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Synthesis of Benzo[*f*]quinoline Derivatives by Three-Component Condensation of Tetronic Acid with Naphthalen-2-amine and Formaldehyde

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Abstract—New derivatives of benzo[*f*]furo[3,4-*b*]quinoline, spiro[benzo[*f*]quinoline-2,3′-furan], and benzo[*f*]-quinoline-2-carboxylic acid were synthesized with high selectivity by three-component condensation of tetronic acid with naphthalen-2-amine and formaldehyde.

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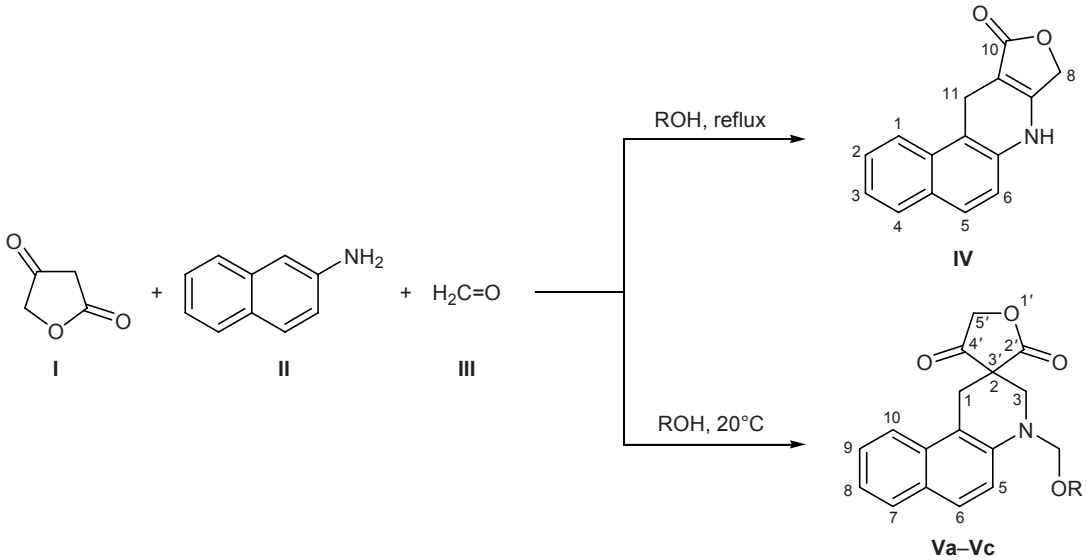
Benzo[*f*]quinoline derivatives exhibit versatile biological activity, which stimulates synthesis of new compounds of this series [1]. Various substituted benzo[*f*]quinolines were shown to possess antibacterial properties [2], inhibit choline esterase [3], 5-α-reductase [4], and HIV reverse transcriptase (HIV-1 RT) [5], and block dopamine receptors [6].

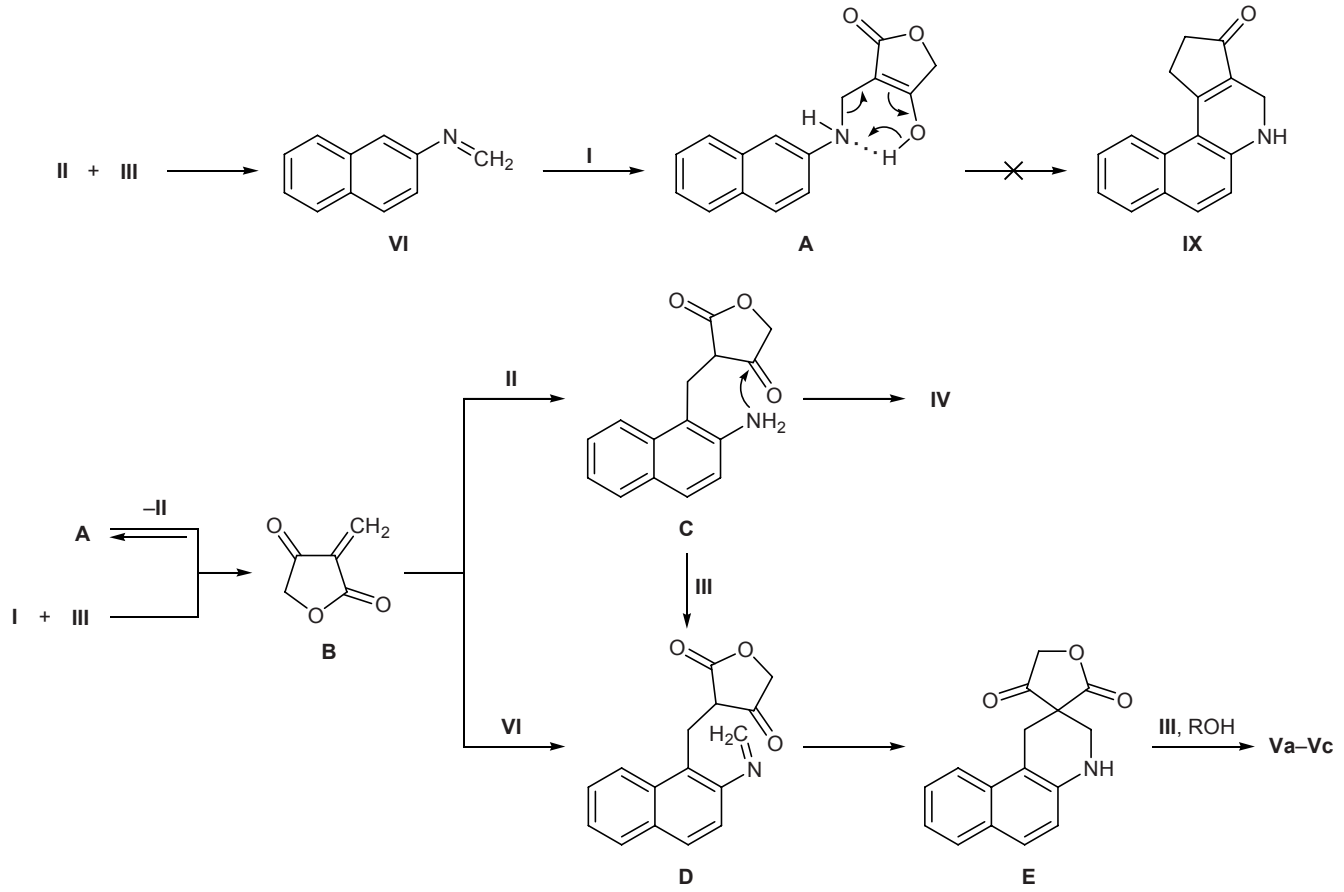
Tetronic acid (**I**, tetrahydrofuran-2,4-dione) is a structural fragment of a number of compounds exhibiting antibiotic, cytotoxic, antitumor, pesticidal, and other kinds of biological activity [7] and is used in the synthesis of natural compounds and their biologically active analogs [8]. Compounds in which tetronic acid fragment is fused to a heterocyclic system attract

Scheme 1.



R = Me (**a**), Et (**b**), *i*-Pr (**c**).

Scheme 2.



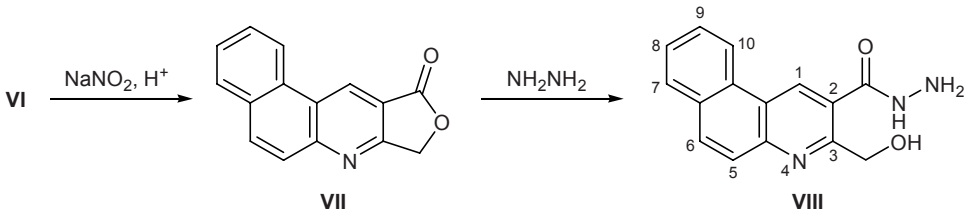
specific attention. Some derivatives of such polycyclic system showed anticancer [9], antirheumatic [10], antiarrythmic [11, 12], and enzyme inhibitory activity [13].

We previously proposed a simple and efficient one-pot procedure for the synthesis of spiro-fused benzo[*f*]-quinoline derivatives via cascade heterocyclization of cyclic β-dicarbonyl compounds with naphthalen-2-amine in the presence of excess formaldehyde [14, 15]. With a view to extend the synthetic potential of this reaction and obtain new benzo[*f*]quinoline derivatives having a tetronic acid fragment in the present work we examined three-component condensation of tetronic acid (**I**) with naphthalen-2-amine (**II**) and formaldehyde (**III**). We found that, depending on the reaction conditions and reactant ratio, selective formation of partly hydrogenated benzo[*f*]quinoline derivatives **IV** and **V** differing in the mode of fusion of tetronic acid fragment is possible (Scheme 1).

The condensation performed with equimolar amounts of the reactants in boiling aliphatic alcohol resulted in the formation of 65% of dihydrobenzo[*f*]-furo[3,4-*b*]quinoline derivative **IV**. When the condensation was performed at room temperature using excess formaldehyde (molar ratio **I**:**II**:**III** = 1:1:6 and more), the products were *N*-alkoxymethyl-substituted spiro[benzo[*f*]quinoline-2,3′-furan]-2′,4′-diones **Va**–**Vc** whose yield attained ~80%.

Probable mechanisms for the formation of compounds **IV** and **V** are shown in Scheme 2. In the first step, the condensation of formaldehyde (**III**) with naphthalen-2-amine (**II**) gives Schiff base **VI**. Addition of tetronic acid (**I**) at the polarized C=N bond in **VI** yields intermediate β-amino ketone **A**, and reversible elimination of amine **II** from the latter generates α,β-unsaturated ketone **B** in which the double C=C bond is activated due to conjugation with two carbonyl groups. Intermediate **B** could also be formed directly from formaldehyde and tetronic acid according to Knoevenagel. Next follows irreversible electrophilic substitution of hydrogen in position *1* of naphthalen-2-amine (**II**) by the action of unsaturated ketone **B**, and amino ketone **C** thus formed undergoes (at elevated temperature) thermal intramolecular cyclization to dihydrobenzo[*f*]furo[3,4-*b*]quinoline **IV** via nucleophilic

Scheme 3.



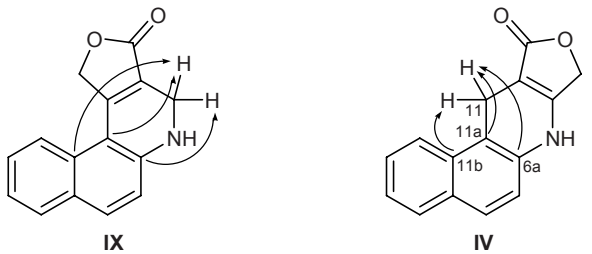
attack by the amino group on the ketone carbonyl carbon atom. If the reaction is carried out at room temperature, the cyclization is slow, while the presence of excess formaldehyde favors its reaction at the free amino group of amino ketone **C** with formation of Schiff base **D**. Intermediate **D** can also be formed by reaction of α,β-unsaturated ketone **B** at the aromatic ring of Schiff base **VI**. Spirocyclic system **E** arises as a result of intramolecular attack by nucleophilic carbon atom in the dicarbonyl fragment at the azomethine carbon atom. The subsequent Mannich type [16] reaction of amine **E** with formaldehyde and alcohol (used as solvent) yields compounds **Va**–**Vc** (Scheme 2).

It should be emphasized that the intramolecular cyclization of amino ketone **C** involves exclusively the ketone carbonyl group in the tetronic acid fragment, so that reactive lactone moiety is retained in the resulting polycyclic product **IV**. The presence of a lactone fragment in molecule **IV** was proved by chemical transformations. For this purpose, compound **IV** was oxidized with sodium nitrite in acetic acid to benzo[*f*]furo-[3,4-*b*]quinolin-10(8*H*)-one **VII**, and treatment of the latter with hydrazine hydrate in isopropyl alcohol led to the formation of 3-hydroxymethylbenzo[*f*]quinoline-2-carbohydrazide (**VIII**) (Scheme 3). This transformation scheme may be considered to be a convenient method for the preparation of difficultly accessible 2-substituted benzo[*f*]quinoline derivatives.

The structure of the newly synthesized compounds was confirmed by their IR and NMR spectra. The IR spectrum of dihydrobenzo[*f*]furo[3,4-*b*]quinoline **IV** contained a strong absorption band at 1720 cm^{-1} due to lactone carbonyl group and two strong absorption bands at 1527 and 1695 cm^{-1}, which were assigned to stretching vibrations of the double C=C bond neighboring to the nitrogen atom. Also, N–H stretching vibration band was observed at 3319 cm^{-1}. Spirocyclic compounds **Va**–**Vc** displayed in the IR spectra two carbonyl absorption bands at 1741 (ketone) and 1793 cm^{-1} (lactone). The IR spectrum of hydrazide **VIII** was characterized by the presence of a number of difficultly identifiable absorption bands in the region 1540–1636 cm^{-1}, stretching vibrations of the NH group gave rise to a sharp peak at 3332 cm^{-1}, and a strong broadened band at 3261 cm^{-1} corresponded to stretching vibrations of the hydroxy group.

In the aromatic region (δ 7.4–7.9 ppm) of the ^{1}H NMR spectrum of dihydrobenzo[*f*]furo[3,4-*b*]quinoline **IV** we observed a set of signals with an overall intensity corresponding to 6H. Enantiotopic methylene protons on C^{11} gave one singlet at δ 3.87 ppm. Likewise, a two-proton singlet at δ 4.86 ppm belonged to the methylene protons on C^8; the downfield position of this signal is related to deshielding effect of the neighboring oxygen atom. The NH signal appeared as a broadened singlet at δ 9.79 ppm.

In keeping with our previous data [17], intramolecular cyclization of amino ketone **A** could give 4,5-dihydrobenzo[*f*]furo[3,4-*c*]quinolin-3(1*H*)-one (**IX**) which is isomeric to dihydrobenzo[*f*]furo[3,4-*b*]quinoline **IV**. Therefore, additional spectroscopic studies were performed to elucidate the product structure. The use of two-dimensional COSY, HSQC, and HMBC correlation techniques allowed us to unambiguously assign, respectively, all ^{1}H signals, signals from CH carbon atoms, and signals belonging to quaternary carbon atoms. Here, the key signals were those from C^{11b} (s, δ_C 131.96 ppm), C^{6a} (s, δ_C 134.06 ppm), C^{11a} (s, δ_C 111.28 ppm), and 11-H (s, 2H, δ 3.87 ppm). In the NOESY spectrum of the product we observed correlations between 11-H, on the one hand, and C^{11b}, C^{6a}, and C^{11a}, on the other. No such correlations are possible for structure **IX**. The above data provide unam-



Possible correlations in the two-dimensional NMR spectra of compounds **IV** and **IX**.

biguous proofs of the dihydrobenzo[*f*]furo[3,4-*b*]quinoline structure of the product (see figure).

The ^{1}H NMR spectrum of compound **VII** lacked signal assignable to NH proton, while a two-proton singlet was present at δ 5.55 ppm due to methylene protons on C^8. The 11-H proton gave a sharp singlet at δ 9.72 ppm; its downfield position is related to strong steric shielding. Hydrazide **VIII** displayed in the ^{1}H NMR spectrum seven one-proton signals in the aromatic region (δ 7.7–9.3 ppm), and their multiplicities were consistent with the substitution pattern in the benzoquinoline fragment (singlet from 1-H, four doublets from 5-H, 6-H, 7-H, and 10-H, and two triplets from 8-H and 9-H). The alcoholic hydroxy proton appeared as a singlet at δ 10 ppm, a singlet at δ 4.65 ppm was assigned to the methylene group on C^3, and NH protons gave rise to relatively narrow multiplets at δ 4.90 and 5.36 ppm (2H and 1H, respectively).

The ^{1}H NMR spectra of spiro derivatives **Va**–**Vc** contained signals typical of the corresponding alkoxy groups. Aromatic protons resonated as a set of unresolved signals in the region δ 7.1–7.9 ppm with an overall intensity of 6H. A two-proton singlet at δ 3.34 ppm corresponded to methylene protons on C^1, while methylene protons on C^3 displayed a typical *AB* pattern (two one-proton doublets at δ 3.6–3.8 ppm with a coupling constant ^2J of 13 Hz). Analogous doublet signals were observed at δ 4.6–4.9 ppm (^2J = 17.5 Hz) due to 5′-H protons in the tetronic acid fragment. Protons in the NCH_2O fragment were strongly deshielded by the neighboring nitrogen and oxygen atoms, and their signals appeared even more downfield, at δ 4.7–5.0 ppm (*AB* system, ^2J = 11 Hz).

EXPERIMENTAL

The IR spectra were recorded in KBr on a Nicolet Protege-460 spectrometer with Fourier transform. The ^{1}H NMR spectra were obtained on Bruker AC-500 (500 MHz), Tesla BS-567 (100 MHz), and Bruker DRX-500 (500.13 for ^{1}H, 125.75 MHz for ^{13}C) instruments using DMSO-d_6 as solvent (unless otherwise stated); the chemical shifts were measured relative to tetramethylsilane as internal reference. The melting points were determined on a Kofler hot stage.

8,11-Dihydrobenzo[*f*]furo[3,4-*b*]quinolin-10(7*H*)-one (IV). A mixture of 1.43 g (0.01 mol) of naphthalen-2-amine (**II**) and 0.3 g (0.01 mol) of paraformaldehyde in 30 ml of isopropyl alcohol (methyl or ethyl alcohol can also be used without appreciable change of the product yield) was heated under reflux until it became homogeneous (~5 min), a hot solution of 1.00 g (0.01 mol) of tetronic acid (**I**) in 15 ml of isopropyl alcohol was added in one portion, and the mixture was heated for 1 h under reflux. The precipitate was filtered off, washed with acetone, and recrystallized from dimethylformamide. Yield 1.55 g (65%), mp >300°C. IR spectrum, ν, cm^{-1}: 3319 (N–H), 2800–3000 (C–H_{aliph}); 1720 (C=O); 1695, 1527 (C=C–N); 1214, 1012 (C–O). ^{1}H NMR spectrum, δ, ppm: 3.87 s (2H, 11-H), 4.86 s (2H, 8-H), 7.10 d (1H, 6-H, J = 8.7 Hz), 7.41 d.d.d (1H, 3-H, J = 8.1, 6.8, 1.1 Hz), 7.55 d.d.d (1H, 2-H, J = 8.5, 6.8, 1.4 Hz), 7.71 d.d (1H, 1-H, J = 8.5, 0.8 Hz), 7.76 d (1H, 5-H, J = 8.7 Hz), 7.84 d.d (1H, 4-H, J = 8.1, 1.4 Hz), 9.79 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 20.33 t (C^{11}), 65.15 t (C^8), 92.26 s, 111.28 s (C^{11a}), 117.29 d (C^6), 122.03 d (C^1), 123.64 d (C^3), 126.70 d (C^2), 127.83 d (C^4), 127.99 d (C^5), 129.82 s, 131.96 s (C^{11b}), 134.06 s (C^{6a}), 158.47 s, 172.63 s (C^{10}). Found, %: C 75.89; H 4.66; N 5.93. $C_{15}H_{11}NO_2$. Calculated, %: C 75.94; H 4.67; N 5.90.

4-Alkoxymethyl-1,4-dihydro-3*H*-spiro[benzo[*f*]-quinoline-2,3′-furan]-2′,4′(5′*H*)-diones Va–Vc (*general procedure*). A mixture of 1.43 g (0.01 mol) of naphthalen-2-amine and 2.10 g (0.07 mol) of paraformaldehyde in 15 ml of methanol, ethanol, or propan-2-ol was stirred for 40 min at room temperature. A solution of 1.00 g (0.01 mol) of tetronic acid in 30 ml of the same alcohol was slowly added (over a period of 30–40 min), and the mixture was stirred for 1 h. The precipitate was filtered off, the mother liquor was to left to stand on exposure to air (to allow most solvent to escape), and an additional portion of the product was filtered off. The product was purified by recrystallization from the corresponding alcohol.

4-Methoxymethyl-1,4-dihydro-3*H*-spiro[benzo-[*f*]quinoline-2,3′-furan]-2′,4′(5′*H*)-dione (Va). Yield 2.46 g (79%), mp 154°C. IR spectrum, ν, cm^{-1}: 2800–3000 (C–H_{aliph}); 1793, 1740 (C=O); 1268, 1260, 1077, 1054 (C–O–C). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.34 s (2H, 1-H), 3.41 s (3H, OCH_3), 3.62 d and 3.78 d (1H each, 3-H, J = 13 Hz), 4.63 d and 4.83 d (1H each, 5′-H, J = 17.5 Hz), 4.72 d and 4.91 d (1H each, NCH_2O, J = 11 Hz), 7.15–7.82 m (6H, H_{arom}). Found, %: C 69.44; H 5.49; N 4.52. $C_{18}H_{17}NO_4$. Calculated, %: C 69.44; H 5.50; N 4.50.

4-Ethoxymethyl-1,4-dihydro-3*H*-spiro[benzo[*f*]-quinoline-2,3′-furan]-2′,4′(5′*H*)-dione (Vb). Yield 2.83 g (87%), mp 138°C. IR spectrum, ν, cm^{-1}: 2800–3000 (C–H_{aliph}); 1793, 1741 (C=O); 1269, 1260, 1074, 1056 (C–O–C). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm:

1.26 t (3H, $CH_2C\mathbf{H}_3$, J = 8 Hz), 3.34 s (2H, 1-H), 3.60 d and 3.76 d (1H each, 3-H, J = 13 Hz), 3.64 q (2H, $C\mathbf{H}_2CH_3$, J = 7.5 Hz), 4.63 d and 4.83 d (1H each, 5′-H, J = 17.5 Hz), 4.70 d and 4.90 d (1H each, NCH_2O, J = 11 Hz), 7.15–7.82 m (6H, H_{arom}). Found, %: C 70.12; H 5.92; N 4.28. $C_{19}H_{19}NO_4$. Calculated, %: C 70.14; H 5.89; N 4.31.

4-Isopropoxymethyl-1,4-dihydro-3*H*-spiro-[benzo[*f*]quinoline-2,3′-furan]-2′,4′(5′*H*)-dione (Vc). Yield 2.81 g (83%), mp 130°C. IR spectrum, ν, cm^{-1}: 2800–3000 ($C–H_{aliph}$); 1792, 1740 (C=O); 1055, 1271, 1260, 1075 (C–O–C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.19 s and 1.26 s [3H each, $CH(C\mathbf{H}_3)_2$], 3.34 s (2H, 1-H), 3.58 d and 3.77 d (1H each, 3-H, J = 13 Hz), 3.80 m [1H, $C\mathbf{H}(CH_3)_2$], 4.62 d and 4.86 d (1H each, 5′-H, J = 17.5 Hz), 4.75 d and 4.93 d (1H each, NCH_2O, J = 11 Hz), 7.15–7.85 m (6H, H_{arom}). Found, %: C 70.73; H 6.24; N 4.09. $C_{20}H_{21}NO_4$. Calculated, %: C 70.78; H 6.24; N 4.13.

Benzo[*f*]furo[3,4-*b*]quinolin-10(8*H*)-one (VII). A solution of 0.28 g (0.004 mol) of sodium nitrite in 2 ml of water was added to a suspension of 0.47 g (0.002 mol) of compound **IV** in a mixture of 4 ml of acetic acid and 1 ml of concentrated hydrochloric acid. The mixture was stirred for 30 min and neutralized, and the precipitate was filtered off and recrystallized from dimethylformamide. Yield 0.39 g (84%), mp 244°C. IR spectrum, ν, cm^{-1}: 1745 (C=O); 1202, 1014 (C–O). ^1H NMR spectrum, δ, ppm: 5.55 s (2H, 8-H), 7.62–8.35 m (5H, H_{arom}), 9.05 m (1H, 6-H), 9.73 s (1H, 11-H). Found, %: C 76.60; H 3.86; N 5.98. $C_{15}H_9NO_2$. Calculated, %: C 76.59; H 3.86; N 5.95.

3-(Hydroxymethyl)benzo[*f*]quinoline-2-carbohydrazide (VIII). A mixture of 0.3 g of compound **VII** and 0.3 g of hydrazine hydrate in 5 ml of isopropyl alcohol was heated for 1 h under reflux. The precipitate was filtered off and recrystallized from 20 ml of isopropyl alcohol. Yield 0.31 g (91%), mp 223°C. IR spectrum, ν, cm^{-1}: 3332 (N–H), 3261 (O–H), 1542, 1612, 1636 (C=O), 1061 (C–O). ^1H NMR spectrum, δ, ppm: 4.65 s (2H, $C\mathbf{H}_2OH$), 4.90 m (2H, $NHN\mathbf{H}_2$), 5.36 m (1H, $N\mathbf{H}NH_2$), 7.75 t (1H, 9-H, J = 8 Hz), 7.81 t (1H, 8-H, J = 8 Hz), 7.97 d (1H, 5-H, J = 10 Hz), 8.11 d (1H, 7-H, J = 8 Hz), 8.21 d (1H, 6-H, J = 10 Hz), 8.87 d (1H, 10-H, J = 8 Hz), 9.29 s (1H, 1-H), 10.00 s (1H, OH). Found, %: C 67.39; H 4.86; N 15.79. $C_{15}H_{13}N_3O_2$. Calculated, %: C 67.40; H 4.90; N 15.72.

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