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A Study on the Biological and Medicinal Significance of Pyrimidines and Related Heterocycles

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Abstract – The biological importance of one of the most essential heterocycles, the pyrimidine, is discussed in this paper. The majority of physiologically and medicinally essential substances containing pyrimidine and its derivatives have been covered. The current study focuses on pyrimidine and its numerous derivatives as antimicrobial agents, which is a significant chemical moietys.

Keywords – Pyrimidine derivatives, Heterocycles, biological significance, Pyrimidines, medicinal significance.

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INTRODUCTION

Pyrimidine pharmacophores are an important and vital component of DNA and RNA, and they play an important role in a variety of biological processes. They also have significant chemical and pharmacological usefulness as antibiotics, antibacterial, cardiovascular, agrochemical, and veterinary products.

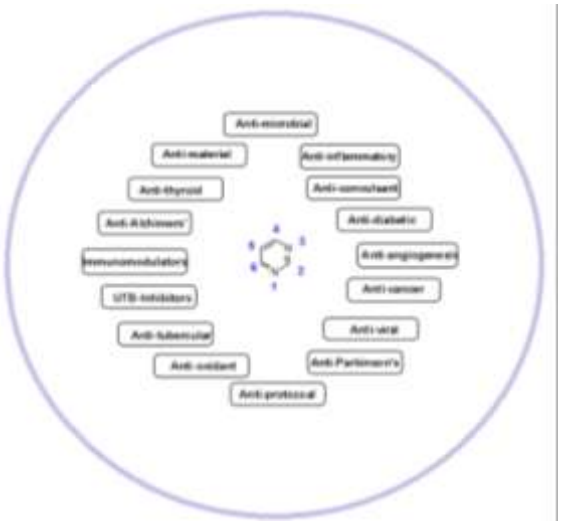


Figure 1.1: Diverse biological importance of pyrimidines

Pyrimidines are heterocyclic aromatic compounds with two nitrogen atoms at positions 1 and 3 in the six-membered rings, analogous to benzene and pyridine. Heterocycles with a pyrimidine moiety are of particular concern since they represent a large class of natural and synthetic goods, many of which have biological and therapeutic applications. Substituted purines and pyrimidines are abundant in living species and were among the first organic chemists to investigate them. Pyrimidines are biologically essential heterocycles that are by far the most common members of the diazine family, with uracil and thymine being components of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA), respectively, and cytosine being found in both.

Antifungal agents such as azoles, antiviral agents such as nonnucleoside reverse transcriptase inhibitors, and multiple antibacterial agents such as -lactams and quinolones have all been shown to benefit from structural alteration of antimicrobial drugs to which resistance has formed. It's not shocking, then, that major pharmaceutical firms have continued to focus their attention on developing antimicrobial agents in proven groups in reaction to antimicrobial resistance. However, it has been noted that, with the latest pipeline of chemotherapeutics, researchers are approaching the end game in terms of parent structure alterations. As a result, a proposal has been made for the introduction of new medication groups that operate on separate target sites than those already in operation. Since their molecular subunits are used in many natural products such as antioxidants, hormones, and antibiotics, heterocyclic compounds are common in nature and have drawn substantial interest in the design of biologically active molecules and advanced organic chemistry. Often belonging to the heterocyclic compound family, nitrogen-containing heterocycles are a significant class of compounds in medicinal chemistry, as well as a biological and industrial contribution that aids in the understanding of life processes. Azine or pyridine is a completely

unsaturated membered six-ring comprising nitrogen; with two nitrogen atoms, it is diazine; with a nitrogen at 1,2-position, it is pyridine; with a nitrogen at 1,3-position, it is pyrimidine; and with a nitrogen at 1,4-position, it is pyrazine. The present study, on the other hand, would concentrate on the importance of the pyrimidine class of antimicrobial agents, as well as clinical and in vitro applications of pyrimidine derivatives, in order to aid in the discovery of more potent and efficient antimicrobial agents.

Figure 1.2: Pyridine and different isomeric forms of diazine family

Furthermore, the pyrimidine skeleton can be found in many natural ingredients, such as vitamin B1 (thiamine), as well as many industrial drugs, such as barbituric acid and Veranal, which are hypnotics.

Pyrimidine is a heterocyclic aromatic organic compound with two nitrogen atoms at positions 1 and 3 of the six-member ring, equivalent to benzene and pyridine. It is isomeric with two other diazine forms.

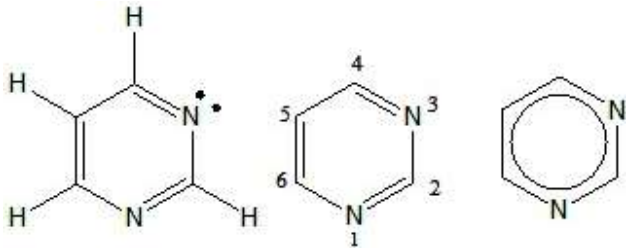


Figure 1.3: Pyrimidine

Purine, on the other hand, is a heterocyclic aromatic chemical compound made up of a pyrimidine and an imidazole group fused together.

The two types of nitrogenous bases are purines and pyrimidines. These bases are the foundation for the basic genetic code and are used in both deoxyribonucleotides and ribonucleotides. Substituted purines and their tautomers are often referred to as purines. Purine is the most abundant nitrogen-containing heterocycle in existence, with prominent purines. Purines make up half of the bases in nucleic acids, adenine and guanine, so the amount of purines formed naturally on Earth is immense. These bases form hydrogen bonds with their pyrimidine counterparts, thymine and cytosine, in DNA. Complementary base pairing is the term for this. The isolation of alloxan can be tracked back to the beginning of pyrimidine chemistry.

1. Purines:

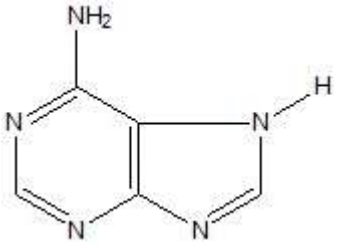


Figure 1.4: Adenine

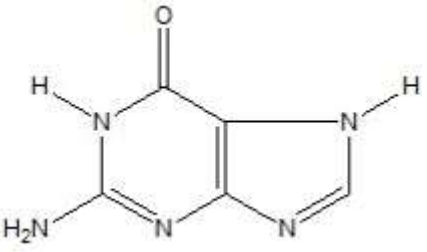


Figure 1.5: Guanine

2. Pyrimidines:

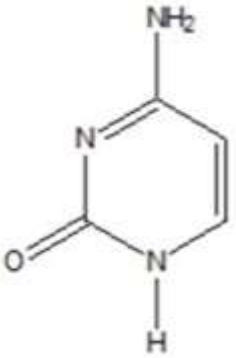


Figure 1.6: cytosine

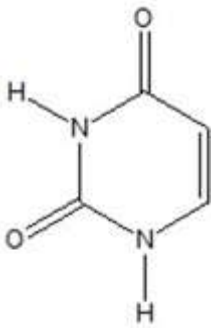


Figure 1.7: uracil

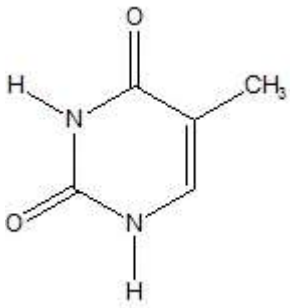


Figure 1.8: Thymine

In DNA and RNA, these bases form hydrogen bonds with their complementary purines. As a result, the purines adenine (A) and guanine (G) are paired with the pyrimidines thymine (T) and cytosine (C). Adenine: uracil and guanine: cytosine are the adenine: uracil and guanine: cytosine pairs that form in RNA instead of T. For Watson-Crick base pairing, these hydrogen bonding modes are used. Other hydrogen bonding forms ("wobble pairings") are present in both DNA and RNA, but the additional 2'-hydroxyl group in RNA extends the hydrogen bonding structures available to RNA. Synthetic pyrimidines may also be produced in the laboratory. The Biginelli reaction is a classic procedure for pyrimidine synthesis.

Chemical Properties: The ring pi electrons grow less energetic as the amount of nitrogen atoms in the ring rises, making electrophilic aromatic substitution more complex whereas nucleophilic aromatic substitution becomes simpler. The replacement of the amino group by chlorine in 2-aminopyrimidine and its reversal Reductions in pyrimidine resonance stabilisation can lead to ring cleavage and addition reactions rather than substitutions. The Dimroth rearrangement is an example of such a manifestation. N-alkylation and N-oxidation are more difficult in pyrimidines than in pyridine, and they are therefore less simple. Protonated pyrimidine has a Pka value of 1.23, while pyridine has a value of 5.30.

Organic Synthesis: Chemical synthesis can also be used to make pyrimidines in the field. The classic Biginelli reaction is one form. Many other approaches, such as the synthesis of 2-thio-6-methyluracil from thiourea and ethyl acetoacetate or 4-methylpyrimidine from 4, 4-dimethoxy-2-butanone and formamide, depend on the condensation of carbonyls with amines.

Vitamins including thiamine, riboflavin, and folic acid contain the pyrimidine ring. Antiviral, anticancer, antifungal, antimalarial, sedative, hypnotic, anticonvulsant, anthelmintic, and antithyroid activities have all been discovered in pyrimidine compounds.

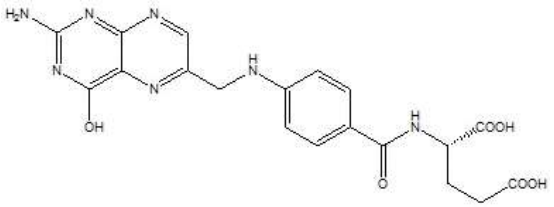


Figure 1.9: Folic Acid

LITERATURE REVIEW

Sanjiv Kumar et al. (2019) Pyrimidine nucleus is a significant pharmacophore with promising pharmacological properties. Physicochemical and spectral analysis is used to validate the chemical properties of a sequence of pyrimidine scaffolds. The antimicrobial potential of the synthesised compounds was tested against Gram positive and negative bacteria, as well as fungal organisms. They were also tested against a human colorectal carcinoma cell line for anticancer activity (HCT116). Although the antimicrobial ability of compounds Ax2, Ax3, Ax8, and Ax14 was found to be superior against the measured microorganisms, the antiproliferative action of compounds Ax7 and Ax10 was found to be superior against HCT116. Molecular docking of the pyrimidine derivatives Ax1, Ax9, and Ax10 with the CDK8 (PDB id: 5FGK) protein revealed moderate to better docking results inside the binding pocket. Ax8 and Ax10, which have important antimicrobial and anticancer functions, may be used as lead compounds in the synthesis of new antimicrobial and anticancer agents, respectively.

Sanjiv Kumar et al. (2018) Heterocyclic compounds have a wide range of molecular diversity and have been shown to be widely and cost-effective therapeutic agents. Comprehensive studies into the therapeutic ability of heterocycles compounds have shown their enormous importance in disease pathophysiology. The heterocyclic pyrimidine nucleus, which is an important base portion of deoxyribonucleic acid's genetic content, has shown a variety of biological activities. The aim of this analysis is to look at the work that has been done on the therapeutic potentials of pyrimidine scaffolds, which are useful for medical applications in the modern millennium.

Ajmal R.Bhat et al. (2017) The most important tasks in N-heterocyclic chemistry are the syntheses of bioactive annulated pyrimidine derivatives, since these compounds have shown to be very desirable and useful for the creation of new molecular structures of possible drugs with differing pharmacological activities. The one-pot multicomponent synthesis of annulated nitrogen- and oxygen-containing heterocycles including pyrano [2, 3-d] pyrimidines, pyrido [2, 3-d] pyrimidines, and pyrido [2, 3-d; 5-6-d]dipyrimidines is summarised in this analysis article. The chemistry of the domino

Knoevenagel-Michael addition process is used to create the synthetic technique.

Sahu, m. et al. (2016) Pyrimidines have an important role in medicine and they have a wide range of biological properties. As possible bioactive molecules, their associated fused heterocycles are of concern. Anticonvulsant, analgesic, sedative, anti-depressive, antipyretic, anti-inflammatory, antiviral, anti-HIV, antimicrobial, and anti-tumor activities have all been identified for pyrimidine derivatives. As a result, the focus of this analysis is on research on various biological activities of pyrimidine analogues that has recently been published in the scientific literature.

Selvaraj Mohana Roopan et al. (2016) this work attempts to summarise the literature on different pyrimidine analogue synthetic procedures. Pyrimidine and its fused pyrimidine compounds are heterocyclic scaffolds that have anticancer, anxiolytic, antioxidant, antiviral, antifungal, anticonvulsant, antidepressant, and antibacterial properties. According to World Health Organization statistics, cancer is a leading cause of death worldwide, necessitating the development of an appropriate cancer treatment. The researchers were inspired to create a sequence of pyrimidine heterocycles after reading that pyrimidine motifs are anticancer agents.

MEDICINAL PROPERTIES OF PYRIMIDINES

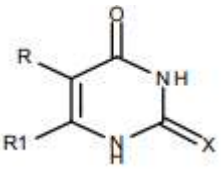
One potential explanation for their extensive medicinal uses is the inclusion of pyrimidine base in thymine, cytosine, and uracil, which are important building blocks of nucleic acids DNA and RNA. Pyrimidines are one of the most powerful groups of drugs, with substantial in vitro action against unrelated DNA and RNA, viruses such as polioviruses, diuretic, antitumor, anti-HIV, and cardiovascular effects. The substances containing the pyrimidine nucleus have a broad variety of pharmacological functions, according to the literature review. Moreover, pyrimidine analogues have been found to have antibacterial, antifungal, antileishmanial, anti-inflammatory analgesic, antihypertensive, antipyretic, antiviral, antidiabetic, antiallerggic, anticonvulsant, antioxidant, antihistaminic, herbicidal, and anticancer properties, and several pyrimidine derivatives have been reported to have potential central nervous system (CNS) activity.

MEDICINAL SIGNIFICANCE OF PYRIMIDINES

Several pyrimidine derivatives have been produced as chemotherapeutic agents during the past two decades and have seen widespread clinical use.

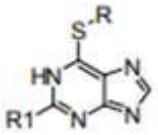
Antineoplastics and anticancer agents

There are several antimetabolites that are pyrimidine-based. They typically have structural similarities to the endogenous substrates they oppose. The pyrimidine ring or the pendant sugar groups can be modified structurally. 5-fluorouracil3, 4 (5-FU), a pyrimidine derivative, was one of the first metabolites developed. 5- Thiouracil also has certain anticancer properties.

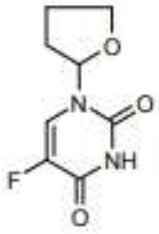


X = O, R = F, R_1 = H, 5-fluorouracil
X = O, R = SH, R_1 = H, 5-thiouracil

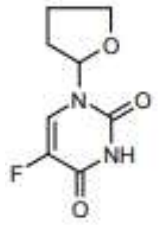
Since Woods and Fildes proposed the antimetabolite hypothesis in 1940, antineoplastic compounds with the guanine nucleus (such as azathioprine mercaptopurine, thioguanine, tegafur, and others) were discovered. The use of natural cellular metabolites is inhibited by these medications.

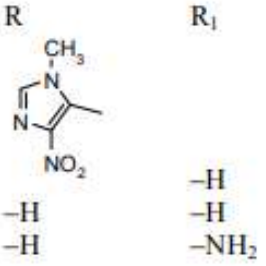


Azathioprine

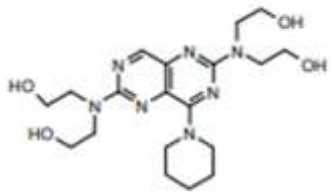


Tegafur

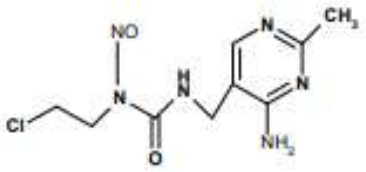




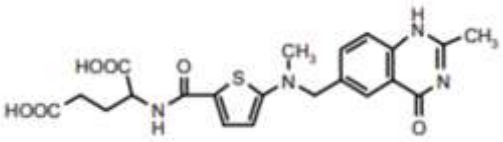
In recent years, there have been even more, such as mopidamo, nimustine, raltitrexed, uramustine, and trimetrixate.



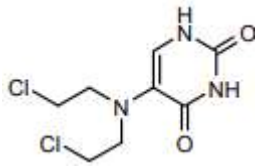
Mopidamol



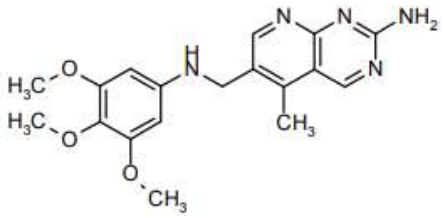
Nimustine



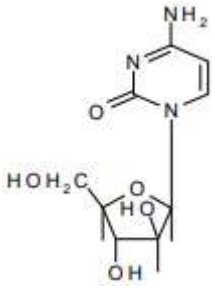
Raltitrexed



Uramustine

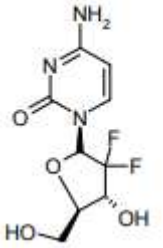


Trimetrexate glucuronate



Ara-C

1-b-D-Arabinosylcytosine16 (Ara-C) is another pyrimidine antimetabolite of which the sugar has a beta configuration and is arabinose. It is mostly used as an anticancer drug, but it also has important beneficial results in herpes virus infections and encephalitis patients. Gemcitabine, a pyrimidine antimetabolite, has shown to be effective against stable tumours in mice.



Gemcitabine

PYRIMIDINES AS ANTI-CANCER AGENT

Cancer is a life-threatening illness that affects over six million people worldwide per year. Humans' lifestyles also changed dramatically, increasing the likelihood of contracting several cancers. A constant attempt has been made to classify anti-cancer molecules from both natural and synthetic sources [8]. P21 Activated Kinases (PAKs), MCF-7 kinase, PKCK2 kinase, JAK1-3 kinase, FLT1 kinase, FLT3-4 kinase, CHK1 kinase, Aurora-A kinase, MGC-803 kinase, EC-109 kinase, B16-F10 kinase, etc. are some

Ma designed, synthesised, and tested 1, 2, 3-triazole–pyrimidine–urea derivatives for anticancer action. MGC-803, EC-109, MCF-7, and B16-F10 cell lines were used to analyse the synthesised compounds. Almost all of the synthesised substances were shown to have mild to strong activity toward all cancer cell lines. However, compounds 7, 8, and 9 inhibited B16-F10 development effectively (IC50 = 32 nM, 35 nM, and 42 nM, respectively). Compound 7 also caused cellular apoptosis in a concentration-dependent fashion, according to a flow cytometry report. Any of the 2, 4-diaminopyrimidine derivatives were synthesised by Qin and evaluated for biological activities such as anti-proliferation, Aurora kinase inhibition, and cell cycle results. When opposed to the VX-680 regulation, all of the synthesised compounds had higher cytotoxicity against tumour cell lines. Compound 10 had the largest cytotoxicity (IC50=0.5-4.0 M) and a selectivity for Aurora A over Aurora B of more than 35-fold. Molecular docking study also indicated that this compound had a greater structure and energy exchange with Aurora-A than Aurora-A. Furthermore, compound 10 caused HeLa cancer cell lines to enter the G2/M cell cycle. As a result, these synthetic compounds have the ability to be developed further as anticancer Aurora A inhibitors. Ethyl 2-(benzylidene)-7-methyl-3-oxo-2,

3-dihydro-5H-thiazolo [3, 2-a] pyrimidine-6-carboxylate derivatives were designed, synthesised, and characterised by Jin. Compound 11 was discovered to be an active and selective inhibitor of PKCK2 with an IC50 of 0.56 M, which is 2.2-fold higher than the IC50 of 1.24 M for 4, 5, 6, 7-tetrabromobenzotriazole (TBB). Compound 11 and TBB had Ki values of 0.78 M and 2.70 M for PKCK2, respectively. As a result, compound 11 inhibited endogenous PKCK2 kinase and demonstrated encouraging antiproliferative behaviour that warrants further investigation.

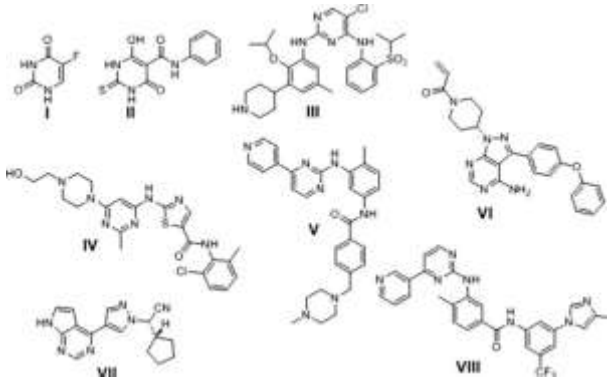
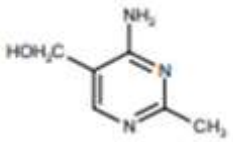


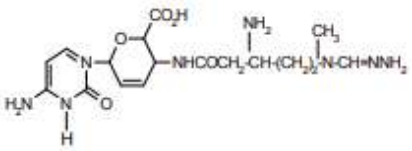
Figure 1.10: Anticancer drugs have pyrimidine ring in their structure.

ANTIBIOTICS

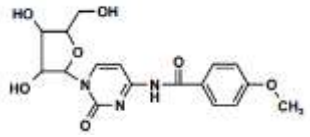
Pyrimidine antibiotics come in a variety of forms. Bacimethrin (5-hydroxymethyl-2-methoxypyrimidin-4-amine) is the most basic of them all, and it works against a variety of staphylococcal infections. Gourgetin, a cytosine analogue, kills mycobacteria as well as a variety of Gram-positive and Gram-negative bacteria. Amicetin and plicacetin, two more cytosine compounds, have action against acid-fast and Gram-positive bacteria, as well as several other species.



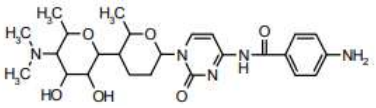
Bacimethrin



Gourgetin



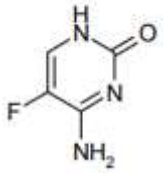
Amicetin



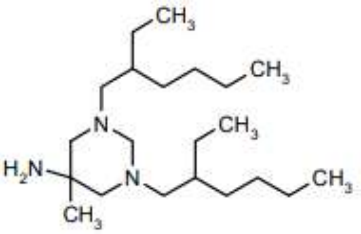
Plicacetin

ANTIFUNGALS

Pyrimidines have antifungal effects as well. Flucytosine is a fluorinated pyrimidine that is used as a nucleosidal antifungal agent to treat severe systemic infections triggered by sensitive Candida albicans and Cryptococcus strains. Hexitidine is most often used to treat aphthous ulcers.



Flucytosine



Hexitidine

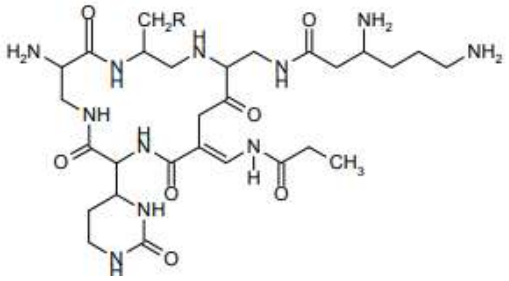
ANTHELMINTIC DUGS

Anthelmintic medicines (or antihelmintic drugs) refer to a class of antiparasitic medications used to manage parasitic worm infections (also known as helminths). Helminthiasis is a pathological disease that affects people who are sick or infested with helminths**.**

ANTITUBERCULAR DRUGS

In particular, some of the most powerful anti-mycobacterial medications, such as isoniazid and ethambutol, have been shown to prevent the biogenesis of cell walls controlled by covalently connected mycolic acids, arabinogalactan, and peptidoglycan (AGP), with glycolipids such as - trehalose monomycolate complementing the mycolic acids (TMM)

Capreomycin, developed by Streptomyces capreolus, is a pyrimidine-containing second-line bacteriostatic antituberculin medication.



Capreomycin

CONCLUSION:

Pyrimidines have their own special position in our lives. This heterocyclic moiety is extremely important in biology and medicine. A wide range of pyrimidine medicines have different therapeutic properties. This piques medicinal chemists' curiosity in the pyrimidine moiety in antimicrobial drug production. It would also ensure the implementation of effective methods for the creation of essential heterocyclic chemistry research areas.

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