Journal of Young Pharmacists, 2025; 17(1):26-35.
https://www.jyoungpharm.org

Review Article

The Impact of Novel Purine, Pyrimidine and Folate Analogues on Cancer Treatment: A Review

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ABSTRACT

The primary goal of this review is to highlight the anti-cancer activity of class of Anti-metabolites derivatives particularly emphasizing purine, pyrimidine and pteridine/folate antagonists as chemotherapeutic agents. The most of the anticancer agents contain heterocyclic moiety in their chemical structure, including purines, pyrimidine and pteridine/folate antagonists which is important in elucidating their mechanism of action and effectiveness against cancer. The etiology and statistical data explore the pivot role for designing drugs in chemotherapy. The derivatives categorized under anti-metabolites usually disrupt essential cellular processes by mimicking endogenous molecules. These agents interfere with DNA or RNA synthesis thereby causing cell death in rapidly dividing tumor cells. As per this present review study, the structure requirements for anti-tumor activity were analyzed through structure activity relationship that explores the pivot role for the synthesis of new purine, pyrimidine and pteridine based drugs in chemotherapy on cancer prevalence for the future benefit and this class of antimetabolites shows some prominent therapeutic properties both *in vivo* and *in vitro*, providing an additional rationale for its use in the maintenance therapy and also in the management of wide variety of disorders, predominantly cancer. In this review, we have also tabulated the clinical significance of purines, pyrimidines and folate-based drugs such as Thioguanine, Mercaptopurine, 5-Fluorouracil and Methotrexate against various cancer types, discussing their efficacy and impact on patient outcomes. In the context of anticancer therapy, this review provides a comprehensive summary about the substitution in the anti-metabolites drugs their synthesis has potential benefit in the medical and pharmaceutical aid.

Keywords: Anti-folate, Anti-metabolites, Cancer, Purine, Pyrimidine.

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Received: 10-09-2024;
Revised: 25-09-2024;
Accepted: 30-11-2024.

INTRODUCTION

The quick developments of aberrant cells that proliferate beyond their typical limits and have the ability to infect nearby bodily regions before spreading to different organs; this latter phase is known as metastasis. The main reason why people die from cancer is because of widespread metastases.[1] According to World Health Organization's cancer probability estimates, ten million mortalities across worldwide, or approximately 1:6 ratio deaths attributed to cancer in the year of 2020. The most common cancers are found in the prostate, lungs, colon, breast and rectum. About one-third of cancer-related fatalities are linked to alcohol dependency, increased BMI, low fruit and vegetable adaptation in diet and sedentary lifestyles. About 30% of cancer incidences in low- and lower capital countries are caused by cancer-causing diseases whereas; Hepatitis and HPV. Numerous tumours can be curative whether they are diagnosed priory and addressed appropriately.[2] The interplay of an individual's hereditary factors with three external agents led to the growth of the pre-cancerous lesion into a malignant tumour. These agents included; Ionizing radiation, ultraviolet light are examples of physical carcinogens, Inhalation of tobacco, alcohol, arsenic (impure drinking water), aflatoxin (food contaminants) and asbestos are examples of chemical carcinogens, viruses and bacterial or parasitic diseases are examples of biological carcinogens.[3] Chemotherapy might be employed for meta statics, combinations, adjuvants and used for neoadjuvant situations. An adjuvant treatment is one that is administered prior to the primary treatment. One type of medication that can be utilized in addition to starting aid to prevent and/or limits proliferation of tumour cells is adjuvant therapy. Adjuvant therapy is currently the accepted standard of

DOI: 10.5530/jyp.20251471

care for cancers of the breast, lungs, colon and ovaries. Combining chemotherapy and radiation therapy is used to shrink the tumour before undergoing surgery or attempting a curative outcome for tumours of the head and neck, lung and anal regions.[4]

In 2020, the most common types of new cancer cases (measured in terms of millions) were

The cases of breast cancer were 2.26, tumour of lung was 2.21, colon including rectum was 1.93, prostate neoplasm was 1.41, dermal tumour (non-mela-noma) was 1 lakh 20 thousand and stomach malignancy 1.09 million.[5] The main reasons for fatalities from cancer; The organ with the maximum mortality effect was in the colon and rectum 9 lakhs, liver 8 lakhs, stomach 7 lakhs, breast 6 lakhs and lung 1.80 million approximately. Cervix carcinoma is the frequent type of neoplasm out their people in 23 different nations. According to WHO statistics, almost 400,000 young people were reported to get cancer annually. In 2020, male individuals are more prone to develop lung, prostate and colorectal cancers and NCI reported that 43% of all types of cancer were diagnosed in men. For female, three most prevalent cancers are breast, colorectal and lung was reported to develop in over 50% of all new cancer diagnosed in female in the year of 2020. According to the American Cancer Society's data report, 6 lakhs tumour mortalities and nearly new 1 lakh reported case of tumours were enrolled in the United States of America in the year 2023.[6] The primary reason for the dramatic increase in cancer incidence is most likely age-related increases in the risk of various malignancies. Age-related declines in cellular repair systems are concomitant with an increase in overall risk.[7]

The pathogenesis of cancer progresses from an earlier stage of cancer to a tumour of malignancy over the course of several stages. The very first phase, known as initiation, is characterized by a mutation in a cell's DNA that turns oncogenes, which promote cell development, active, or tumour suppressor genes, which inhibit cell growth, inactive. During the second step, known as promotion, a small cluster of aberrant cells is formed by the mutant cells being encouraged to divide and grow quickly. The abnormal cells continue to divide and expand in the third stage, which is referred to as progression, until they create a tumour thereby infiltrating nearby tissues and invade to different parts of body throughout the circulation/ via lymphatic systems.[8]

Important components of a significant amount of anti-cancer drugs now on the market are heterocyclic compounds. Their abundance in nature, as well as the capacity to communicate with a variety of cellular systems with processes, constitutes part which makes them popular in the design of anti-cancer drugs.[9] Heterocyclic-based medications are versatile enough to target several metabolic pathways and cellular processes involved in the pathophysiology of cancer. The enormous group of molecules known as heterocycle-based compounds has an unmatched degree of interactional flexibility. Particularly, the nitrogen-based heterocycles are essential for the synthesis of anticancer drugs (Table 1). Research has shown that indoles are among the most effective nitrogen heterocycles because they can trigger cell death in a range of cancer cell types.[10] Two of the most important original indole-based anticancer medications were vincristine and vinblastine, which were identified due to their ability to suppress tubulin polymerization. Oxygen-containing heterocycles are also present in a number of anti-cancer drugs. One of the first medications to be discovered paclitaxel; curative for cancer and its action involves preventing the development of cancer cells during their mitotic phase by depolymerizing microtubule polymers.[11,12]

ANTI-METABOLITES

Purine and pyrimidine core with their equivalent nucleoside and pteridine cofactors, which are employed in several stages of purine and pyrimidine biosynthesis, have structural counterparts in the form of antimetabolites. Obstructing with the process of extraction of the components of Deoxyribonucleic acid is the definition of antimetabolites. Thus, their primary mode of action involves depleting nucleotides, which subsequently inhibits DNA replication. Nevertheless, some of them have the ability to be deceitfully inserted into nucleic acids, causing structural anomalies that result in cell death through different pathways, such as DNA breaks.[13]

Pyrimidine analogues are mainly act by three possible mechanisms by structural modification on the pyrimidine ring: Enzymes/ kinases inhibition which is involves in biosynthesis of pyrimidine, Insertion in to DNA or RNA that leads to miscoding, DNA polymerase inhibition. Fluorouracil, Cytarabine, Floxuridine are common examples as a pyrimidine derivative (Figure 1).[14,15]

Purine nucleoside analogues, however, have the ability to cause cancer cells to cease functioning. Certain nucleoside transporters allow purine nucleoside analogues to enter cells. After entering the cell, a nucleoside kinase phosphorylates producing a monophosphate metabolite in the process. Nucleoside monophosphate kinase then catalyses a second phosphorylation step, while nucleoside diphosphate kinase catalyses a third phosphorylation step. Apoptosis may result from the integration into DNA if it causes DNA strand breaks, stops chain extension, or aggregates mutations. Thioguanine, Mercaptopurine are well known drugs available in the market (Figure 2).[16]

These are important class of anti-tumour drugs structurally similar to folates, antifolates are necessary one-carbon donors for DNA synthesis in mammalian cells. Analogues of folic acid prevent thymidine from being formed, which leads to the build-up of UMP and high levels of UTP.[17] This imbalance in the purine nucleotide pool causes DNA synthesis to slow down. These compounds bind to thymidylate synthase and dihydrofolate reductase, thereby inhibiting cell division and cycle

advancement. Methotrexate is an important class of antifolates they act by inhibiting the enzyme dihydrofolate reductase.[18]

ROLE OF ANTI-METABOLITES IN VARIOUS BIOLOGICAL ACTIONS

One of the key heterocyclic moieties available naturally means purine ring system. Purines are essential for gene transcription, protein synthesis, cellular metabolism and genetic material replication. Likewise, they have been shown to have antiviral, cardiotonic, antineoplastic, antitubercular, antiulcer and antibacterial qualities. It is believed that alkylguanine derivatives play a major part in the development of malignancy, mutation, including cell death. These conjugates induce mutations that produce the GC to AT transition. It is possible to efficiently inactivate the O-alkylguanine-DNA-Alkyltransferase (AGT) protein, which coordinates the inclusion of either thymine or cytosine with no stopping DNA replication. This increases the *in vitro* chemotherapeutic effectiveness of alkylating drugs.[19]

Antimetabolites based on pyrimidines have a wide distribution. The endogenous substrates they antagonize are typically structurally connected to them. Either the pendant sugar groups or the pyrimidine ring may have undergone structural change. Thiouracil and its alkyl derivatives are effective in treating hyperthyroidism with least side effects.[14] It was ultimately confirmed that pyrimidine analogues are potent inhibitors of DHFR (Dihydrofolate reductase) of malarial plasmodia. Sulfadiazine, sulfamerazine and sulfadimidine are pyrimidine derivatives of sulfa medications that are utilized in cases of acute UT infections, CSF meningitis and penicillin allergy. Because of its antiviral activity, pyrimidine derivatives have recently attracted a lot of attention. 5-Iodode oxyuridine acts as a highly selective antiviral agent.[20]

The first pteridine acid inhibitor, Methotrexate [MTX], became known and its phenomenal potential to cure a range of individual cancers motivated researchers to search for other folate analogues (Figure 3). The structural derivative of pteridine acid; Methotrexate blocks action of an enzyme folate reductases, so obstructing the transformation of the folic acid to tetra-hydrofolic acids, it was crucial for metabolic activity and cell division.[21] When combined with other antiblastoma medications, methotrexate is suggested for the treatment of acute juvenile leukaemia, chorionepithelioma of the uterus, breast, lung, testicular and other malignant tumours in adults, as well as for immunosuppressive purposes. Pemetrexed, a novel antifolate, is an antimetabolite that has the ability to combat mesothelioma and certain types of lung cancer.[22] It is believed to impact numerous targets, such as DHFR, glycinamide ribonucleotide formyltransferase and thymidylate synthetase, which in turn results in a reduction in the production of purines also pyrimidines.[23]

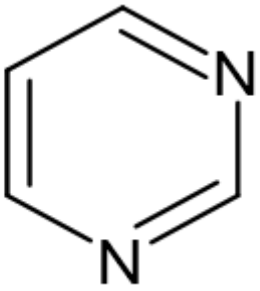


Figure 1: Chemical Structure of Pyrimidine.

STRUCTURE ACTIVITY RELATIONSHIP

Pyrimidine compounds hold a significant position in nucleic acid chemistry, with their variations such as uracil, thymine, cytosine, adenine and guanine serving as essential components for DNA and RNA. This accounts for the wide-ranging pharmacological effects observed in pyrimidine derivatives.[24] Out of these medicinal properties, the anticancer potential of pyrimidines has been extensively documented. Structural modification of antimetabolites on the pyrimidine ring leads to inhibition of kinase enzyme involved in the biosynthesis of pyrimidine (Figure 4). Substitution on the purine antimetabolites results in the inhibition of synthesis and metabolism of purine nucleotides. Anti-folates were designed on the basis of differences between

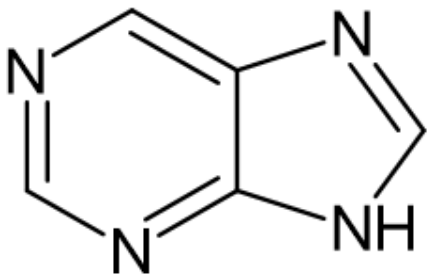


Figure 2: Chemical Structure of 9H-Purine.

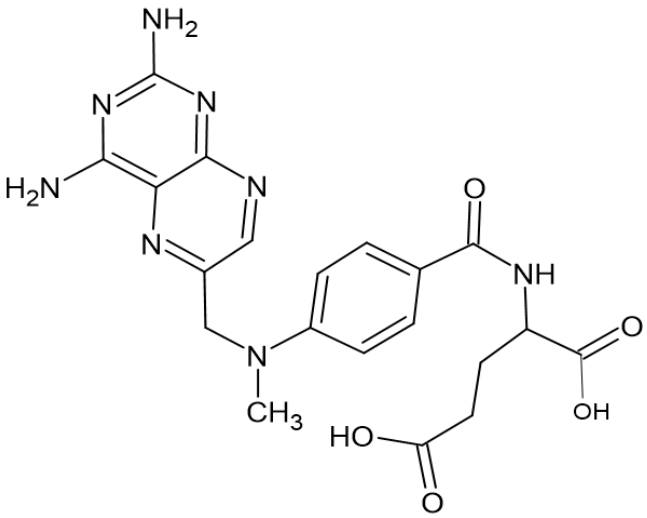


Figure 3: Chemical Structure of anti-folate drug Methotrexate.

the folate influx system in certain tumours and also in normal tissues (Figure 5).[25]

REVIEW OF LITERATURE

Shaaban OG *et al.*, (2018) were reported that the novel purines with a substituted 8-position and incorporating a pyrazole component were synthesized and assessed for their potential anticancer and antioxidant properties. The reduced cytotoxic activity and anticancer activity was shown by 1a and 1b (Figure 6) against tumour cell line A549 (lung cancer) by inducing apoptosis to cancer cell lines respectively.[43]

Hao EJ *et al.*, (2021) was reported about the synthesis of potent anticancer agents reduced colon cancer cell growth *in vitro*. The reaction involved in the synthesis was asymmetric synthesis and according to Structure-Activity-Relationship (SAR) demonstrated wherein 2a (Figure 7) emerged as the most potent, displaying significant inhibitory effects against both HCT-116 and SW480 strains, with IC_{50} value of 0.89 and 1.15 µM, respectively.[44]

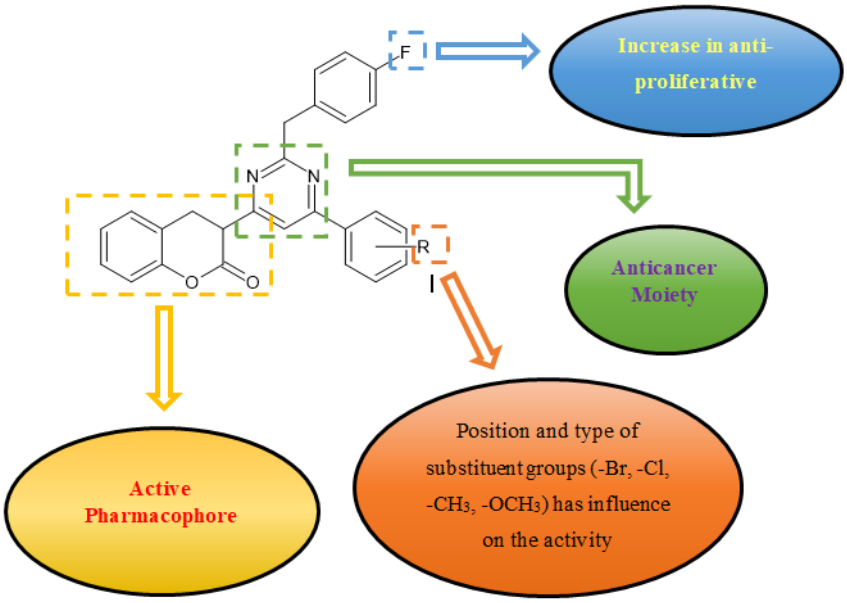


Figure 4: Structure Activity Relationship Coumarin derived pyrimidine derivatives.

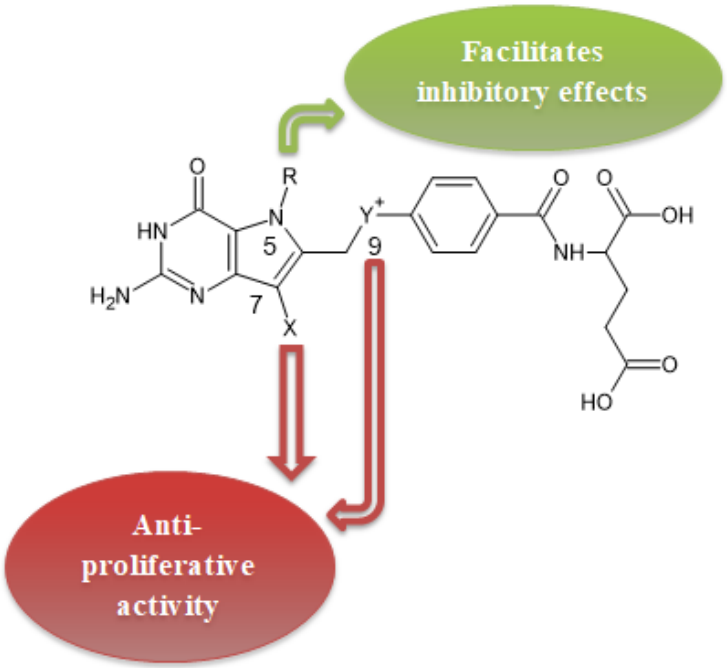
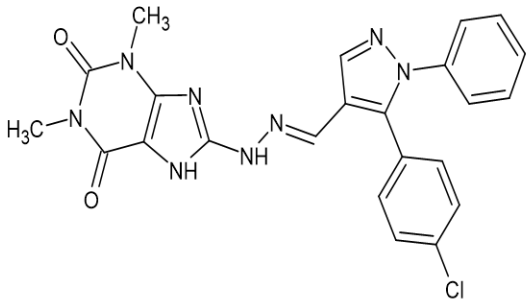


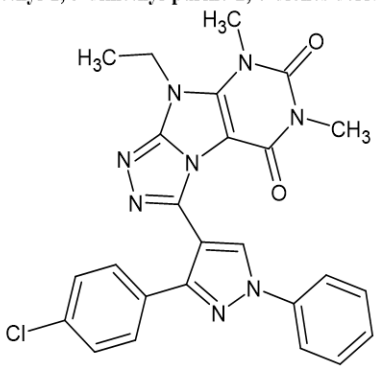
Figure 5: Structure Activity Relationship for anti-folate derivatives.

Nepali K *et al.*, (2020) was reported the synthesis and assessment for a sequence of Histone Deacetylase (HDAC) blockers featuring a purine/purines isostere were synthesized and it involves multistep synthetic approach. *In vitro* studies on cytotoxicity indicate that compound 3a (Figure 8), a benzamide derivative, effectively defeated the proliferation of triple-negatives breast tumour strains MDA-MB-231 (IC_{50} of 1.48 mM) and MDA-MB-468 (IC_{50} of 0.65 mM), as well as liver tumour strains HepG2 (IC_{50}=2.44 mM).[45]

Khalifa ME *et al.*, (2020) were reported that nine novel compounds based on purine were conceptualized and synthesized via consecutive reactions involving the initial compound, 8-amino-substituted purine and a variety of reagents involves multistep reaction. Despite derivative 4a (Figure 9) exhibiting potent

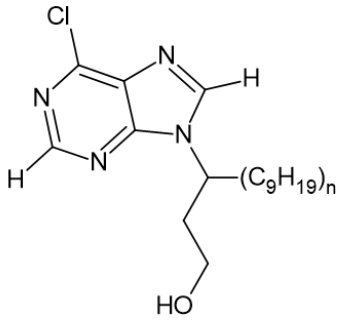


1a; 8-{2-(3-aryl-1-phenyl-1H-pyrazolo-4-phenyl)-methylene-hydrazinyl}-7-ethyl-1, 3-dimethyl-purine-2, 6-diones derivatives



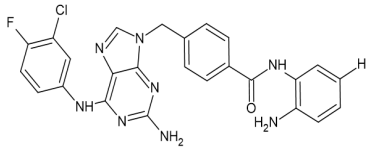
1b; 3-{3-aryl-1-phenyl-1H-pyrazolo-4-phenyl}-9-ethyl-5, 7-dimethyl-5H-(1, 2, 4)triazolo-[4, 3]-purine-6, 8-diones

Figure 6: Chemical Structure of derivatives 1a and 1b showing potential anti-cancer activity.



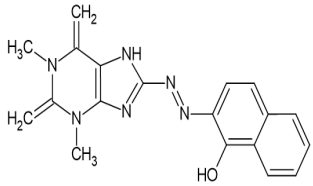
2a; {3-[6-Chloro-9H-purin-9-yl]-dodecane-1-ol}

Figure 7: Chemical Structure of derivative 2a effective against colon cancer.



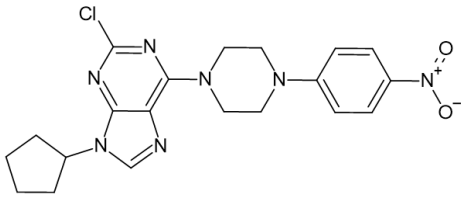
3a; 4-{[2-amino-6-[(3-chloro, 4-fluoro-phenyl)-amino)-9H-purino-9-yl)-methyl]-N-[2-amino-phenyl] benzamide

Figure 8: Chemical Structure of derivative 3a effective against breast and lung cancer.



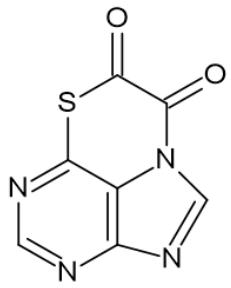
4a; 8-{(2-Hydroxy-naphthalene-1-yl)-di-azenyl}-1,3-di-methyl-3,7-di-hydro-1H-purine-2,6-dione

Figure 9: Chemical Structure of derivative 4a as an anti-cancer agent.

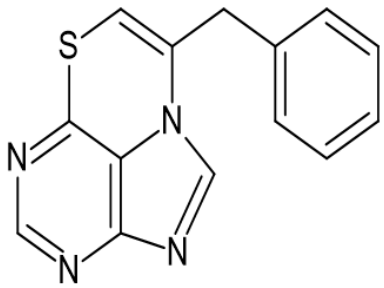


5a; {2-Chloro-9-cyclic-pentyl-6-[4-(4-nitro-phenyl)-piperazin-1-phenyl]-9H-purine}

Figure 10: Chemical Structure of derivative 5a as an anti-cancer agent.



6a; {1, 4}-thia-azino[4,3,2]-purine-7, 8-diones



6b; 7-benzyl-{1,4}thia-azino{4,3,2}-purines

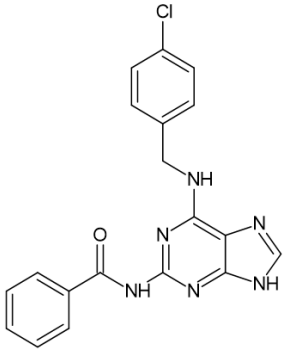
Figure 11: Chemical Structure of derivatives 6a and 6b as anti-cancer agents.

activity at low concentrations (IC_{50} of 26.16 μM), it still poses risks to normal cell strains.[46]

O. Salas C *et al.*, (2019) were reported that devised, produced and assessed innovative derivatives of 2,6,9-trisubstituted purines with the aim of determining their potential as antitumor agents. The reaction involves 3 steps employing 2-(fluoro)-6-chloropurine as a basic material Compound 5a (Figure 10) exhibited promising efficacy compared to the currently available drug, cisplatin.[47]

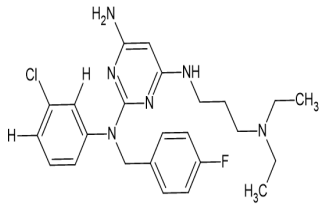
Hassan AY *et al.*, (2017) were reported the synthesis of novel fused purine analogues and investigated for anticancer activity wherein compounds 6a and 6b (Figure 11), resulted in significant anticancer potency against nearly all cell lines tested. Various fused purine analogues have been synthesized using different chemical reactions employing 6-mercaptopurine as a starting material.[48]

Wang X *et al.*, (2019) were reported the synthesis of new 2, 6-di-substituted purines analogues as major anti-cancer agents. The reaction involved is nucleo-philic substitutions of 6-(chloro)-9H-purino-2-amine with benzoyl-chloride as



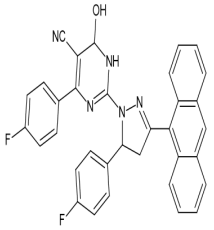
7a; *N*-{6-{[(4-chloro-phenyl)-methyl]-amine}-9*H*-purino-2-yl}-benzamide

Figure 12: Chemical Structure of derivative 7a effective against different cancer cell strains.



8a; N-2-{3-chloro-phenyl}-N-4-(3-(diethyl-amino)-propyl)-N-2-(4-fluoro-benzyl)-pyrimidyl-2,4,6-tri-amine

Figure 13: Chemical Structure of derivative 8a as an anti-cancer agent.



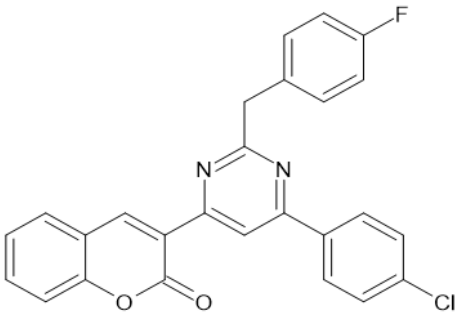
9a; 2-{3-Anthracene-9-phenyl-5-(4-fluoro-phenyl)-4, 5-di-hydro-pyrazolo-1-yl}-4-(4-fluoro-phenyl)-6-oxo-1, 6-di-hydro-pyrimidyl-5-carbonitrile

Figure 14: Chemical Structure of derivative 9a as an anti-cancer agent.

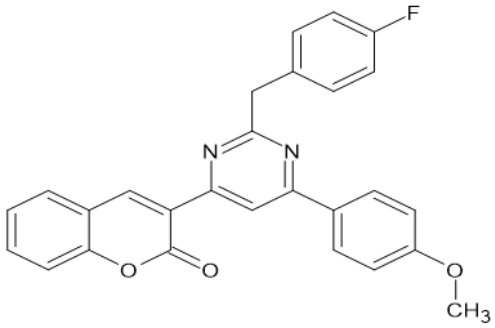
Structure Activity Relationship for anti-folate derivatives.

Table 1: Clinical significance of various brands of purine antagonists.

Name of the Drug	Clinical Significance
Thioguanine	Acute blood cancers in children and adults, Leukemia myelogenous chronica, ulcerative colitis in particular, an inflammatory bowel condition, psoriasis, Mice with colorectal cancer that is immune-therapy-resistant.[26]
Mercaptopurine	Beneficial in the management of myelo-monocytes blood cancers, acute lympho-blastic leukaemia, and myeloid leukaemia.[27]
Fludarabine	Acute-myeloid leukaemia and chronic-lymphocyte leukaemia respond well to its therapy.[28]
Pentostatin	For curing of hairy cell-leukaemia, chronic-lymphocytic leukaemia, (steroid-refractory acute and chronic graft against hostage disease.[29]
Cladribine	To cure leukaemia, Chronic-lymphocytic leukaemia, histiocytosis, Erdheim-Chester disease.[30,31]
Fluorouracil	Beneficial in the therapy of carcinomas of breast, colon and rectum, pancreatic, stomach, skin and basal cell carcinomas.[32]
Cytarabine	Treatment of acute and chronic leukaemia, meningeal leukaemia, acute and chronic lymphocytic leukaemia.[33]
Floxuridine	In the management of gastrointestinal adenocarcinoma, liver cancer.[34]
Capecitabine	Effective in treating acute granulocytic leukaemia of adult and children, metastatic breast cancer, carcinoma of gall bladder, hepatocellular carcinoma.[35]
Gemcitabine	Treatment for pancreatic, breast, bladder, ovarian cancer, cervical cancer, Hodgkin's disease, head and neck carcinoma.[36]
Methotrexate	Treatment of breast cancer disabling psoriasis,[37] rheumatoid arthritis,[38] pediatric poly articular juvenile idiopathic arthritis,[39] Leukaemia,[40] Acute myeloid leukaemia, lung cancer.
Calcium folinate/ Leucovorin	For treating gastric carcinoma, osteosarcoma, colorectal carcinoma and pregnancy anemia.[41]
Azathiopurine	Treatment of Rheumatoid Arthritis and in the management of Crohn disease, Atopic dermatitis, multiple sclerosis.[42]

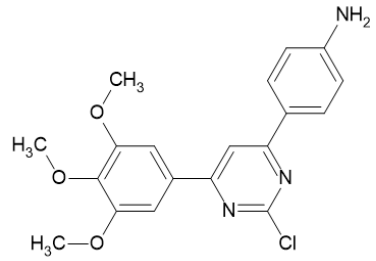


10a; 3-{6-(4-chloro-phenyl)-2-{(4-fluoro-phenyl)-methyl]-pyrimidyl-4-yl}-2*H*-1-benzopyrano-2-one



10b; {3-(2-(4-fluoro-benzene)-6-(4-methoxy-phenyl)-pyrimidino-4-yl}-2H-chromen-2-ones]

Figure 15: Chemical Structure of derivatives 10a and 10b as anti-cancer agents.



11a; 4-{2-chloro-6-(3,4,5-tri-methoxy-benzyl)-pyrimidyl-4-yl}-aniline

Figure 16: Chemical Structure of derivative 11a as an anti-cancer agent.

well as 2-methoxy-benzoyl chloride in presence of pyridines. Compound 7a (Figure 12) demonstrated outstanding inhibition of cell proliferation across three different cancer cell strains (as IC_{50} value of 1.77±0.35 mM for HCT-116, 1.51±0.19 mM for SW480and 1.25±0.38 mM for MDA-MB-231) respectively.[49]

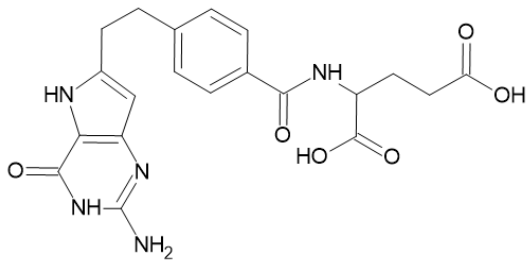
Madia VN *et al.*, (2021) were reported the synthesis of pyrimidine analogues and tested towards five human tumour cell Strains. It is a multistep synthesis whereas among all the synthesized second series 8a (Figure 13) below compound of aminopyrimidine derivatives exhibited excellent activity with the EC_{50s}=10-26 µM.[50]

Ahmed NM *et al.*, (2019) were reported the synthesis and investigated new sequence of substituted pyrimidino analogues as anti-tumour agents. Compound 9a (Figure 14) exhibited significant efficacy against Hep-G2 and Huh-7 cell strains (as IC_{50} value of 5.34 and 6.13 µg/mL), akin to the activity of Doxorubicin (DOX).[51]

Hosamani KM *et al.*, (2015) were reported the microwave-assisted synthesis of coumarins derived pyrimidines derivatives as potential anti-cancer drugs. Of these, compound demonstrated strong efficacy towards the A549 cell strain, compared to the reference drug cisplatin. Meanwhile, compounds 10a and 10b (Figure 15) displayed exceptional activity towards the MDAMB-231 cell strain, surpassing the potent of Cisplatin with an IC_{50}<10 mM.[24]

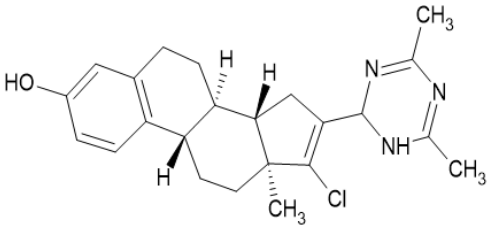
Kumar B *et al.*, (2018) were reported the various substituted pyrimidines bridging combretastatin compounds had been synthesised and assessed in the current investigation. The intermediates chalcone were synthesized by aldol condensation further reacted with pyrimidine derivatives to derive final products. Compound 11a (Figure 16) were strongest in the series, as of IC_{50} towards of these 2 cancer cell types of 4.63 mM and 3.71 mM respectively.[52]

Tian C *et al.*, (2017) were reported that by using MTS technique GI_s data, a range of novel 6-substituted pyrimidino analogues have been investigated for its potential anticancer activity. These are most potent substance, 12a (Figure 17), had GI_{50} values of 8.92, 1.72 and 0.73 micromolar towards HL-60, H-1299 and A-549 cells, respectively.[53]



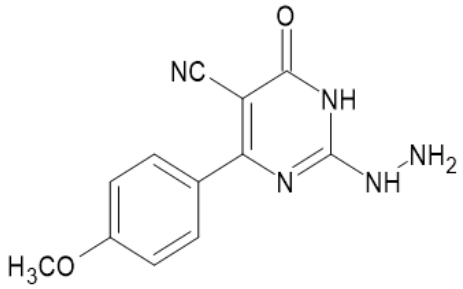
12a; {4-(2-(2-Amino-4-hydroxy-5H-pyrolo-[3, 2-pyrimidin-6-yl)-ethyl)-benzoyl}-glutamic-acid

Figure 17: Chemical Structure of derivative 12a as an anti-cancer agent.

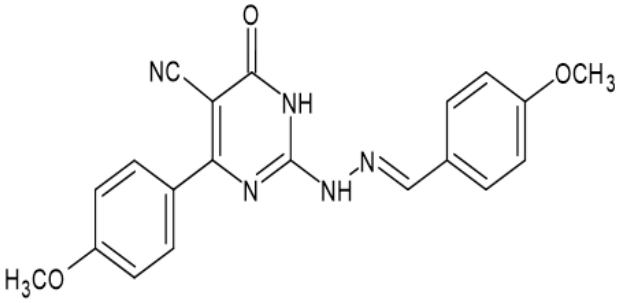


13a; 16-{4, 6-di-methyl-1, 2-di-hydro-1,3, 5-tria-azin-2-yl)-17-chloro-11, 3, 5, 16-estra-tetraen-3-ol

Figure 18: Chemical Structure of derivative 13a effective against breast cancer.



14a; 2-hydra-zin-yl-4-{4-methoxy-phenyl}-6-oxo-1, 6-di-hydro-pyrimidino-5-carbo-nitrile

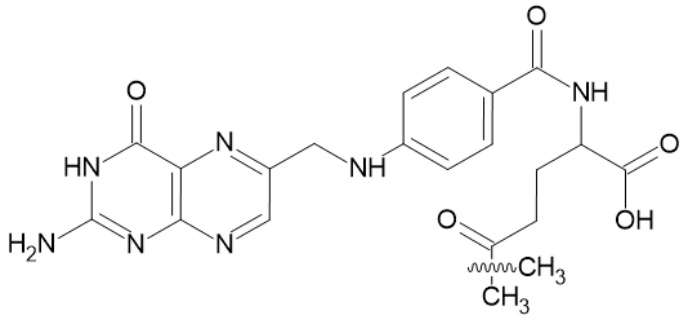


14b; 2-aceto-hydr-azinyl-4-{4-methoxy-phenyl}-6-oxo-1,6-di-hydro-pyrimidino-5-carbo-nitrile

Figure 19: Chemical Structure of derivatives 14a and 14b as anti-cancer agents.

Scherbakov AM *et al.*, (2018) were reported the synthesis of variety of new pyrimidines as potential anticancer agent particularly breast cancer cell strains. The IC_{50} value of derivative of Compound 13a (Figure 18) found to be 7.4 for MCF-cell strain demonstrated selectivity as an ERα modulator, exhibiting the most potent antiproliferative effects against hormone-dependent breast cancer.[54]

Mohamed MM *et al.*, (2017) were reported that the newly developed pyrimidine derivatives anti-tumour activity was performed *in vitro*. It was discovered that are more effective



15a; Folic acid derived paclitaxel conjugates

Figure 20: Chemical Structure of derivative 15a as an anti-cancer agent.

scaffolds towards the 2 cell strains were compounds 14a and 14b (Figure 19) showing IC_{50} value of 25.52 and 25.73 against HePG-2 and MCF-7 respectively.[55]

Dai Y *et al.*, (2020) were reported that the synthesis and evaluation of folic-acid peptides derived paclitaxel derivatives. FAP7TX 15a (Figure 20) exhibited greater ability in inducing cell toxicity (with an IC_{50} of 2.92±0.2 mM), disrupting cell membranes and promoting apoptosis in MCF-7/PTX cells.[56]

CONCLUSION

This review illustrates the effects of antimetabolites as antineoplastic agent. Heterocyclic compounds possess good amount of anticancer activity, we particularly focused on antimetabolites either purine and pyrimidine or folate analogues have a profound impact on human health. The structural modification affects the activity on purine, pyrimidine and folic acid analogues is crucial for designing compounds with enhanced anticancer efficacy. Researchers can aim to optimize the chemical structure to improve bioavailability, specificity and overall therapeutic potential. As per the study conducted on pyrimidines and purines containing analogues have a particular, effective and individual role in combating various cancers, including those of the breast, prostate, lung, colon and liver, in that order. We can conclude that this class of antimetabolites shows some prominent therapeutic properties both *in vivo* and *in vitro* and

the synthesis of these provides an additional rationale for its use in the pharmaceutical research and also in the management of wide variety of disorders, predominantly cancer.

ACKNOWLEDGEMENT

The authors extend their appreciation to in-charge of Central Library, Faculty of Pharmacy, Sri Adichunchanagiri College of Pharmacy, Adichunchanagiri University, BG Nagara for providing access to the journals also digital library services. We offer thanks to SACCP Principal, Chemistry Department Head & other faculty members for clarifying the doubts during the review process.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

BMI: Body Mass Index; **HPV:** Human Papillomavirus; **WHO:** World Health Organization; **NCI:** National Cancer Institute; **DNA:** Deoxyribonucleic acid; **RNA:** Ribonucleic acid; **UMP:** Uridine Monophosphate; **UTP:** Uridine Triphosphate; **UTI:** Urinary Tract Infections; **CSF:** Cerebrospinal fluid; **IC_{50}:** Half Maximal Inhibitory Concentration; **GI_{50}:** Growth Inhibition 50%.

SUMMARY

The most prevalent malignancies include breast, lung, colon, prostate, and rectal cancers. Cancer is still the top cause of death globally and is characterized by aberrant cell development and spread. Cancer risk factors include poor diet, high body mass index, and alcohol use. Treatment and diagnosis at an early stage can be curative. Cancer progresses via three stages, which are triggered by environmental factors such as radiation, tobacco, and viruses, as well as genetic abnormalities. Adjuvant therapy and other forms of chemotherapy are essential components of treatment. In the creation of anticancer drugs, heterocyclic compounds-especially nitrogen-based indoles-are essential. Purine and pyrimidine analogues are examples of antimetabolites that prevent DNA replication, which kills cancer cells. Methotrexate and other anti-folates interfere with the metabolic functions of cancer cells. Antimetabolites' structural modifications increase their anticancer effectiveness by focusing on particular enzymes involved in nucleotide biosynthesis.

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Cite this article: Ramakrishna JK, Gowda PSKR, Rahamanulla A, Nagaraju PK, Ramesh B, Chandramouli M. The Impact of Novel Purine, Pyrimidine and Folate Analogues on Cancer Treatment: A Review. J Young Pharm. 2025;17(1):26-35.