APPLICATION OF TOPOLOGICAL INDICES IN PREDICTING THE PROPERTIES OF SELECTED ANTIMICROBIAL AND IMMUNOSUPPRESSIVE COMPOUNDS

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ABSTRACT

Rapid advances in technology have increased attention to computational methods as effective tools for predicting the physicochemical properties of biologically active compounds, such as lipophilicity, among others. Therefore, there is a great need to develop new and accurate in silico models that can be based on structural descriptors such as topological indices. These are sets of numerical descriptors that characterize the molecule under study. It is possible to represent it in the form of a graph, in which atoms are vertices and edges are covalent bonds. The arrangement of the individual elements of a graph is closely related to the topology and geometry of the molecule under study, and this results in a correlation with its pharmacokinetic properties [1].

AIM OF THE WORK

The aim of this work was to calculate topological indices for selected groups of antimicrobial and immunosuppressive drugs and to evaluate the usefulness of these structural descriptors for predicting selected ADME/T properties of the studied molecules.

METHODS AND MATERIALS

In this study, topological indices based on the adjacency matrix were calculated: Gutman (M, M^v), Randić ($^0\chi$, $^1\chi$, $^0\chi^v$, $^1\chi^v$) and topological indices based on the distance matrix: Wiener (W), Rouvray-Crafford (R) and Pyka (A, ^0B, ^1B). These indices were calculated according to their authors' formulas [1-4]. The drug groups studied were antimicrobial compounds (delafloxacin, linezolid, sutezolid, ceftazidime) and immunosuppressive (everolimus, zotarolimus) compounds. Linear regression analysis was used to obtain the results presented in Figures 1-3, which were performed using Statistica 13.3 software. The data used to calculate the correlations were the values of lipophilicity parameters obtained experimentally by the reversed-phase thin-layer chromatography (RP-TLC) technique using the stationary phases - $RP2F_{254}$, $RP18F_{254}$ and $RP18WF_{254}$ chromatographic plates and the mobile phases - a mixture of ethanol with water, acetonitrile with water and propan-2-ol with water, the values of lipophilicity parameters obtained using various computer algorithms, such as: properties dependent methods (AlogPs, MlogPs), principle of isolating carbons (ACD/logP), atom-based methods (AClogP, XlogP2, XlogP3), atom based and fragment contribution ($logP_{KOWWIN}$), fragment contribution methods (milogP, AlogP), taken from the Virtual Computational Chemistry Laboratory program and online database [5,6]. The physicochemical parameters of the tested substances were taken from the online database [7].

RESULTS

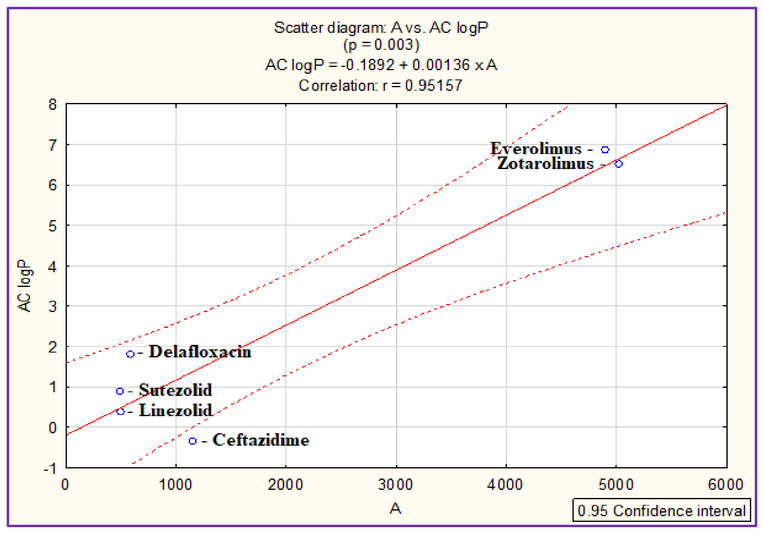

Fig. 1 Correlation plot between the value of the topological index A and the value of the computationally obtained lipophilicity parameter AC logP for the tested compounds (p=0.003).

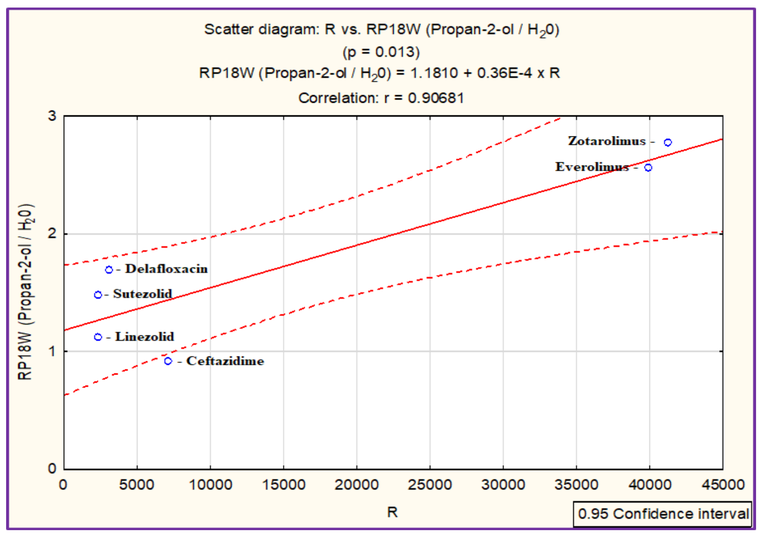

Fig. 2 Correlation plot between the value of the topological index R and the value of the experimentally obtained lipophilicity parameter RP18W (Propan-2-ol / H_20) for the tested compounds (p=0.013).

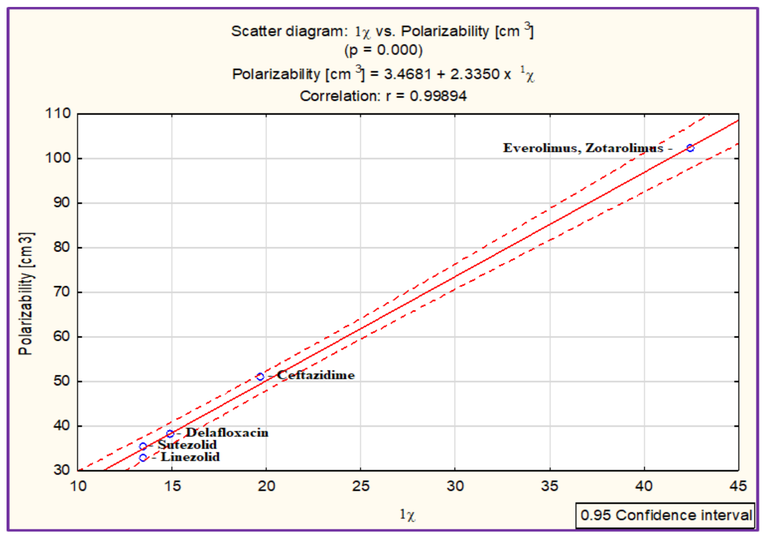

Fig. 3 Correlation plot between the value of the topological index $^1\chi$ and the value of the physicochemical property „Polarizability" for the tested compounds (p=0.000).

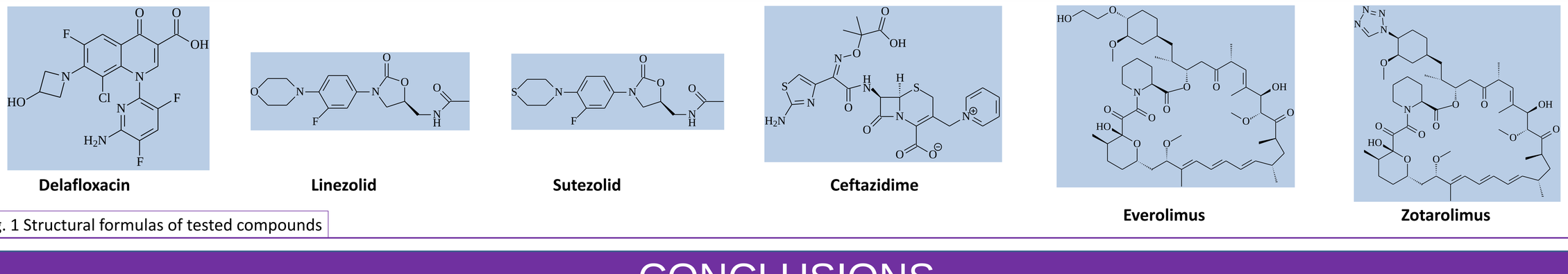

Fig. 1 Structural formulas of tested compounds

CONCLUSIONS

Examples of high-strength linear correlation plots between the values of topological indices and the values of lipophilicity parameters obtained by the experimental method and by using computer algorithms and physicochemical parameters are shown in Fig. 1-3. The performed studies suggests that structural descriptors such as topological indices can be a useful tool for predicting selected important ADME/T properties of drug substances, such as lipophilicity, for example. Our proposed method is fast, easy to use and economical. It is characterized by high efficiency, as can be seen in the posted Fig. 3, where the p-value is 0.000 and this indicates very strong correlation. The proposed method avoids costly laboratory experiments to test ADME/T properties by experimental methods.

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