Preparation and characterization of chalcone compounds.

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Abstract

The research includes Preparation of chalcones Preparation of chalcones in alkaline medium and reacting two types of ketones, Acetylnaphthalene-2 and 4-morpholino acetophenone, with four types of aldehydes, as eight types of new chalcones were prepared (H1, H4, H5, H6, H8) The compounds were identified by FT-IR, proton nuclear magnetic resonance spectra (^{1}HNMR) and electron aerosol ionization mass spectrometry (ESI), where this was confirmed by the compositions of the new chalcones prepared. The biological activity of the prepared compounds was studied for two types of pathogenic bacteria for humans, which are bacteria Gram-negative *Escherichia coli*, and Gram-positive bacteria *Staphylococcus aureus* that cause skin infections. Where the compound gave the highest efficacy compound H8 against both types of pathological bacteria under test, followed by compound H4 and then compound H6.

Key word: chalcone, biological activity

Introduction The chalcon

Organic compounds belonging to the family of flavones also known as 1,3-diarylprop-2-en-1-one. It occurs naturally in the form of unsaturated α, β-ketones with two aromatic rings (A, B) (1), and is widely spread in vegetables, fruits, spices, tea, etc. The carbonyl, the alkene double bond adjacent to the carbonyl appears in two positions (E)Trans and (Z)Cis.(2)

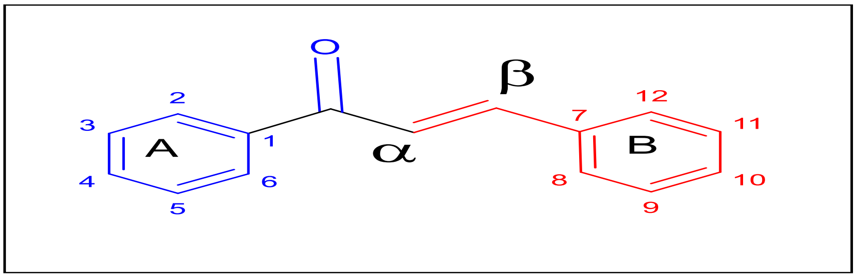
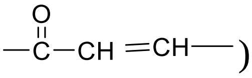


Figure (1-1): represents the structure of the chalcone

Presence of the effective group ( $-\overset{O}{\overset{\|}{C}}-CH=CH-$) In the composition of chalcone, it has a wide range of biological activities (3), so it occupies an important place in medical and biological chemistry because of its therapeutic properties that fight cancer and infections (4), germs and viruses (5), antioxidants and fungi (6), combating HIV HIV, tuberculosis and tumors, as well as an analgesic (7), combating high blood pressure, irregular heartbeat, gout, combating anxiety, convulsions, obesity and combating diabetes (8,9)

In addition, pyrazole, oxazoline, oxazine pyrimidine, and others are considered because they contain successive double bonds that lead to delocalization of electrons by π, and this reduces their electrophilic property

When chalcones interact with reagents searching for the nucleus to(10).

prepare heterogeneous cyclic compounds, they act as a reagent searching for electrons according to Michael’s addition reaction, where in the cyclocondensation reaction the chalcones act as a binary detector searching for electrons interacting with a binary detector searching for the nucleus as in the general equation below (2 - 1).(11)

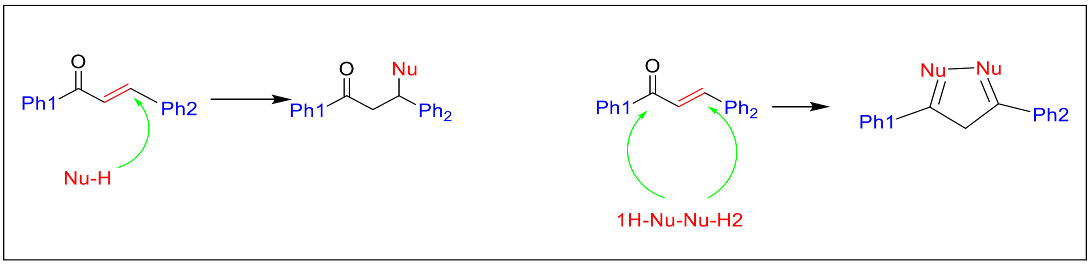


Figure (2-1): It represents a general equation for the interaction of the gallcon with the reagents searching for the nucleus

Chalcone shapes

Chalcones are elastic molecules that are dominant in many conformations and whose properties depend on proper ring substitution. Chalcones stereochemical properties exist as isomers

E-(trans) or Z-(cis) depend on the hydrogen atoms of the Cα = CB double bond. In most cases, the E-(trans) isomer is the most thermodynamically stable, making it the predominant coordination of chalcones, while the Z isomer due to the effects The strong separation between the carbonyl group and the B ring, the formation of the Z isomer is unstable.In addition, the chalcone is photosensitive in the solution due to the double bond and this leads to the conversion of the E form to the Z form in the solution.The cyclic compensators also affect the isomerism equilibrium ratio and rate when the mixture is purified. EZ Experimentally, the only stereoisomer that is produced in the solid state is the E-isomer in the following figure

(3-1).(12-17)

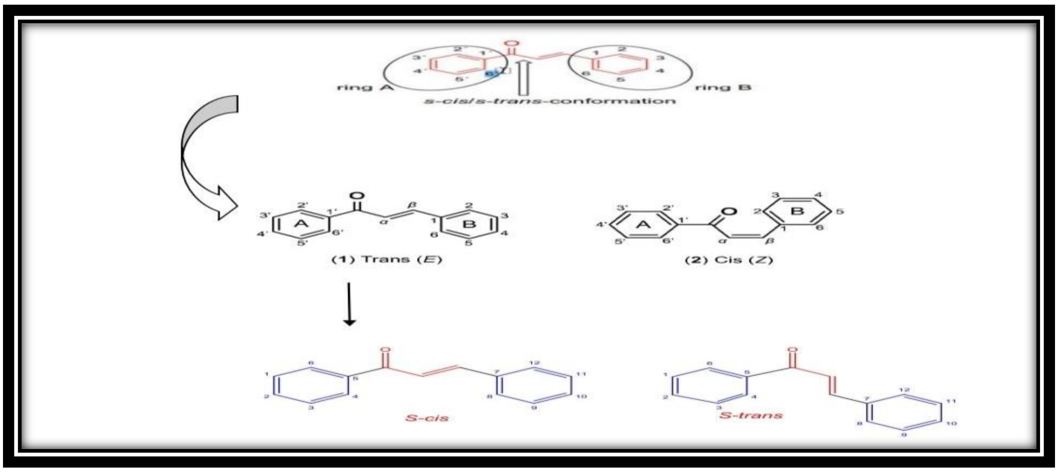


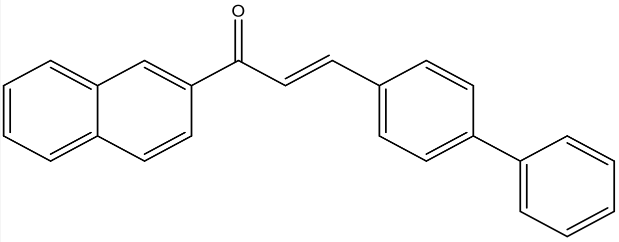
Figure (1-3): The structure of the chalcone (cis, trans)

The equilibrium ratio and rate of E-(trans) or Z-(cis) isomers depends on the structure and properties of the environment, for example temperature and solvent, steric effect between substituents on ethyl carbon atoms and carbonyl group and field effects between C=C and C=O groups On the other hand, it is the Z-(cis) isomer where it is non-planar due to the steric barrier between the H atoms. Also due to the barrier between the carbonyl oxygen and the phenyl ring, the Z-(cis)-isomer showed non-planarity experimentally and theoretically while the (s-trans) is the isomer The most stable chalcone has been confirmed as the most stable isomer using X-ray crystal structures.(18-23)

Methods of preparation chalcones

It was used in the basic way by Claisen-Schmidt condensation (24-27) to prepare eight types of chalcone. Where 0.001mol of ketone substitute was mixed with 0.001mol of aldehyde in a 100ml round flask equipped with a magnetic stirrer, then 20ml of absolute ethanol was added as a solvent, then after leaving the mixture for a short period under stirring until the dissolution was confirmed, 5ml of a 15% sodium hydroxide solution was added in batches. The mixture was mixed for (2-3) hours, then the reaction mixture was left in the refrigerator for (12) hours, after that it was added to a mixture of (70 ml) of cold distilled water in batches, where a precipitate was formed representing the resulting substance. The precipitate was washed with distilled water and recrystallized from absolute ethanol. To confirm the reaction, TLC thin layer chromatography was used, and the sublimation mixture was ethyl acetate: hexane (1:3). And the physical properties of the prepared chalcones are shown in Table (1)

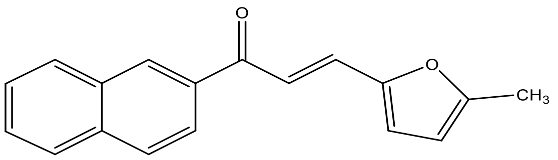
Preparation of compound H1



(*E*)-3-([1,1'-biphenyl]-4-yl)-1-(naphthalen-2-yl)prop-2-en-1-one
Chemical Formula: $C_{25}H_{18}O$
Molecular Weight: 334.42

Where it was prepared by reacting 0.170g (0.001mol) of the compound 2-Acetylnaphthalene with 0.182g (0.001mol) Biphenyl-4-Carboxaldehyde and it gives a yellowish white powder at a melting point (139-137C).

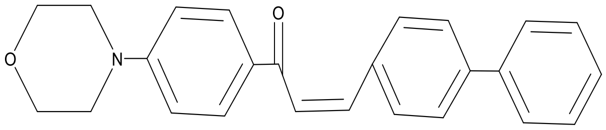
Preparation of compound H4



(*E*)-3-(5-methylfuran-2-yl)-1-(naphthalen-2-yl)prop-2-en-1-one
Chemical Formula: $C_{18}H_{14}O_2$
Molecular Weight: 262.31

It was prepared by reacting 0.170 g (0.001 mol) of 2-Acetylnaphthalene compound with 0.110 g (0.001 mol) 5-methylfuran-2-carbaldehyde, giving a gray powder with a melting point. (85-87°C)

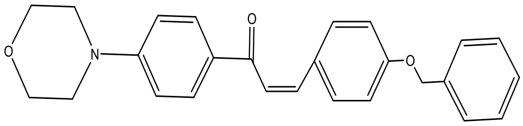
Preparation of compound H5



(*Z*)-3-([1,1'-biphenyl]-4-yl)-1-(4-morpholinophenyl)prop-2-en-1-one
Chemical Formula: $C_{25}H_{23}NO_2$
Molecular Weight: 369.46

It was prepared with 0.205 g (0.001 mol) of 4-morpholino acetophenone. With 0.182g (0.001mol) of Biphenyl-4-Carboxaldehyde, it gives a yellow powder at a melting point of (210-212C°).

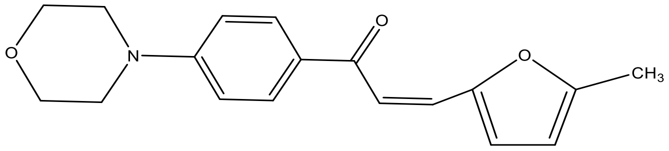
Preparation of compound H6



(*Z*)-3-(4-(benzyloxy)phenyl)-1-(4-morpholinophenyl)prop-2-en-1-one
Chemical Formula: $C_{26}H_{25}NO_3$
Molecular Weight: 399.49

It was prepared with 0.205 g (0.001 mol) of 4-morpholinoacetophenone. with 0.212 g (0.001 mol) of 4(Benzylox) Benzaldehyde giving a light yellow powder At melting point(157-158C°

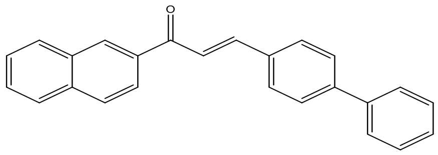
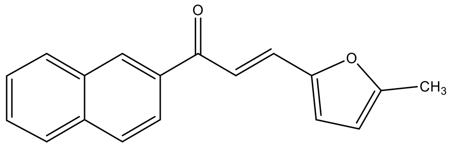
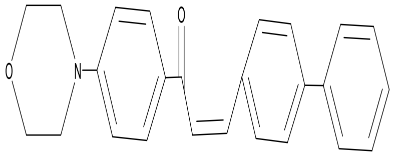
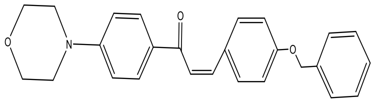
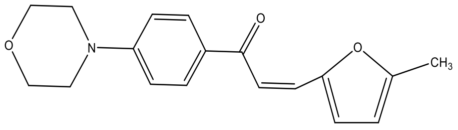
Preparation of compound H8



(*Z*)-3-(5-methylfuran-2-yl)-1-(4-morpholinophenyl)prop-2-en-1-one
Chemical Formula: $C_{18}H_{19}NO_3$
Molecular Weight: 297.35

It was prepared by reacting 0.205 g (0.001 mol) of 4-morpholino acetophenone with 0.110 g (0.001 mol) of 5-methylfuran-2-carbaldehyde (it gives a brown powder at a melting point of(191-193°C)

Table (1): Physical properties and chemical composition of prepared chalcones

Code	Compound	m.p	color	Time	Cofactor
H1	 (*E*)-3-([1,1'-biphenyl]-4-yl)-1-(naphthalen-2-yl)prop-2-en-1-one Chemical Formula: $C_{25}H_{18}O$ Molecular Weight: 334.42	**137-139°C**	**yellowish white**	**2 hours**	**Ethanol**
H4	 (*E*)-3-(5-methylfuran-2-yl)-1-(naphthalen-2-yl)prop-2-en-1-one Chemical Formula: $C_{18}H_{14}O_2$ Molecular Weight: 262.31	**85-87°C**	**ashen**	**5 hours**	**Ethanol**
H5	 (*Z*)-3-([1,1'-biphenyl]-4-yl)-1-(4-morpholinophenyl)prop-2-en-1-one Chemical Formula: $C_{25}H_{23}NO_2$ Molecular Weight: 369.46	**210-212°C**	**yellow**	**6 hours**	**Ethanol**
H6	 (*Z*)-3-(4-(benzyloxy)phenyl)-1-(4-morpholinophenyl)prop-2-en-1-one Chemical Formula: $C_{26}H_{25}NO_3$ Molecular Weight: 399.49	**157-158°C**	**light yellow**	**7 hours**	**Ethanol**
H8	 (*Z*)-3-(5-methylfuran-2-yl)-1-(4-morpholinophenyl)prop-2-en-1-one Chemical Formula: $C_{18}H_{19}NO_3$ Molecular Weight: 297.35	**191-193°C**	**brown**	**6 hours**	**Ethanol**

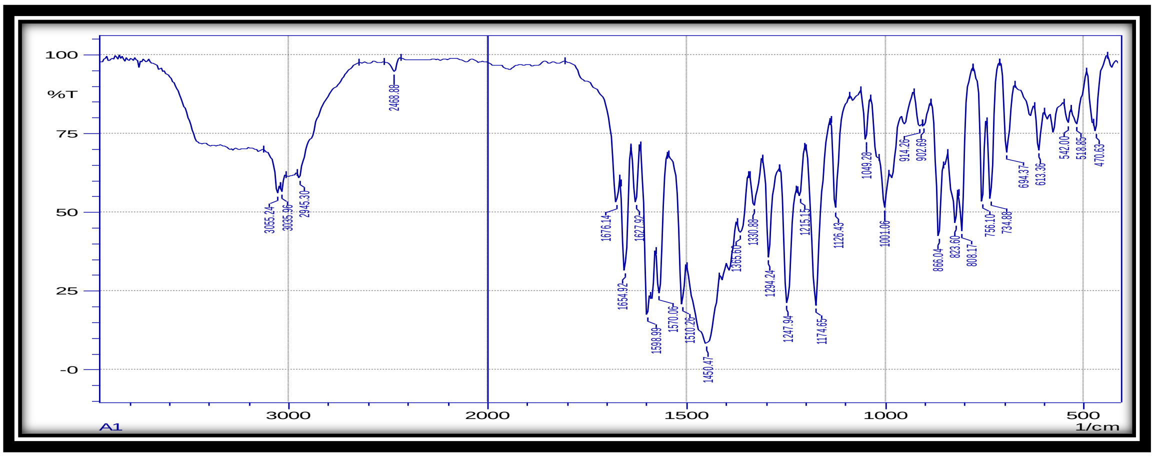
Results and Discussion

1-Infrared spectra of the prepared chalcone compounds.

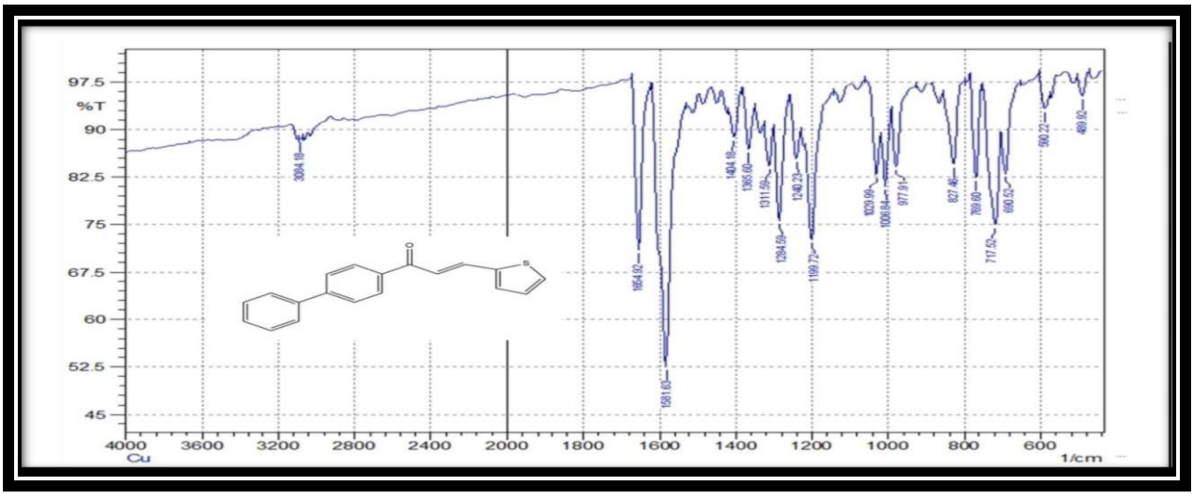
The infrared spectra of the prepared compounds (H1, H4, H5, H6, H8) are shown in the following figure (from (3-3) to (3-10)) And the indications are shown in the following table (1-3), where the appearance of a beam at the range(3097-3050 cm^{-1}) The stretching is due to the bonding of the aromatic C-H protons and the appearance of a bundle at the range (2915-1-2994 cm^{-1}) The appearance of a beam at the range (1064-1625 cm-1) due to carbonyl C=O. The appearance of a signal at the range 1593-1533 cm-1) back to C=C And the appearance of a signal at (1284-1220 cm-1) dating back to C-O for compounds H4, H6, H8, and the appearance of a signal at the range (1485-1404 cm-1) dating back to C-C in the area of functional aggregates. The fingerprint area was characterized by the appearance of single bonds at the lower range. From 1-400cm. (24-27)

Table (2) shows the data of the most important bands of the infrared spectra of the prepared chalcones

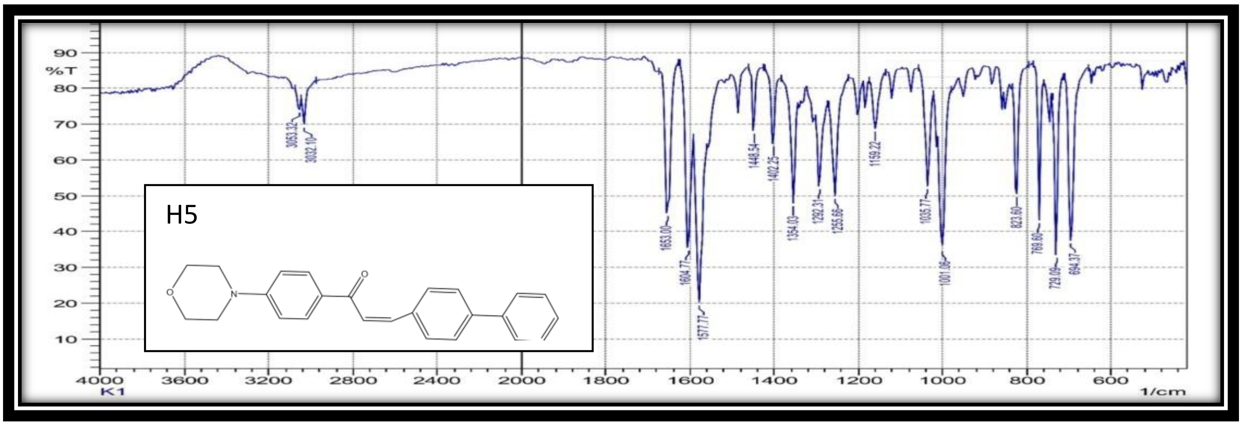
compound symbol	C-H Aromatic cm^{-1}	C-H Aliphatic cm^{-1}	C=O cm^{-1}	C=C cm^{-1}	C-C cm^{-1}	C-O cm^{-1}	C-S cm^{-1}
H1	3050	2915	1651	1570	1450	-	-
H4	3053	2941	1643	1566	1436	-	-
H5	3053	-	1653	1577	1448	1220	-
H6	3084	-	1664	1581	1404	1284	-
H8	3097	-	1656	1533	1485	1284	-


100
%T
75
50
25
-0
3000
2000
1500
1000
500
1/cm
A1
3055.24
3035.96
2945.30
2468.88
1676.14
1654.92
1627.92
1598.99
1570.06
1510.26
1450.47
1365.60
1330.88
1294.24
1247.94
1215.15
1174.65
1126.43
1049.28
1001.06
914.26
902.69
866.04
823.60
808.17
756.10
734.88
694.37
613.36
542.00
518.85
470.63

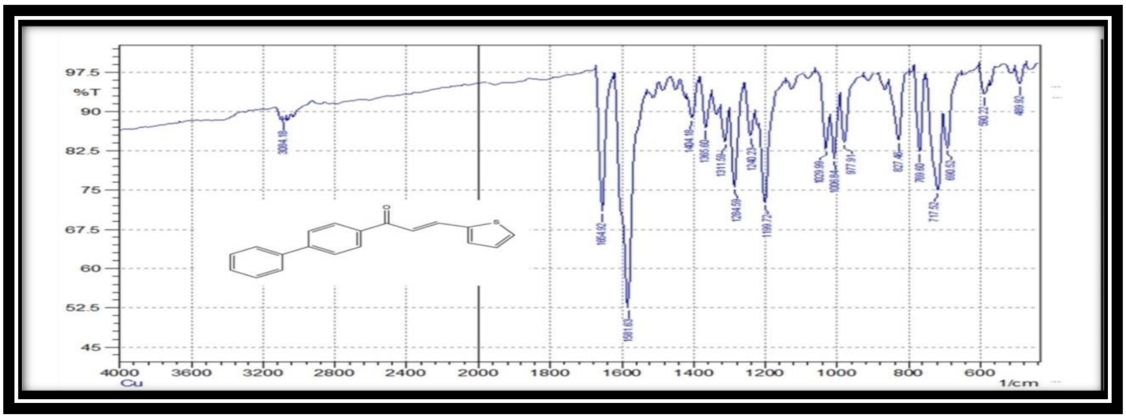
H1


97.5
%T
90
82.5
75
67.5
60
52.5
45
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
1/cm
Cu
S
O
3084.18
1654.92
1581.63
1404.18
1365.60
1311.59
1284.59
1240.23
1199.72
1029.99
1006.84
977.91
827.46
769.60
717.52
690.52
590.22
489.92

H4


90
%T
80
70
60
50
40
30
20
10
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
1/cm
K1
H5
O
N
O
3053.32
3032.10
1653.00
1604.77
1577.77
1448.54
1402.25
1354.03
1292.31
1255.66
1159.22
1035.77
1001.06
823.60
769.60
729.09
694.37

H5



H6

H8

2-Electron Sputtering Ionization Mass Spectrometer(ESI)

The mass spectra of the ionization by electronic spraying of the compounds prepared from (H1,H4,H5,H6,H8) are shown in the figure from (3-31) to (3-38) matching the molecular weight of the proposed formulas. (H5, H6)) as for the second figure, the molecular weight with a sodium molecule in compounds (H1,H4, H8)(24-27)As shown in the following table

Table (3) shows the mass spectra of the ionization by electronic spraying of the prepared chalcones

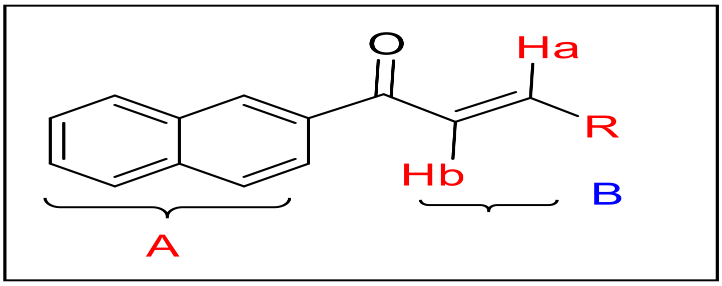
compound symbol	or[M+Na]$^{+1.-1}$ [2M+Na]$^{+1.-1}$	Chalcone molecular weight
H1	**358**	**334**
H4	**285**	**262**
H5	**761**	**369**
H6	**821**	**399**
H8	**321**	**297**

3- ^{1}H NMR spectra of chalcones

NMR techniques are used to confirm the proposed structures of the compounds.

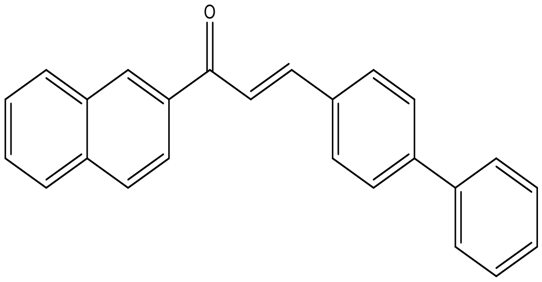
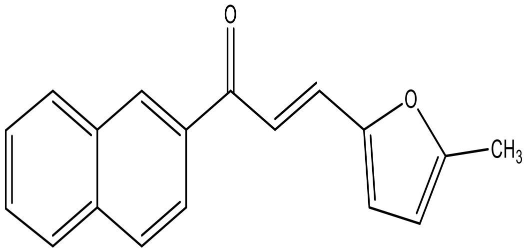
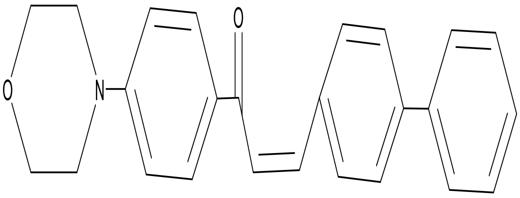
Nuclear magnetic resonance spectra to study the compounds at a frequency of (400 and 500) MHz in DMSO solvent, CDCl3. There are two types of isomers in the chalcone. All sources and published research confirmed that the trans isomer is dominant. Chalcone structures are more stable. Chalcone compounds are characterized by three regions of chemical displacement of protons. (α-H, β-H)Ha, Hb With protons (2-Acetylnaphthalene, 4-morpholino acetophenone)A and B (various aromatic aldehydes) in all compounds, the olefin protons are characterized by two double signals with a coupling constant (J=15-16Hz).

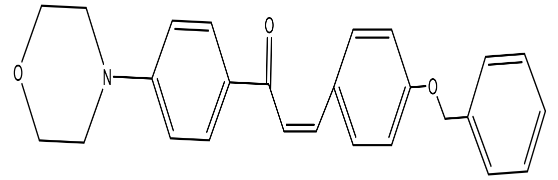
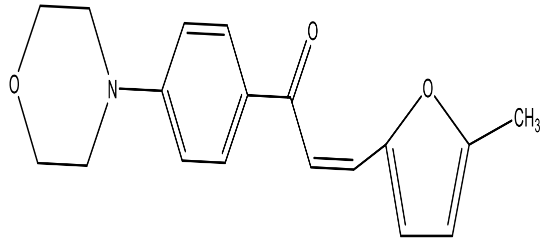
Whereas, the olefin protons have an overlapping signal with the A protons at a displacement of (6.2-8.5) PPM for all compounds, and there are other peaks that appear R-B and differ in the chemical displacement depending on the R that interferes with the A protons and the Ha, Hb protons. This causes difficulty in distinguishing the Ha, Hb protons because of the overlap Strong with cyclic protons of A,B (24-27)

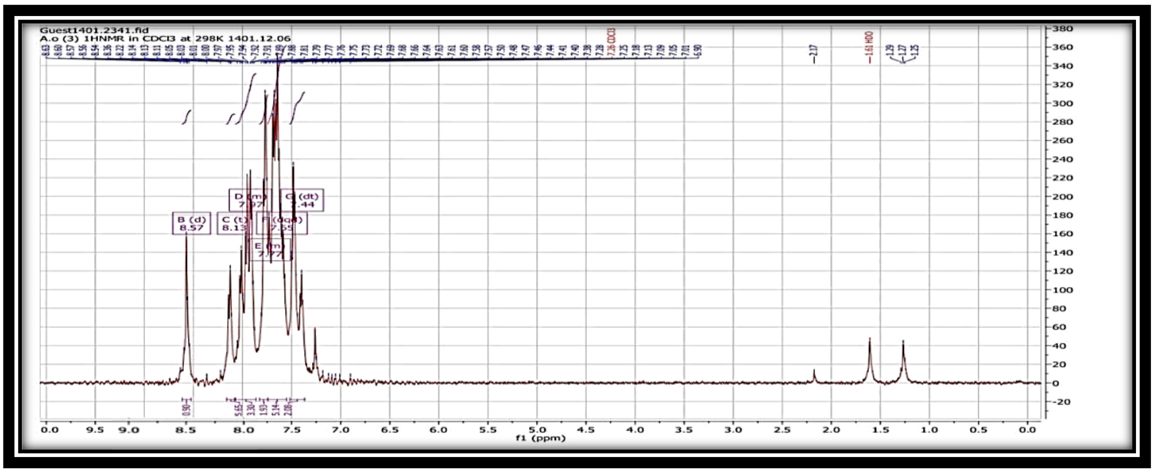


All ^{1}HNMR spectroscopy of the prepared compounds are characterized by the appearance of a strong signal at (7.2ppm) due to CDCl3 and the appearance of a signal at (1.5ppm) due to water

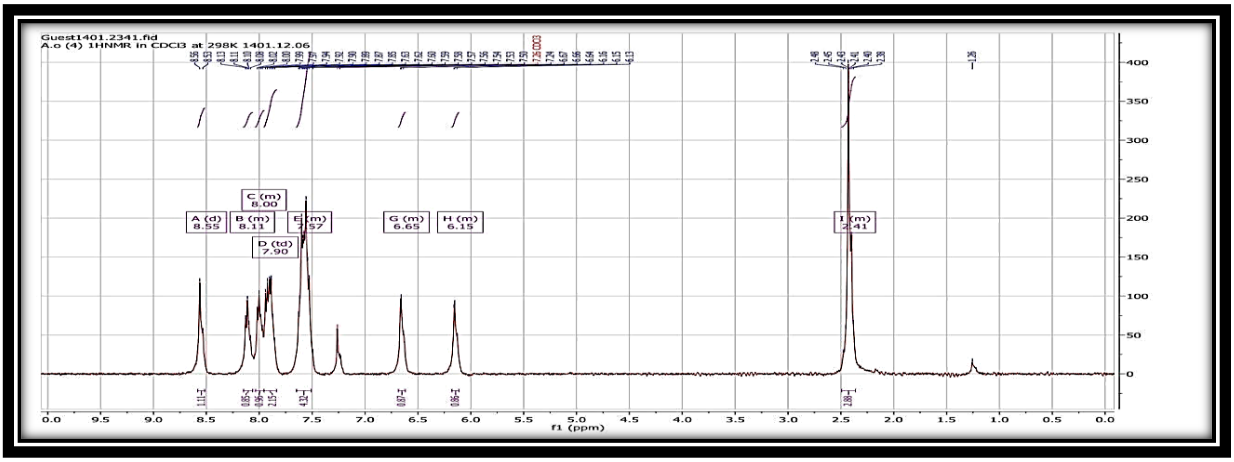
Table (4) the most important chemical displacements in ppm units for the 1HNMR spectra of the prepared chalcone compounds

Symbol	Compound	chemical displacements
H1		δ=8.57-7.44 (dd,2H,CH=CH) δ =8.13-7.55(m,16H,Ar-H)
H4		δ=2.41(m,3H,CH3) δ=8.55-7.90(dd,2H,CH=CH) δ=8.11-6.15(m,9H,Ar-H)
H5		δ= 3.88-3.34(dd,8H,-CH$_2$-CH$_2$-) δ= 8.04-6.93(dd,2H,CH=CH) δ= 7.84-7.38(m,13H,Ar-H)

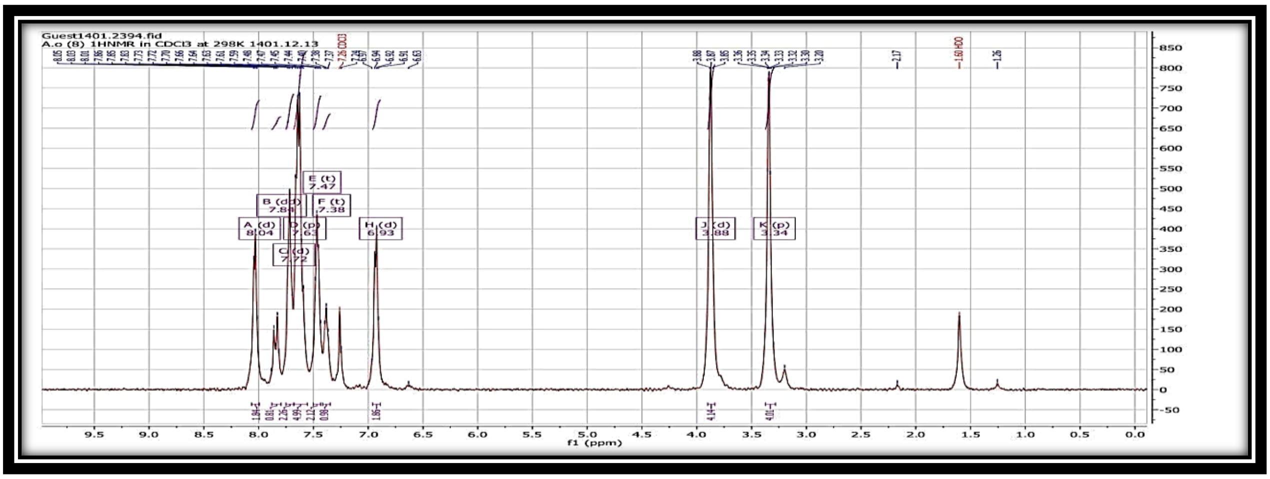
H6		δ= 3.87-3.33(mm,8H,-CH_2-CH_2-) δ =5.11(dd,2H,OCH_2) δ =7.01-6.29(dd,2H,CH=CH) δ= 8-7.25(m,13H,Ar-H)
H8		δ= 2.38(d,3H,CH3) δ =3.86-3.32(mm,8H,-CH_2-CH_2-) δ= 7.52-7.25(dd,2H,CH=CH) δ =8.01-6.11(m,6H,Ar-H)



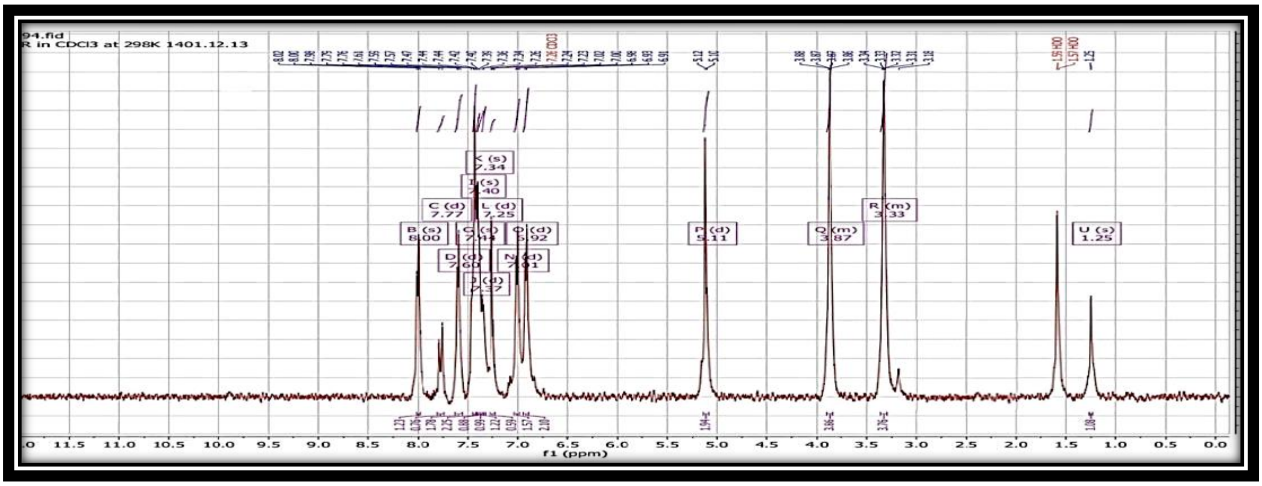
H1



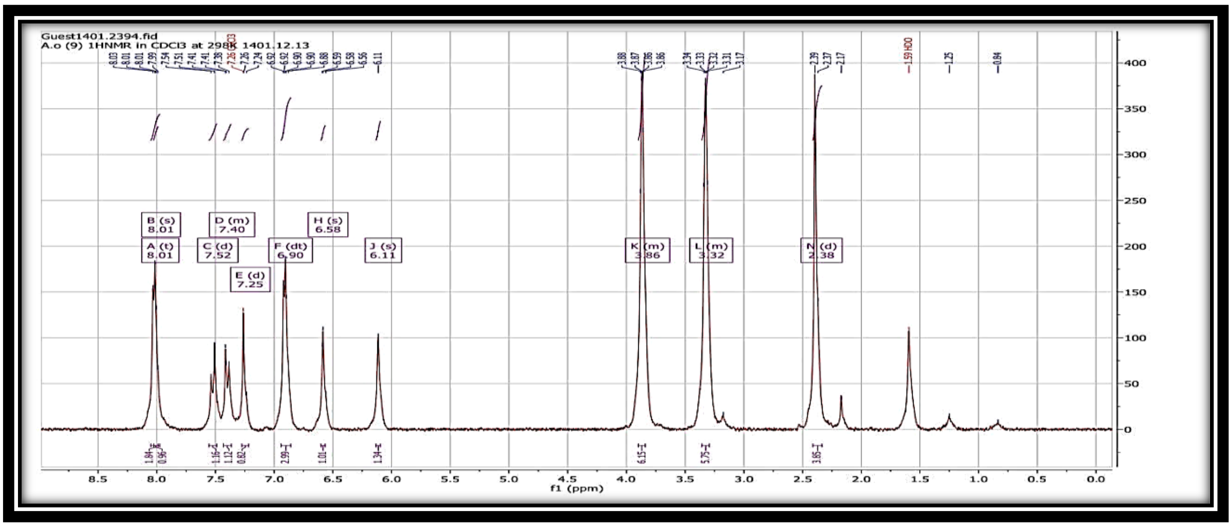
H4


Guest1401.2394.fid
A.o (8) 1HNMR in CDCl3 at 298K 1401.12.13
A (d) 8.04
B (dd) 7.84
C (d) 7.72
D (p) 7.63
E (t) 7.47
F (t) 7.38
H (d) 6.93
J (d) 3.88
K (p) 3.34
f1 (ppm)

H5


94.fid
R in CDCl3 at 298K 1401.12.13
K (s) 7.34
I (s) 7.40
C (d) 7.77
L (d) 7.25
B (s) 8.00
O (d) 6.92
D (d) 7.60
N (d) 7.01
J (d) 7.37
P (d) 5.11
Q (m) 3.87
R (m) 3.33
U (s) 1.25
f1 (ppm)

H6


Guest1401.2394.fid
A.o (9) 1HNMR in CDCl3 at 298K 1401.12.13
B (s) 8.01
A (t) 8.01
D (m) 7.40
C (d) 7.52
E (d) 7.25
F (dt) 6.90
H (s) 6.58
J (s) 6.11
K (m) 3.86
L (m) 3.32
N (d) 2.38
f1 (ppm)

H8

4- biological activity chalcone

The biological activity of some chemical compounds was tested in the microbiology laboratory for postgraduate studies in the Department of Life Sciences, College of Education for Pure Sciences - University of Basra against two types of pathogenic bacteria for humans, which are Gram-negative Escherichia coli and Gram-positive Staphylococcus aureus. It was obtained from patients attending Al-Fayhaa General Hospital in Basra Governorate, and the biological activity was tested by the Agar well diffusion method according to the method of (Balouiri et al. (2016) with some minor modifications(28,29,30)

The inhibitory ability of some of the tested chemical compounds, which was represented by the emergence of zones of inhibition of bacterial growth (the area free of bacterial growth around the pits of acres) indicates the ability of these chemical compounds to kill pathogenic bacteria under test, with varying degrees according to the different diameters of the inhibition zones measured (the most effective chalcone compounds are Compound H8 against both types of pathogenic bacteria under test, followed by compound H4 and then compound H6)

And there are compounds that did not affect the pathogenic bacteria tested at all, i. Caused by pathological bacteria, especially since these bacteria were resistant to more than three types of antibiotics, according to the preliminary tests conducted in the above-mentioned laboratory against antibiotics, or to combine these compounds with antibiotics to increase their effectiveness against pathological bacteria and activate them (Al-Saady, 2021), and this requires conducting more tests on these chemical compounds to know their cytotoxicity on normal cells and the extent of their negative effects on them, and to determine half the lethal dose, IC50, for normal cells, as well as to study the possibility of its effect on cancer cells.

Effective compound mm (5-10) damper diameter*

Good Effective Composite mm (10-20) Retarding Diameter*

* Retarding with a diameter of more than (20) mm is a highly effective compound As in the following figure

Table (5) represents the biological activity **values of chalcone compounds for both types of bacteria staph and E.COli**

numbering	compound symbol	just change the phrase by (zone of inhibition)	
		Staphylococcus aureus	*Escherichia coli*
1	H1	0	10
2	H8	7	17
3	H6	10	10
4	H4	10	12
5	DMSO	0	0

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