

Drug Design—A Rational Approach

INTRODUCTION

'Drug design' or '*tailor-made compound*' aims at developing a drug with high degree of chemotherapeutic index and specific action.

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.

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.

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, demcloxycycline, 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

: phenyl- butazone undergoes *in vivo* hydroxylation to oxyphenbutazone.

3. CONCEPT OF 'LEAD'

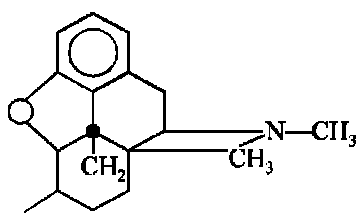
Another school of thought views '**drug design**' as the vital process of envisioning and preparing specific new molecules that can lead more efficiently to useful drug discovery. This may be considered broadly in terms of two types of investigational activities. These include :

- (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.

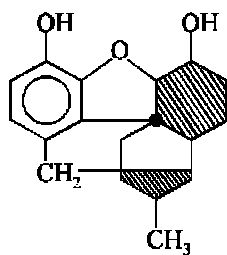
3.1 Examples

(i) Narcotic Analgesics

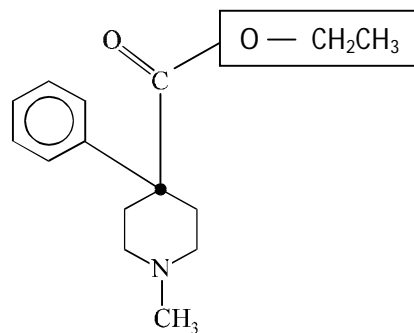
In the year 1939, Schaumann first identified and recognized the presence of a quaternary-carbon-atom in the morphine molecule, in the field of drug design of narcotic analgesics. Intensive research further led to the evolution of pethidine (meperidine) which incidentally combines both the properties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



Morphine

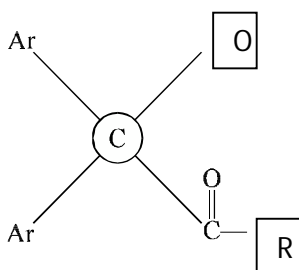


Morphine
(Schaumann's Model)



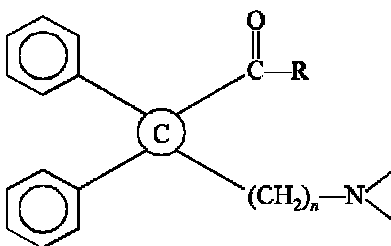
Pethidine
(Meperidine)

Ehrhardt suggested a general formula relevant to the analgesic activity in 1949 as stated below :



where, Ar is the aromatic ring, X the basic side chain and (—C—) carbonyl function in the form of an ester, ketone or an amide.

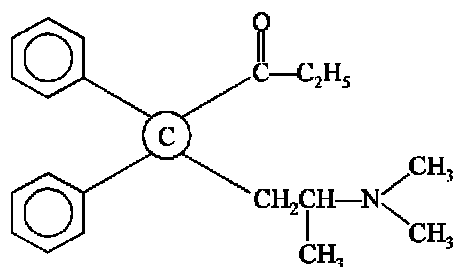
Later on, the above general formula was modified slightly as follows :



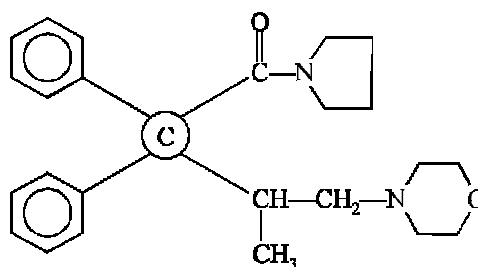
which successfully led to the development of the following *three* narcotic analgesics, namely : methadone, dextromoramide and dextropropoxyphene.

(ii) Antipyretic Analgesics

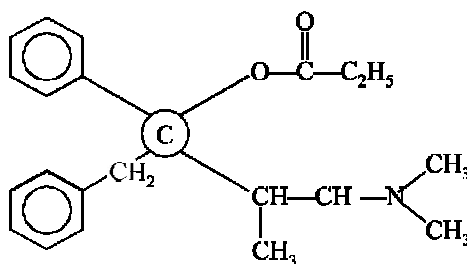
Another fruitful approach in drug design is the meticulous screening of the metabolite for probable pharmacological activity. The most interesting example is the bio-oxidation of acetanilide into *para*-aminophenol which subsequently on chemical manipulation has yielded better tolerated antipyretic-analgesics like paracetamol and phenacetine.



Methadone

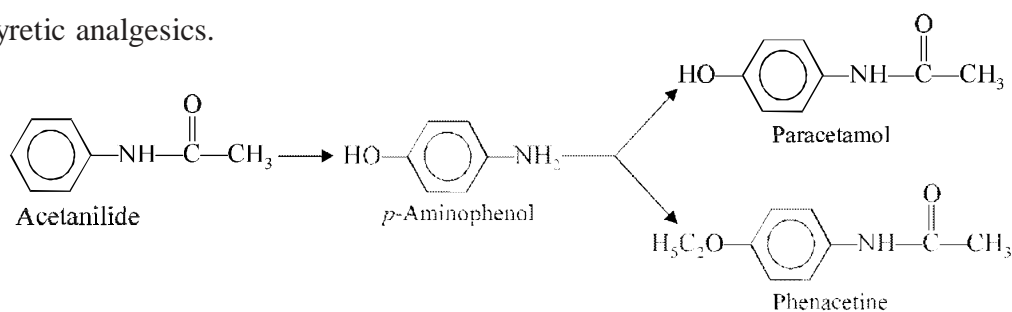


Dextomoramid



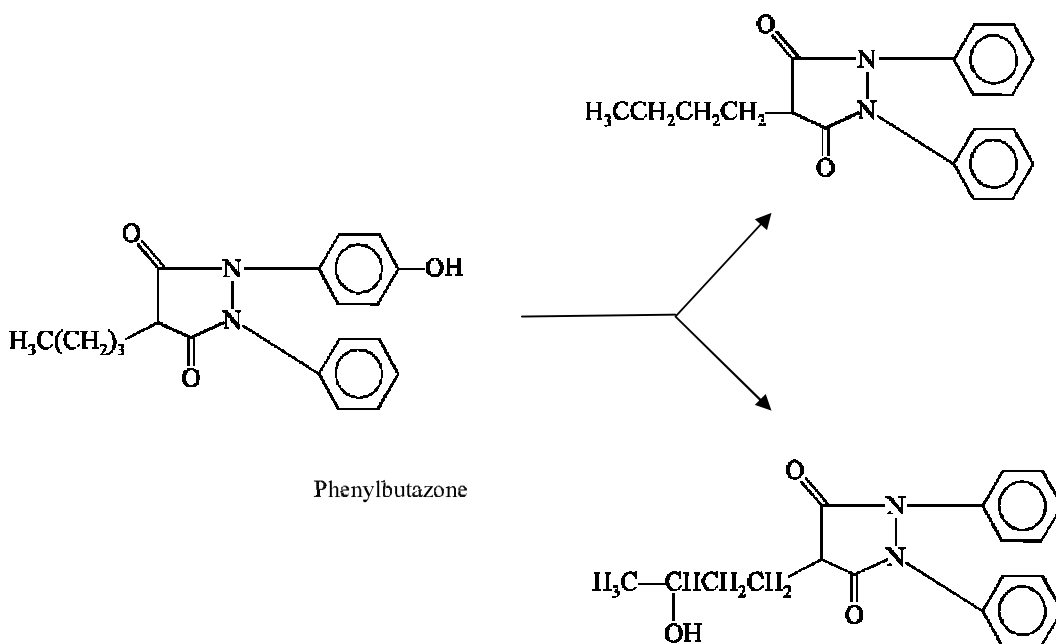
Dextropropoxyphen

Quite recently phenacetine has been withdrawn completely because of its toxic after effects, though it dominated the therapeutic field for over 30 years as a potent antipyretic analgesics.



(iii) Antirheumatic Drugs

The study of the metabolite conversion of the antirheumatic drug phenylbutazone resulted in the introduction of a better tolerated drug oxyphenylbutazone as an antirheumatic drug and phenylbutazone alcohol as an uricosuric agent.



4. FACTORS GOVERNING DRUG-DESIGN

A few cardinal factors governing the efficacy towards the evaluation of drug design include :

- (a) The smaller the expenditure of human and material resources involved to evolve a new drug of a particular value, the more viable is the design of the programme.
- (b) Experimental animal and clinical screening operations of the new drugs.
- (c) Relationships between chemical features and biological properties need to be established retrospectively.
- (d) Quantitative structure-activity relationships (QSARs) vary to an appreciable extent in depth and sophistication based on the nature of evaluation of structure or activity. A purposeful relation of structural variables must include steric factors, electronic features of component functional groups and, in general, the molecule as a whole.
- (e) The trend to synthesize a huge number of newer medicinal compounds indiscriminately for exploratory evaluation still prevails which exclusively reflects the creative genuineness and conceptual functions of a highly individualized expression of novelty by a medicinal chemist.
- (f) Introduction of functional groups in a molecule that need not essentially resemble metabolites, but are capable of undergoing bonding interactions with important functional groups of biochemical components of living organisms affords an important basis for

exploration.

(g) Disease etiologies and various biochemical processes involved prove useful.

5. RATIONAL APPROACH TO DRUG DESIGN

A rational approach to drug design may be viewed from different angles, namely :

5.1. Quantum Mechanical Approach

Quantum mechanics (or wave mechanics) is composed of certain vital principles derived from fundamental assumptions describing the natural phenomena effectively. The properties of protons, neutrons and electrons are adequately explained under quantum mechanics. The electronic features of the molecules responsible for chemical alterations form the basis of drug molecule phenomena.

5.2. Molecular Orbital Approach

Based on the assumption that electrons present in molecules seem to be directly linked with orbitals engulfing the entire molecule which set forth the molecular orbital theory. The molecular orbital approach shows a dependence on electronic charge as evidenced by the study of three volatile inhalation anaesthetics, and also on molecular conformation as studied with respect to acetylcholine by such parameters as bond lengths and angles including torsional angles.

Molecular orbital calculations are achievable by sophisticated computers, and after meticulous interpretations of results the molecular structure in respect of structure-activity analysis is established.

5.3. Molecular Connectivity Approach

This approach establishes the presence of structural features like cyclization, unsaturation, skeletal branching, and the position and presence of heteroatom in molecules with the aid of a series of numerical indices. For example : an index was determined to possess a correlative factor in the SAR study of amphetamine-type hallucinogenic drugs.

Molecular connectivity approach has some definite limitations, such as, electronegativity variance between atoms, non-distinguishable entity of *cis-trans*

isomerism.

5.4. Linear Free-Energy Approaches

This method establishes the vital link between the proper selection of physicochemical parameters with a specific biological phenomenon. However, such a correlation may not guarantee and allow a direct interpretation with regard to molecular structure, but may positively offer a possible clue towards the selection of candidate molecules for synthesis.

6. DRUG-DESIGN : THE METHOD OF VARIATION

Under this method a new drug molecule is developed from a biologically active prototype. The various advantages are as follows :

- (a) At least one new compound of known activity is found.
- (b) The new structural analogues even if not superior may be more economical.
- (c) Identical chemical procedure is adopted and hence, considerable economy of time, library and laboratory facilities.
- (d) Screening of a series of congener (*i.e.*, member of the same gene) gives basic information with regard to pharmacological activity.
- (e) Similar pharmacological technique for specific screening may be used effectively. The cardinal objectives of the method of variation are :
 - To improve potency
 - To modify specificity of action
 - To improve duration of action
 - To reduce toxicity
 - To effect ease of application or administration or handling
 - To improve stability
 - To reduce cost of production

Once the molecular structure of the compound in question is drawn on the drawing board, one takes into consideration such information as the following :

- a) variation of functional groups and their proximity to one another
- b) various probable rotational and spatial configurations
- c) possibility of steric hindrance between various portions of the molecule in different configurations in space ; and
- d) probability of electronic interactions between various portions of the molecule including such matters as inductive and mesomeric effects, hyper-conjugation, ionizability, polarity, possibility of chelation, asymmetric centres and zwitterion formation.

7. Research and Development Strategies

It has been proved beyond any reasonable doubt that the 'rate of success' in drug discovery is exclusively dependent on the ability to identify, characterize novel, patentable newer 'target-drug- molecules' usually termed as New Chemical Entities (NCEs), which essentially possess the inherent capability and potential in the management and control of a specific disease/ailment ; besides, being efficacious and safer in character. With the advent of latest technological advancements in the specialized areas related to genomics and combinatorial chemistry an appreciable advancement has been accomplished in the R & D strategies. It is, however, pertinent to mention here that a proprietary NCE status, position and recognition is an absolute must not only to ensure marketing exclusively but also to aptly justify the huge investment in the ensuing R & D process thereby making medicinal chemistry a more or less core element of the entire 'drug discovery process'.

Interestingly, the 'drug discovery process' may be categorized into four distinct heads, namely : (i) Target identification and selection,

(ii) Target optimization,

(iii) Lead identification, and

(iv) Lead optimization.

The concerted efforts encompassing various intangible and critical methodologies that ultimately relate to the activities, expertise, wisdom and integration of the individual

scientist directly or indirectly involved in 'drug discovery process' virtually leads to advance drug discovery profiles.*

In short, the qualified success in the 'drug discovery process' predominantly revolves around the following cardinal factors, namely :

- Articulated project management processes
- Prioritization
- Well-defined aims and objectives
- Company organization(s) and culture
- Resourcing modus operandi
- Prompt decision making factors.

8. MOLECULAR HYBRIDISATION

The molecular hybridisation essentially embodies the synthesis of strategically designed of alto- gether newer breeds of 'bioactive agents' either from two or even more compounds having different characteristic features by the aid of covalent-bond synthesis.

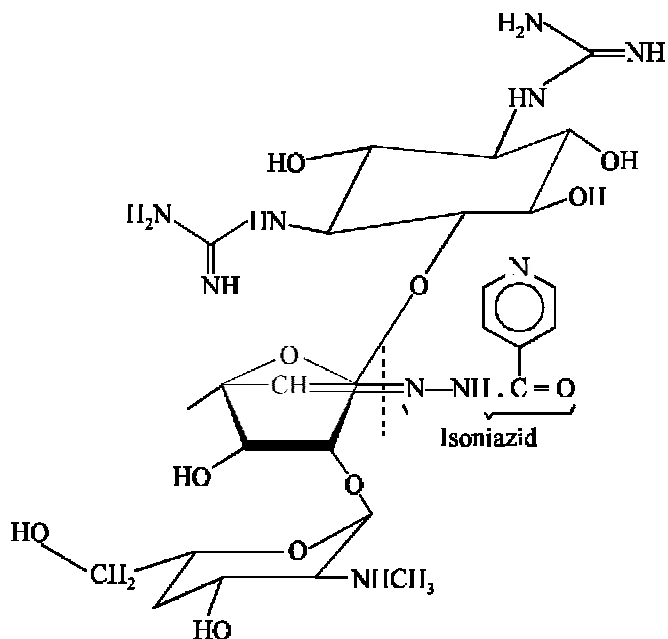
Necki (1886) first conceived the interesting 'salol principle', whereby he exploited the benefi- cial properties of phenols and carboxylic acids possessing potent antibacterial characteristic features into the 'design' of newer drug molecules with better and improved pharmacological activities by means of simple esterification.

A few typical examples wherein the hyberdisation was accomplished commencing from two 'bioactive entities' i.e., implementation of the full-salol principle occurred, as stated under :

Examples :

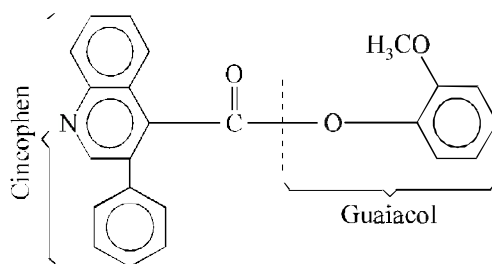
(a) Antibacterial Agent : Streptoniazid ;

A molecule of streptomycin and a molecule of isoniazid by means of a strong double bond between C and N with the elimination of a mole of water. The 'hyberdised molecule' exhibits a significant potentiated antibacterial and tuberculosstatic agent.



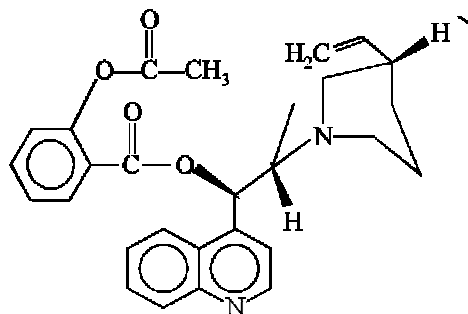
(b) **Antitussive Expectorant Drug : Guaiacyl phenyl cinchoninate ;**

A mole each of cincophen and guaiacol gets hybridised by forming an ester-linkage and losing a mole of water. The new product shows an improved antitussive and expectorant activity.



(c) **Antipyretic-Analgesic Agent : Quinine acetylsalicylate ;**

Hybridisation takes place between a mole of acetylsalicylic acid (i.e., aspirin) and quinine (i.e., a potent antimalarial agent) to lose a mole of water ; and the resulting hybridised product potentiates the antimalarial activity along with substantial antipyretic—analgesic activity.



9. RIGIDITY AND FLEXIBILITY VS DRUG DESIGN :

It has been observed beyond any reasonable doubt whatsoever that the structure-activity relationship invariably affords certainly a molecular complementary prevailing evidently between the bioactive compound and the probable receptor site. At this point in time two different situations may usually crop up, namely :

- (a) increased rigidity — that may ultimately lead to improved potencies ; and
- (b) increased flexibility—that may give rise to better and improved activity.

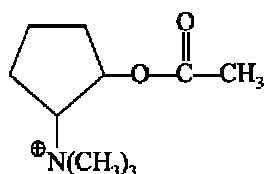
These two aforesaid situations shall now be discussed with typical examples so that one may have a better understanding of these aspects vis-a-vis drug design of newer targetted drug molecules.

9.1. Increased Rigidity

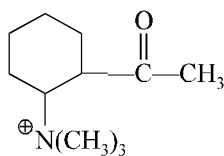
There are a plethora of ‘drug molecules’ which are inherently flexible in nature i.e., they can assume a wide-range of shapes (spatial arrangements). Of these structural variants quite a few are absolutely not so favourably acceptable for reaction at a specific ‘receptor site’. Therefore, the ‘design’ or ‘search’ for a relatively more rigid structural analogue essentially having the required, correct and desired ‘dimensions’ must be looked into in order to obtain a more potent drug substance.

Besides, the actual distance existing between two vital functional moieties may be almost fixed arbitrarily in rigid molecular structural variants. These restructured and strategically positioned newer targetted-drug molecules may be subjected to vigorous and critical examinations by the aid of several sophisticated latest physicochemical analytical devices, such as : X-Ray diffraction analysis ; Optical Rotary Dispersion (ORD) ; NMR-spectroscopy ; Mass Spectroscopy ; FTIR-Spectrophotometry and the like.

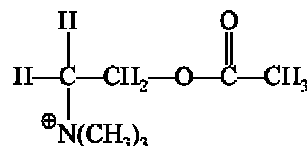
Examples : Structural analogues of acetylcholine (ACh) i.e., a short-acting cholinergic drug, with ‘increased rigidity’ having 5- or 6- membered saturated rings were synthesized ; and their activities were compared using ACh as the reference drug :



**MODIFIED ACh
WITH 5-MEMBERED
CYCLIC RING
(A)**

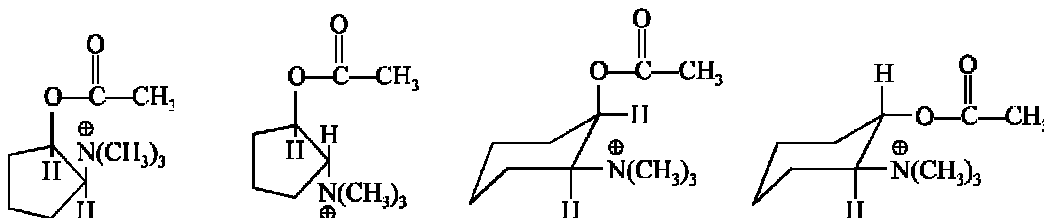


**MODIFIED ACh
WITH 6-MEMBERED
CYCLIC RING
(B)**



**ACETYLCHOLINE ACh
(AN OPEN-CHAIN COMPOUND)**

Interestingly, either of the two structural analogues (A) and (B) can be further resolved into their respective *trans*- and *cis*-isomers i.e., spatially rearranged structures, as given below :



It has been observed that the 'intraatomic distance' between 'O' and 'N' atoms for the *cis*- isomers (A & B) ranged between 2.5—2.9 Å ; whereas, between the corresponding *trans*- isomers (A & B) varied between 2.9—3.7 Å. Furthermore, the relative cholinergic activities of the *cis*-isomers were found to be greater than the corresponding *trans*-isomers using ACh as the reference drug.

The results of these findings have been summarized in the following table, wherefrom certain important clues may be derived with regard to some important functional group(s) located on the en- zymes and the existing distances between such moieties.

S. No.	Drugs	Intra-Atomic Distances between 'O' and 'N' (Å)	Relative cholinergic Activit
1.	ACh	—	1.00
2.	A- <i>cis</i> -	2.51	1.43
3.	A- <i>trans</i> -	3.45	1.07
4.	B- <i>cis</i> -	2.5—	1.14
5.	B- <i>trans</i> -	2.9—	1.06

Thus, A-*cis*— is found to be almost 50% more active than ACh, and B-*cis*-only upto 15%

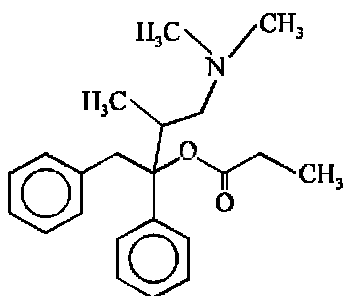
than ACh. However, the corresponding *trans*-isomers of A and B did not show any improvement in their cholinergic activities.

Increased Flexibility

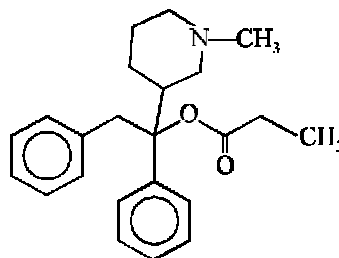
The problems encountered invariably with less flexible, rigid and compact molecules being that their manoeuvrability are comparatively much less. In other words, they either possess little or practically negligible capacity to have them rearranged to a more favoured conformation that may ultimately give rise to enhanced bioactivity.

Example :

Propoxyphene (I) is an open-chain structural analogue having narcotic analgesic activity ; whereas, its corresponding cyclic analogue (II) is almost found to be devoid of the pharmacological activity.



**PROPOXYPHENE
(I)
(ACTIVE)**



**PROPOXYPHENE CYCLIC ANALOGUE
(II)
(INACTIVE)**

10. 'TAILORING' OF DRUGS

With the advent of enormous in-depth knowledge of 'modern chemistry', the 'tailoring' of drugs has become a skilful art that may result fruitful results through specific modes of attack on a drug molecule.

Various configurational and stereochemical changes afford flexibility and overall dimension of a drug molecule. Such alterations may be conveniently achieved through different means and ways, namely : ring fission or fusion, formation of lower or higher homologues, introduction of optically active centres, formation of double bonds towards geometrical isomerism, and lastly introduction of bulky groups towards restricted rotation or the removal and replacement of such groups.

Alterations of various physical and chemical characteristics through the insertion of newer functional moieties or by the replacement of such groups already present by others that essentially differ in degree or in type. These types of changes may be effectively brought about by : isosteric replacement, changes of orientation or position of given moieties, introduction of polar character of

given functional groups or replacement of other groups with different electrical features, and finally such changes which either promote or inhibit the presence of different electronic conditions achieved through inductive effects, mesomeric effects, tautomerism, chelation, hyperconjugation, etc.

Probable Questions for B. Pharm. Examinations

1. Justify the following statements :
 - (a) Drug design aims at developing a drug with high degree of chemotherapeutic index and specific action.
 - (b) From the practical view-point it is the '*Exploitation of Leads*' wherein rational approaches to drug-design have been mostly productive with fruitful results.
2. Discuss the various '*factors governing drug-design*'.
3. Elaborate the 'rational approach to drug design' with regard to Quantum Mechanics (or Wave Mechanics), Molecular Orbital Theory, Molecular Connectivity and Linear Free-Energy Concepts.
4. Enumerate the various cardinal objectives of '*the Methods of Variation*' giving appropriate examples.
5. The first synthetic oestrogen *trans*-diethylstilbestrol came into existence by applying the principle of 'drug-design through disjunction' from 'oestradiol'. Explain.
6. The development of 'ganglionic block agent' is exclusively based on the '*principle of mixed molecular*' as drug design through conjunction.
7. '*Tailoring of Drugs*' is the outcome of a unique blend of skillful and involving various configurational and stereochemical changes attributing its flexibility and overall dimension. Explain.
8. Discuss the various possible approaches in designing newer drugs by applying variation of a '*biologically active prototype*'.
9. Bio-oxidation and acetanilide and metabolic conversion of phenylbutazone gave rise to two better tolerated drug molecules used frequently and profusely in the therapeutic armamentarium. Explain.
10. Differentiate the basic concepts of '*analogues*' and '*prodrugs*' with the help of suitable examples of parent drug molecule(s).

RECOMMENDED READINGS

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2. **Foye's Principles of Medicinal Chemistry**, Williams DA and Lemke T.L. (Eds), Lippincot Williams & Wilkins, New York, 5th edn., 2002.
3. Kenny BA *et al.* **The Application of high throughput Screening to novel lead discovery**, *Prog. Drug Res.*, **41** : 246-269, 1998.
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5. Williams M., **Strategies for Drug Discovery**, *NIDA Research Monograph*, **132** : 1-22,1993.

