Type II Diabetes (T2DB) is one of the worldwide problems characterized by ineffective insulin signal transduction as a result of insulin resistance and impaired glucose homeostasis. Protein Tyrosine Phosphatase 1B (PTP1B), an enzyme in phosphatase family that share a conserved structure in their catalytic domain, is a major regulator of the signal transduction. The enzyme functions by dephosphorylation of insulin receptor and insulin receptor substrate. Genetic and experimental evidences suggested that the enzyme is an attractive drug target for Type II Diabetes. Many research groups have attempted to develop inhibitors of PTP1B. However, none of them has made it to the drug market due to inefficiency to function. Development of PTP1B inhibitor has proven rather difficult owing to three main challenges, i.e. potency, selectivity, and cell permeability. Here, we report a novel strategy that possibly overcomes those main challenges. I describe the development of potential exo-affinity labeling agents targeting PTP1B function, investigation of potency of the agents which were reported as IC50 values, as well as kinetics study of those compounds against the enzyme.