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Study of the Interaction of Protein Tyrosine Phosphatase (PTP1B) with SNA Similar by Molecular Modeling

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Abstract

Protein tyrosine phosphatase 1B is a unique enzyme which is included in the family of protein tyrosine phosphatase (PTP).It is encoded by the protein tyrosine phosphatase non-receptortype1) PTPN1 gene in humans. Protein tyrosinephosphatase 1B (PTP1B) is a negative regulator of the pathway of insulin signaling andis considered as an important therapeutic target for the treatment of type 2 diabetes mellitus. Inphysiological conditions for long-term energy store two hormones which are crucial: insulin and leptin .Insulin controls the pathways responsible for lipogenes and glucose uptake and leptin regulates peripheral energy expenditure and food intake .Our job is to study the interaction of the enzyme PTP1Bas a new target for type diabetes 2, and similar inhibitors SNA downloaded from PubChem.

1. Introduction

There searches and the synthesis of the new components which are active pharmacologically, and which are increasingly involved with in a study of molecule modeling.

Thanks to the information technology development in the recent years and precisely to the rise of in tensive parallel computing, the molecule modeling has become an important challenge [1] .The molecule modeling consists of the construction of tree-dimensional models from data.

The interactions between the molecules are the basic of the majority of the biological mechanism .The details of those interactions, at the level of molecules ,are very important, and they could be studied by crystallography of x-ray or nuclear magnetic resonance(NMR)[2].

Docking is a method of molecule modeling which calculates the preferable orientation of a molecule towards a second one when they are linked to as table complex. Knowing the preferable orientation serves to predict the union solidarity between two molecules [3].

Most of time, the receiver is a protein which contains one or many specific active sites ,more or less accessible depending on the case .The ligand is generally a small flexible molecule .So, the docking permits to predict the potential of a ligand with a protein [2]. Protein tyrosine phosphatase non-receptor type 1 also called protein-tyrosine phosphatase1B (PTP1B) is an enzyme that is a member of the family of protein tyrosine phosphatase (PTP). In humans, it is en coded by the gene PTPN1 [4].

Protein tyrosine phosphatase1B (PTPN1) is a negative regulator of the insulin pathway signaling, it is considered as an important therapeutic target for the treatment of diabetes

mellitus type 2 [5]. In physiological case for storage for long term of energy two hormones are crucial: in sulin and leptin. Insulin controls the responsible passages of lipo genesis and the glucose capturation and it regulates the leptin, it has also been implicated in the development of breast cancer have been explored as a potential therapeutic arget in this way[6,8].

2. Materials and Methods

Rcsb protein data bank which allows the downloading of protein structure of Tyrosine-protein phosphatase1bas pdb files [9].

The similar molecules are uploaded to the base thanks to PubChem given SNA derivatives, and then madedata mining of these molecules with the Knime-2.7.0 software [10];if the molecules have the Lipinski's rule was then visualization of the enzyme with the Chimera1.8.1 software [11],and making the docking with Chimera software .We use the program of molegro to visualize (display) the active sites of the protein and calculated their surfaces and volumes.

3. Ligands Structures

Banks data base pubchem [12] which allows the downloading of structures from a variety of vendors as SDF files was used in this screen downloading similar compounds. Are(CID126038,CID11232973,CID10337076,CID9797843, CID50937085,CID9997262,CID73744231,CID40578925,CI D21121561,CID10019885,CID164046,CID132244,CID2503 3706)to study the inhibitory activity of similar compounds of SNA. The general formula for SNA is ($C_{28}H_{35}F_4N_3O_{11}P_2$), similar compounds is of formula ($C_{20}H_{16}O_5$).

Lipinski rule is known as Pfizer rule of five (cinq) or simply the rule's five (cinq) (R05); it is a base rule to evaluate or determinate if a chemical component with pharmacological activities or biological has properties that would make it a likely oral drug (medicines) in humans. The rule has been formulated by Christopher A .Lipinski in 1997, based on the observation that drugs administered orally are relatively smaller and moderate lylipophilic [13, 14].

4. Results and Discussion

In the first part 14 components have been analyzed (similar molecules of SNA), with knime program which gives us a curve which represents the components which verify lipinski's rule.

According to the curve, we have found the14molecules which verify lipinski's rule, which are between 0 and 5.

The study of the interaction between enzyme of protein tyrosine phosphatase1B (fig04) and the chosen inhibitors was done by docking molecular chimera program [11].

The download of PTP1B was made from the database Protein Data Bank (www.rcsb.org/pdb) (access code: 2CM2) [15].

To deepen the interaction mode and these activity of the four ligands with the enzyme, the molecular modeling was realized by the chimera program.

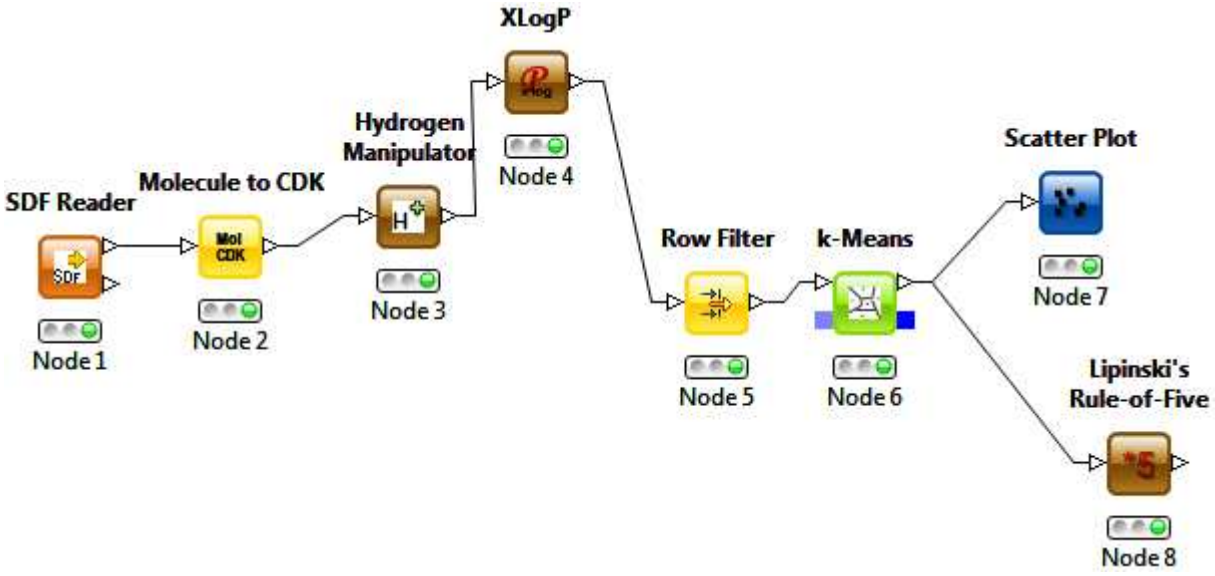


Fig. 1. *Data mining KNIME for data base preparation for the virtual screening.*

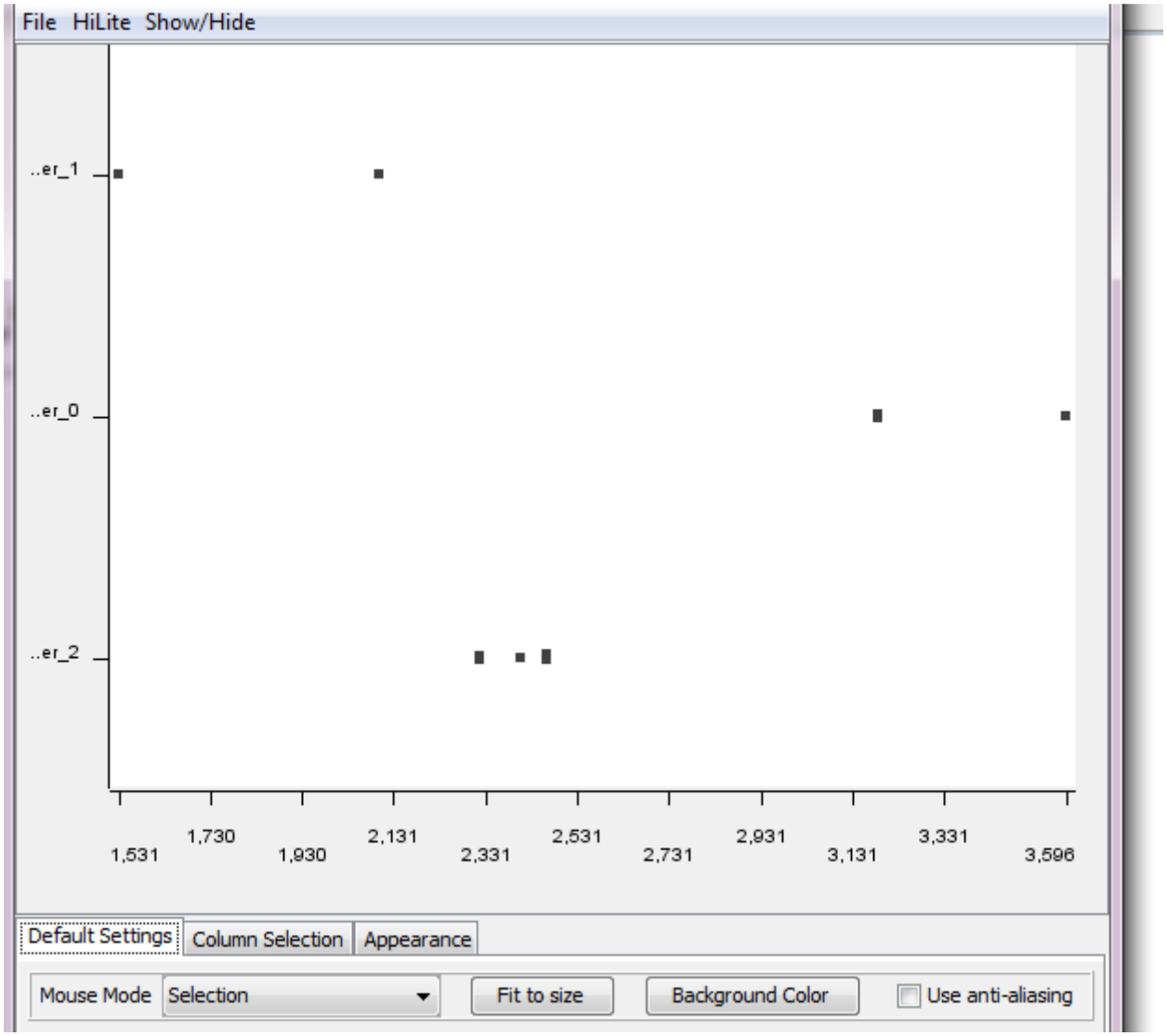


Fig. 2. *The control curve of the Lipinski rule.*

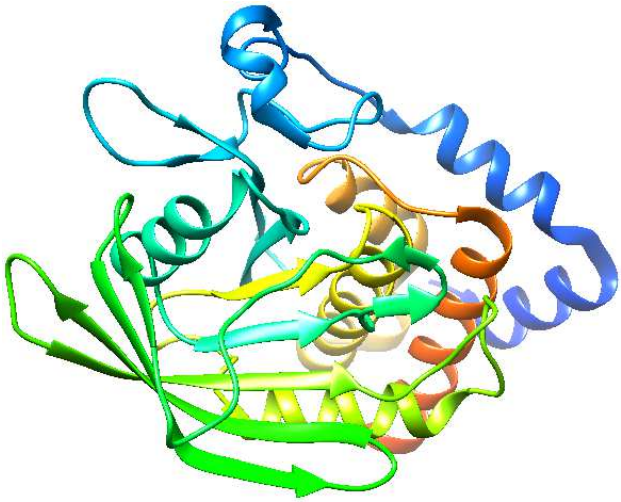


Fig. 3. *Protein tyrosinephosphatase1B.*

Molegro virtual docker program [16,17,18]was used to detect cavities of our enzyme which are five (tab01).

Table 1. *Chemical propertieso four cavities.*

cavities	Volume(A^3)	Surface(A^3)
Cavity1	27.14	90.88
Cavity2	23.04	93.44
Cavity3	23.04	106.24
Cavity4	13.31	61.44
Cavity5	10.24	48.64

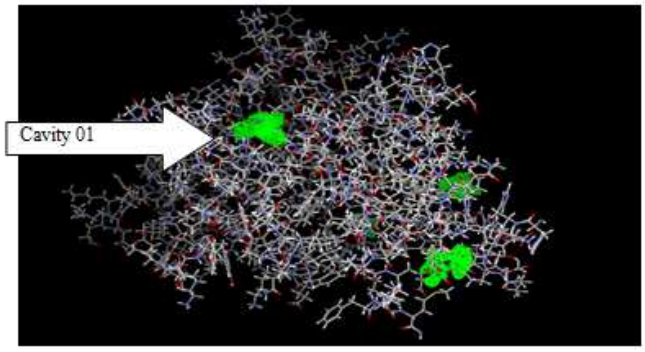


Fig. 4. *The graphic interface with the identified cavities with molegro.*

The volume of the cavity 01(27.24A^3)shown that it is more elevate then the other cavities ,cavity 1have been chosen for the coming studies (fig05).

Docking:

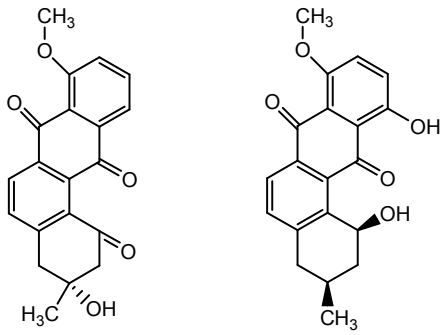
Docking molecular used to predict the structure of a formed complex of a protein and a ligand, the formation of this complex is formed on the recognition of the three-dimensional structure of ligand by a receiver site [2].

In this study, the complex enzyme-substrat umis done using chimera program (tab2).

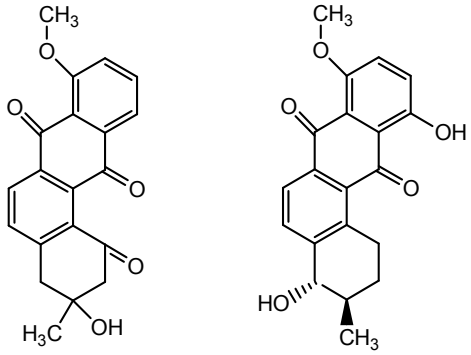
Table 2. *Energies corresponds to our compounds.*

Compounds	Energies(Kcal/mol)
S0	-9.1
S1	-9.1
S2	-9.1
S3	-9.1
S4	-9.1
S5	-9.2
S6	-9.2
S7	-9.7
S8	-9.8
S9	-9.6
S10	-9.7
S11	-9.8
S12	-9.6
S13	-9.5

The following inhibitors have been chosen (CID: 25033706; CID: 132244; CID: 164046; CID: 73744231). And which are the weakest energies .The chemical structure of those molecules has been represented in (fig5).



(S_{08})cid: 25033706 (S_{11})cid: 132244



(S_{07})cid:164046 (S_{12})Cid:73744231

Fig. 5. *Similar to the more stable SNA.*

Table 3. *The representation of the chemical link between amino acids of the active site and the inhibitors atoms.*

atomes/molecules	S7	S12	S11	S8
O1	PHE 182=3.551 GLY 183=3.017	THR 138=2.664 GLU 97=3.406	PHE 182=3.565 GLY 183=3.048	THR138=2.233 GLU 97=3.409
O2	GLN 266=2.846	GLU 97=3.011 THR 138=2.792	ARG 221=2.095 TRP 179=3.475	GLU 97=3.012 THR 138=2.791
O3	TRP 179=3.413 GLN 266=3.559		ARG 221=2.013 GLN 266=3.480	
O4	GLN 266=2.998		GLN 262=2.805 GLY 220=3.431	
O5	GLN 262=2.781 GLY 220=2.954	LEU 140=3.017 THR 138=2.792 GLU 97=2.525	GLN 262=2.807 GLY 220=2.924	GLU 97=2.521 LEU140=3.017 THR 138=2.792

The measured distances vary between 2.013A° and 3.565A° of the entire studied complex.

The interactions between2.5A°and3.5A°are considered as elevated and cells between 3.1Å and 3.55Å are assumed to be

average. The superior interactions (3.55)are weak or absent [19].

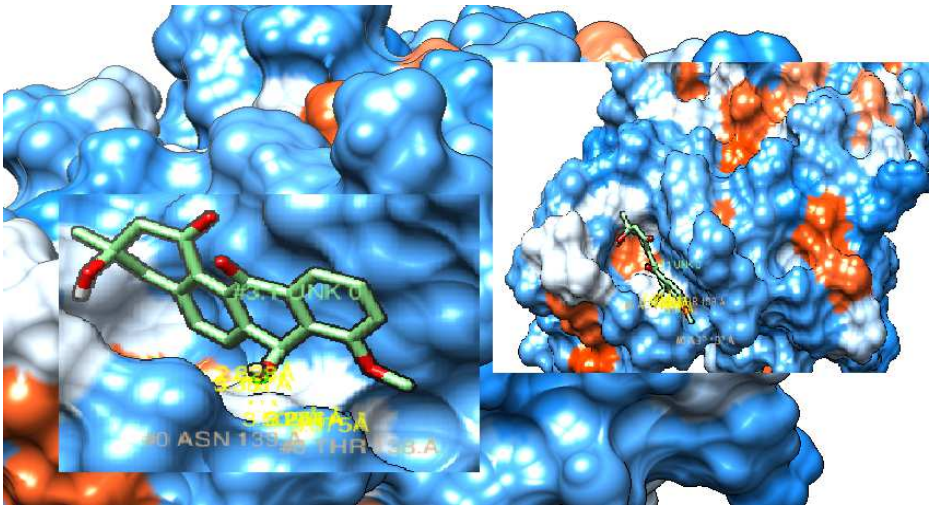


Fig. 6. *The different bonds between amino acids inactive site and inhibitor.*

5. Conclusion

The analysis of molecular docking gives place at the prospective identification of ligands.

Based on the analysis, we take four more stable molecules, and see the bonds according with the active site of our enzyme, hence, in present study, it can be concluded that molecules S8, S11, S8, S12 have the potential to inhibit the activity of ptp1b but the calculus of the distances of bindings also ensures that S11 show a very strong binding with ptp1b at active site

The most stable molecule is$S_{11}$is the lowest energy and also the bonds smaller.

It appears that theS_{11}molecule has a better contribution to the inhibition for slowing the progression of type diabetes2 disease.

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