

# Computational Identification of Prenylated Isoflavanones as Natural PTPN1 Inhibitors for Antidiabetic Drug Discovery

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## INFO ARTIKEL

Received 30 September 2024

Accepted 30 November 2024

Key words:

PTP1B;

molecular docking;

prenylated isoflavanones;

antidiabetic agents;

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## ABSTRACT

Protein tyrosine phosphatase non receptor type 1 (PTPN1) is a key negative regulator of insulin signaling and a validated therapeutic target for antidiabetic drug development. This study investigates the binding potential of three prenylated isoflavanones platyisoflavanone A, sophoraisoflavanone A, and erpogein D against PTP1B using molecular docking. Redocking of the native ligand yielded a low RMSD value (0.2953 Å), confirming the reliability of the docking protocol. All three compounds demonstrated strong predicted affinities and sub-micromolar  $K_i$  values, with platyisoflavanone A showing the highest potency. Interaction analysis revealed that the isoflavanones occupy the catalytic pocket and engage key residues such as Tyr46, Asp48, Phe182, Ile219, and Gln262, supported by extensive hydrophobic contacts from the prenyl substituent. These findings indicate that prenylated isoflavanones possess structural features compatible with PTP1B inhibition and represent promising natural scaffolds for further development of antidiabetic agents.

## Introduction

Natural products remain an indispensable reservoir for the discovery of new therapeutic agents, particularly in the treatment of metabolic disorders such as type 2 diabetes mellitus. Among the diverse classes of plant secondary metabolites, prenylated isoflavanones have attracted increasing scientific interest due to their structural richness and broad pharmacological potential. *Erythrina poeppigiana* (Fabaceae), a species widely distributed in tropical regions, is known to produce a variety of bioactive flavonoids and isoflavonoids. Recent phytochemical investigations have successfully isolated three structurally related prenylated isoflavanones: platyisoflavanone A, erpogein D, and sophoraisoflavanone A which were initially reported for their antimalarial activity and later recognized for their promising multitarget pharmacological profiles.[1]

Computational studies have further expanded the biological relevance of these compounds. A previous in silico investigation demonstrated that all three isoflavanones exhibit favorable drug-likeness properties, high

gastrointestinal absorption, and compliance with Lipinski's criteria [2] More importantly, SwissTargetPrediction consistently identified Tyrosine-protein phosphatase non-receptor type 1 (PTPN1) as the top predicted target for platyisoflavanone A, erpogein D, and sophoraisoflavanone A, with probability values approaching unity. This strong and recurrent prediction suggests a high degree of structural compatibility between these natural compounds and known ligands of PTPN1[3] The same study also highlighted additional targets associated with inflammation and cell proliferation; however, PTPN1 remained the most dominant and biologically relevant target across all three molecules [4]

PTPN1, also known as Protein Tyrosine Phosphatase 1B (PTP1B), is a well-established negative regulator of insulin signaling. By dephosphorylating the insulin receptor and IRS-1, PTP1B attenuates downstream metabolic pathways essential for glucose uptake and homeostasis. Overexpression or hyperactivity of PTP1B has been strongly associated with insulin resistance, obesity, and impaired glucose tolerance. Consequently, selective

inhibition of PTP1B has emerged as a compelling therapeutic strategy for restoring insulin sensitivity and managing type 2 diabetes. The availability of high-resolution crystallographic data particularly the 1ECV structure, which captures PTP1B in complex with a small-molecule inhibitor provides an ideal framework for structure-based drug design and molecular docking studies.[5]

Given the strong computational evidence linking prenylated isoflavanones to PTP1B and considering the central role of PTP1B in metabolic regulation, the present study focuses on evaluating the antidiabetic potential of platyisoflavanone A, erypogein D, and sophoraisoflavanone A through molecular docking against the PTP1B structure (1ECV).[6] By analyzing binding affinities, interaction patterns, and structural complementarity, this work aims to determine whether these natural compounds can serve as viable lead candidates for PTP1B inhibition and subsequent modulation of insulin signaling.

## Material and Method

### *Ligand Preparation*

Three prenylated isoflavanones platyisoflavanone A, erypogein D, and sophoraisoflavanone A were selected based on previous phytochemical studies reporting their biological potential. The two-dimensional structures of all compounds were drawn using ChemDraw Professional and subsequently exported into Chem3D for three-dimensional optimization. Geometry minimization was performed using the MMFF94 force field, which is widely applied for small-molecule conformational refinement due to its balanced treatment of steric, electrostatic, and torsional parameters. The minimization process ensured that each ligand adopted a low-energy conformation suitable for docking simulations.

Following minimization, the optimized structures were saved in MOL format and converted into PDBQT using AutoDock Tools. During conversion, polar hydrogens were added, Gasteiger charges were assigned, and rotatable bonds were defined according to the default Vina protocol. All ligands were treated as flexible molecules.

### *Protein Preparation*

The crystal structure of Protein Tyrosine Phosphatase 1B (PTP1B) was retrieved from the Protein Data Bank (PDB ID: 1ECV). This structure contains PTP1B complexed with a small-molecule inhibitor, providing a well-defined catalytic pocket for structure-based docking. The protein was prepared using AutoDock Tools by removing water molecules, deleting the co-crystallized ligand, and adding polar hydrogens. Kollman charges were assigned, and non-polar hydrogens were merged. The prepared receptor was saved in PDBQT format.

### *Docking Protocol*

Molecular docking simulations were performed using AutoDock Vina v1.2.7, which employs an iterated local search global optimizer and an empirical scoring function to estimate binding affinity. A configuration file was prepared specifying the receptor and ligand files, grid box dimensions, and grid center coordinates. The grid box was set to fully encompass the catalytic pocket of PTP1B, with dimensions of  $40 \times 40 \times 40$  Å and a spacing of 0.375 Å, consistent with the native ligand's binding region.

The exhaustiveness parameter was set to 100 to ensure thorough sampling of ligand conformations. For each ligand, Vina generated multiple binding poses ranked by predicted binding affinity (kcal/mol). The best pose (lowest binding energy) was selected for further analysis.

### *Validation of Docking Procedure*

To ensure reliability of the docking protocol, the native ligand from 1ECV was removed and re-docked into its original binding site. The predicted pose was compared with the crystallographic pose using RMSD values. An RMSD below 2.0 Å was considered indicative of successful validation. This procedure confirmed that the docking setup accurately reproduced the native binding mode of PTP1B.

### *Interaction Analysis*

The top-ranked binding poses of each ligand were visualized using BIOVIA Discovery Studio Visualizer. Two-dimensional interaction

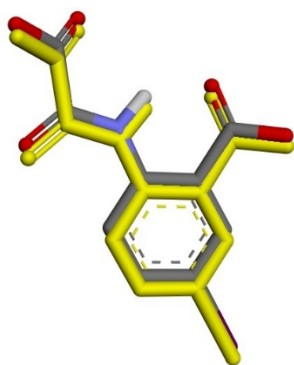
diagrams were generated to identify hydrogen bonds, hydrophobic contacts,  $\pi$ -interactions, and electrostatic interactions between the ligands and key residues within the PTP1B catalytic pocket.

## Result and discussion

### Molecular Docking Results

To ensure the reliability of the docking protocol, a redocking procedure was performed using the native ligand present in the PTP1B crystal structure 1ECV[7]. The native ligand was removed from the binding pocket and subsequently re-docked using the same grid parameters and scoring function applied to the test compounds. AutoDock Vina successfully reproduced the crystallographic binding orientation, yielding a heavy-atom RMSD of 0.2953 Å relative to the native pose (Figure 1).

This RMSD value well below the commonly accepted threshold of 2.0 Å demonstrates that the docking configuration accurately captures the geometric and energetic characteristics of the PTP1B active site [8]. The close alignment between the predicted and experimental poses confirms that the grid box placement, receptor preparation, and scoring parameters are appropriate for evaluating ligand binding within the catalytic pocket of PTP1B.



**Figure 1.** Redocking overlay of native ligand in 1ECV

### Binding Affinity of Prenylated Isoflavanones

Following successful redocking validation, molecular docking simulations were performed to assess the binding strength of the three prenylated isoflavanones platyisoflavanone A, erypogein D, and sophoraisoflavanone A toward the catalytic pocket of PTP1B (1ECV).

AutoDock Vina generated nine poses for each ligand, with the top-ranked pose selected based on the lowest predicted binding free energy ( $\Delta G$ ).

Platyisoflavanone A exhibited the strongest affinity with a  $\Delta G$  of  $-8.233$  kcal/mol, followed closely by sophoraisoflavanone A ( $-8.155$  kcal/mol) and erypogein D ( $-7.917$  kcal/mol). These values fall within the sub-micromolar potency range typically associated with natural PTP1B inhibitors. To further contextualize these results, inhibition constants ( $K_i$ ) were calculated from the docking energies using the standard thermodynamic relationship  $K_i = e^{\Delta G/RT}$ . The resulting  $K_i$  values  $0.29 \mu\text{M}$ ,  $0.33 \mu\text{M}$ , and  $0.47 \mu\text{M}$ , respectively indicate that all three compounds possess strong predicted inhibitory potential against PTP1B.

**Table 1.** Binding affinities and calculated  $K_i$  values of prenylated isoflavanones against PTP1B (1ECV)

| Ligand                | Binding Affinity (kcal/mol) | $K_i$ ( $\mu\text{M}$ ) |
|-----------------------|-----------------------------|-------------------------|
| Platyisoflavanone A   | $-8.233$                    | $0.29 \mu\text{M}$      |
| Sophoraisoflavanone A | $-8.155$                    | $0.33 \mu\text{M}$      |
| Erypogein D           | $-7.917$                    | $0.47 \mu\text{M}$      |
| Native ligand         | $-9.061$                    | $0.25 \mu\text{M}$      |

The close clustering of  $K_i$  values suggests that the prenylated isoflavanone scaffold is inherently compatible with the PTP1B active site, likely due to its combination of aromatic rings, hydrogen-bonding groups, and hydrophobic prenyl substituents. Among the three ligands, platyisoflavanone A demonstrates the most favorable predicted potency, consistent with its more extensive interaction network observed in subsequent binding-pose analyses.

### Binding Pose Analysis

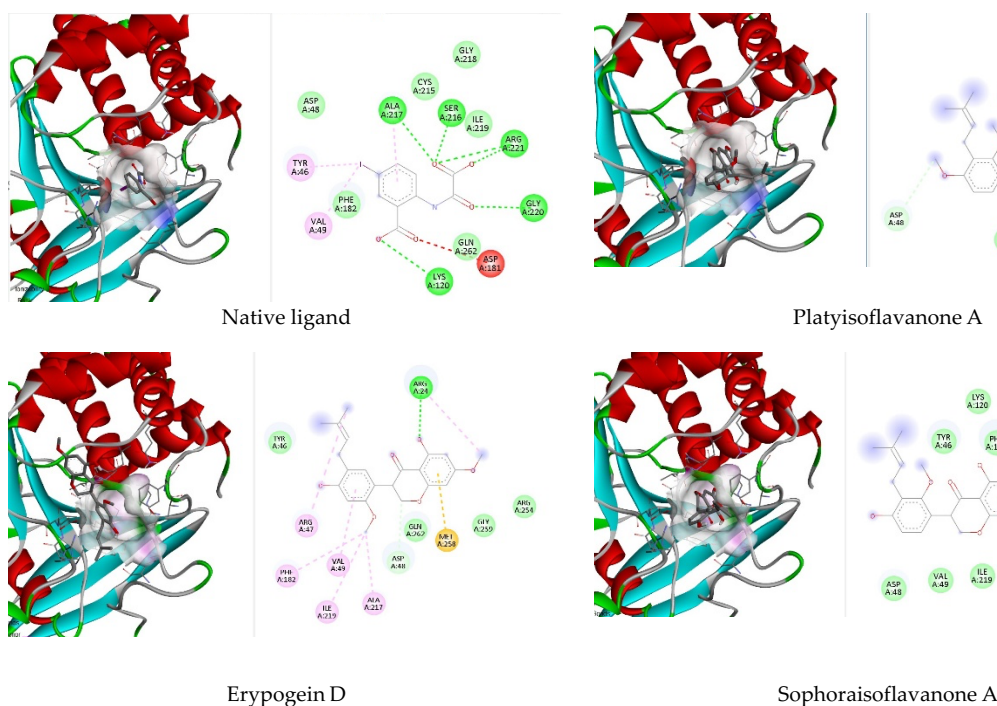
The binding poses of platyisoflavanone A, erypogein D, and sophoraisoflavanone A were analyzed and compared with the native ligand of PTP1B (1ECV). All ligands occupied the canonical catalytic pocket, overlapping with the native inhibitor's binding region validated by

redocking (RMSD = 0.2953 Å). The interactions primarily involved residues Asp48, Val49, Phe182, Ala217, Ile219, and Gln262, which are

known to govern substrate recognition and catalytic regulation.

**Table 2.** Comparative interaction profile of prenylated isoflavanones and native ligand with PTP1B (1ECV)

| Compound              | Hydrogen Bond Interactions | Bond            | Van Der Waals                                                                              | Observation                                                                                                                            |
|-----------------------|----------------------------|-----------------|--------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| Native ligand (1ECV)  | Ala127, Arg221, Lys 120    | Ser216, Gly220, | Gly 218, Cys215, Asp48, Ile219, Phe182, Gln262,                                            | Compact binding within catalytic pocket; strong polar anchoring and aromatic stacking stabilize the complex.                           |
| Platyisoflavanone A   |                            |                 | Val49, Ile219, Gln262, Gly220, Arg 221, Cys 215, Asp 181, Phe182, Tyr 46, Lys 120, Ser216, | Deep insertion into the pocket; prenyl group enhances hydrophobic packing; strongest overall affinity ( $\Delta G = -8.233$ kcal/mol). |
| Erypogein D           | Arg24                      |                 | Arg 254, Gly 259, Gln 262, Tyr46, Ile 219, Val 49, Asp48, Arg45                            | Similar orientation to native ligand; additional polar contacts with Lys120 and Arg221 increase stability.                             |
| Sophoraisoflavanone A | Asp181                     |                 | Asp48, Val49, Ile219, Gln262, Gly220, Cys215, Arg 221, Ser216, Phe182, Tyr 46, Lys 120     | Slightly shifted pose toward the hydrophobic rear pocket; fewer hydrogen bonds lead to weaker binding ( $\Delta G = -7.917$ kcal/mol). |



**Figure 2.** 2D and 3D overlay of native ligand and docked isoflavanones

Table 2 and Figure 2 summarize the interaction patterns formed by the native PTP1B ligand and the three prenylated isoflavanones. Overall, all compounds occupy the catalytic pocket and interact with key residues involved in ligand recognition. The native ligand shows a balanced combination of hydrogen-bonding and hydrophobic contacts, reflecting its compact and well-anchored binding mode. In comparison, the three isoflavanones rely more

heavily on van der Waals and hydrophobic interactions particularly with residues such as Val49, Ile219, Phe182, Tyr46, and Gln262 while forming fewer hydrogen bonds. These differences in interaction profiles correspond to variations in binding orientation and predicted affinity among the compounds.

The comparative interaction analysis highlights how the three prenylated isoflavanones platyisoflavanone A,

sophoraisoflavanone A, and erypogein D engage the catalytic pocket of PTP1B relative to the native ligand[9]. While the native ligand displays a balanced combination of hydrogen-bonding and hydrophobic interactions, the three natural compounds rely predominantly on hydrophobic contacts with key residues such as Val49, Ile219, Phe182, Tyr46, and Gln262. This pattern reflects the influence of the prenyl substituent, which enhances hydrophobic anchoring within the pocket.

Platyisoflavanone A exhibits the broadest interaction network, engaging both catalytic and rear-pocket residues, consistent with its strongest binding affinity. Sophoraisoflavanone A maintains the core interactions of the native ligand but introduces additional contacts with Arg24, Arg45, and Arg254, suggesting a slightly shifted yet stable orientation. Erypogein D interacts widely across the pocket but forms fewer hydrogen bonds, resulting in a more flexible pose and slightly lower affinity. Overall, the interaction profiles indicate that all three compounds successfully mimic the native ligand's binding pattern while introducing additional hydrophobic stabilization[10]

The SAR analysis reveals that the prenylated isoflavanone scaffold is structurally well-suited for PTP1B inhibition. The aromatic core of the isoflavanones facilitates  $\pi$ - $\pi$  stacking with residues such as Phe182 and Tyr46, while the phenolic and carbonyl groups provide opportunities for hydrogen bonding with Asp48, Asp181, and Gln262. The presence of the prenyl group significantly enhances hydrophobic interactions, allowing deeper insertion into the catalytic pocket and stronger engagement with residues like Val49, Ile219, and Cys215.

Platyisoflavanone A benefits from an optimal balance of aromatic, polar, and hydrophobic features, resulting in the most favorable binding affinity. Sophoraisoflavanone A introduces additional polar contacts that stabilize its pose despite fewer hydrophobic interactions[11]. Erypogein D, while structurally similar, forms fewer polar anchors and relies more heavily on hydrophobic packing, which may explain its slightly weaker affinity. These observations suggest that

modifications enhancing hydrogen-bonding capacity or optimizing prenyl positioning could further improve inhibitory potency[12]

PTP1B is a well-established negative regulator of insulin signaling, and its inhibition has long been pursued as a therapeutic strategy for improving insulin sensitivity and glucose homeostasis[13]. The strong binding affinities and favourable interaction profiles observed for the three prenylated isoflavanones indicate that these natural compounds may serve as promising lead candidates for antidiabetic drug development[14]

Their ability to mimic the native ligand's interaction pattern while introducing additional hydrophobic stabilization suggests that the isoflavanone scaffold is compatible with the structural requirements of PTP1B inhibition[15]. The sub-micromolar  $K_i$  values further support their potential biological relevance. These findings align with previous computational predictions identifying PTPN1 as a primary target for these compounds, reinforcing their mechanistic plausibility.

Future work may include molecular dynamics simulations to assess binding stability, in vitro enzyme inhibition assays to validate computational predictions, and structural optimization to enhance potency and selectivity. Collectively, the results position prenylated isoflavanones as attractive natural scaffolds for the development of novel PTP1B inhibitors with potential antidiabetic applications.

## Conclusion

The docking study shows that the three prenylated isoflavanones platyisoflavanone A, sophoraisoflavanone A, and erypogein D bind favorably to the catalytic pocket of PTP1B. Redocking validation confirms the reliability of the docking protocol. All three compounds exhibit strong predicted affinities and sub-micromolar  $K_i$  values, with platyisoflavanone A showing the highest potency. Their interaction profiles closely mimic the native ligand, supported by extensive hydrophobic contacts and key polar interactions. These results indicate that prenylated isoflavanones represent promising

natural scaffolds for developing PTP1B inhibitors with potential antidiabetic relevance.

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