Synthesis and Spectroscopic Characterization of a New Series of Thiazolidin-4-One Compounds from Heterocyclic Schiff Bases

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***Abstract*–The present work includes synthesis, characterization, and investigation of the biological activity of a new series of thiazolidin-4-one derivatives. The synthetic routes have been divided into four main steps as follows: The first step is the preparation of (4-(4'-chlorobenzyloxy)phenyl)ethanone) as a starting material, by the reaction of p-hydroxyacetophenone with p-chlorobenzyl chloride in the presence of anhydrous K_2CO_3 in absolute ethanol. The second step of this work is synthesis of (4-[4'-(4''-chlorobenzyloxy)phenyl]-thiazol-2-amine), it was achieved by the reaction of (4-(4'-chlorobenzyloxy)phenyl) ethanone) with thiourea in the presence of iodine. The third step includes the synthesis of heterocyclic Schiff bases, by treatment of (4-[4'-(4''-chlorobenzyloxy)phenyl]-thiazol-2-amine) and different substituted benzaldehydes in absolute ethanol using glacial acetic acid as catalyst. The fourth and final step of synthesis process is the synthesis of a series of Thiazolidin-4-one, by the reaction of the synthesized imines with mercaptoacetic acid in dry benzene. The structures of the synthesized products were assigned on the basis of (Fourier transform infrared, ^{1}H-nuclear magnetic resonance (NMR), ^{13}C-NMR, and ^{13}C-DEPT-135) spectroscopy. The synthesized compound was evaluated for antibacterial activity, against two types of bacteria, *Escherichia coli* (Gram-negative) and *Staphylococcus aureus* (Gram-positive). The results showed the high sensitivity of the synthesized compounds against both types of bacteria.**

***Index Terms*—Antibacterial activity, Cyclization, Thiazole, Thiazolidin-4-one.**

I. Introduction

The chemistry of heterocyclic compounds is as logical as of aliphatic or aromatic compounds. Heterocyclic chemistry is the chemistry which deals with the compound having heteroatom such as oxygen, nitrogen, and sulfur in the core structure, in many cyclic compounds that we studied so far benzene, naphthalene, cyclohexanol, and cyclopentadiene the rings are made up only of carbon atoms; such compounds are called homocyclic compounds. The heterocyclic compound shows a number of pharmacologically and biologically active compounds.

Thiazolidines are a class of heterocyclic organic compounds with a five membered saturated ring with a thioether group and an amine group. It is a sulfur analog of oxazolidine [1]. 4-thiazolidinones are important derivatives of thiazolidine with a carbonyl group at the 4-position which belongs to an important group of heterocyclic compounds containing sulfur and nitrogen in a five-membered ring. Substituents in the 2-, 3-, and 5-position may be varied [2]. 4-thiazolidinones and their derivatives are an important class of compounds in organic and medical chemistry. 4-thiazolidinone derivatives have different uses and importance, for example, they were used as stabilizers of polymeric materials, and also as intermediates in organic synthesis furthermore 4-thiazolidinones give good pharmacological uses [3], they have been known to possess a wide range of biological activities, such as anti-inflammatory [4,5], antioxidant [6], antitumor, [7], anticancer [8], anticonvulsant [9], anti HIV [10], antiviral, antifungal, antibacterial, and antitubercular [5,11,12].

II. Experimental

A. Instruments

a. Melting points were determined by BUCHI B-540 electrothermal melting point apparatus.
b. IR-Spectra were recorded on a Bio-Rad Merlin, Fourier transform infrared (FT-IR) spectroscopy Mod FTS 3000, in which solid materials were taken as a KBr disc special for spectroscopy.
c. The ^{1}H-nuclear magnetic resonance (NMR), ^{13}C-NMR, and ^{13}C-DEPT-135 spectra were recorded on a Bruker Ultrashield (300 MHz) with TMS as internal reference and in Al-Albayt University and University of Jordan for Science and Technology, (400 MHz), and the solvents which had been used were $CDCl_3$ and dimethyl sulfoxide.

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B. Experimental: Preparation of Starting Materials

Synthesis of (4-(4'-chlorobenzyloxy)phenyl)ethanone) (1) [13]

A mixture of 4-hydroxy acetophenone (6.82 g and 0.05 mole), 4-chlorobenzyl chloride (9.15 g, 0.057 mole), and anhydrous K_2CO_3 (13.80 g and 0.10 mole) in 100.00 mL absolute ethanol was refluxed with stirring for 7.5 H. The solution was cooled, then poured into cold water. A solid product was immediately formed, filtered off, washed several times with water and cold ethanol, dried and recrystallized from absolute ethanol to obtain white crystals of (4-(4'-chlorobenzyloxy)phenyl)ethanone) (1). m.p = (93–94°C), yield = (90%), IR (cm^{-1}): C=Ostr. 1668; C-O-C 1253 and 1172 asym. and sym. Str.

Synthesis of(4- [4'- (4''- chlorobenzyloxyphenyl]-thiazol-2- amine) (2) [14,15]

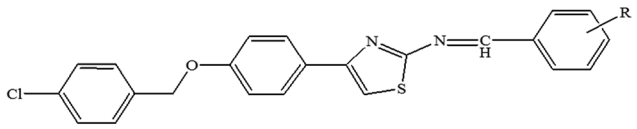
Thiourea (3 g, 0.04 mole) and I_2 (5 g, 0.02 mole) were triturated and mixed with (4-(4'-chlorobenzyloxy)phenyl) ethanone) (1) (5.2 g, 0.02 mol), the mixture was heated on a water bath at 70°C with occasional stirring for 9 H, the solid was triturated and mixed with Et_2O to remove unreacted 4(4-(4'-chlorobenzyloxy)phenyl)ethanone) (1), washed with aqueous thiosulfate (5%) to remove excess iodine and then with water. The crude product was dissolved in hot water, filtered to remove the impurity, and 2(4-[4'-(4''-chlorobenzyloxy)phenyl]-thiazol-2-amine) (2) was precipitated by addition of ammonia solution. The product was recrystallized from ethanol to give yellow crystals of the desired product. m.p = (177–179°C), Yield = (69%), IR: [N-Hstr. 3442, 3284, 3120]; [C-H str. (aromatic) 3020]; [C-Hstr.(aliphatic) 2887]; [C=Nstr. 1629]; [C=Cstr. 1600].

Synthesis of N-(substituted benzylidene)-4-[4'-(4''-chloro benzyloxy)-phenyl] thiazole-2-amine(3a-j) Schiff bases [16]

In round bottom flask (3.16 g, 0.01 mol) of (4-[4'-(4''-chlorobenzyloxy)phenyl]-thiazol-2-amine) (2) was dissolved in 40 mL of absolute ethanol, appropriate aldehyde (0.01 mol) was added to the mixture with a few drops of glacial acetic acid. The reaction mixture was refluxed from 5.30 to 7.30 h and was monitored using thin-layer chromatography (TLC) and cooled, the products were precipitated and filtered off, recrystallized from absolute ethanol. The yield and melting points of Schiff bases are summarized in Table I.

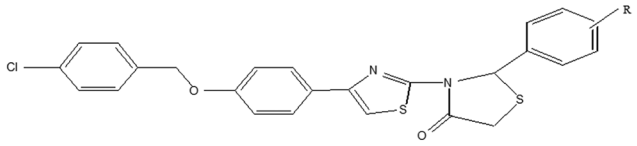
TABLE I
SOME PHYSICAL PROPERTIES OF THE SYNTHESIZED IMINES (3A-J)

Prod.	R	Color	m.p/°C	M.wt (g/mol)	Yield %	Time (h)
a	4-NO_2	orange	132–134	449.51	73	6
b	4-F	Light yellow	136–138	422.5	76	5.3
c	4-Cl	Yellow	140–142	438.96	71	6
d	4-Br	Yellow	120–122	483.414	70	6.15
e	4-OCH_3	Bright yellow	184–186	434.5	47	7.3
f	4-N $(CH_3)_2$	Yellow	221–223	447.51	52	7
g	CH_3	Light yellow	181–182	418.51	66	6.3
h	2-F	yellow	129–131	422.5	69	5
i	3-NO_2	Bright yellow	141–142	449.51	65	5.3
j	2-Cl	Bright yellow	124–126	438.96	63	5.3



Synthesis of 2-(substitutedphenyl)-3-[4-[4'-(4''-chlorobenzyloxy)-phenyl] 1,3-thiazol-2-yl] thiazolidin-4-one (4 a-j)[17,18]

To a solution of compounds (3a-j) (0.005 mol) in benzene 30 mL, mercaptoacetic acid (0.006 mol) was added slowly with stirring. The mixture was refluxed from 15.30 to 18 h; the reaction was monitored by TLC. The solvent was removed under vacuum, and the reaction mixture was neutralized with cold saturated sodium bicarbonate solution until CO_2 evolution. The product was kept at room temperature for 24 h. The formed products were filtered off and washed 3 times with distilled water and recrystallized from absolute ethanol to give the desired compounds. Percentage of yields and melting points of the synthesized thiazolidinone derivatives were summarized in Table II.



Antibacterial susceptibility for the synthesized compounds

Muller-Hinton medium was prepared using nutrient agar preservation of pure culture, then sterilized by autoclave, and

TABLE II
SOME PHYSICAL PROPERTIES OF THE SYNTHESIZED THIAZOLIDIN-4-ONES (4A-J)

Prod.	R	Color	m.p°C	M.wt (g/mol)	Yield %	Time (h)
a	4-NO_2	Brown	170–172	537.5	64	16.30
b	4-F	Yellow	138–140	510.5	69	16
c	4-Cl	Yellow	133–135	526.1	61	16.30
d	4-Br	Milky	164–166	571.414	59	16.30
e	4-OCH_3	Orange	151–153	522.5	50	18
f	4-N $(CH_3)_2$	Brown	133–135	535.5	56	17.30
g	4-CH_3	Brown	127–129	506.5	59	17
h	2-F	Light yellow	132–134	510.5	64	15.30
i	3-NO_2	Orange	151–153	537.5	61	16
j	2-Cl	Deep brown	150–152	526.1	57	16

TABLE III
THE ANTIBACTERIAL ACTIVITY DATA OF SOME PREPARED COMPOUNDS

Compounds	Zone of inhibition in mm	
	Gram-positive *Staphylococcus aureus*	Gram-negative *Escherichia coli*
4 a	+++	+++
4b	++++	+++
4c	++++	+++
4d	++++	+++
4e	++++	++
4f	++++	++++
4g	+++	+++
4h	++++	++++
4i	++++	++
4j	+++	++++

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poured in Petri dish to a depth of 4 mm. Activation of each type of bacteria, before culturing on the nutrient agar in the nutrient broth which was used for dilution of bacterial and cultivation of culture was isolates, for 24 h in 37°C, then inoculation of the plates. Then, culturing the bacteria on nutrient agar. Application of the thiazolidin-4-one derivatives disks, each disk was prepared by mixing a substance with KBr powder (1:10) by pressing under pressure. The prepared disk was placed on the surface of the cultured media with each of the above bacteria. The incubated plates were incubated for 24 h at 37°C, after inhibition zone diameter as shown in Table III.

III. Results and Discussion

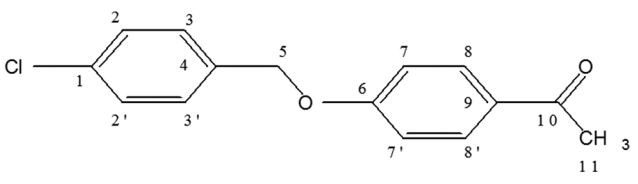
A. Characterization of (4-(4'-Chlorobenzyloxy)(Phenyl) Ethanone) (1)

The first step of the present work has been started by preparation of 4-(4'-chlorobenzyloxy) acetophenone compound through the reaction of p-chlorobenzyl chloride with p-hydroxyacetophenone in the presence of anhydrous K_2CO_3 in ethanol In FT-IR spectrum the strong evidence for obtaining the (4-(4'-chlorobenzyloxy)(phenyl)ethanone) (1) is disappearance of a broad band at 3600–3200cm^{-1} for hydroxyl group of 4-hydroxyacetophenone, and shifting the band of carbonyl group from 1660 to 1668cm^{-1}, two weak bands at 2927 and 2872cm^{-1} belongs to the (-CH_2-) group [19,20].

The ^{1}H-NMR spectrum of (4-(4'-chlorobenzyloxy)(phenyl) ethanone) (1), showed two singlet signals at 2.5 and 5.2 ppm for the three protons of (-CH_3), and two protons of O-CH_2 group, respectively. Two doublet signals at 7.1 and 7.95 ppm and two fused doublets at 7.5 ppm which belong to the eight protons of aromatic rings.

The ^{13}C-NMR spectrum, showed eleven singlet peaks, three signals at 26.84, 69.09, and 196.7 ppm attributed to the carbon atom of -CH_3, -O-CH_2, and C=O groups, and also the other eight signals at 115.11, 128.95, 130.01, 130.64, 130.9, 133.06, 136, and 162.4 ppm belongs to the $C_{7,7'}$, $C_{3,3'}$, $C_{2,2'}$, $C_{8,8'}$, C_9, C_1, C_4, and C_6, respectively.

The ^{13}C-DEPT-135 showed the disappearance of five non-protonated carbons (C_1, C_4, C_6, C_9, and C_{10}) which appeared in the ^{13}C-NMR spectrum also showed downward signal at δ (67.7) for the di-protonated carbon atom (-O-CH_2-) group, the upward signal at δ (25.5) for tri-protonated carbon atom of -CH_3 group, four different upward signals at 113.7, 127.6, 128.7, and 129.6 ppm attributed to the monoprotonated carbon atom (-CH-) in two aromatic rings ($C_{7,7'}$, $C_{3,3'}$, $C_{2,2'}$, and $C_{8,8'}$), respectively.



(1)

B. Characterization of 2-Amino-4-[4'-(4''-Chlorobenzyloxy Phenyl)]-Thiazole (2)

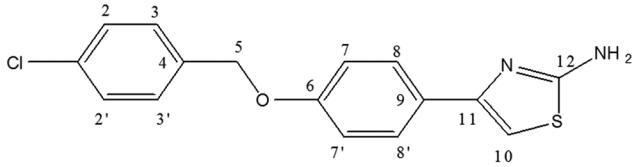
The second step of this work includes preparation of 2-amino thiazole that was synthesized from the reaction of 4-(4'-chlorobenzyloxy) acetophenone and thiourea in the presence of excess iodine as reducing agent. Synthesized compound was identified by spectral methods: FT-IR, ^{1}H-NMR, ^{13}C-NMR, and^{13}C-DEPT-135 spectra.

In FT-IR spectrum of the newly synthesized compound, the disappearance of carbonyl group band at 1668cm^{-1} and appearance of three bands at 3442, 3284, and 3120cm^{-1} corresponding to asymmetric(N-H)stretching, symmetric(N-H)stretching, and overtone(N-H) bending, respectively, and also the appearance of cyclic band C=N at 1629cm^{-1}, C=C aromatic band at 1600cm^{-1}, and C-S-C band at 692cm^{-1}, confirmed the expected structure [21,22].

The^{1}H-NMR spectrum showed the appearance of multiple signals of eight protons of two phenyl ring at δ (7.06-7.78) ppm and the singlet signal of two protons of -O-CH_2 group at δ (5.17) ppm, also the singlet signal at δ (6.89) ppm belongs to two protons of amine group and one proton of thiazole ring [23].

In the ^{13}C-NMR spectrum, which showed 12 singlet peaks of 12 types carbons in the different chemical shifts, C_5 at (68.84) ppm attributed to the carbon atom of -O-CH_2 group, C_{12} at 168.5 ppm, C_{11} at 150.08 ppm, and C_{10} at 99.98 ppm for thiazole ring, and also the other eight signals at 115.21, 127.5, 128.69, 128.8, 129.9, 132.8, 136.6, and 157.88 ppm were fitted to the $C_{7,7'}$, $C_{8,8'}$, $C_{3,3'}$, C_9, $C_{2,2'}$, C_1, C_4, and C_6, respectively [24].

The ^{13}C-DEPT-135 showed five upward signals one for CH of C_{10} which is the position 5 of thiazole ring at 98.65 ppm and illustrate four different upward signals at 113.84, 125.95, 127.56, and 128.65 ppm attributed to mono-protonated types of carbon atom (-CH-) in two phenyl rings ($C_{7,7'}$, $C_{8,8'}$, $C_{3,3'}$, and $C_{2,2'}$, respectively, also showed downward signal at δ (67.45) for di-protonated carbon atom (-O-CH_2) group, but the disappearance of six non-protonated carbons (C_1, C_4, C_6, C_9, C_{11}, and C_{12}) which appeared in the normal ^{13}C-NMR is a good evidence for confirming the expected structure



(2)

C. Characterization of N-(substituted benzylidene)-4-[4'-(4''-Chlorobenzyloxy)-Phenyl] Thiazole-2-Amine(3a-j)

The third step of this work is a synthesis of the Schiff bases from the reaction between the 2-amino thiazole with a number of substituted benzaldehydes. The method involves mixing of the solution of the two reactants in absolute ethanol and using glacial acetic acid as a catalyst to accelerate the reaction under the reflux condition.

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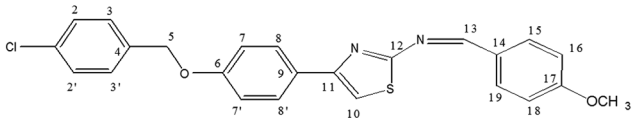
The formation of the new Schiff bases (3a-j) was confirmed on the basis of their spectral methods: FT-IR, ^{1}H-NMR, ^{13}C-NMR, and ^{13}C-DEPT-135.

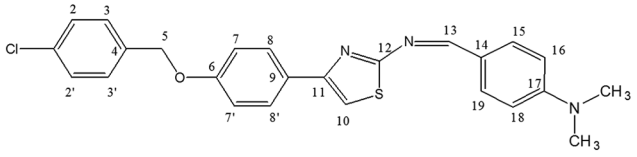
In FT-IR spectra of compounds (3a-j), the disappearance of the characteristic bands for the amino group from IR spectral data at 3442, 3284, and 3120cm^{-1} for NH_2 stretching vibration, and the absence of aldehydic carbonyl group of reactants, is an indication for the formation of Schiff bases. Produce the signal in the range of 1616–1595cm^{-1} and 2860–2850cm^{-1} which belongs to the HC=N, C-H stretching, respectively. The C-H (aromatic) str. at 3090–3010cm^{-1}, C=C str. 1540–1440cm^{-1}. Two strong bands appeared in the range of 1261–1153cm^{-1} which belongs to -O-CH_2 group. As an example in the compounds (3 e, g), the appearance of a (CH=N) absorption bands at 1595, 1597cm^{-1} for azomethine bands, and C-H (azomethine) at 2850 and 2850 which belongs to 3 e, g, respectively, is the strong evidence for the formation of Schiff bases. From the ^{1}H-NMR spectra of imines (3a, e, f, g, h, i), a singlet signal for the proton of (CH=N-) group is observed at 8.7-9.2 ppm, and the multiple signal of aromatic protons occurs in range (6.7–8.3) ppm. (Chandramouli *et al.*, 2012), as an example in compound (3e), there are two singlet signal at 3.85 and 5 ppm integrated to (-OCH_3 and -O-CH_2-) protons in this order, and the multiple signal for protons of aromatic ring at 6.9–8 ppm, and a singlet signal for the proton of (CH=N-) group is observed at 8.9 ppm. In compound (3g) showed a singlet signal at (2.3) ppm due to three protons of CH_3 group and the singlet signal at δ (5.1 ppm) for benzylic protons, and a singlet signal for the proton of CH=N- group appeared at δ (9 ppm), and the multiplet signals at δ (6.9–7.9) ppm for protons of aromatic ring [25].

In the ^{13}C-NMR spectrum of compound (3e), the signal for carbon of (-OCH_3) group appeared at δ (55.28) ppm and the signal for carbon of (-O-CH_2) group appeared at δ (68.13) ppm, whereas the C_{13} carbon atom of (CH=N) group appears at δ (163.65) ppm, and the signals for three carbons of thiazole ring appears at 114.05, 148.8, and 162.98 ppm were fitted to the C_{10}, C_{11}, and C_{12}, and signals in the aromatic region for carbons in three phenyl ring appears at 133.42, 131.54, 128.08, 135.47, 157.7, 114.37, 127.18, 129.18, 126.4, 132.16, 114.26, and 169.6 ppm were fitted to the C_1, $C_{2,2'}$, $C_{3,3'}$, C_4, C_6, $C_{7,7'}$, $C_{8,8'}$, C_9, C_{14}, $C_{15,19}$, $C_{16,18}$, and C_{17}, respectively. In compound (3g) shows that 18 singlet peaks of carbon in the different chemical shifts, the signal for carbon of -CH_3 group appeared at δ (21.8) ppm and the signal for carbon of -O-CH_2 group appeared at δ (68.9) ppm, whereas the C_{13} carbon atom of CH=N group appears at δ (170.1) ppm, C_{12} at (165) ppm, C_{11} at (149.9) ppm, C_{10} at (115.1) ppm for thiazole ring, and 12 signals in the aromatic region for carbons in three phenyl ring appears at 136.2, 132.95, 129.9, 137.4, 158.5, 127.1, 127.9, 130.2, 128.8, 132.6, 134.4, and 144 ppm were fitted to the C_1, $C_{2,2'}$, $C_{3,3'}$, C_4, C_6, $C_{7,7'}$, $C_{8,8'}$, C_9, C_{14}, $C_{15,19}$, $C_{16,18}$, and C_{17}, respectively [16].

The ^{13}C-DEPT-135 of compound (3e) showed the disappearance of eight non-protonated carbons (C_1, C_4, C_6, C_9, C_{11}, C_{12}, C_{14}, and C_{17}) which appeared in the normal ^{13}C-NMR also showed the upward signal at δ (55.03) for tri-protonated carbon atom of -OCH_3 group, and demonstrate the downward signal at δ (67.87) for di-protonated carbon atom (-O-CH_2) group, the upward signal at δ (163.42) for mono-protonated carbon atom of -CH=N- group.



(3e)



(3g)

D. Characterization of 2-(substituted phenyl)-3-[4-[4'-(4''-chlorobenzyloxy)- phenyl] 1,3-thiazol-2-yl] thiazolidin-4-one(4 a-j)

The fourth step of this work is a synthesis of a new series of biological active heterocyclic thiazolidin-4-one derivatives. Thiazolidin-4-ones (4a-j) were synthesized from the reaction of the synthesized Schiff bases (3a-j) with mercaptoacetic acid in benzene, heating under reflux. See Scheme 1.

The formation of the synthesized new thiazolidin-4-ones (4a-j) was confirmed on the basis of their spectral methods: FT-IR, ^{1}H-NMR, and^{13}C-DEPT-135.

The general feature of the IR spectra of thiazolidin-4-ones (4a-j) consists of the appearance of strong, sharp bands at 1699.2–1683.9cm^{-1} which belong to carbonyl groups of the thiazolidin-4-ones structure that is considered as evidence of the formation of the described products [26]. The disappearance of (C=N) band for imines in the range of 1616–1595cm^{-1} in all 4-thiazolidinones is also good evidence for the occurrence of thiazolidinones compound. As an example, compound (4 e) the disappearance of a band at 1595cm^{-1} for (C=N) group of imine, shows a signal for the carbonyl group of thiazolidin-4-one (C=O) at 1687.7cm^{-1}, and also in the compound (4 h), showed the strong band at 1699.2cm^{-1} relation to the (C=O) group, and the absence of C=N (azomethine) absorption band at 1610.4cm^{-1}.

The ^{1}H-NMR spectra of some thiazolidinones (4a, e, f, g, h, i) showed two signals at 3.7–4.4 ppm as two doublets due to the non equivalent geminal protons assigned for S-CH_2 which is good evidence for obtaining the products. The proton of S-CH-N group assigned as C_{15} in thiazolidinone ring appears around (6) ppm. In compound (4 h) (Fig. 1), the disappearance of CH=N signals at (9.2) ppm, appeared two doublet signals at δ (4.1 and 4.3) ppm for two protons of the CH_2 group and a singlet signal at (5.1 ppm) for benzylic protons. A singlet signal at δ (6.1) ppm which belong to CH group assigned as C_{15}, and aromatic protons were observed at δ (6.9-7.5) ppm). The ^{13}C-DEPT-135 spectrum of compounds (4 h) (Fig. 2) showed the disappearance of nine non-protonated carbons (C_1, C_4, C_6, C_9, C_{11}, C_{12}, C_{13}, C_{16}, and C_{17}) which appeared in the normal ^{13}C-NMR also showed two downward signals at δ (36.92 and 65.38) ppm belongs to -CH_2- and -O-CH_2- group, and also the upward signal at

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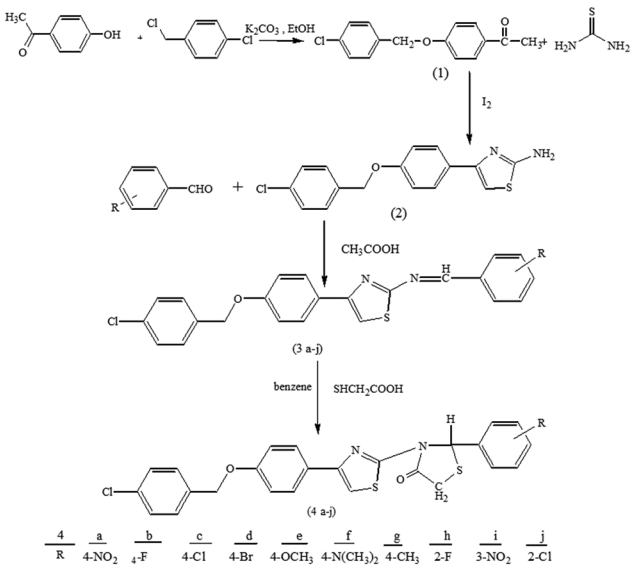
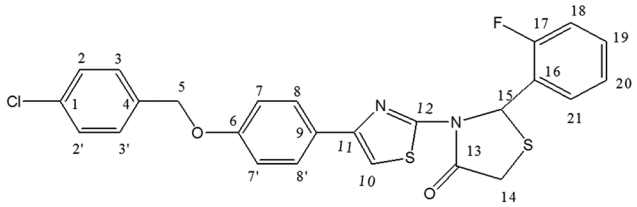


Scheme 1. The preparation of 4-thiazolidinone compounds.

δ (54.49) for mono-protonated carbon atom of -CH- group of thiazolidin-4-one. The other eight upward signals are attributed to mono-protonated carbons of three benzene rings.



(4h)

E. Screening of the synthesized thiazolidin-4-one compounds for their antibacterial activity against two strains of bacteria

The antibacterial activities for synthesized thiazolidinone derivatives were carried out using disc agar diffusion method, by measuring the zone of inhibition in mm. The synthesized thiazolidinone compounds were tested against

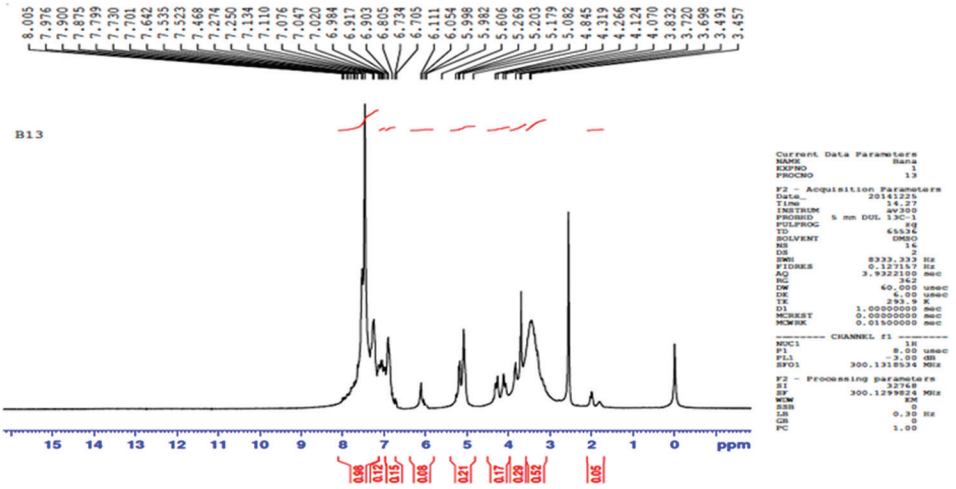


Fig. 1. H-nuclear magnetic resonance spectrum of compound (4 h).

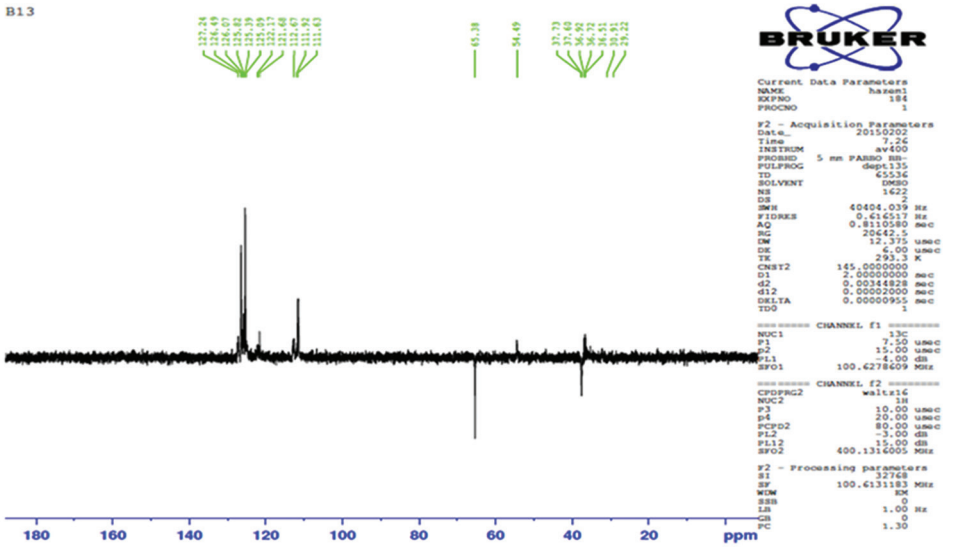


Fig. 2. 13C-DEPT-135-nuclear magnetic resonance spectrum of compound (4 h).

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the *Staphylococcus aureus* (Gram-positive) bacteria and *Escherichia coli* (Gram-negative) bacteria (Table III).

According to the reported procedure (El-masry, *et al.*, 2000) highly active ++++ (inhibition zone >34 mm; active +++ (inhibition zone 25–34 mm); moderately active ++ (inhibition zone 19–25 mm); slightly active + (12–19 mm); and inactive – (inhibition zone <12 mm).

IV. Conclusions

1. It was concluded that the cyclization reaction needs more time to give the reaction product than other reactions.
2. The electron withdrawing group on benzaldehydes leads to the formation of imines and thiazolidin-4-ones in higher yields than electron donating group.
3. The prepared thiazolidinone derivatives are biological active against both types of bacteria *S. aureus* and *E. coli*. The results of biological activity for synthesized compounds were showed a good effect against *S. aureus* (Gram-positive) and *E. coli* (Gram-negative).

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