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IN-SILICO DESIGN AND PHARMACOKINETIC PREDICTION STUDIES OF NOVEL BENZOTHIAZOLE CLUBBED OXADIAZOLE DERIVATIVES FOR ANTI-DIABETIC ACTIVITY

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ABSTRACT

Diabetes is one of the pre-dominant metabolic disorders all over the world. It is an increasingly important condition globally and robust estimates of its prevalence are required for allocating resources. In this regard, we have designed and evaluated a small library of twenty derivatives of benzothiazole clubbed oxadiazole in search of potent anti-diabetic agents through *in-silico* studies using Glide 5.5 extra precision (XP) maestro Schrodinger software. Compounds 5A, 5B, 5J and 5K shows excellent activities on PPAR-γ and compounds 5A, 5B, 5D, 5H, 5J, 5K and 5L showed good activities on α-glucosidase and α-amylase than standard drug acarbose. Comparatively designed compounds shows least activity on DPP4 receptor. Molecular docking studies were done to assess the binding mode and interactions of synthesized hits at binding site of receptors. Results of in-silico studies showed that most of the compound have excellent drug likeness properties, pharmacokinetic profile and are preferable as an orally available drug. Here in we conclude benzothiazole incorporating oxadiazole could be considered as promising scaffolds towards the development of novel antidiabetic agents.

KEYWORDS: Benzothiazole, oxadiazole, anti-diabetic potential, *in-silico* studies, Schrodinger.

INTRODUCTION

Diabetes mellitus is one of the most common chronic diseases in nearly all countries and continues to increase in numbers and significance, as economic development and urbanization lead to changing lifestyles characterised by reduced physical activity and increased obesity. Type 2 diabetes mellitus (T2DM) or non-insulin dependent diabetes mellitus (NIDDM) is considered as one of the life threatening disease with an increasing occurrence globally. It is predominantly an effect based on diet and social habits, described by reduced insulin sensitivity where by reduced uptake of glucose from blood. Prolonged exposure to high glucose level in blood can lead to irreversible damage to eyes, nerves, kidney and heart. The International Diabetes Federation (IDF) estimated that the global prevalence of diabetes is predicted to grow from 415 million at present to 642 million by 2040.[1] Therefore, effective therapeutic strategies against type 2 diabetes are important priorities for public health.

Currently, there are different class of hypoglycemic agents are used. Among those targets the four most important anti-diabetic targets are α-glucosidase, α-amylase, PPAR-γ and DPP4. α-glucosidase is one of the potential therapeutic approaches that reduce absorption of glucose and delay carbohydrate digestion hence maintaining blood glucose level. Several types of α-glucosidase inhibitors have been marketised including acarbose, voglibose and miglitol. However due to numerous side effects of these drugs, medicinal chemists are continuously in struggles to discover new α-glucosidase inhibitors. Peroxisome proliferator-activated receptors form a subfamily of the nuclear hormone receptor super family which is effectively indulged in regulating the genes expression involved in glucose and lipid metabolism. It has the highest expression level in adipocytes and its activation regulates the carbohydrates metabolism and decreases blood lipids levels through the increase in the expression of the target genes involved in glucose and lipids metabolism. DPP4 is a serine protease expressed in most tissues. DPP4 regulates insulin secretion by the inactivation of GIP and GLP-1 through removing two amino acids from the N terminus of both hormones. Enhancing the duration of endogenous incretin hormone by inhibiting DPP4 function is now a validated approach in treatment of type 2 diabetes.[2-5] In this study we have designed and evaluated the anti-diabetic potential of twenty derivatives of benzothiazole clubbed oxadiazole through *in-silico* studies.

Benzothiazole is a heterocyclic compound with diverse range of biologically activity. Benzothiazole and its derivatives shows numerous activities such as

antimicrobial,[6] antitumor,[7] analgesic and anti-inflammatory,[8] antileishmanial,[9] antidiabetic,[10] antiviral[11] and anti-tubercular[12] activities. Structurally, benzothiazole skeleton is a fusion of benzene ring and thiazole moiety. It has the ability to control diabetes mellitus. Since, it is involved in inhibition of 11-hydroxysteroid dehydrogenase type 1, it has the ability to stimulate insulin secretion and has known hypoglycaemic mechanism.[13] Oxadiazoles are five-membered ring heterocyclic compounds containing oxygen and nitrogen atoms. Nucleus exists in four possible isomer forms but 1, 3, 4-oxadiazole is widely explored for various applications. 1,3,4-Oxadiazole improves diabetes by means of anti-oxidative action.[14] Thus based on the aforementioned points, it was thought worthwhile to prepare new anti-diabetic agent having integrated benzothiazole ring and 1,3,4-oxadiazole with an objective to obtain biologically active, safer and relatively low costs anti-diabetic agents.

MATERIALS AND METHODS

ACD/ChemSketch

ACD/ChemSketch is a molecular modelling program used to create and modify images of chemical structures. Also, this software allows molecules and molecular models displayed in two and three dimensions, to understand the structure of chemical bonds and the nature of functional groups. Chemical structures and SMILES notations of the compounds were obtained by using ACD labs Chemsketch version 12.0 (www.acdlabs.com/resources/freeware/chemsketch/).

Molinspiration

Molinspiration offers free on-line cheminformatics software for calculation of important molecular properties such as partition coefficient (Log P), Topological polar surface area (TPSA), Hydrogen bond donors and acceptors, rotatable bonds, number of atoms, molecular weight and violation of Lipinski's rule of five and to predict bioactivity scores for drug targets including enzymes and nuclear receptors, kinase inhibitors, GPCR ligands and ion channel modulators.[29] SMILES notations of the selected derivatives were fed in the online Molinspiration software (https://www.molinspiration.com/) to predict the drug likeness properties. Lipinski's rule of five is used in drug design and development to predict oral bioavailability of potential lead or drug molecules.

Pharmacokinetic parameters and toxicity potential

ADME refers to the absorption, distribution, metabolism and excretion of a molecule in an organism. All these factors are important for a molecule which acts as a drug. Having favourable ADME characteristics is the most pre-requisite for drug development. The identification and elimination of unfavourable compounds makes the research process more cost-effective and efficient.For this reason, prediction of the pharmacokinetic properties of the new drug candidates as early as possible in the drug development process is very important.[15]

PkCSM software

pkCSM provides a platform for the analysis and optimization of pharmacokinetic and toxicity properties implemented in a user-friendly, freely available web interface (http://structure.bioc.cam.ac.uk/pkcsm). This is a novel method for predicting and optimizing small-molecule pharmacokinetic and toxicity properties which relies on distance-based graph signatures. The method adapted the Cutoff Scanning concept to represent small-molecule structure and chemistry (expressed as atomic pharmacophores–node labels) in order to represent and predict their pharmacokinetic and toxicity properties, building 30 predictors divided into five major classes: absorption (seven predictors), distribution (four predictors), metabolism (seven predictors), excretion (two predictors), and toxicity (10 predictors).

Molecular docking studies

Molecular docking is one of the most applied virtual screening methods in drug design. In the field of molecular modelling, docking predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex with minimum energy. In this study, molecular docking study was performed using the Schrodinger Maestro interface running on Linux 16.04 operating system. The structure of the ligand was built using the Schrödinger Maestro interface and was then submitted to the Protein Preparation Wizard protocol of the Schrödinger Suite 2016 Update 2. The ligands were prepared using LigPrep 3.8 to correctly assign the protonation states at pH 7.4 ± 1.0, as well as the atom types.Ligand preparation involves 2D or 3D structures and producing their low energy states in maestro format using OPLS 2005 force field, with the possibilities to extend each input structure by generating variation on ionization states. Bond orders were assigned and hydrogen atoms were added to the structures. PDB ID's of the four receptors α-glucosidase, α-amylase, PPAR-γ and DPP4 are as follows 3TOP, 1B2Y, 4EMA and 4A5S and were downloaded from protein data bank with suitable resolution. The protein chain with standard drug was selected and other chain was deleted along with residual water molecules which were beyond 5 Å; leaving behind water molecules near the ligand to yield energy minimized protein structures. These energy minimized protein structures were then used to generate grid which used reference drug as a ligand to signify the binding sites within the receptor target. Finally docking was carried out using Glide software with Extra precision and write XP descriptor information. During this procedure, favourable ligand poses were then generated to determine their spatial fit into the active site of receptor and those who fitted best were then evaluated and minimized for generating glide scores. The Glide score, hydrogen bonds and pi-pi interactions formed with the surrounding amino acids were used to predict the binding affinities and proper alignment of these compounds at the active site of the receptors.

RESULTS AND DISCUSSION

Structure of proposed ligand containing benzothiazole clubbed oxadiazole is shown in Figure 1.

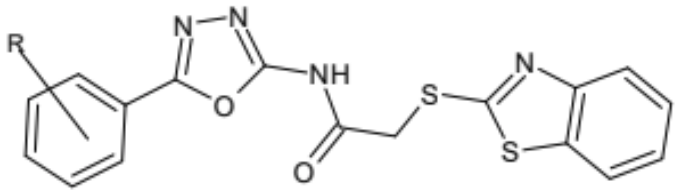

Figure: 1 Designed ligand.

Proposed compounds were designed and evaluated by various in-silico tools such as Chemsketch, Molinpiration, pkCSM, Maestro Schrodinger etc.

Theoretical determination of drug-likeness properties

We predicted the drug likeliness profile of the compounds through analysis of pharmacokinetic properties of the compounds by using molinspiration online property toolkit. Based on the results obtained from molinspiration it was observed that all of the proposed compounds obeyed Lipinski rule of five. According to the Lipinski's rule of five new molecule designed for oral route should have a MW < 500, log Po/w < 5, No more than 5 hydrogen bond donors and No more than 10 hydrogen bond acceptor. None of the proposed derivatives show violation of rule. The results are presented in Table 1.

Table 1: Lipinski rule analysis of proposed derivatives.

S. No	Compound code	R	Molecular weight	Log P	H bond donors	H bond acceptors
1	5A	2,3-dihydroxy	400.44	3.13	8	3
2	5B	3,4-dihydroxy	400.44	2.92	8	3
3	5C	2,5-dihydroxy	400.44	3.12	8	3
4	5D	2,4-dihydroxy	400.44	3.12	8	3
5	5E	3,4-dimethoxy	428.5	3.54	8	1
6	5F	2-hydroxy-4-methoxy	414	3.65	8	2
7	5G	2-hydroxy-5-methoxy	414.47	3.65	8	2
8	5H	3-hydroxy-4-methoxy	414.47	3.23	8	2
9	5I	2-hydroxy	384.44	3.62	7	2
10	5J	3-hydroxy	384.44	3.41	7	2
11	5K	4-hydroxy	384.44	3.41	7	2
12	5L	4-amino	383.46	2.96	7	3
13	5M	3-amino	383.46	2.94	7	3
14	5N	4-nitro	413.44	3.85	9	1
15	5O	2-nitro	413.44	3.85	9	1
16	5P	4-chloro	402.89	4.57	6	1
17	5Q	4-fluro	402.89	4.57	6	1
18	5R	4-methyl	382.47	4.34	6	1
19	5S	4-methoxy	398.46	3.95	7	1
20	5T	3-methoxy	398.47	3.92	7	1

Theoretical determination of ADME properties

ADME parameters of proposed compounds (5A-5T) are calculated with the help of pkCSM software. Results shows that most of the dervatives exhibit good ADME properties. Table 2 presents predicted ADME properties of the compounds. The Caco-2 cell line is composed of human epithelial colorectal adrenocarcinoma cells and is widely used as an in-vitro model of the human intestinal mucosa to predict absorption of orally administered drug. The steady state volume of distribution (VDss) is the theoretical volume that the total dose of a drug would need to be uniformly distributed to give the same concentration as in blood plasma. Total body clearance and unbound fraction of the drug is also calculated. Predicted value of these parameters for the proposed compounds exhibit with in the limits. Thus, it can be suggested that the designed compounds may possess a good pharmacokinetic profile, increasing their pharmacological importance.

Table 2: ADME prediction by pkCSM software.

S. No	Compound code	Intestinal absorption (% absorbed)	Caco2 permeability (Log Papp)	VDss distribution (Log L/Kg)	Fraction unbound (Fu)	Clearance (logml/min/kg)
1	5A	90.79	1.27	0.51	0.5	0.063
2	5B	100	0.48	0.22	0	0.151
3	5C	93.92	0.25	0.39	0	0.247
4	5D	94.89	0.15	0.18	0.1	0.305
5	5E	88	1.02	0.02	0.04	0.464
6	5F	87	0.95	0.14	0.09	0.47
7	5G	95	1.14	0.03	0.04	0.41
8	5H	92.81	1.32	0.18	0.4	0.31
9	5I	96	0.29	0.28	0	0.29
10	5J	100	0.43	0.22	0.25	0.16
11	5K	100	0.37	0.17	0.09	0.10
12	5L	89.38	0.98	0.01	0.25	0.05
13	5M	89.36	0.89	0.03	0.03	0.065
14	5N	100	0.23	0.21	0	0.23
15	5O	100	0.49	0.50	0.15	0.31
16	5P	90.89	1.27	0.13	0.07	0.08
17	5Q	90.85	1.25	0.14	0.1	0.15
18	5R	91.56	1.30	0.12	0.36	0.17
19	5S	92.78	1.3	0.02	0.51	0.26
20	5T	93.48	1.19	0.03	0.44	0.32

Toxicity prediction

The application of in silico methods is increasing with the prediction of toxic risks to human and the environment. The mutagenic and carcinogenic effects of designed compounds on human body were predicted using pkCSM software and results showed that all of the compounds are non-toxic. (Table 3).

Table 3: Toxicity prediction of analogs.

S. No	Compound code	Mutagenicity	Carcinogenicity
1	5A	No risk	No risk
2	5B	No risk	No risk
3	5C	No risk	No risk
4	5D	No risk	No risk
5	5E	No risk	No risk
6	5F	No risk	No risk
7	5G	No risk	No risk
8	5H	No risk	No risk
9	5I	No risk	No risk
10	5J	No risk	No risk
11	5K	No risk	No risk
12	5L	No risk	No risk
13	5M	No risk	No risk
14	5N	No risk	No risk
15	5O	No risk	No risk
16	5P	No risk	No risk
17	5Q	No risk	No risk
18	5R	No risk	No risk
19	5S	No risk	No risk
20	5T	No risk	No risk

Molecular docking studies

Molecular docking studies of 20 derivatives of benzothiazole clubbed oxadiazole was carried out to explore the possible binding interaction as well as to compare the binding pattern of these designed compounds to the standard ligand using Glide 5.5 extra precision (XP) maestro Schrodinger software. Docking studies were conducted on four important anti-diabetic receptors which are α-glucosidase, α-amylase, PPAR-γ and DPP4. The designed compound shows most potent activity on PPAR-γ. Also shows good activity on α-glucosidase and α-amylase and least activity on DPP4 receptor. The docking scores of the derivatives are shown in Table 4.

Table 4: Docking scores of proposed derivatives.

S. No	Compound code	α-Glucosidase	α - Amylase	PPAR-γ	DPP4
1	5A	-8.6	-7.5	-9.8	-8.9
2	5B	-8.8	-7.9	-9.9	-9.2
3	5C	-6.9	-6.5	-9.0	-7.1
4	5D	-8.6	-7.9	-8.9	-7.4
5	5E	-7.2	-7.0	-8.8	-6.2
6	5F	-7.0	-5.0	-7.8	-6.4
7	5G	-7.3	-5.8	-7.7	-6.5
8	5H	-8.7	-7.0	-10.1	-9.3
9	5I	-6.7	-5.1	-9.1	-7.2
10	5J	-8.6	-5.2	-10.2	-5.6
11	5K	-8.9	-6.8	-10.5	-6.9
12	5L	-8.5	-8.2	-9.8	-6.7
13	5M	-6.1	-7.7	-8.8	-9.1
14	5N	-6.1	-5.8	-8.0	-8.7
15	5O	-6.1	-5.5	-7.8	-6.5
16	5P	-6.7	-5.7	-7.7	-6.6
17	5Q	-6.7	-5.6	-6.3	-6.6
18	5R	-7.0	-5.7	-8.8	-6.7
19	5S	-8.7	-8.0	-8.5	-6.8
20	5T	-7.3	-6.6	-9.0	-7.5
21	ACARBOSE	-8.5	-8.4	-	-
22	ROSIGLITAZONE	-	-	-8.8	-
23	VILDAGLIPTIN	-	-	-	-9.5

Yeast α-glucosidase (EC 3.2.1.20) has been widely used to screen bioactive compounds targeting α- glucosidase. The optimized compounds were docked into the B chain of enzyme (PDB-3TOP).From the docking calculation study, it was observed that the top ranked conformations of almost all compounds were well accommodated inside the active site of α-glucosidase enzyme. Compounds 5A, 5B,5D, 5H, 5J, 5K and 5L showed potent activity on both α-glucosidase and α-amylase. Binding interacions of compounds 5A and 5D are shown in figure-2. The structural features observed in this group for the active nature of compounds are the presence of electron donating groups like –OH and -OCH_3 group. 2D representation of compounds showing good docking score on α-amylase (1B2Y) is shown in figure-3. A comparative docking study on α-glucosidase (3TOP) receptor was carried out with the help of Acarbose which was taken as standard. The 2D and 3D representation of Acarbose is shown in figure-4. Compounds 5A, 5B, 5J, 5K showed highest docking score (-10.4,-10.3,-10.2 and -10.5 respectively) in the active sites of the PPAR- γ comparable to that of Rosiglitazone (-8.8). Most potent analogues in these series are having hydroxyl, methoxy and chloro substitutions at ortho and para positions. Docked pose of compound 5K is shown in figure-5. Binding interactions of Rosiglitazone on 4EMA is shown in figure-6. The proposed compounds shows comparatively less activity on DPP4 receptor. Among the 20 derivatives the top most compound showing good docking score on DPP4 receptor were found to be 5B and 5H. Binding interactions of compound 5B on DPP4 receptor is shown in figure-7.Interacting amino acid residues were found to be TYR662, TYR 666, TYR547, TYR631, VAL 546, TRP629, LYS554.

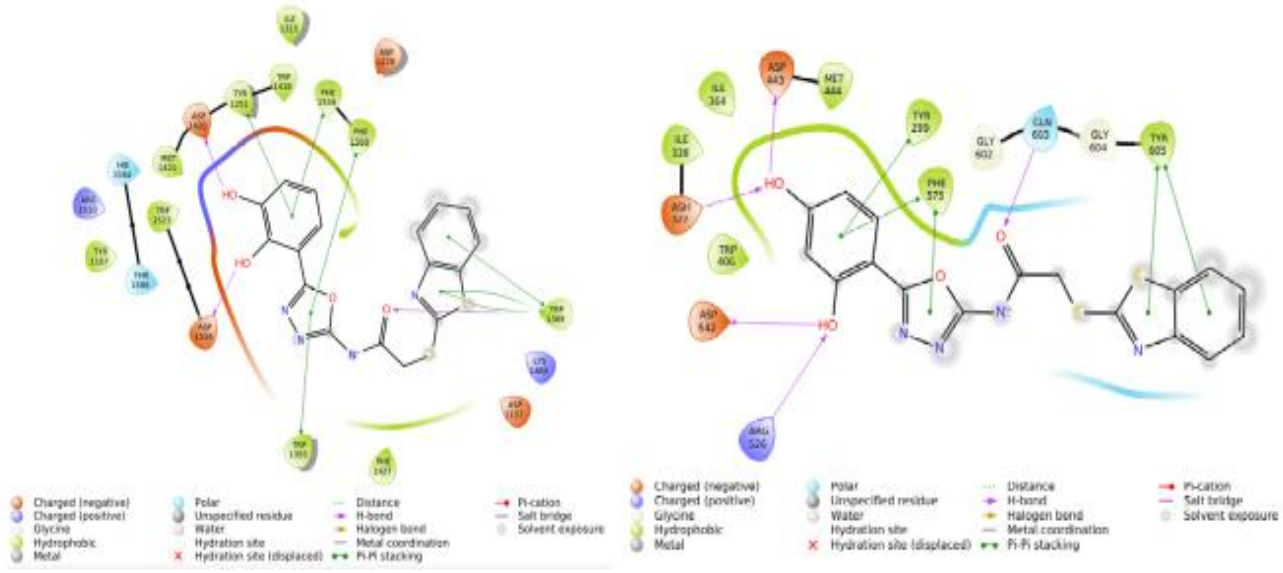

Figure 2: 2D binding interactions of compounds 5A& 5D on 3TOP.

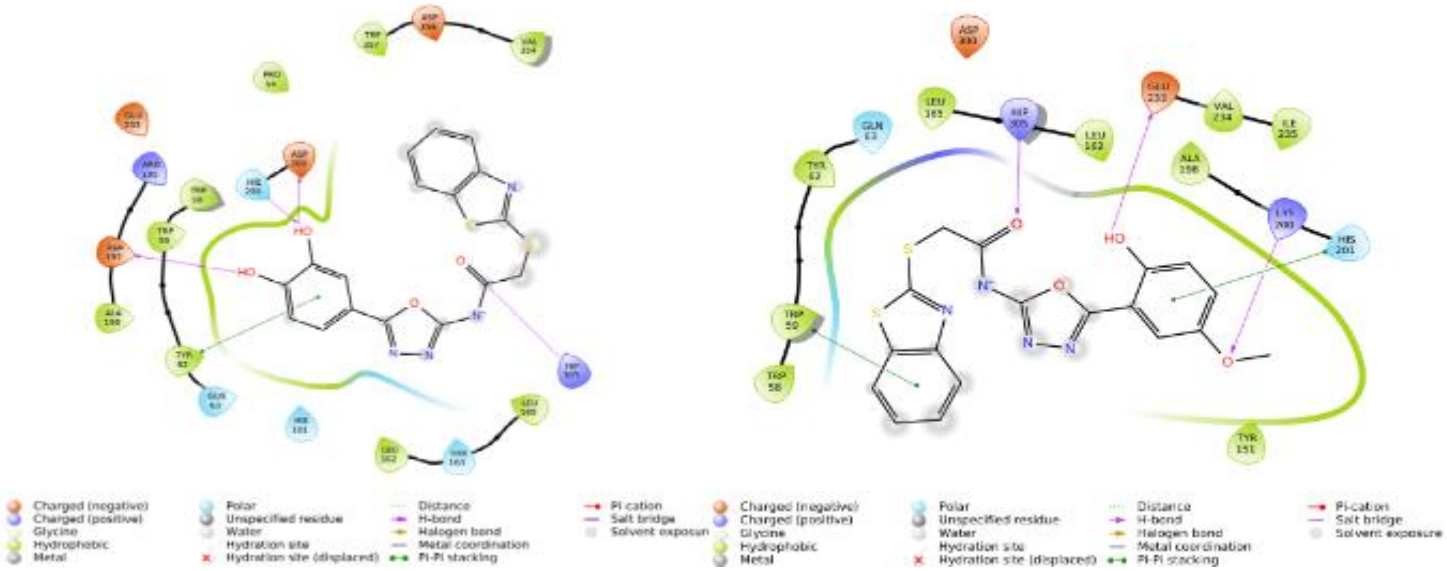

Figure 3: 2D binding interactions of compounds 5B & 5G on 1B2Y.

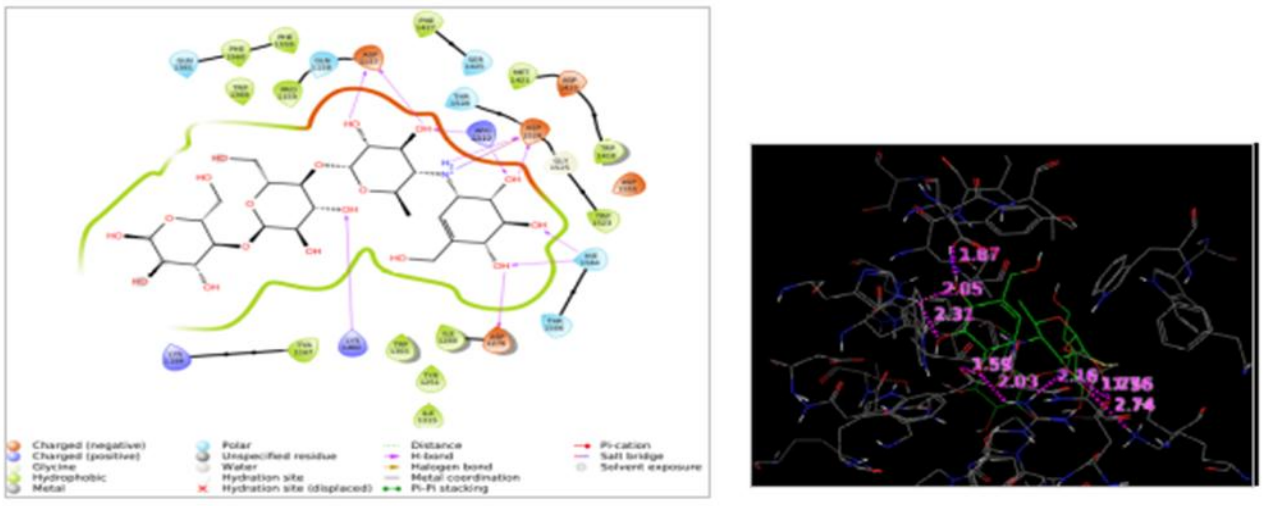

Figure 4: 2D & 3D binding interactions of Acarbose on 3TOP.

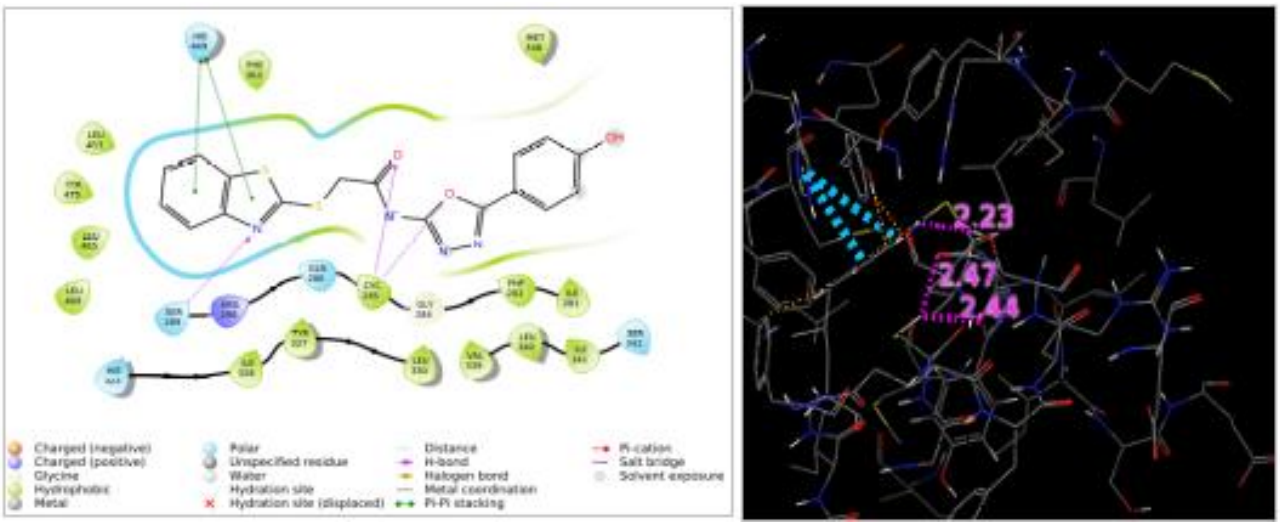

Figure 5: 2D & 3D Binding interaction of 5K on 4EMA.

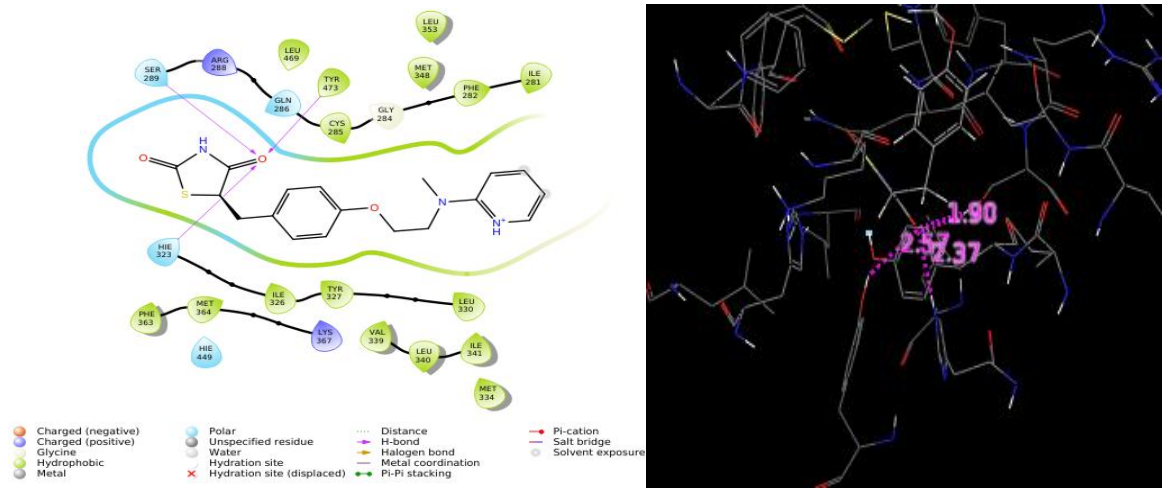

Figure 6: Binding interaction of Rosiglitazone on 4EMA.

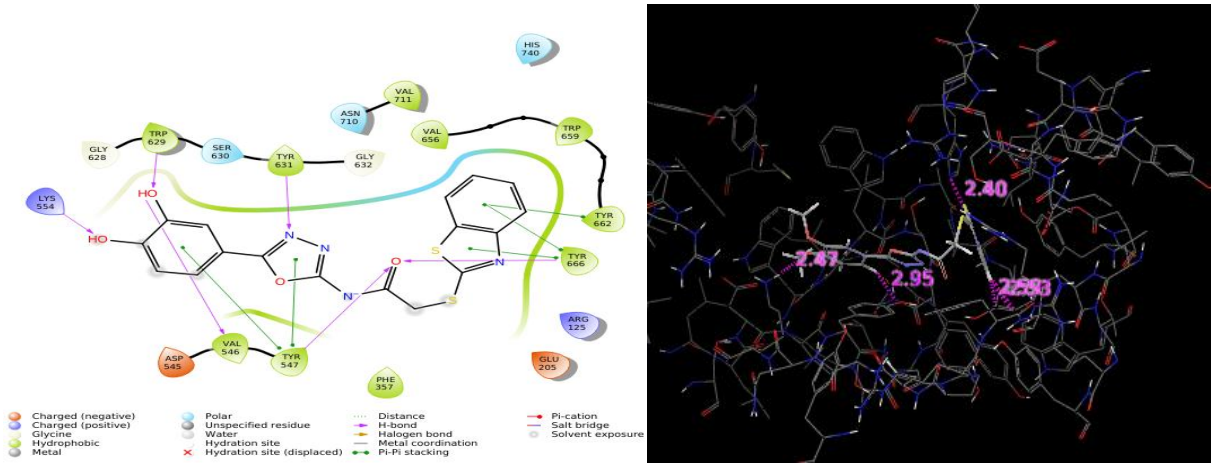

Figure 7: Binding interactions of compound 5B on 4A5S.

On the basis of results obtained from molecular docking studies a clear structure activity relationship could be drawn. It suggest that,

- Presence of disubstituted phenyl ring attached to oxadiazole ring showed better results as compared to the compounds having monosubstituted phenyl ring.
- Presence of electron donating groups such as -OH, -OCH_3 improves anti-diabetic action when compared with electron withdrawing groups.
- The presence of amide linkage connecting benzothiazole and oxadiazole nucleus shows good anti-diabetic potential.

CONCLUSION

In present study, we have designed and evaluated twenty derivatives of benzothiazole clubbed oxadiazole derivatives against four most important anti-diabetic receptors such as α-glucosidase,α-amylase, PPAR-γ and DPP4 through *in-silico* studies. All compounds obeyed lipinski rule of five which suggest that these compound have excellent drug likeness properties and are preferable as an orally acting drug. Results of ADME prediction conclude that synthesized compounds may possess a good pharmacokinetic profile, increasing their pharmacological importance. All of the compounds were found to be non-toxic on toxicity studies. Molecular docking study reveals that compounds 5A,5B,5J and 5K shows excellent activities on PPAR-γ with a docking score of -10.4,-10.3,-10.2,-10.5 respectively which is comparable with standard. Compounds 5A, 5B, 5D, 5H, 5J, 5K and 5L showed good activities on α-glucosidase and α-amylase than standard drug acarbose. It was found that proposed compound are less active on DPP4 receptor. Thus, based on the in silico Drug likeness, ADME evaluation and molecular docking study, it can be suggested that benzothiazole incorporating oxadiazole derivatives can further be explored with a view to obtain potential antidiabetic agents with minimal side effects.

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