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"A COMPREHENSIVE STUDY OF ANTICANCER DRUG AND THEIR INTERACTION WITH DNA"

Author : 1 Ms Veenu Gupta, 2 Mr. Sourabh Gupta, 3 Dr Shilpi Srivastava
Department of Chemistry, Kalinga University, Raipur -Chhatisgarh

ABSTRACT
Cancer is the third most lethal disease in the world after cardiovascular, parasitic and infectious diseases, based on reports from American Cancer Society (ACS) . In 2011, nearly 13 million people are diagnosed with cancer and hence, cancer continues to be a great threat to people now . Thus, the medical needs for cancer remain one of the most demanding areas in scientific research. Several studies have been carried out to prevent and treat cancers. Che- moprevention is defined as pharmacological intervention with synthetic or naturally occurring compounds that may inhibit or prevent carcinogenesis. Cancer treatment involves surgery, radiation and drugs. Surgery-the first line of therapy, is used for early stage of cancer. Radiotherapy is most often applied in a localised setting and conjunction with surgical procedures. The last one, drugs are implemented with chemotherapy (CTX), which employs a wide group of drugs that have cytotoxic effects. The anticancer drugs inhibit cell division and proliferation and are less selectivity towards cancer cells. Thus, these drugs not only destroy cancer cells but also destroy normal cells.

ANTICANCER DRUGS — BENEFICIAL EFFECTS

Anticancer or chemotherapy drugs are chemicals that can denature cancer cells by arresting their growth. Though anticancer drugs affect dividing cancer cells, normal cells are also affected in the course of the event. The most affected cells are:

- Bone marrow,
- Gonads (sex organs),
- Gastrointestinal tract, and
- Skin (hair follicle cells).

In addition to the above organs, liver and kidneys (slow proliferating cells) are affected since they are the organs of metabolism or target organs of toxicity.

Today, more than 100 different drugs have been used for chemotherapy, either alone or in combination with other treatments. For several years, the most effective drugs used in chemotherapy were considered to be DNA damaging agents . These drugs can be divided into different categories based on their mechanism of action. They are summarized in Figure 1.

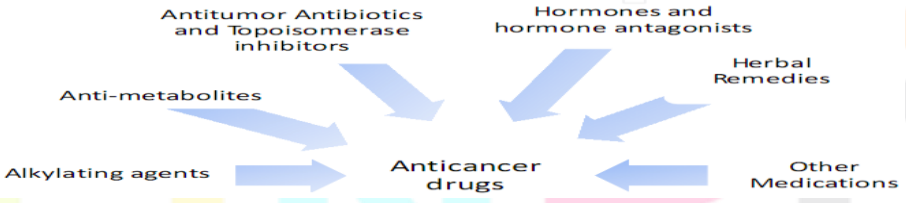


Figure 1. Classification of anticancer drugs

Alkylating agents (Figure 2)

This class of drugs directly damages DNA by adding methyl or other alkyl groups onto nucleotide bases [6] and thereby inhibit their correct utilization by base pairing leading to mutation, DNA fragmentation as well as inhibition of DNA replication and transcription. They also disrupt cell respiration and intermediary metabolism by alkylation of proteins and enzymes. The anticancer drugs that contain alkylating agents are cyclophosphamide, ifosfamide, melphalan, and chlorambucil.

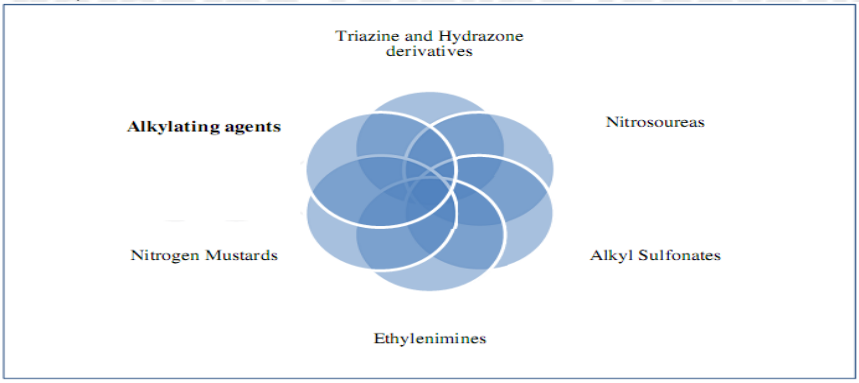


Figure 2. Family of alkylating agents

Anti-metabolites (Figure 3)

Inhibitors of DNA synthesis inhibit essential biosynthetic processes or are incorporated into DNA, RNA, proteins and other macromolecules. These drugs (Figure 3) are either structural analogues for heterocyclic bases or agents interfering with folate metabolism. DNA building blocks include heterocyclic bases and folic acid. They inhibit main steps in the formation of purine and pyrimidine bases as well as nucleotides. This class of drugs includes antifolates (methotrexate, pemetrexed) [8], antipyrimidines (5-fluorouracil, capecitabine, eniluracile, hydroxyur- ea) and antipurines (6-mercaptopurine, 6-thioguanine).

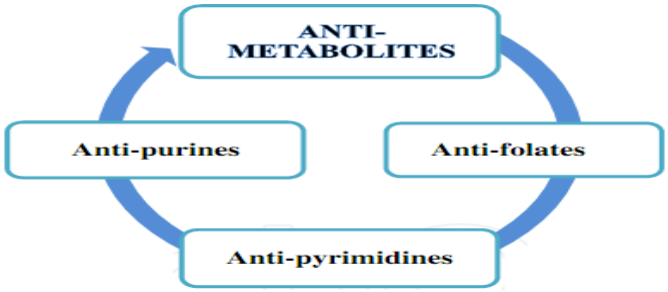


Figure 3. Anti-metabolites

Antitumor Antibiotics and Topoisomerase Inhibitors

Antitumor antibiotics and topoisomerase inhibitors are obtained from the cultures of various microorganisms. Examples:

- Doxorubicin (Adriblastina),
- Daunorubicin (Remember Cerubi),
- Bleomycin (Bleoc's),
- Mitomycin,
- Mithramycin,and
- Epirubicin.

Furthermore, topoisomerase inhibitors have been used to interfere with the action of topoiso- merase I and II enzymes. These enzymes regulate the changes in DNA structure which includes DNA replication, transcription, recombination, and chromatin remodelling. The important inhibitors are camptothecin, irinotecan, topotecan for Topoisomerase I; Etoposide (VP-16), teniposide, doxorubicin, daunorubicin, ellipticine etc, for Topoisomerase II. These drugs inhibit the ability of the topoisomerase to cleave nucleic acid molecules. Although these types of drugs have important clinical efficacy, they have undesired and/or adverse effects such as drug resistance, poor bioavailability problems and myelosuppression. Furthermore, some of them lead to disruption or stabilization of DNA, so that these are also called as topoisomerase poisons. The other inhibitors of topoisomerase bind to enzyme or DNA and interrupt the catalytic activity of the enzyme and prevent the enzyme binding actions.

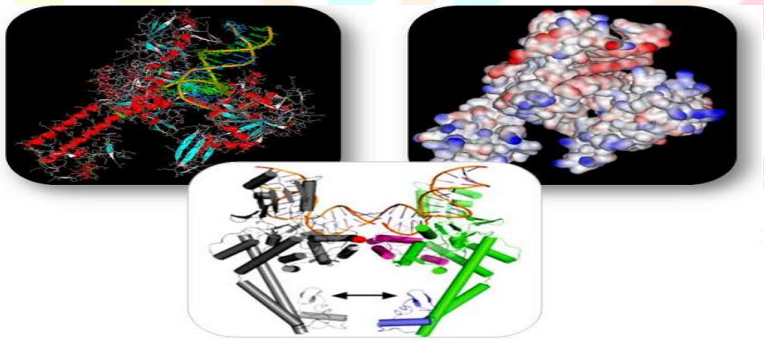


Figure 4. Structure of DNA-Topoisomerase II

Bi-and ter-benzimidazole derivatives constitute a new class of DNA Topo I and II inhibitors. In addition, a camptothecin derivative with a benzoxazole ring is shown significantly more potent than camptothecin as an inhibitor of DNA Topo I . It is of the opinion that a fused ring system in the chemical structure is critical and important for the biological activity.

For example, 2-(4-aminophenyl)benzothiazoles, are observed by Shi et al., exhibit potent anti-tumour activity against some cell lines (breast, ovarian, colon, and renal cell lines). Choi et al. also synthesized a series of 2-(4-aminophenyl)benzothiazole and evaluated the Topo II inhibitory activity. There are studies on the inhibitory effects of some novel fused heterocyclic compounds, (benzimidazole, benzoxazole, benzothiazole, and oxazole(4,5-b)pyridine derivatives) on eukaryotic DNA Topo II (Figure 4) in a cell-free system . These compounds displayed more potent inhibitory activities than the reference drug etoposide (Table 1, Figure 5). Molecular modelings of the possible structural motifs of the fused heterocyclic compounds given in Table 1 have been studied to expose their binding mode to eukaryotic DNA topoisomerase II by molecular docking studies. The interactions involved in the anti-tumour activities of fused heterocyclic compounds lead to the rational design of novel eukaryotic DNA topoisomerase II-targeted drugs .

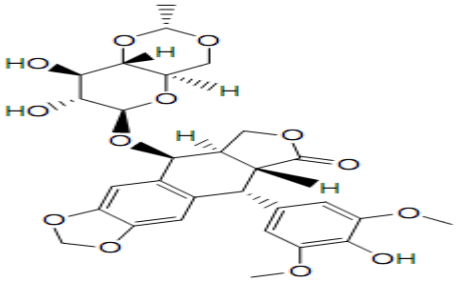
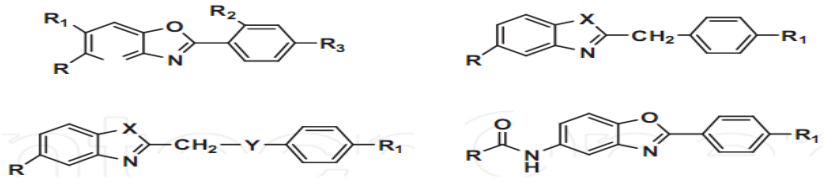


Figure 5. The structure of the reference drug-etoposide



Herbal remedies

These drugs show their effects on mitosis during metaphase by preventing the formation of the spindle. Etoposide VP-16 (Vepesid), an effective anticancer drug, is applied to treat a broad spectrum of human cancers for more than two decades. Unfortunately, its wide therapeutic application is often hindered by multidrug resistance (MDR), low water solubility and toxicity. New derivatives of benzoxazoles, benzimidazoles and related fused heterocyclic compounds, exhibited significant eukaryotic DNA topoisomerase II inhibitory activity, were synthesized and exhibited better inhibitory activity even compared with the drug etoposide (Figure 5) .

Other examples are:

- Vinblastine (Velber A),
- Vincristine (Oncovin),
- Podophyllotoxin,
- Teniposide (VM26-Bristol),and
- Vindesin(Eldisine).

Hormones and hormone antagonists

Hormone antagonists are used for tumors caused by hormones or hormonal imbalance. Examples:

- Glucocorticoid hormones and Estrogens.

The endogenous estrogens in women are steroid hormones. Possible consequences of the lack of estrogen in postmenopausal women are frequently reported, including postmenopausal symptoms, increased risks of osteoporosis, coronary heart disease and Alzheimer's disease. On the other hand, the cumulative exposure to estrogen encourages development of female reproductive cancers. Such examples include breast cancer and uterus cancer, which are found associated with hormone replacement therapy, early menarche and late menopause. The contribution of estrogens in various physiological and pathological pathways depends on the binding to estrogen receptors. It also activates transcription of estrogen responsive genes. The anti-cancer drug benzodihydro [α]carbazole (BDHC), which is widely used to treat breast cancer, and for which the primary target is the human estrogen receptor (hER). This study reveals a brief introduction of BDHC therapy for breast cancer and the related mechanistic pictures of small compounds signaling through hER by using QSAR and docking methods. They were applied to understand the nature of 5,6-dihydro11-alkylbenzo [α]carbazole derivatives (Table 2) and to investigate the interactions of homolog series with binding sites on selected a-chains of human estrogen receptors (hER).

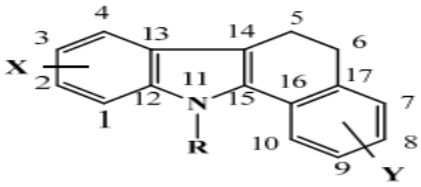


Table 2. Relative Binding Activities (RBA) of 11-Alkyl–6,11-dihydrohydroxy-5H-benzo [α]carbazoles

X, Y = OH

Compound	R	Position of X	Position of Y	RBA[a]	logRBA*
1	CH_3	3	9	9,6	1,60
2	C_2H_5	3	9	30	1,10
3	C_3H_7	3	9	38	1,00
4	C_2H_5	3	8	13	1,47
5	C_2H_5	4	9	1,3	2,47
6	C_2H_5	4	8	1,9	2,30
7	C_2H_5	2	9	9,7	1,59
8	C_2H_5	2	8	0,7	2,73
9	C_2H_5	3		1,8	2,32
10	C_2H_5		8	0,06	3,80
11	C_2H_5		9	0,8	2,68

Furthermore, the X-ray structure of 17β-estradiol in hER was superimposed on compound 2 and 3 on the docked structure (Figure 6).

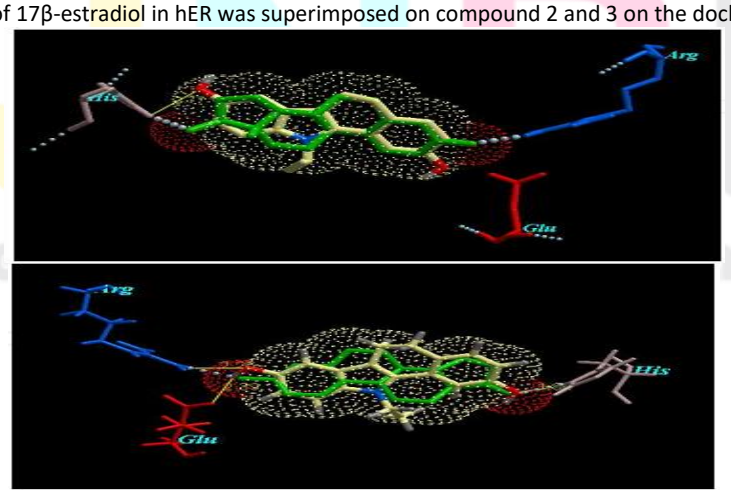


Figure 6. Estradiol (green) superimposed on compound 2 and 3 in the a-chain's binding site of hER. Key residues and H-bonds are shown by yellow lines and blue dotted lines

Other hormonal antagonists are:

- Progestins,
- GnRH (gonadotropin releasing hormone), and
- Antiandrogens

Other medicines

Medicines that are used as anticancer drugs are:

• Platinum-based drugs (cisplatin, carboplatin),
• L-Asparaginase (Crasnit's),
• Hydroxyurea (Hydrea), and
• Amsacrine (Amsidyl).

Many of the CTX drugs that are employed are naturally occurring compounds extracted from plants, while others are synthetic. Genotoxic agents bind to DNA and directly and/or indirectly affect the replication which induces the apoptosis. These agents are also divided into three important subunits-alkylating agents, intercalating agents and enzyme inhibitors. Etoposide is an enzyme inhibitor which inhibits topoisomerase II and prevents resealing of DNA that leads to cell death. However, this drug structure exhibits undesired effect for treatment of the disease. Due to this reason, different methods have been improved to evaluate the adverse effects of etoposide, the most effective and potent drug. There are two approaches to evaluate the adverse effects of the potent drugs-first one, is synthetic way. Researchers try to find derivatives of this drug agent with the conventional way. In the another approach, they use novel and rational drug design, discovery and development methods which are more economic and minimize time and labor by using computer models, compared with the usual conventional methods.

Harmful (or toxic) effects of anticancer drugs

An understanding of toxicity or adverse effects of anticancer compounds is important to design effective and potent drug combinations and also to interpret toxicological profile of new chemical entities. Most cytotoxic anticancer agents are evaluated at the maximum tolerated dose levels. The toxicity of these compounds is often a manifestation of their mechanism of action and their effect on growing normal cells such as hair follicle cells, gastrointestinal surface epithelial cells, and stem cells.

Toxicity or adverse effects of anticancer drugs include the following:

• Bone marrow depression due to damage for the growing stem cells causes a reduction in the white blood cell, platelet, and red cell counts. These, in turn, could cause suscept- ibility to infections, excessive bleeding, and anemia. In addition, certain drugs cause unique and severe bone damage, such as the osteonecrosis of the jaw associated with bisphosphonates [40].
• Damage to growing cells may cause temporary loss of hair (alopecia), skin rashes, changes in the color and texture, or loss of fingernails and toenails. These toxicities are usually reversible.
• Surface epithelial damage to the gastrointestinal tract may result in ulcers, stomatitis, difficulty in swallowing (dysphagia), vulnerability to oral infections such as candidiasis, and changes in saliva secretion. In addition, nausea, vomiting, diarrhea, or constipation occur commonly.
• Some drugs may cause kidney damage due to extensive cell destruction, purine catabolism, and deposition of urates in the renal tubules. The activity of drugs depends on the individual physiological system and the mode of renal handling of drugs.
• Cinnamaldehyde (an anticancer drug) at a dose level of 73.5 mg / kg body weight / day induced histopathological changes of kidney accompanied by increased activity of marker enzymes and an imbalance in the antioxidant status, in rats. Cinnamaldehyde induced renal damage, is due to the reactive oxygen species that formed while in the free radical scav- enging reactions.
• In addition, liver damage may occur due to large blood supply. Metabolic conditions of the liver and the kidney are usually monitored for possible correlation to drug levels in the blood and dosage adjustments, since these are the major drug elimination sites or the target organs of toxicity.
• Certain symptoms and adverse effects associated with cancer could be secondary to disease progression. For example, cancer metastases to the bones could cause chronic pain due to the proliferation of cancer cells in the bones and the associated bone remodeling and destruction. Also, tumors that compress veins, the use of central vein catheter, and relative immobility of the patient could lead to deep vein thrombosis with potential pulmonary embolism.
• Drugs such as paclitaxel and vincristine could cause peripheral neuropathy. Similarly, anthracyclines are known for rare but severe cardiotoxicity .

Thus, adverse effect and dose-limiting toxicity of anticancer compounds could be a manifes- tation of either their mechanisms of action or unrelated toxicities common to a given chemical entity of compounds (anthracyclines and etoposide). A close attention to monitor the emergence of known side effects of anticancer drugs, as well as those observed in the preclinical animal toxicology studies, ensures patient safety in early oncology drug clinical trials.

Especially, chemotherapy has been integrated into treatment programs with surgery and radiation therapy. The major problem of the clinical efficacy in chemotherapy is because of toxicity of the anticancer drugs to the normal tissues of the body. Rapidly proliferating tissues such as bone marrow, gastrointestinal tract, hair follicle, etc are the major sites of acute toxicities. In addition, chronic and cumulative toxicities may also occur. There are measures and agents which can improve the toxicities of anticancer drugs. Furthermore, current challenges of anticancer drug development include the significant time and cost involvement, and the low success rates. These issues lead to increasing efforts of the pharmaceutical industry toward increasing the effectiveness of the drug discovery and development process to minimize failure of drug candidates at later stages of development. It also includes develop- ment of high throughput preclinical screening methods (computational molecular modeling techniques) and biological assays with greater specificity and predictability. Increasing emphasis is being placed on developing a mechanistic understanding of the physicochemical and biological phenomena involved in drug development such as chemical structure and polymorph stability, and pharmacokinetics. The use of mathematical models to explain the mechanisms of drug degradation and predict the outcomes of formulation and process changes and scale-up is increasingly being adopted such as Quantitative Structure Activity Relationships (QSAR). This chapter summarises the beneficial and harmful (toxicity) effects of anticancer drugs and other measures adopted for its management. Proper handling of anticancer agents is the utmost importance at the earlier phase because it has an affiliation with the course of treatment and outcome of the patient in his physical, mental and social wellbeing. Because of these reasons, computer aided drug design and discovery are used to reduce the side effects of the anticancer drugs. These procedures result in effective therapeutic options for chemotherapy. On general consideration, antioxidants (vitamins) play a significant role to ameliorate the toxicity. Thus, fruits and vegetables in the diet might protect human health from toxic effects of drugs at certain extent [50]. While in chemotherapy, if the patients are given vitamin rich food (vegetables, fruits, etc), then toxicity of the chemotherapeutic drugs can be prevented at certain extent.

Some basic Facts about Cancer

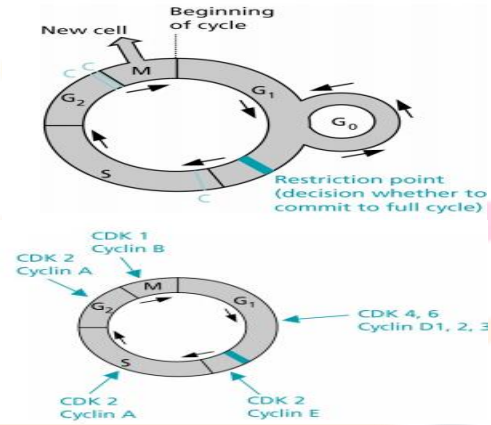
• Cancer cells have lost the normal regulatory mechanisms that control cell growth and multiplication
• Cancer cell have lost their ability to differentiate (that means to specialize)
• Benign cancer cell stay at the same place
• Malignant cancer cells invade new tissues to set up secondary tumors, a process known as metastasis
• Chemicals causing cancer are called mutagens
• Cancer can be caused by chemicals, life style (smoking), and viruses
• Genes that are related to cause cancer are called oncogenes. Genes that become onogenic upon mutation are called proto-oncogenes.

The Hallmarks of Cancer

• Self-sufficiency in growth signals (e.g. via activation of the H-Ras oncogene)
• Insensitivity to growth inhibitory (anti-growth) signals (lose retinoblastoma suppressor)
• Evasion of programmed cell death (apoptosis) (produce IGF survival factors)
• Limitless replicative potential (turn on telomerase)
• Sustained angiogenesis (produce VEGF inducer)
• Tissue invasion and metastasis (inactivate E-cadherin)
• Inactivation of systems that regulate in response to DNA damage.

Phases of the Cell Cycle

• **G1 phase (gap 1):** Cell grows in size and prepares to copy its DNA in response to various growth factors
• S phase (synthesis): Replication of DNA, copying of the chromosome
• **G2 phase (gap 2):** Preparation for cell division. Check copied DNA and repair damaged copies.
• **M phase (mitosis):** Formation of the mitotic spindle, and separation into two individual cells (cell division).
• Progression through the cell cycle is controlled by cyclin-dependent kinases (CDKs).
• Binding of cyclin with its associated kinase triggers to move the cell cycle to another phase
• Inhibitory proteins are present that can modify the effect of cyclins. These include p15 and p16 that block activity of the cyclin D-CDK complex. Another regulator is p21 that is controlled by the tumor suppressor protein p53.
• Over-active cyclins or CDKs have been associated with many tumors. Excessive production of cyclins or CDKs or insufficient production of CDK inhibitors leads to disruption of the normal regulation of the cell cycle.

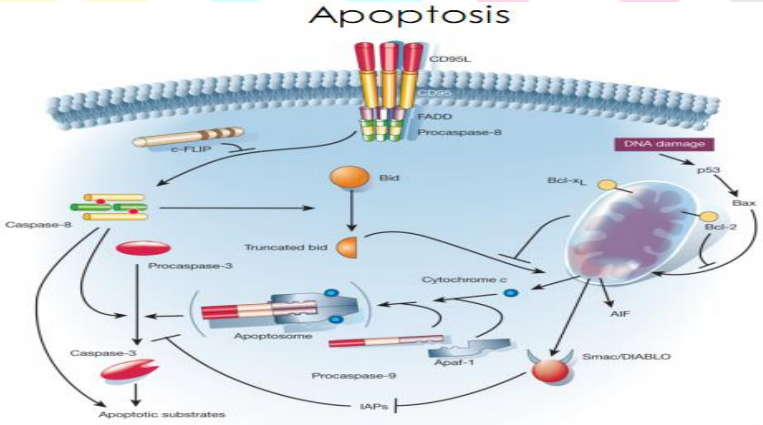


Cell Death

• Necrosis is the uncontrolled (pathological) cell death. In contrast with apoptosis, cleanup of cell debris by phagocytes of the immune system is generally more difficult. There are many causes of necrosis including injury, infection, cancer, infarction, toxins and inflammation. Necrosis can arise from lack of proper care to a wound site. Usually cell outlines do not stay intact, and cell debris is released into the environment
• Apoptosis is the programmed cell death. It is used by organisms to control the number of cells and tissue size. The cells during apoptosis shrink, but no uncontrolled release of cell debris into the environment occurs. The immune system usually "cleans up" the dying cells, and the content is recycled. Apoptosis is triggered by an extracellular signal to the CD95 receptor. In response to that signal a set of cysteine proteases, called caspases are activated, that are largely responsible for the morphological changes observed.

Routes for Apoptosis

• Two pathways for activation: i) at the plasma membrane via external ligands upon binding to the death receptor or ii) via the mitochondrial pathway
• Binding of external ligands such as tumor necrosis factor receptor (TNFα) to Fas receptors of the TNF superfamily induces receptor oligomerization and formation of a death-inducing signaling complex. This complex recruits, via the adaptor molecule FADD (Fas-associated death domain) multiple Pro-caspase-8 molecules, resulting in caspase-8 activation that finally results in caspase-3 activation
• In the mitochondrial pathway release of apoptogenic factors such as cytochrome c, Apaf-1, caspase-9-containing apoptosome complex and inhibitors-of-apoposis proteins trigger caspase-3 activation
• Links between the two pathways exist. For example, caspsase-8 results in cleavage of Bid, a Bcl-2 family protein, which translocates to the mitochondria to release cytochrome c.



Regulators of Apoptosis

• The Bcl-2 family of factors regulate caspase activation either negatively (e.g. Bcl-2, Bcl-XL, MCL1) or positively (e.g. Bcl-XS, Bax, BAD, BAK, BID)
• The inhibitors of apoptosis proteins (IAP) retard apoptosis

• Upstream modulators are oncogenes such as c-myc, that activates apoptosis in a manner important in cancer therapy • the tumor suppressor p53 induces apoptosis under certain circumstances

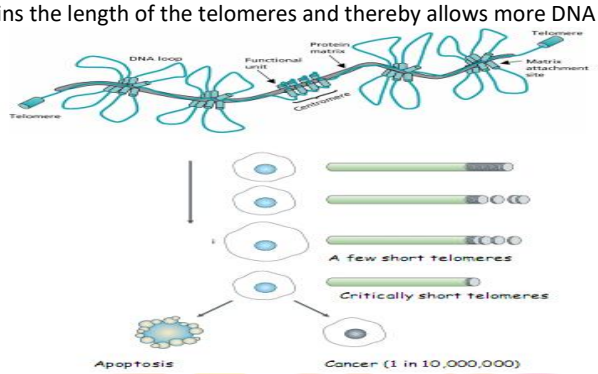
Triggers	Regulators	Executioners
· DNA damage	· p53	· Apaf-1
· cytokine star vation	· death domain factors	· caspases
· hypoxia	· Bcl-2 family	
· detachment	· Myc/oncogenes	
· temperature	· cytokine-responsive kinases	
· death receptor	· cytochrome c	

Telomeres:

• Cancer cells are often called immortal since there seems to be no limit for how often they can divide

• Life-time of normal cells is limited to 50-60 cell divisions. This is regulated by telomeres. The telomeres are at the 3' end of the chromosomes. After each replication about 50-100 base pairs are lost

• At some point telomeres are too short to be effective and the DNA becomes unstable thereby limiting replication. Cancer cells possess an enzyme called telomerase which maintains the length of the telomeres and thereby allows more DNA replications.



Tissue Invasion

• In malignant cancers cells cancer cells break away from the primary tumor site, invade a blood or lymphatic vessel, to form metastasis sites

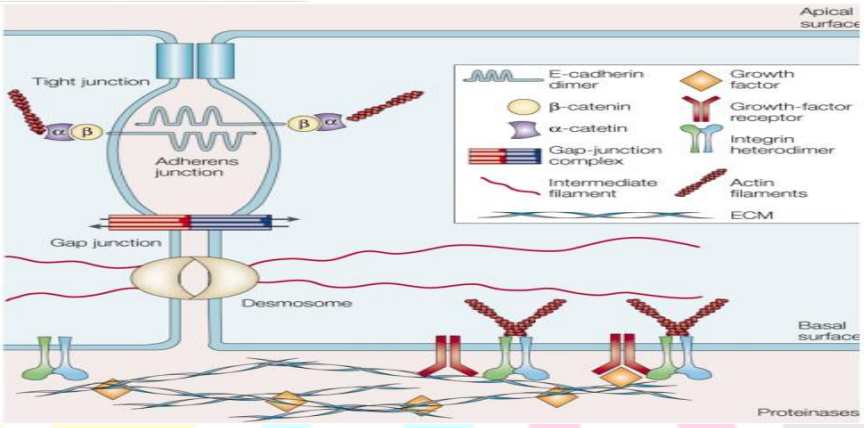
• Usually, cells only stick to similar cells. The signature on the cell-surface is transmitted via cell-adhesion molecules (e.g. cadherins). Moreover, cells are connected to each other via mounting them on the extracellular matrix (EM).

• Adhesion to the EM involves molecules called integrins.

• The protein matrix metalloproteinase degrades the extracellular matrix, and therefore is important for leaving the site of the primary tumor and attaching to the secondary site.

• If a non-cancer cell is detached from the extracellular matrix it stops growing and apoptosis is triggered.

• In metastized cells cell adhesion molecules are missing, so that they can leave the site of the primary tumor.



Angiogenesis

• Tumors are quickly growing tissue that needs to have good blood supply.

• Angiogenesis refers to the formation of new blood vessels

• Tumor cells release growth factors such as vascular endothelial growth factor (VEGF) or fibroplast growth factor (FGF-2) leading to sprouting and extension of existing capillaries

• In healthy tissue repair of injured tissues is controlled by angiogenesis inhibitors such as angiostatin and thrombospondin

• Blood vessels arising from angiogenesis are abnormal in that they are disorganized in structure and leaky.

• These cells display integrins on their surface to protect the newly formed cells from apoptosis

• Before angiogenesis can start the basement membrane around the blood vessel has to be broken down (carried out by matrix metalloproteinase (MMPs))

Strategies for Anti-Cancer Therapeutics

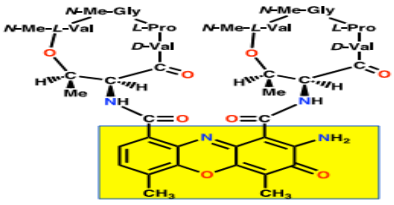
Therapeutic target or modality	Targeted process	Mechanism of action of therapeutics	Target example (drug)
Transformation	Apoptosis	Activation of apoptosis pathways	BCL2
	Signalling	Interference with signal transduction, response	ABL (Gleevec; Novartis)
	Invasion/metastasis	Inhibition of tumour spread	Cathepsin K
Immortalization	Senescence	Induction of senescence	Telomerase
Host	Angiogenesis	Interference with blood supply of tumour	VEGF (Avastin; Genentech/Roche)
	Tumour-associated membrane proteins	Antibody-directed cytotoxicity	CD20 (Rituxan; Biogen Idec/ Genentech)
Traditional cytotoxics	Replication/ cytokinesis	Interference with DNA synthesis, cell division	Microtubules (Taxol)
	Metabolism	Reduction of essential metabolite	Thymidylate synthase (5-FU)
Neocytotoxics	Protein turnover	Inhibition of acceleration of protein degradation	Proteasome (Velcade; Millennium Pharmaceuticals)
	Epigenetics	Remodelling chromatin, DNA methylation	HDAC interactions
	Stress response	Interference with cellular stress buffering	ATPase/chaperone superfamily

Drugs directly interacting with DNA Intercalating agents

Mechanism of action

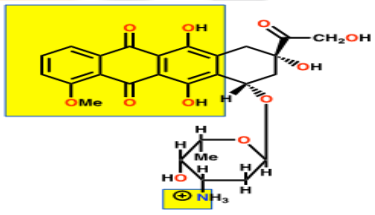
- Contain planar aromatic or heteroaromatic ring systems
- Planar systems slip between the layers of nucleic acid pairs and disrupt the shape of the helix
- Preference is often shown for the minor or major groove
- Intercalation prevents replication and transcription
- Intercalation inhibits topoisomerase II (an enzyme that relieves the strain in the DNA helix by temporarily cleaving the DNA chain and crossing an intact strand through the broken strand.

Intercalating agents



Dactinomycin

(Extra binding to sugar phosphate backbone by cyclic peptide)

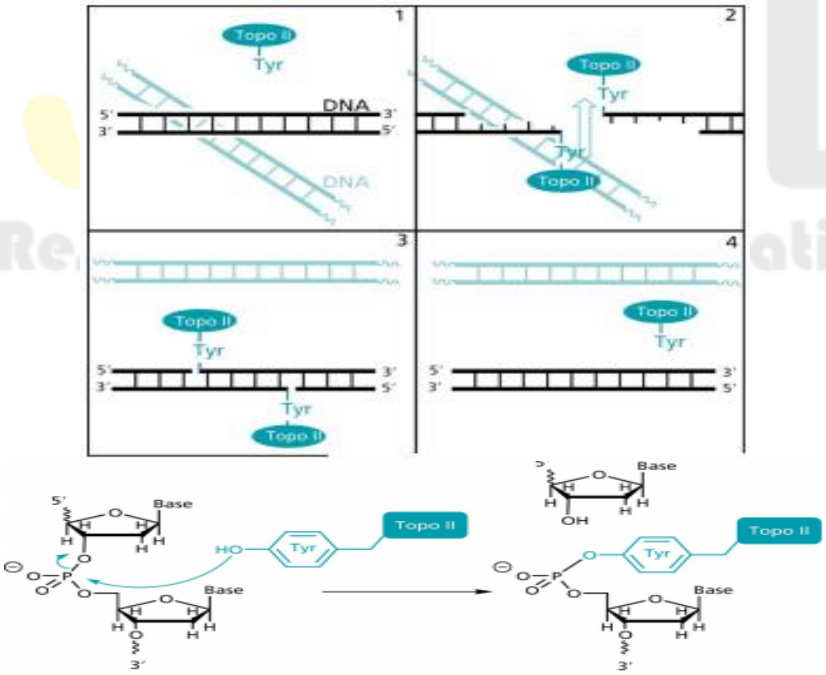


Doxorubicin (Adriamycin)

(Extra binding to sugar phosphate backbone by NH_3)

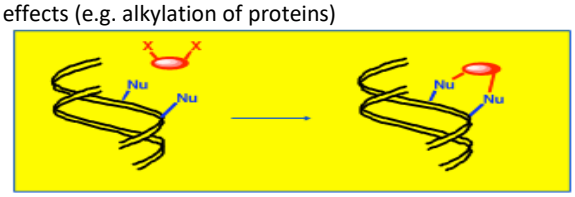
Intercalating reagents (II)

- During replication, supercoiled DNA is unwound by the helicase. The thereby created tension is removed by the topoisomerase II, that cuts and rejoins the DNA strands.
- When doxorubicin is bound to the DNA it stabilizes the DNA-topo II complex at the point where the enzyme is covalently bound

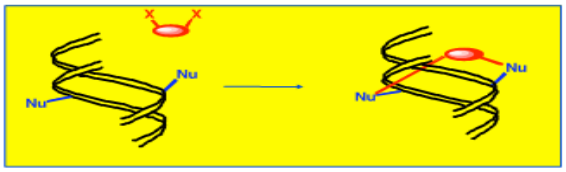


Drugs directly interacting with DNA Alkylating agents

- Contain highly electrophilic groups
- Form covalent bonds to nucleophilic groups in DNA
- Attack N-1 and N-3 of adenine and N-3 of cytosine, and in particular N-7 of guanine bases
- Prevent replication and transcription
- Useful as anti-tumour agents
- Toxic side effects (e.g. alkylation of proteins)

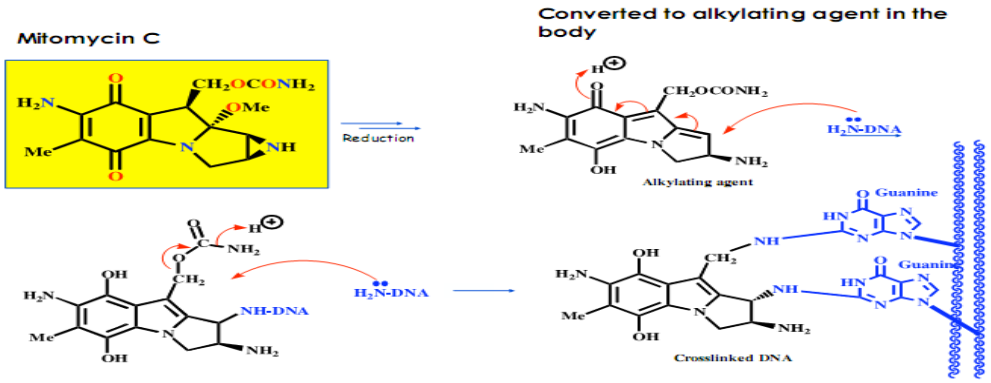


Intrastrand cross linking



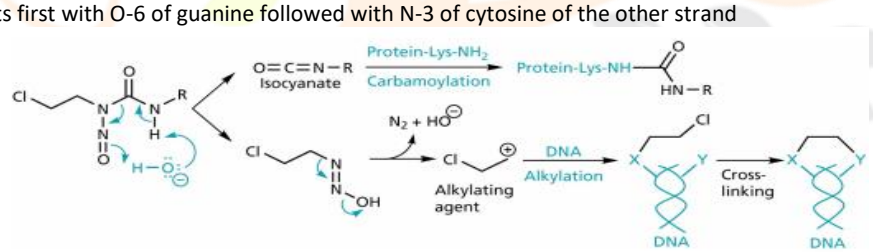
Interstrand cross linking

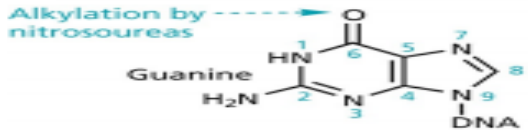
Alkylating Drugs: Mitomycin C

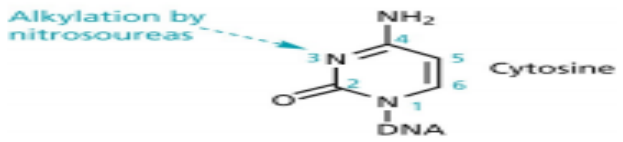


Nitrosoureas

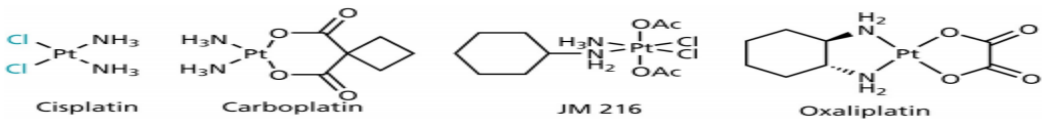
- Lomustine and carmustine are lipid-soluble and can cross the blood-brain barrier
- The drugs decompose to form alkylating and carbamoylating
- The formed isocyanate reacts with lysine NH3 groups thereby inactivating DNA repair enzymes
- The alkylating agent reacts first with O-6 of guanine followed with N-3 of cytosine of the other strand



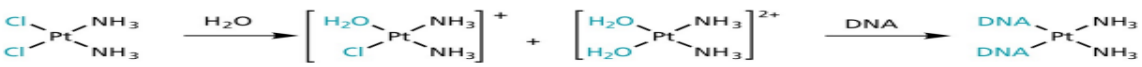


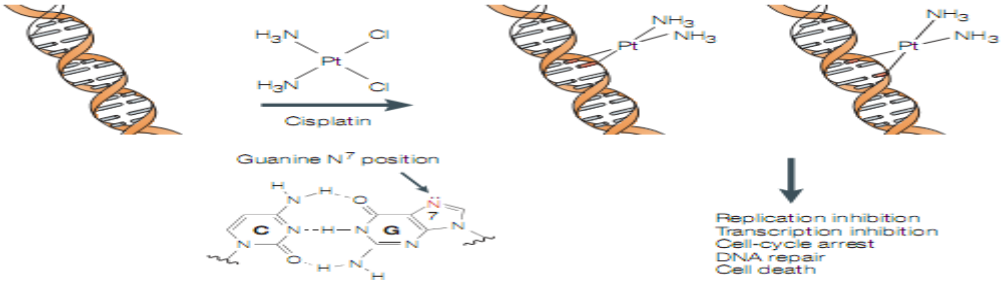


Pt-Alkylating agents:

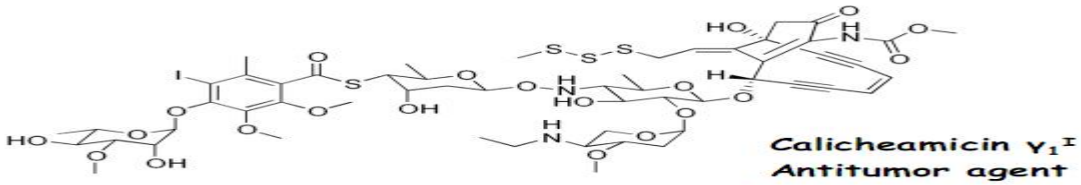


- Binds to DNA in regions rich in guanine units
- Intrastrand links rather than interstrand
- Inhibits transcription
- In solution the Cl- ligands are exchanged against water to result in positively charged ligands that bind to the DNA (to N-7 or O-6 of adjacent guanine groups)
- Results in localized unwinding of the DNA





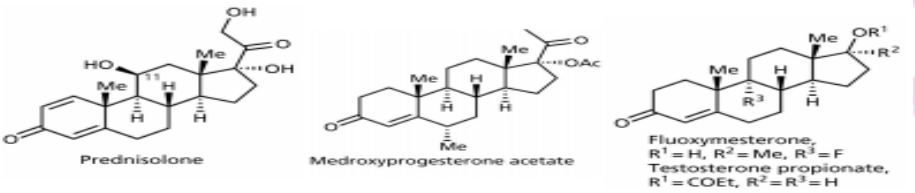
DNA chain cutters



- Generates DNA diradical
- DNA diradical reacts with oxygen
- Results in chain cutting

Hormone-based Anti-Cancer Therapies

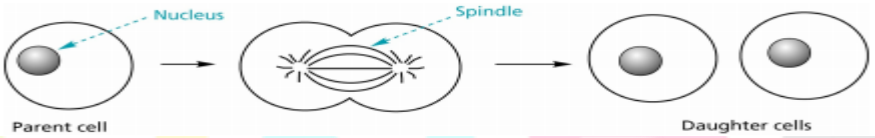
- Steroid hormones bind to nuclear receptors and act as transcription factors
- If the cancer requires a specific hormone, a hormone resulting in the opposite effect can be administered
- Used: glucocorticoides (hormones involved in the biosynthesis of glucose, e.g. prednisolone), oestrogens, progestins (e.g. medroxyprogesterone acetate), analogues of the luteinizing hormone-releasing hormones (LHRH)



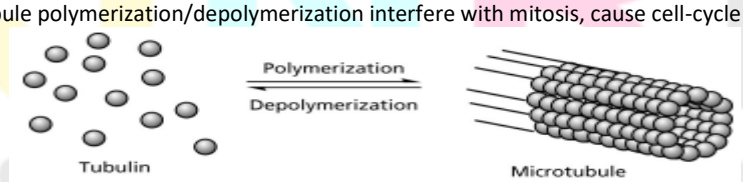
1 2 3 4 5 6 7 8 9 10	
pyroGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2	LHRH
pyroGlu-His-Trp-Ser-Tyr-(D-Leu)-Leu-Arg-Pro-ethylamide	Leuprolide
pyroGlu-His-Trp-Ser-Tyr-(D-(t-Bu)Ser)-Leu-Arg-Pro-Azgly-NH_2	Goserelin

Drugs acting on structural proteins

- Mitosis is a ordered series of events in which identical copies of the genome are moved to discrete locations within the dividing cell
- The mitotic spindle is very important for that event. The filaments in the mitotic spindle are formed from microtubule



- Microtubule are cytoskeletal elements present in all eukaryotic cells.
- They are composed of α- and β-subunits
- Both, formation (polymerization) and destruction (depolymerization) of microtubules are important for proper execution of cell division
- Drugs interfering with microtubule polymerization/depolymerization interfere with mitosis, cause cell-cycle arrest and trigger apoptosis



Cell cycle – specific agents

The major cytotoxic activities of anticancer drugs in this class are seen in a particular phase of the cell cycle. These agents are technically phase-specific drugs rather than cycle-specific agents. It was noted in animal species that these particular agents produced a greater cell kill if an amount of drug were divided and given in multiple, repeated fractions rather than as a large single dose. These agents are then also termed 'schedule dependent. Examples of S-phase dependent drugs are antimetabolites like methotrexate, 5-fiurourocil and G (dependents are asparagine and corticosteroids.

Cell cycle (phase) - Nonspecific agents

In contrast, the cell cycle (phase)-nonspecific agents are equally effective in large tumor in which the growth fraction, labelling index and mitotic index are low. Moreover, drugs in this group are not schedule dependent but are dose dependent. In other words, the degree of cell kill is directly proportional to the absolute dose given, a single bolus injection generally kills the same number of cells as repeated fractions totalling the same amount. Examples include alkylating agents like cyclophosphamide, antitumor antibiotics like doxorubicine, nitrosureas like BCNU, cisplatin.

The utilisation of cancer chemotherapy breaks down into three major categories.

1. Curative to some degree in clinically evident disseminated malignancy, eg: childhood leukemia, Hodgkin's disease.
2. Curative to some degree in clinically evident localised and regional malignancy in combination with surgery and/or irradiation, eg: breast cancer, osteogenic sarcoma.

3. Palliative in clinically evident disseminated malignancy (prolongation ofsurvival), eg: ovarian cancer, multiple myeloma, breast cancer

In the past two decades, considerable progress has been made in the understanding of some important factors that influence the effectiveness of chemotherapy. They include:

1. The log-kill hypothesis
2. Cell kinetics of both normal and malignant cells.
3. The mechanism of action of different cytotoxic drugs and their effect on the cell cycle.
4. The influence of drug scheduling (pharmacokinetics).
5. Drug toxicity, especially the effects on the hematopoietic and immune systems.
6. Selectivity of cytotoxic drugs for certain histological cell types.
7. Drug resistance.

The ability to cure cancer with local means - surgery or radiotherapy - is hindered by the presence of viable metastasis outside the treatment field. Malignant tumors, as they grow, may invade their surrounding stroma and will pass through the basement membrane. During this process it would constantly shed cells. Some of these cells are able to establish metastatic clones even before the primary mass reaches a clinically detectable level. In such instances systemic therapy of cancer using chemical agents has been proved to be useful. Drugs can in some instances cure by themselves or help to cure when combined with surgery and radiotherapy. For a wide range ofdisseminated cancers, drugs can achieve clinical remissions and regressions which impact favourably on quality of life as well as survival.

Strategies to optimise cancer chemotherapy

As the fundamental advances continue in the chemotherapy of neoplastic disorders, the greatest progress in the recent past is in the conceptual therapeutic developments. These include:

a) The design of more effective regimens for concurrent administration of drugs, including combinations of neoplastic agents with biologic response modifiers.

b) The increased use of adjuvant and neoadjuvant chemotherapy.

c) The greater insight into mechanisms of resistance to antineoplastic agents.

d) The acquisition of knowledge of mechanism of action of many antitumor agents, which facilitates the design of new methods to prevent or minimise drug toxicity.

e) Increased knowledge about such vital processes as tumor initiation and the dissemination, implantation and growth of metastasis.

Vexing problems with current chemotherapeutic approaches

Major obstacles to the cure of neoplastic diseases using chemotherapeutic agents are:

1. Development of multidrug resistance,
2. Tumor heterogeneity, and
3. Dose dependent host tissue toxicity.

Tumor heterogeneity and development of multidrug resistance are the two unresolved problems in cancer research and no clear cut understanding in this regard has been achieved till date. Besides the above two, the inherent problem of non-specificity of chemotherapeutic agents is a major area of research interest. This non-specificity is due to very subtle metabolic differences that exist between a cancerous and a normal cell. So, unlike in a bacterial infection, a cancer chemotherapeutic agent cannot exclusively act on the metabolic pathways of cancer cells while leaving the rapidly dividing normal cells unaffected.

Methods developed to enhance specificity of chemotherapeutic agents

Antineoplastic agents are, therefore, neither specific nor targeted to cancer cells. Improved delivery of anticancer drugs to tumor tissues, thus, appears to be a challenging and achievable effort. Significant efforts have been directed towards the improvement of anticancer drug delivery in the recent years. Chemical modifications such as altering the partitition coefficient, preparation of prodrugs, binding of immunological ligands has met with little success. Physical approaches for the delivery of anticancer drugs consist of microparticulate drug carriers (liposomes, niosomes, microspheres, nanoparticles), magnetic microcapsules, implantable pumps and reservoirs etc.

CONCLUSION

The present study has enabled us to understand some of the features of drug binding with DNA. Analysis of the factors involved in the sequence specific intercalation of drug within sequences of DNA has understood from the stacking interactions. The stacking energies of small aromatic molecules computed with different level of theories could demonstrate the appropriate method for the computation of stacking interactions of large molecules. The studies on the stacking interaction of benzene and pyridine molecules have been found useful to assess the level of theoretical calculations. The extent of dispersion forces included in various calculations from the relative variation of stacking interactions of aromatic molecules is well explained. The results ofMP2 calculations on the stacking of benzene rings are found similar to that of the reported CCSD(T) calculations. The MP2/6-31G+(d,p) and MP2/6-31+G(df,p) are found feasible for explaining the n-% type of stacking interactions, and these methods can be applied to the computation of larger stacked molecules instead of using other high level expensive techniques.