Trends in Bioinformatics

ISSN 1994-7941

science alert

ANSInet
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http://ansinet.com

Trends in Bioinformatics 8 (1): 26-36, 2015
ISSN 1994-7941 / DOI: 10.3923/tb.2015.26.36

Maestro 9.4 as a Tool in the Structure Based Screening of Glycoalkaloids and Related Compounds, Targeting Aldose Reductase

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ABSTRACT

Diabetes mellitus is one of the alarming common diseases of this century. In India, according to the statistics of the International Diabetes Federation, 87 million of people are affected by Diabetes mellitus and this number is expected to cross 100 million by 2030. This has created a thrust for the development of new medicines. Recently, ban of pioglitazone, an oral anti-diabetic drug by Drugs Technical Advisory Board (DTAB) on account of its side effects, portrays the need for developing new drugs with less or no side effects. Cheminformatics tools assist in screening several millions of compounds and providing lead compounds in drug designing. This paper focuses on screening of lead compounds in arriving at newer drugs for Diabetes mellitus. Aldose reductase a cytosolic enzyme is the receptor to which selected lead compounds are docked. Glycoalkaloids (present in bitter melon) and related compounds were docked onto aldose reductase and based on the GLIDE score, structural modifications were carried out to arrive at the highest GLIDE score. A commercially available molecule recommended for Type 2 Diabetes mellitus was also taken for reference. Glycoalkaloids were found to possess high GLIDE score compared to standard. In order to analyze the competence of the Schrodinger software a comparison was made with an internet freeware Hex 6.3 version. The flexible receptor docking of Schrodinger was found to be more advantageous than the Hex 6.3.

Key words: Diabetes mellitus, aldose reductase, glycoalkaloids, GLIDE score

INTRODUCTION

Human life span is on an increase and aging is also postponed in recent days. Innovative medicines play a profound role along with nutrition, sanitation and other public health measures in increasing the average life span of man. Still there are many of the most common human diseases that are not effectively treated by existing therapies. With the improved technologies, researchers are focusing on genes and proteins responsible for genetic disorders and common polygenic diseases such as diabetes, heart disease etc. The increased pressure from the cost of clinical investigations and insufficient sources of financial support in research promotes cheminformatics (Hughes *et al.,* 2011; Van de Waterbeemd and Gifford, 2003; Guttula *et al*., 2011; Umamaheswari *et al*., 2012).

In order to facilitate the speed and cost involved in the drug discovery, a number of computational methods are used. The successfulness of the methods depend on number of factors like ligand structure, target receptor structure etc. In molecular modeling, the crystal structure,

conformation and the orientation of lead molecule provides the binding energy of the target receptor and finally results in docking scores which aids in arriving at the best docked ligand structure. Thus docking studies play a significant role in rational designing of drugs and aids drug discovery process (Rother *et al*., 2006; Anusuya and Natarajan, 2012; Rask-Andersen *et al*., 2011; Akhila *et al*., 2012).

Diabetes mellitus is a threatening disease that leads to death in humans. According to World Health Organisation (WHO) nearly 200 million people all over the world suffer from diabetes and this number is likely to be doubled by 2030. Diabetes mellitus can be categorized into two types: Type-1 and type-2. Type 2 Diabetes Mellitus (T2DM) is a metabolic disorder that has affected more than 87 million people in India. It is characterized by the impairment of insulin secretion from pancreatic beta cells and insulin resistance in peripheral tissues such as liver, skeletal muscle and adipose tissue, finally leading to hyperglycemia (Sivaperuman and Dhas, 2013; Reddy *et al*., 2012; Vaidya *et al*., 2013; Rummey *et al*., 2006; Fatchiyah *et al*., 2013; Annapurna *et al*., 2013). According to the Indian Diabetic Federation, more than 100 million are likely to be victims of Diabetes mellitus by 2030.

Biguanides, thiazolidinediones, metformin, sulfonylurea, meglitinides, miglitol, acarbose etc. are the commercially available anti-diabetic drugs. These medications may have side-effects like digestive discomfort, lactic acidosis, headache, dizziness, hypoglycemia, liver cell injury, neurological defects etc. Hence there is thrust for natural products possessing anti-diabetic activity. Understanding the interaction of drugs with the biological processes ensures safe medication. Management of diabetes is thus still a challenge to the medical system (Angadi *et al*., 2013; Williams and Pickup, 1991; Senthilraja *et al*., 2013; Wallach *et al*., 2010). Recently, the growth in the sales of anti-diabetic molecules has increased by lifestyle ailments in India. The anti-diabetic subclass, a combination of Metformin and Glimepiride registered a growth of 8.1% than anti-infective drugs (Times of India, 18 June 2014).

Plants are good source of secondary metabolites which find use in pharmaceutical research. In past years, more than 40% of commercially available new drugs were from natural products. The anti-diabetic drug-metformin was developed based on the use of *Galega officinalis*. Hence analysis of the phytoconstituents of plants with anti-diabetic potency may provide lead for discovery of hypoglycemic molecules (Bibi *et al*., 2013; Wang *et al*., 2013; Suhitha *et al*., 2012; Handral *et al*., 2012; Noor *et al*., 2013).

Aldose Reductase (AR) is a monomeric reduced Nicotinamide Adenine Dinucleotide (NAD) phosphate. In 1956, Hers reported the glucose reducing activity of aldose reductase, the first rate limiting enzyme in polyol pathway which reduces glucose to sorbitol with NADPH as cofactor. The conversion of sorbitol to fructose is aided by sorbitol dehydrogenase enzyme. This pathway is responsible for the utilization of glucose if the consumption is less than 3%. The activity of the pathway increases as the glucose consumption increases to 30%. These abnormalities lead to the accumulation of sorbitol and leads to oxidative stress and tissue injury during diabetes (Madeswaran *et al*., 2012; Ammiraju *et al.,* 2012; Jain *et al*., 2011; Vepuri *et al*., 2012).

Considering the need for newer antidiabetic drugs and in an endeavour to introduce new antidiabetic drugs, molecular docking studies of selected chemical constituents of 10 different medicinally important plants has been carried out to understand the binding mechanisms of these bioactive constituents with aldose reductase protein (receptor) using XP docking program of Maestro, version 9.4, Schrödinger software. The results of the study revealed the most probable phytoconstituent-protein interactions. Synthetic drug-metformin was used as standard for

comparison. Vicine compound present in *Momordica charantia* was found to possess good anti-diabetic activity compared to that of standard metformin. Isomers of vicine were also generated and docked with the receptor aldose reductase and found to have similar GLIDE score as that of vicine.

MATERIALS AND METHODS

Selection of ligands: The phytoconstituents of ten different traditionally used anti-diabetic plants were analyzed. Plants such as *Allium cepa* (Onion), *Allium sativum* (Garlic), *Trigonella foenum-graecum* (Fenugreek leaves), *Momordica charantia* (Bitter melon), *Murraya koeingii* (Curry leaves) and *Tinospora cordiflora* (Shindila kodi) were found to possess metabolites with structure in part resemblance to metformin. The compounds present in the aforesaid plants are as follows: S-methyl cysteine sulfoxide and diphenyl amine (*Allium cepa*), Allin (*Allium sativum*), 4-hydroxyisoleucine (*Trigonella foenum-graecum*), vicine (*Momordica charantia*), mahanine, mahanimbicine, mahanimbine, koenidine and girinimbin (*Murraya koeingii*) and magnoflorine (*Tinospora cordiflora*).

These compounds were docked with aldose reductase using Maestro version, 9.4 -Schrödinger software. The binding energy of the docked structures was compared to that of metformin.

Preparation of ligand: The selected ligands were sketched in MarvinSketch (Freeware) and saved as MDL molfiles [V2000]. Lipophilicity (Log P) of drugs is essential in drug designing. The logP value of zwitterions is calculated from the logD at the isoelectric point using MarvinSketch software. The effect of hydrogen bonds on logP is also considered when there is formation of a six membered ring between suitable donor and acceptor atoms. As the logD values are pH-dependent, the logD calculation relies on the pKa prediction process. It means that the calculated logP will only provide reasonable prediction for a few types of structures. The ligands selected for the docking studies were based on the lopP values.

Consequently, ligand preparation was done using LigPrep (Schrödinger) from the application menu. The 2D structures of the ligands with bond directions were converted by LigPrep to the full 3-dimensional structure by assigning the force field as OPLS-2005. LigPrep can generate the expected ionized forms at significant concentrations corresponding to the pH 7.0±3.0 and generate the tautomers based on probability to recognize counter ions for removal and to add or remove hydrogens to achieve charge neutrality. It generates 32 stereochemical structures per ligand. Considering all the reasonable ionization states of ligands, the lowest energy conformer is important for docking studies. Each ligand after LigPrep was saved as separate files A, B, C, D, E, F, G, H, I, J, K, L, M, N, O, P, Q and Metformin as file Z.

Preparation of protein: The three dimensional crystal structure of human Aldose reductase complexed with ligand tolrestat ($C_{16}H_{14}F_3NO_3S$) (PDB id: 2FZD) was extracted from the Protein Data Bank (PDB) (Fig. 1). Prior to docking the ligands onto the protein's active site, the protein was prepared using protein preparation wizard of Schrodinger's molecular docking software. During this protein preparation all water molecules and hetero atoms are removed. Hydrogen atoms were added to the protein, including those necessary to define the correct ionization and tautomeric states of amino acid residues such as LEU 15, GLN 59, GLU 60, GLU 64, LYS 85, GLU 126, THR 135, ILE 137, GLN 146, LEU 152, GLY 193, LEU 152, GLY 193, LYS 194,

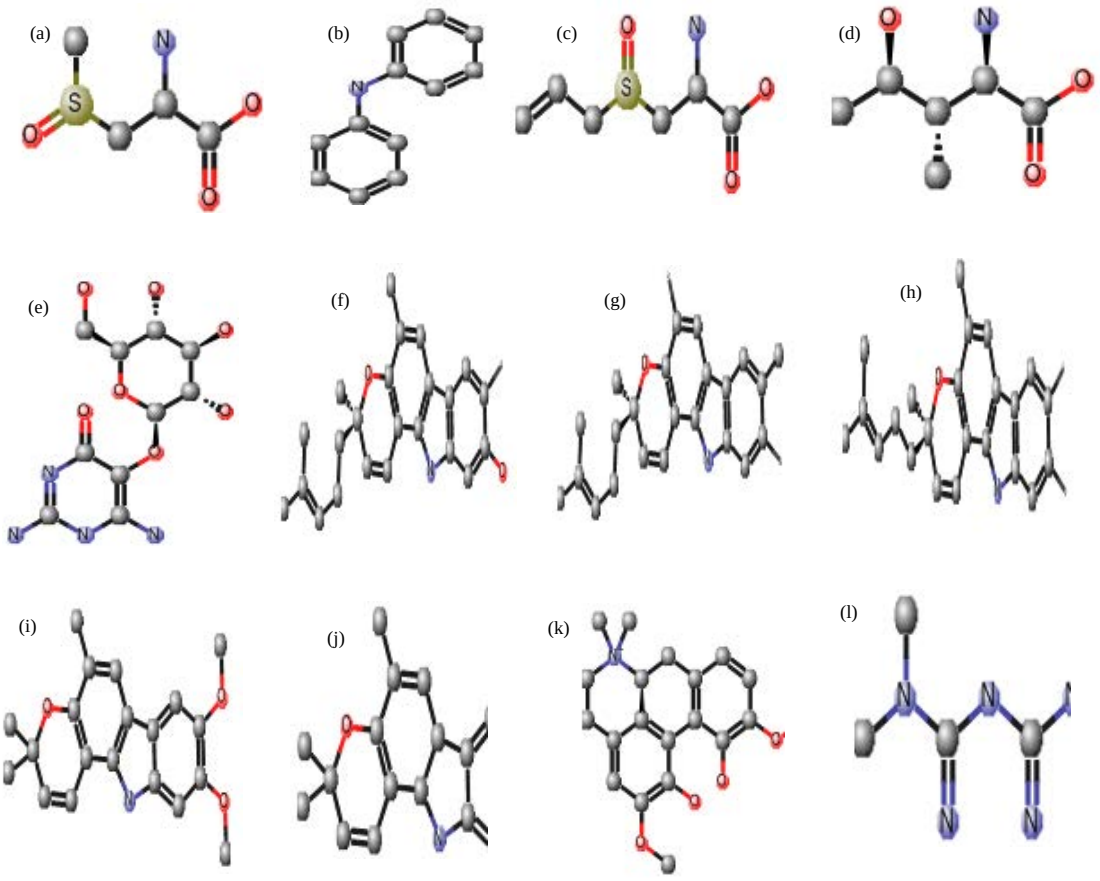

Fig. 1(a-l): 2D structures of the ligands and metformin, (a) S-methyl cysteine sulfoxide, (b) Diphenyl amine, (c) Allin, (d) 4-Hydroxyisoleucine, (e) Vicine, (f) Mahanine, (g) Mahanimbicine (h) Mahanimbine, (i) Koenidine, (j) Girinimbin, (k) Magnoflorine and (l) Metformin

LYS 242, THR 244 and GLN 267. The active site of the protein was defined for generating the grid. The screened ligands were then docked into the prepared grid, for which "standard precision mode" was selected. No constraints were defined.

Molecular docking: Docking was carried out using GLIDE (Grid-Based Ligand Docking with Energies) software. GLIDE searches for favourable interaction between one or more ligand molecules and a receptor molecule. The combination of position and orientation of a ligand relative to receptor, along with its conformation in flexible docking, is referred to as a ligand pose. The ligand pose that GLIDE generates, pass through a series of hierarchical filters that evaluate the ligands interaction with the receptor. The initial filters test the spatial fit of the ligand to define active site and examine the complementarily of ligand-receptor interactions using a grid-based method patterned after the empirical ChemScore function. Poses that pass these initial screens enter the final stage of the algorithm which involves evaluation and minimization of a grid approximation to the OPLS-AA non-bonded ligand-receptor interaction energy. Final scoring is

then carried out on the energy-minimized poses. GLIDE Score is based on the ChemScore but includes a steric clash term and adds buried polar atoms devised by Schrödinger to penalize electrostatic mismatches: G score = 0.065*vd W+0.130* Coul+Lipo+H bond+Bury P+Rot B+Site (Schrodinger Suite, 2011).

These PDB structures were used for docking studies using Hex 6.3 version software. The structure of metformin and vicine complexes was identified via docking and their relative stabilities were evaluated using molecular dynamics and their binding affinities, using free energy simulations.

The parameters used for the docking process were:

- Correlation type-Shape only
- FFT Mode-3D fast lite
- Grid dimension-0.6
- Receptor range-180
- Ligand range-180
- Twist range-360
- Distance range-40

The Metformin and vicine were docked with the receptor aldose reductase using the above parameters.

RESULTS AND DISCUSSION

Plant metabolites like flavonoids, alkaloids, glycosides and β-sitosterol were studied for their potential against the inhibitor PPAR*γ* (Peroxisome Proliferator-Activated Receptor), GLUT-4 (Glucose Transporter-4) and SGLT2 (Sodium Glucose co-Transporter-2) (Annapurna *et al*., 2013). Flavonoids like biochanin, butein, esculatin, fisetin and herbacetin showed excellent binding interactions with aldose reductase using Autodock 4.2 were reported (Madeswaran *et al*., 2012). Cheminformatics serves as a tool in analyzing the mechanism of inhibition of these phytoconstituents against the receptor. There are only few reports on the molecular docking studies of the secondary metabolites like myrcene, citral, geraniol from *C. citrates* against aldose reductase (Saraswathi *et al*., 2011), gymnemagenin of *Gymnema sylvestre* inhibiting the enzyme DPP-IV (Kamble *et al*., 2012) etc., for the treatment of Diabetes mellitus. Molecular modeling study of ten compounds from *Cuminum cyminum* was achieved by GOLD, AutoDock vina, eHiTS, PatchDock and MEDock (Muppalaneni and Rao, 2011). Schrodinger software has been successfully used by Pfizer in synthesizing a new drug molecule. This has been investigated to choose this software for the present study.

The 2D structures of the eleven ligands and metformin are shown in Fig. 1. The physical parameters and LogP values of the molecules from different plant foods viz. s-methyl cysteine sulfoxide and diphenyl amine *(Allium cepa*), Allin (*Allium sativum*), 4-hydroxyisoleucine (*Trigonella foenum-graecum*), vicine (*Momordica charantia*), mahanine, mahanimbicine, mahanimbine, koenidine and girinimbin *(Murraya koeingii*) and magnoflorine (*Tinospora cordiflora*) are given in Table 1.

The docking results (Table 2) revealed compound vicine (Fig. 2), a significant constituent in bitter gourd to have a higher GLIDE score compared to the other compounds and Metformin. Analysis of the structure of vicine reveals a pyrimidine nucleus. Pyrimidine nucleoside is found to induce hypoglycemia in non-diabetic fasting rats by intraperitoneal administration (Raman and Lau, 1996).

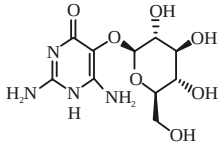

Fig. 2: Structure of vicine

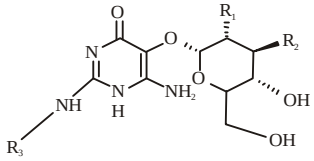

Fig. 3: Structural modification of vicine, R_1 = -OCH_3-ligand M, R_1 = -OCH_3, R_2 = -OCH_3-ligand N, R_1 = -OH, R_2 = -OH, R_3 = -$COCH_3$-ligand O, R_1 = -OH, R_2 = -OH, R_3 = -C_6H_5-ligand P, R_1 = -OH, R_2 = -OH, R_3 = -$C_6H_4NH_2$-ligand Q

Table 1: Physical parameters and LogP values of the selected ligands

Plants	Compounds	Ligand name	Molecular formula	Molar mass (g mol^{-1})	Log P
Allium cepa	s-methyl cysteine sulfoxide	A	$C_4H_9NO_3S$	151.18	-4.27
	Diphenyl amine	B	$C_{12}H_{11}N$	169.22	3.73
Allium sativum	Allin	C	$C_6H_{11}NO_3S$	177.22	0.89
Trigonella foenum-graecum	4-Hydroxyisoleucine	D	$C_6H_{11}NO_3$	147.17	-2.81
Momordica charantia	Vicine	E	$C_{10}H_{16}N_4O_7$	304.25	-4.11
Murraya koeingii	Mahanine	F	$C_{23}H_{25}NO_2$	347.45	5.76
	Mahanimbicine	G	$C_{23}H_{25}NO$	331.45	6.24
	Mahanimbine	H	$C_{23}H_{25}NO$	331.45	6.12
	Koenidine	I	$C_{20}H_{21}NO_3$	323.39	4.15
	Girinimbin	J	$C_{18}H_{17}NO$	263.33	4.42
Tinospora cordiflora	Magnoflorine	K	$C_{20}H_{20}NO_4$	342.40	-1.47
Anti-diabetic drug	Metformin	Z	$C_4H_{11}N_5$	129.16	-2.02

Table 2: GLIDE score and GLIDE energy of eleven ligands and metformin

Ligands	Compounds	GLIDE score (kcal mol^{-1})	GLIDE energy (kcal mol^{-1})
A	S-methyl cysteine sulfoxide	-4.47	-15.12
B	Diphenyl amine	-1.20	-17.02
C	Allin	-1.60	-24.87
D	4-Hydroxyisoleucine	-5.37	-16.06
E	Vicine	-6.64	-35.89
F	Mahanine	-1.19	-17.02
G	Mahanimbicine	-2.70	-20.20
H	Mahanimbine	-0.30	-24.28
I	Koenidine	-0.90	-26.64
J	Girinimbin	-2.70	-27.48
K	Magnoflorine	-3.70	-29.71
Z	Metformin	-5.69	-17.36

Mulling over the structure-activity of the pyrimidine nucleus, the structure of vicine was modified by replacing the -OH and -NH_2 groups with different functional groups (Fig. 3). Replacement of -OH groups by methoxy groups (ligand M, N) and substitution of acetyl, phenyl and primary amine groups to the -NH_2 position (ligand O, P and Q), respectively are expected to yield high GLIDE score than the parent compound. But the substituted structures possess low GLIDE score than the vicine. This may be due to the bulkiness of the substituted groups which create a barrier in docked pose of the proposed ligands. The substituted structure of vicine may not have

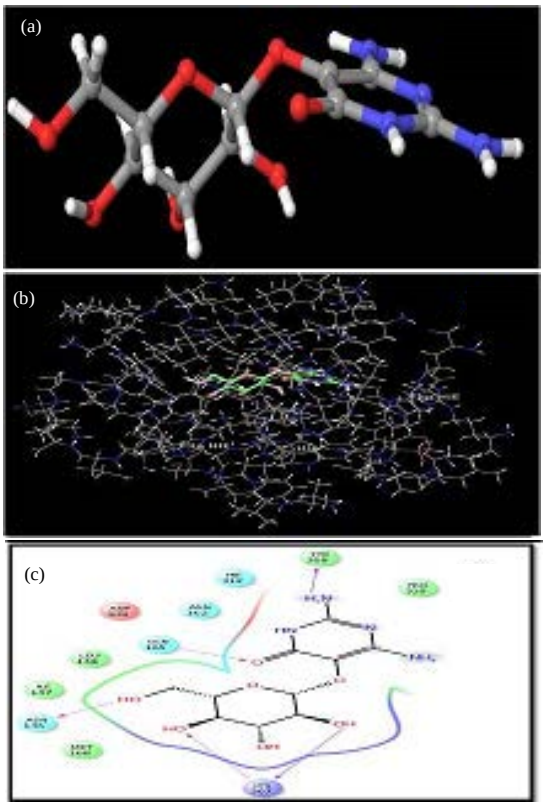

Fig. 4(a-c): (a) 3D structure, (b) Docked poses and (c) 2D interactions of vicine with protein-aldose reductase

Table 3: GLIDE Score and GLIDE Energy of modified structure of vicine

Ligands	GLIDE score (kcal mol^{-1})	GLIDE energy (kcal mol^{-1})
M	-4.00	-29.71
N	-6.00	-35.26
O	-5.25	-38.07
P	-5.14	-29.25
Q	-4.26	-36.44

exactly fitted into the pocket of the receptor aldose reductase. The replacement of adjacent -OH groups by -OCH_3 (ligand N) gave similar GLIDE score of 6.0 (Table 3).

The high GLIDE score of 6.6 for vicine results from the better docked poses of the ligand with the receptor. The 3D structure, 2D interactions and docked poses of vicine with the receptor aldose reductase are shown in Fig. 4. From Fig. 4b, it is clearly shown that there is good interaction between the protein and ligand molecule. The 2D interactions (Fig. 4c) revealed the amino acids like LYS 307 and ASN 136 to interact with the ligand through co-ordinate bonding with the hydroxyl groups. The free primary amine group (-NH_2) gets coordinated to the amino acid TYR 309 and the carbonyl group to GLN 165 by Vander Waal forces. This has given a better docking pose resulting in high GLIDE score. The GLIDE score and GLIDE energy of eleven ligands and metformin are given in Table 2. The proposed inhibitor might be more effective since it simulates the residual interaction with the respective residues like Asn 136, GLN 165, LYS 307 and TYR 309 by satisfying the properties of Lipinski's rule of 5.

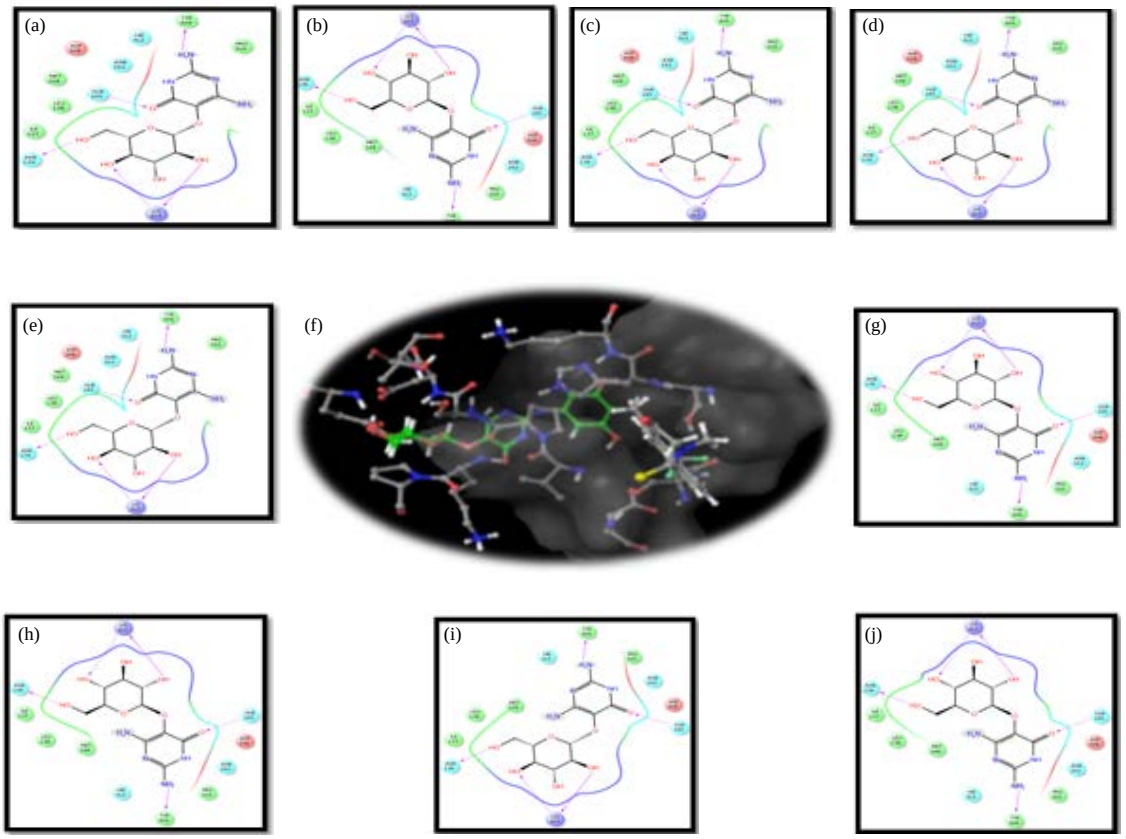

Fig. 5(a-j): Two dimensional interactions of the nine isomers of vicine with G score, (a) G score = -6.64, (b) G score = -6.52, (c) G score = -6.44, (d) G score = -6.52, (e) G score = -6.64, (f) Vicine with G score, (g) G score = -6.46, (h) G score = -6.52, (i) G score = -6.41 and (j) G score = -6.61

In some cases, the drug efficacy depends on the percentage of isomers generated from the parent compound. Enantiomers of Thalidomide had conflicting drug activity and hence banned in 1961. The nature and activity of the drug may change according to the isomers. Hence the possible isomers were generated for vicine to find out the efficacy of the drug against aldose reductase. The nine isomers of vicine with similar GLIDE score of 6.4-6.6 revealed that the interactions with protein molecule would be the same and small variation in the docking score may be attributed to the change in the plane of axis and rotation of the ligands. The Two dimensional interactions of the nine isomers of vicine with Gscore and the docked pose for the high GLIDE score is shown in Fig. 5.

The docking results of metformin and vicine using Hex 6.3 software showed an increase in the energy values (-136.32) which means metformin was more compatible with the receptor than the vicine (134.20). However, the binding site of vicine was similar to that of metformin which means that functional groups involved were the same and only the steric compatibility leads to the decreased energy values. This indicates that the docking was not flexible to give better docking pose with high energy score.

The modes of interaction of ligands with receptor vary depending on the functional groups and structure of the ligands. Traditionally used plants may provide lead compounds that can be exploited in drug discovery. Maestro provides flexible docking and also superior to Hex 6.3 internet software. Hence the use of docking software may cut down million and millions of rupees involved in the preliminary wet lab studies.

CONCLUSION

In silico studies of eleven ligands revealed that the glycoalkaloids (vicine) possess good GLIDE score against the receptor aldose reductase comparable with that of standard drug metformin for the treatment of Type-2 Diabetes mellitus. Flexible docking of Schrodinger software was found to be more advantageous than other internet freeware.

ACKNOWLEDGMENTS

The authors are grateful to Avinashilingam Institute for Home Science and Higher Education for Women University, Coimbatore-43 for providing research facilities and special thanks to the Department of Biochemistry, Biotechnology and Bioinformatics of University, for providing access to GLIDE software.

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