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Structure-Based Virtual Screening of Natural Compounds for Inhibition of Protein Tyrosine Phosphatase 1B: A Promising Therapeutic Approach in Diabetes Management

Ahmad Salah Alkathiri

Abstract

Background: Diabetes is a metabolic disorder characterized by an imbalance in insulin synthesis or utilization, resulting in elevated blood glucose levels. Type 2 diabetes (T2D) is characterized by high blood glucose levels, which are primarily caused by insulin resistance, resulting in a variety of complications and a significant impact on vital organs. The primary function of protein tyrosine phosphatase 1B (PTP1B) is to regulate the signaling pathways of insulin and leptin, both of which are involved in cellular metabolism and glucose homeostasis. PTP1B catalyzes the de-phosphorylation of active insulin receptors and insulin receptor substrates, resulting in insulin signaling downregulation.

Methods: In this study, natural compounds from the ZINC database were screened against the PTP1B protein using the PyRx 0.8 tool. The physicochemical and drug-likeness characteristics of the top five screened compounds were investigated using the SwissADME web tool.

Results: The compounds ZINC899884, ZINC56981, ZINC252509722, ZINC1843029, and ZINC21789 interacted and bound with PTP1B protein strongly, and their binding energies were higher than those of the control compounds. Furthermore, these compounds exhibit favorable drug-like properties.

Conclusion: This study suggests the potential use of these compounds as PTP1B inhibitors for diabetes management. However, additional experimental studies are needed to optimize them as PTP1B inhibitors.

Introduction

Diabetes is a metabolic condition marked by an imbalance in insulin synthesis or usage, resulting in elevated blood glucose levels [1]. It has been expected that the incidence of diabetes will rise by approximately 64% by 2025, affecting around 53.1 million people [2]. The global prevalence of diabetes in adults was predicted to be 285 million (6.4%) in 2010, and this figure is expected to climb to roughly 439 million (7.7%) by 2030 [3]. Type 2 diabetes (T2D) is becoming more common all over the world, particularly in underdeveloped and developing countries. It is estimated that around 463 million adults currently suffer from diabetes, with the number expected to rise to 700 million by 2045 [4]. Saudi Arabia, the Middle East's largest country with a population of around 33.3 million [5], is experiencing a widespread surge of diabetes among its adult population. Diabetes affects over one-fourth of adults in the country, and this figure is anticipated to rise dramatically by 2030 [6].

T2D is defined by high blood glucose levels, which are mostly due to insulin resistance (IR), resulting in multiple problems and a severe influence on important organs [7]. One well-established treatment approach for treating hyperglycemia involves lowering the activity of protein tyrosine phosphatase 1B (PTP1B), which can improve IR [8]. PTP1B is a protein tyrosine phosphatase family enzyme that is abundantly expressed in different organs such as the liver, muscles, and adipose tissue, all of which are insulin targets [9]. Its principal function is to regulate the signaling pathways of insulin and leptin, both of which are important hormones involved in cellular metabolism and glucose homeostasis. PTP1B catalyzes the de-phosphorylation of active insulin receptors and insulin receptor substrates, resulting in the down-regulation of insulin signaling [10]. PTP1B over activity contributes to IR, which leads to hyperglycemia and metabolic abnormalities, which are the fundamental underlying causes of T2D [11]. Hence, PTP1B emerges as a prospective therapeutic target, and its inhibition has been recommended as a potentially useful treatment for T2D.

The drug development process poses significant challenges in the pharmaceutical industry due to the considerable time and financial investments required to navigate through all the phases of creating a new drug. To address this, computer-aided drug design (CADD) has emerged as a widely used approach to streamline the drug development process. Using CADD, researchers can optimize their experimental focus, reducing the time and expenses associated with drug development. Among the different in silico techniques, virtual screening (VS) stands out as a strong and valuable technology with great promise in drug design [12]. This study aimed to find possible natural PTP1B inhibitors using the in-silico tools.

Methods

Target protein retrieval and preparation

The crystal structure of the PTP1B (PDB ID: 2CNG), refined at a 1.90 Å resolution, was obtained from the Protein Data Bank. Following that, the co-crystallized ligand, IZE, also known as BDBM13474, which is a PTP1B inhibitor, was removed from the protein structure, and the clean protein structure was minimized using the discovery studio visualizer 2020 and saved in .pdb format.

Natural compound library preparation and virtual screening

The ZINC database was used to obtain a collection of 2700 naturally occurring compounds in '.sdf' file format. These compounds' structures were minimized by employing a Universal Force Field (UFF) and prepared for further VS. VS is a drug development computer approach used to identify prospective compounds with promising pharmacological activity from huge compound libraries. It applies drug design theoretical principles as well as computer technology and specific software applications [13]. The major goal is to systematically filter novel lead chemicals from large molecular databases. Using the PyRx 0.8 tool [14], the prepared compound library was screened against the PTP1B.

Physiochemical and ADMET properties

The physicochemical and drug-likeness characteristics of the top five screened compounds were investigated using the SwissADME web tool. With the help of this efficient tool, it was possible to thoroughly assess and estimate the different properties connected to these compounds, which provided important insights into their chemistry and potential as treatment candidates [15].

Results

Virtual screening of natural compounds

To identify a potential natural inhibitor of PTP1B, a VS methodology was utilized. A library of 2700 natural compounds, obtained from the ZINC database, underwent virtual screening. Here in this study, co-crystallized ligand (BDBM13474), and two well-known PTP1B inhibitors, namely Erythribyssin A [16] and Formylchromone [17] were used as positive controls. The XYZ coordinates, specifically 2.124500, 9.759750, and 46.315444 were derived from the co-crystallized ligand.

Targeting the active site residues of PTP1B, 2700 natural compounds were computationally screened, and several compounds with higher binding energies than the positive controls used in this study were identified as possible candidates. The top 15 compounds that interacted with important PTP1B residues and had binding energies greater than the control are listed in Table 1.

Compounds	Binding Affinity (kcal/mol)
ZINC899884	-8.5
ZINC56981	-8.5
ZINC252509722	-8.1
ZINC1843029	-8
ZINC21789	-8
ZINC14681317	-7.9
ZINC14760151	-7.9
ZINC18847036	-7.7
ZINC26829933	-7.5
ZINC34733778	-7.5
ZINC100014157	-7.5
ZINC26832397	-7.4
ZINC33832263	-7.4
ZINC34226709	-7.3
ZINC34645716	-7.3
BDBM13474	-7.2
Erythribyssin A	-7.1
Formylchromone	-7

Table 1: Top 15 screened compounds having higher binding affinity value than the control.

The binding energies of all 15 compounds were found to be lower than those of the control compounds, indicating a stronger affinity for the target protein PTP1B. Furthermore, these compounds exhibited interactions with a significant number of the key residues of PTP1B. Following a thorough analysis and visualization of the interactions between the docked complexes, the top five hits (Figure 1) in this study, which demonstrated more effective binding by interacting with crucial PTP1B residues, are thoroughly discussed.

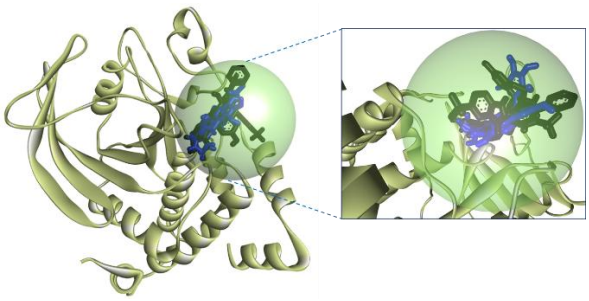

Figure 1: 3D visualization of docked poses of control compounds (black) and top 5 hits (blue) in the binding pocket of PTP1B.

The co-crystallized ligand (BDBM13474), Erythribyssin A, and Formylchromone, which were used as positive controls, have been shown to interact with key PTP1B residues like (Asp48, Ile219, Gln262, Gly220, Arg221, Cys215, Phe182, Ser216, Asp181, and Tyr46) (Figure 2).

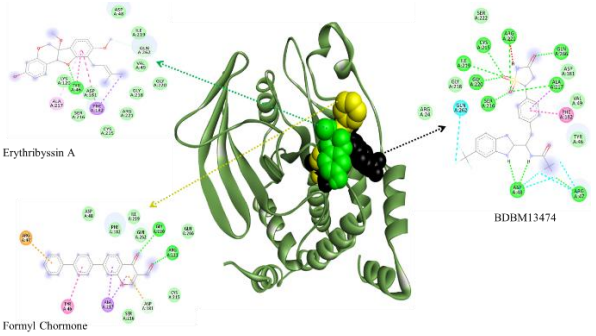

Figure 2: Binding poses and 2D interacting residues of PTP1B with control compounds.

The analysis focused on the interaction profiles of the top 5 hits, specifically ZINC899884, ZINC56981, ZINC252509722, ZINC1843029, and ZINC21789 within the active site residues of PTP1B. This analysis included both 3D interactions (Figure 3) and 2D interactions (Figure 4).

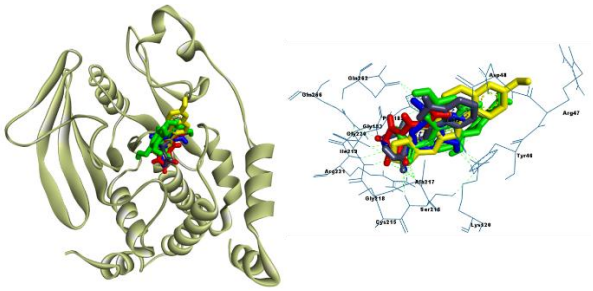

Figure 3: Binding poses of top 5 hits, ZINC899884 (green), ZINC56981 (grey), ZINC252509722 (yellow), ZINC1843029 (red), and ZINC21789 (blue) in the binding pocket of PTP1B.

ZINC899884 interacted with Asp48, Phe182, Ala217, Gln262, Ile219, Gly220, Gly218, Ser216, Cys215, Arg221, Asp181, Tyr46, Lys120, and Arg47 residues of PTP1B protein. Gly220, Ser216, Arg221, and Tyr46 residues were involved in H-bonding with ZINC899884 (Figure 4A). ZINC56981 interacted with Gly218, Cys215, Ser216, Arg221, Asp181, Gln266, Phe182, Ala217, Val49, Gln262, Asp48, Tyr46, Ile219, and Gly220 residues of PTP1B protein. Among them, Gly218, Ser216, Arg221, and Gln262 H-bonded with ZINC56981 (Figure 4B). ZINC252509722 binds with the Glu115, Asp181, Lys120, Tyr46, Phe182, Gly220, Ser216, Ala217, Ile219, Arg221, Cys215, Gly218, Val49, Gln262, and Asp48 residues of PTP1B protein. Gln262, Ala217, Ser216, Tyr46, Lys120, and Asp181 residues were involved in H-bonding with ZINC252509722 (Figure 4C). ZINC1843029 was found to interact with Ile219, Val49, Gln262, Ser216, Gly218, Ala217, Arg221,

Molecule	Physicochemical Properties						Lipophilicity					
	MW	RB	HBA	HBD	MR	TPSA	iLOGP	XLOGP3	WLOGP	MLOGP	Silicos-IT Log P	Consensus Log P
ZINC899884	284.26	0	5	1	72.74	57.15	2.48	2.61	2.41	1.71	2.6	2.36
ZINC56981	218.25	4	3	3	62.26	65.12	1.33	-0.55	1.38	-1.38	1.96	0.55
ZINC252509722	406.38	5	11	5	88.45	164.37	2.98	-1.8	-2.42	-2.12	-2.57	-1.19
ZINC1843029	158.12	2	3	4	39.55	113.32	-0.29	-2.17	-2.94	-1.85	-2.03	-1.85
ZINC21789	184.15	2	5	3	43.79	86.99	0.97	0.86	0.59	0.18	0.28	0.57

[RB=number of rotatable bonds; HBA= Hydrogen bond acceptor; HBD= Hydrogen bond donor; MR=Molar Refractivity].

Table 2: Predicted Physicochemical Properties and Lipophilicity of top 5 compounds (ZINC899884, ZINC56981, ZINC252509722, ZINC1843029, and ZINC21789).

Molecule	Water Solubility			Pharmacokinetics							
	ESOL Class	Ali Class	Silicos-IT class	GI absorption	BBB permeant	Pgp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor
ZINC899884	S	S	S	High	Y	Y	Y	Y	X	Y	Y
ZINC56981	Very S	Very S	S	High	Y	X	X	X	X	X	X
ZINC252509722	Very S	Very S	S	Low	X	Y	X	X	X	X	X
ZINC1843029	Highly S	Highly S	S	Low	X	X	X	X	X	X	X
ZINC21789	Very S	S	S	High	X	X	X	X	X	X	X

[Soluble=S; NO=X; Yes=Y]

Table 3: Predicted Water Solubility and Pharmacokinetics of top 5 compounds (ZINC899884, ZINC56981, ZINC252509722, ZINC1843029, and ZINC21789).

Molecule	Drug likeness						Medicinal Chemistry			
	Lipinski	Ghose	Veber	Egan	Muegge	Bioavailability Score	PAINS	Brenk	Lead likeness	Synthetic Accessibility
ZINC899884	0	0	0	0	0	0.55	0	0	0	3.7
ZINC56981	0	0	0	0	0	0.55	0	0	1	2.2
ZINC252509722	1	1	1	1	2	0.11	0	0	1	5.8
ZINC1843029	0	4	0	0	3	0.55	0	1	1	2.42
ZINC21789	0	0	0	0	1	0.55	1	1	1	1.5

Table 4: Predicted drug-likeness and medicinal chemistry properties of top 5 compounds (ZINC899884, ZINC56981, ZINC252509722, ZINC1843029, and ZINC21789).

and Ser216 residues make the H-bond with ZINC1843029 (Figure 4D). Further, ZINC21789 interacted with Tyr46, Val49, Gln262, Phe182, Ile219, Gln266, Asp181, Gly220, Cys215, Arg221, Gly218, Ser216, Ala217, and Lys120 residues of PTP1B protein. Among them, Gln262, Gly220, Arg221, Ser216, and Ala217 residues were H-bonded with ZINC21789 (Figure 4E).

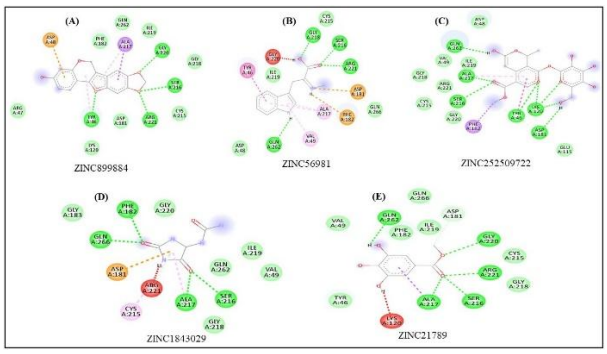

Figure 4: Interacting residues of PTP1B with ZINC899884 (A), ZINC56981 (B), ZINC252509722 (C), ZINC1843029 (D), and ZINC21789 (E).

Physicochemical, pharmacokinetics and drug likeness assessment

properties falling within this zone demonstrate oral bioavailability. Figure 5 illustrates the physiochemical properties as bioavailability radar of the five selected hits. ZINC252509722 and ZINC21789 exhibited minimal deviation from the designated pink region, within which the molecular radar plot must entirely reside in order to be classified as drug-like (Figure 5).

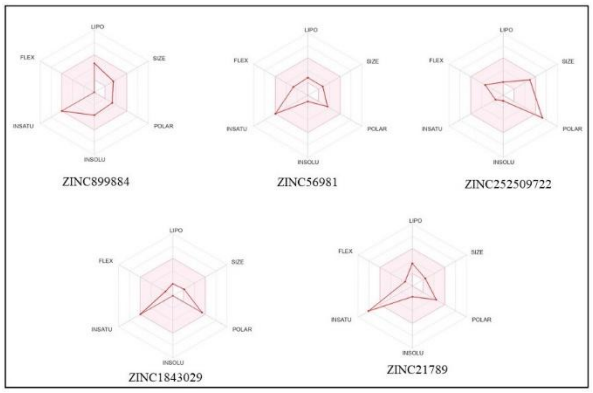

Figure 5: Bioavailability radar for top 5 hits (ZINC899884, ZINC56981, ZINC252509722, ZINC1843029, and ZINC21789).

The lipophilicity of all five selected molecules is below 5, suggesting that these molecules have the potential to be investigated as orally active compounds.

Table 2 provides a summary of the physicochemical properties and various lipophilicity scores.

Water-soluble molecules are highly advantageous in numerous drug development endeavors, primarily due to their convenient handling and formulation properties. The selected 5 compounds exhibited favorable water solubility across all parameter classes, namely ESOL, Ali, and Silicos-IT. The pharmacokinetic properties of the selected compounds were also predicted. The study revealed that the gastrointestinal absorption rates of ZINC899884, ZINC56981, and ZINC21789 were observed to be significantly high, whereas ZINC252509722 and ZINC1843029 exhibited notably low absorption rates. These results indicate that ZINC899884, ZINC56981, and ZINC21789 are characterized by a favorable ability to be absorbed efficiently from the intestinal tract. The compounds ZINC899884 and ZINC56981 have demonstrated the ability to cross the blood-brain barrier (BBB). Further pharmacokinetic characteristics of the compounds, including their capacity to inhibit cytochrome P450 enzymes (CYPs), suggest that they do not exhibit any interaction with any specific isoform of cytochrome P450. This implies that these isoforms do not play a role in the biotransformation process of the selected molecule (Table 3).

Lipinski's rule, which meets the requirements of an ideal drug molecule, is the generally recognized physicochemical property guideline. The selected molecules' bioavailability Score was 0.55, except ZINC252509722 (0.11), which violated one of Lipinski's rules, indicating that these molecules can be synthesized and advanced to the next stage of the drug development pipeline. The findings indicate that all of the compounds exhibit a favorable drug-likeness score, demonstrating minimal or no violations of the drug-likeness criteria under investigation (Table 4).

Discussion

The link between insulin resistance and T2D, as well as the significance of tyrosine (Tyr) phosphorylation in regulating insulin receptor signaling, has sparked significant scientific interest in the regulation of tyrosine phosphorylation homeostasis [18]. PTP1B is a notable contender among the numerous tyrosine phosphatases implicated in this process. Hence, there is a strong emphasis on targeting PTP1B and developing novel PTP1B inhibitors as a viable therapeutic method for improving insulin sensitivity in diabetes treatment while avoiding the unwanted weight gain associated with thiazolidinediones [19]. Nonetheless, the practical utility of currently available synthetic PTP1B inhibitors has been limited due to dose-dependent side effects and failure to pass Phase II clinical trials. Furthermore, natural molecules with enhanced pharmacodynamic and pharmacokinetic properties may offer advantages over their synthetic counterparts.

The efficiency of ligand-target protein interactions is determined by the minimal binding energy obtained in molecular docking analyses [20-22]. The top five compounds, ZINC899884, ZINC56981, ZINC252509722, ZINC1843029, and ZINC21789 exhibited lower binding energies than the positive controls, indicating a strong affinity between PTP1B and these top compounds.

Natural products have demonstrated their ability to benefit human health [23]. According to WHO, approximately 80% of the population in developing countries continues to rely on traditional or folk medicines derived primarily from plant sources for disease prevention and treatment. When compared to modern pharmaceuticals, traditional medicinal practices using plant-derived extracts have demonstrated superior cost-effectiveness, clinical efficacy, and a lower incidence of adverse effects. Current diabetes treatments primarily aim to regulate and reduce blood glucose levels to within the normal range. However, many modern drugs have significant adverse effects that can lead to serious medical complications during treatment. Hence, traditional medicines have been long utilized and are considered crucial as alternative therapeutic modalities [24].

PTP1B is an enzyme that dephosphorylates active insulin receptors and insulin receptor substrates, resulting in insulin signaling downregulation. This study looks for natural compounds that target the PTP1B protein. The compounds ZINC899884, ZINC56981, ZINC252509722, ZINC1843029, and ZINC21789 exhibited strong binding to the PTP1B protein, as well as exhibited good drug-like properties. This study suggests that ZINC899884, ZINC56981, ZINC252509722, ZINC1843029, and ZINC21789 warrant further research as potential PTP1B inhibitors for diabetes management.

Conflict of Interest

The authors declare that there is no conflict of interest.

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