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Molecular Modeling of Structurally Diverse Compounds as Potential Therapeutics for Transmissible Spongiform Encephalopathy

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Abstract : Prion is a protein substance whose certain form is considered as infectious agent. It is presumed to be the cause of the transmissible spongiform encephalopathies (TSEs). The protein it is composed of, called PrP, can fold in structurally distinct ways. At least one of those 3D structures is transmissible to other prion proteins. Prions can be found in brain tissue of healthy people and have certain biological role. The structure of prions naturally occurring in healthy organisms is marked as PrPc, and the structure of infectious prion is labeled as PrPSc. PrPc may play a role in synaptic plasticity and neuronal development. Also, it may be required for neuronal myelin sheath maintenance, including a role in iron uptake and iron homeostasis. PrPSc can be considered as an environmental pollutant. The main aim of this study was to carry out the molecular modeling and calculation of molecular descriptors (lipophilicity, physico-chemical and topological descriptors) of structurally diverse compounds which can be considered as anti-prion agents. Molecular modeling was conducted applying ChemBio3D Ultra version 12.0 software. The obtained 3D models were subjected to energy minimization using molecular mechanics force field method (MM2). The cutoff for structure optimization was set at a gradient of 0.1 kcal/Åmol. The Austin Model 1 (AM-1) was used for full geometry optimization of all structures. The obtained set of molecular descriptors is applied in analysis of similarities and dissimilarities among the tested compounds. This study is an important step in further development of quantitative structure-activity relationship (QSAR) models, which can be used for prediction of anti-prion activity of newly synthesized compounds.

Keywords : chemometrics, molecular modeling, molecular descriptors, prions, QSAR
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