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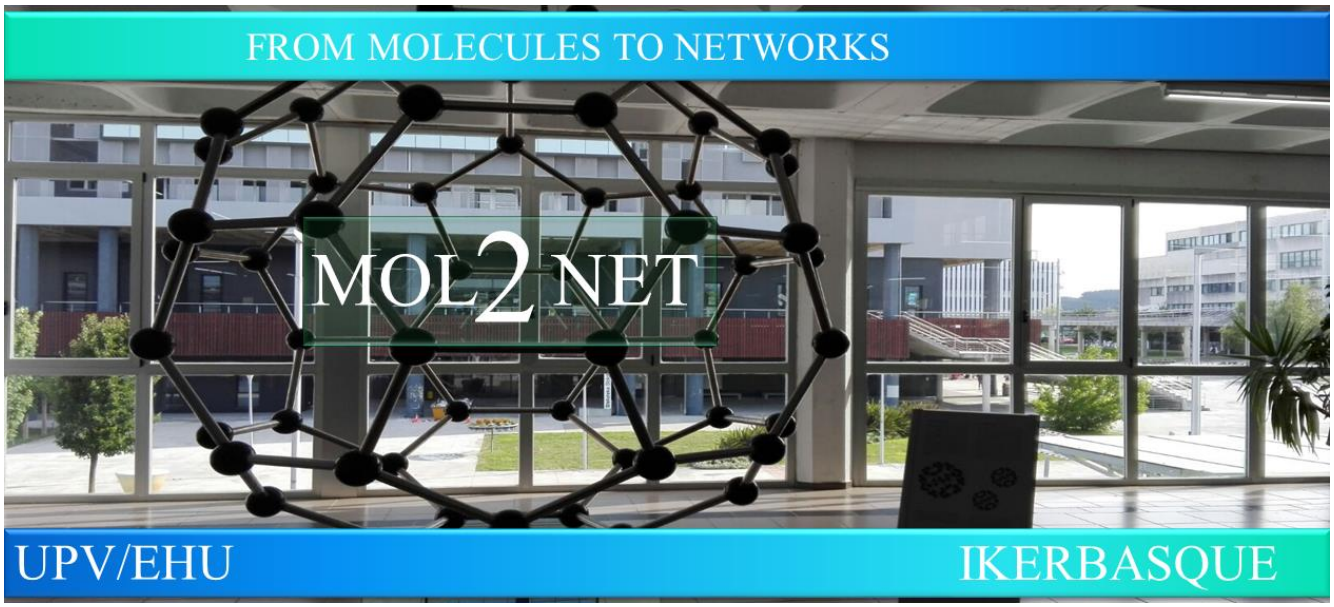

Modern approaches of computer support for virtual screening of antioxidants

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For the first time, the mathematical and theoretical foundations of a complex approach to the creation of a computer program for the virtual screening of NO scavengers in a number of newly synthesized compounds were developed. Approaches to the implementation of the software complex are described. In our work, for the first time, the antioxidant activity of 532 xanthine derivatives was evaluated in vitro for NO inhibition. For the first time, with the help of semi-empirical quantum chemical methods, the main descriptors of the frontier molecular orbitals of xanthine derivatives have been substantiated by their influence on the ability of these compounds to bind NO. This research aims to assess the in vitro antioxidant properties of 532 xanthine derivatives with regard to NO inhibition. The dependence of antioxidant activity on the quantum chemical parameters of xanthine derivatives was analyzed using machine learning algorithms using the following models: Linear Regression, Support Vector Machine Regression, Random Forest Regression, Gradient Boosting Regression, K-Nearest Neighbors

Regression. As a result of our analysis, we tested several models for solving regression problems. The best models without optimization turned out to be the "Support Vector Machine Regression" and "K-Nearest Neighbors Regression" models. When optimizing the studied models, the Gradient Boosting Regression model showed the best generalizing ability with an error within 16%. This model can be used for the prediction of antioxidant activity based on quantum chemical parameters. The model's quality can be further improved by increasing the training and test samples, as well as expanding the features to deepen the model and improve the generalization ability. A program of virtual screening of substances with the properties of NO scavengers has been developed and created. In the process of testing the new synthesized xanthine derivatives, a computer program made it possible to predict the most pronounced properties of the NO scavenger in 8-benzylaminotheophilinyl-7-acetic acid hydrazide (C-3). In vitro experiments confirmed the prediction of the properties of the NO scavenger in C-3 (267.3%). Addition of C-3 (10^{-5} M) to the incubation mixture leads to a decrease in nitrotyrosine by 45% and oxidized glutathione by 53.2% concomitantly with an increase in the concentration of reduced glutathione by 43.8% and increase in the activity of GSH-dependent enzymes - GPR by 337% and GR by 195% ($p < 0.05$). It should be noted that the antioxidant effect of C-3 is accompanied by an increase in concentration of HSP_{70} by 34.7%. By regulating the level of NO and its cytotoxic forms, C-3 is able to reduce the suppression of GSH, which determines the concentration of HSP_{70}. In terms of potency, C-3 is significantly superior to Mexidol (10^{-5}M). The obtained results in vitro confirm the results of the NO scavenger's C-3 compound obtained as a result of the virtual screening..

Scientific novelty. For the first time as a result of optimization of purposeful search of NO scavengers among xanthine derivatives and creation of a computer program of virtual screening with the help of machine learning algorithms using the "Gradient Boosting" model, as well as in vitro and in vivo experiments revealed 8-benzylaminotheophilinyl-7-acetic acid hydrazide (C-3). It was first shown that C-3 in the model of myocardial infarction and ICH inhibits the expression of eNOS and iNOS mRNA in the brain and myocardium, and in the ICH model increases the concentration of HSP70 in the brain of experimental animals and improves working and reference memory in experimental animals.

The practical significance of the results. The created program of virtual screening of NO scavengers can be used to optimize the targeted search for new antioxidants among newly synthesized compounds and to plan the synthesis of new substances.

Web applications have a number of advantages over standard desktop applications. Namely:

- Web applications are more cost-efficient and easier to use. Using web-based applications, enterprises and companies can reduce the cost of maintaining IT departments that are responsible for installing software and servicing it. In this case, all you need is a computer with a browser and Internet or corporate network connection to use the program.
- Web application updates are much cheaper and simpler. The cost of software maintenance is always of great importance. Updating it is very similar to installing it, so the benefits that have been mentioned apply in this situation as well.

- Web applications are more versatile and practical for the end user. It is enough to install a web application on a server running under any modern operating system, and users will be able to use it via the Internet on any computer or mobile device.
- Web applications facilitate the organization of data storage. If there is a need to access the same data from different places, then it is much easier to organize their storage in one place, instead of scattering them across different databases. This eliminates the need for synchronization and increases the degree of their security.

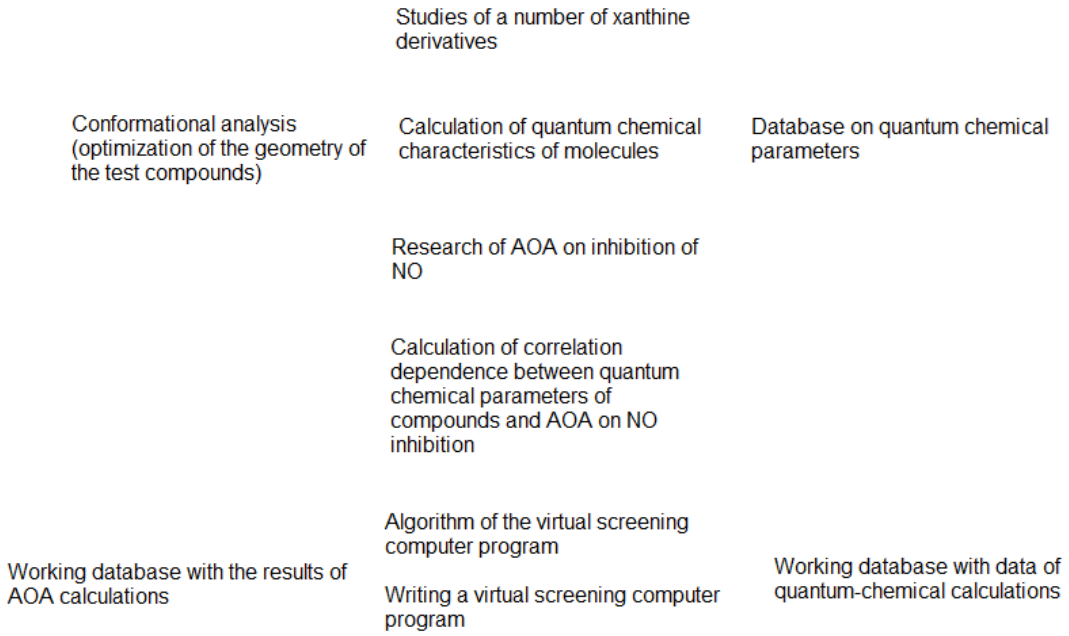

Fig. 1. Scheme of the electron-topological approach for studying the structure-antioxidant activity relationship.

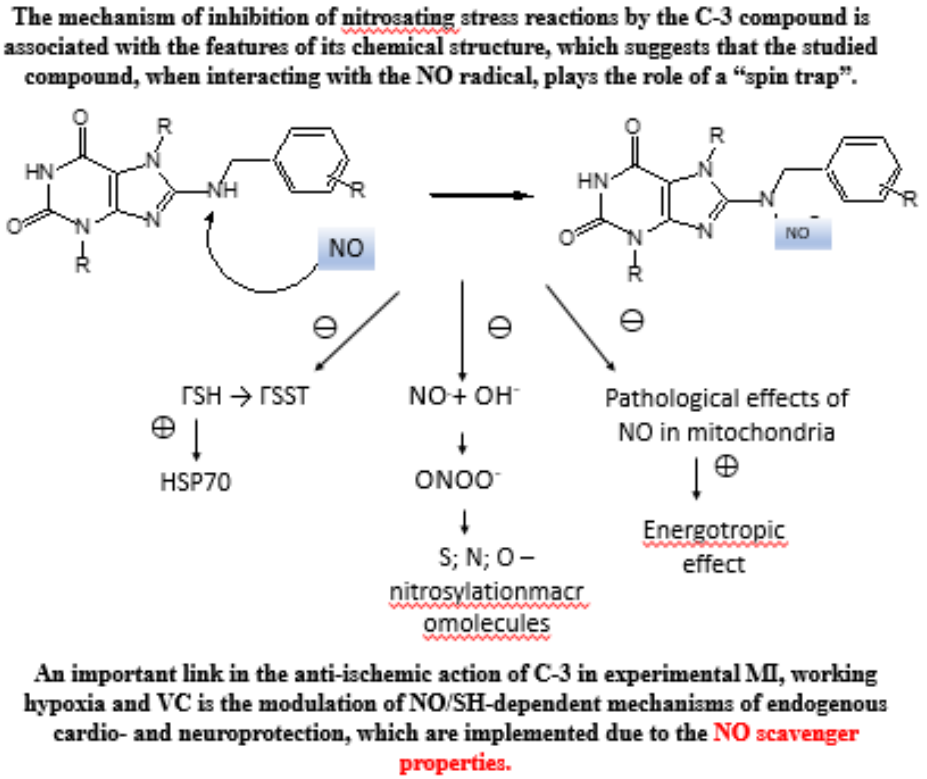

Fig.2. Hypothetical mechanism of action of the new compound C-3

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