wjpls, 2016, Vol. 2, Issue 5, 209-221. Research Article ISSN 2454-2229

World Journal of Pharmaceutical and Life Sciences WJPLS

www.wjpls.org

SJIF Impact Factor: 3.347

IN SILICO EVALUATION FOR GLUCOKINASE SENSITIZER OF SOME NOVEL LIGNANDS AS POTENTIAL ANTIHYPERGLYCEMIC AGENTS

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Article Received on 26/08/2016 Article Revised on 16/09/2016 Article Accepted on 06/10/2016

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ABSTRACT

Glucokinase could indeed serve as pacemaker of glycolysis & could be an attractive target for type-2 diabetes. Binding modes of a series of Some Novel Lignands as protein Glucokinase (Hexokinase 4) (PDB ID:1V4S) Sensitizer have been identified by molecular modeling techniques. We have performed docking and ADME predictions of this Sensitizer with Hexokinase 4 enzyme. ADME predictions of 6 top selected compounds were done with Medchem desiner with version 2.0. The results indicate that Protein-ligand interactions were studied using Glucokinase protein PDB ID1V4S, obtained from Protein data bank to evaluate the affinity of various Glucokinase modulating analogues towards ligand binding site and to study the extent of correlation between experimental values and computational dock scores, to proposed a new compounds with Glibenclamide, Glipizide, Glimipiride, Gliclazide as the standard. The information generated from the present study should be useful in the design of more potent Glucokinase (Hexokinase 4) (PDB ID:1V4S) Sensitizer as antidiabetic agents.

KEYWORDS: Antidiabetic, Docking, ADME, Diabetes mellitus Type 2.

INTRODUCTION

Diabetes mellitus is one of the major disease currently affecting millions people worldwide and the number is growing rapidly. Type 2 diabetes poses a major health problem globally,

especially in many developing countries.[1] It is brought about when the cells in the muscles, liver, and fat tissues fail to utilize insulin effectively. Human body has to maintain the blood glucose level at a very narrow range, which is done with insulin and glucagon.[2] The function of glucagon is causing the liver to release glucose from its cells into the blood, for the production of energy.[3] Glucokinase is an enzyme that facilitates phosphorylation of glucose to glucose-6-phosphate. Glucokinase occurs in cells in the liver, pancreas, gut, and brain of humans and most other vertebrates. In each of these organs it plays an important role in the regulation of carbohydrate metabolism by acting as a glucose sensor, triggering shifts in metabolism or cell function in response to rising or falling levels of glucose, such as occur after a meal or when fasting. Mutations of the gene for this enzyme can cause unusual forms of diabetes or hypoglycemia.

Glucokinase (GK) is a hexokinase isozyme, related homologously to at least three other hexokinases.[4] All of the hexokinases can mediate phosphorylation of glucose to glucose-6-phosphate (G6P), which is the first step of both glycogen synthesis and glycolysis. However, glucokinase is coded by a separate gene and its distinctive kinetic properties allow it to serve a different set of functions. Glucokinase has a lower affinity for glucose than the other hexokinases do, and its activity is localized to a few cell types, leaving the other three hexokinases as more important preparers of glucose for glycolysis and glycogen synthesis for most tissues and organs. Because of this reduced affinity, the activity of glucokinase, under usual physiological conditions, varies substantially according to the concentration of glucose.[5] The sulfhydryl groups of several cysteines surpmound the glucose binding site. All except cys 230 are essential for the catalytic process, forming multiple disulfide bridges during interaction with the substrates and regulators. At least in the beta cells, the ratio of active to inactive glucokinase molecules is at least partly determined by the balance of oxidation of sulfhydryl groups or reduction of disulfide bridges. These sulfhydryl groups are quite sensitive to the oxidation status of the cells, making glucokinase one of the components most vulnerable to oxidative stress, especially in the beta cells.[6]

MATERIALS AND METHODS

a) Molecular Modeling Studies

Molecular modeling studies have been carried out using HEX 5.1 & MVD (Grid-based Ligand Docking with Energetics) software Molegro Virtual Docker version 5.5 workspace was used for all the steps involved in ligand preparation, protein preparation and docking.

ACD Chem Sketch is chemical drawing software developed by ACD LAB. The software is user-friendly, provides all details of drawn structures and helped to calculate chemical properties, design professional reports and presentations.

b) Ligand Preparation

The ligands used in this study were prepared using ARGUS LAB (Optimized Potential Liquid Simulations for All Atoms) force fields for energy minimization.

c) Protein Preparation

The X-ray crystal structures retrieved from PDB database as raw could not be suitable for molecular docking studies. A typical PDB structure consists only of heavy atoms, waters, Cofactors, metal ions and can be of multimeric. These structures do not have the information about bond orders, topologies or formal atomic charges. So, the raw PDB structure should be prepared in a suitable manner for docking. Protein Preparation Wizard of MVD (Grid-based Ligand Docking with Energetics) software Molegro Virtual Docker version 5.5 workspace was used to process and prepare the protein. This also follows the Optimized Potential for Liquid Simulations-All Atoms (OPLS-AA) force fields for energy minimization.

ADMET Study by Medchem desiner 2.0

Lipinski Rule of Five Lipinski rule of 5 helps in distinguishing between drug like and non drug like molecules[15]. It predicts high probability of success or failure due to drug likeness for molecules complying with 3 or more of the following rules

- Molecular mass less than 500 Dalton
- High lipophilicity (expressed as LogP less than 5)
- Less than 5 hydrogen bond donors
- Less than 10 hydrogen bond acceptors
- Molar refractivity should be between 40-130

These filters help in early preclinical development and could help pass up costly late-stage preclinical and clinical failures. In this study, we also calculated all five parameters for all the designed compounds.

RESULTS AND DISCUSSION

According to Seifert and Lang, the aim of virtual screening is to “enable the initiation of a medicinal chemistry program with a reasonable probability for identifying a lead compound”.

A virtual screening approach should therefore find at least one active molecule which can then be further used in medicinal chemistry. Following this definition, the presented screening was successful, leading to the identification of an active molecule, of which the activity and toxicity can be modified by slight structural changes. This investigation was to deteMine the comparative efficacy & docking affinity of commonly used Anti-diabetic, reported molecules & my proposed molecules on targeting 3D model 1V4S structure, using in silico techniques by different computational drug designing Sources & softwares i.e, RCSB protein data bank, molinspiration, chem sketch, hex 5.1 , argus lab , mdl mol file, brookhaven pdb file, etc. was docked with energy minimized marketed anti-diabetic, reported molecules & proposed molecules by using docking software HEX5.1.The inhibitors binding efficacy & affinities were deteMined using HEX docking scoring (Etotal negative value) fitness function. The application on computational science (In silico drug designing) to phaMaceutical research is a discipline, which is phenomenal.

Docking was used to investigate whether Marketed type II diabetic drug and Newly proposed derivatives could bind to one of the same binding sites on the kinase domain of the insulin receptor or not. While the latter binding site seems to be too small for the compounds, they should be able to bind to the pocket between the a C helix and the b-sheets of the N-teMinal lobe of the kinase domain. This binding pocket is large enough in size and contains several amino acids which could contribute to the binding of the compounds. In this simple & elegance studies revealed efficacy of 04 marketed anti-diabetic , 25 reported anti-diabetic molecules & 05 proposed molecules were targeted against GLUCOKINASE(HEXOKINASE 4) (PDB ID:1V4S). After accessing all docking results it can be observed that the proposed molecule (DPM5) with IUPAC name 6-[3-Isopropoxy-5-(4-methane sulfonyl-phenoxy)-Nicotinic acid have the better docking affinity, compared to marketed best Anti-Diabetic agent's (Glimipiride, Etotal: -327.60 & Glipizide, Etotal: -290.20). While proposed DPM5(Etotal:-33824.) found appreciable docking score higher than marketed prescribed Anti-Diabetic Agents, (Glibenclamide) which were usually used in TYPE II diabetics. So Present observation strengthened the hypothesis for development of new Anti-diabetic agents which can sensitize GLUCOKINASE(HEXOKINASE 4) (PDB ID:1V4S) enzyme for its insulin stimulatory .It proves that the ability of the glucokinase sensitizing enzyme by the Proposed Anti-Diabetic Molecules.Finally it can be concluded from this reported studies, molecule like molecule (DPM5) 6-[3-Isopropoxy-5-(4-methane sulfonyl-phenoxy)-Nicotinic acid may be a new class of potent anti-diabetic analogue for type II diabetes.

Hydrogen Bond Intreaction of proposed Molecules & marketed Drug Against 1V4S Protein

Name Of Compounds	Protein Residue
RPM_{04}	CYS-230,ARG-63,VAL-452,SER-411
GLIBENCLAMIDE	CYS-230,SER-151,ARG-63,GLU-300, LYS-296, THR-332, LYS-169
GLIMIPERIDE	CYS-230,GLU-300,SER-411,VAL-452,LEU-451
GLIPIZIDE	CYS-230,GLU-300,TRP-167,GLY-295,THR-332
GLICLAZIDE	CYS-230,THR-82,GLY-229,THR-228, LYS-169

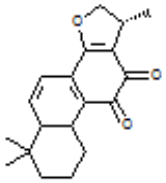
Table 1: Structure and physiochemical properties of docked compounds with standard Glibenclamide, Glipizide, Glimipiride, Gliclazide.

Code	Log p	Molecular weight(Daltons)	Hydrogen Bond Donor	Hydrogen Bond Acceptor	Lipinski Rule	E.Total
M_1	3.797	298.384	0	3	Followed	-237.38
M_2	3.368	368.389	2	6	Followed	-271.16
M_3	3.006	336.39	1	4	Followed	-242.03
M_4	3.791	278.31	0	3	Followed	-244.78
M_5	0.591	288.215	3	7	Followed	-206.31
M_6	0.82	290.274	5	6	Followed	-227.34
M_7	-1.689	127.19	4	4	Followed	-187.38
M_8	0.041	127.19	4	3	Followed	-162.78
M_9	4.363	266.342	2	2	Followed	-273.86
M_{10}	3.161	256.26	3	4	Followed	-239.17
M_{11}	1.631	318.329	5	6	Followed	-224.88
M_{12}	3.22	220.354	1	2	Followed	-204.41
M_{13}	2.346	286.243	4	6	Followed	-236.49
M_{14}	6.692	346.913	0	3	Followed	-273.16
M_{15}	3.169	226.233	0	3	Followed	-194.93
M_{16}	3.808	302.373	4	4	Followed	-249.00
M_{17}	-0.516	128.178	4	4	Followed	-139.84
M_{18}	-2.421	207.228	5	6	Followed	-213.00
M_{19}	0.382	352.413	0	5	Followed	-251.81
M_{20}	2.844	234.297	1	3	Followed	-201.74
M_{21}	4.153	336.347	2	5	Followed	-252.39
DPM_1	3.71	412.51	2	6	Followed	-338.24
DPM_2	2.835	334.396	1	5	Followed	-247.45
DPM_3	4.92	498.492	3	8	Followed	-312.04
DPM_4	0.788	434.402	4	10	Followed	-286.24

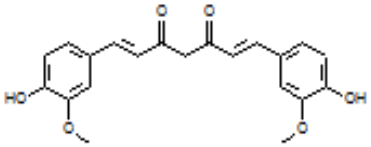
Serial number	Marketed Molecule	E_{total} Of the Molecule
1	Glibenclamide	-309.20
2	Glipizide	-290.88
3	Glimepiride	-327.60
4	Gliclazide	-233.31

Chemical Moeities Effective Against Type-Ii *Diabetes*

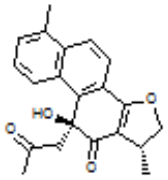
M1:- Cryptotanshione[7]



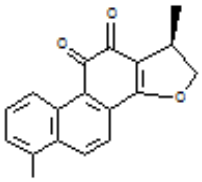
M2:- Curcumin[8]



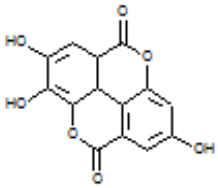
M3:- Shenol A[9]



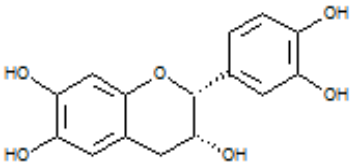
M4:- Dihydrotanshinove[10]



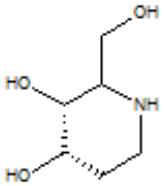
M5:- Ellagic Acid[11]



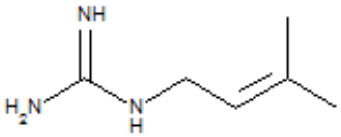
M6:- Epicatechin[12]



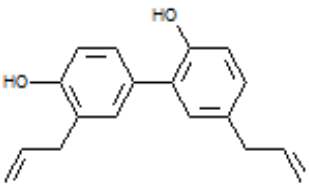
M7:- Fogomine[13]



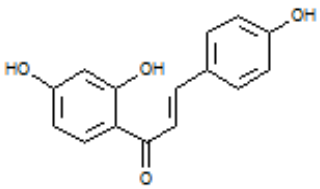
M8:-Gulegine[14]



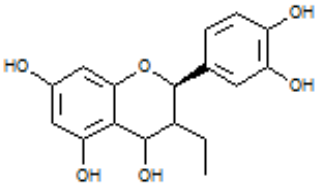
M9:- Honokiol[15]



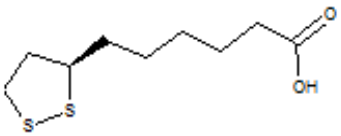
M10:- Isoliquiritigenin[16]



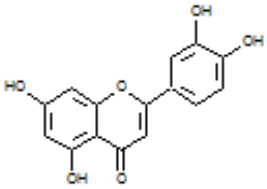
M11:-Leucopelargonidin[17]



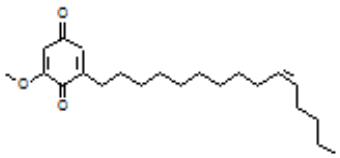
M12:-Lipoic Acid [18]



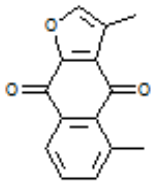
M13:-Luteolin[19]



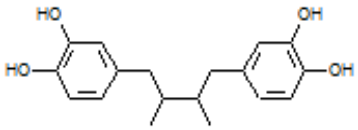
M14:-Maesanin[20]



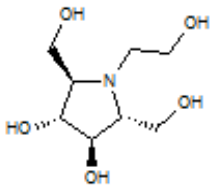
M15:-Maurine[21]



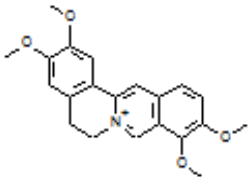
M16:-Mesopropaol [22]



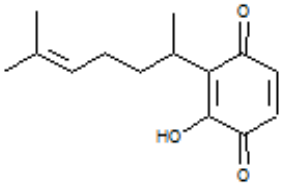
M17:- N Hydroxy Ethyl 1 4 Dideoxy 1 4 Imino D Arabinitol[23]



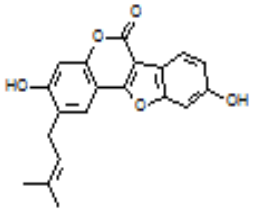
M18:-Palmatine[24]



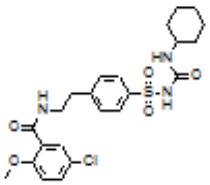
M19:-Perezone[25]



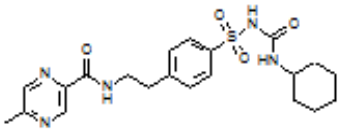
M20:-Pesoralidin[26]



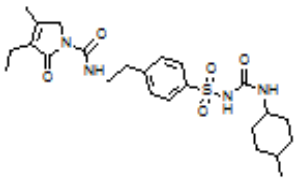
Marketed Drugs



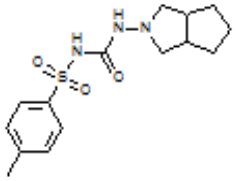
GLIBENCLAMIDE



GLIPIZIDE



GLIMEPIRIDE

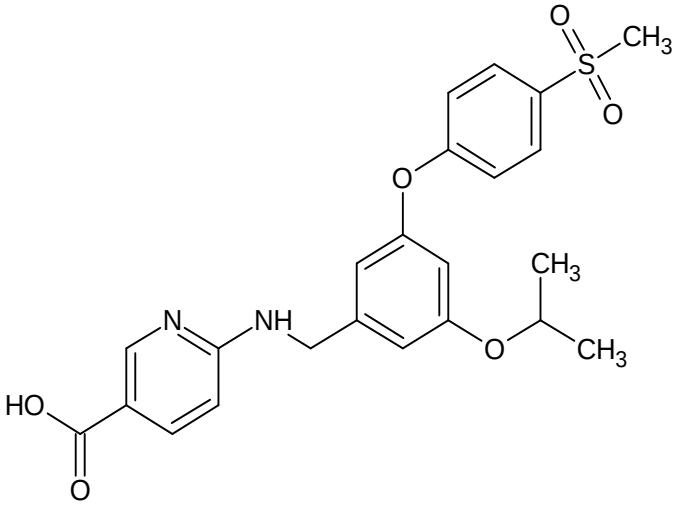


GLICLAZIDE

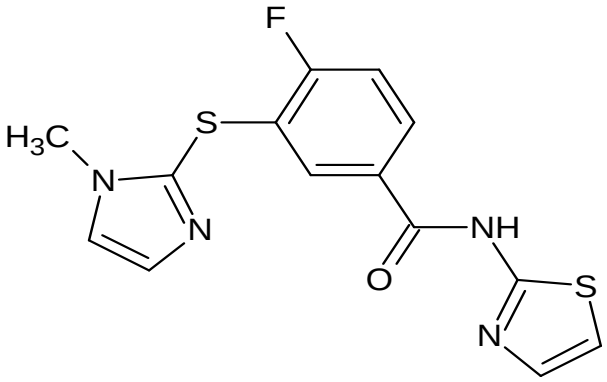
Proposed Future Molecule Effective Against

TYPE-II *DIABETES*

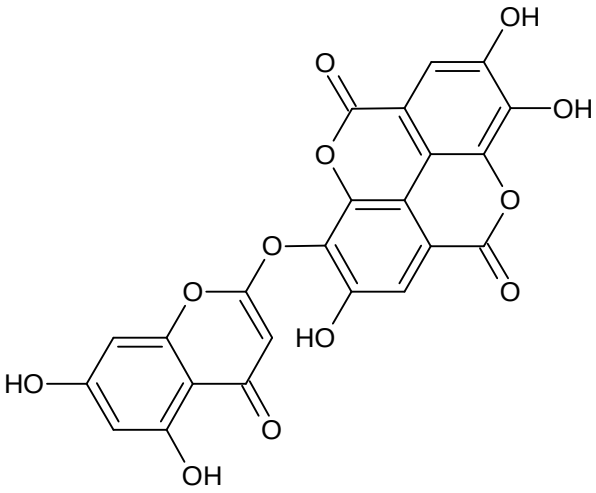
DPM_1:-



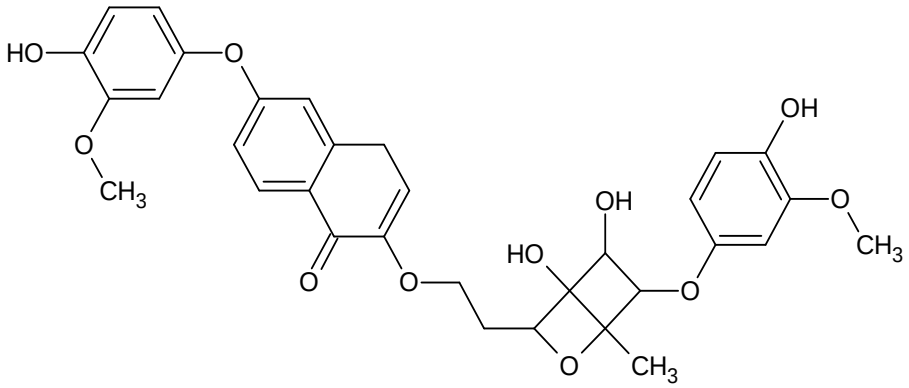
DPM_2:-



DPM_3:-



DPM_4:-



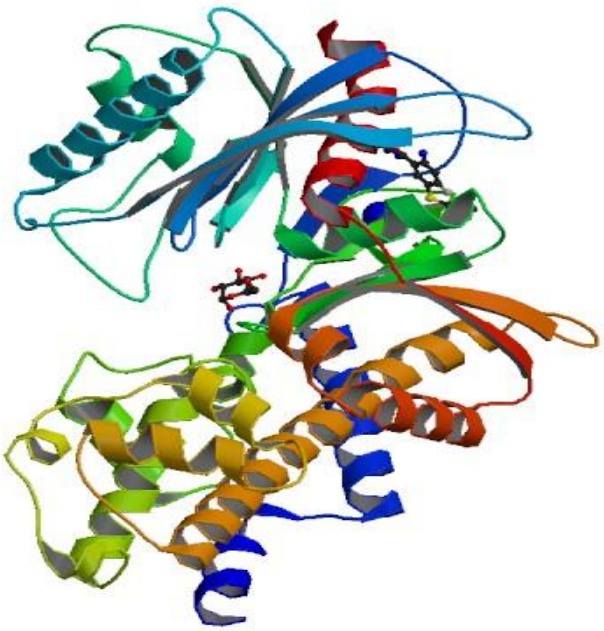


Fig 1: 1V4S (Receptor)

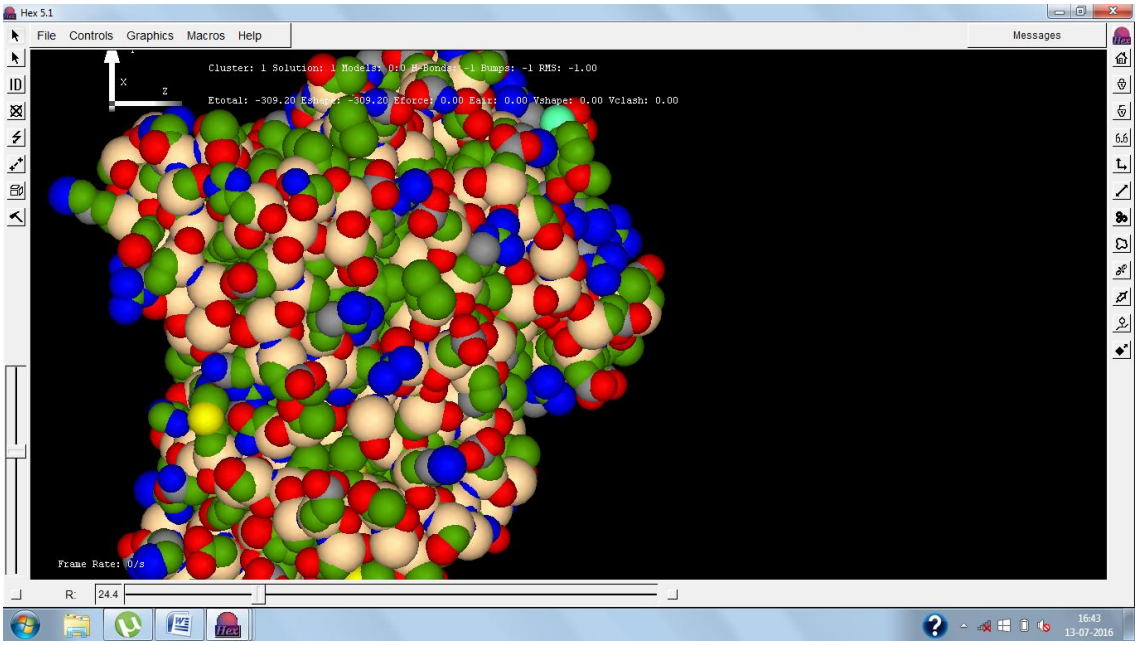


Fig 2: Glipizide(Standard Drug)-docked with 1V4S.

Docking Result of all Proposed molecule

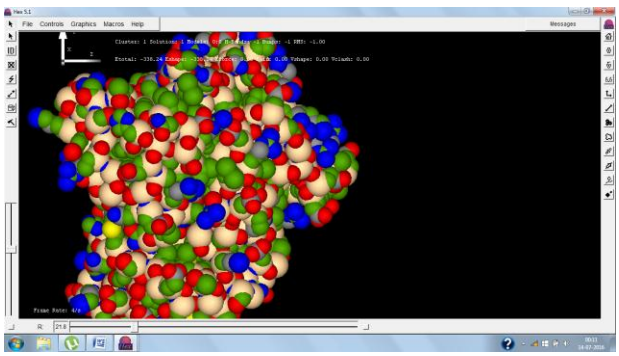


Fig 3: DPM 1

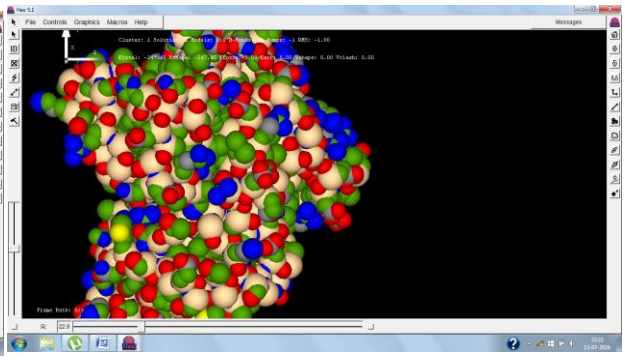


Fig 4: DPM 2

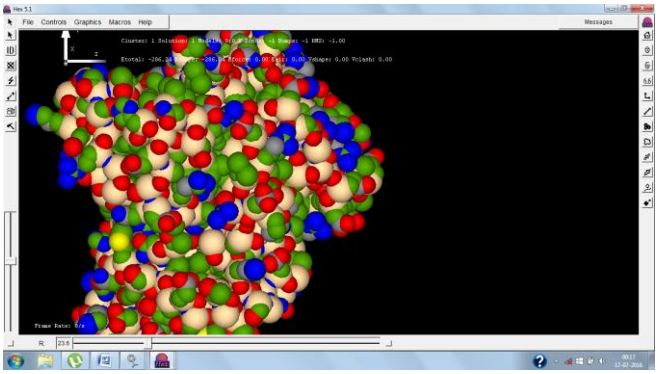


Fig 5: DPM 3

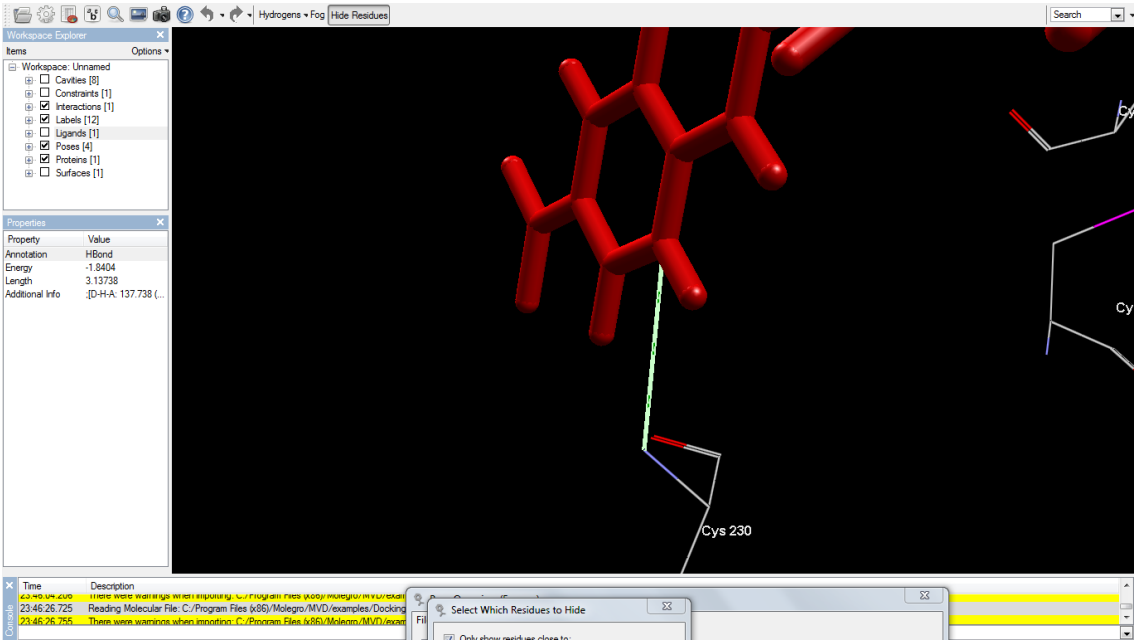


Figure.7 Binding mode of Compound DPM 5 in the active site of with Glucokinase (1V4S) along with interacting amino cys 230.

CONCLUSION

In conclusion, from the present findings, it is well documented that Out of 30 compounds DPM1 showed better docking valu compaired to standard marketed molecule ,so DPM1 plays a part in the management of diabetes , it may be useful in the treatment of anti hyperglycemic in diabetic patients. The potential binding sites of the proposed anti-diabetic agent's was found that Cys-230,Glu-300,Lys-296,Ser-340,Ser-411,Arg-63.The binding Site of the Standard marketed Drugs was found to be Cys-230,Ser-151,Arg-63,Glu-300,Ser-411,Lys-296.This Proves that the effective binding sites are present in selected proposed anti diabetic agent's,when compared with the standard anti-diabetic drug's. Finally, we propose these compounds as anti-diabetic agents as hit structures for design more potent and specific drugs. Moreover, further exploration for detailed mechanism of action of these compounds is required to be investigated before declaring them as safe as well as potent therapeutic agents. However, the data reported in this thesis may be a helpful guide for the medicinal chemists and the researchers who are working in this area.

ACKNOWLEDGEMENTS

The authors are grateful to the Principal and management of Institute of pharmacy & technology, salipur, for providing necessary facilities to carry out this research work.

REFERENCES

1. Iwanishi M and Kobayashi M. Effect of pioglitazone on insulin receptors of skeletal muscles from high-fat-fed rats. Metabolism, 1993; 42: 1017-21.
2. Zimmet P K G, Alberti K G and Shaw J. Global and societal implications of the diabetes epidemic. Nature, 2001; 41: 782–7.
3. Deepal V S, Suresh Kumar P, Vadivukkarasi B and Florida T, Molecular docking studies on selected phytocompounds from different Andrographis sp against PPAR-γ and C/EBP-α receptors for type-2-diabetes. Asian Journal of PhaMaceutical and Clinical Research, 2013; 6(2): 196-9.
4. Hypothesis: structures, evolution, and ancestor of glucose kinases in the hexokinase family". April 2001.
5. Glucokinase Activators in Diabetes Management.
6. Akhila S and Aleykutty N A. Docking Studies on Identified Constituents of Helicteres isora as Antidiabetic Agents International Journal of Computer Applications, 2012; 45.
7. Khan MM, Saxena R, Puri Anju, Chander R, Khanna Ak, Saxena Ak & saxena JK-Regulation of Glycogen metabolism by antidyslipidemic action of gemfibrozil & cholestyramine in dy slipidemic diabetic hamster model., 2008.
8. Gupta, Asheesh; Raghubir, Ram, Energy metabolism in the granulation tissue of diabetic rats during cutaneous wound healing., 2005.
9. Kasimu R, Basnet P, Tezuka Y, Kadota S, Namba T. Danshenols A and B, new ALR2 inhibitors from the root of salvia miltiorhiza bunge". Chem PhaM. 1997.
10. Ahamad R, Sriivasta SP, Maurya R, Rajendra SM, Arya KR & Srivastava A- mild antihyperglycaemic activity in Eclipta alba, Berberis aristata, Batula utilis, Cedrus deodara,Myristica fragrans, TeMinalia Chebula., 2008.
11. Ueda H, Kawanishi K , Moriyasu M Effects of ellgic acid and 2-(2,3,6-trihydroxy-4-carboxyphenyl)ellagic acid on sorbitol accumulation in vitro and in vivo., 2004.
12. Grover JK, Vat V, Yadav SS. Pterocarpus marsupium extract (Vijaysar) prevented the alteration in metabolic patterns induced in the noMal rat by feeding an adequate diet containing fructose as sole carbohydrate". Diabetes Obes Metab.2005.
13. Obatomi Dk, Oye AAA,jangber ZN, Temple Metabolia & Renal Changes Following The Ingestion of African Mistletoe extract in Rats. PHytother., 1998.
14. OjeWole JAO Anti-inflammatory & anti Diabetic properties of sclerocarya birrea (A.Rich.) Hochst. Stem-bark aqueous extract in Mice & rats., 2004.

15. Okyar A,Can A,Akev N,Baktir G,Sutlupinar N. Effects of Aloe vera leaves on blood glucose level in type I & type II diabetic rat models.Phytother., 2001.
16. Aida K,Tawata M,Shindo H,Onaya T,Sasaki H, Yamaguchi T, Chin M,Mitsuhashi H Isoliquiritigenin : a new ALR2 inhibitor from glycyrrhizae radix.plant Med., 1990.
17. Augusti KT. Antidiabetic effects of a glycoside of leucopelargonidin isolated from Ficus bengalensis linn. Cherian. Indian J. Exp. Biol., 1993.
18. Orhan DD, Aslan M, Sendogdu N, Ergun F, Yesilada E. Evaluation of the hypoglycaemic effects and antioxidant activity of three Viscum album subspecies (European mistletoe) in streptozotocin-diabetic rats:. J. Ethnopha Mcol., 2005.
19. Haraguchi H, Ohmi I. Matsuda H, Cai H,Kubo M,Tosa H, Linuma M Study on anti-cataract drugs from natural sources. effects of Buddlejae flos on in virto ALR2 Activity. biol. phaM., 1995.
20. Haraguchi H,Ohmi I. Inhibition of ALR2 by maesanin & related p- benzoquinone derivatives & effects on other enzymes. Bioorg Med. Chem., 1996.
21. Alarcon-Aguilar FJ, Hernandez-Galicia E, Campos- Sepulveda AE, Xolalpa-Molina S,Rivas –Vilchis GF, Vazquez-Carrillo LI, Roman-Ramos R.Evaluation of the hypoglycaemic effect of Cucurbita ficifolia bouche. In different experimental models. J. Ethnopha Macol., 2002.
22. Luo J, Chuanng T, Cheung J, Quan J, Tsai J, Sullivan C, Hector RF, Reed MJ, Meszaros K, King SR, Carlson TJ, Reaven GM Masoprocol ;a new antihyperglycemic agents agent isolated from the creosote bush. Eur. J. Pha Macol., 1998.
23. Pari L, Ramakrishnan R, Venkateswaran S. Antihyperglycemic effect of Diamd, a herbal foMulation, in experimental diabetes in rats". J Pha Macol., 2001.
24. Polyxeni Alexiou & Vassilis J. Demopoulos Chemistry & Activity. Medicinal plants used for the treatment of Diabetes And Its long term complications., 2010.
25. Alarcon-Aguilar FJ, Roman-Ramos R, Jmenez-Estrada M, Reyes-Chilpa R, Gonzalez-Paredes B. Flores-Saenz JL Effects of three mexican madicinal plants on blood glucose levels in healthy mice & rabbits. J.Ethnopha Macol.,1997.
26. Reddy SV, Tiwari AK, kumar US,Rao RJ, Rao JM Free radical scavenging, enzyme inhibitory constituents from from antidiabetic Ayurvedic medicinal plant Hydnocarpus wightiana Blume, Phytother. Res., 2005.