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MATHEMATICAL MODELS OF SPASMOLYTIC ACTIVITY OF DITERPENOID ALKALOIDS

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

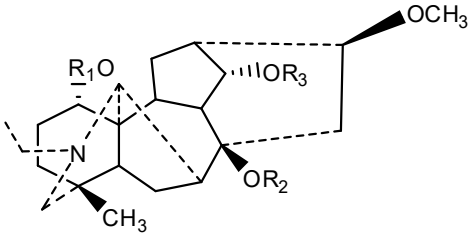
Introduction

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 reducing the possibility of detection by the simple test method opens the way to different spectrums of research

Model Building

73 diterpene alkaloids were selected in order to create mathematical models representing the spasmolytic activity of the compounds mentioned above and their various derivatives:



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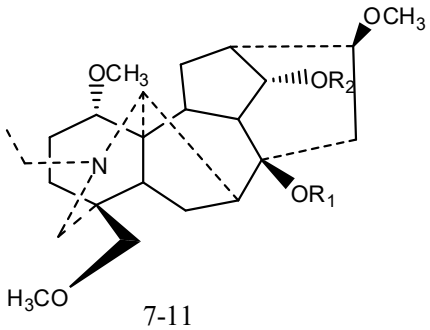

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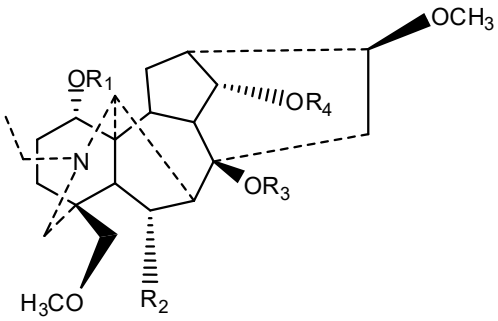

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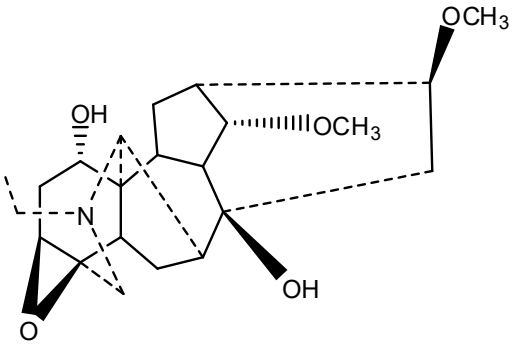

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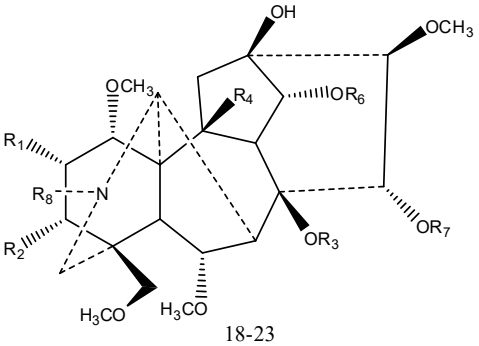

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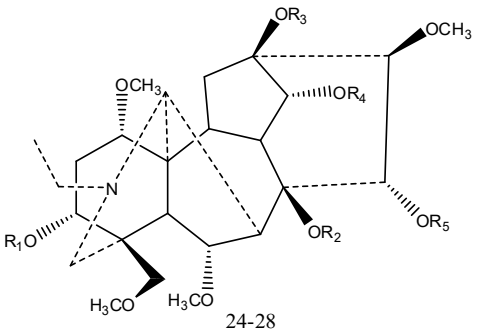

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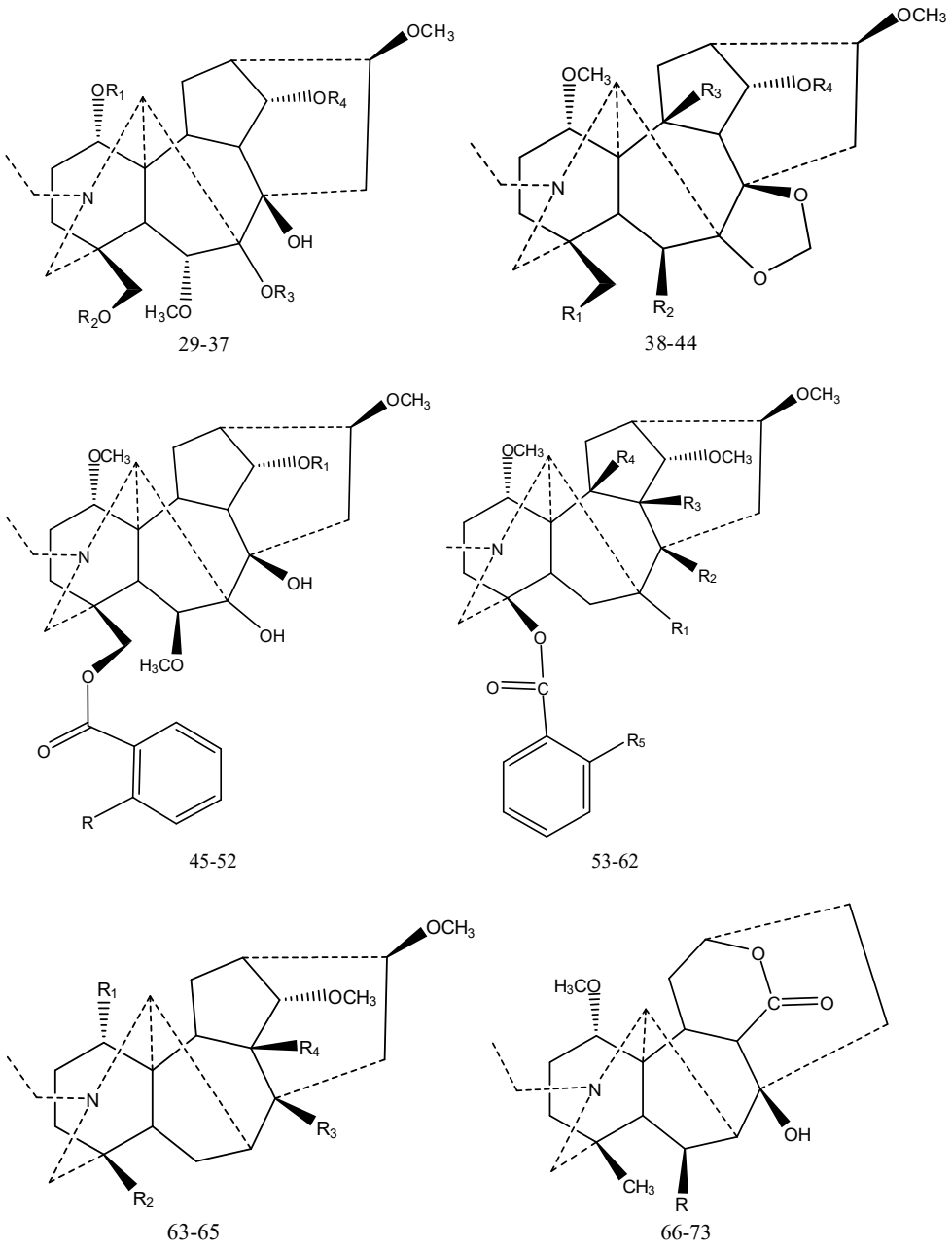


2 – picture. Properties of diterpene alkaloids.

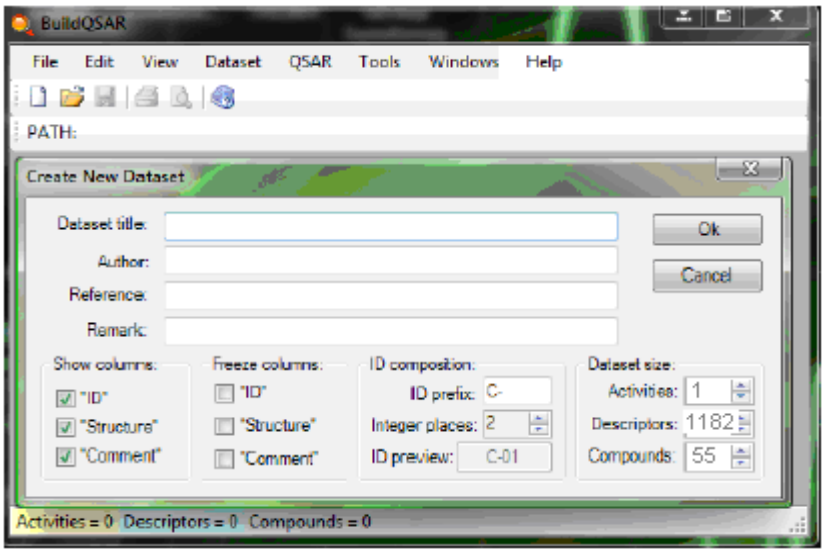
The initial geometries of these compounds were prepared using the HyperChem program and the descriptors were calculated. It is known that today there are more than 6000 types of descriptors, and the program DRAGON [89] created by Italian scientists is used to calculate them. We used DRAGON web version, one of the first versions of this program, which can calculate only 1497 descriptors. A total of 1497 descriptors in 18 categories were calculated in this

complex, taking into account the components, topology, electronic structure and other properties of the compounds.

The obtained descriptors of diterpene alkaloids were saved in Microsoft Excel 2010 through the DRAGON web version program, and the pEC50 spasmolytic activity values of the compounds and the relationship models between the descriptors were carried out in the BuildQSAR program. Results of EC50 values of diterpene alkaloids pEC50converted to values.

Descriptor Calculation

The process of finding mathematical models was carried out in the BuilDQsar program. Initially, a new window was opened showing the descriptor number (1182) and the combination number (55) in this program:



3 – picture. Overview of BuildQSAR

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). 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)

Single and Multiple Descriptor Models

The research resulted in satisfactory mathematical models consisting of 5-6 descriptors representing the spasmolytic activity of diterpenoid alkaloids.

Single Descriptor Model: E2s (WHIM component accessibility index weighted by atomic electronegativity states).

Multiple Descriptor Models: include descriptors Mor31e, GATS3v, HATS6v, BELp1, D/Dr10, G1v, IVDE, and others.

1 – 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,	0.814	0.549	33.295	0.610	0.590	0.573

GATS3v						
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

Conclusion

For the first time, the spasmolytic activity of diterpenoid alkaloids was studied using the QSAR method. Mathematical models consisting of 5-6 descriptors representing the spasmolytic activity of these compounds were found.

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