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Review Article

Review: Anticancer Activity Of Pyrazole

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ABSTRACT

The study of pharmaceutical chemistry is devoted to the search for and development of novel therapeutic medicines. While inorganic substances like antacids, mineral supplements, and radiopharmaceuticals continue to play a significant role in therapy, organic molecules with more focused pharmacological actions are gaining ground. The five and six-membered heterocyclic nitrogen-containing systems, which have demonstrated their effectiveness in fields like anti-bacterial, fungicidal, anti-inflammatory, anticonvulsant, diuretics, and anti-histaminic treatments, are among the most significant in ongoing research. These systems include pyrazole, imidazole, triazoles, thiazolidine, and pyrazole. One endocyclic double bond and two neighboring nitrogen atoms make up the ring of the basic, five-membered heterocyclic molecule known as pyrazoline. The use of pyrazole derivatives as herbicides and active medicines has a long history in the agrochemical and pharmaceutical sectors, and the recent success of pyrazole COX-2 inhibitors has brought attention to the significance of these heterocyclic rings in medicinal chemistry. The more practical microwave method of synthesis has been used by many researchers to create novel pyrazoline derivatives. The distinctive template of pyrazolone is linked to a variety of biological functions, and this review highlights some of them, including anticancer, anti-diabetic, and anti-inflammatory effects.

INTRODUCTION

The study of pharmaceutical chemistry is devoted to the search for and development of novel therapeutic medicines. While inorganic substances like antacids, mineral supplements, and radiopharmaceuticals continue to play a significant role in therapy, organic molecules with more focused pharmacological actions are gaining ground. The five and six-membered heterocyclic nitrogen-containing systems, which have demonstrated their effectiveness in fields like anti-bacterial, fungicidal, anti-inflammatory, anticonvulsant, diuretics, and anti-histaminic treatments, are among the most significant in ongoing research. These systems include pyrazole, imidazole, triazoles, thiazolidine, and pyrazole.

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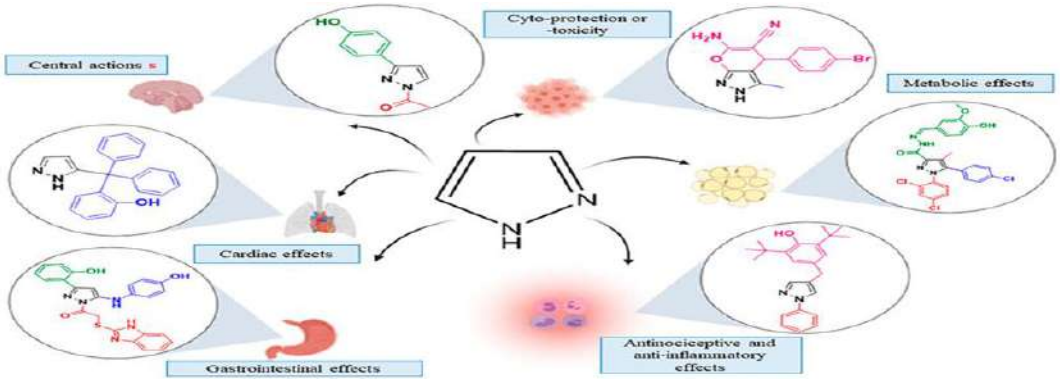
One endocyclic double bond and two neighboring nitrogen atoms make up the ring of the basic, five-membered heterocyclic molecule known as pyrazoline. The use of pyrazole derivatives as herbicides and active medicines has a long history in the agrochemical and pharmaceutical sectors, and the recent success of pyrazole COX-2 inhibitors has brought attention to the significance of these heterocyclic rings in medicinal chemistry. The more practical microwave method of synthesis has been used by many researchers to create novel pyrazoline derivatives. The distinctive template of pyrazolone is linked to a variety of biological functions, and this review highlights some of them, including anticancer, anti-diabetic, and anti-inflammatory effects.



Ludwig Knorr first used the word "pyrazole" in 1883. It designates a group of basic organic compounds with an aromatic ring found in the heterocyclic series. Three carbon atoms and two neighboring nitrogen atoms make up the 5-membered ring structure of these molecules. Although they are uncommon, they are categorized as alkaloids because of the pharmacological effects they have on people. The first organic pyrazole, 1-pyrazolyl-alanine, was discovered in waterm elon seeds in 1959. Pyrazole derivatives have a long history of use in agrochemicals and pharmaceuticals as active medicinal ingredients and herbicides. These heterocyclic rings are significant in medicinal chemistry, as seen by the recent success of pyrazole COX-2 inhibitors Pyrazole-containing pharmaceutical active compounds are crucial in medicinal chemistry, as was discovered through a thorough examination of this family of heterocyclic lead. Small biomolecules that include pyrazole have been produced as potential therapeutic agents for the treatment of neurodegenerative illnesses, particularly those that target the pathologies involved in Parkinson's and Alzheimer's diseases. Due to their intriguing pharmacological characteristics, pyrazole complexes have recently received increased attention as biomolecules. It is possible to identify this heterocycle in a variety of well-known medications that fall into several categories and have a range of therapeutic effects. Pyrazole is π – excess aromatic heterocycle. Electrophilic substitution reaction occurs at position 4 and nucleophilic attack at positions 3 and 5. [fig 1]

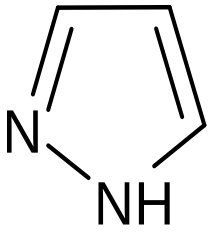


Fig no.1 Structure of Pyrazole

The pyrazole diversely substituted by aromatic and heteroaromatic groups possess number of biological activities, which makes them particularly interesting. Pyrazoles are derived from natural or biological sources. Artificial pyrazole derivatives are utilized often in several fields. Applications range widely, from medicines to agrochemicals. Not fewer than 33

pyrazole-containing medications are available for the treatment of a variety of illnesses, from bacterial infections to cancer and neurological disorders.

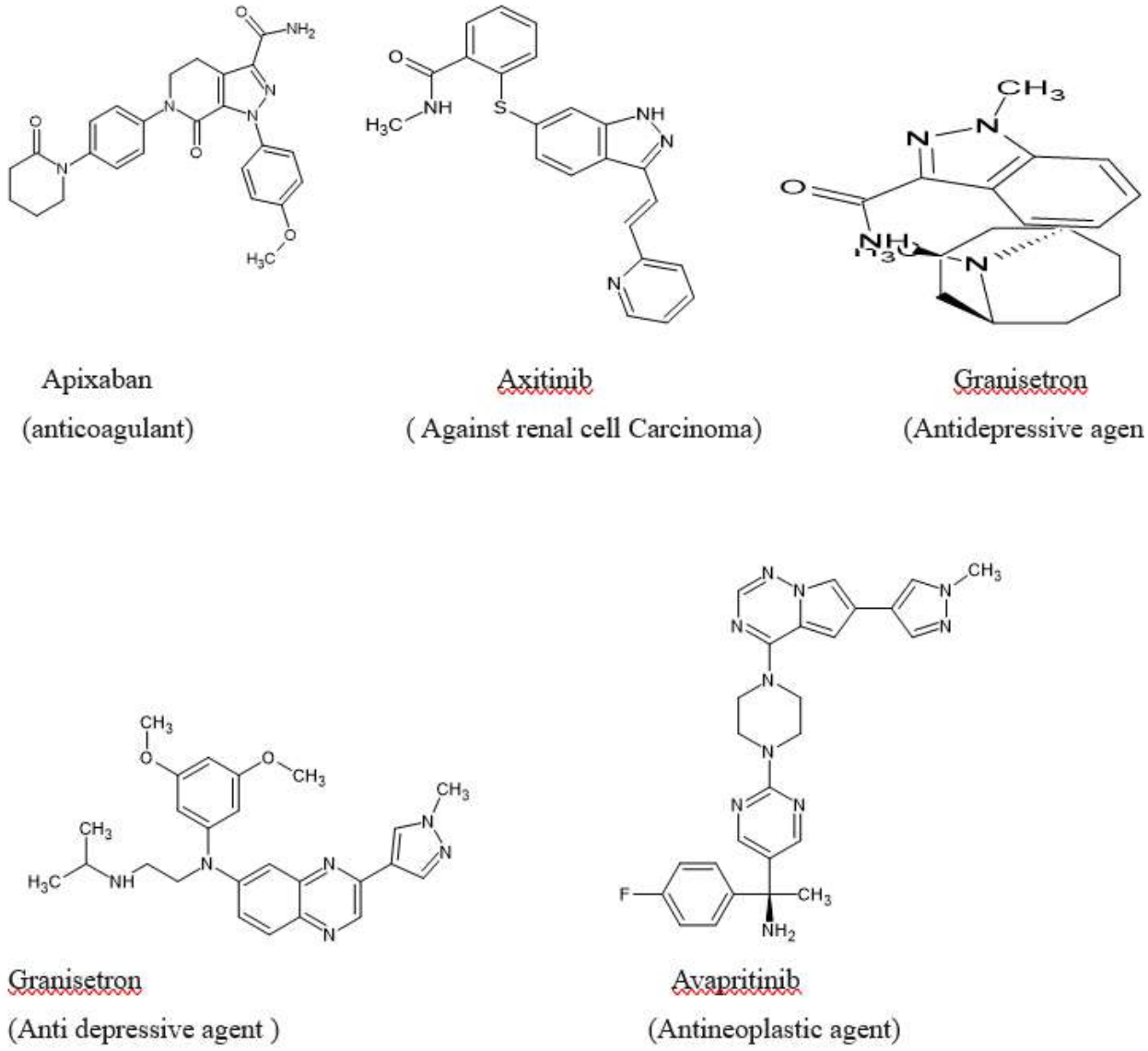


Figure 2. Representative FDA approval pyrazole – containing medicines

Biological activity of pyrazole

Anticancer

Cancer is still responsible for over nine million of all reported deaths worldwide, despite the advances in antineoplastic drug development. Therefore, tremendous efforts are being exerted by the medicinal community to discover novel potent, yet selective, chemotherapeutic anticancer agents. Many heterocyclic compounds have drawn the medicinal chemists' attention due to their anticancer activities and their diverse biological activities. Geographically, Asia is the continent with the highest number of cancer cases, followed by Europe. The World Health Organization reported that worldwide total morbidity and mortality was 6.2 million in 1997, 7.4 million in 2004, and 7.6 million in 2008, It means 13% of all deaths were due to cancer and that the global cancer rate could increase by 50% to 15 million new cases by 2030. According to the World Health

Organization, more than 70% of all cancer deaths occur in low- and middle-income countries. Worldwide, the most prominent cancer types in men are lung, bronchus, prostate, colon, and rectum, and in women are lung, bronchus, breast, colon, and rectum. Due to increasing pollution and the use of carcinogens, this fatal disease is increasing in prevalence. A key feature of cancerous cells is their uncontrolled proliferation; thus, the inhibition of proliferative pathways is believed to be an effective strategy to fight cancer. The ester and amide derivatives of 1-phenyl-3-(thiophen-3-yl)-1H-pyrazole-4-carboxylic acid (Scheme 15) synthesized by Inceler et al.56 exhibited anticancer activities against various cancer cell lines. Among all the synthesized amide derivatives, compounds 70c and 70f possess the best inhibitory effects on cell growth. By fusing pyrimidine, carboxyhydrazide, and ferrocenyl molecules with the pyrazole cap, many derivatives of pyrazole are created, all of which are very potent against lung cancer cells. Ohki et al. (2002) created the 1-(3,5-difluorophenyl)-N-(E) -3-(1-pyrimidin-2-yl)-1H-pyrazol-4-yl-piperidin-4-amine pyrimidinyl pyrazole derivative as a new scaffold for an anti-tumor agent, which also demonstrated antiproliferative activity against human lung cancer cell lines and inhibited tubulin polymerization. A number of unique small molecules of the chemical ethyl1-[20-hydroxy30-aroxypropyl] were described by Wei et al. in 2006. compounds of 3-aryl-1H-pyrazole-5-carboxylate, which have the ability to inhibit lung cancer cell proliferation. Novel 1-arylmethyl-3-aryl-1H-pyrazole-5-carbohyrazide derivatives were created by Xia et al. in 2007 and were used to trigger cell death and suppress the development of A549 cells.A549 cell proliferation is being inhibited by a novel class of 1-(3-(4-chlorophenoxy)phenyl)-3-(4-chlorophenyl)-1H-pyrazole-5 carbohydrazide, according to Fan et al. (2008).

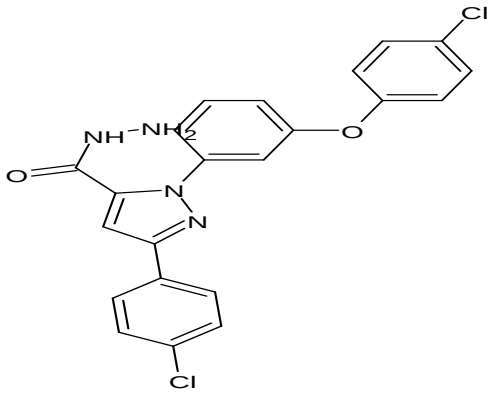
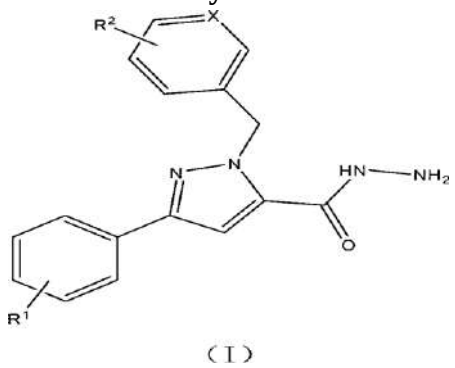


Fig 3. 1-(3-(4-chlorophenoxy)phenyl)- 3-(4-chlorophenyl) 1H-pyrazole-1H-pyrazole-5-carbohydrazide5



(I)

(fig 4) 1-arylmethyl-3-aryl-1H-pyrazole-1H- -carbohyrazide

Balbi et al (2011) prepared a novel pyrazole derivatives 5- methoxy-2-(1-(pyridine-2-yl)-1H-pyrazol-5-yl)phenol and reported their antiproliferative activity in human ovarian adenocarcinoma A2780 cells, human lung carcinoma A549 cells, and murine P388 leukemia cells. Lv et al (2010) reported and synthesized two series of pyrazole derivatives 4,5-dihydro-5-(4-methoxyphenyl)-3-(3,4-dimethylphenyl)pyrazole-1-caboxamide which are designing for potential EGFR kinase inhibitors, as well as antiproliferative activity against MCF-7 with potent inhibitory activity in tumor growth inhibition, would be a potential anticancer activity. Bandgar et al (2010) developed a new series of 3, 5-diaryl pyrazole derivatives 1-(3,5-dichlorophenyl)-4-(4,5-dihydro-1H-imidazol-2-yl)- 1H-pyrazol-5-amine and evaluated for their

anticancer activity.7

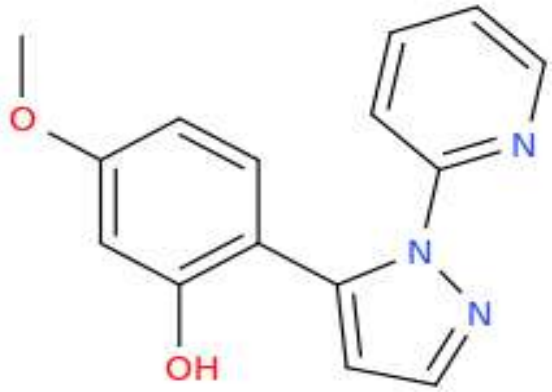
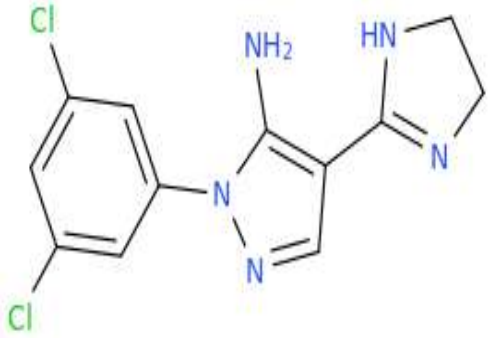
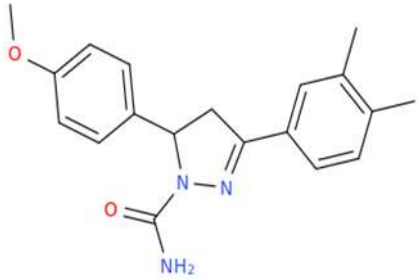


fig 7 5- methoxy-2-(1-(pyridine-2-yl)-1H-pyrazol -5-yl)phenol



1-(3,5-dichlorophenyl)-4-(4,5-dihydro-1H-yl)1H-pyrazol-5-amine



Nassar (2010) synthesized new pyrazoline derivatives by aldol condensation reaction between 3-indolaldehyde 1 and 4-methoxyacetophenone 2 afforded chalcone compounds. Some of the synthesized new compounds were screened against antitumor activity and they have been found to have promosing anticancer activity. Zahran et al (2010) synthesized 2-Aryl1H-indole-3-carbaldehyde derivatives by Claisen–Schmidt condensation with acetophenone derivatives under microwave irradiation condition compared with the conventional heating to afford excellent yields of trans substituted indolylchalcones which subjected to condensation reaction with phenylhydrazine to afford their indolylpyrazoline analogues. The antitumor activity of the synthesized compounds was examined and evaluated against human hepatocellular carcinoma cell line (Hep-G2) as well as the half maximal inhibitory concentration (IC50). Most of them showed high potent antitumor activity. Compound (A) having 4-chloro substitution showed excellent anticancer activity (IC50 = 4.94 mM) against HeLa (human cervix carcinoma cell lines), which implied that lipophilic and electron-withdrawing halobenzyl groups are beneficial for cytotoxic activity against HeLa cell lines. Sankappa Rai U. et al.101 synthesized a new series of pyrazole chalcones (111a–111e) exhibiting anticancer activities against MCF-7 and HeLa cell lines. Compound 111c showed the highest inhibition in human MCF-7 and HeLa cell lines; its highest activity was attributed to the 4-fluoro-phenyl and 5-fluoro-pyridin moieties. The cis-restricted 3-aminopyrazole (fig 3) analogues of combretastatins synthesized by Tsyganov et al.53 as anticancer agents selectively target microtubules. Microtubules are responsible for the formation of the mitotic spindle, which is essential for proper chromosomal separation during cell division. The reported compounds possess antiproliferative and microtubule-destabilizing activities. Molecules, with 3,4,5-trimethoxy groups on ring exhibited the highest antimitotic microtubule-destabilizing effect in sea urchin embryo assay. These compounds also showed considerable cytotoxicity against a panel of 60 human cancer cell lines. In addition, compound inhibited the growth of multidrug-resistant, P-glycoprotein-overexpressing ovarian cancer cells, suggestive of their potential as anticancer agents.

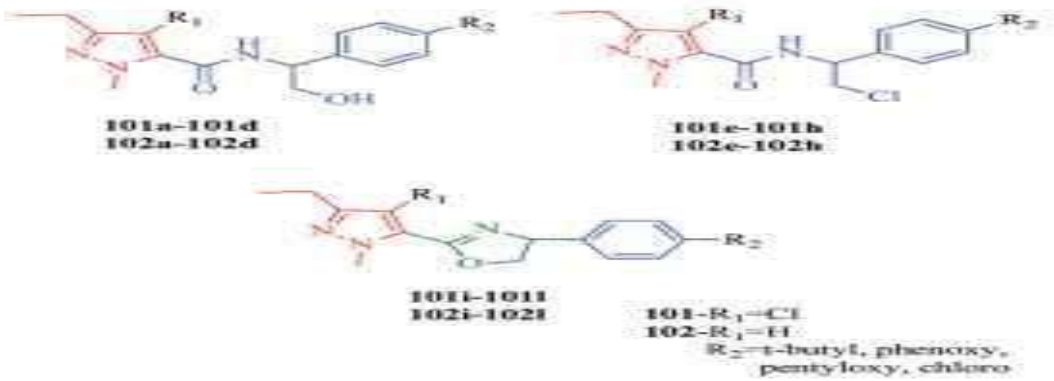


Fig 9 .Pyrazole derivatives as insectisidal and acaricidal agent

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