DOI 10.1007/s10593-016-1827-5

Chemistry of Heterocyclic Compounds **2016**, *52*(1), 58–67

Synthesis of 1-functionalized di- and tetramethyl-3,4-dihydrobenzofuro[3,2-*g*]- and [2,3-*h*]isoquinoline derivatives

Tatyana S. Vshivkova[1], Aleksei A. Gorbunov[1], Olga A. Maiorova[1], Pavel A. Slepukhin[2,3], Maxim L. Isenov[2], Yurii V. Shklyaev[1]*

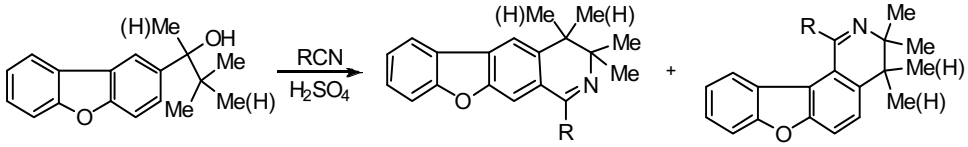
[1] *Institute of Technical Chemistry, Ural Branch, Russian Academy of Sciences, 3 Akademika Koroleva St., Perm 614013, Russia; e-mail: yushka@newmail.ru*

[2] *I. Ya. Postovskii Institute of Organic Synthesis, Ural Branch, Russian Academy of Sciences, 22 S. Kovalevskoi St./ 20 Akademicheskaya St., Yekaterinburg 620219, Russia; e-mail: slepukhin@ios.uran.ru*

[3] *Ural Federal University named after the first President of Russia B. N. Yeltsin, 19 Mira St., Yekaterinburg 620002, Russia.*

Translated from Khimiya Geterotsiklicheskikh Soedinenii, 2016, *52*(1), 58–67

Submitted November 13, 2015
Accepted December 14, 2015



Linear and angular 1-substituted derivatives of 3,3-di- and 3,3,4,4-tetramethyl-3,4-dihydrobenzofuroisoquinoline were obtained under Ritter reaction conditions, and the stereochemical features of these compounds were analyzed.

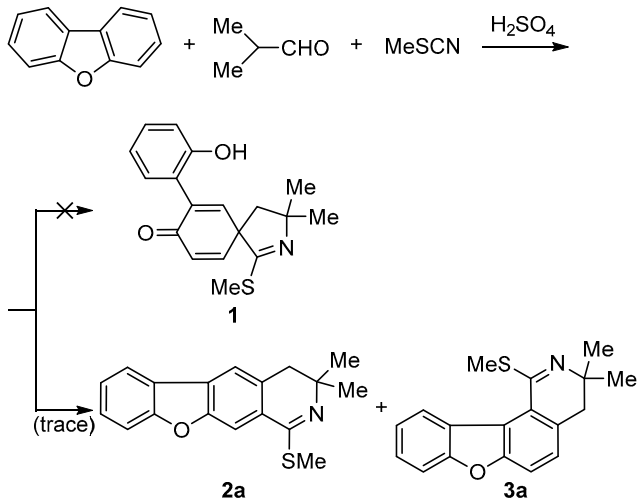
Keywords: 3,4-dihydrobenzofuro[3,2-*g*]isoquinolines, 3,4-dihydrobenzofuro[2,3-*h*]isoquinolines, Ritter reaction.

Fused ring systems containing two heterocycles have long attracted the attention of researchers. For example, derivatives of α-, β-, and γ-carbolines form a large group of alkaloids,[1] which includes isocryptolepin.[2] Derivatives of pyrido[4,3-*b*]carbazole, such as ellipticine, are well known natural compounds.[3,4] The anticancer alkaloid lamellarin is another example of annulated heterocycles that contain various heteroatoms.[5]

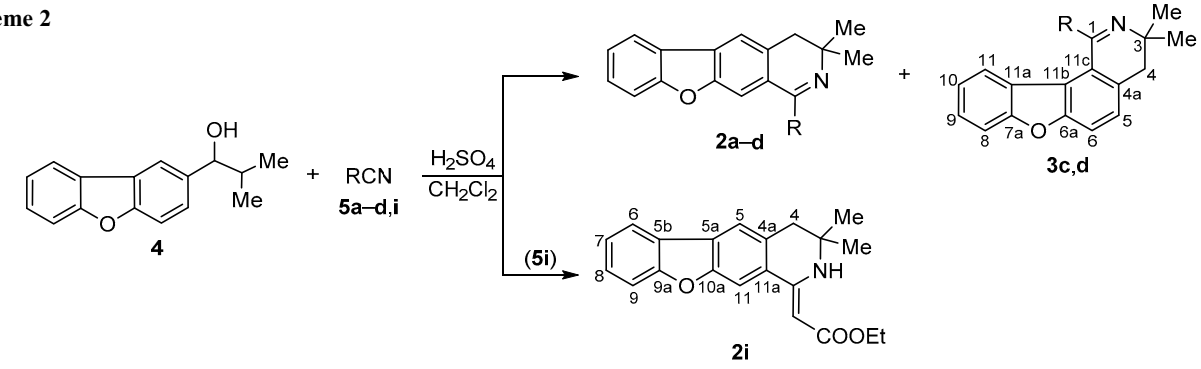
We have previously shown that the condensation of arenes containing electron-donating substituents at an *ortho* position with α-branched aldehydes and nitriles in concentrated sulfuric acid gave 3,4-dihydroisoquinoline derivatives.[6–13]

In the current work, we studied the possibility of preparing 1-R-3,3-dimethyl- and 1-R-3,3,4,4-tetramethyl-3,4-dihydrobenzofuroisoquinolines as heterocyclic systems with two different heteroatoms in separate rings, starting from dibenzofuran under the Ritter reaction condition. The reaction could be assumed to follow a similar mechanism as the reactions of structurally related compounds, anisole,[14] *ortho*-substituted anisoles,[15,16] and 2,6-dialkylphenols[17] with α-branched aldehydes and nitriles. This mechanism would have resulted in derivatives of 2-azaspiro[4.5]deca-1,6,9-trien-8-ones **1** (Scheme 1). The interaction of dibenzofuran, isobutyraldehyde, and methylthiocyanate in concentrated sulfuric acid medium was found to produce trace amounts of the regioisomeric 3,3-dimethyl-3,4-dihydrobenzofuroisoquinolines **2a** and **3a** (as a 7:1 mixture according to GC-MS analysis of the

Scheme 1



Scheme 2



a R = SMe, **b** R = Me, **c** R = 2-Py, **d** R = 2-$H_2NC_6H_4$, **i** R = CH_2COOEt

reaction mixture). Increasing the reaction duration from 1 to 4 h did not significantly change the yield of compounds **2a** and **3a**, and products of type **1** were not detected.

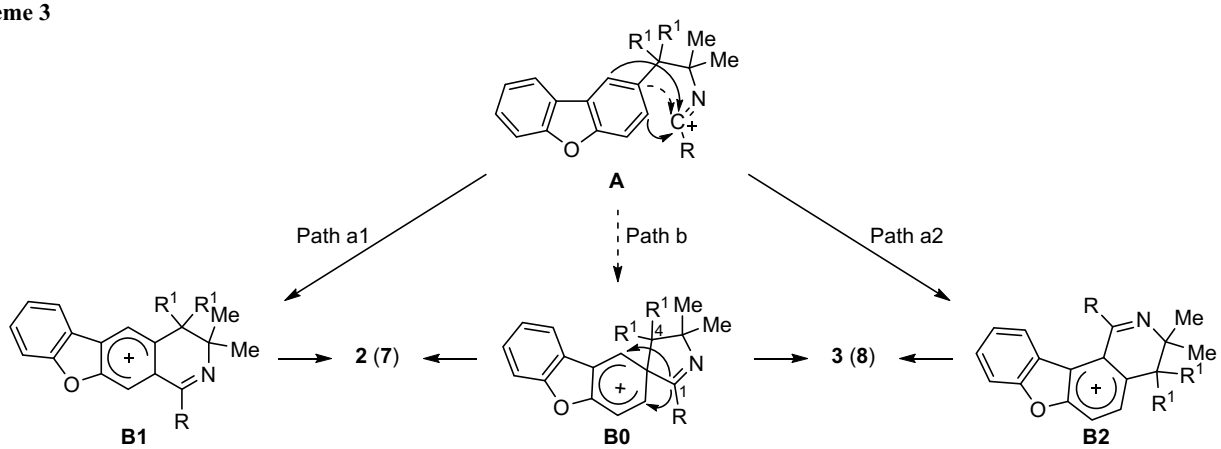
In order to increase the yields of 3,3-dimethyl-3,4-dihydrobenzofuroisoquinolines **2** and **3**, a linear synthesis was performed starting from 1-(dibenzo[*b*,*d*]furan-2-yl)-2-methylpropan-1-ol (**4**) and nitriles **5a**–**d**,**i** in concentrated sulfuric acid (Scheme 2). Procedures have been described in the literature for the preparation of benzofuro-[2,3-*g*]isoquinolines,[18–20] benzofuro[2,3-*h*]isoquinolines,[21] and benzofuro[3,2-*g*]isoquinolines,[22–24] while no examples were found for the synthesis of 3,4-dihydrobenzofuro[3,2-*g*]- and [2,3-*h*]isoquinolines.

The reaction products were formed in 31–80% total yield and were purified by crystallization (**2b**,**i**) or separated by column chromatography. The ratio of isomers **2** and **3** depended on the properties of nitrile: for aliphatic nitriles, regioselective formation of compounds of type **2** was observed, but aromatic nitriles gave a mixture of regioisomers **2** and **3** in 1:0 to 1:2 ratio. The structure of compounds **2a**–**d**,**i** and **3c**,**d** was established from IR, ^{1}H and ^{13}C NMR, mass spectrometry, and elemental analysis data. The structure of compounds **2i** and **3c** was additionally confirmed by COSY, HSQC, and HMBC 2D NMR experiments, that enabled a complete assignment of all ^{1}H and ^{13}C NMR signals. ^{1}H NMR spectra of compounds **2a**–**d**,**i** and **3c** contained a singlet due to the CH_3 group at the C-3 atom and a singlet of the 4-CH_2 group. ^{1}H NMR spectrum of compound **3d** contained two 3-CH_3 singlets at 0.93 and 1.50 ppm, while the 4-CH_2 protons gave two doublets at 2.66 and 2.88 ppm with the geminal spin-spin coupling constant of 15.0 Hz. The aromatic H-6 proton signal in ^{1}H NMR spectra of the linear molecules **2a**–**d**,**i** was observed in the downfield region of 7.74–7.92 ppm (the numbering of atoms is presented in Scheme 2). The analogous H-11 proton in the spectra of angular molecules **3c**,**d** was observed at an upfield position (5.84 and 6.29 ppm, respectively), indicating the proximity of aromatic ring of the substituent at position 1 to the H-11 proton in benzofuran system, and confirming the proposed structure of 3,4-dihydrobenzofuro[2,3-*h*]isoquinolines **3c**,**d**.

The proposed reaction mechanism involves the formation of carbimmonium ion **A**[6] and an attack by its electrophilic center at one of the *ortho* positions (paths a1, a2), or an *ipso* attack with the formation of the spiro-σ-complex **B0** (path b), followed by 1,2-sigmatropic shift at the C(1)–arene bond,[25] which also can proceed in two directions (Scheme 3).

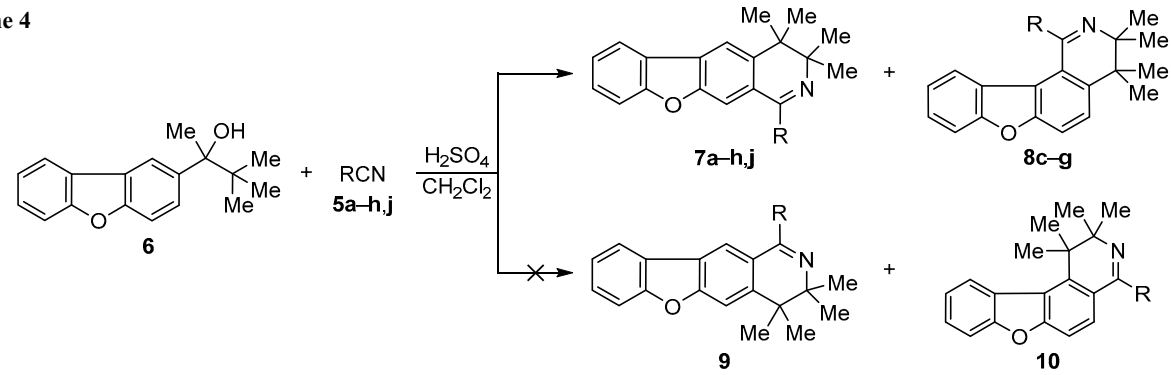
Shklyaev with coworkers[25] have shown that the molecule of 2-(4-methoxyphenyl)-3,3-dimethylbutan-2-ol containing four adjacent methyl groups reacted with nitriles, forming 1-R-6-methoxy-3,3,4,4-tetramethyl-3,4-dihydroisoquinolines, i.e., the mutual arrangement of methoxy group and alkyl chain in the ring had changed, likely due to the reaction occurring analogously to path b, followed by a sigmatropic shift at the C(4)–arene bond. We attempted to

Scheme 3



2, **3** R^1 = H; **7**, **8** R^1 = Me

Scheme 4



a R = SMe, **b** R = Me, **c** R = 2-Py, **d** R = 2-$H_2NC_6H_4$, **e** R = Ph, **f** R = 2-$MeOC_6H_4$, **g** R = 2-BrC_6H_4, **h** R = $CH_2CH(Me)_2$, **j** R = CH_2COOMe

change the regioselectivity of heterocyclization reaction also in the case of dibenzofuran by introducing additional methyl groups in the carbinol. We established that the reaction of 2-(dibenzo[*b,d*]furan-2-yl)-3,3-dimethylbutan-2-ol (**6**) with nitriles **5a**–**h**,**j** in concentrated sulfuric acid gave a mixture of regioisomers **7** and **8** (Scheme 4), while compounds of types **9** and **10** were not detected. Therefore, we consider it more likely that the reaction occurs by paths a1, a2. This was confirmed by semiempirical modeling of the reaction pathway by the PM3 method. According to calculations, the intermediates **B1** and **B2** were more stable by 2–5 kcal/mol compared to **B0**.

The mixtures of regioisomers **7** and **8** formed with the total yields of 33–68% were separated by column chromatography (the ratio of isomers **7** and **8** was from 1:0 to 1:10 and depended on the character of nitriles in a similar way as in the case of compounds **2** and **3**). The structure of compounds **7a**–**h**,**j** and **8c**–**g** was established from IR, ^{1}H and ^{13}C NMR, mass spectroscopy, and elemental analysis data. The structure of compounds **7e**,**f** and **8c** (Figs. 1–3) was proved by X-ray structural analysis.

The molecules presented in Figures 1–3 were chiral due to the non-planar half-chair conformation of dihydropyridine ring and the orientation of substituent at position 1 out of the dibenzofuran ring plane. As indicated by the considered computational models, all compounds **8** in this regard are similar to compound **8c**, while compounds **7** are similar to compounds **7e**,**f**. The crystals of these compounds belonged to centrosymmetric space groups. The lack of molecular symmetry elements and the apparently high energy barriers to the inversion of

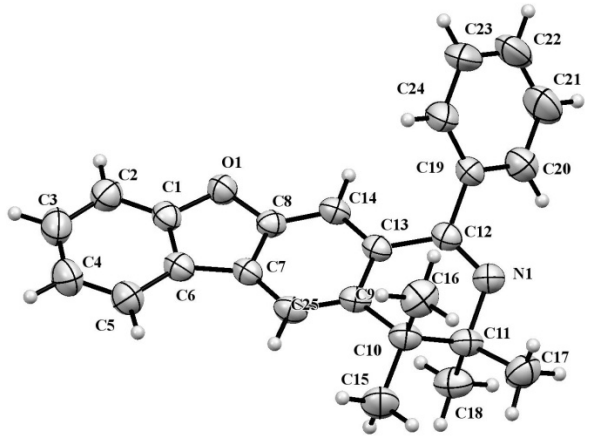


Figure 1. Structure of compound **7e** with atoms represented by thermal vibration ellipsoids of 50% probability.

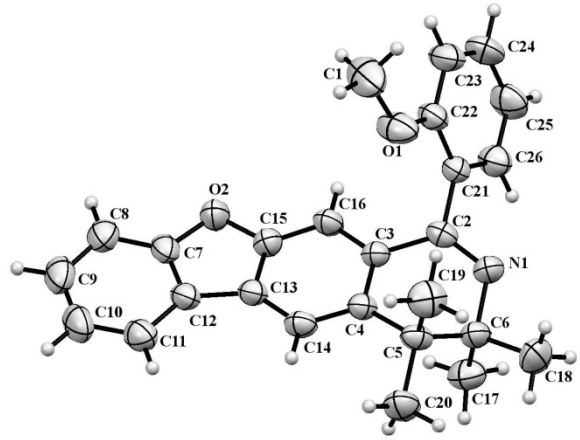


Figure 2. Structure of compound **7f** with atoms represented by thermal vibration ellipsoids of 50% probability.

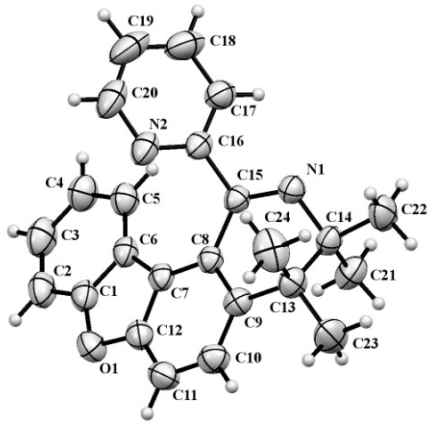


Figure 3. Structure of compound **8c** with atoms represented by thermal vibration ellipsoids of 50% probability.

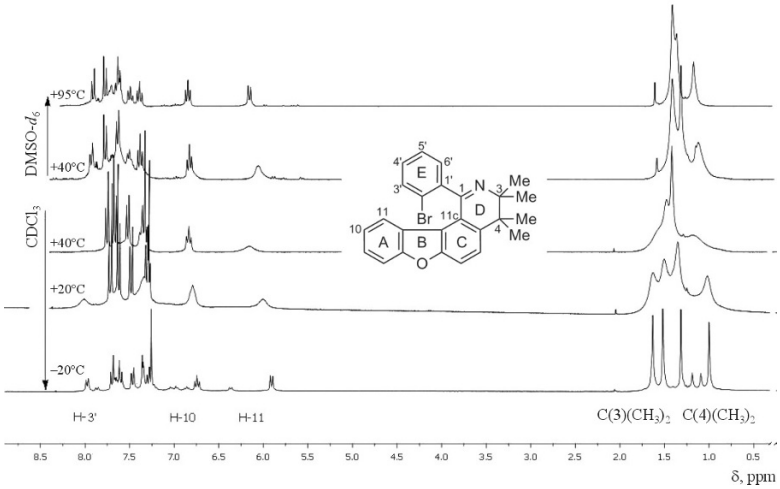


Figure 4. ^{1}H NMR signal evolution for compound **8g** over the temperature range from –20 to +95°C.

dihydropyridine ring, as discussed below, point to cocrystallization of two enantiomeric forms, i.e., the crystals of compounds **7e**,**f** and **8c** are racemates.

The angular molecules of compounds **8c**–**g**, similarly to compound **3c**, gave ^{1}H NMR spectra with H-11 and H-10 proton signals shifted upfield (5.89–6.75 ppm), that we explained by shielding of these atoms by the aromatic ring E (Fig. 4), confirmed by X-ray structural analysis data for compound **8c**. Thus, the measured distance between the center of pyridine ring and the H-11 atom (in the structural experiment this proton was located at the C(5) atom, Fig. 3) was 2.75 Å, comparable to the length of hydrogen bonds. It is entirely possible that a proton at such distance interacts with the π-electron system of aromatic ring.

^{1}H NMR spectra of compounds **7c**–**h**,**j** and **8c**,**e**–**g** acquired at room temperature showed a significant broadening of signals from four methyl groups C(3)(CH$_3$)$_2$ and C(4)(CH$_3$)$_2$, while the spectra of compounds **8f**,**g** also featured broadening of H-11, H-10, and H-3' signals (atom numbering is given in Fig. 4). This can be attributed to the D ring inversion (half-chair – half-chair inversion), accompanied by oscillations of substituent at position 1. This inversion is not degenerate in the case of compounds **7d**,**f**, **8f**,**g** with substituted aryl groups and compounds **7c**, **8c** with pyridyl groups. The inversion energy barriers for compounds **7**, **8** were established as the energy differences between conformers and the transition states, and according to semiempirical PM3 calculations were found to be 6–7 kcal/mol for compounds **7** and 9–10 kcal/mol for compounds **8**. Analogous calculations for 3,3-dimethyl derivatives gave much lower values: 1–2 kcal/mol for compounds **2** and 3–4 kcal/mol for compounds **3**. The three times higher energy barrier, in our opinion, explains the qualitative difference between the narrow signals of dimethyl derivatives and the broadened signals of tetramethyl derivatives: the rate of conformational change at room temperature, as reflected by dynamic NMR data, corresponds to fast exchange rate in the first case and moderate exchange rate in the second case.

The example of compounds **7d**–**g** was used to study the temperature dependence of ^{1}H NMR spectra for the linear molecules **7**. The evolution of upfield part in ^{1}H NMR

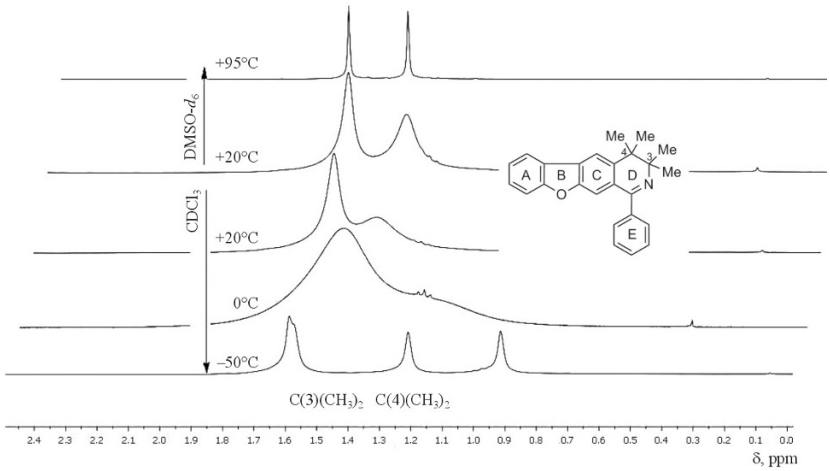


Figure 5. ^{1}H NMR signal evolution for compound **7e** over the temperature range from –50 to +95°C.

spectrum of compound **7e** is shown in Figure 5. The axial and equatorial methyl groups were observed at –50°C as four slightly broadened singlets, and the signals of vicinal groups were closer together. The equatorial and axial signals merged at around 0°C, and the narrow singlets at 95°C corresponded to geminal methyl groups. The coalescence of signals for compounds **7f**,**g** was observed at higher temperatures (30–40°C), pointing to slower inversion.

The temperature evolution of ^{1}H NMR spectra for the angular compounds **8** was studied in the case of compounds **8c**,**d**,**g**. Compound **8d** was different than the rest of the series, because its methyl groups gave four narrow signals at room temperature, instead of only below 0°C. The slower inversion was likely associated with the existence of a hydrogen bond between the ring nitrogen atom and the *ortho*-amino group. A noticeable signal broadening occurred only above 40°C, but coalescence – at approximately 100°C. For compounds **8c**,**g**, coalescence was observed at approximately 50°C.

The changes in ^{1}H NMR spectrum of compound **8g** are shown in Figure 4. The broadened signals of H-11, H-3', and H-10 protons observed in the downfield region of spectrum at +20°C were transformed at +95°C into two doublets and a triplet, respectively. The four broadened methyl group signals did not fully evolve into two broadened singlets over the same temperature interval. When the temperature was decreased to –20°C, a weaker secondary series of signals was clearly observed due to another conformer (integrated intensity ratio ~10:3), that can also be considered as rotational isomer with the opposite position of bromine atom (see the Supplementary information file).

The possibility of aryl group rotation around the C(1)–C(1') bond at position 1 of the angular molecules **8d**–**g** must be rejected, since semiempirical PM3 calculations involving variation of the torsion angle C(11c)–C(1)–C(1')–C(2') showed more than 240 kcal/mol energy disadvantage of the eclipsed conformer (at approximately 180° angle), compared to the preferred conformer (at approximately 90° angle), when rotating through the less hindered side. This energy barrier was substantial also for compounds **7d**–**g** and **8c**, reaching 32–49 kcal/mol, but for compound **7c** it was only 5 kcal/mol, which was already comparable to the calculated energy barrier to inversion. Crystals of the linear compound **7f** and angular compound **8c** lacked rotational isomers according to X-ray structural analysis: the substituents apparently occupied only one, energetically favored position (Figs. 2 and 3).

We have thus shown that the interaction of 1-(dibenzo[*b,d*]furan-2-yl)-2-methylpropan-1-ol or 2-(dibenzo[*b,d*]furan-2-yl)-3,3-dimethylbutan-2-ol with aliphatic nitriles under the Ritter reaction conditions occurred regioselectively, forming 1-substituted 3,3-di- and 3,3,4,4-tetramethyl-3,4-dihydrobenzofuro[3,2-*g*]isoquinolines, while reactions with aromatic nitriles gave a mixture of the respective 3,3-di- and 3,3,4,4-tetramethyl-3,4-dihydrobenzofuro[3,2-*g*]- and [2,3-*h*]isoquinolines. The presence of four instead of two methyl groups in the annulated dihydropyridine ring slowed its inversion (half-chair – half-chair transition), observed as a broadening of certain ^{1}H NMR signals.

Experimental

IR spectra were recorded for thin films on a Bruker IFS-66/S FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury plus 300 instrument (300 and 75 MHz, respectively) in $CDCl_3$, with HMDS as internal standard (0.055 ppm). Dynamic ^{1}H NMR experiments were performed on a Varian Mercury plus 300 instrument (300 MHz) in $CDCl_3$ (from –50 to +40°C) and in DMSO-d_6 (20–95°C). Two-dimensional NMR experiments (^{1}H–^{13}C HSQC, ^{1}H–^{13}C HMBC, and ^{1}H–^{1}H COSY) for compounds **3c** and **2i** were performed on a Bruker Avance III HD spectrometer (400 MHz). Mass spectra and chromatograms were recorded on an Agilent Technologies 6890N/5975B GC-MS instrument (HP-5ms column, 30 m × 0.25 mm, 0.25 μm, carrier gas – helium, EI ionization, 70 eV). The analysis of compounds **2i** and **7j** revealed decarbethoxylation products, formed by thermal decomposition of compounds in the evaporator, which were identical chromatographically and by mass spectra to compounds **2b** and **7b**, respectively. Elemental analysis was performed on a Leco CHNS-932 analyzer. Melting points were determined on a Stuart SMP40 apparatus. The reaction progress and purity of the obtained compounds were controlled by TLC on Sorbfil plates (UV-254), visualization under UV light and by 0.5% solution of *para*-chloranil in toluene. Silica gel from Alfa Aesar (0.06–0.20 mm) was used for column chromatography. Computational modeling of molecules was performed with the HyperChem 7.01 (trial version) software. The transition states between the inversed forms were identified by the synchronous transit method.

1-(Dibenzo[*b,d*]furan-2-yl)-2-methylpropan-1-one. Isobutyryl chloride (11 ml, 105 mmol) was added to a stirred suspension of $AlCl_3$ (16.0 g, 120 mmol) in dichloroethane (40 ml), while cooling in ice bath. A solution of dibenzofuran (16.8 g, 100 mmol) in dichloroethane (40 ml) was then added, while maintaining at 20°C. The mixture was stirred for 1 h, left overnight at room temperature, and then carefully poured on crushed ice (60 g). The quenched mixture was treated with concd. HCl (4 ml) and the layers were separated. The aqueous layer was extracted with dichloroethane. The organic layer and extracts were washed with water, then with 2% NaOH solution (25 ml) and again with water, and dried over anhydrous Na_2SO_4. Dichloroethane was removed by distillation.[26a] The product was purified by distillation at 248–249°C (18 mmHg). Yield 17.5 g (73%), white precipitate, mp 55–57°C (MeOH) (mp 57°C[27]). IR spectrum, ν, cm^{-1}: 3063, 2971, 1678, 1591, 1198. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.27 (6H, d, *J* = 6.6, $2CH_3$); 3.67 (1H, sept, *J* = 6.6, CH); 7.37 (1H, td, *J* = 7.8, *J* = 1.2, H Ar); 7.48 (1H, td, *J* = 7.8, *J* = 1.2, H Ar); 7.58 (1H, dd, *J* = 7.8, *J* = 1.2, H Ar); 7.59 (1H, d, *J* = 9.0, H Ar); 7.99 (1H, dd, *J* = 7.8, *J* = 1.2, H Ar); 8.10 (1H, dd, *J* = 9.0, *J* = 1.8, H Ar); 8.58 (1H, d, *J* = 1.8, H Ar). ^{13}C NMR spectrum, δ, ppm: 19.2; 35.2; 111.3; 111.6; 120.7; 121.3; 123.1; 123.5; 124.3; 127.6; 127.7; 131.1; 156.5; 158.4; 203.3. Mass spectrum, *m*/*z* (I_{rel}, %): 238 $[M]^+$ (19), 195 $[M–C_3H_7]^+$ (100), 167 $[M–COC_3H_7]^+$

(23), 139 (34). Found, %: C 80.39; H 5.82. $C_{16}H_{14}O_2$. Calculated, %: C 80.65; H 5.92.

1-(Dibenzo[*b,d*]furan-2-yl)-2-methylpropan-1-ol (4). A solution of 1-(dibenzo[*b,d*]furan-2-yl)-2-methylpropan-1-one (19.0 g, 80 mmol) in EtOH (100 ml) was added to a stirred and cooled suspension of $NaBH_4$ (3.0 g, 80 mmol) in EtOH (40 ml). The mixture was stirred for 2 h at 30°C, then for 1 h at 20–25°C. Ethanol was removed by distillation, then 10% aqueous NaOH solution (30 ml) was added. The mixture was extracted with Et_2O and dried over anhydrous Na_2SO_4. Et_2O was removed by distillation. Yield 13.1 g (68%), white precipitate, mp 64–66°C (hexane). IR spectrum, ν, cm^{-1}: 3405, 3054, 2961, 2874, 1595, 1474, 1196. ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.81 (3H, d, *J* = 6.6, CH_3); 1.46 (3H, d, *J* = 6.6, CH_3); 1.95 (1H, br. s, OH); 1.98–2.09 (1H, m, $(CH_3)C\underline{H}$); 4.51 (1H, d, *J* = 7.2, $C\underline{H}OH$); 7.24–7.57 (4H, m, H Ar); 7.90–7.95 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 18.3; 19.0; 35.5; 80.0; 111.0; 111.5; 118.4; 120.5; 122.5; 124.0; 124.1; 125.7; 127.0; 138.3; 155.5; 156.4. Mass spectrum, *m*/*z* (I_{rel}, %): 240 $[M]^+$ (12), 197 $[M–C_3H_7]^+$ (100), 169 (79), 141 (16), 139 (19), 115 (11). Found, %: C 79.68; H 6.68. $C_{16}H_{16}O_2$. Calculated, %: C 79.97; H 6.71.

1-(Dibenzo[*b,d*]furan-2-yl)-2,2-dimethylpropan-1-one. Trimethylacetyl chloride (12.5 ml, 105 mmol) was added to a stirred suspension of $AlCl_3$ (16.0 g, 120 mmol) and dibenzofuran (16.8 g, 100 mmol) in dichloroethane (60 ml), while cooling with ice water. The further procedure followed the synthesis of 1-(dibenzo[*b,d*]furan-2-yl)-2-methylpropan-1-one. The product was purified by distillation at 192–193°C (5 mmHg). Yield 15.3 g (61%), white crystals, mp 60.5–61.0°C (hexane). IR spectrum, ν, cm^{-1}: 3064, 2972, 1673, 1593, 1469. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.43 (9H, s, $3CH_3$); 7.37 (1H, td, *J* = 7.5, *J* = 1.2, H Ar); 7.49 (1H, td, *J* = 7.5, *J* = 1.2, H Ar); 7.56 (1H, d, *J* = 8.4, H Ar); 7.58 (1H, d, *J* = 8.4, H Ar); 7.91 (1H, dd, *J* = 8.7, *J* = 1.8, H Ar); 7.98 (1H, dd, *J* = 7.5, *J* = 0.9, H Ar); 8.38 (1H, d, *J* = 1.8, H Ar). ^{13}C NMR spectrum, δ, ppm: 28.2; 28.4; 44.1; 111.0; 111.8; 120.8; 121.4; 123.1; 123.8; 124.0; 127.7; 128.1; 133.1; 156.7; 157.4; 207.7. Mass spectrum, *m*/*z* (I_{rel}, %): 252 $[M]^+$ (5), 195 $[M–C_4H_9]^+$ (100), 167 $[M–COC_4H_9]^+$ (15), 139 (29). Found, %: C 80.65; H 6.70. $C_{17}H_{16}O_2$. Calculated, %: C 80.93; H 6.39.

2-(Dibenzo[*b,d*]furan-2-yl)-3,3-dimethylbutan-2-ol (6). A solution of MeI (5.2 ml, 84 mmol) in Et_2O (20 ml) was added dropwise to a cooled suspension of Mg (1.75 g, 72 mmol) in Et_2O (10 ml). The mixture was then heated on a water bath for 30 min, stirred, and treated by dropwise addition of 1-(dibenzo[*b,d*]furan-2-yl)-2,2-dimethylpropan-1-one (15.0 g, 60 mmol) in Et_2O (20 ml). After the addition was complete, the mixture was heated on a water bath for additional 2 h and left overnight. Crushed ice (7 g) was added and the quenched mixture was washed with 30% aqueous NH_4Cl solution. The ether layer was separated, while the aqueous layer was extracted with Et_2O (3×20 ml). The combined ether layers were washed with water and dried over anhydrous Na_2SO_4. Ether was evaporated,[26b] and the residue was purified by distillation at 203°C (5 mmHg). Yield 11.2 g (70%), white crystals, mp 82–83°C (hexane). IR spectrum, ν, cm^{-1}: 3574, 3480, 3057, 2969, 1594, 1470. ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.95 (9H, s, $3CH_3$); 1.67 (3H, s, CH_3); 1.76 (1H, s, OH); 7.29 (1H, td, *J* = 7.5, *J* = 1.2, H Ar); 7.36–7.44 (2H, m, H Ar); 7.51 (2H, t, *J* = 7.5, H Ar); 7.92 (1H, d, *J* = 7.5, H Ar); 8.02 (1H, d, *J* = 1.2, H Ar). ^{13}C NMR spectrum, δ, ppm: 25.7; 25.8; 38.1; 78.7; 109.8; 111.6; 119.1; 120.5; 122.5; 123.1; 124.5; 126.5; 126.9; 140.8; 154.9; 156.5. Mass spectrum, *m*/*z* (I_{rel}, %): 268 $[M]^+$ (0.3), 211 $[M–C_4H_9]^+$ (68), 193 $[M–H_2O–C_4H_9]^+$ (15). Found, %: C 80.34; H 7.54. $C_{18}H_{20}O_2$. Calculated, %: C 80.56; H 7.51.

Reaction of 1-(dibenzo[*b,d*]furan-2-yl)-2-methylpropan-1-ol (4) or 2-(dibenzo[*b,d*]furan-2-yl)-3,3-dimethylbutan-2-ol (6) with nitriles 5a–j (General method). A mixture of nitrile **5a–j** (2.0 mmol) and compound **4** or **6** (2.0 mmol) in CH_2Cl_2 (1 ml) was added dropwise to stirred, cooled (5–10°C) 93% H_2SO_4 (1 ml). The reaction mixture was stirred for 1 h at 20–25°C, then poured on crushed ice (15–20 g) that was mixed with aqueous ammonia (6 ml). The mixture was extracted with CH_2Cl_2 (3×10 ml), the combined extracts were washed with H_2O and dried over anhydrous Na_2SO_4. The solvent was removed by distillation, and the residue was crystallized or separated by chromatography.

3,3-Dimethyl-1-methylsulfanyl-3,4-dihydrobenzofuro[3,2-*g*]isoquinoline (2a) was obtained from compounds **4** and **5a**. Purification by crystallization. Yield 340 mg (57%), light-yellow crystalline powder, mp 130–132°C (EtOH). IR spectrum, ν, cm^{-1}: 1660, 1596, 1566, 1514. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.22 (6H, s, 3-$(CH_3)_2$); 2.46 (3H, s, SCH_3); 2.83 (2H, s, 4-CH_2); 7.31 (1H, t, *J* = 7.5, H Ar); 7.45 (1H, t, *J* = 7.8, H Ar); 7.54 (1H, d, *J* = 8.1, H Ar); 7.66 (1H, s, H-5); 7.87 (1H, s, H-11); 7.89 (1H, d, *J* = 7.8, H-6). ^{13}C NMR spectrum, δ, ppm: 12.4; 28.2; 39.6; 56.1; 108.0; 111.7; 119.5; 120.8; 122.7; 123.4; 125.9; 127.2; 127.6; 130.6; 154.7; 157.0; 160.0. Mass spectrum, *m*/*z* (I_{rel}, %): 295 $[M]^+$ (38), 294 $[M–H]^+$ (23), 280 $[M–CH_3]^+$ (100), 206 (31). Found, %: C 73.26; H 5.86; N 4.41; S 10.61. $C_{18}H_{17}NOS$. Calculated, %: C 73.19; H 5.80; N 4.74; S 10.85.

1,3,3-Trimethyl-3,4-dihydrobenzofuro[3,2-*g*]isoquinoline (2b) was obtained from compounds **4** and **5b** and purified by chromatography (eluent 15:1 CH_2Cl_2–acetone). Yield 160 mg (31%), light-yellow crystalline powder, mp 105–107°C (EtOAc–hexane). R_f 0.25 (CH_2Cl_2–acetone, 10:1). IR spectrum, ν, cm^{-1}: 2963, 2923, 1623, 1570, 1454. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.23 (6H, s, 3-$(CH_3)_2$); 2.46 (3H, s, 1-CH_3); 2.83 (2H, s, 4-CH_2); 7.34 (1H, td, *J* = 7.5, *J* = 0.9, H Ar); 7.47 (1H, td, *J* = 7.8, *J* = 0.9, H Ar); 7.57 (1H, d, *J* = 8.7, H Ar); 7.68 (2H, s, H-5,11); 7.93 (1H, d, *J* = 7.5, H-6). ^{13}C NMR spectrum, δ, ppm: 23.6; 27.9; 39.3; 54.1; 108.7; 111.8; 119.7; 120.9; 122.9; 123.6; 127.6; 127.7; 131.1; 155.1; 157.1. Mass spectrum, *m*/*z* (I_{rel}, %): 263 $[M]^+$ (100), 262 $[M–H]^+$ (20), 248 $[M–CH_3]^+$ (85), 222 $[M–C_3H_5]^+$ (13), 221 $[M–C_3H_6]^+$ (72), 220 (29), 207 $[M–C_4H_8]^+$ (15), 206 (16), 205 (28). Found, %: C 82.11; H 6.75; N 5.00. $C_{18}H_{17}NO$. Calculated, %: C 82.10; H 6.51; N 5.32.

3,3-Dimethyl-1-(pyridin-2-yl)-3,4-dihydrobenzofuro-[3,2-*g*]isoquinoline (2c) and **3,3-dimethyl-1-(pyridin-2-yl)-3,4-dihydrobenzofuro[2,3-*h*]isoquinoline (3c)** were obtained from compounds **4** and **5c**. The mixture was separated by column chromatography (eluent 20:1 CH_2Cl_2–acetone).

Compound 2c. Yield 160 mg (25%), white crystalline powder, mp 109–111°C (EtOAc–hexane). R_f 0.23 (10:1 CH_2Cl_2–acetone). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.28 (6H, s, 3-$(CH_3)_2$); 2.92 (2H, s, 4-CH_2); 7.24–7.33 (2H, m, H Ar); 7.39 (1H, td, *J* = 7.7, *J* = 1.2, H Ar); 7.46 (1H, d, *J* = 7.8, H Ar); 7.51 (1H, s, H-5); 7.69 (1H, s, H-11); 7.74–7.81 (2H, m, H Ar); 7.88 (1H, d, *J* = 7.5, H Ar); 8.62 (1H, d, *J* = 4.8, H Py). ^{13}C NMR spectrum, δ, ppm: 27.4; 39.2; 55.2; 111.7 (2C); 119.7; 120.9; 122.7; 123.7 (2C); 124.0; 126.0 (2C); 127.7; 132.1; 137.0; 148.5; 154.7; 157.1; 157.5; 162.8. Mass spectrum, *m*/*z* (I_{rel}, %): 326 $[M]^+$ (32), 311 $[M–CH_3]^+$ (100), 270 $[M–C_4H_8]^+$ (39). Found, %: C 80.75; H 5.49; N 8.46. $C_{22}H_{18}N_2O$. Calculated, %: C 80.96; H 5.56; N 8.58.

Compound 3c. Yield 360 mg (55%), white crystalline powder, mp 138–140°C (EtOH). R_f 0.40 (10:1 CH_2Cl_2–acetone). IR spectrum, ν, cm^{-1}: 1585, 1564, 1464. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.37 (6H, s, 3-$(CH_3)_2$); 2.94 (2H, s, 4-CH_2); 5.84 (1H, d, *J* = 7.8, H-11); 6.79 (1H, td, *J* = 7.7, *J* = 1.2, H-10); 7.28 (1H, td, *J* = 7.8, *J* = 1.2, H-9); 7.32–7.40 (2H, m, H-5, H-5 Py); 7.49 (1H, d, *J* = 8.1, H-8); 7.65 (1H, d, *J* = 8.4, H-6); 7.86 (1H, td, *J* = 7.8, *J* = 1.8, H-4 Py); 8.00 (1H, d, *J* = 7.5, H-3 Py); 8.49 (1H, d, *J* = 4.2, H-6 Py). ^{13}C NMR spectrum, δ, ppm: 26.6 (CH_3); 39.4 (4-CH_2); 54.4 (C-3); 110.8 (C-8); 113.6 (C-6); 121.0 (C-11a(C-11b)); 121.5 (C-10); 122.3 (C-11b (C-11a)); 123.1 (C-3 Py); 123.3 (C-11); 123.6 (C-5 Py); 126.3 (C-9); 126.8 (C-5); 133.1 (C-4a,11c); 136.8 (C-4 Py); 149.1 (C-6 Py); 155.4 (C-6a); 156.2 (C-7a); 158.3 (C-2 Py); 162.7 (C-1). Mass spectrum, *m*/*z* (I_{rel}, %): 326 $[M]^+$ (36), 311 $[M–CH_3]^+$ (100), 270 $[M–C_4H_8]^+$ (44). Found, %: C 80.69; H 5.58; N 8.51. $C_{22}H_{18}N_2O$. Calculated, %: C 80.96; H 5.56; N 8.58.

2-(3,3-Dimethyl-3,4-dihydrobenzofuro[3,2-*g*]isoquinolin-1-yl)aniline (2d) and **2-(3,3-dimethyl-3,4-dihydrobenzofuro[2,3-*h*]isoquinolin-1-yl)aniline (3d)** were obtained from compounds **4** and **5d**. The mixture was separated by column chromatography (eluent 6:1 hexane–EtOAc).

Compound 2d. Yield 270 mg (40%), light-yellow crystals, mp 127.5–128.5°C (2-PrOH). R_f 0.20 (6:1 hexane–EtOAc). IR spectrum, ν, cm^{-1}: 3456, 3329, 2965, 2928, 1612, 1554, 1491. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.27 (6H, s, 3-$(CH_3)_2$); 2.87 (2H, s, 4-CH_2); 4.92 (2H, br. s, NH_2); 6.67–6.74 (2H, m, H Ar); 7.11–7.19 (2H, m, H Ar); 7.28 (1H, t, *J* = 7.5, H Ar); 7.37–7.48 (2H, m, H Ar); 7.42 (1H, s, H-5); 7.68 (1H, s, H-11); 7.89 (1H, d, *J* = 7.8, H Ar). ^{13}C NMR spectrum, δ, ppm: 27.8; 39.1; 54.9; 99.9; 111.8; 116.9; 117.1; 119.7; 120.9; 121.7; 122.8; 123.5; 126.0; 127.1; 127.8; 129.8; 130.8; 132.2; 146.6; 154.7; 157.1; 164.4. Mass spectrum, *m*/*z* (I_{rel}, %): 340 $[M]^+$ (30), 339 $[M–H]^+$ (100), 323 $[M–NH_3]^+$ (8). Found, %: C 80.88; H 5.91; N 8.17. $C_{23}H_{20}N_2O$. Calculated, %: C 81.15; H 5.92; N 8.23.

Compound 3d. Yield 160 mg (23%), light-yellow crystalline powder, mp 179–181°C (2-PrOH). R_f 0.45 (6:1 hexane–EtOAc). IR spectrum, ν, cm^{-1}: 3456, 3321, 2967, 2928, 1611, 1583, 1552, 1491. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.93 (3H, s) and 1.50 (3H, s, 3-$(CH_3)_2$); 2.66 (1H, d, *J* = 15.0) and 2.88 (1H, d, *J* = 15.0, 4-CH_2); 5.53 (2H, br. s, NH_2); 6.29–6.34 (2H, m, H Ar); 6.74–6.79 (2H, m, H Ar); 6.88 (1H, d, *J* = 6.9, H Ar); 7.03 (1H, t, *J* = 6.9, H Ar); 7.16–7.24 (2H, m, H Ar); 7.36 (1H, d, *J* = 8.7, H Ar); 7.53 (1H, d, *J* = 7.8, H Ar). ^{13}C NMR spectrum, δ, ppm: 23.2; 31.5; 40.0; 54.4; 100.0; 110.9; 113.7; 117.1; 117.8; 121.6; 122.1; 123.1; 125.6; 127.0; 127.1; 130.2; 130.9; 133.7; 155.8; 156.5; 164.4. Mass spectrum, *m*/*z* (I_{rel}, %): 340 $[M]^+$ (100), 339 $[M–H]^+$ (73), 325 $[M–CH_3]^+$ (64), 324 $[M–NH_2]^+$ (33), 323 $[M–NH_3]^+$ (15), 284 $[M–C_4H_8]^+$ (30), 283 (42). Found, %: C 80.87; H 5.75; N 8.02. $C_{23}H_{20}N_2O$. Calculated, %: C 81.15; H 5.92; N 8.23.

Ethyl (3,3-dimethyl-3,4-dihydrobenzofuro[3,2-*g*]isoquinolin-1(2*H*)-ylidene)acetate (2i) was obtained from compounds **4** and **5i**. Purification by crystallization. Yield 360 mg (53%), light-yellow crystalline powder, mp 163–164°C (EtOH). IR spectrum, ν, cm^{-1}: 3265, 2964, 1645, 1602, 1566, 1175. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz) (the atom numbering is given in Scheme 2): 1.32 (6H, s, 3-$(CH_3)_2$); 1.37 (3H, t, *J* = 6.9, $OCH_2C\underline{H}_3$); 2.97 (2H, s, 4-CH_2); 4.22 (2H, q, *J* = 6.9, $OC\underline{H}_2CH_3$); 5.25 (1H, s, =C<u>H</u>CO_2Et); 7.34 (1H, td, *J* = 7.8, *J* = 0.9, H-7); 7.49 (1H, td, *J* = 7.8, *J* = 0.9, H-8); 7.57 (1H, d, *J* = 7.8, H-9); 7.68 (1H, s, H-5); 7.88 (1H, s, H-11); 7.92 (1H, d, *J* = 7.8, H-6); 9.12 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 14.6 ($OCH_2\underline{C}H_3$); 28.4 (CH_3); 42.7 (4-CH_2); 49.0 (C-3); 58.8 ($O\underline{C}H_2CH_3$); 78.2 (=<u>C</u>HCO_2Et); 108.3 (C-11); 112.0 (C-9); 120.4 (C-5); 120.9 (C-6); 122.4 (C-7); 123.0 (C-5a); 125.8 (C-4a); 127.4 (C-5b); 127.5 (C-8); 129.6 (C-11a); 154.7 (C-1(C-10a)); 155.0 (C-1(C-10a)); 156.7 (C-9a); 170.8 (C=O). Found, %: C 74.93; H 6.27; N 4.09. $C_{21}H_{21}NO_3$. Calculated, %: C 75.20; H 6.31; N 4.18.

3,3,4,4-Tetramethyl-1-(methylsulfanyl)-3,4-dihydrobenzofuro[3,2-*g*]isoquinoline (7a) was obtained from compounds **6** and **5a**. Purification by crystallization. Yield 370 mg (57%), white crystals, mp 77–78°C (EtOH). IR spectrum, ν, cm^{-1}: 3060, 2975, 2925, 1601, 1456. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.18 (6H, s, 3-$(CH_3)_2$); 1.31 (6H, s, 4-$(CH_3)_2$); 2.46 (3H, s, SCH_3); 7.33 (1H, td, *J* = 7.5, *J* = 0.9, H-7); 7.45 (1H, td, *J* = 7.8, *J* = 1.5, H-8); 7.55 (1H, d, *J* = 8.1, H-9); 7.86 (1H, s, H-5); 7.89 (1H, s, H-11); 7.95 (1H, br. d, *J* = 7.8, H-6). ^{13}C NMR spectrum, δ, ppm: 12.4; 23.7; 39.5; 61.7; 107.9; 111.8; 116.0; 120.8; 122.8; 123.9; 126.3; 126.7; 127.7; 141.1; 154.3; 157.2; 159.1. Mass spectrum, *m*/*z* (I_{rel}, %): 323 $[M]^+$ (13), 308 $[M–CH_3]^+$ (100), 251 (10), 219 (10), 218 (12). Found, %: C 74.03; H 6.60; N 4.40; S 9.68. $C_{20}H_{21}NOS$. Calculated, %: C 74.27; H 6.54; N 4.33; S 9.91.

1,3,3,4,4-Pentamethyl-3,4-dihydrobenzofuro[3,2-*g*]-isoquinoline (7b) was obtained from compounds **6** and **5b**. Purification by crystallization. Yield 190 mg (33%), light-yellow crystals, mp 129–130°C (EtOAc). IR spectrum, ν, cm^{-1}: 3060 (br. s), 2973, 2924, 1630, 1575, 1457. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.32 (6H, s, 3-CH_3); 1.89 (6H, s,

4-CH_3); 2.49 (3H, s, 1-CH_3); 7.35 (1H, t, J = 7.5, H-7); 7.47 (1H, t, J = 7.8, H-8); 7.57 (1H, d, J = 8.4, H-9); 7.66 (1H, s, H-5); 7.92 (1H, s, H-11); 7.97 (1H, d, J = 7.5, H-6). ^{13}C NMR spectrum, δ, ppm: 23.3; 23.6; 24.1; 38.9; 59.5; 108.5; 111.8; 116.0; 120.8; 122.9; 123.9; 126.2; 126.8; 127.6; 141.7; 154.4; 157.2; 160.5. Mass spectrum, *m*/*z* (I_{rel}, %): 291 $[M]^+$ (81), 290 $[M–H]^+$ (44), 276 $[M–CH_3]^+$ (41), 249 $[M–C_3H_6]^+$ (27), 248 $[M–C_3H_7]^+$ (37), 235 $[M–C_4H_8]^+$ (62), 234 $[M–C_4H_9]^+$ (100), 233 (18). Found, %: C 82.21; H 7.33; N 4.55. $C_{20}H_{21}NO$. Calculated, %: C 82.44; H 7.26; N 4.81.

3,3,4,4-Tetramethyl-1-(pyridin-2-yl)-3,4-dihydrobenzofuro[3,2-*g*]isoquinoline (7c) and **3,3,4,4-tetramethyl-1-(pyridin-2-yl)-3,4-dihydrobenzofuro[2,3-*h*]isoquinoline (8c)** were obtained from compounds **6** and **5c**. The mixture was separated by column chromatography (eluent 4:1 hexane–EtOAc).

Compound 7c. Yield 35 mg (impurity of compound **8c** with 20% of ^{1}H NMR signal intensity). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.30 (6H, br. s, 3-CH_3); 1.42 (6H, br. s, 4-CH_3); 7.31–7.40 (3H, m, H Ar); 7.45 (1H, td, J = 7.8, J = 1.2, H Ar); 7.51 (1H, d, J = 7.5, H Ar); 7.53 (1H, s, H-5); 7.84 (1H, dd, J = 6.6, J = 1.5, H Ar); 7.97 (1H, s, H-11); 7.98 (1H, d, J = 6.9, H Ar); 8.70 (1H, d, J = 4.5, H Py). Mass spectrum, *m*/*z* (I_{rel}, %): 354 $[M]^+$ (13), 339 $[M–CH_3]^+$ (100), 298 $[M–C_4H_8]^+$ (19), 297 $[M–C_4H_9]^+$ (11), 296 (18).

Compound 8c. Yield 326 mg (46%), colorless crystals, mp 186–186.5°C (EtOH). R_f 0.31 (2:1 hexane–EtOAc). IR spectrum, ν, cm^{-1}: 3060, 2975, 1582, 1464. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.97 (3H, br. s, CH_3); 1.24 (3H, br. s, CH_3); 1.52 (3H, br. s, CH_3); 1.66 (3H, br. s, CH_3); 5.89 (1H, d, J = 8.1, H-11); 6.75 (1H, td, J = 8.1, J = 1.2, H-10); 7.23 (1H, ddd, J = 8.0, J = 7.5, J = 1.2, H-9); 7.31 (1H, ddd, J = 7.4, J = 4.8, J = 1.2, H-5 Py); 7.44 (1H, d, J = 7.8, H-5); 7.56 (1H, d, J = 8.7, H-8); 7.66 (1H, d, J = 8.4, H-6); 7.80 (1H, td, J = 7.7, J = 1.2, H-4 Py); 7.93 (1H, d, J = 7.8, H-3 Py); 8.46 (1H, d, J = 4.8, H-6 Py). ^{13}C NMR spectrum, δ, ppm: 21.5; 22.3; 24.2; 25.0; 39.5; 60.3; 111.1; 114.2; 120.9; 121.6; 121.8; 123.2; 123.3; 123.6 (2C); 123.8; 126.6; 137.0; 143.0; 149.4; 155.0; 156.5; 158.5; 162.4. Mass spectrum, *m*/*z* (I_{rel}, %): 354 $[M]^+$ (20), 339 $[M–CH_3]^+$ (100), 298 $[M–C_4H_8]^+$ (19), 297 $[M–C_4H_9]^+$ (13), 296 (23). Found, %: C 81.01; H 6.23; N 7.84. $C_{24}H_{22}N_2O$. Calculated, %: C 81.33; H 6.26; N 7.90.

2-(3,3,4,4-Tetramethyl-3,4-dihydrobenzofuro[3,2-*g*]isoquinolin-1-yl)aniline (7d) and **2-(3,3,4,4-tetramethyl-3,4-dihydrobenzofuro[2,3-*h*]isoquinolin-1-yl)aniline (8d)** were obtained from compounds **6** and **5d**. The mixture was separated by column chromatography (eluent 5:1 hexane–EtOAc).

Compound 7d. Yield 380 mg (51%), yellow crystals, mp 203–205°C (EtOAc). R_f 0.34 (5:1 hexane–EtOAc). IR spectrum, ν, cm^{-1}: 3441, 3342, 1607, 1452. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.28 (6H, br. s, 3-CH_3); 1.41 (6H, br. s, 4-CH_3); 4.89 (2H, br. s, NH_2); 6.71–6.78 (2H, m, H Ar); 7.14–7.22 (2H, m, H Ar); 7.32 (1H, t, J = 7.4, H Ar); 7.42 (1H, s, H-5); 7.43 (1H, t, J = 7.8, H Ar); 7.51 (1H, d, J = 8.1, H Ar); 7.95 (1H, s, H-11); 7.97 (1H, d, J = 7.2, H Ar). ^{13}C NMR spectrum, δ, ppm: 23.4; 38.5; 60.3; 111.6; 111.8; 115.3; 116.9; 117.2; 120.8; 122.1; 122.8; 123.8; 126.3; 126.4; 127.7; 129.8; 130.6; 142.5; 146.5; 154.1; 157.2; 164.2. Mass spectrum, *m*/*z* (I_{rel}, %): 368 $[M]^+$ (35), 367 $[M–H]^+$ (100), 353 $[M–CH_3]^+$ (13). Found, %: C 81.21; H 6.56; N 7.53. $C_{25}H_{24}N_2O$. Calculated, %: C 81.49; H 6.57; N 7.60.

Compound 8d. Yield 130 mg (17%), light-yellow crystals, mp 163–165°C (2-PrOH). R_f 0.63 (5:1 hexane–EtOAc). IR spectrum, ν, cm^{-1}: 3469, 3344, 1606, 1459. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.93 (3H, s, CH_3); 1.21 (3H, s, CH_3); 1.46 (3H, s, CH_3); 1.57 (3H, s, CH_3); 5.64 (2H, br. s, NH_2); 6.34 (1H, t, J = 7.5, H-10); 6.49 (1H, d, J = 8.1, H-11); 6.82 (1H, d, J = 8.0, H Ar); 6.84 (1H, d, J = 8.0, H Ar); 6.88 (1H, t, J = 7.8, H Ar); 7.08 (1H, t, J = 7.8, H Ar); 7.23 (1H, t, J = 7.5, H Ar); 7.42 (1H, d, J = 8.7, H Ar); 7.50 (1H, d, J = 8.4, H Ar); 7.62 (1H, d, J = 8.7, H Ar). ^{13}C NMR spectrum, δ, ppm: 20.7 (CH_3); 22.0 (CH_3); 24.0 (CH_3); 24.9 (CH_3); 38.9; 59.1; 110.2; 113.0; 116.5; 117.2; 120.6; 121.5; 122.5; 122.7; 123.1; 125.1; 126.3; 129.5; 130.0; 142.7; 146.2; 154.6; 156.1; 163.3. Mass spectrum, *m*/*z* (I_{rel}, %): 368 $[M]^+$ (100), 367 $[M–H]^+$ (29), 353 $[M–CH_3]^+$ (69), 352 $[M–NH_2]^+$ (81), 337 $[M–CH_3–NH_2]^+$ (19), 336 $[M–CH_3–NH_3]^+$ (15), 325 (35), 312 $[M–C_4H_8]^+$ (35), 311 $[M–C_4H_9]^+$ (42), 310 (36). Found, %: C 81.23; H 6.62; N 7.56. $C_{25}H_{24}N_2O$. Calculated, %: C 81.49; H 6.57; N 7.60.

3,3,4,4-Tetramethyl-1-phenyl-3,4-dihydrobenzofuro[3,2-*g*]isoquinoline (7e) and **3,3,4,4-tetramethyl-1-phenyl-3,4-dihydrobenzofuro[2,3-*h*]isoquinoline (8e)** were obtained from compounds **6** and **5e**. The mixture was separated by column chromatography (eluent 5:1 hexane–EtOAc).

Compound 7e. Yield 280 mg (40%), white crystals, mp 144–145°C (EtOH). R_f 0.64 (5:1 hexane–EtOAc). IR spectrum, ν, cm^{-1}: 3061, 2974, 1612, 1568. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.29 (3H, br. s, CH_3); 1.42 (9H, br. s, 3CH_3); 7.35 (1H, td, J = 7.4, J = 1.2, H Ar); 7.36 (1H, s, H-5); 7.43–7.49 (4H, m, H Ar); 7.52 (1H, d, J = 7.8, H Ar); 7.57–7.61 (2H, m, H Ar); 7.98 (1H, s, H-11); 7.99 (1H, d, J = 7.8, H Ar). ^{13}C NMR spectrum, δ, ppm: 23.1 (2C); 24.1 (2C); 38.9; 60.4; 111.4; 111.8; 116.0; 120.9; 122.9; 123.9; 126.3; 127.7; 128.3 (2C); 128.8 (2C); 129.1; 139.5; 142.6; 154.1; 157.3. Mass spectrum, *m*/*z* (I_{rel}, %): 353 $[M]^+$ (100), 352 $[M–H]^+$ (100), 338 $[M–CH_3]^+$ (22), 337 (14), 322 (12), 310 $[M–C_3H_7]^+$ (23), 298 (17), 297 $[M–C_4H_8]^+$ (80), 296 $[M–C_4H_9]^+$ (80), 295 (16), 282 (24), 281 (58). Found, %: C 85.06; H 6.50; N 4.04. $C_{25}H_{23}NO$. Calculated, %: C 84.95; H 6.56; N 3.96.

Compound 8e. Yield 30 mg (4%), white crystalline powder, mp 172.5–174°C (2-PrOH). R_f 0.75 (5:1 hexane–EtOAc). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.85 (3H, br. s, CH_3); 1.14 (3H, br. s, CH_3); 1.42 (3H, br. s, CH_3); 1.57 (3H, br. s, CH_3); 6.01 (1H, d, J = 8.1, H Ar); 6.67 (1H, td, J = 7.7, J = 1.2, H Ar); 7.00–7.60 (2H Ar, not localized); 7.16 (1H, td, J = 7.8, J = 1.2, H Ar); 7.30–7.37 (3H, m, H Ar); 7.48 (1H, d, J = 8.4, H Ar); 7.59 (1H, d, J = 8.4, H Ar); 7.99 (1H, br. s, H Ar). ^{13}C NMR spectrum, δ, ppm: 20.8; 22.5; 24.6; 25.4; 39.8; 60.0; 111.0; 114.1; 115.4 (2C);

121.9; 123.4; 123.5; 125.2 (2C); 126.9; 128.2; 129.6; 129.8; 140.4; 143.6; 155.2; 156.6. Mass spectrum, *m/z* (I_{rel}, %): 353 $[M]^+$ (52), 352 $[M–H]^+$ (21), 310 $[M–C_3H_7]^+$ (19), 297 $[M–C_4H_8]^+$ (54), 296 $[M–C_4H_9]^+$ (100), 295 (13), 282 (16), 281 (55). Found, %: C 84.66; H 6.67; N 3.69. $C_{25}H_{23}NO$. Calculated, %: C 84.95; H 6.56; N 3.96.

1-(2-Methoxyphenyl)-3,3,4,4-tetramethyl-3,4-dihydrobenzofuro[3,2-g]isoquinoline (7f) and **1-(2-methoxyphenyl)-3,3,4,4-tetramethyl-3,4-dihydrobenzofuro[2,3-*h*]isoquinoline (8f)** were obtained from compounds **6** and **5f**. The mixture was separated by column chromatography (eluent 5:1 hexane–EtOAc).

Compound 7f. Yield 290 mg (38%), colorless crystals, mp 202.5–203.5°C (EtOAc). R_f 0.25 (5:1 hexane–EtOAc). IR spectrum, ν, cm^{-1}: 2979, 2967, 2937, 1612, 1600, 1571. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.16 (6H, br. s, 3-$(CH_3)_2$); 1.46 (6H, br. s, 4-$(CH_3)_2$); 3.64 (3H, s, OCH_3); 6.93 (1H, d, *J* = 8.1, H Ar); 7.05 (1H, td, *J* = 7.5, *J* = 0.9, H Ar); 7.10 (1H, s, H-5); 7.30–7.50 (5H, m, H Ar); 7.95 (1H, s, H-11); 7.97 (1H, d, *J* = 8.1, H Ar). Mass spectrum, *m/z* (I_{rel}, %): 383 $[M]^+$ (45), 382 $[M–H]^+$ (36), 368 $[M–CH_3]^+$ (12), 353 $[M–CH_2O]^+$ (29), 352 $[M–CH_3O]^+$ (100), 327 $[M–C_4H_8]^+$ (13), 326 $[M–C_4H_9]^+$ (14), 312 (18). Found, %: C 81.32; H 6.42; N 3.74. $C_{26}H_{25}NO_2$. Calculated, %: C 81.43; H 6.57; N 3.65.

Compound 8f. Yield 160 mg (21%), colorless crystals, mp 154–155°C (hexane). R_f 0.43 (5:1 hexane–EtOAc). ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.98 (3H, br. s, CH_3); 1.26 (3H, br. s, CH_3); 1.49 (3H, br. s, CH_3); 1.61 (3H, br. s, CH_3); 3.03 (3H, s, OCH_3); 6.10 (1H, br. s, H-10); 6.65 (1H, br. s, H-11); 6.73 (1H, t, *J* = 7.5, H Ar); 7.19–7.25 (2H, m, H Ar); 7.37–7.42 (2H, m, H Ar); 7.53 (1H, d, *J* = 8.4, H Ar); 7.60 (1H, d, *J* = 8.4, H Ar); 7.86 (1H, br. s, H Ar). Mass spectrum, *m/z* (I_{rel}, %): 383 $[M]^+$ (22), 353 $[M–CH_2O]^+$ (28), 352 $[M–CH_3O]^+$ (100), 337 (13), 327 $[M–C_4H_8]^+$ (11), 326 $[M–C_4H_9]^+$ (21), 311 (13). Found, %: C 81.23; H 6.47; N 3.72. $C_{26}H_{25}NO_2$. Calculated, %: C 81.43; H 6.57; N 3.65.

1-(2-Bromophenyl)-3,3,4,4-tetramethyl-3,4-dihydrobenzofuro[3,2-g]isoquinoline (7g) and **1-(2-bromophenyl)-3,3,4,4-tetramethyl-3,4-dihydrobenzofuro[2,3-*h*]isoquinoline (8g)** were obtained from compounds **6** and **5g**. The mixture was separated by column chromatography (eluent 50:1 CH_2Cl_2–acetone).

Compound 7g. Yield 380 mg (44%), white crystals, mp 216–218°C (EtOAc). R_f 0.10 (20:1 hexane–acetone). IR spectrum, ν, cm^{-1}: 2973, 1608, 1568, 1449. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.18 (3H, br. s, CH_3); 1.44 (3H, br. s, CH_3); 1.50 (6H, br. s, $2CH_3$); 7.01 (1H, s, H-5); 7.21–7.32 (2H, m, H Ar); 7.38–7.47 (4H, m, H Ar); 7.60 (1H, d, *J* = 8.1, H Ar); 7.94 (1H, d, *J* = 7.8, H Ar); 7.96 (1H, s, H-11). ^{13}C NMR spectrum, δ, ppm: 22.5; 23.5; 24.2; 38.8; 60.7; 110.3; 111.7; 116.2; 120.8; 122.1; 122.8; 123.8; 125.7; 126.6; 127.6; 127.7; 129.9; 130.7; 132.9; 140.3; 141.4; 154.2; 157.2; 163.9. Mass spectrum, *m/z* (I_{rel}, %): 431 $[M]^+$ (10), 375 $[M–C_4H_8]^+$ (15), 374 $[M–C_4H_9]^+$ (10), 352 $[M–Br]^+$ (100), 337 $[M–CH_3–Br]^+$ (41), 322 (16), 294 (13), 293 (12), 279 (16). Found, %: C 69.13; H 5.07; N 3.20. $C_{25}H_{22}BrNO$. Calculated, %: C 69.45; H 5.13; N 3.24.

Compound 8g. Yield 170 mg (20%), colorless crystals, mp 153.5–154.5°C (EtOAc). R_f 0.23 (20:1 hexane–acetone). IR spectrum, ν, cm^{-1}: 2977, 2934, 1626, 1602, 1587, 1462. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.01 (3H, br. s, CH_3); 1.36 (3H, br. s, CH_3); 1.47 (3H, br. s, CH_3); 1.60 (3H, br. s, CH_3); 5.99 (1H, br. s, H-11); 6.75 (1H, br. s, H-10); 7.10–7.80 (1H Ar, not localized); 7.20–7.26 (3H, m, H Ar); 7.43 (1H, dd, *J* = 7.8, *J* = 0.6, H Ar); 7.55 (1H, d, *J* = 8.4, H Ar); 7.64 (1H, d, *J* = 8.4, H Ar); 7.93 (1H, br. s, H-3'). ^{13}C NMR spectrum, δ, ppm: 20.9; 23.1; 23.6; 25.2; 39.3; 60.0; 111.1; 114.3; 120.7; 122.0; 123.1; 123.8; 124.0; 126.9; 128.3; 130.4; 132.5; 133.8; 141.9; 155.2; 156.6; 163.0. Mass spectrum, *m/z* (I_{rel}, %): 431 $[M]^+$ (7), 374 $[M–C_4H_9]^+$ (10), 352 $[M–Br]^+$ (100), 337 $[M–CH_3–Br]^+$ (34), 322 (13), 294 (10), 293 (9), 279 (16). Found, %: C 69.68; H 4.82; N 3.07. $C_{25}H_{22}BrNO$. Calculated, %: C 69.45; H 5.13; N 3.24.

1-Isobutyl-3,3,4,4-tetramethyl-3,4-dihydrobenzofuro[3,2-g]isoquinoline (7h) was obtained from compounds **6** and **5h** and purified by chromatography (eluent 7:1 hexane–EtOAc). Yield 323 mg (49%), thick colorless oil. R_f 0.40 (7:1 hexane–EtOAc). IR spectrum, ν, cm^{-1}: 2969, 2932, 2868, 1624, 1573. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.00 (6H, d, *J* = 6.6, $CH(C\underline{H}_3)_2$); 1.18 (6H, br. s, 3-$(CH_3)_2$); 1.32 (6H, br. s, 4-$(CH_3)_2$); 2.06–2.19 (1H, m, $C\underline{H}(CH_3)_2$); 2.68 (2H, d, *J* = 6.6, $C\underline{H}_2CH(CH_3)_2$); 7.33 (1H, td, *J* = 7.5, *J* = 0.9, H-7); 7.45 (1H, td, *J* = 7.5, *J* = 1.5, H-8); 7.55 (1H, d, *J* = 8.4, H-9); 7.64 (1H, s, H-5); 7.92 (1H, s, H-11); 7.95 (1H, d, *J* = 7.8, H-6). Mass spectrum, *m/z* (I_{rel}, %): 333 $[M]^+$ (64), 332 $[M–H]^+$ (44), 318 $[M–CH_3]^+$ (100), 291 $[M–C_3H_6]^+$ (70), 290 $[M–C_3H_7]^+$ (60), 277 $[M–C_4H_8]^+$ (14), 276 $[M–C_4H_9]^+$ (53), 262 (14); 261 (19), 260 (13), 249 (21), 248 (12), 235 (39), 234 (89), 233 (32), 231 (19), 220 (25), 219 (35), 217 (72). Found, %: C 82.96; H 8.42; N 4.12. $C_{23}H_{27}NO$. Calculated, %: C 82.84; H 8.16; N 4.20.

Methyl 2-(3,3,4,4-tetramethyl-3,4-dihydrobenzofuro[3,2-g]isoquinolin-1(2*H*)-ylidene)acetate (7j) was obtained from compounds **6** and **5j**. Purification by crystallization. Yield 400 mg (57%), light-yellow crystals, mp 146–147°C (EtOH). IR spectrum, ν, cm^{-1}: 3281, 2977, 1648, 1602, 1447. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.34 (12H, br. s, 3-$(CH_3)_2$, 4-$(CH_3)_2$); 3.71 (3H, s, OCH_3); 5.17 (1H, s, =$C\underline{H}CO_2Me$); 7.31 (1H, td, *J* = 7.5, *J* = 1.2, H-7); 7.43 (1H, td, *J* = 7.4, *J* = 1.2, H-8); 7.52 (1H, d, *J* = 8.1, H-9); 7.80 (1H, s, H-5); 7.90 (1H, s, H-11); 7.92 (1H, d, *J* = 7.5, H-6); 9.03 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 24.4; 41.0; 50.1; 54.7; 76.8; 108.2; 111.7; 116.3; 120.7; 122.8; 123.6; 126.5; 127.5; 127.8; 140.3; 154.5; 155.3; 157.1; 171.5. Found, %: C 75.27; H 6.60; N 3.67. $C_{22}H_{23}NO_3$. Calculated, %: C 75.62; H 6.63; N 4.01.

X-ray structural analysis of compounds 7e,f and 8c. Monocrystals of compounds **7e**,**f** and **8c** were obtained by crystallization from acetone. X-ray diffraction experiments were performed at 295(2) K on an Xcalibur-3 diffractometer with CCD detector (MoKα radiation, graphite monochromator, ω-scanning). The structures of compounds were solved by direct method with SHELXS-97 software.[28] Parameters were refined by using SHELXL-97 software in anisotropic approximation (isotropically for hydrogen

atoms). The crystallographic data for compounds **8c**, **7f,** and **7e** were deposited at the Cambridge Crystallographic Data Center (deposits CCDC 1434242, CCDC 1434243, and CCDC 1434244, respectively).

The Supplementary information file, containing drawings of conformers for compound **8g**, is available online at http://link.springer.com/journal/10593.

This work received financial support from the Russian Foundation for Basic Research (grant 13-03-00184).

References

1. Smirnova, O. B.; Golovko, T. V.; Granik, V. G. *Pharm. Chem. J.* **2011**, *44*, 654. [*Khim.-Farm. Zh.* **2010**, *44*(12), 6.]
2. Cimanga, K.; De Bruyne, T.; Pieters, L.; Vlietinck, A. *Tetrahedron Lett.* **1996**, *37*, 1703.
3. Ramkumar, N.; Raghavendra, M. S.; Nagarajan R. *Synlett* **2014**, *25*, 2791.
4. Meesala, R.; Ezzat, M. O.; Mordi, M. N.; Mansor, Sh. M. *Synlett* **2014**, *25*, 2176.
5. Nakao, Y.; Fusetani, N. *J. Nat. Prod.* **2007**, *70,* 689.
6. Shklyaev, Yu. V.; Nifontov, Yu. V. *Russ. Chem. Bull*., *Int. Ed*. **2002**, *51*, 844. [*Izv. Akad. Nauk*, *Ser. Khim.* **2002**, 780.]
7. Glushkov, V. A.; Rozhkova, Yu. S.; Vakhrin, M. I.; Shklyaev, Yu. V. *Chem. Heterocycl. Compd.* **2005**, *41*, 1022. [*Khim. Geterotsikl. Soedin.* **2005**, 1198.]
8. Shklyaev, Yu. V.; Ismagilov, R. R.; Rozhkova, Yu. S.; Fatykhov, A. A.; Abdrakhmanov, I. B.; Tolstikov, A. G. *Russ. Chem. Bull*., *Int. Ed*. **2004**, *53*, 906. [*Izv. Akad. Nauk*, *Ser. Khim.* **2004**, 869.]
9. Shklyaev, Yu. V.; Gilev, M. Yu.; Maiorova, O. A. *Russ. J. Org. Chem.* **2009**, *45*, 1843. [*Zh. Org. Khim.* **2009**, 1845.]
10. Kharitonova, A. V.; Gorbunov, A. A.; Shklyaev, Yu. V. *Russ. J. Appl. Chem.* **2010**, 1489. [*Zh. Prikl. Khim.* **2010**, 1383.]
11. Shklyaev, Yu. V.; Vshivkova, T. S.; Maiorova, O. A.; Gorbunov, A. A. *Russ. J. Org. Chem.* **2012***, 48*, 257. [*Zh. Org. Khim.* **2012**, 267.]
12. Shklyaev, Yu. V.; Yeltsov, M. A.; Rozhkova, Yu. S.; Tolstikov, A. G.; Dembitsky, V. M. *Heteroat. Chem.* **2004**, *15*, 486.
13. Shklyaev, Yu. V.; Gorbunov, A. A.; Rozhkova, Yu. S.; Vshivkova, T. S.; Vazhenin, V. V.; Maiorova, O. A.; Tolstikov, A. G.; Dembitsky, V. M. *Heteroat. Chem.* **2005**, *16*, 192.
14. Glushkov, V. A.; Ausheva, O. G.; Shurov, S. N.; Shklyaev, Yu. V. *Russ. Chem. Bull*., *Int. Ed*. **2002**, *51*, 894. [*Izv. Akad. Nauk*, *Ser. Khim.* **2002**, 822.]
15. Nifontov, Yu. V.; Glushkov, V. A.; Ausheva, O. G.; Shklyaev, Yu. V. *Russ. J. Org. Chem.* **2002**, *38*, 1387. [*Zh. Org. Khim.* **2002**, 1437.]
16. Plekhanova, I. V.; Stryapunina, O. G.; Glushkov, V. A.; Karmanov, V. I.; Maiorova, O. A.; Shklyaev, Yu. V. *Russ. J. Org. Chem.* **2009***, 45*, 360. [*Zh. Org. Khim.* **2009**, 372.]
17. Rozhkova, Yu. S.; Khmelevskaja, K. A.; Shklyaev, Yu. V.; Ezhikova, M. A.; Kodess, M. I. *Russ. J. Org. Chem.* **2012**, *48*, 69. [*Zh. Org. Khim.* **2012**, 75.]
18. Campaigne, E.; Ashby, J. *J. Heterocycl. Chem.* **1969**, *6*, 875.
19. Elmes, B. C.; Swan, J. M. *Aust. J. Chem*. **1969**, *22*, 1963.
20. Umeda, R.; Nishida, H.; Otono, M.; Nishiyama, Yu. *Tetrahedron Lett.* **2011**, *52*, 5494.
21. Hayama, T.; Kawamura, M.; Mizuki, Yu.; Ito, H.; Haketa, T. WO Patent 2014199637 A1.
22. Fujiwara, A. N.; Acton, E. M. Goodman, L. *J. Heterocycl. Chem.* **1969**, *6*, 379.
23. Ma, B.; Fiordelsiso, J.; Wu, Y.; Kwong, R. US Patent 20110266526 A1
24. Langendoen, A.; Koomen, G.-J.; Pandit, U. K. EU Patent 0257701.
25. Shklyaev, Yu. V.; Rozhkova, Yu. S.; Perevoshchikova, A. N.; Gorbunov, A. A. *Russ. Chem. Bull.*, *Int. Ed.* **2014**, *63*, 2087. [*Izv. Akad. Nauk*, *Ser. Khim.* **2014**, 2087.]
26. (a) *Organicum* [Russian translation]; Kost, A. N., Ed.; Mir: Moscow, 1965, p. 308. (b) ibid., p. 491.
27. Buu-Hoi, Ng. Ph.; Royer, R. *Recueil des Travaux Chimiques des Pays-Bas et de la Belgique* **1948**, 67, 175.
28. Sheldrick, G. M. *Acta Crystallogr*., *Sect. A: Found. Crystallogr.* **2008**, *A64*, 112.