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Synthesis, Characterization, Docking studies, Evaluation of Thiazinyl-thiazolidinone derivatives as potential in vitro antidiabetic and antioxidant agents.

Ramarajan Rajalakshmi [1],*, Rajavel Santhi[2], Thangaraj Elakkiya[3]

[1]Associate professor, Department of chemistry, Annamalai University, India

[2, 3] Research Scholar, Department of chemistry, Annamalai University, India

chemrajalaksmi@gmail.com

Abstract

A new series of thiazinyl-thiazolidinone synthesized by reacting involving condensation of aromatic aldehyde and ketone yields the corresponding chalcone. Amino thiazine is expected to form by reaction involving thiourea with chalcone in basic medium. Amino thiazine condenses with aldehyde yields the corresponding Schiff bases. Finally the Schiff bases reaction involving with thioglycolic acid in presence of zinc chloride catalyst to give the thiazolidinone derivatives. All the synthesized compounds were evaluated by FT-IR and ^{1}H NMR spectroscopic techniques. All the compounds were tested in vitro antidiabetic and antioxidant activity. Molecular docking studies were carried out 2HR7 protein.

Key words: *Thiazine, thiazolidinone, antidiabetic, antioxidant, molecular docking.*

1. Introduction

Heterocyclic compound with atoms like oxygen, sulphur and nitrogen may enhance the activity. Thiazolidinone possess wide range of biological actions from antibacterial to anticancer [1-5]. Various recent new drug developments in thiazolidinone derivatives show better effect and less toxicity. Moreover the possible improvements in the activity can be achieved by slight modifications in the substituents on the thiazolidinone nucleus. This has been noticed so far, that the introduction of another heterocyclic moiety into the thiazolidinone nuclei will enhance the biological activities [6-7]. Thiazolidinone is considered to be one of the most important heterocyclic compounds .This is because the thiazolidinone derivatives occupy an important place in the field of pharmacology. The 4-thiazolidinone ring system in a core structure is used in medicine as practical life. Compounds such as pioglitazone (hypoglycemic), etozoline (antihypertensive), ralitoline (anticonvelsent) and thiazolidomycin activity against sterptomyces species based on this pharmacophore.

Over the past few years, thiazolidinone and their derivatives have been extensively researched in the field of research. Thiazolidinone analogs have various medicinal properties such as antibacterial [8], antifungal [9], antioxidant 10], antidiabetic [11], anticancer [12], anti HIV [13], and anti-inflammatory [14].Several methods for the synthesis of 4-thiazolidinones are widely reported in the literature. The main synthetic routes to 1, 3-thiazolidin-4-ones involve three components that are an amine, a carbonyl compound, and a mercapto-acid [15-18]. The classical synthesis reported can be either a one-pot three-component condensation [19-20] or a two-step process [21-22]. The reactions begin by formation of an imine (the nitrogen of amine attacks the carbonyl of aldehyde or ketone), which undergoes attack by generated sulfur nucleophile, followed by intramolecular cyclization on elimination of water. The use of hazardous media such as benzene [23], 1, 4-dioxane [24], dimethylformamide (DMF) [25] and DMSO [26] has been reported in this cyclo condensation. It also has been observed that the rate of cyclo condensation can be increased by microwave heating [27-28].In this article we present a new class of structurally thiazolidinone derivatives, incorporating two heterocyclic compounds with known biological function such as thiazine and 4-thiazolidinone derivatives.

2. Experimental

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Chemistry

2.1. General procedure for (E)-3-(4-methoxyphenyl)-1-(pyridin-3-yl) prop-2-en-1-one **(3e)**

Chalcone is obtained by the reaction involving equal mol of aromatic aldehyde and ketone in presence of base catalyst. The reaction was completed is confirmed by TLC test. After the reaction was completed, the reaction mixture was poured into water. The solution was cooled and the product was filtered and recrystallized using ethanol.

2.2 General procedure for 4-(4-methoxyphenyl)-6-(pyridin-3-yl)-6H-1, 3-thiazin-2-amine **(4e)**

4-(4-methoxyphenyl)-6-(pyridin-3-yl)-6H-1, 3-thiazin-2-amine is obtained by the reaction involving chalcone and thiourea under reflux with stirrer in presence of alkali medium. After the reaction mixture was poured into ice water keep it 0ºC for 48 hrs. The precipitate obtained was filtered and re-crystallized with ethanol.

2.3 General procedure for (6E)-N-(4-methoxybenzylidene)-4-(4-methoxyphenyl)-6-(pyridin-3-yl)-6H-1, 3-thiazin-2-amine **(6q)**

The reaction mixture of amine react and aromatic aldehyde was dissolved in ethanol. The mixture was refluxed in presence of acetic acid as a catalyst. The reaction mixture was poured into water. The precipitate was collected and re-crystallized using ethanol.

2.4 General procedure for 2-(4-methoxyphenyl)-3-(4-(4-methoxyphenyl)-6-(pyridin-3-yl)-6H-1, 3-thiazin-2-yl) thiazolidin-4-one **(7q)**

The final compound thiazolidinone was obtained by the reaction involving Schiff bases with thioglycolic acid dissolved in dry benzene. The mixture was refluxed in presence of Lewis catalyst (zinc chloride). After the complete the reaction mixture of benzene was removed by distillation to give crude solid, which was dissolved in methanol. When the reaction mixture is passed through sodium bicarbonate, the non reactive acid is separated, after evaporate the solution in air condition. The precipitate solid was formed and recrystallized from methanol to give thiazolidinone.

3. Spectral Data

3.1 2-(4-chlorophenyl)-3-(4-(4-chlorophenyl)-6-(pyridin-3-yl)-6H-1, 3-thiazin-2-yl) thiazolidin-4-one

This compound was obtained as light orange solid. Yield: 82%. Mp: 282-312. IR (KBr, cm-1): 3024 (Ar-CH); 1712 (C=O); 1524 (C=C);888 (C-S);1443 (C-N);1623 (C=N); ^{1}H NMR (δ) (DMSO): 3.33 (s, 2H, -SC<u>H</u>$_2$,thiazolidinone);5.92 (s, 1H, NC<u>H</u>, thiazolidinone); 4.57 (d, 1H, S-C<u>H</u>, C_6 of oxazine); 6.32 (d, 1H, C=C<u>H</u>, C_5 of oxazine);6.62-8.54 (m,12H, Ar-H). ^{13}C NMR (δ): 34.22 (C_5 of thiazolidinone); 171.33 (CO cyclic); 46.35 (C2 of thiazolidinone), 160.43 (C2 of oxazine); 143.35(C4 of oxazine); 112.39 (C5 of oxazine); 36.02 (C6 of oxazine); 120-150 (17C, Ar-C).

3.2 2-(4-bromophenyl)-3-(4-(4-bromophenyl)-6-(pyridin-3-yl)-6H-1, 3-thiazin-2-yl) thiazolidin-4-one

This compound was obtained as light orange solid. Yield: 86%. Mp: 290-310. IR (KBr, cm-1): 3023 (Ar-CH); 1710 (C=O); 1519 (C=C);889 (C-S);1445 (C-N);1622 (C=N); ^{1}H NMR (δ) (DMSO): 3.34 (s, 2H, -SC<u>H</u>$_2$,thiazolidinone);5.83 (s, 1H, NC<u>H</u>, thiazolidinone); 4.49 (d, 1H, S-C<u>H</u>, C_6 of oxazine); 6.31 (d, 1H, C=C<u>H</u>,C_5 of oxazine);6.60-8.59 (m,12H, Ar-H). ^{13}C NMR (δ): 34.66 (C_5 of thiazolidinone); 171.46 (CO cyclic); 46.54 (C_2 of thiazolidinone), 160.53 (C_2 of oxazine); 143.15(C4 of oxazine); 112.49 (C5 of oxazine); 36.12 (C6 of oxazine); 120-150 (17C, Ar-C).

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3.3 2-(4-fluorophenyl)-3-(4-(4-fluorophenyl)-6-(pyridin-3-yl)-6H-1, 3-thiazin-2-yl) thiazolidin-4-one

This compound was obtained as light orange solid. Yield: 84%. Mp: 280-300. IR (KBr, cm-1): 3024 (Ar-CH); 1711 (C=O); 1526 (C=C);886 (C-S);1446 (C-N);1624 (C=N); ^{1}H NMR (δ) (DMSO): 3.38 (s, 2H, -SCH_2,thiazolidinone);5.84 (s, 1H, NC<u>H</u> thiazolidinone); 4.48 (d, 1H, S-C<u>H</u>, C_6 of oxazine); 6.32 (d, 1H, C=C<u>H</u>, oxazine)6.60-8.56 (m,12H, Ar-H). ^{13}C NMR (δ): 34.62 (C5 of thiazolidinone); 171.33 (CO cyclic); 46.35 (C2 of thiazolidinone), 160.43 (C_2 of oxazine); 143.35(C_4 of oxazine); 112.39 (C_5 of oxazine); 36.02 (C_6 of oxazine); 120-150 (17C, Ar-C).

3.4 3-(6-(pyridin-3-yl)-4-p-tolyl-6H-1, 3-thiazin-2-yl)-2-p-tolylthiazolidin-4-one

This compound was obtained as light orange solid. Yield: 81%. Mp: 280-310. IR (KBr, cm-1): 3021 (Ar-CH); 1716 (C=O); 1523 (C=C);884 (C-S);1443 (C-N);1621 (C=N); ^{1}H NMR (δ) (DMSO): 3.33 (s, 2H, -SCH_2,thiazolidinone);5.83 (s, 1H, NC<u>H</u>, thiazolidinone); 4.48 (d, 1H, S-C<u>H</u>, C_6 of oxazine); 6.32 (d, 1H, C=C<u>H</u>, oxazine);2.36(s,3H,C-CH_3);6.60-8.70 (m,12H, Ar-H). ^{13}C NMR (δ): 34.22 (C5 of thiazolidinone); 171.33 (CO cyclic); 46.35 (C2 of thiazolidinone), 160.23 (C2 of oxazine); 143.45(C4 of oxazine); 112.39 (C5 of oxazine); 36.02 (C6 of oxazine); 24.34(C-<u>C</u>H_3 120-150 (17C, Ar-C).

3.5 2-(4-methoxyphenyl)-3-(4-(4-methoxyphenyl)-6-(pyridin-3-yl)-6H-1, 3-thiazin-2-yl) thiazolidin-4-one

This compound was obtained as light orange solid. Yield: 78%. Mp: 277-310. IR (KBr, cm-1): 3022 (Ar-CH); 1712 (C=O); 1523 (C=C);884 (C-S);1441 (C-N);1627 (C=N); ^{1}H NMR (δ) (DMSO): 3.34 (s, 2H, -SCH_2,thiazolidinone);5.83 (s, 1H, NC<u>H</u>, thiazolidinone); 4.51 (d, 1H, N-C<u>H</u>, C_6 of oxazine); 6.33 (d, 1H, C=C<u>H</u>, oxazine)3.73(S,3H,O-CH_3);6.60-8.70 (m,12H, Ar-H). ^{13}C NMR (δ): 34.22 (C5 of thiazolidinone); 171.33 (CO cyclic); 46.34 (C2 of thiazolidinone), 160.43 (C2 of oxazine); 143.35(C4 of oxazine); 112.39 (C5 of oxazine); 36.02 (C6 of oxazine); 55.56(O-<u>C</u>H_3) 120-150 (17C, Ar-C).

3.6 2-(4-nitrophenyl)-3-(4-(4-nitrophenyl)-6-(pyridin-3-yl)-6H-1, 3-thiazin-2-yl) thiazolidin-4-one

This compound was obtained as light orange solid. Yield: 84%. Mp: 283-310. IR (KBr, cm-1): 3024 (Ar-CH); 1709 (C=O); 1526 (C=C);887 (C-S);1441 (C-N);1626 (C=N); ^{1}H NMR (δ) (DMSO): 3.33 (s, 2H, -SCH_2,thiazolidinone);5.84 (s, 1H, NC<u>H</u>, thiazolidinone); 4.48 (d, 1H, N-C<u>H</u>, C_6 of oxazine); 6.32 (d, 1H, C=C<u>H</u>, oxazine);6.60-8.70 (m,12H, Ar-H). ^{13}C NMR (δ): 34.12 (C5 of thiazolidinone); 171.33 (CO cyclic); 46.35 (C2 of thiazolidinone), 160.33 (C2 of oxazine); 143.45(C4 of oxazine); 112.39 (C5 of oxazine); 36.02 (C6 of oxazine); 120-150 (17C, Ar-C).

4. RESULTS AND DISCUSSION

Chalcone were synthesized by aromatic aldehyde and aromatic ketone in presence of sodium hydroxide catalyst. Amino thiazine synthesized by thiourea and compound 3a-3f in basic medium using reflux condition. The Schiff bases synthesized by reaction involving aromatic aldehyde compound 4a-4f and in presence of acetic acid. The Schiff bases on further cyclization with thioglycolic acid in presence of Lewis catalyst will give expected the

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thiazolidinone derivatives. FT-IR results help to confirm the functional group of the title compounds. For all synthesized compounds (7m-7r) a strong absorption appeared at 1710cm^{-1} was assigned to the carbonyl group of thiazolidinone ring. The absorption band at 1598cm^{-1} and 1623cm^{-1} was attributed to the C=N in the oxazine ring. The absorption band at 3058cm^{-1} was assigned to the aromatic stretching frequency of C-H functional group. FT-IR spectrum of compound 7p and 7q the absorption band around at 2963 was assigned to the methyl and methoxy functional group. Compound 7q is chosen as a representative compound to expound the spectral features of the synthesized compounds. The singlet peak appear at 3.28ppm was assigned to the methelene proton (1H) between the carbonyl compound and sulfur in the thiazolidinone. The peak at 5.97ppm was assigned to the methyl proton (singlet, 1H) between the sulfur and nitrogen in the thiazolidinone. The doublet proton appeared at the 4.54ppm was assigned to the methelene proton (1H) binding to the thiazine and pyridine ring. The doublet proton appeared at 6.34ppm was attributed to the oxazine not joined with any substitution. A sharp singlet appeared at 3.67ppm was confirmed to the methoxy proton. A multiplet proton (12H) appeared at the range of 6.65 to 8.57 was assigned to the aromatic proton. Compound 7q is chosen as a representative compound to expound the spectral features of the synthesized compounds. The singlet peak appear at 3.28ppm was assigned to the methelene proton (1H) between the carbonyl compound and sulfur in the thiazolidinone. The peak at 5.97ppm was assigned to the methyl proton (singlet, 1H) between the sulfur and nitrogen in the thiazolidinone. The doublet proton appeared at the 4.54ppm was assigned to the methelene proton (1H) binding to the thiazine and pyridine ring. The doublet proton appeared at 6.34ppm was attributed to the oxazine not joined with any substitution. A sharp singlet appeared at 3.67ppm was confirmed to the methoxy proton. A multiplet proton (12H) appeared at the range of 6.65 to 8.57 was assigned to the aromatic proton.

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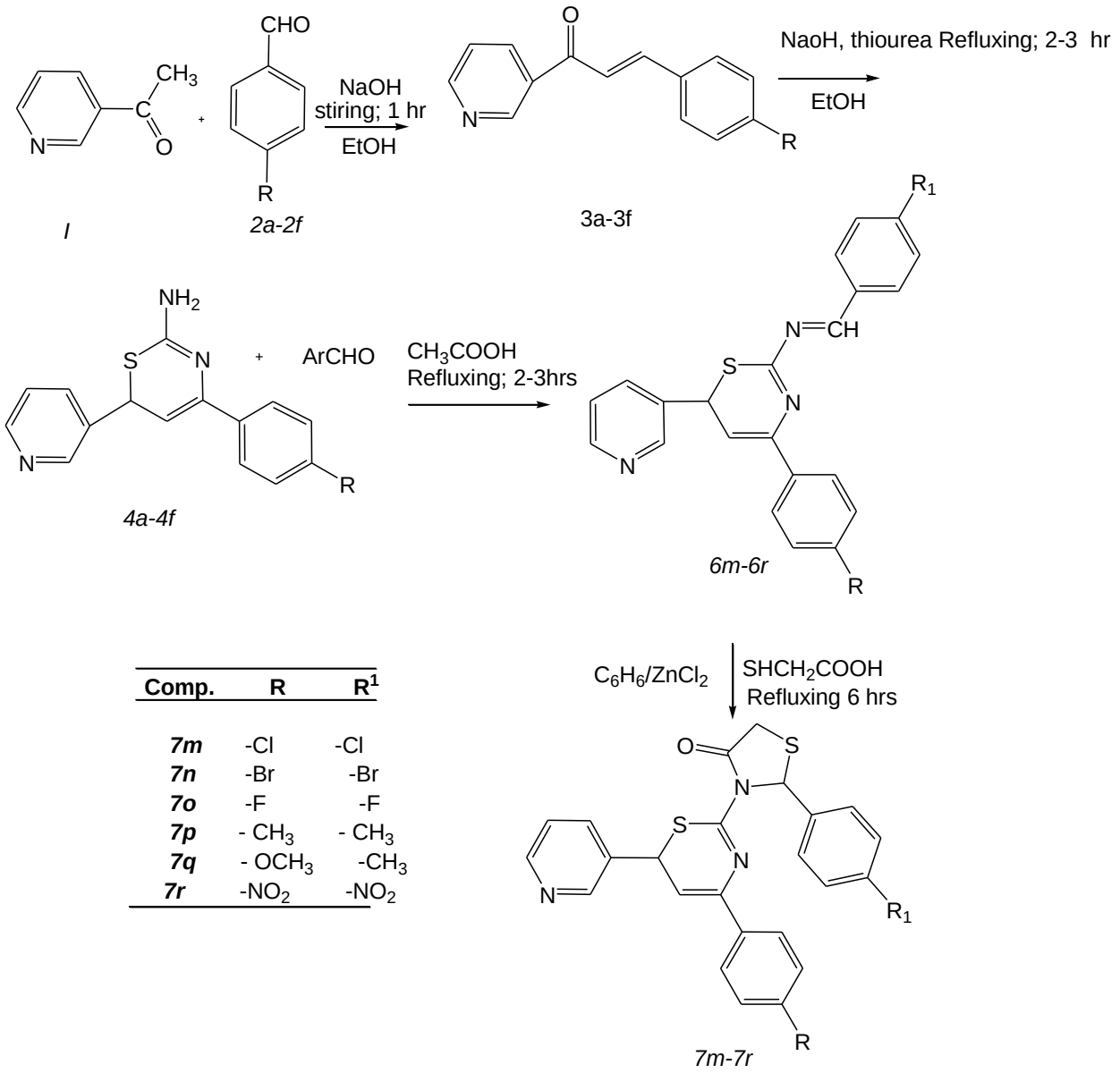


Comp.	R	R[1]
7m	-Cl	-Cl
7n	-Br	-Br
7o	-F	-F
7p	- CH_3	- CH_3
7q	- OCH_3	-CH_3
7r	-NO_2	-NO_2

5. Biological evaluation

5.1. Antioxidant Screening (In Vitro)

5.1.1. DPPH Radical Scavenging Activity

Percentage of antioxidant activity of all synthesized compounds was evaluated in DPPH free radical assay. The DPPH free radical assay was assessed according to the method described by Braca et al [29]. The test was performed in three times and % scavenging activity was calculated using the equation below.

% of scavenging = [(A control) - (A sample)/A control] x 100

Where A control is the absorbance of the control reaction and A sample is the absorbance of the test compound.

All the synthesized compounds evaluated in vitro antioxidant activity; all synthesized compounds IC_{50} values compared standard drug ascorbic acid. All the tested compounds IC_{50} values are listed in table 1. Compound

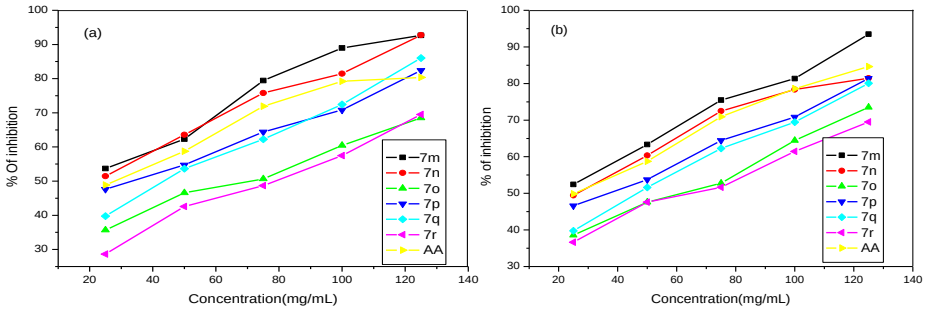
7m and 7n is the most active their IC_{50} values are 14.33(μg/mL) and 17.83(μg/mL). Compound 7o and 7r have the lowest active compared to standard drug.IC_{50} value of compound 7o and 7r is 67.61(μg/mL) and 76.68(μg/mL) respectively. Compound 7p and 7q have the moderate activity their IC_{50} values are 34.23(μg/mL) and 46.26(μg/mL) respectively. Standard drug ascorbic acid IC_{50} values are 21.68(μg/mL).

5.1.2. Nitric oxide (NO) method

All compounds have highly activated compared to standard drug. IC_{50} value of standard drug ascorbic acid is 23.19(μg/mL). Compound 7m and 7n have most active their IC_{50} values are 17.02(μg/mL) and 19.22(μg/mL) respectively. Remaining compound 7o, 7p, 7q and 7r have moderate activity their IC_{50} values are 59.53 (μg/mL), 36.44 (μg/mL), 48.67 (μg/mL) and 64.46 (μg/mL) respectively.

Table 1- *In vitro* antioxidant activity **7m-7r** using DPPH and NO free radical

Compound	IC50(μg/mL)	
	DPPH	No
7m	14.33	17.02
7n	17.83	19.22
7o	67.61	59.53
7p	34.23	36.44
7q	46.26	48.67
7r	76.68	64.46
Ascorbic acid	21.68	23.19



6. In vitro antidiabetic assay

6.1. Alpha-amylase inhibition activity

The inhibitory activity of alpha amylase was assessed according to Xiao method [30].Alpha amylase inhibition activity was calculated using the following formula.

Inhibitory activity (%) =1-Asorbance of the sample-Absorbance of the blank

Absorbance of control

The IC 50 value obtained by the equation indicates the concentration of the compounds that inhibit activity of the alpha amylase.

All the synthesized compounds evaluated in vitro antidiabetic activity their IC_{50}values are listed in table 2. The standard drug acarbose IC_{50} values are 16.89 (µg/mL). The IC_{50} values of compounds 7n (bromo) and 7p (methyl) are 13.02 (µg/mL) and 15.95 (µg/mL) respectively. Compound 7q (methoxy) and 7r (nitro) have lowest IC_{50} values are 53.78 and 50.62(µg/mL). Compound 7m (chloro) and 7o (flouro) have the moderate activity compared to standard drug their IC_{50} values are 23.1 and 27.24(µg/mL).

6.2. Alpha -Glucosidase inhibition activity

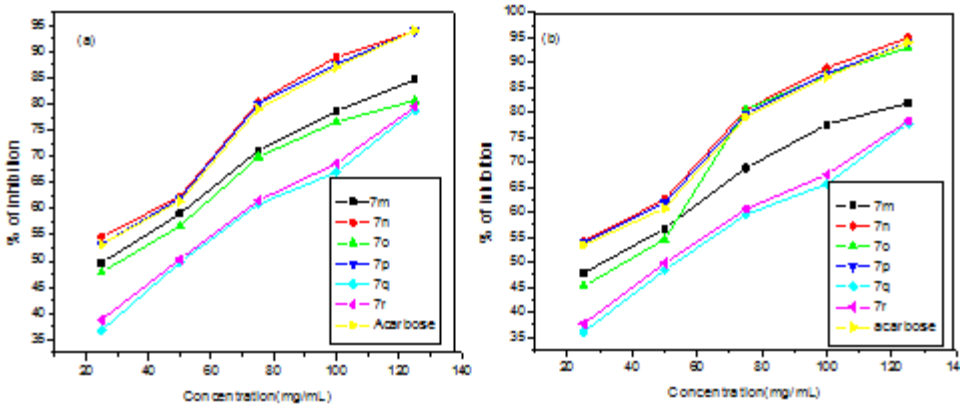
All the IC_{50} values are listed in table 2; these IC_{50} values are similar to α-amylase IC_{50}values. The entire synthesized compound evaluated in vitro antidiabetic activity using standard drug acarbose. All synthesized compounds IC_{50} value compared to standard drug. The IC_{50} value of standard drug acarbose is 17.13(µg/mL). 4-Bromosubstitution compound most active compared all synthesized compound with IC_{50} values are 14.24(µg/mL).

Next methyl substitution is the most effective with an IC_{50} value of 15.14(μg/mL). Chloro and flouro substitution have the moderate their IC_{50} values are 28.42(μg/mL) and 31.9(μg/mL) respectively. Methoxy and nitro substitution have the lowest activity compared to all synthesized compounds and standard drug. Their IC_{50} values are 56.5(μg/mL) and 52.8(μg/mL) respectively.

Table 2 *In vitro* antidiabetic activity (**7m–r)** using α-amylase and α-glucosidase.

Compound	IC50(μg/mL)	
	α-Amylase	α-Glucosidase
7m	23.56	28.76
7n	13.67	13.54
7o	27.78	31.45
7p	15.76	16.67
7q	54.67	45.67
7r	49.89	47.78
Acarbose	16.54	17.67

Fig 2. Antidiabetic activity results using a) alpha-amylase and b) alpha-glucosidase.



7. Molecular docking studies

The main purpose of molecular docking is to find the interaction and binding attraction between the synthesized compounds and the receptor. The molecular docking scores and binding energy are listed in table 3. The glide energy results are -30.041 to 37.099. Compound 7m has the highest negative docking score of -6.155kcal/mol with glide energy -34.494kcal/mol compared to the docking study results of all synthesized compounds. Compound 7p has the lowest negative docking score of -4.328kcal/mol with glide energy -33.06kcal/mol. remaining four compounds has the moderate docking scores varies from -4.988 to -5.969 kcal/mol. Compound 7m involved π-π stacking interaction of phenyl ring with PHE88 residue of the enzyme and H-bond interaction of pyridine ring with water molecule. Compound 7n not involved interaction of synthesized compounds with amino acid residue but it had involved in vitro antidiabetic test showed good activity. Compound 7o showed π-π stacking interaction of phenyl ring and thiazine ring with PHE96 residue of the enzyme. Phenyl ring and ARG118 interaction involved π-cation interaction with docking score of -5.049kcal/mol. Compound 7p involved π-π stacking interaction of phenyl ring with PHE88.Compound 7q not involved any interaction but it had involved in vitro antidiabetic test showed good activity. Finally compound 7r involved π cation interaction between the phenyl ring and ARG 118.

Table 3
Molecular docking result based on glide energy, hydrogen bonding and ligand interaction of acarbose enzyme for the tested compounds **7h–m** (PDB: 2HR7)

Compound	Docking score (kcal/mol)	Number of hydrogen bonds	Interacting residues of 2HR7
7m	-5.811	1	PHE88,
7n	-6.155	-	-
7o	-5.049	2	PHE96,ARG118

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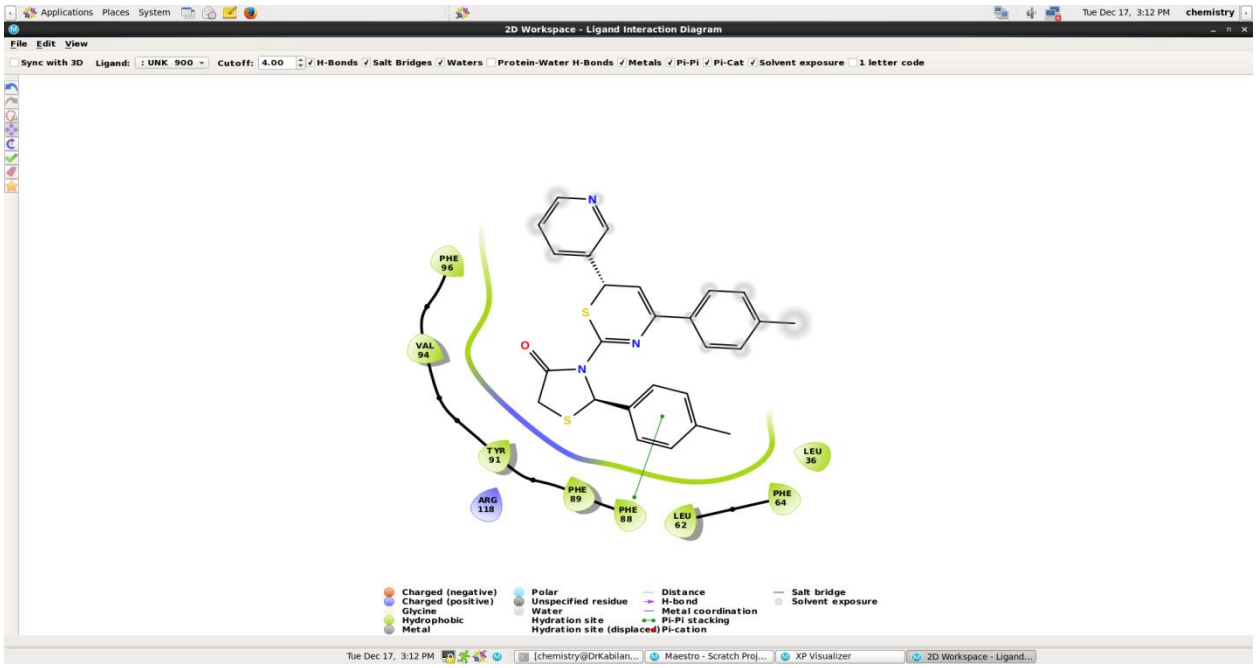
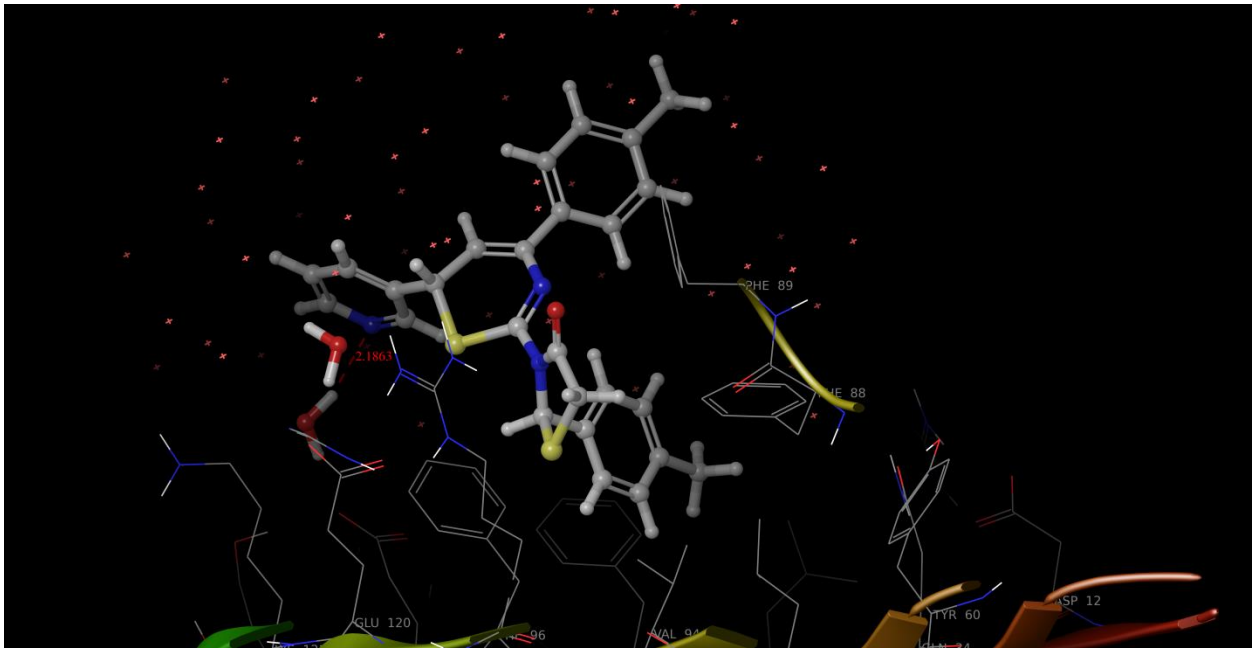
7p	-5.969	1	PHE88,
7q	-4.328	-	-
7r	-4.988	1	ARG118

Fig.3. Ligand interaction of compound 7p into Acarbose active site **(PDB ID: 2HR7)** in two dimensional structures and three dimensional structures.





8. Conclusion

In conclusion, we have prepared a series of thiazinyl-thiazolidinone derivatives. All the synthesized compounds were evaluated in vitro antidiabetic and anti oxidant activity. These compounds have significant inhibitory activities.

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