Abstract

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This project presents computational studies of various biological systems comprising of antioxidant compounds and metallo-complexes, anti-anthrax, and anti-endotoxins. These studies utilizes quantum chemistry for providing a physicochemical description of the molecular structures and data mining techniques for correlating the relationships that exists been the molecular structures and biological/chemical activities and properties.

Antioxidants play crucial roles in scavenging oxidative damages arising from reactive oxygen species. Bond dissociation enthalpy (BDE) of phenolic O-H bond has well been accepted as an indicator of antioxidant activity since phenols donate the hydrogen atom to the free radicals thereby neutralizing its toxic effect. The BDEs from a data set of 39 antioxidant phenols were modeled using computationally inexpensive quantum chemical descriptors with multiple linear regression (MLR), partial least squares (PLS), and support vector machine (SVM). The molecular descriptors of the phenols were derived from calculations at the following theoretical levels: AM1, HF/3-21g(d), B3LYP/3-21g(d), and B3LYP/6-31g(d). Results indicated that when MLR and PLS were used as the regression methods, B3LYP/3-21g(d) gave the best performance with leave-one-out cross-validated correlation coefficients (r) of 0.917 and 0.921, respectively, while the semiempirical AM1 provided slightly lower r of 0.897 and 0.888, respectively. When SVM was used as the regression method no significant difference in the accuracy was observed for models using B3LYP/3-21g(d) and AM1 as indicated by r of 0.968 and 0.966, respectively. The quantitative structure-property relationship (QSPR) model of BDE discussed in this study offers great potential for the design of novel antioxidant phenols with robust properties.

Superoxide anions are reactive oxygen species that can attack biomolecules such as DNA, lipids and proteins to cause many serious diseases. This study reports the synthesis of copper complexes of nicotinic acid with related pyridine derivatives. The copper complexes were shown to possess superoxide dismutase (SOD) and antimicrobial activities. The copper complexes exerted SOD activity in range of 49.07-130.23 microM. Particularly, copper complex of nicotinic acid with 2-hydroxypyridine was the most potent SOD mimic with an IC(50) of 49.07 microM. In addition, the complexes exhibited antimicrobial activity against Bacillus subtilis ATCC 6633 and Candida albicans ATCC 90028 with MIC range of 128-256 microg/mL. The SOD activities were well correlated with the theoretical parameters as calculated by density functional theory at the B3LYP/LANL2DZ level of theory. Interestingly, the SOD activity of the copper complexes was demonstrated to be inversely correlated with the electron affinity, but was well correlated with both HOMO and LUMO energies. The vitamin-metal complexes described in this report are great examples of the value-added benefits of vitamins for medicinal applications.

Nicotinic acid (also known as vitamin B3) is a dietary element essential for physiological and antihyperlipidemic functions. This study reports the synthesis of novel mixed ligand complexes of copper with nicotinic and other select carboxylic acids (phthalic, salicylic and anthranilic acids). The

tested copper complexes exhibited superoxide dismutase (SOD) mimetic activity and antimicrobial activity against Bacillus subtilis ATCC 6633, with a minimum inhibition concentration of 256 microg/mL. Copper complex of nicotinic-phthalic acids (CuNA/Ph) was the most potent with a SOD mimetic activity of IC(50) 34.42 microM. The SOD activities were observed to correlate well with the theoretical parameters as calculated using density functional theory (DFT) at the B3LYP/LANL2DZ level of theory. Interestingly, the SOD activity of the copper complex CuNA/Ph was positively correlated with the electron affinity (EA) value. The two quantum chemical parameters, highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO), were shown to be appropriate for understanding the mechanism of the metal complexes as their calculated energies show good correlation with the SOD activity. Moreover, copper complex with the highest SOD activity were shown to possess the lowest HOMO energy. These findings demonstrate a great potential for the development of value-added metallovitamin-based therapeutics.

Quantitative structure-activity relationship (QSAR) models were constructed for predicting the inhibition of furin-dependent processing of anthrax protective antigen of substituted guanidinylated aryl 2,5-dideoxystreptamines. Molecular descriptors calculated by E-Dragon and RECON were subjected to variable reduction using the Unsupervised Forward Selection (UFS) algorithm. The variables were then used as input for QSAR model generation using partial least squares and back-propagation neural network. Prediction was performed via a two-step approach: (i) perform classification to determine whether the molecule is active or inactive, (ii) develop a QSAR regression model of active molecules. Both classification and regression models yielded good results with RECON providing higher accuracy than that of E-DRAGON descriptors. The performance of the regression model using E-Dragon and RECON descriptors provided a correlation coefficient of 0.807 and 0.923 and root mean square error of 0.666 and 0.304, respectively. Interestingly, it was observed that appropriate representations of the protonation states of the molecules were crucial for good prediction performance, which coincides with the fact that the inhibitors interact with furin via electrostatic forces. The results provide good prospect of using the proposed QSAR models for the rational design of novel therapeutic furin inhibitors toward anthrax and furin-dependent diseases.

Bacterial lipopolysaccharides (LPS), also known as endotoxins, are major structural components of the outer membrane of Gram-negative bacteria that serve as a barrier and protective shield between them and their surrounding environment. LPS is considered to be a major virulence factor as it strongly stimulates the secretion of pro-inflammatory cytokines which mediate the host immune response and culminating in septic shock. Quantitative structure-activity relationship studies of the LPS neutralization activities of anti-endotoxins were performed using charge and quantum chemical descriptors. Artificial neural network implementing the back-propagation algorithm was selected for the multivariate analysis. The predicted activities from leave-one-out cross-validation were well correlated with the experimental values as observed from the correlation coefficient and root mean square error of 0.930 and 0.162, respectively. Similarly, the external testing set also yielded good predictivity with correlation coefficient and root mean square error of 0.983 and 0.130. The model holds great potential for the rational design of novel and robust compounds with enhanced neutralization activity.

Keywords: Drug design, data mining, machine learning, quantum chemistry, computational chemistry