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Review Paper

Pharmacological Activities of Pyrazole and Its Derivatives: A Review

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ABSTRACT

Pyrazole is an important five-membered nitrogen-containing heterocyclic scaffold that has attracted considerable attention in medicinal chemistry due to its broad spectrum of pharmacological activities. Pyrazole derivatives exhibit diverse biological properties, including antimicrobial, antidiabetic, anti-Alzheimer's, anti-obesity, anti-tubercular, anti-inflammatory, anti-leishmanial, antidepressant, and anticancer activities. Structural flexibility, ease of functionalization, and favourable interactions with multiple biological targets make the pyrazole nucleus a valuable pharmacophore for drug design. Extensive structure–activity relationship (SAR) studies have demonstrated that both electronic and steric factors significantly influence the biological efficacy of pyrazole-based compounds. Recent advances in synthetic methodologies have further expanded the chemical diversity and therapeutic potential of pyrazole derivatives. This review provides a comprehensive overview of the pharmacological activities of pyrazole-containing compounds, highlighting key structural features, and recent developments that support their continued relevance in modern drug discovery.

INTRODUCTION

Pyrazole is an aromatic heterocyclic compound consisting of a five-membered ring structure containing three carbon atoms and two adjacent nitrogen atoms (**Fig-1**). The molecular formula of pyrazole is $C_3H_4N_2$. The name “pyrazole” was first proposed by Ludwig Knorr in 1883.

Pyrazole derivatives demonstrate a wide spectrum of biological and pharmacological properties such

as anticancer, anti-inflammatory, antimicrobial and analgesic activities. Molecules possessing the pyrazole nucleus exhibit unique structural characteristics that make them highly valuable scaffolds in modern medicinal chemistry. Numerous pyrazole-based derivatives are employed as pharmacophoric units in several therapeutic agents ^[1]. In 1959, the first natural pyrazole, 1-pyrazolyl-alanine, was isolated from seeds of watermelons ^[2].

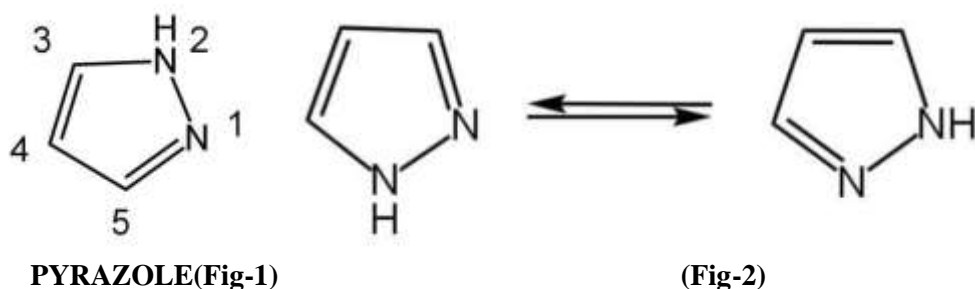
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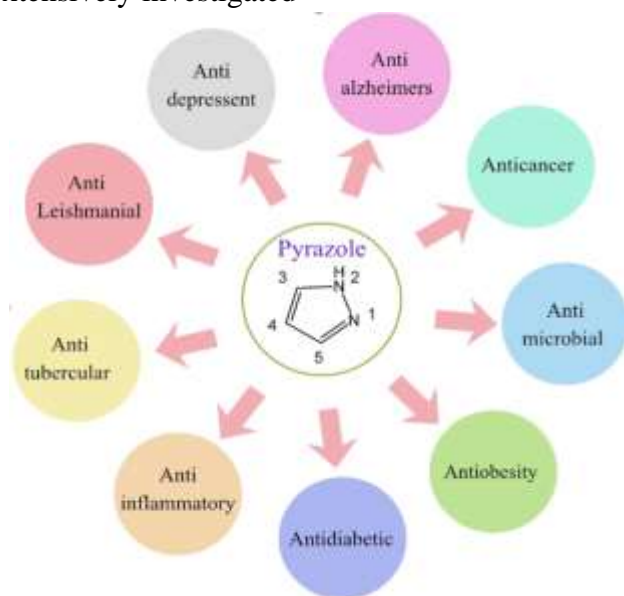




Pyrazole occurs as a colourless crystalline solid with a melting range of 69–70°C and a boiling point between 186–188°C, which is influenced by intermolecular hydrogen bonding. The compound exists in two rapidly interconvertible tautomeric forms, rendering them inseparable (**Fig-2**). A detailed review has highlighted that pyrazole-containing pharmacophores significantly contribute to the development of bioactive molecules in medicinal chemistry ^[3].

In recent years, pyrazole-based systems have gained significant scientific attention owing to their remarkable pharmacological properties. Among the azole family, pyrazole derivatives represent one of the most extensively investigated

classes of compounds. Incorporation of the pyrazole nucleus into diverse chemical structures has been shown to impart a wide range of biological activities and functional attributes. Consequently, pyrazole derivatives find applications not only in medicinal chemistry, but also in technological fields and agricultural science ^[4]. This review focuses on biologically active pyrazole compounds that possess significant therapeutic potential. Pyrazole-containing molecules are well recognized for their broad spectrum of biological activities and their importance as heterocyclic structures in medicinal chemistry ^[5, 6, 7].



(Fig-3 pyrazole containing different pharmacological activities)

A survey of existing literature shows that pyrazole derivatives exhibit a wide range of pharmacological properties (**Fig-3**).

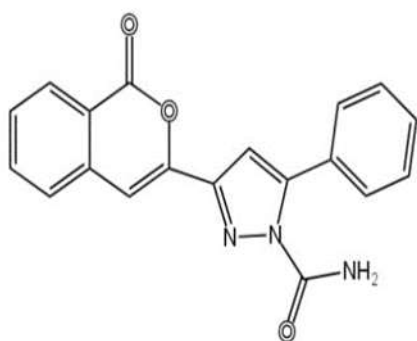
PHARMACOLOGICAL ACTIVITIES

Antimicrobial Activity:

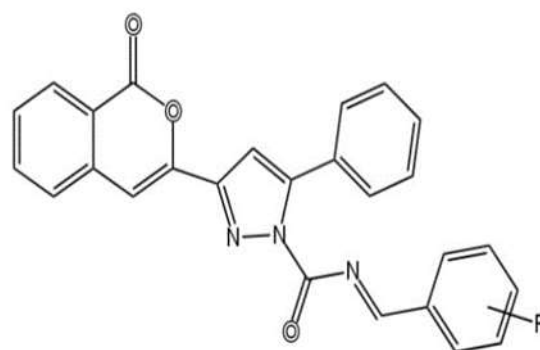
Most infectious diseases in the environment are caused by microorganisms. Even hospital intensive-care units often face contamination,

particularly from Gram-positive bacteria. Therefore, there is a growing need to develop antibiotics with improved resistance-fighting properties. In this context, the present study aims to design and develop potent antimicrobial drug-related compounds [8]. In vitro antimicrobial screening of the newly synthesized compounds was performed using the agar diffusion method. The evaluation included two fungal strains—*Candida albicans* (ATCC 10231) and *Aspergillus niger* (ATCC 16404)—and four bacterial strains: two Gram-positive bacteria (*Staphylococcus aureus* (ATCC 29213) and *Bacillus subtilis* (ATCC 6051)), and two Gram-negative bacteria (*Klebsiella pneumoniae* (ATCC 700603) and

Escherichia coli (ATCC 25922)). Standard antibiotic Chloramphenicol and the antifungal agent Clotrimazole were used as reference controls to assess the potency of the test compounds under identical conditions [9]. The variations in the effectiveness of different compounds against microorganisms may depend on factors such as the impermeability of microbial cell walls or structural differences in microbial ribosomes [10]. The results suggest that the antimicrobial activity of the synthesized compounds is influenced both by the bacterial cell wall composition and by the structural features of the pyrazole derivatives themselves.



(Fig-4)

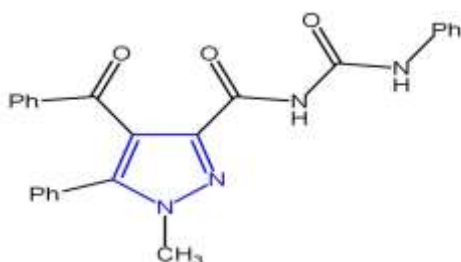


(Fig5)

Heterocyclic compounds containing pyrazole derivatives have demonstrated notable antimicrobial activity. Newly synthesized tri-substituted pyrazole derivatives exhibit measurable antimicrobial effects (Fig-4, 5) [11]. According to Balouiri et al. (2016), the antibacterial properties of the selected compounds were evaluated in vitro using the micro-dilution method at various concentrations. In the present study, this method was applied to assess activity against both Gram-negative (*Escherichia coli* ATCC 25922) and Gram-positive (*Staphylococcus aureus* ATCC 25923) bacteria. Over the past two decades, Malek et al. have designed and synthesized numerous pyrazole derivatives and extensively evaluated their antimicrobial activity.

Chalcones, which contain an α,β -unsaturated ketone linked to a phenyl group, have attracted considerable attention for their notable antibacterial and antifungal properties, primarily attributed to the α,β -unsaturated ketone moiety. Similarly, 3,5-diaryl-4,5-dihydro-1H-pyrazole derivatives, belonging to the 2-pyrazoline class, have also gained increasing research interest in recent years due to their promising biological potential [12]. Akbas et al. synthesized a series of 1H-pyrazole-3-carboxylic acid derivatives (Fig-4) and evaluated their antibacterial activity against *Bacillus cereus*, *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas putida*. Among the tested compounds, compound (Fig-6) exhibited the highest activity, showing effective

antibacterial action against both Gram-positive and Gram-negative bacteria [13].

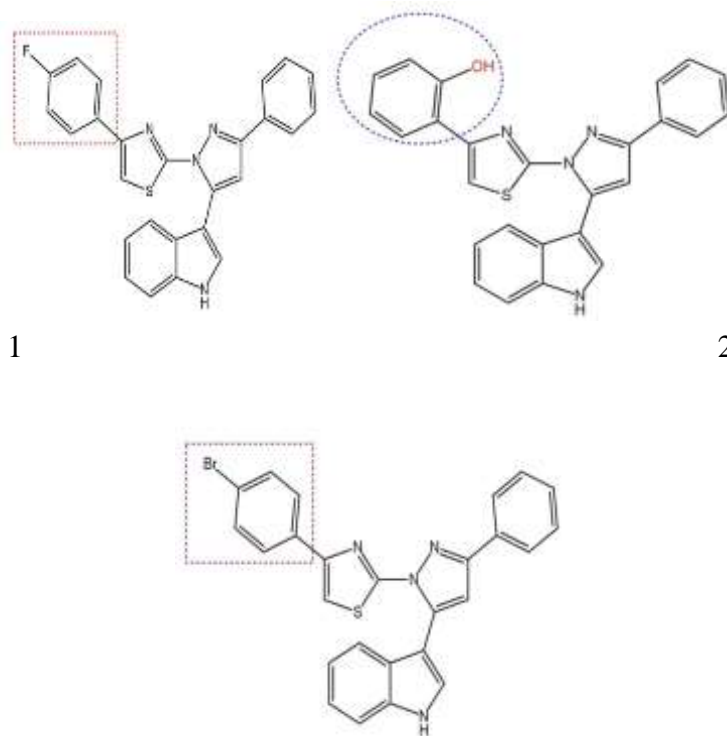


(Fig-6)

Antidiabetic Activity:

Cottineau et al. (2002) reported the development of a new series of substituted pyrazole-4-carboxylic acids for evaluating their antidiabetic activity. Their findings showed that 3-methoxy-1H-pyrazole-4-carboxylic acid emerged as the

most potent hypoglycemic agent among the synthesized compounds [14]. Several pyrazole derivatives have shown promising antidiabetic potential. Among the synthesized compounds, 2-(5-(1H-indol-3-yl)-3-phenyl-1H-pyrazol-1-yl)-4-(4-bromophenyl) thiazole exhibited the strongest antihyperglycemic activity, with an IC_{50} value of 236.1 $\mu\text{g/mL}$. This was compared with the reference drug acarbose, which displayed an IC_{50} of 171.8 $\mu\text{g/mL}$. Furthermore, compounds E, F, and G, containing fluoro, bromo, and hydroxyl substituents on the phenyl ring attached to the thiazole-pyrazole core, also demonstrated significant inhibitory activity (Fig-7) [15].



(Fig-7)

Additionally, novel urea and thiourea derivatives were synthesized through reactions of pyrazoles with the corresponding isocyanates or isothiocyanates. Further cyclization of the thiourea intermediates led to the formation of cyclic compounds, some of which exhibited strong

antimicrobial activity, while others showed significant hypoglycemic effects [16]. The study by Abdel-Baky et al. proved that chitosan-quinoline Schiff base derivative possesses antibacterial and antioxidant effects and has high competence as an anti-diabetic agent through the inhibition of α -

amylase and α -glucosidase enzymes^[17]. Sharon et al. developed a novel series of 5-[(5-aryl-1H-pyrazol-3-yl) methyl]-1H-tetrazole derivatives and evaluated their antihyperglycemic activity *in vivo*.

Anti-Alzheimer's activity:

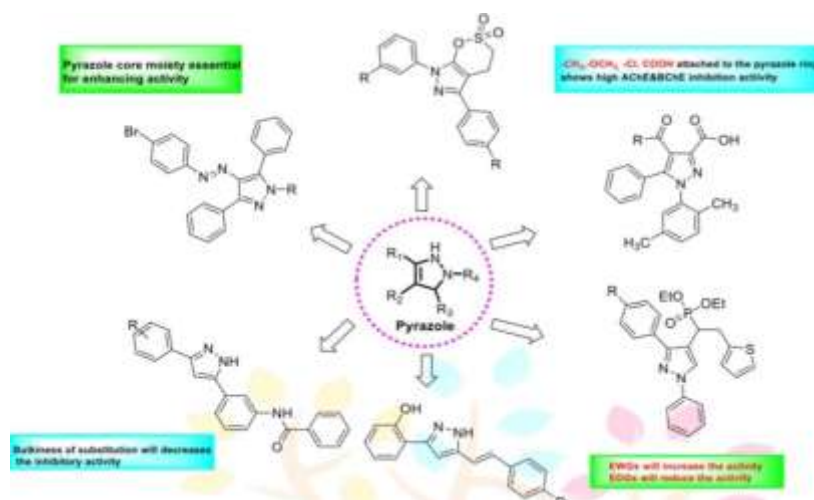
Alzheimer's disease (AD) is a progressive neurodegenerative disorder and a common form of dementia. It is characterized by symptoms such as memory loss and neuronal degeneration. Several factors, including cardiovascular disease, advanced age, and psychosocial influences, contribute to the development of Alzheimer's disease^[18]. The pyrazole moiety has shown promising potential in anti-Alzheimer's drug discovery. Pyrazole derivatives are known to target several key pathways involved in neurodegeneration and the progression of Alzheimer's disease (AD). These compounds can inhibit important enzymes such as acetylcholinesterase (AChE), monoamine oxidase (MAO), and β -secretase, all of which play critical roles in AD pathogenesis. In addition, pyrazole derivatives exhibit neuroprotective effects by reducing neurodegeneration, amyloid- β (A β) aggregation, and tau protein phosphorylation, which are major hallmarks of AD progression^[19]. The wide range of pharmaceutical applications of pyrazoles has driven significant progress in their synthetic methodologies. Over the past decade, numerous efficient and versatile approaches such as transition-metal catalysis, photoredox reactions, one-pot multicomponent processes, the use of novel reactants, and innovative reaction mechanisms—have contributed substantially to the synthesis and functionalization of pyrazole derivatives. The pyrazole compounds discussed herein demonstrate considerable promise as

prospective candidates for the development of novel neurodegenerative therapeutics^[20].

Structure–activity relationship (SAR) studies were carried out with a focus on the pyrazole core and its substitution pattern (**Fig-8**). Variations in cholinesterase inhibitory activity among the synthesized analogs were attributed to differences in substitution within the core structure of the molecules. These structural features strongly influenced inhibitory potency, with additional variability arising from the nature and positional arrangement of substituents on the aryl rings. Smaller substituents on the pyrazole ring were found to enhance inhibitory activity against both acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) when compared to bulkier groups. Moreover, the presence of electron-withdrawing substituents such as fluoro (–F), chloro (–Cl), and bromo (–Br) significantly increased activity, whereas electron-donating groups (EDGs) including methyl (–CH₃) and methoxy (–OCH₃) led to reduced inhibition. These findings indicate that both electronic and steric factors play a crucial role in modulating cholinesterase activity.

In a study reported by Shaikh et al. (2020), novel N-substituted pyrazole-based α -aminophosphonate derivatives were synthesized and evaluated for their anti-cholinesterase potential. Among these, compound 8 (IC₅₀ = 0.055 mM) and compound 9 (IC₅₀ = 0.017 mM) demonstrated strong inhibitory activity against AChE. The remaining analogs exhibited moderate to significant inhibition of BChE, outperforming standard drugs such as galantamine and rivastigmine. Overall, this study identified several promising lead compounds with considerable potential for further development as therapeutic agents targeting Alzheimer's disease^[21].



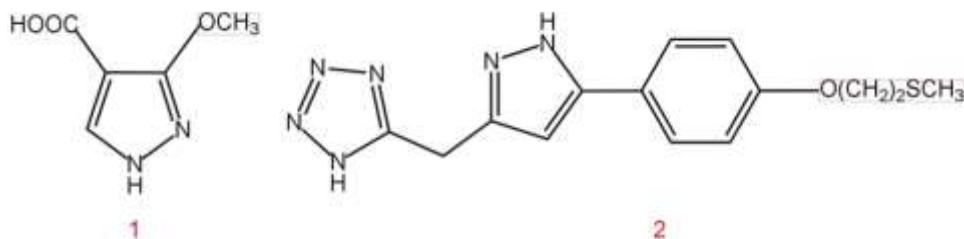


(Fig-8: SAR analysis of Pyrazole heterocyclic derivatives for AD)

Anti-obesity Activity:

Obesity is recognized not only as a chronic and progressive disease but is also associated with an increased risk of numerous health conditions, including diabetes mellitus, cardiovascular diseases, non-alcoholic fatty liver disease (NAFLD), subfertility, renal disorders, obesity-hypoventilation syndrome (OHS), gastroesophageal reflux disease (GERD), various

cancers, and Coronavirus disease 2019 (COVID-19). Obesity markedly elevates the risk of several chronic health conditions, including type 2 diabetes mellitus, coronary artery disease, stroke, non-alcoholic fatty liver disease, sleep apnea, osteoarthritis, and certain types of cancer (Fig-9) [22].



(Fig-9)

Several pyrazole-based derivatives have demonstrated anti-obesity activity, as the pyrazole moiety is recognized as an important pharmacophore exhibiting a wide range of biological effects [23]. Pyrazole-based compounds exhibit anti-obesity effects through different biological mechanisms:

Inhibition of pancreatic lipase, leading to reduced dietary fat absorption
 Regulation of adipogenesis and lipogenesis
 Activation of AMP-activated protein kinase (AMPK)

Modulation of peroxisome proliferator-activated receptors (PPARs)

Appetite suppression via central nervous system pathways
 In recent years, several pyrazole and substituted pyrazole derivatives have demonstrated promising anti-obesity activity through multiple mechanisms, including pancreatic lipase inhibition, appetite regulation, modulation of lipid metabolism, and interaction with metabolic enzymes. Kumar et al. synthesized a series of substituted pyrazole derivatives and evaluated their pancreatic lipase inhibitory activity. Several compounds showed significant inhibition comparable to orlistat, indicating their potential as fat absorption blockers [24]. Similarly,

Abdel-Maksoud et al. reported pyrazole-based hybrids exhibiting potent lipase inhibition and reduced triglyceride levels in vivo [25]. Sharma et al. designed novel pyrazole analogues that demonstrated significant reduction in body weight gain and serum lipid levels in high-fat diet-induced obese rats. The activity was attributed to modulation of lipid metabolism enzymes [26]. In another study, El-Shehry et al. reported pyrazole derivatives that reduced adipose tissue mass and improved lipid profiles in experimental animals [27].

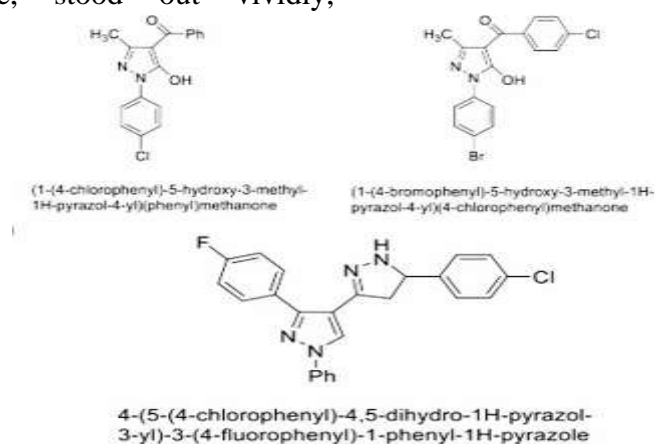
Anti-tubercular activity:

Against the dark, persistent shadow cast by *Mycobacterium tuberculosis*, pyrazole scaffolds emerged like bold strokes of colour on a restless canvas. Manetti et al. (2006) painted the first decisive form, revealing a chlorophenyl-substituted pyrazole whose activity burned steadily, arresting bacterial growth at an MIC of 25 $\mu\text{M}/\text{mL}$ [28]. The vision deepened in the hands of Castagnolo et al. (2008), who reshaped the molecular landscape with brominated hues at the N1 position. Their compound, enriched with a p-bromophenyl presence, stood out vividly,

demonstrating pronounced inhibition against the H37Rv strain, as though structure itself guided potency [29].

Shelki et al. (2012) introduced fluorinated highlights into the pyrazole framework, and among these shimmering forms, a pyrazoline derivative shone with particular intensity. It suppressed the resilient H37Rv strain at a striking MIC of 6.25 $\mu\text{g}/\text{mL}$, suggesting precision carved through chemical contrast [30]. In 2013, Fullam et al. explored the rhythmic repetition of diaryl pyrazoles, targeting the arylamine N-acetyltransferase enzyme. One compound, bearing methoxy substitutions, flowed smoothly across the biochemical canvas, halting *M. tuberculosis* growth with an MIC below 10 $\mu\text{g}/\text{mL}$ [31]. Maurya et al. (2013) investigated a series of substituted pyrazole derivatives and assessed their in vitro anti-tubercular activity against the *Mycobacterium tuberculosis* H37Rv strain [32].

Finally, Pathak et al. (2014) broadened the scene with diaryl-substituted pyrazoline ethanones, their work echoing layered brushstrokes that collectively affirmed the enduring promise of pyrazole derivatives against the H37Rv strain (**Fig-10**) [33].



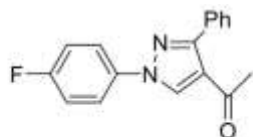
(Fig- 10)

Anti-inflammatory Activity:

Inflammation is a multi-stage process that in the critical step is supposed to be powered by acutely released arachidonic acid and its prostaglandin-

like metabolites. Two cyclooxygenase (COX) isozymes are known to catalyse the rate-limiting stage of prostaglandin synthesis, COX-I and COX-II [34]. Nonsteroidal anti-inflammatory

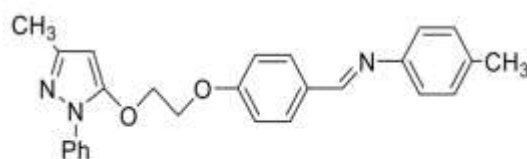
drugs (NSAIDs) alleviate pain by counteracting the cyclooxygenase (COX) enzyme. Some common example of NSAIDs is aspirin, ibuprofen, and naproxen [35]. A series of 1-(4-substituted-phenyl)-3-phenyl-1H-pyrazole-4-carbaldehydes were prepared and tested for their anti-inflammatory and analgesic activities. Among the prepared compound exhibited the maximum anti-inflammatory activity (**Fig-11**) [36].



1-(1-(4-fluorophenyl)-3-phenyl-1H-pyrazol-4-yl)ethanone

(Fig-11)

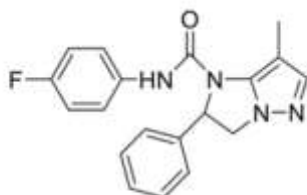
A novel series of pyrazole derivatives were reported by Tewari et al (2014) and evaluated in vivo for their anti-inflammatory activity. Among the compounds N-(4-(2-(3-methyl-1-phenyl-1H-pyrazol-5-yl)oxy)benzylidene)-4-methylbenzenamine showed comparable anti-inflammatory (**Fig-12**) [37].



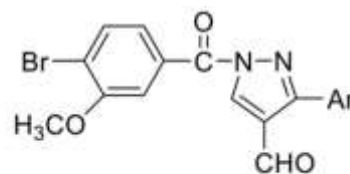
(E)-N-(4-(2-(3-methyl-1-phenyl-1H-pyrazol-5-yl)oxy)benzylidene)-4-methylbenzenamine

(Fig-12)

Brullo et al, (2012) reported and synthesized the anti-inflammatory evaluation of new 2,3-dihydroimidazo[1,2-b] pyrazole derivatives in which compound N-(4-fluorophenyl)-2,3-dihydro-7-methyl-2-phenylimidazo[1,2-b]pyrazole-1-carboxamide showed an interesting dual activity inhibiting both Fmlp-Ome and IL8-induced chemotaxis with IC50 values of 3.8 and 1.2 Nm, respectively [38]. Freddy et al (2001) have synthesized the series of 1-(3-bromo-4-methoxybenzyl)-4-formyl-3-(substituted phenyl) pyrazole and their anti-inflammatory activity (**Fig-13**) [39].



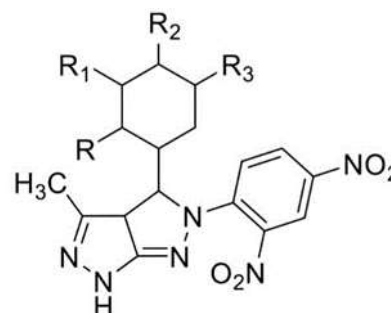
N-(4-fluorophenyl)-2,3-dihydro-7-methyl-2-phenylimidazo[1,2-b]pyrazole-1-carboxamide



1-(3-bromo-4-methoxybenzyl)-4-formyl-3-(substituted phenyl) pyrazole

(Fig-13)

Bhaskar et al (2007) have reported the synthesis of 4,5-disubstituted-3-methyl-1,3a,4,5-tetrahydropyrazolo[3,4-c] pyrazoles and their anti-inflammatory activity [40]. Nargund et al (1992) evaluated the fluorinated phenyl styryl ketones and Nphenyl-5-substituted aryl-3-P-(fluorophenyl) pyrazoline and reported anti-inflammatory activity in vivo (**Fig-14**) [41].

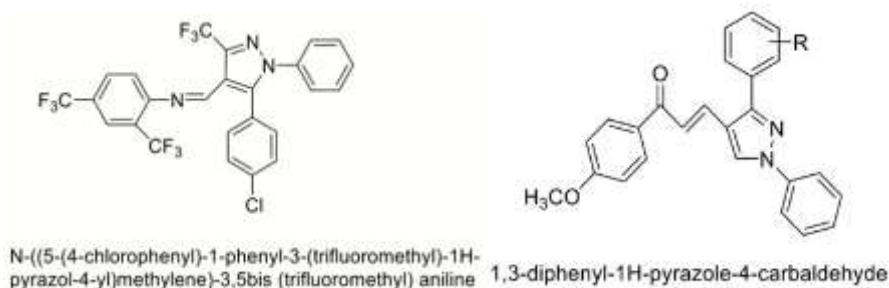


4,5-disubstituted-3-methyl-1,3a,4,5-tetrahydropyrazolo[3,4-c] pyrazoles

(Fig-14)

Sayed et al (2012) reported a series of new pyrazole derivatives characterized as N-((5-(4-chlorophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)methylene)-3,5-bis(trifluoromethyl) aniline which exhibited optimal anti-inflammatory activity as compared with reference drugs diclofenac sodium and celecoxib. Bandgar et al (2009) evaluated the series of novel 1-(2,4-

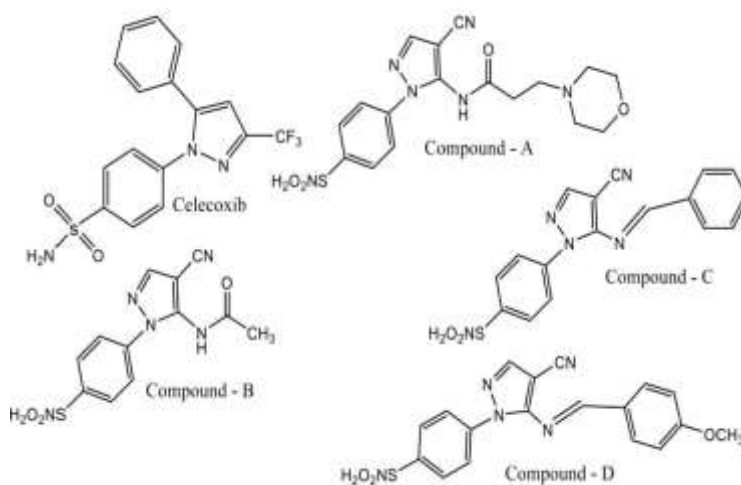
dimethoxy-phenyl)-3-(1,3-diphenyl-1H-pyrazol-4-yl)-propenone by the Claisen-Schmidt condensation of 1-(2,4-dimethoxy-phenyl)-ethanone and substituted 1,3-diphenyl-1H-pyrazole-4-carbaldehyde. All the synthesized compounds were evaluated for anti-inflammatory activity (Fig-15) [42].



(Fig-15)

Anti-inflammatory activities as pain is a hallmark of tissue damage and inflammatory processes (Baral et al., 2019), pyrazole analogs with antinociceptive and anti-inflammatory activities are important to analgesic drug development. The pyrazole compounds with fluorine at para, meta and ortho positions on the phenyl ring

demonstrated an antinociceptive effect in the previous studies (de Oliveira et al., 2017; Florentino et al., 2019). This effect was associated with the activation of the opioid receptor and blockage of the acid-sensing ion channel subtype 1 α (ASIC-1 α).



(Fig-16)

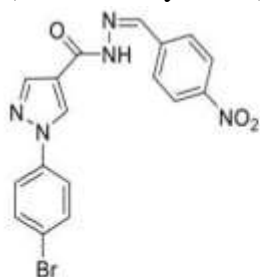
Pyrazole substituted with nitro and bromo groups inhibited pain response (60%) better than compounds and with benzofuran carbaldehyde (35 and 50%, respectively) [43]. Pyrazole based compounds, such as celecoxib, are well-known for their significant anti-inflammatory properties,

making them valuable in the pharmaceutical industry [44] (Fig-16). Recent research focuses on derivatives that inhibit both COX and 5-Lipoxygenase (5-LOX), thereby reducing both prostaglandins and leukotrienes, which potentially

offers higher efficacy with fewer gastric side effects [45].

Anti leishmanial Activity:

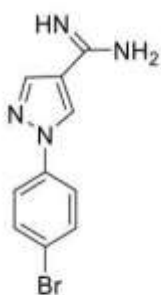
Several studies have demonstrated the potential of pyrazole derivatives as anti-leishmanial agents. Bernardino et al. (2006) synthesized 1H-pyrazole-4-carbohydrazides and evaluated their in vitro leishmanicidal activity. Among the tested derivatives, (Z)-N-(4-nitrobenzylidene)-1-(4-



(Z)-N-(4-nitrobenzylidene)-1-(4-bromophenyl)-1H-pyrazole-4-carbohydrazide

(Fig-17)

Santos et al. (2011a) synthesized 1-aryl-1H-pyrazole-4-carboximidamide derivatives and evaluated their anti-leishmanial potential in vitro. The compound 1-(4-bromophenyl)-1H-pyrazole-4-carboxamide showed promising activity, indicating scope for further structural optimization (Fig-19) [48]. In a subsequent study, Dos Santos et

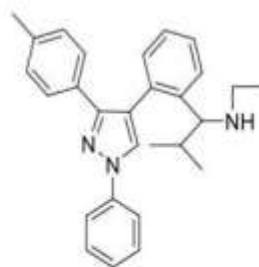


1-(4-Bromophenyl)-1H-pyrazole-4-carboxamide

(Fig-19)

Bekhit et al. (2014) synthesized a new series of 1H-pyrazole derivatives and assessed their in vitro activity against Leishmania aethiopica promastigotes. The compound (E)-3-(3-phenyl-1-

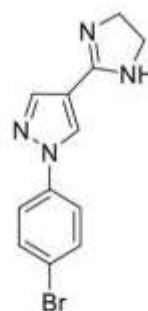
bromophenyl)-1-pyrazole-4-carbohydrazide exhibited the highest activity against Leishmania amazonensis, L.chagasi, and L.braziliensis (Fig-17) [46]. Dardari et al. (2006) reported a novel pyrazole derivative, N-ethyl-2-methyl-1-(2-(1-phenyl-3-p-tolyl-1H-pyrazol-4-yl) phenyl)propan-1-amine, which showed potent inhibition of Leishmania tropica, L.major, and L.infantum, with IC₅₀ values of 0.50, 0.65 and 0.42 µg/mL, respectively (Fig-18) [47].



N-ethyl-2-methyl-1-(2-(1-phenyl-3-p-tolyl-1H-pyrazol-4-yl)phenyl)propan-1-amine

(Fig-18)

al. (2011b) reported 1-aryl-4-(4,5-dihydro-1H-imidazol-2-yl)-1H-pyrazoles, among which 1-(4-bromophenyl)-4-(4,5-dihydro-1H-imidazol-2-yl)-1H-pyrazole was the most active against promastigote forms of L. amazonensis (IC₅₀ = 15 µM) (Fig-20) [49].

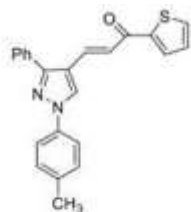


1-(4-Bromophenyl)-4-(4,5-dihydro-1H-imidazol-2-yl)-1H-pyrazole

(Fig-20)

p-tolyl-1H-pyrazol-4-yl)-1-(thiophen-2-yl) prop-2-en-1-one displayed the highest activity, with an IC₅₀ value of 0.08 µg/mL (Fig-21) [50]. Figarella et al. (2020) evaluated pyrazole derivatives for

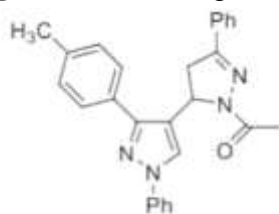
antiparasitic activity against *Leishmania mexicana* and *Trypanosoma cruzi*. Only (2-hydroxy-5-methyl phenyl)(1-phenyl-1H-pyrazol-4-yl) methanone showed selectivity toward L.



(E)-3-(3-phenyl-1-p-tolyl-1H-pyrazol-4-yl)-1-(thiophen-2-yl)prop-2-en-1-one

(Fig-21)

Tuha et al. developed a new series of pyrazole derivatives and identified 1-(4,5-dihydro-3-phenyl-5-(1-phenyl-3-p-tolyl-1H-pyrazol-4-yl)pyrazol-1-yl)ethanone as the most potent compound, showing superior activity against *Leishmania donovani* compared to standard drugs such as miltefosine and amphotericin B deoxycholate (Fig-23)^[52]. Reviriego et al. (2017)

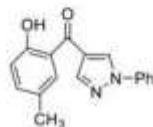


1-(4,5-dihydro-3-phenyl-5-(1-phenyl-3-p-tolyl-1H-pyrazol-4-yl)pyrazol-1-yl)ethanone

(Fig-23)

Santos et al. (2013) synthesized a series of pyrazole-thiosemicarbazone hybrids and evaluated their activity against *Leishmania amazonensis*. Several compounds demonstrated significant inhibition of promastigote growth, which was attributed to interference with parasite redox balance and mitochondrial dysfunction, highlighting the importance of sulphur-containing substituents in enhancing activity^[54]. Pereira et al. (2014) reported the synthesis of pyrazole-linked amidines and assessed their leishmanicidal activity against *L. infantum*. Some derivatives exhibited low micromolar IC₅₀ values and showed reduced cytotoxicity toward mammalian macrophages,

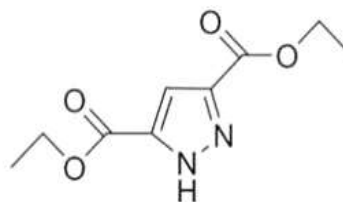
mexicana, with a selectivity index of 3, although its IC₅₀ value was comparatively higher (Fig-22)^[51].



(2-hydroxy-5-methylphenyl)(1-phenyl-1H-pyrazol-4-yl)methanone

(Fig-22)

synthesized simple dialkyl pyrazole-3,5-dicarboxylates and evaluated their activity against *T. cruzi*, *L. infantum*, and *L. braziliensis*. Diethyl-1H-pyrazole-3,5-dicarboxylate exhibited high efficacy against the tested protozoa, highlighting the relevance of this scaffold in Anti-leishmanial drug development (Fig-24)^[53].



Diethyl 1H-pyrazole-3,5-dicarboxylate

(Fig24)

indicating favourable selectivity indices and potential for further development^[55].

Silva et al. (2016) evaluated a new class of pyrazole-based chalcone analogues against *Leishmania braziliensis*. The study revealed that electron-withdrawing groups on the aromatic ring significantly enhanced antiparasitic activity, possibly through inhibition of parasite enzymes involved in energy metabolism^[56]. Alves et al. (2018) synthesized pyrazole-benzofuran hybrids and screened them for in vitro activity against *L. amazonensis* amastigotes. The most active compound induced apoptosis-like cell death in parasites and showed better efficacy than pentamidine in intracellular models^[57]. Costa et al.

(2019) explored metal-complexed pyrazole derivatives, particularly copper(II)-pyrazole complexes, for anti-leishmanial activity. These complexes demonstrated enhanced potency compared to free ligands, suggesting that metal coordination can improve cellular uptake and biological activity [58]. Moreira et al. (2021) reported pyrazole-based inhibitors of trypanothione reductase, a key enzyme in *Leishmania* survival. Selected compounds showed potent enzyme inhibition and effective suppression of *L. donovani* promastigote growth, supporting enzyme-targeted pyrazole design as a rational therapeutic strategy [59]. Kumar et al. (2022) synthesized a library of substituted pyrazole sulphonamides and evaluated their activity against *L. major*. Several derivatives displayed strong in vitro activity with acceptable safety profiles, emphasizing the relevance of sulphonamide moieties in improving anti-leishmanial potency [60].

Antidepressant Activity:

Several pyrazole and pyrazoline derivatives have demonstrated significant antidepressant-like activity in preclinical studies using validated animal models such as the forced swim test (FST) and tail suspension test (TST). These models are widely accepted for screening antidepressant efficacy and are sensitive to clinically effective antidepressant drugs. Reduction in immobility time observed with pyrazole derivatives in these tests indicates their potential antidepressant effect [61,62]. Mechanistic investigations suggest that the antidepressant activity of pyrazole derivatives is primarily mediated through modulation of the monoaminergic system. Some substituted pyrazoles act as monoamine oxidase (MAO) inhibitors, particularly MAO-A, leading to increased synaptic concentrations of serotonin and norepinephrine. This mechanism is consistent with the pharmacological action of several established

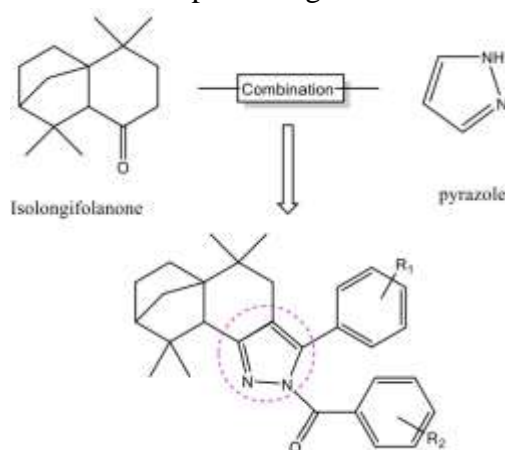
antidepressant agents [63,64]. In addition, certain pyrazole derivatives have been reported to influence dopaminergic neurotransmission, further contributing to their antidepressant profile [65]. Structure-activity relationship (SAR) studies indicate that substitution at specific positions on the pyrazole ring plays a crucial role in determining antidepressant potency. Electron-donating and electron-withdrawing groups on the aromatic ring attached to the pyrazole nucleus have been shown to enhance CNS penetration and receptor binding affinity, thereby improving antidepressant activity [66]. Pyrazoline derivatives, which are partially saturated analogues of pyrazole, have also exhibited notable antidepressant effects, suggesting that both ring saturation and substitution pattern are important determinants of activity [67]. Overall, accumulated pharmacological evidence supports the potential of pyrazole derivatives as antidepressant agents. Their ability to modulate monoamine levels, combined with favourable behavioural outcomes in animal models, highlights the pyrazole scaffold as a valuable lead structure for the development of novel antidepressant drugs. However, further studies focusing on toxicity, pharmacokinetics, and clinical evaluation are necessary to establish their therapeutic applicability [68].

Anticancer Activity:

Various pyrazole derivatives have been synthesized by linking pyrimidine, carboxyhydrazide, and ferrocenyl moieties to the pyrazole core, and these compounds have demonstrated notable effectiveness against lung carcinoma cells. Balbi et al. (2011) synthesized a novel pyrazole derivative, 5-methoxy-2-(1-(pyridin-2-yl)-1H-pyrazol-5-yl) phenol and reported its antiproliferative activity against human ovarian adenocarcinoma (A2780) cells, human lung carcinoma (A549) cells, and murine P388 leukaemia cells [69].



Bernardino et al. (2006) synthesized a series of 1H-pyrazole-4-carbohydrazide derivatives and evaluated their in vitro leishmanicidal activity. Among the compounds tested, (Z)-N-(4-nitrobenzylidene)-1-(4-bromophenyl)-1H-pyrazole-4-carbohydrazide exhibited the highest activity against *Leishmania amazonensis*, *L. chagasi*, and *L. braziliensis* species [70]. Cancer remains a major global health concern and is currently the second leading cause of mortality worldwide [71]. Numerous pyrazole derivatives have demonstrated promising anticancer activity.



(Fig-25: Pyrazole ring containing isolongifolanone derivatives with antitumor activity)

In particular, isolongifolanone-based derivatives incorporating a pyrazole moiety have been identified as potential candidates for anticancer therapy (Fig-25) [72]. Pyrazole-pyrimidine compounds and their bioisosteres are heterocyclic structures known to exhibit a wide range of biological activities, including notable antitumor effects [73]. Additionally, a series of 4-benzoyl-1,5-diphenyl-1H-pyrazole-3-carbonyl thiourea derivatives have demonstrated significant anticancer activity, highlighting their potential as therapeutic agents for the treatment of leukaemia, liver cancer, and colon cancer [74]. After cardiovascular diseases, cancer is the second leading cause of mortality and morbidity worldwide, accounting for approximately 13% of global deaths [75]. It is characterized by the

uncontrolled proliferation of abnormal cells. Although chemotherapy and radiation therapy remain effective treatment options, their use is often limited due to significant adverse effects on normal cells [76]. Consequently, the search for novel, potent, selective, and safer anticancer agents continue to be a major focus in the field of medicinal chemistry [77]. Perina M. et al. reported the development of ring-fused pyrazole derivatives of dihydrotestosterone that target prostate cancer cells through the down regulation of androgen receptors (AR) [78]. In their study, steroidal pyrazoles derived from the natural sex hormone 5 α -dihydrotestosterone were synthesized, and a ring-fused 1,5-disubstituted pyrazole (compound 3d) was identified as the lead compound. This compound exhibited potent androgen receptor antagonistic activity by effectively suppressing AR signalling.

CONCLUSION

Pyrazole derivatives represent a versatile and highly promising class of heterocyclic compounds in medicinal chemistry. The extensive literature reviewed in this article clearly demonstrates that the pyrazole scaffold possesses significant therapeutic potential across a wide range of disease conditions, including infectious diseases, metabolic disorders, neurodegenerative diseases, inflammation, parasitic infections, cancer, and central nervous system disorders. Overall, pyrazole-based molecules continue to serve as valuable lead structures for the development of novel and safer drugs.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this review article.

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