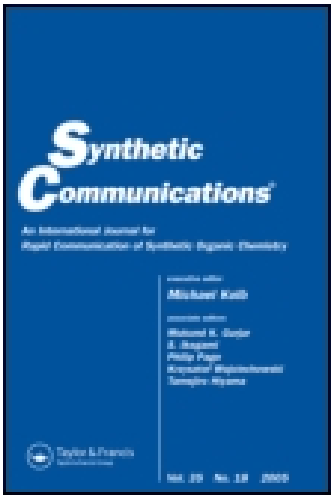

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Synthesis of Alkyl and Aryl Substituted Benzo[h]Naphtho[1,2-b][1,6]naphthyridines

K. Prabha [a] & K. J. Rajendra Prasad [a]

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

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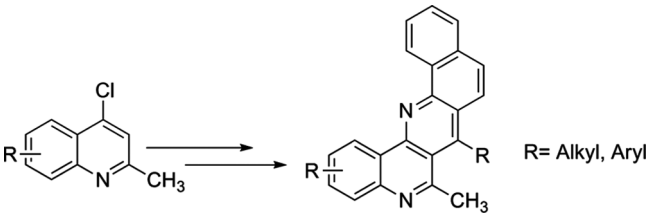
SYNTHESIS OF ALKYL AND ARYL SUBSTITUTED BENZO[*h*]NAPHTHO[1,2-*b*][1,6]NAPHTHYRIDINES

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

GRAPHICAL ABSTRACT



Abstract *The reaction of 4-chloro-2-methylquinolines and 1-naphthylamine under neat conditions yielded 2-methyl-*N*-(1-naphthyl)quinolin-4-amines. These potential intermediates on reaction with aliphatic and aromatic carboxylic acids yielded the respective 7-alkyl and -aryl substituted benzo[*h*]naphtho[1,2-*b*][1,6]naphthyridines. The highly deshielded protons in the final compounds were assigned on the basis of 2D NMR studies.*

Keywords 4-Chloro-2-methylquinolines; 2-methyl-N-(1-naphthyl)quinolin-4-amines; 6-methyl-7-substituted-benzo[*h*]naphtho[1,2-*b*][1,6]naphthyridines; 1-naphthylamine

INTRODUCTION

Among various heterocyclic compounds, quinoline-based drugs such as chloroquine and primaquine are well known for their antimalarial properties against *Plasmodium falciparum*.[1] Moreover, the quinoline nucleus has found broad application in drug development for the treatment of MCH (melanin-concentrating hormone)–receptor–related disorders;[2] cell proliferative diseases;[3] transmissible spongiform encephalopathies;[4] malignant tumors such as stomach cancer, brain tumors, and large intestine cancer,[5] and bacterial infections in mammals.[6] Some of the anilinoquinolines are also considered as synthetic antimalarials.[7,8] Literature studies point out that the reaction of chloroquinolines was aimed to get substituted quinolines possessing biological activity,[9,10] including the amination reaction to derive the respective anilinoquinolines.

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

Naphthyridines have received considerable attention over the past years because of their wide range of biological activities including anti-inflammatory,[11,12] antifungal,[11,12] anti-arrhythmic,[13] anti-alalgesic,[14] anti-HIV,[15] and anticancer[16] activities. Particularly some of the dibenzonaphthyridines (*i.e.*, quinoline dimers), act as potent and selective 3-phosphoinostide-dependent kinase-I inhibitors.[17] The naphthonaphthyridine ring system is a rare heterocycle compared with simple[18,19] as well as benzonaphthyridines,[20] and it is envisioned that naphtho[2,1-*c*][2,7] naphthyridines, which contained both naphthalene rings and naphthyridine moieties, may afford unique biological activities, like the spiro[naphto[2,1-*c*][2,7] naphthyridine-5,4′-piperidine] derivatives that inhibit lipid peroxidation.[21] Naphthonaphthyridines were synthesized from 2-aminobenzo[*f*]-quinoline and glycerol in the presence of H_2SO_4,[22] by the Skraup reaction of 3-aminobenzo[*h*]quinoline with ketone,[23] from a multicomponent reaction[24,25] of aromatic aldehydes, 2-naphtylamines, and piperidone derivatives, and by several other methods.[26,27]

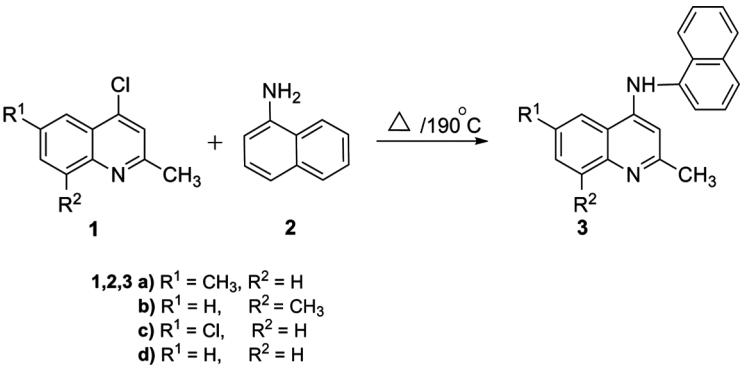
Recently, dibenzonaphthyridines have been synthesized by a reaction in which anilinoquinolines were exploited as potential intermediates.[28–30] In continuation, herein we report a mild and efficient synthesis of alkyl and aryl substituted benzonaphthonaphthyridines utilizing 4-chloro-2-methylquinolines and involving naphthylaminoquinolines as potential intermediates.

The present investigation was aimed to study the reaction of 4-chloro-2-methylquinolines **1** and 1-naphthylamine **2** to get the 2-methyl-*N*-(1-naphthyl)quinolin-4-amine **3**, which in turn can be utilized as potential intermediates to derive the alkyl and aryl substituted benzonaphthonaphthyridines **4** and **5**.

In view of these considerations, 4-chloro-2,8-dimethylquinoline (**1b**) was reacted with 1-naphthylamine **2** under neat conditions at 190 °C for half an hour to obtain a single product. In its infrared (IR) spectrum, NH stretching vibration was observed at 3437 cm^{-1}. Its ^1H NMR spectrum showed the presence of two methyl groups at δ 2.50 and δ 2.77 for C_2-CH_3 and C_8-CH_3 respectively. The peculiar C_3-H appeared as a singlet at δ 6.12. All the 10 aromatic protons appeared at δ 7.54–8.86 while two broad singlets (each for one proton) integrated at δ 11.21 and δ 12.65 and were assigned C_4-NH amino form and N_1-H imino form. The ratio of amino to imino form was found to be 1:1. ^{13}C NMR spectra confirmed the presence of 21 carbons. From the elemental analysis, the molecular formula was found to be $C_{21}H_{18}N_2$ and its mass spectrum showed the molecular ion peak at m/z 298. From these details, the structure of the compound was confirmed as 2,8-dimethyl-*N*-(1-naphthyl)quinolin-4-amine (**3b**). The reaction sequence was extended to other quinoline derivatives (**1a,c,d**) to afford the corresponding 2-methyl-*N*-(1-naphthyl) quinolin-4-amines (**3a,c,d**) (Scheme 1). The compounds **3a**, **3b**, and **3d** were identical with the compounds reported earlier,[31] but our procedure described here is ecofriendly because it involves solvent-free conditions.

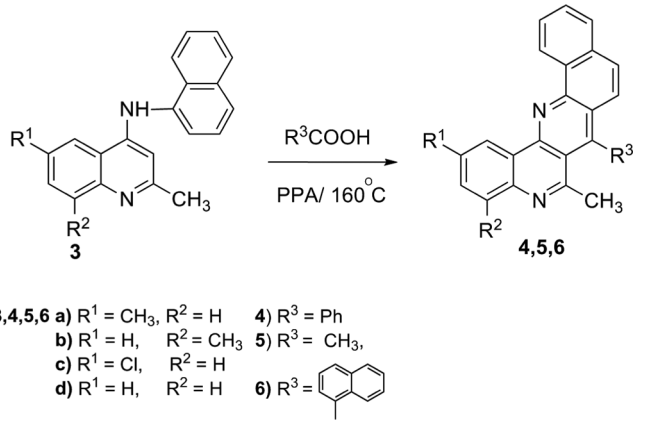
Having obtained the potential intermediates **3**, the synthesis of alkyl and aryl substituted benzonaphthonaphthyridines was intended, employing alkyl and aryl carboxylic acids under acidic condition.

Hence 2,8-dimethyl-*N*-(1-naphthyl)quinolin-4-amine (**3b**) was reacted with benzoic acid in the presence of polyphosphoric acid as catalyst (Scheme 2). The reaction yielded a single product. Its IR spectrum did not show the presence of a NH group. Its ^1H NMR spectrum exhibited two singlets each at δ 2.35 and δ 2.86 for C_4-CH_3



Scheme 1. Preparation of 2-methyl-*N*-(1-naphthyl)quinolin-4-amine **3**.

and C_6-CH_3 respectively. All the aromatic protons resonated at δ 7.27–7.81 except for two proton doublets, which were very much deshielded at δ 9.37 ($J = 7.50$ Hz) and δ 9.68 ($J = 8.00$ Hz). With the help of advanced NMR studies such as correlation spectroscopy [H,H-COSY, C,H-COSY heteronuclear single-quantum correlation (HSQC)], and heteronuclear multiple-bond correlation (HMBC) correlations, the deshielded proton at δ 9.37 was assigned to C_1-H while the proton at δ 9.68 was assigned C_{13}-H. A one-proton doublet at δ 9.37 ($J = 7.50$ Hz) and a six-proton multiplet at 7.51–7.61 have H,H-COSY connections. The proton at δ 9.37 was characteristics of C_1-H while the multiplet was assigned to C_2, C_8, C_9, C'_3, C'_4, and C'_5-H. A one-proton doublet at δ 9.68 ($J = 8.00$ Hz) and a one proton triplet at δ 7.77 ($J = 7.50$ Hz) have H,H-COSY connections, which are characteristic of C_{13}-H and C_{12}-H respectively. The assignment of coupling protons for all the other aromatic protons using H,H-COSY is mentioned in Table 1. From the C,H-COSY (HSQC) spectrum, the values of C_1 and C_{13} carbons were assigned as δ 122.3 and δ 125.9 respectively. The values of all other carbons holding protons are denoted in Table 2. The peculiar C_1-H has HMBC connectivity with C_2-H while the C_{13}-H have connectivities with



Scheme 2. Preparation of 6-methyl-7-substituted-benzo[*h*]naphtho[1,2-*b*][1,6]naphthyridines **4**, **5**, and **6**.

Table 1. ^{1}H NMR and their coupling protons of the compound **4b** assigned by H,H-COSY

Entry	^{1}H NMR (δ)	Coupling protons (δ)
1	2.35 (s, 3H, C_4-CH_3)	—
2	2.86 (s, 3H, C_6-CH_3)	—
3	7.27 (d, 1H, C_3-H, $J = 9.50$ Hz)	7.51–7.61 (m, 6H which includes C_2-H)
4	7.35 (d, 2H, C'_2 & C'_6-H, $J = 7.20$ Hz)	7.51–7.61 (m, 6H which includes C'_3 & C'_5-H)
5	7.51–7.61 m, 6H which includes C_2, C'_3 & C'_5-H)	7.27 (d, 1H, C_3-H, $J = 9.50$ Hz) 7.35 (d, 2H, C'_2 & C'_6-H, $J = 7.20$ Hz)
6	7.70 (t, 1H, C_{11}-H, $J = 7.50$ Hz)	7.77 (t, 1H, C_{12}-H, $J = 7.50$ Hz) 7.81 (d, 1H, C_{10}-H, $J = 7.50$ Hz)
7	7.77 (t, 1H, C_{12}-H, $J = 7.50$ Hz)	7.70 (t, 1H, C_{11}-H, $J = 7.50$ Hz) 9.68 (d, 1H, C_{13}-H, $J = 8.00$ Hz)
8	7.81 (d, 1H, C_{10}-H, $J = 7.50$ Hz)	7.70 (t, 1H, C_{11}-H, $J = 7.50$ Hz)
9	9.37 (d, 1H, C_1-H, $J = 7.50$ Hz)	7.51–7.61 (m, 6H which includes C_2-H)
10	9.68 (d, 1H, C_{13}-H, $J = 8.00$ Hz)	7.77 (t, 1H, C_{12}-H, $J = 7.50$ Hz)

C_{11}, C_{13a}, and C_{13b} carbons. The connectivity of all other protons with the carbons is denoted in Table 3. The HMBC connectivity is diagrammatically shown in Fig. 1.

Its ^{13}C NMR spectrum showed the appearance of 28 carbon signals, and the mass spectrum identified the molecular ion peak at m/z 384. The molecular formula was deduced as $C_{28}H_{20}N_2$ from its elemental analysis data. All these spectral and analytical details attest to the structure of the compound as 4,6-dimethyl-7-phenylbenzo[*h*]naphtho[1,2-*b*][1,6]naphthyridine (**4b**). The generality of the reaction was tested against other 2-methyl-*N*-(1-naphthyl)quinolin-4-amines (**3a,c,d**) in order to get the corresponding benzonaphthonaphthyridines (**4a,c,d**). A similar set of reactions was also extended to other carboxylic acids (i.e., acetic acid and 1-naphthoic acid) in which the 2-methyl-*N*-(1-naphthyl)quinolin-4-amines **3** was reacted with acetic acid and 1-naphthoic acid in the presence of polyphosphoric acid (PPA) at 160 °C to get 6,7-dimethylbenzo[*h*]naphtho[1,2-*b*] [1,6]naphthyridines **5** and 6-methyl-7-(naphthalen-1-yl)benzo[*h*]naphtho[1,2-*b*][1,6]naphthyridines **6** respectively (Scheme 2). In the present case, also the C_1-H and C_{13}-H were deshielded around ~9.25 and ~9.79 respectively. The numbering of the core skeleton of the benzo[*h*]naphtho[1,2-*b*][1,6] naphthyridine moiety is represented in Fig. 2.

Table 2. ^{1}H NMR and their carbon of the compound **4b** assigned by C,H-COSY (HSQC)

Entry	^{1}H NMR (δ)	^{13}C NMR (δ)
1	2.35 (s, 3H, C_4-CH_3)	29.5 (C_4)
2	2.86 (s, 3H, C_6-CH_3)	17.8 (C_6)
3	7.27 (d, 1H, C_3-H, $J = 9.50$ Hz)	127.7 (C_3)
4	7.35 (d, 2H, C'_2 &C'_6-H, $J = 7.20$ Hz)	130.0 (C'_2 & C'_6)
5	7.51–7.61 (m, 6H, C_2, C_8, C_9, C'_3, C'_4, C'_5-H)	131.8 (C_2), 125.1 (C_8), 124.2 (C_9), 128.5 (C'_3, C'_5), 128.4 (C'_4)
6	7.70 (t, 1H, C_{11}-H, $J = 7.50$ Hz)	129.5 (C_{11})
7	7.77 (t, 1H, C_{12}-H, $J = 7.50$ Hz)	127.3 (C_{12})
8	7.81 (d, 1H, C_{10}-H, $J = 7.50$ Hz)	127.6 (C_{10})
9	9.37 (d, 1H, C_1-H, $J = 7.50$ Hz)	122.3 (C_1)
10	9.68 (d, 1H, C_{13}-H, $J = 8.00$ Hz)	125.9 (C_{13})

Table 3. HMBC connectivity of the protons with the carbons of the compound **4b**

Entry	^{1}H NMR	HMBC ^2J, ^3J
1	2.35 (s, 3H, C_4-CH_3)	C_3, C_4, C_{4a}
2	2.86 (s, 3H, C_6-CH_3)	C_6, C_{6a}
3	7.27 (d, 1H, C_3-H, $J = 9.50$ Hz)	C_{4a}
4	7.35 (d, 2H, C'_2 & C'_6-H, $J = 7.20$ Hz)	C'_3, C'_4, C'_5
5	7.51–7.61 (m, 6H, C_2, C_8, C_9, C'_3, C'_4, C'_5-H)	C_1, C_3, C_4, C_7, C_{7a}, C_{9a}, C_{10}, C'_1, C'_3, C'_4, C'_5
6	7.70 (t, 1H, C_{11}-H, $J = 7.50$ Hz)	C_{9a}, C_{10}, C_{12}, C_{13}
7	7.77 (t, 1H, C_{12}-H, $J = 7.50$ Hz)	C_{10}, C_{13a}
8	7.81 (d, 1H, C_{10}-H, $J = 7.50$ Hz)	C_{9a}, C_{13a}
9	9.37 (d, 1H, C_1-H, $J = 7.50$ Hz)	C_2
10	9.68 (d, 1H, C_{13}-H, $J = 8.00$ Hz)	C_{11}, C_{13a}, C_{13b}

The reason for the two protons being deshielded might be the interaction of these protons with the nitrogen atom at the 14th position.

The plausible mechanism for the conversion of **1** to **4,5,6** might be as shown in Scheme 3.

Amination of 4-chloro-2-methylquinolines **1** with 1-naphthylamine **2** under neat conditions at 190 °C afforded the 2-methyl-*N*-(1-naphthyl)quinoline-4-amines

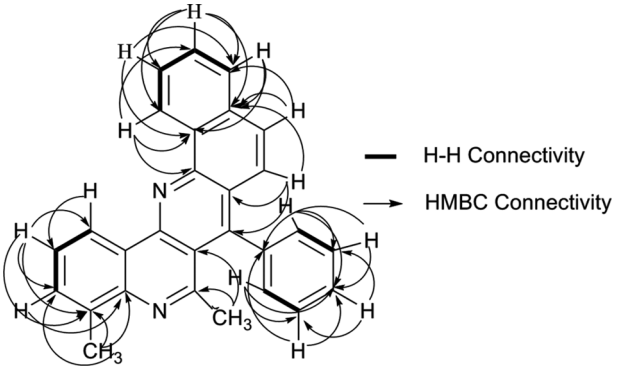


Figure 1. Bold lines represent H,H-COSY and arrows represent HMBC connectivity of compound **4b**.

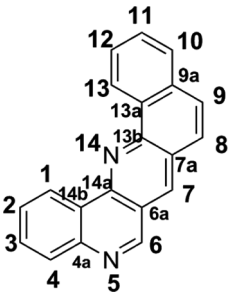
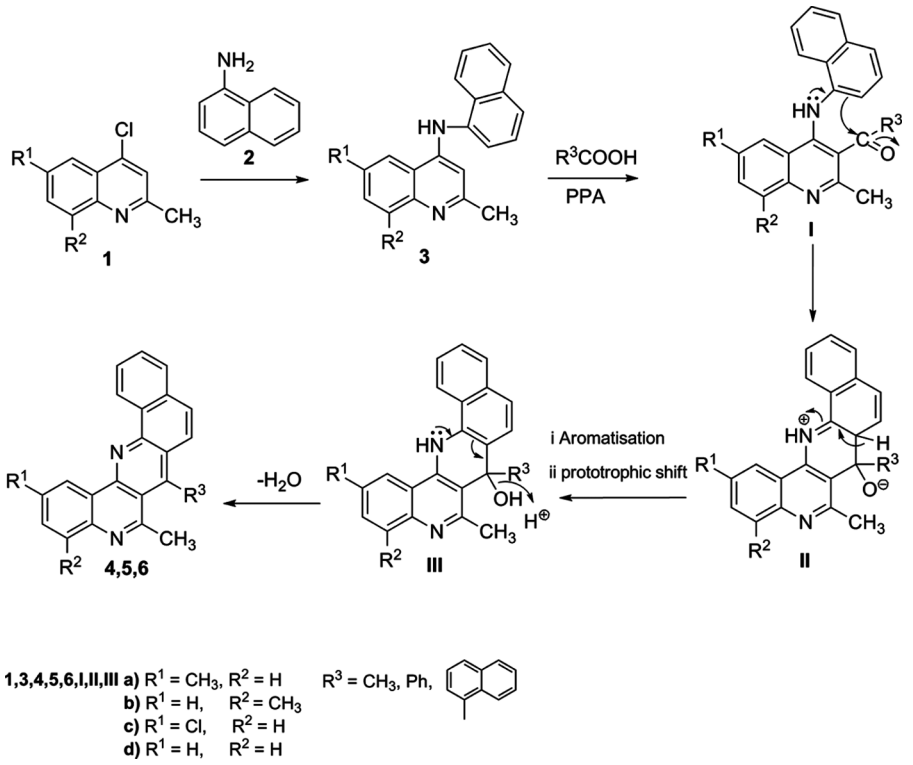


Figure 2. Numbering of the benzo[*h*]naphtho[1,2-*b*][1,6]naphthyridine core.



Scheme 3. Mechanism for the formation of the final benzonaphthonaphthyridines.

3. The 2-methyl-*N*-(1-naphthyl)quinolin-4-amines **3** on acylation with alkyl or aryl carboxylic acids at the 3rd position of the quinoline moiety yielded the intermediate **I**. The intermediate **I** on internal electrophilic cyclization at the C_3-carbonyl carbon through the β-position of the naphthylamino moiety gave the intermediate **II**, which on aromatization and prototropic shift followed by the elimination of H_2O molecule through the intermediate **III** ended up in the formation of final products **4**–**6**.

From the experimental work it is concluded that the reaction of 4-chloro-2-methylquinolines **1** and 1-naphthylamine **2** yielded 2-methyl-*N*-(1-naphthyl)quinolin-4-amines **3**, which were utilized as potential intermediates to prepare 7-substituted benzonaphthonaphthyridines **4**–**6** where the substituents hold alkyl and aryl moieties.

EXPERIMENTAL

Melting points (mp) were determined on a Mettler FP 51 apparatus (Mettler Instruments, Switzerland) and are uncorrected. They are expressed in degrees centigrade (°C). IR spectra were recorded on Schimadzu FTIR-8201PC spectrophotometer (Schimadzu, Japan) using KBr disc. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AV 400 [400-MHz(^{1}H) and 100-MHz(^{13}C)] spectrometers, and 2D-NMR were recorded on Bruker AV 500 [500-MHz (^{1}H) and 125-MHz (^{13}C)]

spectrometers using tetramethylsilane (TMS) as an internal reference. The chemical shifts are expressed in parts per million (ppm). Mass spectra (MS) were recorded on an AutoSpec EI+Shimadzu QP 2010 Plus GC-MS mass spectrometer. Micro analyses 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 thin-layer chromatography (TLC) with plates coated with silica gel G using petroleum ether and ethyl acetate as developing solvents.

2-Methyl-N-(1-naphthyl)quinolin-4-amine (3)

General procedure. 4-Chloro-2-methylquinoline (**1**, 0.004 mol) was heated with 1-naphthylamine (**2**, 0.004 mol) under neat conditions at 190 °C for half an hour. The product was washed with water, dried, adsorbed, and purified using silica-gel column chromatography and eluted with ethylacetate–methanol (99:1) mixture to get **3**, which was then recrystallized using methanol.

Compound 3a. Brown solid; mp 295–297 °C; yield: 0.870 g (73%). IR ν_{max} (cm^{-1}) : 3431 (NH), 1603, 1520, 1148; ^{1}H NMR (DMSO-d_6) δ: 2.47 (s, 3H, C_2-CH_3), 2.59 (s, 3H, C_6-CH_3), 6.15 (s, 1H, C_3-H), 7.55–8.03 (m, 8H, C_7-, C_8-, C'_2-, C'_3-, C'_4-, C'_5-, C'_6-, and C'_7-H), 8.10 (dd, 1H, C'_8-H $J_o = 7.75$ Hz and $J_m =$ 3.50 Hz), 8.76 (s, 1H, C_5-H), 10.94 (b s, 1H, C_4-NH amino form), 14.47 (b s, 1H, N_1-H imino form). The ratio of amino and imino form was found to be 1:1. ^{13}C NMR (DMSO-d_6) δ: 20.1 (C_6-CH_3), 21.6 (C_2-CH_3), 100.5 (C_3), 116.4 (C'_2), 120.3 (C_5), 123.0 (C'_4), 123.1 (C_{4a}), 125.8 (C'_8), 126.8 (C'_{8a}), 127.4 (C'_7), 127.6 (C'_6), 129.0 (C'_3), 129.1 (C'_5), 129.8 (C_8), 133.8 (C_7), 134.6 (C_6), 135.6 (C'_{4a}), 136.9 (C'_1), 137.6 (C_{8a}), 154.2 (C_4), 155.8 (C_2); MS: m/z (%) 298 (M^+, 85), 297 (100), 283 (20), 268 (15), 124 (10), 105 (18), 89 (15), 51 (30). Anal. calcd. for $C_{21}H_{18}N_2$: C, 84.53; H, 6.08; N, 9.39. Found : C, 84.42; H, 6.13; N, 9.45%.

Compound 3b. Brown solid; mp 297–299 °C; yield: 0.894 g (75%). IR ν_{max} (cm^{-1}): 3437 (NH), 1598, 1525, 1144; ^{1}H NMR (DMSO-d_6) δ: 2.50 (s, 3H, C_2-CH_3), 2.77 (s, 3H, C_8-CH_3), 6.12 (s, 1H, C_3-H), 7.54–7.87 (m, 8H, C_6-, C_7-, C'_2-, C'_3-, C'_4-, C'_5-, C'_6-, and C'_7-H), 8.11 (d, 1H, C'_8-H $J = 8.50$ Hz), 8.86 (d, 1H, C_5-H $J = 8.50$ Hz), 11. 21 (b s, 1H, C_4-NH amino form), 12.65 (b s, 1H, N_1-H imino form). The ratio of amino and imino form was found to be 1:1; ^{13}C NMR (DMSO-d_6) δ: 19.4 (C_8-CH_3), 21.5 (C_2-CH_3), 100.8 (C_3), 116.4 (C'_2), 121.0 (C_5), 123.0 (C'_4) 122.9 (C_{4a}), 125.8 (C'_8), 126.8 (C'_{8a}), 127.4 (C'_7), 127.6 (C'_6), 129.0 (C'_3), 129.1 (C'_5), 129.0 (C_6), 133.5 (C_7), 135.6 (C'_{4a}), 136.3 (C_8), 136.9 (C'_1), 140.2 (C_{8a}), 154.8 (C_4), 155.9 (C_2). MS: m/z (%) 298 (M^+, 80), 297 (100), 283 (15), 268 (12), 123 (15), 105 (20), 65 (18), 51 (35). Anal. calcd. for $C_{21}H_{18}N_2$: C, 84.53; H, 6.08; N, 9.39. Found: C, 84.65; H, 5.99; N, 9.36%.

Compound 3c. Brown solid; mp 294–296 °C; yield: 0.858 g (72%); IR ν_{max} (cm^{-1}) : 3430 (NH), 1596, 1540, 1131. ^{1}H NMR (DMSO-d_6) δ: 2.47 (s, 3H, C_2-CH_3), 6.17 (s, 1H, C_3-H), 7.56–8.06 (m, 8H, C_7-, C_8-, C'_2-, C'_3-, C'_4-, C'_5-, C'_6-, and C'_7-H), 8.10 (dd, 1H, C'_8-H $J_o = 8.02$ Hz and $J_m = 2.50$ Hz), 9.05 (s, 1H, C_5-H), 10. 94 (b s, 1H, C_4-NH amino form), 14.63 (b s, 1H, N_1- H imino form). The ratio of amino and imino form was found to be 1:1. ^{13}C NMR (DMSO-d_6) δ: 21.9

(C_2-CH_3), 101.0 (C_3), 116.4 (C'_2), 120.0 (C_5), 123.0 (C'_4), 123.2 (C_{4a}), 125.8 (C'_8), 126.8 (C'_{8a}), 127.4 (C'_7), 127.6 (C'_6), 129.0 (C'_3), 129.1 (C'_5), 130.1 (C_8), 133.2 (C_7), 133.8 (C_6), 135.6 (C'_{4a}), 136.9 (C'_1), 137.8 (C_{8a}), 154.0 (C_4), 155.8 (C_2). MS: m/z (%) 320 ($M+2$, 26), 318 (M^+, 80), 317 (100), 302 (20), 287 (25), 247 (15), 123 (10), 88 (40), 51 (65). Anal. calcd. for $C_{20}H_{15}ClN_2$: C, 75.35; H, 4.74; N, 8.79. Found : C, 75.38; H, 4.82; N, 8.71%.

Compound 3d. Brown solid; mp 296–298 °C; yield : 0.840 g (74%); IR ν_{max} (cm^{-1}) : 3423 (NH), 1587, 1520, 1115; ^{1}H NMR (DMSO-d_6) δ: 2. 48 (s, 3H, C_2-CH_3), 6.10 (s, 1H, C_3-H), 7.56–8.12 (m, 9H, C_6-, C_7-, C_8-, C'_2-, C'_3-, C'_4-, C'_5-, C'_6-, and C'_7-H), 8.14 (d, 1H, C'_8-H, $J=8.00$ Hz), 8.96 (s, 1H, C_5-H $J=7.50$ Hz), 11.10 (b s, 1H, C_4-NH amino form), 14.60 (b s, 1H, N_1-H imino form). The ratio of amino and imino form was found to be 1:1. ^{13}C NMR (DMSO-d_6) δ 21.5 (C_2-CH_3) 101.1 (C_3), 116.4 (C'_2), 121.3 (C_5), 123.0 (C'_4), 122.6 (C_{4a}), 125.8 (C'_8), 126.8 (C'_{8a}), 127.4 (C'_7), 127.6 (C'_6), 129.0 (C'_3), 129.1 (C'_5), 129.1 (C_6), 130.5 (C_8), 133.3 (C_7), 135.6 (C'_{4a}), 136.9 (C'_1), 139.7 (C_{8a}), 154.6 (C_4), 155.6 (C_2). MS: m/z (%) 284 (M^+, 95), 283 (100), 269 (25), 268 (15), 253 (10), 124 (20), 89 (22), 44 (35). Anal. calcd. for $C_{20}H_{16}N_2$: C, 84.48; H, 5.67; N, 9.85. Found : C, 84.56; H, 5.70; N, 9.74%.

Preparation of 6-Methyl-7-phenylbenzo[h]naphtho[1,2-b][1,6] naphthyridine (4)

General procedure. 2-Methyl-*N*-(1-naphthyl)quinolin-4-amine (**3**, 0.002 mol) and benzoic acid (0.0025 mol) were added to polyphosphoric acid (6 g of P_2O_5 in 3 mL of H_3PO_4) and heated at 160 °C for 3 h. The reaction was monitored using TLC. After the completion of the reaction, it was poured into ice water, neutralized with saturated sodium bicarbonate solution to remove excess benzoic acid, extracted with ethyl acetate, and purified by column chromatography using silica gel. The product eluted with petroleum ether–ethyl acetate (99:1) mixture to get **4**, which was recrystallised using methanol.

Compound 4a. Colorless needles; mp 205–207 °C; yield : 0.330 g (43%). IR ν_{max} (cm^{-1}) : 1616 (C=N), 1608, 1560, 1471; ^{1}H NMR ($CDCl_3$) δ: 2.26 (s, 3H, C_2-CH_3), 2.90 (s, 3H C_6-CH_3), 7.27–7.94 (m, 12H, C_3-, C_4-, C_8-, C_9-, C_{10}-, C_{11}-, C_{12}-, C'_2-, C'_3-, C'_4-, C'_5-, and C'_6-H), 9.45 (d, 1H, C_1-H, $J=2.40$ Hz), 9.68 (d, 1H, C_{13}-H $J=8.00$ Hz). ^{13}C NMR ($CDCl_3$) δ: 17.8 (C_6-CH_3), 29.9 (C_2-CH_3), 117.9 (C_{6a}), 122.5 (C_1), 124.1 (C_9), 125.0 (C_8), 125.2 (C_{7a}), 125.9 (C_{13}), 126.4 (C_{14b}), 127.3 (C_{12}), 127.6 (C_{10}), 128.0 (C_4), 128.4 (C'_4), 128.5 (C'_3 & C'_5), 128.6 (C_3), 129.5 (C_{11}), 130.0 (C'_2 & C'_6), 131.1 (C_2), 131.3 (C_{9a}), 133.9 (C_{13a}), 139.3 (C'_1), 143.4 (C_7), 144.4 (C_{4a}), 147.4 (C_{13b}), 147.6 (C_{14a}), 158.6 (C_6); MS: m/z (%) 384 (M^+, 100), 383 (20), 369 (10), 354 (12), 221 (10), 123 (5), 65 (10), 51 (10). Anal. calcd. for $C_{28}H_{20}N_2$: C, 87.47; H, 5.24; N, 7.29. Found: C, 87.41; H, 5.28; N, 7.31%.

Compound 4b. Colorless prisms; mp 202–205 °C; yield: 0.338 g (41%); IR ν_{max} (cm^{-1}) : 1621 (C=N), 1601, 1561, 1480. ^{1}H NMR ($CDCl_3$) δ: 2.35 (s, 3H, C_4-CH_3), 2.86 (s, 3H, C_6-CH_3), 7.27 (d, 1H, C_3-H, $J=9.50$ Hz), 7.35 (d, 2H, C'_2 & C'_6-H, $J=7.20$ Hz) 7.51–7.61 (m, 6H, C_2, C_8, C_9, C'_3, C'_4, C'_5-H), 7.70 (t, 1H, C_{11}-H, $J=7.50$ Hz), 7.77 (t, 1H, C_{12}-H, $J=7.50$ Hz), 7.81 (d, 1H, C_{10}-H, $J=7.50$ Hz), 9.37

(d, 1H, C_1-H $J = 7.50$ Hz), 9.68 (d, 1H, C_{13}-H, $J = 8.00$ Hz). ^{13}C NMR ($CDCl_3$) δ: 17.8 (C_6-CH_3), 29.5 (C_4-CH_3), 117.9 (C_{6a}), 122.3 (C_1), 124.1 (C_9), 124.5 (C_2), 125.0 (C_8), 125.2 (C_{7a}), 125.9 (C_{13}), 126.2 (C_{14b}), 127.3 (C_{12}), 127.6 (C_{10}), 127.7 (C_3), 128.4 (C'_4), 128.51 (C'_3 & C'_5), 129.5 (C_{11}), 130.0 (C'_2 & C'_6), 131.3 (C_{9a}), 133.9 (C_{13a}), 136.1 (C_4) 139.3 (C'_1), 143.4 (C_7), 147.4 (C_{13b}), 147.6 (C_{14a}), 147.7 (C_{4a}), 158.6 (C_6). MS: m/z (%) 384 (M^+, 100), 383 (28), 369 (5), 354 (5), 222 (10), 123 (15), 65 (6), 51 (5). Anal. calcd. for $C_{28}H_{20}N_2$: C, 87.47; H, 5.24; N, 7.29. Found: C, 87.58; H, 5.18; N, 7.24%.

Compound 4c. Colorless needles; mp 206–208 °C; yield: 0.323 g (40%); IR ν_{max} (cm^{-1}): 1622 (C=N), 1605, 1547, 1463; ^{1}H NMR ($CDCl_3$) δ: 2.90 (s, 3H C_6-CH_3), 7.25–7.94 (m, 12H, C_3-, C_4-, C_8-, C_9-, C_{10}-, C_{11}-, C_{12}-, C'_2-, C'_3-, C'_4-, C'_5-, and C'_6-H), 9.29 (d, 1H, C_1-H, $J = 2.40$ Hz), 9.63 (d, 1H, C_{13}-H, $J = 8.00$ Hz); ^{13}C NMR ($CDCl_3$) δ: 17.8 (C_6-CH3), 117.9 (C_{6a}), 122.2 (C_1), 124.1 (C_9), 125.0 (C_8), 125.2 (C_{7a}), 125.9 (C_{13}), 126.4 (C_{14b}), 127.3 (C_{12}), 127.6 (C_{10}), 128.2 (C_4), 128.4 (C'_4), 128.51 (C'_3 & C'_5), 128.8 (C_3), 129.5 (C_{11}), 130.0 (C'_2 & C'_6), 130.3 (C_2), 131.3 (C_{9a}), 133.9 (C_{13a}), 139.3 (C'_1), 143.4 (C_7), 144.4 (C_{4a}), 147.4 (C_{13b}), 147.6 (C_{14a}), 158.6 (C_6). MS: m/z (%) 406 (M + 2, 35), 404 (M^+, 100), 389 (18), 375 (12), 369 (5), 222 (18), 123 (10), 65 (12), 51 (15). Anal. calcd. for $C_{27}H_{17}ClN_2$: C, 80.09; H, 4.23; N, 6.91. Found: C, 80.12; H, 4.29; N, 6.97%.

Compound 4d. Colorless prisms; mp 201–203 °C; yield: 0.310 g (42%); IR ν_{max} (cm^{-1}) : 1618 (C=N), 1607, 1549, 1467; ^{1}H NMR ($CDCl_3$) δ: 2.88 (s, 3H, C_6-CH_3), 7.37–8.13 (m, 13H, C_2-, C_3-, C_4-, C_8-, C_9-, C_{10}-, C_{11}-, C_{12}-, C'_2-, C'_3-, C'_4-, C'_5-, and C'_6-H), 9.61 (d, 1H, C_1-H, $J = 7.40$ Hz), 9.79 (d, 1H, C_{13}-H, $J = 9.00$ Hz); ^{13}C NMR ($CDCl_3$) δ: 17.8 (C_6-CH_3), 117.9 (C_{6a}), 122.5 (C_1), 124.1 (C_9), 124.3 (C_2), 125.0 (C_8), 125.2 (C_{7a}), 125.9 (C_{13}), 126.2 (C_{14b}), 126.6 (C_4), 127.3 (C_{12}), 127.6 (C_{10}), 127.7 (C_3), 128.4 (C'_4), 128.51 (C'_3 & C'_5), 129.5 (C_{11}), 130.0 (C'_2 & C'_6), 131.3 (C_{9a}), 133.9 (C_{13a}), 139.3 (C'_1), 143.4 (C_7), 147.4 (C_{13b}), 147.6 (C_{14a}), 147.7 (C_{4a}) 158.6 (C_6). MS: m/z (%) 370 (M^+, 100), 369 (85), 341 (32), 293 (10), 263 (15), 124 (10), 64 (10), 44 (25). Anal. calcd. for $C_{27}H_{18}N_2$: C, 87.54; H, 4.90; N, 7.56. Found: C, 87.66; H, 4.81; N, 7.53%.

6,7-Dimethylbenzo[h]naphtho[1,2-b][1,6]naphthyridine (5)

General procedure. An appropriate mixture of 2-methyl-*N*-(1-naphthyl) quinolin-4-amine (**3**, 0.002 mol) and acetic acid (0.0025 mol) was added to polyphosphoric acid (6 g of P_2O_5 in 3 mL of H_3PO_4) and heated at 160 °C for 3 h. The reaction was monitored using TLC. After the completion of the reaction, it was poured into ice water, extracted with ethyl acetate, and purified by column chromatography using silica gel. The product was eluted with petroleum ether–ethyl acetate (99:1) mixture to get **5**, which was recrystallized using methanol.

Compound 5a. Colorless prisms; mp 184–186 °C; yield: 0.218 g (34%); IR ν_{max} (cm^{-1}) : 1623 (C=N), 1591, 1522, 1437; ^{1}H NMR ($CDCl_3$) δ: 2.53 (s, 3H, C_2-CH_3), 2.71 (s, 3H, C_6-CH_3), 3.12 (s, 3H, C_7-CH_3), 7.61–7.99 (m, 7H, C_3-, C_4-, C_8-, C_9-, C_{10}-, C_{11}-, and C_{12}-H), 9.25 (d, 1H, C_1-H, $J = 2.00$ Hz), 9.51 (d, 1H, C_{13}-H, $J = 8.00$ Hz). ^{13}C NMR ($CDCl_3$) δ: 16.9 (C_6-CH_3), 24.4 (C_7-CH_3), 29.1 (C_2-CH_3), 118.1 (C_{6a}), 122.5

(C_1), 124.1 (C_9), 125.2 (C_8), 125.4 (C_{7a}), 125.9 (C_{13}), 126.4 (C_{14b}), 127.3 (C_{12}), 127.6 (C_{10}), 128.0 (C_4), 128.8 (C_3), 129.5 (C_{11}), 131.1 (C_2), 131.1 (C_{9a}), 133.9 (C_{13a}), 139.1 (C_7), 144.4 (C_{4a}), 147.4 (C_{13b}), 147.6 (C_{14a}), 158.6 (C_6). MS: m/z (%) 322 (M^+, 100), 307 (80), 291 (15), 278 (15), 277 (42), 124 (10), 105 (20), 65 (28). Anal. calcd. for $C_{23}H_{18}N_2$: C, 85.69; H, 5.62; N, 8.69. Found: C, 85.79; H, 5.68; N, 8.54%.

Compound 5b. Colorless needles; mp 183–185 °C; Yield: 0.231 g (36%); IR ν_{max} (cm^{-1}) : 1626 (C=N), 1587, 1520, 1439; ^{1}H NMR ($CDCl_3$) δ: 2.38 (s, 3H, C_2-CH_3), 2.92 (s, 3H, C_6-CH_3), 3.34 (s, 3H, C_7-CH_3), 7.64–8.15 (m, 7H, C_2-, C_3-, C_8-, C_9-, C_{10}-, C_{11}-, and C_{12}-H), 9.25 (dd, 1H, C_1-H $J_o = 8.00$ Hz and $J_m = 1.50$ Hz),), 9.71 (d, 1H, C_{13}-H, $J = 8.00$ Hz); ^{13}C NMR ($CDCl_3$) δ_C: 16.9 (C_6-CH_3), 24.4 (C_7-CH_3), 29.8 (C_4-CH_3), 118.1 (C_{6a}), 122.3 (C_1), 124.1 (C_9), 125.2 (C_8), 125.4 (C_{7a}), 125.9 (C_{13}), 126.4 (C_{14b}), 127.3 (C_{12}), 127.4 (C_2), 127.6 (C_{10}), 128.6 (C_3), 129.5 (C_{11}), 131.1 (C_{9a}), 133.9 (C_{13a}), 134.2 (C_4), 139.1 (C_7), 147.4 (C_{13b}), 147.6 (C_{14a}), 147.8 (C_{4a}), 158.6 (C_6). MS: m/z (%) 322 (M^+, 100), 321 (55), 307 (38), 290 (10), 278 (8), 277 (28), 124 (15), 105 (18), 65 (25). Anal. calcd. for $C_{23}H_{18}N_2$: C, 85.69; H, 5.62; N, 8.69. Found: C, 85.66; H, 5.56; N, 8.78%.

Compound 5c. White solid; mp 186–188 °C; Yield: 0.205 g (30%); IR ν_{max} (cm^{-1}) : 1627 (C=N), 1585, 1518, 1442; NMR ($CDCl_3$) δ_H: ^{1}H NMR (500 MHz $CDCl_3$) δ: 2.66 (s, 3H, C_6-CH_3), 3.09 (s, 3H, C_7-CH_3), 7.59–8.00 (m, 7H, C_3-, C_4-, C_8-, C_9-, C_{10}-, C_{11}-, and C_{12}-H), 9.21 (d, 1H, C_1-H, $J = 2.00$ Hz), 9.49 (d, 1H, C_{13}-H, $J = 8.00$ Hz). ^{13}C NMR ($CDCl_3$) δ: 16.9 (C_6-CH_3), 24.4 (C_7-CH_3), 118.1 (C_{6a}), 122.2 (C_1), 124.1 (C_9), 125.2 (C_8), 125.4 (C_{7a}), 125.9 (C_{13}), 126.4 (C_{14b}), 127.3 (C_{12}), 127.6 (C_{10}), 128.0 (C_4), 128.6 (C_3), 129.5 (C_{11}), 131.0 (C_2), 131.1 (C_{9a}), 133.9 (C_{13a}), 139.1 (C_7), 144.4 (C_{4a}), 147.4 (C_{13b}), 147.6 (C_{14a}), 158.6 (C_6). MS: m/z (%) 344 (M + 2, 30), 342 (M^+, 100), 341 (60), 327 (10), 307 (12), 291 (10), 126 (15), 106 (12), 65 (25). Anal. calcd. for $C_{22}H_{15}ClN_2$: C, 77.19; H, 4.39; N, 8.19. Found: C, 77.10; H, 4.45; N, 8.24%.

Compound 5d. Colorless prisms; mp 182–184 °C; yield: 0.203 g (23%); IR ν_{max} (cm^{-1}) : 1622 (C=N), 1592, 1525, 1444; ^{1}H NMR ($CDCl_3$) δ: 2.75 (s, 3H, C_6-CH_3), 3.11 (s, 3H, C_7-CH_3), 7.64–8.16 (m, 8H, C_2-, C_3-, C_4-, C_8-, C_9-, C_{10}-, C_{11}-, and C_{12}-H), 9.27 (d, 1H, C_1-H $J_o = 8.00$ Hz and $J_m = 1.50$ Hz), 9.75 (d, 1H, C_{13}-H, $J = 8.00$ Hz). ^{13}C NMR ($CDCl_3$) δ: 16.9 (C_6-CH_3), 24.4 (C_7-CH_3), 118.1 (C_{6a}), 122.5 (C_1), 124.3 (C_9), 124.5 (C_2), 125.2 (C_8), 125.4 (C_{7a}), 125.9 (C_{13}), 126.4 (C_{14b}), 127.3 (C_{12}), 127.6 (C_{10}), 128.2 (C_4), 128.6 (C_3), 129.5 (C_{11}), 131.1 (C_{9a}), 133.9 (C_{13a}), 139.1 (C_7), 147.4 (C_{13b}), 147.6 (C_{14a}), 147.8 (C_{4a}), 158.6 (C_6). MS: m/z (%) 308 (M^+, 100), 307 (85), 293 (20), 279 (15), 202 (18), 124 (10), 106 (20), 44 (35). Anal. calcd. for $C_{22}H_{16}N_2$: C, 85.69; H, 5.23; N, 9.08. Found: C, 85.79; H, 5.06; N, 9.15%.

6-Methyl-7-(naphthalen-1-yl)benzo[h]naphtho[1,2-b][1,6] naphthyridine (6)

General procedure. 2-Methyl-*N*-(1-naphthyl)quinolin-4-amine (**3**, 0.002 mol) and 1-naphthoic acid (0.0025 mol) were added to polyphosphoric acid (6 g of P_2O_5 in 3 mL of H_3PO_4) and heated at 160 °C for 3 h. The reaction was monitored using TLC. After the completion of the reaction, it was poured into ice water, neutralized

with saturated sodium bicarbonate solution to remove excess of 1-naphthoic acid, extracted with ethyl acetate, and purified by column chromatography using silica gel. The product was eluted with petroleum ether–ethyl acetate (99:1) mixture to get **6**, which was recrystallized using methanol.

Compound 6a. Colorless needles; mp 222–224 °C; yield: 0.346 g (40%); IR ν_{max} (cm^{-1}) : 1620 (C=N), 1606, 1565, 1476; ^1H NMR ($CDCl_3$) δ: 2.21 (s, 3H, C_2-CH_3), 2.91 (s, 3H C_6-CH_3), 7.43–8.30 (m, 14H, C_3-, C_4-, C_8-, C_9-, C_{10}-, C_{11}-, C_{12}-, C'_2-, C'_3-, C'_4-, C'_5-, C'_6-, C'_7-, and C'_8- H), 9.43 (d, 1H, C_1-H, $J = 2.40$ Hz), 9.74 (d, 1H, C_{13}-H, $J = 8.00$ Hz). ^{13}C NMR ($CDCl_3$) δ: 18.0 (C_6-CH_3), 29.9 (C_2-CH_3), 117.9 (C_{6a}), 119.4 (C'_2), 122.5 (C_1), 124.1 (C_9), 125.0 (C_8), 125.2 (C_{7a}), 125.9 (C_{13}), 126.4 (C_{14b}), 127.3 (C_{12}), 127.6 (C_{10}), 127.8 (C'_8), 127.9 (C'_3) 128.0 (C_4), 128.1 (C'_4), 128.3 (C'_5), 128.4 (C'_6), 128.5 (C'_7), 128.6 (C_3), 129.5 (C_{11}), 131.1 (C_2), 131.3 (C_{9a}), 132.6 (C'_{8a}), 133.9 (C_{13a}), 134.1 (C'_{4a}), 137.1 (C'_1), 143.4 (C_7), 144.4 (C_{4a}), 147.4 (C_{13b}), 147.6 (C_{14a}), 158.6 (C_6). MS: m/z (%) 434 (M^+, 100), 419 (15), 404 (14), 378 (12), 307 (18), 221 (10), 123 (5), 65 (10). Anal. calcd. for $C_{32}H_{22}N_2$: C, 88.45; H, 5.10; N, 6.45. Found: C, 88.38; H, 5.15; N, 6.47%.

Compound 6b. Colorless prisms; mp 225–227 °C; yield: 0.356 g (41%); IR ν_{max} (cm^{-1}) : 1625 (C=N), 1600, 1567, 1481; ^1H NMR ($CDCl_3$) δ: 2.30 (s, 3H, C_4-CH_3), 2.89 (s, 3H, C_6-CH_3), 7.44–8.32 (m, 14H, C_2-, C_3-, C_8-, C_9-, C_{10}-, C_{11}-, C_{12}-, C'_2-, C'_3-, C'_4-, C'_5-, C'_6-, C'_7-, and C'_8- H), 9.39 (d, 1H, C_1-H, $J = 7.50$ Hz), 9.74 (d, 1H, C_{13}-H, $J = 8.00$ Hz). ^{13}C NMR ($CDCl_3$) δ: 17.8 (C_6-CH_3), 29.5 (C_4-CH_3), 117.9 (C_{6a}), 119.4 (C'_2), 122.3 (C_1), 124.1 (C_9), 124.5 (C_2), 125.0 (C_8), 125.2 (C_{7a}), 125.9 (C_{13}), 126.2 (C_{14b}), 127.3 (C_{12}), 127.6 (C_{10}), 127.7 (C_3), 127.8 (C'_8), 127.9 (C'_3), 128.1(C'_4), 128.3 (C'_5), 128.4 (C'_6), 128.5 (C'_7), 129.5 (C_{11}), 131.3 (C_{9a}), 132.6 (C'_{8a}), 133.9 (C_{13a}), 134.1 (C'_{4a}), 136.1 (C_4), 137.1 (C'_1), 143.4 (C_7), 147.4 (C_{13b}), 147.6 (C_{14a}), 147.7 (C_{4a}) 158.6 (C_6). MS: m/z (%) 434 (M^+, 100), 433 (28), 418 (5), 404 (20), 307 (10), 123 (15), 65 (6), 51 (5). Anal. calcd. for $C_{32}H_{22}N_2$: C, 88.45; H, 5.10; N, 6.45. Found: C, 88.49; H, 5.08; N, 6.43%.

Compound 6c. Colorless needles; mp 228–230 °C; yield: 0.318 g (35%). IR ν_{max} (cm^{-1}) : 1623 (C=N), 1600, 1549, 1462. ^1H NMR ($CDCl_3$) δ: 2.91 (s, 3H C_6-CH_3), 7.40–8.33 (m, 14H, C_3-, C_4-, C_8-, C_9-, C_{10}-, C_{11}-, C_{12}-, C'_2-, C'_3-, C'_4-, C'_5-, C'_6-, C'_7-, and C'_8- H), 9.36 (d, 1H, C_1-H, $J = 2.40$ Hz), 9.71 (d, 1H, C_{13}-H, $J = 8.00$ Hz). ^{13}C NMR ($CDCl_3$) δ: 17.8 (C_6-CH_3), 117.9 (C_{6a}), 119.4 (C'_2), 122.2 (C_1), 124.1 (C_9), 125.0 (C_8), 125.2 (C_{7a}), 125.9 (C_{13}), 126.4 (C_{14b}), 127.3 (C_{12}), 127.6 (C_{10}), 127.8 (C'_8), 127.9 (C'_3), 128.1 (C'_4), 128.2 (C_4), 128.3 (C'_5), 128.4 (C'_6), 128.5 (C'_7), 128.8 (C_3), 129.5 (C_{11}), 130.3 (C_2), 131.3 (C_{9a}), 132.6 (C'_{8a}), 133.9 (C_{13a}), 134.1 (C'_{4a}), 139.3 (C'_1), 143.4 (C_7), 144.4 (C_{4a}), 147.4 (C_{13b}), 147.6 (C_{14a}), 158.6 (C_6). MS: m/z (%) 456 (M + 2, 35), 454 (M^+, 100), 419 (18), 405 (12), 342 (5), 280 (18), 123 (10), 65 (12), 51 (15). Anal. calcd. for $C_{31}H_{19}ClN_2$: C, 81.84; H, 4.20; N, 6.15. Found: C, 81.79; H, 4.24; N, 6.11%.

Compound 6d. Colorless prisms; mp 218–220 °C; yield: 0.308 g (37%). IR ν_{max} (cm^{-1}): 1619 (C=N), 1609, 1550, 1470. ^1H NMR ($CDCl_3$) δ: 2.88 (s, 3H, C_6-CH_3), 7.41–8.34 (m, 15H, C_2-, C_3-, C_4-, C_8-, C_9-, C_{10}-, C_{11}-, C_{12}-, C'_2-, C'_3-, C'_4-, C'_5-, C'_6-, C'_7-, and C'_8- H), 9.47 (d, 1H, C_1-H, $J = 7.40$ Hz), 9.79 (d, 1H, C_{13}-H, $J = 9.00$ Hz). ^{13}C NMR ($CDCl_3$) δ: 17.8 (C_6-CH_3), 117.9 (C_{6a}), 119.4 (C'_2), 122.5

(C_1), 124.1 (C_9), 124.3 (C_2), 125.0 (C_8), 125.2 (C_{7a}), 125.9 (C_{13}), 126.2 (C_{14b}), 126.6 (C_4), 127.3 (C_{12}), 127.6 (C_{10}), 127.7 (C_3), 127.8 (C'_8), 127.9 (C'_3), 128.1 (C'_4), 128.3 (C'_5), 128.4 (C'_6), 128.5 (C'_7), 129.5 (C_{11}), 131.3 (C_{9a}), 132.6 (C'_{8a}), 133.9 (C_{13a}), 134.1 (C'_{4a}), 139.3 (C'_1), 143.4 (C_7), 147.4 (C_{13b}), 147.6 (C_{14a}), 147.7 (C_{4a}), 158.6 (C_6). MS: m/z (%) 420 (M^+, 100), 419 (85), 405 (32), 343 (10), 273 (15), 174 (10), 64 (10), 44 (25). Anal. calcd. for $C_{31}H_{20}N_2$: C, 88.54; H, 4.80; N, 6.66. Found: C, 88.60; H, 4.76; N, 6.62%.

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