De novo Design of Human Cu/Zn Superoxide Dismutase ligands in Relation to Amyotrophic Lateral Sclerosis/ QSAR Studies of Cyclazocine Series Compounds

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ABSTRACT

Recently, it has been discovered that a region of human Cu/Zn superoxide dismutase (SOD-1) appears to be critical to its aggregation, which is implicated in the pathogenic mechanism of neurodegenerative diseases such as familial amyotrophic lateral sclerosis (FALS). In the first part of this dissertation, SOD-1 inhibitors targeting at cysteine-111 region were de novo designed. Methylguanidinium group was firstly identified as the seed structure. Inhibitor candidates were then generated by "growing" algorithm. The protein ligand binding affinity and biological availability were evaluated. The Gauss-Connolly surface visually demonstrated the complementary properties between designed inhibitors and the binding pocket. Orotic acid (OA) and its derivatives stood out as the highest scoring hits for 2D database searching. Docking results showed strong interactions between SOD-1 and OA. Under oxidative aggregation condition, 0.1 mM orotate blocked the aggregation of both WT and pathogenic mutant SOD-1. This successful implementation of designing anti-aggregation ligand for SODs provided a hope for future drug design that may be used to treat ALS. Furthermore, another two potential binding sites related to the ends of the SOD-1 beta-barrel were proposed for designing inhibitors which may have synergistic effects in preventing the aggregation of SOD-1.

In the second part of this dissertation, Quantitative Structure-Activity Relationship (QSAR) models were developed to predict cyclazocine series compounds' binding activity for opioid κ receptor. Comparative Molecular Field Analysis (CoMFA) was first tried to identify the structural requirements and conformation for binding. Based

on CoMFA results some new structures were suggested with little increased inhibitory activity.

To overcome the shortcomings of CoMFA, alignment-free QSAR models were built using different descriptors, including Transferable Atom Equivalent (TAE) descriptors, Property Encoded Surface Translator (PEST) descriptors, MOE 2D and internal 3D (i3D) descriptors and Autocorrelation Descriptors (PAD). PEST descriptors gave the best results, with PLS performing better than KPLS. The inclusion of feature selection greatly improves the modeling results. Among the most important feathers, FUK and EP were the best. From the most satisfactory result, PEST descriptors reflected the electronic property as well as shape information complementarily of the receptors and the binding site, and have promising application in QSAR modeling.