Synthesis and Prediction of the Ubiquinol-cytochrome *c* Reductase Inhibitory Activity of 3,4-Dihydroisoquinolines and 2-Azaspiro[4.5]decanes (Spiropyrrolines)

Anna N. Perevoshchikova,[a]* Daria V. Eroshenko,[a] Maksim V. Dmitriev,[b] Victoria V. Grishko,[a] and Yurii V. Shklyaev[a]

[a]Institute of Technical Chemistry of Ural Branch of the Russian Academy of Sciences, Academician Korolev Street 3, 614013 Perm, Russia
[b]Perm State National Research University, Bukirev Street 15, 614990 Perm, Russia
E-mail: annper87@gmail.com
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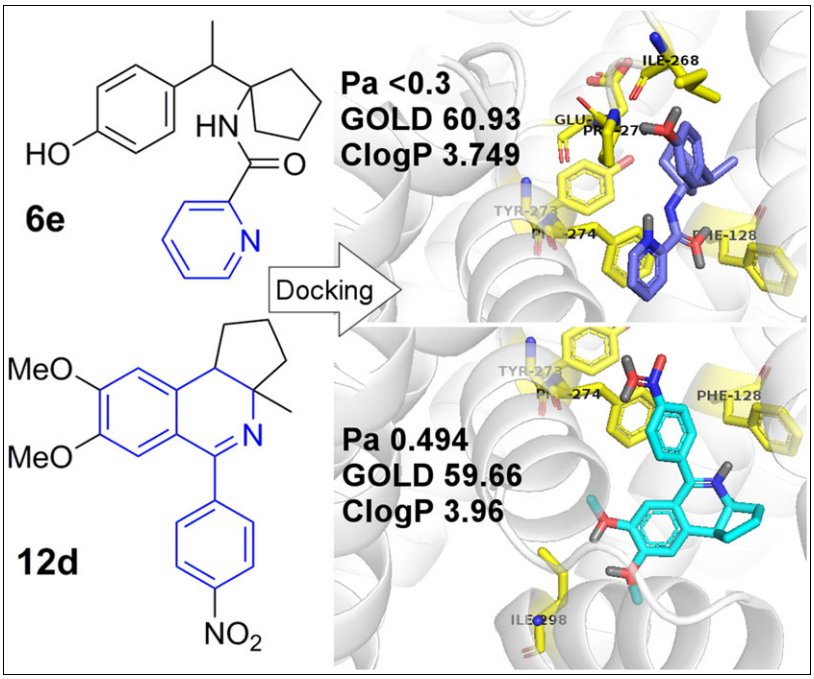

Isoquinolines rank as the second largest group among the plant alkaloids. Natural isoquinolines and synthetic isoquinoline derivatives exhibit numerous biological activities. In this study, the approaches to synthesis of new 3,4-dihydroisoquinoline and 2-azaspiro[4.5]decane (spiropyrroline) derivatives annelated by C(3)–C(4) bonds with a cyclohexyl or cyclopentyl moiety have been developed. In accord with the results of biological activity prediction by the PASS software, molecular docking was carried out on the ubiquinol-cytochrome *c* reductase (bc_1 complex) model. Compounds **6e** and **12a**,**d** were found out as potential Q_0 site inhibitors of the bovine bc_1 complex.

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INTRODUCTION

Isoquinoline derivatives evince a wide range of biological activities. For example, partially hydrogenated isoquinoline derivatives can act as antagonists of dopamine receptors, exhibit antiproliferative, antitumor, anthelmintic, analgesic, antimicrobial, antibacterial, and other activities [1–7]. In synthesis of 3,4-dihydroisoquinolines and their derivatives, the most frequently used reactions are those of Bischler–Napieralsky, Pictet–Spengler, and Pomeranz–Fritsch [8]. The Ritter reaction, along with a possibility of forming amides in the classical variant of the reaction [9], can also be used in synthesis of 3,4-dihydroisoquinoline and 2-azaspiro[4.5]decane (spiropyrroline) derivatives [10,11].

Earlier, we showed that the Wagner–Meerwein rearrangement of 1-(4-methoxyphenyl)-2,2-dimethylpropan-1-ol, 3,3-dimethyl-2-phenylbutane-2-ol and 1-(4-methoxyphenyl)-1-(1-methylcyclohexyl)ethan-1-ol allows to obtain a carbocation, whose interaction with nitrile leads to the formation of heterocyclic compounds [12–14].

In the presented work, a possibility of the synthesis new 3,4-polyalkyl derivatives of 3,4-dihydroisoquinoline by interaction of nitriles with insufficiently studied 1-cycloalkyl-1-(4-methoxyphenyl)ethane-1-ol and 1-(4-methoxyphenyl)-1-(1-methylcyclopentyl)ethane-1-ol, as well as 4-(1-cyclobutenyl-ethyl)-1,2-dimethoxybenzene was explored. Potential biological activity of synthesized compounds was studied by the *in silico* methods.

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RESULTS AND DISCUSSION

Chemistry. New carbinols **1–3** synthesized by the standard methods [14–16] underwent interaction with nitriles **4a–f** in the presence of 94% sulfuric acid (Scheme 1).

In the case of carbinol **1**, the cycloalkyl moiety was supposed to expand at the expense of the Wagner–Meerwein rearrangement, but the cyclopentyl part, apparently, was not sterically stressed markedly, with 6-methyl-13,14-azadispiro [4.1.5.2]tetradec-8,11,13-trien-10-ones **5a–c** obtained as products of the Ritter reaction. Earlier [17,18], we had shown a similar dependence in the formation of spiropyrrolines for some substituted alkoxyphenylcarbinols. According to GC/MS, the reaction of compound **1** with 2-cyanopyridine resulted in the formation of compounds **5e** and **6e** mixed at the ratio 2: 1. Compounds **5e**,**f** were unstable, and in the process of chromatographic purification on silica gel turned into products of the dienone-phenolic rearrangement—amides **6e**,**f**. In the ^{1}H NMR spectra of compounds **5a–c** and **6e**,**f**, a signal of the methyl group was observed as a doublet (J = 7.2–7.5 Hz) in the 0.82–0.84 ppm range for spiropyrrolines **5a–c** and in the range of 1.18–1.31 ppm for amides **6e** and **6f**, and the proton signal at C(6) was in the form of a quadruplet (J = 7.2–7.5 Hz, J = 14.55–15.0 Hz) in the 2.56–2.59 ppm range for spiropyrrolines **5a–c** or in the range of 3.60–3.66 ppm for amides **6e** and **6f**.

With carbinol **2** used, a 1,2-sigmatropic shift of the cyclopentane ring was observed with the formation of hexahydrofenanthridine derivatives **7a–f**, instead of the expected migration of the methyl group [14]. The *cis*-configuration of the methyl groups was found out by the X-ray diffraction analysis performed for crystalline isocarbostyril **10** (Fig. 1) synthesized from compound **7b** (Scheme 2). Thus, we succeeded in ascertaining the structure of the remaining compounds **7a**,**c–f** and confirming the location of the methoxy group at position 9 for this series of compounds. The ^{1}H NMR spectra of compounds **7a–f** at 6.61–6.75 ppm include a doublet of doublets of H(8), a doublet of H(10) is located at 6.85–6.93 ppm, and a doublet of H(7) at 7.09–7.57 ppm.

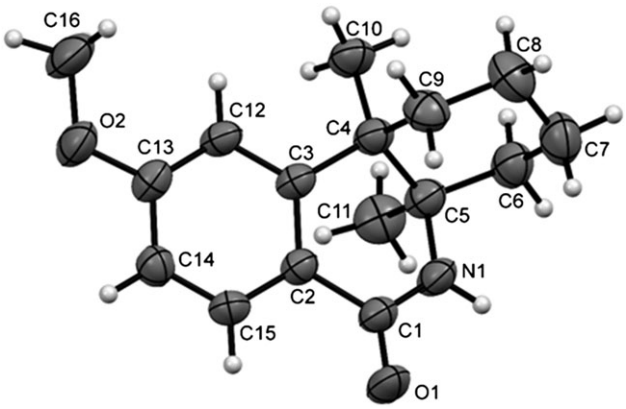
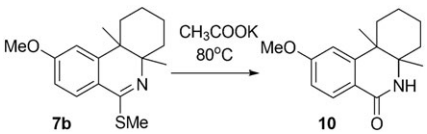


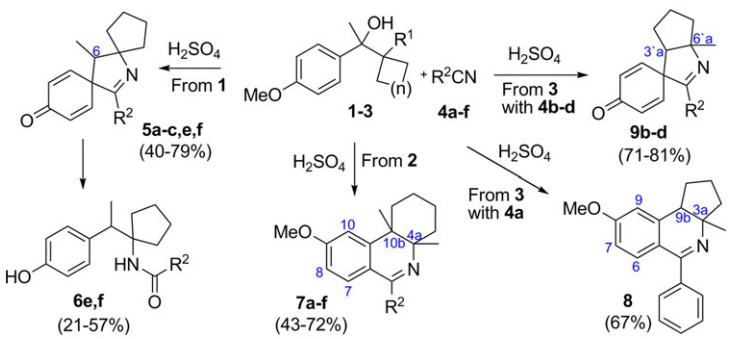
Figure 1. The structure of compound **10** according to X-ray diffraction data.

Scheme 2. Obtaining compound **10**.



In the reaction with carbinol **3**, 2-azaspiro[4,5]decans **9b–d** were isolated as the main products. In the ^{1}H NMR spectra of compounds **9b–d**, the singlet of the methyl group in the range of 1.52–1.62 ppm and the doublet of doublets at 2.53–2.61 ppm indicate the methyl group as being located at the C(6′a) atom, and the proton at C(3′a). Thus, during the reaction, the Wagner–Meerwein rearrangement proceeds twice and results in the expansion of the ring and migration of the methyl group. The structures of compounds **9c**,**d** were confirmed by X-ray structural analysis (Fig. 2).

Scheme 1. **1**: n = 2, R^1 = H; **2**: n = 2, R^1 = CH_3; **3**: n = 1, R^1 = H; **4a–f**, **5a–d**, **6e**,**f**, **7a–f**, **9b–d**: R^2 = Ph(**a**), SMe(**b**), CH_2COOEt(**c**), 4-$NO_2C_6H_4$(**d**), 2-Py(**e**), Me(**f**). [Color figure can be viewed at wileyonlinelibrary.com]



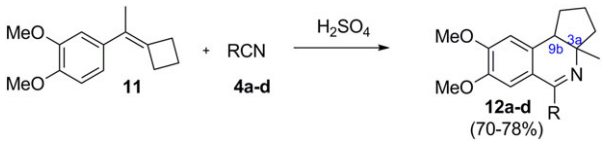
The reaction with benzonitrile **4a** resulting in only isoquinoline **8** was an exception. The ^{1}H NMR spectrum of compound **8** at 1.13 ppm includes a singlet with an integral intensity equaling 3 that is assigned to the signal of the methyl group at the atom C(3a) and a triplet at 2.75 ppm (J = 9.6 Hz) to the proton signal at C(9b). This phenomenon again indicates the double proceeding of the Wagner–Meerwein rearrangement. The signals of protons of the aromatic part of compound **8** are located as those for compounds **7a–f** at 6.65 ppm—doublet of doublets of H(7) (J = 8.4 Hz, J = 2.7 Hz), at 6.76 ppm—doublet of H(9) (J = 8.4 Hz), and doublet of H(6)—at 7.14 ppm (J = 8.7 Hz); thus, the methoxy group is in position 8.

We did not succeed in receiving carbinol of type **3** with two methoxy groups in the aromatic part. In all cases, styrene **11** was formed which, when reacts with nitriles **4a–d**, forms, as expected, the annelated 3,4-dihydroisoquinolines **12a–d** (Scheme 3). The signal of the methyl group at C(3a) position in the ^{1}H NMR spectra of compounds **12a–d** is also presented as singlet in the range of 1.05–1.20 ppm, like for compound **8**, and the signal of the proton at C(9b) is observed as triplet at 2.64–2.76 ppm(J = 9.0–9.6 Hz), with all these signals also indicating the double proceeding of the Wagner–Meerwein rearrangement. The structure of compound **12c** was confirmed by X-ray diffraction (Fig. 3).

Thus, the formation of products **8**, **9b–d**, and **12a–d** indicates the double proceeding of the Wagner–Meerwein rearrangement followed by the Ritter heterocyclization in accord with Scheme 4.

Biology. Keeping in mind that the structure of synthesized compounds contained heterocyclic pharmacophoric moieties, we tried to predict their potential biological activities by the *in silico* methods. So the online service "Prediction of Activity Spectra for Substances" (PASS) predicting over 4000 kinds of biological activity was opted because of its high (about 95%) accuracy [19]. The main observation of the PASS prediction was a high degree of probability (Pa 0.545–0.884) of ubiquinol-cytochrome *c* reductase inhibitory

Scheme 3. 4a–d and **12a–d**: R = Ph(**a**), SMe(**b**), CH_2COOEt(**c**), 4-$NO_2C_6H_4$(**d**). [Color figure can be viewed at wileyonlinelibrary.com]



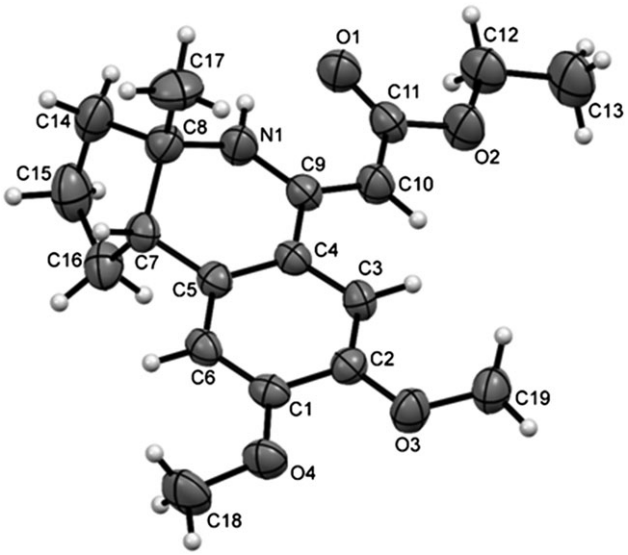


Figure 3. The structure of compound **12c** according to X-ray diffraction data.

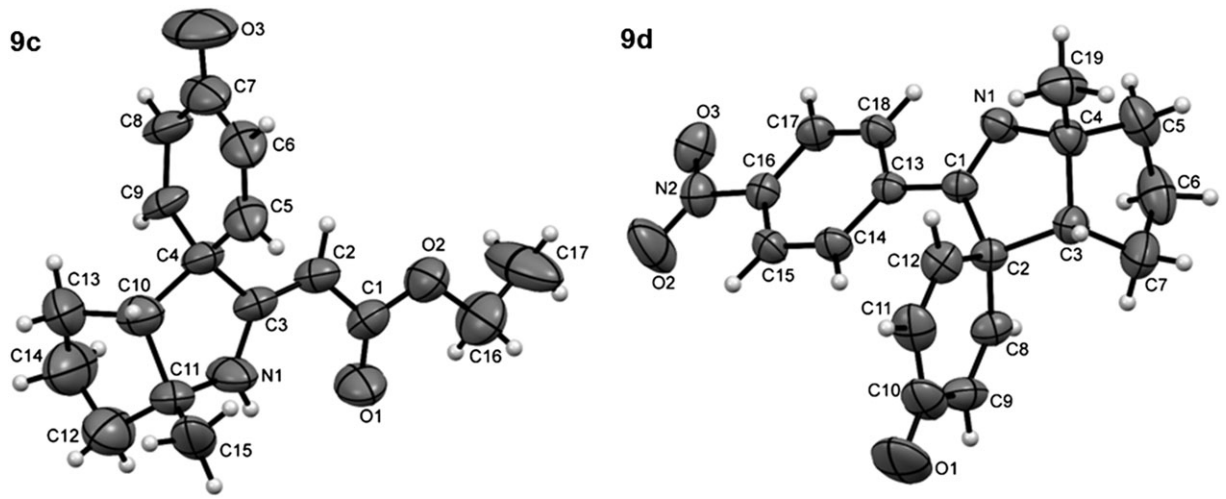
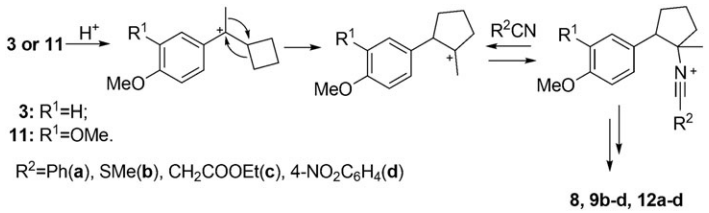


Figure 2. The structures of compounds **9c**,**d** according to X-ray diffraction data.

Scheme 4. Possible reaction mechanism.



activity for compounds **5a**–**c**, **6f**, **7a**,**b**,**d**,**f**, **8**, **9b**,**d**, and **12a** among synthesized derivatives (Table S1).

Ubiquinol-cytochrome *c* reductase, or the cytochrome bc_1 complex (EC 1.10.2.2, bc_1), has been identified as a promising target for agricultural fungicides [20] and antimalarial drugs [21] due to its important role in the cellular respiratory chain [22]. The binding to Q_0 pocket of the bc_1 complex has been known as the crucial step for the action of several conventional inhibitors [23]. Possible ligand-receptor interactions for each of the synthesized compounds with the Q_0 binding site of the bc_1 complex were investigated in detail by the docking studies with the GOLD software widely used for virtual screening [24]. The crystal structures of the bovine bc_1 complex with conventional inhibitor class P (AZ, MOAS, myxothiazol, UHDBT, and stigmatellin) bonded at the Q_0 site were downloaded from the Protein Data Bank. The GOLD scores between all synthesized compounds and the targeted protein were calculated (Table S1). As the compounds **6e**,**f**, **7a**–**f**, **8**, **9b**–**d**, **10**, and **12a**–**d** have chiral centers, 37 synthetically possible enantiomers were applied in docking simulations. We did not find out any correlation between the PASS prediction activity and the GOLD data not only for the synthesized compounds but also for conventional inhibitors (particularly, AZ and MOAS) (Table S1), probably due to the presence of asymmetric centers in the structure of these compounds that create additional restrictions for accurate prediction of biological activity by PASS software designed for 2D structures [25].

The results of molecular docking showed three compounds (**6e**, **12a**, and **12d**) to have the highest GOLD score exceeding 57 at molecular docking within the bc_1 complex co-crystallized with myxothiazol (PDB: 1SQP) (Table 1). Comparison of the structures of compounds **12a** and **12d** with high GOLD scores revealed that the 3,4-dihydroisoquinoline structure with an aromatic substituent at the first position should presumably be essential for bc_1 complex inhibitory activity. Conformations of the dihydropyridine ring and aromatic radical of the compound **12a** and **12d** were similar to the myxothiazol's heterocycles (Fig. 4c,d). The absence of an aromatic fragment (**12b**) or replacement of the planar 3,4-dihydroisoquinoline structure (**12d**) with the non-planar one of spiropyrroline (**9d**) resulted in a decrease in the calculated GOLD score values (Table S1). The presence of the alkyl and alkoxy substituents did not significantly influence the GOLD score. The docking study also revealed the (*S*,*S*)-enantiomers of **12a**,**d** to be better in the binding site as compared with (*R*,*R*)-enantiomer of these compounds.

Along with the compounds **12a** and **12d**, the highest GOLD score (60.93) was calculated for the product of dienone-phenolic regrouping—amide **6e**. But, in this case, conformation of only the pyridine radical of compound **6e** was similar to the one of the thiazole rings of myxothiazol (Fig. 4b). The GOLD score for the (*S*)- and (*R*)-enantiomers of compound **6e** equaled 59.58 and 60.93, respectively, suggesting more affinity to the (*R*)-enantiomer.

According to the structural information determined by the crystallographic studies [23], myxothiazol has a high potency as bc_1 complex inhibitor because its thiazole rings form the π–π stacking with the phenyl group of Phe274 (Fig. 4a) [26,27]. Similarly to myxothiazol, the π–π interaction between the Phe274 and the aromatic

Table 1

Molecular docking of the compounds **6e** and **12a**,**d** with amino acid residues within Q_0 pocket of the bc_1 complex (PDB: 1SQP).

Ligands	GOLD score	π–π stacking with Phe274, Å	H-bonds with amino acid residues
Myxothiazol	99.03	Yes, 3.639	Glu271, Tyr273
6e	60.93	Yes, 3.425	Pro270, Ile268, Phe128
12a	57.22	Yes, 3.002	Ile146
12d	59.66	Yes, 3.159	Ile298, Pro270

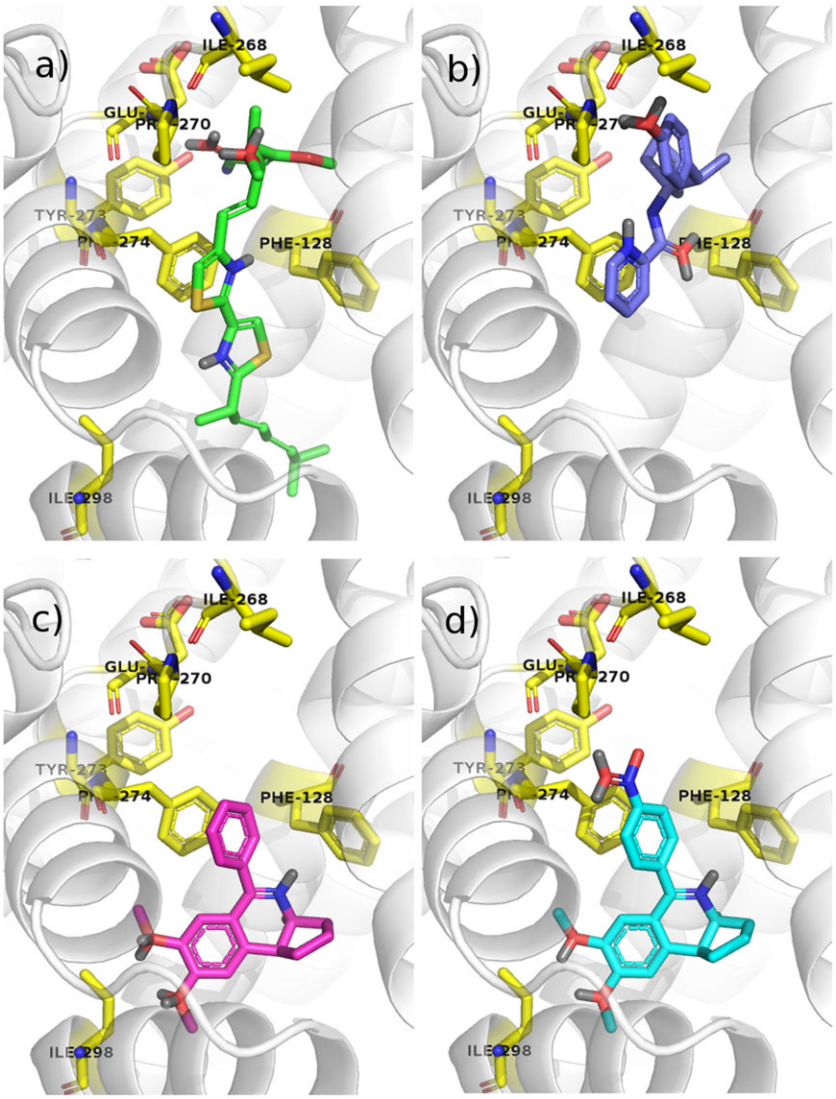


Figure 4. Comparison of the binding modes of myxothiazol and compounds **6e** and **12a**, **d**: (a) the simulated binding model of bc_1 in complex with myxothiazol; (b) the simulated binding model of bc_1 in complex with compound (*R*)-**6e**; (c) the simulated binding model of bc_1 in complex with compound (*S,S*)-**12a**; (d) the simulated binding model of bc_1 in complex with compound (*S,S*)-**12d**. [Color figure can be viewed at wileyonlinelibrary.com]

radical of compounds **12a**,**d** was observed as well (Table 1). These π–π stacking interactions are possible because of conformational flexibility of Phe274 side chain [28]. As shown in Table 1, besides the π–π stacking, compounds **12a**,**d** form hydrogen bonds with amino acid residues of protein within Q_0 pocket. Unlike myxothiazol that forms H-bond with Glu271 and Tyr273, compound **12a** formed H-bond with Ile146 and **12d** formed H-bond with Ile298. The heteroaromatic fragment of molecule **6e** also resulted in the π–π stacking interaction with Phe274 (Fig. 4b, Table 1). However, the conformation of compound **6e** within Q_0 pocket differs from that of compounds **12a**,**d** by the presence of three H-bonds with Pro270, Ile268, and Phe128 within the active site of the bovine bc_1 complex (Table 1).

The GOLD score data for the potential inhibitors of bc_1 complex **6e** and **12a**,**d** have been supported by the calculated Lipinski parameters [29] (Table S2). The predicted octanol/water partition coefficient (ClogP) is useful for the estimation of the hydrophobic interactions within the Q_0 pocket formed by the side chains of Phe274, Phe128, Ile146, Pro270, Ala277, Leu294, Met124, and Ile298 [30]. The ligand-protein interactions may be possible because of the high value of predicted lipophilicity (ClogP ranging from 3.96 to 4.22) of the synthesized compounds **6e** and **12a**,**d**. Interestingly, the ligands **6e** and **12d** showed highest potential inhibitor efficiency for bc_1 complex due to the similar ClogP values (3.749 and 3.96, respectively) and correlating high GOLD scores values (60.93 and 59.66, respectively).

Methods and materials. ***Prediction of activity spectra for substances.*** A dataset consisting of 20 compounds were processed through the PASS online service [19] (www.pharmaexpert.ru/passonline/). As a scoring function, the PASS estimates the probability of the presence (Pa) and the absence (Pi) of each activity in the range from 0 to 1. The Pa value was used as the main criterion; therefore, only activities with Pa > Pi were considered.

Molecular docking. Molecular docking studies were carried out on a laptop PC with Intel® Core™ i3-6100 QM CPU at 3.70 GHz, RAM 8 GB operating under the Windows 7 Professional OS. Briefly, the 3D crystal structures of bovine bc_1 complex with azoxystrobin (AZ), β-methoxyacrylate stilbene (MOAS), myxothiazol, 5-undecyl-6-hydroxy-4,7-dioxobenzothiazole (UHDBT), and stigmatellin were downloaded from the RCSB Protein Data Bank (PDB code 1SQB, 1SQQ, 1SQP, 1SQV, and 1SQX, respectively) [23] and loaded into the GOLD 5.0.1 version (CCDC Software, http://www.ccdc.cam.ac.uk/products) [31]. All types of atoms, charges, and bond hybridization were carefully checked. Protons were added, and all crystallographic water molecules were removed. The native ligand was removed, and the binding site was defined as all atoms within 5 Å of the crystallographic ligand. The GOLD software was benchmarked by docking AZ, MOAS, myxothiazol, UHDBT, and stigmatellin into the native binding site of the bc_1 complex [32].

The ChemBio3D Ultra 14.0 software (Perkin Elmer) was used to draw the 3D structures of synthesized compounds that were further pre-optimized with MM2 force field and saved in mol2 file format. The docking was performed 10 times using standard parameters, and the GOLD score was determined. Conformation of the ligands with the highest GOLD score value was selected as the best and then compared with the conformation of native co-crystallized ligand by the PyMOL Molecular Graphics System 2.0 (Schrödinger LLC).

To assess compliance of the compounds **6e** and **12a**,**d** with the Lipinski rule of five [14], their molecular weight (Mw) and octanol/water partition coefficient (ClogP) were calculated using the ChemBioDraw 14.0 software (Perkin Elmer).

EXPERIMENTAL

All commercially available materials and reagents were purchased from Alfa Aesar with no further purification. Melting points were measured in open capillaries on the Stuart SMP40 melting point device without further correction. The IR spectra were recorded on Fourier spectrometers, models FCM-1201 or Bruker IFS-66/S, in petroleum jelly. ^{1}H and ^{13}C NMR spectra were recorded on the Varian Mercury Plus 300 or Bruker DRX 400 Hz spectrometers, with chemical shifts and coupling constants (J) expressed in parts per million (ppm) and hertz (Hz), respectively. Mass spectra were acquired on the Agilent Technology 6890N/5975B mass spectrometer (ionization potential 70 eV). Microanalyses (C, H, and N) were carried out on the Leco CHNS-932 elemental analyzer. The reactions and purity of the compounds obtained were overseen by TLC on Sorbfil plates, with the use of 0.5% solution of chloranil in toluene and UV light.

General procedure for synthesis of 1–3 and 11. To a freshly prepared 0.036 mole solution of CH_3MgI in Et_2O, a solution of 0.030 mole of corresponding ketone in 10 mL of Et_2O was added dropwise and stirred at such a rate that the mixture was slightly boiling. With the remaining amount of ketone added, the reaction mixture was additionally refluxed for 2 h. The reaction mass was then cooled with ice and hydrolyzed by slow dropping into 35 mL of saturated NH_4Cl solution. After separation of the phases, the aqueous phase was extracted with Et_2O (3 × 15 mL). The combined extracts were washed with water and dried over $MgSO_4$, whereupon the solvent was distilled off. The residue (**3** and **11**) was distilled at appropriate temperature or isolated by column chromatography (**1** and **2**). The yield of compounds **1–3** and **11** equaled 52–93%.

General procedure for synthesis of 5a–c, **6e**,**f**, **7a–f**, **8**, **9b–d**, **10**, **and 12a–d**. A mixture composed of 1 mmol of carbinol **1–3** or styrene **11** and 1 mmol of nitrile was added dropwise to 1 mL of 92% H_2SO_4 while vigorously stirred and cooled with ice water. The reaction mixture was then stirred for 20 min at room temperature, poured into a mixture of crushed ice with 4 mL of aqueous ammonia, and extracted with CH_2Cl_2 (3 × 5 mL). The combined extracts were washed with water, dried over $MgSO_4$, whereupon the solvent was distilled off. The reaction product was isolated by column chromatography or crystallization from a suitable solvent.

Compound **10** was obtained from **7b**. Compound **7b** (0.2 g) was mixed with 1 mL of freshly prepared CH_3COOK and heated for 10 h at 80°C. The mixture was then hydrolyzed with 2 mL of ammonia, washed with hexane, and crystallized from ethyl acetate.

The structures of all the synthesized compounds were confirmed by ^{1}H NMR, ^{13}C NMR, GC/MS, IR, and elemental analysis; X-ray diffraction analysis for compounds **9c**,**d**, **10**, and **12c** was carried out.

6-Methyl-13-phenyl-14-azadispiro[4.1.5.2]tetradeca-8,11,13-trien-10-one (5a). Yield 79%, white crystals, mp 156–158°C (from ethyl acetate). IR: 3325, 2960, 2872, 1643, 1600, 1514 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.82 (d, 3H, C(6)H$\underline{CH_3}$, J = 7.2 Hz), 1.40–2.20 (m, 8H, C(1)H_2, C(2)H_2, C(3)H_2, C(4)H_2), 2.59 (q, 1H, H(6), J = 14.6, 7.2 Hz), 6.42 (dd, 1H, H(9), J = 1.8, 9.9 Hz),

6.49 (dd, 1H, H(11), J = 1.5, 10.2 Hz), 6.80 (dd, 1H, H(8), J = 2.7, 9.9 Hz), 6.89 (dd, 1H, H(12), J = 2.8, 9.9 Hz), 7.20–7.40 (m, 3H, H_{Ar}(3), H_{Ar}(4), H_{Ar}(5)), 7.63 (d, 2H, H_{Ar}(2), H_{Ar}(6), J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 9.29 (C(6)H<u>C</u>H$_3$), 25.09, 26.54, 34.01, 40.55 (C(1)H_2, C(2)H_2, C(3)H_2, C(4)H_2), 53.07 (C(6)), 64.73 (C(7)), 84.35 (C(5)), 127.61, 128.50, 130.20, 130.73, 131.35 (C(9), C(11), C_{Ar}(2), C_{Ar}(3), C_{Ar}(4), C_{Ar}(5), C_{Ar}(6)), 148.55, 152.12 (C(8), C(12)), 166.16, 185.61 (C(10), C(13)). MS, (*m/z*, %): 291 $[M]^+$ (0.14), 188 $[M-C_6H_5CN]^+$ (27), 173 (33), 147 (26), 145 (18), 131 (10), 121 (15), 107 (16), 103 (100), 91 (14), 77 (17), 76 (34), 50 (16). *Anal*. Calcd for $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.33; H, 7.16; N, 4.80.

6-Methyl-13-(methylthio)-14-azadispiro[4.1.5.2]tetradeca-8,11,13-trien-10-one (5b). Yield 45%, yellow-white crystals, mp 75°C (eluent: hexane-ethyl acetate 10:1). IR: 3042, 2958, 2930, 2872, 1667, 1579 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.84 (d, 3H, C(6)H<u>C</u>H$_3$, J = 7.2 Hz), 1.20–2.10 (m, 8H, C(1)H_2, C(2)H_2, C(3)H_2, C(4)H_2), 2.38 (s, 3H, SCH_3), 2.59 (q, 1H, H(6), J = 14.7, 7.2 Hz), 6.30–6.45 (m, 2H, H(8), H(12)), 6.60–6.75 (m, 2H, H(9), H(11)). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 9.43, 13.38 (C(6)H<u>C</u>H$_3$, SCH_3), 24.27, 25.86, 34.03, 40.23 (C(1)H_2, C(2)H_2, C(3)H_2, C(4)H_2), 52.78 (C(6)), 64.63 (C(7)), 85.10 (C(5)), 130.73, 131.07 (C(9), C(11)), 146.23, 149.38 (C(8), C(12)), 166.65, 185.29 (C(10), C(13)). MS, (*m/z*, %): 261 $[M]^+$ (2), 189 (15), 188 $[M-CH_3SCN]^+$ (100), 173 (27), 147 (15), 145 (14), 131 (19), 126 (13), 121 (72), 120 (38), 108 (16), 107 (33), 92 (17), 91 (33), 82 (14), 81 (29), 77 (12), 67 (29). *Anal*. Calcd for $C_{17}H_{23}NOS$: C, 68.93; H, 7.33; N, 5.36; S, 12.27. Found: C, 68.78; H, 7.51; N, 5.45; S, 12.18.

Ethyl 2-(6-methyl-10-oxo-14-azadispiro[4.1.5.2]tetradeca-8,11-dien-13-ylidene)ethanoate (5c). Yield 40%, white crystals, mp 99°C (eluent: hexane-acetone 5:1). IR: 3338, 2963, 2875, 1663, 1600 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.84 (d, 3H, C(6)H<u>C</u>H$_3$, J = 7.5 Hz), 1.20 (t, 3H, OCH$_2$<u>C</u>H$_3$, J = 7.2 Hz), 1.50–2.00 (m, 8H, C(1)H_2, C(2)H_2, C(3)H_2, C(4)H_2), 2.56 (q, 1H, H(6), J = 15.0, 7.2 Hz), 4.05 (q, 2H, O<u>C</u>H$_2$CH$_3$, J = 14.1, 7.2 Hz), 4.27 (s, 1H, =CH–), 6.27 (dd, 1H, H(9), J = 1.8, 9.9 Hz), 6.36 (dd, 1H, H(11), J = 9.9, 1.8 Hz), 6.68 (dd, 1H, H(8), J = 2.7, 9.9 Hz), 6.78 (dd, 1H, H(12), J = 3.0, 9.9 Hz), 8.23 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 8.82, 14.25 (C(6)H<u>C</u>H$_3$, OCH$_2$<u>C</u>H$_3$), 23.17, 24.81, 34.80, 39.48 (C(1)H_2, C(2)H_2, C(3)H_2, C(4)H_2), 48.54 (C(6)), 56.41 (C(7)), 58.51 (O<u>C</u>H$_2$CH$_3$), 72.94 (C(5)), 77.97 (=CH–), 129.23, 130.44 (C(9), C(11)), 146.47, 149.32 (C(8), C(12)), 160.95, 170.11, 185.08 (C(10), C(13), C=O). *Anal*. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.50; H, 7.74; N, 4.81.

N-{1-[1-(4-Hydroxyphenyl)ethyl]cyclopentyl}pyridine-2-carboxamide (6e). Yield 21%, yellow oil (eluent: hexane-ethyl acetate 5:1). IR: 3346, 3060, 2966, 2937, 2875, 1662, 1614, 1591, 1515 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.31 (d, 3H, CH<u>C</u>H$_3$, J = 7.2 Hz), 1.10–2.50 (m, 8H, C(<u>C</u>H$_2$)$_4$), 3.66 (q, 1H, <u>C</u>HCH$_3$, J = 7.2, 15.0 Hz), 6.30–9.10 (m, 10H, H_{Ar}(2), H_{Ar}(3), H_{Ar}(5), H_{Ar}(6), H_{Py}(3), H_{Py}(4), H_{Py}(5), H_{Py}(6), OH, NH). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 16.60 (CH<u>C</u>H$_3$), 22.99, 23.26, 33.82, 34.84 (C(<u>C</u>H$_2$)$_4$), 43.16 (<u>C</u>HCH$_3$), 68.96 (<u>C</u>(CH$_2$)$_4$), 113.75, 114.42 (C_{Ar}(3), C_{Ar}(5)), 121.62, 125, 92 (C_{Py}(3), C_{Py}(5)), 129.32, 129.81 (C_{Ar}(2), C_{Ar}(6)), 134.65 (C_{Ar}(1)), 137.41 (C_{Py}(4)), 147.77 (C_{Py}(6)), 150.14 (C_{Py}(2)), 154.96 (C_{Ar}(4)), 163.76 (C=O). MS, (*m/z*, %): 310 $[M]^+$ (0.07), 189 (100), 171 (13), 106 (21), 78 (40). *Anal*. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14; N, 9.03. Found: C, 73.75; H, 7.08; N, 9.10.

N-{1-[1-(4-Hydroxyphenyl)etyl]cyclopentyl}acetamide (6f). Yield 57%, white crystals, mp 131°C (eluent: hexane-ethyl acetate 5:1). IR: 3330, 2953, 2922, 2851, 1744, 1636, 1618, 1544 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.18 (d, 3H, CH<u>C</u>H$_3$, J = 7.5 Hz), 1.30–2.00 (m, 8H, C(<u>C</u>H$_2$)$_4$), 1.77 (s, 1H, COCH$_3$), 3.60 (q, 1H, <u>C</u>HCH$_3$, J = 7.2, 14.4 Hz), 6.67 (d, 2H, H_{Ar}(3), H_{Ar}(5), J = 8.8 Hz), 6.97 (d, 2H, H_{Ar}(2), H_{Ar}(6), J = 8.8 Hz), 7.09 (s, 1H, OH), 9.07 (bs, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 16.39 (CH<u>C</u>H$_3$), 22.83 (CO<u>C</u>H$_3$), 22.93, 23.59, 32.75, 33.06 (C(<u>C</u>H$_2$)$_4$), 41.12 (<u>C</u>HCH$_3$), 67.79 (<u>C</u>(CH$_2$)$_4$), 114.42 (C_{Ar}(3), C_{Ar}(5)), 129.42 (C_{Ar}(2), C_{Ar}(6)), 134.22 (C_{Ar}(1)), 155.45 (C_{Ar}(4)), 169.02 (C=O). MS, (*m/z*, %): 247 $[M]^+$ (0.2), 126 $[C_5H_8NHCOCH_3]^+$ (51), 84 $[C_5H_8NH]^+$ (100). *Anal*. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.58; H, 8.69; N, 5.41.

9-Methoxy-4a,10b-dimethyl-6-phenyl-1,2,3,4,4a,10b-hexahydrophenanthridine (7a). Yield 56%, dark yellow oil (eluent: hexane-ethyl acetate 10:1). IR: 3417, 3200, 2928, 2858, 1665, 1514, 1216 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.8–1.9 (m, 14H, C(1)H_2, C(2)H_2, C(3)H_2, C(4)H_2, C(4a)CH_3, C(10b)CH_3), 3.79 (s, 3H, OCH_3), 6.61 (dd, 1H, H(8), J = 8.4, 2.7 Hz), 6.93 (d, 1H, H(10), J = 2.4 Hz), 7.09 (d, 1H, H(7), J = 8.4 Hz), 7.30–7.55 (m, 5H, HAr). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 21.08, 22.28, 29.52, 35.01 (C(1), C(2), C(3), C(4)), 14.26, 21.44 (C(4a)<u>C</u>H$_3$, C(10b)<u>C</u>H$_3$), 38.39 (C(4a)), 55.01 (OCH_3), 59.16 (<u>C</u>(10b)), 109.01, 111.04, 129.88 (C(7), C(8), C(10)), 120.49 (C(6a)), 127.93, 128.34 (C_{Ar}(2), C_{Ar}(3), C_{Ar}(4), C_{Ar}(5), C_{Ar}(6)), 128.31 (C_{Ar}(1)), 139.98, 161.59, 163.53 (C(6), C(9), C(10a)). MS, (*m/z*, %): 319 $[M]^+$ (80), 318 (100), 304 $[M-CH_3]^+$ (16), 290 (20), 265 (19), 264 (54), 248 (17), 242 (23), 236 (14). *Anal*. Calcd for $C_{22}H_{25}NO$: C, 82.72; H, 7.89; N, 4.38. Found: C, 82.96; H, 7.71; N, 4.16.

9-Methoxy-4a,10b-dimethyl-6-(methylthio)-1,2,3,4,4a,10b-hexahydrophenanthridine (7b). Yield 72%, light yellow oil (eluent: hexane-ethyl acetate 10:1). IR: 3157, 2927, 2855, 1604, 1485, 1246 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.70–1.80 (m, 14H, C(1)H_2, C(2)H_2, C(3)H_2, C(4)H_2, C(4a)CH_3, C(10b)CH_3), 2.42 (s, 3H, SCH_3),

3.81 (s, 3H, OCH_3), 6.75 (dd, 1H, H(8), J = 8.6, 2.7 Hz), 6.85 (d, 1H, H(10), J = 2.7 Hz), 7.57 (d, 1H, H(7), J = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 12.08 (SCH_3), 14.09, 22.16 (C(4a)$\underline{CH_3}$, C(10b)$\underline{CH_3}$), 21.18, 22.20, 29.66, 35.98 (C(1), C(2), C(3), C(4)), 38.95 (C(4a)), 55.16 (OCH_3), 60.47 (C(10b)), 109.54, 111.05, 126.17 (C(7), C(8), C(10)), 121.04 (C(6a)), 147.49, 158.47, 161.75 (C(6), C(9), C(10a)). MS, (*m*/*z*, %): 289 $[M]^+$ (30), 275 $[M\text{-}CH_3 + 1]^+$ (19), 274 $[M\text{-}CH_3]^+$ (100), 256 (13), 234 (17). *Anal*. Calcd for $C_{17}H_{23}NOS$: C, 70.54; H, 8.01; N, 4.84; S, 11.08. Found: C, 70.63; H, 8.18; N, 4.60; S, 11.01.

Ethyl 2-(9-methoxy-4a,10b-dimethyl-1,2,3,4,4a,5-hexahydrophenanthridin-6(10bH)-ylidene)acetate (7c). Yield 50%, yellow-green oil (eluent: hexane-ethyl acetate 5:1). IR: 3270, 2974, 2935, 2863, 1737, 1663, 1643, 1600, 1484, 1288 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.58–1.74 (m, 17H, C(1)H_2, C(2)H_2, C(3)H_2, C(4)H_2, C(4a)CH_3, C(10b)CH_3, $CH_2\underline{CH_3}$), 3.94 (s, 3H, OCH_3), 4.40 (q, 2H, $O\underline{CH_2}CH_3$, J = 7.2 Hz), 5.06 (s, 1H, =CH–), 6.65–7.00 (m, 2H, H(8), H(10)), 7.65 (d, 1H, H(7), J = 8.8 Hz), 8.97 (bs, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 13.55, 14.22, 20.06 (C(4a)$\underline{CH_3}$, C(10b)$\underline{CH_3}$, $OCH_2\underline{CH_3}$), 20.69, 21.85, 34.56, 35.07 (C(1), C(2), C(3), C(4)), 53.46 (C(4a)), 54.74 (OCH_3), 57.80 ($O\underline{CH_2}CH_3$), 61.04 (C(10b)), 75.10 (–CH=), 110.27, 110.88, 126.51 (C(7), C(8), C(10)), 120.36 (C(6a)), 148.32, 154.79, 161.53, 170.93 (C(6), C(9), C(10a), C=O). *Anal*. Calcd for $C_{20}H_{27}NO_3$: C, 72.92; H, 8.26; N, 4.25. Found: C, 72.86; H, 8.43; N, 4.19.

9-Methoxy-4a,10b-dimethyl-6-(4-nitrophenyl)-1,2,3,4,4a,10b-hexahydrophenanthridine (7d). Yield 48%, yellow oil (eluent: hexane-ethyl acetate 10:1). IR: 3107, 3076, 3054, 2827, 2860, 2233, 1941, 1807, 1692, 1528, 1350 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.60–2.00 (m, 14H, C(1)H_2, C(2)H_2, C(3)H_2, C(4)H_2, C(4a)CH_3, C(10b)CH_3), 3.83 (s, 3H, OCH_3), 6.64 (dd, 1H, H(8), J = 8.4, 2.7 Hz), 6.90–7.40 (m, 2H, H(7), H(10)), 7.66 (d, 2H, H_{Ar}(2), H_{Ar}(6), J = 8.7 Hz), 8.24 (d, 2H, H_{Ar}(3), H_{Ar}(5), J = 8.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 21.02, 22.31, 29.58, 34.97 (C(1), C(2), C(3), C(4)), 14.28, 21.32 (C(4a)$\underline{CH_3}$, C(10b)$\underline{CH_3}$), 38.53 (C(4a)), 55.22 (OCH_3), 59.92 (C(10b)), 109.50, 111.56, 129.32 (C(7), C(8), C(10)), 119.63 (C(6a)), 123.63, 129.51 (C_{Ar}(2), C_{Ar}(3), C_{Ar}(5), C_{Ar}(6)), 130.21 (C_{Ar}(1)), 146.30, 147.84, 162.08, 162.16 (C(6), C(9), C(10a), C_{Ar}(4)). MS, (*m*/*z*, %): 364 $[M]^+$ (100), 363 (91), 349 $[M\text{-}CH_3]^+$ (18), 335 (22), 317 (21), 310 (25), 309 (65), 242 (32). *Anal*. Calcd for $C_{22}H_{24}N_2O_3$: C, 72.50; H, 6.64; N, 7.69. Found: C, 72.76; H, 6.36; N, 7.48.

9-Methoxy-4a,10b-dimethyl-6-(pyridin-2-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine (7e). Yield 61%, yellow oil (eluent: hexane-acetone 5:1). IR: 3453, 3296, 3219, 3057, 2931, 2859, 1694, 1606, 1566, 1491 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.80–1.90 (m, 14H, C(1)H_2, C(2)H_2, C(3)H_2, C(4)H_2, C(4a)CH_3, C(10b)CH_3), 3.82 (s, 3H, OCH_3), 6.66 (dd, 1H, H(8), J = 8.8, 2.7 Hz), 6.92 (d, 1H, H(10), J = 2.4 Hz), 7.25 (d, 1H, H(7), J = 4.5 Hz), 7.27–7.40 (m, 1H, H_{Py}(5)), 7.69 (dd, 1H, H_{Py}(3), J = 9.0, 1.8 Hz), 7.77 (td, 1H, H_{Py}(4), J = 7.5, 1.8 Hz), 8.65 (m, 1H, H_{Py}(6)). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 20.72, 21.96, 29.14, 34.68 (C(1), C(2), C(3), C(4)), 13.53, 20.96 (C(4a)$\underline{CH_3}$, C(10b)$\underline{CH_3}$), 38.19 (C(4a)), 54.66 (OCH_3), 59.23 (C(10b)), 109.11, 110.74, 129.61 (C(7), C(8), C(10)), 119.49 (C(6a)), 122.79, 123.32, 136.26, 147.92 (C_{Py}(3), C_{Py}(4), C_{Py}(5), C_{Py}(6)), 157.85, 161.48, 161.76, 166.25 (C(6), C(9), C(10a), C_{Py}(2)). MS, (*m*/*z*, %): 320 $[M]^+$ (22), 306 $[M\text{-}CH_3 + 1]^+$ (23), 305 $[M\text{-}CH_3]^+$ (100), 264 (27). *Anal*. Calcd for $C_{21}H_{24}N_2O$: C, 78.71; H, 7.55; N, 8.74. Found: C, 78.76; H, 7.73; N, 8.65.

9-Methoxy-4a,6,10b-trimethyl-1,2,3,4,4a,10b-hexahydrophenanthridine (7f). Yield 43%, red-orange oil (eluent: hexane-ethyl acetate 5:1). IR: 3291, 3081, 2929, 2858, 1704, 1631, 1605, 1492, 1241 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.73–1.77 (m, 14H, C(1)H_2, C(2)H_2, C(3)H_2, C(4)H_2, C(4a)CH_3, C(10b)CH_3), 2.43 (s, 3H, C(6)CH_3), 3.85 (s, 3H, OCH_3), 6.76 (dd, 1H, H(8), J = 8.5, 2.6 Hz), 6.89 (d, 1H, H(10), J = 2.6 Hz), 7.48 (d, 1H, H(7), J = 8.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 21.07, 22.07, 29.48, 35.19 (C(1), C(2), C(3), C(4)), 21.75, 22.90 (C(4a)$\underline{CH_3}$, C(10b)$\underline{CH_3}$), 29.11 (C(6)$\underline{CH_3}$), 38.53 (C(4a)), 55.01 (OCH_3), 58.38 (C(10b)), 109.54, 110.92, 127.18 (C(7), C(8), C(10)), 120.97 (C(6a)), 147.99, 160.30, 161.70 (C(6), C(9), C(10a)). MS, (*m*/*z*, %): 257 $[M]^+$ (85), 256 (35), 243 $[M\text{-}CH_3 + 1]^+$ (18), 242 $[M\text{-}CH_3]^+$ (100), 228 (50), 214 (23), 203 (42), 202 (43), 188 (27), 187 (34), 174 (21). *Anal*. Calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9.01; N, 5.44. Found: C, 79.18; H, 9.13; N, 5.29.

8-Methoxy-3a-methyl-5-phenyl-2,3,3a,9b-tetrahydro-1H-cyclopenta[c]isoquinoline (8). Yield 67%, yellow oil (eluent: hexane-ethyl acetate 5:1). IR: 2951, 2864, 1664, 1606 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.13 (s, 3H, C(3a)CH_3), 1.45–2.50 (m, 6H, C(1)H_2, C(2)H_2, C(3)H_2), 2.75 (t, 1H, C(9b)H, J = 9.6 Hz), 3.82 (s, 3H, OCH_3), 6.65 (dd, 1H, H(7), J = 8.4, 2.7 Hz), 6.76 (d, 1H, H(9), J = 8.4 Hz), 7.14 (d, 1H, H(6), J = 8.7 Hz), 7.30–7.55 (m, 5H, H_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 25.36 (C(2)), 28.10 (C(3a)$\underline{CH_3}$), 31.24 (C(1)), 40.37 (C(3)), 46.60 (C(9b)), 55.24 (OCH_3), 65.76 (C(3a)), 111.29 (C(9)), 115.98 (C(7)), 127.41, 127.70, 128,03, 128.32 (C_{Ar}(2), C_{Ar}(3), C_{Ar}(5), C_{Ar}(6)), 128.34 (C(5a)), 129.28 (C(6)), 130.69 (C_{Ar}(4)), 133.51 (C_{Ar}(1)), 143.29 (C(9a)), 156.42 (C(5)), 166.21 (C(8)). MS, (*m*/*z*, %): 291 $[M]^+$ (100), 290 $[M\text{-}H]^+$ (87), 276 $[M\text{-}CH_3]^+$ (21), 263 (73), 262 (28), 248 (15), 178 (17). *Anal*. Calcd for $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.49; H, 7.39; N, 4.75.

6a′-Methyl-2′-(methylthio)-4′,5′,6′,6a′-tetrahydro-3a′H-spiro[cyclohexa[2,5]diene-1,3′-cyclopenta[b]pyrrol]-4-one (9b). Yield 71%, yellow oil (eluent: hexane-ethyl acetate 5:1). IR: 3381, 3295, 2956, 2870, 1666, 1593 cm^{-1}. ^{1}H

NMR (300 MHz, $CDCl_3$), δ: 1.45–2.10 (m, 6H, C(4′)H_2, C(5′)H_2, C(6′)H_2), 1.52 (s, 3H, C(6a′)CH_3), 2.37 (s, 1H, SCH_3), 2.53 (dd, 1H, H(3a′), J = 8.1, 4.2 Hz), 6.23 (dt, 1H, H(2), J = 0.9, 9.9 Hz), 6.39 (dt, 1H, H(6), J = 0.9, 10.2 Hz), 6.68 (dd, 1H, H(3), J = 2.85, 9.9 Hz), 6.79 (dd, 1H, H(5), J = 3.0, 10.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 13.91 (C(5′)), 25.42 (SCH_3), 28.42 (C(4′)), 30.54 (C(6a′)CH_3), 40.54 (C(3a′)), 58.29 (C(6′)), 63.25 (C(3′)), 85.97 (C(6a′)), 127.43 (C(5)), 130.51 (C(3)), 146.32 (C(6)), 150.45 (C(2)), 167.00 (C(2′), 184.83 (C(4)). MS, (*m/z*, %): 247 $[M]^+$ (1.7), 175 (13), 174 (100), 159 (21), 146 (32), 133 (11), 131 (28), 120 (71), 107 (19), 91 (18), 77 (17), 73 (18), 655 (13), 55 (33), 41 (15), 39 (17). *Anal*. Calcd for $C_{14}H_{17}NOS$: C, 67.98; H, 6.93; N, 5.66; S, 12.96. Found: C, 67.94; H, 6.89; N, 5.85; S, 12.88.

Ethyl 2-(6a′-methyl-4-oxo-3a′,4′,5′,6′-tetrahydro-1′H-spiro[cyclohexa[2,5]diene-1,3′-cyclopenta[b]pyrrole]-2′(6a′H)-ylidene)acetate (9c). Yield 78%, orange crystals, mp 169–170°C (from acetone). IR: 3323, 3115, 2968, 1658, 1605 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.00–2.10 (m, 12H, C(6a′)CH_3, C(4′)H_2, C(5′)H_2, C(6′)H_2, OCH_2CH_3), 2.40–2.50 (m, 1H, H(3a′)), 4.12 (q, 2H, OCH_2CH_3, J = 7.2 Hz), 4.23 (s, 1H, =CH–), 6.16 (d, 1H, H(2), J = 9 Hz), 6.35 (d, 1H, H(6), J = 10.2 Hz), 6.75–6.90 (m, 2H, H(3), H(5)), 7.93 (1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 14.33 (OCH_2CH_3), 25.53 (C(4′)), 28.78 (C(6a′)CH_3), 30.48 (C(5′)), 41.78 (C(6′)), 54.47 (C(3′)), 55.97 (C(3a′)), 58.62 (OCH_2CH_3), 72.37 (C(6a′)), 77.43 (=CH–), 126.09, 129.59 (C(3), C(5)), 147.07, 150.78 (C(2), C(6)), 162.48 (C(2′)), 170.36 (C=O), 184.89 (C(4)). *Anal*. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 71.18; H, 7.45; N, 4.69.

X-ray diffraction analysis of compound 9c. The cell parameters and the set of experimental reflections of a sample of compound **9c** were measured on a single crystal X-ray diffractometer equipped with the Xcalibur Ruby CCD detector by the ω-2θ scanning method on monochromatized MoK_α-radiation at T = 295 (2) K.

Absorption is taken into account empirically using the algorithm SCALE3 ABSPACK [33]. The structure was solved by a direct statistical method and refined by the full-matrix least-squares method in the anisotropic approximation for all non-hydrogen atoms. The hydrogen atoms of the NH groups are refined independently in the isotropic approximation; the rest are placed in geometrically calculated positions and included in the refinement using the riding model. All calculations to determine and refine the structures were performed using the program SHELXL-97 [34]. To analyze the compound **9c** with the gross formula $C_{17}H_{21}NO_3$, an orange crystal with a size of 0.55 × 0.30 × 0.20 mm was used. Crystal rhombic, space group $P2_12_12_1$, a 9.468 (2), b 9.704 (4), c 17.245 (6) Å, V 1584.5 (9) $Å^3$, d_{calc} 1.205 g/cm^3, Z 4. The soft restrictions SADI, DFIX, SIMU, and DELU are imposed on the geometric and anisotropic parameters of the part of a disordered atom. Final refinement results: R_1 0.0649, wR_2 0.1626 for 2224 reflections with $I > 2\sigma(I)$; R_1 0.0988, wR_2 0.1936 for all 3492 independent reflections, S 1.031. Summary of data CCDC 1833626.

6a′-Methyl-2′-(4-nitrophenyl)-4′,5′,6′,6a′-tetrahydro-3a′H-spiro[cyclohexa[2,5]diene-1,3′-cyclopenta[b]pyrrol]-4-one (9d). Yield 81%, colorless crystals, mp 163°C (from acetone). IR: 3323, 3115, 2968, 1658, 1605 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.40–2.25 (m, 6H, C(4′)H_2, C(5′)H_2, C(6′)H_2), 1.62 (s, 3H, C(6a′)CH_3), 2.61 (dd, 1H, H(3a′), J = 7.35, 4.65 Hz), 6.41 (dd, 1H, H(2), J = 1.8, 9.9 Hz), 6.48 (dd, 1H, H(6), J = 1.8, 9.9 Hz), 6.91 (dd, 1H, H(3), J = 3.0, 9.9 Hz), 6.98 (dd, 1H, H(5), J = 3.0, 9.9 Hz), 7.80–7.90 (dm, 2H, H_{Ar}(2), H_{Ar}(6)), 8.10–8.20 (dm, 2H, H_{Ar}(3), H_{Ar}(5)). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 25.26 (C(5′)), 27.85 (C(6a′)CH_3), 31.02 (C(4′)), 40.16 (C(6′)), 59.46 (C(3a′)), 62.08 (C(3′)), 85.07 (C(6a′)) 123.28 (C_{Ar}(3), C_{Ar}(5)), 127.91 (C(5)), 128.64 (C_{Ar}(2), C_{Ar}(6)), 130.69 (C(3)), 139.22 (C_{Ar}(1)), 147.93 (C(6)), 148.71 (C_{Ar}(4)), 151.35 (C(2), 164.27 (C(2′)), 184.33 (C(4)). MS, (*m/z*, %): 322 $[M]^+$ (0.01), 174 (100), 159 (24), 146 (45), 131 (35), 120 (99), 102 (30), 55 (49). *Anal*. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.67; H, 5.78; N, 8.55.

X-ray diffraction analysis of compound 9d. The cell parameters and the set of experimental reflections of a sample of compound **9d** were measured on a single crystal X-ray diffractometer equipped with the Xcalibur Ruby CCD detector by the ω-2θ scanning method on monochromatized MoK_α-radiation at T = 295 (2) K.

Absorption is taken into account empirically using the algorithm SCALE3 ABSPACK [33]. The structure was solved by a direct statistical method and refined by the full-matrix least-squares method in the anisotropic approximation for all non-hydrogen atoms. The hydrogen atoms of the NH groups are refined independently in the isotropic approximation; the rest are placed in geometrically calculated positions and included in the refinement using the riding model. All calculations to determine and refine the structures were performed using the programs OLEX2 [35] and SHELXL-2014 [36]. To analyze the compound **9d** with the gross formula $C_{19}H_{18}N_2O_3$, a colorless crystal measuring 0.48 × 0.29 × 0.23 mm was used. The crystal is monoclinic, space group $P2_1/c$, a 7.1536 (11), b 13.054 (2), c 17.546 (3) Å, β 91.225 (17)°, V 1638.0 (5) $Å^3$, d_{calc} 1.307 g/cm^3, Z 4. Final refinement results: R_1 0.0538, wR_2 0.1365 for 2937 reflections with $I > 2\sigma(I)$; R_1 0.0715, wR_2 0.1520 for all 3900 independent reflections, S 1.031. Summary of data CCDC 1833628.

9-Methoxy-4a,10b-dimethyl-1,2,3,4,4a,5-hexahydrophenanthridin-6(10bH)-one (10). Yield 60%, colorless crystals, mp 138°C (from ethyl acetate). ^{1}H

NMR (400 MHz, $CDCl_3$), δ: 1.17, 1.32 (both s, 6H, C(4a)CH_3, C(10b)CH_3), 1.37–1.84 (m, 8H, C(1)H_2, C(2)H_2, C(3)H_2, C(4)H_2), 3.85 (s, 3H, OCH_3), 5.83 (bs, 1H, NH), 6.82 (dd, 2H, H(8), H(10), J = 7.3, 2.2 Hz), 8.06 (dd, 1H, H(7), J = 9.6, 2.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 21.15, 21.80, 29.95, 36.01 (C(1), C(2), C(3), C(4)), 24.01, 24.21 (C(4a)$\underline{CH_3}$, C(10b)$\underline{CH_3}$), 41.17 (C(4a)), 55.31 (OCH_3), 56.90 (C(10b)), 110.51, 111.02, 130.34 (C(7), C(8), C(10)), 120.07 (C(6a)), 14951, 163.32, 165.07 (C(6), C(9), C(10a)). MS, (*m*/*z*, %): 259 $[M]^+$ (20), 245 $[M\text{-}CH_3 + 1]^+$ (17), 244 $[M\text{-}CH_3]^+$ (100), 203 (83), 202 (18).

X-ray diffraction analysis of compound 10. The cell xparameters and the set of experimental reflections of a sample of compound **10** were measured on a single crystal X-ray diffractometer equipped with the Xcalibur Ruby CCD detector by the ω-2θ scanning method on monochromatized MoK_α-radiation at T = 295 (2) K.

Absorption is taken into account empirically using the algorithm SCALE3 ABSPACK [33]. The structure was solved by a direct statistical method and refined by the full-matrix least-squares method in the anisotropic approximation for all non-hydrogen atoms. The hydrogen atoms of the NH groups are refined independently in the isotropic approximation; the rest are placed in geometrically calculated positions and included in the refinement using the riding model. All calculations to determine and refine the structures were performed using the programs OLEX2 [35] and SHELXL-2014 [36]. To analyze the compound **10** with the gross formula $C_{19}H_{25}NO_4$, a colorless crystal measuring 0.58 × 0.42 × 0.34 mm was used. The crystal is monoclinic, pr. Gr. $P2_1/n$, a 11.034 (2), b 8.8730 (16), c 18.402 (3) Å, β 95.943 (18)°, V 1792.0 (6) Å3, d_{calc} 1.228 g/cm^3, Z 4. Final refinement results: R_1 0.0489, wR_2 0.1269 for 3038 reflections with $I > 2\sigma(I)$; R_1 0.0701, wR_2 0.1404 for all 4209 independent reflections, S 1.076. Summary of data CCDC 1833629.

7,8-Dimethoxy-3a-methyl-5-phenyl-2,3,3a,9b-tetrahydro-1H-cyclopenta[c]isoquinoline (12a). Yield 76%, yellow oil (eluent: hexane-ethyl acetate 2:1). IR: 2945, 2862, 1603, 1507 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.13 (s, 3H, C(3a)CH_3), 1.40–2.50 (m, 6H, C(1)H_2, C(2)H_2, C(3)H_2), 2.70 (t, 1H, C(9b)H, J = 9.6 Hz), 3.65, 3.91 (both s, 6H, 2xOCH_3), 6.60–6.85, 7.30–7.65 (both m, 7H, H(6), H(9), H_{Ar}(2), H_{Ar}(3), H_{Ar}(4), H_{Ar}(5), H_{Ar}(6)). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 22.65, 34.97, 42.06 (C(1), C(2), C(3)), 24.72 (C(3a)$\underline{CH_3}$), 45.74 (C(9b)), 55.84, 55.91 (2xOCH_3), 65.62 (C(3a)), 111.26, 111.99 (C(6), C(9)), 128.06, 128.09, 128.44, 128.61, 128.78 (C_{Ar}(2), C_{Ar}(3), C_{Ar}(4), C_{Ar}(5), C_{Ar}(6)), 118.46 (C(5a)), 134.80, 139.62 (C(9a), C_{Ar}(1)), 146.75, 150.95 (C(7), C(8)), 162.96 (C(5)). MS, (*m*/*z*, %): 321 $[M]^+$ (100), 320 (68), 306 $[M\text{-}CH_3]^+$ (46), 294 (12), 293 (58), 292 (16), 165 (16). *Anal*. Calcd for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.24; H, 7.38; N, 4.30.

7,8-Dimethoxy-3a-methyl-5-(methylthio)-2,3,3a,9b-tetrahydro-1H-cyclopenta[c]isoquinoline (12b). Yield 70%, white crystals, mp 102–103°C (from hexane). IR: 2929, 2859, 1659, 1596 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.05 (s, 3H, C(3a)CH_3), 1.15–2.35 (m, 6H, C(1)H_2, C(2)H_2, C(3)H_2), 2.40 (s, 1H, SCH_3), 2.64 (t, 1H, C(9b)H, J = 9.6 Hz Hz), 3.84 (s, 6H, 2xOCH_3), 6.64, 7.19 (both s, 2H, H(6), H(9)). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 12.22 (SCH_3), 22.88, 34.94, 42.61 (C(1), C(2), C(3)), 24.70 (C(3a)$\underline{CH_3}$), 45.94 (C(9b)), 55.82, 56.00 (2xOCH_3), 66.93 (C(3a)), 108.12, 110.94 (C(6), C(9)), 119.02 (C(5a)), 132.99 (C(9a)), 147.15, 150.89 (C(7), C(8)), 157.62 (C(5)). MS, (*m*/*z*, %): 291 $[M]^+$ (35), 290 $[M\text{-}H]^+$ (22.7), 277 (17), 276 $[M\text{-}CH_3]^+$ (100), 243 (8.5), 159 (4.0), 115 (3.3), 41 (3.4). *Anal*. Calcd for $C_{16}H_{21}NO_2S$: C, 65.95; H, 7.26; N, 4.81; S, 11.00. Found: C, 65.94; H, 7.19; N, 4.87; S, 10.88.

Ethyl 2-(7,8-dimethoxy-3a-methyl-2,3,3a,4-tetrahydro-1H-cyclopenta[c]isoquinolin-5(9bH)-ylidene)acetate (12c). Yield 78%, colorless crystals, mp 142–143°C (from acetone). IR: 3105, 2955, 2617, 1721, 1644, 1597 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.20 (s, 3H, C(3a)CH_3), 1.30 (t, 3H, $OCH_2\underline{CH_3}$, J = 7.2 Hz), 1.50–2.20 (m, 6H, C(1)H_2, C(2)H_2, C(3)H_2), 2.73 (t, 1H, C(9b)H, J = 9.6 Hz), 3.83, 3.89 (both s, 6H, 2xOCH_3), 4.05–4.30 (m, 2H, $O\underline{CH_2}CH_3$), 5.06 (s, 1H, =CH–), 6.64, 7.15 (both s, 2H, H(6), H(9)), 8.80 (bs, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 14.54 ($OCH_2\underline{CH_3}$), 22.02, 33.76, 41.11 (C(1), C(2), C(3)), 25.60 (C(3a)$\underline{CH_3}$), 49.01 (C(9b)), 55.66, 55.69 (2xOCH_3), 58.20 ($O\underline{CH_2}CH_3$), 59.85 (C(3a)), 76.13 (=CH–), 107.89, 111.17 (C(6), C(9)), 118.59 (C(5a)), 131.97 (C(9a)), 147.49 (C(8)), 151.08 (C(7)), 154.91 (C(5)), 171.00 (C=O). *Anal*. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.73; H, 7.71; N, 4.39.

X-ray diffraction analysis of compound 12c. The cell parameters and the set of experimental reflections of a sample of compound **10** were measured on a single crystal X-ray diffractometer equipped with the Xcalibur Ruby CCD detector by the ω-2θ scanning method on monochromatized MoK_α-radiation at T = 295 (2) K.

Absorption is taken into account empirically using the algorithm SCALE3 ABSPACK [33]. The structure was solved by a direct statistical method and refined by the full-matrix least-squares method in the anisotropic approximation for all non-hydrogen atoms. The hydrogen atoms of the NH groups are refined independently in the isotropic approximation; the rest are placed in geometrically calculated positions and included in the refinement using the riding model. All calculations to determine and refine the structures were performed using

the program SHELXL-97 [34]. To analyze the compound **12c** with the gross formula $C_{19}H_{25}NO_4$, a colorless crystal with a size of 0.58 × 0.42 × 0.34 mm was used. The crystal is monoclinic, space group $P2_1/n$, a 11.034 (2), b 8.8730 (16), c 18.402 (3) Å, β 95.943 (18)°, V 1792.0 (6) Å^3, d_{calc} 1.228 g/cm^3, Z 4. Final refinement results: R_1 0.0489, wR_2 0.1269 for 3038 reflections with $I > 2\sigma(I)$; R_1 0.0701, wR_2 0.1404 for all 4209 independent reflections, S 1.076. Summary of data CCDC 1833627.

7,8-dimethoxy-3a-methyl-5-(4-nitrophenyl)-2,3,3a,9b-tetrahydro-1H-cyclopenta[c]isoquinoline (11d). Yield 76%, yellow crystals, mp 178–179°C (from acetone). IR: 3442, 3334, 3114, 2937, 2860, 1665, 1599, 1515 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.16 (s, 3H, C(3a)CH_3), 1.40–2.50 (m, 6H, C(1)H_2, C(2)H_2, C(3)H_2), 2.76 (t, 1H, C(9b)H, J = 9.0 Hz), 3.69, 3.96 (both s, 6H, 2xOCH_3), 6.59, 6.80 (both s, 2H, H(6), H(9)), 7.72 (d, 2H, H_{Ar}(2), H_{Ar}(6), J = 8.4 Hz), 8.29 (d, 2H, H_{Ar}(3), H_{Ar}(5), J = 8.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 22.61, 35.03, 41.97 (C(1), C(2), C(3)), 23.61 (C(3a)$\underline{CH_3}$), 45.58 (C(9b)), 55.90, 55.97 (2xOCH_3), 66.17 (C(3a)), 111.06, 111.51 (C(6), C(9)), 117.42 (C(5a)), 123.40, 123.41, 129.50, 129.51 (C_{Ar}(2), C_{Ar}(3), C_{Ar}(5), C_{Ar}(6)), 134.96 (C(9a)), 145.98 (C_{Ar}(1)), 146.99 (C(7)), 147.94 (C_{Ar}(4), 151.56 (C(8)), 161.33 (C(5)). MS, (*m/z*, %): 366 $[M]^+$ (100), 365 $[M-H]^+$ (38), 351 $[M-CH_3]^+$ (46), 339 (13), 338 (56), 337 (16), 305 (13). *Anal*. Calcd for $C_{21}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 7.65. Found: C, 68.90; H, 6.21; N, 7.48.

CONCLUSION

In the course of this study, the reaction of 2-(4-methoxyphenyl)-1-(cycloalkyl)ethan-1-ols containing four alkyl substituents in the aliphatic part of the molecule with nitriles in accord with the Ritter reaction was confirmed to proceed with the Wagner–Meerwein rearrangement resulting in the formation of 3,3,4,4-tetraalkyl-3,4-dihydroisoquinoline derivatives. For carbinols containing a cyclobutyl radical, the Wagner–Meerwein rearrangement proceeds twice and leads, depending on the number of methoxy groups in the aromatic part, to the formation of annelated spiropyrrolines and 3,4-dihydroisoquinolines. Structural analysis of the synthesized compounds using the PASS software showed most of them to have potential activity against ubiquinol-cytochrome *c* reductase. Virtual screening of 37 possible 3D structures of the synthesized compounds by molecular docking showed the compounds (*R*)-**6e** and (*S*,*S*)-**12d** to be potential inhibitors of ubiquinol-cytochrome *c* reductase. These findings pose the task to develop a stereospecific synthesis of these compounds.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.