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Synthesis and Identification of New Azolidine-4-one Derived from Creatinine and Study their Anticancer and Antioxidant Effects

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Abstract

Creatinine and Schiff`s bases are well known for their diverse range of biological activities and are thought to be emerging and useful therapeutic targets for the treatment of several diseases. The present work was aimed at the synthesis of new imidazolidine-4-one, thiazolidine-4-one, and oxazolidine-4-one derivatives derived from creatinine and to illustrate their influence on a colon cancer cell line and assess their antioxidant activity. Creatinine was reacted with α-chloroethyl acetate to produce 2-ethyl acetate creatinine **1**. Then, the reaction of compound **1** with *n*-propyl bromide afforded *N*-propyl-2-ethylacetate creatinine **2**. Compound **2** was then reacted with hydrazine hydrate to give hydrazide derivative **3**. Schiff bases **4-6** were synthesized *via* the reaction of compound **3** with aromatic aldehydes (benzaldehyde and *p*-hydroxybenzaldehyde) and a ketone (*p*-amino acetophenone) in the presence of glacial acetic acid as a catalyst. Finally, Schiff bases **4-6** were treated with 2-aminoacetic acid to synthesize imidazolidine-4-one derivatives **7-9**, with 2-thioglycolic acid to prepare thiazolidine-4-one derivatives **10-12**, and with glycolic acid to synthesize oxazolidine-4-one derivatives **13-15**. The newly synthesized compounds were identified using FT-IR and ^{1}H NMR spectroscopy. In addition, the antioxidant and anticancer activities of some of the synthesized compounds were evaluated *in vitro* and showed good results.

Keywords: Schiff bases, Imidazolidine-4-one, Thiazolidine-4-one, Oxazolidine-4-one, Antioxidant activity, Anticancer activity.

تحضير وتشخيص مشتقات جديدة من ازوليدين-4-اون المشتقة من الكرياتينين ودراسة مضادات السرطان و مضادات الاكسدة لها

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الخلاصة

الكريانين وقواعد شيف معروفة جيدا بفعاليتها البيولوجية ويعتقد انها اهداف علاجية ناشئة و مفيدة لعلاج العديد من الامراض . الهدف من هذا البحث هو تحضير مشتقات جديدة من ايميدازوليدين-4-اون, ثايازوليدين-4-اون و اوكسازوليدين-4-اون المشتقة من الكرياتينين. و لتوضيح تاثيرها على خط خلايا سرطان القولون وتقييم نشاطها المضاد للأكسدة . تم تحضير 2-اثيل خلات كرياتينين **1** من تفاعل الكرياتينين مع اثيل اسيتات

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الكلور. بعد ها تم تحضير المركب N–بروبيل 2–اثيل خلات كرياتينين من تفاعل المركب **1** مع بروميد البروبيل . بعدها المركب **2** تمت مفاعلته مع الهيدرازين المائي للحصول على مشتق الهيدرازايد **3**. تم تحضير قواعد شيف **4–6** من تفاعل المركب **3** مع الالديهايدات الاروماتية (بنزلديهايد، بارا–هيدروكسي بنزالديهايد) و كيتون (بارا –امينو اسيتوفينون) وبوجود بضع قطرات من حامض الخليك الثلجي كامل مساعد. في النهاية قواعد شيف **4–6** تم مفاعلتها مع 2–امينو حامض الخليك لتحضير مشتقات ايميدازوليدين–4–اون **7–9** مع حامض الثايوكلايكولك للحصول على مشتقات الثايازوليدين–4–اون **10–12** و مع حامض الكلايكولك لتحضير مشتقات اوكسازوليدين–4–اون **13–15** تم تشخيص المركبات الجديدة المحضرة من خلال التحليل الطيفي بالأشعة تحت الحمراء والرنين النووي المغناطيسي لذرة الهيدروجين. بالإضافة الى ذلك، تم تقييم الفعالية المضادة للأكسدة والمضادة للسرطان في المختبر لبعض المركبات المحضرة حيث أظهرت نتائج جيدة.

1. Introduction

Hugo Schiff described the first synthesis of Schiff`s bases in the nineteenth century [1]. Schiff`s base compounds are an important and well-studied class due to their wide range of biological applications, simplicity of synthesis, and chelating properties [2]. Imidazolidin-4-one is a five-ring heterocyclic molecule that contains nitrogen and carbon atoms and a carbonyl group. The cyclic addition of Schiff`s base compounds to alanine yields these imidazolidin-4-one compounds [3]. In the biological and pharmacological fields, these compounds are extremely useful [4]. Thiazolidine-4-one has taken a special place in the field of medical chemistry because of its wide use in biological activities [5]. Thiazolidinones-4-one are produced by cyclizing acyclic compounds or by interconvertibly substituting appropriately substituted thiazolididine derivatives [6]. The biological activities of thiazolidine-4-one include anti-diabetic effects, antioxidant, antimicrobial, anticonvulsant, antitumor, antimalarial, and anti-inflammatory effects [7-9]. 4-Oxo-oxazolidines are a type of five-membered ring heterocyclic molecules that contain two heteroatoms, oxygen at position 1 and nitrogen at position 3, as well as a carbonyl group at position 4 in the ring. The reaction of glycolic acid with imine has been used to produce oxazolidine-4-one. These compounds have various biological applications [10]. The aim of this research was to synthesize new imidazolidine-4-one, thiazolidine-4-one, and oxazolidine-4-one derivatives from creatinine, explain how they affect colon cancer cell lines, and evaluate their antioxidant activity.

2. Experimental part

2.1. Materials and instruments

Sigma-Aldrich and Fluka companies supplied all solvents and starting materials for the synthesized compounds, which were used without further purification. The synthesized compounds were measured using a Gallen Kamp capillary melting point instrument that was uncorrected. FT-IR measurements were done using a Shimadzu FTIR-8400S with a potassium bromide disc, while ^{1}H NMR spectra were recorded at 400 MHz on a Bruker spectrophotometer type ultra-shield with TMS as an internal standard. TLC was used to monitor the reactions (ethyl acetate and petroleum ether as an eluent), and visualize them with iodine.

2.2. Methods of the synthesis of compounds

*Synthesis of 2-ethyl acetate creatinine **(1)***

This compound was synthesized using a modified procedure from the literature [11]. In a round-bottomed flask, creatinine (1.13 g, 10 mmol,), α-chloroethyl acetate (1 mL, 10 mmol,), and potassium carbonate (2.07 g, 15 mmol) in 1,4-dioxane (20 mL) were refluxed for 24 hours. The reaction mixture was then cooled to room temperature, and the solid crude material was filtered and recrystallized from ethanol. The physical properties of the synthesized compound **1** are shown in Table 1.

Synthesis of N-propyl-2-ethyl acetate creatinine ***(2)***

A mixture of compound **1** (1.99 g, 10 mmol), *n*-propyl bromide (1 mL, 6 mmol) and potassium carbonate (2.07 g, 15 mmol) in absolute 1,4-dioxane (20 mL) was refluxed for 24 hours. After cooling the reaction mixture, the solid crude material was filtered and recrystallized from ethanol [12]. The physical properties of synthesized compound **2** are shown in Table 1.

Synthesis of hydrazide derivative ***3***

A solution of compound **2** (10 mmol) in ethanol absolute (10 mL) was added to hydrazine hydrate (1.5 mL, 30 mmol, 99%). After that, the reaction mixture was refluxed for 6 hours. The solvent was then evaporated, and the precipitate was washed with water before recrystallization from ethanol [13]. The physical properties of compound **3** are listed in Table 1.

Synthesis of Schiff`s bases ***4-6***

A solution of benzaldehyde, *p*-hydroxybenzaldehyde or *p*-aminoacetophenone (5 mmol) and hydrazide derivative **3** (5 mmol) was dissolved in ethanol absolute (20 mL), and a few drops of glacial acetic acid were added. The reaction mixture was then refluxed for 6 hours before cooling to room temperature, and the solid crude material was filtered and recrystallized from ethanol [14]. The physical properties of the title compounds **4**-**6** are listed in Table 1.

Synthesis of imidazolidine-4-one derivatives ***7-9***

A mixture of Schiff`s bases **4**-**6** (1 mmol) and 2-aminoacetic acid (75 mg, 1 mmol) was dissolved in dry 1,4-dioxane (10 mL). The reaction mixture was then refluxed for 14-16 hours. The solid crude material was filtered and recrystallized from ethanol [15]. The physical properties of the prepared compounds **4**-**6** are listed in Table 1.

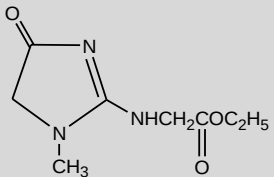
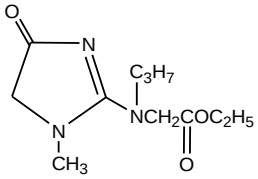
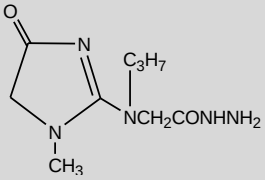
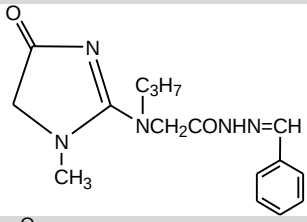
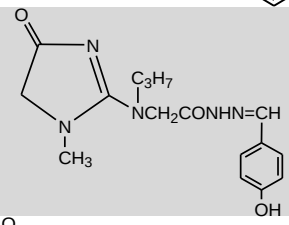
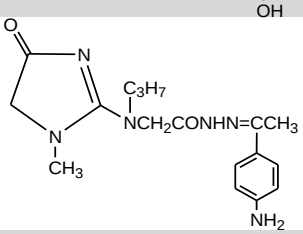
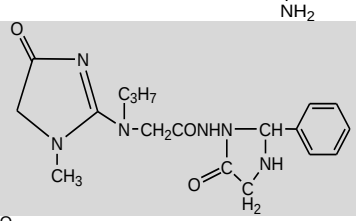
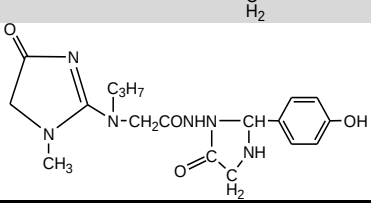
Synthesis of thiazolidine-4-one derivatives ***10-12***

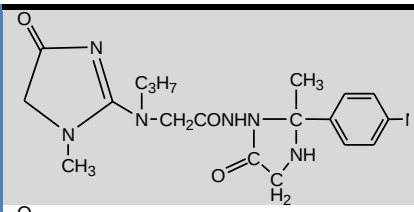
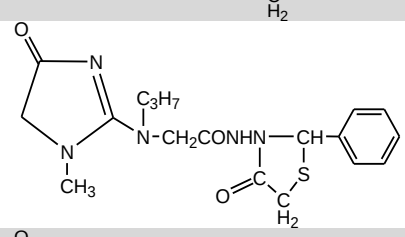
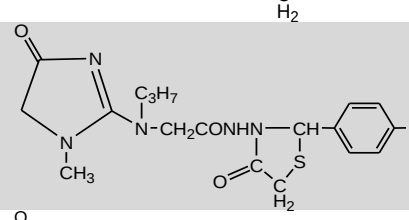
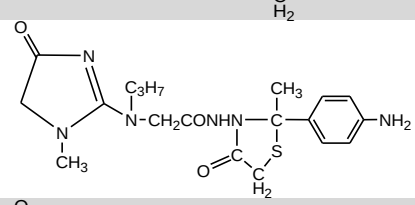
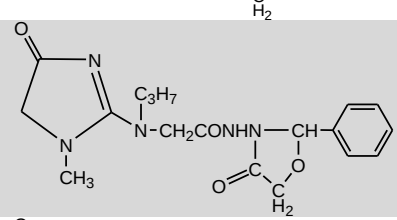
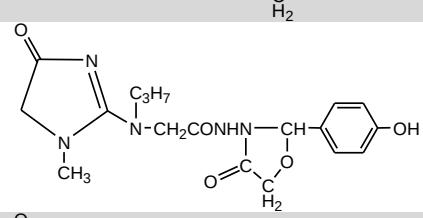
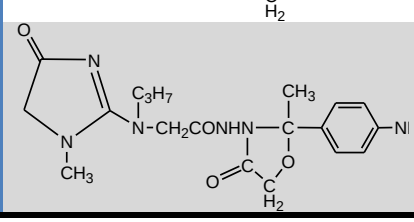
A mixture of Schiff`s bases **4**-**6** (2 mmol), 2-mercaptoacetic acid (184 □L, 2 mmol), and anhydrous zinc chloride (210 mg, 1.6 mmol) in dry 1,4-dioxane (10 mL). The reaction mixture was then refluxed for 8-10 hours. The mixture was poured into crushed ice, and the solid crude material was filtered and recrystallized from ethanol [16]. The physical properties of the prepared compounds **10**-**12** are listed in Table 1.

Synthesis of oxazolidine-4-one derivatives ***13-15***

A mixture of Schiff`s bases **4**-**6** (2 mmol) and 2-hydroxyacetic acid (152 □L, 2 mmol) was dissolved in dry 1,4-dioxane (10 mL). Anhydrous zinc chloride (210 mg, 1.6 mmol) was then added. The reaction mixture was then refluxed for 7-9 hours before cooling to room temperature. The solid crude material was filtered and recrystallized from ethanol [17]. The physical properties of the title compounds **13**-**15** are listed in Table 1.

Table 1: Physical properties of compounds 1-15

Compound number	Compound structure	Molecular formula	M.wt (g.mol^{-1})	Yield (%)	m.p.	Color
1		$C_8H_{13}N_3O_3$	199.20	91	209-210	Yellow
2		$C_{11}H_{19}N_3O_3$	241.28	88	223-224	Yellow
3		$C_9H_{17}N_5O_2$	227.26	85	212-213	White
4		$C_{16}H_{21}N_5O_2$	315.37	80	75-77	Deep yellow
5		$C_{16}H_{21}N_5O_2$	331.37	73	175-177	Yellow
6		$C_{17}H_{24}N_6O_2$	344.41	88	95-97	Red
7		$C_{18}H_{24}N_6O_3$	372.42	71	138-140	Yellow
8		$C_{18}H_{24}N_6O_4$	388.42	85	195-197	Yellow

9		$C_{18}H_{25}N_7O_3$	387.44	90	110-112	Orange
10		$C_{18}H_{23}N_5O_3S$	389.47	75	205-207	Orange
11		$C_{18}H_{23}N_5O_4S$	405.47	83	188-190	Yellow
12		$C_{18}H_{24}N_6O_3S$	404.49	85	110-122	Deep orange
13		$C_{18}H_{23}N_5O_4$	373.41	77	78-80	Orange
14		$C_{18}H_{23}N_5O_5$	389.41	80	138-140	Yellow
15		$C_{18}H_{24}N_6O_4$	388.42	65	125-127	Red

Antioxidant capacity

The α,α-diphenyl-β-picrylhydrazyl (DPPH) method is commonly used because its free radicals are stable at room temperature as well. It is a rapid way to assay antioxidant compounds. The antioxidant activity of the synthesized compounds 5, 8 and 11 was tested in ethanol (1 mL) at different concentrations (25, 50, and 100 ppm). Following this, a DPPH ethanol solution (1 mL) was added to each concentration. The mixture was incubated in the dark for 30 minutes, and UV-VIS spectroscopy was used to calculate compound absorption versus standard vitamin C at 517 nm [18].

Anticancer activity

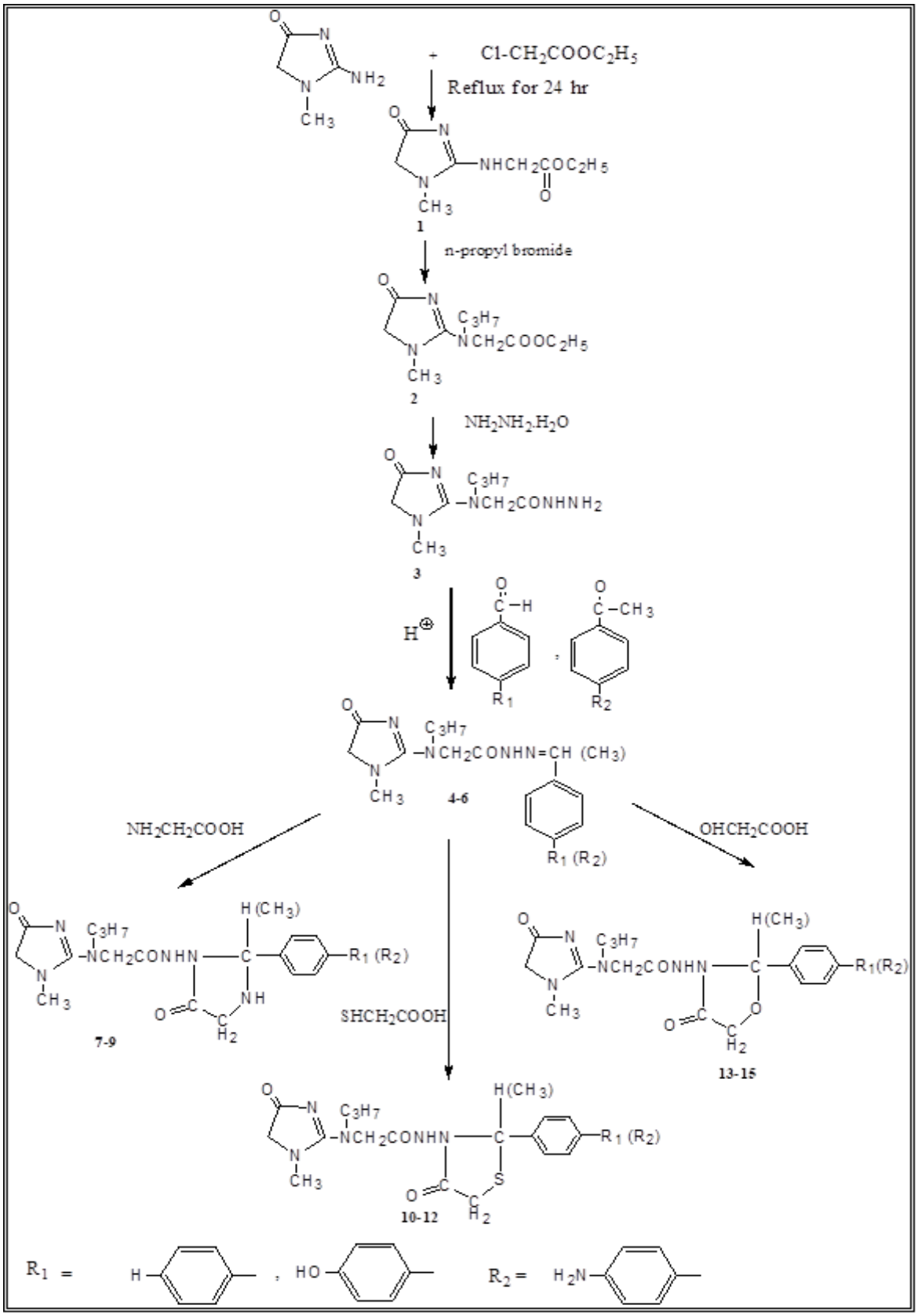
Using an MTT assay, the cytotoxic activity of compound **7** on the tumor cell line $CaCO_2$ was assessed compared with the normal cell line WRL-68. The cells were grown in 96-well

microplates, each with a final capacity of 200 μL. The microplate was then incubated for 24 hours at 37°C with 5% CO_2. After that, various concentrations of compound **7** were administered to each cell, and the cells were incubated for 24 hours at 37°C with 5% CO_2. Finally, MTT solution (10 μL) was then added, and the absorbance was measured at 575 nm using an ELISA reader [19].

3. Results and discussion

3.1. Chemistry

Scheme 1 illustrates the synthetic route of all the prepared compounds **1-15**. Creatinine was reacted with chloromethyl acetate in the presence of potassium carbonate as a base to afford the corresponding ester **1** in 91% yield. *N*-Propyl-2-ethylacetate creatinine 2 was obtained in a very good yield (88%) by the reaction of compound **1** with *n*-propyl bromide. The FT-IR spectrum of compound **1** showed a new band at 1745 cm^{-1} that is related to the C=O ester group. Another band at 3278 cm^{-1} belongs to the NH, and the NH_2 band disappeared (Table 2). The FT-IR spectrum of compound **2** revealed the disappearance of the NH band, while compound **3** showed the appearance of the C=O band of hydrazide at 1690 cm^{-1}, the NH band at 3284 cm^{-1}, and the NH_2 band at (3415 asymmetric and 3367 symmetric); these bands and others are shown in Table 2.



Scheme 1: Synthetic rote of the prepared compounds **1-15**

Table 2: FT-IR spectral data (υ, cm^{-1}) of the synthesized compounds **1-3**

Compound number	C=N C-N	C-H Aliphatic	C=O Cyclic amide C=O Hydrazide	NH	C=O Ester C-O-C Ester	NH_2
1	1639 1338	Asymmetric 2981 Asymmetric 2875	1668 -	3278	1745 1118	-
2	1639 1332	Asymmetric 2937 Asymmetric 2870	1670 -	-	1740 1116	-
3	1643 1338	Asymmetric 2941 Asymmetric 2808	1720 1690	3284	-	Asymmetric 3415 Symmetric 3367

The reaction of hydrazide **3** with aromatic aldehydes and ketone gave the corresponding Schiff bases **4-6** in 73-88% yields. As indicated in Table 3, the FT-IR spectra of these compounds showed the presence of C=N bands at 1643-1650 cm^{-1}.

Table 3: FT-IR spectral data (υ, cm^{-1}) of the synthesized Schiff bases **4-6**

Compound number	C-H Aliphatic	C=O Cyclic amide C=O Amide	C=N C-N	C-H Aromatic	C=C Aromatic	C-H Aliphatic	N-H	Others
4	Asymmetric 2950 Symmetric 2891	1720 1699	1643 1325	3049	1573 1487	3164	3257	----
5	Asymmetric 2937 Symmetric 2883	1704 1685	1650 1338	3002	1579 1512	3100	3271	3400 (OH)
6	Asymmetric 2979 Symmetric 2935	1710 1699	1650 1332	3001	1573 1540	3186	3309	NH_2 Asymmetric 3431 Symmetric 3398

Schiff`s bases **4-6** were then treated with 2-aminoacetic acid [20], thioglycolic acid [21], and glycolic acid to produce imidazolidine-4-ones **7-9**, thiazolidine-4-ones **10-12**, and oxazolidine-4-ones **13-15**, respectively. Each product of 5-17 is likely to be a mixture of two enantiomers (Scheme 1). The FT-IR spectral data of these compounds showed the presence of a characteristic band that was caused by the C=O cyclic amide of the imidazolidine-4-one, thiazolidine-4-one, and oxazolidine-4-one rings. Additionally, the formation of C-S bands in thiazolidin-4-one derivatives **10-12**, as shown in Table 4

Table 4: FT-IR spectral data (υ, cm^{-1}) of the synthesized compounds **7-15**

Compound number	C-H Aliphatic	C=O Cyclic amide C=O Amide	C=N C-N	C-H Aromatic	C=C Aromatic	N-H	C-S	Others
7	Asymmetric 2968 Symmetric 2885	1710 1681	1641 1336	3050	1602 1556	3286	-	----
8	Asymmetric 2966 Symmetric 2937	1699 1679	1639 1336	3050	1558 1530	3284	-	3431 (OH)
9	Asymmetric 2968 Symmetric 2904	1720 1700	1639 1334	3050	1573 1502	3294	-	NH_2 Asymmetric 3425 Symmetric 3390
10	Asymmetric 2981 Symmetric 2883	1720 1699	1650 1338	3001	1575 1520	3250	649	-
11	Asymmetric 2977 Symmetric 2879	1720 1701	1650 1342	3050	1577 1514	3220	648	3413 (OH)
12	Asymmetric 2979 Symmetric 2879	1714 1699	1640 1319	3039	1577 1515	3336	648	NH_2 Asymmetric 3411 Symmetric 3373
13	Asymmetric 2941 Symmetric 2879	1701 1680	1640 1334	3010	1577 1512	3236	-	-
14	Asymmetric 2941 Symmetric 2881	1710 1699	1640 1338	3010	1604 1579	3259	-	3342 (O-H)
15	Asymmetric 2906 Symmetric 2827	1718 1701	1645 1363	3022	1595 1544	3200	-	NH_2 Asymmetric 3334 Symmetric 3321

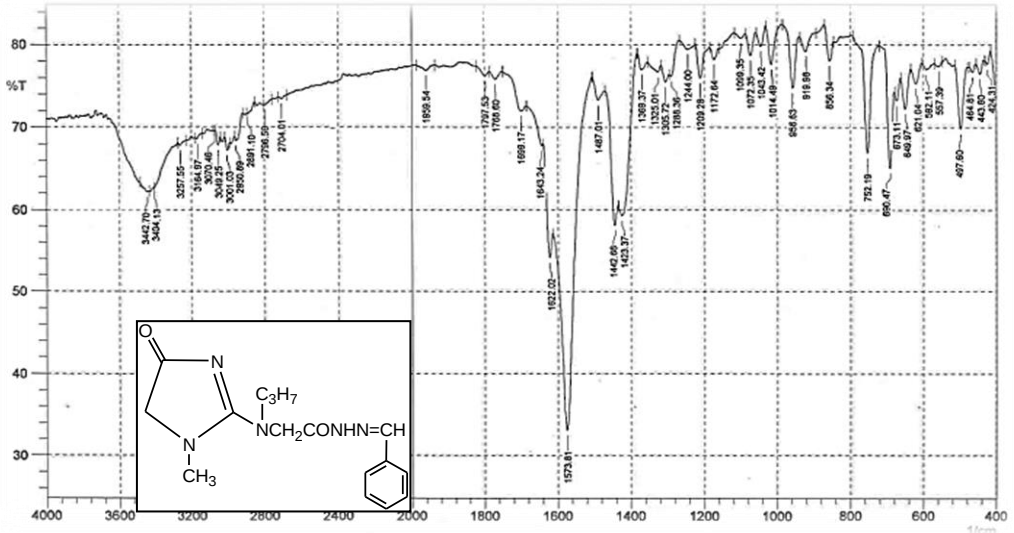


Figure 1: FT-IR spectrum of compound **4**

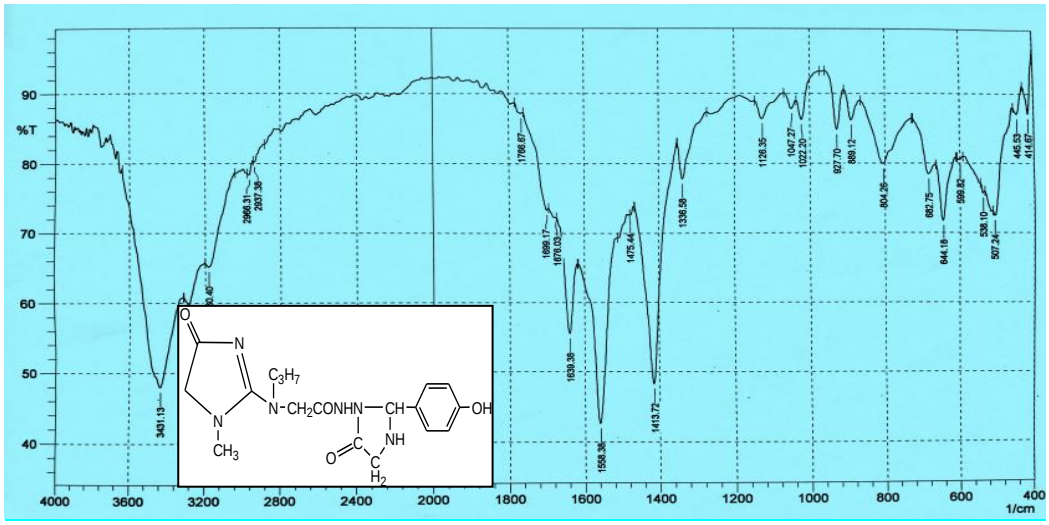


Figure 2: FT-IR spectrum of compound **8**

-

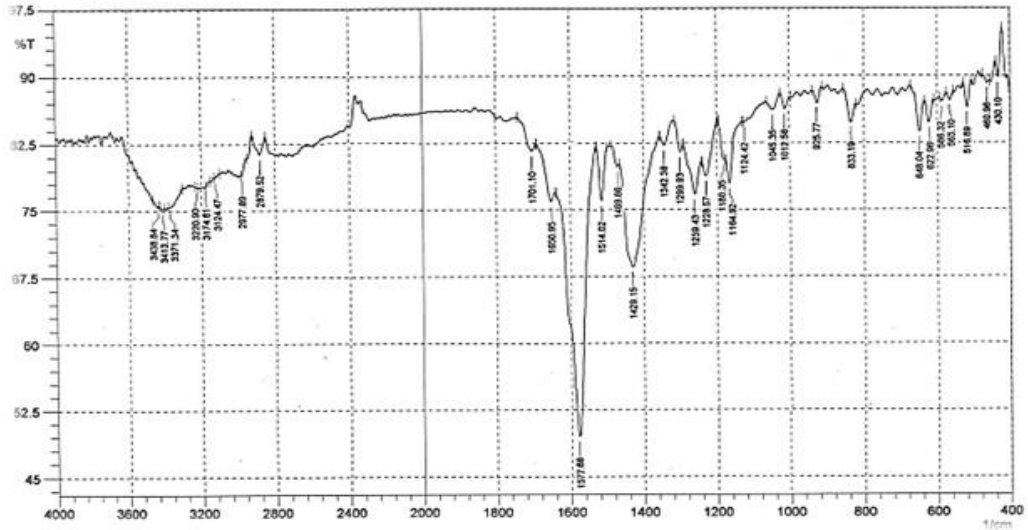


Figure 3: FT-IR spectrum of compound **11**

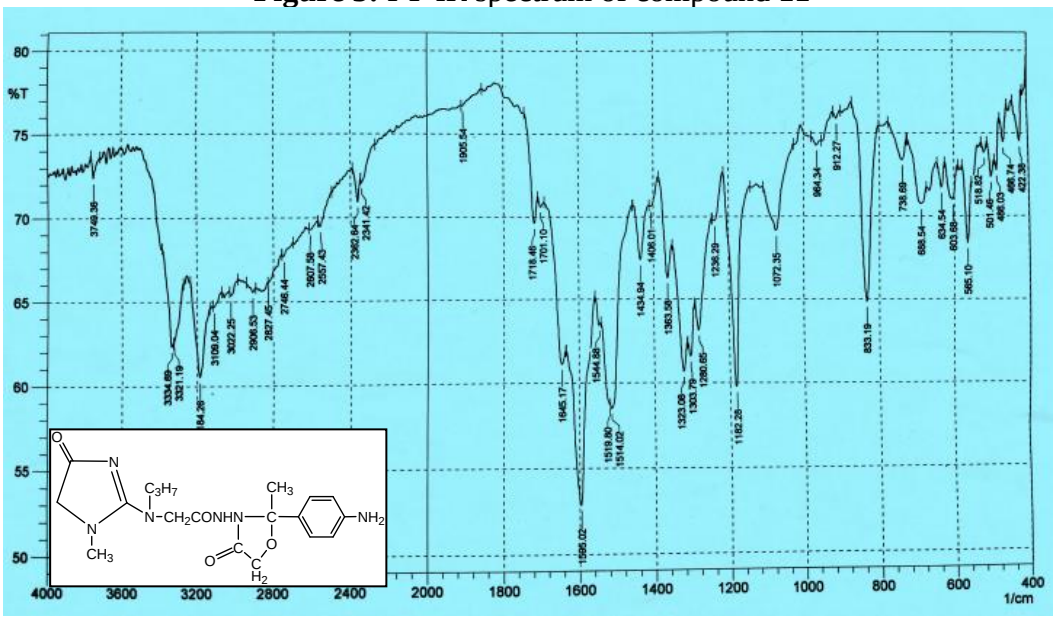
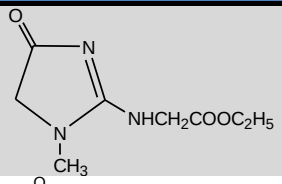
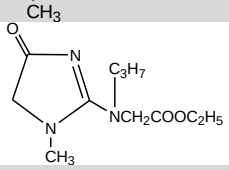
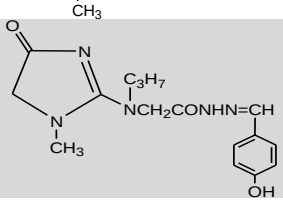
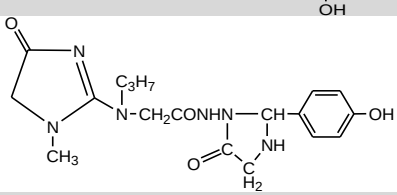
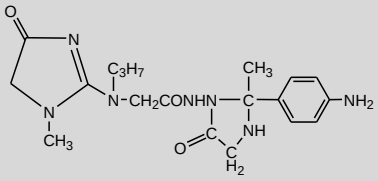
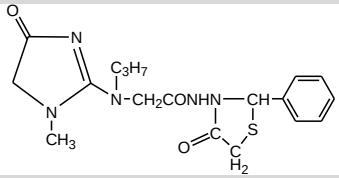
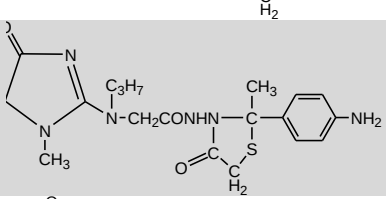
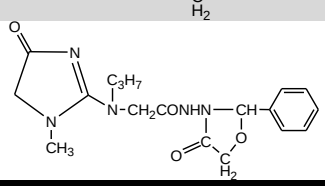


Figure 4: FT-IR spectrum of compound **15**

The ^{1}H NMR spectra of compounds (1, 3, 5, 8, 9, 10, 12, and 13) are listed in Table 5.

Table 5: The ^{1}H NMR of compounds **1**, **3**, **5**, **8**, **9**, **10**, **12**, and **13**

Compound number	Compound structure	^{1}H NMR spectral data (□□□ppm)
1		**1.7 (3H, CH_3), 2.9 (3H, CH_3), 3.3 (2H, CH_2), 3.4 (2H, CH_2), 3.6 (2H, CH_2), 7.5 (1H,NH)**
3		**1.2 (3H, CH_3), 1.6 (3H, CH_3), 2.9 (3H, CH_3), 3.0 (2H, CH_2), 3.3 (2H, CH2), 3.4 (2H, CH_2), 3.5 (2H, CH_2), 3.6 (2H, CH_2), 3.7 (2H, CH_2)**
5		**1.1 (3H, CH_3), 1.2 (3H, CH_3), 2.5 (2H, CH_2), 3.4 (2H, CH_2), 3.5 (2H, CH_2), 4.0 (2H, CH_2), 6.9-7.7 (5H, Ar-H and iminic-H), 8.5 (1H, NH), 10.1 (1H, OH)**
8		**1.2 (3H, CH_3), 1.3 (3H, CH_3), 2.5 (2H, CH_2), 2.9 (1H, CH), 3.3 (2H, CH_2), 3.4 (2H, CH_2),), 3.5 (2H, CH_2), 3.8 (2H, CH_2), 4.2 (1H, NH), 6.8-7.8 (4H, Ar-H), 8.5 (1H, NH), 10.2 (1H, OH)**
9		**1.2 (3H, CH_3), 1.3 (3H, CH_3), 2.3 (3H, CH_3), 2.5 (2H, CH_2), 2.9 (2H, CH_2), 3.5 (2H, CH_2), 3.6 (2H, CH_2), 3.8 (2H, CH_2), 3.8 (2H, NH_2), 4.1 (1H, NH), 6.5-7.6 (4H, Ar-H), 8.1 (1H, NH)**
10		**1.2 (3H, CH_3), 1.7 (3H, CH_3), 2.7 (1H, CH_2), 3.2 (2H, CH_2), 3.3 (2H, CH_2), 3.5 (2H, CH_2), 3.6 (2H, CH_2), 6.5-7.9 (5H, Ar-H), 8.2 (1H, NH)**
12		**1.2 (3H, CH_3), 1.3 (3H, CH_3), 2.3 (3H, CH_3), 2.5 (2H, CH_2), 3.0 (2H, CH_2), 3.3 (2H, CH_2), 3.5 (2H, CH_2), 3.6 (2H, CH_2), 4.1(2H, NH_2), 6.5-7.7 (4H, Ar-H), 8.5 (1H, NH)**
13		**1.2 (3H, CH_3), 2.1 (3H, CH_3), 2.5 (2H, CH_2), 2.7 (1H, CH_2), 3.3 (2H, CH_2), 3.5 (2H, CH_2), 3.9 (2H, CH_2), 6.5-7.9 (5H, Ar-H), 8.7 (1H, NH)**

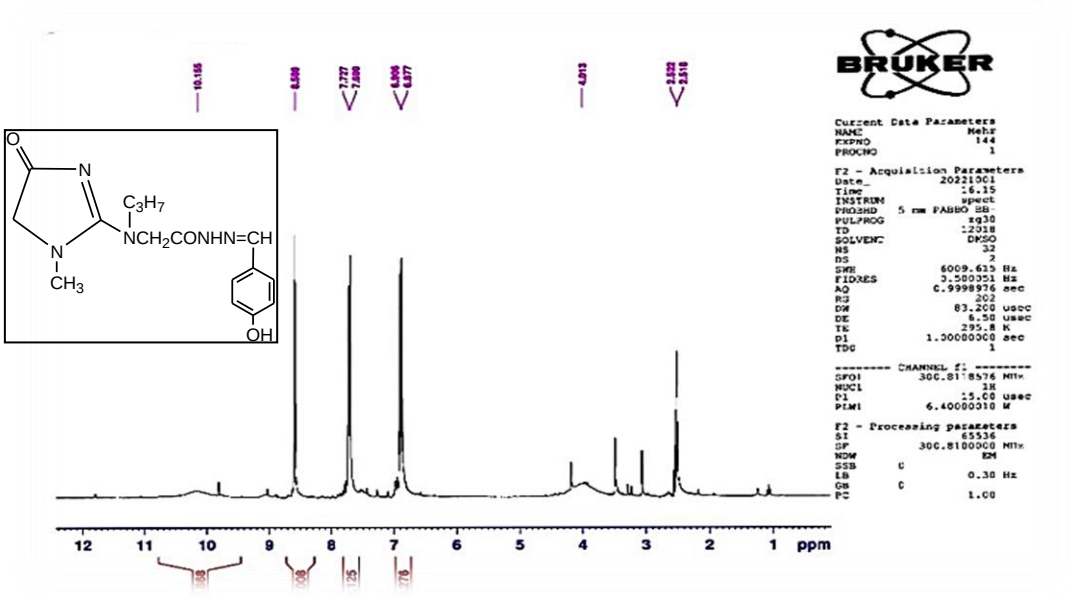


Figure 5: ^{1}H NMR spectrum of compound **5**

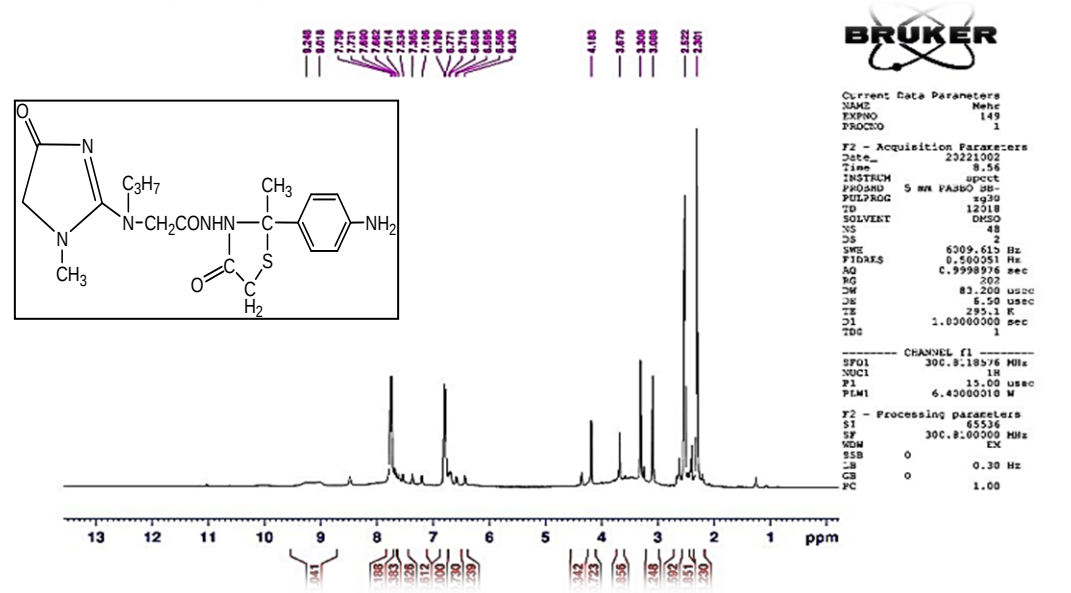


Figure 6: ^{1}H NMR spectrum of compound **12**

3.2. Antioxidant capacity

The antioxidant activity is calculated by determining the decrease in absorbance at different concentrations due to the elimination of DPPH. Some of the synthesized compounds exhibited dose-dependent DPPH scavenging activity. According to Table 6 and Figure 7, the DPPH scavenging of the evaluated compounds (5, 8, and 11) ranged from (0.014, 0.06, and 0.01) for compound 5 at different concentrations (25, 50, and 200 ppm, respectively). For compound 8, the scavenger capacities were 0.014, 0.038, and 0.093. Compounds **8** and **11** therefore exhibited DPPH scavenger activity; whereas compound **5** exhibited extremely low DPPH scavenger activity when compared to compounds **8** and **11**.

Table 6 : The scavenger activities of compounds **5**, **8**, **11**, and vitamin C using DPPH method

Compound concentration	25 ppm	50 ppm	100 ppm
5	0.014	0.06	0.01
8	0.014	0.038	0.052
11	0.014	0.038	0.093
Vitamin C	0.45	0.67	0.8

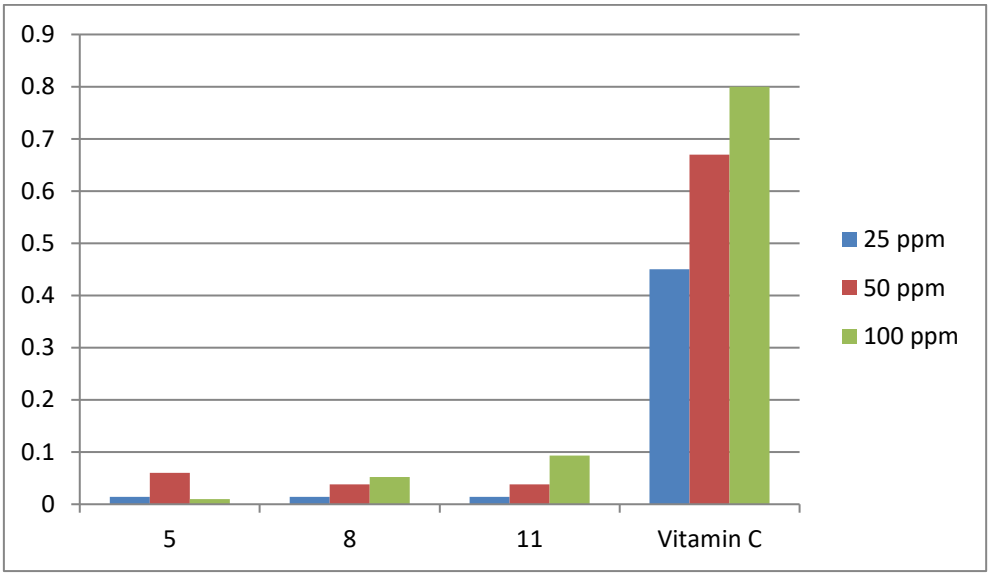


Figure 7 : DPPH scavenger activities of compounds **5**, **8**, and **11** compared with vitamin C

Cytotoxic effect of compound 7 on Caco-2 cancer cell line using MTT assay

The cytotoxic effect of compound **7** on the cancer cell line (Caco-2) in comparison to the normal cell line (WRL-68) was evaluated using the MTT assay [22]. A decrease in cell viability was seen in a dose-dependent pattern because of the cytotoxic effect of compound **7** on Caco-2 cells at concentrations ranging from 25 to 400 µg/mL (Table 7). The lowest Caco-2 cell viability was seen at 400 µg/mL (58.6±1.97), whereas the maximum Caco-2 cell viability was attained at 25 µg/mL (85.9±2.14), as shown in Figure 8.

Table 7: The cytotoxic effect of compound **7** on WRL68 and CaCo2 cell line

Concentration µg mL^{-1}	Cell viability (%) ± SD	
	WRL68	CaCo2
400	82.6± 2.3	**58.6± 1.97**
200	90.7±1.57	**65.895±1.7**
100	90.08± 1.04	**71.6± 0.41**
50	93.8± 1.10	**83.835±6.21**
25	94.63±0.48	**85.9± 2.14**

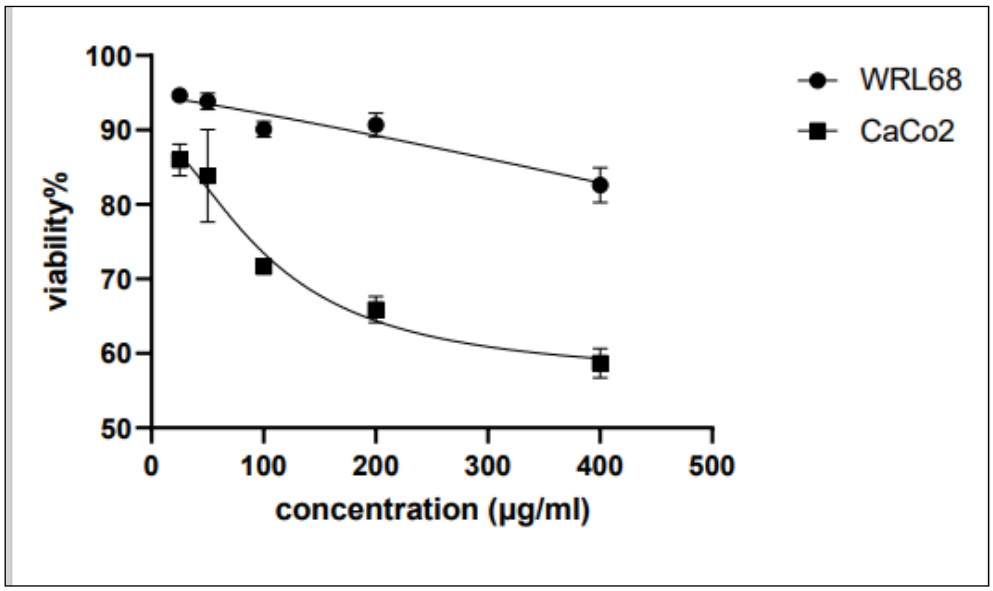


Figure 8: Cytotoxic effect of compound **7** on Caco-2 and WRL-68 cell

4. Conclusion

In the present study, new imidazolidine-4-one and thiazolidine-4-one derivatives have been synthesized from Schiff bases and hydrazide derivatives. These new compounds were identified based on spectral data (FT-IR and ^{1}H NMR spectroscopy). In addition, the synthesized compounds have good anticancer activity (*in vitro*) and an antioxidant effect.

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