Synthesis and Characterization of Some New 4-Oxothiazolidine-2-Carboxylic Acid Derivatives With the Evaluation of Their Biological Activity.

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Abstract

Reaction of 2-alkylthiazolidine-4-carboxylic acid [**1**] with methanol in presense drops of sulfuric acid gave the ester: methyl 2-alkylthiazolidine-4-carboxylate [**2**], then converted this ester to the acid hydrazide: 2-alkylthiazolidine-4 carbohydrazide [**3**] which was reacted with glyoxylic acid to give Schiff base: 2-[2-(2-alkylthiazolidine-4-carbonyl)hydrazono]acetic acid [**4**]. Schiff's bases (4) were reacted with thioglycolic acid to give 3-(2-alkylthiazolidine-4-carboxamido)-4- oxothiazolidine-2 - carboxylic acid [**5**].

The spectral methods of the prepared compounds were characterized by FT.IR, ^{1}HNMR (just for compounds 5), and Uv-Vis, besides melting points were recorded and the purity was checked through T.L.C. technique. Antibacterial activity for some of the synthesized compounds were screened.

Keywords : Heterocyclic compounds, Sulfur amino acid, Thiazolidine, Carboxylic acids, Schiff's bases.

تحضير و تشخيص بعض مشتقات 4- أوكزوثايازوليدين-2- حامض كاربوكسيلي جديدة و دراسة فعاليتها البايولوجية

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الخلاصة

ان تفاعل أسترة 2-ألكيل ثايازوليدين -4- حامض كاربوكسيلي [**1**] مع كحول المثيل بوجود قطرات من حامض الكبريتيك المركز أعطى الأستر : مثيل 2 -ألكيل ثايازوليدين -4- كاربوكسيليت [**2**] ، ثم مفاعلة الأستر مع هيدرازين ليعطي هيدرازيد الحامض : 2- ألكيل ثايازوليدين -4-كاربوهيدرازيد [**3**]، الذي يتفاعل مع حامض كلايوكسيلك ليعطي قواعد شيف : 2-(2-(2- ألكيل ثايازوليدين-4 - كاربونيل) هيدرازونو) حامض الأسيتك[**4**].تم مفاعلة قواعد شيف مع حامض ثايوكلايكولك لتعطي مشتقات الثايازوليدين : 3-(2- ألكيل ثايازوليدين-4 -كاربوكسأمايد)-4 -أوكسوثايازوليدين-2 -حامض كاربوكسيلي [**5**].

تم متابعة التفاعل بواسطة كروموتوغرافيا الطبقة الرقيقة ، وشخصت المركبات المحضرة بواسطة أطياف الأشعة تحت الحمراء و طيف الرنين النووي المغناطيسي فقط للمركبات (5) وأطياف الأشعة فوق البنفسجية-المرئية ، بالأضافة الى قياس درجات الأنصهار، كما تم أختبار الفعالية البيولوجية لبعض البكتريا.

الكلمات المفتاحية : مركبات حلقية غير متجانسة، حامض أميني كبريتي، ثايازوليدين، أحماض كاربوكسيلية، قواعد شيف.

Introduction

A large family of heterocyclic compounds of which certain volatile derivatives are known for their applications in flavor and food chemistry are thiazolidines [1], The structures identified so far from natural sources and foodstuffs [2], especially in cooked meat [1,3], and in some exotic fruits such as guava and cupuacu [3,4]. The coupling reaction of cysteine or cysteamine with aliphatic and aromatic aldehydes or ketones formed thiazolidines[5-9]., They have played a pivotal role in the organic, bio-medical, organic chemistry and natural products for more than an anti-microbial material such as penicillin, cephalosporin, narcodicins, thienamicyn been prepared from thiazolidines [10-12]. The presence of the thiazolidine ring of penicillin and its derivatives related to the first recognition of its occurrence in nature [13]. Thiazolidine-4- one representing the prevailing scaffold in drug discovery [14].

The biological activity of thiazolidine-4-one referred to presence of one carbonyl group in thiazole at 4th position[13,15]., they are basically known for their antidiabetic activity, anticancer, antimicrobial, and anti-inflammatory[14-22].

The different pharmacological properties such as antibacterial [23], antimycobacterial [24], anticonvulsant [25] or anti-inflammatory activity [26] were occured by 4-oxothiazolidine ring, It is reported that the introduction of arylidene moities in different locations of the thiazolidinone ring enhance the biological activity [27-30].The excellent antioxidant activity in comparison with ascorbic acid showed by most of the Schiff bases and thiazolidine-4 -ones [31,32]. The aim of this work is to prepare and characterize new series of oxothiazolidine-2- carboxylic acid derivatives starting with cysteine, which expected to have a biological activity.

Experimental Part

A-Techniques:

1- Hot stage ***Gallen Kamp*** melting point apparatus, melting points were measured and were uncorrected.

2- KBr disk on a ***SHIMADZU*** FT.IR 8300 spectrophotometer in the range (4000-400) cm^{-1}, FT.IR spectra were recorded

3- Uv-Vis varian Uv-Cary-100 spectrophotometers, Uv-Vis spectra were recorded in DMSO as solvent.

4- BRUKER-400 MHz operating at 300 MH_Z with tetra methyl silane as internal standard in DMSO-d^6 as a solvent, ^{1}HNMR spectra were recorded, measurements were made at Chemistry Department, AL-Al-Bayt University- Jordan.

5- Fertigfollen precoated sheets type Polygram Silg, Thin Layer Chromatography (TLC) was carried out, and the plates were developed with iodine vapor.

6- The biological activity was performed at environmental laboratory, Baghdad University.

B-Materials:

Chemicals employed were of analytical reagent and used without further purification .

Synthesis of: 2-Alkylthiazolidine-4 - carboxylic acids (1) [33,34].

In absolute ethyl alcohol (20 mL) a solution of aldehyde (0.01 mol) was added at (0-10) ^{0}C to a stirred solution of DL-cysteine hydrochloride anhydrous (0.01mol, 1.575gm)

and anhydrous potassium acetate (0.01mol, 0.98gm) in absolute ethyl alcohol (25 mL). After stirring for (5-6 hrs.) at (0-10) ^{0}C, the excess solvent was evaporated ,then the remains was treated with sodium bicarbonate then excess of distilled water to produce crystals which were filtered, dried to gave bright yellow- brown crystals; Re-crystallized from ethanol.

Synthesis of: Methyl 2-alkylthiazolidine-4 - carboxylates (2) [35].

2- Alkylthiazolidine-4- carboxylic acid (1) (0.005 mol) was refluxed with (25 mL) of absolute methanol and few drops of conc. H_2SO_4 for (5 hrs.). The mixture was left to cool and filtered to give yellow crystals ; Re-crystallized from ethanol.

Synthesis of: 2-Alkylthiazolidine-4 -carbohydrazides (3) [36].

To a solution of (0.01 mol) of methyl 2- alkylthiazolidine- 4- carboxylate (2) in (20 mL) absolute ethyl alcohol was added (0.01mol, 0.5 gm, 0.5 mL) of hydrazine hydrate (90%). The mixture was refluxed under anhydrous conditions for (4-5 hrs.); excess solvent was distilled off, then the resulting solid was separated from the cold filtered and re-crystallized from ethanol.

Synthesis of: 2-[2-(2-Alkylthiazolidine-4 -carbonyl)hydrazono]acetic acids (4) [37,38].

Schiff's bases (4) have been prepared in accordance to method reported.

In absolute ethyl alcohol (20 mL) a solution of 2-alkylthiazolidine-4-carbohydrazides(3) (0.01 mol) was slowly added to a solution of glyoxylic acid (0.01mol) + 2 drops of glacial acetic acid in absolute ethyl alcohol (15 mL). After stirring for (1hr.), the mixture was refluxed for a period of (5 hrs.). The mixture was filtered after cooling and washed with cold ethanol and re-crystallized from ether.

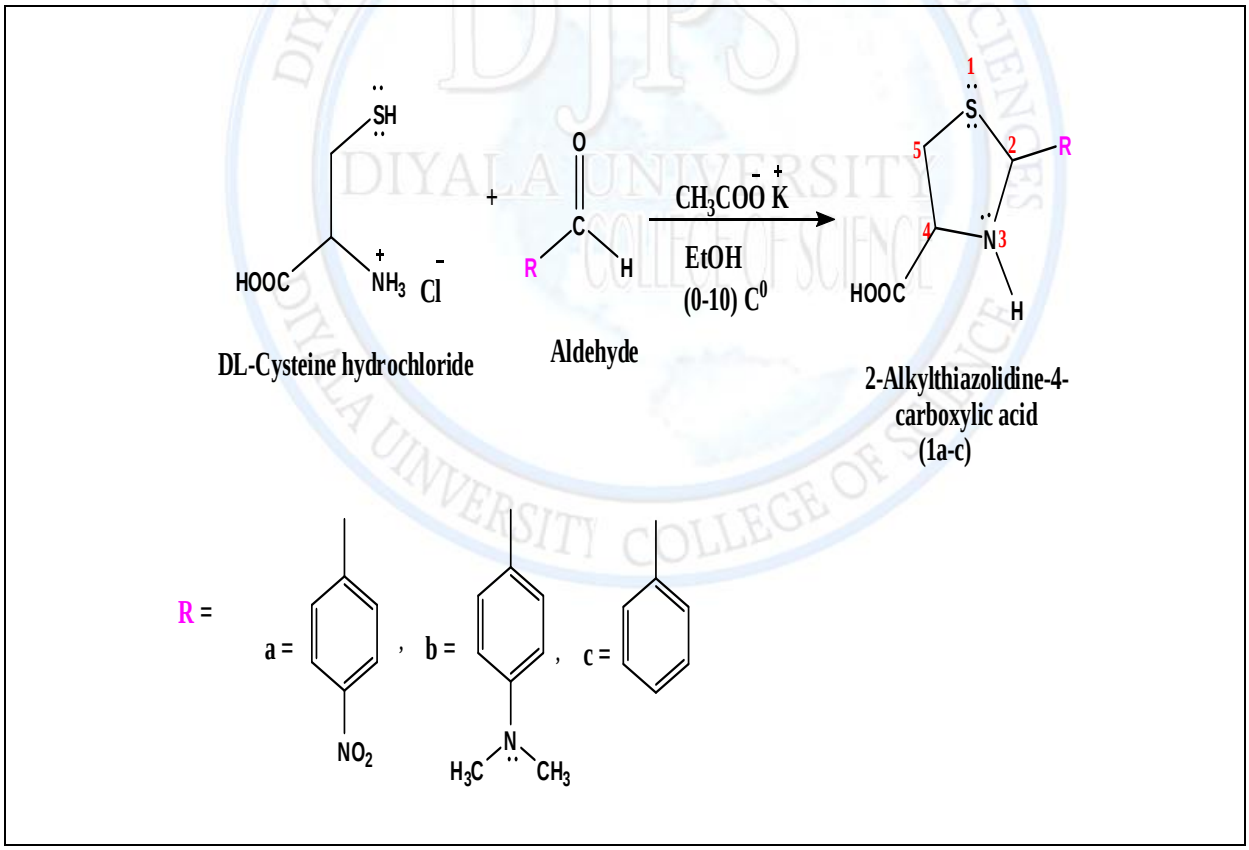
Synthesis of: 3-(2-Alkylthiazolidine-4 -carboxamido)-4 -oxothiazolidine-2 -carboxylic acids (5) [39].

In dry benzene (10 mL) 2-Mercaptoacetic acid (0.005 mol, 0.35mL) was added slowly to (0.005 mol) of Schiff's bases (4). The addition continued about (10 second) while stirring the mixture was then refluxed for (10 hrs.). Excess solvent was evaporated and the residue was treated with sodium bicarbonate to produce compounds (5) precipitate as solid and re-crystallized from ethanol.

Results and Discussion

The first step in scheme (1) involved synthesis of thiazolidine-4- carboxylic acid derivatives by the reaction of benzaldehyde or substituted benzaldehyde with DL-cysteine hydrochloride anhydrous and potassium acetate anhydrous in absolute ethanol [33,34].

These compounds have been diagnosed mediated through the FT.IR spectra and other physical properties (table 1).



Scheme- 1

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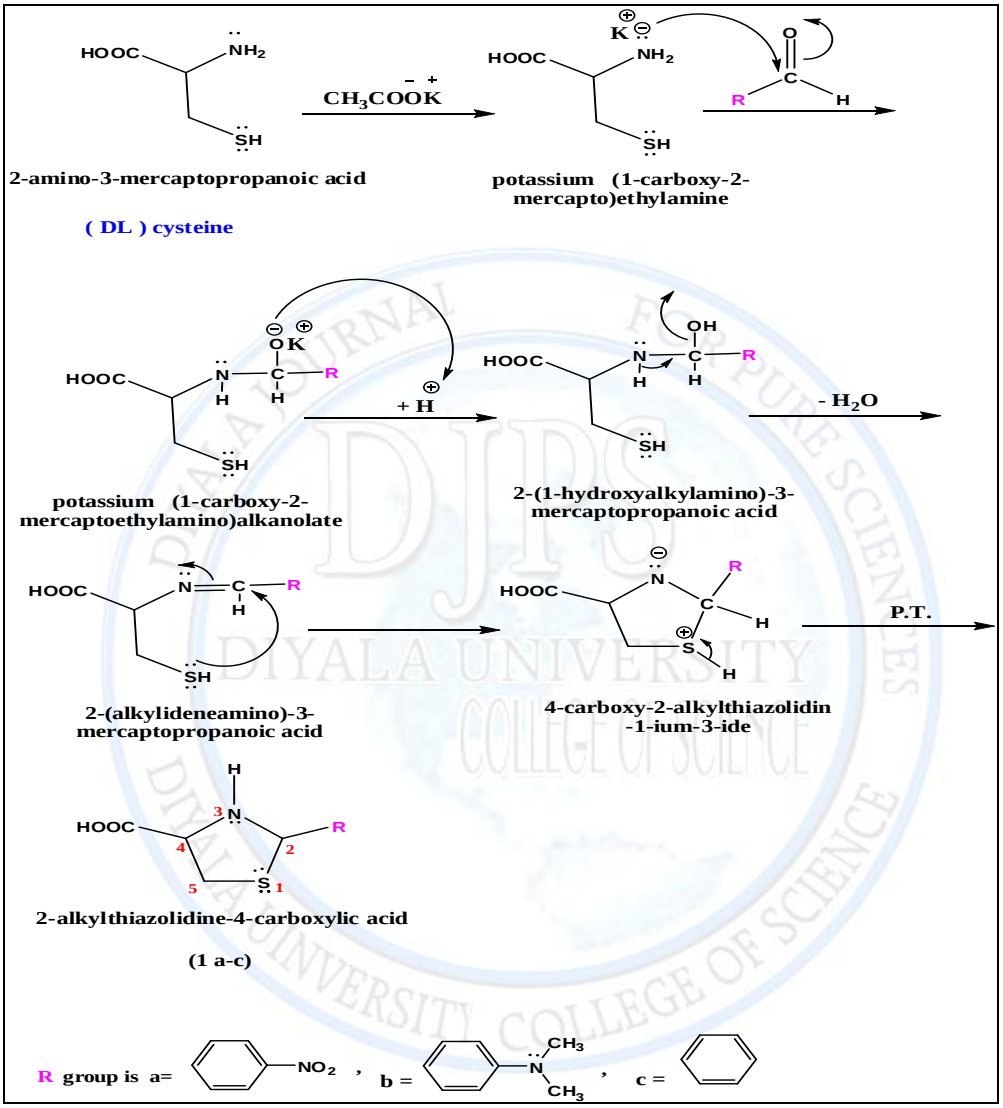
The suggested mechanism of the reaction is shown in scheme below**:**

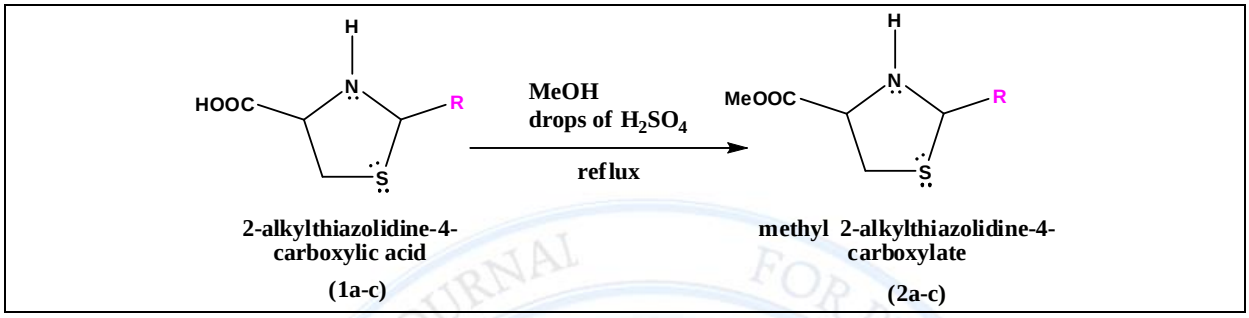


Scheme-2

The FT.IR spectra of compounds (1), showed disappearances of stretching bands of (NH_2) , (SH), and (C=O) of aldehyde, and appearance of stretching band of (NH) which interference with (OH) of carboxylic acid at (3367-3341) cm^{-1} , (table -2) [40].

Thiazolidine-4- carboxylic acid derivatives (1) were converted to esters (2) by reaction with absolute methanol in presence of H_2SO_4 drops by (esterfication reaction) (Scheme-3)[35,41].

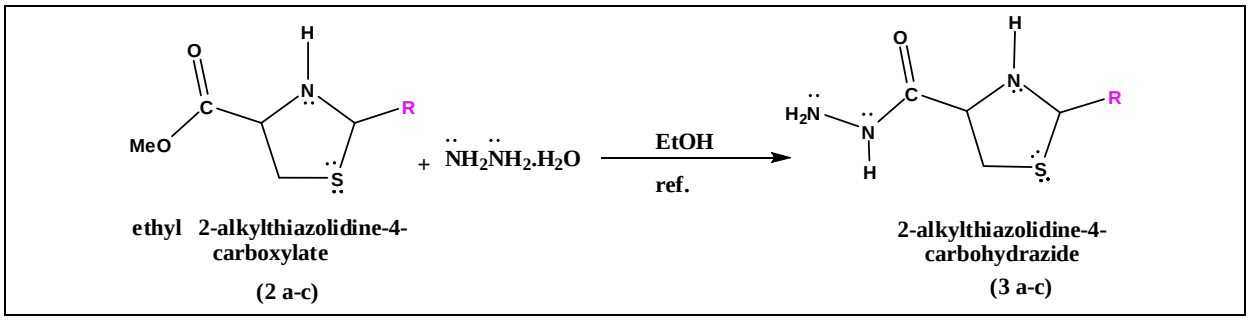
The products were characterized by FT.IR spectroscopy (table-3), and other physical properties (table-1).



Scheme -3

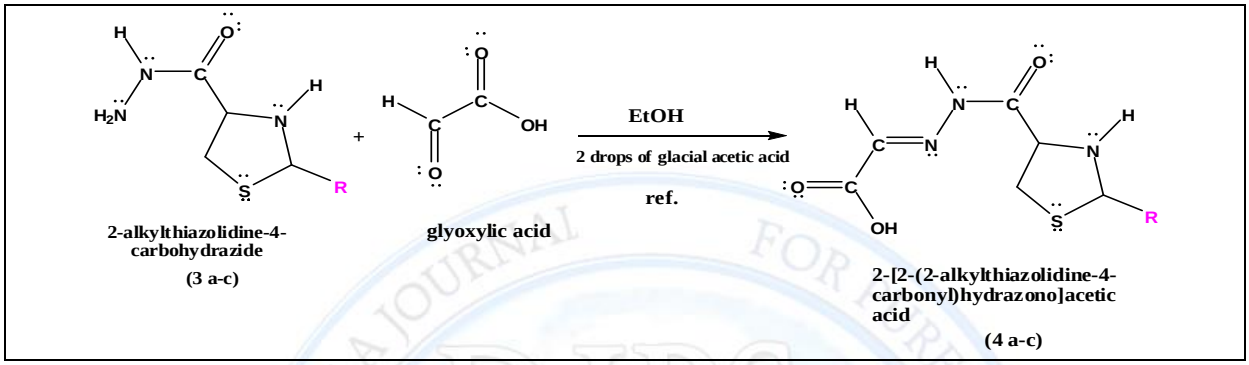
The mechanism of this condensation is known and it is acid catalyzed [42,43].

The FT.IR spectra of compounds (2) showed disappearance of (OH) bands. The reaction of hydrazine hydrate with ester is one of the most common reaction to synthesize the acid hydrazide , it is a tetrahedral nucleophilic substitution reaction [44,45]. FT.IR spectra of the hydrazide derivative compounds (3) showed the appearance of the characteristic absorption in the region (3443-3359) cm^{-1} due to the asymmetric and symmetric stretching vibration of the group (-HN-NH_2) , and the disappearance of absorption (1769-1743) cm^{-1} due to the stretching vibration of carbonyl group of ester , while showed appearance of absorption band at (1686-1675) cm^{-1} of compound (3) due to stretching vibration of amide II band [40,45], (table-4). (Table-1) showed the physical properties of these compounds.



Scheme -4

The mechanism of this reaction is known [45].The treatment of acid hydrazides [3] with glyoxylic acid afforded the correspondding Schiff's base that was identified as compound (4) on the basis of its spectral data (Scheme-5).



Scheme-5

The mentioned compounds were synthesized from the condensation reaction of equimolar quantity of primary amine with glyoxylic acid in absolute ethyl alcohol with few drops of glacial acetic acid; It is the major method to prepare Schiff's bases [46].

Compounds (4) containing imine bond have been synthesized for preparing another derivatives like thiazolidine because these derivatives have a wide range of biological activity[47] and industry[48]. Compounds (4) were characterized by FT.IR , and other physical properties (table-1). The FTIR spectra showed the disappearance of (NH_2) stretching vibration presence in the spectra of acid hydrazides [3] at (3463-3346) cm^{-1}, and showed a broad band of (NH) group at (3442-3257) cm^{-1} which was overlap with absorption of (OH) of acid group, (1685-1670) cm^{-1} due to (C=O) group of amide II, and (1636-1610) cm^{-1} due to (C=N) of Schiff's base. The mechanism of this reaction is known [45]., For a long time imines have been used successfully in the synthesis of nitrogen containing heterocycles [49].

Thiazolidine-4 -one ring derivatives (5) were synthesized by refluxing equimolar amounts from the imine (4) with thioglycolic acid in dry benzene., Cyclization occur where thiol group in 2-mercaptoacetic acid attack as a nucleophile the carbon of C=N [50,51]. When compound (4) reacted with 2-mercaptoacetic acid in dry benzene to produce compound (5), which was characterized by FT.IR , ^{1}HNMR spectra , besides the TLC and physical properties (table-1).

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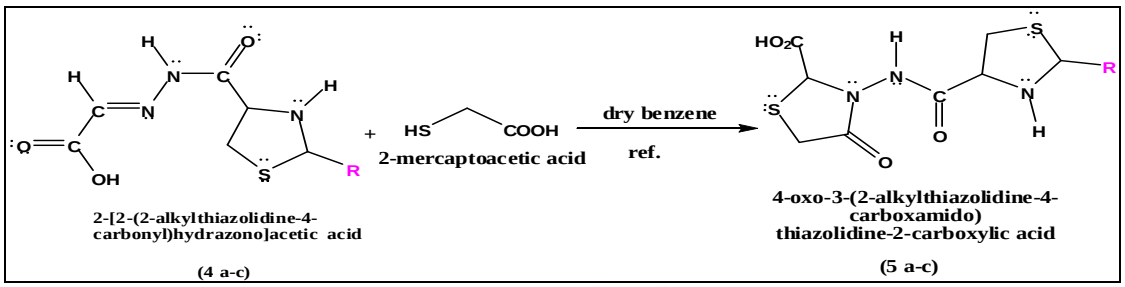
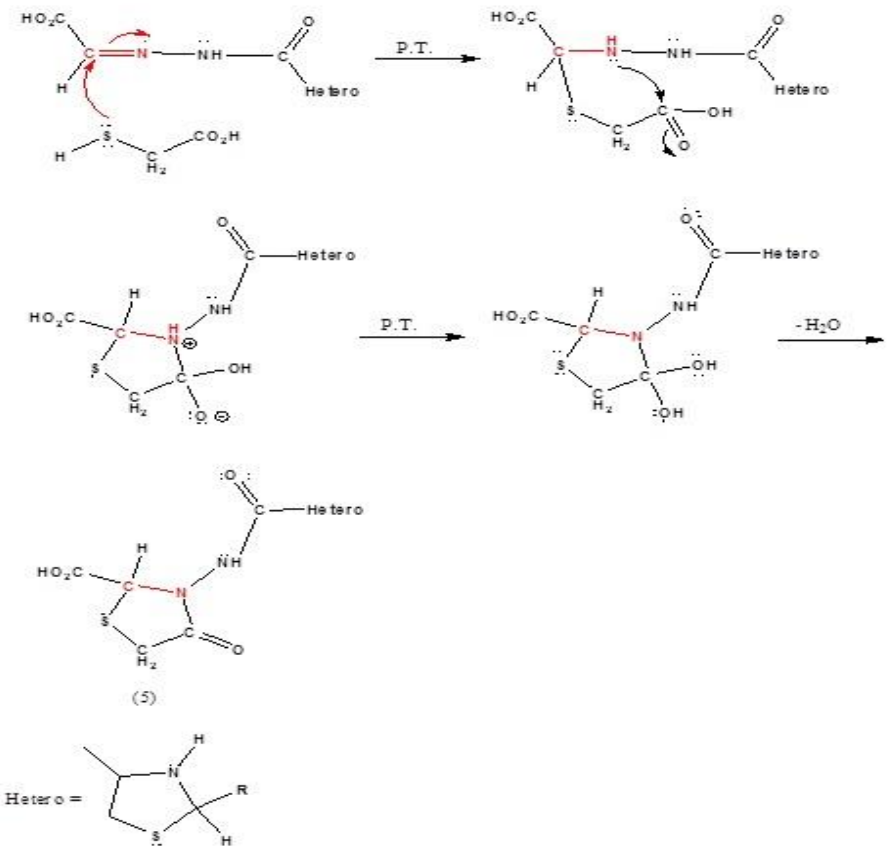


Scheme-6

Compounds (5) showed in the spectrum of FT.IR spectrum the carbonyl group stretching band at (1716-1709) cm^{-1} due to thiazolidin-4-one ring and this was the most characteristic evidence for the success of cyclization step.A broad band for (NH) group at (3456-3226) cm^{-1} which was overlap with absorption of (-OH) group, also shows bands at (3063-3038) cm^{-1}, (2981 and 2856) cm^{-1} attributed to υ(C-H) aromatic, and stretching vibrations of (C-H) aliphatic group; Besides the disappearance of the (C=N) group (1626-1610) cm^{-1} for imine. Compound (5a) showed the ^{1}HNMR spectrum the following characteristic chemical shifts (DMSO-d^{6}) ppm. Protons of methylene (CH_2) of thiazolidine-4-one ring appeared at (δ= 3.71); Protons of methine (CH) of thiazolidine-4-one ring appeared at (δ= 5.44), protons of methylene (CH_2) of substituted thiazolidine ring appeared at (δ= 2.96), protons of methine (CH) of thiazolidine ring appeared at (δ= 3.18,and 6.73); Protons of (NH) group appeared at(δ= 2.509); Protons of (NH) of secondary amide group appeared at (δ= 10.367); Protons of aromatic ring appeared at the range (δ=7.48-8.042) as a multiplate and signal at (δ= 13.559) belong to (OH) of carboxylic acid group (figure-1). Compound (5b) showed ^{1}HNMR spectrum the following characteristic chemical shifts (DMSO-d^{6}) ppm. Protons of methylene (CH_2) and methine (CH) of thiazolidine-4-one ring appeared at (δ= 4. 13),(δ= 4.53) respectively, protons of methylene (CH_2) and methine (CH) of substituted thiazolidine ring appeared at (δ= 2.54), (δ= 3.54), and (δ= 4.84) respectively; Protons of (NH) group appeared at(δ= 2.5); Protons of (NH) of secondary amide group appeared at (δ= 7.142); Protons of

aromatic ring appeared at the range (δ=6.27-6.52) as a multiplate peaks and signal at (δ= 9.272) belong to (OH) of carboxylic acid group (figure-2)., While the ^{1}HMNR spectrum of compound (5c) showed the following characteristic chemical shifts (DMSO-d^{6}) ppm. Protons of methylene (CH_2) and methine (CH) of thiazolidine-4-one ring appeared at (δ= 3.85),(δ= 5.51) respectively; Protons of methylene (CH_2) and methine (CH) of substituted thiazolidine ring appeared at (δ= 2.67),(δ= 3.84), and (δ= 6.35) respectively; Protons of (NH) group appeared at (δ= 2.05); Protons of (NH) of secondary amide group appeared at (δ= 8.031); Protons of aromatic ring appeared at the range (δ=7.27-7.36) as a multiplate peaks and signal at(δ=12.34) belong to (OH) of carboxylic acid group (figure-3).

The proposed mechanism of this reaction is presented in the scheme below:



Scheme-7

UV-Vis. absorption peaks values for compounds (1c, 2b, 3a, 4b, 5a) were shown in (table-7).

Biological screening: Antibacterial activity test:

According to the disc diffusion method the antibacterial test was performed. The antimicrobial activity *in vitro* against two strains of Gram negative and positive bacteria (***Escherichia Coli*** , and ***Staphococcus aureus***) were assayed for compounds (1a,2b,3c,4c,and 5b) . By autoclaving for 15min. at 121 ºC the prepared agar and Petri dishes were sterilized. From the dish culture of the tested microorganisms the agar plates were surface inoculated uniformly. The middle-reinforced distanced appropriately separately slots made every 6 mm in diameter. These holes were filled with 0.1 ml of the prepared compounds (10mg of the compound dissolved in 1mL of the solvent DMSO which was used as a solvent.

These plates were incubated at 37 ° C for 24 hr for bacteria. Inhibition were examined areas resulting from various vehicles. Preliminary results of the tests are For ***St.*** (**G^+**), compound (4c) showed highest activity, while compounds (1a,2b) showed no activity on this bacteria. Compounds (3c,5b) showed slightly activity ; For ***E.coli*** (**G^-**), compound (3c) have very slightly effect on this bacteria; While compounds (1a,2b,4c, and 5b) have effect on this bacteria (table-8).

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Table no. (1): Physical properties of the prepared compounds.

Comp.	Molecular Formula	Molecular Weight (gm/mol)	Yield %	M.P. C^0	Color
1a	$C_{10}H_{10}O_4N_2S$	254	95	205-207	yellow
1b	$C_{12}H_{16}O_2N_2S$	252	83	232-234	light brown
1c	$C_{10}H_{11}O_2NS$	209	86	197-199	light yellow
2a	$C_{11}H_{12}O_4N_2S$	268	86	143-145	light yellow
2b	$C_{13}H_{18}O_2N_2S$	266	77	125-128	Yellowish brown
2c	$C_{11}H_{13}O_2NS$	223	79	221-223	light yellow
3a	$C_{10}H_{12}O_3N_4S$	268	77	179- 181	yellow
3b	$C_{12}H_{18}ON_4S$	266	75	161-163	light brown
3c	$C_{10}H_{13}ON_3S$	223	73	156-158	yellow
4a	$C_{12}H_{12}O_5N_4S$	324	71	243-245	yellow
4b	$C_{14}H_{18}O_3N_4S$	322	73	259-261	yellow
4c	$C_{12}H_{13}O_3N_3S$	279	70	292-294	yellow
5a	$C_{14}H_{14}O_6N_4S_2$	398	59	219-221	yellow
5b	$C_{16}H_{20}O_4N_4S_2$	396	51	315-317	yellow
5c	$C_{14}H_{15}O_4N_3S_2$	353	45	229-232	light yellow

Table no. (2): FT.IR spectral data of the prepared compounds (1a - c).

Comp.	ᵛCH aro.	ᵛCH ali.	ᵛC=O acid	ᵛOH acid	ᵛC=C aro.	Others
1a	3060	2970	1754	3367	1554	C-O 1354 C-S 729 C-N 1266 N-H bend. 1595 NO_2 1535, 1373
1b	3043	2926, 2895	1750	3354	1532	C-O 1324 C-S 725 C-N 1265 N-H bend. 1634
1c	3052	2931	1731	3341	1535	C-O 1331 C-S 732 C-N 1243 N-H bend. 1640

Table no. (3): FT.IR spectral data of the prepared compounds (2a - c).

Comp.	υCH aro.	υCH ali.	υC=O ester	υNH	υC=C aro.	Others
2a	3055	2963	1769	3365	1565	C-O 1323 C-S 725 C-N 1254 N-H bend. 1611 NO_2 564,1309
2b	3050	2918, 2876	1751	3351	1558	C-O 1319 C-S 720 C-N 1261 N-H bend. 1623
2c	3029	2927	1743	3354	1553	C-O 1335 C-S 719 C-N 1236 N-H bend. 1632

Table no. (4): FT.IR spectral data of the prepared compounds (3a - c).

Comp.	υCH aro.	υCH ali.	υC=O amide II	υNH2 , N-H	υC=C aro.	Others
3a	3056	2965	1686	3463-3350	1577	C-S 720 C-N 1251 N-H bend. 1622 NO_2 1540,1380
3b	3050	2927, 2915	1681	3441-3346	1561	C-S 725 C-N 1247 N-H bend. 1623
3c	3034	2918	1676	3438-3359	1587	C-S 715 C-N 1255 N-H bend. 1620

Table no. (5): FT.IR spectral data of the prepared compounds (4a - c).

Comp.	υCH aro.	υCH ali.	υC=O amide II	υN-H Interferance with O-H acid	υC=O acid	υC=N imine	Others
4a	3045	2967	1685	3440-3257	1759	1636	C-S 725 C-N 1257 N-H bend. 1612 NO_2 1567,1303
4b	3051	2923, 2917	1670	3420-3271	1737	1610	C-S 720 C-N 1261 N-H bend. 1642
4c	3022	2965	1673	3442-3265	1712	1622	C-S 743 C-N 1268 N-H bend. 1643

Table no. (6): FT.IR spectral data of the prepared compounds (5a - c).

Comp.	ᵛCH aro.	ᵛCH ali.	ᵛC=O amide II	ᵛC=O acid	ᵛC=O oxothiazolidine ring	ᵛN-H, O-H acid	Others
5a	3063	2981	1656	1767	1716	3445-3231	C-S 724 C-N 1266 N-H bend. 1581 NO_2 1565,1323
5b	3055	2947,2925	1673	1736	1710	3454-3226	C-S 733 C-N 1273 N-H bend. 1627
5c	3038	2951,2856	1691	1747	1709	3427-3233	C-S 712 C-N 1251 N-H bend. 1665

Table no. (7): UV.-Visible spectral data of the prepared compounds.

Comp.	λ_{Max} (nm)
1c	202
2b	226
3a	245
4b	298, 307
5a	340, 361

Table no. (8): Antibacterial activities of some of the synthesized compounds

Comp. no.	*E.coli*	*Staphococcus aureus*
1a	+	-
2b	+	-
3c	-	+
4c	+	++
5b	+	+

- = No inhibition = inactive.
+ = (5-10) mm = slightly active.
++ = (11-20) mm = moderately active.

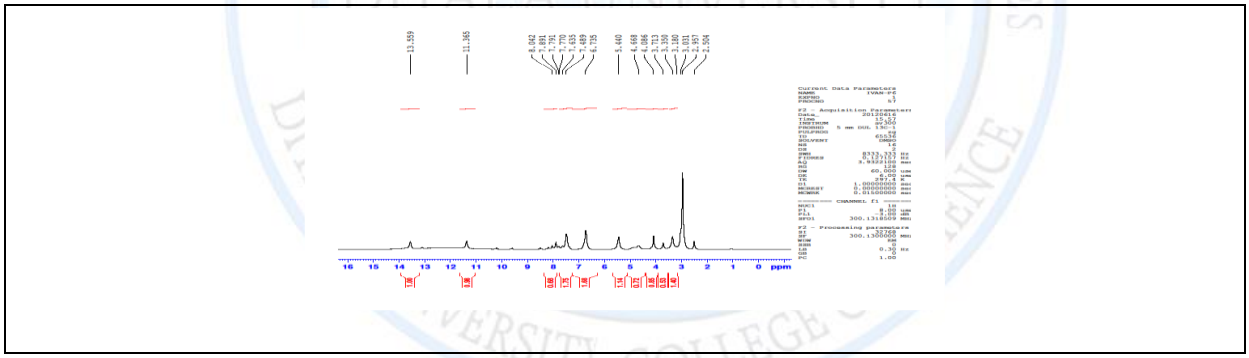

Figure no. (1): ^{1}HNMR spectrum of compound (5a).

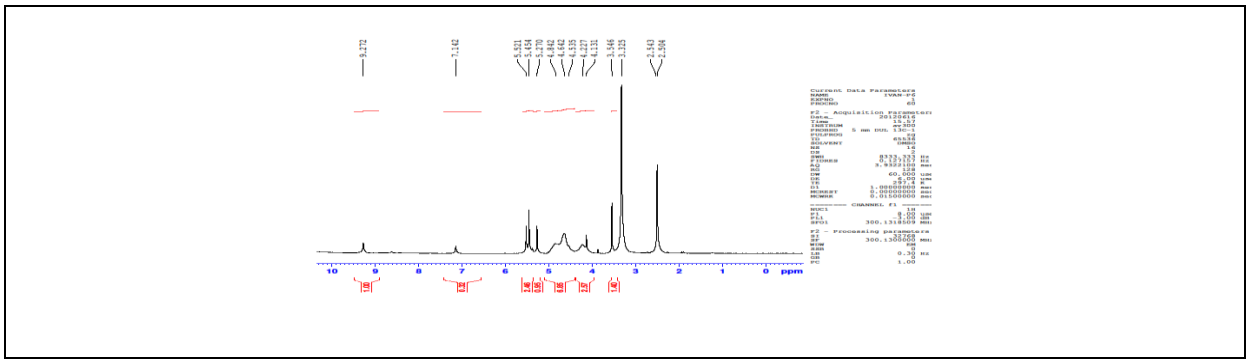

Figure no. (2): ^{1}HNMR spectrum of compound (5b).

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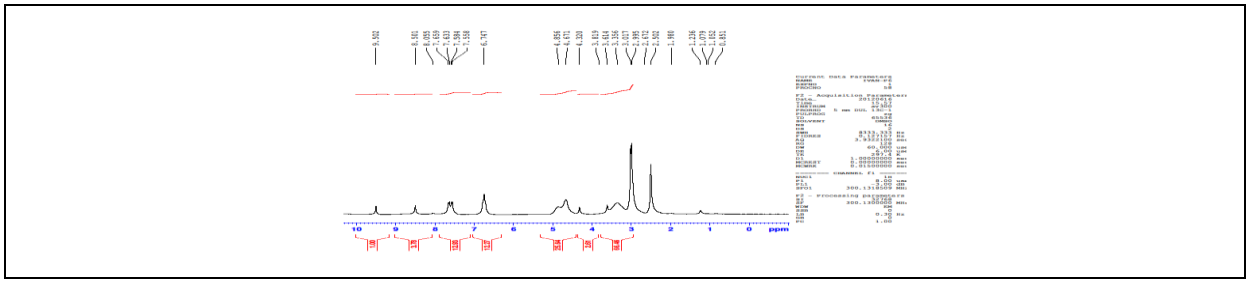
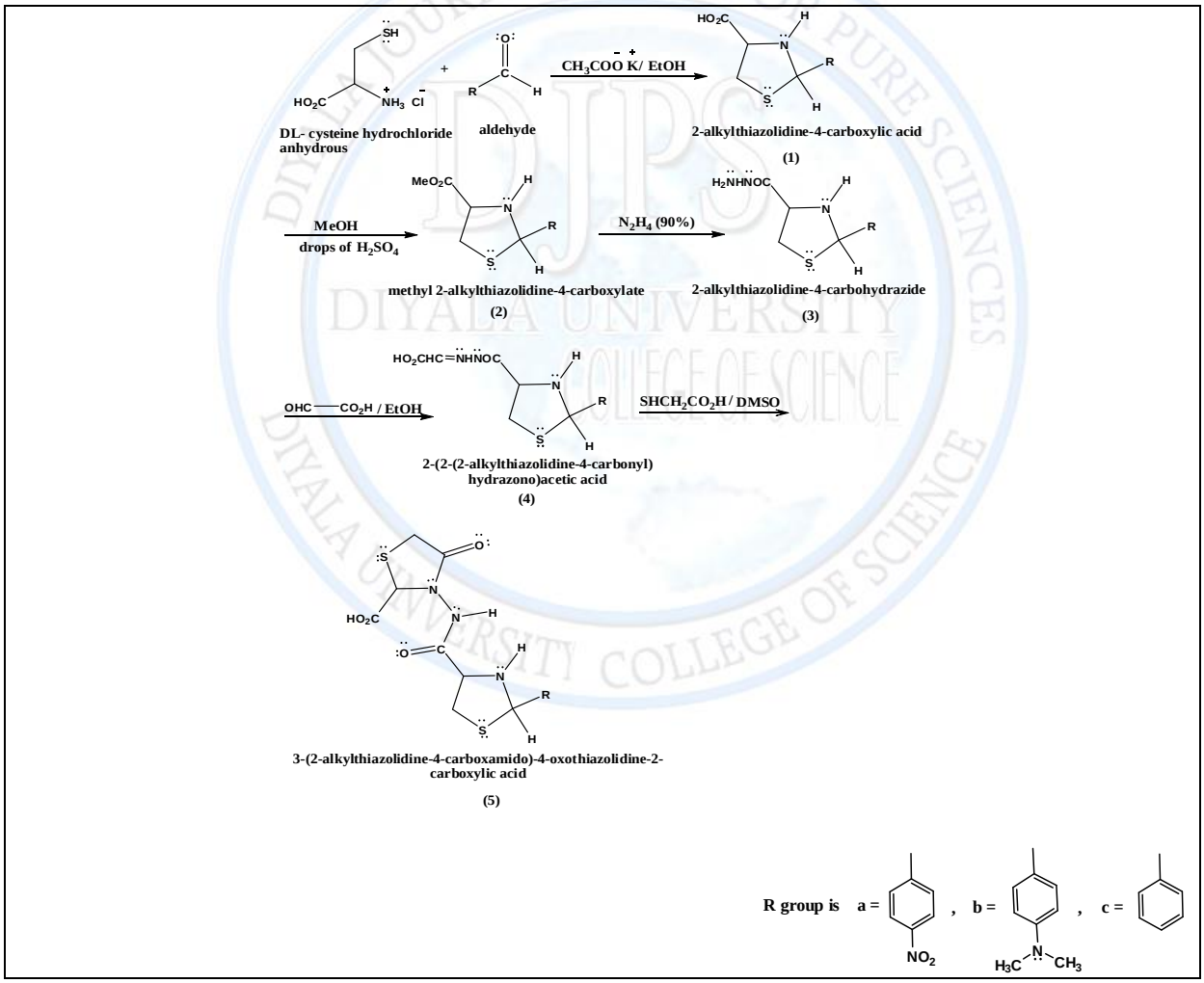


Figure no. (3): ^{1}HNMR spectrum of compound (5c).



Scheme- 8