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Synthesis and Characterization of Three New Heterocyclic Compounds Derived From The Succinic Anhydride and Vanillin Esterification

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Abstract:In this paper, we synthesized three heterocyclic compounds derived from the esterification reaction of succinic anhydride and vanillin and then the condensation reaction between the esterification product with 4-nitroanillin to obtain the azomethine compound,bis (2-methoxy-4-((E)-(4-nitrophenylimino)methyl)phenyl) succinate. The three new heterocyclic compounds were synthesized from the reaction of azomethine compound with succinic anhydride,phthalic anhydride and maleic anhydride. The progress of the synthesized reaction was followed by the (TLC) method, and determined the melting point of these synthesized compounds. These synthesized compound were identifiedby FT-IR, H-NMR and ^{13}C-NMR Spectrophotometric techniques.

Key Words: Vanillin esterification , Vanillin Schiff's bases, heterocyclic compounds .

1-Introduction :

New heterocyclic compounds were created that are thought to have biological activity as an antibacterial agent due to the biological activity of vanillin and succinic anhydride against some types of bacteria like E. coli. [1].

Vanillin, a phenolic aldehyde present in white solid acicular crystals, is extracted from the pods of the vanilla plant. Through condensation reactions with aromatic and aliphatic amines, it is utilized to create Schiff base compounds. These compounds have the general formula R1HC = N-R2, where R1 and R2 are alkyl or aryl groups, and are distinguished by the azomethine group (-C=N-)[2]. Because an electron pair is present on the nitrogen atom, the aryl group, which can be either homogeneous or heterogeneous, is referred to as an imine or an azomethine. The azomethine group is easily synthesized and has many chemical and biological uses. [3,4].

The necessity for a new source of therapeutic chemicals and the hunt for new alternative substances to treat these diseases resulted from the appearance of new breeds and the growing resistance of many diseases to the treatments used to treat them. These chemicals include Schiff bases compounds, which have demonstrated numerous effective medicinal applications as tumor

therapies as well as antibacterial, antimicrobial, germicidal, and antifungal agents. Moreover, antipyretics [5-7].

The medical and industrial significance of heterocyclic organic molecules stems from their diverse compositional features. They are widely used in medicine and can effectively treat cancer disorders. They can be found in significant amounts in biological substances such as vitamins, enzymes, antimicrobials, antifungals, oxidants, and herbicides [8-14].

This effort comprises the synthesis of novel chemicals that, when investigated in the medical field, are anticipated to have medicinal uses for treating a wide variety of microorganisms.

1. Materialsand Methods

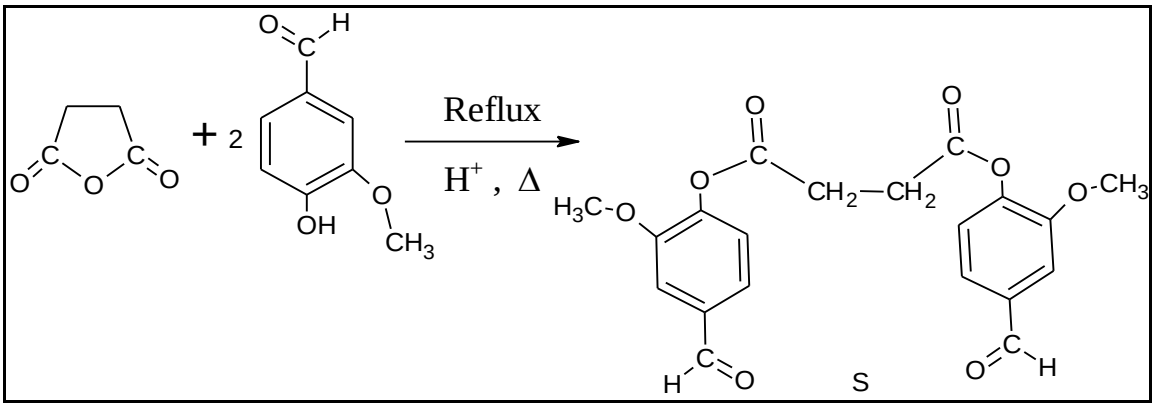
1.1. Chemicalsand Instruments

The following compounds are employed, and all of them are of extremely high purity: vanillin (purity 99), phthalic anhydride (purity 99.5%), maleic anhydride (purity 99%), succinic anhydride (purity 99.8%), and dimethyl formamide (98%).The BDH firm provided these chemicals, whereas the MERCK company supplied 4-nitro aniline (purity 99%), diethyl ether (purity 99%), and thionyl chloride (purity 99.8%).

The following tools were employed to investigate the new heterocyclic compounds: a melting point apparatus of type Gallenkamp MFB-600, an NMR instrument of type Varian-Ultra Shield-300 MHz Switzerland, with DMSO-d6), and an infrared spectrophotometer (FT-IR) IRAffinity-1S (Shimadzu, Japan).

2.2.Synthesis of vanillin esterification(compound S)

A solution of 0.06 mol of vanillin dissolved in 100 ml of dioxane was combined with 0.03 mol of succinic anhydride dissolved in the same solvent in a 250 ml round-bottom flask. The reaction was then run for 4–5 hours at a temperature between 100 and 110 °C, following the conclusion of the reaction's duration. As seen in scheme1, the solvent is extracted using a rotary evaporator, the precipitate is gathered and cleaned with diethyl ether, and a brown-colored vanillin ester(S) is produced [15].



Scheme 1: Vanillin ester(S) synthesis

2.3.Synthesis of Ester Schiff Bases (A):

The ester compound (S) prepared in Scheme 1 was reacted with (0.006 mol) dissolved in 100 ml of dimethyl formamide and mixed with (0.003 mol) of 4-nitro aniline in a 250 ml round-bottomed flask. Three drops of glacial acetic acid were added, and the reaction was refluxed for four hours at (95-100) 0C to create a Schiff base bis (2-methoxy-4-((E)-(4-

nitrophenylimino)methyl)phenyl) succinate (A). The solid product is then obtained by removing the solvent using a rotary evaporator, followed by an acetone wash and drying[16, 17]. The prepared Schiff base has a melting point of 170 0C. Scheme 2 illustrates the reaction of preparation.

2.4.Synthesis of bis(2-methoxy-4-(4-(4-nitrophenyl)-1,5-dioxo-1,3,4,5-tetrahydrobenzo[e][1,3]oxazepin-3-yl)phenyl) succinate(B)

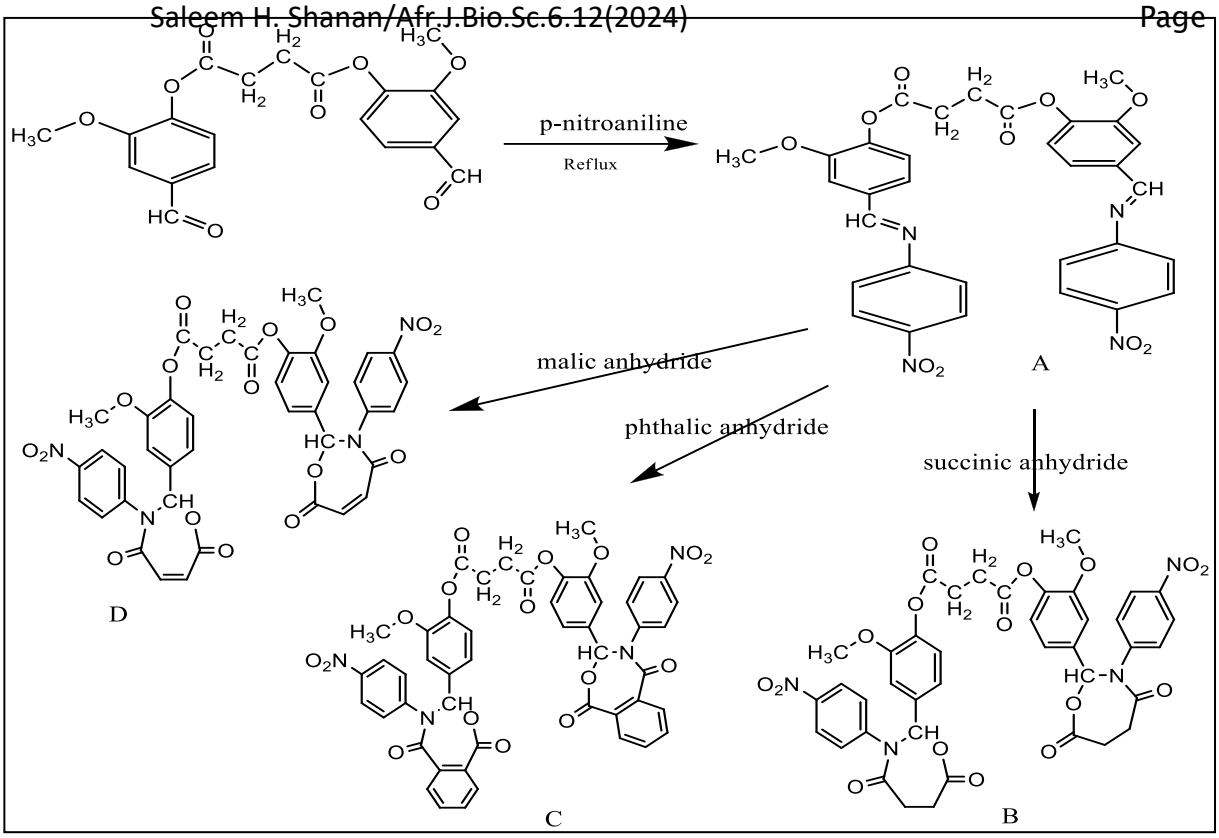
The compound bis(2-methoxy-4-(3-(4-nitrophenyl)-4,7-dioxo-2,3,4,7-tetrahydro-1,3-oxazepin-2-yl)phenyl) succinate (A1) was prepared by mixing a solution of 0.002 mol of succinic anhydride with a solution of succinic anhydride (0.004 mol) in 150 ml of DMF in a 250 ml round-bottomed flask with stirring and heating at a temperature of 110-80 0C. TLC followed the progress of the reaction. The precipitate was collected after evaporating the solvent in a rotary evaporator and was dried and recrystallized using diethyl ether[17] shows scheme2. The melting point of the compound for product A1 is 166 ^{0}C.

2.5.Synthesis of bis(2-methoxy-4-(4-(4-nitrophenyl)-1,5-dioxo-1,3,4,5-tetrahydrobenzo[e][1,3]oxazepin-3-yl)phenyl) succinate (C)

Compound A (0.002 mol) and phthalic anhydride (0.004 mol) were dissolved in 100 milliliters of DMF while stirring. The mixture was then heated to (90–110 0C) for 20–24 hours. The solvent was then removed using a rotary evaporator device, and the product was filtered, collected, dried, and recrystallized using a benzene solvent, as per scheme 2. The compound has a melting point of 185^{0}C.

2.6.Synthesis of compound D

A solution of 0.006 mol of maleic anhydride mixed with a solution of 0.003 mol of compound A after dissolving them in 100 ml of DMF. The mixture was left with stirring and heating at a temperature of 80-100 °C for hours, after that, the solvent was removed and the product was collected, dried, and recrystallized in diethyl ether solvent[19-23], the melting point of the resulting compound is 175 0C. Scheme2 show the preparations diagram.



Scheme2: Synthesis of Schiff base A,Synthesis of heterocyclic compound B,C and D

Antibacterial effectiveness of heterocyclic compounds:

The disk diffusion method was used to examine the activity of the synthesized heterocyclic compounds as antibacterial against Gram-positive bacteria (***Staphylococcus*** *aureus*) and Gram-negative bacteria (***Escherichia coli***), the agar and petri plates were sterilized by autoclave at 121°C for 15 minutes. Then the agar was poured onto the discs and left to solidify. Then 4 holes (6 mm) were made, and 0.1 ml of the solution of the prepared compounds (0.01 g in 2 ml of Dimethylformamide) was added to each hole, and these plates were incubated at (37 ° C) for 24 hours[19,20].

3.Resultsanddiscussion :

3.1. ***Investigation study ofheterocyclic compounds:***

3.2.Study of compound S by infrared spectroscopy (FT-IR):

The new ester derivative compounds (S) of vanillin with succinic anhydride which was synthesized and identified in a previous study by (Shanan & Kadem,2021)and used as a starting

material to prepare a Schiff base A, which was used to prepare the new heterocyclic compounds (B, C and D) in this work. To confirm that the compound (S)was obtained in its correct form, it was studied using infrared spectroscopy (FT-IR), which shows the bond stretching of these compounds in IR (KBr cm-1) including: 3050 (C-H, Ar-H Str), 1255 (C-O-C Str, ether), 1225 (C-O Str), 1751 (C=O Str, ester group), 1724 (C=O Str, aldehyde group)[15].

3.3.Characterization of azomethine compound A:

The new compound ((2-methoxy-4-((E)-(4-nitrophenylimino)methyl)phenyl)succinate (A) whichwas obtained via the reaction of ester derivative (S) with4-nitroaniline was identified by FT-IR as shown in figure1.This figure show the disappearance of the first amine group at (3400-3550cm^{-1}) and the appearance of the imine group (C=N) at (1635cm^{-1})[21], the melting point of this schiff base(m.p) =177 ^{0}C .

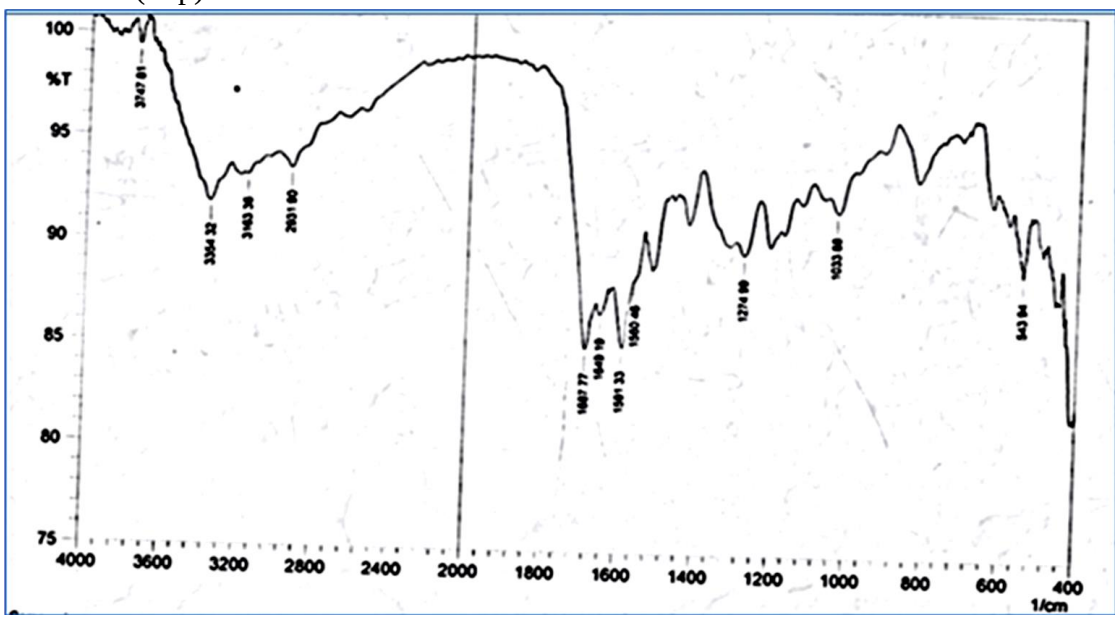


Figure1:The FT-IR spectrum of schiff base A

3.4.Characterization of heterocyclic compound B,C and D:

The new heterocyclic compounds(A1) which synthesized through the reaction of the prepared Schiff base (A)with succinic anhydride was characterized by FT-IR spectra, which show the disappearance of imine group C=N band and appearance of C-N band at 1274 cm^{-1} and C=O lactone at 1980cm^{-1},C-O at 1471 cm^{-1}as shown in figure 2-A.

The H-NMR spectrums of (A1) show the integration and multiplicity patterns of compound A1 in DMSO exhibits signals at 4.2ppm due to H-C-N proton,CH_3 –ether protons at 3.2ppm,H-aromatic protons at 7.2-7.66 ppm, and CH_2CH_2 protons at 2.4ppm[22] as in figure2-B.

The ^{13}C-NMR spectrum of A1 compound show peak signals at44.9 for CH_3-ether carbon, aromatic C appearance at 125-132ppm, CH=N carbon at 120ppm,carbonyl Carbon at 168 and ether carbon at 55.8 ppm as shown in figure 2-C.

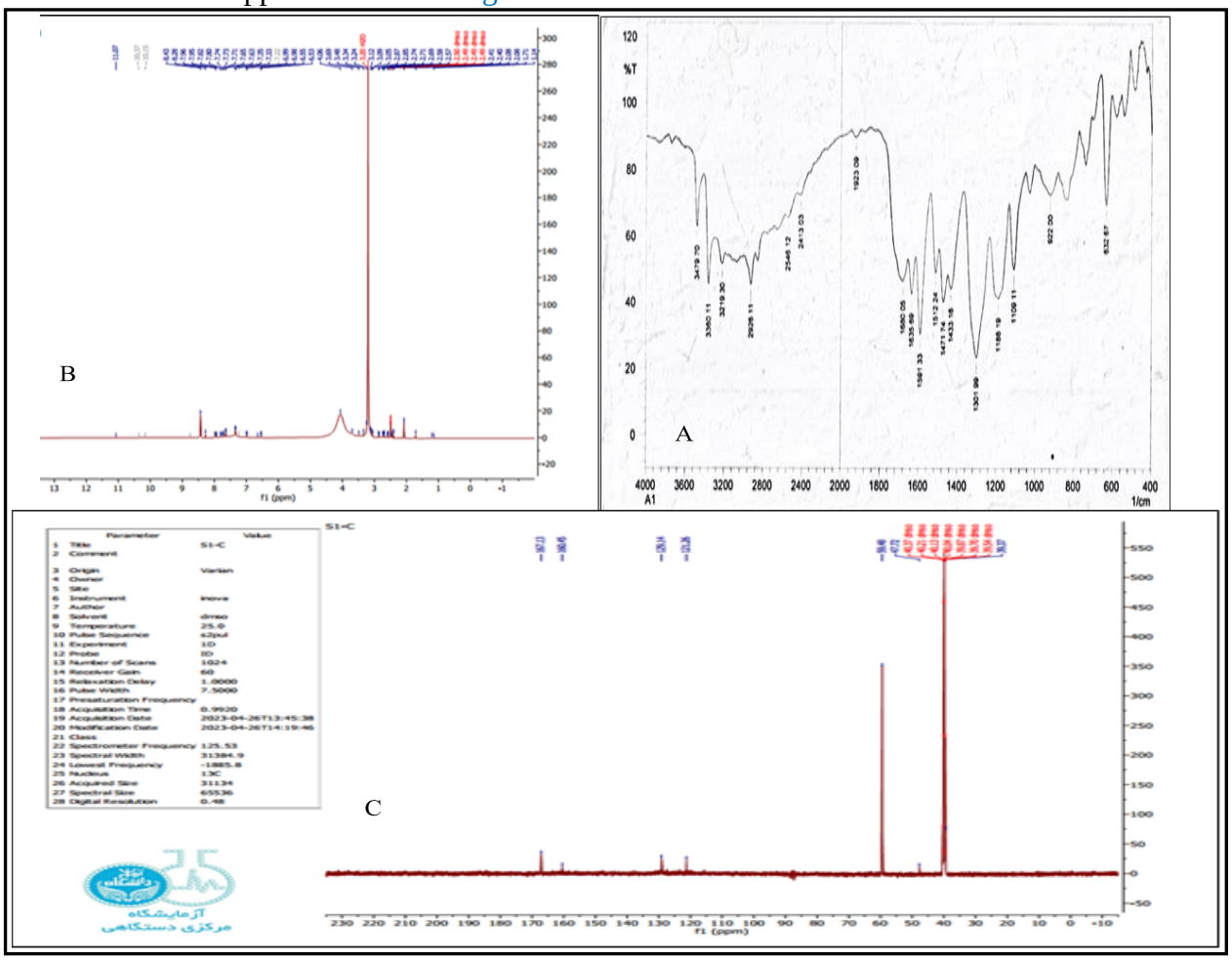


Figure2 :FT-IR(A),^{1}H-NMR(B) and ^{13}C-NMR(C) spectrum for heterocyclic compound B

TheFT-IR spectrum of new heterocyclic compounds(A2) which synthesized through the reaction of the prepared Schiff base, A with phthalic anhydride show the disappearance of imine group C=N at 1640 cm^{-1} and appearance of C-N bond band at1150-1200cm^{-1} and C=O lactone at 1668cm^{-1},C-O at 1462 cm^{-1} see figure 3-A.

Figure 3-Bshow the ^{1}HNMR spectrum of compound C, show signals at 4ppm due the proton of HC-N lactone, 3.5 ppm due to CH_3 –ether proton, H-aromatic protons at 7.06 -7.8, CH_2CH_2 protons at 2.71 and CH=CH heptane ring protons at 6.46 and 6.94 ppm.

^{13}C-NMR spectrum of compound A2 show signal at 88 due to HC-N lactone carbon ,CH_3 – ether carbon at 40 ppm, H-aromatic carbon at 111-139, CH_2 alkyl carbon at 29.1,CH=CH heptane ring carbon at 120-134,C-carbonyl carbon at 160-167 and C-carbonyl carboxyl carbon at171ppm[23] as in figure3-C.

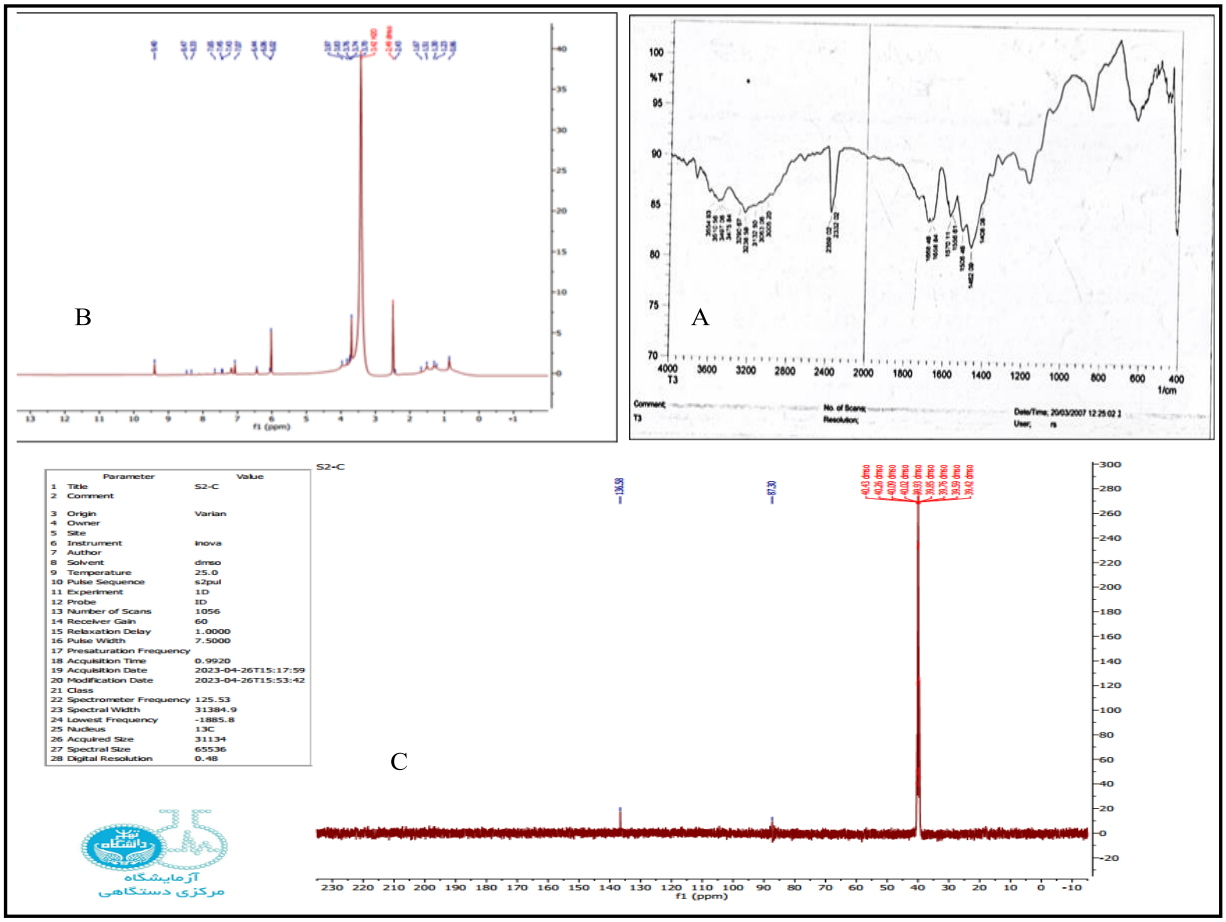


Figure3 :FT-IR(A),^{1}H-NMR(B) and 13C-NMR(C) spectrum for heterocyclic compound C

The FT-IR spectrum of compound D show the disappearance of C=N band and appearance of C-N band at 1213cm^{-1}, C=O lactone band at 1676cm^{-1}and C-O at 1481cm^{-1},see figure 4-A.

The^{1}H-NMR spectrums of (A3) show the signals of protons and their positions in the ^{1}H-NMR spectra in DMSO which exhibits signals at 4.5ppm attributed to CH-N proton, CH_3 –ether proton at 3.8,H-aromatic proton at 7.12-8.24 and CH_2 alkyl proton at 2.7ppm[24]as shown in figure 4-B.

The^{13}C-NMR spectrums of (D) show the signals of protons and their positions in the ^{13}C-NMR spectra in DMSO which exhibits signals at 87ppm attributed to CH-N lactone carbon, CH_3–ether carbon at 55.8, aromatic carbon at 111.4-151.1 and CH_2 alkyl carbon at 29.1ppm, as in figure 4-C.

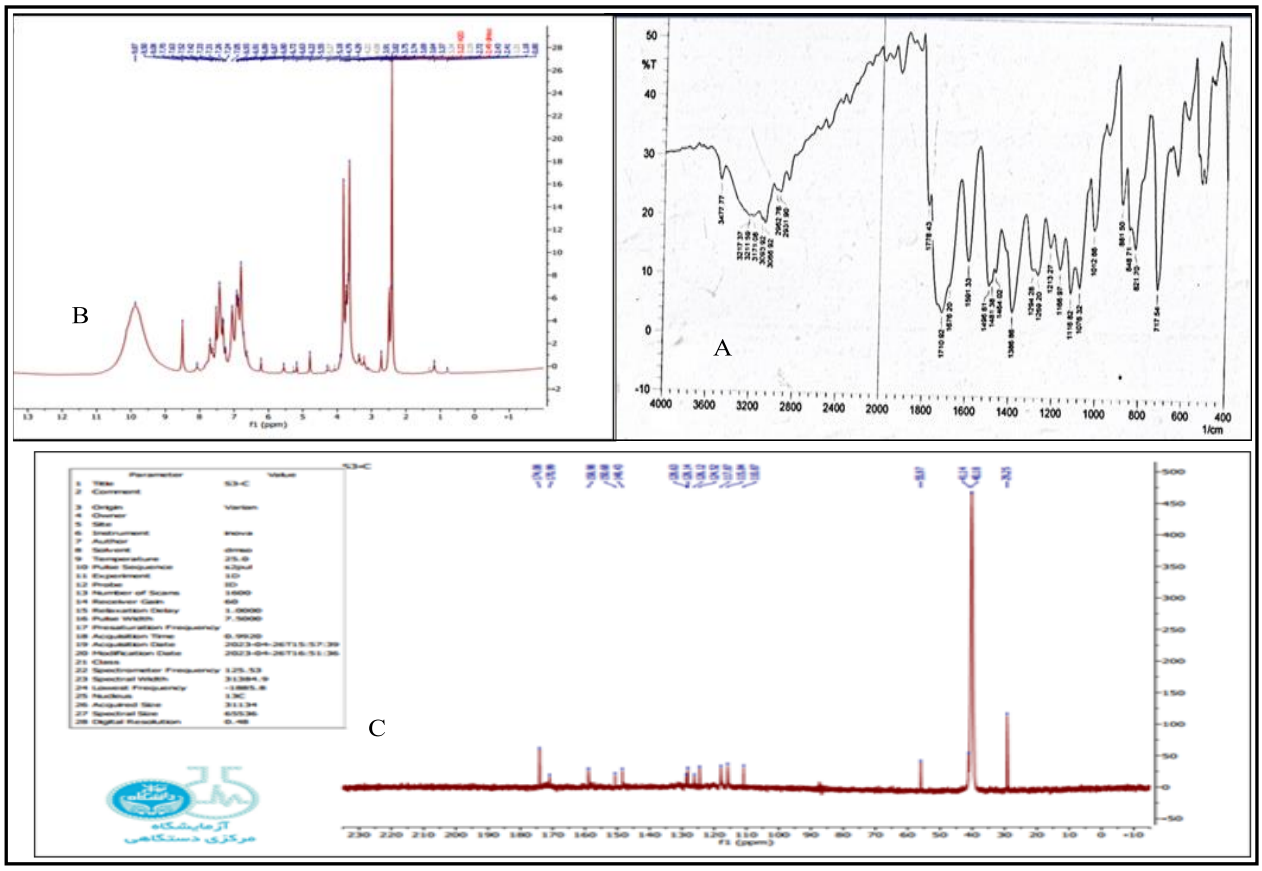


Figure4 :FT-IR(A),^{1}H-NMR(B) and 13C-NMR(C) spectrum for heterocyclic compound D

Antibacterial activity of heterocyclic compounds:

The antibacterial activity was carried out by disk diffusion method using Gram-positive bacteria (*Escherichia coli*) and Gram-negative bacteria (*Staphylococcus aureus*) .Table1 show the results that was obtained for these compounds activity which showed good antibacterial activity for most of the tested compounds compare to the ciprofloxacin drug[25].

Table1: The heterocyclic compounds activity as antibacterial

Compound No.	Inhibition Zone(mm)	
	E.coli	*Staphylococcus*

A1	20	24
A2	24	23
A3	21	22
Ciprofloxacin	12	15

Conclusions:

The Schiff bases which prepared from nitrobenzene consider as a raw material for preparing three heterocyclic compounds that contain an atom of nitrogen or oxygen through the addition reaction process, and these prepared compounds have a high antibacterial activity against of the ***E. coli***and ***Staphylococcus*** compared to the ciprofloxacin antibiotic drug.

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ConflictofInterestand CompliancewithEthicalStandards*:*There are no conflicts of interest and Thisarticledoesnotcontainanystudiesinvolvinghumanoranimalsubjects.

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