Article

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Preparation, Characterization, and Antibacterial Evaluation of New Derivatives of Nicotinic and Mefenamic Acids

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ABSTRACT

A new series of heterocyclic derivatives of nicotinic and mefenamic acids was obtained by reacting the hydrazine of nicotinic and mefenamic acids with p-nitrophenyl isocyanate, O-mercaptobenzoic acid. The derivatives hydrazone was obtained by reacting a new azo compound containing a free acytal group with nicotinic and mefenamic acids hydrazide and the reaction was monitored by TLC technique. The chemical structures of the intermediate and the final compounds were characterized by measuring melting points, ^{13}C-NMR, ^{1}H-NMR, and FT-IR. Antibacterial studies of some of the compounds were performed. The impact of the biological activity of these compounds was examined against two bacteria types, (*Staphylococcus aureus*) and (*Acinetobacter baumannii*).

Keywords: , Hydrazide ,Schiff base, Azo, azetidin

Introduction:

Nonsteroidal anti-inflammatory drugs (NSAIDs) rank among the most widely utilized medications in both human and veterinary healthcare. Their widespread use stems from their ability to alleviate pain, reduce fever, and combat inflammation. Examples include nicotinic and mefenamic acids, which are recognized for their therapeutic efficacy in managing various conditions.

Mefenamic acid (MA), also known as Ponstan or chemically as 2-(2,3-dimethylphenyl)amino]benzoic acid. MA is structurally similar to the aromatic amino acid group[(1-3)]. MA, which is derived from anthranilic acid, hinders cell growth and triggers apoptotic cell death in certain human carcinoma cell lines. In addition to their usual pain-relieving and

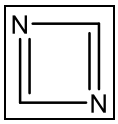
fever-reducing effects, research indicates that NSAIDs have the potential to be used as a therapeutic treatment for carcinoma cell lines and Alzheimer's disease

Nicotinic acid which named niacin or vitamin B3 shown Difference in lipoprotein levels and blood lipids levels made it must a more ability to increase the concentration of high-density lipo protein and to wide use of nicotinic acid and also importance in the pitch of study and development to prove its effectiveness. Ability to reduce the risk of heart attacks, atherosclerotic diseases, and high blood pressure diseases associated with kidney disease. Despite these benefits, unwanted side effects have limited their use, and possibly the most common bulging effect is skin rash[(4)]. The term "Schiff's base" derives from the German scientist Hugo Schiff, who first identified in 1864 the chemicals resulting from the interaction of primary amines with carbonyl compounds.

Per IUPAC standards, Schiff bases were categorized as imines compounds, including a hydrocarbonyl group on nitrogen atom, denoted as R2C = NR′ (where R′ ≠ H). They are considered by many to be synonymous with azomethines.
Azo dyes are distinguished by a nitrogen–nitrogen double bond (–N=N–), a structural feature that imparts valuable properties in textile applications. Incorporating heterocyclic compounds containing nitrogen, oxygen, or sulfur plays a crucial role in enhancing dye coloration, resulting in a diverse range of shades with varying intensities. In contemporary applications, azo dyes containing heterocyclic moieties demonstrate superior coloring characteristics, improved thermal stability, increased tinctorial strength, and more favorable solvatochromic behavior compared to those synthesized from simple aromatic amines. [(5)].

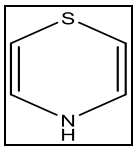
Nitrogen-containing heterocyclic compounds serve as a fundamental foundation for therapeutic drug discovery in medicinal chemistry. The ability of nitrogen to establish hydrogen bonds with biological targets enhances its significance in pharmaceutical applications. In drug design efforts, quaternary rings are gaining importance as essential bioactive frameworks. Their role extends beyond biological activity, enhancing physicochemical properties and facilitating structural exploration into previously uncharted areas of chemical space. [(6,7)]

Diazetidin: Diazetidin is a heterocyclic ring and includes its composition on two carbon atoms and two nitrogen atoms (Figure 1).



Fig(1): Structure of Diazetidine

Thiazines: Thiazines are characterized by a six-membered ring containing both nitrogen and sulfur atoms (Figure 2), a structural feature considered essential for their antifungal, anticonvulsant, and antiviral properties. The simplicity and versatility of the thiazine core, combined with its ease of synthesis, position thiazines, and their derivatives as valuable sources of biologically active compounds.



Fig(2): Structure of 1,4-thiazine

Chemistry

Materials and Methods:

The chemicals used in this study were of the highest available purity and were obtained from Fluka and Merck. Melting points were ascertained utilizing an electro-thermal 9300 melting point equipment (United Kingdom). TLC (Thin-layer chromatography) was performed using silica gel plates, with compound spots detected through exposure to iodine vapor. The infrared spectrum FTIR Shimadzu model (8400) was also measured using the range 600-4000 cm^{-1} as well as the ^{13}C-NMR and ^{1}H-NMR-spectra (ppm) until the prepared compounds using a nuclear magnetic resonance spectrometer Bruker –Ultra Shield 300 MHz Tehran university/Iran.

Synthesis of isonicotinohydrazide, ethyl 2-((2,3-dimethylphenyl)amino) benzohydrazide [I1,M1][8]

A solution containing 0.001 mol of nicotinic acid and mefenamic acid was prepared by dissolving the mixture in (30 mL) of absolute ethanol, followed by the addition of (1 mL) sulfuric acid. The mixture was refluxed for 6 hours at 75°C. A hydrazine hydrate (0.001 mol.) was added, and the sediments were recrystallized with ethanol.

I1: white powder , the yield was 76%, the melting point was 159-161℃, and the R_f value was 0.86 (Ethanol-Benzene 3:2)

M1: white crystals ,the yield 76% , the melting point of 244-246 °C and an Rf value of 0.92 (ethanol-benzene 3:2).

Synthesis of [Azo 2] [9] 2-((4-acetylphenyl)diazenyl)-2-(1H-benzo[d]imidazole-2-yl)acetonitrile

The compound (Azo2) "2-((4- acetylphenyl)diazenyl)-2-(1H-benzo[d]imidazol-2-yl)acetonitrile " was prepared by dissolving (0.001mol) of p-amino acetophenone in a mixture of 5 mL HCl and 10 mL distilled water. An ice bath of 0 to 5 °C was utilized for cooling the mixture, and then a solution of (0.001mol) sodium nitrite in 10 mL cooled distilled water was introduced dropwise. The solution was allowed to stand for 20 minutes until it stabilized to form the diazonium salt, followed by adding the diazonium salt to a solution of (0.001mol) 2-benzimidazolyl acetonitrile and 20 mL of sodium hydroxide solution 5% with the addition of 50 mL of ethanol absolute at a temperature of 0°C. The mixture is stirred for about 20 minutes, filtered, and left to dry.

Azo2: yellow solid , 55% yield , 288-290 °C melting point .

Synthesis of N'-(1-(3-(((1H-benzo[d]imidazol-2-yl)(cyano)methyl)diazenyl) phenyl)ethylidene)benzohydrazide, (S)-N'-(1-(3-(((1H-benzo[d]imidazol-2-yl)(cyano)methyl)diazenyl)phenyl)ethylidene)-2-((2,3-dimethyl phenyl)amino) benzohydrazid [I1S3, M1S3][10]

The Schiff base compounds (I1S3, M1S3) were synthesized by reacting (0.001 mol) of compound (I1 or M1) with (0.001 mol) of Azo2 in (25 mL) of ethanol. Three drops of glacial acetic acid were utilized to promote the reaction, and the liquid was refluxed for 17 and 12 hours, accordingly. The resulting precipitates were then purified through recrystallization using ethanol.

I1S3: yellow powder, yield %73, melting point 150-152℃, and R_f value 0.93 (Ethanol-Benzen3:2

M1S3: yield 83% ,Dark yellow , melting point of 169-171 °C , R_f value of 0.95 (ethanol-benzene 3:2).

Synthesis of N-(2-(4-(((1H-benzo[d]imidazol-2-yl)(cyano)methyl)diazenyl)phenyl) -2-methyl-3-(4-nitrophenyl)-4-thioxo-1,3-diazetidin-1-yl)isonicotinamide,N-(2-(4-(((1H-benzo[d]imidazol-2-yl)(cyano) methyl)diazenyl)phenyl)-2-methyl-3-(4-nitrophenyl)-4-thioxo-1,3-diazetidin-1-yl)-2-((2,3-dimethylphenyl)amino) benzamide (I1S3E,M1S3E)[11]

In a 100 mL round-bottom flask, 0.001 mol of Schiff base (I1S3, M1S3) was dissolved in 25 mL of anhydrous 1,4-dioxane. 0.001 mol of phenyl isocyanate was injected dropwise while preserving a 0–5°C temperature. The reacting solution was agitated at ambient temperature for three hours prior to refluxing for 24 and 28 hours. Following completion, the product was filtered and purified through recrystallization using ethanol.

I1S3E : Dark orange, yield 74%, melting point 218-220°C, R_f. value of 0.78 (ethanol-benzene 3:2).

M1S3E: yellow ,yield 77%, melting point 244-246 °C , R_f. value of 0.75(ethanol-benzene 3:2).

Synthesis of N-(2-(4-(((1H-benzo[d]imidazol-2-yl)(cyano)methyl)diazenyl) phenyl)-2-methyl-4-oxo-2H-benzo[e][1,3]thiazin- 3(4H)-yl)isonicotinamide , N-(2-(4-(((1H-benzo[d]imidazol-2-yl)(cyano)methyl)diazenyl)phenyl)-2-methyl-4- Synthesis of oxo-2H-benzo[e][1,3]thiazin-3(4H)-yl)-2-((2,3-dimethylphenyl) amino)benzamide (I1S3C,M1S3C)[12]

A derivative of Schiff base (I1S3-M1S3) (0.001mol) dissolved in 30 mL dry Benzene was combined with 2-mercapto benzoic acid (0.001mol) was dissolved in(3ml) of DMF. 5 drops of tri-ethyl amine were added after that which it was heated and reflux for a period of time (43-31) hours at a temperature of 50C. With interaction monitoring by TLC(ethanol: benzene)(2:3),then it was filtered, the filtrate was extracted, dried and recrystallized with absolute ethanol.

I1S3C: Brown , yield 64% ,melting point 225-227°C, R_f. value of 0.83 (ethanol-benzene 3:2).

M1S3C: Dark Brown , yield 55% ,melting point 244-246 °C, R_f. value of 0.82 (ethanol-benzene3:2).

Biological activity Anti-bacterial activity

Research on the biological activity of certain synthesized compounds was conducted at the Amin Center for Advanced Biotechnology and Research / Holy Shrine of Imam Ali. This investigation

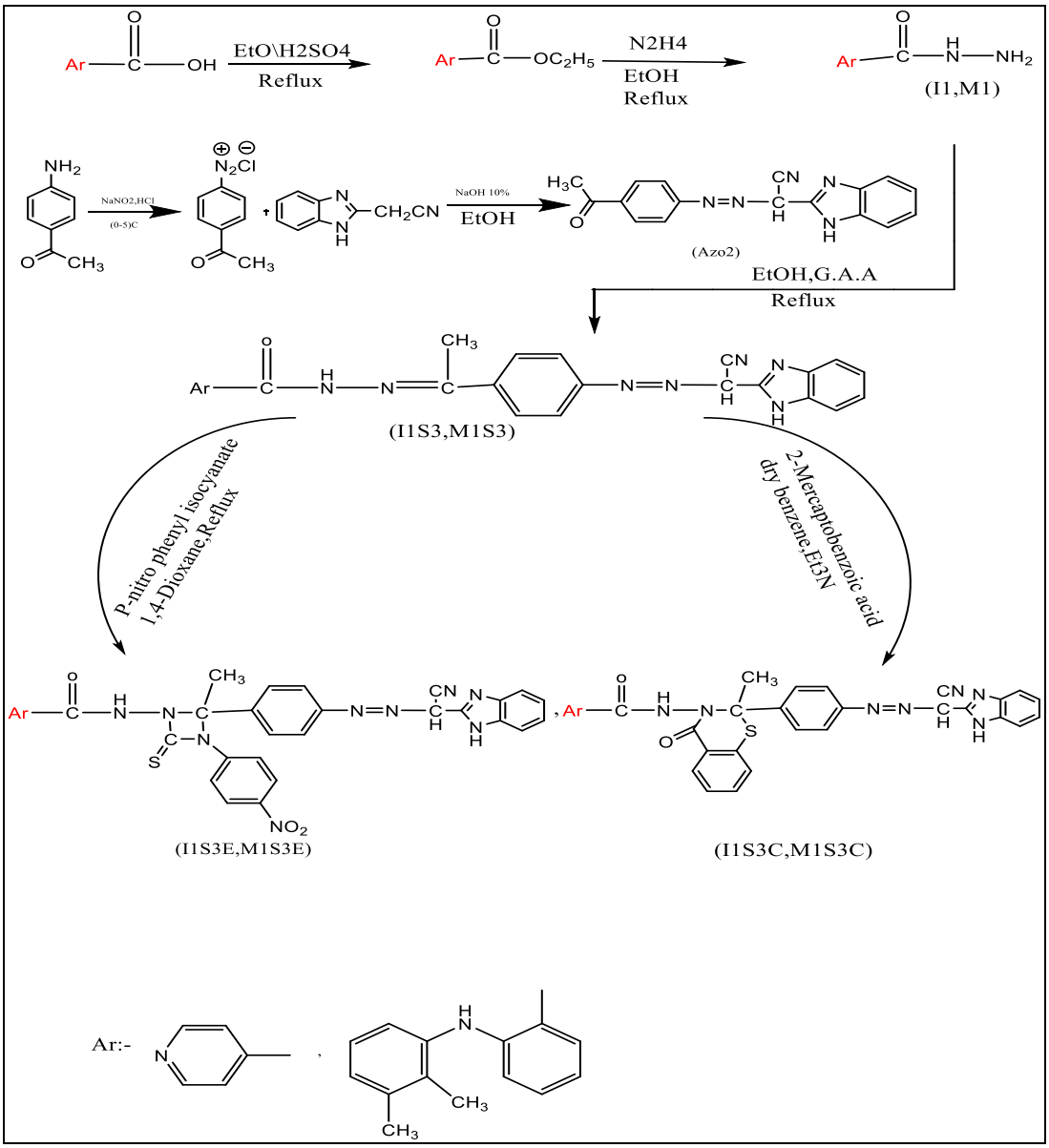
involved testing against two strains of pathogenic bacteria: the Gram-negative *Acinetobacter baumannii* and the Gram-positive *Staphylococcus aureus*.

Solutions of the synthesized compounds were prepared to assess their biological activity against two bacterial strains. Each compound was dissolved in 5 mL of dimethyl sulfoxide (DMSO) at concentrations of 0.125, 0.25, 0.5, and 1 µg/mL. The prepared bacterial cultures were evenly distributed across the surface of Mueller-Hinton Agar plates using a loopful technique to ensure uniform spreading.

Four wells, each measuring 9 mm in diameter, were formed in the agar plates with a cork borer disinfected with alcohol. Ample separation was maintained between the wells to avert the overlap of inhibitory zones. 0.1 mL of the prepared solutions was meticulously poured into each well using a micropipette. The plates were thereafter maintained at 37°C for 24 hours. Subsequent to incubation, the widths of the inhibitory zones produced by the compounds were quantified using a millimeter ruler.

Results and Discussion

The compounds I1- M1S3C were synthesized according to the chemical procedures outlined in Scheme 1. The current study included the use of a compound (mefenamic acid, nicotinic acid) as a starting material to prepare derivatives of the azetidin ring and thiazin, Where the prepared compounds were identified by a number of spectra: FTIR(cm^{-1}),^{1}HNMR(δ ppm) and ^{13}CNMR(δ ppm). The biological activity of all the prepared compounds was also evaluated. This research involved the examination of two strains of pathogenic bacteria. These pathogenic bacteria were isolated and identified in the laboratory through microscopic and biochemical analyses. The study focused on two distinct bacterial types: the Gram-positive Staphylococcus aureus and the Gram-negative Acinetobacter baumannii.



Scheme 1. Synthesis of ring azetidin and thiazin (I1S3E,M1S3E,I1S3C,M1S3C)

TABLE 1.Physical properties of the prepared compounds.

Comp.	M.F	Colour	m.p℃	Yield%
I1	$C_6H_7N_3O_1$	White powder	159-161	76
M1	$C_{15}H_{17}N_3O_1$	White crystal	244-246	76
Azo2	$C_{17}H_{13}N_5O_1$	Yellow soild	288-290	55
I1S3	$C_{23}H_{18}N_8O_1$	Yellow soild	150-152	73
M1S3	$C_{32}H_{28}N_8O_1$	Dark yellow	169-171	83
I1S3E	$C_{29}H_{22}N_9O_3S_1$	Dark orange	218-220	74
M1S3E	$C_{39}H_{32}N_9O_3S_1$	Yellow	244-246	77
I1S3C	C30H22N8O2S1	Brown	225-227	64
M1S3C	C39H32N8O2S1	Dark brown	244-246	55

Interpretation of Synthesis Results

I1,M1 was synthesized by heating nicotinic acid,mefenamic acid with absolute ethanol, presenting concentrated sulfuric acid to produce an ester derivative, and after that converting it to a hydrazide derivative by reaction with hydrazine hydrate. FT-IR analysis[13] showed that the stretching as well as the 3115,3309 cm^{-1}, 3302-3448 cm^{-1}, and 1649 cm^{-1} that many attributed to NH, NH_2, and C=O, respectively, as shown in Fig. 3and 4. The ^{1}H-NMR spectrum for compound M1 showed singlet for NH_2 protons of hydrazide at δ5.28 ppm and singlet for NH proton of hydrazide at δ 9.88 ppm. ^{13}C-NMR showed the ethyl ester peaks' disappearance while revealing the amide's carbonyl at δ 169.06 ppm. Figs. 5 and 6 show the ^{1}H-NMR and ^{13}C-NMR spectra of M1.

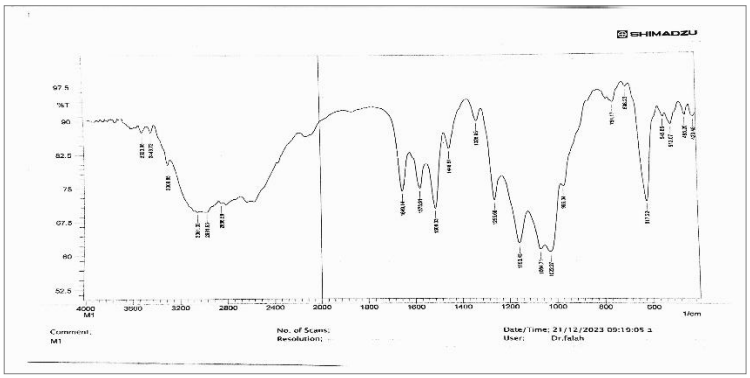


FIG. 3. FTIR of compound M1.

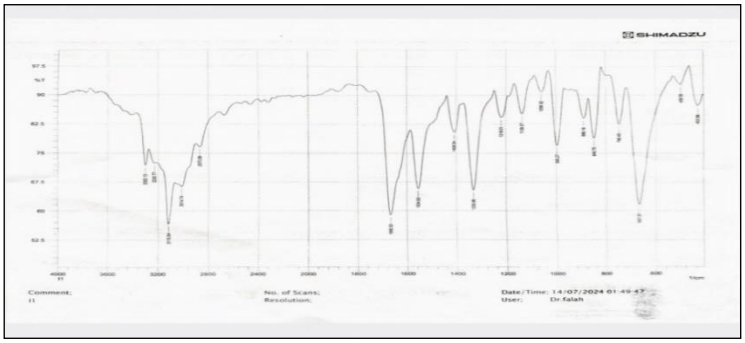


FIG.4. FTIR of compound I1.

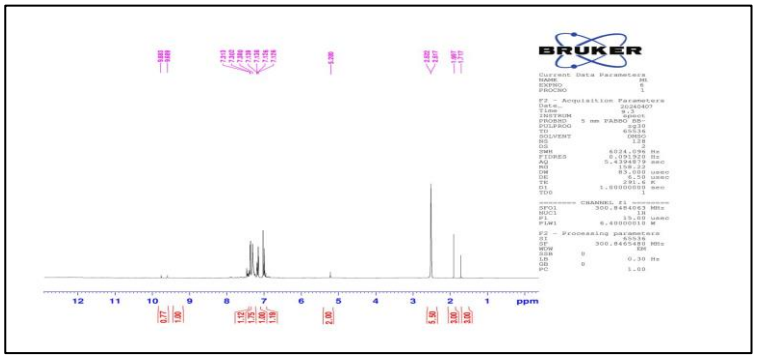


FIG. 5: ^{1}HNMR Spectra of M1.

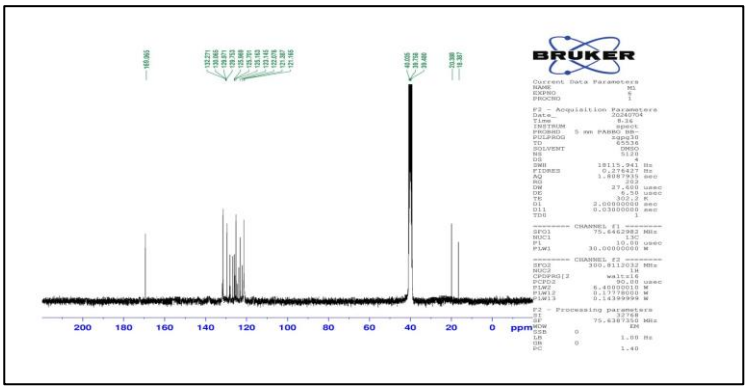


FIG.6. ^{13}C-NMR Spectra of M1.

Azo2 compound was prepared through a coupling reaction between diazonium salt and 2-benzimidazolyl acetonitrile. The disappearance of the primary amine group band in the FT-IR spectrum of compound (I1,M1)coupled with the appearance of new bands at 1490 cm^{-1} for N=N, 1662 cm^{-1} for C=O (ketone) in the FT-IR spectrum of Azo2, confirmed its formation. Figs. 7 show the FTIR spectra of Azo2.

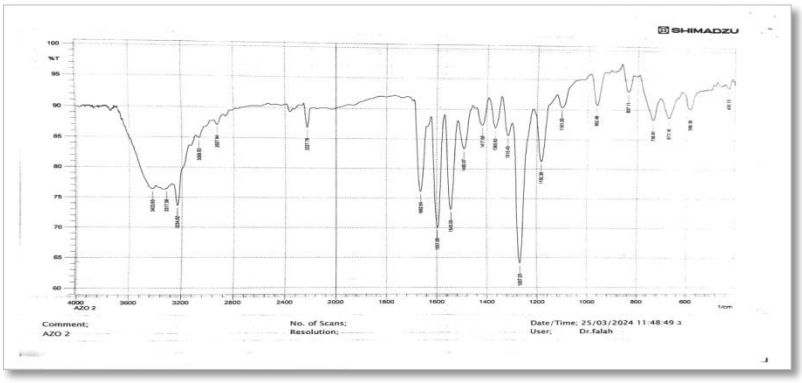


FIG.7. FTIR Spectra of Azo2.

Compound (I1S3,M1S3) was prepared by condensation reaction between compound (I1,M1) and compound Azo2. The disappearing bands of the primary amine group of compound I1,M1 in the FTIR spectrum(14) for compound I1S3,M1S3 indicated a characteristic broad absorption band at 3257, and 3415cm^{-1} due to NH stretching of amide. They showed the disappearance of the absorption band for the NH_2 group, 1670,1678 cm^{-1} due to -C=O amide, and 1595,1600 cm^{-1} due to the C=N imine group in the compound I1S3,M1S3 respectively as shown in Fig. 8 and 9. The ^{1}H-NMR spectrum for compound M1S3 showed the disappearance of the broad singlet for NH_2 protons of hydrazid at δ 5.28 ppm. ^{13}C-NMR displayed the peak of -C=N imine at δ 157.77,157.97 ppm for I1S3,M1S3 . respectively Figs. 10 and 11 displayed the ^{13}C-NMR and ^{1}H-NMR spectra of I1S3,M1S3 fig 12 and 13.

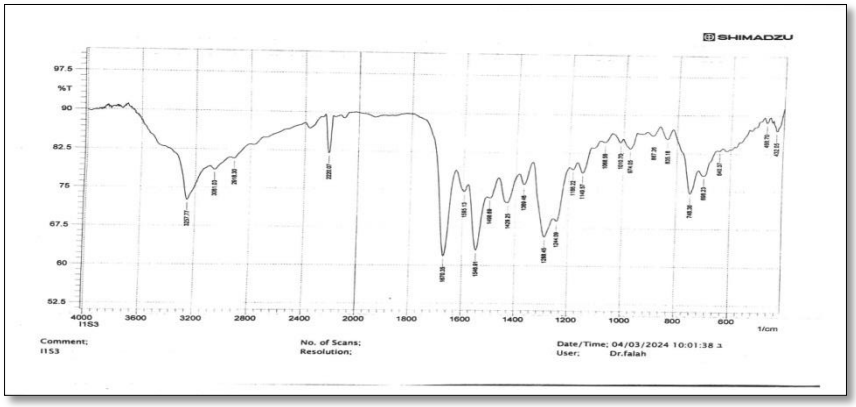


FIG. 8: FTIR Spectra of I1S3.

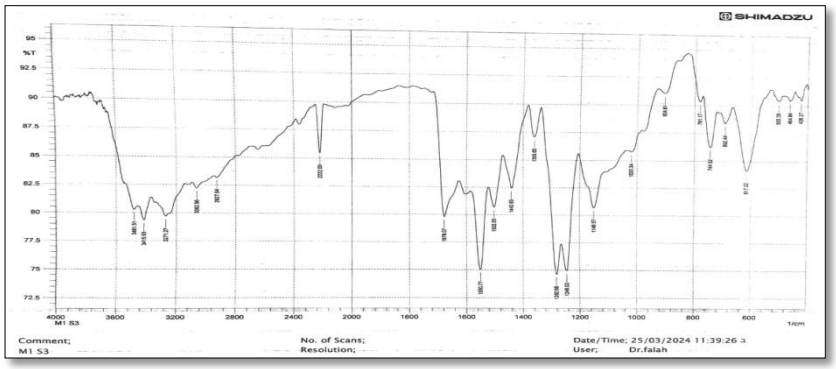


FIG. 9. FTIR Spectra of M1S3.

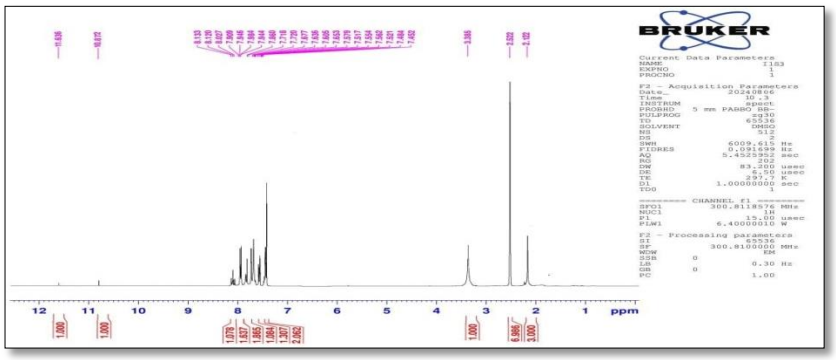


FIG.10. HNMR Spectrum of Comp.I1S3

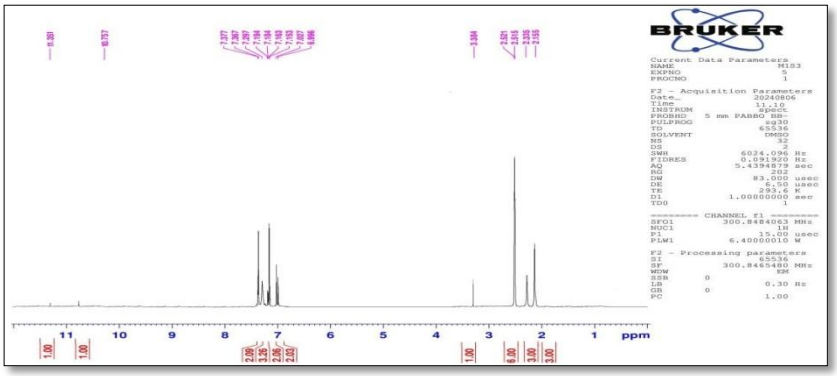


FIG. 11. HNMR Spectrum of Comp.M1S3.

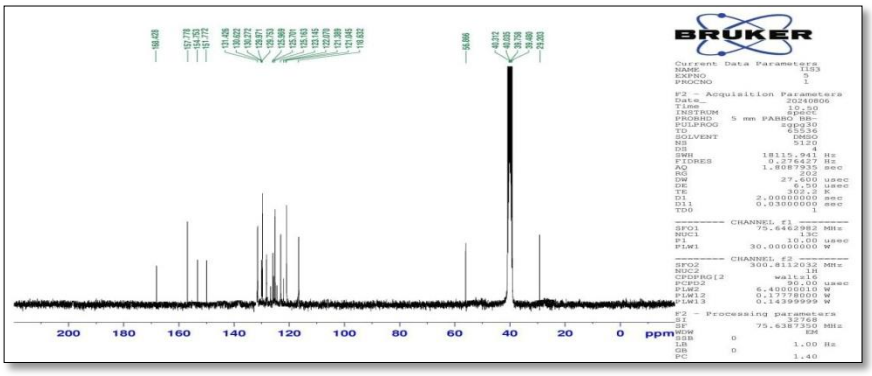


FIG.12: ^{13}C-NMR Spectrum for I1S3

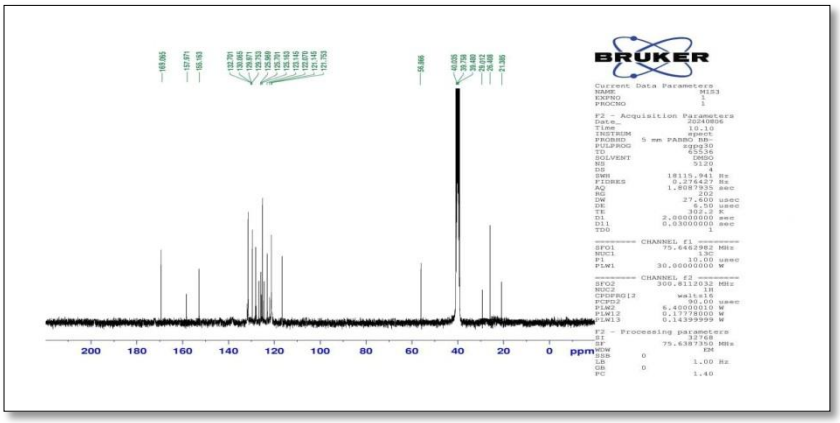


FIG.13. ^{13}CNMR Spectra for M1S3.

Compound (I1S3E, M1S3E) were prepared by cyclization reaction of compound (I1S3,M1S3) with P-Nitro phenyl isocyanate. The disappearance of imine (-C=N-) group of compound (I1S3,M1S3) in the FT-IR spectrum [(15)] for compound(I1S3E, M1S3EE) were observed. The imine group band at 1595,1600 cm^{-1} disappeared, while new peaks appeared at 1656, 1651 cm^{-1} for -C=O amide, 1257,1251 cm^{-1} for C=S , Fig 14and 15. The ^{1}H-NMR spectrum analysis revealed the absence of the distinctive singlet peak associated with imine protons. Additionally, a singlet peak appeared at (2.31 ppm), corresponding to the CH_3 proton in the quaternary rings. ^{13}C-NMR showed the peak (-C-N) of the Quadruple rings at 78.58 while appearing to peak at 173.42 C=S for azetidin. Figs. 16 and 17 show the ^{1}H-NMR and ^{13}C-NMR spectra.

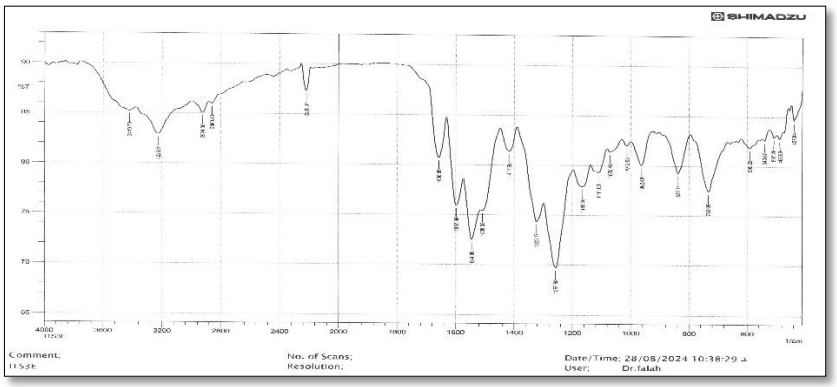


FIG. 14. FTIR Spectra of M1S3

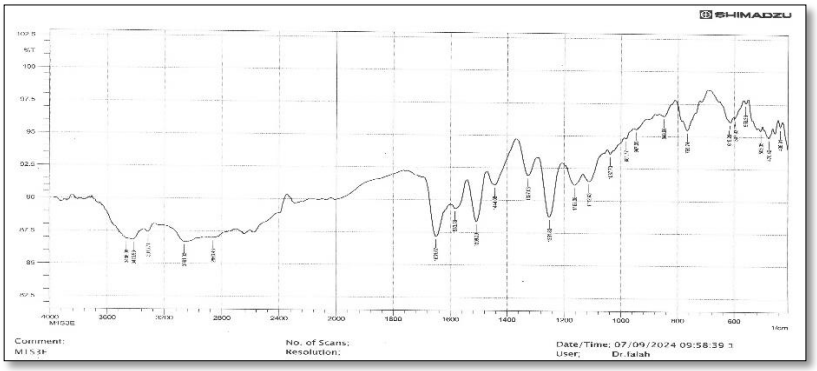


FIG. 15. FTIR Spectra of M1S3E.

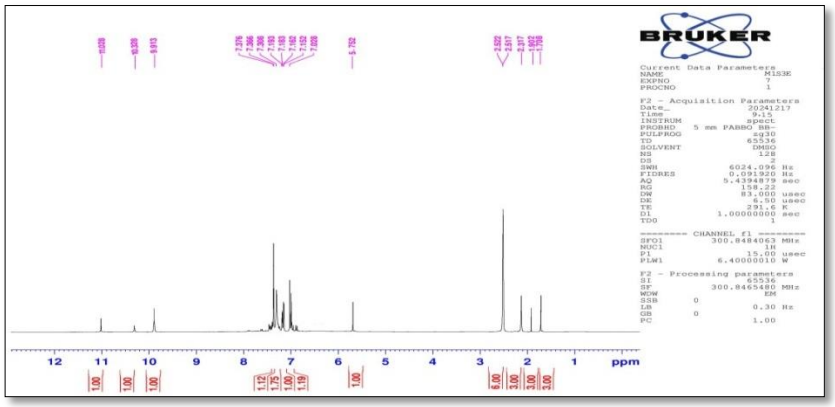


FIG.16. HNMR Spectrum of Comp.M1S3E

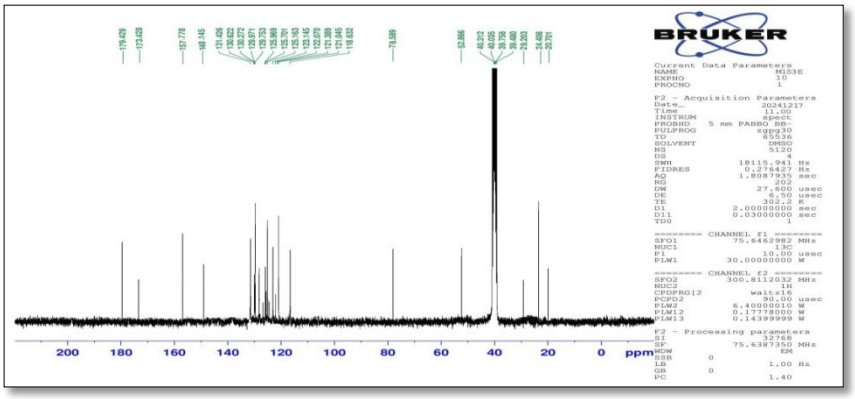


FIG. 17. ^{13}C-.NMR Spectrum of Comp.M1S3E

Compound (I1S3C,M1S3C) were prepared by cyclization reaction of compound (I1S3,M1S3) with 2-mercaptobenzoic acid . The disappearance of imine (-C=N-) group of compound (I1S3,M1S3) in the FT-IR spectrum[16-19] for compound(I1S3C, M1S3C) were observed. The imine group band at 1595,1600 cm^{-1} disappeared, while new peaks appeared at 1666 cm^{-1} for -C=O, ,Fig 18and 19. The ^{1}H-NMR spectrum of I1S3C demonstrated the disappearance of the characteristic singlet peak corresponding to imine protons. Meanwhile, a singlet peak emerged at (1.81 ppm), representing the CH_3 proton in the hexagonal ring (Fig. 20). ^{13}C-NMR showed the peak (-C-N) of the hexagonal rings at 56.86 while appearing to peak at 170.06 C=O for thiazine . Figs. 21,^{13}C-NMR spectra of I1S3C.

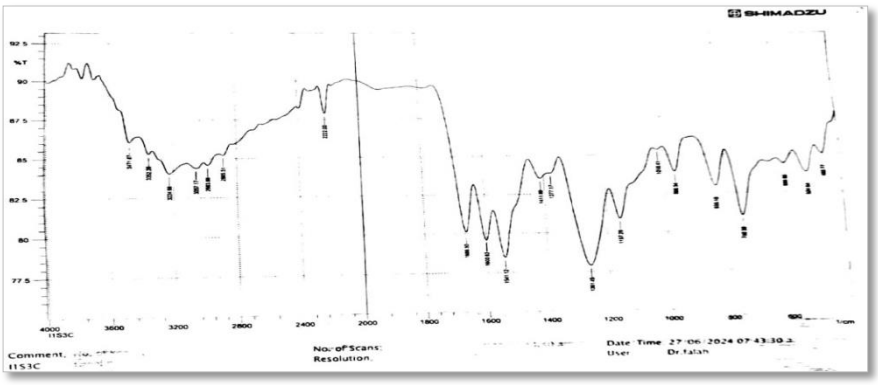


FIG. 18. FTIR Spectra of I1S3C.

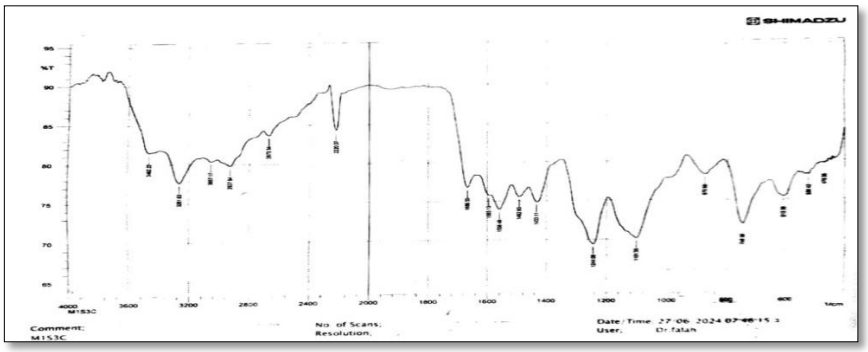


FIG. 19. FTIR Spectra of M1S3C

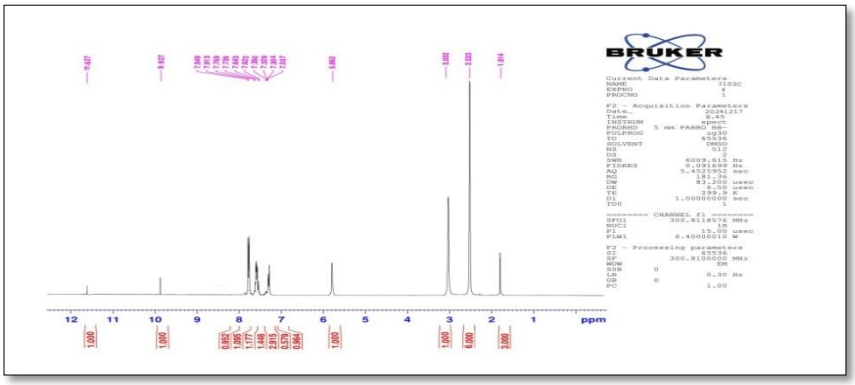


FIG. 20. HNMR Spectrum of Comp.I1S3C.

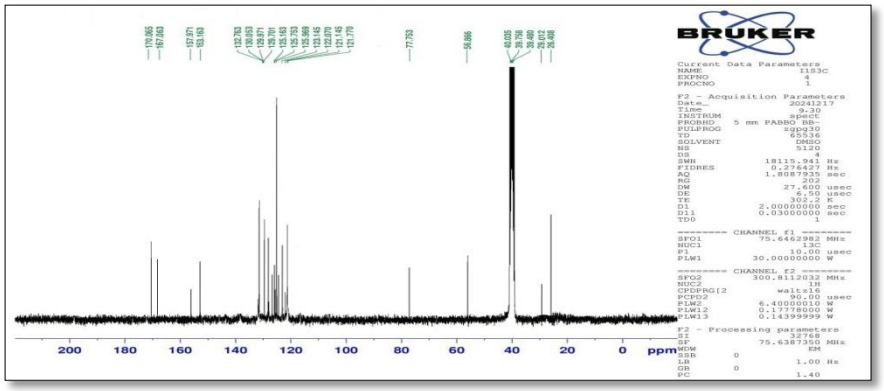


FIG. 21. ^{13}CNMR Spectrum of Comp.I1S3C

Study of Biological Activity Against Bacteria

The biological activity [20]of some organic compounds(I1S3E,I1S3C,M1S3C) was studied to determine their antibacterial activity for two types of pathogenic bacteria after they were isolated and diagnosed from pathological cases and their properties were proven .The first type is Gram-positive bacteria *(Staphylococcus aureus*) ,while the seconed type is gram-negative bacteria (*Acinetobacter baumannii*) .it gave a high percentage of inhibition when concentration of 1µg/Ml .Likewise,the organic compounds(I1S3E,I1S3C,M1S3C) as in Table2.

TABLE 2.Biological activity against Bacteria millimeter of prepared compounds

Mate	Con. µg/Ml	*Acinetobacter baumannii*	*Staphylococcus aureus*
Control		0	0
I1S3E	1	25	20
	0.5	20	14
	0.25	15	0
	0.125	12	0
I1S3C	1	25	23
	0.5	19	18
	0.25	13	12
	0.125	11	0
M1S3C	1	19	24
	0.5	14	18
	0.25	0	14
	0.125	0	11

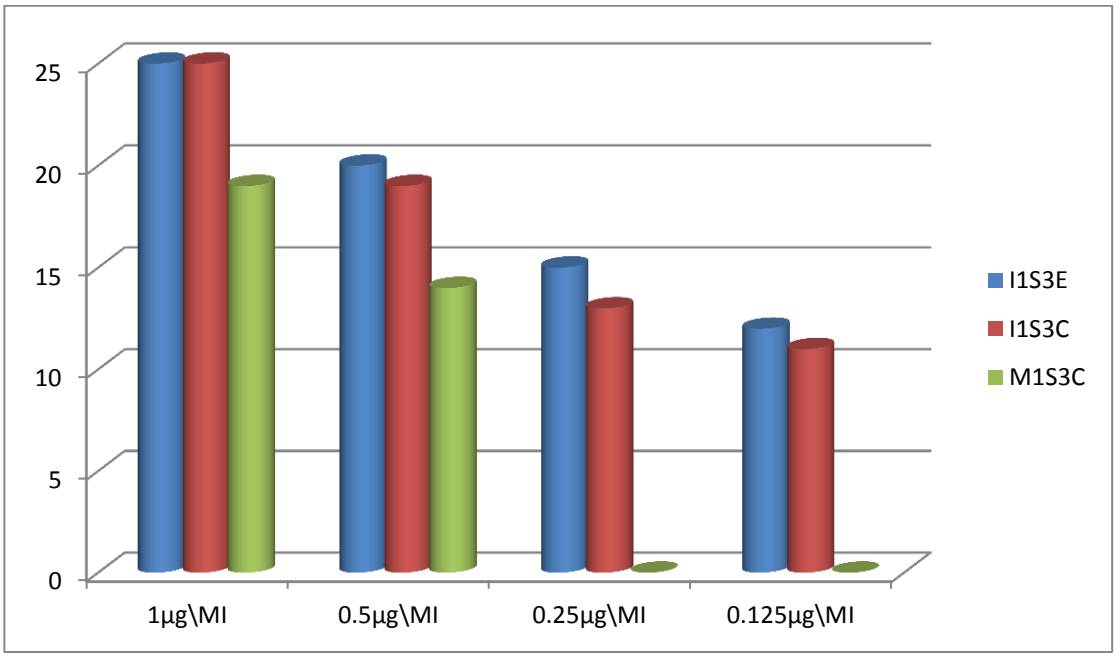


FIG. 22 Antibacterial evaluation of some synthetic compounds against *Acinetobacter baumannii*

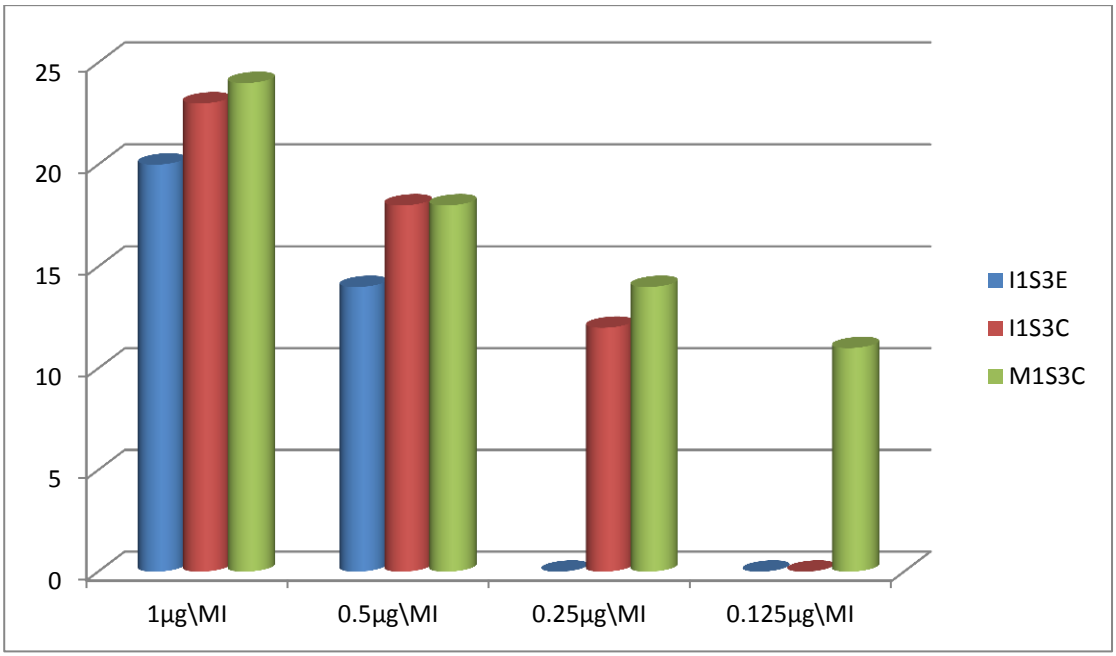


FIG. 23 Antibacterial evaluation of some synthetic compounds against *Staphylococcus aureus*

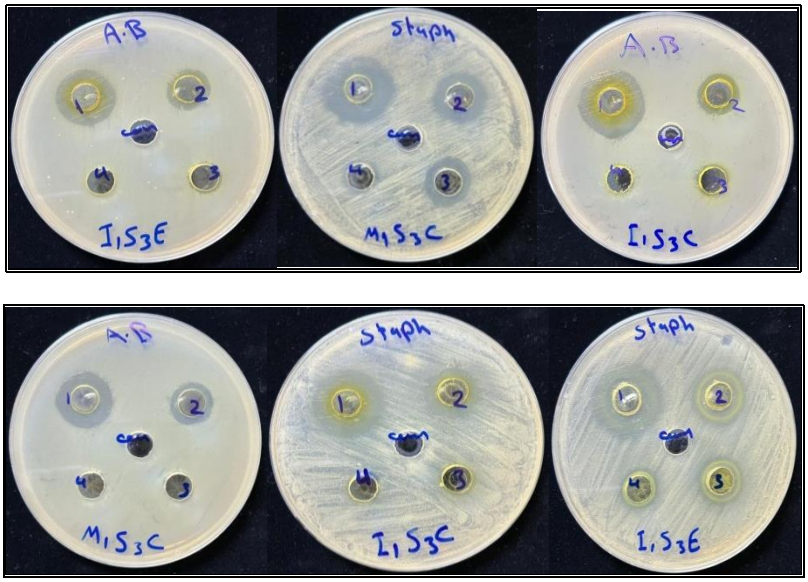


FIG.24: Show the inhibition of the prepared compounds (I1S3E,I1S3C,M1S3C) of the bacteria *Staphylococcus aureus* and bacteria *Acinetobacter baumannii*

Conclusions

In this study, several new heterocyclic derivatives were prepared from the reaction of mefenamic and nicotinic acids with p-nitrophenyl isocyanate , O-mercaptobenzoic acid. These derivatives were found to be stable at room temperature, the others exhibited high melting points. All these derivatives were confirmed

through spectroscopic analysis. Additionally, biological evaluation of the antibacteria *Staphylococcus aureus* and bacteria *Acinetobacter baumannii* a properties was investigated

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