Synthesis of some new heterocyclic compounds by High-Speed,Microwaveirradiation and pharmacological evaluation

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Abstract

A series of substituted chalcones (1-4) were synthesized and used to prepare some new membered heterocyclic compounds (Pyrimidinones)(5-12) by their condensation with urea and thiourea, and four membered heterocyclic compounds (Pyrazolines) (13-16) by their condensation with 2,4-dinitrophenyl hydrazine also, four membered heterocyclic compounds (isoxazolines) (17-20) by their condensation with aminohydroxide hydrochloride.

All reactions were carried out under microwave irradiation (MW1) is described. The synthesized compounds are characterized by FTIR and C.H.N analysis. We also study the biological activity for prepared compounds against four types of bacteria & one type of the fungi .

Keyword : Synthesis by High- Speed Microwave irradiationchalcones.

تحضير بعض المركبات الحلقية الجديدة بواسطة اشعاع المايكرويف الفائق السرعة ودراسة فعاليتها البايولوجية .

هاله ادريس إبراهيم

الملخص

يتضمن البحث تحضير سلسلة من الجالكوناتالمعوضة (1-4) والتي استخدمت لتحضير مركبات حلقية غير متجانسة (البايريميدينونات) (5-12) بتكاثفها مع اليوريا او الثايويوريا، وكذلك استخدمت لتحضير اربع مركبات حلقية غير متجانسة (البايرازولينات) (13-16) بتكاثفها مع 2،4- ثنائي فينيل هيدرازين ، وأيضا"استخدمت لتحضير اربع مركبات حلقية غير متجانسة (اوكسزازوليزات) (17-20) بتكاثفها مع اوكسيد امين الهيدروكلور ايد .كل التفاعلات اجريت باستخدام المايكرويف، وشخصت المركبات باستخدام مطيافية

الاشعة تحت الحمراء (IR) ،والتحليل الدقيق للعناصر (C.H.N) . كذلك درست الفعالية البايولوجية للمركبات المحضرة ضد أربعة أنواع من البكتويا ونوع من الفطريات .

Introduction

Chalcones constitute an important class of natural products belonging to the flavonoid family, which have been reported to possess spectrum of biological activities, including anti-bacterial, anti-fungal, anti-inflammatory, antitumor, insect anti-feed and anti-mutagenic[1-4].

Bacteria are becoming resistant to ever more anti-microbial agents. Currently, bacterial resistance is combated the discovery of new drugs. However, micro-organisms are becoming resistant more quickly than new drugs are being found, thus future research in anti-microbial therapy may focus on finding ways to overcome resistance to antimicrobial, or methods to treat infections with alternative means thiohydrations have been proven to have anticonvulsant activity[4].

Compounds that comprise the hydration moiety exhibit pharmacological properties[5-8]. Similarly many natural and synthetic products containing heterocyclic rings, such as pyrazdes[9], was reported to possess various pharmacological activities. The pyrazoline, pyrimidinone, oxazoline and their derivatives represent one of the most biological active classes of compounds, and its nucleus is associated with diverse pharmacological activities such as potent GNRH receptor antagonists[10] for medicinal and pharmaceutical application[11], as anti-inflammatory, anti-arthritic agents[12] and other biological activities[13].

Microwave induced organic reaction enhancement [MORE] chemistry is gaining popularity as a nonconventional technique for rapid organic synthesis, important features of this technique are easy access to very high temperature, good control over energy input in a reaction, higher yields and rapid synthesis of the organic compounds. The effect of microwave irradiation is due to the combination of both thermal and thermal effects. It is characterized by spectacular accelerations produced in many reactions which cannot be

observed in classical heating[10-12]. The synthesized compounds were purified by recrystallized and chromatography. The compounds were characterized by IR and CHN analysis.

Experimental

General procedure for the synthesis of chalcones (1-4) by microwave irradiation methods (MWI)[22]

Equimolar quantities (0.01 mole) of acetyl heterocyclic compounds and respective aldehydes (0.01mole) were mixed and dissolved in minimum amount (3ml) of alcohol [13] to this mixture an aqueous potassium hydroxide solution (0.003mole) was added slowly and mixed, the entric reaction mixture was microwave irradiation .

Condensation reaction of chalcones (1-4) with thiourea or urea (5-12) [23]

Equimolar irradiation (0.01 mole) of chalcones, thiourea or urea (0.01mole) were mixed and dissolved in abs. ethanol then added (0.01 gm) of sodium in ethanol., the enteric reaction mixture was microwave irradiation in catalyst scientific microwave oven. The physical data of compounds (5-12) are given in table (1) .

Condensation reaction of chalcones (1-4) with 2,4-dinitrophenyl hydrazine (13-16) [24]

Equimolar quantities (0.01 mole) of chalcones in acetic acid and(0.01mole) 2,4-dinitro phenyl hydrazine derivatives was added slowly and mixed, the enteric reaction mixture was microwave irradiation, the physical data of compounds (13-16) are given in table (1) .

Condensation reaction of chalcones (1-4) with amino hydrochloride hydroxide (17-20) [25]

Equimolar quantities of (0.01 mole) of chalcones and (0.01mole) amino hydrochloride hydroxide are

mixed in abs. ethanol and (10ml) of 10% NaOH. was added slowly and mixed. The enteric reaction mixture was microwave irradiation. The physical data of compounds (17-20) are given in table (1) .

Table 1: physical properties for prepared compounds (1-20)

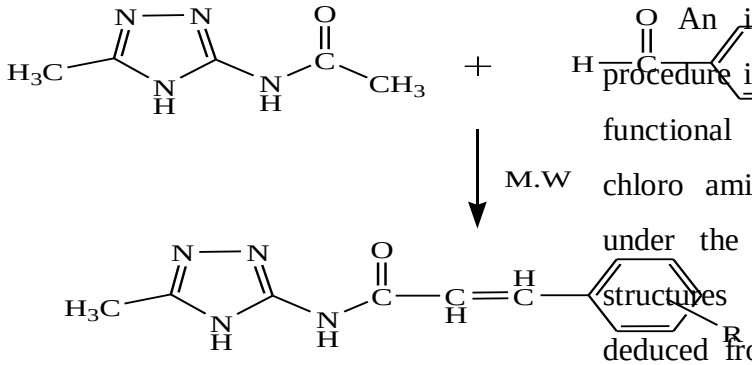
Compounds no.	m.p (^{o}C)	Yield %	Color
1	110-112	79	Light yellow
2	108-110	80	Green
3	100-102	78	Yellow
4	111-113	70	Orange
5	272-273	69	Off yellow
6	278-280	76	Peal yellow
7	268-270	74	White
8	270-271	67	Orange
9	170-172	75	Yellow
10	180-182	74	White
11	177-178	72	Yellow
12	167-168	68	Peal yellow
13	150-152	69	Orange
14	160-162	70	Orange
15	148-150	80	Off yellow
16	150-151	83	Green
17	195-196	70	Off yellow
18	186-188	76	Whit
19	190-192	77	Orange
20	184-185	68	Off Orange

Table 2 : (C.H.N.) analysis data for some prepared compounds.

Comp. no.	Mol. Formula	Analysis found (cal.) %		
		C	H	N
1	$C_{12}H_9ON_4$	64.00(63.89)	4.00(4.01)	24.88(24.80)
2	$C_{12}H_9O_2N_4$	59.75(59.37)	3.73(3.39)	23.24(24.22)
5	$C_{13}H_{13}ON_6$	57.99(58.26)	4.83(4.71)	31.23(31.98)
7	$C_{13}H_{12}ON_4Cl$	51.48(51.15)	3.96(3.39)	27.72(27.53)
9	$C_{13}H_{12}SN_4$	51.82(51.24)	4.31(4.93)	27.90(27.07)
13	$C_{18}H_{15}O_4N_8$	53.07(53.84)	3.68(3.36)	27.52(27.27)
17	$C_{12}H_{12}ON_5$	59.50(59.13)	4.96(4.77)	28.93(28.86)

Results and discussion

The synthesis of the chalcones was accomplished according to the Claisen – Schemidt condensation of 3-acetyl-5-methyl-1,2,4-traizole with appropriate aromatic aldehyde according to(scheme 1), and the (C.H.N.) analysis data are recorded in table (2) . The corresponding proceeded smoothly and good to excellent yields (70-80)%.



1: R = H , 2: R = 4-OH , 3: R = 3-Cl , 4: R = 4-Br

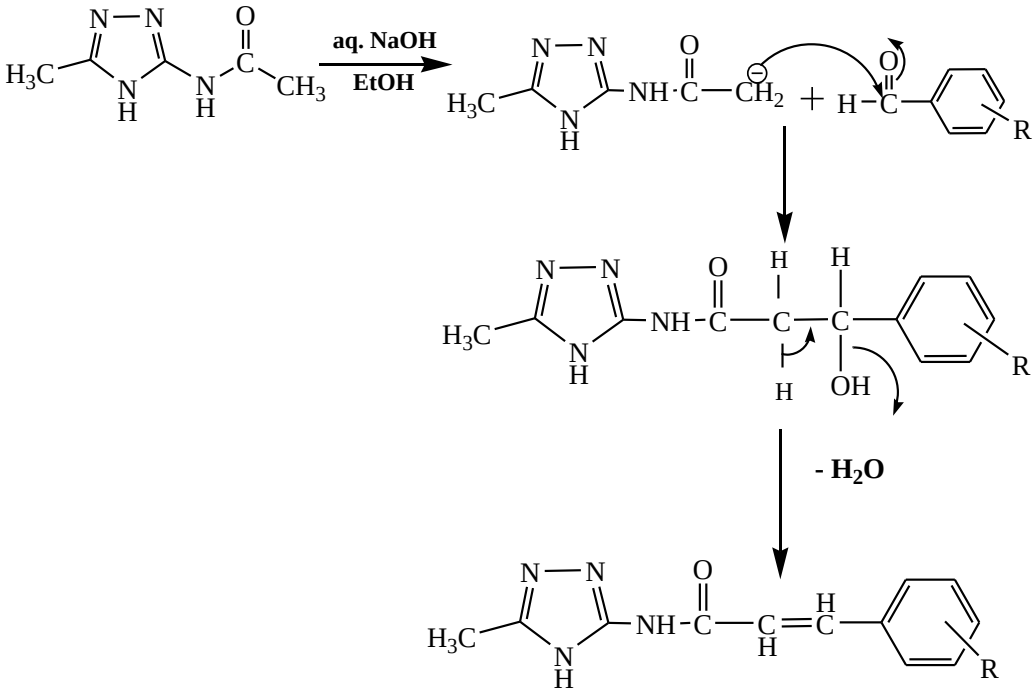
Scheme (1)

An important feature of this procedure is the survival of variety of functional groups such as hydroxyl, chloro amide, isomethene and ether under the reaction conditions. The structures of the products were deduced from their IR and elemental

analysis. For example the IR spectrum of compound (3) exhibited characteristic band absorption of conjugated C=O group at 1658.87 cm^{-1}. The absorptions bands at (1593, 1512, 1463) cm^{-1} were assigned to the exited of C=C , (1620) cm^{-1} to N=C, aromatic ring in (1100, 1110) cm^{-1}indicated to the two substitutions.

The structures of these chalcones were identified from their IR spectra in table (2).

The mechanism of this reactions is known, it may be outlined at follows in scheme (2)



1: R = H , 2: R = 4-OH , 3: R = 3-Cl , 4: R = 4-Br

Scheme (2)

Table 2: The FT-IR selected bands of prepared compounds

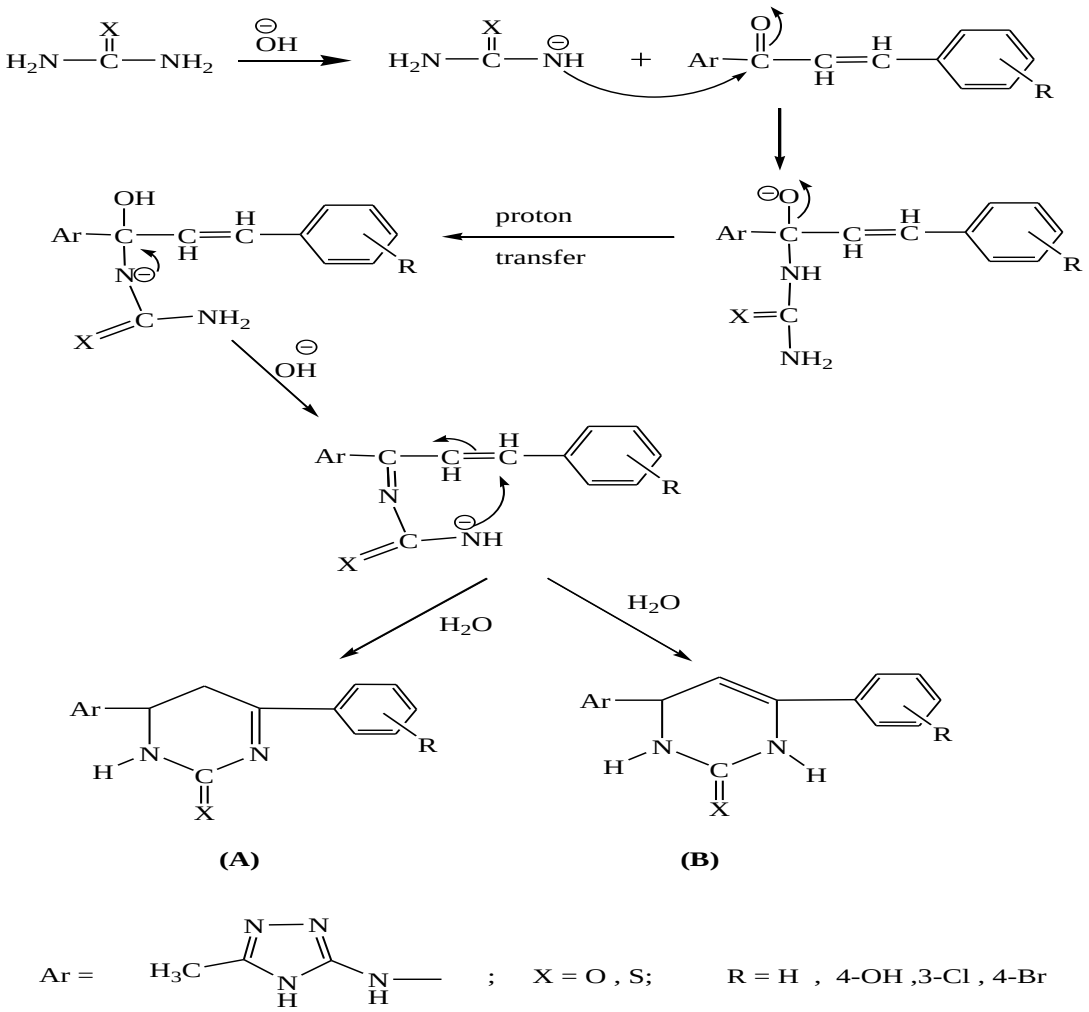
Comp. no.	R	IR (KBr) ν cm^{-1}				
		C=O	C=N	C=C	NH	Other group
1	H	1662	1591	1585	3444	-----
2	4-OH	1667	1633	1600	3448	3433
3	3-Cl	1659	1620	1593	3420	880-920
4	4-Br	1658	1624	1593	3432	860-910

The introduction of aromatic moiety into the terminal position of the conjugated system (C=C-C=O), as in chalcones appear to increase its polar as in character and therefore its tendency to undergo condensation reaction with nucleophiles. Thuschalcones (1-4) condensation with urea, thiourea 2,4-dintitro phenyl hydrazine and NH_2OH-HCl under microwave irradiation it takes only 5-6 min.

Microwave irradiation facilitates the polarization of the molecule under irradiation causing rapid reaction to occur.

The actions of urea and thiourea on the chalcones were studied. The condensation of chalcones (1-4) with urea leads to the corresponding substitute pyrimidinonces (5-8), and with thiourea lead to the substituted thiopyrimidinonces (9-12). The formation of these compounds may proceed through one of two routes:- Claisen or Michael routes [18]

Rot 1:- Claisen addition:-

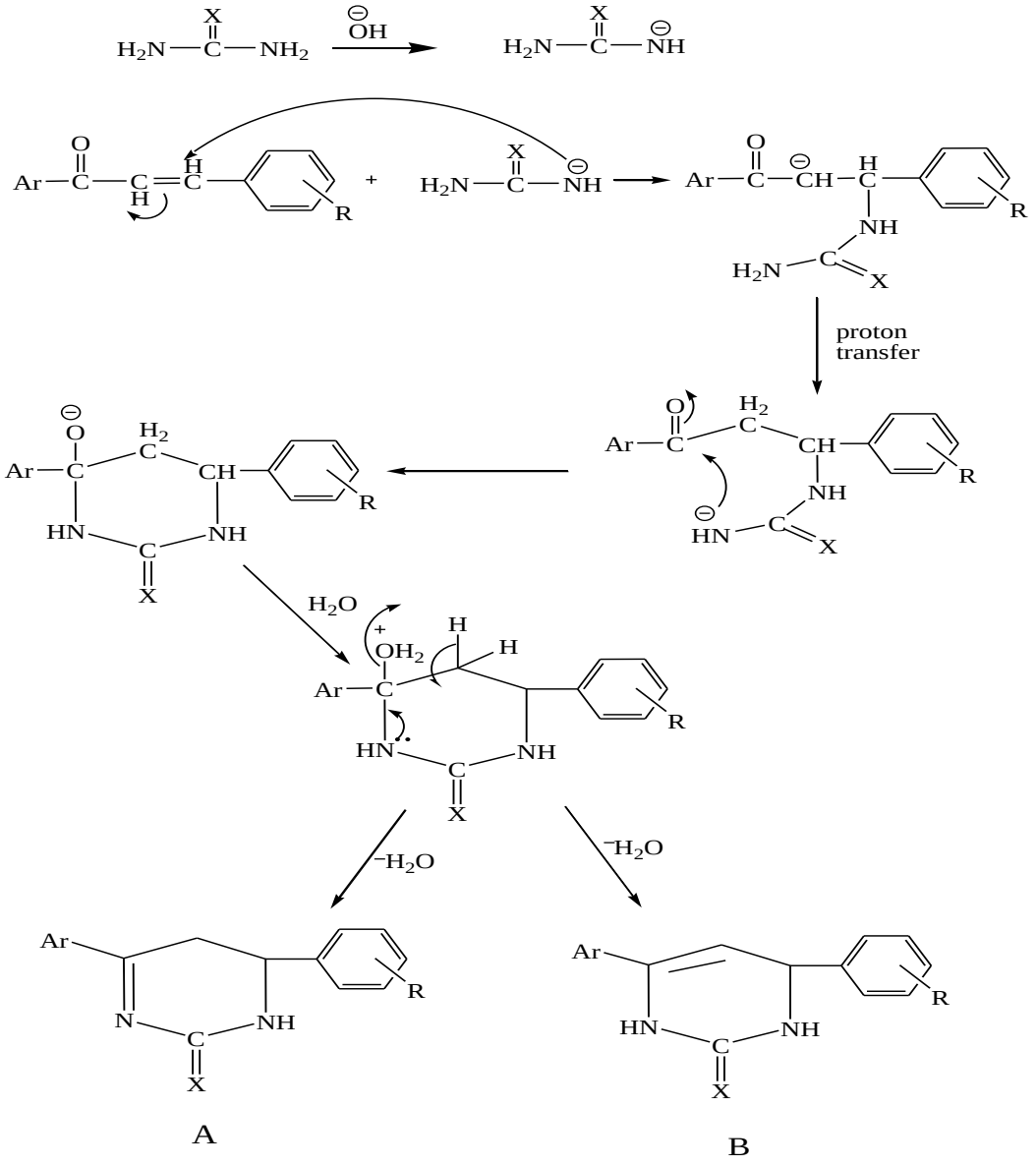


Scheme (2A)

The theoretical studies for the heat of formation and steric energy of the products illustrate that this reaction proceeds via Michael addition to form the most stable product (B).

The structures of pyrimidinonces (5-12) were supported by IR spectroscopy. The IR spectra in Table 3 of compounds (5-12) showed absorption peaks at (3444-3422)cm^{-1} , (1617-1600) cm^{-1} and (1684-1670) cm^{-1} assigned to NH, C=C and C=O bonds stretching respectively.

Route 2 : Micheal addition



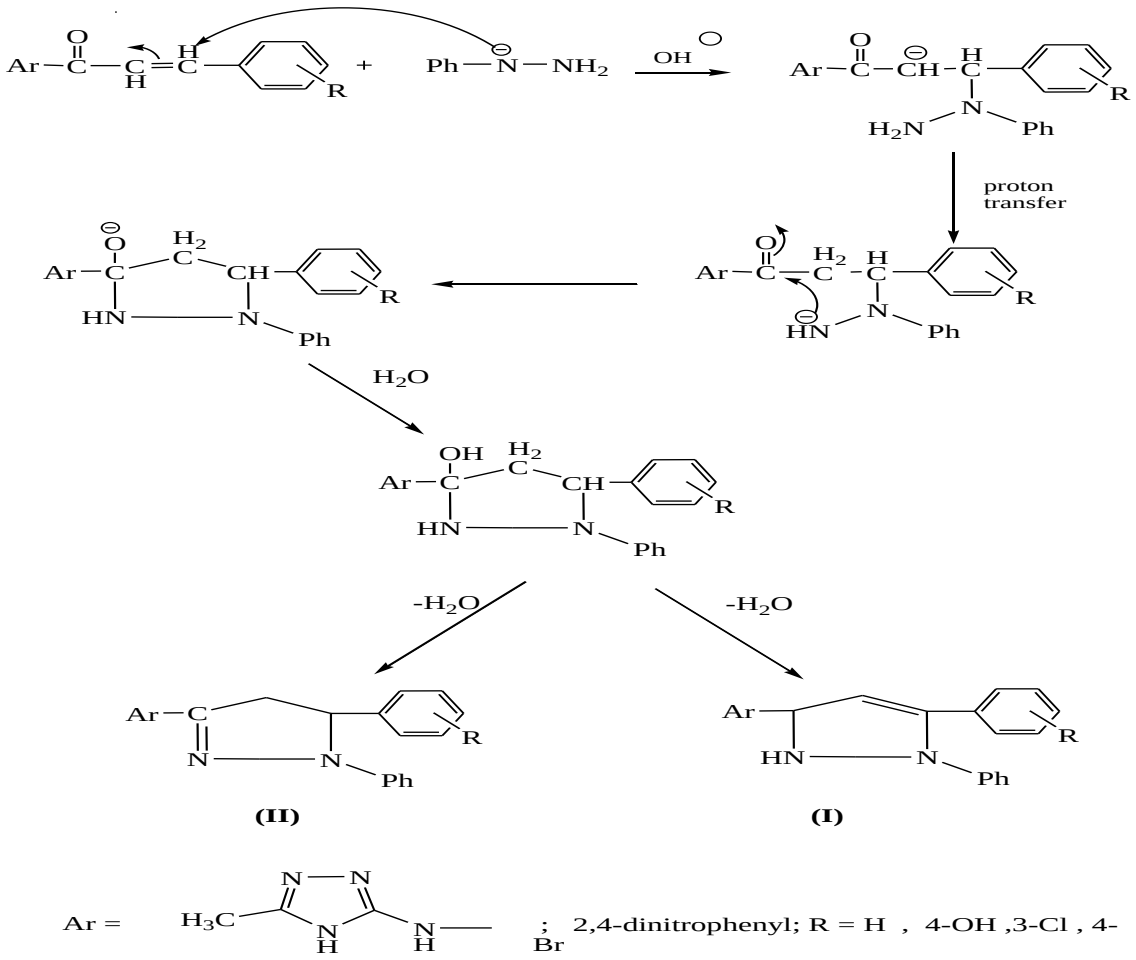
Scheme (2B)

Table3: The FT-IR spectra of compounds (5-12)

Comp. no.	R	IR (KBr) ν cm^{-1}						
		N-H	C=O	C=N	C=C	C=S	CH Alpha	CH arom.
5	H	3440	1765	1690	1593	-----	2922	3070
6	4-OH	3458	1772	1684	1696	-----	2920	3073
7	3-Cl	3426	1738	1656	1628	-----	2924	3070
8	4-Br	3446	1720	1654	1633	-----	2400	3070
9	H	3402	1753	1632	1571	1283	2725	3218
10	4-OH	3420	1760	1650	1590	1280	2720	3200
11	3-Cl	3395	1720	1618	1560	1286	2624	3183
12	4-Br	3390	1714	1612	1562	1282	2688	3180

Chalcones (1-4) condensed with2,4-nitrophenyl hydrazine yield the corresponding pyrazolines (13-16) either through claisen addition or Michael addition.

The previous literature (19) illustrated through the theoretical study for the heat of formation and steric hindrance energy for similar compounds that this reaction proceed exclusively via Michael addition to form the most stable product (II) scheme (3)



Ar = ; 2,4-dinitrophenyl; R = H , 4-OH ,3-Cl , 4-Br

Scheme (3)

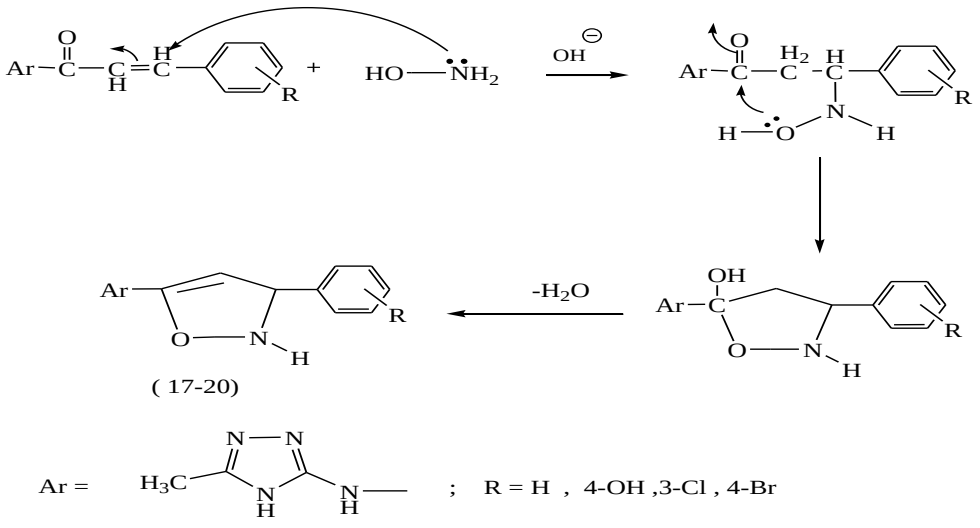
The structure of the pyrazolidines (13-16) was supported by IR spectroscopy , which showed characteristic absorption peaks at (1611-1600)cm^{-1} , (3411-3399) cm^{-1}attributed of the pyrazoilne ring bonds the absence of absorption peak for the C=O bond stretching supported the formation of structure I.

Table 4:The FT- IR spectra of compounds (13-16)

Comp. no.	-R	C=N	C=C	NH	CH Alpha	CH arom	$-NO_2$
13	H	1600	1618	3440	2937	3080	1323 1270
14	4-OH	1685	1623	3448	2945	3082	1369 1240
15	3-Cl	1643	1605	3420	2934	3073	1344 1225
16	4-Br	1674	1618	3438	2941	3085	1340 1274

Chalcones (1-4) condensed with NH_2-OH .HCl yield the corresponding isooxazolenes (17-20). The reaction was followed by the disappearance of (C=O) absorption band of chalcones. The structure of these isooxazlenes were identified form their IR spectra in table 5, and the appearance of the (-O-C) stretching at (1077)cm^{-1}.

The mechanism of this condensation is known and base catalyzed , it may be out lined at follows scheme (4)



Scheme (4)

Table 5:- FT- IR spectra of compounds (17-20)

Comp. no.	-R	C=N	C=C	C-O	C-H Alpha	C-H arom	N-H
17	H	1568	1542	1076	2921	3190	3452
18	4-OH	1610	1583	1077	2927	3185	3446
19	3-Cl	1600	1567	1032	2924	3071	3420
20	4-Br	1605	1566	1054	2924	3075	3432

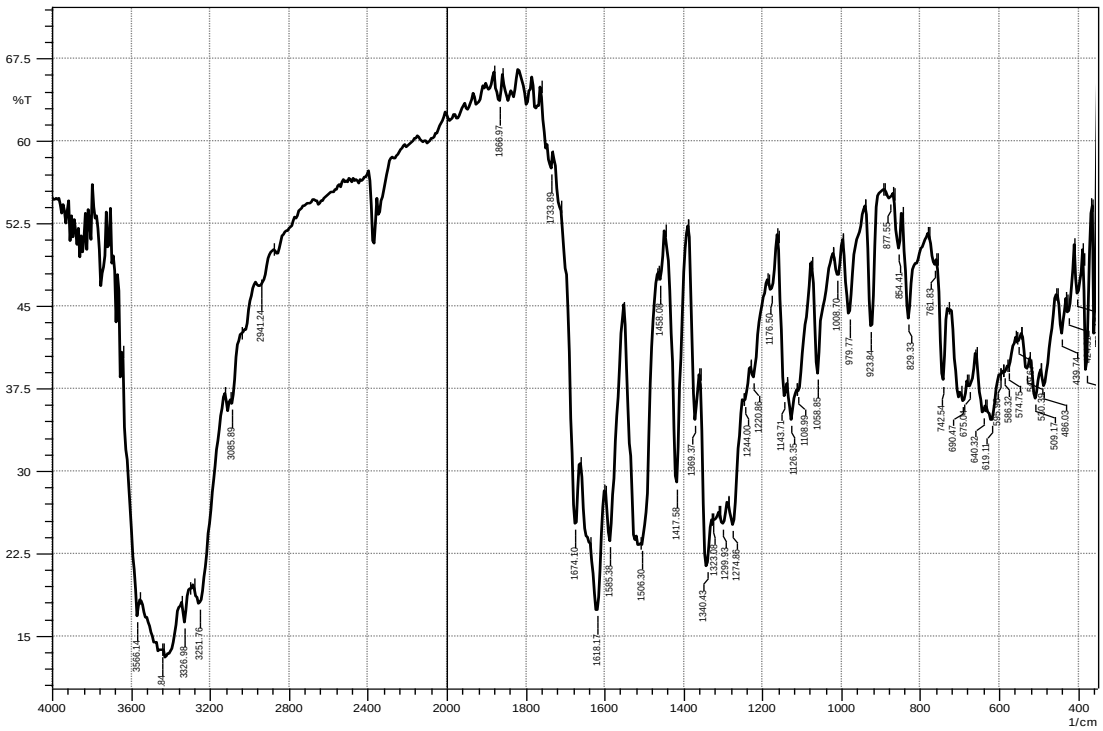


Fig (1): FT-IR spectra of compound 3 .

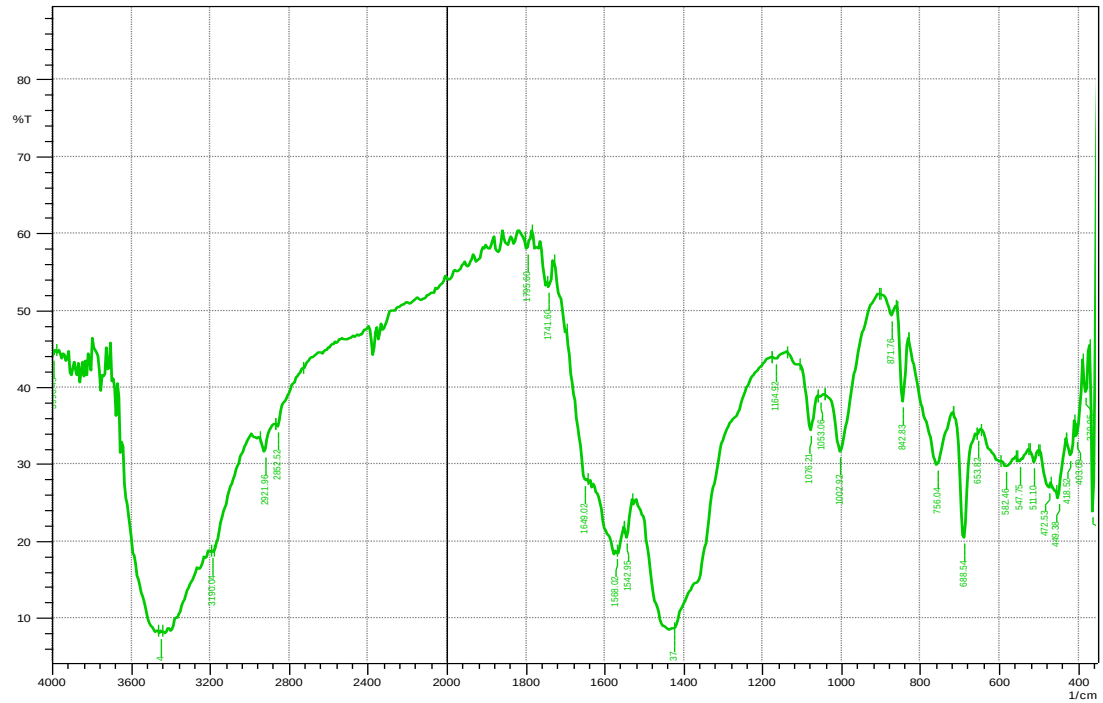


Fig (2): FT-IR spectra of compound 8 .

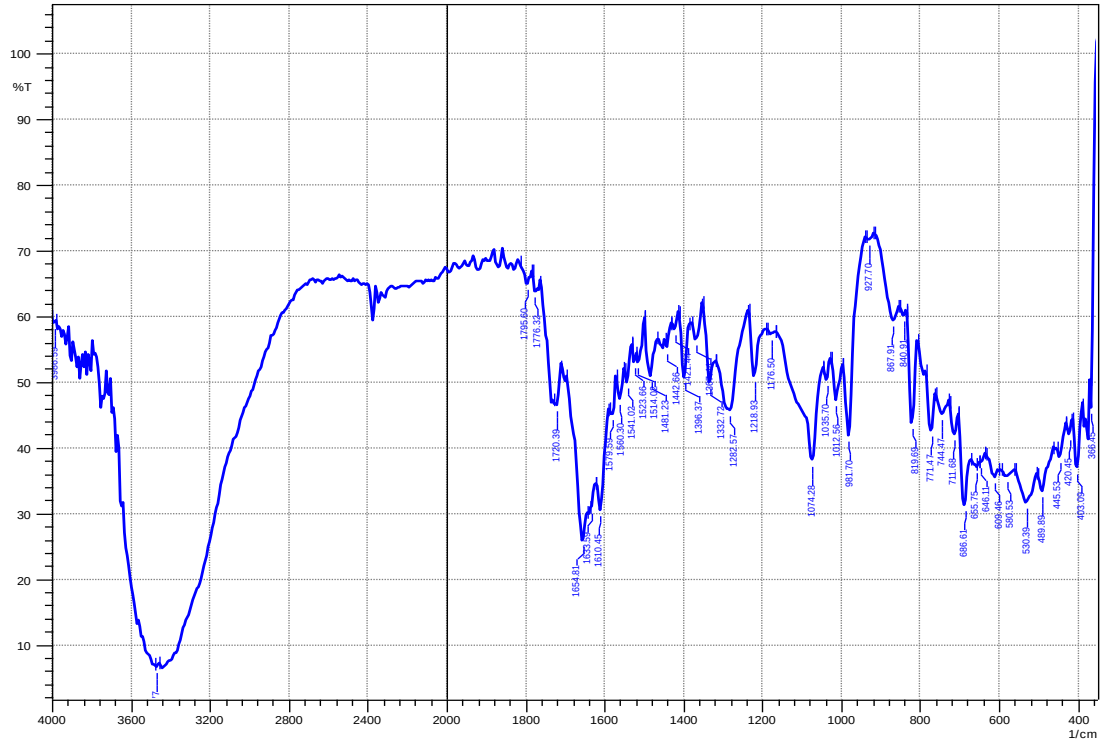


Fig (3): FT-IR spectra of compound 9 .

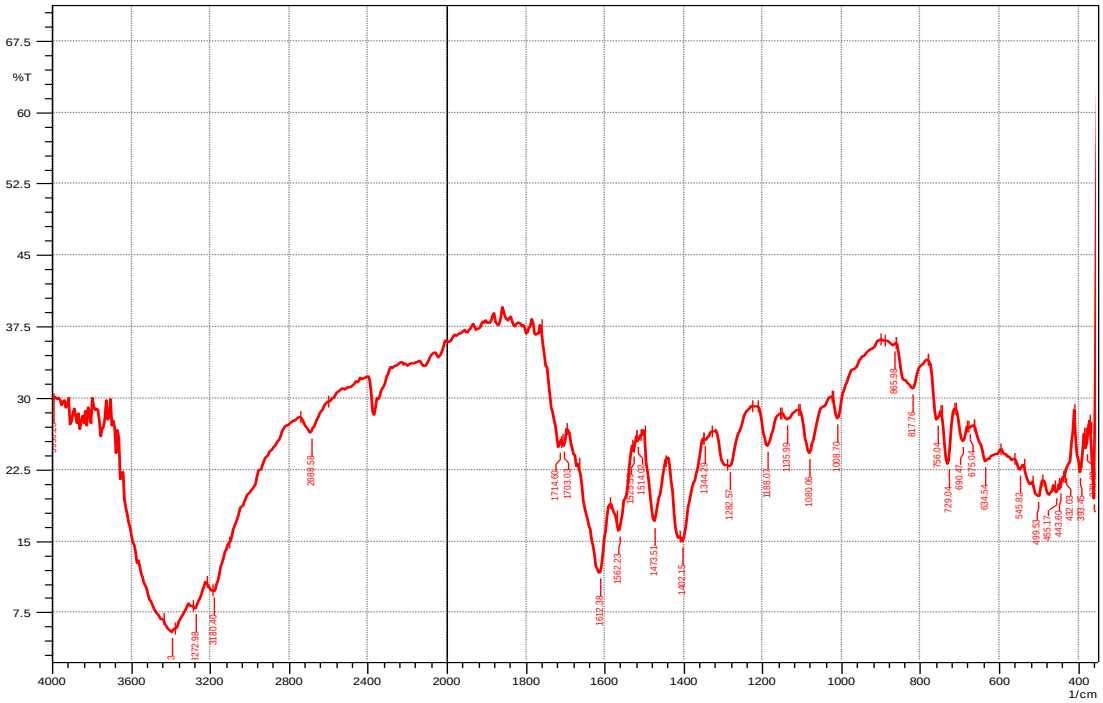


Fig (4): FT-IR spectra of compound 10 .

Biological activity

The prepared compounds were screened for their antibacterial activity against four microoganisms including { staphococcus aurous & streptococcus pyogenes} types of (Gram positive) bacteria & [E.coli& Pseudomonas aeruginosa] types of (Gram negative) bacteria. Biological activity against the fungus (Candida albicans) were studied also.The prepared citraconamic acids &citaconimides showed different biological activities against the studied types of bacterial & fungi as shown in table (6) .It was noticaeable that biological activity of these compounds depend on nature of substituents in their molecules thus compounds (6) (10) & (14,18) showed high biological activity due to the presence of electron releasing substituents (- OH) .

While compounds (7,8,11,12.15.16,19,20)which substituted with electron with drawing substituents (CL)& (Br) showed slight activity against S. aureus&S.pyogenes but were inactive against other bacteria & fungi . Also compounds (13,14,15,16) which were substituted with (No_2) group showed no activity against S . aureus ,S . pyogenes& fungi but slight activity against E.Coli&aeruginosa **.**

Table6 : Antibacterial & antifungal activity of prepared compounds.

Comp. no.	Gram- positive bacteria		Gram- negative bacteria		Fungi
	Staphylococcus aureus	Streptococcus pyogenes	Escherichia coli	Pseudomonas aeuroginosa	Candida albicans
5	+ +	+ +	+	+	+
6	+ + +	+ + +	+	+	+
7	–	–	+	+	–
8	–	–	+	+	–
9	+	+	+	+	+
10	+ + +	+ + +	+	+	+ +
11	–	–	+	–	–

12	_	+	_	_	_
13	+ +	+	+ +	+ +	+ +
14	+ + + +	+ + + +	+ + +	+ + +	+ + +
15	+	+	_	_	+
16	_	_	+	_	+
17	+ +	+ +	+ + +	+ +	+ + +
18	+ + + + +	+ + +	+ + + + +	+ + + +	+ + +
19	_	_	+	_	_
20	+	_	_	+	+

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