African Journal of Biological Sciences

Review Article

PTP1B: A multifaceted target for drug development of various human disorders

Shubham V. Pawar*, Anagha Joshi, Mukul Tambe

SCES's Indira College of Pharmacy, Tathawade, Pune, India

***Corresponding Author:**Shubham V. Pawar, SCES's Indira College of Pharmacy, Tathawade, Pune, India; Email ID: svpawar127@gmail.com; Mob.: (+91) 9011919695

Article History
Volume 6, Issue 5, 2024
Received: 22 May 2024
Accepted: 03Jun 2024
doi:*10.48047/AFJBS.6.5.2024.10637-10650*

Abstract

Protein Tyrosine Phosphatase 1B (PTP1B) stands as a pivotal enzyme in cellular signallingpathways, exerting significant influence on metabolism, insulin sensitivity, and cellular proliferation. This review comprehensively explores the pharmacological and chemical dimensions of PTP1B, highlighting its crucial role in regulating cellular processes. The structural elucidation of PTP1B has unveiled key insights into its function and inhibition. Its catalytic domain, featuring a conserved signature motif, serves as a target for pharmacological intervention. Various small molecule inhibitors have been developed to modulate PTP1B activity, with promising implications for treating metabolic disorders such as diabetes and obesity. Additionally, the structural diversity of PTP1B inhibitors offers opportunities for rational drug design and optimization. Beyond their therapeutic relevance, PTP1B inhibitors have emerged as valuable tools for probing cellular signallingnetworks. By selectively perturbing PTP1B function, researchers can dissect the intricate interplay between tyrosine phosphorylation and dephosphorylation events, shedding light on disease mechanisms and identifying novel drug targets. Furthermore, the review explores the diverse applications of PTP1B inhibitors in preclinical and clinical settings, ranging from basic research to drug discovery endeavours. The multifaceted roles of PTP1B inhibitors extend beyond metabolic disorders, encompassing cancer, inflammation, and neurodegenerative diseases. In conclusion, this review underscores the pivotal importance of PTP1B in cellular physiology and disease pathogenesis. By elucidating its pharmacological and chemical aspects, this comprehensive examination provides valuable insights into the development and application of PTP1B-targeted therapies for a myriad of human ailments.

Key Words: PTP1B, Allosteric Inhibitors, T2DM, Obesity, Cancer.

Introduction

Protein Tyrosine Phosphatase 1B (PTP1B), a regulatory protein encoded by the PTPN1 gene, wields significant influence over cellular signaling pathways, encompassing a diverse range of cellular processes, such as growth, metabolism, and differentiation. This review aims to elucidate the multifaceted functions of PTP1B, delve into the underlying mechanisms of its actions, and explore its clinical implications in health and disease (Tonks, 2006).Due to its pivotal role in regulating signaling pathways relevant to metabolic disorders, cancer, and inflammatory diseases, PTP1B has emerged as a highly sought-after target for therapeutic intervention. Consequently, extensive research has been devoted to developing pharmacological strategies to hinder PTP1B activity, culminating in the identification of numerous small molecule inhibitors and promising therapeutic candidates.

Small molecule inhibitors of PTP1B primarily target the enzyme's catalytic domain and competitively inhibit its phosphatase activity. These inhibitors are designed to mimic the structure of phosphotyrosine substrates and interact with the active site of PTP1B, thereby blocking its enzymatic function. Several classes of PTP1B inhibitors have been developed, including aryl sulfonamides, benzofuran derivatives, biphenylcarboxylic acids, and salicylic acid derivatives (Zhang et al., 2017; Krishnan et al., 2018).

Mechanism of Action

PTP1B inhibitors have a therapeutic effect by preventing the dephosphorylation of crucial signallingmolecules, such as insulin receptor substrates (IRS) and receptor tyrosine kinases (RTKs). This results in increased insulin signalling, improved glucose metabolism, and reduced inflammation. By inhibiting PTP1B activity, these inhibitors promote insulin sensitivity, glucose uptake, and glycogen synthesis in insulin-responsive tissues, thereby alleviating insulin resistance and hyperglycemia that are associated with obesity and type 2 diabetes mellitus (T2DM) (Klaman et al., 2000; Owen et al., 2015).

Clinical Development

Several PTP1B inhibitors have advanced into clinical development for the treatment of metabolic disorders and cancer. These inhibitors have undergone preclinical testing for safety, efficacy, and pharmacokinetic properties in animal models and early-phase clinical trials in human subjects. While some PTP1B inhibitors have shown promising results in preclinical studies, their clinical development has been hampered by challenges such as off-target effects, poor bioavailability, and limited efficacy in human trials. Further research is needed to optimize the pharmacokinetic and pharmacodynamic properties of PTP1B inhibitors and evaluate their long-term safety and efficacy in larger clinical trials(Goldstein, 2002; Zhang et al., 2004).

Role in Signal Transduction

Signal transduction is an indispensable process through which cells convert external signals into internal responses, ultimately regulating a myriad of cellular functions, including proliferation, differentiation, and metabolism. PTP1B plays a pivotal role in signal transduction by functioning as a negative regulator of tyrosine phosphorylation events (Elchebly et al., 1999).

Dephosphorylation of Receptor Tyrosine Kinases (RTKs)

RTKs are cell surface receptors activated upon ligand binding, leading to tyrosine phosphorylation in their cytoplasmic domains. This event initiates downstream signallingcascades for cell growth, survival, and differentiation. PTP1B negatively regulates RTK signallingby dephosphorylating activated receptors, thereby attenuating downstream pathways. (Neel and Tonks, 1997).

Modulation of Insulin Signalling pathway

PTP1B plays a key role in insulin signalling, facilitating insulin receptor autophosphorylation and insulin receptor substrate protein phosphorylation. This initiates a cascade of downstream signalling events, regulating glucose uptake, glycogen synthesis, and gene expression.

PTP1B's dephosphorylation of specific tyrosine residues on IRS proteins can contribute to insulin resistance in obesity and type 2 diabetes mellitus (Elchebly et al., 1999).

Regulation of Janus Kinase (JAK) Signalling

JAKs, also known as cytoplasmic tyrosine kinases, are responsible for transmitting signals from cytokine receptors to the nucleus, where they regulate immune responses, hematopoiesis, and inflammation. Recent studies have shown that the protein tyrosine phosphatase 1B (PTP1B) interacts directly with and dephosphorylates JAKs, negatively regulating the JAK-STAT signalling pathway. Dysregulation of PTP1B-mediated JAK dephosphorylation has been linked to inflammatory diseases and cancer (Tiganis, 2013).

Crosstalk with Other Signallingpathways

PTP1B interacts with various signalling pathways, including receptor tyrosine kinases (RTKs), insulin signalling components, and Janus kinases (JAKs). It also influences signalling events by modulating the activity of other protein phosphatases or scaffolding proteins involved in signal transduction. For example, it has been demonstrated to dephosphorylate components of growth factor receptor-mediated signalling pathways, such as the epidermal growth factor receptor (EGFR) pathway (Julien et al., 2011).

Regulation of Insulin Signalling

Insulin signalling, crucial for glucose uptake, glycogen synthesis, and lipid metabolism, operates by binding to its receptor and activating downstream signalling pathways, like the PI3K-Akt and MAPK pathways. PTP1B, a negative regulator, dephosphorylates key components of the insulin signalling cascade, such as IRS proteins, attenuating insulin signalling and leading to insulin resistance and impaired glucose metabolism (Elchebly et al., 1999).

Regulation of Energy Homeostasis

PTP1B plays a significant role in maintaining energy balance by regulating appetite, energy expenditure, and body weight in the hypothalamic neurons of the central nervous system. Genetic and pharmacological manipulation of PTP1B in animal models has demonstrated its potential as a target for combating obesity and related metabolic disorders (Zhang et al., 2004).

Regulation of Appetite

PTP1B is located in the ARC and VMH, which are essential for appetite regulation. Research indicates that when PTP1B is absent or blocked in these areas, neuropeptide signalling is affected, leading to increased POMC and reduced AgRP/NPY expression. As a result, food intake decreases and resistance to obesity induced by diet improves.(Bence et al., 2006; Tsou et al., 2014).

Impact on Body Weight Regulation

PTP1B plays a crucial role in the regulation of body weight by integrating signals from peripheral tissues and the CNS to modulate energy balance. Genetic deletion or inhibition of PTP1B results in reduced adiposity, improved insulin sensitivity, and resistance to diet-induced obesity. Conversely, overexpression of PTP1B in the CNS leads to hyperphagia, obesity, and metabolic dysfunction, highlighting the importance of PTP1B in the central regulation of body weight (Elchebly et al., 1999; Zabolotny et al., 2002).

Implications in Obesity and Metabolic Disorders

The dysregulation of protein tyrosine phosphatase 1B (PTP1B) has been linked to obesity and metabolic disorders. PTP1B overexpression and activity have been observed in obesity, insulin resistance, and type 2 diabetes mellitus (T2DM), leading to dysregulated energy balance and metabolic dysfunction. Pharmacological inhibition or genetic deletion of PTP1B has shown promise in improving energy homeostasis, insulin sensitivity, and body weight control in preclinical models, suggesting its potential as a therapeutic target for obesity and related metabolic disorders (Julien et al., 2007; Zabolotny et al., 2008; Owen et al., 2015). PTP1B, which affects glucose metabolism, also regulates lipid metabolism. Research on PTP1B-deficient mice indicates that PTP1B plays a role in adipogenesis, lipid storage, and

energy balance, as they exhibit reduced adiposity, increased energy expenditure, and improved lipid profile. PTP1B modulates the activity of key regulators of lipid metabolism, such as PPARγ and SREBPs, through its interactions with insulin signalling pathways (Klaman et al., 2000). PTP1B is a critical regulator of energy balance and metabolism, and increased levels of it are associated with obesity and insulin resistance (Klaman et al., 2000; Cheng et al., 2002). This results in impaired insulin signaling, glucose intolerance, and dysregulated lipid metabolism. Genetic deletion or inhibition of PTP1B improves insulin sensitivity, glucose tolerance, and energy balance in animal models of obesity and T2DM, indicating its potential as a therapeutic target for metabolic disorders. Insulin signalling, crucial for glucose uptake, glycogen synthesis, and lipid metabolism, operates by binding to its receptor and activating downstream signalling pathways, like the PI3K-Akt and MAPK pathways. PTP1B, a negative regulator, dephosphorylates key components of the insulin signalling cascade, such as IRS proteins, attenuating insulin signalling and leading to insulin resistance and impaired glucose metabolism (Elchebly et al., 1999; Zabolotny et al., 2008). PTP1B also negatively regulates insulin signaling by dephosphorylating insulin receptor substrate (IRS) and attenuating downstream signaling events. Elevated PTP1B expression and activity contribute to the development of insulin resistance and T2DM. Pharmacological inhibition or genetic deletion of PTP1B improves insulin sensitivity and glucose homeostasis, suggesting its potential as a therapeutic target for T2DM(Klaman et al., 2000; Owen et al., 2015).

Role in Various Diseases

PTP1B has been linked to the development of various diseases, including obesity, T2DM (type 2 diabetes mellitus), cancer, and inflammatory disorders. Dysregulation of PTP1B activity results in abnormal signalling pathways, metabolic dysfunction, and immune system dysregulation, emphasizing its importance as a potential target for therapy in these diseases.

Cancer

PTP1B has been identified as a potential regulator of cancer development, with its role depending on the cellular context. While it can inhibit growth factor signalling and suppress tumor growth in some cases, its overexpression has been linked to oncogenic phenotypes like enhanced cell proliferation, survival, and metastasis. PTP1B also modulates signalling pathways involved in tumor progression, such as receptor tyrosine kinase (RTK) and Janus kinase (JAK) signalling. Targeting PTP1B may offer therapeutic benefits in cancer treatment by inhibiting tumor growth and metastasis(Julien et al., 2007; Tonks et al., 2006).

Inflammatory Disorders

PTP1B has been linked to the regulation of immune responses and inflammatory signalling pathways. Increased PTP1B expression and activity have been observed in inflammatory disorders such as rheumatoid arthritis, inflammatory bowel disease, and atherosclerosis. PTP1B regulates cytokine signalling pathways through its interactions with Janus kinases (JAKs) and signal transducer and activator of transcription (STAT) proteins. Pharmacological inhibition or genetic deletion of PTP1B attenuates inflammatory responses and improves disease outcomes in preclinical models, suggesting its potential as a therapeutic target for inflammatory disorders (Zabolotny et al., 2002; Zhang et al., 2004).

Chemistry:

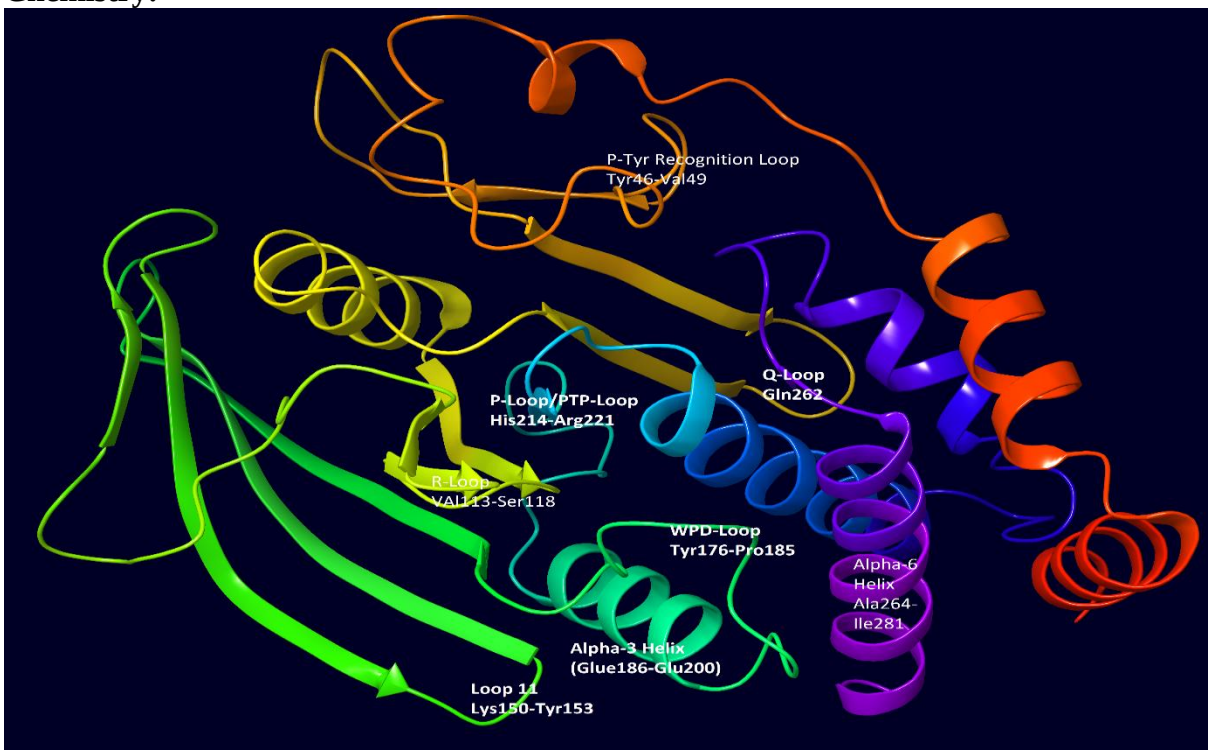

Fig:1Protein Structure of PTP1B

Researchers have conducted studies using computer-based methods to examine the interactions and mechanisms of six various natural compounds with PTP1B, utilizing docking and molecular dynamics simulations to assess inhibition (Baskaran &Baddireddi, 2019). The first crystal structure of PTP1B, a non-receptor PTP, was reported in 1994 (Barford et al., 1994). PTP1B's structure comprises three domains, including the N-terminal Catalytic Domain, Regulatory Domain, and C-terminal Domain (Villamar-Cruz et al., 2021; Simoncic et al., 2006). The PTP1B enzyme consists of 435 amino acids and has an approximate molecular weight of 45 kDa.

PTP1B comprises eight alpha helices and twelve beta strands, as reported by Tautz et al. (2013). Its structure contains a catalytically active site that is surrounded by various loops, including the WPD loop, Qloop, pTyr-loop, and E-loop, among others, as described by Yang et al. (2001). PTP1B has a unique pattern that features a specific conserved Catalytic WPD loop, which is shared by other PTPs from various microorganisms. This presents a challenge in developing potential drugs that are selective for the enzyme, as it shows significant similarity to TCPTP, as noted by Barford et al. (1995) and Fauman and Saper (1996). Studies have demonstrated that the activity of PTP1B is regulated by conformational changes in the WPD loop.The availability of substrate to the WPD loop facilitates enzyme activity, leading to conformational changes that enable the WPD loop to assume a closed conformation (Wiesmann et al., 2004). This activation is bolstered by other domain regions, including the R-loop, P loop, pTyr recognition loop, Q-loop, S-loop, Loop 11, α-3 helix, α-6 helix, and α-7 helix (FIG:211) (Yang et al., 2001; Olmez and Alaknet, 2011). The amino acids that designate the Loops are given in following table:

Name of Loop	**Amino Acid with Sequence number**
WPD loop	Tyr176-Pro185
R-loop	Val113-Ser118
P loop	His214-Arg221
pTyr recognition loop	Tyr46-Val49
Q- loop	Gln262
S-loop	Leu204-Gly209
Loop 11	Lys150-Tyr153

α-3 helix	Glu186-Glu200
α-6 helix	Ala264-Ile281
α-7 helix	Ser285-Ser295)

Researchers have developed various inhibitors aimed at the catalytic active site, but only a few have progressed to clinical trials. The challenge of selectivity, due to structural similarity with other PTPs, as well as issues with permeability and a conserved active site, has hindered the development of inhibitors. However, Wiesmann et al. identified a non-catalytic inhibitor that targets an allosteric site located approximately 20 Å away from the catalytic site. This site comprises the α-3 helix, α-6 helix, and α-7 helix. Some studies have shown that inhibition of the allosteric site induces a conformational change in the enzyme that renders it inactive, distorting the WPD loop (Wiesmann et al., 2004; Olmez and Alaknet, 2011).
The details of Allosteric inhibitors are given in the following section.

Allosteric inhibition of PTP1B

Wiesmann et al. in 2004 initially uncovered a novel allosteric site during their examination of a few Benzofuran derivatives on PTP1B. During this study, compound 1**(Fig:2)** did not exhibit time-dependent inhibition, and it displayed significant reversibility and a consistent low compound-to-protein stoichiometry. The mechanism of this binding was confirmed through X-ray crystallography, and the first allosteric inhibition of PTP1B was reported. The benzofuran-based compounds 1 and 2 **(Fig:2)** were found to exhibit allosteric inhibition, with IC50 values of 22 and 8uM, respectively, which is 40-fold greater than benzbromarone, a previously reported inhibitor (Wiesmann Et al 2004).

Further, Kamerlin et al. (2006) investigated the mechanism of the novel allosteric inhibitors i.e. compound 3 **(Fig:2)**through targeted molecular dynamics. The molecular dynamics simulation of the complex revealed that the closure of the WPD loop was completely prevented, leading the enzyme to adopt a catalytically inactive conformation. This inactivation is attributed to the inhibition of the α3-helix rearrangement relative to the α7-helix (Kamerlin et al., 2006). Subsequently, Kamerlin et al. (2007) extended this allosteric inhibition study. They utilized the compound for the development of force field parameters and examined the mobility of the WPD loop with the inhibitors. Results indicated that the said inhibitor significantly reduced the mobility of the WPD loop and restricted flexibility in the S loop of the enzyme (Kamerlin et al., 2007).

In the year 2008, a study was conducted by Muthusamy et al. to investigate the tannins present in Cichorium intybus and their impact on glucose uptake and PTP1B inhibition. The study analyzed both the methanolic extract of Cichorium intybus (CME) and the detannified extract (CME/DT) using radiolabeled glucose uptake and lipid accumulation assays to examine the effects on glucose transport and adipocyte differentiation in 3T3-L1 cells, respectively. The results showed that CME failed to inhibit glucose uptake in inhibitor-treated cells, while CME/DT showed the opposite effect. Additionally, the study found that the PTP1B enzyme was inhibited by CME, while CME/DT did not exhibit this activity. This suggested that the tannins present in the extract were responsible for inhibiting the PTP1B enzyme. The effects of CME and CME/DT on the insulin signallingcascade were further examined using immunoprecipitation and western blot techniques. The results indicated that the important markers of insulin signalling, such as IR beta and IRS1, were phosphorylated when treated with CME, whereas their expression was very low in the presence of CME/DT. This suggested that the tannins present in the extract exhibited PTP1B inhibition activity (Muthusamy et al., 2008).In 2010, researchers performed solvent-solvent fractionation on CME and subsequently subjected it to 2-deoxy-D3 [H]-glucose uptake studies. Based on the results, the butanol-soluble fraction was isolated for column chromatography, which led to the identification of CGA. (Muthusamy et al., 2010) Subsequently, in 2012, Baskaran et al. investigated the molecular interactions between PTP1B allosteric site and compound 5, CGA(4) and CHA(6) **(Fig:2)**, which are caffeoyl derivatives. Using computational tools, they

performed molecular docking and dynamic studies, demonstrating that the ligand-protein complex was stable and restricted the mobility of the WPD loop, thereby inactivating the enzyme. (Baskaran et al., 2012).

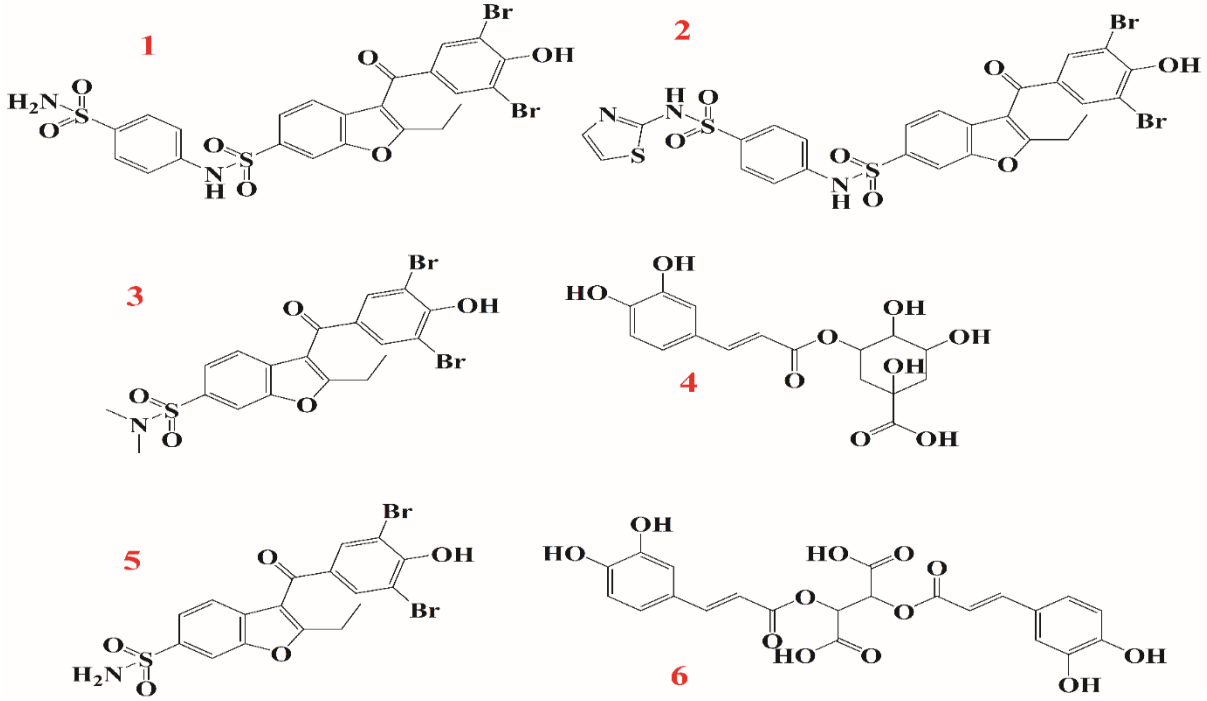

Fig:2 PTP1B Allosteric Inhibitors (Compound no 1-6)

Building upon the work of Weismann et al., Tang et al. designed and synthesized 15 novel sulfathiazole-based derivatives from compound 1**(Fig:3)**. Among these, six compounds exhibited significant PTP1b inhibitory activity, demonstrating selectivity over other PTPs. Among these, compound 7 (X= , L=, R1=, R2= R3=)**(Fig:3)** was found to be the most active, with an IC50 value of 3.2uM and displaying non-competitive inhibition of PTP1B. Additionally, the compound was found to have insulin-sensitizing effects when tested in vivo in insulin-resistant mice, as reported by Tang et al. (2013).Krishnan et al (2014) demonstrated the binding of the previously reported phosphatase PTP1B inhibitor, Trodusquemine (8) **(Fig:3)**, to the allosteric site, which distorted the C terminus. Subsequent research revealed that this inhibitor antagonized HER2 signallingand inhibited tumorigenesis in breast cancer. Furthermore, the authors identified two sites, Alpha 9 and Alpha 7 extended, where Trodusquemine (8) **(Fig:3)**, a cholestane-based compound, bound to the space between these two sites and distorted the enzyme, resulting in its inactivity.

The inhibitory activity of lupine triterpenes, including Lupeol, lupenone, betulin, and betulinic acid (09) **(Fig:3)**, was investigated for their potential to inhibit PTP1B by Jin et al. (2016). The researchers conducted molecular docking and MD studies to evaluate the binding allosteric site of these triterpenes and found that they demonstrated hydrophobic interactions with amino acids Ala189, Leu192, Phe196, Phe280, Trp291, and Leu294 present in the allosteric site. The enzyme inhibition assay revealed that all these triterpenes were non-competitive inhibitors of PTP1B enzyme, with IC 50 values of 5.6 uM, 13.7 uM, 15.3 uM, and 1.5 uM, respectively.

Ottanàand co-workers designed and synthesized novel (4-oxothiazolidin-3-yl)methyl benzoic acid derivatives (10) **(Fig:3)** for PTP1B allosteric inhibition. Two different series with substitutions at C2 and different aryl substitutions at C5 of Thiazolidine-4-one were designed. In vitro studies on PTP1b showed that all compounds possessed significant inhibitory activity. Out of these compounds, three compounds were the most effective PTP1B inhibitors, with IC50 values ranging from 1.5 µM to 1.9 µM. The study also revealed that some compounds exhibited reversible binding with PTP1B enzyme, while the remaining compounds showed a mixed pattern of inhibition, both reversible and irreversible. Kinetic studies of the designed molecules were conducted to determine the type of inhibition, which revealed that the compounds inhibit the enzyme in both competitive and non-competitive manners. Furthermore, the insulin mimetic activity of the compounds on HEP G2 cells showed that compounds from series 5 increased IR beta phosphorylation levels, indicating that these compounds behaved as insulin mimetics. However, compounds from series did not exhibit such activity (Ottanà et al, 2016).

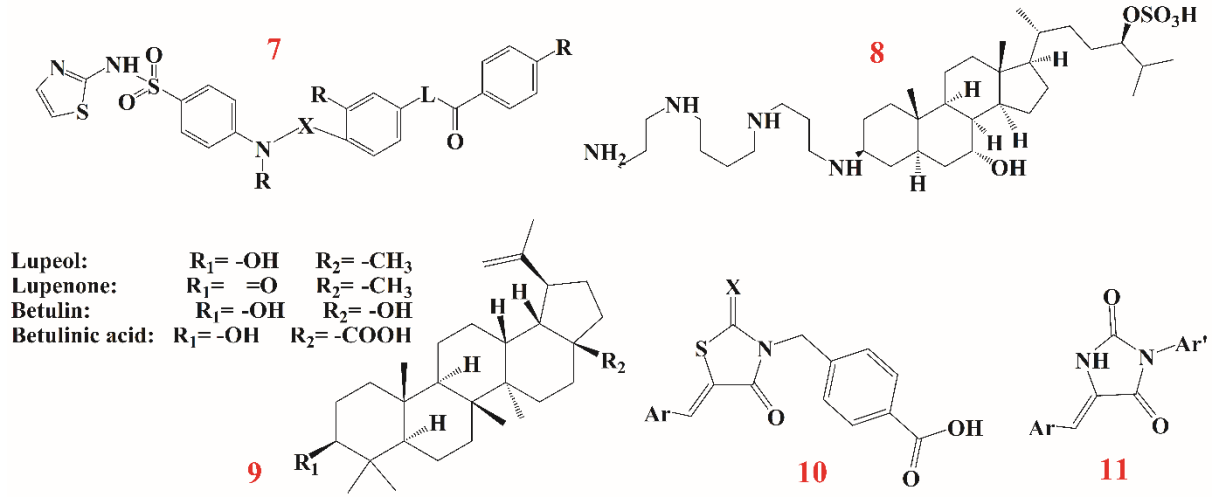

Fig:3 PTP1B Allosteric Inhibitors (Compound no 7-11)

In 2019, Ottana et al. introduced a new series of 3-aryl-5-arylidene-2-thioxo-4-imidazolidinones (11) **(Fig:3)**, which replaced the thiazolidine ring with an imidazole ring. These non-carboxylate PTP1B inhibitors were found to be reversible and non-competitive at micromolar concentrations, as revealed by kinetic studies. Furthermore, docking studies showed that these molecules fit into the allosteric site of PTP1B. It was also discovered thatthese agents acted as insulin sensitizing agents when evaluated by cellular assays on liver HEPG2 cells. The study was conducted by Ottana et al. (2019).

In 2017, Zargari et al investigated the binding of three flavonoids—Morin (MOR)(14), 2′-Methoxykurarinone (MOK) (13), and 6,8-diprenylorobol (DPO) (12) **(Fig:4)**—at the allosteric site of the PTP1B enzyme. The molecular interaction between these flavonoids and the enzyme was examined through molecular docking and dynamics studies, as well as free energy landscape and cluster analysis. According to the molecular docking analysis, DPO had the lowest binding energy of -8.3 kcal/mol, followed by MOK (-6.5 kcal/mol) and MOR (-5.3 kcal/mol). The molecular dynamics study also yielded positive results for all three flavonoids, as demonstrated by the cluster analysis cutoff at 1.15 A (Zargari et al, 2017).

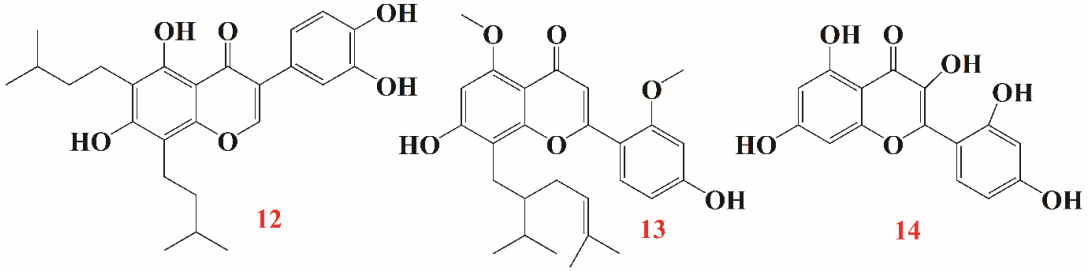

Fig:4 PTP1B Allosteric Inhibitors (Compound no 12-14)

Kostrzewa et al. (2018) examined small peptide-like molecules (15-18) **(Fig:5)** for their capacity to inhibit PTP1B activity at an allosteric site. Through molecular docking studies of four dipeptides and tripeptides, the researchers identified specific amino acids that bound to the allosteric site. These compounds were assessed for their ability to inhibit PTP1B using an in-vitro assay, which showed that they reduced enzymatic activity and decreased the viability of MCF7 breast cancer cells in the presence of the inhibitors (Kostrzewa et al., 2018).

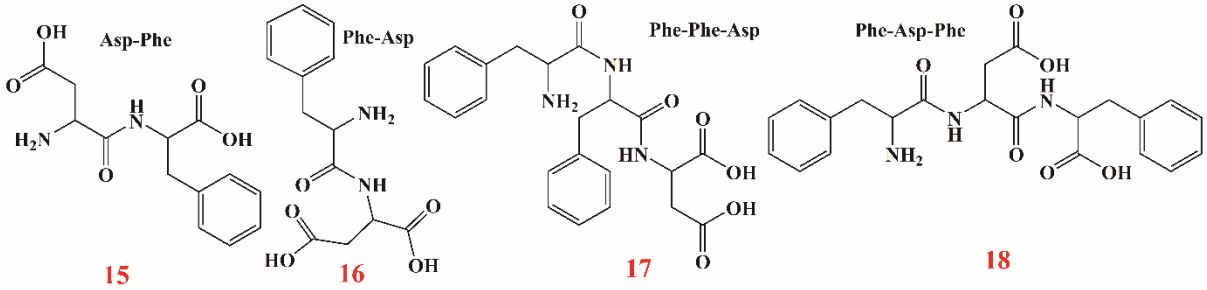

Fig:2 PTP1B Allosteric Inhibitors (Compound no 15- 18)

Researchers, including Morishita et al. (2017), designed a library of novel substituted benzoylsulfonamide compounds (19)**(Fig:6)** for the purpose of testing them as inhibitors of PTP1B. Among these compounds, 19**(Fig:6)**displayed potent and selective inhibitory activity against the PCP1B enzyme, with an IC50 value of 0.25 µM. Additionally, 18K was determined to be a non-competitive inhibitor that binds to the allosteric site of the enzyme. The oral absorption of 19**(Fig:6)** was found to be high, resulting in a significant reduction of blood glucose levels with no reported significant side effects (Morishita et al., 2017).

In 2017, Punthasee and colleagues investigated the conjugate composed of 5-aryl-1,2,5-thiadiazolidin-3-one 1,1-dioxide**(20)(Fig:6)**previously designed with an electrophilic α-bromoacetamide. The time-dependent loss of activity of PTP1B was observed with one of the compounds 20. Mass spectrometry of the inactivated enzyme revealed that the modification at C121 was the primary change in the structure, which suggests allosteric inhibition of the enzyme. (Punthasee et al, 2017)

In 2018, Eto et al conducted a pharmacological evaluation of bipenyl-benzoylsulfonamide compounds**(19) (Fig:6)** against the PTP1B enzyme for their inhibitory effects. The compound **19(Fig:6)** was found to inhibit PTP1B with an IC50 value of 0.28 ± 0.01 mM. Furthermore, it was observed that this compound increased the phosphorylation of IR signallingat the same concentration where it inhibited PTP1B, indicating its potential to reduce insulin resistance. However, the compound did not show adipocyte differentiation. The study's highlight was that compound **19(Fig:6)** inhibits PTP1B at an allosteric site without PPARS agonist activity, which enhances its impact as an antidiabetic agent by improving insulin signallingin hepatic cells and muscles. Additionally, the compound demonstrated anti-obesity effects, which is a difficulty faced by many antidiabetic agents (Eto et al, 2018).

Qin et al (2018) conducted a study on Flavonolignans from Silubum Marianum**(21) (Fig:6)**, and a total of nine compounds were evaluated for their non-competitive inhibitory effect on PTP1B. The kinetic analysis of compounds 1 to 5 demonstrated the non-competitive inhibition of PTP1B, and the molecular docking study further supported the inhibitory activity against the PTP1B enzyme. The results of this study were published in (Qin et al, 2018)

Shinde et. Al in 2018 developed a receptor-based pharmacophore. In this virtual screening protocol authors used two pharmacophores for identification of PTP1B inhibitor which must determine selectivity and permeability toward enzyme. the molecular docking and MD studies were performed to establish the allosteric inhibition mechanism of enzyme. For the same 23 molecules had potential inhibitory activity and out of them 10 was found to possess good permeability with potential inhibitory property. This study had given idea about the presence of hydrophobic region, hydrogen bond acceptor region and hydrogen bond donor

region. It also indicated the exact distance between all the regions.The study had well explained the use of receptor-based pharmacophore generation for a potent and selective inhibitor targeting allosteric site. (Shinde et al., 2018).

Shi et al. (2019) investigated a N-atom augmented product of radicicol. The inhibition of PTP1B through allosteric site was evaluated by molecular docking studies, Mutagenesis and enzymological studies. Out of several compounds, compound **22(Fig:6)** showed an increased insulin signallingand glucose uptake in a dose-dependent manner. The authors suggested that pyrrolopyrazoloisoquinolone can be modified to increase the potency and selectivity of the agents (Shi et al., 2019).

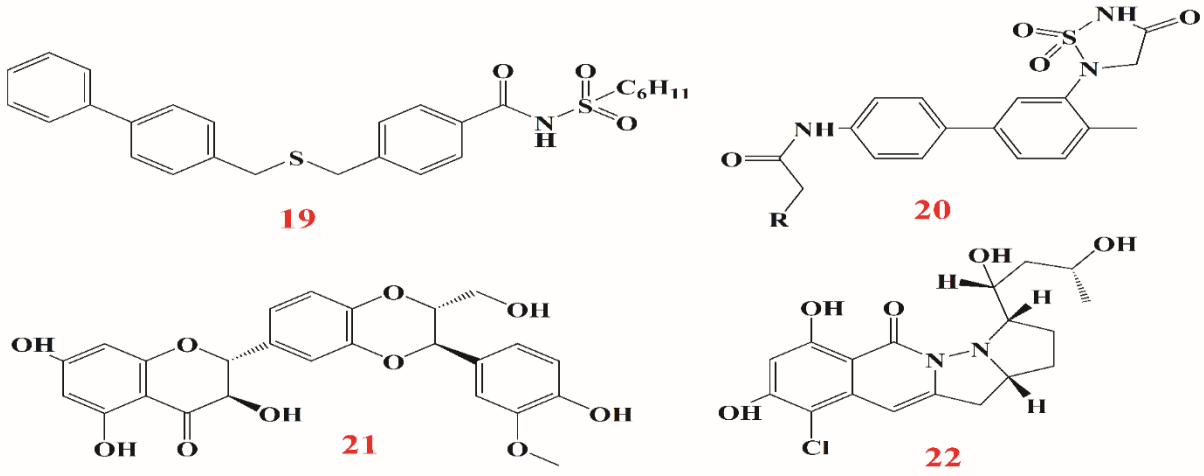

Fig:6 PTP1B Allosteric Inhibitors (**Compound no 19-22**)

In 2019, Bhaskaran et al. selected six natural products based on their in-vitro antidiabetic activity for further evaluation. The study aimed to examine the potential of Aloe emodin glycoside (AEG)**(23)**, 3β-taraxerol (3BT)**(24) (Fig:7)**, chlorogenic acid (CGA)**(4)**, cichoric acid (CHA)(6)**(Fig:3)**, (3β)-stigmast-5-en-3-ol (SGS)**(25)**, and methyl lignocerate (MLG)**(26)(Fig:7)** as PTP1B allosteric inhibitors through molecular docking, molecular dynamic simulation, and homology modelling. The results of the study showed that AEG, 3BT, CGA, and CHA bound more effectively to the allosteric site of PTP1B than SGS and MLG. The docking study comparison of these compounds on the active site and allosteric site indicated that the compounds exhibited favourable binding at the allosteric site. The study findings emphasized the significance of the α-7 helix of PTP1B and its coordination with the WPD loop, Loop11, α-3 helix, and α-6 helix (Bhaskaran et al 2019).

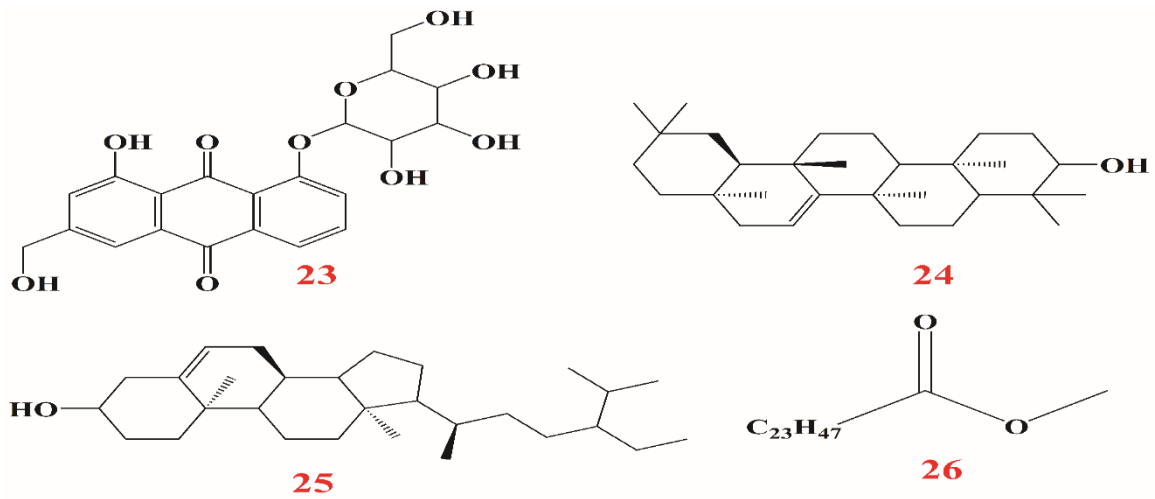

Fig:7 PTP1B Allosteric Inhibitors (Compound no 23-26)

In 2022, Friedman et al employed a terpanoid called amorphadiene (AD)**(27)(Fig:8)**, which had been previously isolated from a microbial culture, for the purpose of PTP1B inhibition. The researchers conducted an evaluation of the allosteric inhibition of PTP1B by **27** through molecular dynamics simulations. The simulations suggested that AD**(27)** bound to two adjacent sites on the allosteric influence C terminus. This binding was distinct from that of other allosteric inhibitors. Upon binding to this site, AD**(27)** distorted the α7 helix, which initiated the closure of the WPD loop and resulted in the observed inhibitory activity. The authors of the study proposed that the AD**(27)** scaffold could be utilized for the development of novel derivatives (Friedman et al, 2022).**(Fig:8)**

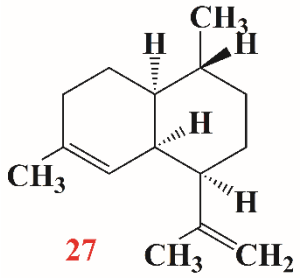

Fig:8 PTP1B Allosteric Inhibitors (Compound no 27)

Discussion

This review article delves into the complex pharmacological and chemical aspects of the Protein Tyrosine Phosphatase 1B (PTP1B) enzyme, emphasizing its significance as a potential therapeutic target for various diseases. Through a comprehensive analysis, several key points emerge. The review explores the pharmacological aspects of PTP1B, including its role in cellular signaling pathways and its involvement in diseases such as obesity, diabetes, and cancer. By elucidating the mechanisms underlying PTP1B's action, the article provides valuable insights into its potential as a therapeutic target for these conditions. In-depth analysis of the chemical structure of PTP1B and its catalytic mechanism enhances our understanding of its function within cellular signaling networks. By elucidating the interactions between PTP1B and its substrates, the review elucidates the molecular basis of its regulatory role in cellular processes. The article also discusses the development of inhibitors and modulators targeting PTP1B, highlighting their potential for therapeutic intervention. By summarizing the structure-activity relationships of known inhibitors, the review provides valuable insights into the design and optimization of novel PTP1B-targeted therapeutics. The review also explores the clinical implications of targeting PTP1B in the treatment of metabolic disorders, cancer, and autoimmune diseases. By examining preclinical and clinical studies, the article evaluates the efficacy and safety of PTP1B inhibitors in therapeutic applications, providing valuable guidance for future drug development efforts.

Conclusion

In conclusion, your review article provides a comprehensive overview of the pharmacology and chemistry of the PTP1B enzyme, highlighting its significance as a therapeutic target in various diseases. Through a detailed analysis of its structure, function, and pharmacological relevance, the article underscores the potential of PTP1B inhibitors and modulators for the treatment of metabolic disorders, cancer, and autoimmune diseases. By synthesizing existing knowledge and identifying future research directions, your review contributes to the advancement of PTP1B-targeted drug discovery efforts, paving the way for the development of innovative therapeutics with clinical utility.

Funding

Nil

Conflict of interest

None

References

1. Anika J. Friedman, Evan T. Liechty, Levi Kramer, Ankur Sarkar, Jerome M. Fox, and Michael R. Shirts The Journal of Physical Chemistry B 2022 126 (42), 8427-8438.
2. Barford D, Jia Z, Tonks NK (1995) Protein tyrosine phosphatases take off. Nat Struct Mol Biol 2: 1043–1053.
3. Barford, D.; Flint, A.J.; Tonks, N.K. Crystal structure of human protein tyrosine phosphatase 1B. Science 1994, 263, 1397–1404.
4. Baskaran S.K. &Baddireddi S. L., Journal of Molecular Modeling (2019) 25:272
5. Bence, K. K. et al. (2006). Neuronal PTP1B regulates body weight, adiposity and leptin action. Nature Medicine, 12(8), 917–924.
6. Cheng, A. et al. (2002). Attenuation of leptin action and regulation of obesity by protein tyrosine phosphatase 1B. Developmental Cell, 2(4), 497–503.
7. Elchebly, M. et al. (1999). Increased insulin sensitivity and obesity resistance in mice lacking the protein tyrosine phosphatase-1B gene. Science, 283(5407), 1544–1548.
8. Fauman EB, Saper MA (1996) Structure and function of theprotein tyrosine phosphatases. Trends biochem sci 21: 413–417.
9. Goldstein, B. J. (2002). Protein-tyrosine phosphatase 1B (PTP1B): a novel therapeutic target for type 2 diabetes mellitus, obesity and related states of insulin resistance. Current Drug Targets, 3(6), 359–375.
10. J. Yang, T. Niu, A. Zhang, A.K. Mishra, Z.J. Zhao, G.W. Zhou, Relation between the flexibility of the WPD loop and the activity of the catalytic domain of protein tyrosine phosphatase SHP-1, J. Cell. Biochem. 84 (1) (2001) 47-55.
11. Julien, S. G. et al. (2007). Protein tyrosine phosphatase 1B deficiency or inhibition delays ErbB2-induced mammary tumorigenesis and protects from lung metastasis. Nature Genetics, 39(3), 338–346.
12. Julien, S. G. et al. (2011). Protein tyrosine phosphatases in cancer: friends and foes! Progress in Molecular Biology and Translational Science, 106, 253–306.
13. Klaman, L. D. et al. (2000). Increased energy expenditure, decreased adiposity, and tissue-specific insulin sensitivity in protein-tyrosine phosphatase 1B-deficient mice. Molecular and Cellular Biology, 20(15), 5479–5489.
14. Krishnan, N. et al. (2018). Protein tyrosine phosphatases as potential therapeutic targets. Acta Pharmaceutica Sinica B, 8(5), 699–713.
15. Morishita K, Shoji Y, Tanaka S, Fukui M, Ito Y, Kitao T, Ozawa SI, Hirono S, Shirahase H. Novel Non-carboxylate Benzoylsulfonamide-Based Protein Tyrosine Phosphatase 1B Inhibitors with Non-competitive Actions. Chem Pharm Bull (Tokyo). 2017;65(12):1144-1160.
16. Navasona Krishnan, Dorothy Koveal, Daniel H Miller, Bin Xue, Sai DipikaaAkshinthala, Jaka Kragelj, Malene Ringkjøbing Jensen, Carla-Maria Gauss, Rebecca, Martin Blackledge, Senthil K Muthuswamy, Wolfgang Peti & Nicholas K Tonks, "Targeting the disordered C terminus of PTP1B with an allosteric inhibitor", nature chemical biology, 2014, 10, 558-566.
17. Neel, B. G., & Tonks, N. K. (1997). Protein tyrosine phosphatases in signal transduction. Current Opinion in Cell Biology, 9(2), 193–204.
18. Olmez EO, Alakent B (2011) Alpha helix plays an important role in the conformational stability of PTP1B. J Biomol Struct Dyn 28(5):675–693.
19. Ostrzewa T, Sahu KK, Gorska-Ponikowska M, Tuszynski JA, Kuban-Jankowska A. Synthesis of small peptide compounds, molecular docking, and inhibitory activity evaluation against phosphatases PTP1B and SHP2. Drug Des Devel Ther. 2018, 12: 4139–4147.
20. Owen, C. et al. (2015). Targeting the protein tyrosine phosphatase 1B for the treatment of obesity. Current Opinion in Drug Discovery & Development, 18(4), 449–457.

21. PuminanPunthasee, Adrian R. Laciak, Andrea H. Cummings, Kasi ViswanatharajuRuddraraju, Sarah M. Lewis, Roman Hillebrand, Harkewal Singh, John J. Tanner, and Kent S. Gates, Biochemistry 2017 56 (14), 2051-2060
22. Qin, N., Sasaki, T., Li, W., Wang, J., Zhang, X., Li, D., … Koike, K. (2018). Identification of flavonolignans from Silybum marianum seeds as allosteric protein tyrosine phosphatase 1B inhibitors. Journal of Enzyme Inhibition and Medicinal Chemistry, 33(1), 1283–1291.
23. Rosaria Ottanà, Paolo Paoli, Alexandra Naß, Giulia Lori, Venera Cardile, Ilenia Adornato, Archimede Rotondo, Adriana Carol Eleonora Graziano, Gerhard Wolber, Rosanna Maccari, "Discovery of 4-[(5-arylidene-4-oxothiazolidin-3-yl)methyl]benzoic acid derivatives active as novel potent allosteric inhibitors of protein tyrosine phosphatase 1B: In silico studies and in vitro evaluation as insulinomimetic and anti-inflammatory agents", European Journal of Medicinal Chemistry, 127, 2017, 840-858.
24. Rosaria Ottanàa, Paolo Paolib, Giulia Lorib, Ilenia Adornatoa, Santo Previtia, Alexandra Naß, Gerhard Wolber, Rosanna Maccari, "Design and evaluation of non-carboxylate 5-arylidene-2-thioxo-4- imidazolidinones as novel non-competitive inhibitors of protein tyrosine phosphatase 1B", Bioorganic Chemistry 92 (2019) 103211, 1-12.
25. Sarath Kumar Baskaran, Nabajyoti Goswami, Sudhagar Selvaraj, Velusamy Shanmuganathan Muthusamy, and Baddireddi Subhadra Lakshmi, "Molecular Dynamics Approach to Probe the Allosteric Inhibition of PTP1B by Chlorogenic and Cichoric Acid", J. Chem. Inf. Model. 2012, 52, 8, 2004–2012.
26. SarathKumar, B., Lakshmi, B.S. In silico investigations on the binding efficacy and allosteric mechanism of six different natural product compounds towards PTP1B inhibition through docking and molecular dynamics simulations. *J Mol Model* **25**, 272 (2019).
27. Kamerlin,S.C.L., and Boresch, R.R.S. "A targeted molecular dynamics study of WPD loop movement in PTP1B", Biochemical and Biophysical Research Communications 345 (2006) 1161–1166.
28. Shinde RN, Kumar GS, Eqbal S, Sobhia ME (2018) Screening and identification of potential PTP1B allosteric inhibitors using in silico and in vitro approaches. PLoS ONE 13(6), 1-20.
29. Simoncic, P.D.; McGlade, C.J.; Tremblay, M.L. PTP1B and TC-PTP: Novel roles in immune-cell signallingThis paper is one of a selection of papers published in this Special issue, entitled Second Messengers and Phosphoproteins—12th International Conference. Can. J. Physiol. Pharmacol. 2006, 84, 667–675.
30. Taoda Shi, E. M. Kithsiri Wijeratne, Cristian Solano, Andrew J. Ambrose, Alison B. Ross, Charles Norwood, Charles K. Orido, Tigran Grigoryan, Joseph Tillotson, Minjin Kang, Gang Luo, Bradley M. Keegan, Wenhao Hu, Brian S. J. Blagg, Donna D. Zhang, A. A. Leslie Gunatilaka, and Eli Chapman, Biochemistry 2019 58 (30), 3225-3231
31. Tautz, L.; Critton, D.A.; Grotegut, S. Protein Tyrosine Phosphatases: Structure, Function, and Implication in Human Disease. Phosphatase Modul. 2013, 1053, 179–221.
32. Tiganis, T. (2013). PTP1B and TCPTP—nonredundant phosphatases in insulin signalling and glucose homeostasis. FEBS Journal, 280(2), 445–458.
33. Tonks, N. K. (2006). Protein tyrosine phosphatases: from genes, to function, to disease. Nature Reviews Molecular Cell Biology, 7(11), 833–846.
34. Tsou, R. C. et al. (2014). Disruption of protein tyrosine phosphatase 1B expression in the hypothalamus promotes energy expenditure and protects against obesity. Molecular Metabolism, 3(2), 172–183.

35. V.S. Muthusamya, S. Ananda, K.N. Sangeethaa, S. Sujathaa, Balakrishnan Arunb, B.S. Lakshmi, "Tannins present in Cichorium intybus enhance glucose uptake and inhibit adipogenesis in 3T3-L1 adipocytes through PTP1B inhibition", Chemico-Biological Interactions 174 (2008) 69–78.
36. V. S. Muthusamy, C. Saravanababu, M. Ramanathan, R. Bharathi Raja, S. Sudhagar, S. Anand and B. S. Lakshmi, "Inhibition of protein tyrosine phosphatase 1B and regulation of insulin signallingmarkers by caffeoyl derivatives of chicory (Cichorium intybus) salad leaves," British Journal of Nutrition (2010), 104, 813–823.
37. Villamar-Cruz, O.; Loza-Mejía, M.A.; Arias-Romero, L.E.; Camacho-Arroyo, I. Recent advances in PTP1B signalling in metabolism and cancer. Biosci. Rep. 2021, 41, BSR20211994.
38. Wiesmann C, Barr KJ, Kung J, Zhu J, Erlanson DA, et al. (2004) Allosteric inhibition of protein tyrosine phosphatase 1B. Nat Struct Mol Biol 11: 730–737.
39. Yan-Bo Tang, Dianyun Lu, Zheng Chen, Chun Hu, Ying Yang, Jin-Ying Tian, Fei Ye, Li Wu, Zhong-Yin Zhang, Zhiyan Xiao, "Design, synthesis and insulin-sensitising effects of novel PTP1B inhibitors", Bioorganic & Medicinal Chemistry Letters 23 (2013) 2313–2318.
40. Yuma Ito, Masaki Fukui, Mamoru Kanda, Ko Morishita, Yoshimichi Shoji, Tatsuya Kitao, Eiichi Hinoi, Hiroaki Shirahase, "Therapeutic effects of the allosteric protein tyrosine phosphatase 1B inhibitor KY-226 on experimental diabetes and obesity via enhancements in insulin and leptin signalling in mice" , Journal of Pharmacological Sciences, 137 (1) 2018,38-46.
41. Zabolotny, J. M. et al. (2008). Protein-tyrosine phosphatase 1B expression is induced by inflammation in vivo. Journal of Biological Chemistry, 283(21), 14230–14241.
42. Zargari, F., Lotfi, M., Shahraki, O., Nikfarjam, Z., &Shahraki, J. (2018). Flavonoids as potent allosteric inhibitors of protein tyrosine phosphatase 1B: molecular dynamics simulation and free energy calculation. *Journal of Biomolecular Structure and Dynamics*, *36*(15), 4126–4142.
43. Zhang, E. E. et al. (2004). PTP1B inhibits leptin signal transduction in vivo. Developmental Cell, 2(4), 489–495.
44. Zhang, S. et al. (2017). Protein tyrosine phosphatase 1B (PTP1B) inhibitors from natural products: A patent review (2006–2016). Expert Opinion on Therapeutic Patents, 27(10), 1129–1145.