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# 3,28-Bis-*O*-polyfluorobenzoylbetulin. Synthesis, Molecular Structure, and Cytotoxicity

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**Abstract**—Treatment of betulin with 2,3,4,5-tetrafluoro- and pentafluorobenzoyl chlorides in triethylamine afforded 3,28-bis-*O*-polyfluorobenzoylbetulins. According to the X-ray diffraction data, all six-membered rings in the 3,28-bis-*O*-pentafluorobenzoylbetulin molecule appear in a *chair* conformation, and the five-membered ring has an *envelope* conformation with the $C^{17}$ atom deviating from the plane formed by the other four carbon atoms. Unlike betulin itself, the obtained bis-esters showed no cytotoxic effect on human lung adenocarcinoma cell line A549 and human glioblastoma cell line U251.

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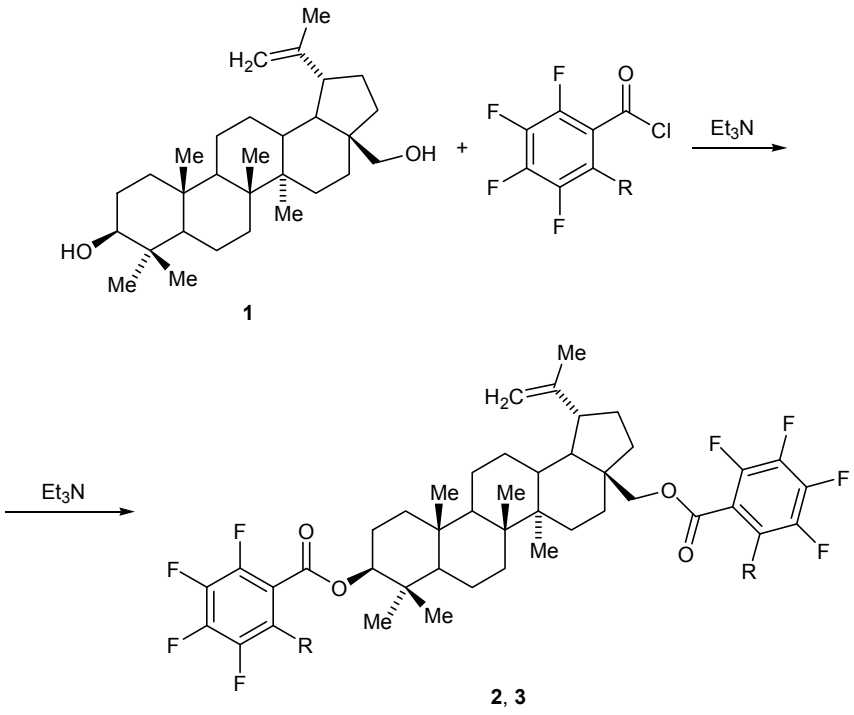
The chemistry of terpenoids in Russia has a long history, and considerable advances have been achieved in this field [1]. Betulin (**1**) is a pentacyclic triterpenoid of the lupane series, and it has been extensively studied in recent time in many research centers of Novosibirsk, Ufa, Perm, Moscow, and St. Petersburg. Betulin exhibits high and diverse biological activity, in particular anti-inflammatory, choleretic, antiviral, antitumor, immunomodulatory, etc. [2, 3], and efficiently inhibits chemically induced carcinogenesis *in vivo* [4]. Betulin is among the most accessible terpenoids; its concentration in *Betula Pendula* Roth. birch bark reaches 35% [2]. The ease of isolation and purification of betulin provides the possibility of obtaining new biologically active compounds based thereon. Esterification of betulin at the hydroxy groups on $C^3$ and $C^{28}$ afforded a wide series of *O*-acyl derivatives some of which turned out to be promising as hepatoprotective, anti-inflammatory, antiulcer, immunomodulatory, and anti-HIV agents [5–7].

Betulin esters containing fluorine atoms in the acyl moiety have been studied to a considerably lesser extent than their nonfluorinated analogs. Up to now, only a few 28-*O*- and 3,28-bis-*O*-fluoroacyl betulin derivatives have been synthesized [8–11]. Taking into account that more than 20% of commercial pharmaceuticals contain fluorine atoms [12], we have synthesized 3,28-bis-*O*-(2,3,4,5-tetrafluorobenzoyl)betulin **2** and 3,28-bis-*O*-(pentafluorobenzoyl)betulin **3** by reaction of betulin with a slight excess of 2,3,4,5-tetrafluoro- or pentafluorobenzoyl chloride in triethylamine (Scheme 1). Compounds **2** and **3** were isolated in 78 and 69% yield, respectively, as light brown solids readily soluble in benzene, chloroform, and methylene chloride and poorly soluble in hexane, ethyl acetate, acetone, and ethanol.

The structure of **2** and **3** was confirmed by IR, $^1H$, $^{13}C$, and $^{19}F$ NMR, and ESI mass spectra. The $^{19}F$ NMR spectra of **2** and **3** contained two sets of signals with equal intensities, indicating the presence of two polyfluorobenzoyloxy groups on $C^3$ and $C^{28}$. Signals of fluorines in the 2,3,4,5-tetrafluorobenzoyloxy group on $C^{28}$ of **2** were located at $\delta_F$ –133.79, –137.86, –147.44, and –153.36 ppm, and those of the 2,3,4,5-tetrafluorobenzoyloxy group on $C^3$, at $\delta_F$ –134.08, –138.11, –147.94, and –153.57 ppm. Likewise, the pentafluorobenzoyloxy group on $C^{28}$ of **3** was represented by signals at $\delta_F$ –137.94, –148.67, and –160.37 ppm, and

**Scheme 1.**




**2**, R = H; **3**, R = F.

that on $C^3$, at $\delta_F$ –138.59, –149.43, and –160.55 ppm. In the $^1H$ NMR spectra of these compounds, the $CH_2O$ protons resonated as two doublets at δ 4.60, 4.14 ($^2J$ = 11.0 Hz) (**2**) and 4.62, 4.17 ppm ($^2J$ = 11.0 Hz) (**3**). These signals were shifted 0.8 ppm downfield from the corresponding signals of initial betulin; analogous downfield shift was observed in the spectrum of 3,28-bis-*O*-trifluoroacetylbetulin [9]. The signal of 3-H (d.d) was located even in a weaker field than that in the spectrum of 3,28-bis-*O*-trifluoroacetylbetulin [9] by 1.57 ppm (δ 4.75 ppm, $^3J$ = 10.8, 5.1 Hz) (**2**) and 1.63 ppm (δ 4.81 ppm, $^3J$ = 11.3, 5.0 Hz) (**3**). The $^{13}C$ chemical shifts of **2** and **3** almost did not differ from those reported for 3,28-bis-*O*-trifluoroacetyl-

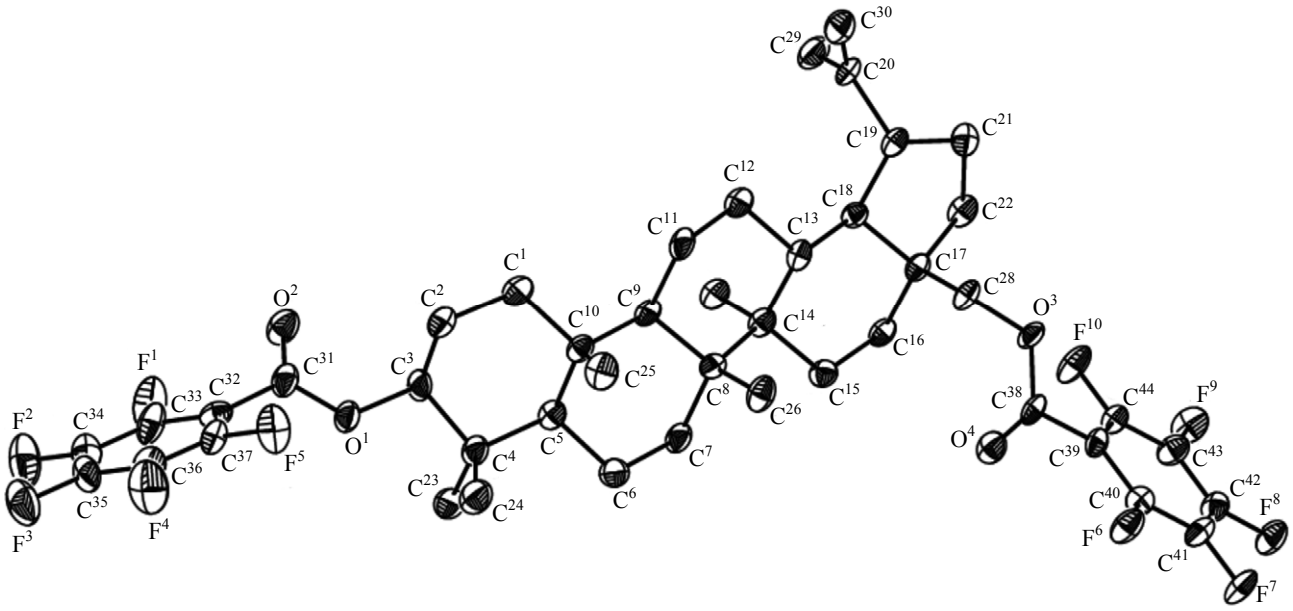



**Fig. 1.** Structure of the molecule of lup-20(29)-ene-3β,28-diyl bispentafluorobenzoate (**3**) according to the X-ray diffraction data.

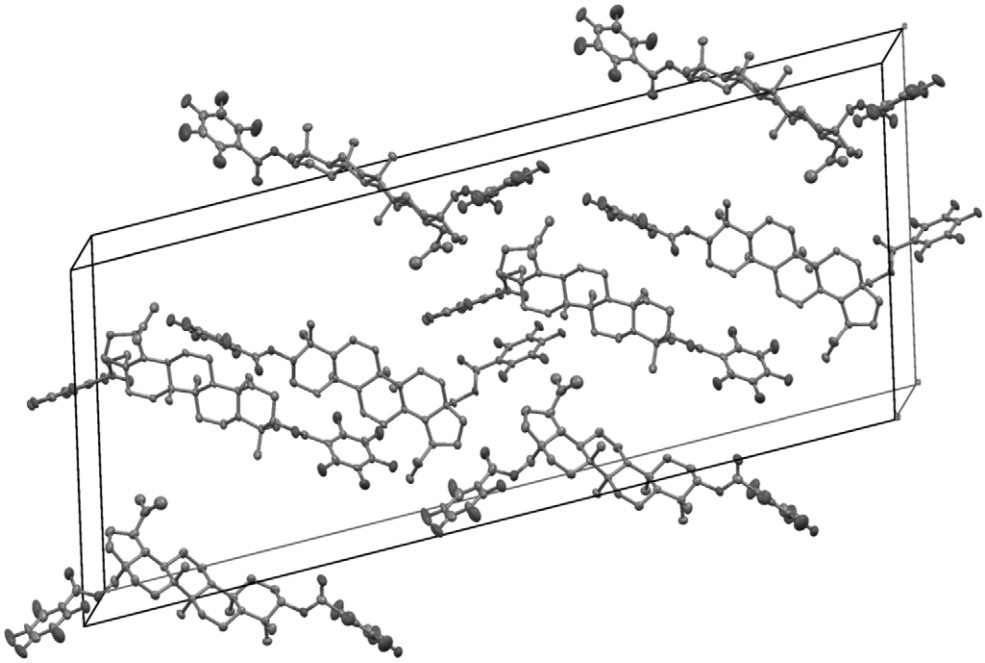


**Fig. 2.** A fragment of crystal packing of lup-20(29)-ene-3β,28-diyl bispentafluorobenzoate (**3**).

betulin [10]; exceptions were the signals of $C^3$ and $C^{28}$ which appeared 2–3 ppm upfield.

The molecular structure of 3,28-bis-*O*-(pentafluorobenzoyl)betulin **3** was determined by X-ray analysis. Single crystals of **3** were obtained by crystallization from ethyl acetate–acetone (1 : 1). Compound **3** crystallized in the chiral point symmetry group (*C*2) with two independent molecules in a unit cell (Fig. 1). The structures of two independent molecules were almost identical; the only difference was mutual arrangement of the $C_6F_5CO_2$ substituents on $C^3$ and $C^{28}$ with respect to the pentacyclic skeleton. The bond lengths and dihedral angles in the betulin fragments of two independent molecules coincided with each other within the experimental error and were similar to those found for other betulin derivatives, e.g., 3,28-bis-*O*-trifluoroacetylbetulin [9] and 3,28-*O*-diacetylbetulin [13]. All six-membered rings adopt a *chair* conformation, but the more flexible five-membered ring, unlike the above noted betulin bis-esters, has an *envelope* conformation with the $C^{17}$ atom deviating by ~0.7 Å from the plane formed by the $C^{18}$, $C^{19}$, $C^{21}$, and $C^{22}$ atoms.

The observed difference in the torsion angles determining orientation of the $C_6F_5CO_2$ groups with respect to the central part of molecule **3** is likely to originate from the difference in the intermolecular interaction systems. The prefluorinated substituents in one of the two independent molecules form mainly short C–H···F contacts with the pentacyclic skeleton, whereas one $C_6F_5$ group of the second molecule is involved in a series of short C···C and F···F contacts with the perfluorinated substituent of the neighboring molecule (Fig. 2).

The cytotoxicity of 3,28-bis-perfluorobenzoate **3** *in vitro* was studied in comparison to betulin **1** against human lung adenocarcinoma A549 and human glioblastoma U251 cell lines. The cytotoxic activity was quantitatively expressed by the cell viability percentage at concentrations of the tested compounds of 5, 10, and 15 μM (Table 1). The cell viability was estimated by counting their overall amount in wells in 48 h after addition of compound **1** or **3** (sulforhodamine B assay). The results showed no effect of compound **3** on the survival of A549 and U251 cells up to a concentration of 15 μM. Further increase of the

**Table 1.** Effect of compounds **1** and **3** on the viability of A549 and U251 tumor cells

| Compound no. | Concentration, μM | Cell viability, % | |
|---|---|---|---|
| | | A549 | U251 |
| **1** | 5 | 95.1±7.2 | 93.2±5.7 |
| | 10 | 75.5±4.5 | 51.0±6.8 |
| | 15 | 32.8±1.1 | 20.4±4.0 |
| **3** | 5 | 102.0±7.6 | 105.8±10.7 |
| | 10 | 93.9±8.7 | 100.0±13.1 |
| | 15 | 101.0±1.9 | 94.5±7.0 |

concentration was impossible because of low solubility of compounds **2** and **3**. On the other hand, betulin showed an appreciable cytotoxic effect even at a concentration of 10 μM. Thus, the acylation of betulin at the 3-OH and 28-OH groups with perfluorobenzoyl residues suppresses the cytotoxic activity against the examined cancer cell lines. Analogous results have recently been obtained [11] by studying the cytotoxicity of betulin and its mono- and bis-esters with different benzoyl groups (including 4-fluorobenzoyl and 4-trifluoromethylbenzoyl) against several human tumor cell lines (MGC-803, PC3, Bcap-37, A375, MCF-7) by MTT assay.

## EXPERIMENTAL

The $^{1}H$, $^{13}C$, and $^{19}F$ NMR spectra were recorded on a Bruker Avance 400 spectrometer at 400.13, 100.61, and 375.50 MHz, respectively, using $CDCl_3$ as solvent. Signals in the $^{13}C$ NMR spectra were assigned on the basis of DEPT and $^{1}H$–$^{13}C$ HMQC experiments. The $^{19}F$ chemical shifts are given relative to $CFCl_3$. The IR spectra were measured from solutions in chloroform on a Shimadzu FTIR-8400S spectrometer. The mass spectra (electrospray ionization) were obtained on a Bruker micrOTOF 10223 instrument; samples were introduced as solutions in methanol. The elemental compositions were determined with a Carlo Erba 1106 analyzer. The optical rotations were measured at λ 589 nm on an Optical Activity AA-55 polarimeter using a 3-mL cell.

Crystallographic data for ester **3**. Monoclinic crystal system, space group *C*2; $C_{44}H_{48}F_{10}O_4$, *M* 830.82; unit cell parameters (120 K): $a$ = 51.449(9), $b$ = 7.1538(14), $c$ = 22.116 (3) Å; β = 105.379(13)°; $V$ = 7848(2) Å$^3$; $d_{calc}$ = 1.406 g/cm$^3$; $Z$ ($Z'$) = 8 (2). Intensities of 27321 reflections ($R_{int}$ = 0.0793) were measured on a Bruker Smart APEX II CCD automated diffractometer at 120 K (Mo $K_\alpha$ radiation, graphite monochromator, ω-scanning, $2\theta_{max}$ = 58°). The structure was solved by the direct method and was refined against $F^2$ by the full-matrix least-squares method in anisotropic–isotropic approximation using 17170 reflections. The positions of hydrogen atoms were determined by difference electron density syntheses and were refined according to the riding model. Final divergence factors: $wR_2$ = 0.1630; $R_1$ = 0.0707 [for 8342 reflections with $I > 2\sigma(I)$]; goodness of fit 0.951. The calculations were performed using SHELXTL PLUS software package [14]. The X-ray diffraction data for compound **3** were deposited to the Cambridge Crystallographic Data Centre (CCDC entry no. 1834265).

**Betulin (1)** was isolated by extraction from the bark of *Betula Pendula* Roth. birch. The outer birch bark with a moisture content of less than 5% was finely crumbled and Soxhlet extracted with a 1 : 1 mixture of petroleum ether (bp 70–100°C) and toluene. The extract was cooled to 10°C, and the precipitate was filtered off and dried in air. The crude product (yellowish powder) was recrystallized twice from ethanol. Loose white powder, mp 251–252°C; published data [15]: mp 256–258°C. According to the $^{1}H$ NMR data, the product contained ≥95% of the main substance.

Pentafluorobenzoic and 2,3,4,5-tetrafluorobenzoic acids were commercial products (P&M) with a purity of 99%. The corresponding acid chlorides were prepared by treatment of the acids with phosphorus pentachloride (pure grade, *Reakhim*) [16].

**2,3,4,5-Tetrafluorobenzoyl chloride.** Yield 69%, bp 63°C (13 mm). $^{19}F$ NMR spectrum, $\delta_F$, ppm: –133.79, –136.80, –143.14, –152.59.

**Pentafluorobenzoyl chloride.** Yield 78%, bp 60°C (20 mm). $^{19}F$ NMR spectrum, $\delta_F$, ppm: –137.62 (2F), –145.14 (1F), –159.10 (2F).

Triethylamine was preliminarily dried over solid sodium hydroxide, distilled, and stored over metallic sodium.

**Lup-20(29)-ene-3β,28-diyl bis-2,3,4,5-tetrafluorobenzoate (2).** 2,3,4,5-Tetrafluorobenzoyl chloride, 2.4 g (11.29 mmol), was added dropwise with stirring to a suspension of 2.0 g (4.52 mmol) of betulin in 20 mL of triethylamine, cooled to 5°C. The mixture was stirred for 20 h at room temperature and for 2 h at 60°C, washed with 5% aqueous HCl (100 mL), and extracted with 80 mL of chloroform. The extract was washed with distilled water and dried over $MgSO_4$, the solvent was distilled off on a rotary evaporator, and the residue was recrystallized from ethanol and dried under reduced pressure. Yield 2.8 g (78%), mp 116–118°C, $[\alpha]_D^{20}$ = –23.3° ($c$ = 0.013, $CHCl_3$). IR spectrum, ν, cm$^{-1}$: 1719 (C=O), 1627 (C=C), 1239 (C–F). $^{1}H$ NMR spectrum, δ, ppm: 0.92 s, 0.95 s, 0.98 s, 1.04 s, and 1.10 s (15H, $CH_3$); 1.73 s (3H, 30-H), 0.81–2.10 m (24H, CH, $CH_2$), 2.51 m (1H, 19-H), 4.14 d and 4.60 d (2H, 28-H, $^{2}J_{HH}$ = 11.0 Hz), 4.64 d and 4.74 d (2H, 20-H), 4.75 d.d (1H, 3-H, $^{3}J_{HH}$ = 5.1, 10.8 Hz), 7.63 m (1H, $H_{arom}$). $^{13}C$ NMR spectrum, $\delta_C$, ppm: 14.79 ($C^{27}$), 16.06 ($C^{26}$), 16.16 ($C^{25}$), 16.61 ($C^{24}$),

18.18 ($C^6$), 19.13 ($C^{30}$), 20.83 ($C^{11}$), 23.61 ($C^2$), 25.16 ($C^{12}$), 27.04 ($C^{15}$), 28.01 ($C^{23}$), 29.50 ($C^{16}$), 29.70 ($C^{21}$), 34.11 ($C^7$), 34.54 ($C^{22}$), 37.11 ($C^{10}$), 37.75 ($C^{13}$), 38.03 ($C^4$), 38.38 ($C^1$), 40.94 ($C^8$), 42.79 ($C^{14}$), 46.59 ($C^{17}$), 47.75 ($C^{19}$), 48.81 ($C^{18}$), 50.29 ($C^9$), 55.39 ($C^5$), 64.87 ($C^{28}$), 83.79 ($C^3$), 110.08 ($C^{29}$), 113.05 and 113.25 ($CH_{arom}$), 115.09 and 115.55 ($C_{arom}$); 140.10, 142.11, 142.59, 142.72, 145.21, 146.59, 147.79, 149.16 m (FC); 149.86 ($C^{20}$), 161.92 and 162.58 (C=O). $^{19}$F NMR spectrum, $\delta_F$, ppm: –133.79, –137.86, –147.44, –153.36 [28-OC(O)$C_6HF_4$]; –134.08, –138.11, –147.94, –153.57 [3-OC(O)$C_6HF_4$]. Mass spectrum: *m*/*z* 817.3480 $[M + Na]^+$. Found, %: C 66.60; H 6.44. $C_{44}H_{50}F_8O_4$. Calculated, %: C 66.49; H 6.34. *M* + Na 817.3474.

**Lup-20(29)-en-3β,28-diyl bispentafluorobenzoate (3).** Pentafluorobenzoyl chloride, 1.3 g (5.63 mmol), was added dropwise with stirring to a suspension of 1.0 g (2.25 mmol) of betulin in 10 mL of triethylamine, cooled to 5°C. The mixture was stirred for 20 h at room temperature and for 3 h at 60°C, washed with 5% aqueous HCl (50 mL), and extracted with chloroform (50 mL). The extract was washed with distilled water and dried over $MgSO_4$, the solvent was distilled off on a rotary evaporator, and the residue was recrystallized from ethanol, and dried under reduced pressure. Yield 1.3 g (69%), mp 138–140°C, $[\alpha]_D^{20} = –13.4°$ (*c* = 0.013, $CHCl_3$). IR spectrum, ν, $cm^{-1}$: 1731 (C=O), 1655 (C=C), 1227 (C–F). $^1$H NMR spectrum, δ, ppm: 0.87 d (1H, 5-H, $^3J_{HH}$ = 9.78 Hz), 0.91 s (6H), 0.98 s (3H), 1.03 s (3H), 1.05–2.09 m (23H, CH, $CH_2$), 1.10 s (3H), 1.73 s (3H, $C^{30}H_3$), 2.50 m (1H, 19-H), 4.17 d and 4.62 d (2H, 28-H, $^2J_{HH}$ = 11.04 Hz), 4.64 d and 4.74 d (2H, 29-H), 4.81 d.d (1H, 3-H, $^3J_{HH}$ = 5.0, 11.3 Hz). $^{13}$C NMR spectrum, $\delta_C$, ppm: 14.79 ($C^{27}$), 16.04 ($C^{26}$), 16.14 ($C^{25}$), 16.46 ($C^{24}$), 18.16 ($C^6$), 19.12 ($C^{30}$), 20.82 ($C^{11}$), 23.65 ($C^2$), 25.14 ($C^{12}$), 26.95 ($C^{15}$), 27.84 ($C^{23}$), 29.43 ($C^{16}$), 29.55 ($C^{21}$), 34.08 ($C^7$), 34.42 ($C^{22}$), 37.09 ($C^{10}$), 37.76 ($C^{13}$), 37.92 ($C^4$), 38.38 ($C^1$), 40.92 ($C^8$), 42.77 ($C^{14}$), 46.50 ($C^{17}$), 47.72 ($C^{19}$), 48.83 ($C^{18}$), 50.26 ($C^9$), 55.40 ($C^5$), 65.54 ($C^{28}$), 84.63 ($C^3$), 110.09 ($C^{29}$), 136.00–147.20 ($C_{arom}$), 149.80 ($C^{20}$), 159.51 and 158.86 (C=O). $^{19}$F NMR spectrum, $\delta_F$, ppm: –137.94 (2F, *o*-F), –148.67 (1F, *p*-F), –160.37 (2F, *m*-F) [28-OC(O)$C_6F_5$]; –138.59 (2F, *o*-F), –149.43 (1F, *p*-F), –160.55 (2F, *m*-F) [3-OC(O)$C_6F_5$]. Mass spectrum: *m*/*z* 853.3250 $[M + Na]^+$. Found, %: C 63.47; H 5.96. $C_{44}H_{48}F_{10}O_4$. Calculated, %: C 63.61; H 5.82. *M* + Na 853.3285.

**Cytotoxicity assay of betulin and lup-20(29)-ene-3β,28-diyl bispentafluorobenzoate (3) *in vitro*.** Human lung adenocarcinoma A549 and human glioblastoma U251 cell lines were obtained from the Russian Vertebrate Cell Culture Collection (Institute of Cytology, Russian Academy of Sciences, St. Petersburg, Russia). Cells were cultivated at 37°C in a humid atmosphere containing 5% of $CO_2$ in DMEM complete medium (Biolot, Russia) with addition of 10% of fetal bovine serum (Gibco), 2 mmol of a solution of L-glutamine, 100 unit/mL of penicillin, and 100 mg/mL of streptomycin. The cells were recultured 3 times a week. Tests were carried out between the 3rd and 7th reculture.

The cultured A549 and U251 cells were inoculated in 96-well microplates in amounts of 8000 and 18000 cells per well, respectively (cell suspension volume 100 μL), and incubated for 24 h before the addition of compounds to be tested. Stock solutions of **1** and **3** were prepared by dissolving the compounds in acetone to a concentration of 1 mM and were stored at 4°C. Solutions with concentrations of 10, 20, and 30 μM were prepared immediately before addition to wells using complete culture medium and were added in an amount of 100 μL to the wells containing cultured cells, so that the final concentrations of **1** and **3** in the wells were 5, 10, and 15 μM, and the final concentration of acetone therein did not exceed 1.5%, which did not affect the cell viability. All experiments were carried out in triplicate. Those wells to which only complete culture medium (100 μL) was added without a compound to be tested were used as control. Wells containing 200 μL of complete culture medium were used as blanks. The microplates were incubated for 48 h at 37°C in a humid atmosphere containing 5% of carbon dioxide.

The cells in wells were fixed by adding a solution of trichloroacetic acid, the wells were then repeatedly washed with running water, and a 0.4% solution of sulforhodamine B was added in keeping with the manufacturer protocol (TOX6, Sigma). The unbound dye was removed by washing with 1% acetic acid, and the bound dye was dissolved in Tris [2-amino-2-(hydroxymethyl)propane-1,3-diol, 10 mM]. The optical density of the content of the wells was measured at λ 510 nm against blank using a BioTeck Instruments Epoch microplate reader (US).

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