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A REVIEW: ANTICANCER ACTIVITY OF PYRIMIDINE ANALOGUES

KOMPALLY SAI PREETHI 1*, TARANUM FATHIMA 2, ABBAGONI AKSHITHA 3, J.V.C.SHARMA 4, K.Chandana 5

1.student 2. Assistant professor 3.student 4. Principal 5.student

JOGINPALLY B R PHARMACY COLLEGE, YENKAPALLY(V), MOINABAD, TELANGANA, INDIA

Abstract :

Pyrimidine ring is the building unit of nucleic acids (DNA & RNA) , it's related chemical structures possess various pharmacological functions, in which anticancer activity is mostly reported . Nowadays cancer has become serious global health challenge , so the researchers have focused on developing anticancer analogues . Pyrimidine , a fortunate scaffold , is a part of living organisms which plays major role in cancer pathogenesis and it is also pointed as a valuable compound in the cancer treatment. There are many innovative pyrimidine derivatives designed and produced for the last few years with specific anticancer activity . This review article mainly focuses on the pyrimidine analogues and their anticancer activity . The present compulsion can be extremely beneficial for the future medical chemists focusing on the design and synthesis of anticancer drugs .

Key words : pyrimidine ring , anticancer activity, cancer pathogenesis , medical chemists .

INTRODUCTION :

- The pyrimidine ring system has wide existence in nature as substituted and ring fused compounds .
- Although pyrimidine derivatives such as uric acid and alloxan were known in the early 19th century , laboratory synthesis of a pyrimidine was not outranged until 1879. The systematic study of pyrimidines started in the year 1887 by pinner , who synthesized derivatives by condensing ethyl acetoacetate with amidines .
- Pinner first proposed the name “ pyrimidine “ in 1885.
- The parent compound was first prepared by Gabriel and colman in 1900 by conversion of Barbituric acid to 2,4,6- trichloro pyrimidine followed by reduction using zinc dust in hot water.

Since years pyrimidine nucleus has emerged as an essential pharmacophore interacting with the synthesis and also with the major functions of nucleic acids. Pyrimidine ring is the building unit of DNA & RNA , hence it's derivatives exhibits various pharmacological activities such as antiviral , anticancer , especially anti – HIV , anti malarial , antimicrobial and anti – inflammatory .

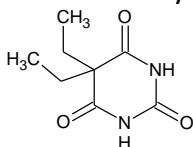
Pyrimidines are the most important six membered heterocyclic compounds containing two nitrogen atoms . Pyrimidines are present among the three isomeric diazines .



pyrimidine

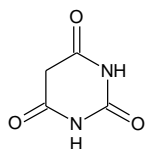
Several pyrimidines have been extracted from the nucleic acid hydrolyzed. The nucleic acids are found to be essential constituents of all cells and also of living matter ; cytosine is found to be present in both types of nucleic acids i.e.. ribonucleic acid (RNA) & deoxyribonucleic acid (DNA), and where as uracil is present only in RNA and thymine only in DNA.

Pyrimidine ring is found in vitamin B1 , Barbituric acid (2,4,6 – trihydroxy pyrimidine) and its derivatives such as veranal which are usually used as hypnotics.



Barbituric acid

veranal



Compounds having pyrimidine nucleus possess broad range of biological activity like 5-fluorouracil as anticancer , idoxuridine and triflouridine as antiviral , zidovudine and stavudine as anti- HIV ; trimethoprim , sulphamethiazine , sulphadiazine as antibacterial , phenobarbitone as sedative , hypnotic and anticonvulsant etc...

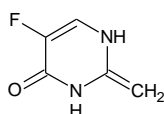
As a result of remarkable biological activity of pyrimidine derivatives , intensive research has been carried out on anticancer activity . so , the present review highlights the anticancer activity of pyrimidine derivatives.

Pyrimidine antagonists acts to block pyrimidine containing nucleotides synthesis and also leads to the stoppage of DNA synthesis and inhibition of cell division.

Literature review :

Pyrimidine belongs to an electron rich nitrogen containing heterocycle . Synthetic adaptability of pyrimidine allows generation of structurally modified derivatives which generally includes analogues derived from substitution of the aryl ring , and derivatization of pyrimidine nitrogen and substitution at of carbon at 2,4,5 & 6 positions.

Human cells have the capacity to salvage pyrimidines for the production of deoxyribonucleotides that are used for the synthesis of DNA and analogues of these nucleotide precursors have proven to be an important class of anticancer agents .

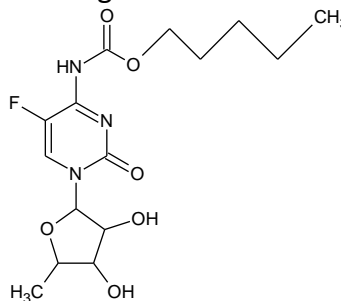


Fluorouracil :

- Heidelberger and colleagues et. al synthesized fluorouracil (anticancer drug) and tested for it's selective activity and hypothesized that Fluorouracil will selectively kill tumour cells ; it is used as a potent treatment for colorectal , breast , stomach and pancreatic cancer.

1)Capecitabine :

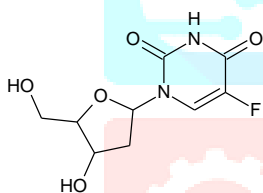
- It is presently approved for its use in the treatment of stage 3 colon cancer and metastatic breast cancer



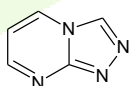
. It is a prodrug of fluorouracil administered orally

2)Floxuridine :

- It is an excellent substrate for thymidine kinase and it is converted by this enzyme directly to F-dUMP.
- It is more potent inhibitor of cell growth than Fluorouracil and it is not converted to ribonucleotide metabolites.
- But it is not widely used .



- El.sayed.et al , Zhao et. al designed and synthesized derivatives of the (1,2,4) triazolo (4,3-a) pyrimidine ring system and tested against anti tumour activity. Special potent anticancer activity against human

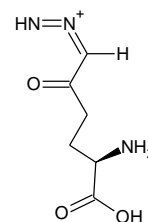
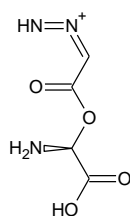


[1,2,4]triazolo[4,3-a]pyrimidine

colorectal cancer cell.

- Sridhar et.al synthesized compounds 2-amino-4-(2',5'-dimethyl-3'-furyl)-6(aryl)pyrimidines (4 a-n) in good yields and tested against the cell lines for their anticancer activity. Some of the compounds have significant anticancer activity against cancer cell lines out of all the compounds , 4b containing 4- chlorophenyl substitution on 6 th position of pyrimidine nucleus showed maximum activity.
- A series of thienopyrimidine derivatives linked to thiosemicarbazide moiety was synthesized , characterised and evaluated for their in vivo anticancer activity against two human cancer cell lines (like prostate and colon cancer cell lines) . compounds 5b & 5d showed higher cytotoxic activity against both the cancer cell lines.
- Levenberg et .al found that 6-diazo-5 oxo – norleucine and azaserine to be inhibitors of glutamine in a specific reaction concerned with inosinic acid synthesis . His studies in the laboratory had proven that

6-diazo-5-oxo norleucine subsequently depresses the utilisation of both ureidosuccinic as well as urotic acid for the synthesis of cytosine moiety of nucleic acids in some mammalian tissues including H.S.H 1 and H.E.P.H 3 tumours .

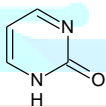


azaserine

6-diazo -5-

oxonorleucine

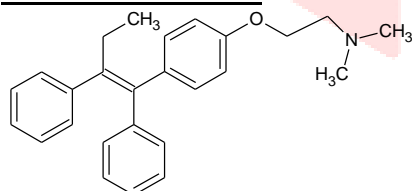
- A number of nucleosides and 5-fluorouracil was applied orderly as a remedy for breast cancer , gastro intestinal tract tumours was tested by Maccoss and Robins et.al and reported .
- El.sayed et.al synthesized glycosylthio five and six membered heterocyclic with anticancer activity and reported.
- Cieplik , pogorelnik et.al synthesized drugs which affects DNA biosynthesis that had received much attention and among them pyrimidine derivatives remains the most effective.
- Mohammed et.al synthesized pyrimidinone pyrimidinones and tested against various cell lines , which showed interesting pharmacological properties as anti tumour .



pyrimidin-2(1H)-one

Although there have been several developing advances in various therapeutic strategies for cancer treatment , the cytotoxicity of drugs remains the backbone for the treatment of cancer proven by Butler et.al.

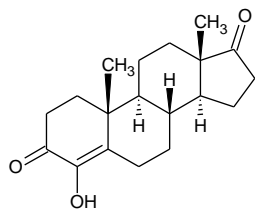
Breast cancer :



Tamoxifen

Jameera Begum et.al synthesized antiestrogen compound tamoxifen which is considered to be an absolute leader in the endocrine therapy of hormone dependent breast cancer.

Carlini et.al synthesized aromatase inhibitors such as Formestane and exemestane with various specific anticancer activity.

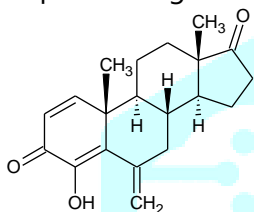


Formestane

Formestane, formerly sold under the brand name **Lentaron** among others, is a steroidal, selective aromatase inhibitor which is used in the treatment of estrogen receptor-positive breast cancer in postmenopausal women.

Exemestane

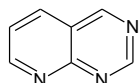
Exemestane, sold under the brand name **Aromasin** among others, is a medication used to treat breast cancer. It is a member of the class of antioestrogens known as aromatase inhibitors. Some breast cancers require estrogen to grow.



Pyrimidines possessing anticancer activity :

Coco et.al synthesized a new class of 6 – thioxopyrimidine derivatives and its molecular structures were confirmed by IR , NMR and elemental analysis study . This synthesized derivatives was evaluated for their in – vitro anticancer potential against multiple panels of 60 human cancer cell lines by sulforhodamine B assay . All the synthesized 6- thioxopyrimidine derivatives exhibited potential anticancer activity .

M.D Gavilan et.al proposed the synthesis of (1,3,5- tetra hydro -4-1-benzoxazepine -3-yl) pyrimidines and tested for its anticancer activity . This study showed that the synthesized compound contained required anti tumour activity .



pyrido[2,3-*d*]pyrimidine

Pyrido (2,3-d) Pyrimidines

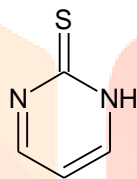
N.R. Mohamed et.al synthesized pyrido (2,3-d) pyrimidines and he evaluated the corresponding compound against in-vivo anti- tumour activity on lung and liver carcinoma cells . The result confirmed that compounds having moderate action against lung carcinoma cell lines.

P.shanmugasundaram et .al synthesized the compound pyrido (2,4-d) pyrimidine Carboxylate and tested for its cytotoxic activity using three human cancer cell lines such as Colon cancer , liver cancer , cervical cancer and its evaluation showed that the synthesized compound contains significant anticancer activity.

H.T.Abdel Mohsen et.al focused his study on the synthesis of novel benzimidazole pyrimidine conjugates and stated that this compound possess potent anti tumour activity .

- Alagarswamy et.al reported anticancer activity of some substituted (1,3,4) thia diazolo thieno (3,2-e) pyrimidine -5(4H) – ene . This compound showed significant anticancer activity towards lung , breast and other cancer.

Abdulla et . al synthesized 2- thioxypyrimidine derivatives . This newly prepared compound was evaluated for its anticancer activity against two human tumour cell lines like cervix carcinoma cell line (hela) & breast



pyrimidine-2(1H)-thione

carcinoma cell line (MCF 7) respectively.

M.M Ghoraba et.al described novel thiazolo (4,5-b) pyrano (2,3-d) pyrimidine derivatives and this compound has evaluated for its in vivo anticancer activity against human breast cancer cell line .

M.Bakavolia reported cytotoxic effects of triazolopyrimidoxadiazine moiety on various malignant cancer cell lines including human breast cancer cell line (MCF-7) and hepatocellular carcinoma with different concentrations (50-500 micro gram) . The result reported showed compound decreased cell viability of cells as a concentration dependent manner .

Pyrimidines as antineoplastic agents :

Therefore the chemistry of pyrimidines has become increasingly important as a result of several recent developments in medicinal chemistry.

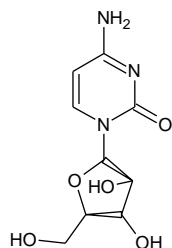
The pyrimidine derivatives are used as antineoplastic agents , are a diverse group of agents with similar structures but with little bit different mechanism of action , activities and spectrum of activity .

These agents are nucleoside analogues and which are considered as antimetabolites inhibiting nucleoside triphosphates in the synthesis of nucleic acids DNA or RNA or both .

These agents may be derivatives of cytosine (azacitidine, decitabine, cytarabine , gemcitabine) or uracil (fluorouracil , floxuridine) which demonstrates a wide range of antineoplastic activity in cell and animal models .

Fluorouracil & floxuridine have more typical antineoplastic activity and these are the agents which are essential for several solid tumours.

Cytarabine and gemcitabine are the analogues of cytosine but they are used in different forms of cancer ;

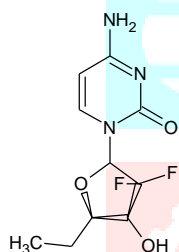


Cytarabine

Cytarabine is used for leukemias and lymphomas ; while gemcitabine is used in case of solid tumour chemotherapy.

Cytarabine, also known as **cytosine arabinoside (ara-C)**, is a chemotherapy medication used to treat acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), chronic myelogenous leukemia (CML), and non-Hodgkin's lymphoma

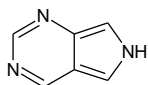
Gemcitabine, with brand names including **Gemzar**,^[1] is a chemotherapy medication.^[2] It treats cancers including testicular cancer,^[3] breast cancer, ovarian cancer, non-small cell lung cancer, pancreatic cancer, and bladder cancer.



Gemcitabine

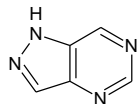
Some of the patented pyrimidines ;

1. Chuckowree et.al patented fused pyrimidines as phosphatidylinositol -3- kinase (PI3K) inhibitors . synthesized compounds were subjected to PI3K biochemical screening assay. Compound inhibition of PI3K was determined by radiometric assay using purified , recombinant enzyme and ATP .
2. Ibrahim et.al filed patent on fused pyrrolo pyrimidine compounds for kinase modulations , useful for the treatment of diseases associated with the activity of Fms kinase and kit protein kinases including Breast cancer , prostate cancer ,lung and ovarian cancer etc.
3. Lori et.al filed a patent on substituted pyrrolo (3,4-d) pyrimidines as tumour growth

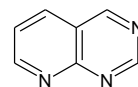


inhibitors .

4. Hogberg et.al filed a patent on novel pyrimidine derivatives as tubulin inhibitors.
5. Gokaroju et.al filed a patent on substituted 4-(selenophen -2(or3) -yl amino) pyrimidine derivatives , having anti-proliferative activity against a panel of human cancer cell lines.
6. Mao et.al filed a patent on pyrazolopyrimidine derivatives as an inhibitor of various types of cancer cells and thus they are useful to treat Cancer related to the dysregulation of kinase pathway .



7. Liang et.al filed a patent on 4-urea – phenyl substituted 6- morpholin -4-yl- pyrazolo (3,4-d) pyrimidine derivatives as an potent and selective inhibitors of mTOR kinase which is the major regulator of cell growth .
8. Burgdorf et .al filed a patent on pyrido pyrimidine derivatives as protein kinase inhibitors



pyrido[2,3-d]pyrimidine

that can be employed for the treatment of cancer.

Anticancer activity :

The anticancer activity of the synthesized compounds was studied on human prostatic adenocarcinoma (PC3) , human colorectal carcinoma (HCT 116) and human breast adenocarcinoma (MCF7) cell lines in addition to their effect on human normal retinal pigmented epithelial cell line (RPE1) using the MTT assay (mosmann ,1983 ; El- Ansary et.al , 2015).

Various mechanisms of anticancer pyrimidines patented during the last few years ;

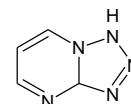
It involves ;

1. Phosphorylase / Nucleosidase inhibitors (PNP , MTAP , MTAN inhibitors)
2. Tyrosine kinase inhibitors (HER2K , RON inhibitors)
3. Inositol kinase inhibitors (PI3 kinase inhibitors)
4. Histone de acetylase inhibitors
5. Lysophosphatidic acid acyltransferase beta inhibitor
6. Serine / threonine – protein kinase inhibitors
7. Autotaxin (Ats) inhibitor
8. Heat shock protein 90 (HSP 90) inhibitor
9. Dual-specificity protein kinase inhibitor (MPSI kinase inhibitor)

Newly substituted oxo- and thioxopyrimidine, thiazolo pyrimidines and pyrimidine thioglycoside derivatives were synthesized and structurally characterised. The newly prepared compounds showed cytotoxic activity against HCT-116 and PC-3 cell lines showing moderate to good activities.

Natural hormones (estrone, 3 beta – acetoxyandrostene, 3- keto-17 beta – hydroxyandrostene) were transformed into the corresponding derivatives, the modified steroidal pyrimidines and dihydrotriazines in moderate to high yields using a two-step sequence involving the Vilsmeier – Haack reaction and condensation with amides such as guanidine and acetimidamide. The newly synthesized compounds showed remarkable cytotoxic activity against breast and prostate cancer cells. Further more lead compounds reported selectivity towards ER alpha in MCF-7 breast cancer cells.

New substituted pyrimidine and thiazolo pyrimidine glycosides as well as their acyclic analogues were synthesized and tested for their anticancer activity. Some of the synthesized compounds showed potent



activity and thiazolo pyrimidine derivative has been shown to be selective to cancer cells.

Conclusion : Pyrimidine ring derivatives has been found to be potent compounds against various anticancer activity. Several compounds of pyrimidine derivatives was synthesized and structurally characterised. The prepared compounds showed effective cytotoxic activity against various human cancer cell lines revealing their potent activities. Pyrimidine analogues showed maneuverability and versatility which grabbed the interest of medicinal chemists in the pyrimidine skeleton in the medical field.

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