Case study: Nutraceutical

Phosphorylation Vs Glycosylation in targets of hexosamine biosynthetic pathway

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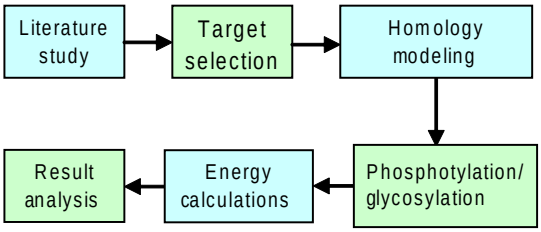
Customer type

A leading nutraceutical company

Software modules

BioPredicta

VLife Engine



Application

Side effect analysis

Techniques

Homology modeling

Residue modifications

Energy analysis

Background:

Phosphorylation and o-Glycosylation are two important cellular events that control many signaling pathways. It has been reported that the actions of phosphorylation and o-glycosylation are complementary to each other. Phosphorylation occurs on serine, threonine or tyrosine residues and o-glycosylation occurs on serine or threonine residues. Phosphorylation and o-glycosylation modifications are reciprocal and occur at same or adjacent residues.

Design challenge:

Insulin resistance is marked by reduced ability of insulin to move glucose from blood into cells for use as energy or storage for future use. Hexosamine biosynthetic pathway has a significant role in insulin resistance where UDP-N-acetyl glucosamine is the end product. This UDP-N-acetyl glucosamine acts as a substrate for o-glcosylation of proteins involved in insulin signalling pathway. This modification results in the altered functioning of these proteins and ultimately results in insulin resistance. The aim of this project was to find the targets in insulin signaling pathway that can undergo o-glycosylation preferably over phosphorylation.

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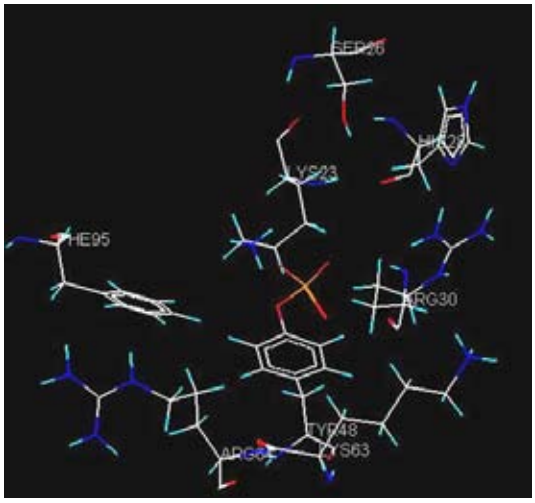
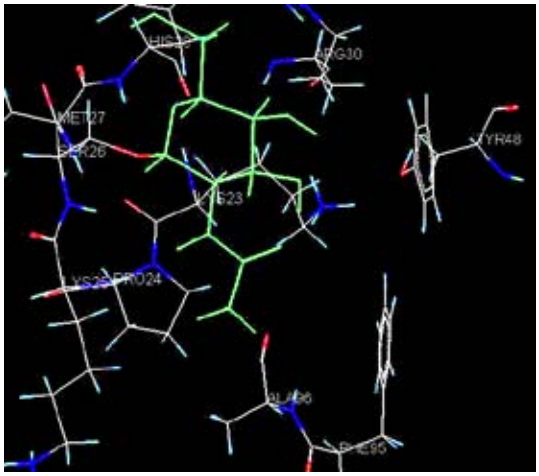


Phosphorylation of IRS1



Glycosylation of IRS1

Project work:

The key enzymes involved in insulin signaling pathway were collected from literature sources and in-house database. The structures for these enzymes were obtained from Protein Data Bank. Homology modeling was carried out for those enzymes which do not have crystal structures. The phosphorylation and glycosylation sites on these enzymes were determined using web servers Phosphosite (http://www.phosphosite.org/), YinOYang (http://www.cbs.dtu.dk/services/YinOYang/) and NetOGlyc (http://www.cbs.dtu.dk/services/NetOGlyc/). Phosphorylation and glycosylation on respective residues were carried out using VLifeMDS.

Result analysis:

The stabilisation energy for posphorylation or glycosylation is determined using the formula

$\Delta Eph = Eph - (Eapo + Ep)$

$\Delta Egly = Egly - (Eapo + Eg)$

where,

ΔEph – energy of phosphorylation

$\Delta Egly$ – energy of glycosylation

Eapo – energy of apo protein

Eph – energy of phosphorylated protein

Egly – energy of glycosylated protein

Ep = energy of phosphate group

Eg = energy of N-acetyl glucosamine

Based on these energies the targets that can get glycosylated preferably over phosphorylation were determined in hexosamine biosynthetic pathway.

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