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Synthesis and Characterization of Chelating Phenolic Polymers Containing Metoclopramide Hydrochloride Drug

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Abstract

This study in volved synthesis of the chelating phenolic polymers functionalized by Mannich base functional groups. The work included two parts ; part one syntheses of Mannich bases monomers formed by the condensation reaction of P-hydroxy benzaldehyde with different secondary amines and Primary amine (Metoclopramide hydrochloride) have been synthesized. Then part two included synthesis of phenolic chelating polymers containing Mannich bases by condensation Mannich bases which prepared in part one with P-hydroxy benzaldehyde and phenol. These chelating polymers were characterized through (FT-IR) and(^{1}H-NMR) spectroscopy so measured the thermal stability and study the biological activity of some of the synthesized compounds .

Keywords : Metoclopramide drug , chelating phenolic polymers, Mannich bases

1. Introduction

The importance of chelate resins in due to their high efficiency in extraction processes, their high selectivity towards some metal ions, As well as their ease of use for separation and the wide analytical applications that these resins enjoy. Chelated polymers are polymers that contain special functional groups that contain two or more electron donors such as (Oxygen, Nitrogen, Sulfur)[1]. One of the highly effective resins is phenol formaldehyde (P.F.) resin, which can be obtained from the reaction of phenol with formaldehyde. This resin has wide uses in the industrial field, especially the formation of plastics and resin adhesives. [2]. The characteristic of (P.F.) resin clued high mechanical; thermal and weather stability [3]. So, the lower processing_rate and required higher curing temperature compared to other thermosetting adhesives limit the application of (P.F.) resins for use their in imbibation and adhesives [4].

In this paper a new series of phenol formaldehyde, resin was prepared by reaction phenol and formaldehyde with Mannich bases, Mannich bases are famous compounds for along time, and interest in these compounds continues because of their effectiveness in pharmacological aspects and their industrial applications such as polymers used in paint and coating as well as their applications in various fields and includes organic compounds that contain the active group (CH_2N) [5]. They have been studied intensively mainly due to its application in organic synthesis particularly for preparing dyes, industrial , pharmaceutical and antimicrobial such as antibacterial [6], anticancer [7], anti-inflammatory[8] and anticonvulsant [9-10],so primary amine used to prepared Mannich bases is Metoclopromide hydrochloride. It is chemically – 4 – amino-5-choro-N-2(diethyl amino) ethyl – 2 – methoxy benzamide hydrochloride [11]. Is one of psychopharmacological

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agents, it is used as antiemetic in pharmaceutical preparations and it derivatives have used as anticancer [12], antibacterial [13], antifungal and antiviral[14-15].

2. Chemicals and Methods

In this work the chemicals used were sourced from ((Sigma, BDH, Merch, Aldrich ND Fluka)), so are used without from purification. SMP3 uses digital Stuart Scientific to record the Melting points apparatus and are uncorrected. (FT-IR) spectrum was registered in (SHIMADZU) (FT-IR-8400) Fourier transform infrared spectrophotometer in the ((4000-6000)) cm^{-1} spectral range internal reference measurements.so(^{1}H-NMR) spectra were recorded on Bruker ((500 MHz)) instrument using ((DMSO-d6)) and ((TMS)) which is internal reference measurement were made at chemistry department in Al albayt University , Jordan.

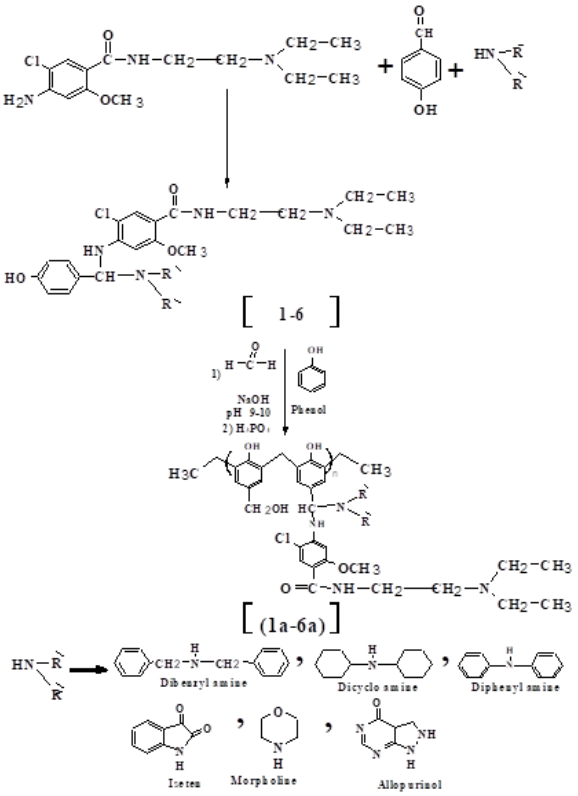
3. Method for the synthesis of Mannich bases [5]

In round bottom flask was placed solution of metoclopramide (0.002mol) in (10 ml) of DMF with (0.002 mol) of different second amines such as(Dibenzyl amine, Dicycl amine, Diphenyl amine, Iseten, Morphene and Allopurinol) and Formaldehyde (0.02 mol) . has been refluxed for (3 hr). Solvent used was evaporated then residue poured in ice water with stirring. The precipitate was recrystallized from DMSO after filtering. The physical properties for products (1- 6) in table (1).

4. General methods for the synthesis of Phenol-Formaldehyde [3]

The batch polymerization process was used to prepare phenol-formaldehyde resin with a molar ratio (1: 2: 2) of phenol and formaldehyde by adding 6% of the catalyst on a total origan.

Phenol was mixed in flask with formaldehyde and prepared Mannich bases in the presence of the catalyst. The heater is switched off when the temperature of the mixture rises to (70) ° C, and to complete the polymerization reaction, the mixture is reheated to 90 ° C to restore the resulting heat and reside in (93-95)ºC for 1 hr were synthesized with the same procedure. The physical properties of resins (1a- 6a) are listed in table (2).

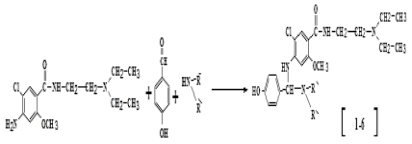


Scheme (1)

5. Result and Discussion

In this study comparison the synthesis of the chelating phenolic polymers functionalized by Mannich bases have been functional groups.

This work included four parts, part one: novel Mannich bases have been synthesized by reaction between Metoclopramide, parahydroxy benzaldehyde and different secondary amine (1-6) which evaluated them for antifungal activity.



It is nucleophilic addition reaction to the carbonyl group and includes all amines by means of acompound containing an active proton and carbonyl group in the presence of aprimary or secondary.The product structures of all the newly synthesized compounds were confirmed from during suitable spectral technique as in (^{1}H-NMR and FT-IR).

In FT-IR spectrum for compound (2.) figure (1) appear absorption band of (3348) cm^{-1} return to υ ((N-H)) the amide , other bands in (2980, 2800, 1631, 3398

and 1496) cm^{-1} which are return to υ (C-H) arom., υ (C-H) aliph., υ (C=O) and υ (O-H) of phenol and υ (CN) respectively. So, the FT-IR spectrum of compound (6) figure (2) showed absorption disappearance of υ (NH_2) for amine appearance of band at (3456 cm^{-1} due to υ (O-H), another bands appeared in((1585, 3221 cm^{-1}, 1458, 3120 and 2881-2061)) cm^{-1}which are return to υ (C= O), υ (N-H), υ (C-N), υ (C-H) aromatic and υ (C-H) aliphatic successively.

During the ^{1}H-NMR spectra, the signals of the competent prepared derivatives were verified on the basis of their chemical shifts, multiplication and pairing constant.

(^{1}H-NMR) spectrum of compound (4) figure (5) appear signals at phenyl proton δ(7.03-7.76) ppm. 1 H proton of (CONH) at δ(6.34) ppm, 3H protons of (O-CH_3) were at around δ(1.11) ppm. 1 H proton of (OH) at δ (9.78) ppm, 1H proton of (–NH–C) at δ (8.30) ppm and 4 H protons at (-CH_2-CH_2-) at δ (3.48-3.96) ppm, 5H protons of (N-CH_2-CH_3) at δ (2.86) ppm, Also, morphelin cyclic protons showed signals (6.59-6.97) ppm and (4.53-4.84) ppm belongs to (N-CH_2) and (O-CH_2) protons respectively.

So, The 1H-NMR spectrum of compounds(5) figure (6) showed a singlet beak at (0.99)ppm for the proton of methyl groups (CH3-O). The protons of the aromatic ring[16,17] are also observed at (6.62-7.79) ppm.δ (8.46) ppm return to (CONH), (9.75) due to (OH) phenolic group, (8.19) ppm return to (NH-C) and (3.90) due to 5H protons for (N-CH_2-CH_3). Also, appeared signals in δ (4.82) ppm belong to (4 H) protons of (-CH_2-CH_2-).

Part two

In this work involved phenol formaldehyde (PF) resin (Phenolic chelating polymers) was synthesized via batch polymerization with phenol, formaldehyde and Mannich bases which prepared in part one (1-6) , scheme (1).

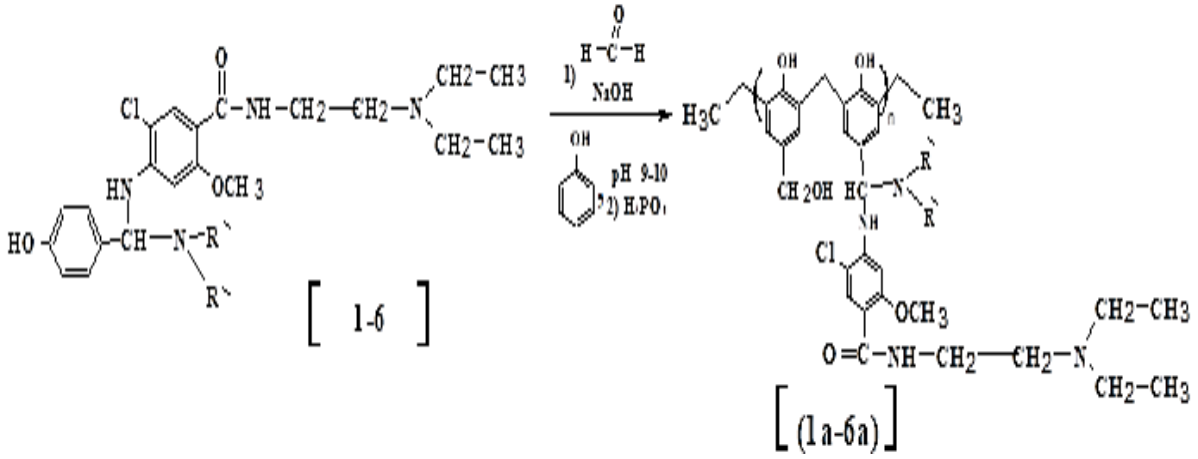
The condensation state also affects the structure of the resin, Since the aromatic phenol ring containing ortho and para position, has the ability to condense with formaldehyde, but the position is more related than the position ortho.

The existence of one para position and two ortho position in an aromatic ring generally could result to a phenol process of (phenol formaldehyde) resin synthesis. The catalysts can make more formaldehyde resin containing especially (ortho) hydroxyl methyl groups. So however, in thormaldehyde or methylol towards phenol (ortho) positions to excess the ratio ortho on para substituted positions bring about more reactive functional groups or more un reacted par apositions in the treatment stage, that may become shorter the treatment time and excess the cross-linking degree for cured (phenol formaldehyde) resin [1,4].

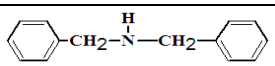
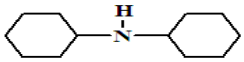
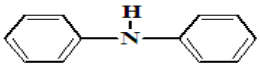
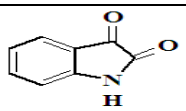
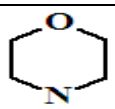
In general, the new derivatives for phenol formaldehyde resin was characterized by physical properties, spectroscopic data, tables (1), (2). The FT-IR spectrum of polymer (2a), Figure (3) shows bands in: [(3007),(2885), (1593), (3259), (3313) and (1481)] cm^{-1} back to υ (C-H) arom., υ (C-H) aliph., υ (C= C), stretching band for υ (N-H), υ (O-N) and υ (C-N). Also polymer (6a), Figure (4) shows bands at [(3097),(2912-2951), (1593), (3267), (3387) and (1477)] cm^{-1} due to υ (C-H) arom., υ (C-H) aliph., υ (C= C), υ (N-H), υ (O-H) and υ (C-N) successively.

While ^{1}H-NMR spectral data of polymer (5a), figure (7) showed signals in δ (6.42-7.53) ppm retun to arom. ring proton; δ (9.65) ppm, return to (OH) phenolic group, (8.48) ppm return to (-CONH), (1.22) ppm return to δ (O-CH_3), δ (3.75) ppm return to (5H) protons for (N-CH_2-CH_3). So appeared signals at δ (2.75) ppm belong to (-CH2-) proton and δ (4.67) ppm belong to (CH_2-OH) proton.

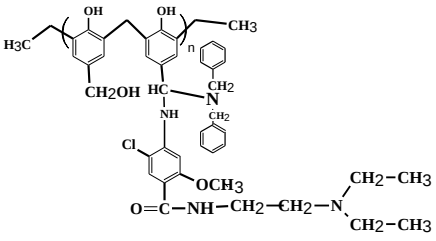
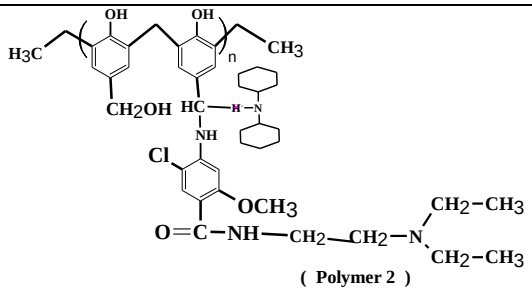
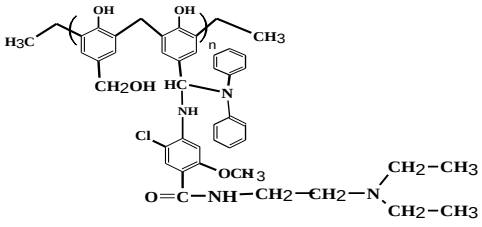
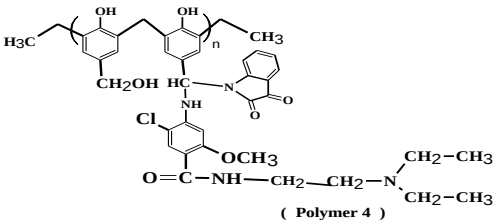
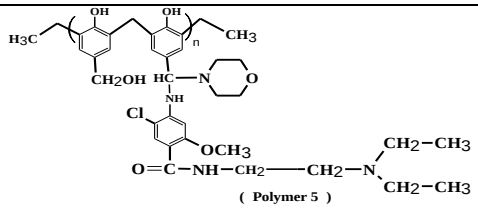
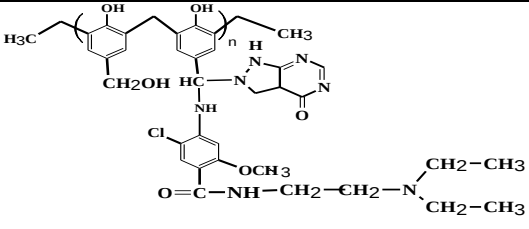
While, Part three: In this study, a thermal weighing technique was used to measure the thermal stability of phenol formaldehyde resins by using a programmed heating rate to measure the change in the sample weight. The converted weight can be measured as a function of the temperature taken from (phenol formaldehyde resin) by the programmed heating rates [(10.0 c^o / min)] by an inactive atmosphere [N2 gas 50 (ml / min)]. that gave worthy information for the thermal stability of phenol formaldehyde resins. So from TGA and DSc curves figures (8) to figure (13) showed the results of prepped polymer (1a-6a5) which indicated the high thermal resistance and appeared their step of weight loss temperature.



Table(1) show physical properties of prepared Mannich bases (1-6)

Comp. No.	Comp. structure	M. P. C°	Color	Yield%	Molecular formula	
1	 Dibenzyl amine	140-142	Yellow	63.72	$C_{14}H_{15}N$	197.22
2	 Dicyclo amine	132-134	Faint Yellow	43.63	$C_{12}H_{23}N$	181.31
3	 DiPhenylamine	240-243	Yellow	56.58	$C_{12}H_{11}N$	169.22
4	 Iseten	164-166	Brown	65	$C_8H_5NO_2$	147.13
5	 Morpholine	200-202	Orange	43.2	C_4H_9NO	87.12
6	 Allopurinol	160-162	Dark Orange	66	$C_5H_6N_4O$	138.12

Table(2) physical properties data of prepared resins (1a-6a)

Comp. No.	Compound structure	Color	Yield%
1a.	 (Polymer 1)	Dark orange	152
2a.	 (Polymer 2)	Pala orange	147.9
3a.	 (Polymer 3)	Brown	57.23
4a.	 (Polymer 4)	Reddish brown	40.06
5a.	 (Polymer 5)	Yellowish Brown	5.45
6a.	 (Polymer 6)	Dark red	8.25

Table(3) (FT-IR) spectrum for all product compounds

Com. No.	υ C-H arom. cm^{-1}	υ C-H aliph. cm^{-1}	υ C=O cm^{-1}	υ C=C cm^{-1}	υ N-H cm^{-1}	υ O-H cm^{-1}	υ C-N cm^{-1}	Others cm^{-1}
1.	3050	2943	–	1597	3205	3317	1496	--
2.	2980	2800	_	1631	3321	3398	1450	--
3.	3050	2951-2978	--	1600	3348	3456	1458	--
4.	3097	2947	--	1681	3178	3344	1462	--
5.	3120	2881-2981	--	1585	3221	3456	1458	--
6.	2974	2800	--	1597-1678	3224	3402-3344	1454	--
1a.	3059	2912	--	1589	3263	3471	1473	--
2a.	3007	2885	_	1593	3259	3313	1481	--
3a	3090	2887	--	1597	3250	3417	1477	--
4a.	3163	2935	--	1593	3236	3406	1477	--
5a.	3097	2912-2951	_	1593	3267	3387	1477	--
6a.	3024	2927	--	1612	3297	3394	1481	--

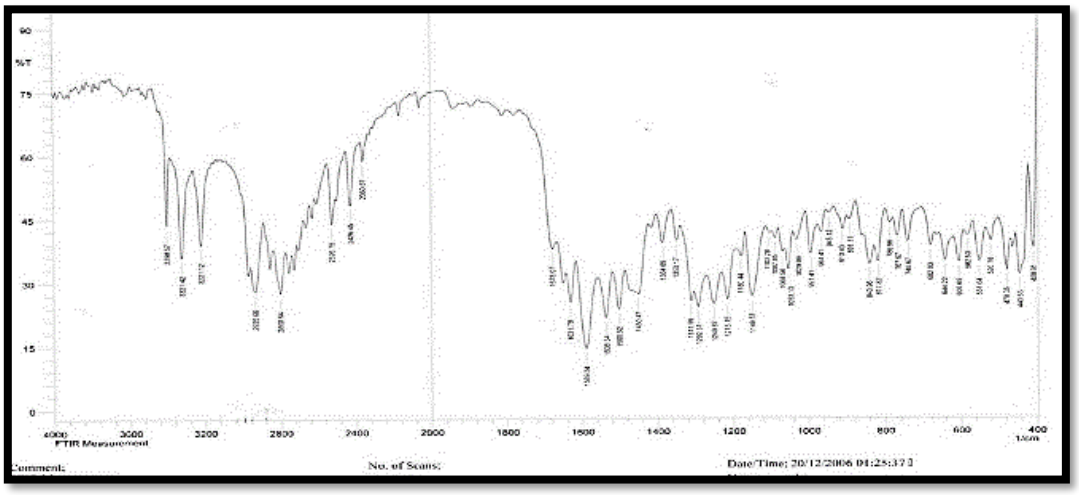


Fig. 1 :show(FT-IR) for prepared compound (2)

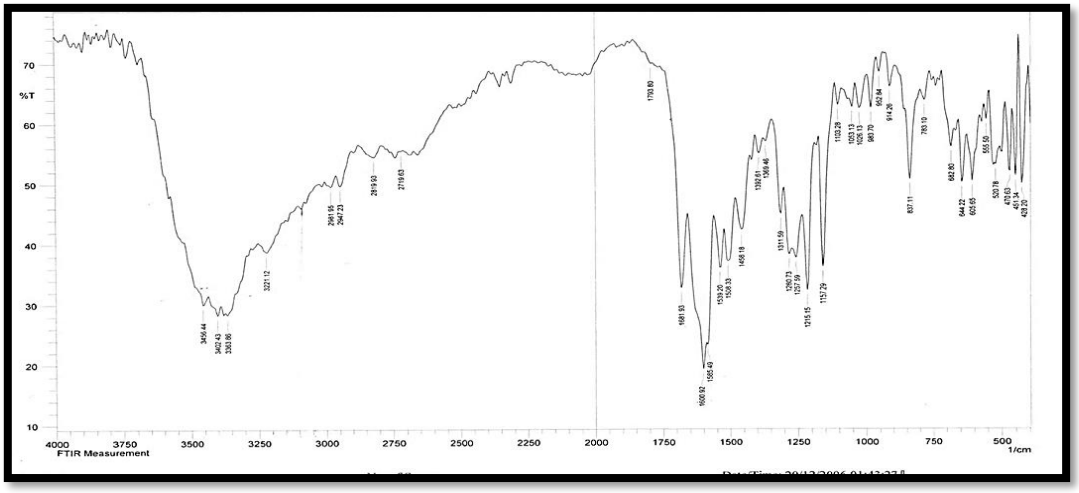


Fig. 2: Show(FT-IR) for prepared compound (6)

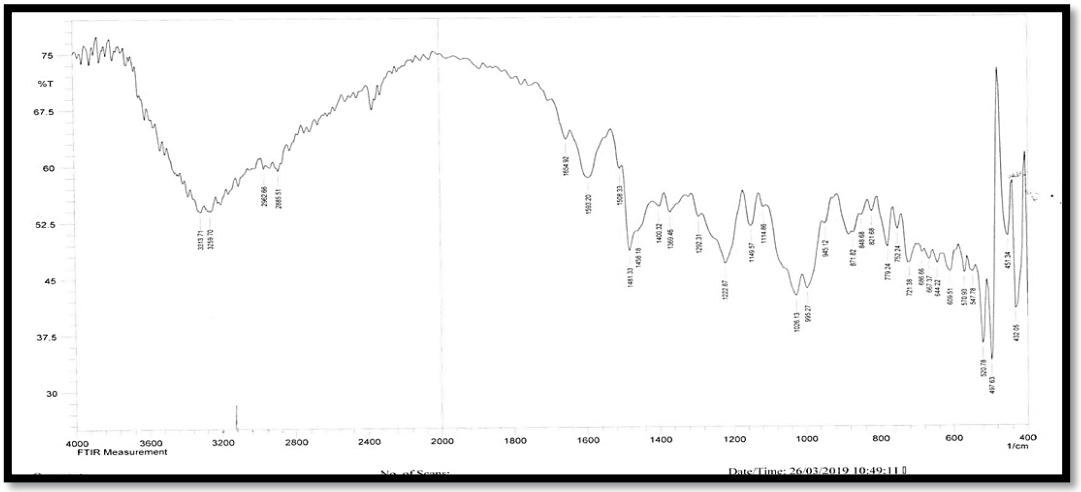


Fig. 3: Show (FT-IR) for prepared compound (2a)

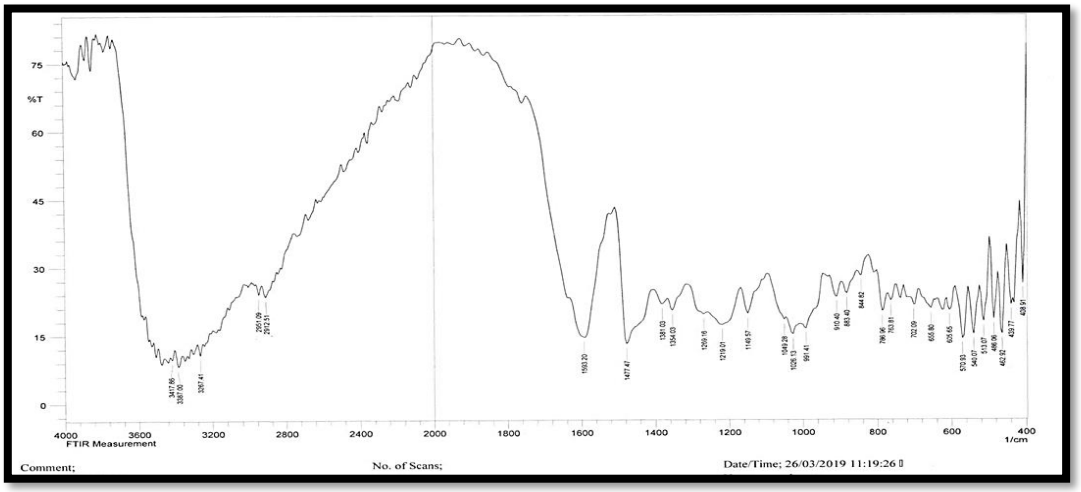


Fig. 4 : Show(FT-IR) for prepared compound (6a)

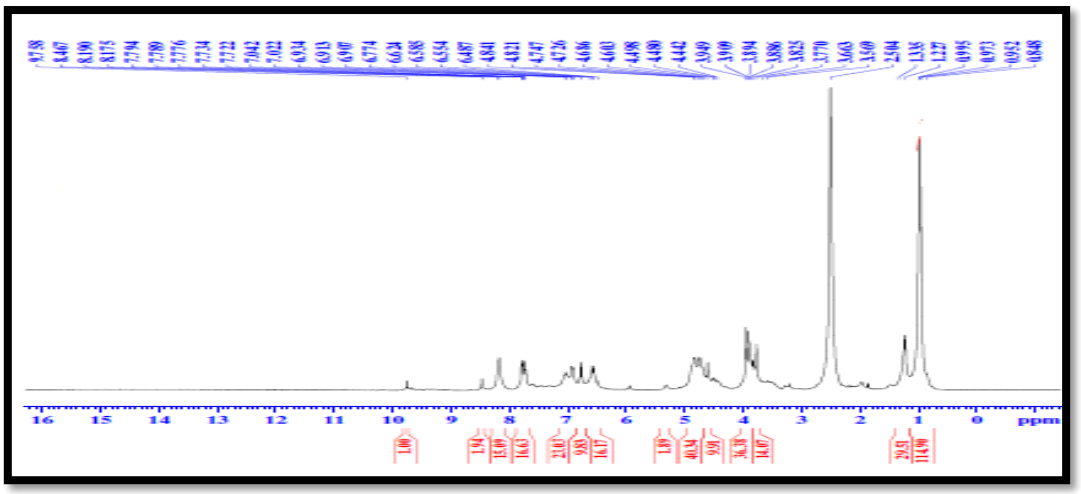


Fig. 5 :Show (^{1}H-NMR) spectral for prepared compound (4)

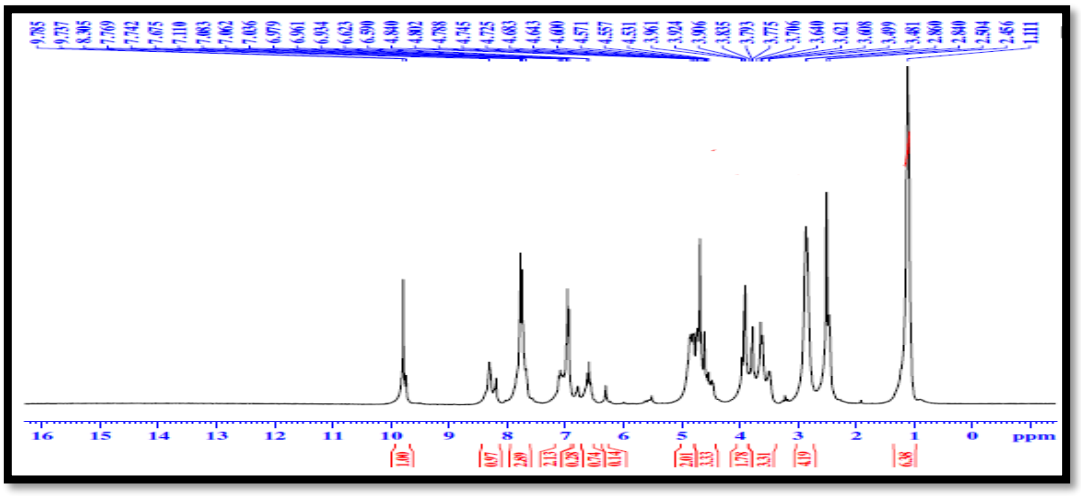


Fig. 6: Show(^{1}H-NMR) spectral for prepared compound (5)

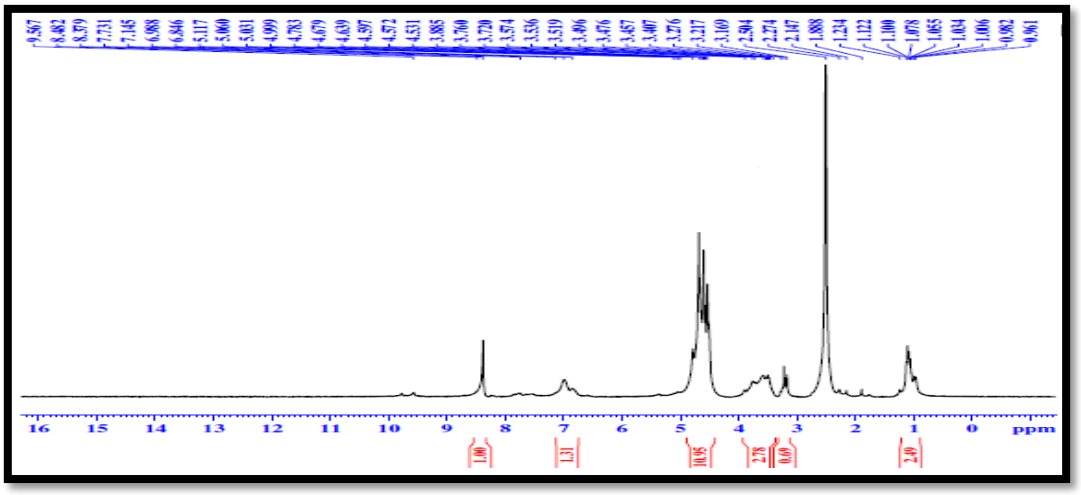


Fig. 7: Show (^{1}H-NMR) spectral for prepared compound (5a)

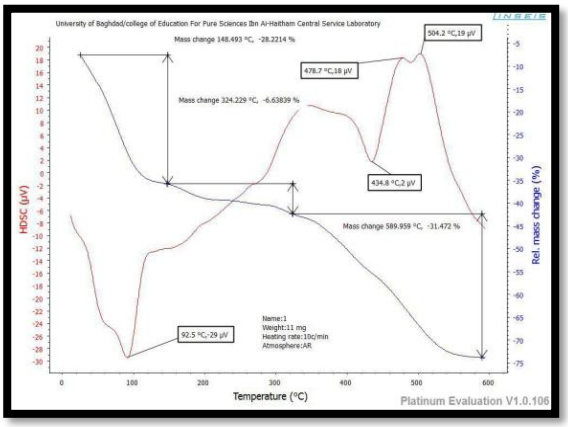


Fig. 8 :Show DSC , TGA analyses of prepared compound (1a)

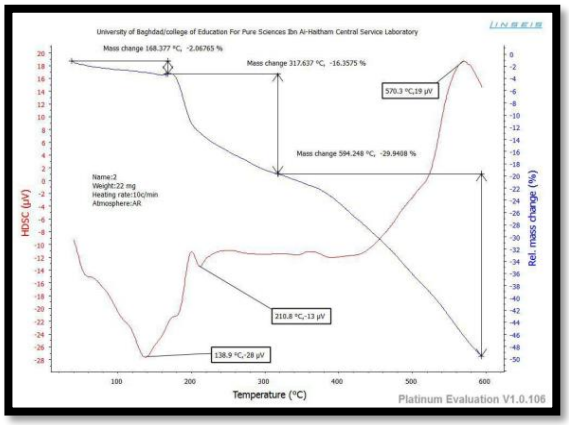


Fig. 9: Show DSC , TGA analyses of prepared compound (2a)

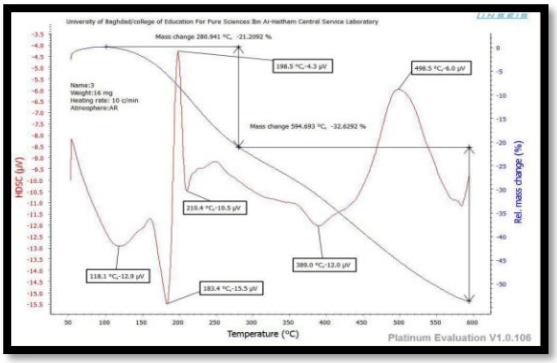


Fig. 10: Show DSC , TGA analyses of prepared compound (3a)

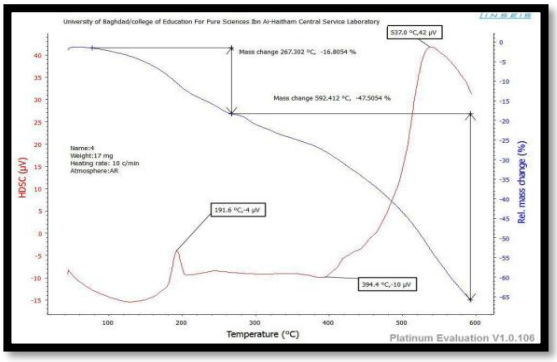


Fig. 11 : Show DSC , TGA analyses of prepared compound (4a)

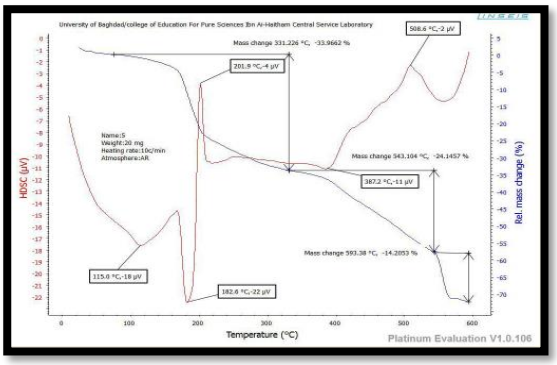


Fig. 12 : Show DSC , TGA analyses of prepared compound (5a)

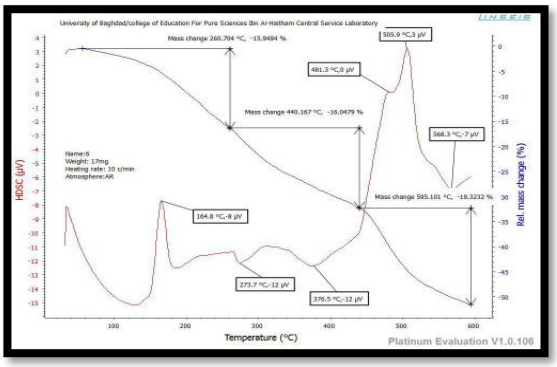


Fig. 13 : Show DSC , TGA analyses of prepared compound (6a)

6. Part four

While part four includes antibacterial activity. The preliminary study of the synthesized compounds to determine their biological effectiveness for future use as pharmaceuticals or drugs , The new compounds were evaluated for their antibacterial activities[18,19] against two types of bacteria gram positive, namely Staphylococcus aureus, Bacillus subtillus , Bacillus cereus, and against gram – negative bacteria namely, Pseudomonas aeruginosa, Klebsiella peneumoniae, Acintobacter baumannii as well as Candida albicans summarized in table (4) . two Gram-positive bacteria *(Staphelococcus aureus and Staphelococcusepidermidis),* two Gram-negative bacteria (*Escherichia coli* and *Proteus vulgaris*) at a concentration 10mg/disk.

DMSO was used as solvent for all compounds (Mannich bases) and as control. The table (4) showed the efficiency of synthesized compounds against certain species without others, different inhibition zones size against tested bacteria strains was observed, the result showed that synthesized compounds have high activity against gram positive and gram negative bacteria for compound (5) better than from all the compound which products or compound (5) exhibited excellent and highest activity against all kinds of bacteria as well as candida albicans and that due to the activity of Mannich bases compounds. Inhibition zones resulted from all tested compounds which shown in the table (4).

Table (4) Antimicrobial and antifungal inhibition zone (mm) of some of the synthesized compounds

Comp.	Inhibition zone (mm) at 10 mg/ml against						
	Gram positive			Gram negative			Fungi
	Staphylococcus aureus	Bacillus subtillus	Bacillus cereus	Pseudomonas aeruginosa	Klebsiella pneumoniae	Acinetobacter baumannii	Candida albicans
1.	20	17	16	20	18	30	18
2.	19	18	17	23	19	30	17
3.	20	20	20	19	17	27	22
4.	25	24	26	23	22	33	26
5.	29	25	27	28	27	33	31
6.	23	24	24	23	22	33	27

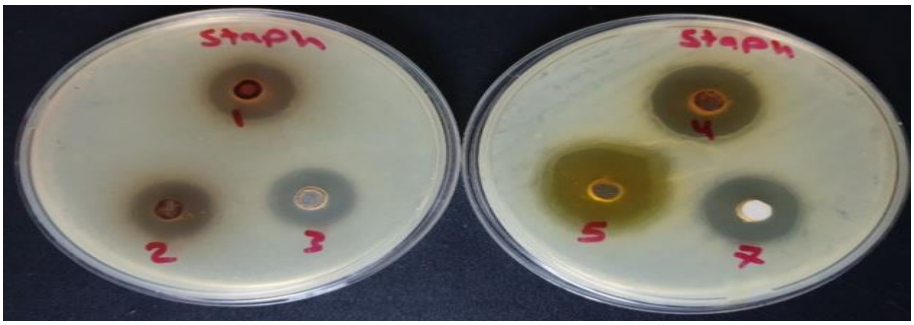


Fig. 14: Effect of comp. (1-6) in (Staphylococcus aureus)

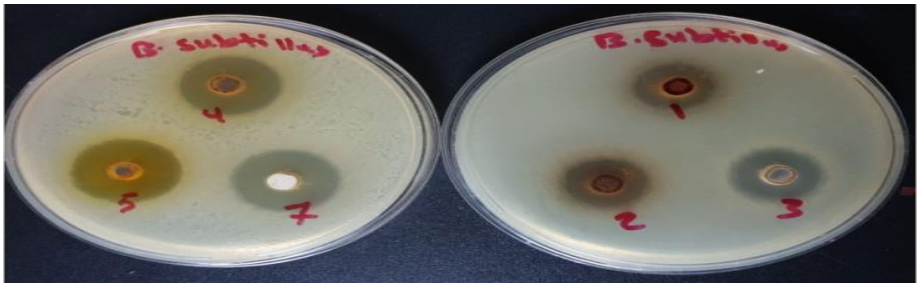


Fig. 15: Effect of comp. (1-6) in (Bacillus subtillus)

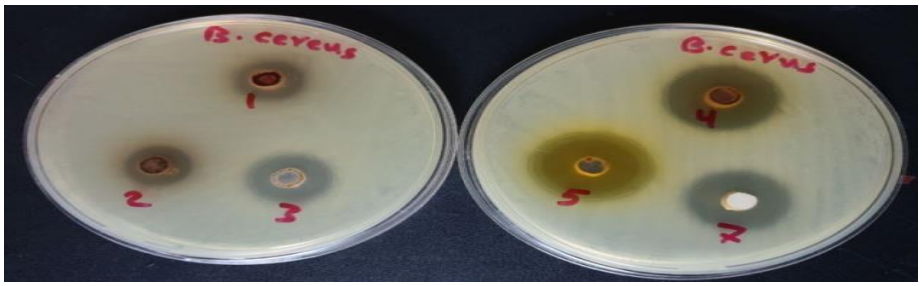


Fig. 16: Effect of comp. (1-6) in (Bacillus cereus)

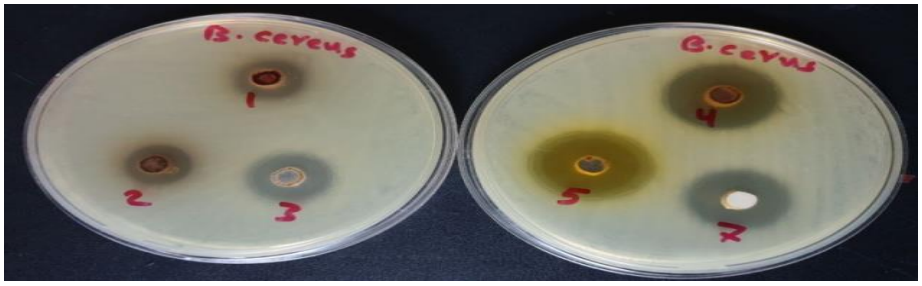


Fig. 16: Effect of comp. (1-6) in (Bacillus cereus)

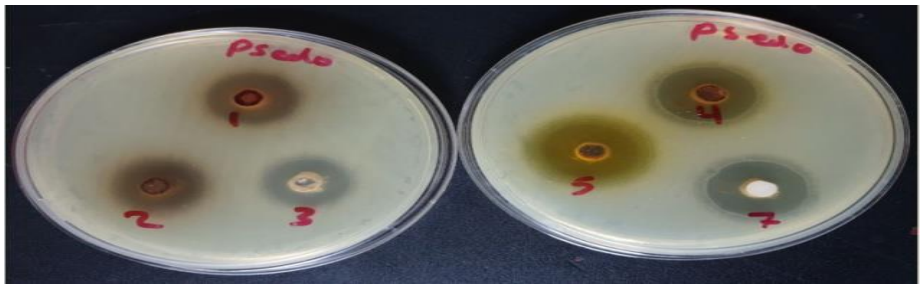


Fig. 17: Effect of comp. (1-6) in (Pseudomonas aeruginosa)

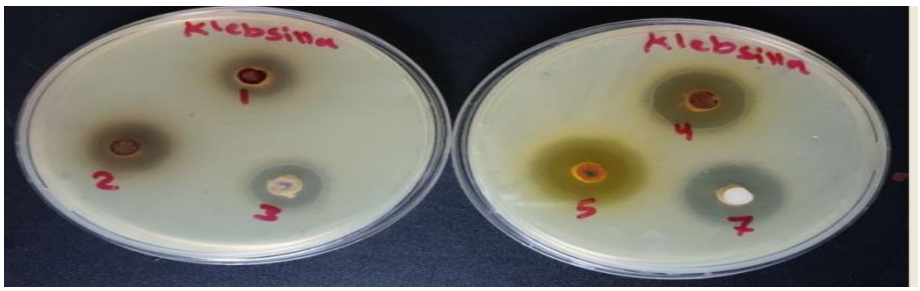


Fig. 18: Effect of comp. (1-6) in(Klebsiella pneumonia)

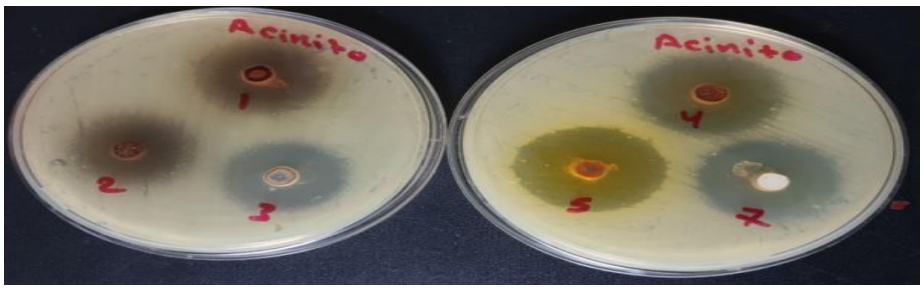


Fig. 19: Effect of comp. (1-6) in (Acinetobacter baumannii)

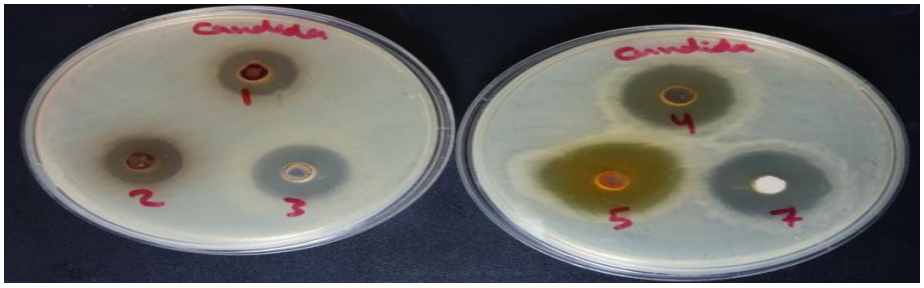


Fig. 20: Effect of comp. (1-6) in (Candida albicans)

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