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# Synthesis, characterization, molecular docking study and anti-bacterial activity of new 4-thiazolidinone derivatives

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**Abstract**
In the current work, a series of compounds containing of thiazolidinone derivatives (AD6-AD10) prepared by reacting Schiff base with thioglycolic acid in dioxane and characterization by using spectroscopic techniques FT-IR, $^{1}$H-NMR, $^{13}$C-NMR and CHN spectral technique Antibacterial behaviors inspected against various bacteria, including *Staphylococcus epidermidis* and *Staphylococcus aureus* Gram (+) ve, *Klebsiella pneumonia* and *Escherichia coli* Gram (-) ve. *Insilico* molecular docking study performed for the active compound where the compounds showed good docking score with a good binding mods.

**Keywords:** 4-Thiazolidinone, molecular docking, antibacterial

## Introduction

Thiazolidinone compounds are one of the thiazolidine derivatives, and they are heterocyclic molecules that contain sulphur and nitrogen, and when they have a carbonyl section in the -4-site [1], they are called thiazolidinedione-4-on [2]. These systems show more stability than thiophene, as they are stable towards acid at moderate temperatures [3]. The researchers were interested in preparing the thiazolidinediones, using thiocyclic acid to obtain the thiazolidine -2-on ring while preserving the active carboxyl group [4]. Thiazolidinone derivatives were prepared from the reaction of Schiff bases with thioglycolic acid [5]. A thiazolidine compound was prepared from hydrazones derived from 2-hydrazinobenzothiazole with thioglycolic acid in the presence of zinc chloride and THF as a solvent [6]. The thiazolidinediones are biologically active [7]. It is essential because it contains an atom of sulfur and nitrogen [8]. Its medical and therapeutic importance has increased recently because it contains many influential groups that enter into the chemistry of drugs [9]. the chemistry of toxins, and many other medical uses [10]. A series of anti-diabetic agents have been developed and studied, mainly the level of sugar in the blood and the extent to which the cell reduces its activities in resisting obesity genetically [11], and this means that cells sometimes become resistant to insulin [12] as it causes a significant breakthrough in anti-diabetic treatment by increasing sensitivity to insulin for that [13]. They are also called "insulin sensitizers"[14] and have been used to treat diarrhea [15] and to kill parasites of the type (Toxoplasma gondi) [16]. Thiazolidinediones are effective against Staphylococcus aureus, Klebsiella pneumonia & Eschcrshia Coli [17]. The thiazolidine-4-en compounds have a broad biological activity spectrum [18]. The focus was on thiazolidinediones. It is an anti-HIV [19], anti-diabetic [20], diuretic [21], anti-inflammatory [22], anti-tuberculosis [23], and anti-fungal [24]. Thiazolidinone compounds were also included in industrial chemistry and analytical chemistry [25]. Many studies were conducted on their use as heavy metal removers and pollutants [26], especially dyes, and they were also used in manufacturing chemical fertilizers [27]. This study aimed to prepare five compounds of thiazolidinediones, characterize them by physical and spectroscopic methods, and study their biological activity and molecular modeling.

## Experimental part

### 1. Chemistry

Melting points of all new thiazolidinone compounds were tested through utilizing open capillary tube apparatus (Staurt SMP10). Infrared analysis data were detected using KBr disc on an FT-IR -8400s (SHIMADZU) at chemistry lab at the college of science, Tikrit university. $^{1}$H NMR and $^{13}$C NMR spectra were detected in deuterated solvent in 400 MHz ($^{1}$H NMR) and 100MHz ($^{13}$C NMR). The chemical shift was schemed in $\delta$ppm by using tetramethyl silane (TMS) as a reference. Elemental analysis (CHNS) accomplished by' EuroEA 3000 / apparatus.

### 1.1. Preparation of Thiazolidinone Derivatives (AD6-AD10)

0.02 mole of the imine derivatives dissolved in 25ml Diethylene dioxide and warmed with stirring for ten minutes in a 100 ml round flask fitted with a condenser placed in a water bath, after which 0.04 mol of $ZnCl_2$ anhydrous dissolved in 10 ml of Diethylene dioxide was added as a catalyst to (0.04 mol) of thiol acetic acid dissolved in 20 ml of Diethylene dioxide. The mixture was introduced drop by drop, and after mixing the reaction components, it was noticed that it became cloudy immediately after addition. Then, the course of the reactions was followed up using thin layer chromatography and using Benzene: Methanol (6:4) and endorsement was done with iodine, and after the reflux period ended, part of the solvent was evaporated to give a residue, the precipitate was filtered and washed with distilled water after which it was left to dry and then re-washed from chloroform [28]. Table 1 depicts a few of the physical properties of the compounds prepared.

**3-(4-(4-(2-oxo-5-phenylpyrrolidin-1-yl)benzyl)phenyl)-2-phenylthiazolidin-4-one(AD6):**

Dark yellow; Yield 70%; m.p: 245-247 ºC; $R_f$=0.7 ($CHCl_3$: benzene, 1:3); IR (KBr), $v_{max}/cm^{-1}$: 3068 (C-H aromatic), 2927, 2892 (C-H), 1680 (C=O), 1603, 1470 (C=C Ar),1264(C-N), 692 (C-S).

**2-(4-fluorophenyl)-3-(4-(4-(2-(4-fluorophenyl)-5-oxopyrrolidin-1-yl)benzyl)phenyl)thiazolidin-4-one (AD7)**

Dark yellow; Yield 76%; m.p: 229-231 ºC; $R_f$=0.67 ($CHCl_3$:benzene, 1:3);); IR(KBr), $v_{max}/cm^{-1}$: 3080 (C-H aromatic), 2927, 2892 (C-H), 1680 (C=O), 1603, 1470 (C=C Ar),1264(C-N), 692 (C-S).

**2-(4-chlorophenyl)-3-(4-(4-(2-(4-chlorophenyl)-5-oxopyrrolidin-1-yl)benzyl)phenyl)thiazolidin-4-one(AD8)**

Yellow; Yield 72%; m.p: 212 - 214 ºC; $R_f$=0.8 ($CHCl_3$: benzene, 1:3);); IR(KBr), $v_{max}/cm^{-1}$: 3068 (C-H aromatic), 2987, 2901 (C-H), 1646 (C=O), 1600, 1484 (C=C Ar),1272 (C-N), 692 (C-S).

**2-(4-nitrophenyl)-3-(4-(4-(2-(4-nitrophenyl)-5-oxopyrrolidin-1-yl)benzyl)phenyl)thiazolidin-4-one(AD9)**

Brown; Yield 65%; m.p: 236-238 ºC; $R_f$=0.75 ($CHCl_3$: benzene, 1:3);); IR(KBr), $v_{max}/cm^{-1}$: 3072(C-H aromatic), 2971, 2901 (C-H), 1684 (C=O), 1598, 1472 (C=C Ar), 1513,1342 ($NO_2$ asym, sym) 1249 (C-N), 690 (C-S),

**2-(4-methoxyphenyl)-3-(4-(4-(2-(4-methoxyphenyl)-5-oxopyrrolidin-1-yl)benzyl)phenyl)thiazolidin-4-one(AD10)**

light yellow; Yield 70%; m.p: 223 -225 ºC; $R_f$=0.83 ($CHCl_3$: benzene, 1:3);); IR(KBr), $v_{max}/cm^{-1}$: 3063 (C-H aromatic), 2960, 2894 (C-H), 1692 (C=O), 1588, 1510 (C=C Ar),1257(C-N), 1094 (C-O), 692 (C-S).

**Biological activity**

Antibacterial potency of new synthesized thiazolidine molecules were detected by the disk diffusion method against four bacteria: *Staphylococcus epidermidis* and *Staphylococcus aureus* Gram (+) ve, and *Klebsiella pneumonia* and *Escherichia coli* Gram (-) ve,. Later, the disks were submerge in DMSO (which was used as a pessimistic monitor) and dried out in an incubator prior to using them in bacteria cultures. For two days, the plates were incubated at 37°C. zone of inhibition (ZOI) was noted and calculated. The antibiotics *ciprofloxacin*, *ampicillin*, and *amoxicillin* were utilized as a reference samples at three doses [29, 30].

***Insilico* studies**

**1. Molecular docking study**

Molecular docking investigation for new thiazolidine derivatives that have high activity against of *Staphylococcus epidermidis* and *Staphylococcus aureus*, *Klebsiella pneumonia* and *Escherichia coli* (AD7, AD8, AD10) via employing Auto Dock 4.2.6 programs, Klebsiella pneumoniae AcrB(PDB:ID:8FFS) biotin carboxylase (PDB:ID: 3jzf), biotin protein ligase (PDB:ID: 4dq2), protein FtsZ (ftsZ) (PDB:ID: 4M8I) were obtained from RCSB, PDB (Protein Data Bank) site. The minimization energy of new compounds were accomplished by using MM2 in chem3D program. The ligand and protein preparation were achieved by Auto DockTools-1.5.6 program. Finally, Discovery Studio 2020 Client was used to visualize 2D and 3D binding modes.

**Results and discussion**

**1. Chemistry**

This organic synthesis scenario includes reaction of Schiff base derivatives with mercapto acetic acid to produce of 1,3-thiazolidine-4-one derivatives (AD6-AD10). As clarifying in figure 1:

The FT-IR range for thiazolidinone derivatives (AD6-AD10) to the absence the peak of imin group (HC=N), and emersion of new peaks at (3051-3080) $cm^{-1}$ attributed to the (C-H) aromatic, besides, a band at (2913-2987) $cm^{-1}$ and (2844-2901) $cm^{-1}$ attributed to (C-H) aliphatic, and bands at (1646-1694) $cm^{-1}$ attributed to the (C=O) lactam, bands at (1586-1603) $cm^{-1}$ and (1470-1513) $cm^{-1}$ indicated to the aromatic ring (C=C), band at (1249-1272) $cm^{-1}$ refer to (C-N), and band at (674-708) $cm^{-1}$ attributed to (C-S).

The $^1$H-NMR spectrum of synthesized compounds (AD6-AD10) revealed : multiple signals at **δ**= 7.01-8.16 ppm, attributed to aromatic protons, a singlet signal at 6.46-6.63 ppm represent the methane (CH) proton of thiazolidine ring at 2 positions, singlet peak at range **δ**= 3.93 – 4.02 ppm attributed to methylene protons($CH_2$) at C5 in thiazolidine ring, the singlet signal at **δ**= 3.83-3.93 ppm that spacer linkage between two benzene ring, the singlet peaks at **δ**= 3.79 ppm refer to protons of methoxy group (-OCH3) in AD10 compounds, the signal at **δ**= 3.36 ppm represent of HDO exchangeable proton, the signals at **δ**= 2.49 – 2.51 ppm attributed to DMSO exchangeable protons. As depicted in figure 2:

$^{13}$C-NMR spectral data revealed: appearanc of (C=O) cabons of thiazolidine ring at **δ**= 171.6 ppm. The aromatic carbons were appeared at **δ**= 116.14 – 163.98 ppm, signal at **δ**= 64.95 – 64.97 ppm. represent of methine carbon (CH) of C5 in thiazolidine ring, signal at **δ**= 46.29 – 49.76 ppm refer to methylene (CH2) carbon spacer that linking two benzene ring, signal at **δ**= 31.72 – 33.51 ppm due to (CH2) carbon in 5 position of thiazolidine ring, the (-OCH3) carbon in AD10 compound was appeared at **δ**= 58.35 ppm. As depicted in the figure2.

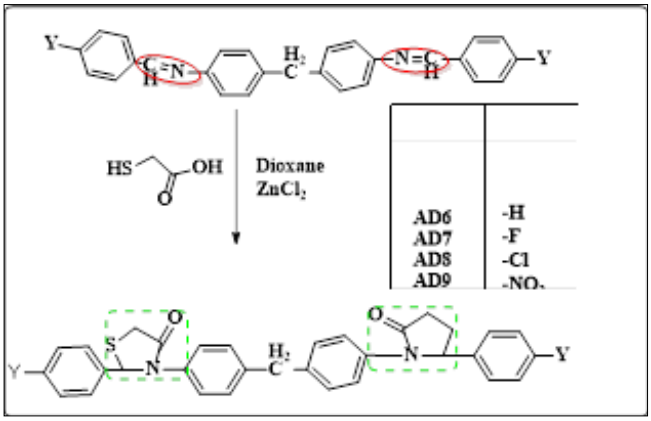


**Fig 1:** Route of Prepared Compounds (AD6-AD10)

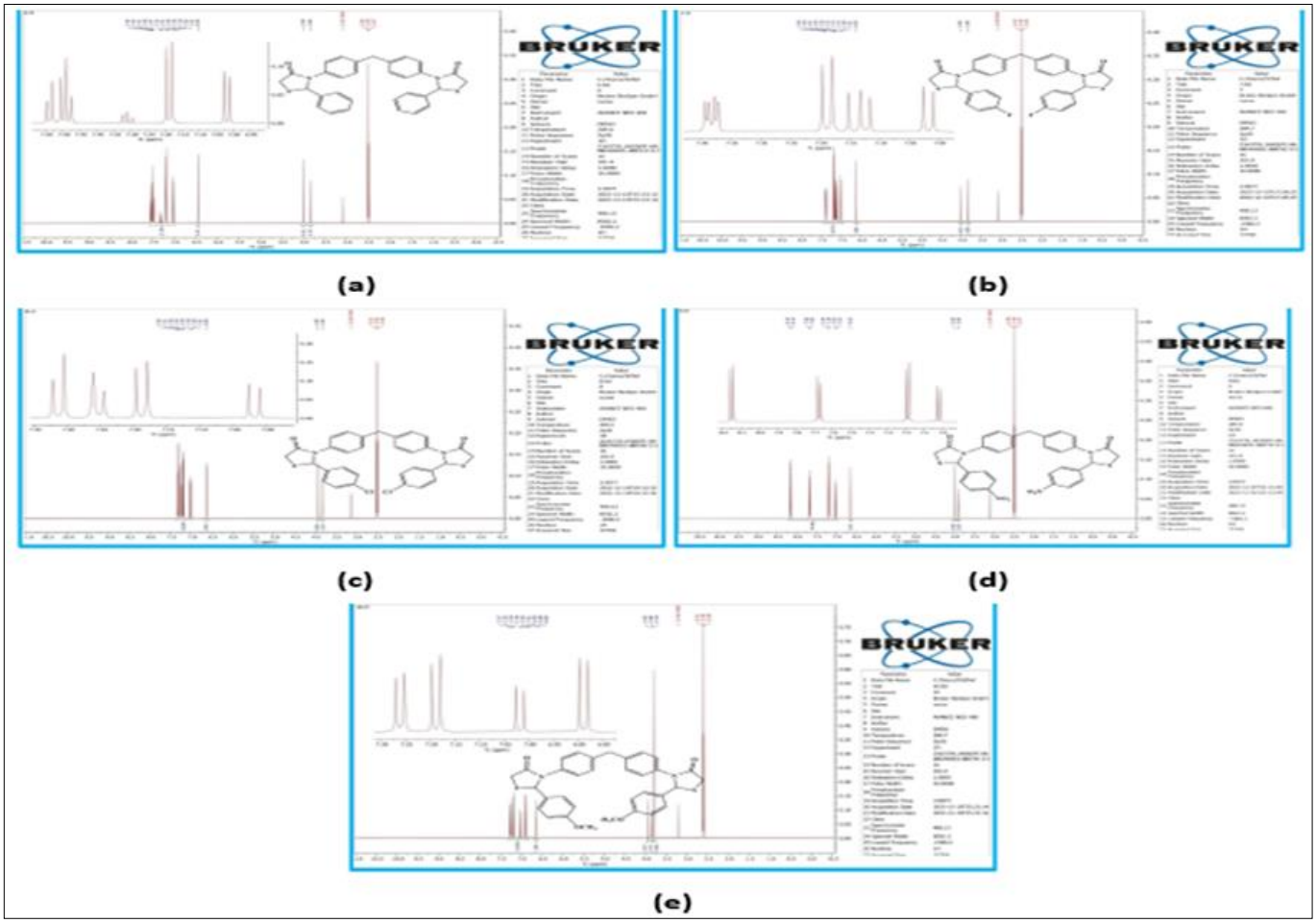


**Fig 2:** $^{1}$H-NMR Spectrum of Compound (a) AD6 (b) AD7 (c) AD8 (d) AD9 (e) AD10

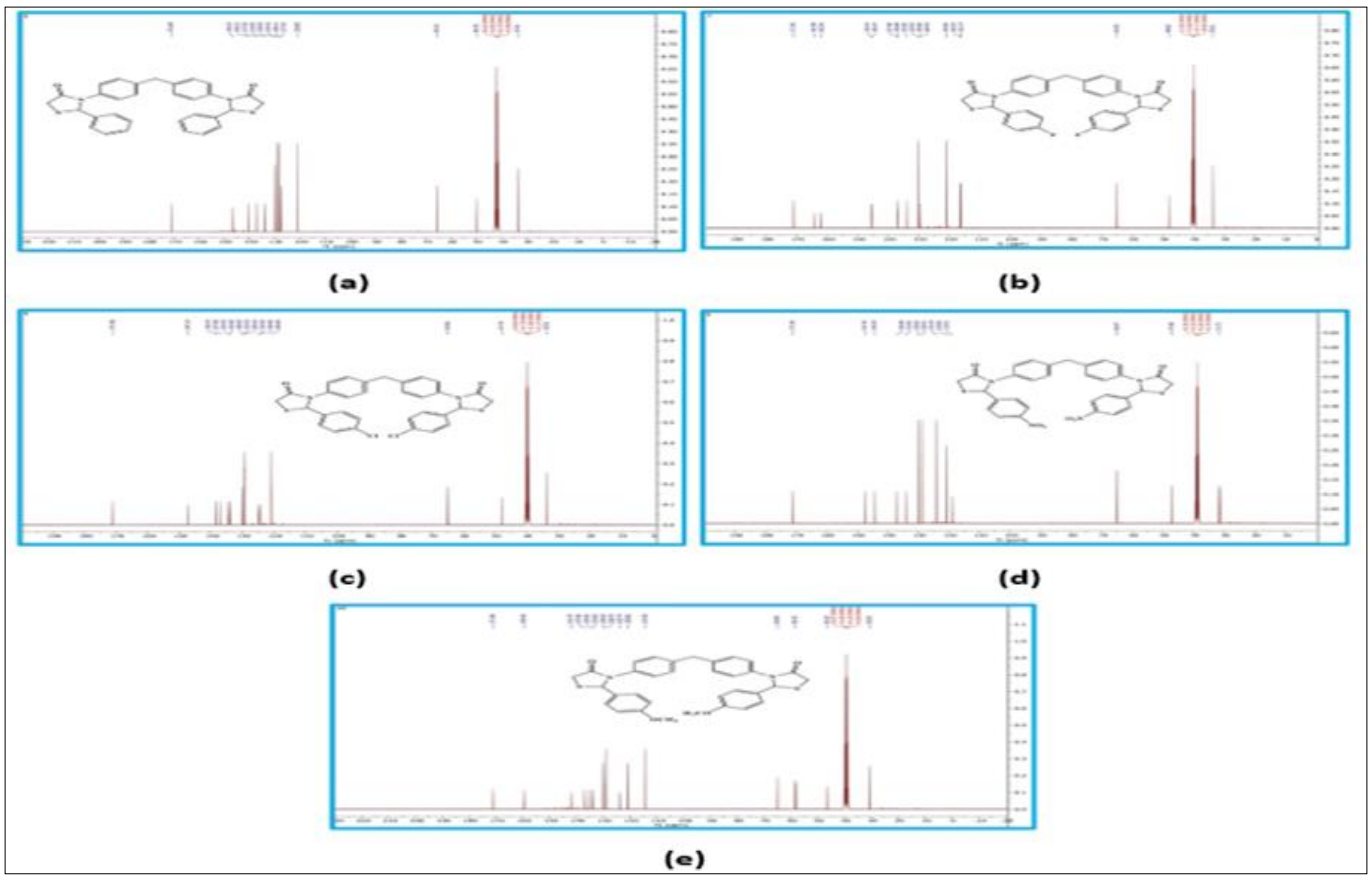


**Fig 3:** $^{13}$C-NMR Spectrum of Compound (a) AD6 (b) AD7 (c) AD8 (d) AD9 (e) AD10

The prepared compounds (AD6-AD10) were diagnosed using the element analysis technique for the compounds, and the outcomes indicated that the obtained values, which were found to be close or identical to the calculated values, and this proves the accuracy and validity of the prepared compounds (AD6-AD10), as shown in Table 4.

**Table 3:** Elemental Analysis (CHNS) Values for the Prepared Compounds (AD6-AD10)

| Comp. No. | Molecular Formula | Found | | | | Calculated | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | C% | H% | N% | S% | C% | H% | N% | S% |
| AD6 | $C_{31}H_{26}N_2O_2S_2$ | 71.05 | 5.10 | 5.31 | 11.94 | 71.24 | 5.01 | 5.36 | 12.2 |
| AD7 | $C_{31}H_{24}F_2N_2O_2S_2$ | 66.72 | 4.36 | 4.94 | 11.39 | 66.65 | 4.33 | 5.01 | 11.48 |
| AD8 | $C_{31}H_{24}Cl_2N_2O_2S_2$ | 63.11 | 4.15 | 4.71 | 10.94 | 62.94 | 4.09 | 4.74 | 10.84 |
| AD9 | $C_{31}H_{24}N_4O_6S_2$ | 60.69 | 4.00 | 9.21 | 10.58 | 60.77 | 3.95 | 9.14 | 10.47 |
| AD10 | $C_{33}H_{30}N_2O_4S_2$ | 67.90 | 5.14 | 4.73 | 10.89 | 68.02 | 5.19 | 4.81 | 11.00 |

## 2. Biological part

Antibacterial potency of the new thiazolidine derivatives (AD6-AD10) was tested against gram-negative and gram-positive bacteria. As per the outcomes offered in Table 6 and Figure 8, these compounds can inhibit the growth of the used bacteria. However, it was found that the ability to inhibit has a direct association with the concentration of prepared compounds (AD6-AD10).

**Table 4:** Antibacterial potency outcomes of new thiazolidine derivatives (AD6-AD10) and reference drugs.

| Comp. symbol | *E. Coli* | | | *K, Pneumonia* | | | *S. Aureus* | | | *S. Epidermidis* | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0.0001 | 0.01 | 0.1 | 0.0001 | 0.01 | 0.1 | 0.0001 | 0.01 | 0.1 | 0.0001 | 0.01 | 0.1 |
| AD6 | 6 | 11 | 19 | 0 | 5 | 13 | 2 | 4 | 8 | 6 | 8 | 15 |
| AD7 | 7 | 14 | 20 | 6 | 9 | 16 | 8 | 15 | 20 | 9 | 13 | 18 |
| AD8 | 8 | 15 | 20 | 10 | 14 | 20 | 9 | 20 | 20 | 8 | 14 | 19 |
| AD9 | 6 | 12 | 17 | 5 | 13 | 8 | 5 | 10 | 16 | 4 | 9 | 13 |
| AD10 | 9 | 18 | 20 | 7 | 11 | 19 | 6 | 15 | 20 | 3 | 9 | 16 |
| *Ampicillin* | 10 | 16 | 24 | 7 | 17 | 21 | 8 | 14 | 18 | 9 | 15 | 19 |
| *Amoxicillin* | 8 | 13 | 18 | 6 | 13 | 18 | 9 | 15 | 17 | 7 | 15 | 20 |
| *Ciprofloxacin* | 9 | 15 | 20 | 9 | 14 | 16 | 9 | 12 | 18 | 8 | 16 | 19 |
| Blank disk | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

## 3. Molecular docking study

Molecular docking modeling process was done for the molecules (AD7, AD8, AD10) against the binding site Klebsiella pneumoniae AcrB(PDB:ID:8FFS), biotin carboxylase (PDB:ID: 3jzf), biotin protein ligase (PDB:ID: 4dq2), protein FtsZ (ftsZ) (PDB:ID: 4M8I) to interpretation of inhibitor effect of these compounds, the obtained results were showed: the compounds (AD8, AD10) showed high docking score with the binding site of Klebsiella pneumoniae AcrB(PDB:ID:8FFS), while the compounds (AD7, AD8) showed good binding mods with the binding groove of biotin protein ligase (PDB:ID: 4dq2). as depicted in figures (6-11), table (5) showed the docking score and H-bond binding mods:

**Table 5:** The docking results of antibacterial compounds with the binding site of Klebsiella pneumoniae AcrB (PDB:ID:8FFS) biotin carboxylase (PDB:ID: 3jzf), biotin protein ligase (PDB:ID: 4dq2), protein FtsZ (ftsZ) (PDB:ID: 4M8I)

| Comp. No. | PDB:ID | Docking Score(kcal/mol) | Residue Involve H-bond |
|---|---|---|---|
| AD10 | 3jzf | -7.9 | ARG:B:338 |
| AD8 | 8FFS | -10.1 | ARG:B:619 |
| AD10 | 8FFS | -11.2 | |
| AD7 | 4dq2 | -7.9 | ASN:A:179, SER:A:318, MET:A:195 |
| AD8 | 4dq2 | -7.9 | ASN:A:179, SER:A:318 |
| AD8 | 4M8I | -9.6 | ILE:A:228 |

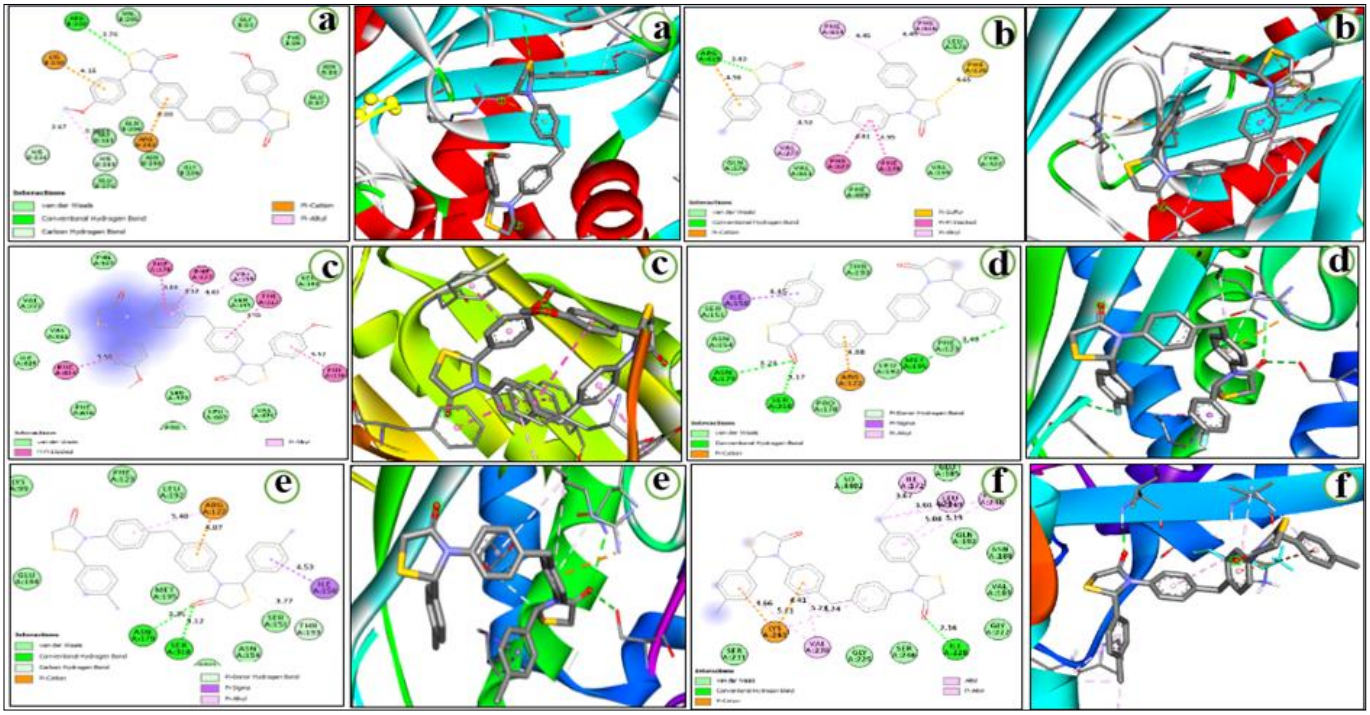

**Fig 4:** 3D and 2D images of interaction: (a) (AD10) with biotin carboxylase (PDB:ID: 3jzf) (b): (AD8) with Klebsiella pneumoniae AcrB (PDB:ID:8FFS) (c): (AD10) with Klebsiella pneumoniae AcrB (PDB:ID:8FFS), (d): (AD7) with biotin protein ligase (PDB:ID: 4dq2), (e): (AD8) with biotin protein ligase (PDB:ID: 4dq2). (f): (AD8) with protein FtsZ (ftsZ) (PDB:ID: 4M8I).

## Conclusions

Finally, we developed and synthesized new chemical derivatives containing of thiazolidine moiety with reasonable yields, AD7, AD8, AD10 derivatives showed antibacterial activity against of four type of pathogenic bacteria. docking studies suggested the new compounds acts as a good inhibitory agent against tested types of bacteria.

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