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Synthesis, Characterization and Antibacterial Evaluation of Some New Heterocyclic Compounds Derived from 2- (1,1-Dimethyl-1, 3-Dihydro-2H-Benzo[e]Indol-2-Ylidene) Malonaldehyde

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ABSTRACT

Using the conventional method, six New Heterocyclic compounds Derived from 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)malonaldehyde. The chemical structure of the compounds were confirmed and characterized by spectroscopic techniques (FT-IR, and ^{1}H-NMR). Their purities have been tested by thin layer chromatography (TLC). New compounds (1-7) with concentrations (200, 150, 100, 50) ppm were screened for their antibacterial activity against *E. coli and S. aureus* by the agar well diffusion method, which revealed different results.

Keywords: : Malonoaldehyde, Schiff bases, indole derivatives ,antibacterial activity.

I. INTRODUCTION

Heterocyclic compounds are a class of chemical substance that is used in a variety of biological applications [1]. The heterocyclic ring can be found in the skeletons of many biological compounds, including DNA and RNA, chlorophyll, hemoglobin, vitamins, and more [2]. Many heterocyclic compounds, such as Benzimidazole derivatives, have been utilized to treat a number of ailments as antibacterial herbicides, urinary antiseptics, and anti-inflammatory agents [3]. Pyrazole derivatives have already been demonstrated to have a variety of biological activities [4], including antibacterial, antifungal, [5] and antiviral properties [6]. Antihelmintic and antiparasitic properties[7] . Indole and many of its derivatives are among the most intriguing nitrogen heterocycles due to their broad range of biological activities [8], which include antifungal [9], anti-diabetic [10], anti-inflammatory [11], anti-bacterial [12], and anti-allergic (Aboul-Enein In the pharmaceutical industry and chemical synthesis, indole and its analogs are important heterocycles and bioactive intermediates due to their wide range of pharmacological properties [13]. In addition, C-3-substituted indole is a crucial step in the production of pharmacologically active molecules [14]. Indole (2, 3-benzopyrrole) possesses ten electrons, making it a heterocycle with an abnormally large amount of electrons that functions as a weak base [15]. Among the . Electrophilic substitution at C-3 in a five-membered ring, which is aided by electron release from the heteroatom, is one of the most prevalent indole reactions. The indole skeleton's N-H bond is slightly acidic. A strong base is employed to deprotonate the N-H proton. As a result, for N-substitution reactions as alkylations, acylations, and transition metal catalyzed arylation, basic conditions are required [16].

Vuillemin used the term "antibiotic" in 1889 to describe the active component complex in the antibiosis process. The Greek words "anti" and "bios" mean "against" and "life" respectively. Antibiotics, according to Benedict and Langlykke, are a biochemical compound produced by or adjusted by a live plant that is capable of suppressing the life activities of viruses in minute concentrations. Antibiotics were once a simple matter, created by a single virus that prevented the growth of other bacteria [17]. Antibiotics are also known as antibacterial drugs. Antiviral medicines [18] are pharmaceuticals that prevent viruses from reproducing. Antibiotics are chemotherapeutic drugs that kill or stop bacteria from growing. These chemical compounds are used to treat disease by eliminating the bacteria that cause it.

II. EXPERIMENTAL

1- Chemistry part

Materials and methods

General procedures were used to purify and identify the produced chemicals, including:

- Thin Layer Chromatography is a type of chromatography that uses a thin layer (TLC),
- Melting Temperature,
- Infrared Fourier-Transform Spectroscopy (FT-IR),
- ^{1}H-NMR.

Synthesis methods

1-Synthesis of Malonaldehyde 2-(1,1-dimethyl-1,3-dihydro-2H-benzoe]indol-2-ylidene) (A1).

N,*N*-dimethyl formamide (DMF) (3ml) was cooled in an ice bath then added drop wise of (1.3ml) Phosphoryl chloride (POCl3) with stirring under 5°C, then a solution of (1 g, 4.7 mmol) 1,1,2- trimethyl-1H-benzo[e]indole in DMF (3ml) was added dropwise, the reaction mixture was stirred in ice path for 1h. then reflux for 3h. at 88 ºC. The resulting solution was added to icy distilled water and neutralized with 25% NaOH aqueous, the yellow precipitate was formed

filtered off and dried in oven. Recrystyled by ethanol to afford pure yellow precipitate **[19]** .Yield (1.242 g, 98 %). m.p 206-208 ^{o}C.. FT-IR data (cm^{-1}): 3130 υ (N-H), 2969 υ (C-H aliphatic), 2740 υ(CH aldehyde), 1680 υ (C=O), 1509-1456 υ (C=C), 1209 υ (C-N), 748 υ (C-H bending). ^{1}H NMR (400MHz, DMSO, *δ* in ppm): *δ* = 13.14 (s, 1H, N*H*), 9.79 (s, 2H, C*H*=O), 7.69-7.38 (6H, Ar-*H*) and 1.68 (s, 6H, 2xCH_3) .

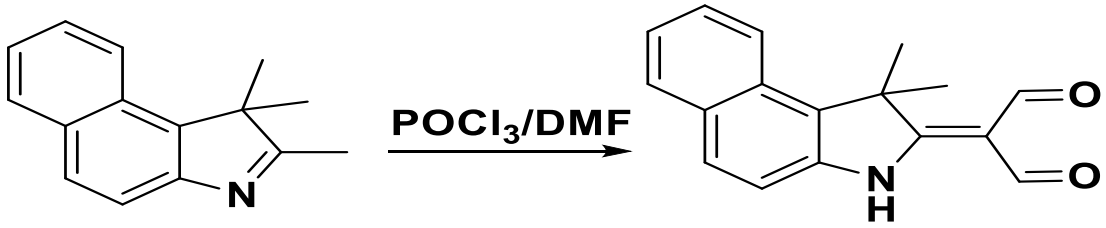


figure (1. 1): The synthetic pathway of 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)malonaldehyde(A1).

2-Synthesis of (2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-((4 hydroxyphenyl) imino)propanal (A2).

Glacial acetic acid (1 ml) were added to solution of Malonaldehyde 2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene) and (0.411g, 3.7 mmol) 4-hydroxy aniline were dissolved in ethanol (30 ml) prepared as a solution and then the mixture reaction was refluxed in a water bath at 78oC for 20 h. A solvent was reduced to one quarter; a dark brown precipitate was formed, filtrated off, washed with water, and dried up in an oven at 50 ºC. The purity of this compound was determined by using TLC (3:1) hexane: ethyl acetate, which gave one spot. Yield (1.2g 89%), m.p 150-152°C. FT-IR data in (cm^{-1}): 3185 υ(N-H), 3049 (CH aromatic) 2973 υ(CH aliphatic), 1650 υ(C=O), 1632 υ(CH=N), 1528-1491υ(C=C), 1354 υ(CH_3), 1264 υ(CN), , and 751 υ(C-H bending). **^{1}H NMR** (400 MHz, DMSO, *δ* in ppm): *δ* = 14.23 (s, 1H, NH), 9.46 (s, 1H, *H*C=O), 9.09 (s, 1H, OH), 8.96 (s, 1H, *H*C=N), 6.83-8.17 (m, 10H, Ar-*H*), and 1.96 (s, 6H, 2x CH_3).

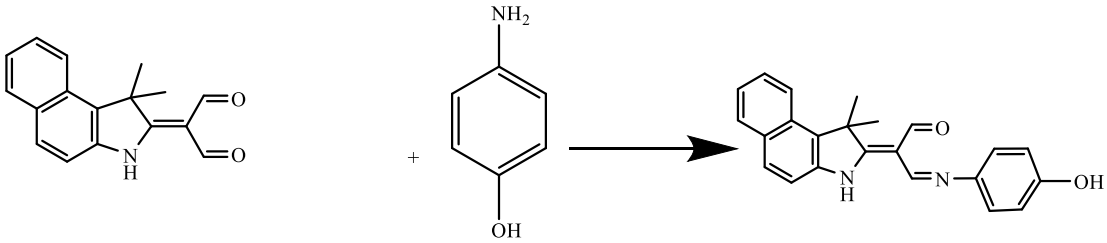


figure (3. 2): The synthetic pathway of Synthesis of (2-(1,1-dimethyl-1,3-dihydro-2H benzo[e]indol-2-ylidene)-3-(4 hydroxyphenyl) imino)propanal .(A2).

3-Synthesis of 2-[3,3-dimethyl-2,3-dihydro-1H-indol-2-ylidene]-3-iminopropanal (A3).

A mixture of (1 g, 2.21mmol) of 2-(3,3-dimethyl-1,3-dihydro-indol-2-ylidene)-malonaldehyde and (0.426g 2.21 mmol) of 4-amminoantipyrene was dissolved in 35 ml of ethanol and then 1ml of glacial acetic acid was added to the solution. The mixture was refluxed in water bath at 78ºC for 10h. (3:1) hexane: ethyl acetate, which gave one spot. Yield: (1.65g, 97 %), m.p. 168-170 ºC. FT-IR data in (cm-1): 3420 υ(N-H), 3052 (CH aromatic) 2966 υ(CH aliphatic), 2856 υ(CH aldehyde), 1656 υ(C=O), 1594 υ(CH=N), 1527-1492 υ(C=C), 1292 υ(CN), , and 752 υ(C-H bending). **^{1}H NMR** (400 MHz, DMSO, *δ* in ppm): *δ* = 13.87 (s, 1H, NH), 9.64 (s, 1H, *H*C=O), 8.1 (s, 1H, *H*C=N), 7.40-8.04 (m, 11H, Ar-*H*), 1.95 (s, 3H, N-CH_3), and 1.81 (s, 9H, 2x CH_3).

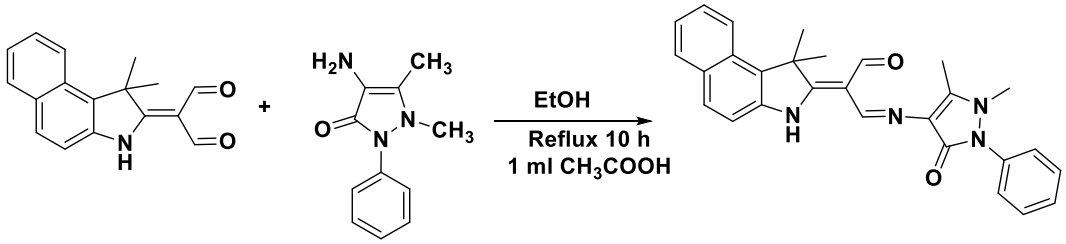


Figure (1. 3): The synthetic pathway of 2-[3,3-dimethyl-2,3-dihydro-1H-indol-2-ylidene]-3-iminopropanal (A3).

4-Synthesis of 3-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)imino)-2-(1,1 dimethyl-3-pentyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)propanal.(A4)

A (1g, 2.21mmol) of 2-(3,3-dimethyl-1,3-dihydro-indol-2-ylidene)-malonaldehyde was dissolved in DMF 20 ml, then (0.3 g K_2CO_3 that dissolving in water) was added, and then (0.335 g, 2.21mmol) of halide (Bromo pentane) was added to the mixture with continuous stirring for a quarter of an hour, the mixture was refluxed for 15h, The organic layer was then washed with water and dried after being extracted with ethyl acetate (32 x 5mL).The purity of this compound was determined by using TLC (3:1) hexane: ethyl acetate, which gave one spot. Yield: (0.73 g, 63 %), m.p. 118-120 ºC. FT-IR data in (cm^{-1}): 3052 (CH aromatic) 2926 υ(CH aliphatic), 3864 υ(CH_2), 1664 υ(C=O), 1621 υ(CH=N), 1518-1452 υ(C=C), 1354 υ(CH_3), 1205 υ(CN), , and 747 υ(C-H bending). **^{1}H NMR** (400 MHz, DMSO, *δ* in ppm): 9.64 (s, 1H, *H*C=O), 8.16 (s, 1H, *H*C=N), 7.37-8.03 (m, 11H, Ar-*H*), 3.34 (t, 2H, N-CH_2), 1.94 (s, 3H, N-CH_3), 1.87 (m, 6H, N-CH_2), 1.48 (s, 9H, 2x C*H*$_3$) and 0.85 (m, 3H, $CH_2\underline{CH_3}$).

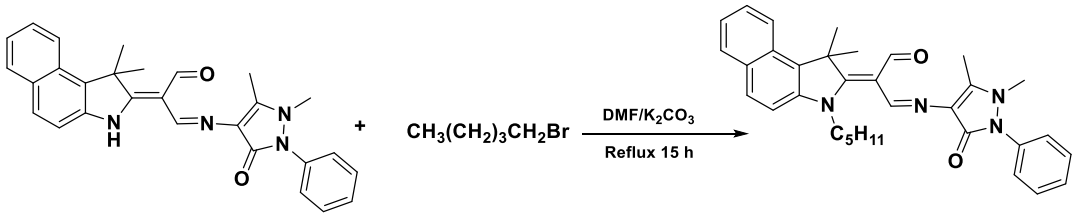


Figure (1. 4): The synthetic pathway of 3-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)imino)-2-(1,1 dimethyl-3-pentyl-1,3-dihydro-2H-benzo[e]indol- ylidene)propanal.(A4).

5-Synthesis of (2E)-2-(1,1-dimethyl-3-octyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)imino)propanal.(A5)

A (1g, 2.21mmol) of 2-(3,3-dimethyl-1,3-dihydro- indol-2-ylidene)-malonaldehyde was dissolved in DMF 20 ml, then (0.3 g K_2CO_3 that dissolving in water) was added, and then (0.426 g, 2.21mmol) of halide (Bromo octane) was added to the mixture with continuous stirring for a quarter of an hour, the mixture was refluxed for 15h, then extracted with ethyl acetate (3×25mL) and the organic layer was washed with water, and then dried. The purity of this compound was determined by using TLC (3:1) hexane: ethyl acetate, which gave one spot. Yield: (0.70 g56 %), m.p. 128-130 ºC. FT-IR data in (cm^{-1}): 3056 (CH aromatic) 2926 υ(CH aliphatic), 2853 υ(CH_2), 1670 υ(C=O), 1621 υ(CH=N), 1519-1457 υ(C=C), 1351 υ(CH_3), 1206 υ(CN), , and 751 υ(C-H bending).

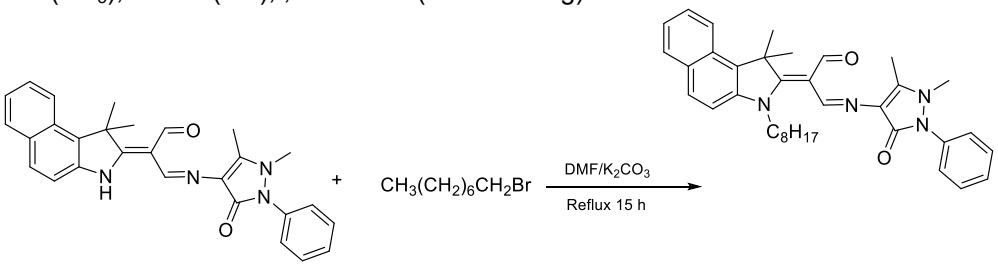


figure (1. 5): The synthetic pathway of (2E)-2-(1,1-dimethyl-3-octyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)imino)propanal.(A5)

6-Synthesis of 4-(((2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-oxo propylidene)amino)benzoic acid.(A6)

Amixture of (1g ,3 .76mmol) of 2-(3,3-dimethyl-1,3-dihydro-indol-2-ylidene)-malonaldehyde and (0.621g, 3.76mmol) of 4-aminoethylbenzoate was dissolved in ethanol (25-30 ml), , then added glacial acetic acid 2ml to the solution. The mixture was refluxed in water bath at 78ºC for 10h. TLC (3:1) hexane: ethyl acetate yielded one spot, which was used to determine the purity of this chemical. Yield: (1.2 g,77 %), m.p. 102-104 ºC. FT-IR data in (cm^{-1}): 3132 υ(N-H), 3052 (CH aromatic) 2976 υ(CH aliphatic), 2716 υ(CH aldehyde), 1717 υ(C=O ester) 1674 υ(C=O aldehyde), 1607 υ(CH=N), 1510-1456 υ(C=C), 1365 υ(CH_3), 1239 υ(CN), , and 753 υ(C-H bending). **^{1}H NMR** (400 MHz, DMSO, *δ* in ppm): *δ* = 13.47 (s, 1H, NH), 9.53 (s, 1H, *H*C=O),8.80 (s, 1H, *H*C=N), 7.48-8.20 (m, 10H, Ar-*H*), and 1.84 (s, 3H, C*H*$_3$).

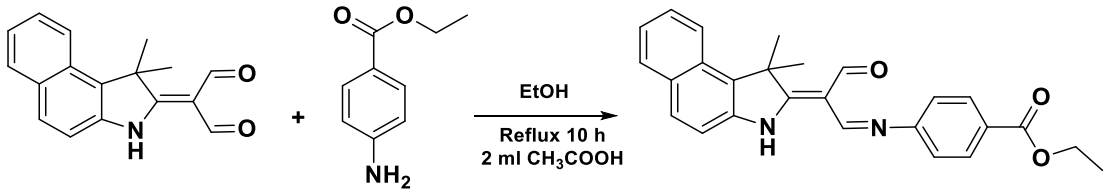


Figure (1. 6): The synthetic pathway of 4-(((2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)-3-oxo propylidene)amino)benzoic acid.(A6)

7-Synthesis of 6-[(5E)-3,3-dimethyl-4-methylidene-5-(prop-2-en-1-ylidene)pyrrolidin-2-ylidene]-3,6-dihydro-2H-1,4-diazepine.(A7)

A (1 g,3.76 mmol) 2-(3,3-dimethyl-1,3-dihydro-indol-2-ylidene)-malonaldehyde dissolved in 15 ml ethanol . then (0.3 g K_2CO_3 of after dissolving in water) was added and (0.225g,3.76 mmol) of ethane-1,2-diamine that dissolved in 10 ethanol added to the mixture. The mixture was refluxing for 15h in water bath at 78ºC. The purity of this compound was determined by using TLC (3:1) hexane: ethyl acetate, which gave one spot. Yield: (0.7 g, 64 %), m.p. 150-152 ºC. FT-IR data in (cm-1): 3232 υ(N-H), 3052 (CH aromatic) 2969 υ(CH aliphatic), 1620 υ(CH=N), 1584-1448 υ(C=C), 1398 υ(CH_3), 1252 υ(CN), , and 749 υ(C-H bending). **^{1}H NMR** (400 MHz, DMSO, *δ* in ppm): *δ* = 12.88 (s, 1H, NH), 8.35 (s, 1H, *H*C=N), 7.39-8.13 (m, 6H, Ar-*H*), 3.83(t, 4H , NCH_2), and 1.92 (s, 6H, 2x C*H*3).

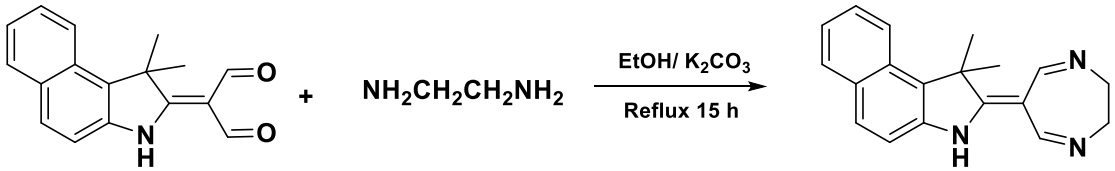
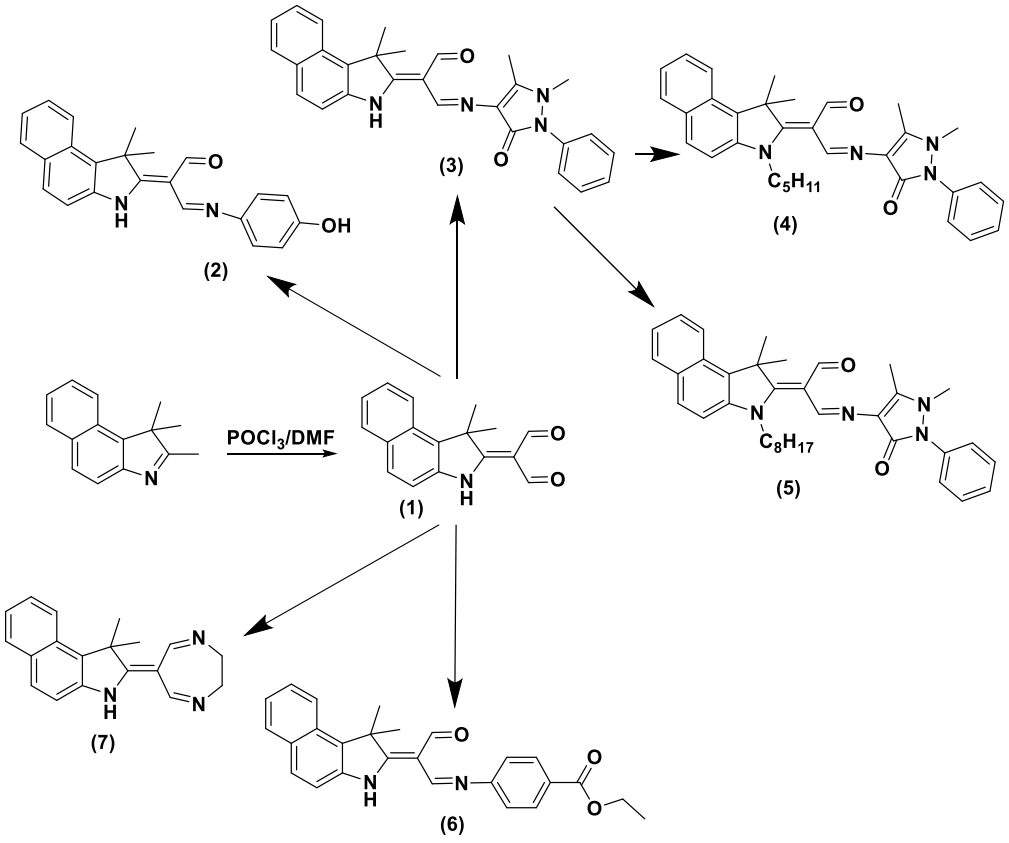


Figure (1. 7): The synthetic pathway of 6-[(5E)-3,3-dimethyl-4-methylidene-5-(prop-2- en-1-ylidene)pyrrolidin-2-ylidene]-3,6-dihydro-2H-1,4-diazepine.(A7)



Scheme of new synthesized compounds (1-6)

2- Biological part

Material and Methods

Staphylococcus aureus isolates were cultured on Blood agar and Mannitol salt agar. *Escherichia coli* isolates were cultured on MacCkonky agar and Eosin Methylene blue.

MacFarland turbidity standard

The preparing solution from the company (Biomeriex) was used in calibrating the number of bacterial cells, as it gives an approximate number of cells 1.5 x 10^8 cells/ml.

1- Muller Hinton agar

This medium was prepared by dissolving 38 gm in 1L of distillated water and sterilized by autoclave at 121 °C and under pressure 15 pounds for 15 minutes cooled and poured into sterile dishes and kept in the refrigerator until use.

2- Determination the Antimicrobial activity of compounds by agar well diffusion method

1- A number of bacteria colonies were transported by loop to prepare the suspended bacteria and put it in tubes contain brain heart infusion broth to activate the bacteria. The tubes were incubated for (18 - 24) h at 37 °C. The suspended bacteria was compared to the standard MacFarland solution (1.5 x $10^{8)}$ 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.

2- A holes were made with a diameter of 5 mm in the culture media by using sterilized a cork borer

3- 100 µl of the material (concentration50/100/150/200ppm) were added to each hole individually by micropipette. After then, incubate the dishes at 37 °C for 24 h. The positive control represented by adding sterile distilled water. After then, incubate the dishes at 37 °C for 24 h.

4-The effectiveness of each concentration was determined by measuring the diameter of the inhibition zone around each hole.

III. RESULTS AND DISCUSSION

1-Chemistry results

The new synthesized compounds were subjected to TLC; spectral studies like ^{1}HNMR, and FTIR, and their results are discussed below. The physical properties such as the percentage yield and melting point of the compounds are represented in Table No.1

Table (1): Physical properties of the synthesized compounds

Comp. No.	Molecular formula	%Yield	Melting Point ºC	TLC Rf (cm)
1	$C_{17}H_{15}NO_2$	98%	208-210	0.6
2	$C_{23}H_{20}N_2O_2$	89%	150-152	0.3
3	$C_{28}H_{26}N_4O_2$	97%	168-170	0.7
4	$C_{33}H_{36}N_4O_2$	63%	118-120	0.7
5	$C_{36}H_{42}N_4O_2$	56%	128-130	0.5
6	$C_{26}H_{24}N_2O_3$	77%	102-104	0.5
7	$C_{19}H_{19}N_3$	64%	150-152	0.3

FT-IR Study

The FT-IR spectra of the new five synthesized compounds showed the absorption band of the new functional group (imine group CH=N) at 1632, 1594,1621,1621 and 1607 cm^{-1} for the compounds 2, 3,4,5 and 6 respectively which approved the chemical structure of the synthesized compounds. A strong absorption band appeared at 1650-1674 cm^{-1} for all the compounds related to the carbonyl C=O group. Whereas the absorption band appeared at 16205 were belonged to the CH=N group for compound 7. All of these bands are confirmed the chemical structures of the synthesized compounds .

NMR Study

^{1}H-NMR,spectra were reported in DMSO (dimethyl sulfoxide) with chemical shifts in ppm and using TMS (tetramethylsilane) as standard.The ^{1}H-NMR results for compound (1) Fig. (1) shown single signals at 13.14 ppm was belonged to proton of (NH) of indole ring . A singlet signal at 9.79 ppm was referred to proton atom of aldehyde (C=O) group. Signals were appeared in the region between (7.69-7.38) ppm were assigned to protons of aromatic ring for (2) compound . Finally peak at 1.96 ppm was belonged to six protons of two methyl groups. ^{1}H NMR results of other compounds are discussed and listed in table (2).

Table. (2): The chemical shift in ppm to ^{1}H NMR results of compounds

No	**NH**	HC=O	CH=N	Ar-H	2xCH3	Other
1	13.14	9.79	-	7.69-7.38	1.68	-

2	14.23	9.46	8.69	6.83-8.17	1.96	9.09 O-H
3	13.87	9.64	8.1	7.40-8.04	1.81	1.95 N-CH_3
4	13.22	9.43	8.4	7.23-8.5	1.61	-
5	13.31	9.39	8.2		1.75	-
6	13.47	9.53	8.80	7.48-8.20	1.95 1.84 CH_3	4.21 OCH_3
7	12.88	-	8.35	7.39-8.13	1.92	-

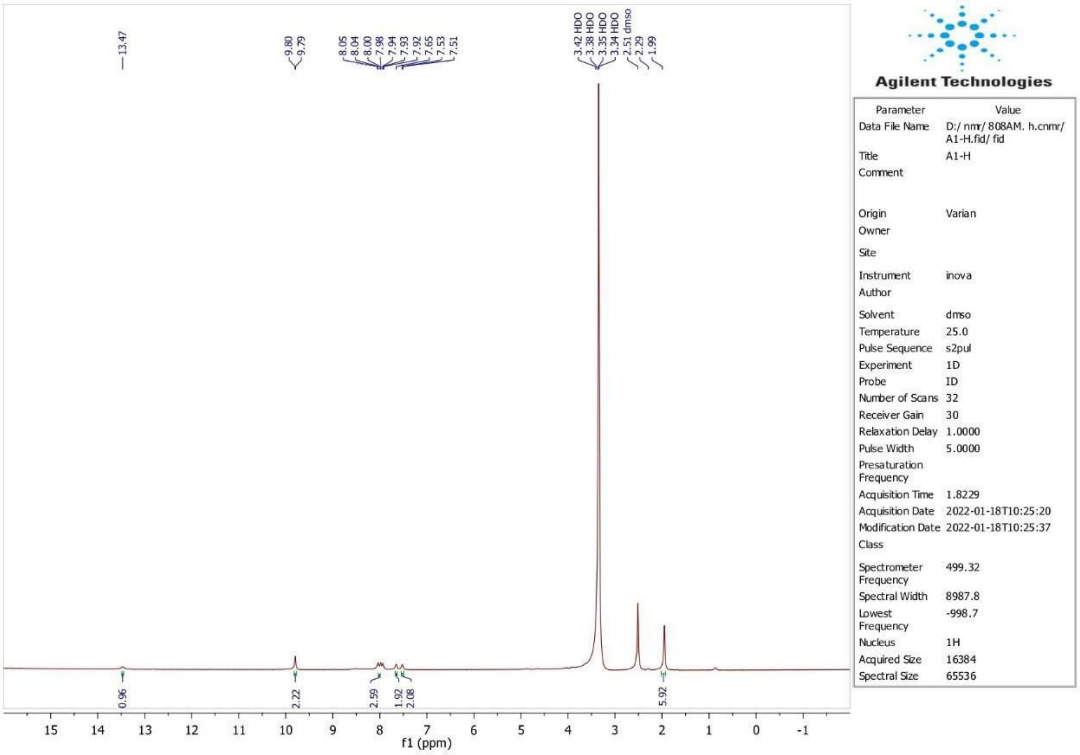


Figure (2-1): 1H NMR spectrum of compound 1

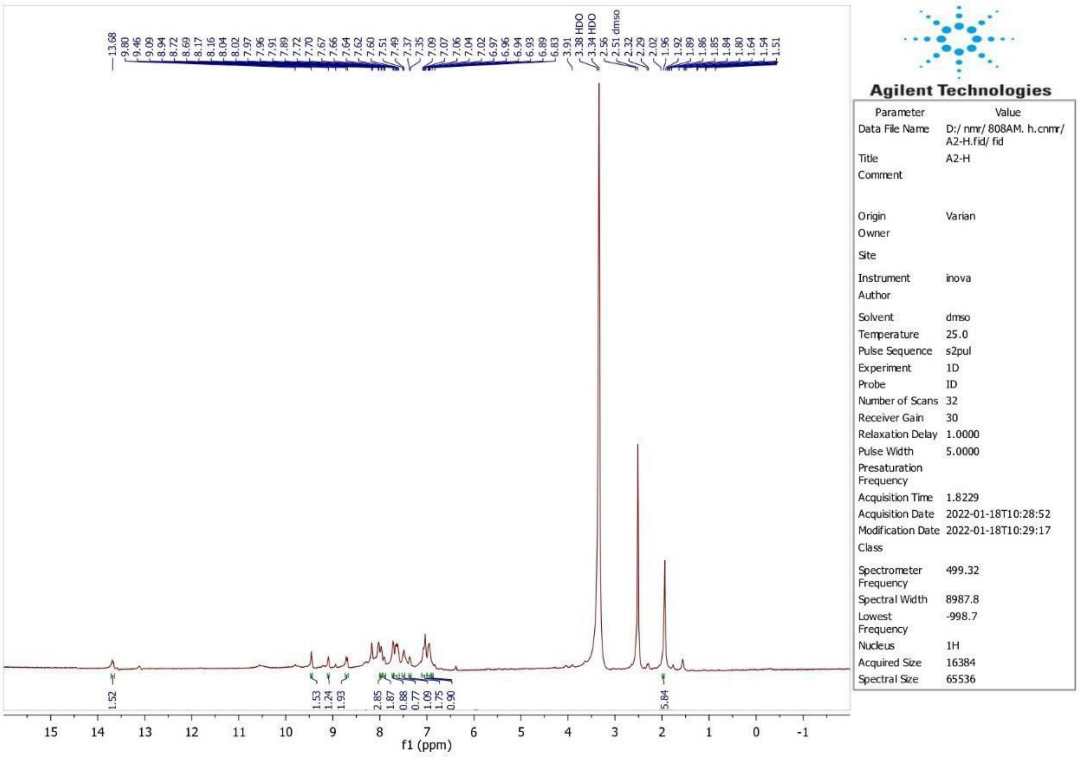


Figure (2-2): 1H NMR spectrum of compound 2

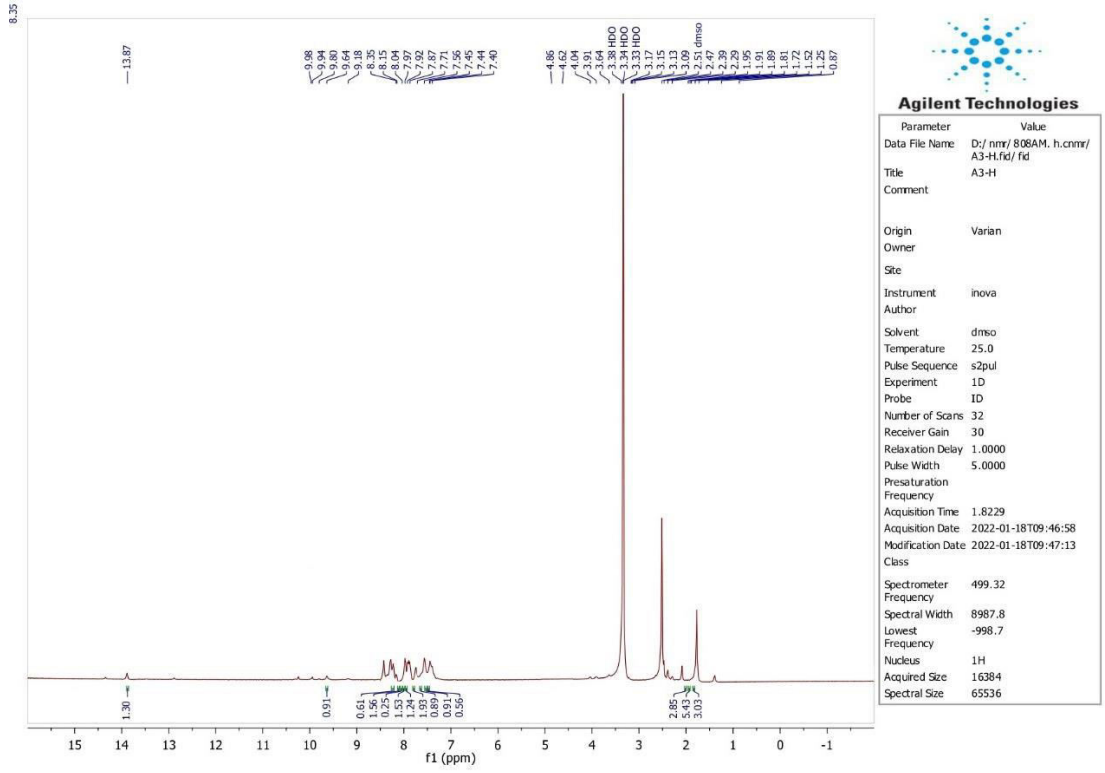


Figure (2-3): 1H NMR spectrum of compound 3

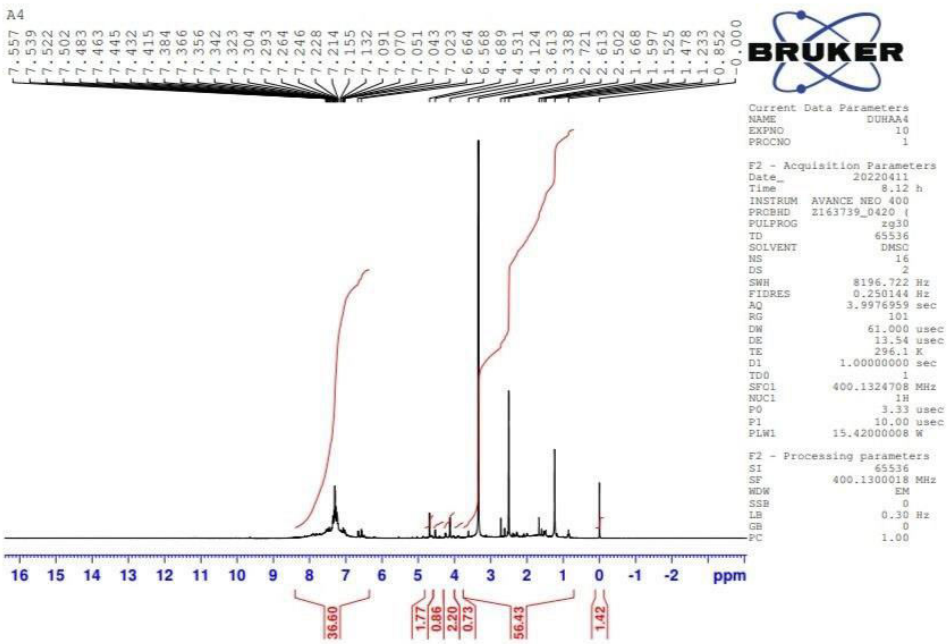


Figure (2-4): 1H NMR spectrum of compound 4

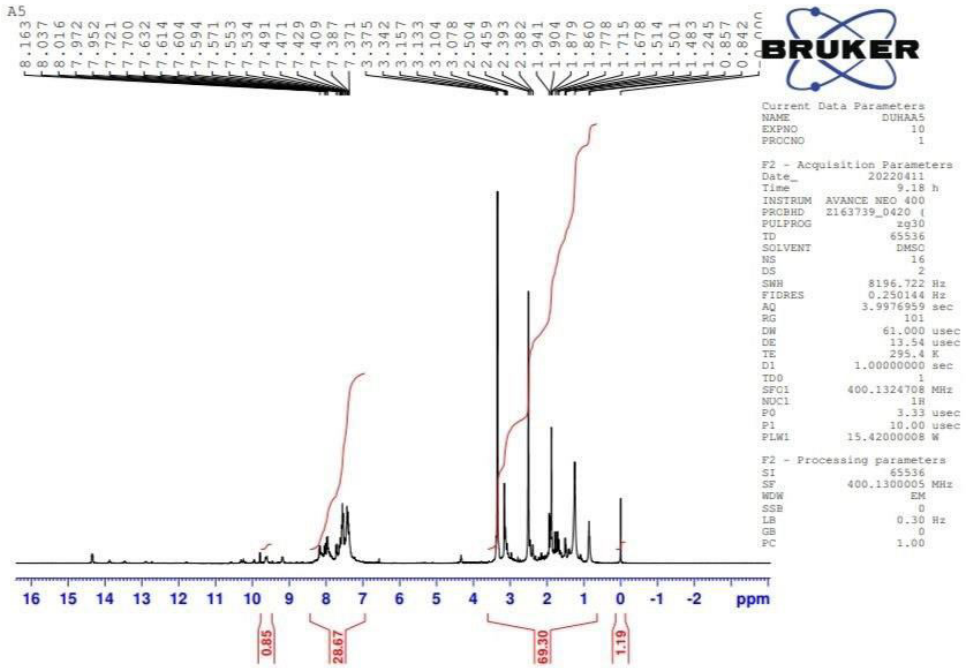


Figure (2-5): 1H NMR spectrum of compound 5

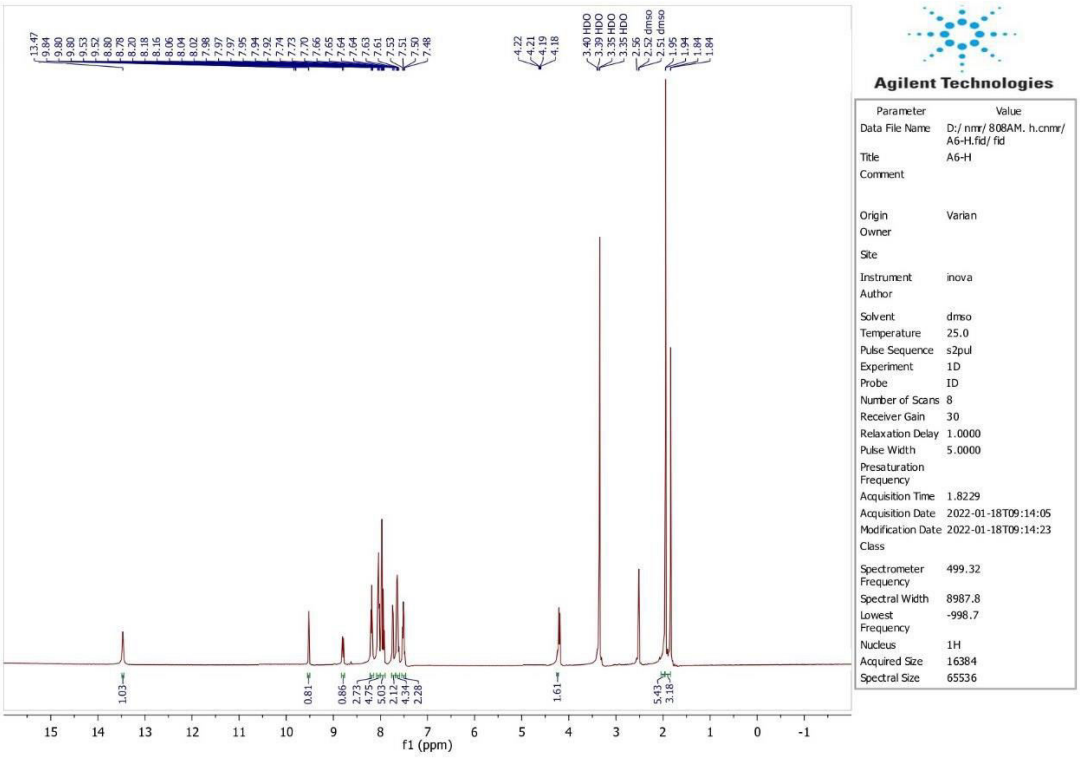


Figure (2-6): 1H NMR spectrum of compound 6

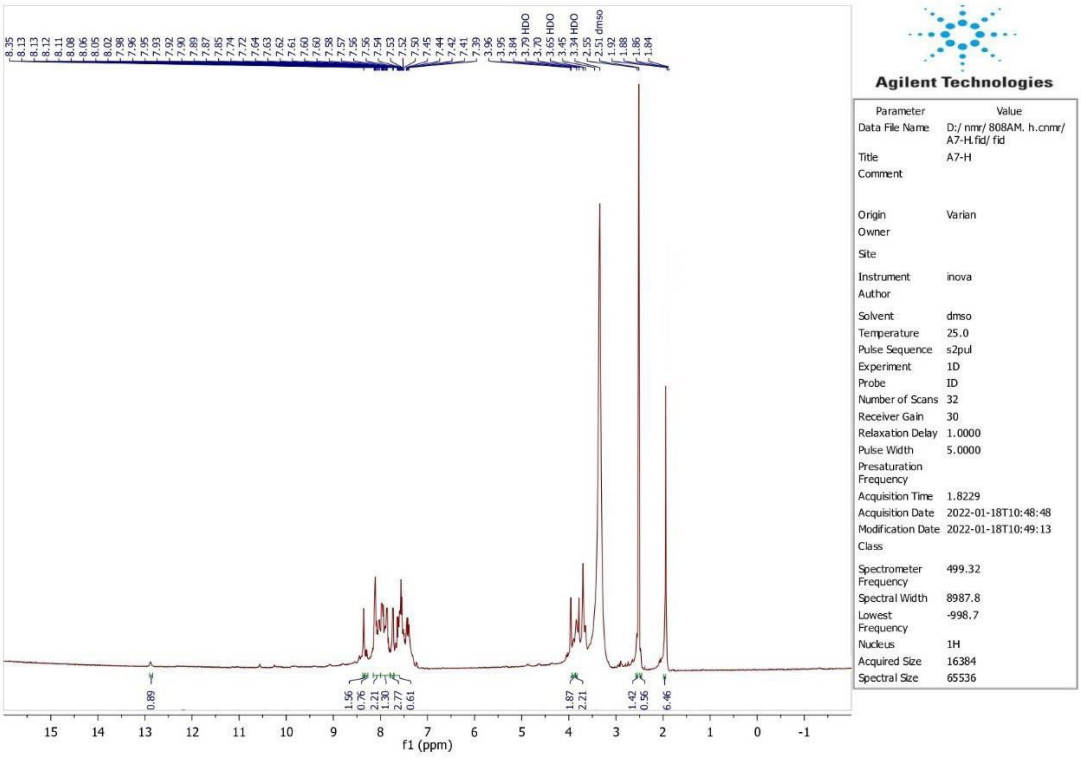


Figure (2-7): 1H NMR spectrum of compound 7

1- Biological results

The antibacterial activity of newly compounds 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 6. The results are reported in Table 3. According to the screening results, the compounds have no inhibitory action against both E. coli and S. aureus bacteria.

Table (3): Antibacterial activity of compounds (1-7).

MICROORGANISM TESTED MATERIALS	*E. COLI*				*S. AUREUS*			
	200 ppm	150 ppm	100 ppm	50 ppm	200 ppm	150 ppm	100 ppm	50 ppm
1	12	11	11	11	19	17	16	15
2	14	11	11	11	26	19	18	17
3	12	11	12	12	17	15	15	15
4	-	-	-	-	18	16	14	13
5	20	18	15	12	30	28	24	17
6	-	-	-	-	13	12	11	11
7	15	11	11	11	22	15	14	13

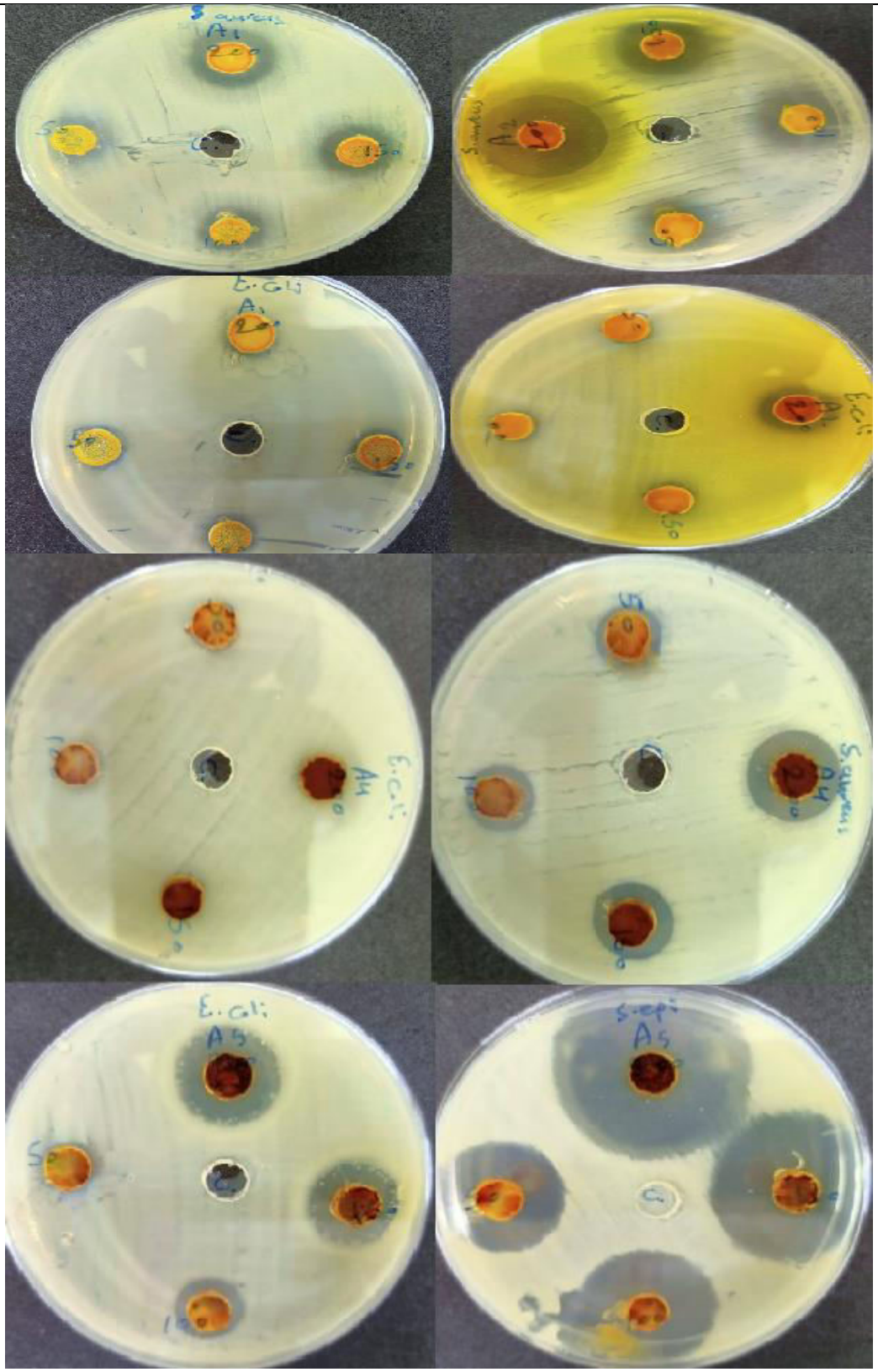


Figure (): Effects of the tested compounds (1,2,4,5) against S. aureus and E. coli.

IV. CONCLUSIONS

2-(1,1-dimethyl-1,3-dihydro-2H-benzo[e] indol-2-ylidene) malonaldehyde derivatives were synthesized in this study. These compounds were characterized utilizing diverse spectroscopic methods like FT-IR, ^{1}H-NMR, In addition to measurement some of their physical properties. Antibacterial activity of the produced compounds was evaluated, and

it was shown to be good to acceptable against two types of bacteria: gram negative (*E. coli*) and gram positive bacteria (*S. aureus)*.

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