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Pharmaceutical Importance of Pyrazoline Derivatives: A Mini Review

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Abstract.

Pyrazoline has become an interesting subclass of nitrogen containing heterocycles with large number of pharmacological significance. This review provides a small survey relating to the advantages of pyrazoline and its derivatives in pharmaceutical field, specifically as anticancer, anticonvulsant, anti-inflammatory and antimalarial agents.

Keywords: pyrazoline, heterocycles, pharmaceutical significance.

1. INTRODUCTION

Pyrazoline and its derivatives are member of nitrogen containing heterocycles [1]. In their structure, two nitrogen atoms are present in five-membered ring (Figure 1). This nucleus contains a C=N double bond [2]. Pyrazoline derivatives have been found in natural products in the form of vitamins, alkaloids and pigments [3]. In the last decade, great attention has been paid on the pyrazoline derivatives due to their unique molecular structure with simplicity of preparation and wide application in pharmaceutical field. They have shown interesting pharmacological activities such as anticancer [4], anti-inflammatory [5], antimicrobial [6], antioxidant [7] and antidepressant [8].

In continuation of the development of pyrazolines as promising candidate for drugs, a comprehensive data result regarding their status in global research community is urgently required. This paper summarizes recent progress in pharmacological activities of synthesized pyrazoline and its derivatives.

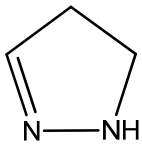

Figure 1. Basic structure of pyrazoline

2. PHARMACOLOGICAL ACTIVITIES OF PYRAZOLINES

2.1 Anticancer

A series of benzochalcones bearing pyrazoline nucleus was developed by Shin *et al.* [9]. From evaluation of their anti-colorectal cancer potency, **1** was denoted as the most potent compound with IC_{50} value of 2.40 µM. Cell cycle progression can be blocked through dysregulation of cell cycle regulatory cyclin B1 and proteins p21 [9]. This induced apoptosis of cancer cells. Some novel fluorine containing hydroxypyrazoline derivatives were prepared by Dinesha *et al*. and were evaluated for in vitro anticancer activity [10]. Among the prepared compounds, **2** showed promising cytotoxic effect with IC_{50} value of 1.86 and 2.45 µM against MCF-7 and MDA-MB-231 breast adenocarcinoma cancer cell lines, respectively. Garazd *et al*. evaluated some new 6-pyrazolinylcoumarins for possible anticancer performance [11]. The results highlighted that compound **3** has the highest activity with certain sensitivity profile toward Leukemia cell lines (CCRF-CEM and MOLT-4).

A novel series of 3,5-disubstituted pyrazolines was designed and tested for their in vitro anticancer activity [12]. Compound **4** revealed a noticeable effect against human non-small-cell lung cancer cell line (A549). At concentration of 22.13 µM this compound caused 50% inhibition of cell growth. The authors concluded the introduction of alkoxy and fluorine functionalities exhibited higher activity than unsubstituted pyrazolines [12]. Design of novel quinoline-based 4,5-dihydro-1*H*-pyrazoles and anticancer evaluation against 60 different human cancer cell lines was presented by Ramirez-Prada *et al*. [13]. In this study, compound **5** was selected as the best candidate for anticancer agent with selective activity against Leukemia (K-562, RPMI-8226, SR), CNS cancer (SF-295), Melanoma (MDA-MB-435, SK-MEL-5), Ovarian cancer (OVCAR-4, NCI/ADR-RES), Renal cancer A498 and breast cancer (MCF-7, T-47D, MDA-MB-468) cell lines with GI50 (growth inhibition) values below 1.0 µM. Recently, some new 2,4-disubstituted-1,3-thiazoles integrated with pyrazoline moieties were developed by Sadashiva *et al.* [14]. Compound **6** (IC_{50}: 5.0 µM) exhibit higher activity than standard drug Cisplatin (IC_{50}: 10.0 µM).

2.2 Anticonvulsant

Rao *et al.* designed novel 1,3,5-trisubstituted-2-pyrazoline derivatives and investigated for their anticonvulsant activity [15]. Among the screened compound, **7** was found to be protective against scMet and MES-induced seizures in the dose range of 30-300 mg/kg. The data highlighted that compounds with electron-donating group such as methoxy and chlorine functionalities on aromatic ring at position 5 of pyrazoline nucleus significantly enhanced anticonvulsant efficacy [15]. Three new structures in the form of 3-substituted-*N*-aryl-6,7-dimethoxy-3a,4-dihydro-3*H*-indeno[1,2-*c*]pyrazole-2-carboxamide analogs were prepared by Ahsan [16]. The anticonvulsant and neuroprotective activity were examined based on ADD protocol and the author found that compound **8** showed the best action with IC_{50} value of 159.20 ± 1.21 µM. Currently, Beyhan *et al.* promoted 3,5-disubstituted-4,5-dihydro-1*H*-pyrazole-1-carbothioamides as potential anticonvulsant agent [17]. The analysis revealed that compound **9** exhibited noteworthy performance in pentylenetetrazole induced seizure (PTZ) test.

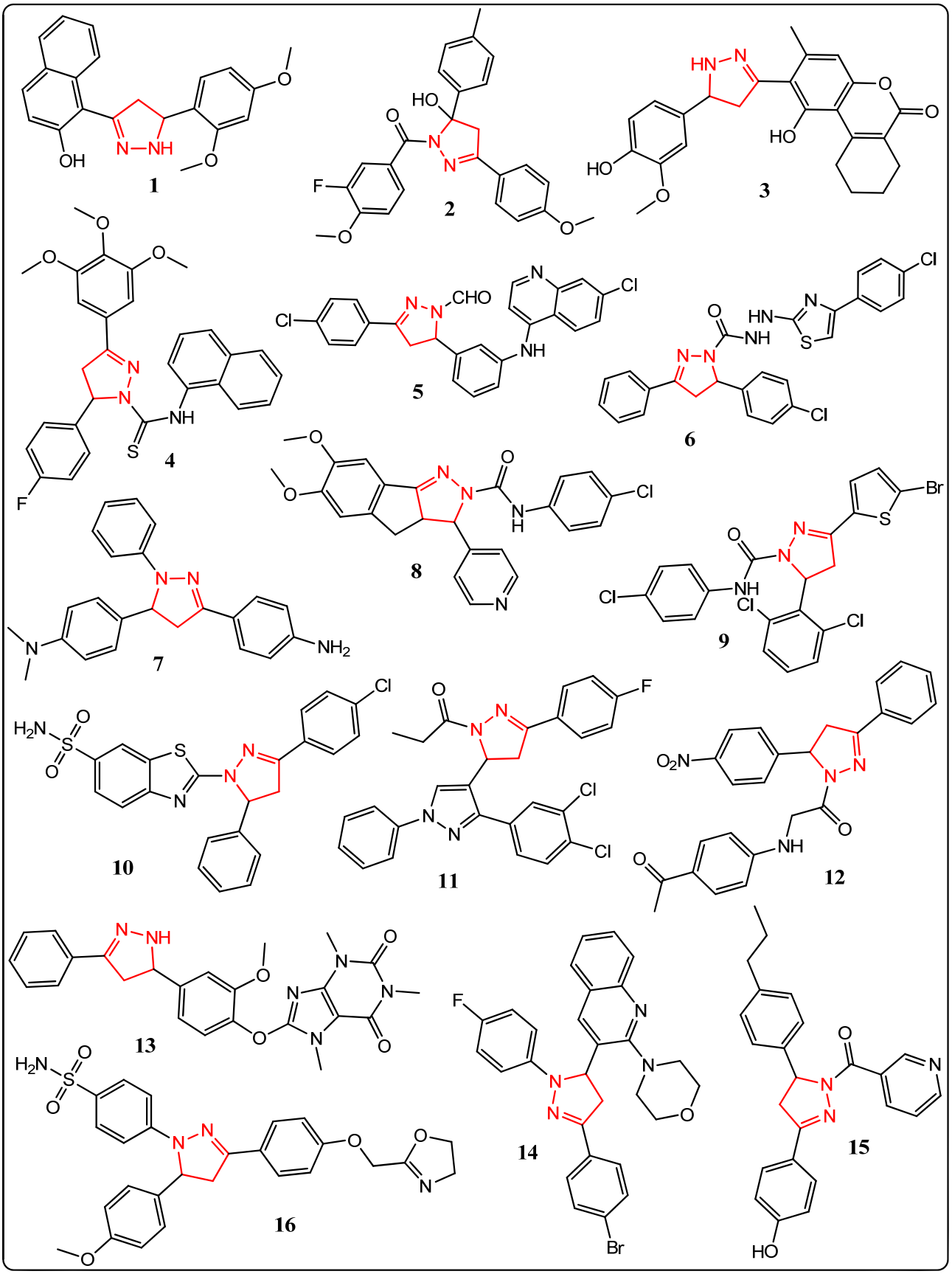

Figure 2. Structure of compound 1-16

2.3 Anti-inflammatory

Synthesis and anti-inflammatory screening of pyrazolines linking benzothiazole scaffold was done by Kharbanda *et al.* [18]. Of the synthesized compounds, **10** was reported to exhibit most remarkable activity with suppression of the COX-2 enzyme activity and TNF-α production. This compound was non-toxic and non-ulcerogenic. Several derivatives of pyrazolyl-pyrazoline were developed by Viveka *et al.* and profiled for in vitro anti-inflammatory efficacy [19]. Compound **11** (percentage inhibition of oedema: 75.56% at dose of 50 mg/kg) was found to be most active within the developed molecules and compared with standard drug Diclofenac sodium (percentage inhibition: 76.56%). The authors highlighted that *N*-acylated and nitro substituted *N*-phenyl pyrazolyl-pyrazolines showed a very promising performance [19]. Abdel-Sayed *et al.* developed 1,3,5-trisubstituted pyrazoline derivatives and screened for their cyclooxygenase inhibitory activity and related method for anti-inflammatory evaluation [20]. Compound **12** having an excellent selectivity inhibited COX-2 with IC_{50} value of 10 μM and selectivity index > 10.

2.4 Antimalarial

A facile synthesis of caffeine-based chalcones, pyrazolines and pyrazolo[3,4-*b*][1,4]diazepines as antimalarial agents was performed by Insuasty *et al.* [21]. On pyrazolines series, compound **13** displayed an outstanding growth inhibition percentage 85.2 ± 5.4% with IC_{50} value of 13.7 ± 2.1 μM. A novel class of organic compound containing pyrazoline-morpholinoquinoline hybrid for possible antimalarial candidate was investigated by Karad *et al.* [22]. Upon evaluation, compound **14** exhibited superior antiplasmodial action with IC_{50} of 0.015 μM, higher activity compared to standard drugs Chloroquine (0.062 μM) and Quinine (0.826 μM). Recently, Mishra *et al.* developed a series of new 1,3,5-trisubstituted pyrazoline derivatives from the reaction of chalcones with nicotinic acid hydrazides [23]. After screening, compound **15** showed better antimalarial activity than the chloroquine against MRC-2 and RKL-9 *Plasmodium falciparum* strains with IC_{50} values of 0.022 and 0.192 μM, respectively. Potential antimalarial agents from a class of 4,5-dihydrooxazole-pyrazoline hybrid compounds was synthesized by Pandey *et al.* [24]. After deep screening against *Plasmodium berghei* mouse model, compound **16** was denoted as the most potent agent with IC_{50} of 0.322 μM.

3. Conclusion

Pyrazoline, a five-membered nitrogen bearing heterocyclic system can be denoted as pharmaceutically important molecules. The synthesis technique and exploration of pharmacological activities of pyrazolines have become a trending topic. Review result highlighted that there were several pyrazoline derivatives displayed significant pharmacological activity and have higher activities compared to standard commercial drugs.

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