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Synthesis, Characterization of Chitosan para- hydroxyl Benzaldehyde Schiff Base Linked Maleic Anhydride and the Evaluation of Its Antimicrobial Activities

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Abstract:

Current research included preparation, characterization of some new chitosan- hydroxy benzaldehyde-Schiff bases with maleic anhydride. The present study aimed to the synthesis and characterization of novel chitosan Schiff base compounds using para- hydroxy benzaldeh and maleic anhydride. The derivative of the schiff-chitosan base, which is associated with different drugs, has been replaced with different amino and hydroxy drugs. The derivative is characterized by different analytical techniques. The results of FT-IR studies clearly indicate construction of the chief amine group in chitosan and the emergence of new bands that correspond to the association of maleic anhydride with the chitosan base. TGA, ^{1}H-NMR, biological studies acquired two types of bacteria Gram +ve *(Bacillus, Staphylococcus aureus)* and two bacteria Gram -ve *(Escherichia coli, Pseudomonas aeruginosa)* and yeast like fungi *(Candida albicans).*

Keywords: Antimicrobial, Chitosan derivatives, maleic anhydride**,** Schiff base, Polymerization**.**

Introduction:

Chitosan natural biopolymer can be considered as an abundant second natural polymer besides cellulose [1]. Polymer science exploits various strategies[2] to design novel polymer-based hydrogels and drug delivery systems and genes and scaffolds for [3] tissue engineering, toxic substances and mineral chelation. Chemical modification of chitosan is a popular protocol for obtaining new chitosan derivatives with biofunctional properties, so that their applications can be expanded [4]. Once the chitin deacetylation point reaches about 50% (depending on the source of the polymer), it dissolves in an aqueous acidic medium called chitosan.

Chitosan is at ease to work with chitin because of the proton amino groups in dilute acid solutions, particularly acetic acid, which leads to solubility[5]. Chitosan has high, biodegradation biocompatibility, and antifungal movement due to chemical modification of chitosan is usually done in large quantities, randomly reacting with its subunits with unusual biological activity and physicochemical properties that have been functional for drugs and food[6]. Chitosan vinyl monomer grafting is one way to obtain the chemical modification of this amino polysaccharide. The Schiff base containing imine groups can be prepared by the interaction between the active carbonyl groups and the amino groups. Acylation, removal, carboxymethyl, sulfur, butyrate and p-chitosan formation were achieved by standard biological production techniques[7]. A very important class of Schiff bases is composed of compounds derived from aromatic aldehydes, much work has been done on the Schiff bases based on chitosan and their complexes. Many researchers investigated the antioxidant activity of five Schiff bases of chitosan and carboxymethyl CS which were related to the concentrations of active hydroxyl and amino groups in the molecular chains[8].

While maleic anhydride is not a normal phenyl monomer, it has been reported to polymerize in water in the presence of poly (N-phenylpyrrolidinone) coupled potassium persulfate [9]. In line with the high reactivity of the amino groups, they must be threatened with extinction to induce the functional reaction that takes place across the

hydroxyl groups. Several methods are envisaged, but to date the most common is the N-phthaloylation of chitosan [10-12]. In this work, we synthesize a new derivative of the CS Schiff base by inoculating maleic anhydride as a spacer using open-loop polymerization.

Material and Methods:

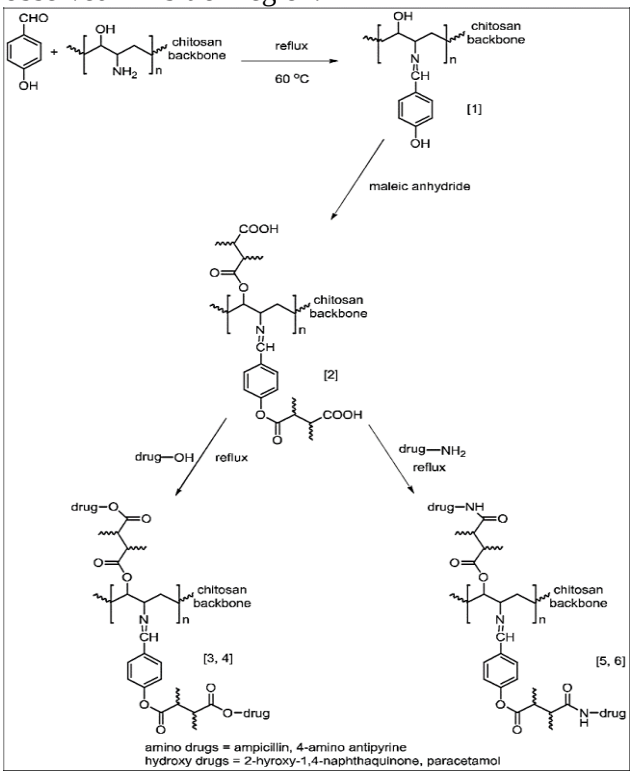
Chitosan was supplied from Sinopharm Chemical Reagent Co., Ltd, China, *p*-hydroxy benzaldehyde was obtained commercially from Aldrich (UK), Maleic anhydride and other solvents were provided from Chemicals (China) and they were distilled before use. FTIR spectra were recorded in the spectral range (500-4000) cm^{-1} using potassium bromide disks on Shimadzu FTIR-8400 infrared spectrometer. Bruker instrument (400MHz) was applied to measure ^{1}H-NMR spectra using deuterated dimethyl sulfoxide as solvent and Tetra methyl silane as internal standard reference. Differential scanning calorimetric (DSC) and thermal gravimetric analysis (TGA) were performed in Geological Survey and Mining, Bagdad, Iraq. The antimicrobial examination was checked in the Biology Department, College of women, University of Baghdad

Synthesis of Chitosan Schiff Bases Substituted with Different Drugs

Chitosan 2g. was dissolved in acetic acid about 15ml. in conc. 0.2N and mixed with stirrer at room temperature for 30min. until complete dissolving and the appearance of gelatin solution viscous (A) then *p*-hydroxy benzaladehyde was combined to the mixture. The combination was moved and heated under water bath at 60°C for 6hrs. Ethanol was used to wash off the mixture then it was dried to room temperature (B). Maleic anhydride 3g. was dissolved in acetone20ml. and then added to the 4.5g. of (B) product. After dissolving in 40 ml of acetone the mixture was refluxed about 6 hrs with stirring with 60^{o}C. The mixture was washed with ethanol absolute and dried . The product (B) was dissolved in ethanol absolute 2drops of thionylchloride and it was heated about 10min. and then mixed with 1gof ampicillin dissolved in 5ml. of absolute ethanol and refluxed about 4hrs at 60^{o}C. The same procedure was used to prepare other derivatives of amino and hydroxy drugs.

Antimicrobial Activity

The tested compounds [1-6] have been prepared at 100 mg/ml concentrations by using dimethyl sulfoxide (DMSO) for solvent. Agar diffusion method has been used for determining antimicrobial activity. The culture medium has been inoculated with one of the bacteria or fungus that is suspended in nutrient broth. Wells of six mm diameter have been perforated in agar with fresh bacteria or fungi separately and filled with 100 µl of each concentration. For control, DMSO is used. The incubation is performed at 37°C for one day. Solvent controls have been maintained and growth areas of inhibition have been observed. Antimicrobial activity has been assessed by measuring the diameter of the observed inhibition region.



Scheme 1. Synthetic pathways for newly prepared derivatives (1-6) are presented

Results and Discussion:

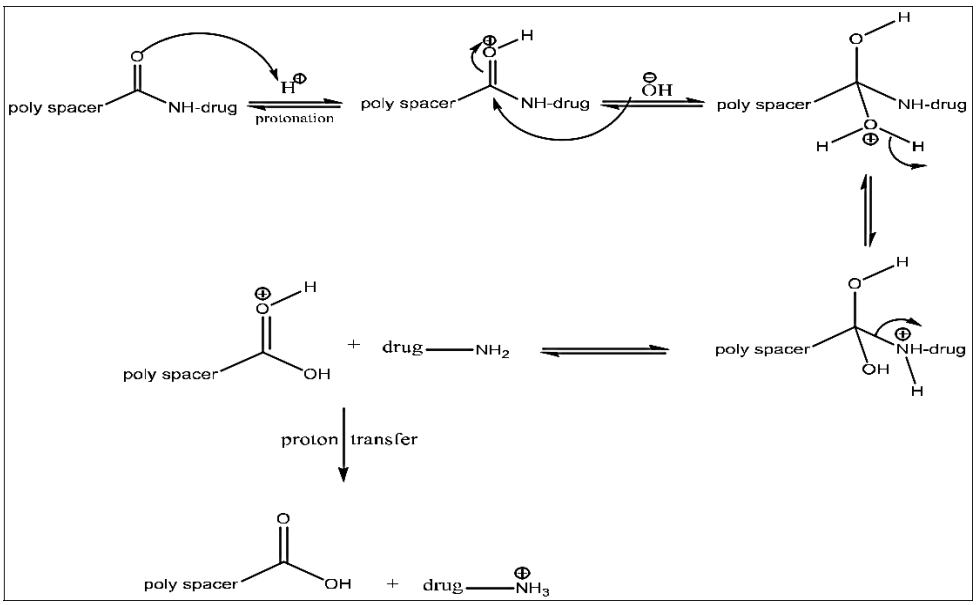
Infrared (IR) spectroscopy is based on the absorption of infrared radiation in chemical bonds. The bond is related to permanent dipole moment change (such as stretching and bending). FTIR is often used as a useful tool in identifying specific functional groups or chemical bonds present in a substance. Having a Peaking at a specific wavelength indicates the presence of a specific chemical bond. FTIR Spectra for all prepared derivatives showed the characteristic peaks as shown below.

A detailed FT-IR spectral representation of a chitosan / para- hydroxy benzaldehyde Schiff base is shown in Fig. 1. Absorption peak was observed at 3591 cm^{-1} that corresponds to the intermolecular hydrogen-bound hydrogen stretching, and NH in secondary amides. The peak obtained at 2883.20 cm^{-1} and 1600cm^{-1} confirms the presence of homozygous CH. It extends in the methylene group

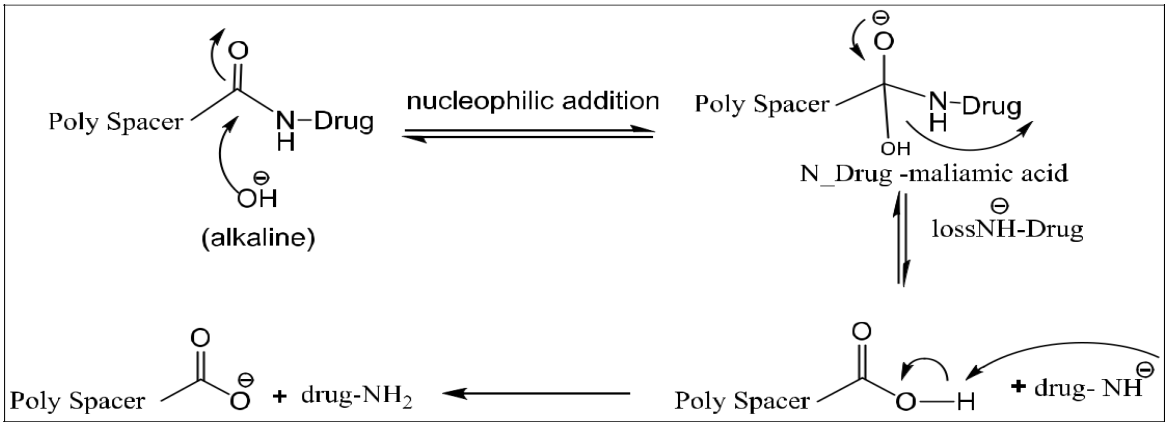
and C = O and extends in the amides (amide-I domain) respectively. Specific absorption ranges were obtained at 1540.71 cm^{-1}, corresponds to the curvature of NH in the secondary amides (amide domain II), and in 1461.55, 896.16 cm^{-1} in-plane curvature is visible, C-H curvature is symmetrical in CH3 at 1151.29 cm^{-1}, peak at 1053.45 cm^{-1} corresponds to the C-O-C joint and 1245.98 cm^{-1}, the C-O span and at 779.15 cm^{-1} C-H the bend is seen straight. FT-IR spectra of Schiff's base of chitosan / para- hydroxy benzaldehyde are represented in Fig. 2. The observed absorption peak a 3450 cm^{-1} corresponds to the OH-stretch between hydrogen-bound molecules, and the NH-expansion in the secondary Amides. The peaks obtained at 2922.79 cm^{-1} and 1605 cm^{-1} confirm the presence of an aliphatic CH stretch in the methylene group and C = O and expanded in the amides (amide-I range) respectively are represented in Figs. 3,4. They were specific absorption ranges.

What was obtained at 1587.76 cm^{-1} corresponds to the curvature of NH in the secondary amides (amide band II), and at 1457.81, 864.5 cm^{-1} OH flexion at visual level, symmetric C-H flexion in CH_3 at 1151 cm^{-1}, height at 1017.38 cm^{-1} corresponds to the C-O-C bond and 1274.78 cm^{-1}, the C-O stretch and at 781.15 cm^{-1} C-H bending is observed are represented in Fig .5.

Therefore, the FTIR results clearly show the formed interaction between the chitosan matrix and aldehydes. The formation of new imine bonds was confirmed by the apex in the range of 1627 and 1645 cm-1 for both Mixtures. Also, variable peaks were observed in the mixtures compared to FTIR pure chitosan Emphasizing the formation of Schiff bases from chitosan[13-15].



Scheme 2. Hydrolysis of polymHydrolysis of polymer drugs in acidic



Scheme 3. Hydrolysis of polymHydrolysis of polymer drugs in basic

Synthesis of new Schiff bases of chitosan polymers and study drug release in different medium is the main aim of the research.

Mechanism reaction included amine group in chitosan attacks the carbon carbonyl group of aldehyde to form Schiff bases in scheme 1. Then the products CS reacts with maleic anhydride to form copolymer ofCS –CO Maliamid. Schiff bases compounds have been characterized by (FT-IR) spectra. These spectra showed disappearance of bands due to NH_2 symmetric and asymmetric and appearance of bands due to $\upsilon_{C=N}$ group in the spectral range[16-17] 1600-1622cm^{-1} Scheme 2

Hydrolysis of polymer drugs in acidic Scheme3Hydrolysis of polymer drugs in basic. All information of Fourier transform infrared spectral data of compounds 5 are listed in Tab.1.

Table 1. FT-IRspectral data of synthesized compounds [1-5] [18-21]

Comp. No	υ_{C-H} Haromatic	$\upsilon_{C=N}$	$\upsilon_{C=C}$	υ_{C-N}	Others bands
1	3100	1600	1549	1444	OH-3591
2	3098	1605	1550	1450	OH-acid3450
3	3100	1610	1560	1478	
4	3100	1622	1549	1450	
5	3100	1610-1615	1550	1450	

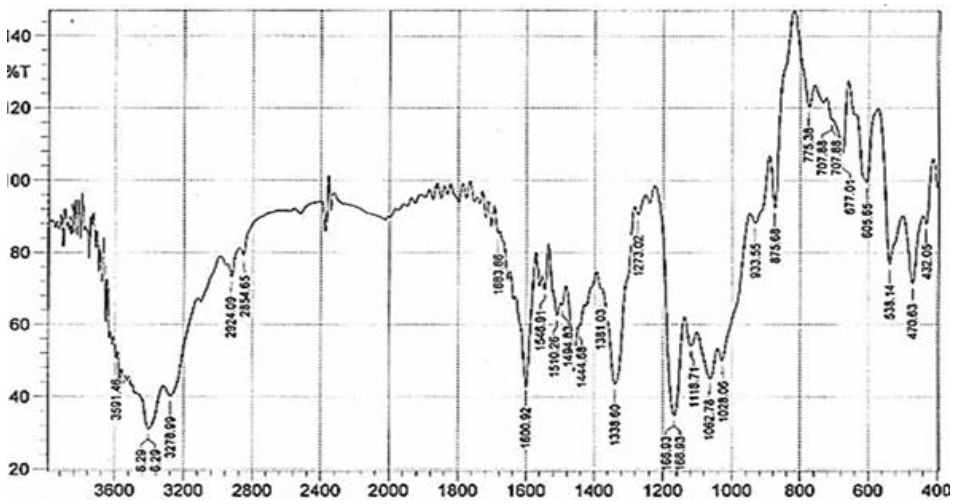


Figure 1. FTIR spectrum for compound C1

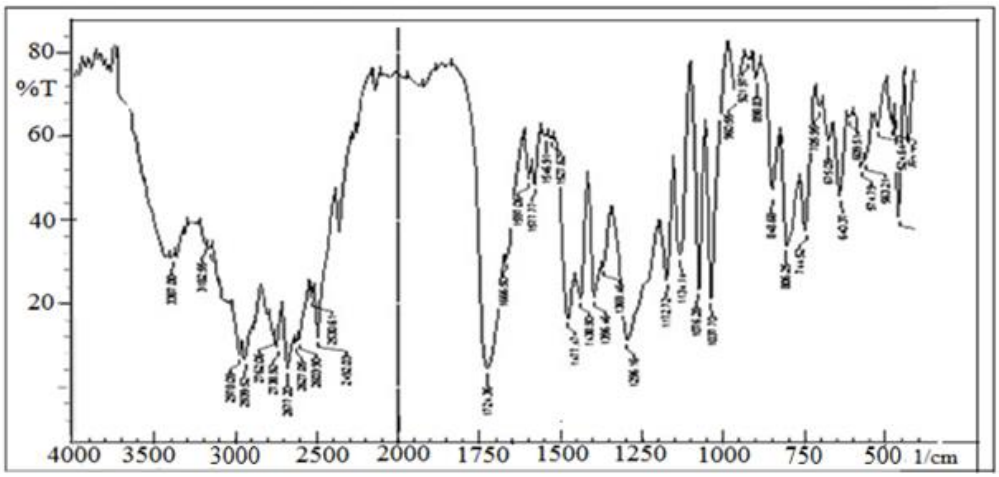


Figure 2. FTIR spectrum for compound C2

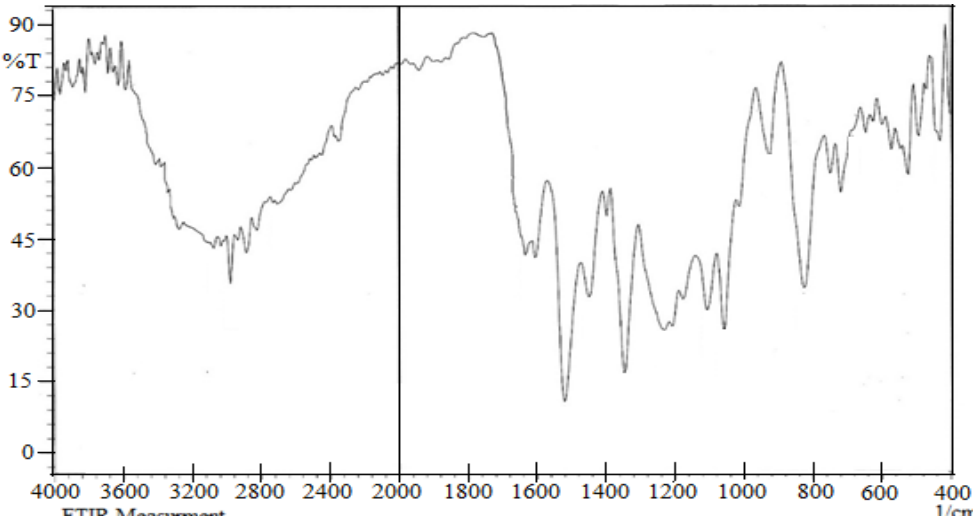


Figure 3. FTIR spectrum for compound C3

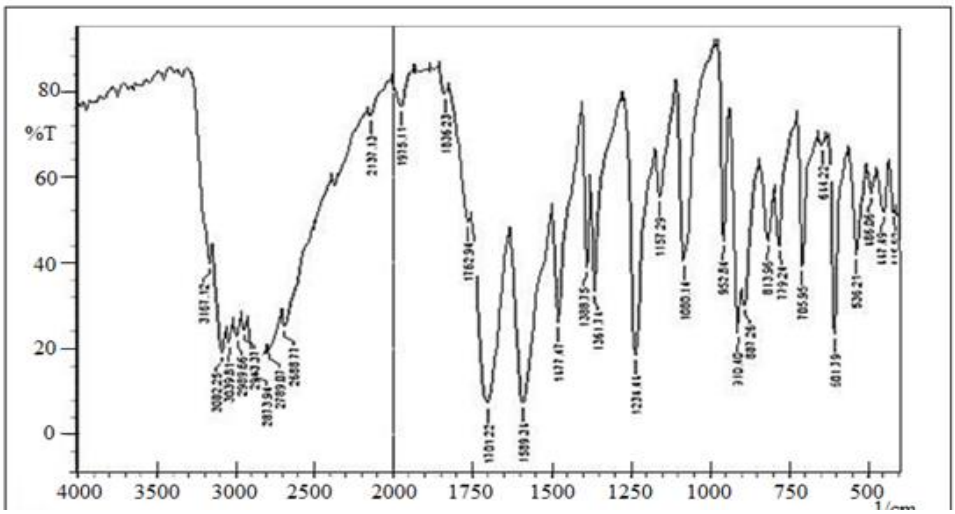


Figure 4. FTIR spectrum for compound C4

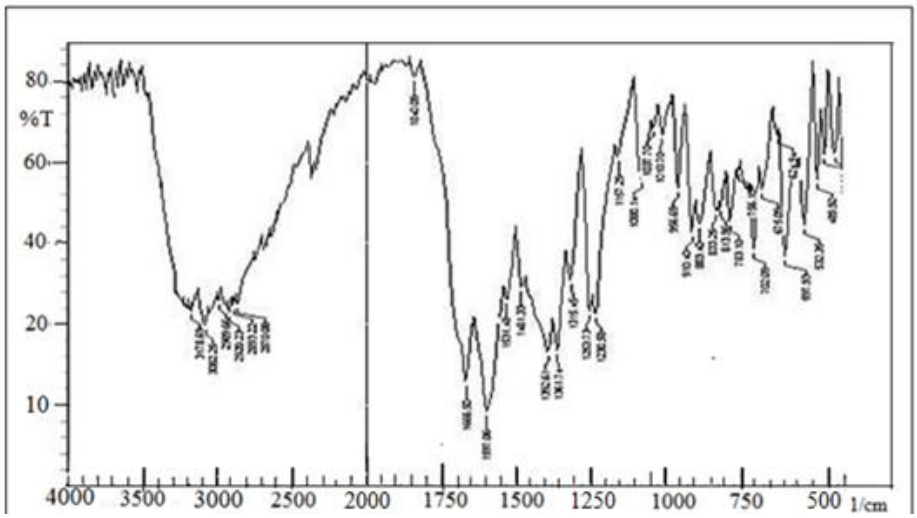


Figure 5. FTIR spectrum for compound C5

^{1}H-NMR spectrum of chitosan derivatives Figs. 6-10 respectively shows the important chemical characteristics of shifts (DMSO-d_6, ppm) as listed in Tab. 2.It displayed signals attributed for protons of (CH=N) azo methane, (CH_2) methylene, (CH) aliphatic, (CH) aromatic in all compounds besides appearances of some characteristic signals due to protons of (-OH) alcoholic[18], protons of (-OH) phenolic in compound1 protons of (-OH) carboxylic in compound 2and finally protons of (-NH) amide in compounds 4,5 respectively[19-21].

Table 2. ^{1}H-NMR spectral data (δppm) of synthesized compounds [1-5].

Comp. No.	^{1}H-NMR parameters (δppm)
1	2.95-3.04 (t, 6H, CH_2 methylene), 3.34-3.37 (t, 2H, CH), 4.65 (s, 1H, OH alcoholic), 6.61-7.67 (m, 4H, Ar-H), 7.98 (s, 1H, CH=N), 9.44 (s, 1H, OH phenolic).
2	2.87-3.11 (t, 6H, CH_2 methylene). 3.50-3.69 (t, 2H, CH), 6.63-7.80 (m, 4H, Ar-H), 8.18 (s, 1H, CH=N), 11.45 (s, 2H, OH carboxylic).
3	2.90-3.20 (t, 6H, CH_2 methylene), 3.44-3.74 (t, 2H, CH), 6.78-7.23 (m, 4H, Ar-H), 8.23 (s, 1H, CH=N).
4	2.86-3.22 (t, 6H, CH_2 methylene), 3.59-3.69 (t, 2H, CH), 6.57-7.25 (m, 4H, Ar-H), 8.55 (s, 1H, CH=N).
5	2.91-3.25 (t, 6H, CH_2 methylene), 3.73-3.83 (t, 2H, CH), 6.70-7.77 (m, 4H, Ar-H), 8.23 (s, 1H, CH=N), 9.14 (s, 2H, NH).

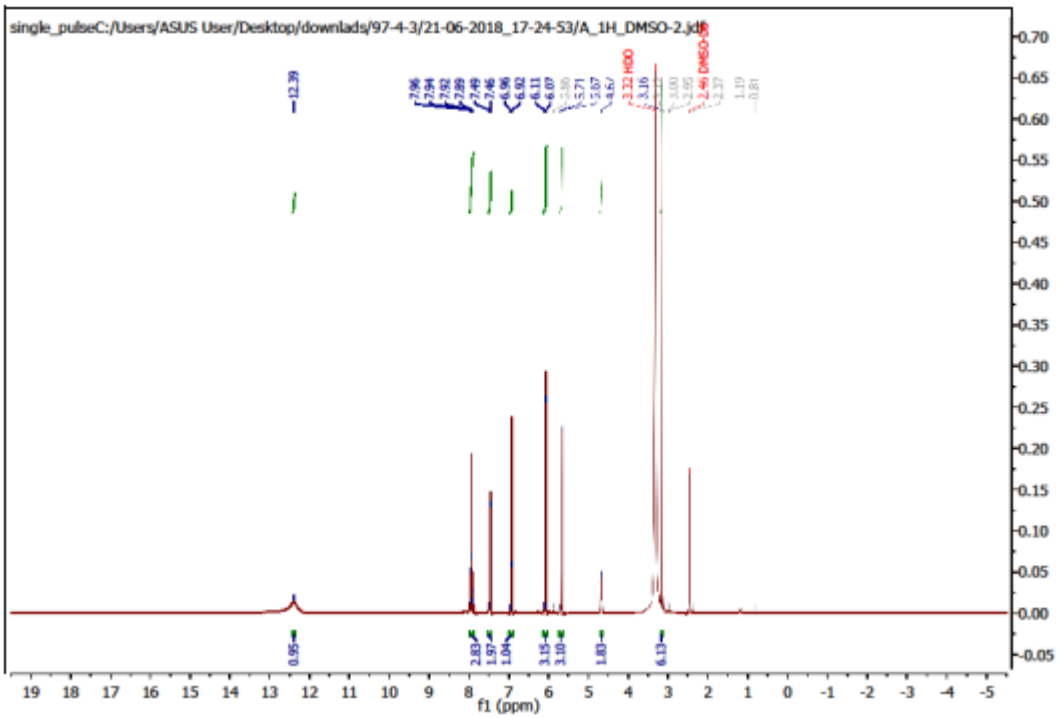


Figure 6. H-NMR spectrum for compound (C1)

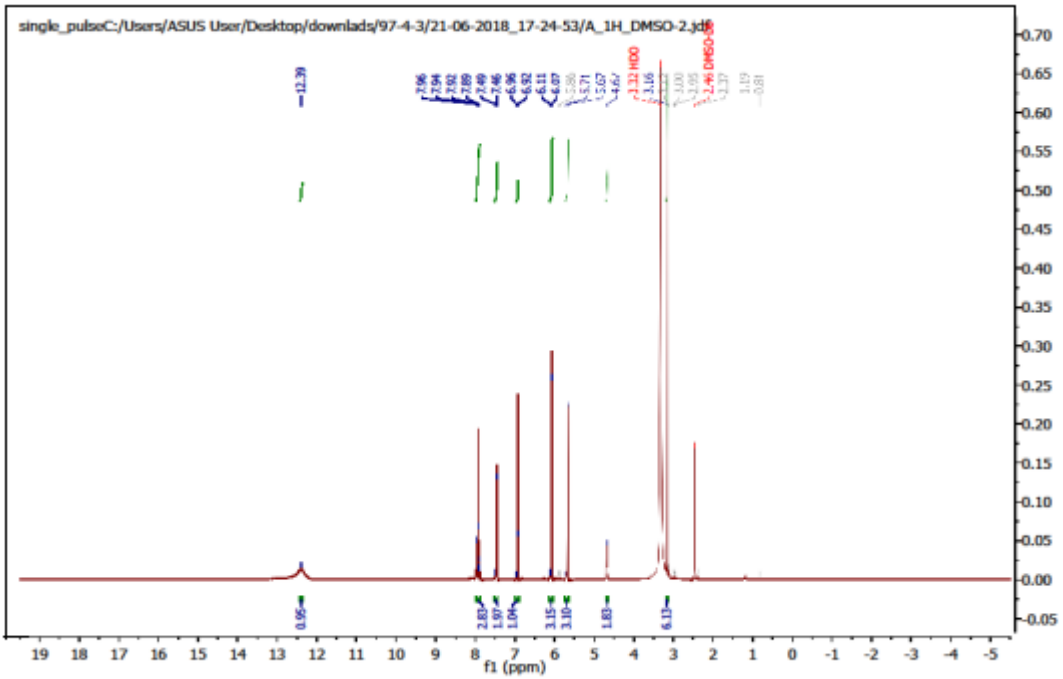


Figure 7. H-NMR spectrum for compound (C2)

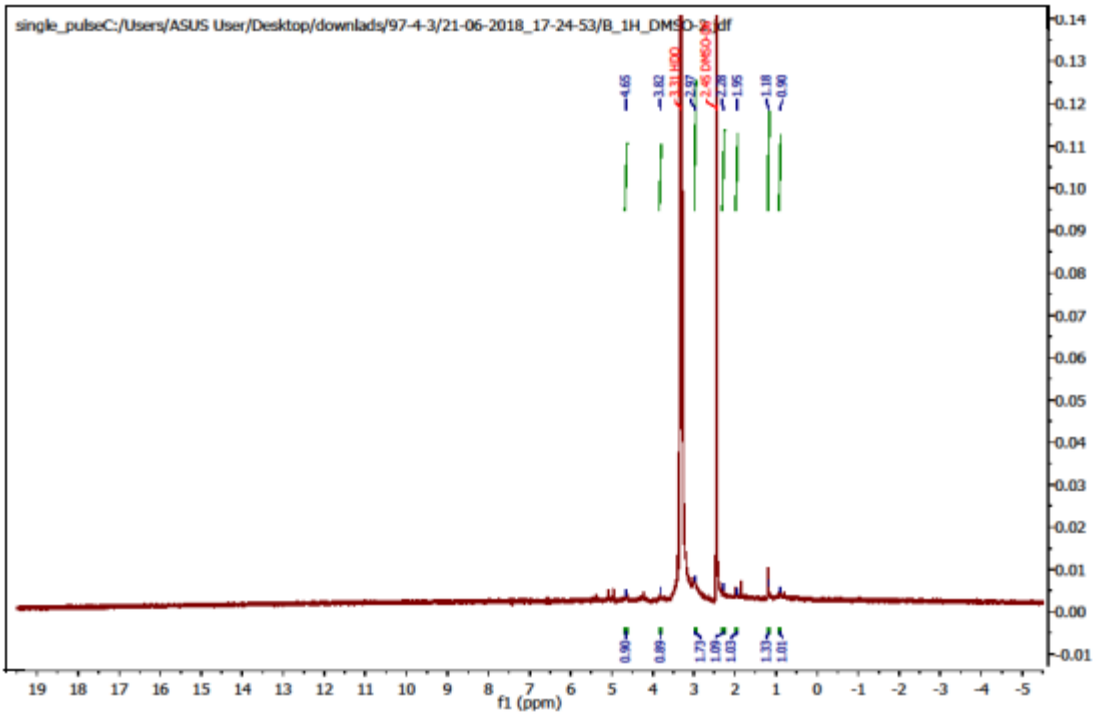


Figure 8. H-NMR spectrum for compound (C3)

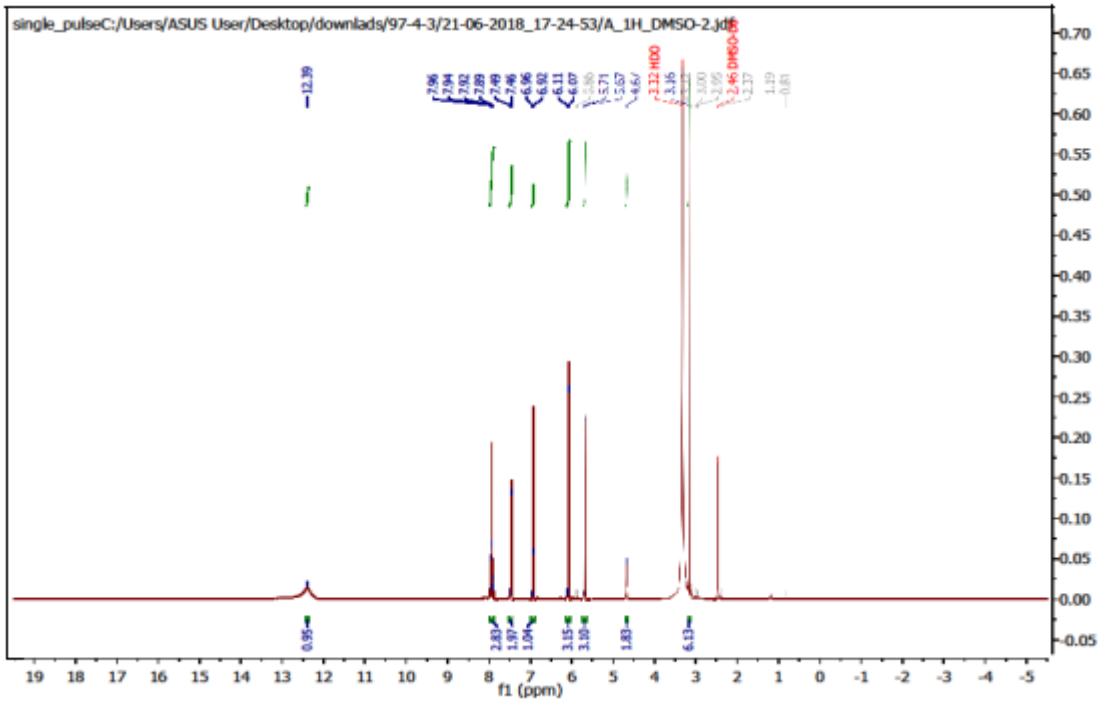


Figure 9. H-NMR spectrum for compound (C4)

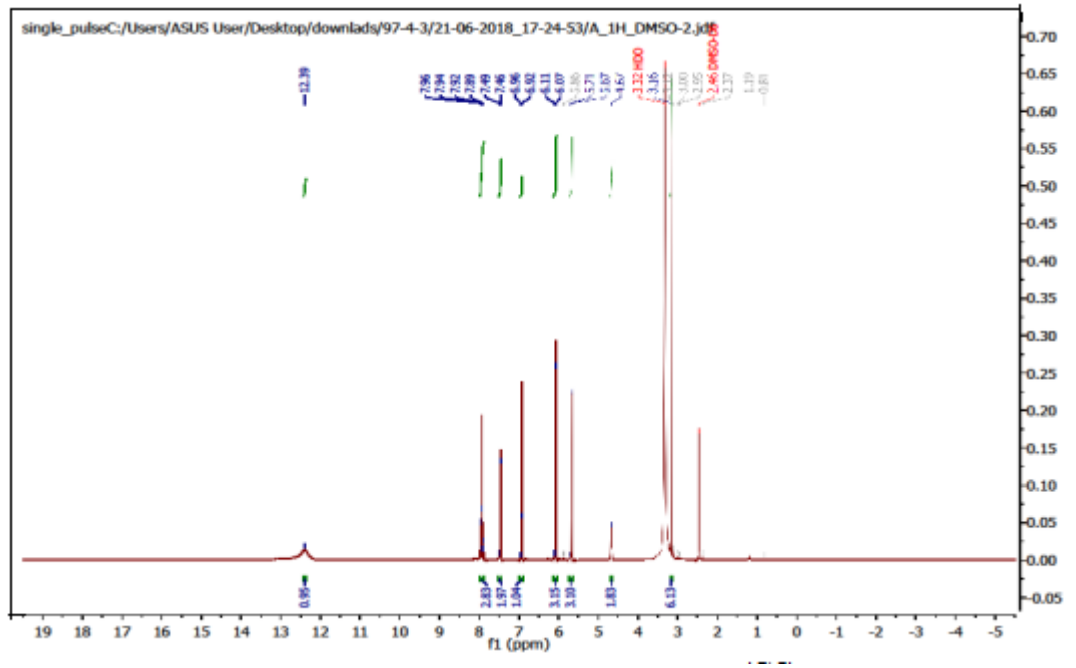


Figure 10. H-NMR spectrum for compound (C5)

The dynamic oxidation properties of the synthesized polymers have been characterized by thermal analysis by difference scanning calorimetric (DSC) and thermo gravimetric analysis (TGA). In the current research 10-20mg was possessed from the synthesized polymers under a controlled temperature rate of 10ºC/minusing inactive atmosphere (nitrogen gas 50ml/min.Thus the temperature thermo grams versus lose weight were noted and analyzed. Consequently the thermal stability of the synthesized derivatives was tested using thermo gravimetric technique by scaled the changing of sample weight at a controlled temperature rate. The weight changing was checked as a function of temperature which provided valuable information on thermal stability of the synthesized compounds. Thermo gravimetric analysis is employed. The samples are subjected to

tested samples weight loss and thermal decomposition for some prepared polymers resulting in Figs. 11, and 12 respectively. The dissociation of active groups linking oxygen with elementary droplet can be attributed to polymer degradation[22].

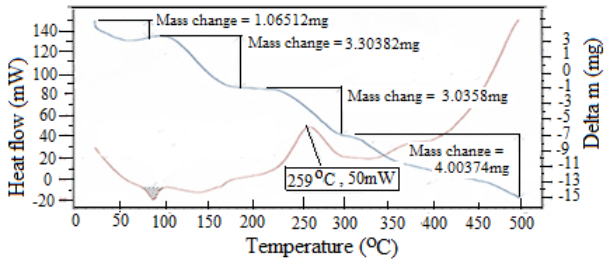


Figure 11. (DSC) and (TGA) analysis for compound (2)

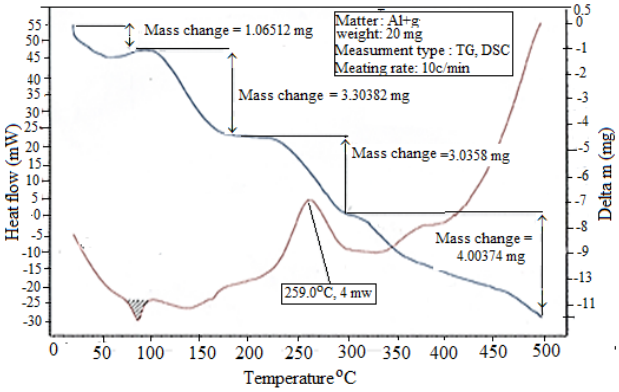


Figure 12. (DSC) and (TGA) analysis for compound (5)

The Antimicrobial Activity:

The inhibition zone of the newly synthesized polymers of chitosan derivatives attached with amino and hydroxy drugs 1-5 were observed and measured. The biological activates of prepared compounds were tested on two types of negative bacteria dye gram (*Escherichia coli EA*, *Pseudomonas aeruginosa PA*) beside two types of positive bacteria dye gram (*Staphylococcus Aureus SA*, *Bacillus subtilis BS*) and against yeast likes fungi (*candida albicans CA*) fungi using ager well diffusion method. The results of this study are summarized in Tab. 3.

Table 3. The effectiveness of bacteria against the prepared compounds [1-5].

Comp. No.	**G (+ve) Inhibition area diameter (mm.)**		**G (+ve) Inhibition area diameter (mm.)**		***Fungi* Inhibition area diameter (mm.)**
1	12	Nil	10	8	Nil
2	14	Nil	12	10	12
3	16	10	15	14	20
4	14	18	17	15	24
5	18	12	17	20	10
Control (DMSO)	0	0	0	0	0

The data given in Tab. 3 indicate most of the synthesized derivatives tested confirm varying grades of antibacterial activity against Gram-negative bacteria and Gram-positive bacteria strains, in similitude to the scale in each case which exposed that these derivatives are bioactive.

Control solution of dimethyl sulfoxide gives no inhibition zone in each case against both bacterial isolates. 4and 5 exhibited a high level of anti-bacterial effectiveness up against G+ positive bacteria (SA, BS) and against G- negative bacteria (EC, PA). Moreover compound 6 show highly activity against Gram-positive bacteria (SA). Furthermore some other synthesized compounds such as 3 and 4 have acceptable degree of activity against the tested pathogenic bacteria. As for the effectiveness of anti-fungus the mentioned compounds 3 and 4 showed highest efficiency.

The structure antimicrobial activity relationship (SAR) of the newly prepared polymers detect that the activity maximum was achieved in compounds 3, 4, and 5 having both amino and hydroxy drugs moieties attached with azomethane derivative of chitosan polymeric chain.

Conclusions:

New synthesized polymers were derived from chitosan attached with both amino and hydroxy drugs were synthesized and structurally characterized by using different spectroscopic techniques. The synthetic route produced schiff bases containing ampicillin, 4-amino antipyrine, 2-hyroxy-1,4-naphthaquinone and paracetamol portable on a linear polysaccharide chain of chitosan. The dynamic oxidation properties of the synthesized polymers have been characterized by thermal analysis by difference scanning calorimetric (DSC) and thermo gravimetric analysis (TGA) compounds was high thermal stability . The structure antimicrobial activity of the newly prepared polymers detect that the activity maximum was achieved in compounds 3, 4, and 5 having both amino and hydroxyl drugs moieties attached with azomethane derivative of chitosan polymeric chain. This compound have many application in medicine field because control release compared normal drugs.

Authors' declaration:

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are mine ours. Besides, the Figures and images, which are not mine ours, have been given the permission for re-publication attached with the manuscript.

- Ethical Clearance: The project was approved by the local ethical committee in University of Baghdad.

Authors' contributions statement:

S. A. A., S. H. A. contributed to the design and implementation of the research, S. A. A. prepared of new chitosan- hydroxy benzaldehyde-Schiff bases with maleic anhydride and performed the analysis of the results IR,^{1}H-NMR. S. H. A. prepared schiff-chitosan base associated with different drugs performed the analysis of the results TGA .Both of them drafted the manuscript and designed the figures. manufactured the samples and characterized them with spectroscopy, performed the characterization.. aided in interpreting the results and worked on the manuscript.

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تحضير، تشخيص قاعدة شف، بارا هيدروكسي بنزوالديهايد كيتوسان مرتبط مع الماليئيك اللامائي وتقييم فعاليتها الميكروبية

سناء عبد الصاحب عبد الكريم **سناء هتور عواد**

قسم الكيمياء, كلية العلوم للبنات, جامعة بغداد, بغداد, العراق

الخلاصة:

يتضمن البحث الحالي تحضير وتشخيص بعض قواعد شف لكيتوسان - هيدروكسي بنزالديهايد- مع أنهيدريد المالئيك. هدفت الدراسة الحالية إلى تخليق وتشخيص مركبات قواعد شف لكيتوسان الجديدة باستخدام بارا هيدروكسي بنزالده و أنهيدريد المالئيك. تم استبدال مشتقات قواعد شف لكيتوسان بالاتحاد مع أدوية مختلفة امينيه و هيدروكسيليه. المشتقات الناتجه تم تميزها بتقنيات تحليلية مختلفة. تشير نتائج التحليل بالأشعة تحت الحمراء بوضوح إلى تكوين مجموعة الأمين الرئيسية في الكيتوسان وظهور روابط جديدة تتوافق مع ارتباط أنهيدريد المالئيك بقاعدة شف لكيتوسان. بواسطة (التحليل النووي المغناطيسي للبرتون ^{1}H-NMR,)و(التحاليل الحرارية TGA)تم دراسة الفعالية البايلوجية للمركبات الناتجة بواسطه نوعين من(البكتريا الموجبة *Bacillus, Staphylococcus aureus*)و البكتريا السالبة*Escherichia coli, Pseudomonas aerugino*)ونوع واحد من بكتريا الخميرة مثل (الفطريات *Candida (albicans*.

الكلمات المفتاحية: مضاد للبكتريا, مشتقات الكيتوسان, انهيدريد المالئيك, قواعد شف ,البلمرة