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Co-crystallized ligand based designing and synthesis of some heterocyclic derivatives of chalcone as "protein-tyrosine phosphatase 1B" inhibitors

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Protein tyrosine phosphatase 1B (PTP1B) is an important target for diabetes since inhibition of PTP1B offers therapeutic benefits in insulin resistant diabetes. Unfortunately, no drugs are approved or available in market as PTP1B inhibitor and finding of such type of anti-diabetic agents is still in progress. However, computational modeling, based on the interaction between co-crystallized ligand and macromolecular receptor has presented some structural features required for PTPIB inhibitory activity. Considering these structural features of co-crystallized ligand bound with 3D crystal structure of PTP1B receptor we have designed some chalcones and their heterocyclic derivatives as PTP1B inhibitors. Preliminary substituted chalcones have been investigated but only one phenyl ring of these derivatives shows interaction with PTP1B receptor in molecular docking study. To overcome this problem, some heterocyclic derivatives of chalcone have been designed. These heterocyclic derivatives show interactions similar to co-crystallized ligand, which means both terminal rings exhibit interactions with macromolecular receptor in molecular docking study. Moreover, some of the synthesized heterocyclic derivatives of chalcone show potent inhibitory activity when tested *in vitro* and compound **AD-4** ((*E*)-3-(3-nitrophenyl)-1-(pyridin-4-yl)prop-2-en-1-one) is observed as the most prominent inhibitory agent with 75.06% inhibition of PTP1B. Potent derivative **AD-4** also exhibits significant anti-hyperglycemic activity during *in vivo* evaluation in animal model.

Keywords: Anti-hyperglycemic, Chalcone, Heterocycles, PTP1B, Insulin, Diabetes