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Mechanisms and anticancer therapeutic potential of 1,3,4-trisubstituted pyrazole derivatives (mini review)

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Abstract: **With their diverse range of biological actions, 1,3,4-trisubstituted pyrazoles have become significant compounds in medicinal chemistry, especially in the study of cancer. Since 1,3,4- trisubstituted pyrazole derivative have been demonstrated to have analgesic, anti-inflammatory, and anticancer actions, this study focuses on their pharmacological characteristics. Compounds that block cyclin-dependent kinases (CDKs) are notable examples because they cause cell cycle arrest and apoptosis in multiple cancer cell lines. Disrupting angiogenesis and tumor progression, these compounds have also shown encouraging inhibitory efficacy against vascular endothelial growth factor receptors (VEGFRs). According to recent research, several 1,3,4-trisubstituted pyrazoles have strong cytotoxic effects against a variety of cancer types, including solid tumors and leukemia, with IC_{50} value in the lower micromolar ranges. Furthermore, by specifically targeting important enzymes involved in the growth of cancer, some derivatives have been demonstrated to increase the effectiveness of already available chemotherapeutics. The promise of 1,3,4-trisubstituted pyrazoles as lead compounds for the creation of innovative anticancer treatments is highlighted in this review, which also emphasizes the need for more research to completely clarify their therapeutic potential due to their complex methods of action.**

Keywords: **1,3,4-trisubstituted pyrazole, anticancer, VEGFR, CDK.**

I. INTRODUCTION

Pyrazole is a heterocyclic compound with five atoms that contains two nitrogen atoms at positions one and two. Because of its wide range of biological functions and potential for medicinal use, it has been the subject of much literary research [1, 2]. Numerous pharmacological effects, such as anti-inflammatory, analgesic, antipyretic, anticonvulsant, antidepressant, anticancer, antibacterial, and antifungal qualities, have been found for pyrazole derivatives [3-5] **(Figure 1)**.

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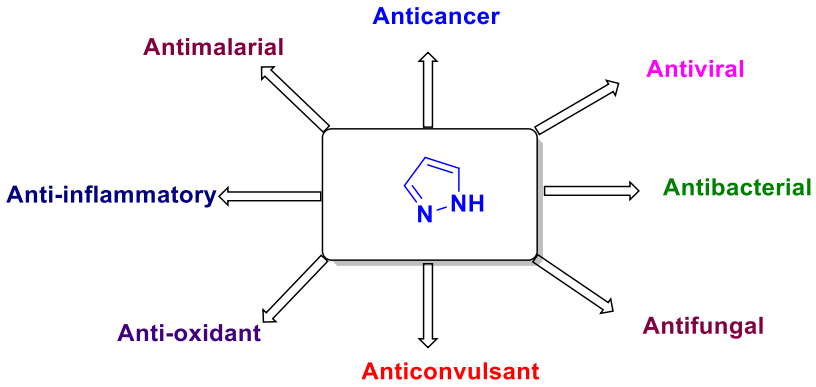

Figure 1. Different biological activities of Pyrazole

For instance, the pyrazole derivative celecoxib **(Figure 2)** is used as a non-steroidal anti-inflammatory medicine (NSAID) to treat arthritis related pain in addition to inflammation. It decreases the synthesis of prostaglandins that resulted in inflammation and specifically inhibits the activity of the cyclooxygenase-2 (COX-2) enzyme. [6]. Similarly, another pyrazole derivative that has anti-inflammatory qualities through blocking COX enzymes is pirazolac **(Figure 2)**. Additionally, numerous medications containing pyrazoles have been authorized for the treatment of various tumor types. [7], like crizotinib (Figure 2), which treat metastatic non-small cell lung cancer by blocking protein kinases that promote angiogenesis and tumor development [8]. Another illustration is the pyrazole derivative ruxolitinib (Figure 2), which is used to treat intermediate to high-risk myelofibrosis [9].

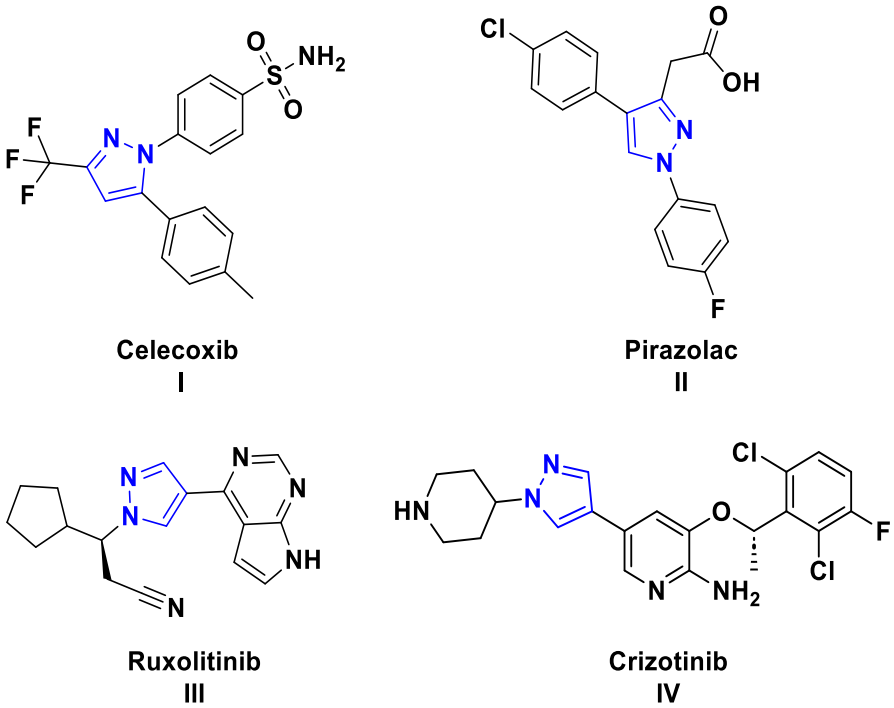

Figure 2. Clinically used Pyrazole derivatives.

By creating stable complexes with transition metal ions including copper, iron, and zinc, pyrazole derivatives have been investigated for their metal chelating capabilities in addition to their pharmacological effects. By focusing on metalloenzymes implicated in tumor formation, these metal complexes have been studied for their possible application in cancer treatment. [10]. The biological activities and therapeutic potential of 1,3,4-trisubstituted pyrazole derivatives will be the particular focus of this review, along with an emphasis on their mechanisms of action and uses in the development of new anticancer drugs.

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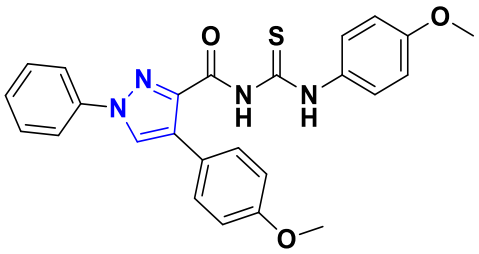
II. BODY OF ARTICLE

2.1 Mechanisms of action of Pyrazole moiety as anticancer

N-substituted pyrazoles have been utilized for their potential as agents against leukemia [11, 12], tumors [13, 14], proliferation [15], angiogenesis [16], DNA interaction [17], apoptosis [18], autophagy [19], and tubulin [14]. Through the inhibition of several enzymes, proteins, and receptors that are essential for cell proliferation, they have demonstrated impressive anticancer effects. Cyclin-dependent kinase (CDK) is one of the targets of pyrazole. [14], vascular endothelial growth factor receptor (VEGFR) [20], and tumor growth factor (TGF)-b type [21].

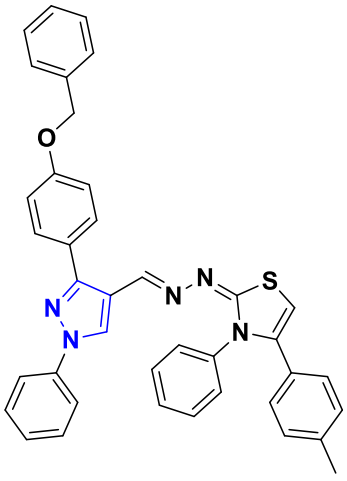
2.1.1 CDK inhibitors

A family of kinases known as CDKs controls the course of the cell cycle and is frequently dysregulated in cancer. CDKs are desirable targets for the development of anticancer drugs because their inhibition can result in cell cycle arrest and apoptosis [22-24]. Compounds based on pyrazoles have demonstrated encouraging inhibitory effects on CDKs, which can reduce the development of tumors and the proliferation of cancer cells [25, 26]. A study conducted by Sun, J., Lv, X. H., et al [27] investigated pyrazole-carboxamide derivatives and found that compound **V** has a substantial inhibitory effect on CDK2 with an IC_{50} of 25 nM. With an IC_{50} range of 0.75 µM to 4.21 µM, this compound efficiently suppresses the growth of cancer cell lines H460, MCF-7, and A549.

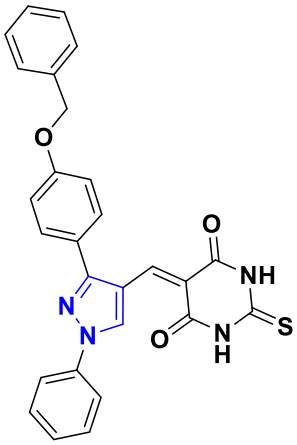


V IC_{50} = 25 nM

A number of new 1,3,4-trisubstituted pyrazoles [28], have been synthesized and investigated for their ability to inhibit various HepG2, UO-31, and HCT116 cancer cell lines. **VIa** and **VIb** showed the strongest anticancer effects among the substances that were studied. In contrast to compound **VIb**, which exhibited IC_{50} values of 1.2 µM, 1.8 µM, and 1.5 µM, respectively, compound **VIa** demonstrated IC_{50} values of 1.5 µM against HCT116, 2.0 µM against UO-31, and 1.8 µM against HepG2. Subsequent research showed that both substances caused HepG2 cells to underwent cell cycle arrest and apoptosis during the G2/M phase. With IC_{50} values of 2.38 µM and 1.52 µM, respectively, **VIa** and **VIb** significantly reduced CDK1 activity, suggesting their potential as effective

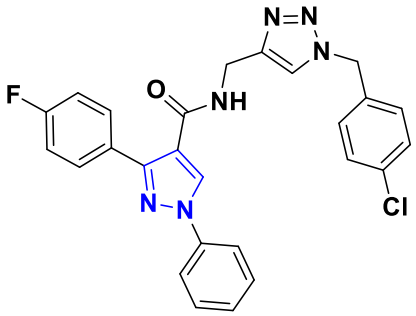


VIa IC_{50}= 2.38 µM



VIb IC_{50}= 1.52 µM

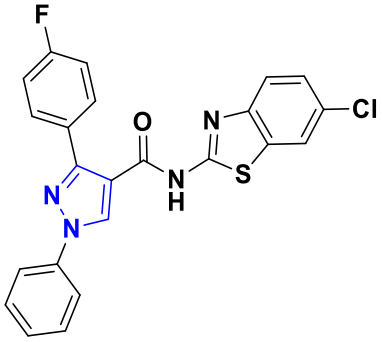
As CDK1/Cdc2 inhibitors, a number of new N-((1-benzyl-1H-1,2,3-triazol-4-yl) methyl)-1,3-diphenyl-1H-pyrazole -4-carboxamide hybrids were synthesized [29]. With a GI_{50} value ranging from 0.13 to 0.7 µM, compound **VII** demonstrated strong growth inhibitory effect against cancer cell lines (MIAPaCa-2, MCF-7, and HeLa), exceeding the control medication nocodazole (0.81–0.95 µM). At a concentration of 50 nM, compound **VII** decreased CDK1 overexpression in MCF-7 cells and resulted in cell cycle arrest at the G2/M phase, according to flow cytometry.



VII IC_{50} = 50 nM

2.2.2 VEGFR inhibitors

Angiogenesis depends on vascular endothelial growth factor (VEGF), which is bound by VEGF receptors (VEGFRs) on cell surfaces to support angiogenesis, tumor development, and metastasis. [30, 31]. Therapeutic drugs that target the VEGF/VEGFR pathway can stop the growth of cancer by interfering with the production of blood vessels and the spread of metastasis [32, 33]. An example of that approach, Reddy, T. S., et al [34] synthesized a series of new pyrazolo-benzothiazole hybrids and evaluated their cytotoxic effects on a range of cancer cell lines, including glioblastoma (U87MG), colon (HT-29), prostate (PC-3), lung (A549), and a normal human embryonic kidney cell line (Hek-293T). With IC_{50} values ranging from 3.17 to 6.77 µM, compound **VIII** demonstrated strong cytotoxicity against all tested cancer cell types. Additionally, compound **VIII** showed antiangiogenic qualities in an *in vivo* model utilizing transgenic zebrafish (Tg(flila:EGFP)) and significant in vitro inhibitory effects on VEGFR-2 with an IC_{50} value of 97 nM.



VIII IC_{50} = 97 nM

Pyrazole-pyrazole compounds were developed by Dawood et al., who then assessed their in vitro inhibitory effects on MCF7 cells [20]. With an IC_{50} of 16.50 µM, compound **IX** had the most activity among the investigated compounds, whereas the reference medication, tamoxifen, had an IC_{50} of 23.31 µM. Furthermore, a few of these pyrazole compounds efficiently lower VEGFR-2 levels. Interestingly, hybrid **IX** showed 78% suppression of VEGFR-2 (IC_{50} = 0.82 µM), making it a viable option for anti-breast cancer treatment that targets this receptor. Subsequent research showed that compound **IX** suppressed development in the G2/M phase and caused pre-G1 apoptosis through the activation of caspase-3, showcasing notable pro apoptotic activity.

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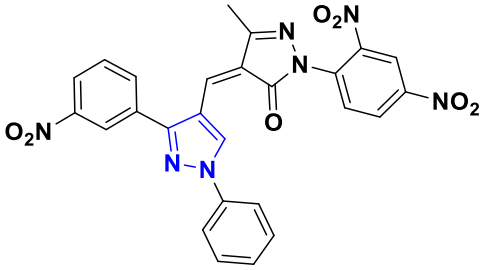
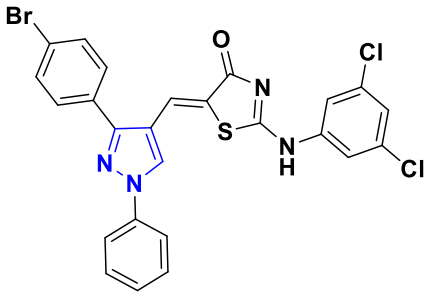


IX IC_{50} = 0.82 µM

2.2.3 Topoisomerase inhibitors

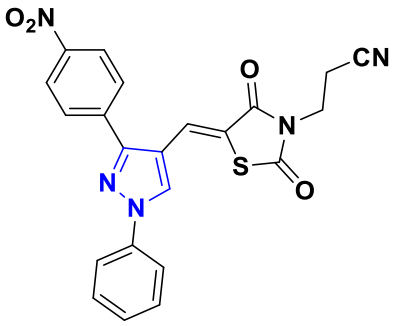
By enabling the temporary cleavage and rejoining of DNA strands during replication, transcription, and recombination processes, DNA topoisomerases specifically type IIA isoforms are acknowledged as promising targets in the treatment of cancer. These enzymes are essential in reducing the torsional strain of DNA [35-37]. Several tumor cells have been found to exhibit dysregulation of type IIA topoisomerases, which is typified by elevated expression and activity in contrast to their non-transformed counterparts [38-40].

In a work by Bhat et al. [41] a new group of thiazolidinone-pyrazole hybrids was designed and synthesized. The compounds' anticancer properties against MDA-MB231 cells were assessed *in vitro*. With an IC_{50} value of 29.8 µM, compound X showed the most inhibitory action among the compounds tested against MDA-MB231 cells. These results highlight how important dichloro-substituents are for enhancing the compounds' efficacy on the arylamino thiazolidinone nucleus.

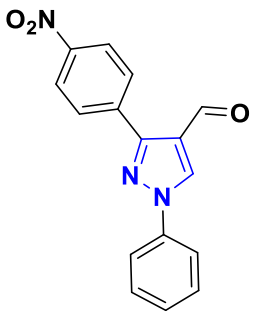


X IC_{50} = 29.8 µM

Alshammari et al. [42] developed a new derivative of pyrazole-tethered thiazolidine-2,4 -dione as part of a research. The antitumor activity of intermediate and final compounds was assessed by the researchers using MCF7 and SW480 cell lines. With IC_{50} values of 190 and 170 µg/mL, respectively, compounds **XIa** and **XIb** demonstrated strong inhibitory action against SW480 cells among the investigated compounds. Similarly, with IC_{50} values of 90 and 140 µg/mL, respectively, these substances demonstrated significant cytotoxicity against MCF7 cells.



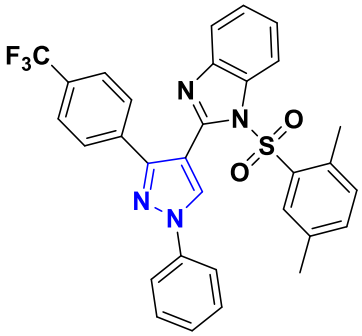
XIa



XIb

2.2.4 Tubulin polymerization inhibition

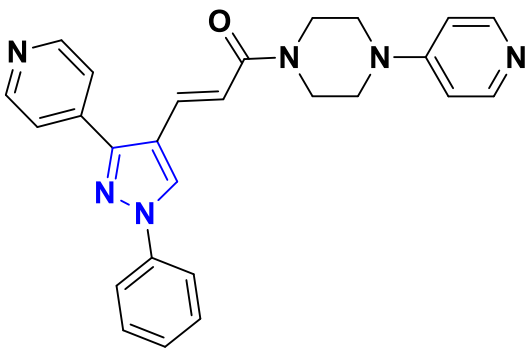
Microtubules are ubiquitous hollow tubular structures in cells that are made up of the small protein component tubulin [43]. Tubulin is essential for eukaryotic cell processes such motility, trafficking, signaling, and proliferation because it polymerizes to form microtubules. It has thus emerged as a primary target in the creation of anticancer drugs [44]. Tumor cells divide rapidly through tubulin polymerization. Cytotoxic medications that prevent tubulin polymerization have therefore been developed and are crucial components of chemotherapy [45]. Colchicine, which bound to tubulin and prevented microtubule production, was the first known chemical to exclusively target microtubules [46]. Wang et al. [47] synthesized and developed novel pyrazole-benzene sulfonamide hybrids grafted with benzimidazole, and assessed their anticancer potential in vitro as potential inhibitors of tubulin polymerization. With IC_{50} values ranging from 0.15 to 0.33 µM, compound **XII** had the strongest antiproliferative effect against A549, HeLa, HepG2, and MCF7 cell lines when compared to colchicine and CA-4 as positive controls. With an IC_{50} of 1.52 µM, compound **XII** similarly demonstrated significant inhibitory effects on tubulin assembly *via* binding to the tubulin's colchicine site. Similar to CA-4, compound **XII** was shown to suppress tubulin polymerization through a concentration-dependent mechanism. Compound **XII** as well.



XII

2.2.5 PI3K/AKT and MAPK/ERK inhibitor

PI3K/AKT and MAPK/ERK are two crucial signaling pathways in cancer. Inhibiting or blocking these two crucial mechanisms simultaneously is an interesting cancer therapeutic approach [48-50]. A group of 1,3-diarylpyrazole acrylamide derivatives were tested for their in vitro anticancer properties against lung cancer cell lines (A549), malignant mesothelioma (SPC212), and mesothelial cells (MeT-5a) by Demiroglu-Zergeroglu et al [51] Compound **XIII** showed exceptional antiproliferative efficacy among the produced compounds. At doses greater than 10 µM over a 24-hour period, compound **XIII** was shown to dramatically suppress the phosphorylation with the expression of ERK1/2 and AKT proteins and to start caspase-dependent death in SPC212 cells. Furthermore, it was shown that compound **XIII** induced G2/M cell cycle arrest in a way that was dependent on both cell and dosage, with SPC212 cells are more susceptible compared to A549 cells. Consequently, compound **XIII** had strong inhibitory effects on the MAPK/ERK and PI3K/AKT pathway, suggesting that it may be used as an anticancer therapy.



XIII

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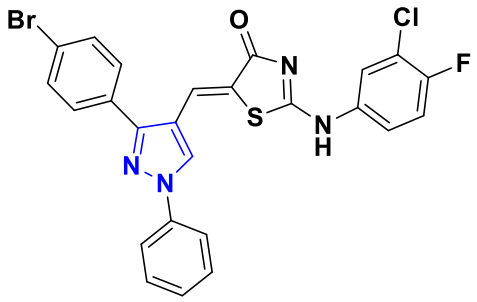
2.2.6 MDM2 inhibitors

MDM2 is a significant inhibitor of the tumor suppressor gene p53. MDM2 overexpression has the ability to attach to p53 and stop its transcriptional activity, which encourages tumor development. Tiny molecule inhibitors that target the MDM2-p53 link have been designed in order to effectively eactivate the p53 pathway and produce anticancer effects. [52-54].

A new series of thiazolidinone pyrazole hybrids was developed and manufactured by Bhat et al. [55] who evaluated the compounds' anticancer effects on Ehrlich ascites carcinoma (EAC) and MDA-MB231 cells *in vitro* and *in vivo*. Compound **XIV** showed better cytotoxicity against EAC than the reference medication, which had an IC_{50} of 1954.4 µM, with an IC_{50} of 901.3 µM. Molecular docking experiments showed that compound **XIV** has a high binding affinity for the MDM2 protein.



XIV

III. CONCLUSION

1,3,4-trisubstituted pyrazole derivatives are a potential family of compounds in medicinal chemistry with a wide range of biological effects, particularly in the field of anticancer medicine. Their many mechanisms of action, such as the inhibition of crucial enzymes like cyclin-dependent kinases (CDKs) and vascular endothelial growth factor receptors (VEGFRs) among others, demonstrate their potential as powerful anticancer medications. In addition to having potent cytotoxic effects on several cancer cell lines, these chemicals can also disrupt angiogenesis and induce apoptosis, making them valuable leads for therapeutic development.

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