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β-Carbolines: synthesis of harmane, harmine alkaloids and their structural analogs by thermolysis of 4-aryl-3-azidopyridines and investigation of their optical properties

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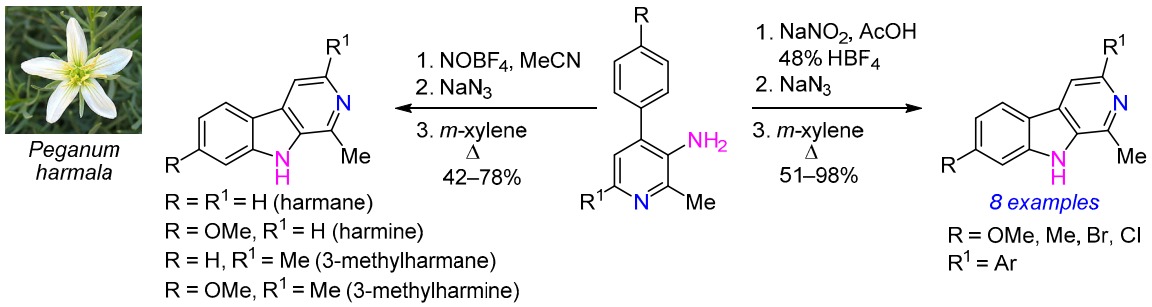


Interest in β-carbolines is caused by the biological activity of these compounds and the use of their fluorescent properties in the study of their interaction with DNA and other biological targets, as well as with drug delivery vehicles. A new general method for the synthesis of harmane, harmine, and their structural analogs by thermolysis of substituted 4-aryl-3-azidopyridines was developed, and their optical properties were studied.

Keywords: alkaloids, 3-amino-4-arylpyridines, 4-aryl-3-azidopyridines, asymmetric Hantzsch pyridines, harmane, harmine, substituted β-carbolines, fluorescence of β-carbolines.

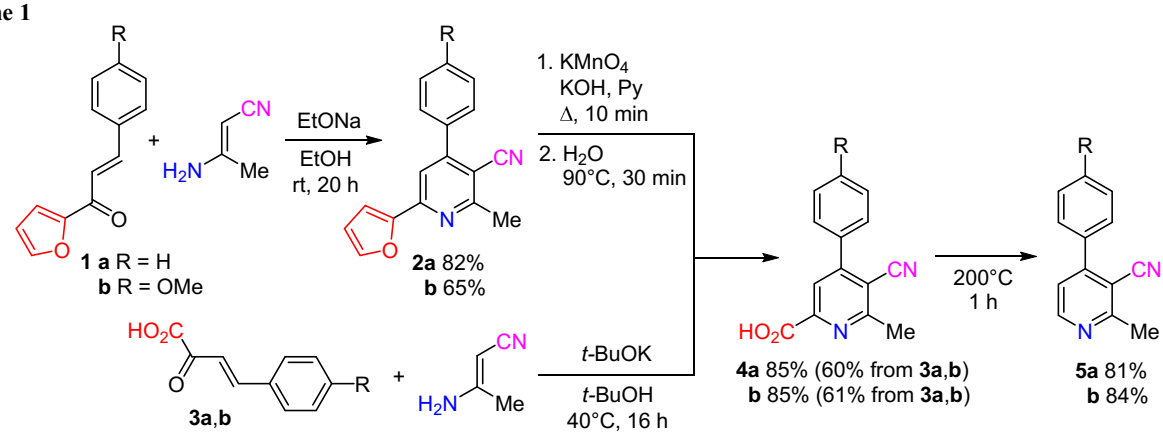
One of the valuable gifts of nature to humanity is its tireless synthesis of alkaloids, which have long been used to treat various diseases. β-Carboline alkaloids are produced by several plants, including *Peganum harmala*, the main components of its extract being harmane, harmine, harmaline, and harmalol. *Peganum harmala* extract has been used since ancient times to treat syphilis, malaria, hysteria, neuralgia, Parkinson's disease, rheumatism, as well as for the preparation of hallucinogenic drinks and tobacco. In China, *Peganum harmala* has been used to treat cancer and malaria for more than 100 years.[1]

Harmane and harmine possess a wide spectrum of biological activity.[2] Harmine exhibits a high ability to intercalate in DNA; it acts as a powerful and specific inhibitor of tyrosine kinase DYRK1A, a promising target in antitumor therapy; exhibits an affinity for neurotransmitters, which makes this alkaloid a promising compound for the development of drugs for the treatment of neurodegenerative diseases, such as Alzheimer's disease. It increases the induction of connective tissue growth factor CCN2 in HCS-2/8 human chondrocyte cells and osteoarthritic articular chondrocytes and, therefore, has a chondrogenic and chondroprotective effect.[3] Harmane exhibits sedative, antidepressant, antiplatelet, antioxidant, hypotensive, antidiabetic, antinociceptive, anti-parasite effect, acts as acetylcholinesterase and myeloperoxidase inhibitor.[4]

β-Carboline alkaloids and their derivatives have a pronounced antiviral activity. In particular, 9-methylharmine disrupts the maturation and release of particles of Dengue fever virus into the extracellular environment, while harmane and its derivatives exhibit antiviral activity against HIV.[5]

In 2014, a piezochrome luminescent material, a molecular donor–acceptor–donor triad, was synthesized on

Scheme 1



the basis of harmane, which has acidochromic and piezochromic fluorescence and is a promising molecular switch.[6]

Harmane was used as a fluorescent molecular probe to study transport proteins by stationary fluorimetry. Harmane, harmine, and harmine derivatives are promising photosensitizers for the photodynamic therapy of cancer.[7]

The main methods for the synthesis of β-carbolines (9*H*-pyrido[3,4-*b*]indoles) are the classic Pictet–Spengler and Bischler–Napieralski reactions, as a result of which tetrahydro- and dihydro-β-carbolines are obtained from tryptamines and tryptophanes which then undergo dehydrogenation of the pyridine ring. Both steps of these reactions are constantly being improved.[8] The Pictet–Spengler reaction also uses gramines whose dialkylamino group is substituted by the action of C-nucleophiles, either with or without activation.[9] Under similar conditions, biomimetic synthesis of β-carbolines from tryptophan and arylglycines was performed.[10]

Modern methods for the synthesis of β-carbolines are represented by a number of reactions: the Ru-catalyzed photoredox synthesis of 1-acyl-β-carbolines from tryptamines and terminal alkynes; Pd-catalyzed Buchwald–Hartwig arylation of 2-chloroaniline with 3-bromopyridine followed by the intramolecular Heck reaction; Pd-catalyzed Ulmann cross coupling of 2-iodocyclohex-2-en-1-one with 4-iodo-3-nitropyridine to form 2-(3-nitropyridin-4-yl)cyclohex-2-en-1-one, its reductive cyclization followed by dehydrogenation of 6,7,8,9-tetrahydro-5*H*-pyrido[3,4-*b*]indole; Pd-catalyzed annulation of 3-iodo-1*H*-indole-2-carboxaldehyde imine with terminal and internal alkynes; Ru-catalyzed [2+2+2] cycloaddition of *O*,*N*-dialkynylamides with nitriles; Ru-catalyzed thermolysis of 2-(2-azidoaryl-1-methylpyridinium triflate, which completes with the insertion of nitrene into the C–H bond of pyridine.[11] Most of the above methods for producing β-carbolines use expensive and toxic catalysts, the use of which is less than ideal.[12]

We were able to implement a new method for the synthesis of harmane, harmine alkaloids and their structural analogs, in which 3-cyano-2-methylpyridines **5a**,**b** were used as starting compounds. In order to increase the yield, the previously described synthesis of pyridines **4a**,**b** from 4-aryl-2-oxobut-3-enoic acids **3a**,**b** was optimized by replacing MeCN with commercially available 3-aminocrotononitrile.[13] Alternative synthesis of pyridine-6-carboxylic acids **4a**,**b** from compounds **1a**,**b** using the single-step Hantzsch reaction for the synthesis of pyridines **2a**,**b** with the subsequent oxidation of the furyl substituent of pyridine turned out to be more efficient and better reproducible (oxidation of the furyl substituent of pyridines **2a**,**b** by $KMnO_4$ in pyridine with KOH is more effective than in Me_2CO with $KMnO_4$).[14] Above methods provide pyridines **4a**,**b** in high yields (Scheme 1).

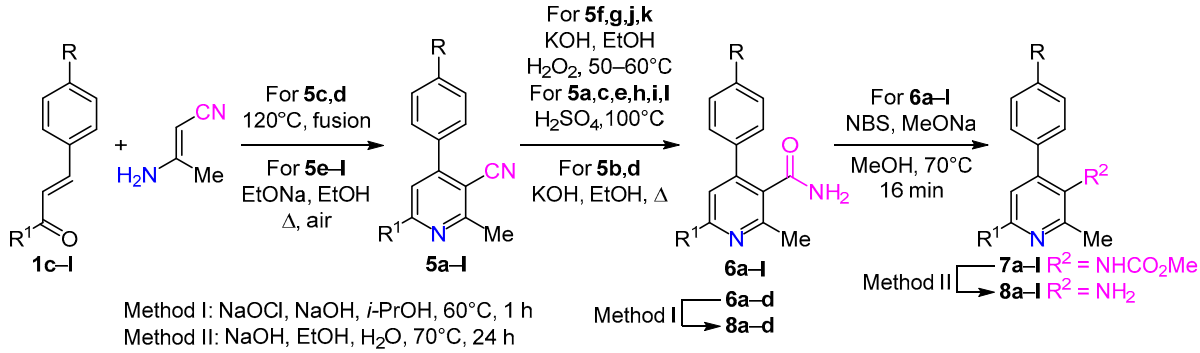
The known synthesis of 2-methylpyridines **5a**,**b** according to Katritzky et al. is multistage and time-consuming.[15] In our case, 4-aryl-3-cyano-2-methylpyridines **5a**,**b** were obtained by decarboxylation of pyridines **4a**,**b** by heating without solvent (Scheme 1).

3-Cyano-2,6-dimethylpyridines **5c**,**d** were obtained by fusion of benzalacetone (**1c**) and anisalacetone (**1d**) with 3-aminocrotononitrile. The synthesis of amides **6a**,**c** was carried out by incomplete hydrolysis of the cyano group of pyridines **5a**,**c** by heating in concentrated H_2SO_4, and the synthesis of amides **6b**,**d** by the Radzishevsky hydrolysis of the corresponding pyridines **5b**,**d**.[16] For the synthesis of 3-aminopyridines **8a**–**d**, the classical (NaOCl, NaOH) and modified (NBS, MeONa) Hoffmann reactions were employed.[17] Modified Hoffman reactions yielded 4-aryl-2-methylpyridin-3-ylcarbamates **7a**–**l**, from which 3-aminopyridines **8a**–**l** were synthesized (Scheme 2).

Harmane, harmine, and their structural analogs **10a**–**l** were synthesized by thermolysis of 4-aryl-3-azidopyridines **9a**–**l** in xylene. In turn, 4-aryl-3-azidopyridines **9a**–**l** were obtained from diazonium salts of 3-aminopyridines **8a**–**l**. Diazonium salts of 3-aminopyridines **8a**,**c**,**d** were obtained by treatment with $NOBF_4$ in MeCN at –10°C, whereas compounds **8b**,**e**–**l** were accessed using $NaNO_2$ in a mixture of AcOH and HBF_4 (diazonium salts were not isolated). As a result of the substitution of the diazo group in the pyridyldiazonium salts with the azide group by nucleophilic substitution with NaN_3, 3-azidopyridines **9a**–**l** were formed. 3-Azidopyridines **9a**–**d** were obtained in quantitative yields, isolated, and characterized, whereas the unstable 3-azidopyridines **9e**–**l** were isolated by extraction with *m*-xylene and used without further purification (Scheme 3).

β-Carbolines contain the acidic proton of the pyrrole ring of indole and the nitrogen atom of the pyridine ring in

Scheme 2



1c–l, **5–8 a** R = H, R^1 = H; **b** R = OMe, R^1 = H; **c** R = H, R^1 = Me; **d** R = OMe, R^1 = Me; **e** R = H, R^1 = 4-BrC_6H_4; **f** R = OMe, R^1 = 4-$MeOC_6H_4$; **g** R = OMe, R^1 = 4-BrC_6H_4; **h** R = Cl, R^1 = Ph; **i** R = Me, R^1 = 4-MeC_6H_4; **j** R = H, R^1 = 4-$MeOC_6H_4$; **k** R = OMe, R^1 = Ph; **l** R = Cl, R^1 = 4-MeC_6H_4

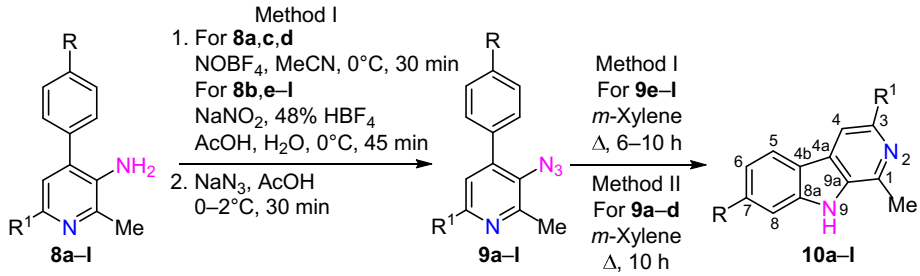
their structure, which in the basic state have pK_a 16 (pyrrole NH) and pK_a 7 (pyridine N). The electronic excitation of carbolines to the first singlet excited state increases the acidity and basicity of both centers by 4–7 pK_a units. A change in the acid-base properties of carbolines upon excitation makes possible double proton transfer and the implementation of the phototautomerization process.[18]

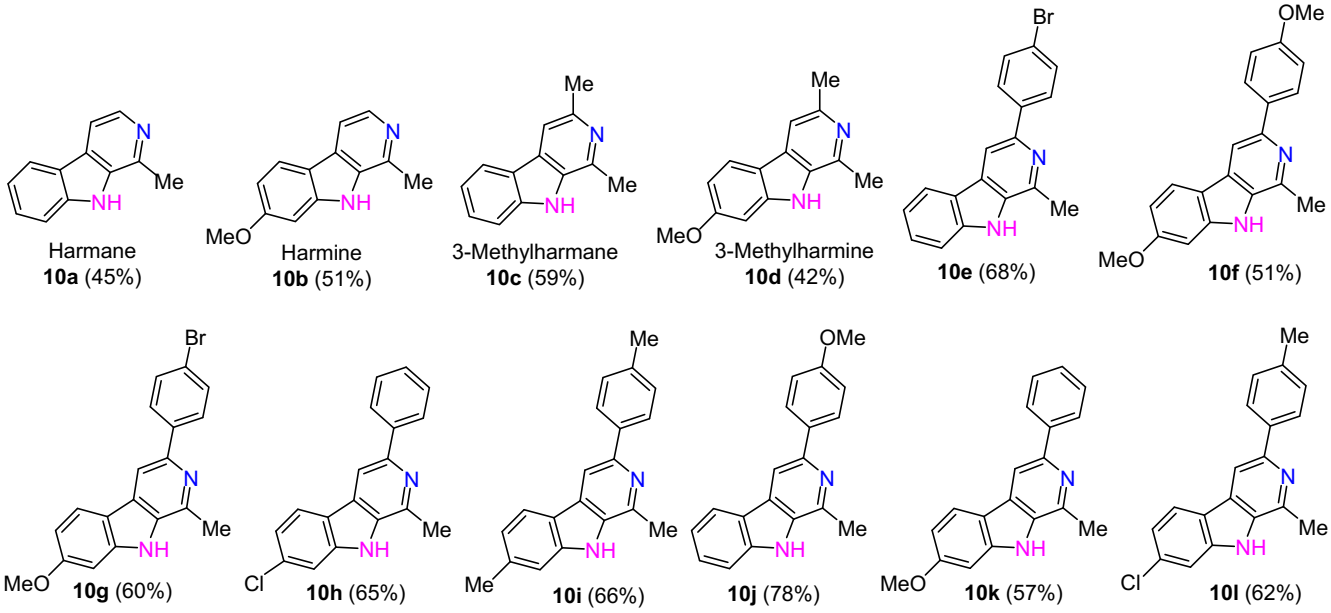
It is known that harmine, norharmane, and other β-carboline alkaloids easily protonate and deprotonate forming a cation, anion, and zwitterion,[18] which have different absorption and fluorescence spectra (Scheme 4).

For example, the maxima in the luminescence spectra for various acid-base forms of harmine **10b** are at 420 (cation H_2CB^+), 372 (neutral form HCB), 435 (anion CB^-), and 482 nm (zwitterion HCB^{+-}),[19] which makes it possible to use it as a fluorescent probe for biological research,[7] responsive to changes in the pH of the medium and the external environment.[20]

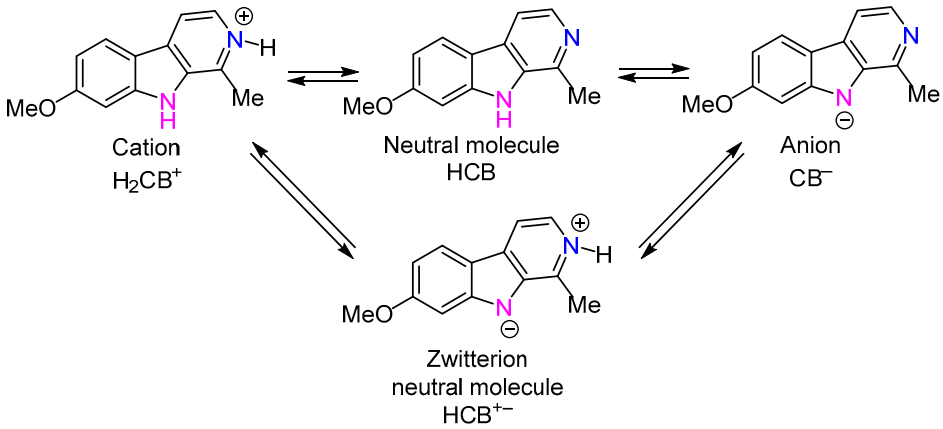
The absorption spectra of compounds **10a**–**d** in EtOH solution are a superposition of neutral and protonated form signals. Therefore, treatment of these solutions with radiation with different wavelengths leads to different

Scheme 3





Scheme 4



excitations in each of these forms and, as a result, to a change in the fluorescence spectra. For example, when compound **10d** is irradiated with a 300 nm light, the signals of the neutral form with maxima of 361 and 374 nm, as well as of protonated forms with a maximum of 407 nm are observed in the fluorescence spectrum (Fig. 1). At the same time, when the solution is irradiated with light with a wavelength of 325 nm, the broadened signal with a maximum at 414 nm corresponding to the protonated form is the main one (Fig. 1).

Only the neutral form signals are observed in the fluorescence spectra of compounds **10a**–**d** recorded in aprotic solvents such as DMSO and CH_2Cl_2. When acid (CF_3CO_2H) is added to the β-carboline **10d** solution, only the protonated signal is observed (Figs. S26 and S27, see the Supplementary information file). A similar picture is observed for all alkyl-substituted β-carbolines **10a**–**d**. At the same time, in the fluorescence spectra of solutions of aryl-substituted β-carbolines **10e**–**l** (recorded in EtOH), the signal of the neutral form with a maximum at 370–390 nm is the main signal (Fig. S13, see the Supplementary information file). When these compounds are irradiated with radiation with different wavelengths, it practically does not change. In the short-wavelength region of the absorption spectra, there are two intense peaks related to the π–π and n–π transitions.[19] For example, for compound **10k** (Fig. 1), the maxima of these transitions are at 257 and 279 nm, respectively.

Signals of various acid-base forms are registered in the absorption and fluorescence spectra of aqueous ethanol solutions (H_2O–EtOH, 9:1) of compound **10k** recorded at various pH values (Figs. S28 – S31, see the Supplementary information file). When acidifying a solution of compound **10k** by 2 N H_2SO_4 in the absorption spectra, a transition from the form HCB to the form H_2CB^+ is noticeable. However, the absorption spectrum changes slightly with increasing pH of the medium. At the same time, at pH up to 4.5, only the H_2CB^+ form exists in the solution with a maximum emission at 425 nm. At pH 4.5–6.6, the protonated form H_2CB^+ transforms into the neutral form HCB, and at pH 6.6–9.5 only the neutral form HCB with maximum emission at 374 nm is present in solution. At pH 9.5, the neutral form HCB begins to transform into the deprotonated form CB^- with a maximum emission at 485 nm.

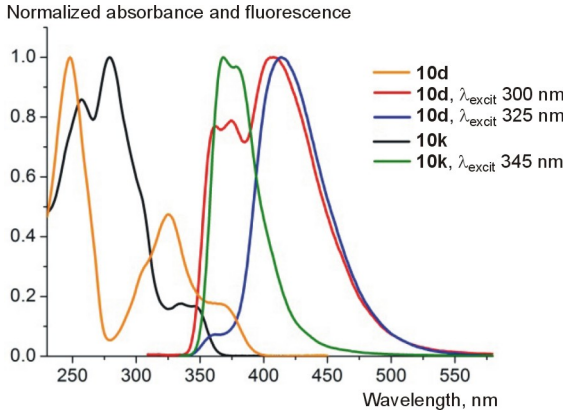


Figure 1. Absorption and fluorescence spectra of EtOH solutions of compounds **10d**,**k**.

We determined the values of pK_a 5.53 (H_2CB^+/HCB) and pK_a 11.56 (HCB/CB^-) for compound **10k** (Figs. S32 and S33, see the Supplementary information file). The pK_a value (H_2CB^+/HCB) was determined graphically[19] from the absorption (λ 373 nm) and fluorescence (λ 374 nm) spectra, whereas pK_a (HCB/CB^-) was determined only from the fluorescence spectra (λ 374 nm), since the absorption spectrum did not change for this transition (Fig. 2; Figs. S32 and S33, see the Supplementary information file).

A comparison of these data with the known values for harmine **10b**[19] (pK_a 7.75 (H_2CB^+/HCB), pK_a 12.5 (HCB/CB^-)) shows that the introduction of any substituent at position C-3 has a significant effect on the acid-base properties of the molecule and can be used to tune fluorescent probes based on these compounds.

To conclude, we have developed a general method for the synthesis of harmane, harmine alkaloids and their structural analogs from available precursors. It was found that thermolysis of 4-aryl-3-azidopyridines completes with the formation of β-carbolines by the insertion of nitrene in the C–H bond of the aryl substituent.

Experimental

IR spectra were registered on a Simex FT-801 FT-IR spectrometer in KBr pellets. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker DRX-400 spectrometer (400 and 100 MHz, respectively) in $CDCl_3$ or DMSO-d_6, using

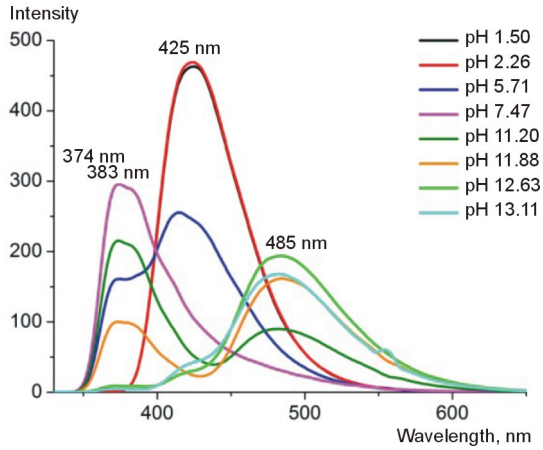


Figure 2. Dependence of the fluorescence spectrum of compound **10k** on the pH of the solution in H_2O–EtOH, 9:1, concentration 5.8 μM , excitation wavelength 278 nm.

residual solvent signals ($CDCl_3$: 7.26 ppm for ^1H nuclei and 77.0 ppm for ^{13}C nuclei; DMSO-d_6: 2.50 ppm for ^1H nuclei and 39.5 ppm for ^{13}C nuclei) to assign chemical shifts. Elemental analysis was performed on a Carlo Erba EA 1106 CHN-analyzer. Absorption spectra were recorded on a PerkinElmer Lambda 750 diode-array spectrophotometer, photoluminescence spectra were recorded on a Cary Eclipse fluorescence spectrophotometer. In both cases, the concentration of the solutions of the studied compounds in the corresponding solvents was below 10^{-5} mol/dm^{-3}. The molar coefficient of absorption was determined by a literature method.[21,22] The quantum yield of the luminescence of the studied compounds was determined relative to quinine sulfate using the comparison method.[23,24] Melting points were determined on a Boetius heating bench and are uncorrected. Monitoring of the reaction progress and assessment of the purity of synthesized compounds were done by TLC on Silufol UV-254 plates. 60–120 μ silica gel was used for column chromatography.

Chalcones **1a**,**b**,[25a] **1c**,**d**,[25b] **1e**,**g**,**h**,**k**,[25c] **1f**,**j**,[25d] **1i**,[25e] **1l**[25f] synthesized by the Claisen–Schmidt condensation of the corresponding acetophenones and aromatic aldehydes. Synthesis of compounds **3a**,**b**[26] and **5a**,[15,27a,b] **5b**,[27a] **5c**,[27b] **5f**–**k**,[27d] was done in accordance with published methods.

Synthesis of methyl (4-aryl-2-methylpyridin-3-yl)-carbamates 7a–l (General method). Amide **6a–l** (1.00 mmol) and NBS (0.19 g (1.05 mmol) were added to a solution of MeONa, obtained from Na (0.31 g) and anhydrous MeOH (16 ml). The reaction mixture was stirred and heated (70°C) for 6 min, then NBS (0.09 g, 0.53 mmol) was added, and heating was continued for 10 min. After the completion of the reaction, the solvent was evaporated under reduced pressure, the residue was diluted with H_2O and, with cooling, neutralized with 50% AcOH. The resulting oil was triturated with cooling, and, if necessary, left in the refrigerator overnight. The resulting crystals were filtered off, washed with H_2O, and purified by recrystallization.

Methyl (2-methyl-4-phenylpyridin-3-yl)carbamate (7a). Yield 0.18 g (76%), colorless crystals, mp 161–162°C (petroleum ether). IR spectrum, ν, cm^{-1}: 3161 (NH), 2989, 2949, 2764, 1729 (C=O), 1594, 1535, 1262, 1236, 1192, 1064, 835, 759, 700, 620, 579. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.57 (3H, s, 2-CH_3); 3.66 (3H, br. s, NHCOOC$\underline{H}_3$); 6.36 (1H, br. s, N$\underline{H}$COOCH$_3$); 7.12 (1H, d, *J* = 5.0, H-5); 7.33–7.35 (2H, m, H Ph); 7.39–7.47 (3H, m, H Ph); 8.43 (1H, d, *J* = 5.0, H-6). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.4; 52.6; 122.5; 125.7; 128.3 (2C); 128.4; 128.6 (2C); 137.0; 147.1; 147.4; 155.0; 157.4. Found, %: C 69.47; H 5.79; N 11.59. $C_{14}H_{14}N_2O_2$. Calculated, %: C 69.41; H 5.82; N 11.56.

Methyl [4-(4-methoxyphenyl)-2-methylpyridin-3-yl]-carbamate (7b). Yield 0.25 g (90%), colorless crystals, mp 137–138°C (petroleum ether). IR spectrum, ν, cm^{-1}: 3266 (NH), 2955, 2839, 1703 (C=O), 1610, 1514, 1306, 1264, 1248, 1184, 1071, 1028, 823. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.55 (3H, s, 2-CH_3); 3.67 (3H, br. s, NHCOOC$\underline{H}_3$); 3.83 (3H, s, OC$\underline{H}_3$); 6.42 (1H, br. s, N$\underline{H}$COOCH$_3$); 6.93–6.97 (2H, m, H Ar); 7.11 (1H, d, *J* = 5.1, H-5); 7.25–7.28 (2H, m, H Ar); 8.37 (1H, d, *J* = 5.1, H-6). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.1; 52.7; 55.3; 114.2 (2C); 122.7; 128.9 (2C); 129.6 (2C); 146.7; 147.3; 155.0; 157.0; 159.9. Found, %: C 66.22; H 5.95; N 10.31. $C_{15}H_{16}N_2O_3$. Calculated, %: C 66.16; H 5.92; N 10.29.

Methyl (2,6-dimethyl-4-phenylpyridin-3-yl)carbamate (7c). Yield 0.24 g (94%), colorless crystals, mp 132–133°C (petroleum ether). IR spectrum, ν, cm^{-1}: 3164 (NH), 2953, 2773, 1720 (C=O), 1593, 1530, 1388, 1264, 1248, 1202, 1098, 877, 752, 699, 599. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.52 (3H, s, 2-CH_3); 2.54 (3H, s, 6-CH_3); 3.62 (3H, br. s, NHCOOC$\underline{H}_3$); 6.03 (1H, br. s, N$\underline{H}$COOCH$_3$); 6.97 (1H, s, H-5); 7.28–7.32 (2H, m, H Ph); 7.35–7.43 (3H, m, H Ph). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.1; 23.9; 52.6; 122.2; 126.2; 128.3 (2C); 128.4; 128.6 (2C); 137.2; 147.8; 155.2; 156.2; 156.4. Found, %: C 70.22; H 6.33; N 10.95. $C_{15}H_{16}N_2O_2$. Calculated, %: C 70.29; H 6.29; N 10.93.

Methyl [4-(4-methoxyphenyl)-2,6-dimethylpyridin-3-yl]carbamate (7d). Yield 0.27 g (95%), colorless crystals, mp 102–103°C (petroleum ether). IR spectrum, ν, cm^{-1}: 3271 (NH), 3001, 2958, 2839, 1704 (C=O), 1610, 1515, 1386, 1268, 1189, 1076, 1032, 864, 841, 777, 711, 600, 548, 515. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.52 (3H, s, 2-CH_3); 2.53 (3H, s, 6-CH_3); 3.64 (3H, br. s, NHCOOC$\underline{H}_3$); 3.82 (3H, s, OC$\underline{H}_3$); 6.05 (1H, br. s, N$\underline{H}$COOCH$_3$); 6.91–6.95 (3H, m, H Ar, H-5); 7.22–7.26 (2H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.0; 23.8; 52.6; 55.3; 114.1 (2C); 122.2; 126.3; 129.4; 129.6 (2C); 147.5; 155.3; 156.1; 156.4; 159.8. Found, %: C 67.17; H 6.30; N 9.81. $C_{16}H_{18}N_2O_3$. Calculated, %: C 67.12; H 6.34; N 9.78.

Methyl [6-(4-bromophenyl)-2-methyl-4-phenylpyridin-3-yl]carbamate (7e). Yield 0.33 g (83%), colorless crystals, mp 175–176°C (EtOH). IR spectrum, ν, cm^{-1}: 3204 (NH), 3008, 2959, 1736 (C=O), 1591, 1527, 1455, 1408, 1371, 1251, 1093, 1064, 1007, 915, 837, 757, 697. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.68 (3H, s, 2-CH_3); 3.65 (3H, br. s, NHCOOC$\underline{H}_3$); 6.21 (1H, br. s, N$\underline{H}$COOCH$_3$); 7.36–7.41 (2H, m, H Ph); 7.41–7.48 (3H, m, H Ph); 7.51 (1H, s, H-5); 7.57 (2H, d, *J* = 8.4, H Ar); 7.88 (2H, d, *J* = 8.4, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.2; 52.8; 119.8; 122.1; 123.9; 128.1; 128.3 (2C);

128.8 (4C); 131.9 (2C); 136.9 (2C); 147.8; 153.5; 154.9; 157.1. Found, %: C 60.53; H 4.33; N 7.09. $C_{20}H_{17}BrN_2O_2$. Calculated, %: C 60.47; H 4.31; N 7.05.

Methyl [4,6-bis(4-methoxyphenyl)-2-methylpyridin-3-yl]carbamate (7f). Yield 0.34 g (89%), colorless crystals, mp 148–149°C (EtOH). IR spectrum, ν, cm^{-1}: 3295 (NH), 2959, 2841, 1700 (C=O), 1611, 1512, 1457, 1374, 1290, 1257, 1240, 1064, 1027, 840. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.59 (3H, s, 2-CH_3); 3.69 (3H, br. s, NHCOOC$\underline{H}_3$); 3.84 (3H, s, OCH_3); 3.85 (3H, s, OCH_3); 6.04 (1H, br. s, N$\underline{H}$COOCH$_3$); 6.95–6.99 (4H, m, H Ar); 7.30–7.32 (2H, m, H Ar); 7.43 (1H, s, H-5); 7.92–7.95 (2H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.7; 52.7; 55.3; 114.0 (2C); 114.1 (2C); 118.8; 126.6; 128.3 (2C); 129.6 (2C); 129.7; 131.7; 147.2; 155.0; 155.2; 156.9; 159.7; 160.4. Found, %: C 69.89; H 5.90; N 7.37. $C_{22}H_{22}N_2O_4$. Calculated, %: C 69.83; H 5.86; N 7.40.

Methyl [6-(4-bromophenyl)-4-(4-methoxyphenyl)-2-methylpyridin-3-yl]carbamate (7g). Yield 0.38 g (90%), colorless crystals, mp 143–144°C (EtOH). IR spectrum, ν, cm^{-1}: 3400 (NH), 2952, 2838, 1729 (C=O), 1601, 1493, 1408, 1242, 1064, 1015, 837, 768. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.64 (3H, s, 2-CH_3); 3.62 (3H, br. s, NHCOOC$\underline{H}_3$); 3.85 (3H, s, OCH_3); 6.61 (1H, br. s, N$\underline{H}$COOCH$_3$); 7.02–7.10 (2H, m, H Ar); 7.25–7.28 (2H, m, H Ar); 7.45 (1H, s, H-5); 7.55–7.57 (2H, m, H Ar); 7.86–7.88 (2H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.8; 52.5; 55.9; 111.3 (2C); 119.9 (2C); 121.5; 123.2; 126.3; 128.6 (2C); 130.4; 131.2 (2C); 131.8; 137.8; 144.5; 153.6; 155.7; 156.6. Found, %: C 58.97; H 4.51; N 6.53. $C_{21}H_{19}BrN_2O_3$. Calculated, %: C 59.03; H 4.48; N 6.56.

Methyl [4-(4-chlorophenyl)-2-methyl-6-phenylpyridin-3-yl]carbamate (7h). Yield 0.31 g (87%), colorless crystals, mp 161–162°C (EtOH). IR spectrum, ν, cm^{-1}: 3203 (NH), 3135, 2955, 1715 (C=O), 1601, 1548, 1488, 1447, 1339, 1067, 1016, 883, 834, 774, 692, 594. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.62 (3H, s, 2-CH_3); 3.67 (3H, br. s, NHCOOC$\underline{H}_3$); 6.06 (1H, br. s, N$\underline{H}$COOCH$_3$); 7.30–7.33 (2H, s, H Ar); 7.37–7.47 (5H, m, H Ph); 7.48 (1H, s, H-5); 7.96–7.98 (2H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.7; 52.8; 119.3; 127.0 (2C); 127.9; 128.7 (2C); 128.9 (2C); 129.0; 129.7 (2C); 130.1; 134.6; 135.9; 138.8; 146.7; 155.0; 155.6. Found, %: C 68.02; H 4.83; N 7.91. $C_{20}H_{17}ClN_2O_2$. Calculated, %: C 68.09; H 4.86; N 7.94.

Methyl [2-methyl-4,6-bis(4-methylphenyl)pyridin-3-yl]carbamate (7i). Yield 0.29 g (83%), colorless crystals, mp 158–159°C (EtOH). IR spectrum, ν, cm^{-1}: 3231 (NH), 3031, 2922, 1694 (C=O), 1592, 1524, 1457, 1379, 1266, 1189, 1059, 827. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.34 (3H, s, CH_3); 2.35 (3H, s, CH_3); 2.47 (3H, s, 2-CH_3); 3.54 (3H, br. s, NHCOOC$\underline{H}_3$); 7.26–7.28 (4H, m, H Ar); 7.37–7.39 (2H, m, H Ar); 7.65 (1H, s, H-5); 7.99–8.01 (2H, m, H Ar); 8.88 (1H, br. s, N$\underline{H}$COOCH$_3$). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 20.7; 20.8; 21.3 (2-CH_3); 51.8; 118.6; 126.5 (2C); 127.8; 128.3 (2C); 128.8 (2C); 129.2 (2C); 134.5; 135.5; 137.5; 138.4; 148.2; 153.7; 155.2; 157.2. Found, %: C 76.32; H 6.42; N 8.12. $C_{22}H_{22}N_2O_2$. Calculated, %: C 76.28; H 6.40; N 8.09.

Methyl [6-(4-methoxyphenyl)-2-methyl-4-phenylpyridin-3-yl]carbamate (7j). Yield 0.28 g (79%), colorless crystals, mp 167–168°C (EtOH). IR spectrum, ν, cm^{-1}: 3172 (NH), 3001, 2951, 2834, 1721 (C=O), 1608, 1516, 1458, 1376, 1255, 1174, 1067, 1038, 841, 770, 696. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.61 (3H, s, 2-CH_3); 3.66 (3H, br. s, NHCOOC$\underline{H}_3$); 3.85 (3H, s, OCH_3); 5.98 (1H, br. s, N$\underline{H}$COOCH$_3$); 6.95–7.01 (2H, m, H Ar); 7.36–7.47 (6H, m, H Ph, H-5); 7.93–7.97 (2H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.7; 52.7; 55.3; 114.1 (2C); 118.7; 126.6; 128.3 (2C); 128.4 (3C); 128.7 (2C); 131.7; 137.6; 147.6; 155.1; 155.2; 156.9; 160.5. Found, %: C 72.43; H 5.77; N 8.07. $C_{21}H_{20}N_2O_3$. Calculated, %: C 72.40; H 5.79; N 8.04.

Methyl [4-(4-methoxyphenyl)-2-methyl-6-phenylpyridin-3-yl]carbamate (7k). Yield 0.33 g (95%), colorless crystals, mp 167–168°C (EtOH). IR spectrum, ν, cm^{-1}: 3288 (NH), 3033, 2747, 2842, 1698 (C=O), 1609, 1616, 1446, 1254, 1064, 10223, 833, 770, 701. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.62 (3H, s, 2-CH_3); 3.69 (3H, br. s, NHCOOC$\underline{H}_3$); 3.85 (3H, s, OCH_3); 6.04 (1H, br. s, N$\underline{H}$COOCH$_3$); 6.96–7.00 (2H, m, H Ar); 7.30–7.34 (2H, m, H Ph); 7.36–7.46 (3H, m, H Ph); 7.50 (1H, s, H-5); 7.97–7.99 (2H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.7; 52.7; 55.3; 114.2 (2C); 119.6; 127.0 (2C); 127.3; 128.7 (2C); 128.8; 129.6; 129.7 (2C); 133.5; 139.1; 147.2; 155.3; 157.1; 159.8. Found, %: C 72.43; H 5.76; N 8.08. $C_{21}H_{20}N_2O_3$. Calculated, %: C 72.40; H 5.79; N 8.04.

Methyl [4-(4-chlorophenyl)-2-methyl-6-(4-methylphenyl)pyridin-3-yl]carbamate (7l). Yield 0.31 g (84%), colorless crystals, mp 166–167°C (EtOH). IR spectrum, ν, cm^{-1}: 3219 (NH), 3140, 2953, 1714 (C=O), 1601, 1488, 1446, 1337, 1234, 1069, 1016, 818, 589. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.39 (3H, s, CH_3); 2.62 (3H, s, 2-CH_3); 3.67 (3H, br. s, NHCOOC$\underline{H}_3$); 6.01 (1H, br. s, N$\underline{H}$COOCH$_3$); 7.24–7.26 (2H, m, H Ar); 7.30–7.33 (2H, m, H Ar); 7.40–7.44 (2H, m, H Ar); 7.46 (1H, s, H-5); 7.87–7.89 (2H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.3; 21.6; 52.8; 119.0; 126.8; 126.9 (2C); 128.9 (2C); 129.5 (2C); 129.7 (2C); 129.9; 134.6; 135.9; 136.0; 139.1; 146.8; 155.1; 155.6. Found, %: C 68.69; H 5.25; N 7.60. $C_{21}H_{19}ClN_2O_2$. Calculated, %: C 68.76; H 5.22; N 7.64.

Synthesis of 3-amino-4-arylpyridines 8a–l (General procedure). Method I. 2 M Aqueous NaOH (3.7 ml) was added to a solution of amide **6a**–**d** (1 mmol) in *i*-PrOH (10 ml). Then 12% aqueous NaOCl (2.5 ml) was added in portions over 5 h (0.5 ml every hour). The resulting mixture was heated at 60°C for 1 h. After the completion of the reaction, *i*-PrOH was evaporated under reduced pressure, the residue was diluted with H_2O, and the formed oil was extracted with EtOAc. The organic layer was dried over $MgSO_4$, evaporated under reduced pressure, and the residue was purified by recrystallization.

Method II. Carbamate **7a**–**l** (1.00 mmol) was added to a solution of NaOH (0.30 g) in H_2O (0.8 ml) and EtOH (2.2 ml). The reaction mixture was stirred for 24 h at 70°C, then cooled to room temperature, and diluted with H_2O. The precipitated crystals were filtered off and purified by recrystallization. Compound **8j** was isolated as hydrochloride salt. This was done by dissolving the residue in the form of an oil in EtOH (2 ml) and adding 36% HCl (0.2 ml) with cooling.

2-Methyl-4-phenylpyridin-3-amine (8a). Yield 0.16 g (84%, method I), 0.15 g (80%, method II), yellow crystals, mp 66–67°C (petroleum ether). IR spectrum, ν, cm^{-1}: 3417, 3311 (NH_2), 3216, 2912, 1639, 1591, 195, 1474, 1417, 1258, 1228, 1076, 1026, 984, 828, 780, 752, 709, 600, 544. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.37 (3H, s, 2-CH_3); 3.63 (2H, br. s, NH_2); 6.82 (1H, d, *J* = 4.9, H-5); 7.28–7.39 (5H, m, H Ph); 7.89 (1H, d, *J* = 4.9, H-6). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 20.7; 122.6; 128.1; 128.5 (2C); 129.0 (2C); 133.3; 137.3; 137.5; 138.7; 143.9. Found, %: C 78.19; H 6.55; N 15.25. $C_{12}H_{12}N_2$. Calculated, %: C 78.23; H 6.57; N 15.21.

4-(4-Methoxyphenyl)-2-methylpyridin-3-amine (8b). Yield 0.15 g (72%, method I), 0.15 g (72%, method II), colorless crystals, mp 138–139°C (petroleum ether). IR spectrum, ν, cm^{-1}: 3424, 3310 (NH_2), 3198, 2834, 1629, 1517, 1250, 1180, 1029, 823, 568. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.47 (3H, s, 2-CH_3); 3.76 (2H, br. s, NH_2); 3.84 (3H, s, OCH_3); 6.91 (1H, d, *J* = 5.0, H-5); 6.97–7.01 (2H, m, H Ar); 7.34–7.37 (2H, m, H Ar); 7.94 (1H, d, *J* = 5.0, H-6). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 20.4; 55.3; 114.5 (2C); 122.9; 129.2; 129.7 (2C); 133.6; 138.0 (2C); 143.4; 159.5. Found, %: C 72.90; H 6.54; N 13.04. $C_{13}H_{14}N_2O$. Calculated, %: C 72.87; H 6.59; N 13.07.

2,6-Dimethyl-4-phenylpyridin-3-amine (8c). Yield 0.17 g (84%, method I), 0.15 g (76%, method II), colorless crystals, mp 80–81°C (petroleum ether). IR spectrum, ν, cm^{-1}: 3432, 3319 (NH_2), 3216, 3061, 2916, 1625, 1552, 1463, 1270, 1236, 1019, 956, 868, 744, 698, 592, 552. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.47 (3H, s, 2-CH_3); 2.48 (3H, s, 6-CH_3); 3.63 (2H, br. s, NH_2); 6.81 (1H, s, H-5); 7.36–7.48 (5H, m, H Ph). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 20.2; 22.8; 122.3; 128.2; 128.5 (2C); 129.1 (2C); 135.1; 135.4; 137.3; 142.8; 146.2. Found, %: C 78.70; H 7.16; N 14.10. $C_{13}H_{14}N_2$. Calculated, %: C 78.75; H 7.12; N 14.13.

4-(4-Methoxyphenyl)-2,6-dimethylpyridin-3-amine (8d). Yield 0.15 g (66%, method I), 0.18 g (81%, method II), colorless crystals, mp 115–116°C (petroleum ether). IR spectrum, ν, cm^{-1}: 3423, 3336 (NH_2), 3220, 2835, 1613, 1511, 1460, 1290, 1246, 1173, 1035, 833, 558. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.44 (3H, s, 2-CH_3); 2.45 (3H, s, 6-CH_3); 3.56 (2H, br. s, NH_2); 3.84 (3H, s, OCH_3); 6.76 (1H, s, H-5); 6.96–6.99 (2H, m, H Ar); 7.33–7.36 (2H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 20.5; 23.1; 55.3; 114.5 (2C); 122.2; 129.7 (2C); 134.6; 135.3; 143.0; 146.6; 159.5. Found, %: C 73.59; H 7.03; N 12.30. $C_{14}H_{16}N_2O$. Calculated, %: C 73.66; H 7.06; N 12.27.

6-(4-Bromophenyl)-2-methyl-4-phenylpyridin-3-amine (8e). Yield 0.31 g (91%, method II), colorless crystals, mp 122–123°C (EtOH). IR spectrum, ν, cm^{-1}: 3464, 3375 (NH_2), 3212, 2935, 1616, 1551, 1491, 1454, 1425, 1376, 1349, 1233, 1178, 1069, 1008, 885, 829, 746, 701. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.62 (3H, s, 2-CH_3); 3.94 (2H, br. s, NH_2); 7.36 (1H, s, H-5); 7.41–7.54 (7H, m, H Ar, H Ph); 7.81–7.83 (2H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 20.3; 120.2; 122.2; 127.9 (2C); 128.5 (2C); 128.6; 129.3 (2C); 131.7 (2C); 135.0; 137.0; 137.5; 143.4; 144.7. Found, %: C 63.77; H 4.42; N 8.30. $C_{18}H_{15}BrN_2$. Calculated, %: C 63.73; H 4.46; N 8.26.

4,6-Bis(4-methoxyphenyl)-2-methylpyridin-3-amine (8f). Yield 0.22 g (70%, method II), colorless crystals, mp 87–88°C (EtOH). IR spectrum, ν, cm^{-1}: 3465, 3376 (NH_2), 2963, 2837, 1610, 1512, 1293, 1249, 1029, 840. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.43 (3H, s, 2-CH_3); 3.76 (3H, s, OCH_3); 3.80 (3H, s, OCH_3); 4.62 (2H, br. s, NH_2); 6.91–6.94 (2H, m, H Ar); 7.05–7.07 (2H, m, H Ar); 7.31 (1H, s, H-5); 7.42–7.45 (2H, m, H Ar); 7.88–7.91 (2H, m, H Ar). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 21.4; 55.1; 55.2; 113.8 (2C); 114.4 (2C); 118.1; 126.5 (2C); 129.7 (2C); 129.8; 132.1; 132.3; 137.2; 143.2; 143.7; 158.7; 158.9. Found, %: C 75.00; H 6.30; N 8.76. $C_{20}H_{20}N_2O_2$. Calculated, %: C 74.98; H 6.29; N 8.74.

6-(4-Bromophenyl)-4-(4-methoxyphenyl)-2-methylpyridin-3-amine (8g). Yield 0.36 g (97%, method II), colorless crystals, mp 185–186°C (EtOH). IR spectrum, ν, cm^{-1}: 3450, 3381 (NH_2), 3005, 2957, 2834, 1622, 1551, 1491, 1462, 1243, 1177, 1117, 1020, 831, 757. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.43 (3H, s, 2-CH_3); 3.75 (3H, s, OCH_3); 4.58 (2H, br. s, NH_2); 7.14–7.16 (2H, m, H Ar); 7.20–7.23 (2H, m, H Ar); 7.37 (1H, s, H-5); 7.52–7.54 (2H, m, H Ar); 7.90–7.92 (2H, m, H Ar). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 21.3; 55.4; 119.7 (2C); 119.8; 120.1 (2C); 120.9; 125.9; 127.2 (2C); 130.2; 131.3 (2C); 138.6; 139.2; 141.5; 143.1; 156.3. Found, %: C 61.85; H 4.61; N 7.61. $C_{19}H_{17}BrN_2O$. Calculated, %: C 61.80; H 4.64; N 7.59.

4-(4-Chlorophenyl)-2-methyl-6-phenylpyridin-3-amine (8h). Yield 0.27 g (92%, method II), colorless crystals, mp 127–128°C (EtOH). IR spectrum, ν, cm^{-1}: 3442, 3363 (NH_2), 3035, 2938, 1598, 1489, 1386, 1232, 1088, 1014, 757, 694, 594. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.45 (3H, s, 2-CH_3); 4.86 (2H, br. s, NH_2); 7.24–7.28 (1H, m, H Ar); 7.35–7.41 (3H, m, H-5, H Ar); 7.52–7.57 (4H, m, H Ar); 7.95–7.97 (2H, m, H Ar). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 21.5; 118.8; 125.3 (2C); 127.1; 128.4 (2C); 128.9 (2C); 130.5 (2C); 130.8; 132.5; 136.6; 137.9; 139.2; 143.4; 143.7. Found, %: C 73.27; H 5.15; N 9.53. $C_{18}H_{15}ClN_2$. Calculated, %: C 73.34; H 5.13; N 9.50.

2-Methyl-4,6-bis(4-methylphenyl)pyridin-3-amine (8i). Yield 0.25 g (85%, method II), colorless crystals, mp 106–107°C (EtOH). IR spectrum, ν, cm^{-1}: 3465, 3376 (NH_2), 2963, 2837, 1610, 1512, 1293, 1249, 1029, 840. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.30 (3H, s, 2-CH_3); 2.36 (3H, s, CH_3); 2.44 (3H, s, CH_3); 4.68 (2H, br. s, NH_2); 7.17–7.19 (2H, m, H Ar); 7.30–7.32 (2H, m, H Ar); 7.34 (1H, s, H-5); 7.38–7.40 (2H, m, H Ar); 7.84–7.86 (2H, m, H Ar). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 20.7; 20.8; 21.4; 118.5; 125.2 (2C); 128.3 (2C); 129.0 (2C); 129.6 (2C); 132.3; 134.7; 136.2; 136.6; 137.1; 137.6; 143.3; 143.7. Found, %: C 83.26; H 6.95; N 9.74. $C_{20}H_{20}N_2$. Calculated, %: C 83.30; H 6.99; N 9.71.

6-(4-Methoxyphenyl)-2-methyl-4-phenylpyridin-3-amine hydrochloride (8j). Yield 0.25 g (86%, method II), yellow crystals, mp 201–202°C (EtOH). IR spectrum, ν, cm^{-1}: 3459, 3297 (NH_2), 3215, 1625, 1513, 1439, 1291, 1262, 1187, 1088, 1026, 835, 781, 738, 705, 602. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.73 (3H, s, 2-CH_3); 3.43 (2H, br. s, NH_2); 3.82 (3H, s, OCH_3); 7.07–7.10 (2H, m, H Ar); 7.51–7.61 (5H, m, H Ar); 7.66 (1H, s, H-5); 7.88–7.91 (2H, m, H Ar). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 16.3; 55.5;

114.3 (2C); 123.4; 124.0; 128.4 (2C); 129.3 (2C); 129.4 (2C); 129.5; 135.0; 138.6; 138.8 (2C); 140.8; 160.8. Found, %: C 69.88; H 5.81; N 8.59. $C_{19}H_{19}ClN_2O$. Calculated, %: C 69.83; H 5.86; N 8.57.

4-(4-Methoxyphenyl)-2-methyl-6-phenylpyridin-3-amine (8k). Yield 0.23 g (80%, method II), colorless crystals, mp 134–135°C (EtOH). IR spectrum, ν, cm^{-1}: 3459, 3372 (NH_2), 2961, 2837, 1611, 1510, 1444, 1349, 1286, 1247, 1170, 1104, 1025, 976, 873, 830, 775, 688, 593. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.34 (3H, s, 2-CH_3); 3.70 (3H, s, OCH_3); 4.63 (2H, br. s, NH_2); 6.95–6.98 (2H, m, H Ar); 7.16 (1H, t, *J* = 7.2, H Ar); 7.27–7.29 (3H, m, H Ar, H-5); 7.33–7.35 (2H, m, H Ar); 7.84–7.86 (2H, m, H Ar). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 21.4; 55.2; 114.4 (2C); 118.9; 125.2 (2C); 127.0; 128.4 (2C); 129.7 (2C); 130.1; 132.1; 137.9; 139.3; 143.4; 143.5; 158.9. Found, %: C 78.61; H 6.27; N 9.68. $C_{19}H_{18}N_2O$. Calculated, %: C 78.59; H 6.25; N 9.65.

4-(4-Chlorophenyl)-2-methyl-6-(4-methylphenyl)pyridin-3-amine (8l). Yield 0.24 g (78%, method II), colorless crystals, mp 114–115°C (EtOH). IR spectrum, ν, cm^{-1}: 3490, 3403 (NH_2), 3084, 2931, 1615, 1491, 1454, 1429, 1396, 1379, 1233, 1180, 1089, 823. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.30 (3H, s, CH_3); 2.44 (3H, s, 2-CH_3); 4.80 (2H, br. s, NH_2); 7.17–7.19 (2H, m, H Ar); 7.36 (1H, s, H-5); 7.51–7.56 (4H, m, H Ar); 7.84–7.86 (2H, m, H Ar). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 20.7; 21.4; 118.4; 125.1 (2C); 128.9 (2C); 129.0 (2C); 129.7; 130.5 (2C); 130.9; 132.5; 136.2; 136.5; 136.6; 137.6; 143.6. Found, %: C 73.93; H 5.57; N 9.03. $C_{19}H_{17}ClN_2$. Calculated, %: C 73.90; H 5.55; N 9.07.

3-Azido-4-(4-methoxyphenyl)-2-methylpyridine (9b). A cooled solution of 48% HBF_4 (3.5 ml) was added dropwise with cooling to 0°C to a solution of 3-aminopyridine **8b** (1.0 mmol) in AcOH (5 ml) and H_2O (2 ml). The reaction mixture was stirred for 30 min, then a cooled solution of $NaNO_2$ (83 mg, 1.2 mmol) in H_2O (1 ml) was added dropwise. The reaction mixture was kept at 0°C for 45 min, then NaN_3 (78 mg, 1.2 mmol) was added in portions at the same temperature. The reaction mixture was stirred for 30 min, diluted with H_2O, and neutralized with ammonia. The precipitated crystals were filtered off, washed with H_2O, and purified by recrystallization. Yield 0.23 g (96%), colorless crystals, mp 65–66°C (petroleum ether). IR spectrum, ν, cm^{-1}: 3012, 2966, 2838, 2134 (N_3), 1607, 1464, 1269, 1174, 1096, 1035, 834, 548. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.61 (3H, s, 2-CH_3); 3.85 (3H, s, OCH_3); 6.99–7.01 (2H, m, H Ar); 7.06 (1H, d, *J* = 5.1, H-5); 7.40–7.42 (2H, m, H Ar); 8.29 (1H, d, *J* = 5.1, H-6). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.2; 55.3; 114.2 (2C); 123.4; 128.0; 130.0 (2C); 132.4; 143.1; 145.3; 152.6; 160.2. Found, %: C 65.04; H 5.07; N 23.35. $C_{13}H_{12}N_4O$. Calculated, %: C 64.99; H 5.03; N 23.32.

Synthesis of 4-aryl-3-azido-2-methylpyridines 9a,c,d (General method). A solution of amine **8a**,**c**,**d** (1.0 mmol) in MeCN (0.5 ml) was added dropwise to a stirred solution of $NOBF_4$ (129 mg, 1.1 mmol) in MeCN (2 ml) at –10°C for 15 min. The reaction mixture was warmed to 0°C and stirred for 30 min. The mixture was again cooled to –10°C, and a solution of NaN_3 (76 mg, 1.1 mmol) in H_2O (1 ml) was added for 30 min. The reaction mixture was warmed to 0°C and stirred for 30 min, diluted with H_2O, and extracted with Et_2O. The extract was dried over $MgSO_4$, concentrated, and the product was purified by column chromatography on silica gel, eluent $CHCl_3$–EtOAc, 9:1, and recrystallized from petroleum ether.

3-Azido-2-methyl-4-phenylpyridine (9a). Yield 0.17 g (80%), colorless crystals, mp 35–36°C (petroleum ether). IR spectrum, ν, cm^{-1}: 3060, 3025, 3010, 2971, 2922, 2135 (N_3), 1584, 1537, 1464, 1437, 1296, 1219, 1152, 1096, 1073, 880, 847, 828, 752, 696. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.63 (3H, s, 2-CH_3); 7.09 (1H, d, *J* = 4.9, H -5); 7.43–7.52 (5H, m, H Ph); 8.33 (1H, d, *J* = 4.9, H-6). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.2; 123.4; 128.6 (2C); 128.7 (2C); 128.9; 132.4; 135.7; 143.4; 145.2; 152.6. Found, %: C 68.59; H 4.76; N 26.61. $C_{12}H_{10}N_4$. Calculated, %: C 68.56; H 4.79; N 26.65.

3-Azido-2,6-dimethyl-4-phenylpyridine (9c). Yield 0.21 g (94%), colorless crystals, mp 41–42°C (petroleum ether). IR spectrum, ν, cm^{-1}: 2930, 2920, 2116 (N_3), 1606, 1513, 1296, 1248, 1150, 1095, 1070, 878, 844, 755, 699. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.54 (3H, s, 2-CH_3); 2.60 (3H, s, 6-CH_3); 6.95 (1H, s, H-5); 7.41–7.49 (5H, m, H Ph). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.0; 23.6; 123.0; 128.6 (2C); 128.7 (2C); 128.8; 129.8; 135.9; 143.8; 151.7; 154.2. Found, %: C 69.58; H 5.38; N 24.95. $C_{13}H_{12}N_4$. Calculated, %: C 69.62; H 5.39; N 24.98.

3-Azido-4-(4-methoxyphenyl)-2,6-dimethylpyridine (9d). Yield 0.24 g (96%), colorless crystals, mp 34–35°C (petroleum ether). IR spectrum, ν, cm^{-1}: 2932, 2839, 2119 (N_3), 1609, 1514, 1291, 1251. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.52 (3H, s, 2-CH_3); 2.58 (3H, s, 6-CH_3); 3.85 (3H, s, OCH_3); 6.92 (1H, s, H-5); 6.97–7.00 (2H, m, H Ar); 7.38–7.42 (2H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.0; 23.6; 55.3; 114.1 (2C); 122.9; 128.1; 129.9 (3C); 143.4; 151.7; 154.2; 160.0. Found, %: C 66.08; H 5.59; N 22.07. $C_{14}H_{14}N_4O$. Calculated, %: C 66.13; H 5.55; N 22.03.

Synthesis of 1-methyl-β-carbolines 10a–l (General procedure). Method I. 48% HBF_4 (3.5 ml) was added dropwise to a solution of aminopyridine **8e**–**l** (1.0 mmol) in a mixture of AcOH (5 ml) and H_2O (2.1 ml). The reaction mixture was stirred for 30 min, then a cooled solution of $NaNO_2$ (83 mg, 1.2 mmol) in H_2O (3 ml) was added dropwise. The reaction mixture was stirred at 0°C for 45 min, and the precipitated crystals of diazonium tetrafluoroborate were filtered off. The diazonium salt was suspended in AcOH (10 ml), and NaN_3 (78 mg, 1.2 mmol) was added in portions at 0–2°C. The reaction mixture was stirred for additional 30 min and then diluted with H_2O. The oily azidopyridine **9a**–**l** was extracted with *m*-xylene (27 ml), and the extract was dried over $MgSO_4$. The drying agent was filtered off, and the filtrate was heated under reflux for 6–10 h (TLC control). The solvent was evaporated under reduced pressure, and β-carboline was purified by recrystallization from EtOH.

Method II. A solution of 4-aryl-3-azidopyridine **9a**–**d** (1 mmol) in *m*-xylene (27 ml) was heated under reflux for 10 h. After the completion of the reaction, *m*-xylene was evaporated under reduced pressure. The residue was dissolved in EtOH (2 ml), and 36% HCl (0.2 ml) was

added. The formed carbolinium hydrochloride was filtered off, dissolved in H_2O, and the solution was neutralized with aqueous ammonia. The formed crystals were filtered off and recrystallized from MeCN.

1-Methyl-9*H*-pyrido[3,4-*b*]indole (harmane) (10a). Yield 82 mg (45%, method II), colorless crystals, mp 236–237°C (MeCN) (mp 233–235°C,[11c] mp 235–236°C[28]). IR spectrum, ν, cm^{-1}: 3131 (NH), 3064, 2971, 2883, 1625, 1568, 1504, 1322, 1236, 882, 820, 750. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.74 (3H, s, CH_3); 7.21 (1H, ddd, *J* = 7.9, *J* = 6.9, *J* = 1.0, H-6); 7.52 (1H, ddd, *J* = 8.2, *J* = 6.9, *J* = 1.3, H-7); 7.58 (1H, dt, *J* = 8.2, *J* = 0.9, H-8); 7.91 (1H, dd, *J* = 5.4, *J* = 0.5, H-4); 8.15–8.18 (2H, m, H-3,5). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 20.5; 112.1; 112.9; 119.4; 121.2; 121.9; 127.1; 128.1; 134.5; 137.6; 140.4; 142.2. Found, %: C 79.07; H 5.50; N 15.39. $C_{12}H_{10}N_2$. Calculated, %: C 79.10; H 5.53; N 15.37.

7-Methoxy-1-methyl-9*H*-pyrido[3,4-*b*]indole (harmine) (10b). Yield 0.11 g (51%, method II), colorless crystals, mp 253–254°C (MeCN) (mp 262–264°C,[29a] mp 252°C (MeOH, $CHCl_3$)[29b]). IR spectrum, ν, cm^{-1}: 3150 (NH), 2967, 2887, 1627, 1566, 1453, 1327, 1281, 1201, 1164, 1025, 816. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.70 (3H, s, CH_3); 3.84 (3H, s, OCH_3); 6.83 (1H, dd, *J* = 8.7, *J* = 2.3, H-6); 7.02 (1H, d, *J* = 2.2, H-8); 7.78 (1H, d, *J* = 5.3, H-4); 8.03 (1H, d, *J* = 8.8, H-5); 8.12 (1H, d, *J* = 5.3, H-3); 11.45 (1H, br. s, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 20.3; 55.5; 94.8; 109.3; 112.2; 114.9; 122.8; 127.5; 134.6; 137.9; 141.4; 142.0; 160.3. Found, %: C 73.49; H 5.68; N 13.25. $C_{13}H_{12}N_2O$. Calculated, %: C 73.56; H 5.70; N 13.20.

1,3-Dimethyl-9*H*-pyrido[3,4-*b*]indole (3-methylharmane) (10c). Yield 0.12 g (59%, method II), colorless crystals, mp 186–187°C (MeCN) (mp 182–184°C,[30a] mp 179°C (petroleum ether, $CHCl_3$)[30b]). IR spectrum, ν, cm^{-1}: 3129 (NH), 3071, 2964, 1626, 1573, 1505, 1454, 1336, 1250, 1150, 1012, 968, 903, 749, 646, 587. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.55 (3H, s, 3-CH_3); 2.71 (3H, s, 1-CH_3); 7.17 (1H, t, *J* = 6.9, H-6); 7.46–7.55 (2H, m, H-7,8); 7.72 (1H, s, H-4); 8.11 (1H, d, *J* = 7.4, H-5); 11.37 (1H, br. s, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 20.3; 23.8; 110.9; 111.8; 118.9; 121.0; 121.6; 127.6; 128.0; 132.8; 140.7; 140.9; 145.2. Found, %: C 79.52; H 6.18; N 14.25. $C_{13}H_{12}N_2$. Calculated, %: C 79.56; H 6.16; N 14.27.

7-Methoxy-1,3-dimethyl-9*H*-pyrido[3,4-*b*]indole (3-methylharmine) (10d). Yield 95 mg (42%, method II), colorless crystals, mp 207–208°C (CH_3CN). IR spectrum, ν, cm^{-1}: 3316 (NH), 2957, 2919, 1628, 1572, 1480, 1460, 1377, 1331, 1281, 1165, 1134, 1102, 1026, 949, 872, 823, 569. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.51 (3H, s, 3-CH_3); 2.65 (3H, s, 1-CH_3); 3.83 (3H, s, OCH_3); 6.78 (1H, dd, *J* = 8.6, *J* = 2.2, H-6); 6.98 (1H, d, *J* = 2.2, H-8); 7.60 (1H, s, H-4); 7.96 (1H, d, *J* = 8.6, H-5); 11.24 (1H, br. s, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 20.1; 23.8; 55.5; 94.7; 108.9; 110.5; 114.8; 122.7; 128.6; 132.9; 140.2; 142.4; 145.6; 160.2. Found, %: C 74.24; H 6.28; N 12.41. $C_{14}H_{14}N_2O$. Calculated, %: C 74.31; H 6.24; N 12.38.

3-(4-Bromophenyl)-1-methyl-9*H*-pyrido[3,4-*b*]indole (10e). Yield 0.23 g (68%, method I), colorless crystals, mp 235–236°C (EtOH). IR spectrum, ν, cm^{-1}: 3157 (NH), 3087, 1623, 1561, 1492, 1449, 1348, 1244, 1080, 1006, 891, 831, 738. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.83 (3H, s, CH_3); 7.23–7.27 (1H, m, H-6); 7.51–7.55 (1H, m, H-7); 7.59–7.61 (1H, m, H-8); 7.63–7.66 (2H, m, H Ar); 8.13–8.16 (2H, m, H Ar); 8.27 (1H, d, *J* = 7.8, H-5); 8.59 (1H, s, H-4); 11.64 (1H, br. s, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 20.7; 109.1; 112.1; 119.4; 120.6; 121.4; 121.9; 128.0 (3C); 128.2; 131.4 (2C); 134.1; 139.3; 140.9; 141.7; 143.6. Found, %: C 64.17; H 3.87; N 8.36. $C_{18}H_{13}BrN_2$. Calculated, %: C 64.11; H 3.89; N 8.31.

7-Methoxy-3-(4-methoxyphenyl)-1-methyl-9*H*-pyrido-[3,4-*b*]indole (10f). Yield 0.16 g (51%, method I), colorless crystals, mp 190–191°C (EtOH). IR spectrum, ν, cm^{-1}: 3363 (NH), 2937, 2838, 1633, 1518, 1469, 1344, 1161, 1108, 1031, 920, 817, 610, 557. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.76 (3H, s, CH_3); 3.78 (3H, s, OCH_3 Ar); 3.85 (3H, s, OCH_3); 6.83 (1H, dd, *J* = 8.6, *J* = 2.0, H-6); 6.99–7.01 (3H, m, H-8, H Ar); 8.05–8.11 (3H, m, H-5, H Ar); 8.30 (1H, s, H-4). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 20.7; 55.3; 55.5; 94.9; 107.6; 109.2; 114.1 (2C); 115.4; 122.9; 127.5 (2C); 128.9; 133.1; 133.7; 140.7; 142.5; 145.5; 159.0; 160.4. Found, %: C 75.48; H 5.72; N 8.85. $C_{20}H_{18}N_2O_2$. Calculated, %: C 75.45; H 5.70; N 8.80.

3-(4-Bromophenyl)-1-methyl-7-methoxy-9*H*-pyrido-[3,4-*b*]indole (10g). Yield 0.22 g (60%, method I), colorless crystals, mp 257–258°C (EtOH). IR spectrum, ν, cm^{-1}: 3220 (NH), 3164, 2836, 1624, 1514, 1464, 1344, 1266, 1107, 1007, 882, 827, 785, 733, 627. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.80 (3H, s, CH_3); 4.04 (3H, s, OCH_3); 6.76 (1H, d, *J* = 8.2, H-6); 7.17 (1H, d, *J* = 8.2, H-8); 7.44–7.48 (1H, m, H-5); 7.62–7.64 (2H, m, H Ar); 8.04–8.06 (2H, m, H Ar); 8.36 (1H, s, H-4). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 20.7; 55.7; 100.6; 104.8; 110.7; 110.8; 120.8; 127.5; 128.3 (2C); 129.5; 131.6 (2C); 133.4; 139.5; 141.4; 142.2; 144.1; 156.7. Found, %: C 62.10; H 4.15; N 7.67. $C_{19}H_{15}BrN_2O$. Calculated, %: C 62.14; H 4.12; N 7.63.

7-Chloro-1-methyl-3-phenyl-9*H*-pyrido[3,4-*b*]indole (10h). Yield 0.19 g (65%, method I), colorless crystals, mp 184–185°C (EtOH). IR spectrum, ν, cm^{-1}: 3410 (NH), 3161, 3057, 1625, 1467, 1066, 907, 806, 762, 700. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.83 (3H, s, CH_3); 7.26 (1H, dd, *J* = 8.4, *J* = 1.8, H-6); 7.34 (1H, t, *J* = 7.3, H Ph); 7.47 (2H, t, *J* = 7.6, H Ph); 7.59 (1H, d, *J* = 1.6, H-8); 8.15–8.17 (2H, m, H Ph); 8.29 (1H, d, *J* = 8.4, H-5); 8.55 (1H, s, H-4); 11.70 (1H, br. s, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 20.6; 108.9; 111.5; 119.5; 120.3; 123.3; 126.0 (2C); 127.3; 127.7; 128.4 (2C); 132.2; 134.2; 139.9; 141.3; 141.7; 145.5. Found, %: C 73.80; H 4.44; N 9.60. $C_{18}H_{13}ClN_2$. Calculated, %: C 73.85; H 4.48; N 9.57.

1,7-Dimethyl-3-(4-methylphenyl)-9*H*-pyrido[3,4-*b*]-indole (10i). Yield 0.19 g (66%, method I), yellow crystals, mp 167–168°C (EtOH). IR spectrum, ν, cm^{-1}: 3425 (NH), 3270, 2918, 2856, 1631, 1565, 1508, 1462, 1344, 1154, 1034, 869, 816. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.40 (3H, s, CH_3 Ar); 2.53 (3H, s, 7-CH_3); 2.79

(3H, s, 1-CH_3); 7.10 (1H, d, *J* = 8.0, H-6); 7.25–7.28 (3H, m, H-8, H Ar); 7.96–8.00 (3H, m, H-5, H Ar); 8.13 (1H, s, H-4); 8.22 (1H, br. s, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 20.4; 21.2; 22.2; 109.1; 111.6; 120.1; 121.4; 121.8; 126.7 (2C); 129.3 (2C); 129.5; 133.7; 137.2; 138.1; 138.6; 140.9; 141.0; 147.7. Found, %: C 83.84; H 6.32; N 9.76. $C_{20}H_{18}N_2$. Calculated, %: C 83.88; H 6.34; N 9.78.

3-(4-Methoxyphenyl)-1-methyl-9*H*-pyrido[3,4-*b*]indole (10j). Yield 0.23 g (78%, method I), colorless crystals, mp 256–257°C (EtOH). IR spectrum, ν, cm^{-1}: 3144 (NH), 2837, 1622, 1605, 1500, 1463, 1344, 1292, 1240, 1173, 1114, 1027, 886, 832, 736. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.82 (3H, s, CH_3); 3.80 (3H, s, OCH_3); 7.00–7.04 (2H, m, H Ar); 7.20–7.24 (1H, m, H-6); 7.50–7.54 (1H, m, H-7); 7.57–7.59 (1H, m, H-8); 8.09–8.13 (2H, m, H Ar); 8.26 (1H, d, *J* = 7.8, H-5); 8.45 (1H, s, H-4); 11.53 (1H, br. s, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 20.7; 55.1; 108.0; 112.0; 113.9 (2C); 119.1; 121.5; 121.9; 127.3 (2C); 127.8; 128.4; 132.9; 133.6; 140.9; 141.3; 145.0; 158.9. Found, %: C 79.11; H 5.56; N 9.74. $C_{19}H_{16}N_2O$. Calculated, %: C 79.14; H 5.59; N 9.72.

7-Methoxy-1-methyl-3-phenyl-9*H*-pyrido[3,4-*b*]indole (10k). Yield 0.16 g (57%, method I), colorless crystals, mp 242–243°C (EtOH). IR spectrum, ν, cm^{-1}: 3169 (NH), 2951, 2836, 1628, 1461, 1161, 820, 741, 702. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.78 (3H, s, CH_3); 3.85 (3H, s, OCH_3); 6.85 (1H, dd, *J* = 8.6, *J* = 2.2, H-6); 7.03 (1H, s, H-8); 7.32 (1H, t, *J* = 7.3, H Ph); 7.45 (2H, t, *J* = 7.6, H Ph); 8.11–8.14 (3H, m, H-5, H Ph); 8.40 (1H, s, H-4); 11.48 (1H, br. s, NH). ^{13}C NMR spectrum (DMSO-d_6) δ, ppm: 20.7; 55.5; 94.9; 108.6; 109.3; 115.4; 123.0; 126.3 (2C); 127.5; 128.7 (2C); 128.8; 134.0; 140.4; 140.9; 142.5; 145.4; 160.4. Found, %: C 79.12; H 5.57; N 9.74. $C_{19}H_{16}N_2O$. Calculated, %: C 79.14; H 5.59; N 9.72.

7-Chloro-1-methyl-3-(4-methylphenyl)-9*H*-pyrido[3,4-*b*]-indole (10l). Yield 0.17 g (55%, method I), colorless crystals, mp 191–192°C (EtOH–MeCN, 1:1). IR spectrum, ν, cm^{-1}: 3434 (NH), 1626, 1571, 1467, 1311, 1252, 1062, 932, 907, 904, 601. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.33 (3H, s, CH_3 Ar); 2.42 (3H, s, CH_3); 7.18–7.23 (3H, m, H-6, H Ar); 7.46 (1H, s, H-8); 7.87 (2H, d, *J* = 8.0, H Ar); 7.97 (1H, d, *J* = 8.4, H-5); 8.05 (1H, s, H-4); 10.23 (1H, br. s, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 19.8; 21.2; 109.8; 111.4; 120.3; 120.3; 122.6; 126.7 (2C); 128.5; 129.4 (2C); 133.5; 133.9; 137.4; 137.5; 141.0; 141.5; 147.5. Found, %: C 74.35; H 4.96; N 9.16. $C_{19}H_{15}ClN_2$. Calculated, %: C 74.39; H 4.93; N 9.13.

Supplementary information file containing the description of synthesis and physicochemical characteristics of compounds **2a**,**b**, **4a**,**b**, **5a**–**e**,**l**, and **6a**–**l**, as well as absorption and fluorescence spectra of compounds **10a**–**l** can be accessed at http://link.springer.com/journal/10593.

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