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A REVIEW ON PYRIMIDINES AND PROTEIN KINASE INHIBITORS AS ANTICANCER AGENTS

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ABSTRACT
The anticancer potential of fused pyrimidine scaffolds has been evidenced number of research articles, patent literature and different enzymes/receptors/targets involved targeting as anticancer agents. A new series of pyrimidine and fused pyrimidines derivatives reported as major focused area at present for researchers all over the globe. Cellular kinases are important role in cell proliferation & differentiation of cell and human genome encodes huge number of protein kinases that transfer a γ-phosphate group from ATP to serine, threonine, or tyrosine residues and many of these kinases are associated with human cancer initiation and progression which is second most targeted groups for ligands, after the G-protein-coupled receptors. The review, provide an in depth analysis of activation mechanisms for kinases in cancer, highlight recent successes in drug discovery, and demonstrate the clinical impact of selective kinase inhibitors the information provider in development of novel agents in relation to oncology and to meet the challenges for kinase-targeted cancer therapies.

KEYWORDS: Pyrimidine, protein kinase, anticancer, binding site.

INTRODUCTION
Cancer is a disease characterized by uncontrolled multiplication and spread of abnormal forms of the body's own cells. Cancer can divide into types based on where it begins which are Carcinomas, sarcoma Leukemia's and Lymphomas.[1] As a cancerous tumor grows, the bloodstream or lymphatic system may carry cancer cells to other parts of the body. During this process, the cancer cells grow and may develop into new tumors. This is known as metastasis. The use of chemotherapy to treat cancer began at the start of the 20th century with attempts to narrow the universe of chemicals that might affect the disease by developing methods to screen chemicals using transplantable tumors in rodents. It was, however, four World War II–related programs, and the effects of drugs that evolved from them, that provided the impetus to establish in 1955 the national drug development effort known as the Cancer Chemotherapy National Service Center. The ability of combination chemotherapy to cure acute childhood leukemia and advanced Hodgkin's disease in the 1960s and early 1970s overcame the prevailing pessimism about the ability of drugs to cure advanced cancers and facilitated the study of adjuvant chemotherapy.[2]

Synthetic drugs are like fused pyrimidine derivatives play important role for the treatment of cancer. Pyrimidine derivatives are an important class of nitrogen heterocycles that have attracted more attention in the last decades. Due to their utilities as a precursor for the construction of condensed heterocyclic systems, they represent an interesting pharmacophore for pharmaceutical products.[3-8]

PYRIMIDINES AS ANTICANCER AGENTS
Pyrimidine derivatives have diversified activities such as antiviral,[9] antitumorm[10] antifolate,[11] antibacterial,[12] antifungal,[13] CNS active,[14] diuretic,[15] uricosuric,[16] diabetogenic, analgesic[17] anti-inflammatory[18] antioxidant,[19] New strains of microbes have been reported to threaten millions of people around the world every year,[20] Several pyrimidine derivatives have long ago been identified as antifolates[21] (Fig: 1) and targeting nucleic acids as effective anticancer agents.[22]

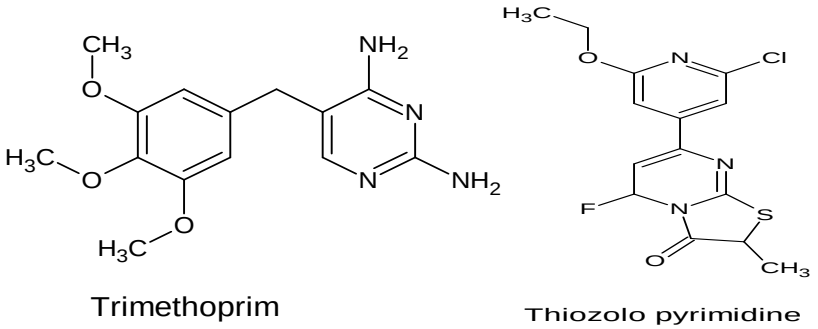

Fig: 1.

Cellular Kinase Targets As Anticancer Activity

Moreover, pyrimidine derivatives display usefulness in the fields of chemotherapy. Pyrimidine-based antimetabolites structurally related to the endogenous substrates as 5-Fluorouracil (5-FU) and 5-thiouracil (Fig: 2) were early recognized as effective therapies for cancer. It was reported that the chemotherapeutic efficacy of pyrimidine derivatives is related to their ability to inhibit vital enzymes responsible for DNA biosynthesis as dihydrofolate reductase (DHFR)[23] thymidylate synthetase (TSase), thymidine phosphorylase (TPase) and reverse transcriptase (RTase).[24] Further, pyrimidine and fused pyrimidine derivatives show biologically important activities because of their structural resemblance to purine-pteridine systems. Due to their severe toxicity and limited selectivity, the search for more potent and selective anticancer agents is highly interested (Fig: 3).

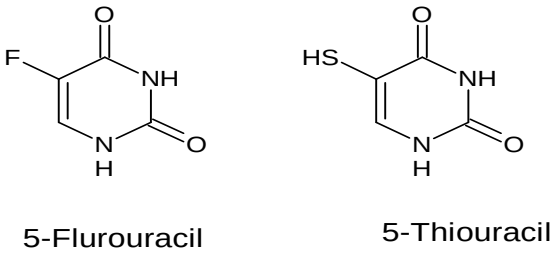

Fig: 2.

Marketed Drugs Containing Pyrimidine Nucleus**:-**

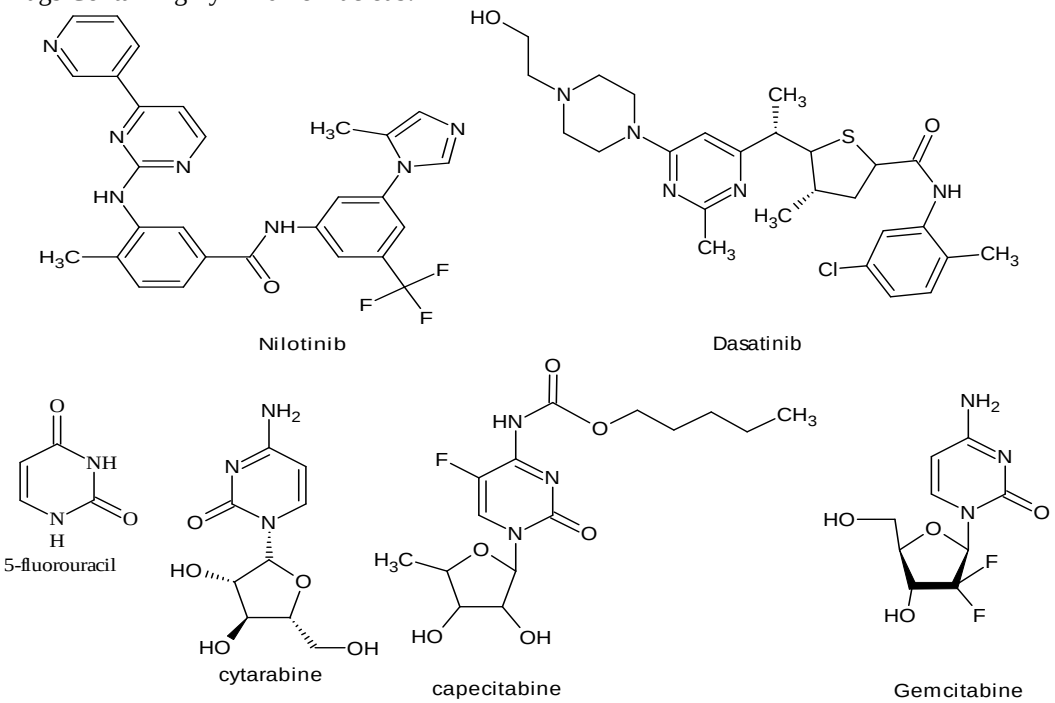

Figure: 3.

Membrane-spanning receptor tyrosine kinases control cell growth and differentiation. Tyrosine kinase is a subclass of protein kinase, that transfer a phosphate group to a tyrosine residue in a protein this have important faction in signal transduction. The binding of growth factors such as insulin, epidermal growth factor, and platelet-derived growth factor to the extracellular domain of this transmembrane receptor switches the kinase activity of catalytic domain. This signaling cascade is altered in cancer cell, which cause over expression of TK receptors. There are tyrosine receptor kinases and non receptor tyrosine kinases were mafor

targets for ligands. The list of FDA-approved kinase inhibitors and their drug targets were given below.[25] [Table: 1]

Table 1: Targets of Ligands towards cellular kinases.

Drug target	Protein substrate	Drug
ALK	Tyrosine	Crizotinib, Ceritinib, Alectinib, Brigatinib
BCR–Abl	Tyrosine	Bosutinib, Dasatinib, Imatinib, Nilotinib, Ponatinib
B-Raf	Serine/threonine	Vemurafenib, Dabrafenib
BTK	Tyrosine	Ibrutinib
CDK family	Serine/threonine	Palbociclib, Sorafenib, Ribociclib
c-Met	Tyrosine	Crizotinib, Cabozantinib
EGFR family	Tyrosine	Gefitinib, Erlotinib, Lapatinib, Vandetanib, Afatinib, Osimertinib
JAK family	Tyrosine	Ruxolitinib, Tofacitinib
MEK1/2	Dual specificity	Trametinib
PDGFR α/β	Tyrosine	Axitinib, Gefitinib, Imatinib, Lenvatinib, Nintedanib, Pazopanib, Regorafenib, Sorafenib, Sunitinib
RET	Tyrosine	Vandetanib
Src family	Tyrosine	Bosutinib, Dasatinib, Ponatinib, Vandetanib
VEGFR family	Tyrosine	Axitinib, Lenvatinib, Nintedanib, Regorafenib, Pazopanib, Sorafenib, Sunitinib
JAK family	Thymidylate synthase	Raltitrexed, Fluorouracil

The tyrosine kinase receptors have multi domain extracellular Ligands for specific Ligand, a signal pass transmembrane hydrophobic helix and tyrosine kinase domain. The receptor tyrosine kinases are not only cell surfaces transmembrane receptors, but are also enzymes having kinase activity. Cytoplasm portion contains a tyrosine kinase domain. The kinase domain has regulatory sequence both on the N and C terminal end. The first non-receptor tyrosine kinases identified was the SRC. Non-receptor tyrosine kinase receptor has additional signaling or protein-protein interacting domains such as SH_2, SH_3, and the Ph domain.[26] Each tyrosine kinase receptor attached with an adenosine triphosphate (ATP) and the energy reach phosphate group is transferred to the amino acid tyrosine by this activation of tyrosine kinase and phosphorylation of tyrosine residue lead to activation. Schematic representation of mode of action of tyrosine kinase of intracellular signaling pathway is given below.[27]

ROLE OF PROTEIN KINASES

Targeting the kinases harboring oncogenic transformational capacity and metastasis has led to a notable change in the clinical management of cancer (Fig: 4) and mechanism actions of some kinase inhibitors [Table 2]. Hundreds of kinases play overlapping and intricate roles in cell transformation, tumor initiation, survival and proliferation. Diving kinases while justifying their coinciding functionalities is difficult.[28]

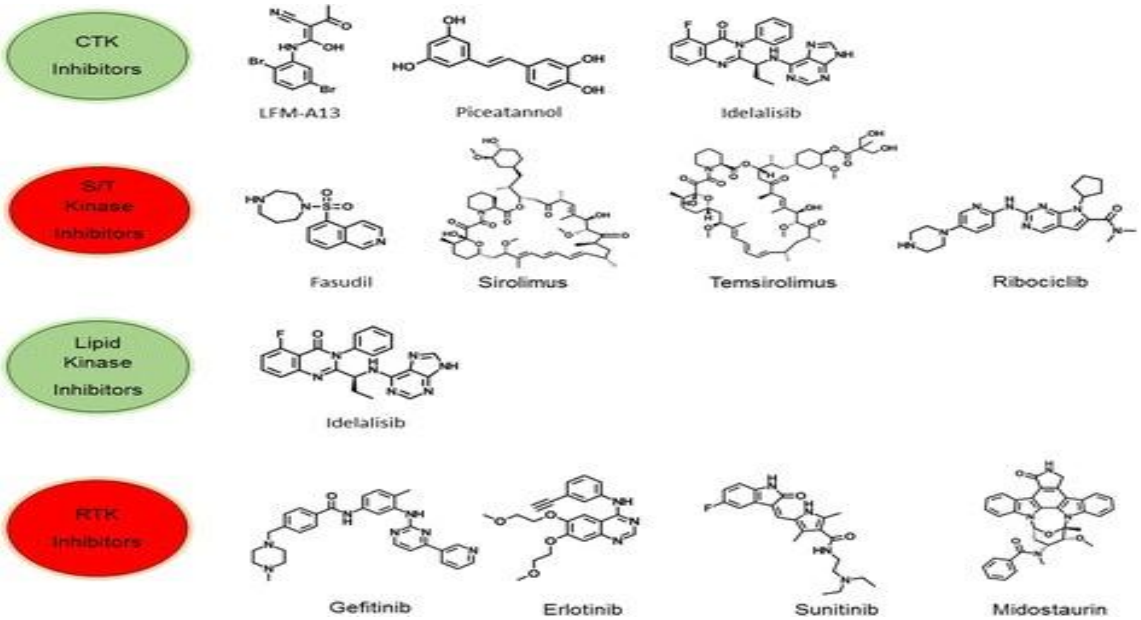

Figure 4:

Table 2: Classification of small molecule kinase inhibitors.

Class of Kinase Inhibitor	Mechanism of Action	Examples
Type I	Competes for the substrate and binds in the ATP-binding pocket of the active conformation	Bosutinib, Cabozantinib, Ceritinib, Crizotinib, Gefitinib, Pazopanib, Ruxolitinib, Vandetanib
Type II	Type II inhibitors bind to the DFG-Asp out protein kinase conformation, which corresponds to an inactive enzyme	Imatinib, Sorafenib, Axitinib, Nilotinib
Type III (Allosteric Inhibitor)	Occupy a site next to the ATP-binding pocket so that both ATP and the allosteric inhibitor can bind simultaneously to the protein.	Trametinib, GnF2
Type IV (Substrate Directed Inhibitors)	Undergo a reversible interaction outside the ATP pocket and offer selectivity against targeted kinases	ONO12380
Type V (Covalent Inhibitor)	Bind covalently (irreversible)to their protein kinase	Afatinib, Ibrutinib, HK1–272

CONCLUSION: The human genome encodes 538 protein kinases that transfer a γ-phosphate group from ATP to serine, threonine, or tyrosine residues. Many of these kinases are associated with human cancer initiation and progression. The recent developments of cellular kinase inhibitors targeting various types of cancer has proven successful in chemotherapy and based on the review protein-targeted drug discovery significantly useful in order to meet the challenges for cancer therapies.

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