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Triterpenic Acid Amides as a Promising Agent for Treatment of Metabolic Syndrome

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Abstract: A series of triterpenic acid amides were synthesized incorporating a 2-ethoxy-3-phenylpropanoic acid pharmacophore fragment. The synthesized compounds were tested for their ability to improve glycemic control and to counter lipid abnormalities in C57BL/6 mice placed on a high-fat/high-cholesterol diet. Of all tested compounds, the dihydrobetulonic derivative (**16b**) had the most pronounced effect in decreasing blood glucose levels, total cholesterol (TC), and high-density lipoproteins (HDL). All the synthesized compounds displayed a relatively safe profile in the animal studies carried out in this work.

Keywords: type 2 diabetes mellitus; hypoglycemic activity; natural product; triterpenic amides; glucose tolerance; total cholesterol

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1. Introduction

Type 2 diabetes or diabetes mellitus is a complex disease with pleiotropic clinical manifestations directly connected to a more general cluster of conditions referred to as metabolic syndrome. Diabetic dysfunctions, characterized by hyperglycemia, result from a combination of factors: insulin resistance, inadequate insulin secretion, and excessive or inappropriate glucagon secretion. In the last two decades, a new class of promising anti-diabetic pharmacological targets has emerged, comprised of a subfamily of nuclear receptors activated by peroxisome proliferators (PPARs). The activation of these receptors has been shown to normalize metabolic dysfunctions and reduce cardiovascular risk factors associated with type 2 diabetes [1]. Among the different activators, dual PPAR-α,γ agonists (glitazars) are of particular interest for the treatment of metabolic syndrome since they combine the hypolipidemic and hypoglycemic properties of α and γ-agonists [2].

A number of dual PPAR agonists, demonstrating promising results in animal studies, have been tested in clinics. However, to date, only one, saroglitazar (Figure 1), has been approved in India [3]. All the others—ragaglitazar, muraglitazar, tesaglitazar, aleglitazar (Figure 1)—failed to gain regulatory approval, primarily due to adverse side effects, that include hepatotoxicity, cardiotoxicity, and gastrointestinal toxicity [4,5].

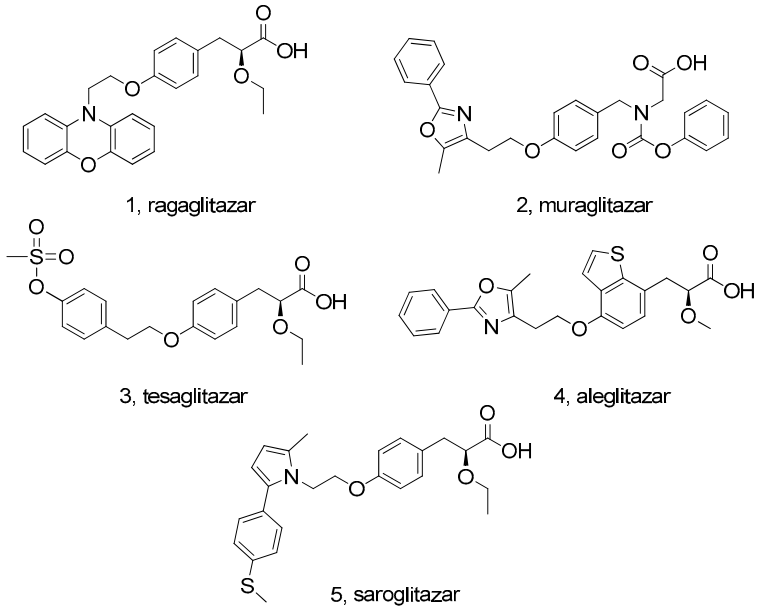


Figure 1. Chemical structures of selected glitazars (**1–5**).

Glitazars' adverse side effects may in principle be reduced by chemically modifying their pharmacophore groups. Among the possible modifications, the introduction of fragments derived from natural compounds is of particular interest.

Natural compounds are a well-known starting point for the synthesis of many drugs [6] and the introduction of natural pharmacophores can significantly improve their inherent properties. In this work, we focused on triterpenic acids and their derivatives, such as ursolic, corosolic, glycerrhetinic, as well as betulonic acids and their lipophilic derivatives. Lipophilic fragments are of particular interest in the case of PPARs because PPARs are actively expressed in the liver and in adipose tissues [7]. Triterpenic acids and their derivatives have both hepatoprotective and anti-diabetic properties [8–11], while being at the same time of little toxicity [12]. These favorable characteristics may be explained by the presence of a steroid nucleus, thought to be important for strong hypoglycemic effects [13] and their significant lipophilicity.

The triterpenic acids (Figure 2) chosen in this work are known to have hypoglycemic properties. Thus, certain lupane-type triterpenoids, such as betulonic **6a** and dihydrobetulonic **6b** acids, have been shown to possess alpha-glucosidase inhibitory activities [14,15]. Glycyrrhetinic acid **7a** is known to have several targets for its hypoglycemic actions: PPAR-γ, C/EBP-α, MAPK activation and pHSL [16]. In the case of ursolic acid **8a**, the validated targets include PPAR-α, SREBP-1c, HSL translocation, perilipin A expression, ATGL and others. Glycyrrhetinic acid derivatives have been reported to possess therapeutic antidiabetic potential [17]. Of particular, recent interest is corosolic acid **8b** that has a pronounced antidiabetic effect with a confirmed mechanism of AMPK activation and α-amylase inhibition [18]. Some derivatives of corosolic acid have also been shown to have pronounced hypoglycemic activity in vivo [19].

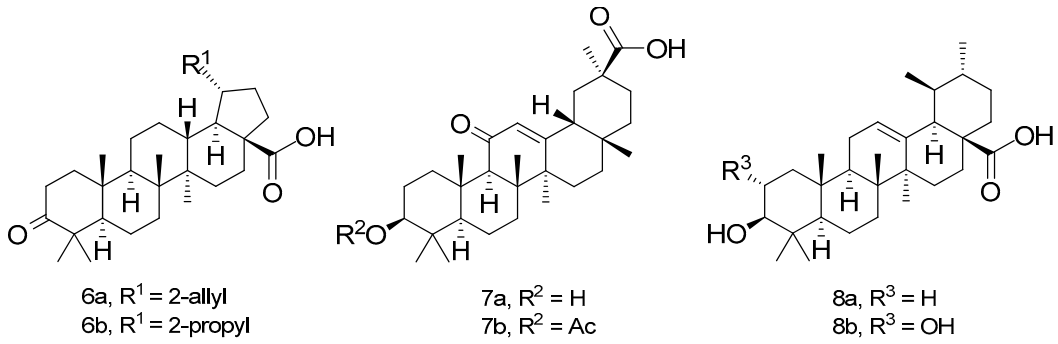


Figure 2. Triterpene acids, scaffolds for creating new compounds.

As the basis of the synthesis of new compounds, we have chosen the 2-ethoxy-3-phenylpropanoic acid pharmacophoric fragment, a common structural fragment for most of the glitazars tested in clinics. The newly synthesized compounds were tested for their ability to improve glycemic control and to counter lipid abnormalities in vivo, in C57/BL/6 mice placed on a high fat diet with the addition of cholesterol and cholate.

Our approach to the fine-tuning of the pharmacological activity consisted in the modification of the glitazars pharmacophore fragment at the level of the phenolic hydroxyl group in the tyrosol fragment, as exemplified by tesaglitazar. We hypothesized that, just like with other existing glitazars, modifications in this portion of the molecule would not affect its binding to the receptor, but may lead to desirable pharmacokinetic and pharmacodynamic properties. The choice of amide bonding as a means to join the new pharmacophores is based on its known stability in biological environments, available protocols to create amide bonds and the possibility to incorporate numerous acids of natural origin. The presence of a spacer is important in two aspects. On the one hand, it provides some flexibility to the molecule, promoting enhanced binding to the receptor. On the other hand, the aminoethanol fragment constitutes a minimal requirement for the establishment of the amide bond linking the glitazars pharmacophore fragment at the level of the phenolic hydroxyl group. It should also be noted that corosolic acid on its own acts as a dual PPAR agonist. It is therefore of interest to study the influence of related terpene acids on the PPAR binding of their derivatives.

2. Materials and Methods

2.1. Chemistry

The analytical and spectral studies were conducted in the Chemical Service Center for the collective use of SB RAS.

The ^{1}H and ^{13}C-NMR spectra of the compounds in $CDCl_3$ solutions were measured in a Bruker AV-400 spectrometer (400.13 and 100.61 MHz, respectively). The residual signals of the solvent were used as references (δH 2.48, δC 39.52 ppm for DMSO-d_6 and δH 7.27, δC 77.1 ppm for $CDCl_3$). Chemical shift measurements were calculated in ppm and the coupling constants (J) in hertz (Hz). The mass spectra (70 eV) were recorded on a DFS Thermo Scientific high-resolution mass spectrometer. Column chromatography employed Merck silica gel (63–200 μ). Thin-layer chromatography was performed on TLC Silica gel 60F254, Merck (Darmstadt, Germany). The melting temperatures of the compounds were determined using a Koffler table.

Synthesis of compounds **10, 11, 17, 8b, 18a–d** and spectra for **13, 14, 15a–f, 16a–f** are presented in Supplementary (Figure S1–S12).

All chemicals were used as received unless otherwise noted. Reagent-grade solvents were redistilled prior to use. Synthetic starting materials, reagents and solvents were purchased from Sigma-Aldrich (St. Louis, MO, USA), Acros Organics (Geel, Belgium) and AlfaAesar (Heysham, UK).

Ursolic, betulonic and dihydrobetulonic acids were purchased from the Departmental Pilot of NIOCH SB RAS. Acetylglycyrrhetinic acid was donated by colleagues from the Department of Medicinal Chemistry at NIOCH SB RAS. Corosolic acid was synthesized from ursolic as described [20] and so was the reference compound tesaglitazar **3** [21]. The obtained spectral data coincide with those found in literature.

2.1.1. Synthesis of Tert-butyl 2-(4-(2-hydroxyethyl)-phenoxy)-ethylcarbamate (11)

Tert-butyl 2-bromoethylcarbamate **10** 3.42 g (15.3 mmol) and 4-(2-hydroxyethyl)-phenol **9** 1.51 g (11 mmol) were dissolved in 10 mL DMF in a 25-mL flask. K_2CO_3 3.02 g (35 mmol) and catalytic amounts of TBAB were then added. The reaction was let to proceeded for 120 h with stirring in an inert atmosphere at 40 °C. The reaction was monitored by TLC in a $CHCl_3$:EtOAc:MeOH—8:1:1 system. The reaction mixture added to water (60 mL), stirred for 15 min, and extracted with 3 × 25 mL of Et_2O. The ether layer was washed with a KOH solution and dried over $MgSO_4$. Purification was carried out by precipitation in cooled Et_2O.

Material obtained: white powder, 2.75 g. Yield 89%. Mp: 96–98 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.42 (s, 9 H), 2.78 (t, *J* = 6.6, 2 H), 3.49 (d, *J* = 4.9, 2 H), 3.78 (t, *J* = 6.5, 2 H), 3.96 (t, *J* = 5.0, 2 H), 5.03 (br.s., 1 H), 6.81 (d, *J* = 8.6, 2 H), 7.11 (d, *J* = 8.4, 2 H). ^{13}CNMR: 28.34 (3 C), 66.24, 67.01, 68.67, 79.35, 80.21, 129.85 (2 C), 130.47 (2 C), 130.86, 155.85, 157.21. *m*/*z* (measured): 281.1627 $[M]^+$. $C_{15}H_{23}NO_4$. *m*/*z* (calculated): M 281.1625.

2.1.2. Synthesis of (S)-ethyl3-(4-(4-(2-(tert-butoxycarbonylamino)-ethoxy)-phenoxy)-phenyl)-2-ethoxypropanoate (13)

Tert-butyl 2-(4-(2-hydroxyethyl)-phenoxy)-ethyl carbamate **11** 1.91 g (6.8 mmol), *(S)*-ethyl-2-ethoxy-3-(4-hydroxyphenyl) propanoate **12** 1.78 g (7.5 mmol) and PPh_3 1.96 g (7.5 mmol) were dissolved in 60 mL THF in a 100 mL flask, DIAD 1.47 mL (7.5 mmol) was then added dropwise. The solution was cooled to 0 °C and stirred for 24 h. The reaction was monitored by TLC in a $CHCl_3$:EtOAc:MeOH—8:1:1 system. The reaction mixture was then extracted with EtOA and washed with a saturated solution of NaCl. The organic phase was dried over $MgSO_4$. Purification was achieved through a two-stage column chromatography on silica gel: first with a hexane:EtOAc—4:1 system, and then using $CHCl_3$:MeOH –100:2.

Material obtained: yellow oil, 2.89 g. Yield 85%.^{1}H-NMR (300 MHz, $CDCl_3$): 1.17 (t, *J* = 7.0, 3 H), 1.23 (t, *J* = 7.1, 3 H), 1.46 (s, 9 H), 2.95 (d, *J* = 6.6, 2 H), 3.03 (t, *J* = 7.1, 2 H), 3.35 (dd, *J* = 9.1, 7.0, 1H), 3.48–3.67 (m, 2 H), 3.93–4.05 (m, 3 H), 4.07–4.22 (m, 4 H), 4.92–5.10 (m, 1 H), 6.78–6.89 (m, 4 H), 7.15 (d, *J* = 8.6, 2 H), 7.20 (d, *J* = 8.6, 2 H).^{13}C NMR: 14.09, 14.95, 28.26 (3 C), 34.77, 38.34, 40.00, 60.64, 66.04, 67.02, 68.69, 79.32, 80.27, 114.25 (4 C), 129.13, 129.89 (2 C), 130.25 (2 C), 130.63, 155.78, 157.12, 157.44, 172.41. *m*/*z* (measured) 501.2726 $C_{28}H_{39}NO_7$ $[M]^+$. *m*/*z* (calculated): M 281.1625. M 501.2725.

2.1.3. Synthesis of 2-(4-(2-(4-((S)2-ethoxy-3-propanoate)-phenoxy)-ethyl)-phenoxy) ethanamine (14)

Trifluoroacetic acid 4.43 mL (58 mmol) was added dropwise with vigorous stirring to a cooled solution of *(S)*-ethyl-3-(4-(4-(2-(tert-butoxycarbonylamino)-ethoxy)-phenoxy)-phenyl)-2-ethoxy propanoate **13** 2.91 g (5.8 mmol) in 80 mL of CH_2Cl_2. The mixture was then purged with argon and left overnight. The solvent was evaporated, the crude product was dissolved in EtOAc and washed with saturated solution of $NaHCO_3$. The product was used without further purification.

Material obtained: yellow oil, 2.14 g. Yield 92%. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.13 (t, *J* = 7.0, 3 H), 1.25 (t, *J* = 7.1, 3 H), 2.98 (d, *J* = 6.6, 2 H), 3.03 (t, *J* = 7.1, 2 H), 3.35 (dd, *J* = 9.1, 7.0, 1 H), 3.76 (m, 2 H), 3.89–4.01 (m, 3 H), 4.02–4.18 (m, 4 H), 4.92–5.10 (br.s, 2 H) 6.79 (m, 4 H), 7.15 (d, *J* = 8.6, 2 H), 7.13 (d, *J* = 8.6, 2 H). ^{13}C-NMR: 14.15, 14.87, 34.78, 38.41, 40.11, 60.67, 66.09, 67.04, 68.63, 80.25, 114.19 (4 C), 129.15, 129.89 (2 C), 130.24 (2 C), 130.64, 157.15, 157.47, 172.42. *m*/*z* (measured): 401.2202 $[M]^+$. C_{23} $H_{31}NO_5$. *m*/*z* (calculated): M 401.2201.

2.1.4. General Procedure for the Synthesis of [triterpenoic]-2-(4-(2-(4-((S)2-ethoxy-3-propanoate)-phenoxy)-ethyl)-phenoxy) ethanamides (15a–f)

Amine **14** 1.1 g (2.75 mmol) and the corresponding acids **6–8** (2.5 mmol) were dissolved in 20 mL of DMF in a 50-mL round-bottom flask HBTU. 0.72 g (1.9 mmol) was added, followed with DIPEA 0.54 g (4.2 mmol), added dropwise while cooling in an ice bath). The mixture was purged with argon and stirred at room temperature for 5 h. It was subsequently poured into water, acidified with 10% hydrochloric acid to pH~2–3 and extracted with EtOAc. The organic phase was washed with a saturated solution of $NaHCO_3$ and dried over $MgSO_4$. Purification was carried out by column chromatography on silica gel using the hexane:EtOAc—3:1 system.

N-[3-Oxolup-20(29)-en-28-oyl]-2-(4-(2-(4-((S)2-ethoxy-3-propanoate)-phenoxy)-ethyl)-phenoxy) ethanamide (**15a**)

Material obtained: yellow oil, 1.86 g. Yield 89%. ^{1}H-NMR (400 MHz, CDCl3): 0.81 (d, *J* = 12.6, 3 H), 0.87–1.26 (m, 20 H), 2.90 (m, 2 H), 2.99 (t, *J* = 6.7, 2 H), 3.27–3.37 (m, 1 H), 3.50–3.7 (m, 3 H), 3.92 (t, *J* = 6.5, 1 H), 3.99 (t, *J* = 4.6, 2 H), 4.03–4.17 (m, 4 H), 4.63 (m, 1 H), 6.08 (br.s., 1 H), 6.79 (dd, *J* = 12.2, 8.6, 4 H), 7.10 (d, *J* = 8.3, 2 H), 7.16 (d, *J* = 8.3, 2 H).^{13}C-NMR: 14.12 (s, 3 C), 14.41, 14.97 (s, 3 C), 15.73 (d, 2 C), 19.39 (d, 2 C), 21.26, 25.45, 26.33–26.86 (m, 1 C), 29.23, 30.70, 34.10, 36.74, 37.70, 38.18, 38.34 (2 C), 40.45, 42.39, 46.74, 47.20, 49.79, 55.62, 60.32, 60.70 (2 C), 66.07 (2 C), 68.65, 80.26, 109.38, 114.15 (4 C), 129.15, 129.93 (2 C), 130.28 (4 C), 150.66, 157.13, 157.40, 172.47, 176.33, 218.23. *m*/*z* (measured): 837.5543 $[M]^+$. C_{53} $H_{75}NO_7$. *m*/*z* (calculated): M 837.5543.

N-[3-Oxolup-28-oyl]-2-(4-(2-(4-((S)2-ethoxy-3-propanoate)-phenoxy)-ethyl)-phenoxy) ethanamide (**15b**)

Material obtained: yellow oil, 1.78 g. Yield 85%.^{1}H-NMR (400 MHz, $CDCl_3$): 0.73 (t, *J* = 6.3, 3 H), 0.77–1.07 (m, 14 H), 2.92 (m, 2 H), 2.99 (t, *J* = 6.7, 2 H), 3.27–3.37 (m, 1 H), 3.50–3.59 (m, 1 H), 3.64 (d, *J* = 4.7, 2 H), 3.93 (t, *J* = 6.5, 1 H), 3.99 (t, *J* = 4.6, 2 H), 4.05–4.15 (m, 4 H), 6.04 (br.s., 1 H), 6.80 (dd, *J* = 12.2, 8.6, 4 H), 7.12 (d, *J* = 8.3, 2 H), 7.17 (d, *J* = 8.3, 2 H). ^{13}C NMR: 14.11 (s, 2 C), 14.21 (s, 2 C), 14.33, 14.50, 14.96 (s, 2 C), 15.72, 19.43, 20.90, 21.26, 22.89, 26.44, 29.23, 29.85, 34.00, 34.74, 36.67, 37.63, 38.32, 38.52, 39.44, 40.47, 42.55, 44.31, 47.19, 49.07, 49.51, 54.74, 56.15, 60.69, 66.06, 66.85, 68.63, 80.24, 114.13 (2 C), 114.31 (2 C), 116.35, 129.15, 129.91 (2 C), 130.28 (2 C), 130.69, 157.10, 157.39, 172.46, 176.51, 180.80, 218.21. *m*/*z* (measured): 839.5700 $[M]^+$. C_{53} $H_{77}NO_7$. *m*/*z* (calculated): M 839.5699.

[3*β*-. acetoxy-11-oxo-18*β*-H-olean-12-ene]-2-(4-(2-(4-((S)2-ethoxy-3-propanoate)-phenoxy)-ethyl)-phenoxy) ethanamide (**15c**)

Material obtained: yellow oil, 1.72 g. Yield 78%. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.70 (s, 3 H), 0.88 (s, 6 H), 1.07–1.31 (m, 21 H), 2.06 (s, 3 H), 2.17 (dd, *J* = 12.9, 4.1, 1 H), 2.36 (s, 1 H), 2.76–2.97 (m, 6 H), 3.01 (t, *J* = 7.0, 2 H), 3.28–3.40 (m, 1 H), 3.52–3.64 (m, 1 H), 3.64–3.74 (m, 2 H), 3.95 (m, *J* = 6.7, 6.7, 1 H), 4.00–4.22 (m, 7 H), 4.52 (dd, *J* = 11.4, 5.0, 1 H), 5.70 (s, 1 H), 6.10 (t, *J* = 5.6, 1 H), 6.80 (d, *J* = 8.7, 2 H), 6.87 (d, *J* = 8.6, 2 H), 7.14 (d, *J* = 8.6, 2 H), 7.19 (d, *J* = 8.6, 2 H). ^{13}C-NMR: 14.21, 15.06, 16.41, 16.66, 17.33, 18.60, 21.32, 23.30, 23.53, 26.34, 28.01, 28.37, 29.50, 31.51, 31.79, 32.64, 34.86, 36.90, 37.40, 38.01, 38.45, 38.76, 39.08, 41.75, 43.12, 43.65, 45.31, 47.93, 54.97, 60.78, 61.69, 66.17, 66.76, 68.78, 77.20, 80.39, 80.57, 114.25 (2 C), 114.50 (2 C), 128.48, 129.22, 130.04 (2 C), 130.35 (2 C), 130.83, 157.09, 157.52, 169.06, 171.03, 172.56, 175.98, 199.88. *m*/*z* (measured): 895.5598 $[M]^+$. $C_{55}H_{77}NO_9$. *m*/*z* (calculated): M 895.5596.

[3ß-. hydroxy-urs-12-ene]-2-(4-(2-(4-((S)2-ethoxy-3-propanoate)-phenoxy)-ethyl)-phenoxy) ethanamide (**15e**)

Material obtained: yellow oil, 1.70 g. Yield 81%. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.15 (t, *J* = 7.1, 3 H), 1.21–1.48 (m, 20 H), 2.93 (d, *J* = 7.0, 2 H), 3.01 (t, *J* = 7.1, 2 H), 3.30–3.38 (m, 1 H), 3.53–3.68 (m, 4 H), 3.91–4.02 (m, 3 H), 4.05–4.19 (m, 10 H), 5.3 (m, 1 H), 6.46 (t, *J* = 5.0, 1 H), 6.81 (m, 4 H), 7.13 (d, *J* = 8.6, 2 H), 7.20 (d, *J* = 8.6, 2 H). ^{13}C-NMR: 14.21, 15.06, 15.56,

16.86, 17.20, 18.18, 21.22, 23.14, 24.84, 27.82, 28.06, 30.48, 30.88, 32.65, 34.88, 38.41, 39.02, 39.48, 39.76, 42.43, 47.47, 47.93, 49.09, 52.96, 53.80, 55.00, 60.80, 66.16, 66.49, 68.80, 78.90, 80.35, 108.16, 114.21 (2 C), 120.48, 124.58, 125.92, 127.09, 128.38, 129.26, 130.09 (2 C), 130.39 (2 C), 130.72, 136.78, 139.32, 157.12, 157.51, 172.55, 173.36, 178.30. *m*/*z* (measured): 839.5700 $[M]^+$. C_{53} $H_{77}NO_7$. *m*/*z* (calculated): M 839.5699.

[2*α*,3ß-. dihydroxy-urs-12-ene]-2-(4-(2-(4-((S)2-ethoxy-3-propanoate)-phenoxy)-ethyl)-phenoxy) ethanamide (**15f**)

Yellow oil, 1.39 g. Yield 65%. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.68 (s, 3 H), 0.94 (s, 3 H), 1.00 (s, 3 H), 1.07 (s, 3 H), 1.16 (t, *J* = 7.0, 3 H), 1.22 (t, *J* = 7.1, 3 H), 1.77 (d, *J* = 12.8, 2 H), 1.83–2.06 (m, 6 H), 2.44–2.59 (m, 2 H), 3.02 (t, *J* = 7.0, 2 H), 3.30–3.40 (m, 1 H), 3.52–3.72 (m, 4 H), 3.92–4.01 (m, 3 H), 4.09 (t, *J* = 7.0, 2 H), 5.31 (br.s., 1 H), 6.47 (t, *J* = 5.1, 1 H), 6.77–6.85 (m, 4 H), 7.14 (d, *J* = 8.5, 2 H), 7.20 (d, *J* = 8.3, 2 H). ^{13}C NMR: 14.22, 15.06, 16.47, 16.71, 16.93, 17.21, 18.20, 21.22, 23.17, 23.34, 24.81, 27.81, 28.58, 29.69, 34.92, 37.21, 38.01, 38.41, 38.64, 39.07, 39.58, 39.79, 42.51, 46.52, 47.48, 47.96, 53.85, 55.10, 60.81, 66.17, 66.53, 68.81, 68.86, 76.58, 77.42, 80.33, 83.89, 114.20 (2 C), 114.30 (2 C), 125.72, 129.32, 130.11 (2 C), 130.42 (2 C), 130.85, 139.40, 157.43, 157.59, 172.55, 178.20. *m*/*z* (measured): 855.5649 $[M]^+$. C_{53} $H_{77}NO_8$. *m*/*z* (calculated): M 855.5648.

2.1.5. Hydrolysis of [triterpene]-2-(4-(2-(4-((S)2-ethoxy-3-propanoic)-phenoxy)-ethyl)-phenoxy) ethanamides (**16a–f**)

In a 25 mL flask, 0.51 mmol of the corresponding ester **15a–f** was dissolved in MeOH:THF:H_2O—1:2:1 system. The solution was cooled to 0 °C, and 2.3 mmol of LiOH monohydrate was added in portions with vigorous stirring. After 2 h, extracted with EtOAc, and the aqueous layer was acidified with 10% hydrochloric acid to pH ~2–3. The organic layer was dried with $MgSO_4$. Purification was carried out by column chromatography in the $CHCl_3$:MeOH—100:2 system.

N-[3-Oxolup-20(29)-en-28-oyl]-2-(4-(2-(4-((S)2-ethoxy-3-propanoic)-phenoxy)-ethyl)-phenoxy) ethanamide (**16a**)

Material obtained: brown powder, 0.32 g. Yield 79%. Mp: 122–124 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.83 (d, *J* = 11.7, 6 H), 0.91–1.08 (m, 10 H), 2.30–2.52 (m, 3 H), 2.90–3.15 (m, 5H), 3.47 (d, *J* = 7.4, 1 H), 3.54–3.77 (m, 3 H), 4.03 (br. s., 3 H), 4.10 (t, *J* = 6.4, 2 H), 4.55–4.80 (m, 2 H), 6.11 (br. s., 1 H), 6.75–6.90 (m, 4 H), 7.15 (d, *J* = 7.8, 2 H), 7.20 (d, *J* = 7.8, 2 H). ^{13}C-NMR: 14.15, 14.48, 15.02, 15.72, 15.85, 19.39, 19.52, 20.96, 21.30, 25.52, 26.54, 29.31, 30.78, 33.46, 33.64, 34.06, 34.85, 36.79, 37.77, 37.85, 38.23, 38.68, 39.51, 40.52, 42.48, 46.88, 47.27, 49.84, 54.83, 55.76, 60.40, 66.65, 66.90, 68.74, 79.76, 109.49, 114.30 (2 C), 114.45 (2 C), 128.75, 130.01, 130.47 (2 C), 130.80 (2 C), 150.67, 157.19, 157.61, 176.43, 218.65. *m*/*z* (measured): 809.5230 $[M]^+$. $C_{51}H_{71}NO_7$. *m*/*z* (calculated): M 809.5229.

N-[3-Oxolup-28-oyl]-2-(4-(2-(4-((S)2-ethoxy-3-propanoic)-phenoxy)-ethyl)-phenoxy) ethanamide (**16b**)

Material obtained: white powder, 0.34 g. Yield 84%. Mp: 119–120 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.71–1.01 (m, 18 H), 1.17 (t, *J* = 7.0, 3 H), 1.50–1.92 (m, 7 H), 2.15–2.29 (m, 1 H), 2.29–2.53 (m, 3 H), 2.86–3.11 (m, 4 H), 3.34–3.48 (m, 1 H), 3.55–3.77 (m, 3 H), 3.97–4.06 (m, 3 H), 4.10 (t, *J* = 7.1, 2 H), 6.14 (t, *J* = 5.5, 1 H), 6.76–6.90 (m, 4 H), 7.11–7.24 (m, 4 H). ^{13}C-NMR: 14.26, 14.44, 15.12, 15.76, 15.85, 19.34, 19.57, 20.91, 21.32, 25.76, 26.54, 29.32, 30.77, 33.45, 33.63, 34.05, 34.82, 36.76, 37.74, 37.87, 38.21, 38.64, 39.52, 40.55, 42.45, 46.86, 47.21, 49.82, 54.84, 55.76, 60.42, 66.63, 66.94, 68.75, 79.71, 109.41, 114.34 (2 C), 114.45 (2 C), 128.72, 130.09, 130.48 (2 C), 130.87 (2 C), 150.67, 157.14, 157.61, 176.44, 218.66. *m*/*z* (measured): 811.5387 $[M]^+$. $C_{51}H_{73}NO_7$. *m*/*z* (calculated): M 811.5387.

[3β-. acetoxy-11-oxo-18β-H-olean-12-ene]-2-(4-(2-(4-((S)2-ethoxy-3-propanoic)-phenoxy)-ethyl)-phenoxy) ethanamide (**16c**)

Material obtained: colorless oil, 2.09 g. Yield 85%. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.70 (s, 3 H), 0.88 (s, 6 H), 1.08–1.20 (m, 12 H), 1.33–1.40 (m, 6 H), 1.52–1.85 (m, 6 H), 2.06 (s, 3 H), 2.17 (dd, *J* = 13.2, 3.6, 1 H), 2.77–2.85 (m, 1 H), 2.88–3.09 (m, 4 H), 3.41 (dd, *J* = 9.0, 7.1, 1 H), 3.60 (dd, *J* = 8.9, 7.1, 1 H), 3.67 (q, *J* = 4.9, 2 H), 3.97–4.05 (m, 3 H), 4.08 (t, *J* = 7.1, 2 H), 4.52 (dd, *J* = 11.6, 4.8, 1 H), 5.72 (s, 1 H), 6.20 (t, *J* = 5.4, 1 H), 6.80 (d, *J* = 8.6, 2 H), 6.85 (d, *J* = 8.6, 2 H), 7.14 (d, *J* = 8.6, 2 H), 7.18 (d, *J* = 8.6, 2 H). ^{13}C-NMR: 15.00, 16.39, 16.64, 17.29, 18.57, 21.31, 23.27, 23.49, 26.30, 26.34, 27.99, 28.36, 29.44, 31.45, 31.75, 32.60, 34.15, 34.84, 36.87, 37.36, 37.82, 37.98, 38.72, 39.09, 41.66, 43.11, 43.65, 45.31, 47.89, 54.93, 56.68, 60.41, 66.65, 68.73, 79.89, 80.61, 114.28 (2 C), 114.48 (2 C), 128.42, 128.82, 130.01 (2 C), 130.42 (2 C), 130.79, 157.05, 157.60, 169.25, 171.14, 176.16, 200.02. *m*/*z* (measured): 867.5285 $[M]^+$. C_{53} $H_{73}NO_9$. *m*/*z* (calculated): M 867.5284.

[3β-. hydroxy-11-oxo-18β-H-olean-12-ene]-2-(4-(2-(4-((S)2-ethoxy-3-propanoic)-phenoxy)-ethyl)-phenoxy) ethanamide (**16d**)

Material obtained: orange powder, 0.04 g. Yield 10%. Mp: 112–114 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.64–0.74 (m, 3 H), 0.80 (s, 3 H), 1.00 (s, 3 H), 1.06–1.22 (m, 12 H), 1.29–1.50 (m, 9 H), 1.54–1.70 (m, 4 H), 2.16 (dd, *J* = 11.9, 5.3, 1 H), 2.32 (s, 1 H), 2.75–2.84 (m, 1 H), 2.88–3.10 (m, 4 H), 3.24 (dd, *J* = 10.7, 5.3, 1 H), 3.36–3.47 (m, 1 H), 3.53–3.75 (m, 3 H), 3.98–4.06 (m, 3 H), 4.09 (m, *J* = 7.2, 7.2, 2 H), 5.68 (s, 1 H), 6.20 (t, *J* = 5.1, 1 H), 6.80 (d, *J* = 8.6, 2 H), 6.86 (d, *J* = 8.6, 2 H), 7.14 (d, *J* = 8.5, 2 H), 7.18 (d, *J* = 8.6, 2 H *m*/*z* (measured): 825.5180 $[M]^+$. $C_{51}H_{71}NO_8$. *m*/*z* (calculated): M 825.5179.

[3ß-. hydroxy-urs-12-ene]-2-(4-(2-(4-((S)2-ethoxy-3-propanoic)-phenoxy)-ethyl)-phenoxy) ethanamide (**16e**)

Material obtained: colorless oil, 0.33 g. Yield 81%. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.48–0.76 (m, 9 H), 0.82–1.10 (m, 15 H), 1.33–1.56 (m, 10 H), 3.20 (dd, *J* = 11.2, 3.9, 1 H), 3.36–3.52 (m, 2 H), 3.54–3.71 (m, 1 H), 3.84–4.13 (m, 6 H), 4.58 (br. s., 1 H), 5.29 (br. s., 1 H), 6.45–6.55 (m, 1 H), 6.81 (t, *J* = 7.9, 4 H), 7.14 (d, *J* = 8.5, 2 H), 7.20 (d, *J* = 8.5, 2 H).^{13}C NMR: 15.08, 15.61, 16.86, 17.20, 18.13, 21.21, 23.07, 24.68, 26.51, 27.77, 27.97, 29.67, 30.87, 32.65, 35.02, 36.63, 37.22, 38.06, 38.39, 38.52, 39.04, 39.43, 39.79, 42.43, 47.42, 48.05, 53.92, 54.89, 66.09, 66.36, 69.06, 77.20, 79.39, 80.05, 114.00 (2 C), 114.13 (2 C), 125.97, 128.74, 130.07 (3 C), 130.36, 130.59 (2 C), 139.00, 157.03, 157.61, 173.61, 178.18. *m*/*z* (measured): 811.5387 $[M]^+$. $C_{51}H_{73}NO_7$. *m*/*z* (calculated): M 811.5385.

[2α,3ß-. dihydroxy-urs-12-ene]-2-(4-(2-(4-((S)2-ethoxy-3-propanoic)-phenoxy)-ethyl)-phenoxy) ethanamide (**16f**)

Material obtained: white crystals, 0.29 g. Yield 69%. Mp: 130–132 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.47–0.60 (m, 6 H), 0.71–0.78 (m, 3 H), 0.81–0.90 (m, 3 H), 0.93–1.01 (m, 6 H), 1.06 (s, 3 H), 1.71–1.98 (m, 6 H), 2.19 (s, 1 H), 2.62–2.66 (m, 1 H), 2.93–3.10 (m, 5 H), 3.30–3.68 (m, 5 H), 3.88–4.18 (m, 7 H), 5.31 (br. s., 1 H), 6.50 (d, *J* = 3.5, 1 H), 6.76–6.85 (m, 4 H), 7.10–7.16 (m, 2 H), 7.20 (d, *J* = 8.5, 2 H). ^{13}C NMR: 15.16, 16.25, 16.66, 16.81, 17.24, 18.12, 21.26, 23.07, 23.17, 24.66, 27.73, 28.38, 29.22, 30.91, 32.67, 34.92, 37.34, 37.84, 38.00, 38.25, 39.07, 39.15, 39.52, 39.84, 42.56, 46.53, 47.52, 48.16, 53.88, 55.06, 66.12, 66.46, 67.93, 69.18, 80.89, 84.62, 113.98 (2 C), 114.35 (2 C), 125.73, 127.84, 130.01 (2 C), 130.09, 130.28, 130.53 (2 C), 130.72, 139.01, 156.93, 157.82, 178.03. *m*/*z* (measured): 827.5336 $[M]^+$. $C_{51}H_{73}NO_8$. *m*/*z* (calculated): M 827.5335.

2.2. Biology

2.2.1. Animals

C57Bl/6 mice weighing 20–25 g were obtained from the SPF vivarium of the ICG SB RAS. Animals were kept under standard conditions with free access to water and food, in humidity and temperature-controlled rooms, under standard 12 h light/12 h

dark cycle. All manipulations involving animals was carried out in strict accordance with the legislation of the Russian Federation, Order of the Ministry of Health of the Russian Federation No. 199n of 04/01/2016 and the provisions of Directive 2010/63/EU of the European Parliament and of the Council of the European Union of 09.22.2010 on the protection of animals used for scientific purposes. Each experimental group consisted of 8 animals.

2.2.2. High Fat Diet

Standard pelleted feed containing 250 Kcal/100 g was supplemented with 2.5% cholesterol (CAS 57885, Acros Organics), 0.5% cholic acid (CAS 81254, ABCR), 0.1% 6-propyl -2-thiurocyl (CAS 51525, Sigma-Aldrich), and 20% fat in the form of butter. The final caloric content of the feed was set at 545 Kcal/100 g. Tesaglitazar **3** was used as a control due to the chemical similarity with novel compounds, the tesaglitazar moiety being a part of their chemical structure. The animals were kept on this diet for 6 weeks and subsequently divided into the following groups: (1) HF diet; (2) HF diet + Tesaglitazar **3** 15 mg/kg; (3) HF diet + **16a** 30 mg/kg; (4) HF diet + **16b** 30 mg/kg; (5) HFdiet + **16c** 30 mg/kg; (6) HF diet + **16e** 30 mg/kg; (7) HF diet + **16f** 30 mg/kg; (8) Standard chew + Vehicle (water distilled + two drops of tween 80). The test substances were mixed with 2 drops of Tween 80, diluted in distilled water, then introduced once a day by oral gavage for 5 weeks.

2.2.3. Oral Glucose Tolerance Test

The oral glucose tolerance test was carried out on the 32 day of the experiment, one day after the last administration of the compounds and after 12 h fasting. The same oral glucose load (2.5 g/kg) was used in all experimental groups. Blood glucose values were measured using a OneTouch Select blood glucose meter (LifeScan Inc., Milpitas, CA, USA) before dosing (0) and 30, 60, 90, 120 min after the glucose load. The area under the glycemic curve was calculated using Tai's model [22].

2.2.4. Biochemistry

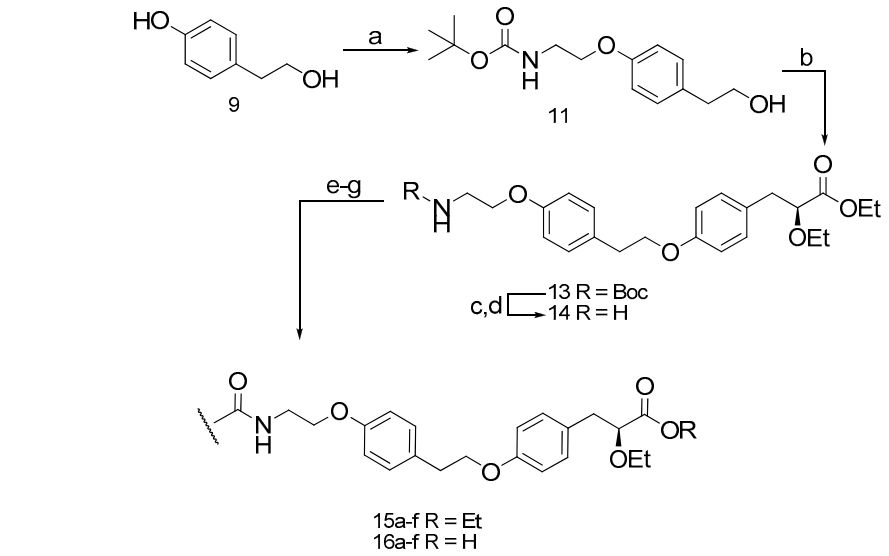
After 5 weeks of treatment mice were decapitated and trunk blood was collected. The serum was isolated by centrifugation at 1640$\times$ *g* for 15 min. Serum total cholesterol (TC), total triglyceride (TG), high density and low-density lipoproteins (HDL and LDL), Glucose (Glu) and Alkaline phosphatase (ALP) levels were measured in all groups using standard diagnostic kits (Vector Best, Novosibirsk, Russia) and a Stat Fax 3300 spectrophotometer (Awareness Technology Inc., Palm City, FL, USA).

Statistical analysis was performed using Mann–Whitney U test. Results were calculated as averages $\pm$ SEM. $p < 0.05$ was considered to be statistically significant.

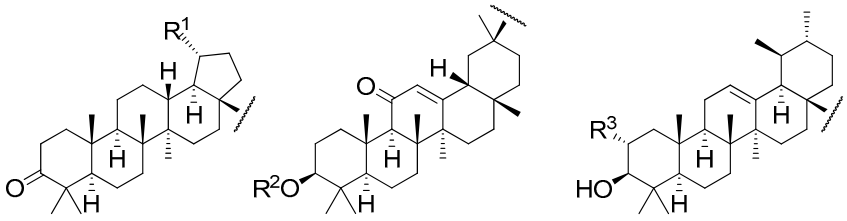
3. Results

3.1. Chemistry

The synthetic route used for the preparation of the new triterpenic acid amides is presented in Scheme 1. *Tert*-butyl N-[2-[4-(2-hydroxyethyl)-phenoxy]-ethyl] carbamate **11** was obtained in 88% yield by the reaction of tyrosol **9** with an excess of bromide **10** in DMF in the presence of potassium carbonate and catalytic amounts of tetra-n-butylammonium bromide (TBAB). The conditions of the reaction are common with those of nucleophilic substitution. However, the elevated temperature at which the reaction took place led to a decrease in the yield of the target compound due to side reactions of bromide **10**. At the same time, a decrease in the reaction temperature led to a significant increase in the reaction time. We found that **10** can be obtained in 88% yield when the reaction is carried out for seven days at 40 °C.



a) BocNHCH$_2$CH$_2$Br **(10)**, K_2CO_3, DMF, 40 °C, 120 h; b) (*S*)-ethyl 2-ethoxy-3-(4-hydroxyphenyl)propanoate **(12)**, PPh_3, DIAD, THF; c) CF_3COOH, CH_2Cl_2; d) $NaHCO_3$; e) **6-8**, HBTU, DIPEA, DMF; f) LiOH, THF/MeOH/H_2O; g) HCl, H_2O.



R^1 = 2-allyl
15a 89%
16a 79%
R^1 = 2-propyl
15b 85%
16b 84%

15c R^2 = Ac 78%
16c R^2 = Ac 85%
16d R^2 = H 10%

15e R^3 = H 81%
16e R^3 = H 81%
15f R^3 = OH 65%
16f R^3 = OH 69%

Scheme 1. The synthetic route for synthesis of compounds **16a–f**.

Compound **13** was obtained in 85% yield, using an adapted procedure [23] through the reaction of tyrosol derivative **11** with (*S*)-ethyl 2-ethoxy-3-(4-hydroxyphenyl) propanoate **12** in the presence of diisopropylazodicarboxylate (DIAD) and triphenylphosphine in THF.

Free amine **14** was obtained in 92% yield using an adapted procedure [24] upon sequential treatment of trifluoroacetic acid on amine **13** with methylene chloride and an aqueous $NaHCO_3$ solution. The condensation of this resulting amine **14** with acids **6–8** in the presence of (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) and N,N-diisopropylethylamine (DIPEA) in DMF using an adapted procedure [25] led to the production of novel amides **15a–f** in yields of 65–89% under mild conditions. The resulting compounds **15a–f** were hydrolyzed with lithium hydroxide using an adapted procedure [26] and the reaction mixture was subsequently acidified, leading to the formation of acids **16a–f** in yields of 69–85%. Because the rate of hydrolysis of the acetyl group in the glycyrrhetinic moiety is much lower compared to the rate of hydrolysis of the ester group in the phenylpropanoic acid moiety, it is possible to isolate **16c** in 85% yield as the main product when the reaction is carried out for approximately 2 h under cooling.

3.2. Biology

To assess the pharmacological activities, the newly synthesized compounds were administered by oral gavage at a dose of 30 mg/kg for five weeks to mice placed on a high-fat diet with the addition of 2.5% cholesterol and 0.5% cholate (HF diet). This dose was determined according to preliminary experiments with similar molecules (data not

published). Tesaglitazar **3** was used as a positive control at a dose of 15 mg/kg, to take into account its lower molecular weight. The changes in animal body weights were monitored throughout the experiment (Figure 3).

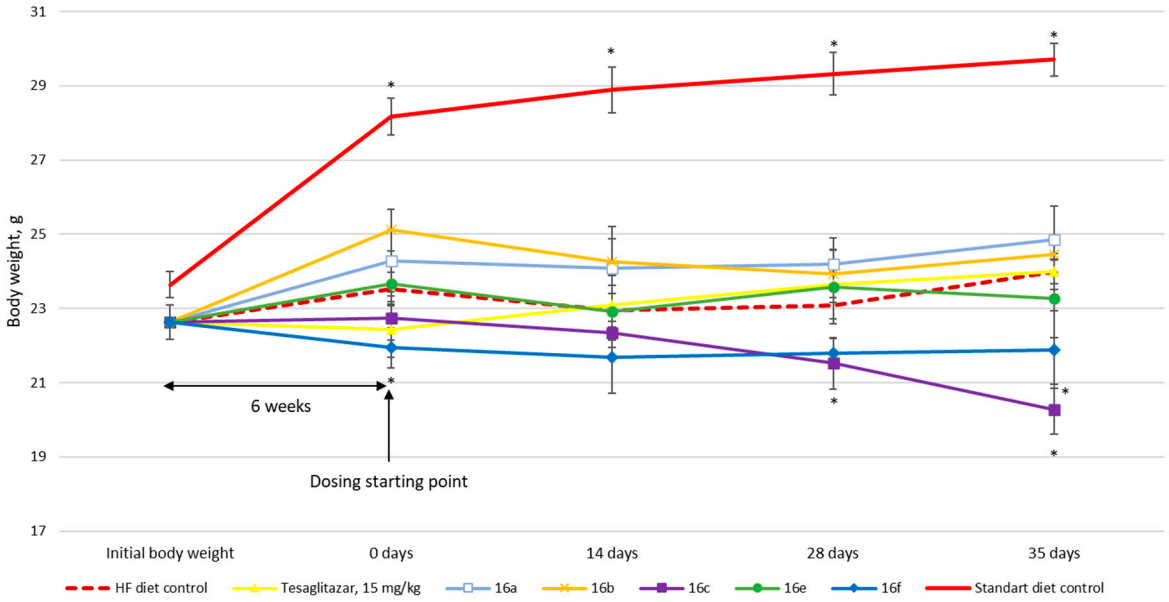


Figure 3. Dynamics of changes in body weight of animals during the experiment. * $p < 0.05$ compare to HF diet control. 6 week—period on HF-diet prior to introduction of testing compounds. Dosing starting point—first introduction of tesaglitazar, **16a**, **16b, 16c**, **16e**, **16f**. **16a–f** were introduced at a dose of 30 mg/kg.

An oral glucose tolerance test (OGTT) was carried out 32 days post administration of the tested compounds (Figures 4 and 5). The experiment was concluded after 36 days, and blood was drawn for biochemical analyses (Table 1).

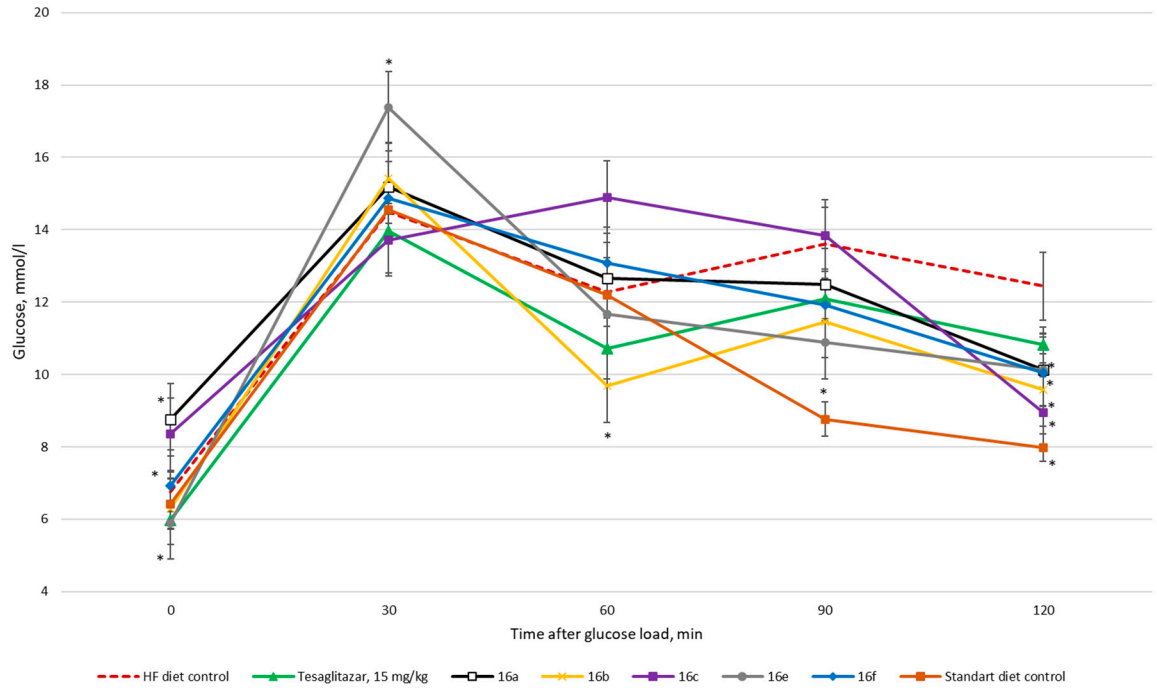


Figure 4. Oral glucose tolerance test results. **16a–f** were introduced at a dose of 30 mg/kg. * $p < 0.05$ compare to HF diet control.

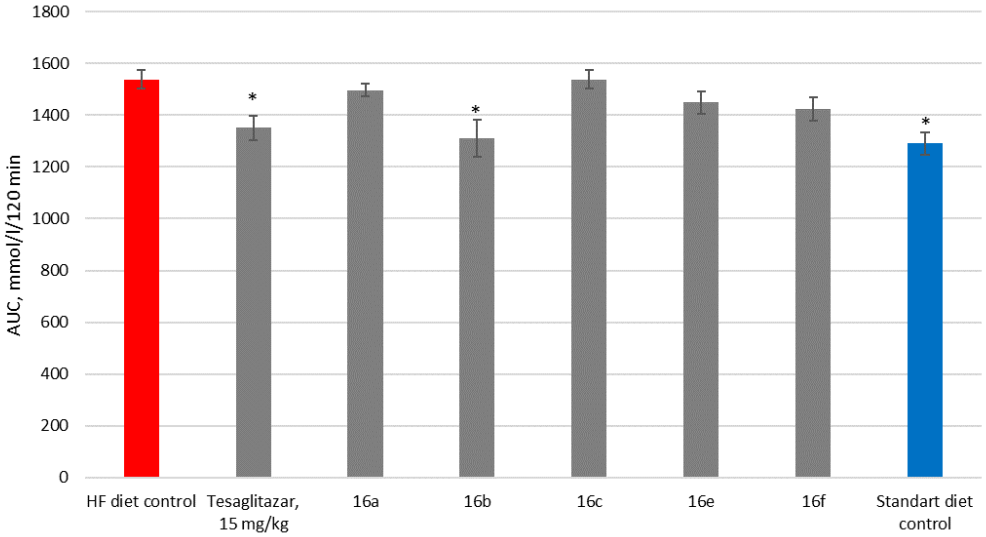


Figure 5. OGTT results. Area under glycemic curve (AUC). **16a–f** were introduced at a dose of 30 mg/kg. * $p < 0.05$ compare to HF diet control.

Table 1. Blood biochemical parameters at the end of the experiment (36 days).

	TC, mmol/L	TG, mmol/L	HDL, mg/dL	LDL, mg/dL	GlU, mmol/L	ALP, U/L
HF diet	4.29 ± 0.16	0.57 ± 0.07	213.51 ± 16.61	19.84 ± 2.57	6.76 ± 0.32	196.54 ± 8.86
3	4.88 ± 0.18 *	0.39 ± 0.02 *	201.60 ± 5.73	18.54 ± 0.93	7.55 ± 0.54	492.76 ± 34.74 *
16a	4.03 ± 0.22	0.37 ± 0.04 *	173.79 ± 10.85	24.93 ± 1.49	7.62 ± 0.77	190.33 ± 13.71
16b	3.71 ± 0.23 *	0.64 ± 0.09	156.43 ± 13.05 *	17.76 ± 1.89	5.51 ± 0.44 *	184.25 ± 9.49
16c	3.88 ± 0.27	0.57 ± 0.04	153.81 ± 11.02 *	18.03 ± 2.69	6.72 ± 0.48	208.80 ± 26.77
16e	4,28 ± 0.47	0.40 ± 0.04	184.95 ± 20.59	20.72 ± 6.87	5.71 ± 0.64	342.70 ± 80.70
16f	3.83 ± 0.29	0.65 ± 0.05	158.378 ± 10.15 *	17.60 ± 1.12	6.71 ± 0.49	223.06 ± 22.87
SD control	2.41 ± 0.18 *	0.79 ± 0.05 *	108.64 ± 6.11 *	11.01 ± 1.18 *	6.38 ± 0.28	180.53 ± 7.06

TC—total cholesterol, TG—triglycerides, HDL—high-density lipoproteins, LDL—low-density lipoproteins, GLU—glucose, ALP—alkaline phosphatase, HF—high fat diet, SD—standard diet. * $p < 0.05$ compare to HF diet control.

4. Discussion

In this study, we synthesized new triterpenic acid amides, that incorporate a 2-ethoxy-3-phenylpropanoic acid pharmacophore fragment, convenient for glitazars. Betulonic, dihydrobetulonic, glycyrrhetinic, ursolic, and corosolic acids were chosen for synthesis due to their antidiabetic potential.

The newly synthesized compounds were administered per os at a dose of 30 mg/kg for 5 weeks to mice placed on a high-fat diet with the addition of cholesterol and cholate taking tesaglitazar 3 as a positive control.

As can be seen in Figure 3, the body weight of animals maintained on the HF diet was noticeably inferior to that of animals in the standard diet (SD) control group. The weight lost in this case is directly a consequence of the high content of cholesterol and cholic acid in the diet. Usually these additives used to produce more pronounced fatty liver disease in mice [27]. Animals treated with tesaglitazar **3** differed from the other groups in their persistent tendency to gain body weight. The opposite trend was observed in the animals treated with **16c**. Administration of **16f** did not significantly affect animal body weight at any point of the experiment. The dynamics of the changes in body weight in groups **16a**, **16b**, **and 16e** resembled that of the HF diet control group. Thus, if the dynamics of body weight are assumed to reflect acute toxicity, all the tested compounds, except for **16c**, exhibit negligible toxic effects during the experiment.

Based on the oral glucose tolerance test, the HF diet resulted in impaired glucose tolerance (HF diet control vs. SD after 60 min, Figure 4). A significant decrease in the concentration of blood glucose was observed only in the reference compound **3** and **16b** groups. The lower values of their areas under the glycemic curve (AUC, Figure 5) do not differ from the values obtained in the control group (SD). Interestingly the greatest decrease in glucose was observed after **16b** administration exceedingly early, only 60 min after the start of the experiment (Figure 4). Conversely, **16c** administration caused an increase in blood glucose levels 60 and 90 min after glucose administration. This observation may be explained by a delay in insulin synthesis/release by pancreatic beta cells.

The mice maintained on the HF diet developed hyperlipidemia, as demonstrated by a significant increase in the blood levels of total cholesterol (TC) and carrier lipoproteins (HDL) (Table 1). At the same time, the level of triglycerides (TG) was decreased, a finding that may be explained by a lower synthetic function of the liver and some hepatotoxic effects of the diet.

Administration of tesaglitazar **3** further reduced this parameter, while causing increased levels of TC and alkaline phosphatase (ALP). This finding can be considered a hepatotoxic effect since the introduction of other substances did not cause similar changes. Interestingly, the changes in biochemical parameters did not affect the body weight of the animals, which continued to gain weight throughout the experiment (Figure 3).

The desired hypolipidemic effect was found in mice treated with **16b**. Their blood TC and HDL levels were significantly lower than those of the control group (HF diet). In addition, these animals also displayed the lowest glucose level, a finding that speaks in favor of a dual effect of **16b** on lipid and carbohydrate metabolisms, absent in any of the other groups. ALP activities in these animals remained at the control level of mice maintained on both on HF and on SD diets. The absence of any ALP increase, which is associated with cholestasis, suggests that **16b** is less toxic than reference compound **3**. Administration of **16f** and **16c** led to a decrease in high density lipoproteins (HDL) cholesterol, without causing a significant decrease in TC, although the values are remarkably close to **16b**. It is possible that these substances have a lower affinity for receptors than **16b** and that a higher dose may be required to obtain a similar response.

5. Conclusions

A series of triterpenic acid amides were synthesized incorporating a 2-ethoxy-3-phenylpropanoic acid pharmacophore fragment. The synthesized compounds were administered orally at a dose of 30 mg/kg for 5 weeks to mice placed on a high-fat/high-cholesterol diet (HF diet). All the synthesized compounds, except for one (**16c**) appeared to have negligible toxic effects throughout the experiment. A significant decrease in blood glucose in the blood of animals, matching the levels in the control group (SD) was observed in animals receiving either the reference drug **3** or the dihydrobetulonic acid derivative **16b**. The HF diet-associated increase in the blood of total cholesterol (TC) and carrier lipoproteins (HDL) and associated decrease in the level of triglycerides (TG) was effectively prevented by the administration of compound **16b**, with full or partial normalization of these blood parameters in the relevant animals. Administration of tesaglitazar caused a further decrease in triglycerides (TG) levels and an increase in TC and alkaline phosphatase (ALP).

In conclusion, the newly synthesized dihydrobetulonic (**16b**) derivative is able to improve both lipid and carbohydrate metabolism and is thus a promising drug candidate, deserving further investigation.

Supplementary Materials: The following are available online at https://www.mdpi.com/2218-0532/89/1/4/s1. Figure S1. 1H NMR spectrum of compound **11**. Figure S2. 1H NMR spectrum of compound **11**. Figure S3. 1H NMR spectrum of compound **15a**. Figure S4. 1H NMR spectrum of compound **15b**. Figure S5. 1H NMR spectrum of compound **15c**. Figure S6. 1H NMR spectrum of compound **15e**. Figure S7. 1H NMR spectrum of compound **15f**. Figure S8. 1H NMR spectrum of compound **16a**. Figure S9. 1H NMR spectrum of compound **16b**. Figure S10. 1H NMR spectrum of

compound **16c**. Figure S11. 1H NMR spectrum of compound **16e**. Figure S12. 1H NMR spectrum of compound **16f**. All 13C NMR can be found below 1H NMR spectrum.

Author Contributions: Chemistry investigation, V.F., M.B., and S.K. under the supervision of O.L.; in vivo investigation, D.B. and M.S.B. under the supervision of M.K. and T.G.T.; methodology, V.F. and N.F.S.; project administration, O.L.; supervision, O.L.; writing—original draft, S.K., O.L., and M.K.; writing—review and editing, O.L., M.K., and N.F.S. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of N.N. Vorozhtsov Institute of Organic Chemistry SB RAS (protocol no. P-12-122019-14 approved 17.12.2019).

Informed Consent Statement: Not applicable.

Data Availability Statement: Data is contained within the article or supplementary material.

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Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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