







## Synthesis and Investigation the Biological Activity of Some New Alkenes Based on Thiazolidin-4-One Compounds

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### Abstract

This work has been done to prepare a series of new alkene compounds derived from 4-thiazolidinones by substituting different aldehydes, P-acetamido-phenol, and 2-mercapto-benzoimidazole, which were used as starting materials to form ester [I]<sub>a,b</sub> and then make hydrazides [II]<sub>a,b</sub>, which were used to prepare 1, 3, and 4-oxadiazoles [III]<sub>a,b</sub>, which were then used for prepared Schiff bases [IV]<sub>a-f</sub>. The next step was the synthesis of 4-thiazolidinone derivatives [V]<sub>a-f</sub> from Schiff bases. The final step was the synthesis of alkenes [VII]<sub>a-f</sub>, the prepared derivatives were identified with spectral methods (FT-IR, <sup>1</sup>H-NMR, mass, and CHNS). The antibacterial activity of the prepared derivatives was evaluated against four types of bacteria, positive gram (*Staphylococcus aureus* and *Enterococcus faecalis*.) and negative gram (*E. coli* and *Pseudomonas aeruginosa*). The final compounds gave high to moderate efficacy against *Enterococcus faecalis* bacteria, molecular modeling study against one of the SARS human coronavirus proteins was tested for synthesis compounds. Compound [VII]<sub>c</sub> had a high bonding strength with the target protein, wherever it was -8.08 Kcal/mole followed by the compound [VII]<sub>a</sub>. in the bonding strength energy, which was -7.65Kcal/mole.

**Keywords:** Alkenes, antibacterial activity, molecular docking, Schiff bases, thiazolidin-4-ones.

### 1. Introduction

Heterocyclic compounds (i.e., containing heterogeneous atoms such as nitrogen, sulfur, and oxygen) are important in various fields of science such as medicine, industry, agriculture, and pharmaceuticals [1–3]. There is much interest in these compounds and their new derivatives. 1,2,3-Thiosolidinones, a class of heterocyclic compounds with five members, hold significant biological and medical importance due to their incorporation of elements such as oxygen, nitrogen, and sulfur. In addition to the carbonyl group on C5, S at location 1, N at location 3, and CH<sub>2</sub> at location 2, 4, and 5 are found with ring structure, which increase their effectiveness against many microorganisms as well as diseases [4,5], like the nucleus of 4-thiazolidine is included in the composition of diabetes medications [6], it also expands the



targets of its work to include antiviral, antifungal, anti-parasitic, and anti-cancer [7], anti-tuberculosis [8,9], antibacterial [10], and anticonvulsant activity [11]. This work prepared new compounds of alkenes containing a 4-thiazolidine nucleus, evaluated their biological activity, and conducted molecular modeling.

## 2. Materials and Methods

### 2.1 Instrumental

All chemicals were employed without purification; a specific company supplied them. The melting point was measured by using Gallen Kamp uncorrected melting point with open capillaries, FT-IR by using Shemazdo (1800, KBr dis. in  $\text{cm}^{-1}$ ),  $^1\text{H-NMR}$  with Burker NMR, 400 MHz, C.H.N.S. analysis with LECO CHNS-923, and Mass with Agilent Technology (HP), MS Model 5973 Network mass Selective Detector with Electron Impact (EI) 70 eV, Analyzer: Quadrupole at Tehran University.

### 2.2 Compound [I]<sub>a</sub>

A combination of P-acetamidophenol [a] (0.15 g, 0.01 mole) and ethyl  $\alpha$ -chloroacetate (1.23 mL, 0.01 mole) in (15 mL) of dry-acetone refluxed for 6 hours in the presence of anhydrous  $\text{K}_2\text{CO}_3$  (1.38 g, 0.01 mole). Then the finished mixture is cooled and placed on crushed ice. The white solid product was filtered and recrystallized from Et-OH after drying. yield 85%, m.p. 78°C [12], FT-IR ( $\text{cm}^{-1}$ ): 3387 for sec. amide ( $\nu$ -NH str.), 3002 ( $\nu$  arom.-CH str.), 2939, 2866 ( $\nu$  aliph. C-H str.), 1743 ( $\nu$  C=O) carbonyl ester, 1681 ( $\nu$  amide C=O), 1523 ( $\nu$  C=C), 1315( $\nu$  C-N), 1242, and 1211( $\nu$ - C-O-C ), 829 ( $\nu$  P-substitution).

### 2.3 Compound [I]<sub>b</sub>

Heating combination of 2-mercaptobenzoimidazol [b] (0.355 g, 0.001 mole), ethyl- $\alpha$ -Chloro-acetate (0.001 mole), and molten sodium-acetate (0.247 g, 0.003 mole) into absolute EtOH 5 mL for 4 hours After cooling the final mixture and immersing it in extremely cold water, we filter, dry, and recrystallize the resulting product in Et-OH. [13,14], yield 93%, m.p. 86-88°C, FTIR ( $\text{cm}^{-1}$ ):3125 ( $\nu$  NH), 3080 ( $\nu$  arom.-CH), 2954, 2866 ( $\nu$  aliph.CH), 1735 ( $\nu$  C=O) ester, 1601 ( $\nu$  C=N), 1504 ( $\nu$  C=C); 1215 ( $\nu$  C-O-), 759 ( $\nu$  C-S-C).

### 2.4 General procedure for synthesis hydrazide derivatives [II]<sub>a,b</sub>

Hydrazine hydrate 80% (8 mL) has been added to a solution of ester compounds [I]<sub>a,b</sub> (0.03 mole) in ethanol at 12.5 mL and refluxed for 5–6 hours. After that, cool the mixture, off-white filter the product, dry it, and then recrystallize from EtOH [12-14].

#### 2.4.1 Compound [II]<sub>a</sub>

Molecular formula:  $\text{C}_{10}\text{H}_{13}\text{N}_3\text{O}_3$ , yield 89%, m.p. 155-157°C, White color, FT-IR ( $\text{cm}^{-1}$ ): 3340-3190 ( $\nu$ -NH<sub>2</sub>,-NHSec.amide), 3055 ( $\nu$  arom.-CH), 2924-2830 ( $\nu$  aliph. C-H-), 1643 ( $\nu$  C=O str.), 1570 ( $\nu$  C=C), 1357 ( $\nu$ -C-N-), 1230 ( $\nu$  C-O-C).

#### 2.4.2 Compound [II]<sub>b</sub>

Molecular formula:  $\text{C}_9\text{H}_{10}\text{N}_4\text{OS}$ , yield 89%, m.p.78-80°C, colour off white, FT-IR ( $\text{cm}^{-1}$ ): 3345-3184 ( $\nu$  -NH-,NH<sub>2</sub> str.), 3020 ( $\nu$  arom. CH str.), 2862,2820 ( $\nu$  aliph.CH str.), 1651( $\nu$  C=O), 1616 ( $\nu$  C=N str.), 1554 ( $\nu$  C=C), 732 ( $\nu$  S-C).

### 2.5 General procedure for preparation 1, 3, 4-Oxadiazol derivatives [III]<sub>a, b</sub>

A combination of hydrazine type [II]<sub>a,b</sub> (0.01 mole) and 4-aminobenzoic acid (0.01 mole, 1.37 g) in phosphorus oxychloride (5 mL) then refluxed for 6 hours. Once the reaction is complete, place the continent on the crushed ice. By using a solution of  $\text{NaHCO}_3$  the mixture was neutralized. Et-OH washed, filtered, and recrystallized the yellow product [15–17].

**2.5.1 Compound [III]<sub>a</sub>**

Molecular formula: C<sub>17</sub>H<sub>16</sub>N<sub>4</sub>O<sub>3</sub>, yield 75%, m.p. 258-260°C, yellow powder, FT-IR (cm<sup>-1</sup>) 3383-3200 (ν -NH<sub>2</sub> str., -NH str.), 3070 (ν arom. C-H), 2839 (ν aliph.-C-H-), 1678 (ν C=O) sec. amide, 1647 (ν C=N), 1600 (ν C=C), 1323 (ν C-N), 1249 (ν C-O), 846 (ν p-substitution) [18].

**2.5.2 Compound [III]<sub>b</sub>**

Molecular formula: C<sub>16</sub>H<sub>13</sub>N<sub>5</sub>OS, yield 75%, m.p. 190–192 °C, greenish powder, FT-IR (cm<sup>-1</sup>), 3340–3221 (ν -NH<sub>2</sub> str., -NH str.) The secondary amine has the following properties: 3020 (ν arom. CH str.), 2943-2831 (ν aliph. CH str.), 1645 (ν C=N), 1600 (ν C=C), 1257 (ν C-O), 837 (ν p-substitution), and 744 (ν C-S), according to [19].

**2.6 General procedure for synthesizing Schiff bases [IV]<sub>a-f</sub>**

Schiff's bases for the prepared amines [III<sub>a</sub> and III<sub>b</sub>] were prepared by the general method (0.01 mole) from aldehydes (benzaldehyde, 5-bromo-2-hydroxybenzaldehyde, and 3-ethoxy-2-hydroxybenzaldehyde) and a few drops from glacial acetic acid in ethanol (15 mL), then added (0.01 mole) from synthesis amines (III<sub>a</sub> and III<sub>b</sub>), refluxed for 6 hours, then filtered the precipitate wash with methanol and recrystallization from ethanol.

**2.6.1 Compound [IV]<sub>a</sub>**

Molecular formula: C<sub>24</sub>H<sub>20</sub>N<sub>4</sub>O<sub>3</sub>, yield 85%, light orange crystals, M.p. 165-167°C, FT-IR ν, cm<sup>-1</sup>, 3232 (ν NH str.) Sec. amide, 3070 (ν arom. CH str.), 1685 (ν C=O str.) amide, 1654 (ν C=N) azomethine, 1564 (ν arom.C=C), 1215 (ν C-O str.).

**2.6.2 Compound [IV]<sub>b</sub>**

Molecular formula: C<sub>24</sub>H<sub>19</sub>BrN<sub>4</sub>O<sub>4</sub>, yield 80%, brown product, m.p. 240-242°C, FT-IR ν, cm<sup>-1</sup>, 3413-3170 (ν OH str.), 3332 (ν NH str.) Sec. amide, 3070 (ν arom. CH str.), 1670 (ν C=O str.) amide, 1650 (ν C=N str.) azomethine, 1573 (ν arom. C=C str.), 1226 (ν C-O str.), 702 (ν C-Br str.). Mass: *m/z*=507, 495, 452, 368, 291, 269, 171, 199, 120, 92, 57.

**2.6.3 Compound [IV]<sub>c</sub>**

Molecular formula: C<sub>26</sub>H<sub>24</sub>N<sub>4</sub>O<sub>5</sub>, yield 85%, light orange crystals, m.p. 130-132°C, FT-IR ν, cm<sup>-1</sup>, 3400-3332 (ν OH str.), 3217-3130 (ν NH str.) amide, 3066 (ν arom.CH str.), 2927, 2898 (ν aliph.CH str.), 1643 (ν C=N) azomethine, 1548 (ν arom. C=C), 1222 (ν C=O).

**2.6.4 Compound [IV]<sub>d</sub>**

Molecular formula: C<sub>23</sub>H<sub>17</sub>N<sub>5</sub>OS, yield 85%, orange product, m.p. 194-196°C, FT-IR ν, cm<sup>-1</sup>, 3332 (ν NH str.) imidazole ring, 3055 (ν arom. CH str.), 1610(ν C=N) azomethine, 1600 (ν arom. C=C), 1068 (ν C=O), 744 (ν C-S).

**2.6.5 Compound [IV]<sub>e</sub>**

Molecular formula: C<sub>23</sub>H<sub>16</sub>BrN<sub>5</sub>O<sub>2</sub>S, yield 85%, light brown product, m.p. 252-254°C, FT-IR ν, cm<sup>-1</sup>, 3190 (ν OH str.), 3348 (ν NH str.) imidazole ring, 3051 (ν arom.CH str.), 2978 (ν aliph. CH str.), 1651 (ν C=N) azomethine, 1600 (ν arom.C=C str.), 1260 (ν C-O), 744 (ν C-S), 624 (ν C-Br). <sup>1</sup>H-NMR δ ppm: (N-H) at 10.44 (s,1H), (OH) at δ8.91 (s,1H), (CH=N) at 8.6 (s,1H), Ar-H at 8.22 -6.62 (m,11H arom.), (S-CH<sub>2</sub>) at 4.63, 4.21 (s, 2H). C.H.N.S. Found %: C, 54.40; H 3.20; N 13.70; S 6.30. Calculated%: C, 54.55; H 3.18 ; N 13.83; S, 6.33. Mass: *m/z*= 468.

**2.6.6 Compound [IV]<sub>f</sub>**

Molecular formula: C<sub>25</sub>H<sub>21</sub>N<sub>5</sub>O<sub>3</sub>S, yield 85%, orange product, m.p. 248-250°C, FT-IR ν, cm<sup>-1</sup>, 3217 (ν OH str.), 3336 (ν NH str.) imidazole ring, 3062 (ν arom.CH), 1647 (ν C=N) azomethine, 1597 (ν arom. C=C), 1249 (ν C-O), 740 (ν C-S).

**2.7 Synthesis of Thiazolidin-4-one derivatives [V]<sub>a-f</sub>**

The 4-Thiozolidinone derivatives were prepared according to the previously used method [20, 21].

**2.7.1 Compound [V]<sub>a</sub>**

Molecular formula: C<sub>26</sub>H<sub>22</sub>N<sub>4</sub>O<sub>4</sub>S, yield 85%, off white powder, m.p. 267-269°C, FT-IR  $\nu$ , cm<sup>-1</sup>, 3332-3224 ( $\nu$  NH str.) Sec. amide, 3055 ( $\nu$  arom. CH str.), 2968 ( $\nu$  aliph. CH str.), 1739 ( $\nu$  C=O) thiazolidin-4 ring, 1670 ( $\nu$  C=O) for amide, 1562 ( $\nu$  arom. C=C str.), 1219 ( $\nu$  C-O), 744 ( $\nu$  C-S).

**2.7.2 Compound [V]<sub>b</sub>**

Molecular formula: C<sub>26</sub>H<sub>21</sub>BrN<sub>4</sub>O<sub>5</sub>S, yield 79%, light yellow powder, m.p. 240-242°C, FT-IR  $\nu$ , cm<sup>-1</sup>, 3200 ( $\nu$  OH str.), 3373 ( $\nu$  NH str), Sec. amide, 3070 ( $\nu$  arom. CH str.), 1672 ( $\nu$  C=O) thiazolidin-4 ring, 1593 ( $\nu$  arom. C=C str.), 1226 ( $\nu$  C-O), 777 ( $\nu$  C-S), 709 ( $\nu$  C-Br). <sup>1</sup>H-NMR 400 MHz  $\delta$  ppm: 10.20 (N-H, s, 1H), 7.69-6.54 (m, 11H arom.), 6.44-8.01 (s, 1H, OH), 5.52 (2H, S-CH<sub>2</sub>), 5.08 (1H, N-CH-S), 3.67 (s, 2H, OCH<sub>2</sub>), 2.15 (s, 3H, CH<sub>3</sub>). C.H.N.S. Found %: C 53.60; H, 3.59; N, 9.60; S 5.50. Calculated %: C, 53.71; H 3.64; N 9.64; S, 5.51.

**2.7.3 Compound [V]<sub>c</sub>**

Molecular formula: C<sub>28</sub>H<sub>26</sub>N<sub>4</sub>O<sub>6</sub>S, yield 85%, pale yellow, m.p. 260-262°C, FT-IR  $\nu$ , cm<sup>-1</sup>, 3411-3330 ( $\nu$  OH str.), 3350 ( $\nu$  NH str.) Sec. amide, 3059 ( $\nu$  arom. CH str.), 2873 ( $\nu$  aliph. C-H str.), 1740 ( $\nu$  C=O str.) carbonyl ring, 1700 ( $\nu$  C=O) amide, 1597 ( $\nu$  arom. C=C str.), 1249 ( $\nu$  C-O str.), 736 ( $\nu$  C-S).

**2.7.4 Compound 3-(4-(5-(((1H-Benzo[d]imidazol-2-yl)thio)methyl)-1,3,4-Oxadiazol-2-yl)phenyl)-2-phenylthiazolidin-4-one [V]<sub>d</sub>**

Molecular formula: C<sub>25</sub>H<sub>19</sub>N<sub>5</sub>O<sub>2</sub>S<sub>2</sub>, yield 85%, pale yellow, m.p. >310°C, FT-IR  $\nu$  (cm<sup>-1</sup>), 3344 ( $\nu$  N-H str.) imidazole ring, 3062 ( $\nu$  arom. C-H str.), 1720 ( $\nu$  C=O) carbonyl-ring, 1640 ( $\nu$  C=N str.) ring, 1597 ( $\nu$  arom. C=C), 1273 ( $\nu$  C-O), 744 ( $\nu$  C-S).

**2.7.5 Compound [V]<sub>e</sub>**

Molecular formula: C<sub>25</sub>H<sub>18</sub>BrN<sub>5</sub>O<sub>3</sub>S<sub>2</sub>, yield 85%, light brown product. m.p. 280-282 °C, FT-IR  $\nu$ , cm<sup>-1</sup>, 3236 ( $\nu$  OH str.), 3346 ( $\nu$  NH str.) imidazole, 3095 ( $\nu$  arom. CH str.), 1722 ( $\nu$  C=O str.) ring, 1600 ( $\nu$  arom. C=C str.), 1648 ( $\nu$  C=N) ring, 1250 ( $\nu$  C-O), 744 ( $\nu$  C-S), 702 ( $\nu$  C-Br str.). <sup>1</sup>H-NMR 400 MHz,  $\delta$  ppm: 10.39 (s, 1H, N-H), 8.03 (s, 1H, OH), 8.05-6.45 (m, 11H arom.), 4.45 and 5.53 (s, 3H, (S-CH<sub>2</sub> and N-CH-S of ring), 3.73 (s, 2H, SCH<sub>2</sub>). C.H.N.S. Found %: C 51.70; H, 3.10; N, 12; S 11.02. Calculated %: C 51.73; H, 3.13; N, 12.06; S 11.05.

**2.7.6 Compound [V]<sub>f</sub>**

Molecular formula: C<sub>27</sub>H<sub>23</sub>N<sub>5</sub>O<sub>4</sub>S<sub>2</sub>, yield 85%, light brown product, m.p. > 310°C, FT-IR  $\nu$ , cm<sup>-1</sup>, 3217 ( $\nu$  OH str.), 3345 ( $\nu$  NH str.) imidazole, 3062 ( $\nu$  arom. CH str.), 1720 ( $\nu$  C=O) ring, 1600 ( $\nu$  arom. C=C str.), 1642 ( $\nu$  C=N) oxadiazole ring, 1246 ( $\nu$  C-O), 744 ( $\nu$  C-S). <sup>1</sup>H NMR 400 MHz, DMSO  $\delta$  ppm: 10.35 (s, 1H, NH), 8.03 (s, 1H, OH), 5.48, 5, 95 (1H, -NCHS-), 7.80-6.88 (m, 11H arom.), 3.64 (s, 2H, S-CH<sub>2</sub>), 4.05 (2H, CH<sub>2</sub>), 3.64-3.28 (5H, CH<sub>3</sub>CH<sub>2</sub>), 2.46 (3H, CH<sub>3</sub>). C.H.N.S. Found %: C, 59.35; H, 4.20; N, 12.76; S 11.70. Calculated %: C, 59.43; H 4.25; N 12.84; S, 11.75.

**2.8 General procedure for preparation of aldehydes [VI]<sub>a-c</sub>**

The aldehydes used in this reaction was prepared by references [22–25]. 4-methoxyphenyl 4-formyl benzoate VI a, off-white powder, m.p. 76-78 °C. 4-formylphenyl 4-butoxybenzoate VI b, off-white powder, m.p. 174-176 °C. 5'-formyl-2'-mydroxy-3'-methoxy-[1,1'-biphenyl]-4-yl)4-methoxybenzoate VI c, off-white powder, m.p. 118-120 °C.

**2.9 General procedure Synthesis of alkene from thiazoldin-4-one derivatives [VII]<sub>a-f</sub>**

The compound [V]<sub>a-f</sub> (0.01 mole) was mixed with (0.015 mole) from aldehydes [VI] in 1 mL of pyridine, then the mixture was put in reflux for 4 hours. After cooling, the reaction product solidifies in the reaction flask and forms a precipitate in crushed ice. The product was filtrated, washed with water, dried, and recrystallized with ethanol [14].

**2.9.1 Compound [VII]<sub>a</sub>**

Molecular formula: C<sub>44</sub>H<sub>38</sub>N<sub>4</sub>O<sub>7</sub>S, Yield 75%, off-white powder, m.p. 84-86 °C, FT-IR  $\nu$ , cm<sup>-1</sup>, 3332 ( $\nu$  NH str.) Sec. amide, 3070 ( $\nu$  arom. CH str.), 1726 ( $\nu$  C=O str.) ester, 1701 ( $\nu$  C=O) amide, 1654 ( $\nu$  C=N) ring, 1625 ( $\nu$  C=C) alkene, 1602 ( $\nu$  arom. C=C), 1209 ( $\nu$  C-O), 745 ( $\nu$  C-S). <sup>1</sup>H-NMR400MHZ,  $\delta$  ppm: 10.03 (s,1H,NH), 8.68-7.11 (m, 21H arom.) and (s, 1H) C=CH, 5.30 (s, 1H) CH,4.11 (s,2H), 4.08 (t,2H)OCH<sub>2</sub>, 2.46 (s,3H) CH<sub>3</sub>C=O, 1.76 and 1.75 (m, 6H), 1.44 (s, 3H) CH<sub>3</sub>. C.H.N.S. Found %: C, 59.65; H, 3.76; N, 6.72; S 3.77. Calculated %: C, 60.08; H 3.81; N 6.84; S 3.91.

**2.9.2 Compound [VII]<sub>b</sub>**

Molecular formula: C<sub>41</sub>H<sub>31</sub>BrN<sub>4</sub>O<sub>8</sub>S, yield 73%, yellow powder, m.p. 86-88°C, FT-IR  $\nu$ , cm<sup>-1</sup>, 3180( $\nu$  OH str.), 3363 ( $\nu$  NH str.) Sec. amide, 3070 ( $\nu$  arom. CH str.), 1730 ( $\nu$  C=O) ester, 1697 ( $\nu$  C=O)amide,1640( $\nu$  C=N) 1631 ( $\nu$  C=C str.)alkene, 1602 ( $\nu$  arom. C=C), 1211 ( $\nu$  C-O), 761( $\nu$  C-S), 649 ( $\nu$  C-Br).<sup>1</sup>H-NMR400MHZ,  $\delta$ : 10.03 (s,1H,NH), 8.57 (s,1H) OH, 8.12- 7.14 (m, 20H arom.) and (s,1H) C=CH, 5.06 (s, 1H) CH, 3.88 (5H) OCH<sub>2</sub> and OCH<sub>3</sub>, 2.13 (s, 3H) CH<sub>3</sub>C=O. C.H.N.S. Found % : C, 60.05; H, 3.76; N, 6.75; S 3.65. Calculated %: C, 60.08; H,3.81;N 6.84; S 3.91.

**2.9.3 Compound [VII]<sub>c</sub>**

Molecular formula: C<sub>50</sub>H<sub>42</sub>N<sub>4</sub>O<sub>11</sub>S, yield 85%, brown powder, m.p. 124-126°C, FT-IR  $\nu$ , cm<sup>-1</sup>, 3120 ( $\nu$  OH str.), 3350 ( $\nu$  NH str.) Sec. amide, 3070 ( $\nu$  arom. CH str.), 1724( $\nu$  C=O)ester, 1691 ( $\nu$  C=O) amide, 1630 ( $\nu$  C=C) alkene, 1212 ( $\nu$  C-O).<sup>1</sup>H-NMR400MHZ,  $\delta$  ppm: 9.99 (s,1H,NH), 8.07 (s,1H) OH and (s, 1H) C=CH, 8.06-7.10 (m, H arom.), 5.07 CH, 3.87-3.84 (s, 2H) OCH<sub>2</sub>, OCH<sub>3</sub>, 2.44(s, 3H) CH<sub>3</sub>CO, 1.22(t, 3H) CH<sub>3</sub>. C.H.N.S. Found % : C 66. 20; H,4.57; N, 6.15;S 3.44. Calculated %: C 66.21; H, 4.67; N, 6.18; S 3.54.

**2.9.4 Compound [VII]<sub>d</sub>**

Molecular formula: C<sub>43</sub>H<sub>35</sub>N<sub>5</sub>O<sub>5</sub>S<sub>2</sub>, yield 85%, yellow powder, m.p. 76-78°C, FT-IR  $\nu$ , cm<sup>-1</sup>, 3404 ( $\nu$  NH str.) imidazole ring, 3062 ( $\nu$  arom. CH str.), 1726 ( $\nu$  C=O) ester, 1690 ( $\nu$  C=O) amide,1629( $\nu$  C=C str.) alkene, 1652 ( $\nu$  C=N) ring, 1602 ( $\nu$  arom. C=C str.), 1390 ( $\nu$  C-N str.), 1213 ( $\nu$  C-O), 757 ( $\nu$  C-S).<sup>1</sup>H-NMR400MHZ,  $\delta$  ppm: 10.0(s,1H,NH), 8.19-7.13(m, 21H arom.), 6.75-8.66 for ( C=CH), 5.52 (s, 1H) CH, 5,62 (s, 2H) SCH<sub>2</sub>,4.09 (2H. OCH<sub>2</sub>), 1,23 (s, 2H) CH<sub>2</sub>,0.85 (s, 3H) CH<sub>3</sub>. C.H.N.S. Found %: C67.20; H, 4.45; N, 9.09; S 8.20. Calculated%: C 67.43; H 4.61; N, 9.14; S, 8.37.

**2.9.5 Compound [VII]<sub>e</sub>**

Molecular formula: C<sub>40</sub>H<sub>28</sub>BrN<sub>5</sub>O<sub>6</sub>S<sub>2</sub>, yield 85%, brown powder, m.p. 150-152°C, FT-IR  $\nu$ , cm<sup>-1</sup>, 3201 ( $\nu$  OH str.), 3384( $\nu$  NH str.) imidazole ring, 3062 ( $\nu$  arom. CH str.), 1730 ( $\nu$  C=O) ester, 1695 ( $\nu$  C=O str.) amide, 1629 ( $\nu$  C=C)alkene, 1652 ( $\nu$  C=N) ring, 1602 ( $\nu$  arom. C=C str.), 1357 ( $\nu$  C-N), 1213 ( $\nu$  C-O), 761 ( $\nu$  C-S), 688 ( $\nu$  C-Br).<sup>1</sup>H-NMR400MHZ,  $\delta$  ppm: 10.0 (s,1H,NH), 8.58 (s,1H) OH, 7.378.09 (m, 19-H-arom.) and C=CH, 5.8 (s, 2H) SCH<sub>2</sub>, 2.29 (d, 2H) CH<sub>2</sub>, 1.84 CH<sub>2</sub>CH<sub>3</sub>. C.H.N.S. Found %: C 58.47; H 3.35; N 8.47; S 7.69. Calculated %: C 58.68; H 3.45; N 8.55; S 7.83.

### 2.9.6 Compound [VII]<sub>f</sub>

Molecular formula: C<sub>49</sub>H<sub>39</sub>N<sub>5</sub>O<sub>9</sub>S<sub>2</sub>, Yield 85%, pale yellow powder, m.p. 224-226°C, FT-IR  $\nu$ , cm<sup>-1</sup>, 3201 ( $\nu$  OH str.), 3361 ( $\nu$  NH str.) imidazole ring, 3070 ( $\nu$  arom.CH str.), 1722 ( $\nu$  C=O) ester, 1691 ( $\nu$  C=O str.) amide, 1630 ( $\nu$  C=C str.) alkene, 1654 ( $\nu$  C=N)ring, 1604 ( $\nu$  arom. C=C str.), 1382 ( $\nu$  C-N), 1209 ( $\nu$  C-O), 761 ( $\nu$  C-S). <sup>1</sup>H-NMR400MHz  $\delta$  ppm: 10.03 (s, 1H, NH), 9.20 (s, 1H) OH, 8.67-7.11 (m, H-arom.) and 7.21 (s, 1H) C=CH, 5.82 CH, 4.12 SCH<sub>2</sub> and OCH<sub>2</sub>, 1.75, 1.72 and 1.41 (m, 3CH<sub>2</sub>), 0.96(t, 3H), 4.29 (s, 3H) OCH<sub>3</sub>. C.H.N.S. Found %: C 64.80; H, 4.25; N, 7.62; S 7. Calculated%: C 64.96; H, 4.34; N, 7.73; S 7.08.

### 2.10 The antibacterial assay

Using the plate-agar method and Mueller-Hinton culture medium, the biological activity of the prepared compounds was evaluated against two types of Gram-positive (*Enterococcus faecalis* and *Staphylococcus aureus*) bacteria and two types of Gram-negative (*E. coli* and *Pseudomonas aeruginosa*) bacteria.

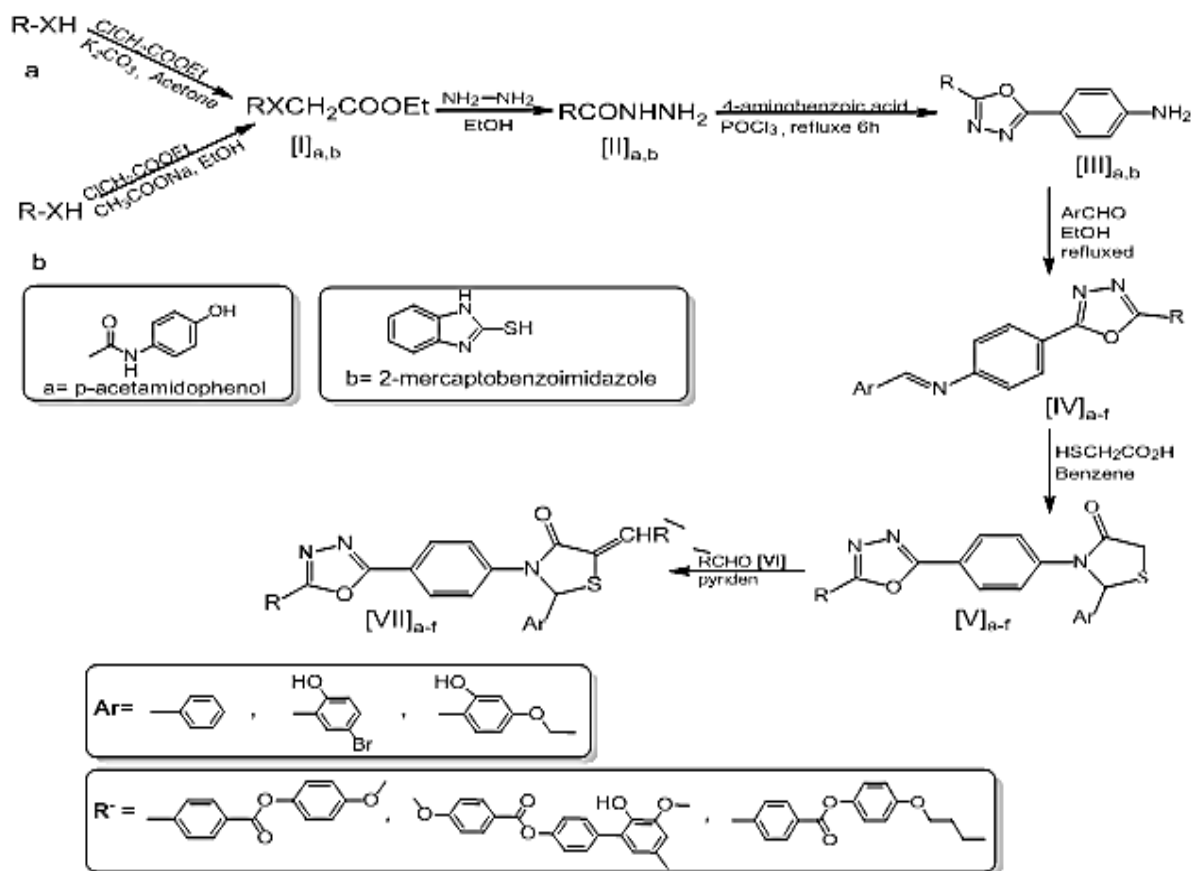
### 2.11 Molecular modelling for synthesis alkenes

The structures of the derivatives were prepared using the Chem. Office.15 program and used the program MOE 2014 for a molecular modeling study of derivatives prepared with one of the Corona virus proteins (2W2G). The 3D structure for the studied protein was obtained from the Protein Database Bank ([www.rcsb.org](http://www.rcsb.org)).

## 3. Results and Discussion

Starting with Paracetamol and 2-mercaptobenzimidazole, the ester was prepared for it Ia and Ib. Then the resulting esters were reacted via hydrazine hydrate (NH<sub>2</sub>-NH<sub>2</sub>) EtOH to produce hydrazides [II]a, [II]b, which were converted to 1,3,4-oxadiazoles [III]a and [III]b, then reacted with 4-aminobenzoic acid in the presence of a POCl<sub>3</sub>. The later compounds condensed with aldehydes (Benz aldehyde, 3-ethoxybenzaldehyde, and 5-bromo-2-hydroxybenzaldehyde) led to the formation of Schiff bases compounds [IV]a-f. Thiazolidin-4-ones derivatives V a-f obtained via reacting Schiff compounds and 2-mercapto acetic acid in benzene under reflux. The final compounds [VII]a-f were synthesized via reflux of the resulting thiazolidine-4-ones derivatives [V]a-f with aldehydes (4-methoxyphenyl 4-formyl benzoate, 5'-formyl-2'-Hydroxy-3'-Methoxy-[1,1-Biphenyl]-4-yl)4-methoxy benzoate, and 4-formyl phenyl 4-butoxy benzoate) [VI]a-c in the presence of pyridine, the synthesis route of these reactions is shown in **Scheme 1**. Spectrophotometric methods confirmed new structure derivatives (FTIR, <sup>1</sup>H-NMR, Mass, and C.H.N.S analysis). FTIR spectrum for [I] a and [I] b show the bands appearance at 1743 cm<sup>-1</sup>, and 1735 cm<sup>-1</sup> attributed to carbonyl ester str. str. In hydrazide compounds, II appearance two bands between (1651-1643) and the band in (3309-3194 cm<sup>-1</sup>) to the  $\nu$  C=O and  $\nu$  (-NH<sub>2</sub>, NH) for IIa,b besides to bands at  $\nu$ (3340-3220) cm<sup>-1</sup> which indicate the  $\nu$ (-NH<sub>2</sub>) group. Schiff bases IVa-f were identified via the azomethine group absorption band at 1604-1610 cm<sup>-1</sup>. The <sup>1</sup>H-NMR spectrum for IVe show single at 10.22 $\delta$  attributed to NH imidazole ring proton, a singlet at 8.91 $\delta$  due to OH proton, singlet at 8.61 $\delta$  due to azomethine group proton C=NH, multiply singlets at 8.22-6.62 $\delta$  for 11 aromatic protons, and singlet at 4.63, 4.21 $\delta$  due to S-CH<sub>2</sub> protons. For 4-thiazolidine derivatives Va-f, their formation can be confirmed by FT-IR, the disappearance of the azomethine adsorption band, and the appearance of the carbonyl-group  $\nu$  C=O for a five-membered ring of thiazolidine-4-one at 1715-1712 cm<sup>-1</sup>. The <sup>1</sup>H-NMR spectrum for Vb shows single at  $\delta$  10.20 $\delta$  due to N-H amide proton in paracetamol, multiply signals at 6.4-8.01 $\delta$  attributed to 12 aromatic protons +OH proton, singlet at 5.04 $\delta$  for O-CH<sub>2</sub> protons, singlet at  $\delta$ 5.52 ppm for  $\nu$

NCH-S in the ring of the thiazolidine-4-one ring, and single at  $\delta$  3.67 ppm due to  $\text{CH}_2$  methyl protons in ring and finally three protons of  $\text{CH}_3$  appeared at  $\delta$  2.19 ppm.



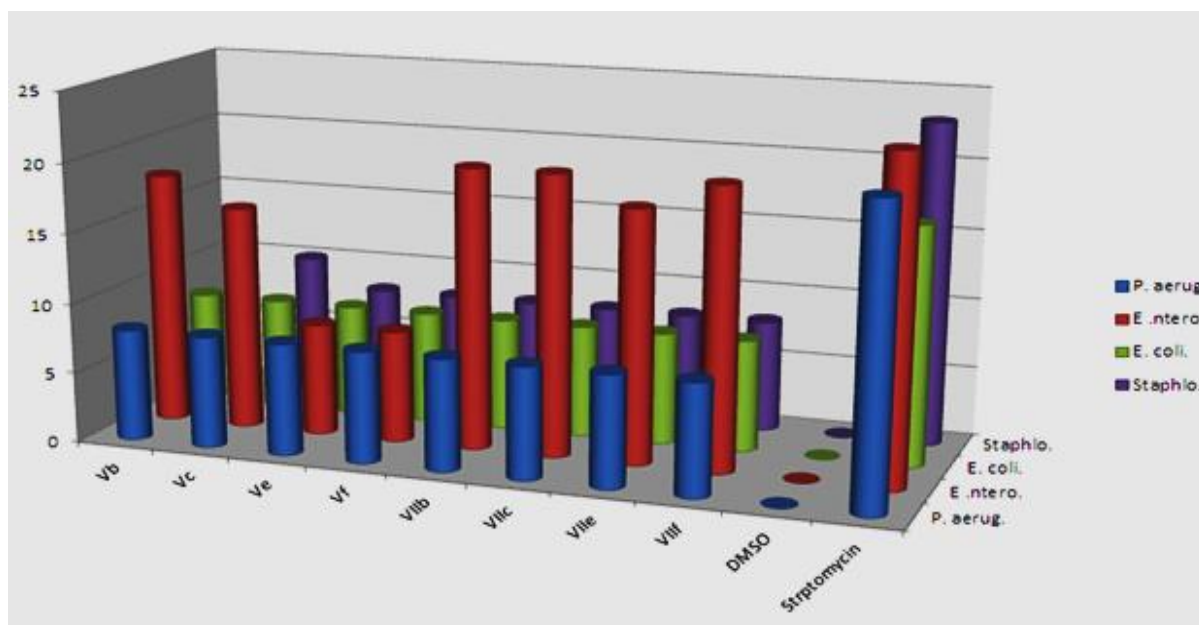
**Scheme 1.** Synthetic route for the new thiazolidin-4-ones derivatives.

While  $^1\text{H-NMR}$  for Ve displays single at  $\delta$  10.39 ppm due to NH proton imidazole ring, multiply singles at 8.05-6.45 ppm for 11 aromatic protons and OH proton, at  $\delta$  4.45, 5.53 ppm singles due to S- $\text{CH}_2$  and NCHS of ring proton, besides to a singles at 3.37 for  $\text{CH}_2$  proton in the ring, single. The  $^1\text{H-NMR}$  for Vf show single at  $\delta$  10.35 ppm imidazole ring proton, multiply singles at  $\delta$  8.6-6.46 ppm due to 11 aromatic protons and OH proton, also two singles at  $\delta$  5.48, 5.95 ppm for S $\text{CH}_2$  proton and NCHS proton, and single at  $\delta$  4.05 ppm due to O-CH 2 proton, where single at  $\delta$  3.64 ppm refer to  $\text{CH}_2$  protons in the ring. The final compounds VII a-f were characterized by FT-IR, which showed sharp bands for C=O (ester) derivatives in the range 1724-1730  $\text{cm}^{-1}$ , alkene band C=C in the range 1631-1625  $\text{cm}^{-1}$ , and suitable band around 1209-1211  $\text{cm}^{-1}$  for C-O ester linkage. The  $^1\text{HNMR}$  spectra for derivatives VII a-f are as below; derivative VIIa single at  $\delta$  10.03 ppm for NH proton, multiply singles at  $\delta$  7.0-8.05 ppm refers to the 21 aromatic protons, which interfere with the alkene proton signal C=CH, single at  $\delta$  5.27 ppm due to CH ring proton, single at  $\delta$  4.11 ppm attributed to  $\text{OCH}_2$  proton and  $\text{OC}_2\text{H}_5$  protons, two singles at  $\delta$  (1.43 and 1.71) ppm due to two  $2\text{CH}_2$  protons and  $\text{COCH}_3$  protons, single at  $\delta$  0.94 ppm for  $\text{CH}_2\text{CH}_3$  protons. VII b has single at  $\delta$  10.03 ppm for NH proton, single at  $\delta$  8.57 ppm for OH proton, multiply signals at  $\delta$  8.12-7.14 resulting from the overlapping signals of the 18 aromatic protons and the alkene proton C=CH, single at  $\delta$  5.06 ppm due to CH ring proton, two signals at  $\delta$  3.88, and 3.69 ppm for  $\text{OCH}_2$  and  $\text{OCH}_3$  protons respectively, finally singlet at  $\delta$  2.13 ppm single due to  $\text{CH}_3\text{C=O}$ . VII d has single at  $\delta$  10.0 due to NH proton, overlapping signals of 19 aromatic protons with that of

alkene C=CH at  $\delta$  7.37-8.09 ppm, single at  $\delta$  5.8 ppm for SCH<sub>2</sub>, also singlet at 3.82 ppm due to OCH<sub>3</sub> protons. VIIe has single at 10.0ppm due to NH proton, at 8.58 ppm single due to OH proton, multiply singlets at  $\delta$  8.09-7.12 ppm for aromatic protons that interact with alkene proton C=CH, single at  $\delta$  5.8 ppm for SCH<sub>2</sub> protons, single at  $\delta$  2.29 due to CH<sub>2</sub> protons, single at  $\delta$  1.84 ppm for CH<sub>2</sub>CH<sub>3</sub> protons.

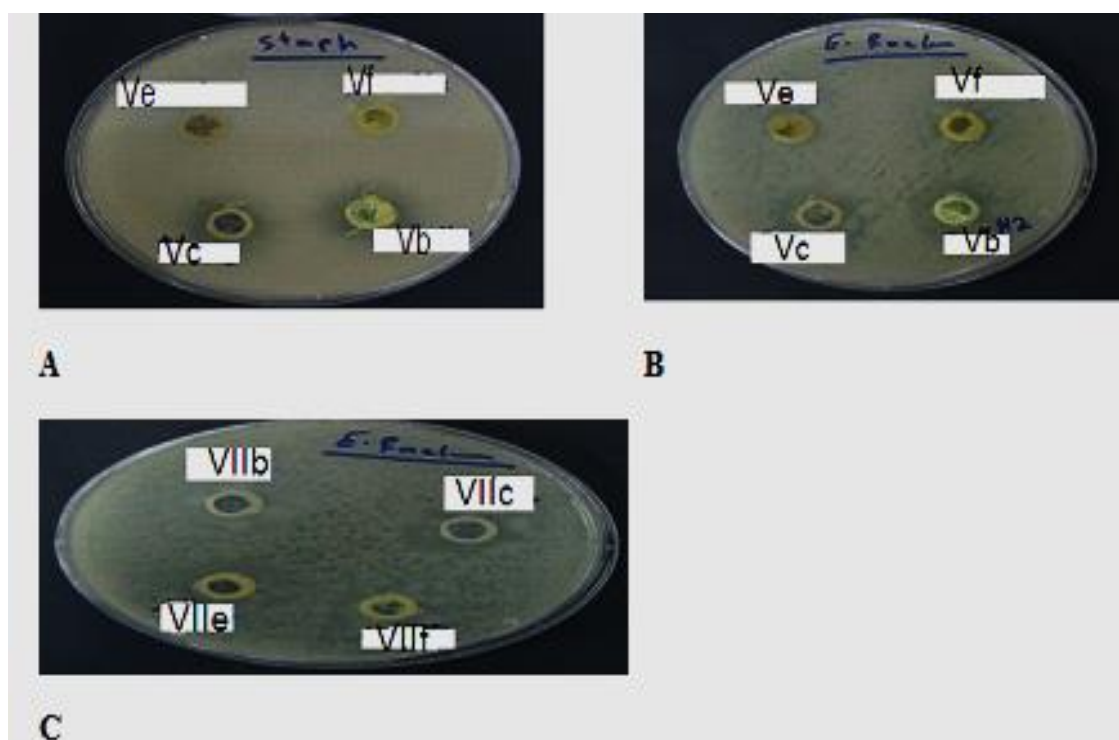
### 3.1 Antibacterial activity

Using the plate-agar method, the newly synthesized derivatives were investigated for their biological activity against four different species of bacteria, including two gram-positive (*Enterococcus faecalis* and *Staphylococcus aureus*) and two gram-negative (*E. coli* and *Pseudomonas aeruginosa*) [26-28]. Four compounds of the derivatives containing the 4-thiazolidine rings [V]b, [V]c, [V]e, and [V]f were tested and compared with four of the alkenes [VII] b, [VII]c, [VII] e, and [VII]f prepared from them. The results showed that all the compounds under test had no biological activity against bacteria, *Pseudomonas aeruginosa*, and *E. coli*, whereas, compounds [V]b, and [V]c had moderate activity towards *Staphylococcus*, while the rest of the compounds under test had no efficacy against it. **Figure 1** shows the results diagram. The compounds under test were characterized by having moderate to somewhat high activity against *Enterococcus faecalis*, except for two compounds Ve, and V f that had weak effectiveness. The results of the derived alkenes [VII] b, [VII] c, [VII]e, and [VII]f were significantly higher than the compounds prepared from them [V] b, [V]c, [V]e, and [V]f. **Table 1** shows results in mm for zone inhibition and **Figure 2** displays the results on petri dishes.



**Figure 1.** The results diagram of antibacterial activity against synthesis derivatives (Vb, Vc, Ve, Vf, VIIb, VIIc, VIIe, and VIIf ).





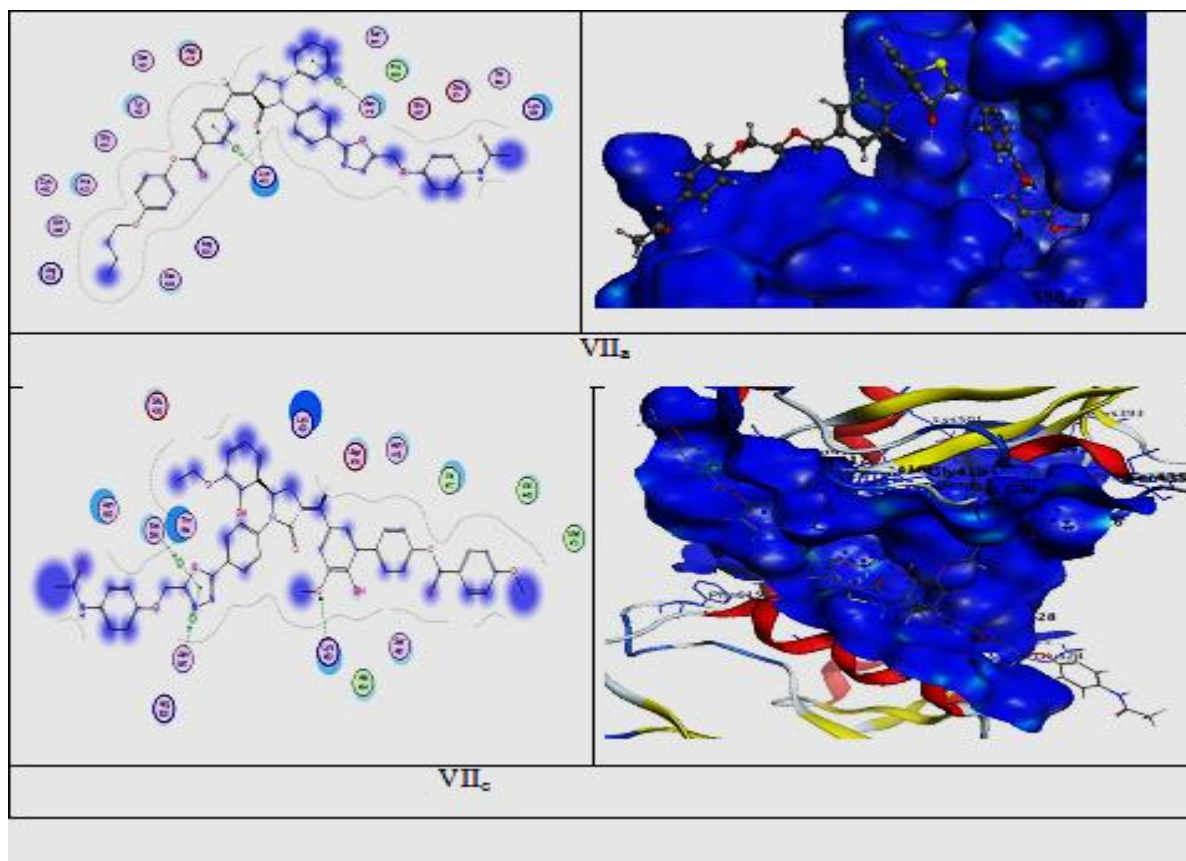
**Figure 2.** The Bacterial culture dishes. A: results of  $V_b$ ,  $V_c$ ,  $V_e$ , and  $V_f$ ) against *staphylo*. B: results of  $V_b$ ,  $V_c$ ,  $V_e$ , and  $V_f$ ) against *Enterococcus faecalis* . C: results of ( $VII_b$ ,  $VII_c$ ,  $VII_e$ , and  $VII_f$  ) against *Enterococcus faecalis*.

### 3.2 Molecular docking study

I was studying the molecular modeling of the compounds prepared [VII]a-f with one of the Coronavirus proteins 2W2G (human SARA coronavirus unique) [29-32]. Molecular modeling was studied for the compounds with the large pocket, which was isolated from the studied protein (2W2G), where the binding energy was within the range of -8.08 kcal/mol, -6.78 kcal/mol; **Table 2** shows score docking results. [VII]a -7.65 kcal/mol as dock score with interaction by H-bond at LYS463 and  $\pi$ -H interaction at ASN418 and LYS491. [VII] b with - 6.78 as dock score conceded as the lowest with ASN418 by  $\pi$ -H interaction. [VII]c has the highest dock score with -8.08 kcal/mol., H-bond at LYS463, and  $\pi$ - H interaction with ASN597 and SER598. [VII]f has a -7.07 kcal/mol. Dock score with SER626, MET428, ARG628, and GLY491 with two H-bond and  $\pi$ -interaction. **Table 1** shows the modeling values and interactions with the studied protein. **Figure 3** shows some compounds with the studied protein in two dimensions.

**Table 1.** The dock score and interaction for synthesis compounds.

Com.	Dock-Score Kcal/mol.	Interaction residues
$VII_a$	-7.65	LYS463, ASN418, LYS463
$VII_b$	-6.78	ASN418
$VII_c$	-8.08	LYS463, ASN597, SER598
$VII_f$	-7.07	SER626, MET428, ARG628, GLY491



**Figure .3.** The 2D interaction and protein target surface for VII<sub>a</sub>, and, VII<sub>c</sub>,

#### 4. Conclusion

In this study, new compounds derived from thiazolidine-4-ones were successfully prepared and identified by spectrophotometric methods. In their bacterial activity assay, where it was found that some of these compounds have high effectiveness against the studied bacteria, while others do not have any effectiveness, the results of the derived alkenes (VII<sub>b</sub>, VII<sub>c</sub>, VII<sub>e</sub>, and VII<sub>f</sub>) were significantly higher than the compounds prepared from them (V<sub>b</sub>, V<sub>c</sub>, V<sub>e</sub>, and V<sub>f</sub>). *Enterococcus faecalis* provided the best results. Some of the prepared compounds (VII<sub>a</sub>, VII<sub>b</sub>, VII<sub>c</sub>, and VII<sub>f</sub>) had good binding when doing molecular modeling against one of the SARS human coronavirus proteins where the binding energy was within the range of -8.08 kcal/mole to 6.78 kcal/mole.

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#### Conflict of Interest

The authors declare that they have no conflicts of interest.

#### Funding

No founding.

## Ethical Clearance

This work has been approved by the Scientific Committee at the University of Baghdad/ College of Education for Pure Science (Ibn Al-Haitham).

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