

# New Method of Preparation of Carboxy-Protected Amino Acid Conjugates of Glycyrrhizinic Acid

L. A. Baltina Jr., A. I. Fairushina, and L. A. Baltina

Ufa Institute of Chemistry of the Russian Academy of Sciences, pr. Oktyabrya 71, Ufa, 450054 Russia  
e-mail: baltina@anrb.ru

Received August 13, 2015

**Abstract**—A method for preparation of carboxy-protected amino acid conjugates of glycyrrhizinic acid with the use of *N*-hydroxybenzotriazole, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, and methyl esters of L-amino acids (phenylalanine, tyrosine, leucine, isoleucine, and methionine) in 85–90% yield was developed. The structure of the prepared compounds was confirmed by IR and <sup>13</sup>C NMR spectra.

**Keywords:** glycyrrhizinic acid, amino acids methyl esters, glycopeptides, *N*-hydroxybenzotriazole, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide

**DOI:** 10.1134/S1070363216040113

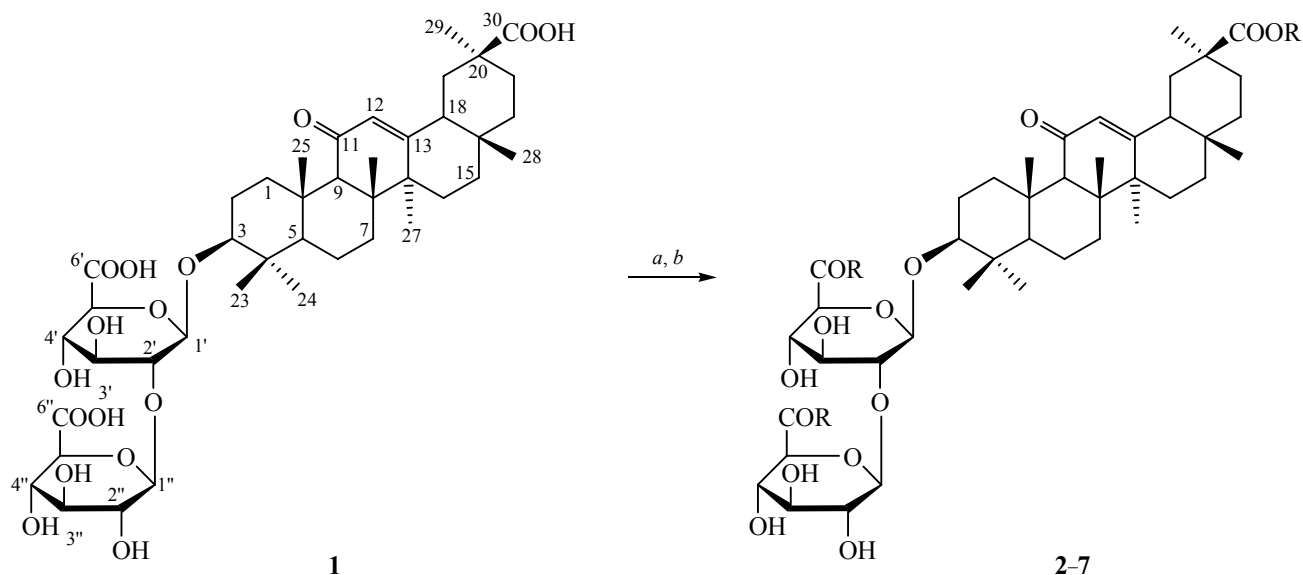
Chemical modification of polyfunctional natural compounds with the known biological activity is a promising approach to the synthesis of new compounds of medicinal application [1, 2]. Glycyrrhizinic acid **1** is the main triterpenoid glycoside of the roots of *Glycyrrhiza glabra* L. and *Glycyrrhiza uralensis* Fisher; it is known to possess high and various biological activity like anti-inflammatory, antiulcer, antioxidant, antitoxic, hepatoprotective, antimicrobial, antitumor, etc. [3] It is also one of the leading natural compounds which are promising for medicine as the base for creation of new antiviral drugs; chemical modification of the glycoside fragment in its molecule opens wide possibilities for preparation of valuable biologically active compounds [4–8].

Earlier we showed that the conjugates of glycyrrhizinic acid with amino acids and dipeptides proved to be promising for medicine as anti-AIDS agents [9], inhibitors of Epstein–Barr virus [10], anti-SARS CoV-agents [11], inhibitors of influenza virus A/H1N1/pdm2009 [12], and as immunostimulators [13, 14]. Various methods were developed for the preparation of amino acid conjugates of glycyrrhizinic acid with the use of *N*-hydroxybenzotriazole (HOBt) or the system *N*-hydroxysuccinimide–*N,N'*-dicyclohexylcarbodiimide and the complex of pentafluorophenol with *N,N'*-dicyclohexylcarbodiimide for the activation of carboxy group of glycoside [15–18].

In the present work we report on a new preparation method of glycyrrhizinic acid conjugates with methyl esters of L-amino acids.

The procedure for preparation of carboxy-protected amino acid conjugates of glycyrrhizinic acid with the use of *N*-hydroxybenzotriazole and *N,N'*-dicyclohexylcarbodiimide (DCC) in dioxane or tetrahydrofuran medium at the molar ratio **1** : HOBt : DCC = 1 : (3.5–4.0) : (3.4–4.0) with the formation of activated tris-(oxybenzotriazole) ester **2** has been known [15, 16]; after separation of precipitated *N,N'*-dicyclohexylurea compound **2** reacted with methyl, benzyl, and 4-nitrobenzyl esters of amino acids in the presence of tertiary amine like *N*-methylmorpholine, triethylamine, and tributylamine. The yield of carboxy-protected conjugates of glycyrrhizinic acid containing three amino acid residues was 82–94%. Although *N,N'*-dicyclohexylurea formed in the reaction course is very poorly soluble in organic solvents, sometimes it could not be completely removed from the reaction mixture that led to contamination of the target product. Water-soluble carbodiimides like 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide were found to be more suitable as condensing reagents. It did not provide dicyclohexylurea, and its product of water addition remained in the aqueous phase at the workup of the reaction mixture with water. Earlier 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide was not applied to the synthesis of amino acid conjugates of glycyrrhizinic acid.

Scheme 1.



*a*, HOBt, DEC; *b*, HA, *N*-ethylmorpholine. HA = L-PheOMe·HCl, L-TyrOMe·HCl, L-LeuOMe·HCl, L-IleOMe·HCl, L-MetOMe·HCl. R = 2-oxybenzotriazolyl (2), L-PheOMe (3), L-TyrOMe (4), L-LeuOMe (5), L-IleOMe (6), L-MetOMe (7).

Methyl esters of L-amino acids (phenylalanine, tyrosine, leucine, isoleucine, and methionine) in the form of hydrochlorides were used in the present work as amino acid components. The condensation was done in dimethylformamide with the use of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (DEC) hydrochloride at the molar ratio of the reagents **1** : HOBt : amino acid : DEC = 1 : (3.5–4.0) : (3.5–4.0) : (3.5–4.0) mmol in the presence of an excess of *N*-ethylmorpholine for 24 h.

The yield of carboxy-protected conjugates **3–7** reached 85–90% (Scheme 1). The structure of the obtained compounds was confirmed by IR and  $^{13}\text{C}$  NMR spectra as well as by comparison of  $R_f$  and  $[\alpha]_D^{20}$  values with those of known compounds [16, 17].

In conclusion, a new method for preparation of conjugates of glycyrrhizinic acid with esters of amino acids based on activation of the carboxy groups of the glycoside by means of *N*-hydroxybenzotriazole and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide allowed preparation of the target compounds in a quantitative yield.

## EXPERIMENTAL

IR spectra were recorded on an IR Prestige-21 spectrophotometer (Shimadzu) from suspensions of the

samples in mineral oil.  $^{13}\text{C}$  NMR spectra were registered on a Bruker AMX-300 spectrometer operating at 75.5 MHz and using tetramethylsilane as an internal reference. Optical rotation was measured on a Perkin-Elmer 341 polarimeter ( $l = 1$  dm). TLC was done on Sorbfil plates (Sorbpolimer) with the use of the following solvent systems: chloroform–methanol–water (45 : 10 : 1) (A) or chloroform–ethanol (5 : 1) (B). Column chromatography was performed on silica gel (50–160  $\mu\text{m}$ , IMID Ltd., Russia).

Purification of the solvents was accomplished according to known procedures [19]. Glycyrrhizinic acid was isolated from the roots of *Glycyrrhiza uralensis* Fisher of the Siberian populations [20]. *N*-Hydroxybenzotriazole, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, and hydrochlorides of L-amino acids methyl esters were purchased from Sigma-Aldrich (USA), Alfa Aesar (England), and Chemapol (Hungary), respectively.

**General procedure for preparation of glycyrrhizinic acid conjugates 3–7.** *N*-Hydroxybenzotriazole (0.48–0.54 g, 3.5–4.0 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.67–0.77 g, 3.5–4.0 mmol) were added to a cooled solution of glycyrrhizinic acid (0.82 g, 1 mmol) in 15–20 mL of DMF. The reaction mixture was stirred for 1 h at 0–5°C, then 5–6 h at 22–24°C. Then

hydrochloride of amino acid ester (3.5–4.0 mmol) and *N*-ethylmorpholine (0.6–0.8 mL, 5.0–7.0 mmol) were added and the reaction mixture was kept for 24 h at 22–24°C. Next, the reaction mixture was diluted with cold water and acidified with citric acid to pH ~3–4. The precipitate was filtered off, washed with water, dried, and re-precipitated from aqueous ethanol.

**3-*O*-{2-*O*-[*N*-(β-D-Glucopyranosyluronoyl)-L-(1-methoxy-1-oxopropan-3-phenyl-2-yl)carbamoyl]-*N*-(β-D-glucopyranosyluronoyl)-L-(1-methoxy-1-oxopropan-3-phenyl-2-yl)carbamoyl}-(3β,20β)-11-oxo-30-*N*-[(1-methoxy-1-oxopropan-3-phenyl-2-yl)carbamoyl]-30-norolean-12-ene (3).** Yield 90%, white powder, *R*<sub>f</sub> 0.72 (A),  $[\alpha]_{\text{D}}^{20}$  35° (*c* = 0.04, EtOH)  $\{[\alpha]_{\text{D}}^{20}$  30° (*c* = 0.02, EtOH) [16]}. IR spectrum,  $\nu$ , cm<sup>-1</sup>: 3600–3200 (OH, NH), 1742 (COOMe), 1662 (C=O), 1652 (Ph), 1535 (CONH). <sup>13</sup>C NMR spectrum (CD<sub>3</sub>OD),  $\delta_{\text{C}}$ , ppm: 202.6 (C<sup>11</sup>), 178.6 (C<sup>30</sup>), 171.5 (C<sup>6'</sup>), 171.3 (C<sup>13</sup>, C<sup>6</sup>), 129.1 (C<sup>12</sup>), 104.8 (C<sup>1'</sup>), 104.6 (C<sup>1</sup>), 90.8 (C<sup>3</sup>), 80.8 (C<sup>2</sup>), 77.8 (C<sup>5'</sup>), 77.1 (C<sup>5</sup>), 75.9 (C<sup>3'</sup>), 75.5 (C<sup>3'</sup>, C<sup>2'</sup>), 73.5 (C<sup>4</sup>, C<sup>4'</sup>), 63.0 (C<sup>9</sup>), 56.4 (C<sup>5</sup>), 48.2 (C<sup>18</sup>), 46.7 (C<sup>8</sup>), 45.1 (C<sup>20</sup>), 44.5 (C<sup>14</sup>), 42.5 (C<sup>19</sup>), 40.6 (C<sup>4</sup>), 40.5 (C<sup>1</sup>), 33.8 (C<sup>7</sup>), 38.5 (C<sup>22</sup>), 38.0 (C<sup>10</sup>), 33.0 (C<sup>17</sup>), 32.7 (C<sup>21</sup>), 29.2 (C<sup>28</sup>), 28.5 (C<sup>23</sup>), 28.4 (C<sup>29</sup>), 27.6 (C<sup>16</sup>), 27.5 (C<sup>2</sup>, C<sup>15</sup>), 23.9 (C<sup>27</sup>), 19.4 (C<sup>26</sup>), 18.5 (C<sup>6</sup>), 17.4 (C<sup>25</sup>), 17.1 (C<sup>24</sup>); PheOMe: 173.4, 173.0, 172.8, 137.5–128.2, 54.8, 54.6, 54.5, 53.0, 52.9, 52.8, 38.4, 38.2. Found N, %: 3.4. C<sub>72</sub>H<sub>95</sub>N<sub>3</sub>O<sub>19</sub>. Calculated N, %: 3.2.

**3-*O*-{2-*O*-[*N*-(β-D-Glucopyranosyluronoyl)-L-(1-methoxy-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)carbamoyl]-*N*-(β-D-glucopyranosyluronoyl)-L-(1-methoxy-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)carbamoyl}-(3β,20β)-11-oxo-30-*N*-[(1-methoxy-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)carbamoyl]-30-norolean-12-ene (4).** Yield 86%, white powder, *R*<sub>f</sub> 0.59 (B),  $[\alpha]_{\text{D}}^{20}$  45° (*c* = 0.02, MeOH)  $\{[\alpha]_{\text{D}}^{20}$  41° (*c* = 0.24, MeOH) [16]}. IR spectrum,  $\nu$ , cm<sup>-1</sup>: 3600–3200 (OH, NH), 1732 (COOCH<sub>3</sub>), 1652 (C=O), 1615 (Ph), 1596, 1538, 1516 (CONH), 1500 (Ph). <sup>13</sup>C NMR spectrum (CD<sub>3</sub>OD),  $\delta_{\text{C}}$ , ppm: 202.7 (C<sup>11</sup>), 173.6 (C<sup>30</sup>), 171.4 (C<sup>6'</sup>), 171.3 (C<sup>6</sup>), 170.6 (C<sup>13</sup>), 128.3 (C<sup>12</sup>), 106.6 (C<sup>1'</sup>), 105.1 (C<sup>1</sup>), 90.9 (C<sup>3</sup>), 81.1 (C<sup>2</sup>), 77.8 (C<sup>5'</sup>), 77.5 (C<sup>5</sup>), 76.1 (C<sup>3'</sup>, C<sup>3''</sup>), 75.5 (C<sup>2'</sup>), 73.7 (C<sup>4</sup>, C<sup>4'</sup>), 63.4 (C<sup>9</sup>), 56.8 (C<sup>5</sup>), 48.4 (C<sup>18</sup>), 47.0 (C<sup>8</sup>), 45.2 (C<sup>20</sup>), 44.8 (C<sup>14</sup>), 42.7 (C<sup>19</sup>), 40.9 (C<sup>4</sup>), 40.6 (C<sup>1</sup>), 39.3 (C<sup>10</sup>, C<sup>22</sup>), 33.2 (C<sup>17</sup>), 32.4 (C<sup>21</sup>), 26.8 (C<sup>2</sup>), 18.5 (C<sup>6</sup>), 34.1 (C<sup>7</sup>), 27.9 (C<sup>16</sup>), 29.2 (C<sup>29</sup>), 28.8 (C<sup>28</sup>), 28.5 (C<sup>23</sup>), 27.6 (C<sup>15</sup>), 24.3 (C<sup>27</sup>), 19.6 (C<sup>26</sup>), 17.4 (C<sup>25</sup>), 17.0 (C<sup>24</sup>); TyrOMe: 173.2, 173.1, 172.2, 157.8, 131.8–116.7, 63.4, 62.9,

62.7, 55.2, 55.1, 55.0, 53.2. Found N, %: 2.9. C<sub>72</sub>H<sub>95</sub>N<sub>3</sub>O<sub>22</sub>. Calculated N, %: 3.1.

**3-*O*-{2-*O*-[*N*-(β-D-Glucopyranosyluronoyl)-L-(1-methoxy-5-methyl-1-oxopentan-2-yl)carbamoyl]-*N*-(β-D-glucopyranosyluronoyl)-L-(1-methoxy-5-methyl-1-oxopentan-2-yl)carbamoyl}-(3β,20β)-11-oxo-30-*N*-[(1-methoxy-5-methyl-1-oxopentan-2-yl)carbamoyl]-30-norolean-12-ene (5).** Yield 80%, white powder, *R*<sub>f</sub> 0.72 (B),  $[\alpha]_{\text{D}}^{20}$  40° (*c* = 0.04, EtOH)  $\{[\alpha]_{\text{D}}^{20}$  35° (*c* = 0.02, EtOH) [16]}. IR spectrum,  $\nu$ , cm<sup>-1</sup>: 3600–3200 (OH, NH), 1740 (COOCH<sub>3</sub>), 1660 (C=O), 1540 (CONH). <sup>13</sup>C NMR spectrum (CD<sub>3</sub>OD),  $\delta_{\text{C}}$ , ppm: 202.4 (C<sup>11</sup>), 175.8 (C<sup>30</sup>), 171.8 (C<sup>13</sup>), 170.7 (C<sup>6'</sup>), 170.4 (C<sup>6</sup>), 129.2 (C<sup>12</sup>), 106.4 (C<sup>1'</sup>), 105.3 (C<sup>1</sup>), 90.7 (C<sup>3</sup>), 81.6 (C<sup>2</sup>), 77.6 (C<sup>5'</sup>), 77.3 (C<sup>5</sup>), 76.9 (C<sup>3'</sup>), 76.3 (C<sup>3</sup>), 76.0 (C<sup>2'</sup>), 73.5 (C<sup>4'</sup>), 73.1 (C<sup>4''</sup>), 63.2 (C<sup>9</sup>), 56.5 (C<sup>5</sup>), 48.2 (C<sup>18</sup>), 46.7 (C<sup>8</sup>), 45.1 (C<sup>20</sup>), 44.5 (C<sup>14</sup>), 42.5 (C<sup>19</sup>), 40.9 (C<sup>4</sup>), 40.7 (C<sup>1</sup>), 38.4 (C<sup>22</sup>), 38.1 (C<sup>10</sup>), 33.8 (C<sup>7</sup>), 33.0 (C<sup>17</sup>), 32.2 (C<sup>21</sup>), 29.2 (C<sup>29</sup>), 28.8 (C<sup>28</sup>), 28.4 (C<sup>23</sup>), 27.6 (C<sup>2</sup>), 27.4 (C<sup>16</sup>), 26.6 (C<sup>15</sup>), 23.9 (C<sup>27</sup>), 19.4 (C<sup>26</sup>), 18.5 (C<sup>6</sup>), 17.4 (C<sup>25</sup>), 17.1 (C<sup>24</sup>); LeuOMe: 174.8, 174.2, 173.3, 52.9, 52.7, 52.3, 52.0, 51.8, 40.6, 40.4, 31.8, 31.7, 31.6, 23.4, 23.3, 20.2, 14.4, 14.2, 14.0. Found N, %: 3.6. C<sub>63</sub>H<sub>101</sub>N<sub>3</sub>O<sub>19</sub>. Calculated N, %: 3.5.

**3-*O*-{2-*O*-[*N*-(β-D-Glucopyranosyluronoyl)-L-(1-methoxy-3-methyl-1-oxopentan-2-yl)carbamoyl]-*N*-(β-D-glucopyranosyluronoyl)-L-(1-methoxy-3-methyl-1-oxopentan-2-yl)carbamoyl}-(3β,20β)-11-oxo-30-*N*-[(1-methoxy-3-methyl-1-oxopentan-2-yl)carbamoyl]-30-norolean-12-ene (6).** Yield 85%, white powder, *R*<sub>f</sub> 0.76 (A),  $[\alpha]_{\text{D}}^{20}$  40° (*c* = 0.04, EtOH)  $\{[\alpha]_{\text{D}}^{20}$  40° (*c* = 0.02, EtOH) [16]}. IR spectrum,  $\nu$ , cm<sup>-1</sup>: 3600–3200 (OH, NH), 1742 (COOCH<sub>3</sub>), 1661 (C=O), 1527 (CONH). <sup>13</sup>C NMR spectrum (CD<sub>3</sub>OD),  $\delta_{\text{C}}$ , ppm: 202.6 (C<sup>11</sup>), 178.8 (C<sup>30</sup>), 172.7 (C<sup>6</sup>, C<sup>6'</sup>), 171.2 (C<sup>13</sup>), 129.1 (C<sup>12</sup>), 105.1 (C<sup>1'</sup>), 104.9 (C<sup>1</sup>), 90.3 (C<sup>3</sup>), 81.6 (C<sup>2</sup>), 77.6 (C<sup>5'</sup>), 77.2 (C<sup>5</sup>), 76.3 (C<sup>3'</sup>), 76.0 (C<sup>3</sup>), 75.4 (C<sup>2'</sup>), 73.4 (C<sup>4'</sup>), 73.2 (C<sup>4''</sup>), 63.0 (C<sup>9</sup>), 56.3 (C<sup>5</sup>), 48.2 (C<sup>18</sup>), 46.7 (C<sup>8</sup>), 44.9 (C<sup>20</sup>), 44.5 (C<sup>14</sup>), 42.5 (C<sup>19</sup>), 40.7 (C<sup>4</sup>), 40.3 (C<sup>1</sup>), 38.7 (C<sup>22</sup>), 38.0 (C<sup>10</sup>), 33.8 (C<sup>7</sup>), 32.1 (C<sup>21</sup>), 32.8 (C<sup>17</sup>), 29.2 (C<sup>29</sup>), 28.9 (C<sup>28</sup>), 28.4 (C<sup>23</sup>), 27.6 (C<sup>16</sup>), 27.4 (C<sup>2</sup>), 26.6 (C<sup>15</sup>), 23.8 (C<sup>27</sup>), 19.4 (C<sup>26</sup>), 18.5 (C<sup>6</sup>), 17.3 (C<sup>25</sup>), 17.1 (C<sup>24</sup>); IleOMe: 174.0, 173.2, 173.1, 58.3, 58.0, 57.6, 52.8, 52.7, 52.6, 17.0, 16.2, 16.0, 12.0, 11.9, 11.4. Found N, %: 3.4. C<sub>63</sub>H<sub>101</sub>N<sub>3</sub>O<sub>19</sub>. Calculated N, %: 3.5.

**3-*O*-{2-*O*-[*N*-(β-D-Glucopyranosyluronoyl)-L-(1-methoxy-4-methylthio-1-oxobutan-2-yl)carbamoyl]-**

***N*-( $\beta$ -D-glucopyranosyluronoyl)-L-(1-methoxy-4-methylthio-1-oxobutan-2-yl)carbamoyl}-(3 $\beta$ ,20 $\beta$ )-11-oxo-30-*N*-[(1-methoxy-4-methylthio-1-oxobutan-2-yl)carbamoyl]-30-norolean-12-ene (7). Yield 90%, cream powder,  $R_f$  0.68,  $[\alpha]_D^{20}$  30° ( $c = 0.04$ , EtOH)  $\{[\alpha]_D^{20}$  29° ( $c = 0.03$ , EtOH) [16]}. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 3600–3200 (OH, NH), 1740 (COOCH<sub>3</sub>), 1660 (C=O), 1540 (CONH). <sup>13</sup>C NMR spectrum (CD<sub>3</sub>OD),  $\delta_C$ , ppm: 202.7 (C<sup>11</sup>), 178.2 (C<sup>30</sup>), 171.7 (C<sup>6'</sup>); 171.5 (C<sup>13</sup>, C<sup>6</sup>), 129.3 (C<sup>12</sup>), 105.4 (C<sup>1''</sup>), 105.2 (C<sup>1'</sup>), 90.8 (C<sup>3</sup>), 82.0 (C<sup>2</sup>), 77.8 (C<sup>5''</sup>), 77.3 (C<sup>5'</sup>), 76.5 (C<sup>3''</sup>), 76.2 (C<sup>3'</sup>), 76.1 (C<sup>2''</sup>), 73.6 (C<sup>4''</sup>), 73.5 (C<sup>4'</sup>), 63.3 (C<sup>9</sup>), 56.6 (C<sup>5</sup>), 48.4 (C<sup>18</sup>), 46.9 (C<sup>8</sup>), 45.0 (C<sup>20</sup>), 44.8 (C<sup>14</sup>), 42.7 (C<sup>19</sup>), 40.9 (C<sup>4</sup>), 40.6 (C<sup>1</sup>), 38.9 (C<sup>22</sup>), 34.6 (C<sup>8</sup>), 27.0 (C<sup>2</sup>), 38.3 (C<sup>10</sup>), 33.3 (C<sup>17</sup>), 32.3 (C<sup>21</sup>), 29.5 (C<sup>29</sup>), 28.7 (C<sup>23</sup>), 27.9 (C<sup>28</sup>), 27.7 (C<sup>16</sup>), 26.3 (C<sup>15</sup>), 24.2 (C<sup>27</sup>), 19.9 (C<sup>26</sup>), 18.7 (C<sup>6</sup>), 17.6 (C<sup>25</sup>), 17.4 (C<sup>24</sup>); MetOMe: 174.8, 173.6, 172.9, 53.4, 53.1, 52.9, 52.8, 52.7, 52.6, 31.8, 31.7, 31.4, 31.2, 15.7, 15.6. Found N, %: 3.3; S, %: 8.5. C<sub>60</sub>H<sub>95</sub>N<sub>3</sub>O<sub>19</sub>S<sub>3</sub>. Calculated N, %: 3.4; S, %: 8.9.**

#### ACKNOWLEDGMENTS

This work was financially supported by the Russian Science Foundation (grant no. 14-03-01307).

#### REFERENCES

- Battler, M.S., *Nat. Prod. Rep.*, 2005, vol. 22, p. 162. DOI: 10.1039/b402985m.
- Mahato, S.B., *Stud. Nat. Prod. Chem.*, 2000, vol. 23, p. 487. DOI: 10.1016/S1572-5995(00)80136-2.
- Tolstikov, G.A., Baltina, L.A., Grankina, V.P., Kondratenko, R.M., and Tolstikova, T.G., *Solodka: bioraznoobrazie, khimiya, primeneniye v meditsine* (Glycyrrhiza: Biodiversity, Chemistry, Application in Medicine), Novosibirsk: Geo, 2007.
- Chattopadhyay, D. and Naik, T.N., *MiniRev. Med. Chem.*, 2007, vol. 7, p. 275. DOI: 10.2174/138955707780059844.
- Pompei, R., Laconi, S., and Ingianni, A., *MiniRev. Med. Chem.*, 2009, vol. 9, p. 996. DOI: 10.2174/138955709788681636.
- Graebin, C.S., Verli, H., and Guimaraes, J.A., *J. Braz. Chem. Soc.*, 2010, vol. 21, p. 1595. DOI: 10.1590/S0103-50532010000900002.
- Baltina, L.A., Kondratenko, R.M., Baltina, L.A., Jr., Plyasunova, O.A., Pokrovskii, A.G., and Tolstikov, G.A., *Pharm. Chem. J.*, 2009, vol. 42, no. 10, p. 539. DOI: 10.1007/s11094-010-0348-2.
- Baltina, L., *Curr. Med. Chem.*, 2003, vol. 10, no. 2, p. 155. DOI: 10.2174/0929867033368538.
- Baltina, L.A., Jr., Kondratenko, R.M., Baltina, L.A., Baschenko, N.Z., and Plyasunova, O.A., *Russ. J. Bioorg. Chem.*, 2009, vol. 35, no. 4, p. 510. DOI: 10.1134/S1068162009040141.
- Lin, J.Ch., Cherng, J.M., Hung, M.S., Baltina, L.A., Baltina, L.A., Jr., and Kondratenko, R.M., *Antiviral Res.*, 2008, vol. 79, p. 6. DOI: 10.1016/j.antiviral.2008.01.160.
- Hoefer, H., Baltina, L.A., Michaelis, M., Kondratenko, R.M., Baltina, L.A., Jr., Tolstikov, G.A., Doerr, H.W., and Cinatl, J., *J. Med. Chem.*, 2005, vol. 48, no. 4, p. 1256. DOI: 10.1021/jm0493008.
- Baltina, L.A., Jr., Stolyarova, O.V., Baltina, L.A., Kondratenko, R.M., Fedorova, V.A., Orshanskaya, Yu.A., and Zarubaev, V.V., *Chem. Nat. Compd.*, 2014, vol. 50, no. 2, p. 317. DOI: 10.1007/s10600-014-0941-9.
- Kondratenko, R.M., Baltina, L.A., Vasil'eva, E.V., Nasyrov, Kh.M., Kireeva, R.M., Baschenko, N.Zh., Fridman, S.M., Baltina, L.A., Jr., and Tolstikov, G.A., *Russ. J. Bioorg. Chem.*, 2004, vol. 30, no. 2, p. 148. DOI: 10.1023/B:RUBI.0000023100.52170.6b.
- Baltina, L.A., Ryzhova, S.A., Vasil'eva, E.V., Tolstikov, G.A., Sakhautdinova, G.M., and Zarudii, F.S., *Russ. J. Bioorg. Chem.*, 1994, vol. 20, no. 12, p. 778.
- Baltina, L.A., Ryzhova, S.A., Vasil'eva, E.V., and Tolstikov, G.A., *Russ. J. Bioorg. Chem.*, 1994, vol. 20, no. 1, p. 40.
- Baltina, L.A., Ryzhova, S.A., Vasil'eva, E.V., Kapina, A.P., and Tolstikov, G. A., *Russ. J. Gen. Chem.*, 1993, vol. 63, no. 9, p. 1490.
- Baltina, L.A. and Tolstikov, G.A., *Zh. Obshch. Khim.*, 1991, vol. 61, no. 5, p. 1227.
- Ryzhova, S.A., Baltina, L.A., and Tolstikov, G.A., *Russ. J. Gen. Chem.*, 1996, vol. 66, no. 1, p. 157.
- Gordon, A.J., and Ford, R.A., *Sputnik khimika* (The Chemist's Companion), Moscow: Mir, 1976.
- Stolyarova, O.V., Baltina, L.A., Jr., Mikhailova, L.R., Gabbasov, T.M., Baltina, L.A., and Tolstikov, G.A., *Chemistry for Sustainable Development*, 2008, vol. 16, p. 563.