IRSTI 76.31.35; 76.31.33

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In silico analysis of anticancer effects of anabasine derivatives

Abstract. *In the paper a review of using of different derivatives of anabasine is represented. As well results of computer QSAR investigations of N-(anabazinil)-isobutyric acid, N-(anabazinil)-isovaleric acid, N-(anabazinil)-trimethylacetic acid, N-(anabazinil)-crotonic acid, N-(anabazinil)-chloroacetic acid are represented. For in silico analysis PASS, Molinspiration, OSIRIS software has been used. The results obtained show that summarizing all predictions N-(anabazinil)-isobutyric acid and N-(anabazinil)-chloroacetic acid are acceptable structures for creation new more active and effective derivatives as antitumor medicines. However, considering Cl-containing derivative it was concluded, that this molecule should be changed for decreasing parameters of toxicity with remaining the prospective bioactivity. Most given structures are corresponding to Lipinski's rule and drug-likeness filters and can be considered as basic structures for constructing some new effective anticancer medicines.*

Keywords: *anabasine, N-(anabazinil)-isobutyric acid, N-(anabazinil)-isovaleric acid, N-(anabazinil)-trimethylacetic acid, N-(anabazinil)-crotonic acid, N-(anabazinil)-chloroacetic acid, in silico, PASS, Molinspiration, OSIRIS Property Explorer, Lipinski rule.*

DOI: 10.32523/2616-7034-2021-134-1-6-19

Introduction. Anabasine is well known alkaloid. It is a prospective synthon for modification and synthesis of new bioactive substances [1]. This alkaloid shows expressed anti-tuberculosis and insecticidal properties [2]. The potential of its using in chemical syntheses is still not fully revealed. The introduction of pharmacophore fragments into its structure, such as thiourea, furan, thiazoline, and others, allows the search for new anabasine derivatives with potential antibacterial activity [3, 4].

Anabasine $C_{10}H_{14}N_2$ is an alkaloid of the pyridine series contained in Echinochloa leafless *(Anabasis aphylla L.)*, and tobacco [5, 6]. In its pharmacological properties, anabasine is similar to nicotine, cytisine and lobelin. For example, anabasine hydrochloride is a medicine which reduces the need for nicotine. Anabasine sulfate is used as an insecticide for treatment of fruit and vegetable crops. Anabasine can be used as a raw material for obtaining of nicotinic acid.

Insecticidal properties of anabasine are very important. Thus, in folk medicine Anabasis has been used by the local population for a long time: the powder obtained from the stem of Anabasis – for wounds dusting, water infusion of green parts of Anabasis – against lice, scabies and ringworm of livestock, a decoction of the roots was used to treat tuberculosis [7, 8]. Anabazine was one of the widely used insecticidal means of pest control of such industrial crops, vegetable and melon crops

(aphids, fleas, copperheads, whiteflies, etc.). However, due to its high toxicity (LD 8-10 mg/kg), it was discontinued in the 60s of the last century.

In order to overcome the high toxicity of some natural alkaloids, there are methods of their chemical modification that lead not only to a decrease in toxicity, but also allow you to influence the pharmacological activity of the original medicinal substance [9]. For example, only the inclusion of a -CH3 group into the anabasine structure (N-methylanabasine) leads to a 4-fold decrease in toxicity and a 25-fold decrease in the excitatory effect on respiration compared to the initial alkaloid [10]. Introduction of sulphur into molecule of physiologically active substances not only gives a significant decrease in toxicity due to the easy oxidability of its derivatives in the human body, but also leads to occurrence of other activities

In the paper [11] biological activity of salts of dithioacids of phosphorus based on alkaloid anabasine is reported. Studies of the specific activity and toxicity of anabazine thiosalts in the laboratory of experimental tumor therapy of the KazNRI of Oncology and Radiology showed that the drugs had different activity in relation to experimental animal tumors. Anabasinium 0.0-diethyl-, 0.0-dibutyl (dithiophosphates) and Anabasinium N-piperidyl-O-isopropyl dithiophosphate were studied in vivo in mice with inoculated lymphocytic leukemia P-388. Treatment was started in 24 hours after tumor transplantation, drugs in doses of 1 mg/kg; 10 mg/kg; 20 mg/kg; 50 mg/kg; 100 mg/kg were administered intraperitoneally for 5 days. The results of research showed that the presented drugs are low-toxic and have a pronounced antitumor activity in the range of 56-94%, especially Anabazinium N-piperidyl-O-isopropyl dithiophosphate. The greatest therapeutic effect on Ehrlich's tumors was a dose of 10 mg/kg, causing inhibition of tumor growth up to 88-94 %, without showing high toxicity. The same effect has Anabasine 0,0-diethyldithiophosphate. As a result of clinical studies of chemotherapy drugs, doses of 10 mg/kg and 20 mg/kg showed the greatest therapeutic effect, causing inhibition of tumor growth up to 88-94% and without high toxicity [11].

Now, an approach for investigations of medicines based on in vitro/in vivo methods are commonly accepted. During last 40 years in the N.N. Blokhin Russian Scientific Center of Oncology of RAMS is used a three-stage system for seeking of novel substances with anticancer effects:

1) screening human cancer cells of various histogenesis using in vitro methods;

2) screening for transplantable tumor material taken from rats or mice;

3) comprehensive study with transplantable and induced animal tumor material and heterotransplants of human cancer material in mice [12].

It is well-known that creation of novel pharmaceuticals takes extensive financial expenditure. It takes about 10-15 years and around 500 million USD when developing a new pharmaceutical. Furthermore, up to 80% of these finances can be spent on fruitless solutions at the preclinical and clinical steps of pharmaceutical elaboration [12].

Introduction of new computer technologies for forecasting and their implementation to evaluate the probably activities of substances, with following examination of the studied matters in compliance with the prediction results can give the opportunity of a holistic study of the bioactivity of chemical compounds [13]. Computerized toxicity simulations can be used for prediction the anticipated toxicity and influence on human health; the values of important toxicity characteristics derived based on machine simulation and from animal experiments are quite close when appropriate injection route is chosen. Computer models are developed on the basis of statistical analysis of toxicological data accessible for lots of chemicals. These models are used for prediction toxicity of studied chemicals, o the basis of quantitative associations between structure and activity, so called Quantitative Structure - Activity Relationship or QSAR [14, 15]. The software for computer forecasting of biological activity of organic chemicals called PASS (Prediction of Activity Spectra for Substances) works based on aforementioned principle [16]. Description of the organic compound structure in PASS based on the structural formula. The program makes it possible real time forecasting the spectrum of bioactivities of organic chemical on the basis of structural formula in format of MOL file in the Internet [17]. The

forecasting result is presented in form of an ordered list of the corresponding activities names and probabilities Pa - "to be active" and Pi - "to be inactive" for the studied pharmaceuticals. This makes it possible to join data on bioactive compounds taken from multiple resources in single training sample. The obtained list can be sorted in descending or ascending order of the Pa – Pi discrepancy [18].

One of the basic indicator for the realizability of following producing chemicals is the accordance of structure of the substance to "Lipinski's rule five" (drug-likeness) [19, 20]. In compliance with the rule, a compound can be considered as a potential drug when its molar weight is less than 500; log P less than 5; the hydrogen donor number less than 5 (defined as the sum of OH and NH); amount of hydrogen acceptors less than 10 (defined as the sum of O and N atoms). The Molinspiration program is usually applied to define the specified characteristics and to estimate the molecular polar surface area.

The Osiris property explorer software is often applied for forecasting of compound safety [21]. It computes the physical and chemical (molecular weight, solubility, log P), toxic characteristics (reproductive toxicity, irritating effect, tumorgenicity, mutagenicity) as well drug-likeness of chemicals. A positive drug-likeness value from 0,1 to 10 means that the structure includes fragments that are usually included in drugs. The "drug score" index, accounting all the characteristics, makes it possible to estimate the potential of the studied chemical as a drug (from 0 to 1).

The Molinspiration program can be used for prediction of bioactivity of the substance. For example, in order to define antitumor activity it is often used likeness to kinase inhibitors. Kinase inhibitor - a substance that blocks a type of enzyme called a kinase [22]. Human cells have many different kinases, and they help control important functions, such as cell signaling, metabolism, division, and survival. Certain kinases are more active in some types of cancer cells and blocking them may help keep the cancer cells from growing. Kinase inhibitors may also block the growth of new blood vessels that tumors need to grow. Some kinase inhibitors are used to treat cancer [23].

Today along with the "rule of five" there are additional filters, which are sets of indicators characterizing the molecular properties of the compounds:

1) bioavailability: molecular weight <500; log P <5; the number of hydrogen bond donors <5; the number of hydrogen bond acceptors <10; number of rotating bonds <10; polar surface area (PSA) <200; the number of condensed aromatic rings <5 or >6 [24];

2) Ghose filter: molecular weight 160-480; the number of atoms 20-70; log P from -0.4 to 5.6; molecular refraction 40-130 [25];

3) lead likeness: molecular weight <450; number of rings <4; number of rotating bonds <10; the number of hydrogen bond donors <5; the number of hydrogen bond acceptors <8 [26];

4) Muegge filter: molecular weight 200-600; number of rings <7; number of rotating bonds <15; the number of hydrogen bond donors <5; the number of hydrogen bond acceptors <10; log P from -2 to 5; PSA <150 [27];

5) Veber filter: number of rotating bonds <10; PSA <140 [28].

Additional program for prediction of ADME/Tox (absorption, distribution, metabolism, elimination and toxicity) properties is web-based application PreADMET [29]. A significant bottleneck remains in the drug discovery procedure, in particular in the later stages of lead discovery, is analysis of the ADME and overt toxicity properties of drug candidates [30]. Over 50% of the candidates failed due to ADME/Tox deficiencies during development [31]. To avoid this failure at the development a set of in vitro ADME/Tox screens has been implemented in most pharmaceutical companies with the aim of discarding compounds in the discovery phase that are likely to fail further down the line [32]. Even though the early stage in vitro ADME reduces the probability of the failure at the development stage, it is still time-consuming and resource-intensive [33]. Thus, a web-based application called PreADMET has been developed in response to a need for rapid prediction of drug-likeness and ADME/Tox data [34].

Earlier in the article [35] it was presented synthesis and characterization of the number of N-acylated derivatives of anabasine, including N-(anabazinil)-isobutyric acid, N-(anabazinil)-isovaleric acid,

N-(anabazinil)-trimethylacetic acid and others, which are perspective as drugs, potentially as antitumor medications.

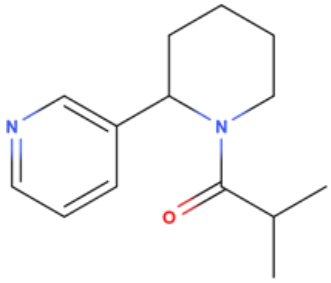
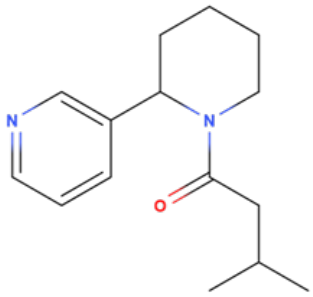
In the paper results of *in silico* investigations of anabasine derivatives: N-(anabazinil)-isobutyric acid (1), N-(anabazinil)-isovaleric acid (2), N-(anabazinil)-trimethylacetic acid (3), N-(anabazinil)-crotonic acid (4), N-(anabazinil)-chloroacetic acid (5) are presented. The analysis was carried out for revealing antitumor activity and for defining drug-likeness of these derivatives as a potential base for creation a new effective antitumor medication.

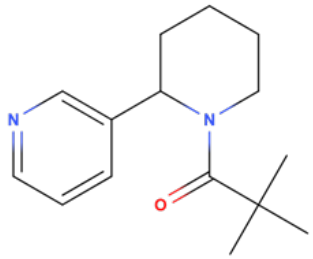
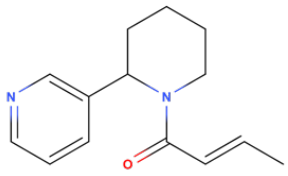
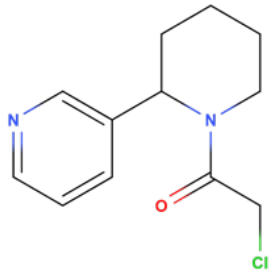
Materials and Methods

Considered compounds and their structures are represented in Table 1.

Table 1

Investigated compounds

№	Name	Structural formula
1	N-(anabazinil)-isobutyric acid	 *Formula* $C_{14}H_{20}N_2O$ *Systematic name* 2-Methyl-1-(2-(pyridin-3-yl)piperidin-1-yl)propan-1-one *Canonical SMILES* CC(C)C(=O)N1CCCCC1C2=CN=CC=C2 *Isomeric SMILES* CC(C)C(=O)N1CCCCC1C2=CN=CC=C2 *PubChem Compound ID* 3822923
2	N-(anabazinil)-isovaleric acid	 *Formula* $C_{15}H_{22}N_2O$ *Systematic name* 3-methyl-1-(2-(pyridin-3-yl)piperidin-1-yl)butan-1-one *Canonical SMILES* CC(C)CC(=O)N1CCCCC1C2=CN=CC=C2 *Isomeric SMILES* CC(C)CC(=O)N1CCCCC1C2=CN=CC=C2 *PubChem Compound ID* 24284658

3	N-(anabazinil)-trimethylacetic acid	 *Formula* $C_{15}H_{22}N_2O$ *Systematic name* 2,2-dimethyl-1-(2-(pyridin-3-yl)piperidin-1-yl)propan-1-one *Canonical SMILES* CC(C)(C)C(=O)N1CCCCC1C2=CN=CC=C2 *Isomeric SMILES* CC(C)(C)C(=O)N1CCCCC1C2=CN=CC=C2 *PubChem Compound ID* 24285002
4	N-(anabazinil)-crotonic acid	 *Formula* $C_{14}H_{18}N_2O$ *Systematic name* 1-(2-(pyridin-3-yl)piperidin-1-yl)but-2-en-1-one *Canonical SMILES* C/C=C/C(=O)N1CCCCC1C2CCCNC2 *Isomeric SMILES* O=C(/C=C/C)N1CCCCC1C1=CN=CC=C1 *PubChem Compound ID* -
5	N-(anabazinil)-chloroacetic acid	 *Formula* $C_{12}H_{15}ClN_2O$ *Systematic name* 2-Chloro-1-(2-(pyridin-3-yl)piperidin-1-yl)ethan-1-one *Canonical SMILES* C1CCN(C(C1)C2=CN=CC=C2)C(=O)CCl *Isomeric SMILES* C1CCN(C(C1)C2=CN=CC=C2)C(=O)CCl *PubChem Compound ID* 14619404

Structural formulas as well as MOL-files have been generated using internet resource «http://molview.org/».

IUPAC names of structures 1-5 generated with ChemDrawUltra from CambridgeSoft.

PASS forecasting has been carried out on http://pharmaexpert.ru/PASSonline/predict.php.

Molinspiration data were obtained from https://www.molinspiration.com/cgi-bin/properties using SMILES for generation of molecule models.

OSIRIS Property Explorer software (https://www.organic-chemistry.org/prog/peo/) was used for analysis.

Results and Discussion

1. PASS forecasting for anticancer activity

The PASS software was used for forecasting of antitumor activity of the investigated compounds (Table 2). We considered only Pa > Pi causes. Antineoplastic and kinase inhibitor properties were selected for analysis.

It was revealed that the structures 1, 3, 4 and 5 can show some activity against non-Hodgkin's lymphoma and with lower probability – against bone cancer. The lowest relevance for antineoplastic properties was shown for structure 2. The highest relevance - structure 5 with chlorine in the structure.

Table 2

Results of PASS antitumor activity forecasting

№	Chemical	Anticancer activity (Pa, %)
1	N-(anabazinil)-isobutyric acid	0,365 Antineoplastic (non-Hodgkin's lymphoma) 0,286 Kinase inhibitor 0,258 Antineoplastic (bone cancer) 0,237 Antineoplastic alkaloid 0,163 Cancer procoagulant inhibitor 0,157 Protein kinase B alpha inhibitor 0,086 TTK protein kinase inhibitor
2	N-(anabazinil)-isovaleric acid	0,279 Preneoplastic conditions treatment 0,277 Cancer associated disorders treatment 0,266 Antineoplastic (bone cancer) 0,254 Kinase inhibitor 0,237 Antineoplastic (multiple myeloma) 0,214 Antineoplastic alkaloid 0,2 Antimetastatic 0,178 Cancer procoagulant inhibitor 0,074 TTK protein kinase inhibitor 0,052 MAP-kinase-activated kinase 1 inhibitor
3	N-(anabazinil)-trimethylacetic acid	0,325 Antineoplastic (non-Hodgkin's lymphoma) 0,284 Kinase inhibitor 0,241 Antineoplastic (bone cancer) 0,239 Antineoplastic alkaloid 0,219 Antineoplastic (small cell lung cancer) 0,166 Antineoplastic (ovarian cancer) 0,164 Choline kinase inhibitor 0,137 Protein kinase B alpha inhibitor 0,123 Cancer procoagulant inhibitor 0,092 TTK protein kinase inhibitor

4	N-(anabazinil)-crotonic acid	0,321 Antineoplastic (non-Hodgkin's lymphoma) 0,313 Antineoplastic alkaloid 0,287 Cancer associated disorders treatment 0,257 MAP kinase kinase 4 inhibitor 0,23 Antineoplastic (bone cancer) 0,189 p21-activated kinase 1 inhibitor 0,167 Antineoplastic enhancer 0,161 p21-activated kinase inhibitor
5	N-(anabazinil)-chloroacetic acid	0,474 Antineoplastic (non-Hodgkin's lymphoma) 0,457 Antineoplastic 0,378 Antineoplastic (multiple myeloma) 0,278 Antineoplastic (breast cancer) 0,266 Kinase inhibitor 0,261 Antineoplastic (bone cancer) 0,188 Antineoplastic alkaloid 0,17 Cancer procoagulant inhibitor 0,156 Antineoplastic (bladder cancer) 0,125 Protein kinase B alpha inhibitor 0,091 Antineoplastic, alkylator 0,08 TTK protein kinase inhibitor

2. Molinspiration data

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

Compound / **Property**	**N-(anabazinil)-isobutyric acid**	**N-(anabazinil)-isovaleric acid**	**N-(anabazinil)-trimethylacetic acid**	**N-(anabazinil)-crotonic acid**	**N-(anabazinil)-chloroacetic acid**
	1	**2**	**3**	**4**	**5**
An octanol-water partition coefficient miLogP	2,04	2,57	2,62	1,66	1,52
polar surface area TPSA	33,20	33,20	33,20	32,34	33,20
Number of atoms	17	18	18	17	16
Molecular mass MW	232,33	246,35	246,35	236,36	238,72
Hydrogen bond acceptors (all nitrogen or oxygen atoms) nON	3	3	3	3	3

ISSN(Print) 2616-7034 eISSN 2663-130X

Hydrogen bond donors (the total number of nitrogen–hydrogen and oxygen–hydrogen bonds) nOHNH	0	0	0	1	0
Number of violations of Lipinski rule nviolations	0	0	0	0	0
Number of rotating bonds nrotb	2	3	2	2	2
Volume	234,80	251,60	251,03	247,17	215,19

We have checked complience 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 of investigated structures according to different rules

Drug-likeness	**N-(anabazinil)-isobutyric acid**	**N-(anabazinil)-isovaleric acid**	**N-(anabazinil)-trimethylacetic acid**	**N-(anabazinil)-crotonic acid**	**N-(anabazinil)-chloroacetic acid**
Rule of 5 (Lipinski)	100%	100%	100%	100%	100%
Bioavailability	100%	100%	100%	100%	100%
Ghose filter	50%	50%	50%	50%	50%
Lead likeness	100%	100%	100%	100%	100%
Muegge filter	100%	100%	100%	100%	100%
Veber filter	100%	100%	100%	100%	100%

Table 4 shows that all derivatives pass through the filters and are potentially appropriate structures for drug production.

The Molinspiration software was used for calculation of bioactivity score (Table 5). Usually, the less value of bioactivity scores a substance show, the more active it in that field. It is well-known, that usually anticancer drugs are good kinase inhibitors, so this bioactivity is an appropriate criterion for forecasting of anticancer activity of medications. From the table it is clear that all of the studied compounds show a kinase inhibitor activity. The most active is N-(anabazinil)-chloroacetic acid with bioactivity score for Kinase inhibitor of -0.65. The least active as a kinase inhibitor is N-(anabazinil)-trimethylacetic acid. The obtained results show correlation with PASS analysis, where Cl-containing derivative was the most prospective as an antineoplastic agent.

Table 5

Molinspiration analysis of bioactivity score

Bioactivity	N-(anabazinil)-isobutyric acid	N-(anabazinil)-isovaleric acid	N-(anabazinil)-trimethylacetic acid	N-(anabazinil)-crotonic acid	N-(anabazinil)-chloroacetic acid
GPCR ligand	0.02	0.11	0.07	0.18	-0.37
Ion channel modulator	-0.07	0.11	-0.05	0.15	-0.14
Kinase inhibitor	-0.61	-0.53	-0.51	-0.60	-0.65
Nuclear receptor ligand	0.69	-0.65	-0.56	-0.70	-0.97
Protease inhibitor	-0.23	-0.02	-0.23	0.10	-0.61
Enzyme inhibitor	-0.09	-0.03	-0.04	0.09	-0.33

3. OSIRIS Property Explorer analysis

OSIRIS Property Explorer is a program used for obtaining predictions about toxic effects (mutagenicity, tumorgenicity, irritant, reproductive effects) as well as some critical properties of molecules and analytical criteria as drug-likeness and drug-score calculated on the basis of molecule structure. The results of analysis of studied structures using OSIRIS Property Explorer are represented in Table 6.

Drug-likeness represents similarity of studied structure to conventionally used drugs. It's positive value points that the molecule has mostly fragments, which are often present in conventional drugs. From this point of view, both N-(anabazinil)-isobutyric acid and N-(anabazinil)-chloroacetic acid are prospective with the values of druglikeness of 1.61 and 1.7 correspondly.

The drug score combines drug-likeness, cLogP, logS, molecular mass and toxicity risks in one handy value that may be used to judge overall potential of compound to qualify for a drug [36]. From the point of view of toxicity N-(anabazinil)-chloroacetic acid is characterized as a high-risk compound. Therefore, despite its prospective bioactivity – Cl-containing derivative is a significantly risky medication.

Table 6

Results of analysis of studied compounds using OSIRIS Property Explorer software

Properties	N-(anabazinil)-isobutyric acid	N-(anabazinil)-isovaleric acid	N-(anabazinil)-trimethylacetic acid	N-(anabazinil)-crotonic acid	N-(anabazinil)-chloroacetic acid
Mutagenicity	0	0	0	0	1
Tumorgenicity	0	0	0	0	1
Irritant	0	0	0	1	1
Reproductive effects	0	0	0	0	1

cLogP	2.24	2.7	2.81	2.07	1.8
Solubility	-1.77	-2.04	-1.95	-2.04	-1.74
Molweight	232.0	246.0	246.0	236.0	238.0
TPSA	33.2	33.2	33.2	32.34	33.2
Druglikeness	1.61	1.47	-2.23	-1.95	1.7
Drug-Score	0.86	0.82	0.5	0.42	0.11

Conclusion. Thus, research carried out show that after generalization of all predictions N-(anabazinil)-isobutyric acid and N-(anabazinil)-chloroacetic acid are prospective structures for obtaining more effective and active derivatives for obtaining of anticancer preparations. However, considering Cl-containing derivative it can be concluded, that this molecule should be changed for decreasing parameters of toxicity with remaining the prospective bioactivity. Most given structures are corresponding to Lipinski rule and drug-likeness filters and can be considered as the bases for constructing new highly effective antitumor preparations.

Acknowledgements and Funding. This research has been funded by the Science Committee of the Ministry of Education and Science of the Republic of Kazakhstan (Grant No. AP05132861)

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Анабазин туындыларының ісікке қарсы белсенділігін In silico талдау

Аннотация. Мақалада анабазиннің әртүрлі туындыларын қолдануға шолу жасалады. Сондай-ақ, N-(анабазинил)-изобутир қышқылы, N-(анабазинил)-изовалериан қышқылы, N-(анабазинил)-триметилацет қышқылы, N-(анабазинил)-кротон қышқылы, N-(анабазинил) - хлорацет қышқылы in silico зерттеулерінің нәтижелері ұсынылған. In silico талдау үшін PASS, Molinspiration, OSIRIS бағдарламалары қолданылды. Жүргізілген зерттеулер N-(анабазинил)-изобутир және N-(анабазинил)-хлорацет қышқылдарының барлық болжамдарын жинақтағаннан кейін ісікке қарсы препараттарды алу үшін неғұрлым тиімді және белсенді туындыларды алу үшін перспективалы құрылым болып табылатынын көрсетті. Алайда, құрамында Cl бар туынды қарастырғанда, болжанған биоактивтілікті сақтай отырып, уыттылық параметрлерін азайту үшін осы молекуланы өзгерту қажеттілігі туралы қорытынды жасалды. Жоғарыда аталған құрылымдардың көпшілігі Липинский ережесіне және есірткіге ұқсас сүзгілерге сәйкес келеді және жаңа жоғары тиімді ісікке қарсы препараттарды құрудың негізі ретінде қарастырылуы мүмкін.

Түйін сөздер: анабазин, N-(анабазинил)-изобутир қышқылы, N-(анабазинил)-изовалериан қышқылы, N-(анабазинил)-триметилацет қышқылы, N-(анабазинил)-кротон қышқылы, N-(анабазинил) - хлорацет қышқылы, in silico, PASS, Molinspiration, OSIRIS Property Explorer, Липинский ережесі.

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In silico анализ противоопухолевой активности производных анабазина

Аннотация. В статье представлен обзор применения различных производных анабазина. Также представлены результаты in silico исследования N-(анабазинил)-изомасляной кислоты, N-(анабазинил)-изовалериановой кислоты, N-(анабазинил)-триметилуксусной кислоты, N-(анабазинил)-кротоновой кислоты, N-(анабазинил)-хлоруксусной кислоты. Для анализа in silico были использованы программы PASS, Molinspiration, OSIRIS. Проведенные исследования показывают, что после обобщения всех прогнозов N-(анабазинил)-изомасляная и N-(анабазинил)-хлоруксусная кислоты являются перспективными структурами для получения более эффективных и активных производных для получения противоопухолевых препаратов. Однако при рассмотрении Cl-содержащего производного был сделан вывод о необходимости изменения этой молекулы для снижения параметров токсичности при сохранении предполагаемой биоактивности. Большинство приведенных структур соответствуют правилу Липинского и фильтрам лекарственного подобия и могут рассматриваться как основы для построения новых высокоэффективных противоопухолевых препаратов.

Ключевые слова: анабазин, N-(анабазинил)-изомасляная кислота, N-(анабазинил)-изовалериановая кислота, N-(анабазинил)-триметилуксусная кислота, N-(анабазинил)-кротоновая кислота, N-(анабазинил)-хлоруксусная кислота, in silico, PASS, Molinspiration, OSIRIS Property Explorer, правило Липинского.

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