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Synthesis of Triazolylisatins Glycoconjugates and Some Ammonium Hydrazones on Their Basis

A. V. Bogdanov[a,*], O. V. Andreeva[a], M. G. Belenok[a], A. D. Voloshina[a], K. I. Enikeeva[b], A. V. Samorodov[b], and V. F. Mironov[a]

[a] *A.E. Arbuzov Institute of Organic and Physical Chemistry, Federal Research Center "Kazan Scientific Center of Russian Academy of Sciences," Kazan, 420088 Russia*
[b] *Bashkir State Medical University, Ufa, 450000 Russia*
**e-mail: abogdanov@inbox.ru*

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Abstract—The click reaction of propargylisatins with some azido-sugars was used to synthesize new isatin derivatives, in which the carbohydrate residue is linked to the 2,3-dioxindole scaffold via the 1,2,3-triazole ring. A number of water-soluble acylhydrazones with different cation site were obtained on their basis. It was shown that the newly obtained compounds do not exhibit hemotoxic action and have a significant antiaggregatory and anticoagulant activity at the level of reference drugs such as acetylsalicylic acid and pentoxifylline.

Keywords: isatin, glycoconjugates, click reactions, hydrazones, antimicrobial activity, hemotoxicity

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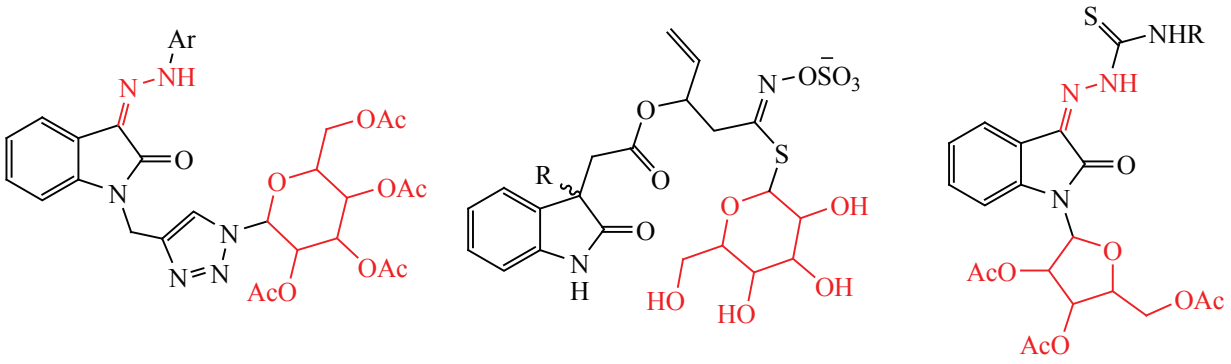
Combination of several pharmacophore fragments in the molecule is one of the most popular modern strategies for the development of new drugs [1–4]. The presence of three highly reactive sites (the lactam nitrogen atom, the ketone group, and position 5 of the heterocycle) makes isatin a convenient scaffold for such molecular modification in order to obtain new types of structures with different physiological activity [5–11]. In accordance with this concept, in recent years, the direction of the search for bioactive compounds in which isatin unit is attached to the pharmacophore fragment via 1,2,3-triazole linker has begun to develop. It has been shown that many compounds of this type exhibit various types of activity: anticancer, antituberculosis, antimicrobial, antidiabetic, etc. [12–17]. On the other hand, it is also known that the approach based on the introduction of a carbohydrate residue into the target molecule is one of the promising pathways for the targeted synthesis of bioactive substances [18–26]. To date, there are few works on the synthesis and study of the biological activity of isatin derivatives containing a monosaccharide residue both at the endocyclic nitrogen atom and at the substituent periphery (Scheme 1) [27–34].

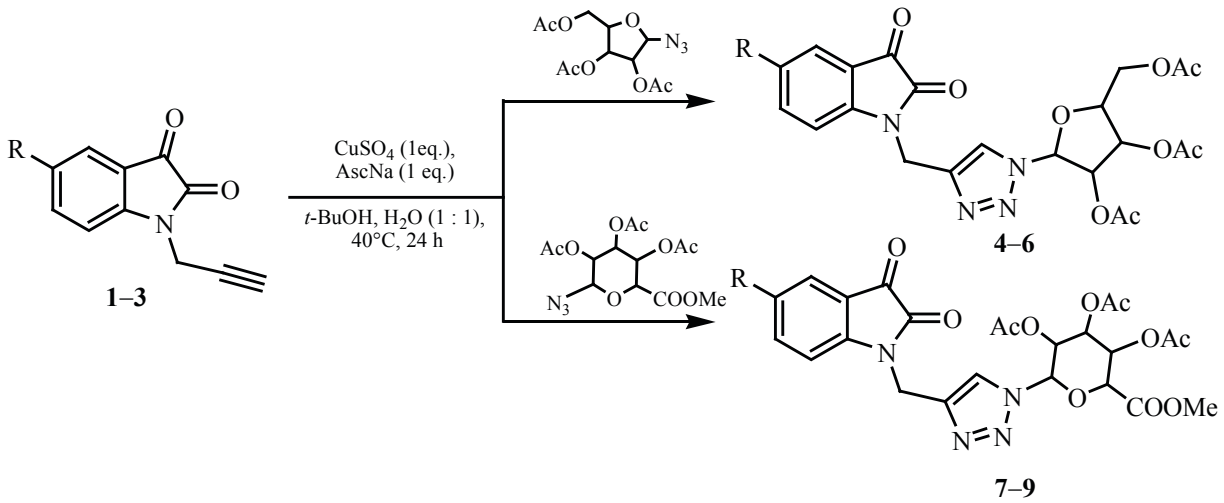
Based on the data on the peculiarities of the preparation and study of the biological activity of water-soluble isatin hydrazones [35–40], herein we proposed a two-stage synthesis of new isatin derivatives containing ribose and glucuronic acid fragments. At the first stage, 5-substitted glycotriazolylisatines **4**–**9** were obtained in high yields by the azide-alkine cycloaddition reaction (Scheme 2).

Structure and composition of the new compounds was unambiguously proven using NMR, IR spectroscopy, mass spectrometry, and elemental analysis data. For example, in the ^{1}H NMR spectra of isatins **4**–**9** in the low-field region, there are signals from the protons of the benzo fragment and a singlet related to the only proton of the triazole ring. It should be noted that in the spectra of derivatives **4**–**7**, **9** recorded in deuterochloroform, this signal manifests in the 7.81–7.95 ppm range, while in the spectrum of compound **8** recorded in DMSO-d_6, this signal is shifted to a weaker field (8.47 ppm). Preservation of all acetyl groups and the methoxycarbonyl one in compounds **4**–**6** and **7**–**9** is evidenced by the presence of three singlets at 2.05–2.11 ppm and four ones at 1.54–2.07 ppm, respectively. The anomeric protons resonate in the 5.88–6.34 ppm region as single doublets

Scheme 1.



Scheme 2.



R = H (**1**, **4**, **7**), OMe (**2**, **5**, **8**), F (**3**, **6**, **9**).

with a coupling constant of $^{3}J_{HH}$ 3.5–3.6 and 8.9–9.3 Hz in the case of ribofuranosyl and glucopyranuronate derivatives, respectively. It indicates that the β-orientation of the anomeric center of all the obtained compounds is preserved. In addition, ^{13}C NMR spectra contain downfield signals of carbon atoms of carbonyl groups: five for ribosyl derivatives and six for glucuronic ones.

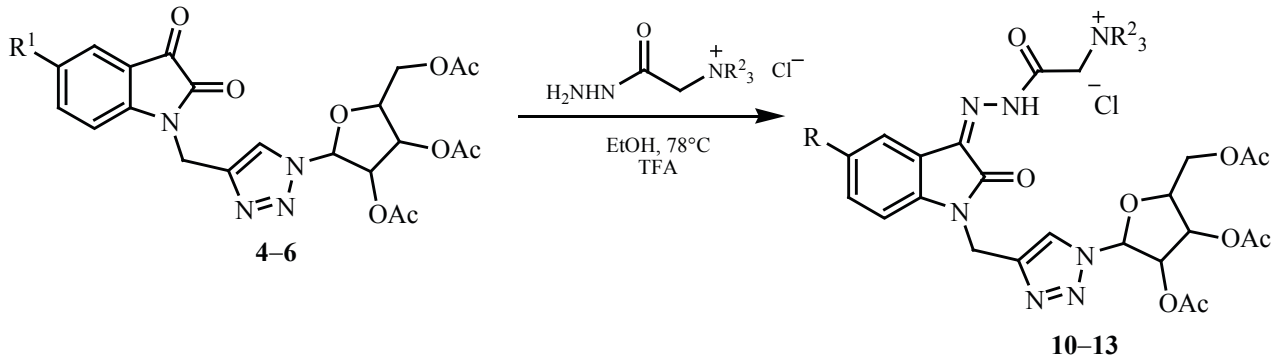
In order to obtain water-soluble isatin derivatives, we synthesized acylhydrazones **10**–**13** containing an acylated ribose fragment by the condensation reaction of Girard reagents T and P with triazolylisatins **4**–**6** (Scheme 3).

To assess the relationship between the structure of the carbohydrate residue and biological activity, derivatives **14**–**17** containing a methyl glucuronate fragment were obtained under the conditions described above (Scheme 4). It should be noted here that, in comparison with the ribosyl derivatives, the solubility of compounds **14**–**17** in water was significantly lower.

Despite the possibility of *cis* and *trans* isomerism relative to the exocyclic C=N bond [41–43] of compounds **10**–**17**, it was not possible to establish isomeric ratio due to the coincidence of the chemical shifts of all signals in the ^{1}H and ^{13}C NMR spectra. The presence of both isomers is evidenced only by the broadening of some signals: methylene protons of the hydrazone substituent, the triazole proton, and the H^{4} proton of the oxindole ring.

To our surprise, the obtained salts **10**–**17** did not show significant antimicrobial activity against both gram-positive and gram-negative bacteria (*Staphylococcus aureus*, *Bacillus cereus*, *Escherichia coli*, *Pseudomonas*

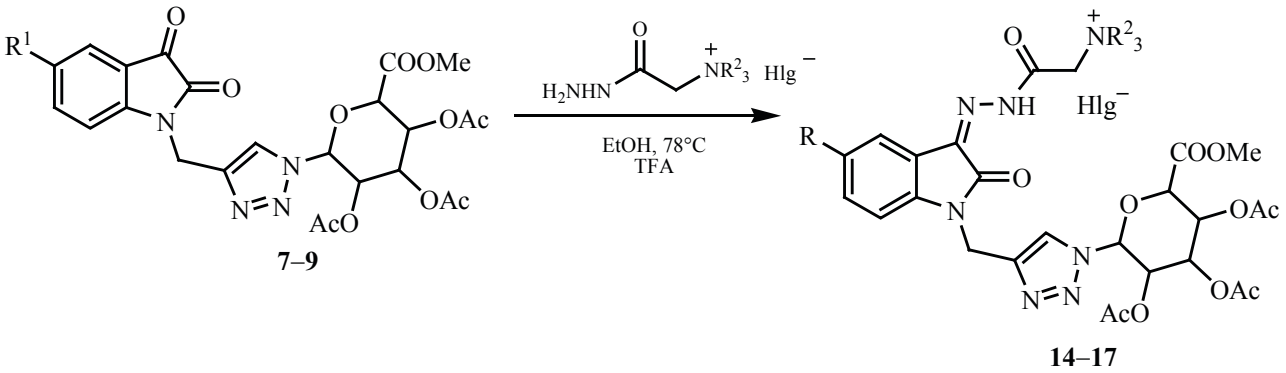
Scheme 3.



4–6 **10–13**

R^1 = H, NR^2_3 = NMe_3 (**10**); R^1 = OMe, NR^2_3 = NMe_3 (**11**); R^1 = F, NR^2_3 = NMe_3 (**12**); R^1 = H, NR^2_3 = N⟨⟩ (**13**).

Scheme 4.



7–9 **14–17**

R^1 = H, NR^2_3 = NMe_3, Hlg = Cl (**14**); R^1 = OMe, NR^2_3 = NMe_3, Hlg = Cl (**15**); R^1 = F, NR^2_3 = NMe_3, Hlg = Cl (**16**); R^1 = H, NR^2_3 = $NMeEt_2$, Hlg = Br (**17**).

aeruginosa, *Aspergillus niger*, *Trichophyton mentagrophytes*) and against the yeast-like fungus. At the same time, the study of the hemolytic activity of isatins **4**–**9** and acylhydrazones **10**–**17** indicated the absence of hemotoxicity, with the exception of methoxyl derivatives **11** and **15**. For these compounds, the maximum hemolysis degree was 7.8% at a concentration of 125 μm/mL.

When searching for new drug candidates, not only their efficacy and low toxicity are important, but also determining the possibility of side effects. There is evidence of withdrawal from the market of some drugs, clinical trials of which did not include the determination of their effect on the hemostatic system [44, 45]. Thus, when determining the target type of biological activity of new compounds, it seemed appropriate to study their antiaggregatory and anticoagulant activities. We have investigated the antiaggregatory and anticoagulant activities of ammonium salts **10**–**17**. The data obtained (Table 1) indicated the absence of a negative effect of the tested compounds on the hemostatic system.

Compounds **10**, **15**, and **17** exhibited greater antiaggregation activity than acetylsalicylic acid, and pyridinium salt **13** exceeded pentoxifylline in terms of antiaggregation activity. It should be noted that acetylsalicylic acid does not affect the latent period of collagen-induced platelet aggregation; however, all tested compounds shortened the lag period in the range of 12.4–21.5% relative to the control (i.e., they affect the platelet release reaction). At the same time, all tested compounds reduce the rate of platelet aggregation, increasing the time to reach the maximum amplitude (except for compound **13**). Compounds **10**, **13**, **15**, **17** showed anticoagulant activity, but it was less than 10, and they were inferior to sodium heparin.

Table 1. Effect of compounds **10–17** on platelet aggregation and hemostasis (median[a] 0.25–0.75)

Compound	lag-phase lengthening, s	Maximum amplitude relative to control, %	Aggregation rate relative to control, %	Time to reach maximum amplitude relative to control, %	APTT relative to control[b], %
10	–13.7 (12.5–16.4)[c, d, e]	–27.1 (22.3–30.2)[d, f, g]	–62.5 (58.7–65.3)[e, f, h]	+83.3 (76.4–89.2) [e, f, h]	+7.5 (3.7–9.6)[c, i]
11	–6.4 (5.3–8.2)[c, d, e]	–4.3 (3.2–5.3)[d, e]	–12.5 (8.4–14.3)[c, g]	+14.7 (12.5–16.1) [c, g]	+4.2 (3.1–5.7)[i]
12	–2.3 (1.4–4.2)[e]	–3.3 (1.7–6.4)[d, e]	–18.7 (14.5–23.1)[c, d, g]	+38.9 (35.4–42.3) [f, h]	+3.1 (2.5–4.8)[i]
13	–23.6 (20.1–28.9)[e, f, h]	–42.8 (38.5–44.3)[f, h]	–61.7 (56.9–64.2) [e, f, h]	–35.9 (31.4–40.2) [e, f, h]	+8.7 (6.4–10.5)[c, i]
14	–3.4 (2.7–4.5)[e]	–1.5 (1.1–3.4) [e, h]	–24.1 (20.4–25.6) [d, f, g]	+43.5 (40.1–47.6) [f, h]	+2.7 (1.9–3.4)[i]
15	–21.4 (20.8–24.6) [e, f, h]	–34.2 (31.2–37.6)[f, g, h]	–44.9 (40.3–46.2)[f, g, h]	+35.1 (32.4–39.7) [f, h]	+9.2 (7.5–12.6)[c, i]
16	–3.1 (2.7–4.5)[e]	–1.7 (1.2–2.6)[e, h]	–32.3 (30.1–37.5) [f, h]	+55.7 (47.4–60.3) [f, g, h]	+8.5 (6.7–11.9)[c, i]
17	–12.5 (9.4–15.3) [c, d, e]	–22.2 (18.7–24.3)[d, f, g]	–36.4 (34.5–38.9) [f, h]	+11.6 (8.7–13.5)[c, g]	+11.3 (8.7–13.4)[c, i]
Acetylsalicylic acid	–2.1 (1.1–2.6)	–13.7 (10.8–16.4)[c]	–10.5 (7.6–12.3)[c]	+10.5 (8.7–13.4)[c]	–
Pentoxifylline	+32.4 (28.7–35.6)[f, h]	–48.4 (42.7–56.5)[f, h]	–34.9 (28.7–39.6)[f]	+32.1 (27.6–36.4) [d,f]	–
Heparin sodium	–	–	–	–	+20.3 (19.7–21.4)

[a] Median—average value.
[b] APTT—activated partial thromboplastin time, number of replicates $n = 6$.
[c] $p \le 0.05$ relative to control.
[d] $p \le 0.05$ relative to acetylsalicylic acid.
[e] $p \le 0.001$ relative to pentoxifylline.
[f] $p \le 0.001$ relative to control.
[g] $p \le 0.05$ relative to pentoxyfilline.
[h] $p \le 0.001$ relative to acetylsalicylic acid.
[i] $p \le 0.05$ relative to heparin sodium.

In conclusion, the absence of hemotoxicity and the high antiaggregatory and anticoagulant activity of the new glycosyl-containing isatin-3-acylhydrazones create the prerequisites for further searching for effective anticancer or antiviral agents based on these glycoconjugates. In addition, in order to improve the antimicrobial activity of such water-soluble ammonium salts, the need for a deep design of their structures by wider variation of both the substituents in the benzo moiety of the heterocycle and the carbohydrate residue became obvious.

EXPERIMENTAL

IR spectra were recorded on a Bruker Vector-22 spectrometer from KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance-400 (400 and 100.6 MHz, respectively) and Bruker Avance-600 (600 and 150 MHz, respectively) relative to the residual signals of the deuterated solvent. MALDI mass spectra were recorded on an UltraFlex III TOF/TOF mass spectrometer. ESI mass spectra were recorded on an Amazon X mass spectrometer (Bruker Daltonik GmbH, Bremen, Germany). Melting points were measured on an SMP10 Stuart instrument. Elemental analysis was performed using a CHNS-3 analyzer.

General procedure for the synthesis of isatins 4–9. Solutions of $CuSO_4$ (5 mmol) in 2 mL of water and Na ascorbate (5 mmol) in 2 mL of water were added successively to a mixture of equimolar (5 mmol) amounts

of propargylisatin **1**–**3** and the corresponding azide in a *tert*-butanol–water mixture (1:1). The resulting mixture was stirred for 24 h at 40°C. The solution was then concentrated under reduced pressure, the residue was treated with water and extracted with dichloromethane. The organic layer was dried with $MgSO_4$. Compounds **4**–**9** were obtained in pure form after removal of the solvent.

1-{[1-(2′,3′,5′-Tri-*O*-acetyl-β-D-ribofuranosyl)-1*H*-1,2,3-triazol-4-yl]methyl}-1*H*-indole-2,3-dione (4). Yield 82%, mp 90°C. IR spectrum, ν, cm^{-1}: 3245, 2939, 1742, 1614, 1471, 1436, 1371, 1227, 1108, 1042. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.05 s (3H, CH_3), 2.10 s (3H, CH_3), 2.11 s (3H, CH_3), 4.22 d. d (1H, CH_2O, A-part of AB-system, $^2J_{HH}$ 12.4, $^3J_{HH}$ 4.4 Hz), 4.34 d. d (1H, CH_2O, B-part of AB-system, $^2J_{HH}$ 12.4, $^3J_{HH}$ 3.0 Hz), 4.44–4.48 m (1H, CH), 5.03 s (2H, NCH_2, AB-system, $^2J_{HH}$ 20.8 Hz), 5.56 d. d (1H, CH, $^3J_{HH}$ 5.4, $^3J_{HH}$ 5.4 Hz), 5.78 d. d (1H, CH, $^3J_{HH}$ 5.3, $^3J_{HH}$ 3.6 Hz), 6.11 d (1H, CH, $^3J_{HH}$ 3.6 Hz), 7.12 d. d. d (1H, H^5, $^3J_{HH}$ 7.5, $^3J_{HH}$ 7.5, $^4J_{HH}$ 0.6 Hz), 7.31 d. d (1H, H^7, $^3J_{HH}$ 8.5, $^4J_{HH}$ 0.6 Hz), 7.58–7.60 m (2H), 7.83 s (1H, CH=). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 20.38 (CH_3), 20.41 (CH_3), 20.6 (CH_3), 35.2 (CH_2), 62.7 (CH), 70.6 (CH), 74.4 (CH), 90.3 (CH), 111.4 (CH), 117.6, 122.5 (CH), 124.1 (CH), 125.4 (CH), 138.6 (CH), 142.3, 150.1, 158.0, 169.2, 169.4, 170.3, 182.9. Mass spectrum (MALDI), *m*/*z*: 509 $[M + Na]^+$. Found, %: C 54.23; H 4.39; N 11.42. $C_{22}H_{22}N_4O_9$. Calculated, %: C 54.32; H 4.56; N 11.52.

5-Methoxy-1-{[1-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-1*H*-1,2,3-triazol-4-yl]methyl}-1*H*-indole-2,3-dione (5). Yield 93%, mp 153°C. IR spectrum, ν, cm^{-1}: 3240, 2941, 1740, 1616, 1474, 1436, 1377, 1222, 1111, 1040. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.06 s (3H, CH_3), 2.11 s (6H, $2CH_3$), 3.79 s (3H, OCH_3), 4.22 д. д (1H, CH_2O, A-part of AB-system, $^2J_{HH}$ 12.4, $^3J_{HH}$ 4.4 Hz), 4.36 d. d (1H, CH_2O, B-part of AB-system, $^2J_{HH}$ 12.4, $^3J_{HH}$ 3.0 Hz), 4.45–4.48 m (1H, CH), 5.03 s (2H, NCH_2, AB-system, $^2J_{HH}$ 21.5 Hz), 5.56 d. d (1H, CH, $^3J_{HH}$ 5.5, $^3J_{HH}$ 5.5 Hz), 5.78 d. d (1H, CH, $^3J_{HH}$ 5.2, $^3J_{HH}$ 3.6 Hz), 6.10 d (1H, CH, $^3J_{HH}$ 3.6 Hz), 7.13–7.16 m (2H), 7.24 d (1H, H^7, $^3J_{HH}$ 9.0 Hz), 7.81 s (1H, CH=). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 20.16 (CH_3), 20.22 (CH_3), 34.8 (CH_3), 40.0 (CH_2), 55.9 (CH_3), 62.4 (CH_2), 70.1 (CH), 73.3 (CH), 79.8 (CH), 89.0 (CH), 109.2 (CH), 112.2 (CH), 118.1, 123.7 (CH), 123.8 (CH), 142.1, 143.9, 155.8, 157.8, 169.1, 169.4, 169.8, 183.2. Mass spectrum (MALDI), *m*/*z*: 517 $[M + H]^+$, 539 $[M + Na]^+$, 555 $[M + K]^+$. Found, %: C 53.34; H 4.50; N 10.69. $C_{23}H_{24}N_4O_{10}$. Calculated, %: C 53.49; H 4.68; N 10.85.

5-Fluoro-1-{[1-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-1*H*-1,2,3-triazol-4-yl]methyl}-1*H*-indole-2,3-dione (6). Yield 83%, mp 113°C. IR spectrum, ν, cm^{-1}: 3223, 2945, 1750, 1618, 1468, 1434, 1370, 1228, 1123, 1040. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.07 s (3H, CH_3), 2.11 s (6H, $2CH_3$), 4.22 d. d (1H, CH_2O, A-part of AB-system, $^2J_{HH}$ 12.4, $^3J_{HH}$ 4.5 Hz), 4.36 d. d (1H, CH_2O, B-part of AB-system, $^2J_{HH}$ 12.4, $^3J_{HH}$ 3.0 Hz), 4.45–4.49 m (1H, CH), 5.03 s (2H, NCH_2, AB-system, $^2J_{HH}$ 20.4 Hz), 5.56 d. d (1H, CH, $^3J_{HH}$ 5.5, $^3J_{HH}$ 5.5 Hz), 5.78 d. d (1H, CH, $^3J_{HH}$ 5.2, $^3J_{HH}$ 3.5 Hz), 6.11 d (1H, CH, $^3J_{HH}$ 3.5 Hz), 7.29–7.34 m (3H), 7.83 s (1H, CH=). Mass spectrum (MALDI), *m*/*z*: 527 $[M + Na]^+$. Found, %: C 52.23; H 4.09; N 11.00. $C_{22}H_{21}FN_4O_9$. Calculated, %: C 52.38; H 4.20; N 11.11.

1-{[1-(2′,3′,4′-Tri-*O*-acetyl-5′-methoxycarbonyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methyl}-1*H*-indole-2,3-dione (7). Yield 91%, mp 210°C. IR spectrum, ν, cm^{-1}: 3116, 2959, 1750, 1760, 1613, 1472, 1438, 1375, 1246, 1217, 1114, 1042. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.69 s (3H, CH_3), 1.96 s (3H, CH_3), 2.00 s (3H, CH_3), 3.61 s (3H, CH_3), 4.77 d (1H, CH, $^3J_{HH}$ 10.0 Hz), 4.98 s (2H, NCH_2), 5.19 d. d (1H, CH, $^3J_{HH}$ 9.7, $^3J_{HH}$ 9.6 Hz), 5.57 d. d (1H, CH, $^3J_{HH}$ 9.4, $^3J_{HH}$ 9.3 Hz), 5.62 d. d (1H, CH, $^3J_{HH}$ 9.3, $^3J_{HH}$ 9.2 Hz), 6.34 d (1H, CH, $^3J_{HH}$ 9.1 Hz), 7.06 d (1H, H^7, $^3J_{HH}$ 7.9 Hz), 7.13 d. d (1H, H^5, $^3J_{HH}$ 7.4, $^3J_{HH}$ 7.4 Hz), 7.57 d (1H, H^4, $^3J_{HH}$ 7.1 Hz), 7.61 d. d (1H, H^6, $^3J_{HH}$ 7.6, $^3J_{HH}$ 7.3 Hz), 8.52 s (1H, CH=). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 19.8 (CH_3), 20.2 (CH_3), 20.3 (CH_3), 35.0 (CH_2), 52.7 (CH_3), 68.5 (CH), 69.9 (CH), 71.5 (CH), 73.0 (CH), 83.8 (CH), 111.1 (CH), 117.7, 123.2 (CH), 123.6 (CH), 124.6 (CH), 138.2 (CH), 142.4, 150.0, 157.9, 166.6, 168.4, 169.4, 169.6, 183.1. Mass spectrum (MALDI), *m*/*z*: 567 $[M + Na]^+$, 583 $[M + K]^+$. Found, %: C 52.89; H 4.36; N 10.19. $C_{24}H_{24}N_4O_{11}$. Calculated, %: C 52.94; H 4.44; N 10.29.

5-Methoxy-1-{[1-(2′,3′,4′-tri-*O*-acetyl-5′-methoxycarbonyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]-methyl}-1*H*-indole-2,3-dione (8). Yield 87%, mp 171°C. IR spectrum, ν, cm^{-1}: 3135, 2955, 1753, 1627, 1600, 1492, 1439, 1376, 1223, 1112, 1041. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.68 s (3H, CH_3), 1.94 s (3H, CH_3), 1.98 s (3H, CH_3), 3.59 s (3H, CH_3), 3.73 s (3H, CH_3), 4.73 d (1H, CH, $^3J_{HH}$ 10.0 Hz), 4.94 s (2H, NCH_2), 5.17 d. d (1H, CH, $^3J_{HH}$ 9.7, $^3J_{HH}$ 9.6 Hz), 5.54 d. d (1H, CH, $^3J_{HH}$ 9.5, $^3J_{HH}$ 9.2 Hz), 5.60 d. d (1H, CH, $^3J_{HH}$ 9.6,

$^3J_{HH}$ 9.1 Hz), 6.31 d (1H, CH, $^3J_{HH}$ 8.9 Hz), 6.97 d (1H, H^7, $^3J_{HH}$ 8.6 Hz), 7.13 d (1H, H^4, $^4J_{HH}$ 2.6 Hz), 7.18 d. d (1H, H^5, $^3J_{HH}$ 8.6, $^4J_{HH}$ 2.6 Hz), 8.47 s (1H, CH=). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 20.0 (CH_3), 20.4 (CH_3), 20.5 (CH_3), 35.2 (CH_2), 53.0 (CH_3), 56.3 (CH_3), 68.7 (CH), 70.1 (CH), 71.7 (CH), 73.2 (CH), 84.0 (CH), 109.6 (CH), 112.5 (CH), 118.3, 123.4 (CH), 124.3 (CH), 142.7, 144.0, 156.2, 158.2, 166.9, 168.7, 169.8, 169.9, 183.6. Mass spectrum (MALDI), *m*/*z*: 597 [*M* + Na]$^+$. Found, %: C 52.09; H 4.43; N 9.67. $C_{25}H_{26}N_4O_{12}$. Calculated, %: C 52.27; H 4.56; N 9.75.

5-Fluoro-1-{[1-(2′,3′,4′-tri-*O*-acetyl-5′-methoxycarbonyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methyl}-1*H*-indole-2,3-dione (9). Yield 84%, mp 230°C. IR spectrum, ν, cm^{-1}: 3117, 2958, 1749, 1622, 1488, 1465, 1375, 1216, 1168, 1119, 1046. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.79 s (3H, CH_3), 2.05 s (3H, CH_3), 2.07 s (3H, CH_3), 3.77 s (3H, CH_3), 4.32 d (1H, CH, $^3J_{HH}$ 9.8 Hz), 5.02 d (1H, NCH^a, $^2J_{HH}$ 15.7 Hz), 5.07 d (1H, NCH^a, $^2J_{HH}$ 15.7 Hz), 5.36 d. d (1H, CH, $^3J_{HH}$ 9.6, $^3J_{HH}$ 9.5 Hz), 5.37 d. d (1H, CH, $^3J_{HH}$ 9.4, $^3J_{HH}$ 9.3 Hz), 5.48 d. d (1H, CH, $^3J_{HH}$ 9.3, $^3J_{HH}$ 9.2 Hz), 5.88 d (1H, CH, $^3J_{HH}$ 9.3 Hz), 7.21 d. d (1H, H^7, $^3J_{HH}$ 8.7, $^4J_{FH}$ 3.7 Hz), 7.30–7.33 m (2H, H^4, H^6), 7.95 s (1H, CH=). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 20.0 (CH_3), 20.4 (CH_3), 20.5 (CH_3), 35.4 (CH_2), 53.2 (CH_3), 68.9 (CH), 70.3 (CH), 71.6 (CH), 75.0 (CH), 85.6 (CH), 112.3 d (C^4, $^2J_{FC}$ 24.3 Hz), 112.7 d (C^7, $^3J_{FC}$ 7.1 Hz), 118.3 d (C^{3a}, $^3J_{FC}$ 7.1 Hz), 121.8 (CH), 124.7 d (C^6, $^2J_{FC}$ 24.0 Hz), 142.4, 146.1 d (C^{7a}, $^4J_{FC}$ 1.7 Hz), 157.7 d (C^2, $^5J_{FC}$ 1.1 Hz), 159.5 d (C^5, $^1J_{FC}$ 246.1 Hz), 166.0, 168.6, 169.2, 169.6, 182.3 d (C^3, $^4J_{FC}$ 1.8 Hz). Mass spectrum (MALDI), *m*/*z*: 585 [*M* + Na]$^+$, 601 [*M* + K]$^+$. Found, %: C 51.02; H 4.01; N 9.79. $C_{24}H_{23}FN_4O_{11}$. Calculated, %: C 51.25; H 4.12; N 9.96.

General procedure for the synthesis of acylhydrazones 10–17. Three drops of trifluoroacetic acid were added to a mixture of equimolar (5 mmol) amounts of the isatin derivative and 1,2,3-thiadiazolylcarbohydrazide in 5 mL of ethanol freshly distilled over BaO. The reaction mixture was refluxed for 3 h. After spontaneous cooling to room temperature, the precipitate was filtered off, washed with absolute diethyl ether, and dried in a vacuum of 12 mmHg.

2-[2-(1-{[1-(2′,3′,5′-Tri-*O*-acetyl-β-D-ribofuranosyl)-1*H*-1,2,3-triazol-4-yl]methyl}-2-oxoindolin-3-ylidene)hydrazinyl]-*N*,*N*,*N*-trimethyl-2-oxoethylammonium chloride (10). Yield 82%, mp 168°C. IR spectrum, ν, cm^{-1}: 3368, 3219, 3025, 2939, 1721, 1685, 1615, 1470, 1370, 1231, 1154, 1106, 1042. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.91 s (3H, CH_3), 1.96 s (3H, CH_3), 2.00 s (3H, CH_3), 3.36 s (9H, $3CH_3$), 4.34 d (2H, OCH_2, $^3J_{HH}$ 5.3 Hz), 4.70–4.71 m (1H, CH), 4.77–4.78 m (1H, CH), 4.88–4.89 m (1H, CH), 4.92 br. d (1H, CH, $^3J_{HH}$ 4.6 Hz), 5.02 s [2H, $CH_2C(O)$], 5.07 s (2H, NCH_2), 7.19 d. d (1H, H^5, $^3J_{HH}$ 7.7, $^3J_{HH}$ 7.7 Hz), 7.24 d (1H, H^7, $^3J_{HH}$ 7.8 Hz), 7.44–7.49 m (1H, H^6), 7.63–7.66 m (1H, H^4), 8.19 s (1H, CH=), 12.64 s (1H, NH). Mass spectrum (MALDI), *m*/*z*: 600 [*M* – Cl]$^+$. Found, %: C 50.80; H 5.20; Cl 5.41; N 15.29. $C_{27}H_{34}ClN_7O_9$. Calculated, %: C 50.98; H 5.39; Cl 5.57; N 15.41.

2-(2-{1-[1-(2′,3′,5′-Tri-*O*-acetyl-β-D-ribofuranosyl)-1*H*-1,2,3-triazol-4-yl]methyl}-5-methoxy-2-oxoindolin-3-ylidene)hydrazinyl]-*N*,*N*,*N*-trimethyl-2-oxoethylammonium chloride (11). Yield 97%, mp 210°C (dec.). IR spectrum, ν, cm^{-1}: 3402, 3186, 3016, 2963, 1749, 1685, 1620, 1488, 1460, 1368, 1293, 1232, 1160, 1040. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.91 s (3H, CH_3), 1.94 s (3H, CH_3), 2.03 s (3H, CH_3), 3.34 s (9H, $3CH_3$), 3.80 s (3H, CH_3), 4.61–4.62 m (2H, OCH_2), 4.98 s [2H, $CH_2C(O)$], 5.05 s (2H, NCH_2), 5.19–5.21 m (1H, CH), 5.54 d. d (1H, CH, $^3J_{HH}$ 5.9 Hz, $^3J_{HH}$ 5.8 Hz), 5.69 d. d (1H, CH, $^3J_{HH}$ 5.1 Hz, $^3J_{HH}$ 5.0 Hz), 5.94 d (1H, CH, $^3J_{HH}$ 5.3 Hz), 7.13 d. d (1H, H^6, $^3J_{HH}$ 8.6, $^4J_{HH}$ 2.5 Hz), 7.20–7.23 m (2H, H^7, H^4), 8.38 s (1H, CH=), 12.64 s (1H, NH). Mass spectrum (MALDI), *m*/*z*: 630 [*M* – Cl]$^+$. Found, %: C 50.32; H 5.29; Cl 5.27; N 14.63. $C_{28}H_{36}ClN_7O_{10}$. Calculated, %: C 50.49; H 5.45; Cl 5.32; N 14.72.

2-[2-(1-{[1-(2′,3′,5′-Tri-*O*-acetyl-β-D-ribofuranosyl)-1*H*-1,2,3-triazol-4-yl]methyl}-5-fluoro-2-oxoindolin-3-ylidene)hydrazinyl]-*N*,*N*,*N*-trimethyl-2-oxoethylammonium chloride (12). Yield 90%, mp 138–140°C. IR spectrum, ν, cm^{-1}: 3354, 3231, 3024, 2929, 1749, 1692, 1624, 1483, 1373, 1232, 1158, 1044. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.97 s (3H, CH_3), 1.98 s (3H, CH_3), 2.06 s (3H, CH_3), 3.63 s (9H, $3CH_3$), 4.33 d (2H, OCH_2, $^3J_{HH}$ 11.5 Hz), 4.42 s (2H, NCH_2), 4.92–4.96 m (1H, CH), 5.35–5.39 m (1H, CH), 5.56–5.58 m (1H, CH), 5.75–5.80 m (1H, CH), 6.13 s [2H, $CH_2C(O)$], 7.05–7.09 m (2H, H^7, H^6), 7.42–7.46 m (1H, H^4), 7.97 s (1H, CH=), 12.46 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 20.2 (CH_3), 20.3 (CH_3), 21.0 (CH_3), 34.5 (CH_2), 53.5 (CH_3), 61.7 (CH_2), 62.4 (CH_2), 70.1 (CH), 73.3 (CH), 79.8 (CH), 89.0 (CH), 108.1 (CH), 112.1 (CH), 118.4 (CH), 120.1, 123.9 (CH),

134.5, 139.3, 141.6, 158.8 d (C^5, $^1J_{FC}$ 239.6 Hz), 160.1, 166.3, 169.2, 169.4, 169.8. Mass spectrum (MALDI), *m*/*z*: 618 [*M* – Cl]$^+$. Found, %: C 49.41; H 4.88; Cl 5.37; N 14.87. $C_{27}H_{33}ClFN_7O_9$. Calculated, %: C 49.58; H 5.09; Cl 5.42; N 14.99.

1-{2-[2-(1-{[1-(2′,3′,5′-Tri-*O*-acetyl-β-D-ribofuranosyl)-1*H*-1,2,3-triazol-4-yl]methyl}-2-oxoindolin-3-ylidene)hydrazinyl]-2-oxoethyl}pyridinium chloride (13). Yield 90%, mp 168°C. IR spectrum, ν, cm^{-1}: 3403, 3227, 3138, 2969, 1747, 1691, 1636, 1615, 1490, 1470, 1374, 1230, 1154, 1105, 1043. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.01 s (3H, CH_3), 2.09 s (3H, CH_3), 2.10 s (3H, CH_3), 4.15–4.19 m (1H, CH), 4.37–4.40 m (2H, CH_2), 4.94 s (2H, NCH_2), 5.59–5.61 m (1H, CH), 5.79 br. s (1H, CH), 6.24 br. s (1H, CH), 6.67 s [2H, $CH_2C(O)$], 7.02–7.08 m (2H, H^7, H^5), 7.25–7.27 m (1H, H^6), 7.55–7.58 m (1H, H^4), 7.92–7.99 m (2H, 3-Py), 8.31–8.37 m (1H, 4-Py), 9.46–9.48 m (2H, 2-Py), 8.05 s (1H, CH=), 12.57 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 20.2 (CH_3), 20.6 (CH_3), 21.0 (CH_3), 34.5 (CH_2), 60.6 (CH_2), 61.1 (CH_2), 70.1 (CH), 73.3 (CH), 83.7 (CH), 91.7 (CH), 110.8 (CH), 118.6, 120.6 (CH), 123.4 (CH), 127.67, 127.70 (CH), 132.1 (CH), 135.1, 143.0, 146.2 (CH), 146.5 (CH), 146.6 (CH), 160.2, 167.5, 169.2, 169.6, 171.9. Mass spectrum (MALDI), *m*/*z*: 620 [*M* – Cl]$^+$. Found, %: C 52.90; H 4.47; Cl 5.26; N 14.73. $C_{29}H_{30}ClN_7O_9$. Calculated, %: C 53.09; H 4.61; Cl 5.40; N 14.95.

***N*,*N*,*N*-Trimethyl-2-oxo-2-[2-(2-oxo-1-{[1-(2′,3′,4′-tri-*O*-acetyl-5′-methoxycarbonyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methyl}indolin-3-ylidene)hydrazinyl]ethylammonium chloride (14).** Yield 93%, mp 200–202°C. IR spectrum, ν, cm^{-1}: 3400, 3215, 3128, 3009, 2960, 1760, 1680, 1616, 1471, 1455, 1367, 1290, 1222, 1152, 1106, 1042. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.66 s (3H, CH_3), 1.94 s (3H, CH_3), 1.98 s (3H, CH_3), 3.22 s (9H, $3CH_3$), 3.59 s (3H, CH_3), 4.74 d (1H, CH, $^3J_{HH}$ 10.1 Hz), 4.94 s [2H, $CH_2C(O)$], 5.04 s (2H, NCH_2), 5.18 d. d (1H, CH, $^3J_{HH}$ 9.8, $^3J_{HH}$ 9.7 Hz), 5.54 d. d (1H, CH, $^3J_{HH}$ 9.5, $^3J_{HH}$ 9.5 Hz), 5.63 d. d (1H, CH, $^3J_{HH}$ 9.4, $^3J_{HH}$ 9.3 Hz), 6.33 d (1H, CH, $^3J_{HH}$ 9.2 Hz), 7.09 d (1H, H^7, $^3J_{HH}$ 7.6 Hz), 7.16 d. d (1H, H^5, $^3J_{HH}$ 7.5, $^3J_{HH}$ 7.4 Hz), 7.42 d. d (1H, H^6, $^3J_{HH}$ 8.2, $^3J_{HH}$ 7.6 Hz), 7.64 br. s (1H, H^4), 8.49 s (1H, CH=), 12.57 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 20.1 (CH_3), 20.5 (CH_3), 21.4 (CH_3), 34.8 (CH_2), 53.1 (CH_3), 54.1 (CH_3), 63.3 (CH_2), 68.8 (CH), 70.1 (CH), 71.8 (CH), 73.3 (CH), 84.0 (CH), 110.9 (CH), 119.0, 121.5 (CH), 123.6 (CH), 123.9 (CH), 132.6 (CH), 142.5, 143.1, 160.5, 166.5, 167.0, 168.8, 169.9, 170.0, 172.8. Mass spectrum (MALDI), *m*/*z*: 658 [*M* – Cl]$^+$. Found, %: C 51.20; H 5.19; Cl 5.02; N 14.30. $C_{29}H_{36}ClN_7O_{10}$. Calculated, %: C 51.37; H 5.35; Cl 5.23; N 14.46.

***N*,*N*,*N*-Trimethyl-2-oxo-2-[2-(2-oxo-1-{[1-(2′,3′,4′-tri-*O*-acetyl-5′-methoxycarbonyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methyl}-5-methoxyindolin-3-ylidene)hydrazinyl]ethylammonium chloride (15).** Yield 98%, mp 161–163°C (dec.). IR spectrum, ν, cm^{-1}: 3434, 3215, 3010, 2957, 1758, 1688, 1551, 1488, 1439, 1370, 1293, 1218, 1168, 1124, 1041. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.70 s (3H, CH_3), 1.96 s (3H, CH_3), 1.99 s (3H, CH_3), 3.25 s (9H, $3CH_3$), 3.60 s (3H, CH_3), 3.77 s (3H, CH_3), 4.78 d (1H, CH, $^3J_{HH}$ 9.9 Hz), 4.99 br. s [2H, $CH_2C(O)$], 5.03 s (2H, NCH_2), 5.20 d. d (1H, CH, $^3J_{HH}$ 9.5, $^3J_{HH}$ 9.4 Hz), 5.57 d. d (1H, CH, $^3J_{HH}$ 9.6, $^3J_{HH}$ 9.5 Hz), 5.67 d. d (1H, CH, $^3J_{HH}$ 9.0, $^3J_{HH}$ 8.8 Hz), 6.37 d (1H, CH, $^3J_{HH}$ 8.5 Hz), 6.99–7.07 m (2H, H^7, H^6), 7.15–7.22 m (1H, H^4), 8.52 s (1H, CH=), 12.63 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 19.5 (CH_3), 19.89 (CH_3), 19.93 (CH_3), 34.3 (CH_2), 52.4 (CH_3), 55.3 (CH_3), 61.7 (CH_2), 68.1 (CH), 69.5 (CH), 71.1 (CH), 72.6 (CH), 83.4 (CH), 106.6 (CH), 111.3 (CH), 117.3 (CH), 119.2, 122.8 (CH), 135.0, 136.2, 141.9, 155.7, 159.8, 166.2, 167.9, 168.9, 169.1, 169.2. Mass spectrum (MALDI), *m*/*z*: 688 [*M* – Cl]$^+$. Found, %: C 49.59; H 5.15; Cl 4.78; N 13.46. $C_{30}H_{38}ClN_7O_{12}$. Calculated, %: C 49.76; H 5.29; Cl 4.90; N 13.54.

***N*,*N*,*N*-Trimethyl-2-oxo-2-[2-(2-oxo1-{[1-(2′,3′,4′-tri-*O*-acetyl-5′-methoxycarbonyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methyl}-5-fluoroindolin-3-ylidene)hydrazinyl]ethylammonium chloride (16).** Yield 86%, mp 192°C. IR spectrum, ν, cm^{-1}: 3402, 3233, 3122, 3022, 2958, 1758, 1688, 1624, 1484, 1443, 1373, 1226, 1157, 1106, 1042. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.67 s (3H, CH_3), 1.93 s (3H, CH_3), 1.96 s (3H, CH_3), 3.49 s (9H, $3CH_3$), 3.61 s (3H, CH_3), 4.57 d (1H, CH, $^3J_{HH}$ 10.1 Hz), 4.96 d (1H, NCH^a, $^2J_{HH}$ 15.9 Hz), 5.01 d (1H, NCH^a, $^2J_{HH}$ 15.9 Hz), 5.15 s [2H, $CH_2C(O)$], 5.21 d. d (1H, CH, $^3J_{HH}$ 9.7, $^3J_{HH}$ 9.6 Hz), 5.48 d. d (1H, CH, $^3J_{HH}$ 9.3, $^3J_{HH}$ 9.2 Hz), 5.53 d. d (1H, CH, $^3J_{HH}$ 9.5, $^3J_{HH}$ 9.4 Hz), 6.21 d (1H, CH, $^3J_{HH}$ 9.1 Hz), 7.01–7.05 m (2H, H^6, H^7), 7.37–7.40 m (1H, H^4), 8.15 s (1H, CH=), 12.60 s (1H, NH). Mass spectrum (MALDI), *m*/*z*: 676 [*M* – Cl]$^+$. Found, %: C 48.80; H 4.78; Cl 4.87; N 13.59. $C_{29}H_{35}ClFN_7O_{11}$. Calculated, %: C 48.91; H 4.95; Cl 4.98; N 13.77.

***N*,*N*-Diethyl-*N*-methyl-2-oxo-2-[2-(2-oxo-1-{[1-(2′,3′,4′-tri-*O*-acetyl-5′-methoxycarbonyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methyl}indolin-3-ylidene)hydrazinyl]ethylammonium chloride (17).** Yield 81%, mp 168°C. IR spectrum, ν, cm^{-1}: 3425, 3229, 3151, 2982, 2955, 1758, 1717, 1690, 1616, 1470, 1441, 1377, 1219, 1156, 1106, 1040. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.30 t (6H, $2N^+CH_2\underline{CH}_3$, $^3J_{HH}$ 6.8 Hz), 1.70 s (3H, CH_3), 1.97 s (3H, CH_3), 2.01 s (3H, CH_3), 3.18–3.23 m (4H, $2N^+\underline{CH}_2CH_3$), 3.59–3.66 m (6H, OCH_3, N^+CH_3), 4.79 d (1H, CH, $^3J_{HH}$ 10.0 Hz), 4.83 s [2H, $CH_2C(O)$], 5.05–5.11 m (2H, NCH_2), 5.22 d. d (1H, CH, $^3J_{HH}$ 9.8, $^3J_{HH}$ 9.6 Hz), 5.59 d. d (1H, CH, $^3J_{HH}$ 9.9, $^3J_{HH}$ 9.4 Hz), 5.68 d. d (1H, CH, $^3J_{HH}$ 9.7, $^3J_{HH}$ 9.5 Hz), 6.38 d (1H, CH, $^3J_{HH}$ 9.9 Hz), 7.14–7.21 m (2H, H^5, H^7), 7.45–7.47 m (1H, H^6), 7.69 br. s (1H, H^4), 8.54 s (1H, CH=), 12.61 s (1H, NH). Mass spectrum (MALDI), *m*/*z*: 686 $[M - Br]^+$. Found, %: C 48.41; H 5.19; Br 10.22; N 12.67. $C_{31}H_{40}BrN_7O_{11}$. Calculated, %: C 48.57; H 5.26; Br 10.42; N 12.79.

AUTHOR INFORMATION

A.V. Bogdanov, ORCID: http://orcid.org/0000-0002-2483-4742

O.V. Andreeva, ORCID: http://orcid.org/0000-0001-5518-8395

M.G. Belenok, ORCID: http://orcid.org/0000-0002-0906-8226

A.D. Voloshina, ORCID: http://orcid.org/0000-0002-3540-8554

K.I. Enikeeva, ORCID: http://orcid.org/0000-0002-5995-2124

A.V. Samorodov, ORCID: http://orcid.org/0000-0001-9302-499X

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CONFLICT OF INTEREST

V.F. Mironov is a member of the Editorial Board of the Russian Journal of General Chemistry. The other authors declare no conflict of interest.

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