Egypt. J. Chem. **Vol. 64,** No. 6 pp. 2925 - 2936 (2021)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Synthesis and Characterization of some Tetrazole Derivatives and Evaluation of their Biological Activity

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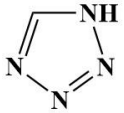
Abstract

This research included synthesizing a series of heterocyclic compounds where the compound 2-chloroacetohydrazide was synthesized from ethyl chloroethanoate with Hydrazine hydrate 95%. The reaction was carried out in the cold condition. 2-(pyrimidin-2-ylamino)acetohydrazide was prepared by reaction A1 with 2-amino pyrimidine in absolute ethanol using Potassium hydroxide (KOH); then reaction 2-(pyrimidin-2-ylamino) acetohydrazide with different aldehydes to produce Schiff bases derivatives A3 –A14 which was introduced in two different synthetic methods the first was synthesized. Then tetrazole derivatives [A15-A19] were synthesized from the hydrozone reactor (Schiff bases) [A3-A14] prepared by reaction Schiff base with sodium azide. In a second way, derivatives 2, 3-dihydroquinozoline-4-one [A20-A24] were synthesized from the interaction of some of Schiff's bases in the third step with anthralenic acid (2-amino benzoic acid) using 1,4-dioxane as a solvent; the synthetic compounds were diagnosed with some spectral methods, such as UV, FTIR, 1H-NMR and quantitative analysis of the elements (C.H.N.S.). Some synthetic compounds on the growth of four types of bacterial isolates known to be resistant to antibiotics were studied. Amoxicillin and Ampicillin were used as control samples, and some of the prepared compounds showed good inhibiting efficacy against the used bacteria (Escherichia coli, Klebsiella pneumonia, Staphylococcus aureus, and Staphylococcus epidermidis)

Keywords: heterocyclic compounds, ring-closing reaction, tetrazole, 2-amino pyrimidine

Introduction

Tetrazolates are five-ring heterogeneous compounds containing four nitrogen atoms and one carbon atom as well as hydrogen atoms, and the simplest of them is the compound (Tetrazole) with The formula CH_2N_4 [1] is shown below



The nitrogen-rich conjugated system characterizes tetrazoles with both acceptor and electronic donor features [2]. The planar structure works on stabilizing negative charge by delocalization, which is considered appropriate for the receptor-ligand interaction. Tetrazolate anions are lipophilicity more than carboxylates, which improve the passing of drug molecules out of cell membranes. On the other hand, tetrazoles exhibit resistance against metabolic degradation paths consequently possesses a more extended period of action [3]. Tetrazoles and their heterocyclic analogs are important pharmacophores in medicinal chemistry due to their unique structure and favorable pharmacokinetic profile. Their pharmacological profile involves anti-hypertensive, anti-analgesic, anti-allergic, and anti-ulcer activities [4-6]. Tetrazoles-based heterocycles have enormous synthetic use and work as a precursor for synthesizing strong heterocycles, involving explosives, pharmaceuticals, and propellants [7-8]. Heterocyclic analogs of tetrazoles work as the first confirmed treatment for dopamine D2 receptors [9-10]. Tetrazoles based heterocycles work as strong antimicrobial and anticancer agents [11]. Jackman et al. mentioned the robust cytotoxicity and growth inhibitory action of tetrazoles-involving-drugs. Tetrazoles based drugs have an incomplete interfering spectrum of antitumor action and toxicity profile in comparison with tomudex and possibly other Thymidylate synthase inhibitors presently being examined clinically [12].

Leishmaniasis is an animal disease originally that is transmitted between vertebrates and people by sandflies. A literature reconnaissance shows

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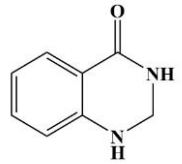
Receive Date: 26 December 2020, Revise Date: 02 January 2021, Accept Date: 14 March 2021

DOI: 10.21608/EJCHEM.2021.54356.3165

tetrazoles based heterocycles as robust anti-leishmanial agents. In this case, Pyrazolyl-based tetrazoles are revealed to be efficient cytotoxicity and antileishmanial agents [13]. Likewise, Fai~oes et al. mention the synthesis, antileishmanial potential, and oral bioavailability of 5-[5-amino-1-(40 - methoxyphenyl)1H-pyrazole4-yl]1H-tetrazole utilizing a rational medication design program [14]. Lately, Viviane et al. stated the anti-leishmanial potential of arylpyrazole based tetrazoles. The synthesized arylpyrazole based tetrazoles displayed strong and unconventional anti-leishmanial reaction [15]. These compounds are considered one of the most effective cyclic compounds because they possess four free pairs of electrons for four nitrogen atoms, so they are among the electron propellant compounds [16]. Hydroquinazolin-4-one is a hexagonal ring containing two nitrogen atoms and a carbonyl group containing a carbonyl group at site 4 called hydroquinazolin 4-one [17].



2,3-dihydroquinazolin-4(1*H*)-one

Materials and Methodology

All the chemicals used in this work were of the highest purity and supplied without further purification in Thin Layer Chromatography (TLC). All reactions were monitored by thin-layer chromatography Silica gel/TLC with fluorescent indicator 254 nm; layer thickness 0.2 mm; 20 × 20 cm aluminum cards were used. Ethyl acetate: n-hexane (3:7), ethanol: dioxane (1:1), and methanol: chloroform (1:9) was the adopted solvent system. R_f value (Ethanol: Dioxin 1:1). Besides, it was checked by pro-coated sheets with silica–gel as an immobile phase. Appropriate solvent (ethanol), as mobile phase (Melting points), was specified by Stuart melting point SMP10 Spectr (FT-IR) were by KBr disk on SHIMADZU FT-IR-8300 spectrophotometer in Ibn Sina Company and College of Sciences for Women at University of Baghdad. ^{1}H-NMR measurements were obtained from Moscow University of Russia, operated at 500 MHZ in DMSO-d6. Elemental analysis (C.H.N.S) was measured in the College of Education for Pure Science/ University of Babylon. Biological activity was conducted out in Biology Laboratory at the University of Baghdad, College of Science for Women.

Synthesis Methods and Preparation of 2-chloroacetohydrazide [A1] (18)

0.16mol, 9gm, 9ml of aqueous hydrazine (95.5%) was added gradually with continuous stirring to a mixture of ethyl chloroacetate (0.16mol, 10gm, 10ml) in (5ml) of absolute ethanol in a round bottom flask equipped with a magnetic stirrer and an ice bath. The addition was gradual with continuous stirring until a white precipitate was formed. The end of the reaction was monitored by using the TLC technique, and after the end of the reaction, the precipitate was collected by filtration, recrystallized with absolute ethanol, and dried at a temperature of 100C, yield 81% and m.p of (160-162) the retention factor was (R_f) (0.78) and yellow-dark.

Preparation of the compound [A2] (19)

0.1mol 11.5gm 2-chloroacetohydrazide A1 was dissolved in (30ml) of absolute ethanol and added to (0.1mol, 10gm) of 2-amino-primidine in (15ml of absolute ethanol in the presence of potassium hydroxide KOH (2.8gm). The mixture was refluxed for (14-15) hours, and the completion of the reaction was monitored using the TLC technique. After the reaction's completion, the mixture was left to cool down, then the precipitate was filtered, the product was recrystallized with chloroform and dried at a temperature of 100C, and the percentage of the product was 81% and a melting point of (208-210). Besides, the handicap factor, Rf = 0.80, and it was a light yellow color.

Preparation of Hydrosons (Schiff's rules) [A3-A14] [20]

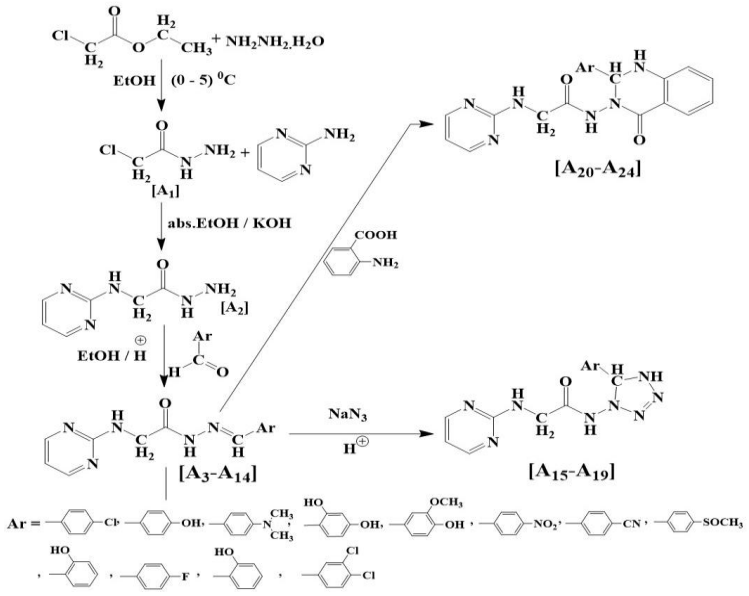
Solution (2gm, 0.01mol) of the compound [A2] in (15ml) of absolute ethanol was added to (0.01mol) of the various aldehydes. After adding four drops of glacial acetic acid, the mixture was refluxed for 6 hours) Moreover, the reaction was confirmed by using a TLC technique. After completion of the reaction, the resulting mixture was cooled slowly, and then the precipitate was filtered and collected, recrystallized with absolute ethanol, and dried at 100C. Table (1) shows some of the physical properties, percentage, and R_f of Schiff's base compounds [A3-A14].

Preparation of some Tetrazol Derivatives [A15-A19] [21]

(0.2gm, 0.05mol) of some Schiff's bases derivatives [A3-A14] were dissolved in (10ml) tetrahydrofuran (THF) with (0.05mol, 0.04gm.) of sodium azide in (5ml) of solvent. The mixture was refluxed for (5-9) hours, and the reaction was confirmed by using the TLC technique. The mixture was cooled, filtered, washed with cold water, recrystallized with absolute ethanol, and dried at 100C. Table (1) shows some of the physical properties, percentage, and R_f of tetrazol derivatives [A15-A19].

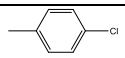
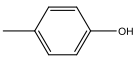
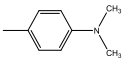
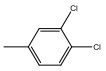
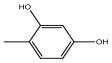
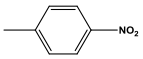
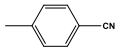
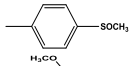
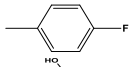
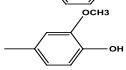
Preparation of some 2,3-dihydroquinosulin4-one derivatives [A20-A24] [22]

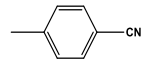
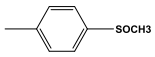
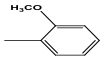
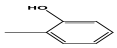
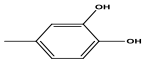
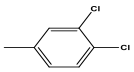
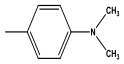
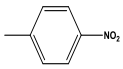
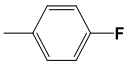
0.0006mol of some Schiff bases derivatives [A3-A14] was dissolved in (10ml) of (1,4-dioxane) and added to (0.0006mol, 0.095gm) of anthranilic acid dissolved in (5ml) of (1,4 - dioxane), then the mixture was refluxed for (14-16) hours, and the reaction was monitored by using TLC technology. The mixture was cooled, and then filtered, washed with cold water, recrystallized with absolute ethanol, and dried at a temperature of 100C. Table (1) shows some of the physical properties, R_f of the 2,3,-dihydroquinosoline-4-one derivatives [A20-A24].



Scheme 1. prepared derivatives [A1-A24]

Table-1 Physical properties of prepared compounds [A1-A24], R_F

Comp. No.	Ar	Molecular Formula/ M.Wt g/mol	Color	M.P. (0C)	Yield (%)	R_f (1:1)
A_3		$C_{13}H_{12}N_5OCl$ 288	Light yellow	238-240	68	0.68
A_4		$C_{13}H_{13}N_5O_2$ 271.1	brown	189-191	73	0.69
A_5		$C_{15}H_{19}N_6O$ 300.1	Red	260-262	62	0.61
A_6		$C_{13}H_{11}N_5OCl_2$ 324.1	Dark yellow	270-272	84	0.83
A_7		$C_{13}H_{13}N_5O_3$ 357.6	Yellowish green	244-246	65	0.64
A_8		$C_{15}H_{15}N_5O_3$ 298.1	Yellow	212-114	75	0.73
A_9		$C_{13}H_{12}N_6O_3$ 300.1	Brown	246-248	79	0.79
A_{10}		$C_{14}H_{12}N_6O$ 280.1	Yellow	284-286	82	0.81
A_{11}		$C_{14}H_{15}N_5O_2S$ 317.1	Dark yellow's	260-262	78	0.77
A_{12}		$C_{14}H_{15}N_5O_2$ 285.1	yellowish-green	272-274	59	0.55
A_{13}		$C_{13}H_{12}N_5OF$ 273.1	Pall yellow	225-227	55	0.54
A_{14}		$C_{13}H_{13}N_5O_2$ 271.1	Yellowish green	290-292	81	0.80
A_{15}		$C_{14}H_{14}N_8O_3$ 340	Pall yellow	186-188	68	0.67

A_{16}		$C_{14}H_{12}N_9O$ 322	Yellowish green	170-172	88	0.87
A_{17}		$C_{14}H_{15}N_7O_2S$ 345	Yellow	240-242	64	0.63
A_{18}		$C_{14}H_{11}N_8O_2$ 413	Black	173-175	79	0.78
A_{19}		$C_{13}H_{13}N_8O_2$ 399	Pall brown	150-152	65	0.64
A_{20}		$C_{20}H_{18}N_6O_4$ 406	Pall yellow	144-146	79	0.71
A_{21}		$C_{20}H_{16}N_6O_2Cl_2$ 443	Dark yellow	215-217	76	0.64
A_{22}		$C_{22}H_{22}N_7O_2$ 416	Brown	300-302	71	0.83
A_{23}		$C_{20}H_{18}N_7O_4$ 420	dark brown	278-280	62	0.63
A_{24}		$C_{20}H_{18}N_6O_2F$ 393	yellow	186-188	66	0.60

Chloroacetohydrazide [A1] [18]

The compound [A1] was prepared by reacting one mole of aqueous hydrazine with one mole with ethyl chloroethanoate. The reaction of the preparation of 2-chloracetohydrazide was carried out according to [23].

When studying the infrared (FT-IR) spectrum for the compound 2-chloroacetohydrazide [A1], two stretch bands of the (NH_2) group were observed, which appeared as sharp and medium-intensity bands at (3259) cm^{-1} and at (3335) cm^{-1}, and the appearance of two bands. Symmetric and asymmetric stretching respectively of the aliphatic (CH) group, which appears as sharp and medium-intensity bands at (2941 and 2800) cm^{-1}; a strong band of (C=O) amide group at (1641) cm^{-1}. (C-Cl) at (833) cm^{-1} and a strong band of (NN) appeared at (1070) cm^{-1}, as these bands were identical to what is found in the literature [24]. In the proton nuclear magnetic resonance spectrum of the compound 2-chloroacetohydrazide, a single signal was observed at (8.75) ppm attributed to the proton of a group (NH), and a single signal was observed at (4.22) ppm related to the protons of a group (NH_2), and there was also a single signal in the region at (4.05). The ppm refers to the proton group (CH_2) [26]. The spectra are shown in Figure (1a), which shows the ultraviolet spectrum of the compound [A1], Figure (1b) shows the infrared spectrum of the compound [A1], and Figure (1c) shows the proton NMR spectrum for the same compound.

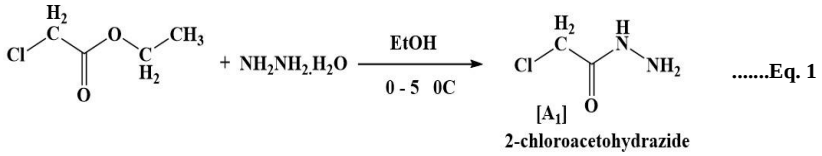
Compound [A2] [19]

The compound [A2] was prepared by one mole of the compound 2-amino-primidine with one mole of 2-chloroacetohydrazide in a basic medium using absolute ethanol as a solvent and as in the following equation.

Moreover, when viewing the infrared (FT-IR) spectrum of the compound (A2), it was observed that two (NH_2) stretch bands appeared as sharp and medium-intensity bands at (3249) cm^{-1} and at (3309) cm^{-1}, and the appearance of a (CH) aromatic and incident band. At (3064) cm^{-1}, and the emergence of a strong band of (C=O) amide bonds at (1679) cm^{-1}, and the emergence of two symmetric and an asymmetric stretching band of the aliphatic group (CH) that appear as sharp and medium-intensity band at (2964) cm^{-1}, and the emergence of a strong band of the aromatic pinch (C=C) at (1614) cm^{-1}, and a strong band of (NN) at (1066) cm^{-1}, and a strong band of (C=N) in the pyrimidine at (1542) cm^{-1} (25).

When viewing the proton NMR spectrum of the compound [A2], it was observed that a triple signal appeared at (8.46) ppm, attributed to the proton of the group (NH), and the presence of a doublet signal (7.95) ppm was observed in the spectrum. (a) group protons (CH-Pyi), and a triple signal was observed at (6.79) ppm belonging to the group proton (CH-Pyi') (b), and a single signal was observed at (6.22 ppm) attributed to a group proton (c) (NH) associated with the pyrimidine ring. The spectrum also showed a signal in the region (4.15) ppm belonging to the protons of the group (NH_2) (f), and the spectrum also showed the presence of a signal in the region (3.56)

ppm related to the protons Group (CH_2) (d), (27). The spectra are shown in Fig. (2a), which shows the ultraviolet spectrum of the compound [A2], Fig. (2b) shows the infrared spectrum of the compound [A2], and Fig. (2c) shows the NMR spectrum of the component [A2].



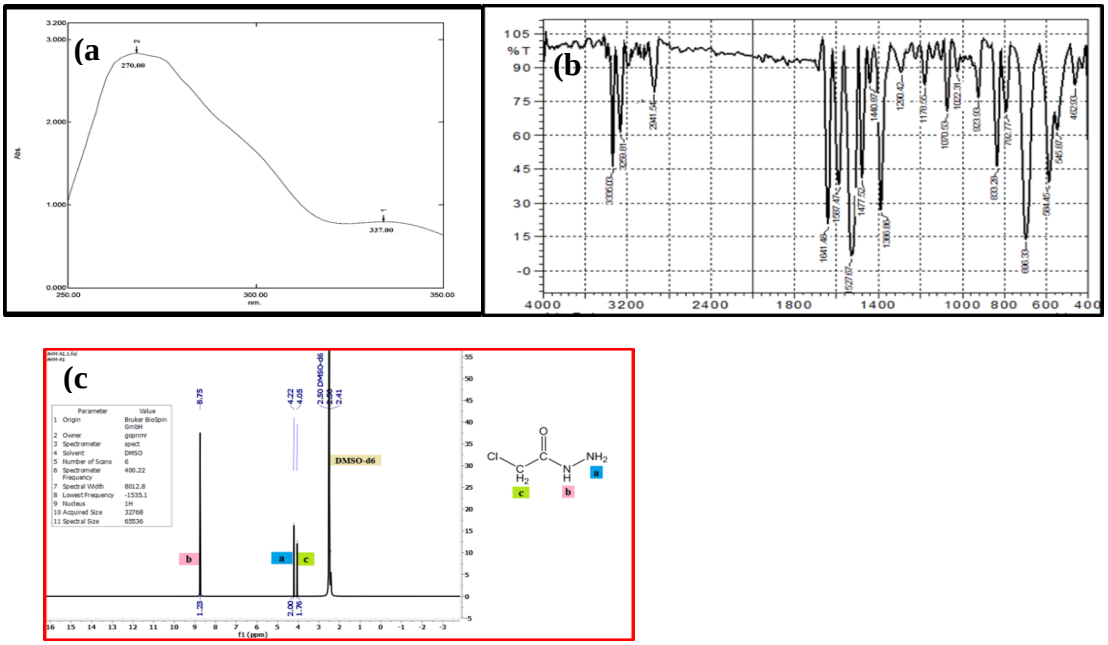


Fig. 1. shows (a) the ultraviolet spectrum of the compound [A1], (b) shows the infrared spectrum of the compound [A1], and (c) shows the proton NMR spectrum for the same compound

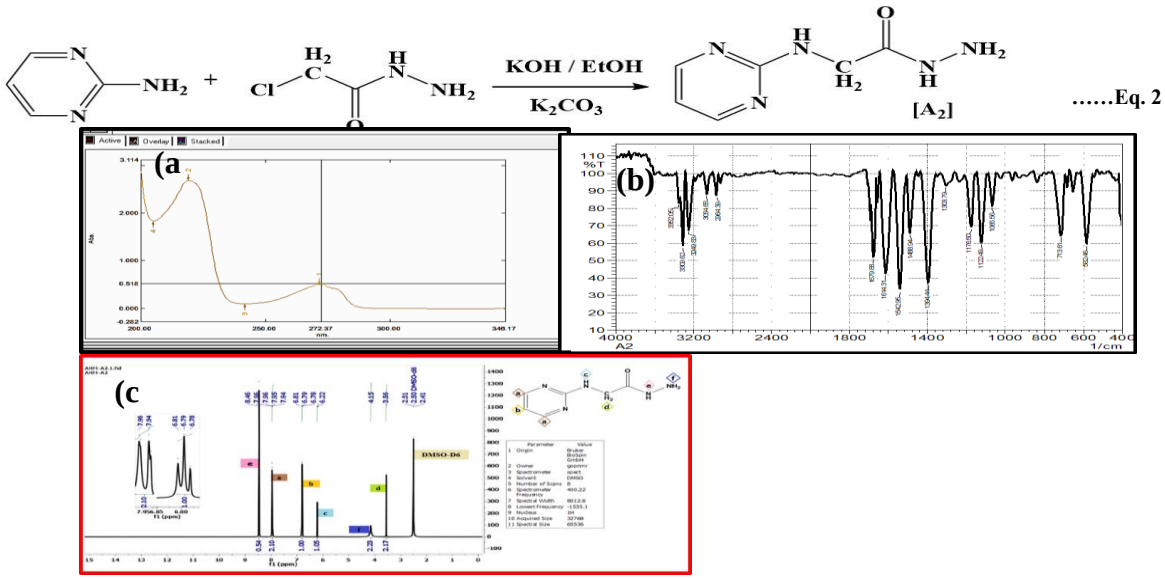


Fig. 2. Shows (a) the ultraviolet spectrum of the compound [A2], (b) shows the infrared spectrum of the compound [A2], and (c) shows the NMR spectrum of the component [A2].

Schiff's bases derivatives [A3-A14] [20]

Schiff bases [A3-A14] were prepared from the reaction of one mole of the aromatic benzaldehyde substitutes with one mole of the compound [A2] in the presence of ethanol as a solvent (23) as shown in the following equation:

When viewing the infrared (IR) spectrum of the prepared Schiff bases compounds [A3-A14], it was noticed that the two amine group (NH_2) stretching bands that appeared at (3309) and (3352) cm^{-1} can be assigned to the compound [A2] were disappeared. A medium stretch band at (1618-1653) cm^{-1} belongs to the group (C=N), and the appearance of the same strong band at (1548-1597) cm^{-1} belongs to a group (C=N) present in the pyrimidine ring. The (1502-1625) cm^{-1} is due to the stretching of the aromatic (C=C) coupling, in addition to the absorption bands at the range (3005-3090) cm^{-1} due to the stretching of (CH) aromatic bond. The appearance of an absorption band at the range (3164-3225) cm^{-1} is related to stretching (NH), as shown in Table (2). The values of the absorbances in the ultraviolet spectrum of derivatives of Schiff base (A3-A14), Figure (3 a and b) which show the ultraviolet and the FTIR spectrum of the one compound [A10] respectively, and Figure (3c) and figure (4) show the proton NMR spectrum of the two compounds [A10, A11] as a model for Schiff's rules, where these bands were close to what is found in the literature (25).

When studying the nuclear magnetic resonance spectrum [1H-NMR] of the compound [A10], it was observed that a single signal appeared at (11.37) ppm attributed to the proton of the group (NH), (e), and the appearance of a single signal at (8.34) ppm is attributed to the proton of a group (N=CH), (f). The presence of a binary signal in the region (7.90 ppm) also appeared in the spectrum due to the protons of the group (CH-Pyi) (a). The region (7.08-7.65) ppm belongs to the protons of the aromatic benzene ring (CH-Ar) (g, h), and a triple signal was observed at (6.58) ppm belonging to the proton of the group (CH-Pyi ') (b). The emergence of a single signal at (5.88) ppm attributed to the proton of the group (NH) (c) associated with the pyrimidine ring. It appeared in the spectrum also the presence of a single signal in the region (4.26) ppm belonging to the group protons (CH2) (26, 27), and Fig. (4c) shows the proton NMR spectrum of the compound [A10].

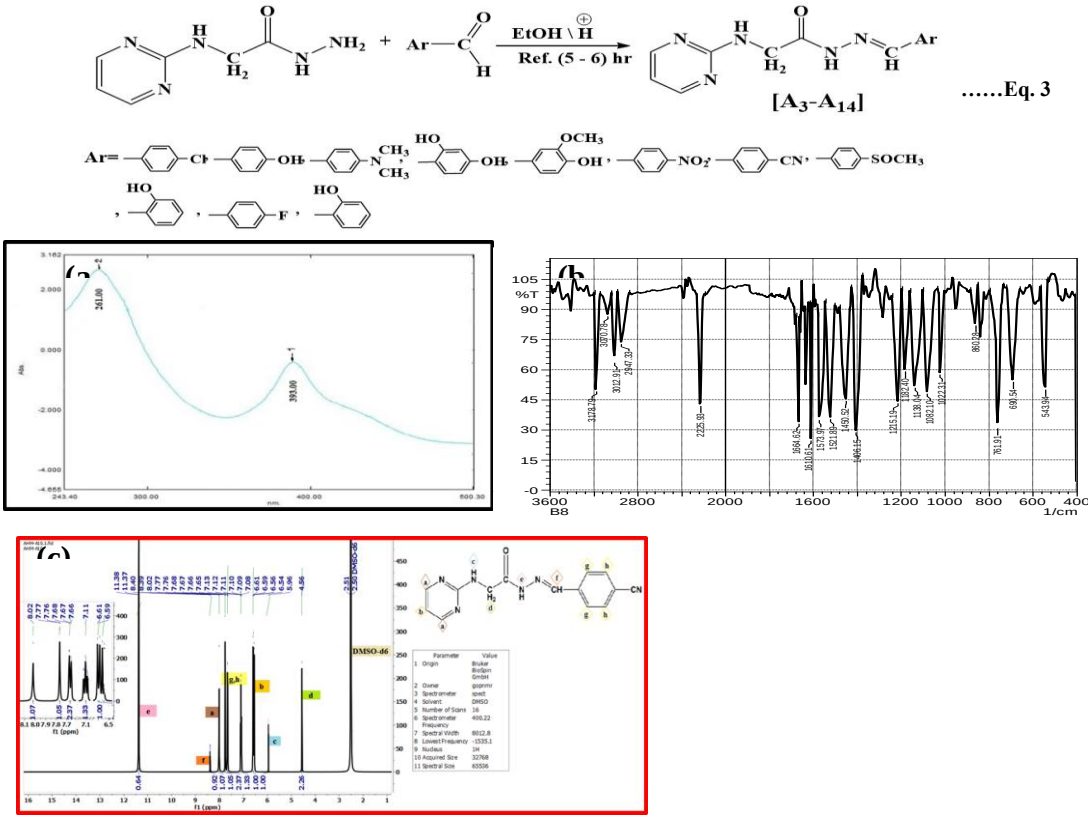


Fig. 3. Shows (a) the ultraviolet, (b) the FTIR spectrum, and (c) the proton NMR spectrum for the compound [A10]

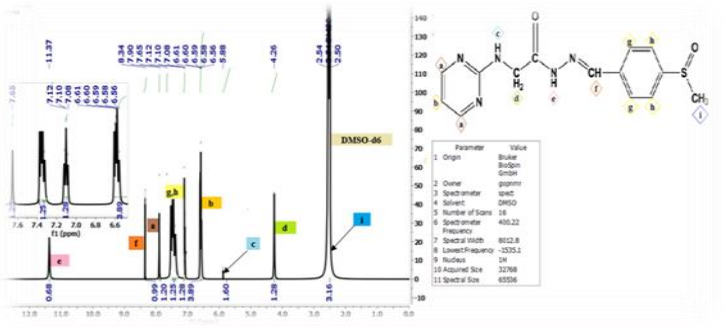
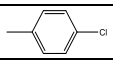
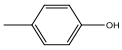
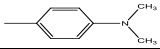
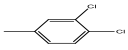
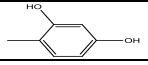
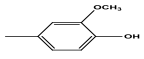
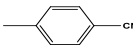
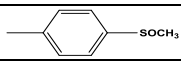
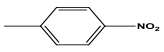
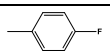
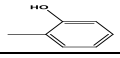


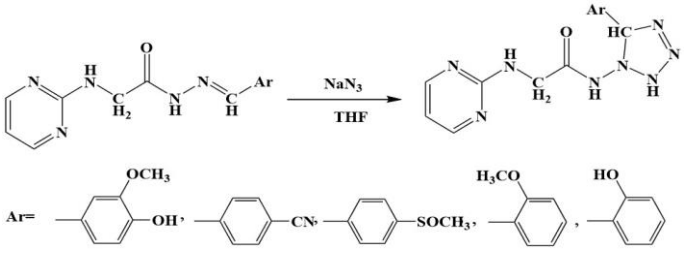
Fig. 4. Shows the proton NMR spectrum for the compound [A11].

Table 2. Infrared absorption (cm^{-1}) and absorbance values in the ultraviolet spectrum of the Ultraviolet base derivatives [A3-A13]

Comp. No.	Ar	$_1\lambda$ max $_2\lambda$ max EtOH	IR (KBr) cm^{-1}					
			ν C=N)(Schiff	ν(C-H) Arom. Aliph.	ν (C=C) Arom.	ν (C=N) Pyi.	ν (C=O) Amid	Others
A_3		261 393	1640	3059 2933	1620	1583	1644	3164ν (NH) 813ν (C-Cl)
A_4		248 398	1635	3063 2848	1625	1581	1670	3167ν (NH) 3416ν (OH)
A_5		217 342	1642	3053 2993	1606	1556	1674	3178ν (NH)
A_6		218 390	1647	3090 2941	1620	1570	1666	3184 ν (NH) 813ν (C-Cl)
A7		239 309	1653	3009 2860	1622	1577	1662	ν (NH)3184ν (OH) 3475
A_8		242 317	1629	3005 2958	1612	1570	1664	OH,3479,ν CH3asy.sy. 1429,1383ν (NH)3201
A_9		217 370	1629	3005 2958	1612	1579	1664	OH,3479,ν CH_3asy.sy. 1429,1383ν (NH)3201
A_{10}		261 393	1631	3012 2947	1610	1573	1664	ν (NH) ,2225ν (CN) 3178
A_{11}		239 309	1618	3070 2933	1585	1548	1666	ν (NH) 570 , νCS 3225,SO,960
A_{12}		216 320	1627	3051 2941	1527	1575	1666	NO_2 asy.sy. ν 1520,1355ν (NH),3201,
A_{13}		224 370	1624	3045 2955	1527	1572	1680	3149 ν (NH) 979ν (C-F)
A_{14}		212 380	1629	3061 2945	1502	1597	1683	3173 ν (NH) 3506,ν (OH)

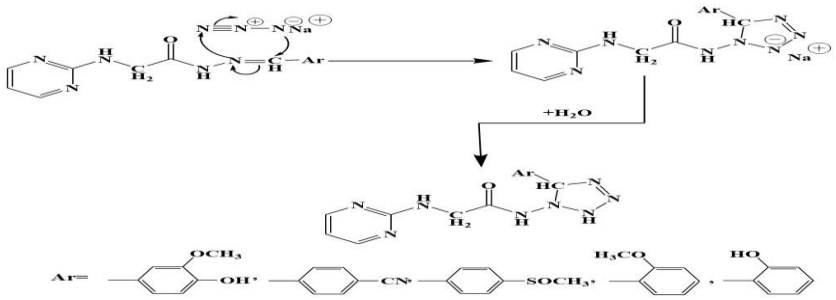
Tetrazol derivatives [A15-A19] [21]

The tetrazol derivatives [A15-A19] were prepared from the reaction of one mole of the prepared Schiff bases [A3-A14] with one mole of sodium azide (NaN3) in tetrahydrofuran (THF) (23) to give a heterocyclic five members ring of tetrazol derivatives [A15-A19], as shown in the following equation:



…..Eq. 4

The following scheme illustrates the proposed mechanism for preparing tetrazol derivatives [A15-19]:



Scheme 2. Mechanism of preparing tetrazol derivatives [A15-A19]

When viewing the infrared spectrum, it was observed that a medium band appeared in the range (3143-3195) cm^{-1} due to the stretching of the (NH) group, and the emergence of two absorption bands in the range (3006-3053) cm^{-1} due to the stretching of the aromatic (CH) afferent. In addition to the emergence of absorption bands at the range (2921-2993) cm^{-1} due to the stretching of the aliphatic (CH) bond, in addition to the emergence of two bands at the range (1614-627) cm^{-1} due to the vibration. (C=C) aromaticity, and the emergence of an intermediate band at the range (1373-1487) cm^{-1} belonging to the group (N=N), and the emergence of other bands at the range (1280-1214) cm^{-1} attributed to the range of (CN) as well as the emergence of absorption bands at the range (1014-1087) cm^{-1} due to the stretching of the (NN) coupling, and the emergence of absorption bands at the range (1664-1687) cm^{-1} due to the stretching of the (C=O) amide bond, and the emergence of another band at the range (1560-1596) cm^{-1}, which is attributed to the stretch of pinching (C=N) in the pyrimidine ring where these bands were close to what is found in the literature (24,25), and as in Table (3), which shows the results of infrared absorption (cm^{-1}). The absorption values in the ultraviolet spectrum of tetrazol derivatives [A15-A19], and Figure (5a) show the infrared spectrum. For compound [A17] as a model for this group.

When studying the proton NMR spectrum of the compound [A17], it was observed that a single signal appeared at (8.90) ppm attributed to the proton of the group (e) (NH). It appeared in the spectrum also the presence of a binary signal in the region (8.50) ppm belongs to the protons of the group (a) (CH-Pyi), and it appeared in the spectrum also the presence of multiple signals at (7.50 - 7.61) ppm related to the protons of the aromatic ring (g, h) (CH-Ar), and a triple signal was also observed. At (6.74) ppm belonging to the proton of (CH-Pyi ') (b), a triple signal was also observed at (5.94) ppm attributed to the proton of the group (c) (NH) associated with the pyrimidine ring, as well as the emergence of a signal A single at (5.03) ppm refers to the proton of the carbon atom for the five-membered ring, (f) (CH). The appearance of two equivalent signals was observed at (3.81) ppm due to the protons of the two-fold group (CH_2) (d). A single signal was observed in (3.26) ppm is attributed to the proton of the methylation group (j) (CH_3), and the appearance of a binary signal at (2.93) ppm refers to the proton of the nitrogen atom (i) (NH) for the pentagonal ring (27). Fig. (5 b) as an example of ^{1}HNMR for [A17]

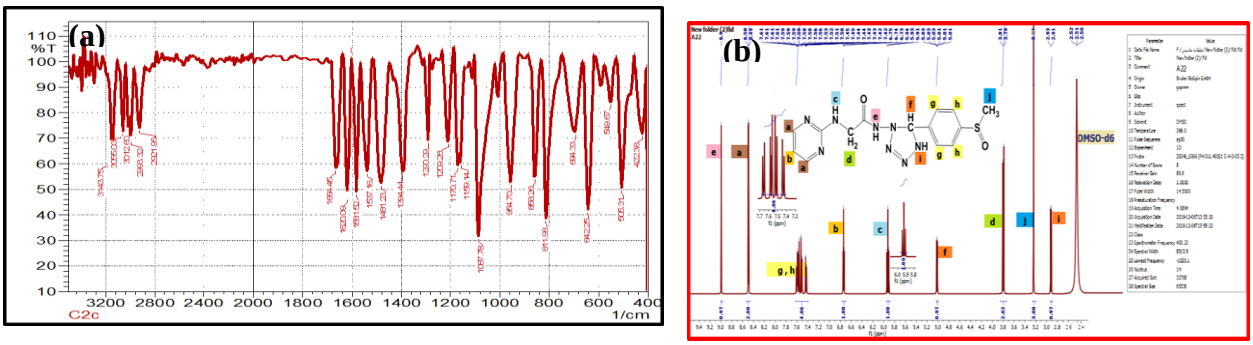
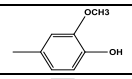
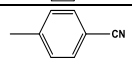
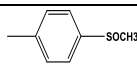
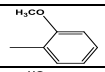
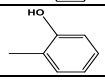


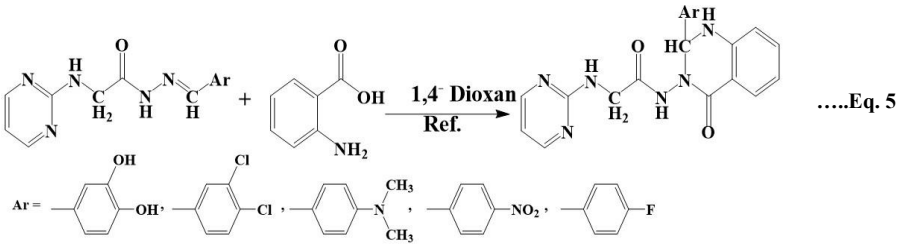
Fig. 5. shows (a) Infrared spectrum, (b) the proton NMR spectrum for the compound [A17].

Table 3. Infrared absorption results (cm-1) and absorbance values in the ultraviolet spectrum of tetrazole derivatives [A15-A19]

Comp. No.	Ar	λ max$_1$ λ max$_2$ Aceton	IR (KBr) cm^{-1}							
			ν (C=O) Amid.	ν (N-H)	ν(C-H) Arom., Aliph.	ν (C=C) Arom.	ν (N=N)	ν (C-N)	ν (N-N)	Others
A_{15}		216 340	1687	3143	3006 2921	1622	1487	1286	1041	ν (OH).(3529), ν (C=N) 1570 (C-O-C)1382
A_{16}		255 391	1674	3155	3029 2964	1614	1460	1201	1014	ν (CN).(2244) ν (C=N).Pyi 1560
A_{17}		234 385	1664	3143	3021 2993	1620	1481	1209	1087	ν (C-S,S-O).642,811 ν(C-O).1290(C=N)1581
A_{18}		239 308	1668	3195	3053 2970	1627	1373	1203	1037	(C-O).(1272) ν(C=N).(1596)
A_{19}		242 377	1668	3155	3012 2955	1614	1487	1207	1027	ν (OH).(3512). ν(C=N)Pyi.(1588)

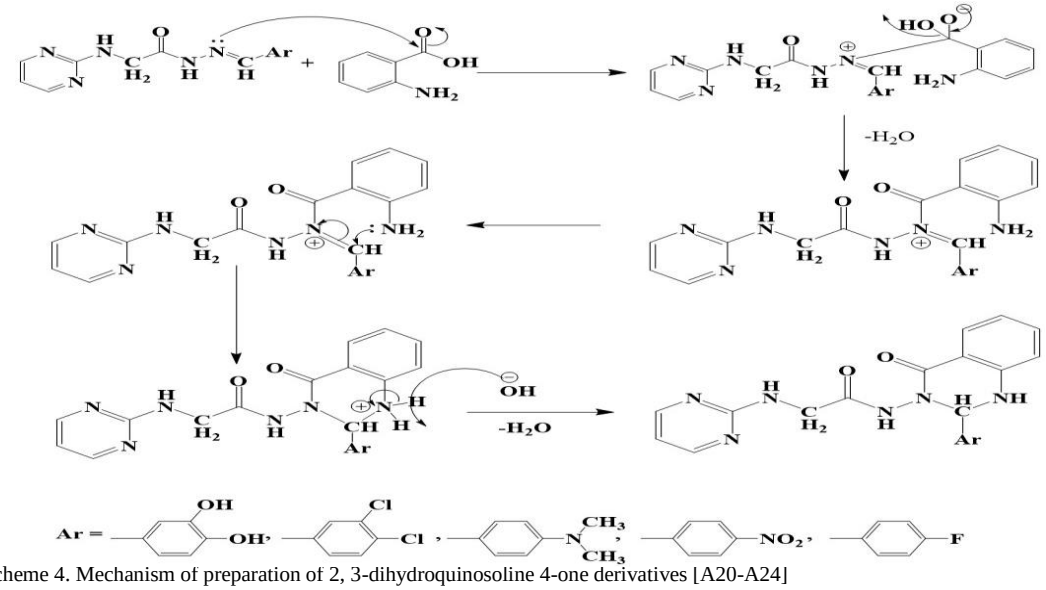
Preparation of some 2,3-dihydroquinosulin4-en derivatives [A20-A24] [22]

The 2,3-dihydroquinosulin 4-en derivatives [A20-A24] were prepared from the reaction of one mole of the prepared Schiff bases [A3-A14] with one mole of anthranilic acid in 1,4-dioxane as a solvent to give a hexagonal heterocyclic of 2,3-dihydroquinosulin4-one derivatives [A20-A24], as shown in the following equation:



.....Eq. 5

The following scheme illustrates the known mechanism (23) for preparing 2, 3-dihydroquinosulin4-en derivatives [A20-A22]:



Scheme 4. Mechanism of preparation of 2, 3-dihydroquinosoline 4-one derivatives [A20-A24]

When studying the infrared spectrum, it was observed that the medium band at (1564-1583) cm^{-1} could be assigned to the group (C=N) appeared, and the emergence of a strong band at the frequency (1660-1685) cm^{-1} related to the stretch of the carbonyl lactam bond (C=O), and a sharp absorption band was

observed at the range (3143-3220) cm^{-1} due to stretching the (NH) bond, and the emergence of absorption bands at the range (3012-3078) cm^{-1} is due to (CH) aromatic, as well as the appearance of the absorption band at the range (2904-2981) cm^{-1} due to the stretching of the aliphatic (CH) bond. The appearance of the band at the range (1608-1628) cm^{-1} is due to the vibration of the aromatic pistons (C=C), and the appearance of the same intermediate band at the range (1296-1402) cm^{-1} belongs to the (CN) group, and other bands appear at the range (1002-1037) cm^{-1} attributed to the hardness stretch (NN). These packages were close to what was found in (24.25), as in Table (4), which shows the results of infrared absorption (cm^{-1}), and Figure (6 a and b) that shows infrared spectrum and the proton NMR spectrum for the compound [A22] as a model for the group.

Elemental analysis (C.H.N.S), the accurate elemental analysis measurement was performed for some of the prepared compounds, and the measurements were identical or close to the calculated ratio and as shown in Table (5).

Evaluation of the biological activity of some prepared compounds.

Some of the prepared compounds' biological efficacy was evaluated, as the heterocyclic compounds exhibited different biological efficacy against the positive bacteria for the Gram stain and the negative for the Gram stain. The effect of the compounds prepared in this research was evaluated on four types of bacteria, namely: Escherichia coli, Klebsiella pneumonia, Staphylococcus aureus, and Staphylococcus epidermidis. This bacterium was chosen due to its medical importance as it causes many diseases and differs in its resistance to antibiotics. The biological effectiveness of some compounds prepared using the drilling method, the tablet method, and measuring the inhibition level was measured. The results indicate that the prepared compounds can inhibit bacteria's growth in their two types, positive and negative for the Cram stain, in different proportions, as shown in Table (6).

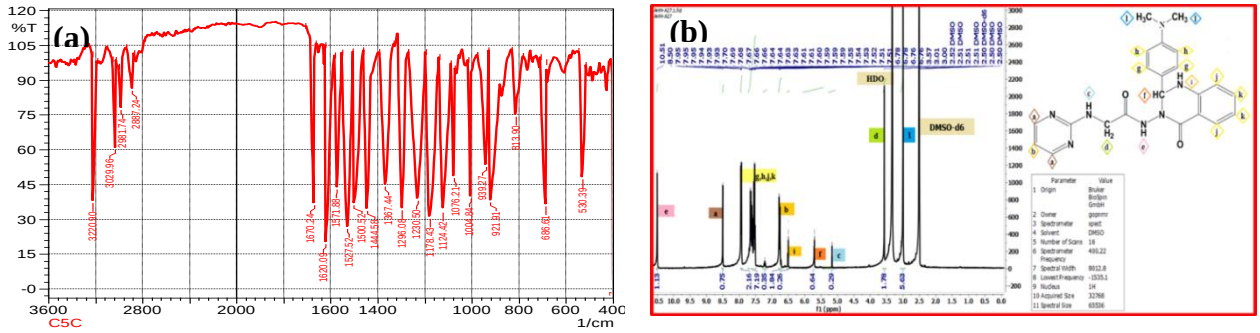


Fig. 6. shows (a) Infrared spectrum, (b) the proton NMR spectrum for the compound [A22].

Table (4) Infrared absorption results (cm^{-1}) and absorbance values in the ultraviolet spectrum of the 2, 3-dihydroquinosoline 4-En derivatives [A20-A24]

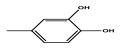
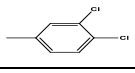
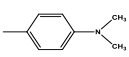
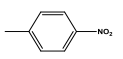
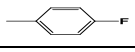
Comp. No.	Ar	λmax$_1$ λmax$_2$ THF	IR (KBr) cm^{-1}							
			ν (C=N) Pyi.	ν (N-H)	ν(C-H) Arom., Aliph.	ν (C=O)	ν (C=C)	ν (C-N)	ν (N-N)	Others
A_{20}		262 385	1583	3143	3078 2970	1660	1627	1402	1026	ν (OH).(3529)
A_{21}		261 360	1575	3209	3012 2904	1679	1620	1382	1037	ν (C-Cl). asy. (935) sym. (1126)
A_{22}		210 365	1571	3220	3029 2981	1670	1620	1296	1004	ν N (CH_3) asy. (1444) sym. (1367)
A_{23}		241 375	1564	3195	3058 2975	1685	1608	1301	1002	ν (NO_2). asy. (1330) sym. (1525)
A_{24}		239 301	1581	3201	3035 2927	1668	1628	1338	1016	ν (C-F). (1112)

Table 5. Elemental analysis (C.H.N.S) for the compound [A1, A2, A10, A11, A17, and A22]

Comp. No.	Molecular Formula	Found				Calculated			
		C%	H%	N%	S%	C%	H%	N%	S%
A_1	$C_2H_5N_2OCl$	22.13	4.64	25.81	.....	22.05	4.60	25.79	.....
A_2	$C_6H_9N_5O$	43.11	5.43	41.89	…….	43.6	5.35	41.79	……
A_{10}	$C_{14}H_{12}N_6O$	59.99	4.32	29.89	.....	67.59	4.22	29.88	.....
A_{11}	$C_{14}H_{15}N_5O_2S$	52.98	4.76	22.07	10.10	52.88	4.73	22.2	10
A_{17}	$C_{14}H_{16}N_8O_2S$	46.66	4.48	31.09	8.90	46.69	4.50	30.12	8.91
A_{22}	$C_{22}H_{23}N_7O_2$	63.30	5.55	23.49	……	63.40	5.45	23.55	……

Table 6. The antibacterial activity of the prepared compounds in the growth of several negative and positive bacteria (the diameter of the inhibition circuit is measured in mm

Comp. No.	Conc. mg/ml	E. Coil	K. Pneumonia	S. Aureus	S. Epidermidis	Inhibition Zone(mm)
A_1	25	-	++	-	-	0
	50	+	+++	+	+	1-2
	100	+	+++	++	+	1-4
A_2	25	+	++	+	+	1-2
	50	++	+++	++	+++	1-5
	100	+++	+++	+++	+++	4-5
A_6	25	+	+	++	+	1-4
	50	+++	++	++	+++	2-5
	100	+++	+++	+++	+++	4-5
A_7	25	+	+	-	++	0-2
	50	+++	++	+	+++	1-5
	100	+++	+++	++	+++	2-5
A_{16}	25	-	-	-	+	2
	50	++	+	+	++	1-4
	100	+++	++	++	++	2-4
A_{17}	25	-	-	-	-	0
	50	+	+	++	++	1-3
	100	+++	++	++	++	2-4
A_{24}	25	-	-	-	-	0
	50	+	+	+	+	1-2
	100	++	++	++	++	2-4
Amoxicillin	25	2.5	3	2.7	2.8	3
Ampicillin	50	2	2.5	2.5	3.7	4
Blank disk	100	0	0	0	0	0

= (-)no damping (++) = 2 - 4 mm damping

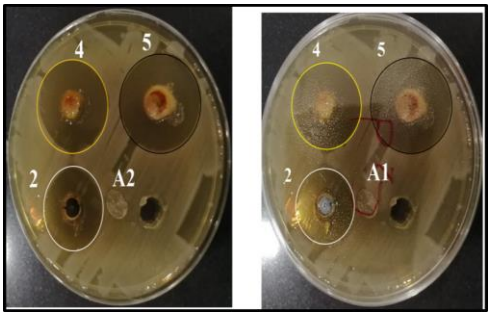


Fig. 7. The inhibitory activity of [A2, A1] against bacteria *Klebsiella pneumonia*

2-1= (+)mm damping (+++) = 4 - 5 mm damping

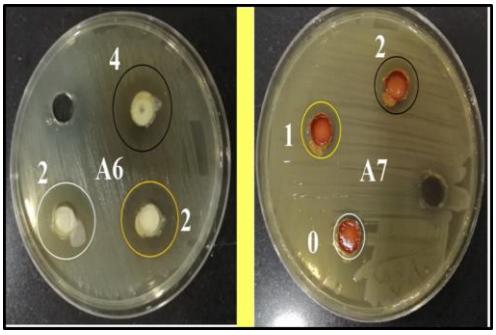


Fig. 8. The inhibitory activity of the [A7, A6] against Bacteria *Staphylococcus aureus*

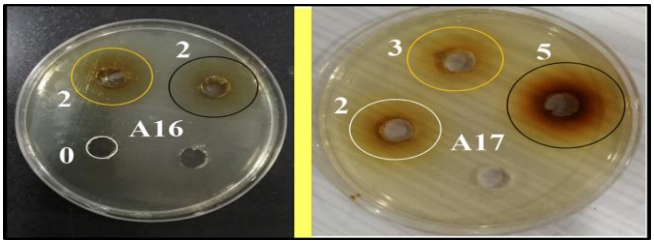


Fig. 9. The inhibitory activity of [A16-A17] against Escherichia coli bacteria

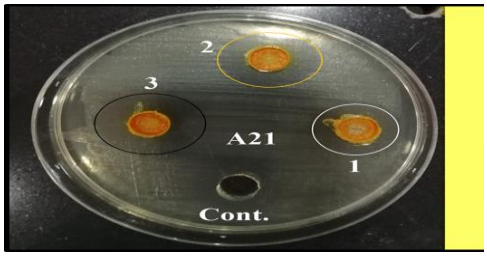


Fig. 10. The inhibitory activity of [A21] against bacteria *Staphylococcus epidermidis*

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تحضير وتشخيص بعض مشتقات التيترازول وتقييم فعاليتها البايولوجية

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الخلاصة

تضمن هذا البحث تحضير سلسلة من مركبات حلقية غير متجانسة حيث تم تحضير المركب2-chloroacetohydrazide من تفاعل أثيل كلورو إيثانوات مع الهيدرازين المائي (95%) وقد أجري التفاعل تحت ظروف باردة ،تم تحضير 2-(pyrimidin-2-ylamino)acetohydrazide بالتفاعل 2-chloroacetohydrazide مع 2-أمينو بيريميدين في إيثانول مطلق باستخدام هيدروكسيد البوتاسيوم (KOH)، ثم تفاعل 2-(pyrimidin-2-ylamino)acetohydrazide مع ألدهيدات مختلفة لإنتاج مشتقات قواعد شيف A14- A3 والتي تم إدخالها بطريقتين تخليقيتين مختلفتين تم تصنيع الأولى. ثم تم تصنيع مشتقات تترازول [A15-A19] من مفاعل الهيدروزون (قواعد شيف) [A14-A3] المحضر بتفاعل قاعدة شيف مع أزيد الصوديوم. في الطريقة الثانية ، تم تصنيع المشتقات 2 ، 3-ثنائي هيدروكوينوزولين-4-وان [A24-A20] من تفاعل بعض قواعد شيف في الخطوة الثالثة مع حمض ألانثرانلك (2-حمض أمينو بنزويك) باستخدام 1.4-ديوكسان كمذيب، تم تشخيص المركبات التركيبية ببعض الطرق الطيفية، مثل الأشعة فوق البنفسجية، FTIR، H-NMR1 والتحليل الكمي للعناصر (CHNS). تمت دراسة تأثير بعض المركبات الصناعية على نمو أربعة أنواع من العزلات البكتيرية المعروفة بمقاومتها للمضادات الحيوية. تم استخدام الأموكسيسيلين والأمبيسيلين كعينة تحكم ، وأظهرت بعض المركبات المحضرة فعالية تثبيط جيدة ضد البكتيريا المستخدمة,*Klebsiella pneumonia, Escherichia coli* (*Staphylococcus aureus, and Staphylococcus epidermidis*).