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Hypothesis

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Molecular docking and virtual screening for novel protein tyrosine phosphatase 1B (PTP1B) inhibitors

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Abstract:
Protein tyrosine phosphatase 1B (PTP1B) functions as major negative regulator of insulin and leptin signaling pathways. In view of this, PTP1B is an significant target for drug development against cancer, diabetes and obesity. The aim of the current study is to identify PTP1B inhibitors by means of virtual screening with docking. 523,366 molecules from ZINC database have been screened and based on DOCK grid scores and hydrogen bonding interactions five new potential inhibitors were identified. ZINC12502589, ZINC13213457, ZINC25721858, ZINC31392733 and ZINC04096400 were identified as potential lead molecules for inhibition of PTP1B. The identified molecules were subjected to Lipinski's rule of five parameters and found that they did not violate any rule. More specific analysis of pharmacological parameters may be scrutinized through a complete ADME/Tox evaluation. Pharma algorithm was used to Calculate ADME–Tox profiles for such molecules. In general, all the molecules presented advantages and as well as disadvantages when compared to each other. No marked difference in health effects and toxicity profiles were observed among these molecules.

Keywords: PTP1B, Lead-like, Virtual Screening, ADME-Tox, ZINC database

Background:
Protein tyrosine phosphatases 1B (PTP1B) is a non-receptor phospho-tyrosine protein phosphatase, which is considered as a major negative regulator of both insulin- and leptin- simulated signal transduction **[1, 2].** Previous studies have revealed that the lack of PTP1B can enhance insulin sensitivity, improve glycaemic control, and resist to high fat diet-induced obesity **[3, 4].** Besides, using PTP1B antisense oligonucleotides to treat diabetic mice could reduce the PTP1B expression level, and subsequently normalize blood glucose, finally improving insulin sensitivity **[5, 6].** It is suggested that PTP1B inhibitors may enhance insulin and leptin sensitivity and act as effective therapeutics for type II diabetes, insulin resistance, as well as obesity. Therefore, PTP1B has been a potential drug target for type II diabetes and obesity **[7]**. Considering the importance of PTP1B in type II diabetes and obesity the development of PTP1B inhibitors began in early 1990 and continues today **[7, 8].** In an effort to develop a small, potent and selective PTP1B inhibitor, we used iterative structure based drug design to identify and optimize lead molecule entity. In the present study, we identified novel classes of PTP1B inhibitors by means of a structure-based drug design protocol involving virtual screening with docking. 523,366 molecules from ZINC database have been screened and based on DOCK grid scores five new inhibitors were identified. The identified molecules were subjected for ADME/T analysis.

Methodology:
The docking library for PTP1B comprising about 523,366 molecules was constructed from the latest version of the ZINC

database provided by Shoichet Laboratory, Department of Pharmaceutical Chemistry, University of California, San Francisco (UCSF) **[9].**

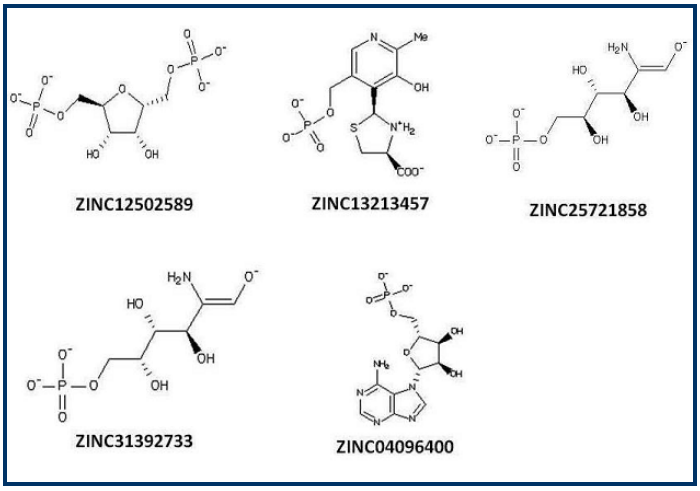

Figure 1: Structures of the five lead molecules with their respective Ids.

Virtual screening of PTP1B inhibitors

The 3-D coordinates in the X-ray crystal structure of PTP1B complexed with a 1, 2, 3, 4- Tetrahydroisoquinolinyl sulfamic acids inhibitor (PDB code: 2F71) **[10]** were selected as the receptor model in the virtual screening. After removing the ligand and solvent molecules, hydrogen atoms were added to each protein atom. We used the UCSF DOCK 6.2 program **[11]** in the virtual screening of PTP1B inhibitors. Residues within a radius of 4 Å around the center of the 1,2,3,4-Tetrahydroisoquinolinyl sulfamic acid binding in the PTP1B structure were defined as the active site to construct a grid for the virtual screening. The position and conformation of each molecule were minimized by the anchor fragment orientation as well as by the torsion minimization method implemented in the DOCK 6.2 program **[11].** Hundred conformations and a maximum of 100 anchor orientations for each molecule were generated, and the binding energy of all the docked conformations were minimized by 100 iterations using the standard approach as described **[12].**

ADME/T evaluation

Pharmacokinetics is a term used in the pharmacology which gives idea about Absorption, Distribution, Metabolism and Excretion / Toxicity (ADME/T) of a drug molecule. It has found that more than 50% drugs are fail during clinical trial due to their weak ADME properties **[13].** Recent advancements in Computational studies and the overall drug discovery process have rapidly generated large numbers of potential pharmacologically active compounds waiting for optimization and pre-clinical ADMET evaluation. Thus before clinical trail ADME and toxicity property must be tested. For this analysis we have used Pharma-algorithm server http://pharma-algorithms.com/webboxes/ **[14].** The Lipinski's rule of five parameters was obtained by using the Molinspiration program **[15].**

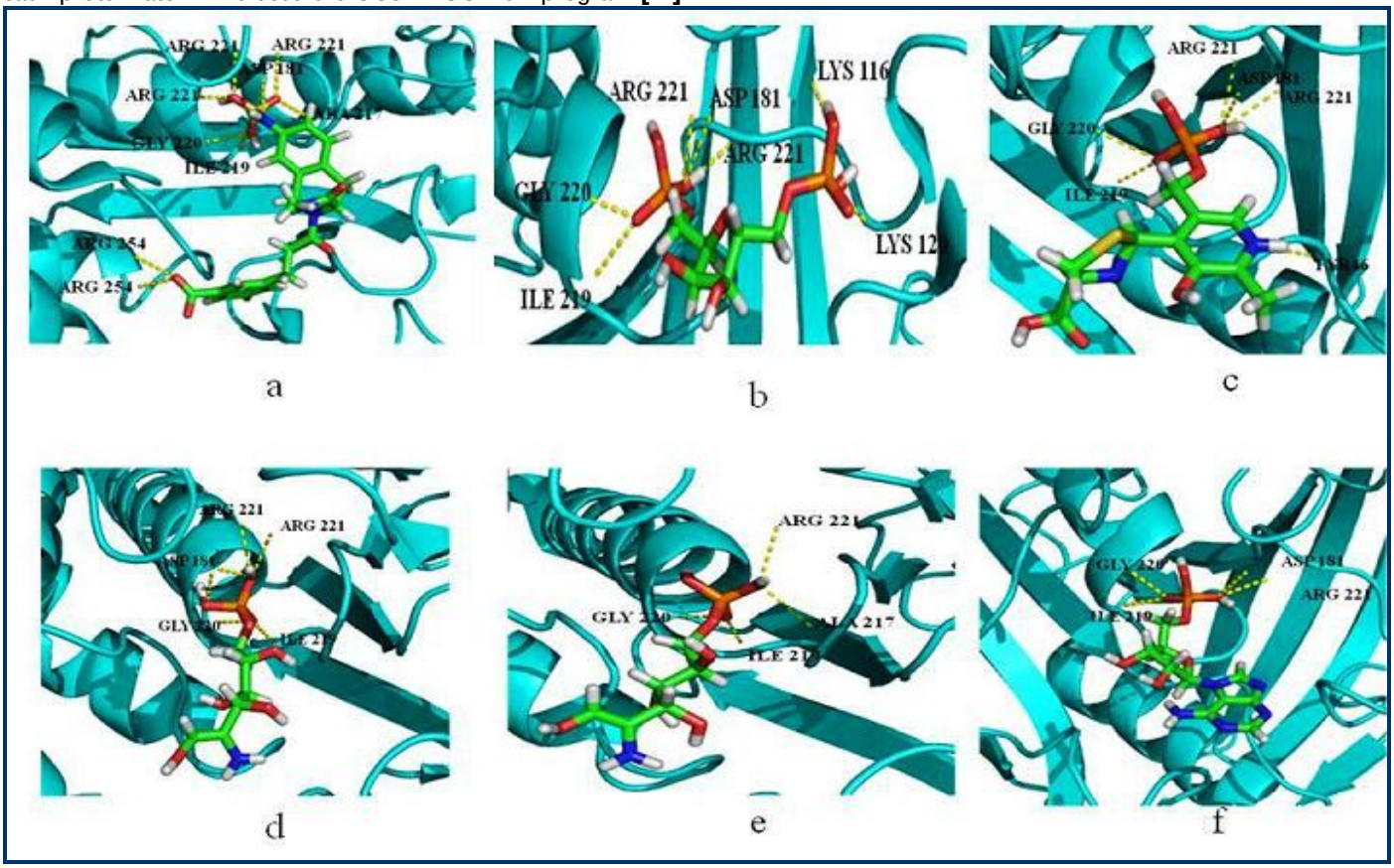

Figure 2: Binding modes of the five potential ligands to the active site of PTPIB: **(a)** (1,2,3,4-Tetrahydroiso quinolinyl sulfamic acid, **(b)** ZINC12502589**, (c)** ZINC13213457, **(d)** ZINC25721858, **(e)** ZINC31392733 and **(f)** ZINC04096400

Results and Discussion:

Virtual screening

In the first step of research, the 1, 2, 3, 4-Tetrahydroisoquinolinyl sulfamic acids inhibitor, was docked with PTP1B using Dock 6.2, and the complex was analyzed for the putative functional amino acid residues that are involved in hydrogen bonding. The obtained complex results are summarized in **Table 1 (see supplementary material) & Figure 2a**. It was observed that, eight residues (ARG'24, ARG'254, TYR'20, ASP'181, ARG'221, ALA'217, GLY'220, and ILE'219) form eleven hydrogen bonds were formed with the inhibitor. This particular binding site was utilized for Virtual Screening of molecules from the Zinc database. As a result, 88 lead molecules were identified that had better DOCK grid scores than 1,2,3,4-Tetrahydroisoquinolinyl sulfamic acid, and these were compared with its binding conformation; eventually 5 lead molecules were identified as potential lead molecules for inhibition of PTP1B based on their hydrogen bonding interactions. The chemical names of the five lead compounds **(Figure 1)** are: 2,5-Anhydroglucitol-1,6-Biphosphate (ZINC12502589); (2S,4S)-2-[3-hydroxy-2-methyl-5-(phosphonooxymethyl)-4-pyridyl]thiazolidine-4-carboxylic (ZINC13213457); [(2S,3R,4R,5R)-5-amino-2,3,4-trihydroxy-6-oxo-hexyl] (ZINC25721858); aldehydo-D-glucosamine 6-phosphate (ZINC31392733); and 7-(5-phospho-alpha-D-ribosyl)adenine (ZINC04096400). The chemical structures of these lead molecules are illustrated in **Figure 1**, and the binding modes of these five lead molecules and their interacting residues are shown in **(Figure 2a–f) & Table 1 (see supplementary material).**

ADME–Tox evaluation

Absorption, Distribution, Metabolism, Excretion and Toxicity (ADME/Tox) are main five parameters to test the drug likeness of a molecule was tested by the pharma algorithm **[16].** Thus, the algorithm gives an overview about the oral bioavailability, absorption and the toxic effect of drug like molecule. By this study, it becomes easy to optimize the lethal doses of any molecule without killing any animal, which reduces the cost **[17].** Oral bioavailability of drug must be low, and shows the oral bioavailability of all five ligands **Table 2.** Lipinski *et al.* **[18]** have proposed a series of rules imposing limitations on logP (the logarithm of octanol/water partition coefficient), molecular weight, and the number of hydrogen bond acceptors and donors, known as 'rule of five'. The rule states that most 'drug-like' molecules have logP ≤5, molecular weight ≤500, and molar refractivity between 40-130, number of hydrogen bond acceptors ≤10, and number of hydrogen bond donor's ≤5. Molecules violating more than one of these rules may have problems with bioavailability. **Table 2 (see supplementary materials)** shows that compounds did not violate any rule. More specific analysis of pharmacological parameters may be scrutinized through a complete ADME–Tox evaluation. **Table 2** depicts some specific parameters related to absorption, distribution, metabolism, excretion and toxicity for the predicted compounds. In general, all compounds presented advantages and disadvantages when compared to each other. No marked difference in health effects and toxicity profiles were observed among the compounds.

Conclusion:

PTP1B is an important target for drug development against cancers, diabetes and obesity. Using structure based drug design protocol involving virtual screening with docking studies five new inhibitors for PTP1B were identified namely ZINC12502589, ZINC13213457, ZINC25721858, ZINC31392733 and ZINC04096400. The identified molecules were subjected to Lipinski's rule of five parameters and the molecules did not violate any rule. Pharma algorithm was used to Calculate ADME–Tox (absorption, distribution, metabolism, excretion and toxicity). In general, all the molecules presented advantages and as well as disadvantages when compared to each other. No marked difference in health effects and toxicity profiles were observed among these molecules. Considering both the binding affinity and bioavailability, we recommend these molecules as potential inhibitors for PTP1B, although further experimental investigation regarding the oral bioavailability should be pursued to confirm that these inhibitors can function effectively in humans.

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Supplementary material:

Table 1: Results for the five lead molecules and 1,2,3,4-Tetrahydroisoquinolinyl sulfamic acid, obtained using UCSF DOCK

Lead molecules[a]	DOCK grid scores (kcal/mol)[b]	Amino acids involved in interactions	No. of HBs[c]
1,2,3,4-Tetrahydroiso quinolinyl sulfamic acid	-46.615	ARG'254, ASP'181, ARG'221, ALA'217, GLY'220, and ILE'219	9
ZINC12502589	-75.358	LYS'116, LYS'120, ASP'181, ARG'221,GLY'220 and ILE'	7
ZINC13213457	-62.822	TYR'20, ASP'181, ARG'221, GLY'220 and ILE'219	6
ZINC25721858	-58.170	ASP'181, ARG'221, GLY'220 and ILE'219	6
ZINC31392733	-55.584	ALA'217, ARG'221, GLY'220 and ILE'219	4
ZINC04096400	-58.471	ILE'219, GLY'220, ARG'221 and ASP'181	4

a Ligand IDs are from the ZINC database
b UCSF DOCK grid score
c Number of hydrogen bonds formed

Table 2: ADME–Tox parameters calculated for the reference and proposed compounds

ADME–Tox	ZINC04096400	ZINC12502589	ZINC13213457	ZINC25721858	ZINC31392733
logP	4.945	2.599	0.463	5.318	5.273
Molecular weight	345.208	320.083	347.265	256.127	256.127
No of Hydrogen bonds acceptors	10	9	8	8	8
No of Hydrogen bonds donors	4	2	2	5	5
Log sol. pH 1.7 (stomach)	-0.86	0.49	-1.94	-0.67	-0.67
Log sol. pH 4.6 (duodenum)	-0.85	0.49	-1.53	-0.6	-0.6
Log sol. pH 6.5 (jejunum, ileum)	0.46	0.49	0.46	0.59	0.59
Log sol. pH 7.4 (blood)	0.46	0.49	0.46	0.59	0.59
Log sol. pH 8.0 (colon)	0.46	0.49	0.46	0.59	0.59
% Oral bioavailability	<30	<30	<30	<30	<30
Absorption rate k_a min^{-1})	ka= 0	ka= 0	ka= 0	ka= 0	ka= 0
LD50 rat / mouse (mg / kg, oral)	850 / 7600	42000 / 240000	2700 / 4500	3200 / 3600	3200 / 3600
LD50 rat / mouse (mg / kg, intraperitoneal)	350 / 1500	4600 / 18000	2300 / 1400	1300 / 690	1300 / 340
LD50 mouse (mg / kg, intravenous)	900	2700	1400	690	690
LD50 mouse (mg / kg, subcutaneous)	17000	1800000	7400	4800	4800
Ames test (genotoxicity, %)	0.33	0.05	0.33	0.13	0.13
Prob. of blood effect	0.78	0.56	0.56	0.85	0.85
Prob. of cardiovascular system	0.92	0.26	0.29	0.96	0.96
Prob. of gastrointestinal system	0.54	0.35	0.23	0.47	0.47
Prob. of kidney effect	0.93	0.16	0.46	0.31	0.31
Prob. of liver effect	0.7	0.11	0.39	0.39	0.39
Prob. of lung effect	0.47	0.12	0.06	0.3	0.3