In Silico Design, Synthesis and *In Vitro* Antidiabetic Activity of Novel 5-Furyl-1,3,4-Thiadiazolimines

Sherin A. Hameed[1]*, Joyamma Varkey[2], P Jayasekhar[3]

[1] College of Pharmaceutical Sciences, Government Medical College, Thiruvananthapuram, Kerala

[2]College of Pharmaceutical Sciences, Government Medical College, Alappuzha.

[3]College of Pharmacy, National University of Science and Technology, Sultanate of Oman

Email:- sherinirshad@gmail.com

ABSTRACT - Postprandial hyperglycemia plays an important role in the development of T2DM. The promising therapeutic approach is to decrease hyperglycemia by decreasing the postprandial rise in blood glucose concentration. In our study, a series of novel 5-furyl- 1,3,4-thiadiazol-2-imine derivatives were designed and those with good Physico-chemical properties were synthesized by oxidative cyclization between aryl acid and thiosemicarbazide using phosphorous oxychloride and subsequent treatment with aromatic aldehydes with varying substituents. Docking studies with the human pancreatic alpha-amylase enzyme in complex with myricetin (PDB ID: 4GQR) and peroxisome proliferator-activated receptor gamma (PPARgamma) (PDB ID: 1FM6) were done to predict the protein-ligand binding modes. The compounds SA07, SA03 and SA04 showed significantly high docking scores while SA01, SA05 and SA06 showed moderate scores. All derivatives were subjected to *in vitro* anti-diabetic screening using chromogenic dinitro salicylic acid method (α amylase inhibition assay). Significant percentages of inhibition were reported for SA03, SA07 and SA04 with acarbose as standard. Molecular docking revealed that synthesized derivatives and target proteins were actively involved in binding before and after systemic absorption and had a significant correlation with their biological activity.

KEYWORDS: 1,3,4-thiadiazole, docking, α- amylase, anti-diabetic

INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic diseases in which there are high blood sugar levels or hyperglycemia over a prolonged period. DM is one of the prime concerns of morbidity and mortality around the globe with an expected projection of 366 million cases in 2030 compared to 171 million in 2000 [1]. It is ranked seventh among the leading causes of death and is considered third when its fatal complications are taken into account [2]. India was declared as the "diabetes capital of the world" by WHO in 2013. DM is a condition in which the pancreas no longer produce enough insulin or cells stop responding to insulin that is produced so that the glucose in the blood cannot be absorbed in to the cells of the body [3]. Between two types of diabetes, type 2 is more prevalent than type 1, with more than 90% of the total diabetic patients suffering from it. Postprandial hyperglycemia plays an important role in the development of T2DM [4]. The promising therapeutic approach is to decrease hyperglycaemia by decreasing the postprandial rise in blood glucose concentration. This is achieved by retarding the digestion and absorption of ingested carbohydrates through the inhibition of carbohydrate hydrolysing enzymes such as α-amylase and α- glucosidase [5]. Currently, experimental T2DM drug discovery is focused on compounds with insulin-sensitizing activity that acts via several mechanisms.

1, 3, 4-thiadiazole, a five membered ring system containing sulphur and nitrogen atom have become a considerable class of heterocycles and a great area for researchers because of their wide range of biological activity. Versatile biological activities of this moiety is probably due to strong aromaticity of the ring system, which provide good *in vivo* stability and least toxicities for higher vertebrates, including humans. When different functional groups are attached to thiadiazole nucleus, it may interact with biological receptors and produce an outstanding property [6]. Literature survey revealed that 1,3,4-thiadiazole and its derivatives possesses wide range of therapeutic activities like antimicrobial [7], antifungal [8], antitubercular [9], [10], anti-inflammatory [11], wound healing, diuretic [12], antiulcer, antidiabetic [13], anticonvulsant [14], anticancer [15], anti-leshmanial, antidepressant, antioxidant, radio-protective, and antiviral activities [16]. Thiadiazole moiety acts as a "hydrogen binding domain" and "two-electron donor system". They occur in four isomeric form viz., 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, 1,3,4-thiadiazole [17], [18].

1,2,3-thiadiazole **1,2,5-thiadiazole** **1,2,4-thiadiazole** **1,3,4-thiadiazole**

In silico approaches are being used today in drug discovery to assess the ADMET properties of compounds at the early stages of discovery and development. ACD Lab Chemsketch, PASS (Prediction of Activity Spectra for Substances), Osiris property calculator, Pre-ADMET prediction, Molinspiration and SwissADME are some of the software which helps pharmaceutical scientists to select the best candidates for development as well as to reject those with a low probability of success [19]. The three-dimensional structure of a protein or protein-ligand complex is helpful in lead identification using molecular modeling. Discovery studio, AUTODOCK, Glide, and SwissDOCK are some of the software providing docking analysis. Discovery Studio is a suite of software for simulating small molecule and macromolecule systems. It is developed and distributed by Dassault Systemes BIOVIA (formerly Accelrys) [20].

Our present study includes the *in silico* screening of a series of 5-furyl-1,3,4-thiadiazole-2-imine compounds, their docking studies with targets like the human pancreatic alpha-amylase enzyme in complex with myricetin (PDB ID: 4GQR), peroxisome proliferator-activated receptor gamma (PPARgamma) (PDB ID: 1FM6) and *in vitro* screening for anti-diabetic activity by α-amylase inhibition assay.

EXPERIMENTAL METHODS

The *in silico* modeling of all proposed compounds were carried out by using Molinspiration (21), ACDLAB Chemsketch (22), Pre ADMET, Osiris property calculator (24), and PASS (Prediction of Activity Spectra for Substances) (25) to predict the physiological and biological parameters.

All the chemicals used for synthesis were of laboratory reagent grade and were obtained from Sigma-Aldrich and S.D. fine chemicals Ltd. Melting points were determined in open capillaries in the electrical melting point apparatus and are uncorrected. Analytical thin-layer chromatography was performed on precoated silica gel plates (Merck) to establish the identity of reactants and products monitored in-between reactions as well as at the end for completion of the reaction. The spots were visualized by iodine vapours in an enclosed chamber. Infra-Red spectra of compounds were recorded on 1) Perkin Elmer Spectrum Two FT-IR spectrometer in the range of 4000-200 cm-1. Proton (1H) Nuclear Magnetic Resonance Spectra of compounds were recorded on Bruker Advance II 400 NMR Spectrophotometer using DMSO solvent.

Synthesis of selected derivatives

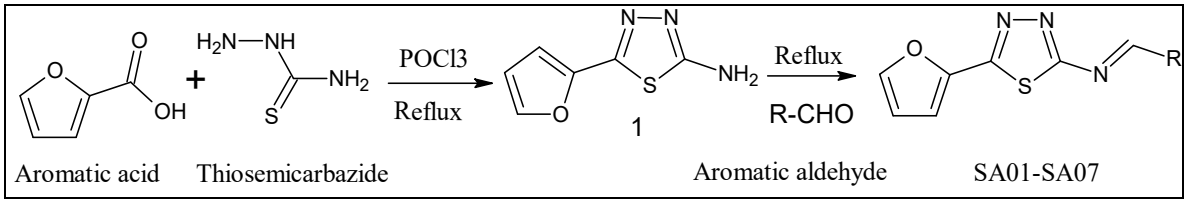

Fig 1: Scheme for the synthesis

Step 1 Synthesis of 2-amino-5 furyl-1,3,4-thiadiazole [26].

An equimolar amount of mixture of 2-furoic acid (0.1mole) and thiosemicarbazide (0.1mole), in $POCl_3$ (excess), was heated for half an hour, water (90ml) added and reaction mixture refluxed till the completion of reaction (TLC), cooled to room temperature, poured to ice-cold water, neutralized with saturated KOH solution, and recrystallized from 95% ethanol.

Step 2 Synthesis of 5-furyl-1,3,4-thiadiazol-2-imine derivatives (SA01-SA07) [27].

To the compound 1(0.01M) in 20ml ethanol, selected aldehyde (0.01M) in 15ml ethanol was added and refluxed for 5-6hr. The volume of resultant solution was reduced to half by distillation under reduced pressure. The resulting solution was poured on crushed ice and kept overnight below 20˚c for crystallization. The solid which got separated was dried and recrystallized from ethanol.

Molecular docking

Docking Analysis was performed using docking software Discovery studio 2018 for identifying the binding affinity of proposed compounds with two targets by Library docking method

The human pancreatic alpha amylase enzyme in complex with myricetin with **PDB id: 4GQR** were retrieved from Protein Data Bank (PDB) with a resolution of $1.2A^0$ [28]. The protein consists of a single polypeptide chain with sequence length of 496 amino acids. The binding sites of protein interaction with its native ligand are Trp

59, Gln63, Asp197 and Glu233. Docking analysis were performed by selecting binding site from receptor cavities in the target protein using charmm/charmm36 as force field.

The crystal structure of the heterodimer of the human retinoid X receptor alpha and peroxisome proliferator-activated receptors gamma (PPARgamma) ligand binding domains respectively bound with 9-cis retinoic acid and rosiglitazone and co-activator peptides were retrieved from PDB with **PDB ID: 1FM6** with a resolution of 2.1A ^{0}. The active site selected for the studies are Phe 282, Cys285, Ser289, Leu330, Met364, His449, Tyr473, the binding site of rosiglitazone.

***In vitro* anti-diabetic activity (α-Amylase Inhibition assay) [29].**

Porcine pancreatic α amylase (PPA) was used for the preliminary screening of α amylase inhibitors from the compounds using the chromogenic dinitro salicylic acid (DNSA) method. A total of 500µL of 0.02 M sodium phosphate buffer (pH 6.9 with 0.006 M NaCl) containing 20 mg/mL of α- amylase and varying concentration (25, 50, 75, & 100µg/ml) of extract as inhibitor were pre-incubated at 25ºC for 10 min. After the pre-incubation, 500 µL of a 1% starch solution in 0.02 M sodium phosphate buffer (pH 6.9) was added to each tube at timed intervals. The reaction was stopped using 1.0 mL of DNSA colour reagent. The test tubes were incubated for 5 min, cooled., diluted by adding 10ml distilled water and the absorbance was measured at 540nm. Varying concentrations of acarbose (1mg/ml stock) were treated as standard.

$$\%\ of inhibition = \frac{B-A*100}{(B-C)}$$

A- OD of test sample

B- OD of blank with starch and alpha amylase

C- OD of Control with starch only,

RESULTS AND DISCUSSION

Seven 1,3,4- thiadiazole derivatives were screened for best physico-chemical parameters using different software. All derivatives were screened for RO5 compliance using Chemsketch and Molinspiration software and were found to obey Lipinski's rule of 5 (RO5). The results were detailed in Table 1. Molecular parameters of proposed derivatives were further evaluated using Ghose filter and Viber filter. Ghose filter rule stated that compounds with Partition coefficient log P in (−0.4 to +5.6) range, Molar refractivity from 40 to 130, Molecular weight from 180 to 480 and Number of atoms from 20 to 70 (includes H-bond donors [e.g. OHs and NHs] and H-bond acceptors [e.g. Ns and Os]) give more druglikeness character. While Veber rule stated that for a compound predicted to have good oral bioavailability then the rotatable bond count should be less than or equal to 10 and polar surface area should be less than or equal to 140. All the proposed derivatives obeyed the Ghose and Veber filter rules.

All the proposed derivatives have TPSA value less than140 angstroms. This parameter is significant to correlate proposed derivatives with the human intestinal absorption, Caco-2 monolayer's permeability, and blood brain barrier penetration. Percentage of absorption (% ABS) was estimated using the equation: % ABS=109−(0.345×TPSA), according to Zhao et al. ADME parameters were shown in Table 2.

Seven derivatives were synthesized conventionally and their structures were confirmed by IR and 1H-NMR spectra. The details of different substitution, melting point, % yield and spectral details were given in Table 3.

Docking studies were performed with human pancreatic alpha amylase enzyme (4GQR) to find out alpha amylase inhibiting activity and with peroxisome proliferator-activated receptor gamma (PPARgamma) (1FM6) to find out the antidiabetic activity after systemic absorption. Docking analysis report as shown in Table 4 revealed that except SA02 all others have good interaction with the binding site of human pancreatic alpha amylase enzyme. The compounds SA07, SA03 and SA04 showed good docking score while SA01, SA05 and SA06 moderate score. Docking with PPARgamma showed that compound SA07 and SA04 have maximum docking score.

In vitro anti-diabetic screening results as given in Table 5 showed maximum percentage of inhibition for SA03and SA07 which have maximum docking score also. Thus *in vitro* anti-diabetic analytical report compliments docking analysis results. Percentage of inhibition shown by various derivatives were compared with standard acarbose, shown in figure 5.

Both in vitro and docking studies showed that SA02, (*Z*)-*N*-[5-(furan-2-yl)-1,3,4-thiadiazol-2-yl]-1-phenylmethanimine which is a derivative with unsubstituted phenyl ring attached to imine linkage have least docking score. SA03 which is chemically (*Z*)-1-(2,4-dichlorophenyl)-*N*-[5-(furan-2-yl)-1,3,4-thiadiazol-2-yl] methanimine and SA07, (*E*)-1-(furan-2-yl)-*N*-[5-(furan-2-yl)-1,3,4-thiadiazol-2-yl] methanimine; both exhibited maximum docking score with alpha amylase as well as good percentage of inhibition. Presence of electron donating groups at 2nd and 4th position of phenyl ring contributed more to get strong receptor interaction. Highly aromatic furyl ring also give much hydrogen bonding interaction with the receptor resulting significant alpha amylase inhibitory action.

Table 1: Evaluation of RO5 with Molinspiration and Chemsketch software.

Code	Molecular formula	MiLog P	nHAc	nHDo	Volume	M.Ref Cm^3	nrot b	TPSA	Mol.Wt	No: of atoms
SA01	C15H14N4OS	3.35	5	0	259.99	85.97	4	54.53	298.36	35
SA02	C13H9N3OS	3.25	4	0	214.09	73.17	3	51.29	255.30	27
SA03	C13H7C12N3OS	4.53	4	0	241.16	82.37	3	51.29	324.19	27
SA04	C16H15N3O4S	2.88	7	0	290.73	90.61	6	78.99	345.37	39
SA05	C13H9N3O2S	3.19	5	1	222.11	74.02	3	71.52	271.29	28
SA06	C13H8N4O3S	3.18	7	0	237.42	78.83	4	97.11	300.29	29
SA07	C11H7N3O2S	2.50	5	0	195.66	65.34	3	64.43	245.26	24

Table 2: ADME parameters calculated by Pre-ADMET software.

Code	BBB	Caco2	HIA	MDCK	PPB	SP	%ABS
SA01	1.21	36.53	99.12	20.81	91.86	-3.47	90.19
SA02	1.56	31.50	98.76	239.22	95.86	-3.42	91.30
SA03	2.91	54.97	98.45	72.59	100	-3.39	91.30
SA04	0.42	27.17	96.99	2.93	93.68	-3.94	81.75
SA05	0.81	10.17	95.57	78.68	98.00	-3.66	84.33
SA06	0.11	1.54	88.09	2.04	90.64	-3.52	75.50
SA07	0.68	29.95	95.2	209.74	86.9	-3.69	86.77

Table 3: Physico-spectral details of synthesised compounds

Code	-R	mp ˚c	% yield	Spectral analysis	
				IR spectral details Peaks at nm	Nmr spectral details chemical shifts at (400 MHz,DMSO δ ppm)
SA01	4-N,N-dimethyl phenyl	201	62	3104 (Ar-C-H), 2919 (C-H), 1635 (N=CH), 1521 (C=C), 1268 (C-N, $N(CH_3)_2$, 883 (N-N), 688 (C-S-C)	2.93 (s, 6H, CH_3), 6.6-7.8 (7H, Ar-H), 8.87 (s, 1H, N=CH),
SA02	-phenyl	236	65	3015(Ar-C-H), 2923(C-H), 1635 (N=CH), 1503(C=C), 1103 (C-H, Furan), 883(N-N), 684(C-S-C)	6.7-8.3 (m, 8H, Ar-H) 8.99 (s, 1H, N=CH)
SA03	2,4-dichorophenyl	220	57	3022 (Ar-C-H), 2917 (C-H), 1518 (C=C), 1630 (N=CH), 888 (N-N), 692(C-S-C)	6.7-7.9 (s, 6H, Ar-H), 9.0(s, 1H, N=CH)
SA04	3,4,5-trimethoxyphenyl	208	48	3274 (Ar-C-H), 2919 (C-H), 1688 (N=CH), 1503 (C=C), 1242 (C-O), 881 (N-N), 689 (C-S-C)	3.7-3.9(s 9H, CH_3),6.8-7.7 (m,5H, Ar-H), 8.9 (s, 1H, N=CH)
SA05	2-hyroxyphenyl	192	55	3682 (OH), 3134(Ar-C-H) 2923 (C-H), 1605 (N=CH), 1500 (C=C), 888 (N-N), 688 (C-S-C)	6.7-8.0 (m, 7H,Ar-H), 8.9 (s, 1H, N=CH)
SA06	3-nitrophenyl	185	60	3115 (Ar-C-H), 2924 (C-H), 1613 (N=CH), 1530 (Ar-NO_2), 889(N-N), 690 (C-S-C)	6.7-8.7(m, 7H,Ar-H), 8.7(s, 1H, N=CH)
SA07	2-furyl	251	43	3130 (Ar-C-H) 2916 (C-H), 1630 (N=CH), 1495 (C=C), 887 (N-N), 686 (C-S-C)	6.5-7.9 (m, 6H, Ar-H), 8.82 (s, 1H, N=CH)

Table 4: Docking analysis report with human pancreatic alpha amylase enzyme (4GQR) and peroxisome proliferator-activated receptor gamma (PPARgamma) (1FM6)

SL:No.	**Ligand**	**Docking score**	**Interacting Residue 4GQR**	Docking score	Interacting Residue**(1FM6)**
1	SA01	54.5996	Trp59, Asp197, Glu233 (3WHB)	81.12	Met364,Ser289, Arg288,His323
2	SA02	50.9353	No H bond interaction	71.42	Met364, Ser289
3	**SA03**	**64.7517**	Ala198, A:His201, Ala198	76.15	Met364, ser289
4	**SA04**	**63.3986**	Trp59, Asp197, Asp197, Glu233	**94.54**	Gln286,Ser289, Arg288,Phe282 (Whb)
5	SA05	54.1312	Asp197	73.68	Met364,Ser289
6	SA06	59.1726	His201	87.49	Tyr473, Gln286
7	**SA07**	**68.025**	Trp59 whb	**95.50**	His449, Ser289

Table 5: Report of *in vitro* antidiabetic screening.

µl/ml	**% of inhibition(Each value expressed as Mean±SEM)**							
	Acarbose	**SA01**	**SA02**	**SA03**	**SA04**	**SA05**	**SA06**	**SA07**
25	24.35	40.46±3.65	29.09±2.56	69.09±3.89	35.52±1.17	12.4±1.483	37.45±2.73	83.64±2.34
50	48.71	47.15±0.85	37.4±3.93	85.45±3.22	42.47±1.61	30.15±4.47	39.79±2.06	87.27±2.23
75	76.92	51.83±4.09	46.82±2.27	90.91±2.46	64.09±1.94	47.61±2.58	41.13±1.93	89.09±2.87
100	93.58	54.18±4.61	53.5±1.89	94.55±1.80	76.44±0.98	56.34±2.56	45.15±1.24	92.73±1.53

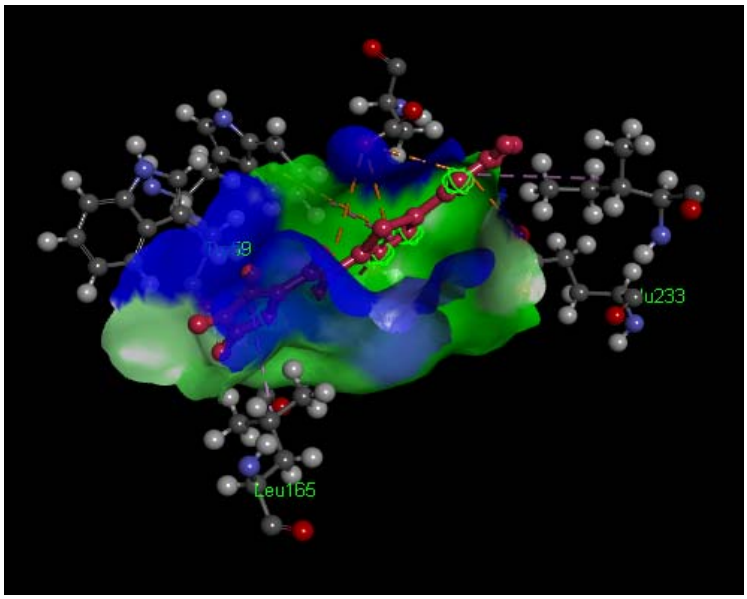

Fig 1: 3D view

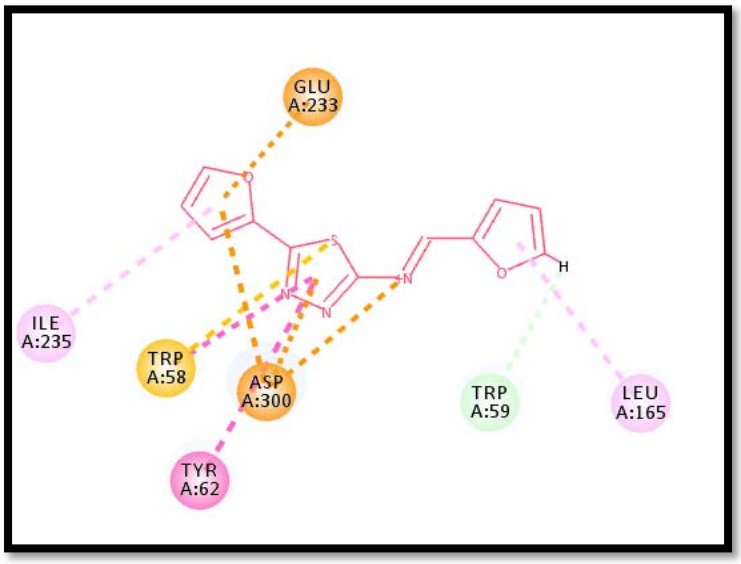

Fig 2: 2D view

Interaction of SA07 which have maximum docking score with 4GQR were shown in figure 1 and 2

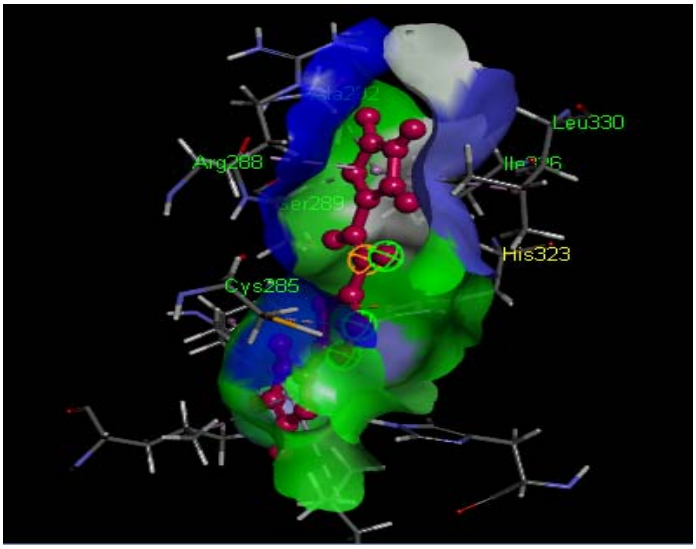

Fig 3: 3D view

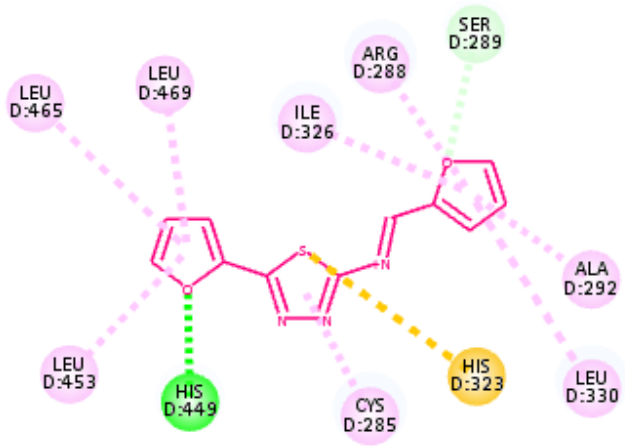

Fig 4: 2D view

Interaction of SA07 which have maximum docking score with 1FM6 were shown in figure 3 and 4

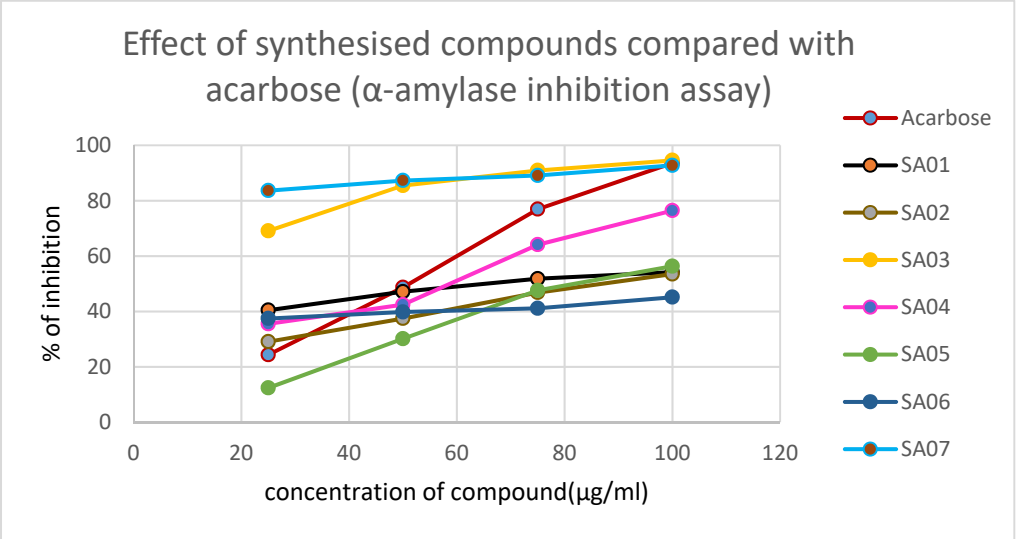

Figure 5: Comparison of percentage of inhibition shown by synthesised compounds.

CONCLUSION

The designed and synthesized 5-furyl-1,3,4-thiadiazol-2-imine derivatives showed good docking score and *in vitro* anti-diabetic activity. *In silico* physico chemical prediction studies confirmed that the majority of the title compounds possessed the druglikeness character. *In vitro* screening results suggested that compounds in which phenyl ring with electron donating groups at 2, 4th position (SA03) and that with furyl ring (SA07) attached to imine linkage exhibited significant alpha-amylase inhibitory activity. The docking studies with PPAR gamma receptor proved that the proposed compound SA07 and SA04 have best docking score, thus giving insight to antidiabetic activity after systemic absorption also. Compounds namely SA03, SA07 and SA04 having significant docking score and percentage of inhibition, can be selected for further optimisation and can be explored for *in vivo* activity in the mere future thus resulting in the development of novel anti-diabetic drugs with better pharmacological profile.

CONFLICT OF INTERESTS:

The authors declare that there is no conflict of interests regarding the publication of this paper.

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