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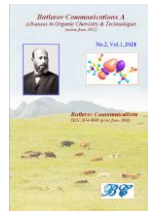

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Quantum chemical analysis of alkilarylsulfonamides interactions with α-carboangidrase hCA II

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Abstract

A quantum-chemical calculation of a number of alkyl-substituted benzenesulfonyl-amides was performed at the level of the DFT M06/6-311++G** (SMD) theory to determine the atomic electrostatic potential on sulfamide nitrogen atoms, the Hirschfeld charge on these atoms, the energies of the boundary orbitals, followed by the determination of the electronic chemical potential, rigidity and electrophilicity of the molecules of these compounds. A comparison was made between the quantum-chemical parameters of alkylbenzenesulfonyl-amide molecules and their inhibitory ability when interacting with α-carbonic anhydrase hCA II. It was found that the inhibition of α-carbonic anhydrase hCA II by alkyl-substituted benzenesulfonylamides is determined to a greater extent by the interaction of alkyl substituents with the amino acid environment of the active site of the enzyme than by the acidic properties of the sulfonylamides themselves, probably due to the comparability of the electronic and steric effects of the substituents. This is indicated by the discovered one-parameter relationships between the logarithm of the binding constant of α-carbonic anhydrase and the effective volume of alkyl substituents, the number of carbon atoms in the substituent, the accessible surface of the substituent, and the relative nucleophilicity of sulfonylamides with respect to Zn^{+2}. These dependences are inconsistent with the concept of inhibition of α-carbonic anhydrase by the anionic form of sulfonylamides; however, this contradiction is apparent due to the predominance of the hydrophobic interaction of the linker of the inhibitor with the amino acid environment of the active center of the enzyme over the Coulomb interaction of the anionic center of sulfonylamide (sulfonamide nitrogen atom) with zinc cation. These dependences have a quite definite physical meaning and are able to predict the result of inhibition of carbonic anhydrase by alkyl-substituted benzenesulfonamides of various classes, as well

as to indicate the relationship between different types of interactions in the inhibition of carbonic anhydrase both by coordinating the lone pair of electrons of the sulfamide nitrogen atom and zinc cation in the active enzyme center of carbonic anhydrase, and the determining role of hydrophobic interactions of the carbon skeleton of the carrier of the sulfamide group with the amino acid environment of the sulfonylamide molecule. The revealed one-parameter correlation ratios have correlation coefficients that exceed those for the literature multi-parameter ratios, which often have no physical meaning.

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