ISSN: 0975 -8542

Journal of Global Pharma Technology

Available Online at: www.jgpt.co.in

RESEARCH ARTICLE

# Synthesis, Characterization and Antibacterial Study of New 4-Thiazolidinone and Tetrazole Compounds Derived from Thiosemicarbazone and Hydrazones

**Israa A. Mosa*, Rasmia M. Rumez, Jumbad H. Tomma**

*Department of Chemistry, College of Education for Pure Science, Ibn Al-Haitham, University of Baghdad, Baghdad, Iraq.*

***Corresponding Author: Israa A. Mosa**

## Abstract

A new 4-thiazolidinone, substitutedbenzylidene-thiazolidinone and tetrazole were synthesized from thiosemicarbazone and hydrazone. The thiosemicarbazone was prepared by the reaction of thiosemicarbazide with aldehyde derivative from L-ascorbic acid in absolute ethanol using glacial acetic acid as a catalyst. 1, 3-thiazolidin-4-ones were synthesized from the condensation of thiosemicarbazones with chloroacetic acid in presence of anhydrous sodium acetate. A 1, 3- thiazolidine-4-one was reaction with several 4-substitutedaldehydes to produce new derivatives with a double bond at the position-5 of the 4-thiazolidinone ring. While the tetrazole compounds were synthesized by 1, 3-cycloaddition reaction of sodium azide and hydrazone compounds in dimethylformamide. The hydrazone compounds were prepared by the reaction of phenylhydrazine or substituted phenylhydrazine with aldehyde derivative from L-ascorbic acid in absolute ethanol using glacial acetic acid as a catalyst. The structures of newly synthesized compounds were established on the basis of spectroscopy data.

**Keywords:** *L-Ascorbic acid, 4-Thiazolidinone, Alken, Thiosemicarbazone, Tetrazole, Hydrazone.*

## Introduction

In present era heterocyclic compounds are associated with wide range of biological and pharmacological activities [1, 4]. Thiazolidinones are considered as a biologically important active scaffold that possesses almost all types of biological activities. Thiazolidinone, a saturated form of thiazole with carbonyl group at fourth carbon, has been considered as wonder nucleuses which possess all types of biological activities.

Its derivatives belong to the most frequently studied moieties and its presence in penicillin was the first recognition of its occurrence in nature [5], several substituted thiazolidinone have been found to be possessed a number of biological activities like antibacterial [6, 7], anticancer [8, 9], anti-tubercular [10, 11], antifungal [12, 13], anti-inflammatory [14], antiviral [15, 16], and analgesic [17].Due to this vital role it was thought to synthesized 4-thiazolidinone derivatives and tetrazole derivatives. Derivatives of 4-thiazolidinnone were synthesized by various methods. However, a conventional method for such synthesis was frequently used. It is involve the cyclo-condensation reaction one-pot method was convenient for synthesis 4-thiazolidinone. This method includes the reaction of enamines with ethyl-2-bromopropionate [18].

A common synthetic path is the cyclization of thiourea or thiosemicarbazide derivatives with halo-esters or thiolglycolic acids in the presence of inorganic base in polar solvents. The cyclization reaction was carried out by conventional method [19] or microwave irradiation techniques [20]. Tetrazole and its derivatives have attracted much attention because of their applications agriculture, medicine and biochemistry [21] such as antihypertensive, antialergic, antibiotic and anticonvulsant agents [22, 23].

## Experimental

### Instruments

Uncorrected melting points were determined by using Hot-Stage, Gallen Kamp melting point apparatus. $^1$HNMR spectra were recorded in DMSO-$d_6$ on Varian (500 MHz) I nova NMR spectrometer, at Tahran University, Iran. The chemical shifts were recorded as values in ppm using tetramethylsilane (TMS) as internal standard. FT-IR spectra were recorded using KBr discs on a Shimazu (IR prestige-21) Fourier Transform Infrared spectrophotometer and Shimadzu IR Affinity-1-Fourier Transform Infrared spectrophotometer. Some reactions and the purity of the synthesized compounds were monitored by using TLC (silica gel).

### General Procedures

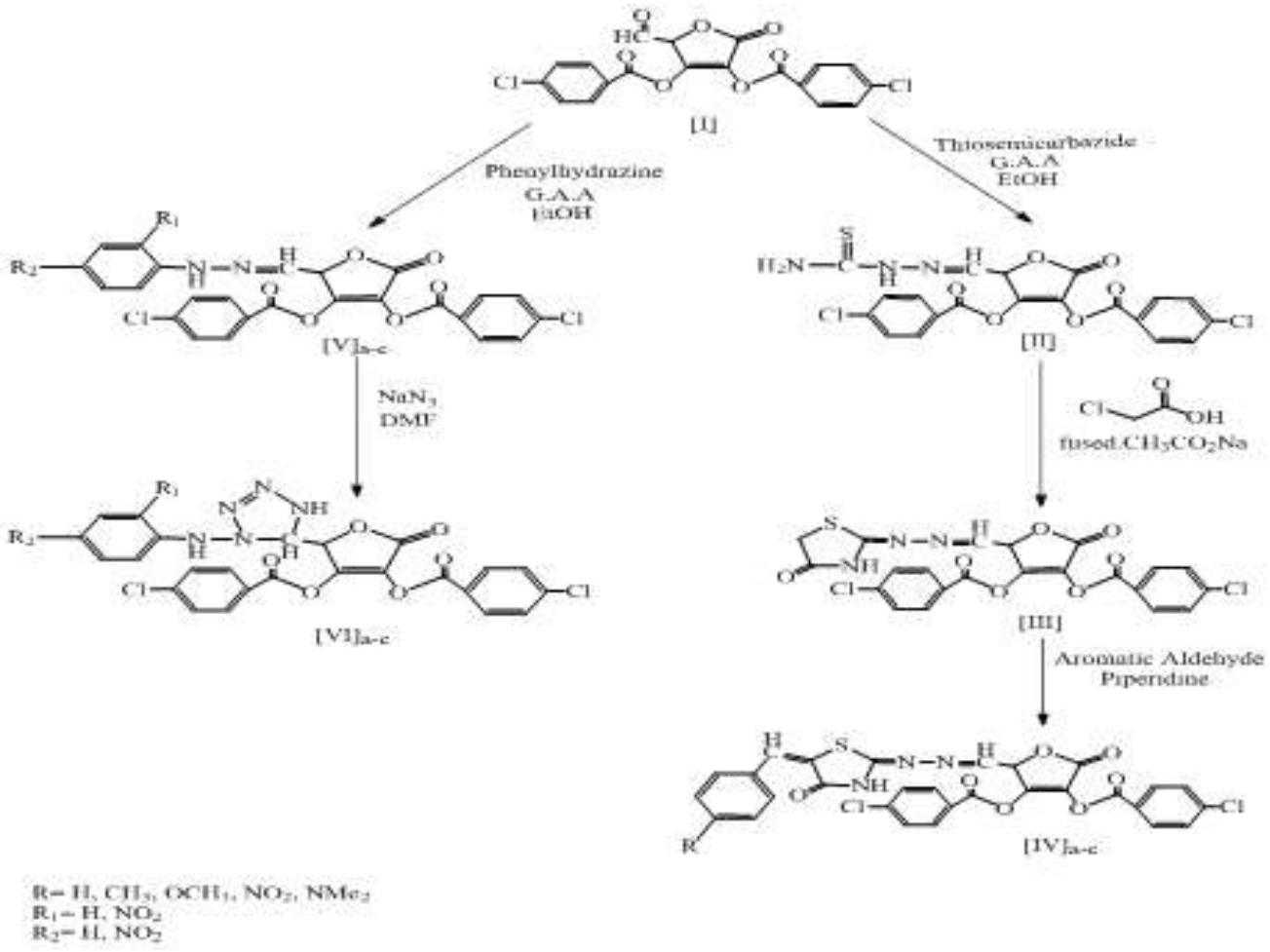
All new heterocyclic derivatives were synthesized according to Scheme (1)

### Synthesis of 2-formyl-5-oxo-2, 5-dihydrofuran-3, 4-diyl bis (4-chlorobenzoate) [I] [24]

To a mixing solution of ($NaIO_4$) (4.7 g, 22 mmol) in 60 ml of distilled water at (0˚C), a solution of 2,3-*O*-di(4-chlorobenzoyl)-L-ascorbic acid that derived from L-ascorbic (10g, 22 mmol) in 60 ml of absolute ethanol was added dropwise. After stirring for (15) minutes, added (0.5ml) of ethylene glygol as dropwise, mixing was persistent at room temperature for (2 hours). The mixture was filtered and to the filtrate, (40ml) of water was added then the yield was extracted by ethyl acetate, the product dried by anhydrous magnesium sulfate, then filtered and the solvent was evaporated and the residue recrystallized from chloroform to product compound [I].

### Preparation of Thiosemicarbazone [II] [25]

Thiosemicarbazide (0.091g, 0.001mol) was added to a solution of aldehyde derived from L-ascorbic acid (compound [I]) (0.421g, 0.001mol) in absolute ethanol (4ml) and two drops of glacial acetic acid. The reactants were heated under reflux for 6 hrs. The product was cooled (to room temperature) and the solid was filtered, dried and recrystallized from ethanol.



**Scheme 1: Synthetic route for target compounds [II] to [VI] a-c**

### Synthesis of thiazolidinone Compound [III]

A mixture of thiosemicarbazone [II] (0.16g, 0.0003mol), chloroacetic acid (0.001mol, 0.09g) and fused sodium acetate (0.003mol, 0.25g) in absolute ethanol (3ml) was refluxed for 6 hrs. The reaction mixture was poured onto ice water and the precipitate was filtered, washed with water, dried and recrystallized from ethanol. The nomenclature and physical properties of this compound was listed in Table (1).

### Synthesis of Compounds [IV] a-e

A mixture of compound [III] (0.1g, 0.0002mol) and benzaldehyde (0.0002mol) was refluxed in presence of piperidine (0.5ml) for 3 hrs. The reaction mixture was cooled at room temperature, and poured onto ice water. The the yield was extracted by (10ml) of chloroform with washing diethyl ether.

### Preparation of Hydrazones [V]a-c

Phenylhdrazine and substituted phenylhydrazine (0.001mol) was added to a solution of aldehyde derived from L-ascorbic acid (compound [I]) (0.421g, 0.001mol) in absolute ethanol (4ml) and two drops of glacial acetic acid. The reactants were heated under reflux for 6 hrs. The product was cooled to room temperature and the solid was filtered, dried and recrystallized from ethanol.

### Preparation of Tetrazole Derivatives [VI] a-c

To a stirring solution of Schiff bases [V]a-c (0.0002mol), sodium azide (0.01g, 0.0002mol) in 2ml of dimethylform amid was added. The mixture was refluxed for 10 hrs with stirring then cooled at room temperature and the precipitate was filtered, washed with cold water recrystallization from ethanol.

**Table 1: Physical properties of compounds [1] to [VI] c**

| Comp. No. | R | Color | Yield% | m.p. C° | Name |
|---|---|---|---|---|---|
| [I] | | Yellow | 74 | 198-200 | 2-formyl-5-oxo-2,5-dihydrofuran-3,4-diyl bis(4-chlorobenzoate) |
| [II] | | Pale brown | 57 | 130-133 | 2-((2-carbamothioylhydrazineylidene)methyl)-5-oxo-2,5-dihydrofuran-3,4-diyl bis(4-chlorobenzoate) |
| [III] | | Brown | 58 | 167-170 | 2-oxo-5-(((4-oxothiazolidin-2-ylidene)hydrazineylidene)methyl)-2,5-dihydrofuran-3,4-diyl bis(4-chlorobenzoate) |
| [IV]a | H | Brown | 72 | Gummy | 2-(((5-((E)-benzylidene)-4-oxothiazolidin-2-ylidene)hydrazineylidene)methyl)-5-oxo-2,5-dihydrofuran-3,4-diyl bis(4-chlorobenzoate) |
| [IV]b | $CH_3$ | Brown | 81 | Gummy | 2-(((5-((E)-4-methylbenzylidene)-4-oxothiazolidin-2-ylidene)hydrazineylidene)methyl)-5-oxo-2,5-dihydrofuran-3,4-diyl bis(4-chlorobenzoate) |
| [IV]c | $OCH_3$ | Brown | 75 | Gummy | 2-(((5-((E)-4-methoxybenzylidene)-4-oxothiazolidin-2-ylidene)hydrazineylidene)methyl)-5-oxo-2,5-dihydrofuran-3,4-diyl bis(4-chlorobenzoate) |
| [IV]d | $NO_2$ | Brown | 83 | Gummy | 2-(((5-((E)-4-nitrobenzylidene)-4-oxothiazolidin-2-ylidene)hydrazineylidene)methyl)-5-oxo-2,5-dihydrofuran-3,4-diyl bis(4-chlorobenzoate) |
| [IV]e | $NMe_2$ | Brown | 75 | Gummy | 2-(((5-((E)-4-(dimethylamino)benzylidene)-4-oxothiazolidin-2-ylidene)hydrazineylidene)methyl)-5-oxo-2,5-dihydrofuran-3,4-diyl bis(4-chlorobenzoate) |
| [V]a | H | Brown | 59 | 123-125 | 2-oxo-5-((2-phenylhydrazineylidene)methyl)-2,5-dihydrofuran-3,4-diyl bis(4-chlorobenzoate) |
| [V]b | 2,4-[$NO_2$] | Orange | 60 | 116-120 | 2-((2-(2,4-dinitrophenyl)hydrazineylidene)methyl)-5-oxo-2,5-dihydrofuran-3,4-diyl bis(4-chlorobenzoate) |
| [V]c | 4-$NO_2$ | Orange | 63 | 138-140 | 2-((2-(4-nitrophenyl)hydrazineylidene)methyl)-5-oxo-2,5-dihydrofuran-3,4-diyl bis(4-chlorobenzoate) |
| [VI]a | H | Brown | 90 | 108 dec | 2-oxo-5-(1-(phenylamino)-4,5-dihydro-1H-tetrazol-5-yl)-2,5-dihydrofuran-3,4-diyl bis(4-chlorobenzoate) |
| [VI]b | 2,4-[$NO_2$] | Brown | 66 | 130 dec | 2-(1-((2,4-dinitrophenyl)amino)-4,5-dihydro-1H-tetrazol-5-yl)-5-oxo-2,5-dihydrofuran-3,4-diyl bis(4-chlorobenzoate) |
| [VI]c | 4-$NO_2$ | Brown | 72 | 305 dec | 2-(1-((4-nitrophenyl)amino)-4,5-dihydro-1H-tetrazol-5-yl)-5-oxo-2,5-dihydrofuran-3,4-diyl bis(4-chlorobenzoate) |

## Results and Discussion

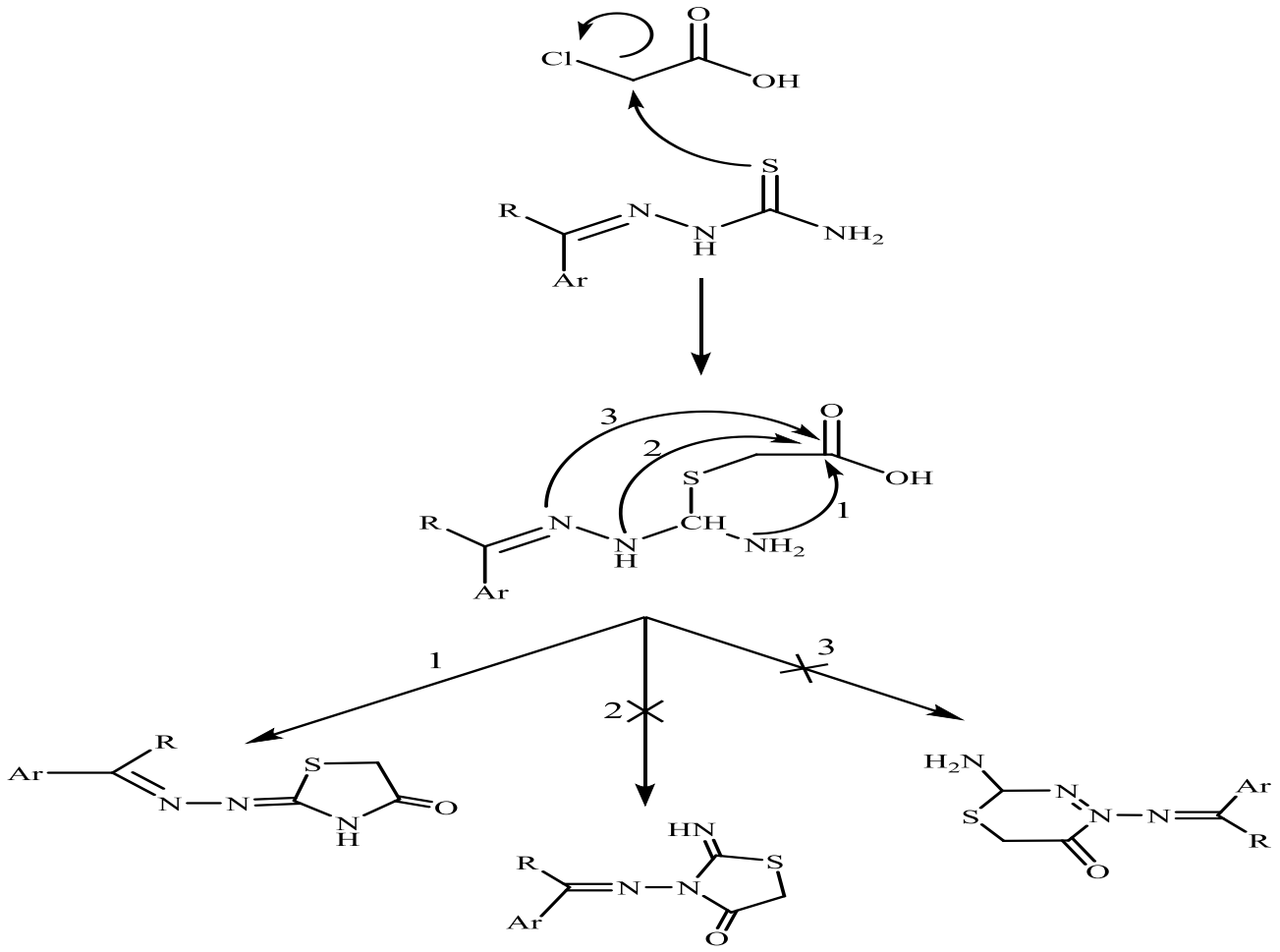
In the present work, we report the synthesis of new alkene derivatives of 4-thiazolidinone and tetrazole compounds derived from L-ascorbic acid. The target compounds were derived from aldehyde [I] the compound [I] was characterized by FTIR, $^{1}$HNMR, $^{13}$C-NMR and Mass spectroscopy, compound [1]

afford a positive Tolen's test by occurrence a silver mirror [49]. The FTIR spectrum of compound [I], showed the following bands, stretching bands at (2843-2727)$cm^{-1}$ for (C-H) aldehydic, stretching bands at (3093-2983)$cm^{-1}$ for (C-H) aromatic, at (2937-2843)$cm^{-1}$ for (C-H) aliphatic, stretching band at 1728 $cm^{-1}$ for (C=O) groups, and (900-600)$cm^{-1}$ for (C-H) aromatic bending (O.O.P). Thiosemicarbazone [II] which obtained from the reaction of aldehyde which derived from L-ascorbic acid with thiosemicarbazide, Scheme (1).

The thiosemicarbazone [II] was charaterized by FTIR and mass spectroscopy, the IR characteristic absorption bands are listed in Table (2). Three new stretching absorption bands at (3367-3170)$cm^{-1}$ are due to $NH_2$ and NH groups, while the stretching absorption band due to C=N group appeared at 1643 $cm^{-1}$. However, the spectrum of this compound showed the disappearances of carbonyl stretching absorption of the starting material (aldehyde) and $NH_2$ group of thiosemicarbazide. The resulted thiosemicarbazone [II] was cyclized successfully to 4-thiazolidinone [III]. The mass spectrum of this compound, showed a molecular ion (M-1) (m/z=493) and many characteristic fragmentations at (m/z= 353, 318, 304, 288 and 203).

The procedure includes the reaction of thiosemicarbazone with chloroacetic acid and anhydrous sodium acetate in ethanol under reflux. The disappearance of starting materials was monitored by TLC. The cyclization mechanism may proceed as in Scheme (2). The first step of the reaction includes the removal proton from NH via sodium acetate resulted in conversion of the resulted intermediate to partially or totally to thiol form [26].



**Scheme 2: The suggested mechanism for synthesis 4-thiazoldinones**

The second step include a nucleophilic attack by thiol on carbon atom (that bears a good leaving group CH-Cl) will result the formation of C-S bond. This step is followed by an attack $NH_2$ on carbon atom of carbonyl group resulted in formation of five member heterocyclic ring. The carbonyl group at position 4 of the ring may be formed by losing a molecule of water. The FTIR spectrum of the product confirmed the formation of the 4-thiazolidinone [III], Table (2) the spectrum showed the disappearances of $NH_2$ group

bands of thiosemicarbazone [II] together with appearances of new characteristic bands at 3325 $cm^{-1}$ and 1714 $cm^{-1}$ related to stretching vibration of N-H and C=O of lactam groups, respectively.

The mass spectrum of this compound, showed many characteristic fragmentations at (m/z= 507, 463, 381, 335, 304 and 185). By another step of our plan is to introduce a double bond at position 5 of the thiazolidinone ring. To give alkene compounds [IV] $_{a-e}$. This step was carried out via reaction of thiazolidinone [III] with benzaldehyde and substituted benzaldehyde in presence of piperidine (which was a base to remove the most acidic proton at position 5 of the ring).

The resulted carbanion would easy attack the carbon of the carbonyl group of the benzaldehyde and substituted benzaldehyde to produce the alkene [IV] $_{a-e}$. The structure of the resulted products were confirmed by their FTIR spectra which showed a stretching vibration band for olefinic double bond (C=C) in the region (1635-1631) $cm^{-1}$. The most characteristic absorption bands of the products are listed in Table (2). Furthermore, $^1$HNMR spectrum of compound $[IV]_c$ (in DMSO as solvent) showed a singlet signal at δ 8.28 ppm for a proton of NH group and complicated signals between in the region δ 6.8-7.9 ppm due to sixteen protons.

Eight of aromatic protons, one olefinic proton (CH=) and one proton of imine groups (CH=N). A sharp singlet signal appeared at δ 3.85 ppm due to three a liphatic proton of methoxy group ($OCH_3$). Also the spectrum showed a doublet signals at δ 1.50 ppm for a proton of lactone ring. While the $^1$HNMR spectrum of compound $[IV]_e$ ( in DMSO as solvent) showed a singlet signal at δ 9.67 ppm for one proton of NH group a complicated signals between in the region δ 6.5-8.0 ppm due to sixteen protons. Eight of them are aromatic protons, one olefinic protons (CH=) and one protons of imine groups (CH=N).

A signal appeared at δ 2.87 ppm due to six aliphatic protons of ($CH_3$-N-$CH_3$) group. Besides to, appeared a signal at δ 1.43 ppm for a protone of lactone ring. The new Schiff bases (hydrazones) $[V]_{a-c}$ were synthesized by refluxing equimolare of aldehyde derived from L-ascorbic acid with phenylhydrazine or substituted phenylhydrazine in absolute ethanol with some drops of glacial acetic acid (GAA). These Schiff bases $[V]_{a-c}$ were

identified by FTIR and $^1$HNMR spectroscopy.

FTIR absorption spectra showed the disappearance of absorption bands due to $NH_2$ and C=O groups of the starting materials together with appearance of new absorption bands in the region (1639-1612)$cm^{-1}$ which is assigned to azomethine group (C=N) stretching. The other FTIR spectral data were listed in Table (3).

$^1$HNMR spectrum in DMSO of hydrazone $[V]_b$ showed a sharp signal at δ 9.99 ppm for one proton could be attributed to the NH group, and a complicated signals between in the region δ(7.55-8.8) ppm that could be attributed to the eleven aromatic protons and the one proton of imine groups (CH=N) appeared at δ 9.11 ppm. One sharp singlet signal at δ 1.21 ppm for proton of lactone ring. Tetrazole derivatives [VI] were obtained by addition reaction of $NaN_3$ to hydrazone $[V]_{a-c}$ in dry dimethyl formamide.

These compounds were identified by FTIR and $^1$HNMR spectroscopy. The FTIR spectra Table (3) showed the disappearance of absorption stretching band of imine group with appearance of new absorption stretching band in the region (1548-1516)$cm^{-1}$ which are assigned to N=N stretching [27]. $^1$HNMR spectrum of compound $[VI]_a$ (in DMSO as solvent), showed two a singlet signals at δ 8.50 ppm and δ 4.65 ppm for two protons of NH(exo) and NH(endocyclic) respectively. And many signals for thirteen aromatic protons appeared in the region δ(7.3-7.9) ppm. Also the spectrum showed two doublet signals at δ 2.92 and δ 1.3 ppm for CH of tetrazole ring and lactone ring, respectively.

## Biological Activity

The antibacterial activity of the synthesized compounds was performed according to the agar diffusion method [28]. The synthesized compounds were tested against E.coli and Staph. Aureus. Each compound was dissolved in DMSO to give concentration 1ppm. The plates were then incubated at 37 °C and examined after 24 hrs. The zones of inhibition formed were measured in millimeter and are represented by a numbers depending upon the diameter and clarity as in Table 4. All the compounds exhibit the highest to low against of the one types of the

bacteria (gram +), this could be related to the presence of the imine linkage or thiazolidinone and hydrazone moiety.

**Table 2: FTIR data of compounds [II], [III] and [IV] $_{a-e}$**

| Comp. No. | v $NH_2$,NH asym, sym | v C-H arom. | v C-H aliph. | v C=O | v C=N | v C=C | v C=S | v C-Cl | v C-S |
|---|---|---|---|---|---|---|---|---|---|
| [II] | 3367-3170 | 3099 | 2974-2848 | 1726, 1708 | 1643 | 1591 | 1276 | 758 | |
| [III] | 3325 | 3093 | 2980-2927 | 1726, 1714 | 1662 | 1593 | - | 759 | 756 |
| $[IV]_a$ | 3236 | 3070 | 2935-2854 | 1728 | 1635 | 1616 | - | 748 | 710 |
| $[IV]_b$ | 3300 | 3200 | 2931-2854 | 1710 | 1631 | 1612 | - | 756 | 709 |
| $[IV]_c$ | 3248 | 3205 | 2935-2854 | 1710 | 1632 | 1612 | - | 759 | 732 |
| $[IV]_d$ | 3236 | 3150 | 2935-2858 | 1716 | 1631 | 1600 | - | 756 | 721 |
| $[IV]_e$ | 3236 | 3100 | 2935-2854 | 1755 | 1635 | 1600 | - | 756 | 690 |

**Table 3: FTIR data of compounds $[V]_{a-c}$, $[VI]_{a-c}$**

| Comp. No. | v NH | v C-H alph. | v C=O | v C=N | v C=C | v N=N | v C-Cl | Other |
|---|---|---|---|---|---|---|---|---|
| $[V]_a$ | 3200 | 2974-2820 | 1720 | 1639 | 1593 | - | 759 | |
| $[V]_b$ | 3320 | 2926-2850 | 1724 | 1635 | 1589 | - | 759 | v $NO_2$: 1589-1311 |
| $[V]_c$ | 3236 | 2981-2835 | 1720 | 1635 | 1593 | - | 759 | v $NO_2$: 1504-1323 |
| $[VI]_a$ | 3142 | 2927-2854 | 1716 | - | 1593 | 1548 | 756 | |
| $[VI]_b$ | 3120 | 2927-2856 | 1735 | - | 1587 | 1530 | 742 | v $NO_2$: 1543-1330 |
| $[VI]_c$ | 3251 | 2920-2889 | 1725 | - | 1593 | 1516 | 752 | v $NO_2$: 1546-1307 |

**Table 4: Antibacterial activity of the synthesized compounds [II]-[VI] $_{a-c}$**

| Comp. No. | E. Coli(G-) | Staphylococci aurus (G+) |
|---|---|---|
| [II] | - | 16 |
| [III] | - | 11 |
| $[IV]_a$ | - | 20 |
| $[IV]_b$ | - | 14 |
| $[IV]_c$ | - | 19 |
| $[IV]_d$ | 17 | 20 |
| $[IV]_e$ | - | 20 |
| $[V]_a$ | - | 21 |
| $[V]_b$ | - | 17 |
| $[V]_c$ | - | - |
| $[VI]_a$ | - | - |
| $[VI]_b$ | - | - |
| $[VI]_c$ | - | - |

## Conclusion

In conclusion, new compounds of 4-thiazolidinone derivatives and tetrazole derivatives were synthesized from thiosemicarbazone and different hydrazones those derived from L-ascorbic acid and they were characterized by different spectral studies.

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