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Molecular Modeling Approaches to Discover Novel PTP1B Inhibitors for Treatment of Type 2 Diabetes Therapy

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Type 2 diabetes, also known as non-insulin dependent diabetes or adult diabetes, is characterized by a deficiency in insulin signaling in spite of normal elevated levels of insulin. Protein tyrosine phosphatase 1B (PTP1B) regulates insulin signaling by dephosphorylating tyrosine residues in the kinase regulatory domain of the insulin receptor. It is one of the best therapeutic targets for the treatment of type 2 diabetes. In the past 10 years, many inhibitors of PTP1B have been discovered and designed as drug candidates of PTP1B. However, most inhibitors have poor membrane permeability because they are highly charged due to phosphonate mimetics. In addition, the structural feature of active site in PTP1B is caused the difficulty of designing potent inhibitors with acceptable membrane permeability. In this study, quantitative structure–activity relationship model was generated for initial screening to identify potential PTP1B inhibitors from chemical databases. It was based on experimental datasets about IC50 values of PTP1B inhibitors. For a secondary screen, the candidate compounds were selected using pharmacophore model. This model allowed us to identify candidate compounds with structural characteristics essential for potent PTP1B inhibition. Finally, we performed molecular docking calculation to clarify the specific interactions at the molecular level between the selected candidate compounds and PTP1B providing insights into binding affinities and interaction mechanisms. This study highlights the importance of novel PTP1B inhibitors in the treatment of type 2 diabetes using computational methodologies in overcoming the challenges of inhibitor design, particularly concerning membrane permeability.