Raf. J. Sci.,Vol.28, No.2 Special Issue for the Third Scientific Conference of Chemistry, pp.37-46, 2019

Synthesis and Biological Activity of some New Nitrogenous Heterocyclic Compounds Derived from Azachalcone

Munera Y. Roof *Department of Chemistry/College of Science University of Mosul*
E –mail: mounerayo @yahoo.com

Shakir M. Saied *Department of Dentistry Al-Noor University College*
E –mail: shakirmsaied@ yahoo.com

(Received 1 /8/ 2018 ; Accepted 25 / 10 / 2018)

ABCTRACT

A series of heterocyclic compounds containing oxygen and nitrogen atoms, isoxazoline II(a-d) and another containing two nitrogen atoms, pyrazolinesIII(a-d) and phenylpyrazolines IV(a-d) were prepared by the reaction of a proper azachalcones I(a-d) with hydroxylaminehydrochloride, hydrazine hydrate or phenylhydrazine. These heterocyclic compounds were characterized by ^{1}H-NMR , CHN , IR and UV spectra in addition to their some physical properties. Also, these prepared compounds were screened for their biological activities and a theoretical calculation which shows that the product IVa obtained from 1,2 – rout was energetically more stable by 1.3967 kcal/mole than that came from 1,4 – rout, thus the reaction proceed via 1,2 – addition.

Keywords : azachalcone, isoxazoline, pyrazoline, biological activity.

تحضير والفعالية البايولوجية لبعض المركبات الحلقية الغير المتجانسة الجديدة والمشتقة من الازاجالكونات

الملخص

يتضمن البحث تحضير سلسلة من المركبات الحلقيـة غيـر المتجانـسة الحاويـة علـى ذرتـي اوكـسيجين ونتـروجين ايزواوكسازولين II(a-d) او الحاوية على ذرتي نتروجين البايرازولين III (a-d) والفنيـل بـايرازولينIV (a-d) مـن تفاعـل الازاجالكون المناسبI (a-d) مع هيدروكسيل امين او الهيدرازين او فنيل الهيدرازين على التوالي. تم تشخيص المركبات بواسطة اطياف ^{1}H-NMR, IR, CHN و UV إضافة إلى بعض خواصها الفيزياوية وفحص الفعالية البايولوجيـة لجميـع المركبـات المحضره، كما تم حساب قيم الطاقة للناتج IVa واثبتت ان ميكانيكة التفاعل تتم بميكانيكية إضافة (1,2).

الكلمات الدالة: ازجالكون، ايزوكسازولين، بايرازولين، الفعالية البايولوجية.

INTRODUCTION

Study for the improvement of novel biological activity agents is becoming the main importance in many investigate laboratories all over the world with the plan to find out newer, additional effective molecules, with elevated specificity and reduced toxicity than the existing ones(Shih *et al.*, 2018). Five membered rings contain two nitrogen molecules or one nitrogen and other oxygen which were found to be a extremely significant pharmacophore in many therapeutic agents (Gunkara and Ocal, 2018; Rajanarendar *et al.,* 2007). In addition, the incorporation of these moiety into a pharmacologically-active pyridyl molecule resulted in many cases in improving the therapeutic profile of the parent

compound (Abedalazem *et al*., 2015). Hundreds or even thousands of isooxazoles and pyrazolines nitrogen-containing five-membered heterocyclic compounds have been prepared by many procedures (Gunkara *et al*., 2018; Patel *et al*., 2016; Sharma *et al*., 2014), while pyrazoline derivatives prepared by the addition of hydrazine hydrate or phenylhydrazine to azachalcones, isoxazolines were prepared by the addition of hydroxyl amine hydrochloride to these chalcones (Sharma *et al*., 2014; Patel *et al*., 2016; Bhimwal *et al*., 2011).

These five membered ring nitrogenous or oxygenous heterocyclic derivatives have widespread potential biological activities such as, antimicrobial (Kotla *et al*., 2012; Hassan *et al*., 2013), antitumoractivites (Mntoya *et al*., 2014), antiinflammatory (Venkataraman *et al*., 2010), antibacterial(Bhimwal *et al*., 2011; Patel *et al*., 2016), anticancer agents (Gunkara *et al*., 2018) and antitubercular activity (Bishnoi *et al*., 2013). These titles of the heterocyclic compounds appeared of interest to synthesis using azachalcones derivatives as synthons.

EXPERIMENTAL

Melting points were determined on an electrothermal Stuart melting point SM P30 and were uncorrected. ^{1}H-NMR spectra of some synthesized compounds were recorded on NMReady 60 Pro-User Manual/Version 1.0 at central service laboratory, University of Baghdad. The chemical shifts are reported in δ values (ppm) relative to tetramethylsilane and quoted as *s*(singlet), *d*(doublet), *t*(triplet), *br*(broad) and *m*(multiplet). Infrared absorption spectra were recorded on Bruker spectrophotometer from college of Pharmacy, University of Mosul. Elemental analysis (CHN) obtained via EuroEA-3000/Italy Elemental analyzer from the central service laboratory, University of Baghdad. Ultra-Violet spectra (UV spectra) obtained via Spectro UV-Vis Auto,UV-2602, from college of Agriculture, University of Mosul. All heterocyclic products II(a-d), III(a-d) and IV(a-d) have been tested for their biological activity at college of Sciences-Mosul University, through agar diffusion method.

The starting azachalcones (3-(pyridine-2-yl)-1-(p-tolyl,bromo, chloro or fluro)prop-2-en-1-one) I(a-d) were prepared according to a previous work (Raoof, 2005).

Synthesis of 3-(4-substituted phenyl)-5-(2`-pyridyl)-4,5-dihydro isoxazoline II(a-d)(Joshi *et al*., 2012) :

Equimolar mixture of aproper azachalcones 1(a-d) (2.5mmol), hydroxylamine hydrochloride (2.5mmol, 0.17 gm) and sodium acetate (2.5mmol, 0.21gm) in ethanol(20ml) is refluxed for 6-7 hours. The mixture was concentrated under atmospheric pressure, then poured into ice water. The precipitates obtained were filtered off, washed with water and crystallized with suitable solvent to afford a solid compounds II(a-d). Tables (1and 2) show some physical properties and spectral data of these compounds respectively:

Table 1: Physical properties of compounds II(a-d)

Compd. No.II	R	Solvent of crystallization	M.P. C°	Yield %	color	Molecular formula
a	CH_3	Ether	139-141	33	yellow	$C_{15}H_{14}N_2O$
b	Br	EtOH-H_2O	152-156	70	brown	$C_{14}H_{11}N_2OBr$
c	Cl	Benzene	136-139	29	yellow	$C_{14}H_{11}N_2OCl$
d	F	EtOH	130(dec.).	19	brown	$C_{14}H_{11}N_2OF$

Table 2: Spectral data of compounds II(a-d)

Compd. No.II	R	UV($CHCl_3$) $\lambda_{max.}$ nm	IR(KBr)cm^{-1}	^{1}H-NMR (DMSO)δ-ppm	CHN	
					Calculated	Found
a	CH_3	275	3034 $CH_{arom.;}$ 2920 C- 1667 C=N; 1587 1123 C-O	6.65-7.68(m),8H 5.27-5.58(m),1H 3.65-4.15(db),1H 2.94(d), 1H 2.29(s), 3H	C 75.6 H 5.9 N 11.7	78.7 5.6 12.8
b	Br	268	3054 $CH_{arom.;}$ 2999 1678 C=N; 1582 1056 C-O			
c	Cl	268	3107 $CH_{arom.;}$ 2717 1675 C=N; 1587 1048 C-O	7.07-8.44 4.95-5.39(t),1H 2.70-3.06 (m),2H	C 65 H 4.2 N 10.8	60.8 4.28 8.57
d	F	290	3131 $CH_{arom.;}$ 2820 1682 C=N ; 1544 1093 C-O			

Synthesis of [3-(4-substituted phenyl)-5-(2`-pyridyl)]-4,5-dihydro pyrazolines III(a-d) (Chincholkar *et al.,* 1979; Venkataraman *et al*., 2010):

A mixture of a proper azachalcone (2.5mmol), hydrazine hydrate(5mmol, 0.25gm), either in pyridine to prepare compounds III(a and b)(method A), or in ethanol to prepare compounds III(c and d)(method B) was refluxed for 6-7 hrs. The mixture was poured into ice water, the precipitate formed washed with water, dried and crystallized with suitable solvent to afford amorphous solid of compounds III(a-d). Tables (3 and 4) showed some physical properties and spectral data of these compounds respectively.

Table 3: Physical properties of compounds III(a-d)

Compd. No.III	R	Solvent of crystallization	M.P. C°	Yield %	color	Molecular formula
a	CH_3	EtOH-H_2O	75-80 decomp.	30	brown	$C_{15}H_{15}N_3$
b	Br	EtOH	152-155	28	yellow	$C_{14}H_{12}N_3Br$
c	Cl	Ether	101-110 decomp.	28	brown	$C_{14}H_{12}N_3Cl$
d	F	EtOH-H_2O	67-70 decomp.	25	yellow	$C_{14}H_{12}N_3F$

Table 4 : Spectral data of compounds III(a-d)

Compd. No.III	R	UV($CHCl_3$) $\lambda_{max.}$ nm	IR(KBr)cm^{-1}	^{1}H-NMR (DMSO)δ-ppm	CHN	
					calculated	Found
a	CH_3	260	3270 NH; 3020 $CH_{arom.;}$ 2870 C H_{alip} 1660 C=N 1560 C=$C_{arom;}$ 1310 C-N	8.53-8.44(br),1H; 7.91-7.34(m),8H; 4.25 (m),1H; 3.69(db),2H; 2.51(s), 3H	C 75.9 H 6.3 N 17.7	74 5.8 16.2
b	Br	280	3210 NH 3055 $CH_{arom.;}$ 2905 $CH_{aliph;}$ 1677 C=N; 1584 C=$C_{arom\ ;}$ 1285 C-N	8.52-8.45(br),1H 8.11-7.40 (m),8H 3.80 (m), 1H 3.60-3.52(db), 2H	C 55.6 H 4.0 N 13.9	52.4 3.5 12.75
c	Cl	300	3462 NH 3020 $CH_{arom.}$ 2900 $CH_{aliph.}$ 1685 C=N 1604 C-$C_{arom.}$ 1375 C-N			
d	F	288	3413 NH; 3078 $CH_{arom.}$ 2850 $CH_{aliph.}$ 1601 C=N 1508 C=$C_{arom,}$ 1232 C-N			

Synthesis of 1-phenyl[3-(4-substituted phenyl)-5-(2`-pyridyl)]-4,5-dihydro pyrazoline IV(a-d): (Sharma *et al*., 2014)

A mixture of proper azachalcones (2.5mol), phenyl hydrazine (2.5mol,0.27gm) and 10 ml glacial acetic acid was refluxed for 3-4 hrs., the mixture was then poured into ice-water. The residue was filtered off, washed with water, dried and crystallized from suitable solvent to afford a solid compounds IV(a-d). Tables(5 and 6) showed some physical properties and spectral data respectively of these compounds.

Table 5 : Some physical properties of compounds IV(a-d)

Compd. No.IV	R	Solvent of crystallization	M.P. C°	Yield %	color	Molecular formula
a	CH_3	EtOH	118-119	35	white	$C_{21}H_{19}N_3$
b	Br	EtOH	155-159	25	yellow	$C_{20}H_{16}N_3Br$
c	Cl	EtOH	138-140	30	yellow	$C_{20}H_{16}N_3Cl$
d	F	$(Me)_2O$	158-162	18	yellow	$C_{20}H_{16}N_3F$

Table 6: Spectral data of compounds IV(a-d)

Compd. No.IV	R	UV($CHCl_3$) $\lambda_{max.}$ nm	IR(KBr)cm^{-1}	^{1}H-NMR (DMSO)δ-ppm	CHN	
					calculated	Found
a	CH_3	258	3127 $CH_{arom.}$; 2833 CH_{alip} 1598 C=N ; 1512 C=C_{arom} 1332 C-N	7.32-8.53(m), 13H 5.47-5.81(t), 1H 3.05-4.26(m), 2H 2.80 (s), 3H	C 80.5 H 6.07 N 13.4	77.0 6.11 10.3
b	Br	290	3015 $CH_{arom.}$; 2920 $H_{aliph.}$ 1630 C=N; 1550 C=$C_{arom.}$ 1358 C-N			
c	Cl	260	3050 $CH_{arom.}$; 2900 $CH_{aliph.}$ 1589 C=N; 1572 C-$C_{arom.}$ 1319 C-N	6.67-7.80(m), 13H 5.33-5.64(m),1H 2.96-4.16 (m),2H	C 72.1 H 4.8 N 12.6	72.13 4.8 12.3
d	F	278	3046 $CH_{arom.}$; 2857 $CH_{aliph.}$; 1593 C=N ; 1549 C=$C_{arom.}$; 1238 C-N			

BIOLOGICAL ACTIVITY

The procedure followed for tested the titles heterocyclic products is simply that a filter disk impregnated with an antibiotic which is applied to the surface of anagar plate containing the organism to be tested and the plate is incubated at 37°C for 24-48 hours. AS the substance diffuses from the filter paper into the agar, the concentration decreases. At some particular distance from each disk, the antibiotic is diluted to the point that is no longer inhibits microbial growth. The effectiveness of particular antibiotic is shown by the presence of growth inhibition zones. These zones appear as clear areas surrounding the disk from the substances with antimicrobial activity. Measur the zone sizes to the nearest millimeter using a ruler and the results reported as (++), (+), (±) or (-), Table(7). Dimethyl sulfoxide (DMSO) was used as a solvent for the compounds, blank paper disk of DMSO also was used as control.

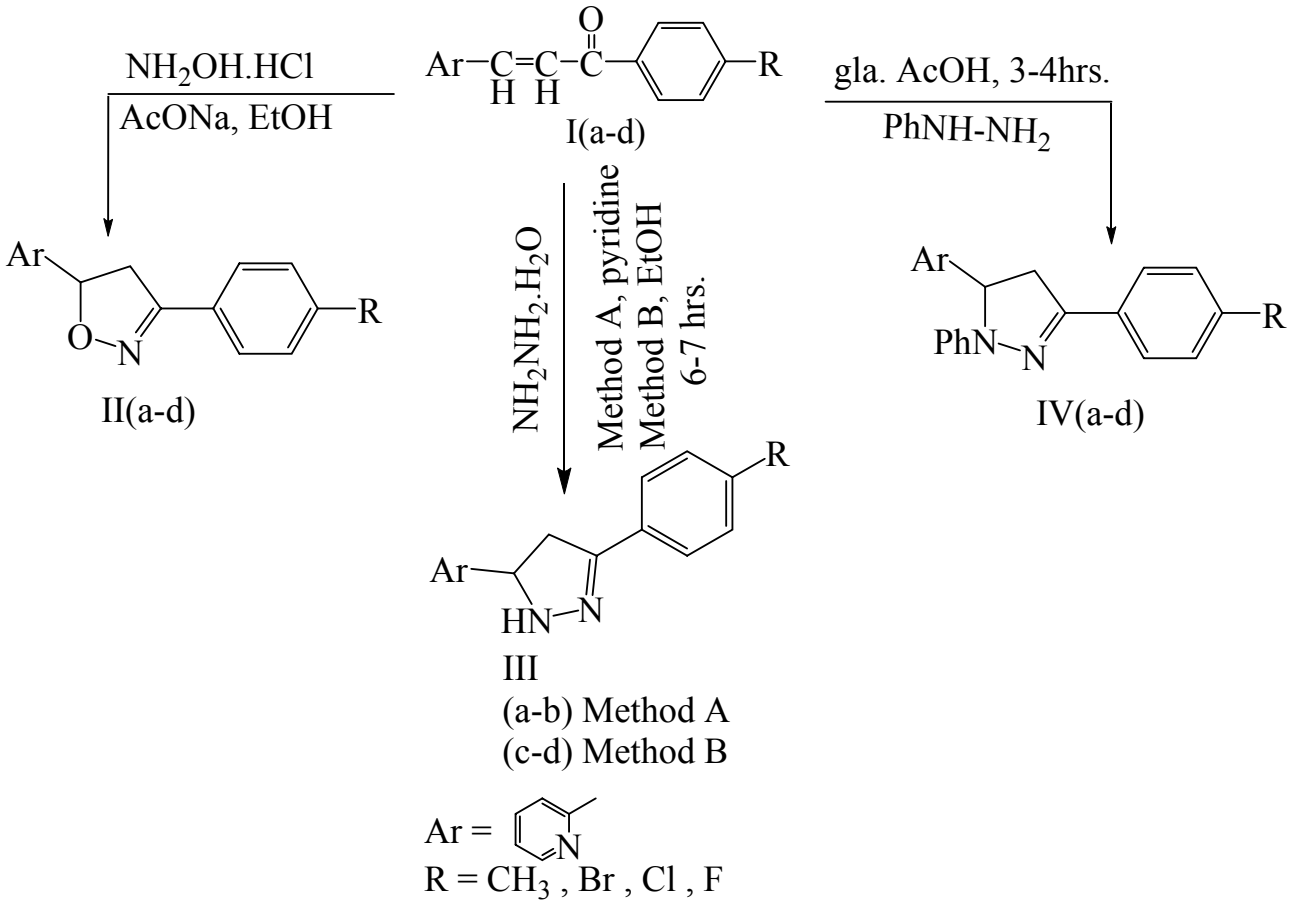
Table 7 : Biological activity for products (II-IV)

Comp.No.	E-coli	Staphylococcus-aureus	Pseudomonas-aeruginosa
IIa	++	±	-
IIb	-	-	-
IIc	+	+	-
IId	+	+	-
IIIa	++	+	-
IIIb	+	+	-
IIIc	-	+	-
IIId	±	+	-
IVa	+	+	-
IVb	+	-	-
IVc	-	+	-
IVd	±	-	-

Note: (++) = sensitive, more than 20 mm, (+) = intermediate, 10-20mm, (±) = weak, 5-10mm, (-) = resistant, no inhibition,

RESULS AND DISCUSSION

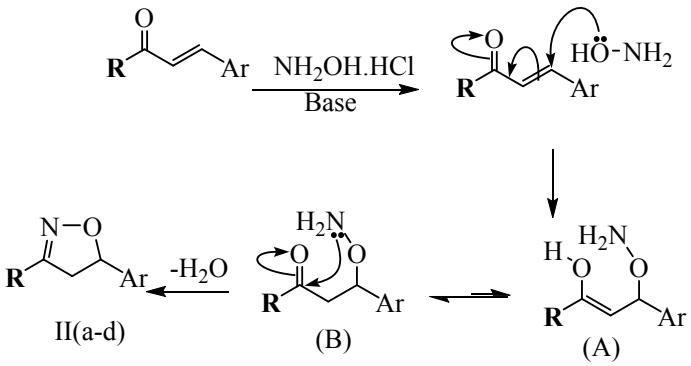
A suitable synthesis of aimed heterocyclic compounds were accomplished by the route outlined in Scheme (1) :



Scheme 1: Synthesis heterocyclic compounds containing N,O or N, N-atoms

In this work, the synthesis of isoxazolines II(a-d) from the cyclization of starting azachalcones and hydroxylamine hydrochloride was carried out as shown in Scheme (1). In order to achieve this aim, sodium acetate as a base was used.

The nucleophile ($HONH_2$) attack carbon number (4) of α,β-unsaturated carbonyl compound via 1,4 – Michael addition giving intermediate (A) which cyclized via intermolecular addition to produce intermediate (B), the driving force for ring formation was the water elimination (Raoof *et al.*, 2013; Levai, 2005; Levai *et al.*, 2007). The proposed mechanism was illustrated in Scheme (2) (Shah and Desai, 2007) :



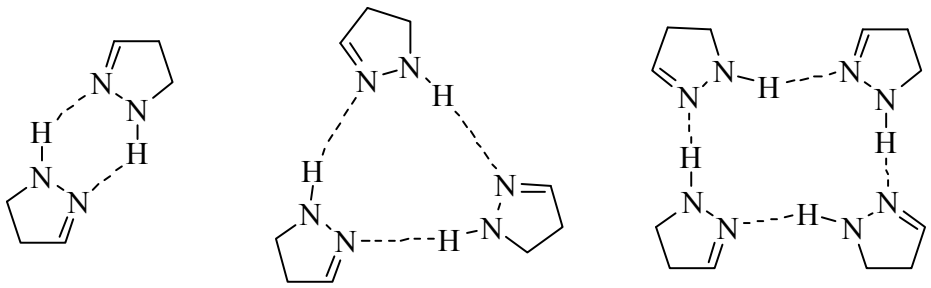
Scheme 2: The preposed mechanism for cyclization

The UV spectral data for the products II(a-d) showed a blue shift in λ_{max} values (268-290), indicating that these products was less conjugated than staring materials (Raoof, 2005). The IR spectra of these products showed the major absorption band at (1667-1682) cm^{-1} for C=N, (Azarifar and Shaebanzadeh, 2002; Daood and Ahmed, 2015; Bhimwal *et al.,* 2011). Other absorption bands were represented in Table (2). The ^{1}H-NMR spectra of compounds (IIa and c) were in agreements with the suggested structures. For the product IIa appeared signals at: δ (6.65-8.54)ppm (m, 8H, Aryl and Pyridyl-H), (5.27-5.58)ppm (m,1H, CH oxazoline ring), (3.65-4.15)ppm (db, 1H, CH_2oxazoline ring), 2,9ppm (db, 1H, CH_2 oxazoline ring)and 2.29 ppm (s, 3H, CH_3), (Shah *et al.,* 2007), while compound IIc appeared as signals at: δ(7.07-8.44) ppm (m, 8H, Aryl and Pyridyl-H), (4.95-5.39) ppm (t, 1H, CH oxazoline ring) and (2.70-3.06) ppm (m, 2H, CH_2 oxazoline ring). The elemental analysis calculated for the product (IIa) $C_{15}H_{14}N_2O$(%) : C,75.6; H,5.9; N,11.7; found: C,78.7; H,5.6; N,12.8 and for the product (IIc) $C_{14}H_{11}N_2OCl$(%): C,65; H,4.2; N,10.8; found: C,60.8; H,4.27; N,8.57. It should be noted that the results of the CHN analyses are affected by many contaminants present in the sample like, (moisture, solvent, dust). Therefore, the values determined experimentally might not correspond to the theoretical values (Swamy and Agasimundi, 2008; Arora *et al.,* 2012).

Reaction of azachalcones I(a-d) with hydrazine hydrate using pyridine (method A) or ethanol (method B) gave pyrazoline derivatives III(a-b and c-d) respectively. The mechanism is the same as suggested for synthesis of compounds II as shown by Scheme (2).

The UV spectral data show a blue shift in λ_{max} values (260-300), indicating that these products are less conjugated than starting materials and the reaction take place. The IR spectra showed absorptions bands at (3210-3462) cm^{-1} and (1601-1685) cm^{-1} for NH and C=N respectively, (Table 4). The ^{1}H-NMR spectra of compounds III(a and b) gave signals at (8.52-8.44) ppm (br, 1H, NH), (Shah *et al.,* 2007), (8.11-7.34)ppm (m., 8H, Aryl and Pyridyl-H), (4.25-3.80)ppm (m, 1H, CH pyrazoline ring) and (3.69-3.52)ppm(db, 2H, CH_2pyrazoline ring). The compound IIIa gave an additional signal at 2.51ppm(s, 3H, CH_3 group). The analysis C,H,N calculated for the product IIIa $C_{15}H_{15}N_3$(%) : C,75.9; H,6.3; N,17.7; found : C,74.3; H5.8; N,16.2, while for the product IIIb $C_{14}H_{12}N_3Br$(%) : C,55.6; H,4; N,13.9; found : C,52.4; H,3.5; N,12.7.

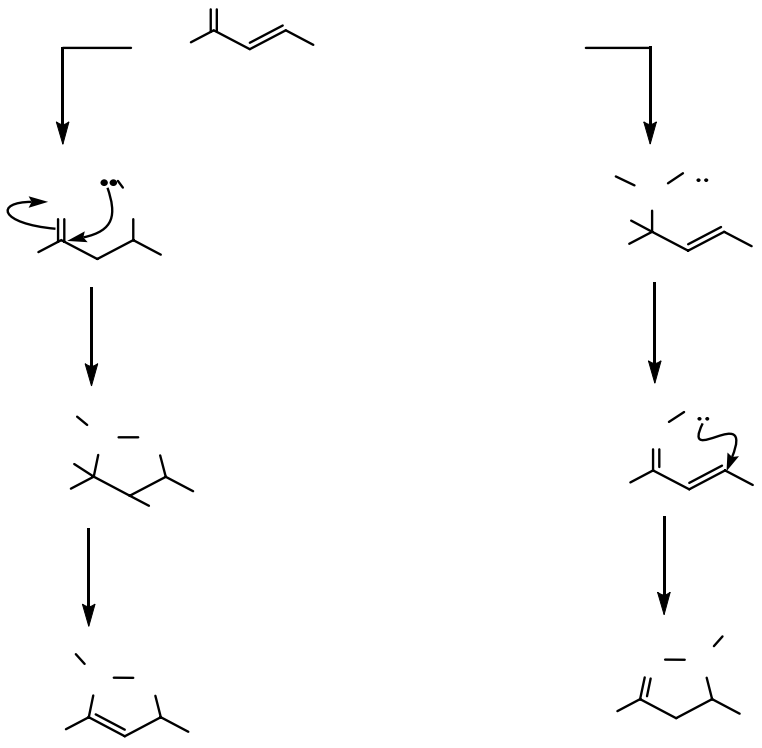
Unfortunately, the yield of these compounds are low, these results can be attributed to the ability of the N – unsubstituted pyrazoline molecule to form an intermolecular hydrogen bonding, which can lead to at least five motifs such as dimers trimers and tetramers as the following (Ahmed, 2011):



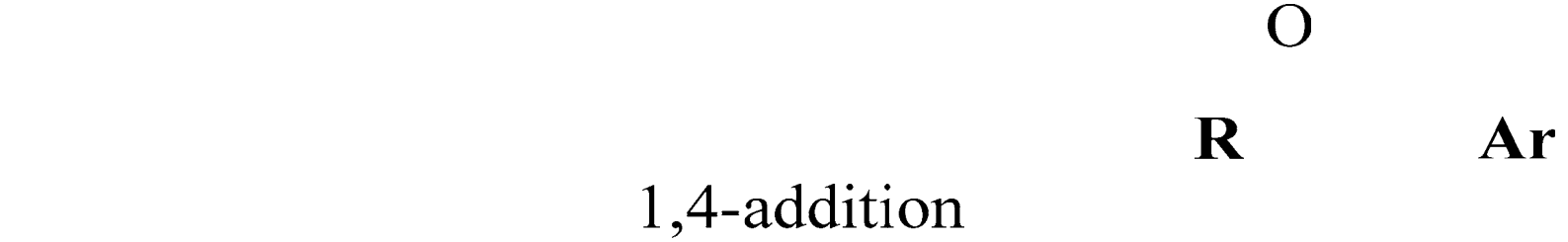
dimer trimer tetramer

Phenylpyrazoline derivatives IV(a-d) obtained by the addition of phenylhydrazine to the proper acceptor (activated α, β-unsaturated carbonyl compounds) through 1,4- conjugate addition or at the carbonyl carbon 1,2 – addition to form intermediate, which then undergoes cyclization process to form the product, Scheme (3).

Theoretical calculations (for product IVa which choosed as representative for these serious) showed that the product obtained from 1,2 – rout was energetically more stable by 1.3967 kcal/mole than that came from 1,4 – rout; thus, we suggest that reaction proceed via 1,2–addition (Al-Kadhimi *et al.*,2013):



Scheme 3: mechanism of 1,4 and 1,2 addition



The UV spectral data show a blue shift in λ_{max} values (258-290)nm . the IR spectra showed the most important absorption band at (1589-1630) cm^{-1} belong to C=N stretching, (Al-Kadhimi *et al.,* 2013), (Table 6). The ^{1}H-NMR spectra of compounds IV (a and c) appeared signals at : δ(8.53-6.67)ppm (m,13H, Aryl and Pyridyl-H), (4.95-5.81)ppm (m, 1H, CH pyrazoline ring)) and (2.96-4.26)ppm (m, 2H, CH_2pyrazoline ring). The product IVa gives additional signal at 2.80ppm (s, 3H, CH_3) . The analysis C,H,N calculated for the product IVa $C_{21}H_{19}N_3$(%) : C,80.5; H,6.07; N,13.4; found : C,77.3; H.6.11; N,10.3, while for the product (IVc) $C_{20}H_{16}N_3Cl$(%) : C,72.1; H,4.8; N,12.6; found : C,72.13; H,4.8; N,12.3 .

Antimicrobial activity of the prepared compounds II, III, IV(a-d) was examined by the agar diffusion method used free different bacterial species, i.e. *E-Coli, Staphylococcus aureus* and *Pseudomonas aeruginosa*. The prepared compounds show higher activity towards *E. coli* and *Staph. aureus* compared to the pseudomonas aeruginosa, (Table 7) (Nowakowska *et al*., 2001).

ACKNOWLEDGMENT

The authors are thankful to Ms. Shbaba /College of Science – Biological department for the biological screening of the preparing compounds.

REFERENCES

Abdelazem, A.Z.; Lee, S.H. (2015). Synthesis and biological evaluation of new pyrimidine-4-yl-ethanol derivatives as ROS1 kinase inhibitors. *J.Enzyme Inhibition and Midic. Chem.,* **90**, 195-208.

Ahmed, S.A.Q.S. (2011). Synthesis of various heterocyclic compounds from α,β-unsaturated ketones. M.Sc. Thesis, College of Scince. Mosul University.

Al-Kadhimi, A.H.; Al-Khayate, A.K.; Al-Dulyme, M.G. (2013). Synthesis and characterization of some new pyrazoline derivatives from chalcones bearing benzofurane moiety. *The First Scie. Conference the College of Sciences,*pp.283-292 www.iasj.net/iasj?func=f.

Arora, V.; Arora, P.; Lamba, H.S.(2012). Synthesis and biological activities of some 3,5- disubstituted pyrazoline derivatives of 2- acetyl naphthalene. *International J. Pharm. and Pharmaceut. Sci.,* **4**(4),2012.

Azarifar, D.; Shaebanzadeh, M. (2002). Synthesis and characterization of new 3,5-dinaphthyl substituted 2-pyrazolines and study of their antimicrobial activity. *J. Molecules,***7**(12),885-895.

Bhimwal, R.; Sharma, A.K.; Jain, A. (2011). Synthesis, characterization and In-vitro antimicrobial evaluation of some novel isoxazoline derivatives. *J. Advanced Pharm. Education and Research*, **1**(5), 251-258.

Bishinoi, A.; Singh, S.; Tiwari, A.K.; Srivastava, K.; Raghuvir, R.; Tripathi, C.M. (2013). Synthesis, characterization and biological activity of new cyclization products of 3-(4-substituted benzylidene-2H-pyrido [1,2-a] pyrmidine-2,4-(3H)-diones. *J.Chem. Sci*., **125**(2), 305-312.

Chincholkar, M.M.; Jamode, V.S. (1979). Synthesis of pyrazoline Part II, 72p. Shodhganga. inflibnet.ac.in/bitstream.

Dawood, R.S.; Ahmed, K.T. (2015). Synthesis and characterization of new pyrazoline and isoxazoline derivatives based on fluorine. *Tikrit J. Pure Sci.,***20**(2), 121-126.

Gunkara, O.T.; Ocal, N. (2018). Synthesis of new N-phthalimide substituted tricyclic imide containing isoxazoline and bispiro functional group as possible anticancer agents. *J. Turkish Chem. Soc.*, **5**(1), 73-48.

Hassan, S.Y. (2013). Synthesis, antibacterial and antifungal activity of some new pyrazoline and pyrazole derivatives. *J. Molecules*.**18**(3), 2683-2711.

Joshi, V.D.; Kshirsagar, M.D.; Singhal, S. (2012). Synthesis and biological evaluation of some novel isoxazoles and benzodiazepines. *J. Chem. and Pharmaceut. Research*. **4**(6), 3234-3238.

Kotla, V.V.; Dalavai, V.K.; Chunduri, V.R. (2012). Synthesis and biological activity studies of some novel pyrazoline derivatives. *J. Der. Pharma. Chem.*, **4**(5), 2003-2008.

Levai, A. (2005). Synthesis of chlorinated 3,5-diaryl-2-pyrazolines by the reaction of chlorochalcones with hydrazines. ARKIVOC (Archive for Organic Chemistry)344p.

Levai, A.; Katalin, E.K.; Jekő, J.(2007). "Synthesis of Tricyclic Fused Pyrazolines by the Reaction of 3-arylidenechromanones and 3-arylidene-1-thiochromanones with Hydrazine". ARKIVOC; (viii) pp.26-39.

Mntoya, A.; Quiroga, J.; Abonia, R.; Nogueras, M.; Cobo, J.; Insuasty, B. (2014). Synthesis and in vitro antitumor activity of a novel series of 2-pyrazoline derivatives bearing the 4-aryloxy-7-chloroquinoline fragment. *J. Molecules*, **19**, 18656-18675.

Nowakowska, Z.; Wyrzykiewicz, E.; Kedzia, B. (2001). Synthesis and antimicrobial properties of N-substituted derivatives of (E) -4-azachalcones. *J. II Farmaco*. **56**(4), 325-329.

Patel, A.J.; Patel, M.P. (2016). Synthesis and antimicrobial studies of new pyrazoline/ isoxazoline derivatives bearing quinoline moiety using Ultrasound Irradiation. *Indian J. Advances in Chem. Sci.*, **4**(4), 409-420.

Rajanarendar, E.; Ramesh, P.; Kalyan Rao, E.; Mohan, G.; Srinivas, M. (2007)." p-TsOH Catalysed KSF Solid Supported Michael Addition with Substituted Isoxazoles and their Reductive Cyclisation to Isoxazolo[4,5b]azepines". ARKIVOC ; xiv: pp.266-75

Raoof, M.Y. (2005). Astudy on some azachalcones condensation reactions. Ph.D. Thesis, College of Scince. Mosul University, pp.15- 18.

Raoof, M.Y.; Saied, S.M.; AL.Gawady, M.S. (2013). Synthesis of some3-chloro-2,3-dimethyl-1-phenylpyrazolidin-5-one (Chlorophenazone) Derivatives. Kirkuk University, *J. Sci. Studies,* **8**(2), 34-42.

Shah, T.; Desai, V. (2007). Synthesis and antibacterial studies of some novel isoxazoline derivatives. *J. Serb.Chem.Soc.*,**72**(5), 443-449.

Sharma, S.; Kaur, S.; Bansal, T.; Gaba, J. (2014). Synthesis of bioactive pyrazoline derivatives. *J. Chem. Sci. Trans*., **3**, 861-875.

Shih, T.L.; Liu, M.H.; Kuo, Ch.F.(2018). Halo substituted chalcones and azachalcones inhibited lipopoly saccharited stimulated Pro-Inflammatory responses through the TLR_4-Mediated Pathway. *Molecules*, **23**,597, www.mdpi.com.

Swamy, P.M.G.; Agasimundin, Y.S. (2008). Synthesis and antimicrobial screening of certain substituted chalcones and isoxazolines bearing hydroxyl benzofuran. *Rasayan J. Chem*., **1**(2), 421-428.

Venkataraman, S.; Jaia, S.; Shah, K.; Upmanyu, N. (2010). Synthesis and biological activity of some novel pyrazolines. *J. Acta Poloniae Pharmaceutica-Drug Research,* **67**(4), 361-366.