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

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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, nuclear 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), GC-MS, H and 13C NMR and FT-IR spectra confirmed the formation of 2-pyrazoline ring with substitution at N1,C5 and C3. The spin-spin coupling constants (J) for the multiple peaks at HNMR spectra pointed to the de shielded aromatic protons in α and β protons of the prepared chalcone. Interestingly, some new family of pyrazolines 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 carbonyl 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.
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.

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 C₃H₆N₂ and molar mass 70.095 g·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].

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.

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.

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

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

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

**Chalcones**

Chalcones, the precursors of flavonoids and iso flavonoids, 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].

**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.

**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 α, β-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].
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-Naptho - 1,2-C-pyrazoles was an anti-fertility agent for female mammals [37]. Additionally, the metal ligand stability constants of UO2 (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  | ![Structure](image1.png) Dimethyl amino-1,5-dimethyl-2,4-phenyl pyrazol -3-one (amino pyrine ). | Anti pyretic and analgesic | [42] |
| 2  | ![Structure](image2.png) [1H-pyrazole (3,4-d) pyrimidin-4-ol (Allopurinol). | Treatment of gout | [44] |
| 3  | ![Structure](image3.png) [ (methy phenyl)-3-(tri fluoro methyl -4)-5]-4-pyrazo-1-yl benzene sulfonamide ] ( celecoxib ). | Non-steroidal anti-inflammatory drug (NSAID) | [45] |
| 4  | ![Structure](image4.png) Dt hydro-1,5- dimethyl -2-phenyl3-H; 1,2-pyrazole3-one (phenazone). | Analgesic | [46] |
| 5  | ![Structure](image5.png) 5-amino-2-[3-(4-di chloro phenyl ) ethyl] -4H-pyrazol-3-one (Mizuloline). | 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-ido- 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 thiocarbamoyl derivatives were investigated for antiamoebic activity [41]. The square planar of palladium (II) complexes [Pd(NS)₂] (NS = uni-negatively charged acetone Schiff bases of S-methyl- and S-benzyldithiocarbazate) 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, thiosemicabzide, 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-1 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 Tahran 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, 2. 20 mL, 20. 0 mmol) and crushed KOH (1. 12 g, 20. 0 mmol) were added. Aqueous NH₃ (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 C₁₂H₁₀BrNO, m. p =105-108) 0C, (97-99 0C 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 0C; FW=276. 31, C14H10BrNO: IR (KBr, γ/cm-1): 1689 [(C=O)], 1558 [(C=C)], 1591 [(C=N-Pyridine)]. 1H NMR (500 MHz, DMSO) δ 8.77 – 8.75 (d,1H, Ar, 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).

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

A mixture of (0.01 mole, 2.62 gm) 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.

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 0C; FW = 374.

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 cm-1 assigning to α-β 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 1685,1610 and 1500 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+. 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; C14H10BrNO 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; C16H15BrN4S 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+ and 79Br+, figure 5.
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 - CH3 moiety, which point to the processing of Claisen-Shmidt 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 –CH2- 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 thiiamide - NH2, attached directly
to N1 atom of pyrazoline ring. As well as, the multiple and doublet-doublet peaks at (3.7-4.22) ppm attributed to the adjacent and geminal protons H-C-CH2 moiety, which confirms the formation of a reduced ring of pyrazole [65, 66]. The doublet-doublet peaks at (6.5-7.56) ppm and multiple peaks at (7.8-7.42) ppm were belonged to aromatic protons of 4-bromophenyl and 2-pyridyl rings respectively, figure 7. This newly synthesized pyrazoline may interact with some neurotransmittances that elevated in neurodegenerative diseases, such as dopamine, glutamate and γ-amino butyric acid through hydrogen bonding and electrostatic interactions via the dentate system of N-S and N-N donor atoms. These interactions need further evaluations.

![Figure 6. HNMR spectrum of chalcone in d6-DMSO solvent.](image)

![Figure 7. HNMR spectrum of 2-pyrazoline ligand.](image)
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-hydroxide solution as a further reaction 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.

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CONFLICT OF INTERESTS

Authors declare that no conflict of interests.

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