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SYNTHESIS AND IN SILICO APPROACH OF SUBSTITUTED PYRIMIDINE DERIVATIVES AS A NOVEL INHIBITOR- A REVIEW

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Abstract:

In recent years, the development of novel inhibitors has gained significant attention in various fields, particularly in the pharmaceutical industry. Substituted Pyrimidine derivatives have emerged as promising candidates for designing potent inhibitors due to their versatile chemical properties and potential biological activities. This review provides a comprehensive overview of the synthesis and in silico approaches employed for the design of substituted Pyrimidine derivatives as inhibitors. The review begins by highlighting the significance of Pyrimidine derivatives in drug discovery and their structural diversity. It emphasizes the role of computational tools and techniques in rational drug design, including molecular docking, molecular dynamics simulations, and quantitative structure-activity relationship (QSAR) studies. The integration of experimental and computational methods offers a synergistic approach for the identification and optimization of effective inhibitors. Furthermore, the review delves into the synthetic strategies employed for the preparation of substituted Pyrimidine derivatives. It discusses various synthetic routes, such as condensation, cyclization, and functionalization, showcasing their potential for generating diverse chemical libraries. The comprehensive understanding presented in this review is expected to inspire further advancements in the field of inhibitor design and contribute to the development of innovative therapeutic agents.

Keywords: substituted Pyrimidine derivatives, inhibitor design, molecular docking, molecular dynamics simulations, QSAR studies.

1. INTRODUCTION

The investigation of heterocycles is an evergreen field in the branch of natural science and dependably pulls in the consideration of researchers working in the region of natural products as well as in the synthetic organic chemistry. Also, numerous valuable medications have risen up out of the fruitful examinations did in this branch [1]. Moreover, terrific advances have been made encouragement the learning of relationship between chemical structure and biological activity. Indeed, this propensity is reflected by the voluminous information accessible in heterocyclic chemistry. Thus, the successful applications in various fields ensure a limitless scope for the development of structurally novel compounds of this type with a wide range of physico-chemical and biological properties.

Fig. 1: Structure of Pyrimidine

Bicyclic nitrogen-containing heterocyclic compounds, such as purines, quinazolines, pteridines and Pyrimidines are well-known pharmacophores in drug discovery. Amongst different heterocyclic systems, the chemistry of Pyrimidines constitutes a very important class of compounds. Pyrimidines are important components in the synthesis of DNA, RNA, glycoprotein and membrane lipids, all of which are vital for the growth and maintenance of cells [2]. Specifically, Pyrimidine derivatives incorporate an extensive number of natural products, pharmaceuticals and functional materials. Examples of marketed drugs with a bicyclic core structure including Pyrimidine core substructure are shown in (Fig. 1).

2. Mode of Biological Action

Apoptogenic effect of Pyrimidine derivatives on murine leukemia cells increased proliferative activity of tumor cells is closely related to the increased activity of essential enzymes that participate in Pyrimidine metabolism. The interest in studying the inhibitors of nucleic acid metabolism is connected to the fact that a large number of these compounds have found important applications in the therapy of cancer, viral infections and some other diseases. The most important representatives of these inhibitors are 5-fluorouracil and its nucleosides. In the light of the recent findings concerning the role of apoptosis and of tumor cell enzymes in cancer chemotherapy, the interest in Pyrimidine derivatives has greatly increased [3]. Thio- and hydrazine- Pyrimidines have been developed as potential antimetabolites and the compounds obtained are structurally very similar to the natural Pyrimidine bases uracil and cytosine. Some of them demonstrate biological activity, including antibacterial and antitumor action. In the course of investigation of wide spectrum of Pyrimidine derivatives it has been found that 2-thio-4- hydrazinouracil show the highest activity. This compound inhibits the growth of various microorganisms; it displays an inhibitory effect on the final stages of Pyrimidine nucleotide synthesis, on the conversation of orotate into uridine nucleotides, on cytosine triphosphate synthase reaction and on the maturation of 45 S pre- RNA.

2.1 The problem

Cancer is a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020. The most common in 2020 (in terms of new cases of cancer) were: breast (2.26 million cases); lung (2.21 million cases); colon and rectum (1.93 million cases); prostate (1.41 million cases); skin (non-melanoma) (1.20 million cases); and stomach (1.09 million cases) [4-6].

2.2 What causes cancer?

Cancer arises from the transformation of normal cells into tumour cells in a multi-stage process that generally progresses from a pre-cancerous lesion to a malignant tumour. These changes are the result of the interaction between a person's genetic factors and three categories of external agents, including: physical carcinogens, such as ultraviolet and ionizing radiation;chemical carcinogens, such as asbestos, components of tobacco smoke, alcohol, aflatoxin (a food contaminant), and arsenic (a drinking water contaminant); and biological carcinogens, such as infections from certain viruses, bacteria, or parasites.

WHO, through its cancer research agency, the International Agency for Research on Cancer (IARC), maintains a classification of cancer-causing agents. The incidence of cancer rises dramatically with age, most likely due to a build-up of risks for specific cancers that increase with age. The overall risk accumulation is combined with the tendency for cellular repair mechanisms to be less effective as a person grows older.

2.3 Risk factors for cancers

Tobacco use, alcohol consumption, unhealthy diet, physical inactivity and air pollution are risk factors for cancer and other noncommunicable diseases.

Some chronic infections are risk factors for cancer; this is a particular issue in low- and middle-income countries. Approximately 13% of cancers diagnosed in 2018 globally were attributed to carcinogenic infections, including Helicobacter pylori, human papillomavirus (HPV), hepatitis B virus, hepatitis C virus, and Epstein-Barr virus (2).

Hepatitis B and C viruses and some types of HPV increase the risk for liver and cervical cancer, respectively. Infection with HIV increases the risk of developing cervical cancer six-fold and substantially increases the risk of developing select other cancers such as Kaposi sarcoma.

2.4 Reducing the cancer burden

Between 30 and 50% of cancers can currently be prevented by avoiding risk factors and implementing existing evidence-based prevention strategies. The cancer burden can also be reduced through early detection of cancer and appropriate treatment and care of patients who

develop cancer. Many cancers have a high chance of cure if diagnosed early and treated appropriately [7-9].

3. Preventing cancer

Cancer risk can be reduced by: not using tobacco; maintaining a healthy body weight; eating a healthy diet, including fruit and vegetables; doing physical activity on a regular basis;n avoiding or reducing consumption of alcohol; mgetting vaccinated against HPV and hepatitis B if you belong to a group for which vaccination is recommended.

3.1 Early detection

Cancer mortality is reduced when cases are detected and treated early. There are two components of early detection: early diagnosis and screening.

3.2 Early diagnosis

When identified early, cancer is more likely to respond to treatment and can result in a greater probability of survival with less morbidity, as well as less expensive treatment. Significant improvements can be made in the lives of cancer patients by detecting cancer early and avoiding delays in care.

Early diagnosis consists of three components: being aware of the symptoms of different forms of cancer and of the importance of seeking medical advice when abnormal findings are observed; access to clinical evaluation and diagnostic services; and timely referral to treatment services. Early diagnosis of symptomatic cancers is relevant in all settings and the majority of cancers. Cancer programmes should be designed to reduce delays in, and barriers to, diagnosis, treatment and supportive care.

3.3 Screening

Screening aims to identify individuals with findings suggestive of a specific cancer or pre-cancer before they have developed symptoms. When abnormalities are identified during screening, further tests to establish a definitive diagnosis should follow, as should referral for treatment of cancer is proven to be present. HPV test (including HPV DNA and mRNA test), as preferred modality for cervical cancer screening; and mammography screening for breast cancer for women aged 50–69 residing in settings with strong or relatively strong health systems. Quality assurance is required for both screening and early diagnosis programmes.

3.4 Treatment:

A correct cancer diagnosis is essential for appropriate and effective treatment because every cancer type requires a specific treatment regimen. Treatment usually includes surgery, radiotherapy, and/or systemic therapy (chemotherapy, hormonal treatments and targeted biological therapies). Proper selection of a treatment regimen takes into consideration both

the cancer and the individual being treated. Completion of the treatment protocol in a defined period of time is important to achieve the predicted therapeutic result.

Determining the goals of treatment is an important first step. The primary goal is generally to cure cancer or to considerably prolong life. Improving the patient's quality of life is also an important goal. This can be achieved by support for the patient's physical, psychosocial and spiritual well-being and palliative care in terminal stages of cancer [10].

3.5 Palliative care:

Palliative care is treatment to relieve, rather than cure, symptoms and suffering caused by cancer and to improve the quality of life of patients and their families. Palliative care can help people live more comfortably. It is particularly needed in places with a high proportion of patients in advanced stages of cancer where there is little chance of cure.

Relief from physical, psychosocial, and spiritual problems through palliative care is possible for more than 90% of patients with advanced stages of cancer.

Improved access to oral morphine is strongly recommended for the treatment of moderate to severe cancer pain, suffered by over 80% of people with cancer in the terminal phase [11].

3.5 WHO response:

WHO and IARC collaborate with other UN organizations, inlcuing the International Atomic Energy Agency, and partners to: Increase political commitment for cancer prevention and control; coordinate and conduct research on the causes of human cancer and the mechanisms of carcinogenesis; monitor the cancer burden (as part of the work of the Global Initiative on Cancer Registries); identify "best buys" and other cost-effective, priority strategies for cancer prevention and control; develop standards and tools to guide the planning and implementation of interventions for prevention, early diagnosis, screening, treatment and palliative and survivorship care for both adult and child cancers; strengthen health systems at national and local levels to help them improve access to cancer treatments; The International Agency for Research on Cancer (IARC link is external)) estimates that globally, 1 in 5 people develop cancer during their lifetime, and 1 in 8 men and 1 in 11 women die from the disease. These new estimates suggest that more than 50 million people are living within five years of a past cancer diagnosis. Ageing populations globally and socio-economic risk factors remain among the primary factors driving this increase.

Breast cancer represents 1 in 4 cancers diagnosed among women globally. Colorectal, lung, cervical, and thyroid cancers are also common among women [12].

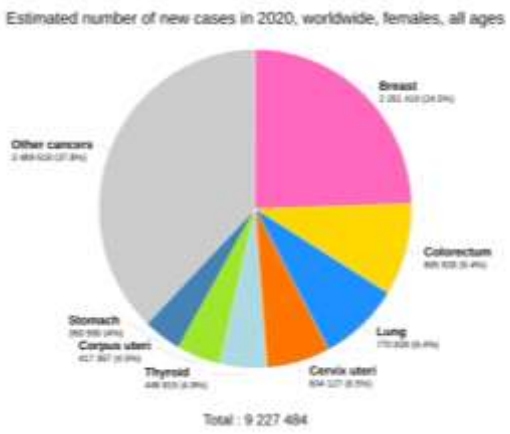

Figure 2 : Estimated Number of Female categories of all ages

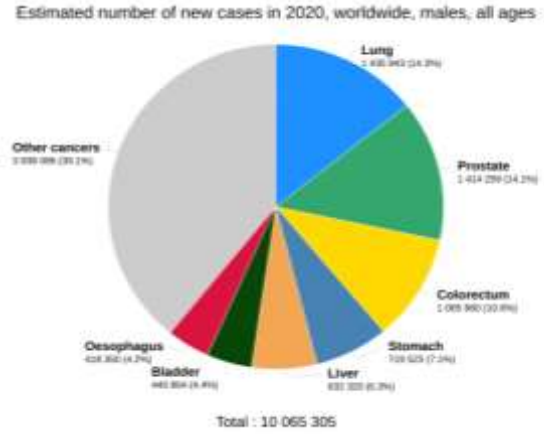

Figure 3 : New cases of all age group Cancers

4. Conclusion:

Earlier procedures involved purely randomized search procedures for drug discovery, in which the experience and intuition of medicinal chemists played vital role in reducing the stochastic nature of search techniques. In view of ever increasing number of chemical compounds this is too time consuming, guarantees too little success and is too expensive. All these necessitated the development of a new logical and scientific approach in drug discovery.

Molecular docking characterizes an important technique in computational biology wherein molecular modeling techniques are used to predict the interaction between any macromolecule (protein) with therapeutically interesting molecules. The capability of protein to interact with small molecules administers a significant part of the protein's dynamics which may enhance/ inhibit its biological function. In an attempt to find new inhibitors of the enzymes, many researchers synthesize a virtual library of compounds, and dock them into the active site cavity of respective enzyme to study their potency. The major drawback associated with such practices is that molecules thought to be potent would necessitate sophisticated syntheses.

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