SYNTHESIS AND SPECTROSCOPIC DISTINCTION OF BENZONAPHTHONAPHTHYRIDINE AND ITS ISOMER

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GRAPHICAL ABSTRACT

Abstract Distinction of benzo[h]naphtho[1,2-b][1,6]naphthyridine and its isomeric benzo[b]naphtho[1,2-h][1,6]naphthyridine is well explained on the basis of various spectroscopic techniques. Initially these isomers were prepared from their respective chloroquinolines via anilinoquinolines as potential intermediates. Spectroscopic dissimilarities of their precursors and intermediates have also been considered and compared with the final benzonaphthonaphthyridine isomers.

Keywords Benzo[h]naphtho[1,2-b][1,6]naphthyridine; benzo[b]naphtho[1,2-h][1,6]naphthyridine; 4-chloro-2-methylbenzo[h]quinoline; 4-chloro-2-methylquinoline; N-(naphthyl)quinolin-4-amine; N-o-tolylbenzo[h]quinolin-4-amine; spectral distinction

INTRODUCTION

The presence of a quinoline and benzoquinoline ring system in numerous natural products possessing a wide range of pharmacological activities has attracted a great deal of attention from synthetic as well as medicinal chemists. Besides broad medicinal applications as antimalarial, antibacterial, antiaggressive, and anti-inflammatory agents, they are also useful as agrochemicals.\textsuperscript{[1–3]} The DNA topo-isomerase inhibitory activity of benzoquinolines is due to their high binding affinity with DNA and hence they can display cytotoxic and antitumor activities.\textsuperscript{[4]} Numerous synthetic strategies have been developed for the construction of quinolines\textsuperscript{[5–7]} and benzoquinolines\textsuperscript{[8–10]} because of their therapeutic importance. Proton tautomerism plays an important role in many fields of chemistry, especially biochemistry.\textsuperscript{[11–13]}
Even though isomers in heterocyclic compounds are difficult to distinguish, their biological roles have some distinction. For example, in spite of the structural similarity of the quinoline methanol isomers (quinine and quinidine), quinine was not phototoxic in the mouse when screened for in vitro using the Candida albicans inhibition test.[14] This type of isomers is able to be differentiated by spectral techniques. For example, enantiomeric differentiation of oxygenated bicyclo[2.2.1]heptane derivatives was done by $^{13}$C NMR spectroscopy using lanthanide shift reagent.[15] Different mass spectrometric methods, stable isotope labelling, and theoretical calculations have allowed us to structurally characterize and differentiate the isomeric ion structures produced by the two heteroaromatic isomers 3-methyl-1,2-benzoxazole and 2-methyl-1, 3-benzoxazole.[16] The naphthonaphthyridine ring system is a rare heterocycle compared with simple[17] benzonaphthyridines as well as those,[18] that contain both naphthalene ring and naphthyridine moieties, which may afford unique biological activities. Only a few synthetic strategies have been developed for the synthesis of naphthonaphthyridines,[19,20] In this context the present work describes the distinction between benzo$[h]$naphtho[1,2-b][1,6]naphthyridine and its isomer benzo$[b]$ naphtho[1,2-b][1,6]naphthyridine. However, spectroscopic distinction of quinolinamines and benzonaphthonaphthyridines is not well explained in literature. Also their starting materials, quinolinamines and benzoquinolinamines, were also taken into account. We undertook this study because of the biological significance of one isomer over the other and the importance of naphthonaphthyridines.[21]

RESULTS AND DISCUSSION

Initially we reported the synthesis of compounds 3–6.[22] In this communication we report the preparation of novel hetero-substituted benzonaphthonaphthyridines by utilizing the intermediate 3, which are depicted in the Scheme 1.

To get hetero-substituted benzo$[h]$naphtho[1,2-b][1,6]naphthyridines, the potential intermediate 3 was reacted with pyridine-3-carboxylic acid in the presence of polyphosphoric acid (PPA) at 110 °C for an hour to give a pale yellow product (Scheme 1). From its infrared (IR) spectrum the bands at 1699 cm$^{-1}$, 1644 cm$^{-1}$, and 1549 cm$^{-1}$ were due to three C=N groups. Its $^1$H NMR spectrum showed two singlets at $\delta$ 2.41 and $\delta$ 2.88, indicating the presence of C4 & C6 methyl protons. All other aromatic protons appeared in the region between $\delta$ 7.17 and 9.71. Its

![Scheme 1. Synthesis of benzo$[h]$naphtho[1,2-b][1,6]naphthyridines 7, 8, and 9.](image-url)
$^{13}$C NMR spectrum showed the presence of 27 carbons. From the analytical data, molecular formula of the compound was deduced as C$_{27}$H$_{19}$N$_{3}$. All the spectral and analytical details attest the compound as 4,6-dimethyl-7-(pyridin-3-yl)benzo[h]-naphtho[1,2-b][1,6]naphthyridine (7). The same reaction was extended to other hetero-carboxylic acids such as furan-2-carboxylic acid and thiophen-2-carboxylic acid with 3 to get the corresponding furan- and thieno-substituted benzo[h]-naphtho[1,2-b][1,6]naphthyridines 8 and 9.

**Synthesis of Benzo[b]naphtho[1,2-h][1,6]naphthyridines**

Next we have aimed to synthesize benzo[b]naphtho[1,2-h][1,6]naphthyridine, which was an isomeric (position isomer) compound of benzo[h]naphtho[1,2-b]-[1,6]naphthyridine. With the aim to construct these naphthyridine derivatives, 4-chloro-2-methylbenzo[h]quinoline (13) was taken as a starting precursor. Compound 13 was reacted with o-toluidine (14) under neat conditions at 190 °C for half an hour to afford a single product (Scheme 2). The IR spectrum of the compound showed absorption bands at 3420 cm$^{-1}$ and 1628 cm$^{-1}$, which were due to the presence NH and C=N functional groups. Two singlets in its $^1$H NMR spectrum resonated at $\delta$ 2.24 and 2.73 and correspond to C$_2$ and C$_2$ methyl protons respectively. A one-proton singlet at $\delta$ 6.33 was evidence for peculiar C$_3$-H of the benzooquinoline moiety. All other aromatic protons resonated in the region between $\delta$ 7.38 and 9.28. One-proton two broad singlets at $\delta$ 10.63 and $\delta$ 13.49 were due to C$_4$-NH amino form and C$_1$-NH imino form (ratio 1:1). Its $^{13}$C NMR spectrum showed the presence of 21 carbons. Its molecular formula from the elemental analysis was found to be C$_{21}$H$_{18}$N$_2$ and its molecular ion peak was shown at m/z 298 from its mass spectrum. On the basis of spectral and analytical details the structure of the compound was confirmed as 2-methyl-$N$-o-tolylbenzo[h]quinolin-4-amine (15).

With the intention of getting the cyclized product, the intermediate 15 was reacted with benzoic acid in the presence of PPA catalyst at 160 °C for 3 h to afford a single product (Scheme 3). The product was analyzed by various spectral techniques. IR spectrum showed the absorption bands at 1625 cm$^{-1}$ and 1567 cm$^{-1}$, which were due to two C=N functional groups. The $^1$H NMR spectrum of 16 exhibited two singlets each at $\delta$ 2.46 and 3.13 for C$_6$—CH$_3$ and C$_{11}$-CH$_3$ respectively. All the aromatic protons resonated at $\delta$ 7.37–8.08 except for two proton doublets, which were very much deshielded at $\delta$ 9.36 ($J$ = 8.00 Hz) and $\delta$ 9.46 ($J$ = 9.00 Hz). With the help of advanced NMR studies such as correlations spectroscopy (H,H-COSY) (Table 1), C,H-COSY (HSQC) (Table 2), and heteronuclear multiple bond correlation (HMBC) correlations (Table 2), the deshielded proton at $\delta$ 9.36 was assigned for C$_4$-H while the proton at $\delta$ 9.46 for C$_{13}$-H. A one-proton doublet at $\delta$ 9.36
(\(J = 8.00\) Hz) and a two-proton multiplet between 7.72 and 7.73 have H,H-COSY connection. The proton at \(\delta 9.36\) was characteristic of C\(_4\)-H while the multiplet was assigned for C\(_3\), C\(_{10}\)-H. A one-proton doublet at \(\delta 9.46\) (\(J = 9.00\) Hz) and a one-proton doublet at \(\delta 8.08\) (\(J = 9.00\) Hz) have H-H COSY connections, which are characteristic of C\(_{13}\)-H and C\(_{14}\)-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\(_4\) and C\(_{13}\) carbons were assigned as \(\delta 124.7\) and \(\delta 122.1\) respectively. The values of all other carbons holding protons are denoted in Table 2. The peculiar C\(_4\)-H has HMBC connectivity with C\(_2\) while the C\(_{13}\)-H has connectivities with C\(_{4b}\), C\(_{14a}\) carbons. The connectivity of all other protons with the carbons is denoted in Table 2. The HMBC connectivity

| Table 1. \(^1\)H NMR and their coupling protons of the compound 16 assigned by \(^1\)H-\(^1\)H COSY |
|-------------------------------|-------------------|
| \(^1\)H NMR \((\delta)\)     | Coupling protons \((\delta)\) |
| 1 2.46 (s, 3H, C\(_6\)-CH\(_3\)) | —                              |
| 2 3.13 (s, 3H, C\(_{11}\)-CH\(_3\)) | —                              |
| 3 7.37 (t, 1H, C\(_9\)-H, \(J = 7.50\) Hz) | 7.60–7.61 (m, 3H, which includes C\(_8\)-H), 7.72–7.73 (m, 2H, which includes C\(_{10}\)-H) |
| 4 7.41–7.44 (m, 3H, C\(_3\)'', C\(_4\)'', C\(_5\)' - H) | 7.41–7.44 (m, 3H which includes C\(_3\)'', C\(_4\)'', C\(_5\)' - H), 7.60–7.61 (m, 3H, which includes C\(_3\)'', C\(_4\)'', C\(_5\)' - H) |
| 5 7.60–7.61 (m, 3H, C\(_2\)'', C\(_3\)'', C\(_4\)-H) | 7.41–7.44 (m, 3H, which includes C\(_3\)'', C\(_4\)'', C\(_5\)' - H), 7.37 (t, 1H, C\(_9\)-H, \(J = 7.50\) Hz) |
| 6 7.69 (t, 1H, C\(_2\)-H, \(J = 7.50\) Hz) | 8.03 (d, 1H, C\(_{14}\)-H, \(J = 7.50\) Hz) |
| 7 7.72–7.73 (m, 2H, C\(_3\), C\(_{10}\)-H) | 9.36 (d, 1H, C\(_2\)-H, \(J_p = 8.00\) Hz, \(J_m = 8.00\) Hz), 7.69 (t, 1H, C\(_{14}\)-H, \(J = 7.50\) Hz), 7.37 (t, 1H, C\(_9\)-H, \(J = 7.50\) Hz) |
| 8 8.03 (d, 1H, C\(_1\)-H, \(J = 7.50\) Hz) | 7.69 (t, 1H, C\(_2\)-H, \(J = 7.50\) Hz) |
| 9 8.08 (d, 1H, C\(_{13}\)-H, \(J = 9.00\) Hz) | 9.46 (d, 1H, C\(_{15}\)-H, \(J = 9.00\) Hz) |
| 10 9.36 (d, 1H, C\(_2\)-H, \(J_p = 8.00\) Hz, \(J_m = 1.50\) Hz) | 7.72–7.73 (m, 2H which includes C\(_3\)-H) |
| 11 9.46 (d, 1H, C\(_{13}\)-H, \(J = 9.00\) Hz) | 8.08 (d, 1H, C\(_{14}\)-H, \(J = 9.00\) Hz) |
and numbering of the benzo[h]naphtho[1,2-b][1,6]naphthyridine moiety 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. From its elemental analysis the molecular formula was deduced as C$_{28}$H$_{20}$N$_{2}$. All these spectral and analytical details attest to the structure of the compound as 6,11-dimethyl-7-phenylbenzo[b]naphtho[1,2-b][1,6]naphthyridine (16). Similar reaction was also extended to other carboxylic acids i.e., acetic acid and 1-naphthoic acid) to get 6,7,11-trimethylbenzo[b]naphtho[1,2-b][1,6]naphthyridines 17 and 6,11-dimethyl-7-(naphthalen-1-yl)benzo[b]naphtho[1,2-b][1,6]naphthyridine 18, respectively. In all cases the C$_4$-H and C$_{13}$-H were deshielded. The reason for the two protons to get deshielded might be the interaction of these protons with the nitrogen atoms at 5 and 12 positions.

The same reaction was carried out using heterocarboxylic acid to get the corresponding hetero-substituted benzo[b]naphtho[1,2-b][1,6]naphthyridine derivatives. In this connection the intermediate 15 was reacted with pyridine-2-carboxylic acid in the presence of PPA as catalyst to give a single product (Scheme 3). The IR spectrum of product showed stretching frequencies at 1626 cm$^{-1}$, 1595 cm$^{-1}$, and 1568 cm$^{-1}$ due to the presence of three C=N groups. In its $^1$H NMR spectrum the two methyl protons resonated as two singlets at $\delta$ 2.41 and $\delta$ 3.07 respectively. The rest of the aromatic protons appeared in the region between $\delta$ 7.22 and $\delta$ 9.52. The $^{13}$C NMR spectrum revealed the presence of 27 carbons. On the basis of data obtained

| No | $^1$H NMR (δ) | $^{13}$C NMR (δ) | HMBC $^2$J, $^3$J |
|----|---------------|------------------|------------------|
| 1  | 2.46 (s, 3H, C$_6$-CH$_3$) | 29.7 (C$_6$-CH$_3$) | C$_6$ |
| 2  | 3.13 (s, 3H, C$_{11}$-CH$_3$) | 18.4 (C$_{11}$-CH$_3$) | C$_{10}$, C$_{11}$, C$_{11a}$ |
| 3  | 7.37 (t, 1H, C$_{4p}$H, $J=7.50$ Hz) | 126.9 (C$_4$) | C$_{10}$, C$_8$ |
| 4  | 7.41–7.44 (m, 3H, C$_4'$, C$_4''$, C$_5''$ – H) | 128.3 (C$_4'$, C$_4''$, C$_5''$) | C$_3$, C$_4$, C$_5'$, C$_6'$ |
| 5  | 7.60–7.61 (m, 3H, C$_3'$, C$_3''$, C$_2$-H) | 128.5 (C$_3'$, C$_3''$), 127.1 (C$_8$) | C$_{10}$ |
| 6  | 7.69 (t, 1H, C$_{2}$-H, $J=7.50$ Hz) | 127.4 (C$_2$) | C$_4$, C$_{14a}$ |
| 7  | 7.72–7.73 (m, 2H, C$_3$, C$_{10}$-H) | 126.5 (C$_3$), 131.1 (C$_{10}$) | C$_{1}$, C$_2$, C$_{4a}$, C$_9$ |
| 8  | 8.03 (d, 1H, C$_1$-H, $J=7.50$ Hz) | 127.8 (C$_1$) | C$_{2}$, C$_3$, C$_{4a}$ |
| 9  | 8.08 (d, 1H, C$_{1a}$-H, $J=9.00$ Hz) | 127.0 (C$_{14}$) | C$_{1}$, C$_{4a}$, C$_{13}$ |
| 10 | 9.36 (d, 1H, C$_{2}$-H, $J_o=8.00$ Hz, $J_m=8.00$ Hz) | 124.7 (C$_4$) | C$_2$ |
| 11 | 9.46 (d, 1H, C$_{1b}$-H, $J=9.00$ Hz) | 122.1 (C$_{13}$) | C$_{4b}$, C$_{14a}$ |

Table 2. $^1$H NMR and their carbon assigned by C,H-COSY (HSQC) and HMBC connectivity of the protons with the carbons of the compound 16.

Figure 1. HMBC connectivity and numbering of compound 16.
from elemental and spectral analyses the structure of the compound was confirmed as 6,11-dimethyl-7-(pyridin-3-yl)benzo[h]naphtho[1,2-h][1,6]naphthyridine (19).

Similar reaction condition was extended to other heterocarboxylic acids such as furan-2-carboxylic acid and thiophen-2-carboxylic acid to get the corresponding hetero-substituted benzo[h]naphtho[1,2-h][1,6]naphthyridines 20 and 21 (Scheme 3). The identities of the compounds were established on the basis of their spectral data and elemental analysis.

**Spectroscopic Distinction of Benzo[h]naphtho[1,2-b][1,6]-naphthyridine and Its Isomeric Benzo[b]naphtho[1,2-h][1,6]-naphthyridine**

IR and $^{13}$C NMR and also mass spectra of the two isomeric structures (6 and 16) do not find substantial difference. Interestingly, $^1$H NMR spectra of the respective isomers show little variation, hence we thought to compare and investigate the $^1$H NMR spectra of the starting precursors (1 and 13), intermediates (3 and 15), and the final compounds (5 and 16) respectively.

In 4-chloro-2,8-dimethylquinoline (1) the deshielded proton is C$_5$-H, while in the case of 4-chloro-2-methylbenzo[h]quinoline (13), besides C$_5$-H at $\delta$ 8.09, C$_{10}$-H is much deshielded to $\delta$ 9.32. This is due to the spatial interaction of the C$_{10}$-H with the nitrogen at the 1st position (Fig. 2).

The intermediates from which benzonaphthonaphthyridines were derived have spectroscopic differences, particularly in the $^1$H NMR spectrum. The intermediate 3, which was derived from 4-chloro-2,8-dimethylquinoline (1), has the same deshielding effect for the C$_5$-H, while in the case of another intermediate (15), in addition to C$_5$-H, one more deshielding proton is observed at C$_{10}$-H, as in starting precursors 3. Both of the intermediates have amino and imino tautomerism for the C$_4$-NH in the same region (Fig. 3).

Upon annulation reaction with benzoic acid, the intermediate 15, which already had one deshielded proton at $\delta$ 9.36 due to C$_{10}$-H, generates one more deshielded proton at $\delta$ 9.46 due to C$_{13}$-H in its final structure (16). The cyclization of the intermediate 3, which does not possess deshielded a proton, generates two deshielded protons around $\delta$ 9.37 and $\delta$ 9.68 for C$_{17}$- and C$_{14}$-H respectively in final compound 5 (Fig. 4). The reason for the C$_{10}$-H in compound 13 and in the intermediate 15 to be much deshielded around $\delta$ 9.30 is its spatial interaction with the nitrogen atom, and upon cyclization, its C$_5$ position is changed to C$_{13}$ and the C$_{10}$ changes to C$_4$. C$_{10}$-H in the intermediate (i.e., C$_4$-H in the final product), however, experiences the same

![Figure 2](image-url). $^1$H NMR comparison of deshielded protons in compounds 1 and 13.
spatial effect while the C5-H of the intermediate does not experience such effect because of the rotation of the N-aryl ring and its cyclization restricts the rotation and changes the position to C13 in which the spatial effect is observed.

Moreover, the C5-H and C6-H of the benzo[h]quinoline (13) and tolylbenzo[h]quinolin-4-amine (15) has peculiar coupling constant values around 9.00 Hz and the same prevails as C13-H and C14-H in the final compound (16). In the case of 4-chloro-2-methylquinoline (1) and 2-methyl-N-(1-naphthyl)quinoline-4-amine (3) no such positions were found having higher coupling constant values. However, the C8 and C9 positions of the final benzo[h]naphtho[1,2-b][1,6]naphthyridine (5) merged as multiplets with other aromatic protons.

The deshielded protons (C4 and C13) of compound 16 do not show much difference, whereas the same (C1 and C13) in compound 6 showed a difference in theoretically calculated geometrical parameters. It was thought that there might be some difference in the C-C-C-N dihedral angle (shown in bold lines, Fig. 5) of compound 6. Hence geometrical parameters were calculated theoretically for the two compounds 5 and 16. For the compound 5 the two C-C-C-N dihedral angles were calculated as 1.853 and 21.001, whereas for compound 16 they were 1.730 and 1.905. From this observation we conclude that the greater value of bond angle in compound 5 makes the C13 proton deshield very high in the region of δ 9.68.

From the point of 13C NMR spectrum, there are no substantial changes in carbon values to distinguish between the two benzonaphthonaphthyridines. The mass spectra of the two compounds 5 and 16 did not show variation. In the fragmentation pattern of the two compounds, all the values are nearly the same and the mass fragmentation pattern of 6 and that of 16 are given in the Supplementary Data.

Figure 3. 1H NMR comparison of the potential intermediates 3 and 15.

Figure 4. 1H NMR comparison of highly deshielded protons in compounds 5 and 16.
CONCLUSION

In conclusion, the synthesis and spectroscopic study of benzo[h]naphtho[1,2-b][1,6]naphthyridine and its isomer benzo[h]naphtho[1,2-h][1,6]naphthyridine have been carried out, and they were distinguished using 2D-NMR studies and theoretically calculated parameters. Complete investigation of $^1$H NMR of chloroquinolines and quinolinamines was also done for the study.

EXPERIMENTAL

Melting points (mp) were determined on a Mettler FP 51 apparatus (Mettler Instruments, Switzerland) and are uncorrected. They are expressed in degree centigrade (°C). A Nicolet Avatar Model FT-IR spectrophotometer was used to record the IR spectra (4000–400 cm$^{-1}$). $^1$H NMR and $^{13}$C NMR spectra were recorded on Bruker AV 400 [400 MHz ($^1$H) and 100 MHz ($^{13}$C)] and AV 500 [500 MHz ($^1$H) and 125 MHz ($^{13}$C)] spectrometer using tetramethylsilane (TMS) as an internal reference. The chemical shifts are expressed in parts per million (ppm). Mass spectra (MS) were recorded on Auto Spec EI+Shimadzu QP 2010 PLUS GC-MS mass spectrometer. Microanalyses were performed on a Vario EL III model CHNS analyzer (Vario, Germany). The solvent and reagents used for the preparations were of reagent grade and were purified by standard methods. Thin-layer chromatography (TLC) was performed using glass plates coated with silica gel-G containing 13% calcium sulfate as binder. Ethyl acetate and petroleum ether were used as developing solvents.

Preparation of 6-Methyl-7-(pyridin-3-yl)benzo[h]naphtho[1,2-b][1,6]-naphthyridine (7), General Procedure

2-Methyl-N-(1-naphthyl)quinolin-4-amine (3, 2 mmol) and pyridine-3-carboxylic acid (2.5 mmol) were added to polyphosphoric acid (6 g of P$_2$O$_5$ in 3 mL of H$_3$PO$_4$) and heated at 110°C for 1 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 pyridine-3-carboxylic acid / thiophen-2-carboxylic acid / furan-2-carboxylic acid, extracted with ethyl acetate, and purified by column chromatography using silica gel. The product was eluted with petroleum ether–ethyl acetate (97:3) mixture to get 7, which was recrystallized using methanol.
Compound 7

Pale yellow prisms; mp: 248–250 °C; yield: 48%; IR (KBr, cm⁻¹) \( \nu_{\text{max}} \): 1699, 1644, 1549 (C=N); \(^1\)H NMR (500 MHz, CDCl₃) (ppm) \( \delta_H \): 2.41 (s, 3H, C₄-CH₃), 2.88 (s, 3H, C₆-CH₃), 7.17 (d, 1H, C₃-H, \( J = 9.00 \) Hz), 7.25 (t, 1H, C₅′-H, \( J = 8.50 \) Hz, \( J = 5.00 \) Hz), 7.38 (t, 1H, C₂-H \( J = 8.50 \) Hz), 7.60 (d, 1H, C₁₂-H, \( J = 7.50 \) Hz), 7.71 (2d, 2H, C₁₁-H, \( J = 8.00 \) Hz), 7.80 (dd, 1H, C₄′-H, \( J = 8.50 \) Hz, \( J = 5.00 \) Hz), 7.93 (s, 1H, C₂₀-H), 8.20 (d, 1H, C₁₀-H \( J = 8.00 \) Hz), 9.31 (d, 1H, C₁-H \( J = 8.00 \) Hz), 9.71 (d, 1H, C₁₃-H \( J = 8.00 \) Hz); \(^{13}\)C NMR (125 MHz, CDCl₃) (ppm) \( \delta_C \): 19.7 (C₆-CH₃), 27.1 (C₄-CH₃), 118.1 (C₆ₐ), 122.3 (C₁), 124.1 (C₉), 124.6 (C₂), 125.2 (C₈), 125.4 (C₇ₐ), 125.9 (C₁₃), 126.4 (C₁₄ₐ), 127.3 (C₁₂), 127.6 (C₁₀), 128.5 (C₃′), 128.9 (C₃), 129.5 (C₁₁), 131.1 (C₉ₐ), 132.4 (C₅′), 133.9 (C₁₃ₐ), 134.2 (C₄), 134.6 (C₄′), 139.1 (C₃), 142.4 (C₄′), 147.4 (C₆′), 147.8 (C₁₃ₐ), 148.5 (C₁₄ₐ), 149.0 (C₄ₐ), 159.1 (C₆), MS (385) \( m/z \) (%) 385 (M⁺, 98). Anal. calcd. for C₂₇H₁₉N₃ (385): C, 84.13; H, 4.97; N, 10.90. Found: C, 84.20; H, 4.91; N, 10.89%.

Preparation of 2-Methyl-N-phenylbenzo[h]quinolin-4-amine (15), General Procedure

4-Chloro-2-methylbenzo[h]quinoline (13, 4 mmol) was reacted with o-toluidine (4 mmol) under neat condition at 190 °C for half an hour. The product was washed with water, dried, adsorbed, purified using silica-gel column chromatography, and eluted with ethylacetate–methanol (95:5) mixture to get 15, which was then recrystallized using methanol.

Compound 15

Brown solid; mp: >300 °C. Yield: 75%. IR (KBr, cm⁻¹) \( \nu_{\text{max}} \): 3420 (NH), 1628 (C=C-N), 1146. \(^1\)H NMR (500 MHz, DMSO-d₆) (ppm) \( \delta_H \): 2.24 (s, 3H, C₂₀-CH₃), 2.73 (s, 3H, C₂₂-CH₃), 6.33 (s, 1H, C₃-H), 7.38–7.95 (m, 6H, C₃₀–C₆₀, C₈, C₉-H), 8.20 (d, 1H, \( J = 9.00 \) Hz, C₆-H), 8.23 (dd, 1H, \( J_o = 8.00 \) Hz, \( J_m = 2.50 \) Hz, C₇-H), 8.60 (d, 1H, \( J = 9.00 \) Hz, C₃-H), 9.28 (dd, 1H, \( J_o = 8.00 \) Hz, \( J_m = 2.00 \) Hz, C₁₀-H), 10.63 (s, 1H, C₄-NH amino form), 13.49 (s, 1H, C₁-NH imino form, ratio of amino form to imino form is 1:1). \(^{13}\)C NMR (125 MHz, DMSO-d₆) (ppm) \( \delta_C \): 17.8 (C₂₀-C₂₂), 20.5 (C₂₂-CH₃) 102.6 (C₃), 113.6 (C₈), 119.2 (C₄₀), 124.0 (C₅) 127.9 (C₄), 128.1 (C₁₀) 128.2 (C₅), 128.6 (C₈), 128.7 (C₉), 129.1 (C₇), 129.4 (C₃′), 130.1 (C₉′), 132.1 (C₅′), 134.6 (C₁₀ₐ), 135.8 (C₆ₐ), 137.2 (C₃′), 140.7 (C₁₀ₐ), 154.0 (C₄), 154.2 (C₂). Anal. calcd. for C₂₁H₁₉N₃ (385): C, 84.13; H, 4.97; N, 9.39. Found: C, 84.42; H, 6.13; N, 9.45%.

Preparation of 6-Methyl-7-phenylbenzo[B]naphtho[1,2-h][1,6]-naphthyridine (16), General Procedure

2-Methyl-N-phenylbenzo[h]quinolin-4-amine (15) (2 mmol) and benzoic acid (2.5 mmol) were added to polyphosphoric acid (6 g of P₂O₅ in 3 mL of H₃PO₄)
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 benzoic acid / acetic acid / 1-naphthoic acid, extracted with ethyl acetate, purified by column chromatography using silica gel, and eluted with petroleum ether–ethyl acetate (99:1) mixture to get 16, which was recrystallized using methanol.

**Compound 16**

Pale yellow solid; mp: 206–208 °C; yield: 51%; IR (KBr, cm<sup>−1</sup>) vmax: 1625 (C=O), 1567, 1531, and 1485; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) (ppm) δ<sub>H</sub>: 2.46 (s, 3H, C<sub>6</sub>-CH<sub>3</sub>), 3.13 (s, 3H, C<sub>11</sub>-CH<sub>3</sub>), 7.37 (t, 1H, C<sub>9</sub>-H, J = 7.50 Hz), 7.41–7.44 (m, 3H, C<sub>3</sub>'<sup>0</sup>, C<sub>4</sub>'<sup>0</sup>, C<sub>5</sub>'<sup>0</sup>-H), 7.60–7.61 (m, 3H, C<sub>2</sub>', C<sub>6</sub>', C<sub>8</sub>-H), 7.69 (t, 1H, C<sub>1</sub>-H, J = 7.50 Hz), 7.72–7.73 (m, 2H, C<sub>3</sub>, C<sub>10</sub>-H), 8.03 (d, 1H, C<sub>1</sub>-H, J = 7.00 Hz), 8.08 (d, 1H, C<sub>14</sub>-H, J = 7.50 Hz), 9.36 (d, 1H, C<sub>4</sub>'-H, J<sub>o</sub> = 8.00 Hz, J<sub>m</sub> = 1.50 Hz), 9.46 (d, 1H, C<sub>13</sub>-H, J = 9.00 Hz); ^<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) (ppm) δ<sub>C</sub>: 18.4 (C<sub>11</sub>-CH<sub>3</sub>), 29.7 (C<sub>6</sub>-CH<sub>3</sub>), 121.12 (C<sub>6a</sub>), 122.08 (C<sub>13</sub>), 122.28 (C<sub>7a</sub>), 124.74 (C<sub>4</sub>), 125.98 (C<sub>12b</sub>), 126.51 (C<sub>3</sub>), 126.91 (C<sub>9</sub>), 127.06 (C<sub>14</sub>), 127.06 (C<sub>8</sub>), 127.42 (C<sub>2</sub>), 127.78 (C<sub>1</sub>), 128.34 (C<sub>3</sub>'<sup>0</sup>, C<sub>4</sub>'<sup>0</sup>, C<sub>5</sub>'<sup>0</sup>), 128.52 (C<sub>2</sub>'<sup>0</sup> & C<sub>6</sub>'<sup>0</sup>), 129.97 (C<sub>14a</sub>), 130.74 (C<sub>14a</sub>), 131.14 (C<sub>10</sub>), 134.64 (C<sub>11</sub>), 135.15 (C<sub>10</sub>'), 137.48 (C<sub>7</sub>) 139.40 (C<sub>11a</sub>), 146.35 (C<sub>4</sub>'), 149.01 (C<sub>12a</sub>), 159.40 (C<sub>6</sub>); MS: m/z (%) 384 (M<sup>+</sup>, 100), 383 (35), 369 (20), 354 (8), 65 (6), 51 (5). Anal. calcd. for C<sub>28</sub>H<sub>20</sub>N<sub>2</sub> (384): C, 87.47; H, 5.24; N, 7.29. Found: C, 87.40; H, 5.29; N, 7.31%.

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**SUPPLEMENTAL MATERIAL**

Supplemental data for this article can be accessed on the publisher’s website.

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