WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 6, Issue 11, 1034-1051. Research Article ISSN 2277– 7105

# ANALYSIS AND EVALUATION OF A POTENTIAL LIGAND ON SULFONYLUREA RECEPTOR (SUR1) FOR TREATMENT OF DIABETES MELLITUS TYPE (II) EMPLOYING MOLECULAR SIMULATIONS

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Article Received on
07 August 2017,
Revised on 27 August 2017,
Accepted on 17 Sep. 2017
DOI: 10.20959/wjpr201711-9735

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## ABSTRACT

Nowadays most of the drugs used in the treatment of type-2 diabetes target the sulfonylurea receptor stimulating insulin release. Targeting sulfonylurea may provide an important help for the development of drugs against type-2 diabetes. However, absence of tertiary structure of sulfonylurea limits the possibilities of structure based drug designing. In the present work, we have explored the 3D structure of sulfonylurea receptor using homology approach and in silico ADME (absorption, distribution, metabolism and excretion) predictions. Based on the active sites we have screened the glibenclamide [*IUPAC name: 5-chloro-N-(4-[N-(cyclohexylcarbamoyl)sulfamoyl]phenethyl)-2-methoxybenzamide*] inhibitor as well as our proposed ligand molecule [*IUPAC name: N-(cyclohexylcarbamoyl)-3-[(7-imino-1-oxo-4,7- dihydro-1H-inden-4-yl)methyl]-benzenesulfonamide*] against modeled protein using different docking programmes and ADME predictions are also done for understanding the pharmacokinetic properties. The proposed ligand molecule [*IUPAC name: N- (cyclohexylcarbamoyl)-3-[(7-imino-1-oxo-4,7-dihydro-1H-inden-4-yl)methyl] benzenesulfonamide*] shows better binding efficiency with greater binding energy, BE=-7.98. It binds with 3 hydrogen bonds with the receptor protein, heat of formation is also greater (Hf=- 73.476) also having greater aqueous solubility (Log S=-3.44), partition coefficient is lowered (cLog P=2.79), topological surface area, (TPSA=116.19) is increased, all these values support that the proposed ligand is highly efficient and potent for treatment of diabetes mellitus type (II) than the present drug- glibenclamide [*IUPAC name: 5-chloro-N-(4-[N- (cyclohexylcarbamoyl)sulfamoyl]phenethyl)-2-methoxybenzamide*].

**KEYWORDS:** Glibenclamide, Docking, ADME, Type-2 diabetes.

## INTRODUCTION

Diabetes (type-2) is a chronic disorder affecting millions of diabetic patients all over the world and today India leads the world with the largest number of diabetics. The disease is associated with long-term dysfunction, damage and failure of various organs, therefore it affects almost every physiological system of the body.

The Management of diabetes mellitus (Type II) is one of the biggest challenge all over the world[1-2] including India where it is estimated that 19.4 million individuals are affected by the non-insulin dependent diabetes mellitus (NIDDM), which is likely to go up to 57.2 million by the year 2025.[3] India leads the world today with the largest number of diabetics in any given country. In the 1970s, the prevalence of the diabetes among the urban Indians was reported to be 2.1 percent, which has now risen to about 12.1 percent. Moreover there is an equally large pool of individuals with impaired glucose tolerance (IGT). Many of them may eventually develop NIDDM with furtherance of the disease.[3]

Diabetes mellitus type 2 represents the final stage of a chronic and progressive syndrome representing a heterogeneous disorder caused by various combinations of insulin resistance and decreased pancreatic-cell function caused by both genetic and acquired abnormalities.[1–8] Currently, type 2 diabetes mellitus is diagnosed when the underlying metabolic abnormalities consisting of insulin resistance and decreased-cell function cause elevation of plasma glucose above 126 mg/dl (7 mmol/liter) in the fasting state and/or above 200 mg/dl (11.1 mmol/liter) 120 min after a 75-g glucose load.[7] However, the fact that many newly diagnosed type 2 diabetic subjects already suffer from the so called “late complications of diabetes” at the time of diagnosis[9] indicates that the diagnosis may have been delayed and in addition, that the pre- diabetic condition is harmful to human health and requires increased awareness of the general public.

β -Cell dysfunction is initially characterized by impairment in the first phase of insulin secretion during glucose stimulation and may antedate the onset of glucose intolerance in type 2 diabetes.[10] Initiation of the insulin response depends upon the trans-membranous transport of glucose and coupling of glucose to the glucose sensor. The glucose/glucose sensor complex then induces an increase in glucokinase by stabilizing the protein and impairing its degradation. The induction of glucokinase serves as the first step in linking

intermediary metabolism with the insulin secretory apparatus. Glucose transport in cells of type-2 diabetes patients appears to be greatly reduced, thus shifting the control point for insulin secretion from glucokinase to the glucose transport system.[11] This defect is greatly improved by the sulfonylureas.[12,13]

Sulfonylureas are drugs that stimulate secretion of insulin from the pancreatic -cells[14] and are therefore used extensively in the treatment of type-2 diabetes. It is well established that sulfonylureas stimulate insulin release by interacting with the high-affinity 140-kDa SUR-1 protein of the ATP-regulated $K^+$ channel at the cytoplasmic leaflet of the plasma membrane. This interaction closes the channel, causing membrane depolarization, the opening of voltage-gated L- type $Ca^{2+}$ channels, an increase in cytoplasmic-free $Ca^{2+}$ concentration and the activation of the secretory machinery. Sulfonylureas also stimulate insulin exocytosis by directly interacting with the secretory machinery and not via closure of the plasma membrane ATP-regulated $K^+$ channel.[15] This effect may constitute part of the therapeutic benefits of sulfonylureas and contribute to their hypoglycemic action in diabetes.

Nevertheless, studies have clearly demonstrated that the second-generation sulfonylurea glibenclamide accumulates progressively in the β-cell. Moreover, autoradiography studies have shown that sulfonylureas are internalized by the β -cell and bind to intracellular sites such as secretory granules.[16-17]

Glibenclamide is a second-generation sulphonylurea which has been widely used in the management of non-insulin dependent diabetes mellitus in Europe since 1969 and in the United States since 1984, where it is known as glyburide.[18] Many aspects of its clinical pharmacology remain incompletely characterised. Recent reports have emphasised the danger of hypoglycaemia with glibenclamide, even at low dose, especially in the elderly people.[19] Drug interactions and impaired renal function are suspected to contribute to hypoglycaemic episodes, but little is known about their effect on glibenclamide pharmacokinetics.[20] These problems and the lack of understanding of the dose-response relationship for the drug, complicate the clinical use of the drug. A number of reports have drawn attention to inter-individual variations in absorption, steady state circulating concentrations and elimination rates, features that have been also noted with other sulphonylureas.[18] The effect of food on the bioavailability of glibenclamide is unclear, some reports report no effect[21], whilst others demonstrate distinct alterations in drug absorption.

## MATERIALS AND METHODS

All computations and molecular modeling were carried out on the IBM Workstation with Fedora 7 operating system using MODELLER9v8, Autodock4.0, iGEMDOCK and Molegro Virtual Docker (MVD2012.5.5 version) and GROMACS 4.0.1 package.

### *Sequence alignment and molecular modeling of SUR-1 Receptor*

The protein sequence of Sulfonylurea receptor (SUR-1) in fasta format was obtained from the NCBI database.[22] (Accession No. AAB02278). Protein-BLAST algorithm[23] against Protein DataBank[24] was carried out for the sequence homology search, in order to identify homologous sequences with known 3-D structure. Blast-p (protein query–protein database) program was run with BLOSUM62 as a scoring matrix[25], word size 3, gap penalty of 11 and gap extension penalty of 1. High resolution crystal structure of homologous protein as a template was considered for homology modeling. The Blast-p alignments were further refined by using Clustal *W* 2.0.10 program[26] with default parameters. The sequence and 3D structure of template protein were extracted from the PDB database. Crystal structure of ATP-binding cassette (ABC)-transporter haemolysin (Hly)B (PDB ID: 2FF7.A)[27] was obtained as the best hit amongst 39 hits according to its sequence identity score, lowest E-value and highest resolution. The 3D structure of SUR-1 receptor was generated by MODELLER 9v8[28] and SWISS-MODEL server.[29] Homology modeling of SUR-1 receptor was performed in the following steps: template selection from Protein Data Bank (PDB), sequence-template alignment, model building, model refinement and validation.[30]

### *Protein Structure validation*

MODELLER generated several preliminary models which were ranked based on their DOPE scores. Some models having low DOPE score were selected and stereo-chemical property of each models was assessed by PROCHECK.[31] This server has been used for the validation of modeled SUR-1 receptor structure. PROCHECK analysis of the model was done to check whether the residues are falling in the most favored region in the Ramachandran's plot or not. The model with the least number of residues in the disallowed region was selected for further studies. Quality of models was evaluated with respect to energy and stereochemical geometry. ProSA-Web server[32] was used to evaluate energy and Verify 3D[33] to evaluate the local compatibility of the model related to good protein structure.

PROCHECK analysis of the modeled protein showed that 94.17% of the residues were found in allowed regions of Ramachandran plot (Fig. 1, Table 1). Among the 355 residues 270 residues found in most favored region, 25 in additional allowed region, 3 in generously allowed region and 1 residue in prohibited region. The statistical score of the Ramachandran plot shows that 90.3% are in the most favored region, 8.4% in additional allowed region, 1.0% in generously allowed region and 0.3% in prohibited region. The above results indicate that the protein model is reliable (Table: 2). Verify 3D score profile access the quality of the model. Verify 3D profile of the modeled protein, residues have an averaged 3D-1D score greater than zero should be considered reliable. The computability score for all the residues in the modeled protein are above zero.

**Preparation of Ligand**

According to the several studies, it is found that Sulfonylurea is the basic drug which helps to stimulate β-cells to synthesize insulin for the treatment of Diabetes Mellitus Type II.

It was found that several Drugs like Glibenclamide, Glimepiride, Gliclazide etc. are the drugs which are based on sulfonylurea compound used for Diabetes Mellitus Type II disease.

Keeping this study in mind the structure of new proposed ligand has been prepared on the base of Sulfonylurea, similarly as the other drugs has been made.

Such structure (Fig. 2 and Fig. 3) has been drawn with the help of ACD LABS Chem Sketch software (34-37) which is then converted into pdb file with the help of a converter Open Bable.

The properties of ligand has been calculated both with the help of off-line tools as well as on-line webserver such as ACD LABS Chemsketch, MOPAC 2012 (semiempirical PM7 calculations) which are listed in table 2.

**Molecular Docking**

Molecular docking was performed on SUR-1receptor with Glibenclamide and new proposed Ligand using different docking programmes- AutoDock 4.0[38], iGEMDOCK[39] and Molegro Virtual Docker (MVD2012.5.5 version).[40]

***Semiempirical Molecular dynamics Studies***

The semiempirical molecular dynamic studies of both Glibenclamide and the new ligand proposed have been done using semiempirical quantum chemistry package MOPAC 2012 PM7.[41-42]

***RESULTS AND DISCUSSION HOMOLOGY MODELING OF SUR-1***

The SUR-1 has (Accession No. AAB02278) is 1581 amino acids long and shows structural similarity with the crystal structure of ATP-binding cassette (ABC)-transporter haemolysin (Hly)B (PDB ID: 2FF7.A). ATP-binding cassette (ABC)-transporter haemolysin (Hly)B was selected as a template on the basis of lowest e-value (0.00e-1) and maximum identity (45.5%) (Data shown in table 3). MODELLER 9v8 was used to generate the homology model of SUR-1 according to the crystal structure of 2FF7.A. In total five models were generated and the discrete optimize potential energy (DOPE) was calculated using "model-single.top" script. The model no. 3 (PBP.B99990003.pdb) having maximum score was consider as a best model of SUR1. Pymol software was used to visualize the model to find out the maximum numbers of helixes, turns and sheets in the protein.

***Molecular Docking Analysis***

The two dimensional structure of glibenclamide were taken from pubchem server[43] of NCBI and converted it into 3D coordinate *via* CORINA server.

The ligand was docked against modeled protein via mentioned Autodock docking software. The Lamarkian genetic algorithm[44] was used in AutoDock to perform the automated molecular dockings. Default parameters were used except number of runs. The docking of ligand with SUR-1 receptor was performed in two steps. In the preliminary step, docking was performed to identify the potential binding sites on SUR-1 receptor and in the second step of docking, whole surface of protein was covered with very large grid maps, created by AutoGrid. The X, Y, Z dimensions of the grid were set to 72 Å with grid points separated by 0.375 Å.

The interaction of these Ligands with modeled protein was selected on the basis of binding energy, intermolecular energy, inhibition constant and Hydrogen bonding interaction. These values along with the hydrogen bond forming residues are presented in table 4. The Ligand that shows smaller dissociation constant and higher binding energy,

intermolecular energy with SUR- 1 receptor, was considered to be a better drug. The new proposed ligand was bound on the active amino acid LYS-1384, THR-1508, GLN-1426 of SUR-1 receptor and 3 hydrogen bond was formed with -7.98 Kcal/mol binding energy and 246.08 μM inhibition constant (Fig. 4). While the Glibenclamide Ligand was bound on the active amino acid THR-1508, GLN-1426 of SUR-1 receptor and 2-hydrogen bond was formed with -4.86 Kcal/mol binding energy and 274.47 μM inhibition constant. The new ligand proposed was found to be the most potent Drug against the SUR-1 receptor amongst Glibenclamide used drug molecules in this study.

Another reason for better performance of the proposed ligand is that it does not contain any toxic element-Chlorine (Cl) as the Glibenclamide have and it follows the "Lipinski's rule of five for drug likeness". This is the reason that Proposed Ligand does not show any toxicity. Our data revealed that the new ligand proposed was found to be the best antibiotic against Diabetes Mellitus Type-II.

Again for checking the Autodock results, docking was performed with iGEMDOCK for the molecular docking analysis of SUR-1 receptor with Glibenclamide and New Proposed Ligand. iGEMDOCK is a suite of automated docking/screening tools. The interface of iGEMDOCK has two main tags, docking/screening tag and post-analyzing tag. The docking/screening tag is designed to predict how chemical molecules bind to a receptor of known 3D structure. The predicted protein-ligand poses can be further analyzed in the post-analyzing tag. This helps to explore better binders. The architecture of iGEMDOCK consists of four major modules. The docking/screening and post-analyzing modules contain several components to make the screening/analyzing procedure smoothly. The predicted or clustered protein-ligand complexes can be visualized in the visualization module. The parallel processing module provides the parallel computation of screening jobs.

Molecular docking was performed on SUR-1 receptor with Glibenclamide and New Proposed Ligand using iGEMDOCK. The interaction of these Ligands with modeled protein was selected on the basis of binding energy, Van der Waals force and Hydrogen bonding interaction. These values along with the hydrogen bond energy are presented in table 4.

The Ligand showing higher binding energy, intermolecular energy with SUR-1 receptor, was considered to be a better drug. The New Proposed Ligand was bound on the SUR-1 receptor

with -110.515 Kcal/mol binding energy. While the Glibenclamide Ligand was bound on the SUR-1 receptor with -94.2688 Kcal/mol binding energy. New Proposed Ligand was found to be the most potent Drug against the SUR-1 receptor amongst Glibenclamide used drug molecules in this study. The molecular docking studies performed using Igemdock shown in table 4 evidently describes the good correlation between ligand molecules to modeled protein of SUR-1 receptor. Our data revealed that the New Proposed Drug was found to be the best antibiotic against Diabetes Mellitus Type-II.

Similarly Molecular Docking was also performed with Molegro Virtual Docker. The MVD2012.5.5 version used for calculating the MolDock score of SUR-1 receptor with Glibenclamide and New Proposed Ligand. The docking of ligand with SUR-1 receptor was performed in two steps. In the preliminary step, docking was performed to identify the potential binding sites on SUR-1 receptor and in the second step of docking, whole surface of protein were covered with very large grid maps, created by MolGrid. The dimensions of the grid resolution were set to 0.30 Å. The center of grid dimension was set to X=264.44, Y=117.85, Z=-91.02 with the Radius=9. The number of runs was set to be 10 with the other as default. The interaction of these Ligands with modeled protein was selected on the basis of binding energy are shown in table 4.

The Ligand showing higher binding energy with SUR-1 receptor, was considered to be a better drug. The New Proposed Ligand was bound on the SUR-1 receptor with -33.2641 Kcal/mol binding energy. While the Glibenclamide Ligand was bound on the SUR-1 receptor with –22.4152 Kcal/mol binding energy. New Proposed Ligand was found to be the most potent Drug against the SUR-1 receptor amongst Glibenclamide used drug molecules in this study. The values of molecular docking studies performed and presented, evidently describes the good correlation between ligand molecules to modeled protein of SUR-1 receptor. Our data revealed that the New Proposed Drug was found to be the best antibiotic against Diabetes Mellitus Type- II.

***Semiempirical Molecular dynamics Studies***

After applying Merck Molecular Force Field (MMFF), in 500 steps, 10e-7 convergence using Steepest Descent algorithm semiempirical PM7 calculations have been done, the results obtained have been shown in table 2.

On the basis of above table 2 it is clear that the heat of formation in case of the new ligand is greater than the heat of formation in the case of the patented drug/ligand-Glibenclamide. Thus the new ligand is more stable and potent than Glibenclamide as it is also clear from the total energy, ionization potential, etc given in the table 2.

The result of the above experiment shows that the Proposed Ligand [*IUPAC name: N- (cyclohexylcarbamoyl)-3-[(7-imino-1-oxo-4,7-dihydro-1H-inden-4-yl)methyl]-benzenesulfonamide*] has high binding affinity as compared with Glibenclamide on the basis of binding energy, intermolecular energy, inhibition constant and Hydrogen bonding interaction. The New Proposed Ligand was bound on the active amino acid LYS-1384, THR-1508, GLN- 1426 of SUR-1 receptor and 3 hydrogen bond while the Glibenclamide was bound on the active amino acid THR-1508, GLN-1426 of SUR-1 receptor and 2 hydrogen bond. Based on this, it can be concluded that the new proposed ligand have higher binding affinity with the receptor than the Glibenclamide. This shows that the Proposed Ligand works much better than the Glibenclamide over the SUR1 receptor.

***Figures***

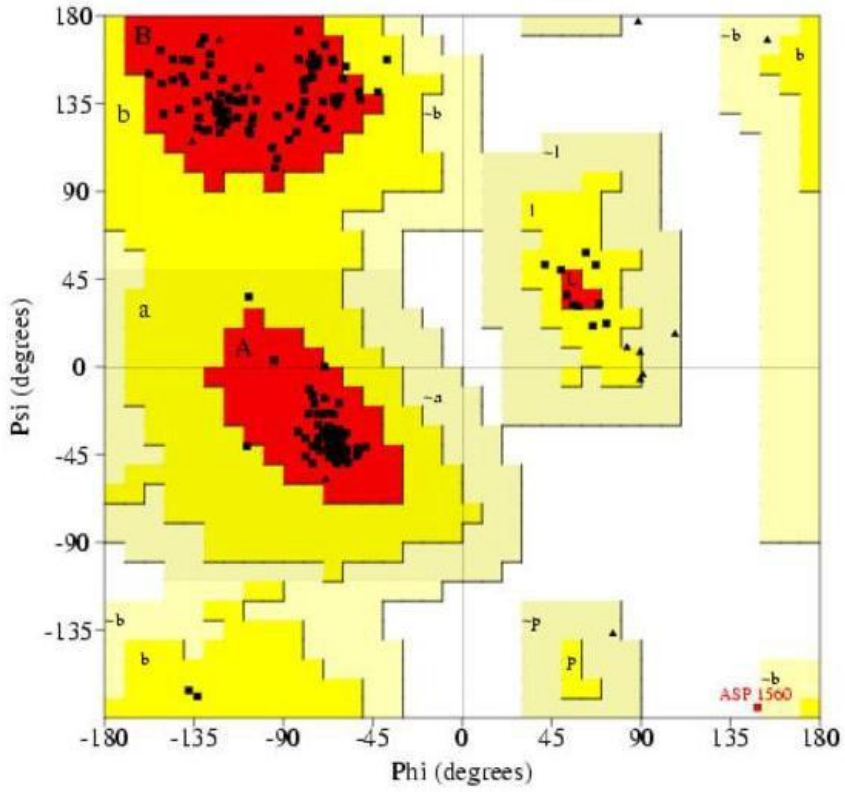


**Fig. 1.**

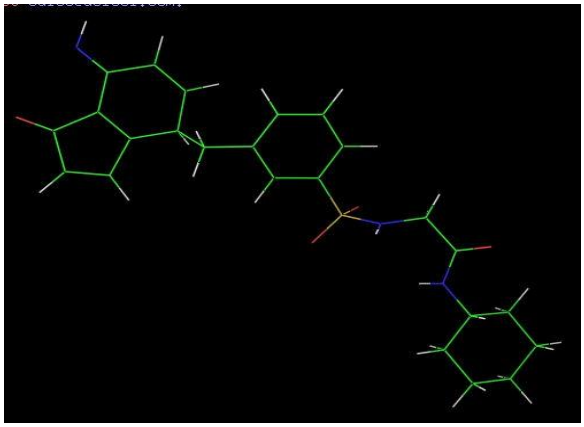

**Fig. 2.**

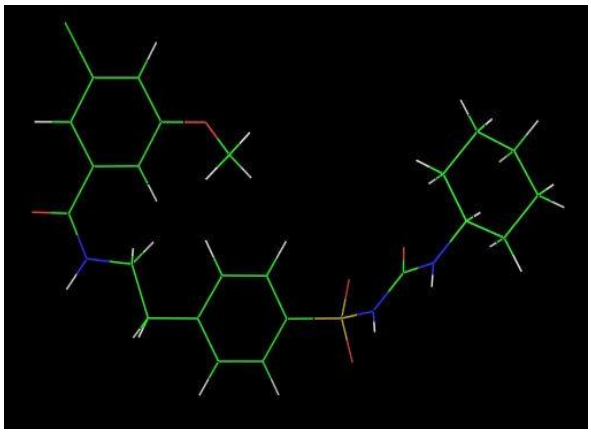

**Fig. 3.**

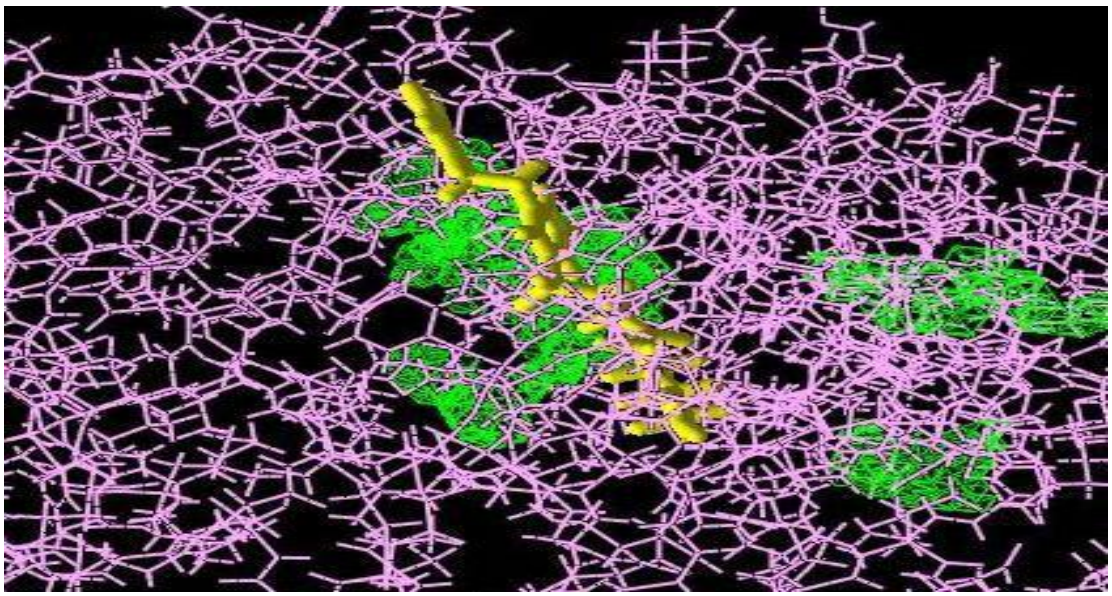

**Fig. 4.**

***Figure captions:***

**Fig. 1: Ramachandran's map of SUR1 of *Homo sapience.***

**Fig. 2: 3-D Structure of Proposed Ligand Fig. 3: 3-D Structure of Glibenclamide.**

**Fig. 4: The interaction of high affinity potent new proposed ligand with SUR-1 receptor of Diabetes Mellitus Type-II.**

**Table 1.**

| S. No. | Ramachandran Plot statistics | Modeled Protein | Template |
|---|---|---|---|
| **1** | % Amino acid in most favored regions | 93.1 | 93.9 |
| **2** | % Amino acid in additional allowed regions | 14.0 | 12.0 |
| **3** | % Amino acid in generously allowed regions | 0.0 | 2.0 |
| **4** | % Amino acid in prohibited regions | 1.0 | 0.0 |

**Table 2.**

| S. No. | Properties | Properties of Glibenclamide | Properties of New Proposed Ligand |
|---|---|---|---|
| **1.** | Molecular Formula | $C_{23}H_{28}ClN_3O_5S$ | $C_{23}H_{25}N_3O_4S$ |
| **2.** | Formula Weight | 494.004 | 439.527 |
| **3.** | Composition | C (55.920%), H (5.710%), Cl (7.180%), N (8.510%), O (16.190%), S (6.490%) | C (62.850%). H (5.730%), N (9.560%), O (14.560%), S (7.300%) |
| **4.** | Molar Refractivity | 126.900$cm^3$ | 117.830 $cm^3$ |
| **5.** | Molar Volume | 362.900$cm^3$ | 309.500 $cm^3$ |
| **6.** | Parachor | 1015.300$cm^3$ | 862.300 $cm^3$ |
| **7.** | Index of Refraction | 1.616 | 1.686 |
| **8.** | Surface Tension | 61.200 dyne/cm | 60.200 dyne/cm |
| **9.** | Density | 1.360 $g/cm^3$ | 1.410 $g/cm^3$ |
| **10.** | Polarizability | 50.300 $cm^3$ | 46.710 $cm^3$ |
| **11.** | Monoisotopic Mass | 493.144 Da | 439.157 Da |
| **12.** | Nominal Mass | 493 Da | 439 Da |
| **13.** | cLog P | 3.990 | 2.790 |
| **14.** | Log S | -5.400 | -3.440 |
| **15.** | TPSA | 113.600 | 116.190 |
| **16.** | Heat of formation | -200.752 KCal/Mol =-839.94663 KJ/Mol | -73.476 KCal/Mol =-307.424 KJ/Mol |
| **17.** | Total energy | -5683.203 EV | -5077.938 EV |
| **18.** | Electronic energy | -52650.766 EV | -43156.966 EV |
| **19.** | Core-core repulsion | 46967.564 EV | 38079.028 EV |
| **20.** | Dipole | 8.291 Debye | 3.773 Debye |
| **21.** | No. of filled levels | 89 | 81 |
| **22.** | Ionization potential | 9.268 EV | 9.682 EV |
| **23.** | HOMO LUMO energies (EV) | -9.268 -0.588 | -9.682 -1.864 |

**Table 3.**

| S. No. | Model predicted through MODELLER | DOPE score KJmol$^{-1}$ | Overall quality factor ERRAT |
|---|---|---|---|
| **1.** | PBP.99990001 | -12225.373 | 78.710 |
| **2.** | PBP.99990002 | -12225.373 | 78.710 |
| **3.** | PBP.99990003 | **-20151.761** | **93.562** |
| **4.** | PBP.99990004 | -20016.876 | 91.953 |
| **5.** | PBP.99990005 | -20128.563 | 92.392 |

**Table 4.**

**The interaction energies (Kcal/mol) of SUR-1 receptor and Ligands obtained from the molecular docking using:**

| Autodock | | | iGEMDOCK | | | | Molegro Virtual Docker | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Ligands** | **Binding Energy (BE)** | **Inter- moleculear Energy (Kcal/mol)** | **Inhibition constant (Ki) µM** | **Ligand Efficiency** | **Hydrogen Bonds** | **Residues** | **Total Energy** | **VDW** | **H Bond** | **Aver Con Pair** | **Mol Dock SE** | **Rerank Score** |
| **Glibenclamide** | -4.860 | -7.250 | 274.470 | -0.150 | 2 | THR-1508 GLN-1426 | -110.515 | -110.515 | -24.500 | 34.129 | -33.264 | 9.277 |
| **New Proposed** | -7.980 | -7.270 | 264.080 | -0.150 | 3 | LYS-1384 | -94.269 | -94.2688 | -16.900 | 20.424 | -22.415 | 12.671 |

## CONCLUSIONS

In the present study, we built the 3 D structure of SUR-1 using homology modeling. The protein structure taken for this study was verified for its quality. The two Ligands namely Glibenclamide [*IUPACname:5-chloro-N-(4-[N-(cyclohexylcarbamoyl)sulfamoyl]phenethyl)-2- methoxybenzamide*] and the new proposed ligand [*IUPAC name: N-(cyclohexylcarbamoyl)-3- [(7-imino-1-oxo-4,7-dihydro-1H-inden-4-yl)methyl]-benzenesulfonamide*] were designed for the studies, and used for binding with SUR-1 receptor. Top ranked docking analysis and in silico ADME calculations reveal that, new proposed ligand binds at the active sites with higher binding energy and lower inhibition constant. The best docking confirmation shows residues LYS-1384, THR-1508 and GLN-1426 are involved in new proposed ligand binding with 3 hydrogen bonds. On the basis of binding energy that is -7.98, cLog P =2.79, molecular weight=439.527, aqueous solubility that is Log S=-3.44, topological surface area, TPSA=116.19, heat of formation Hf=-73.476, it can be said that the new ligand designed and proposed has been found to be the optimum and most effective inhibitor against Diabetes Mellitus Type-II. This information will be very helpful for the new drug designing against Diabetes Mellitus Type-II.

The results obtained in this paper suggests that attempts to synthesize this new drug molecule proposed and determination of its clinical parameters including its efficacy and cytotoxicity and invivo testing may be of significant importance.

### Conflict of Interest

The authors declared no conflict of interest.

## ACKNOWLEDGEMENT

The authors gratefully acknowledge the Department of Chemistry, University of Allahabad, Allahabad for their support.

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