Chemistry and synthesis of Bis Pyrazole derivatives and their biological activity: a review

W F. Rodhan*, S S. Kadhum, Z Z M Ali, A G Eleiwi, R F Abbas, I R Mohamed and Z A Hussein

1Mustansiriyah University, College of Science, Department of Chemistry, Baghdad-Iraq

*Corresponding: wafaa77@uomustansiriyah.edu.iq

Abstract. Pyrazole derivatives were used for all kinds of biological celerity like used for a core structure in a large of compounds that possess important pharmacological agents such as a potent anti-inflammatory, anti-obesity drug rimonabant, antitumor and analgesic. Various bis-pyrazole derivatives were introduced a great contribution not only in the synthetic chemistry but also used in the healthful chemistry field. In this review, we reported the different methods have been used for synthesis of pyrazole derivatives with some of them being used in the biological field.

Key Words: pyrazole, Bis-pyrazole derivatives, synthesis, biological activities.

1. Introduction

Pyrazole is a heterocyclic five membered ring compound containing nitrogen atoms in 1 and 2 positions (figure 1). Pyrazole has interesting biological activities such as tumour cell growth activation [1]. Anti leishmanial [2,3], anti-inflammatory agents analgesic activity, antimicrobial activity [4-6], anti-inflammatory activity [7,8], α glycosidase inhibitory [9], anti bacterial activity [10,11], antioxidant activity[12, 13], and anticancer agents[14-16]. Bispyrazol is an important moiety in therapeutic chemistry due to its biological activities and its versatile synthesis methods. Synthesis of bis-pyrazole derivatives has received much attention from many researchers. Bis-pyrazole playing as essential role in the medicinal chemistry fields such as anticancer agents[17,18], anti inflammatory, antimicrobial activity (figure 2).

Figure 1. Pyrazole
In the last studies, Synthesis of bis-pyrazole derivatives and few novel bis-pyrazole derivatives had found a unique application in the last years and fitted with their biological importance.

2. General methods of synthesis
Ludwig knorr in 1883 studied Pyrazole moieties and substituted pyrazole, and pechmann synthesis (scheme 1) [19, 20].

3. Synthesis of Bis pyrazole
Diana et al. studied a novel operation for the integration of bis pyrazole derivatives by the condensation of ketones with terephthaldehyde to form chalcones, and then
3.1. Reaction with NH₂.NH₂ (scheme 2) [21].

[Diagram]

Scheme 2. Synthesis of bis pyrazole derivatives from chalcone.

3.2. Bisenieks et al. described a new approach for the synthesis of bis-pyrazolyl methanes by the reaction of 3,5-diacyl-1,4-dihydropyridine with NH₂.NH₂ in solvent (scheme 3) [22].

[Diagram]

Scheme 3. Synthesis of bis pyrazole from pyrimidones.

3.3. Bis pyrazole also synthesis by Abul Ghafoor et al., when stirring the ethanolic mixture of cyano acetamide and adding aldehydes (scheme 4) [16].

[Diagram]

Scheme 4. Synthesis of bis pyrazoles with alkyl and aryl aldehyde.
3.4. Salah et al., successfully prepared some new bis pyrazole derivatives derivatives containing hydro phosphoryl unit from phosphonic dihydrazide (1) with acetophenone derivatives then treatment with Vilsmeier-Haack reagent (scheme 5)[23].

![Scheme 5](image)

Scheme 5. Synthesis of bis-pyrazole containing phosphoryl unit.

3.5. Michael et al., described a method to synthesis of some bis-pyrazole this method involved formation of bis-β-diketones then condensation with hydrazine to prepare of new bis-pyrazole from alyl-and xylyl-linked bis (β-diketone) precursors (Scheme 6) [24].

![Scheme 6](image)

Scheme 6. General synthesis of bis-ppyrazole ligands.

3.6. In the last few years, some new bis-pyrazole derivatives prepared by the reaction between chalcone derivatives and phenylhydrazine, and using these compounds as anti-instigative and germicide, (scheme 7) [25, 26].
3.7. New bis pyrazole imitatives have been composites by Ravindra et al., the synthesis was achieved using microwave, by the mixture of 3,5-bis-(4-hydroxy-3-methoxy-benzylidene-1-phenyl piperidine-2,6-diones and hydrazine hydrate in a yield 46-87% , (scheme 8) [27].

Scheme 7. Synthesis pathways of bis pyrazole derivatives from chalcone.

3.8. Nadia et al. proposed a simple, convenient and efficient method for preparation of bis-pyrazole as antimicrobial agent by reaction of phenylene diamines with cyano ethyl acetate,(scheme 9) [28].
3.9. Meliha et al. reported a scheme involves the synthetic procedure for the synthesis of bis-pyrazole compounds according to previous studies as anti-cancer and cytotoxic agents as illustrated in scheme (10). One symmetrical structure called 1,4-phenylene-bis—N-thio carbamoyl pyrazole and 1,4-phenylene-bis-pyrazole thiazole derivatives have been synthesized (Scheme 10). [18].

3.10. Some of bis-pyrazole derivatives had Synthesized and used as anti-tumour with potent apoptosis installation effects DNA harm. This approach included synthesis of pyrazole oxime combination exhibited span of anti-tumour (scheme 11) [17].
Scheme 11. Procedure for synthesis of bis pyrazole oxime reagents and conditions: (i) EtOH, EtONa, -12h, 72-80%. (ii) Hydrazine hydrate, HOAc, EtOH, rt, 12hr. (iii) Me₂SO₄, Na₂CO₃ , CH₂Cl₂, reflux, 4hr. (v) LiALH₄, THF, 1hr. (vi) SOCl₂, CH₂Cℓ₂, 20 min, rt, 1hr. (vii) Transposed phenols, NaOH, EtOH, reflux 2-3 hr, DMSO, 10-18hr. (viii) NH₂OH-HCL KOH, reflux, 6-17hr. (ix) K₂CO₃, Cs2CO3, MeCN, reflux, 12-18hr.

3.11. The importance of bis –pyrazole derivatives had appeared when it was prepared by its ligands with metal complexities, synthesized of a novel sequence of pyrazole –platinum (II) complexes as a potential anti-cancer influence [29]. The corresponding pyrazole reaction was added to the reaction mixture (K₂PtCl₄+KI) (Scheme 12).

Scheme12. Synthesis of a novel sequence of pyrazole –platinum(II)complexes.
4. Pharmacological activities

4.1. Antibacterial and antifungal activity
N-(2-(5-Br-1H-indazole-1-yl)-phenyl)-3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carboxamide (compound 1) showed upper anti-fungal movement towards the seven phytopathogenic [30]. While compound 2 exhibited excellent activities towards bacteria and fungi sepsis [31]. Finally, compound 3 showed the good activity towards E.coli, Pseudomonas aeruginosa, Staphylococcus epidermidis and Staphylococcus aureus[32].

4.2. Antitumor Activity
A new group of bis-pyrazole has observed to have the property to act as an anti-cancer celerity, compound 4 exhibited the weak results against enzyme activity (B-Raf inhibitor) [33]. The compound 5 was used as an anti-tumour agent against Ehrlich ascites carcinoma tumour cells [34] and compound 6 also used as a potent anti-cancer [35]. A sequence of bis-pyrazole imitative was used to their ability to act as anti-cancer rapidity (compound 7) [36].
4.3. Anti inflammatory and antiviral activity

Some of bispyrazole derivatives were Prepared and explored as anti-inflammatory celerity (complex 8) [37], and most of these derivatives were showed excellent antiviral activity (compound 9 and 10) [38, 39].
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