DRUG DESIGN

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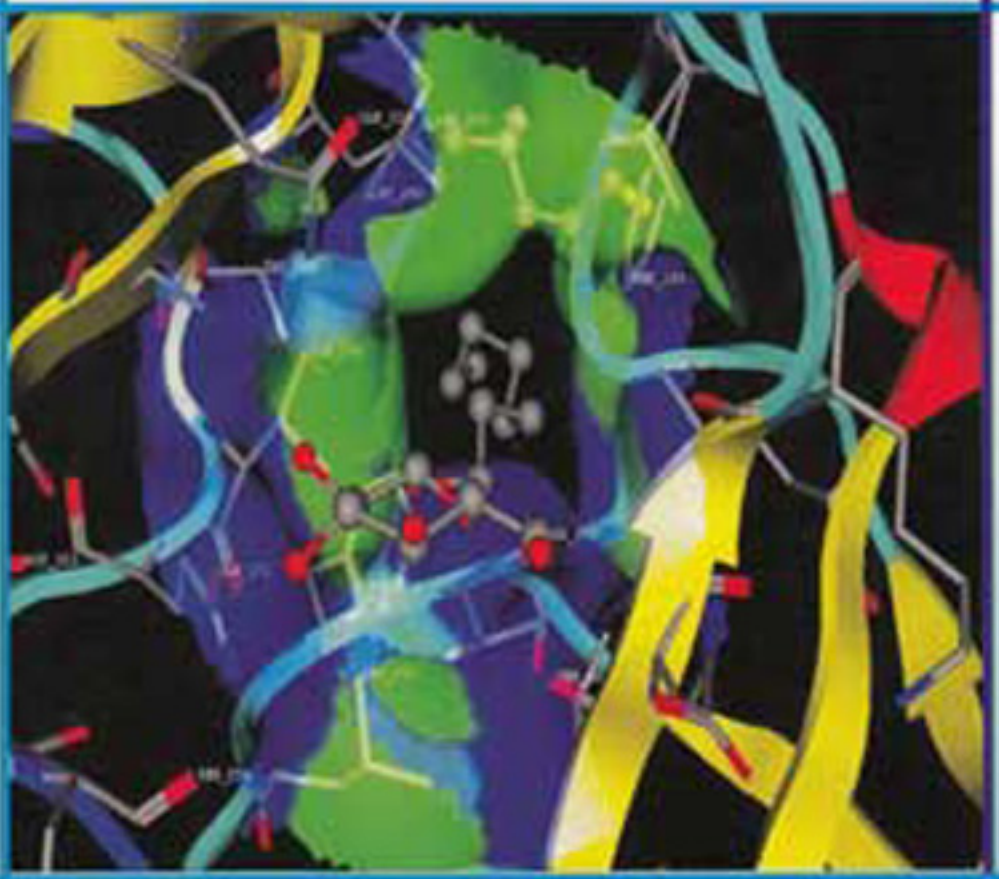

NIRALI PRAKASHAN
ADVANCEMENT OF KNOWLEDGE

DRUG DESIGN

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PREFACE

The chemical and physical properties of any molecule are governed by its structural features and biological activity does not stand exception to this. Inspite of the early recognition of this principle by Crum-Brown and Fraser, the quantitative relationship between the structure and properties of a molecule could not be established on a firm basis for almost a century. However, during last three decades, different approaches were designed to utilise the structural information coded in these physico-chemical properties as a quantitative descriptors of biological activity.

These approaches may be used effectively in drug design depending upon the institution, experience and general scientific awareness of the reader.

This text is an outgrowth of the medicinal chemistry courses taught at various Universities in India. In this book we have tried to provide a coherent and rational account of the principles underlying every aspect of drug design. Special chapters are devoted on Enzyme Inhibitors and Anti-Aids Agents to explain the strategy of the discovery and development of drugs. Since the basic principles of drug design remain sufficiently immutable, separate chapters were included to elaborate advances in the field of CVS - drugs and drugs affecting functioning of various neurotransmitter systems.

We wish to place on record our sincere thanks to our publisher Mr. D. K. Furia for his kind co-operation. Authors are greatly indebted to their colleagues for their generous help and criticism. They also wish to acknowledge indebtedness to all who have assisted with the completion of the book.

Suggestions from all corners of the profession are welcome. Authors are responsible for any deficiencies or errors that remained and would be grateful if readers would call them to our attention.

Pune **Authors**

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1

DRUG DESIGN

1.1 INTRODUCTION

Drug design is an integrated developing discipline which portends an era of 'tailored drug'. It involves the study of effects of biologically active compounds on the basis of molecular interactions in terms of molecular structures or its physico-chemical properties involved. It studies the processes by which the drugs produce their effects, how they react with the protoplasm to elicit a particular pharmacological effect or response, how they are modified or detoxified, metabolised or eliminated by the organism.

Disposition of drugs in individual regions of biosystems is one of the main factors determining the place, mode and intensity of their action. The biological activity may be "positive" as in drug design or "negative" as in toxicology. Thus, drug design involves either total innovation of lead or an optimization of already available lead. These concepts are the building stones upon which the edifice of drug design is built up.

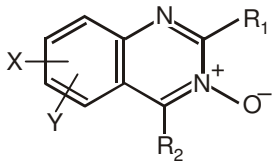
The current trend in the drug design is to develop new clinically effective agents through the structural modification of a lead nucleus. The lead is a prototype compound that has the desired biological or pharmacological activity but may have many undesirable characteristics, like high toxicity, other biological activity, insolubility or metabolism problems. Such organic leads once identified, are easy to exploit. This process is rather straight forward. The real test resides with the identification of such lead compounds and the optimum bioactive positions on the basic skeleton of such leads.

The examples of drug discovery without a lead are quite few in number. The most prominent examples include penicillium and librium. In 1928, Alexander Fleming noticed a green mold growing in a culture of *Staphylococcus aureus,* and where the two had converged, the bacteria were lysed. This led to the accidental discovery of penicillin, which was produced by the mold. Dr. Ronald Hare, colleague of Dr. Fleming, found that very special conditions were required to produce the phenomenon initially observed by Fleming. Another extraordinary circumstance was that the particular strain of the mold on Fleming culture was a relatively good penicillin producer, although most strains of that mold (Penicillium) produce no penicillin at all. The mold presumably came from the laboratory just below Fleming's laboratory where research on molds was going on. Thus, the discovery of penicillin could be possible because a combination of all unlikely events took place simultaneously.

The full extent of the value of penicillin was not revealed until late 1940s because of emergence of the sulphonamide antibacterials in 1935 and the outbreak of World War II. Thereafter the original mold (Penicillium notatum) was replaced by Penicillium chrysogenum because of relatively low yield of penicillin from the former. The correct structure of penicillin was reported in 1943 by Sir Robert Robinson (Oxford) and Karl Folkers (Merck). Once the structure was known, penicillin became lead nucleus for future analogs.

Yet another example of drug discovered without a lead is librium, the first benzodiazepine tranquilizer. A series of quinazoline-3-oxides (1) was synthesized by

Dr. Leo Sternbach at Roche in a program to develop a new class of tranquilizer drugs. Since, none of these compounds was found to be active, the scheme was terminated in 1955. However, a vial from the above scheme which remained untested was found in 1957 during a general laboratory cleanup.

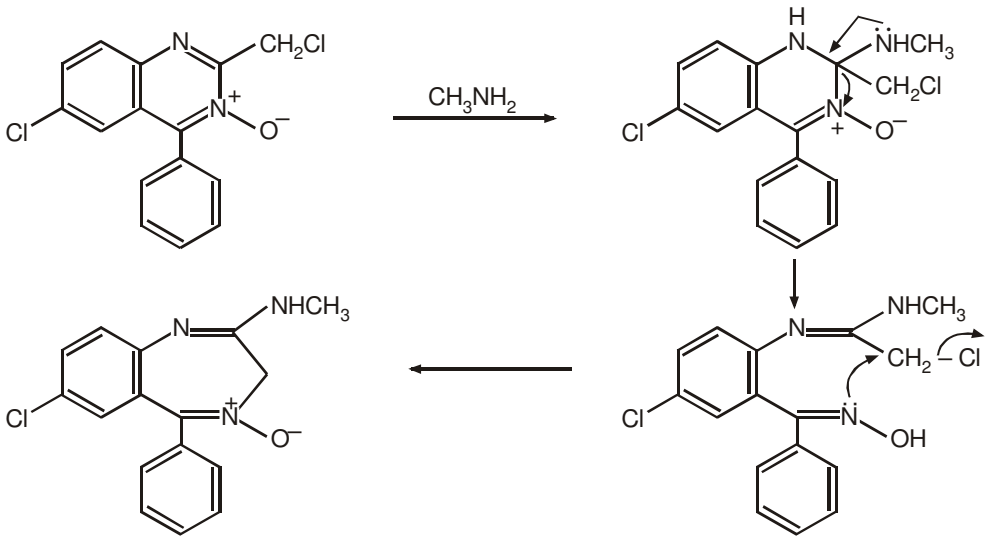


(1)

The compound (2) present in it, was submitted for pharmacological testing to complete official formalities. Surprisingly, it gave very promising results during preliminary screening for tranquilizing activity. It was found to be benzodiazepine-4-oxide, presumably produced in an unexpected reaction of the corresponding chloromethyl quinazoline-3-oxide with methylamine.

If that vial had not been found in the laboratory cleanup, the benzodiazepines may not have been discovered for many years to come. Thus, librium once identified as a lead, was then became exploited to develop future analogs like diazepam. The latter is about 10 times more potent than the lead.

The alkylating agents stood as the first systematic approach to cancer chemotherapy, especially in leukaemia where leukocytes multiply in an uncontrolled fashion. They were developed to lower down high toxicity of mustard gas whose anti-leucocytic action was evidenced when a ship loaded with mustard gas was bombed in an Italian harbour. The military personnel who came in contact with this gas showed an unusually low white blood cell count.



(2) Librium

1.2 METHODS OF LEAD DISCOVERY

There are several approaches which can be employed for lead identification. In order to identify a lead nucleus in a given series, the whole series should be analysed for a particular biological activity. Once the lead is identified, it can be structurally modified to improve the potency. There is a difference between the terms, activity and potency. Activity is the particular pharmacological activity while potency is the strength of that effect. Following are some of the important methods which can be used for lead identification.

(a) Random screening :

In this method, all compounds (including synthetic chemicals and natural products of plant, marine and microbial origin) from a given series are tested. Inspite of budgetary and manpower overuse, this method may be used to discover drugs or leads that have unexpected activities. Antibiotics like, streptomycin and tetracyclines were found out by this method.

A successful random search for antibacterial action was conducted by several pharmaceutical companies in the 1950s. They tested soil samples from all over the world, which resulted in the discovery of many novel structures and some spectacularly useful groups of antibiotics, notably the tetracyclines.

Recently, the large scale automated testing of microbial mutants has been done in combination with recombinant DNA techniques to speed up the efficient discovery and production of new antibiotics.

(b) Non-random screening :

It is a modified form of random screening which was developed because of budgetary and manpower restrictions. In this method, only such compounds having similar structural skeletons with that of lead, are tested.

(c) Drug metabolism studies :

Metabolism of drug occurs as an attempt by metabolizing enzymes to cut short the period of stay of the drug in the body. Structural modifications (i.e. metabolic biotransformation) are done in drug molecule by the enzymes to increase its polarity. It is brought about regardless of whether the resulting drug metabolite possesses more activity or toxicity. The discovery of sulfanilamide is reported through the metabolic studies of prontosil.

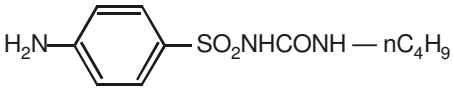
The antipyretic action of acetanilide was discovered by chance when a nurse by mistake dispensed acetanilide to a patient. Due to its toxicities, acetanilide could not stand in the market. Metabolic studies showed that the toxicities are due to its in vivo metabolite, p-aminophenol. These observations led to development of phenacetin and paracetamol.

(d) Clinical observations :

Many times the drug possesses more than one pharmacological activities. The main activity is called as therapeutic effect while rest of the actions are known as side-effects of the drug. Such drug may be used as lead compound for structural modifications to improve the potency of secondary effects.

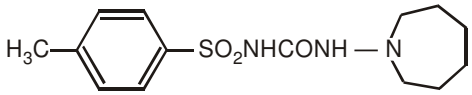
Sulphonamide oral hypoglycemics arose directly from the clinical observation, in 1942, that a sulphathiazole derivative, which was being used specifically for treating typhoid, lowered the blood sugar drastically. The pronounced hypoglycemia exerted by

5 - isopropyl - 2 sulphanilamido - 1, 3, 4-thiadiazole indicated that an arylsulponyl thiourea moiety ($ArSO_2 - NH - C (= N) - S$) present in thiadiazoles is responsible for their blood glucose lowering effect. This observation led to the development of carbutamide by Franke and Fuchs through opening of thiazole ring to give a thiourea moiety in which = S was then replaced by = O.



Tolbutamide

In order to nullify the toxicity and antibacterial activity of the 4-amino group, it was replaced by other substituents resulting into tolbutamide, chlorpropamide and tolazamide.

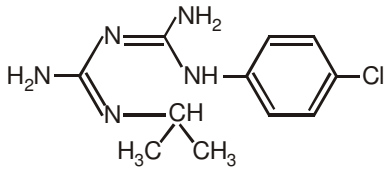


Tolazamide

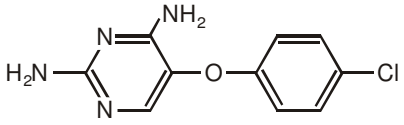
Using 4-methylhistamine as a lead, Ganellin and his colleagues developed H_2 - receptor antagonists with a side-chain terminating in a thiourea group. Because of severe side-effects seen in these thiourea derivatives, thiourea group was bioisosterically replaced by guanidine. Cyanoguanidine when introduced into the side-chain, resulted into cimetidine.

A series of aminoalkyl derivatives of iminodibenzyl was synthesized as analgesics, sedative and anti-histaminics by Hafliger and Schindler in 1951. Imipramine, one of the compounds, appeared to be potential anti-depressant during clinical studies by Kuhn in 1957. Many tricyclic anti-depressants, therefore were synthesized.

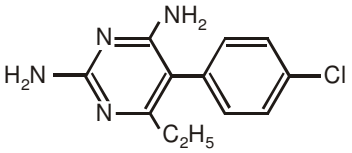
Similarly, due to the antifolate activity shown by chlorguanide, various diamino-pyrimidines were synthesized. Pyrimethamine was designed by deleting the bridging between two rings.



Chlorguanide

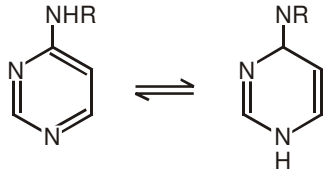


Diaminopyrimidine



Pyrimethamine

With the knowledge of antimalarial activity of sulfapyrimidines at hand, British medicinal chemists F.L. Rose and F.H.S. Curd



Proton tautomerism in aminopyrimidines

spotted a tautomeric proton shift in aminopyrimidines which was supposed to be an essential prerequisite for potent antimalarial activity as per Schonhofer's hypothesis proposed for amino-quinolines. Less toxicity may be expected from pyrimidine series when compared with quinolines/acridines, as the former are components of nucleotides.

(e) Rational approaches to lead discovery :

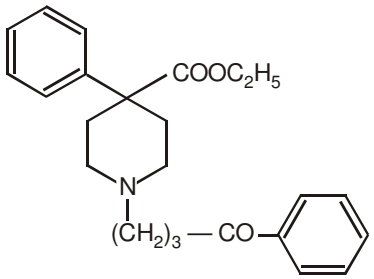
The knowledge about the receptors and their mode of interaction with drug molecules plays an important role in drug design. This knowledge may be used to develop conformationally bioactive skeletons having exact three-dimensional complementarity to a receptor. Greater potency, higher selectivity and less adverse effects are expected by reducing the flexibility of the drug structure. For example, replacement of a terminal N, N-diethylamino group by piperidino exploits the decreasing valency angle at the tertiary nitrogen of the latter so that access of the basic group to anionic sites might be improved. This modification leads to the development of major tranquilizers, local anaesthetics, antihistaminics and spasmolytics. Incorporating a rigid ring leads to altered pharmacokinetic and pharmacodynamic features due to altered pKa of the amine and lipophilicity of the molecule.

This approach is of greater importance in identification of lead nucleus. It involves the use of signs and symptoms of the disease. Most diseases, atleast in part, arise from an imbalance of particular endogenous bioactive substances in the body. These imbalances may be corrected by agonism or antagonism of a receptor or by inhibition of a particular enzyme. Once the real site of such imbalance is identified, the natural enzyme substrate or endogenous substance may be used as a lead nucleus. For example, endogenous hormones, progesterone and 17 β-estradiol were used for developing oral contraceptives. The development of an anti-inflammatory drug, indomethacin from the lead nucleus, serotonin resulted at Merck with a belief that serotonin is a possible mediator of inflammation.

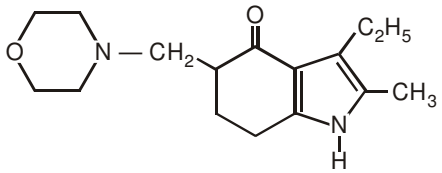
Medicinal chemistry has many examples of the development of successful therapeutics based on an exploration of endogenous compounds. The treatment of diabetes mellitus, for example, is based upon the administration of insulin, the hormone that is functionally deficient in this disease. The current treatment of Parkinson's disease is based upon the observation that the symptoms of Parkinson's disease arise from a deficiency of dopamine, an endogenous molecule within the human brain. Since, dopamine cannot be given as a drug, since it fails to cross the blood-brain barrier and enter the brain, its biosynthetic precursor, L-DOPA, has been successfully developed as an anti-Parkinson's drug.

Analogously, the symptoms of Alzheimer's disease arise from a relative deficiency of acetylcholine within the brain. Current therapies for Alzheimer's-type dementia are based upon the administration of cholinesterase enzyme inhibitors that prolong the effective half-life of remaining acetylcholine molecules within the brain.

Paul A. J. Janseen developed meperidine derivatives by replacing methyl group on piperidine nitrogen by alkyl aryl keto groups. While searching for a better substituent to replace carbethoxy group, tertiary alcohol group was finally selected.



Substitution of the aryl nucleus by halogens and pseudohalogens (F_3C) demonstrated that fluorine para to the keto group was optimal for neuroleptic potency. Out of several hundreds of analogs, haloperidol was selected in 1958 finally for clinical trial. Haloperidol was subjected to various molecular modifications to enhance neuroleptic activity at the expense of analgetic properties. For example, tetrahydropyridyl and piperazinyl rings were used to replace piperidine ring.



Molindone

Since the aminobutyrophenones are δ–aminoketones, homologs were synthesized. Molindone, a Mannich base of pyrrole ketone, is used as an antipsychotic.

In rational drug design, this cycle of "design-test-redesign-retest" can go on for several iterations until the optimized molecule is achieved.

In a chance test, numbing on the tongue was exerted by 2-dimethylamino-2-aceto-toluidine, an intermediate in the synthesis of gramine. This led to the synthesis of various anilides to get local anaesthetics. The presence of two sterically hindering ortho methyl groups protect the anilide linkage from hydrolysis and increase the duration of action of lidocaine. This principle was extended further to develop mepivacaine and dimethisoquine.

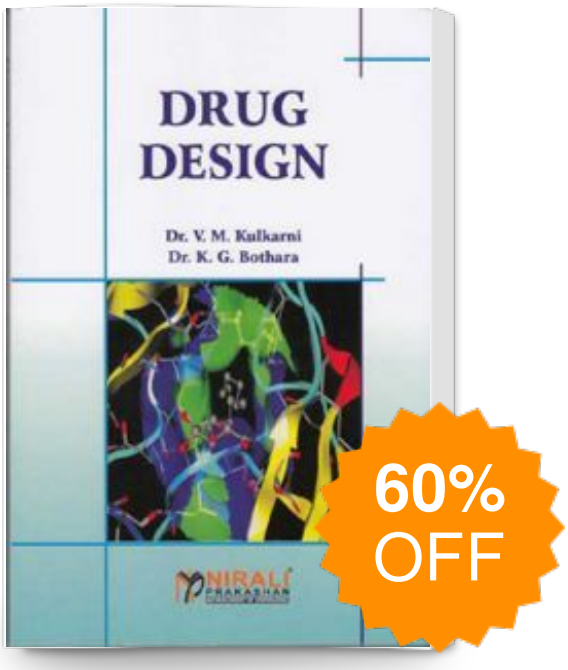
In Postwar France, the Berthier Pharmaceutical Company in Grenoble began to pursue a sideline project of producing soothing liquid bismuth preparations for acute tonsillitis. Being dissatisfied with the commonly used oils, they elected to use the physiologically inert valproic acid as a solvent for their bismuth compounds. Valproic acid is now used in the treatment of epilepsy and (migraine).

In 1962, Pierre Eymard, a graduate student at the University of Lyon, synthesized a series of Khellin. Khellin is a biologically active substance that occurs in the fruit of the wild Arabian Khell plant and which has been used for centuries for the treatment of kidney stones. When attempts to produce a solution of these Khellin compounds failed, advice was sought from H. Meunier of the nearby Laboratory, Berthier. In the view of Berthier's recent interest in valproic acid as a non-toxic inert solvent, Eymard's Khellin derivatives were dissolved in valproic acid and they were studied for anticonvulsant activity. These preliminary studies revealed profound anticonvulsant activity. The antiepileptic action of valproic acid was thus discovered completely by accident, with the first successful clinical trial occuring in 1963.

Bromine was discovered in seawater in 1826. Recognizing its chemical similarity to iodine, French physicians immediately exploited it as an iodine alternative for the treatment of numerous conditions, including syphilis and thyroid goiter. Although no beneficial effects were reported for either bromine or its potassium salt, their widespread use eventually helped to recognize the depressant effect of potassium bromide on the nervous system.

In 1857, Sir Charles Locock, the physician, with the view that epilepsy arose from excessive sexuality, introduced bromide to suppress the supposed

Drug Design



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