Binding of Donepezil to Acetylcholinesterase: A Computational Study via Response Surface Methodology

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Abstract:
Donepezil is an oral medication used to improve cognition and behavior in people involved with Alzheimer's disease (AD). Response surface method (RSM) is an efficient computational technique for simultaneous estimation of factor effects on response, the subject not considered in traditional one-factor-at-each-time approaches. Within the present project, donepezil, an AChE inhibitor, was subjected to analysis of variance (ANOVA) incorporated into RSM statistical package. The aim was to mathematically model and estimate the effectiveness of determinant factors on in silico target binding accuracies with regard to validated experimental binding affinities of donepezil within AChE binding site.
RSM was applied to model the influence of six independent factors on AutoDock driven binding accuracies of donepezil vs validated experimental AChE inhibitory affinities. Three distinctive levels (-1, 0 and +1) were assigned for each factor under study (A: torsion degrees for drug, B: grid spacing, C: quaternion degrees for drug, D: No. rotatable bonds, E: initial drug conformation and F: target conformation) and ANOVA was performed for each endpoint (response: ΔpKi) on the basis of Box-Behnken matrix comprising 54 independent runs. ΔpKi was defined as the numerical difference between docking and experimental binding affinities. All statistical analysis and modeling procedure were performed via Box-Behnken method incorporated into Design-Expert (DOE) software-v.7. Docking simulations were done by AutoDock4.2. ANOVA results exhibited that quadratic model could best describe the relationship among dependent variable (ΔpKi) and independent ones (factors A to F) with R2 values of 0.9943. Model p-value of 0.0001 indicated that the developed model was significant. Mathematical model in terms of significant factors (p-value of 0.05) and their coded levels was as follows:
5.25+0.22B-0.19f-0.22BF=ΔnH
The most significant model terms with regard to response were found to be grid spacing (distance between autogrid adjacent points) and target conformation. Moreover BF (grid spacing×target conformation) was the significant interactive term of model. Target conformation may be translated into the induced fit models of the enzyme. Moreover; desirable solutions to achieve minimized responses (minimum differences between in silico and in vitro results) were offered. Identification of determinant methodological and structural variables might provide the comparative qualitative/quantitative exploration of donepezil in binding to its target. The outputs of this study may assist in development of optimized docking technique toward rational design of more selective and potent donepezil analogues as AChE inhibitors.

Key Words: Alzheimer, Donepezil, Response Surface Method, Docking