

## Messmer High School SMART Team 2015-2016

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### PTP1B Inhibitors for Type 2 Diabetes Treatment

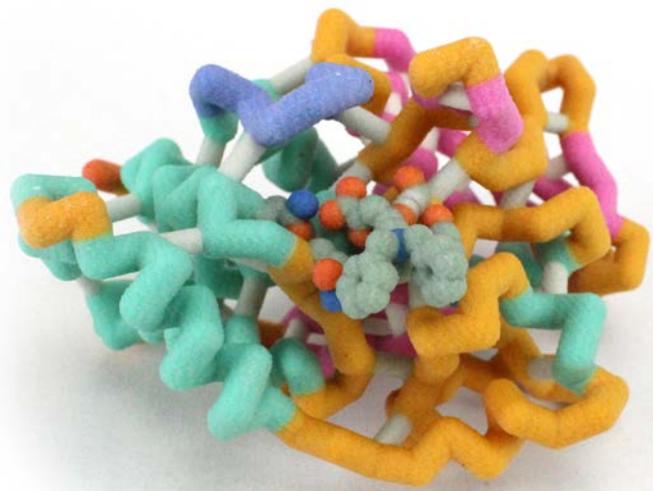
**PDB:** 3EB1

**Primary Citation:** Sijiu Liu, Li-Fan Zeng, Li Wu, Xiao Yu, Ting Xue, Andrea M. Gunawan, Ya-Qiu Long, and Zhong-Yin Zhang. (2008). Targeting Inactive Enzyme Conformation: Aryl Diketoacid Derivatives as a New Class of PTP1B Inhibitors. *JACS Articles*, **130**, 17075-17084.

**Format:** Alpha carbon backbone

**RP:** Zcorp with plaster

**Abstract:** People with diabetes have difficulty regulating their blood sugar leading to the malfunctions of the heart, kidney, nerves, and brain if their blood sugar is too high. Most diabetics use insulin to control their condition. Insulin binds to its surface receptor in muscle and fat cells to trigger removal of sugar from the blood. Protein tyrosine phosphatase 1B (PTP1B) affects blood sugar regulation by dephosphorylating the insulin receptor and reducing its activity. Studying PTP1B can help us understand how its inhibitors can slow down the removal of phosphate from the insulin receptor, affecting the blood sugar regulation process. PTP1B normally functions to remove the phosphate group from the insulin receptor. Since PTP1B ordinarily reduces insulin receptor activity, blocking PTP1B could increase insulin sensitivity. The PTP1B active site has a highly positive binding pocket which binds to the highly negative phosphates on the phosphorylated insulin receptor. Many of the current inhibitors of PTP1B act by binding to this active site. However, these inhibitors have difficulty penetrating the cell membrane because of their formal charge, and are unable to inhibit PTP1B inside cells. LZP25 avoids this issue by not having a formal negative charge, but instead a polar area of similar size to phosphate. Binding to the PTP1B active site pocket (sites Ser216, Ala217, Ile219, Gln262, Gln266), its bulky side groups then prevent a key loop in the enzyme active site from closing. If PTP1B is inhibited in the insulin pathway by a potential drug based on LZP25, people who have type 2 diabetes as a result of insufficient insulin receptor activity could better regulate their blood sugar. If the insulin receptor would signal appropriately, the body's normal control of blood sugar would improve, preventing problems with the heart, kidney, nerves, and brain. Messmer Catholic High School SMART (Students Modeling A Research Topic) Team has designed a model of PTP1B with LZP25 using 3D printing technology to investigate their structure/function relationships.



### Specific Model Information:

- Protein Name: Tyrosine-protein phosphatase non-receptor type 1 (PTP1B)
- PDB File: 3EB1.pdb
  
- Helix is colored turquoise
- Beta sheets are colored magenta
- Non-motive portions are colored orange
- H-bonds are colored ivory
- Struts are colored light grey and are magnetic
  - Amino acids Ser216, Ala217, Ile219, Gln262, Gln266, are displayed because they form the binding sites for compound LZP25.
- WPD loop is colored medium purple
  - Amino Acids 179-187 are highlighted in medium purple because they usually close to remove the phosphate group.
- Hydrophobic bond is colored yellow and are magnetic
  - The hydrophobic bond of amino acid TYR 46 with the phenyl ring of LZP25 (in the PDB known as LZQ322) is highlighted in yellow because it forms a 4th docking site for LZP25.

<http://cbm.msoc.edu/smartTeams/index.php>

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