

Inhibition of Insulin Amyloid Fibrillization by Glyco-Acridines: In vitro and in silico study

*Quan Van Vuong^{1, ‡}, Zuzana Bednarikova^{2,3 ‡}, Andrea Antosova², Pham Dinh Quoc Huy^{1,4},
Katarina Siposova², Mai Suan Li^{1,4,*} and Zuzana Gazova^{2,5*}*

¹Institute for Computational Science and Technology, Tan Chanh Hiep Ward, District 12, Ho Chi Minh City, Vietnam

²Department of Biophysics, Institute of Experimental Physics, Slovak Academy of Sciences, Watsonova 47, 040 01 Kosice, Slovakia

³Department of Biochemistry, Faculty of Sciences, Safarik University, Srobarova 2, 041 54 Kosice, Slovakia

⁴Institute of Physics, Polish Academy of Sciences, Al. Lotnikow 32/46, 02-668 Warsaw, Poland

⁵Department of Medical and Clinical Biochemistry and LABMED, Faculty of Medicine, Safarik University, Kosice, Slovakia

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ABSTRACT. The amyloid fibril formation of insulin causes formation of protein deposits at the sites of insulin injection and is obstacle in its storage and delivery for diabetes treatment. We investigated the ability of small molecules, aromatic glyco-acridine derivatives, to prevent insulin fibrillization by experimental and computational techniques. The fluorescence spectroscopy and atomic force microscopy have shown that glyco-acridines interfere with insulin aggregation with inhibitory activity depending on compound structures. The binding free energies estimated by all-atom molecular dynamics simulations indicate that the non-polar interaction is a key factor controlling the binding affinity of glyco-acridine derivatives to insulin. For the first time we have introduced geometrical descriptors allowing to distinguish the binding affinities of stereo-isomers. The binding free energies correlate with the distance between planes of the acridine tricyclic core and side parts in unbound and bound states. In addition the aromatic part of glyco-acridines is critical in directing the ligand to interact with the receptor. Our findings may have implications in the drug design and provide a basis for developing new small molecule inhibitors that are efficient in therapy of amyloid-related diseases.