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STRUCTURE BASED DRUG DESIGNING FOR DIABETES MELLITUS (IRAK PROTEIN)

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ABSTRACT

We have address a specific suitable ligand for diabetes mellitus (IRAK Protein). We have been retrieved the Protein which is responsible for diabetes mellitus and target binding site has been identified using PROSITE tool of Expasy server. The list of drugs are retrieved which are used to treat diabetes mellitus and the best drug ligand has been identified based on molecular docking. We have done the comparative study of drugs and also docking studies have been performed using HEX v. 6.12 and iGEMDOCk softwares . These findings suggest the use of various softwares related with drug designing which are easily available.

Kewords : IRAK Protein, HEX v. 6.12, Docking , TIIDM

[I]INTRODUCTION

Drug design is the approach of finding drugs by design, based on their biological targets. Drugs may be defined that bind in to active region and inhibit this key molecule. Various freely available softwares are there but it depends on our choice of interest which to use and also depends on criteria for the study. As the diabetes is one of the deadliest disease for so long hence we have concentrated on this IRAK protein which is one of the causative agent. Diabetes mellitus is a complex, Multifactor and polygenic disease likely to be caused by one or more gene alterations action in combination with non-genetic factors [1]. We have focused on Type II Diabetes Mellitus (TIIDM).

Drug Design

There are three basic tasks any docking procedure must accomplish: 1) characterization of the binding site; 2) positioning of the ligand into the binding site and 3) evaluating the strength of interaction for a specific ligand-receptor complex. There are many small molecule databases in public domain such as ZINC, Pubchem, ChemDB, Chem Spider, KEGG ligand database and Drug Bank for virtual screening. The procedure of structure based VS through docking has become crucial when it is necessary to test a database of thousands of compounds against one or more protein targets in a feasible time. However these drugs would also have to be designed in such a

way as not to affect any other important molecules that may be similar in appearance to the key molecules [2].

Ligand

We have taken 1st generation grug into consideration. As TIIDM can not be controlled by diet alone we have to give drugs for the same. Acetohexamide is one of the drug choice . If acetoheaxamide will be a overdose it cause symptoms include hunger, nausea, anxiety, cold sweats, weakness, drowsiness and coma.

[II] MATERIALS AND METHODS

The Protein sequence which is responsible for diabetes mellitus retrieved from NCBI. This IRAK protein has 712 amino acids and 3 hits in the sequence. Then the lists of drugs for diabetes mellitus are retrieved from drug bank and analyzed the hydrophobic activity for each drugs. We have taken (to Acetohexamide) 80 percent similarity ligands for study. Hydrophobic activity is calculated by Lipinsky filter tool [3-4]. The distribution of the Log P and Log S values for each drugs shows the highest hydrophobic activity of the drug. The structure of the protein retrieved from Protein data bank and binding sites of the receptor was calculated by PROSITE tool. The structure of the various drugs were taken from drug bank and both the structures were docked by Hex v 6.12 [5] and iGEMDOCk tools[6]. Finally all the results are compared and discussed. These are the ligands which are taken into consideration Acetohexamide, Zinc_1514, Zinc_1516 Zinc_2194, Zinc_155274, Zinc_5929621.

[III] RESULTS AND DISCUSSION:

3.1 PROSITE Analysis (4):

It also shows that the positions of the binding sites present in the IRAK Protein (212-521,218-239,336-348).The position 218 and 226 is for NP_BIND and the proton acceptor site is present in the position 340.

3.2 Lipinski Rule of Five Analysis

1. Acetohexamide

Molecular Weight = 304.00
Hydrogen Bond Donor = 0
Hydrogen Bond Acceptor = 0
LogP = 0.000
Molar Refractivity = 0.000

2. Zinc_1514

Molecular Weight = 295.00
Hydrogen Bond Donor = 1
Hydrogen Bond Acceptor = 3
LogP = 2.780
Molar Refractivity = 75.580

3. Zinc_1516

Molecular Weight = 323.00
Hydrogen Bond Donor = 1
Hydrogen Bond Acceptor = 3
LogP = 3.561
Molar Refractivity = 84.814

4. Zinc_2194

Molecular Weight = 281.00
Hydrogen Bond Donor = 1
Hydrogen Bond Acceptor = 3
LogP = 2.390
Molar Refractivity = 70.963

5. Zinc_155274

Molecular Weight = 309.00
Hydrogen Bond Donor = 0
Hydrogen Bond Acceptor = 3
LogP = 3.126
Molar Refractivity = 80.207

6. Zinc_5929621

Molecular Weight = 309.00
Hydrogen Bond Donor = 1
Hydrogen Bond Acceptor = 3
LogP = 3.026
Molar Refractivity = 80.127

Table 1. LOG P value

Sr. no.	Drug Name	LOG P
1	Acetohexamide	1.72
2	Zinc_1514	2.780
3	Zinc_1516	3.561
4	Zinc_2194	2.390

5	Zinc_155274	3.126
6	Zinc_5929621	3.026

The drug Acetohexamide has lowest LOG P vale(1.72) Zinc _1514 has very low Log P value (2.780) and So on The value goes on Increasing indicates reduction in hydrophobic activity

Table 2. Result of PROSITE Analysis

HITS in IRAK Protein	3
Position of HITS in Protein	212-521,218-239,336-348
NP_BIND	218,226(ATP by similarity)
BINDING	239 (ATP by similarity)
ACT_SITE	340 Proton acceptor(By similarity)
Patterns	2
Profiles	1
Protein kinase domain Distinct Patterns	PS50011
Protein kinase ATP Binding region	PS00107
Serine/Threonine kinase active site region	PS00108

Table 2 shows that 3 hits present in the Protein including 2 patterns and 1 profile. It also shows
that the positions of the binding sites present in the IRAK Protein (212-521,218-239,336-348).The position 218 and 226 is for NP_BIND and the proton acceptor site is present in the position 340. PK ATP binding region is PS00107.

Table 3: Comparison B.E. of two softwares

iGEMDOCK v2.1	Energy	HEX v6.12	Energy
2NRU-Acetohexamide-0.pdb	-116.04	2NRU-zinc_1516	-282.27
2NRU-zinc_5929621-0.pdb	-113.81	2NRU-zinc_5929621	-264.45
2NRU-zinc_2194-0.pdb	-94.55	2NRU-zinc_155274	-257.54
2NRU-zinc_1516-0.pdb	-37.7	2NRU-zinc_2194	-242.69
2NRU-zinc_155274-0.pdb	-35.64	2NRU-zinc_1514	-236.63
2NRU-zinc_1514-0.pdb	89.24	2NRU-Acetohexamide	-201.71

Table 3 Shows that where the binding/docking energy of 2NRU-Acetoxamide is also least in iGEMDOCK and The docking energy of 2NRU-Acetoxamide in Hex is accordingly more as compared to iGEMDOCK and Zinc_1514 shows value lesser than zinc_5929621 and zinc_1516.

3.3 Docking

With HEX v 6.12

Figure 1. Screen shot of Receptor

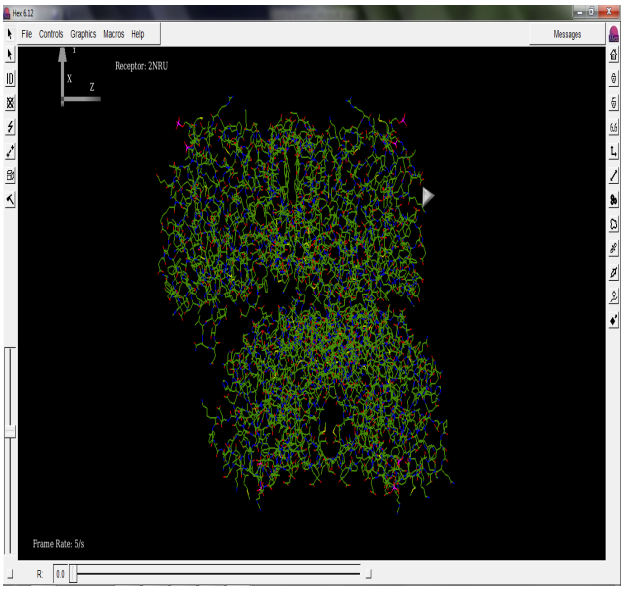


Figure 2. Screenshot of Ligand and Receptor

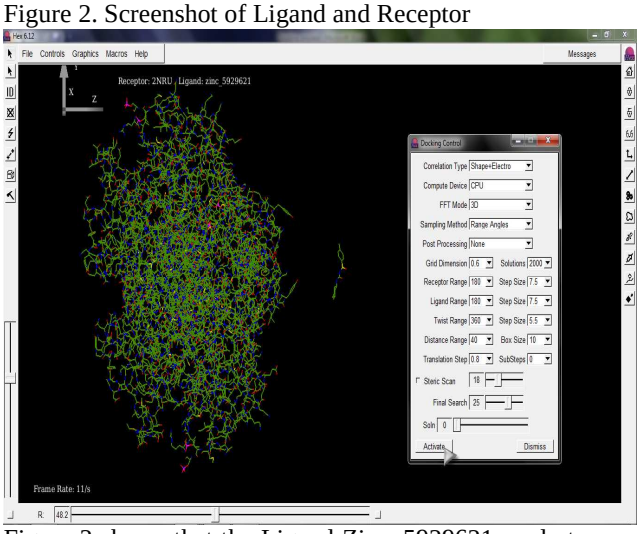
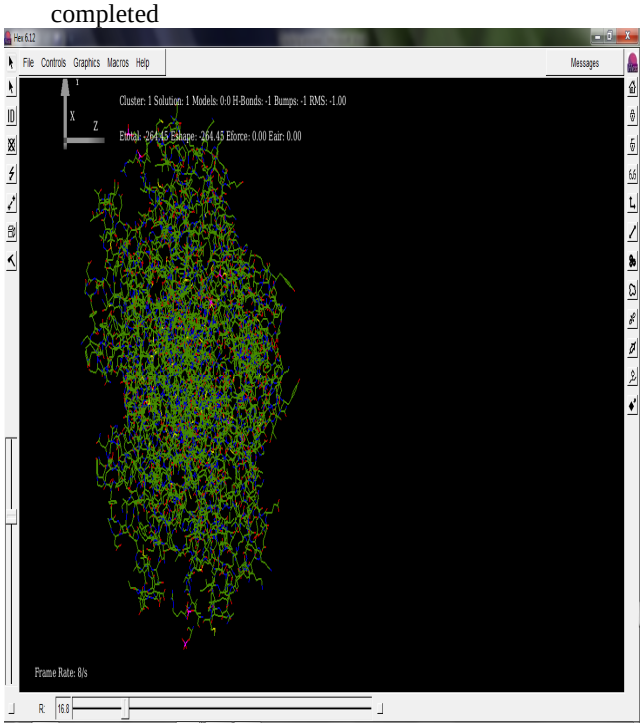


Figure 2 shows that the Ligand Zinc_5929621 ready to bind with the receptor IRAK Protein through Hex v 6.12 tool.

Figure 3. Screenshot After The Docking process completed



The docked Eforce and Etotal values are displayed in this screenshot of Figure 3.

Figure 4. Screenshots of iGEMDOCk

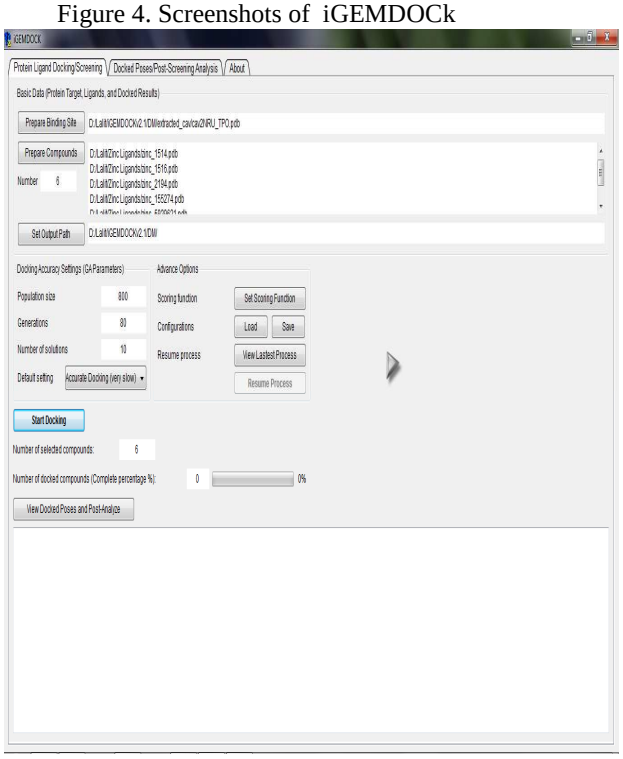


Figure 5. Screenshot of Docking Process

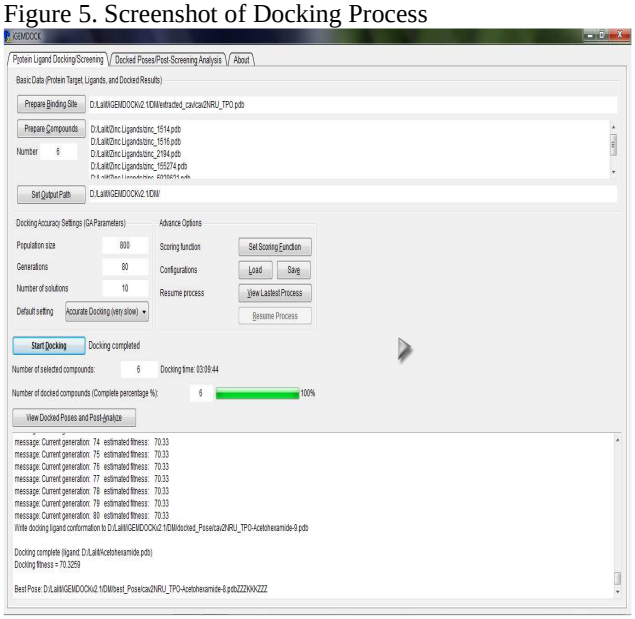
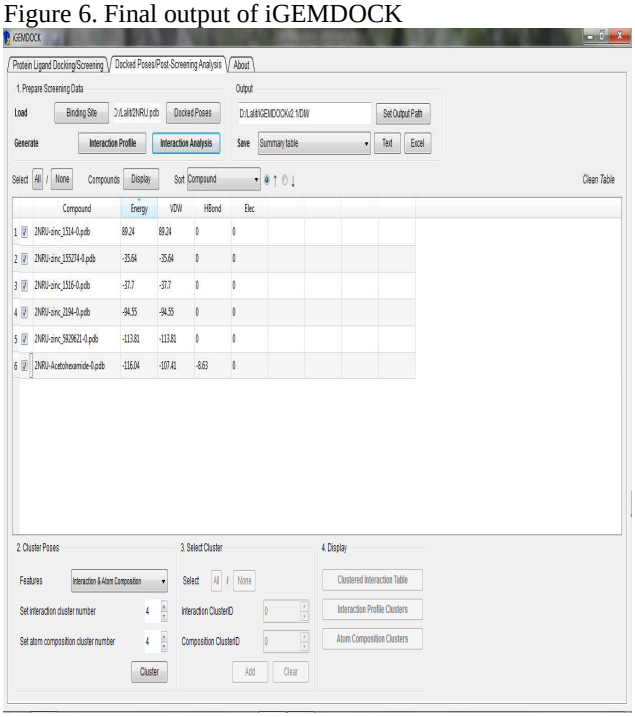


Figure 6. Final output of iGEMDOCK



[IV] CONCLUSION

In this article, we have observed results on the basis of hydrophobic effect on Log P value and the IRAK Protein has 3 active sites. The docked results were identified by molecular docking method. The list of drugs are collected from zinc

database which are used to treat Diabetes mellitus and identified the best drug based on hydrophobic activity. From the above data and the result of docking & Lipinski Rule of Five, we can predict that, iGEMDOCK can used as best docking method, because the LogP value of Acetohexamide as well as Zinc_5929612 is less.

[V] REFERENCES

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