

# The Utilities of Pyrazolines Encouraged Synthesis of a New Pyrazoline Derivative via Ring Closure of Chalcone, for Optimistic Neurodegenerative Applications

Rusul S. Sabah\*, Zahraa S. Al-Garawi, Mahmoud N. Al-Jibouri

Department of Chemistry, College of Science, Mustansiriyah University, Baghdad, IRAQ.

\*Correspondent contact: [rusul.saadsabah96@gmail.com](mailto:rusul.saadsabah96@gmail.com)

## Article Info

Received  
02/08/2021

Accepted  
14/10/2021

Published  
10/03/2022

## ABSTRACT

Pyrazolines and its derivatives have been extensively studied as coordinated ligands of high potential applications in diverse chemical and biological systems. This work explores some methods of synthesis of pyrazolines, such as the preparation of pyrazole derivatives via chalcones. It also demonstrates that 2-pyrazoline complexes were biologically active and have had a range of clinical applications. Palladium (II) complex of pyrazole was active as antitumor when tested against murine mammary adenocarcinoma (LM3). Copper (II) and Cobalt (II) complex are biologically active in the living system as biomolecules or co factors. Based on these information, we tried here to synthesis a new 2-pyrazoline from (E)-3-(4-bromophenyl)-1-(pyridin-2-yl)prop-2-en-1-one. The newly synthesized pyrazoline was characterized using mass spectroscopy, nucleic magnetic resonance spectroscopy NMR and Fourier transform infrared spectroscopy FTIR. The characterization results showed that 2-pyrazoline has successfully synthesized. The microanalyses (C, H, N, S), GC-MS, H and <sup>13</sup>C NMR and FT-IR spectra confirmed the formation of 2-pyrazoline ring with substitution at N1, C-3 and C-5 and the spin-spin coupling constants (J) for the multiple peaks at HNMR spectra pointed to the de shielded aromatic protons in  $\alpha$  and  $\beta$  protons of the prepared chalcone. Interestingly, some new family of pyrazoles that have isosteres of Zonisamide have been previously showed activity toward treating neuroglial disorders such as epilepsy and autism. Thus, we synthesized and well characterized pyrazole here to be considered later for studying its potency to moderate some neurodegenerative disorders. On the other hand, the reviewed literature here showed that pyrazoline could negatively interact with some neurotransmitters through hydrogen bonding and electrostatic interactions with the amino and carboxylic ends of the functional ends of the neurotransmitters. Therefore, this new trend of the promising candidate 2- pyrazoline have to be further investigated.

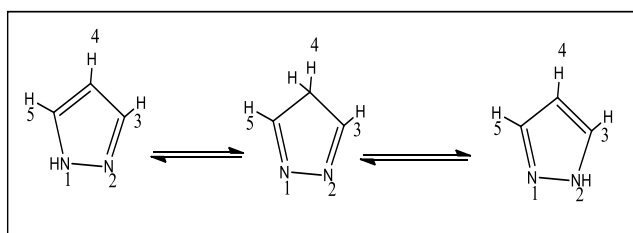
**KEYWORDS:** 2-Pyrazoline ligands; chalcones; clinical applications; spectroscopic studies.

## الخلاصة

تمت دراسة Pyrazolines ومشتقاتها على نطاق واسع كروابط منسقة لتطبيقات محتملة كفوءة في أنظمة كيميائية وبيولوجية متنوعة. في هذه الدراسة، نحاول استكشاف بعض طرق تخليق البيرازولين، مثل تحضير مشتقات البيرازول باستخدام الجالكون، إذ لوحظ أن مشتقات 2-pyrazoline نشطة بيولوجيًا ولديها مجموعة من التطبيقات السريرية. كان معقد البلاديوم (II) مع البيرازول نشطًا كمضاد للأورام عند اختباره ضد سرطان الغدة الثديية (LM3). أما معقدات النحاس (II) والكوبالت (II) فقد كانت نشطة بيولوجيًا في النظام الحي كعوامل مشتركة. بناءً على هذه المعلومات السابقة نشرها، حاولنا هنا تحضير معقد جديد للـ 2-pyrazoline من (E)-3-(4-bromophenyl)-1-(pyridin-2-yl) prop-2-en-1-one. تم تشخيص البيرازولين المحضر حديثًا باستخدام التحليل الطيفي الشامل، والتحليل الطيفي بالرنين النووي المغناطيسي NMR والتحليل الطيفي بالأشعة تحت الحمراء FTIR. أظهرت نتائج التشخيص أن 2-بيرازولين قد تم تصنيعه بنجاح وأكدت التحليلات الدقيقة (CHNS) و GC-MS و H و <sup>13</sup>C NMR و FT-IR تشكيل حلقة 2-pyrazoline مع الاستبدال في N1 و C-3 و C-5 وثوابت اقتران تدوير (J) من أشارت القيم المتعددة في أطياف HNMR إلى أن البروتونات الأروماتية المحجوبة هي في  $\alpha$  و  $\beta$  البروتونات من الجالكون المحضر. ومن المثير للاهتمام، أن بعض العائلات الجديدة من البيرازولات التي تحتوي على مشابهاة الزونيساميد قد أظهرت في دراسة سابقة نشاطًا بتخفيف الاضطرابات العصبية مثل الصرع والتوحد. ولذلك تم تصميم تركيب البيرازول في هذه الدراسة وتشخيصه باتقان ليتم عليه دراسة سريرية مستقبلية بمجال الاضطرابات الانتكاسية العصبية، من ناحية ثانية بما أن الادبيات التي تم استعراضها هنا قد وضحت أن البيروزولات يمكن أن تتفاعل سلبيًا مع بعض النواقل العصبية من خلال الروابط الهيدروجينية والتفاعلات الكهروستاتيكية مع النهايات الأمينية والكربوكسيلية للنهايات الوظيفية للناقلات العصبية فإن هذا الاتجاه الجديد من قبل المرشح الواعد 2- البيرازولين يجب أن يخضع لمزيد من التحقيقات لتأكيد الفاعلية.

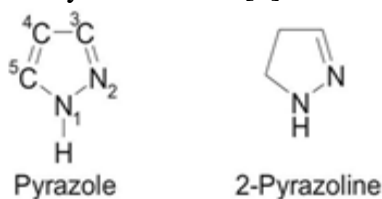
## INTRODUCTION

A pyrazole refers to a simple aromatic ring compound of heterocyclic diazole series has a characteristic 5-member ring structure composed of three carbon atoms and two nitrogen atoms in the adjacent position to the unsaturated parent compound. The pyrazole ring contains two double bonds within the nucleus, imparting an aromatic character to these molecules [1]. As shown in scheme 1.



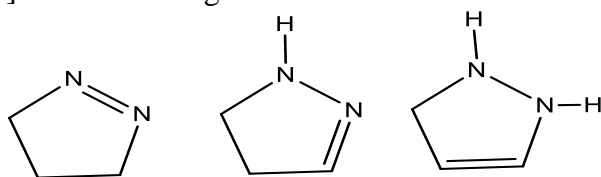
**Scheme 1.** General tautomeric forms of a pyrazole compound.

Pyrazolines are cyclic compounds or ring structure-compounds that have at least two different elements of atoms as members of their rings [2]. These compounds are well-known and they have an important nitrogen-containing five-membered ring with a molecular formula  $C_3H_6N_2$  and molar mass  $70.095 \text{ g}\cdot\text{mol}^{-1}$ . They are also called dihydropyrazoles because they can be viewed as partially reduced pyrazoles. Various methods have been previously worked out for synthesis. Several pyrazoline derivatives have been found to possess diverse biological properties, which has stimulated research activity in this field [3].



**Figure 1.** Structure of pyrazole and 2-pyrazoline.

Pyrazolines have only one double bond within the nucleus and, depending on the position of the double bond, can exist in three separate forms: 1-pyrazoline [1], 2-pyrazoline [4], and 3-pyrazoline [5] as shown in figure 2.



**Figure 2.** Isomers of 1-pyrazoline, 2-pyrazoline and 3-pyrazoline [6].

However, among these tautomeric structures, 2-pyrazoline is the most common one. Pyrazoline derivatives are electron-rich nitrogenous heterocycles, which play an important role in the diverse biological activities. Among pyrazoline derivatives, 3-substituted pyrazolines is the most attractive pyrazoline-type [1].

Metal complexes derived from pyrazole have attracted considerable interest not only due to their extensive coordination chemistry but also to their catalytic and biological properties [1, 4]. The efficacy of a therapeutic agent may be enhanced upon coordination with a metal ion [7]. The coordination bonds between transition metal ions and heterocyclic ligands containing nitrogen atom have proved to be useful for the construction of solid-state architectures and inorganic crystal engineering [8]. Some metal ions is biologically essential, such as cobalt, nickel and copper[9]. The chelating ability of copper (II) and its positive reduction potential allow participation in biological transport

[10]. Cobalt is known to be a central element of metabolically important biomolecules, as such B12, and therefore its bio speciation in biological fluids constitutes a theme worthy of chemical and biological perusal [11]. The utilities of the pyrazoline are of increasing, although its synthesis is more challenging. The needs of a chemically stable compound with a wide range of biological and clinical activities and less toxicity, for pharmaceutical applications. As such, eighteen novels 1-N-substituted-3,5-diphenyl-2-pyrazoline derivatives, a series of twenty 1-(4-sulfamylphenyl)-3-trifluoromethyl-5-indolyl pyrazolines, some 2-naphthyl pyrazolines and exclusive fluorine substituted pyrazoline derivatives were designed, synthesized and screened for cyclooxygenase (COX-1, COX-2) inhibitory, anti-inflammatory, analgesic and antimicrobial activities; some of them possessed acceptable activity [12, 13]. In particular, a series of 1,3,5-trisubstituted pyrazolines appears to have antimalarial properties, in addition to the potential for other applications; these compounds target the malaria parasite by inhibiting the haem detoxification process [14].

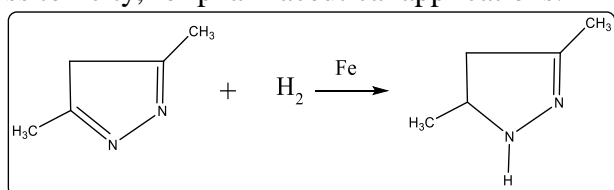
## METHODS OF SYNTHESIS OF IZE PYRAZOLINES

There were many methods described the synthesized 2-pyrazolines as racemates, but

methods for the efficient preparation of enantiomerically enriched 2-pyrazolines are remained limited [15]. However, 2-pyrazolines were synthesized using a Lewis acid catalyzed 1,3-dipolar cycloaddition [16].

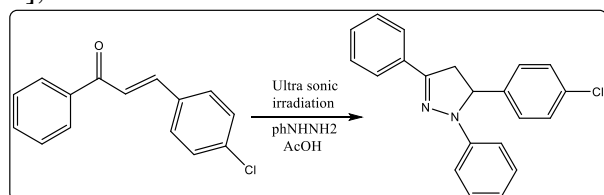
Another method to prepare the substituted 2-pyrazoline [17] was the reduction of pyrazole derivative by a catalyst [18], scheme 2.

The utilities of the pyrazoline are of increasing, although its synthesis is more challenging. The needs of a chemically stable compound with a wide range of biological and clinical activities and less toxicity, for pharmaceutical applications.



**Scheme 2.** Reduction method to isolate 3,5-dimethyl-2-pyrazoline.

The ultrasonic waves was also used to prepare the 1-phenyl pyrazole derivative at room temperature [19], scheme 3.

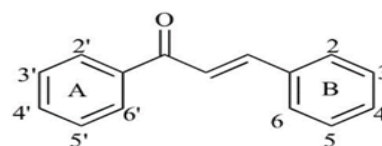


**Scheme 3.** Preparation of pyrazole derivative in glacial acetic acid.

## Chalcones

Chalcones, the precursors of flavonoids and isoflavonoids, are one of the major classes of natural products with widespread distribution in fruits, vegetables, spices, tea and soy-based foodstuff. Naturally occurring chalcones and their synthetic analogues display a wide spectrum of biological activities, (*E*)-3-(4-methoxyphenyl)-1-(benzimidazol-2-yl)prop-2-en-1-one [20].

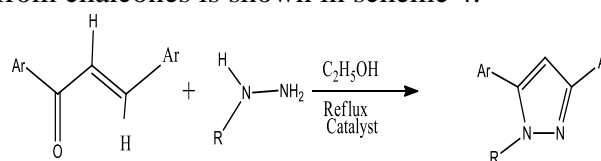
Accordingly, chalcones became an object of continued interest in both academia and industry. Chemically, chalcones or 1,3-diaryl-2-propen-1-ones consist of open-chain flavonoids in which the two aromatic rings are joined by a three-carbon unsaturated carbonyl system [21].



**Figure 3.** Molecular scaffold of chalcone.

## Preparation of pyrazoles from chalcones

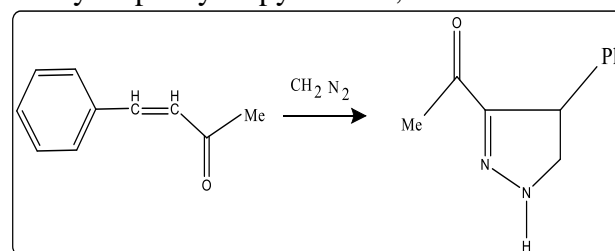
Extensively applicable methodologies to synthesize pyrazoles have been developed and reported. Those include reaction of chalcones with hydrazine and subsequent dehydrogenation [18]. The general way for the preparation of pyrazole from chalcones is shown in scheme 4.



R= phenyl, H, alkyl or aryl

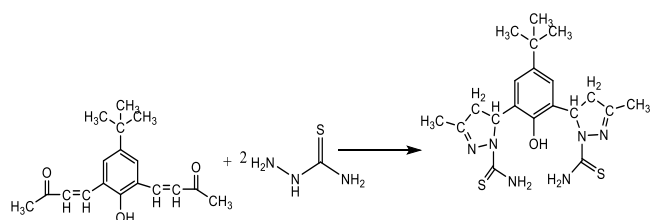
**Scheme 4.** Preparation of pyrazole derivatives via chalcones.

However, the condensation of diazomethane [22] with chalcone derivative resulted in good yield of 3-acetyl-4-phenyl-2-pyrazoline, scheme 5.



**Scheme 5.** Ring Closure of  $\alpha$ ,  $\beta$ -unsaturated ketones via diazomethane.

Recently, Al-jibouri, M. N. and A. Rahman, M. F. [22] adopted novel bis-2-pyrazoline ligands and their metal complexes via ring closure of bis-chalcone of 2,6-diformyl-4-*t*-butyl-phenol with an excess of thiosemicarbazide. These novel ligands and their complexes were well characterized on the basis of elemental analyses and spectra of nuclear magnetic resonance (NMR), Infrared (IR) and electron ionization mass spectroscopy (EI-MS), see scheme 6. The antimicrobial studies of the ligands and metal complexes in DMSO solvent showed promising results due to the significant inhibition zones of the selected micro-organisms of bacteria and fungi [22].



**Scheme 6.** Preparation of bis-2-pyrazoline ligand [23].

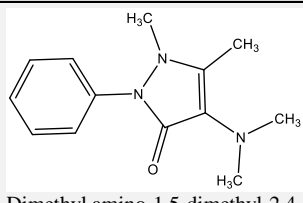
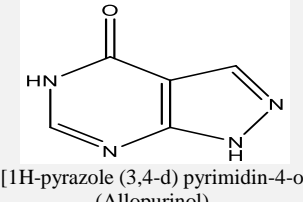
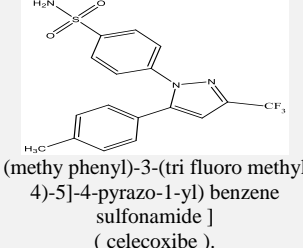
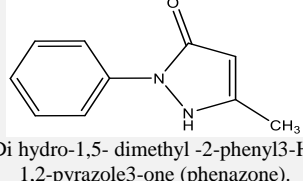
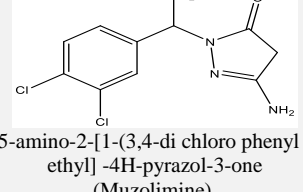
The coordination chemistry of bis pyrazole derivatives is one of the examples derived from acyclic bi nucleated end-off compartment ligands [24]. The binuclear complexes of pyrazole ligands are being biologically attractive and have considerable analytical and industrial importance [25]. In this regard, the bi dentate pyrazole ligands containing S, N and O-donor atoms showed wide spectrum of application as antitumor [26], antiviral and insecticides agents [27], see table 1. The use of transition metal complexes with azo dyes containing strong donor groups has also been used as spray reagent in chromatography.

### Clinical application of pyrazolines

The substituted derivatives of pyrazolines were extensively studied as coordinated ligands because of their importance and high potential in various chemical and biological systems. Pyrazoline derivatives found to act well against bacteria [28] and fungus [29]. The substituted pyrazolines used as anti-mycobacterial [30], anti-tubercula [31], anticancer [32], antitumor [33] and anti-diabetic and their metal ion complexes have special importance in the biochemical systems [34], table 1. Several pyrazole derivatives were applied clinically as nonsteroidal anti-inflammatory drugs (NSAIDs), e. g. , metamizole sodium, phenazone, phenylbutazone, and propiphenazone. Noteworthy selective cyclooxygenase (COX-2) inhibitors containing a pyrazole ring, including celecoxib, which is a relatively safe drug with anti-inflammatory, analgesic, and antipyretic activity. It is also indicated for arthrosis and arthritis. However, currently used pyrazolones are restricted due to some side effect suppression of hematopoiesis, kidney and liver disorders). Therefore, the most recent focus is toward the discovery of new pyrazole derivatives with adequate efficacy and lower toxicity, such as that promising results showed by 3,5-Diaryl-2-pyrazolines [35]. The metal complexes of some pyrazole such as Cu (II), Ni (II) and Co (II) showed antibacterial activities. Pyrimidino pyrazoles

activity was also studied against cancer [36], 3-(4-pyridyl)-2-H-Naphtho - 1,2-C-pyrazoles was an anti-fertility agent for female mammals [37]. Additionally, the metal ligand stability constants of UO<sub>2</sub> (II) and Cu (II) complexes with some substituted sulphonic acids and the complexes of substituted pyrazoles with some lanthanides-metal ions were under investigation [38].

**Table 1.** Some extreme biological active pyrazole derivatives.

No	Structure	Pharmaceutical Importance	Ref.
1	 Dimethyl amino-1,5-dimethyl-2,4-phenyl pyrazol-3-one (amino pyrine).	Anti pyretic and analgesic	[42]
2	 [1H-pyrazole (3,4-d) pyrimidin-4-ol (Allopurinol).	Treatment of gout	[44]
3	 [(methyl phenyl)-3-(tri fluoro methyl - 4)-5-[4-pyrazo-1-yl] benzene sulfonamide ] (celecoxibe).	Non-steroidal anti-inflammatory drug (NSAID)	[45]
4	 Di hydro-1,5- dimethyl -2-phenyl 3-H-1,2-pyrazole 3-one (phenazone).	Analgesic	[46]
5	 5-amino-2-[1-(3,4-di chloro phenyl) ethyl] -4H-pyrazol-3-one (Muzolimine).	Diuretic	[47]

It was reported that chloro substituted pyrazoles complexes (at different concentration and percentage range) [39] were biologically more active compared to the corresponding ligands [22]. Palladium (II) complexes of pyrazole 3,5-dimethyl-4-iodo- pyrazole (HdmIPz) was tested against murine mammary adenocarcinoma (LM3) and lung adenocarcinoma (LP07) cell lines and showed anti-tumor activity [40]. Thus, palladium complexes of

pyrazoline thiocarbonyl derivatives were investigated for antiamebic activity [41]. The square planar of palladium (II) complexes [Pd(NS)<sub>2</sub>] (NS = uni-negatively charged acetone Schiff bases of S-methyl- and S-benzylthiocarbamate) was prepared and screened for their antibacterial, antifungal and cytotoxic activities [42]. In general, the effects of the metal complexes on *Entamoeba histolytica* were more pronounced than those of the corresponding ligands [43]. Recently, pyrazoles find their way in a new trend of application, where they used to treat autism spectrum [42, 44] surveyed 7 novel designs of isosteric rings of pyrazole based on Zonisamide. They discovered that the isosteric rings of pyrazole were able to make a complex with A-type potassium channel and actively blocked it. This A-type potassium channel is a central role in the pathogenesis of autism spectrum.

### Using of chalcone and its derivatives in medicine

Chalcones are well-known intermediates to synthesis of various heterocyclic compounds. Compounds with the chalcone backbone have been informed to possess various biological activities [48]. Chalcones have been reported to possess antimicrobial [49], anti-inflammatory [50], antioxidant and anticancer properties [51]. They were also found to exhibit analgesic [52], platelet anti-aggregation [53], anti-ulcerative, antimalarial [54], antiviral [55]. Anti-leishmanial [56] and anti-hyperglycemic properties [57]. As well as to inhibit the enzymes tyrosinase [58] and aldose reductase [58]. Much attention has been paid to the synthesis of heterocyclic compounds bearing nitrogen-containing rings, like pyrazoline and pyrimidine systems, mainly due to their potential pharmacological activity [35, 59]. A classical synthesis of 2-pyrazolines involves the base catalyzed [60] Claisen-Schmidt condensation of appropriate ketones with suitable aldehydes in the presence of potassium hydroxide in aqueous ethanolic solution at room temperature to give chalcones [61], which undergo a subsequent cyclization reaction with hydrazines [62]. Several alternatives are available for this condensation including that under acidic [62] or basic conditions [63, 64].

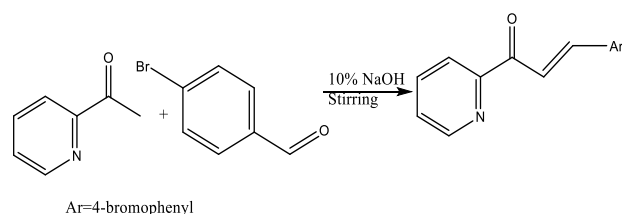
## MATERIALS AND METHODS

### Chemicals and materials

All the chemicals that used in this work were commercially available and used without further purification. Acetone, ammonia, diethyl ether, dimethyl sulfoxide, ethanol, hexane, methanol, thiosemicarbazide, 2-acetylpyridine and 4-Ethyl acetate, sodium hydroxide and Potassium hydroxide were purchased from Fluka with purity 99.8%. Chloroform, bromobenzaldehyde were purchased from Sigma-Aldrich with purity 99.5 - 99.7%. The melting points of prepared compounds were estimated by Stuart-SMP30. The FT-IR spectra of the prepared compounds were recorded in the range (4000-400) cm<sup>-1</sup> on (8400 S-FT-IR SHIMADZU) spectrometer at Babylon University, College of Pharmacy, Babylon, Iraq. The mass spectra of the prepared compound were measured using SHIMADZU GC-DIMS QP2010 ultra and orbitrap LTQ XL-Thermo Fisher scientific mass spectrometer at Mustansiriayah University. The NMR spectra of the prepared chalcone and 2-pyrazoline ligands were measured on 500 MHz Bruker NMR spectrometer at Tahrán University, Faculty of Chemistry, Iran.

### Synthesis of 2-pyrazoline via ring closure of chalcone

The chalcone was prepared according to the modified procedure established in literature [64]. A weight of 1.85 g of 4-bromobenzaldehyde (10.0 mmol) was dissolved in ethanol (50 mL) and 2-acetylpyridine (2.42 g, 20.0 mmol) and crushed KOH (1.12 g, 20.0 mmol) were added. Aqueous NH<sub>3</sub> (32%, 38.5 mL) was slowly added to the reaction mixture, stirred at room temperature overnight. The precipitate was collected by filtration, washed with water (3-10 mL) followed by ethanol (10 mL), re-crystallized from ethanol and finally dried in vacuo. Chemical formula was C<sub>14</sub>H<sub>10</sub>BrNO, m.p. = (105-108) °C, (97-99 °C Literature [64]). The procedure of reaction was followed by thin layer chromatography (TLC) technique using (n-hexane: ethyl acetate (7:3) as eluent. scheme 7.



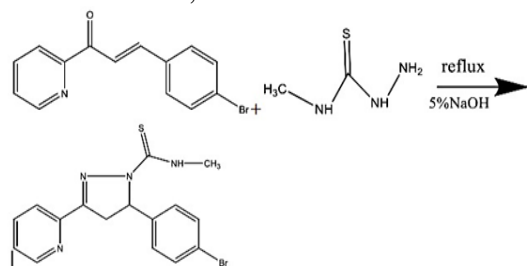
**Scheme 7.** Synthesis of (E)-3-(4-bromophenyl)-1-(pyridin-2-yl)prop-2-en-1-one.

### Synthesis of (E)-3-(4-bromophenyl)-1-(pyridin-2-yl)prop-2-en-1-one

Analysis of chalcone: Yellow and air stable crystalline substance, (Yield 2.06 g (80%); M. p. 103-105 °C; FW=276.31, C<sub>14</sub>H<sub>10</sub>BrNO: IR (KBr,  $\gamma/\text{cm}^{-1}$ ): 1689 [(C=O)], 1558 [(C=C)], 1591 [(C=N-Pyridine)]. <sup>1</sup>H NMR (500 MHz, DMSO)  $\delta$  8.77 - 8.75 (d, 1H, -CH=CH, J=10 Hz), 8.75-8.70 (d, H, CH=CH-C=O), 8.86-8.66 (dd, 2H, Ar, J=12 Hz), 8.05-8.02 (dd, 2H, Ar, J=15 Hz), 7.91-7.89 (m, 2H-Py, J = 10. Hz), 7.78-7.55 (d, 1H, J = 18.1 Hz).

### Synthesis 5-(4-bromophenyl)-N-methyl-3-(pyridin-2-yl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (L)

A mixture of (0.01 mole, 2.89 gm) of chalcone derivative and 4-methylthiosemicarbazide (0.012mole, 0.62gm) with sodium hydroxide (1g in 5ml water) was refluxed in 50ml absolute ethanol for 12 hours. The product was poured into ice water and the crude product, which was separated out (L1), was filtered and re-crystallized from methanol. The crystallized ligand was dried in vacuum desiccator, scheme 8.



**Scheme 8.** Synthesis of 5-(4-bromophenyl)-N-methyl-3-(pyridin-2-yl)-4,5-dihydro-1H-pyrazole-1-carbothioamide.

### Synthesis 5-(4-bromophenyl)-N-methyl-3-(pyridin-2-yl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (L)

Analysis of L1: Dark yellow crystals and air stable, (Yield 2.80 g (75%); M. p. 118-120 °C; FW = 374.

22, C<sub>16</sub>H<sub>15</sub>BrN<sub>4</sub>S: IR (KBr,  $\gamma/\text{cm}^{-1}$ ): [3454: (m, -NH-), 1604: (C=N, Pyrazoline), 1585: (C=N-Pyridine), 1591: (C=N-Pyridine), 1373: (-C=S thioamide)]. <sup>1</sup>H NMR (500 MHz, DMSO)  $\delta$  9.62 (s, 1H, NH-), 8.75-8.06 (dd, 2H, Ar-H, J=10 Hz), 8.00-7.75 (m, 2H, Pyridine-H, J=85 Hz), 7.54-7.49 (dd, 2H, Pyridine, J=25 Hz), 3.50-3.62 (dd, 2H, -CH<sub>2</sub>-Pyrazoline, J = 12. Hz) 3.42-3.40 (m, 1H, -CH-Pyrazoline, J = 10. Hz), 2.45 (s, 1H, -CH<sub>3</sub>-N).

## RESULTS AND DISCUSSION

According to the reviewed utilities of pyrazolines, we tried here to obtain a new 2-pyrazoline via ring closing of chalcones, for neurodegenerative applications. The prepared compounds were characterized using elemental analyses, FT-IR, LC-MS spectroscopy and H NMR technique to confirm the purity of the products. The IR spectrum of chalcone showed strong absorptions at around 1685, 1610 and 1500  $\text{cm}^{-1}$  assigning to  $\alpha$ - $\beta$  unsaturated carbonyl, -CH=CH- of 1,4-disubstituted aromatic ring [64]. The IR spectrum of new 2-pyrazoline ligand showed new features of vibrational modes at around 3100, 15380, 1375 and 1075  $\text{cm}^{-1}$  bands which consistent with stretching of -NH-, -C=N- and -C=S thioamide group attached directly to N1- atom of pyrazoline moiety. The MS spectrum of the prepared chalcone showed a base peak at  $m/e=79$  and 81 with 100% and 98 % relative intensity, which confirmed the cleavage of Br<sup>+</sup>. molecular ion in the gas phase and the molecular ion at  $m/e=289$  and 287 with 67 % intensity is a clearly evidence for the expected chemical formula; C<sub>14</sub>H<sub>10</sub>BrNO with 289 g/mole molecular weight due to the high stability of bromine isotope (81Br) relative to other isotopes in nature, figure 4. However, the spectrum of 2-pyrazoline ligand in figure 5 showed low intensity peaks at  $m/e=374$  and 372 with 30 % relative intensity confirmed the proposed chemical formula of the ligand; C<sub>16</sub>H<sub>15</sub>BrN<sub>4</sub>S that was formed up on ring closure of chalcone with 4-methylthiosemicarbazide. Furthermore the base peak that was shown at around  $m/e=81$  and 79 is consistent with the stable isotopes of 81Br<sup>+</sup> and 79Br<sup>+</sup>, figure 5.

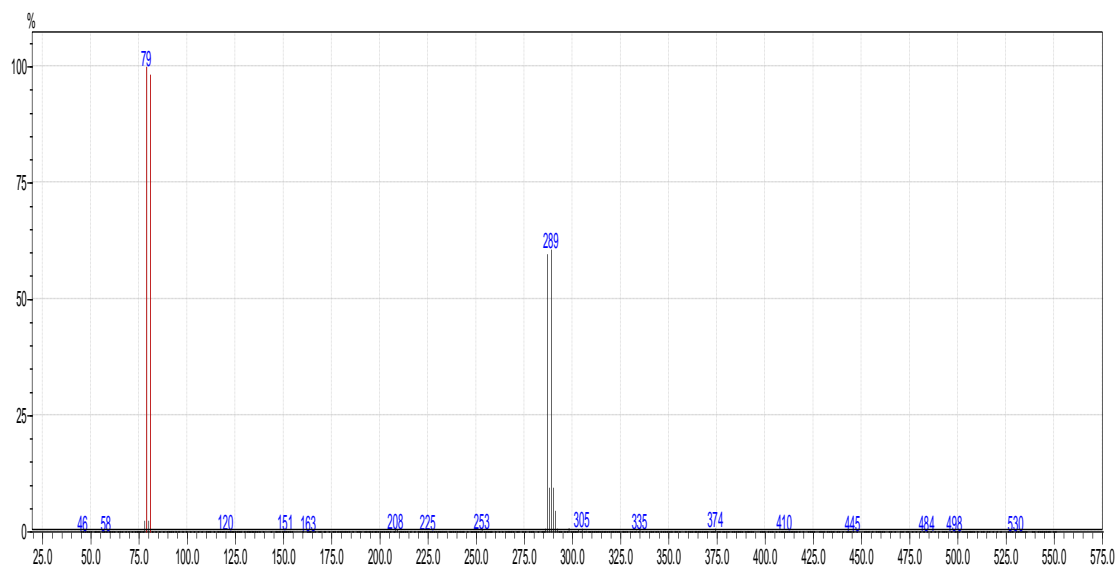


Figure 4. Mass spectrum of chalcone.

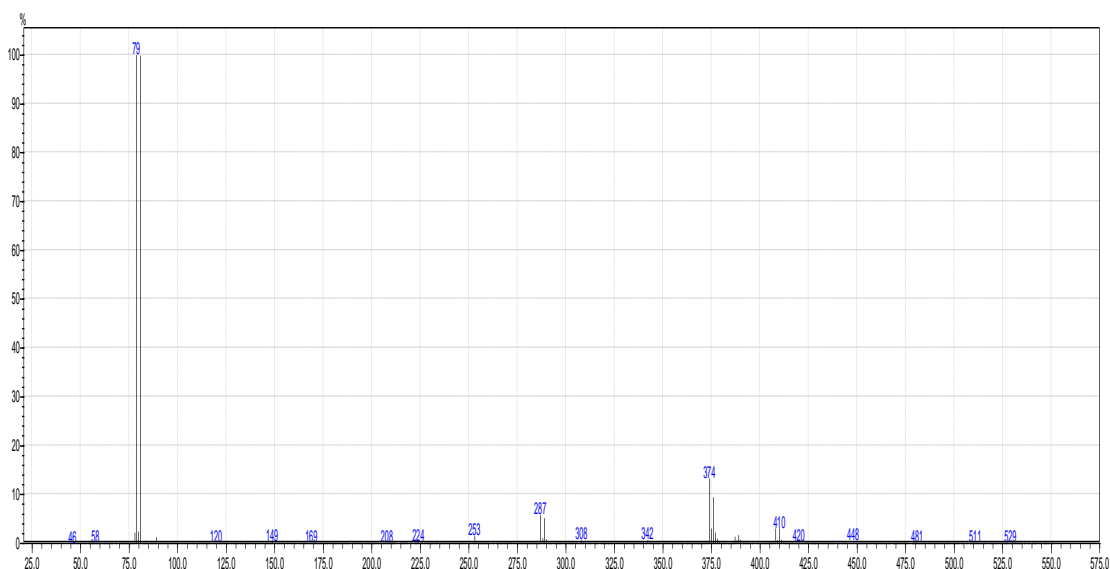


Figure 5. Mass Spectrum of 2- pyrazoline ligan.

The NMR spectra of the prepared chalcone and pyrazoline ligand were carried out at d6-DMSO solvent. The H NMR spectrum of chalcone showed no peaks in the shielding regions of aliphatic -CH<sub>3</sub> moiety, which point to the processing of Claisen-Smidt condensation between 2-Acetyl pyridine with 4-bromobenzaldehyde [65, 66] The doublet-doublet peaks at 6.5-7.11 ppm assigned to nuclear spin of aromatic protons beside absorptions of aromatic of pyridine ring at about 7.7 and 8.01 ppm respectively, figure 6. The calculated spin-

spin coupling constants (J) for the doublet-doublet and other multiple peaks in chalcone and 2-pyrazoline based-ligand exhibited values in a regions (10-18) Hz in chalcone product and (10-25) Hz in the 2-pyrazoline ligand, which confirms the stability of 2-pyrazoline ring through the coupling of germinal -CH<sub>2</sub>- protons with adjacent -CH-N- moiety.

The H NMR spectrum of the new ligand showed weak intensity peak at 8 and 12 ppm assigned to nuclear spin of thiamide -NH<sub>2</sub>, attached directly





## CONCLUSION

Based on previous work, the ring closure of chalcones with hydrazine or thiosemicarbazide is the most common method to synthesis pyrazoline. Isolation of 2-pyrazoline ligand introduced active sites donor systems as Lewis bases in the coordination chemistry. Literature shows that using ultrasonic waves to synthesis of 2-pyrazolines was a good method although the yield was less than the other organic method. The coordination chemistry of ligands of 2-pyrazoline has investigated the participation of isomethine nitrogen atom and thioamide in bonding with the transition metal ions, therefore most ligands of 2-pyrazoline have favored poly dentate system of N-S and N-N donor atoms. The antimicrobial activity of 2-pyrazolines and their metal complexes has been approved in previous studies more than the use of heterogeneous catalysis, due to the ability the pyrazoline derivatives to penetrate the lipo-layers of bacteria and fungi walls through their active sites. Here, we synthesized new chalcone via condensation of 2-acetyl pyridine with 4-bromobenzaldehyde in alkaline medium of sodium hydroxide solution, followed the Micheal addition of the chalcone product with 4-methylthiosemicarbazide to afford the new ligand of 2-pyrazoline to have a promising substituted rings. The latter could work on weakening the neurotransmitters or the ion channels, for treating neurodegenerative disorders. This will be confirmed in the future plan.

## ACNOWLEDGMENT

The authors would like to thank Mustansiriyah University ([www.uomustansiriyah.edu.iq](http://www.uomustansiriyah.edu.iq)) in Baghdad- Iraq for supporting this work.

## CONFLICT OF INTERESTS

Authors declare that no conflict of interests.

## REFERENCES

- [1] Li JT, Zhang XH, Lin ZP. An improved synthesis of 1,3,5-triaryl-2-pyrazolines in acetic acid aqueous solution under ultrasound irradiation. *Beilstein J Org Chem.* 2007;3:11–20.
- [2] M. Nic JJBK. Selectivity:IUPAC. Compendium of Chemical Terminology, (the “Gold Book”). 1997.
- [3] Shaaban MR, Mayhoub AS, Farag AM. Recent advances in the therapeutic applications of pyrazolines. *Expert Opinion on Therapeutic Patents.* 2012;22:253–91.
- [4] Onoa GB, Moreno V, Font-Bardia M, Solans X, Pérez JM, Alonso C. Structural and cytotoxic study of new Pt(II) and Pd(II) complexes with the bi-heterocyclic ligand mepirizole. *J Inorg Biochem.* 1999;75:205–12.
- [5] Abid M, Azam A. Synthesis and antiamebic activities of 1-N-substituted cyclised pyrazoline analogues of thiosemicarbazones. *Bioorganic Med Chem.* 2005;13:2213–20.
- [6] Konar S, Jana A, Das K, Ray S, Golen JA, Rheingold AL, et al. A rare pentanuclear cadmium(II) complex and two new mononuclear zinc(II) complexes of pyrazole derived ditopic ligands-Synthesis, crystal structures and spectral studies. *Inorganica Chim Acta.* 2013;397:144–51.
- [7] Bharti N, Shailendra, Sharma S, Naqvi F, Azam A. New palladium(II) complexes of 5-nitrothiophene-2-carboxaldehyde thiosemicarbazones: Synthesis, spectral studies and in vitro anti-amoebic activity. *Bioorganic Med Chem.* 2003;11:2923–9.
- [8] Navarro JAR, Lippert B. Simple 1:1 and 1:2 complexes of metal ions with heterocycles as building blocks for discrete molecular as well as polymeric assemblies. *Coordination Chemistry Reviews.* 2001;222:219–50.
- [9] Foye WO, Lemke TL W DA. Color Section. *Photosynthesis Research.* 2004;80:5–8.
- [10] Blumberg WE, Peisach J. The optical and magnetic properties of copper in *Chenopodium album* plastocyanin. *BBA - Biophys Incl Photosynth.* 1966;126:269–73.
- [11] Matzapetakis M, Dakanali M, Raptopoulou CP, Tangoulis V, Terzis A, Moon N, et al. Synthesis, spectroscopic, and structural characterization of the first aqueous cobalt(II)-citrate complex: Toward a potentially bioavailable form of cobalt in biologically relevant fluids. *J Biol Inorg Chem.* 2000;5:469–74.
- [12] Fioravanti R, Bolasco A, Manna F, Rossi F, Orallo F, Ortuso F, et al. Synthesis and biological evaluation of N-substituted-3,5-diphenyl-2- pyrazoline derivatives as cyclooxygenase (COX-2) inhibitors. *Eur J Med Chem.* 2010;45:6135–8.
- [13] Jadhav SY, Shirame SP, Kulkarni SD, Patil SB, Pasale SK, Bhosale RB. PEG mediated synthesis and pharmacological evaluation of some fluoro substituted pyrazoline derivatives as antiinflammatory and analgesic agents. *Bioorganic Med Chem Lett.* 2013;23:2575–8.
- [14] Acharya BN, Saraswat D, Tiwari M, Shrivastava AK, Ghorpade R, Bapna S, et al. Synthesis and antimalarial evaluation of 1, 3, 5-trisubstituted pyrazolines. *Eur J Med Chem.* 2010;45:430–8.
- [15] Kou X, Shao Q, Ye C, Yang G, Zhang W. Asymmetric Aza-Wacker-Type Cyclization of N-Ts Hydrazine-Tethered Tetrasubstituted Olefins: Synthesis of Pyrazolines Bearing One Quaternary or Two Vicinal Stereocenters. *J Am Chem Soc.* 2018;140:7587–97.
- [16] Kanemasa S, Kanai T. Lewis acid-catalyzed enantioselective 1,3-dipolar cycloadditions of diazoalkane: Chiral ligand/achiral auxiliary cooperative

- chirality control [4]. *Journal of the American Chemical Society*. 2000;122:10710–1.
- [17] Di Carlo G, Mascolo N, Izzo AA, Capasso F. Flavonoids: Old and new aspects of a class of natural therapeutic drugs. *Life Sciences*. 1999;65:337–53.
- [18] Donnelly DMX. *The Chemistry of Chalcones and Related Compounds*. *Phytochemistry*. 1982;21:2435.
- [19] Yusuf M, Jain P. Synthetic and biological studies of pyrazolines and related heterocyclic compounds. *Arab J Chem*. 2014;7:553–96.
- [20] Ashton WT, Doss GA. A regioselective route to 3-alkyl-1-aryl-1H-pyrazole-5-carboxylates: Synthetic studies and structural assignments. *J Heterocycl Chem*. 1993;30:307–11.
- [21] Turan-Zitouni G, Chevallet P, Kiliç FS, Erol K. Synthesis of some thiazolyl-pyrazoline derivatives and preliminary investigation of their hypotensive activity. *Eur J Med Chem*. 2000;35:635–41.
- [22] Fahad ARM, Abid MN. Synthesis, characterization and antimicrobial activity of some transition metals complexes derived from bis-pyrazoline based ligand. *Malaysian J Sci*. 2019;38:59–71.
- [23] Özdemir A. Synthesis and antimicrobial activity of some pyrazoline derivatives bearing amide moiety. *Marmara Pharm J*. 2013;17:187–92.
- [24] Vicentini CB, Manfredini S, Manfrini M, Bazzanini R, Musiu C, Putzolu M, et al. Synthesis and biological evaluation of a series of substituted pyrazolo[3,4-d]-1,2,3-triazoles and pyrazolo[3,4-d]oxazoles. *Arch Pharm (Weinheim)*. 1998;331:269–72.
- [25] Annigeri SM, Sathisha MP, Revankar VK. Spectroscopic studies of bridged binuclear complexes of Co(II), Ni(II), Cu(II) and Zn(II). *Transit Met Chem*. 2007;32:81–7.
- [26] Syamal A, Maurya MR. Synthesis and characterisation of nickel(II), cobalt(II), manganese(II), copper(II), zinc(II), dioxouranium(VI) and dioxomolybdenum(VI) complexes of tridentate dibasic ONO donor Schiff bases derived from 2-benzothiazolecarbohydrazide and salicylaldehyde/2. *Transit Met Chem*. 1986;11:201–5.
- [27] Yang TH, Silva AR, Shi FN. Six new 3d-4f heterometallic coordination polymers constructed from pyrazole-bridged CuIII<sub>n</sub>III<sub>n</sub> dinuclear units. *Dalt Trans*. 2013;42:13997–4005.
- [28] Ahirwar MK, Gautam N, Shrivastava SP. Synthesis and antimicrobial activity of some pyrazoline derivatives. *Asian J Chem*. 2010;22:5297–302.
- [29] El Sadek MM, Hassan SY, Abdelwahab HE, Yacout GA. Synthesis and bioassay of a new class of furanyl-1,3,4-oxadiazole derivatives. *Molecules*. 2013;18:8550–62.
- [30] Kaplancikli ZA, Turan-Zitouni G, Özdemir A, Revial G. New triazole and triazolothiadiazine derivatives as possible antimicrobial agents. *Eur J Med Chem*. 2008;43:155–9.
- [31] Ali MA, Shaharyar M, Siddiqui AA. Synthesis, structural activity relationship and anti-tubercular activity of novel pyrazoline derivatives. *Eur J Med Chem*. 2007;42:268–75.
- [32] Santhi N, Emayavaramban M, Gopi C, Manivannan C, Raguraman A. Green synthesis and antibacterial evaluation of some 2-pyrazoline derivatives. *Int J Adv Chem*. 2014;2:5–9.
- [33] Jainey PJ, Bhat IK. Antitumor, analgesic, and anti-inflammatory activities of synthesized pyrazolines. *J Young Pharm*. 2012;4:82–7.
- [34] Talegaonkar RS, Burghate AS. pH-metric studies on formation constants of the complexes of substituted thiazolyl Schiff's bases with some lanthanide metal ions. *J Indian Chem Soc*. 2012;89:1585–9.
- [35] Amir M, Kumar S. Synthesis and anti-inflammatory, analgesic, ulcerogenic and lipid peroxidation activities of 3,5-dimethyl pyrazoles, 3-methyl pyrazol-5-ones and 3,5-disubstituted pyrazolines. *Indian J Chem - Sect B Org Med Chem*. 2005;44:2532–7.
- [36] Donnelly D, Geoghegan R, O'Brien C, Philbin E, Wheeler TS. Synthesis of Heterocyclic-Substituted Chromones and Related Compounds as Potential Anticancer Agents. *J Med Chem*. 1965;8:872–5.
- [37] THAKAR KA, GOSWAMI DD, PACHPOR DG. ChemInform Abstract: SYNTHESIS OF FURAL ANALOGS OF SUBSTITUTED FLAVONOIDS. *Chem Informationsd*. 1974;5:11–4.
- [38] Naik AB, Narwade ML. PH-metric studies on formation constants of the complexes of substituted pyrazoles with some lanthanide metal ions and the influence of ionic strengths on complex equilibria in a 70% dioxane-water mixture. *Russ J Coord Chem Khimiya*. 2009;35:932–7.
- [39] Ramteke A, Narwade ML M V. Studies in acoustical properties of chloro substituted pyrazoles in different concentration and different percents in dioxane – water mixture. 4:254–2612. 2012;4:254–61.
- [40] Barra C V. , Rocha F V. , Netto AVG, Shimura B, Frem RCG, Mauro AE, et al. New palladium(II) complexes with pyrazole ligands: Part I. Synthesis, spectral and thermal studies, and antitumor evaluation. In: *Journal of Thermal Analysis and Calorimetry*. 2011. p. 483–8.
- [41] Budakoti A, Abid M, Azam A. Syntheses, characterization and in vitro antimicrobial activity of new Pd(II) complexes with 1-N-substituted thiocarbonyl-3,5-diphenyl-2-pyrazoline derivatives. *Eur J Med Chem*. 2007;42:544–51.
- [42] Nabati M, Bodaghi-Namileh V. Evaluation of Medicinal Effects of Isoxazole Ring Isosteres on Zonisamide for Autism Treatment by Binding to Potassium Voltage-Gated Channel Subfamily D Member 2 (Kv 4. 2). *Adv J Chem A*. 2020;3:462–72.
- [43] Ali I, Wani WA, Khan A, Haque A, Ahmad A, Saleem K, et al. Synthesis and synergistic antifungal activities of a pyrazoline based ligand and its copper(II) and nickel(II) complexes with conventional antifungals. *Microb Pathog*. 2012;53:66–73.
- [44] Akbar Ali M, Mirza AH, Butcher RJ, Tarafder MTH, Keat TB, Ali AM. Biological activity of palladium(II) and platinum(II) complexes of the acetone Schiff bases of S-methyl- and S-benzylthiocarbamate and the X-ray crystal structure of the [Pd(asm<sub>2</sub>)] (asm<sub>2</sub>=anionic form of the acetone Schiff base of S-methylthiocarbamate. *J Inorg Biochem*. 2002;92:141–8.
- [45] Brown AW. Recent Developments in the Chemistry of Pyrazoles. In: *Advances in Heterocyclic Chemistry*. 2018. p. 55–107.
- [46] Naim MJ, Alam O, Nawaz F, Alam MJ, Alam P. Current status of pyrazole and its biological activities. *Journal of Pharmacy and Bioallied Sciences*. 2016;8:2–17.

- [47] Khan MF, Alam MM, Verma G, Akhtar W, Akhter M, Shaquiquzzaman M. The therapeutic voyage of pyrazole and its analogs: A review. *European Journal of Medicinal Chemistry*. 2016;120:170–201.
- [48] Siddiqui ZN, Asad M, Praveen S. Synthesis and biological activity of heterocycles from chalcone. In: *Medicinal Chemistry Research*. 2008. p. 318–25.
- [49] Szliszka E, Czuba ZP, Sędek Ł, Paradyś A, Król W. Enhanced TRAIL-mediated apoptosis in prostate cancer cells by the bioactive compounds neobavaisoflavone and psoralidin isolated from *Psoralea corylifolia*. *Pharmacol Reports*. 2011;63:139–48.
- [50] Rajendra Prasad Y, Lakshmana Rao A, Prasanna L, Murali K, Ravi Kumar P. Synthesis and antidepressant activity of some 1,3,5-triphenyl-2-pyrazolines and 3-(2''-hydroxy naphthalen-1''-yl)-1,5-diphenyl-2-pyrazolines. *Bioorganic Med Chem Lett*. 2005;15:5030–4.
- [51] Rojas J, Payá M, Dominguez JN, Luisa Ferrándiz M. The synthesis and effect of fluorinated chalcone derivatives on nitric oxide production. *Bioorganic Med Chem Lett*. 2002;12:1951–4.
- [52] Nowakowska Z, Kedzia B, Schroeder G. Synthesis, physicochemical properties and antimicrobial evaluation of new (E)-chalcones. *Eur J Med Chem*. 2008;43:707–13.
- [53] Viana GSB, Bandeira MAM, Matos FJA. Analgesic and antiinflammatory effects of chalcones isolated from *Myracrodruon urundeuva* Allemão. *Phytomedicine*. 2003;10:189–95.
- [54] Zhao LM, Jin HS, Sun LP, Piao HR, Quan ZS. Synthesis and evaluation of antiplatelet activity of trihydroxychalcone derivatives. *Bioorganic Med Chem Lett*. 2005;15:5027–9.
- [55] Valla A, Valla B, Cartier D, Le Guillou R, Labia R, Florent L, et al. New syntheses and potential antimalarial activities of new “retinoid-like chalcones.” *Eur J Med Chem*. 2006;41:142–6.
- [56] Jamal H, Ansari WH, Rizvi SJ. Chalcones: Differential effects on glycogen contents of liver, brain and spinal cord in rats. *Biol Med*. 2009;1:107–15.
- [57] Liu M, Wilairat P, Croft SL, Tan ALC, Go ML. Structure-activity relationships of antileishmanial and antimalarial chalcones. *Bioorganic Med Chem*. 2003;11:2729–38.
- [58] Satyanarayana M, Tiwari P, Tripathi BK, Srivastava AK, Pratap R. Synthesis and antihyperglycemic activity of chalcone based aryloxypropanolamines. *Bioorganic Med Chem*. 2004;12:883–9.
- [59] Khatib S, Nerya O, Musa R, Shmuel M, Tamir S, Vaya J. Chalcones as potent tyrosinase inhibitors: The importance of a 2,4-substituted resorcinol moiety. *Bioorganic Med Chem*. 2005;13:433–41.
- [60] Shafiee A, Bagheri M, Shekarchi M, Abdollahi M. The antinociceptive activities of 1-(4-aryl-2-thiazolyl)-3,5-disubstituted-2 pyrazolines in mouse writhing test. *J Pharm Pharm Sci*. 2003;6:359–61.
- [61] Greber G. Vogel's textbook of practical organic chemistry (5th ed. ), revised by Brian S. Furniss, Antony J. Hannaford, Peter W. G. Smith, and Austin R. Tatchell, John Wiley & Sons, New York, 1514 pp. price: \$84. 95. *J Polym Sci Part A Polym Chem*. 1991;29:1223–1223.
- [62] Revanasiddappa BC, Rao RN, Subrahmanyam EVS, Satyanarayana D. Synthesis and biological evaluation of some novel 1, 3, 5-trisubstituted pyrazolines. *E-Journal Chem*. 2010;7:295–8.
- [63] Patel VM, Desai KR. Eco-friendly synthesis of fluorine-containing pyrazoline derivatives over potassium carbonate. *Arkivoc*. 2004;6:123–9.
- [64] Chimenti F, Bizzarri B, Manna F, Bolasco A, Secci D, Chimenti P, et al. Synthesis and in vitro selective anti-*Helicobacter pylori* activity of pyrazoline derivatives. *Bioorganic Med Chem Lett*. 2005;15:603–7.
- [65] Yoon H, Ahn S, Park M, Kim DW, Kim SH, Koh D, et al. <sup>1</sup>H and <sup>13</sup>C NMR spectral assignments of chalcones bearing pyrazoline-carbothioamide groups. *Magn Reson Chem*. 2013;51:500–8.
- [66] Kim B, Ahn S, Lee Y, Koh D, Lim Y. <sup>1</sup>H and <sup>13</sup>C NMR spectral assignments of nineteen 5-(3,5-dimethoxyphenyl)-3-(2-methoxyphenyl)-2-pyrazoline derivatives. *Magn Reson Chem*. 2021;59:478–88.

#### How to Cite

Sabah, R. S., Al-Garawi, Z. S. ., & Al-jibouri, M. N. **The utilities of pyrazolines encouraged synthesis of a new pyrazoline derivative via ring closure of chalcone, for optimistic neurodegenerative applications.** *Al-Mustansiriyah Journal of Science*, 33(1), 21–31, 2022. Doi: <https://doi.org/10.23851/mjs.v33i1.1067>