

# Synthesis of some new Thiazolidine and 1,3,4-Oxadiazole Derived from L-cysteine and Study of Their Biological Activity as Antioxidant and Breast Cancer

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**Abstract:** The study firstly included the synthesis of aldehyde derivatives by reacting p-hydroxy benzaldehyde with ethyl chloroacetate to prepare compound (A), then producing the thiazolidine derivatives by condensing compound (A) with cysteine to obtain (AT). Thiazolidines possess two types of isomers (diastereomers) that are difficult to separate ( cis-(2R,4R) and trans-(2S,2R)). Due to the presence of chiral atoms, an isomer cis/ trans percentages were powerfully dependent on a solvent. The compound (AT) reacts with acetic anhydride for the synthesis of the compound (ATA), then it reacts with hydrazine hydrate to prepare the 3-acetyl-2-[4-(2-hydrazinyl-2-oxoethoxy) phenyl]thiazolidine-4-carboxylic acid (ATAH), which is the basic unit in the synthesis of 1,3,4-oxadiazoles, as the compound (ATAH) reacts with carboxylic acid derivatives in the presence of phosphoryl chloride to synthesis 1,3,4-oxadiazole derivatives (ATAO<sub>1-4</sub>) and interact a compound (ATAH) with potassium hydroxide and carbon disulfide to prepare a compound 3-acetyl-2-{4-[2-(5-mercapto-1,3,4-oxadiazol-2-yl)- 2-oxoethoxy] phenyl} thiazolidine-4-carboxylic acid (ATASO). All synthesis compounds were identified using Mass-EI, FT-IR, and (<sup>1</sup>H, <sup>13</sup>C) NMR Spectra. Antibacterial activity of synthesis compounds was studied against two kinds of bacteria (*E.coil* and *S.aureus*) and studied as an antioxidant, as well the study of the compound with high efficacy in the direction of oxidation anticancer (MCF7) and determine an IC<sub>50</sub>.

**Keywords:** 1,3-thiazolidine derivatives; oxadiazole; anti-bactiral; antioxidant; MCF7.

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## 1. Introduction

Thiazolidine and 1,3,4-oxadiazole are well-known and distinguished compounds widely available due to their different pharmacological efficacy. Researchers have been interested in different ways to prepare compounds containing more than one heterogeneous atom due to their biological and industrial importance [1-5]. Oxadiazole is a class of heterocyclic aromatic pentacyclic compounds that contain oxygen and two nitrogen atoms in the form of heterocyclic atoms [6, 7]. 1,3,4-oxadiazole derivatives have been prepared from hydrazides by condensing it with a carboxylic acid in the presence of phosphoryl chloride (POCl<sub>3</sub>) or condensation with carbon disulfide (CS<sub>2</sub>) and the presence of the base [8-11]. 1,3,4-oxadiazole derivatives are very important in their use in the treatment of many diseases; they were used as antitumor [12, 13], antifungal [14], anti-viral, antioxidant, anticancer, anti-HIV, antimicrobial, antibacterial, and other medicinal applications [15-18]. Thiazolidine is similar

in structure to amino acid (proline) [19] and penicillin. The synthesis of 1,3-thiazolidine-4-carboxylic acid derivatives by the reaction of carbonyl compounds (aldehyde, ketone) with L-cysteine [20-22], it is pharmacologically effective was used to treat many diseases, including antibacterial, antifungal, inflammatory, antihypertensive [23, 24], antioxidant, anticancer (prostate), diabetes, influenza and many other diseases [25-27]. The research study described preparing some new oxadiazole derivatives containing 1,3-thiazolidine and studying them as antibacterial, antioxidant, and anticancer.

## 2. Materials and Methods

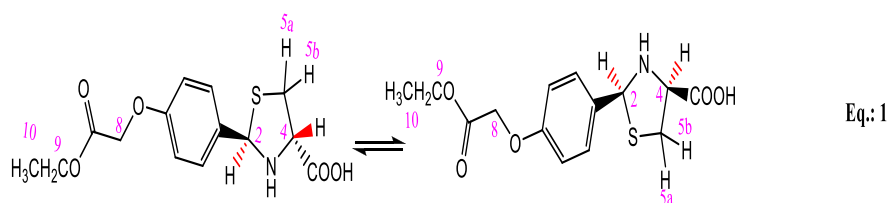
Solvents and chemicals were procured from Sigma. All chemical was at the smallest grade ACS, and chromatography layer TLC analysis of reaction mix was achieved by means of plates aluminum covered by silica gel sheet layers (Merck). The melting point was obtained from a Gallen-kamp melting point device in a capillary tube.  $^1\text{H}$ ,  $^{13}\text{C}$ -nuclear magnetic resonance (NMR) spectral are recorded on (Brucker.400 MHz) in  $\text{CDCl}_3$  or DMSO reference, and the presence of TMS in place of the internal standard:  $\text{CDCl}_3$ :  $\delta$ : 7.2 ppm and DMSO-d $_6$ :  $\delta$ : 2.50, 3.3 ppm as solvent (Iran). The chemical shift was introduced in ppm:  $\delta$ : scale, J: coupling constants value specified in Hz. A splitting was abbreviated follows: d (doublet), s (singlet), dd (doublet of doublet) t(triplet), and m (multiblasy). (EI) Mass spectra (Iran) and FT-IR spectrum (Fourier transform infrared) were recorded on Shimadzu FTIR-8300 (Iraq).

### 2.1. Preparation of Ethyl 2-(4-formyl phenoxy)acetate (A).

A mixture of 1.22 g (10 mmole) of 4-hydroxy benzaldehyde with 2.14 ml (20 mmole) of 2-ethyl Chloro acetate and 1.38 g (10 mmole) of potassium carbonate in a round flask and with (60 ml) acetone as solvent was reflex for (20 h) to form a white precipitate, filter the solution to get rid of the precipitate, evaporation and dried leaving an oil yellow [28].

### 2.2. Synthesis of 2-[4-(2-ethoxy-2-oxoethoxy) phenyl] thiazolidine-4-carboxylic acid (AT).

A mix of (10 mmole) compound (A) and 1.21 g (10 mmole) L-cysteine in ethanol: water (10: 1) is stirred at (20 h) in temperature (20 °C), the yellowish-white precipitate was formed, filtration and washed with diethyl ether, dehydrated and recrystallized by (ethanol: water) to give white crystal [m.p= 143-145°C]. The structure is presented in Scheme1. Thiazolidine has stereoisomers due to the presence of chiral atoms and is difficult to separate, as shown in Equation 1[29].



(2R, 4S) 2-[4-(2-ethoxy-2-oxoethoxy) aryl] thiazolidine-4- carboxylic acid (AT) 54% Trans Isomer (Cis 46 %).

Yield=85%, mp:143-145°C. FT-IR (KBr disk): 3200-2552 (Zwitter ion  $\text{NH}_2^+$ ), 1622s ( $\text{COO}^-$ ).  $^1\text{H}$ NMR (400 MHz, DMSO) (Trans):  $-\delta$ : 1.21 (t, 3H, J=4) ( $\text{H}_{10}$ )(CH $_3$ ), 3.15 (dd, 1H, J=8, 4 Hz) ( $\text{H}_{5a}$ ),  $\delta$ : 3.28 (dd, 1H, J=8, 4Hz) ( $\text{H}_{5b}$ ),  $\delta$ :4.16 (t, 1H, J=8Hz) ( $\text{H}_4$ ),  $\delta$ :4.24 (m, 2H, J=4) ( $\text{H}_9$ )(CH $_2$ ),  $\delta$ :4.74 (s, 2H) ( $\text{H}_8$ ),  $\delta$ :5.45 (s, 1H) ( $\text{H}_2$ ), 6.83-7.5(4H) (HAr), (Cis):  $-\delta$ : 1.22(t)

(H10)(CH<sub>3</sub>), 3.7(t, J=8) (H5a),  $\delta$ : 3.24 dd, J=8, 4 (H5b),  $\delta$ : 3.86 (t, J=8) (H4),  $\delta$ : 4.24(m, 2H) (H9)(CH<sub>2</sub>),  $\delta$ : 4.78 (s, H) (H8),  $\delta$ : 5.56 (s, H) (H2), 6.83-7.5(4H) (HAr) <sup>13</sup>CNMR:  $\delta$ : 14.06 (CH<sub>3</sub>),  $\delta$ :37.9 (C5),  $\delta$ : 60.6 (OCH<sub>2</sub>),  $\delta$ : 64.6(C8),  $\delta$ : 64.8 (C4),  $\delta$ : 70.8 (C2),  $\delta$ : 114-157 (CAr),  $\delta$ :168, 173 (C=O), Mass (EI): Mwt=311.2M<sup>+</sup>, 267.1 peas beak. 2.3. Preparation of 3-Acetyl-2-[4-(2-ethoxy-2-oxoethoxy) phenyl] thiazolidine-4-carboxylic acid (ATA).

Dissolve (10 mmole ) of (AT) in 6 % Na<sub>2</sub>CO<sub>3</sub> (50 ml) cooled in an ice bath at 0°C and follower by dropwise adding of 3.77 ml (40 mmole) acetic anhydride over (10 min). The mixtures were stirred for (1.5 h), the acidification solution by addition 10 % of HCl, and the reaction mixture was extracted by chloroform (2x25 ml). The extract is washed with water and dehydrated over anhydrous (Na<sub>2</sub>SO<sub>4</sub>), evaporation, and dried solvent leaving an oil yellow [30].

(2R, 4R) 3-Acetyl-2-[4-(2-ethoxy-2-oxo ethoxy) phenyl] thiazolidine-4-carboxylic acid (ATA) 85 %Cis Isomer (Trans15 %).

m.p: Oil yellow. FT-IR (NaCl disk): 3415 (OH), 1745,1689(C=O). <sup>1</sup>HNMR (400MHz, CDCl<sub>3</sub>)(Cis)-  $\delta$ :1.21(t, 3H, J=4) (H10) (CH<sub>3</sub>),  $\delta$ :1.96 (s, 3H) (H7),  $\delta$ :3.25 (m, 1H, J=8Hz) (H5a)  $\delta$ :3.43 (d, 1H, J=8Hz) (H5b),  $\delta$ :4.22 (m, 2H, J=4) (H9) (CH<sub>2</sub>),  $\delta$ :4.56 (m, 1H, J=8Hz) (H4),  $\delta$ :4.58 (s, 2H) (H8),  $\delta$ :6.05(s, 1H) (H2), 6.85-7.55 (4H) (HAr),  $\delta$ :12.91(s, 1H) (H6) (OH), (Trans)-  $\delta$ : 1.21(t, 3H) (H10),  $\delta$ : 2.06 (s, 3H) (H7),  $\delta$ : 3.25(t, H) (H5a)  $\delta$ : 3.68 (m, H, J=6Hz) (H5b),  $\delta$ : 4.24(m, 2H) (H9),  $\delta$ : 4.58 (t, H) (H4),  $\delta$ : 4.98(s, 2H) (H8),  $\delta$ : 6.25 (s, H) (H2), 6.85-7.55 (HAr),  $\delta$ :12.92(s, 1H) (H6). <sup>13</sup>CNMR:  $\delta$ :14.06 (CH<sub>3</sub>),  $\delta$ : 23.2 (C7),  $\delta$ : 32.05 (C5),  $\delta$ : 61.8 (OCH<sub>2</sub>),  $\delta$ : 64.4 (C4),  $\delta$ : 65.5 (C8),  $\delta$ : 66.7 (C2),  $\delta$ : 115-157 (C-Ar),  $\delta$ : 169, 171, 173 (C=O).

2.4 Synthesis of 3-acetyl-2-[4-(2-hydrazinyl-2-oxo ethoxy) phenyl] thiazolidine-4-carboxylic acid (ATAH).

A solution of (ATA) in 40 ml ethyl alcohol absolute was an additional 80 % hydrazine hydrate; the reacting mixture was reflexed for a period of (24 h) to form a white precipitate filtration and washed with methanol, the recrystallized by ethanol [31].

(2R, 4S) 3-acetyl-2-(4-(2-hydrazinyl-2-oxoethoxy) phenyl)thiazolidine-4-carboxylic acid (ATAH) 95 %Trans Isomer (Cis 5 %).

m.p: 228-230°C. FT-IR: 3442 (OH), 3317, 3228 (NH<sub>2</sub>), 3182 (NH),1687 (C=O). <sup>1</sup>HNMR (400MHz, DMSO)(Trans)-  $\delta$ :2.07 (s, 3H) (H7),  $\delta$ :3.25 (t, 1H, J=12Hz) (H5a),  $\delta$ :3.40 (t, 1H, J=8Hz) (H5b),  $\delta$ :4.18 (t, 1H, J=8Hz) (H4),  $\delta$ :4.32 (s, 2H) (NH<sub>2</sub>),  $\delta$ :4.48(s, 2H) (H8),  $\delta$ :6.53 (s, 1H) (H2),  $\delta$ :8.54(s, 1H) (NH), 7.06-7.54(m,4H) (HAr),  $\delta$ :12.92 (s, 1H) (H6) (OH), (Cis)  $\delta$ : 2.08(s, 3H) (H7),  $\delta$ : 3.25(t, H) (H5a),  $\delta$ : 3.4(t, H) (H5b),  $\delta$ : (4.18(t, H) (H4),  $\delta$ : 4.52(s, 2H) (H8),  $\delta$ : 6.49 (s, H) (H2),  $\delta$ : 8.63(s, H) (NH), 7.06-7.54(m, 4H) (HAr),  $\delta$ :12.92(s, 1H) (H6). <sup>13</sup>CNMR:  $\delta$ : 22.99(C7),  $\delta$ :35.6(C5),  $\delta$ :63.6(C4),  $\delta$ :66.3(C8),  $\delta$ :71.7 (C2),  $\delta$ :114-157.5 (CAr),  $\delta$ : 166.6, 169.35, 171.68 (C=O). Mass (EI):Mwt= 339.3 M<sup>+</sup> 79 a peas beak.

2.5. Prepare of 3-acetyl-2- {4-[2-(5-mercapto- 1,3,4-oxadiazol-2-yl) -2-oxoethoxy] phenyl} thiazolidine-4-carboxylic acid (ATASO).

A mix of (10 mmole) of ATAH and (10 mmole) of KOH in addition 4 ml (20 mmole) of CS<sub>2</sub> with drops at 0 °C was reserved in absolute ethanol (50 ml), a solution was refluxed for (24 h). The mixtures were concentrated a poured into water ice, before which acidified with

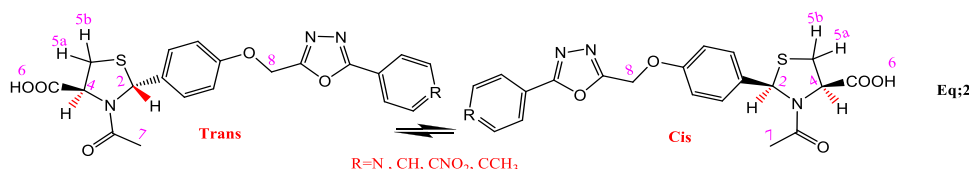
dilute HCl (10%) and formed yellow (beige) precipitates were filtrated, washed by ether, dried, and recrystallized from ethanol [32].

(2R, 4S) 3-acetyl-2-{4-[2-(5- mercapto-1, 3,4-oxadiazol-2-yl)-2-oxoethoxy] phenyl} thiazolidine-4-carboxylic acid (ATAO) 94%Trans Isomer (Cis6%).

Yield:35% m.p: 199-201°C. FT-IR(KBr disk): 3412 (OH), 3100 (NH), 2625 (SH), 1762 (C=O), 1628 (C=N). <sup>1</sup>HNMR (400MHz, DMSO)(Trans)- δ:1.84 (s, 3H) (H7), δ:3.1(m, 1H, J=4Hz) (H5a), δ:3.36 (m, 1H, J=4Hz) (H5b), δ:4.39 (t, 1H, J=8Hz) (H4), δ:4.84 (s, 2H) (H8), δ:6.51 (s, 1H) (H2), 7.1-7.9(4H, d) (HAr), δ: 9.9 (s, 1H) (SH), δ:14.66 (s, 1H) (H6) (OH), (Cis) δ: 2.1(s, 3H) (H7), δ: 3.3(m) (H5a), δ: 3.57(m, H) (H5b), δ: 4.1(t, H) (H4), δ: 4.81(s, 2H) (H8), δ: 6.34(s, H) (H2), 7.1-7.9(4H) (HAr), δ: 9.9s, 1H (9.91s) (SH), δ: 14.65(s, H) (OH). <sup>13</sup>CNMR: δ: 23.6 (C7), δ:34.5 (C5), δ:62.1 (C4), δ:65.2 (C8), δ:70.9 (C2), δ:115-155 (CAr), δ: 161.2 (C=N), δ:169.27, 172.05 (C=O), δ:179.35 (SH-C=N), Mass (EI): Mwt= 381.2 M<sup>+</sup>, 138.2 peas beak.

### 2.6. General methods for synthesis 3-acetyl-2-{4-[2-oxo-2-(5-aryl) -1,3,4-oxadiazol-2-ylethoxy] phenyl} thiazolidine-4-carboxylicacid (ATAO<sub>1-4</sub>).

All compounds were produced using the same practice [33]. A mix of (10 mmole) compound (ATAH) and (10 mmole) aromatic carboxylic acid in (8 ml) POCl<sub>3</sub> was refluxed to 80 °C for (6-8 h) on the water bath, the development of products was examined on TLC [ethanol: ethyl acetate] (2;8), the mixes were concentrated, decanted on crushed ice by stirred and added to it (10 %) of NaHCO<sub>3</sub>, the products solid were filtered, washed by water, dried and then recrystallized from a mixes ethyl acetate: hexane or ethanol. Structure physical data symbols of synthesis compounds (ATAO<sub>1-4</sub>) are given away in Scheme 2 and shown diastomer in Equation 2.



(2R,4S)-3-acetyl-2-{4- [(5-( pyridin-4-yl)-1,3,4-oxadiazol-2-yl) methoxy] phenyl} thiazolidine-4-carboxylic acid (ATAO<sub>1</sub>) 86%Trans Isomer (Cis 14%).

Yield:30 % m.p.: 242-245°C. FT-IR (KBr disk): 3406s (OH), 1675m(C=O), 1639m (C=N). <sup>1</sup>HNMR (400 MHz, DMSO) (Trans)- δ:1.95 (s, 3H) (H7), δ:3.1 (t, 1H, J=8Hz) (H5a), δ:3.43 (d, H, J=12Hz) (H5b), δ:4.17 (t, 1H, J=8Hz) (H4), δ:4.87 (s, 2H) (H8), δ:6.47 (s, 1H) (H2), δ:7.1-8.24(d, 8H) (HAr), δ:12.28 (s, 1H) (H6)(OH), (Cis) δ: 2.08 (s, 3H) (H7), δ: 3.3 (m, H) (H5a), δ: 3.4(m, H) (H5b), δ: 4.4(m, H) (H4), δ: 4.86 (s, 2H) (H8), δ: 6.54(s, H) (H2), δ:7.1-8.24(d, 8H) (HAr), δ: 12.28 (OH). <sup>13</sup>CNMR: δ:21.97 (C7), δ:33.94 (C5), δ:65.22 (C8), δ:71.95 (C4), δ:73.95(C2), δ:115-158 (CAr), δ:162.59, 162.85 (2C=N), δ:169.97, 172.88 (C=O). Mass (EI): Mwt=426 M<sup>+</sup> 43 peas beak.

(2R,4S)-3-acetyl-2-{4- [( 5-phenyl-1,3,4 -oxadiazol-2-yl) methoxy] phenyl} thiazolidine-4-carboxylic acid (ATAO<sub>2</sub>) 78%Trans Isomer (Cis22%).

Yield:33 % m.p: 192-195 °C. FT-IR (KBr): 3415 (OH), 1680 (C=O) , 1630 (C=N). <sup>1</sup>HNMR (400 MHz, DMSO)(Trans)- δ:1.8 (s, 3H) (H7), δ:3.05 (t, H, J=4Hz) (H5a), δ: 3.44 (t,

H, J=4Hz) (H5b),  $\delta$ : 4.32 (t, 1H, J=8Hz) (H4),  $\delta$ :4.84(s, 2H) (H8),  $\delta$ :6.37 (s, 1H) (H2),  $\delta$ :7.2-7.9 (m, 9H) (HAr),  $\delta$ :13.06 (s, 1H) (H6) (OH), (Cis)  $\delta$ : 2.05(s, 3H) (H7),  $\delta$ : 3.3(m, H) (H5a),  $\delta$ : 3.4 (m, H) (H5b),  $\delta$ : 4.53(m,H) (H4),  $\delta$ : 4.86 (s, 2H) (H8),  $\delta$ : 6.17(s, H) (H2),  $\delta$ :7.2-7.9(9H) (HAr),  $\delta$ : 13.08 (OH). Mass (EI): Mwt=425.2 M<sup>+</sup>, 90.2 peas beak.

(2R,4S)-3-acetyl-2-[4-[(5-(4-nitro phenyl)-1,3,4-oxadiazol-2-yl), methoxy] phenyl] thiazolidine-4-carboxylic acid (ATAO<sub>3</sub>) 96 %Trans Isomer (Cis 4 %).

Yield: 40 %, m.p: 209-212°C. FT-IR: 3271 (OH), 1722 (C=O), 1597 (C=N). <sup>1</sup>HNMR(400MHz, DMSO)-(Trans)  $\delta$ :1.96 (s, 3H (H7),  $\delta$ :3.09 (t, H, J=8Hz) (H5a),  $\delta$ :3.56 (t, 1H, J=8Hz) (H5b),  $\delta$ :4.4 (dd, 1H, J=8, 4Hz) (H4),  $\delta$ :4.85 (s, 2H) (H8),  $\delta$ :6.4 (s, 1H) (H2),  $\delta$ :7.1-8.1(d, 8H) (HAr),  $\delta$ :13.49(s, 1H) (H6)(OH),(Cis)  $\delta$ : 2.09(s, 3H) (H7),  $\delta$ : 3.4(m, H) (H5a),  $\delta$ : 3.75(m, H) (H5b),  $\delta$ : 4.57(m, H) (H4),  $\delta$ : 4.86 (s, 2H) (H8),  $\delta$ : 6.36(s, H) (H2),  $\delta$ :7.1-8.1(8H) (HAr),  $\delta$ : 13.5 (OH). <sup>13</sup>CNMR:  $\delta$ : 22.45 (C7),  $\delta$ :34.6 (C5),  $\delta$ :64.9 (C8),  $\delta$ :69.4 (C4),  $\delta$ :73.3 (C2),  $\delta$ :118-156 (CAr),  $\delta$ :162.04, 163.8 (2C=N),  $\delta$ :169.3, 170.5 (C=O), (EI)Mass: Mwt=470.2 M<sup>+</sup>=43.2 peas beak.

(2R,4S)-3-acetyl-2-[4-[ (5-(4-toloyl)-1,3,4-oxadiazol-2-yl) methoxy] phenyl] thiazolidinee-4-carboxylic acid (ATAO<sub>4</sub>) 73 %Trans Isomer (Cis27 %).

Yield:28 % m.p: 205-207 °C. FT-IR KBr: 3327 (OH), 1697 (C=O), 1627 (C=N). <sup>1</sup>HNMR,( 400 MHz, DMSO)-(Trans)  $\delta$ :1.42 (s, 3H)(CH<sub>3</sub>),  $\delta$ :1.84(s, 3H) (H7),  $\delta$ :3.08(m, H, J=8Hz) (H5a),  $\delta$ :3.44 (m, H, J=8Hz) (H5b),  $\delta$ :4.21(t, H, J=8Hz) (H4),  $\delta$ :4.78 (s, 2H) (H8),  $\delta$ :6.36 (s, 1H) (H2),  $\delta$ :6.9-8.1(8H) (HAr),  $\delta$ :12.91(s, 1H) (H6)(OH), (Cis)  $\delta$ :1.43 (s, 3H)(CH<sub>3</sub>),  $\delta$ : 2.04 (s, 3H) (H7),  $\delta$ : 3.32 (m, H) (H5a),  $\delta$ : 3.4(m, H) (H5b),  $\delta$ : 4.2(m, H, 4Hz) (H4),  $\delta$ : 4.82 (s, 2H) (H8),  $\delta$ : 6.32 (s, H) (H2),  $\delta$ :6.9-8.1(8H) (HAr),  $\delta$ : 12.93 (OH). <sup>13</sup>CNMR:  $\delta$ :22.35 (C7),  $\delta$ :33.5 (C5),  $\delta$ :62.1 (C4),  $\delta$ :62.4 (C8),  $\delta$ :66.8 (C2),  $\delta$ :160.2, 164.14 (2C=N),  $\delta$ :169.2, 170.3 (C=O),  $\delta$ :115-155.57 (CAr). Mass (EI): Mwt=439.2 M<sup>+</sup>, 133.3 peas beak.

### 2.7. Antibacterial study.

The antibacterial tests were shown given to the disc diffusion methods. Compounds (AT, ATA, ATAH, ATASO, ATA<sub>01</sub>, ATA<sub>02</sub>, ATA<sub>03</sub> and ATA<sub>04</sub>) were tested for antibacterial action *in vitro* against two kinds of microbial (*S.aureus*, *E.coli*). Which bacteria petridishes were primed agar and sterilized with autoclaving for (15 min), that agar plate was inoculated shallow uniformly from a broth culture of tested microorganisms in a solidified medium properly spread out the hole was made all(6 mm), which hole was filled with (0.1 ml) of a synthesis compounds, the concentrations compounds were synthesized 1000, 500, 250 and 100 ppm and Ampicillin was used for example to anti-biotic bacteria. Dimethyl sulfoxide was used as a solvent, unique of that hole is files with DMSO as controller, to realize an effect of solvent, which dished is incubate at 37 °C for (24 h) [34].

### 2.8. Antioxidant activity.

Compounds synthesis antioxidant activity (AT, ATAH, ATASO, ATA<sub>01</sub>, ATA<sub>02</sub>, ATA<sub>03</sub>, and ATA<sub>04</sub>) was determined to scavenge a very stable 2,2-diphenyl-1-picrylhydrazyl (DPPH) like free radicals giving to Blois method. DPPH inhibition movement is measure spectrophotometric by mix (1 ml) (200  $\mu$ M) DPPH mixture with (1 ml) of dissimilar concentrations (25, 50, 100, 150 and 200  $\mu$ g/ml). Which absorbance's are measured at (517

nm) using UV-Visible and notice the change in DPPH from violet to yellow or colorless, an % inhibition is considered by an equation [35].

$$\text{Inhibition\%} = \frac{A_D - A_S}{A_D} \times 100\%.$$

$A_D$  = Absorption of DPPH

$A_S$  = Absorption of sample

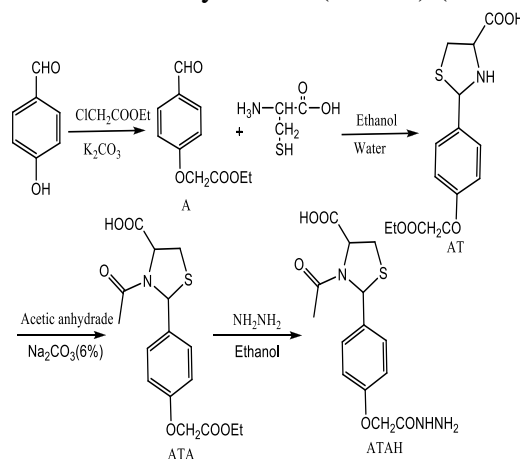
### 2.9. Anticancer (MCF-7).

MCF-7 cancer cells were cultured in a dish containing 96 vacuoles filled with (200  $\mu$ l) of fresh medium for each hole for (24 h) in optimal conditions (37 °C and atmosphere of carbon dioxide at 5 % concentration and in a humid atmosphere). After that, serum media (10 % FBS was+ Antibiotics- penicillin and 100  $\mu$ g/ml streptomycin) and wash the cells twice with buffer phosphate solution (PBS), fresh culture media containing dilute concentrations of the compounds to be tested were used, and the cells were then incubated for (24, 48 and 72 h). Then the prepared compounds were studied in a range of concentrations of (500-15.62  $\mu$ g/ml). Holes in the plate were analyzed for each concentration by adding (10  $\mu$ l) of 5% of freshly prepared (3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide)] (MTT) in PBS in (100 ml) of DMSO, then stirring the plates to facilitate dissolution of the crystals. The absorbances were measured at a wavelength of (570 nm). A Biotech device was used, and the half inhibitory concentration was calculated  $IC_{50}$  [36].

## 3. Results and Discussion

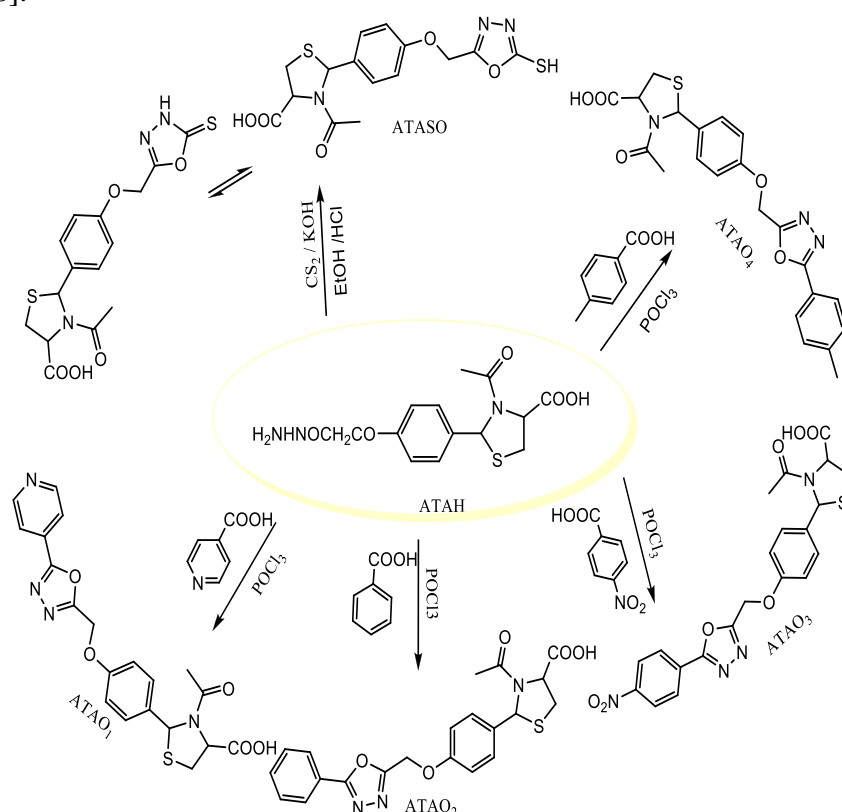
### 3.1. Chemistry.

Compound (A) was synthesized by nucleophile attacking 4-hydroxy benzaldehyde on ethyl chloroacetate and presence  $K_2CO_3$ ; the compound (A) reacts with the amino acid L-cysteine to obtain 2-(4-(2-ethoxy-2-oxoethoxy) phenyl), thiazolidine-4-carboxylic acid (AT) in high yield [17], this reaction from thiazolidine have produced a mixture of diastereomers (trans-(2S,4R) cis-(2R,4R) they cannot be separated, the percentage (cis/ trans) was dependent on a solvent, DMSO main isomer was trans, and in  $CDCl_3$  a major isomer was cis. Which protects an amine group of thiazolidine cycle in compound (AT) by reacting with acetic anhydride to form compound (ATA). The thiazolidine derivatives(ATA) reacts with (80 %) hydrazine ( $NH_2NH_2$ ) and ethanol as solvent to prepare 3-acetyl-2-(4-(2-hydrazinyl-2-oxoethoxy) phenyl) thiazolidine-4-carboxylic acid (ATAH) (Scheme 1) [3].



**Scheme 1.** Synthesis of thiazolidine derivatives.

The 1,3,4-oxadiazole derivative was prepared from compound (ATAH) either through reaction with CS<sub>2</sub> and KOH to synthesize the compound (ATASO) or by condensing it with carboxylic derivatives in the existence of phosphoryl chloride (POCl<sub>3</sub>) to prepare different derivatives in 1,3,4-oxadiazole (ATAO<sub>1-4</sub>) (Scheme2) [8, 37]. The validity structures of the prepared compounds were confirmed using Mass spectra (EI), FT-IR, and NMR spectroscopic as mass spectra are used to determine the molecular weight (M) of compounds. The MWt was consistent with the theoretical values, as the FT-IR technique proved the disappearance of the NH<sub>2</sub> and NH group and the appearance of the C=N groups at the range of 1580-1650 cm<sup>-1</sup>. The <sup>1</sup>HNMR spectra confirmed the disappearance of the signals of NH<sub>2</sub> and NH of the hydrazides groups and the emergence of new signals in the aromatic region. The compound ATAO<sub>4</sub> was characterized by a presence of a signal at 1.46 ppm due to methyl group. ATSO compound showed a signal at 9.9 ppm attributed to SH proton, and <sup>13</sup>CNMR was characterized by the appearance of signals at a range of 160-166 ppm and 179 ppm attributed to the carbon of the C=N group [8].



**Scheme 2.** Prepare 1,3,4-oxadiazole derivatives.

### 3.2. Biological activity.

#### 3.2.1. Antibacterial activity.

The study presented that the synthesized compounds AT, ATAH, ATASO, ATAO<sub>1</sub>, ATAO<sub>2</sub>, ATAO<sub>3</sub>, and ATAO<sub>4</sub> have very good activity usefulness against two kinds of bacteria (*E. coli* and *S. aureus*) unknown compared to Ampicillin anti-biotic revealed in Table 1, the solvent DMSO doesn't have inhibition of bacteriological erosion. Moreover, which result displayed that the compound ATAH, ATASO, and ATAO<sub>1</sub> have the highest inhibition activity of the *E.Coli* bacteria. The ATAO<sub>4</sub> and ATASO showed good activity toward *S. aureus*; the biological activity decreases with lower concentration [38, 39].

**Table 1.** Biological activity of the prepared compounds at concentrations of (1000-100 µg/ml) and area inhibition of (*E. coli*, *S. aureus*).

comp.	Inhibition area (mm) and Concentration (µg/ml)							
	<i>E.Coli</i> (mm)				<i>S.aureus</i> (mm)			
	1000	500	250	100	1000	500	250	100
AT	18	13	9	4	14	10	6	0
ATAH	30	22	16	12	20	11	7	6
ATAO <sub>1</sub>	24	14	10	4	18	12	7	0
ATAO <sub>2</sub>	18	12	6	0	12	8	0	0
ATAO <sub>3</sub>	21	14	10	4	10	8	6	4
ATAO <sub>4</sub>	18	10	9	3	20	16	10	7
ATASO	29	19	14	8	24	16	12	5
Ampicilline	18	12	8	0	13	8	0	0

### 3.2.2. Antioxidant activity.

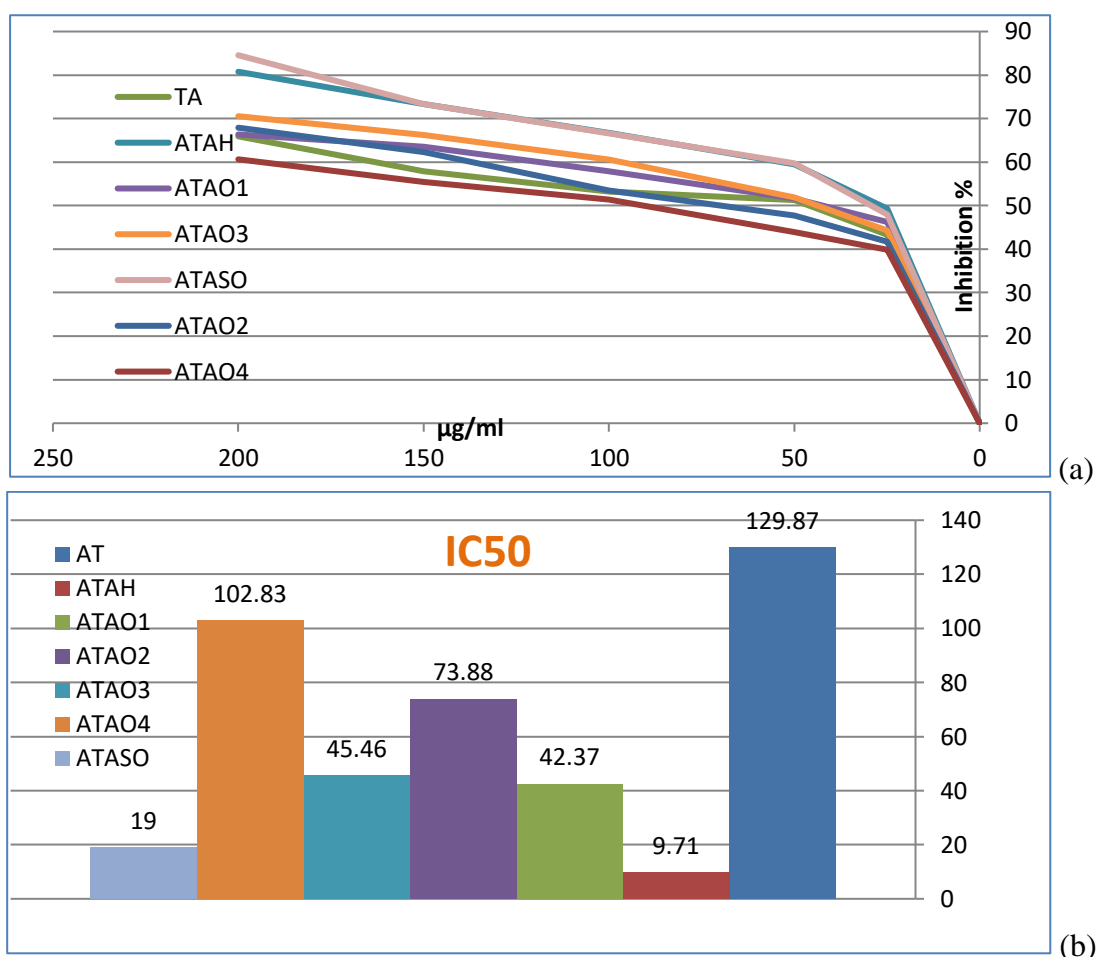
Oxidation was important for several bodily organisms to produce good energy, but radicals reactive as Nitrogen species (RNS) and Oxygen species (ROS) were constantly produced to destroy DNA and RNA, resulting in atherosclerosis mutation, heart diseases, and cancer. However, antioxidant materials are adept at protecting cells from damage caused by radicals. The results exposed that a reaction of prepared compounds with DPPH is dependent on concentration, the effectiveness of synthesized compounds (AT, ATAH, ATAO<sub>1</sub>, ATAO<sub>2</sub>, ATAO<sub>3</sub>, ATAO<sub>4</sub>, and ATASO) are studied in diverse concentrations (25, 50, 100, 150, and 200 µg/ml) and are measured at the absorbance of (517 nm) which is the absorbance of a DPPH solution and change of DPPH purple color to yellow because of the transfer of hydrogen or electron. Which % inhibition at concentration of (200 µg/ml) is (60.65 %, 80.75 %, 66.35 %, 67.9 %, 70.54 %, 66.5 %, 60.64 % and 84.55 %) for compounds (AT, ATAH, ATAO<sub>1</sub>, ATAO<sub>2</sub>, ATAO<sub>3</sub>, ATAO<sub>4</sub> and ATASO) respectively, as (Figure 1, 2 and Table 2). Compounds (ATAH, ATASO, and ATAO<sub>3</sub>) have a high inhibition activity to DPPH. Results displayed that the IC<sub>50</sub> value was persistent by inhibition of prepared compounds with the freest hydrogen atoms as (OH, SH and NH) or free-electron stable. Consequently, the compounds that possess OH, NH, and SH groups are more effective as radical inhibitors due to the ease of hydrogen transfer, and the 1,3,4-oxadiazole ring stabilizes the free radical [40, 41].

Also, some compounds prepared from oxadiazole and thiazolidine derivatives with high inhibition against oxidation were studied as anticancer (MCF-7), and the inhibition value was calculated; the two compounds (ATAO<sub>1</sub>, ATASO) showed good activity against cells with a value of IC<sub>50</sub>= 49.35, 31.51 µg/ml respectively [42, 43], as for compounds were showed for following: ATASO > ATAO<sub>1</sub> > ATAO<sub>3</sub> > ATAO<sub>4</sub>. These results are in agreement with the results of antioxidants, as shown in Figure 2.

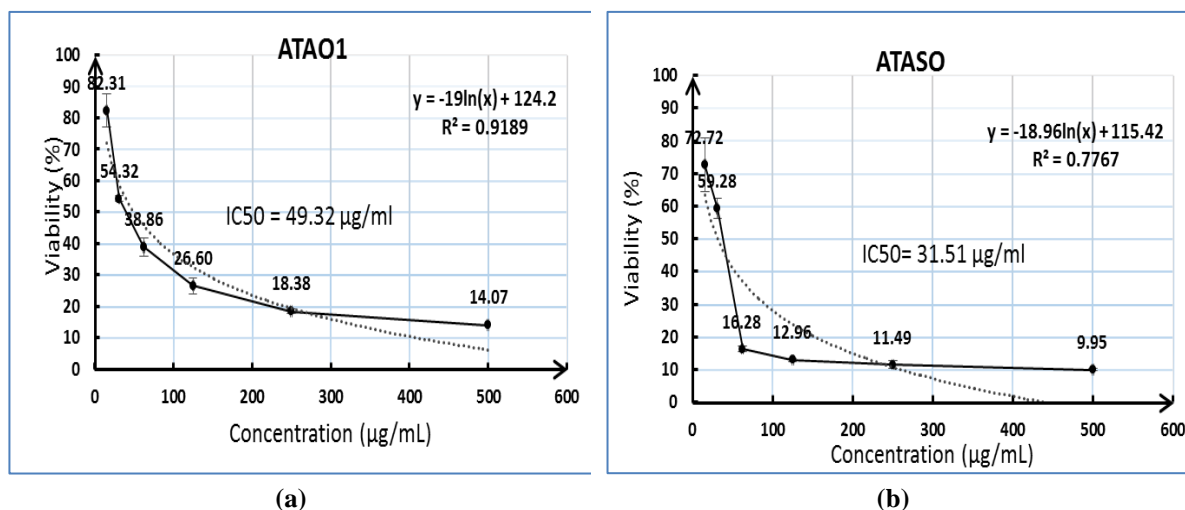
**Table 2.** Percentage of inhibition with concentration and IC<sub>50</sub>.

Inhibition percentage and concentration						
Comp.	200µg/ml	150µg/ml	100µg/ml	50µg/ml	25µg/ml	IC <sub>50</sub> µg/ml
AT	60.65	53.25	44.6	41.54	30.45	129.87 ± 0.56
ATAH	80.75	73.32	66.76	59.5	49.25	9.71 ± 0.78
ATAO <sub>1</sub>	66.35	63.5	57.87	51.64	46.25	42.37 ± 0.83
ATAO <sub>2</sub>	67.9	62.35	53.45	47.67	41.65	73.88 ± 0.87
ATAO <sub>3</sub>	70.54	66.24	60.55	51.85	44.23	45.46 ± 0.92
ATAO <sub>4</sub>	60.64	55.43	51.45	43.87	39.88	102.83 ± 0.73
ATASO	84.55	73.32	66.65	59.78	47.9	19 ± 0.88
S.Acid	90.15	88.52	75.25	65.63	50.55	4.5 ± 0.94





**Figure 1.** DPPH radical scavenging activity of compounds at concentrations (25-200 µg/ml) presents the Percentage inhibition.: **(a)** Percentage inhibition and concentration; **(b)** IC<sub>50</sub>: Half maximal inhibitory concentration for the prepared compounds.



**Figure 2.** The inhibition percentage and IC<sub>50</sub> with concentrations compound (15.5-500 µg/ml): **(a)** The inhibition percentage and IC<sub>50</sub> with concentrations compound ATAO<sub>1</sub>; **(b)** The inhibition percentage and IC<sub>50</sub> with concentrations compound ATASO.

#### 4. Conclusions

Thiazolidine derivative was prepared with good yield, and oxadiazoles were hard obtained from condensate thiazolidine hydrazides with a carboxylic acid. The prepared

compounds thiazolidine and oxadiazole were characterized as having antibacterial and antioxidants and anticancer MCF-7. Then support them using such derivatives as medicine.

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## Conflicts of Interest

There are no battles to declare.

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