm^{-1}: 3245 (NH), 1596 (C=N), 1517, 1112; ^1H NMR (400 MHz, $CDCl_3$), (Fig. S1 & S3, see Supporting Information) δ, ppm: 2.41 (overlapping singlets, 6H, two C4′-CH_3 each for C5 and C7 isomers), 2.56 (s, 3H, C7-CH_3), 2.95 (s, 3H, C5-CH_3; ratio of C5-CH_3 to C7-CH_3 = 3:1), 6.65–6.68 (broad s, 2H, C2-NH each for C5 and C7 isomers), 7.00 (s, 1H, C3-H for C7-isomer), 7.03 (s, 1H, C3-H for C5-isomer; ratio of C3-H for C5 to C7 isomer = 3:1), 7.21–7.96 (m, 12H, C6-, C8-, C2′-, C3′-, C5′-, C6′-H for C5-isomer and C5-, C6-, C2′-, C3′-, C5′-, C6′-H for C7-isomer), 7.61 (t, 1H, C7-H, J = 8.24 Hz for C5-isomer), 7.72 (s, 1H, C8-H for C7-isomer). GC-MS (Figs. S2 & S4; see Supporting Information) exhibited two retention peaks with peak areas in the ratio 3:1. Molecular formula of the isomers: $C_{17}H_{15}ClN_2$.

Preparation of 2-Chloro-5,4′-dimethyl-4-(N-phenylamino)quinoline (3a) and 2-chloro-7,4′-dimethyl-4-(N- phenylamino)quinoline (3b)

Pale yellow prisms ($C_{17}H_{15}ClN_2$); m.p.: 125–129 °C; Yield: 0.733 g (26%); IR (KBr) νmax, cm^{-1}: 3340 (NH), 1600 (C=N), 1529, 1079; ^1H NMR (400 MHz, $CDCl_3$) δ, ppm: 2.43 (overlapping singlets, 6H, two C4′-CH_3 each for C5 and C7 isomers), 2.51 (s, 3H, C7-CH_3), 2.90 (s, 3H, C5-CH_3; ratio of C5-CH_3 to C7-CH_3 = 3:1), 6.68–6.71 (broad s, 2H, C2-NH each for C5 and C7 isomers), 6.42 (s, 1H, C3-H for C7-isomer), 6.49 (s, 1H, C3-H for C5-isomer; ratio of C3-H for C5 to C7 isomer = 3:1), 7.19–7.93 (m, 12H, C6-, C8-, C2′-, C3′-, C5′-, C6′-H for C5-isomer and C5-, C6-, C2′-, C3′-, C5′-, C6′-H for C7-isomer), 7.67 (t, 1H, C7-H, J = 8.24 Hz for C5-isomer), 7.75 (s, 1H, C8-H for C7-isomer). Molecular formula of the isomers: $C_{17}H_{15}ClN_2$.

Preparation of 5,4′,4″-Trimethyl-2,4-bis-(N-phenylamino)quinoline (4a) and 7,4′,4″-trimethyl-2,4-bis-(N- phenylamino)quinoline (4b)

Pale yellow needles ($C_{24}H_{23}N_3$); m.p.: 130–134 °C; Yield: 0.706 g (20%); IR (KBr) νmax, cm^{-1}: 3241 (NH), 1617 (C=N), 1517, 1084; ^1H NMR (400 MHz, DMSO-d_6), (Fig. S3, see Supporting Information) δ, ppm: 2.24–2.26 (m, 12H, C4′-CH_3 and C4″-CH_3 for C5 and C7 isomers), 2.27 (s, 3H, C7-CH_3), 2.90 (s, 3H, C5-CH_3; ratio of C5 to C7 isomers = 5:2), 6.03 (s, 1H, C3-H for C7-isomer), 6.09 (s, 1H, C3-H for C5-isomer; ratio of C5 to C7 isomers = 5:2), 6.96–8.35 (m, 22H, C5, C6, C8, C2′, C3′, C5′, C6′, C2″, C3″, C5″, C6″-H for C7-isomer and C6, C7, C8, C2′, C3′, C5′, C6′, C2″, C3″, C5″, C6″-H for C5-isomer), 9.49–9.51 (broad s, 2H, C2-NH for C5 and C7 isomers), 9.53–9.55 (broad s, 2H, C4-NH for C5 and C7 isomers), 12.53–12.60 (broad s, 2H, N1-H for C5 and C7 isomers). GC-MS (Fig. S4, see Supporting Information) exhibited two retention peaks with peak areas in the ratio 5:2. Molecular formula of the isomers: $C_{24}H_{23}N_3$.

Preparation of 1,9,4′-trimethyl-7-phenyl-6-(N-phenylamino) dibenzo [b,h] [1,6] naphthyridine (5a) and 3,9,4′-trimethyl-7-phenyl-6-(N-phenylamino)dibenzo [b,h] [1,6] naphthyridine (5b).

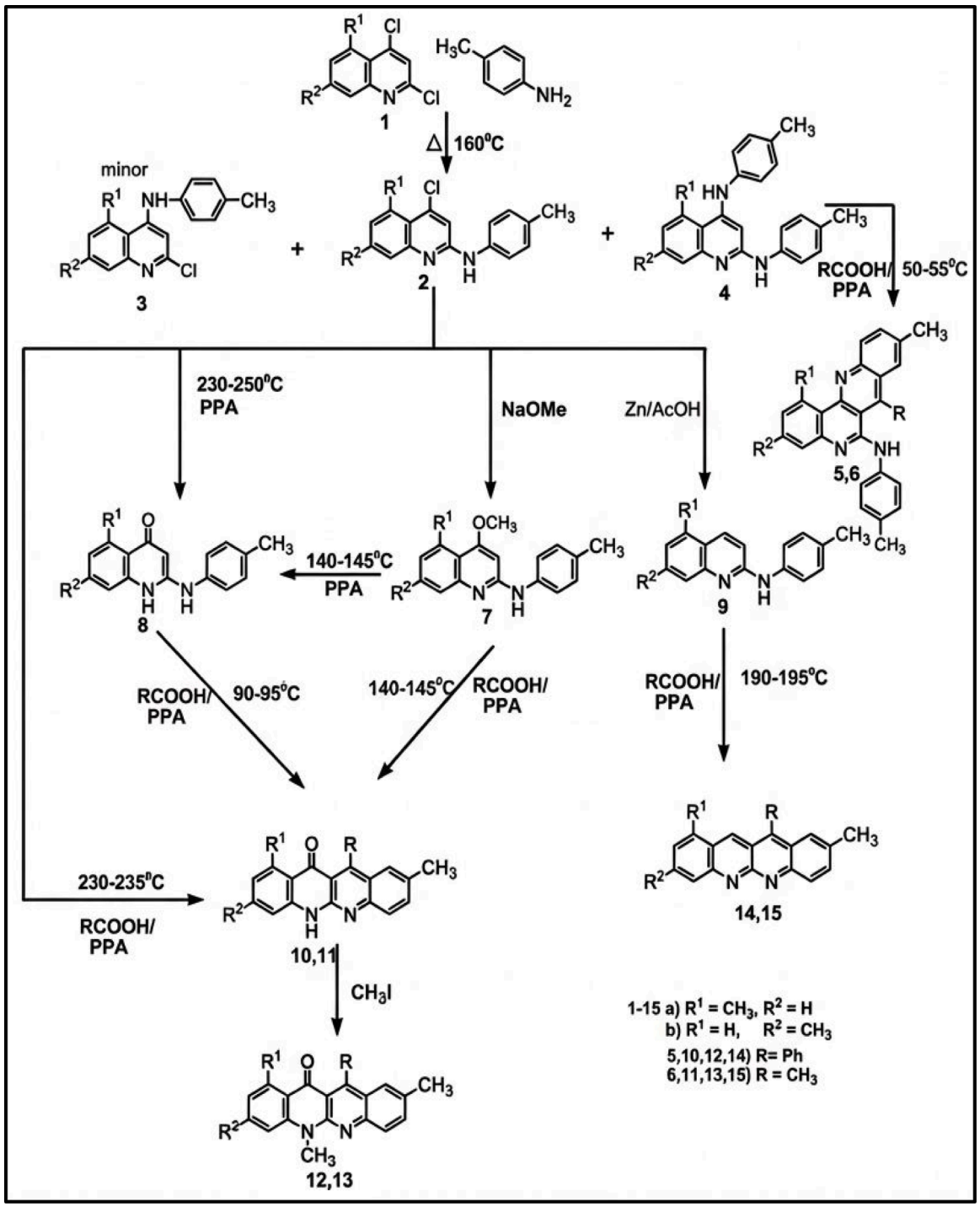
An appropriate mixture of 4′,4″-dimethyl-2,4-bis-(N-phenylamino) quinoline (**4a** and **4b**, 0.001 mol) and benzoic acid (0.0011 mol) was added to polyphosphoric acid (3 g of P_2O_5 in 1.5 mL of H_3PO_4) and maintained at 50–55 °C for 5 hours. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was poured into ice water and neutralized with saturated $NaHCO_3$ solution to remove excess benzoic acid. The precipitate was filtered, dried, and purified by column chromatography over silica gel using petroleum ether:ethyl acetate (99:1) to afford **5a** and **5b**, which were recrystallized from ethyl acetate as orange prisms.

Orange prisms ($C_{31}H_{25}N_3$); m.p.: 253–257 °C; Yield: 0.153 g (35%); IR (KBr) νmax, cm^{-1}: 3420 (NH), 1595 (C=N), 1510, 1353; ^1H NMR (300 MHz, $CDCl_3$, Fig. S5, see Supporting Information) δ, ppm: 2.31 (overlapping singlets, 6H, C4′-CH_3 for C1 and C3 isomers), 2.49 (s, 3H, C9-CH_3 for C1-isomer), 2.50 (s, 3H, C9-CH_3 for C3-isomer; ratio of C1 to C3 isomer = 10:1), 2.63 (s, 3H, C3-CH_3), 3.42 (s, 3H, C1-CH_3; ratio of C1 to C3-CH_3 = 10:1), 6.96–8.09 (m, 31H, C2-, C3-, C4-, C8-, C10-, C11-, C2′-, C3′-, C5′-, C6′-, C2″-, C3″-, C4″-, C5″-, C6″-H and C6-NH for C1-isomer, and C2-, C4-, C8-, C10-, C11-, C2′-, C3′-, C5′-, C6′-, C2″-, C3″-, C4″-, C5″-, C6″-H and C6-NH for C3-isomer), 9.12 (d, 1H, C1-H, J = 8.32 Hz for C3-isomer). Molecular formula of the isomers: $C_{31}H_{25}N_3$.

Preparation of 1,7,9,4′-tetramethyl-6-(N-phenylamino)dibenzo [b,h] [1,6] naphthyridine (6a) and 3,7,9,4′-tetramethyl-6-(N-phenylamino)dibenzo [b,h] [1,6] naphthyridine (6b).

An appropriate mixture of 4′,4″-dimethyl-2,4-bis-(N-phenylamino) quinoline (**4a** and **4b**, 0.0010 mol) and acetic acid (0.0011 mol, 0.1 mL) was added to polyphosphoric acid (3 g of P_2O_5 in 1.5 mL of H_3PO_4) and stirred at 50–55 °C for 5 hours. The reaction was monitored by TLC. Upon completion, the mixture was poured into ice water, extracted with ethyl acetate, adsorbed, filtered, dried, and purified by column chromatography over silica gel using petroleum ether:ethyl acetate (98:2) to afford **6a** and **6b**. The products were recrystallized from ethyl acetate as orange prisms.

Orange prisms ($C_{26}H_{23}N_3$); m.p.: 213–215 °C; Yield: 0.1244 g (33%);



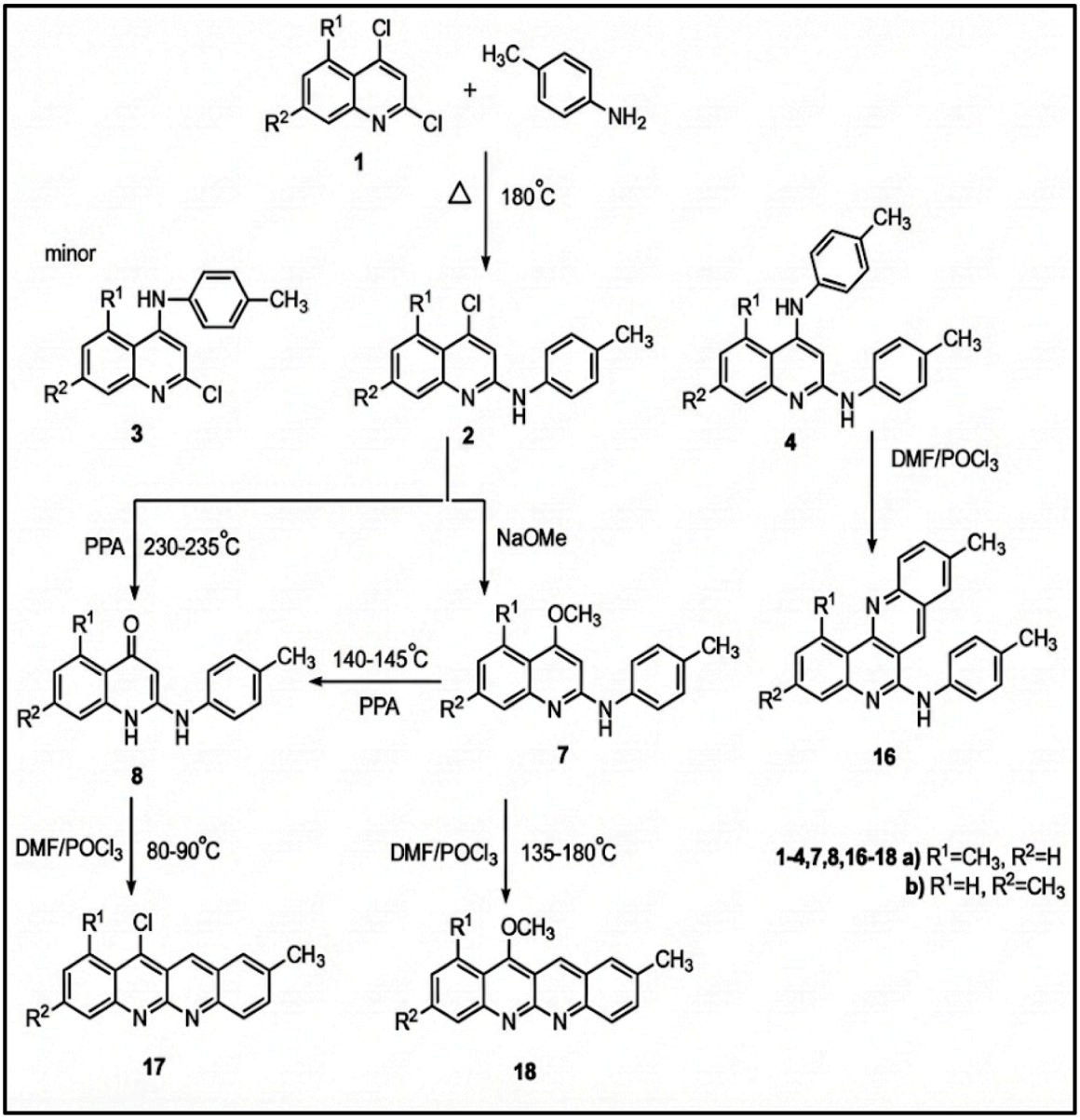
Scheme 2. Regioselective reaction pathway using $POCl_3$ for dibenzo-naphthyridine synthesis, highlighting intermediate stages and reaction parameters.

IR (KBr) νmax, cm^{-1}: 3410 (N-H), 1598 (C=N), 1510, 1341; ^1H NMR (300 MHz, $CDCl_3$, Fig. S6, see Supporting Information) δ, ppm: 2.39 (overlapping singlets, 6H, C4′-CH_3 for C1 and C3 isomers), 2.57 (overlapping singlets, 6H, C9-CH_3 for C1 and C3 isomers), 2.65 (s, 3H, C3-CH_3), 3.08 (s, 3H, C7-CH_3 for C1-isomer), 3.10 (s, 3H, C7-CH_3 for C3-isomer; ratio of C1 to C3 isomers = 8:1), 3.41 (s, 3H, C1-CH_3), 6.91–8.12 (m, 21H, C2-, C3-, C4-, C8-, C10-, C11-, C2′-, C3′-, C5′-, C6′-H, C6-NH for C1-isomer, and C2-, C4-, C8-, C10-, C11-, C2′-, C3′-, C5′-, C6′-H, C6-NH for C3-isomer), 8.98 (d, 1H, C1-H, J = 8.32 Hz for C3-isomer). Molecular formula of the isomers: $C_{26}H_{23}N_3$.

Preparation of 4-methoxy-5,4′-dimethyl-2-(N-phenylamino) quinoline (7a) and 4-methoxy-7,4′-dimethyl-2-(N-phenylamino) quinoline (7b).

4-Chloro-4′-methyl-2-(N-phenylamino)quinoline (**2a** and **2b**, 0.004 mol) was added to a sodium methoxide solution (5 g of sodium in 30 mL of methanol) and heated over a water bath for 10 hours. The reaction was monitored by TLC. Upon completion, the excess methanol was evaporated, and the reaction mixture was poured into ice water and neutralized 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 afford **7a** and **7b**, which were recrystallized from methanol as colorless needles.

Colorless needles ($C_{18}H_{18}N_2O$); m.p.: 138–142 °C; Yield: 0.389 g (35%); IR (KBr) νmax, cm^{-1}: 3387 (NH), 1655, 1521, 1439, 1240 (O-



Scheme 3. Regioselective multistep synthesis of methyl-substituted dibenzo-naphthyridine derivatives *via* $POCl_3$-mediated with labeled intermediates and thermal conditions.

CH_3); ^1H NMR (300 MHz, $CDCl_3$, Fig. S7, see Supporting Information) δ, ppm: 2.35 (overlapping singlets, 6H, C4′-CH_3 for C5 and C7 isomers), 2.47 (s, 3H, C7-CH_3), 2.76 (s, 3H, C5-CH_3; ratio of C7-CH_3 to C5-CH_3 = 2:1), 3.87 (s, 3H, O-CH_3 for C5-isomer), 3.92 (s, 3H, O-CH_3 for C7-isomer; ratio of C5 to C7 isomers = 2:1), 6.27 (s, 1H, C3-H for C7-isomer), 6.39 (s, 1H, C3-H for C5-isomer; ratio of C5 to C7 isomers = 2:1), 6.63–6.71 (broad s, 2H, C2-NH for C5 and C7 isomers), 6.97–7.56 (m, 13H, C6-, C7-, C8-, C2′-, C3′-, C5′-, C6′-H for C5-isomer and C6-, C8-, C2′-, C3′-, C5′-, C6′-H for C7-isomer), 7.87 (d, 1H, C5-H, J = 8.24 Hz for C7-isomer). Molecular formula of the isomers: $C_{18}H_{18}N_2O$.

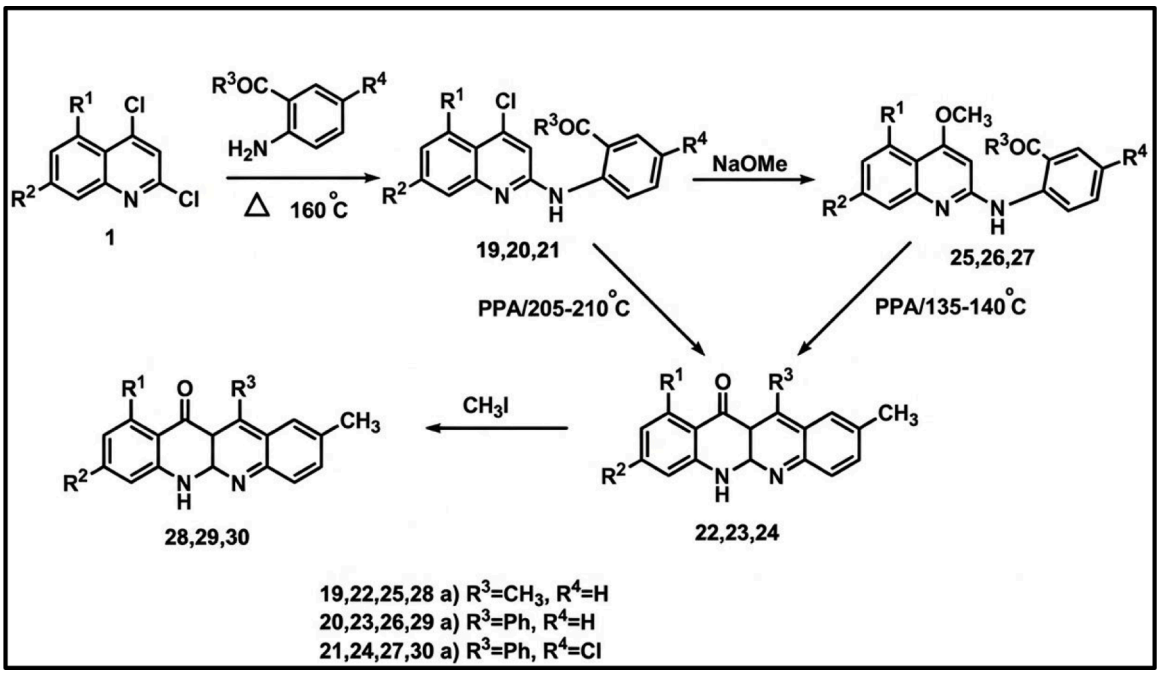
Preparation of 5,4′-dimethyl-2-(N-phenylamino)quinolin-4 (1H)-one (8a) and 7,4′-dimethyl-2-(N-phenylamino)quinolin-4 (1H)-one (8b).

4-Methoxy-4′-methyl-2-(N-phenylamino)quinoline (**7a** and **7b**, 0.001 mol) was added to PPA (3 g of P_2O_5 in 1.5 mL of H_3PO_4) and heated at 140–145 °C for 4 hours. The reaction was monitored by TLC. Upon completion, the reaction mixture was poured into crushed ice. The resulting precipitate was filtered, dried, and purified by column chromatography, eluting with petroleum ether:ethyl acetate (70:30) to afford **8a** and **8b**, which were recrystallized from methanol as a white solid.

White solid ($C_{17}H_{16}N_2O$); m.p.: 280–284 °C; Yield: 0.105 g (40%); IR (KBr) νmax, cm^{-1}: 3468 (NH), 1621 (C=O), 1590, 1510, 1120; ^1H NMR (400 MHz, DMSO-d_6, Fig. S8, see Supporting Information) δ, ppm: 2.32 (overlapping singlets, 6H, C4′-CH_3 for C7 and C5 isomers), 2.40 (s, 3H, C7-CH_3), 2.72 (s, 3H, C5-CH_3; ratio of C5 to C7 isomers = 4:1), 6.20 (s, 1H, C3-H for C7-isomer), 6.26 (s, 1H, C3-H for C5-isomer; ratio of C3-H for C5 to C7 isomer = 4:1), 7.09–7.79 (m, 15H, C6-, C7-, C8-, C2′-, C3′-, C5′-, C6′-H and C2-NH for C5-isomer, and C6-, C8-, C2′-, C3′-, C5′-, C6′-H and C2-NH for C7-isomer), 7.84 (d, 1H, C5-H, J = 8.13 Hz for C7-isomer), 9.41–9.43 (broad s, N1-H for C5 and C7 isomers). Molecular formula of the isomers: $C_{17}H_{16}N_2O$.

Preparation of 5,4′-dimethyl-2-(N-phenylamino)quinoline (9a) and 7,4′-dimethyl-2-(N-phenylamino)quinoline (9b).

4-Chloro-4′-methyl-2-(N-phenylamino)quinoline (**2a** and **2b**, 0.002 mol) was refluxed with activated zinc powder (5 g) in acetic acid (20 mL) for 1 hour. The reaction was monitored by TLC. Upon completion, the reaction mixture was filtered, poured into ice water, and extracted



Scheme 4. Thermally driven $POCl_3$-mediated synthetic route for methyl dibenzo-naphthyridine derivatives showing regioselective intermediate transformations.

Table 2
Correlation of the ratio of the isomeric products obtained from the above reactions (Schemes **2 - 4**).

Isomers	Product ratio	Isomers	Product ratio
1a:1b	3: 1	**16a:16b**	10: 1
2a:2b	3: 1	**17a:17b**	2: 1
3a:3b	3: 1	**18a:18b**	2: 1
4a:4b	5: 2	**19a:19b**	3: 1
5a:5b	10: 1	**20a:20b**	3: 1
6a:6b	8: 1	**21a:21b**	3: 1
7a:7b	2: 1	**22a:22b**	4: 1
8a:8b	4: 1	**23a:23b**	4: 1
9a:9b	1: 1	**24a:24b**	3: 2
10a:10b	3: 2	**25a:25b**	1: 1
11a:11b	3: 1	**26a:26b**	3: 1
12a:12b	5: 1	**27a:27b**	3: 1
13a:13b	2: 1	**28a:28b**	3: 1
14a:14b	1: 1	**29a:29b**	4: 1
15a:15b	1: 1	**30a:30b**	3: 1

with ethyl acetate. The crude product was purified by column chromatography over silica gel, eluting with petroleum ether:ethyl acetate (97:3), to afford **9a** and **9b**, which were recrystallized from ethyl acetate as colorless needles.

Colorless needles ($C_{17}H_{16}N_2$); m.p.: 130–134 °C; Yield: 0.223 g (45%); IR (KBr) νmax, cm^{-1}: 3391 (NH), 1601, 1535, 1400, 1269; ^{1}H NMR (300 MHz, $CDCl_3$, Fig. S9, see Supporting Information) δ, ppm: 2.37 (overlapping singlets, 6H, C4′-CH_3 for C5 and C7 isomers), 2.51 (s, 3H, C7-CH_3), 2.61 (s, 3H, C5-CH_3; ratio of C5 to C7-CH_3 = 1:1), 6.90 (d, 1H, C3-H, J = 9.00 Hz for C7-isomer), 6.99 (d, 1H, C3-H, J = 9.00 Hz for C5-isomer; ratio of C3-H for C5 to C7 isomer = 1:1), 7.11–7.65 (m, 16H, C6-, C7-, C8-, C2′-, C3′-, C5′-, C6′-H and C2-NH for C5-isomer, and C5-, C6-, C8-, C2′-, C3′-, C5′-, C6′-H and C2-NH for C7-isomer), 7.84 (d, 1H, C4-H, J = 9.00 Hz for C7-isomer), 8.08 (d, 1H, C4-H, J = 9.00 Hz for C5-isomer; ratio of C4-H for C5 to C7 isomer = 1:1). Molecular formula of the isomers: $C_{17}H_{16}N_2$.

Preparation of 2,10-dimethyl-12-phenyldibenzo [b,g] [1,8] naphthyridin-11(6H)-one (10a) and 2,8-dimethyl-12-phenyldibenzo [b,g] [1,8] naphthyridin-11(6H)-one (10b).

4-Methoxy-4′-methyl-2-(N-phenylamino)quinoline (**7a** and **7b**, 0.002 mol) was reacted with benzoic acid (2.1 mmol) in the presence of polyphosphoric acid (6 g of P_2O_5 in 3 mL of H_3PO_4) at 140–145 °C for 6 hours. The reaction was monitored by TLC. Upon completion, the reaction mixture was poured into ice, and the excess benzoic acid was neutralized with saturated sodium bicarbonate solution. The mixture was extracted with ethyl acetate, and the crude product was purified by column chromatography over silica gel, eluting with petroleum ether: ethyl acetate (96:4) to afford **10a** and **10b**, which were recrystallized from methanol as pale-yellow needles.

Pale-yellow needles ($C_{24}H_{18}N_2O$); m.p.: 190–194 °C; Yield: 0.140 g (20%); IR (KBr) νmax, cm^{-1}: 3440 (NH), 1619 (C=O), 1560, 1481, 1445; ^{1}H NMR (400 MHz, $CDCl_3$, Fig. S10, see Supporting Information) δ, ppm: 2.37 (overlapping singlets, 6H, C2-CH_3 for C10 and C8 isomers), 2.69 (s, 3H, C8-CH_3), 2.94 (s, 3H, C10-CH_3; ratio of C10-CH_3 to C8-CH_3 = 3:2), 6.90–7.86 (m, 21H, C1-, C3-, C4-, C7-, C9-, C2′-, C3′-, C4′-, C5′-, C6′-H for C8-isomer, and C1-, C3-, C4-, C7-, C8-, C9-, C2′-, C3′-, C4′-, C5′-, C6′-H for C10-isomer), 8.23 (d, 1H, C10-H, J = 7.56 Hz for C8-isomer), 9.57–9.59 (broad s, 2H, N6-H for C8 and C10 isomers). Molecular formula of the isomers: $C_{24}H_{18}N_2O$.

Preparation of 2,10,12-trimethyldibenzo [b,g] [1,8] naphthyridin-11(6H)-one (11a) and 2,8,12-trimethyldibenzo [b,g] [1,8] naphthyridin-11(6H)-one (11b).

4-Methoxy-4′-methyl-2-(N-phenylamino)quinoline (**8a** and **8b**, 0.0020 mol) was reacted with acetic acid (0.0021 mol) in the presence of polyphosphoric acid (6 g of P_2O_5 in 3 mL of H_3PO_4) at 140–145 °C for 6 hours. The reaction was monitored by TLC. Upon completion, the reaction mixture was poured into ice water, extracted with ethyl acetate, and the crude product was purified by column chromatography over silica gel, eluting with petroleum ether:ethyl acetate (95:5) to afford **11a** and **11b**, which were recrystallized from methanol as pale-yellow needles.

Pale-yellow needles ($C_{19}H_{16}N_2O$); m.p.: 154–156 °C; Yield: 0.1036 g (18%); IR (KBr) νmax, cm^{-1}: 3439, 1611, 1543, 1471, 1455; ^{1}H NMR (400 MHz, $CDCl_3$, Fig. 11, see Supporting Information) δ, ppm: 2.50 (overlapping singlets, 6H, C2-CH_3 for C10 and C8 isomers), 2.69 (s, 3H, C8-CH_3), 2.99 (s, 3H, C10-CH_3; ratio of C10 to C8 isomer = 3:1), 3.40 (s, 3H, C12-CH_3 for C10-isomer), 3.42 (s, 3H, C12-CH_3 for C8-isomer; ratio of C10 to C8 isomer = 3:1), 6.96–7.55 (m, 11H, C1-, C3-, C4-, C7-, C8-, C9-H for C10-isomer, and C1-, C3-, C4-, C7-, C9-H for C8-isomer), 8.04

(d, 1H, C10-H, J = 7.89 Hz for C8-isomer), 9.29–9.32 (broad s, 2H, N6-H for C8 and C10 isomers). Molecular formula of the isomers: $C_{19}H_{16}N_2O$.

Preparation of 2,6,10-trimethyl-12-phenyldibenzo [b,g] [1,8] naphthyridin-11(6H)-one (12a) and 2,6,8-trimethyl-12-phenyldibenzo [b,g] [1,8] naphthyridin-11(6H)-one (12b).

2-Methyl-12-phenyldibenzo[b,g][1,8]naphthyridin-11(6H)-ones (**10a** and **10b**, 0.001 mol) were refluxed with methyl iodide (1 mL) in the presence of ignited potassium carbonate (2 g) in acetone (10 mL) for 1 hour. The reaction was monitored by TLC. Upon completion, the excess acetone was evaporated, and the reaction mixture was poured into ice water, neutralized with dilute HCl, and extracted with ethyl acetate. The crude product was purified by column chromatography over silica gel using petroleum ether:ethyl acetate (99:1) as eluant to afford **12a** and **12b**. The compounds were recrystallized from ethanol as pale-yellow prisms.

Pale-yellow prisms ($C_{25}H_{20}N_2O$); m.p.: 182–186 °C; Yield: 0.087 g (24 %); IR (KBr) νmax, cm^{-1}: 1640 (C=O), 1600, 1550, 1473, 1360; ^1H NMR (400 MHz, $CDCl_3$, Fig. S12, see Supporting Information) δ, ppm: 2.39 (overlapping singlets, 6H, C2-CH_3 for C10 and C8 isomers), 2.45 (s, 3H, C8-CH_3), 2.90 (s, 3H, C10-CH_3; ratio of C10 to C8 isomers = 5:1), 4.24 (s, 3H, N6-CH_3 for C10-isomer), 4.26 (s, 3H, N6-CH_3 for C8-isomer; ratio of N6-CH_3 for C10 to C8 isomers = 5:1), 7.08–7.90 (m, 21H, C1-, C3-, C4-, C7-, C9-, C2′-, C3′-, C4′-, C5′-, C6′-H for C8-isomer, and C1-, C3-, C4-, C7-, C8-, C9-, C2′-, C3′-, C4′-, C5′-, C6′-H for C10-isomer), 8.08 (d, 1H, C10-H, J = 7.98 Hz for C8-isomer). Molecular formula of the isomers: $C_{25}H_{20}N_2O$.

Preparation of 2,6,10,12-tetramethyldibenzo [b,g] [1,8] naphthyridin-11(6H)-one (13a) and 2,6,8,12-tetramethyldibenzo [b,g] [1,8] naphthyridin-11(6H)-one (13b).

2,12-Dimethyldibenzo[b,g][1,8]naphthyridin-11(6H)-one (**11a** and **11b**, 0.001 mol) was refluxed with methyl iodide (1 mL) in the presence of ignited potassium carbonate (2 g) in acetone (10 mL) for 1 hour. The reaction was monitored by TLC. Upon completion, the excess acetone was evaporated, and the reaction mixture was poured into ice water, neutralized with dilute HCl, and extracted with ethyl acetate. The crude product was purified by column chromatography over silica gel using petroleum ether:ethyl acetate (99:1) as eluant to afford **13a** and **13b**. The compound was recrystallized from ethanol as pale-yellow prisms.

Pale-yellow prisms ($C_{20}H_{18}N_2O$): m.p. 168–169 °C; Yield: 0.069 g (23%); IR (KBr) ν_max (cm^{-1}): 1644, 1592, 1550, 1473, 1360; ^1H NMR (400 MHz, $CDCl_3$) (Fig. S13, see supporting information) δ (ppm): 2.53 (overlapping singlets, 6H, C2-CH_3 for C10 and C8 isomers), 2.59 (s, 3H, C8-CH_3), 3.00 (s, 3H, C10-CH_3, ratio of C10 and C8 isomers 2:1), 3.36 (s, 3H, C12-CH_3 for C10 isomer), 3.38 (s, 3H, C12-CH_3 for C8 isomer, ratio of C10 and C8 isomers 2:1), 4.04 (s, 3H, N6-CH_3 for C10 isomer), 4.07 (s, 3H, N6-CH_3 for C8 isomer, ratio of C10 and C8 isomers 2:1), 7.05–7.88 (m, 11H, C1-, C3-, C4-, C7-, C8-, C9-H for C10 isomer and C1-, C3-, C4-, C7-, C9-H for C8 isomer), 8.36 (d, 1H, C10-H, J = 7.64 Hz for C8 isomer). Molecular formula of the isomer: $C_{20}H_{18}N_2O$.

Preparation of 2,10-dimethyl-12-phenyldibenzo [b,g] [1,8] naphthyridine (14a) and 2,8-dimethyl-12-phenyldibenzo [b,g] [1,8] naphthyridine (14b).

4′-Methyl-2-(N-phenylamino)quinoline (**9a** and **9b**, 0.001 mol) was reacted with benzoic acid (0.0011 mol) in the presence of polyphosphoric acid (3 g of P_2O_5 in 1.5 mL of H_3PO_4) at 190–195°C for 15 h. Upon completion of the reaction, the excess benzoic acid was neutralized with $NaHCO_3$, and the reaction mixture was poured into ice water, extracted with ethyl acetate, and purified by column chromatography over silica gel using petroleum ether:ethyl acetate (92:8) as the eluent to afford **14a** and **14b**. The products were recrystallized from methanol as dark brown prisms.

Dark brown prisms ($C_{24}H_{18}N_2$): m.p. 210–214°C; Yield: 0.033 g (10%); IR (KBr) νmax (cm^{-1}): 1610, 1575, 1450, 1354, 1196; ^1H NMR (400 MHz, $CDCl_3$) (Fig. S14, see supporting information) δ (ppm): 2.46 (overlapping singlets, 6H, C2-CH_3 for C8 and C10 isomers), 2.52 (s, 3H, C8-CH_3), 2.59 (s, 3H, C10-CH_3; ratio of C10-CH_3 to C8-CH_3 = 1:1), 7.29–8.31 (m, 22H, C1-, C3-, C4-, C7-, C8-, C9-, C2′-, C3′-, C4′-, C5′-, C6′-H for C10 isomer and C1-, C3-, C4-, C7-, C9-, C10-, C2′-, C3′-, C4′-, C5′-, C6′-H for C8 isomer), 8.54 (s, 1H, C11-H for C10 isomer), 8.56 (s, 1H, C11-H for C8 isomer; ratio of C11-H for C10 to C8 isomer = 1:1); Molecular formula of the isomer: $C_{24}H_{18}N_2$.

Preparation of 2,10,12-trimethyldibenzo [b,g] [1,8] naphthyridine (15a) and 2,8,12-trimethyl dibenzo [b,g] [1,8] naphthyridine (15b).

4′-Methyl-2-(N-phenylamino)quinoline (**9a** and **9b**, 0.0010 mol) was reacted with acetic acid (0.0011 mol) in the presence of polyphosphoric acid (3 g of P_2O_5 in 1.5 mL of H3PO4) at 190–195°C for 15 h. After completion of the reaction, the mixture was poured into ice water, extracted with ethyl acetate, and purified by column chromatography over silica gel using petroleum ether:ethyl acetate (92:8) as eluent to afford **15a** and **15b**. The products were recrystallized from methanol as dark brown prisms.

Dark brown prisms ($C_{19}H_{16}N_2$): m.p. 210–212°C; Yield: 0.032 g (12%); IR (KBr) νmax (cm^{-1}): 1609, 1572, 1445, 1353, 1191; ^1H NMR (300 MHz, $CDCl_3$) (Fig. S15, see supporting information) δ (ppm): 2.40 (overlapping singlets, 6H, C2-CH_3 for C8 and C10 isomers), 2.51 (s, 3H, C8-CH_3), 2.60 (s, 3H, C10-CH_3; ratio of C10 to C8 isomers 1:1), 3.18 (overlapping singlets, 6H, C12-CH_3 for C8 and C10 isomers), 7.31–8.11 (m, 12H, C1-, C3-, C4-, C7-, C8-, C9-H for C10 isomer and C1-, C3-, C4-, C7-, C9-, C10-H for C8 isomer; ratio of C10 to C8 isomers 1:1), 8.57 (s, 1H, C11-H for C10 isomer), 8.58 (s, 1H, C11-H for C8 isomer; ratio of C10 to C8 isomers 1:1). Molecular formula of the isomer: $C_{19}H_{16}N_2$.

Preparation of 1,9,4′-trimethyl-6-(N-phenylamino)dibenzo [b,h] [1,6] naphthyridine (16a) and 3,9,4′-trimethyl-6-(N-phenylamino)dibenzo [b,h] [1,6] naphthyridine (16b).

4′,4″-Dimethyl-2,4-bis-(N-phenylamino)quinoline (**4a** and **4b**, 0.001 mol) was added to the Vilsmeier adduct (prepared by adding 12 mL of $POCl_3$ dropwise to a stirred solution of DMF (5 mL) at 0°C, followed by stirring for 15 min) and stirred at room temperature for 5 hours. The reaction was monitored by TLC. After completion, the reaction mixture was poured into ice water. The precipitate was filtered, dried, and purified by column chromatography over silica gel using a petroleum ether:ethyl acetate (99:1) mixture to afford **16a** and **16b**. The products were recrystallized from ethyl acetate as orange prisms.

Orange prisms ($C_{25}H_{21}N_3$): m.p. 253–257°C; Yield: 0.127 g (35%); IR (KBr) ν_max (cm^{-1}): 3427 (NH), 1599 (C=N), 1549, 1358; ^1H NMR (300 MHz, $CDCl_3$) (Fig. S16, see Supporting Information) δ (ppm): 2.38 (overlapping singlets, 6H, C4′–CH_3 for C1 and C3 isomers), 2.68 (overlapping, 6H, C9–CH_3 for C1 and C3 isomers), 2.74 (s, 3H, C3–CH_3), 3.31 (s, 3H, C1–CH_3; ratio of C1 and C3 isomers = 10: 1), 7.22–8.17 (m, 21H, C2-, C3-, C4-, C8-, C10-, C11-, C2′-, C3′-, C5′-, C6′–H and C6–NH for C1 isomer; C2-, C4-, C8-, C10-, C11-, C2′-, C3′-, C5′-, C6′–H and C6–NH for C3 isomer), 8.37 (s, 1H, C7–H for C1 isomer), 8.39 (s, 1H, C7–H for C3 isomer), 8.71 (d, 1H, C1–H, J = 7.67 Hz for C3 isomer). Molecular formula: $C_{25}H_{21}N_3$.

Preparation of 11-chloro-2,10-dimethyldibenzo [b,g] [1,8] naphthyridine (17a) and 11-chloro-2,8-dimethyldibenzo [b,g] [1,8] naphthyridine (17b): General procedure.

4′-Methyl-2-(N-phenylamino)quinolin-4(1H)-one (**8a** and **8b**, 0.002 mol) was stirred with DMF/$POCl_3$ (3.6 mL/8.4 mL) at 85–90°C for 10 h. After completion of the reaction, the mixture was poured into crushed ice, extracted with ethyl acetate, and purified by column chromatography over silica gel. The product was eluted with petroleum ether:ethyl acetate (99: 1) and (93: 7) mixtures to afford the starting materials **2a** and **2b**, and the products **17a** and **17b**, respectively. It was recrystallized from ethanol as colourless needles.

Colourless needles ($C_{18}H_{13}ClN_2$): m.p. 195–196°C; Yield: 0.105 g (18%); IR (KBr) ν_max (cm^{-1}): 1622, 1588, 1518, 1049; ^1H NMR (300 MHz, $CDCl_3$) (Fig. S17, see Supporting Information) δ (ppm): 2.35 (overlapping singlets, 6H, C2–CH_3 for C10 and C8 isomers), 2.63 (s, 3H, C8–CH_3), 2.98 (s, 3H, C10–CH_3; ratio of C10 and C8 isomers = 2: 1), 7.42–8.00 (m, 11H, C1-, C3-, C4-, C7-, C8-, C9-H for C10 isomer, and C1-

, C3-, C4-, C7-, C9-H for C8 isomer), 8.46 (d, 1H, C10-H, J = 7.88 Hz, for C8 isomer), 8.71 (s, 1H, C12-H for C8 isomer), 8.73 (s, 1H, C12-H for C10 isomer; ratio of C10 and C8 isomers = 2: 1); Molecular formula: $C_{18}H_{13}ClN_2$.

Preparation of 11-methoxy-2,10-dimethyldibenzo[b,g] [1,8] naphthyridine (18a) and 11-methoxy-2,8-dimethyldibenzo[b,g] [1,8] naphthyridine (18b).

4-Methoxy-4′-methyl-2-(N-phenylamino)quinoline (**7a** and **7b**, 0.001 mol) was added to a Vilsmeier adduct (prepared by adding $POCl_3$ (12 mL) dropwise to a stirred solution of DMF (5 mL) at 0°C, followed by stirring for an additional 15 minutes) and the reaction mixture was stirred at 50–55°C for 5 hours. The reaction progress was monitored by TLC. After completion, the reaction mixture was poured into ice water, and the resulting precipitate was filtered, dried, and purified by column chromatography over silica gel using a petroleum ether:ethyl acetate (99:1) mixture to afford **18a** and **18b**. The compounds were recrystallized from ethyl acetate as orange prisms.

Orange prisms ($C_{19}H_{16}N_2O$): m.p. 253–255°C; Yield: 0.098 g (34%); IR (KBr) ν_max (cm^{-1}): 1596 (C=N), 1529, 1358; ^1H NMR (300 MHz, $CDCl_3$) (Fig. S18, see Supporting Information) δ (ppm): 2.41 (overlapping singlets, 6H, C2–CH_3 for C10 and C8 isomers), 2.59 (s, 3H, C8–CH_3), 3.11 (s, 3H, C10–CH_3, ratio of C10 and C8 isomers = 2:1), 3.97 (s, 3H, OCH_3 for C8 isomer), 4.05 (s, 3H, OCH_3 for C10 isomer, ratio of OCH_3 for C10 and C8 isomers = 2:1), 7.01–7.89 (m, 11H, C1-, C3-, C4-, C7-, C8-, C9–H for C10 isomer and C1-, C3-, C4-, C7-, C9–H for C8 isomer), 8.54 (d, 1H, C10–H, J = 7.88 Hz for C8 isomer), 8.76 (s, 1H, C12–H for C8 isomer), 8.79 (s, 1H, C12–H for C10 isomer, ratio of C8 and C10 isomers = 2:1); Molecular formula: $C_{19}H_{16}N_2O$.

Preparation of 2-[(2′-acetylphenyl)amino]-4-chloro-5-methylquinoline (19a) and 2-[(2′-acetylphenyl)amino]-4-chloro-7-methylquinoline (19b).

2,4-Dichloroquinoline (**1a** and **1b**, 0.004 mol) was reacted with o-aminoacetophenone (0.004 mol or in excess) under neat conditions at 160°C for half an hour. The product was washed with water, dried, adsorbed onto silica gel, and purified by column chromatography using a petroleum ether:ethyl acetate (98:2) mixture to obtain **19a** and **19b**, which were recrystallized from methanol as colorless prisms.

Colourless prisms ($C_{18}H_{15}ClN_2O$): m.p. 145–147°C; Yield: 0.868 g (70%); IR (KBr) ν_max (cm^{-1}): 3408 (NH), 1632 (C=O), 1591, 1516, 1149; ^1H NMR (400 MHz, $CDCl_3$) (Fig. S19, see Supporting Information) δ (ppm): 2.56 (overlapping singlets, 6H, $COCH_3$ for C5 and C7 isomers), 2.59 (s, 3H, C7-CH_3), 2.92 (s, 3H, C5-CH_3; ratio of C5- and C7-isomers = 3: 1), 7.01 (s, 1H, C3-H for C7-isomer), 7.03 (s, 1H, C3-H for C5-isomer; ratio of C3-H for C5- and C7-isomers = 3: 1), 7.14–7.94 (m, 11H, C6-, C7-, C8-, C3′-, C4′-, C5′-H for C5-isomer and C6-, C8-, C3′-, C4′-, C5′-H for C7-isomer), 8.21 (d, 1H, C5-H, J = 7.65 Hz for C7-isomer), 9.48 (d, 1H, C6′-H, J = 8.61 Hz for C7-isomer), 9.51 (d, 1H, C6′-H, J = 8.61 Hz for C5-isomer; ratio of C6′-H for C5- and C7-isomers = 1: 1), 11.57 (br s, 2H, C2-NH for C5 and C7 isomers); Molecular formula: $C_{18}H_{15}ClN_2O$.

Preparation of 2[(2′-benzoylphenyl)amino]-4-chloro-5-methylquinoline (20a) and 2[(2′- benzoylphenyl)amino]-4-chloro-7-methylquinoline (20b)

2,4-Dichloroquinoline (**1a** and **1b**, 0.004 mol) was reacted with *o*-aminobenzophenone (0.004 mol or in excess) under neat conditions at 160°C for half an hour. The resulting product was washed with water, dried, adsorbed, and purified by silica gel column chromatography using a petroleum ether:ethyl acetate (98:2) mixture as the eluent to afford compounds **20a** and **20b**. The products were then recrystallized from methanol to yield pale yellow prisms.

Pale yellow prisms ($C_{23}H_{17}ClN_2O$): m.p. 168–170°C; Yield: 1.041 g (70%). IR (KBr, νmax cm^{-1}): 3432 (NH), 1635 (C=O), 1578, 1535, 1146. ^1H NMR (400 MHz, $CDCl_3$) (Fig. S20; see Supporting Information) δ (ppm): 2.55 (s, 3H, C7–CH_3), 2.98 (s, 3H, C5–CH_3; ratio of C5 and C7 isomers = 3:1), 7.03 (s, 1H, C3–H for C7 isomer), 7.05 (s, 1H, C3–H for C5 isomer; ratio of C3–H for C5 and C7 isomers = 3:1), 7.13–7.82 (m, 21H, C6–, C7–, C8–, C3′–, C4′–, C5′–, C2″–, C3″–, C4″–, C5″–, C6″–H for C5 isomer and C6–, C8–, C3′–, C4′–, C5′–, C2″–, C3″–, C4″–, C5″–, C6″–H for C7 isomer), 7.89 (d, 1H, C5–H, J = 7.86 Hz, for C7 isomer), 9.19 (d, 1H, C6′–H, J = 8.26 Hz, for C7 isomer), 9.21 (d, 1H, C6′–H, J = 8.24 Hz, for C5 isomer), 11.02 (br s, 2H, C2–NH for C5 and C7 isomers). Molecular formula: $C_{23}H_{17}ClN_2O$.

Preparation of 2-[(2′-benzoyl-4′-chlorophenyl)amino]-4-chloro-5-methylquinoline (21a) and 2-[(2′-benzoyl-4′-chlorophenyl)amino]-4-chloro-7-methylquinoline (21b)

2,4-Dichloroquinoline (**1a** and **1b**, 0.004 mol) was reacted with 2-amino-5-chlorobenzophenone (0.004 mol or in excess) under neat conditions at 160°C for half an hour. The resulting product was washed with water, adsorbed, and purified by silica gel column chromatography using a petroleum ether:ethyl acetate (98:2) mixture as the eluent to afford compounds **21a** and **21b**, which were then recrystallized from methanol to yield colorless prisms.

Colourless prisms ($C_{23}H_{16}Cl_2N_2O$): m.p. 172–174°C; Yield: 1.120 g (69%). IR (KBr, ν_{max} cm^{-1}): 3437 (NH), 1639 (C=O), 1584, 1511, 1158. ^1H NMR (300 MHz, $CDCl_3$) (Fig. S21; see Supporting Information) δ (ppm): 2.54 (s, 3H, C7–CH_3), 2.98 (s, 3H, C5–CH_3), 7.09 (s, 1H, C3–H for C7 isomer), 7.11 (s, 1H, C3–H for C5 isomer; ratio of C5 and C7 isomers = 5:1), 7.30–7.78 (m, 19H, C6–, C7–, C8–, C3′–, C5′–, C2″–, C3″–, C4″–, C5″–, C6″–H for C5 isomer and C6–, C8–, C3′–, C5′–, C2″–, C3″–, C4″–, C5″–, C6″–H for C7 isomer), 7.95 (d, 1H, C5–H, J = 8.40 Hz, for C7 isomer), 9.23 (d, 1H, C6′–H, J = 8.33 Hz, for C5 isomer), 9.25 (d, 1H, C6′–H, J = 8.29 Hz, for C7 isomer), 10.82 (br s, 2H, C2–NH for C5 and C7 isomers). Molecular formula: $C_{23}H_{16}Cl_2N_2O$.

Preparation of 10,12-Dimethyldibenzo[b,g] [1,8] naphthyridin-11(6H)-one (22a) and 8,12-Dimethyldibenzo[b,g] [1,8] naphthyridin-11(6H)-one (22b)

2-[(2′-Acetylphenyl)amino]-4-chloroquinoline (**19a** and **19b**, 0.002 mol) was added to polyphosphoric acid (prepared from 6 g of P_2O_5 in 3 mL of H_3PO_4) and heated at 205–210°C for 5 hours. The reaction progress was monitored by TLC. Upon completion, the reaction mixture was poured into ice water and extracted with ethyl acetate. The organic layer was purified by silica gel column chromatography using a petroleum ether:ethyl acetate (96:4) mixture as the eluent to afford compounds **22a** and **22b**, which were recrystallized from methanol to yield colorless needles.

Colourless needles ($C_{18}H_{14}N_2O$): m.p. 189–191°C; Yield: 0.120 g (22%). IR (KBr, ν_{max} cm^{-1}): 3419 (NH), 1659 (C=O), 1617, 1526, 1483. ^1H NMR (400 MHz, $CDCl_3$) (Fig. S22; see Supporting Information) δ (ppm): 2.47 (s, 3H, C8–CH_3), 2.78 (s, 3H, C10–CH_3; ratio of C10 and C8 isomers = 4:1), 3.17 (s, 3H, C12–CH_3 for C8 isomer), 3.19 (s, 3H, C12–CH_3 for C10 isomer; ratio of C10 and C8 isomers = 4:1), 7.10–8.23 (m, 13H, C1–, C2–, C3–, C4–, C7–, C8–, C9–H for C10 isomer and C1–, C2–, C3–, C4–, C7–, C9–H for C8 isomer), 8.41 (d, 1H, C10–H, J = 8.06 Hz, for C8 isomer), 9.24 (br s, 2H, N6–H for C8 and C10 isomers). Molecular formula: $C_{18}H_{14}N_2O$.

Preparation of 10-Methyl-12-phenyldibenzo[b,g] [1,8] naphthyridin-11(6H)-one (23a) and 8-Methyl-12-phenyldibenzo[b,g] [1,8] naphthyridin-11(6H)-one (23b)

2-[(2′-Benzoylphenyl)amino]-4-chloroquinoline (**20a** and **20b**, 0.002 mol) was added to polyphosphoric acid (prepared from 6 g of P_2O_5 in 3 mL of H_3PO_4) and heated at 205–210°C for 5 hours. The reaction progress was monitored by TLC. Upon completion, the reaction mixture was poured into ice water and extracted with ethyl acetate. The organic layer was purified by silica gel column chromatography using a petroleum ether:ethyl acetate (96:4) mixture as the eluent to afford compounds **23a** and **23b**, which were recrystallized from methanol to yield colorless prisms.

Colourless prisms ($C_{23}H_{16}N_2O$): m.p. 202–203°C; Yield: 0.128 g (19%). IR (KBr, ν_{max} cm^{-1}): 3428 (NH), 1649 (C=O), 1607, 1566, 1463. ^1H NMR (400 MHz, $CDCl_3$) (Fig. S23; see Supporting Information) δ (ppm): 2.49 (s, 3H, C8–CH_3), 2.78 (s, 3H, C10–CH_3; ratio of C10 and C8 isomers = 4:1), 7.00–7.70 (m, 23H, C1–, C2–, C3–, C4–, C7–, C8–, C9–, C2′–, C3′–, C4′–, C5′–, C6′–H for C10 isomer and C1–, C2–, C3–, C4–, C7–,

C9–, C2′–, C3′–, C4′–, C5′–, C6′–H for C8 isomer), 8.15 (d, 1H, C10–H, J = 8.10 Hz, for C8 isomer), 8.55 (br s, 2H, N6–H for C10 and C8 isomers). Molecular formula: $C_{23}H_{16}N_2O$.

Preparation of 2-Chloro-10-methyl-12-phenyldibenzo [b,g] [1,8] naphthyridin-11(6H)-one (24a) and 2-Chloro-8-methyl-12-phenyldibenzo [b,g] [1,8] naphthyridin-11(6H)-one (24b)

2-[(2′-Benzoyl-4′-chlorophenyl)amino]-4-chloroquinoline (**21a** and **21b**, 0.002 mol) was added to polyphosphoric acid (prepared from 6 g of P_2O_5 in 3 mL of H_3PO_4) and heated at 205–210°C for 5 hours. The reaction progress was monitored by TLC. Upon completion, the reaction mixture was poured into ice water and extracted with ethyl acetate. The organic layer was purified by silica gel column chromatography using a petroleum ether:ethyl acetate (96:4) mixture as the eluent to afford compounds **24a** and **24b**, which were recrystallized from methanol to yield colorless prisms.

Colourless prisms ($C_{23}H_{15}ClN_2O$): m.p. 206–208°C; Yield: 0.118 g (16%). IR (KBr, ν_{max} cm^{-1}): 3430 (NH), 1634 (C=O), 1605, 1541, 1485. ^1H NMR (400 MHz, $CDCl_3$) (Fig. S24; see Supporting Information) δ (ppm): 2.45 (s, 3H, C8–CH_3), 2.70 (s, 3H, C10–CH_3; ratio of C10 and C8 isomers = 3:2), 6.91–7.86 (m, 21H, C1–, C3–, C4–, C7–, C8–, C9–, C2′–, C3′–, C4′–, C5′–, C6′–H for C10 isomer and C1–, C3–, C4–, C7–, C9–, C2′–, C3′–, C4′–, C5′–, C6′–H for C8 isomer), 8.11 (d, 1H, C10–H, J = 8.20 Hz, for C8 isomer), 9.23 (br s, 2H, N6–H for C10 and C8 isomers). GC–MS (Fig. S25; see Supporting Information): The spectrum exhibited two retention peaks with peak area ratios of 3:2, corresponding to the two isomers. Molecular formula: $C_{23}H_{15}ClN_2O$.

Preparation of 2- [(2′-Acetylphenyl)amino] -4-methoxy-5-methylquinoline (25a) and 2- [(2′-Acetylphenyl)amino] -4-methoxy-7-methylquinoline (25b)

2-[(2′-Acetylphenyl)amino]-4-chloroquinoline (**19a** and **19b**, 0.004 mol) was added to sodium methoxide (prepared from 2 g of sodium in 15 mL of methanol) and heated on a water bath for 10 hours. The reaction progress was monitored by TLC. Upon completion, excess methanol was evaporated, and the reaction mixture was poured into ice water and neutralized with dilute HCl. The resulting precipitate was filtered, dried, and purified by silica gel column chromatography using a petroleum ether:ethyl acetate (94:6) mixture as the eluent to afford compounds **25a** and **25b**, which were recrystallized from methanol to yield colorless prisms.

Colourless prisms ($C_{19}H_{18}N_2O_2$): m.p. 145–147°C; Yield: 0.820 g (67%). IR (KBr, ν_{max} cm^{-1}): 3411 (NH), 1621 (C=O), 1589, 1519, 1241. ^1H NMR (300 MHz, $CDCl_3$) (Fig. S26; see Supporting Information) δ (ppm): 2.65 (overlapping s, 6H, $COCH_3$ for C5 and C7 isomers), 2.69 (s, 3H, C7–CH_3), 3.03 (s, 3H, C5–CH_3), 4.04 (s, 3H, OCH_3 for C5 isomer), 4.07 (s, 3H, OCH_3 for C7 isomer; ratio of C5 and C7 isomers = 1:1), 6.61 (s, 1H, C3–H for C5 isomer), 6.64 (s, 1H, C3–H for C7 isomer), 7.14–7.94 (m, 11H, C6–, C7–, C8–, C3′–, C4′–, C5′–H for C5 isomer and C6–, C8–, C3′–, C4′–, C5′–H for C7 isomer), 8.30 (d, 1H, C5–H, J = 7.65 Hz, for C7 isomer), 9.50 (d, 1H, C6′–H, J = 8.61 Hz, for C7 isomer), 9.55 (d, 1H, C6′–H, J = 8.61 Hz, for C5 isomer; ratio of C6′–H for C5 and C7 isomers = 1:1), 11.60 (br s, 2H, C2–NH for C5 and C7 isomers). Molecular formula: $C_{19}H_{18}N_2O_2$.

Preparation of 2- [(2′-Benzoylphenyl)amino] -4-methoxy-5-methylquinoline (26a) and 2- [(2′-Benzoylphenyl)amino] -4-methoxy-7-methylquinoline (26b)

2-[(2′-Benzoylphenyl)amino]-4-chloroquinoline (**20a** and **20b**, 0.004 mol) was added to sodium methoxide (prepared from 2 g of sodium in 15 mL of methanol) and heated on a water bath for 10 hours. The reaction progress was monitored by TLC. Upon completion, excess methanol was evaporated, and the reaction mixture was poured into ice water and neutralized with dilute HCl. The resulting precipitate was filtered, dried, and purified by silica gel column chromatography using a petroleum ether:ethyl acetate (95:5) mixture as the eluent to afford compounds **26a** and **26b**, which were recrystallized from methanol to yield pale yellow prisms.

Pale yellow prisms ($C_{24}H_{20}N_2O_2$): m.p. 168–170°C; Yield: 0.971 g (66%). IR (KBr, ν_{max} cm^{-1}): 3439 (NH), 1628 (C=O), 1580, 1238, 1158. ^1H NMR (400 MHz, $CDCl_3$) (Fig. S27; see Supporting Information) δ (ppm): 2.57 (s, 3H, C7–CH_3), 2.89 (s, 3H, C5–CH_3; ratio of C5 and C7 isomers = 3:1), 4.02 (s, 3H, OCH_3 for C5 isomer), 4.04 (s, 3H, OCH_3 for C7 isomer; ratio of C5 and C7 isomers = 3:1), 6.70 (s, 1H, C3–H for C5 isomer), 6.72 (s, 1H, C3–H for C7 isomer), 7.00–7.79 (m, 21H, C6–, C7–, C8–, C3′–, C4′–, C5′–, C2″–, C3″–, C4″–, C5″–, C6″–H for C5 isomer and C6–, C8–, C3′–, C4′–, C5′–, C2″–, C3″–, C4″–, C5″–, C6″–H for C7 isomer), 7.94 (d, 1H, C5–H, J = 8.13 Hz, for C7 isomer), 9.17 (d, 1H, C6′–H, J = 8.05 Hz, for C7 isomer), 9.21 (d, 1H, C6′–H, J = 7.98 Hz, for C5 isomer), 11.05 (br s, 2H, C2–NH for C5 and C7 isomers). Molecular formula: $C_{24}H_{20}N_2O_2$.

Preparation of 2- [(2′-Benzoyl-4′-chlorophenyl)amino] -4-methoxy-5-methylquinoline (27a) and 2- [(2′-Benzoyl-4′-chlorophenyl)amino] -4-methoxy-7-methylquinoline (27b)

2-[(2′-Benzoyl-4′-chlorophenyl)amino]-4-chloroquinoline (**21a** and **21b**, 0.004 mol) was added to sodium methoxide (prepared from 2 g of sodium in 15 mL of methanol) and heated on a water bath for 10 hours. The reaction progress was monitored by TLC. Upon completion, excess methanol was evaporated, and the reaction mixture was poured into ice water and neutralized with dilute HCl. The resulting precipitate was filtered, dried, and purified by silica gel column chromatography using a petroleum ether:ethyl acetate (95:5) mixture as the eluent to afford compounds **27a** and **27b**, which were recrystallized from methanol to yield colourless prisms.

Colourless prisms ($C_{24}H_{19}ClN_2O_2$): m.p. 172–174°C; Yield: 1.125 g (70%). IR (KBr, ν_{max} cm^{-1}): 3432 (NH), 1636 (C=O), 1581, 1521, 1148. ^1H NMR (300 MHz, $CDCl_3$) (Fig. S28; see Supporting Information) δ (ppm): 2.49 (s, 3H, C7–CH_3), 2.89 (s, 3H, C5–CH_3), 3.98 (s, 3H, OCH_3 for C5 isomer), 4.00 (s, 3H, OCH_3 for C7 isomer; ratio of C5 and C7 isomers = 3:1), 6.59 (s, 1H, C3–H for C5 isomer), 6.62 (s, 1H, C3–H for C7 isomer; ratio of C5 and C7 isomers = 3:1), 7.31–7.81 (m, 19H, C6–, C7–, C8–, C3′–, C5′–, C2″–, C3″–, C4″–, C5″–, C6″–H for C5 isomer and C6–, C8–, C3′–, C5′–, C2″–, C3″–, C4″–, C5″–, C6″–H for C7 isomer), 8.06 (d, 1H, C5–H, J = 8.14 Hz, for C7 isomer), 9.20 (d, 1H, C6′–H, J = 8.33 Hz, for C7 isomer), 9.24 (d, 1H, C6′–H, J = 8.29 Hz, for C5 isomer), 11.03 (br s, 2H, C2–NH for C5 and C7 isomers). Molecular formula: $C_{24}H_{19}ClN_2O_2$.

Preparation of 6,10,12-Trimethyldibenzo [b,g] [1,8] naphthyridin-11(6H)-one (28a) and 6,8,12-Trimethyldibenzo [b,g] [1,8] naphthyridin-11(6H)-one (28b)

12-Methyldibenzo[b,g][1,8]naphthyridin-11(6H)-one (**22a** and **22b**, 0.002 mol) was refluxed with methyl iodide (1 mL) in the presence of ignited potassium carbonate (2 g) in acetone (10 mL) for 1 h. The reaction progress was monitored by TLC. Upon completion, the excess acetone was evaporated, and the reaction mixture was poured into ice water and neutralized with dilute HCl. The product was extracted with ethyl acetate and purified by silica gel column chromatography using a petroleum ether:ethyl acetate (99:1) mixture as the eluent to afford compounds **28a** and **28b**. The products were recrystallized from ethanol to yield colorless needles.

Colourless needles ($C_{19}H_{16}N_2O$): m.p. 189–191°C; Yield: 0.115 g (20%). IR (KBr, ν_{max} cm^{-1}): 1649 (C=O), 1615, 1568, 1473. ^1H NMR (400 MHz, $CDCl_3$) (Fig. S29; see Supporting Information) δ (ppm): 2.53 (s, 3H, C8–CH_3), 2.84 (s, 3H, C10–CH_3; ratio of C10 and C8 isomers = 3:1), 3.19 (s, 3H, C12–CH_3 for C8 isomer), 3.21 (s, 3H, C12–CH_3 for C10 isomer; ratio of C10 and C8 isomers = 3:1), 3.90 (s, 3H, N6–CH_3 for C8 isomer), 3.95 (s, 3H, N6–CH_3 for C10 isomer), 7.12–8.01 (m, 13H, C1–, C2–, C3–, C4–, C7–, C8–, C9–H for C10 isomer and C1–, C2–, C3–, C4–, C7–, C9–H for C8 isomer), 8.29 (d, 1H, C10–H, J = 7.89 Hz, for C8 isomer). Molecular formula: $C_{19}H_{16}N_2O$.

Preparation of 6,10-Dimethyl-12-phenyldibenzo [b,g] [1,8] naphthyridin-11(6H)-one (29a) and 6,8-Dimethyl-12-phenyldibenzo [b,g] [1,8] naphthyridin-11(6H)-one (29b)

12-Phenyldibenzo[b,g][1,8]naphthyridin-11(6H)-one (**23a** and **23b**, 0.002 mol) was refluxed with methyl iodide (1 mL) in the presence of ignited potassium carbonate (2 g) in acetone (10 mL) for 1 h. The

reaction progress was monitored by TLC. Upon completion, the excess acetone was evaporated, and the reaction mixture was poured into ice water and neutralized with dilute HCl. The product was extracted with ethyl acetate and purified by silica gel column chromatography using a petroleum ether:ethyl acetate (99:1) mixture as the eluent to afford compounds **29a** and **29b**. The products were recrystallized from ethanol to yield colorless prisms.

Colourless prisms ($C_{24}H_{18}N_2O$): m.p. 202–203°C; Yield: 0.126 g (18%). IR (KBr, ν_{max} cm^{-1}): 1641 (C=O), 1601, 1566, 1483. ^1H NMR (400 MHz, $CDCl_3$) (Fig. S30; see Supporting Information) δ (ppm): 2.49 (s, 3H, C8–CH_3), 2.80 (s, 3H, C10–CH_3; ratio of C10 and C8 isomers = 4:1), 3.97 (s, 3H, N6–CH_3 for C8 isomer), 4.00 (s, 3H, N6–CH_3 for C10 isomer; ratio of C10 and C8 isomers = 4:1), 7.19–7.98 (m, 23H, C1–, C2–, C3–, C4–, C7–, C8–, C9–, C2′–, C3′–, C4′–, C5′–, C6′–H for C10 isomer and C1–, C2–, C3–, C4–, C7–, C9–, C2′–, C3′–, C4′–, C5′–, C6′–H for C8 isomer), 8.19 (d, 1H, C10–H, J = 8.10 Hz, for C8 isomer). Molecular formula: $C_{24}H_{18}N_2O$.

Preparation of 2-Chloro-6,10-dimethyl-12-phenyldibenzo [b,g] [1,8] naphthyridin-11(6H)-one (30a) and 2-Chloro-6,8-dimethyl-12-phenyldibenzo [b,g] [1,8] naphthyridin-11(6H)-one (30b)

2-Chloro-12-phenyldibenzo[b,g][1,8]naphthyridin-11(6H)-one (**24a** and **24b**, 0.002 mol) was refluxed with methyl iodide (1 mL) in the presence of ignited potassium carbonate (2 g) in acetone (10 mL) for 1 h. The reaction progress was monitored by TLC. Upon completion, the excess acetone was evaporated, and the reaction mixture was poured into ice water and neutralized with dilute HCl. The product was extracted with ethyl acetate and purified by silica gel column chromatography using a petroleum ether:ethyl acetate (99:1) mixture as the eluent to afford compounds **30a** and **30b**. The products were recrystallized from ethanol to yield colorless prisms.

Colourless prisms ($C_{24}H_{17}ClN_2O$): m.p. 206–208°C; Yield: 0.146 g (19%). IR (KBr, ν_{max} cm^{-1}): 1668, 1634 (C=O), 1550, 1486. ^1H NMR (400 MHz, $CDCl_3$) (Fig. S31; see Supporting Information) δ (ppm): 2.41 (s, 3H, C8–CH_3), 2.81 (s, 3H, C10–CH_3; ratio of C10 and C8 isomers = 3:1), 4.01 (s, 3H, N6–CH_3 for C8 isomer), 4.08 (s, 3H, N6–CH_3 for C10 isomer; ratio of C10 and C8 isomers = 3:1), 7.21–7.90 (m, 21H, C1–, C3–, C4–, C7–, C8–, C9–, C2′–, C3′–, C4′–, C5′–, C6′–H for C10 isomer and C1–, C3–, C4–, C7–, C9–, C2′–, C3′–, C4′–, C5′–, C6′–H for C8 isomer), 8.23 (d, 1H, C10–H, J = 8.41 Hz, for C8 isomer). Molecular formula: $C_{24}H_{17}ClN_2O$.

CRediT authorship contribution statement

M. Sangeetha: Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **S. Packiaraj:** Writing – review & editing, Visualization, Validation, Data curation. **M. Manoj:** Writing – review & editing, Visualization, Validation. **J. Anitha:** Validation, Investigation. **K. Banupriya:** Writing – review & editing.

Declaration of competing interest

There is no conflict of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2026.145406.

Data availability

Data will be made available on request.

References

[1] K. Okuma, T. Koga, S. Ozaki, Y. Suzuki, K. Horigami, N. Nagahora, K. Shioji, M. Fukuda, M. Deshimaru, One-pot synthesis of dibenzo[*b,h*][1,6]naphthyridines from 2-acetylaminobenzaldehyde: application to a fluorescent DNA-binding compound, Chem. Commun. 50 (2014) 15525–15528, https://doi.org/10.1039/C4CC07807A.

[2] N.G. Sanders, D.J. Meyers, D.J. Sullivan, Antimalarial efficacy of Hydroxyethylapoquinine (SN-119) and its derivatives, Antimicrob. Agents Chemother. 58 (2) (2014) 820–827, https://doi.org/10.1128/aac.01704-13.

[3] V. Sharma, D.K. Mehta, R. Das, Synthetic methods of Quinoline derivatives as potent anticancer agents, Mini. Rev. Med. Chem. 17 (16) (2017) 1557–1572, https://doi.org/10.2174/1389557517666170510104954.

[4] S. Mukherjee, M. Pal, Medicinal chemistry of Quinolines as emerging anti-inflammatory agents: an overview, Curr. Med. Chem. 20 (35) (2013) 4386–4410, https://doi.org/10.2174/09298673113209990170.

[5] A. Dolsak, U. Svajger, S. Lesnik, J. Konc, S. Gobec, M. Sova, Selective toll-like receptor 7 agonists with novel Chromeno[3,4-*d*]imidazol-4(1*h*)-one and 2-(trifluoromethyl)quinoline/quinazoline-4-amine scaffolds, Eur. J. Med. Chem. 179 (2019) 109–122, https://doi.org/10.1016/j.ejmech.2019.06.030.

[6] V. Gasparotto, I. Castagliuolo, G. Chiarelotto, V. Pezzi, D. Montanaro, P. Brun, G. Palu, G. Viola, M.G. Ferlin, Synthesis and biological activity of 7-Phenyl-6,9-dihydro-3*H*-pyrrolo[3,2-*f*]quinolin-9-ones: A new class of antimitotic agents devoid of aromatase activity, J. Med. Chem 49 (6) (2006) 1910–1915, https://doi.org/10.1021/jm0510676.

[7] M.E. Wall, M.C. Wani, C.K. Cook, K.H. Palmer, A.T. McPhail, G.A. Sim, Plant antitumor agents. I. The isolation and structure of Camptothecin, a novel alkaloidal Leukemia and tumor inhibitor from Camptotheca acuminate, J. Am. Chem. Soc. 88 (16) (1966) 3888–3890, https://doi.org/10.1021/ja00968a057.

[8] S.K. Srivatsava, M. Khan and S.P.K. Khanuja, Process for isolation of anticancer agent camptothecin from Nothapodytes foetida, US Patent no. 6893668B2, 2005. https://patents.google.com/patent/US6893668B2/en.

[9] S. Vijayaragavan, S. Mahajan, Docking, synthesis and antimalarial activity of novel 4-anilinoquinoline derivatives, Bioorg. Med. Chem. Lett. 27 (8) (2017) 1693–1697, https://doi.org/10.1016/j.bmcl.2017.03.005.

[10] S. Hostyn, B.U. Maes, G.V. Baelen, A. Gulevskaya, C. Meyers, K. Smits, Synthesis of 7*H*-indolo[2,3-*c*]quinolines: study of the Pd-catalyzed intramolecular arylation of 3-(2-bromophenylamino)quinolines under microwave irradiation, Tetrahedron 62 (19) (2006) 4676–4684, https://doi.org/10.1016/j.tet.2005.12.062.

[11] M. Kidwai, S. Kohli, Synthesis of dibenzo(b,g)-5-methyl-1,8-naphthyridines, Indian J. Chem, Sect. B 40 (2001) 248–249. http://nopr.niscair.res.in/handle/123456789/22226.

[12] E.G. Paronikyan, S.N. Sirakanyan, A.S. Narayan, T.O. Asatryan, K.Z. Markaryan, R. A. Aleksanyan, Synthesis and antiarrhythmic activity of 7-benzyl(ethyl)-1-hydroxy-4-carbamoyl-3-oxo-5,6-dihydro-8H-2,7-naphthyridines, Pharm. Chem. J. 30 (6) (1996) 365–367, https://doi.org/10.1007/BF02219320c.

[13] S.Z. Vatsadze, M.L. Kostochka, V.P. Lezina, V.G. Vinokurov, P.M. Klodt, N.V. Zyk, Synthesis of new derivatives of 5,6,7,8- tetrahydro-1,6-naphthyridines and their pharmacological properties, Russ. Chem Bull, Int. Ed. 54 (2005) 257–258, https://doi.org/10.1007/s11172-005-0247-y.

[14] M.W. Embrey, J.S. Wai, T.W. Funk, C.F. Homnick, D.S. Perlow, S.D. Young, J. P. Vacca, D.J. Hazuda, et al., A series of 5-(5,6)-dihydrouracil substituted 8-hydroxy-[1,6]naphthyridine-7-carboxylic acid 4-fluorobenzylamide inhibitors of HIV-1 integrase and viral replication in cells, Bioorg. Med. Chem. Lett. 15 (20) (2005) 4550–4554, https://doi.org/10.1016/j.bmcl.2005.06.105.

[15] 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, et al., Design and Synthesis of 8-Hydroxy-[1,6]Naphthyridines as Novel Inhibitors of HIV-1 Integrase in Vitro and in Infected Cell, J. Med. Chem. 46 (2003) 453–456, https://doi.org/10.1021/jm025553u.

[16] M. Atanasova, S. Ilieve, B. Galabov, QSAR analysis of 1,4-dihydro-4-oxo-1-(2-thiazolyl)-1,8-naphthyridines with anticancer activity, Eur. J. Med. Chem. 42 (2007) 1184–1192, https://doi.org/10.1016/ejmech.2007.01.029.

[17] M. Manoj, K.J. Rajendra Prasad, Effect of substituents in the syntheses of phenyl-Substituted Dibenzonaphthyridines, J. Heterocycl. Chem. 50 (2013) 1049–1063, https://doi.org/10.1002/jhet.652.

[18] M. Manoj, K.J. Rajendra Prasad, Facile synthesis of alkyl and aryl substituted dibenzo[*b,g*][1,8]naphthyridin-5-ones, Synth. Commun. 40 (22) (2010) 3290–3308, https://doi.org/10.1080/00397910903399708.

[19] M. Sangeetha, M. Manoj, Efficient synthetic route to access linear and angular Dibenzonaphthyridines, Russ. J. Org. Chem. 55 (10) (2019) 1604–1608, https://doi.org/10.1134/S1070428019100221.

[20] F. Zaragoza, H. Stephensen, B. Peschke, K. Rimvall, K, 2-(4-Alkylpiperazin-1-yl) quinolines as a new class of imidazole-free histamine H_3 receptor antagonists, J. Med. Chem. 48 (2005) 306–311, https://doi.org/10.1021/jm040873u.

[21] M. Arockiadoss, S. Savithiri, G. Rajarajan, V. Thanikachalam, H. Saleem, Synthesis, spectroscopic (FT-IR, FT-Raman, UV and NMR) and computational studies on 3*t*-pentyl-2*r*,6*c*-diphenylpiperidin-4-one semicarbazone, Spectro chem, Acta Part A. Mol. Biomol. Spectrosc. 148 (2015) 189–202, https://doi.org/10.1016/j.saa.2015.03.117.