DOI 10.1007/s10593-021-02892-9
Chemistry of Heterocyclic Compounds **2021**, *57*(2), 187–198

Synthesis of 4-ethoxycarbonyl(cyano)-β-carbolines *via* thermolysis of 4-aryl-3(5)-azidopyridine derivatives and the study of their optical and hypoglycemic properties

Viktoriya A. Proshchenkova[1], Vladislav Yu. Shuvalov[2], Larisa V. Glyzdinskaya[1], Alexander S. Fisyuk[2], Sergei A. Chernenko[1], Mikhail V. Khvostov[3], Tatyana G. Tolstikova[3], Marina A. Vorontsova[1], Galina P. Sagitullina[1]*

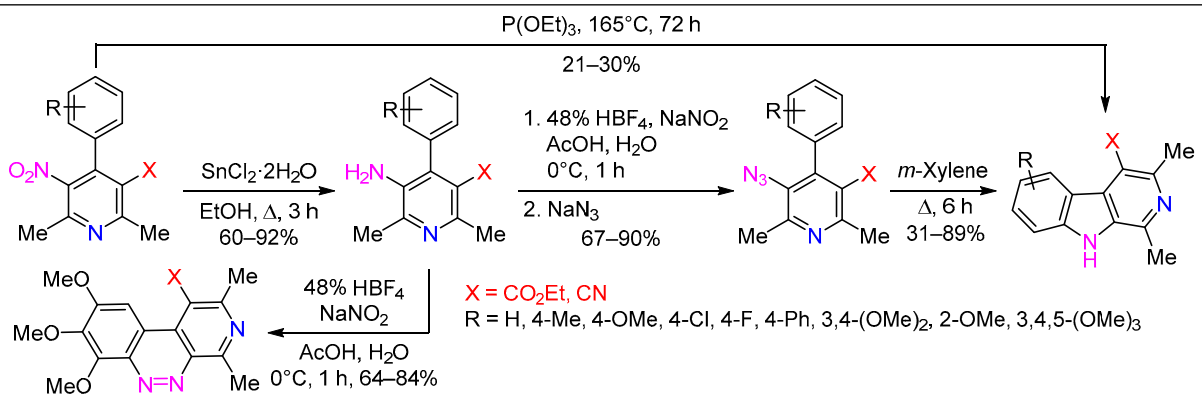
[1] *Dostoevsky Omsk State University, 55a Mira Ave., Omsk 644077, Russia; e-mail: sagitullina@chemomsu.ru*

[2] *Omsk State Technical University, 11 Mira Ave., Omsk 644050, Russia; e-mail: v.y.shuvalov@chemomsu.ru*

[3] *N. N. Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, 9 Akademika Lavrentieva Ave., Novosibirsk 630090, Russia; e-mail: m.khvostov@g.nsu.ru*

Translated from Khimiya Geterotsiklicheskikh Soedinenii, 2021, *57*(2), 187–198

Submitted August 31, 2020
Accepted September 24, 2020



4-Ethoxycarbonyl(cyano)-1,3-dimethyl-β-carbolines were synthesized *via* thermolysis of 4-aryl-3(5)-azidopyridines and their optical and hypoglycemic properties were studied. For the first time, the accessible Hantzsch nitropyridines were used as the starting materials. Diazotization of 3-aminopyridines having a trimethoxyaryl substituent at the C-4 position of the pyridine ring by intramolecular azo coupling afforded 7,8,9-trimethoxy-2,4-dimethylpyrido[3,4-*c*]cinnolines. When evaluating the hypoglycemic properties of the four obtained β-carbolines, it was found that ethyl 7-fluoro-1,3-dimethyl-9*H*-pyrido[3,4-*b*]indole-4-carboxylate, the structure of which contains the fluorine atom, has the highest glucose-lowering action.

Keywords: azidopyridine, Hantzsch nitropyridines, pyrido[3,4-*c*]cinnoline, 9*H*-pyrido[3,4-*b*]indole, azo coupling, Cadogan reaction, cyclization.

The alkaloid norharmane, the simplest β-carboline, exhibits a wide spectrum of biological activity.[1] This makes the norharmane molecule (9*H*-pyrido[3,4-*b*]indole) a pharmacophore. According to P. Gund's definition, a pharmacophore is "a set of structural features in a molecule that is recognized at a receptor site and is responsible for that molecule's biological activity".[2a] The type of biological activity depends on the presence of various substituents in the structure of β-carboline. Harmane and harmine differ from norharmane by the presence of methyl and methoxy groups in their structure. This implies the possibility of a directed change of the biological activity of β-carbolines by introducing various groups into their structures. Biological activity is exhibited not only by natural β-carbolines, but also by their synthetic structural analogs (Fig. 1).[2]

There are three main ways of introducing various groups into the molecule of an organic compound: selecting the synthesis route, transformation of functional groups present in the structure, and the functionalization of the C–H bonds of aromatic rings. Direct functionalization of the C–H bonds of β-carboline by electrophilic substitution reactions is easily accomplished only in the benzene ring, whereas

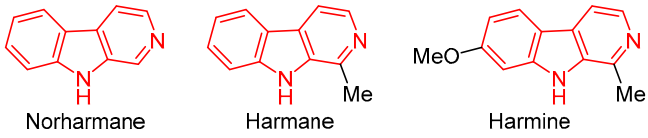


Figure 1. β-Carbolines norharmane and its derivatives harmane and harmine.

the electron-deficient pyridine ring is inert with respect to these reactions. In this regard, methods for the synthesis of β-carbolines with a given set of substituents in the pyridine ring are of great importance.

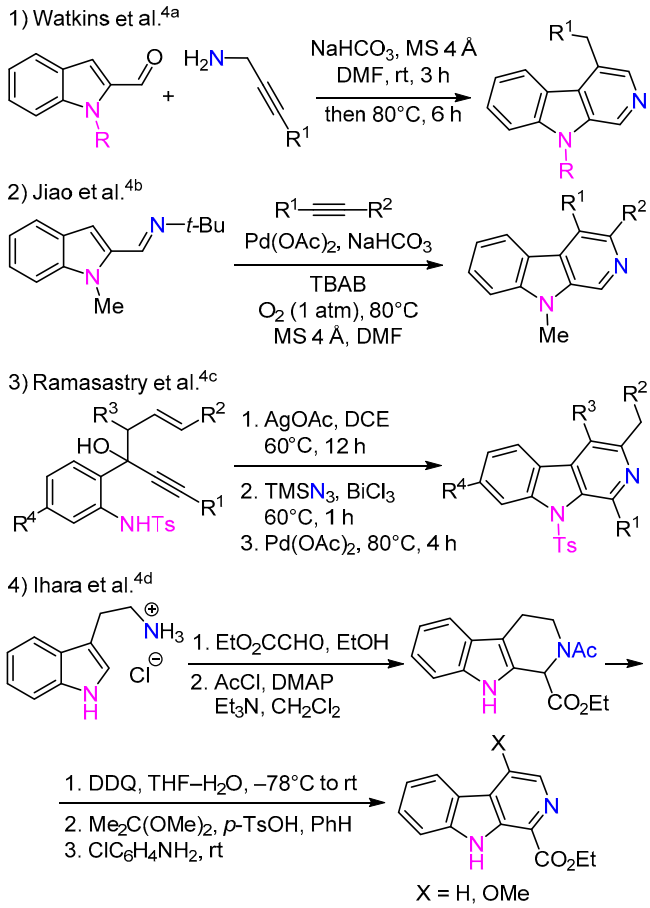
β-Carboline synthesis from tryptophan by the Pictet–Spengler reaction allows access to 1,2,3,4-tetrahydro-β-carbolines which are easily oxidized to aromatic compounds. The presence of a carboxyl group in the structure of β-carboline at the C-3 position of the pyridine ring makes it possible to synthesize a number of compounds by transformation of the carboxyl group.[3] β-Carbolines containing substituents at the C-4 position are synthesized by other methods: 1) by the reaction of indole-2-carbaldehydes and substituted propargylamines with the formation of Schiff bases followed by isomerization of the acetylene group leading to allenes and 6π-azacyclization of the latter to β-carbolines;[4a] 2) by palladium-catalyzed reactions of *N*-substituted indole-2-carbaldehyde *tert*-butylimines with internal alkynes;[4b] 3) by one-pot Ag(I)-, Bi(III)-, and Pd(II)-catalyzed (triple-relay catalysis) cascade of reactions of 5-*exo*-*dig* cyclization of 3-[2-(tosylamino)phenyl]hex-5-en-1-yn-3-ol into indoline, nucleophilic azidation of the double bond of indoline, and thermolysis of azide to nitrene with cyclization to β-carboline;[4c] 4) by the reaction of tryptamine hydrochloride with ethyl glyoxylate followed by acylation at the nitrogen atom of tetrahydro-β-carboline, oxidation by DDQ to 4-oxo-carboline, conversion of the carbonyl group into a methoxy group by reaction with dimethoxypropane in the presence of *p*-TsOH, and aromatization with chloranil (Scheme 1).[4d]

This work describes a new method for the synthesis of β-carbolines with the ethoxycarbonyl group and the cyano group at the C-4 position of the pyridine ring and investigation of the relationship of the optical and biological properties of the obtained β-carbolines with their structure.

The simplicity of the Hantzsch synthesis of nitropyridines was for us an incentive to use them as starting compounds for the preparation of β-carbolines. The Cadogan reaction as a one-step method for the synthesis of β-carbolines appeared to be the most attractive, but did not meet the expectations. When carrying out the Cadogan reaction by fusing nitropyridine **1a** with DPPE as a reducing agent without a solvent, the formation of β-carboline did not occur even in trace amounts.[5] β-Carboline was also not found in the reaction mixture of the catalytic reaction with PPh_3 and $MoO_2Cl_2(dmf)_2$.[6] In the reaction with smaller in volume $P(OEt)_3$, β-carboline **4a** is formed with a low yield (Table 1).

The inefficiency of the reduction of the nitro group of pyridines **1a–c** to nitrene and the closure of the pyrrole ring of β-carboline can be explained by steric obstacles to the

Scheme 1



approach of $P(OEt)_3$ to the nitro group shielded by two substituents (Scheme 2). The low yield of β-carbolines **4a–c** led us to abandon the Cadogan reaction as a route for the synthesis of β-carbolines.

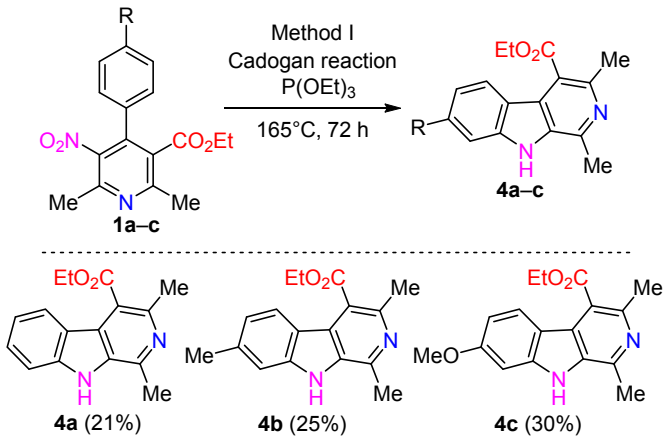
Later, we decided upon thermolysis of 5-azidopyridines **3**, **7 a–h** in *m*-xylene as the method for the synthesis β-carbolines. The starting nitropyridines **1**, **5 a–i** were synthesized by the Hantzsch reaction in two steps (Supplementary information). The reduction of the nitro

Table 1. Optimization of the reaction conditions for the Cadogan reaction for compound **1a***

Entry	Reducing agent (amount)	Solvent	Temperature, °C	Catalyst, 5 mol %	Time, h	Yield, %
1	DPPE (1.1 mmol)	–	150	–	10	0
2	PPh_3 (1.2 mmol)	PhMe	110	$MoO_2Cl_2(dmf)_2$	24	0
3	PPh_3 (1.2 mmol)	*p*-Cymene	177	$MoO_2Cl_2(dmf)_2$	15	0
4	$P(OEt)_3$	–	165	–	50	6**
5	$P(OEt)_3$***	–	165	–	72	21**

* The reactions were carried out with 1 mmol of compound **1a** under an N_2 atmosphere.
** Yields after isolation by chromatography.
*** Sealed vial.

Scheme 2



group of pyridines was carried out with $SnCl_2$ in EtOH (Scheme 3).

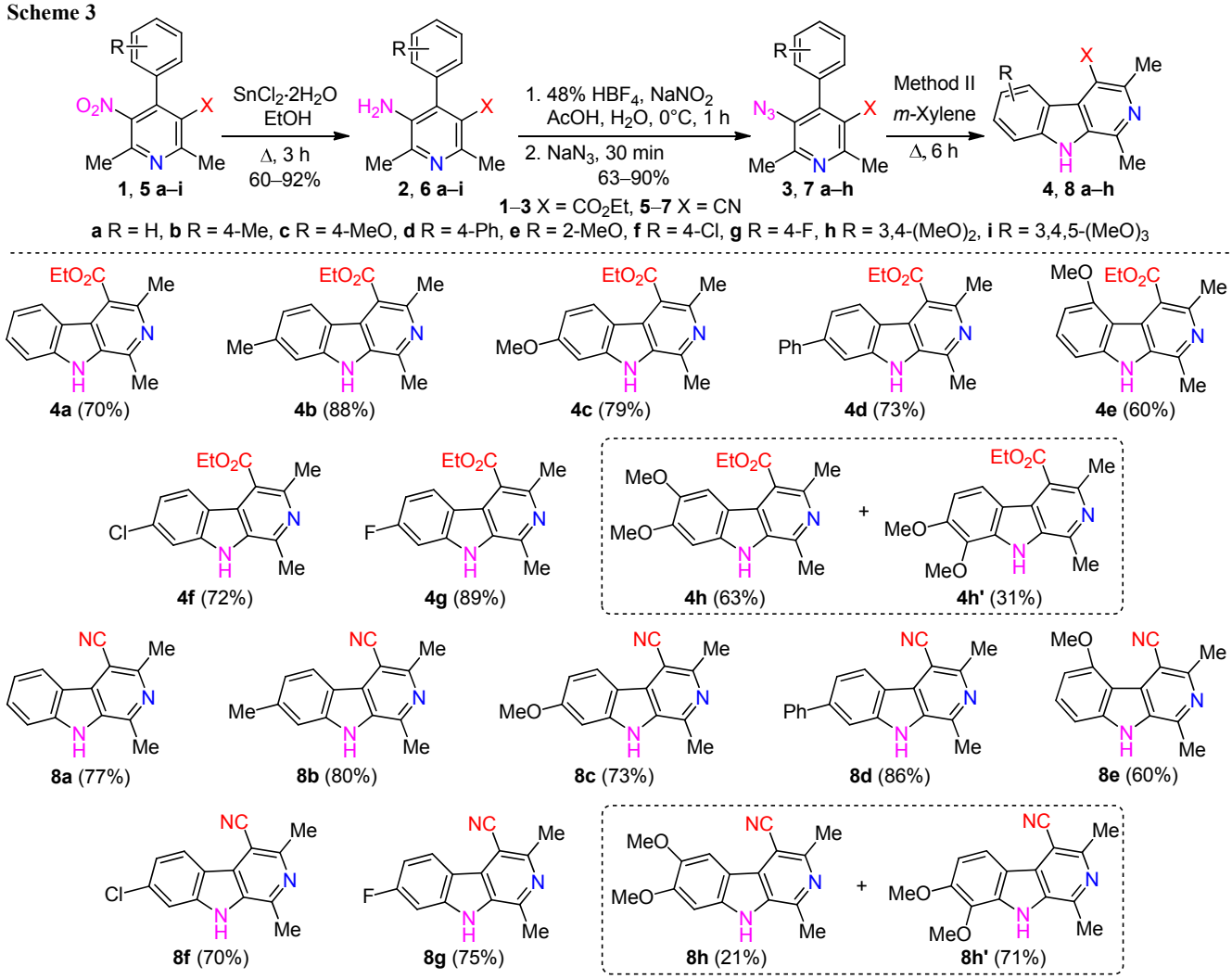
Diazotization of the amino group of pyridines **2**, **6 a–i** by $NaNO_2$ in AcOH and HBF_4 mixture at 0°C gave pyridines with a diazo group, which were not isolated but immediately converted into 5-azidopyridines **3**, **7 a–h** by the action of NaN_3. 5-Azidopyridines **3**, **7 a–h** were isolated in high yields and characterized. Heating compounds **3**, **7 a–h** in *m*-xylene made it possible to obtain β-carbolines **4**, **8 a–h**. Thermolysis of 5-azidopyridines **3h**, **7h** with an asymmetric arrangement of two methoxy groups resulted in the formation of isomeric β-carbolines **4h**, **4h'** and **8h**, **8h'** in 94 and 92% combined yields, respectively (Scheme 3).

Hantzsch nitropyridines were used as starting materials for the synthesis of 3-methylharmane **13a** and 3-methylharmine **13b** (Schemes 4, 5). Hydrolysis of the ester group of pyridines **1a**,**b** yielded compounds **9a**,**b**, which were transformed into nitropyridines **10a**,**b** by decarboxylation. Reduction of the nitro group of pyridines **10a**,**b** yielded 3-aminopyridines **11a**,**b**.

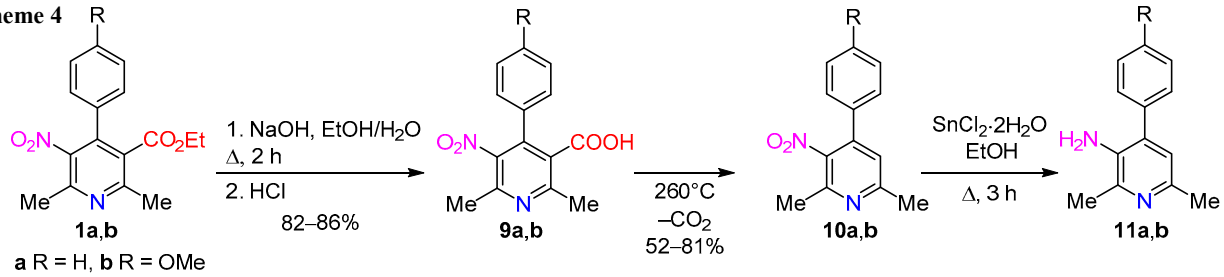
The use of $NOBF_4$ was effective as a diazotizing agent in the synthesis of diazonium salts from 3-aminopyridines **11a**,**b**. Nucleophilic substitution of the diazo group with NaN_3 gave 3-azidopyridines **12a**,**b**. Thermolysis of 3-azidopyridines **12a**,**b** in *m*-xylene afforded 3-methylharmane **13a** and 3-methylharmine **13b**.[7]

Diazotation of 5-aminopyridines **2i**, **6i** with $NaNO_2$ at 0°C is followed by an electrophilic substitution reaction with the formation of pyrido[3,4-*c*]cinnolines **14a**,**b** (Scheme 6). The formation of cinnolines **14a**,**b** takes place as a result of intramolecular azo coupling of the

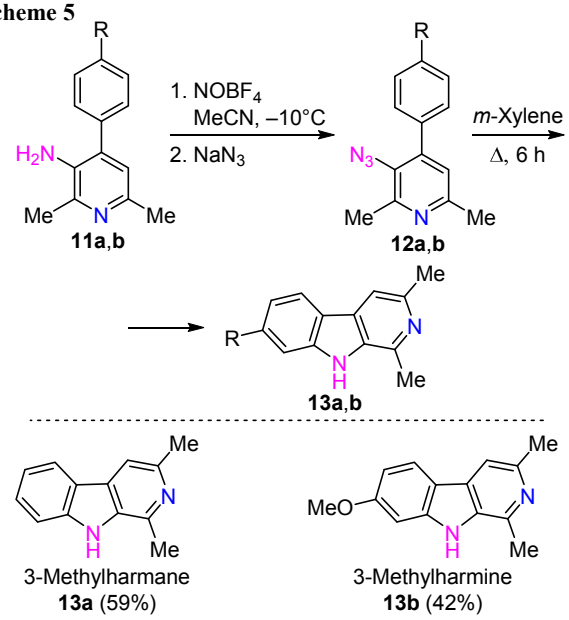
Scheme 3



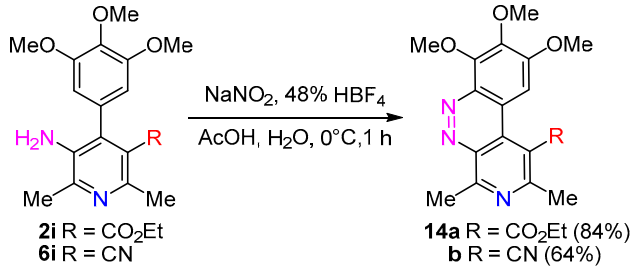
Scheme 4



Scheme 5



Scheme 6



pyridyldiazonium salt with the electron-rich trimethoxybenzene ring.

As noted earlier, β-carboline derivatives are promising in the search for new biologically active agents. Thus, it has been established that compounds of this class can be effective stimulators of insulin secretion[8] which can be used in the treatment of type 2 diabetes mellitus. Based on the preliminary computer screening with the PASS (Prediction of Activity Spectra for Substances)[9] program, we selected compounds **4c**,**g** and **8e**,**h** for hypoglycemic activity evaluation by the glucose tolerance test in mice. It was found that compound **4g** has a statistically significant glucose-lowering effect, comparable to that of vildagliptin (Fig. 2).

Fluorescence spectroscopy is often used to study the mechanisms of the biological activity of β-carbolines.[10] The electronic spectra of 9*H*-pyrido[3,4-*b*]indoles are well studied.[11] However, little is known about the photophysical properties of substituted derivatives. We recently reported that in EtOH solution 1,3-dimethyl-9*H*-pyrido[3,4-*b*]-indoles **13a**,**b** exist in two forms, neutral and protonated, and their fluorescence spectra represent a superposition of the spectra of these two forms.[7] The introduction of an acceptor group into the pyridine ring leads to a decrease in its basicity. The signals of the protonated form appear in the absorption and fluorescence spectra of compounds **4**, **8 a**–**h'** only upon addition of an acid (Fig. 3).

The shape of the peaks in the absorption and fluorescence spectra does not change significantly. The introduction of a carbethoxy group (compound **4a**) and a cyano group (compound **8a**) at the C-4 position of the 1,3-dimethyl-9*H*-pyrido[3,4-*b*]indole predictably leads to an insignificant increase in the fluorescence quantum yield

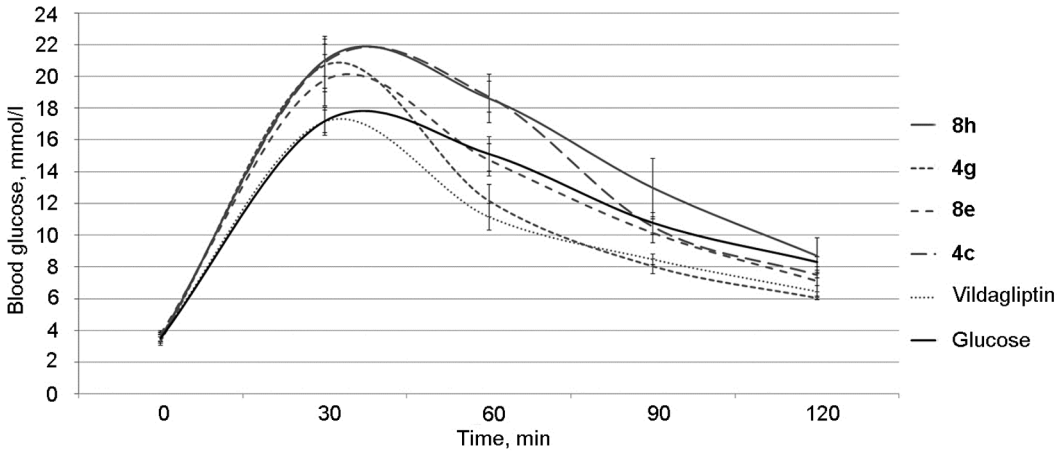


Figure 2. Efficacy of β-carbolines **4c**,**g** and **8e**,**h** in the oral glucose tolerance test. The graph shows the effect of compounds **4c**,**g** and **8e**,**h** on a decrease in blood glucose level over time in CD-1 mice.

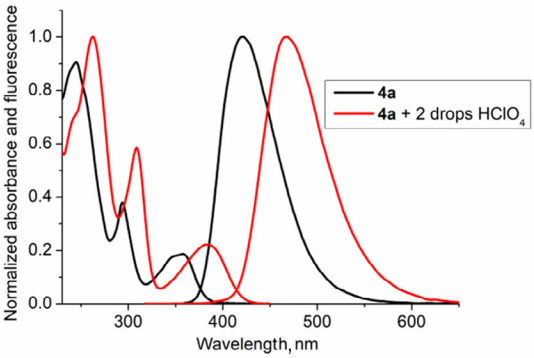


Figure 3. Normalized absorption and fluorescence spectra of solutions of compound **4a** in EtOH (black line) and EtOH + 2 drops of $HClO_4$ (red line).

(by 0.13 and 0.12, respectively) and also to the bathochromic shift in the fluorescence spectra (57–86 nm) (Table S1, Supplementary information file). The introduction of substituents into the benzene ring does not significantly affect the position of the maxima in the absorption and fluorescence spectra of compounds **4b**, **4e**–**g**, **8h**,**h'** (Table S1, Supplementary information file). For compounds **8b**–**g**, the presence of such substituents leads to a hypsochromic shift of the fluorescence maximum by 27–51 nm as compared to 9*H*-pyrido[3,4-*b*]indoles **4a** and **8a**, with the exception of dimethoxy-substituted 9*H*-pyrido-[3,4-*b*]indoles **4h**,**h'**. For these compounds, a redshift of the fluorescence maxima by 46–61 nm and a Stokes shift of 113–120 nm are observed. It should be noted that the introduction of a substituent into the benzene ring, as a rule, leads to a drop in the quantum yield for all compounds **4b**–**h'**, **8b**–**g**,**h'** except for compound **8h**; in this case, a slight increase in the quantum yield is observed (Table S1, Supplementary information file).

To conclude, a new series of β-carboline derivatives was developed and their optical and hypoglycemic properties were studied. 4-Ethoxycarbonyl- and 4-cyano-β-carbolines are excellent base compounds for modeling biological activity by transforming ester and cyano groups into other groups. It was found that ethyl 7-fluoro-1,3-dimethyl-9*H*-pyrido[3,4-*b*]indole-4-carboxylate with a fluorine atom in the pyrido[3,4-*b*]indole ring at a dose of 10 mg/kg has a statistically significant glucose-lowering effect comparable to that of vildagliptin.

Experimental

IR spectra were registered on a Simex FT-801 Fourier transform 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 with the residual solvent signals ($CDCl_3$: 7.26 ppm for ^{1}H nuclei and 77.0 ppm for ^{13}C nuclei; DMSO-d_6: 2.50 ppm for ^{1}H nuclei and 39.5 ppm for ^{13}C nuclei) as internal standard. 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 test compounds were dissolved in EtOH in such a way that the concentration of the resulting solutions was below 10^{-5} mol/dm^3. The molar extinction coefficient was determined according to the described method.[12] The quantum yield of the studied compounds was determined using the comparison method relative to 9,10-diphenylanthracene.[13] 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. Silica gel (60–120 μm) was used for column chromatography.

3-Aminocrotononitrile was supplied by Acros Organics and used without additional purification. The synthesis of ethyl 3-aminobut-2-enoate,[14] nitroenones,[15] 5-nitropyridines **1a** and **5a**,[16] 1-nitropropan-2-one,[17] 1-(diethoxymethyl)-4-methylbenzene,[18] *N*-(4-fluorobenzylidene)butan-1-amine[19] was done according to published methods. Compounds **11**–**13 a**,**b** were described by us earlier.[7]

Synthesis of compounds 2, **6 a–i** (General method). A mixture of nitropyridine **1a–i** or **5a–i** (2 mmol), $SnCl_2 \cdot 2H_2O$ (2.03 g, 9 mmol), and EtOH (2 ml) was heated under reflux for 3 h. The reaction mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. The residue was cooled, and H_2O (52 ml) was added. The resulting mixture was thoroughly triturated until a homogeneous suspension formed, then made alkaline with 10% aqueous NaOH (4.5 ml). Aminopyridine crystals were filtered off or extracted with EtOAc (3×50 ml). The organic layer was dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The resulting residue was recrystallized from an appropriate solvent.

Ethyl 5-amino-2,6-dimethyl-4-phenylnicotinate (2a). Yield 0.32 g (60%), colorless crystals, mp 122–123°C (*n*-heptane). IR spectrum, ν, cm^{-1}: 3433, 3319 (NH_2), 1722 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.87 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 2.48 (3H, s, 6-CH_3); 2.49 (3H, s, 2-CH_3); 3.56 (1H, br. s, NH_2); 3.94 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 7.25–7.27 (2H, m, H Ar); 7.36–7.45 (3H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 13.5; 20.3; 21.2; 61.0; 127.7; 128.5; 128.8 (2C); 129.0 (2C); 132.5; 134.9; 135.9; 142.8; 143.7; 168.1. Found, %: C 71.14; H 6.75; N 10.41. $C_{16}H_{18}N_2O_2$. Calculated, %: C 71.09; H 6.71; N 10.36.

Ethyl 5-amino-2,6-dimethyl-4-(4-methylphenyl)nicotinate (2b). Yield 0.42 g (74%), colorless crystals, mp 105–106°C (*n*-heptane). IR spectrum, ν, cm^{-1}: 3294, 3179 (NH_2), 1721 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.92 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 2.38 (3H, s, CH_3); 2.51 (3H, s, 6-CH_3); 2.52 (3H, s, 2-CH_3); 3.63 (2H, br. s, NH_2); 3.98 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 7.14–7.16 (2H, m, H Ar); 7.24–7.26 (2H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 13.6; 19.8; 20.8; 21.3; 61.1; 128.2; 128.5 (2C); 129.7 (2C); 131.4; 133.2; 136.5; 138.6; 142.3; 143.0; 167.9. Found, %: C 71.87; H 7.13; N 9.81. $C_{17}H_{20}N_2O_2$. Calculated, %: C 71.81; H 7.09; N 9.85.

Ethyl 5-amino-4-(4-methoxyphenyl)-2,6-dimethylnicotinate (2c). Yield 0.54 g (90%), colorless crystals, mp 65–66°C (*n*-heptane). IR spectrum, ν, cm^{-1}: 3299, 3207 (NH_2), 1702 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm

(*J*, Hz): 0.95 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 2.47 (3H, s, 6-CH_3); 2.48 (3H, s, 2-CH_3); 3.57 (2H, br. s, NH_2); 3.82 (3H, s, OCH_3); 3.98 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 6.94–6.97 (2H, m, H Ar); 7.17–7.21 (2H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 13.7; 20.2; 21.1; 55.3; 61.0; 114.4 (2C); 126.7; 128.1; 130.0 (2C); 132.3; 136.3; 142.6; 143.4; 159.7; 168.3. Found, %: C 67.91; H 6.67; N 9.31. $C_{17}H_{20}N_2O_3$. Calculated, %: C 67.98; H 6.71; N 9.33.

Ethyl 5-amino-4-(biphenyl-4-yl)-2,6-dimethylnicotinate (2d). Yield 0.54 g (78%), colorless crystals, mp 132–133°C (PhMe). IR spectrum, ν, cm^{-1}: 3488, 3395 (NH_2), 1724 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.90 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 2.50 (3H, s, 6-CH_3); 2.52 (3H, s, 2-CH_3); 3.65 (2H, br. s, NH_2); 3.98 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 7.34–7.39 (3H, m, H Ar); 7.44–7.47 (2H, m, H Ar); 7.59–7.62 (2H, m, H Ar); 7.66–7.70 (2H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 13.6; 20.3; 21.2; 61.1; 127.0 (2C); 127.6; 127.7 (2C); 128.9 (2C); 129.2 (2C); 132.2; 133.7; 136.0; 140.2 (2C); 141.4; 142.8; 143.7; 168.1. Found, %: C 76.33; H 6.44; N 8.11. $C_{22}H_{22}N_2O_2$. Calculated, %: C 76.28; H 6.40; N 8.09.

Ethyl 5-amino-4-(2-methoxyphenyl)-2,6-dimethylnicotinate (2e). Yield 0.37 g (62%), colorless crystals, mp 119–120°C (*n*-heptane). IR spectrum, ν, cm^{-1}: 3317, 3314 (NH_2), 1720 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.87 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 2.47 (3H, s, 6-CH_3); 2.51 (3H, s, 2-CH_3); 3.48 (2H, br. s, NH_2); 3.77 (3H, s, OCH_3); 3.93 (2H, q, *J* =7.0, $C\underline{H}_2CH_3$); 6.97–7.02 (2H, m, H Ar); 7.08–7.10 (1H, m, H Ar); 7.35–7.39 (1H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 13.6; 20.4; 21.7; 55.9; 60.7; 111.3; 121.2; 123.9; 127.7; 130.2 (2C); 130.5; 136.5; 143.4; 143.9; 156.7; 168.1. Found, %: C 67.92; H 6.68; N 9.31. $C_{17}H_{20}N_2O_3$. Calculated, %: C 67.98; H 6.71; N 9.33.

Ethyl 5-amino-4-(4-chlorophenyl)-2,6-dimethylnicotinate (2f). Yield 0.50 g (82%), colorless crystals, mp 132–133°C (*n*-heptane). IR spectrum, ν, cm^{-1}: 3311, 3211 (NH_2), 1722 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.95 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 2.48 (3H, s, 6-CH_3); 2.49 (3H, s, 2-CH_3); 3.56 (2H, br. s, NH_2); 3.99 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 7.21–7.23 (2H, m, H Ar); 7.41–7.43 (2H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 13.7; 20.2; 21.2; 61.2; 127.6; 129.3 (2C); 130.3 (2C); 131.2; 133.2; 134.7; 135.9; 142.8; 143.8; 167.8. Found, %: 62.99; H 5.65; N 9.14. $C_{16}H_{17}ClN_2O_2$. Calculated, %: C 63.05; H 5.62; N 9.19.

Ethyl 5-amino-4-(4-fluorophenyl)-2,6-dimethylnicotinate (2g). Yield 0.49 g (85%), colorless crystals, mp 150–151°C (petroleum ether). IR spectrum, ν, cm^{-1}: 3308, 3212 (NH_2), 1729 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.92 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 2.40 (3H, s, 6-CH_3); 2.42 (3H, s, 2-CH_3); 3.42 (2H, br. s, NH_2); 3.95 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 7.07–7.13 (2H, m, H Ar); 7.21–7.26 (2H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 13.7; 20.9; 21.8; 60.9; 116.0 (2C, d, *J* = 21.7); 127.4; 130.7; 130.8 (2C, d, *J* = 7.8); 131.0 (d, *J* = 3.5); 135.5; 143.3; 144.3; 162.7 (d, *J* = 248.0); 168.5. Found, %: C 66.72; H 5.96; N 9.76. $C_{16}H_{17}FN_2O_2$. Calculated, %: C 66.65; H 5.94; N 9.72.

Ethyl 5-amino-4-(3,4-dimethoxyphenyl)-2,6-dimethylnicotinate (2h). Yield 0.57 g (87%), colorless crystals, mp 96–97°C (*n*-heptane). IR spectrum, ν, cm^{-1}: 3483, 3392 (NH_2), 1727 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.97 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 2.42 (3H, s, 6-CH_3); 2.44 (3H, s, 2-CH_3); 3.50 (2H, br. s, NH_2); 3.84 (3H, s, OCH_3); 3.89 (3H, s, OCH_3); 3.99 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 6.80–6.84 (2H, m, H Ar); 6.92 (1H, s, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 13.8; 20.8; 21.7; 56.0; 56.0; 60.9; 111.7; 112.3; 121.4; 127.5; 127.6; 131.6; 135.7; 143.2; 144.2; 149.1; 149.4; 168.8. Found, %: C 65.48; H 6.66; N 8.50. $C_{18}H_{22}N_2O_4$. Calculated, %: C 65.44; H 6.71; N 8.48.

Ethyl 5-amino-4-(3,4,5-trimethoxyphenyl)-2,6-dimethylnicotinate (2i). Yield 0.48 g (67%), colorless crystals, mp 140–141°C (*n*-heptane). IR spectrum, ν, cm^{-1}: 3488, 3392 (NH_2), 1711 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.95 (3H, t, *J* = 6.8, $CH_2C\underline{H}_3$); 2.50 (6H, s, 2,6-CH_3); 3.67 (2H, br. s, NH_2); 3.82 (6H, s, OCH_3); 3.86 (3H, s, OCH_3); 4.00–4.04 (2H, m, $C\underline{H}_2CH_3$); 6.50 (2H, s, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 13.7; 20.2; 21.1; 56.2 (2C); 60.9; 61.1; 105.9 (2C); 127.7; 130.1; 132.5; 136.0; 138.1; 142.7; 143.6; 153.8 (2C); 168.2. Found, %: C 63.38; H 6.73; N 7.75. $C_{19}H_{24}N_2O_5$. Calculated, %: C 63.32; H 6.71; N 7.77.

5-Amino-2,6-dimethyl-4-phenylnicotinonitrile (6a). Yield 0.27 g (60%), colorless crystals, mp 170–171°C (*n*-heptane). IR spectrum, ν, cm^{-1}: 3482, 3384 (NH_2), 2228 (CN). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.48 (3H, s, 6-CH_3); 2.67 (3H, s, 2-CH_3); 3.63 (2H, br. s, NH_2); 7.36–7.38 (2H, m, H Ar); 7.45–7.56 (3H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.2; 22.8; 107.2; 117.0; 128.8 (2C); 129.5 (3C); 133.6; 135.9; 136.0; 147.2; 150.2. Found, %: C 75.34; H 5.85; N 18.79. $C_{14}H_{13}N_3$. Calculated, %: C 75.31; H 5.87; N 18.82.

5-Amino-2,6-dimethyl-4-(4-methylphenyl)nicotinonitrile (6b). Yield 0.30 g (63%), colorless crystals, mp 178–179°C (CCl_4). IR spectrum, ν, cm^{-1}: 3468, 3374 (NH_2), 2229 (CN). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.44 (3H, s, CH_3); 2.49 (3H, s, 6-CH_3); 2.68 (3H, s, 2-CH_3); 3.65 (2H, br. s, NH_2); 7.29–7.35 (4H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.2; 21.3; 22.8; 107.2; 117.1; 128.6 (2C); 130.2 (2C); 130.6; 135.9; 136.1; 139.4; 147.2; 150.2. Found, %: C 75.86; H 6.35; N 17.69. $C_{15}H_{15}N_3$. Calculated, %: C 75.92; H 6.37; N 17.71.

5-Amino-4-(4-methoxyphenyl)-2,6-dimethylnicotinonitrile (6c). Yield 0.44 g (86%), colorless crystals, mp 170–171°C (CH_3CN). IR spectrum, ν, cm^{-1}: 3431, 3350 (NH_2), 2225 (CN). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.46 (3H, s, 6-CH_3); 2.64 (3H, s, 2-CH_3); 3.63 (2H, br. s, NH_2); 3.85 (3H, s, OCH_3); 7.04 (2H, d, *J* = 8.4, H Ar); 7.30 (2H, d, *J* = 8.4, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.2; 22.8; 55.3; 107.4; 115.0 (2C); 117.2; 125.6; 130.2 (2C); 135.9; 136.1; 147.1; 150.2; 160.4. Found, %: C 71.20; H 6.01; N 16.52. $C_{15}H_{15}N_3O$. Calculated, %: C 71.13; H 5.97; N 16.59.

5-Amino-4-(4-biphenyl)-2,6-dimethylnicotinonitrile (6d). Yield 0.50 g (84%), colorless crystals, mp 230–231°C (PhMe). IR spectrum, ν, cm^{-1}: 3471, 3375 (NH_2), 2228

(CN). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.50 (3H, s, 6-CH_3); 2.69 (3H, s, 2-CH_3); 3.70 (2H, br. s, NH_2); 7.37–7.49 (5H, m, H Ar); 7.64 (2H, d, *J* = 7.2, H Ar); 7.75 (2H, d, *J* = 7.8, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.3; 22.9; 107.0; 117.1; 127.1 (2C); 127.8; 128.1 (2C); 128.9 (2C); 129.3 (2C); 132.4; 135.5; 135.9; 140.1; 142.3; 147.4; 150.3. Found, %: C 80.18; H 5.70; N 14.02. $C_{20}H_{17}N_3$. Calculated, %: C 80.24; H 5.72; N 14.04.

5-Amino-4-(2-methoxyphenyl)-2,6-dimethylnicotinonitrile (6e). Yield 0.47 g (92%), colorless crystals, mp 183–184°C (CH_3CN). IR spectrum, ν, cm^{-1}: 3437, 3309 (NH_2), 2227 (CN). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.46 (3H, s, 6-CH_3); 2.64 (3H, s, 2-CH_3); 3.57 (2H, br. s, NH_2); 3.80 (3H, s, OCH_3); 7.04–7.10 (2H, m, H Ar); 7.19 (1H, dd, *J* = 7.2, *J* = 1.4, H Ar); 7.42–7.46 (1H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.2; 22.8; 55.7; 108.0; 111.9; 117.2; 121.4; 122.1; 130.4; 131.1; 133.4; 136.4; 147.3; 149.8; 156.5. Found, %: C 71.19; H 6.00; N 16.52. $C_{15}H_{15}N_3O$. Calculated, %: C 71.13; H 5.97; N 16.59.

5-Amino-4-(4-chlorophenyl)-2,6-dimethylnicotinonitrile (6f). Yield 0.43 g (83%), colorless crystals, mp 198–199°C (CCl_4). IR spectrum, ν, cm^{-1}: 3484, 3385 (NH_2), 2227 (CN). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.47 (3H, s, 6-CH_3); 2.65 (3H, s, 2-CH_3); 3.59 (2H, br. s, NH_2); 7.32 (2H, d, *J* = 8.2, H Ar); 7.52 (2H, d, *J* = 8.2, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.2; 22.8; 107.0; 116.8; 129.9 (2C); 130.3 (2C); 132.1; 134.5; 135.7 (2C); 147.6; 150.4. Found, %: C 65.31; H 4.71; N 16.22. $C_{14}H_{12}ClN_3$. Calculated, %: C 65.25; H 4.69; N 16.30.

5-Amino-4-(4-fluorophenyl)-2,6-dimethylnicotinonitrile (6g). Yield 0.31 g (65%), colorless crystals, mp 162–163°C (CCl_4). IR spectrum, ν, cm^{-1}: 3494, 3386 (NH_2), 2231 (CN). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.58 (6H, s, 2,6-CH_3); 4.70 (2H, br. s, NH_2); 7.41–7.49 (4H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 21.1; 21.9; 105.8; 115.9 (2C, d, *J* = 21.7); 116.7; 130.2 (d, *J* = 3.5); 131.0 (2C, d, *J* = 8.7); 132.7; 136.9; 147.0; 147.4; 162.1 (d, *J* = 245.4). Found, %: C 69.63; H 4.98; N 17.37. $C_{14}H_{12}FN_3$. Calculated, %: C 69.70; H 5.01; N 17.42.

5-Amino-4-(3,4-dimethoxyphenyl)-2,6-dimethylnicotinonitrile (6h). Yield 0.45 g (79%), colorless crystals, mp 184–185°C (CH_3CN). IR spectrum, ν, cm^{-1}: 3476, 3382 (NH_2), 2225 (CN). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.46 (3H, s, 6-CH_3); 2.64 (3H, s, 2-CH_3); 3.66 (2H, br. s, NH_2); 3.88 (3H, s, OCH_3); 3.92 (3H, s, OCH_3); 6.87 (1H, s, H Ar); 6.93–7.01 (2H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.2; 22.8; 56.0; 56.1; 107.3; 112.1 (2C); 117.2; 121.5; 125.9; 135.9; 136.0; 147.2; 149.8; 150.0; 150.2. Found; %: C 67.88; H 6.09; N 14.77. $C_{16}H_{17}N_3O_2$. Calculated; %: C 67.83; H 6.05; N 14.83.

5-Amino-2,6-dimethyl-4-(3,4,5-trimethoxyphenyl)nicotinonitrile (6i). Yield 0.51 g (82%), colorless crystals, mp 219–220°C (PhMe). IR spectrum, ν, cm^{-1}: 3439, 3355 (NH_2), 2228 (CN). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.47 (3H, s, 6-CH_3); 2.66 (3H, s, 2-CH_3); 3.49 (2H, br. s, NH_2); 3.87 (6H, s, OCH_3); 3.91 (3H, s, OCH_3); 6.57 (2H, s, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.2; 22.8; 56.4; 60.9; 106.2 (2C); 107.1; 117.1; 128.7; 135.9 (2C); 139.0; 147.3; 150.2; 154.1 (2C). Found, %: C 65.23; H 6.09; N 13.36. $C_{17}H_{19}N_3O_3$. Calculated, %: C 65.16; H 6.11; N 13.41.

Synthesis of 4-aryl-5-azido-2,6-dimethylpyridines 3, **7 a–h**. A solution of the respective aminopyridine **2a–h** or **6a–h** (2 mmol) in AcOH (10 ml) and H_2O (4 ml) was cooled to 0°C, and chilled 48% aqueous HBF_4 (7 ml) was added dropwise. The reaction mixture was stirred for 30 min, then a chilled solution of $NaNO_2$ (2.3 mmol) in H_2O (2 ml) was added dropwise. The reaction mixture was kept at 0°C for 45 min, then NaN_3 (2.3 mmol) was added in portions at the same temperature. The reaction mixture was stirred for 30 min, diluted with H_2O, and neutralized with 10% aqueous NaOH to pH 7. The precipitated crystals were filtered off and washed with chilled H_2O.

Ethyl 5-azido-2,6-dimethyl-4-phenylnicotinate (3a). Yield 0.52 g (87%), colorless crystals, mp 53–54°C (*n*-heptane). IR spectrum, ν, cm^{-1}: 2110 (N_3), 1722 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.89 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 2.53 (3H, s, 6-CH_3); 2.57 (3H, s, 2-CH_3); 3.97 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 7.30–7.32 (2H, m, H Ar); 7.41–7.43 (3H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 13.5; 21.2; 22.1; 61.3; 115.0; 128.4 (2C); 129.0 (3C); 130.3; 133.5; 141.3; 150.6; 152.3; 167.2. Found, %: C 64.88; H 5.46; N 18.95. $C_{16}H_{16}N_4O_2$. Calculated, %: C 64.85; H 5.44; N 18.91.

Ethyl 5-azido-2,6-dimethyl-4-(4-methylphenyl)nicotinate (3b). Yield 0.51 g (82%), colorless crystals, mp 48–49°C (MeOH). IR spectrum, ν, cm^{-1}: 2114 (N_3), 1724 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.94 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$); 2.39 (3H, s, CH_3); 2.52 (3H, s, 6-CH_3); 2.56 (3H, s, 2-CH_3); 4.00 (2H, q, *J* = 7.1, $C\underline{H}_2CH_3$); 7.19–7.24 (4H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 13.6; 21.2; 21.3; 22.1; 61.3; 128.6; 128.9 (2C); 129.1 (2C); 130.4; 130.5; 139.0; 141.4; 150.5; 152.2; 167.4. Found, %: C 65.72; H 5.87; N 18.11. $C_{17}H_{18}N_4O_2$. Calculated, %: C 65.79; H 5.85; N 18.05.

Ethyl 5-azido-4-(4-methoxyphenyl)-2,6-dimethylnicotinate (3c). Yield 0.59 g (90%), colorless crystals, mp 73–74°C (*n*-heptane). IR spectrum, ν, cm^{-1}: 2113 (N_3), 1715 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.99 (3H, t, *J* = 7.2, $CH_2C\underline{H}_3$); 2.54 (3H, s, 6-CH_3); 2.58 (3H, s, 2-CH_3); 3.84 (3H, s, OCH_3); 4.04 (2H, q, *J* = 7.2, $C\underline{H}_2CH_3$); 6.94–6.98 (2H, m, H Ar); 7.23–7.27 (2H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 13.7; 21.0; 21.9; 55.3; 61.4; 113.9 (2C); 115.9; 125.5; 128.9; 130.3 (2C); 144.7; 150.2; 152.0; 160.3; 167.3. Found, %: C 62.51; H 5.59; N 17.10. $C_{17}H_{18}N_4O_3$. Calculated, %: C 62.57; H 5.56; N 17.17.

Ethyl 5-azido-4-(biphenyl-4-yl)-2,6-dimethylnicotinate (3d). Yield 0.66 g (88%), colorless crystals, mp 111–112°C (MeOH). IR spectrum, ν, cm^{-1}: 2129 (N_3), 1736 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 0.83 (3H, t, *J* = 6.9, $CH_2C\underline{H}_3$); 2.49 (3H, s, 6-CH_3); 2.56 (3H, s, 2-CH_3); 3.99 (2H, q, *J* = 6.9, $C\underline{H}_2CH_3$); 7.37–7.50 (5H, m, H Ar); 7.72 (2H, d, *J* = 7.4, H Ar); 7.82 (2H, d, *J* = 7.4, H Ar). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 13.3; 20.0; 20.7; 61.5; 126.6; 126.7 (2C); 128.0 (2C); 128.6; 129.1 (2C); 129.4 (2C); 131.0; 131.8; 139.0; 141.0;

142.3; 148.8; 151.4; 165.9. Found, %: C 71.02; H 5.38; N 15.07. $C_{22}H_{20}N_4O_2$. Calculated, %: C 70.95; H 5.41; N 15.04.

Ethyl 5-azido-4-(2-methoxyphenyl)-2,6-dimethylnicotinate (3e). Yield 0.59 g (90%), colorless crystals, mp 98–99°C (*n*-heptane). IR spectrum, ν, cm^{-1}: 2114 (N_3), 1724 (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.88 (3H, t, *J* = 6.9, $CH_2C\underline{H}_3$); 2.52 (3H, s, 6-CH_3); 2.53 (3H, s, 2-CH_3); 3.78 (3H, s, OCH_3); 3.94 (2H, q, *J* = 6.9, $C\underline{H}_2CH_3$); 6.92–6.98 (2H, m, H Ar); 7.09 (1H, dd, *J* = 7.4, *J* = 1.8, H Ar); 7.36–7.40 (1H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 13.5; 21.2; 22.4; 55.6; 61.0; 110.4; 120.3; 122.6; 128.4; 130.3; 130.6; 130.7; 138.5; 150.9; 152.0; 157.1; 167.2. Found, %: C 62.52; H 5.59; N 17.12. $C_{17}H_{18}N_4O_3$. Calculated, %: C 62.57; H 5.56; N 17.17.

Ethyl 5-azido-4-(4-chlorophenyl)-2,6-dimethylnicotinate (3f). Yield 0.58 g (88%), colorless crystals, mp 85–86°C (MeOH). IR spectrum, ν, cm^{-1}: 2120 (N_3), 1722 (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.98 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$); 2.56 (3H, s, 6-CH_3); 2.61 (3H, s, 2-CH_3); 4.03 (2H, q, *J* = 7.1, $C\underline{H}_2CH_3$); 7.25–7.27 (2H, m, H Ar); 7.42–7.44 (2H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 13.6; 20.8; 21.7; 61.7; 128.6; 128.8 (2C); 130.3 (2C); 130.7; 131.7; 135.5; 140.7; 150.6; 152.3; 166.7. Found, %: C 58.05; H 4.59; N 16.87. $C_{16}H_{15}ClN_4O_2$. Calculated, %: C 58.10; H 4.57; N 16.94.

Ethyl 5-azido-4-(4-fluorophenyl)-2,6-dimethylnicotinate (3g). Yield 0.43 g (69%), colorless crystals, mp 55–56°C (*n*-heptane). IR spectrum, ν, cm^{-1}: 2111 (N_3), 1728 (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.97 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 2.52 (3H, s, 6-CH_3); 2.56 (3H, s, 2-CH_3); 4.01 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 7.11–7.15 (2H, m, H Ar); 7.29–7.32 (2H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 13.7; 21.4; 22.3; 61.4; 115.6 (2C, d, *J* = 22.6); 128.4; 129.6 (d, *J* = 3.5); 130.2; 131.0 (2C, d, *J* = 8.7); 140.0; 150.9; 152.6; 163.1 (d, *J* = 249.7); 167.3. Found, %: C 61.08; H 4.79; N 17.78. $C_{16}H_{15}FN_4O_2$. Calculated, %: C 61.14; H 4.81; N 17.83.

Ethyl 5-azido-4-(3,4-dimethoxyphenyl)-2,6-dimethylnicotinate (3h). Yield 0.58 g (82%), colorless crystals, mp 111–112°C (*n*-heptane). IR spectrum, ν, cm^{-1}: 2110 (N_3), 1729 (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.98 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 2.50 (3H, s, 6-CH_3); 2.54 (3H, s, 2-CH_3); 3.85 (3H, s, OCH_3); 3.90 (3H, s, OCH_3); 4.02 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 6.83–6.91 (3H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 13.8; 21.4; 22.2; 55.9; 56.0; 61.3; 110.9; 112.3; 121.8; 125.9; 128.6; 130.4; 140.7; 148.9; 149.7; 150.5; 152.3; 167.6. Found, %: C 60.70; H 5.70; N 15.79. $C_{18}H_{20}N_4O_4$. Calculated, %: C 60.66; H 5.66; N 15.72.

5-Azido-2,6-dimethyl-4-phenylnicotinonitrile (7a). Yield 0.44 g (89%), colorless crystals, mp 110–111°C (*n*-heptane). IR spectrum, ν, cm^{-1}: 2222 (CN), 2114 (N_3). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.60 (3H, s, 6-CH_3); 2.74 (3H, s, 2-CH_3); 7.41–7.43 (2H, m, H Ar); 7.53–7.54 (3H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.9; 23.5; 108.3; 115.8; 129.0 (2C); 129.1 (2C); 130.2; 130.7; 132.1; 145.7; 155.8; 157.7. Found, %: C 67.40; H 4.43; N 28.07. $C_{14}H_{11}N_5$. Calculated, %: C 67.46; H 4.45; N 28.10.

5-Azido-2,6-dimethyl-4-(4-methylphenyl)nicotinonitrile (7b). Yield 0.45 g (85%), colorless crystals, mp 110–111°C (*n*-heptane). IR spectrum, ν, cm^{-1}: 2228 (CN), 2108 (N_3). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.43 (3H, s, CH_3); 2.59 (3H, s, 6-CH_3); 2.73 (3H, s, 2-CH_3); 7.25–7.38 (4H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.4; 21.8; 23.5; 108.4; 115.9; 128.9 (2C); 129.2; 129.7 (2C); 130.9; 140.3; 146.0; 155.7; 157.7. Found, %: C 68.38; H 4.96; N 26.58. $C_{15}H_{13}N_5$. Calculated, %: C 68.42; H 4.98; N 26.60.

5-Azido-4-(4-methoxyphenyl)-2,6-dimethylnicotinonitrile (7c). Yield 0.48 g (86%), colorless crystals, mp 108–109°C (*n*-heptane). IR spectrum, ν, cm^{-1}: 2224 (CN), 2106 (N_3). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.58 (3H, s, 6-CH_3); 2.72 (3H, s, 2-CH_3); 3.86 (3H, s, OCH_3); 7.04 (2H, d, *J* = 8.4, H Ar); 7.36 (2H, d, *J* = 8.4, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.9; 23.5; 55.3; 108.4; 114.5 (2C); 116.0; 124.2; 130.5 (2C); 131.0; 145.6; 155.7; 157.7; 160.9. Found, %: C 64.45; H 4.71; N 25.12. $C_{15}H_{13}N_5O$. Calculated, %: C 64.51; H 4.69; N 25.07.

5-Azido-4-(biphenyl-4-yl)-2,6-dimethylnicotinonitrile (7d). Yield 0.57 g (88%), colorless crystals, mp 147–148°C (*n*-heptane). IR spectrum, ν, cm^{-1}: 2226 (CN), 2112 (N_3). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.62 (3H, s, 6-CH_3); 2.76 (3H, s, 2-CH_3); 7.36–7.51 (5H, m, H Ar); 7.65 (2H, d, *J* = 7.4, H Ar); 7.76 (2H, d, *J* = 8.2, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.9; 23.6; 108.2; 115.9; 127.2 (2C); 127.6 (2C); 128.0; 128.9 (2C); 129.5 (2C); 130.9; 131.0; 140.0; 143.0; 145.6; 155.9; 157.9. Found, %: C 73.79; H 4.63; N 21.50. $C_{20}H_{15}N_5$. Calculated, %: C 73.83; H 4.65; N 21.52.

5-Azido-4-(2-methoxyphenyl)-2,6-dimethylnicotinonitrile (7e). Yield 0.35 g (63%), colorless crystals, mp 101–102°C (*n*-heptane). IR spectrum, ν, cm^{-1}: 2223 (CN), 2120 (N_3). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.58 (3H, s, 6-CH_3); 2.73 (3H, s, 2-CH_3); 3.84 (3H, s, OCH_3); 7.03–7.11 (2H, m, H Ar); 7.20–7.25 (1H, m, H Ar); 7.50 (1H, t, *J* = 7.2, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.8; 23.4; 55.7; 109.3; 111.3; 115.9; 120.9; 121.0; 130.5; 131.3; 132.0; 143.2; 155.4; 157.0; 157.2. Found, %: C 64.45; H 4.71; N 25.14. $C_{15}H_{13}N_5O$. Calculated, %: C 64.51; H 4.69; N 25.07.

5-Azido-4-(4-chlorophenyl)-2,6-dimethylnicotinonitrile (7f). Yield 0.47 g (82%), colorless crystals, mp 144–145°C (*n*-heptane). IR spectrum, ν, cm^{-1}: 2228 (CN), 2113 (N_3). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.55 (3H, s, 6-CH_3); 2.65 (3H, s, 2-CH_3); 7.54–7.56 (2H, m, H Ar); 7.64–7.66 (2H, m, H Ar). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 21.5; 23.0; 107.4; 110.3; 115.6; 128.7 (2C); 131.0 (2C); 131.1; 134.8; 144.1; 155.5; 157.0. Found, %: C 59.21; H 3.56; N 24.61. $C_{14}H_{10}ClN_5$. Calculated, %: C 59.27; H 3.55; N 24.68.

5-Azido-4-(4-fluorophenyl)-2,6-dimethylnicotinonitrile (7g). Yield 0.40 g (75%), colorless crystals, mp 137–138°C (*n*-heptane). IR spectrum, ν, cm^{-1}: 2226 (CN), 2109 (N_3). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 2.55 (3H, s, 6-CH_3); 2.65 (3H, s, 2-CH_3); 7.39–7.43 (2H, m, H Ar);

7.57–7.60 (2H, m, H Ar). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 21.4; 22.8; 107.5; 115.5; 115.7 (2C, d, *J* = 22.5); 128.5 (d, *J* = 3.5); 130.2; 131.5 (2C, d, *J* = 8.7); 144.3; 155.3; 156.8; 162.8 (d, *J* = 248.0). Found, %: C 62.98; H 3.75; N 26.12. $C_{14}H_{10}FN_5$. Calculated, %: C 62.92; H 3.77; N 26.20.

5-Azido-4-(3,4-dimethoxyphenyl)-2,6-dimethylnicotinonitrile (7h). Yield 0.54 g (87%), colorless crystals, mp 118–119°C (*n*-heptane). IR spectrum, ν, cm^{-1}: 2224 (CN), 2118 (N_3). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.58 (3H, s, 6-CH_3); 2.73 (3H, s, 2-CH_3); 3.90 (3H, s, OCH_3); 3.94 (3H, s, OCH_3); 6.91 (1H, s, H Ar); 7.00 (2H, d, *J* = 1.2, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.9; 23.5; 56.0; 56.2; 108.4; 111.5; 112.3; 116.0; 122.2; 124.4; 131.0; 145.6; 149.4; 150.7; 155.7; 157.7. Found, %: C 62.17; H 4.91; N 22.59. $C_{16}H_{15}N_5O_2$. Calculated, %: C 62.13; H 4.89; N 22.64.

Synthesis of β-carbolines 4 and 8 a–h' (General procedure). Method I. A mixture of nitropyridine **1a–c** (2 mmol) and $P(OEt)_3$ (10 mmol) was heated in a sealed vial (in a nitrogen atmosphere) at 165°C for 72 h. After the completion of the reaction, the mixture was evaporated under reduced pressure. EtOAc was added to the residue, the crystals were filtered off and purified by recrystallization from PhMe.

Method II. A solution of 4-aryl-5-azidopyridine **3a–h** or **7a–h** (2 mmol) in *m*-xylene (54 ml) was heated under reflux for 6 h. After the completion of the reaction, *m*-xylene was evaporated under reduced pressure. The resulting residue was purified by column chromatography (eluent $CHCl_3$–EtOAc–EtOH, 6:3:1) on silica gel.

Ethyl 1,3-dimethyl-9*H*-pyrido[3,4-*b*]indole-4-carboxylate (4a). Yield 0.11 g (21%, method I), 0.38 g (70%, method II), colorless crystals, mp 145–146°C (PhMe). IR spectrum, ν, cm^{-1}: 3136 (NH), 1710 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.48 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$); 2.75 (3H, s, 3-CH_3); 2.76 (3H, s, 1-CH_3); 4.60 (2H, q, *J* = 7.2, $C\underline{H}_2CH_3$); 7.21 (1H, t, *J* = 7.2, H-6); 7.43–7.50 (2H, m, H-8,7); 8.08 (1H, d, *J* = 8.0, H-5); 9.03 (1H, br. s, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 14.2; 20.1; 22.2; 61.6; 111.6; 119.1; 120.2; 120.5; 123.6; 126.3; 128.7; 132.9; 141.1; 142.4; 144.5; 169.1. Found, %: C 71.67; H 5.97; N 10.40. $C_{16}H_{16}N_2O_2$. Calculated, %: C 71.62; H 6.01; N 10.44.

Ethyl 1,3,7-trimethyl-9*H*-pyrido[3,4-*b*]indole-4-carboxylate (4b). Yield 0.14 g (25%, method I), 0.50 g (88%, method II), colorless crystals, mp 167–168°C (petroleum ether). IR spectrum, ν, cm^{-1}: 3349 (NH), 1729 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.47 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$); 2.46 (3H, s, 7-CH_3); 2.73 (3H, s, 3-CH_3); 2.74 (3H, s, 1-CH_3); 4.59 (2H, q, *J* = 7.2, $C\underline{H}_2CH_3$); 7.01 (1H, d, *J* = 8.2, H-6); 7.19 (1H, s, H-8); 7.93 (1H, d, *J* = 8.2, H-5); 9.18 (1H, br. s, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 14.2; 20.0; 22.1; 22.2; 61.6; 111.5; 118.1; 118.7; 122.0; 123.2; 126.4; 133.0; 139.3; 141.7; 142.1; 144.4; 169.2. Found, %: C 72.39; H 6.47; N 9.94. $C_{17}H_{18}N_2O_2$. Calculated, %: C 72.32; H 6.43; N 9.92.

Ethyl 7-methoxy-1,3-dimethyl-9*H*-pyrido[3,4-*b*]indole-4-carboxylate (4c). Yield 0.18 g (30%, method I), 0.47 g (79%, method II), colorless crystals, mp 120–121°C (PhMe). IR spectrum, ν, cm^{-1}: 3137 (NH), 1719 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.47 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$); 2.70 (3H, s, 3-CH_3); 2.73 (3H, s, 1-CH_3); 3.82 (3H, s, OCH_3); 4.59 (2H, q, *J* = 7.2, $C\underline{H}_2CH_3$); 7.13–7.17 (1H, m, H-6); 7.22–7.26 (1H, m, H-8); 7.94–7.97 (1H, m, H-5); 9.01 (1H, br. s, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 14.3; 20.1; 22.6; 55.4; 61.5; 94.2; 109.9; 114.3; 118.1; 124.7; 126.6; 133.0; 141.7; 142.7; 145.1; 160.9; 169.3. Found, %: C 68.49; H 6.10; N 9.36. $C_{17}H_{18}N_2O_3$. Calculated, %: C 68.44; H 6.08; N 9.39.

Ethyl 1,3-dimethyl-7-phenyl-9*H*-pyrido[3,4-*b*]indole-4-carboxylate (4d). Yield 0.50 g (73%, method II), colorless crystals, mp 222–223°C (EtOH). IR spectrum, ν, cm^{-1}: 3418 (NH), 1722 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.41 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$); 2.72 (3H, s, 3-CH_3); 2.95 (3H, s, 1-CH_3); 4.61 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 7.44 (1H, t, *J* = 7.5, H Ar); 7.53 (2H, t, *J* = 7.5, H Ar); 7.66 (1H, dd, *J* = 8.7, *J* = 1.6, H-6); 7.77–7.79 (2H, m, H Ar); 7.88 (1H, s, H-8); 8.13 (1H, d, *J* = 8.7, H-5); 12.82 (1H, br. s, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 14.1; 17.0; 18.4; 62.7; 110.2; 117.6; 119.9; 120.9; 124.6; 127.4 (2C); 127.7; 128.5; 129.4 (2C); 133.4; 139.2; 139.7; 140.8; 143.4; 144.2; 165.8. Found, %: C 76.79; H 5.89; N 8.15. $C_{22}H_{20}N_2O_2$. Calculated, %: C 76.72; H 5.85; N 8.13.

Ethyl 5-methoxy-1,3-dimethyl-9*H*-pyrido[3,4-*b*]indole-4-carboxylate (4e). Yield 0.36 g (60%, method II), colorless crystals, mp 103–104°C (PhMe). IR spectrum, ν, cm^{-1}: 3146 (NH), 1717 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm(*J*, Hz): 1.41 (3H, t, *J* = 6.8, $CH_2C\underline{H}_3$); 2.65 (3H, s, 3-CH_3); 2.66 (3H, s, 1-CH_3); 3.94 (3H, s, OCH_3); 4.48–4.54 (2H, m, $C\underline{H}_2CH_3$); 6.57 (1H, d, *J* = 7.8, H-6); 6.97 (1H, d, *J* = 7.8, H-8); 7.36 (1H, t, *J* = 7.8, H-7); 9.28 (1H, br. s, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 14.2; 19.9; 21.6; 55.5; 61.0; 100.7; 104.2; 110.6; 120.8; 124.0; 129.7; 132.2; 141.0; 142.4; 142.8; 156.5; 170.0. Found, %: C 68.37; H 6.06; N 9.35. $C_{17}H_{18}N_2O_3$. Calculated, %: C 68.44; H 6.08; N 9.39.

Ethyl 7-chloro-1,3-dimethyl-9*H*-pyrido[3,4-*b*]indole-4-carboxylate (4f). Yield 0.44 g (72%, method II), colorless crystals, mp 186–187°C (PhMe). IR spectrum, ν, cm^{-1}: 3156 (NH), 1724 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.48 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$); 2.77 (3H, s, 3-CH_3); 2.83 (3H, s, 1-CH_3); 4.59 (2H, q, *J* = 7.2, $C\underline{H}_2CH_3$); 7.15 (1H, dd, *J* = 8.8, *J* = 1.4, H-6); 7.46 (1H, s, H-8); 7.99 (1H, d, *J* = 8.8, H-5); 9.49 (1H, br. s, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 14.2; 19.8; 22.0; 61.8; 111.7; 118.9; 119.0; 121.2; 124.8; 126.3; 133.2; 134.9; 141.8; 142.3; 144.8; 168.5. Found, %: C 63.53; H 5.00; N 9.23. $C_{16}H_{15}ClN_2O_2$. Calculated, %: C 63.48; H 4.99; N 9.25.

Ethyl 7-fluoro-1,3-dimethyl-9*H*-pyrido[3,4-*b*]indole-4-carboxylate (4g). Yield 0.51 g (89%, method II), colorless crystals, mp 146–147°C (PhMe). IR spectrum, ν, cm^{-1}: 3145 (NH), 1714 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.48 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$); 2.71 (3H, s, 3-CH_3); 2.73 (3H, s, 1-CH_3); 4.59 (2H, q,

J = 7.2, C$\underline{H}_2$CH$_3$); 6.93 (1H, td, *J* = 9.1, *J* = 2.2, H-6); 7.04 (1H, dd, *J* = 9.2, *J* = 2.3, H-8); 8.05 (1H, dd, *J* = 8.8, *J* = 5.5, H-5); 9.01 (1H, br. s, NH). ^{13}C NMR spectrum (CDCl$_3$), δ, ppm (*J*, Hz): 14.3; 20.2; 22.6; 61.6; 97.8 (d, *J* = 26.9); 109.0 (d, *J* = 24.3); 118.0 (d, *J* = 144.8); 125.3 (d, *J* = 10.4); 126.1; 133.4 (d, *J* = 1.7); 141.7; 141.8; 142.4; 145.5; 163.4 (d, *J* = 246.2); 169.1. Found, %: C 67.18; H 5.31; N 9.73. $C_{16}H_{15}FN_2O_2$. Calculated, %: C 67.12; H 5.28; N 9.78.

Ethyl 6,7-dimethoxy-1,3-dimethyl-9*H*-pyrido[3,4-*b*]-indole-4-carboxylate (4h). Yield 0.41 g (63%, method II), colorless crystals, mp 128–129°C (PhMe). IR spectrum, ν, cm^{-1}: 3158 (NH), 1725 (C=O). ^{1}H NMR spectrum (CDCl$_3$), δ, ppm (*J*, Hz): 1.48 (3H, t, *J* = 7.1, CH$_2$C$\underline{H}_3$); 2.71 (3H, s, 3-CH$_3$); 2.73 (3H, s, 1-CH$_3$); 3.89 (3H, s, 7-OCH$_3$); 3.93 (3H, s, 6-OCH$_3$); 4.56 (2H, q, *J* = 6.9, C$\underline{H}_2$CH$_3$); 6.85 (1H, s, H-8); 7.56 (1H, s, H-5); 8.63 (1H, br. s, NH). ^{13}C NMR spectrum (CDCl$_3$), δ, ppm: 14.3; 20.1; 22.7; 56.0; 56.4; 61.4; 94.0; 105.5; 112.8; 117.9; 126.7; 133.0; 136.7; 141.9; 144.9; 145.0; 152.0; 169.3. Found, %: C 65.91; H 6.16; N 8.50. $C_{18}H_{20}N_2O_4$. Calculated, %: C 65.84; H 6.14; N 8.53.

Ethyl 7,8-dimethoxy-1,3-dimethyl-9*H*-pyrido[3,4-*b*]-indole-4-carboxylate (4h'). Yield 0.20 g (31%, method II), colorless crystals, mp 174–175°C (PhMe). IR spectrum, ν, cm^{-1}: 3144 (NH), 1725 (C=O). ^{1}H NMR spectrum (CDCl$_3$), δ, ppm (*J*, Hz): 1.44 (3H, t, *J* = 7.1, CH$_2$C$\underline{H}_3$); 2.70 (3H, s, 3-CH$_3$); 2.74 (3H, s, 1-CH$_3$); 3.94 (3H, s, 8-OCH$_3$); 3.97 (3H, s, 7-OCH$_3$); 4.55 (2H, q, *J* = 7.2, C$\underline{H}_2$CH$_3$); 6.87 (1H, d, *J* = 9.0, H-6); 7.77 (1H, d, *J* = 9.0, H-5); 9.16 (1H, br. s, NH). ^{13}C NMR spectrum (CDCl$_3$), δ, ppm: 14.2; 20.0; 22.4; 56.5; 60.8; 61.4; 107.0; 116.3; 118.3; 119.3; 126.9; 133.3; 133.4; 136.2; 142.3; 145.0; 151.7; 169.0. Found, %: C 65.90; H 6.16; N 8.50. $C_{18}H_{20}N_2O_4$. Calculated, %: C 65.84; H 6.14; N 8.53.

1,3-Dimethyl-9*H*-pyrido[3,4-*b*]indole-4-carbonitrile (8a). Yield 0.34 g (77%, method II), colorless crystals, mp 241–242°C (PhMe). IR spectrum, ν, cm^{-1}: 3285 (NH), 2227 (CN). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.68 (3H, s, 3-CH$_3$); 2.75 (3H, s, 1-CH$_3$); 7.28–7.33 (1H, m, H-7); 7.59–7.62 (2H, m, H-6,8); 8.25 (1H, d, *J* = 8.0, H-5); 11.98 (1H, br. s, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 20.8; 22.4; 95.7; 112.7; 117.7; 118.8; 120.3; 121.3; 126.7; 129.5; 132.1; 141.2; 146.2; 150.2. Found, %: C 76.05; H 4.97; N 18.91. $C_{14}H_{11}N_3$. Calculated, %: C 76.00; H 5.01; N 18.99.

1,3,7-Trimethyl-9*H*-pyrido[3,4-*b*]indole-4-carbonitrile (8b). Yield 0.38 g (80%, method II), colorless crystals, mp 250–251°C (PhMe). IR spectrum, ν, cm^{-1}: 3298 (NH), 2228 (CN). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.49 (3H, s, 7-CH$_3$); 2.66 (3H, s, 3-CH$_3$); 2.73 (3H, s, 1-CH$_3$); 6.90 (1H, d, *J* = 8.4, H-6); 6.99 (1H, s, H-8); 8.09 (1H, d, *J* = 8.4, H-5); 11.75 (1H, br. s, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 20.7; 21.9; 22.3; 95.1; 112.0; 116.5; 117.6; 120.8; 121.8; 126.8; 132.0; 139.4; 141.7; 145.5; 149.8. Found, %: C 76.62; H 5.61; N 17.81. $C_{15}H_{13}N_3$. Calculated, %: C 76.57; H 5.57; N 17.86.

7-Methoxy-1,3-dimethyl-9*H*-pyrido[3,4-*b*]indole-4-carbonitrile (8c). Yield 0.37 g (73%, method II), colorless crystals, mp 263–264°C (PhMe). IR spectrum, ν, cm^{-1}: 3302 (NH), 2226 (CN). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.67 (3H, s, 3-CH$_3$); 2.73 (3H, s, 1-CH$_3$); 3.88 (3H, s, OCH$_3$); 6.90 (1H, d, *J* = 8.4, H-6); 6.99 (1H, s, H-8); 8.09 (1H, d, *J* = 8.4, H-5); 11.80 (1H, br. s, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 20.5; 22.3; 55.4; 94.6; 110.5; 112.5; 117.7; 122.1; 122.8; 127.3; 132.1; 143.1; 144.8; 149.9; 161.1. Found, %: C 71.63; H 5.24; N 16.76. $C_{15}H_{13}N_3O$. Calculated, %: C 71.70; H 5.21; N 16.72.

1,3-Dimethyl-7-phenyl-9*H*-pyrido[3,4-*b*]indole-4-carbonitrile (8d). Yield 0.51 g (86%, method II), colorless crystals, mp 292–293°C (PhMe). IR spectrum, ν, cm^{-1}: 3281 (NH), 2232 (CN). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.71 (3H, s, 3-CH$_3$); 2.79 (3H, s, 1-CH$_3$); 7.42 (1H, t, *J* = 7.3, H Ar); 7.52 (2H, t, *J* = 7.5, H Ar); 7.60 (1H, dd, *J* = 8.4, *J* = 1.5, H-6); 7.74–7.78 (3H, m, H Ar, H-8); 8.31 (1H, d, *J* = 8.4, H-5); 12.13 (1H, br. s, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 20.8; 22.4; 95.4; 110.1; 117.6; 118.0; 119.6; 121.6; 126.5; 127.2 (2C); 127.8; 129.0 (2C); 132.6; 140.3; 141.5; 141.8; 146.0; 150.1. Found, %: C 80.70; H 5.06; N 14.07. $C_{20}H_{15}N_3$. Calculated, %: C 80.78; H 5.08; N 14.13.

5-Methoxy-1,3-dimethyl-9*H*-pyrido[3,4-*b*]indole-4-carbonitrile (8e). Yield 0.30 g (60%, method II), colorless crystals, mp 275–276°C (EtOH). IR spectrum, ν, cm^{-1}: 3282 (NH), 2223 (CN). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.72 (3H, s, 3-CH$_3$); 2.74 (3H, s, 1-CH$_3$); 3.94 (3H, s, OCH$_3$); 6.70 (1H, d, *J* = 8.0, H-6); 7.13 (1H, d, *J* = 8.0, H-8); 7.50 (1H, t, *J* = 8.0, H-7); 11.90 (1H, br. s, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 20.6; 23.3; 54.2; 97.4; 100.4; 104.5; 109.2; 118.3; 125.6; 130.7; 131.7; 142.5; 145.1; 151.4; 156.3. Found, %: C 71.64; H 5.23; N 16.76. $C_{15}H_{13}N_3O$. Calculated, %: C 71.70; H 5.21; N 16.72.

7-Chloro-1,3-dimethyl-9*H*-pyrido[3,4-*b*]indole-4-carbonitrile (8f). Yield 0.36 g (70%, method II), colorless crystals, mp 268–269°C (PhMe). IR spectrum, ν, cm^{-1}: 3280 (NH), 2225 (CN). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.68 (3H, s, 3-CH$_3$); 2.74 (3H, s, 1-CH$_3$); 7.28 (1H, d, *J* = 6.5, H-6); 7.56 (1H, s, H-8); 8.14 (1H, d, *J* = 7.6, H-5); 12.00 (1H, br. s, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 20.6; 22.2; 95.3; 111.9; 117.1; 117.4; 120.4; 122.4; 126.0; 132.2; 133.6; 141.4; 146.2; 150.3. Found, %: C 65.83; H 3.97; N 16.48. $C_{14}H_{10}ClN_3$. Calculated, %: C 65.76; H 3.94; N 16.43.

7-Fluoro-1,3-dimethyl-9*H*-pyrido[3,4-*b*]indole-4-carbonitrile (8g). Yield 0.36 g (75%, method II), colorless crystals, mp 285–286°C (MeOH). IR spectrum, ν, cm^{-1}: 3297 (NH), 2221 (CN). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.72 (3H, s, 3-CH$_3$); 2.77 (3H, s, 1-CH$_3$); 7.08–7.12 (1H, m, H-6); 7.33 (1H, s, H-8); 8.32 (1H, dd, *J* = 8.3, *J* = 5.6, H-5); 11.86 (1H, br. s, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 20.3; 20.0; 95.1; 98.2 (d, *J* = 26.0); 108.6 (d, *J* = 25.1); 115.5; 117.0; 122.7 (d, *J* = 11.3); 126.4; 132.5; 141.8 (d, *J* = 13.9); 145.5; 150.2; 162.8 (d, *J* = 244.5). Found, %: C 70.35; H 4.24; N 17.51. $C_{14}H_{10}FN_3$. Calculated, %: C 70.28; H 4.21; N 17.56.

6,7-Dimethoxy-1,3-dimethyl-9*H*-pyrido[3,4-*b*]indole-4-carbonitrile (8h). Yield 0.12 g (21%, method II), colorless crystals, mp 275–276°C (*i*-PrOH). IR spectrum, ν, cm^{-1}: 3308 (NH), 2219 (CN). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.68 (3H, s, 3-CH_3); 2.72 (3H, s, 1-CH_3); 3.84 (3H, s, 7-OCH_3); 3.92 (3H, s, 6-OCH_3); 7.03 (1H, s, H-8); 7.64 (1H, s, H-5); 11.53 (1H, br. s, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 20.2; 22.1; 55.6; 55.9; 94.1; 94.7; 102.5; 110.6; 117.6; 126.9; 131.7; 137.1; 144.5; 144.7; 149.4; 152.4. Found, %: C 68.38; H 5.34; N 14.88. $C_{16}H_{15}N_3O_2$. Calculated, %: C 68.31; H 5.37; N 14.94.

7,8-Dimethoxy-1,3-dimethyl-9*H*-pyrido[3,4-*b*]indole-4-carbonitrile (8h'). Yield 0.40 g (71%, method II), colorless crystals, mp 230–231°C (*i*-PrOH). IR spectrum, ν, cm^{-1}: 3294 (NH), 2224 (CN). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.70 (3H, s, 3-CH_3); 2.81 (3H, s, 1-CH_3); 3.94 (3H, s, 8-OCH_3); 3.95 (3H, s, 7-OCH_3); 7.15 (1H, d, *J* = 8.8, H-6); 8.00 (1H, d, *J* = 8.8, H-5); 11.70 (1H, br. s, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 20.8; 22.2; 56.6; 60.5; 94.9; 108.3; 114.8; 116.7; 117.5; 127.8; 132.7; 133.9; 136.3; 145.6; 150.0; 152.4. Found, %: C 68.38; H 5.35; N 14.89. $C_{16}H_{15}N_3O_2$. Calculated, %: C 68.31; H 5.37; N 14.94.

Synthesis of 4-aryl-2,6-dimethyl-5-nitronicotinic acids 9a,b (General method). A solution of NaOH (20 mmol) in H_2O (2 ml) was added with stirring to a solution of pyridine **1a**,**b** (4 mmol) in EtOH (10 ml). The reaction mixture was heated under reflux for 2 h and cooled. H_2O was added, and the resulting mixture was acidified with aqueous HCl to pH 3. The formed precipitate was filtered off and recrystallized from EtOH.

2,6-Dimethyl-5-nitro-4-phenylnicotinic acid (9a). Yield 0.89 g (82%), colorless crystals, mp 217–218°C (EtOH). IR spectrum, ν, cm^{-1}: 1729 (C=O), 1542, 1373 (NO_2). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.51 (3H, s, 2-CH_3); 2.57 (3H, s, 6-CH_3); 7.24–7.26 (2H, m, H Ar); 7.45–7.46 (3H, m, H Ar). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 20.2; 22.6; 127.8 (2C); 128.6 (2C); 129.1; 129.5; 131.9; 139.0; 144.9; 148.7; 155.5; 167.2. Found, %: C 61.80; H 4.46; N 10.27. $C_{14}H_{12}N_2O_4$. Calculated, %: C 61.76; H 4.44; N 10.29.

4-(4-Methoxyphenyl)-2,6-dimethyl-5-nitronicotinic acid (9b). Yield 1.04 g (86%), colorless crystals, mp 254–255°C (EtOH). IR spectrum, ν, cm^{-1}: 1725 (C=O), 1537, 1365 (NO_2). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.49 (3H, s, 2-CH_3); 2.55 (3H, s, 6-CH_3); 3.78 (3H, s, OCH_3); 7.00–7.03 (2H, m, H Ar); 7.17–7.20 (2H, m, H Ar). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 20.1; 22.6; 55.2; 114.2 (2C); 123.8; 129.3 (2C); 129.5; 138.7; 145.2; 148.5; 155.3; 160.1; 167.4. Found, %: C 59.54; H 4.65; N 9.25. $C_{15}H_{14}N_2O_5$. Calculated, %: C 59.60; H 4.67; N 9.27.

Synthesis of 2,6-dimethyl-3-nitro-4-phenylpyridines 10a,b (General method). 5-Nitronicotinic acid derivative **9a**,**b** (5 mmol) was heated at 260°C until evolution of CO_2 bubbles stopped. The mixture was cooled to room temperature and purified by column chromatography on silica gel, eluent PhMe. The product was recrystallized from *n*-heptane.

2,6-Dimethyl-3-nitro-4-phenylpyridine (10a). Yield 0.59 g (52%), colorless crystals, mp 40–41°C (*n*-heptane). IR spectrum, ν, cm^{-1}: 1522, 1362 (NO_2). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.58 (3H, s, 2-CH_3); 2.60 (3H, s, 6-CH_3); 7.07 (1H, s, H-5); 7.32–7.35 (2H, m, H Ar); 7.41–7.44 (3H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 20.6; 24.4; 122.3; 127.5 (2C); 129.0 (2C); 129.5; 134.5; 142.4; 145.1; 149.7; 159.8. Found, %: C 68.47; H 5.33; N 12.30. $C_{13}H_{12}N_2O_2$. Calculated, %: C 68.41; H 5.30; N 12.27.

4-(4-Methoxyphenyl)-2,6-dimethyl-3-nitropyridine (10b). Yield 1.04 g (81%), colorless crystals, mp 76–77°C (*n*-heptane). IR spectrum, ν, cm^{-1}: 1527, 1365 (NO_2). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.56 (3H, s, 2-CH_3); 2.59 (3H, s, 6-CH_3); 3.82 (3H, s, OCH_3); 6.94 (2H, d, *J* = 8.0, H Ar); 7.05 (1H, s, H-5); 7.28 (2H, d, *J* = 8.0, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 20.6; 24.4; 55.3; 114.6 (2C); 122.2; 126.6 (2C); 128.9; 142.0; 145.2; 149.6; 159.6; 160.7. Found, %: C 65.13; H 5.50; N 10.88. $C_{14}H_{14}N_2O_3$. Calculated, %: C 65.11; H 5.46; N 10.85.

Synthesis of pyrido[3,4-*c*]cinnolines 14a,b (General method). A solution of aminopyridine **2i** or **6i** (2 mmol) in AcOH (10 ml) and H_2O (4 ml) was cooled to 0°C, and chilled 48% aqueous HBF_4 (7 ml) was added dropwise. The reaction mixture was stirred for 30 min, then a chilled solution of $NaNO_2$ (2.3 mmol) in H_2O (2 ml) was added dropwise, and the resulting mixture was stirred for 30 min. It was diluted with H_2O and neutralized with 10% aqueous NaOH to pH 7. The precipitated crystals were filtered off and washed with chilled H_2O.

Ethyl 7,8,9-trimethoxy-2,4-dimethylpyrido[3,4-*c*]cinnoline-1-carboxylate (14a). Yield 0.62 g (84%), light-yellow crystals, mp 83–84°C (*i*-PrOH). IR spectrum, ν, cm^{-1}: 1719 (C=O), 1537 (N=N). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.43 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$); 2.74 (3H, s, 2-CH_3); 3.36 (3H, s, 4-CH_3); 4.01 (3H, s, 8-OCH_3); 4.11 (3H, s, 9-OCH_3); 4.33 (3H, s, 7-OCH_3); 4.56 (2H, q, *J* = 7.1, $C\underline{H}_2CH_3$); 7.39 (1H, s, H-10). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 14.1; 21.4; 22.8; 56.2; 61.6; 62.3; 63.7; 98.6; 115.7; 120.2; 122.2; 136.9; 139.3; 144.9; 150.4; 153.3; 157.1; 164.0; 170.2. Found, %: C 61.39; H 5.74; N 11.34. $C_{19}H_{21}N_3O_5$. Calculated, %: C 61.45; H 5.70; N 11.31.

7,8,9-Trimethoxy-2,4-dimethylpyrido[3,4-*c*]cinnoline-1-carbonitrile (14b). Yield 0.42 g (64%), light-yellow crystals, mp 184–185°C (*i*-PrOH). IR spectrum, ν, cm^{-1}: 2214 (CN), 1533 (N=N). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.99 (3H, s, 2-CH_3); 3.36 (3H, s, 4-CH_3); 4.12 (3H, s, 8-OCH_3); 4.15 (3H, s, 9-OCH_3); 4.33 (3H, s, 7-OCH_3); 8.73 (1H, s, H-10). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 22.1; 24.8; 56.8; 61.6; 63.7; 98.1; 98.2; 115.3; 118.8; 124.9; 136.2; 139.3; 145.6; 150.1; 157.8; 163.6; 167.5. Found, %: C 63.01; H 5.00; N 17.31. $C_{17}H_{16}N_4O_3$. Calculated, %: C 62.95; H 4.97; N 17.27.

Study of hypoglycemic activity of compounds 4c,g and 8e,h. Compounds **4c**,**g** and **8e**,**h** were administered orally at a dose of 10 mg/kg to CD-1 mice (5 animals per group) 30 min before oral glucose loading (2.5 g/kg). The animals were obtained from the vivarium of the Federal Research Center, Institute of Cytology and Genetics of the

Siberian Branch of the Russian Academy of Sciences, where they were kept under standard vivarium conditions with free access to water and feed. All research work with laboratory animals was carried out in accordance with the generally accepted ethical standards for the treatment of animals which meet the "European Convention for the Protection of Vertebrate Animals used for Experimental or Other Scientific Purposes".[20]

Blood glucose level was measured at the tail incision using a OneTouch Select glucometer (LifeScan Inc., USA) before administration of the test compounds (0 min), as well as 30, 60, 90, and 120 min after glucose administration. Vildagliptin, a dipeptidyl peptidase-4 inhibitor, was used as a positive control. Statistical analysis was performed using the Mann-Whitney U test.[8,9,20]

Supplementary information file containing absorption and fluorescence spectra of compounds **4**, **8 a–h'**, physicochemical characteristics of the starting compounds, as well as the NMR spectra of the synthesized compounds is available at the journal website at http://link.springer.com/journal/10593.

The study was carried out with the financial support of the Russian Foundation for Basic Research within the framework of scientific project No. 19-33-90229.

References

1. (a) Cao, R.; Peng, W.; Wang, Z.; Xu, A. *Curr. Med. Chem.* **2007**, *14*, 479. (b) Homer, J. A.; Sperry, J. *J. Nat. Prod.* **2017**, *80*, 2178. (c) Jarhad, D. B.; Mashelkar, K. K.; Kim, H.-R.; Noh, M.; Jeong, L. S. *J. Med. Chem.* **2018**, *61*, 9791.
2. (a) Sanders, MP A.; McGuire, R.; Roumen, L.; De Esch, I. J. P.; De Vlieg, J.; Klomp, J. P. G.; De Graaf, C. *Med. Chem. Commun.* **2012**, *3*, 28. (b) Camerman, A.; Mastropaolo, D.; Hempel, A.; Camerman, N. *Acta Crystallogr*., *Sect. C*: *Cryst. Struct. Commun.* **2005**, *C61*, o265. (c) Cooper, S. J. *Eur. J. Pharmacol.* **1986**, *120*, 257. (d) File, S. E.; Baldwin, H. A. *Brain Res. Bull.* **1987**, *19*, 293. (e) Yin, W.; Majumder, S.; Clayton, T.; Petrou, S.; VanLinn, M. L.; Namjoshi, O. A.; Ma, C.; Cromer, B. A.; Roth, B. L., Platt, D. M.; Cook, J. M. *Bioorg. Med. Chem.* **2010**, *18*, 7548. (f) Diaz-Arauzo, H.; Evoniuk, G. E.; Skolnick, P.; Cook, J. M. *J. Med. Chem.* **1991**, *34*, 1754.
3. (a) Devi, N.; Kumar, S.; Pandey, S. K.; Singh, V. *Asian J. Org. Chem.* **2018**, *7*, 6. (b) Cox, E. D.; Diaz-Arauzo, H.; Huang, Q.; Reddy, M. S.; Ma, C.; Harris, B.; VcKernan, R.; Skolnick, P.; Cook, J. M. *J. Med. Chem.* **1998**, *41*, 2537. (c) Sahoo, C. R.; Paidesetty, S. K.; Padhy, R. N. *Eur. J. Med. Chem.* **2019**, *162*, 752. (d) Penta, A.; Franzblau, S.; Wan, B., Murugesan, S. *Eur. J. Med. Chem.* **2015**, *105*, 238. (e) Cao, R.; Chen, H.; Peng, W.; Ma, Y.; Hou, X.; Guan, H.; Liu, X.; Xu, A. *Eur. J. Med. Chem.* **2005**, *40*, 991. (f) Ling, Y.; Feng, J.; Luo, L.; Guo, J.; Peng, Y.; Wang, T.; Ge, X.; Xu, Q.; Wang, X.; Dai, H.; Zhang, Y. *ChemMedChem* **2017**, *12*, 1.
4. (a) Uredi, D.; Motati, D. R.; Watkins, E. B. *Org. Lett.* **2018**, *20*, 6336. (b) Ding, S.; Shi, Z.; Jiao, N. *Org. Lett.* **2010**, *12*, 1540. (c) Dhiman, D.; Mishra, U. K.; Ramasastry, S. S. V. *Angew. Chem.*, *Int. Ed.* **2016**, *55*, 7737. (d) Takasu, K.; Shimogama, T.; Saiin, C.; Kim, H.-S.; Wataya, Y.; Ihara, M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1689.
5. Shuvalov, V. Yu.; Rupp, A. S.; Fisyuk, A. S.; Kuratova, A. K.; Nefedov, A. A.; Sagitullina, G. P. *ChemistrySelect* **2019**, *4*, 1696.
6. Shuvalov, V. Yu.; Rupp, A. S.; Kuratova, A. K.; Fisyuk, A. S.; Nefedov, A. A.; Sagitullina, G. P. *Synlett* **2019**, 919.
7. Shuvalov, V. Yu.; Elisheva, V. A.; Belousova, A. S.; Arshinov, E. V.; Glyzdinskaya, L. V.; Vorontsova, M. A.; Chernenko, S. A.; Fisyuk, A. S.; Sagitullina, G. P. *Chem. Heterocycl. Compd.* **2020**, *56*, 73. [*Khim. Geterotsikl. Soedin.* **2020**, *56*, 73.]
8. (a) Cooper, E. J.; Hudson, A. L.; Parker, C. A.; Morgan, N. G. *Eur. J. Pharmacol.* **2003**, *482*, 189. (b) Bahekar, R. H.; Jain, M. R.; Jadav, P. A.; Goel, A.; Patel, D. N.; Prajapati, V. M.; Gupta, A. A.; Modi, H.; Patel, P. R. *Bioorg. Med. Chem.* **2007**, *15*, 5950. (c) Morgan, N. G.; Cooper, E. J.; Squires, P. E.; Hills, C. E.; Parker, C. A.; Hudson, A. L. *Ann. N. Y. Acad. Sci.* **2003**, *1009*, 167. (d) Morgan, N. G.; Chan, S. L. *Curr. Pharm. Des.* **2001**, *7*, 1413.
9. *PASS Online*. http://www.way2drug.com/passonline.
10. (a) Chen, J.; Peng, F.; Zhang, Y.; Li, B.; She, J.; Jie, X.; Zou, Z.; Chen, M.; Chen, L. *Eur. J. Med. Chem.* **2017**, *140*, 104. (b) Gu, H.; Li, N.; Dai, J.; Xi, Y.; Wang S.; Wang, J. *Int. J. Mol. Sci.* **2018**, *19*, 3179. (c) Tadokoro, Y.; Nishikawa, T.; Ichimori, T.; Matsunaga, S.; Fujita, M. J.; Sakai, R. *ACS Omega* **2017**, *2*, 1074. (d) Guan, H.; Liu, X.; Peng, W.; Cao, R.; Ma, Y.; Chen, H.; Xu, A. *Biochem*. *Biophys. Res. Commun.* **2006**, *342*, 894.
11. (a) Balon, M.; Hidalgo, J.; Guardado, P.; Munoz, M. A.; Carmona, C. *J. Chem. Soc.*, *Perkin Trans. 2* **1993**, 99. (b) Perez, M. A. M.; Guzman, M. C. C.; Toledo, J. H.; Almeida, M. B. *J. Chem. Soc*., *Perkin Trans. 2* **1986**, 1573. (c) Wolfbeis, O. S.; Fürlinger, E. *Z. Phys. Chem.* **1982**, *129*, 171. (d) Sanchez-Coronilla, A.; Balon, M.; Munoz, M. A.; Carmona, C. *Chem. Phys.* **2008**, *344*, 72. (e) Tarzi, O. I.; Erra-Balsells, R. *J. Photochem. Photobiol.*, *B* **2006**, *82*, 79.
12. (a) Kumar, A.; Singh, S.; Mudahar, G. S.; Thind, K. S. *Radiat. Phys. Chem.* **2006**, *75*, 737. (b) Williams, A. T. R.; Winfield, S. A.; Miller, J. N. *Analyst* **1983**, *108*, 1067.
13. (a) Allen, M. W. *Measurement of Fluorescence Quantum Yields*; Thermo Fisher Scientific: Madison. Technical note: 52019. (b) Brouwer, A. M. *Pure Appl. Chem.* **2011**, *83*, 2213.
14. Davood, A.; Nematollahi, A.; Iman, M.; Shafiee, A. *Arch. Pharm. Res.* **2009**, *32*, 481.
15. (a) Fel'gendler, A. V.; Aboskalova, N. I.; Berestovitskaya, V. M. *Russ. J. Gen. Chem.* **2000**, *70*, 1087. [*Zh. Obshch. Khim.* **2000**, *70*, 1158.] (b) Dornow, A.; Sassenberg, W. *Liebigs Ann. Chem.* **1957**, *602*, 14.
16. Sagitullina, G. P.; Glizdinskaya, L. V.; Sagitullin, R. S. *Chem. Heterocycl. Compd.* **2005**, *41*, 739. [*Khim. Geterotsikl. Soedin.* **2005**, 858.]
17. Hurd, C. D.; Nilson, M. E. *J. Org. Chem.* **1955**, *20*, 927.
18. Karimi, B.; Seradj, H.; Ebrahimian, G.-R. *Synlett* **1999**, 1456.
19. Sathiyaraj, E.; Selvaganapathi, P.; Thirumaran, S.; Ciattini, S. *J. Mol. Struct.* **2016**, *1119*, 385.
20. *European Convention for the Protection of Vertebrate Animals Used for Experimental and other Scientific Purposes (ETS 123)*; Strasbourg, 1986.