Computer-aided, Rational Design of Potent and Selective Inhibitors of Protein Tyrosine Phosphatase 1B(PTP 1B), a Key Enzyme in the Insulin Signaling Pathway and Novel Therapeutic Target for Obesity and Type 2 Diabetes Mellitus

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Abstract

Protein Tyrosine Phosphatase 1B (PTP1B) has been shown to be a negative regulator of insulin signaling by dephosphorylating key tyrosine residues within the regulatory domain of the â-subunit of the insulin receptor. Recent gene knockout studies in mice have shown these mice to have increased insulin sensitivity and improved glucose tolerance. Furthermore, these mice also exhibited a resistance to diet induced obesity. Inhibitors of PTP1B would have the potential of enhancing insulin action by prolonging the phosphorylated state of the insulin receptor. In addition, recent clinical studies have shown that the haplotype ACTTCAG0 of the PTPN1 gene, which encodes PTP1B, is a major risk contributor to type 2 diabetes mellitus (T2DM). Thus, there is compelling evidence that small molecule inhibitors of PTP1B may be effective in treating insulin resistance at an early stage. Using an *in silico* structure–based approach, we have designed a potent and selective, small peptide inhibitor of PTP1B. The designed peptide is found to satisfy Lipinski's rule of 5 for its suitability as a drug. Therefore, it can be considered to be a suitable lead compound for the development of new drugs in treating insulin resistance at an early stage thereby leading to a prevention strategy for T2DM and obesity.

Key words: Insulin signaling, Insulin resistance, PTP 1B, Structure based drug design.