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QSAR Study on Diverse Compounds for Effects on Thermal Stability of a Monoclonal Antibody

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Abstract : The thermal melting curve of a protein provides information on its conformational stability and could provide cues on its aggregation behavior. Naturally-occurring osmolytes have been shown to improve the thermal stability of most proteins in a concentration-dependent manner. They are therefore commonly employed as additives in therapeutic protein purification and formulation. A number of intertwined and seemingly conflicting mechanisms have been put forward to explain the observed stabilizing effects, the most prominent being the preferential exclusion mechanism. We attempted to probe and summarize molecular mechanisms for thermal stabilization of a monoclonal antibody (mAb) by developing quantitative structure-activity relationships using a rationally-selected library of 120 osmolyte-like compounds in the polyhydric alcohols, amino acids and methylamines classes. Thermal stabilization potencies were experimentally determined by thermal shift assays based on differential scanning fluorimetry. The cross-validated QSAR model was developed by partial least squares regression using descriptors generated from Molecular Operating Environment software. Careful evaluation of the results with the use of variable importance in projection parameter (VIP) and regression coefficients guided the selection of the most relevant descriptors influencing mAb thermal stability. For the mAb studied and at pH 7, the thermal stabilization effects of tested compounds correlated positively with their fractional polar surface area and inversely with their fractional hydrophobic surface area. We cannot claim that the observed trends are universal for osmolyte-protein interactions because of protein-specific effects, however this approach should guide the quick selection of (de)stabilizing compounds for a protein from a chemical library. Further work with a large variety of proteins and at different pH values would help the derivation of a solid explanation as to the nature of favorable osmolyte-protein interactions for improved thermal stability. This approach may be beneficial in the design of novel protein stabilizers with optimal property values, especially when the influence of solution conditions like the pH and buffer species and the protein properties are factored in.

Keywords : thermal stability, monoclonal antibodies, quantitative structure-activity relationships, osmolytes
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