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N.L. Shapekova
R.Z. Safarov

L.N. Gumilyov Eurasian National University, Nur-Sultan, Kazakhstan
(E-mail: shapekova_nl@enu.kz, ruslanbox@yandex.ru)

Computer analysis of the antineoplastic activity of betulin derivatives

Abstract. *The paper provides an overview of the use of various betulin derivatives. There are represented conclusions of in-silico research of betulin, betulinic acid, betulinic diacetate, allobetulinol. There has been used OSIRIS software for in silico analysis PASS, Molinspiration. Obtained results of the study show that after summarizing of all forecasts betulin and betulinic acid are potential compounds for getting more efficient and active products for producing of antitumor pharmaceuticals. Betulin diacetate is proper according to various theoretic terms but has a high probability to be an irritant mediator. Also, this substance shows the worst compliance with Lipinski rule. According to PASS forecast all the investigated compounds have substantial prospect to be used as the basis for producing new highly effective anticancer pharmaceuticals.*
Keywords: *botulin, betulin diacetate, betulinic acid, allobetulinol, in silico, PASS, Molinspiration, OSIRIS Property Explorer, Lipinski rule.*

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Introduction. In pharm chemistry, natural substances and their derivatives are widely used when developing new preparations. One of them is the basic constituent of birch bark - betulin - lupane alcohol. It has substantial synthetic abilities and a multiplicity of pharmacologic influences, which makes it a prospective compound for synthesis of N-containing cyclic compounds with a different types of bioactivity [1–10]. The triterpenoids of a lupan series are interesting for researchers because of the wide range of their biomedical features and availability of the natural compounds: betulin, betulinic and betulonic acids, betulin aldehyde, beta-sitosterol and suberin [11, 12, 21–27, 13–20].

In the study [28] several betulin acyl derivatives were synthesized and their antiviral activity against influenza A (H7N1), herpes simplex type I (VGP-I), ESNO 6 and HIV-1 was studied in comparison with previously synthesized acylates and initial terpenoids. It was found that betulin and betulinic acid acylates in general do not have an advantage in inhibiting the reproduction of all the viruses used in comparison with betulinic acid, at the same time, the structural modification of the C3 and C28 positions of the triterpene backbone allows to slightly change the spectrum of antiviral action.

The cytotoxicity of N - ethyl-and N-methylpiperazinylamides of betulinic and glycyrrhetic acids against human embryonic kidney cells HEK293, lung adenocarcinoma A-549, breast carcinoma MCF-7, neuroblastoma SH-SY5Y in vitro experiments was studied [29]. It was found that the obtained compounds have cytotoxic activity against both conditionally normal cells and cell lines of tumor origin. There is a more pronounced ability of betulinic acid amides to suppress the viability of tumor cells compared to N-ethylpiperazinylamide of glycyrretonic acid.

The conducted experiments [30] clearly indicate that the mechanism of antitumor action of amides and betulonic acid dipeptide is associated with a decrease in the expression of the Cyclin D1 gene in human leukemic cells CEM and MOLT-4, which leads to inhibition of cell division and subsequent apoptosis. The authors also found that under the influence of the studied compounds, the level of hTERT mRNA in leukemic cells decreases. According to the results obtained, one of the mechanisms

of antitumor action of the studied derivatives of plant triterpenes is inhibition of the expression of the hTERT gene. inhibition of this gene expression has been shown to lead to a loss of telomerase activity, which is likely to lead to telomere loss and chromosomal instability, which can also induce apoptosis.

The authors of the study [31] have shown that betulonic acid amides are more active antitumor agents in vitro than betulinic acid ($p < 0.05$), the mechanism of antitumor action of which is associated with the induction of apoptosis. One of the mechanisms is carried out through Fas receptors (CD95) belonging to the family of tumor necrosis factor (TNF) receptors that activate caspase-8, while the other pathway involves cytochrome c, Apaf-1 and caspase-9. The leading role in starting this pathway is played by the family of proteins Bcl-2. The different expression of these proteins and their binding proteins allows for very fine regulation of apoptosis.

The authors [32] studied the cytotoxic activity of 35 new betulinic acid derivatives in vitro, 50 % cytotoxic and inhibitory doses of which were in the ranges from 3.6 ± 1.3 to 98.2 ± 1.8 and from 0.69 ± 0.3 to 125.6 ± 3.1 microns, respectively. The apoptosis-inducing effect of the studied betulinic acid derivatives in human leukemia cells in culture was found. It was found that the greatest inducing effect (apoptosis is manifested in 27% of cells after 72 hours of incubation) is caused by the compound G-49 amide of betulinic acid. The most active derivatives of betulonic acid, which have high cytotoxic activity and induce apoptosis in MT-4 cells, increase the expression of Bcl-2 genes by 2-3 times, Cyclin D1-by 4-9 times. The mechanism of the apoptosis activation pathway by betulinic acid derivatives cannot be determined unambiguously and probably depends on the specific experimental conditions.

Induction of apoptosis under the action of betulin, betulinic acid and their derivatives, as a rule, is associated with the following [33]:

1) with direct regulation of the mitochondrial apoptotic pathway and impaired mitochondrial membrane potential;

2) release of cytochrome c from mitochondria into the cytosol;

3) increase in activated forms of polyribose polymerase, DNA fragmentation.

4) activation of initiator and effector caspases (3, 8 and 9).

The authors of the review study [34] discuss the prospects for the use of triterpenoids of the lupan series in medical practice. Among the native compounds, betulinic acid is of particular importance - a highly effective anti-cancer agent and an inhibitor of enterovirus ESNO6. The most promising semi-synthetic derivatives of the lupane series include amides, ureides, dipeptides and acylates of betulinic, betulonic and 3-oximinobetulonic acids, which have high anti-HIV activity, pronounced antitumor and organ protective effects. it is shown that the production of biologically active additives with betulin extract is actively developing.

Thus, in this work results of in silico study of betulin and its derivatives: betulinic acid, betulin diacetate, allobetulinol are presented. The analysis was carried out for revealing more predominant basic compound for development of biologically active derivatives with anticancer action.

Materials and Methods. Studied chemicals and their structures are given in Table 1.

Structural formulas and mol files generated using open internet resource http://molview.org/.

IUPAC and systematic names of studied compounds generated with ChemDrawUltra from CambridgeSoft.

PASS prediction carried out at web site http://pharmaexpert.ru/PASSonline/predict.php.

Molinspiration properties were taken from https://www.molinspiration.com/cgi-bin/properties with SMILES for generation models of molecules.

OSIRIS Property Explorer program by the link https://www.organic-chemistry.org/prog/peo/ was used for analysis of properties of obtained compounds.

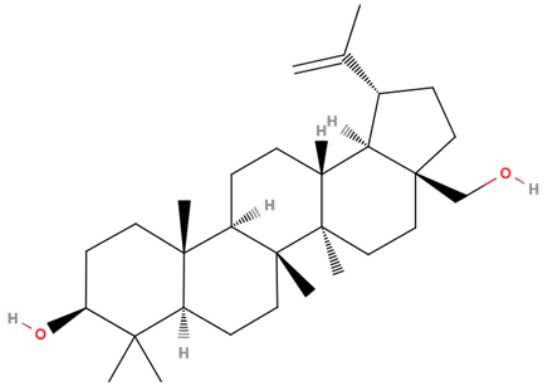
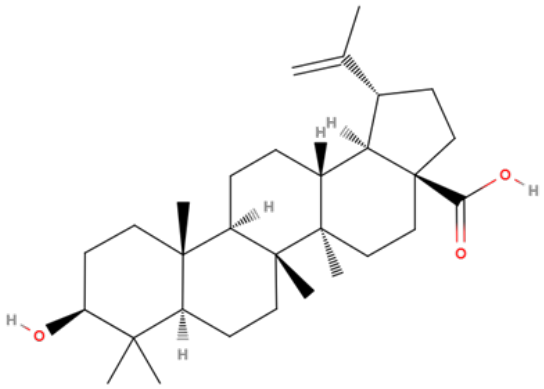
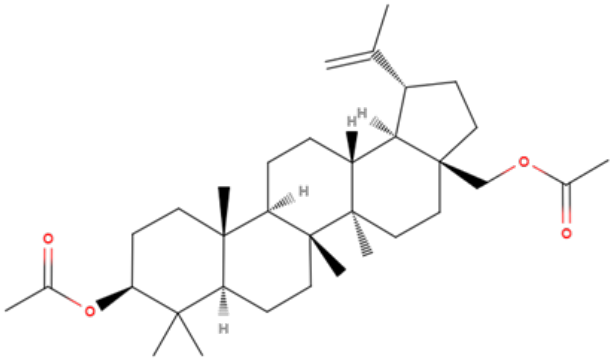
Results and Discussion

1. PASS prediction of anticancer properties

The PASS program used for prediction of anticancer activity of the studied structures (Table 2). It was defined that all the compounds have high possibility for antitumor activity 92.5 - 95.2%. Between directions of cancer betulin is more active against melanoma with 90.3% of probability, betulinic acid shows more activity against melanoma and lung cancer (80.0% and 81.5%), betulin diacetate is more specific to melanoma (88.9%), allobetulinol is effective against colorectal cancer (92.0%).

Table 1

Studied preparations

№	Name	Structural formula
1	Betulin	 *Systematic name* Lup-20(29)-ene-3β,28-diol *Canonical SMILES* CC(=C)C1CCC2(C1C3CCC4C5(CCC(C(C5CCC4(C3(CC2)C)C)(C)C)O)C)CO
2	Betulinic acid	 *Systematic name* (3β)-3-Hydroxy-lup-20(29)-en-28-oic acid *Canonical SMILES* CC(=C)C1CCC2(C1C3CCC4C5(CCC(C(C5CCC4(C3(CC2)C)C)(C)C)O)C)C(=O)O
3	Betulin diacetate	 *Systematic name* (3beta)-Lup-20(29)-ene-3,28-diyl diacetate *Canonical SMILES* CC(=C)C1CCC2(C1C3CCC4C5(CCC(C(C5CCC4(C3(CC2)C)C)(C)C)OC(=O)C)C)COC(=O)C

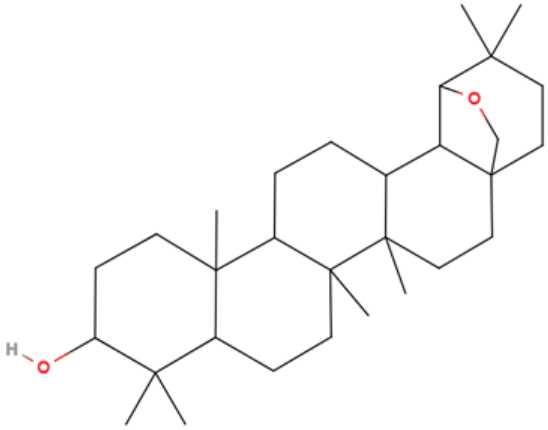
4	Allobetulinol	 IUPAC name (1R,4aR,6aR,6bR,8aR,10S,12aR,12bR,14aR,14bR)-2,2,6a,6b,9,9,12a-heptamethylicosahydro-1H-1,4a-(epoxymethano)picen-10-ol Canonical SMILES CC1(CCC23CCC4(C(C2C1OC3)CCC5C4(CCC6C5(CCC(C6(C)C)O)C)C)C)C

Table 2

Results of PASS antitumor activity forecasting

№	Structure	Anticancer activity (Pa, %)
1	Betulin	0.540 Anticarcinogenical 0.633 Antimetastatical 0.948 Antineoplastical 0.903 Antineoplastical (melanoma) 0.858 Antineoplastical (colorectal cancer) 0.853 Antineoplastical (colon cancer) 0.833 Antineoplastical (lung cancer) 0.803 Antineoplastical (breast cancer) 0.785 Antineoplastical (ovarian cancer) 0.737 Antineoplastical (cervical cancer) 0.698 Antineoplastical (thyroid cancer) 0.661 Antineoplastical (endocrine cancer) 0.596 Antineoplastical (carcinoma) 0.403 Antineoplastical (pancreatic cancer) 0.275 Antineoplastical (squamous cell carcinoma) 0.276 Antineoplastical (lymphocytic leukemia) 0.239 Antineoplastical (glioblastoma multiforme) 0.236 Antineoplastical (liver cancer) 0.181 Antineoplastical (glioma) 0.158 Antineoplastical (lymphoma)
2	Betulinic acid	0.493 Anticarcinogenical 0.624 Antimetastatical 0.925 Antineoplastical 0.230 Antineoplastical (brain cancer) 0.724 Antineoplastical (breast cancer) 0.550 Antineoplastical (carcinoma)

		0.670 Antineoplastical (cervical cancer) 0.789 Antineoplastical (colon cancer) 0.794 Antineoplastical (colorectal cancer) 0.620 Antineoplastical (endocrine cancer) 0.164 Antineoplastical (glioblastoma multiforme) 0.160 Antineoplastical (liver cancer) 0.815 Antineoplastical (lung cancer) 0.158 Antineoplastical (lymphocytic leukemia) 0.800 Antineoplastical (melanoma) 0.708 Antineoplastical (ovarian cancer) 0.413 Antineoplastical (pancreatic cancer) 0.272 Antineoplastical (squamous cell carcinoma) 0.661 Antineoplastical (thyroid cancer)
3	Betulin diacetate	0.514 Anticarcinogenical 0.573 Antimetastatical 0.952 Antineoplastical 0.812 Antineoplastical (breast cancer) 0.648 Antineoplastical (carcinoma) 0.773 Antineoplastical (cervical cancer) 0.876 Antineoplastical (colon cancer) 0.879 Antineoplastical (colorectal cancer) 0.690 Antineoplastical (endocrine cancer) 0.238 Antineoplastical (glioblastoma multiforme) 0.178 Antineoplastical (glioma) 0.210 Antineoplastical (liver cancer) 0.859 Antineoplastical (lung cancer) 0.295 Antineoplastical (lymphocytic leukemia) 0.144 Antineoplastical (lymphoma) 0.889 Antineoplastical (melanoma) 0.835 Antineoplastical (ovarian cancer) 0.389 Antineoplastical (pancreatic cancer) 0.173 Antineoplastical (renal cancer) 0.301 Antineoplastical (squamous cell carcinoma) 0.735 Antineoplastical (thyroid cancer)
4	Allobetulinol	0.460 Anticarcinogenical 0.623 Antimetastatical 0.950 Antineoplastical 0.213 Antineoplastical (brain cancer) 0.573 Antineoplastical (breast cancer) 0.715 Antineoplastical (carcinoma) 0.395 Antineoplastical (cervical cancer) 0.917 Antineoplastical (colon cancer) 0.920 Antineoplastical (colorectal cancer) 0.724 Antineoplastical (endocrine cancer) 0.160 Antineoplastical (glioblastoma multiforme) 0.227 Antineoplastical (liver cancer) 0.883 Antineoplastical (lung cancer) 0.154 Antineoplastical (lymphoma) 0.551 Antineoplastical (melanoma) 0.318 Antineoplastical (multiple myeloma) 0.373 Antineoplastical (non-Hodgkin's lymphoma)

		0.168 Antineoplastical (non-small cell lung cancer) 0.866 Antineoplastical (ovarian cancer) 0.328 Antineoplastical (pancreatic cancer) 0.178 Antineoplastical (renal cancer) 0.202 Antineoplastical (squamous cell carcinoma) 0.773 Antineoplastical (thyroid cancer)

2. Molinspiration analysis

The Molinspiration is used to define key properties of bioactivity of organic compounds based on their structures (Table 3).

Table 3

Parameters of studied compounds computed with Molinspiration

Property	**Betulin**	**Betulinic acid**	**Betulin diacetate**	**Allobetulinol**
An octanol-water partition coefficient miLogP	7,16	7,04	8,45	7,23
polar surface area TPSA	40,46	57,53	52,61	29,46
Number of atoms	32	33	38	32
Molecular mass MW	442,73	456,71	526,80	442,73
Hydrogen bond acceptors (all nitrogen or oxygen atoms) nON	2	3	4	2
Hydrogen bond donors (the total number of nitrogen–hydrogen and oxygen–hydrogen bonds) nOHNH	2	2	0	1
Number of violations of Lipinski rule nviolations	1	1	2	1
Number of rotating bonds nrotb	2	2	6	0
Volume	469,86	472,04	542,89	465,32

We have checked compliance of studied structures with various rules and indicators for possibility of structures to be used as drugs (Lipinski rule, bioavailability, Ghose filter, lead likeness, Muegge filter, Veber filter). The result of the analysis is shown in the Table 4.

Table 4

Drug likeness parameters of studied compounds in compliance with various rules

Drug likeness	**Betulin**	**Betulinic acid**	**Betulin diacetate**	**Allobetulinol**
Lipinski rule	80.0%	80.0%	60.0%	80.0%
Bioavailability	85.7%	85.7%	71.4%	85.7%
Ghose	75.0%	75.0%	50.0%	50.0%
Lead likeness	80.0%	60.0%	60.0%	80.0%
Muegge	85.7%	85.7%	85.7%	85.7%
Veber filter	100.0%	100.0%	100.0%	100.0%

Betulin diacetate passes through fewer filters and is the least proper structure for creation of bioactive derivatives for production of pharmaceuticals. Contrarily betulin is more proper. Betulinic acid also has prospects to be a convenient origin for creation more active derivatives.

The Molinspiration program was applied for computing bioactivity score (Table 5). Typically, the less value of bioactivity score a substance shows, the more active it in that field. It is well-known, that generally anticancer pharmaceuticals are good kinase inhibitors, so this effect is an appropriate criterion for prediction of antitumor activity of biopreparations. From the table all the studied compounds show activity as a kinase inhibitor. The most active is betulinic acid with bioactivity score for Kinase inhibitor of -0.50. The least active kinase inhibitor is allobetulinol.

Table 5

Molinspiration analysis of bioactivity score

Bioactivity	Betulin	Betulinic acid	Betulin diacetate	Allobetulinol
GPCR ligand	0,21	0,31	0,10	0,21
Ion channel modulator	-0,04	0,03	-0,08	0,02
Kinase inhibitor	-0,41	-0,50	-0,48	-0,24
Nuclear receptor ligand	0,85	0,93	0,66	0,49
Protease inhibitor	0,09	0,14	0,06	0,15
Enzyme inhibitor	0,51	0,55	0,38	0,46

3. OSIRIS Property Explorer analysis

OSIRIS Property Explorer is a program used for obtaining forecasts about toxicity properties (reproductive effects, irritant, tumorgenicity, mutagenicity) and critical properties of compounds and analytical criteria as drug-likeness and drug-score computed on the basis of molecule structure. The data on researched structures obtained with OSIRIS Property Explorer are presented in Table 6.

Drug-likeness shows similarity of investigated compound to general used drugs. Positive drug-likeness value means that the molecule structure has mostly fragments, which are usually present in conventional drugs. From this point of view allobetulinol is more prospective with the value of drug likeness of -1.32.

The drug score combines drug likeness, cLogP, logS, molecular mass and toxicity risks in one convenient value that may be used to judge overall potential of compound to qualify for a drug [35].

From the point of view of toxicity betulin, betulinic acid and allobetulinol are characterized as a no risk compounds, betulin diacetate – a medium risk compound.

Table 6

Results of analysis of studied compounds using OSIRIS Property Explorer software

Properties	Betulin	Betulinic acid	Betulin diacetate	Allobetulinol
Mutagenicity	0	0	0	0
Tumorgenicity	0	0	0	0
Irritant	0	0	1	0
Reproductive effects	0	0	0	0
cLogP	6,72	6,37	7,69	6,31
Solubility	-6,3	-6,28	-7,12	-6,49
Molweight	442	456	526	442
TPSA	40,46	57,53	52,6	29,46
Druglikeness	-23,93	-21,49	-20,49	-1,32
Drug-Score	0,15	0,15	0,06	0,18

Conclusion. Thus, research conducted shows that summarizing of all forecasts, betulin and betulinic acid are prospective compounds for creation more effective semiproducts for obtaining of antitumor drugs. Betulin diacetate is proper based on various theoretical conclusions but has a high probability to be an irritant agent. Additionally, it is the least compliant with Lipinski rule. PASS forecast shows that all the investigated compounds have substantial potential to be used as the origin for creation of new highly effective anticancer pharmaceuticals.

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Н.Л. Шәпекова, Р.З. Сафаров

Л.Н. Гумилев атындағы Еуразия ұлттық университеті, Нұр-Сұлтан, Қазақстан

Бетулин туындыларының ісікке қарсы белсенділігін компьютерлік талдау

Аңдатпа. Мақалада бетулиннің әртүрлі туындыларын қолдануға шолу жасалады. Сондай-ақ, бетулин, бетулин қышқылы, бетулин диацетаты, аллобетулинолды in silico зерттеу нәтижелері ұсынылған. In silico талдау үшін PASS, Molinspiration, OSIRIS бағдарламалары қолданылды. Зерттеулер көрсеткендей, барлық болжамдарды жинақтағаннан кейін бетулин мен бетулин қышқылы ісікке қарсы препараттарды алу үшін тиімді және белсенді туындыларды алу үшін перспективалы құрылым болып табылады. Бетулин диацетаты көптеген теориялық жағдайларға сәйкес келеді, бірақ тітіркендіргіш агент ретінде әсер етудің жоғары ықтималдығын көрсетеді. Ол сондай-ақ, Липинский ережесіне ең аз сәйкестікті көрсетеді. PASS болжамын талдау негізінде зерттелген барлық құрылымдар жаңа жоғары тиімді ісікке қарсы препараттарды алу үшін негіз ретінде пайдалану үшін айтарлықтай әлеуетке ие.

Түйін сөздер: бетулин, бетулин қышқылы, бетулин диацетаты, аллобетулин, in silico, PASS, Molinspiration, OSIRIS Property Explorer, Липинский ережесі.

Н.Л. Шапекова, Р.З. Сафаров

Евразийский национальный университет имени Л.Н. Гумилева, Нур-Султан, Казахстан

Компьютерный анализ противоопухолевой активности бетулиновых производных

Аннотация. В статье представлены обзор применения различных производных бетулина, а также результаты in silico исследования бетулина, бетулиновой кислоты, диацетата бетулина, аллобетулинола. Для анализа in silico были использованы программы PASS, Molinspiration, OSIRIS. Проведенные исследования показывают, что после обобщения всех прогнозов бетулин и бетулиновая кислота являются перспективными структурами для получения более эффективных и активных производных для получения противоопухолевых препаратов. Диацетат бетулина является подходящим исходя из многих теоретических условий, но показывает высокую вероятность воздействия в качестве раздражающего агента. Также он проявляет наименьшее соответствие правилу Липинского. На основе анализа прогноза PASS все изученные структуры обладают значительным потенциалом для использования в качестве основы для получения новых высокоэффективных противоопухолевых препаратов.

Ключевые слова: бетулин, бетулиновая кислота, диацетат бетулина, аллобетулинол, in silico, PASS, Molinspiration, OSIRIS Property Explorer, правило Липинского.

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Авторлар туралы мәлімет:

Шәпекова Н.Л. – медициналық ғылымдарының докторы, профессор, Жаратылыстану ғылымдары факультетінің деканы, Л.Н. Гумилев атындағы Еуразия ұлттық университеті, Қажымұқан көшесі 13, Нұр-Сұлтан, Қазақстан.

Сафаров Р.З. – **корреспонденция үшін автор,** химия ғылымдарының кандидаты, химия кафедрасының доцент м.а., Технологиялар трансферті жобалық кеңсесінің бастығы, Л.Н. Гумилев атындағы Еуразия ұлттық университеті, Сәтбаев көшесі 2, Нұр-Сұлтан, Қазақстан.

Shapekova N.L. – Doctor of Medicine, Professor, Dean of the Faculty of Natural Sciences, L.N. Gumilyov Eurasian National University, 13 Kazhymukan str., Nur-Sultan, Kazakhstan.

Safarov R.Z. – **corresponding author,** Candidate of Chemical Sciences, Assoc. Professor of Department of Chemistry, Head of the Technologies Transfer Project office, L.N. Gumilyov Eurasian National University, 2 Satpaev str., Nur-Sultan, Kazakhstan.