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Discovery of novel α-amylase inhibitors using structure-based drug design

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α-Amylase is an endoamylase and belongs to glycoside hydrolase family 13 (GH 13) according to the classification of carbohydrate-active enzymes [1]. It initiates starch hydrolysis into smaller oligomers. Inhibitors of this enzyme are of pharmacological importance as α-amylase is considered as attractive target for treating elevated post-prandial blood glucose levels resulting in obesity and type II diabetes. Besides the application as a drug, it is highly interesting to classify nutritional components, such as food additives or secondary plant metabolites with respect to their modulation of α-amylase.

We present a model that predicts the affinity of small organic molecules to α- amylase. On the basis of available crystal structures (Figure 1) [2], we developed a virtual screening workflow for the identification of novel non- peptidic, non-carbohydrate α-amylase inhibitors. In addition to virtual screening using structure-based 3D pharmacophore models [3], molecular docking and clustering for diversity selection have been applied as post-screening filters. Fourteen virtual hits were purchased and tested in vitro using a kinetic assay with p-Nitrophenyl-α-d-maltopentaoside (PNPG5) as a chromogenic substrate. Three of those fourteen compounds showed concentration-dependent inhibition with promising IC_{50} values (hit rate: 21%).

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References

1. Cantarel BL, Coutinho PM, Rancurel C, Bernard T, Lombard V, Henrissat B: **The carbohydrate-active enzymes database (cazy): An expert resource for glycogenomics.** *Nucleic Acids Res* 2009, **37**:D233-D238.
2. Qin X, Ren L, Yang X, Bai F, Wang L, Geng P, Bai G, Shen Y: **Structures of human pancreatic alpha-amylase in complex with acarviostatins:**

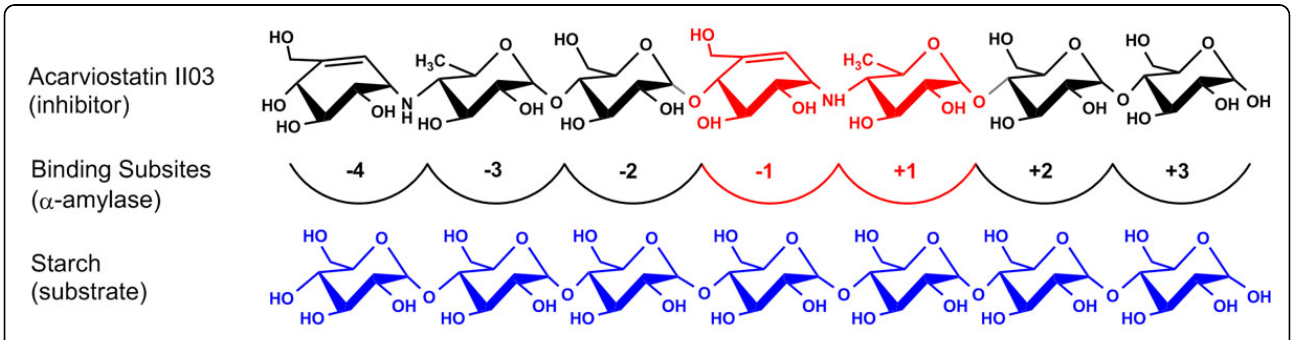

Figure 1 Subsites of α-amylase with Acarviostatin II03 inhibitor, (ki ~ 14 nM) (PDB entry: 3OLE) and starch. Site of cleavage is between subsites -1 and +1.

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Implications for drug design against type II diabetes. *J Struct Biol* 2011, **174(1)**:196-202.

3. Wolber G, Langer T: **Ligandscout: 3-d pharmacophores derived from protein-bound ligands and their use as virtual screening filters.** *J Chem Inf Model* 2005, **45(1)**:160-169.

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