

Tricyclic Terpenoid Derivatives as Potential Protein Tyrosine Phosphatase 1B Inhibitors for Antihyperglycemic Activity: A Review

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Abstract:

Protein tyrosine phosphatase 1B (PTP1B; PTPN1) is a non-receptor protein tyrosine phosphatase that functions as an important negative regulator of insulin receptor signaling. Because excessive PTP1B activity can attenuate insulin receptor and insulin receptor substrate phosphorylation, inhibition of PTP1B has long been investigated as a strategy for improving insulin sensitivity and reducing hyperglycaemia in type 2 diabetes mellitus (T2DM). Natural terpenoids, particularly pentacyclic triterpenes, have emerged as useful chemical starting points because their rigid, lipophilic frameworks can engage hydrophobic regions adjacent to the polar catalytic machinery of PTP1B. Oleanolic acid, ursolic acid, corosolic acid, lupeol, betulinic acid and related scaffolds have demonstrated PTP1B inhibition in biochemical and cellular studies, while chemical modification has produced derivatives with improved potency, selectivity or pharmacological behavior. This review focuses specifically on tricyclic terpenoid derivatives inspired by pentacyclic triterpenoid PTP1B inhibitors in which the oleanolic-acid-derived scaffold was simplified to a smaller tricyclic core. The rationale for terpenoid-based inhibition; the evolution from natural triterpenes to semi-synthetic derivatives and tricyclic analogues; structure activity relationships involving hydrophobicity, acidic functionality, hydrogen-bonding groups and scaffold size; mechanisms of inhibition; selectivity against TCPTP and other phosphatases; cellular glucose uptake; animal evidence; pharmacokinetic and physicochemical limitations; and opportunities for modern medicinal chemistry. The evidence indicates that tricyclic terpenoid derivatives represent promising research scaffolds rather than clinically validated antidiabetic agents. Future progress will likely depend on combining structural biology, quantitative SAR, permeability optimization, metabolic-stability studies, target-engagement biomarkers, and rigorous *in-vivo* pharmacology.

Keywords: Protein Tyrosine Phosphatase 1B; PTP1B; PTPN1; Tricyclic Terpenoids; Insulin Resistance; Type 2 Diabetes Mellitus; Antihyperglycemic Activity.

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Introduction

Diabetes mellitus is a chronic metabolic disease characterized by sustained disturbances in glucose homeostasis and progressive tissue dysfunction. In T2DM, insulin resistance and declining β -cell compensation interact to produce persistent hyperglycaemia [1]. Although multiple therapeutic classes are available, there remains interest in agents that directly improve insulin signaling rather than simply increasing insulin secretion or reducing intestinal glucose absorption. The search for insulin-sensitizing targets has therefore included receptor tyrosine kinases, serine/threonine kinases, lipid phosphatases and protein tyrosine phosphatases [2]. PTP1B is particularly relevant because it is positioned as a negative regulator of insulin signaling. Genetic deletion of PTP1B in mice produced increased insulin sensitivity and

resistance to diet-induced obesity, providing an important proof of concept for pharmacological inhibition [3, 10]. The molecular basis is consistent with PTP1B-mediated dephosphorylation of the insulin receptor and associated signaling proteins. Inhibition can therefore prolong insulin-receptor phosphorylation and facilitate downstream signaling through IRS proteins, PI3K [4] and AKT, ultimately favoring glucose transport and metabolic responses [2,11].

Despite this strong biological rationale, PTP1B has proven difficult to translate into a successful drug target. The catalytic pocket is highly conserved among classical protein tyrosine phosphatases and is strongly polar because it recognizes phosphotyrosine [5]. Highly charged catalytic-site

inhibitors can have poor membrane permeability and may inhibit closely related phosphatases such as TCPTP. Several clinical-stage PTP1B programs were discontinued because of efficacy, selectivity, safety, pharmacokinetic or development issues [3,12–15]. These experiences shifted attention toward alternative binding sites, allosteric inhibition, partial-site occupation and hydrophobic scaffolds that can exploit structural differences surrounding the catalytic pocket.

Terpenoids are attractive in this context. Their compact carbon-rich frameworks provide hydrophobic surfaces that can interact with peripheral pockets while selected oxygenated or acidic substituents provide hydrogen-bonding and electrostatic contacts. Pentacyclic triterpenes such as OA and UA have already been identified as PTP1B inhibitors, and synthetic modification has generated derivatives with submicromolar to low-micromolar potency in biochemical assays [4–8]. The tricyclic terpenoid approach represents a further step, retaining the spatial and physicochemical advantages of a terpenoid-like core while reducing molecular size and potentially improving drug-like properties [9].

The purpose of this review is therefore not to claim that tricyclic terpenoids are established antidiabetic drugs, but to critically examine them as medicinal-chemistry scaffolds for PTP1B inhibition and antihyperglycaemic research. Particular attention is paid to the relationship between enzyme inhibition and functional glucose-lowering activity, because a potent biochemical inhibitor is not necessarily an effective cellular or systemic insulin sensitizer.

A focused narrative literature review was assembled using PubMed/PMC-indexed literature,

peer-reviewed medicinal chemistry and pharmacology articles, and recent reviews of PTP1B inhibitors. Search concepts included combinations of PTP1B, “protein tyrosine phosphatase 1B, triterpene, terpenoid, oleanolic acid, ursolic acid, tricyclic terpenoid, insulin resistance, antihyperglycaemic, glucose uptake, TCPTP, structure–activity relationship, and allosteric inhibitor. Priority was given to primary research describing biochemical inhibition, cellular insulin signaling or glucose uptake, animal antihyperglycaemic effects, and medicinal-chemistry optimization. The central primary article for tricyclic terpenoid derivatives is Yang *et al.* [9]. Earlier oleanolic- and ursolic-acid studies are included because they establish the medicinal-chemistry lineage from natural pentacyclic triterpenes to smaller synthetic scaffolds. Recent structural and mechanistic reviews are used to contextualize active-site, secondary-site and allosteric inhibition [2,16–20].

PTP1B Biology and Its Relationship to Glucose Homeostasis:

PTP1B is encoded by PTPN1 and belongs to the classical non-receptor protein tyrosine phosphatases. It is broadly expressed and is associated with intracellular membranes, including the endoplasmic reticulum through its C-terminal targeting sequence. Functionally, PTP1B can oppose receptor tyrosine kinase signaling by removing phosphate groups from tyrosine residues. In the insulin pathway, PTP1B can attenuate phosphorylation of the insulin receptor and IRS proteins, thereby limiting propagation of the insulin signal [1,2,11]. The overall relationship between PTP1B inhibition and insulin signaling is illustrated in Figure 1.

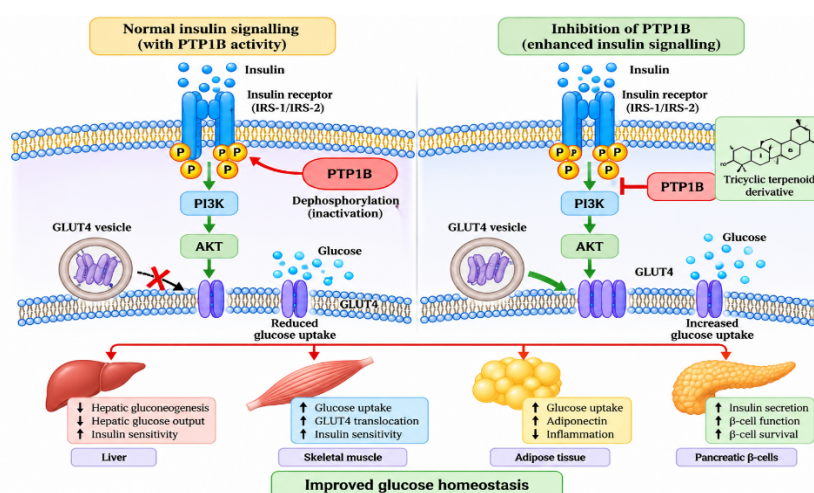


Figure 1: PTP1B inhibition and insulin signaling

The canonical insulin pathway begins when insulin binds the extracellular α -subunit of the insulin receptor, triggering activation of the receptor tyrosine kinase in the β -subunit.

Autophosphorylation creates docking sites for IRS proteins. IRS phosphorylation recruits PI3K, which generates phosphatidylinositol-3,4,5-trisphosphate and activates AKT. In muscle and adipose tissue,

AKT promotes GLUT4 vesicle trafficking to the plasma membrane, increasing glucose uptake. In the liver, insulin signaling suppresses gluconeogenic gene expression and favors glycogen synthesis. PTP1B can reduce the strength or duration of these signals by dephosphorylating key tyrosine residues.

Genetic evidence is central to the target rationale. PTP1B-deficient mice showed enhanced insulin sensitivity and resistance to weight gain under high-energy feeding conditions [10]. Subsequent studies supported tissue-specific roles for PTP1B, including effects in liver, muscle, adipose tissue and the central nervous system. These findings suggested that selective pharmacological inhibition might improve insulin sensitivity while also affecting energy balance.

However, PTP1B is not simply a disease-specific enzyme. It participates in several signaling networks, and complete systemic inhibition may produce consequences that differ from partial, tissue-selective or transient inhibition. This consideration is particularly important when

designing natural-product-inspired molecules, because a broad hydrophobic scaffold may engage multiple proteins. Consequently, target engagement, phosphatase selectivity and phenotypic specificity should be evaluated together rather than relying on a single IC₅₀ value.

Structural Features of PTP1B Relevant to Inhibitor Design: PTP1B contains a well-characterized catalytic domain with a central β -sheet surrounded by α -helices. The active-site architecture includes the phosphate-binding P-loop, WPD loop, Q-loop and pTyr-recognition loop. The catalytic signature contains Cys215, whose thiolate form attacks the phosphorus center of a phosphotyrosine substrate, while Asp181 in the WPD loop acts as a general acid/base [16,17]. Arg221 contributes to recognition of the negatively charged phosphate group. Gln262 participates in the hydrolysis step by coordinating the catalytic water molecule. The principal structural regions relevant to inhibitor design are summarized in Table 1. The major structural regions are illustrated in Figure 2.

Table 1: Structural and functional characteristics of PTP1B relevant to inhibitor design

PTP1B region/site	Representative residues/features	Functional role	Relevance to tricyclic terpenoid inhibitors
Catalytic P-loop	Cys215, Arg221	Phosphate recognition and catalytic dephosphorylation	Polar/acidic substituents may provide anchoring interactions.
WPD loop	Asp181	General acid/base catalysis; dynamic loop closure	Ligands may influence WPD-loop conformation.
Q-loop	Gln262	Positions catalytic water molecule	Potential secondary hydrogen-bonding interactions.
Secondary/B site	Tyr20, Arg24, Phe52, Arg254, Met258	Provides additional substrate/inhibitor contacts	Hydrophobic terpenoid frameworks may occupy adjacent nonpolar regions.
C site	Tyr46, Arg47, Asp48	Peripheral recognition region	Potential source of PTP1B selectivity.
D site	Lys120 and surrounding residues	Auxiliary binding region	Can be exploited to distinguish PTP1B from related PTPs.
Allosteric region	α 3, α 6, α 7 helices and surrounding loop regions	Regulates catalytic-loop dynamics	Compatible with hydrophobic natural-product-derived scaffolds.

Note: PTP1B, protein tyrosine phosphatase 1B; P-loop, phosphate-binding loop; WPD loop, tryptophan–proline–aspartate loop. The listed

regions represent commonly discussed catalytic, secondary and allosteric regions and are not necessarily mutually exclusive binding sites

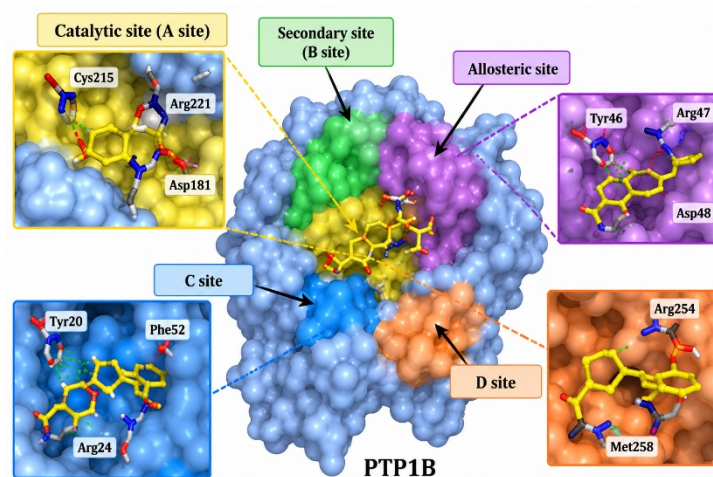


Figure 2: The major structural regions of PTP1B

The high polarity and conservation of the catalytic pocket create two linked medicinal-chemistry problems. First, strong binding often requires acidic or ionizable groups that mimic phosphotyrosine, which can reduce passive membrane permeability. Second, the same catalytic architecture is present in other classical PTPs, making selectivity difficult. TCPTP is particularly challenging because it is highly homologous to PTP1B and participates in immune and growth signaling [2,18]. Structural work has identified secondary and allosteric regions around PTP1B. A-site inhibitors occupy the catalytic pocket; B-site interactions can extend into a secondary aryl-phosphate recognition region; C- and D-site interactions exploit less-conserved residues. Allosteric ligands can bind near the $\alpha 3$, $\alpha 6$ and $\alpha 7$ helices and influence WPD-loop dynamics [16,18,21]. These sites are particularly interesting for terpenoids because their hydrophobic surface can complement nonpolar cavities while strategically positioned polar groups can anchor the scaffold. A key concept is induced or dynamic selectivity. PTP1B and TCPTP may have highly similar catalytic pockets, but their peripheral residues and conformational networks differ. Nonpolar terpenoids have been shown to exploit such differences through allosteric or secondary-site binding, supporting the broader concept that hydrophobic natural-product-like scaffolds can achieve selectivity without requiring a highly charged phosphotyrosine mimic [21].

Terpenoids as PTP1B Inhibitor Scaffolds:

Terpenoids are biosynthetically derived from isoprene units and include monoterpenes, sesquiterpenes, diterpenes, tetraterpenes, triterpenes and tetraterpenes. Within PTP1B research, triterpenoids have attracted particular attention because their rigid, polycyclic frameworks can present a large hydrophobic surface and tolerate

selective functionalization. Reviews of natural PTP1B inhibitors consistently identify terpenoids as one of the major structural classes [4,5,22]. Representative natural and semi-synthetic triterpenoid PTP1B inhibitors are summarized in Table 2. The scaffold progression is summarized in Figure 3.

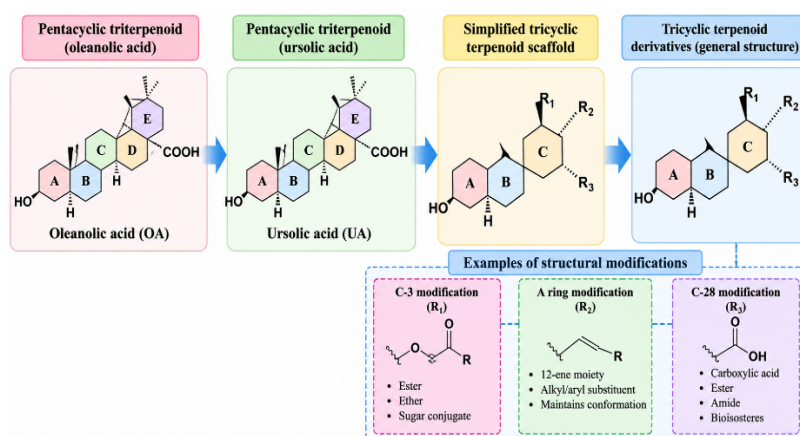
Pentacyclic triterpenes provide an especially useful starting point. OA and UA contain a pentacyclic carbon skeleton with a hydroxyl group near C-3 and a carboxylic acid at C-28. These groups are strategically positioned at opposite ends of a hydrophobic framework. Experimental studies have shown that UA and OA inhibit PTP1B and that chemical derivatization can markedly change potency and cellular activity [6–8]. The importance of the carbon skeleton is demonstrated by the fact that seemingly modest changes in hydroxylation pattern can alter PTP1B potency. In ursane-type triterpenes, UA and CA displayed measurable inhibition, whereas more extensively hydroxylated analogues could be substantially weaker [7]. This suggests that excessive polarity or steric disruption can prevent productive occupation of hydrophobic binding regions. At the same time, carefully introduced polar substituents can improve interactions with catalytic or secondary-site residues. Terpenoid inhibitors should therefore be considered three-dimensional pharmacophores rather than merely hydrophobic molecules. The scaffold defines the spatial relationship between functional groups, while the functional groups determine electrostatic anchoring, hydrogen bonding, solubility and metabolic behavior. This is particularly relevant to tricyclic derivatives, in which removal of two rings can substantially change conformational freedom and the projected distances between pharmacophoric groups.

Table 2: Representative natural and semi-synthetic triterpenoid PTP1B inhibitors

Compound/scaffold	Chemical class	Reported PTP1B activity	Cellular/metabolic evidence	Major observation	SAR
Oleanolic acid (OA)	Pentacyclic triterpenoid	PTP1B inhibitory activity reported	Used as a starting scaffold for insulin-signaling studies	C-3 and C-28 positions are important for optimization.	
Ursolic acid (UA)	Pentacyclic triterpenoid	IC ₅₀ approximately 3-4 μ M in selected studies [7]	Enhanced insulin signaling and glucose uptake reported [6,7]	Hydroxylation pattern affects activity.	
OA derivative 13	Modified OA derivative	Ki = 130 nM [8]	Enhanced insulin receptor phosphorylation and glucose uptake [8]	Modification at C-3/C-28 markedly improved potency.	
OA derivative 3e	Glycosylated OA derivative	IC ₅₀ = 0.56 μ M [23]	Insulin-sensitizing response reported [23]	C-3 carbohydrate and C-28 acidic functionality are important.	
Tricyclic derivative 15	OA-inspired tricyclic derivative	Among stronger inhibitors in Yang <i>et al.</i> [9]	Primarily characterized biochemically	Useful biochemical SAR benchmark.	
Tricyclic derivative 28	OA-inspired tricyclic derivative	Among stronger inhibitors in Yang <i>et al.</i> [9]	Primarily characterized biochemically	Demonstrates importance of optimized substituents.	
Tricyclic derivative 34	OA-inspired tricyclic derivative	Among stronger inhibitors in Yang <i>et al.</i> [9]	Primarily characterized biochemically	Useful biochemical SAR benchmark.	
Tricyclic derivative 25	OA-inspired tricyclic derivative	Moderate PTP1B inhibition [9]	Enhanced insulin-stimulated glucose uptake and antihyperglycaemic activity in a nicotinamide-STZ model [9]	Illustrates balanced optimization of potency and pharmaceutical properties.	

Note: OA, oleanolic acid; UA, ursolic acid; PTP1B, protein tyrosine phosphatase 1B; IR, insulin receptor; Ki, inhibition constant; IC₅₀, half-maximal inhibitory concentration; STZ,

streptozotocin. Numerical values are assay-dependent and should not be compared directly across studies without considering assay conditions.

**Figure 3: The PTP1B scaffold progression**

Oleanolic Acid and the Evolution Toward Tricyclic Derivatives:

OA is a naturally occurring pentacyclic triterpenoid found in numerous medicinal and dietary plants. Its identification as a PTP1B inhibitor created an important bridge between natural-product screening and rational medicinal chemistry. Early work reported an OA-derived competitive inhibitor with substantially improved potency and cellular activity after modification at positions 3 and 28 [8]. Subsequent systematic synthesis demonstrated that changes in the A ring, the 12-ene moiety and the acidic substituent could influence activity [6]. Liu *et al.* synthesized sugar-substituted OA derivatives and observed that both the carbohydrate at C-3 and the acidic chain at C-28 affected PTP1B inhibition and insulin-sensitizing activity. Several derivatives displayed low-micromolar inhibition, with compound 3e reported at 0.56 μM [23]. These findings illustrate an important principle: activity is not governed by one functional group but by the combined spatial arrangement of the triterpene core and appended polar substituents. Other OA derivatives have been evaluated using a combination of biochemical assays, docking and animal models. One study reported cinnamoyl ester and ethyl ether derivatives with enhanced PTP1B interactions and hypoglycaemic effects in a non-insulin-dependent diabetes model [24]. Such work supports the idea that OA can be used as a pharmacophoric template, but it also exposes a recurring challenge: high molecular weight and lipophilicity can compromise solubility and pharmacokinetics. Yang *et al.* subsequently used a structure-based design strategy to simplify the OA-derived architecture. Rather than preserving the entire pentacyclic skeleton, the authors elaborated a smaller tricyclic core and introduced substituents

intended to retain favorable interactions [9]. This is conceptually significant because scaffold simplification can reduce molecular weight, change lipophilicity and improve synthetic accessibility while retaining a three-dimensional hydrophobic platform. The resulting compounds provide a useful case study in the difference between biochemical and pharmacological optimization. Compounds 15, 28 and 34 showed strong enzyme inhibition, but compound 25 was selected for more extensive biological evaluation because it combined moderate inhibition with more favorable pharmaceutical properties. In insulin-resistant HepG2 cells, compound 25 increased insulin-stimulated glucose uptake, and in a nicotinamide-STZ model it showed antihyperglycaemic effects [9]. This demonstrates why medicinal chemistry should optimize a multidimensional profile rather than maximize enzyme potency alone.

Structure-Activity Relationships of Tricyclic Terpenoid PTP1B Inhibitors

Scaffold size and three-dimensionality: The most important conceptual change in the tricyclic series is scaffold contraction. A pentacyclic triterpene contains a broad hydrophobic surface, but not that entire surface contributes to target binding. Removing rings can lower molecular weight and reduce the number of unnecessary hydrophobic contacts. The challenge is to preserve the orientation of key substituents. In a tricyclic scaffold, small changes in ring fusion, stereochemistry or linker length can move a polar group by several angstroms relative to the protein surface. Key SAR relationships are summarized in Table 3. The major SAR vectors are illustrated in Figure 4.

Table 3: Structure-activity relationships reported for oleanolic-acid-derived PTP1B inhibitors

Structural modification	Observed effect on PTP1B activity	Proposed interpretation
Modification at C-3	Can substantially increase or decrease activity depending on substituent	Position can accommodate additional functionality and modulate hydrophobic/H-bonding contacts.
Modification at C-28	Strongly influences activity	Acidic functionality or appropriately positioned H-bonding groups can contribute to binding.
Retention of A ring	Important for activity in several OA series	Maintains three-dimensional scaffold geometry.
Retention of 12-ene moiety	Associated with retention of activity in selected series	May maintain scaffold geometry and hydrophobic interactions.
Introduction of acidic groups	Often improves recognition	Can provide electrostatic/H-bonding interactions.
Excessive hydroxylation	May reduce activity in some series	Increased polarity can disrupt hydrophobic complementarity.
Esterification at C-3	Can enhance activity depending on substituent	Adds hydrophobic/ π -interaction surface and changes molecular geometry.
Sugar substitution at C-3	Can produce potent inhibitors	Activity depends on sugar identity and orientation.
Long acidic chain at C-28	Important in selected glycosylated derivatives	May improve interactions when appropriately spaced.

Note: SAR, structure–activity relationship; OA, oleanolic acid. These trends are series-dependent rather than universal rules. Liu *et al.* reported that

both C-3 carbohydrate and C-28 acidic-chain modifications influenced activity in OA derivatives [23].

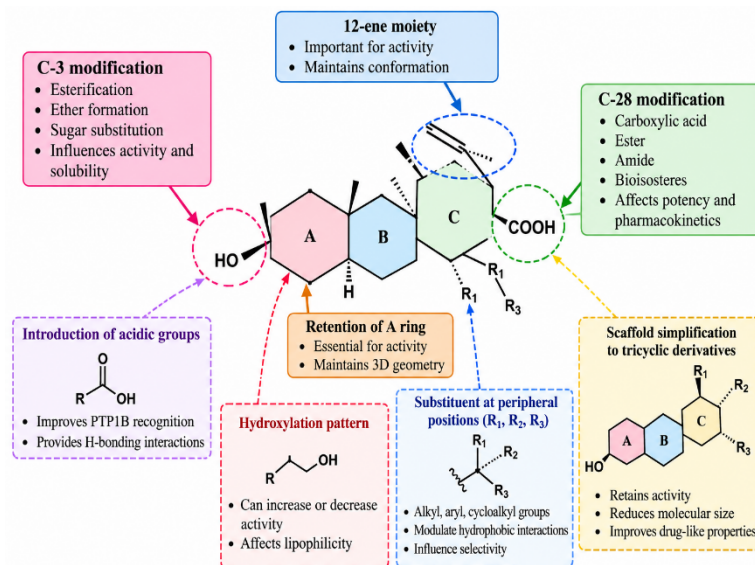


Figure 4: SAR of Tricyclic Terpenoids as PTP1B inhibitors

Hydrophobic interactions: PTP1B contains hydrophobic regions adjacent to the polar catalytic site and within allosteric regions. Terpenoid-like carbon frameworks can interact with residues such as Phe52 and other nonpolar side chains. Studies of nonpolar terpenoids indicate that hydrophobic interactions can be sufficient to stabilize allosteric binding and alter WPD-loop dynamics [21]. This provides a mechanistic basis for using lipophilic scaffolds rather than exclusively phosphate-mimicking inhibitors.

Acidic functionality: The C-28 carboxylic acid of OA and the corresponding acid in related triterpenes can contribute to PTP1B recognition, but the ionized form may reduce membrane permeability. Chemical modification can either preserve the acid for stronger electrostatic interactions or mask it as an ester/prodrug to improve permeability. The trade-off is critical: masking an acid can improve exposure while weakening direct binding. A rational series should therefore compare acids, bioisosteres, esters and ionizable heterocycles rather than assuming one optimal state.

Hydroxyl groups: Hydroxyl groups can provide hydrogen bonds to catalytic or peripheral residues and can increase aqueous compatibility. However, excessive hydroxylation may disrupt hydrophobic complementarity and increase polarity beyond what is compatible with passive cell penetration. Experimental comparisons among ursane-type triterpenes support a non-linear relationship between hydroxylation and PTP1B activity [7].

Aromatic and heteroatom-containing substituents: Synthetic derivatives often introduce aromatic groups, amides, ethers or heterocycles to create additional hydrogen-bond and π -interaction opportunities. Such groups can also tune lipophilicity and metabolic stability. For tricyclic terpenoids, the ideal substitution pattern is likely to be one that preserves the rigid hydrophobic core while adding only the minimum polar functionality required for target engagement and exposure.

Selectivity: Because TCPTP is highly homologous to PTP1B, potency against PTP1B should be accompanied by counter-screening. Interaction with residues that differ between PTP1B and TCPTP, including peripheral residues around the B/C/D regions and the allosteric network, offers a more defensible path to selectivity than simply increasing catalytic-pocket affinity [16,18,21].

Mechanistic Basis of Antihyperglycaemic Activity: The proposed pharmacological sequence for a PTP1B inhibitor is: target binding $\rightarrow$ reduction of PTP1B catalytic or regulatory activity $\rightarrow$ increased persistence of insulin receptor tyrosine phosphorylation $\rightarrow$ stronger IRS/PI3K/AKT signaling $\rightarrow$ improved glucose transporter trafficking and/or suppression of hepatic glucose production. This sequence is biologically plausible and is supported by genetic and pharmacological studies of PTP1B [10,11]. For terpenoid derivatives, however, target engagement must be demonstrated rather than inferred from a fall in glucose. Triterpenoids may have multiple biological activities, including effects on inflammation, lipid metabolism, oxidative stress

and transcription. Therefore, a glucose-lowering phenotype by itself cannot establish PTP1B as the mechanism. A strong mechanistic package should include at least three linked observations. First, the compound should inhibit recombinant PTP1B under controlled kinetic conditions. Second, it should increase insulin receptor phosphorylation or a validated downstream signaling marker in cells. Third, the cellular phenotype should be attenuated by genetic manipulation of PTP1B or reproduced by a mechanistically distinct PTP1B inhibitor. The strongest studies additionally measure direct target engagement *in vivo*. The Yang *et al.* tricyclic study provides an important intermediate level of evidence because compound 25 increased insulin-stimulated glucose uptake in insulin-resistant HepG2 cells and produced antihyperglycaemic activity in a T2DM model [9]. Nevertheless, future work should more explicitly connect the *in-vivo* phenotype to PTP1B target engagement, for

example through tissue PTP1B activity, insulin receptor phosphorylation, AKT phosphorylation, and pharmacokinetic exposure measurements.

Experimental Approaches for Evaluating Tricyclic Terpenoid PTP1B Inhibitors

Biochemical assays: The first screen should use recombinant human PTP1B with a validated substrate such as p-nitrophenyl phosphate or a phosphotyrosine-containing peptide. Dose-response curves should include sufficient concentrations to define an IC₅₀ and, where possible, kinetic analysis should distinguish competitive, noncompetitive, uncompetitive and mixed inhibition. Assay conditions should report enzyme concentration, substrate concentration, buffer, reducing agent, temperature and incubation time because PTP1B contains a redox-sensitive catalytic cysteine. Recommended experimental models and endpoints are summarized in Table 4.

Table 4: Comparison of catalytic-site, secondary-site and allosteric PTP1B inhibitor strategies

Strategy	Principal advantage	Major limitation	Potential relevance to tricyclic terpenoids
Catalytic/A-site inhibition	Direct interaction with catalytic machinery; potentially high potency	Highly conserved and polar site; selectivity/permeability challenges	Acidic or polar substituents may anchor the terpenoid scaffold.
A+B multisite inhibition	Combines catalytic and peripheral interactions	Greater molecular complexity	Terpenoid core can occupy hydrophobic regions while a substituent reaches catalytic/peripheral sites.
Secondary-site inhibition	Potential for improved selectivity	Requires appropriate spatial complementarity	Rigid tricyclic frameworks may occupy hydrophobic peripheral pockets.
Allosteric inhibition	Potential for improved selectivity and physicochemical properties	Binding mode may be difficult to establish	Particularly attractive for hydrophobic terpenoid scaffolds.
C/D-site targeting	Can exploit residues less conserved among PTPs	May produce weaker affinity when used alone	Functional groups can be directed toward selective peripheral residues.

Note: A-site denotes the catalytic phosphate-binding region; B-, C- and D-site terminology follows structural descriptions of PTP1B inhibitor interactions. Docking alone should not be considered definitive evidence of binding mode [16,18,21].

Selectivity panels: PTP1B inhibition should be compared with TCPTP, SHP1, SHP2, LAR and at least one receptor-type PTP. The goal is not merely a numerical selectivity ratio but a mechanistic understanding of why the compound favors PTP1B. Selectivity is especially important for terpenoids because nonspecific hydrophobic interactions can generate apparent inhibition in biochemical systems.

Cellular assays: HepG2 cells are useful for hepatic insulin signaling and were used in the key tricyclic study [9]. Skeletal-muscle models such as L6 myotubes and C2C12 myotubes can evaluate glucose uptake and GLUT4-related responses. CHO cells expressing human insulin receptor can be used to measure receptor phosphorylation. Cellular assays should include insulin-stimulated and basal conditions, cytotoxicity measurements, intracellular exposure considerations and appropriate positive controls.

Glucose uptake and signaling: A compound should be tested for effects on insulin-stimulated glucose uptake, IR phosphorylation, IRS phosphorylation and AKT phosphorylation. If

GLUT4 translocation is relevant, immunofluorescence or surface-transporter assays can be used. For hepatic models, suppression of gluconeogenic signaling and changes in glucose production can complement uptake assays.

Animal models: A staged approach is preferable: pharmacokinetics and tolerability first, followed by a diet-induced insulin-resistance model and then a chemically induced or genetic diabetes model. Nicotinamide-STZ models are commonly used for T2DM-like phenotypes, but they vary in β -cell injury and insulin deficiency. Diet-induced obesity models may better interrogate insulin resistance and obesity. Endpoints should include fasting glucose, glucose tolerance, insulin tolerance, insulin levels, body weight, food intake, liver and adipose histology, and tissue signaling.

Orthogonal target validation: To establish PTP1B dependence, researchers should combine pharmacological and genetic approaches. Knockdown or knockout of PTPN1 can test whether the compound retains activity when the target is absent. Conversely, overexpression can test whether the phenotype is shifted with increased target abundance. Cellular thermal shift assays, activity-based probes or other target-engagement methods can provide direct evidence of intracellular binding.

Pharmacokinetic and Drug-Likeness Considerations: Natural pentacyclic triterpenes are often poorly soluble in aqueous media because of their rigid, hydrophobic structures. Corosolic acid and related compounds have low water solubility, and structural modification or formulation is often needed to improve absorption [26]. This issue is highly relevant to tricyclic derivatives because scaffold simplification can reduce hydrophobic surface area but can also alter crystal packing, lipophilicity and metabolic stability. The ideal tricyclic PTP1B inhibitor should balance several properties: sufficient aqueous solubility for formulation; moderate lipophilicity for membrane penetration; low nonspecific protein binding; adequate metabolic stability; oral exposure; and a concentration at the target tissue above the cellular effective concentration. Excessively lipophilic molecules may accumulate in membranes and adipose tissue, whereas highly polar derivatives may have inadequate permeability. Carboxylic acids require particular attention. The ionized form can provide strong PTP1B interactions but may be poorly permeable. Esterification can increase passive diffusion but introduces a dependence on hydrolysis for activation. Alternative acidic bioisosteres or neutral hydrogen-bonding groups may provide a better balance. Likewise, phenolic

and aliphatic hydroxyl groups can improve binding but may increase glucuronidation or sulfation.

A useful medicinal-chemistry workflow is therefore iterative rather than linear: biochemical potency $\rightarrow$ selectivity $\rightarrow$ cell permeability $\rightarrow$ cellular target engagement $\rightarrow$ microsomal stability $\rightarrow$ plasma stability $\rightarrow$ oral pharmacokinetics $\rightarrow$ efficacy. The tricyclic series is particularly suited to this approach because ring substitution can be systematically varied while preserving the core three-dimensional architecture.

Safety, Selectivity and Translational Challenges:

The history of PTP1B drug discovery shows that attractive preclinical biology does not guarantee clinical success. Several inhibitors reached clinical development but were discontinued because of efficacy, selectivity, safety or pharmacokinetic concerns [3,12–15]. These failures do not invalidate the target, but they emphasize the need for better molecular design. Major translational limitations and research priorities are summarized in Table 5. For terpenoids, safety assessment should consider both on-target and off-target effects. A hydrophobic scaffold may interact with membrane proteins, nuclear receptors or metabolic enzymes. *In vitro* cytotoxicity should therefore be measured across multiple cell types and linked to intracellular exposure. In animal studies, liver enzymes, renal markers, hematology and histopathology should be evaluated rather than relying only on body weight and glucose.

Selectivity over TCPTP deserves particular attention. TCPTP participates in immune and cellular signaling, and broad inhibition may create undesirable consequences. Structural strategies that exploit the B, C, D or allosteric regions of PTP1B are therefore attractive because they can use non-conserved residues or conformational networks [16,18,21]. Another challenge is distinguishing true enzyme inhibition from assay artifacts. Hydrophobic natural products can aggregate at micromolar concentrations and produce apparent inhibition unrelated to specific target binding. Confirmatory experiments should include detergent sensitivity where appropriate, dynamic light scattering or orthogonal biophysical methods, dilution experiments, and counter-screens against unrelated enzymes. Finally, antihyperglycaemic activity should not be interpreted as equivalent to disease modification. Lower glucose in a chemically induced diabetic animal can result from reduced food intake, toxicity, altered absorption or changes in insulin secretion. PTP1B-directed efficacy should therefore be demonstrated through a coherent mechanism involving target engagement and insulin signaling.

Table 5: Major limitations and future research priorities for tricyclic terpenoid PTP1B inhibitors

Current limitation	Potential consequence	Recommended research priority
Limited PTP1B/TCPTP selectivity data	Potential off-target phosphatase inhibition	Expanded phosphatase selectivity panel.
Poor aqueous solubility of many triterpenoids	Low oral exposure	Scaffold simplification and formulation optimization.
High lipophilicity	Nonspecific binding and metabolic liabilities	Controlled reduction of lipophilicity.
Limited intracellular target-engagement evidence	Mechanism remains inferential	Cellular target-engagement assays.
Reliance on docking	Binding mode may be uncertain	Crystallography, mutagenesis and biophysical assays.
Limited PK/PD information	Difficult to relate dose to target exposure	Integrated PK/PD studies.
Limited chronic safety data	Translation remains uncertain	Repeat-dose toxicology.
Variable animal models	Difficult comparison among studies	Standardized insulin-resistance and diabetes models.
Potential multi-target activity	PTP1B attribution may be uncertain	Genetic target validation.
Few advanced lead compounds	Limited translational progress	Multi-parameter medicinal-chemistry optimization.

Note: PK, pharmacokinetics; PD, pharmacodynamics; PTP1B, protein tyrosine phosphatase 1B; TCPTP, T-cell protein tyrosine phosphatase. The priorities reflect both the broader history of PTP1B drug discovery and the specific physicochemical challenges of hydrophobic natural-product-derived scaffolds.

Comparison with Other PTP1B Inhibitor Strategies: Catalytic-site inhibitors often achieve very strong biochemical affinity because they

directly mimic the phosphate-containing substrate. However, they can be highly polar and insufficiently selective. Secondary-site inhibitors extend into less-conserved regions, while allosteric inhibitors seek to alter the enzyme's conformational equilibrium. Natural terpenoids can contribute to the latter two strategies because their hydrophobic surfaces are compatible with nonpolar pockets. The major PTP1B inhibitor-site strategies are compared in Table 6.

Table 6: Comparison of selected oleanolic-acid-derived PTP1B inhibitor studies

Study	Scaffold/series	Key finding	Relevance to tricyclic derivative development
Zhang <i>et al.</i> [8]	OA derivatives	An OA derivative showed $K_i = 130$ nM and enhanced insulin signaling/glucose uptake.	Demonstrated that OA can provide a potent PTP1B pharmacophore.
Liu <i>et al.</i> [23]	Sugar-substituted OA derivatives	Compound 3e showed $IC_{50} = 0.56$ μ M.	Demonstrated importance of C-3 and C-28 optimization.
Ramírez-Espinosa <i>et al.</i> [24]	OA derivatives	Selected derivatives were evaluated in vitro, in vivo and in-silico for PTP1B inhibition.	Linked biochemical activity to whole-animal effects.
Yang <i>et al.</i> [9]	Tricyclic OA-inspired derivatives	Compounds 15, 28 and 34 were strong enzyme inhibitors; compound 25 showed cellular/in-vivo efficacy.	Demonstrated feasibility of scaffold simplification.

Note: OA, oleanolic acid; K_i , inhibition constant; IC_{50} , half-maximal inhibitory concentration. Values from different studies should not be interpreted as a direct potency ranking because experimental conditions differ.

Rational Design Framework for Next-Generation Tricyclic Terpenoid Derivatives: A practical design program can begin from the pharmacophore represented by OA/OA: a rigid hydrophobic framework, one or more hydroxyl groups, and a terminal acidic or hydrogen-bonding

group. The next step is scaffold simplification into tricyclic cores with controlled stereochemistry. Substituents should then be introduced at positions corresponding to the vectors that project toward

PTP1B secondary or allosteric regions. A proposed medicinal-chemistry optimization framework is provided in Table 7. The proposed experimental workflow is summarized in Figure 5.

Table 7: Proposed medicinal-chemistry optimization strategy for next-generation tricyclic terpenoid PTP1B inhibitors

Optimization parameter	Proposed modifications	Desired outcome
Scaffold	Tricyclic versus modified tricyclic cores	Maintain three-dimensional recognition while reducing molecular size.
Acidic group	COOH, amide, ester, bioisosteres	Balance PTP1B affinity with permeability.
Hydroxylation	Positional isomers and selective removal	Optimize H-bonding and lipophilicity.
Hydrophobic substituent	Alkyl, cycloalkyl, aryl, heteroaryl	Improve peripheral/allosteric interactions.
Stereochemistry	Individual stereoisomers	Identify configuration with optimal binding.
Linker length	Short/medium/long linkers	Optimize distance between pharmacophoric groups.
Solubility	Polar substituents or prodrug strategy	Improve formulation and oral exposure.
Selectivity	PTP1B versus TCPTP optimization	Minimize off-target phosphatase activity.
Metabolic stability	Reduce labile ester/ether positions	Improve half-life and exposure.
Cellular activity	Permeability and target engagement	Translate biochemical potency into cellular efficacy.

Note: COOH, carboxylic acid; PTP1B, protein tyrosine phosphatase 1B; TCPTP, T-cell protein tyrosine phosphatase. Optimization should use a

multi-parameter strategy rather than maximizing enzyme potency alone [9].

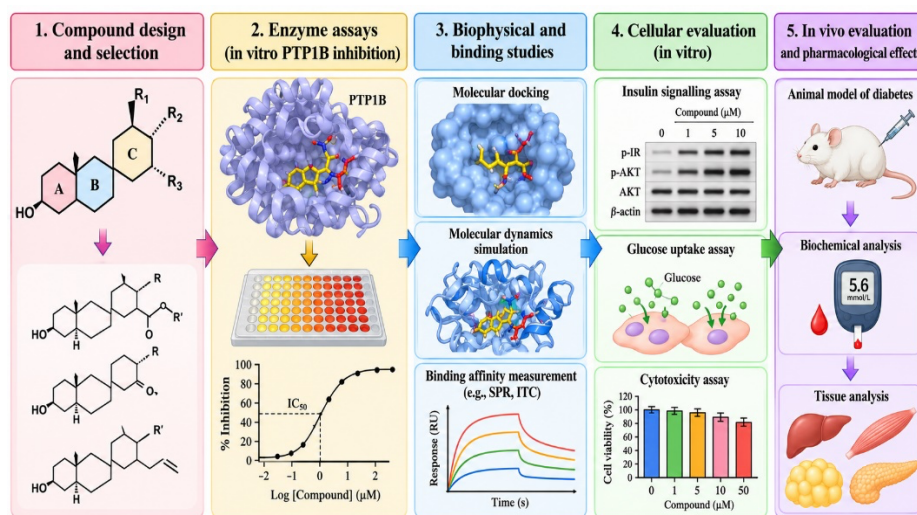


Figure 5: The proposed experimental workflow

A focused library can be organized around four axes. Axis 1 is hydrophobicity, varying alkyl, cycloalkyl, aryl and heteroaryl groups. Axis 2 is polarity, varying hydroxyl, ether, amide and carboxylate groups. Axis 3 is ionization, comparing acids, neutral bioisosteres and weak bases. Axis 4 is rigidity, comparing fused rings with more flexible linkers. This matrix allows quantitative

SAR rather than one-compound-at-a-time optimization. Molecular docking can prioritize binding hypotheses but should not be treated as experimental proof. Docking should be combined with molecular dynamics to assess whether the predicted pose is stable and whether WPD-loop or allosteric-network changes occur. Crystallography or cryo-EM, when feasible, would provide the

strongest evidence for binding mode. Machine-learning approaches can also be applied once a sufficiently consistent dataset is available. Descriptors such as cLogP, topological polar surface area, molecular weight, hydrogen-bond count, rotatable bonds and aromatic surface can be related to PTP1B potency and cellular activity. However, the dataset must be chemically coherent; otherwise, models may learn assay-specific artifacts rather than transferable SAR. A particularly promising strategy is multi-parameter optimization. Instead of maximizing IC₅₀ potency, the optimization objective should include PTP1B/TCPTP selectivity, cell permeability, microsomal stability, aqueous solubility and cytotoxicity. Compound 25 from the Yang study illustrates this principle: it was not the strongest enzyme inhibitor but was prioritized because its overall profile was more favorable [9].

Potential for Multi-Target Antidiabetic Activity:

Diabetes is a systems-level disorder involving insulin resistance, altered hepatic metabolism, dyslipidemia, inflammation and β -cell stress. A tricyclic terpenoid may interact with multiple pathways, which can be either an advantage or a liability. Some natural triterpenes have been reported to affect oxidative stress, inflammation and lipid metabolism in addition to PTP1B [26,27]. Dual inhibition of PTP1B and α -glucosidase is particularly interesting because it could combine insulin sensitization with delayed carbohydrate digestion. Several natural terpenes have been reported to inhibit both enzymes, including OA-related compounds [28]. However, dual activity should be demonstrated quantitatively against both targets and evaluated for whether the combined effect is additive, synergistic or simply coincidental. The multi-target concept should not obscure the primary pharmacological hypothesis. If PTP1B inhibition is the intended mechanism, the compound should retain demonstrable target engagement even if additional activities are present. Conversely, if a triterpenoid has weak PTP1B inhibition but strong activity through another target, it should not be described as a PTP1B-directed antidiabetic lead.

Critical Appraisal of Current Evidence: Overall, the evidence is strongest for the feasibility of PTP1B inhibition by terpenoid-like scaffolds and for the concept that scaffold simplification can improve pharmaceutical properties. Evidence is weaker for selective, durable and target-dependent antihyperglycaemic efficacy in vivo, and there is no clinical evidence establishing tricyclic terpenoid PTP1B inhibitors as effective human antidiabetic medicines. This distinction should be preserved in future publications.

Future Perspectives: *Structure-guided optimization:* Future studies should obtain

experimental structures of representative tricyclic terpenoids bound to PTP1B whenever possible. Structural data would resolve whether the compounds occupy the catalytic pocket, a secondary site or an allosteric region. It would also help explain why some closely related analogues show large potency differences.

Better selectivity: The most important selectivity comparator should remain TCPTP, followed by a broader phosphatase panel. The goal should be to design compounds that exploit PTP1B-specific residues and conformational dynamics. Nonpolar terpenoids may be particularly valuable because they can engage allosteric networks that are less conserved than the catalytic pocket [21].

Pharmacological exposure: Future reports should provide plasma and tissue concentrations alongside efficacy. Without exposure data, it is difficult to determine whether an apparently effective dose is pharmacologically plausible or whether the compound acts through nonspecific effects. Unbound concentration is particularly informative for lipophilic compounds.

Biomarker-guided studies: IR phosphorylation, AKT phosphorylation, PTP1B activity and target occupancy should be measured in liver, skeletal muscle and adipose tissue. These measurements can identify which tissues drive efficacy and whether the compound acts centrally. Such data would also guide formulation and dosing.

Translation to human disease: Before clinical development, tricyclic leads would require robust repeat-dose toxicology, genotoxicity assessment where appropriate, cardiovascular and metabolic safety profiling, and demonstration of oral exposure. The clinical history of PTP1B inhibitors indicates that strong preclinical efficacy is not enough. The development goal should be a selective, orally active, well-tolerated inhibitor with a clearly measurable pharmacodynamic biomarker.

Detailed Medicinal-Chemistry Interpretation of the Tricyclic Strategy: The transition from a pentacyclic triterpene to a tricyclic derivative can be understood as a scaffold-economy problem. A natural product often contains structural features that are useful for biosynthesis or membrane partitioning but are not required for target recognition. Removing non-essential rings can decrease molecular weight and hydrophobic surface area, potentially improving solubility and oral exposure. The difficulty is that natural-product stereochemistry frequently pre-organizes functional groups into a geometry that is difficult to reproduce after simplification. Consequently, ring deletion should be accompanied by a pharmacophore-mapping exercise rather than performed solely to reduce molecular size. For PTP1B, three-

dimensional shape is especially important because the catalytic pocket is deep and the surrounding secondary pockets are spatially organized. A tricyclic core can act as a rigid platform that reduces the entropic cost of binding. If a substituent is pre-oriented toward the B, C or D region, the compound may achieve useful affinity without carrying a highly charged phosphate mimic. This concept is consistent with the observation that nonpolar terpenoids can influence PTP1B through peripheral or allosteric binding networks [21].

Another important design feature is vector control. In fused-ring systems, substituents attached at adjacent carbon atoms can project in markedly different directions depending on stereochemistry. Medicinal-chemistry campaigns should therefore characterize stereoisomers individually rather than assuming that racemic or diastereomeric mixtures behave equivalently. Chiral resolution may reveal substantial potency differences and can also improve the interpretability of molecular modeling. The balance between rigidity and flexibility is similarly important. Excessive rigidity can prevent adaptation to a protein pocket, whereas excessive flexibility increases the entropic penalty for binding and can reduce selectivity. A tricyclic scaffold occupies an intermediate design space: it is more compact than a pentacyclic triterpene but retains sufficient conformational definition to act as a three-dimensional pharmacophore. Substituent optimization should proceed around a clear hypothesis. If an acidic group is intended to interact with Arg221 or a secondary arginine residue, changing it to a neutral ether may reduce affinity. Conversely, if the compound is intended to bind allosterically, a neutral hydrophobic substituent may be preferable. This distinction can be tested by matched molecular pairs and kinetic analysis rather than inferred only from docking scores.

Catalytic-Site Versus Allosteric Terpenoid Inhibition: Classical PTP1B inhibitor programs frequently focused on the catalytic site because it offers a well-defined pocket with strong substrate-recognition determinants. However, the catalytic site is both polar and conserved. This creates the paradox that increasing affinity can simultaneously increase physicochemical burden and cross-reactivity. The development of allosteric inhibitors represents a response to this problem [18,21,33]. Terpenoids are particularly compatible with allosteric concepts because their hydrophobic surfaces can interact with nonpolar protein regions. Trodusquemine, although structurally different from the tricyclic OA-inspired series, illustrates the broader principle that a natural-product-derived hydrophobic scaffold can produce selective, noncompetitive PTP1B inhibition [33]. The lesson for tricyclic terpenoids is not that they must bind

the same site, but that non-catalytic binding is a credible design strategy.

The distinction can be experimentally tested. Competitive inhibition generally produces a change in apparent K_m with minimal change in V_{max} under idealized conditions, whereas noncompetitive or mixed inhibition affects both kinetic parameters. However, kinetic classification alone does not identify a physical binding site. Structural methods, mutagenesis and competition experiments are needed to connect the kinetic phenotype to a binding mode. For tricyclic derivatives, a useful experiment would compare inhibition against wild-type PTP1B and selected site-directed mutants of residues around the catalytic, secondary and allosteric regions. Loss of potency against a mutant supports involvement of that residue, although it does not by itself prove direct contact. Combining mutagenesis with molecular dynamics and structural data can provide a more reliable mechanistic model.

Relationship Between Enzyme Potency and Cellular Activity:

One of the most important lessons from the tricyclic literature is that biochemical potency and cellular activity are related but not identical. A compound can have a low IC_{50} against purified PTP1B and still be weak in cells because of poor permeability, rapid efflux, intracellular sequestration, protein binding or metabolic transformation. Conversely, a compound with only moderate biochemical potency may achieve a useful cellular response if it reaches the target efficiently and has favorable residence time. The selection of compound 25 in the Yang et al. study illustrates this principle [9]. The most potent enzyme inhibitors in the series were not automatically the compounds chosen for full pharmacological evaluation. Instead, a compound with moderate inhibition and more favorable pharmaceutical properties was examined in insulin-resistant HepG2 cells and in a diabetes model. This is an example of profile-based rather than single-parameter optimization. Cellular glucose uptake should also be interpreted carefully. Increased uptake after insulin stimulation is consistent with improved insulin signaling, but it can be influenced by transporter expression, cellular energy state and nonspecific effects. Therefore, glucose uptake should ideally be accompanied by measurements of insulin receptor phosphorylation and AKT activation. Where GLUT4 is relevant, transporter translocation provides an additional mechanistic readout. The same principle applies to hepatocyte models. HepG2 cells are useful for screening but differ from primary human hepatocytes in metabolic phenotype. Follow-up studies could use primary hepatocytes, human skeletal-muscle cells or adipocytes to determine whether the cellular response is tissue-specific. Such experiments would

also help identify whether a compound primarily affects hepatic glucose production or peripheral glucose disposal.

Animal Evidence and Interpretation of Antihyperglycaemic Activity: Animal studies are essential for determining whether biochemical and cellular effects survive the complexity of absorption, metabolism, tissue distribution and endocrine feedback. The nicotinamide-STZ model used in the tricyclic study provides evidence that compound 25 can reduce hyperglycaemia in a diabetic setting [9]. Nevertheless, STZ models vary in the degree of β -cell injury, and therefore the model should be described precisely when interpreting insulin-sensitizing activity. Diet-induced insulin resistance provides a complementary model because it more directly tests metabolic dysfunction associated with excess caloric intake. A compound that improves glucose tolerance without reducing food intake or causing weight loss is particularly informative because it suggests a direct metabolic effect. Conversely, strong reductions in food intake can confound interpretation of glucose lowering.

Glucose tolerance and insulin tolerance tests should be combined with fasting insulin measurements. An improvement in glucose tolerance accompanied by lower fasting insulin can indicate improved insulin sensitivity, whereas a large fall in insulin without improved tolerance may indicate reduced secretion or β -cell toxicity. HOMA-like indices can provide additional information but are less definitive in rodents than direct physiological tests. Tissue pharmacology is another major gap in many natural-product studies. Liver, skeletal muscle and adipose tissue should be examined for insulin receptor phosphorylation, AKT phosphorylation and PTP1B activity. If the compound is designed to be peripheral, central exposure should also be characterized to determine whether hypothalamic PTP1B contributes to the phenotype.

Proposed Structure-Activity Matrix for Future Libraries: A rational future library could use a single tricyclic core and systematically vary five regions: R_1 near the aromatic/hydrophobic vector, R_2 at a hydrogen-bond donor position, R_3 at an acidic or ionizable position, R_4 at a solvent-exposed position and the overall stereochemical configuration. The objective would be to map not only PTP1B potency but also selectivity, permeability and metabolic stability. A first series could compare carboxylic acid, amide, ester and tetrazole-like bioisosteric functionality. The acid may maximize electrostatic binding but reduce permeability; the ester may improve permeability but require hydrolysis; the amide may offer a neutral hydrogen-bonding alternative. These predictions should be tested rather than assumed. A second series could vary hydrophobic substituents

from small alkyl groups through cycloalkyl and aromatic groups. This series would reveal whether the binding site favors compact hydrophobes or extended aromatic surfaces. Excessive lipophilicity should be avoided if it increases nonspecific binding or reduces solubility. A third series could vary hydroxyl placement. The literature suggests that hydroxylation can either help or harm activity depending on position and overall scaffold [7,23]. Positional isomers are therefore particularly informative because they preserve molecular formula while changing hydrogen-bond geometry. A fourth series should deliberately explore allosteric hypotheses. Neutral analogues with reduced catalytic-site charge could be compared with acidic analogues. If neutral analogues retain inhibition and display mixed/noncompetitive kinetics, they may represent a distinct allosteric chemotype deserving structural investigation.

Recommended Reporting Standards for Future PTP1B-Terpenoid Studies: Natural-product PTP1B papers would be substantially more reproducible if they consistently reported enzyme source, catalytic-domain construct, assay buffer, reducing conditions, substrate concentration, enzyme concentration, incubation time and method of IC_{50} calculation. These parameters can materially influence apparent potency. Compound purity should be reported with an analytical method, ideally including HPLC and mass spectrometry. This is especially important for terpenoids because closely related analogues and stereoisomers can co-elute or differ in activity. Structural assignment should include NMR data where new compounds are synthesized. Selectivity should be expressed as a panel rather than a single comparator. At minimum, PTP1B and TCPTP should be measured under comparable conditions. When possible, SHP1, SHP2 and LAR should also be included. A numerical selectivity ratio is more meaningful when assay conditions are matched. Cellular studies should report compound concentration, incubation time, cell viability, insulin concentration and whether glucose uptake is basal or insulin-stimulated. Animal studies should report sex, age, strain, randomization, dosing route, formulation, duration, sample size and exposure. These details are necessary to distinguish pharmacological efficacy from experimental artifacts. Finally, docking figures should not be presented as proof of binding. Docking is hypothesis-generating. Strong claims about binding mode should be supported by biochemical competition, mutagenesis, biophysical binding or structural determination. This is especially important for hydrophobic terpenoids, for which docking can produce plausible but experimentally irrelevant poses.

Overall Synthesis of the Literature: Taken together, the literature forms a coherent medicinal-chemistry progression. First, genetic studies established that PTP1B loss can improve insulin sensitivity [10]. Second, natural-product screening identified triterpenes such as UA and OA as PTP1B-active scaffolds [6–8]. Third, chemical modification demonstrated that potency and

cellular activity could be improved through targeted changes in the triterpene framework [6,23,24]. Fourth, the tricyclic study demonstrated that a smaller terpenoid-inspired architecture can preserve useful activity while improving selected pharmaceutical properties [9]. The integrated pharmacological concept is summarized in Figure 6.

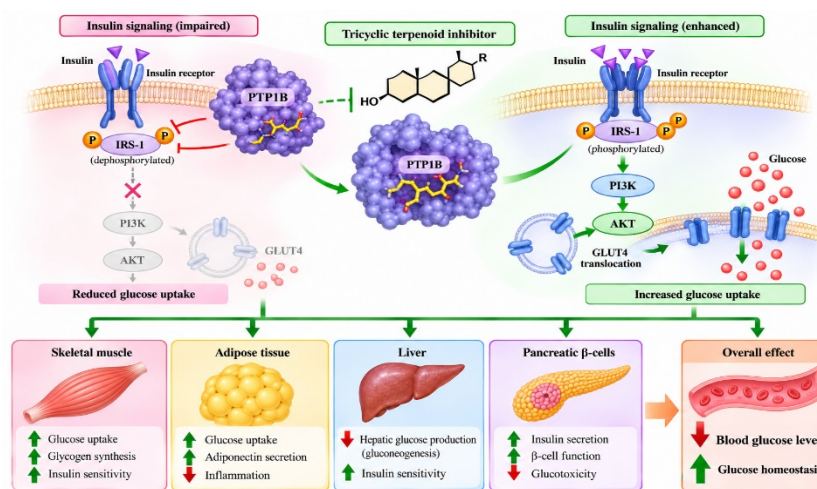


Figure 6: pharmacological concept for PTP1B Inhibitors

At the same time, the literature reveals a translational gap. There is no clinical evidence establishing tricyclic terpenoid PTP1B inhibitors as effective antidiabetic medicines. The broader PTP1B field has repeatedly encountered challenges involving selectivity, bioavailability, efficacy and safety [3,12-15]. Therefore, the main scientific opportunity is not simply to discover more PTP1B inhibitors, but to discover inhibitors with a complete pharmacological profile. The most promising direction is likely a structure-guided, multi-parameter strategy in which the tricyclic scaffold is treated as a tunable platform. The desired lead should combine sufficient PTP1B potency with selectivity over TCPTP, cellular target engagement, oral exposure, acceptable metabolic stability and a measurable pharmacodynamic response. Such a lead would provide a stronger basis for translational development than a compound selected solely on the basis of a low enzyme IC_{50} .

Conclusion

PTP1B remains a compelling molecular target for improving insulin sensitivity because it negatively regulates insulin receptor signaling, and genetic evidence strongly supports the metabolic consequences of reducing PTP1B activity. Natural pentacyclic triterpenes, particularly OA and UA, provided early proof that terpenoid frameworks can inhibit PTP1B and enhance insulin signaling in cellular systems. Medicinal-chemistry studies

subsequently demonstrated that changes at hydroxylated and acidic positions can substantially modify potency and functional activity. The development of smaller tricyclic terpenoid derivatives represents a rational evolution of this scaffold class. The Yang *et al.* study is especially important because it demonstrated that an OA-inspired tricyclic core can yield compounds with strong biochemical inhibition and that balanced optimization can produce a derivative with cellular insulin-sensitizing and *in-vivo* antihyperglycaemic effects. The most important lesson is that the strongest enzyme inhibitor is not necessarily the most useful lead: compound selection must consider selectivity, physicochemical properties, cellular activity, exposure and tolerability. Future work should integrate structure-based design, quantitative SAR, orthogonal target-engagement assays, TCPTP selectivity, ADME optimization and PK/PD modeling. Tricyclic terpenoids should therefore be regarded as promising preclinical scaffolds for PTP1B-directed drug discovery, not as established therapeutic agents. Their value lies in providing a compact, three-dimensional and chemically tunable framework capable of engaging hydrophobic and peripheral regions of PTP1B while offering opportunities to improve drug-like properties relative to larger pentacyclic natural products.

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