American Journal of Applied Sciences 7 (7): 902-905, 2010
ISSN 1546-9239

Density Functional Theory Based Quantitative Structure Activity Relationship Study of 2,5-Bis(1-Aziridinyl)-p-Benzoquinones with Lymphoid Leukemia

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Abstract: Problem statement: QSAR techniques increase the probability of success and reduce time and coast in drug discovery process. The study presented QSAR investigation on 32 bioactive aziridinylbenzoquinones that have activity against lymphoid leukemia. **Approach:** Molecular descriptors, molecular weight, total energy, hardness, chemical potential, electrophilicity index, HOMO and LUMO energies were calculated. Initial geometry optimizations were carried out with the AM1 Hamiltonian. The lowest energy conformations were subjected to single point calculations by the DFT method by employing Beck's Three-Parameter hybrid functional (B3LYP) and pvDZ basis set. Several models for the prediction of biological activity have been drawn up by using the multiple regression technique. **Results:** A model with hapta parametric linear equation with R^2 value of 0.886 was presented. **Conclusion:** The biological activity of the studied compounds can be modeled with quantum chemical molecular descriptors.

Key words: Aziridinyl benzoquenones, lymphoid leukemia, QSAR, DFT, electrophilicity

INTRODUCTION

Quantum chemical descriptors have been extensively used in Quantitave Structure-Activity Relationship studies in biochemistry. Numerous reviews have been published on the applications of quantum chemical descriptors (Parthasarthi *et al*., 2004). The use of quantum chemical descriptors in the development QSAR has received attention due to reliability and versatility of prediction by these descriptors. For the calculation of the quantum chemical molecular descriptor used in QSAR studies, semi empirical methods such as AM1 and PM3 mainly have been used (Cavalli *et al*., 2006; Shaik *et al*., 2005). However, DFT method has been used recently for the prediction of physiochemical and biological properties of organic molecules (Shaik *et al*., 2010; Lei *et al*., 2009; Siu and Che, 2006). A large number of quinones both synthetic and natural occurring have been screened for their antitumor activity in addition to a wide variety of other bioactivities (Bender *et al*., 2007; Bernardo *et al*., 2004; Hargreaves *et al*., 1999). The most prominent chemical feature of these compounds is their ability to undergo redox cycling to generate reactive oxygen species which can damage tumor cell (Fotie *et al*., 2010). Several aziridinylquinones have undergone clinical trials as potential antitumor drugs (Rajski and Williams, 1997; Mayalarp *et al*., 1996; Moret *et al*., 1996; Gupta, 1994). These compounds can be activated toward alkylation as a result of bioreduction by the electron reducing enzymes or by two electron reducing compounds (Aiello *et al*., 2005). Limited number of studies has investigated the QSAR of these quinones. The aim of this study is to build QSAR models using multiple regression method, to investigate the correlations between the experimental biological activity and calculated molecular descriptors of a series of 2,5-Bis(1-aziridinyl)-p-benzoquinones as inhibitors against lymphoid leukemia L1210 in BDF_1 mice.

Theory: Hardness (η), chemical potential (μ) and electronegetivity (χ) are defined as (Bultink *et al*., 2003):

$$\eta = 1/2\left(\frac{\partial^2 E}{\partial N^2}\right)V(r) = 1/2\left(\frac{\partial \mu}{\partial N}\right)V(r) \quad (1)$$

$$\mu = -\chi = -\left(\frac{\partial E}{\partial N}\right)V(r) \quad (2)$$

where, E and V(r) are electronic energy and external potential of an N-electron system, respectively.

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