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

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ABSTRACT

A series of heterocyclic compounds containing oxygen and nitrogen atoms, isoxazoline ІІІ(a-d) and another containing two nitrogen atoms, pyrazolines ІІ(a-d) and phenylpyrazolines ІV(a-d) were prepared by the reaction of a proper azachalcones І(a-d) with hydroxylaminehydrochloride, hydrazine hydrate or phenylhydrazine. These heterocyclic compounds were characterized by 1H-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 ІVа 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.

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 hydroxylamine 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), antitumor activities (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 $\delta$ (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            | CH₃ | Ether                     | 139-141 | 33     | yellow| C₁₅H₁₄N₂O         |
| b            | Br  | EtOH-H₂O                  | 152-156 | 70     | brown | C₁₄H₁₁N₂OBr        |
| c            | Cl  | Benzene                   | 136-139 | 29     | yellow| C₁₄H₁₁N₂OCl        |
| d            | F   | EtOH                      | 130(dec.)| 19     | brown | C₁₄H₁₁N₂OF         |
Synthesis and Biological activities

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

| Compd. No.II | R  | UV(CHCl₃) λmax. nm | IR(KBr)cm⁻¹ | ¹H-NMR (DMSO)δ-ppm | CHN          |
|--------------|----|--------------------|-------------|---------------------|-------------|
|              |    |                    |             |                     | Calculated  | Found       |
| a            | CH₃| 275                | 3034 CH₅N₃; 2920 C-O | 6.65-7.68(m),8H | C 75.6     | 78.7        |
|              |    |                    | 1667 C=N; 1587 | 5.27-5.58(m),1H   | H 5.9      | 5.6         |
|              |    |                    | 1123 C-O     | 3.65-4.15(db),1H         | N 11.7     | 12.8        |
| b            | Br | 268                | 3054 CH₅N₃; 2999 | 2.94(d), 1H       |             |             |
|              |    |                    | 1678 C=N; 1582 | 2.29(s), 3H       |             |             |
|              |    |                    | 1056 C-O     |                   |             |             |
| c            | Cl | 268                | 3107 CH₅N₃; 2717 | 7.07-8.44         | C 65       | 60.8        |
|              |    |                    | 1675 C=N; 1587 | 4.95-5.39(t),1H   | H 4.2      | 4.28        |
|              |    |                    | 1048 C-O     | 2.70-3.06 (m),2H  | N 10.8     | 8.57        |
| d            | F  | 290                | 3131 CH₅N₃; 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             | CH₃| EtOH-H₂O                   | 75-80 decomp. | 30      | brown | C₁₂H₁₅N₃       |
| b             | Br | EtOH                      | 152-155      | 28      | yellow | C₁₄H₁₂N₃Br     |
| c             | Cl | Ether                     | 101-110 decomp. | 28      | brown | C₁₄H₁₂N₃Cl     |
| d             | F  | EtOH-H₂O                  | 67-70 decomp. | 25      | yellow | C₁₄H₁₂N₃F      |
Table 4: Spectral data of compounds III(a-d)

| Compd. No.III | R  | UV(CHCl₃) λmax. nm | IR(KBr) cm⁻¹ | ¹H-NMR (DMSO) δ-ppm | CHN          |
|--------------|----|------------------|--------------|---------------------|-------------|
|              |    |                  |              |                     | calculated  | Found       |
| a            | CH₃| 260              | 3270 NH; 3020 CH₉arom.; 2870 CHaliph; 1660 C=N; 1560 C=C₉arom; 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      | 74          |
| b            | Br | 280              | 3210 NH 3055 CH₉arom.; 2905 CHaliph; 1677 C=N; 1584 C=C₉arom; 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      | 52.4        |
| c            | Cl | 300              | 3462 NH 3020 CH₉arom. 2900 CHaliph. 1685 C=N 1604 C=C₉arom. 1375 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      | 52.4        |
| d            | F  | 288              | 3413 NH; 3078 CH₉arom. 2850 CHaliph. 1601 C=N 1508 C=C₉arom. 1232 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      | 52.4        |

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            | CH₃| EtOH                      | 118-119 | 35      | white | C₂₁H₁₉N₃        |
| b            | Br | EtOH                      | 155-159 | 25      | yellow| C₂₀H₁₆N₃Br       |
| c            | Cl | EtOH                      | 138-140 | 30      | yellow| C₂₀H₁₆N₃Cl       |
| d            | F  | (Me)₂O                   | 158-162 | 18      | yellow| C₂₀H₁₆N₃F        |
Table 6: Spectral data of compounds IV(a-d)

| Compd. No. | R    | UV(CHCl₃) λmax nm | IR(KBr) cm⁻¹ | ¹H-NMR (DMSO) δ ppm | CHN       |
|------------|------|-------------------|--------------|----------------------|-----------|
| a          | CH₃  | 258               | 3127 CH₉ arom. 2833 CH₉ aliph. 1598 C=N ; 1512 C=C₉ 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 CH₉ arom. 2920 CH₉ aliph. 1630 C=N; 1550 C=C₉ arom. 1358 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      |
|            |      |                   |              |                      | 12.3      |
| c          | Cl   | 260               | 3050 CH₉ arom. 2900 CH₉ aliph. 1589 C=N; 1572 C=C₉ 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          |
|            |      |                   |              |                      | 12.3      |
| d          | F    | 278               | 3046 CH₉ arom. 2857 CH₉ aliph. 1593 C=N; 1549 C=C₉ arom. 1238 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          |
|            |      |                   |              |                      | 12.3      |

**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-coll | Staphylococcus-aureus | Pseudomonas-aeruginosa |
|----------|--------|-----------------------|------------------------|
| IIa      | ++     | ±                     | -                      |
| IIb      | -      | -                     | -                      |
| IIc      | +      | +                     | -                      |
| IIId     | +      | +                     | -                      |
| IIIa     | +      | +                     | -                      |
| IIIb     | +      | +                     | -                      |
| IIIc     | -      | +                     | -                      |
| IIIId    | ±      | +                     | -                      |
| IVa      | +      | +                     | -                      |
| IVb      | +      | -                     | -                      |
| IVc      | -      | +                     | -                      |
| IVd      | ±      | -                     | -                      |

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

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 (HONH2) 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):
The UV spectral data for the products II(a-d) showed a blue shift in $\lambda_{max}$ values (268-290), indicating that these products was less conjugated than starting 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: $\delta$ (6.65-8.54)ppm (m, 8H, Aryl and Pyridyl-H), (5.27-5.58) ppm (m, 1H, CH$_2$oxazoline ring), (3.65-4.15) ppm (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: $\delta$(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$_2$O(%) : 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$_2$OCl(%) : 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 $\lambda_{max}$ 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$_2$pyrazoline ring). The compound IIIa gave an additional signal at 2.51 ppm (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$_3$Br(%) : 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 intramolecular hydrogen bonding, which can lead to at least five motifs such as dimers trimers and tetramers as the following (Ahmed, 2011):
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 $\lambda_{\text{max}}$ 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: $\delta$(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$_2$pyrazoline 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$_3$Cl(%) : 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).

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