Abstract

IN SILICO STUDIES OF THE STRUCTURE - ACTIVITY RELATIONSHIP OF SELECTED N-HETEROCYCLIC COMPOUNDS

Currently, the challenge for scientists is to search for compounds that may promote the formation of neoplastic diseases and for compounds with antitumor activity. One of the possible solutions for the development of new active substances is the structural modification of compounds with proven biological activity, which may lead to the formation of a new substance with properties other than its precursor. The most numerous group of carcinogenic compounds are aromatic amines. Polycyclic aromatic amines, nitrosamines, or alkyl anilines show direct mutagenic effects causing cancer in animals and humans. There is also a group of aromatic heterocyclic amines, the carcinogenic effect of which is triggered only by the amine-DNA adduct that is formed in the organism. Predicting the effect of structural changes on the activity of the compound allows the stability, efficacy and possible use of a newly prepared drug product to be assessed. In this case, the first step is to determine the acid-base properties of the compounds and the possibility of equilibria in the solution, which are crucial for understanding the biological activity, solubility, and lipophilicity of the substance, and indicate the possibility of interaction in the environment or a cell of a living organism, for example with DNA.

The work uses computational methods, which are a cheaper alternative to the experiment. Due to the rapid development of theoretical methods in recent years, better and better results are obtained, and the comparison with experimental data allows us to estimate the usefulness of these methods in determining the properties of the tested compounds belonging to a given group. The aim of this study was to determine *in silico* the physicochemical parameters of four selected aromatic heterocyclic amines belonging to the following skeleton derivatives: pyrazine (2-hydrazinopyrazine and its chloride derivative) and anilinesulfonamide (Schiff bases of sulfathiazole and sulfacetamide with a pyrrole ring). Calculations in the gas phase (structural and ionic analysis) were performed using the B3LYP/6-311+G** method for pyrazine derivatives and M06/6-311+ G(2d, 2p) for sulfonamide derivatives. The properties in water described by pKa and logP values were determined using the PCM/B3LYP/6-311+G ** and SMD/M06-2X/6-311+G ** methods for pyrazine derivatives and SMD/M06/6-311++G(2d, 2p) for sulfonamide derivatives. The analysis of the interactions of pyrazine derivatives with DNA was performed using the molecular docking method.

As a result of the calculations, the lowest energy forms of compounds in the gas phase were determined, the energy gaps of the HOMO-LUMO orbitals were determined in order to determine the influence of the substituent on their stability (for pyrazine derivatives); ionic forms were found for all tested compounds in the gas phase in order to establish the full deprotonation path, the values of deprotonation constants (pKa) were calculated based on the proposed path. In addition, for pyrazine derivatives, the possibility of penetration into the cells of the body was verified by determining their lipophilicity (logP) and the possibility of interaction with DNA being a potential molecular target of the tested systems was investigated. The tests were carried out in the gas phase and partly in a water model based on the DFT approach. The work is the first full description of the structure and properties of the studied objects described on the basis of theoretical research. The analysis of the obtained results shows that the use of in silico research in the discussed areas is most appropriate and gives qualitatively satisfactory results.