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(5Z,9Z)-14-[(3,28-Dioxoolean-12-en-28-yl)oxy]tetradeca-5, 9-dienoic Acid with Cytotoxic Activity

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Abstract: For the first time, a synthetic analogue of natural (5Z,9Z)-dienoic acid has been synthesized in the form of a hybrid molecule containing a fragment of oleanolic acid and (5Z,9Z)-tetradeca-5.9-dienedicarboxylic acid, synthesized using a new reaction of Ti-catalyzed homo-cyclomagnesiation 1,2-dienes. The high cytotoxic activity of (5Z,9Z)-14-[(3,28-dioxoolean-12-en-28-yl)oxy]tetradeca-5,9-dienoic acid against tumor cells Jurkat, K562, U937 and HL60 was established. This compound is also an inducer of apoptosis, affects the cell cycle and inhibits human topoisomerase I.

Keywords: hybrid molecules; oleanolic acid; (5Z,9Z)-dienoic acid; cytotoxic activity; apoptosis; cell cycle

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1. Introduction

Oleanolic acid, a pentacyclic triterpenoid of natural origin, found in olive oil, American sweetweed, garlic, Syzygium and other species, is isolated both in free form and as an aglycone of triterpenoid saponins [1–5]. A number of studies have found that oleanolic acid is practically non-toxic as a hepatoprotective drug and has anticancer and antiviral properties [6–11]. In vitro studies have found that oleanolic acid has weak properties against HIV [12] and against hepatitis C, but its more potent synthetic analogues are used as medicines [13]. In addition, an oleanolic acid analogue, a synthetic triterpenoid, has been shown to be a potent inhibitor of inflammatory processes in cells. It works by producing interferon-γ, inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 in macrophages from test mice. They are considered extremely strong phase-2 response inducers (for example, by reducing NADH-ubiquinone oxyreductase and Heme oxygenase-1), and are considered the main defenders of the cell against oxidative and electrophilic stress [14–20].

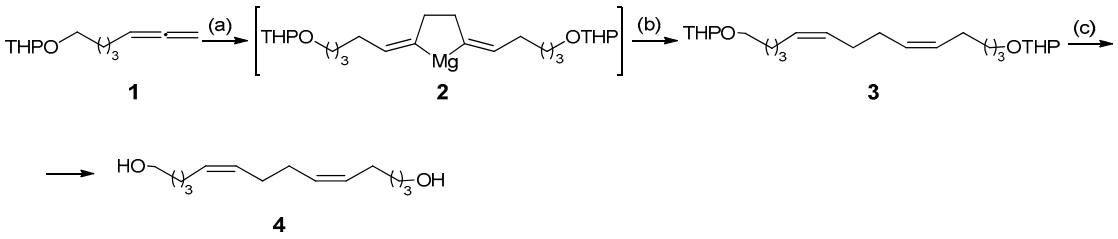
At the same time, our research group, as well as other groups, have shown that natural and synthetic fatty dienoic acids containing a 1Z,5Z-diene fragment in their structure exhibit a wide range of biological activities—antitumor, antibacterial, antiviral and a number of others [21–27], this series of studies showed that among the derivatives of these acids, highly effective inhibitors of human topoisomerase I and II were found [28–33].

In this study, we put forward the idea that a synthesized hybrid molecule containing both a fragment of oleanolic acid and natural (5Z,9Z)-dienoic acid will exhibit high cytotoxicity towards tumor lines and simultaneously inhibit one of the key enzymes of the cell cycle—human topoisomerase I. This strategy has previously shown high efficiency in the synthesis of (5Z,9Z)-dienoic acids containing a steroid fragment [34–55].

2. Results and Discussion

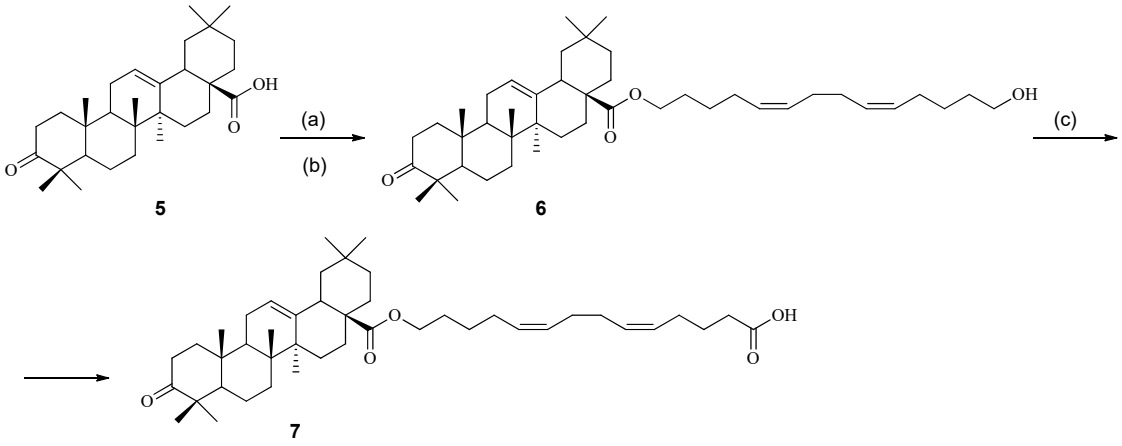
Based on the developed strategy for the total synthesis of (5Z,9Z)-14-[(3,28-dioxoolean-12-en-28-yl)oxy]tetradeca-5,9-dienoic acid, (5Z,9Z)-tetradeca-5,9-dien-1,14-diol (**4**) was originally synthesized using the newly developed reaction homo-cyclomagnesiation of

tetrahydropyran ether of hepta-5,6-dien-1-ol **1** with EtMgBr in the presence of a Cp_2TiCl_2 catalyst (5 mol %) [56–59]. Subsequent deprotection of tetrahydropyranyl-5Z,9Z-diene-1,14-diol **3**, formed after hydrolysis of magnesacyclopentane **2**, in the presence of catalytic amounts of p-toluenesulfonic acid lead to compound **4** (Scheme 1).



Scheme 1. Synthesis of (5Z,9Z)-tetradeca-5,9-diene-1,14-diol. (a): EtMgBr, Mg, Cp_2TiCl_2 (5 mol%), diethyl ether; (b): H_3O^+; (c): *n*-TsOH, $CHCl_3$, MeOH.

The synthesis of target hybrid molecule **7** based on oleanolic and (5Z,9Z)-tetradeca-5,9-dienedicarboxylic acids was carried out through the reaction of 3-oxoolean-12-ene-28-oic acid with an excess of oxalyl chloride (18 eq.) to obtain the corresponding acid chloride, which then reacted in situ with 1,14-*bis*-tetrahydropyranyl-5Z,9Z-diene-1,14-diol **4** (2 eq.) in the presence of DIPEA (2.5 eq.) to obtain compound **6**, the subsequent oxidation of which with the Jones reagent lead to the formation of dienoic acid **7** (Scheme 2). Please see the Supplementary Figures S1 and S2.



Scheme 2. Synthesis of oleanolic acid derivative **7**. Reagents and conditions: (a): oxalyl chloride, anhydrous CH_2Cl_2, rt, overnight; (b): (5Z,9Z)-Tetradeca-5,9-diene-1,14-diol (**4**), DIPEA, anhydrous CH_2Cl_2, overnight, (~70%); (c): Jones reagent, acetone, CH_2Cl_2 (~67%).

According to the data available in the literature [21–35], 5Z,9Z-dienoic acids exhibit high biological activity. In this regard, the first obtained hybrid molecule **7** was investigated for cytotoxic activity against cell lines HL60, Jurkat, K562, U937 (Table 1).

It was found that hybrid molecule **7** has a cytotoxic effect on all selected tumor cell lines, and the cytotoxicity of this compound exceeds the cytotoxicity of oleanolic acid by 14 times when analyzing Jurkat cells, however, the most sensitive culture was K562 cells. For them, the cytotoxic IC50 concentration was 0.007 μM, which is 24 times less than the toxic IC50 value of oleanolic acid.

It should also be noted that, along with oleanolic acid, we studied the cytotoxicity of other precursors of hybrid molecule **7**, namely, (5Z,9Z)-tetradeca-5,9-diene-1,14-diol (**4**) and (5Z,9Z)-14-hydroxytetradeca-5,9-dien-1-yl 3-oxoolean-12-en-28-oate (**6**). It was shown that diol **4** exhibits extremely low cytotoxicity, while alcohol **6**, formed by the addition of diol **4** to oleanolic acid (**5**), leads to a slight increase in the cytotoxicity of the oleanolic acid (Table 1).

Table 1. In vitro cytotoxic activity of hybrid molecule **7** on tumor (Jurkat, K562, U937, HL60) and normal (Hek293, Fibroblasts) cell cultures (μM).

	Jurkat (IC_{50}, μM)	**K562 (IC_{50}, μM)**	**U937 (IC_{50}, μM)**	**Hek293 (IC_{50}, μM)**	**Fibroblasts (IC_{50}, μM)**
Compound **7**	0.014 ± 0.002	0.007 ± 0.001	0.021 ± 0.003	0.127 ± 0.012	0.286 ± 0.022
Compound **6**	0.141 ± 0.012	0.159 ± 0.013	0.117 ± 0.012	0.253 ± 0.024	0.623 ± 0.058
Oleanolic acid (**5**)	0.196 ± 0.018	0.174 ± 0.014	0.131 ± 0.015	0.284 ± 0.027	0.698 ± 0.051
Diol **4**	0.383 ± 0.036	0.362 ± 0.031	0.299 ± 0.028	0.452 ± 0.044	0.874 ± 0.086

The latter fact indicates that hybrid molecule **7** does not undergo enzymatic hydrolysis in the cells and the two parts (compound **5** and a monocarboxylic acid derived from diol **4**) do not induce cytotoxicity separately from each other. At the same time, of course, these data will be refined by us in future extended studies.

It is well known from the literature that cytotoxicity does not always reflect the true mechanism of death of a living cell. Moreover, there is a wide variety of death programs through apoptosis, necroptosis, ferroptosis, etc. Therefore, in our article, when studying the new synthesized molecule, along with cytotoxicity, the induction of apoptosis and cell cycle disturbances were studied to more likely explain how this molecule works in the cell.

Hybrid molecule **7** is an inducer of apoptosis and significantly changes the cell cycle (Figure 1).

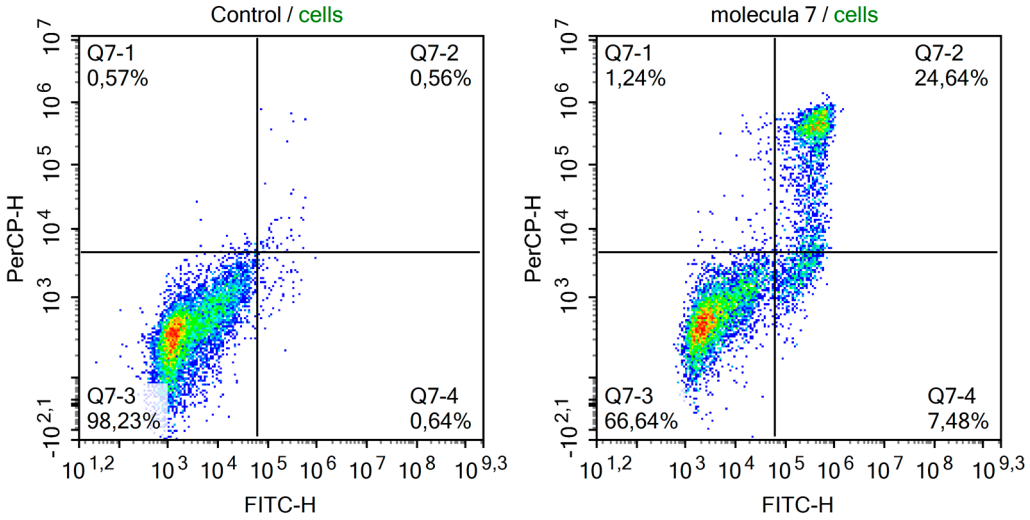


Figure 1. Analysis of apoptosis induction in Jurkat cells during incubation with hybrid molecule **7** at a concentration of 0,5IC_{50} for 24 h. Annexine Alexa Fluor 488 and 7AAD staining.

Figure 1 shows that this hybrid molecule causes the accumulation of cells both in the stage of early apoptosis and in the late stage (7.48 and 24.64%, respectively).

Figure 2 shows histograms of the cell cycle in the cell culture treated with the synthesized compound **7** and the cells of the control sample. Hybrid molecule **7** causes cell cycle arrest in the S phase and also causes the accumulation of the cell population in the G0 phase compared to the control sample.

Thus, the new hybrid molecule **7**, synthesized on the basis of oleanolic and (5Z,9Z)-tetradeca-5.9-dienedicarboxylic acids, has a pronounced cytotoxic effect on various cell lines of lymphoid and myeloid leukemia. This molecule also effectively induces apoptosis and causes cell cycle arrest. All of the above indicates the high anticancer effect of the new hybrid molecule **7**.

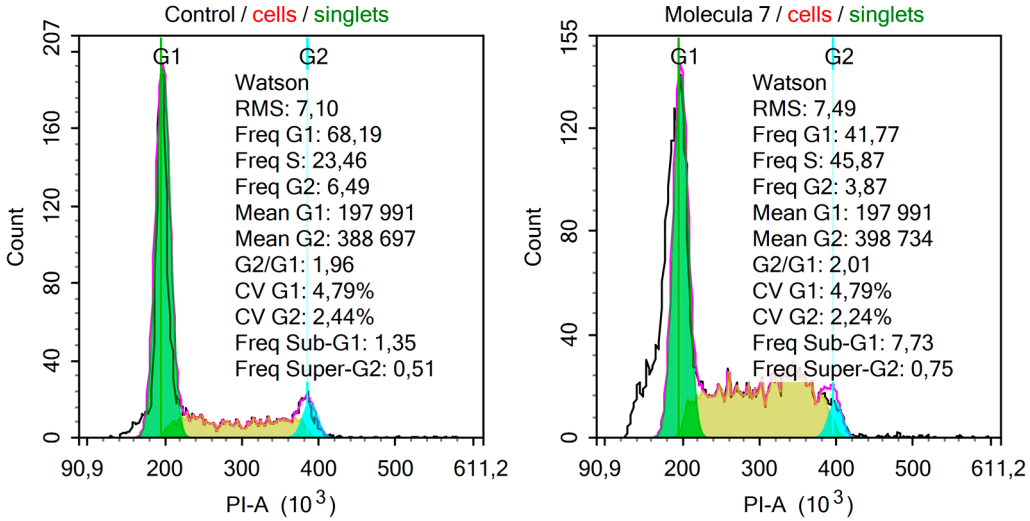


Figure 2. Cell cycle analysis for Jurkat cells treated with compound **7** at a concentration of $0.5IC_{50}$. The incubation time of compounds with cells was 24 h. Propidium iodide staining.

3. Materials and Methods

3.1. Chemistry

The reactions were performed at room temperature in air in round-bottom flasks equipped with a magnetic stir bar. The NMR spectra were recorded on a Bruker Avance 500 spectrometer at 500.17 MHz for 1H and 125.78 MHz for 13C according to standard Bruker procedures. $CDCl_3$ was used as the solvent, and tetramethylsilane, as the internal standard. The mixing time for the NOESY experiments was 0.3 s. Mass spectra were recorded on a Bruker Autoflex III MALDI TOF/TOF instrument with α-cyano-4-hydroxycinnamic acid as a matrix.

^{1}H NMR ($CDCl_3$, 500 MHz) and ^{13}C NMR ($CDCl_3$, 125 MHz) Spectral Data and Synthesis Method for 2,2′-[(5Z,9Z)-tetradeca-5,9-diene-1,14-diylbis(oxy)]bistetrahydro-2H-pyran 3 Are Described in the Literature [60].

^{1}H NMR ($CDCl_3$, 500 MHz) and ^{13}C NMR ($CDCl_3$, 125 MHz) Spectral Data and Synthesis Method for (5Z,9Z)-Tetradeca-5,9-diene-1,14-diol 4 Are Described in the Literature [33].

Synthesis of Oleanolic Acid-5Z,9Z-Dienoic Diol Conjugate 6. To a Solution of 3-oxoolean-12-en-28-oic acid 5 (1.0 mmol) in Anhydrous CH_2Cl_2 (30 mL) at 0 °C, $C_2O_2Cl_2$ (1.5 mL, 18.0 mmol) Was Added. After Stirring at 21–25 °C Overnight, the Mixture Was Evaporated, and Extracted with Dichloromethane (3 × 10 mL). The Residue Acid Chloride Was Dissolved in Dichloromethane (30 mL), and then Diisopropylethylamine (0.4 mL, 2.5 mmol) and Diol 4 (0.45 g, 2.0 mmol) Were Added at 0 °C. After Stirring at Room Temperature for 24 h, the Solvent Was Evaporated, and the Residue Was Purified by Chromatography on SiO_2 Using Hexane/Ethyl Acetate (1/5) as Eluent, Affording the Product 6.

Method of Oxidation of Compound **6** with Jones Reagent is Described in the Literature [34].

(5Z,9Z)-14-Hydroxytetradeca-5,9-dien-1-yl 3-oxoolean-12-en-28-oate 6: White Waxy solid, 0.49 g, 75% Yield. $[\alpha]_D^{22}$ + 39.0 (c 0.79, $CHCl_3$); IR (KBr) ν_{max} 2941, 2862, 1719, 1704, 1458, 1385, 1364, 1261, 1163, 1072, 1034, 974, 825, 729, 649 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.42-5.34 (4H, m, CH=), 5.31 (1H, m, H-12), 4.03 (2H, t, J = 6.5 Hz, CH_2O), 3.65 (2H, t, J = 6.5 Hz, CH_2OH), 2.90-1.14 (23H, m), 2.11–2.05 (8H, m, CH_2CH=), 1.66–1.55 (4H, m, CH_2CH_2CO, CH_2CH_2COH), 1.46–1.40 (4H, m, CH_2), 1.15 (3H, s, H-27), 1.09 (3H, s, H-23), 1.05 (6H, s, H-24, H-25), 0.94 (3H, s, H-30), 0.91 (3H, s, H-29), 0.80 (3H, s, H-26); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 217.8 (C-3), 177.8 (C-28), 143.9 (C-13), 129.9 (CH=), 129.7 (CH=), 129.5 (CH=), 122.1 (C-12), 64.1 (CH2O), 62.8 (CH2OH), 55.3 (C-5), 47.4 (C-4), 46.9 (C-9), 46.7

(C-17), 45.8 (C-19), 41.8 (C-14), 41.4 (C-18), 39.3 (C-1), 39.1 (C-8), 36.8 (C-10), 34.2 (C-2), 33.9 (C-21), 33.1 (C-29), 32.4 (C-22, CH_2CH_2OH), 32.3 (C-7), 30.7 (C-20), 28.2 (CH_2CH_2O), 27.6 (C-15), 27.4 (CH_2CH=), 27.3 (CH_2CH=), 26.9 (CH_2CH=), 26.8 (CH_2CH=), 26.5 (C-23), 26.1 (CH_2), 25.8 (CH_2), 25.7 (C-27), 23.6 (C-30), 23.5 (C-11), 23.0 (C-16), 21.5 (C-24), 19.6 (C-6), 16.9 (C-26), 15.0 (C-25); anal. calcd for $C_{44}H_{70}O_4$: C, 79.71; H, 10.64; found C, 79.65; H, 10.59. MALDI TOF: *m*/*z* 685.459 ([M + Na]$^+$, calcd 685.517).

(5Z,9Z)-14-[(3,28-Dioxoolean-12-en-28-yl)oxy]tetradeca-5,9-dienoic Acid 7: White Waxy Solid, 0.37 g, 53% yield. $[\alpha]_D^{22}$ + 32.0 (c 0.71, $CHCl_3$); IR (KBr) ν_{max} 2929, 2862, 1719, 1706, 1459, 1385, 1261, 1214, 1177, 1163, 1114, 1081, 1032, 801, 757, 667 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.45-5.33 (4H, m, CH=), 5.31 (1H, m, H-12), 4.04 (2H, t, J = 6.5 Hz, CH_2O), 2.91-1.14 (23H, m), 2.37 (2H, t, J = 6.5 Hz, CH_2OH), 2.12–2.05 (8H, m, CH_2CH=), 1.74–1.70 (2H, m, $CH_2CH_2CO_2H$), 1.65–1.60 (2H, m, CH_2CH_2CO), 1.45–1.40 (2H, m, CH_2), 1.15 (3H, s, H-27), 1.09 (3H, s, H-23), 1.06 (6H, s, H-24, H-25), 0.94 (3H, s, H-30), 0.91 (3H, s, H-29), 0.80 (3H, s, H-26); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 217.9 (C-3), 179.1 (CO_2H), 177.8 (C-28), 143.9 (C-13), 130.4 (CH=), 129.8 (CH=), 129.6 (CH=), 128.8 (CH=), 122.1 (C-12), 64.1 (CH_2O), 55.3 (C-5), 47.4 (C-4), 46.9 (C-9), 46.7 (C-17), 45.8 (C-19), 41.8 (C-14), 41.4 (C-18), 39.3 (C-1), 39.1 (C-8), 36.8 (C-10), 34.2 (C-2), 33.9 (C-21), 33.3 (CH_2CO_2H), 33.1 (C-29), 32.4 (C-22), 32.3 (C-7), 30.7 (C-20), 28.2 (CH_2CH_2O), 27.6 (C-15), 27.3 (CH_2CH=), 26.8 (CH_2CH=), 26.5 (C-23, CH_2CH=), 26.1 (CH_2), 25.7 (C-12), 24.6 (CH_2), 23.6 (C-30), 23.5 (C-11), 23.0 (C-16), 21.5 (C-24), 19.6 (C-6), 16.9 (C-26), 15.0 (C-25); anal. calcd for $C_{44}H_{68}O_5$: C, 78.06; H, 10.12; found C, 77.99; H, 10.09. MALDI TOF: *m*/*z* 699.460 ([M + Na]$^+$, calcd 699.496).

3.2. Biological Screening

Cytotoxicity, cell cycle, apoptosis induction and cell culture assays were performed as previously described [22].

4. Conclusions

A new hybrid molecule based on oleanolic and (5Z,9Z)-tetradeca-5,9-dienedicarboxylic acids has been synthesized, which has high cytotoxic activity and also exhibits a pronounced apoptosis-inducing effect on suspension tumor cultures of hematological origin. Also, this hybrid molecule causes the arrest of the cell cycle and the accumulation of the g0 population. Thus, compound **7** is a promising anticancer agent.

Supplementary Materials: The following supporting information can be downloaded online, ^{1}H NMR and ^{13}C NMR spectra of all new compounds.

Author Contributions: Conceptualization, U.M.D.; methodology and validation R.A.T.; performing the chemistry experiments; L.U.D. and R.A.T.; performing the biology experiments; The manuscript was prepared through the contributions R.A.T., L.U.D. and U.M.D. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: The data presented in this study are available in this article.

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Conflicts of Interest: The authors declare no conflicts of interest.

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