Development of a Novel Class of Antidiabetic and Anticancer Agents Targeting PTP1B Enzyme

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Protein Tyrosine Phosphatase 1B (PTP1B), a predominant member of the Protein tyrosine phosphatase (PTP) family of enzymes, serves as a negative regulator of the insulin signal transduction pathways. PTP1B does this by dephosphorylating the pTyr group of active insulin receptor (IR) protein. It also downregulates leptin receptor signaling pathway by dephosphorylating the pTyr group of JAK2 kinase, a signaling event often misregulated in obesity. Recent studies also reveal that PTP1B can also upregulate Src-kinase activity by dephosphorylating a key inhibitory pY529 residue. This leads to the onset and progression of human cancers. Inhibition or down-regulation of PTP1B activity is considered a very attractive therapeutic strategy for the treatment of type 2 diabetes, obesity, and cancer. Natural products derived from medicinal plants have proven an important source of new drug development. In this report, Bakuchiol, a natural product which was isolated from the seeds of CHIBA (Psoralia Corlifolia) was utilized to design a novel class of PTP1B inhibitors. Specifically, a series of a carboxylic acid derivative of Bakuchiol and other small carboxylic acid analogs were synthesized. These inhibitors were then screened against PTP1B enzyme and the IC-50 values were determined by p-nitrophenyl phosphate in-vitro assay. A potent PTP1B inhibitor was identified that, in future, can be used for development of therapeutics for type 2 diabetes, obesity, and cancer.

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