

Drug Design—A Rational Approach

1. INTRODUCTION

In the past few decades there has been a hiatus in the momentum of research and discovery of 'novel medicinal compounds'. This particular trend in drug development perhaps is augmented due to two vital factors, namely: *first*, strict empirical and rational approach to drug design; and *secondly*, high standards of safety and therapeutic efficacy together with tremendous increased costs of research and development and finally the clinical trials.

'Drug design' or 'tailor-made compound' aims at developing a drug with high degree of chemotherapeutic index and specific action. It is a logical effort to design a drug on as much a rational basis as possible thus reducing to the minimum the trial and error approach. It essentially involves the study of biodynamics of a drug besides the interaction between drug molecules and molecules composing the biological objects.

Drug design seeks to explain:

- (a) Effects of biological compounds on the basis of molecular interaction in terms of molecular structures or precisely the physico-chemical properties of the molecules involved.
- (b) Various processes by which the drugs usually produce their pharmacological effects.
- (c) How the drugs specifically react with the protoplasm to elicit a particular pharmacological response.
- (d) How the drugs usually get modified or detoxicated, metabolized or eliminated by the organism.
- (e) Probable relationship between biological activity with chemical structure.

In short, **drug design** may be considered as an integrated whole approach which essentially involves various steps, namely: chemical synthesis, evaluation for activity-spectrum, toxicological studies, metabolism of the drug, *i.e.*, **biotransformation** and the study of the various metabolites formed, assay procedures, and lastly galenical formulation and biopharmaceutics.

The 'drug design' in a broader sense implies random evaluation of synthetic as well as natural products in bioassay systems, creation of newer drug molecules based on biologically-active-prototypes derived from either plant or animal kingdom, synthesis of congeners displaying interesting biological actions, the basic concept of isosterism and bioisosterism, and finally precise design of a drug to enable it to interact with a receptor site efficaciously.

In the recent past, another terminology '**prodrugs**' has been introduced to make a clear distinction from the widely used term '**analogues**'. **Prodrugs** are frequently used to improve pharmacological or biological properties. **Analogues** are primarily employed to increase potency and to achieve specificity of action.

2. ANALOGUES AND PRODRUGS

In the course of **drug design** the *two* major types of chemical modifications are achieved through the formation of **analogues** and **prodrugs**.

An **analogue** is normally accepted as being that modification which brings about a carbon-skeletal transformation or substituent synthesis. *Examples* : **oxytetracycline**, **demclocycline**, **chlortetracycline**, **trans-diethylstilbesterol** with regard to **oestradiol**.

The term **prodrug** is applied to either an appropriate derivative of a drug that undergoes *in vivo* hydrolysis to the parent drug, *e.g.*, **testosterone propionate**, **chloramphenicol palmitate** and the like ; or an analogue which is metabolically transformed to a **biologically active drug**, for instance : **phenylbutazone** undergoes *in vivo* hydroxylation to **oxyphenbutazone**.

3. CONCEPT OF 'LEAD'

Another school of thought views '**drug design**' as the vital process of envisioning and preparing specific new molecules that can lead more efficiently to useful drug discovery. This may be considered broadly in terms of two types of investigational activities. These include :

- (a) **Exploration of Leads**, which involves the search for a new lead ; and
- (b) **Exploitation of Leads**, that requires the assessment, improvement and extension of the lead.

From the practical view-point it is the latter area wherein rational approaches to drug design have been mostly productive with fruitful results.

3.1 Examples

It is worthwhile to look into the right perspective of a few typical and classical examples of **drug design** as detailed below :

(i) Narcotic Analgesics

In the year 1939, Schaumann first identified and recognized the presence of a quaternary-carbon-atom in the morphine molecule, which eventually formed an altogether new basis and opened up a new horizon in the field of **drug design** of narcotic analgesics. Intensive research further led to the evolution of **pethidine (meperidine)** which incidentally combines both the properties of **morphine** and **atropine**. It possesses a quaternary carbon-atom and quite astonishingly a much simpler chemical structure to that of **morphine**.