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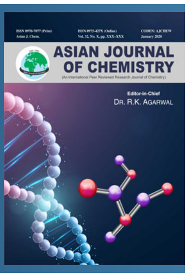

Synthesis, Characterization, Biological Evaluation and Molecular Docking Studies of Some Oxazinyl-Thiazolidinone Derivatives

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A series of new 4-thiazolidinone derivatives of 2-(4-chlorophenyl)-3-(6-(thiophen-2-yl)-4-*p*-tolyl-4*H*-1,3-oxazin-2-yl)-thiazolidin-4-one (**7h-m**) are synthesized because of its wide range of biological activities. ^{1}H & ^{13}C NMR, IR studies were applied for the elucidation of all the synthesized compounds. All the synthesized compounds have been tested for antidiabetic and antioxidant activity *in vitro* method against standard. The analogs **7h-m** was evaluated for α-amylase and α-glucosidase inhibitory potential. The structures of all the compounds have been screened for antioxidant activity using DPPH radical scavenging assay, NO scavenging method. Molecular docking studies were accomplished in addition to understand the binding affinity of those compounds with PDBID 2HR7 which showed that the synthesized derivatives bind in the lively binding site of the target protein

Keywords: Thiazolidinone, Oxazine, Antidiabetic activity, Antioxidant activity.

INTRODUCTION

Diabetes is one of the most damaging human lives in the world and increasing day by day. These disorders are caused by insulin not being properly secreted by the body and some of symptoms obesity, stress, diet, kidney failure and lack of physical activity [1]. Thiazolidinone derivatives have been mostly used to treat diabetes [2,3] and widely used in clinically type 2 diabetes. Different thiazolidinone and related compounds have a higher number of sources of anti-inflammatory [4], antioxidant [5], antitumor [6], antimicrobial [7], antidiabetic [8], antibacterial [9] agents.

The keto group at the 4th position and N-C-S interaction in the thiazolidinone derivatives enhance the pharmacological activity. Thiazolidinone compounds available in two ways one is synthetic another one is natural′s product that bind to plethora of different targets. Such structures have many medicinal properties with different pharmacological effects [10-14]. Recently thiazole, thiazolidinone derivatives have been used as a potent 15 LOX inhibitors, antioxidant and anticancer activity [15]. Thiazolidinone coupled with oxazine is expected to have more biological activities. The pyridine-thiazolidinone derivatives has been well known to have potent anticancer activity [16,17]. In this work, a simple synthetic method of oxazinyl-thiazolidinone derivatives containing biologically potent is described. Moreover, the synthesized compounds were also evaluated for antidiabetic and *in vitro* antioxidant activity.

EXPERIMENTAL

For synthesis, all chemicals were obtained from commercial sources and used as received unless stated otherwise. The melting points are uncorrected and were determined on a MELTEMP II capillary apparatus. IR spectra were meas-ured on a Shimadzu 440 spectrometer using KBr as pallets. ^{1}H NMR spectra were recorded in DMSO-d_6 on a Varian Gemini 200 (400 MHz) spectrometer using TMS as an internal standard.

General synthetic procedure for 4-(4-aryl)-6-(thiophen-2-yl)-4*H*-1,3-oxazin-2-amine (4a-c): 3-(4-Chlorophenyl)-1-(thiophen-2-yl)prop-2-en-1-one (0.01 mol) and urea (0.01 mol) were dissolved in ethanolic NaOH and the reaction mixture was stirred for 2 h. Refluxed the reaction mixture for 6 h and poured into ice water with continuous stirring for 1 h and finally cooled at 0 ºC for 48 h. The solid compound obtained was filtered, washed with water and recrystallized using methanol to give **4a-c**.

General synthetic procedure for *N*-(4-chlorobenzylidene)-4-(4-chlorophenyl)-6-(thiophen-2-yl)-4*H*-1,3-oxazin-2-amine (6h-m): Amine (0.01mol, **4a-c**) was mixed with the corresponding aromatic aldehyde (**5d-g**) in ethanolic solution followed by the addition of acetic acid (5 mL) dropwise. The reaction mixture was refluxed for 3 h. The TLC test is taken to monitor the reaction using petether:ethyl acetate (8:2). The reaction mixture was now cooled to 0 ºC and pour the mixture into ice water. Collect the separated solid, washed with a large quantity of water and recrystallized from ethanol to give **6h-m**.

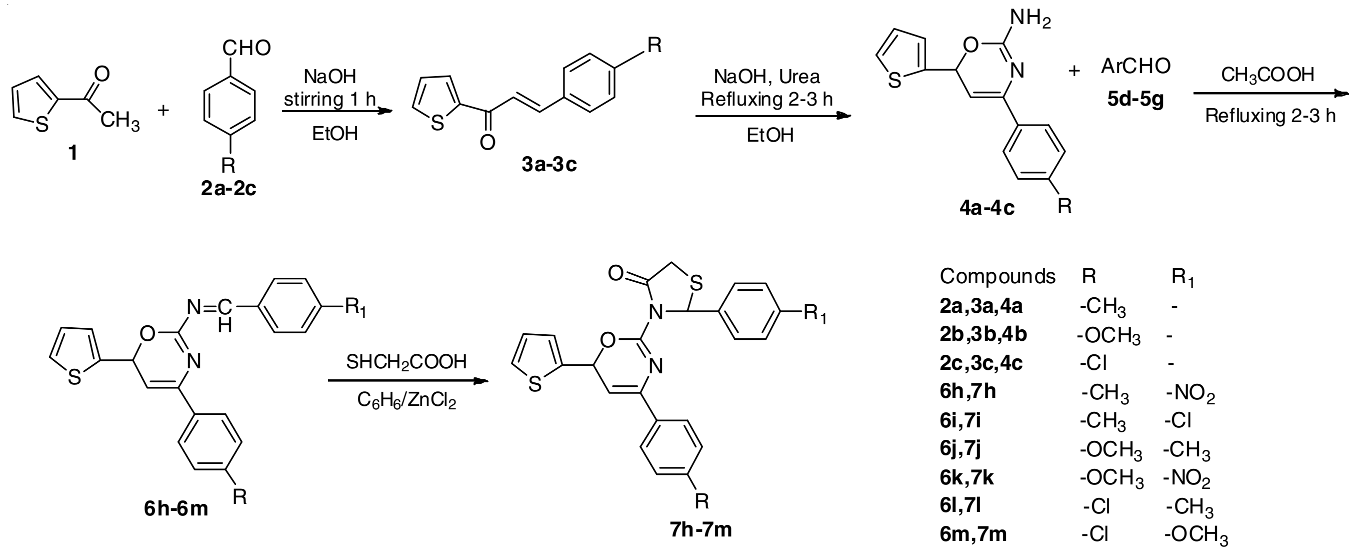
General synthetic procedure for 3-(4-(4-chlorophenyl)-6-(thiophen-2-yl)-4*H*-1,3-oxazin-2-yl)-2-p-tolylthiazolidin-4-one (7h-m): Schiff bases (0.01mol, **6h-m**) with thioglycolic acid (0.01mol) in dry benzene was refluxed for 5 h. The water formed in the reaction was removed by Dean-Stark apparatus. The TLC test was used to monitor the reaction using pet ether: ethyl acetate (8:2). After the completion of the reaction, benzene was removed by distillation to give crude solid, which was dissolved in methanol. The reaction mixture was allowed to pass through sodium bicarbonate solution, thus non-reactive acid is separated and finally remaining solution was allowed to evaporate in air condition. The precipitated solid formed was recrystallized using ethanol to give **7h-m** (**Scheme-I**).

2-(4-Nitrophenyl)-3-(6-(thiophen-2-yl)-4-*p*-tolyl-4*H*-1,3-oxazin-2-yl)thiazolidin-4-one (7h): Light orange solid; m.p. 280-283 ºC; Yield 74%. IR (KBr, ν_{max}, cm^{-1}): 3021 (Ar-CH), 1684 (C=O), 1520 (C=C), 893 (C-S), 1555 (NO_2), 1440 (C-N), 1623 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.38 (s, 2H, -SCH_2, thiazolidinone), 5.92 (s, 1H, NCH, thiazolidinone), 5.19 (d, 1H, N-CH, oxazine), 6.56(d, 1H, C=CH, oxazine), 2.35 (s, 3H, CCH_3), 6.60-8.07 (m, 11H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 34.1 (C_5 of thiazolidinone), 171.2 (CO cyclic), 46.5 (C_2 of thiazolidinone), 155.45 (C_2 of oxazine), 142.34 (C_4 of oxazine), 117.24 (C_5 of oxazine), 69.42 (C_6 of oxazine), 120-145 (Ar-C, 16C). Anal. found (%) for $C_{24}H_{19}N_3O_4S_2$: C, 60.36; H, 4.01; N, 8.80; O, 13.40; S, 13.43.

2-(4-Chlorophenyl)-3-(6-(thiophen-2-yl)-4-*p*-tolyl-4*H*-1,3-oxazin-2-yl)thiazolidin-4-one (7i): Light orange solid; m.p. 279-283 ºC; Yield 80%. IR (KBr, ν_{max}, cm^{-1}): 3021 (Ar-CH), 1683 (C=O), 1523 (C=C), 897 (C-S), 1443 (C-N), 1628 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.39 (s, 2H, -SCH_2, thiazolidinone), 5.94 (s, 1H, NCH, thiazolidinone), 5.16 (d, 1H, N-CH, oxazine), 6.76 (d, 1H, C=CH, oxazine), 2.36 (s, 3H, C-CH_3), 6.60-8.07 (m, 11H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 34.61 (C_5 of thiazolidinone), 173.62 (CO cyclic), 45.35 (C_2 of thiazolidinone), 154.97 (C_2 of oxazine), 142.35 (C_4 of oxazine), 117.39 (C_5 of oxazine), 69.02 (C_6 of oxazine), 120-145 (Ar-C, 16C). Anal. found (%) for $C_{24}H_{19}N_2O_2S_2Cl$: C, 61.72; H, 4.10; Cl, 7.59; N, 6.00; O, 6.85; S, 13.74.

3-(4-(4-Methoxyphenyl)-6-(thiophen-2-yl)-4*H*-1,3-oxazin-2-yl)-2-*p*-tolylthiazolidin-4-one (7j): Light yellow solid; 246-250 ºC; Yield 74%. IR (KBr, ν_{max}, cm^{-1}): 2967 (Ar-CH), 1694 (C=O), 1524 (C=C), 895 (C-S), 1438 (C-N), 1627 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.29 (s, 2H, -SCH_2, thiazolidinone), 5.89 (s, 1H, NCH, thiazolidinone), 5.46 (d, 1H, N-CH, oxazine), 6.32 (d, 1H, C=CH, oxazine), 2.29 (s, 3H, CCH_3), 6.60-8.07 (m, 11H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 33.41 (C_5 of thiazolidinone), 170.52 (CO cyclic), 44.65 (C_2 of thiazolidinone), 155.97 (C_2 of oxazine), 141.95 (C_4 of oxazine), 117.89 (C_5 of oxazine), 69.82 (C_6 of oxazine), 120-145 (Ar–C, 16C). Anal. found (%) for $C_{22}H_{22}N_2O_3S_2$: C, 64.91; H, 4.79; N, 6.06; O, 10.38; S, 13.86.

3-(4-(4-Methoxyphenyl)-6-(thiophen-2-yl)-4*H*-1,3-oxazin-2-yl)-2-4 nitrophenyl)thiazolidin-4-one (7k): Light yellow solid; m.p. 285–293 ºC; Yield 74%. IR (KBr, ν_{max}, cm^{-1}): 3011 (Ar–CH), 1724 (C=O), 1519 (C=C), 883 (C-S), 1555 (NO_2), 1430 (C-N), 1623 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.38 (s, 2H, -SCH_2, thiazolidinone), 5.92 (s, 1H, NCH, thiazolidinone), 5.19 (d, 1H, N-CH, oxazine), 6.46 (d, 1H, C=CH, oxazine), 2.35 (s, 3H, CCH_3), 6.60-8.07 (m, 11H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 34.1 (C_5 of thiazolidinone), 171.2 (CO cyclic), 46.5 (C_2 of thiazolidinone), 155.27 (C_2 of



Compounds	R	R$_1$
2a,3a,4a	-CH_3	-
2b,3b,4b	-OCH_3	-
2c,3c,4c	-Cl	-
6h,7h	-CH_3	-NO_2
6i,7i	-CH_3	-Cl
6j,7j	-OCH_3	-CH_3
6k,7k	-OCH_3	-NO_2
6l,7l	-Cl	-CH_3
6m,7m	-Cl	-OCH_3

Scheme-I: Synthetic route of oxazinyl-thiazolidinone derivatives (**7h-m**) oxazine), 141.57 (C_4 of oxazine), 117.63 (C_5 of oxazine), 69.56 (C_6 of oxazine), 120-145 (Ar-C, 16C). Anal. found (%) for $C_{24}H_{19}N_3O_5S_2$: C, 58.40; H, 3.88; N, 8.51; O, 16.51; S, 12.70.

3-(4-(4-Chlorophenyl)-6-(thiophen-2-yl)-4*H*-1,3-oxazin-2-yl)-2-*p*-tolylthiazolidin-4-one (7l): Light yellow solid; m.p. 278-283 ºC; Yield 68%. IR (KBr, ν_{max}, cm^{-1}): 3021 (Ar–CH), 1684 (C=O), 1520 (C=C), 893 (C-S), 1440 (C-N), 1623 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.38 (s, 2H, $-SCH_2$, thiazolidinone), 5.92 (s, 1H, NCH, thiazolidinone), 5.19 (d, 1H, N-CH, oxazine), 6.34 (d, 1H, C=CH, oxazine), 2.35 (s, 3H, CCH_3), 6.60-8.07 (m, 11H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 34.1 (C_5 of thiazolidinone), 171.2 (CO cyclic), 46.5 (C_2 of thiazolidinone), 154.87 (C_2 of oxazine), 140.57 (C_4 of oxazine), 117.67 (C_5 of oxazine), 69.78 (C_6 of oxazine), 120-145 (Ar-C, 16C). Anal. found (%) for $C_{24}H_{19}N_2O_2S_2Cl$: C, 61.72; H, 4.10; Cl, 7.59; N, 6.00; O, 6.85; S, 13.74.

3-(4-(4-Chlorophenyl)-6-(thiophen-2-yl)-4*H*-1,3-oxazin-2-yl)-2-(4-methoxyphenyl) thiazolidin-4-one (7m): Light yellow solid; m.p. 263-267 ºC; Yield 78%.IR (KBr, ν_{max}, cm^{-1}): 3021 (Ar-CH), 1684 (C=O), 1520 (C=C), 893 (C-S), 1440 (C-N), 1623 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.38 (s, 2H, $-SCH_2$, thiazolidinone), 5.92 (s, 1H, NCH, thiazolidinone), 5.19 (d, 1H, N-CH, oxazine), 6.23 (d, 1H, C=CH, oxazine), 2.35 (s, 3H, CCH_3), 6.60-8.07 (m, 11H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 34.1 (C_5 of thiazolidinone), 171.2 (CO cyclic), 46.5 (C_2 of thiazolidinone), 154.45 (C_2 of oxazine), 140.65 (C_4 of oxazine), 117.68 (C_5 of oxazine), 69.34 (C_6 of oxazine), 120-145 (Ar-C, 16C). Anal. found (%) for $C_{24}H_{19}N_2O_3S_2Cl$: C, 59.68; H, 3.96; Cl, 7.34; N, 5.80; O, 9.94; S, 13.28.

Antioxidant screening

Free radical scavenging activity: This technique measures the facility of the test compounds to scavenge free radicals against DPPH, which produce a violet colour in methanol at 517 nm. The radical scavenging activity (RSA) for methanol solutions of compounds **7h-m** at concentrations 25, 50, 75 and 100 µg/mL containing freshly prepared DPPH solution (0.004% w/v) was carried out and comparison with those of standards ascorbic acid.

in vitro Antidiabetic assay

α-Amylase inhibition activity: Various concentrations (25-125 µg/mL) of tested compounds were prepared by dissolving in distilled water and 1 mL of the enzyme solution added at the same time and incubated at 26 ºC for 15 min. After incubation, 1 mL of starch (0.5%) solution was added to the mixture and further incubated at 25 ºC for 10 min. After the reaction, added 2 mL of 3,5-dinitrosalicylic acid and heated the reaction mixture into the water bath (10 min). After cooling the reaction mixture, the absorbance was measured calorimetrically at 565 nm [18]. The inhibition percentage was calculated using eqn. 1.

$$\text{Inhibition (\%)} = \left(1 - \frac{\text{Absorbance of the untreated (Control)}}{\text{Absorbance of the test well}}\right) \times 100 \quad (1)$$

α-Glucosidase inhibition method: The α-glucosidase inhibitory activity of the synthesized oxazine-thiazolidinone derivatives was evaluated according to the standard method [19]. In a 96-well plate, reaction mixture containing phosphate buffer (100 mM, pH = 6.8), α-glucosidase (0.07 units) and different concentrations (25-125 µg/mL) of tested compounds was preincubated at 37 ºC for 15 min. Then, 5 mM *p*-nitro phenyl-α-D-glucoside (5 mM) was added as a substrate. The reaction mixture was incubated further at 38 ºC for 30 min and finally terminated the reaction by adding 2 mL of Na_2CO_3. The activity of α-glycosidase were determined by measuring the absorbance of *p*-nitrophenol at 405 nm. Acarbose at various concentration 25-125 µg/mL was added as a standard.

RESULTS AND DISCUSSION

In the synthesis of oxazinyl-thiazolidinone derivatives (**7h-m**), acetyl thiophene (**1**) was reacted with various aromatic aldehyde (**2a-c**) in the presence of NaOH as catalyst to obtain chalcone (**3a-c**). The oxazines **4a-c** were synthesized *via* condensation of chalcone derivatives **3a-c** with urea under reflux condition in presence of sodium hydroxide. Intermediate **4a-c** was refluxed with different substituted aldehydes to give Schiff bases in presence of acetic acid. Finally, Schiff bases were refluxed with thioglycolic acid to give thiazolidinone product (**7h-m**). The synthesized compounds were characterized by IR, ^{1}H & ^{13}C NMR and elemental analysis. In the IR spectrum of compound **7h**, the peaks at1728, 1623, 1439 and 896 cm^{-1} are due to carbonyl and C=O, C=N, C-N and C-S stretching, respectively. In the^{1}H NMR spectrum of compound **7h**, two doublet protons at δ 6.29 and 5.19 ppm are due to methine proton in the oxazine ring and the two singlet protons at δ 3.78 and 5.69 ppm in the thiazolidinone ring. ^{13}C NMR spectra of compounds **7h** also supported the fact that cyclic carbonyl group present and a signal appeared in δ 173.67 ppm. The signals at about δ 34.36 and 44.47 ppm were attributed to the C-2 and C-5 carbon of the thiazolidinone ring. Methine carbon atoms of oxazine ring were resonated 117.12 and 141.14 ppm, respectively. The signals resonated at 154.43 ppm have represented the carbon of C=N group in the oxazine ring, respectively and the signal appears at 68.76 ppm have represented the methine carbon atom. The aromatic carbons were resonated between δ 117.12-140.43 ppm.

Antioxidant activity: The results confirmed that compound **7h** established more potent antioxidant activity against the DPPH radicals with IC_{50} value of 6.62 µg/mL, relative to ascorbic acid having IC_{50} value of 22.88 µg/mL (Table-1). In addition compounds **7j, 7l** and **7m** exhibited good potential activity with IC_{50} ranging value of 9.33, 18.16 and 22.07 µg/mL higher than that of the standard ascorbic acid. While other compounds **7i** and **7k** showed modest activities with IC_{50} value of 31.32 and 29.63 µg/mL.

Nitric oxide (NO) radical scavenging activity: The scavenging effects of the tested compounds on NO were measured according to the method of Marcocci *et al*. [20]. The results in Table-1 shows that compounds **7h** and **7j** are more potent as compared to all compounds with IC_{50} values of 6.79 and 6.05 µg/mL, which are far better than standard ascorbic acid having IC_{50} value of 12.61 µg/mL. Compounds **7i** and **7k** are moderately potent having IC_{50} values of 14.22 and 29.26 µ g/mL, respectively. Compounds **7l** and **7m** show the lowest activity

TABLE-1
in vitro ANTIOXIDANT ACTIVITY OF COMPOUNDS **7h-m** USING DPPH AND NO

Compound	IC_{50} (µg/mL)	
	DPPH	NO
7h	6.62	6.79
7i	31.32	14.22
7j	9.33	6.05
7k	29.63	29.26
7l	18.16	53.53
7m	22.07	69.34
Ascorbic acid	22.88	12.61

TABLE-2
in vitro ANTIDIABETIC ACTIVITY OF COMPOUNDS **7h-m** USING α-AMYLASE AND α-GLUCOSIDASE

Compound	IC_{50} (µg/mL)	
	α-Amylase	α-Glucosidase
7h	9.31	1.01
7i	4.08	6.14
7j	39.13	27.29
7k	30.68	16.64
7l	16.51	9.24
7m	53.68	39.12
Acarbose	11.56	17.23

compared to standard with IC_{50} values of 53.53 and 69.34 µg/mL, respectively.

***in vitro* Antidiabetic assay:** The synthesized oxazinyl-thiazolidinones (**7h-m**) were evaluated for *in vitro* antidiabetic activity study against α-amylase and acarbose was used as standard drug. The % inhibition results are represented in Table-2. It was found that all the compounds showed the gradual increase of inhibition as the concentration of the sample increased. From the results, it was found that compounds **7h** and **7i** have shown the maximum inhibition and IC_{50} values 9.31 and 4.08 µg/mL. The IC_{50} values of compounds **7j**, **7k** and **7l** have 39.13, 30.68 and 16.15 µg/mL, respectively were found to be a modest activity, while compound **7m** has shown the IC_{50} value of 53.68 µg/mL, which is the least inhibition activity as compared to acarbose 11.56 µg/mL.

α-Glucosidase inhibition method: The IC_{50} values of synthesized compounds are presented in Table-2. The α-glucosidase study results are consistent with α-amylase inhibition. Many compound in this series were found to be very potent compare to standard. Compounds **7h**, **7i** and **7l** have IC_{50} value of 1.01, 6.14 and 9.24 µg/mL, which showed a better activity compare to standard drug. Among the compounds, **7h** having showed very good inhibition compare with acarbose IC_{50} value 15.79 µg/mL. Compound **7m** having a IC_{50} value of 39.12 µg/mL showed a less activity compare to all the compounds (**7h-m**) and acarbose.

Molecular docking studies: The molecular docking studies of the synthesized oxazinyl-thiazolidinones **(7h-m)** were performed in the Schrödinger docking studies using the PDB code 2HR7 [21]. The molecular docking study was carried out in order to explore the binding affinity of the synthesized compounds in the active site of α-amylase and α-glucisidase enzyme. For the most part, the docking results exhibit that all thiazolidinone derivatives had different substituted groups including electron donating groups (EDG) and electron withdrawing groups (EWG) over benzene ring. The molecular docking glides score, hydrogen bond and interactions are given in Table-3. Three compounds **7h**, **7i** and **7j** showed the highest docking scores (-6.376, -5.902 and -4.973, respectively) among all the compounds. Docking of compound **7h** showed an interaction between phenyl ring and PHE96 (Fig. 1), it had docking score of -6.376 kcal/mol. Compound **7i** (docking score of -5.902 kcal/mol) interaction of phenyl ring with PHE88.

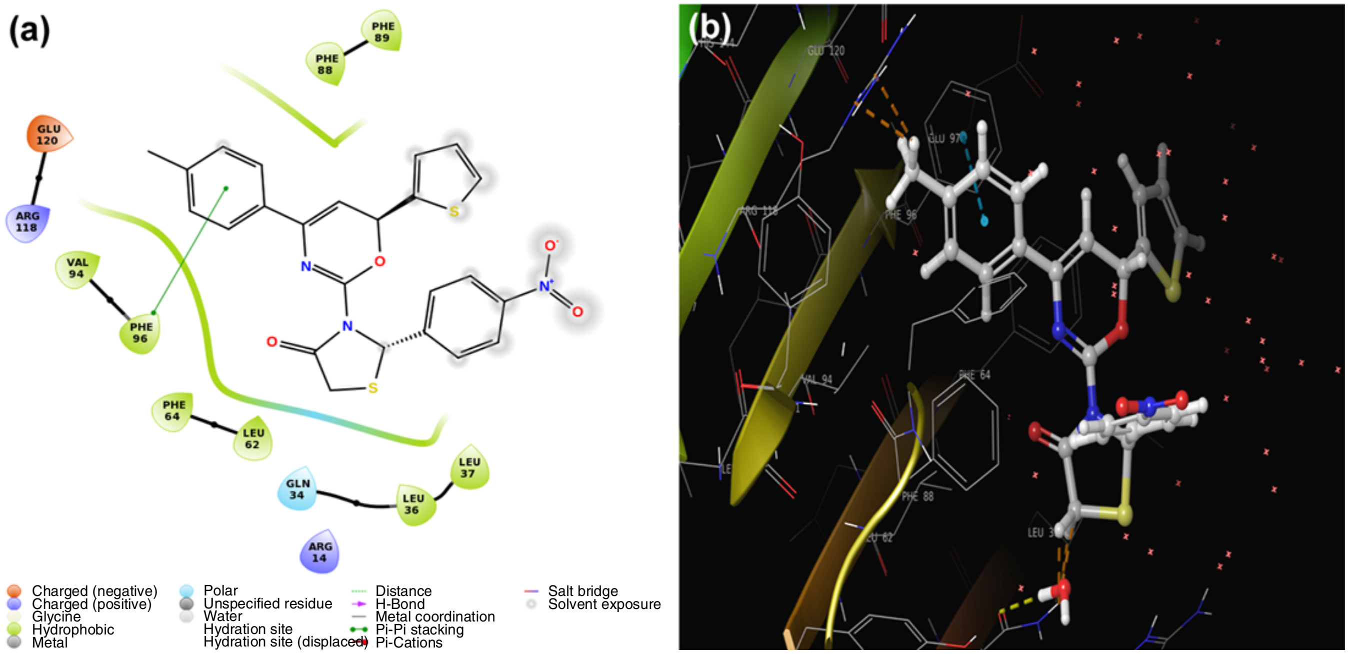


Fig. 1. Docking, glide energy and hydrogen bond of compound **7h** into acarbose active site (PDB ID: 2HR7) in (a) two dimensional structure and (b) three dimensional structure

TABLE-3
MOLECULAR DOCKING RESULT BASED ON GLIDE ENERGY, HYDROGEN BONDING AND 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
7h	-6.376	1	PHE96
7i	-5.902	1	PHE88
7j	-4.973	2	PHE96, GLU97
7k	-4.501	2	PHE88, ARG118
7l	-4.175	2	PHE88, PHE96
7m	-4.138	3	PHE88, PHE89, PHE96

Observation the binding interaction of compound **7j** (docking score of -4.973 kcal/mol) showed phenyl ring and oxazine ring with amino acid PHE96 and the water molecule interaction between oxygen atom of the methoxy group with the GLU97. Compound **7k** was successfully docked with the glide score of -4.501 kcal/mol showed interaction phenyl ring with the amino acid of PHE88 and the oxygen in nitro group interaction with the amino acid ARG118. Additionally and the binding interaction of compound **7l** docking score of -4.175 kcal/mol showed interaction between phenyl ring with amino acid residue PHE88. Finally, compound **7m** exhibited thiophene interacted with PHE88 and methoxy phenyl ring interacted with PHE89 and methyl phenyl ring interacted with PHE96 and the docking score is -4.138 kcal/mol. Among the six compounds investigated, compound **7h** having best antidiabetic activity showed greater binding energy -6.376 kcal/mol compared to other compounds.

Conclusion

In the present work, six new oxazinyl-thiazolidinone derivatives (**7h-m**) were synthesized, characterized and evaluated for their antidiabetic and antioxidant potential. Overall, 2-(4-nitro-phenyl)-3-(6-(thiophen-2-yl)-4-*p*-tolyl-4*H*-1,3-oxazin-2-yl)thiazolidin-4-one **(7h)** was found to be the most potent members of the series.

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CONFLICT OF INTEREST

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

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