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In Silico Design, Toxicity Prediction and Molecular Docking Studies of Oxazole Derivatives against Peroxisome Proliferator Activated Receptor Gamma for the Treatment of Diabetes Mellitus

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Research Article

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ABSTRACT

Diabetes Mellitus (DM) is a serious and common metabolic disorder affecting public health all over the world. Several heterocyclic containing drugs are available in the market to treat DM. However, majority of these drugs show limited therapeutic index and several side effects, therefore new and potent molecules with or without minimum side effects are still required. Among heterocyclic compounds, oxazole derivatives could be fruitful target compounds for DM. In the present work, PPARγ receptor was selected against oxazole as ligand for docking studies using AutoDock 4 with an aim to discover novel compounds. Several in silico analyses of oxazole derivatives like physicochemical properties, drug scores, drug likeness, solubility, and toxicity prediction were investigated using OSIRIS and toxtree freeware. Visualization and analysis were conducted by discovery studio visualization. Results disclose that the derivatives have fine physicochemical properties required for an orally active drug. The docking studies reveal that ligands 4, 9, 13, 14 and 21 show high docking scores of 0.71, 0.85, 0.74, 0.83 and 0.75 as compared to standard drug Rosiglitazone's dock score of 0.80, which specifies that these derivatives possess high affinity and high interaction towards protein 1PRG (human peroxisome proliferator activated receptor gamma). Hence, the designed oxazole derivatives are discovered to have excellent binding affinity in the binding site of target 1PRG, indicating that these compounds could be potential drug candidates for diabetes.

INTRODUCTION

According to the WHO the word "Diabetes" defines a set of metabolic disorders categorized and recognized as hyperglycemia if not treated. It occurs due to defects in insulin action, insulin secretion or both and interferes in metabolism of fat, carbohydrates and proteins. The frequency and death to diabetes is rising worldwide, so to treat chronic non-communicable diseases, there must be proper planning, monitoring and precautions must be taken globally. There are various pathogenic methods involved in the development of diabetes. Diabetes mellitus are majorly of three type:

Type 1 Insulin Dependent Diabetes Mellitus (IDDM) is a chronic autoimmune disorder in which pancreas synthesize little or no insulin. Type 2 DM is a chronic illness also known as Insulin Independent Diabetes Mellitus (NIDDM) affecting the process of blood glucose in body and type 3 or gestational diabetes diagnosed during pregnancy which arises due to intolerance of glucose. Presently there are numerous anti-diabetic drugs available in market including Thiazolidinedione (pioglitazone), Sulfonylureas (glipizide), Meglitinide analogues (repaglinide), GLP-1 receptor agonist (exenatide), DPP-4

inhibitor (sitagliptin), Biguanide (metformin) and alpha glucosidase inhibitor (acarbose). However these drugs cause side effects like nephropathy, cardiovascular problems, kidney defects, chronic joint inflammation, hypoglycemia, liver dysfunction, diarrhea and digestive discomfort. Glucokinase, PPAR, aldose reductase, glycogen phosphorylase, insulin receptor, protein tyrosine phosphate 1-beta, alpha-glucosidase, and Dipeptidyl Peptidase-4 (DPP-4) are some of the receptors that can be used to treat type 2 diabetes. Among these targets, Peroxisome Proliferator Activated Receptor (PPARγ) is a glitazone receptor which controls the genes essential for cell differentiation and several metabolic pathways such as lipid and glucose homeostasis. After stimulating PPARγ, receptor, these indicates insulin sensitization and increase metabolism of glucose. In adipocytes, PPARγ activation enhances the secretion of insulin mediators in peripheral tissues [1]. PPARγ consist of an agonist dependent stimulation domain (AF-2), agonist independent initiated domain (AF-1) and DNA binding domain. Following drug binding to the PPARγ receptor, heterodimerization with retinoid X receptor-α occurs, resulting in the transcription of target protein genes *via* binding of PPRE response element.

The oxazole moiety consists of oxygen in 1 position and nitrogen in 3 position in a five membered ring. It is a weak base aromatic compound possessing three active substitutions at positions C-2, C-4 and C-5.13 Oxazole is therapeutically active moiety showing several activities like antibacterial, antifungal, anti- inflammatory, anticancer, antidepressant and anti-diabetic.

Molecular docking is a form of bioinformatics modeling which includes the interaction of molecules or ligands to provide a stable adduct. These computational tools are effective and useful and depend upon the binding properties of ligand and target proteins and predict the 3D structure of the complex. Through molecular docking techniques, various studies can be identified, such as binding affinity, free energy, active site prediction and stability of complexes.

Computer aided drug design is rapid and cost effective method for novel drug discovery. Nowadays, computational studies are increasing for development of pharmaceuticals which is based upon prediction of Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) properties. Investigating the ADMET properties of molecules can lead to drug discovery and development, as well as selecting the drug by sorting non-drugs by analyzing the “Lipinski rule of 5” resulting to higher class. More than that, molecular docking is used to figure out which lead molecules and binding energy sites are best for drug discovery and development. In this research, we make use of swiss ADME online software that aids in small or bulky molecular structures for drug development and discovery. This software helps in predicting ADME studies, physicochemical properties, pharmacokinetics, drug-likeliness, molecular weight, water solubility and permeability. Recently, the development of new drug and their average mean prices have increased about 2.8 billion U.S dollars. Because of higher costs of *in vitro* and *in vivo* drug development, safety and efficacy, an extensive screening of lead molecules at an earlier stage is required. Hence, scientist prefers computational tools that are beneficial, less tedious, accurate, and economical and helps in screening larger number of compounds. The drug should obey ADMET properties in which toxicity is a necessary parameter to calculate compound threats. In our research, we have taken two important online freeware tools like OSIRIS and Toxtree. Toxicity risk can be predicted by using OSIRIS property explorer which is freely downloaded online. To work in this software we must first develop a java platform that can easily asses toxicity risk and calculate physicochemical properties of novel lead molecules. Toxtree (v3.1.0) is online freely accessible software that estimates the toxic hazards of molecules using decision tree method. The results display carcinogenicity, genotoxicity, skin irritation, mutagenicity, sensitization and biodegradability of compounds.

AutoDock 4 is online automated docking software that aids in displaying the possibility of docking modes as protein-ligand interactions. AutoDock 4 software reads only PDB format files to accelerate the binding energy calculations. In our study, we have used the AutoDock 4 docking tool to check the novel oxazole derivatives as ligands with receptor target 1PRG, and the docking results are analyzed and discussed in this paper [2-8].

AutoDock software is used by several industries, including biopharmaceutical, researchers, academic institutions and other laboratories to discover new compounds. Here, we have docked best lead compounds 4, 9, 13, 14, and 21 with receptor PPARγ (1PRG), and compared them with standard drug rosiglitazone against the similar protein showing binding affinity of -9.77. In our research we have investigated 25 novel oxazole derivatives for their anti-diabetic activity with target receptor protein PPARγ for molecular docking and comparison is made with standard drug rosiglitazone. After the drug- receptor interactions, the binding affinity and binding energy was analyzed using AutoDock freeware. The compounds showing lowest binding energy with standard drug is further being analyzed. The 2D and 3D structure of that compound is then visualized in discovery studio visualization studio visualizer download online freeware.

MATERIALS AND METHODS

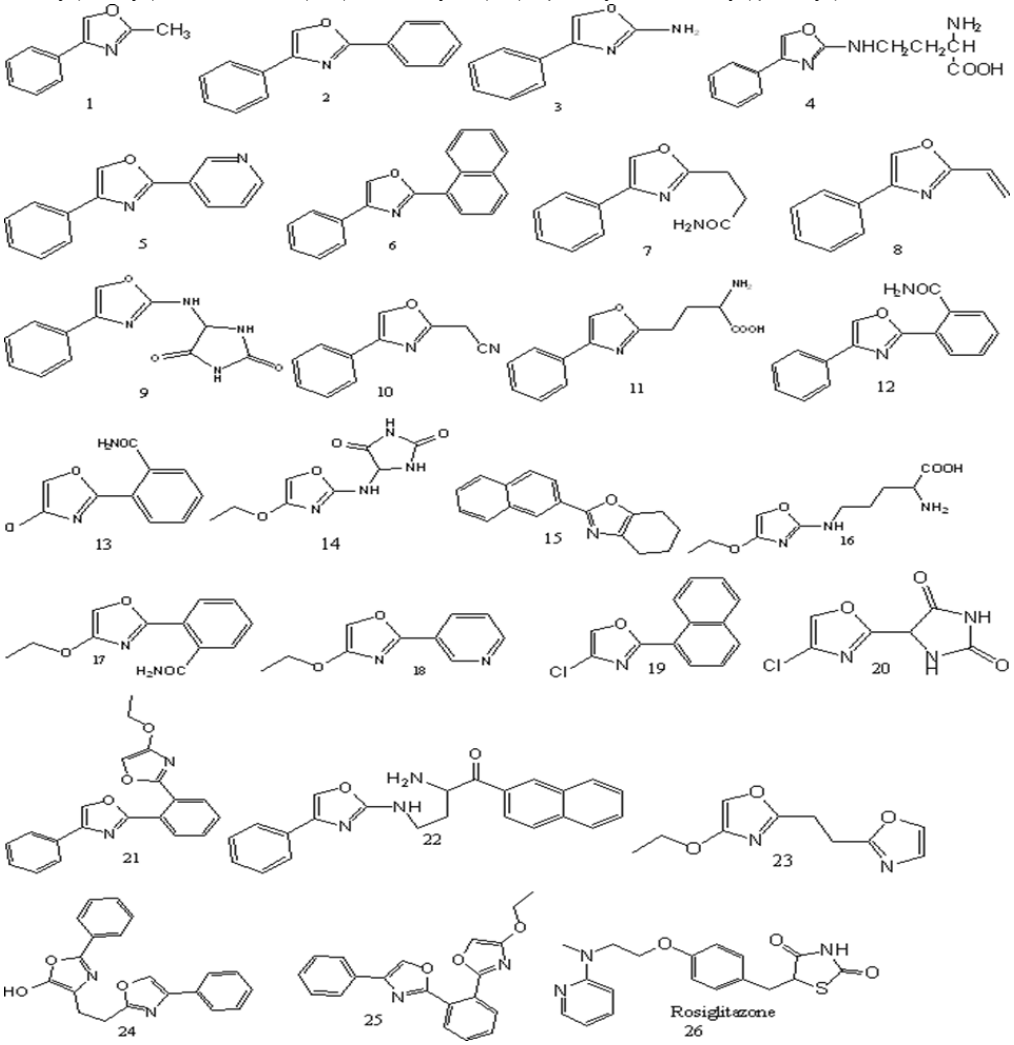
In the present research, several bioinformatics tools have been implemented; discovery studio visualization, open babel, AutoDock 4, Chem Draw 3D 15.1, OSIRIS, toxtree, discovery studio visualizer and swiss ADME [9-13].

Selection of ligand

25 Novel oxazole derivatives were selected and the two-dimensional molecular structures were drawn in Chem Draw 3D professional software, and the structures are saved in PDB file format. Then the selected derivatives were optimized and various physicochemical properties were calculated. These values were then compared with the standard drug rosiglitazone and were designed for molecular docking studies. Figure 1 shows all 25 oxazole derivatives with IUPAC name and standard drug rosiglitazone. Rosiglitazone were selected from PubChem downloaded in SDF format and

converted to a PDB format file.

Figure 1. 2D structures of novel oxazole derivatives with its IUPAC name and standard rosiglitazone (1 to 26). (1) 2-methyl-4-phenyloxazole; (2) 2,4-diphenyloxazole; (3) 4-phenyloxazol- 2-amine; (4) 2-amino-4-((4-phenyloxazol-2-yl)amino)butanoic acid; (5) 4-phenyl- 2-(pyridin-3- yl) oxazole; (6) 2-(naphthalen-1-yl)-4-phenyloxazole; (7) 3-(4-phenyloxazol-2-yl) propanamide; (8) 4-phenyl-2-vinyloxazole; (9) 5-((4-phenyloxazol-2-yl)amino)imidazolidine-2,4-dione;(10)2- (4-phenyloxazol-2-yl)acetonitrile; (11)2-amino-4-(4-phenyloxazol-2-yl)butanoicacid;(12)2-(4-phen yloxazol-2-yl)benzamide; (13)2-(4-chlorooxazol-2-yl)benzamide; (14)5-((4-ethoxyoxazol-2-yl) amino)imidazolidine-2,4-dione;(15)2-(naphthalen-2-yl)-4,5,6,7-tetrahydro benzo[d]oxazole; (16) 2-amino- 5-((4-ethoxyoxazol-2-yl)amino) pentanoic acid; (17) 2-(4-ethoxyoxazol-2-yl)benzamide; (18) 4-ethoxy-2-(pyridin-3-yl)oxazole; (19) 4-phenyloxazol-2- amine; (20) 5-(4-chlorooxazol-2- yl)imidazolidine-2,4-dione;(21) 4-chloro-2-(2-(2-phenyloxazol- 3(2H)-yl)phenyl) oxazole;(22)2- amino-1-(naphthalen-2-yl)-4-((4-phenyloxazol-2-ylamino)butan- 1-one; (23) 4-ethoxy-2-(2-(oxazol- 2-yl)ethyl)oxazole; (24) 2-phenyl-4-(2-(4-phenyloxazol-2-yl) ethyl)oxazol-5-ol; (25)4-ethoxy-2-(2-(4-phenyloxazol-2-yl)phenyl)oxazole; 26. Rosiglitazone.



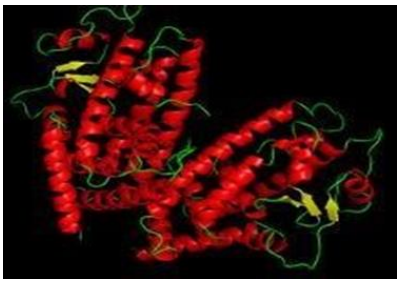
Preparation of ligands

The ligand was prepared by modifying ionization, torsion, removal of water molecules, addition of polar hydrogen and adding kollman charges using AutoDock 4 freeware. Then the ligand was saved in PDBQT file format. The receptor grid was prepared using AutoDock grid tool with grid dimensions of 126x126x126 Å with 0.500 Å spacing [14].

Selection and preparation of target molecule

The crystal structure of target protein PPARγ was downloaded from the protein database, and saved in PDB format. The resolution of protein structure ranges from 2.1 to 2.20 Å. All the oxazole ligands were individually docked into the receptor protein based on ligand protein interactions [15-26]. The 3D structure of receptor is drawn in PyMol shown in Figure 2.

Figure 2. 3D structure of PPARγ (PDB ID: 1PRG) drawn in pymol software.



Prediction of active site by CASTp (Computer Atlas of Surface Topography of protein)

The CASTp is a helpful computational tool and web based software used to identify the active site and topology of PPARγ (Figure 3 and Table 1). The predicted active sites are beneficial for verifying and locating the grid box [27]. The active sites of target with catalytic amino acids were promoted for docking studies and were analyzed by UniProt.

Figure 3. A. Prediction of active site and ligand binding sites using CASTp of PPARγ receptor; B) CASTp results of amino acids showing active site residues for PPARγ highlighted in blue.

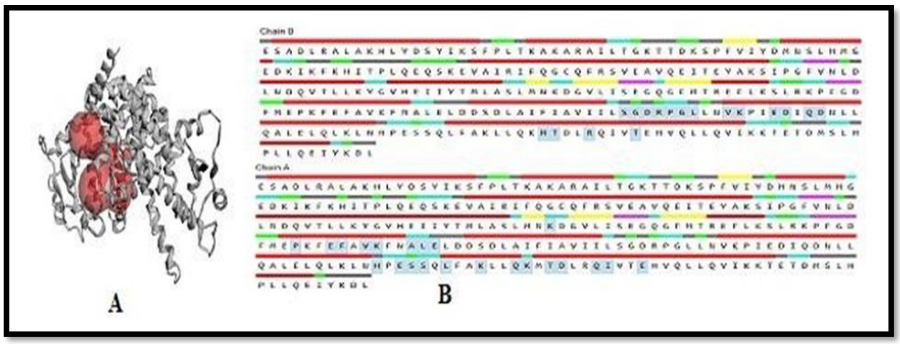


Table 1. Active pocket sites and their residual position of PPARγ were analyzed from CASTp.

Chain	Residue position	Amino acids	Chain	Residue position	Amino acids
A	291	GLU	A	441	ASP
A	336	LYS	A	444	GLN
A	366	PRO	A	445	ILE
A	369	GLU	A	448	GLU
A	370	PHE	B	394	SER
A	372	VAL	B	395	GLU
A	373	LYS	B	396	ASP
A	376	ALA	B	397	ARG
A	377	LEU	B	398	PRO
A	378	GLU	B	399	GLY
A	425	HIS	B	400	LEU
A	427	GLU	B	403	VAL
A	428	SER	B	404	LYS
A	429	SER	B	407	GLU
A	431	LEU	B	408	ASP
A	432	PHE	B	410	GLN
A	434	LYS	B	411	ASP
A	437	GLN	B	439	MET
A	438	LYS	B	440	THR
A	440	THR	B	443	ARG

Prediction of physicochemical properties

Physicochemical properties of ligand and the screening of selected ligands were done through Lipinski's Rule of five. It is used to analyze various physicochemical properties like lipophilicity, polar surface area, H-bond acceptor, H-bond donor, water solubility and refractivity. The values are shown in Table 2.

Analysis of Correlation Coefficient (CC)

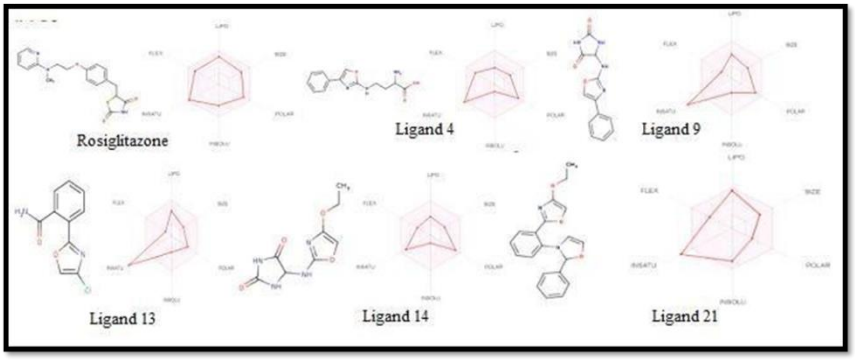
Correlation coefficient is used to identify correlation between two variables and recognize the appropriate attributes for a target cell that is to be investigated. This correlation analysis study is based on identifying certain oxazole derivatives, properties and predicting the dataset with great significant values. As the values of two variables increased, they show a positive correlation, and at opposite ranges of both variables, show negative correlations [28]. The closeness of two selected variable datasets can be calculated by R. The correlation coefficient of various variables lies between 0.9-1, indicating a positive correlation, but if the value of R is less than 0.9, it is called a weak correlation [29].

Prediction of ADME properties

Swiss ADME web based tool is free online software used for screening of pharmacokinetic properties like absorption, distribution, metabolism and excretion. We have also predicted the oral bioavailibity, lipophilicity and solubility of ligand molecules. Structures were drawn on the screen of software, which is then converted into SMILES format as an input file. As we know, that absorption of drugs relies on water solubility, skin permeation (log Kp), P-glycoprotein, gastro- intestinal absorption and permeability, and distribution is influenced by Blood Brain Barrier (BBB). Different CYP models are used to evaluate the distribution and metabolism of oxazole derivatives specifically the CYP1AC2 inhibitor, CYP2C19 inhibitor, CYP2C9 inhibitor, CYP2D6 inhibitor and CYP3A4 inhibitor. Lastly, excretion is influenced by the total clearance. Table 3 shows the predicted results of all the 25 derivatives and the standard drug.

The Swiss ADME software also provides a graphical representation of orally available bioactive drug. This is indicated graphically as a hexagon shown in Figure 4, each of which indicates a parameter crucial for bioavailable drug. The pink hexagonal area describes various properties like lipophilicity, solubility, molecular weight, polarity, flexibility and in saturation [30-35].

Figure 4. Swiss ADME structural features and bioavailability radar of standard rosiglitazone and other docked ligand 4, 9, 13, 14, and 21.



Drug score and toxicity prediction of selected ligands

By using computational drug designing a novel drug molecule can be develop which provide drug with low toxicity for use of oral administration. The drug marketed for oral use must be non-toxic and possess good absorption and dissolution in gastro- intestinal tract to reach the blood. So, drug solubility and dissolution (log S) is an important factor in for drug likeness prediction. Afterwards, these compounds 1 to 25 and standard drug were also simulated for solubility, toxicity, drug score and drug likeness using OSIRIS tool. The properties of these derivatives like mutagenic, tumorigenic, skin irritation, and reproductive effect are coded in colors. High toxicity is indicated by red color, yellow indicates standard drug and green shows no toxicity risk. Table 4 shows OSIRIS data of selected 26 compounds. The blue color indicates the importance of standard ligand 26. Over all the compounds ligand 4, 9, 13, 14, and 21 are highlighted, having excellent drug score and possesses low toxicity [36].

In Table 4 the colour shades represents that the ligand 26 in yellow colour shows standard drug rosiglitazone, ligands 6, 8 in red represents high toxicity risk and green colour represents that ligand 4, 9, 13, 14, and 21 indicates no toxic risk with high drug score [37].

We have also predicted toxicity through the online available software toxtree (v 3.1.0 version) for comparison, which is used to identify, analyze and estimate the toxic hazard using decision tree approach. It is done by entering smiles of the ligand molecule as an input file, and the results collected from Toxtree freeware.

Molecular docking study using autodock 4

Molecular docking of all the selected oxazole derivatives was done by using autodock software. Autodock 4 version used ligand and protein structure in PDB format. The anti-diabetic activity of these molecules was predicted by evaluating the binding energy score and binding affinity when the selected ligand fit to target receptor. All the parameters were evaluated and show that the drug with lowest binding energy gives the excellent interactions. In our study, rosiglitazone was used as standard drug for comparison purpose and was docked with PPARγ receptor to recognize the predicted data. The docking studies reveal that the molecules with lowest negative binding energies are known to be best docked oxazole derivatives with PPARγ. The target protein was prepared in autodock software by removing water and heteroatoms. Then addition of polar hydrogens and Kollman charges was done. Grid was generated using grid box for binding at specific amino acid at the receptor site. Then docking was done after ligand and protein preparation using run autodock option and results were saved as dlg file format [38].

RESULTS AND DISCUSSION

Predicted physicochemical properties of ligand

Structure of oxazole derivatives are given in Figure 1. The physical parameters of selected oxazole derivatives, such as Hydrogen Bond Donor (HBD), Hydrogen Bond Acceptor (HBA), log P, molar refractivity, molecular weight and Lipinski violation are listed in Table 2 In drug discovery and drug design, the main aim is to predict that the selected molecules should be safe, non-toxic and biologically active. So we have investigated 25 ligands and standard drug molecules for toxicity and drug likeness. These physicochemical properties of different derivatives are listed in Table 3. All the compounds obeyed Lipinski's rule of five and Veber's approach, which is an essential rule for analyzing drug likeness and developing a molecule that enhances its oral activity and bioavailability.33 Lipinski rule of five indicates that the compounds should have, molecular weight less than 500 DA, log P should be less than or equal to 5, HBD is less than or equal to 5, HBA is less than or equal to 10 and molar refractivity should be between 40-130. So in Table 2 all the compounds follow this rule and indicate high oral absorption and permeation of compounds. Other than this rule, we have also examined Veber's rule which is needed to predict oral bioavailability. This rule states that the Polar Surface Area (PSA) should be less than or equal to 140 Å and number of rotatable bonds should be less than 12. This rule indicates that the drug can be absorbed easily and permeable. All the data of selected compounds follows these rules are listed in Table 2. From all the 26 lead compounds, ligand 2, 6, 15, 19, 21, 22, 24, and 25 shows log P more than 3 due to presence of bulky aromatic ring substituted in oxazole moiety. Lipophilicity (log P) value should be range in between 0 to 3 which shows excellent bioavailability, solubility and permeability. All the 26 compounds showing log P values between -0.20 to 4.26 are listed in Table 2.

Table 2. Physicochemical properties of the selected ligands.

Ligand	Molecular formula	Molar weight (g/mol)	CLogP value	HBD	HBA	Lipinski violation	Molar refractivity	TPSA (Å2)	RB
1	$C_{10}H_9NO$	159.18	2.31	0	2	0	46.91	26.03	1
2	$C_{15}H_{11}NO$	221.25	3.45	0	2	0	67.38	26.03	2
3	$C_9H_8N_2O$	160.17	1.56	1	2	0	46.34	52.05	1
4	$C_{13}H_{15}N_3O_3$	261.28	0.32	3	5	0	70.14	101.38	6
5	$C_{14}H_{10}N_2O$	222.24	2.7	0	3	0	65.17	38.92	2
6	$C_{19}H_{13}NO$	271.31	4.36	0	2	0	84.88	26.03	2
7	$C_{12}H_{12}N_2O_2$	216.24	1.5	1	3	0	59.43	69.12	4
8	$C_{11}H_9NO$	171.2	2.59	0	2	0	52.03	26.03	2
9	$C_{12}H_{10}N_4O_3$	258.23	0.56	3	4	0	72.97	96.26	3
10	$C_{11}H_8N_2O$	184.19	1.88	0	3	0	51.46	49.82	2
11	$C_{13}H_{14}N_2O_3$	246.26	0.52	2	5	0	65.81	89.35	5
12	$C_{16}H_{12}N_2O_2$	264.28	2.55	1	3	0	75.47	69.12	3
13	$C_{10}H_7N_2O_2Cl$	222.63	1.78	1	3	0	55.04	69.12	2
14	$C_8H_{10}N_4O_4$	226.19	-0.28	3	5	0	58.83	105.59	4
15	$C_{15}H_{13}NO_2$	239.27	3.47	0	3	0	70.74	35.26	3
16	$C_9H_{15}N_3O_3$	213.23	-0.52	3	5	0	54.48	101.38	6
17	$C_{12}H_{12}N_2O_3$	232.24	1.67	1	4	0	61.33	78.35	4

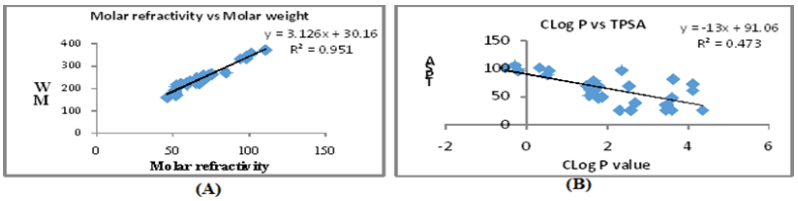
18	$C_{10}H_{10}N_2O_2$	190.2	1.79	0	4	0	51.03	48.15	3
19	$C_{13}H_8NOCl$	229.66	3.6	0	2	0	64.46	26.02	1
20	$C_6H_5N_4O_3Cl$	216.58	-0.2	3	4	0	52.54	96.26	2
21	$C_20H_{18}N_2O_3$	334.37	3.6	0	4	0	98.17	47.73	5
22	$C_{23}H_{21}N_3O_2$	371.43	3.63	2	4	0	110.79	81.15	7
23	$C_{10}H_{12}N_2O_3$	208.21	1.7	0	5	0	52.12	61.29	5
24	$C_{21}H_{18}N_2O_3$	346.38	4.12	1	5	0	98.68	72.29	5
25	$C_20H_{16}N_2O_3$	332.35	4.12	0	5	0	94.17	61.29	5
26	$C_{18}H_{19}N_3O_3S$	357.43	2.36	1	4	0	101.63	96.83	7

Clog P: Lipophilicity; HBD: Number of Hydrogen Bond Donor; HBA: Number of Hydrogen Bond Acceptor; TPSA: Topological Polar Surface Area (Å^2), RB: Number of Rotatable Bonds.

Analysis of correlation coefficient

Various physicochemical parameters are used to analyze correlation coefficient between different compounds like Log P, molecular weight, molar refractivity and total polar surface area shown in Table 2. These parameters are important for the analysis of pharmacokinetics and drug designing and development. By correlating any two parameters and analyzing them by scattered plot diagram in Figure 5. Figure 5indicates correlation plot of molar refractivity *vs.* molecular weight and ClogP *vs.* TPSA of selected 26 compounds. The value of regression (R) was found to be 0.951 and 0.473. Hence, the correlation between molar refractivity and molecular weight exhibiting a high positive correlation, with R-value found to be 0.951. ClogP *vs.* TPSA shows less correlation between variables, that is <1. The selected ligand molecules were predicted for physicochemical parameters and shows that ligand 6, 21, 22, 24, and 25 shows highest values of molar refractivity and Clog P values due to presence of bulky aromatic rings and groups attached with oxazole moiety. Hence these lead 6, 21, 22, 24, and 25 were taken for toxicity predictions.

Figure 5. (A) The correlation plot of molecular weight (MW) (g/mol) *vs.* Molar refractivity; (B) The correlation plot of Topological Polar Surface Area (TPSA) (Å^2) *vs.* ClogP value.



In silico ADME prediction using swiss ADME

The predicted ADME properties of oxazole derivatives using Swiss ADME, an online freely available tool, are listed in Table 3. The Total Polar Surface Area (TPSA) of all 26 ligands ranges from 26-105 Å. The result shows that all ligands obey the Lipinski rule, that is, Total Polar Surface Area (TPSA) less than 150 Å, predicting polarity with effective oral absorption and strong membrane permeation.

Compound absorption can be easily predicted by analyzing the Gastro Intestinal Absorption (GIA) and P-glycoprotein substrate. The results of GIA reveal that all the ligand molecules have high oral absorption. For BBB permeability, except ligand number 4, 9, 11, 14, 16, 17, 20, 22, 24, and 26 all other ligand molecules possess a high BBB permeability level. Results reveal that P-gp substrate or inhibitor is an essential parameter to protect the central nervous system and to prevent multidrug resistant cancer due to stimulation of P-gp substrate in cancer cells. So in our study ligand 5, 6, 22, and 24 show high P-gp expression and can be carcinogenic. Daina, et al. in her article nature scientific reports predicted the consensus estimation of log P and the values obtained for the selected ligands ranges from 4.36to -0.20.19 Compound 6, 24 and 25 shows highest Clog P values, this indicates good bioavailability scores of 4.36 and 4.12, on the other hand decreased Clog P between -5.00 and -11.40 indicates high skin permeation. Interaction of ligands with Cytochrome (CYP) P450 enzyme is crucial for metabolism of ligands in liver.

Cytochrome P450 enzyme is the standard mechanism derived for metabolism based drug-drug interactions in pharmacokinetics, this includes several isoenzyme inhibitors such as CYP1AC2, CYP2C19, CYP3A4, CYP2C9, and CYP2D6. 35 From the result show in Table 3 ligand 2, 5, 6, 8, 12, 15, 19, 21, 22, 24, 25, 26 act as inhibitor of CYP1AC2 and CYP2C19. Compound 15, 21, 22, 24, 25, and 26 inhibit CYP2D6, CYP3A4 and CYP2C9. As we conclude that out of 26 screened ligands, ligand 2, 5, 6, 8, 12, 15, 19, 21, 22, 24, 25, 26 might be metabolized in the liver. At last elimination and excretion of drug molecules can be predicted by solubility and molecular weight of compounds. The results revealed that all the screened molecules follow Lipinski rule of five are said to be drug like (Table 4).

Table 3. Prediction of absorption, distribution, metabolism and excretion parameters of selected oxazole derivatives using Swiss ADME.

Ligand	GI	BBB	P-gp substrate	CYP1AC2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Log K_p
1	High	Yes	No	No	No	No	No	No	-5.57
2	High	Yes	No	Yes	Yes	No	No	No	-5.05
3	High	Yes	No	No	No	No	No	No	-6.11
4	High	No	No	No	No	No	No	No	-4.16
5	High	Yes	Yes	Yes	Yes	No	No	No	-5.82
6	High	Yes	Yes	Yes	Yes	No	No	No	-4.47
7	High	Yes	No	No	No	No	No	No	-6.81
8	High	Yes	No	Yes	Yes	No	No	No	-5.35
9	High	No	No	No	No	No	No	No	-7.04
10	High	Yes	No	No	No	No	No	No	-6.22
11	High	No	No	No	No	No	No	No	-8.47
12	High	Yes	No	Yes	Yes	No	No	No	-6.11
13	High	No	No	No	No	No	No	No	-6.35
14	High	No	No	No	No	No	No	No	-4.54
15	High	Yes	No	Yes	Yes	Yes	Yes	Yes	-4.98
16	High	No	No	No	No	No	No	No	-8.89
17	High	No	No	No	No	No	No	No	-6.62
18	High	Yes	No	No	No	No	No	No	-6.32
19	High	Yes	No	Yes	Yes	No	No	No	-4.71
20	High	No	No	No	No	No	No	No	-7.28
21	High	No	No	Yes	Yes	Yes	Yes	Yes	-5.29
22	High	No	Yes	No	Yes	Yes	Yes	Yes	-5.03
23	High	Yes	No	No	No	No	No	No	-6.36
24	High	No	Yes	Yes	Yes	Yes	Yes	Yes	-5.05
25	High	Yes	No	Yes	Yes	Yes	Yes	Yes	-5.20
26	High	No	No	No	No	Yes	Yes	Yes	-6.27

GI: Gastro Intestinal Absorption; BBB: Blood Brain Barrier Permeation; P-gp: P-glycoprotein substrate; CYP1AC2: Cytochrome P450 family 1 subfamily A member 2 (PDB:2HI4); CYP2C19: Cytochrome P450 family 2 subfamily C member 19 (PDB:4GQS); CYP2C9: Cytochrome P450 family 2 subfamily C member 9 (PDB:1OG2); CYP2D6: Cytochrome P450 family 2 subfamily D member 6 (PDB:5TFT); CYP3A4: Cytochrome P450 family 3 subfamily A member 4 (PDB:4K9T); Log Kp: Skin permeation in cm/s.

Table 4. Drug score and toxicity studies of selected compounds using OSIRIS freeware.

Ligands	Log S	Drug likeness	Drug score	Toxicity			
				Mutagenic	Tumorigenic	Reproductive effect	Irritant
1	-2.47	-0.08	0.69	No	No	No	No
2	-4.99	1.52	0.6	No	Yes	No	No
3	-3.19	0.13	0.69	No	No	No	No
4	-3.49	0.59	0.71	No	No	No	No
5	-3.88	0.56	0.67	No	Yes	No	No
6	-6.59	-1.9	0.25	Yes	Yes	Yes	No
7	-2.45	0.21	0.73	Yes	No	No	No
8	-2.93	-4.28	0.22	Yes	Yes	Yes	No
9	-3.57	3.04	0.85	No	No	No	No

10	-2.78	-6.87	0.28	No	No	No	Yes
11	-2.72	-5.21	0.46	No	No	No	No
12	-5.08	-0.27	0.24	Yes	Yes	No	No
13	-3.8	0.87	0.74	No	No	No	No
14	-2.63	1.17	0.83	No	No	No	No
15	-5.66	-4.26	0.3	No	No	No	No
16	-2.23	-10.53	0.48	No	Yes	No	No
17	-4.14	-2.51	0.21	No	No	No	No
18	-3.26	-1.18	0.56	No	No	No	No
19	-5.31	-2.54	0.33	No	No	No	No
20	-2.29	2.8	0.62	No	No	No	No
21	-6.04	0.41	0.75	No	No	No	No
22	-6.61	-1.38	0.17	No	Yes	No	No
23	-1.56	-3.07	0.5	No	Yes	No	No
24	-5.61	-0.49	0.36	Yes	Yes	Yes	No
25	-7.42	-1.25	0.25	Yes	Yes	Yes	No
26	-3.67	9.14	0.8	No	No	No	No

Drug score and toxicity prediction

The dissolution of drug can be monitored by drug solubility (log S) analysis which plays an important role to know aqueous solubility of drug in gastrointestinal tract and can cross blood brain barrier easily. The dissolution of drug depends mainly on surface area of the compound. Therefore, aqueous solubility (log S) of the drug considered to be higher than -6 which affect drug absorption. The drug score is used to analyze all essential parameters such as drug likeness, molecular weight, Clog P value, and toxicity prediction. If any of the 26 selected ligand molecules shows zero or negative value of drug score, it would be rejected and not considered as drug-like while if the score is greater than zero, it is known to be drug like molecule.

As we know that toxicity is the pivotal parameter to analyze whether the ligand is toxic or non-toxic. In our research toxicity is predicted by online available tool OSIRIS and toxtree. OSIRIS model is used to predict drug score, log S, drug-likeliness and toxicity. *In vitro* and *in vivo* toxicity studies are considered to be tedious and costly. So in silico toxicity and drug-likeliness study of compounds has been effectively studied without excessive animal trials. The OSIRIS software predicts several toxicity parameters such as tumorigenic effect, mutagenicity, reproductive effect, and irritant effect of compounds. Drug can show toxicity with no risk, medium risk, and high risk. In our study, selected ligands are effective and cause no toxicity. The ligand number 6, 8, 24, and 25 show high toxicity risk predicted in Table 5. As we know that any chemical in higher quantities is extremely lethal if taken in higher quantities but perform like a drug when used in therapeutic doses. Hence, an optimum amount will act as a drug.

In our research, standard drug Rosiglitazone shown in Figure 1 (compound 26) to validate the software, which shows drug likeness and drug score is about 0.80 and non-toxicity risk. All ligands show drug score values ranging from 0.1 to 0.9 not less than zero or negative. Compound 4, 9, 13, 14, 21, and 26 show drug score from 0.7 to 0.9, which is closer to 1 and therefore considered as druggable compound, also these are non-toxic (Table 5). Toxtree prediction also conforms the compounds are druggable with no toxicity listed in Table 5. Compound 4, 9, 13, 14, 21, and 26 possess low toxicity risk as estimated by Toxtree method. Cramer's rule indicates that all the above compounds are in high class and Kroes Thresholds of Toxicological Concern (TTC) decision tree estimates the toxicity nature of compounds. The Quantitative Structure Activity Relationship (QSAR) assess the risk for carcinogenicity and skin sensitization through decision tree approach, which prove no risk for above numbered compounds. So it is concluded that among 25 oxazole derivatives, the ligands 4, 9, 13, 14, and 21 are druggable ligands when compared with the standard drug, Rosiglitazone. Hence, in silico methods is an efficient method intended for predicting toxicity.

Table 5. Prediction of toxicity for selected ligands using toxtree freeware.

Ligand	Carmmer's rule	Kroes TTC	Carcinogenicity	Skin sensitization	Protein binding
1	High class	High risk	Yes	No	Yes

2	High class	Low risk	Yes	No	Yes
3	High class	High risk	No	No	Yes
4	High class	Low risk	No	No	Yes
5	High class	High risk	No	No	Yes
6	High class	High risk	Yes	Yes	No
7	High class	Low risk	Yes	No	No
8	High class	High risk	Yes	Yes	No
9	High class	Low risk	No	No	No
10	High class	High risk	Yes	Yes	No
11	High class	Low risk	Yes	Yes	No
12	High class	High risk	Yes	Yes	Yes
13	High class	Low risk	No	No	No
14	High class	Low risk	No	No	No
15	High class	Low risk	Yes	No	No
16	High class	High risk	Yes	Yes	Yes
17	High class	High risk	No	No	Yes
18	High class	High risk	Yes	Yes	Yes
19	High class	High risk	Yes	No	Yes
20	High class	High risk	Yes	No	No
21	High class	Low risk	No	No	No
22	High class	High risk	Yes	No	No
23	High class	High risk	Yes	Yes	Yes
24	High class	High risk	Yes	No	No
25	High class	High risk	Yes	No	No
26	High class	Low risk	No	No	No

Molecular docking study using autodock 4 software

Prior the process of docking studies, the 3D target protein crystal structure of PPARγ (1PRG) was downloaded from PubChem database in SDF format and converted in PDB file format using open babel software. The target protein interaction with ligand was analyzed using autodock 4 and binding energy has been predicted in range from –5.42 to -9.48 Kcal/mol (Table 6). In our study, standard rosiglitazone was docked against 1PRG receptor protein and the binding energy obtained was -9.77 Kcal/mol shown in Figure 6. Among all oxazole derivatives, ligand 4, 9, 13, 14, and 21 show best docking interactions with highest binding energy values ranging -8.13 to -9.48 Kcal/mol against 1PRG when compared with standard rosiglitazone. The picture of 1PRG receptor interaction with ligand 4, 9, 13, 14 and 21 docking was shown in Figure 6 to 11. Hence, we can conclude that compound 4, 9, 13, 14 and 21 indicates highest binding energy with no toxicity and act as a potential anti-diabetic compound compared to standard drug rosiglitazone. The highest docking results of rosiglitazone with ligand 4, 9, 13, 14 and 21 was obtained using autodock 4 and visualized using Discovery Studio Visualizer, a free available software. The standard drug rosiglitazone, which is widely used as anti-diabetic drug available in market, showed the docking score of 0.80 and binding energy value of -9.77 Kcal/mol. For standard drug rosiglitazone, the 2D amino acid interaction is Leu476, Asp475, Tyr340, Ile472, Lys319, His323, Val450, and Leu476 shown in Figure 6B. Molecular docking of ligand 4 with target protein PPARγ receptor showing amino acid residues Cys285, Arg288, His449, Glu369, Ser289, Pro366, Leu469, and Tyr473 represented by green colour showing hydrogen bonding, orange indicates pi cation, pink colour indicates pi-pi interaction and blue is pi donor hydrogen bond in Figure 7A and 7B. Ligand 9 showing amino acd residues Glu291, Glu343, Glu295, Arg288, Val339, and Leu228 in green colour indicates hydrogen bonding with CO and NH, and purple color is sowing pi sigma bond in Figure 8A and 8B. 2D molecular docking of ligand 13 in the receptor binding shows amino acid residues Met329, Ile325, Arg288, Ala292, Ser289 in dotted lines represented by pi-pi interactions by pink lines, and green color shows hydrogen bond with amino acids shown in Figure 9A and 9B. 3D and 2D Molecular docking of ligand 14 with receptor PPARγ shows amino acid residues Leu421, Leu431, Phe432, His425, Lys422, and Ser429 are shown in dotted lines and represented by pi-pi interactions indicated by pink lines, and green color shows hydrogen bond with amino acids shown in Figure 10. 3D and 2D molecular docking of ligand 21 with receptor show amino acid residues Met329, Ala292, Arg288, Ile341, Val339, Leu340, and Glu295 in dotted lines are represented by pi-pi interactions in orange lines, and pink indicates alkyl and pi

alkyl bond in Figure 11. The best docking pose structure of Rosiglitazone and ligand 4, 9, 13, 14, and 21 with PPARγ receptor sites given in Figure 12. The ligand 4, 9, 13, 14, and 21, a novel oxazole derivatives exhibits significant stimulation of PPARγ. Further these screened ligands can be selected for clinical trials and validated for ant-diabetic activity.

Figure 6. Molecular docking of standard rosiglitazone with target PPARγ receptor using discovery studio visualizer and AutoDock 4 (A) structure showing aromatic ring (B) 3D interaction of drug with target protein (C) Interaction of drug with ribbon structure of target protein showing amino acid residues of proteins Leu476, Asp475, Tyr340, Ile472, Lys319, His323, Val450, Leu476.

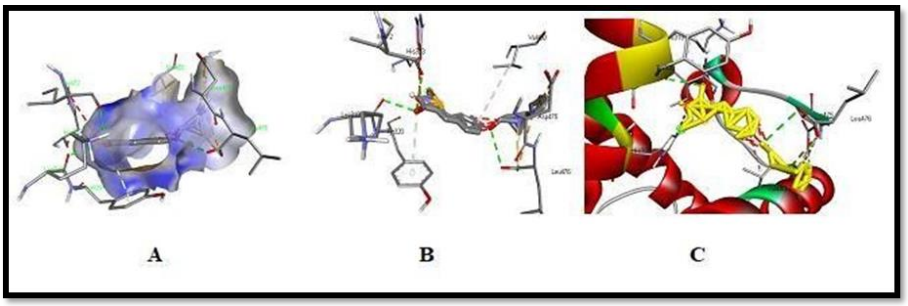


Table 6. The docking minimum binding energies of ligands with PPARγ and interacting residues.

Ligand	Minimum binding energy (Kcal/mol)	RMSD score (Å)	Interacting residues
1	-5.99	63.62	Met364, Cys285, Ile281, His449, Phe282
2	-7.86	62.87	Ile281, Phe264, Cys285, Arg288, Ile341, Sre342
3	-7.48	38.24	Leu431, Phe432, Leu421, Lys422, Ser428, His425
4	-9.46	67.68	Cys285, Arg288, His449, Glu369, Ser289, Pro366, Leu469, Tyr473
5	-8.51	66.31	Cys285, Met364, His449, Ser289
6	-8.49	57.47	Pro227, Glu343, Leu333, Leu340, Val339, Cys285, Arg288, Ile241, Glu295, Leu228
7	-6.62	61.12	Met329, Glu291, Glu343, Pro227, Glu295, Ala292
8	-6.33	67.84	His449, Ser289, Leu465, Leu469, Leu453, Phe363, Met364, Cys285, Phe282, Gln286
9	-8.13	62.85	Glu291, Glu343, Glu295, Arg288, Val339, Leu228
10	-6.99	67.90	Met364, Cys285, His449, Phe363, Phe282, Ser289
11	-8.83	68.10	Met364, Phe282, Phe360, Cys285, His449, Ser289
12	-7.43	54.23	Glu295, Ala292, Pro227, Met329, Leu333
13	-9.48	53.95	Met329, Ile325, Arg288, Ala292, Ser289
14	-8.75	33.89	Leu421, Leu431, Phe432, His425, Lys422, Ser429
15	-9.27	67.34	His449, Arg288, Cys285, Phe282, Met364, Leu356, Ile281
16	-5.42	59.11	Glu291, Glu295, Leu333, Leu228, Pro227, Arg288, Lys265
17	-6.29	59.42	Arg288, Leu228, Glu295, Pro227, Glu295, Leu333, Ala292, Ile326, Met329
18	-6.09	67.98	Phe282, Phe363, His449, Met364, Cys285, Ile281
19	-8.02	60.22	Glu295, Leu475, Arg288, Cys285, Lys265, Leu228
20	-7.02	57.34	Leu421, Leu431, His334, Arg288, Ile326
21	-8.54	54.34	Met329, Ala292, Arg288, Ile341, Val339, Leu340, Glu295

22	-9.54	59.82	Tyr473, Gln286, Asp475, His449, Cys285
23	-5.58	61.48	Glu295, Leu340, Arg288, Ile341, Leu333
24	-9.03	68.92	Phe264, Cys285, Ile341, Leu340, Ser342, Ala292, Gly291, Arg288
25	-6.33	58.22	Leu255, Arg280, Ile281, Ile341, Gly284, Met348, Cys285, Phe264, His266
26 (Rosiglitazone)	-9.77	63.62	Leu476, Asp475, Tyr340, Ile472, Lys319, His323, Val450, Leu476

The ligand 4, 9, 13, 14, 21 as compared with standard drug rosiglitazone shows high binding affinity when docked with receptor is indicated in bold showing amino acid interacting residues (Figures 7-12).

Figure 7. (A) Molecular docking of ligand 4 with target protein PPARγ receptor performed in discovery studio visualizer showing amino acid residues Cys285, Arg288, His449, Glu369, Ser289, Pro366, Leu469, Tyr473; (B) Schematic 2D interaction of ligand 4 with amino acid residues of protein. Green colour indicates hydrogen bonding, orange indicates pi cation, pink colour indicates pi-pi interaction and blue is pi donor hydrogen bond.

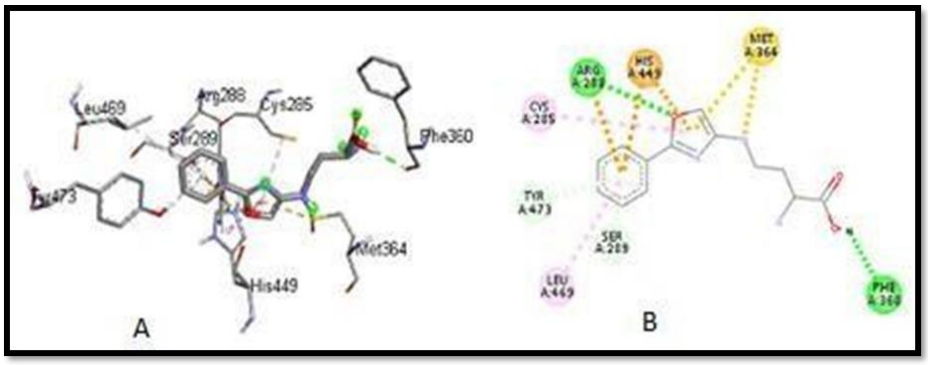


Figure 8. (A) 3D Molecular docking of ligand 9 with target protein PPARγ receptor performed in discovery studio visualizer showing amino acid residues Glu291, Glu343, Glu295, Arg288, Val339, Leu228 (B) Schematic 2D interaction of ligand 4 with amino acid residues of protein. Green colour indicates hydrogen bonding with CO and NH, and purple color is sowing pi sigma bond.

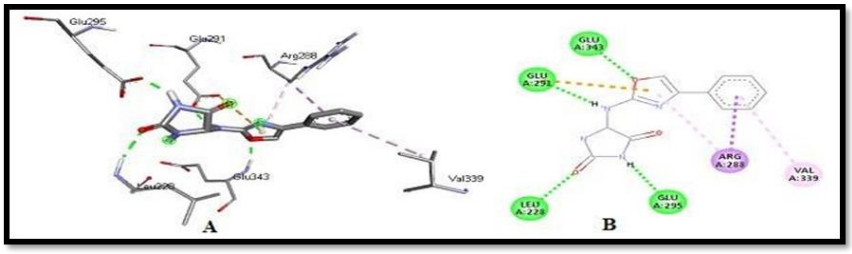


Figure 9. (A) 3D molecular docking of ligand 13 in the receptor binding site performed using discovery studio visualizer. The amino acid residues Met329, Ile325, Arg288, Ala292, Ser289 are shown in dotted lines; (B) Schematic 2D docking of ligand 13 with amino acid residues of receptor protein are represented by pi-pi interactions indicated by pink lines, and green color shows hydrogen bond with amino acids.

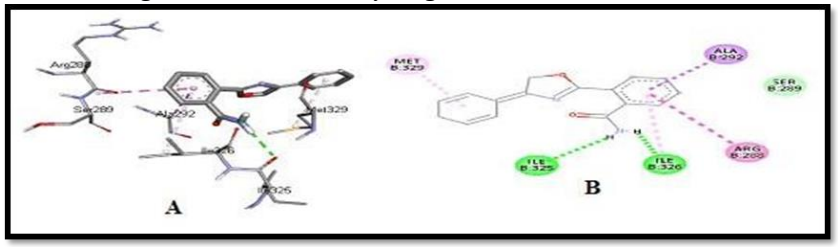


Figure 10. (A) 3D Molecular docking of ligand 14 with receptor PPARγ performed using discovery studio visualizer. The amino acid residues Leu421, Leu431, Phe432, His425, Lys422, Ser429 are shown in dotted lines; (B) Schematic 2D

docking of ligand 14 with amino acid residues of receptor protein are represented by pi-pi interactions indicated by pink lines, and green color shows hydrogen bond with amino acids.

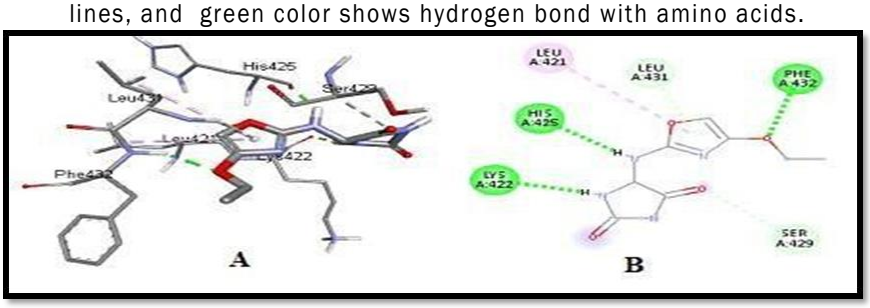


Figure 11. (A) 3D Molecular docking of ligand 21 with receptor PPARγ performed using discovery studio visualizer. The amino acid residues Met329, Ala292, Arg288, Ile341, Val339, Leu340, Glu295 are shown in dotted lines; (B) Schematic 2D docking of ligand 21 with amino acid residues of receptor protein are represented by pi-pi interactions indicated by orange lines, and pink indicates alkyl and pi alkyl bond.

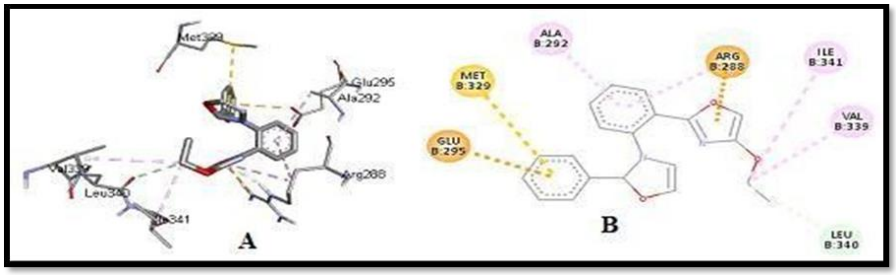


Figure 12. Molecular docking of best docked ligand 4, 9, 13, 14, and 21 indicated within the active site of PPARγ receptor performed in autodock 4 software.

CONCLUSION

Present research exhibit the evaluation data of 25 oxazole derivatives including their physicochemical properties, ADME parameters, drug likeliness, drug score, and toxicity using freely available software such as autodock 4, OSIRIS, discovery studio visualizer, swiss ADME, open babel, toxtree, CASTp and Pymol. Among these ligand 4, 9, 13, 14, and 21 possess drug likeliness properties and best docking energy values using autodock 4 software. Molecular docking of these selected ligands are also seen through discovery studio visualizer showing best docking pose against PPARγ receptor as compared to that of Rosiglitazone as a standard drug. Therefore, it is concluded that oxazole derivative 4, 9, 13, 14, and 21 could be potential anti-diabetic drug candidates.

Conflict of interest

The authors declare no conflict of interest related to the article.

REFERENCES

1. Al-Awar A, et al. Experimental diabetes mellitus in different animal models. J Diabetes Res. 2016:1-12.
2. Halim M, et al. The effects of inflammation, aging and oxidative stress on the pathogenesis of diabetes mellitus (type 2 diabetes). Diabetes Metab Syndr Clin Res Rev. 2019;13:1165-1172.

3. Tan SY, et al. Type 1 and 2 diabetes mellitus: A review on current treatment approach and gene therapy as potential intervention. Diabetes Metab Syndr Clin Res Rev. 2019;13:364-372.
4. Galicia-Garcia U, et al. Pathophysiology of type 2 diabetes mellitus. Int J Mol Sci. 2020;21:6275-6280.
5. Chaudhury A, et al. Clinical review of antidiabetic drugs: Implications for type 2 diabetes mellitus management. Front Endocrinol. 2017;8:1-12.
6. Baynes HW, et al. Classification, pathophysiology, diagnosis and management of diabetes mellitus. J Diabetes Metab. 2015;6:1-9.
7. Inzucchi SE, et al. Oral antihyperglycemic therapy for type 2 diabetes: Scientific review. Jama. 2002;287:360-372.
8. Shah N, et al. Therapeutics for type-2 diabetes mellitus: a glance at the recent inclusions and novel agents under development for use in clinical practice. Ther Adv Endocrinol Metab. 2021;12:1-30.
9. Nguyen ND, et al. Targeted proteins for diabetes drug design. Adv Nat Sci Nanosci Nanotechnol. 2012;3:1-9.
10. Hernandez-Quiles M, et al. PPARgamma in metabolism, immunity, and cancer: Unified and diverse mechanisms of action. Front Endocrinol. 2021;12:1-17.
11. Holm LJ, et al. PPARs and the development of type 1 diabetes. PPAR Res. 2020:1-11.
12. Kume S, et al. Peroxisome proliferator activated receptors in diabetic nephropathy. PPAR Res. 2008:1-11.
13. Zhang HZ, et al. Recent advance in oxazole based medicinal chemistry. Eur J Med Chem. 2018;144:444-492.
14. Kakkar S, et al. A comprehensive review on biological activities of oxazole derivatives. BMC Chem. 2019;13:1-24.
15. Ferreira LG, et al. Molecular docking and structure-based drug design strategies. Molecules. 2015;20:13384-13421.
16. Meng XY, et al. Molecular docking: A powerful approach for structure based drug discovery. Curr Comput Aided Drug Des. 2011;7:146-157.
17. Sabe VT, et al. Current trends in computer aided drug design and a highlight of drugs discovered via computational techniques: A review. Eur J Med Chem. 2021;224:2-14.
18. Veselovsky AV, et al. Strategy of computer aided drug design. Curr Drug Targets Infect Disord. 2003;3:33-40.
19. Daina A, et al. Swiss ADME: A free web tool to evaluate pharmacokinetics, drug likeness and medicinal chemistry friendliness of small molecules. Scientific reports. 2017;7:1-3.
20. Huang HJ, et al. Current developments of computer aided drug design. J Taiwan Inst Chem Eng. 2009;41:623-635.
21. Sander T, et al. OSIRIS, an entirely in house developed drug discovery informatics system. J Chem Infor Model. 2009;49:232-246.
22. Yang H, et al. In silico prediction of chemical toxicity for drug design using machine learning methods and structural alerts. Front Chem. 2018;6:1-30.
23. Valdés-Tresanco MS, et al. AMDock: A versatile graphical tool for assisting molecular docking with Autodock Vina and Autodock4. Bio Direct. 2020;15:1-2.
24. Kapetanovic I, et al. Computer aided drug discovery and development (CADDD): In silico chemico biological approach. Chem Bio Interact. 2008;171:165-176.
25. Khanal P, et al. In silico antidiabetic screening of borapetoside C, cordifolioside A and magnoflorine. Indian J Pharm Sci. 2019;81:550-555.
26. Usha T, et al. Recent updates on computer aided drug discovery: Time for a paradigm shift. Curr Topics Medi Chem. 2017; 17:3296-3307.
27. Fan J, et al. Progress in molecular docking. Quant Biol. 2019;7:83-89.
28. Ranjith D, et al. Swiss ADME predictions of pharmacokinetics and drug likeness properties of small molecules present in Ipomoea mauritiana Jacq. J Pharmacogn Phytochem. 2019;8:2063-2073.
29. Rajalakshmi R, et al. In Silico studies: Physicochemical properties, drug score, toxicity predictions and molecular docking of organosulphur compounds against Diabetes mellitus. J Mol Recognit. 2021;34:2925.
30. Lin X, et al. A review on applications of computational methods in drug screening and design. Molecules. 2020;25:1375.
31. Pinzi L, et al. Molecular docking: Shifting paradigms in drug discovery. Int J Mol Sci. 2019;20:4331.
32. B Fernandes T, et al. Analysis of the Applicability and Use of Lipinskis Rule for Central Nervous System Drugs. Lett in Drug Des Discov. 2016;13:999-1006.
33. Walters WP, et al. Virtual screening an overview. Drug Discov. 1998;3:160-178. [Crossref][Googlescholar][Indexed]
34. Doak BC, et al. Oral druggable space beyond the rule of 5: insights from drugs and clinical candidates. Chem Biol. 2014; 21:1115-1142.
35. Manikandan P, et al. Cytochrome P450 structure, function and clinical significance: A review. Curr Drug Targets. 2018;19:38-54.
36. Srivastava R, et al. Theoretical Studies on the Molecular Properties, Toxicity, and Biological Efficacy of 21 New Chemical Entities. ACS Omega. 2021;6:24891-24901.
37. Kapetanovic I, et al. Computer Aided Drug Discovery and Development (CADDD): In silico chemico biological approach. Chem Biol Interact. 2008;171:165-176.
38. Yuriev E, et al. Challenges and advances in computational docking: 2009 in review. J Mol Recognit. 2011;24:149-164.