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RECENT CHEMICAL ADVANCEMENTS OF PYRAZOLE MOIETY IN ANTICANCER THERAPY

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ABSTRACT

Pyrazole moiety is one of the main scaffold for many anticancer drug candidates.Many pyrazole derivatives have been synthesized which shows their activity against different leukemia cell line, non-small cell lung cancer, colon cancer, prostate cancer, CNS cancer, renal cancer, breast cancer, ovarian cancer and cervix cancer cell line. Literature survey revealed that they have been implemented as antitumor, antileukemic and antiproliferative agent beside their capability to inhibit different types of enzymes which plays important roles in cell division.

KEYWORDS:.

INTRODUCTION

A group of ailment in which uncontrolled growth and spread of abnormal cells occurs in body is known as cancer. If this proliferation of cells is not controlled, it can result in death. External factors (tobacco, infectious organisms, chemicals, and radiation) and internal factors (inherited mutations, hormones, immune conditions, and mutations that occur from metabolism) can be the two causes of cancer. These connecting factors may act together or in sequence to initiate or promote carcinogenesis. Surgery, radiation, chemotherapy, hormone therapy, biological therapy, and targeted therapy etc are used to treat cancer.

Cancer is a major health problem worldwide. The development of new anticancer therapeutic agents is one of the basic goals in medicinal chemistry as according to World health organization cancer causes about 13% of all the death [1].

Cell cycle:

Normal cells grow and divide in an orderly fashion, in accordance with the cell cycle. (Mutations in proto-oncogenes or in tumor suppressor genes allow a cancerous cell to grow and divide without the normal controls imposed by the cell cycle.) The major events in the cell cycle are described in fig.2

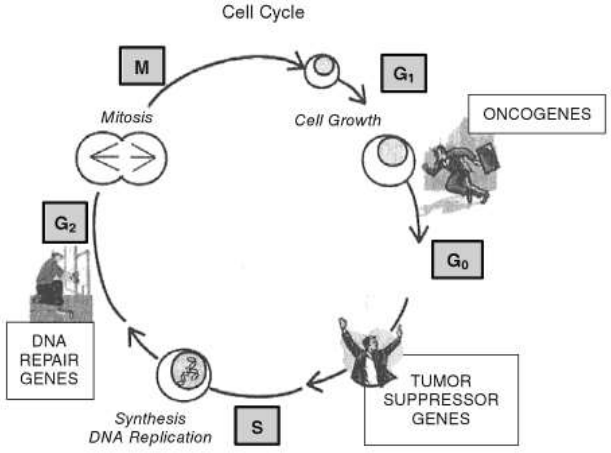


Fig. 2. The cell cycle and placement of major cancer predisposition genes

Several proteins control the timing of the events in the cell cycle, which is tightly regulated to ensure that cells divide only when necessary. The loss of this regulation is the hallmark of cancer. Major control switches of the cell cycle are cyclin- dependent kinases. Each cyclin dependent kinase forms a complex with a particular cyclin, a protein that binds and activates the cyclin-dependent kinase. The kinase part of the complex is an enzyme that adds a phosphate to various proteins required for progression of a cell through the cycle. These added phosphates alter the structure of the protein and can activate or inactivate the protein, depending on its function. There are specific cyclin-dependent kinase/cyclin complexes at the entry points into the G1, S, and M phases of the cell cycle, as well as additional factors that help prepare the cell to enter S phase and M phase. One important protein in the cell cycle is p53, a transcription factor (see the Genes and Development unit) that binds to DNA, activating transcription of a protein called p21. P21 blocks the activity of a cyclin dependent kinase required for progression through G1. This block allows time for the cell to repair the DNA before it is replicated. If the DNA damage is so extensive that it cannot be repaired; p53 triggers the cell to commit suicide. The most common mutation leading to cancer is in the gene that makes p53. Li-Fraumeni syndrome, an inherited predisposition to multiple cancers, results from a germ line (egg or sperm) mutation in p53. Other proteins that stop the cell cycle by inhibiting cyclin dependent kinases are p16 and RB. All of these proteins, including p53, are tumor suppressors.

Normal cells require external growth factors to divide. When synthesis of these growth factors is inhibited by normal cell regulation, the cells stop dividing. Cancer cells have lost the need for positive growth factors, so they divide whether or not these factors are present. Consequently, they do not behave as part of the tissue — they have become independent cells. Normal cells show contact inhibition; that is, they respond to contact with other cells by ceasing cell division. Therefore, cells can divide to fill in a gap, but they stop dividing as soon as there are enough cells to fill the gap. This characteristic is lost in cancer cells, which continue to grow after they touch other cells, causing a large mass of cells to form. Normal cells age and die, and are replaced in a controlled and orderly manner by new cells. Apoptosis is the normal, programmed death of cells. Normal cells can divide only about fifty times before they die. This is related to their ability to replicate DNA only a limited number of times. Each time the chromosome replicates, the ends shorten. In growing cells, the enzyme telomerase replaces these lost ends. Adult cells lack telomerase, limiting the number of times the cell can divide. However, telomerase is activated in cancer cells, allowing an unlimited number of cell divisions. Normal cells cease to divide and die when there is DNA damage or when cell division is abnormal. Cancer cells continue to divide, even when there is a large amount of damage to DNA or when the cells are abnormal. These progeny cancer cells contain the abnormal DNA; so, as the cancer cells continue to divide they accumulate even more damaged DNA.

Pyrazole is characterized by a 5-membered ring structure composed of three carbon atoms and two nitrogen atoms in adjacent positions and to the unsubstituted parent compounds. It is having pharmacological effects on humans and is classified as alkaloids, although they are rare in nature.

Pyrazole plays an important role as antitumor agent because of its good inhibitory activity at various receptor sites such as, EGFR telomerase, ROS Receptor Tyrosine Kinase and Aurora-A Kinase. The pyrazole nucleus includes predominance of inductive effect over mesomeric effect. The substitution at pyrazole nitrogen decreases the basicity due to the steric hindrance to hydration. Because of the presence of diverse properties, easily accessible synthetic pathway and the wide range of biological activities, the pyrazole is centre of attraction for organic chemists [2].

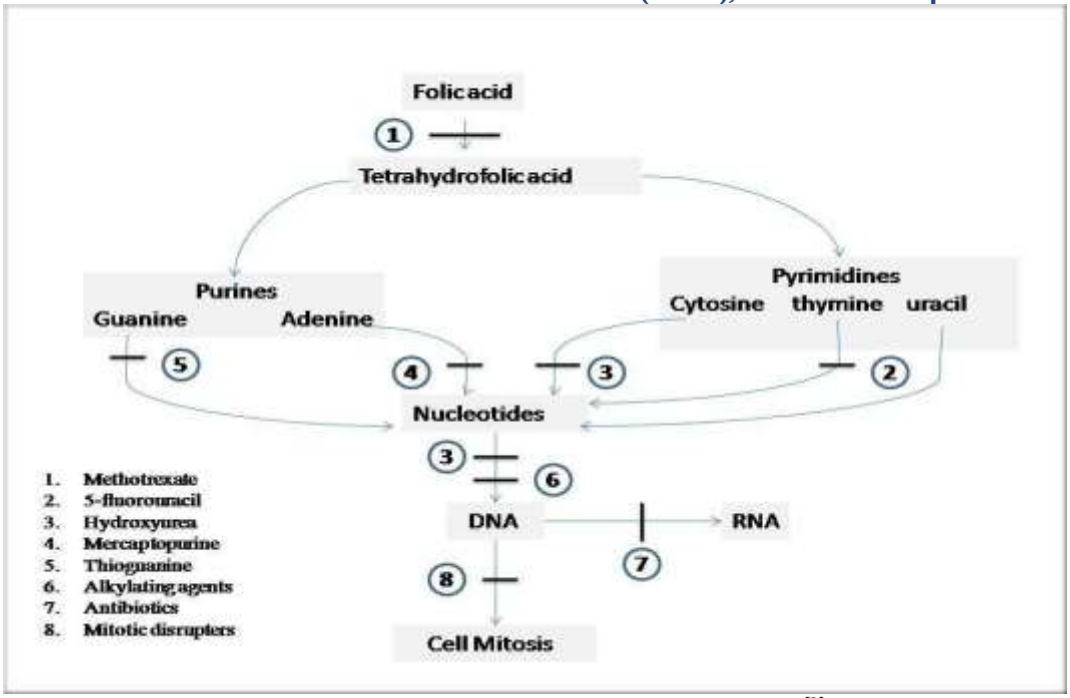
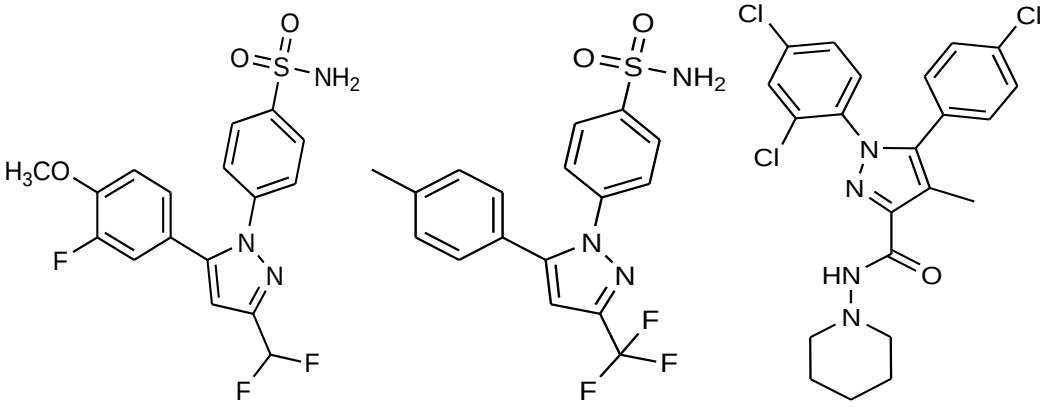


Fig 1: Mechanism of action for Anticancer Drugs [2]

Some pyrazole derivatives with different activities

As proved in the last decade, several pyrazole derivatives have anticancer activity, other activities are also reported for pyrazole nucleus include antitubercular, anticonvulsant, anticancer, antimicrobial, anti-HIV, anti-hepatotoxic, anti-inflammatory, analgesic,[3] and herbicidal.[4] Pyrazole derivatives as wellfeat as A3 adenosine receptor antagonists,[5] neuropeptide YY5 receptor antagonists,[6]hyperlipidemia and thrombopiotinmimetics.[7]



Compound 1: Deracoxib (Anti-inflammatory)
Compound 2: Celecoxib (Anti-inflammatory)
Compound 3: Rimonabant (Anti-obesity)

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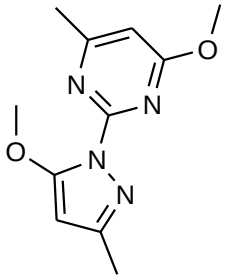
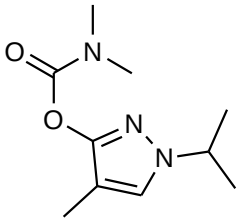
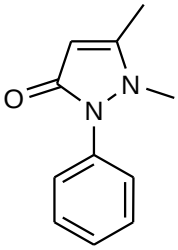


Compound 4: Epirizole (Analgesic,Anti-inflammatory)



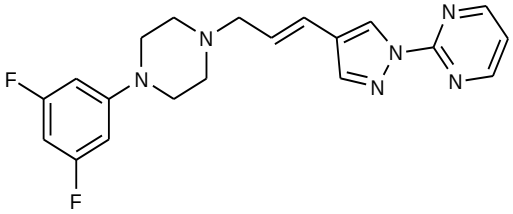
Compound 5: Isolan (Insecticide)



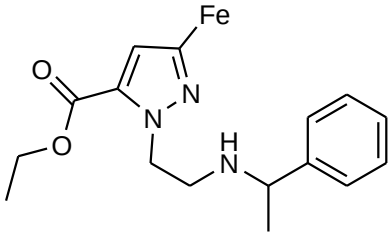
Compound 6: Phenazone (Analgesic)

Pyrazole derivatives with anticancer activity

Various pyrazole derivatives are developed and all are remarkably effective against quite a lot of cellcarcinomas. Manetti F.et al. [8] (compound 7) have analyzed a newscaffold of an antitumor agent, which also showed antiproliferative activity against human lung cancer cell lines and reticenttubulinpolymerization. Schenone S. et al. [9] (compound 8) have studied a series of novel pyrazole derivatives had almost inhibitory effects on the growth of adenocarcinomic human alveolar basal epithelial cells (A549 cells).

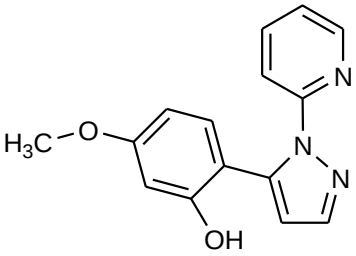


Compound 7

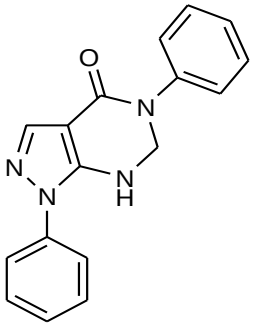


Compound 8

Daidone G. et al. [10] (compound 9) have studied a novel pyrazole derivative and its antiproliferative action in human ovarian adenocarcinoma(A2780 cells), human lung carcinoma cells (A549 cells) and murine P388 leukemia cells. Pevarello P.et al.[11] (Compound 10) have developed a new series of pyrazolo[3,4-d]pyrimidine derivative and tested it for in-vitro anticancer activity against Ehrlich Ascites Carcinoma (EAC) cell line.



Compound 9



Compound 10

Kim D.et al.[12] (compound 11) have synthesized and evaluated 1,3-disubstituted selenolo[3,2-c]pyrazole derivatives for their cytotoxicitycontrary to non-small cell lung cancer (NCI-H226) and A-498 renal cancer cell lines. Zhu G.D.et al. [13] (compound 12) have given a new series of pyrazolo[3,4-d]pyrimidines and pyrazole hydrazones and evaluated them for their antiproliferative activity contrary to human breast adenocarcinoma(MCF-7) cell line.

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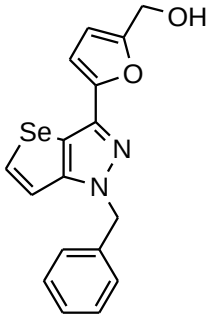
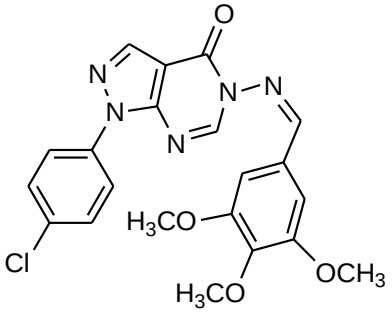
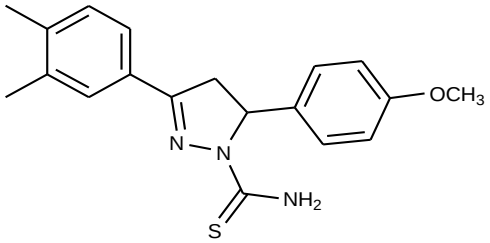


Compound 11

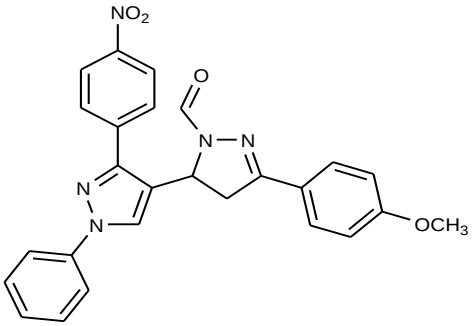


Compound 12

Structure activity relationship of Pyrazole derivatives for anticancer activity:
According to Cheng P. et al [14] compound 13 has methoxy group on phenyl ring at different positions which shows that a strong electron donating substituent on ring at 4th position is more potent against epidermal growth factor receptor inhibitory activity. According to Insuasty L. et al [15] compound 14 has methoxy group on phenyl ring at position four and two pyrazole rings together, having strong activity against cell line of non small cell lung cancer (HOP-92).



Compound 13



Compound 14

According to Luo L. et al [16] compound 15 has electron donating group at 4th position which showed better telomerase inhibitory activity than compound with electron withdrawing substituents. This compound has shown most intoxicating inhibition activity for telomerase and good activity against human melanoma cell (B16-F10).
Ghorab M.M et al [17] have found the scaffold of 3,5-diaryl-1H-pyrazole as a molecular template to synthesize novel growth-inhibitory agents in their study. Their findings suggest that analogs bearing electron-withdrawing groups on one ring while electron-donating groups on another reveal significant activities. In particular, 1, 1'-biphenyl moiety displayed the most potent activity againstovarian cancer cell line(OVCA), human colonic adenocarcinoma cell line (SW620), human non-small cell lung cancer cells(H460) and Human Caucasian gastric adenocarcinoma(AGS)cells with GI(50) values of 0.67, 0.89, 0.73 and 0.79 µM respectively. Cheng P. et al.[14] have found that compound 13 a pyrazole derivative containing thiourea skeleton haspersuasive anticancer activity.Florent T. R. et al.[18] have proposed a novel design by changing the heterocycle for diarylpyrazole structure, various compounds have been synthesized and have been found to be carbonic anhydrase IX inhibitors. Insuasty L. et al.[15] have synthesized noval pyrazolic analogue of chalcones and 3-aryl-4-(3-aryl-4,5dihydro-1H-pyrazole-5-yl)-1-phenyl-1H-pyrazole.Compound16 has chalcone moiety and chlorine group at 4th position of phenyl ring.The compound has shown significant anticancer activity againstNon-small cell lung adenocarcinoma (HOP-92) cell line and cell line SR of leukemia panel.

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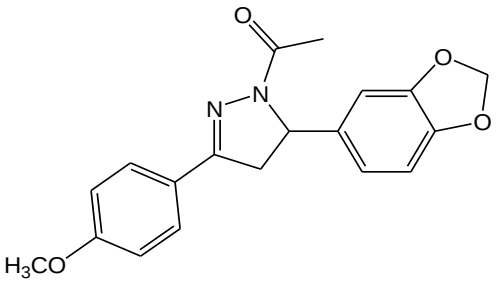
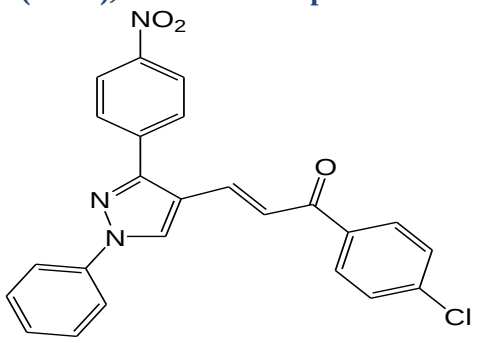
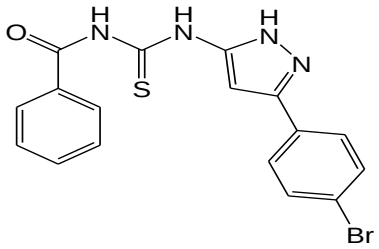


Compound 15

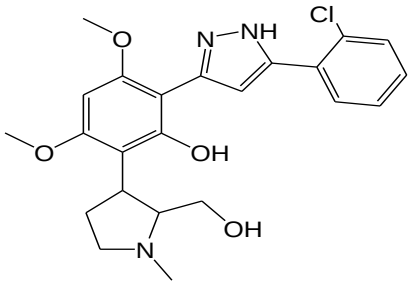


Compound 16

According to Nitulescu G. M. et al.[19] the preeminentanticancer action has been achieved for the compound 17 having an added bromine atom and a pyrazole –NH group free to establish hydrogen bonds. The compound has shown potential antitumor affect, with growth inhibition percents over 50% on 12 cell lines and has been chosen for advance test on a5 fold range of concentration. Totre J. V.et al.[20] have synthesized compound 18 and 19 having halogen atom at 4th position of phenyl ring which was attached to pyrazole in 3,5-diaryl pyrazole system. There study also brings to light that only halogen substituents chlorine and bromine are involved in improving the anticancer activity apart from fluoro substituent.



Compound 17



Compound 18

Liu X. H. et al.[21] have found that Telomerase reverse transcriptase(TERT) protein was express at lower level in MGC -803 cells which were treated with compound 20(helophenyl structure). According to Chistodoulou M. S. et al.[22] presence of hydroxyl group in meta and para position of B-phenyl moiety increasesantiproliferative activity. Zovko T. C. et al. [23] have been synthesized compound 21 (pyrazolone-fused combretastatins). This structure has three parts: First one is, 3, 4, 5 –trimethoxy phenyl moiety, responsible for cytotoxicity. Second one is double bond. This affects both the cytotoxicity and the tubulin binding. And third one is phenol ring. It has property of binding to tubulin.

CONCLUSION

By recent research studies, it has been found that pyrazole is quite a promising scaffold for study in the area of anticancer drugs. This originates the idea to design the pyrazole-based compounds which might show their activity against cancer.

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