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Review Article

PYRIMIDINE: POTENT HETEROCYCLE FOR TREATMENT OF CANCER

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ABSTRACT

Pyrimidine is the parent heterocycle of a very important group of compounds that have been extensively studied due to their occurrence in living system. Pyrimidine ring is the building block of DNA and RNA and thus pyrimidine based chemical architectures exhibit diverse pharmacological activities. Among the reported medicinal attributes of pyrimidines, anticancer activity is most extensively reported. Various synthetic aspects indicated that pyrimidine derivatives are easy to synthesize and has diverse biological and chemical applications. The utility of pyrimidines as synthon for various biologically active compounds have been given good impact to these studies. The pyrimidine derivatives show various biological activities including antitubercular, antioxidant, anti-inflammatory, anticonvulsant, antimicrobial, antibacterial, antiplasmodial, antifungal, anticancer and analgesic activity. The present review article aims to review the work reported on synthesis and anticancer potentials of pyrimidine derivatives during new millennium.

Keywords: Anticancer, Antitubercular, Anti-inflammatory, Pyrimidine derivative, Pharmacological activities.

1. INTRODUCTION

Many heterocycles, namely pyrimidine and pyrimidinone, imidazole, oxazole, thiazole, triazole and pyrazine are bioactive moieties that are ubiquitously present in nature and have been adopted in numerous pharmaceutical products. Vitamin B1, Histidine and alkaloids such as disorazoles, halfordinol, and texamine are a few examples of natural products containing these heterocyclic rings. Antidiabetic drug, glipizide (2,5 substituted pyrazine), antiviral ritonavir (2,4 substituted thiazole) and antihypertensive losartan (N-substituted imidazoles) stand as examples to show the importance of these heterocycles in the pharmaceutical research[1].

Pharmaceutical chemistry is a scientific discipline at the intersection of chemistry and pharmacology involved with designing, synthesizing and developing pharmaceutical drugs. It is a highly interdisciplinary science combining organic with biochemistry, computa-tional chemistry, heterocyclic chemistry, pharmacology, molecular biology, statistics and physical chemistry [2].

Therefore the need for searching ideal drug has resulted in a systematic approach to design and synthesize newer compounds based on the structure activity relationship of some established drugs. The discoveries of novel synthetic heterocyclic compounds are the target of organic scientists to cure the diseases [3].

2. CANCER

Cancer is a class of diseases characterized by irrepressible cell growth. There are over 100 different types of cancer, and each is classified by the type of cell that is initially affected. It harms the body when damaged cells divide uncontrollably to form lumps or masses of tissue called tumors (except in the case of leukemia where cancer prohibits normal blood function by abnormal cell division in the blood stream). Tumors can grow and interfere with the digestive, nervous, and circulatory systems, and they can release hormones that alter body functions. Normal cells in the body follow an orderly path of growth, division, and death. Programmed cell death is called apoptosis, and when this process breaks down, cancer begins to form. Unlike regular cells, cancer cells do not experience programmatic death and instead continue to grow and divide. This leads to a mass of abnormal cells that grows out of control. Cancer is ultimately the result of cells that uncontrollably grow and do not die.

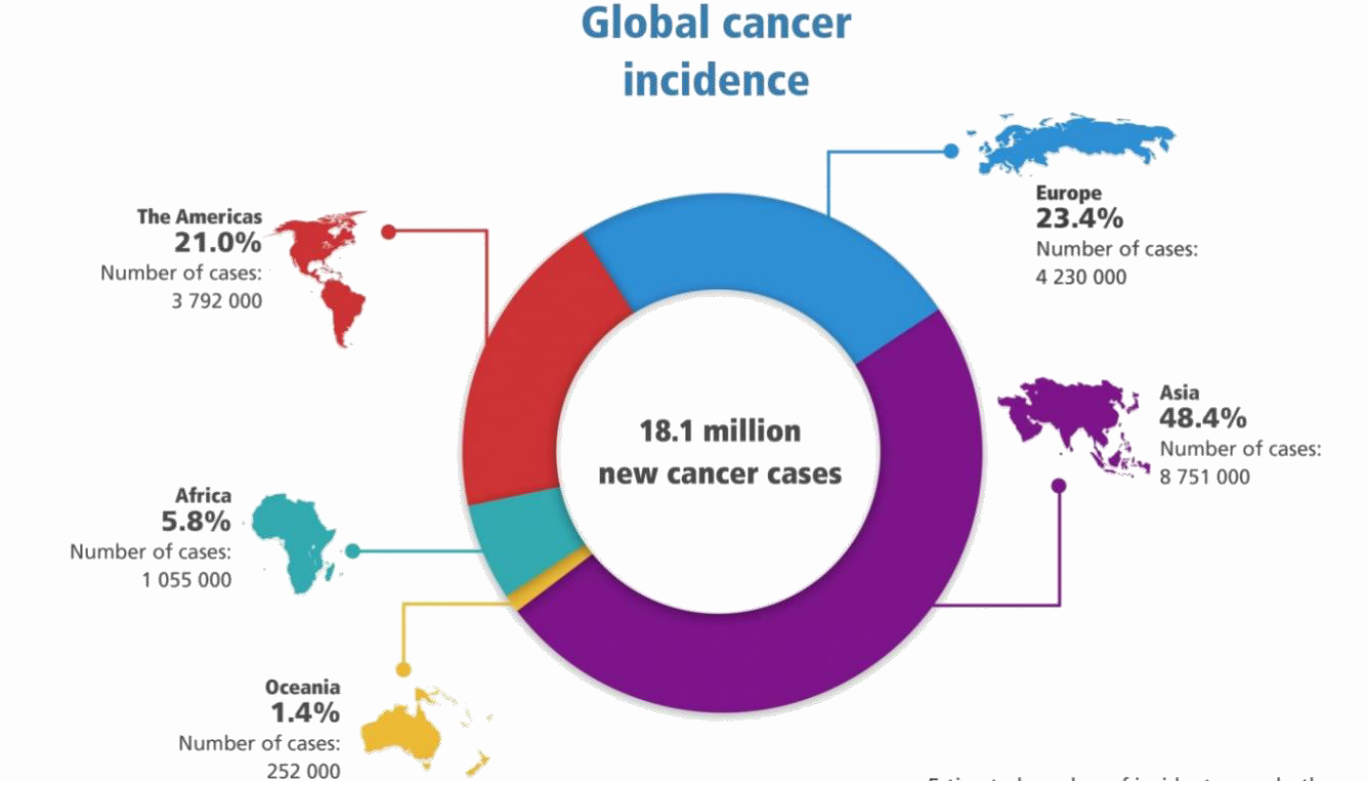


Fig. 1: New Cancer Cases as per Global Cancer Institute [4]

Tumors that stay in one spot and demonstrate limited growth are generally considered to be benign. More dangerous, or malignant, tumors form when two things occur: when a cancerous cell manages to move throughout the body using the blood or lymph systems, destroying healthy tissue in a process called invasion and that cell manages to divide and grow, making new blood vessels to feed itself in a process called angiogenesis. When a tumor successfully spreads to other parts of the body and grows, invading and destroying other healthy tissues, it is said to have metastasized. This process itself is called metastasis, and the result is a serious condition that is very difficult to treat [5].

Cancer is a broad group of various diseases that involving unregulated cell growth. In cancer cells are dividing and grow uncontrollably resulted in malignant tumors and then invade nearby parts of the body. Cancer is a spread to various distant parts of body through the lymphatic system and bloodstream. Cancer encompasses over more than 100 diseases. They having some common properties like,

- abnormal cell growth
- capacity to invade other tissues
- spread to organs via bloodstream or lymphatic system[6].

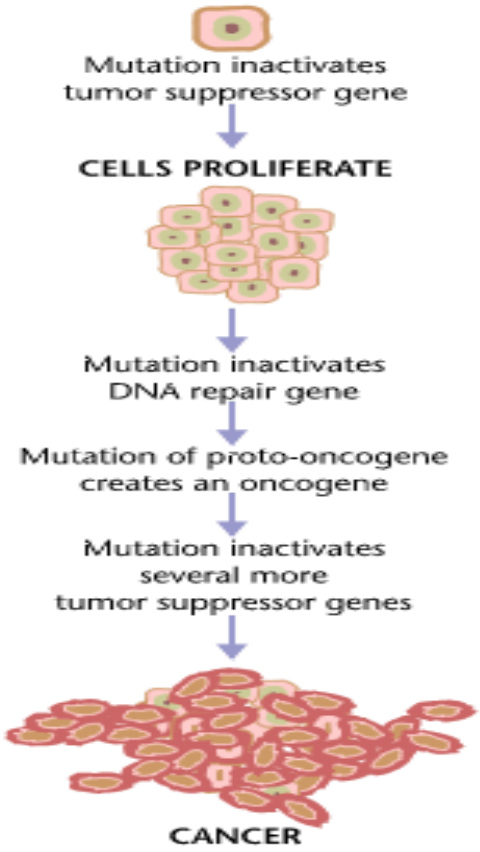


Fig. 2: Pathophysiology of Cancer [7]

3. PYRIMIDINE: A POTENT HETEROCYCLIC SCAFFOLD

Pyrimidine is an aromatic heterocyclic organic compound similar to pyridine. Pyrimidines are the most important six member heterocyclic moiety containing two nitrogen atoms at position 1 and 3. The pyrimidine ring system has wide occurrence in nature as substituted and ring fused compounds and derivatives, including the nucleotides, Vitamin B1 and Alloxan. It is also found in many synthetic compounds such as HIV drug Zidovudine, Barbiturates like barbituric acid and its derivative like Veranal which is used as Hypnotics [8].

Condensed pyrimidine derivatives have been reported as anti-microbial, analgesic, antiviral, anti-inflammatory, anti-HIV, anti-tubercular, anti-tumor, anti-neoplastic, anti-malarial, diuretic, cardiovascular agents.

The biological synthesis of the Pyrimidine derivatives led us to the synthesis of substituted pyrimidines and pyrimidinones. As pyrimidine is a basic nucleus in DNA and RNA, it has been found to be associated with diverse biological activities [9].

Studies on the synthesis and biological properties of pyrimidine derivatives demonstrated that these heterocycles reveal extremely potent biological activity. Pyrimidine derivatives have been found to exhibit cytostatic, immunomodulating and antibacterial activities [10].

There is an urgent and growing need for new classes of antibiotics to maintain the advanced medical procedures we now take for granted. Antibiotics fulfil a critical infection control function in many areas of medicine including during invasive surgery, in cancer chemotherapy, and in the treatment of elderly or immune-compromised patients [11].

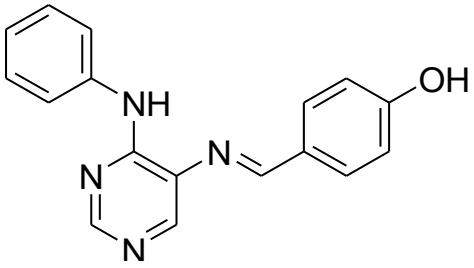
The [4,5-d] isomer of thiazolopyrimidines can be considered as 7-thio analogues of guanine and adenine due to replacement of a nitrogen by a sulfur atom at position 7 of the purine ring. Thiazolo[4,5-d]pyrimidines were reported to possess a broad range of biological activities, including anticancer, antibacterial, analgesic, antidepressant, and antiviral (human cytomegalovirus) properties [12].

Pyrimidine derivatives occupy a distinct and unique place in chemotherapy. The chemotherapeutic efficacy of pyrimidine derivatives is related to their ability to inhibit vital enzymes responsible for DNA biosynthesis as dihydrofolate reductase (DHFR), thymidylate synthetase (TSase), thymidine phosphorylase (TPase) and reverse transcriptase (RTase).

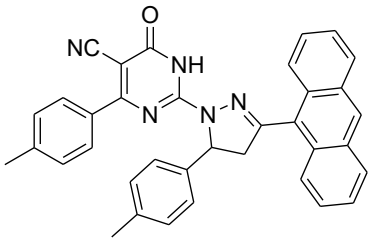
The literature indicated that compound having pyrimidine nucleus possesses broad range of biological activity like 5-fluorouracil as anticancer, Idoxuridine and Triflouridine as antiviral Zidovudine and Stavudine as anti-HIV, Trimethoprim as antibacterial, Minoxidil as antihypertensive and Phenobarbitone as sedative-hypnotics and anticonvulsant [13].

The thiazolo[3,2-a]pyrimidine moiety as a kind of the most important structures, have been shown to display a great diversity of biological activities, including anti-inflammatory, antihypertensive, psycho pharmacological, antimicrobial, antinociceptive, antibacterial, antitumor and anti-HSV-1. They can act as calcium antagonists, diacylglycerol (DG) kinase inhibitors, HIV-1 reverse transcriptase inhibitors, group 2 metabotropic glutamate receptor antagonists and some thiazolo[3,2-a] pyrimidines have been reported as new acetyl cholinesterase (AChE) inhibitors and CDC25B phosphatase inhibitors, used to treat Alzheimer's disease, cancer. At present, the thiazolo [3,2-a] pyrimidine skeleton has been widely used as the core of the drug, which represents ritanserin and setoperone. Therefore, the synthesis of thiazolo[3,2-a]pyrimidine compounds have been attracted wide attention of the chemical workers[14].

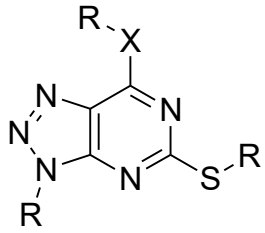
Rao MS *et al* [15] reported anticancer activity of Novel Pyrimidine-4,5-diamine derivatives by using formimidamide benzimidamide and sodium ethoxide. *In silico* modeling was done by using c-Src kinase and p38 MAP kinase complex. Synthesized derivatives possessed significant activity against HeLa cell lines and showed similar activity compared to standard Cisplatin.



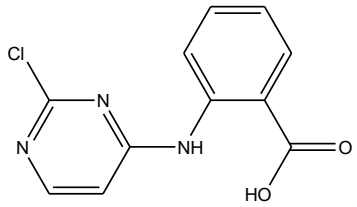
Ahmed NM *et al* [16] have designed and synthesized novel series of pyrimidine pyrazoline-anthracene derivatives and reported anti-liver cancer activity against two hepatocellular carcinoma cell lines HepG2 and Huh-7 as well as normal fibroplast cells by resazurin assay.



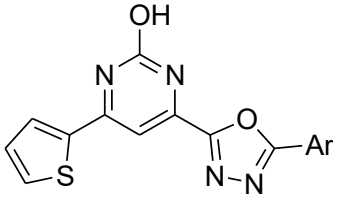
Zhong H.L *et al* [17] have discovered derivatives of [1,2,3] triazolo[4,5-d]pyrimidine as Lysine specific dimethylase 1 (LSD1) inhibitors. They have conducted SARs of the three regions of scaffold and found one of their derivatives potent LSD1 inhibitor and showed certain selectivity to LSD1 over monoamine oxidase. When MGC-803 cells were treated with one of the active compound they found suppressed cell migration.



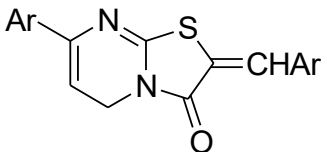
Jadav A *et al* [18] have synthesized novel pyrimidine derivatives as Anticancer agents using 2,4-dichloro-pyrimidine substituted with anthranilic acid.



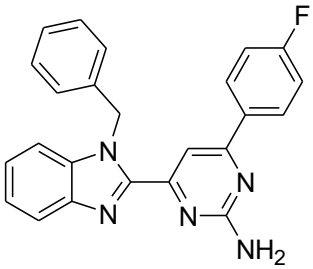
Nermine A.O *et al* [19] have synthesized and evaluated anticancer and antimicrobial activities of some pyrimidine derivatives. They have incorporated several oxadiazole, triazole and thiadiazole moieties into the pyrimidne backbone. They found one of the derivatives having oxadiazole moiety with pyrimidne most potent against breast carcinoma cell line. Pyrimidine carrying substitiuted 1,2,4-triazole 2-thione moiety at position 6, 11 showed the highest cytotoxic activity against colon carcinoma cell line.



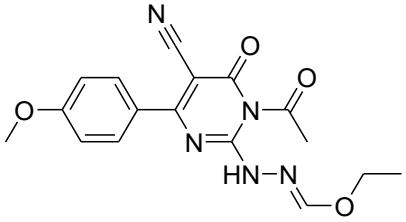
Mahmaud N.M.Y *et al* [20] have synthesized Pyrimidines, their thioglycosides and thiazolopyrimidine derivatives and evaluated anticancer activity. Synthesized compounds were studied for anticancer activity against hepatocellular carcinoma HepG-2, human prostate adenocarcinoma PC-3 and human colorectal carcinoma HCT-116 cells lines. They found some of the compounds showed potent activity against PC-3 and HCT-116 cell lines.



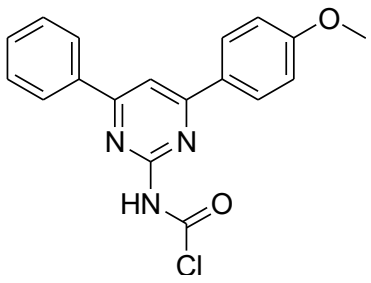
Padhy GK. *et al* [21] have synthesized novel N-benzylbenzimidazole linked pyrimidine derivatives by condensation of N-benzylbenzimidazole chalcones with guanidine hydrochloride. Synthesized compounds were screened for their anticancer activity against human breast cancer cell line MDA-MB-231.



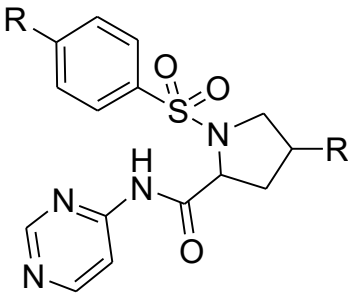
Abbass EM *et al* [22] have synthesized novel pyrimidine derivatives as anticancer agents against HepG2 and HCT-116 cell lines. Molecular docking study was also conducted to reveal the probable interaction with the thymidylate synthase enzyme.



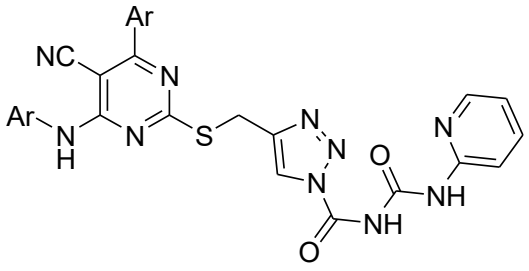
Singh S. *et al* [23] have synthesized substituted pyrimidine derivatives and evaluated their antibacterial activity using agar well diffusion method. Antibacterial activity was evaluated against gram-positive bacteria *Staphylococcus aureus,* gram-negative bacteria *Pseudomonas aeruginosa*. They found potent activity against *Pseudomonas aeruginosa* in compounds having methoxy group.



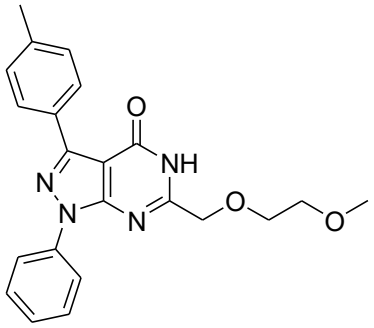
David I.U *et al* [24] synthesized and evaluated anthelmintic activity of pyrimidine derivatives bearing carboxamide and sulphonamide moieties. They found some of the synthesized compound showed potent activity against standard drug Albendazole.



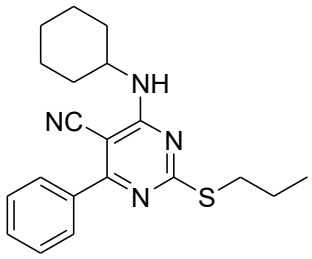
Ma L.Y *et al* [25] synthesized novel 1,2,3-triazole-pyrimidine-urea hybrids as potent anticancer agents. They evaluated anticancer activity against selected four cell lines MGC-803, EC-109, MCF-7 and B16-F10. They found majority of the compounds good to moderate active against all four cell lines. From the study it was concluded that compounds having methoxy groups shown highly potent activity against B16-F10 cell lines.



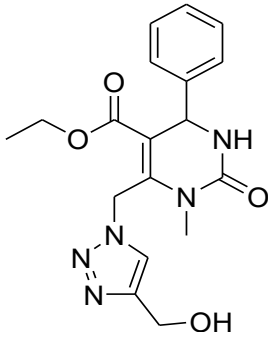
Kosbar TR *et al* [26] (2019) synthesized novel pyrazolo[pyrimidines as potent Telomerase inhibitors and evaluated antitumor assay against Ehrlich ascites carcinoma cells. They have also evaluated for telomerase inhibition by the known telomerase repeat amplification protocol (TRAP) assay.



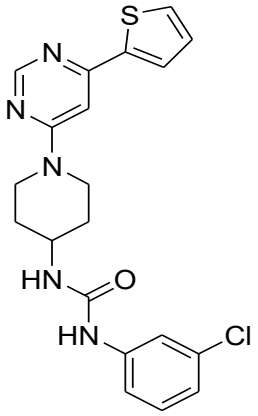
Naseer AA *et al* [27] synthesized novel pyrimidine-5-carbonitrile derivatives as anticancer agents targeting epidermal growth factor receptor. Synthesized compounds were evaluated against four human tumor cell lines colorectal carcinoma (HCT-116), hepato-cellular carcinoma (HepG-2), breast cancer (MCF-7) and non-small cell lung cancer cells (A549). Some of the synthesized compounds were found to have moderate antiproliferative activity against the tested cell lines and more active than the EGFR inhibitor erlotinib.



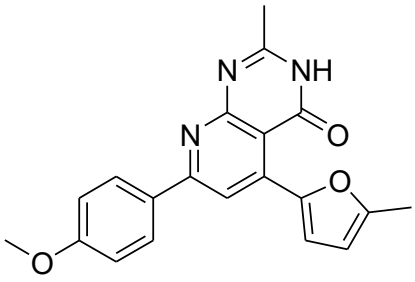
Mostafa AS *et al* [28] synthesized novel dihydro-pyrimidinone derivatives and evaluated anti cancer activities against various cancer cell lines like NCI-H460, SK-MEL-5 and HL-60 (TB) and found to be more safe on normal cells when compared to doxorubicin.



Mule SNR *et al* [29] synthesized novel 4,6-disubstituted pyrimidine derivatives and evaluated as EGFR-TK inhibitors using six different cell lines SIHA, PANC-1 MDA-MB-231, IMR-32, DU145 and A549.



Abedel REM *et al* [30] synthesized pyrido[2,3-d]pyrimidine, pyrido[3,2-e]pyrimidine and terazole[1,5-c]pyrimidine derivatives as potential antimicrobial and anticancer agents. They found synthesized compounds active against colon and liver cancer cell lines.



4. CONCLUSION

In medicinal chemistry, pyrimidine derivatives have been very well known for their therapeutic applications. The presence of a pyrimidine base in Thymine, cytosine and uracil, which are essential binding blocks of nucleic acids, DNA and RNA is one possible reason for their activity. The review article has outlined various pharmacological activities of the pyrimidine scaffold. The scientific information of this manuscript may be worthwhile in encouraging the prospective researchers working on this heterocyclic scaffold.

Conflict of Interest

The authors declare they have no competing interest.

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