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PREPARATION OF HETEROGENEOUS CONGENITAL COMPOUNDS

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Abstract:

The study included the preparation of heterocyclic compounds, as different types of new heterocyclic compounds were prepared, where four types of chalcones (H1, H2, H4, H6) were reacted with three different types of hydrazines (80% Hydazinehydrate and 2,4 dinitro phenyl hydrazine and (thiosemicarbazide dissolved in ethanol) in the presence of three drops of sulfuric acid H2SO4 as a catalyst from 6 hours to 24 hours, and some cases do not need a catalyst, compounds (1N,2N,4N,6N,1S,6H) were prepared, where this was diagnosed Compounds by infrared FT-IR, proton nuclear magnetic resonance spectra (H-NMR) and electrospray ionization mass spectrometry (ESI), as the validity of these structures was confirmed for heterocyclic compounds. The biological activity of the prepared compounds was studied for two types of pathogenic bacteria for humans, which are fecal coliform bacteria. Gram-negative *Escherichia coli*, and Gram-positive bacteria, *Staphylococcus aureus*, that cause skin infections. . It gave the highest efficacy compound 6H against both types of pathological bacteria under test, followed by compound 2N, then compound 6N, and compound 4N, after that, the biological activity of compound 4N was studied, and its biological activity was studied as an inhibitor of cholinesterase in blood serum.

Keywords: Heterocyclic compounds, Biological activity, *E.coli* , *Staph*

INTRODUCTION

Heterocyclic compounds are compounds that contain one or more heterocyclic atoms in their ring structure. Through this definition, we notice that more than 70% of drug and pharmaceutical compounds almost contain at least one of the heterocyclic rings, in addition to many natural compounds that fall under the same definition that contain heterocyclic rings. Examples of basic life compounds are found. In the human body, which contain heterogeneous rings, such as hemoglobin, which contains the pyrrole ring, some amino acids, carbohydrates, and nitrogenous bases. Heterocyclic compounds of Alpyrazole are of great importance in the pharmacological field (1-8). As for the pyrazole compounds, they are heterocyclic compounds containing three carbon atoms and two nitrogen atoms adjacent to them with two double bonds. In general, the two nitrogen atoms are located in position 1 and 2 in each structure. The symmetries of 1H-pyrazole include 4H-pyrazole, 3H-pyrazole, 2H-pyrazole, and 3H, 2H, and 1H indicate the position of the first hydrogen atom or the substituted group according to the numbering system of the pyrazole compounds. The number placed in front of the word dihydro indicates the saturated carbon atom. Dihydro- compounds 2H and 3H-pyrazole must contain one double bond and may be called pyrazoline or dihydro-pyrazoles. Either compounds 4H-pyrazole, it must contain two double bonds and one carbon atom with a tetrahedral shape, which can be called cyclicazine or isopyrazole, and the following figures show the numbering and naming system of the 1H-pyrazole symmetries, Alpyrazole compounds are classified as alkaloids, although they are rare in nature. They have been used to treat allergies, anti-inflammatory, antipyretic, antiarrhythmic, tranquilizing, muscle relaxant, psycoanaeptic, antispasmodic, monoaminoxidase inhibitors, diabetes mellitus, and antibacterial. Also used compounds pyrazole-4-carboxylic acid hydrazine or hydrazine (9-12). Based on the findings of recent studies that many microorganisms cause many different types of diseases, research has tended to study the inhibitory effect of organic compounds on pathogenic bacteria. Pathogenic bacteria are single-celled, prokaryotic, microscopic catnip with specific dimensions and length, and take multiple forms, including spherical, stick, oral, spiral, marketed, and budding bacteria (13-14).

Biological activity, in this study, two types of bacteria were used that cause multiple diseases in humans, some of which are negative. The other is *Escherichia Coli*, represented by (Gram negative) bacteria *Staphylococcus aureus*, represented by (Gram positive) bacteria , Below is a brief look at these two types of bacteria , They are microorganisms and a type of bacteria *Escherichia coli* Gram-negative members of the enteric family are present singly or double in the mucous layer of the colon of mammals and are characterized by their ability to reduce nitrates and ferment many sugars such

as maltose, cocos, lactose, etc., as well as their ability to decompose blood, and then they are responsible for many diseases of the digestive system, urinary Central nervous system and blood poisoning , But *Staphylococcus aureus* They are microscopic living organisms and a type of gram-like wave bacteria that are spherical or oval in cluster shape. These bacteria grow under aerobic conditions and are found on the skin and mucous membranes of humans and animals alike, in addition to their presence sometimes in the upper respiratory tract and intestines. With its ability to grow in highly saline and sugary solutions, and its ability to produce enzymes that dissolve antibiotics containing beta-lactams and dissolve blood, therefore, it causes human diseases of various types, such as dermatitis, food poisoning, osteitis, and other conditions such as blood poisoning. The enzyme acetylcholinesterase is a complex molecule consisting of four similar units, each containing, A monopeptide chain consisting of fifty-seven amino acids and nine carbohydrate chains, this enzyme is found in some tissues and different types of organisms, as it is found in the tissues of mammals, Its presence is concentrated in the central nervous system and blood cells (15-18). The main role of the acetylcholinesterase enzyme is to terminate the transmission of impulses at the synapses, neurotransmitter due to the decomposition of acetylcholine, resulting in acetic acid and choline (19). The aim of the study is to prepare and characterize a number of new heterocyclic compounds, six types of heterocyclic compounds (N1, N2, N4, N6, 1S, 6H) were prepared, biological activity of compounds and heterocyclic compounds. Where the highest heterocyclic compounds gave the activity is compound 6H against both types of pathological bacteria under test, followed by compound 2N and then compound 6N After studying the biological activity of all compounds, compound N4 was chosen and a study of its life effectiveness as an inhibitor of the enzyme Acetylcholinesterase (Acetylcholinesterase enzyme) present in the blood serum.

MATERIALS AND METHODS

1- The general method for the preparation of Alpyrazole

(0.001 mole) of Thiosemicarbazide or 2,4-dinitrophenylhydrazine was added to 0.001 mole of gallcon dissolved in 10 ml of absolute ethanol in a 100 ml round flask equipped with a magnetic stirrer. Then (2-3) drops of concentrated sulfuric acid were added to the mixture, then the reaction was heated and escalated for a period of time. (12) hours with continuous stirring. After the end of the reaction, the mixture was left in the refrigerator for (24) hours to complete sedimentation. The precipitate was dried, crystallized in ethanol, and its melting point was measured. To verify that the reaction occurred, thin layer chromatography (TLC) and a sublimation mixture of ethyl acetate: hexane (3:1) (20) were used.

A- Preparation of compound 1N

The same general method was carried out with a reactance of 0.198 g (0.001 mole). 2,4-dinitrophenylhydrazine with 0.334g (0.001mole) of chalcone H1 dissolved in (10ml) of absolute ethanol and a reddish-brown precipitate was obtained with a melting point at (214-216°C).

B- Preparation of compound 2N

The same general method was carried out with a reactance of 0.198 g (0.001 mole). 2,4-dinitrophenylhydrazine with 0.364g (0.001mole) of chalcone H2 dissolved in (10ml) of absolute ethanol and an orange precipitate was obtained with a melting point at (164-166°C).

C- Preparation of compound 4N

The same general method was carried out with a reactance of 0.198 g (0.001 mole). 2,4-dinitrophenylhydrazine with 0.262 g (0.001 mole) of chalcone H4 dissolved in (10 ml) of absolute ethanol and a dark red precipitate was obtained with a melting point at (114-116°C).

D- Preparation of compound 1S

The same general method was carried out with a reaction of 0.091g (0.001mole) of Thiosemicarbazide with 0.369 g (0.001 mole) of chalcone H5 dissolved in (10 ml) of absolute ethanol and a light orange precipitate was obtained with a melting point at (102-104 °C).

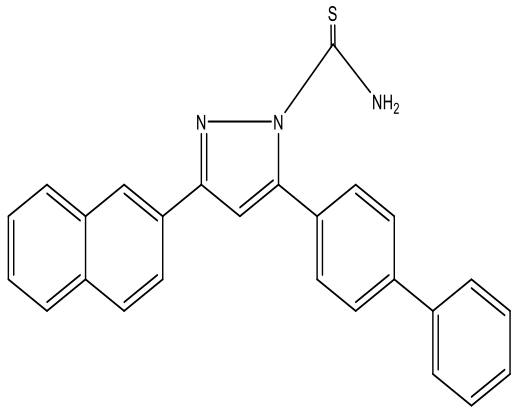
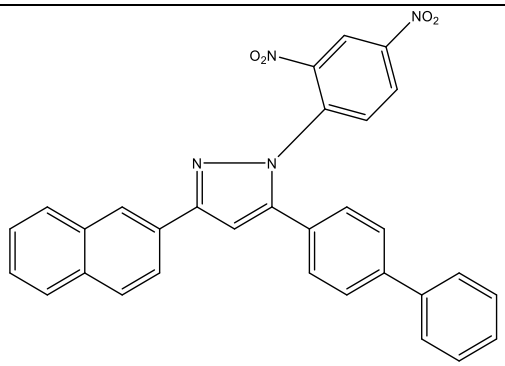
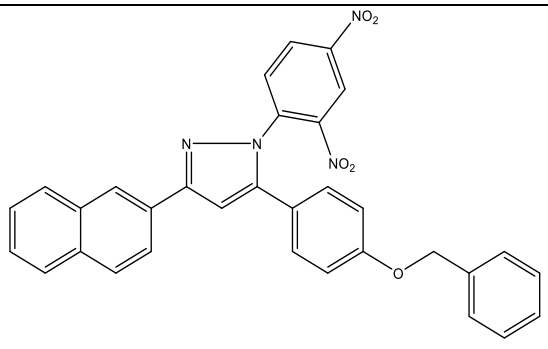
E- Preparation of compound 6N

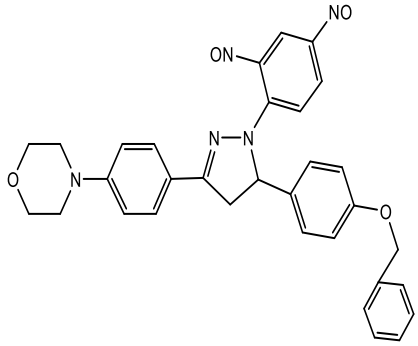
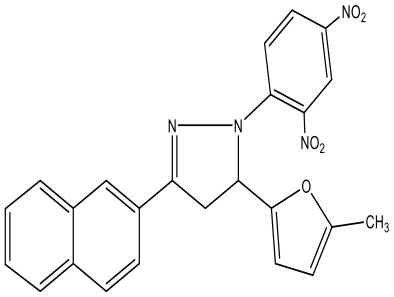
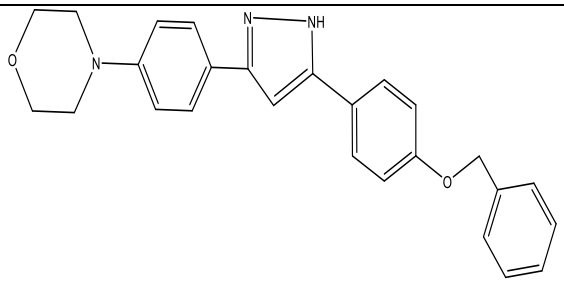
The same general method was carried out with a reactance of 0.198 g (0.001 mole). 2,4-dinitrophenylhydrazine with 0.399 g (0.001 mole) of chalcone H6 dissolved in (10ml) of absolute ethanol and a brown precipitate was obtained with a melting point at (174-176°C).

F- Preparation of compound 6H

The same general method was carried out by reacting 0.032 g (0.001 mole) of Hydrazine with 0.399 g (0.001 mole) of chalcone H6 dissolved in (10 ml) of absolute ethanol and a white precipitate was obtained with a melting point at (206-208°C).

Physical and chemical properties of prepared heterocyclic compounds

code	compound	m.p	color	Time	Cofactor
1S	 5-([1,1'-biphenyl]-4-yl)-3-(naphthalen-2-yl)-1*H*-pyrazole-1-carbothioamide Chemical Formula: $C_{26}H_{19}N_3S$ Molecular Weight: 405.52	206-208°C	light yellow	12 hours	H_2SO_4
1N	 5-([1,1'-biphenyl]-4-yl)-1-(2,4-dinitrophenyl)-3-(naphthalen-2-yl)-1*H*-pyrazole Chemical Formula: $C_{31}H_{20}N_4O_4$ Molecular Weight: 512.53	214-216°C	auburn	8 hours	H_2SO_4
2N	 5-(4-(benzyloxy)phenyl)-1-(2,4-dinitrophenyl)-3-(naphthalen-2-yl)-1*H*-pyrazole Chemical Formula: $C_{32}H_{22}N_4O_5$ Molecular Weight: 542.55	164-166°C	Orang	8 hours	H_2SO_4

6N	 4-(4-(5-(4-(benzyloxy)phenyl)-1-(2,4-dinitrosophenyl)-4,5-dihydro-1*H*-pyrazol-3-yl)phenyl)morpholine Chemical Formula: $C_{32}H_{29}N_5O_4$ Molecular Weight: 547.62 Elemental Analysis: C, 70.19; H, 5.34; N, 12.79; O, 11.69	174-176°C	Brown	12 hours	H_2SO_4
4N	 1-(2,4-dinitrophenyl)-5-(5-methylfuran-2-yl)-3-(naphthalen-2-yl)-4,5-dihydro-1*H*-pyrazole Chemical Formula: $C_{24}H_{18}N_4O_5$ Molecular Weight: 442.43 Elemental Analysis: C, 65.15; H, 4.10; N, 12.66; O, 18.08	114-116°C	Dark red	6 hours	H_2SO_4
6H	 4-(4-(5-(4-(benzyloxy)phenyl)-1*H*-pyrazol-3-yl)phenyl)morpholine Chemical Formula: $C_{26}H_{25}N_3O_2$ Molecular Weight: 411.51	220-222°C	White	6 hours	-

2- SOLUTIONS OF PREPARATION

A- Bufferphosphate

The buffer solution was prepared. Bufferphosphate pH=7.3,0.2M by dissolving (2.8g) of (M.w=141.69 Na2HPO4) in 100ml of distilled water, then adjust the pH by adding drops of HCI hydrochloric acid was used directly. (21)

B- Detector (DTNB)

This reagent was prepared as 5,5-Dithiobis-2-nitrobenzoic acid (O.OO1M).
Dissolve (1g) of DTNB (=396.36 M.W) in (25ml) distilled water with continuous stirring.

C- Baseline solution (Acetyl thiocholine iodide)

(0.017g) of the base material was dissolved in (1ml) of water.

3- Determining the activity of cholinesterase enzyme in human blood serum using the method "WHO" Glossary as a following:

A- (2.25ml) of the buffer solution was placed in a test tube, pH=7.3, and (50 µI) of the DTNB reagent solution and (10 µI) of blood serum were added to it, and the previous ingredients were mixed using the Vortex mixer.
B- Withdraw from the first mixture (2ml) and put it in the measuring cell (3ml), then add the substance to it. The base (34 µI) thiocholin acetyl iodide at a concentration of (0.06M), after which the amount of change in the intensity of

Absorption of the enzyme before and after the addition of the substrate at the wavelength (412 nm) for every three minutes of the reaction of the enzyme and the substrate.

RESULTS AND DISCUSSION

HNMR spectrum(21)

a: Identification of compound 1N

Compound N1 was identified by H-NMR spectroscopy using CDCI3 solvent , It was observed that a multi-signal appeared at the location 8.52-6.81 pmm) (H19) belonging to the aromatic protons. And the appearance of a monomeric signal at 7.86ppm (H1) referring to the CH of the pyrezole ring, and the appearance of a signal of 7.42 (returning to the solvent CDCI3). The appearance of a signal at 1.6)) refers to the H2O band.

b: Characterization of compound 2N

Compound 2N was identified by H-NMR spectroscopy using the solvent DMSO
It was observed that a multi-signal appeared at the site 8.85-6.91 pmm (H19) belonging to the aromatic protons. The appearance of a monomeric signal at 7.56 ppm (H1) due to the CH of the pyrezole ring, the appearance of a signal of 5.17 (H2) to OCH2, the appearance of a signal of 5.04 ppm (returning to the solvent DCM), the appearance of the signal of the DMSO solvent at (2.50 ppm), the appearance of a signal at (3.44 ppm) Return to pack H2O.

c: Identification of compound 1S

Compound 1S was identified by H-NMR spectroscopy using the solvent DMSO, it was observed that a multi-signal appeared at the site 8.99-7.40 pmm (H16) belonging to the aromatic protons. And the appearance of a monomeric signal at 7.19 ppm (H1) belonging to the CH of the pyrezole ring, the appearance of a 4.50 (H2) signal referring to NH2, the appearance of the DMSO solvent signal at (2.50 ppm), and the appearance of a signal at (3.33 ppm) belonging to the H2O bundle.

d: Characterization of compound 4N

Compound 4N was identified by H-NMR spectroscopy using the solvent DMSO , It was noticed that a multi-signal appeared at the location 8.83-7.06 pmm (H12) belonging to the aromatic protons. And the appearance of a binary signal at (2.42ppm) (H2)) due to the CH of the pyrezole ring and the emergence of a signal of (2.42) (H3) to CH3 and the appearance of a triple signal at(6.39ppm) (H1) to CH2 and the appearance of the DMSO solvent signal at (2.50 ppm) the appearance of a signal at (3.33 ppm) returns to packet H2O.

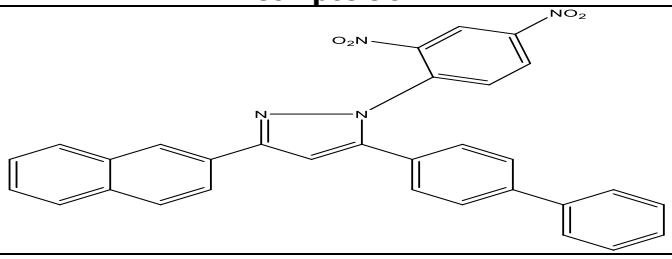
e: Identification of compound 6N

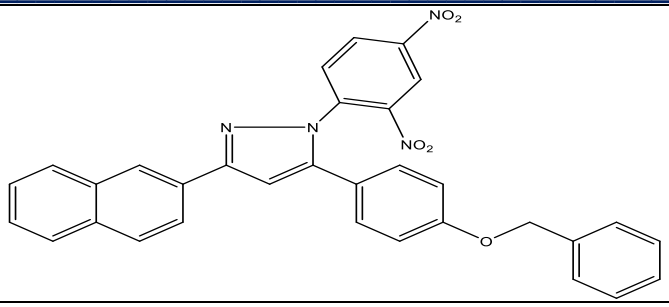
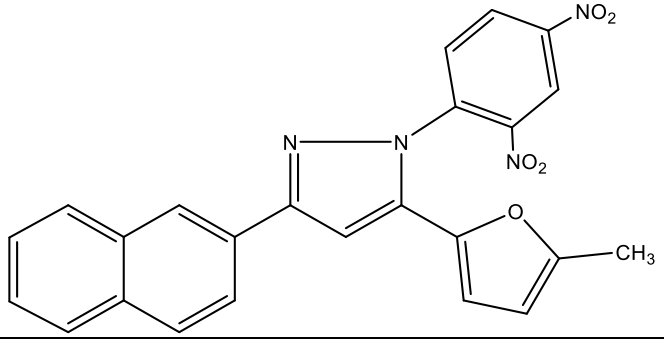
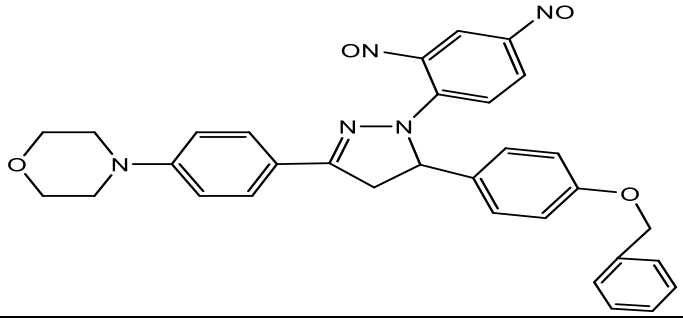
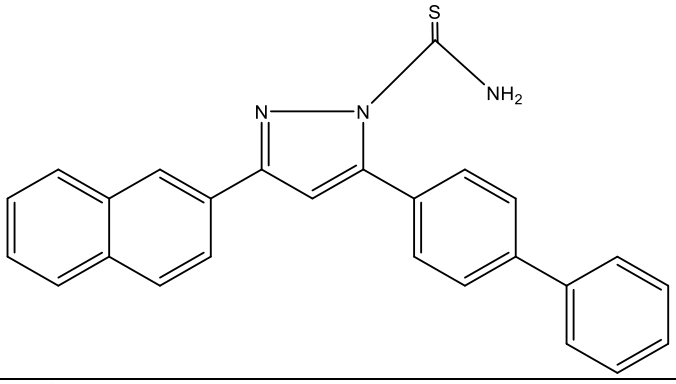
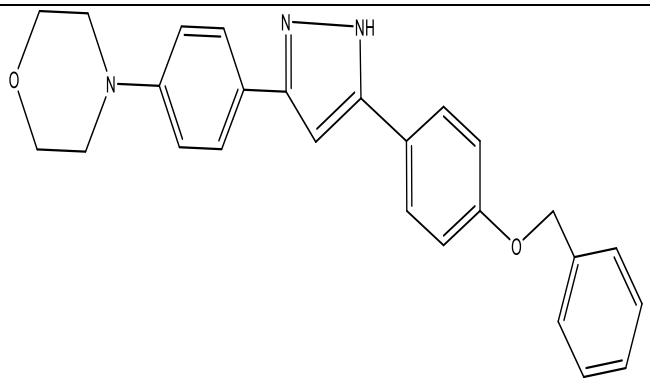
Compound 6N was identified by H-NMR spectroscopy using the solvent DMSO, It was observed that a multi-signal appeared at the location (8.81-6.98 pmm) belonging to (H16) to the aromatic protons, and the emergence of two signals for two bands at the location (3.2) and 3.7) belonging to H8 2(CH2-CH2). The appearance of a binary signal at 3.74ppm (H2) due to the CH of the pyrezole ring, the appearance of a ternary signal (5.12ppm) (H1) to CH2, the appearance of a mono signal (5.28ppm) (H2) to OCH2, the appearance of the DMSO solvent signal at (2.50ppm), and the appearance of a signal at (3.21 ppm) it returns to packet H2O.

f: Identification of compound 6H

Compound 6H was identified by H-NMR spectroscopy using the solvent DMSO, It was observed that a multi-signal appeared at the site 8.01-6.92 pmm (H14) belonging to the aromatic protons, and the emergence of two signals for two bands at (3.2) and 3.8 (returning to H8) 2(CH2-CH2), and the appearance of a mono signal at (7.99 ppm) (H1). refer to NH. And the appearance of a monomeric signal at 6.90ppm (H1) due to the CH of the pyrezole ring, and the appearance of a monomeric signal (H2) at 5.11ppm (referring to OCH2) and the appearance of the DMSO solvent signal at (2.50ppm).

Table (1) the most important chemical displacements in ppm units for the 1HNMR spectra of the prepared heterocyclic compounds

Code	Composition	chemical displacements
1N		δ=8.52-6.81(m,19H,Ar-H) δ=7.86(s,1H,CH)

2N		δ=8.85-6.91(m,19H,Ar-H) δ=7.56 (s,1H,CH) δ=5.04(s,2H,OCH_2)
4N		δ=8.83-7.06(m,12H,Ar-H) δ=2.42(d,1H,CH) δ=6.39 (t,2H,CH_2) δ=2.42(s,3H, CH_3)
6N		δ=8.81-6.98(m,16H,Ar-H) δ=3.74 (d,1H,CH) δ=5.12(t,2H,CH_2) δ=5.28(s,2H,OCH_2) δ=3.7-3.2 (m,8H,-CH_2-CH_2-)
1S		δ=8.99-7.40(m,16H,Ar-H) δ=7.19+ (s,1H,CH) δ=7.99(s,1H,NH) δ= 4.50(s,2H,NH_2)
6H		δ=8.01-6.92(m,13H,Ar-H) δ=6.90 (s,1H,CH) δ=7.99(s,1H,NH) δ= 5.11(s,2H,OCH_2) δ= 3.8-3.2 (m,8H,-CH_2-CH_2-)

2- ESI mass spectrometry

Mass spectrometry of the prepared heterocyclic compounds

The mass spectra of the electrical ionization of the compounds prepared from (N1,N2,N4,N6,1S,6H)) are shown in(Figure 2) conforming to the molecular weight of the proposed formulas. As for the second figure, the molecular weight with a sodium molecule in compounds (N1, N2, N6, 1S, 6H) (98), As shown in the following table.

Table (2) shows the mass spectra of the electro ionization of the prepared heterocyclic compounds

compound symbol	$[M+Na]^{+1.-1}$ $[2M+Na]^{+1.-1}$	The molecular weight of cyclic compounds is heterogeneous
1N	536	512
2N	566	542
4N	905	442
6N	571	547
1S	429	504
6H	435	411

3-

Testing the biological activity of pyrazole heterocyclic compounds(22-23)

The biological activity of some chemical compounds was tested in the microbiology laboratory for postgraduate studies in the Department of Life Sciences, College of Education for Pure Sciences - University of Basra against two types of pathogenic bacteria for humans, which are Gram-negative Escherichia coli and Gram-positive Staphylococcus aureus. It was obtained from patients attending Al-Fayhaa General Hospital in Basra Governorate, and the biological activity was tested by the Agar well diffusion method according to the method of (Balouiri et al. (2016) with some minor modifications as follows:

The bacteria were activated on Nutrient agar culture medium and incubated in the incubator at 37ºC for 24 hours.

1- The bacterial suspension was prepared by filling a loop vector from the bacterial culture at the age of 24 hours and adding it to 10 ml of normal saline, and the concentration of the bacterial suspension was regulated to 0.5 McFarland (1.5 * 108 CFU/ml) and kept in the refrigerator at a temperature of 4ºC until Usage.

2- The bacterial suspension prepared in the paragraph above was spread on Mueller-Hinton agar for the bioactivity test in Petri dishes using cotton swab, and the dishes were left for 10 minutes to dry the bacterial suspension.

3- Holes were made in the dishes with a diameter of 6 mm by means of a cork borer, and 75 microliters of each chemical compound were added by means of a micropipette to these holes, and the dishes were left for a while in the culture room, after which they were incubated in the incubator at a temperature of 37ºC for 24 hours, after which the diameter was measured Zone bacterial growth inhibition and record the results.

4- The control treatment included adding the same volume of DMSO solvent to the wells instead of the chemical solutions and measuring the diameter of the bacterial growth inhibition zone, if any. 83-84)) The inhibitory ability of some of the tested chemical compounds, which was represented by the emergence of zones of inhibition of bacterial growth (the area free of bacterial growth around the pits of acres) indicates the ability of these chemical compounds to kill pathogenic bacteria under test, to varying degrees, according to the different diameters of the zones of inhibition measured (The most effective cyclic compound is compound H6 against both types of pathogenic bacteria under test, followed by compound 3N, compound 6N, and compound N4.

And there are compounds that did not affect the pathogenic bacteria tested at all, i. Caused by pathological bacteria, especially since these bacteria were resistant to more than three types of antibiotics, according to the preliminary tests conducted in the above-mentioned laboratory against antibiotics, or to combine these compounds with antibiotics to increase their effectiveness against pathological bacteria and activate them (Al-Saady, 2021), and this requires conducting more tests on these chemical compounds to know their cytotoxicity on normal cells and the extent of their negative effects on them, and to determine half the lethal dose, IC50, for normal cells, as well as to study the possibility of its effect on cancer cells.

Effective compound mm (5-10) damper diameter*

Good Effective Composite mm (10-20) Retarding Diameter *

* Retarding with a diameter of more than (20) mm is a highly effective compound

Table (3) represents the biological activity values of chalcone and pyrazole compounds for both types of bacteria staph and *E.coli*

sequence	compound symbol	(Damping zone diameter (mm	
		Staphylococcus aureus	*Escherichia coli*
1	6N	15	12
2	2N	20	12
3	1N	0	0
4	4N	20	5
5	6H	30	35
6	1S	0	0
7	DMSO	0	0

4- The effect of compound (4N) on the activity of cholinesterase (Ch.E) in(24) BLOOD SERUM

When starting the study, the compound (N4) was dissolved using DMSO as a solvent, which had no effect on the action of the enzyme.

A standard solution was made for it, and the concentrations prepared from the compound ranged from (10-5m×8-10-5×2) was studied

The effect of this compound on the activity of the cholinesterase enzyme found in human blood serum, and the best inhibition rate was 77.58%.

By determining the activity of the enzyme once without the use of the inhibitor, and again by using the inhibitor. The inhibitory substance, according to the method of action described in the second chapter

The second (1.25 ml) of the buffer solution (1ml) added the inhibitor (practical part). The inhibition percentage of the enzyme was calculated by the concentrations used for the compound (4N).

Depending on the law of the percentage of the inhibitor by comparing the activity of the enzyme with, without and under the inhibitor

The same conditions and as shown in the equation below. (85-88). The findings of the study are shown in the following table (4).

Table (4) shows the effect of compound 4N as an inhibitor

concentration inhibitor M	enzyme activity µmol/ml/3min	inhibition %
None	5.211	0.0
10^{-5}×8	1.220	78.58
10^{-5}×5.8	1.381	73.49
10^{-5}×3.25	1.638	68.56
10^{-5}×2.6	2.399	53.56
10^{-5}×2	2.818	45.92

The rate of inhibition of the enzyme by the inhibitor can be explained by the presence of the CH3-propellant groups. In an inhibitory organic compound, electrons are pushed through resonance to sites from ,That would increase the nucleophile attack on the active site of the enzyme and then reduce or inhibit it , The action of the enzyme is under study.

CONCLUSIONS

The prepared heterocyclic compounds showed significant biological activity against E.Coli and Staph bacteria. Alpyrazole compounds were not affected by the ambient conditions, as it was found to have significant stability towards light and humidity. The ease of preparation of heterocyclic compounds and the difficulty of their purification. The prepared compound (N4) showed its high biological activity as an inhibitor of choline esterase in blood serum.

REFERENCE

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2. Synthesis, Identification and Study of the Anti-microbial activity of Novel Chalcone and Epoxy chalcone compoundsKawkab A Hussein, Nezar L. Shihab, Bahjat A. Saeed. Chemistry Department, College of Education for Pure Science, University of Basrah , Basrah, Iraq

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