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Molecular docking studies of quinoline-3-carbohydrazide as novel PTP1B inhibitors as potential antihyperglycemic agents

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ABSTRACT

Binding modes of a series of quinoline-3-carbohydrazide as protein tyrosine phosphatase 1B (PTP 1B) inhibitors have been identified by molecular modeling techniques. We have performed docking and ADME predictions of these inhibitors with PTP 1B enzyme. As per our literature, we found that PTP1B is highly hydrophobic. The results indicate that quinoline-3-carbohydrazide for addition to hydrogen bonding interactions, Arg24, Asp48, Glu115, Lys116, Lys120, Cys215, Ser216, Ala217 amino acid residues of PTP 1B are responsible for governing inhibitor potency of the compounds. ADME predictions of 6 top selected compounds were done with Qikprop 3.2 tool available in Schrödinger 9.0 ver. The information generated from the present study should be useful in the design of more potent PTP1B inhibitors as antidiabetic agents.

Keywords: PTP1B, ADME predictions, antidiabetic agents.

INTRODUCTION

Diabetes is a chronic condition that occurs when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. By definition, it is classified in to two basic forms Type I and Type II diabetes [1]. With comparison with Cancer and HIV infection, Diabetes has emerged as a major healthcare problem in India. According to Diabetes Atlas published by the International Diabetes Federation (IDF), there were an estimated 40 million persons with diabetes in India in 2007 and this number is predicted to rise to almost 70 million people by 2025. The countries with the largest number of diabetic people will be India, China and USA by 2030. The real burden of the disease is however due to its associated complications which lead to increased morbidity and mortality [2].

Rapid urbanisation and industrialisation have produced advancement on the social and economic front in developing countries such as India which have resulted in dramatic lifestyle changes leading to lifestyle related diseases. The transition from a traditional to modern lifestyle, consumption of diets rich in fat and calories combined with a high level of mental stress has

compounded the problem further. There are several studies from various parts of India which reveal a rising trend in the prevalence of type II diabetes in the urban areas [3].

The main risk factors for diabetes are age, family history, central obesity, physical inactivity and sedentary living, insulin resistance, urbanisation, stress etc. So, the researcher are tried to find out efficient target for treatment of diabetic condition in human being. One of the way choose by researchers are by molecular docking studies. The design of new chemical entities is based on the requirement of active binding site present in the enzyme. The inhibitory action of design compound may be predicted by using different molecular docking softwares that help out for predicting designed molecule's efficiency with respect to binding site.

The targets such as mainly highlighted by researcher are Protein Tyrosine Phosphatase 1-Beta (PTP-1B) [4], Glycogen phasphorylase [5], Dipeptidyl peptidase IV (DPP IV) [6], Glucokinase [7], Peroxisome Proliferator-activated Receptor (PPAR)-γ [8], 3-hydroxy-3-methyl-glutaryl(HMG) Co-A Reductase [9]. Among them we select Protein Tyrosine Phosphatase 1-Beta (PTP-1B) as our target for further studies.

MATERIALS AND METHODS

2.1 ChemBiodraw Ultra 12.0

ChemBiodraw Ultra 12.0 is chemical drawing software developed by Cambridge Pvt. Ltd. The software is user-friendly, provides all details of drawn structures. It helped in calculate chemical properties, design professional reports and presentations.

2.2 ADMET predictions by QikProp 3.2

QikProp is a quick, accurate, easy-to-use absorption, distribution, metabolism, and excretion (ADME) prediction program designed by Professor William L. Jorgensen. QikProp predicts physically significant descriptors and pharmaceutically relevant properties of organic molecules, either individually or in batches. In addition to predicting molecular properties, QikProp provides ranges for comparing a particular molecule's properties with those of 95% of known drugs. QikProp also flags 30 types of reactive functional groups that may cause false positives in high-throughput screening (HTS) assays [10].

2.3. Protein Data Bank (PDB)

Source: www.rcsb.org

The PDB is the single, global archive for information about the 3D structure of biomacromolecules and their complexes, as determined by X-ray crystallography, NMR spectroscopy and cryoelectron microscopy, and includes more than a few Nobel Prize winning structure. PTP1B enzyme was downloaded from Protein data bank with the specific resolution and the PDB id is 1XBO.

2.4. Docking by Glide

The molecular docking tool, Glide (Schrodinger Inc. U.S.A.) software was used for ligand docking studies in to the Protein Tyrosine Phosphatase 1-Beta (PTP-1B) binding pocket. Glide (Grid-based Ligand Docking with Energetic) is one of the most accurate docking tool available for ligand-protein, protein-protein binding studies. Glide was found to produce least number of inaccurate poses and 85% of Glides binding models had an RMSD of 1.4 A^0 or less from native co-crystallized structures [11].

2.5. Protein preparation

A typical PDB structure file consists only of heavy atoms, can contain waters, cofactors, and metal ions, and can be multimeric. The structure generally has no information on bond orders, topologies, or formal atomic charges. Terminal amide groups can also be misaligned, because the X-ray structure analysis cannot usually distinguish between O and NH_2. Ionization and tautomeric states are also generally unassigned. Glide calculations use an all-atom force field for accurate energy evaluation. Thus, Glide requires bond orders and ionization states to be properly assigned and performs better when side chains are reoriented when necessary and steric clashes are relieved [12].

2.6 Ligand preparation

The LigPrep process consists of a series of steps that perform conversions, apply corrections to the structures, generate variations on the structures, eliminate unwanted structures, and optimize the structures. Many of the steps are optional and are controlled by selecting options in the LigPrep panel or by specifying command-line options. The process like convert the structure format (sd format), select the structures, add hydrogen atoms, remove unwanted molecules, neutralize charged groups, generate ionization states, generate tautomers, filter the structures, generate alternative chiralities, generate low-energy ring conformations, remove problematic structures, optimize the geometries and finally convert the output file are performed by during ligand preparation [13].

RESULTS

3.1 PTP 1B as target and design the skeleton of inhibitors

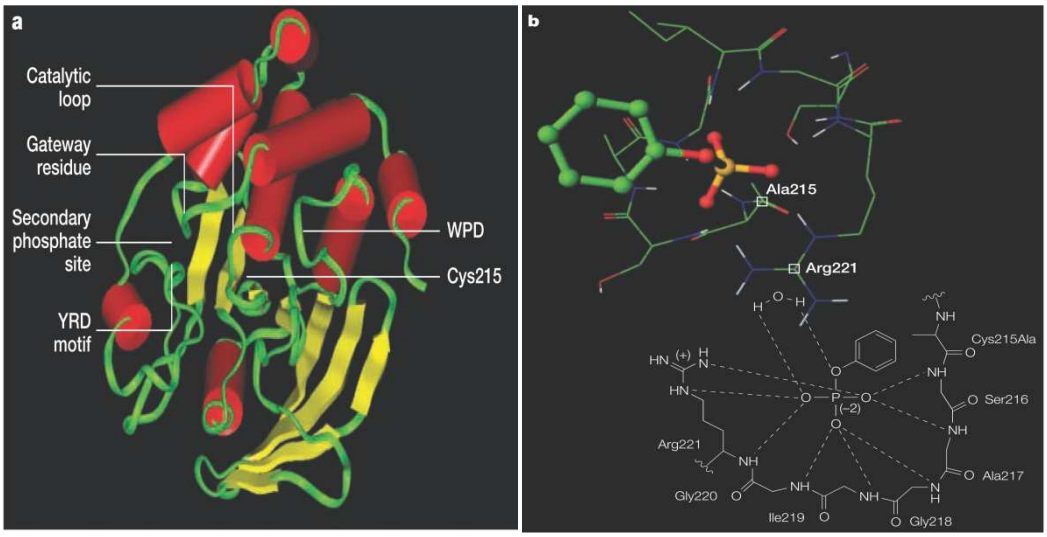


Figure no 1 a. Ribbon view of the crystal structure of protein tyrosine phosphatase 1B (PTP1B), highlighting the main regions of the protein. b. This graphic actually shows the cysteine-to-alanine (Cys215Ala). The line drawing indicates key contacts with the protein amide backbone.

Description of highlighted the main regions of the protein

- **Catalytic loop:**

➢ The base of the catalytic site is defined by the 214–221 PTP signature motifs.

➢ histidine(His) - Cys – Ser - alanine(Ala) - glycine(Gly) - isoleucine(Ile) - Gly- arginine(Arg) (Shown in figure b)

- **WPD loop**

➢ Loop contains Asp181 and Arg224 which maximizes HYDROPHOBIC interactions.

- **Secondary phosphate site**

➢ Catalytically inactive, and provides weaker binding interactions compared with the primary site.

- **YRD motif**

➢ Selectivity at the molecular level

➢ Target interaction with Asp48 and Arg24 to achieve selectivity.

According to researcher studies, we found that some important properties of inhibitors. The properties like (i) For basic antihyperglycemic activity Nitrogen containing ring required; (ii) Molecule should contain phosphate like moiety that one able to bind at catalytic side of enzyme; (iii) Oxygen required for hydrophobic interaction in WPD loop; (iv) Ring nitrogen required for selectivity at active binding site i.e. in the YRD motif.

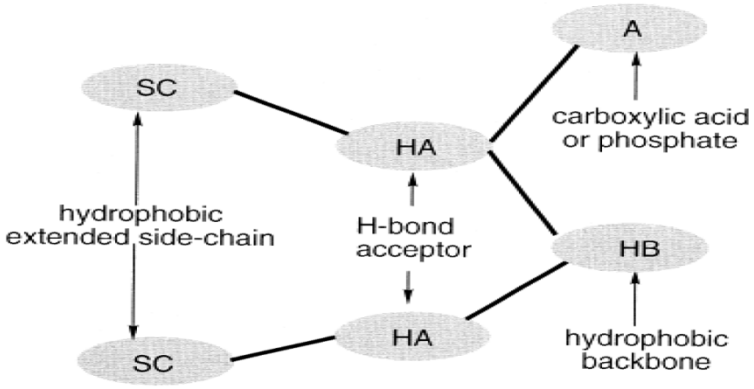


Figure 2 Proposed design skeleton of PTP1B Inhibitors

As requirement and proposed skeleton of PTP1B inhibitors, we design around 100 molecules of quinoline carbohydrazid**e** with respect to active binding site. Among 100 molecules, we select 6 top molecules considered for further studies.

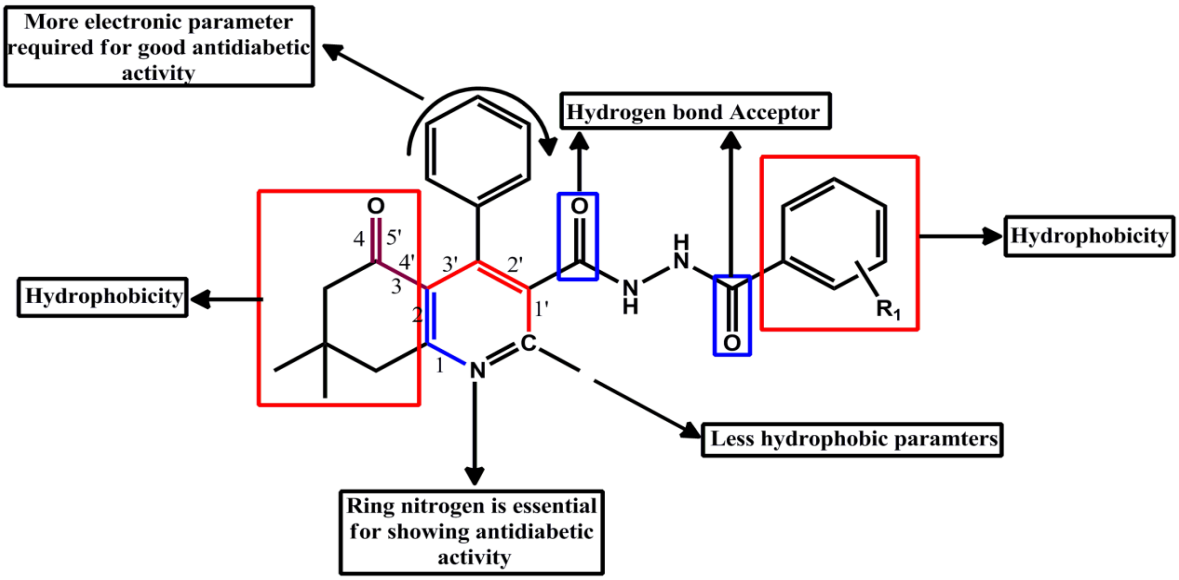


Figure 3 Design of inhibitors according to skeleton

The results of the docking studies are presented in the form of G-score, Energy, Good, Bad and Ugly Van Der Waals (vdw) interactions. The G-scores are presented as negative values, indicating that more the negative values more are the binding interactions. The docking studies were performed for the designed NCEs (as shown in the Table 7.2) with 1XBO enzyme and the results were compared with the ligand IX1 322 present within the receptor. The docked complexes of the designed compounds along with the ligand receptor poses have been shown in the figure 4, 5, 6, 7 and 8. The designed compounds were found to display good binding affinity to the receptor. Yellow dotted line indicates H-bond interactions with receptor.

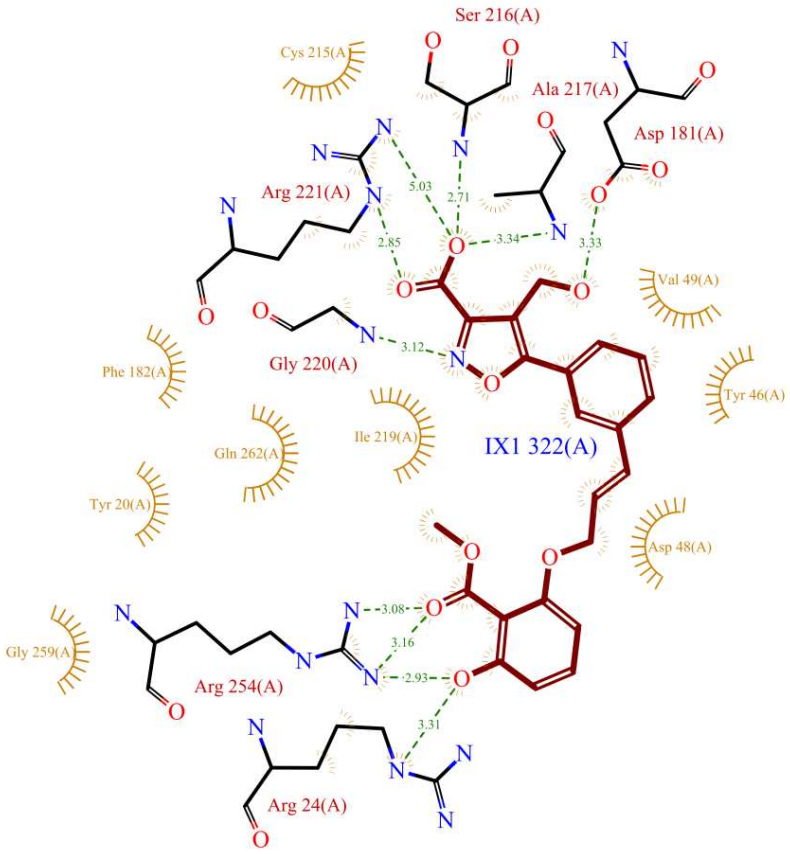
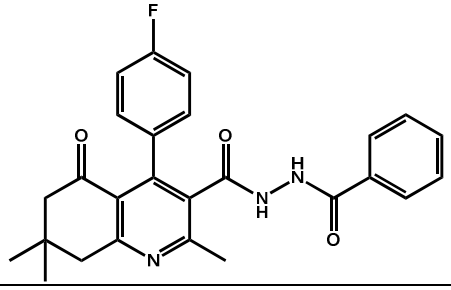
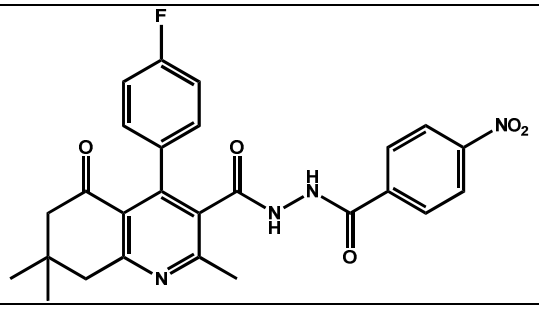
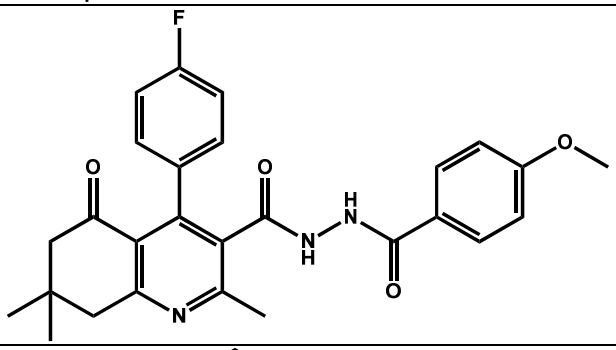
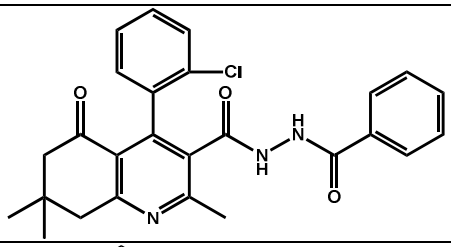
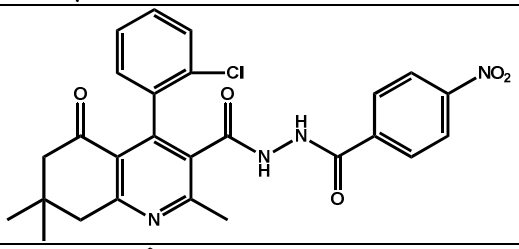
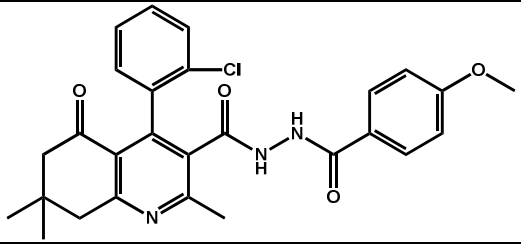


Figure 4 Graphical representation of interaction of ligand IX1 322 at active binding site of 1XBO

3.2 Chemical Structures of designed compounds

Table 3.1 Structures of designed compounds

Sr. No.	Molecule code	Structures of designed compounds
1	5a	

2	**6a**	
3	**7a**	
4	**5b**	
5	**6b**	
6	**7b**	

3.3 Docking and Scoring Function [14]

The ligands were docked with the active site using the 'Extra precision' Glide algorithm. Glide uses a hierarchical series of filters to search for possible locations of the ligand in the active-site region of the receptor. Final scoring of docked ligand is carried out on the energy-minimized poses Glide Score scoring function. Glide Score is based on ChemScore, but includes a steric-clash term and adds buried polar terms devised by Schrödinger to penalize electrostatic mismatches.

GScore = 0.065*vdW + 0.130*Coul + Lipo + Hbond + Metal + BuryP + RotB + Site
Where, vdW: - Van der Waal energy; Coul: - Coulomb energy; Lipo: - Lipophilic contact term; HBond: - Hydrogen-bonding term; Metal: - Metal-binding term; BuryP: - Penalty for buried

polar groups; RotB: - Penalty for freezing rotatable bonds; Site: - Polar interactions at the active site; and the coefficients of vdW and Coul are: - a = 0.065, b = 0.1

Table 1 Results of extra precision docking studies of Compounds (5a-7a, 5b-7b) along with Standard

Sr. No.	Compound code	Glide score	Good Vdw	Bad vdw	Ugly vdw
1	6a	-7.71	278	2	0
2	6b	-6.32	267	1	0
3	Calbiochem	-6.26	241	2	1
4	7a	-5.97	239	0	1
5	7b	-5.85	221	2	0
6	Ertiprotafib	-4.81	201	3	0
7	5a	-3.91	199	1	0
8	5b	-3.67	176	2	0

3.4 Docking images of designed compounds

1. Ertiprotafib docked in PTP-1B pocket

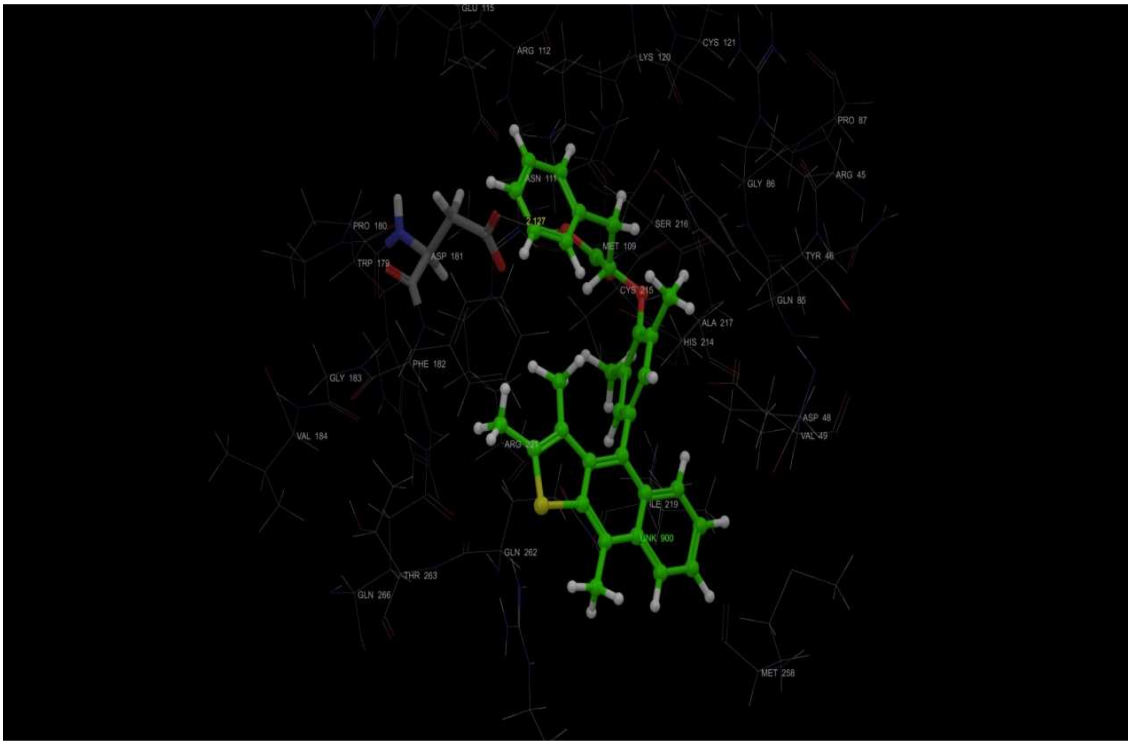


Figure 5 Ertiprotafib docked in PTP-1B pocket

The G-score of the standard ligand **Calbiochem** and **Ertiprotafib** in case of docking with 1XBO were found to be **-6.26** and **-4.81** respectively. The G-score of the designed NCEs were also found to be comparable viz. **-3.67, -3.91, -7.71, -6.32, -5.97** and **-5.83** for the compounds **5a, 5b, 6a, 6b, 7a** and **7b** respectively. Close analysis of these results suggests that designed NCEs have the G-score comparable with that of standard antidiabetic agent, Calbiochem and Ertiprotafib. Besides the G-score, other parameters like energy, and the E-model were also taken into consideration for the evaluation of the docking results; the values of the energy and E-model were found to be significantly closer to the values of the standard Calbiochem and Ertiprotafib.

2. Calbiochem docked in PTP-1B pocket

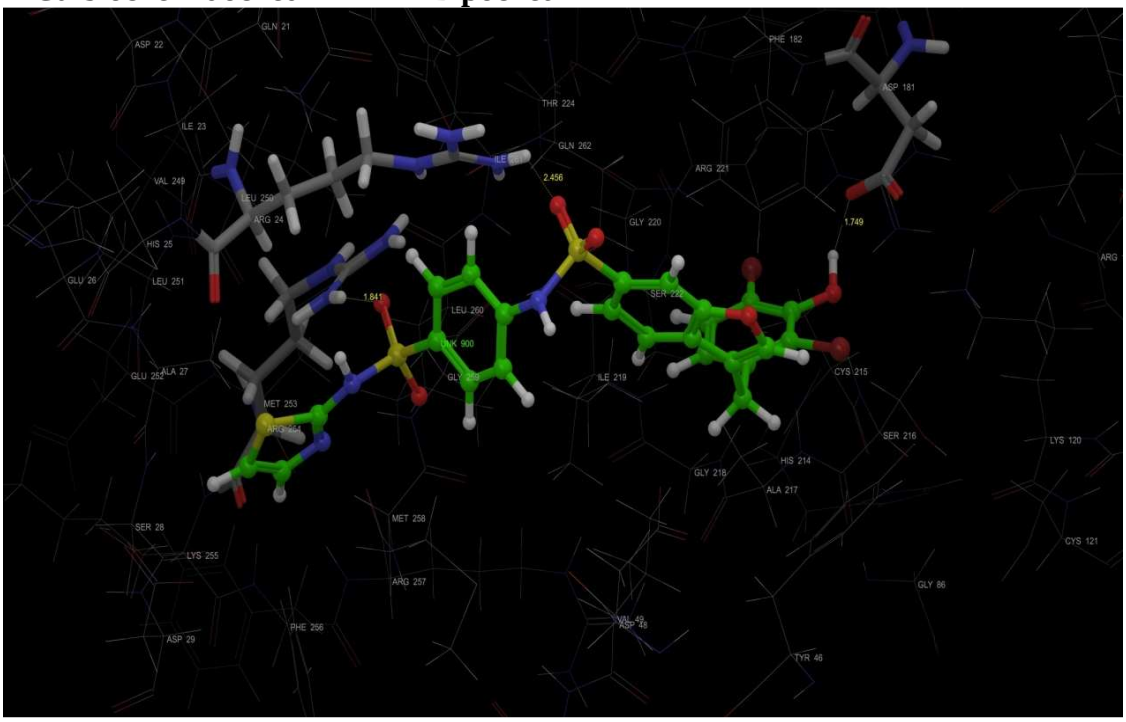


Figure 6 Calbiochem docked in PTP-1B pocket

3. Compound 6a docked in PTP-1B pocket

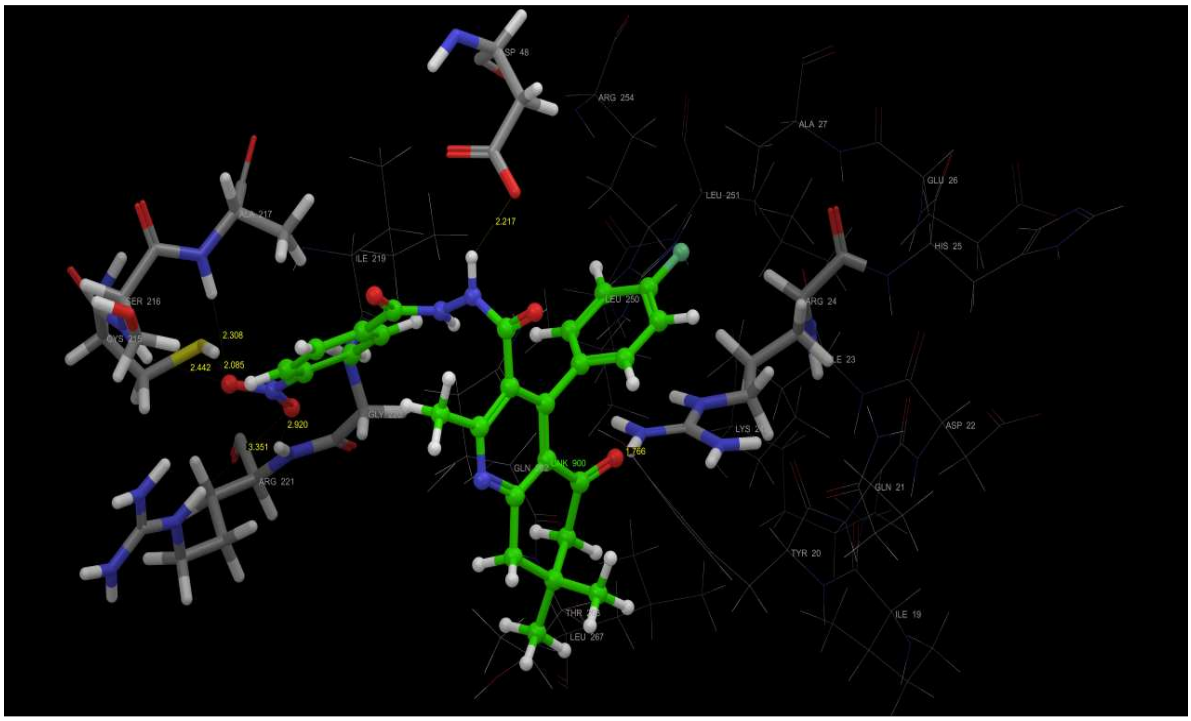


Figure 7 Compound 6a docked in PTP-1B pocket

4. Compound 6b docked in PTP-1B pocket

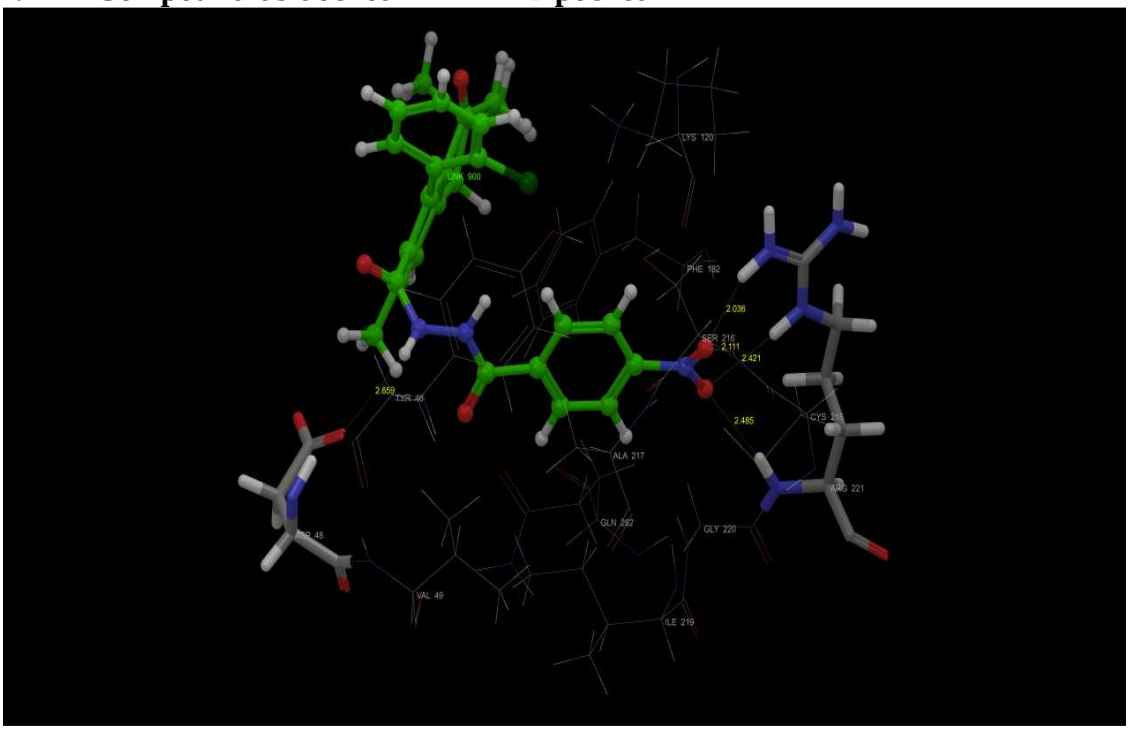


Figure 8 Compound 6b docked in PTP-1B pocket

The number of H-bond interactions in the standard compound, Calbiochem and Ertiprotafib was compared with those of the designed NCEs. In case of docking with 1XBO the numbers of H-bond interactions of the standard compound **Calbiochem** and **Ertiprotafib** was found to be **3** and **2** respectively. While those of designed compounds **5a, 5b, 6a, 6b, 7a** and **7b** were found to be **2, 3, 6, 5, 3** and **3** respectively indicating requirement of additional functional groups which can form possible H-bond interaction with the PTP1B.

It is well established and accepted fact that number of good van der Waals interactions decides the binding affinity for any ligand with receptor enzyme protein. Therefore we have analyzed the binding modes and abilities, considering the number of good, bad and ugly Vander Waals (vdW) interactions of the standard, designed NCEs with IX1 322 active binding site.

In all, the docking scores are the net results of the no. of H-bonds and no. of good van der Waals contacts and penalties due to no. of bad Vander Waals contacts.

3.5 QikProp pharmacokinetic prediction

Table 2 QikProp pharmacokinetic analysis of 5a-7a, 5b-5b

Molecule	Molecular weight	logPo/w	BBB Absorption	% Human Oral Absorption	Rule Of Five	Hepato-toxicity probability
5a	444.504	5.523	-0.536	100	3	0.431
6a	460.959	5.12	-0.434	100	3	0.378
7a	489.502	4.821	-1.704	91.952	3	0.502
5b	505.957	4.431	-1.583	78.757	2	0.392
6b	474.531	5.829	-0.605	100	3	0.278
7b	490.985	5.169	-0.573	100	3	0.259

QikProp pharmacokinetic predicted parameters give information about molecular weight, partition coefficient ($logP_{o/w}$), BBB and % oral absorption values and Lipinski's properties (Rule of Five). We were designed 100 compounds from that best 6 one are mentioned in table 2

DISCUSSION

Computer-assisted drug design (CADD) approach has contributed to the successful discovery of several novel antidiabetic agents. Molecular Docking continues to hold great promise in the field of computer based drug design which screens small molecules by orienting and scoring them in the binding site of a protein. Number of reports citing successful application of CADD in developing specific drugs in different therapeutic areas is expanding rapidly. There are various tools, which can be used for Computer aided drug design such as QSAR, Docking, Homology modeling, ADMET prediction etc. QikProp pharmacokinetic prediction provides us physicochemical properties with it BBB and % oral absorption predictions. These all parameters are helpful to find out bioavailability and toxicity prediction in human body.

CONCLUSION

The major reason for failure of NCEs at latter stages of drug discovery process i.e. drug like pharmacokinetic profile set up, has forced us setting filters like molecular weight, No. of H-bond donors, No. of H- bond acceptors, Polar Surface Area and number of rotatable bonds; so that only drug like NCEs would be generated and resultant NCEs would not have the pharmacokinetic inadequacies. But the thorough analysis of results of docking and QikProp pharmacokinetic analysis studies predicts the safer performance of our designed compounds. The most potent derivatives were subjected to molecular docking studies to get further insights of interactions of NCEs with PTP1B. Finally 6 top compounds with good docking score will be subjected to wet lab work viz., synthesis and evaluation using alloxon induced diabetes mellitus and PTP-1B inhibitor assay studies. The results of dry lab work and wet lab work will be analyzed thoroughly to find out correctness of the rational used for the design of NCEs in general and optimization of pharmacophore for inhibition of PTP-1B.

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