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HOMOLOGY MODELING AND MOLECULAR DOCKING STUDY OF BIOLOGICALLY ACTIVE LIGAND AND SYNTHESIS, CHARACTERIZATION AND INVITRO STUDY OF DERIVATIVES OF METOPROLOL SUCCINATE.

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Abstract: Beta-1 adrenergic receptor (ADRB1_HUMAN) an enzyme plays a critical role in central to the overall regulation of cardiac function. The latest clinical β-blocker trials Beta-1 adrenergic receptor (β1AR) have been shown to play an important role in cardiac disease and heart failure in particular. Metoprolol succinate is essentially useful in the treatment of chest pain. In the present work Metoprolol succinate Complexes has been prepared with transition metals viz; Cu(II), Zn(II), Co(II), Ni(II) and those checked for homology modeling and molecular docking is done for metoprolol succinate. The Metoprolol succinate base inhibitors towards Beta-1 adrenergic receptor (β1AR) is unknown. Hence, the structural bioinformatics study of Beta-1 adrenergic receptor (β1AR) enzyme from human was carried out using homology modeling and molecular docking techniques. The 3D model of Beta-1 adrenergic receptor (β1AR) protein of Homo sapiens were designed using the templet (PDB ID: 2RH1) in Modeller V9.24. The validation of generated model was obtained using several validation methods including Procheck, PROSA, QMean, Errat and Verify3D. The stereo chemical properties of the targeted protein model were validated by using the Ramachandran plot with Procheck server. Towards this end, molecular docking was performed with β1AR and Metoprolol succinate using AutoDock software and Pharmacophore Mapping has been conducted using Accelrys Discovery Studio (DS) to extract a 3D pharmacophore that reflects the important functional groups that are essential for inhibitor binding. This homology modeling and docking study provides clear understanding of β1AR structure and metoprolol succinate, its binding mechanism, thus help in providing the remedial solutions of cardiovascular disease and heart failure caused by malfunctioning of the target protein.

Keywords: **Metoprolol succinate, Homology modeling, Complexes, molecular docking, gout, antimicrobial activity, IR.**

1. INTRODUCTION

Metals have an important place in medicinal chemistry. They have been used in the treatments of diseases since ancient's time. In the list of metals, transitions metals are identified to play very important role in biological processes in the human body. Metal ions influences in the complex form, particularly when the metal is necessary for human body. Complex with the drug as discovery of novel compounds having extra antioxidant, antimicrobial, anti-inflammatory actions [1]. Transition metal complex show a broad application area in antimicrobial activities. When a drug enters the blood stream it binds to plasmatic proteins, namely serum albumin and glycoproteins. This drug–protein binding is reversible in nature in which an equilibrium exists between the bound and free drug molecule. Only the unbound fraction of the drug shows its therapeutic effects in the body. The degree of protein binding varies from drug to drug. The protein binding tendency of a drug is considered to be the most significant factor when its pharmaceutical action is evaluated, as drug efficiency is affected by the degree to which it binds to serum proteins [2]. If drug-binding affinity towards serum protein is weak, then the drug will be metabolized and excreted from the body very quickly, so its therapeutic effect will be low. If the binding affinity of a drug is high then its retention time in the body will be high. This situation results in its toxicity and undesired side effects [3]. So, investigations on drug–protein binding help to determine the rate of absorption, distribution, metabolism and excretion of the drug in the body and to improve drug efficacy for better therapeutic effects.[4] Metoprolol succinate (MS), chemically known as (RS)-1-(isopropyl amino)-3-[4-(2-methoxyethyl)phenoxy]propan-2-ol succinate is a β1-selective (cardioselective) adrenoceptor blocker [5]. It is extensively used in the treatment of hypertension, angina

pectoris, arrhythmia, myocardial infarction, congestive heart failure and also in the prevention of migraine headaches [8]. MS lowers the risk of heart attack by reducing the antagonistic effect of catecholamines on the heart that are released during physical and mental stresses [6]. Due to its selectivity in blocking the β1 receptors in the heart, metoprolol is also prescribed for off-label use in performance anxiety, social anxiety disorder, and other anxiety disorders. As with other pharmaceutical drugs, MS also has some common side effects that include trouble sleeping, tired- ness, abdominal discomfort, abnormally low blood pressure, depression, dizzy and slow heartbeat [7].

2. MATERIALS AND METHODS

2.1 Sequence retrieval and Template selection:

The experimental crystal structure of β1AR of Human is not available in the Protein Data Bank (PDB); hence, its 3D structure was modelled. [8] The protein ID of the target (Beta-1 adrenergic receptor *Homo sapiens*) was retrieved from UniProt Knowledgebase (UniProtKB) [9] with the accession number P08588. Afterwards, the protein ID was submitted to Modeller software to develop a model with sufficient query sequence coverage and sequence identity. The templates were identified using PSI-BLAST [10] against the protein data bank (PDB) parameter. The PDB structure with high percent identity and similarity to be used as templates for homology modeling of both proteins. The protein sequence alignment method was carried out by Clustal W using sequences of template and aligned with target sequences.

2.2 Homology modeling:

The MODELLER (Version 9.12) [11] software was used to homology modeling of protein three-dimensional structures. The user provides an initial alignment of the sequence to be modelled (target) to the sequence(s) of one or more known structures (template). MODELLER then calculates a set of possible structures containing all non-hydrogen atoms and model was generated.

2.3 Model Reputation:

The accuracy of generated models using MODELLER V9.12 were evaluated and verified by SAVES server (Structure Analysis and Verification server) which includes Procheck, ERRAT and Verify 3D [12]. These programs are freely available at the UCLA-DOE LAB server. The Ramachandran plot using Procheck, generates stereo chemical quality and overall G-factors of protein. ERRAT is a program for verifying protein structures that have been determined by X-ray crystallography. Verify3D analyses the compatibility of an atomic model (3D) with its own amino acid sequence (1D). QMean and ProSA server was also used for the analysis of three dimensional structure protein. ProSA (Protein Structure Analysis) server widely used to check 3D models of protein structures for potential errors. The ProSA web server displays two characteristic of input 3D structure which are z-score and a plot of its residue's energies. QMEAN (Qualitative Model Energy Analysis) analysis the composite scoring function describing the major geometrical aspects of protein structures [13].

2.4 Ligand screening:

The PubChem compound database were used to retrieve structure files of ligands compounds for the docking. Lipinski's rule of 5 is necessary screening analysis method for Insilco drug design. Molecular docking analysis was carried out by Autodock 4.0 software. The ligand compounds and 3 oxoacyl synthase II protein were geometrically optimized and docked using docking software of Autodock and inhibit its function. The ligand compound and its analogues were docked with receptor protein using defaults parameters and message box displayed the e-total scores which showed the best score for a particular protein with ligands [14].

2.5 Molecular docking:

Molecular Docking is an important component of computer-assisted drug discovery. It helps in predicting the intermolecular framework formed between a protein and ligand and outputs the appropriate binding between the molecules. Docking was performed by AutoDock 4.2.6 program, [15] using the implemented empirical free energy function and the Lamarckian Genetic Algorithm (LGA). The grid maps were calculated using AutoGrid. In all dockings, a grid map with 60×60×60 points and a grid-point spacing of 1.000 Å was applied [16]. The best conformation with the lowest docked energy was chosen from the docking search. The interactions of complex protein-ligand conformations including hydrogen bonds and bond lengths were analyzed using Pymol software, UCSF Chimera, Molegro Molecular Viewer and Accelrys DS Visualizer software.

3. RESULTS AND DISCUSSION

3.1 Sequence analysis:

The experimental crystal structure of β1AR of Human is not available in the Protein Data Bank (PDB); hence, its 3D structure was modelled. The protein ID of the target (Beta-1 adrenergic receptor *Homo sapiens*) was retrieved from UniProt Knowledgebase (UniProtKB) with the accession number P08588. Afterwards, the protein ID was submitted to Modeller software to develop a model with sufficient query sequence coverage and sequence identity.

The templates were identified using PSI-BLAST against the protein data bank (PDB) parameter. The PDB structure with high percent identity and similarity to be used as templates for homology modeling of both proteins. The protein sequence alignment method was carried out by Clustal W using sequences of template and aligned with target sequences.

The Beta-1 adrenergic receptor (B1AR) protein of *Homo sapiens* plays an important role of mediate the catecholamine-induced activation of adenylate cyclase through the action of G proteins. This receptor binds epinephrine and norepinephrine with approximately equal affinity. Mediates Ras activation through G(s)-alpha- and cAMP-mediated signaling. The homologous structure of Beta-adrenergic receptors sequence was identified by using BLAST tool. The BlastP comparison was done with the protein database and template structure was selected. The wild type *Homo sapiens* B2-adrenergic G protein-coupled receptor protein sequence shows 60% similarity was selected as a template structure for the homology modeling. The sequence alignment of target and template sequence was done by using online version ClustalW as displayed in Fig. 1.

Figure 1. Sequence Alignment of Beta-adrenergic receptors protein and with template PDB ID 2RH1. The alignment shows a similarity of 60 % between the two obtained by using ClustalW program.

3.2 Homology modeling:

The MODELLER (Version 9.12) software was used to homology modeling of protein three-dimensional structures. The user provides an initial alignment of the sequence to be modeled (target) to the sequence(s) of one or more known structures (template). MODELLER then calculates a set of possible structures containing all non-hydrogen atoms and model was generated. MODELLER software is used for homology or comparative modeling of protein three-dimensional structures. MODELLER implements comparative protein structure modeling by satisfaction of spatial restraints, and can perform many additional tasks, including de novo modeling of loops in protein structures, optimization of various models of protein structure with respect to a flexibly defined objective function, multiple alignment of protein sequences and/or structures, clustering, searching of sequence databases, comparison of protein structures, etc.

3.3 Structure analysis:

SAVES server (Structure Analysis and Verification server) which includes Procheck, ERRAT and Verify 3D. These programs are freely available at the UCLA-DOE LAB server (https://services.mbi.ucla.edu/SAVES/). The Ramachandran plot using Procheck, generates stereo chemical quality and overall G-factors of protein. ERRAT is a program for verifying protein structures that have been determined by X-ray crystallography. Verify3D analyses the compatibility of an atomic model (3D) with its own amino acid sequence (1D). QMean and ProSA server was also used for the analysis of three-dimensional structure protein. ProSA (Protein Structure Analysis) server widely used to check 3D models of protein structures for potential errors. The ProSA web server displays two characteristic of input 3D structure which are z-score and a plot of its residues energies. QMEAN (Qualitative Model Energy Analysis) analysis the composite scoring function describing the major geometrical aspects of protein structures.

The 3D Crystal structure of human B2-adrenergic G protein-coupled receptor (2RH1) was used as a template structure to developed 3D structure of Beta-1 adrenergic receptor (B1AR) protein sequence. The alignment file of both sequences was submitted to MODELLER v9.12 to generate required model of target structure as seen in Fig. 2. The 3D structure of Beta-1 adrenergic receptor (B1AR) protein consists of the 164 Alpha helix, 76 strands, 18 beta turns and 219 numbers of random coils. The modeled protein was validate using SAVEs servers which provide Verify3D, ProSA, Errat and PROCHECK analysis. Finally, the structural and stereo chemical properties of the target protein were validated using the score of Ramachandran plot which showed the percentage of residues present in core allowed and disallowed regions. The good quality model would be expected to have over 90% in the most favored region in terms of Ramachandran Plot, in generated model it was found to be 91.9% and only 0.3% of residues were in disallowed region (Fig. 3.). [17] Ramachandran plot score revealed model structure is of good quality. The ERRAT was used to study overall quality factor of protein using statistics of non-bonded interaction between atoms in reported structure. In current case, the ERRAT score of overall quality factor was obtained as 86.55 as described in Fig. 4, which are very much satisfactory for high quality model. The Verify 3D plot predicted 80% of the residues had an averaged 3D-1D score >0.2 that the model was of good quality and very less residues were found in the red region of the graph (Fig. 5.). [18] ProSA and QMean tool confirm the quality and potential error of generated three-dimensional structure as more reliable and within an acceptable range. The range of generated

protein model was 1.48 and z-score of -4.86 which was within the range (Fig. 6 & 7). The above results of entire structure validation program indicate that the homology model is reliable for further study of drug design. [19]

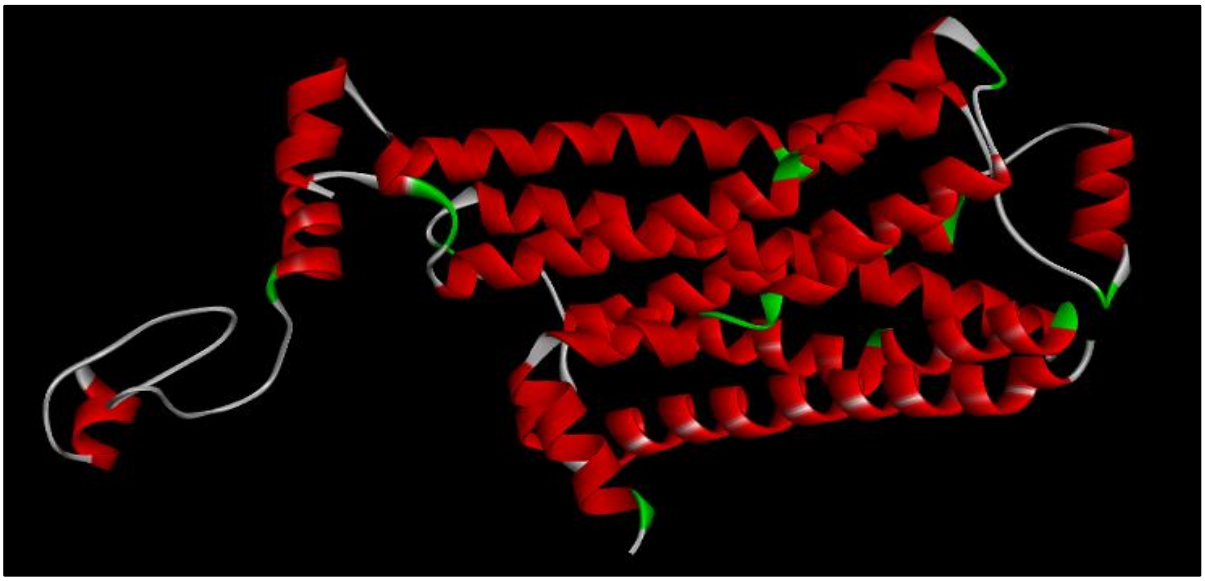


Figure 2. 3D Structure of B1AR generated by Modeller V9.24 using 2RH1 template.

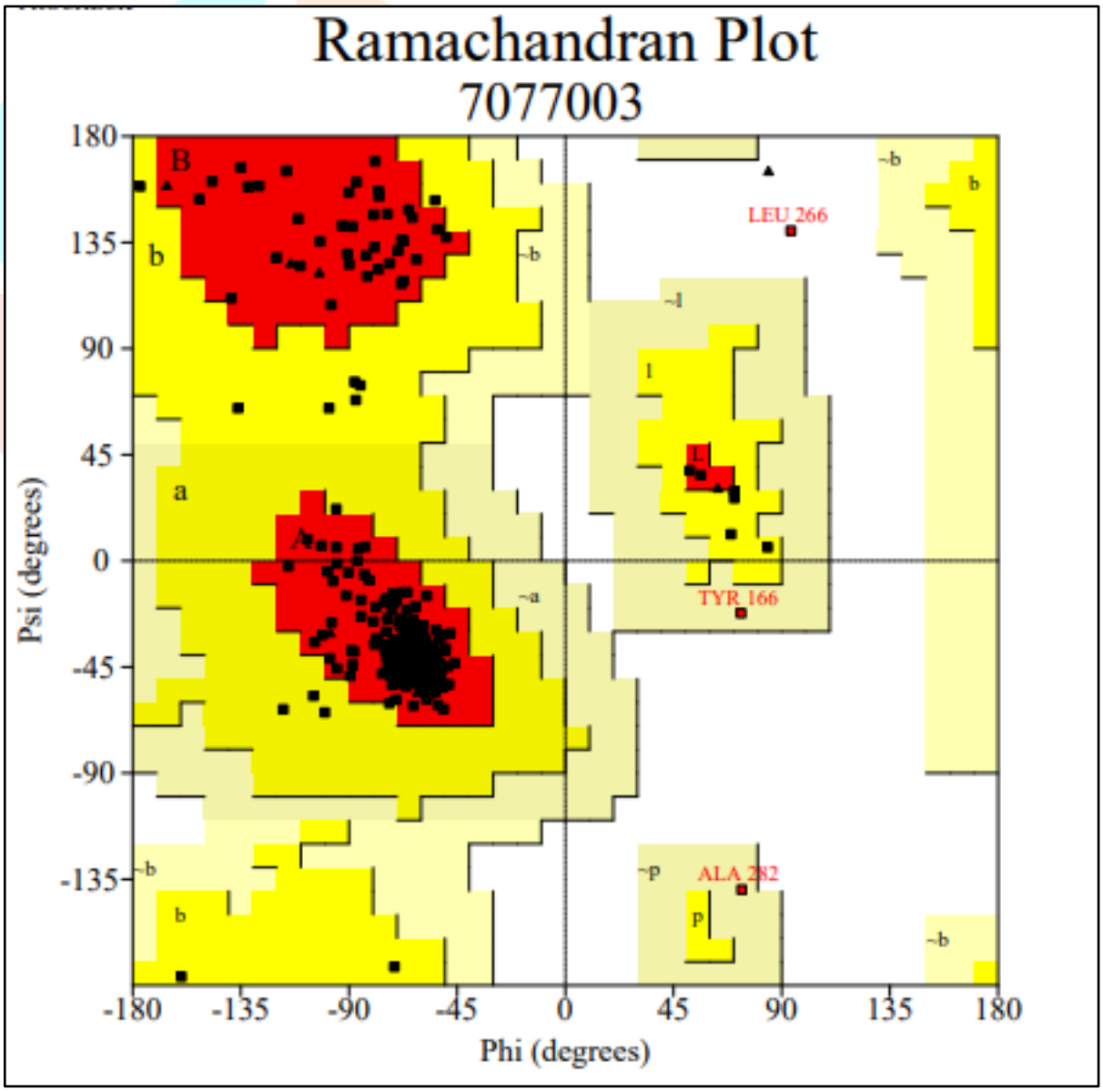


Figure 3. The The Ramachandran plot of B1AR protein [Favoured region: 275 (93.9%), Allowed region: 15 (5.1%) and Outlier region: 1 (0.3%)]. Ramachandran Plot analysis of 3OASII protein which generated from Modeller v9.24. The additionally allowed, generously allowed and disallowed regions are indicated as yellow, light yellow and white fields respectively. But the most favored regions are colored red.

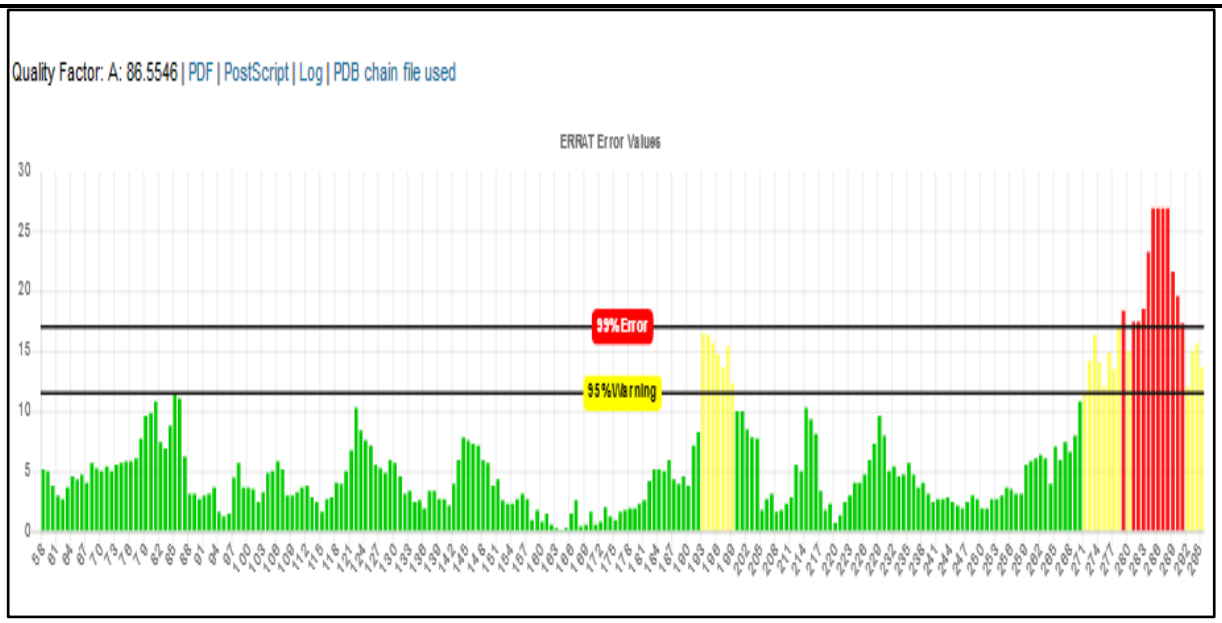


Figure 4. The overall quality factor results of B1AR protein in ERRAT show model quality of 86.55%.

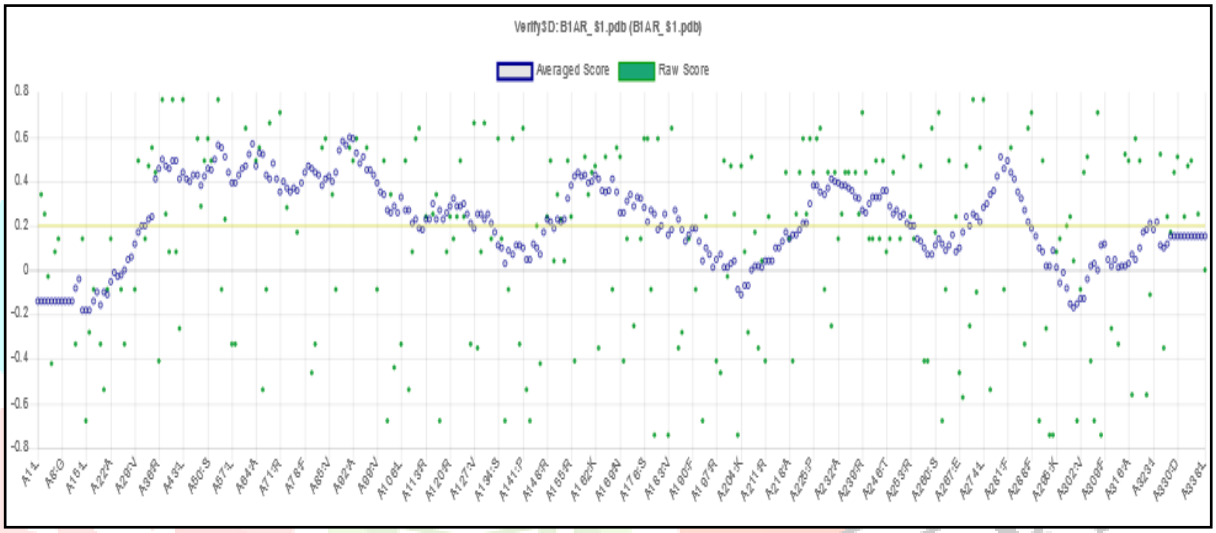


Figure 5. The Verify3D plot of B1AR protein predicted 80% of the residues had a good 3D-1D score.

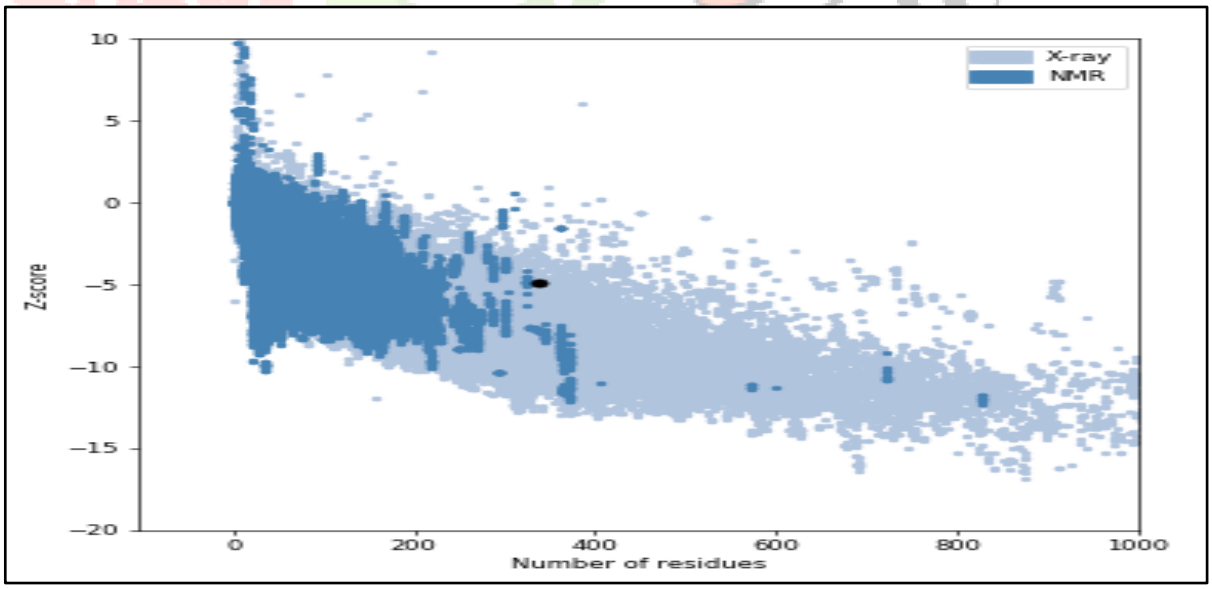


Figure 6. The plot analysis of Prosa program shows groups of structures from different sources (X-ray, NMR) are distinguished by different colors. Overall model quality of B1AR protein shows Z-Score -4.86.

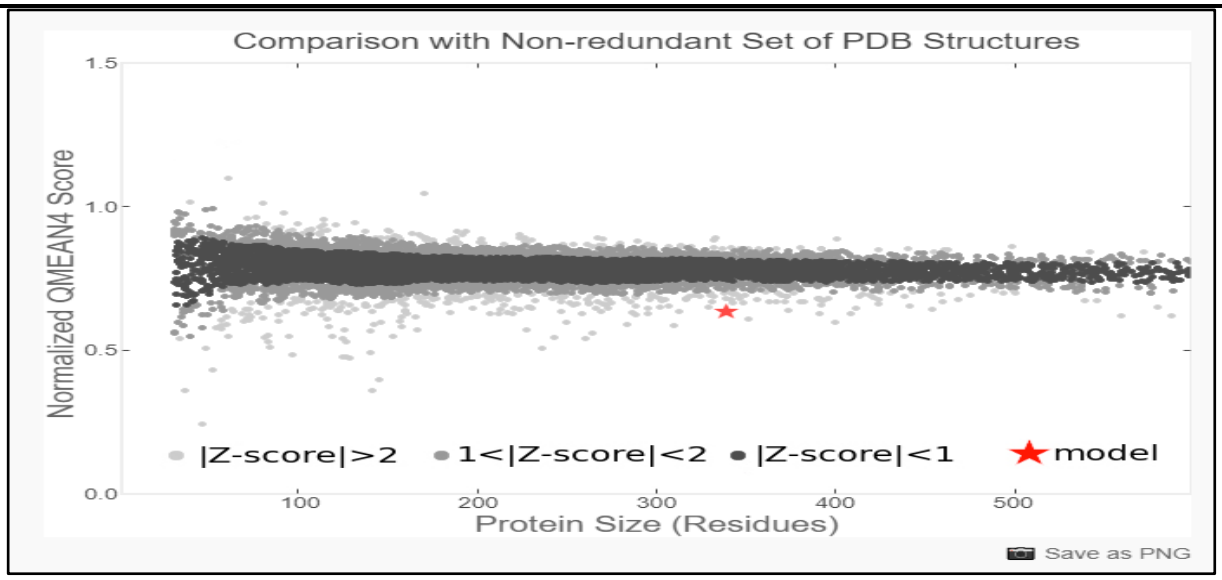
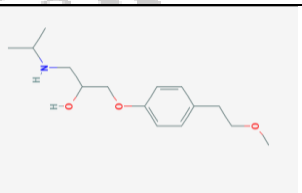


Figure 7. QMEAN analysis of B1AR protein. The plot explain comparison with non-redundant set of PDB structures shows Z-score -3.97.

3.4 Virtual screening of Lead compound:

Virtual ligand screening is useful for successful strategy of structure base drug designing. Five chemical compound Metoprolol Succinate were screened against B1AR protein. These ligand molecules were selected from PubChem compound databases and conversion of SDF to PDB (Protein Data Bank) format carried out using PyMol software. Protein and ligands docking analysis indicates that these molecules can bind to the drug target efficiently and could be potential drug for the heart, renin-secreting tissues of the kidney, parts of the eye responsible for the production of aqueous humor, and to a limited degree in bronchial tissue of the lung. On the basis of binding affinity and drug like properties, Metoprolol Succinate ligands were finally screened. Metoprolol is a specific beta-1 blocker regularly utilized as the succinate and tartrate subsidiaries depending if the plan is intended to be of prompt delivery or expanded delivery. Metoprolol is utilized to treat angina (chest torment) and (hypertension). Metoprolol is additionally used to bring down your danger of death or waiting be hospitalized for cardiovascular breakdown. The molecular weight is 385.5 g/mol, Hydrogen bond donor are 4 and acceptor are 8, rotational bond is 12 in numbers and log p value is 1.6. Metoprolol Succinate were selected as ligands to the docking process with B1AR protein of *Homo sapiens* shown in Table 1. [20, 21]

Table 1: The chemical compound showing ID, name, formula and structure according to their PubChem Compound database.

SN	Compound Name	Compound ID	Molecular Formula	Molecular Weight	Structure
1	Metoprolol Succinate	9800288	$C_{19}H_{31}NO_7$	385.5 g/mol	

3.5 Molecular Docking:

3.5.1 Docking interaction of Metoprolol Succinate & Human Beta1 Adrenergic Receptor (ADRB1):

Molecular docking analysis was carried out by AutoDock 4.2 software. The ligand compounds and Beta-1 adrenergic receptor (B1AR) protein were geometrically optimized and docked using docking software of AutoDock 4.2 and inhibit its function. The ligand compound and its analogues were docked with receptor protein using defaults parameters and message box displayed the binding energy scores which showed the best score for a particular protein with ligands. Molecular Docking is an important component of computer-assisted drug discovery. It helps in predicting the intermolecular framework formed between a protein and ligand and outputs the appropriate binding between the molecules. Docking was performed by AutoDock 4.2 program, using the implemented empirical free energy function and the Lamarckian Genetic Algorithm (LGA). The grid maps were calculated using AutoGrid. In all dockings, a grid map with 60×60×60 points and a grid-point spacing of 1.000 Å was applied. [22] The best conformation with the lowest docked energy was chosen from the docking search. The interactions of complex protein-ligand conformations including hydrogen bonds and bond lengths were analysed using Pymol software, UCSF Chimera, Molegro Molecular Viewer and Accelrys DS Visualizer software. The finest conformation with the lowest docked energy was selected from the docking search. The communications of complex protein–ligand conformations including hydrogen bonds and bond lengths were analyzed using Pymol software, UCSF Chimera, Molegro Molecular Viewer, and Accelrys DS Visualizer software. The protein name is Beta-1 adrenergic receptor (B1AR) and Sequence Length is 477. The protein Organism is *Homo sapiens* and Gene Name is ADRB1. [23]

On carrying out the docking of the β-tubulin (PROTEIN) with Ligand Colchicine and it was detected that the binding energy shown by the β-tubulin and ligand is good at −4.56 kcal/mol. This interaction is more stable as there is one hydrogen bonds formed at Arg164(H) (comparable binding energy, although lower binding energy indicates a good and stable communication) shown in Table 2. In conclusion, Ligand showed better results on docking with the protein. Estimated loss of torsional free energy upon binding

energy is +1.3720 kcal. Minimum electrostatic potential is −29.47 and maximum electrostatic potential is 30.19 as shown in Fig 8 & 9. [24]

Table 2: Docking interaction of Metoprolol Succinate & Human Beta-1 adrenergic receptor (ADRB1)

Protein Name	Ligand Name	Binding Energy (kcal/mol)	No. of H Bonds	Interacting residue	Final Intermolecular Energy (kcal/mol)	vdW + Hbond + desolv Energy (kcal/mol)	Electrostatic Energy (kcal/mol)	Torsional Free Energy (kcal/mol)
Beta-1 adrenergic receptor (ADRB1)	Metoprolol Succinate	-4.56	01 (H1:Distance = 3.16 Å, Strength = -2.18)	LYS347(H1) ASP356 ALA225	-7.24	-7.05	-0.19	+2.68

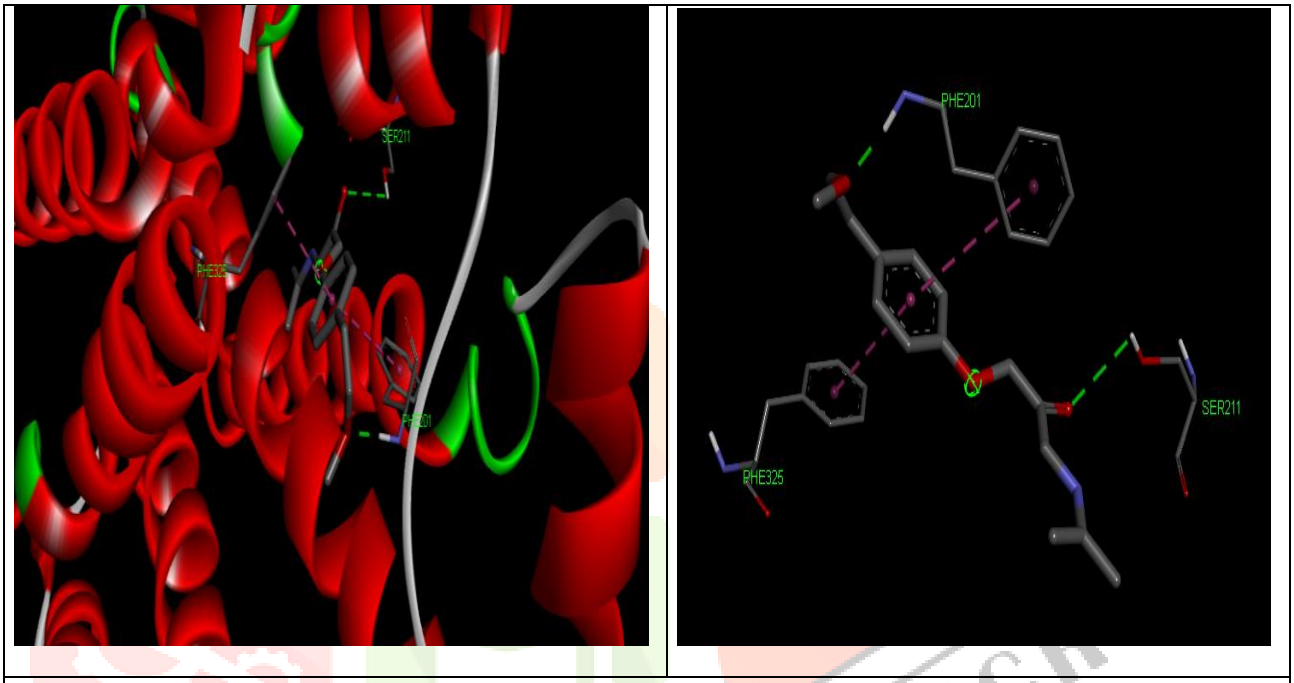


Figure 8. Complex and docking structure of Beta-1 adrenergic receptor (ADRB1) and Metoprolol Succinate as a ligand compound.

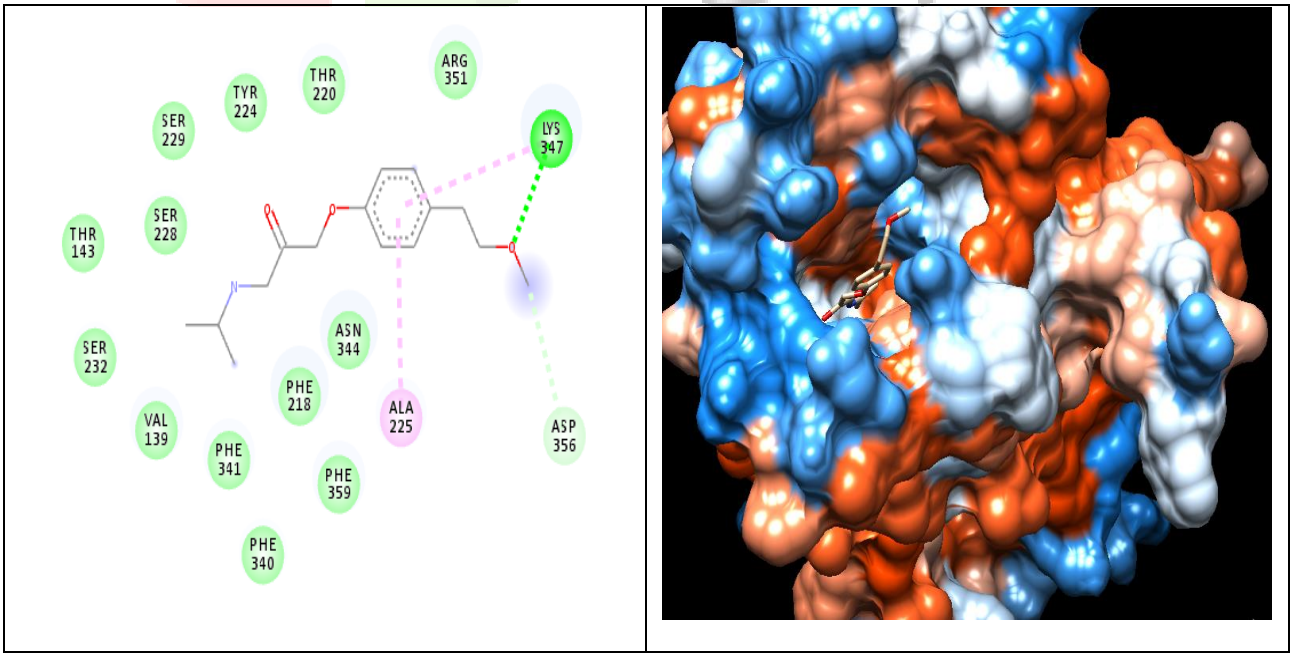


Figure 9. Hydrogen Donor & Acceptor and Electrostatic docking structure of Beta-1 adrenergic receptor (ADRB1) and Metoprolol Succinate as a ligand compound.

3.5.2 Docking interaction of Metoprolol Succinate & Wild turkey Beta1 Adrenergic Receptor (ADRB1):

The protein name is Beta1 Adrenergic Receptor and sequence length is 313. The crystal structure retrieved from Protein Data Bank database and PDB ID is 2VT4. The protein organism is Meleagris gallopavo (Wild turkey) and Beta1 Adrenergic Receptor chain is a protein that in Meleagris gallopavo (Wild turkey) is encoded by the ADRB1 gene. The amino acid information of Beta1 Adrenergic Receptor in which amino acids are 313 out of 258 (906%) is favoured amino acid, 10 (4%) is allowed region and 2 (1%) is disallowed region. This information is related with Ramachandran plot. The Method of analysis is X-Ray diffraction and Resolution is 2.70 Å. The docking analysis done with Metoprolol Succinate and its metal complex. But only Metoprolol Succinate dock with proteins and other metal ligand complexes not attached with selected protein. The Grid arranged at 1.000 Angstroms and Grid Points set as 40 x-points, 40 y-points and 40 z-points.

Table 3: Docking interaction of Metoprolol Succinate & Wild turkey Beta1 Adrenergic Receptor (ADRB1).

Protein Name	Ligand Name	Binding Energy (kcal/mol)	No. of H Bonds	Interacting residue	Final Intermolecular Energy (kcal/mol)	vdW + Hbond + desolv Energy (kcal/mol)	Electrostatic Energy (kcal/mol)	Torsional Free Energy (kcal/mol)
Beta1 Adrenergic Receptor (ADRB1)	Metoprolol Succinate	**-3.48**	01 (H1:Distance= 2.95 Å) 02 (H1:Distance= 3.21 Å)	PHE201(H1) SER211(H2) PHE325	-7.06	-6.99	-0.08	+3.58

On performing the docking of the Beta1 Adrenergic Receptor with Metoprolol Succinate It was observed that the binding energy shown by the Beta1 Adrenergic Receptor protein and Metoprolol Succinate is highest -3.48 kcal/mol binding energy. This interaction observed two hydrogen bond at PHE201 and SER211 shown in Table 3. In comparison to interaction and binding energy showed lower binding energy indicates a good and stable interaction. The components consist of solvent effects, conformational changes in the protein and ligand interaction, free energy due to protein-ligand interactions, internal rotations, association energy of ligand and receptor to form a single complex and free energy due to changes in vibrational modes. A low (negative) energy indicates a stable system and thus a likely binding interaction (Fig. 10-11). [25]

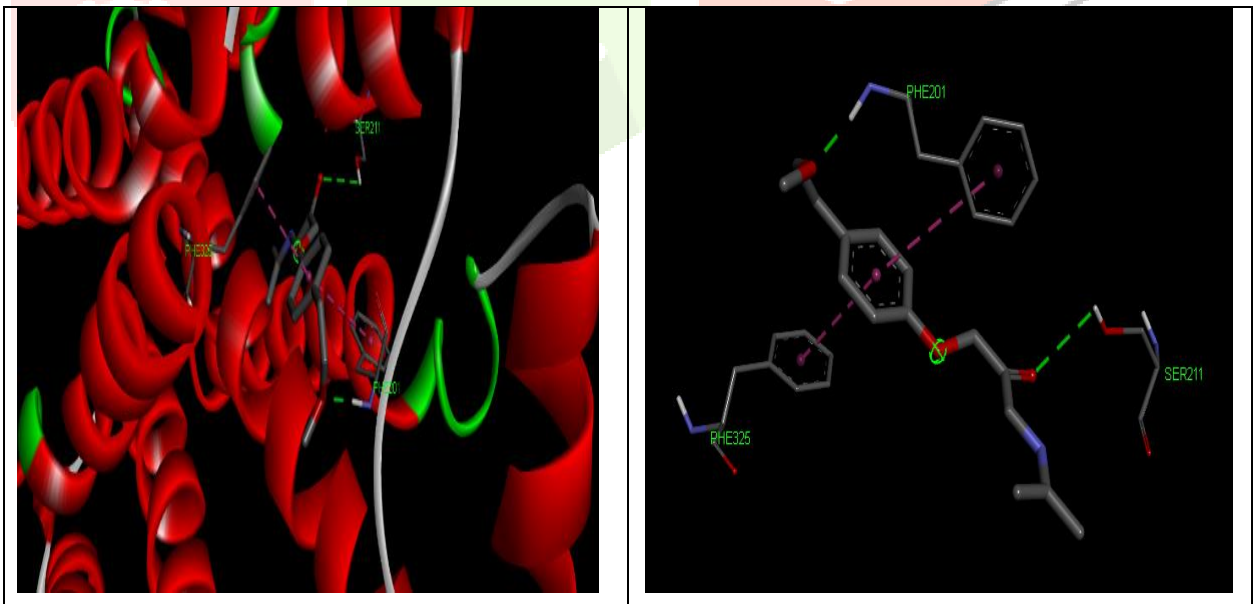


Figure 10. Complex and docking structure of Beta-1 adrenergic receptor (ADRB1) and Metoprolol Succinate as a ligand compound.

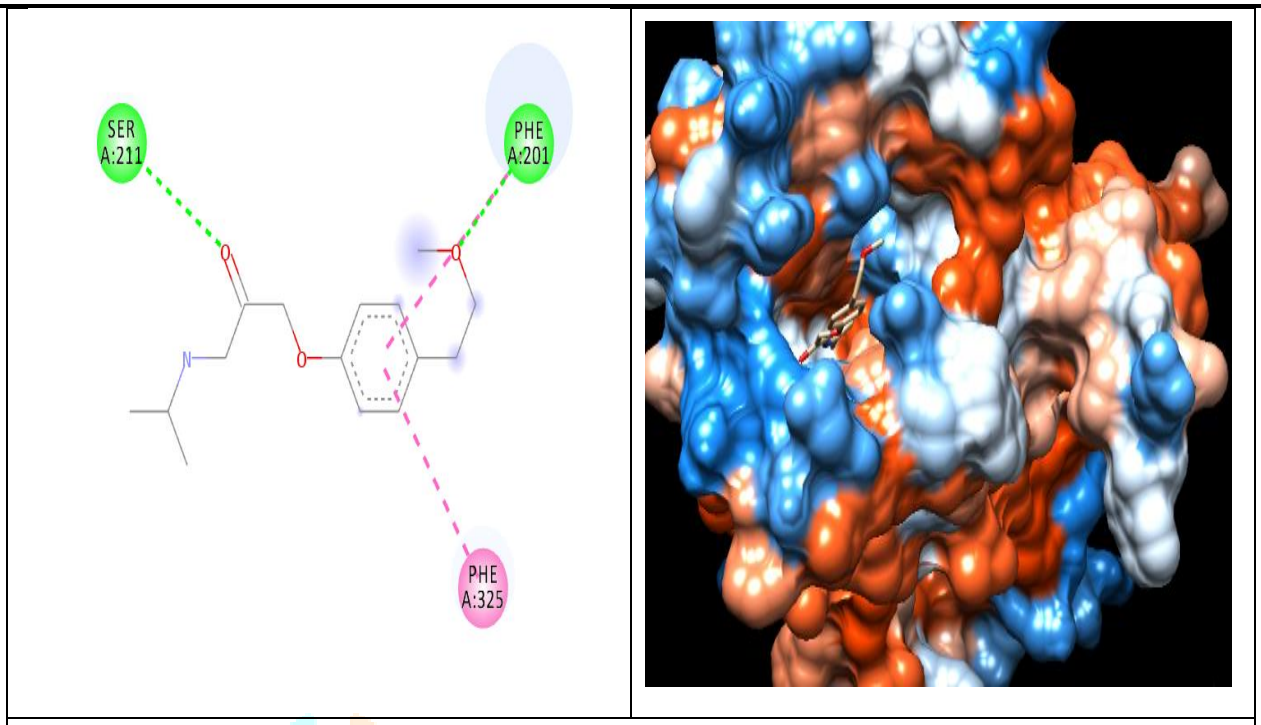


Figure 11. Docking structure of Beta1 Adrenergic Receptor protein and Metoprolol Succinate as a ligand. The interaction of amino acid with ligand shows in figure.

4. CONCLUSIONS

The three-dimensional design of Beta-1 adrenergic receptor protein of Homo sapiens has not been known. The current task was pointed toward discovering novel medication to restrain the Beta-1 adrenergic receptor (B1AR) protein. This examination includes clarification of 3D underlying and physicochemical properties of B1AR protein by means of format based homology displaying. The absence of gem design of B1AR protein incited us to apply in silico methods to start the medication disclosure measure for B1AR protein. This investigation gives clear comprehension of B1AR protein design and its limiting instrument, along these lines help in giving the healing arrangements of cardiovascular, compelling therapy of asthma, malignant growth and different illnesses brought about by breaking down of the objective protein. For homology modeling, the known structure of wild type Homo sapiens B2-adrenergic G protein was used as template. Then SAVEs analysis verification of model using Ramachandran plot showed that most of these residues are in favored regions of the plot and energy minimization were used to refine the structure. The lack of crystal structure of Human Beta-1 adrenergic receptor protein provoked us to apply in silico techniques to initiate the drug discovery process for Beta-1 adrenergic receptor protein. Hence, to understand the characteristics structural features of Beta-1 adrenergic receptor protein and to execute the structure-based drug design strategy for Beta-1 adrenergic receptor protein, template-based homology modeling of wild type Homo sapiens B2-adrenergic G protein coupled applied as template in this study. The model possesses acceptable structural profiles. Furthermore, the binding modes of both Human and Wild Turkey Beta-1 adrenergic receptor protein agonist were determined via molecular docking analysis. Several residues including LYS347, ASP356, ALA225, PHE201, SER211 and PHE325 are involved in direct interactions with the ligand. Among all, LYS347, PHE201 and SER211 provides H-bonding, π- π interactions, respectively, hence found to be crucial residue in ligand binding and for the activation of Beta-1 adrenergic receptor protein. The protein-ligand interaction plays a very significant role in structural based drug designing. The ligands Metoprolol Succinate which was docked with both human and wild turkey protein observed as suitable inhibitor candidates by their docking e-values. We are also investigating the simulation and dynamic behavior forms of Beta-1 adrenergic receptor protein that will be published in future.

DECLARATION OF COMPETING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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