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Synthesis and characterization of new compounds of amic acids derived from cephalosporins, the study of some physical applications and evaluation of their biological activity

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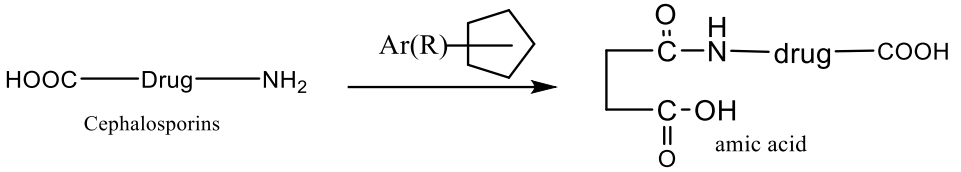
***Abstract*---**In this research, amino acids were prepared from the reaction of cephalosporins with anhydrous acids, and the accuracy of the prepared compositions was confirmed by measuring their physical properties, including melting point, molecular weight and colour, as well as through spectroscopic measurements, including Uv, FTIR, ^{1}H-NMR, ^{13}C-NMR, mass spectrometry, (S.E.M.), (C.H.N.). A study of electrical conductivity and a survey of the biological activity of some prepared compounds and on four types of pathogenic bacteria, two of which are Gram-positive, and two are Gram-negative. They are each of (Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumonia, and Pseudomonas putida). The use of Acker-Hinton's type of culture medium (Molar Hunting Agar) and aqueous solutions of the two compounds [DM7] were also prepared. [DM3] and in concentrations (0.01,0.001,0. 0001,0.00001) mg/ml and by using a solvent dimethyl sulfoxide (DMSO), a sensitivity test was conducted for the bacteria isolates that were used in the study by diffusion method, and using the antibiotics Cefixime, Ceftriaxone, Ampicillin as a control sample.

***Keywords*---**cephalosporins, amino acids, enterococcus faecalis, staphylococcus aureus, klebsiella pneumonia, pseudomonas putida.

Introduction

Amic acids are organic acids that contain two carboxyl groups (COOH) and an amide (CONHR) in the same molecule [1]. Amic acids were prepared from the reaction of primary or secondary, aromatic or aliphatic amines with anhydrous acids such as maleic, phthalic, itaconic, citraconic, succinic and others [3,2].



Amic acids were distinguished by their multiple uses, whether in organic preparations for imides or azoimides or in the field of polymers. They were also used for industrial medicinal or pharmaceutical purposes [4], where they were used to treat arthritis [5] and epilepsy [6,7], and as anti-tuberculosis bacilli and nematodes [8], it was also used in medical diagnosis [9] as well as in studying energy transformations and as an activator of the action of adenosine triphosphate ATP [10]. It was also used in agricultural fields as an industrial growth regulator to produce large-sized vegetables and fruits that resist environmental conditions or long-term storage conditions by spraying them on the growing tops of plants during the germination period [11]. These vegetables and fruits were also characterized as being seedless [12]. It is also used as a pesticide due to its ability to eradicate insects and fungi [13], as well as used to extinguish fires and prevent the spread of flames [14].

Experimental

Chemicals used: All chemicals used in this work were purchased from BDH, Aldrich and Fluka companies and were used without further purification.
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 (400-4000) 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.

Preparation of amic acids [DM7-DM1]

Preparation of the compound (DM7) [15]

In a round-bottom flask with a capacity of 100 ml 0.01 mol (maleic anhydride) was placed and from the separating funnel (0.01 mol) of cephalexin dissolved in benzene was added dropwise and no precipitation occurred. Then the mixture was raised on a water bath for (3) hours, after which the mixture was cooled and the precipitate filtered

Preparation of the compound (DM2) [16]

In a ceramic mortar, 0.01 mole of phthalic anhydride was mixed with 0.01 mole of ceftriaxone, and it was ground well for an hour, then the substance was purified by dissolving it in a solution of sodium bicarbonate and re-precipitating it with dilute hydrochloric acid.

Preparation of the compound (DM3) [17]

In a ceramic mortar, 0.01 mole of phthalic anhydride was mixed with 0.01 mole of ceftriaxone, which was ground well for an hour, before purification, and heated for (7-5) minutes at 150 ^{o}C. Then it cooled, and it formed a long, filamentous, needle-like substance, which was filled with the pot, and the shortest length was 1.6 cm. figure below illustrates this.

Table (1) shows some physical properties of [DM7-DM1] Amic acids

Comp. No.	Molecular Formula	Color	M.P ^{O}C	Yield %
1	$C_{16}H_{17}N_5O_7S_2$	White	165-167 Dec.	88%
2	$C_{18}H_{18}N_8O_7S_3$	White	178-180 Dec.	93%
3	$C_{16}H_{17}N_3O_4S$	orange	186-188	90%
4	$C_{16}H_{19}N_3O_4S$	yellow	175-177	90%
5	$C_{16}H_{15}N_5O_7S_2$	yellow	122-124	92%
6	$C_{15}H_{17}N_5O_6S_2$	white	171-173	88%
7	$C_{16}H_{19}N_3O_5S$	White	153-155	90%

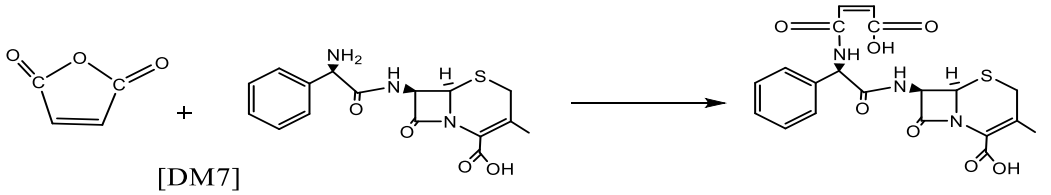
Study of biological activity [18, 19]

This study was used on four types of pathogenic bacteria, two of which are gram positive, and two are gram negative, and they are Staphylococcus aureus and Enterococcus faecalis, Klebsiella pneumoniae, and Pseudomonas putida) are important 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 Life Sciences, and Mueller-Hinton-Akar culture medium was used. Molar Huntin Agar), which 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), and aqueous solutions of two compounds [DM7, DM3] were also prepared. At concentrations of 0.01), 0.001, 0.0001 (0.00001, mg/ml and using a solvent dimethyl sulfoxide (DMSO), a sensitivity test was

performed for the bacterial isolates that were used in the study by the method of diffusion in the nutrient medium of Muler-Hinton agar, which is a transparent nutrient medium with a useful dark yellow color. In testing the sensitivity of microorganisms towards antibiotics, because it contains an animal infusion extracted from casein and starch, it supports the growth of most microbes, microorganisms. At the rate of four holes in each dish, then incubated at 37 ^{0}C for a period of 24 hrs., then the results were read on the next day to show the sensitivity of used derivatives that depend on the diameter of the apparent inhibition in the dishes. About the used pits, as the increase in the diameter of the inhibition means the increase in the biological activity of the prepared compounds and compare that with the diameter of the inhibition for antibiotics.

Results and Discussion

Amic acids were prepared by reacting one mole of cephalosporins with one anhydrous acid.



[DM7]

Discussion of amic acids [DM7-DM1]

The reaction of the amino acids [DM7-DM1] was confirmed by observing the physical changes in the melting point and colour change and the diagnosis of the prepared amino acids [DM7-DM1] by (IR), (^{1}H-NMR) and (^{13}C-NMR) measurements. When studying the infrared (IR) spectrum of amino acids [DM7-DM1], it was noticed that the stretching band of the amine group (NH_2) disappeared in the prepared compounds with the appearance of several bands within the range of (3589-3400) cm-1 that belongs to the imidic (NH) stretch, as well as the appearance of a band within the scope of (3356-3372) cm-1 belonging to the (OH) stretch band Also, a bundle appeared within the field (3223-3120), which belongs to the stretching of the olefinic (CH) group, as well as fortunes appeared within the range (3063), which belongs to the extension of the olefinic group Aromatic (CH) also appeared (2914), which belongs to the stretching of the (CH) aliphatic group, also shows a band within the range (1726) cm-1, which belongs to the stretching frequency of the imide carbonyl group, and the band within The content of (1688) cm-1 is related to the stretching frequency of the carbonyl group of carboxylic acid. A bundle appeared within the range (1626), which belongs to the stretch of the (C=C) olefinic group, as well as a pile seemed within the field (1593-1500) cm-1, which belongs to the stretching frequency of the aromatic (C=C) group, and the beam is within the range (1404-1357) cm-1 belonging to the frequency of the alkyl (CH) group. As for the shafts of curvature of the group (C-N), they appeared in the areas (1237-1201) cm-1, and the rays of curvature of the group (C-O) appeared in the regions (1192-1159) cm 1- As shown in table (2), these packages were close to what is found in the literature [20, 21].

Table (2): Results of the absorption spectra of UV (nm) and IR (cm^{-1}) for (DM1-DM7)

Comp. No.	UV λmax nm DMSO	IR, (KBr), cm^{-1}				
		ν (N-H) ν (NH_2) νOH carboxylic	ν (C-H) olefinic ν (C-H) aromatic ν (C-H) aliphatic	ν(C=O) amide ν(=C-O) carboxylic	ν (C=C) olefinic ν (C=C) aromatic δ (C-H) alkyl	δ(NH_2) δ(CH) aromatic out of plane ν(CN) & ν(CO)
DM1	283	3421 3313	3124, 3066 2937,2899	1735 1654	1614,1599 1535,1502 1414,1390,1369	1319 1205
DM2	287	3522,3423 3336,3300	3275,3119 3068, 2937,2814	1764,1747 1650	1610, 1537,1502 1413,1398, 1367	891,806, 1301 1281,1257
DM3	289	3516,3419 3337,3317	3124.79 3024,2937,2901	1746,1699 1658	1616,1577,1535 1413,1392,1369	1319 1251,1219
DM4	295	3522,3427 3417,3282	3126, 3072 2937,2814	1751 1653	1600,1537,1502 1414,1396,1367	891,806 1305,1284,1257
DM5	283	3522,3414 3375	3159,3120 3068,3026 2970,2933	1752 1689	1612 1589,1516 1465,1400	839,800 1329,1317 1278,1257
DM6	288	3560,3527 3466	3200,3171 3055,3032 2968,2931,2906	1753 1687	1616 1535,1518,1483 1458,1396,1379	868,844,1315 1253,1219
DM7	287	3522,3487 3452,3417	3275.24,3223.16, 3178.79,3140.22 3063.06, 2914.54	1753 1695,1647	1626.05 1593,1537, 1500, 1452,1404	819,798 1357 1280,1259

When performing a 1H-NMR analysis of compound [DM7] shown in figure (4) We note the presence of two bands in the position (9.4-9.0) ppm attributed to the proton of the acidic hydroxyl group (OH), as they appeared within the low range of the spectrum due to negativity of the high electronegativity of the oxygen atom and the bonding of the (OH) group to the electron-distracting carbonyl group, which increases the denudation of the proton from its electrons also, the protons of the benzene ring appeared as two bands in the range (7.82-7.46) ppm, and the first double binary bands appeared at (6.0) ppm belonging to the two olefin

protons. Close to the imide carbonyl group and the second at (5.55-5.0) belongs to the protonated (NH) close to the carbonyl group, and the appearance of bands at the 3.4 site ppm to the protons of alkyl groups [22, 23].

When studying the ^{13}C-NMR spectrum of the compound [DM7] shown in figure (5), It was noted that there were signals at (149.52-110) ppm that were related to the aromatic benzene ring carbons, as well as the appearance of a signal at (70.42) ppm that was attributed to The carbon of the group (CH), aliphatic, and the appearance of a signal at the site (62.68) ppm attributed to the carbon of the group (CH_2), and the formation of movements at the range 39.98-38.27) ppm attributed to the solvent carbonate (DMSO-d^6) [24, 25].

When studying the mass spectrum of the compound [DM7], we notice the appearance of a peak at m/z=303.1 [$C_{14}H_{13}N_3O_5$], and the appearance of a second peak at m/z=285.1 [$C_{14}H_{11}N_3O_4$], the appearance of a third peak m/z=270.2 [$C_{14}H_{10}N_2O_4$], a fourth peak m/z= 256.2 [$C_{14}H_{12}N_2O_3$], a sixth peak m/z=236.1 Overlapping a m/z=232.0 peak [$C_{12}H_{12}N_2O_3$], and a seventh m/z=212.0 peak overlapping a m/z=215.0.0 [$C_{12}H_9NO_3$] peak, an eighth peak m/z=189.0 [$C_{11}H_{11}NO_2$], a ninth peak m/z=170.0 overlapping with a m/z= 173.0 peak [$C_{11}H_{11}NO_2$], and an eighth peak m/z= 189.0 [$C_{11}H_{11}NO_2$], Ten m/z=148.1 [$C_9H_{10}NO$], top eleven m/z= 122.0 [$C_8H_{12}N$], top twelve m/z=104.2 [C_8H_8] It is the peak of the baseline, and the thirteenth peak is m/z=90.4 [C_7H_6], also the fourteenth peak has appeared m/z=76.0 [C_6H_5], and the last peak is at m/z=51.0 [C_4H_3], and that the top of the baseline proves the validity of the compound [26, 27], while the rest of the peaks prove the structural shape of the compound, and figure (6) illustrates this.

Biological activity of some prepared compounds [28, 29]

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 Ceftriaxone, Ampicillin Cefixime, which is a wide classification of antibiotics that have antibacterial activity). Positive and negative, honorable (16), and it also has a large inhibitory diameter as it gives high selectivity when studying the sensitivity of bacteria to the prepared compounds, and since this antibiotic is used to treat many infections and diseases such as urinary tract infections (19-18-17), especially those that occur as a result of infection with colon bacteria and Staphylococcus aureus bacteria. It also treats simple cystitis in females caused by colon bacteria. It treats chronic bacterial prostatitis caused by colon bacteria and infections of the lower respiratory tract, and inflammation of Sinusitis, arthritis, and bone (21-20). It is also used to treat diarrhea caused by colon bacteria and effectively treat typhoid. On different types of chromium-positive and negative bacteria, which recorded a global antagonistic activity against the studied bacteria 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 investigating the biological pathway of these compounds and their side effects. It and the amount of its accumulation in animal tissues and the results based in table (3) indicate that most of the prepared compounds can inhibit the bacteria used by different concentrations of the compounds (0.01,

0.001, 0.0001, 0.00001 mg/ml). Where the diameter of the inhibition ranges from 0 mm, the lowest diameter of inhibition, to 40 mm, the highest diameter of inhibition measured and the table below shows the inhibitory activity of some of the prepared compounds.

Table (3): The inhibitory activity of the two compounds [DM7, DM3] on the growth of several positive and negative bacteria (the diameter of inhibition measured in mm)

Test	*Staph aureus*	*Enterococcus faecalis*	*Pseudomonas putida*	*Klebsiella pneumoniae*	*Antibiotic*
DM3 0.0 1	32	26	32	40	S.a 18
A 0.001	10	20	22	28	E.F 10
B 0.0001	9	10	28	24	P.P 20
C 0.00001	6	4	16	16	K 10
DM7 0. 1	17	16	43	24	P.P 30
A 0.01	7	-	32	20	K 8
B 0.001	-	-	24	-	
C 0.0001	-	-	10	-	

Analysis (SEM) [30,31]

The (SEM) images of the compound DM7 at 10 µm show the surface as scattered layers of rock, where we notice that the trenches have expanded and become more scattered. At 1µm, the surface appears in the form of large rocks scattered with small stones of different densities, interspersed with deep trenches that trap gases within them and spaces between them. At 500 nm, the surface appeared as accumulated rocks, interspersed with deep valleys with voids between them. At 200 nm, the character appeared as large rocks scattered on it with small rock pieces interspersed with holes, phenomenon of nanoparticles became clear.

Microanalysis of the Elements (C.H.N)

A precise analysis of the elements was carried out for some of the prepared compounds, and the measurements were close to the calculated ratio [32], as shown in the following table (4).

Table (4): Microanalysis of the Elements (C.H.N)

Comp.	Molecular	Calculated			Found		
No.	Formula	C%	H%	N%	C%	H%	N%
DM3	$C_{20}H_{19}N_5O_{10}S_2$	43.52	3.83	12.78	43.40	3.46	12..65
DM7	$C_{20}H_{19}N_3O_7S$	53.12	4.53	9.52	53.93	4.30	9.43

Electrical conductivity

Electrical conductivity is widely used in coordination chemistry to find possible ionic formulas. It occurs in a compound when it is a solution or a solid, and the degree of conductivity is more significant when it is the number of ions that it releases in the solution is more, and the conductivity is low in the complex that does not ionize the figure shows the typical properties of electrolytes in aqueous solutions and represents the relationship between the radical molar concentration and molar electrical conductivity [33].

Table (5): Electrical conductivity values of [DM2, DM3, DM7] using the DMSO solvent

Test	DM2	DM3	DM7
Conductivity .us/cm	2.5	2.8	2.6
C°	18.5	19.9	18.9

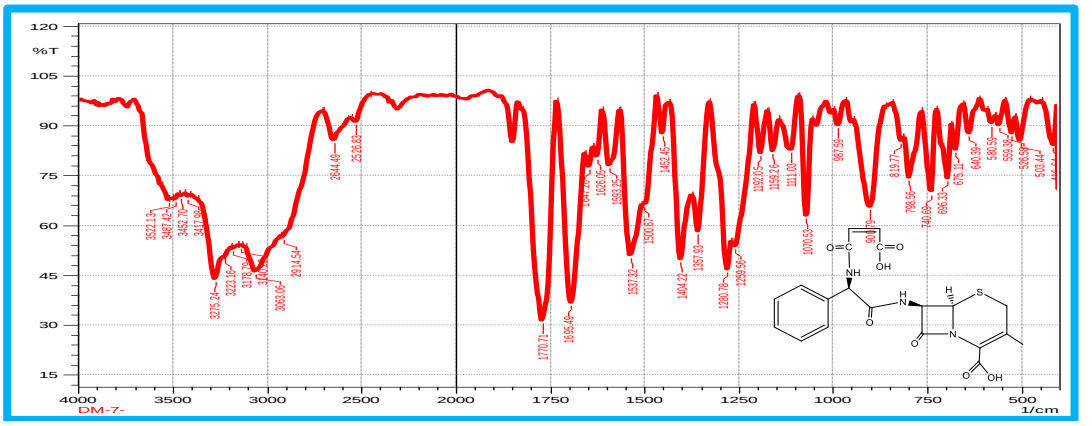


Figure 1: FTIR spectrum of DM7

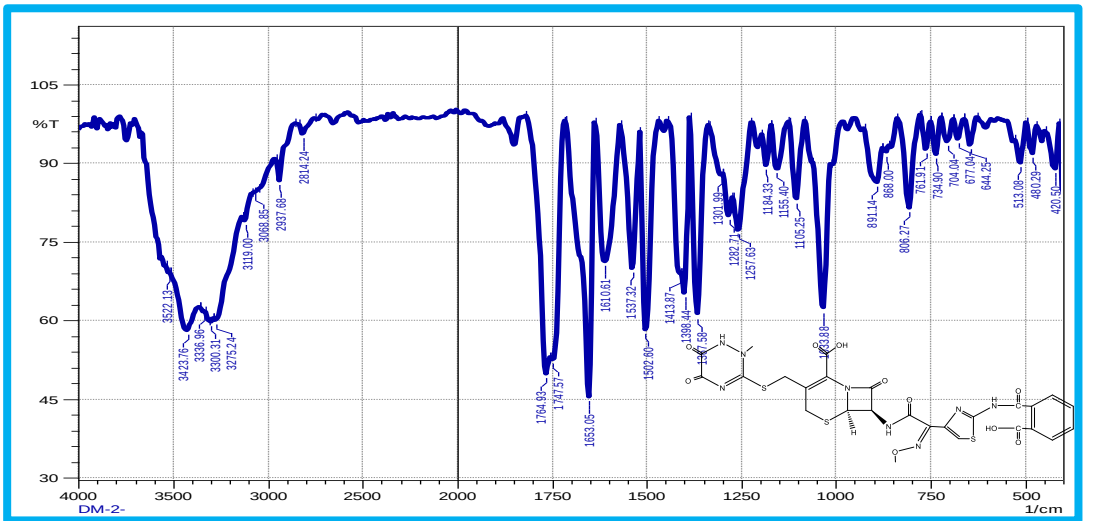


Figure 2: FTIR spectrum of DM2

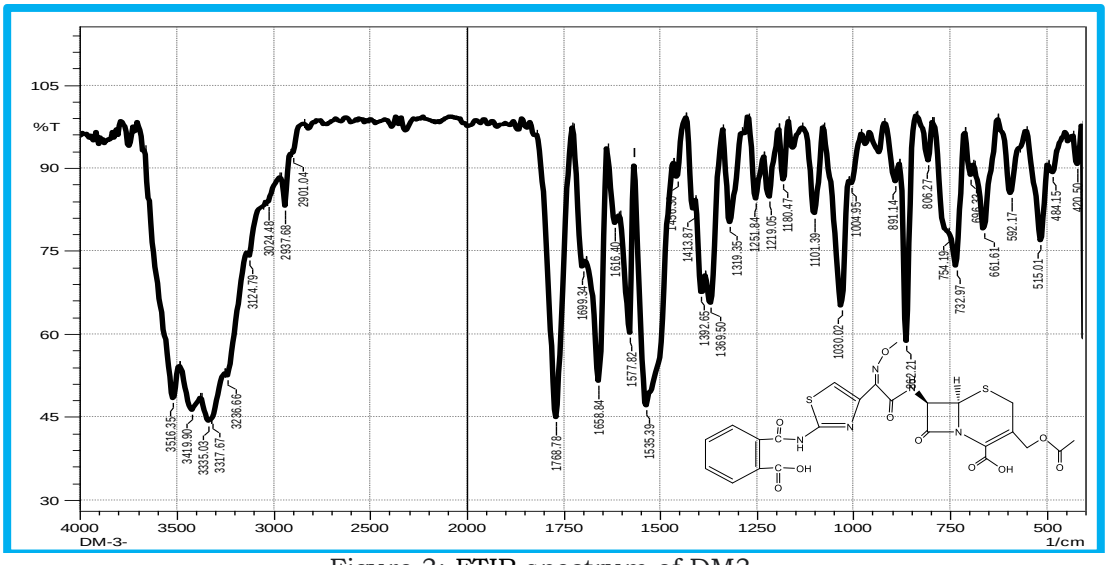


Figure 3: FTIR spectrum of DM3

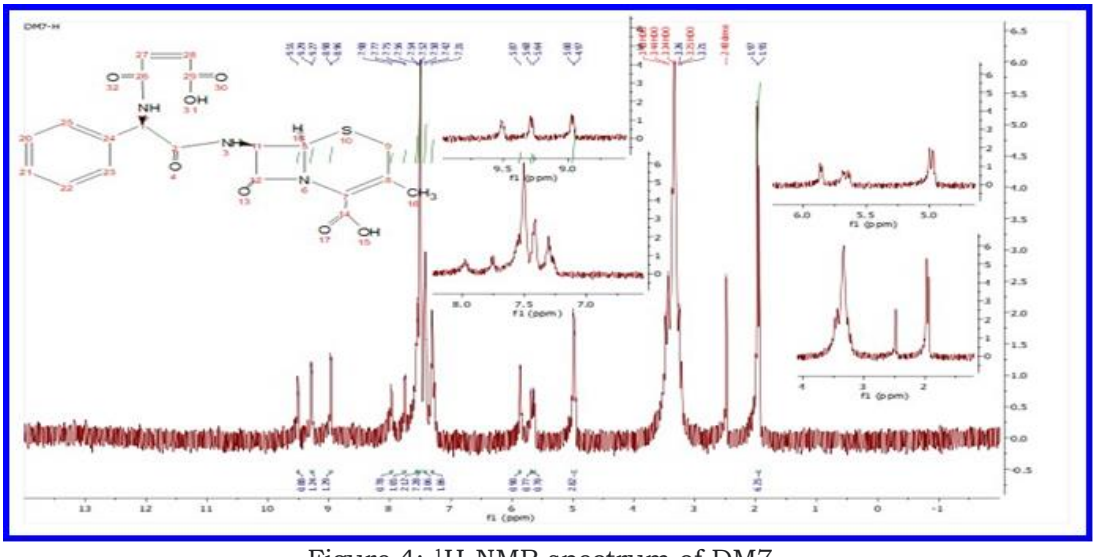


Figure 4: ^{1}H-NMR spectrum of DM7

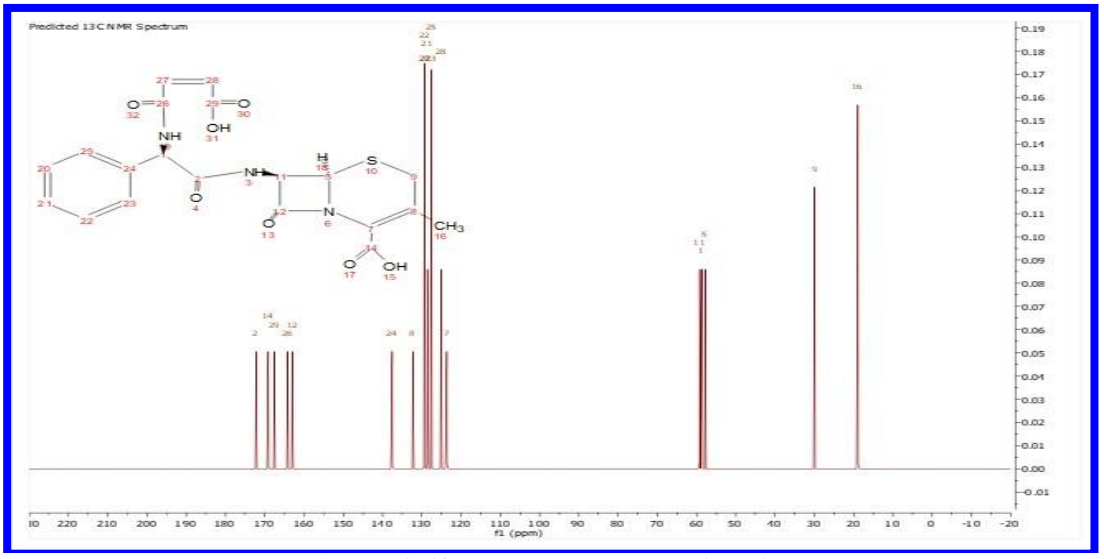


Figure 5: ^{13}C-NMR spectrum of DM7

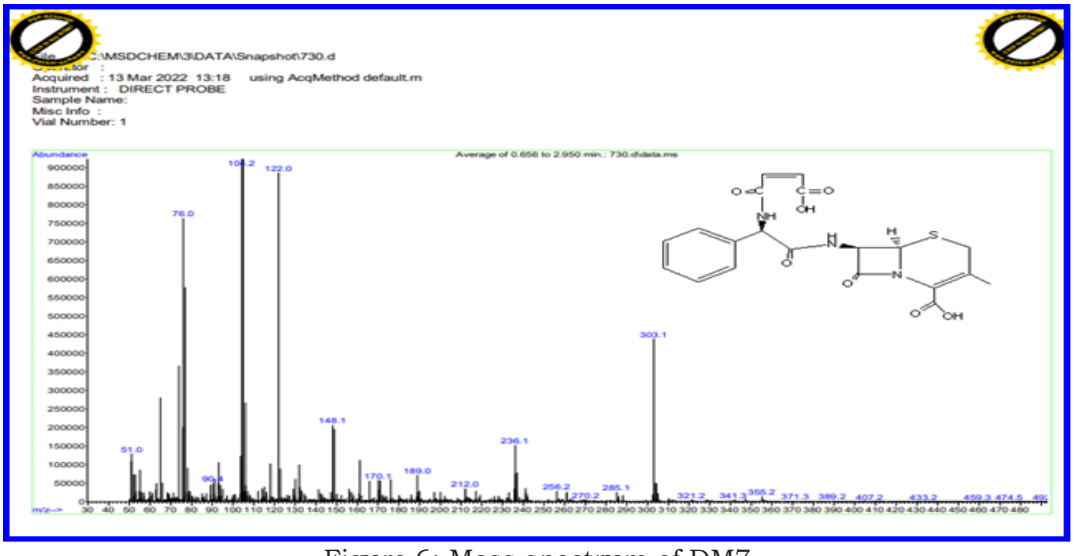


Figure 6: Mass spectrum of DM7

Eager 300 Summarize Results

Date : 2002/01/03 at 01:13:12
Method Name : Nitrogen/Carbon/Hydrogen/Sulphur
Method Filename : N C H S system.mth

Filename	AS Method	Vial
DM7		

#	Group	Sample Name	Type	Weig.	Pro.F	---
57	1	DM7	UNK	3.279	6.25	---

Component name	Element %
Nitrogen%	9.528888702
Carbon%	53.12982178
Hydrogen%	4.531628609
Sulphur%	0

1 Sample(s) in Group No : 1

Component Name	Average	Std. Dev.	% Rel. S. D.	Variance
Nitrogen%	9.528888702	0	0.0000	0.0000
Carbon%	53.12982178	0	0.0000	0.0000
Hydrogen%	4.531628609	0	0.0000	0.0000
Sulphur%	0	0	0.0000	0.0000

Figure 7: C.H.N. of DM7

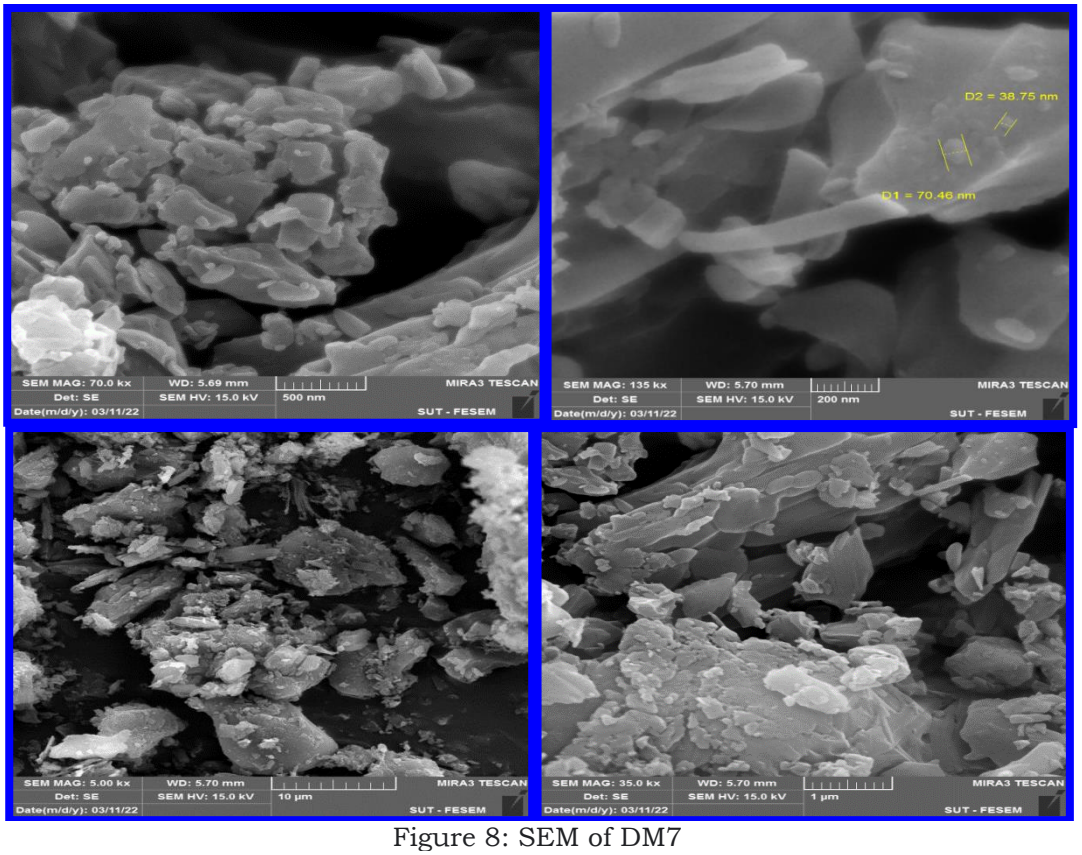


Figure 8: SEM of DM7

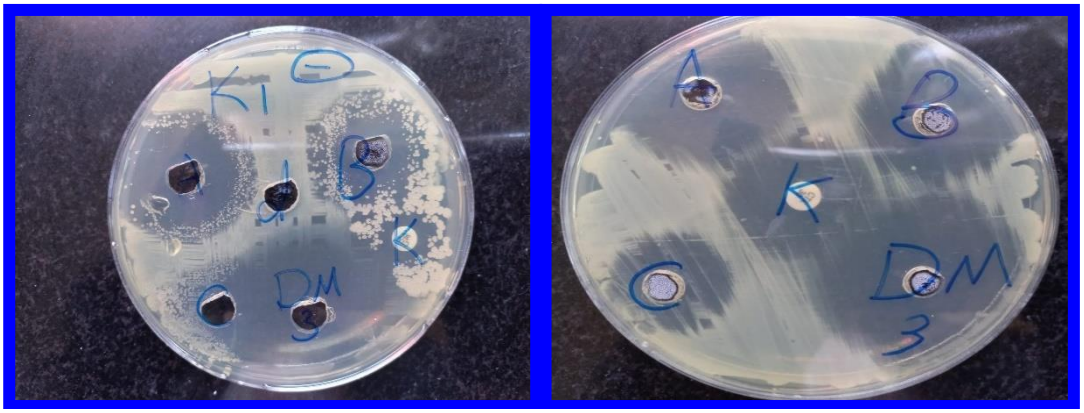


Figure 9: Compound DM3 inhibits the growth of bacteria Enterococcus faecalis and Klebsiella pneumoniae

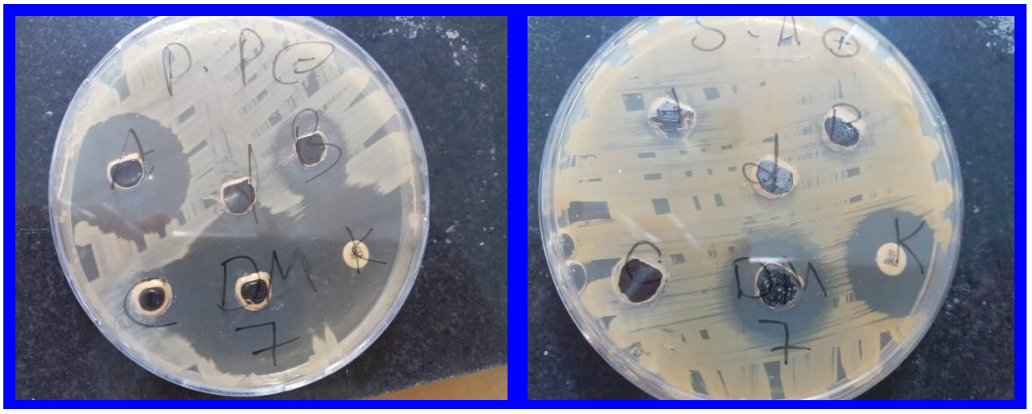


Figure 10: Compound DM7 inhibits the growth of bacteria Pseudomonas putida and Staph aureus

Conclusions

Physical and spectroscopic measurements confirmed the accuracy and validity of the prepared compounds. Therefore, the methods used in the preparation were good, successful and low cost. Through SEM analysis, the surface of the prepared compounds appeared as if they were rocky layers interspersed with deep trenches. The values of the precise analysis of the elements for the prepared compounds were identical or close to the calculated percentage. The vehicles were shown to have good electrical conductivity. The prepared compounds also showed good efficacy against the bacteria used in the study.

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