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Synthesis and Evaluating Antimicrobial Activity for Chalcones Thiophen Compounds

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***Abstract*---**This research included the preparation and characterization of compounds containing chalcones, Schiff bases, and Azo dye: bearing thiophene ring. The compounds (1mk-3mk) had prepared from the reaction acetophenone derivatives with 2-formyl thiophene and, then 2mmk had introduced in two reactions: first, its reaction with some substitutes of benzaldehyde to prepare Schiff bases (4mk-7mk), and the second was the design of a bis azo dye from p-Phenylenediamine with salicylaldehyde to get 8mk, and then reacted with chalcone 2mk to obtain the compound 9mk. The chemical formulas of the prepared compounds were confirmed by spectroscopic methods using UV, infrared, NMR spectroscopy of protons and carbon 13. The antimicrobial activity had tested against *Staphylococcus aureus* and *Candida albicans* in compared with neomycin sulfate and nystatin, and some compounds showed good to moderate inhibition at a concentration of 7.5,10 mg/ml.

***Keywords*---**Azo dye, *Candida albicans,* Schiff bases, *Staphylococcus aureus.*

Introduction

Chalcones are pioneer bioactive compounds in natural products as flavonoids which, are classified α, β-Unsaturated ketones (Li et al., 2019). They occupy an extensive range of pharmacological properties as cytotoxicity on different cancer cell lines, anti-inflammatory (Gaonkar & Vignesh, 2017; Suwito et al., 2014; Nakhjavani et al., 2014), anti-diabetic agents (Hsieh et al., 2012), antimalarial (Domínguez et al., 2005), antimicrobial agents (Choudhary & Juyal, 2011; Gupta & Jain, 2015), antibacterial and antifungal (Andrade et al., 2018; Chu et al., 2018; Dan & Dai, 2020).

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Schiff bases play a vibrant role in numerous biological activities (Andrade et al., 2018). Chalcones containing Schiff bases have notable pharmacological Characteristics due to their many biological activities as their antiproliferative, Anti-Cancer Agents, epilepsy, and Alzheimer's disease (Salem et al., 2019; Koçyiğit et al., 2020). Also, they have liquid crystalline properties (Thaker et al., 2009). A survey of recent literature reveals a lot of research on thiophene chalcones, which has pioneering biological properties such as Anti-inflammatory anti-symptomatic insecticide (Ünver et al., 2019; Duddukuri et al., 2018; Gopi et al., 2017). These observations directed us to synthesize some thiophene chalcones/Schiff bases/azo and evaluate antibacterial and antifungal inhibition against Staphylococcus aureus and Candida albicans. Figure 1 shows the reaction pathway for the preparation of compounds (1mk-9mk):

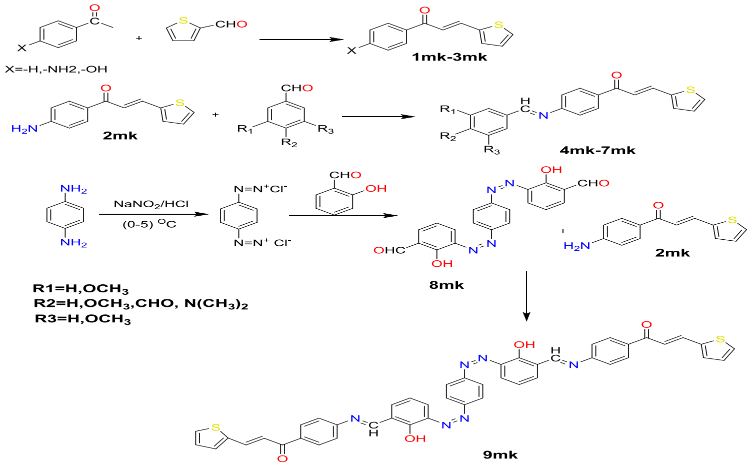


Figure 1. Path way of the preparation of compounds (1mk-9mk**)**

Practical part

Solvents and chemicals had purchased and used from international companies without any purification. The infrared spectra had recorded using a type of device (FTIR-8400S) from the Japanese company Shimadzu, using KBr potassium bromide tablets. The nuclear magnetic resonance spectrum of hydrogen proton (^{1}HNMR) and (^{13}CNMR) was measured in Iran using DMSO solvent) and using a device (Varian 500 MHZ). The flow and purity of the products had traced using Thin Layer Chromatography (TLC). G-fluorescent activated silica gel sheets with a thickness of 0.2 mm were used. The measurement had done using several solvents. The media was sterilized for microorganisms by an autoclave device supplied by the company of Spain and development. The dishes were in the Incubator and had measured in the Microbiology Division/Quality Control Department/The State Company for Pharmaceutical Industry and Medical Appliances - Samarra.

Methods of Preparation

Method of preparing Chalcones (1mk-3mk)

Acetophenone or its substitutes (mol 0.016) had dissolved with (25ml) of absolute ethanol and added to it (10ml) of sodium hydroxide solution 10% in a flask of capacity (100ml). The flask had placed in a bowl containing the ice groats stirred for (5 minutes). Then (0.016mol, 1.5ml) of 2-Tiophene carboxaldehyde had added in the form of drops and gradually with continuous stirring for (6-7) hours at room temperature, leave the mixture for 24 hours in the refrigerator, and then add ice groats. The solution had neutralized with glacial acetic acid 2-3 drops. A precipitate had washed several times with cold water, dried, and recrystallized with ethanol. Table 1: shows some physical properties, percentage, and a molecular formula of compounds Prepared (1mk-3mk): -

Method of preparing Schiff Bases (4mk-7mk)

A chalcone mk2 (0.001 mol, 0.229g) had mixed with (0.001 mol) benzaldehyde or its substitute and dissolved in 20 ml of absolute ethanol. Add to mixture (2-3) drops of glacial acetic acid and rise the mixture for (5-8) minutes in the microwave oven, it is left for 24 hours in the refrigerator, after which it is filtered and left to dry at room temperature, and it is crystallized by ethanol as shown in Table 2.

Method of preparing azo dyes (mk8)

Preparation of diazonium salt:
Para-phenylenediamine (0.18g-0.001mol) had dissolved in a mixture (1.5 ml of distilled water and 1.5 ml of concentrated hydrochloric acid), cooling in an ice bath, then had added an aqueous solution of sodium nitrite (g0.069, mol 0.001), and cool the solution in an ice bath for 5 min, the formation of a red-colored solution had observed. The product had been kept at 0-5°C.

a coupling reaction:
Add 2.5 ml of 10% aqueous sodium hydroxide to (0.002 mol, g 0.21) Salicylic Aldehyde, cool the solution in an ice bath. The previously prepared diazonium salt had added gradually with stirring. Continuous in an ice bath, filter the product and wash the product with distilled water several times with a measurement pH until neutral and then recrystallized with ethanol. Red-colored crystals had formed, with a percentage of 70%, melting point 150-153 ^{O} C, molecular weight 374.36 and molecular formula $C_{20}H_{14}N_4O_4$.

Method of preparing Schiff base (9mk)

A mixture of chalcone 2mk (0.4 g, 0.002 mol) with (0.6 g,0.0016 mol) azo dye 8mk had dissolved in 10 ml absolute ethanol with the addition of 3 drops of glacial acetic acid. A mixture had stirred until dissolution, refluxed for 7-6 hours, and left for 24 hours in the refrigerator, filter precipitate, and let it dry at room temperature, it is crystallized with ethanol, to get a percentage of 69%, melting point 124-127 ^{O} C, molecular weight 796.92 and molecular formula $C_{46}H_{32}N_6O_4S_2$.

Table 1
Some physical properties, yields, and a molecular formula of the compounds (1mk-3mk)

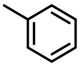
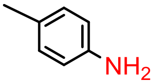
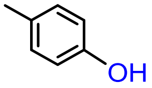
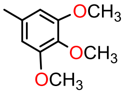
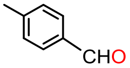
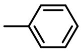
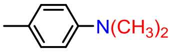
Comp No.	Ar	Molecular Weight g/mole	Molecular Formula	Melting Point °C	Color	Yield %
1mk		214.28	$C_{13}H_{10}OS$	119-120	White	66
2mk		229.06	$C_{13}H_{11}NOS$	125-126	Yellow	73
3mk		230.04	$C_{13}H_{10}O_2S$	116-118	Dark Brown	57

Table 2
Some physical properties, yields, and a molecular formula of the compounds (4mk-7mk)

Comp No.	Ar	Molecular Weight g/mole	Molecular Formula	Melting Point °C	Color	Yield %
4mk		407.48	$C_{22}H_{21}NO_4S$	231-233	Dark Yellow	77
5mk		345.42	$C_{21}H_{15}NO_2S$	196-197	Brown	68
6mk		317.41	$C_{20}H_{15}NOS$	211-213	Dark brown	58
7mk		360.48	$C_{22}H_{20}N_2OS$	204-206	Dark brown	73

Bio-efficiency evaluation
Preparation of the development of bacteria and fungi

- Use culture medium Nutrient broth from dissolving 28g in one liter of distilled water the materials were melted by heating while stirring by a magnetic stirrer, and sterilized by oxidizer Autoclave Under 121 °C and 1.5 pressure for 30 min, cooled and poured into test tubes.
- Use Nutrient agar culture medium from dissolving 28g in 1L of distilled water, and dissolved the materials are heated by stirring with a magnetic stirrer, and sterilization is done by an oxidizer Autoclave under 121 °C and 1.5 pressure for 15 minutes, cooled and poured into 9cm diameter dishes.
- Use of Asbouraud Dextrose agar of 50g per 1L of Distilled water, and dissolve the materials by heating while stirring with the magnetic stirrer,

and sterilizing with a device Autoclave under the same conditions as in (1), cooled and poured into plates with a diameter of 9 cm.

- A type of bacterial isolate had selected within the class of *Staphylococcus aureus*, which is *Staphylococcus aureus* obtained from Microbiology Division/Control Department Specific / State Company for the manufacture of medicines and medical supplies - Samarra, and a type of fungi from A class of yeast is the *Candida mushroom*.

The sensitivity of bacteria and fungi to the prepared compounds

The biological activity of the prepared compounds was tested on one type of bacteria and one type of Fungi by agar-well diffusion method, where 1.5 ml of Bacterial and fungal isolates used and activated in the nutrient medium in a conical flask containing 250 ml of the culture medium in its liquid state at a temperature of 40°C and then stirred well to ensure completely contaminated, poured into petri dishes in an amount of 18ml per plate, and left to solidify at room temperature, and after solidification, etchings were made in the dishes by cylinder metric method according to USP 35 with Cork borer, 100 mml of the prepared compounds of the three concentrations (5,7.5,10) mg/ml in each hole from the drill, put 100 mml of the standard antibiotic Neomycin sulfate at a concentration of 10 mg/ml of bacteria, and also put 40 mml of the prepared compounds for the three concentrations (5,7.5,10) mg/ml in each hole of the drill and put 40 mml of the counter The fungal standard Nystatin at a concentration 10 (mg/ml) of fungi, as the dishes were placed in Incubated at 37 °C for 24 hours, the diameters of the growth inhibition zones were measured Microbial by zone reader for the prepared compounds and this was compared with the diameter of inhibition for standard antibiotics.

Results and Discussion

The chalcones (MK1-MK3) had prepared by the reaction of equal moles of Acetophenone, it substituted with thiophene-2-carboxaldehyde in the base medium, Scheme-2 illustrates the reaction mechanism, which followed the same steps of Claisen-Schmidt condensation, and shown in the Figure.2:

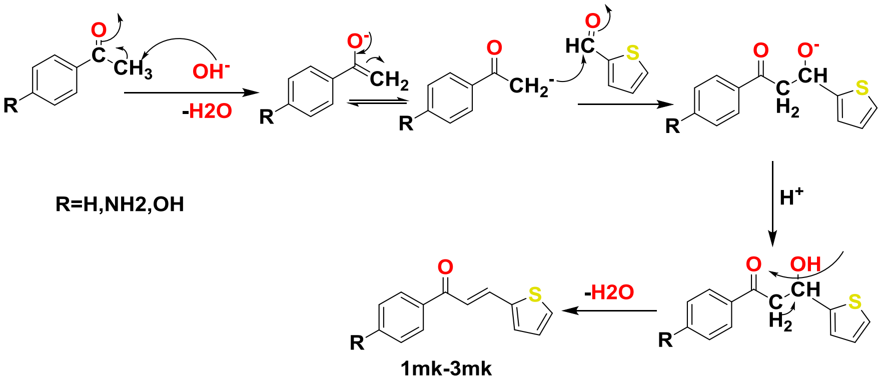


Figure 2. Mechanism of Preparation of (1mk-3mk) chalcones Compounds

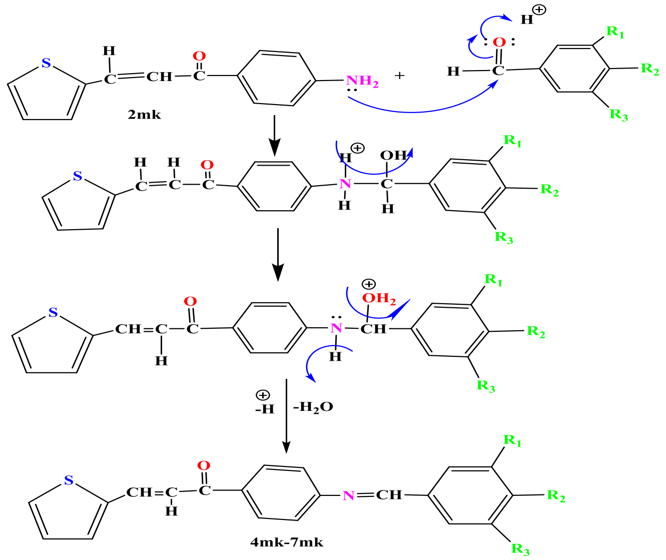
The chalcones compounds (1mk-3mk) had identified in spectroscopic methods. I.R spectra had showed bands at (3037-3115) cm-1, returns to stretching =C-H aromatic, and olefin, (1647-1662) cm-1 returns to stretching C=O. A compound 2mk shows two stretching bands at (3384, 3319) cm-1 for a group -NH2. A compound 3mk shows abord band at 3223 cm-1 refers to the stretching of OH. Table **.3** shows the Infrared absorption bands for prepared compounds, and figure 1, 2 show the infrared spectrum of the compounds (2mk,3mk).

As for the ^{1}HNMR spectrum of the compound 2mk, appeared a signal at 6.15ppm belongs to -NH2 amine group Ha, showed a triple signal at (7.37-7.39) ppm belonging to the Hg proton of the thiophene ring, and it showed Several doublet signals at (7.60-8.85) ppm belongs to protons (Hb-Hf) of the phenyl ring and the protons of the thiophene ring indicated as shown in Figure 3.

The ^{13}C-NMR spectrum of compound 2mk showed eleven signals, where a signal of the carbonyl group C1 appeared at the 187 ppm, C2 attached amino group C-NH2 appeared at 156.1 ppm, C3 appeared at 140.2 ppm, referred to thiophene ring, C4 appeared at 136.9 ppm which belongs to the group C-C = carbon, C5 appeared at 133.2ppm belongs to the carbon connected to the carbonyl group, (C6-C11) appeared at (132.6, 130.3, 128.9, 121.8, 120.7) ppm belongs to the thiophene ring and the benzene ring. Figure 4 illustrates this.

As for the ^{1}HNMR spectrum of the compound 3mk, it showed a single signal at 8.51 ppm belongs to Ha proton of the -OH group attached to the phenyl ring. It showed a doublet signal at (6.71-6.73) ppm belonging to Hb proton attached to a ring Benzene, appeared a triple signal at 7.38 ppm belonging to the Hf proton attached to thiophene ring. The signals (Hc- He) had shown at (6.94-7.98) ppm belongs to the proton of the thiophene ring and the benzene ring, as shown in the following figure 5.

Schiff bases (4mk-7mk) had prepared from mixing equal moles a chalcone 2mk with some Benzaldehyde substitutes with acetic acid as a catalyst using the microwave oven. A reaction follows the mechanism (addition/elimination) where the Nucleophilic addition of amino group on carbonyl then removes a water molecule to obtain the azomethine bond figure 3 illustrates the following:



R1=H,OCH$_3$
R2=H,OCH$_3$,CHO, N(CH$_3$)$_2$
R3=H,OCH$_3$

Figure 3. Assumed Mechanism of Preparation of Compounds (4mk-7mk)

FT-IR spectrum of the compounds (4mk-7mk) had showed an absorption band at (3061-3115) cm^{-1} due to the stretching of the group =CH olefin and aromatic, two or three bands at (1630-1699) cm^{-1} due to stretching C=O, C=N, C=C groups, Table 3 shows the infrared absorption bands of the compounds and the figure 6,7 show the infrared spectrum of the compounds (4mk,7mk).

The ^{1}HNMR spectrum of the observed 4mk compound had studied. The appearance of a single signal at the position of 2.49 ppm belongs to the proton of the solvent used DMSO-d6, a single at 3.35 ppm refers to the water present in the solvent used. It showed a single signal at 8.58ppm belonging to the proton of the imine group CH=N Ha and a doublet signal appeared at (8.17-8.19) ppm belonging to the HC= olefinic group, indicated by Hb, and several doublet signals appeared at (7.47-7.94) ppm belonging to protons of phenyl and thiophene rings denoted by (Hc-Hf), and a signal and triple signal appeared at (7.15-7.37) ppm range, which belongs to the proton of Hh, Hi. It showed two singles signals at (3.74,3.85) ppm belonging to the proton of the methoxy groups CH$_3$-O as shown in Figure 8.

The ^{1}HNMR spectrum of 5mk compound had been studied, the appearance of a single signal at the position of 2.49 ppm belongs to the proton of the solvent used DMSO-d6, single at 3.34ppm refers to the water present in the solvent used. It showed a single signal at 10.09ppm belonging to the CHO aldehyde group Ha, a single signal appeared at 8.80ppm belonging to CH=N imine group Hb, and several doublet signals appeared at (7.43-8.19) ppm belonging to the protons (Hc-Hh) for thiophene and phenyl rings, and a triple signal appeared at the range of (7.18-7.21) ppm Which belongs to the proton of thiophene ring Hk, as shown in Figure 9.

The azo dye 8mk was prepared by preparing the diazonium salt of paraphenylenediamine and then coupling it with Salicylic aldehyde, then prepared Schiff base 9mk by mixing azo dyes with chalcone 2mk, figure 4. shown Mechanism of preparation compound 9mk.

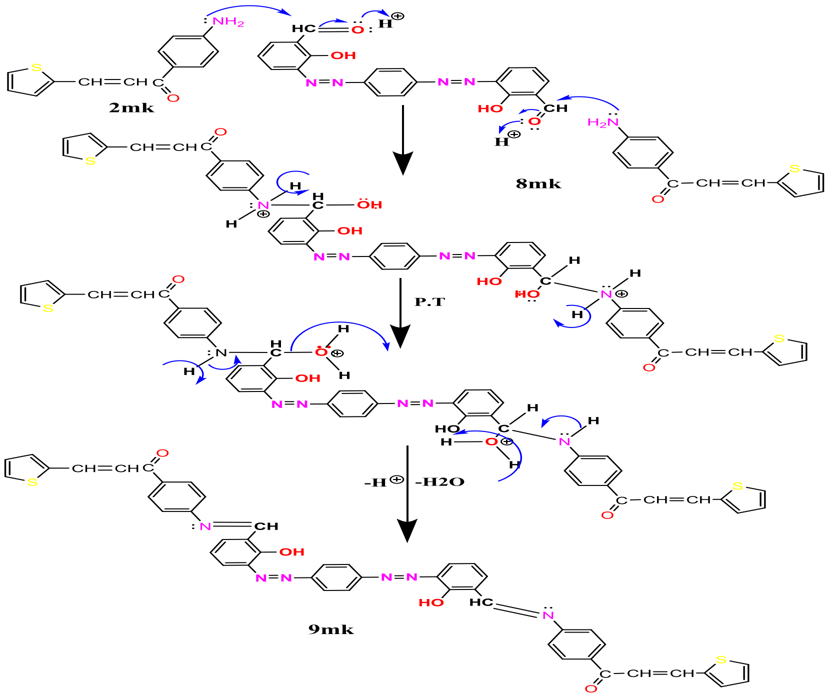


Figure 4. Mechanism of preparation of Schiff base/azo compounds 9mk

The 9mk compound was detected by FT-IR, as the spectrum showed a wide band at the 3313cm^{-1} retractable -OH stretching, bundle at the 3099-3056 cm^{-1} refer to stretching = CH olefinic and aromatic group, bundle at 1660cm^{-1} for stretching carbonyl C=O, a band at 1560 cm^{-1} which belongs to C=N imine group, and a band appeared at 1367cm^{-1} belongs to the azo bridge group as shown in Figure 10.

Table 3
Results of the infrared spectrum of compounds (1mk-8mk)

Comp. No.	**FT-IR(KBr) cm^{-1}**				
	ν NH2 OH	**ν (C-H) Olefin., Arom.&Alph.**	**ν C=O**	**ν C=C C=N**	**ν Others C-O,C-N**
1mk	....	3103 3064	1656	1602 1591	....
2mk	3384 3319	3099 3053	1647	1616 1587	....
3mk	3323	3096 3037	1662	1602 1591	1230 1170
4mk	....	3115 3063	1652	1589 1548	1320 1112
5mk	....	3101 3080	1699 1650	1627 1597	....
6mk	....	3107 3023	1655	1601 1570	....
7mk	....	3137 2964 2923	1650	1596 1550	1313 1164
8mk	3313	3099 3056	1685	1635 1598	1367

The ^{1}HNMR spectrum of the observed 9mk compound has studied the appearance of a single signal at the position of 2.49 ppm belongs to the proton of the solvent used DMSO-d6, a signal in the 3.36ppm position belongs to the water present in the solvent used. It showed a single signal at 9.27ppm belonging to the proton of the imine group HC=N belonging to a proton denoted by Hh and a single signal appeared at 8.86ppm belonging to the -HO group denoted as Hi, a doublet signal appeared at (8.14-8.22)ppm of the thiophene ring referred to as Hd, a doublet signal appeared at (7.83-7.58)ppm refer to protons, denoted by Hf, and a doublet signal appears at 7.78ppm, which returns for the protons of the thiophene ring, referred to as Ha, a triple signal appeared at position (7.20-7.15)ppm It belongs to the protons of the thiophene ring, referred to as Hb, and a triple signal appeared at 6.67ppm belongs to the benzene ring protons, referred to as Hj, and doublet signals appeared at position (7.70-7.51) ppm belongs to the protons of the thiophene ring and the benzene ring, referred to as Hc, He as It is shown in Figure 11.

The ^{13}CNMR spectrum of the compound 9mk showed a signal of carbonyl carbon at 185ppm, which had been indicated by the number C1, and imine carbon signal appeared at 160 ppm, indicated by C12, and signals appeared at 154 ppm for carbon attached -OH indicated C5. It has several signals referred to carbons of phenyl and thiophene rings at (113-140) ppm, as shown in Figure 12.

The evaluation of the biological activity of some prepared compounds

The biological activity of the prepared compounds had evaluated using three concentrations (5,7. 5,10) mg/ml for each compound against one type of bacteria, *Staphylococcus aureus*, and comparing the results with the standard of Neomycin sulphate at a concentration of (10 mg/ml). Also, they had evaluated with the same concentrations mentioned against one type of fungi, *Candida albicans* a class of yeasts, and comparison of results with the standard Nystatin at a concentration of 10 mg/ml.

The compounds showed moderate -good inhibitory activity close to the effectiveness of the antagonist. The compounds 2mk, 3mk, 5mk, and 6MK showed no inhibition at a concentration of 5mg/ml against bacteria, all prepared compounds had no inhibition against fungi at the same concentration, while the compound 4mk showed has good efficacy at a concentration (7.5,10) g/ml against bacteria and fungi as shown in Table. 4,5 and Figure 13,14.

Conclusion

Compounds holding thiophene nucleus with chalcones/ imine/azo groups had obtained from different reactions like Claisen-Schmidt condensation, Schiff, and coupling diazonium. The corresponding compounds showed virtuous against bacteria and fungi which used, that make them a good promising antibacterial and antifungal.

Acknowledgments

The researchers are thankful to everybody who supported the study in the Chemistry Department, College of Education, University of Samarra, and the staff of Quality Control Department /the State Company for Drugs Industry and Medical Appliances in Samarra.

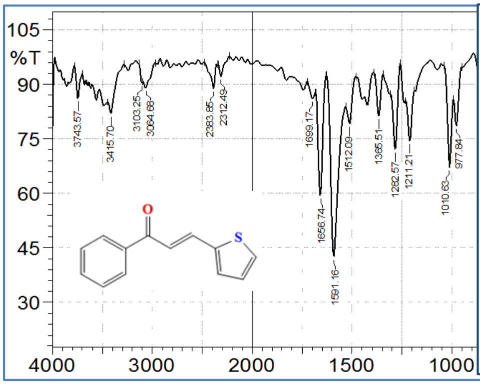


Figure 1. Infrared spectrum of 1mk

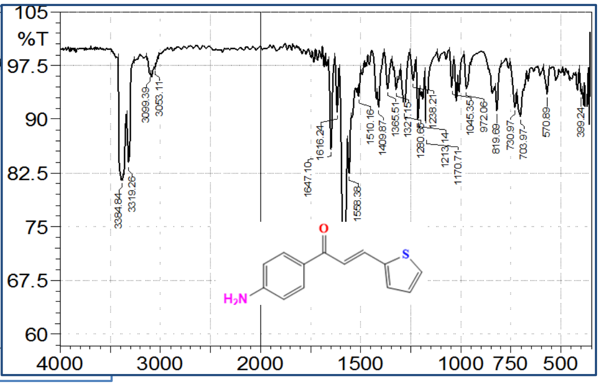


Figure 2. Infrared spectrum of 2mk

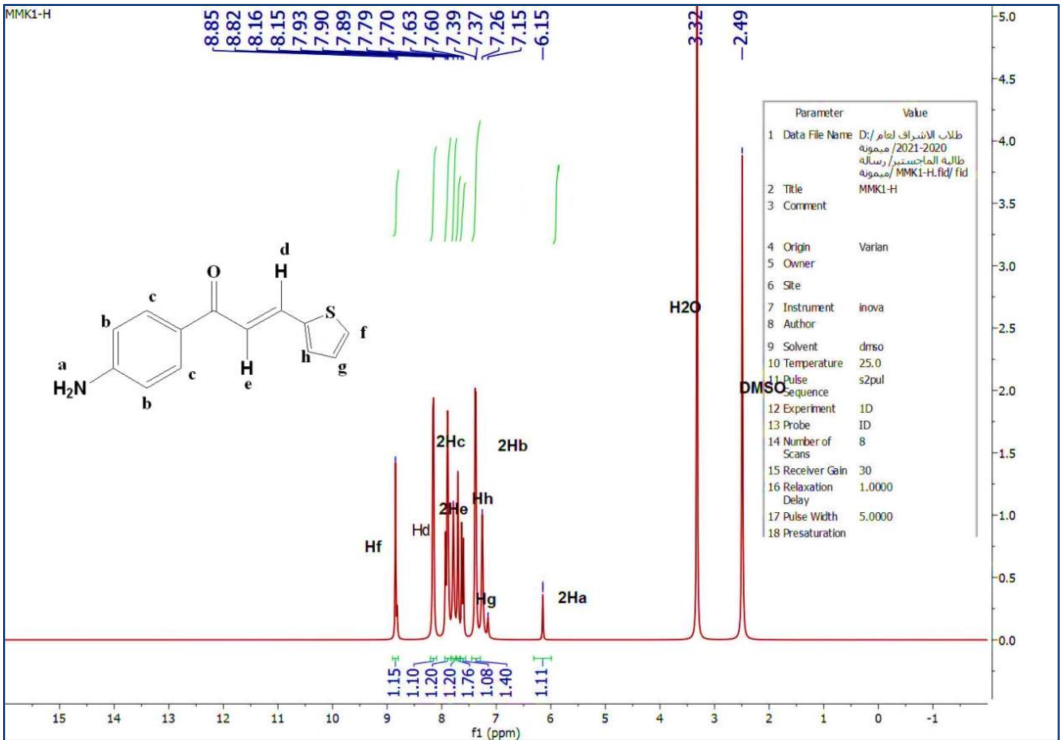


Figure 3. ^{1}HNMR spectrum of compound 2mk

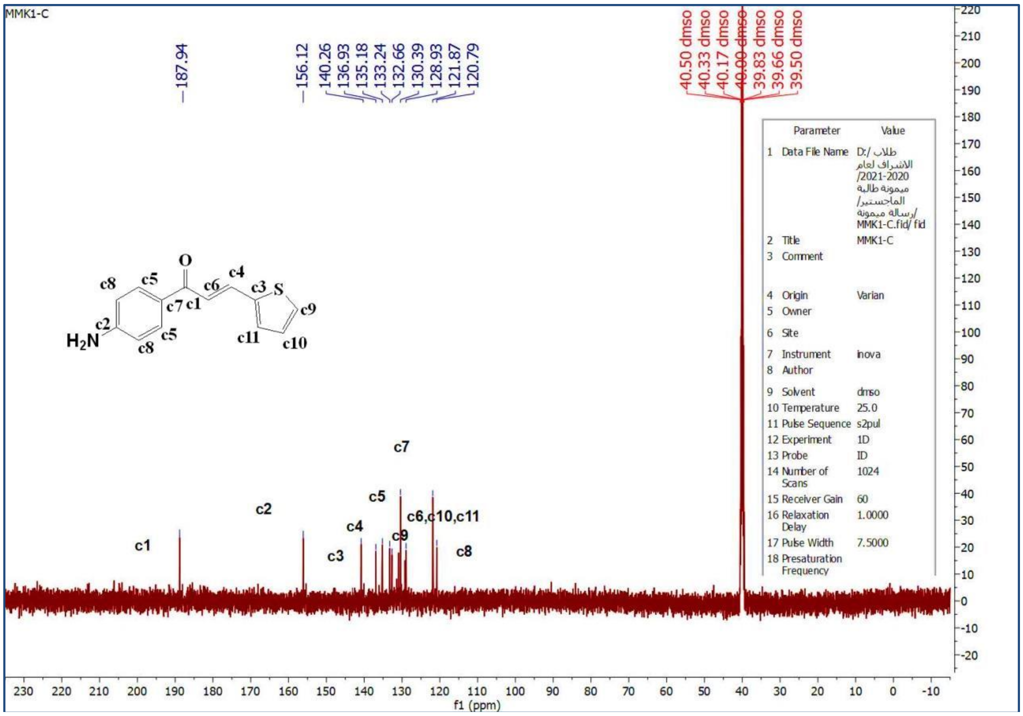


Figure 4. ^{13}CNMR spectrum of compound 2mk

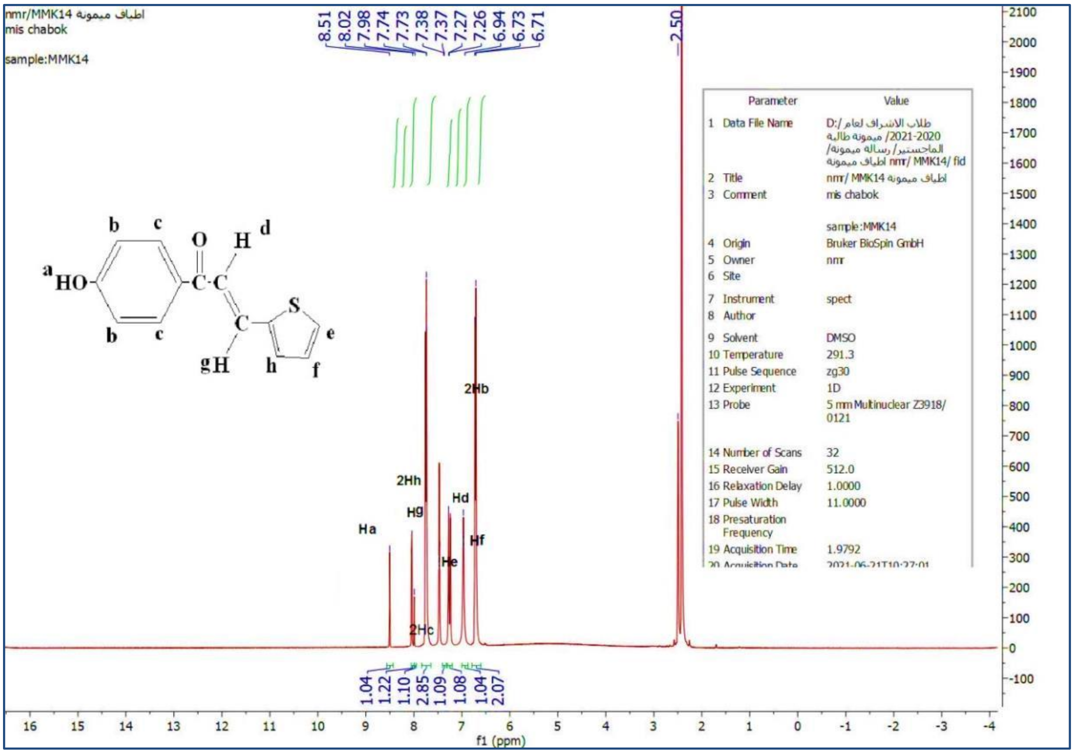


Figure 5. ^{1}HNMR spectrum of compound 3mk

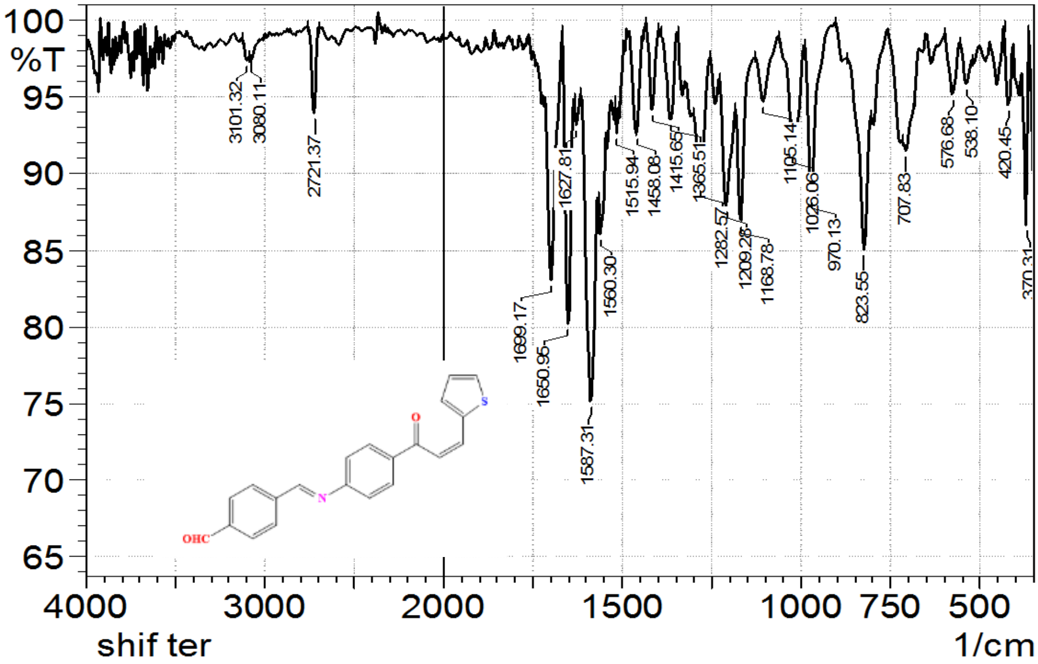


Figure 6. Infrared spectrum of compound 5mk

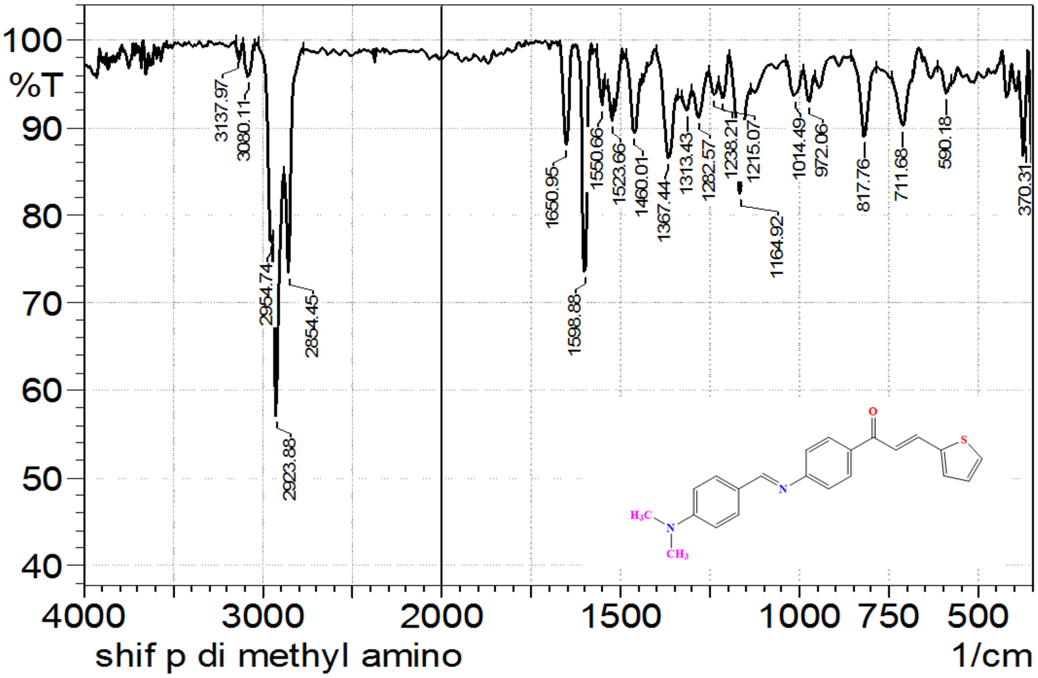
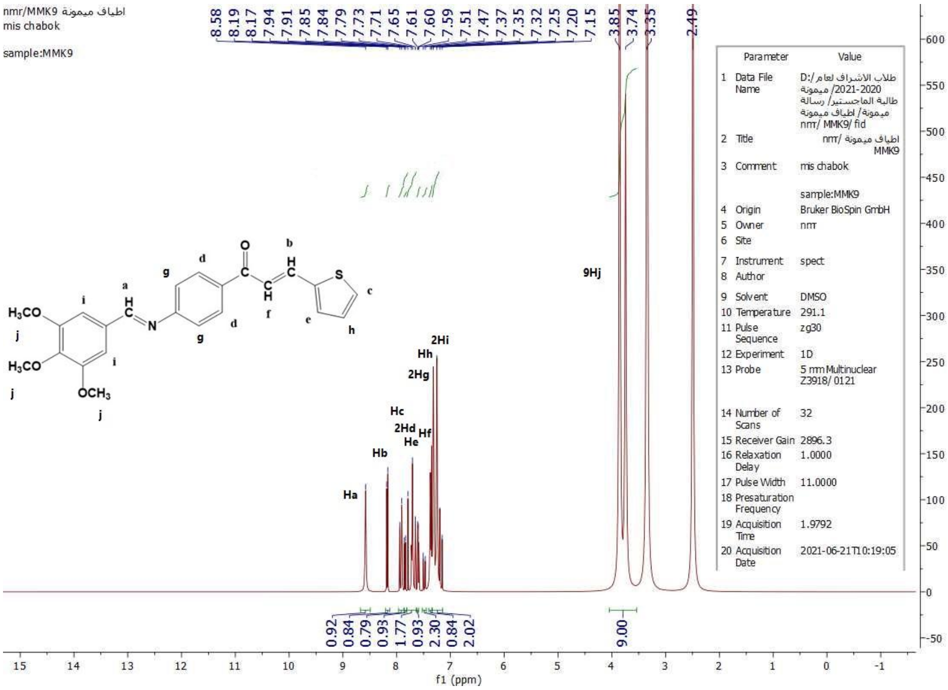


Figure 7. Infrared spectrum for compound 7mk



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2	Title	اطياف ميمونة /nmr MMK9
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5	Owner	nmr
6	Site	
7	Instrument	spect
8	Author	
9	Solvent	DMSO
10	Temperature	291.1
11	Pulse Sequence	zg30
12	Experiment	1D
13	Probe	5 mm Multinuclear Z3918/ 0121
14	Number of Scans	32
15	Receiver Gain	2896.3
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17	Pulse Width	11.0000
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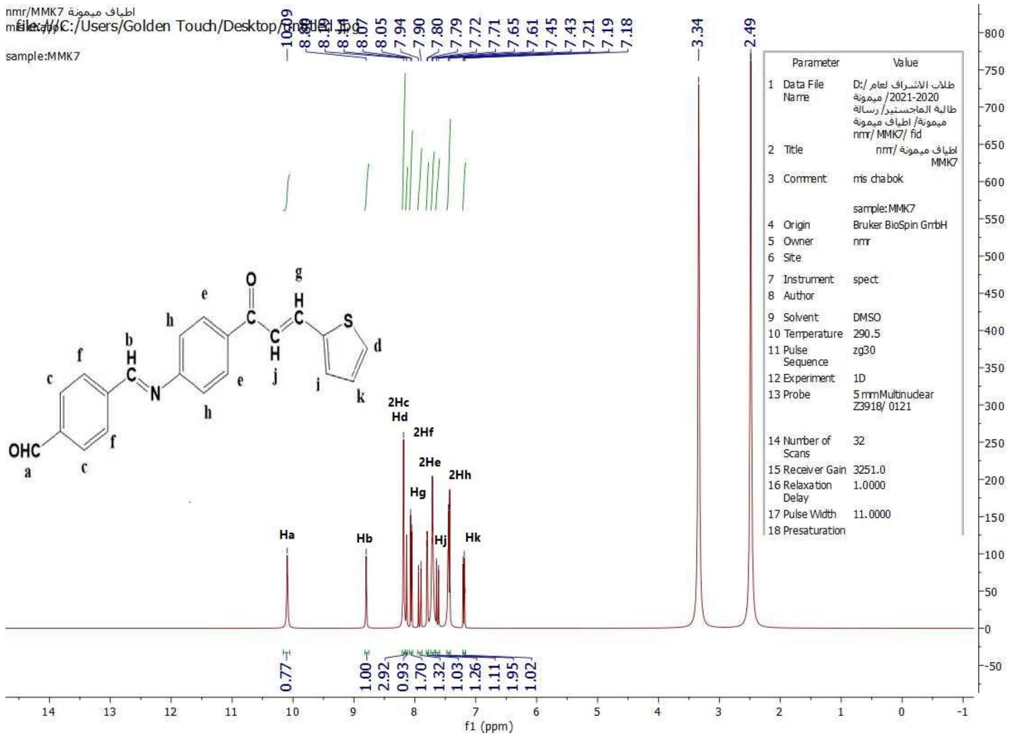
Figure **8**. 1HNMR spectrum of compound 4mk



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3 Comment	ms chabok sample:MMK7
4 Origin	Bruker BioSpin GmbH
5 Owner	nmr
6 Site	
7 Instrument	spect
8 Author	
9 Solvent	DMSO
10 Temperature	290.5
11 Pulse Sequence	zg30
12 Experiment	1D
13 Probe	5 mm Multinuclear Z3918/ 0121
14 Number of Scans	32
15 Receiver Gain	3251.0
16 Relaxation Delay	1.0000
17 Pulse Width	11.0000
18 Presaturation	

Figure 9. ^{1}HNMR spectrum of compound 5mk

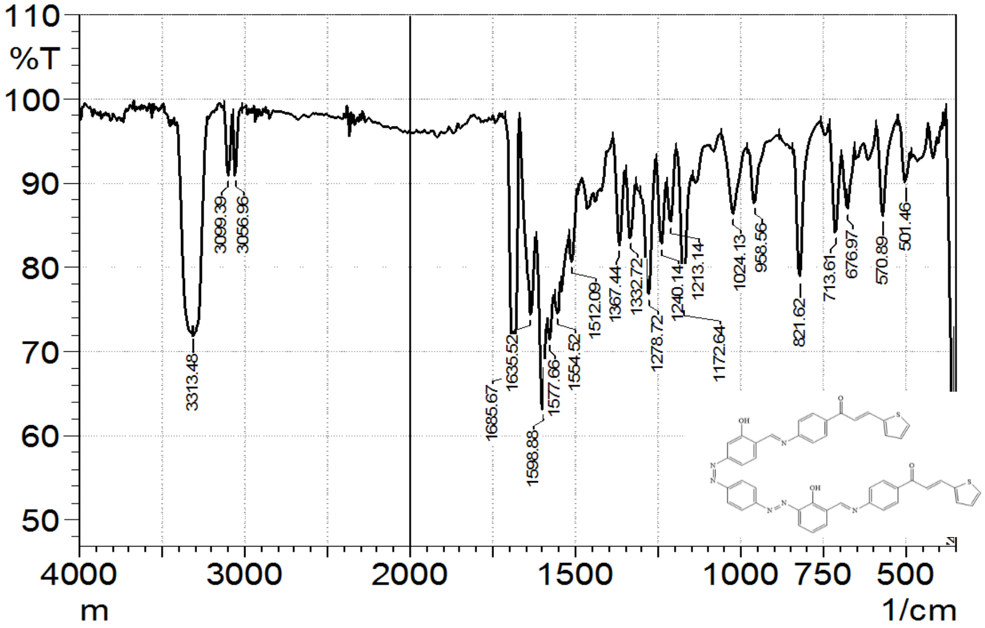
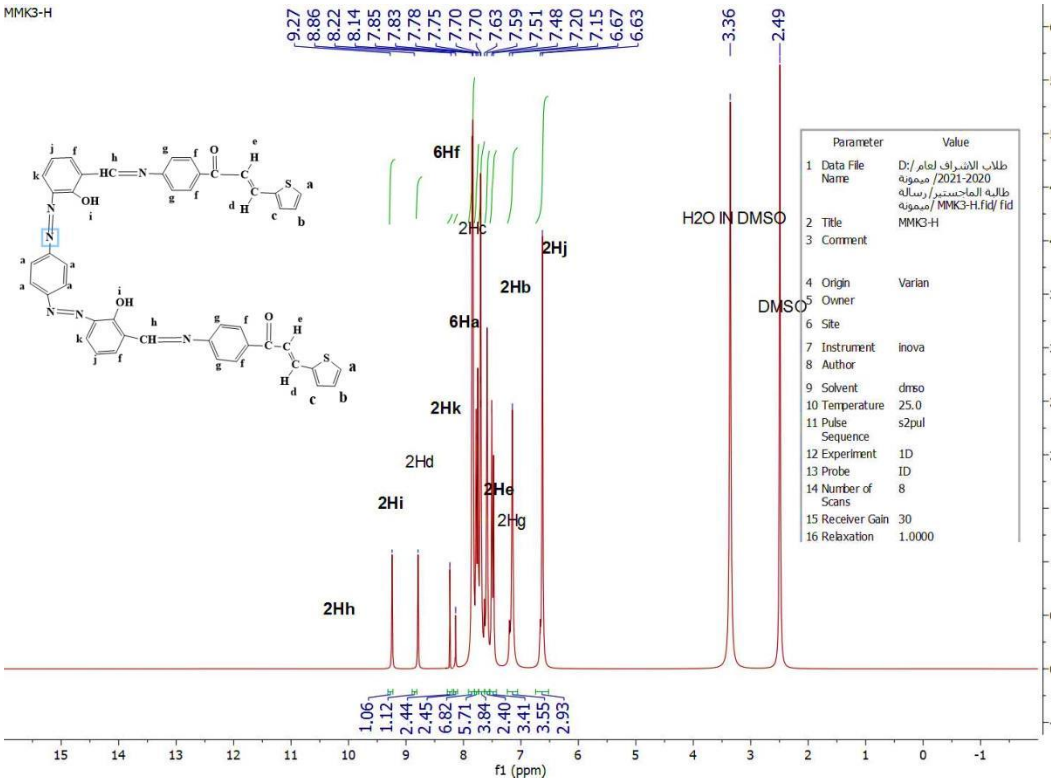


Figure 10. Infrared spectrum for compound 9mk



Parameter		Value
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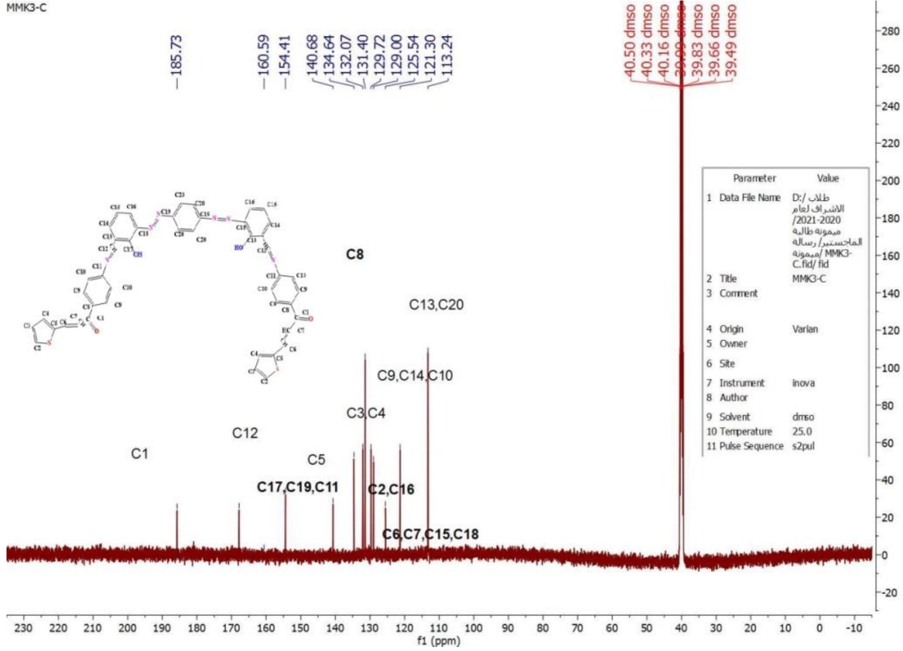
2	Title	MMK3-H
3	Comment	
4	Origin	Varian
5	Owner	
6	Site	
7	Instrument	inova
8	Author	
9	Solvent	dmso
10	Temperature	25.0
11	Pulse Sequence	s2pul
12	Experiment	1D
13	Probe	ID
14	Number of Scans	8
15	Receiver Gain	30
16	Relaxation	1.0000

Figure 11. ^{1}HNMR spectrum of compound 9mk



Parameter		Value
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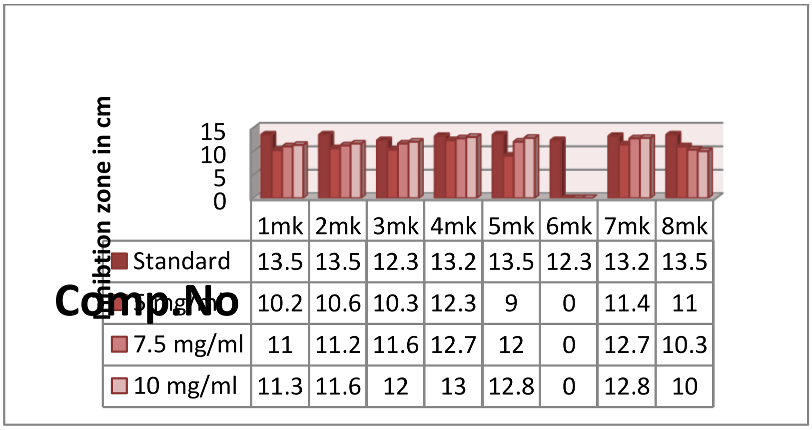
3	Comment	
4	Origin	Varian
5	Owner	
6	Site	
7	Instrument	inova
8	Author	
9	Solvent	dmso
10	Temperature	25.0
11	Pulse Sequence	s2pul

Figure 12. ^{13}CNMR spectrum of compound 9mk

Table 3.
The anti-bacterial activity of the prepared compounds

Comp.No	Standard	5 mg/ml	7.5 mg/ml	10 mg/ml
MK1	13.5	10.2	11	11.3
MK2	13.5	0	11.2	11.6
MK3	12.3	0	11.6	12
MK4	13.2	12.3	12.7	13
MK5	13.5	0	12	12.8
MK6	12.3	0	12.3	12.6
MK7	13.2	11.4	12.7	12.8
MK8	13.5	0	10.3	10

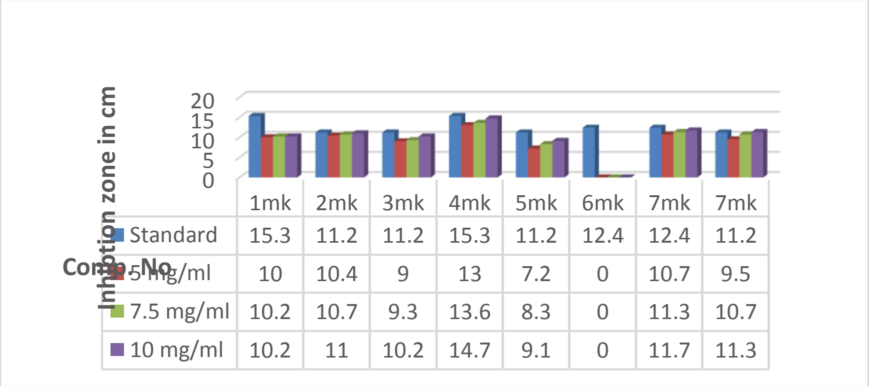


	1mk	2mk	3mk	4mk	5mk	6mk	7mk	8mk
■ Standard	13.5	13.5	12.3	13.2	13.5	12.3	13.2	13.5
■ 5 mg/ml	10.2	10.6	10.3	12.3	9	0	11.4	11
■ 7.5 mg/ml	11	11.2	11.6	12.7	12	0	12.7	10.3
■ 10 mg/ml	11.3	11.6	12	13	12.8	0	12.8	10

Figure 13. Inhibitory activity of 1mk-9mk against bacteria
Figure 14. Inhibitory activity of MK8-MK3 against bacteria.

Table 4
The antifungal activity of the prepared compounds

Comp. No	Standard	5 mg/ml	7.5 mg/ml	10 mg/ml
MK1	15.3	0	10.2	10.2
MK2	11.2	0	10.7	11
MK3	11.2	0	9.3	10.2
MK4	15.3	0	13.6	14.7
MK5	11.2	0	8.3	9.1
MK6	12.4	0	0	0
MK7	12.4	0	11.3	11.7
MK8	11.2	0	10.7	11.3



	1mk	2mk	3mk	4mk	5mk	6mk	7mk	7mk
🟦 Standard	15.3	11.2	11.2	15.3	11.2	12.4	12.4	11.2
🟥 5 mg/ml	10	10.4	9	13	7.2	0	10.7	9.5
🟩 7.5 mg/ml	10.2	10.7	9.3	13.6	8.3	0	11.3	10.7
🟪 10 mg/ml	10.2	11	10.2	14.7	9.1	0	11.7	11.3

Figure 14. The activity against fungi of the prepared compounds

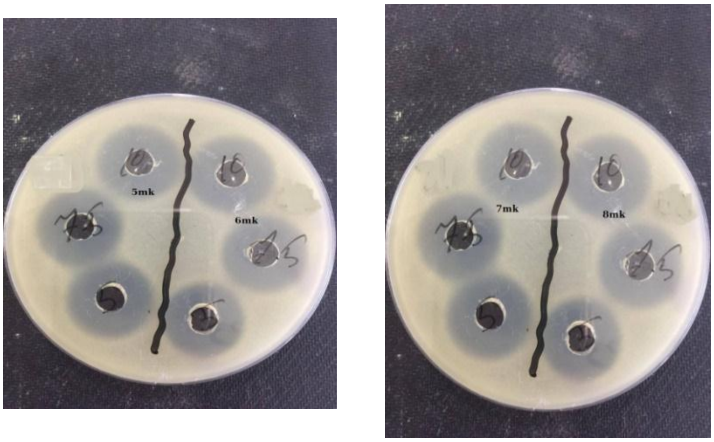


Figure 15. Inhibitory activity of MK6-MK1 against fungi

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