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EFFECT OF BRASSINOSTEROID ESTERS WITH SALICYLIC, SUCCINIC, AND INDOLYLACETIC ACIDS ON THE TUMOR CELL GROWTH

Abstract. The aim of this work is to study the effect of new derivatives of brassinosteroids – their esters with salicylic, succinic, and indolylacetic acids on the growth of tumor cells, on their distribution by cell cycle phases and determination of the type of cell death. It was shown that the activity of the new synthesized compounds differed significantly depending on the substitution nature in the steroid nucleus, amounting to <10 μM in the case of epibrassinolide and epicastasterone salicylates, simultaneously causing the cycle arrest in the G0/G1 phase, a mitochondrial potential decrease, and apoptosis of tumor cells. The results obtained indicate the high activity of salicylates, which effectively suppress the growth of the all studied types of tumors, and the prospects of finding new antitumor agents in this series of compounds.

Keywords: brassinosteroids, biogenic acid esters, tumor cell viability, cell cycle, apoptosis

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ВЛИЯНИЕ ЭФИРОВ БРАССИНОСТЕРОИДОВ С САЛИЦИЛОВОЙ, ЯНТАРНОЙ И ИНДОЛИЛУКСУСНОЙ КИСЛОТОЙ НА РОСТ ОПУХОЛЕВЫХ КЛЕТОК

Аннотация. Работа проведена с целью изучения влияния новых производных брассиностероидов – сложных эфиров с салициловой, янтарной и индолилуксусной кислотой, на рост опухолевых клеток, на распределение их по фазам клеточного цикла и определение типа клеточной гибели. Показано, что активность синтезированных новых соединений существенно различается в зависимости от характера замещения в стероидном ядре, составляя в случае салицилатов эпибрассинолида и эпикастастерона величину IC_{50} < 10 мкМ, одновременно вызывая остановку клеточного цикла в фазе G0/G1, снижение митохондриального потенциала и апоптоз опухолевых клеток. Полученные результаты свидетельствуют о высокой активности салицилатов, эффективно подавляющих рост всех изученных видов опухолей, и перспективности поиска новых противоопухолевых агентов в этом ряду соединений.

Ключевые слова: брассиностероиды, эфиры биогенных кислот, жизнеспособность опухолевых клеток, клеточный цикл, апоптоз

Для цитирования. Влияние эфиров брассиностероидов с салициловой, янтарной и индолилуксусной кислотой на рост опухолевых клеток / О. В. Панибрат [и др.] // Докл. Нац. акад. наук Беларуси. – 2024. – Т. 68, № 1. – С. 28–35. https://doi.org/10.29235/1561-8323-2024-68-1-28-35

Introduction. Brassinosteroids (BS) are plant steroid hormones that play an important regulatory role in various physiological processes, including growth, differentiation, elongation of roots and stems of plants, disease resistance, stress tolerance, and aging. This group of plant steroids includes more than

70 compounds ubiquitous in the plant kingdom [1]. Of all plant hormones, they are the most similar in structure to animal steroid hormones and, like their animal counterparts, BS regulate the expression of numerous genes, affect the activity of complex metabolic pathways, and participate in the regulation of protein and nucleic metabolism. Since the discovery in 1979 of the first representative of this class, brassinolide, the effects of BS and their metabolites in plant organisms have been widely studied. These effects include their influence on the balance of classical phytohormones (auxins, cytokinins, gibberellins, abscisic acid, and ethylene), as well as the additive effect or synergism of their action. At the same time, the synergistic effect was observed not only for a mechanical mixture of classical phytohormones and BS, but also for their synthetic conjugates (Fig. 1). In a number of cases, esters of highly active natural brassinosteroids, epibrassinolide (**1**) and epicastasterone (**2**), and biogenic carboxylic acids – salicylic, succinic and indolylacetic acids were superior in activity to individual ester components, i.e. BS and acid [2–4].

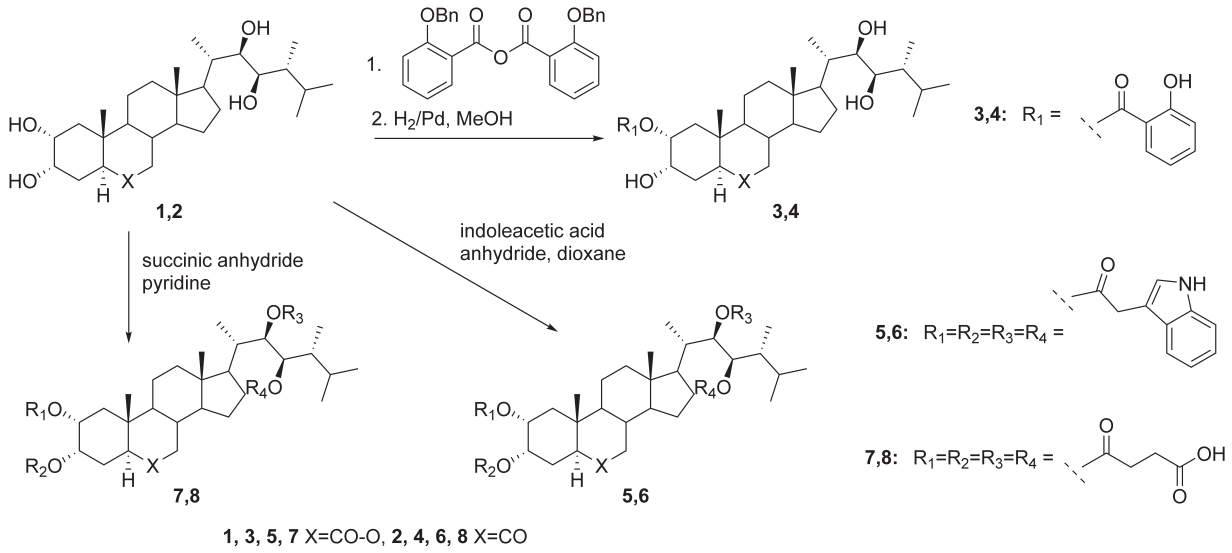

Fig. 1. Synthesis of esters of epibrassinolide (**1**) and epicastasterone (**2**) with succinic, indolylacetic and salicylic acid

In recent years, some potential medical applications of BS have been discovered: antiviral, antitumor, wound healing, immunomodulatory, etc. [5]. It has been shown that natural brassinosteroids and their analogues can inhibit the growth of tumor cells in the micromolar concentration range by increasing the proportion of cells in the G0/G1 phase and decreasing the proportion of cells in the S-phase of the cell cycle. Moreover, hormone-dependent lines turned out to be more sensitive to the action of BS. At the same time, natural brassinosteroids did not affect the growth of normal mammalian cells [6]. In this regard, it seemed interesting to study the effect of BS derivatives containing a phytohormone fragment in their structure as an additional pharmacophore on the development of tumor cells. The success of this direction, in our opinion, can lead to the creation of antitumor agents that selectively affect pathology and do not affect healthy cells. In the present work, we evaluated the effect of previously synthesized conjugates **3**–**8** (Fig. 1) on the division of tumor cells from tumors of various origins.

Experimental. The test substances epibrassinolide (EB) (**1**), epicastasterone (EC) (**2**), EB monosalicylate (**3**), EC monosalicylate (**4**), EB tetraindolyl acetate (**5**), EC tetraindolyl acetate (**6**), EB tetrasuccinate (**7**), and EC tetrasuccinate (**8**) were synthesized in the Laboratory of Steroid Chemistry of the Institute of Bioorganic Chemistry of the National Academy of Sciences of Belarus according to published procedures [2–4]. Salicylic, succinic and indolylacetic acids were purchased from Fluka.

Cultivation of cell culture. To assess the effect of BS esters, the tumor lines A549 (lung carcinoma), MCF-7 (breast adenocarcinoma), Caco-2 (colon cancer), K562 (chronic myelogenous leukemia), HL-60 (acute myelocytic leukemia) obtained from the Russian collection of cell cultures of the Institute of Cytology, Russian Academy of Sciences were used. Human dermal fibroblasts (HDF) were purchased from

the Institute of Biophysics and Cell Engineering of the National Academy of Sciences of Belarus. A549, MCF-7, Caco-2 cell lines and HDF were cultured in high glucose Dulbecco's Modified Eagle Medium (DMEM) (Sigma, USA) and 10 % Fetal Bovine Serum (FBS) (HyClone, USA), 100 units/mL penicillin, 100 μg/mL streptomycin, and amphotericin B (25 μg/mL) (Sigma, USA) at 37 °C, 95 % humidity, 5 % CO_2. K562 and HL-60 cells were cultured in RPMI 1640 medium (Sigma, USA), 10 % FBS (HyClone, USA), 100 units/ml penicillin, 100 μg/ml streptomycin, and amphotericin B (25 μg/ml) (Sigma, USA) at 37 °C 95 % humidity and 5 % CO_2. Cell cultures were maintained at the logarithmic growth stage by routine subculture twice a week.

Characterization of the cytotoxicity of the studied compounds. In the work, compounds were tested at concentrations of 0.1, 1.0, 10.0, and 50.0 μM. The resazurin test was used for analysis [7]. The principle of this method is based on the ability of the mitochondria of living cells in the process of aerobic respiration to reduce the compound resazurin to resorufin, which can fluoresce. The amount of resorufin formed in the cells is directly proportional to the number of living cells present.

Cells were seeded in a 96-well plate at a quantity of 10^4 cells/well (K562, HL-60) and $5 \cdot 10^3$ cells/well (A549, MCF-7, Caco-2, HDF) in 100 μl of medium and test substances were added at concentrations of 0.1, 1.0, 10.0, 50.0 μM. The initial concentration of the compounds was 20 mM in DMSO. 0.25 % DMSO was added to the control. Compounds were diluted to final concentrations sequentially with incubation medium. After 72 h of culturing cells with test compounds under standard conditions, 20 μl of resazurin at a concentration of 250 μM was added to each well of a 96-well plate. After 3 h exposure at 37 °C and 5 % CO_2, cells were reduced from blue resazurin to pink resorufin. The amount of reduced product was measured by fluorescence intensity at an excitation wavelength of 530 nm and an emission wavelength of 590 nm on a Tecan Infinite M200 plate analyzer. Cell viability in the presence of the test compound was calculated using the formula:

$$\text{Viability, \%} = \frac{\text{FL test wells} - \text{Background}}{\text{FL control wells} - \text{Background}} 100\ \%,$$

where FL is fluorescence.

The test compound concentration that causes 50 % inhibition of cell viability (IC_{50}) was calculated graphically from a dose-dependent curve in MS Excel. All experiments were carried out in triplicate, significance $p < 0.05$. Data processing was carried out using the Microsoft Excel program.

Cell cycle assay. MCF-7 cells were seeded at a quantity of $3 \cdot 10^5$ cells/well of a 6-well plate. After 24 hours, BS salicylates (**3** and **4**) were added to the nutrient medium at concentrations of 5 and 10 μM and incubated for 24 hours. Then the cells were detached with 0.25 % trypsin-EDTA solution, washed with phosphate buffer pH = 7.4, and fixed with 70 % ethanol cooled to –20 °C. After 24 hours of fixation at –20 °C, the cells were washed from ethanol, then RNase 100 μg/mL was added and cells were stained with 50 μg/mL PI (propidium iodide) for 40 min in the dark at room temperature [8]. Measurement was performed using a Beckman Coulter FC500 flow cytometer. Data analysis was performed using Kaluza 2.0 Software.

Determination of the mitochondrial potential of cells. MCF-7 cells were seeded in a 96-well plate at a quantity of $5 \cdot 10^3$ cells/well in 100 μl of medium and test substances were added at concentrations of 0.1, 1.0, 10.0, 50.0 μM. The initial concentration of the compounds was 20 mM in DMSO. 0.25 % DMSO was added to the control. Compounds were diluted to final concentrations sequentially with incubation medium. After 24 and 48 h of culturing cells with test compounds under standard conditions, the incubation medium was removed, the cells were washed with phosphate buffer, and then 100 μl of a solution of 3,3′-dihexyloxacarbocyanine iodide ($DiOC_6(3)$) in concentration 0.5 μM was added [9]. After 30 min exposure at 37 °C and 5 % CO_2, the fluorescence of $DiOC_6(3)$ bound to the mitochondrial membrane was measured at an excitation wavelength of 485 nm and an emission wavelength of 515 nm on a Tecan Infinite M200 plate analyzer.

Determination of the type of cell death. MCF-7 cells were seeded at a quantity of $3 \cdot 10^5$ cells per well of a 6-well plate. After 24 hours, BS salicylates (**3** and **4**) were added to the nutrient medium at

concentrations of 5 and 10 μM and incubated for 24 hours. Then the cells were detached with 0.25 % trypsin-EDTA solution, washed with phosphate buffer with pH = 7.4. Cells were stained for the differential determination of apoptosis-necrosis according to the protocol for the Annexin V-FITC Kit (Beckman Coulter, USA) for 30 min in the dark at room temperature [10]. Measurement was performed using a Beckman Coulter FC500 flow cytometer. Data analysis was performed using Kaluza 2.0 Software.

Results and Discussion. The results presented in Table show that only brassinosteroid monoesters with salicylic acid **3** and **4** inhibited the growth of all cell lines at low IC_{50} values (<10 μM) equal to or lower than the IC_{50} values of the widely used universal chemotherapeutic agents cisplatin (Table), 5-FU, etoposide [11; 12]. The IC_{50} values of salicylates of epibrassinolide and epicastasterone did not differ from each other, and there were no significant differences in the suppression of the growth of tumor cells isolated from different types of tumors, i. e. there was no specific action. The only line that proved to be more resistant to the action of compounds **3** and **4** were K562 chronic leukemia cells, which may be due to their increased expression of the BCR/ABL gene, which determines their resistance to apoptosis [13].

IC_{50}, μM of test compounds in relation to tumor cell viability

Compound	Cell line					
	A549	MCF-7	Caco-2	K562	HL-60	Human dermal fibroblasts
1	>50	>50	>50	>50	>50	>50
2	>50	>50	>50	>50	>50	>50
3	3.82 ± 0.31	3.06 ± 0.28	3.62 ± 0.25	7.21 ± 1.03	4.76 ± 0.24	4.94 ± 1.36
4	4.03 ± 0.52	3.04 ± 0.49	3.40 ± 0.64	8.29 ± 0.89	4.70 ± 0.45	7.88 ± 1.98
5	>50	>50	>50	>50	>50	–
6	>50	>50	>50	>50	>50	–
7	>50	>50	>50	>50	>50	–
8	>50	>50	>50	>50	>50	–
Cisplatin	–	22.08 ± 1.06	17.95 ± 0.87	–	–	–
Salicylic acid	>50	>50	>50	>50	>50	>50
Succinic acid	>50	>50	>50	>50	>50	–
Indolylacetic acid	>50	>50	>50	>50	>50	–
EB + salicylic acid mixture (1 mol: 1 mol)	>50	>50	–	–	–	–

The starting natural compounds **1** and **2** did not show such an effect. Previous work has shown that their IC_{50} is in the range of 50–100 μM [6]. Salicylic acid also did not affect the viability of tumor cells. Previously, the antitumor effect of salicylic acid and its metabolites on the growth of the HCT-116 tumor cell line was shown, however, at much higher concentrations from 0.5 to 10 mM [14]. Tetraesters of epibrassinolide and epicastasterone with succinic and indolylacetic acids did not affect the growth of the analyzed tumor cell lines. Experiments on normal dermal fibroblasts showed that IC_{50} of compounds **3** and **4** were slightly higher than those for tumor cells, but also less than 10 μM.

After discovering the effects of salicylates described above, we checked whether a mixture of 1 mol of salicylic acid and 1 mol of EB had a similar effect. It was shown that the mixture of individual components did not affect the growth of the A549 and MCF-7 lines, which indicates the significance of the effect of the chemical structure of compounds **3** and **4**, rather than its individual components. Perhaps the permeability of these compounds through the membrane increases, or this chemical structure has a high affinity for the active center of some enzymes and act as inhibitors of their activity.

In an experiment to establish the effect of compounds **3** and **4** on the cell cycle of the MCF-7 line, it was found that both compounds inhibit it in the S phase and cause cells to accumulate in the G0/G1 phase (Fig. 2), thereby stopping DNA duplication and cell division.

Thus, conjugates **3** and **4** have a pronounced cytostatic effect against the MCF-7 line. These results may indirectly indicate the possibility of compounds **3** and **4** to act as inhibitors of cyclin-dependent kinases (CDKs), which are key enzymes involved in the control of cell transition from one phase to another [15].

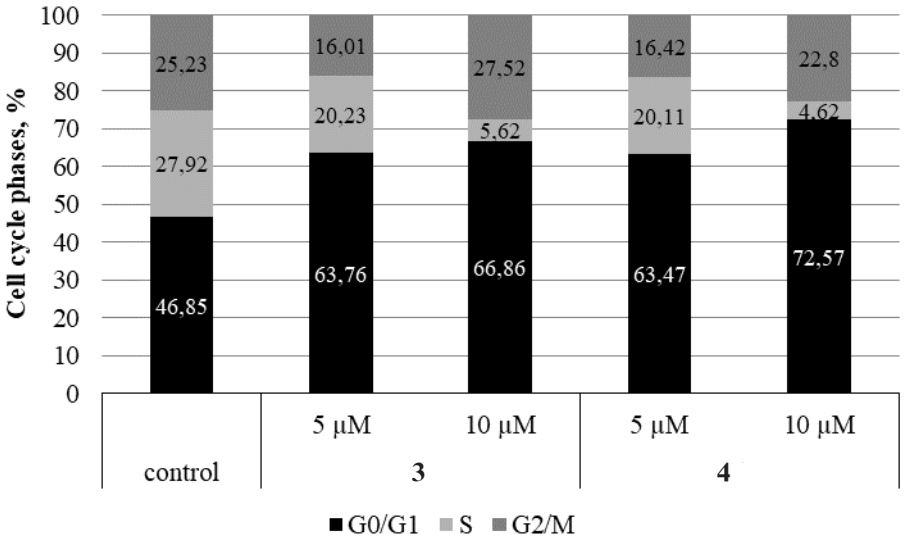

Fig. 2. Distribution of MCF-7 cells by phases of the cell cycle under the action of compounds **3** and **4** within 24 hours

In addition, dose-dependent inhibition of cellular respiration was observed under the action of the studied compounds **3** and **4** (Fig. 3), which was revealed using a positively charged fluorescent label 3,3′-dihexyloxcarbocyanine iodide ($DiOC_6(3)$) capable of specifically binding at low concentrations to negatively charged mitochondrial membrane. The higher the concentration of active compounds and the exposure time, the higher the inhibitory effect. One can see that already after 48 hours, when exposed to a concentration of 10 μM of the studied compounds, almost complete inhibition of the mitochondrial potential of MCF-7 cells occurs, which correlates with the data on the inhibition of their viability.

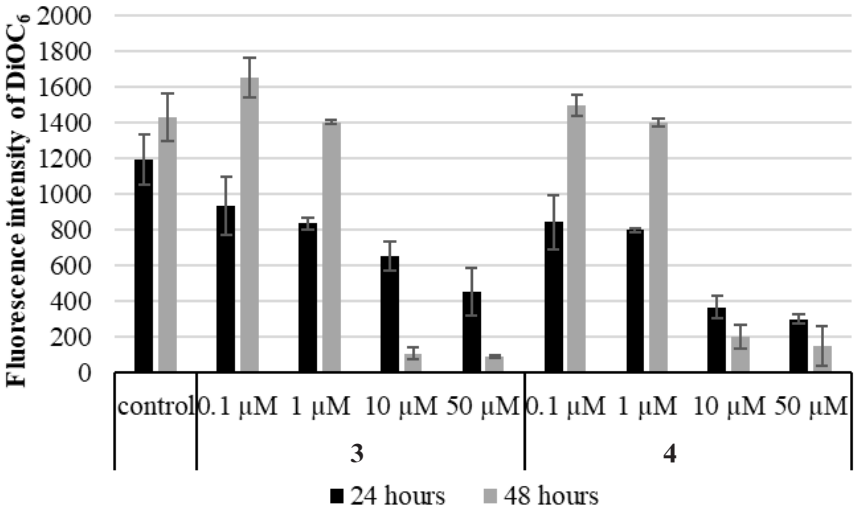

Fig. 3. Changes in the potential of the mitochondrial membrane under the influence of test substances **3** and **4** in MCF-7 cells after 24 and 48 hours

To determine the type of cell death, double staining was carried out with fluorescent dyes Annexin V (during apoptosis, it binds to phosphatidylserine on the outer cell membrane) and PI (stains the DNA of cells only with a broken membrane integrity, which is a sign of necrosis). With an increase in the concentration of the studied compounds, the number of dead cells increases, and all of them pass through early (B4 quadrant) and then late apoptosis (B2 quadrant) (Fig. 4). These data confirm the cytostatic effect of compounds **3** and **4** on MCF-7 cells.

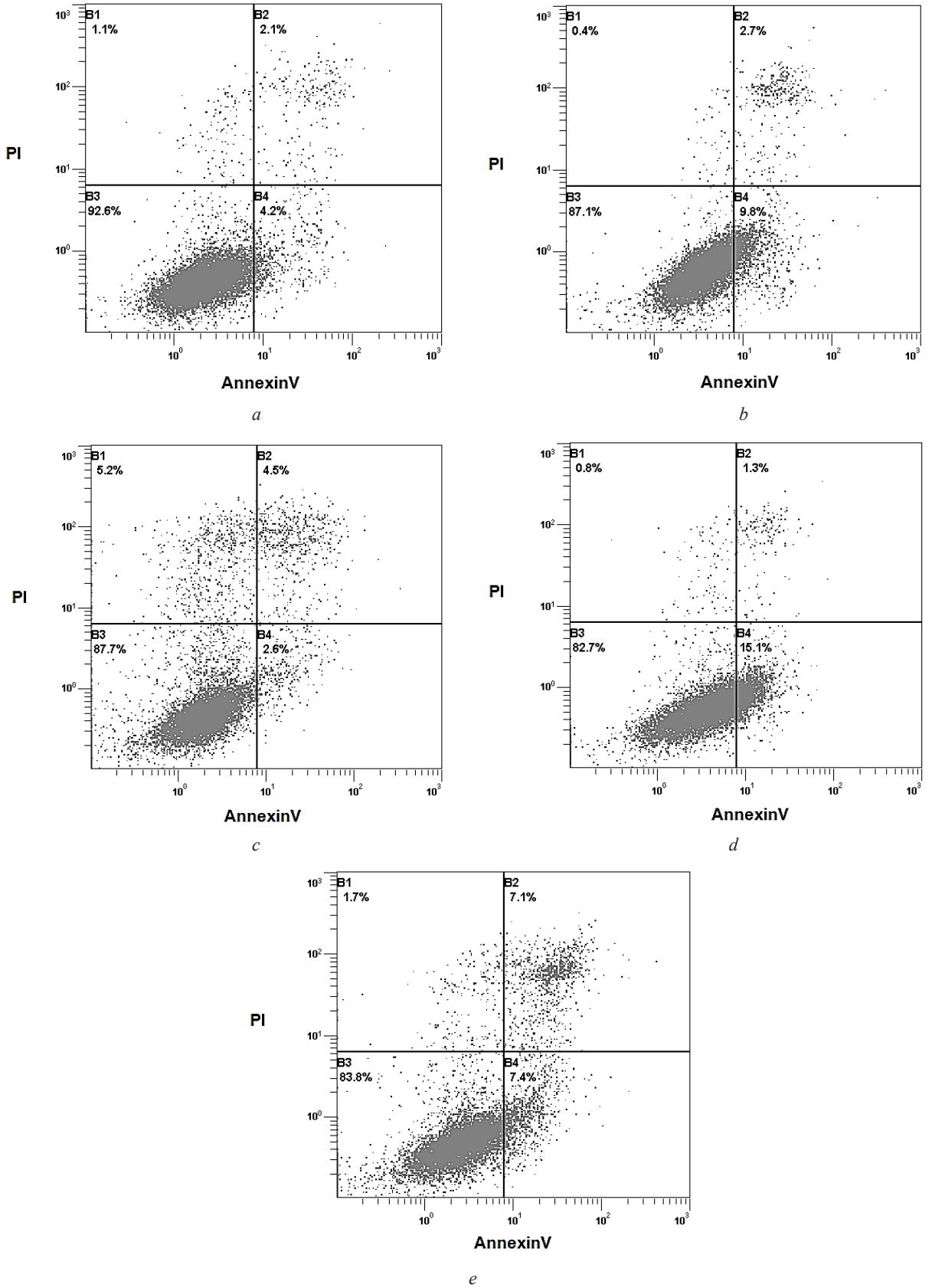

Fig. 4. Differential staining of apoptotic and necrotic MCF-7 cells under the action of compounds **3** and **4** for 24 hours: *a* – control + 0.25 % DMSO; *b* – compound **3** (5 μM); *c* – compound **3** (10 μM); *d* – compound **4** (5 μM); *e* – compound **4** (10 μM). Quadrant B1 – necrosis, quadrant B2 – late apoptosis, quadrant B3 – living cells, quadrant B4 – early apoptosis

Conclusions. Thus, salicylic acid esters of epibrassinolide and epicastasterone **3** and **4** inhibit the growth of tumor cells, while succinic and indolylacetic acids esters **5**–**8** do not affect their growth. This result is obviously related to the peculiarities of the structure of the studied compounds, which provides the IC_{50} value of epibrassinolide and epicastasterone esters with salicylic acid by 10 times less than the IC_{50} value of the starting BS. The data obtained indicate that the mechanism of their action is associated with a cytostatic effect, since both compounds stop the cell cycle, inhibit cellular respiration and induce apoptosis of tumor cells. It should also be noted that the effects of the studied compounds, in contrast to the original brassinosteroids, which more effectively suppressed the growth of hormone-dependent lines (for example, MCF-7) [7], are universal.

The present study of the influence on the development of tumor cells of brassinosteroid derivatives containing in the structure of the molecule a fragment of the phytohormone, salicylic acid, as an additional pharmacophore attached via an ester bond, made it possible to detect a high antitumor activity of new synthesized compounds. We believe that further development of research in this direction has good prospects for the creation of new antitumor agents that selectively affect pathology and do not affect healthy cells.

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