Trehalase is a glycosidase that catalyzes the hydrolysis of trehalose into two molecules of glucose. This enzyme is vital for insects since trehalose is the principal hemolymph sugar and its catabolism results pivotal for physiological processes like energy production and macromolecular biosynthesis. By contrast, the biological relevance of trehalase in mammals has not been elucidated yet since the trehalose intake is occasional. Starting from such observations, trehalase represents an attractive molecular target for the development of inhibitors that can act as novel and selective insecticides.

1) Build a structural model of the insect variant of trehalase.

In this work we have realized a homology model for the Chironomus riparius trehalase, since this insect is a suitable animal model for in vivo experiments. To predict the binding modes of potential inhibitors we adopted an ensemble docking strategy, where the dynamic behavior of the binding site and its surroundings is taken into account during the ligand placement by docking to multiple (4) receptor conformations [1].

2) Propose binding modes and assess the agreement of binding affinities.

We have analyzed a set of ligands comprising casuarine, castanospermine and 11 casuarine derivates. For all of these compounds experimental IC₅₀ were measured [2-4], defining a panel of inhibitors with a wide range of affinities. The best poses obtained were sorted using a consensus ranking algorithm that aggregates affinity evaluations provided from diverse criteria based on empirical docking scores and ΔGbinding calculations [5]. The computational ranking proposed is in good agreement with experimental values (Spearmann’s ρ value 0.815) and it allows to discriminate a potent inhibitor of trehalase enzyme from a weaker one.

Most of the binding geometries of our poses resemble the topology of receptor/ligand interactions found in the crystallographic structures of E. coli trehalase complexes. Energy Decomposition analysis was performed in order to evaluate the per-residue contribution to ΔGbinding and a pattern of 20 aminoacids was identified as relevant for energy stabilization [6]. Such residues demonstrated differential role and importance in the binding modes of different ligands. This fine characterization shed light on how modifications of casuarine derivates can improve or disrupt the complex framework of non-bonding interactions, providing us the basis for future rational drug design tasks.

3) Rationalize the molecular determinants of inhibition.

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REFERENCES