ФАРМАКОЛОГІЯ І ФАРМАЦІЯ

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ANALYSIS OF THE STRUCTURE INFLUENCE OF AMMONIUM HEXAFLUOROSILICATES ON THEIR ANTI-CARIES ACTIVITY

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ANALYSIS OF THE STRUCTURE INFLUENCE OF AMMONIUM HEXAFLUOROSILICATES ON THEIR ANTI-CARIES ACTIVITY
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Currently, ammonium hexafluorosilicates (AHFS) are being studied as promising new type of fluorine-containing agents, which, due to their specific mechanism of anti-caries action, have some advantages compared to known fluoride preparations.

The aim of this study was to identify, on the basis of the developed QSAR models, the main structural factors of AHFS molecules that determine their anti-caries activity, in particular, caries preventive efficacy and mineralization index.

Materials and methods. A training set consisting of 22 AHFS with cations of different types was formed for build QSAR models. SiRMS approach based on the simplex representation of the molecular structure was used for calculate structural descriptors. The calculation of descriptors was carried out at the 2D level of molecular structure modeling. In this case, the molecule is represented by a structural formula, taking into account the connectivity of atoms in the simplex, the type of atoms and the nature of the bond (single, double, triple, aromatic). It should be noted that the structural parameters were calculated only for organic cations (ammonium fragments), since the anion was always the same – SiF_6^{2-}.

Results. 3423 structural descriptors were calculated for each compound. Adequate QSAR PLS models were developed for the caries prevention efficacy and mineralization index of the studied salts. A randomization procedure (*Y-Scrambling*) was used to confirm the non-randomness of the developed QSAR models. An analysis of the relative contributions of different types of descriptors to the calculated values of the studied properties was performed.

Conclusions. As a result of the structural interpretation of the constructed QSAR models' information was obtained regarding the direction of modification of the structures of ammonium hexafluorosilicates to create more effective and promising caries prophylactic agents. Using molecular design, it was possible to construct a new molecule in which a certain balance of the influence of structural factors provides higher values of anti-caries activity characteristics than in the molecules of the training set.

Keywords: anti-caries agents, caries prevention efficacy, mineralization index, SiRMS – simplex representation of molecular structure, QSAR.

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АНАЛІЗ ВПЛИВУ БУДОВИ АМОНІЄВИХ ГЕКСАФТОРОСИЛІКАТІВ НА ЇХ АНТИКАРІЄСНУ АКТИВНІСТЬ
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Мета роботи – на основі розроблених QSAR моделей виявити основні структурні чинники молекул амонієвих гексафторосилікатів (АГФС), що визначають їх антикарієсну активність, зокрема карієс-профілактичну ефективність (КПЕ) і мінералізуючий індекс (МІ). Об'єктом дослідження була вибірка з 22 АГФС. Використовуючи 2D-симплексний підхід, побудовано адекватні QSAR PLS-моделі для КПЕ і МІ досліджуваних солей. Проведено аналіз відносних внесків різних типів дескрипторів

у розрахункові величини досліджуваних властивостей. У результаті структурної інтерпретації побудованих QSAR моделей одержано інформацію щодо напряму модифікації структур амонієвих гексафторосилікатів для створення більш ефективних та перспективних антикарієсних агентів. За допомогою молекулярного дизайну сконструйовано нову молекулу, у якої певний баланс впливу структурних чинників забезпечує більші значення показників антикарієсної активності, ніж у молекул навчальної вибірки.

Ключові слова: антикарієсні агенти, карієс-профілактична ефективність, мінералізуючий індекс, SiRMS – симплексне представлення молекулярної структури, QSAR.

Introduction

As is well known, the so-called “fluoride revolution” [1], that is the widespread implementation of fluoride-based caries prevention methods at municipal and regional levels, the introduction of new fluoride materials and their application technologies in dental practice [2–4], and the elucidation of the mechanisms of the anti-caries action of fluorides [5–7], has led to significant improvements in the dental health status of populations in many countries worldwide. Despite ongoing active research on non-fluoride anti-caries agents (including antibacterial peptides, for example [8], silver nanoparticles [9; 10]), fluoride preparations continue to dominate caries treatment and prevention for caries. Moreover, interest from researchers and clinicians in this type of therapeutic agents has not diminished even after more than 100 years since their discovery [11]. Currently, ammonium hexafluorosilicates (AHFS) [12; 13] are being investigated as promising new fluoride-containing agents. Due to their specific mechanisms of anti-caries action, these compounds possess certain advantages compared to conventional fluoride preparations. It should be noted that both attempts to interpret existing research results on the anti-caries activity of AHFS and predictions of the anti-caries characteristics for new compounds in this series encounter certain difficulties. In this context, studies aimed at identifying relationships between anti-caries activity indicators and the structural characteristics of AHFS using the QSAR formalism undoubtedly represent a valuable and promising research direction.

The aim of the study was to identify, based on the developed QSAR models, the main structural factors of AHFS molecules that determine their anti-caries activity, in particular, caries preventive efficacy (CPE, %) and mineralization index (MI) [14; 15].

Materials and Methods

The dataset used for developing the QSAR models consisted of 22 AHFS with cations of various types, including 15 salts of N-containing heterocyclic cations and 7 arylammonium salts. The properties under study were caries prevention efficacy (CPE) and mineralization index (MI) of the above salts. The structures of the AHFS used in this study, along with their corresponding property values [12, 14, 16] are listed in Table 1.

Table 1

Structures and anti-caries characteristics of AHFS

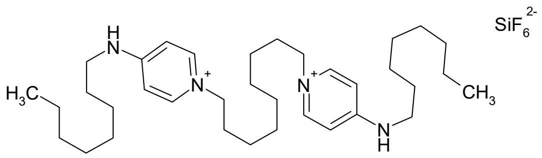
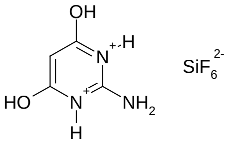
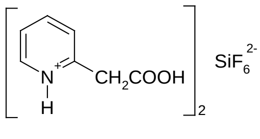
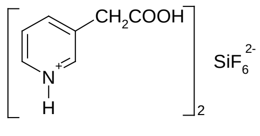
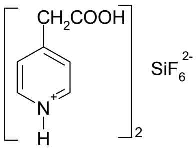
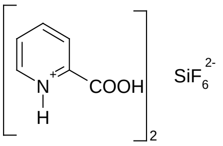
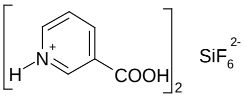
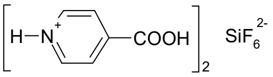
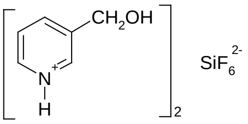
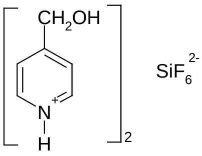
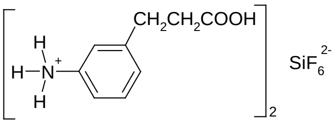
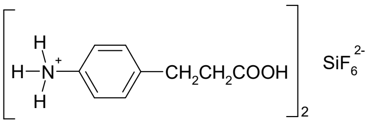
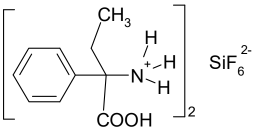
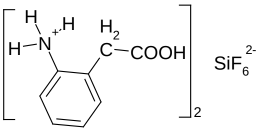
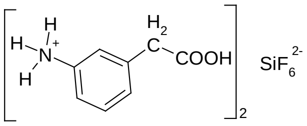
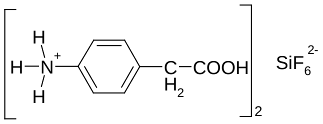
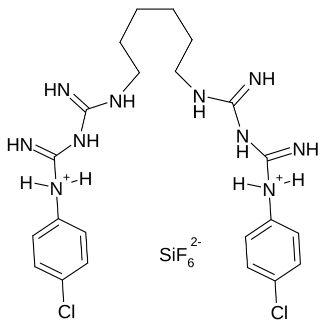
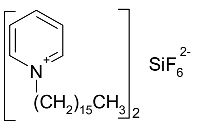
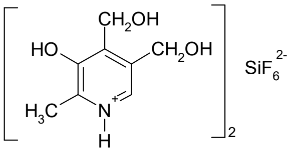
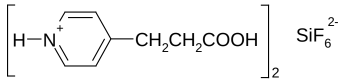
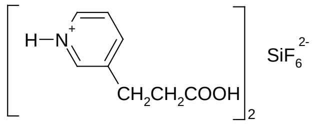
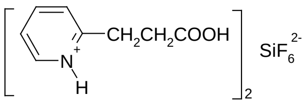
№	Structure of hexafluorosilicate	CPE, %	MI
1		36.4	27.8
2		45.5	39.2
3		6.8	84.6
4		11.4	76.1
5		45.5	50.5

Table 1

6		35.7	45.5
7		37.6	35
8		39.9	33
9		31.7	95.6
10		41.5	105.2
11		23.7	15.1
12		38.5	15.4
13		26.3	16.1
14		28.6	112.8
15		59.5	126.3
16		64.3	123.9

Continuation тable 1

17		79.2	71.5
18		79.2	96.8
19		79.2	100.5
20		39.0	69.25
21		51.2	84.76
22		41.5	74.31

At the previous stage of this study, all molecular structures of the organic cations (ammonium fragments) were modeled using the Molecular Modeling System HyperChem™[1]. For all investigated compounds the structural parameters were calculated using the SiRMS[2] approach [17], which is based on the simplex representation of the molecular structure. This approach has proven effective for solving various QSAR/QSPR tasks [17], in particular, for building QSPR models for the water solubility of similar AHFS and analyzing the influence of H-bond on their water solubility [18].

The SiRMS approach involves isolating and counting different four-atom molecular fragments (simplexes) of fixed composition and structure. In addition to four-atoms, the fragments of other sizes (two-, three- etc.) can also be calculated.

The ability to perform variants of the differentiation of simplex vertexes (atoms) is an important feature of this approach. The differentiation of atoms in these simplexes is performed not only by their labels (atom symbols), but also based on the different atom properties. Different physicochemical characteristics can be used for atom differentiation in a simplex, in particular: atom partial charge, lipophilicity, electronic polarizability, van der Waals (VDW) interaction parameters, the ability to be donor/acceptor of potential H-bond, etc. The details of the calculation of simplex descriptors are described in [17]. The QSAR models developed in the framework of this approach are easily interpreted.

In this study the following schemes of dividing the atom properties into intervals were used in the calculation of simplex descriptors:

electronegativity (en): A <2.19≤ B <2.5≤ C <3 ≤ D;

electronic refraction (rf): A <1.5 ≤ B <3 ≤ C <8 ≤ D;

atomic charge (chg): A <-0.13 ≤ B <-0.02 ≤ C <0.09 ≤ D <0.19 ≤ E <0.30 ≤ F <0.41 ≤ G;

lipophilicity (lip): A <-1.51 ≤ B <-0.96 ≤ C <-0.42 ≤ D <0.13 ≤ E <0.68 ≤ F <1.23 ≤ G;

VDW attraction (attr): A <50 ≤ B <100 ≤ C <250 ≤ D <400 ≤ E <650 ≤ F <2000 ≤ G;

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[1] *HyperChemTM, (2002). HyperCube, Inc. URL: http://www.hypercubeusa.com*

[2] *SiRMS – Simplex Representation of Molecular Structure.*

VDW repulsion (rep): A <20.000 ≤ B <32.000 ≤ C <50.000 ≤ D <100.000 ≤ E.

All atoms corresponding to simplex vertices were also divided into three groups: D – donors of potential H-bond, A – acceptors of potential H-bond and I – indifferent ones.

Integral descriptors, which characterize the molecule as a whole, were used in addition to the calculated local simplex descriptors, in particular, molecular mass, molecular refraction, lipophilicity, equalized electronegativity [17].

The calculation of descriptors was carried out at the 2D level of molecular structure modeling. In this case, the molecule is represented by a structural formula, taking into account the connectivity of atoms in the simplex, the type of atoms and the nature of the bond (single, double, triple, aromatic). It should be noted that the structural parameters were calculated only for organic cations (ammonium fragments) because the anion SiF_6^{2-} was the same in all cases. All values of structural parameters were multiplied by a coefficient (1 or 2) depending on the number of cations in each specific ammonium salt. Thus, a total of 3423 structural descriptors were calculated for the investigated molecules.

The relationships between calculated descriptors and investigated properties were established with the method of partial least squares (PLS) [19]. This statistical method has proven itself well for solving various QSAR/QSPR tasks.

Research results and their discussion

To obtain PLS models, the procedures of Automatic Variable Selection (AVS) and Genetic Algorithm were used. To determine the influence of different structural factors on the CPE and MI in the construction of 2D PLS QSAR models **M1** and **M2**, respectively, all 22 studied hexafluorosilicate cations were included in the training set. Such models **M1** and **M2** are approximated. We tried to use the maximum of the available experimental information that was available to solve the interpretation problem.

At the previous stage mutually-correlated and constant parameters were eliminated and Trend Vector procedures were used to select the initial sets of descriptors for developing of PLS – models [20]. The use of these procedures reduces the count of variables by several times that allows to eliminate the "noise" from the excessive number of descriptors and to obtain more adequate models. Thus, after using the above procedures the number of most significant structural parameters for CPE was 71, and for MI – 68, respectively.

Model **M1** demonstrated the following statistical characteristics: number of latent variables A = 1, coefficient of determination $R^2 = 0.73$, coefficient of determination for cross-validation $Q^2 = 0.66$, standard error for training set S (ws) = 10.4, standard error for cross-validation S (cv) = 12.1.

The *Y-Scrambling* procedure [17] was used to confirm the "nonrandomness" of the developed QSAR models. This procedure consists in creating models by random permutation of the property values. The statistical characteristics of such random models should be significantly lower than statistical parameters for developed real QSAR models. One hundred iterations were carried out by mixing CPE values. The models obtained using the *Y-Scrambling* procedure had low values of $R^2_{(Y\text{-}scr)} = 0.27 \pm 0.03$ and $Q^2_{(Y\text{-}scr)} = 0.11 \pm 0.08$, indicating the non-randomness of the established relationship between the structure of compounds and their CPE values obtained from the previous model **M1**.

Model **M2** had the following adequate statistical characteristics: A = 1, $R^2 = 0.84$, $Q^2 = 0.76$, S (ws) = 14.4, S (cv) = 18.6. As a result of using the *Y – Scrambling* procedure during 100 iterations with random shuffling of MI values, models with low values of $R^2_{(Y\text{-}scr)} = 0.20 \pm 0.03$ and $Q^2_{(Y\text{-}scr)} = 0.09 \pm 0.03$, respectively, were constructed. The results obtained in this case also indicate the non-randomness of the relationship between the structure and mineralization index of investigated compounds obtained from the model **M2**.

It is important to emphasize that models **M1** and **M2** were used for physicochemical and structural interpretation. The structural parameters, their relative contributions, and the total value of these contributions for each atomic property separately for the developed QSAR models **M1** and **M2** to assess the relative influence of various physicochemical factors on the properties of the studied compounds are listed in Table 2. Thus, the relative contribution of simplexes in which the differentiation of vertices corresponds to the atom charges reflects the role of electrostatic factors; the relative contribution of simplexes in which the atoms are differentiated by lipophilicity reflects the role of hydrophobic factors, etc.

An analysis of the relative contributions of different types of descriptors to the calculated CPE value (Model **M1**) (Table 2) showed that electrostatics has the greatest influence, accounting for approximately 79% of the effect on the CPE of the studied compounds. The importance of these factors is evident given the ionic nature of the investigated substances. A noticeable, though somewhat smaller, contribution comes from van der Waals interactions – around 16%.

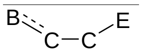
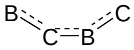
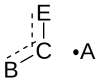
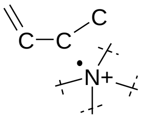
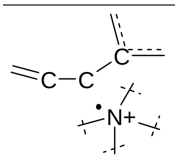
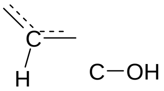
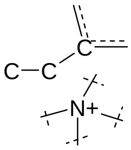
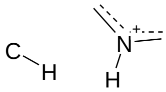
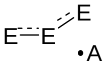
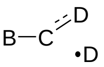
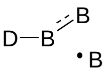
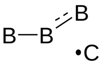
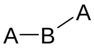
In the case of MI (Model **M2**), the most significant contribution comes from the nature of the atoms, which reflects the individuality of atoms with their full set of properties; this factor accounts for 58% of the influence. Electrostatic interactions also play a substantial role, contributing approximately 33%. Unlike CPE, MI is additionally influenced by lipophilicity, which contributes about 9%.

A structural interpretation of the QSAR models M1 and M2 was subsequently carried out. The relative influence on CPE and MI of certain substituents in the aromatic and heteroaromatic core (Fig. 1), substituents at the quaternary Nitrogen atom (Fig. 2), and the relative position of substituents in the aromatic (heteroaromatic) core (Fig. 3) was analyzed. The provided information clearly shows that the influence of various structural fragments on CPE and MI does not correlate with each other. Therefore, when designing new promising caries-preventive agents, if one seeks to maximize one of the two activity indicators (CPE or MI), the other becomes relatively less significant (Fig. 4).

Nevertheless, through molecular design, we succeeded in identifying a balance of structural factors influencing caries-preventive activity, such that the designed compound

Table 2

Relative influence of some structural parameters on CPE (model M1) and MI (model M2)

	Model M1		Model M2	
Atom property	**Descriptor**	**Contribution, %**	**Descriptor**	**Contribution, %**
Charge	B—B B=C	15.0		18.6
	A—D C—C	14.8	E—E C—C	8.2
		13.0	–	
		11.4	–	
	B=B C—C	7.8	–	
	C=E C=E	6.6	–	
Total		68.6		26.8
Type[1]		5.2		20.0
				11.6
				15.9
	–			10.6
Total		5.2		58.1
Lipophilicity	–			9.2
Electronegativity	–			5.9
VDW repulsion		11.3	–	
		5.0		
Total		16.3		
Electronic refraction		9.9		

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[1] *Reflects the individuality of atom with its full set of properties*

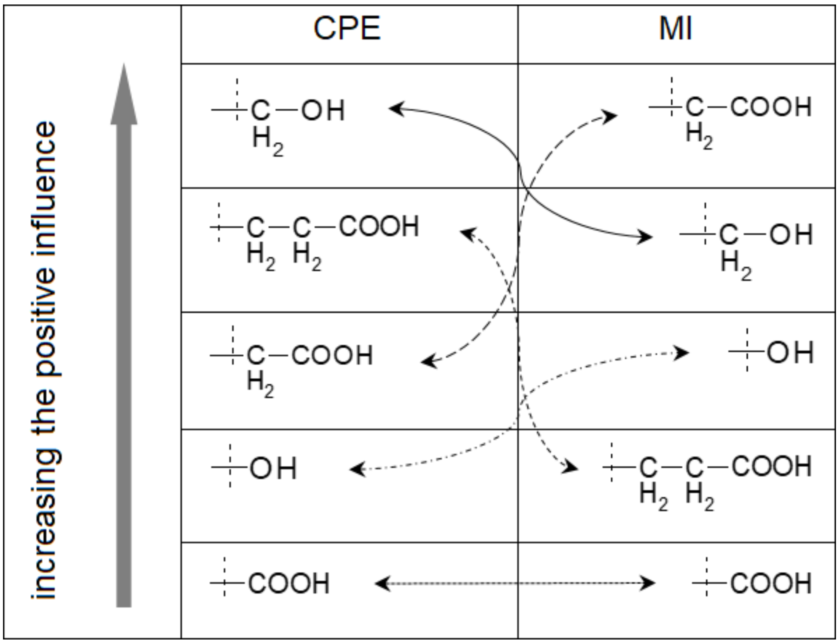


Fig. 1. Relative influence of substituents in the aromatic or heteroaromatic cation core on CPE and MI for investigated salts

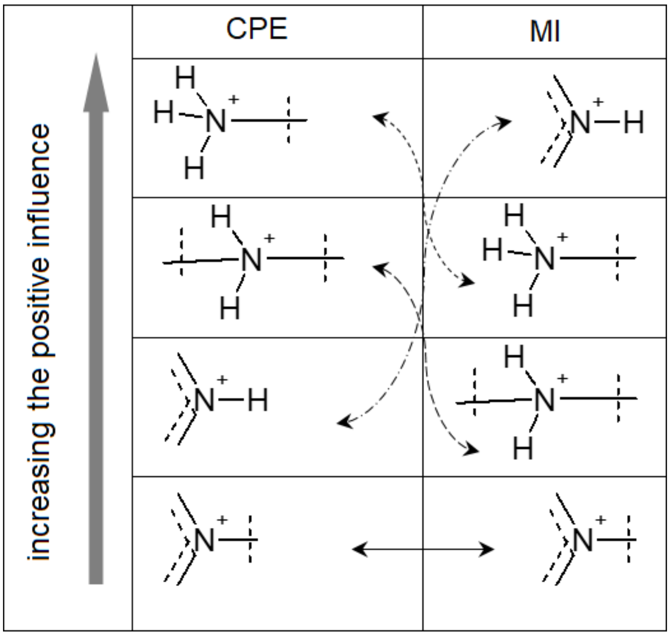


Fig. 2. The sequence of changes in the relative influence of substituents in the N$^+$-containing fragment on CPE and MI

(see Fig. 4, B) exhibits relatively high activity with respect to both parameters.

It should be noted that, in order to assess the parameters of CPE and MI for new substances not included in the training set, QSAR models with proven predictive ability are required. In fact, it is necessary to demonstrate the adequacy of the QSAR models for test sets. For this purpose, a portion of the molecules (specifically, 20% of the total number of molecules in the dataset) is excluded from the model-building process, and the remaining molecules form the training set. After the model is built, it is used to predict the properties of the test compounds.

Given that the full set of studied compounds is relatively small, the method used to evaluate the predictive ability of the constructed QSAR models was based on the formation of test sets using a structural dissimilarity (SD) matrix of the molecules. After calculating the descriptors for all compounds in the sets, the SD matrix was constructed. The measure of SD between molecules M and M' is the Euclidean distance between the molecules in the space of structural parameters S:

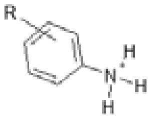
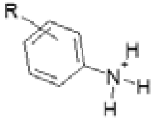
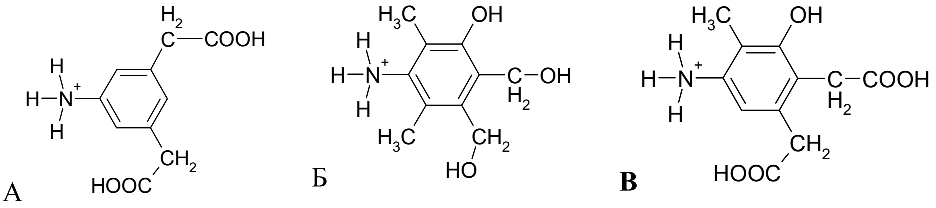
R	CPE		MI	
				
$-COOH$	p > m > o		o >p = m	
$-CH_2-OH$	p > m		p = m	
				
$-CH_2-COOH$	p > m> o	p > m > o	m > o > p	p > м = o
$-CH_2-CH_2-COOH$	p > m > o	p > m	o > m = p	m = p

Fig. 3. Relative influence of some substituents in the aromatic or heteroaromatic cation core on anti-caries activity (CPE and MI) for investigated salts



CPE = 58; MI = **165**　　CPE = **90**; MI = 60　　CPE = **92**; MI = **131**

Fig. 4. Predicted CPE and MI values for new designed molecules

$$SD(M,M')=\sqrt{\sum_{i=1}^{n}(S_i-S'_i)^2}\,,$$

where n – a count of molecules in the studies set.

The entire range of values of the studied properties is divided into specific groups. The number of groups is a tunable parameter; in this study, the number of groups was set to 4, as 20% of the molecules needed to be included in the test set. The test set included compounds from different activity groups that exhibited the minimum total structural dissimilarity (SD) with all structures in the studied dataset. This method of forming the test set ensures representative and diverse training sets, which allows for model building without significant loss of structural information.

Thus, for each property, datasets containing training and test sets were formed. The developed models **M3** (for CPE) and **M4** (for MI) demonstrate sufficient predictive capability. For CPE, model **M3** demonstrated the following statistical characteristics: number of latent variables A = 1, coefficient of determination R^2 = 0.81, cross-validated coefficient of determination Q^2 = 0.61, coefficient of determination for the test set R^2_test = 0.60, standard error for the training set S(ws) = 9.0, standard error for cross-validation S(cv) = 13.6, and standard error for the test set S(ts) = 12.3.

For MI, model **M4** showed the following statistical characteristics: A = 1, R^2 = 0.82, Q^2 = 0.71, R^2_test = 0.74, S(ws) = 15.9, S(cv) = 21.3, and S(ts) = 16.6.

Conclusions

As a result of the study, adequate 2D PLS QSAR models were developed, which not only qualitatively describe the influence of molecular structure on caries-preventive activity (CPE and MI), but also satisfactorily predict the values of these properties for new molecules that are structurally similar to those in the training set.

Through molecular design, a new compound was designed in which a certain balance of structural factors leads to predicted CPE and MI values exceeding those of the molecules in the training set. It is anticipated that future experimental studies will confirm these predictions obtained from the QSAR models.

Thus, the insights gained from the interpretation of the QSAR models highlight potential directions for modifying AHFS structures in order to develop more effective and promising caries-preventive agents.

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