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Synthesis and Identification of Some New Thiazole Derivatives which Derived from Pyrazoline Compounds and Evaluation the Antibacterial Activity of Some of them

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Abstract

In this study some new derivatives of thiazole compounds were successfully prepared in two steps with high yields. The first step included a synthesis of a new series of pyrazoline (1a-1i) using a one-pot three components reaction. The reaction between (acetophenone\4-nitroacetophenone), different substituted benzaldehyde compounds and thiosemicarbazide in absolute ethanol as a solvent with heating at reflux provided the new series of pyrazoline derivatives in a short reaction times. In the second step, the pyrazoline compounds (1a-1i) refluxed with 4-bromophenacyl bromide in absolute ethanol to produce thiazole compounds (2a-2i) in high yields. The Infra-red technique (FT-IR) was used to identify the synthesised compounds and the proton Nuclear Magnetic Resonance technique (^{1}H-NMR) was used to identify som of them.

Keywords: Thiazole, Pyrazoline, one- pot reaction, antibacterial activity.

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تحضير وتشخيص بعض مشتقات الثايازول المشتقة من مركبات البايرازولين وتقييم فعالية البعض منها ضد البكتريا

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الملخص

في هذه الدراسة تم تحضير بعض مشتقات الثايازول الجديدة بخطوتين وبنسب منتوج عالية، حيث تضمنت الخطوة الاولى استخدام طريقة الثلاث متفاعلات في وعاء واحد وذلك من خلال تصعيد كل من (الاستيوفينون او 4-نيترواستيوفينون) والالديهايدات المعوضة والثايوسيميكاربازايد في الايثانول المطلق لانتاج مركبات البايرازولين (1i-1a), اما الخطوة الثانية فتضمنت تصعيد مركبات البايرازولين (1i-1a) مع 4-برومو فينسيل بروميد في الايثانول المطلق لانتاج مركبات الثايازول (2i-2a) وبنسب منتوج عالية . تم استخدام تقنية الاشعة تحت الحمراء (FT-IR) لتشخيص المركبات المحضرة وتقنية طيف الرنين النووي المغناطيسي للبروتون (^{1}H-NMR) لبعض المركبات المحضرة .

الكلمات الدالة : ثايازول، بارازولين، تفاعل خطوة واحدة، فعالية ضد البكتريا.

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1. Introduction:

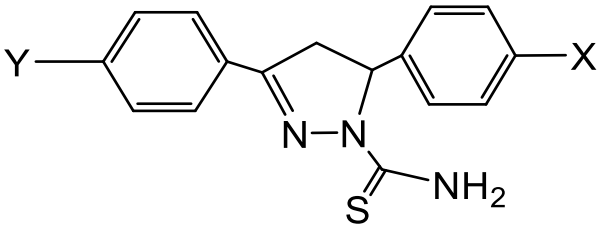
Using a one-pot reaction in organic synthesis considered to be a highly attractive strategy where it has different advantages included simple operation, fewer reaction steps, short reaction times, economic methods and high productivity[1, 2].

Pyrazoline and Thiazole derivatives proved to have a wide range of biological activit [3-10]. The biological activity included anti-inflammatory [3], antifungal [4], antibacterial [5], antioxidant [6], anti-depressant [7], anticancer [8], antiamoebic [9] and anti-tubercular [10]. Arange wide of simple thiazole derivatives synthesized using different protocols starting from amines, however the used strategy in this paper led to provide different thiazoles with high yield in one-pot reaction. The resulted thiazoles expected to have an important biological activity. As a result the biological study conform that thiazoles can work as inhibitor to Escherichia coli.

2. Experimental :

ll chemicals were purchased from Aldrich Chemical Co. Ltd, Lancaster Synthesis Ltd, or Avocado Chemical Co. Ltd. All of the reaction was monitored by TLC (silica plates). Melting points were measured using a Stuart SMP melting point apparatus. Infra-red spectra were recorded as KBr discs (solids) or thin films on NaCl windows or using a NICOLT 100 series FTIR spectrometer. ^{1}H-NMR spectra were recorded on Bruker ultra-shield 300 MHz in Ghazi University in Turkey.

2.1 Synthesis of pyrazoline (1a-1i):



X= Br, Cl, $N(CH_3)_2$, OCH_3, NO_2, H
Y= H, NO_2

Following the procedure in the previous study [11] : a mixture of (acetophenone or 4-nitro acetophenone) (3.5mmol), thiosemicarbazide (5 mmol, 0.45 g), substituted aldehyde (3.5

mmol) and NaOH (4%, 6 mmol) was mixed together in (15 ml) absolute ethanol and refluxed with stirring for appropriate time until complete the reaction which was monitored by TLC and FT-IR. The solution was cooled, the solid product was separated, washed with cold ethanol, dried and recrystallized from toluene to give pyrazoline compounds (1a-1i).

2-1a/5-(4-bromophenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazole-1-carbothioamide:

($C_{16}H_{14}BrN_3S$), m.p. (204-206 °C), yield (71%). IR (cm^{-1}) str.: 3425,3288(NH_2), 1524(C=C), 1599(C=N), 1364(C=S). ^{1}H-NMR (ppm): 3.15(dd, 1H, HH), 3.25-3.29(dd, 1H, HH), 5.55-5.59(dd, 1H, H_9), 7.28-8.36(m, 9H, 2Ar-rings), 8.07(s, 2H, NH_2).

2-1b/5-(4-chlorophenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazole-1-carbothioamide

($C_{16}H_{14}ClN_3S$), m.p. (202-204°C), yield (65%). IR (cm^{-1}) str.: 3435, 3278(NH_2), 1525 (C=C), 1600 (C=N), 1366 (C=S).

2-1c/5-(4-(dimethylamino)phenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazole-1-carbothioamide

($C_{18}H_{20}N_4S$), m.p. (218-220°C), yield (59%). IR (cm^{-1}) str.: 3370,3249 (NH_2), 1506 (C=C), 1559 (C=N), 1368 (C=S).

2-1d/5-(4-methoxyphenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazole-1-carbothioamide

($C_{17}H_{17}N_3OS$), m.p. (174-176°C), yield (48%). IR (cm^{-1}) str.: 3404,3290(NH_2), 1511(C=C), 1603(C=N), 1361(C=S).

2-1e/5-(4-nitrophenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazole-1-carbothioamide

($C_{16}H_{14}N_4O_2S$), m.p.(215-217°C), yield(64%). IR(cm^{-1}) str. : 3491,3363(NH_2), 1490(C=C), 1583(C=N), 1450(C=S).

2-1f/ 3,5-diphenyl-4,5-dihydro-1*H*-pyrazole-1-carbothioamide

($C_{16}H_{15}N_3S$), m.p.(214-216°C), yield(62%). IR(cm^{-1}) str. : 3392,3239(NH_2), 1534(C=C), 1598(C=N), 1368(C=S).

2-1g/5-(4-bromophenyl)-3-(4-nitrophenyl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamide

($C_{16}H_{13}BrN_4O_2S$), m.p.(220-222°C), yield(55%). IR(cm^{-1}) str. : 3435,3280(NH_2), 1490(C=C), 1580(C=N), 1360(C=S).

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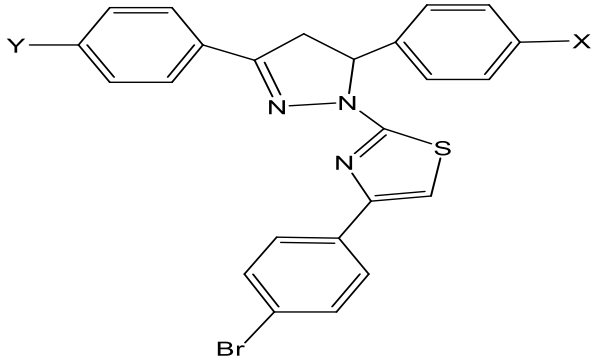
2-1h/5-(4-chlorophenyl)-3-(4-nitrophenyl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamide

($C_{16}H_{13}ClN_4O_2S$), m.p.(217-219°C), yield(60%). IR(cm^{-1}) str. : 3412,3250(NH_2), 1489(C=C), 1600(C=N), 1366(C=S).

2-1i / 5-(4-dimethylamino)phenyl)-3-(4-nitrophenyl)-4, 5-dihydro-1*H*-pyrazole-1-carbothioamide:

($C_{18}H_{19}N_5O_2S$), m.p.(220-222°C), yield(51%). IR(cm^{-1}) str. : 3440,3260(NH_2), 1500(C=C), 1616(C=N), 1370(C=S).

2.2 Synthesis of Thiazole Compounds (2a-2i):



X= Br, Cl, $N(CH_3)_2$, OCH_3, NO_2, H
Y= H, NO_2

A mixture of pyrazoline derivative (1a-1i) (0.5 mmol) and 4-bromophenacyl bromide (0.5mmol, 0.1389g) in absolute ethanol (10ml) was refluxed with stirring for (2-3)hours until complete the reaction, which was monitored by formation of ppt and, the ppt was isolated by filtration, washed with ethanol, dried and purified by recrystallization from toluene and ethanol to give thiazole compounds (2a-2i).

2-2a/4-(4-bromophenyl)-2-(5-(4-bromophenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)thiazole:

($C_{24}H_{16}Br_2N_3S$), m.p.(244-246°C), yield(91%). IR(cm^{-1}) str. :

1485(C=C), 1625(C=N) . ^{1}H-NMR(ppm): 3.07(dd, 1H, HH), 3.27-3.31(dd, 1H, HH), 5.80-5.84(dd, 1H, CH), 7.18-8.26[m, 14H, 3Ar-rings+ CH(thiazole ring)].

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2-2b/4-(4-bromophenyl)-2-(5-(4-chlorophenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)thiazole

($C_{24}H_{16}BrClN_3S$), m.p.(248-250°C), yield(85%). IR(cm^{-1}) str. :

1487(C=C), 1625(C=N) .

2-2c/4-(1-(4-(4-bromophenyl)thiazol-2-yl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-5-yl)-N,N-dimethylaniline

($C_{26}H_{22}BrN_4S$), m.p.(214-216°C), yield(61%). IR(cm^{-1}) str. :

1509(C=C), 1614(C=N).

2-2d/4-**(4-bromophenyl)-2-(5-(4-methoxyphenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)thiazole**

($C_{25}H_{19}BrN_3OS$), m.p.(220-222°C), yield(63%). IR(cm^{-1}) str. :

1490(C=C), 1625(C=N) . ^{1}H-NMR(ppm): 2.80-2.87(dd, 1H, **H**H), 3.04-3.09(dd, 1H, H**H**), 3.74(S, 3H, OCH_3), 5.75-5.79(dd, 1H, CH), 6.87[S, 1H, CH(thiazole ring)], 6.90-8.25(m, 13H, 3Ar-rings).

2-2e/4-(4-bromophenyl)-2-(5-(4-nitrophenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)thiazole

($C_{24}H_{16}BrN_4O_2S$), m.p.(240-242°C), yield(56%). IR(cm^{-1}) str. :

1458(C=C), 1620(C=N).

2-2f/4-(4-bromophenyl)-2-(3-5-diphenyl-4,5-dihydro-1*H*-pyrazol-1-yl)thiazole

($C_{24}H_{17}BrN_3S$), m.p.(210-212°C), yield(51%). IR(cm^{-1}) str. :

1485(C=C), 1623(C=N).

2-2g/ 4-(4-bromophenyl)-2-(5-(4-bromophenyl)-3-(4-nitrophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)thiazole

($C_{24}H_{16}Br_2N_4O_2S$), m.p.(230-232°C), yield(45%). IR(cm^{-1}) str. :

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1460(C=C), 1625(C=N).

2-2h/ 4-(4-bromophenyl)-2-(5-(4-chlorophenyl)-3-(4-nitrophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)thiazole

($C_{24}H_{16}BrClN_4O_2S$), m.p.(227-229°C), yield(52%). IR(cm^{-1}) str. :

1455(C=C), 1622(C=N).

2-2i/ 4-(1-(4-(4-(bromophenyl)thiazol-2-yl)-3-(4-nitrophenyl)-4,5-dihydro-1*H*-pyrazol-5-yl)-N,N-dimethylaniline

($C_{26}H_{22}BrN_5O_2S$), m.p.(218-220°C), yield(57%). IR(cm^{-1}) str. :

1470(C=C), 1620(C=N) . ^{1}H-NMR(ppm): 2.74(S, 6H, $N(CH_3)_2$), 3.06(m, 2H, **C**H_2), 5.81-5.85(dd, 1H, CH), 7.10[S, 1H, CH(thiazole ring)], 6.66-8.10(m, 12H, 3Ar-rings).

2.3 Antibacterial Activity:

The antibacterialial activity of the synthesized compounds was tested *in vitro* against *Escherichia coli*. The microorganism used was obtained from the culture collection of the Department of Microbiology, collage of science, Bagdad University, Iraq. The antimicrobial screening, which is the first stage of antimicrobial drug discovery, was performed by the disc diffusion method [12]. Media for disc sensitivity tests were nutrient agar and Mueller-Hinton agar (MHA), purchased from Difco, (USA). The non-sterile powder of the tested compounds were dissolved in sterile DMSO to yield 2 µg mL–1 passed through 0.2 µm membrane filter (Millipore Corp., USA). The filtrates were dispensed as 2 mL samples into sterile, small screw-capped vials and kept stored at -15 °C. DMSO as a solvent showed various inhibition zone, Table 1 .

3. Result and Discussion:

Pyrazoline derivatives were successfully prepared in one step using a one-pot three components reaction. The used procedure was an attractive synthetic method for the preparation of such compounds. The method required a short time to get the final compounds in high yield with low cost The transformations of pyrazoline compounds to thiazole compounds were achieved by a reaction of the synthesized pyrazoline with 4-bromophenacyl bromide scheme (1), the mechanism in scheme (2) and scheme (3). The IR spectra of

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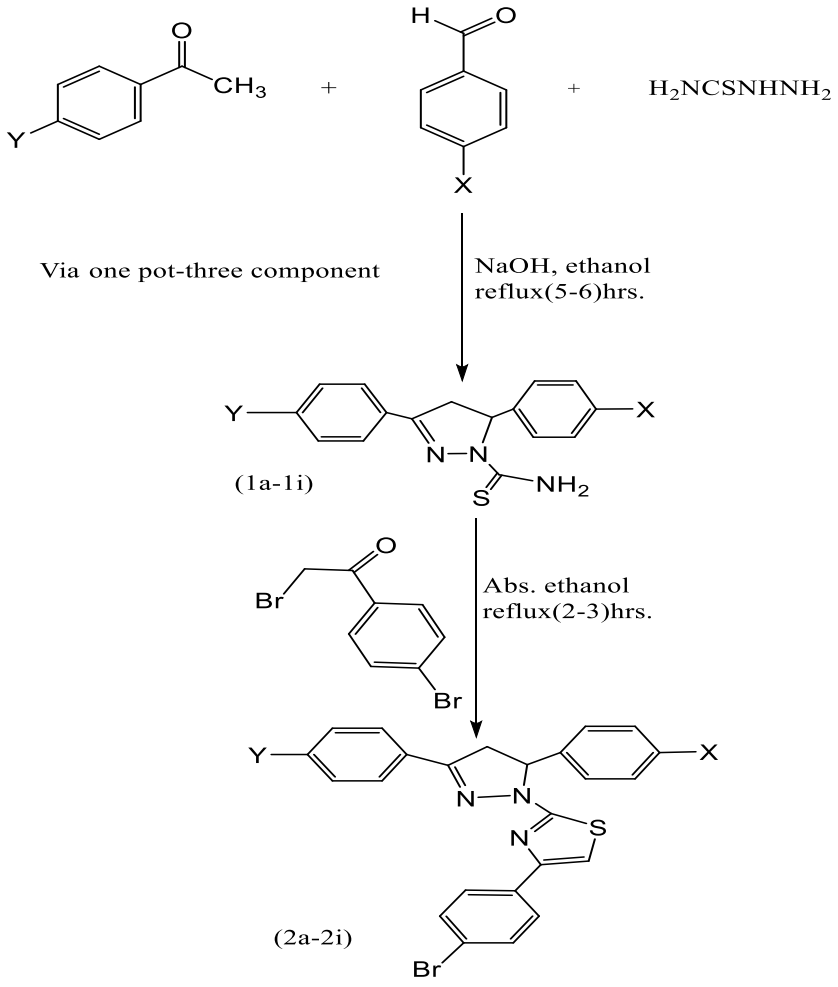
compounds (1a-1i) Fig. 1 showed prominent two peaks at (3200-3400) cm^{-1} belong to (NH_2) stretching of carbothioamide group attached to pyrazoline ring and disappearance of carbonyl group for both (acetophenone or 4-nitroacetophenone) and substituted benzaldehyde. The ^{1}H-NMR of compound (1a) Fig. 2 showed characteristic three doublet to doublet (dd) corresponding to three protons of (CH_2, CH) of pyrazoline ring. In the IR spectra of thiazole compounds, there is good evidence to produce thiazole rings include the disappearance of (NH_2) stretching vibration of thiocarbamide group attached to pyrazoline ring at (3200-3400) cm^{-1} Fig. 3. The ^{1}H-NMR of thiazole compounds (2a, 2d, 2i) Fig. 4,5,6 display characteristic three doublet to doublet (dd) signals corresponding to three protons of (CH_2 and CH) of pyrazoline rings and increase the signal of aromatic rings.



X= Br, Cl, $N(CH_3)_2$, OCH_3, NO_2, H
Y= H, NO_2

Scheme (1)

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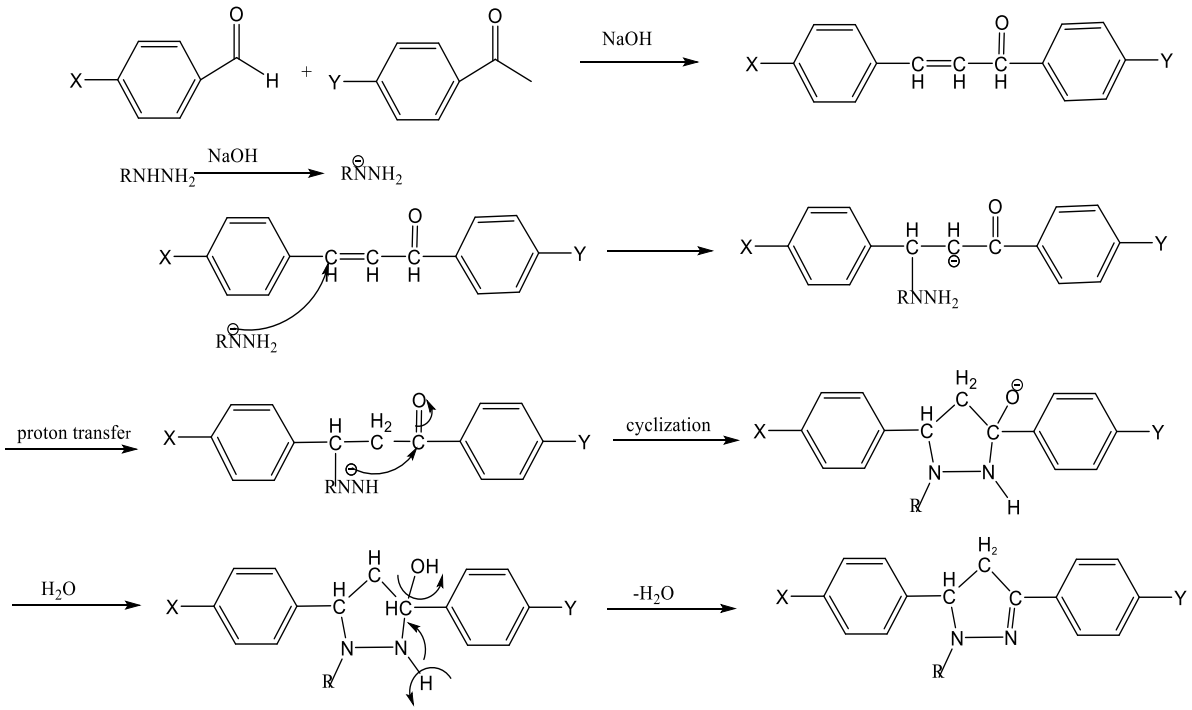

X = Br, Cl, $N(CH_3)_2$, OCH_3, NO_2, H
Y = H, NO_2
R = $CSNH_2$

Scheme (2)

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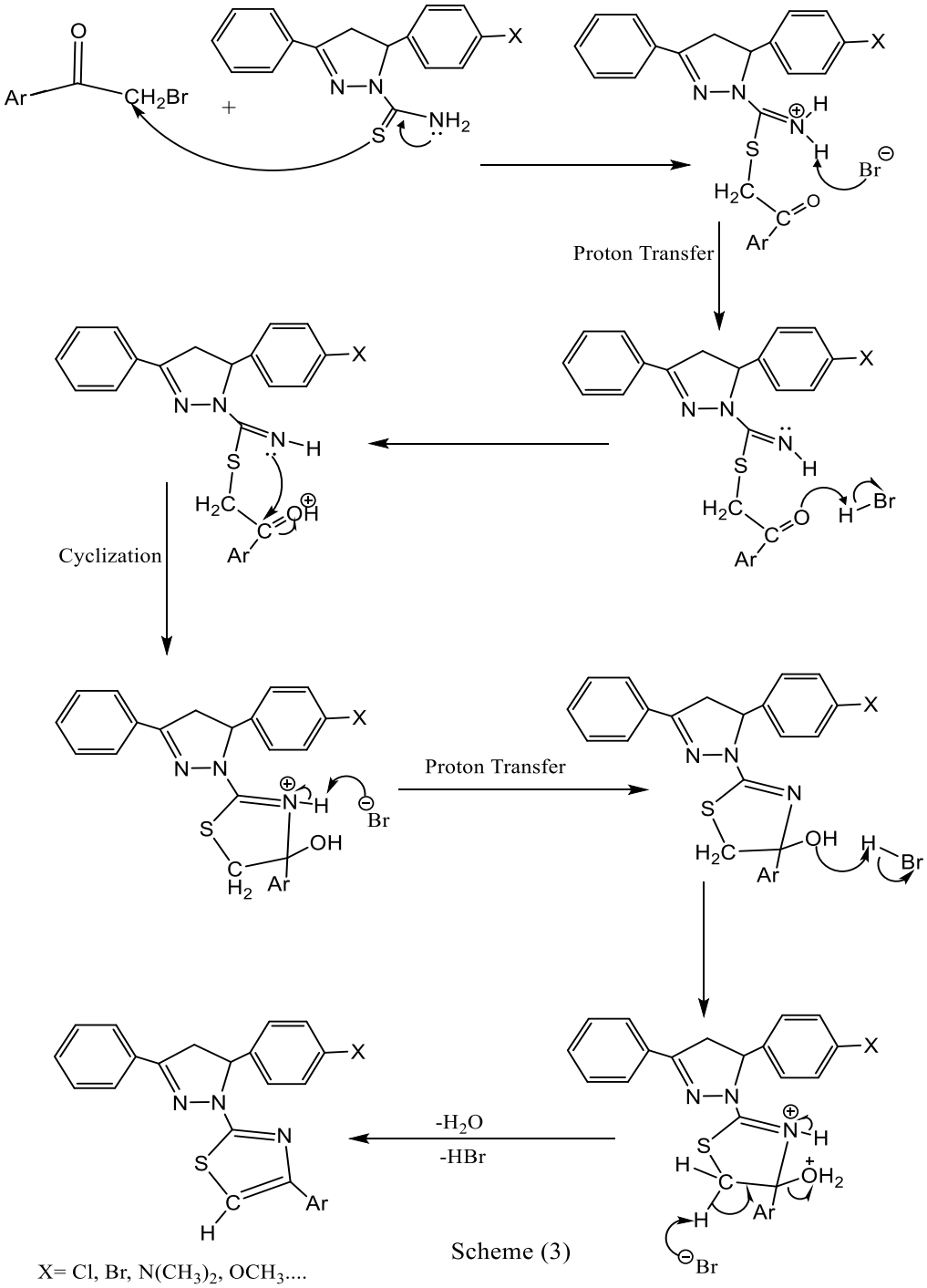

X= Cl, Br, $N(CH_3)_2$, OCH_3....

Scheme (3)

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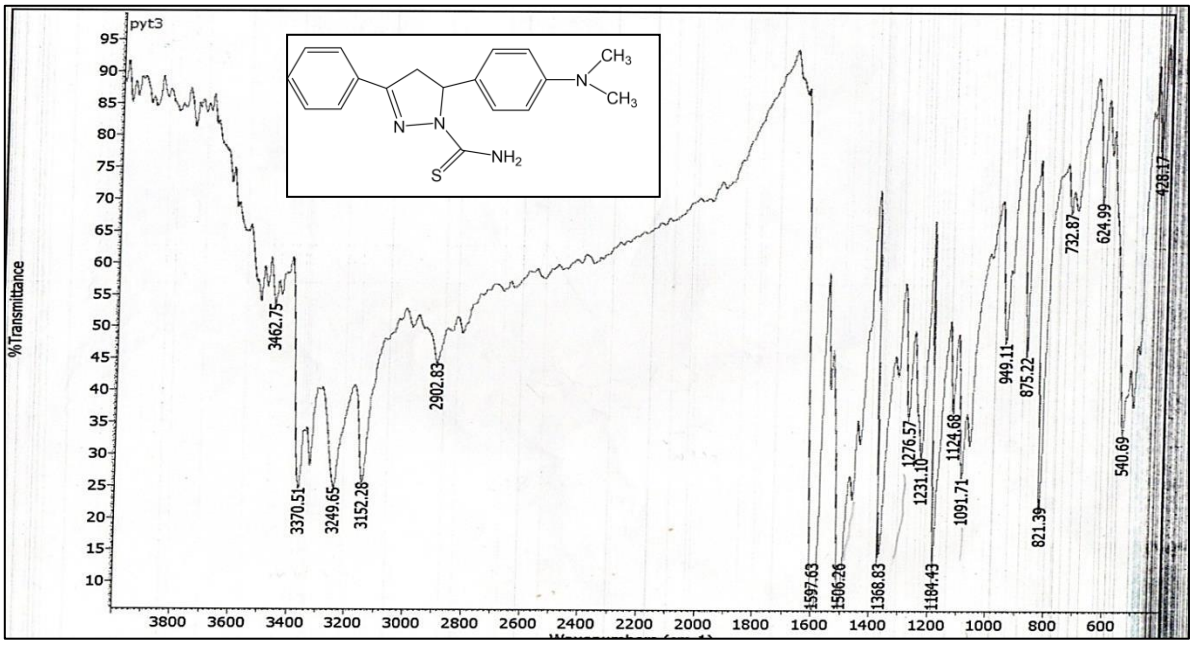

Fig. 1: FT-IR spectrum of compound (1c).

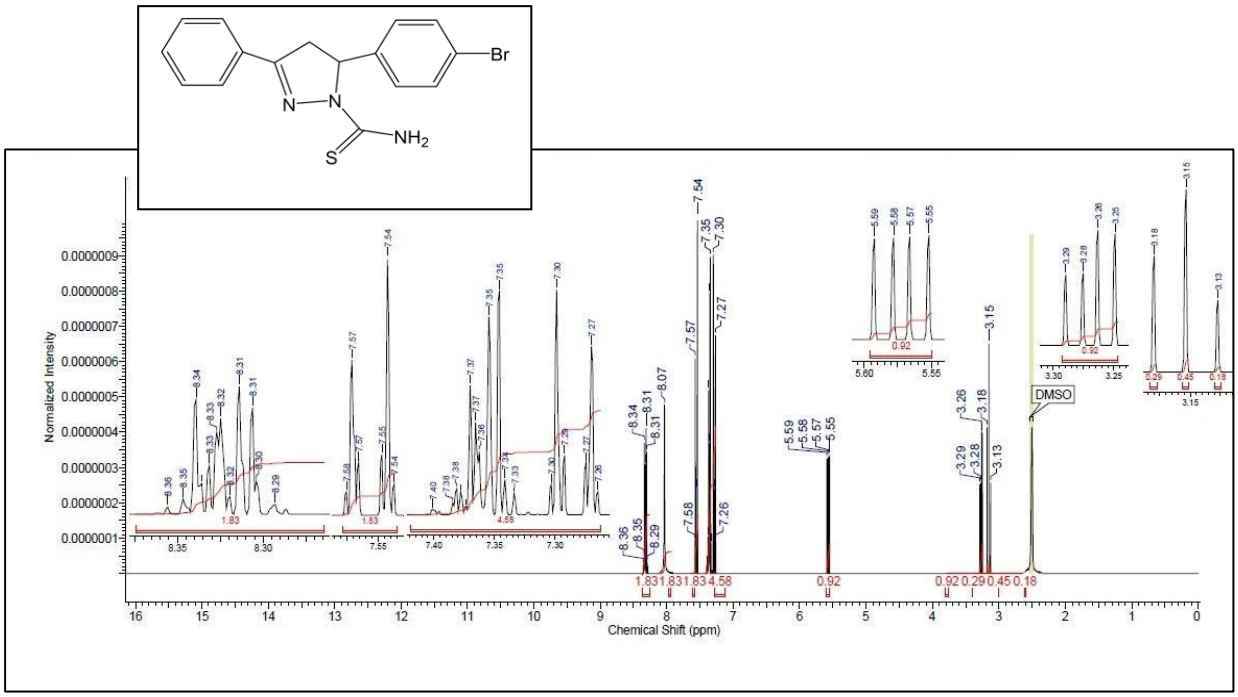

Fig. 2: 1H-NMR spectra of compound (1a).

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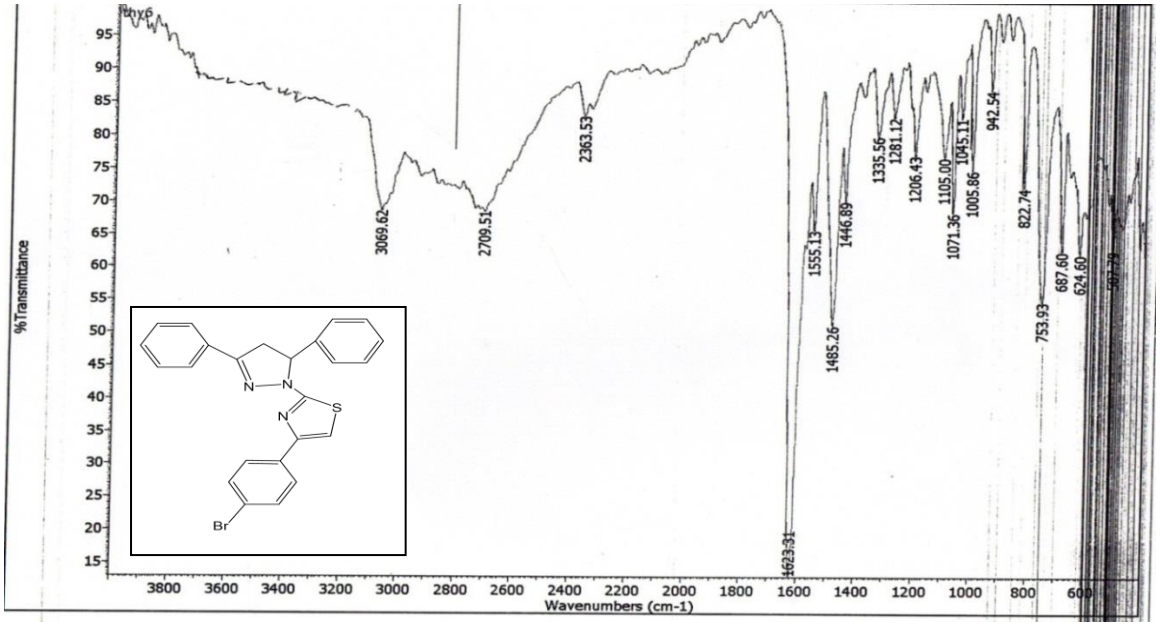

Fig. 3: FT-IR spectra of compound (2f).

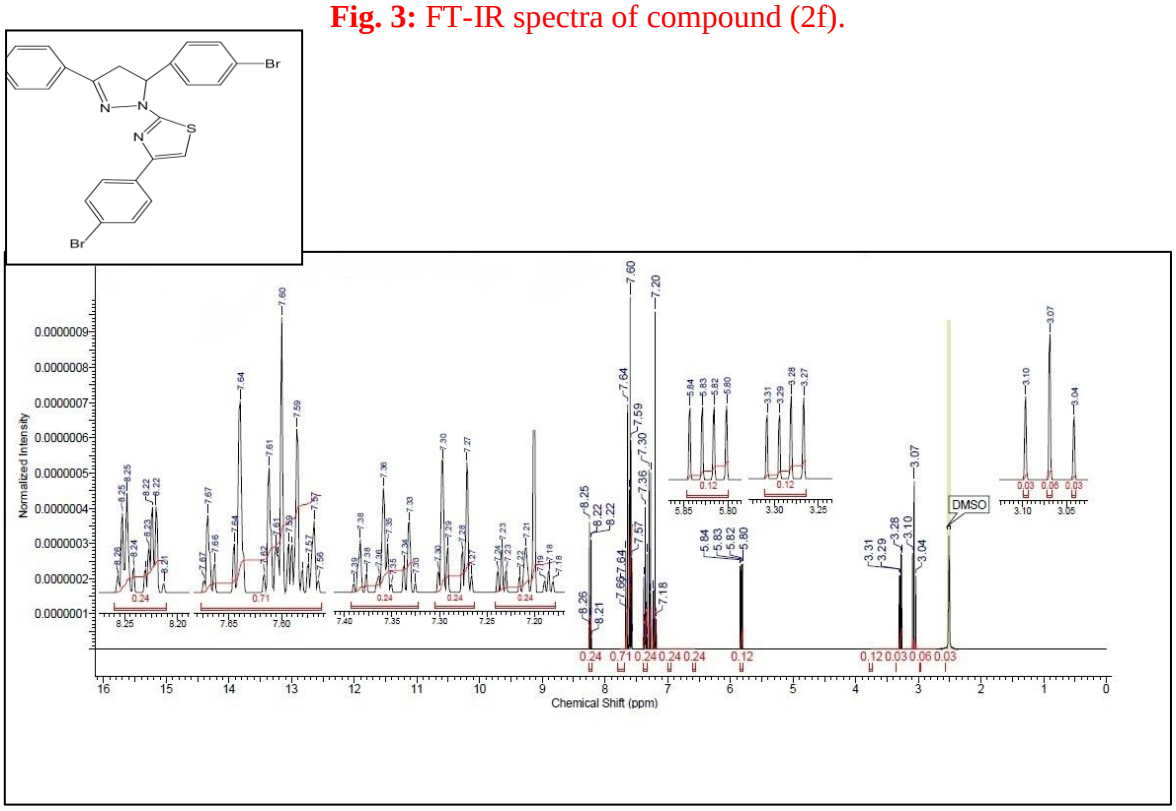

Fig. 4: ^{1}H-NMR spectra of compound (2a).

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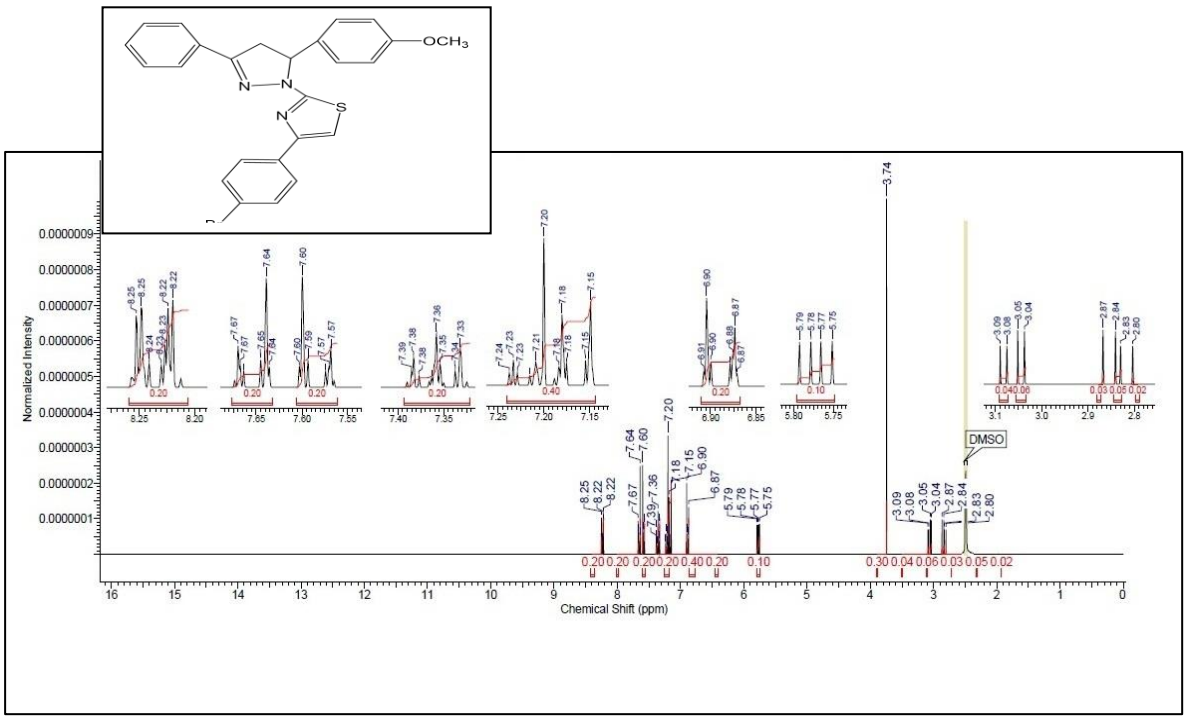

Fig. 5: ^{1}H-NMR spectra of compound (2d).

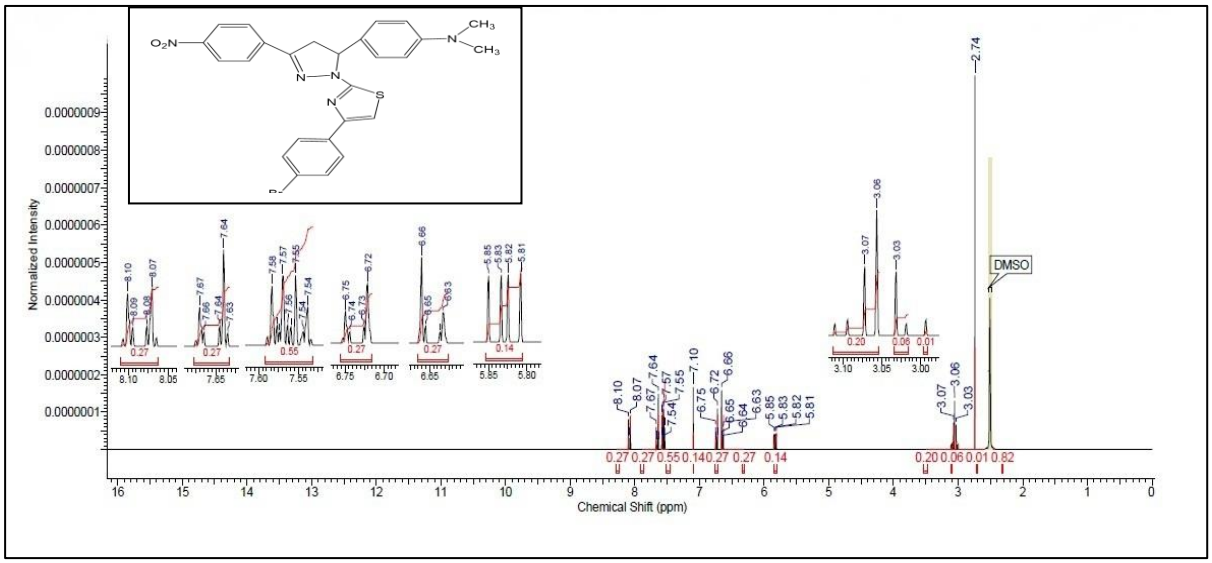

Fig. 6: ^{1}H-NMR spectra of compound (2i).

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Finally antibacterial activity study was done for some of the prepared pyrazoline and thiazole products and it shown in Table 1.

4. Antibacterial activity

As we mentioned before pyrazoline and thiazole compounds have an important biological activity, In this research some of the synthesized compounds were tested against *Escherichia coli* by media for disc sensitivity tests were nutrient agar and Mueller-Hinton agar (MHA) using disc diffusion method. The obtained results are shown in Table 1, and Fig.7:

Table 1: the result of the antibacterial activity of the studied compounds

No.	compound	Inhibition zone(mm)
1	DMSO	8
2	1a	8
3	1b	8
4	1c	8
5	1d	10
6	2a	12
7	2b	9
8	2c	10
9	2d	8
10	2e	13
11	2f	12
12	2i	10

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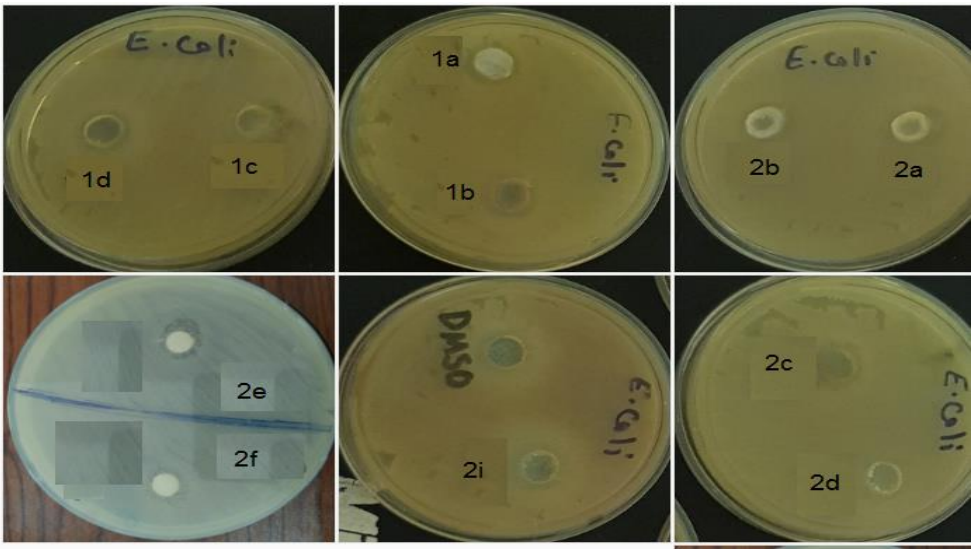

Fig. 7: inhibition zone against by synthesized compounds.

5. Conclusion:

This study deals with the synthesis of substituted pyrazolines via one-pot three components and their transformations to thiazole derivatives.

Synthesis of pyrazoline by three-components between (acetophenone or 4-nitroacetophenone), substituted benzaldehyde and thiosemicarbazide, offers several advantages included fewer reaction steps, simple work-up procedure, require shorter reaction time and high yields.

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