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# Synthesis, Characterization and Antibacterial Activity for 2-(1, 1-dimethyl-1, 3-dihydro-2H-benzo[e]indol-2-ylidene) malonaldehyde Indole

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## Abstract

This study examines a number of indole derivatives (C2-C5), were successfully prepared by the condensation reaction of diamine derivatives such as (3, 4-diaminobenzoic acid, benzene-1, 2-diamine, urea and thiourea) with 2- [1, 1-dimethyl-1, 3-dihydro-2H-benzo[e]indol-2-ylidene] malonaldehyde [C1]. They produced when 1, 1, 2-trimethylbenz[e] indole and POCl3 were combined in the presence of dimethyl forma mide (DMF). Compounds (C2-C3) were prepared by refluxing of compound (C1) with (3, 4-diaminobenzoic acid, benzene-1, 2-diamine), while compounds (C4, C5) were synthesized through the reaction of compound (C1) with urea and thiourea respectively in the presence of hydrochloric acid [HCI] as catalyst, spectroscopic methods such as (FT-IR and nuclear resonance spectroscopy 1H-NMR) were used to confirm the compounds' purity. The agar well diffusion method was used to test new compounds for their, antibacterial activity against E. coli and S. aureus, and the findings were inconsistent.

**Keywords:** Diamine derivatives, Substituted Indole, Antibacterial activity.

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# تحضير، تشخيص و دراسة الفعالية البيولوجية لمركب

# 2-(1, 1-dimethyl-1, 3-dihydro-2H-benzo[e]indol-2-ylidene) malonaldehyde Indole

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## الخلاصة

في هذا البحث تم تحضير سلسلة من مشتقات الإندول ($C_2$-$C_5$) بنجاح عن طريق تفاعل تكثيف مشتقات ثنائي أمين مثل (3،4-ثنائي امينوحامض البنزويك، بنزين-1،2-ثنائي امين ، يوريا ، ثايويوريا) مع 2- ( 1،1-1-dimethyl-،3-dihydro-3-(2H-benzo [e] indol-2-ylidene) malonaldehyde ($C_1$)، والذي تم تحضيره من خلال تفاعل 1،1،2-trimethylbenz [e] indole مع $POCl_3$ بوجود ثنائي ميثيل فورماميد (DMF). تم تحضير المركبات ($C_2$-$C_3$) عن طريق تفاعل المركب ($C_1$) مع (3،4-ثنائي امينوحامض البنزويك، بنزين-1،2-ثنائي امين). بينما تم تحضير المركبات ($C_4$) و($C_5$) من خلال تفاعل المركب ($C_1$) مع اليوريا والثايويوريا على التوالي بوجود حمض الهيدروكلوريك كعامل مساعد. وتم تشخيص المركبات بواسطة بعض تقنيات التحليل الطيفي (FT-IR) والتحليل الطيفي بالرنين النووي المغناطيسي (H-$^1$NMR). تم فحص المركبات الجديدة من حيث نشاطها المضاد للبكتيريا ضد بكتريا *E. coli* و *S. aureus* بواسطة طريقة انتشار الآجار والتي أظهرت نتائج مختلفة.

**الكلمات المفتاحية**: مشتقات ثنائي أمين، الاندول، فعالية بكتيريا.

## Introduction

Heterocyclic compounds are the largest and broadest family of chemical molecules. The majority of scientific disciplines, including medical chemistry and biochemistry, involve heterocyclic molecules. which show biological activities for example antibacterial, antiviral, antifungal, anti-inflammatory, and other therapeutic uses such as and such as anti-tumor [1, 2]. Because of its active in numerous biological processes, it is one of the biological groups of organic chemicals employed in many biological, fields. N-

heterocycles like Alkaloides have been found in several naturally occurring substances that are biologically active. found to play an important role. For example Antibiotics like morphine and vinblastine, penicillin and cephalosporin, in addition to antifungal like cyclosporine , are biologically important substances[3].

For a long time, medicinal chemistry was strongly attracted to the chemistry and biology of heterocyclic molecules. Indole is a significant class of organic heterocyclic compounds that has two-ring structures, consisting of a benzene ring and five pyrrole rings Nitrogen indole is a common ingredient in perfumes and a precursor to many drugs. A tryptophan is an amino acid that contains an indole ring in its structure and is the precursor of the neurotransmitter serotonin[4]. Tryptophan plays a substantial role as a building synthesis in protein biosynthesis. Proteins containing tryptophan have a reducing effect on hormone-related depression and insomnia [5]. The indole Schiff bases were known as a significant type of heterocyclic organic substances with numerous applications in several industries for example anti-inflammatory activity [6], antimicrobial activity [7] antibacterial, antifungal, antitumor activity [8] and antioxidant [9].

## Experimental part

### 1. Materials

were reagent grade and were acquired from Sigma Aldrich and Merck, Alpha and BDH , chemicals are applied as directed.

### 2.Methods of Identification

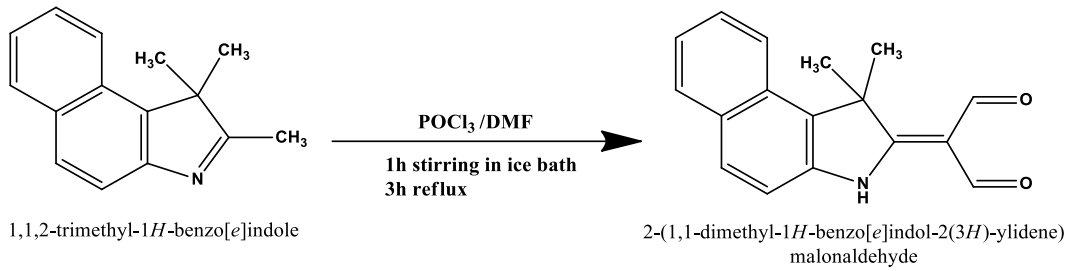
Purification and identification of the synthesized compounds were done by general methods, including:

Melting Point, Fourier-Transform Infrared spectroscopy and $^{1}$H-NMR .

## 3. Synthetic methods.

### 3. 1. Synthesis of 2-(1, 1-dimethyl-1, 3-dihydro-2H-benzo[e] indol-2-ylidene) malonaldehyde ($C_1$)

*N*, *N*-dimethyl form amide (DMF) (10ml) was cooling in an ice bath than (2.3ml) of Phosphoryl chloride ($POCl_3$) with stirring under 5°C. Then a solution of (1 g, 4.7mmol) (1, 1, 2-trimethy -1H-benzo[e]indole) in *N*, *N*-dimethyl form amide DMF (10ml) was dropped into the above mixture, and the reaction mixture was left stirring for an hour in an ice path, reflux for 3hrs. The resulting solution was added to icy distilled water and neutralized with 25 % NaOH aqueous , the yellow precipitate was formation filtered off and dried in oven. Recrystyled by ethanol to afford pure yellow precipitate [10]. Table 1 lists the physical characteristics of compound $C_1$, and the following section contains the synthetic plan (Equation I )




1,1,2-trimethyl-1*H*-benzo[*e*]indole

2-(1,1-dimethyl-1*H*-benzo[*e*]indol-2(3*H*)-ylidene) malonaldehyde

**Equation I:** Synthetic route for compound $C_1$

### 3. 2. Synthesis of (E)-3-(1, 1-dimethyl-1H-benzo[e]indol-2(3H)-ylidene)-3H-benzo[b][1, 4]diazepine-7-carboxylic acid($C_2$)

2-(3, 3-dimethyl-1, 3-dihydro-2H-benzo[glindol-2-ylidene) malonaldehyde (0.1gm, 0.37mmol) was dissolved in aqueous sodium bicarbonate solution (3.32 gm, 39.5mmol in 160 ml water) and 3, 4 diamino benzoic acid (0.05gm, 0.37mmol) was added and 20 hours. Complete of reaction was checked using TLC, mobile phase (1:3 ethyl acetate to hexanes). The solution was acidified with acetic acid and allowed to left overnight afterwards cooled to room temperature. Filtered, water-washed, and dried the precipitate. Table 1 lists the chemical characteristics of compound ($C_2$), and the following is the synthetic plan: (Equation II).

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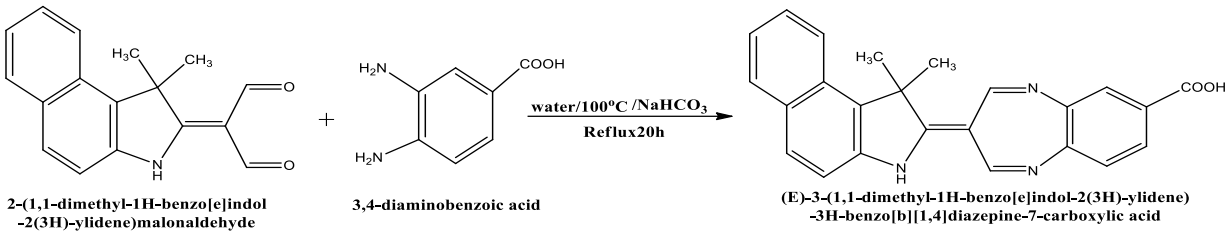
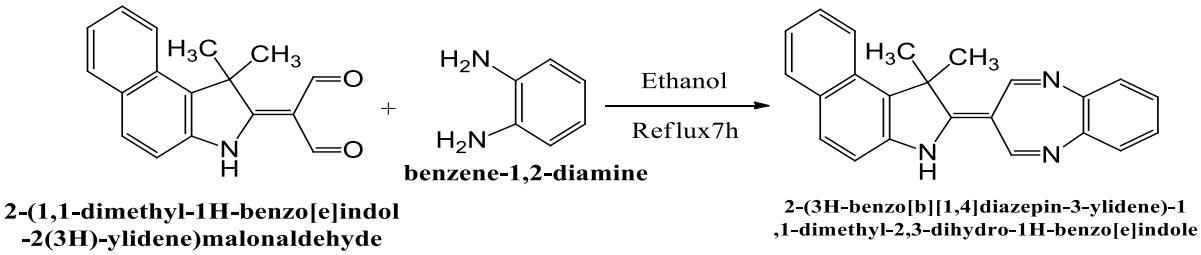



**Equation II:** Synthetic route for compound $C_2$

### 3. 3. Synthesis of 2-(3H-benzo[b][1, 4] diazepin-3-ylidene)- 1, 1-dimethyl-2, 3-dihydro-1H-benzo[e]indole(C3)

A mixture solution (0.1gm, 0.9mmol) of (benzene-1, 2-diamine) and (0.4gm, 0.9mmol) of 2(1, 1-dimethyl-1, 3-dihydro-2H-benzo[e]indol-2-ylidene) malonaldehyde ($C_1$) in 20ml Ethanol contained drops of glacial acidic acid, was left under refluxing at 78 °C for 7hr in the water bath. The solvent was released when the pressure was lowered, and the orange residue was filtered out before being cleaned with hexane and dried in the oven. Complete of reaction was checked using TLC, mobile phase (1:3 ethyl acetate to hexanes). Table 1 lists the physical characteristics of compound ($C_3$), and the following is the synthetic plan: (Equation III).




**Equation III:** Synthetic route for compound $C_3$

### 3. 4. Synthesis of 5-[1, 1-dimethyl-1H-benzo[e]indol-2(3H)-ylidene] pyrimidin-2(5H)-one (C4)

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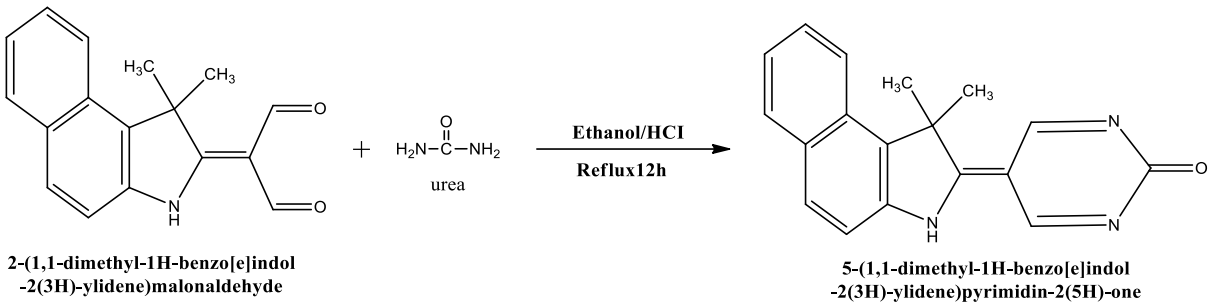
A mixture solution of (0.5gm, 1.88mmol) of 2(1, 1-dimethyl-1, 3-dihydro-2H-benzo[e] indol-2-ylidene) malonaldehyde($C_1$) and (0.1gm, 1.88mmol) of urea dissolved in 20 ml ethanol with couple drops of hydrochloric acid, after 12 hours of refluxing in a water bath, the mixture was filtered out, cleaned with hexane, and dried in an oven while the solvent evaporated under reduced pressure. [TLC (3:1) Hexanes: Ethyl Acetate] was used to assess the purity of this compound. on precoated silica gel, showing spots in the polar regions. Table 1 lists the physical characteristics of compound $C_4$, and the following is the synthetic plan: (Equation IV).




2-(1,1-dimethyl-1H-benzo[e]indol -2(3H)-ylidene)malonaldehyde

5-(1,1-dimethyl-1H-benzo[e]indol -2(3H)-ylidene)pyrimidin-2(5H)-one

**Equation IV:** Synthetic route for compound $C_4$

### 3. 5. Synthesis of 5-(1, 1-dimethyl-1H-benzo[e]indol-2(3H)-ylidene)-pyrimidin -2(5H)-thione ($C_5$)

A mixture of (0.5g, 1.88 mmol) 2-(1, 1-dimethyl-1, 3-dihydro-2H-benzo[e] indol-2-ylidene) malonaldehydeC1 and (0.1g, 1.88mmol) thiourea was dissolved in 30 ml of Ethanol with extra drops of hydrochloric acid (HCI). The mixture was then refluxed in a 78°C water bath for 12hr.TLC (3:1) Hexanes: Ethyl acetate on precoated silica gel was used to determine the purity of new compound, showing spots in the polar regions. Table 1 lists the physical characteristics of compound $C_5$, and the following is the synthetic plan: (Equation V).

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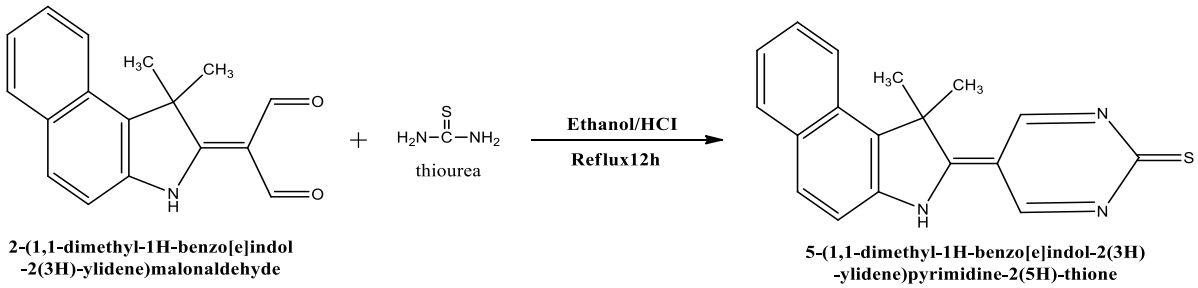


2-(1,1-dimethyl-1H-benzo[e]indol -2(3H)-ylidene)malonaldehyde

5-(1,1-dimethyl-1H-benzo[e]indol-2(3H) -ylidene)pyrimidine-2(5H)-thione

**Equation V:** Synthetic route for compound $C_5$

**Determination of the Antimicrobial activity of synthesized compounds by agar well diffusion method**

Staphylococcus aureus was cultured and identified on Blood agar and Mannitol salt agar. Escherichia coli isolate was cultured and identified on MacCkonky agar and Eosin Methylene blue. MacFarland turbidity standard prepared by the company (Biomeriex) was used in calibrating the number of bacterial cells, as it gives an approximate number of cells 1.5 x 108 cells/ml. The Muller Hinton agar 38 grams were dissolved in 1 liter of distilled water to create the medium and sterilized by autoclave under pressure at 121 °C 15 pounds for 15-20 minutes cooled and poured into sterile dishes and kept in the refrigerator until use. A number of bacteria colonies were transported by a loop to prepare the suspended bacteria and put it in tubes containing brain heart infusion broth to activate the bacteria, The test tubes were kept warm at 37 °C. for (18–24) hours. The suspended bacteria were compared to the standard MacFarland solution (1.5 x 108) cells/ml. After that the bacteria suspended was spread by Sterile Swab, it was spread on the plates containing Muller Hinton agar and then left the plate for a while to dry. Holes were made with a diameter of 5 mm in the culture media by using sterilized a cork borer. 100 µl of the material was added to each hole individually by micropipette. After then, the dishes for 24 hours at 37 °C incubation. The diameter of the inhibitory zone surrounding each hole was measured to assess the potency of each concentration.

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## Results and Discussion

**Chemistry results.**

The new synthesized compounds were subjected to TLC; spectral studies like 1HNMR, and FTIR, and their results are discussed below. The physical properties such as the percentage yield, melting point and color of the compounds (C1- C 5) are represented in Table 1

**Table 1:** Compounds that were produced and their physical characteristics ($C_1$-$C_5$)

| Com. No. | Molecular formula | Molecular weight | Percentage Yield | Melting Point °C | Color |
|---|---|---|---|---|---|
| $C_1$ | $C_{17}H_{15}NO_2$ | 265.31 | 73% | 202-203 | Yellow |
| $C_2$ | $C_{24}H_{19}N_3O_2$ | 283.15 | 91% | > 300 | Brown |
| $C_3$ | $C_{23}H_{19}N_3$ | 337.43 | 96% | 198-200 | Orange |
| $C_4$ | $C_{18}H_{15}N_3O$ | 289.34 | 82% | 130-132 | Brown dark |
| $C_5$ | $C_{35}H_{30}N_4SO_2$ | 570.71 | 92% | 180-184 | Brown |

The synthesis is covered in the first section. of 2 -(1, 1-dimethy l-1, 3-dihydro-benzo [e]indol-2-ylidene) – malonaldehyde (C1), It served as a starting point for the creation of further compounds starting point the compound was recognized by FT-IR, which displayed a distinctive band in the region below. The (N-H) group's stretching vibration includes the band at 3390 cm-1 [11].3065 cm-1 for C-H aromatic [12], 2970 cm-1 to C-H aliphatic [13], 1677 cm-1 for (C= O) [14], 1574-1526 cm-1 for C=C [15], (C-N) band appears at 1206 cm-1, 1392 cm-1 for CH3 bending [16]. Data from the 1H-NMR spectra of chemical Compound (C1) are shown below: 13.47 (s, 1H, NH), 9.80 (s, 2H, 2xCHO), 7.80-8.05 (m, 6H, Ar-H) and 1.99 (s, 6H, 2x CH3). Compound (C1) is reacted by 3, 4-diaminobenzoic acid to obtain compound (C2). By using FT-IR and 1H-NMR spectroscopy, the structures of the compounds thusly synthesized were identified. Data from the FT-IR spectra of chemical Compound (C2) are shown below stretching bands: 3399 cm-1 for (O-H) , 3057cm-1 for (C-H aromatic), 2928-2864 cm-1 for (C-H aliphatic), 1689 cm-1 for (C= O), 1621cm-1 for stretching vibration of C=N , while 1453cm-1 for (C= C) stretching vibration of double bonds, 1375cm-1 for (CH3 group), 1007 cm-1 for (C-O), Data from the 1H-NMR spectra of chemical Compound (C2) are shown below:13.90 (s, 1H.COOH), 11.22 (s, 1H, NH), 8.55 (s, 2H, 2CH=N) 7.36-8.34 (M, 9H, Ar-H), 1.98 (S, 6H, 2xCH3). Compound (C1) was reacted with benzene-1, 2-diamine in absolute ethanol with

addition of (5–6) glacial acetic acid drops to get compound (C3). The FT-IR spectrum of compound (C3) demonstrate the following: The bands at 3408 cm-1 assigned for the stretching vibration of (N-H), 3057cm-1 to the (C-Haromatic), (2956-2932) cm-1 to (C-Haliphatic), 1634 cm-1 for (C=N), 1565cm-1 for (C=C) stretching vibration of double bonds, 1488 cm-1 for (CH3group). Data from the 1H-NMR spectra of chemical Compound (C3) are shown below:

11.2 (s, 1H, NH), 8.65 (s, 2H, 2xCH=N), 7.18-8.22 (M, 10H, Ar-H), 1.98 (s, 6H, 2xCH3). Compound (C1) reacts with urea in absolute ethanol to obtain compound (C4). The FT-IR spectrum of compound (C4) demonstrate the following: The bands at 3392cm-1 assigned for the stretching vibration of (N-H), 2978cm-1 to (C-H aliphatic), 1739cm-1 for(C=O), 1657cm-1for (C=N), 1621cm-1 for (C=C) stretching vibration of double bonds, 1463cm-1 for (CH3 group). Data from the 1H-NMR spectra of chemical Compound (C2) are shown below:11.2(s, 1H, NH), 8.96 (s, 2H, CH=N) 7.39-8.37 (M, 6H, Ar-H) 1.90 (s, 6H, 2xCH3). while as Compound (C1) was reacted with thiourea in absolute ethanol to get compound (C5). The FT-IR spectrum of compound (C5) demonstrate below: The belt at 3282 cm-1 is assigned to the stretch mode of(N-H), 2928 cm-1 to (C-H aliphatic), 2768cm-1 for (C=S), 1645 cm-1for (C=N), 1610-1583 cm-1 for (C=C) stretching vibration, 1463cm-1 for (CH3 group). Data from the 1H-NMR spectra of chemical Compound (C2) are shown below:11.02 (s, 1H, NH), 8.90 (s, 2H, N=CH), 7.43-8.25(m, 6H, Ar-H) 1.65 (s, 6H, 2xCH3).

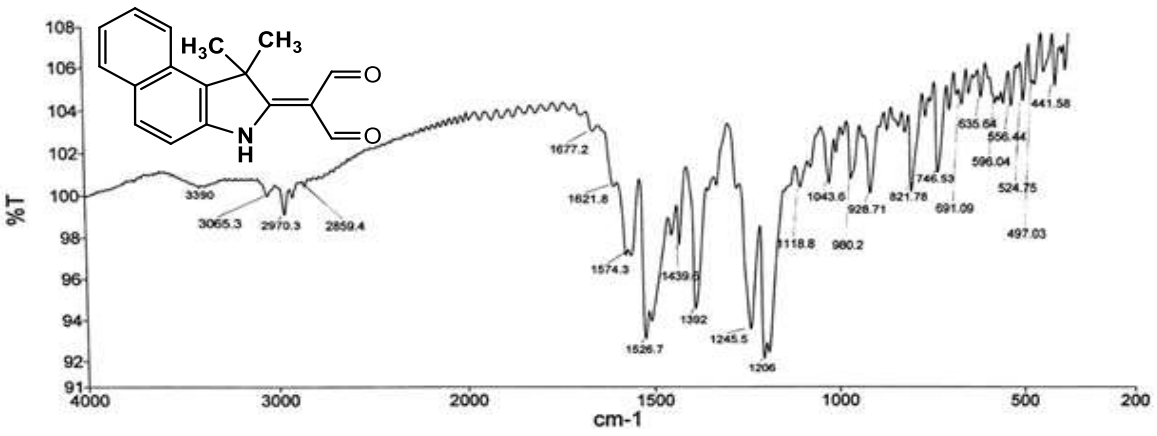


**Figure 1**: The FT-IR spectra of the compound ($C_1$)

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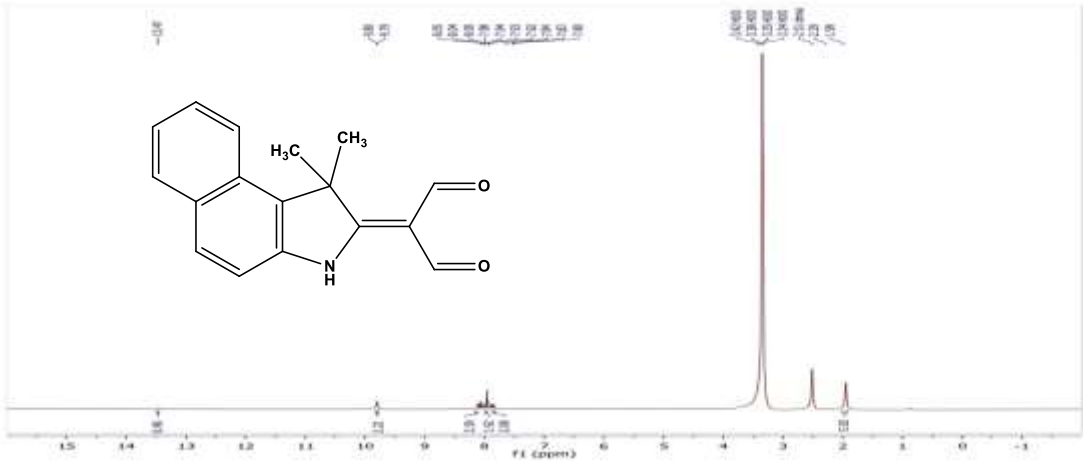


**Figure 2:** The $^{1}$H-NMR spectra of the compound($C_1$).

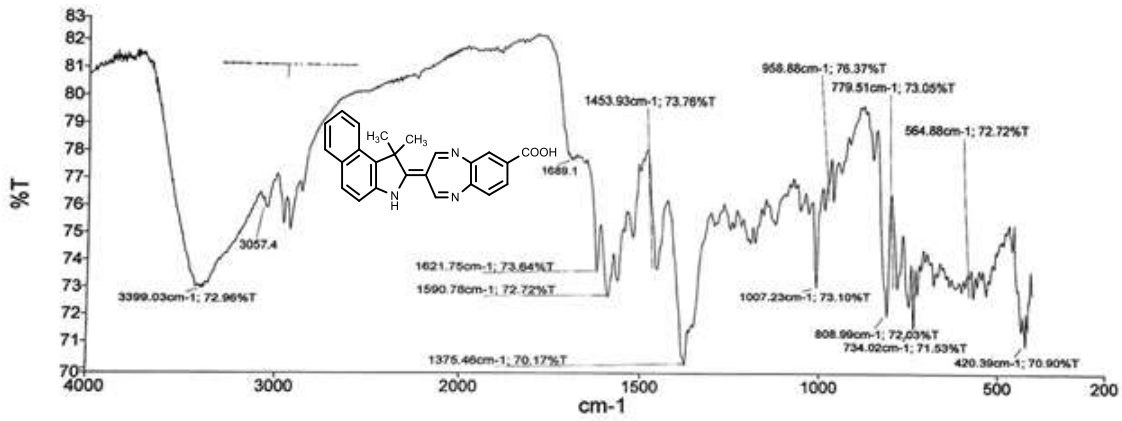


**Figure 3:** The FT-IR spectra of the compound($C_2$).

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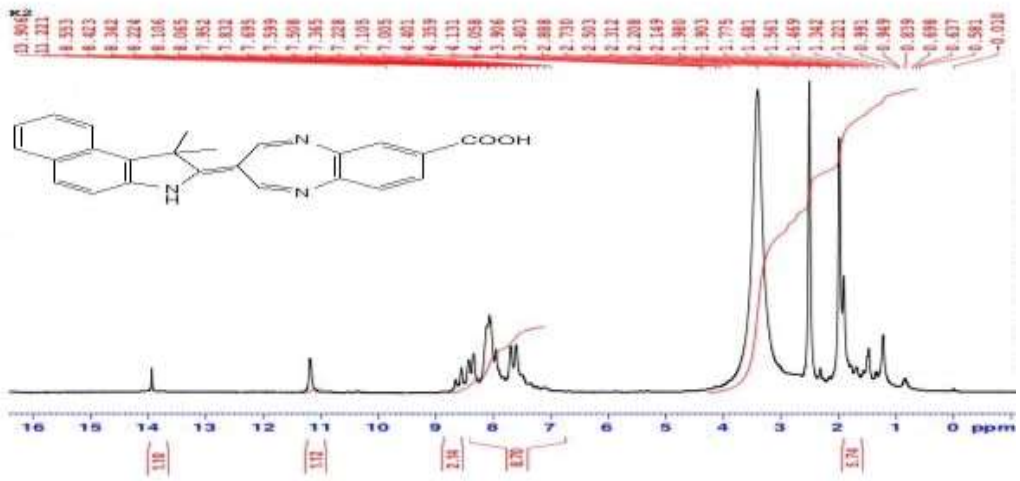


**Figure 4**: The $^{1}$H-NMR spectra of the compound($C_2$).

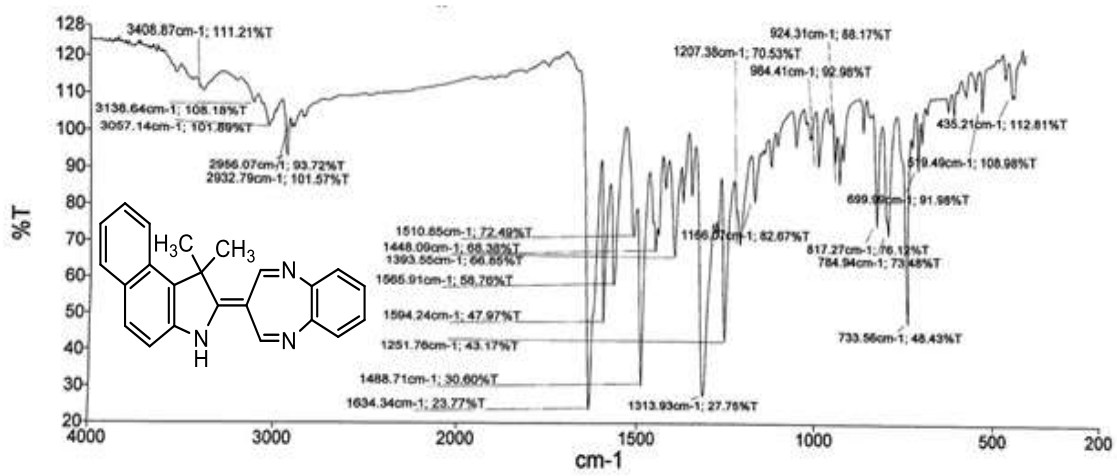


**Figure 5**: The FT-IR spectra of the compound($C_3$).

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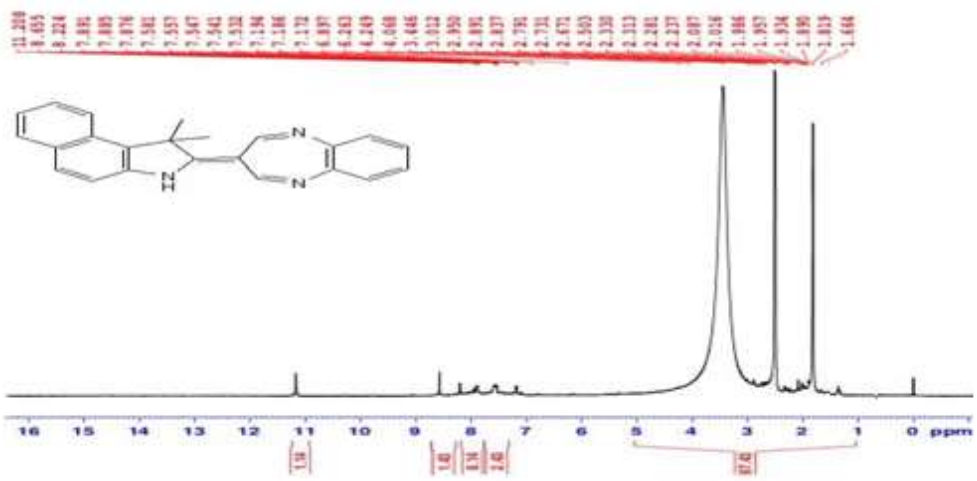


**Figure 6**: The $^{1}$H-NMR spectra of the compound($C_3$).

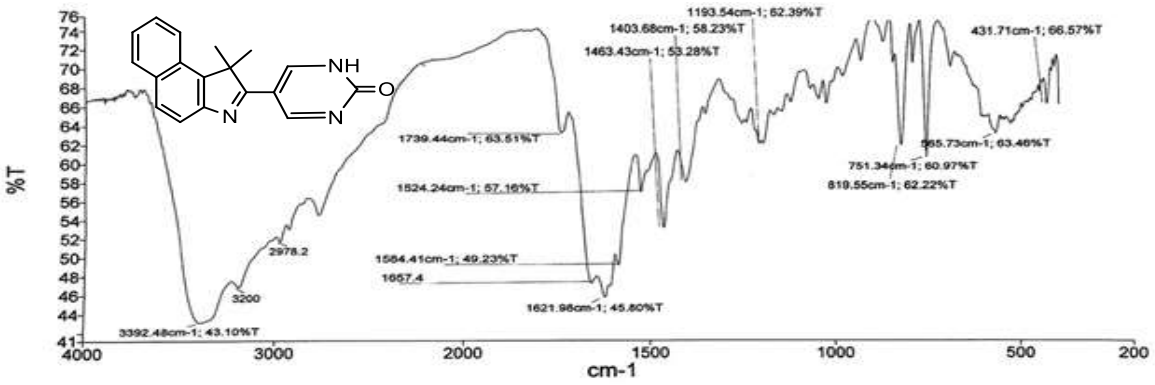


**Figure 7**: The FT-IR spectra of the compound($C_4$).

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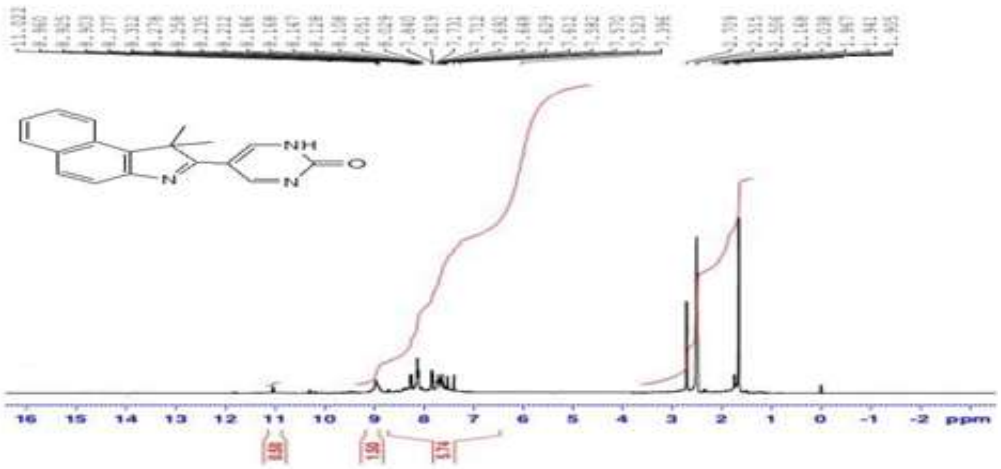


**Figure 8**: The $^{1}$H-NMR spectra of the compound($C_4$).

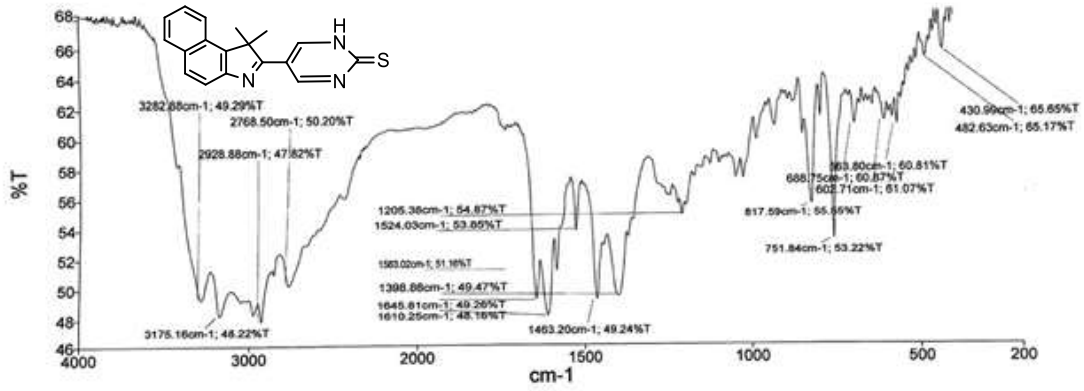


**Figure 9**: The FT-IR spectra of the compound ($C_5$).

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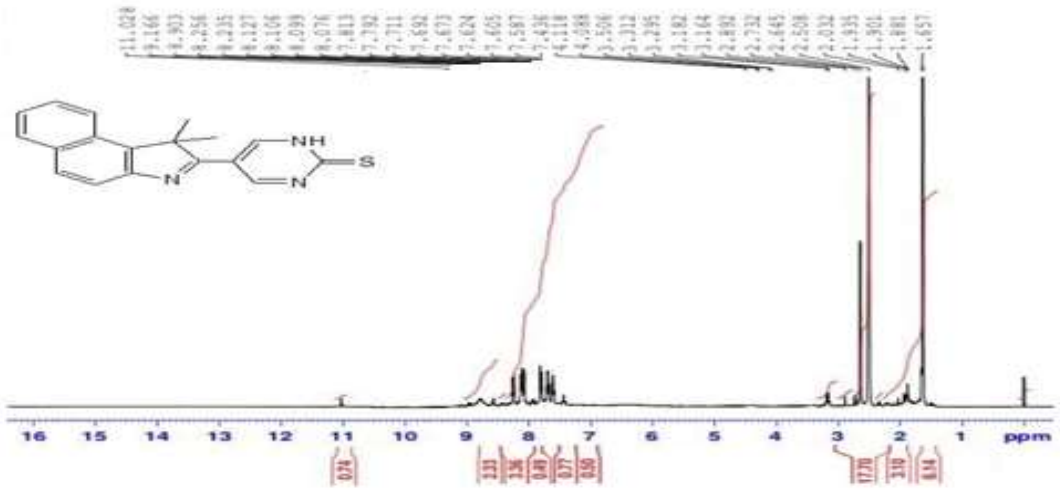


**Figure 10**: The $^{1}$H-NMR spectra of the compound($C_5$).

## Biological results

The antibacterial activity of new compounds with 10mg/ml of Dimethyl sulphoxide (DMSO) as a solvent was examined by using the agar well diffusion method on Muller Hinton agar medium with MacFarland turbidity as a standard solution. The zones of inhibition exhibited by the tested compounds were measured in (mm), as shown in (Figure 11). Table 2 presents the findings. The screening results showed the compounds (**$C_2$**, $C_3$ and **$C_5$**) have moderate action against the microorganisms S. aureus and E. coli, whereas the compound **($C_4$)** has high activity against *S. aureus* bacteria and moderate activity against *E. coli*.

**Table 2**: The inhibition zones of the compounds ($C_2$-$C_5$).

| Tested materials | Microorganism | |
|---|---|---|
| | *E. coli* | *S. aureus* |
| | Diameters of the inhibition (mm) | |
| Compound ($C_2$) | 13 | 19 |
| Compound ($C_3$) | 12 | 17 |
| Compound ($C_4$) | 24 | 31 |
| Compound ($C_5$) | 15 | 25 |

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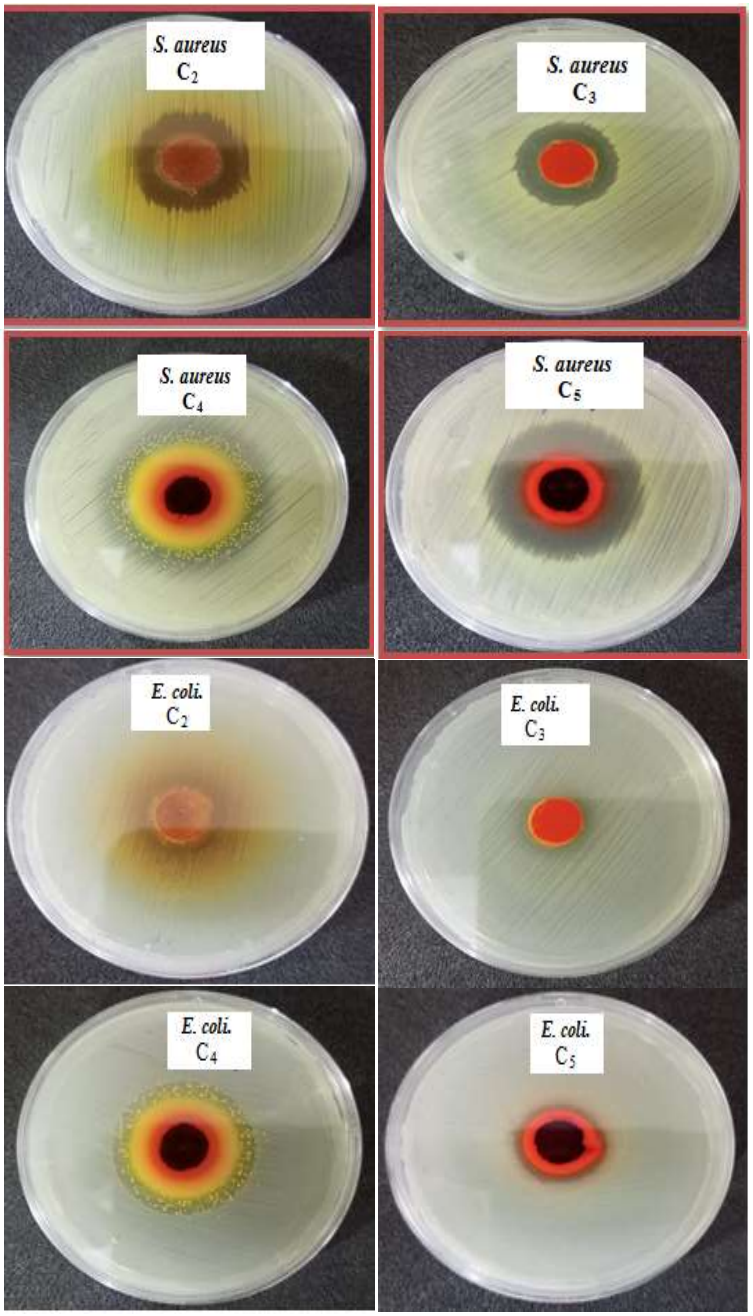


**Figure 11:** Effects of the tested compounds ($C_2$-$C_5$) against *S. aureus and E. coli.*

## Conclusions

The new compounds ($C_2$-$C_5$) were characterized utilizing diverse spectroscopic methods like FT-IR, $^1$H-NMR, In addition to measurement some of their physical properties and antibacterial activity. From the antibacterial experiments, it was observed that all the compounds exhibited moderate activity against two types of bacteria used excluding the compound $C_4$ which has high activity against *S. aureus* and moderate activity against *E. coli*

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