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The diverse pharmacological importance of Pyrazolone Derivatives : A Review

G Mariappan*[1], B.P Saha[1], L. Sutharson[2], Ankit[2], S. Garg[2], Lipika Pandey[1], Deepak kumar[1]

[1]*Department of Pharmaceutical Chemistry, Himalayan Pharmacy Institute, Majhitar, Rangpo, East Sikkim-737136.*

[2]*Department of Pharmacology, Himalayan Pharmacy Institute, Majhitar, Rangpo, East Sikkim-737136.*

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ABSTRACT

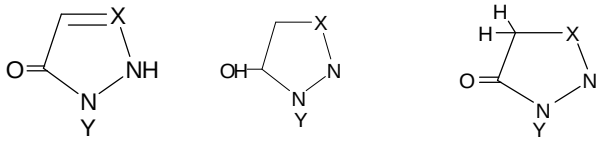
Scientific research programs and reports are continuously pouring in with respect to improvised synthetic techniques to prepare numerous pyrazolone derivatives and with regard to their diverse biological, pharmacological and chemical applications. When pyrazolones were discovered, they were only known as NSAID but in recent times, they are known to exhibit antioxidant, anticancer, antibacterial and several other pharmacological actions. These derivatives were withdrawn from the market because of their adverse effects such as agranulocytosis, skin rashes and blood dyscrasis etc, but recently they are again finding their place in the market and are being extensively used in cerebral ischemia and cardio vascular diseases. Since its introduction into medicine, there have been more than 1000 compounds made in an effort to find others with more potent analgesic action combined with less toxicity. Keeping in view the increasing importance of these derivatives, a need for the review is felt. This review deals with up to-date literature on biological and pharmacological properties of pyrazolone derivatives.

Keywords: Pyrazolones, Edaravone, cardio protective, Antioxidant, Anticancer.

INTRODUCTION

The late 19th century gave rise to the discovery of the three prototypes of modern non-opioid antipyretic and analgesics such as acetaminophen (acetanilide), aspirin and salicylic acid and phenazone[1]. The Chemistry of pyrazolone began in 1883 when Knorr reported the first pyrazolone derivative. The reaction of phenyl hydrazine and ethylacetoacetate resulted in novel structure identified in 1887 as 1-phenyl-3-methyl-5-pyrazolone[2]. The Knorr pyrazole synthesis is the reaction of hydrazines with 1, 3 dicarbonyl compounds to provide the pyrazole or pyrazolone ring system. Pyrazolone is a five membered lactum ring containing two nitrogen and a ketone group in its ring. The prototype molecule, antipyrine was synthesized for clinical use in 1883. The methylated nitrogen derivative aminopyrine was introduced in 1897 and taken off from the market in the 1970s because of its property to form nitrosamines. Dipyrone had been in clinical use since 1922. Antipyrine was the first pyrazolone derivative as a drug introduced in 1887 and as the name implies it was the first agent to reduce fever and used in the treatment of arthritis, musculoskeletal and joint disorder. These derivatives were widely used in medical practice viz antipyrine, aminopyrine, analgin etc. This discovery initiated the beginnings of the great German drug industry that dominated the field for about 40 years. The Compounds like 3-Alkyl-4- arylmethylpyrazol-5-ones are reported to exhibit potent antihyperglycemic activity, while 1-phenyl-3-tetrafluoroethylpyrazol- 5-one is an anxiolytic. Thus, the biological activities of pyrazol-5-ones depend upon the nature of the substituents[3]. 3- methyl -1- phenyl- 2- pyrazolin- 5- one (Edaravone), a strong novel free radical scavenger is used for the treatment of patients with acute brain infarction[4]. Demethylated antipyrine is a novel potent free radical scavenger that has been clinically used to reduce the neuronal damage following ischemic stroke. Demethylated antipyrine exerts neuroprotective effects by inhibiting endothelial injury and by ameliorating neuronal damage in brain ischemia[5].The pharmacological spectrum of pyrazolone compounds are very similar to that of aspirin and some other (NSAID) nonsteroidal anti-inflammatory agents.The drugs containing pyrazolone nucleus are known to display diverse pharmacological activities such as antibacterial, antifungal, anti-inflammatory, analgesic, and antipyretic.

The pyrazolone nucleus has been known to exist in three tautomeric structures.

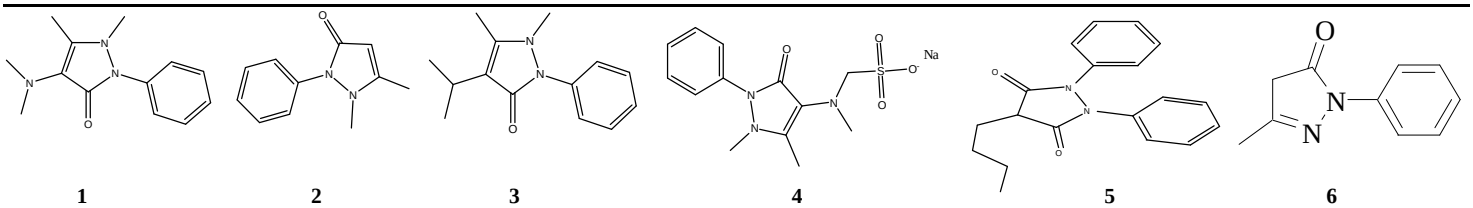


I II III

Strucutre I is present in several substituted pyrazolones which are widely known and used as antipyretic agents. All these compounds are characterized by the presence of a phenyl group attached to nitrogen atom in the 1- position and a methyl group in 3-position. Phenyl group in 1- position and a methyl group in 3-position seem to be essential for antipyretic activity. Several 4, 4-dimethyl derivatives, as well as Pyrazole Blue and Tartrazine, are derived from formula II whereas from structure III several pyrazolone dyes have been derived[6]

Table 1. Pyrazolone derivatives available in the market

Name	Structure	IUPAC Name	Brand Name	Uses
Antipyrine	1	1,2 dihydro-1,5- dimethyl-2-phenyl-3H-pyrazol-3-one	Phenzone Analgesine	Analgesic,Antipyretic
Aminophenazone	2	4-dimethylamino-1,5-dimethyl-2-phenylpyrazol-3-one	Aminopyrin	Analgesic,Antiinflammatory
Propyphenazone	3	1,5-dimethyl-2-phenyl-4-propan-2yl pyrazol-3-one	Pyramidone Anodymin	Analgesic,Antiinflammatory,in rheumatism,in cardiovascular disorder
Metamizole	4	Sod.[(2,3-dihydro-1,5 dimethyl-3-oxo-2-phenyl-1H-pyrazol-4-yl) methylamino] Methanesulfonate	Novalgin Dipyrone Analgin Algozone	Analgesic,Antipyretic,Antiinflammatory
Phenylbutazone	5	4-butyl-1,2-diphenyl-pyrazolidine-3,5 dione	Atropan Azdid Butazolidin Phanyzone	AnalgesicAntipyretic,Antiinflammatory,in rheumatism, in cardiovascular disorder
Edaravone	6	3-methyl-1-phenyl-2-pyrazolin-5-one	Edaravone MCI-186	As antioxidant,In cerebral ischemia,in rheumatism, in cardiovascular disorder



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***Corresponding author.**

G Mariappan
Department of Pharmaceutical Chemistry,
Himalayan Pharmacy Institute, Majhitar,
Rangpo, East Sikkim-737136.
Tel.: +91 9474530205
E-mail:gmariappanhpi@yahoo.co.in

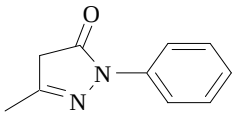
Diverse Pharmacological Properties of Pyrazolones

Aanalgesic anti-inflammatory and antipyretic activity

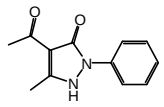
Phenylbutazone, a pyrazolone drug is useful in the treatment of acute gout, rheumatoid arthritis and allied disorders.4-acetyl-1-phenyl-3-methyl pyrazolone

(HAP) and 4-trifluroacetyl-1-phenyl-3-methyl pyrazolone (HTFP) significantly reduces the car rageenan induced inflammation in rats[7].

The selective inhibition of Phospholipase A_2 is crucial in the search of a more efficient anti-inflammatory drug with fewer side effects. Dipyrone a well known pyrazolone inhibitor having anti-inflammatory activity is strongly found to be associated to PLA_2s through three hydrogen bonds where as 1-phenyl-3-methyl-5-pyrazolone presents an interamolecular hydrogen bond that makes difficult the formation of more efficient interactions with PLA_2[8].



3-methyl-1-phenyl-2-pyrazolin-5-one



4-acetyl-1-phenyl-3-methylpyrazolone

Free radicals have some roles in inflammation and systemic and local tissue injuries. Intrathecally administered edaravone, a free radical scavenger, had analgesic effects on inflammatory-induced acute and facilitated pain[9]. Oral dipyrone has been shown to be more effective than an equal dose of aspirin or paracetamol in alleviating postoperative pain, and intravenous dipyrone 2.5g was similar in efficacy to pethidine 50 mg. In patients with acute ureteral or biliary colic, dipyrone 2.5g intravenously was similar in efficacy to indomethacin 50 mg or pethidine 50 mg[10]. pyrazolones exert analgesic effect by inhibiting prostaglandin synthesis. The early phase (1-2 h) inflammation is mainly mediated by histamine, serotonin and increased synthesis of prostaglandins in the damaged tissues surroundings. The late phase is sustained by prostaglandin release and mediated by bradykinin, leukotrienes, polymorph nuclear cells and prostaglandins produced by tissues macrophages. Fever results due to generation of mediators such as IL-1ß, IL-6, interferons and TNF-α cytokines increase the synthesis of prostaglandin which elevates the body temperature. From the results of antipyretics study, it can be suggested that pyrazolone derivatives produce the antipyretic action by inhibiting the prostaglandin synthesis by blocking cycloxygenase isoenzymes, platelet thromboxane synthesis, and prostanoids synthesis[11, 13]. There is increasing evidence that lysosomal enzymes play an important role in the development of acute and chronic inflammation[14, 15]. Most of anti-inflammatory drugs exert their beneficial effect by inhibiting either release of lysosomal enzymes or by stabilizing lysosomal memberane which is one of the major events responsible for the inflammatory process.

Antioxidant/Free radical scavenging activity

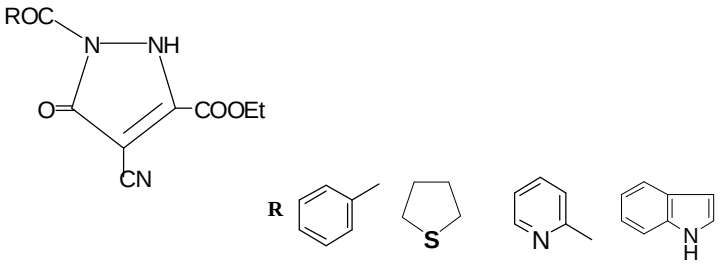
It has been proved that the pyrazolone derivatives have significant antioxidant activity. The quantification of MDA and 4-HNE can be directly correlated with the lipid peroxidation inhibition capacity of the pyrazolone derivatives. The toxic radicals' quantification is also an indicator to monitor the overallprogress of lipid peroxidation which isassociated with myocardial ischemic reperfusion injury[16]. Dipyrone and aminopyrine prevent phorbol-12-myristate-13-acetate-induced neutrophil burst with high efficiency and are highly potent scavengers of HO and HOCl. Mitsubishi-Tokyo Pharmaceuticals Inc (Tokyo, Japan), developed 3-methyl-1-phenyl-2-pyrazolin-5-one (Edaravone) which is a strong novel free radical scavenger. It has been shown that Edaravone reduces or restores the amount of ROS increased by postischemic reperfusion and prevents impairment of the antioxidant defense system[17]. The putative mechanism underlying the antioxidant action of edaravone is as follows- an electron transfer from an edaravone anion to peroxyl radical yields an edaravone radical and peroxyl anion, and this reaction breaks the chain oxidation of lipids. Then, edaravone peroxyl radical transforms to 4, 5-dione by elimination of a hydrogen atom and one electron. Finally, 2-oxo-3- (phenylhydrazono) - butanoic acid (OBP) is produced by the hydrolysis of 4, 5-dione[18].

Structure Activity Relationship (SAR)

- Sterically small substituents such as hydrogen and methyl group did not show any activity, substituents containing carbocyclic moieties such as cyclohexyl, naphthyl, and benzyl maintained or increased the *in vitro* lipid peroxidation-inhibitory activity.
- The activity of 2-substituted compounds largely decreases except for a phenolic hydroxyl analogue.
- The activity is increased by the lipophilic substituents such as alkyl and halogen. Longer alkyl and alkoxy chains show increase in activity.
- A disubstituted halogen analogue increases activity as compared with monosubstituted halogen analogues.
- The introduction of hydrophilic substituents significantly decreased the activity. A phenyl analogue showed excellent activity which was far better than that of a 2-furyl analogue having the lipophilic aromatic group[19].
- The isobutyl group showed increased activity in contrast to the 2-hydroxyethyl group which showed almost no inhibitory activity.
- 4, 4-Disubstituted compounds showed no inhibitory activity, which supports hypothesis that compounds which generate the aromatic hydroxyl group by the keto–enol tautomerization have lipid peroxidation-inhibitory activity.

Anticonvulsant activity and Antidepressant activity

Some 4,4 disubstituted pyrazolone compounds exhibit anticonvulsant activity[20]. For instance, Dipyrone was found to have anticonvulsant activity in three experimental epilepsy models. At a dose of 300 mg/kg i.p., dipyrone blocked the maximal hind limb extension in the electroshock model in Wistar rats, the tonic-clonic component of acute sound-induced seizures and the limbic component of audiogenic kindling in genetically susceptible wistar rats. In the electroshock model higher doses (400 and 500 mg/kg) were also effective but lower doses (100 and 200 mg/kg) were not[21].

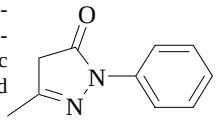


Antihyperglycemic activity

A group of 4-(arylmethyl and heteroarylmethyl)-5-substituted-3-pyrazolone derivatives have been found to have antihyperglycemic activity which is useful in non insulin dependent diabeties mellitus[25].1,2-dihydro-4-[[4-(methylthio)phenyl]methyl]-5-(trifluoromethyl)-3*H*-pyrazol-3-one in oral and subcutaneous glucose tolerance tests, indicated that unlike the renal and intestinal glucose absorption inhibitor phlorizin, it does not effectively block intestinal glucose absorption. Substitution of 4-methylthio, methylsulfinyl, or ethyl to a benzyl group at C4, in combination with trifluoromethyl at C5 of pyrazol-3-one, generated potent antihyperglycemic agents in obese, diabetic db/db mice (16-30% reduction in plasma glucose at 2 mg/kg).5-alkyl-4-(arylmethyl)pyrazol-3-ones (hydroxyl tautomers) have been discovered as potential new oral antidiabetic agents, based on their ability to lower plasma glucose when administered orally to obese, diabetic mice[26, 27].

Role of Pyrazolone in Cardiovascular Disease

Yoshida *et al*. in 2005 reported that Edaravone enhances the expression of eNOS and restores the reduction in eNOS by oxidized low-density lipoprotein in endothelial cells. It shows it prevent cell damage induced by oxidative stress through not only direct ROS scavenging effect but also restoration of reduced eNOS expression[28]. According to French patent application 2529786 a group of 3-phenyl or pyridyl - 5 - pyrazolone derivatives have been discovered which is useful in improving cardiac contractability[31]. It is expected that edaravone has beneficial effects on coronary artery and myocardial cells after ischemic and postischemic myocardial injury in patients with ischemic heart diseases, including acute myocardial infarction and angina pectoris[29, 30].In 1994, Yanagisawa *et al* showed that intravenous infusion of 3methyl-1-phenyl-2-pyrazolin-5-one derivative at a dose of 3 mg/kg attenuates the loss of myocardial creatine kinase activity from the left ventricular free wall in rats subjected to coronary artery occlusion for 10 minutes followed by reperfusion for 24 hours and reduced infarct size by approximately 50% compared with that in the control vehicle group[31]. Minhaz *et al* reported that 3methyl-1-phenyl-2-pyrazolin-5-one derivative attenuated



the myocardial necrotic area by approximately 50% in isolated reperfusion rat heart subjected to coronary artery occlusion. Tsujita *et al*. investigated the effects of edaravone on left ventricular function and infarct size using a randomized, placebo-controlled, open-label protocol in 80 patients with acute myocardial infarction. Intravenous administration of edaravone at a dose of 30 mg for 10 minutes before myocardial reperfusion decreased serum concentrations of creatine kinase-MB isoenzymes, a surrogate point of infarct size, and improved left ventricular ejection fraction in patients with acute myocardial infarction compared with those in the placebo group[30].

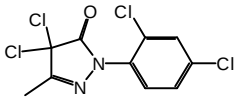
Antimicrobial activity

A new series of 4-arylhydrazono-2-pyrazoline-5-ones were tested in vitro against one Gram-positive and two Gram-negative bacterial strains, two mycobacterial strains and a fungus, *Candida albicans*. Compounds were found to be more active against *Staphylococcus aureus* than the other compounds at a concentration of 15.6 µg/mL[32]. The synthesis of Cu (II) complexes derived from Schiff base ligands obtained by the condensation of 2-hydroxybenzaldehyde or terephtalic aldehyde with 4-aminoantipyrine (4-amino-2, 3-dimethyl-1-phenyl-3-pyrazolin-5-one) was prepared and screened for antimicrobial activity, the qualitative and quantitative antimicrobial activity test results proved that all the prepared complexes are very active, especially against samples of *Ps. aeruginosa*, *A. Boumanii*, *E. coli* and *S. aureus*[33]. Various 1-isonicotinyl-3-methyl-4-(substituted phenyl hydrazono)-2-pyrazolin-5-one compounds were synthesized and evaluated for their antibacterial activity by Amir et al.

Antitumor activity

Cdc25A and B are potential oncogenes and it is due to their overexpression that in various human carcinomas (breast, lung, colorectal, gastric, prostate, head and neck, ovary, lymphomas, and melanomas) and tumor cell lines occurs[34]. In 2004 Korea Research Institute of Chemical Technology synthesized several 3- methyl-4-oximinopyrazolin-5-one scaffold which were found to be Cdc25B inhibitor, out of which 3-Methyl-4-(*O*-methyl-oximino)-1-phenylpyrazolin-5-one and 1,3-dimethyl-4-(*O*-propargyloximino)- pyrazolin-5-one were found to be most potent. The activity decreases when phenyl group at 1-position was modified to bigger aromatic groups[35, 36].

A new derivative of 1-phenyl-3-methyl-5-pyrazolone,4,4-dichloro-1-(2,4-dichloro phenyl)-3-methyl-5-pyrazolone, named TELIN, was chemically synthesized and identified as a potent inhibitor of human telomerase in the cell-free telomeric repeat amplification protocol. It inhibits the telomerase activity at submicromolar level with IC50 of 0.3µM. Kinetic studies showed that binding to telomerase protein, and the mode of inhibition by this substance was competitive–noncompetitive mixed-type with respect to the TS primer, whereas it was uncompetitive or noncompetitive – uncompetitive mixed-type with respect to the three deoxyribonucleosides. TELIN is a specific potent catalytic blocker of telomerase, and is considered to be a valuable substance for medical treatment of cancer and related diseases [37].



4,4-dichloro-1-(2,4-dichlorophenyl)-3-methylpyrazolin-5-one

A new class of VEGFR(vascular endothelial growth factor receptor)-2/KDR kinase inhibitors bearing heterocyclic substituted pyrazolones was designed as KDR kinase inhibition is considered to play an important role in regulating angiogenesis, which is vital for the survival and proliferation of tumor cells. The thiadiazole series of pyrazolones are potent VEGFR-2/KDR kinase inhibitors[38].

Antithrombotic activity

Experimental studies have shown beneficial effects of 3methyl-1-phenyl-2-pyrazolin-5-one derivative (Edaravone) on postischemic reperfusion injury[39, 40]. It has been found to ameliorate infarct size and brain edema in embolization and transient focal, global, and hemispheric ischemia models in adult rats and to attenuate the hypoxic-ischemia encephalopathy in neonatal rats[41]. In Japan, edaravone was approved in April 2001 for treatment of acute brain infarction and subarachnoid hemorrhage in the acute phase. Several investigators have reported that edaravone has beneficial effects on prevention of brain damage in patients with stroke[42].

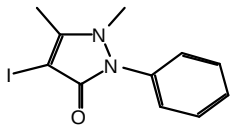
Nafazatrom, a pyrazolone derivative has dual arachidonate enzyme inhibition. It exhibits antithrombotic and thrombolytic action by inhibiting 5-lypoxigenase catabolism of arachidonate. This drug reduces the myocardial infarct size after experimental coronary artery occlusion and reperfusion.

Radioprotective effect

Analgin, antipyrine, and aminopyrine, if administered to mice in large doses 3 h before irradiation (800 R), increases the survival rate and prolonges the life of the dying animals. In combination with cystamine, these compounds increases the chances of survival of the mice after the period of acute intestinal death following irradiation in a dose of 1050 R. Experiments have shown that pyrazolone derivatives considerably increase the resistance to hypoxia of both healthy mice and irradiated mice at various periods of acute radiation sickness[43].

Antiviral activity

In addition to anti-inflammatory and analgesic activity, pyrazolones are known to possess antiviral activity.Saratikov et al discovered that antipyrine and related molecules can possess antiviral activity against a wide range of viruses. Iodoantipyrine or 4-iodo-1, 5-dimethyl-2-phenyl-pyrazol-3-one is an iodinated form of antipyrine. The anti-inflammatory action of Iodoantipyrine produces several effects such as reduction of degranulation of the mast cells; suppression of prostaglandins and arachidonic acid synthesis; membrane stabilizing activity; normalization of liver damage associated enzymes such as ALT and AST; lower intensity of oxidation and phosphorylation processes. This derivative displays antiviral activity against wide range of microorganisms including tick-borne encephalitis virus; hantavirus; influenza type A virus; herpes viruses; hepatitis B and C (HBV and HCV) viruses; Coxsackie A and B enteroviruses; papilloma virus; Venezuelan equine encephalomyelitis (VEE) virus; Rift Valley fever virus; poxviruses; and chlamydia.[44] This compound have been approved by Russia and neighboring countries for prevention and treatment of tick-borne encephalitis (TBE), hemorrhagic fever with renal syndrome (HFRS), and seasonal flu.



4-iodo-1-5-dimethyl-2-phenyl-pyrazol-3-one

Neuroprotective effects

Parkinson's disease is a neurological disorder characterized by the degeneration of nigrostriatal dopaminergic systems. *In vitro* study showed that edaravone significantly ameliorated the survival of TH-positive neurons in a dose-responsive manner. The number of apoptotic cells and HEt-positive cells significantly decreased, thus indicating that the neuroprotective effects of edaravone might be mediated by anti-apoptotic effects through the suppression of free radicals by edaravone. *In vivo* study demonstrated that edaravone-administration at 30 minutes after 6-OHDA (hydroxydopamine) lesion reduced the number of amphetamine-induced rotations significantly than edaravone administration at 24 hours[45].

Hepatoprotective activity

Fulminant hepatic failure is a serious disease that has a poor cure rate unless liver transplantation is performed. 3-methyl-1-phenyl-2-pyrazolim-5-one (edaravone) has the ability to prevent Fas-induced acute liver failure in mice. Edaravone reduces the number of apoptotic hepatocytes and also preventes cytochrome c release and caspase 3 activities, recognized as markers of apoptosis after mitochondrial disruption. Thus it protects hepatocytes from Fas-induced mitochondria-dependent apoptosis by regulating mitochondrial Bcl-xL and Bax[46].These results suggest that edaravone has a marked preventive effect on oxidative stress-induced acute liver injury. The same derivative prevents endotoxin-induced liver injury after partial hepatectomy not only by attenuating oxidative damage, but also by reducing the production of inflammatory cytokines, CINC and iNOS, in part through the inhibition of NF-κB activation.

Spasmolytic effect on smooth muscles

Dipyrone showed a spasmolytic effect on precontracted smooth muscle in vitro model. In a case reported by Hady, it was reported that premedication with dipyrone allowed the bronchoscope to pass through the bronchus more easily and increased the gas exchange in the lungs[47]. Dipyrone was also found to increase the gas exchange in the lungs when given as an analgesic for postoperative pain relief.Resta et al also reported on 2 asthma patients whose airway obstructions improved with dipyrone[48]. The mechanism by which dipyrone relieves bronchospasm is not clearly understood. Although anti-inflammatory properties by way of cyclooxygenase (COX) enzyme and thus prostaglandin synthesis inhibition by NSAIDs is thought to be responsible for

the spasmolytic effect of some NSAIDs, as dipyrone has no or minimal anti-inflammatory effect.

Toxicity and adverse effects

The most frequently reported side effects of the pyrazolone derivatives are skin rashes. Gastrointestinal side effects are rare. Blood dyscrasias, mostly associated with aminopyrine[49]. Side effects, including acute renal failure, liver dysfunction, acute allergic reaction, disseminated intravascular coagulation, thrombocytopenia, leukocytopenia and renal dysfunction.Edaravone should be carefully used in elderly patients and patients with liver disease, renal disease, hematologic disease, or dehydration. Therapeutic usefulness of penylbutazone is limited because it possesses toxic side effects which include peptic ulcer with hemorrhage or perforation, hypersensitivity reactions of the serum sickness type, hepatitis, nephritis, aplastic anemia, leucopenia, agranulocytosis and thrombocytopenia[50].Hence it is necessary to modify the structure of pyrazolones to minimize the side effect and to improve its therapeutic application.

CONCLUSION

Pyrazolone derivatives are gaining importance through their diverse biological and pharmacological properties. In this review, we have described that pyrazolone derivatives are not only having NSAID action but they also possess other pharmacological activities such as antioxidant, antihyperglycemic, antitumour, anticonvulsant, hepatoprotective, neuroprotective, antiviral, antithrombotic, antimicrobial and radioprotective effects. These derivatives have beneficial effects on myocardial and vascular injury following ischemia and reperfuion in patients with acute myocardial infarction and also in atherosclerosis in the chronic phase .This review article may enlighten the medicinal chemists who are aspiring to discover a versatile drug candidate for the benefit of mankind.

REFERENCES

1. Brune MD, Kay. ''The early history of non-opioid analgesics'', Acute Pain. 1997, 1(1), 33-40.
2. Knorr L: Ber Dtsch Chem. Ges. 1883,16,2597
3. Sil Diptesh, Kumar Rishi, Sharon Ashoke, Maulik Prakas R, Ram Vishnu Ji. ''Stereoselective alkenylation of a 1,3-disubstituted pyrazol-5-one through ring transformation of 2H-pyran-2-ones'', Tetrahedron Lett. 2005, 46(22), 3807-3809.
4. Yukihito Higashi, Daisuke Jitsuikia, Kazuaki Chayamab, Masao Yoshizumia.Edaravone (3-Methyl-1-Phenyl-2-Pyrazolin-5-one), A Novel Free Radical Scavenger, for Treatment of Cardiovascular Diseases, Recent Patents on Cardiovascular Drug Discovery. 2006, 1, 85-93.
5. Metabocard for Demethylated antipyrine (HMDB06240), Human metabolome Database, creation date 2007, 05-22.
6. Fernanda misani, Fiordalisi. ''Anticonvulsant pyrazolone'', United State Patent Office. Patented Jan. 19, 1965; 3,166,475.
7. Georgewill OA, Georgewill UO, Nwankwoala RNP. ''Antinflammatory activity of a new pyrazolon drug'', The Internet J. of Pharmacol., 2009, 7 (1).
8. Silva S.L. Da, Comar J M, Oliveira K M T, Bezerra E R M, Calgarotto A.K, BaldossoP A, Veber C L, Villar J A F P, Oliveira A R M, Marangoni S. ''Molecular modeling of the inhibition of the enzyme PLA_2 from snake venom dipyrone and 1-phenyl-3-methyl-5- pyrazolone'', Int. J. Quant. Chem., 2008, 108 (13), 2576-2585.
9. Nishiyama T, Ogawa M. ''Intrathecal edaravone, a free radical scavenger, is effective on inflammatory-induced pain in rats'', Acta. Anaesthesiol. Scand. 2005, 49(2), 147-151.
10. Brogden RN. Pyrazolone derivatives., Drugs. 1986, 32 (4), 60-70.
11. Graham G G, Scott, K F. ''Mechanisms of action of paracetamol and related Analgesics'', Inflammopharmacol., 2003, 11, 401– 413.
12. Bentur Y, Cohen O.''Dipyrone overdose'', J. Toxicol. Clin. Toxicol. 2004 42, 261– 265.
13. Anderson A J, Bocklehurst W E, Wills A L. ''Evidence for the role of lysosomes in the formation of prostaglandin during Carrageenan-induced inflammation in rat'', Pharmacol. Res. Comm. 1971, 3, 13-17.
14. Jannoff A, Zweifach BW. ''Production of inflammatory changes in the micro circulation by cationic proteins extracted from lysosomes'', J. Exp. Med. 1964, 120, 747-764.
15. Mariappan G, Saha B P, Bhuyan N R, Bharti P R, Kumar Deepak. '' Evaluation of antioxidant potential of pyrazolone derivatives'', J. Adv. Pharm. Tech. Res. 2010, 1(2), 260-267.
16. Yamaguchi T, Oishi K, Uchida M, Echizen H: Edaravone, a radical scavenger, may enhance or produce antiproliferative effects of fluvastatin, amlodipine, ozagrel, GF109203X and Y27632 on cultured basilar artery smooth muscle cells, Biol Pharm Bull, 2003, 26, 1706-1710.
17. Yamamoto Y, Kuwahara T, Watanabe K. ''Antioxidant activity of 3-methyl-1-pheneyl-2- pyrazolin-5-one'', Redox Report. 1996, 2, 333-338.
18. Kazutoshi Watanabe, Yasuhiro Morinaka, Katsuhiko Iseki, Toshiaki Watanabe, Satoshi Yuki, Hiroyoshi Nishi.''Structure–activity relationship of 3-methyl-1-phenyl-2-pyrazolin- 5-one (edaravone)'', Redox Report. 2003, 8.
19. Fernanda misani Fiordalisi. ''Anticonvulsant pyrazolone'', United State Patent Office. Patented Jan. 19, 1965; 3,166,475.
20. Doretto MC, Garcia-Cairasco N, Pimenta NJG, Souza DA, Tatsuo M. A.K.F. ''Dipyrone, a novel anticonvulsant agent? Insights from three experimental epilepsy Models'', Neuro Report. 1998, 9 (10), 2415-2421.
21. Abdel-Aziz Mohamed, Abuo-Rahma Gamal El-Din A, Hassan Alaa A. ''Synthesis of novel pyrazole derivatives and evaluation of their antidepressant and anticonvulsant activities'', Eur. J. Med. Chem. 2009, 44.3480–3487.
22. Krall RL, Penry JK, White BG, Kupferberg HJ, Swinyard EA. Epilepsia.1978 19, 409–428.
23. Steru L, Chermat R, Thierry B, Simon P. Psychopharmacol. 1985, 85, 367–370.
24. Kees Kenneth L, Fitzgerald John J, Steiner Kurt E, Mattes James F, Mihan Brenda, Tosi Theresa, Mondoro Diane, McCaleb Michael L. ''New potent antihyperglycemic agents in db/db mice: synthesis and structure-activity relationship studies of (4-substituted benzyl)(trifluoromethyl) pyrazoles and –pyrazolones'', J. Med. Chem. 1996, 39:3920- 3928.
25. Kees KL, Caggiano TJ, Steiner, K. E, Fitzgerald, J. J, Kates M. J., Christos T. E, Kulishoff J. M, Moore R. D, McCaleb M. L. Studies on New Acidic Azoles as Glucose- Lowering Agents in Obese, Diabetic db/db Mice. J. Med. Chem. 1995, 38, 617-628.
26. Das Nirupam, Verma Abhilasha, Shrivastava Prabhat K, Shrivastava Sushant K.''Synthesis and biological evaluation of some new aryl pyrazol-3-one derivatives as potential hypoglycemic agents'', Ind. J. chem. 2008, 47B, 1555-1558.
27. Yoshida H, Sasaki K, Namiki Y, Sato N, Tada N. ''Edaravone, a novel radical scavenger, inhibits oxidative modification of lowdensity lipoprotein (LDL) and reverses oxidized LDL-mediated reduction in the expression of endothelial nitric oxide synthase'', Atherosclerosis, 2005, 179, 97-102.
28. Minhaz U, Tanaka M, Tsukamoto H, et al. ''Effect of MCI-186 on postischemic reperfusion injury in isolated rat heart'', Free Radic. Res. 1996, 24, 361-3677.
29. Tsujita K, Shimomura H, Kawano H, et al. ''Effects of edaravone on reperfusion injury in patients with acute myocardial infarction'', Am. J. Cardiol. 2004, 94, 481-484.
30. Yanagisawa A, Miyagawa M, Ishikawa K, Murota S. ''Cardioprotective effect of MCI-186 (3-methyl-1-phenyl-2- pyrazolin-5-one) during acute ischemia-reperfusion injury in rats'', Int. J. Angiology. 1994, 3, 12-15.
31. Kuçukguze Guniz, Rollas Sevim, Erdeniz Habibe, Kiraz Muammer, Ekinci A, Cevdet, Vidin Aylin. **''**Synthesis, characterization and pharmacological properties of some 4- arylhydrazono-2-pyrazoline-5-one derivatives obtained from heterocyclic amines''. Euro. J. Med. Chem. 2000; 35(7-8): 761-771.
32. Tudor Rosu, Simona Pasculescu, Veronica Lazar, Carmen Chifiriuc, Raluca Cernat. ''Copper(II) Complexes with Ligands Derived from 4-Amino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one'' Synthesis and Biological Activity, Molecules. 2006, 11.
33. Min Jung Seo, Jung Ki Kim, Bum Suk Son, Bo Gan Song, Zaesung No, Hyae Gyeong Cheon, Kwang-Rok Kim, Young Sun Sohn, Hyoung Rae Kim. ''Novel 3-Methyl-4-(O-substituted-oximino)-pyrazolin-5-ones as a Potent Inhibitors of Cdc25B Phosphatase,''Bull. Korean Chem. Soc. 2004, 25(8), 1121.
34. Vicentini CB, Veronese AC, Giori P, Baraldi PG, Guarneri M. Inter. J. Peptide & Protein Research. 1980, 16, 48.
35. Jelich K, Kraemer W, Brandes W, Haenssler G, Reinecke P U. S. Pat. 1987, 4666933 A.
36. Kakiuchi Y, Sasaki N, Satoh-Masuoka M, Murofushi H, Murakami-Murofushi K. '' A novel pyrazolone, 4,4-dichloro-1-(2,4-dichlorophenyl)-3-methyl-5-pyrazolone, as a potent catalytic inhibitor of human telomerase'', Biochem. Biophys. Res. Commun. 2004, 320(4), 1351-1358.
37. Tripathy R, Ghose A, Singh J, Bacon ER, Angeles TS, Yang SX, Albom MS, Aimone LD, Herman JL, Mallamo JP. ''1,2,3-Thiadiazole substituted pyrazolones as potent KDR/VEGFR-2 kinase inhibitors'', Bioorg. Med. Chem. Lett. 2007, 17(6), 1793-1798.
38. Nishi H, Watanabe T, Sakurai H, Yuki S, Ishibashi A. ''Effect of MCI-186 on brain edema in rats'', Stroke .1989, 20, 1236-1240.
39. Oishi R, Itoh Y, Nishibori M, Watanabe T, Nishi H, Saeki K. ''Effect of MCI-186 on ischemia-induced changes in monoaminemetabolism in rat brain'', Stroke. 1989, 20, 1557- 1564.
40. Ross R. The pathogenesis of atherosclerosis., N. Engl. J. Med .1999, 340, 115-126.
41. Edaravone Acute Infarction Study Group: Effect of a novel free radical scavenger, edaravone (MCI-186), on acute brain infarction. Randomized, placebo-controlled, double-blind study at multicenters, Cerebrovasc Dis. 2003, 15, 222-229.
42. Ogasawara K, Inoue T, Kobayashi M, Endo H, Fukuda T, Ogawa A. ''Pretreatment with the free radical scavenger edaravone prevents cerebral hyperperfusion after carotid endarterectomy'', Neurosurgery. 2004, 55, 1060-1067.
43. Piskarev AV, Nesterenko VS. ''Radioprotective effect of some pyrazolone Derivatives'', Bull. Exp. Bio. Med. 1975, 80(1).
44. Evstropov AN, Yavorovskaya VE, Vorob''ev ES, Khudonogova ZP, Medvedeva SG, Filimonov VD, Prishchep TP, Saratikov AS. ''Synthesis and antiviral activity of antipyrine derivatives'', Pharm. Chem. Jour. 1992, 26(5), 426-430.
45. Yuan Wen Ji, Yasuhara Takao, Shingo Tetsuro, Muraoka Kenichiro, Agari Takashi, Kameda Masahiro, Uozumi Takashi, Tajiri Naoki, Morimoto Takamasa, Jing Meng, Baba Tanefumi, Wang Feifei, Leung Hanbai, Matsui Toshihiro, Miyoshi Yasuyuk, Date Isao. ''Neuroprotective effects of edaravone-administration on 6-OHDA-treated dopaminergic neurons'', BMC Neuroscience. 2008, 9, 75.
46. Takeshi Miyasou, A-Hon Kwon, Katsushige Tsuji, Zeyu Qiu, Tadayoshi Okumura, Yasuo Kamiyama. ''Edaravone prevents fas-induced fulminant hepatic failure in mice by regulating mitochondrial BCL-XL and BAX'', Shock. 2008, 30(2), 212-216.
47. Hady S: Dipyrone in Asthma, Br. Med. Jour. 1973, 1(5855), 744.
48. Resta O, Foschino-Barbaro MP, Carnimeo N, Bavoso P, Picca V. ''Asthma Relieved By Acetylsalicylic Acid And Nonsteroid Anti-Inflammatory Drugs'', Respiration. 1984, 46, 121-127.
49. Brogden RN: Pyrazolone Derivatives, Drugs.1986, 32(4), 60- 70.
50. Georgewill OA, Georgewill UO, Nwankwoala RNP. ''Antinflammatory activity of a new pyrazolon drug'', The Internet J. Pharmacol., 2009; 7 (1).

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