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وحماية المستهلك

SYNTHESIS, CHARACTERIZATION AND STUDY THE BIOLOGICAL ACTIVITIES OF NEW HETEOCYCLIC COMPOUNDS CONTAINIG CREATININE

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ABSTRACT

This work included the synthesis of new heterocyclic compounds containing creatinine moiety (A4-A9). These compounds were synthesized from reaction of Schiff bases (A2, A3) with glycine, thioglycolic acid, and glycolic acid to produce imidazolidine-4-one (A4, A5), thiazolidine-4-one A6, A7, and oxazolidine-4-one (A8, A9) respectively. FTIR and ^{1}HNMR were used to identify these compounds. *In vitro* experiments, the antimicrobial properties of compounds (A1, A2, and A4) were evaluated and showed good results.

Keywords: Schiff bases, imidazolidine-4-one, thiazolidine-4-one, oxazolidine-4-one, anti-microbial activity.

تحضير، تشخيص و دراسة الفعالية البيولوجية لمركبات حلقية غير متجانسة جديدة حاوية على الكرياتينين

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الخلاصة

تضمن هذا العمل تحضير مركبات حلقية غير متجانسة جديدة حاوية على جزء الكرياتينين (A4-A9). تم تحضير هذه المركبات من مفاعلة قواعد شيف (A3, A2) مع الكلايسين ،حامض ثايوكلايكولك وحامض الكلايكولك للحصول على ايميدازوليدين-٤-اون (A5, A4)، ثايازوليدين-٤-اون (A7, A6) و اوكسازوليدين-٤-اون (A9, A8)على التوالي. تم استخدام مطيافية FTIR و ^{1}HNMR لتشخيص هذه المركبات. في تجارب مختبرية، تم تقييم الخصائص المضادة للبكتريا للمركبات (A2, A1, A4) واظهرت نتائج جيدة.

الكلمات المفتاحية : قواعد شيف; ايميدازوليدين-٤-اون; ثايازوليدين-٤-اون; اوكسازوليدين-٤-اون; الفعالية المضادة للمايكروبات.

INTRODUCTION

Schiff base molecules containing (carbon-nitrogen) double bonds have attracted an abundance of interest because of their simplicity in synthesis and wide range of uses **(Yassen & Al-Azzawi, 2023; Gatea &Al-Tamimi, 2022)**. Schiff bases additionally have applications in a wide range of other fields, such as chemical analysis, anti-corrosion, ligands for metal complexes, and dyes **(Mahmood, 2021)**. However, Sulfur and nitrogen-containing heterocyclic molecules are essential in therapeutic chemistry applications **(Etivand *et al.*, 2019)**.

One of the heterocyclic compounds with a carbonyl group, nitrogen atoms, and carbon atoms in its structure is imidazolidine-4-one. These compounds have many uses in pharmacology and therapy (**Aftan *et al.*, 2021; Dalaf *et al.*, 2021)**.

Thiazolidin-4-one derivatives are a major class of heterocyclic compounds due to the possibility of medical uses, including antimicrobial, anticancer antifungal, cardiovascular effect s, antitubercular, and anticonvulsant activities **(Trotsko, 2021; Sachin, 2021)**.

Oxazolidinones are efficient bioactive molecules, versatile optical subordinates, and essential synthesis intermediates for natural and bioorganic pigments, and agricultural pesticides **(Abid & Abbass, 2017; Bhat *et al.*, 2011)**. The aim of this research is to synthesize new imidazolidine-4-one, thiazolidine-4-one, and oxazolidine-4-one derivatives from creatinine. In addition, the antimicrobial effects for some of them have been studied.

MATERIALS AND METHODS

Materials and instrumentation

Merck, Sigma/Aldrich, and CDH provided all of the chemicals and solvents that were used in this work. The Merck Company provided the thin layer chromatography and the spots were recognized by iodine vapors. The melting points were recorded using Gallen Kamp equipment. The Fourier transform infrared (FT-IR) spectra of the compounds in a KBr disc have been recorded using a Shimadzu FTIR-8400s Fourier transform infrared spectrophotometer. On a Bruker spectrophotometer (400 MHz), spectrum data for several of the produced substances were measured.

Synthesis of acid hydrazide A1 (Ismail & Al-Tamimi, 2020)

Creatinine derivative was prepared according to the literature procedure **(Ali *et al.*, 2022).** A 1.5 ml of hydrazine hydrate in absolute ethanol (0.03 mol, 99 %), and creatinine derivative (0.01 mol, 2.89 g) were mixed followed by reflux for 6 h, then the precipitate was washed with water. After evaporation of the solvent a recrystallization with ethanol was done. The physical properties of compound A1 is listed in Table (1).

Synthesis of Schiff bases A2, A3 (Ayyash, 2020)

Compound A1 and benzaldehyde/ *p*-hydroxybenzaldehyde/ (0.005 mole) were dissolved in 20 mL of ethanol absolute. Glacial acetic acid was introduced in very small amounts. After that, the reaction mixture was refluxed for six hours. The reaction was then cooled; the formed precipitate after cooling was filtered and recrystallized by ethanol. The physical properties of compounds A2 and A3 are listed in Table (1).

Synthesis of Imidazolidine-4-one derivatives A4, A5 (Muhiebes & Al-Tamimi, 2021)

In a round-bottomed flask, 10 ml of 1,4-dioxane, (0.001 mol, 0.075 g) of glycine, and 0.001 mol of Schiff bases A2/A3 were added. After that, the reaction mixture was heated at 80 ^{0}C for (14–16) hours. The precipitate was then filtered and recrystallized using ethanol. The physical properties of compounds A4 and A5 are listed in Table (1).

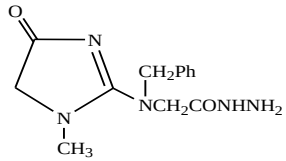
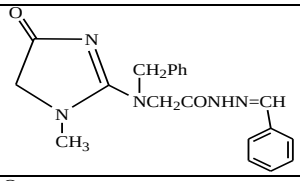
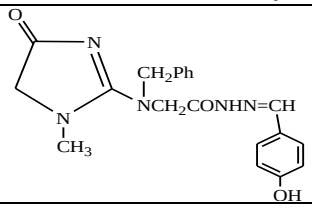
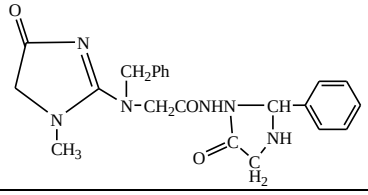
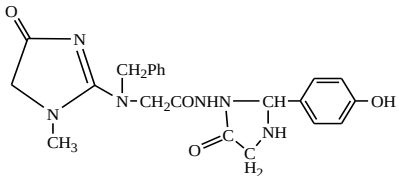
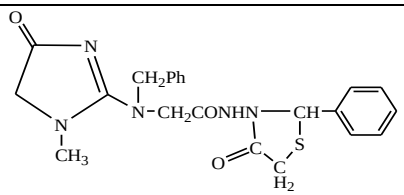
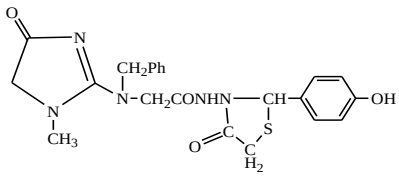
Synthesis of thiazolidine-4-one derivatives A6, A7 (Gupta *et al.*, 2016)

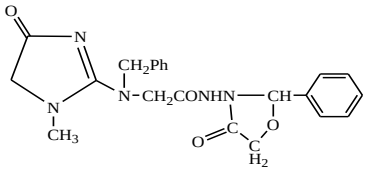
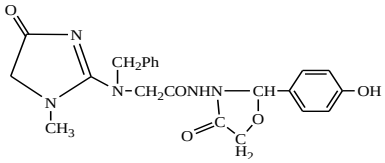
Schiff bases A2/A3 (0.002 mol), thioglycolic acid (0.002 mol, 0.184 ml), and anhydrous zinc chloride (0.0016 mol, 0.21 g) were dissolved in (10) ml of dry 1,4-dioxane. The mixture was heated at 80 ^{0}C for (8–10) hours. The precipitate that resulted from pouring the reaction liquid over crushed ice was filtered, dried, and then recrystallized from ethanol. The physical properties of compounds A6 and A7 are listed in Table (1).

Synthesis of oxazolidine-4-one derivatives A8, A9 (Vivek & Pandurangan, 2014)

As glycolic acid (0.002 mol, 0.152 ml) and Schiff bases A2/A3 (0.002 mol) had been thoroughly mixed in dry 1,4-dioxane (10 ml), then anhydrous zinc chloride (0.0016 mol, 0.21g) was added. After that, the mixture was heated at 80 ^{0}C for (7-9) hours. It took some time for the combination to cool to room temperature. From ethanol, the solid products were recrystallized which their physical properties are presented in Table (1).

Table (1): Physical properties of compounds A1-A9.

Compound No.	Compound structure	Molecular formula	M.wt	Yield %	M.P	Color
A1		$C_{13}H_{17}O_2N_5$	275.31	80	185-187	Pale Yellow
A2		$C_{20}H_{21}N_5O_2$	363.41	94	99-100	Yellow
A3		$C_{20}H_{21}N_5O_3$	379.41	75	190-192	Yellow
A4		$C_{22}H_{24}N_6O_3$	420.46	75	195-197	Yellow
A5		$C_{22}H_{24}N_6O_4$	436.46	80	200-202	Orange
A6		$C_{22}H_{23}N_5O_3S$	437.15	77	175-177	Orange
A7		$C_{22}H_{23}N_5O_4S$	453.51	85	199-200	Yellow

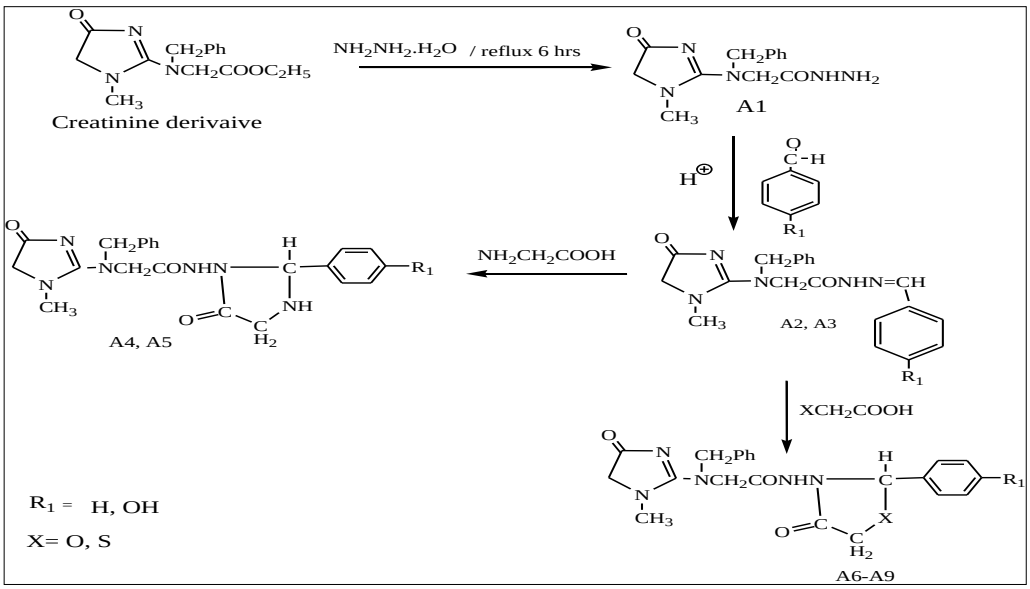
A8		$C_{22}H_{23}N_5O_4$	421.45	75	218-220	Red
A9		$C_{22}H_{23}N_5O_5$	437.45	73	205-207	Green

Biological evaluation (Khorsheed *et al.*, 2020)

Some of the synthesized compounds (A1, A2, A4, and A9) were examined for their antimicrobial effects using the agar diffusion method on two kinds of bacteria (*Staph. aureus* and *Escherichia coli*) and two types of fungi (*Candida albicans* and *Aspergillus flavus*). These sterile agar media were poured over Petri dishes, allowed to set, and then, by using the tidy triangular loop, microbe suspensions were applied to the surface. The synthesized compounds were applied serially using a micropipette and allowed to diffuse for an hour. These plates underwent a 24-hour incubation period at 37 °C. The zone of inhibition in the cup was studied and quantified in mm.

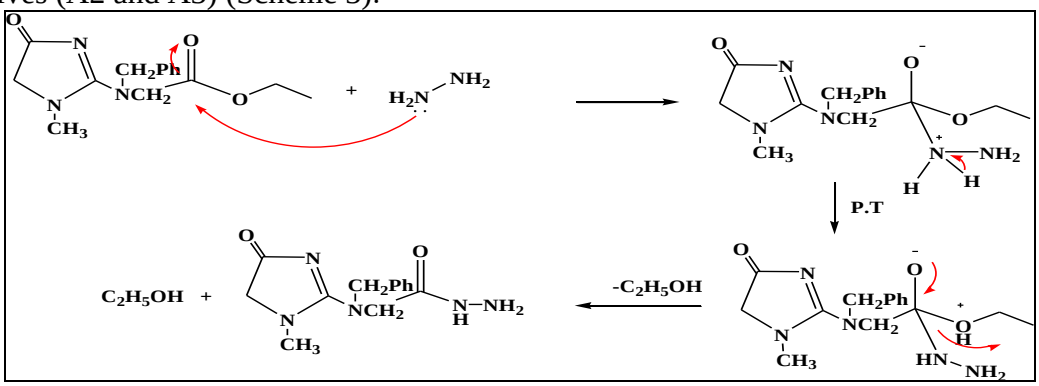
RESULTS AND DISCUSSION

Scheme (1) illustrates the synthetic routes of compounds A1-A9.

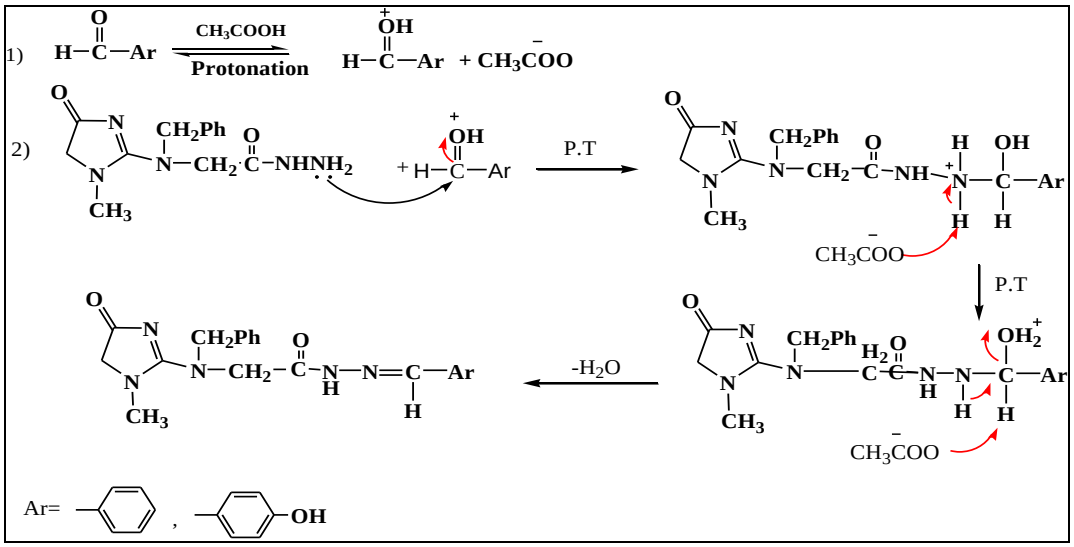


Scheme (1): Routs synthesis of compounds A1-A9.

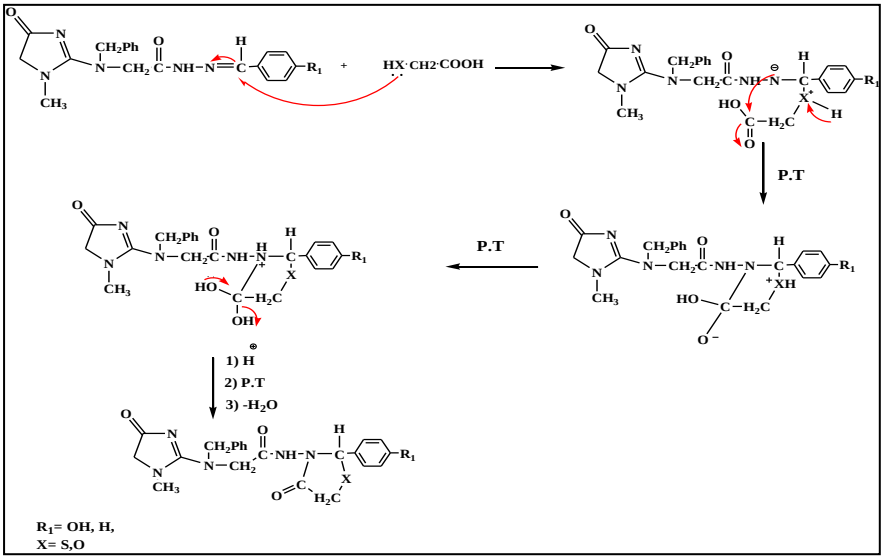
The derivative of creatinine was reacted with hydrazine hydrate to form acid hydrazide derivative A1(Scheme 2) which then reacted with aromatic aldehydes to form Schiff bases derivatives (A2 and A3) (Scheme 3).



Scheme (2): The mechanism for synthesis of hydrazide derivative A1.



Scheme (3): The chemical steps for the synthesis of Schiff bases A2 and A3 Then, the resulting Schiff bases were given a cyclization with glycine, thioglycolic acid, and glycolic acid to produce imidazolidine-4-one (A4, A5), thiazolidine-4-one (A6, A7), and oxazolidine-4-one (A8, A9) compounds respectively (Scheme 4).



Scheme (4): The mechanism of reaction for compounds A6-A9

The FITR of the compound revealed the appearance of the N-H band, NH_2 band, and (C=O) band of hydrazide. While, in Schiff bases the existence of C=N bands were revealed, as shown in Table (2) which includes these bands as well as additional bands.

Table (2): The FT-IR Spectral data of compounds A1-A3 cm^{-1}

Compound number	C-H υ aliphatic	C=O υ cyclic amide C=O amide	υC=N C-N υ	C-H υ aromatic	C=C υ aromatic	(N-H) υ	Others
A1	Asym 2983 sym 2812	1718 1668	1643 1334	3018	1575 1502	3257	(NH_2) Asym. 3419 Sym 3375
A2	Asym 2979 Sym 2820	1700 1680	1640 1340	3050	1571 1550	3274	------
A3	Asym 2979 Sym 2937	1720 1699	1640 1336	3050	1573 1514	3353	(O-H) 3427

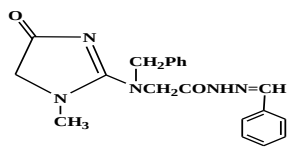
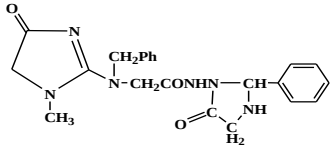
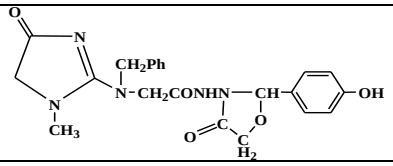
The FTIR data for the synthesized compounds (A4-A9) revealed the creation of C-S bands in thiazolidine-4-one as well as the presence of a distinctive band that was brought on by the C=O cyclic amide of the imidazolidine-4-one, thiazolidine-4-one, and oxazolidine-4-one rings. These bands are listed in Table (3) along with some others.

Table (3): The FT-IR Spectral data of the synthesized compounds A4-A9 in cm^{-1}.

Compound number	C-H υ aliphatic	C=O υ cyclic amide C=O amide	ring υC=N C-N υ	C-H υ aromatic	C=C υ aromatic	(N-H) υ	υ C-S υ C-O	Others
A4	Asym 2975 sym 2997	1710 1680	1637 1334	3050	1573 1502	3294	----- -----	----
A5	Asym 2968 Sym 2880	1699 1679	1639 1336	3033	1602 1556	3286	------ ------	(O-H) 3433 **υ**
A6	Asym 2948 Sym 2887	1710 1689	1643 1330	3050	1623 1575	3280	649 -----	---
A7	Asym 2941 Sym 2881	1710 1670	1641 1338	3002	1606 1575	3220	648 -------	(O-H) 3340 **υ**
A8	Asym 2937 Sym 2885	1710 1690	1647 1332	3050	1622 1573	3220	----- 1253	------
A9	Asym 2939 Sym 2850	1700 1679	1666 1336	3050	1606 1591	3253	----- 1228	**υ** (O-H) 3332

The ^{1}H-NMR spectra of compounds A2, A4, and A9 are listed in Table (4).

Table (4): The ^{1}H-NMR of compounds A2, A4, and A9

Compound number	Compound structure	^{1}H-NMR spectral data
A2		1.2 (s, 3H, N-$\underline{CH_3}$); 2.5 (t, 2H, $\underline{CH_2}$C=O); 3.3 (s, 2H, CH_3-N-$\underline{CH_2}$); 3.8 (t, 2H, $\underline{CH_2}$-Ph); 6.3 (s, 1H, N=$\underline{CH}$); (7.5-7.9) (m, 10 H aromatic); 8.7 (s, 1H,NH)
A4		1.2 (s, 3H, N-$\underline{CH_3}$); 3 (d, 1H, N-$\underline{CH}$-Ar); 3.3 (t, 2H ,$\underline{CH_2}$C=O); 3.5 (s, 2H, $\underline{CH_2}$-C=O of imidazolidine ring); 3.5 (s, 2H, CH_3-N-$\underline{CH_2}$); 3.9 (t, 2H, $\underline{CH_2}$-Ar); (7.4-8.1) (m, 10H aromatic); 8.6 (s, 1H, C-NH proton of imidazolidine ring); 9.2 (s, 1H, NH)
A9		1.1 (s, 3H, N-$\underline{CH_3}$); 2.5(s, 3H, Ar-C$\underline{CH_3}$); 3.2 (t, 2H, $\underline{CH_2}$C=O); 3.3 (s, 2H, $\underline{CH_2}$-C=O of oxadiazolidine ring); 3.5 (s, 2H, CH_3-N-$\underline{CH_2}$); 3.9 (t, 2H, $\underline{CH_2}$-Ph); (6.8-7.7) (m, 11H, aromatic); 8.5 (s, 1H, NH); 10.1 (s, 1H, OH)

Biological activity

The synthetic compounds (A1, A2, and A4) demonstrated different biological effects against the gram-positive and gram-negative bacteria *staphylococcus aureus* and *Escherichia coli* with amoxicillin as standard as well as the two types of fungi *Aspergillus flavus* and *Candida albicans* in comparison to the standard fluconazole drug. As seen in the results, compound A1 has the highest activity against *staphylococcus aureus*, *Escherichia coli*, and *Aspergillus flavus*, *Candida albicans* **(Hussein *et al.*, 2022).** While, compounds A2, and A4 showed moderate activity against *Staphylococcus aureu*s and inactive against *Escherichia coli* and fungi, as shown in Table (5).

Table (5): Antimicrobial activity of compounds A1, A2, and A4.

Compound Number	*Staphylococcus*	*Escherichia coli*	*C.albicans*	*Aspergillus flavus*
	Conc. (0.02 g/ml) Inhibition zone diameter (mm)	**Conc. (0.02 g/ml) Inhibition zone diameter (mm)**	**Conc. (0.02 g/ml) Inhibition zone diameter (mm)**	**Conc. (0.02 g/ml) Inhibition zone diameter (mm)**
A1	15	30	25	20
A2	11	-	-	-
A4	11	-	-	-
Amoxicillin	32	-	-	-
Fluconazole	-	-	25	27

CONCLUSIONS

In the present research, new hydrazide derivative A1 and Schiff bases (A2, A3) were used to synthesize new imidazolidine-4-one (A4, A5), thiazolidine-4-one derivatives (A6, A7), and oxazolidine-4-one compounds (A8, A9). The identification of these new compounds was based on spectrum data (FT-IR and 1H-NMR). Additionally, the antibacterial activities of several of the produced compounds A1, A2, and A4 were assessed. The results revealed that compound A1 has activity against *Escherichia coli* which the slandered Amoxicillin do not have, as well as an antifungal activity.

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