Asian J. Pharm. Res. Vol 10, Issue 1, 1-7, 2020.

e-ISSN 2231 – 363X
Print ISSN 2231 – 3621

Asian Journal
of
PHARMACEUTICAL RESEARCH
Journal homepage: - www.ajprjournal.com

REVIEW ON ANTICANCER AND ANTIDIABETIC ACTIVITY OF PYRAZOLINES

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ABSTRACT

Pyrazolines are the five-membered heterocyclic having two adjacent nitrogen atoms in the ring with single endocyclic double bond and are basic in nature. Pyrazoline, among the various 5-membered heterocyclic compounds have been dragging the attention because of their pharmacological actions exhibited by these compounds. Pyrazoline derivatives display many tremendous biological actions and activities including antidiabetic, anticancer, anti-hypertensive, antiprotozoal, antitumour, anti-HIV, antidepressant and anticonvulsant activities. The study of pyrazoline derivatives towards biological evaluation been an interesting field of pharmaceutical chemistry. Diabetes is a group of metabolic disorder that are characterized by the high blood glucose level which are characterized by hyperglycemia that results from the defect in insulin secretion. Comparison of standard insulin with compounds with phenyl ring or pyrazoline has been done for evaluating the decrease in the glucose level. Cancer is not a single disease, but a combination of large group of diseases which are characterized by the uncontrolled and rapid and pathological proliferation of abnormally transferred cells. Pyrazoline have wide application in the treatment of various cancer types including mouth, oesophagus, brain and bone. Synthesized pyrazoline substituted benzene sulfonyl urea, 1,3thiazole derivatives has been then screened for their potential antiproliferative and in-vitro anticancer evaluation.

Key words: Pyrazoline, Anticancer, Anti-diabetic.

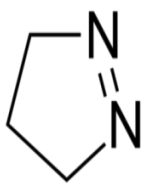
INTRODUCTION

A variety of the medicinal compounds contains heterocyclic ring system. From the current medicinal chemistry investigation it was observed that pyrazoline is one such important heterocyclic system has been gained importance due to the broad range of biological activities.

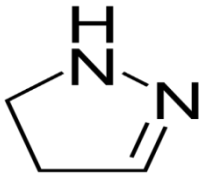
Pyrazoline, among the various derivatives of heterocyclic 5-membered compounds, has attracted its attention due to its various pharmacological activities associated with it. Pyrazolines are the five-membered heterocyclic having two adjacent nitrogen atoms in the ring with single endocyclic double bond and are basic in nature.

Over the years, a great deal of research has been conducted on the synthesis and biological activities of various pyrazoline derivatives. Pyrazoline derivatives are having enormous biological activities such as antimicrobial, anti-inflammatory, analgesic, antipyretic, antidepressant, anti-tuberculosis, anti-antibiotic, anthelmintic, anti-convulsant, antihypertensive, anti-diabetic, anti-tumor, anti -HIV, local anesthetic, antioxidant, insecticide and also selective tranquilizing activity.

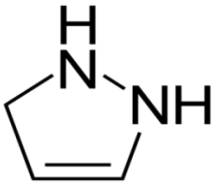
The history of pyrazoline shows that it has attracted many chemists to explore pyrazoline as a biologically active molecule. The study of the biological evaluation of pyrazoline derivatives has been an interesting area of pharmaceutical chemistry.



1-Pyrazoline



2-Pyrazoline



3-Pyrazoline

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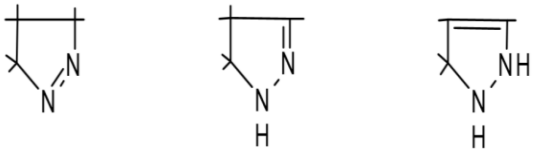
Like the discovery of interesting inventions in the world of science, pyrazolines were also accidentally discovered. When studying the reactivity of phenylhydrazine via ketones and aldehydes, Fischer and Knoevnagel in 1877 condensed acrolein with phenylhydrazine and obtained 1-phenyl pyrazoline instead of hydrazones.



1 - pyrazoline 2 - pyrazoline 3 - pyrazoline

Pyrazoline derivatives are having enormous biological activities such as antimicrobial, anti-inflammatory, analgesic, antipyretic, antidepressant, anti-tuberculosis, anti-antibiotic, anthelmintic, anti-convulsant, antihypertensive, anti-diabetic, anti-tumor, anti -HIV, local anesthetic, antioxidant, insecticideand also selective tranquilizing activity. Attention has focused on pyrazoles for their application in dyes, drugs and anesthetics. Pyrazoles are mainly used in the medical and agricultural fields, but they have also been used as antioxidants in fuels.

DIABETES MELLITUS

Diabetes is a metabolic disorders characterized by high blood sugar over a prolonged period which are characterized by hyperglycemia resulting from the defect in insulin secretion. The phenyl or pyrazoline compound have shown to be better hyperglycemic agent than the standard insulin for reducing blood glucose levels. It is an autoimmune disease caused by an attack on the body of its own pancreas by antibodies. In people with type 1 diabetes, damage to the pancreas does not produce insulin. The main cause of MD is the absolute deficiency of insulin secretion by the beta cells of the pancreas. Symptoms of this type of MD are the autoimmune pathological process occurring in the pancreatic islet and genetic disorders. Symptoms of beta cell destruction include the production of anti-islet autoantibodies to glutamic acid decarboxylase and autoantibodies to insulin. Type 2 diabetes mellitus is the most common form of diabetes, accounting for 95% of diabetes in adults. They are also called as "onset diabetes in adults", but with epidemic of obesity and overweight in case of children. Type 2 diabetes is also called "non-insulin dependent diabetes"

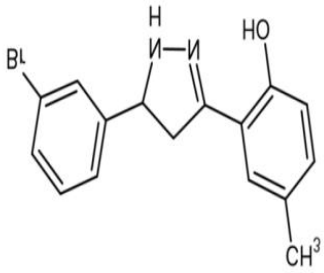
CANCER

Cancer is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body. These contrast with a benign tumor, which does not spread. Possible signs and symptoms include a lump, abnormal bleeding, prolonged cough, unexplained weight loss, and a change in stool. While these symptoms may indicate cancer, they may also have other causes. More than 100 types of cancer affect humans.

Tobacco use is responsible for approximately 22% of cancer deaths. An additional 10% is due to obesity, poor diet, lack of physical activity or excessive alcohol consumption. Other factors include certain infections, exposure to ionizing radiation and environmental pollutants. In developing countries, 15% of cancers are caused by infections such as Helicobacter pylori, hepatitis B, hepatitis C, infection with human papillomavirus, Epstein-Barr virus and l virus immunodeficiency HIV.

Cancer is not a single disease, but a large group of diseases characterized by an uncontrolled, rapid and pathological proliferation of abnormally transformed cells. Pyrazolines are not only useful in the treatment of various types of cancer, including the brain, bones, mouth, esophagus, liver, but some of them also act as chemopreventive agents for cancer. Synthetic benzenesulfonylureas substituted for pyrazoline, 1,3thiazolone derivatives and steroid derivatives were examined for their potential antiproliferative and anticancer in vitro evaluation.

Anticancer Activity: In 2003, Nimavat K *et al.*, [1] synthesized 1- substituted aryl 5- (3'-bromo phenyl) pyrazolines and were taken for primary cancer screening against batteries of cell lines derived from human solid tumors of the NCL cell - H 460 (lung), MCF - 7 (breast) and SF-268 (CNS).



Dmytro Havrylyuk and coworkers in 2009 [2] reported the synthesis of thiazolone-based pyrazoline and evaluated their anticancer activity in vitro. Most of them have shown anticancer activity on leukemia, melanoma, lung, colon, CNS, ovarian, renal and prostate and breast cell lines. Among them, the most effective anticancer compound has been shown to be active with a selective influence on colon cancer cell lines, in particular on HT29.

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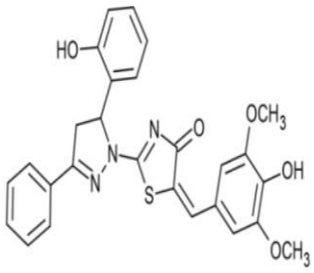
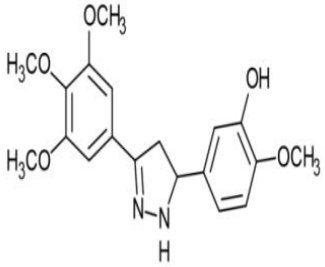
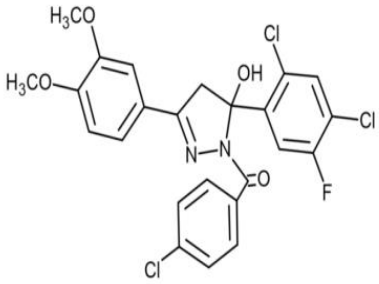


Design of 3, 4, 5-trimethoxy or 2,5-dimethoxypyrazolines N-acetylated and non-acetylated as anticancer agent were reported by Johnson Marlie *et al.*, in 2007 [3]. A non-acetylated derivative has the most active compound in the series, with IC50 values of 2.1 and 0.5 µM in the cell lines B16 and L1210 respectively. In contrast, a similar compound with an N-acetyl pyrazoline ring showed low activity in studies on cell lines.

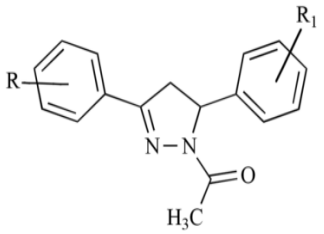


In 2008, Rao B. Sooryanarayana and coworkers [4] synthesized a series of 1-aroyl-3-aryl5-hydroxy-5-(2, 4-dichloro-5-fluro phenyl) pyrazoline and then screened for their antiproliferative activity and found their results.

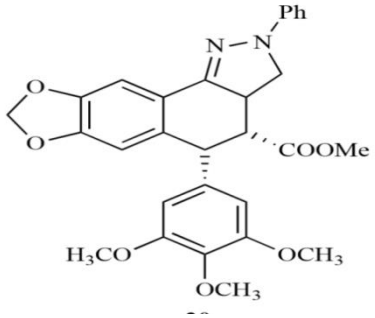


A series of benzimidazo-[1,2-c]-quinazolines were prepared and its anticancer activity was examined in 1994 by Brana and co-workers. Kumar *et al.*, 2009 [5], taking into account the fact that chalcones were considered as an excellent scaffold as starting raw material for the synthesis of different classes of heterocyclic nitrogen compounds such as pyrazolines, thiophenes and pyramidines, etc. These heterocyclic compounds derived from chalcones have a wide range of pharmaceutical importance which includes antibacterial, antifungal, antiviral, antiparasitic, anti-tuberculosis, herbicide, fungicidal, analgesic, antipyretic, antioxidant, anticancer, anticonvulsant, antidiabetic, antidepressant and anti-inflammatory drugs.

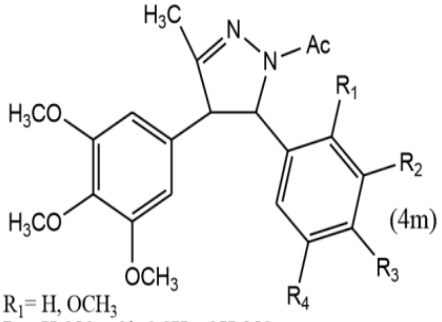
A series of substituted pyrazolines were prepared and its anticancer activity was examined in 2005 by Manna and co-workers. Evaluate their ability to inhibit multi-mediated resistance by P-gycoprotien by direct binding to a purified protein domain containing an ATP binding site and an interaction region with the modulator. The compounds bind to P-glycoportin with greater affinity.



Jose MG *et al.*,1995 [6] synthesized a series of pyrazole derivatives fused from cyclolignanas and evaluated the cytotoxic activities when cultured in culture of murine leukemia cells P-388 and of colon carcinoma HT-29 and of pulmonary carcinoma A-549. They showed IC50 values in micromolar levels, despite the absence of a lactone group in their structures.



In 2011 M. Lee and coworkers [7] synthesized methylpyrazoline analogs from combretastatin A-4 were tested for cytotoxicity against growth of cancer cells in culture using a 72 h MTT continuous exposure test in vitro.



R_1= H, OCH_3
R_2= H, NO_2, Cl, OCH_3, OH, NO_2
R_3= H, CH_3, Cl, Br, NO_2, OCH_3
R_4= H, OCH_3
R_5= H

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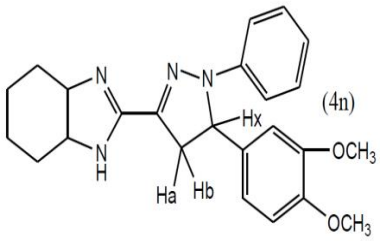
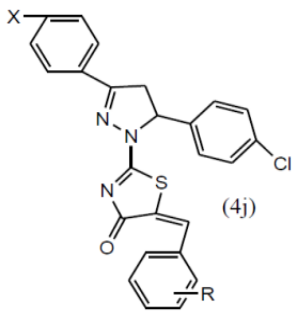
Banday *et al.*, 2010 [8] have synthesized pregnenolone 17pyrazolinyl derivatives and their evaluation as potential anticancer agents against various human cancer cell lines. Various compounds have shown significant cytotoxic activity against the HT-29, HCT-15, 502713 cell lines.

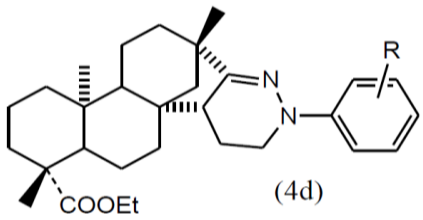


Nadia *et al.*,2013 [9] synthesized a series of 1,3-thiazolone derivatives carrying a pyrazoline fragment and screened for their anti-tumor activity in vitro against the human breast adenocarcinoma cell line (MCF-7). Five of the compounds tested were found to have good anti-tumor activity compared to the reference drug, doxorubicin.



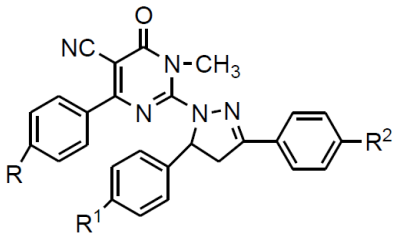
X= Br, Cl
R= H, 4-Cl, 2-OCH_3, 4-OCH_3, 2-NO_2, 3-NO_2

In 2013, S L Zhu *et al.*, [10] studied cytotoxic activity in vitro against four human tumor cell lines of isosteviol derivatives containing heterocyclic fragments of pyrazoline and were evaluated for their anticancer activity against various cell lines. It has been revealed that the introduction of heterocyclic fragments of pyrazoline into isosteviol is beneficial for cytotoxic activities.



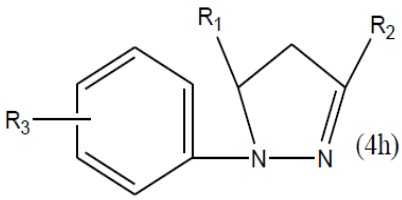
R= H, o-F, m-F, p-F

Derivatives of pyrazolinyl-dihydropyrimidine were synthesized and studied for their antiproliferative activity against the cell lines A 549 (lung), HT 29 (colon), MCF 7 and MDA-MB 231 (breast) by Awadallah *et al.*, in 2013 [11]. Certain compounds have shown high activity against three of the cell lines.



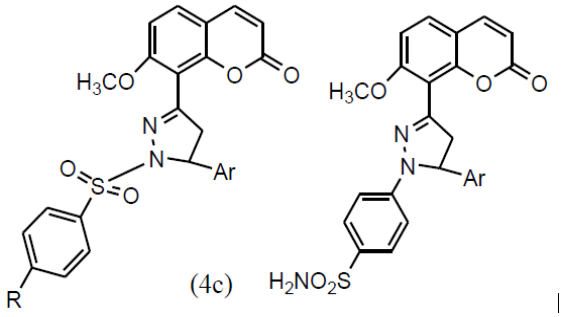
4(f), R_1= F , R_2= CH_3
4(g), R_1= OCH_3 , R_2= OCH_3

M. Abdel-Halim *et al.*, 2013 [12] pyrazoline derivatives were synthesized with scaffolds of 1,3,5-tri-substituted pyrazoline and 1,3,4,5-tetra-substituted pyrazoline and examined for their inhibitory effects on human tumor cell lines.



R_1= 4-chlorophenyl, 3-chlorophenyl, 2-chlorophenyl, 4-bromophenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 4-fluorophenyl
R_2= 4-methoxyphenyl, 3-methoxyphenyl, 2-methoxyphenyl,2,4-dimethoxyphenyl, 2-ethoxyphenyl, t-butylphenyl
R_3= 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 4-bromophenyl

K.M Amin *et al.*, 2013[13] reported the synthesis of two groups of novel coumarin pyrazoline hybrids and endowed with phenylsulfonyl moiety and demonstrated their antitumor potency for the screened compounds.



Certain steroid derivatives of pyrazolinyl C-17 were synthesized and tested their cytotoxic activity against brine shrimp and three human cancer cell lines (NCI-H460, HeLa and HepG2) in 2013 by N.J. Fan and

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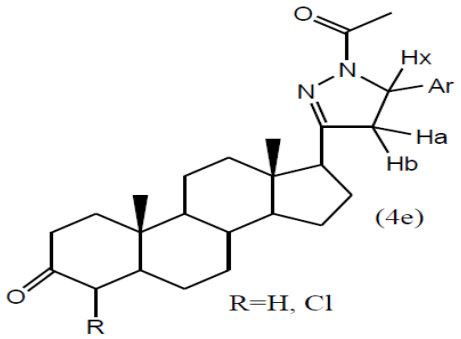
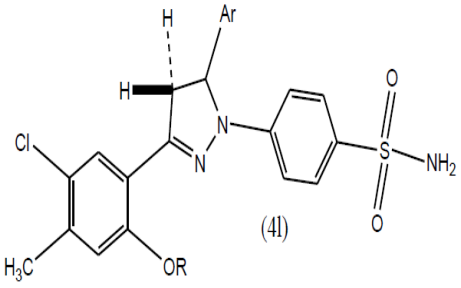
coworkers [14]. Some of these synthetic compounds have shown significant cytotoxic activity.

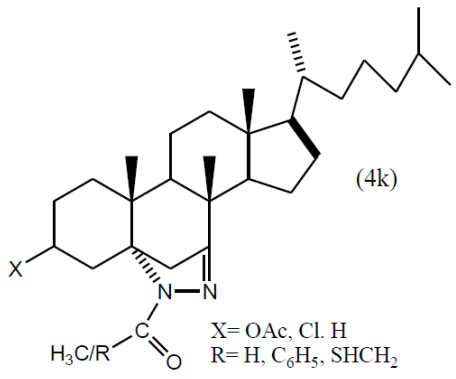


R. Bashir *et al.*, 2011 [15] reported the synthesis of 1,3,5-trisubstituted pyrazolines containing benzene sulfonamide and evaluated the antitumor activity. Certain compounds have shown considerable antitumor activities against the entire tumor cell lines tested.



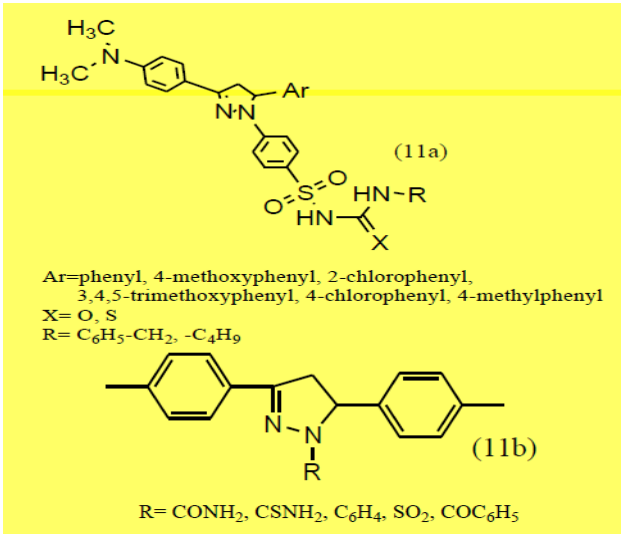
R= H, CH_3
Ar= phenyl, 2-chlorophenyl,ethylenephenyl, 3,4,5-trimethoxyphenyl, 3-hydroxyphenyl, N,N-dimethylaminophenyl, 2-hydroxyphenyl, Clphenyl, 3,4-dimethoxyphenyl

Shamsuzzaman *et al.*, in 2013 [16] synthesized steroid derivatives containing pharmacologically attractive pyrazoline fragments and screened for in vitro anticancer evaluation. The compounds exhibited moderate to good cytotoxicity on cervical cancer and leukemia cell lines 32. All of the compounds were found to be non-toxic to normal cell lines.



Antidiabetic Activity: Syed Ovais *et al.*,in 2014 [17] have synthesized new derivatives of benzenesulfonylurea / thiourea substituted by pyrazoline. The compounds showed moderate to good anti-hyperglycemic activity in normal hyperglycemic rats fed with glucose at a dose of 0.05 mM / kg bw.

N. Santhi *et al.*, 2013[17] synthesized 1,3,5-triaryl-2pyrazolines and studied their anti-diabetic activity and was found to be a better hypoglycemic agent than standard drug insulin for reducing blood glucose levels.



In the same year Emayavaramban *et al.*,[18] carried out in vivo evaluation and confirm the antidiabetic effect of the oral administration of the pyrazoline derivative with different doses of 25, 50 and 100 mg / kg on the percentage of variation of the glycemia and in the prevention of weight loss, decrease urine volume and get the effect of oral administration on the weight of the heart, kidneys, liver of an untreated mouse.

Razzaq *et al.*,in 2008 [19] carried out in silico studies to assess the potential of compounds that prove to be anti-diabetic. The docking study is the calculation technique for exploring the possible binding modes of a ligand on a receptor, an enzyme or any other binding site. This method is used to predict the best orientation of the molecule or ligand towards a protein to form a stable and good complex, 6 compounds (1a, 1b, 2a, 2b, 3a, 3b) have been anchored in the protein. Based on the docking results, 3 compounds (1a, 3a, 2b) show anti-diabetic activity. Compound 1a showed 2 hydrophobic interactions with residues such as Lys513, Lys 534 and Lys 776. The molecule has a strong Van der Waal interaction with Glu510 and Asp777. On this basis, the molecule is assumed to be anti-diabetic. Based on the docking results, 3a appears to have 1 H bond with the Arg547 residue, 2 a hydrophilic interaction with Lys765 and Glu767. There is a Van der Waals interaction between the ligand and the Glu767 residue. Compound 2b has 4 Van der Waals interactions with Lys513, Lys775 and Lys534. They also have a hydrophobic interaction with the amino acid Asp777.

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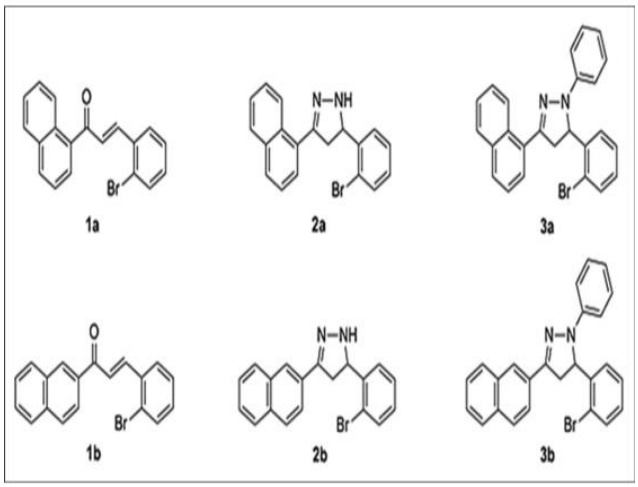

CONCLUSION

This review gives an outlook on the research developments regarding Pyrazoline moiety. This heterocyclic moiety has great biological and medicinal significance. A large array of pyrazoline derivatives possesses a variety of medicinal properties. Pyrazoline is considered as an important lead compound in drug discovery and drug development. Pyrazoline occupy a distinct and unique place in the field of medicine. This article also provides a base for the future research work regarding possible modifications in Pyrazoline moiety and its implementation in drug discovery. Pyrazolines are the five-membered heterocyclic with two adjacent nitrogen atoms in the ring with a single endocyclic double bond which are basic in nature. Pyrazoline derivatives have enormous biological activities such as antimicrobial, anti-inflammatory, analgesic, antipyretic, antidepressant, anti-tuberculosis, anti-antibiotic, anthelmintic, anti-convulsant, antihypertensive, anti-diabetic, anti-tumor, anti -HIV, local anesthetic, antioxidant, insecticide, selective tranquilizing activity. Pyrazoline is a biologically important compound and, therefore, attracts various medicinal chemists. This study gives valuable information for further development of more potent anticancer agents and antidiabetic agents.

ACKNOWLEDGEMENT

Nil

CONFLICT OF INTEREST

No interest.

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