Sys Rev Pharm 2021;12(3):270-285
A multifaceted review journal in the field of pharmacy

Synthesis And Antibacterial Evaluation Of Some New 1, 5- Benzooxazepines Derivatives

Mohammad M.Al-Tufah[1] , **Khalid A. Al-Badrany**[2] , **Saad Salim Jasim**[3]

[1] Directorate of Education, Kirkuk, Ministry of Education,Iraq.
[2] Chemistry Department, College of Education for Pure Sciences, University of Tikrit, Tikrit, Iraq.
[3] Chemistry Department, College of Education for Pure Sciences, University of Kirkuk, Kirkuk, Iraq.
Corresponding author: Mohammad M.Al-Tufah E-mail: Mohamadmd282@gmail.com

ABSTRACT

Ten new chalcones were prepared in three steps, firstly phthalic anhydride reacted with 4- amino acetophenone to produce 2-(4-acetyl phenyl carbamoyl) benzoic acid (M1), secondly [2-(4-acetyl phenyl carbamoyl) benzoic acid (M1)] suffers from the loss of a water molecule via reaction with (anhydrous sodium acetate and acetic anhydride) to produce 2-(4-acetyl phenyl) isoindoline-1,3-dione (M2), thirdly (M2) condensed with various substituted benzaldehydes affording chalcones (M3- M12) were reacted with 2-aminophenol to produce 1, 5-benzooxazepines compounds (M13- M22).

The prepared compounds were characterized by determination of melting point, FT-IR and some of the prepared compounds have been characterized by (1H-NMR and 13C-NMR) techniques, the antibacterial activity of some of the compounds have also been evaluated.

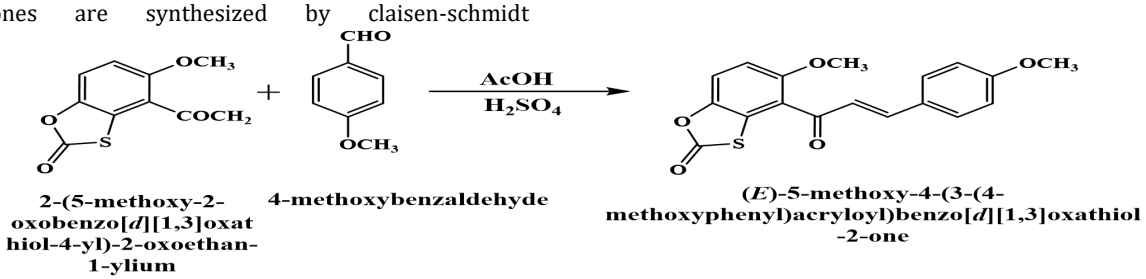
Keywords: Chalcones, Benzoxazepines, phenylcarbamoyl, antibacterial

Correspondence:
Mohammad M.Al-Tufah
Directorate of Education, Kirkuk, Ministry of Education,Iraq.

*Corresponding author: Mohammad M.Al-Tufah email-address: Mohamadmd282@gmail.com

INTRODUCTION

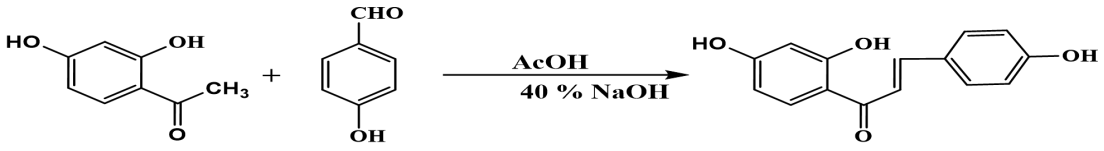
Aldol condensations represent an important class of carbon-carbon bond formation reactions both in nature and in synthetic chemistry[1]. Chalcones are 1,3-diphenyl-2-propene-1-one, in which two aromatic rings are linked by a three carbon α, β-unsaturated carbonyl system [2]. Chalcones are synthesized by claisen-schmidt condensation of aldehyde and ketone by base catalyzed or acid catalyzed followed by dehydration to yield chalcones [3]. In the presence of sulfuric acid **(scheme 1)** the reaction of 4-methoxybenzaldehyde with 4-acetyl-5-methoxybenzo[d][1,3]oxathiol-2-one gives the next product [4].



2-(5-methoxy-2-oxobenzo[*d*][1,3]oxathiol-4-yl)-2-oxoethan-1-ylium **4-methoxybenzaldehyde** **(*E*)-5-methoxy-4-(3-(4-methoxyphenyl)acryloyl)benzo[*d*][1,3]oxathiol-2-one**

scheme 1. Using sulfuric acid to prepare the chalcone compound

The reaction of 2,4-Dihydroxy acetophenone with 4-hydroxybenzaldehyde (scheme 2) produces chalcone compound [5].



2,4-Dihydroxy acetophenone **4-hydroxybenzaldehyde** **(*E*)-1-(2,4-dihydroxyphenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one**

scheme 2. The effect of sodium hydroxid on chalcone compound formation.

Chalcones have also been synthesized using different catalyst such as natural phosphate lithium nitrate [6], KF/natural phosphate [7], $SOCl_2$ [8], Na_2CO_3 [9], silica chloride [10] , $Ba(OH)_2$ / LiOH [11] and by Suzuki reaction [12]. Many chalcones are found to have medicinal and pharmaceutical applications ranging from antitumor[13], anti-inflammaotry[14] , antifungal[15], antimalarial [16], antimicrobial[17] and anticancer[18].

Benzoxazepines are a sevenmembered unsaturated heterocyclic compounds that contains two hetero atoms (oxygen and nitrogen) [19]. The 1,5-benzoxazepines (1, 2,3) are important nitrogen- and oxygen-containing seven membered heterocyclic compounds in drug research since they possess diverse bioactivities[20] figere 1:

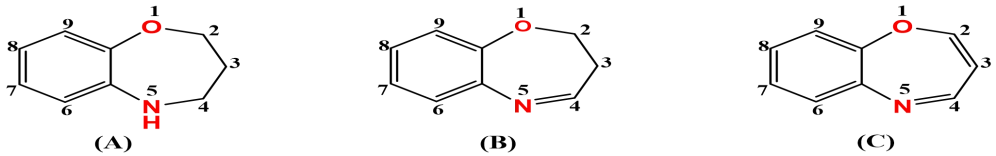
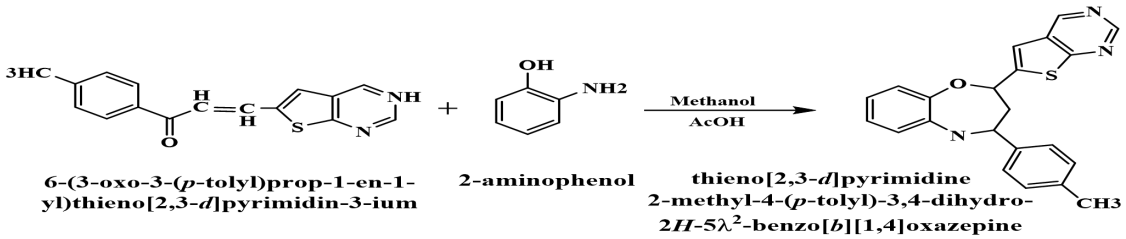


Figure 1 : General structures 1,5-benzoxazepine

These compounds have been synthesized by condensation of chalcone and 2-aminophenol in presence of glacial acetic acid[21](**Scheme 3**)



Scheme 3. Synthesized of 1, 5- Benzoxazepines Containing Thieno [2, 3-d] Pyrimidine Nucleus

Oxazepine derivatives have biological activities such as antibacterial [22]antifungal[23], Anti-cancer [24]), enzyme inhibitors, [25] and analgesic[26]. The 1,4-oxazepines are the parent core of medicinally important drugs like amoxapine, loxapine and sintamil[27]

METHODOLOGY

Materials

Aminophenol, 4–Aminoacetophenone, acetone, anhydrous sodium acetate, phthalic anhydride, sodiumhydroxide, ethanol, acetic anhydride and all aromatic aldehydes are providing from Aldrich and Fluka, BDH they used without further purification. Melting points of the compounds were recorded on electrothermal melting point apparatus (uncorrected). FT-IR spectrum was recorded on Shimadzu FTIR-8400 spectrophotometer as KBr disc. ^{1}HNMR and ^{13}CNMR spectra were registered on Bruker spectroscopic ultra-shield magnets 300 MHz instruments using tetramethylsilane (TMS) as an standard and Dimethyl Sulfoxide -d_6 as a solvent.

General procedure for the synthesis of 2-((4-acetylphenyl)carbamoyl)benzoic acid[28] (M_1)

(0.01 mol) 1.4g of phthalic anhydride was dissolved in (40 mL) of acetone in a round-bottom flask fitted with dropping funnel. then equimolar amount (0.01 mol) 1.35 g of p-amino acetophenone was dissolved in (20 ml) of acetone and added dropwise with stirring for (4) hours, The produced precipitate was purified by filtered and recrystallized from ethanol. Compound (**M_1**) was obtained as a White powder with a yield of 82%.

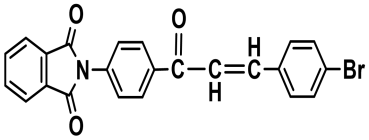
General procedure for the synthesis of 2-(4-acetylphenyl)isoindoline-1,3-dione[28] (M_2)

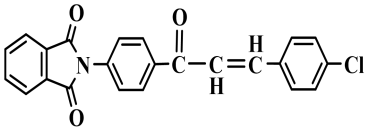
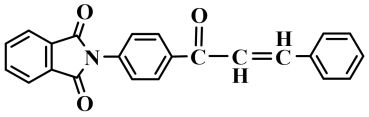
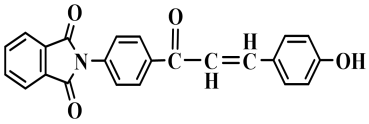
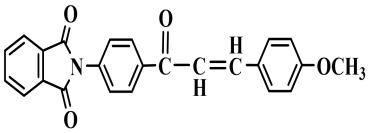
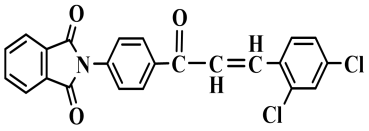
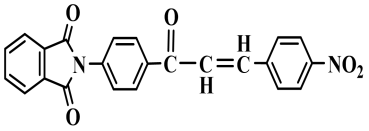
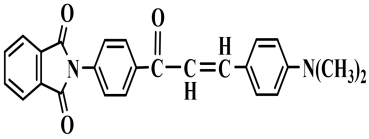
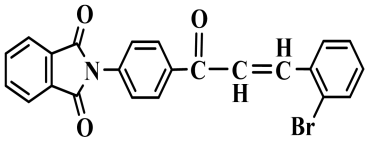
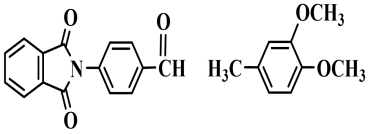
Compound (**M_2**) (0.02 mol, 5.66 g) in (50 mL) of acetic anhydride was mixed with (0.25 g) of anhydrous sodium acetate and refluxed for (4) hours with stirring. The reaction mixture was was cooled to room temperature then poured into crushed ice with stirring and the obtained precipitate was filtered, dried and recrystallized from acetone. Compound (**M_2**) was obtained as a White powder with a yield of 87%.

General procedure for the synthesis of chalcones [29] (M_3-M_{12}).

To a stirred mixture of compound **M_2** (0.008 mol, 2.12g) and substituted benzaldehydes (0.008 mol in absolute ethanol (30 ml), a solution of aqueous potassium hydroxide (15 ml, 40%) was added. The mixture was stirred for (6-8) hours at room temperature, The resulting mix kept in a good conditions until the morning of the next day at room temperature, poured into crushed snow, neutralized by dil HCl and recrystlized from ethanol to give the corresponding chalcone derivative. The structural formulae, names, meltin points, colors and percentage of yields for the synthesized chalcones are recorded in Table **1**.

Table (1): Shows the physical properties of the compounds (M_3-M_{12}).

Comp. No	Structural formula	Nomencclature	M.p C°	Yield %	Color
M_3		2-(4-((E)-3-(4-bromophenyl)acryloyl) phenyl)isoindoline-1,3-dione	186-188	87	Yellow

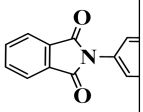
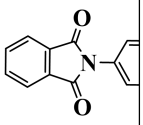
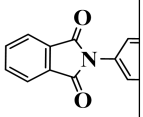
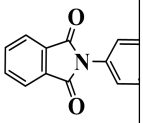
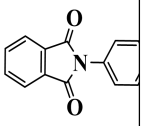
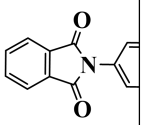
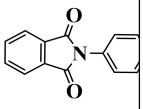
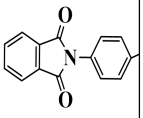
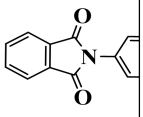
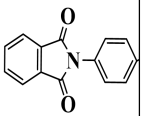
M_4		2-(4-((E)-3-(4-chlorophenyl)acryloyl) phenyl)isoindoline-1,3-dione	206-208	88	Light Yellow
M_5		2-(4-((E)-3-phenylacryloyl)phenyl) isoindoline-1,3-dione	196-198	81	Light Yellow
M_6		2-(4-((E)-3-(4-hydroxyphenyl)acryloyl)phenyl)isoindoline-1,3-dione	214-216	71	Light Yellow
M_7		2-(4-((E)-3-(4-methoxyphenyl)acryloyl)phenyl)isoindoline-1,3-dione	165-167	91	Yellow
M_8		2-(4-((E)-3-(2,4-dichlorophenyl)acryloyl)phenyl)isoindoline-1,3-dione	202-204	86	Light Yellow
M_9		2-(4-((E)-3-(4-nitrophenyl)acryloyl)phenyl)isoindoline-1,3-dione	159-161	73	Dark Brown
M_{10}		2-(4-((E)-3-(4-(dimethylamino) phenyl)acryloyl)phenyl)isoindoline-1,3-dione	108-110	89	Reddish Orang
M_{11}		2-(4-((E)-3-(2-bromophenyl)acryloyl) phenyl)isoindoline-1,3-dione	112-124	84	Yellow
M_{12}		2-(4-((E)-3- (3,4-dimethoxy)acryloyl)phenyl)isoindoline-1,3-dione	148-150	92	Yellow

General procedure for the synthesis of 1,4-oxazepines derivatives[30] (M_{13}-M_{22}).

The ethanol solution (20 ml) of compounds (**M_3-M_{12}**) (0.05 mol) was added to 2-aminophenol (0.05 mol) with (5ml) 10% NaOH and refluxed for (6) hr. after refluxing solvents were distilled off under reduced pressure and the solid thus obtained were recrystallised from ethanol. The structural formulae, names, melting points, colors and percentage of yields for the synthesized oxazepin derivatives are recorded in Table **2**.

Table 2: Shows the physical properties of the compounds (M_{13}-M_{22}).

Comp. No	Structural formula	Nomencclature	M.p °C	Yield %	Color

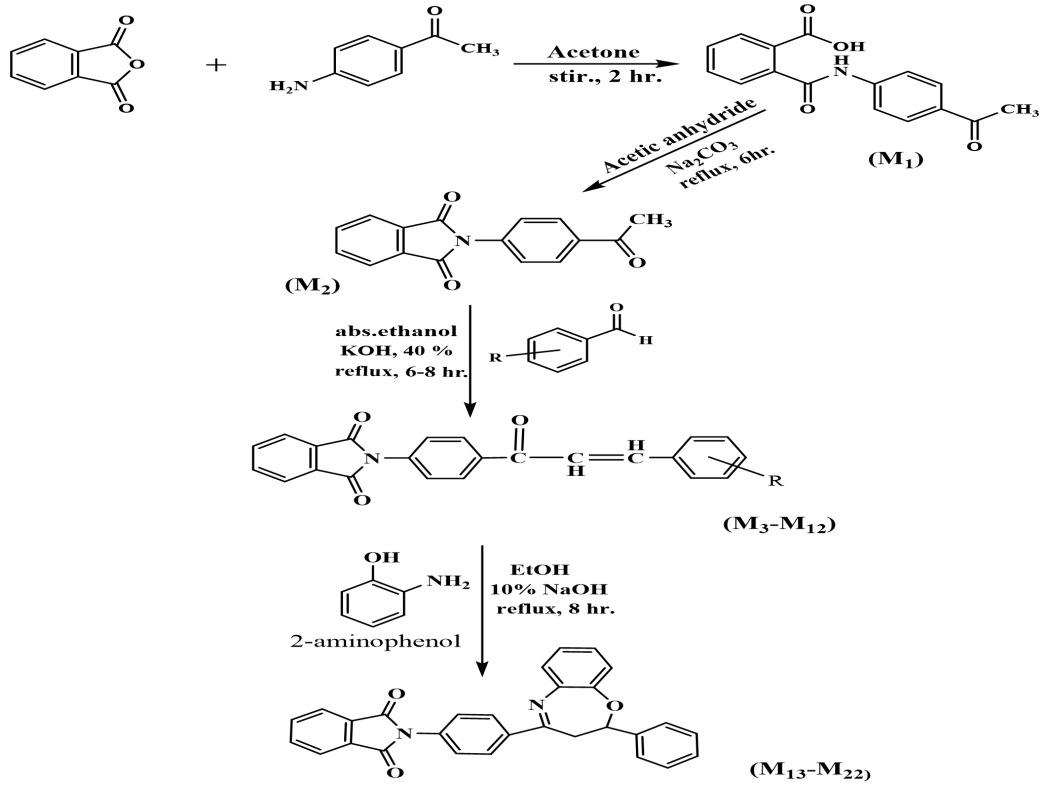
M_{13}		2-(4-(2-(4-bromophenyl)-2,3-dihydrobenzo[b][1,4]oxazepin-4-yl)phenyl)isoindoline-1,3-dione	140-142	71	Brown
M_{14}		2-(4-(2-(4-chlorophenyl)-2,3-dihydrobenzo[b][1,4]oxazepin-4-yl)phenyl)isoindoline-1,3-dione	135-137	51	Yellow
M_{15}		2-(4-(2-phenyl-2,3-dihydrobenzo[b][1,4]oxazepin-4-yl)phenyl)isoindoline-1,3-dione	104-106	58	Yellow
M_{16}		2-(4-(2-(4-hydroxyphenyl)-2,3-dihydrobenzo[b][1,4]oxazepin-4-yl)phenyl)isoindoline-1,3-dione	156-158	66	Orang
M_{17}		2-(4-(2-(4-methoxyphenyl)-2,3-dihydrobenzo[b][1,4]oxazepin-4-yl)phenyl)isoindoline-1,3-dione	113-115	64	Brown
M_{18}		2-(4-(2-(2,4-dichlorophenyl)-2,3-dihydrobenzo[b][1,4]oxazepin-4-yl)phenyl)isoindoline-1,3-dione	133-135	68	Orang
M_{19}		2-(4-(2-(4-nitrophenyl)-2,3-dihydrobenzo[b][1,4]oxazepin-4-yl)phenyl)isoindoline-1,3-dione	183-185	65	Brown
M_{20}		2-(4-(2-(4-(dimethylamino)phenyl)-2,3-dihydrobenzo[b][1,4]oxazepin-4-yl)phenyl)isoindoline-1,3-dione	147-150	48	Brown
M_{21}		2-(4-(2-(2-bromophenyl)-2,3-dihydrobenzo[b][1,4]oxazepin-4-yl)phenyl)isoindoline-1,3-dione	152-154	36	Brown
M_{22}		2-(4-(2-(3,4-dimethoxyphenyl)-2,3-dihydrobenzo[b][1,4]oxazepin-4-yl)phenyl)isoindoline-1,3-dione	110-112	44	Brown

Bacterial activity evaluation

In this study we investigated antibacterial activity of compounds (**M_8, M_9, M_{13}, M_{14}, M_{17}, M_{18}, M_{19},** and **M_{22}**) which were examined for activity against some bacterias like (gr + *Staphylococcus aureus* and *Staphylococcus epidermidis* and the second type was the gr –*Escherichia coli*, *Pseudomonas aeruginosa*), the concentrations of compounds were (0. 01 , 0.001 ,0.0001) mg/ml, using DMSO as a solvent using, Agar well-diffusion method[31] and the obtained results were compared with control group (Norfloxacin and ciprofloxacine) .

RESULTS AND DISCUSSION

The following **scheme 4** show the reaction sequence for the compounds that has been synthesized.

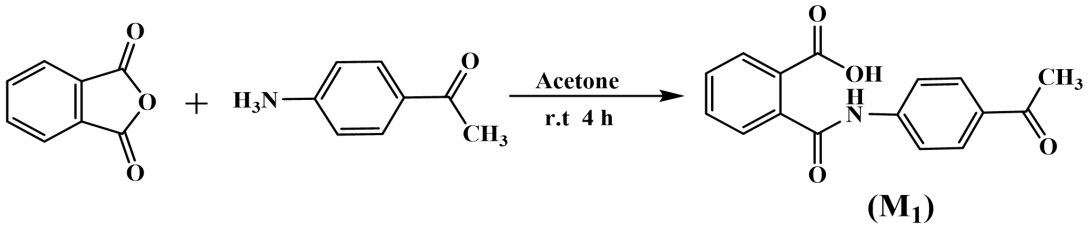


R: = H, 2- Br, 4- Br, 4- Cl, 4- OH, 4- OCH_3, 4- NO_2, 4- $N(CH_3)_2$, 2,4-diCl, 3,4- diOCH_3

Schem 4 : Represents the prepared compounds

Identification of compound (M_1)

Compound (**M_1**) (**Scheme 5**) were synthesized according to the reaction between phthalic anhydride and 4-aminoacetophenone In the presence of the acetone as a solvent.



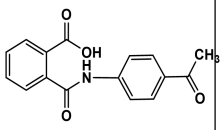
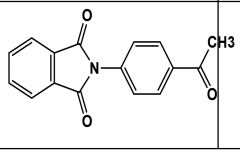
Scheme 5: Structureof the synthesized compound (**M1**)

Compound (**M_1**) given a bands in FT-IR spectrum at (3483)cm^{-1}, (3238)cm^{-1} and (2926)cm^{-1} denotes to stretching vibration of (N-H) bond, (OH) bond and (C-H)alf. bond, other absorbtion appeared at (1708)cm^{-1} ,(1674)cm^{-1}, (1647)cm^{-1} and(1320)cm^{-1}denotes to (C=O) of carboxylic, (C=O) of ketone, (C=O) of amide group and (C-N) group. Not figure **2** and table **3** .

^{1}H-NMR spectrum for compound (**M_1**), (in Dimethyl Sulfoxide -d6 as a solvent) exhibit : 13.09 δ (S, H,OH) ; 10.68 δ (S, H,NH) ; (7.98-7.56) δ (d,8H,Ar-H); 2.43 δ (S, 3H,CH_3), Not figure **3**.

^{13}CNMR spectrum of compound (**M_1**), (in Dimethyl Sulfoxide -d_6 as a solvent) exhibit a signals at δ(26.9) ppm denotes to (CH_3) group, the signals at δ (119,127,130,133,138 and 144) ppm denotes the carbons of aromatic ring and the signal at δ (167.7) pmm denotes to (C=O) Carbonyl group, the signaln at δ (168.3) pmm denotes to amid carbnyl group (N-C=O), another signal at δ(198) pmm denotes to (C=O) ketone group. Note figure **4**.

Table 3: Shows the IR data of compound (M_1 , M_2)

Comp. No.	Compound Structure	FT-IR (KBr) cm^{-1}						
		υ(N-H) amide	υ(O-H) Carboxylic	υ(C=O) carboxylic	υ(C=O) keton	υ(C=O) amide	υ(C=O) imide	υ(C-N) imide
M_1		3483	3238	1708	1674	1647	-	1326
M_2		-	-	-	1708	-	1672 1647	1365

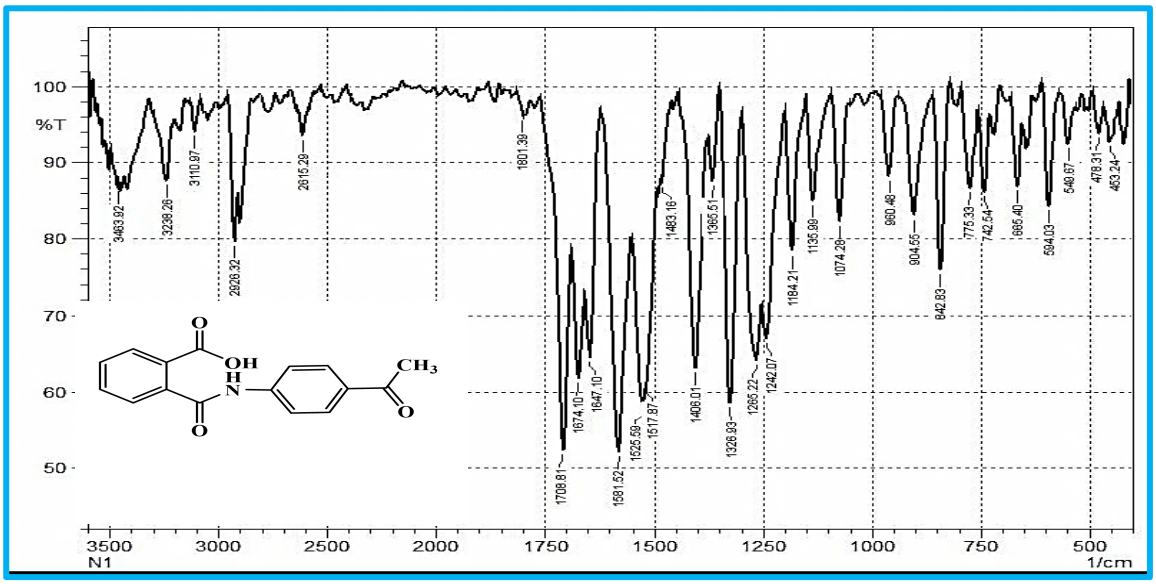


Fig. 2: FT-IR spectrum of compound (M_1)

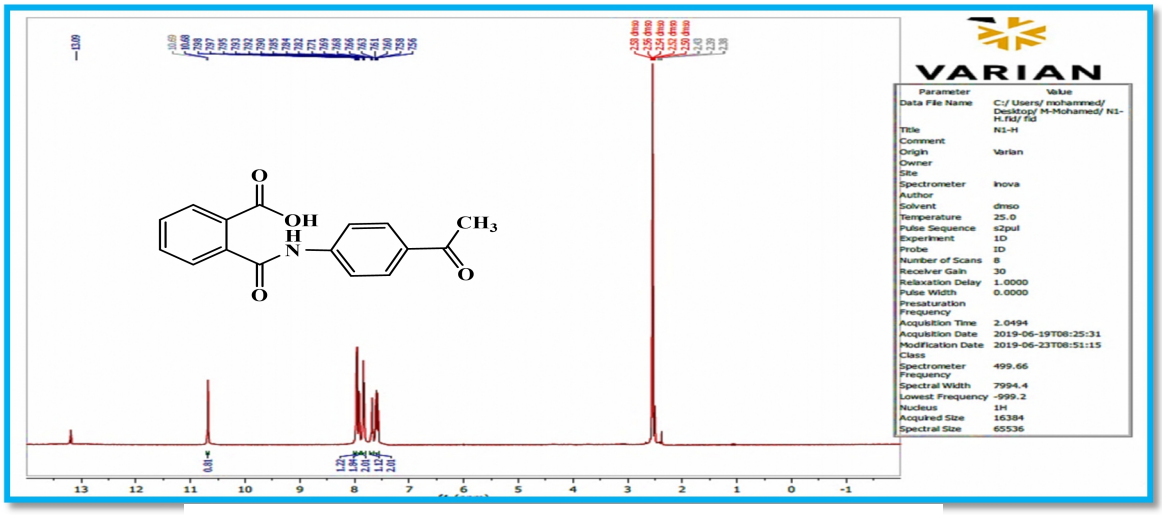


Fig. 3: ^{1}H-NMR specrum of compound (M_1)

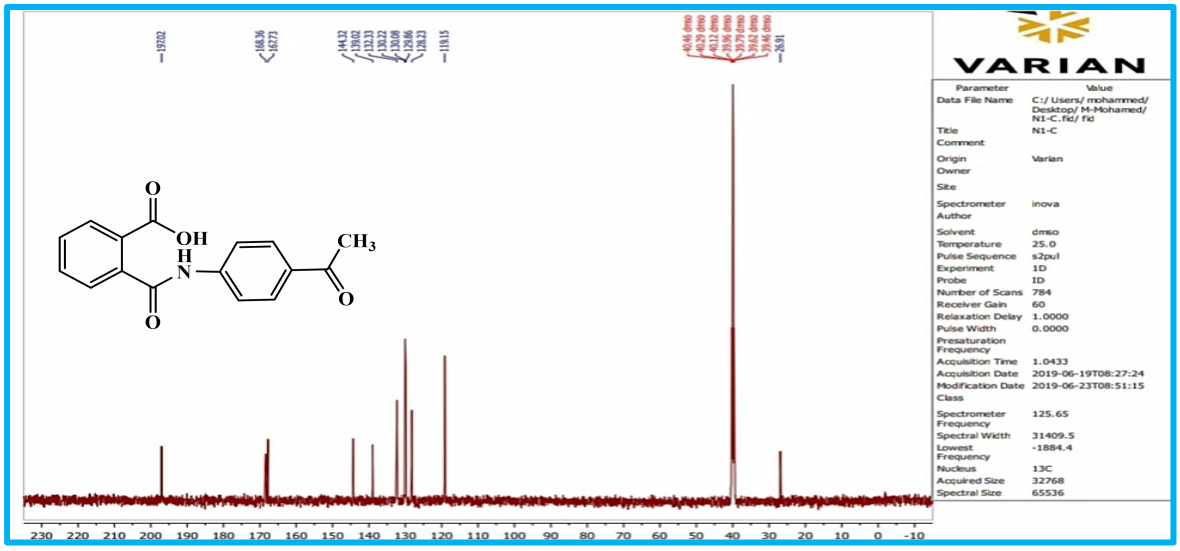
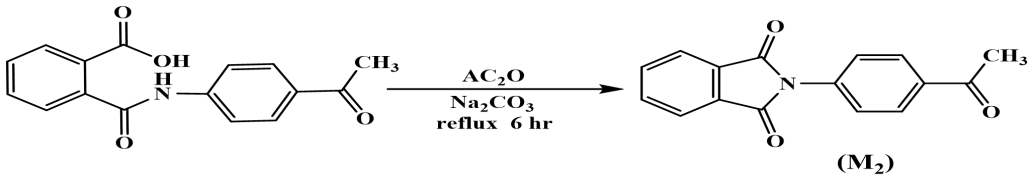


Fig. 4: ^{13}C-NMR spectrum of compound (M_1)

Identification of compound (M_2)

Compound (M_2) (**Scheme 6**) were synthesized via reaction a mixture of 2-(4-acetyl phenyl carbamoyl) benzoic acid with (anhydrous sodium acetate and acetic anhydride).



Scheme 6: Structureof the synthesized compound (M_1)

Compound (M_2) given a bands in FT-IR spectrum at (1708)cm^{-1}, (1672,1647)cm^{-1} and (1365)cm^{-1} denotes to stretching vibration of (C=O) of ketone d, (C=O) of imide group and (C-N) group. Not figure **5** and table **3**.

^{1}H-NMR spectrum for compound **(M_2)**, (in Dimethyl Sulfoxide -d6 as a solvent) exhibit : 2.75 δ (S, 3H,CH_3) ;; (8.18-7.56) δ (d,8H,Ar-H). Not figure **6**. while ^{13}C-NMR spectrum of compound (M_2) exhibit an signal at δ(27.2) ppm denotes to (CH_3) group, and the signals at(124, 127, 129, 132, 135, and 136) pmm denotes to the carbons of aromatic system, an signal at δ(167.0) ppm denotes to imide carbonyl group (C=O), an signal at δ(197) ppm denotes to carbonyl group (C=O) of ketone. Note figure **7**.

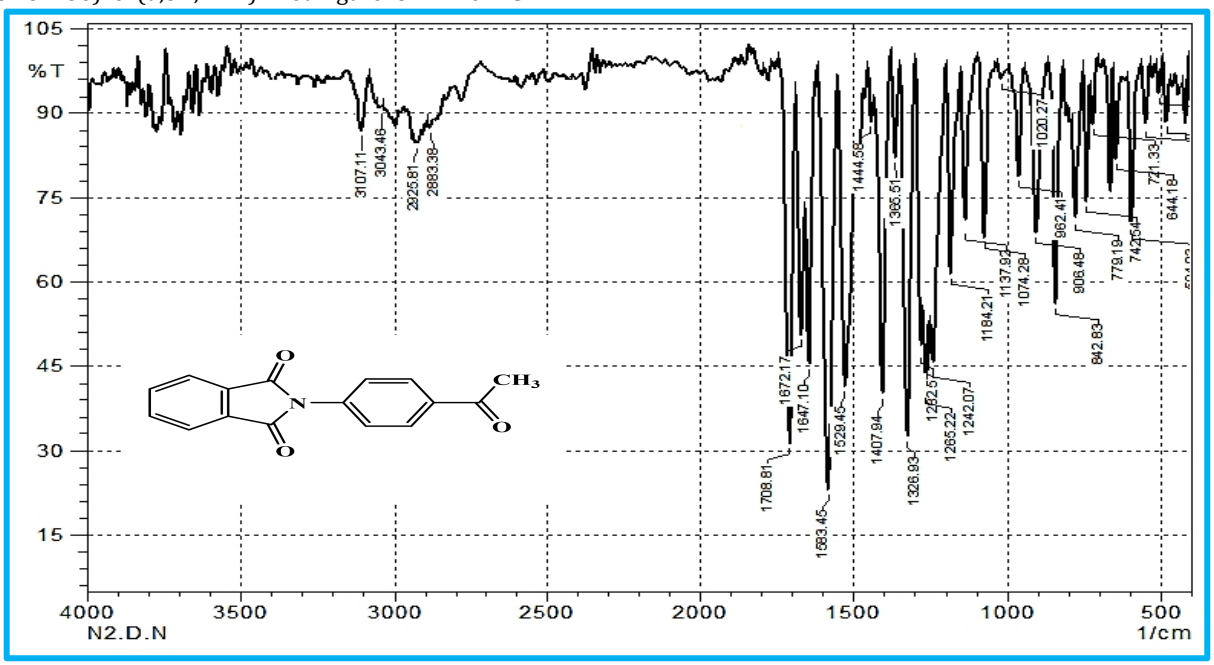


Fig. 5: FT-IR spectrum of compound (M_2)

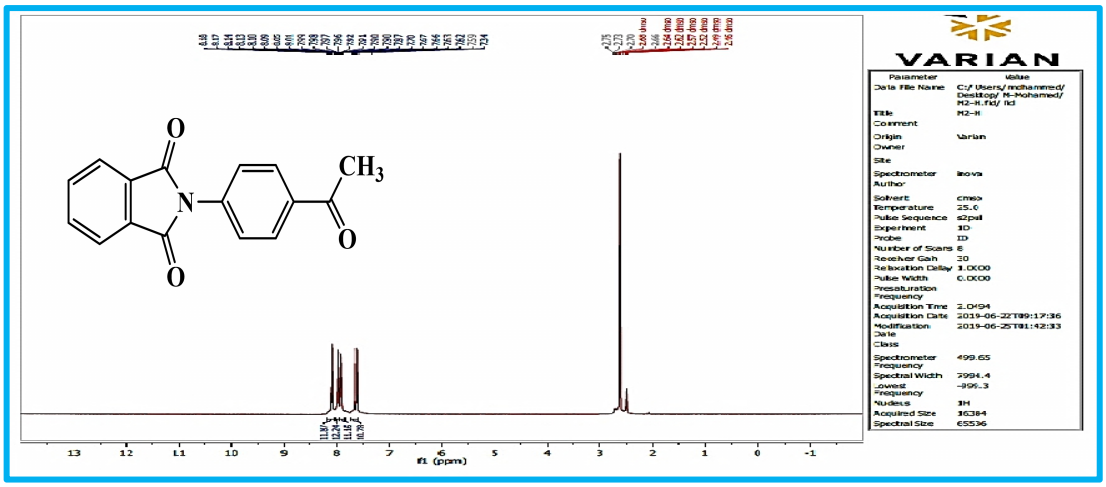


Fig. 6: ^{1}H-NMR specrum of compound (M_2)

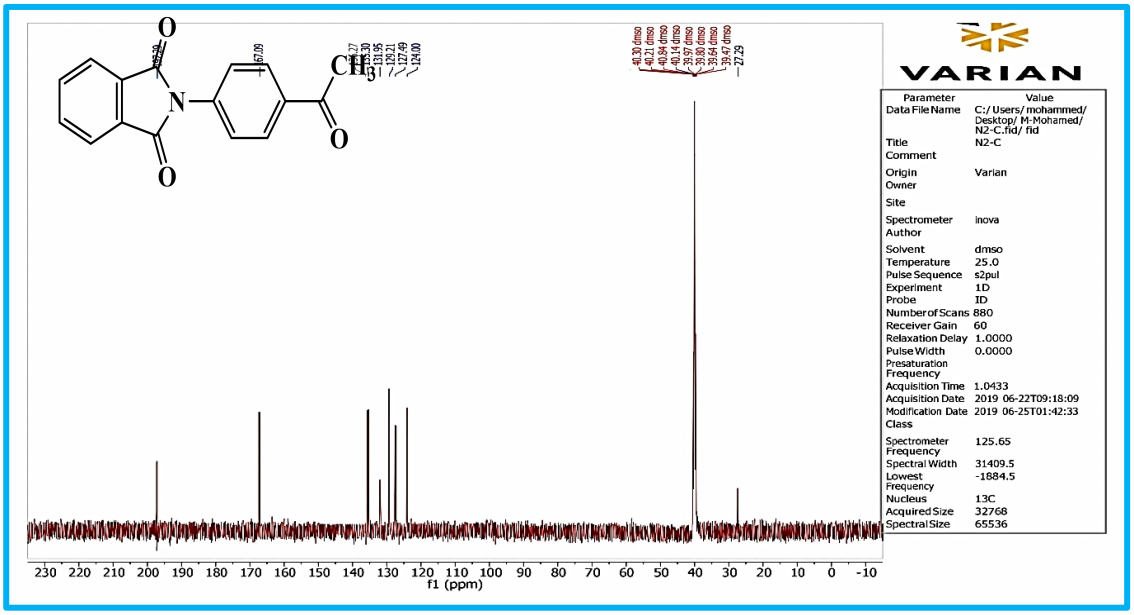
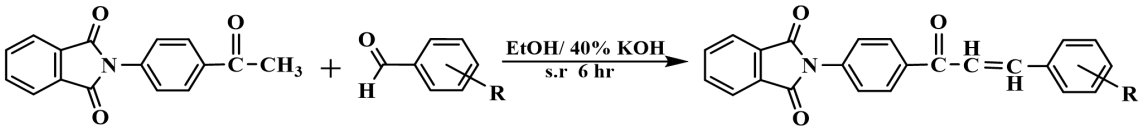


Fig. 7: ^{13}C-NMR specrum of compound (M_2)

Identification of chalcone compounds (M_3 – M_{12})

The compounds (**M_3-M_{12}**) (**Scheme7**) were synthesized according to the reaction of compound (**M_2**) with different aromatic aldehydes in absolute ethanol a solution of aqueous potassium hydroxide (40 %)



R= 4-Br, 4-Cl, H, 4-OH, 4-OCH_3,2,4-DiCl, 4-NO_2, 4-$N(CH_3)_2$, 2-Br, 3,4-diOCH_3 **(M_3-M_{12})**

Scheme 7: Structureof the synthesized compound (**M_3-M_{12}**)

IR spectrum of compound (**M_6**) exhibited bands at (3128)$^{cm-1}$ denotes to streching vibration of (= C-H) of aromatic ring and the double bond of α-β unsaturated group and the bands at (1681)$^{cm-1}$, ,(1655)$^{cm-1}$,(1583,1525)$^{cm-1}$, (1325)$^{cm-1}$ denotes to stretching vibration of υ(C=O) of ketone, υ(C=C) of aliphatic, υ(C=C) of aromatic, and υ(C-N) of imid group respectively the other compounds showed an asymptotic absorbtions of compound (**M_6**). Note figures **8** and table **4**.

^{1}H-NMR spectrum for compound (**M_6**), (in Dimethyl Sulfoxide-d6 as a solvent) exhibit a signal at δ (10.69) pmm indicate to the protons of the (OH) groups amd multiple signal at δ(8.16-6.81) pmm denotes to the protons of aromatic system and the olefinic protons. Note figure **9**.

^{13}C-NMR spectrum of compound (**M_6**) (in dimethyl Sulfoxide -d6 as a solvent) exhibit an signals at δ (119,128,129,130,132.23,132.31.139 and 144) pmm

denotes to the aromatic and olfinic carbons,the signals at δ(167) pmm denotes to the carbon of carbonyl of imide group, an signal at δ(197) pmm denotes to the carbon of carbonyl group,. Note figures **10**.

Table 4: Shows the IR data of compound (M_3-M_{12})

Comp. No.	R	IR (KBr) cm-1				
		υ (=C-H) Alip.	υ (C=O) Ketone	υ (C=C) Alip.	υ (C-N)	Other
M_3	4-Br	3055	1663	1625	1226	υ (C-Br) 661
M_4	4-Cl	3042	1690	1640	1235	υ (C-Cl) 785
M_5	H	3035	1700	1637	1261	-
M_6	4-OH	3066	1672	1649	1271	υ (C-OH) 3269
M_7	4-OCH_3	3059	1658	1598	1218	υ CH_3 2925.2802
M_8	2,4-diCl	3059	1652	1598	1220	υ C-Cl 811
M_9	4-NO_2	3062	1673	1607	1245	υ (NO2) 1450, 1327
M_{10}	4-$N(CH_3)_2$	3044	1678	1610	1266	υ CH_3 2970,2842
M_{11}	2-Br	3067	1680	1625	1226	υ (C-Br) 670
M_{12}	3,4-diOCH_3	3033	1675	1630	1247	υ CH_3 2935,2840

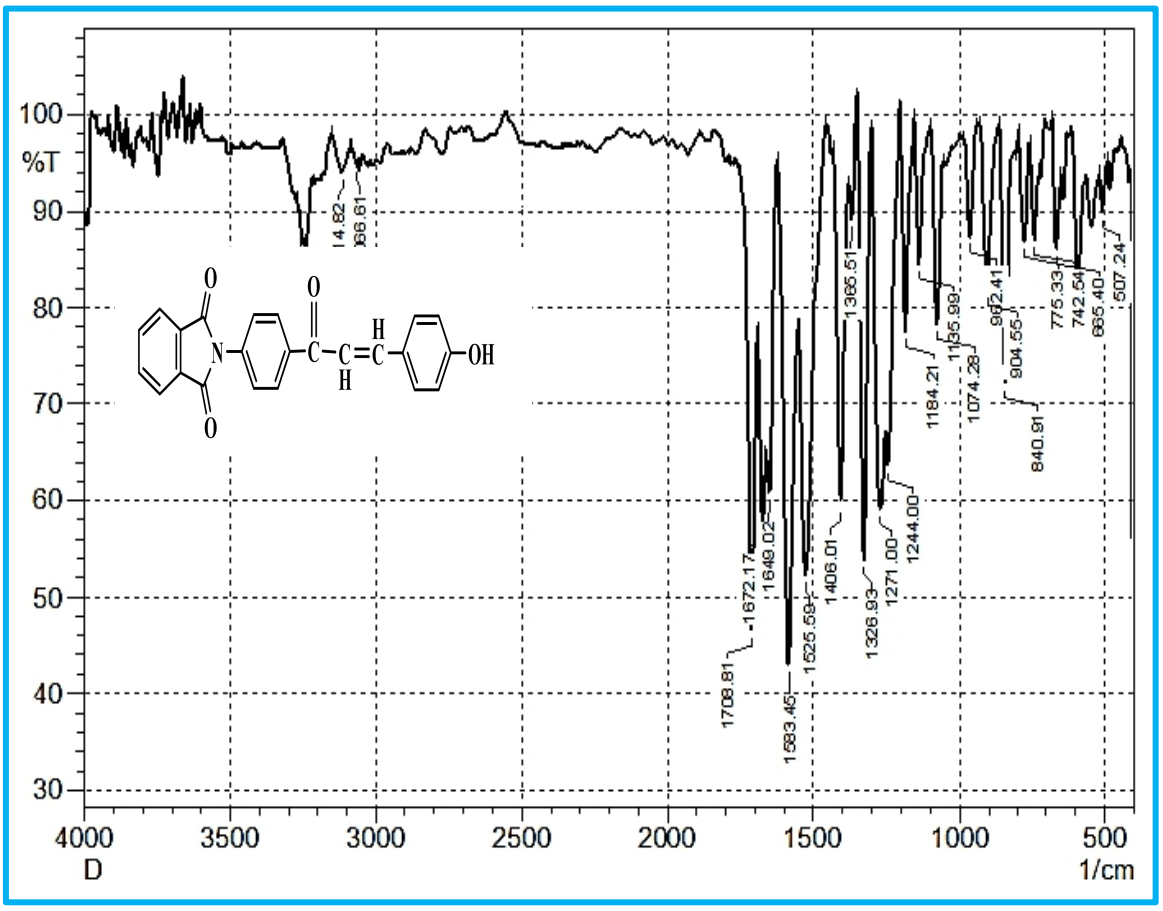


Fig. 8: FT-IR spectrum of compound (M_6)

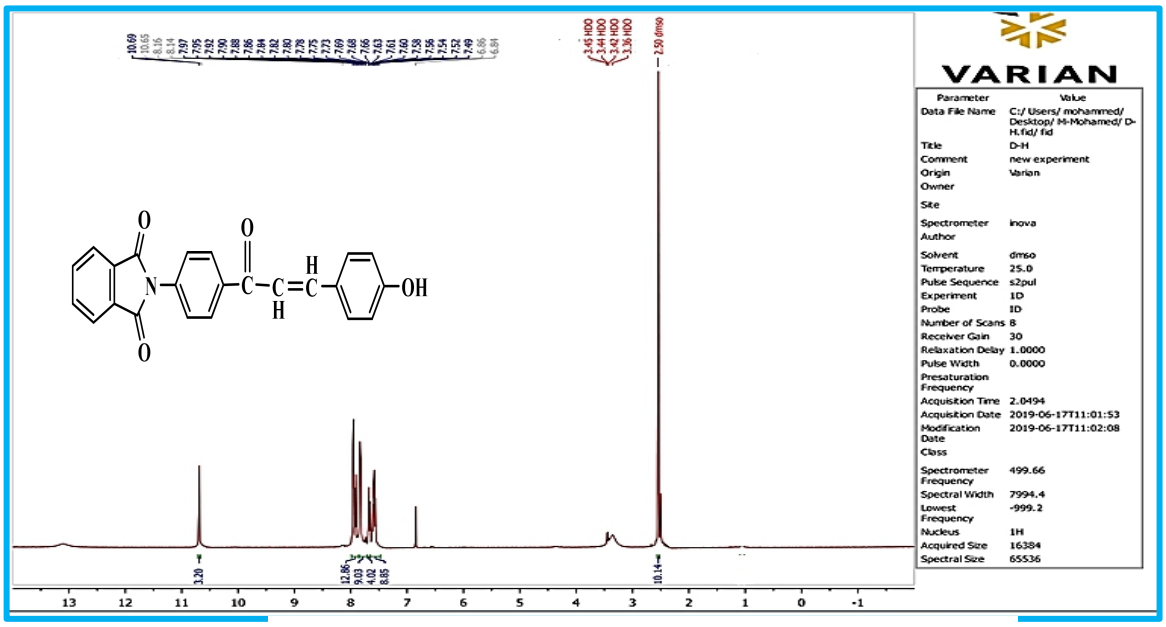


Fig. 9: ^{1}H-NMR specrum of compound (M_6)

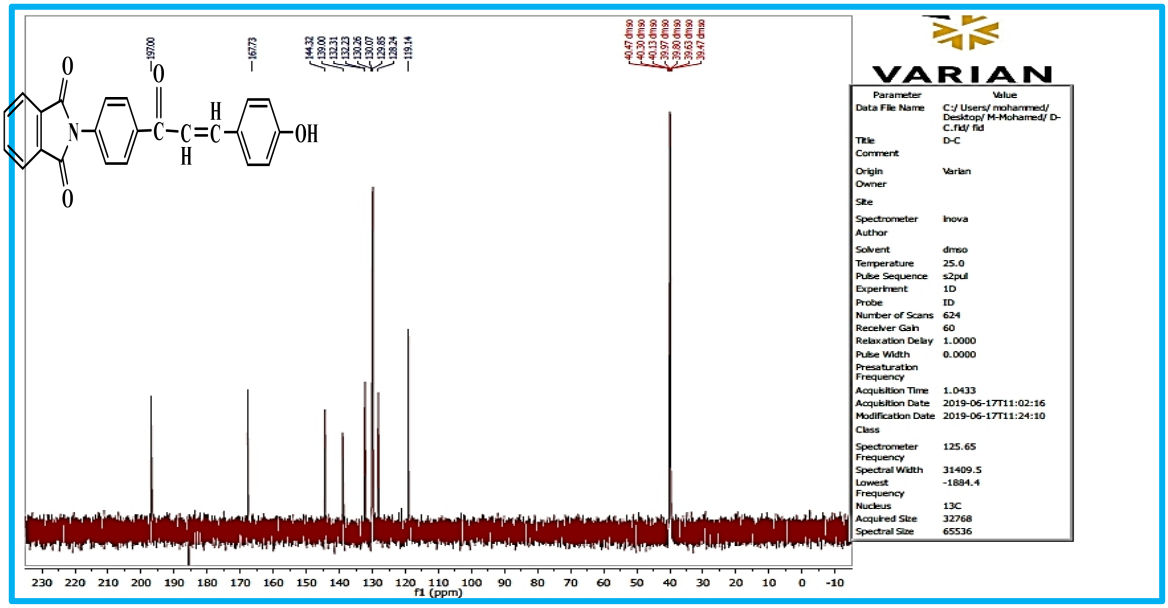
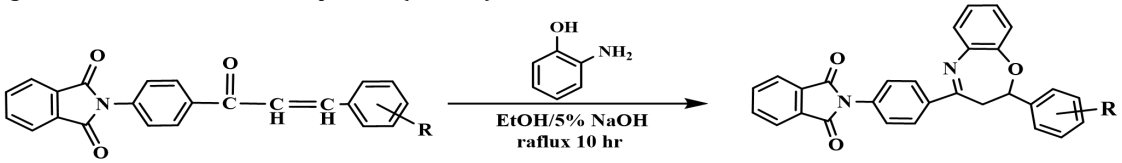


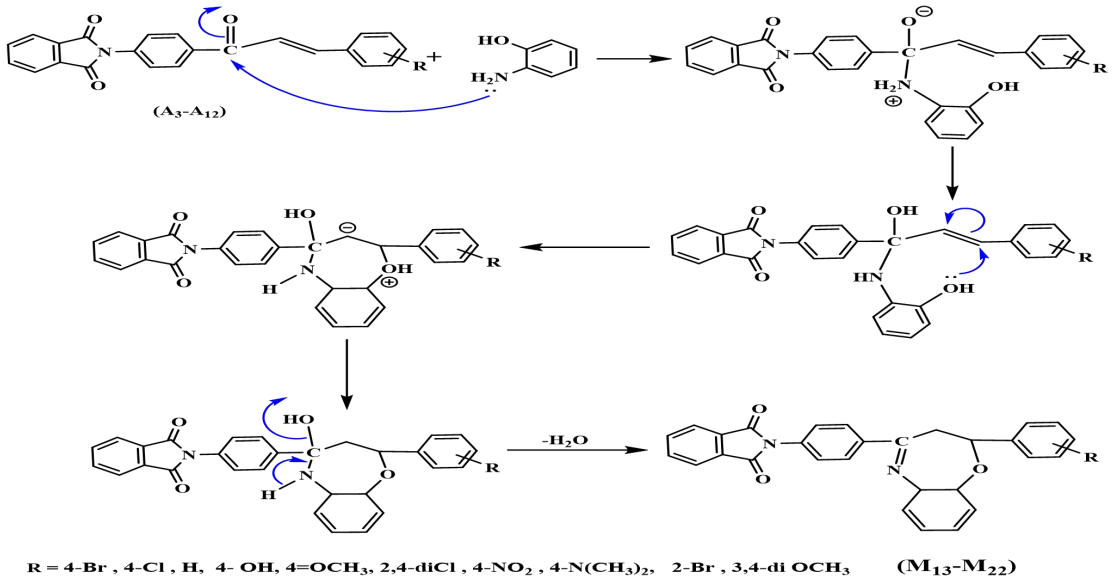
Fig. 10: ^{13}C-NMR specrum of compound (M_6)

Identification of 1,4-oxazepines derivatives (M_{13} – M_{22})
The compounds (M_{13}-M_{22}) (**Scheme 8**) was synthesized according to the reaction between compounds (M_3-M_{12}) with 2-aminophenol in solution of alcoholic sodium hydroxide 5%.



Scheme 8: Structureof the synthesized compound (M_{13}-M_{22})

The suggested mechanism[32] of this reaction is illustrated as in **scheme 9**:



Scheme 9 : A plausible mechanism pathway for the formation of 1,5-Benzoxaazepines (M_{13}-M_{22})

IR spectrum of compound (**M_{20}**) exhibited bands at (2935,2833)$^{cm-1}$ denotes to streching vibration of (C-H) alf. and (1708,1672)$^{cm-1}$, (1587)$^{cm-1}$, (1517,1481)$^{cm-1}$,(1253)$^{cm-1}$denotes to stretching vibration of υ(C=O) of imide, υ(C=N) group, υ(C=C) of aromatic ring, and υ(C-N) group respectively the other compounds showed an asymptotic absorbtions of compound (**M_{20}**). Note figures **11** and table **5**.

^{1}H-NMR spectrum for compound (**M_{20}**), (in Dimethyl Sulfoxide-d6 as a solvent) exhibit a multiple signal at δ(8.70-6.03) pmm denotes to the protons of aromatic system, signal at δ (4.43-4.40) pmm indicate to the proton of the (CH) , signal at δ (2.99-3.04) pmm indicate to the protons of the (CH_2) groups and signal at δ (2.53) pmm indicate to the protons of the (CH_3) groups. Note figure **12**.

^{13}C-NMR spectram of compound (**M_{20}**) in Dimethyl Sulfoxide -d6 as a solvent exhibit an signal at δ(57.33) ppm denotes to the carbon of methyl group, an signal at δ(64.14)pmm denotes to the carbon in position (3) of oxazipen ring, the signal at δ(70.84) pmm denotes to the carbon in position (2) of oxazipen ring , the signal at δ(159.05-111.52) pmm denotes to the carbon atoms in aromatic system and the carbon in position (4) in oxazipen ring, an signal at δ(186.30) ppm denotes to the to the carbons of imid group (- CO-N). Note figures **13**.

Table 5: Shows the IR of compound (M_{13}-M_{22}).

Comp. No.	R	IR (KBr) cm^{-1}						
		υ (C-H) Ar	υ (C-H) Aliph.	υ (C=O) imide	υ (C=N) Ar	υ (C-N)	υ (C-O-C)	Others
M_{13}	4-Br	3056	2927 2874	1712 1655	1612	1273	1087	υ (C-Br) 548
M_{14}	4-Cl	3064	2920 2854	1716 1663	1633	1267	1067	υ (C-Cl) 729
M_{15}	H	3073	2914 2864	1723 1668	1624	1266	1093	-
M_{16}	4-OH	3070	2920 2887	1723 1668	1587	1265	1084	υ (C-OH) 3330
M_{17}	4-OCH_3	3055	2927 2833	1708 1672	1587	1253	1075	υ CH_3 2935,2833
M_{18}	2,4-diCl	3086	2916 2884	1733 1667	1627	1273	1068	υ C-Cl 674
M_{19}	4-NO_2	3104	2974 2852	1724 1669	1596	1252	1097	υ (NO_2) 1412,1337
M_{20}	4-$N(CH_3)_2$	3036	2927 2833	1708 1672	1587	1253	1072	υ CH_3 2927,2833
M_{21}	2-Br	3047	2927 2836	1734 1645	1614	1271	1088	υ (C-Br) 545
M_{22}	3,4-diOCH_3	3048	2924 2877	1707 1664	1622	1252	1096	υ CH_3 2924,2877

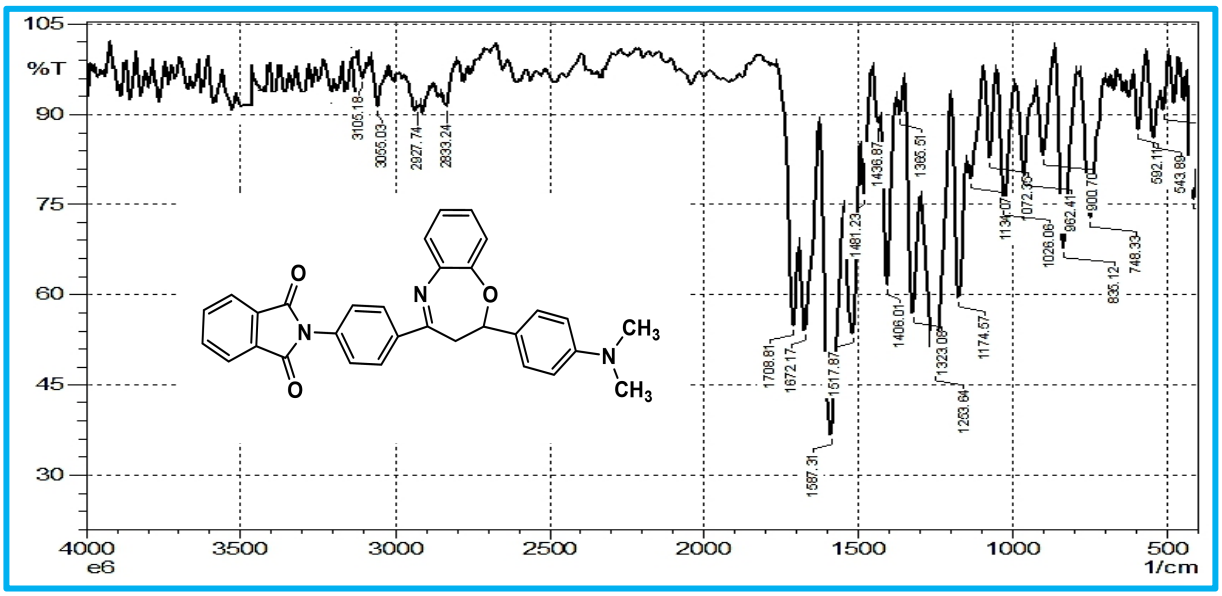


Fig. 11: FT-IR spectrum of compound (M_{20})

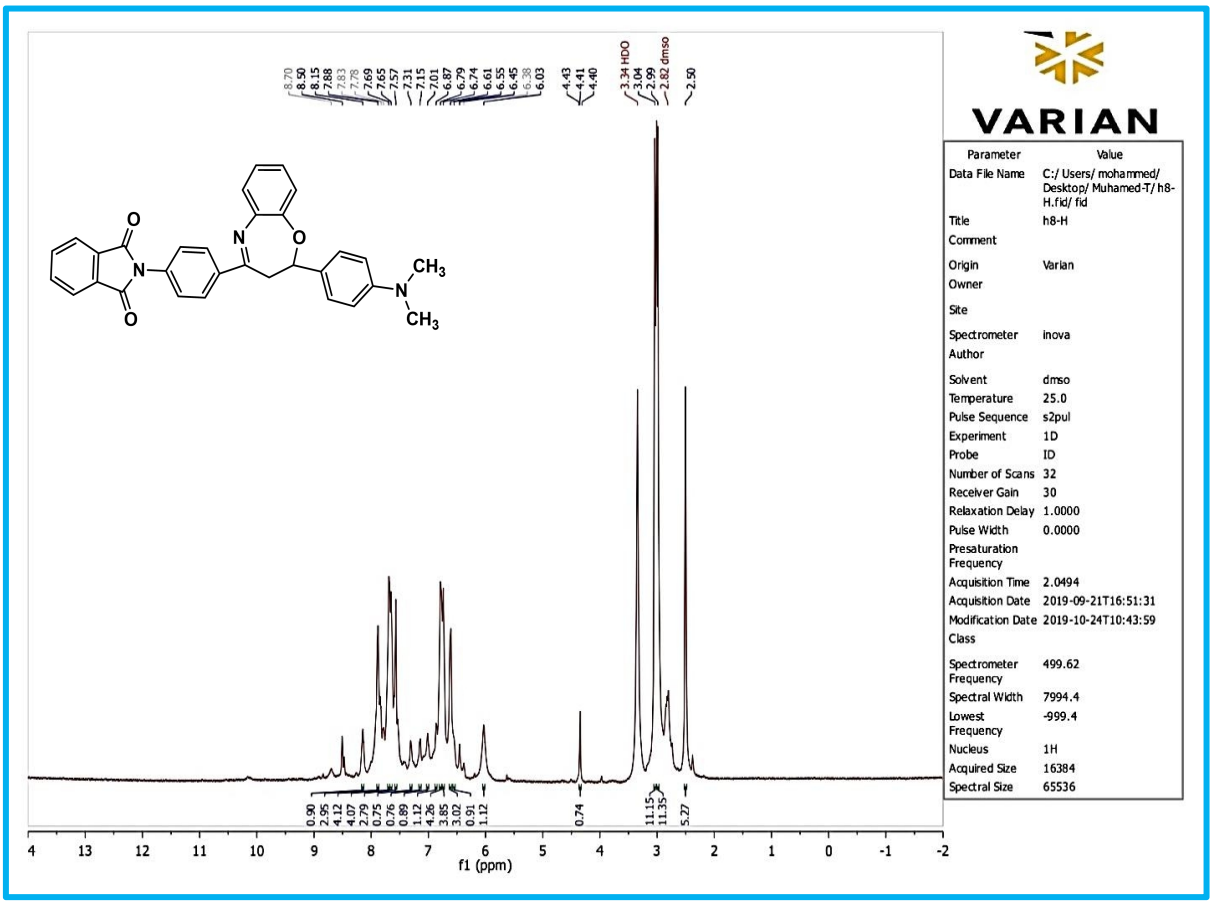


Fig. 12: ^{1}H-NMR specrum of compound (M_{20})

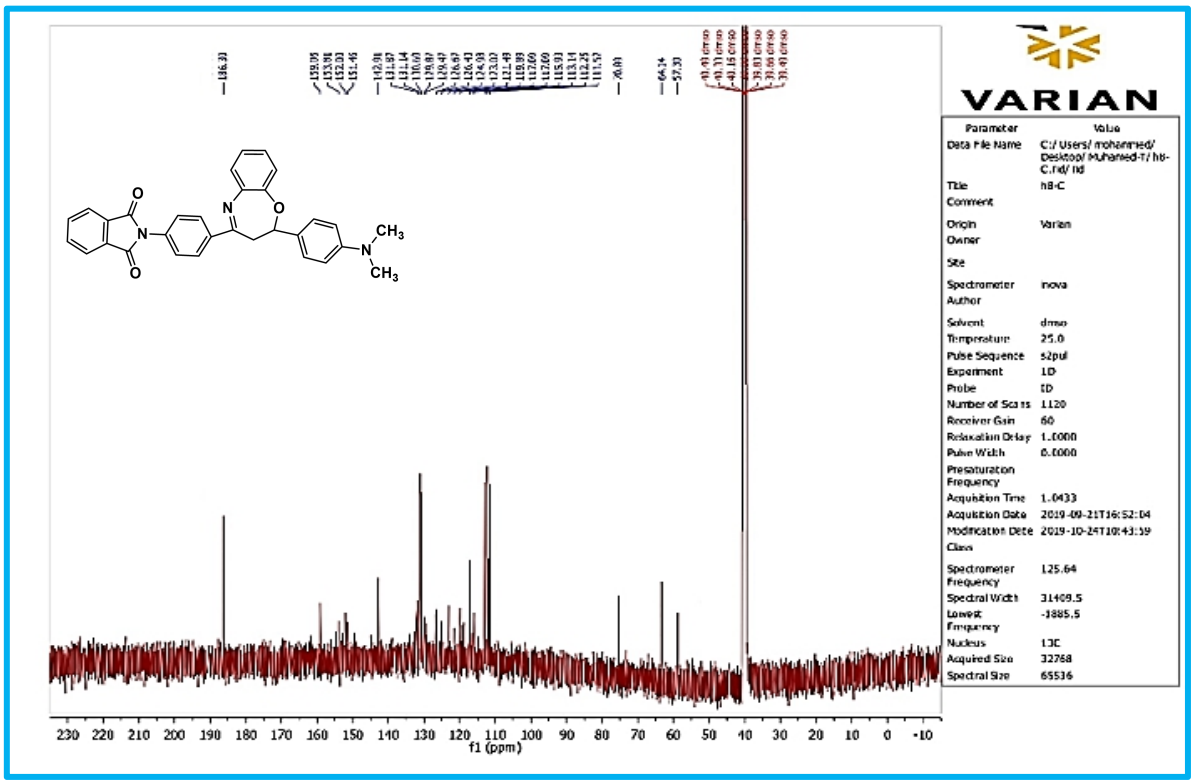


Fig. 13: ^{13}C-NMR specrum of compound (M_{20})

Evaluation Of Biological Activity

The antimicrobial activities of the synthesized compounds were determined in vitro against several pathogenic representative microorganism Gram-positive bacteria [*Staphylococcus aureus* and *Staphylococcus epidermidis*] and the second type was the Gram-negative bacteria like [*Escherichia coli*, *Pseudomonas aeruginosa*], using Agar well-diffusion method[33]. Ciprofloxacin and Norfloxacin were used as standard drugs for studying the potential activities of these compounds. The compounds under the test were injected using a loop onto plates containing Nutrient Agar (NA) media and brooded at 37C° for 24 hours. The agar diffusion was carried out by prepared bacterial suspensions in distilled water, The effect of the compounds under the test against all tested bacterias are shown in table(**6-7**) and figures (**14 - 18**)

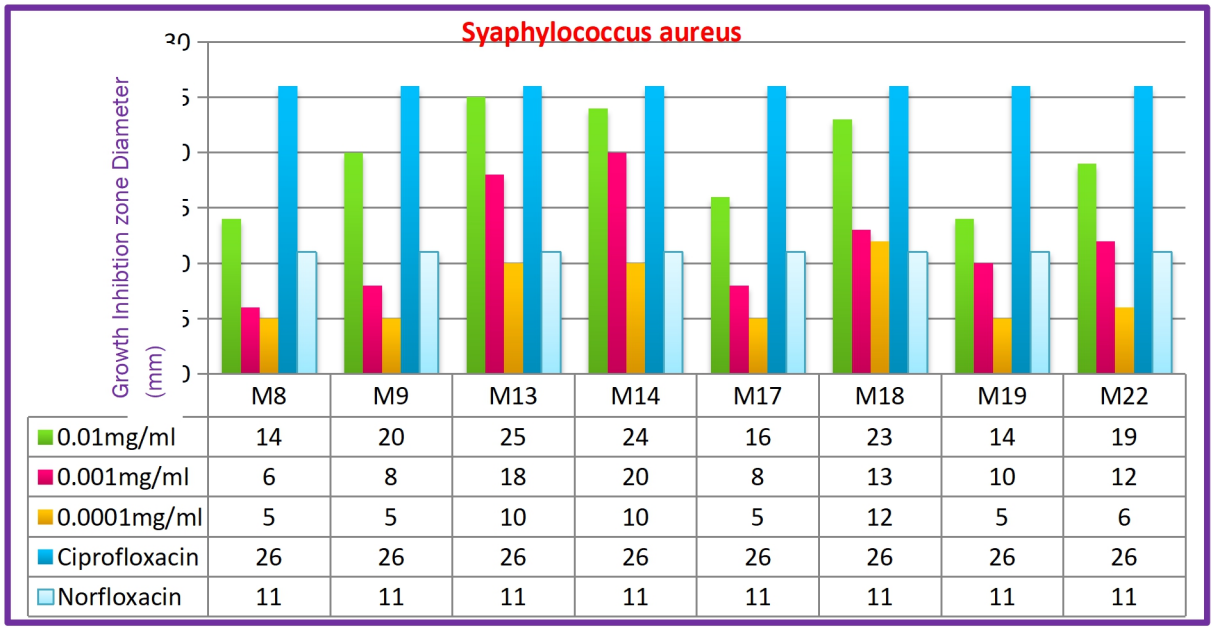
Table 6: Shows antimicrobial activity of the some prepared compounds.

Compound. no.	Conc.mg/ml	Staph. Aureus	Staph. Epidermidis	E. coli	Pseudomonas aeruginosa
M_8	0.01	14	15	0	0
	0.001	6	5	0	0
	0.0001	5	5	0	0
M_9	0.01	20	20	0	0
	0.001	8	10	0	0
	0.0001	5	5	0	0
M_{13}	0.01	25	28	0	0
	0.001	18	18	0	0
	0.0001	10	12	0	0
M_{14}	0.01	24	35	0	0
	0.001	20	22	0	0
	0.0001	10	20	0	0
M_{17}	0.01	16	12	0	0
	0.001	8	6	0	0
	0.0001	5	5	0	0
M_{18}	0.01	23	30	0	0
	0.001	13	18	0	0
	0.0001	12	10	0	0
M_{19}	0.01	14	15	0	0
	0.001	10	10	0	0

	0.0001	5	6	0	0
M_{22}	0.01	22	26	0	0
	0.001	19	12	0	0
	0.0001	12	6	0	0

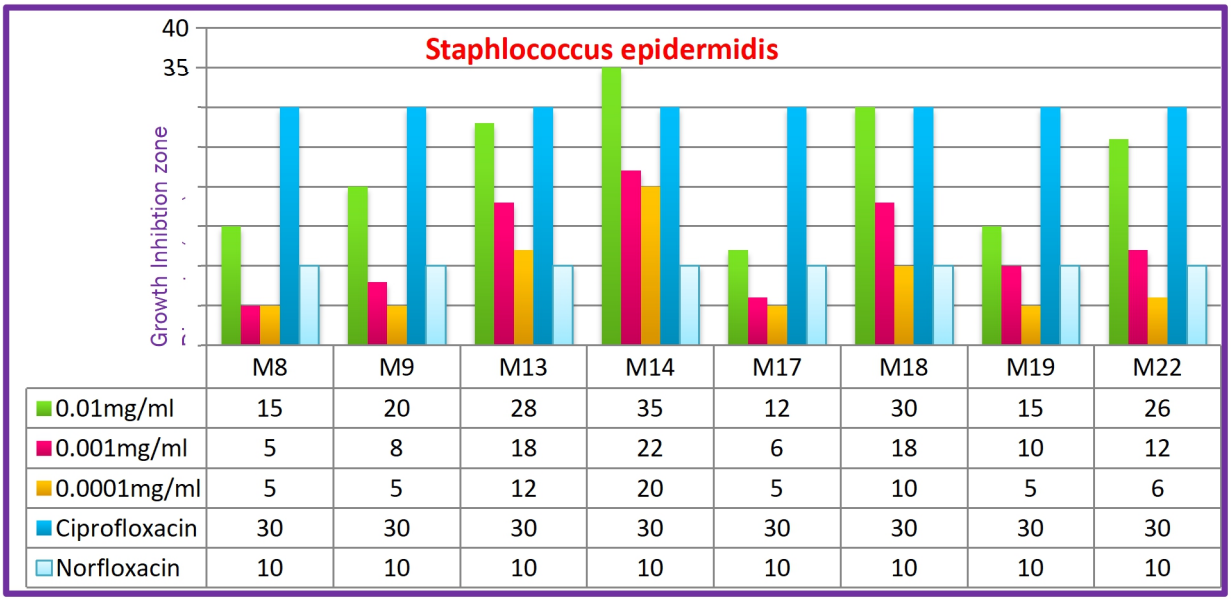
No.	Name	Conc.	Staph. Aureus	Staph. Epidermidis	E. coli	Pseudomonas aeruginosa
1	10 mg/disk	Ciprofloxacin	26	30	22	24
2	10/20 mg/disk	Norfloxacin	11	10	12	11

Table 7 : The bacterial activity of antibiotic (control sample) against bacteria.



	M8	M9	M13	M14	M17	M18	M19	M22
0.01mg/ml	14	20	25	24	16	23	14	19
0.001mg/ml	6	8	18	20	8	13	10	12
0.0001mg/ml	5	5	10	10	5	12	5	6
Ciprofloxacin	26	26	26	26	26	26	26	26
Norfloxacin	11	11	11	11	11	11	11	11

Fig.**14** . Differential effect and different concentrations of compounds studied against bacteria (**S. Aureus**)



	M8	M9	M13	M14	M17	M18	M19	M22
0.01mg/ml	15	20	28	35	12	30	15	26
0.001mg/ml	5	8	18	22	6	18	10	12
0.0001mg/ml	5	5	12	20	5	10	5	6
Ciprofloxacin	30	30	30	30	30	30	30	30
Norfloxacin	10	10	10	10	10	10	10	10

Fig.**15** . Differential effect and different concentrations of compounds studied against bacteria (**S. Epidermidis**)

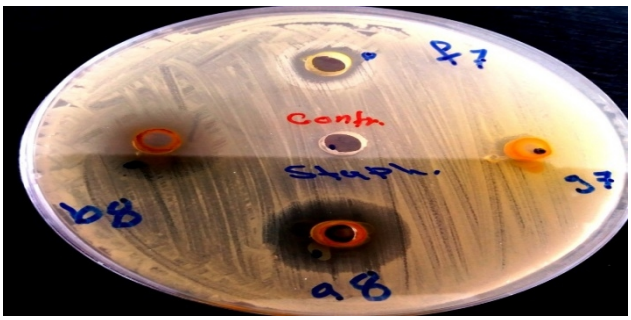


Fig. 16a. Compound (M_{13} and M_{14}) inhibits growth of bacteria S. Aureus(0.01

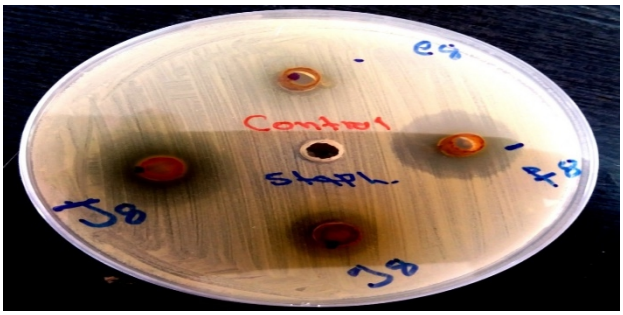


Fig. 16b. Compound (M_{19} and M_{22}) inhibits growth of bacteria S. Aureus(0.01 mg/ml)

Fig. 17a. Compound (M_{13}) inhibits growth of bacteria S. Epidermidis (0.01 mg/ml)

Fig. 17b. Compound (M_{14}, M_{17}, M_{18} and M_{19}) inhibits growth of bacteria S.

Fig. 18a. Compound (M_{22}) inhibits growth of bacteria S. Epidermidis (0.01 mg/ml)

Fig. 18b. Compound (M_{13}, M_{14}, M_{17} and M_{18}) inhibits growth of bacteria S.

REFERENCE

1. Younis, Firas M. "Preparation of Number of Chalcone Compounds From 6-formyl-5-methoxy-1, 3-benzoxathiol." *College Of Basic Education Researches Journal* 11.2 (2011): 711-721.
2. Ugwu, David I., et al. "Syntheses and pharmacological applications of chalcones: a review." *Int. J. Chem. Sci* 13.1 (2015): 459-500.
3. Chetana, B. Patil, S. K. Mahajan, and A. Katti Suvarna. "Chalcone: a versatile molecule." *J Pharm Sci Res* 1.3 (2009): 11-22.
4. Konieczny, M. T., Konieczny, W., Sabisz, M., Skladanowski, A., Wakieć, R., Augustynowicz-Kopeć, E., & Zwolska, Z. (2007). Acid-catalyzed synthesis of oxathiolone fused chalcones. Comparison of their activity toward various microorganisms and human cancer cells line. *European journal of medicinal chemistry*, *42*(5), 729-733.
5. Murti, Yogesh, A. Goswam, and Pradeep Mishra. "Synthesis and antioxidant activity of some chalcones and flavanoids." *Inter J Pharm Tech Res* 5 (2013): 811-818.
6. Sebti S, Solhy A, Somabh A, Kossir A, Oamimoun H, 2002. Dramatic activity enhancement of natural phosphate
7. catalyst by lithium nitrate: An efficient synthesis of chalcones. Catalysis Communication, 3: 335-339.
8. Macquarrie DJ, Nazih R, Sebti S, 2002. KF/natural phosphate as an efficient catalyst for synthesis of 2'-hydroxychalcones and flavanones. Green Chemistry, 4: 56-59
9. Petrov O, Ivanova Y, Gerova M, 2008. SOCl2/EtOH: Catalytic system for synthesis of chalcones. Catalysis Communication, 9: 315- 317.
10. Perozo-Rondon E, Martin Aranda RM, Casal B, Duran-Valle CJ, Lau WN, Zhang XF, Yeung KL, 2006. Sonocatalysis in solvent free conditions: An efficient eco-friendly methodology to prepare chalcones

using a new type of amino grafted zeolites. Catalysis Today, 114: 183-187.
11. Hazarkhani, H., Kumar, P., Kondiram, K. S., & Shafi Gadwal, I. M. (2010). Highly selective Claisen–Schmidt condensation catalyzed by silica chloride under solvent-free reaction conditions. *Synthetic Communications®*, *40*(19), 2887-2896.
12. Rao, M. S., Kotesh, J., Narukulla, R., & Duddeck, H. (2004). Synthesis and spectroscopic characterization of some chromanochalcones and their dihydro derivatives. *Arkivoc*, (14), 96-102.
13. Calvino V, Picallo M, Lopez-peinado AJ, Martin-Aranda RM, Duran-valle CJ, 2006. Ultrasound accelerated Claisen–Schmidt condensation: A green route to chalcones. Applied Surface Science, 252: 6071-6074.
14. Yin, D. L., Liang, Y. J., Zheng, T. S., Song, R. P., Wang, J. B., Sun, B. S., ... & Liu, L. X. (2016). EF24 inhibits tumor growth and metastasis via suppressing NF-kappaB dependent pathways in human cholangiocarcinoma. *Scientific reports*, *6*(1), 1-11.
15. Zhu, H., Xu, T., Qiu, C., Wu, B., Zhang, Y., Chen, L., ... & Liang, G. (2016). Synthesis and optimization of novel allylated mono-carbonyl analogs of curcumin (MACs) act as potent anti-inflammatory agents against LPS-induced acute lung injury (ALI) in rats. *European Journal of Medicinal Chemistry*, *121*, 181-193.
16. Hassan, A. Y., El-Hifnawi, H. N., & Ahmed, W. M. (2019). Design, Synthesis and in Vitro Evaluation of Antimicrobial and Anticancer Activity of Some Novel α, β-Unsaturated Ketones and their Corresponding Fused Pyridines. *Journal of Advanced Pharmacy Research*, *3*(3), 117-133.
17. Singh, P., Anand, A., & Kumar, V. (2014). Recent developments in biological activities of chalcones: a mini review. *European journal of medicinal chemistry*, *85*, 758-777.
18. Ünver, Y. A. S. E. M. İ. N., Tuluk, M., Kahriman, N. U. R. A. N., Emirik, M. U. S. T. A. F. A., Bektaş, E., & Direkel, Ş. (2019). New Chalcone Derivatives with Schiff Base-Thiophene: Synthesis, Biological Activity, and Molecular Docking Studies. *Russian Journal of General Chemistry*, *89*(4), 794-799.
19. Castaño, L. F., Cuartas, V., Bernal, A., Insuasty, A., Guzman, J., Vidal, O., ... & Balíková-Novtoná, G. (2019). New chalcone-sulfonamide hybrids exhibiting anticancer and antituberculosis activity. *European journal of medicinal chemistry*, *176*, 50-60.
20. Azeez, H. J., & Qadir, K. M. (2017). Synthesis and Spectroscopic Characterization of a New Series of Benzo [E][1, 3] Oxazepine Compounds from Schiff Bases. *Science Journal of University of Zakho*, *5*(1), 101-106.
21. M .Ahmad,O .Hedar ,G .Y.Yusef ; Australian Jour of Basic and Applied Scie. Vol (5) No(3) ,pp192-198 .(2011).
22. Prabhakar, Virupakshi, et al. "DESIGN, SYNTHESIS AND STRUCTURAL ELUCIDATION OF NOVEL 1, 5-BENZOOXAZEPINES CONTAINING THIENO [2, 3-d] PYRIMIDINE NUCLEUS AND ITS BIOLOGICAL ACTIVITY SCREENING." *HETEROCYCLIC LETTERS* 7.1 (2017): 121-140.
23. Kais, R., and S. Adnan. "Synthesis, Identification and Studying Biological Activity of Some Heterocyclic Derivatives from 3, 5-Dinitrosalicylic Acid." *Journal of Physics: Conference Series*. Vol. 1234. No. 1. IOP Publishing, 2019.
24. H. M. Serrano-Wu, R. D. Laurent, Y. Chen, S. Huang, R. K. Lam, A. J. Matson, C. E. Mazzucco, M. T. Stickle, P. T. Tully, S. H. Wong, M. D. Vyas, N. B. Balasubramanian, *Bioorg. Med. Chem. Lett.* 2002, 12, 2757.
25. Min Xie, Ren G. Lapidus, Mariola Sadowska, Martin J. Edelman, Ramachandra S. Hosmanea, "Synthesis, anticancer activity, and SAR analyses of compounds containing the 5:7-fused 4,6,8-triaminoimidazo[4,5-e][1,3]diazepine ring system". Bioorganic & Medicinal Chemistry, 24(12), 2595 (2016).
26. Patent Evaluation, "Tricyclic Antihistamines with Potent Anti-Allergic Activity", Journal of Current Opinion on Therapeutic Patents 2(1), 11 (1992).
27. Martin Kratzel, "Synthesis of 5a,11b-propanonaphtho[1,2-e][1,2]oxazepines as potential opioid analgesics", J. Chem. Soc., Perkin Trans. 1, 0, 1541 (1994).
28. Ashram, Muhammad, and Firas F. Awwadib. "A new, simple and efficient method for the synthesis of tricyclic [1, 3] oxazolo [3, 2-d][1, 4] benzoxazepine,[1, 3] oxazino [3, 2-d][1, 4] benzoxazepine, pyrimido [1, 2-d][1, 4] benzoxazepine and their derivatives." *Organic Chemistry* part v (2019): 142-151.
29. Abd Al-Razzak, M. S., & Al-Azzawi, A. M. (2014). Synthesis, characterization and antimicrobial screening of new Schiff bases linked to phthalimidyl phenyl sulfonate moiety. *Baghdad Science* Journal, 11(2),(446-438)
30. Al-Tufah, M. M., Jasim, S. S., & Al-Badrany, K. A. (2020). Synthesis and Antibacterial Evaluation of some New Pyrazole Derivatives. *Medico Legal Update*, *20*(3), 1395-1399.
31. Verma, Purnima, Sarita Gupta, and V. Yadav. "Catalyst-free and facile green synthesis of some novel oxazepine derivatives." *Der Chemica Sinica* 6 (2015): 86-89.
32. Al-Badrany, Khalid A., Amar S. Mohammed, and Yuosra K. Alasadi. "Synthesis of some new 1, 3, 4-oxadiazole compounds derived from 1H-imidazole and study their biological activity." *Eurasian Journal of Biosciences* 13.1 (2019): 501-507.
33. Yadav, N., Yadav, V. B., Ansari, M. D., Sagir, H., Verma, A., & Siddiqui, I. R. (2019). Catalyst-free synthesis of 2, 3-dihydro-1, 5-benzothiazepines in a renewable and biodegradable reaction medium. *New Journal of Chemistry*, *43*(18), 7011-7014.
34. Sharshira EM, Hamada NMM (2011) Synthesis and *in Vitro* Antimicrobial Activity of Some Pyrazolyl-1-carboxamide Derivatives Molecules, 16(9): 7736-45. https://doi.org/10.3390/molecules16097736.