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Virtual and Real Screening of Natural Products to Find Effective Modulators of Protein Tyrosine Phosphatase PTP1B

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The protein tyrosine phosphatase 1B (PTP1B) is an important negative regulator of the insulin receptor. Elchebly M. et al showed that PTP1B knockout mice enhanced insulin sensitivity and were completely healthy and resistant to weight gain when put on a high fat diet (1). This makes PTP1B a promising target for diabetes type 2 and metabolic syndrome.

Aim of our study is to identify effective and natural product-derived inhibitors of PTP1B.

As a straightforward approach we built structure-based 3D pharmacophore models of the active site of PTP1B. From more than 100 models generated with the program LigandScout 8 representative models with different restrictivities were chosen for a virtual screening approach. In silico hits were obtained by screening the natural products database (NPD) with Catalyst 4.11 fast flexible search. In a second step these hits were evaluated by a literature survey to select promising candidates for pharmacological studies. These substances were tested on a colorimetric enzyme assay. Thereby, e.g. the compound docosanedioic acid from *Limonium sp.* could be identified as an in vitro PTP1B inhibitor. It showed a clear inhibition with an IC_{50} of 1,022 µM. This compound and other promising inhibitors of the enzyme assay were tested on human hepatoma cells. Stronger phosphorylation of the insulin receptor was taken as a sign for inhibition of PTP1B.

A selection of promising substances will be further characterized with respect to their mode of inhibition and their selectivity on PTP1B. Thus an inhibition of other phosphatases involved in insulin signalling like TC-PTP, SHP-2, RPTPα, and LAR will be excluded.

[1] Elchebly M, Payette P, Michaliszyn E, Cromlish W, Collins S, Loy AL, Normandin D, Cheng A, Himms-Hagen J, Chan CC, Ramachandran C, Gresser MJ, Tremblay ML, Kennedy BP. Increased insulin sensitivity and obesity resistance in mice lacking the protein tyrosine phosphatase-1B gene. Science. 1999; 283: 1544–1548. doi:10.1126/science.283.5407.1544

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