Investigation of Inhibition Properties of Human Dihydrofolate Reductase: A DFT-based QSAR Study

Sedat Karabulut[1], Natalia Sizochenko[2], Adnan Orhan[3] and Jerzy Leszczynski[2]

[1]Department of Chemistry and Biochemistry, University of Windsor, ON, Email: Sedat.Karabulut@uwindsor.ca
[2]Interdisciplinary Nanotoxicity Center, Department of Chemistry and Biochemistry, Jackson State University, USA
[3]Schoof of Medecine and Department Obstetrics & Gynecology, ludag University, Turkey

Diaminopyrimidine derivatives are frequently used as inhibitors of human dihydrofolate reductase (DHFR), treatment of human immunodeficiency virus is one of the well-known one. Dicyclic and tricyclic potential inhibitors of human dihydrofolate reductase (totally 47) were analyzed using the quantitative structure-activity (QSAR) analysis supported by DFT-based and DRAGON-based descriptors. A good correlation was generally obtained. Factors responsible for inhibition process were identified and discussed. The resulting model was validated via cross validation and Y-scrambling procedure.

As a result of multiple linear regression (MLR), mass-related descriptors and Sanderson electronegativity-related descriptors observed which provide the best correlations with the investigated phenomena. These descriptors reflect results from QSAR studies based on characteristics of human DHFR inhibitors.