RECENT ADVANCES IN ANTICANCER DRUGS

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Summary

In normal cells, the rate of new cell growth is kept in balance with the rate at which old cells die. In cancer cells this balance is disrupted either by the loss of normal growth control or the loss of a cells ability to undergo programmed cell death, known as apoptosis. Normal cycling cells that cease to proliferate enter the resting phase, or *G1*, and their exit into the replicative phases is strongly dependent on the presence of growth factors and nutrients. However, once the cells enter the replicative phase of the cell cycle, they become irrevocably committed to completing cell division. Hence, the conditions that lead to exit from *G1* and entry into *S* are tightly regulated and are frequently misregulated in neoplastic cells that exhibit uncontrolled proliferation. Both tryptamine and piperazine were combined in rigid framework to form Octahydropyrazino[2',1':6,1]pyrido[3,4-b]indole and it is substituted at 2 position to form the compounds which may be active as *antihistamines, antipsychotic, PDE-5 inhibitor* and *anticancer.* Anticancer drugs exploit quantitative differences between the host and cancer cells and adverse reactions to anticancer drugs are often caused by the death of normal cells in tissues with a high growth fraction. The therapeutic index of these drugs is very low and serious adverse reactions occur at therapeutic doses. This is an important factor limiting the use of anticancer drugs.

Keywords: Cancer, Cell Cycle, Advancement in anticancer drugs, Novel anticancer drug.

CANCER: AN INTRODUCTION

Abnormal cell proliferation mediated by disruption of normal cell cycle mechanism is a hallmark of virtually all cancer cells **[1]**. Cancer, a Phenomenon of Immortality which is second major cause of death in US.

A cell needs to divide in order to preserve the organism that it supports. In normal cells, the rate of new cell growth is kept in balance with the rate at which old cells die. In cancer cells this balance is disrupted either by the loss of normal growth control or the loss of a cells ability to undergo programmed cell death, known as apoptosis. When it comes to cell division, cancer cells break just about all the rules **[2]**.

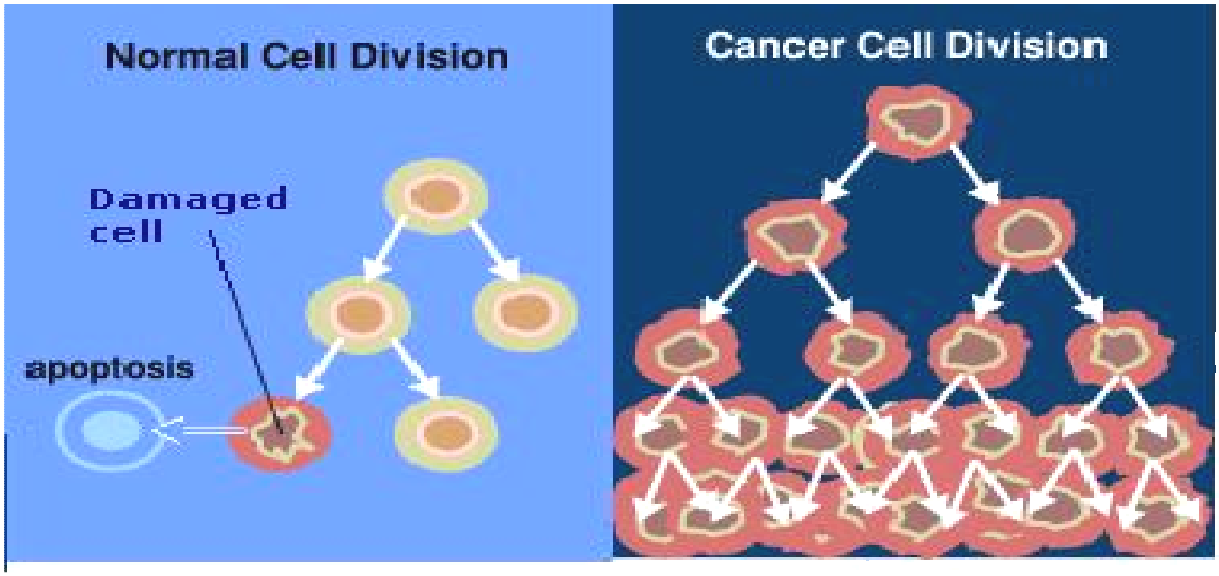


Fig: 1 Comparison of normal and cancer cell division

While cancer is clearly associated with an increase in cell number, alterations in mechanisms regulating new cell birth, or cell proliferation, are only one facet of the mechanisms of cancer.

Tumor cell biology:

Cell division is divided into four phases: *G1, S, G2, and M.* The entire process is punctuated by two spectacular events, the replication of DNA during S phase and chromosome segregation during mitosis or *M* phase. Of the four cell cycle phases, three can be assigned to replicating cells and only the *G1*phase, and a related quiescent phase, *GO*, are nonreplicative in nature. Normal cycling cells that cease to proliferate enter the resting phase, or *G1*, and their exit into the replicative phases is strongly dependent on the presence of growth factors and nutrients. However, once the cells enter the replicative phase of the cell cycle, they become irrevocably committed to completing cell division. Hence, the conditions that lead to exit from *G1* and entry into *S* are tightly regulated and are frequently misregulated in neoplastic cells that exhibit uncontrolled proliferation. There are two restriction points in cell cycle *1*. Between *G1* and *S 2*. Between *G2* and *M* phase. Passage across these restriction point, or R point, is controlled by cell cycle proteins, cyclins and cyclin dependent kinases (CDKs), which physically associate to form a protein kinase that drives the cell cycle forward.

Cancer is a variety of distinct diseases and that defective genes cause this diseases. Further, gene defects are diverse in nature and can involve either loss or gain of gene functions. Conceptually, this process can be divided into three distinct stages: initiation, promotion, and progression. Following are major characteristics that distinguish cancer cell from normal cell -:

1. Uncontrolled proliferation.
2. Dedifferentiation and loss of function
3. Invasiveness
4. Metastasis.

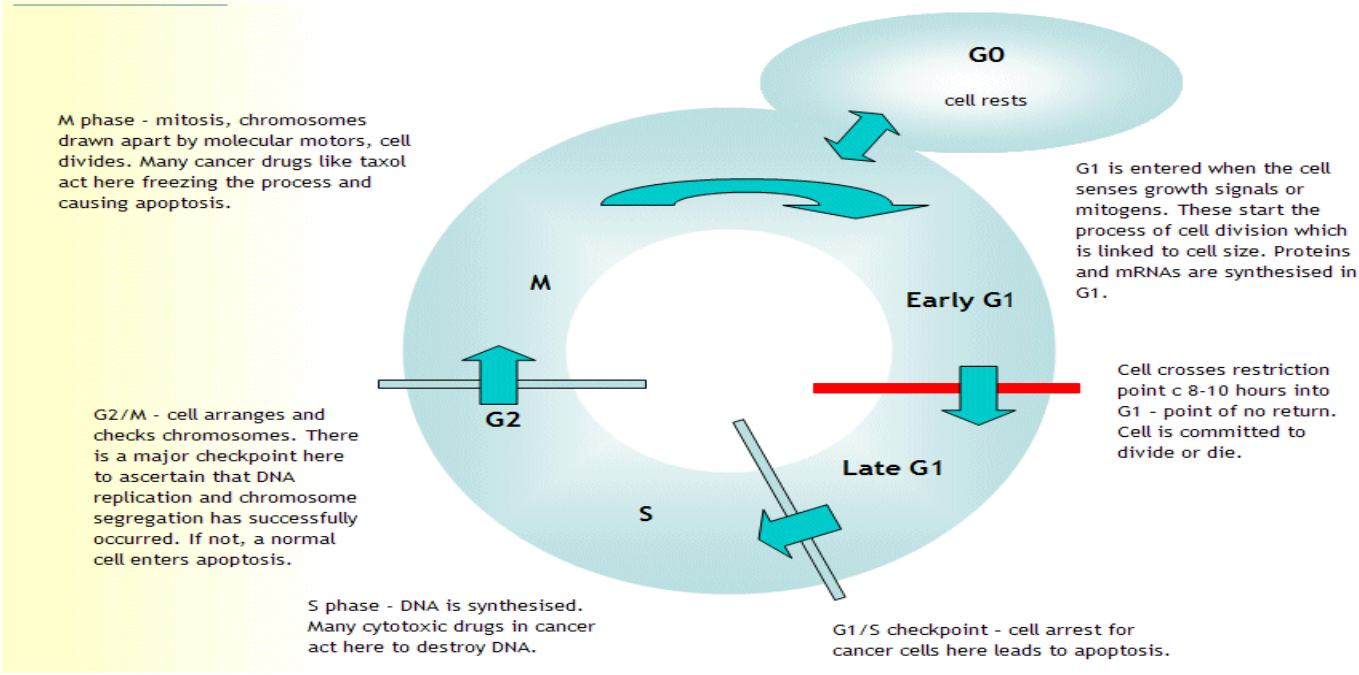


Fig: 2 Cell cycle phases

TREATMENT STRATEGIES

The treatment given for cancer is highly variable and dependent on a number of factors including the type, location and amount of disease and the health status of the patient. *Chemotherapy, Radiation, Surgery, Hormonal Treatments, Specific Inhibitors, Antibodies, Biological Response Modifiers* and *Vaccines* are commonly used agents for cancer treatment.

Drugs have played a significant role in the control of several of the less common cancers. To produce a cure, therapy must eliminate all cancer cells, whether at the primary site, extended to local regional areas, or metastatic to other regions of the body. Anticancer drugs act according first order kinetics **[3]**, they kill a percentage of the cancer cells (e.g. 99.99%) and thus they generally produce remission rather than a cure. Repeated treatments are needed to reduce the number of cells to undetectable levels.

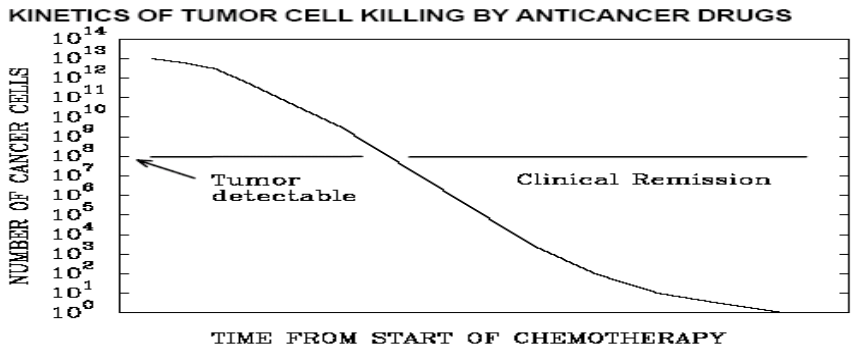


Fig: 3 Kinetics of tumor cell killing by anticancer drugs

So a number of neoplastic diseases can be cured with drugs alone or with drugs in combination with other modalities. Adjuvant chemotherapy in combination with surgery and/or radiotherapy has increased survival rates for a number of solid tumors. Tumors with a high fraction of cells undergoing DNA replication (i.e. a high growth fraction) are most susceptible to anticancer drugs while other more slowly growing tumors of the lung, breast, GI tract and reproductive tract are less sensitive to drugs and usually treated by combinations of surgery, radiation therapy and drugs. An understanding of the cell cycle and growth kinetics is essential for the proper use of anticancer drugs.

SELECTIVE TOXICITY OF ANTICANCER DRUGS

Anticancer drugs exploit quantitative differences between the host and cancer cells and adverse reactions to anticancer drugs are often caused by the death of normal cells in tissues with a high growth fraction. The therapeutic index of these drugs is very low and serious adverse reactions occur at therapeutic doses. This is an important factor limiting the use of anticancer drugs.

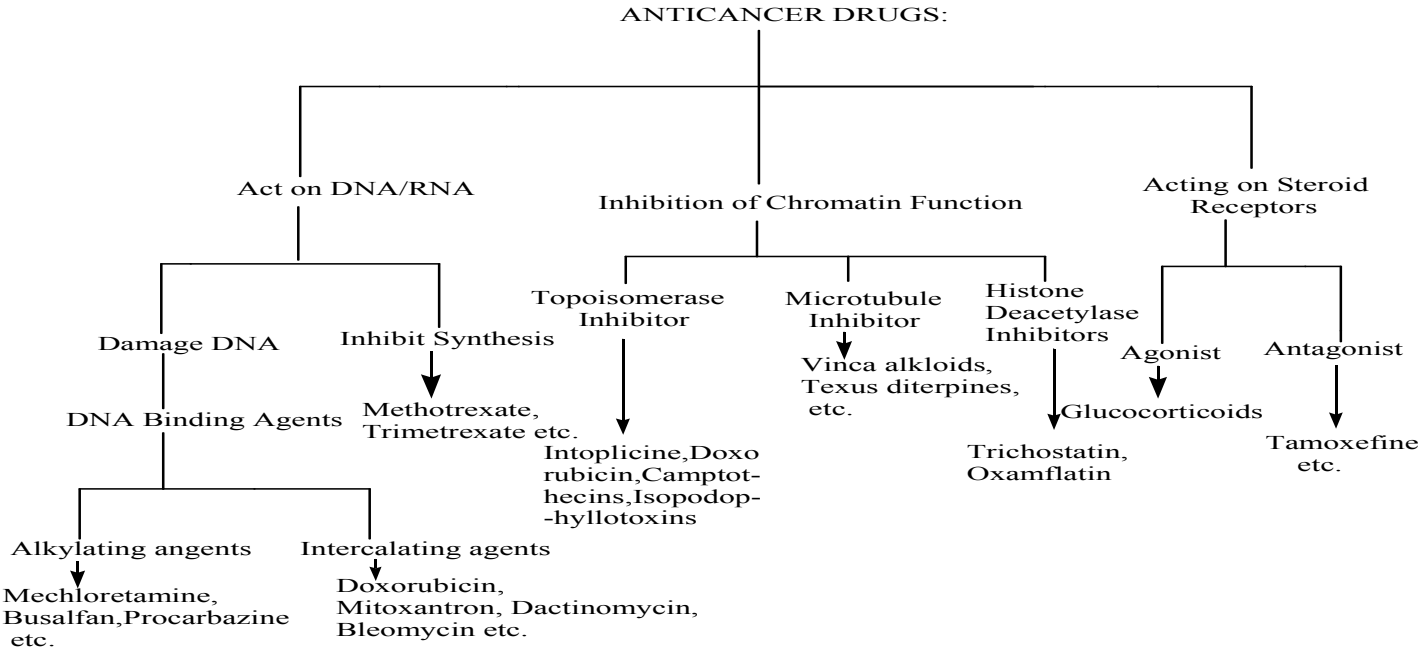
1. Common acute toxicities: As anticancer drugs cannot differentiate between rapidly growing normal cells and cancer cells so these drugs have common acute toxicity on like gastrointestinal mucosa, bone marrow, hair and reproductive function - infertility occurs often, in both males and females.

2. Chronic Toxicities: Cardiomyopathy, Neurotoxicity, Nephrotoxicity, Carcinogenesis and Mutagenesis are common type of chronic adverse effect of anticancer drugs.

NOVEL ANTICANCER DRUGS

Modern chemotherapy of cancer began in the 1940's with the discovery and use of the nitrogen mustard as alkylating agents to treat leukemia's and lymphomas. Many new drugs have subsequently been discovered or designed to have antineoplastic activity. The market for anticancer agents was estimated at about US $10 billion and continues to escalate. The ideal chemotherapeutic drug would target and destroy only cancer cells without adverse effects or toxicities on normal cells. Unfortunately, no such drug exists. Many drugs are effective only if cells are in cell cycle. Agents, which act preferentially on tumor cells in a given phase of the cell cycle, are called cell cycle phase specific.

Anticancer drugs can be classified into following categories [4, 5]:

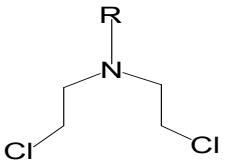


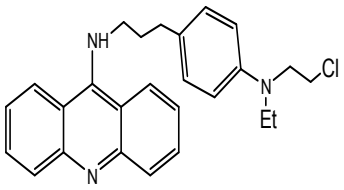
RECENT DEVELOPMENT OF ANTICANCER DRUGS

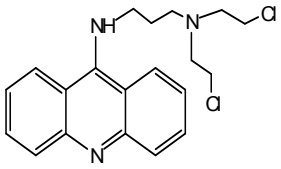
The major chemotherapeutics agents in clinical use exert their primary action on a variety of targets such as DNA/RNA (alkylation, intercalation, topoisomerase inhibition etc.), purine or pyridine metabolism or microtubule assembly. But all these having a common pitfall that is a narrow therapeutic index between cancer cells and that of normal cells. To overcome these limitation in each categories of anticancer drugs following are recent development **[6]**.

1. Alkylating agents: Many of the limitations with the alkylating agents like acting with other cell components etc. could in principle be ameliorated by targeting the mustard moiety more specifically to the DNA-affinic carrier molecule. This could mean less chance of losing active drug by reaction with other cell components, rendering less effective the development of cellular resistance. A higher proportion of bifunctional alkylating agent delivered intact to the DNA would also contribute to a higher proportion of cross-links over to monoalkylation events. The attachment to acridine carriers might serve to target the reactive center to DNA. They showed that such "targeted mustards" such as acridine mustard, quinacridine-linked mustard were more potent than the corresponding untargeted moiety against ascitic tumors *in vivo*, recent work showed that such targeting by an intercalator could also drastically modify the pattern of DNA alkylation by the mustard. Thus, whereas untargeted mustards react largely at the N-7 of guanines in runs of guanines, quinacrine mustard also alkylates at guanines in 5'-GT sites.

Structure of Alkylating agents







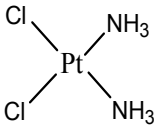
R=CH_3; Mechlorethamine Acridine mustard Quinacridine-linked mustard

R= $(CH_2)_3COOH$; Chlorambucil, R=CH (NH_2) COOH; Melphalan

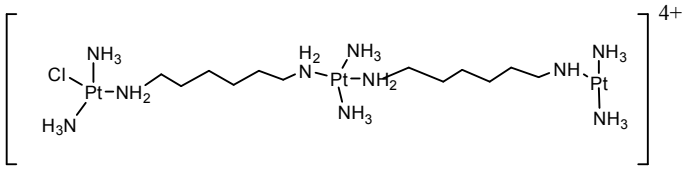
Alkylating agents

2. Platinum Complex: The tetra cationic triplatinum complex BBR 346, a new structural class of DNA-modifying anticancer agents. It reacts with DNA faster than does cisplatin, suggesting rapid cellular uptake and nuclear access. BBR 3464 was 30-fold more cytotoxic than cisplatin in L1210 cells and showed no cross-resistance in sublines resistant to cisplatin because of impaired accumulation and lower DNA binding.

Structure of Platinum complex



Cisplatin

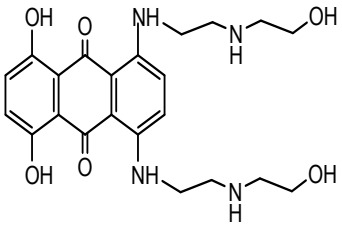


BBR 346

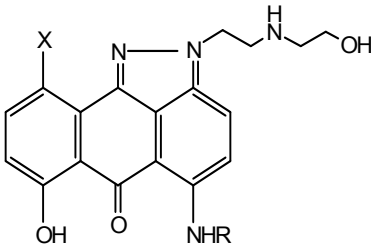
Platinum complex

3. Topoisomerase Inhibitors: Topoisomerase II (topo II) is a ubiquitous nuclear enzyme that modulates topological relationships with in the genome of eukaryotic cells, topo II adjusts and stabilizes DNA during replication, transcription, and recombination, and also functions in chromosomal condensation and segregation reactions. Unlike other members of the topoisomerase super family, topo II is required for proper cell function because it possesses the ability to catenate and decatenate DNA. The essential nature of topo II coupled with its elevated expression in tumor cells make it an exceptional target for chemotherapy. In fact, two of the most widely utilized anticancer drugs, etoposide and adriamycin inhibit topo II. The development of analogs of mitoxantrone has been driven largely by the requirement for lower cardiotoxicity **[7]**. Two broad classes of analogs were synthesized, the first are close analogs of mitoxantrone, where the tricyclic chromophore has been maintained and variations occur in the side-chains or the chromophore atoms. Preclinical studies showed Teloxantrone has a better therapeutic index and lower cardiotoxicity than mitoxantrone. The second broad class are tetracyclic compounds, primarily the *imidazoacridinones* **[8]** and the *anthrapyrazoles*. In this class the activity was maximal

with alkylamino side chains at the N-2 and C-5 position with two to three carbon spacers between proximal and distal nitrogens and showed they induced less oxygen consumption than doxorubicin in the rat liver microsomal system. These compounds bind very tightly to DNA by intercalation. Examples are losoxantrone and piroxantrone etc.



Mitoxantrone



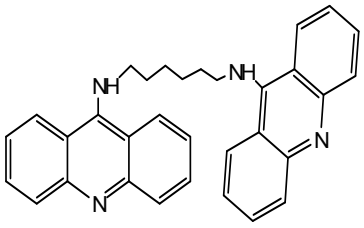
X=OH, R=$(CH_2)_2NHCH_3$; Teloxantrone

X=H, R=$(CH_2)_2NH(CH_2)_2OH$; Losoxantrone

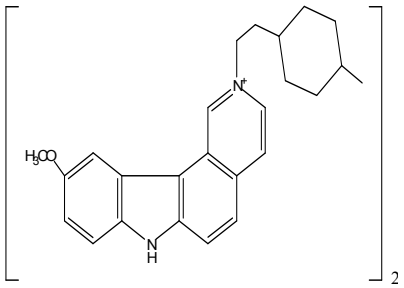
X=OH, R=$(CH_2)_3NH_2$; Piroxantrone

Mitoxantrone and its analogs

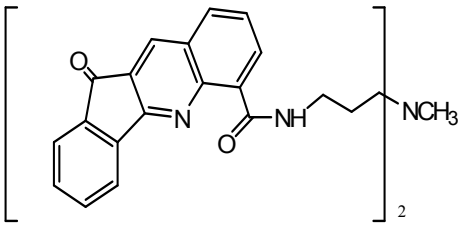
The early SAR suggesting a positive correlation between cytotoxic potency and the strength of DNA binding and because bis-intercalation would theoretically greatly increase DNA binding, many dimeric compounds designed as bis-intercalators were evaluated as anticancer drugs. The bis(acridine) was selected for clinical trial but had significant *CNS* toxicity and the bis (el1ipticine) analog ditercalinium had unacceptable mitochondrial toxicity. More recently, several series of dimers of more lipophilic chromospheres have shown potent and broad-spectrum activity against a variety of human solid tumor cell lines, both in culture and as xenografts in nude mice. Several series of bis analogs of tri- and polycyclic carboxamides, including acridines, phenazines and indenoquinolines are also potent cytotoxic agents and dual topoI/II inhibitors. SAR studies of these compounds show that both chromophore substitution and linker chain variations can significantly affect potency. The dicationic bis(phenazine) XR5944 is of particular interest, with subnanomolar potency in a range of human cell lines and active in multidrug-resistant cell lines *in-vitro* and *in-vivo.*



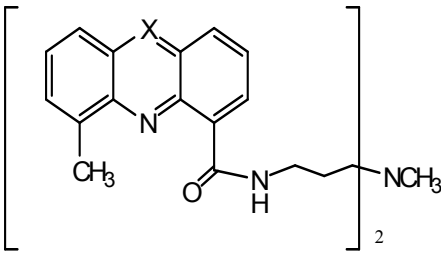
Bis (acridine) derivative



Ditercalinium



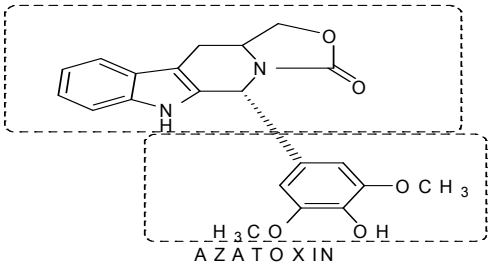
Indenoquinolines



Phenazines Derivatives

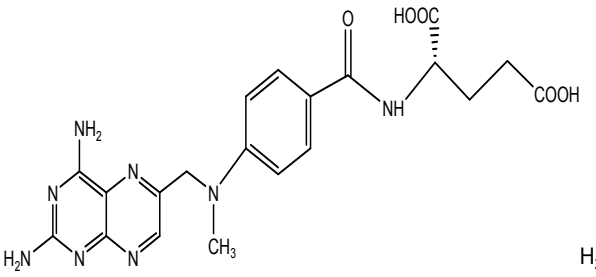
Topoisomerase inhibitors

Azatoxin, a compound designed as a hybrid of etoposide and ellipticine, inhibits topo II action and also halts tubulin polymerization at variable concentrations **[9]**.

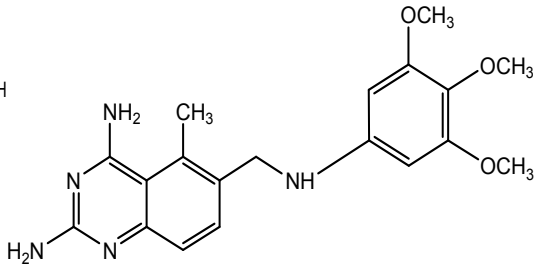


4. **Antimetabolite:** These compounds were designed to circumvent resistance to methotrexate that arises by reduced folate uptake or reduced polyglutamylation. They are relatively lipophilic compounds, lacking a glutamate residue, that get into cells by passive diffusion. The first examples to receive clinical evaluation were *Trimetrexate and Piritrexim and Nolatrexed.*

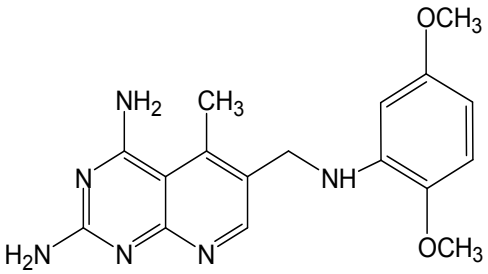
Structure of Antimetabolites agent



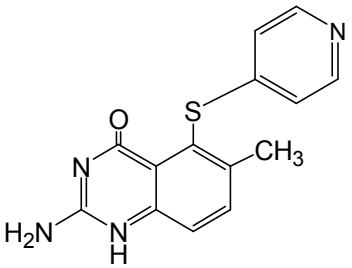
Methotrexate



Trimetrexate



Piritrexim



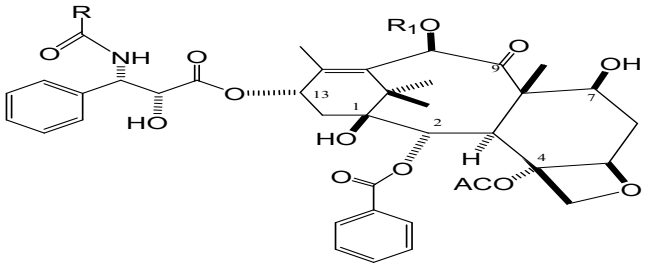
Nolatrexed

Antimetabolites

5. **Microtubules Inhibitors:** Microtubules provide a cytoskeleton for cells so that they can maintain their shapes. They also form a sort of "rails," along which the chromosomes move during mitosis. These microtubules are constructed by the controlled polymerization of

monomeric tubulin proteins of α and β. Dimeric vinca alkaloids interfere with polymerization, thus preventing cell division by preventing the formation of new microtubles. The taxus alkaloids on the other hand promote the polymerization into new microbules but stabilize these and prevent their remodeling. This prevents cell growth and repair. These mechanisms are competable with the modes of action of other antitumor agents thereby allowing for synergy when combine with these substances in cocktails.

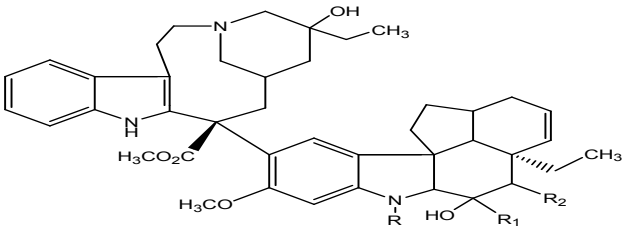
Vindisine is an analog prepared from vinblastine. Its antitumor spectrum is more closely similar to that of vincristine but it is a myelosuppressant and neurotoxicity. Vinflunine is also a vinca alkaloid analog yet to come to market.



R=Ph; R_1 =$COCH_3$ Paclitexal

R=tBu; R_1 =H Docetaxel

Taxus alkaloids



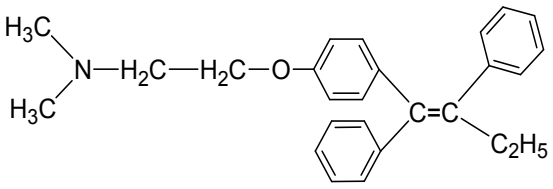
Vinca alkaloids

Table: 1 Compounds of Vinca alkaloids

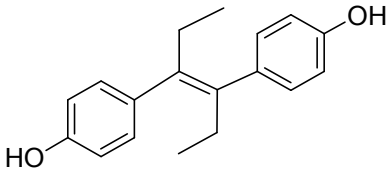
Compound	R	R_1	R_2
Vinblastin	CH_3	CO_2CH_3	$OCOCH_3$
Vincristine	CHO	CO_2CH_3	$OCOCH_3$
Vindesine	CH_3	CO_2NH_2	OH

6. ***Steroidal hormones receptor agonist/antagonist:*** Since sex hormones are concerned with stimulation and control of proliferation and function of certain tissues, including the mammary and prostate glands so cancer arising from these tissues can stimulated or inhibited by appropriate change in hormone balance. Adrenal corticosteroids are also useful in treatment of several types of cancer. Steroid hormones bind to receptor proteins in the cancer cells, forms steroid-receptor complex that ultimately binds directly to nuclear nonhistone protein associated with DNA to activate transcription of associated genes.

Estrogen hormones agonist like diethylstilbestrol and estrogen hormones antagonist like tamoxifen has been approved for clinical use.



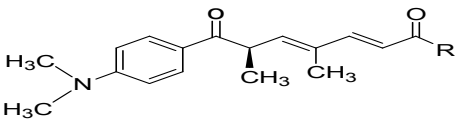
Tamoxifen

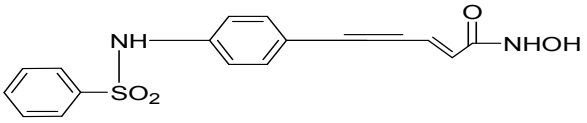


Diethylstilbestrol

Acting on steroidal hormone receptor

7. Histone deacetylase inhibitors [10]: Histones are small basic proteins that, by complexing with DNA, form the nucleosome core. Repetitive units of this nucleosome led to the chromatin in which all the human genome is packaged. The structural modification of histones is regulated mainly by acetylation/deacetylation of the N-terminal tail and is crucial in modulating gene expression, because it affects the interaction of DNA with transcription-regulatory non-nucleo-somal protein complexes. The balance between the acetylated/deacetylated states of histones is mediated by two differentsets of enzymes: histone acetyltransferases (HATs) and histone deacetylases (HDACs). HATs preferentially acetylate specific lysine substrates while HDACs restore the positive charge on lysine residues by removing acetyl groups and thus are involved primarily in the repression of gene transcription by compacting chromatin structure. Inhibition of HDACs represents a new strategy in human cancer therapy since these enzymes play a fundamental role in regulating gene expression and chromatin assembly. They are potent inducers of growth arrest, differentiation and apoptosis of tumor cells. A wide variety of HDACs of both natural and synthetic origin has been reported like depsispeptide FK228, natural HDACs (trichostatin (TSA), depudecin, trapoxins, apicidins) as well as sodiumbutyrate, phenylbutyrate and suberoylanilide hydroxamic acid (SAHA).





R= NHOH Trichostatin A Oxamflatin R=OH Trichostatic Acid

Histone deacetylase inhibitors

MODE OF ACTION OF ANTICANCER DRUGS

Abnormal expression of proto-oncogenes can take several forms; their protein product may be aberrant or is over or under expressed. Thus, two fundamentally different genetic mechanisms exist consisting of, one of them is enhanced or aberrant oncogene expression second is decreased activity of tumor suppressor. A number of oncogene are known and are grouped based on function. One category is related with growth factor producers and another category is related with growth receptor **[11].**

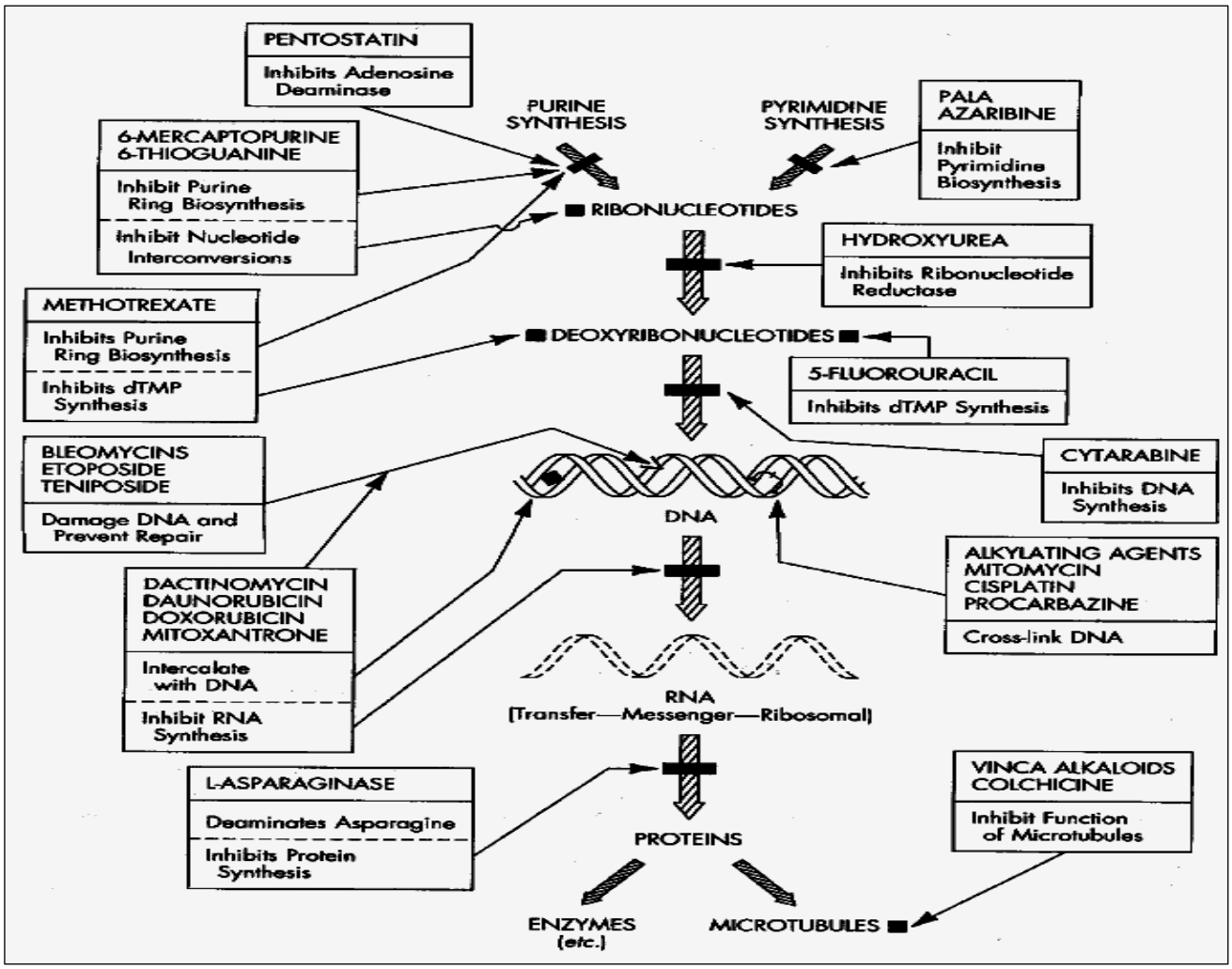
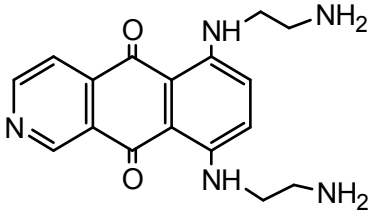
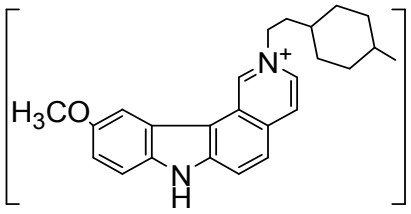
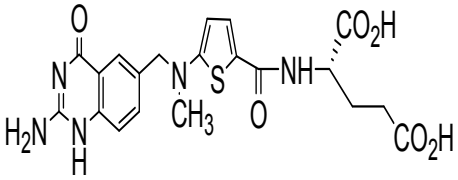
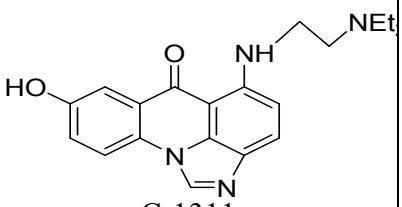
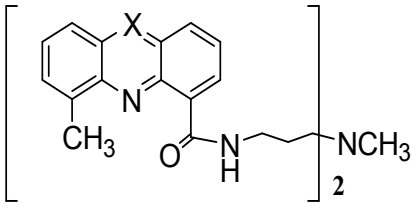
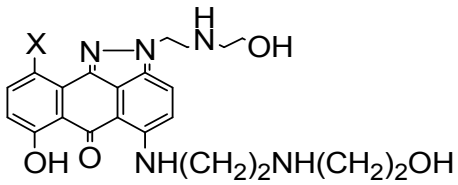
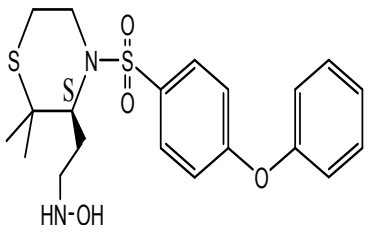
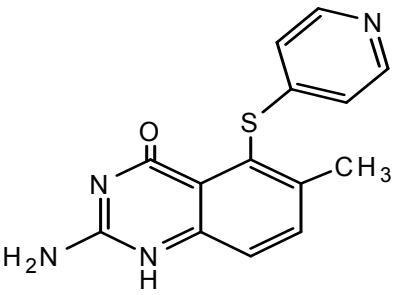
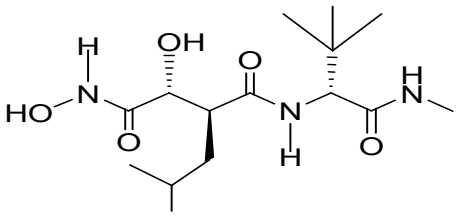


Fig: 3 Mode of action of anticancer drugs

CLINICAL TRIALS & FUTURE ASPECTS OF ANTICANCER DRUGS

Table: 2 Molecules under investigation/clinical trial:

Phase I	Phase II	Phase III
 BBR 2778	 Ditercalinium	 Raltitrexed
 C-1311	 XR5944	 Losoxantrone
 Prinomastate, AG3340	 Nolatrexed	 Marimastate

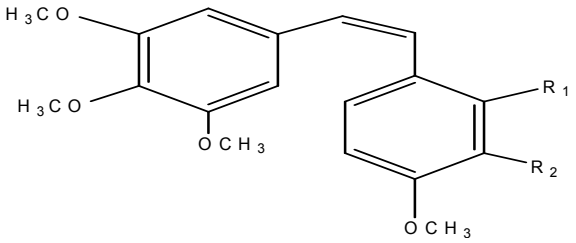
Other molecules under clinical trial:

1. Combretastatin: i. R_1= R_2= H, Combretastatin A-1

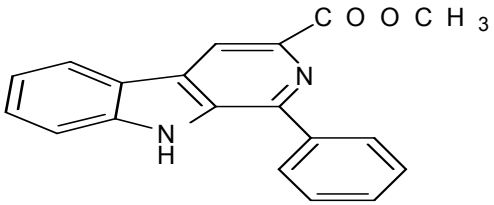
ii. R_1= R_2= OPO_3Na_2 ,Combretastatin A-1p

iii. R_1= H, R_2 = OH, Combretastatin A-4

iv. R_1= H, R_2= OPO_3Na_2, Combretastatin A-4p



2. 1 - aryl - 1,2,3,4 - tetra hydro - 9H- pyrido (3,4 -b) indole - 3 - carboxylic ester:



3. 2-substituted1,2,3,4,6,7,12,12aoctahydropyrazino[1',2':1,6]pyrido[3,4-b]indole

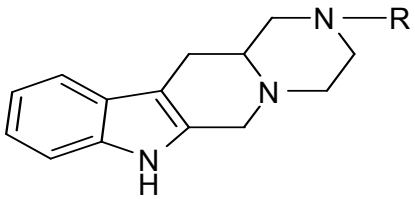
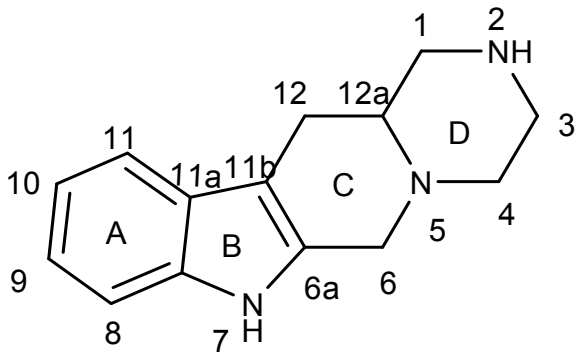


Table: 3 Drugs used in cancer chemotherapy

Generic Name (Structure)	Trade Name	Originator	Chemical Class
Mechlorethamine	Mustargen	Merck	Aliphatic mustard
Cisplatin	Cisplatin	Bristol-Myers	Platinum complex
Temozolomide	Temodar	Shering-Plough	Triazene
Mitoxantrone	Novantrone	Wyeth	Anthracenedione
Intoplicine	----------	Ilex	Pyridoindole
Raltitrexed	Tomudex	Lilly	----------
Nolatrexted	Thymitaq	Zarix	----------

Since tryptamine is a naturally occurring monoamine which acts as a precursor for other compounds including indole, beta-carboline and ergoline alkaloids and auxins which are biologically active in neurological disorders and cancer. While Piperazine incorporates the ethylenediamine substructure have a myriad of biological activity such as H_1 antagonist, antihypertensive and neuroleptic etc. So both tryptamine and piperazine were combined in rigid framework to form Octahydropyrazino[2',1':6,1]pyrido[3,4-b]indole and it is substituted at 2 position to form the compounds which may be active as *antihistamines, antipsychotic, PDE-5 inhibitor* and *anticancer.*



Octahydropyrazino[2',1':6,1]pyrido[3,4-b]indol

Conclusion

Normal cycling cells that cease to proliferate enter the resting phase, or *G1*, and their exit into the replicative phases is strongly dependent on the presence of growth factors and nutrients. However, once the cells enter the replicative phase of the cell cycle, they become irrevocably committed to completing cell division. Hence, the conditions that lead to exit from *G1* and entry into *S* are tightly regulated and are frequently misregulated in neoplastic cells that exhibit uncontrolled proliferation. There are two restriction points in cell cycle between *G1* and *S2*, Between *G2* and *M* phase. Passage across these restriction point, or R point, is controlled by cell cycle proteins, cyclins and cyclin dependent kinases (CDKs), which physically associate to form a protein kinase that drives the cell cycle forward. Anticancer drugs act according first order kinetics, they kill a percentage of the cancer cells (e.g. 99.99%), and thus, they generally produce remission rather than a cure.

From above literature we concluded that both tryptamine and piperazine were combined in rigid framework to form Octahydropyrazino[2',1':6,1]pyrido[3,4-b]indole and it is substituted at 2 position to form the compounds which may be active as *antihistamines, antipsychotic, PDE-5 inhibitor* and *anticancer.* Ditercalinium, Losoxantrone, Nolatrexed and more are discovered as anticancer drug.

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