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Tetrazole Derivatives (Preparation, Organic Analysis, Biotic Evaluation, Nano-Study)

Sabrean Farhan Jawad[a], Dr. Nagham Mahmood Aljamali[*b]

[a]*Lecturer, Department of Pharmacy, Al-Mustaqbal University College, Babylon, Iraq*

[*b]*Professor ,Ph. D, Organic Chemistry ,Synthetic Chemistry Field, Iraq*

Abstract

Micro-organisms are the causes of many diseases, so we find a lot of research in the field of studying the biological efficacy of compounds on various types of pathogenic bacteria. Nowadays there are increasing numbers of infections caused by bacteria that are resistant to most of the antibacterial treatments currently available, for this causes we prepared series tetrazole derivative from different heterocyclic compounds like (tetrazole, thiadiazole, oxadiazole, oxazole, imidazole, triazole, thiazole . General studies have been steered for the derivatives to conclude their chemical configurations via spectroscopic performances (FT.IR, H.NMR, Mass)–spectra, also Biotic Evaluation, Nano- study and other laboratory measurements. Some cyclic compounds are used as antimicrobials, and this is what we have proven in our research, as it has been proven that they are compounds that kill microorganisms or stop their growth. Antimicrobial drugs can be divided according to the microorganisms that they can work against. For example, antibiotics are used against bacteria and antifungals are used against fungi.

Keyword: tetrazole; thiadiazole; oxadiazole; oxazole; imidazole; triazole, thiazole, fungi; bacteria.

1. Introduction

Due to the importance of cyclic tetrazol compounds and their derivatives, they have become the focus of researchers' attention. In many studies [1-3], many researchers have used tetrazol derivatives as anti-hyperglycemic agents [4-5]. The efficacy of tetrazol derivatives was applied to two samples of laboratory mice, one with high blood sugar and the other healthy, and laboratory experiments were conducted. By comparing the two groups under study, the researchers concluded that the used tetrazol [6-11] derivatives affect the amount of insulin secreted from the pancreatic gland. When comparing the results, they found that the cyclic tetrazol derivatives significantly reduce the percentage of blood sugar . Some studies [12-20] have proven the effectiveness of triazole derivatives as anti-corrosion materials and materials used as stable dyes when linked to azo groups, and color-blocking groups that increase the intensity of color when dyeing [21-25]. Through the research it was concluded that when the three prepared compounds are combined [26-29] , they appear as a wonderful cathode that inhibits corrosion and is striped [30-33].

EXPERIMENTAL PART:

Several spectrophotometric devices were chosen to prove the structures of the prepared derivatives of triazole and associated with cyclic compounds of sulfur, nitrogen and oxygen, and they were measured at Kashan University. The measurements were with high accuracy and the purity of the compounds was also high.

Manufacturing of Aldamine Compound {1}:

*Corresponding author e-mail; dr.nagham_mj@yahoo.com ; (Dr. Nagham Aljamali).
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4-N,N-dimethylamino aniline (0.01) mole reacted with ammonium thiocyanate (0.01)mole with (10)ml from (Br2) in presence of glacial acetic acid with stirring for (1 hr), then by separation ,drying ,recrystallization to provide 2- aminobenzothiazole derivative which (0.01 mole) reacted with p-formal ethylbenzoate in presence of drops of (Glac.acetic) with refluxing (3 hrs), then separation ,drying ,recrystallization to Compound {1} approving to procedures [5, 6]

Manufacturing of Tetrazole Compound {2}:

Aldamine compound {1} (0.01 mole) reacted with sodium azide in cyclization reaction, then separation ,drying ,recrystallization to Compound {2} approving to procedures [5, 6].This is the most common method for preparing tetrazol from sodium azide, as it is available, less expensive, higher yield, and higher purity. Therefore, many researchers resort to using this method in preparation.

Manufacturing of Tetrazole-Triazole Compound {3}:

Tetrazole-Benzoate derivative {2} (0.01 mole) reacted with thiosemicarbazide (0.01 mole) in presence of (5% NaOH) in cyclization reaction in two steps, then separation ,drying ,recrystallization to Compound {3} approving to procedures [5, 6] .

Manufacturing of Tetrazole- Thiadiazole Compound {4} :

Tetrazole-Benzoate derivative {2} (0.01 mole) reacted with thiosemicarbazide (0.01 mole) in presence of sulfuric acid in cyclization reaction in two steps, then separation ,drying ,recrystallization to Compound {4} approving to procedures [5, 6] .

Manufacturing of Tetrazole- Imidazole Compound {5}:

Tetrazole-Benzoate derivative {2} (0.01 mole) condensed with O-phenyl diamine (0.01 mole) for (9 hrs) in presence of (3 N) of hydrochloric acid in cyclization reaction, then separation ,drying ,recrystallization to Compound {5} approving to procedures [5, 6].

Manufacturing of Tetrazole-Thiazole Compound {6}:

Tetrazole-Benzoate derivative {2} (0.01 mole) condensed with O-mercaptoaniline (0.01 mole) for (8 hrs) in presence of (3 N) of hydrochloric acid in cyclization reaction, then separation ,drying ,recrystallization to Compound {6} approving to procedures [5, 6]

Manufacturing of Tetrazole- Imidazole Compound {5} :

Tetrazole-Benzoate derivative {2} (0.01 mole) condensed with O-phenyl diamine (0.01 mole) for (9 hrs) in presence of (3 N) of hydrochloric acid in cyclization reaction, then separation ,drying ,recrystallization to Compound {5} approving to procedures [5, 6].

Manufacturing of Tetrazole-Thiazole Compound {6} :

Tetrazole-Benzoate derivative {2} (0.01 mole) condensed with O-mercaptoaniline (0.01 mole) for (8 hrs) in presence of (3 N) of hydrochloric acid in cyclization reaction, then separation ,drying ,recrystallization to Compound {6} approving to procedures [5, 6]

Manufacturing of Tetrazole-Oxazole Compound {7} :

Tetrazole-Benzoate derivative {2} (0.01 mole) condensed with O-aminophenol (0.01 mole) for (9 hrs) in presence of (3 N) of hydrochloric acid in cyclization reaction, then separation ,drying ,recrystallization to Compound {7} approving to procedures [5, 6]

Manufacturing of Tetrazole- Oxadiazole Compound {8}:

Tetrazole-Benzoate derivative {2} (0.01 mole) condensed with semicarbazide (0.01 mole) for (26 hrs) in presence of sulfuric acid in cyclization reaction in two steps, then separation ,drying ,recrystallization to Compound {8} approving to procedures [5, 6] . This method considers simple procedure for synthesis as this compounds by using closing agents in acidic medium.

RESULTS AND DISCUSSION:

Several diagnostic techniques have been accomplished, including automated and bio-diagnostics, as well as laboratory diagnostics for the composition of the prepared derivatives. The prepared compounds and derived from the tetrazol ring were characterized by the accuracy of their diagnosis by spectroscopic methods, the purity of the product, its high percentage, and its bright colors, which gave a clear color gradation [34-39] in the

spectra as a result of containing aggregates with a Fig.(2):^{1}H-.NMR-revealing of compound{8}clear color depth. All spectra have proven the exact composition of the compounds:

FT.IR- Revealing:

This chemical revealing gave strong data of constructions of formatted Tetrazole-derivatives through appearance clear bands at (3200 -3230)cm^{-1} in all prepared compounds respectively for amine group in tetrazole cycle., while appearance band at (2328) cm^{-1} for (SH) thiol group in compound {3} ,appearance bands at (3310 ,3340) cm^{-1} for amine group in compound {4}., appearance band at (3300) cm^{-1} for amine group in imidazole ring in compound {5} , appearance bands at (3325 ,3350) cm^{-1} for amine group in compound {8}., all spectral revealing approving to literature [14].

^{1}H.NMR- Revealing:

This chemical revealing gave strong data of constructions of formatted Tetrazole-derivatives through appearance clear peaks at δ (4.10 – 4.92) in all prepared compounds respectively for proton atom of amine group (NH) in tetrazole cycle., while appearance peak at δ (12. 34) for (SH) thiol group in compound {3} ,appearance peak at δ (4.96) for amine group (NH2) in compound {4}., appearance peak at δ (5. 05) for amine group in imidazole ring in compound {5} , appearance peak at δ (4.98) for amine group in compound {8}., Also appearance signals for protons for aromatic and heterocyclic part form compounds represented by benzothiazole ring in figurs of spectra , all spectral revealing approving to literature [14].

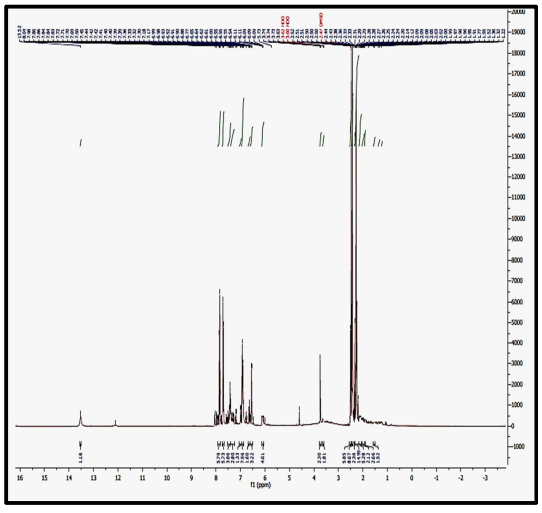


Fig.(1):H.NMR-revealing of Compound{3}

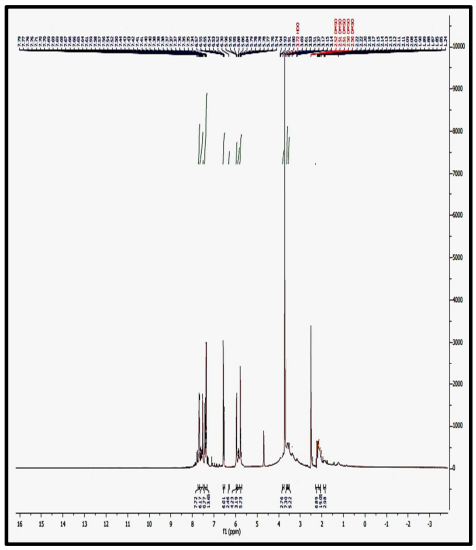
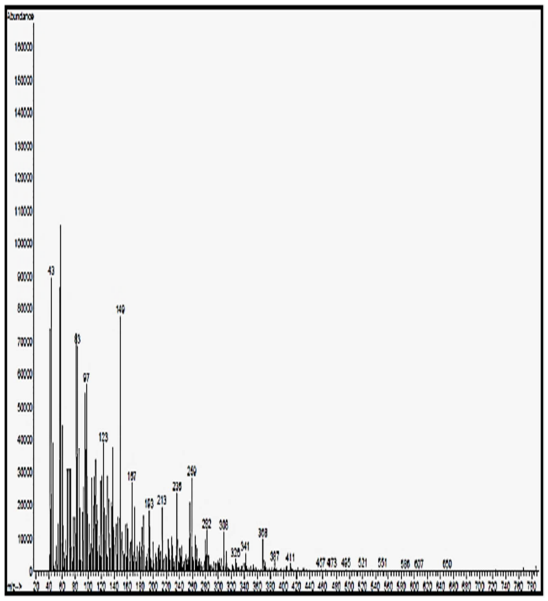


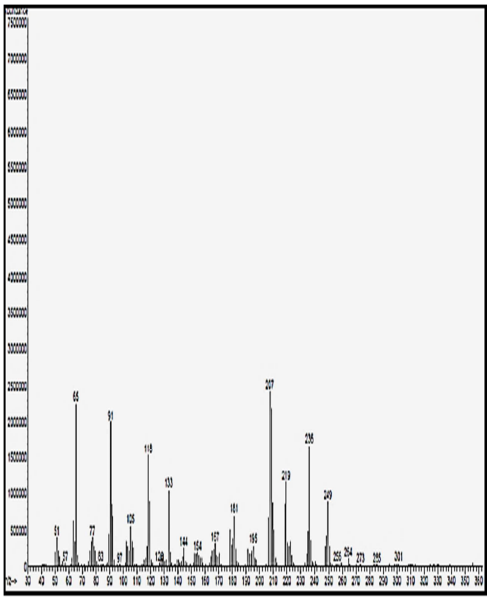
Fig.(2):H.NMR-revealing of Compound{8}

Mass – Revealing:

The revealing of the tetrazole derivatives of (thiadiazole, oxadiazole, triazole, thiazole, imidazole,..) gave additional indication of formatted compounds {1-8} that appeared fractions of functional groups in same molecular weight., every spectral revealing approving to literature [14], some figures (3, 4):



Fig(3): Mass revealing of Compound {4}



Fig(4): Mass revealing of Compound {7}

Evaluation of the efficacy of compounds against Bacteria [39]:

Micro-organisms are the causes of many diseases, so we find a lot of studies in the field of studying the biological efficacy of compounds on various types of pathogenic bacteria. Nowadays there are increasing numbers of infections caused by bacteria that are resistant to most of the antibacterial treatments currently available .,In this study, we used types of bacteria that are among the causes of many human diseases, some of them is Gram positive, represented by (Staphylococcus aureus , Streptococcus pneumonia), and the second type is Gram negative, represented by (E.Coli) at (three concentrations : 20 , 40 , 80 micro gram) with blank [6] solvent (DMSO).

Evaluation of the efficacy of compounds against Fungi [6]:

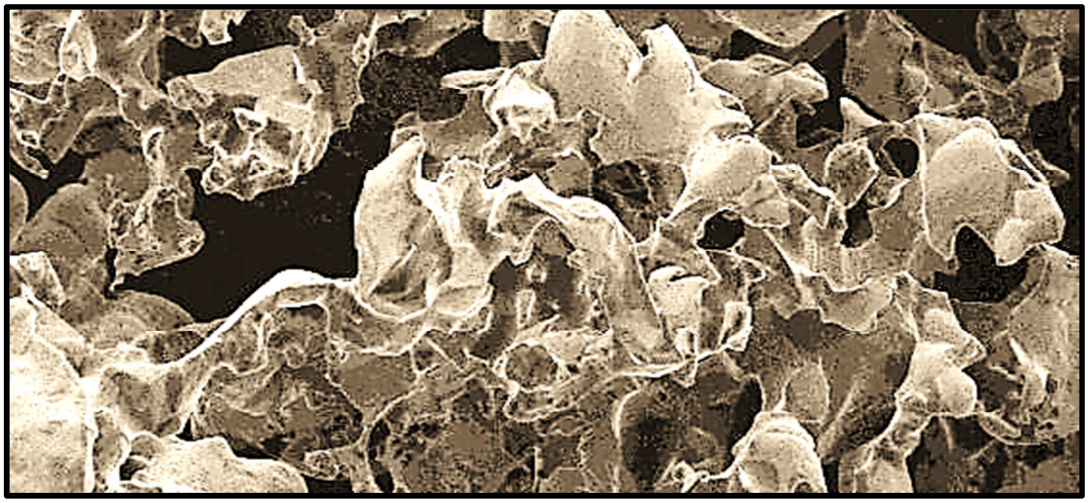
Although fungal products have been used in traditional and folk medicines perhaps since prehistoric times, the ability to identify beneficial properties and then extract active ingredients began with the discovery of penicillin by Alexander Fleming in 1928. Since that time, many antibiotics have been discovered. Additional vitality the potential of fungi to synthesize bioactive molecules useful in a wide range of clinical therapies has been exploited. Pharmacological research has succeeded in isolating antifungals, antivirals and antiprotozoals from fungi [40-44]. The fungus with probably the longest record of medicinal use is the clear Ganoderma, known in Chinese as "ling ji" ("spirit plant") and in Japanese as "menintake". In ancient Japan, the grifola mushroom was equal to its weight in silver although there were no significant medicinal benefits proven to affect humans. The chaga mushroom was used in Russia as early as the 16th century and was mentioned in Alexander Solzhenitsyn's The Cancer Wing. It has also been used in many folk medicine traditions to treat a wide range of ailments. Research has demonstrated the presence of a range of therapeutically important compounds in a range of lichen species but it is believed that none are currently in use in mainstream medicine., Compounds that kill microbes are called microbicides [44-48], while compounds that stop microbes are called bacteriostatic agents. The use of antimicrobial drugs to treat infection is known as antimicrobial chemotherapy while the use of antimicrobial drugs to prevent infection [49-54] is known as antimicrobial prophylaxis.

Nano- Study

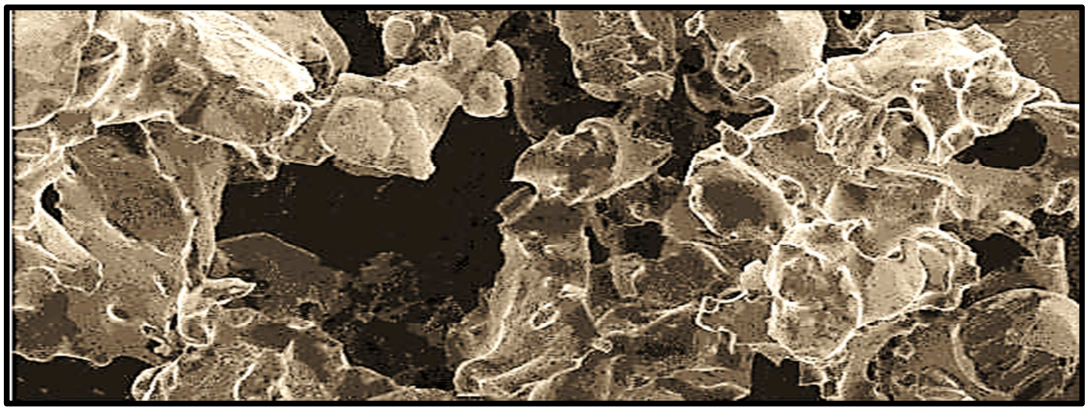
Studying of Nano- Application carried out via using Scanning Electron Microscopy (SEM) that appeared good results about nano-dimensions of the prepared compounds with the scanning microscope technology to find out the nano-dimensions of the compounds, whether they are suitable for medical applications. The results of the examination proved that it possesses nanoscale properties according to methods [32, 52] that qualify it to be successful pharmaceutical compounds.

Fig(5):Nano-Dimension of Tetrazole Derivative {3}

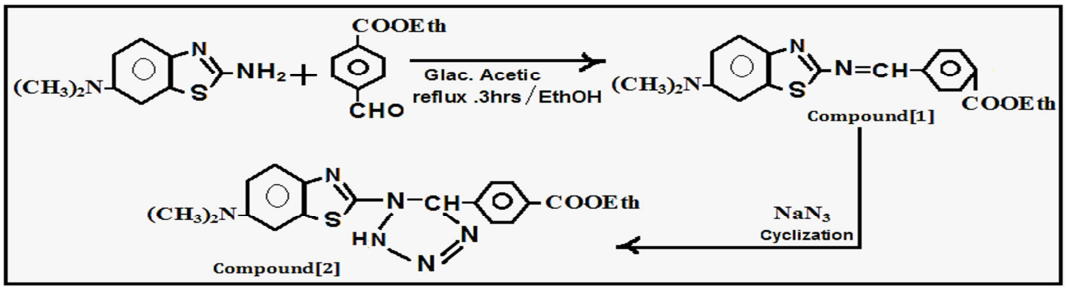
Fig(6):Nano-Dimension of Tetrazole Derivative {4}



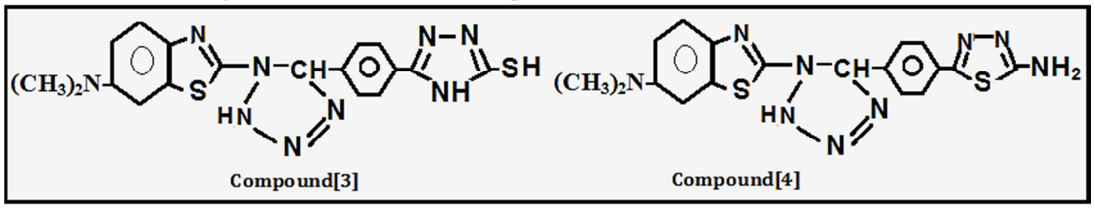
Fig(7):Nano-Dimension of Tetrazole Derivative {5}



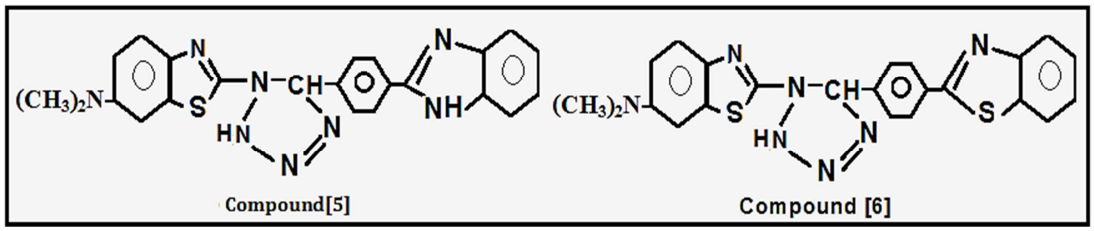
Fig(8):Nano-Dimension of Tetrazole Derivative {6}



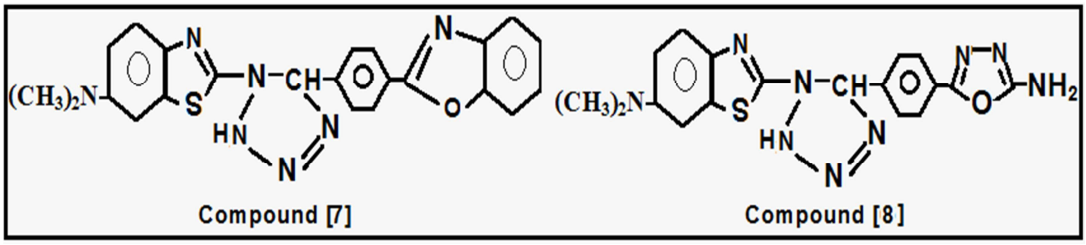
Pattern.1: Manufacturing of Aldamine and Tetrazole Compounds {1, 2}



Pattern.2: Manufacturing of Tetrazole Compounds {3, 4}



Pattern.3: Manufacturing of Tetrazole Compounds {5 ,6}



Pattern.4: Manufacturing of Tetrazole Compounds {7, 8}

Table.1
Evaluation of the efficacy of compounds against Bacteria in Conc. (40 micro gram)

Compounds	*Staphylococcus aureus*	*Streptococcus pneumonia*	*Escherichia.Coli*
Compound {1}	+	+	+
Compound {2}	+	+	+
Compound {3}	+++	+++	+++
Compound {4}	+++	+++	+++
Compound {5}	+++	+++	++
Compound {6}	+++	+++	+++
Compound {7}	++	++	++
Compound {8}	++	++	++

(+) : inhibition (4-7) mm
(++) : inhibition (8-12) mm
(+++) : inhibition (13-16) mm

Table.2
Evaluation of the efficacy of compounds against Fungi in Conc. (50 micro gram)

Compounds	*Fungi : A.flevus*	*Fungi : A. neger*
Compound {1}	+	+
Compound {2}	+	+
Compound {3}	+++	+++
Compound {4}	+++	+++
Compound {5}	+++	+++
Compound {6}	++	++
Compound {7}	+	+
Compound {8}	++	++

(+) : inhibition (4-7) mm
(++) : inhibition (8-12) mm
(+++) : inhibition (13-16) mm

Conclusions:

Some cyclic compounds are used as antimicrobials, and this is what we have proven in our research, as it has been proven that they are compounds that kill microorganisms or stop their growth. Antimicrobial drugs can be divided according to the microorganisms that they can work against. For example, antibiotics are used against bacteria and antifungals are used against fungi. It can also be divided according to function. Compounds that kill microbes are called microbicides, while compounds that stop microbes are called bacteriostatic agents. The use of antimicrobial drugs to treat infection is known as antimicrobial chemotherapy while the use of antimicrobial drugs to prevent infection is known as antimicrobial prophylaxis.

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