

Bibliography

7. BIBLIOGRAPHY

1. Michael L. Mohler; Yali He; Zhongzhi Wu; Dong Jin Hwang; Miller, D. D., Recent and Emerging Anti-Diabetes Targets. *Med. Res. Rev.* **2009**, 29, 125-195.
2. Moller, D. E., New drug targets for type 2 diabetes and the metabolic syndrome. *Nature* **2001**, 414, 821-827.
3. International Diabetes Federation, IDF Diabetes Atlas. 5th edn. Brussels, Belgium: International Diabetes Federation, 2011.
4. Zhang, Z.-Y., Protein tyrosine phosphatases: Structure and Function, Substrate Specificity, and Inhibitor Development. *Annu. Rev. Pharmacol. Toxicol.* **2002**, 42, 209-234.
5. Andres Alonso; Joanna Sasin; Nunzio Bottini; Ilan Friedberg; Iddo Friedberg; Andrei Osterman; Adam Godzik; Tony Hunter; Jack Dixon; Mustelin, T., Protein Tyrosine Phosphatases in the Human Genome. *Cell* **2004**, 117, 699-711.
6. Sheng Zhang; Zhang, Z.-Y., PTP1B as a drug target: recent developments in PTP1B inhibitor discovery. *Drug Discov. Today* **2007**, 12, 373-381.
7. Lydia Taberero; A. Radu Aricescu; E. Yvonne Jones; Szedlacsek, S. E., Protein tyrosine phosphatases: structure–function relationships. *FEBS Journal* **2008**, 275, 867–882.
8. Tiago A. S.Brandao; Alvan C. Hengge; Johnson, S. J., Insights into the Reaction of Protein-tyrosine Phosphatase 1B crystal structures for transition state analogs of both catalytic steps. *J. Biol. Chem.* **2010**, 285, 15874–15883.
9. Andersen, J. N., A genomic perspective on protein tyrosine phosphatases: gene structure, pseudogenes, and genetic disease linkage. *The FASEB Journal* **2004**, 18, 8-30.
10. Tootle, T. L.; Silver, S. J.; Davies, E. L.; Newman, V.; Latek, R. R.; Mills, I. A.; Selengut, J. D.; Parlikar, B. E. W.; Rebay, I., The transcription factor Eyes absent is a protein tyrosine phosphatase. *Nature* **2003**, 426, 299-302.

11. Rayapureddi, J. P.; Kattamuri, C.; Steinmetz, B. D.; Frankfort, B. J.; Ostrin, E. J.; Mardon, G.; Hegde, R. S., Eyes absent represents a class of protein tyrosine phosphatases. *Nature* **2003**, 426, 295-298.
12. Li, X.; Ohgi, K. A.; Zhang, J.; Kronos, A.; Bush, K. T.; Glass, C. K.; Nigam, S. K.; Aggarwal, A. K.; Maas, R.; Rose, D. W.; Rosenfeld, M. G., Eya protein phosphatase activity regulates Six1-Dach-Eya transcriptional effects in mammalian organogenesis. *Nature* **2003**, 426, 247-254.
13. Combs, A. P., Recent Advances in the Discovery of Competitive Protein Tyrosine Phosphatase 1B Inhibitors for the Treatment of Diabetes, Obesity, and Cancer. *J. Med. Chem.* **2009**, 53, 2333-2344.
14. Chatterjee, S.; Goldstein, B. J.; Csermely, P.; Shoelson, S. F.; Brigham; M.A., W. S. H. B., Phosphopeptide Substrates and Phosphonopeptide Inhibitors of Protein-Tyrosine Phosphatases. Defense Technical Information Center 1992.
15. Zhang, Z. Y.; Maclean, D.; McNamara, D. J.; Sawyer, T. K.; Dixon, J. E., Protein Tyrosine Phosphatase Substrate Specificity: Size and Phosphotyrosine Positioning Requirements in Peptide Substrates. *Biochemistry.* **1994**, 33, 2285-2290.
16. Burke, T. R.; Smyth, M. S.; Nomizu, M.; Otaka, A.; Roller, P. R., Preparation of fluoro- and hydroxy-4-(phosphonomethyl)-D,L-phenylalanine suitably protected for solid-phase synthesis of peptides containing hydrolytically stable analogs of O-phosphotyrosine. *J. Org. Chem.* **1993**, 58, 1336-1340.
17. Burke Jr, T. R.; Ye, B.; Yan, X.; Wang, S.; Jia, Z.; Chen, L.; Zhang, Z. Y.; Barford, D., Small molecule interactions with protein-tyrosine phosphatase PTP1B and their use in inhibitor design. *Biochemistry.* **1996**, 35, 15989-15996.
18. Kole, H.; Smyth, M.; Russ, P.; Burke Jr, T., Phosphonate inhibitors of protein-tyrosine and serine/threonine phosphatases. *Biochem. J.* **1995**, 311, 1025.
19. Ye, B.; Burke, T. R., Synthesis of a difluorophosphonomethyl-containing phosphatase inhibitor designed from the X-ray structure of a PTP1B-bound ligand. *Tetrahedron* **1996**, 52, 9963-9970.

20. Burke, T. R.; Ye, B.; Yan, X.; Wang, S.; Jia, Z.; Chen, L.; Zhang, Z.-Y.; Barford, D., Small Molecule Interactions with Protein-Tyrosine Phosphatase PTP1B and Their Use in Inhibitor Design. *Biochemistry* **1996**, *35*, 15989-15996.
21. Puius, Y. A.; Zhao, Y.; Sullivan, M.; Lawrence, D. S.; Almo, S. C.; Zhang, Z. Y., Identification of a second aryl phosphate-binding site in protein-tyrosine phosphatase 1B: a paradigm for inhibitor design. *Proceedings of the National Academy of Sciences* **1997**, *94*, 13420-13425.
22. Yao, Z. J.; Ye, B.; Wu, X. W.; Wang, S.; Wu, L.; Zhang, Z. Y.; Burke, T. R., Structure-based design and synthesis of small molecule protein-tyrosine phosphatase 1B inhibitors. *Bioorg. Med. Chem.* **1998**, *6*, 1799-1810.
23. Groves, M. R.; Yao, Z. J.; Roller, P. P.; Burke Jr, T. R.; Barford, D., Structural basis for inhibition of the protein tyrosine phosphatase 1B by phosphotyrosine peptide mimetics. *Biochemistry* **1998**, *37*, 17773-17783.
24. Liu, D. G.; Gao, Y.; Voigt, J. H.; Lee, K.; Nicklaus, M. C.; Wu, L.; Zhang, Z. Y.; Burke, T. R., Acylsulfonamide-containing PTP1B inhibitors designed to mimic an enzyme-bound water of hydration. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3005-3007.
25. Taylor, S. D.; Kotoris, C. C.; Dinaut, A. N.; Wang, Q.; Ramachandran, C.; Huang, Z., Potent non-peptidyl inhibitors of protein tyrosine phosphatase 1B. *Bioorg. Med. Chem.* **1998**, *6*, 1457-1468.
26. Kotoris, C. C.; Wen, W.; Lough, A.; Taylor, S. D., Preparation of chiral α -monofluoroalkylphosphonic acids and their evaluation as inhibitors of protein tyrosine phosphatase 1B. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1271-1281.
27. Chen, L.; Wu, L.; Otaka, A.; Smyth, M. S.; Roller, P. P.; Burke, T. R.; Denhertog, J.; Zhang, Z. Y., Why Is Phosphonodifluoromethyl Phenylalanine a More Potent Inhibitory Moiety Than Phosphonomethyl Phenylalanine Toward Protein-Tyrosine Phosphatases. *Bioche. Biophys. Res. Commun.* **1995**, *216*, 976-984.

28. Guo, X. L.; Shen, K.; Wang, F.; Lawrence, D. S.; Zhang, Z. Y., Probing the molecular basis for potent and selective protein-tyrosine phosphatase 1B inhibition. *J. Biol. Chem.* **2002**, *277*, 41014-41022.
29. Burke, T. R.; Yao, Z.-J.; Liu, D.-G.; Voigt, J.; Gao, Y., Phosphoryltyrosyl mimetics in the design of peptide-based signal transduction inhibitors. *Pept. Sci.* **2001**, *60*, 32-44.
30. Gao, Y.; Wu, L.; Luo, J. H.; Guo, R.; Yang, D.; Zhang, Z.-Y.; Burke Jr, T. R., Examination of novel non-phosphorus-containing phosphotyrosyl mimetics against protein-tyrosine phosphatase-1B and demonstration of differential affinities toward Grb2 SH2 domains. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 923-927.
31. Leung, C.; Grzyb, J.; Lee, J.; Meyer, N.; Hum, G.; Jia, C.; Liu, S.; Taylor, S. D., The difluoromethylenesulfonic acid group as a monoanionic phosphate surrogate for obtaining PTP1B inhibitors. *Bioorg. Med. Chem. Lett.* **2002**, *10*, 2309-2323.
32. Romsicki, Y.; Reece, M.; Gauthier, J. Y.; Asante-Appiah, E.; Kennedy, B. P., Protein tyrosine phosphatase-1B dephosphorylation of the insulin receptor occurs in a perinuclear endosome compartment in human embryonic kidney 293 cells. *J. Biol. Chem.* **2004**, *279*, 12868-12875.
33. Hussain, M.; Ahmed, V.; Hill, B.; Ahmed, Z.; Taylor, S. D., A re-examination of the difluoromethylenesulfonic acid group as a phosphotyrosine mimic for PTP1B inhibition. *Bioorg. Med. Chem.* **2008**, *16*, 6764-6777.
34. Dufresne, C.; Roy, P.; Wang, Z.; Asante-Appiah, E.; Cromlish, W.; Boie, Y.; Forghani, F.; Desmarais, S.; Wang, Q.; Skorey, K., The development of potent non-peptidic PTP-1B inhibitors *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1039-1042.
35. Lau, C. K.; Bayly, C. I.; Gauthier, J. Y.; Li, C. S.; Therien, M.; Asante-Appiah, E.; Cromlish, W.; Boie, Y.; Forghani, F.; Desmarais, S., Structure based design of a series of potent and selective non peptidic PTP-1B inhibitors. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1043-1048.

36. Dang, Q., Organophosphonic acids as drug candidates. *Expert Opin. Ther. Pat.* **2006**, 16, 343-348.
37. Shen, K.; Keng, Y. F.; Wu, L.; Guo, X. L.; Lawrence, D. S.; Zhang, Z. Y., Acquisition of a specific and potent PTP1B inhibitor from a novel combinatorial library and screening procedure. *J. Biol. Chem.* **2001**, 276, 47311-47319.
38. Boutselis, I. G.; Yu, X.; Zhang, Z. Y.; Borch, R. F., Synthesis and cell-based activity of a potent and selective protein tyrosine phosphatase 1B inhibitor prodrug. *J. Med. Chem.* **2007**, 50, 856-864.
39. Schubert, H. L.; Fauman, E. B.; Stuckey, J. A.; Dixon, J. E.; Saper, M. A., A ligand-induced conformational change in the Yersinia protein tyrosine phosphatase. *Protein science: a publication of the Protein Society* **1995**, 4, 1904.
40. Liotta, A. S.; Kole, H. K.; Fales, H. M.; Roth, J.; Bernier, M., A synthetic tris-sulfotyrosyl dodecapeptide analogue of the insulin receptor 1146-kinase domain inhibits tyrosine dephosphorylation of the insulin receptor in situ. *J. Biol. Chem.* **1994**, 269, 22996-23001.
41. Kole, H. K.; Garant, M. J.; Kole, S.; Bernier, M., A peptide-based protein-tyrosine phosphatase inhibitor specifically enhances insulin receptor function in intact cells. *J. Biol. Chem.* **1996**, 271, 14302-14307.
42. Hippen, K.; Jakes, S.; Richards, J.; Jena, B.; Beck, B.; Tabatabai, L.; Ingebritsen, T., Acidic residues are involved in substrate recognition by two soluble protein tyrosine phosphatases, PTP-5 and rrbPTP-1. *Biochemistry* **1993**, 32, 12405-12412.
43. Desmarais, S.; Jia, Z.; Ramachandran, C., Inhibition of protein tyrosine phosphatases PTP1B and CD45 by sulfotyrosyl peptides. *Arch. Biochem. Biophys.* **1998**, 354, 225-231.
44. Ham, S. W.; Park, J.; Lee, S. J.; Yoo, J. S., Selective inactivation of protein tyrosine phosphatase PTP1B by sulfone analogue of naphthoquinone. *Bioorg. Med. Chem. Lett.* **1999**, 9, 185-186.

45. Masaya Imoto; Hideaki Kakeya; Tsutomu Sawa; Chigusa Hayashi; Masa Hamada; Tomio Takeuchi; Umezawa, K., Dephostatin, A Novel Protein Tyrosine Phosphatase Inhibitor Produced by Streptomyces Taxonomy, Isolation, and Characterization. *J. Antibiot.* **1993**, *46*, 1342-1346.
46. Hideaki Kakeya; Masaya Imoto; Yoshikazu Takahashi; Hiroshi Naganawa; Tomio Takeuchi, K. U., Dephostatin, A Novel Protein Tyrosine Phosphatase Inhibitor Produced by Streptomyces II. Structure Determination. *J. Antibiot.* **1993**, *46*, 1716-1719.
47. Watanabe, T.; Suzuki, T.; Umezawa, Y.; Takeuchi, T.; Otsuka, M.; Umezawa, K., Structure-activity relationship and rational design of 3, 4-dephostatin derivatives as protein tyrosine phosphatase inhibitors. *Tetrahedron* **2000**, *56*, 741-752.
48. Sarmiento, M.; Wu, L.; Keng, Y. F.; Song, L.; Luo, Z.; Huang, Z.; Wu, G. Z.; Yuan, A. K.; Zhang, Z. Y., Structure-based discovery of small molecule inhibitors targeted to protein tyrosine phosphatase 1B. *J. Med. Chem.* **2000**, *43*, 146-155.
49. Malamas, M. S.; Sredy, J.; Moxham, C.; Katz, A.; Xu, W.; McDevitt, R.; Adebayo, F. O.; Sawicki, D. R.; Seestaller, L.; Sullivan, D., Novel benzofuran and benzothiophene biphenyls as inhibitors of protein tyrosine phosphatase 1B with antihyperglycemic properties. *J. Med. Chem.* **2000**, *43*, 1293-1310.
50. Andersen, H. S.; Iversen, L. F.; Jeppesen, C. B.; Branner, S.; Norris, K.; Rasmussen, H. B.; Møller, K. B.; Møller, N. P. H., 2-(oxalylamino)-benzoic acid is a general, competitive inhibitor of protein-tyrosine phosphatases. *J. Biol. Chem.* **2000**, *275*, 7101-7108.
51. Iversen, L. F.; Andersen, H. S.; Branner, S.; Mortensen, S. B.; Peters, G. H.; Norris, K.; Olsen, O. H.; Jeppesen, C. B.; Lundt, B. F.; Ripka, W.; Møller, K. B.; Møller, N. P., Structure-based design of a low molecular weight, nonphosphorus, nonpeptide, and highly selective inhibitor of protein-tyrosine phosphatase 1B. *J. Biol. Chem.* **2000**, *275*, 10300-7.

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52. Wrobel, J.; Li, Z.; Sredy, J.; Sawicki, D. R.; Seestaller, L.; Sullivan, D., Synthesis and PTP1B Inhibition of Novel 4-Aryl-1-oxa-9-t hiacyclopenta [b] fluorenes. *Bioorg. Med. Chem. Lett.* **2000**, 10, 1535-1538.
53. Malamas, M. S.; Sredy, J.; Gunawan, I.; Mihan, B.; Sawicki, D. R.; Seestaller, L.; Sullivan, D.; Flam, B. R., New azolidinediones as inhibitors of protein tyrosine phosphatase 1B with antihyperglycemic properties *J. Med. Chem.* **2000**, 43, 995-1010.
54. Bleasdale, J. E.; Ogg, D.; Palazuk, B. J.; Jacob, C. S.; Swanson, M. L.; Wang, X. Y.; Thompson, D. P.; Conradi, R. A.; Mathews, W. R.; Laborde, A. L., Small molecule peptidomimetics containing a novel phosphotyrosine bioisostere inhibit protein tyrosine phosphatase 1B and augment insulin action. *Biochemistry* **2001**, 40, 5642-5654.
55. Larsen, S. D.; Barf, T.; Liljebris, C.; Paul, D.; Ogg, D.; O'Sullivan, T. J.; Palazuk, B. J.; Schostarez, H. J.; Stevens, F. C.; Bleasdale, J. E., Synthesis and biological activity of a novel class of small molecular weight peptidomimetic competitive inhibitors of protein tyrosine phosphatase 1B. *J. Med. Chem.* **2002**, 45, 598-622.
56. Larsen, S.; May, P.; Bleasdale, J.; Liljebris, C.; Schostarez, H.; Barf, T., Preparation of substituted phenylalanine derivatives as protein tyrosine phosphatase inhibitors. WO Patent 9,911,6061999.
57. Liljebris, C.; Larsen, S. D.; Ogg, D.; Palazuk, B. J.; Bleasdale, J. E., Investigation of potential bioisosteric replacements for the carboxyl groups of peptidomimetic inhibitors of protein tyrosine phosphatase 1B: identification of a tetrazole-containing inhibitor with cellular activity. *J. Med. Chem.* **2002**, 45, 1785-1798.
58. Liljebris, C.; Martinsson, J.; Tedenborg, L.; Williams, M.; Barker, E.; Duffy, J. E. S.; Nygren, A.; James, S., Synthesis and biological activity of a novel class of pyridazine analogues as non-competitive reversible inhibitors of protein tyrosine phosphatase 1B (PTP1B). *Bioorg. Med. Chem.* **2002**, 10, 3197-3212.
59. Arabaci, G.; Yi, T.; Fu, H.; Porter, M. E.; Beebe, K. D.; Pei, D., α -Bromoacetophenone derivatives as neutral protein tyrosine phosphatase

- inhibitors: structure–Activity relationship. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3047-3050.
60. Xin, Z.; Oost, T. K.; Abad-Zapatero, C.; Hajduk, P. J.; Pei, Z.; Szczepankiewicz, B. G.; Hutchins, C. W.; Ballaron, S. J.; Stashko, M. A.; Lubben, T., Potent, selective inhibitors of protein tyrosine phosphatase 1B. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1887-1890.
61. Szczepankiewicz, B. G.; Liu, G.; Hajduk, P. J.; Abad-Zapatero, C.; Pei, Z.; Xin, Z.; Lubben, T. H.; Trevillyan, J. M.; Stashko, M. A.; Ballaron, S. J., Discovery of a potent, selective protein tyrosine phosphatase 1B inhibitor using a linked-fragment strategy. *J. Am. Chem. Soc.* **2003**, *125*, 4087-4096.
62. Zhang, Y. L.; Keng, Y. F.; Zhao, Y.; Wu, L.; Zhang, Z. Y., Suramin is an active site-directed, reversible, and tight-binding inhibitor of protein-tyrosine phosphatases. *J. Biol. Chem.* **1998**, *273*, 12281-12287.
63. Liang, F.; Huang, Z.; Lee, S. Y.; Liang, J.; Ivanov, M. I.; Alonso, A.; Bliska, J. B.; Lawrence, D. S.; Mustelin, T.; Zhang, Z. Y., Aurintricarboxylic acid blocks in vitro and in vivo activity of YopH, an essential virulent factor of *Yersinia pestis*, the agent of plague. *J. Biol. Chem.* **2003**, *278*, 41734-41741.
64. Shim, Y. S.; Kim, K. C.; Chi, D. Y.; Lee, K. H.; Cho, H., Formylchromone derivatives as a novel class of protein tyrosine phosphatase 1B inhibitors. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2561-2563.
65. McCain, D. F.; Wu, L.; Nickel, P.; Kassack, M. U.; Kreimeyer, A.; Gagliardi, A.; Collins, D. C.; Zhang, Z. Y., Suramin derivatives as inhibitors and activators of protein-tyrosine phosphatases. *J. Biol. Chem.* **2004**, *279*, 14713-14725.
66. Shrestha, S.; Shim, Y. S.; Kim, K. C.; Lee, K. H.; Cho, H., Evans Blue and other dyes as protein tyrosine phosphatase inhibitors. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1923-1926.
67. Zhao, H.; Liu, G.; Xin, Z.; Serby, M. D.; Pei, Z.; Szczepankiewicz, B. G.; Hajduk, P. J.; Abad-Zapatero, C.; Hutchins, C. W.; Lubben, T. H., Isoxazole carboxylic

- acids as protein tyrosine phosphatase 1B (PTP1B) inhibitors. *Bioorg. Med. Chem. Lett.* **2004**, 14, 5543-5546.
68. Wang, Q.; Dubé, D.; Friesen, R. W.; LeRiche, T. G.; Bateman, K. P.; Trimble, L.; Sanghara, J.; Pollex, R.; Ramachandran, C.; Gresser, M. J., Catalytic inactivation of protein tyrosine phosphatase CD45 and protein tyrosine phosphatase 1B by polyaromatic quinones. *Biochemistry* **2004**, 43, 4294-4303.
69. Shim, Y. S.; Kim, K. C.; Lee, K. A.; Shrestha, S.; Lee, K. H.; Kim, C. K.; Cho, H., Formylchromone derivatives as irreversible and selective inhibitors of human protein tyrosine phosphatase 1B. Kinetic and modeling studies. *Bioorg. Med. Chem.* **2005**, 13, 1325-1332.
70. Black, E.; Breed, J.; Breeze, A. L.; Embrey, K.; Garcia, R.; Gero, T. W.; Godfrey, L.; Kenny, P. W.; Morley, A. D.; Minshull, C. A., Structure-based design of protein tyrosine phosphatase-1B inhibitors. *Bioorg. Med. Chem. Lett.* **2005**, 15, 2503-2507.
71. Combs, A. P.; Yue, E. W.; Bower, M.; Ala, P. J.; Wayland, B.; Douty, B.; Takvorian, A.; Polam, P.; Wasserman, Z.; Zhu, W., Structure-based design and discovery of protein tyrosine phosphatase inhibitors incorporating novel isothiazolidinone heterocyclic phosphotyrosine mimetics. *J. Med. Chem.* **2005**, 48, 6544-6548.
72. Yue, E. W.; Wayland, B.; Douty, B.; Crawley, M. L.; McLaughlin, E.; Takvorian, A.; Wasserman, Z.; Bower, M. J.; Wei, M.; Li, Y., Isothiazolidinone heterocycles as inhibitors of protein tyrosine phosphatases: synthesis and structure-activity relationships of a peptide scaffold. *Bioorg. Med. Chem.* **2006**, 14, 5833-5849.
73. Combs, A. P.; Glass, B.; Galya, L. G.; Li, M., Asymmetric Synthesis of the (S)-1,1-Dioxido-isothiazolidin-3-one Phosphotyrosine Mimetic via Reduction of a Homochiral (R)-Oxido-isothiazolidin-3-one. *Org. Lett.* **2007**, 9, 1279-1282.
74. Douty, B.; Wayland, B.; Ala, P. J.; Bower, M. J.; Pruitt, J.; Bostrom, L.; Wei, M.; Klabe, R.; Gonneville, L.; Wynn, R.; Burn, T. C.; Liu, P. C. C.; Combs, A. P.;

- Yue, E. W., Isothiazolidinone inhibitors of PTP1B containing imidazoles and imidazolines. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 66-71.
75. Moretto, A.; Kirincich, S.; Xu, W.; Smith, M.; Wan, Z. K.; Wilson, D.; Follows, B.; Binnun, E.; Joseph-McCarthy, D.; Foreman, K., Bicyclic and tricyclic thiophenes as protein tyrosine phosphatase 1B inhibitors. *Bioorg. Med. Chem.* **2006**, *14*, 2162-2177.
76. Klopfenstein, S. R.; Evdokimov, A. G.; Colson, A. O.; Fairweather, N. T.; Neuman, J. J.; Maier, M. B.; Gray, J. L.; Gerwe, G. S.; Stake, G. E.; Howard, B. W., 1, 2, 3, 4-Tetrahydroisoquinolinyl sulfamic acids as phosphatase PTP1B inhibitors. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1574-1578.
77. Wan, Z. K.; Lee, J.; Xu, W.; Erbe, D. V.; Joseph-McCarthy, D.; Follows, B. C.; Zhang, Y. L., Monocyclic thiophenes as protein tyrosine phosphatase 1B inhibitors: capturing interactions with Asp48. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4941-4945.
78. Wan, Z. K.; Follows, B.; Kirincich, S.; Wilson, D.; Binnun, E.; Xu, W.; Joseph-McCarthy, D.; Wu, J.; Smith, M.; Zhang, Y. L., Probing acid replacements of thiophene PTP1B inhibitors. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2913-2920.
79. Wilson, D. P.; Wan, Z. K.; Xu, W. X.; Kirincich, S. J.; Bruce, C.; Joseph-McCarthy, D.; Foreman, K.; Moretto, A.; Wu, J.; Zhu, M., Structure-based optimization of protein tyrosine phosphatase 1B inhibitors: from the active site to the second phosphotyrosine binding site. *J. Med. Chem.* **2007**, *50*, 4681-4698.
80. Hill, B.; Ahmed, V.; Bates, D.; Taylor, S. D., Enantioselective Synthesis of Protected 1-4-[Sulfonamido (difluoromethyl)] phenylalanine and 1-4-[Sulfonamido (methyl)] phenylalanine and an Examination of Hexa- and Tripeptide Platforms for Evaluating pTyr Mimics for PTP1B Inhibition. *J. Org. Chem.* **2006**, *71*, 8190-8197.
81. Combs, A. P.; Zhu, W.; Crawley, M. L.; Glass, B.; Polam, P.; Sparks, R. B.; Modi, D.; Takvorian, A.; McLaughlin, E.; Yue, E. W., Potent benzimidazole sulfonamide protein tyrosine phosphatase 1B inhibitors containing the

- heterocyclic (S)-isothiazolidinone phosphotyrosine mimetic. *J. Med. Chem.* **2006**, *49*, 3774-3789.
82. Sparks, R. B.; Polam, P.; Zhu, W.; Crawley, M. L.; Takvorian, A.; McLaughlin, E.; Wei, M.; Ala, P. J.; Gonneville, L.; Taylor, N., Benzothiazole benzimidazole (S)-isothiazolidinone derivatives as protein tyrosine phosphatase-1B inhibitors. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 736-740.
83. Cho, S. Y.; Baek, J. Y.; Han, S. S.; Kang, S. K.; Ha, J. D.; Ahn, J. H.; Lee, J. D.; Kim, K. R.; Cheon, H. G.; Rhee, S. D., PTP-1B inhibitors: Cyclopenta [d][1,2]-oxazine derivatives. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 499-502.
84. Zhang, W.; Hong, D.; Zhou, Y.; Zhang, Y.; Shen, Q.; Li, J.; Hu, L.; Li, J., Ursolic acid and its derivative inhibit protein tyrosine phosphatase 1B, enhancing insulin receptor phosphorylation and stimulating glucose uptake. *Biochim. Biophys. Acta (BBA)-General Subjects* **2006**, *1760*, 1505-1512.
85. Shrestha, S.; Bhattarai, B. R.; Chang, K. J.; Lee, K. H.; Cho, H., Methylene-disalicylic acid derivatives: New PTP1B inhibitors that confer resistance to diet-induced obesity. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2760-2764.
86. Shrestha, S.; Bhattarai, B. R.; Lee, K. H.; Cho, H., Mono- and disalicylic acid derivatives: PTP1B inhibitors as potential anti-obesity drugs. *Bioorg. Med. Chem.* **2007**, *15*, 6535-6548.
87. Bhattarai, B. R.; Shrestha, S.; Ham, S. W.; Kim, K. R.; Cheon, H. G.; Lee, K. H.; Cho, H., 2-O-Carboxymethylpyrogallol derivatives as PTP1B inhibitors with antihyperglycemic activity. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5357-5360.
88. Dixit, M.; Tripathi, B. K.; Tamrakar, A. K.; Srivastava, A. K.; Kumar, B.; Goel, A., Synthesis of benzofuran scaffold-based potential PTP-1B inhibitors. *Bioorg. Med. Chem.* **2007**, *15*, 727-734.
89. Adams, D. R.; Abraham, A.; Asano, J.; Breslin, C.; Dick, C. A. J.; Ixkes, U.; Johnston, B. F.; Johnston, D.; Kewnay, J.; Mackay, S. P., 2-Aryl-3,3,3-trifluoro-

- 2-hydroxypropionic acids: A new class of protein tyrosine phosphatase 1B inhibitors. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6579-6583.
90. Hu, H. G.; Wang, M. J.; Zhao, Q. J.; Yu, S. C.; Liu, C. M.; Wu, Q. Y., Synthesis of mangiferin derivatives and study their potent PTP1B inhibitory activity. *Chinese Chem. Lett.* **2007**, *18*, 1323-1326.
91. Jung, M.; Lee, Y.; Park, M.; Kim, H.; Kim, H.; Lim, E.; Tak, J.; Sim, M.; Lee, D.; Park, N., Design, synthesis, and discovery of stilbene derivatives based on lithospermic acid B as potent protein tyrosine phosphatase 1B inhibitors. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4481-4486.
92. Seiner, D. R.; LaButti, J. N.; Gates, K. S., Kinetics and mechanism of protein tyrosine phosphatase 1B inactivation by acrolein. *Chem. Res. Toxicol.* **2007**, *20*, 1315-1320.
93. Stuibler, M.; Zhao, L.; Aubry, I.; Schmidt-Arras, D.; Böhmer, F. D.; Li, C. J.; Tremblay, M. L., Cellular inhibition of protein tyrosine phosphatase 1B by uncharged thioxothiazolidinone derivatives. *Chem. Biochem.* **2006**, *8*, 179-186.
94. Lin, L.; Shen, Q.; Chen, G. R.; Xie, J., Synthesis of triazole-linked β -C-glycosyl dimers as inhibitors of PTP1B. *Bioorg. Med. Chem.* **2008**, *16*, 9757-9763.
95. Lin, L.; Shen, Q.; Chen, G. R.; Xie, J., β -C-Glycosiduronic acids and β -C-glycosyl compounds: New PTP1B inhibitors. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6348-6351.
96. Srinivasan, R.; Tan, L. P.; Wu, H.; Yao, S. Q., Solid-phase assembly and in situ screening of protein tyrosine phosphatase inhibitors. *Org. Lett.* **2008**, *10*, 2295-2298.
97. Kumar, A.; Ahmad, P.; Maurya, R. A.; Singh, A.; Srivastava, A. K., Novel 2-aryl-naphtho [1,2-d]oxazole derivatives as potential PTP-1B inhibitors showing antihyperglycemic activities. *Eur. J. Med. Chem.* **2009**, *44*, 109-116.
98. Kumar, A.; Maurya, R. A.; Sharma, S.; Ahmad, P.; Singh, A.; Tamrakar, A.; Srivastava, A. K., Design and synthesis of 3, 5-diarylisoxazole derivatives as

- novel class of anti-hyperglycemic and lipid lowering agents. *Bioorg. Med. Chem.* **2009**, *17*, 5285-5292.
99. Forghieri, M.; Laggner, C.; Paoli, P.; Langer, T.; Manao, G.; Camici, G.; Bondioli, L.; Prati, F.; Costantino, L., Synthesis, activity and molecular modeling of a new series of chromones as low molecular weight protein tyrosine phosphatase inhibitors. *Bioorg. Med. Chem.* **2009**, *17*, 2658-2672.
100. Lakshminarayana, N.; Rajendra Prasad, Y.; Gharat, L.; Thomas, A.; Ravikumar, P.; Narayanan, S.; Srinivasan, C.; Gopalan, B., Synthesis and evaluation of some novel isochroman carboxylic acid derivatives as potential anti-diabetic agents. *Eur. J. Med. Chem.* **2009**, *44*, 3147-3157.
101. Qiu, W. W.; Shen, Q.; Yang, F.; Wang, B.; Zou, H.; Li, J. Y.; Li, J.; Tang, J., Synthesis and biological evaluation of heterocyclic ring-substituted maslinic acid derivatives as novel inhibitors of protein tyrosine phosphatase 1B. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6618-6622.
102. Singh, F. V.; Parihar, A.; Chaurasia, S.; Singh, A. B.; Singh, S. P.; Tamrakar, A. K.; Srivastava, A. K.; Goel, A., 5, 6-Diarylanthranilo-1, 3-dinitriles as a new class of antihyperglycemic agents. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2158-2161.
103. Comeau, A. B.; Critton, D. A.; Page, R.; Seto, C. T., A focused library of protein tyrosine phosphatase inhibitors. *J. Med. Chem.* **2010**, *53*, 6768-6772.
104. Scior, T.; Guevara-García, J. A.; Melendez, F.; Abdallah, H. H.; Do, Q. T.; Bernard, P., Chimeric design, synthesis, and biological assays of a new nonpeptide insulin-mimetic vanadium compound to inhibit protein tyrosine phosphatase 1B. *Drug Des. Dev. Ther.* **2010**, *4*, 231.
105. Lu, L.; Wang, S.; Zhu, M.; Liu, Z.; Guo, M.; Xing, S.; Fu, X., Inhibition protein tyrosine phosphatases by an oxovanadium glutamate complex, $\text{Na}_2[\text{VO}(\text{Glu})_2(\text{CH}_3\text{OH})](\text{Glu}=\text{glutamate})$. *BioMetals* **2010**, *23*, 1139-1147.
106. Yuan, C.; Lu, L.; Wu, Y.; Liu, Z.; Guo, M.; Xing, S.; Fu, X.; Zhu, M., Synthesis, characterization, and protein tyrosine phosphatases inhibition activities of

- oxovanadium (IV) complexes with Schiff base and polypyridyl derivatives. *J. Inorg. Biochem.* **2010**, 104, 978-986.
107. Kumar, A.; Sharma, S.; Tripathi, V. D.; Maurya, R. A.; Srivastava, S. P.; Bhatia, G.; Tamrakar, A.; Srivastava, A. K., Design and synthesis of 2, 4-disubstituted polyhydroquinolines as prospective antihyperglycemic and lipid modulating agents. *Bioorg. Med. Chem.* **2010**, 18, 4138-4148.
108. Ye, D.; Zhang, Y.; Wang, F.; Zheng, M.; Zhang, X.; Luo, X.; Shen, X.; Jiang, H.; Liu, H., Novel thiophene derivatives as PTP1B inhibitors with selectivity and cellular activity. *Bioorg. Med. Chem.* **2010**, 18, 1773-1782.
109. Gupta, S.; Pandey, G.; Rahuja, N.; Srivastava, A. K.; Saxena, A. K., Design, synthesis and docking studies on phenoxy-3-piperazin-1-yl-propan-2-ol derivatives as protein tyrosine phosphatase 1B inhibitors. *Bioorg. Med. Chem. Lett.* **2010**, 20, 5732-5734.
110. Qian, S.; Li, H.; Chen, Y.; Zhang, W.; Yang, S.; Wu, Y., Synthesis and Biological Evaluation of Oleanolic Acid Derivatives As Inhibitors of Protein Tyrosine Phosphatase 1B. *J. Nat. Prod.* **2010**, 73, 1743-1750.
111. Lakshminarayana, N.; Prasad, Y. R.; Gharat, L.; Thomas, A.; Narayanan, S.; Raghuram, A.; Srinivasan, C.; Gopalan, B., Synthesis and evaluation of some novel dibenzo [b, d] furan carboxylic acids as potential anti-diabetic agents. *Eur. J. Med. Chem.* **2010**, 45, 3709-3718.
112. Tang, Y. H.; Hu, M.; He, X. P.; Fahnbulleh, S.; Li, C.; Gao, L. X.; Sheng, L.; Tang, Y.; Li, J.; Chen, G. R., Monosaccharide as a Central Scaffold Toward the Construction of Salicylate-Based Bidentate PTP1B Inhibitors via Click Chemistry. *Chem. Inform.* **2011**, 42.
113. Song, Z.; He, X. P.; Jin, X. P.; Gao, L. X.; Sheng, L.; Zhou, Y. B.; Li, J.; Chen, G. R., 'Click'to bidentate bis-triazolyl sugar derivatives with promising biological and optical features. *Tetrahedron Lett.* **2011**, 52, 894-898.

114. Song, Z.; He, X. P.; Li, C.; Gao, L. X.; Wang, Z. X.; Tang, Y.; Xie, J.; Li, J.; Chen, G. R., Preparation of triazole-linked glycosylated α -ketocarboxylic acid derivatives as new PTP1B inhibitors. *Carbohydr. Res.* **2011**, *346*, 140-145.
115. He, X. P.; Li, C.; Jin, X. P.; Song, Z.; Zhang, H. L.; Zhu, C. J.; Shen, Q.; Zhang, W.; Sheng, L.; Shi, X. X., Microwave-assisted construction of triazole-linked amino acid–glucoside conjugates as novel PTP1B inhibitors. *New J. Chem.* **2011**, *35*, 622-631.
116. Sun, L. P.; Shen, Q.; Piao, H. H.; Ma, W. P.; Gao, L. X.; Zhang, W.; Nan, F. J.; Li, J.; Piao, H. R., Synthesis and biological evaluation of (\pm)-3-(2-(2-fluorobenzyloxy) naphthalen-6-yl)-2-aminopropanoic acid derivatives as novel PTP1B inhibitors. *Eur. J. Med. Chem.* **2011**, *46*, 3630-3638.
117. Xie, J.; Tian, J.; Su, L.; Huang, M.; Zhu, X.; Ye, F.; Wan, Y., Pyrrolo[2,3-c]azepine derivatives: A new class of potent protein tyrosine phosphatase 1B inhibitors. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4306-4309
118. Jiang, B; Shi, D.; Cui, Y.; Guo, S. D., Synthesis and biological evaluation of bromophenol derivatives as protein tyrosine phosphatase 1B inhibitors. *Arch. Pharm. (Weinheim, Germany)* **2012**, *345*, 444-453.
119. Shi, D.; Li, J.; Jiang, B.; Guo, S.; Su, H.; Wang, T., Bromophenols as inhibitors of protein tyrosine phosphatase 1B with antidiabetic properties, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2827-2832.
120. Kumar, A.; Sharma, S.; Gupta, L. P.; Ahmad, P.; Srivastava, S. P.; Rahuja, N.; Tamrakar, A. K.; Srivastava, A. K., Synthesis of propiophenone derivatives as new class of antidiabetic agents reducing body weight in db/db mice, *Bioorg. Med. Chem.* **2012**, *20*, 2172-2179.
121. Kafle, B.; Cho, H., Isoxazolone derivatives as potent inhibitors of PTP1B, *Bulletin of the Korean Chem. Soc.* **2012**, *33*, 275-277.
122. Joshi, P.; Deora, G. S.; Rathore, V.; Tanwar, O.; Rawat, A. K.; Srivastava, A. K.; Jain, D., Identification of ZINC02765569: a potent inhibitor of PTP1B by vHTS *Med. Chem. Res.* **2013**, *22*, 28-34.

123. Basu, S.; Prasad, U. V.; Barawkar, D. A.; De, S.; Palle, V. P.; Menon, S.; Patel, M.; Thorat, S.; Singh, U. P.; Sarma, K. D.; et al, Discovery of novel and potent heterocyclic carboxylic acid derivatives as protein tyrosine phosphatase 1B inhibitors, *Bioorg. Med. Chem. Lett.* **2012**, 22, 2843-2849.
124. Ottana, R.; Maccari, R.; Amuso, S.; Wolber, G.; Schuster, D.; Herdinger, S.; Manao, G.; Camici, G.; Paoli, P., New 4-[(5-arylidene-2-arylimino-4-oxo-3-thiazolidinyl)methyl]benzoic acids active as protein tyrosine phosphatase inhibitors endowed with insulinomimetic effect on mouse C2C12 skeletal muscle cells, *Eur. J. Med. Chem.* **2012**, 50, 332-343.
125. Deora, G. S.; Karthikeyan, C.; Moorthy, N. S. Hari N.; Rathore, V.; Rawat, A. K.; Tamrakar, A. K.; Srivastava, A. K.; Trivedi, P., Design, synthesis and biological evaluation of novel arylidene-malononitrile derivatives as non-carboxylic inhibitors of protein tyrosine phosphatase 1B, *Med. Chem. Res.* **2013**, 22, 5344-5348.
126. Tang, Y-B.; Lu, D.; Chen, Z.; Hu, C.; Yang, Y.; Tian, J-Y.; Ye, F.; Wu, L.; Zhang, Z-Y.; Xiao, Z., Design, synthesis and insulin-sensitizing effects of novel PTP1B inhibitors, *Bioorg. Med. Chem. Lett.* **2013**, 23, 2313-2318.
127. Chandrasekharappa, A. P.; Badiger, S. E.; Dubey, P. K.; Panigrahi, S. K.; Manukonda, S. Reddy V. V. V., Design and synthesis of 2-substituted benzoxazoles as novel PTP1B inhibitors, *Bioorg. Med. Chem. Lett.* **2013**, 23, 2579-2584.
128. Aher, N. G.; Kafle, B.; Cho, H., Thiazolidinone derivatives as competitive inhibitors of protein tyrosine phosphatase 1B PTP1B, *Bull. Korean Chem. Soc.* **2013**, 34, 1275-1277.
129. Wang, Z.; Liu, Z.; Lee, W.; Kim, S-N.; Yoon, G.; Cheon, S.H., Design, synthesis and docking study of 5-(substituted benzylidene)thiazolidine-2,4-dione derivatives as inhibitors of protein tyrosine phosphatase 1B, *Bioorg. Med. Chem. Lett.* **2014**, 24, 3337-3340.

130. Zhi, Y.; Gao, L.-X.; Jin, Y.; Tang, C.-L.; Li, J.-Y.; Li, J.; Long, Y.-Q., 4-Quinolone-3-carboxylic acids as cell-permeable inhibitors of protein tyrosine phosphatase 1B, *Bioorg. Med. Chem.* **2014**, *22*, 3670-3683.
131. Yin, J.-P.; Tang, C.-L.; Gao, L.-X.; Ma, W.-P.; Li, J.-Y.; Li, Y.; Li, J.; Nan, F.-J., Design and synthesis of paracaseolide A analogues as selective protein tyrosine phosphatase 1B inhibitors, *Org. Biomol. Chem.* **2014**, *12*, 3441-3445.
132. Wang, W.-L.; Huang, C.; Gao, L.-X.; Tang, C.-L.; Wang, J.-Q.; Wu, M.-C.; Sheng, L.; Chen, H.-J.; Nan, F.-J.; Li, J.-Y.; et al, Synthesis and biological evaluation of novel bis-aromatic amides as novel PTP1B inhibitors, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 1889-1894.
133. Tang, Y.-B.; Liu, J.-Z.; Zhang, S.-E.; Du, X.; Nie, F.; Tian, J.-Y.; Ye, F.; Huang, K.; Hu, J.-P.; Li, Y.; et al, 3-Phenylpropanoic Acid-Based Phosphotyrosine (pTyr) Mimetics: Hit Evolution to a Novel Orally Active Protein Tyrosine Phosphatase 1B (PTP1B) Inhibitor, *Chem. Med. Chem.* **2014**, *9*, 918-921.
134. Tang, Y.H.; Hu, M.; He, X.P.; Fahnbulleh, S.; Li, C.; Gao, L.X.; Sheng, L.; Tang, Y.; Li, J.; Chen, G.R., Monosaccharide as a Central Scaffold Toward the Construction of Salicylate-Based Bidentate PTP1B Inhibitors via Click Chemistry. *Bull. Korean Chem. Soc.* **2011**, *32*, 1000-1006.
135. Zhang, W.; Hong, D.; Zhou, Y.; Zhang, Y.; Shen, Q.; Li, J.Y.; Hu, L.H.; Li, J., Ursolic acid and its derivative inhibit protein tyrosine phosphatase 1B enhancing insulin receptor phosphorylation and stimulating glucose uptake. *Biochim. Biophys. Acta* **2006**, *1760*, 1505–1512.
136. Galaktionov, K.; Beach, D., Specific activation of cdc25 tyrosine phosphatases by B-type cyclins: evidence for multiple roles of mitotic cyclins *Cell*, **1992**, *67*, 1181–94.
137. Janice, M. Z.; Young-Bum, K.; Odile, D. P.; Jason, K. K.; Michael, A. P.; Olivier, B.; Lori, D. K.; Shubhangi, K.; Gerald, I. S.; Barbara, B. K.; Benjamin, G. N., Overexpression of the LAR (leukocyte antigen-related) protein-tyrosine

- phosphatase in muscle causes insulin resistance, *Proc. Natl. Acad. Sci. U S A.*, **2001**; *98*, 5187–5192.
138. Corinne, B.; Nathalie, D.; Frédéric, L.; Nathalie, S.-L.; Jean-Pierre, E.; Katarina, B.; Louis, B.; Nicole, V.; Christiane S.' sst2 Somatostatin Receptor Mediates Negative Regulation of Insulin Receptor Signaling through the Tyrosine Phosphatase SHP-1 *J. Biol. Chem.* **1998**, *273*, 7099-7106.
139. Geraldine, F.; Frederic, L.; Jean-Pierre, E.; Audrey, F.; Eric, V.; Frederic, V.; Nathalie S.-L.; Lucien P.; Louis B.; Christiane S., Critical Role of Src and SHP-2 in sst2 Somatostatin Receptor-mediated Activation of SHP-1 and Inhibition of Cell Proliferation *Mol. Biol. Cell.* **2003**, *14*, 3911–3928.
140. Brown-Shimer, S.; Johnson, K.A.; Lawrence, J.B.; Johnson, C.; Bruskin, A.; Green, N.R.; Hill, D.E., Molecular cloning and chromosome mapping of the human gene encoding protein phosphotyrosyl phosphatase 1B *Proc. Natl. Acad. Sci.* **1990**, *13*, 5148–5152.
141. Glide, version 5.9, Schrödinger, LLC, New York, NY, 2013.
142. LigPrep, version 2.6, Schrödinger, LLC, New York, NY, 2013.
143. Schrödinger Suite 2013 Protein Preparation Wizard; Epik version 2.3, Schrödinger, LLC, New York, NY, 2013; Impact version 5.8, Schrödinger, LLC, New York, NY, 2013; Prime version 3.1, Schrödinger, LLC, New York, NY, 2013.
144. Sastry, G. M.; Adzhigirey, M.; Day, T.; Annabhimoju, R.; Sherman W. J. *Comput. Aid. Mol. Des.* **2013**, *27*, 221.