STUDY OF SPASMOLYTIC ACTIVITY OF DITERPENE ALKALOIDS BY QSAR METHOD

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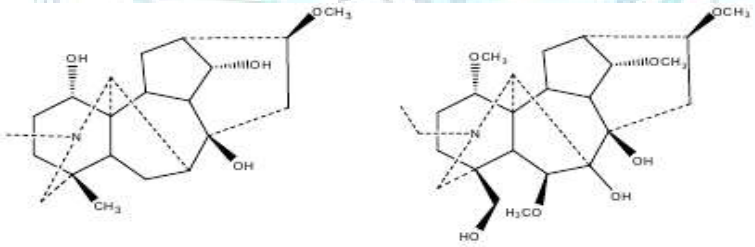
Annotation: Study of diterpene alkaloids and their spasmolytic activity by QSAR method. This method has led to the emergence of new sciences, rational computer design of medicinal substances, and bioinformatics. Along with the terms in vitro and in vivo, the term in silico (in silicon “silicon”) also appeared.
Key words: QSAR, descriptors, drug, diterpene alkaloid, in Vitro, in Vivo
Annotatsiya. Diterpen alkaloidlarining spasmolitik faolligini QSAR usuli bilan o‘rganish. Ushbu usul yangi fanlar, dori vositalarini ratsional kompyuter dizayni va bioinformatikaning paydo bo‘lishiga olib keldi. In vitro va in vivo atamalari bilan birga in silico (silitsiy “silicon”) atamasi ham paydo bo‘ldi.
Kalit so‘zlar: QSAR, descriptorlar, dori, diterpen alkaloid, in vitro, in vivo.
Аннотация. Исследование спазмолитической активности дигерпиновых алкалоидов методом QSAR. Этот метод привел к появлению новых наук, рационального компьютерного дизайна лекарственных веществ и биоинформатики. Наряду с терминами in vitro и in vivo, появился также термин in silico (от лат. «silicon» — кремний).
Ключевые слова: QSAR, дескрипторы, лекарство, дигерпиновый алкалоид, in vitro, in vivo.

INTRODUCTION

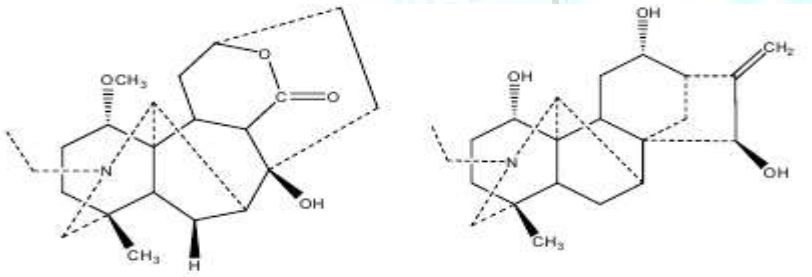
Currently in many areas of natural sciences depending on the quantitative changes in research methods the field of substance detection has changed. Physiologically active chemical compound finding has moved from a simple state to a multifactorial state. Currently using the most modern technologies and chemistry, biology and them medicine without being aware of the latest advances in related sciences it is unimaginable to get a tool. Finding new drugs and molecular genetics in the service of creation (enzymes or receptors to identify and clone genes that produce used), HTS (high-throughput) methods (chemical compounds fast and quality bioscreening, as well as hundreds to thousands high-speed computer technology for compound synthesis). Despite the advances in screening flow incorporated into combinatorial chemistry, unexpected biological intermediates are formed causes a decrease in the rate of absorption of the active drug. According to statistical data, 50% of medicinal products about 100,000 are natural compounds, half of which are from plants is extracted [1]. This is the molecular skeleton of plant matter so diverse (5,750 structures in 135,500 viewed compounds skeletons) by

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reducing the possibility of detection by the simple test method opens the way to different spectrums of research. [2]. In addition all advanced pharmaceutical companies in developed countries fills the library of national compounds every year, 90% of them are aimed at the synthesis of synthetic compounds, while 10% part focused on the screening of natural compounds [1]. That's the statistics a study of biological activity shows that 3% of natural compounds is considered sufficient to do [2]. Thus, based on natural compounds Bioorganic and natural compounds are still getting new medicinal preparations is an urgent problem of chemistry, and its development has peaks. Diterpene alkaloids are found in Aconitum, Delphinium, and Consolida plant species belonging to the Ranunculaceae family and have antiarrhythmic, antispasmodic, and other biological activities [95]. Diterpene alkaloids (aconitine alkaloids) are found in the composition of plants of the Garryceae, Rosaceae, Compositae, Escaloniaceae family. About 200 representatives of diterpene alkaloids are known to science, of which alkaloids such as lycoctonin and perhydrophenanthrine with molecular structure S19 and S20 have been widely studied.



Aconitine Lycoctonin



Heteratizin Napelline

1 – picture. Basic structure of diterpene alkaloids.

Heterethizine alkaloids and lappaconitine alkaloids are found in the form of amino alcohol, complex ester and other alkaloid modifications. Diterpene alkaloids containing bonds with acid residues at positions 6, 8, 14, 18 or modifications are generally considered toxic. Most often, S19 alkaloids are divided into aconitine (V) and lycoctone types.

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METHODS

Ph.D. in the Laboratory of Alkaloid Chemistry of the Institute of Chemistry of Plant Substances of the UzFA. B.S. Salimov studied the diterpene alkaloids in the above-mentioned plants, determined their structures, and determined their biological activities at the department of pharmacology and toxicology of Moscow State University. F.M. Tursunkhodjaeva and f.f.d. F.N. It was studied by Djakhangirov in Vitro method. As a result of in vitro studies, spasmolytic properties of diterpene alkaloids such as aconitine, lycoctonine, napellin and heteratizin were studied.

Table 1. EC50 values of some diterpene alkaloids determined in pharmacological studies

Alkaloids belonging to the caracolin type	EC50	Alkaloids of the lappaconitine type	EC50
Caracolin	540	Lappaconitine	65
1-O-Benzoylcaracholine	82	Sepaconitine	77
1-O-benzoyl-14-O-acetylcaracholine	0.39	Ranaconitine	36
1-O-acetyl-14-O-benzoylcaracholine	0.58	Septefin	17
1-O-Benzoylcarasamine	18	8,9-O-Diacetylappacanitine	16

In this scientific work, based on the pharmacological research of diterpene alkaloids, the structure-activity mathematical model was created using the QSAR (Quantitative Structure Activity Relationship) method. It is known that the QSAR method is one of the theoretical (In Silico) methods for the creation of new medicinal compounds aimed at reducing the cost of laborious, time-consuming and expensive pharmacological research, and has been widely used in recent years.

RESULTS

A satisfactory result was not obtained when searching for a model with 1 descriptor in the BuilDQsar program. The resulting models are considered satisfactory in cases where the correlation coefficient is R2>0.7 or greater. However, among the hundreds of one-descriptor models obtained, the model with the highest correlation coefficient was the model containing the E2s (2nd component accessibility WHIM index/ weighted by atomic electrotopological states) descriptor (Table 5). However, the correlation coefficient of this model is R=0.674 (R2=0.45).

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Table 5 lists two-descriptor models including Mor31e, GATS3v, and HATS6v, E2s descriptors. The R2 values of these models are also less than 0.7. Similarly, it was found that R2 values of mathematical models consisting of three descriptors are less than 0.7. It was found that the correlation coefficient of the mathematical model consisting of four descriptors found as a result of research is less than 0.7. Satisfactory mathematical models showing spasmolytic activity of diterpene alkaloids were obtained in models with 5 and 6 descriptors (Table 6). Descriptors included in these models include:

Mor31e (3D MoRSE – signal / weighted by Sanderson electronegativities)

D/Dr10 (topological descriptors – distance / detouring index of order 10)

BELp1 (BCUT descriptors – lowest eigenvalue n. 1 Burden matrix / weighted by atomic polarizabilities)

G1v (WHIM descriptors – 1st component symmetry directional WHIM index / weighted by atomic van der Waals volumes)

IVDE (topological descriptors – mean information content vertex degree equality)

MATS3p (2D autocorrelations – Moran autocorrelation – lag 3 / weighted by atomic polarizabilities)

GATS3v (2D autocorrelations – Geary autocorrelation – lag 3 / weighted by atomic van der Waals volumes)

GATS8e (2D autocorrelations – Geary autocorrelation – lag 8 / weighted by atomic Sanderson electronegativity)

E2s (WHIM descriptors – 2nd component accessibility directional WHIM index / weighted by atomic electrotopological states)

2 – Table.

1, 2, 3, 4, and 5 descriptor models with higher correlation coefficients generated in BuildQsar

Model descriptor	R	S	F	p	Q2	SPress
One descriptor model						
E2s	0.674	0.684	44.190	0.413	0.710	0.703
A model with two descriptors						
Mor31e, GATS3v	0.740	0.629	31,537	0.502	0.660	0.648
HATS6v,E2s	0.739	0.631	31.193	0.500	0.662	0.649
Three-descriptor model						
BELp1, E2s, GATS3v	0.814	0.549	33.295	0.610	0.590	0.573

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GATS3p, E2s, BELp1	0.810	0.554	32,475	0.604	0.595	0.578
GATS3v, E2s, BELv1	0.809	0.556	32.111	0.597	0.600	0.583
A model with four descriptors						
BELv1,GATS3p, E2s, MATS8e	0.831	0.500	32,944	0.667	0.551	0.530
BELp1,GATS3p, E2s, MATS8e	0.830	0.502	32,714	0.667	0.551	0.530
BELe1,GATS3p E2s, MATS8e	0.826	0.509	31,483	0.639	0.573	0.552
A five-descriptor model						
BELp1,D/Dr10, MATS3p, G1v, E2s	0.88	0.464	32,467	0.699	0.529	0.504
BELp1,D/Dr10 GATS3v, G1v, E2s	0.875	0.466	32.101	0.698	0.529	0.504

Correlation of spasmolytic activity values determined in the experiment and calculated based on the following 5-descriptor model is presented in the figure:

Y1=- 15.2262 BELp1 + 0.0093 D/Dr10 - 6.3206 GATS3v + 23.6437 G1v - 7.6414 E2s + 38.7512, R2=0.79

DISCUSSION

For the first time, the spasmolytic activity of diterpene alkaloids was studied by QSAR analysis method. Dividing diterpene alkaloids into working and test groups, a mathematical model was created based on the working group. It was also checked based on the test group. As a result of the research, mathematical models consisting of 5-6 descriptors representing the spasmolytic activity of diterpene alkaloids were found. At the moment, mathematical models that take into account quantum chemical descriptors are being developed.

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