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CURRENT STATUS OF PYRAZOLE AND IT'S BIOLOGICAL ACTIVITES

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Abstract :

Pyrazole is a five membered and two-nitrogen containing heterocyclic ring. These structures have been investigated in the development of novel compounds with hypoglycemic,analgesic,antimicrobial, anticonvulsant, antidepressant, antimyco-bacterial, antioxidant, antiviral, insecticidal, anti-inflammatory and anti-tumor activities. Pyrazole is a multipurpose lead compound developed by chemical architecture for effective molecules which are biologically active. Several synthetic routes are accorded to the development of pyrazole containing reactions to afford a novel molecule which is an enormous opportunity in the field of medicinal chemistry.The aim of this review is to provide an overview of diverse pharmacological activities of pyrazole moity.This review highlighted recent report of biological activity of pyrazole. The purpose of this review was to collate literature work reported by researchers on pyrazole for their various pharmacological activities and also reported recent efforts made on this moity. It is expected that this review will be helpful in future research and for new thoughts in the quest for rational designs for developing more promising pyrazoles.

Key words :Pyrazole, Heterocyclic, Development, Synthesis

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1. Introduction :

Heterocyclic compounds are a highly valuable and unique class of compounds. These compounds demonstrate a broad spectrum of physical, chemical and biological characteristics[1,2].In nature, heterocyclic compounds are widely distributed and display an important part in metabolism owing to their structural nucleus occurring in various natural products, including hormones, antibiotics, alkaloids, vitamins and many others[3,4]. Pyrazole derivatives have a long history of application in agrochemicals and pharmaceutical industry as herbicides and active pharmaceuticals. The recent success of pyrazole COX-2 inhibitor has further highlighted the importance of these heterocyclic rings in medicinal chemistry. A systematic investigation of this class of heterocyclic lead revealed that pyrazole containing pharmacophore active agents play important role in medicinal chemistry. The prevalence of pyrazole cores in biologically active molecules has stimulated the need for elegant and efficient ways to make these heterocyclic lead[5].

Amongst heterocyclic compounds, nitrogen-containing heterocycles are extensively found as a core framework in a huge library of heterocycles and show several employments in natural science and other areas of science.[6] Additionally, nitrogen-containing heterocycles have striking structural features and they are widely observed in natural products, for instance, vitamins, hormones and alkaloids.[8] Pyrazole **1** is known to be one of the most potential families of nitrogen-containing compounds. Pyrazole derivatives exhibit a broad spectrum of biological profiles, for instance, anti-tubercular, anti-AIDS, anti-malarial anti-microbial, antitumor anticancer,and antifungal. In addition, pyrazoles have also been found as promising anti-hyperglycemic, anti-depressant, anti-convulsant, anti-pyretic,anti anxiety and insecticidal agents. Bipyrazole shows diuretic, cytotoxic and cardiovascular efficacy. It has achieved great attention since the privileged framework is frequently observed as a bioactive component in commercially available medicines, for example, Floxan (anti-inflammatory medicine), pyrazomycin (anticancer),difenamizole (anti-inflammatory drug), and deramaxx (NSAID) (Figure 1).[22,23] It is also utilized in paint and photographic industries and in the development of heat resistant resins. The corresponding 3-oxygenated derivative, pyrazolone.[9]

2. PHARMACOLOGICAL ACTIVITY :

For a very long time, the usefulness and great therapeutic value of pyrazole nucleus have been recognized and widest range of activities of this nucleus evaluated. However, as the first synthetic organic compound having pyrazoline-5-one nucleus, to find use as an important drug. Phenylbutazone as a prototype of pyrazolidinedione is a very potent anti-inflammatory agent, but its use is now banned in some countries. Later on, many modifications of pyrazole nucleus were attempted and several compounds have been synthesized which serves as the basis for the treatment of different diseases like-inflammation, pain, cancer, tuberculosis, and diseases caused by bacteria.[10]

2.1 Anti-inflammatory activity :

Bekhit *et al.* (2008) reported a series of thiazolyl and thiadiazolyl derivatives of 1*H*-pyrazole and their anti-inflammatory activity. They observed that the compounds were more active than the standard indomethacin and the active compound were found selective towards COX-2 enzyme.[11]A series of compound was synthesized by Balbi *et al.* (2007) 5-(2,6,6- Trimethyl-2-cyclohexen-1-yl)ethenyl-1H-pyrazole were also be found to be potent inhibitors of neutrophil chemotactic responsiveness which could be considered as lead compounds and compared to standard Diclofenac.[12]Hall *et al.* (2008) reported compounds in a series of methylene linked pyrazole as EP1 receptor antagonist and discovered compounds of amide, reversed amide and carbamate derivatives and identified as brain penetrant compounds and both demonstrated efficacy in the CFA model of inflammatory pain.[13] A combinatorial library of 3, 5-diaryl pyrazole derivatives were synthesized and evaluate them for anti-inflammatory activity against TNF-α and IL- 6. Out of 15 reported compounds few compound showed anticancer activity (61–73% at 10 μM concentration) And IL-6 inhibition (47% and 42% at 10 μM concentration) as in comparison to standard flavopiridol (72-87% inhibition at 0.5 μM) and dexamethasone (85% inhibition at 1 μM concentration), respectively by Bandgar *et al*. (2010).[14] Abdel-Hafez *et al*. (2009) prepared novel pyrazole-NO hybrid molecules 2-(4-(4-benzoyl-1, 5-diphenyl-1H-pyrazole-3- carbonyl)piperazin-1-yl)-2-oxoethyl nitrate and evaluated them for nitric oxide release, antibacterial and anti-inflammatory activities. Compound **7** exhibited highest percentage of NO release using Griessdiazotization method. Some of the tested compounds are reported with significant anti-inflammatory activitycompared to indomethacin using carrageenan induced paw edema method. Structural modification as reported through nitrate ester or oxime hybrids has resulted better anti-inflammatory activity with less ulcerogenic liability.[15]Synthesised a series of 4-thiazolyl pyrazolyl and studied there, COX-1, COX-2,ulcerogenic effect and acute toxicity, by Bekhit *et al.* (2010) and Docking study of compounds A, B and C on active site of the human COX-2 enzyme and DNA-gyrase B has revealed that compounds A, B and C exhibited good anti-inflammatory activity with no or minimal ulcerogenic effect. Compound B and C are reported as most potent and selective towards COX-2 compared to indomethacin.[16]

2.2. Anticancer activity :

Christodoulou *et al*. (2010) Synthesised a series of tri substituted pyrazole derivatives and PIFA-mediated conversion of molecules bearing the fused pyrazolo [4,3-c]quinolone ring system and evaluated them for anti-angiogenic activity by using *in vitro* assays for endothelial cell proliferation and migration, and in the chicken chorioallantoic membrane (CAM) assay. Compounds having fused pyrazolo [4, 3-c]quinoline motifs emerged asnpotent anti-angiogenic compounds, and also inhibit the growth of human breast (MCF-7) and cervical (Hela) carcinoma cells *in vitro*.[17] Bonesi *et al.* (2010) Prepared a series of chalcones and their pyrazoles derivatives and investigated them for Angiotensin I-Converting Enzyme (ACE) inhibitory activity. They have reported the chalcone (a) with highest activity (IC50 0.219 mM), while the most potent pyrazole was (b) (IC50 0.213 mM).[18] Lv *et al.* (2010) designed two series of pyrazole derivatives and evaluated for their potential EGFR kinase inhibitors activity. Compound 3-(3, 4-dimethylphenyl)-5-(4-methoxy phenyl)-4,5-dihydro-1*H*-pyrazole- 1-carbothioamide is most potent with IC50 of 0.07 μM, as compared to positive control erlotinib.[19]

2.3. Antimicrobial Activity :

A new series of fused pyrazole-pyrimidine derivatives was synthesized by Samir Bondock *et al.* (2010).The given compound was found to exhibit the most potent *in-vitro* antifungal activity with MICs (6.25 μ/ml) against *A. fumigatus* & *F. Oxysporum* comparable with Chloroamphenicol.[20]Smaail *et al.* (2010**)** synthesized novel pyrazole derivatives and these derivatives were evaluated for their antimicrobial activity determined by agar plate diffusion technique. The antibacterial activity was determined by agar plate method against E.Coli strains *Saccharomyces cereviseae* and *Fusarium oxysporum f. sp.ablicans*. Streptomycin was used as reference
compound in performing antimicrobial assay. These derivatives were found to be most potent.[21]

2.4. Anticonvulsant and Antidepressant Activity :

Chimenti *et al.* (2004) Synthesised a novel series of 1-acetyl-3-(4-hydroxy- and 2,4-dihydroxyphenyl)-5-phenyl-4,5-dihydro-(1*H*)-pyrazole derivatives and investigated them ability to selectively inhibit the activity of the A and B isoforms of monoamine oxidase (MAO). The new synthesized compound proved to be more reversible,potent, and selective inhibitors of MAO-A than of MAO-B.[12] Abdel-Aziz *et al.* (2009) Described two synthetic paths for the formation of diacylhydrazines, 5amino-1-substiuted pyrazole-3,3,4-tricarbonitriles and oxadiazole, pyrazoline derivatives, showing antidepressant activity using tail suspension behavioural despair test and anticonvulsant activity against PTZ induced seizures in mice. Compound **a** and **b** showed antidepressant activity compared to imipramine and their antidepressant activity were twice the activity of imipramine at 10mg/kg dose level. Compounds **c**, **d** and **e** exhibit protective effect against clonic seizures induced by i.p.injection of PTZ at a dose level of 20 mg/ kg.[22].

2.5 Antiviral Activity :

Osama *et al.* (2009) synthesized 4, 5-disubstituted pyrazole derivatives . The derivative containing R= Cl group showed the potent antiviral activity against a broad panel of viruses in different cell culture (HEL Cell cultures).[23]Aymn E. Rashad *et al.* (2008) synthesized substituted pyrazole derivatives. These derivatives showed promising antiviral activity against hepatitis A virus and Herpes Simplex virus type-1 using plaque infective assay.

2.6 ACE-Inhibitory Activity:

Macro *et al.* (2010) synthesized a series of pyrazole derivatives and investigated their potential activity as Angiotensin-I-converting enzymes inhibitory activity by performing assay. This derivative of pyrazole showed effective ACE-inhibitory activity with 0.123 mM IC50 value.[24] A new molecule designed and developed a series of COX-2 inhibitors. Gao *et al.* (2011) prepared compounds were screened for their biological activity, indicated that the synthesized new compounds a and b display similar strong inhibitory effectiveness in the MDA-MB-435 human cancer cell line in comparison with the parent compound celecoxib.

3.Conclusion :

Pyrazole have lots of pharmaceutical application in new drug synthesis.Besides having anti-cancer,anti-inflammatory,anti-microbial, antiviral activities pyrazole also posses some anti-influenzial activity also.Now a days,some research is going on for establish a relationship of pyrazole derivative as a cannabinoid receptor antagonist.On the other hand some research is also going on for innovate some new eco-friendly process of pyrazole synthesis.After analyzing the biological and pharmaceutical activity of pyrazole I hope pyrazole is going to be a master key of curing different complex diseases.Till today all the reports regarding pyrazole synthesis and its pharmaceutical activity is very impressive and in future pyrazole will take a big platform in new drug synthesis.

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