CHAPTER-FIRST

INTRODUCTION
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In animal kingdom, we the human being claim ourselves to be the most intelligent and well developed animal in every respect and also claim to have acquired so much knowledge and efficiency and have power to reveal the mysteries of nature. But in spite of all these claims we forget that all discoveries inventions and development have brought so many miseries and ailments to us and other living being. To treat those ailments the man is striving to find out some aid from nature to cure and eliminate those miseries and diseases and since the very begining of life this process is going on. We should not forget that the life of each and every creature has become so complicated and in simplifying it we have created so many problem for ourselves and they have become mysteries for the human life. Life originated as a single cell and there after climate and geographical changes brought so
many changes that gradually resulted to say a perfect human being. For each and every ailments & problems man tried to search out means to cure and remove it, but in this process problems and miseries multiplied so many times and fatal disease have developed which were unknown in the past, damaging vital organs of the body.

Our forefathers knew and we have learnt from smitries and pious books that wounded soldiers were cured within hours by application of herbal medicines without any side effect. But this knowledge was never handed over to coming generation. This was a special branch of science but that science was never transferred by expert to their disciples and that resulted in a great vaccum and that knowledge ended with the death of particular individual.

The principle "survival of the fittest" was known to our ancestors and this actuated them to thinkout
about it as necessity is the mother of invention and thought actuated them to made new inventions and discoveries revealed so many new elements in the field of science and medicine. Initially it was in very crude form but by continuous process of multiplication of knowledge in sciencere and hard labour of individual so many important advancement were made in every field of science and medicine. The mystery of nature was being exploded and revealed to man step by step so many treatment in so many form to cure and heal the diseases were discovered. The success in this field also originated so many problem for the human body and so many remedies were discovered and collectivename for those remedies were given as "Drugs".

Drugs means nothing but a means to cure and heal some disease and remove some problem and for different ailments and diseases different means in different forms were evolved. For a particular ailment a
particular medicine was discovered. In this process recovery of the patient was the main object and that too without any side effect of medicine to individual or patient. This process is still going on and no one can claim that some thing has been discovered and that is the end.

The most important approaches currently employed to obtain subsystem or primising lead compounds are as follows.¹²

(1) Investigation of drug metabolites.

(2) Discovery and exploration of side effects.

(3) Modification of natural compounds.

(4) Mass screening.

(5) Chemical modification of natural, endogenous substances.

(6) Haphazard discoveries.

All these procedures are rather empirical, and much is being left to accident. Obviously attempts
should be made to predict the properties of new subsystems from knowledge on already investigated subsystem or, in other words, to develop method for theoretical level generation.

A review of the problems arising from the search for novel drugs poses the following questions:-

(1) How can one obtain that derivative of a known lead exhibiting the most favourable properties with the simplest, safest and most favourable properties with the simplest, safest and most rational strategy or, in other words, with the minimum number of analogues and of test?

(2) Upon what criteria is the selection of appropriate sub-systems to be based and how can the properties of known lead compounds be used for finding new leads or predicting reasonably correctly biological properties in other sub-systems?
(3) What strategy is to be followed to gather the maximum information about biological properties with the minimum of tests, what test should be done and in what order? How is the flow of substances and information to be organized?

To answer the questions an extensive knowledge of specific features of the interactions of drugs and biosystems and thus of structure activity relationships is required. The theoretical techniques employed for establishing such features are collectively described as quantitative structure activity analysis, the principles of which are illustrated in figure 1.1
Fig 1.1 Principle of quantitative structure activity relationship.

The basic data underlying this concept are obtained characterizing a sample of compounds in terms of their biological properties and their physico-chemical properties. The resulting biological activity parameters and molecular parameters are related, since biological activity is dependent on molecular structure and the resulting properties. Mathematical analysis
reveals such connections in the form of quantitative structure activity relationships (QSARs).

QSAR can be constructed for different purposes and according to different methods. Structure response relationships describe the connections between the magnitude of a given biological effect and the drug structure in a set of congeners, they can therefore be employed to optimize the effect on the basis of structural variations. In structure selectivity relationships a new dimension becomes apparent & the simultaneous consideration of a variety of biological effects may allow an integral optimization. Structure effect relationships describe connections between the structure and the nature of the biological effects to be expected. They may, in principle, lead to the prediction of new compounds. By considering time and/or drug concentration as additional parameters, complex structure-activity time and/or drug concentration as
additional parameters, complex structure-activity concentration relationships are obtained which extend significantly the total body of information, and are especially important in such cases where links between a biological effect and time or drug concentrations are highly complicated and/or dependent on drug structure. Complex structure activity-biosystem relationships represent an extension of structure selectivity relations and, to some extent, also permit inter and extrapolations in the space of biosystems.

The technique for QSAR have been studied by different workers (ref.3 to 10) on different types of drugs.

The present thesis deals with the application of QSAR technique to antitumor agents.

**Cancer and Antitumor Drugs**

Cancer is not one disease, but a group of diseases affecting different organs and system of body.
Although there are a number of known causes of cancer, such as exposure to carcinogenic hydrocarbons or to excessive radiation, cellular mutation of unknown origin may be important in many cases. The numerous different forms of cancer possess certain common features:

"It is a disease typified by abnormal and uncontrolled cell division, frequently at a rate greater than that of most normal body cells."

Neither and etiology of cancer nor the manner in which it causes death (in the vast majority of cases) is understood, despite the efforts that have been devoted over the years to studies of these phenomenon. The incidence of and mortality from cancer have risen steadily ever since reliable statistics on the subject have become available.

The different forms of cancer can be categorised as-
(1) Skin cancer.

(2) Breast cancer

(3) Gynecologic cancer

(4) Respiratory tract cancer.

(5) Alimentary tract cancer.

(6) Genitourinary tract cancer.

(7) Melanoma.

(8) Childhood solid tumor.

(9) Soft tissue sarcomas.

(10) Bone and cartilage tumor.

(11) Brain and peripheral nervous system tumor.

(12) Tumor of eye.

(13) Cancer of head and neck.

The techniques used for treatment of cancer are-

(1) Nuclear Medicine

(2) Chemotherapy.

(3) Cancer surgery

(4) Radiation therapy
(5) Immunology
(6) Combination therapy
(7) Endocrine therapy.

The different chemotherapeutic agents for the treatment of cancer are-

1- Antimetabolite:-

An antimetabolite interferes with the formation of a normal cellular metabolite. This interference may result from the inhibition of an enzyme or enzymes or from incorporation, as a fraudulent building unit, into macromolecules such as proteins or nucleic acids.

Most antimetabolites have resulted from on or in some cases two bioisosteric or other small changes in the structure of a metabolite (eg. F for H₂S or CH₂ for O, NH₂ for OH, S for - CH= CH-), although the results of such a change can not be predicted accurately.
The details of these enzyme inhibitions and the anticancer activity of the antimetabolites are discussed in the following sections.

(a) **Folic Acid Antagonists:**

Folic acid (N-[p-1 amino-4 hydroxy-6 petridi-nyl methyl] amino] benzoyl]-L glutemic acid) must be reduced to 1, L-tetrahydrofolic acid" before it can serve as a coenzyme. The folic acid coenzymes participate at three places in the nucleic acid biosynthetic pathway. A number of aminopterine and methotrexate derivative halogenated in the benzene ring have been prepared\textsuperscript{12,13} and a few of these are significantly less toxic and more effective than the parent compounds against Leukemia.\textsuperscript{14}

A series of six 2,4 diaminoquanzoline analogous of folic acid which bear close structural resemblance to methotrexate were synthesized\textsuperscript{15}. Each of the compounds
was a potent inhibitor of dihydrofolate reductase (DHFR) from rat liver or leukemia cells.

(b) **Glutamine Antagonists:**

Azaserine\textsuperscript{16} (O-diazo-acetyl-L-serine and DON\textsuperscript{17} (6-diazo-5-oxo-L-norleucine), two carcinolytic compounds first isolated from culture broths of steromyces and latter synthesized\textsuperscript{18,19} derive their biological activity from interference with the metabolic processes in which glutamine is involved as a cofactor. Azaserine inhibited formate incorporation into the tissues of tumor bearing mice.

(c) **Pyrimidine Antagonists:**

(i) Azapyrimidines-5-Azuracil (1,3,5 triazine- 2,4, (1-H, 3-H) dione and 5-azaorotic acid have shown the ability to inhibit adenocarcinoma 755 but not leukemia L-1210. The most active of these azapyrimidines, 5-azacytidine (2-amino 1-β-D-ribofluranosyl-1,3,5- triazine-4-one) was found to
be quite effective\textsuperscript{20} against leukemia in AKR mice\textsuperscript{21} producing some cure.

Novel fluorine substituted diaza analogues of 5-azacytidine (AZC) and 5-aza-2-deoxycytidine (3-deaza-cytosines) have been synthesized and tested\textsuperscript{22} for antitumor activity.

Baire K.W. et al\textsuperscript{23} have synthesized a series of the analogous of (1-Pyrenyl methyl) amino alcohol. Binding studies have shown that the presence of additional basic amino groups in the side chain enhances DNA binding due to electrostatic interactions.

The antitumor activity of methyl substituted 7-H, pyridocarbamazole monomer and dimer were studied by Leon, P., and coworkers.\textsuperscript{24}

(ii) Fluoropyrimidines- Most of the possible halogenated pyrimidines have been prepared but only the fluorinated pyrimidines and their
nucleosides which readily metabolize uracil, cytosine and nucleosides have significant anticancer activity.

(d) Ribonucleoside Diphosphate reductase inhibitor:

Hydroxy urea have shown activity against a number of animal neoplasms\textsuperscript{25} and some activity against cancers.

A series of N-(2-fluoroethyl)-N- nitrosourea has been synthesized\textsuperscript{26}, the anticancer activity of these nitrosoureas was determined against the murine tumors B\textsubscript{16} melanoma and Lewis lung carcinoma and was found to be significant.

(E) Purine Antagonists:

(1) Thiopurines- of the unnatural purines that have been evaluated for anticancer activity, 6-meracaptopurine [purine-6 (1H) thioone, MP] and 6-thio-guanine [2 aminopurine-6 (1H)- thioone, TG] are
by far the most active against a variety of experimental neoplasms and in treatment of human disease.\textsuperscript{27} 

A series of 3-Diazaguanine Nuclcosides and Nuclcotides was synthesized\textsuperscript{28} and they were found to be potent antitumor agents.

(2) \textbf{Platinum compounds:}

Metal complexes have been investigated for their chemotherapeutic activity for many years. However the first heavy metal containing complex, to have had significant success in the treatment of cancer is the platinum compound cis-dichloro-diamino platinum II (DDP). A number of platinum complexes were tested for their antitumor properties in mice bearing the sarcoma 180, during the course of which DDP was found to cause complete regression of established tumor.
(3) Derivatives of Triazines and Hydrazines

(I) 5- (3,3-Dimethyl-1-triazino) imidazole-4- carboxamide

Triazinoimidazole carboxamides were synthesized and evaluated for antitumor activity in several experimental animal tumors of the carcinostatic but labile 5- diazoimidazole-4- carboxamide, an intermediate in transformation of 5- amino- imidazole-4-carboxamide to 2 azahypoxathine. The dimethyl derivative demonstrated marked inhibitory effects against sarcoma 180, adeno-carcinoma 755 and Leukemia L-1210.

The in-vivo antitumor activity and in-vitro metabolic dealkylation have been measured\textsuperscript{29} for an homologous series of 3-alkyl-1- (4- carbamoyl phenyl)-3-methyl- triazones and are found to be potent antitumor agents.
(II) **N-isopropyl-α-(2-methylhydrazino)-p-toluamide Hydrochloride.**

It has become an established agent during the past decade for the treatment of advanced Hodgkin's disease\(^{30}\) either alone or in combinations with other antitumor agents.

(4) **Plant Alkaloids**

Three drugs are the most important alkaloids used in the treatment of cancer, demecolcine (colcimide), vinblastine (Velban) and (Oncovin).\(^{31}\)

(5) **Antracycline Antibiotics:**

A substances isolated from a soil actinomycetes, called actinomycin, has besides antibacterial activity some antitumor activity.\(^{32}\)

(6) **Antitumor Antibiotic therapy:**

Antitumor antibiotics are defined as microbial products that inhibit the growth of experimental
animal tumors. The first antibiotic with antitumor activity was isolated by Gasio in 1896.\textsuperscript{33}

(7) **Asparaginase**

Asparaginase isolated from *Escherichia\textsuperscript{34} coli* was an effective as antitumor agent as guinea pig serum. Subsequently the demonstration of antitumor activity against autochihonous canine lymphosarcoma substantially heightened interest in possible activity against human tumor.

The target of anticancer drug is obviously cancer cells, but there is little information on unique characteristics of cancer cell that might be exploitable in the persuit of new agents. Despite this lack of any well defined metabolic basis for design, however useful new agents are being produced, most of them related in some way to active agents that have been conceived or discovered empirically.
The best the chemist can do, even today, is search blindly through random synthetics, antibiotic beers and plant and animal extracts or examine past successes for clues to future.

(8) **Alkylating agents:**

The use of alkylating agents in the chemotherapy of cancer is an outgrowth of investigations performed during World War II in an effort to seek and understand the effects of war gases upon biological systems. There are mainly six types of alkylating agents.35

(1) Aziridines
(2) 2 Chloro ethyl amines
(3) Epoxides
(4) N-Alkyl-N-Nitrosourea
(5) Triazine
(6) Alkyl Alkane sulphonates

Basically this thesis is based on theoretical drug designing using regression analysis methodology.
Which ultimately will helpfull to synthesized some new drug molecules, which utlimately can be used to cure cancer. Thus a series of some new anticancer drugs can obtained which should be the drugs of new generation and ultimately be used to cure the desease cancer.
References:


