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RESEARCH ARTICLE

SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITY EVALUATION OF NEW PYRIDAZINES CONTAINING IMIDAZOLIDINE MOIETY

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A B S T R A C T

This paper contained the synthesis of some new derivatives of pyridazine from the reaction of pyridazine-3,6-diol (1) with chloroacetyl chloride in chloroform with presence of potassium carbonate as catalyst to obtain: 2,2'- [pyridazine-3,6-diylbis (oxy)]diacetyl chloride (2), then converted (2) to acid hydrazide by the reaction with hydrazine hydrate (85-90%) in absolute ethanol to yield : 2,2'-[pyridazine-3,6-diylbis(oxy)]diacetohydrazide (3), which reacted with 3-nitrobenzaldehyde in presence of absolute ethanol and drops of glacial acetic acid to give the corresponding Schiff base : *N* '-(3-nitrobenzylidene)-2-[6-(2-((*Z*)-2-(3-nitrobenzylidene) hydrazinyl)-2-oxoethoxy] pyridazine -3-yloxy)acetohydrazide (4)., Then the target compounds were prepared from the cyclization reaction of compound (4) with different amino acids namely (DL-alanine, DL-valine, and DL-aspartic acid), in THF to yield: 2,2'-(pyridazine-3,6-diylbis(oxy)) bis [N-(4-alkyl-2-(3-nitrophenyl)-5-oxoimidazolidine-1-yl)acetamide](5a,b,c). The synthesized compounds were elucidated by some spectroscopy methods IR,UV and ^{1}HNMR, besides the melting points. TLC was used to check the products. Their biological activities of prepared compounds (5a,b,c) were also studied against two types of bacteria (*Staphococcus aureus* , and *E.Coli*).

INTRODUCTION

Nitrogen-containing heterocyclic compounds are one of the most fruitful and extensively developing fields of heterocyclic chemistry. These compounds exhibit various kinds of biological activities. During the past decades increasing interest in the synthesis and biological activities of pyridazine derivatives has been observed [1–3]. Pyridazine compounds have been reported to possess varied biological activities such as antimicrobial [4], antihypertensive [5], anticancer [6], anti-inflammatory[7] and antifungal activities [8]. These facts have promoted us to synthesize some novel pyridazine derivatives. Recently, pyridazinone nucleus has been extensively studied in the search for new and selective medicinal agents as drugs acting on the cardiovascular system [9]. Furthermore, a number of thienopyridazines have been claimed to possess interesting biological and pharmacological activities such as, anticancer [10]., Pyridazines can also be used as novel therapeutic agents to target Alzheimer's disease and other neurodegenerative diseases like Parkinson [11]. Recent studies indicate pyridazine derivatives can be used in the treatment of dermatitis, prostate cancer, and dry eye disorders [12]. Moreover, pyridazines are pharmaceutically acceptable acid-addition salts that are used as an active component in cardio tonic compositions to increase cardiac contractility[13].

Imidazolidines, a saturated imidazole (tetrahydroimidazole), have been reported to have important biological activities including potential α-adrenergic receptor agonist[14], antimicrobial,antiparasitic [15,16], oral hypoglycaemic [17], antiarrhythmic, anticonvulsant [18,19], anti-inflammatory and analgesic[20-23].

The aim of this work is to synthesize and characterize new pyridazine derivative containing Imidazolidine cycle and to study its spectral and biological activities against some of micro- organisms.

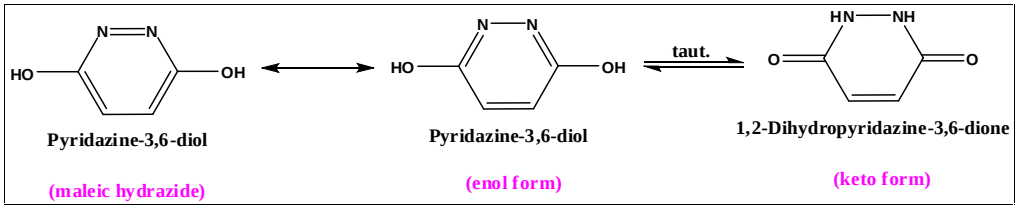
Experimental

Instruments

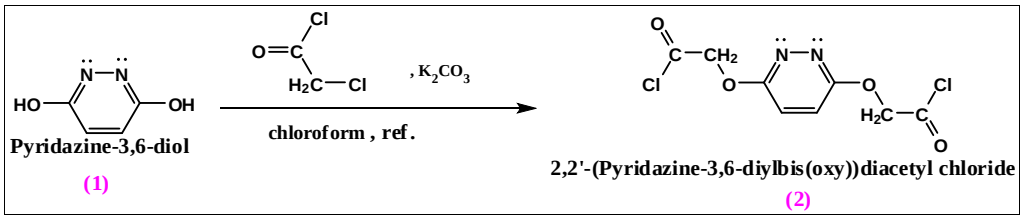
1- All melting points are uncorrected in degree centigrade and were determined on ***Gallenkamp*** electric melting point apparatus.
2- FT.IR spectra were recorded (KBr disk) on a ***SHIMADZU*** FT.IR8300spectrophotometer in the range (4000 - 400) cm^{-1}.
3- Uv/Vis spectra were recorded on Uv/Vis varian Uv-Cary-100 spectrophotometers in DMSO as solvent.
4- ^{1}HNMR spectra were determined on a ***BRUKER***- 400 MHz operating 300 MH_Z spectrometer with tetramethylsilane (TMS) as an internal standard, and the chemical shifts are in δ ppm using deuterated dimethylsulfoxide (DMSO-d^6) as a solvent., measurements were made at Chemistry Department, Al al-Bayt University- Jordan.

5- The reactions progress was monitored by thin-layer chromatography (TLC) using Fertigfollen precoated sheets type Polygram Silg, and the plates were developed with iodine vapor.

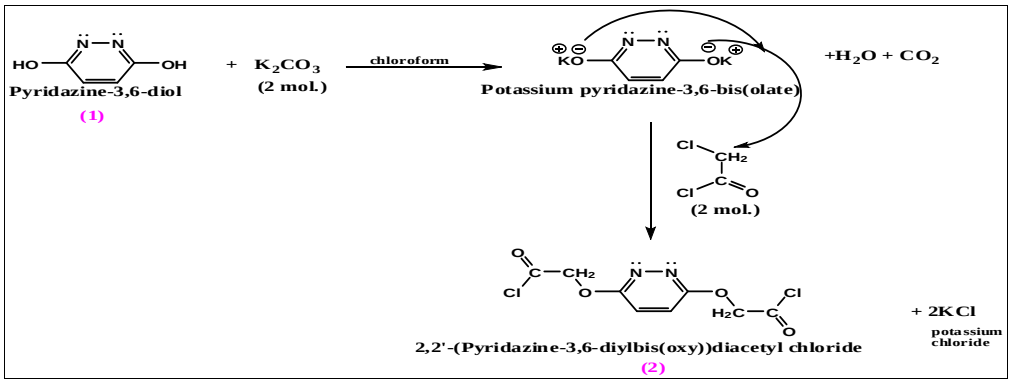
6- The biological activity was performed by environmental laboratory, Baghdad University.



Scheme 1 Structural formula of maleic hydrazide



Scheme 2



Scheme 3

Synthesis of : 2,2'- [pyridazine-3,6-diylbis(oxy)]diacetyl chloride (2) [24].

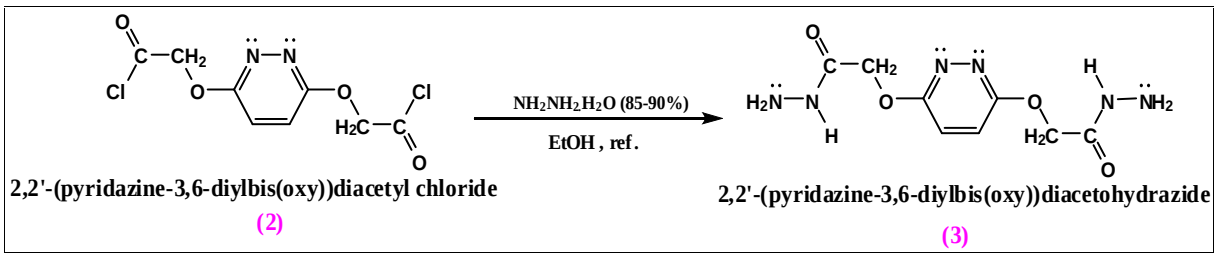
A solution of chloroacetyl chloride (0.02 mol), in chloroform (15 mL), was added to the solution of pyridazine-3,6-diol (0.01 mol) and (0.02 mol) potassium bicarbonate in chloroform (20 mL) at (5) ^{0}C temperature with stirring during (30 minutes). Then, the reaction mixture was refluxed for (5 hrs.), then cooled and poured onto water (25 mL). The solid Formed was filtered off, and re-crystallized from ethanol to give yellow crystals.

Synthesis of: 2,2'-[pyridazine-3,6-diylbis(oxy)] diacetohydrazide (3) [25,26]

To a solution of (0.005 mol) of compound (2) in absolute ethanol (20 mL) was added (0.01mol) of hydrazine hydrate (85-90%).The mixture was refluxed under anhydrous conditions for (10 hrs.); Excess solvent was distilled off. The resulting solid then was filtered and re-crystallized from ethanol. The compound was separated as shining dark yellow crystals.

Synthesis of: *N* '-(3-nitrobenzylidene)-2-[6-(2-((*Z*)-2-(3-nitrobenzylidene) hydrazinyl) -2-oxoethoxy] pyridazine -3-yloxy)acetohydrazide (4) [27-30].

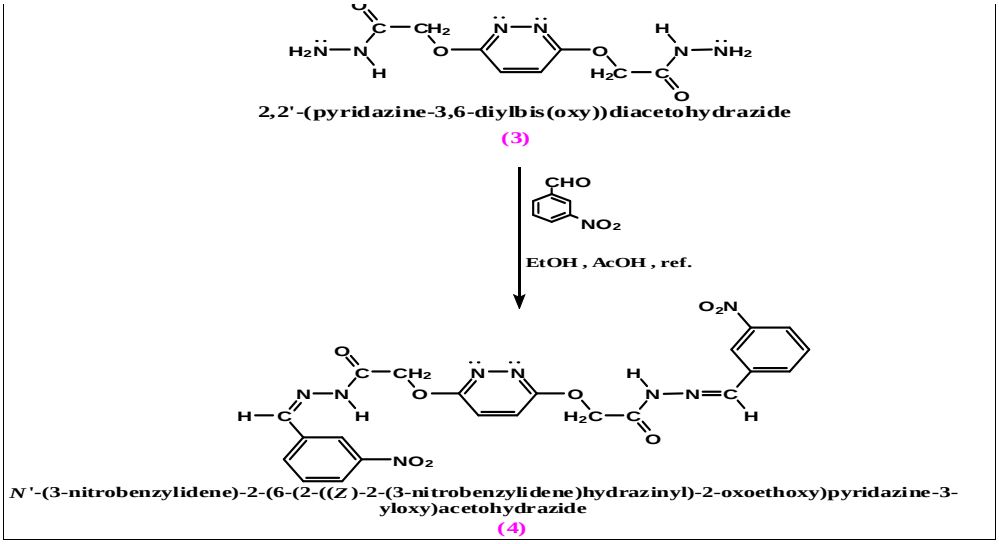
A mixture of compound (3) (0.005) and 3-nitrobenzaldehyde (0.01 mol), in absolute ethanol (20 mL) with few drops of glacial acetic acid was refluxed for (6 hrs.). After completion of the reaction, The resulting mixture was cooled , filtered to get solid, which was re-crystallized from ethanol.



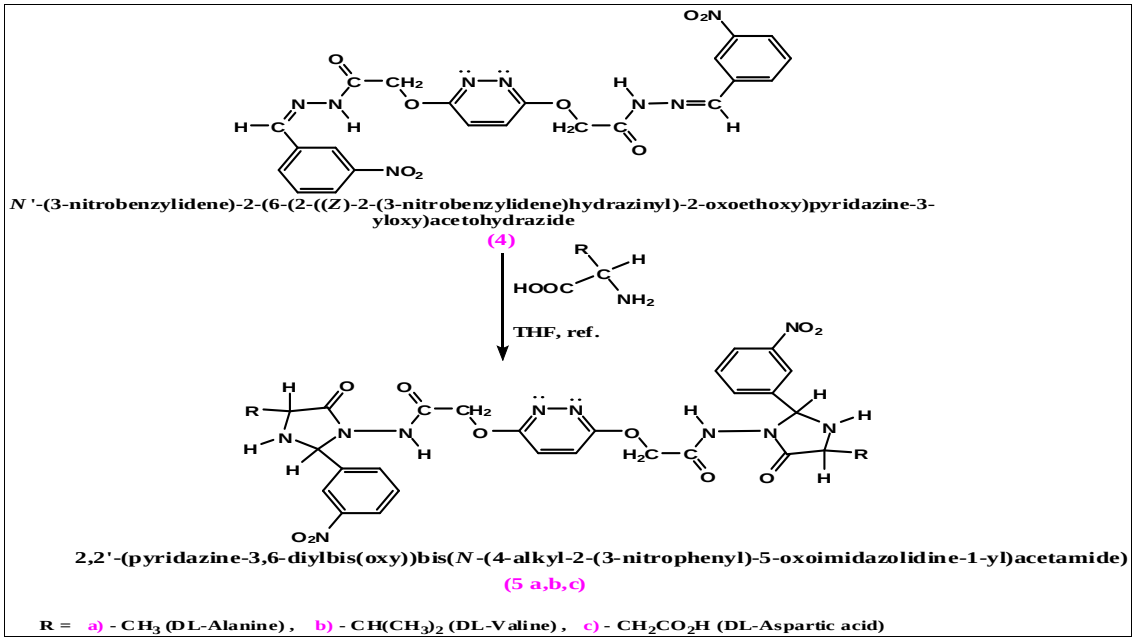
Scheme 4

Synthesis of : 2,2'-(pyridazine-3,6-diylbis(oxy))bis[*N*-(4-alkyl-2-(3-nitrophenyl)-5-oxoimidazolidine-1-yl)acetamide] (5 a,b,c) [31,32].

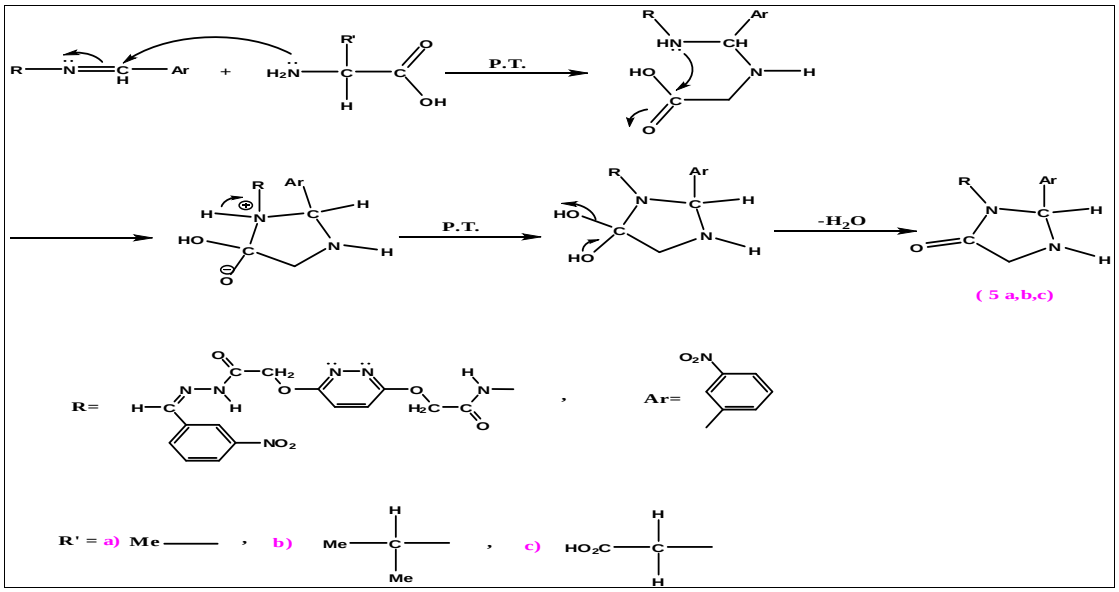
A mixture of Schiff base (0.01mol) and appropriate amino acid (0.02mol) in (25 mL) THF was refluxed with stirring for (24 hrs.), then cooled to room temperature, the precipitate was



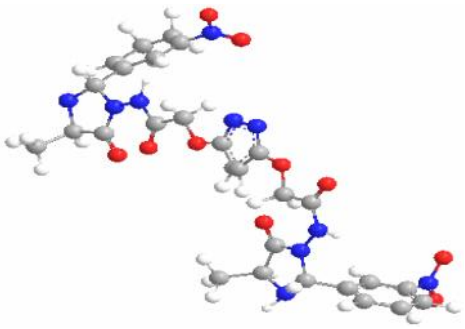
Scheme 5



Scheme 6

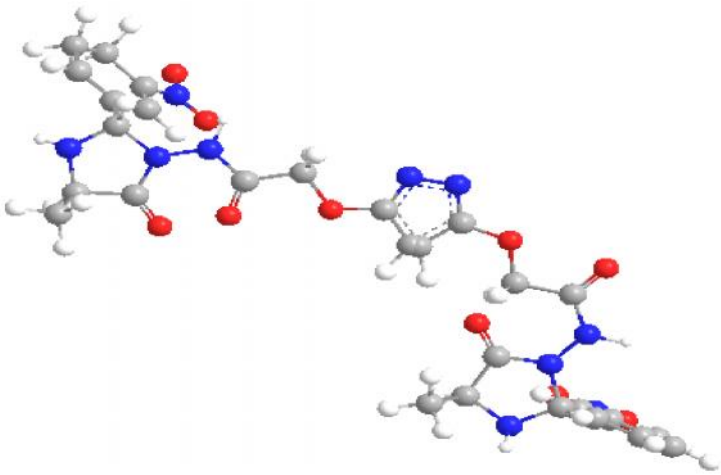


Scheme 7



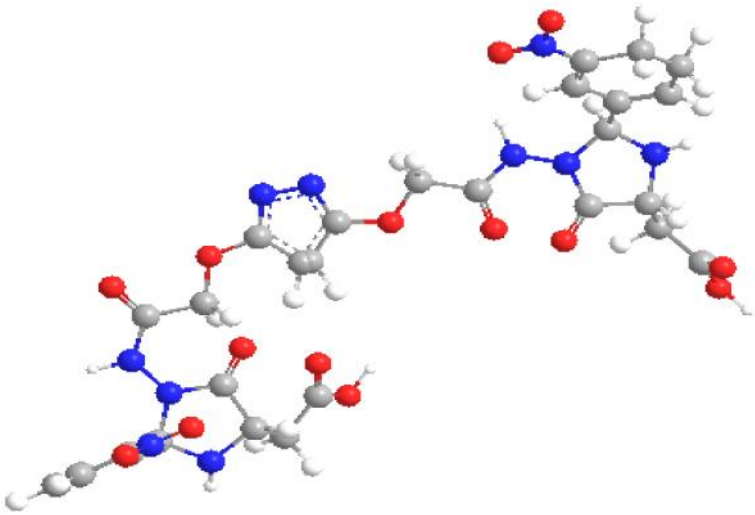
***N*-(4-Methyl-2-(3-nitrophenyl)-5-oxoimidazolidin-1-yl)-2-(6-(2-(4-methyl-2-(5-nitrocyclohexa-1,5-dienyl)-5-oxoimidazolidin-1-ylamino)-2-oxoethoxy)pyridazin-3-yloxy)acetamide**

(5a)



***N*-(4-Isopropyl-2-(3-nitrophenyl)-5-oxoimidazolidin-1-yl)-2-(6-(2-(4-isopropyl-2-(5-nitrocyclohexa-1,5-dienyl)-5-oxoimidazolidin-1-ylamino)-2-oxoethoxy)pyridazin-3-yloxy)acetamide**

(5b)



2-(1-(2-(6-(2-(4-(Carboxymethyl)-2-(3-nitrophenyl)-5-oxoimidazolidin-1-ylamino)-2-oxoethoxy)pyridazin-3-yloxy)acetamido)-2-(5-nitrocyclohexa-1,5-dienyl)-5-oxoimidazolidin-4-yl)acetic acid

(5c)

Filtered and re-crystallized from ethanol.

RESULTS AND DISCUSSION

The infrared study is the important method in the identification of absorbed peaks of the resulting functional groups effective and which are found within the structural formula of the prepared compounds., The difference in the intensity of the main functional groups of absorption peaks is an indication of the occurrence of interaction [33]. The starting material used is pyridazine-3, 6-diol (1) which have the structural formula given by the following equilibrium shown in (scheme-1).

Pyridazine-3,6-diol has many names are: maleic hydrazide, maleic acid hydrazide, and 3,6-dihydroxypyridazine., The enol form which behave as nucleophile react with the

Table 1 physical properties of the prepared compounds

Comp. no.	Molecular Formula	Molecular Weight (gm/mol)	Yield %	M.P. ^{0}C	Color
2	$C_8H_6N_2O_4Cl_2$	265	65	105-107	yellow
3	$C_8H_{12}N_6O_4$	256	63	157-159	dark yellow
4	$C_{22}H_{18}N_8O_8$	522	66	233-235	yellowish brown
5a	$C_{28}H_{30}N_{10}O_{10}$	666	76	257-259	brown
5b	$C_{32}H_{38}N_{10}O_{10}$	722	57	221-223	light brown
5c	$C_{30}H_{30}N_{10}O_{14}$	754	59	247-250	yellow

Compound (2) was converted to acid hydrazide by addition of excess hydrazine hydrate ($NH_2NH_2.H_2O$ 85-90 %) in ethanol to a solution of compound (2) in ethanol to give 2,2'-[pyridazine-3,6-diylbis(oxy)]diacetohydrazide (3), (scheme-4) [37].

The mechanism of this reaction is known [38,39]. The products were characterized by FT.IR spectroscopy (table-2), and other physical properties (table-1). The FT.IR spectra of

Table 2 FT.IR spectral data of the prepared compounds

Comp. no.	CH aro.	CH ali.	C=O	NH_2, NH	C=N imine	Others
2	3045	2954	acetyl chloride 1762	-	-	C-O 1247 C-Cl 710
3	3059	2959	acid hydrazide 1673	3437-3321	-	C-O 1253 N-H bend. 1582
4	3037	2963	acetohydrazide 1682	3329	1589	C-O 1267 N-H bend. 1612 NO_2 1541,1336
5a	3033	2965, 2869	amide II 1674 oxoimidazolidine 1737	3342	-	C-O 1170 N-H bend. 1589 NO_2 1543,1329
5b	3032	2919, 2863	amide II 1685 oxoimidazolidine 1736	3359	-	C-O 1197 N-H bend. 1623 NO_2 1534,1342
5c	3061	2973, 2895	amide II 1681 oxoimidazolidine 1743 acid 1733	3350	-	C-O 1223 N-H bend. 1631 OH acid 3167 O acid 1267 NO_2 1556,1339

Table 3 UV Visible spectral data of the prepared compounds

Comp. no.	λ_{Max} (nm)
5a	286
5b	267
5c	243, 365

Table 4 Antibacterial activities of some of the synthesized compounds

Comp.no.	*E.coli*	*Staphococcus aureus*
5a	+	-
5b	+	-
5c	+	+

electrophiles such as acetyl or alkyl halide or their derivatives to form a good products [34].

The first step in (scheme -2) involved the reaction of enol form of pyridazine-3,6-diol (1) with chloroacetyl chloride in presence of potassium carbonate as catalyst to yield: 2,2'-[pyridazine-3,6-diylbis (oxy)]diacetyl chloride (2) [35,36]., This compound was characterized through the FT.IR spectrum and other physical properties (tables-1 and 2).

The FT.IR spectrum of compound (2) showed disappearance of stretching band of (OH) group of the starting material, and appearance new stretching bands of (C=O), and (C-Cl) at (1726) cm^{-1}, (710) cm^{-1} respectively, (fig. 2) [33].

compound (3), showed appearances of stretching bands of (NH_2) ,and (NH), at (3437-3321) cm^{-1} , (fig.3) [33].

Compound (3) was reacted with 3-nitrobenzaldehyde in absolute ethanol to form Schiff base:

N'-(3- nitrobenzylidene)-2-[6-(2-((*Z*)-2-(3-nitrobenzylidene) hydrazinyl)-2-oxoethoxy] pyridazine -3-yloxy)acetohydrazide (4), (scheme-5) [40].

The mechanism of this reaction is known [39,41]. The products were characterized by FT.IR spectroscopy (table-2), and other physical properties (table-2). The FT.IR spectra of compounds (4), showed disappearances of stretching bands of (NH_2) at (3437-3321) cm^{-1}, and appearance of stretching band of imine group (N=C) at (1589) cm^{-1} (fig. 4) [33].

The treatment of acetohydrazide (4) with different amino acids in tetrahydrofuran (THF), afforded the corresponding pyridazine derivatives containing imidazoline ring that was identified as compound (5 a,b, and c) on the basis of its spectral data (scheme- 6),[42].

Compounds (5) were characterized by physical properties , FT.IR (table 1, and 2) (figs.5,6, and 7), and ^{1}HNMR for compound (5a). FTIR spectra showed the disappearance of imine group (C=N) stretching vibration presence in the spectrum of acetohydrazide, and showed appearances of stretching bands of (NH) at(3359-3342) cm^{-1}, (1737-1733)

cm^{-1} due to (C=O) group of oxoimidazoline ring., and (3167) cm^{-1} due to (OH) group in compound (5c)., The (C=O amide II) was overlap with absorption band of (C=O carboxylic acid) group, (figs. 5,6, and 7) [33].

The proposed mechanism of this reaction described in scheme below:

The ^{1}HNMR spectrum of compound (5a), (fig.8) shows the following characteristic chemical shifts: Protons of (CH_3) group at δ (2.957) ppm , proton of amine group (NH) at δ (3.180) ppm , protons of methine groups (CH) at δ (3.350, and 5.440) ppm respectively, protons of methelene group (CH_2) at δ (4.086) ppm , protons of pyridazine ring at δ(6.735) ppm , proton of secondary amide at δ (11.365) ppm , and protons of aromatic rings appeared at the range δ (7.489-8.042) ppm.

UV-Vis. spectra of compounds (5a, 5b, and 5c) showed intense maxima at (243 nm - 386 nm) referring to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ electronic transition respectively (table 3).

Biological screening: Antibacterial activity test

In this work, the antibacterial test was performed according to the disc diffusion method. Compounds (5a,5b, and 5c) were assayed for their antimicrobial activity *in vitro* against two strains of Gram negative (G -) and positive (G +) bacteria (***Escherichia Coli*** , and ***Staphococcus aureus***). Prepared agar and Petri dishes were sterilized by autoclaving for 15min. at 121 ºC. The agar plates were surface inoculated uniformly from the broth culture of the tested microorganisms. In the solidified medium suitably spaced apart holes were made all 6mm in diameter. These holes were filled with 0.1 mL of the prepared compounds (10mg of the compound dissolved in 1ml of DMSO solvent); DMSO was used as a solvent. These plates were incubated at 37 ºC for 24hr for bacteria. The inhibition zones caused by the various compounds were examined. The results of the preliminary screening tests are : For ***St.*** ($\mathbf{G^+}$), compound (5c) showed slightly activity, while compounds (5a,5b) showed no activity on this bacteria.,Compounds (5a,5b, and 5c) showed slightly activity ; For ***E.coli*** ($\mathbf{G^-}$), (table-4).

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