Chapter 11
Correlation of the Drug Activities of Some Anti–Tubercular Chalcone Derivatives in Terms of the Quantum Mechanical Reactivity Descriptors

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ABSTRACT

Under the QSPR/QSAR paradigm, a comparative study is made of the known drug activity of as many as 15 anti-tubercular drugs vis-à-vis the computed quantum mechanical global reactivity descriptors like global hardness, global softness and global electrophilicity index. The comparative study reveals that the experimentally determined activity of drug molecules, including its variation with side substitution on the parent moiety, correlate nicely with the theoretical descriptors. The global electrophilicity index of a molecule may be useful in predicting the mechanism of the drug receptor interaction. In addition, the authors predicted the QSAR models to correlate the antitubercular activities with quantum mechanical descriptors like global hardness, electronegativity, global softness, and global electrophilicity index. The multilinear model using all four global descriptors computed through PM3 method, effectively predicts the antitubercular activities for a series of chalcone derivatives. The high value of $R^2$ (0.961) supports the validity of that particular model. A nice correlation between the predicted and experimental activities validates the effort.

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INTRODUCTION

The central idea of chemistry is that the physical and chemical properties of molecules are determined by its geometrical as well as electronic structures. It is expected that all the chemical, biological and physical properties of a molecule must be coded in its structural formula. The challenge of fundamental science is to correlate structure with property. The drug is a molecule and bacteria are also bio-molecules and the interaction between the two is a chemical process and will occur in accordance with the fundamental laws of chemistry. It is reasonable to assume that nature has given a clue of the drug activity of molecules in their structure and it is the task of a scientist to locate and identify it and to link it with the process of curing i.e. the healing mechanism. The action of the potent carcinogens lies in their chemical formula and the electronic structures.

The branch of theoretical science which is engaged in studying the relationship between structure and property is labeled as Quantitative Structure Activity Relationship (QSAR) and Quantitative Structure Property Relationship (QSPR). Thus the jargon of the trade of Quantitative structure-activity relationships (QSAR) and Quantitative structure property relationships (QSPR) is the correlation of properties with structure in terms of some mathematical descriptors. The QSAR modeling is born in the toxicology field (Hansch & Leo, 1979). The central axiom of structure –toxicity modeling is that the toxicity of molecules is governed by their properties, which in turn are determined by their structures. The ultimate goal of QSAR/QSPR studies is to establish a direct relationship between structure and activity/property of bio-active compounds with some theoretical as well as experimental descriptors. The theoretical descriptors have quantum mechanical origin and are more reliable than the experimental descriptors as because there is no statistical fluctuation in the theoretical descriptors.

The quantum mechanical descriptors that are useful in QSAR/QSPR studies are the following: - (1) charge densities on atomic sites, (2) the dipole moment, (3) eigen values of the frontier orbitals, the HOMO and LUMO, (4) the HOMO-LUMO gap, (5) the chemical potential ($\mu$) or electronegativity ($\gamma$), (6) the global hardness ($\eta$), (7) the global softness $S$, (8) electrophilicity index ($\omega$). Of these, electrophilicity index ($\omega$), has special relevance in the present context because ligands binding phenomena are of general interest in catalysis and drug design and protein and DNA functioning. In addition to this list, some density functional theoretic local descriptors can also be invoked in this study. These are fukui functions and local softness and local philicity indices. The descriptors mentioned previously (Parr, Donnelly, Levy, & Plake, 1978; Parr & Pearson,1983; Parr & Yang,1984, 1989; Yang & Parr,1983; Parr, Szentpaly, & Liu,1999; Chattaraj, Maiti, & Sarkar, 2003; Chattaraj & Roy, 2007) play a critical role in correlating the structure with reactivity and the site selectivity of various bio-active molecules (Chatterje, Balaji, Matsunaga, & Mizukami, 2006; Roos, Loverix, de Proft, Wyns, & Geerlings, 2003).

In recent times, tuberculosis is one of the most common infectious diseases and it is a great threat to a large percentage of the world population. A recent survey reveals that in every year about two million deaths are caused due to the highly infective bacilli Mycobacterium tuberculosis (Blumberg, Michael, Leonard, & Jasmer, 2005; DeAngelis & Flanagin, 2005; DeAngelis & Flanagin, 2005; Dye, Watt, Bleed, Hosseini, & Raviglione, 2005). On the basis of the report of “World Health Organization” (WHO), it is clear that if the proper steps are not taken to control this diseases, by 2020 AD, nearly 70 million will die due to the infection (WHO, 2007). The main chemotherapeutic agents against TB are isonicotinic acid hydrazide, rifampicin, ethambutol, streptomycin, pyrazinamide, fluoroquinolones, ethionamide etc (Khasnobis, Escuyer, & Chatterjee, 2002). However, due to its serious
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