مجلة الدراسات التربوية والعلمية - كلية التربية - الجامعة العراقية
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doi.org/10.52866/esj.2023.03.22.08

Preparation and Characterization of Some New Compounds Derived from 2-amino-4,6 dimethoxy pyrimidine and Some Drugs, Evaluation of biological activity and its molecular docking

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Abstract:

In this research included the synthesis of Schiff base [NG1-NG3] through the reaction of the substituted aromatic amine with aldehyde or keton group, synthesis of azo dye [NG4-NG5] by the reaction of dapsone's diazonium salt with amines at (0-5) 0C, ,and characterization of the synthesized compounds by using spectroscopic techniques FT-IR, 1H-NMR using DMSO-d6 as a solvent, SEM, in addition, melting point. This work also included a studyBiological activity Biological activity and study of Molecular docking of the prepared compounds with proteins has also been studied using the Auto Dock v4.2 program in an attempt to find out the inhibitory potential of the compounds and the places of these compounds with the active site of the protein and compare them with the practical results obtained .

Keywords: *Azo Dyes, 2-amino-4,6 dimethoxy pyrimidine , Staphylococcus Aureus, Klebsiella Pneumonia, .*

تحضير وتشخيص بعض المركبات الجديدة المشتقة من -2 امينو4,6- ثنائي ميثوكسي بيريميدين وبعض الادوية وتقييم الفعالية البيايولوجية والارساء الجزيئي لها

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مستخلص

تضمن هذا البحث تخليق قاعدة شيف [NG1-NG3] من خلال تفاعل الأمين العطري البديل مع مجموعة الألدهيد أو كيتون ، وتكوين صبغة الآزو [NG4-NG5] عن طريق تفاعل ملح الديازونيوم مع الأمينات عند (0-5)°C، وتوصيف المركبات المركبة باستخدام تقنيات التحليل الطيفي FT-IR ، 1H-NMR باستخدام DM-SO-d6 كمذيب ، SEM ، بالإضافة إلى نقطة الانصهار. تضمن هذا العمل أيضًا دراسة النشاط البيولوجي ودراسة النشاط البيولوجي ودراسة الالتحام الجزيئي للمركبات المحضرة بالبروتينات كما تمت دراسة باستخدام برنامج Auto Dock v4.2 في محاولة لمعرفة الإمكانات المثبطة للمركبات وأماكن وجود هذه المركبات مع الموقع النشط للبروتين ومقارنتها بالنتائج العملية التي تم الحصول عليها .

الكلمات المفتاحية: اصباغ الازو، 2- امينو 4-6 ثنائي ميثوكسي بيريميدين ، المكورات العنقودية الذهبية ، الكليبسيلا الرئوية .

1. Introduction:

Azo compounds are a family of chemical compounds that is getting a lot of interest in scientific circles. They are brightly colored and have long been used as dyes and paints [1]. Furthermore, their excellent thermal and optical properties have been extensively studied in applications such as visual recording medium, toner, and ink-jet printing [2]. As a result, much research on the synthesis and spectrum characteristics of various azo has been published. In addition, the azo compounds have been described as an antidiabetic anti-neoplastic antibacterial [3], and anticancer agent [4]. Add to it that azo compounds are known to impede DNA, RNA, carcinogenesis, and protein production [5]. The industrially prepared azo dyes are of the largest varieties, as they can bind to the substance to be dyed and give it distinctive colors [6]. Some of the azo dyes are unaffected by light, oxygen, washing, or acids and bases [7]. Azo dyes are named because they contain the azo group [8]. The azo group consists of two nitrogen atoms linked by a double bond (-N=N-). It has SP^2 hybridization, bonded with aromatic or aliphatic carbon atoms [9]. Azo dyes may contain one azo group called mono azo dyes, or they may be dichotomous may have more than two azo groups called triple azo dyes [10]. According to the IUPAC system, goose dyes are defined as diamide derivatives HN=NH [11], containing two aryl groups and being the most stable, while the -N=N- group is called the Azo group [12]. There is also another classification based on the method of applying these dyes on an industrial scale. The dyes are grouped as dispersed, acidic, basic, or reactive [13]. The main factors that show colors are the presence of unsaturated groups in the molecule, and just as the axochromic groups are essential in increasing the intensity of the color, they give the dye molecule acidic or essential qualities as it expands its ability to contact the substance to be dyed [14]. The azomethine group (-HC=N-) is present in Schiff bases. Hugo Schiff originally described them in 1864 as condensation products of ketones or aldehydes with primary amines. Schiff base formation is usually catalyzed by acids, bases, or heat [15].Schiff bases are employed as intermediates in amino acid synthesis or ligands to create metal complexes with various structures [16, 17]. Aromatic aldehydes, particularly those with

a sound conjugation system, produce persistent Schiff bases, while aliphatic aldehydes are unstable and polymerize quickly [18]. Schiff base ligands with hydrazone moiety have gotten a lot of interest recently because of their ease of synthesis, which leads to varied various structures and beneficial functions, particularly biological ones [19].

2. Experimental:

2.1. Chemicals used: All chemicals used in this work were purchased from BDH, Aldrich

and Fluka companies and were used without further purification.

2.2. Devices used: The melting points were measured using Electrothermal Melting Apparatus 9300. The FT-IR spectra were captured using a Shimadzu FT-IR 8400S spectrophotometer with a (4000-400) cm^{-1} by KBr disc. DMSO-d_6 as solvents were used to capture ^{1}H-NMR and ^{13}C-NMR spectra on Bruker instruments running at (400) MHZ.

2.3. Preparation of Schiff bases

2.3.1.1 Preparation of the compound (NG1) [20]

(0.01 mol; 0.26 g) of 2-amino-6,4-dimethoxypyrimidine dissolved in 10 ml of ethanol was added to (0.01 mol; 0.3 g) of aldehyde to a round flask with a capacity of (100) ml, and (8) drops of icy acetic acid were added to it. The mixture was escalated at (110) ^{o}C for (4) hours, then the mixture was cooled in ice for (30 minutes) and the precipitate was filtered, then recrystallized using ethanol.

2.3.1.2 Preparation of the compound (NG2) [20]

(0.01 mol; 1.00 g) of 2-amino-6,4-dimethoxypyrimidine dissolved in 20 ml of methanol was added to (0.01 mol; 1.18 g) of aldehyde to a round flask with a capacity of (250) ml, and (15) drops of icy acetic acid were added to it. The mixture was escalated at (130) ^{o}C for (4) hours, then the mixture was cooled in ice for (30 minutes) and the precipitate was filtered, then recrystallized using ethanol.

2.3.1.3 Preparation of the compound (NG3)[20]

(0.01 mol; 0.29 g) of acetophenone was dissolved in 5 ml of methanol and 8 drops of icy acetic acid were added to it, and (0.01 mol; 0.3 g) of 2-amino-6,4-dimethoxypyrimidine dissolved in 8 ml of methanol was added to a round flask with a capacity of (100) ml. 30 minutes) and filtered and recrystallized using ethanol.

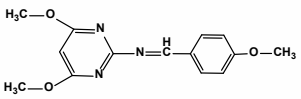
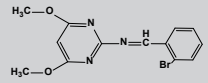
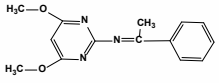
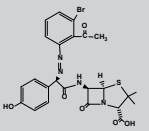
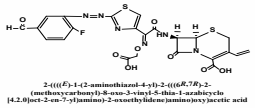
2.3.2. Preparation of the compound azo dye (NG4) [21,22]:

In a round flask (100 mL) (0.01 mol; 0.62 g) sodium nitrite was dissolved in (25 mL) distilled water in an ice bath (0-5) 0°C. To (0.01 mol; 0.36 g) of hydrochloric acid, and in a flask of (100 ml) capacity, (0.01 mol; 1.82 g) of one of the amoxicillins was dissolved in (25 ml) of distilled water, then (0.01 mol; 0.75 g) 4-bromobenzaldehyde was added from the separation funnel, the contents of the baker were filtered on sodium nitrite drop by drop while maintaining the temperature. As the distillation continues, we notice the color of the solution changing from transparent to maroon. After the distillation was completed, the stirring was continued for a full hour without heating. The mixture is raised for (3) hours, then filtered and dried. The rest of the chemical compound [NG5] was prepared in the same way.

Table (1) shows some physical properties of compounds.

Comp. No.	Molecular Formula	Color	M.P ^{O}C	Yield %
NG1	$C_{14}H_{15}N_3O_3$	Pink	267-269	66
NG2	$C_{13}H_{12}BrN_3O_2$	White	272-274	67
NG3	$C_{14}H_{15}N_3O_2$	Orange	83-85	62
NG4	$C_{24}H_{23}BrN_4O_6S$	Yellow	145-147	89
NG5	$C_{23}H_{17}FN_6O_8S_2$	Dark Red	260-262	91

Table (2): Shows the prepared compounds

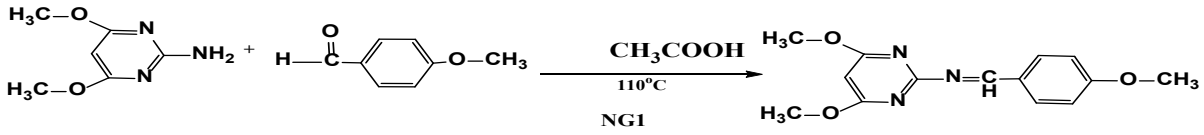
Comp. NO.	Structure & Name
NG1	 *N*-(4,6-dimethoxypyrimidin-2-yl)-1-(4-methoxyphenyl)methanimine
NG2	 1-(2-bromophenyl)-*N*-(4,6-dimethoxypyrimidin-2-yl)methanimine
NG3	 *N*-(4,6-dimethoxypyrimidin-2-yl)-1-phenylethan-1-imine
NG4	 (2*S*,5*R*,6*R*)-6-((*R*)-2-(2-acetyl-3-bromophenyl)diazenyl)-2-(4-hydroxyphenyl)acetamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid
NG5	 2-(((*E*)-1-(2-aminothiazol-4-yl)-2-(((6*R*,7*R*)-2-(methoxycarbonyl)-8-oxo-3-vinyl-5-thia-1-azabicyclo [4.2.0]oct-2-en-7-yl)amino)-2-oxoethylidene)amino)oxy)acetic acid

2.4. Study of biological activity [23, 24]:

This Study was used on two types of pathogenic bacteria, which are gram-positive, and are gram-negative, and they are: *Staphylococcus aureus* and, *Klebsiella pneumonia*, essential in the medical field because of their resistance to antibiotics. These bacteria were taken from the laboratories of the College of Education for Pure Sciences, Department of Bio-Sciences, and a Mueller-Hinton-Agar culture medium was used. Molar Huntin Agar) is used to measure the biological activity of antibiotics and chemicals for medical uses and is used to measure and determine the minimum inhibitor (MIC). Aqueous solutions of the two compounds [DM66, DM70] were also prepared. At concentrations of (0.01, 0.001, 0.0001 mg/mL) and using a solvent dimethyl sulfoxide (DMSO), a sensitivity test was performed for the bacterial isolates that were used in Study by diffusion method in the nutrient medium of Mueller-Hinton agar, which is a transparent nutrient medium with a dark yellow color. D in the sensitivity test of microorganisms towards antibiotics because it contains an animal infusion extracted from casein and starch.

3. Results and Discussion:

The Schiff basae were prepared from the reaction of one mole of 2-amino-6,4-dimethoxypyrimidine with one mole of 4-methoxybenzaldehyde.



3.1. Spectroscopic interpretation (FT-IR .,^{1}H-NMR, ^{13}C-NMR, Mass)

When studying the infrared spectrum (FT-IR) of Schiff bases [NG1], in Figure (1) it was observed that the expansion band of the amine group (NH2) and the carbonyl group (C = O) disappeared in the prepared compounds, with the appearance of several bands within the range (1602 cm^{-1}) belonging to the expansion group (C = N), with the appearance of two bands in the range (1510-1453 cm^{-1}) is due to dilatation of the aromatic bond (C=C), and the beam is within the field (1411-1371 cm^{-1}) belonging to the frequency of the alkyl (C.H.) group. As for the (C-N) group, curvature beams appeared in

the areas (1303-1246 cm^{-1}) and group curvature beams. (C-O) appeared in areas (1186-1122) cm^{-1}, and as shown in table (2), these bundles were close to what is found in the literature [25].

The infrared spectrum of the prepared [NG2] Schiff bases showed in Figure (2) that it was observed that the expansion band of the amine group (NH2) and the carbonyl group (C = O) disappeared in the prepared compounds, the appearance of band within the range (1583 cm^{-1}) and the elongation of the azomethin group (C = N), when the band appeared (3060 cm^{-1}) and (11523-1456cm^{-1})in the range denotes the (=C-H) ,(C=C) stretching aromatic groups, respectively, as well as an expansion band in the range (2985–2947 cm-1) belonging to the (CH) aliphatic bond stretching[26].

The infrared spectrum of the prepared [NG3] Schiff bases showed in Figure (3) that it was observed that the expansion band of the amine group (NH2) and the carbonyl group (C = O) disappeared in the prepared compounds, the appearance of band within the range (1585 cm^{-1}) and the elongation of the azomethin group (C = N), when the band appeared (3022 cm^{-1}) and (1452cm^{-1})in the range denotes the (=C-H) ,(C=C) stretching aromatic groups, respectively, as well as an expansion band in the range (2995–2910 cm-1) belonging to the (CH) aliphatic bond stretching[26].

The IR spectrum of the compound [NG4] shown in figure (4), the disappearance of the stretching band of the amine group (NH2), as well as the appearance of the (NH) imide stretching band that appears in the range (3335-3313) cm-1, and the beam is within the range of (1664cm-1) cm-1 due to the stretching frequency of the carbonyl group of the carboxylic acid, and the appearance of a stretching band (N=N) at (1514cm-1) as for the rest of the bands They retained their regular positions within their natural ranges along the series prepared for azo dyes [27].

When studying the proton NMR - 1H NMR of the compound [NG1] shown in Figure (5), a single signal appears in the range of (6.85) ppm due to imine protonation through the effect of electron withdrawal by rosette and induction of the nitrogen atom. A signal appeared within the range (7.35–7.95) ppm, belonging to the aromatic ring protons. A signal appeared at (5.54) ppm belonging to the protons of the pyrimidine ring, at (3.86) ppm belong-

ing to the protons of the ring-linked methoxy group, in addition to a signal at (2.4) ppm belonging to the protons of the terminal methoxy group.

When studying the (NMR) of the compound [NG3] shown in figure (6), signals with integration within the range (7.3-7-1) ppm back to the protons of the aromatic ring. The spectrum also showed multiple signals at the location (6.34-6.75) ppm belonging to the protons of the pyrimidine ring, and also signals appeared at the location (3.8-3.7) ppm belonging to the protons of the methyl group associated with the pyrimidine ring and displaced by the influence of the neighboring group that withdraws electrons.

When studying the 13C-NMR spectrum of the compound [NG3] shown in Figure (7), a signal at (171) ppm belongs to the carbonate of the pyrimidine ring, and the signal at (168) belongs to the imine group, and multiple signals appeared at (127-128).) ppm due to the carbonization of the benzene ring, with a strong signal appearing at (53) ppm due to the methoxy groups attached to the (129) pyrimidine ring. [28].

The mass spectrum of the compound [NG1M.Wt = 273] shown in figure (8), has several fissions, as a peak appeared at m/z=250 [$C_{12}H_{17}N_3O_3$], a second peak at m/z=234 [$C_{12}H_{16}N_3O_2$],a third peak at m/z=219 [$C_{11}H_{14}N_3O_2$], and a fourth peak at m/z=209 [$C_{10}H_{15}N_3O$] , the fifth peak at m/z=194 [$C_9H_{12}N_3O_2$] , the sixth peak at m/z=183 [$C_8H_{11}N_3O_2$] , the eighth peak at m/z=168 [$C_7H_9N_3O_2$] , the eighth peak at m/z=155 [$C_6H_9N_3O_2$] , the ninth peak at m/z=140 [$C_6H_8N_2O_2$] and Tenth peak at m/z=130 [$C_5H_{10}N_2O_2$], eleventh peak at m/z=115 [$C_5H_9NO_2$], twelfth peak at m/z=130 [$C_5H_9NO_2$], thirteenth peak at m/z=101 [C4H7NO2], fourteenth peak at m/z=85 [C_4H_7NO], and fifteenth peak at m/z = 73 [C_3H_7NO] which is the base peak, the sixteenth peak at m/z=60 [C_3H_8O], and the last peak at m/z=46 [C_2H_6O], and the baseline peak proves the validity of the compound, while the rest of the peaks prove the structural form of the compound [29].

3.2. SEM analysis of the scanning electron microscope:

The technique (SEM) is used to take an image of the surfaces of materials, as it is a focused beam of high-energy electrons to generate a variety of signals on the surface of solid samples, where the different signals emanating from the sample reveal in-

formation about the sample, including the external shape and crystal structure, whether it is nanomaterials or not, and a two-dimensional image is created that displays the differences in these properties, and conventional areas whose width ranges from about 1cm to 5µm can be imaged in scanning mode. (with a resolution potential of 50 to 100 nm, magnification ranges from 20X to about 30,000X) also capable of performing analyzes of the locations of selected points on the sample, this approach is particularly important for SEM and crystal structure.

The SEM analysis of the compound [NG1= $C_{14}H_{15}N_3O_3$] shown in Figure (9) showed that (200nm) was used for the cross-sectional area and the magnification power (MAG: 20.00KX). The radii shown in the Gaussian Fit curve, where the peak of the radii of the compound particles was (383.10 nm) [30,31].

The SEM analysis of the compound [NG4= $C_{24}H_{23}BrN_4O_6S$] shown in Figure (10) showed that (500nm) was used for the cross-sectional area and the magnification power (MAG: 5.00KX). The radii shown in the Gaussian Fit curve, where the peak of the radii of the compound particles was (66.96 nm).

3.4. Thermal analysis study:

The compound (NG1) shown in figure (11) The curve shows the gravimetric decomposition technique that it decomposes in two stages, where it shows the gravimetric thermal decomposition of the compound and the critical temperature at which the maximum transformation of the compound (maximum weight loss) and the practical and theoretical percentage lost from each stage are indicated by the mechanics, as it is noted through the curve that the first gravimetric decomposition starts at a temperature of 152 and ends at a temperature of 154, which indicates the stability of the compound before these two degrees, and it was also shown that the total practical weight lost% (71.56) and the remaining % (28.44). Theoretically, the total lost weight is (69.57) and the remaining % is (30.43), and the remainder is (C_2O_4).

3.5 Spectroscopy diffraction X-ray(XRD)

The results indicated for the studied compound [NG5],) shown in figure (12), that the average nanosize was in the range of (1.10 - 54.56 nm), and this shows the results of the SEM of these compounds by having nanoscale clusters.

3.6. The molecular docking: [32,33]

The study of the molecular docking of the prepared organic derivatives gave the number and types of bonds through which these prepared derivatives are linked with the residues of amino acids that are found in the active site of the enzyme Calprotectin, as the study showed that the compound NG4 interacts with the residues of amino acids that are present in the active site of the enzyme Calprotectin by forming three types of bonds, which are two hydrogen bonds that link the residues of the amino acids THR18,LEU2 located in the active site of the enzyme With the double electron of the ring's sulfur atom pentameric as well as with a hydrogen atom of the hydroxyl group offset on the aromatic ring of the compound, and two pi-alkyl bonds linking the amino acid residues MET1, LYS43 which is located in the site of the characteristic activities with the electronic pairs of the aromatic ring of the distinctive and distinctive numbers of the distinctive numbers, shown in figure (13).

7.5. Biological activity of some prepared compounds: [34]

The study of the biological activity of the compounds prepared with certain concentrations showed that most of these compounds have antagonistic activity against the types of bacteria studied, compared to the antibiotic , Ampicillin which are a broad-spectrum antibiotic with an antibacterial activity). It has both positive and negative bacteria, and it also has a large inhibitory diameter as it gives a high selectivity when studying the sensitivity of bacteria to the prepared compounds, and since this antibiotic is used to treat many diseases and infections such as urinary tract, especially those that occur as a result of infection with colon bacteria and Staphylococcus aureus bacteria, as well as simple cystitis in females caused by coliform bacteria, and prostatitis caused by colon bacteria in addition to infections of the lower respiratory tract, sinus inflammation, arthritis and bones. It is also used to treat diarrhea caused by colon bacteria and is also effective in treating typhoid. Therefore, two compounds of the compounds prepared in this research [NG2, NG3] were studied on different types of chromium-positive and negative bacteria, which recorded a global antagonistic activity against the bacteria studied, and compared with the mentioned antibiotics, it is possible to use

these compounds as a treatment for the same infections and pathological conditions above, after examining the biological path of these compounds, their side effects, and the amount of their accumulation in animal tissues. different compounds (0.01, 0.001, 0.0001, mg/ml), where the diameter of the inhibition ranges between (0 mm minimum diameter of inhibition to 14 mm maximum diameter of inhibition measured) and the table below It shows the inhibitory activity of some of the prepared compounds, and the figures show that the value of the inhibition varies according to the compound, and this is due to the low baseline and because of the presence of resonance, shown in figure (14) .

Table (7): The inhibitory activity of the two compounds [NG2, NG3] in the growth of a number of positive and negative bacteria (the diameter of inhibition measured in mm)

Test	Staph aureus			Klebsiellia pneumoniae		
	0.01	0.001	0.0001	0.01	0.001	0.0001
NG1	13	13	-	12	12	-
NG2	12	13	13	11	13	-
NG3	14	-	-	14	-	-
NG4	14	13	12	14	14	-
NG5	6	3	5	-	-	-

3.8. Dyeing operations:[35,36]

One of the main applications of dyes is their use as dyes with better properties than ordinary dyes. A dye is a colored substance that can give its color to another meaning, provided that it meets several conditions, namely that it has a special ability to dye the body, to have intense color and stable properties against the influence of chemical and natural factors such as fastness to light and washing. Azo dyes [NG4, NG5] were used in the dyeing process, in which an appropriate amount of azo dye was dissolved in a suitable solvent. The resulting solutions were used to dye equal weight pieces of cotton, wool, cloth, brocade, and wood, as iron was used to fix the dye. When washed with water, it showed apparent stability and had good strength against soap and washing powder, as shown in Figure (15,16) [34, 35].

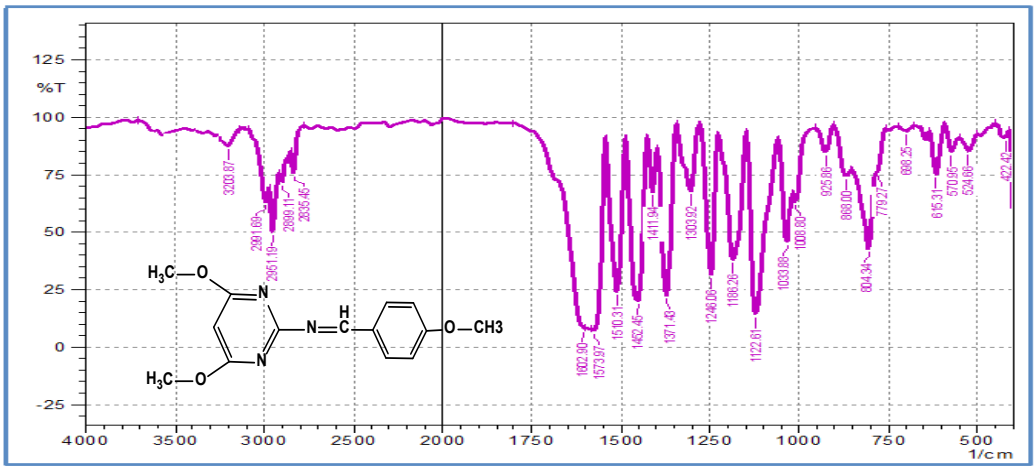


Figure 1: FTIR spectrum of NG1

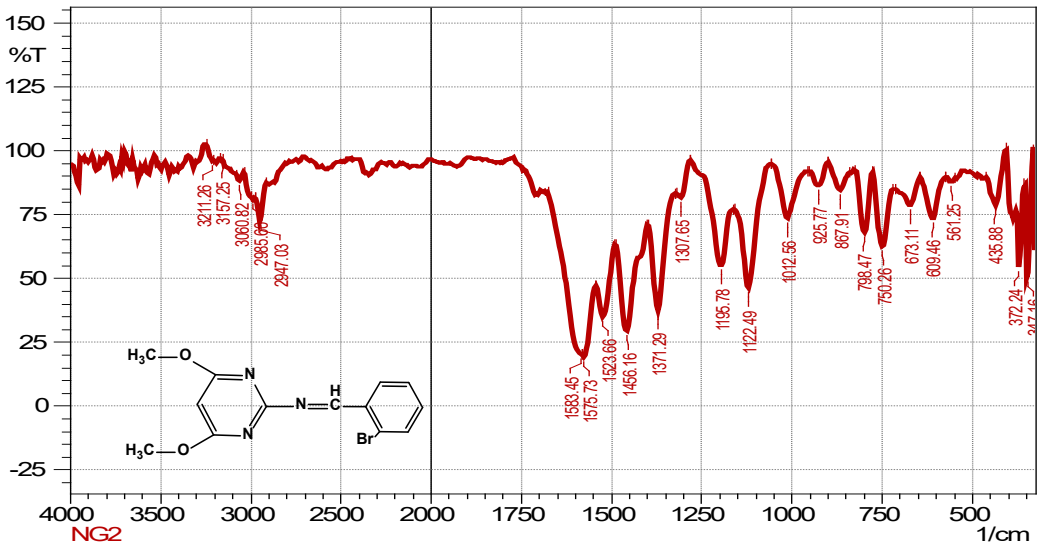


Figure 2: FTIR spectrum of NG2

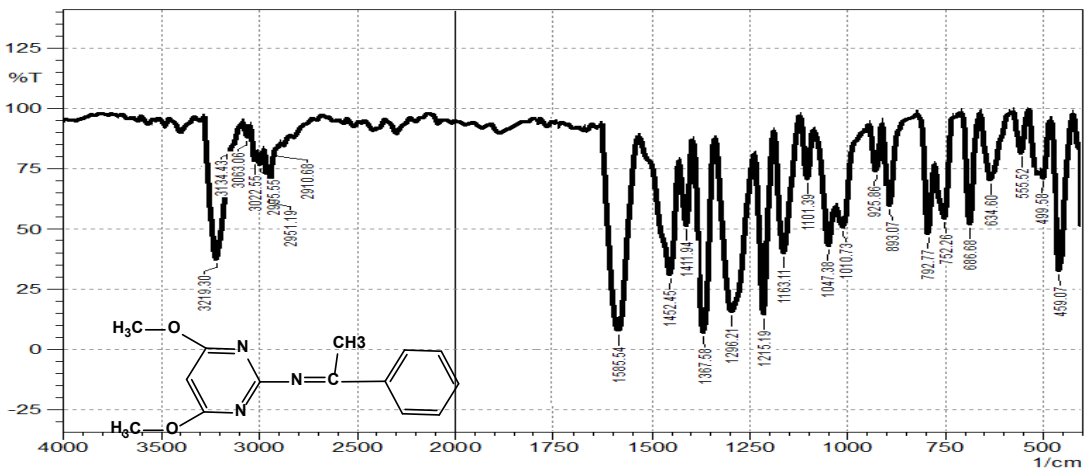


Figure 3: FTIR spectrum of NG3

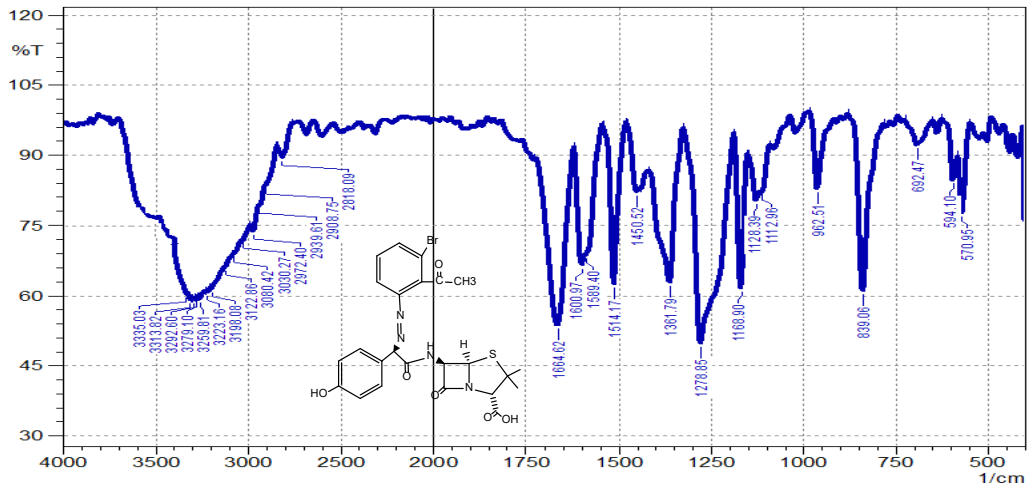


Figure 4: FTIR spectrum of NG4

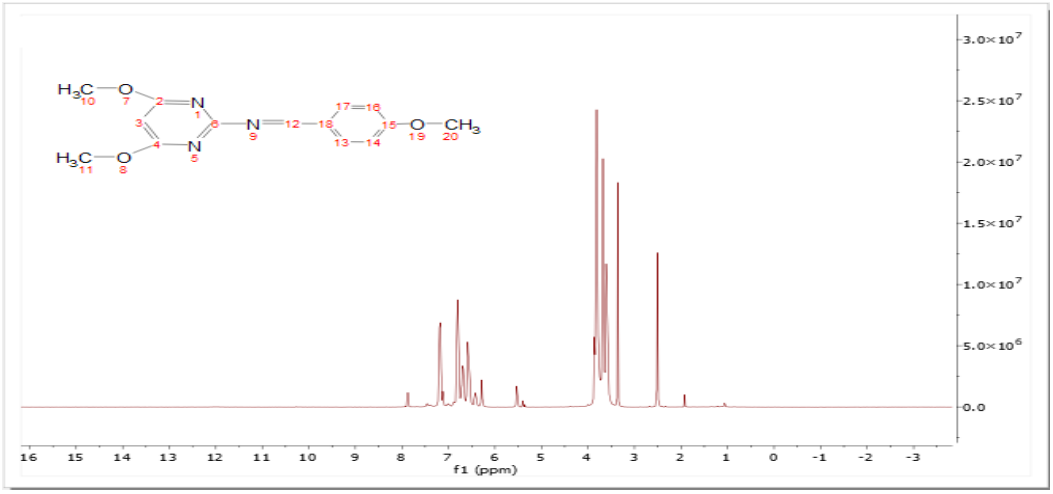


Figure 5: ^{1}H-NMR spectrum NG1

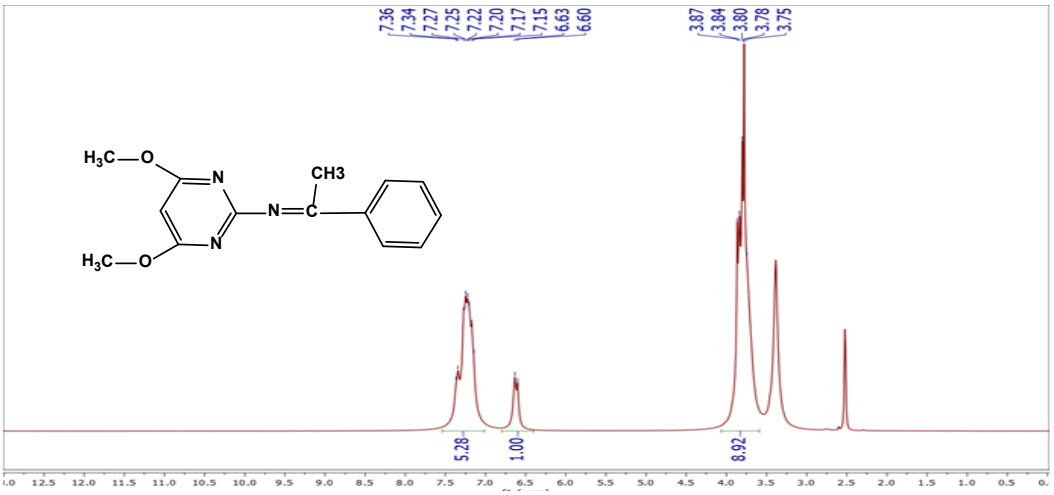


Figure 6: ^{1}H-NMR spectrum NG3

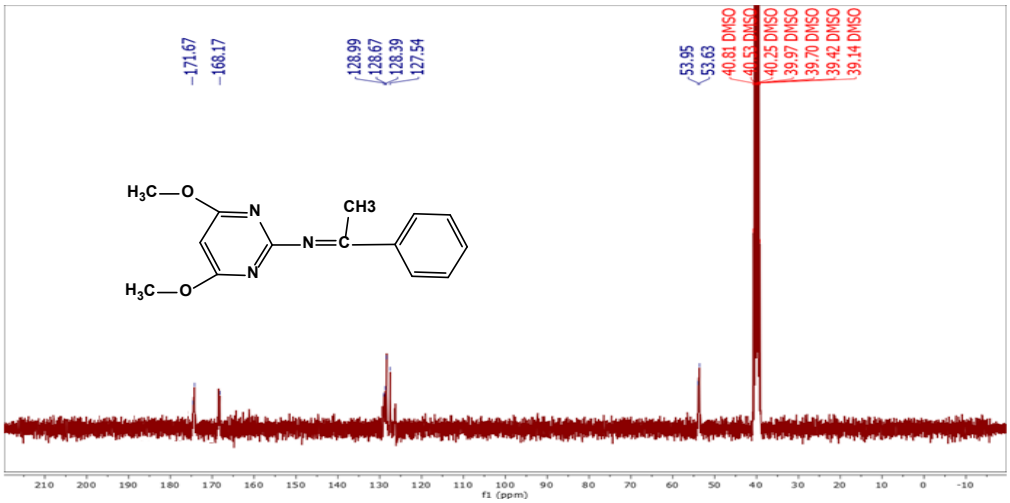


Figure 7: ^{13}C-NMR spectrum of NG3

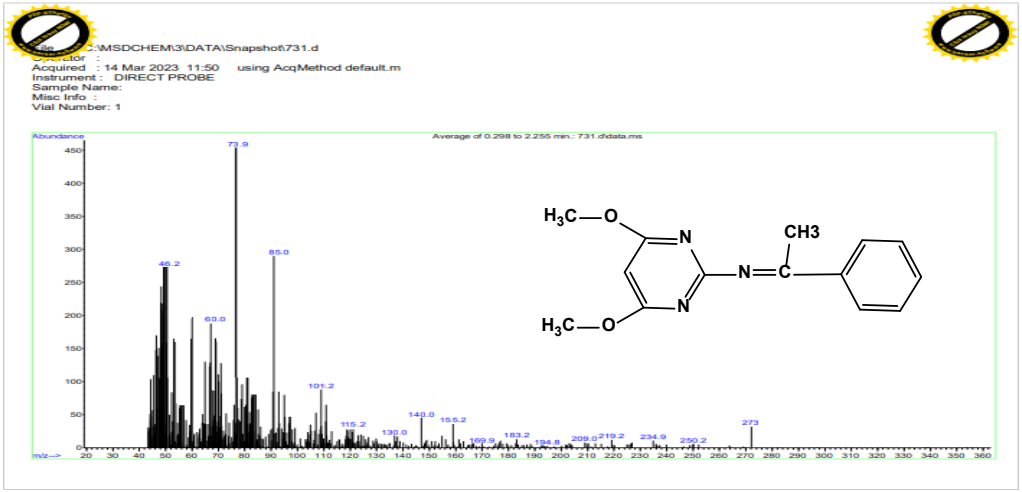


Figure 8: Mass spectrum of NG3

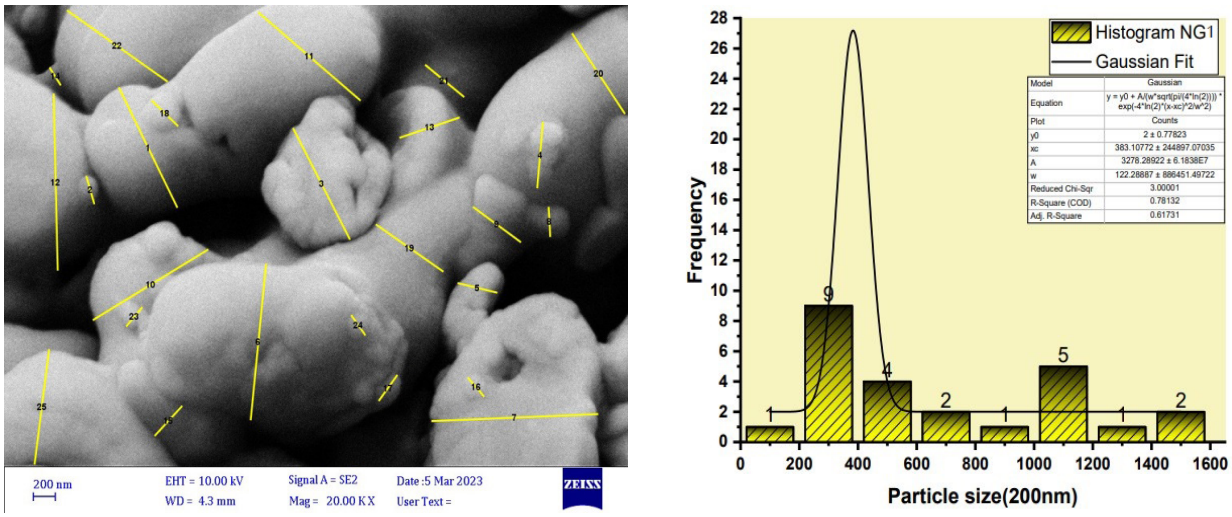


Figure 9: SEM of NG1

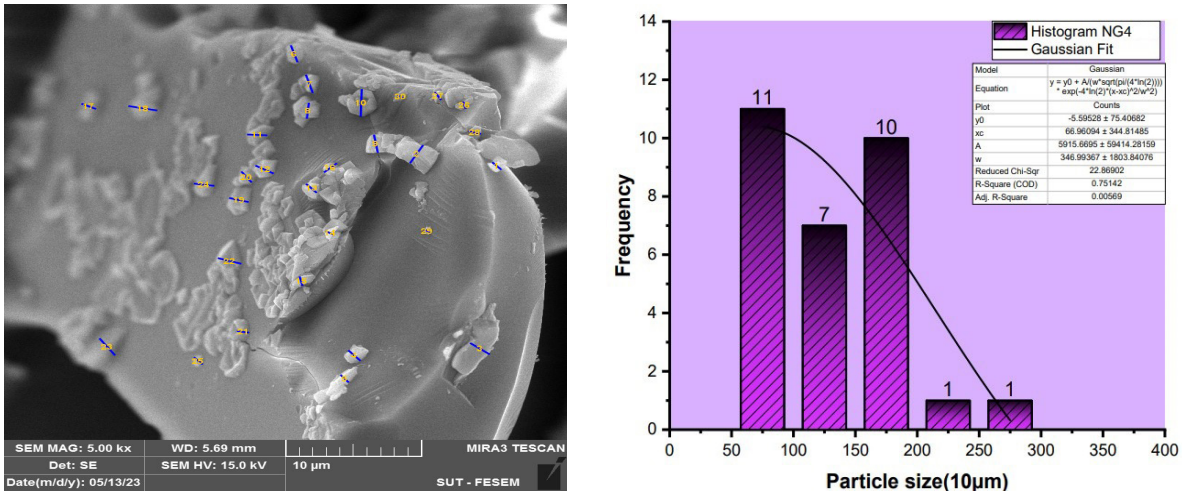


Figure 10: SEM of NG4

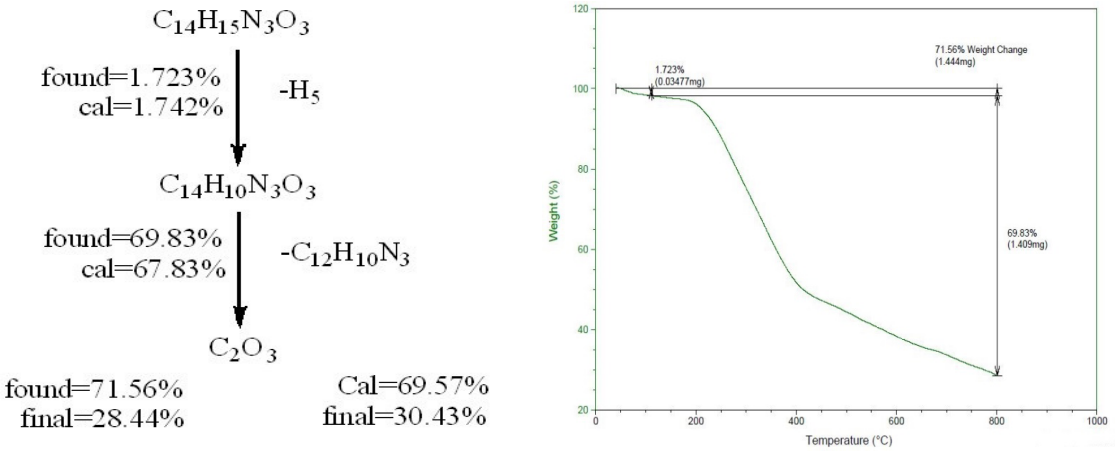


Figure 11: Gravimetric pyrolysis stages of [NG1] compound

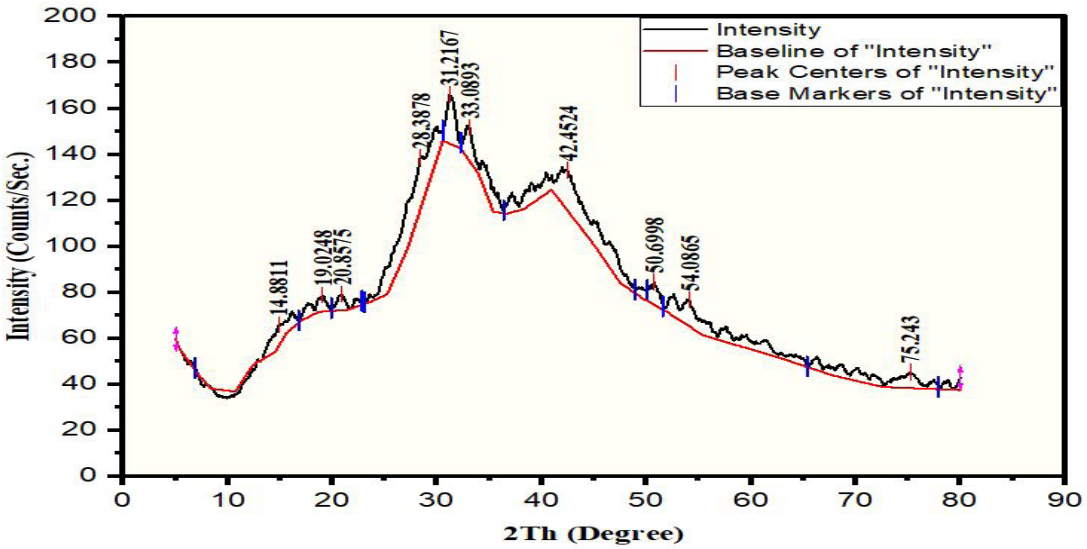
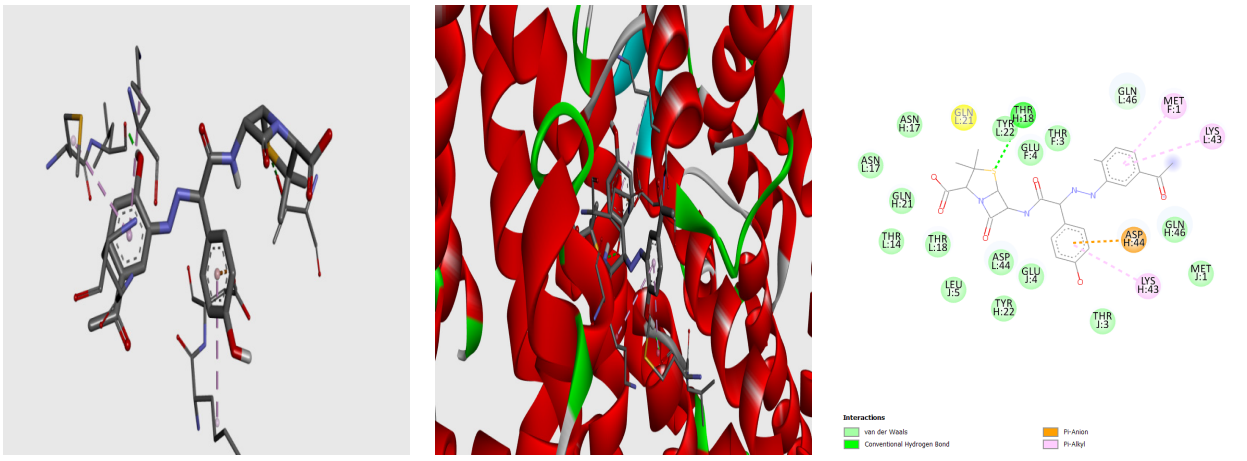


Figure 12: XRD of NG5



Figur 13: Interactions between NG4 and Calprotectin in 3D and 2D dimensions

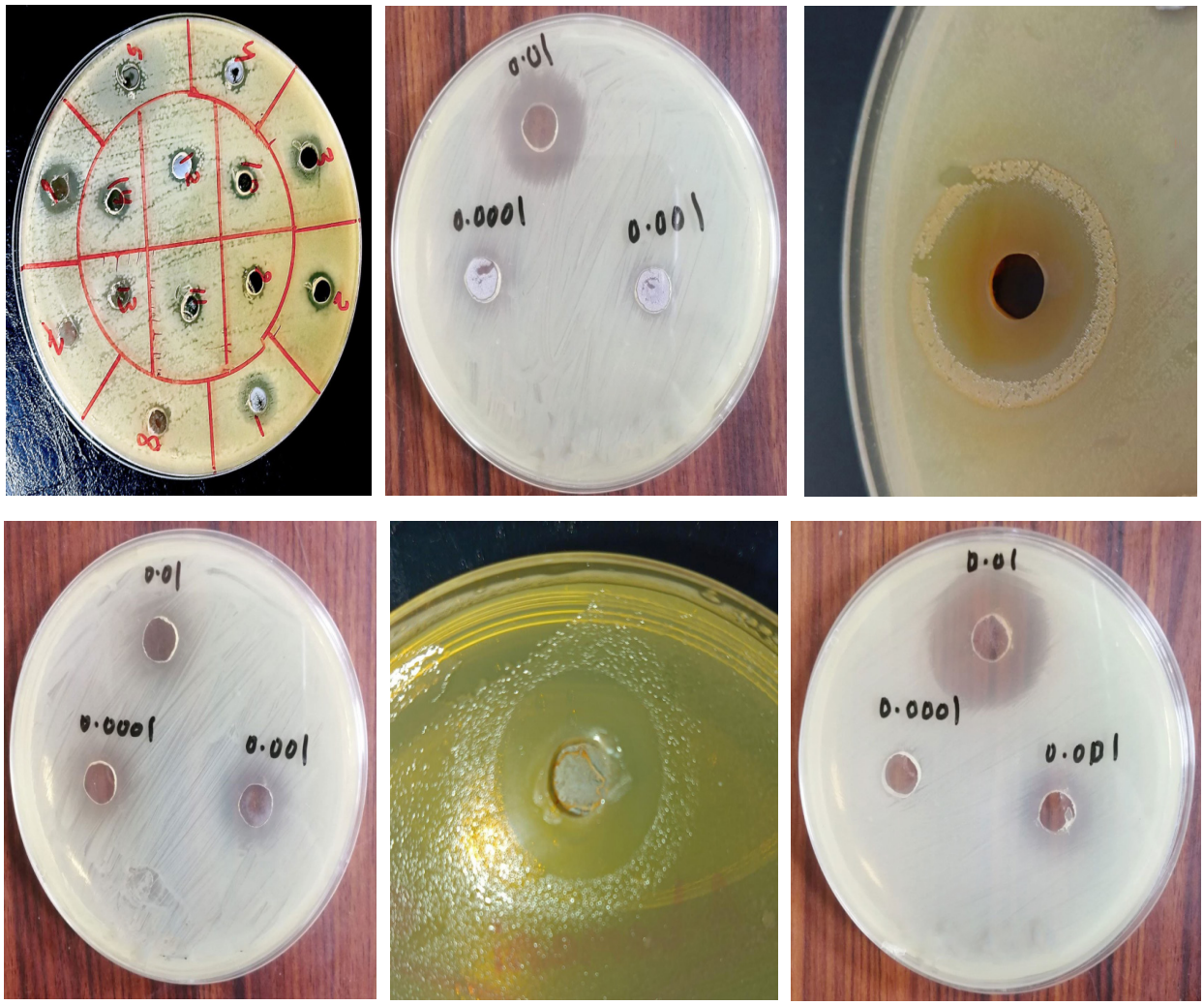


Figure 14: Compound NG2,NG3 inhibits the growth of all used bacteria

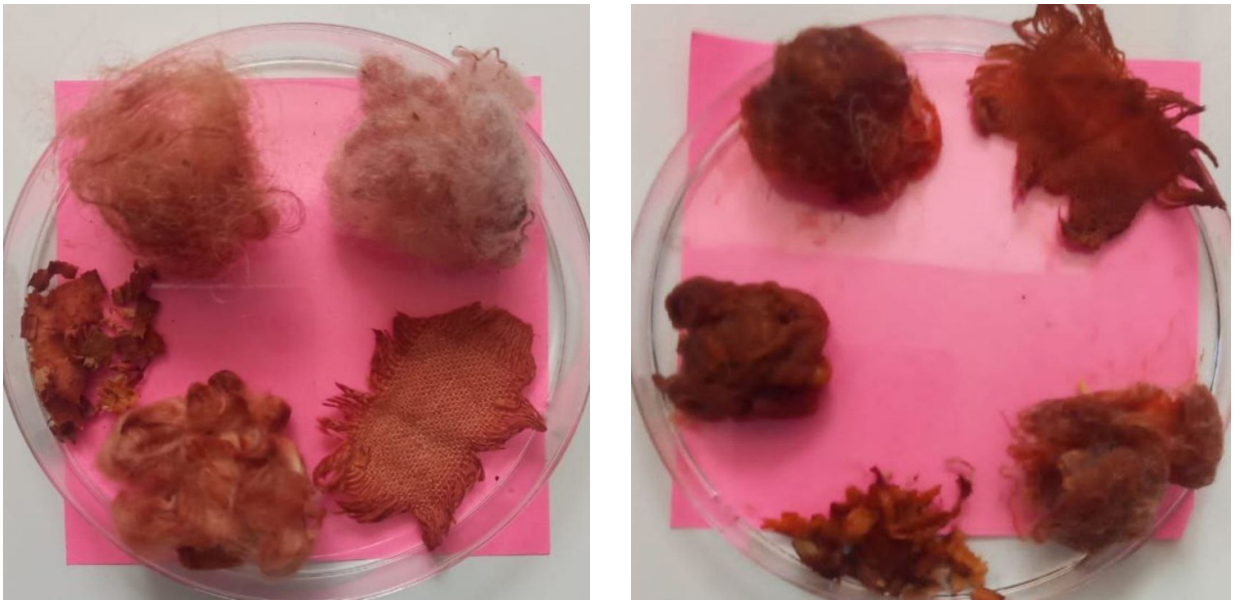


Figure 15: Dyeing process for compound [NG4] before and after washing with water

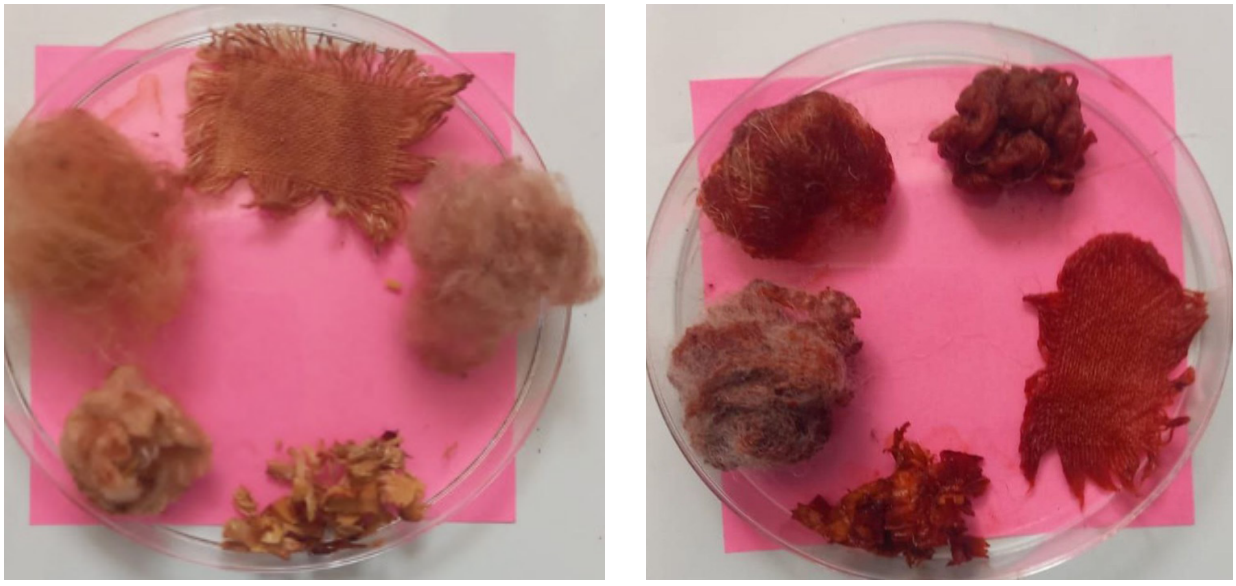


Figure 16: Dyeing process for compound [NG5] before and after washing with water

4. Conclusions:

The physical and spectroscopic measurements confirmed the accuracy and validity of the prepared compounds. Therefore, the methods used in preparation were good, successful, and low cost. Through SEM analysis, the surface of the as-prepared composites appeared as if they were rock layers interspersed with deep trenches. .

The prepared compounds also showed good efficacy against the bacteria used in the study. The prepared azo dyes also showed good synthetic stability for their dyes, as it was observed that the dyes were not removed by washing and they maintained their stability. It gave the results of molecular association and the types of acids present in the compounds attached to the prepared compounds with the amino acid residues present in the structural site.

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