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Recent Advances On Antiproliferative and Anti-inflammatory Potential Of Pyrazoline Derivatives

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Abstract: Pyrazolines are nitrogen-containing five-membered heterocyclic scaffolds that have attracted considerable interest in medicinal chemistry due to their diverse antioxidant, analgesic, anti-inflammatory, antiviral, antimicrobial, antimalarial, anticonvulsant, antitumor, and antidiabetic activities. The presence of this moiety in several marketed drugs against various diseases has proved its significance in the pharmaceutical industry. The present review summarizes the recent progress of pyrazoline against cancer and inflammation. The information will benefit researchers in their study as it will provide new ideas for rational drug development strategies for more effective pyrazoline derivatives as anticancer and anti-inflammatory agents.

Keywords: pyrazolines; anticancer; anti-inflammatory; drug development.

1. Introduction

Heterocyclic compounds serve as building blocks for synthesizing important bioactive agents with improved efficacies over recent centuries [1]. Among them, pyrazolines are important in medicinal chemistry as they exhibit diverse pharmacological potential [2]. Pyrazoline, a reduced form of pyrazole, is a five-membered ring with two nitrogen atoms in the ring. It exists in three isomeric forms: 1-pyrazoline (**1**), 2-pyrazoline (**2**), and 3-pyrazoline (**3**), which differ in the position of the double bond [3](Fig1). Among the isomeric forms, 2-pyrazoline has a special role in medicinal chemistry and drug discovery, attributed to its higher stability and pharmacological actions [4].

Pyrazoline is either synthesized by cyclization of σ,β-unsaturated ketones with hydrazine, or phenylhydrazine in an acidic medium like glacial acetic acid using Knovenagel and Fischer reactions or cyclization of chalcones with hydrazine in a basic medium like triethylamine using a Michael reaction [5,6]. Besides, they are isosteres for imidazole, thiazole, and oxazole. Pyrazolines are known to display numerous bioactivities such as anti-inflammatory, antitumor, antibacterial, antifungal, antidiabetic, antioxidant, anticonvulsant, antidepressant, and analgesic [7-10].

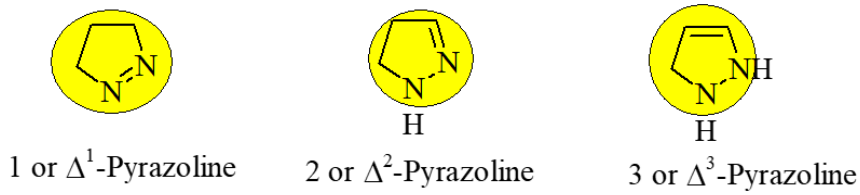

Figure 1. Five-membered nitrogen heterocycles

Pyrazoline pharmacophore can be found in many therapeutic drugs that treat various ailments (Fig.2) [11,12]. Antipyrine, aminopyrine, phenylbutazone, celecoxib, and famprazone are analgesics and anti-inflammatory drugs [13,14]. Crizotinib and Ibrutinib act as anticancer agents for tyrosine kinase receptor inhibition and targ*et al*K, MET, and ROS1 kinases [15]. Ramifenazone is a cyclooxygenase inhibitor [14], and Tozasertib VX-680 is an aurora kinase inhibitor and an effective anti-cancer drug candidate [16].

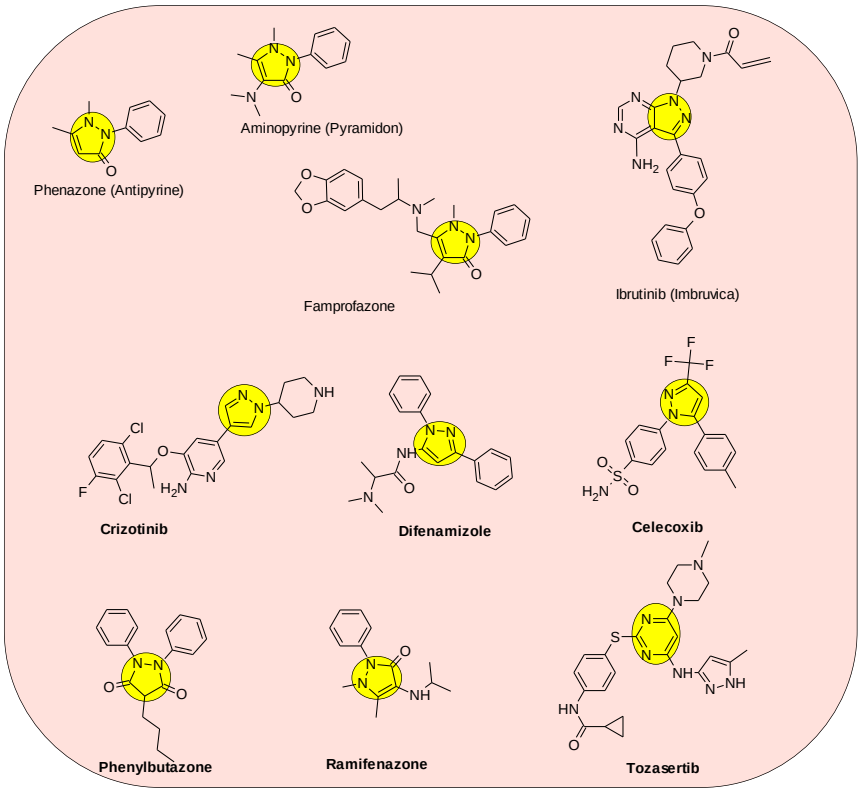

Figure2. Pyrazoline-containing anticancer and anti-inflammatory drugs.

Cancer and inflammation are linked to each other [17]. Recent studies report that inflammation is the precursor of tumor progression. Cancer, the leading cause of mortality globally, involves transforming normal cells into abnormal proliferative cells that tend to spread all over the body [18]. Furthermore, it is associated with drug resistance and unwanted adverse effects. Moreover, cancer is associated with severe infections and chronic inflammation. It is also evident that inflammatory cells play a critical role in developing the tumor microenvironment, which is necessary for the neoplastic process, fostering proliferation, survival, and migration. In this context, anti-inflammatory treatment has been fruitful against early neoplastic development and malignant advancement in cancer prevention [19].

The current review article summarizes the anticancer and anti-inflammatory activities of synthesized pyrazoline derivatives for the past five years (2019-2023). The provided information will be beneficial for future studies and in searching for rational drug development strategies to synthesize more potent anti-inflammatory and anticancer pyrazoline derivatives.

2. Anticancer Potential of Pyrazoline Derivatives

Mansour *et al*., in 2020, reported pyrazoline hybrids containing thiazoline scaffolds as promising cytotoxic agents[20]. Amongst them, hybrid **1** bearing a halogen atom at the *para* position displayed promising cytotoxicity with IC_{50} 6.52, 6.71, and 6.19 μM against MCF7, HepG2, and HCT116 cell lines (Fig. 3).

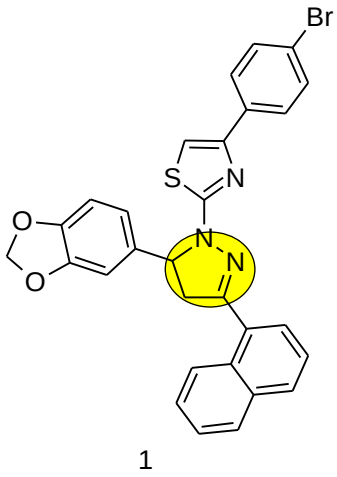

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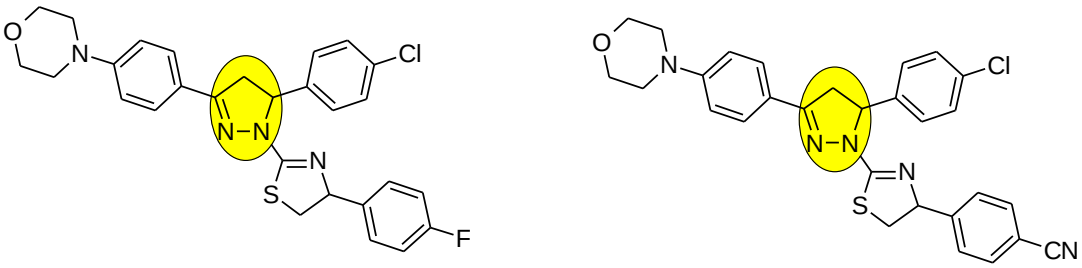
Figure 3. Cytotoxic agents pyrazoline derivatives.

Thiazolyl pyrazoline derivatives 2 and 3, reported by Sever *et al*. in 2019 exhibited an antiproliferative effect with IC_{50} values of 8.95 and 10.76 μM against A549 cell line and IC_{50} 9.59 and 8.05 μM against MCF7 cell lines, compared to erlotinib with IC_{50} 22.35μM (A549) and 8.24 (MCF7) (Fig. 4) [21].



2 **3**

Figure 4. Thiazolyl pyrazoline derivatives.

Matiadis *et al*. [22] in 2020 reported curcumin-pyrazoline hybrid 4 as a potent antiproliferative candidate with an IC_{50} of 53.09 μM, compared to the standard drug doxorubicin (IC_{50} 85.11 μM) towards MCF7 cell line (Fig. 5).

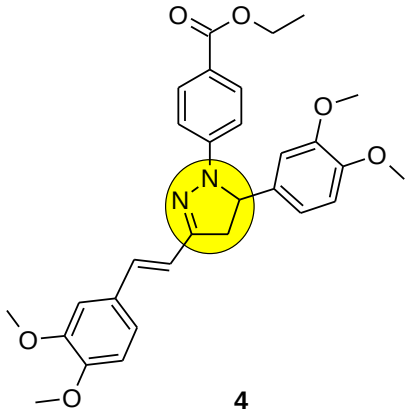


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Figure 5. curcumin-pyrazoline hybrid.

In 2020, Shu *et al.* [23]. reported hybrid 5 containing indole-pyrazoline with better topoisomerase 1 inhibitory activity than the standard drug Camptothecin dosed dependently (Fig. 6).

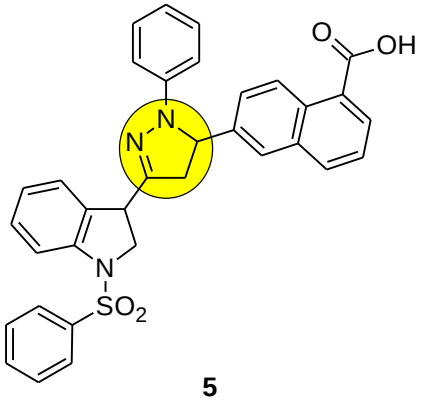

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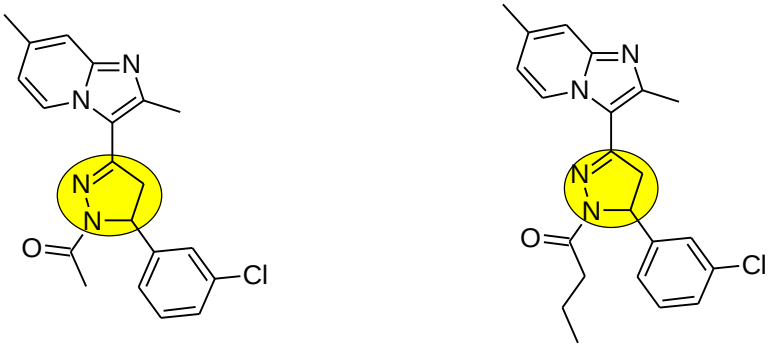
Figure 6. indole-pyrazoline inhibitory.

Kuthyala *et al*. synthesized imidazopyridine-pyrazoline hybrids 6 and 7 as anticancer agents. Compounds 6 and 7 displayed significant cytotoxicities against lung A549 carcinoma with IC_{50} 43.56 and 44.49 µM, respectively (Fig.7) [24].



6 **7**

Figure 7. Imidazopyridine-pyrazoline anticancer agents.

Xu *et al*. reported pyrazoline derivatives 8 bearing a benzothiophene nucleus emerged as a potent cytotoxic compound with IC_{50} = 3.57 µM towards liver HCT-116, in comparison to cisplatin, which displayed IC_{50} = 8.45 µM. Also, it caused the induction of apoptosis by arresting HepG2 cells in the G2/M phase (Fig. 8) [16].

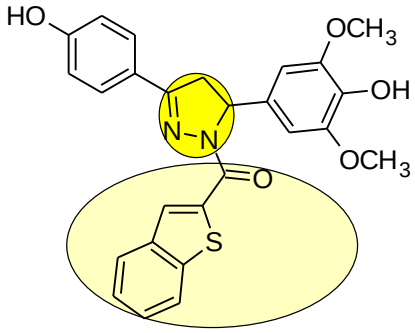


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Figure 8. Pyrazoline-benzothiophene cytotoxic compound.

Quinoline-pyrazoline hybrid 9, reported by Charris *et al*. in 2019, exhibited a promising selectivity index with IC_{50} values of 3.17 and 0.94 µM (24 h) against Jurkat E6.1 and HL_{60} cell lines, respectively (Fig.9) [25].

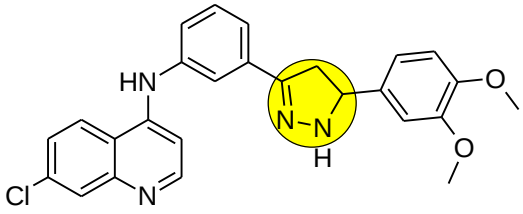

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Figure 9. Quinoline-pyrazoline anticancer hybrid.

Pyrazoline derivative 10-bearing thiazole and quinoline exhibited remarkable anticancer activity with IC_{50} of 0.277, 0.16, and 1.27 µM towards MCF7, HeLa, and DLD1 carcinomas, respectively. Also, it displayed EGFR inhibition with IC_{50} 31.80 nm, compared to control gefitinib (IC_{50} 29.16 nm) (Fig. 10) [26].

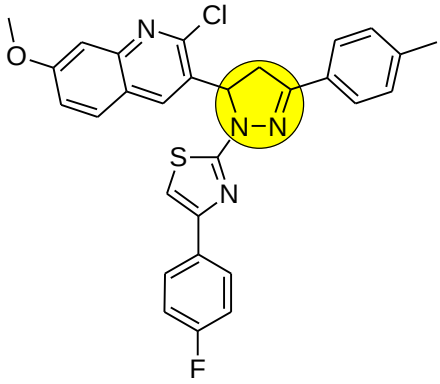

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Figure 10 Anticancer targeting pyrazoline.

Quinolinone-pyrazoline hybrid 11 has been identified as a RAD51-BRCA2 gene disruptor by Bagnolini *et al*. in 2020 (Fig. 11) [27].

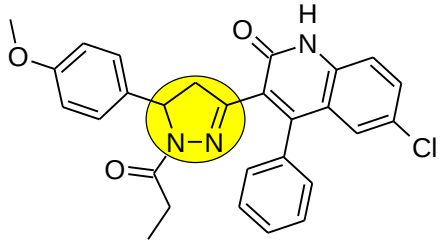

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Figure 11. Quinolinone-pyrazoline molecule.

El-Sakka *et al*. in 2019 reported Pyrazoline-quinazolinone derivatives **12** that caused cytotoxicity of HepG2 cells with IC_{50} of 194 µM (Fig. 12) [28].

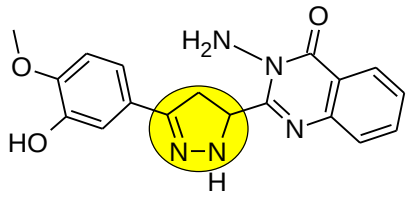

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Figure 12. Pyrazoline-quinazolinone derived anti-cancer agent.

Indole-pyrazoline hybrid 13 reported by Qi *et al* displayed selectivity against colorectal HCT119 and HT29 with GI50 values of 1.37 and 1.22 µM, respectively (Fig. 13) [29].

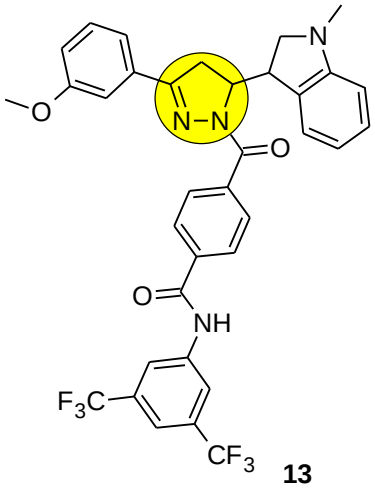

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Figure 13. Indole-pyrazoline hybrid.

Kocyigit *et al*. reported tetrahydro-methanoisoindolodione incorporated pyrazoline derivative 14 as an anticancer agent with an IC_{50} value of 50.05 µM against C6 rat gliocarcinoma cells (Fig.14) [30].

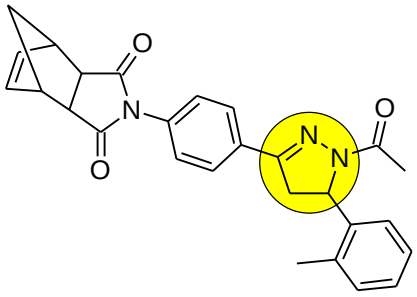

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Figure 14. Tetrahydro-methanoisoindolodione incorporated pyrazoline derivative.

Pyrazoline derivative 15 bearing indole C-glycoside reported by Kumari *et al*. exhibited promising cytotoxicity against MCF-7 (IC_{50} 4.67 µM) and less activity against MDA-MB-231 (IC_{50} 35.5 µM) (Fig. 15) [31].

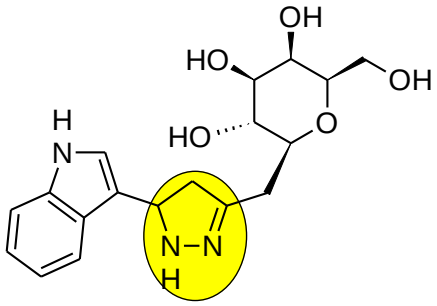

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Figure 15. Pyrazoline- indole C-glycoside derivative.

Santosh *et al*. reported thiazole-bearing pyrazoline derivative 16, which exhibited moderate cytotoxicity towards MDA-MB-231 and colon HT-29 with IC_{50} values of 24.78 and 26.64 µM, respectively (Fig. 16) [32].

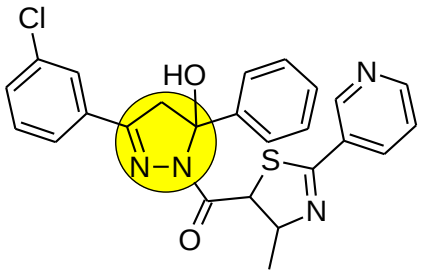

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Figure 16. Thiazole-bearing pyrazoline derivative.

Benzothiazole-linked pyrazoline hybrid 17 reported by Tugrak *et al*. displayed moderate cytotoxicity with IC_{50} values in the range 10.8-26.0 μM towards squamous adenocarcinomas Ca9-22, HSC-4, HSC-2 and HSC-3 (Fig. 17) [33].

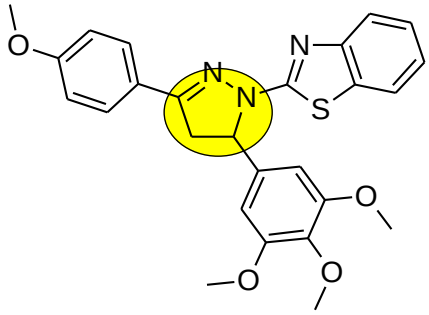

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Figure 17. Benzothiazole-linked pyrazoline hybrid

Pyrazoline derivative 18 bearing a pyrimidinone and anthracene moieties emerged as potent antiproliferative agents against hepatocellular HepG2 carcinoma with an IC_{50} 4.22 μg/mL, comparable to doxorubicin (IC_{50} 5.43 μg/mL) (Fig. 18) [34].

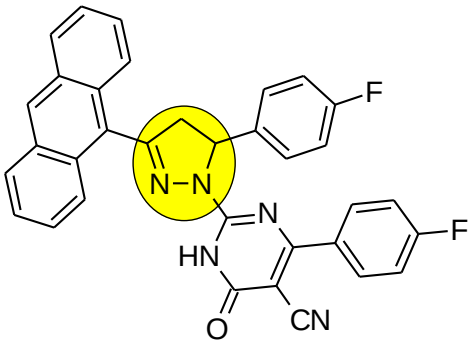

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Figure 18. Pyrazoline bearing a pyrimidinone and anthracene derivative.

Shaik *et al*. reported chalcone-isoxazole pyrazoline conjugate 19 as a promising cytotoxic molecule towards prostate DU-145 exhibiting IC_{50} of 2 μg/mL and non-toxic to normal human L02 cells (Fig. 19) [35].

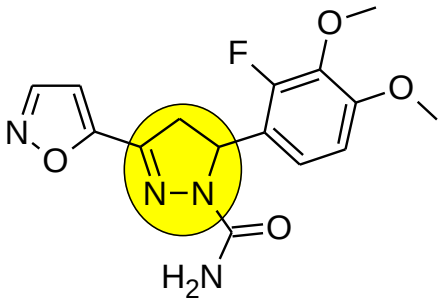

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Figure 19. Chalcone-isoxazole pyrazoline conjugate.

Triazole tethered naphthalimide pyrazoline derivative 20 reported by Kumar *et al*. exhibited inhibitory activity with IC_{50} of 62.23 µM, compared to tamoxifen (IC_{50} of 50 µM) (Fig. 20) [36].

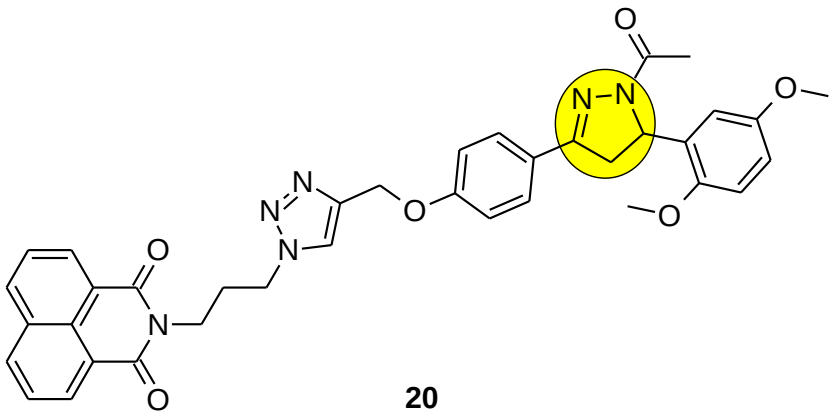

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Figure 20. Triazole tethered naphthalimide pyrazoline derivative.

Silveri *et al*. reported N-carbothioamide pyrazoline 21 (Fig. 21) bearing triazole sulphonamide moiety as cytotoxic against HeLa and MCF-7 with IC_{50} 8.33 and 11.08 µg/mL, respectively [37].

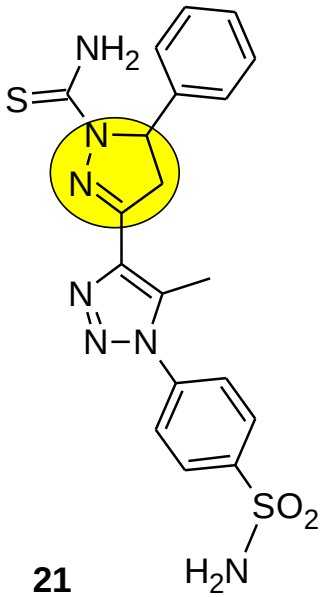

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Figure 21. N-carbothioamide pyrazoline bearing triazole sulphonamide molecule.

Nawaz *et al*. reported carboxamide-linked pyrazoline derivatives 22 and 23 with better cytotoxicity with IC_{50} 10.3 and 4.6 µM, respectively, compared to doxorubicin against lung

A549 cancer cell line[38]. Also, these compounds inhibited the EGFR enzyme with IC_{50} 6.5 and 3.65 µM and induced apoptosis as indicated by DAPI, Annexin V-FITC, and propidium iodide staining. Furthermore, these compounds were safe up to the dose of 500 mg/kg b.w. (Fig. 22).

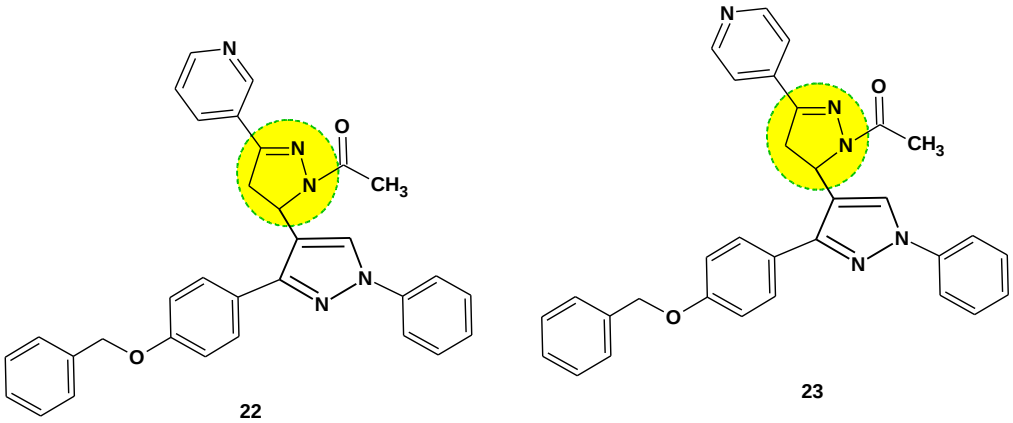

Figure 22. Carboxamide-linked pyrazoline derivatives.

Fakhry *et al*. reported thiazolyl-pyrazoline conjugates 24 and 25 as the potent anticancer agents towards MCF-7 with IC_{50} 4.08 and 5.64 µM, respectively, compared to lapatinib (IC_{50} = 5.88 µM) [39]. Both of them showed remarkable inhibition effects against EGFR (IC_{50} = 0.024 and 0.005 µM) and HER2 (IC_{50} = 0.047 and 0.022 µM), in comparison to reference drug lapatinib (IC_{50} = 0.007 and 0.018 µM). They also showed the ability to induce apoptosis by cell cycle arrest in the G1 and G1/S phases, respectively. Furthermore, *in silico* studies showed their necessary binding with the important amino acids required for EGFR and HER2 inhibition (Fig.23)

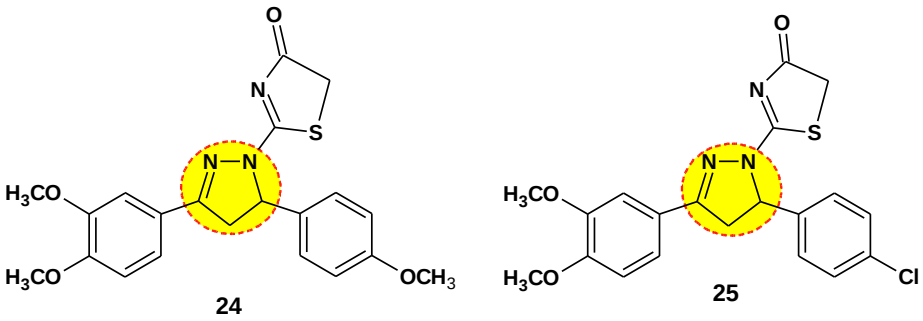

Figure 23. thiazolyl-pyrazoline conjugates the potent anticancer agents.

Pyrazole-linked pyrazoline hybrid 26 was reported by Rana *et al.* [40]. demonstrated remarkable anticancer potential against the cervical HeLa cancer cell line with an IC_{50} of 23.6 µM and the lung A549 cancer cell line with an IC_{50} of 37.59 µM (Fig. 24).

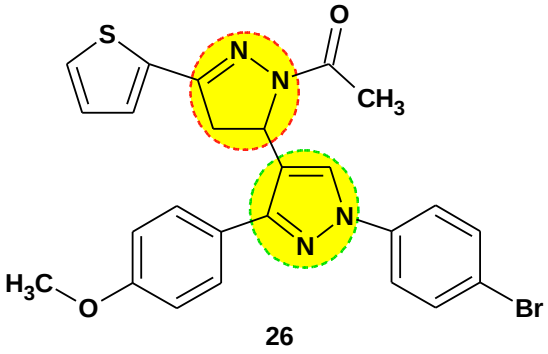

Figure 24. Pyrazoline hybrid.

Novel pyrazoline-thiazolidinone derivative 27 reported by Elewa *et al.* [41]. emerged as a strong cytotoxic candidate against HCT-116 and MCF-7 cells with IC_{50} 3.08 and 5.05µM, compared to reference drug doxorubicin (IC_{50}= 8.92 and 7.27µM). Besides, it was found to be non-toxic with higher IC_{50} values against WISH cells (Fig. 25).

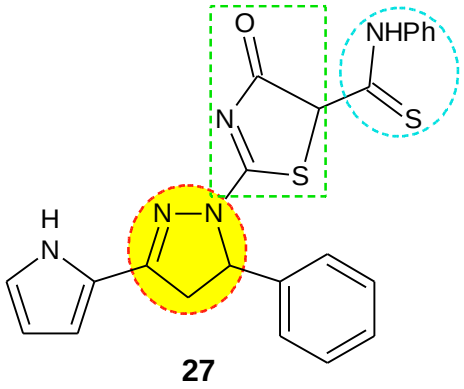

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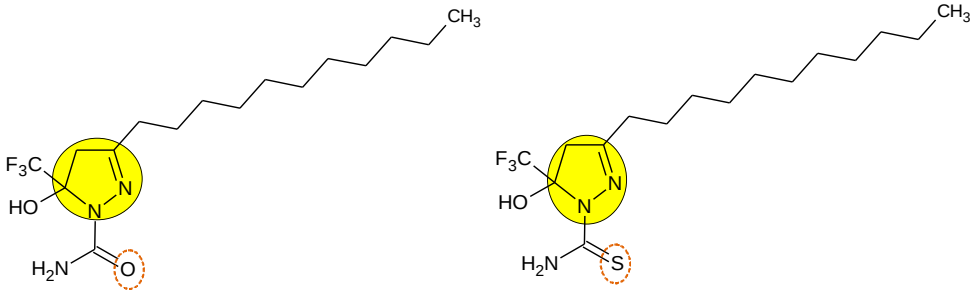
Figure 25. Novel pyrazoline-thiazolidinone derivative.

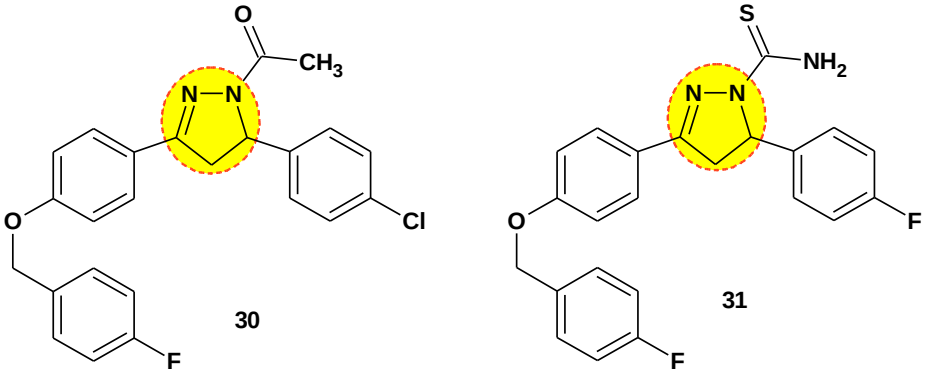
Antiqueira-Santos *et al* [42]. reported that pyrazoline fatty-chain derivatives 28 and 29 bearing a lipophilic chain produced an excellent effect on the viability of B16F10 cells (Fig. 26).



28 29

Figure 26. Pyrazoline chain bearing a lipophilic chain derivative.

Alkamaly *et al.* [43]. reported pyrazoline hybrids 30 and 31 with promising anticancer activities (IC_{50} = 1.30–7.18 µM) as compared to doxorubicin (IC_{50} = 5.12–7.33 µM) towards prostate PC3, hepatocellular HepG2, and breast MDA-MB-231 carcinoma cells. Also, they were non-toxic against normal WI-38 cells. Furthermore, compounds 30 and 31 have emerged as strong dual inhibitors against EGFR (IC_{50} 0.21 and 0.23 µM) and VEGFR2 (0.22 and 0.21 µM). However, they exhibited moderate inhibitory effects for HER2 and FGFR2. Interestingly, these two compounds promoted apoptosis by upregulating Bax, caspase-3, and p53 and downregulating Bcl-2 (Fig. 27).



30 31

Figure 27. pyrazoline hybrids.

Bakar *et al*. synthesized fused pyrazoline derivatives 32 (IC_{50} 21.4 ± 1.32 μM) and 33 (IC_{50} 25.96 ± 5.84 μM) with selective inhibition towards MDA-MB-231 cell line, comparable to the reference drug, Tamoxifen (IC_{50} 42.66 ± 2.19 μM) [44]. These compounds displayed low sensitivity against the noncancerous breast cell line (MCF-10A) (Fig. 28).

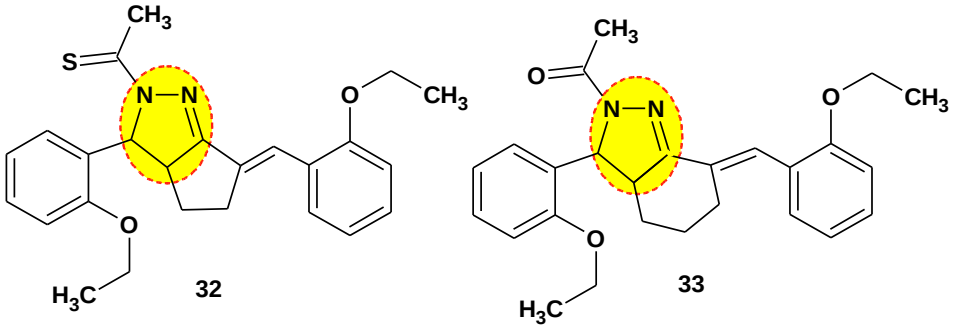


Figure 28. Pyrazoline derivatives.

Thiazolyl pyrazoline hybrids 34 and 35, reported by Abdelsalam *et al*., exhibited promising cytotoxicity towards A549 cells with IC_{50} values of 4.2 and 2.9 μM, respectively. These hybrids also exerted EGFR inhibition with IC_{50} values of 40.7 and 32.5 μM and VEGFR-2 inhibition with IC_{50} values of 78.4 and 43.0 μM, respectively (Fig. 29)[45].

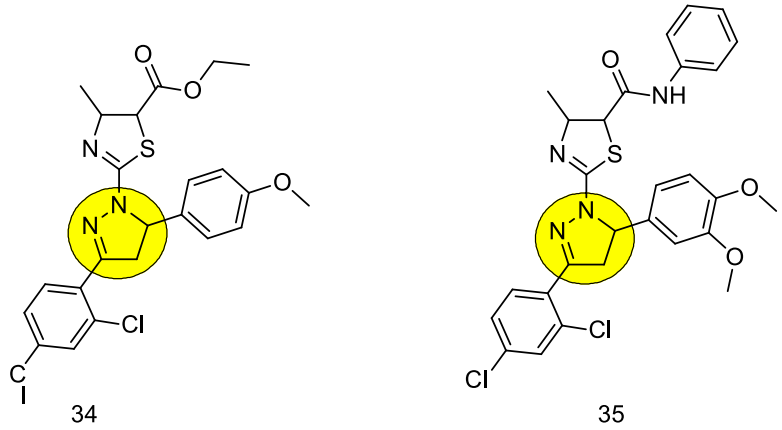


Figure 29. Thiazolyl pyrazoline hybrids.

N-phenyl pyrazoline derivative 36 reported by Mustofa *et al*.displayed a cytotoxic effect in cervical HeLa cells with IC_{50} of 4.7 μM via suppressing EGFR expression, tumor size, and cancer stem cell marker CD133 (Fig. 30) [46].

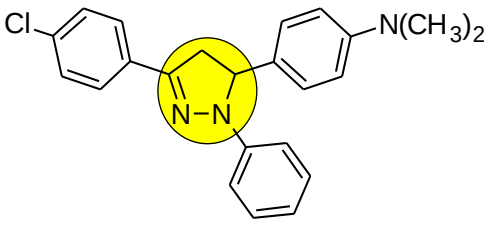


Figure 30. *N*-phenyl pyrazoline molucule.

Halim *et al*. have reported 4-chlorophenoxy pyrazoline derivative 37 as a promising cytotoxic agent with an IC_{50} of 4.77 μM, compared to staurosporine against the MCF-7 cell line (Fig. 31) [47].

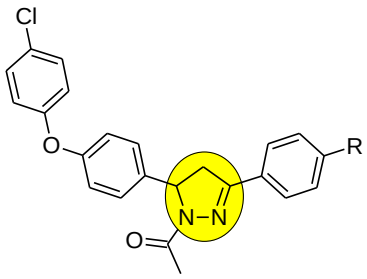


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Figure 31. Chlorophenoxy pyrazoline derivative.

Mansour *et al*. in 2019 reported that thiazolyl-pyrazoline derivative 38 linked to benzo[1,3]dioxole moiety has shown a notable inhibitory effect on HCT-116 cancerous cells with an IC_{50} value of 6.19 μM (Fig. 32) [20].

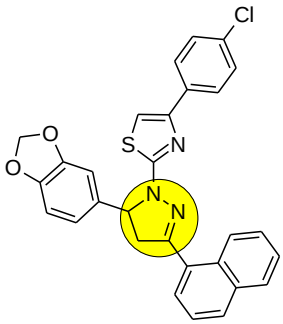

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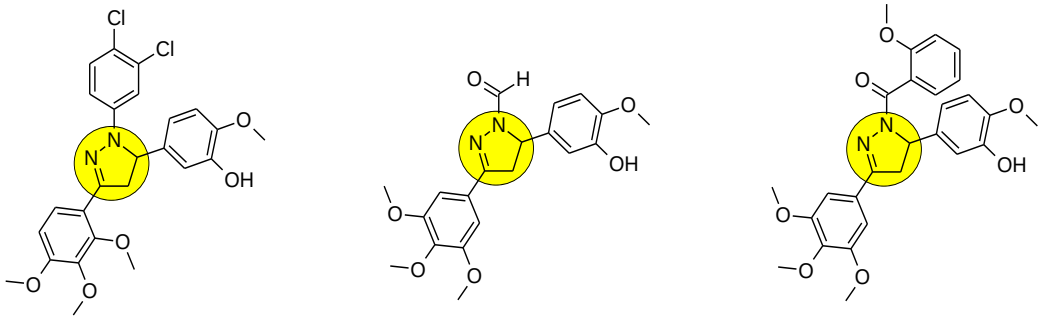
Figure 32. Thiazolyl-pyrazoline derivative.

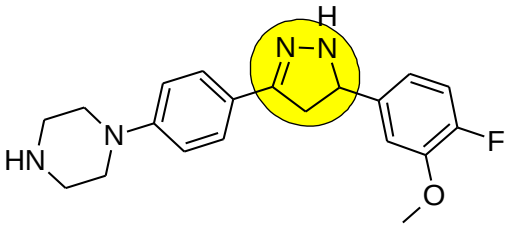
Pyrazoline derivatives of Combretastatin-A4 39, 40, and 41 reported by Shringare *et al*. exhibited excellent antiproliferative activity against MCF-7 with GI_{50} ranging from 0.1 to 0.9 μM (Fig. 33)[48, 49].



39 **40** **41**

Figure 33. Pyrazoline molucules.

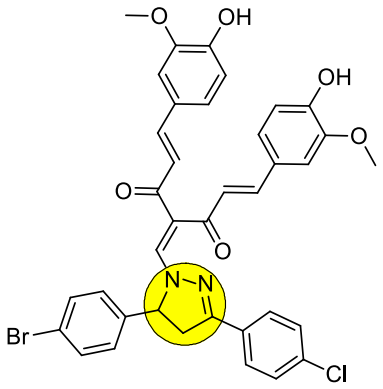
Pyrazoline-bearing piperazine conjugate 42 remarkably increases growth inhibition against many cancer cell lines by NCI. It was also found to be a potent VEGFR-2 inhibitor with IC_{50} 0.57 μM, comparable to Sorafenib (IC_{50}=0.51 μM) (Fig.34) [49].



42

Figure 34. Pyrazoline-bearing piperazine.

Pyrazoline analog of curcumin 43 reported by Chaudhary exhibited strong cytotoxicity against HeLa cells with an IC_{50} of 8.7 µg/mL and triggered apoptosis via cleavage caspase-3 enzyme (Fig. 35) [50].

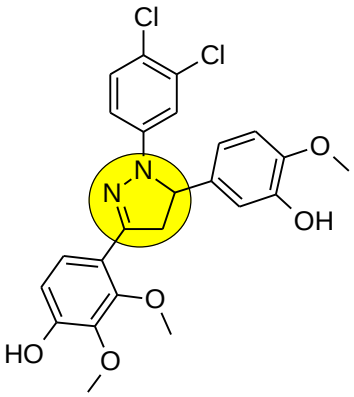


43

Figure 35. Pyrazoline analog of curcumin.

3. Anti-inflammatory Potential of Pyrazoline Derivatives

Shringare *et al.* reported pyrazoline derivatives of Combretastatin-A4 44 and 45 as good anti-inflammatory agents (Fig. 36) [49].



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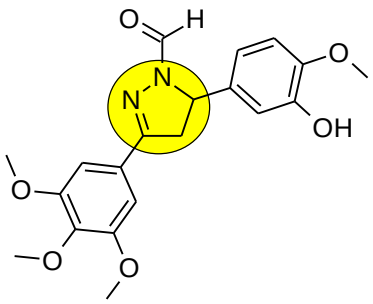
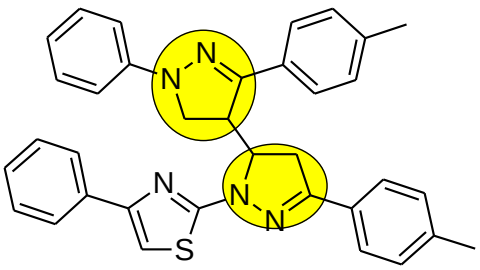


45

Figure 36. Pyrazoline derivatives of Combretastatin-A4 anti-inflammatory agents.

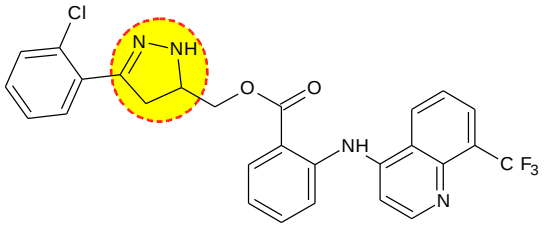
1-Thiazolyl-2-Pyrazolines 46 reported by Raut *et al*. exhibited excellent anti-inflammatory activity with 91.74% protein denaturation inhibition, compared to the standard drug, diclofenac sodium (90.21%) (Fig. 37) [51].



46

Figure 37. Thiazolyl-2-Pyrazolines.

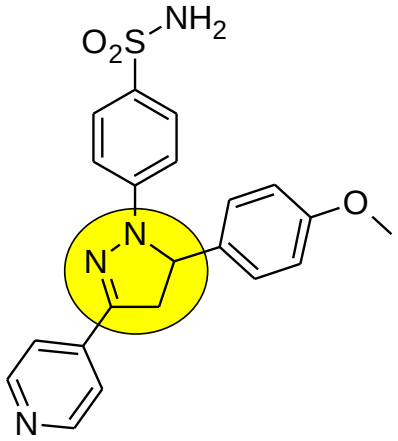
Taher *et al*. reported pyrazole and pyrazoline derivative 47 as COX-2 inhibitors (Fig. 38) [53].



47

Figure 38. Pyrazole and pyrazoline derivative.

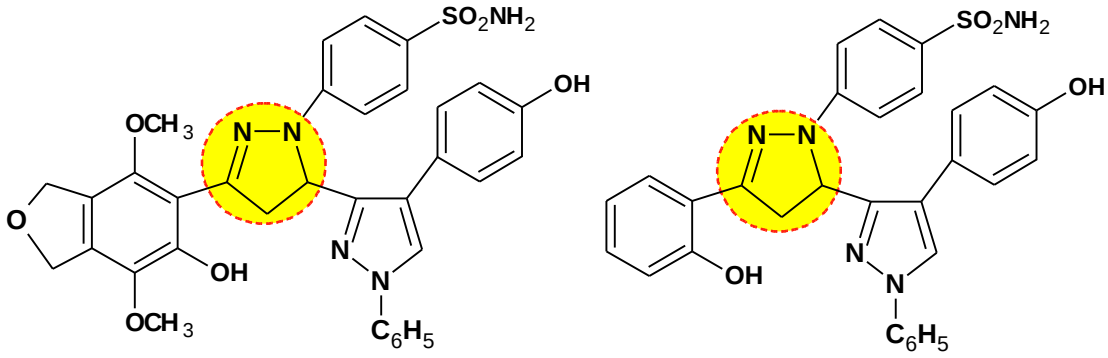
Pyrazoline-bearing benzenesulfonamide 48, reported by Rauf *et al*., exhibited good anti-inflammatory activity using the egg-white paw edema method[53]. Compound 48 caused 29.78% inhibition at 300 min, compared to the standard drug celecoxib (22.67% inhibition) (Fig. 39).



48

Figure 39. Pyrazoline-bearing benzenesulfonamide molcule

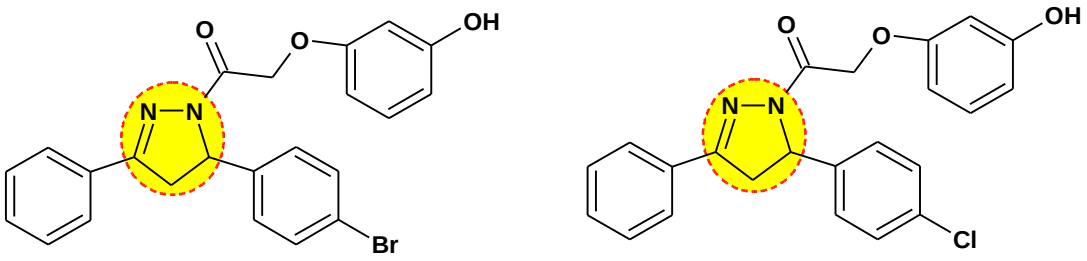
Pyrazolyl pyrazolines (49) and (50), as reported by Ragab *et al*., displayed remarkable anti-inflammatory action gastroprotection without any ulcerogenicity[54]. Also, these compounds inhibited prostaglandin (PGE2) synthesis with 44.23% and 51.4%, besides TNF-α inhibition with 33.48% and 41.41%, respectively (Fig. 40).



49 **50**

Figure 40. Pyrazolyl pyrazolines.

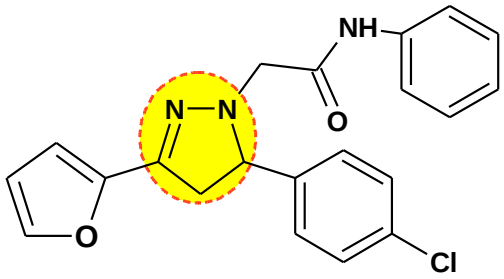
2-pyrazoline derivatives having resorcinol/guaiacol moiety 51 and 52 demonstrated superior anti-inflammatory efficacy compared to the standard drug, indomethacin (Fig. 41) [55, 56].



51 52

Figure 41. 2-pyrazoline derivatives having resorcinol/guaiacol moiety.

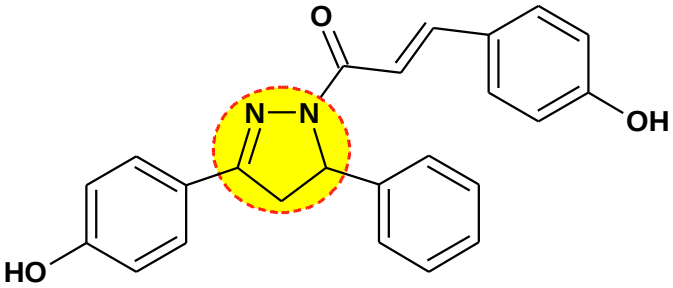
N-substituted pyrazoline derivatives 53 bearing furan moiety, reported by Kanaan *et al*., displayed anti-inflammatory activity by producing a considerable decrease in paw edema compared to diclofenac sodium (Fig. 42) [57].



53

Figure 42. *N*-substituted pyrazoline derivatives.

Bhadoriya *et al*. reported *N*-substituted diaryl-pyrazoline 54 as a potent anti-inflammatory agent with 69.88 percent inhibition of denaturation of protein Fig. 43) [58].



54

Figure 43. *N*-substituted diaryl-pyrazoline anti-inflammatory agent.

4. Conclusions

In conclusion, the review highlights the synthesis of pyrazolines with their potency as anticancer and anti-inflammatory agents. It will benefit the researchers by developing novel molecules with more potency, better selectivity, and minimum side effects. Thus, this article is a useful supplement and will contribute to the further development and synthesis of medicinally important pyrazoline derivatives.

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Conflicts of Interest

The authors declare no conflict of interest.

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