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Synthesis Characterization Biological Activity of Heterocyclic Compounds

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Abstract - To get Schiff bases derivatives malonic acid di hydrazide was reacted with CS2 / KOH, followed by hydrazine hydrate. This produced 1,2,4-triazole, which was then reacted with various substituted benzaldehydes. Thiazolidines were produced via the reaction of Schiff bases with thioglycolic acid. A similar reaction between Schiff bases and glycine yielded imidazolidinone. FT-IR, 1 H-NMR, Uv/vis spectra, melting temperatures, and T.L.C. purity checks were used to describe the compounds. Antibacterial activity was tested on a subset of the produced compounds.

Keywords - Synthesis, Heterocyclic Derivatives, Chalcone, Antibacterial and Biological

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INTRODUCTION

Heterocyclic compounds provide a variety of roles in supporting life and are found almost everywhere in nature Because of the wide range of physiological functions they perform, these chemicals are very important. Antibiotics, heme, vitamin B complex, heme, chlorophyll, various plant pigments, amino acids, proteins, enzymes, medicines, DNA, and dyestuffs all include heterocyclic rings Research into new methods for the construction of heterocyclic five-membered rings like unit isoxazoles and pyrazoles six-membered rings like oxazine and thiazine, and seven-membered rings like 1,3-oxazipene is constantly being driven by the central importance of hetero cycles in natural product chemistry and pharmacology.

These are the biologically and pharmacologically active isoxazoles, pyrazoles, oxazine, and thiazine's that were synthesized from chalcones, the primary intermediate products (There are no restrictions on the other class reactions, and they produce the usual 1,3-oxazepine rings that originate from Schiff's bases. Two units of imine accumulating as a two-membered part is added to a five-membered portion, such as maleic or phthalic anhydrides, to obtain a seven-membered hetero cycle; this is the type of cyclo another reaction used in the agglomeration of the 1,3-oxazepine ring.

The role of heterocyclic molecules in biological activity has grown in recent years. Oxygen, nitrogen, sulfur, and other common hetero atoms form rings in heterocyclic compounds. Numerous heterocyclic compounds, such as alkaloids, antibiotics, amino acids, vitamins, hemoglobin, hormones, and a vast range of synthetic medications and colors, are vital to life and may be found both in nature and in a wide range of non-natural chemicals. Heterocyclic compounds' chemical structures are largely responsible for their biological action. The pharmaceutical industry has begun to pay more attention to heterocyclic compounds, especially those with five or six members. To a similar extent, heterocyclic molecules with nitrogen, Sulphur, and oxygen as hetero atoms are useful in the development of new pharmaceuticals. Triazole and other five-membered ring heterocyclic compounds. These could have a 1, 2, or 3-triazole structure. Furan and pyran, two examples of oxygen-containing heterocyclic compounds with five and six members, respectively. Vitamin B6 (pyridoxine), a derivative of pyridine, is crucial for amino acid metabolism and is found in all members of the vitamin B group.

LITERATURE REVIEW

Nadia Sadiq Majeed, et.al (2018) Chalcone was used as a starting point for the chemical synthesis and subsequent biological analysis of four new heterocyclic derivatives (Pyrazole, Isoxazole, Oxazine, and Thiazine). Second, Schiff's bases derived from an azo molecule were used to create certain 1,3-oxazipene derivatives. In the last phase, we examined the compounds' antibacterial activity against four types of pathogenic gram-positive and gram-negative bacteria. All compounds had extraordinary biological activity, even when compared to conventional antibiotics as ampicillin and ciprofloxacin. These compounds were identified and confirmed with the use of FT- IR, 1HNMR, 13CNMR, and elemental analysis.

Arihant. R. Shah, et.al (2015) In the presence of pyridine, chalcone was reacted with 5-bromo o-phenylenediamine to produce a new benzodiazepine

derivative. The first chalcones were synthesized via claisen-schimidt condensation of 4-acetyl-5-methyl-2-(4-methylphenyl)-2,4-dihydro-3Hpyrazol-3-one and various substituted aldehydes. IR, 1H-NMR, Mass spectrometry, and elemental analysis have all been used to describe the structures of the newly synthesized Benzodiazepine derivatives. Antimicrobial efficacy assessments were performed on the produced drugs.

R kais et.al (2019) In this research, a new thiadiazol compound, 2-(5-amino-1,3,4-thiadiaz0l-2- yl)-4,6-dinitrophenol, (1) is synthesized by reacting 3,5-dinitrosalicylic acid with thiosemicarbazone in phosphoric chloride; (2) is obtained by reacting (1) with 2-Bromobenzaldehyde; (3) is a Schiff base. The compounds (-lactam, thiazolidine, imidazolidine, tetrazole, and oxazepane) may be synthesized from (2) by reacting it with (chloroacetylchloride), (thioglycolic acid), (glycine), (sodium azide), and (phthalic anhydride). Melting points, 1 H-NMR, 13C-NMR, and FT-IR spectra were used to identify the newly synthesized compounds. Then, the synthesized derivatives were tested for their biological activity against two different types of bacteria.

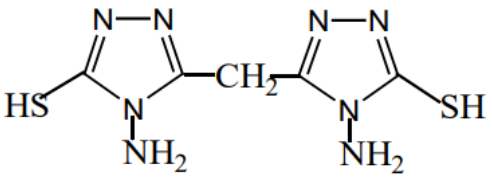
Mohammed alwan farhan , et.al (2022) Four novel compounds, including two schiff bases, were synthesized in this study. These chemicals were produced by reacting 5-Amino-1,3,4-thiadiazole-2-thiol (I1-I4) with heterocyclic isatin. Schiff bases (I3 and I4) were created by the condensation of the I2 molecule with aromatic aldehydes such 4-nitrobenzaldehyde and 4-hydroxybenzaldehyde. FT-IR, 1H-NMR, and 13C-NMR were used to describe these compounds. The physical qualities were evaluated. All of the synthetic substances were tested for their biological efficacy.

Safa thaer flayyih ali, et.al (2016) In the first stage of the synthesis described in this article, the Schiff base is prepared by reacting benzaldehyde derivatives (2-hydroxybenzaldehyde and 4-bromobenzaldehyde) with 4,4-diaminodiphenylsulphon (DDS). These were the starting materials for making heterocyclic compounds. Then, the oxazepine and oxazepane derivatives were made ready. Using (maliec, phthalic, and succinic) anhydride on Schiff base. Melting point, FT-IR, 1H NMR, and C13NMR were used to describe the heterocyclic compounds.

EXPERIMENTAL / TECHNIQUES

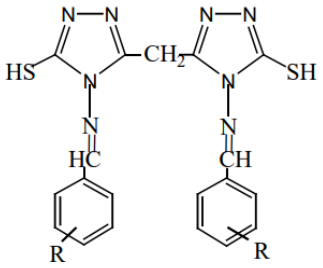
1. Stuart Melting point device was used to take the uncorrected melting point readings.
2. The college of Ibn Al-Haitham used a Shimadzu FT-IR-8300 spectrophotometer to capture infrared (IR) spectra.
3. a Uv/vis spectrophotometer, the Uv-Cary-100, was used to record spectra in the (ISSC).
4. The Chemistry Department at AL-Bayt University in Jordan took 4.1 H-NMR spectra at 300 MHz using tetra methyl silane as an internal standard in DMSO-d6 as a solvent.
5. The Chemical Department, College of Science, Babylon University used the Euroea Elemental Analyzer, Italia, to conduct the Elemental Analysis (C.H.N.S.).
6. Fertigfollen precoated sheets of the polygram Silg type were used for the TLC, and the plates were developed in iodine vapour.

1-Synthesis of bis 3-mercapto -4-amino - 5-methylene 5-yl -1,2,4-triazole



Malonic acid dihydrazide (21g, 0.01mole), carbon disulfide (25ml), and potassium hydroxide (2.23g,0.01mole) were dissolved in 100% ethanol (50ml), and the mixture was refluxed for five hours while being stirred. The ethanol was then concentrated using a rotary evaporator to eliminate any remaining water. A white precipitate, yielding 85%, was obtained by adding 20 ml of hydrazine hydrate to the crude, allowing it to reflux for 4 hours, before being cooled, diluted with 20 ml of distilled water, and acidified with diluted HCL.

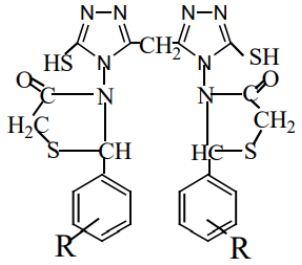
2-Synthesis of Schiff Bases



R = 3-NO2, 4-N(CH3)2, 2-Chloro ,4-NO2, 4-OH and Vaniline.

Absolute ethanol (15 ml) and the necessary aldehyde (0.09 mol) were combined with three drops of glacial acetic acid (0.03 mol) and allowed to reflux in a water bath for three hours. After cooling the reaction mixture to room temperature, the precipitate was separated by filtration, dried, and recrystallized in ethanol to yield yellow crystals.

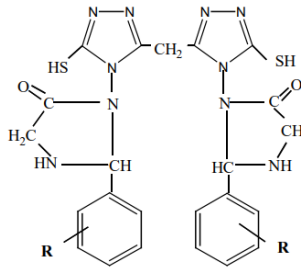
3-Synthesis of Compounds



R = 3-NO2, 4-N(CH3)2, 4-NO2, 4-OH and Vaniline .

To Schiff bases (0.001 mol), mercapto acetic acid (0.002 mol) in dry benzene (7.5 ml) was progressively added. After (10 second) further addition and stirring, the mixture was left to reflux for 10 hours. Compounds were precipitated from ethanol using sodium bicarbonate and then re- crystallized after the excess solvent was evaporated.

4-Synthesis of bis [3-mercapto-2-methylene-2yl)-4-imidazolin-4-one



R= 3-NO2, 4-N(CH3)2, 4-NO2, 4-OH and Vaniline.

After 24 hours of refluxing at room temperature, the combination of 0.01mol Schiff base and 0.02mol glycine in 20 ml THF was cooled to room temperature, and the precipitate was filtered and recrystallized from a 25/75 mixture of ethanol and THF.

Table (1). Yields and physical data of the synthesized compounds.

Compound No.	R_f	Yield %	Color	Recryst. Solvent
1	0.68-0.78	73	White	Ethanol
2	-	71	White	Ethanol/H_2O
3	-	65	Yellow	Ethanol
4	-	72	red	Ethanol
5	-	74	Orange	Ethanol
6	-	73	Orange	Ethanol/H_2O
7	-	66	Pale yellow	Ethanol
8	-	70	Yellow	Ethanol
9	-	75	Yellow	Ethanol/H_2O
10	-	79	Yellow	Ethanol
11	-	60	Yellow	Ethanol
12	-	92	Yellow	Benzene
13	-	70	Yellow	Ethanol/H_2O
14	-	81	Yellow	Ethanol/H_2O
15	-	65	Yellow	Ethanol
16	-	83	Yellow	Ethanol
17	-	90	Yellow	Ethanol
18	-	60	White	Benzene

Table (2): C.H.N.S. analysis for some prepared compounds.

Comp. No.	C.H.N .S .analysis Calc /Found.			
2	24.59 /24.1	3.27/3.00	45.90/45.4	26.22/26.00
3	44.70/44.30	2.74/2.40	27.45/27.00	12.54/12.00
9	46.46/46.00	3.03/3.0	23.56/23.10	10.77/10.20
14	44.23/44.00	3.20/3.00	26.92/26.30	10.25/10.0
4	45.61/45.01	5.13/4.80	27.66/26.10	12.64/12.01
10	54.91/54.30	5.08/4.90	23.72/23.40	10.84/10.20
15	52.25/52.00	5.16/4.90	27.09/26.09	10.32/10.00

Table (3). Spectral data for the newly synthesized compounds.

Compound No.	Spectral data FT-IR /Uv λmax
1	IR (KBr. cm^{-1}). 3309, 3221 ($NH-NH_2$ asym. sym-stretch) and 1660 (C=O) amide I.
2	IR (KBr. cm^{-1}). 1610 (C=N), and 2470 (S-H). 3363, 3309, 3174 (NH_2 asym. sym-stretch and NH), 1608 (C=N), 1568 (C=C) /276,624
3	IR (KBr. cm^{-1}). 1608 (C=N), 1568 (C=C) .
4	IR (KBr. cm^{-1}). 1706 (C=N cyclic stretch of triazole ring) and 1601(C=N).
5	IR (KBr. cm^{-1}). 2528 (S-H), 3055 (C-H) aromatic and 1616 (C=N)
6	IR (KBr. cm^{-1}). 1612 (C=N) and 3020 (C-H) aromatic.
7	IR (KBr. cm^{-1}). 3113 (NH), 3080 (C-H) aromatic and 1610 (C=N).
8	IR (KBr. cm^{-1}).3305, 3221, 3149 three groups of (N-H), 1240 (C=S) and 1643 (C=O).
9	IR (KBr. cm^{-1}).1602 (C=N), 3395 (N-H) and 700 (C-S-C)./ λmax 276,236,283.
10	IR (KBr. cm^{-1}).1600 (C=N), 3400 (N-H) and 1240 (C=S)/ λmax 412,276,238,352,240.
11	IR (KBr. cm^{-1}). 3627 (O-H), 3369, 3128 (NH-NH) and 698 (C-S-C).
12	IR (KBr. cm^{-1}). 3300 (N-H), 1670 (C=O), 1645 (C=O) amide I and 3090, 3060 (C-H) aromatic.
13	IR (KBr. cm^{-1}).1602 (C=N), 3375 (N-H) and 1240, 1026 (C-O-C asym. sym-stretch).
14	IR (KBr. cm^{-1}). 1608 (C=N) and 3433 (O-H)./ λmax 310,340,283.
15	IR (KBr. cm^{-1}). 3431 (O-H), 3300, 3210 (NH-NH). /λmax 276,212,224.
16	IR (KBr. cm^{-1}). 3274 (O-H), 1737 (C=O) pyrazole ring, 1661 (C=O) amide I and 2979 (C-H) aliphatic.
17	IR (KBr. cm^{-1}). 3215 (N-H), 1641 (C=O) and 3064 (C-H) aromatic.
18	IR (KBr. cm^{-1}). 3192 (N-H), 1676 (C=O), and 1600 (C=N) .

DATA ANALYSIS

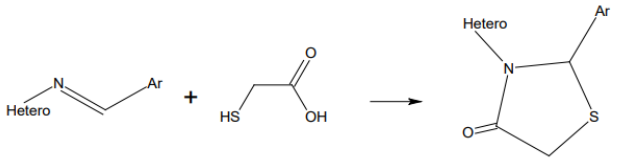
Here, malonic acid di hydrazide served as a building block for further synthesis. Thus, compound was produced by treating compound with carbon disulfide, potassium hydroxide, and hydrazine hydrate, as described by Young and Wood the NH2 asymmetric and symmetric stretching bands can be seen at 3363, 3309, and 3174 cm-1 in the IR spectra of this molecule, as can the C=N band at 1608 cm-1 and the C=C band at 1568 cm-1. Protons of the (N- H) tautomeric of the triazole ring shifted to (9.25) and (CH2) protons shifted to (4.4) in the 1 H-NMR spectrum of compound. As a result of the NH2 (amino group), the protons are located at (9.78,7.60). The Schiffs bases (3-6) were obtained by condensing compound (2) with various substituted benzaldehydes in 100% ethanol (scheme I. Table 3).

Characterization of a 2-Synthesized 4N-[substituted benzylidene]-5-mercapto -2-methyl-2yl1,2,4-triazole

Compound was reacted with the proper aldehydes in 100% ethanol and glacial acetic acid to produce the named compounds. The vast variety of biological activity and industrial of their derivatives has led to their synthesis from imine-bonded compounds, which have been used in the preparation of additional derivatives such as thiazolidine and imidazolines. The most common technique for preparing Schiff bases is the condensation reaction of an equimolar amount of primary amine with the suitable aromatic aldehydes. Melting points, FT-IR spectra, and, in the case of some of the compounds in question, C.H.N.S. analyses were all used to describe the compounds in question. Using amino triazole

as an example, the FT-IR spectra revealed all the proposed bonds, including those for the aromatic (C=C), endocyclic (C=N), and exocyclic imine group, with the absence of two absorption bands owing to (-NH2) stretching. The stretching band at the area (1219-1250) cm-1 was seen in all the produced compounds (Schiff bases) because of the presence of the (=NN=C-) cyclic group. You can get spectral data for any other constituent in table (1). The following distinctive chemical shifts (DMSOd6) ppm are seen in the 1 H-NMR spectra of molecule. At (2.9-3.7) the C-H proton was first seen, followed by the N-H proton at (δ13.5), and finally the S-H proton at 11.36. Multiplet peaks for the protons of aromatic rings with p-substitutions (2 rings) occurred in the region (6.7-8.3).

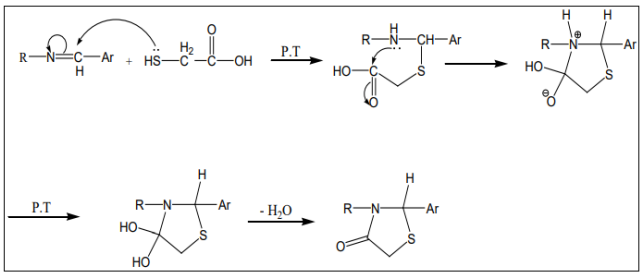
3. Synthesis and characterization of 4N- [(substituted aminophenyl)]-4'-oxo-1̂,3̀-thiazolidin2-yl]-3-mercapto-2-methyl-1,2,4-triazol



Hetero = triazole (2) , Ar = substituted phenyl.

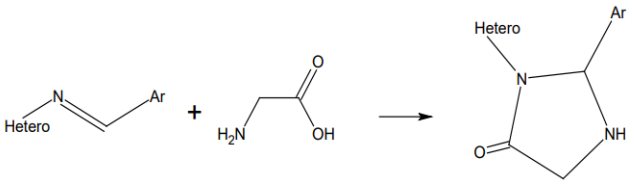
In addition to their widespread biological action, thiazolidinones have significant economic value as a polymeric material stabilizer. For quite some time, hetrocycles containing nitrogen have been synthesized using imines with great success. Equimolar quantities of the imine were refluxed with thioglycolic acid in dry benzene to produce the 4-thiazolidinone derivatives in addition to C.H.N.S. analysis and TLC, the m.p. and FT-IR, 1 H-NMR of the produced compounds were analyzed.

Table 3 of the C.H.N.S. study confirms the proposed layout. Compound [9]'s FT-IR spectrum reveals the telltale evidence for the successful completion of the cyclization step: the emergence of the stretching band of the carbonyl group at (1710 cm-1) owing to the thiazolidinone ring. The stretching vibrations of the (C-H) aromatic and (C-H) aliphatic groups are shown by the bands at (3089 cm-1) and (2924 and 2854 cm-1) in Fig. In addition to the band at 1600 cm1 owing to the (C=N) of the triazole ring, the (C=C) band appears at about 1512 cm1. The C=N group of Schiff base disappears at 1600cm-1, whereas the O-H wide band stretching vibration of mercaptocetic acid disappears at 3500-3000cm-1. Below is a diagram of the putative mechanism for this reaction:



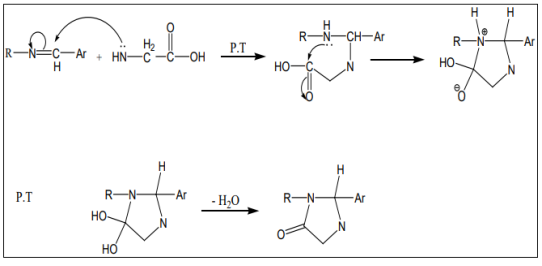
The following (DMSO-d6) ppm chemical shifts are seen in the 1 H-NMR spectra of molecule. At (4.22), protons of thiazolidinone's (CH2) were first seen. The NH proton first showed up with a value of (9.2). The multiplate peaks at (7.2-8.1) were identified as protons of m-substituted aromatic rings, while the signal at (3.54) was identified as CH2 between triazole rings. Protons of the aromatic rings emerge at (7.7-8.5), the NH proton appears at (13.94), and the OH proton appears at (10.3) in the 1 H-NMR spectrum of compound.

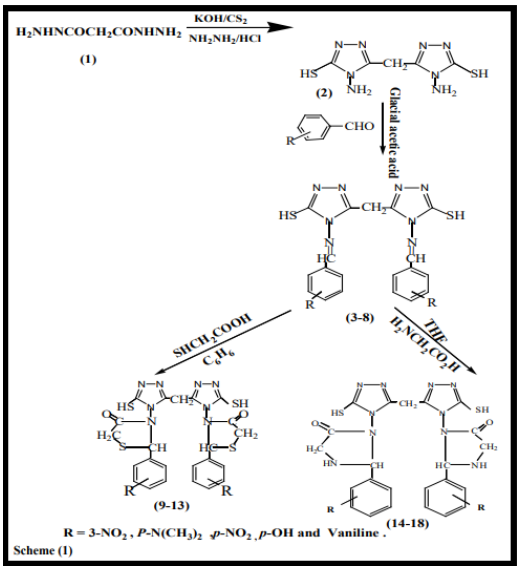
Bis [3-mercapto-2-methylene-2yl]: 4-
characterizationImidazolin-4-one, -4-



The NH vibration at 3320 cm-1 and the elimination of the C=N band at 1600 cm-1 in the FTIR spectra of the product obtained by heating Schiff base derivatives with glycine (amino acetic acid) in THF identify the compound as a derivative of imidazolidine. The 1 H-NMR spectrum, which places the product's protons at (δ 6.7- 7.6) ppm because of aromatic proton content. The (N-H) imidazole proton was discovered at δ (8.59) and the N-H toutomeric proton showed up at (δ 9.5) ppm.

What follows is a description of the suggested mechanism for this reaction.





Biological screening: Antibacterial activity test.

The disc diffusion technique was used to test for antibacterial activity in this study. Antimicrobial activity of compounds [1], [4], [10], [17], and [18] against Escherichia coli, Klebsiella pneumoniae, and Proteus vulgaris was tested in vitro. Autoclaving the prepared agar and Petri plates at 121 degrees Celsius for 15 minutes ensured their sterility. The studied microorganisms' broth cultures were used to evenly inoculate the agar plates. Holes, all measuring 6mm in diameter, were drilled at regular intervals into the cemented material. The synthesized compounds (10mg diluted in 1ml of DMSO solvent) were injected into the holes at a concentration of 0.1 ml. Bacteria were allowed to grow on these plates for 24 hours at 37 degrees Celsius. Different drugs' inhibition spheres were analyzed. Initial screening findings are summarized in Table (4).

Table (4): Results of antibacterial activity of the tested compounds.

compound No.	*Escherichia Coli*	*Klebsiella Pneumonia*	*Proteus Vulgaris*
[1]	+	+	-
[4]	-	-	+
[10]	++	+	-
[17]	-	++	-
[18]	++	++	+

Note: - = No inhibition = inactive., + = (5-10) mm = slightly active., ++ = (11-20) mm = moderately active

CONCLUSIONS

Natural compounds include nucleic acids, plant alkaloids, and chlorophyll all contain heterocyclic systems. Because of its usefulness in both pharmaceuticals and industrial research, heterocyclic compounds are often regarded as a key class of organic chemicals. In the fight against

infectious illnesses, nothing is more crucial than progress in the research and development of antibiotics targeting bacterial pathogenesis. Because of their contents, which include organic heterocyclic rings that include sulphuer atoms, compounds (F2) and (F4) are the most effective biologically. Studying their biological activity revealed that all of them were very effective even at low concentrations, but compound proved to be the most active of the bunch. In the early days of organic chemistry, the molecules in this class were referred to as uric acid metabolites, but it wasn't until the work of pinner that the ring system was systematically studied. Pinner also gave the unproven parent body the name pyrmidine.

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