M.Sc. Final Year

Chemistry, Paper V

MEDICINAL CHEMISTRY

मध्यप्रदेश भोज (मुक्त) विश्वविद्यालय – भोपाल

MADHYA PRADESH BHOJ (OPEN) UNIVERSITY – BHOPAL

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SYLLABI-BOOK MAPPING TABLE

Medicinal Chemistry

Syllabi	Mapping in Book
Unit I **Drug Design:** Development of new drugs, procedures followed in drug design, Concept of lead compound and lead modification, concepts of prodrugs and soft drugs, Structure Activity Relationship (SAR), factors affecting bioactivily, resonance, inductive effect, isosterism, bio-isosterism, spatial considerations. Theories of drug activity: occupancy theory, rate theory, induced fit theory. Quantitative structure activity relationship. History and development of QSAR. Concepts of drug receptors. Elementary treatment of drug receptor interactions. Physicochemical parameters: Lipophilicily, partition coefficient, electronic ionization constants, steric, Shelton and surface activity parameters and redox potentials. Free-Wilson analysis, Hansch analysis, relationships between FreeWilson and Hansch analysis, LD-50, ED-50 (Mathematical derivations of equations excluded).	**Unit-1:** Drug Design **(Pages 3-22)**
Unit II **Phormocokinetics:** Introduction to drug absorption, disposition, elimination using pharmacokinetics, important pharmacokinetic parameters in defining drug disposition and in therapeutics. Mention of uses of pharmacokinetics in drug development process. **Phormocodynomics:** Introduction, elementary treatment of enzyme stimulation, enzyme inhibition, sulphonamides, membrane active drugs, drug metabolism, xenobiotics, biotransformation, significance of drug metabolism in medicinal chemistry.	**Unit-2:** Pharmacokinetics and Pharmacodynamics **(Pages 23-37)**
Unit III **Antineoplastic Agents:** Introduction, cancer chemotherapy, special problems, role of alkylating agents and antimetabolites in treatment of cancer. Mention of carcinolytic antibiotics and mitotic inhibitors. Synthesis of mechlorethamine, cyclophoshamide, melphalan, uracil, mustards, and 6-mercaptopurine. Recent development in cancer chemotherapy. Hormone and natural products. **Cardiovascular Drugs:** Introduction, cardiovascular diseases, drug inhibitors of peripheral sympathetic function, central intervention of cardiovascular output. Direct acting arteriolar dilators. Synthesis of amyl nitrate, sorbitrate, diltiazem, quinidine, veropamil, methyldopa, atenolol, oxyprenolol.	**Unit-3:** Antineoplastic Agents and Cardiovascular Drugs **(Pages 39-69)**
Unit IV **Local Antiinfective Drugs:** Introduction and general mode of action. Synthesis of sulphonamides, furazolidone, nolidixic acid, ciprofloxacin, norfloxocin, dapsone, amino salicylic acid, isoniazid, ethionamide, ethambutol, fluconozole, econozole, griseofulvin, chloropquin. **Psychoactive Drugs:** The Chemotherapy of Mind: Introduction, neurotransmitters, CNS depressants, general anaesthetics, mode of action of hypnotics, sedatives, anti-anxiety drugs, benzodiozipines, buspirone, neurochemistry of mental diseases. Antipsychotic drugs - the neuroleptics, antidepressants, butyrophenones, serendipity and drug development, stereochemical aspects of psychotropic drugs.	**Unit-4:** Antiinfective Drugs and Psychoactive Drugs **(Pages 71-102)**

Synthesis of diazepam, oxazepam, Clonazepan, alprazolam, phenytoin, Ethosuximide, trimethadione, barbiturates, thiopental sodium, glutethimide.

Unit V

Antibiotics: Cell wall biosynthesis, inhibitors, β-lactam rings, antibiotics inhibiting protein synthesis. Synthesis of penicillin G, penicillin V, ampicillin, amoxycillin, chloramphenicol, cephalosporin, tetracycline and streptomycin.

Unit-5: Antibiotics
(Pages 103-128)

CONTENTS

INTRODUCTION

NOTES

The International Union for Pure and Applied Chemistry (IUPAC) defines medicinal chemistry as a "chemistry-based discipline, also involving aspects of biological, medical and pharmaceutical sciences. It is concerned with the invention, discovery, design, identification and preparation of biologically active compounds, the study of their metabolism, the interpretation of their mode of action at the molecular level and the construction of structure-activity relationships.

Medicinal chemistry involves the creation and refinement of molecules for the purpose of creating or improving drugs. It is grounded in synthetic organic chemistry, a discipline in which scientists combine small molecules to create new ones. While other areas of pharmaceutical science focus on the analysis and testing of molecules, medicinal chemistry concentrates primarily on the design of molecules. As such, it's ideal for scientists who prefer taking a hands-on, creative approach to their work.

This book, *Medicinal Chemistry*, has been divided into five units with special emphasis on the different aspects of medicinal chemistry. The book written strictly in SIM (self-instructional material) format for students of distance learning. Each unit starts with an Introduction and Objectives. Then, the detailed content is presented in an understandable and organized manner. Each unit has a set of Check Your Progress Questions to test the readers' understanding of the topics covered. A Summary along with a list of Key Words and a set of Self-Assessment Questions and Exercises is also provided at the end of each unit for effective recapitulation. Each unit also has a list of books for Further Readings.

UNIT 1 DRUG DESIGN

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Structure

1.0 INTRODUCTION

Drug designing projects have always been the biggest challenge for the pharmaceutical companies. The probable statistics suggest that human body has about 35000 open reading frames in its genome which generate approx. 500,000 proteins. Among these generated proteins only 10 thousand proteins have been identified crystallographically. So, while designing the drug we still have 4 lakh 90,000 unknowns which can lead to failure of all the scientific efforts in designing a novel therapeutic approach to treat a disease. Moreover, developing a drug for rare diseases become burdensome for pharmaceutical companies because the

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manufacturing cost can never be covered by the product sales. Physiology of human body has never been simple. The biological systems are difficult to understand hence it is not surprising that most of the time drugs are heterocyclic, contain multiple function groups and have moderate molecular weight. These challenges of organic synthesis are the determining factors for production of a drug. Usually, it's observed that researchers do a computational analysis on all the probable compounds check the toxicity, selectivity, bioavailability, intellectual property, efficacy, and rate of absorption in body. These analyses narrow down the search for prospective derivatives for a drug. This unit will explain the process of development of new drugs including the procedures involved. It will introduce the concepts of lead compound, lead modification, prodrugs and soft drugs along with the history and development of QSAR. It will discuss physicochemical parameters for a drug.

1.1 OBJECTIVES

After going through this unit, you will be able to:

- Describe the designing and development of drugs
- Discuss about the factors affecting the bioactivity of a drug
- Explain all the theories of drug activity
- Analyse physicochemical parameters for a drug

1.2 DEVELOPMENT OF NEW DRUGS

Developing a new drug has always been challenging. In past decades, it was easy to bring a drug to market as regulatory policies were quite lenient. Now with growing demand and better healthcare the approval of drugs have come difficult.

Practice of medicinal chemistry is nothing new. Several thousand years ago people used herbs, berries and roots as medicine. Some of these were successful in clinical trials in lab but it was not until 100 to 150 years back that people got to know about active components present in natural sources.

The historical records of countries like China and India have some evidences of therapeutic use of plant concoctions. Use of opium pepper add sub potential analgesic agent is not surprising. In 1928, the accidental discovery of penicillin by Alexander Fleming vasaki achievement. Thereafter a new era of pharmaceuticals started.

For development of a new drug, metabolites from plant products are extracted and screened for its activity.

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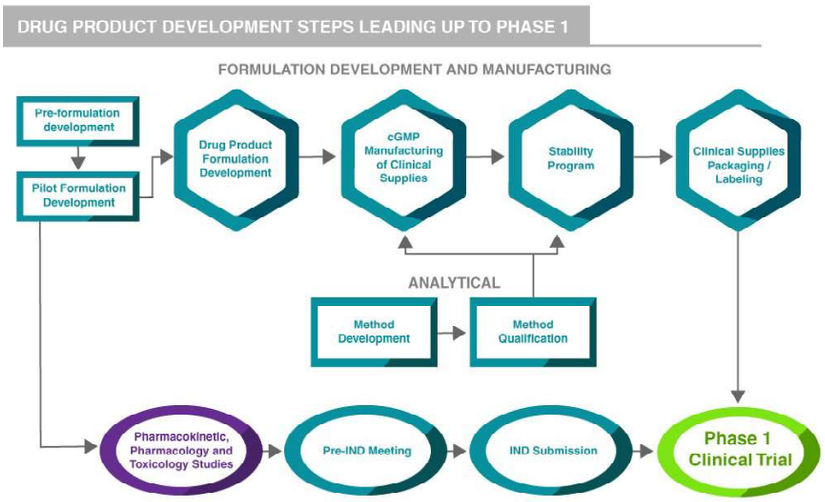

Fig. 1.1 *Drug Product Development Steps Leading Up to Phase 1*

Once the prototype is ready it is sent for preclinical development followed by clinical trials. If a drug is proved as safe then it is approved by FDA and launched in market.

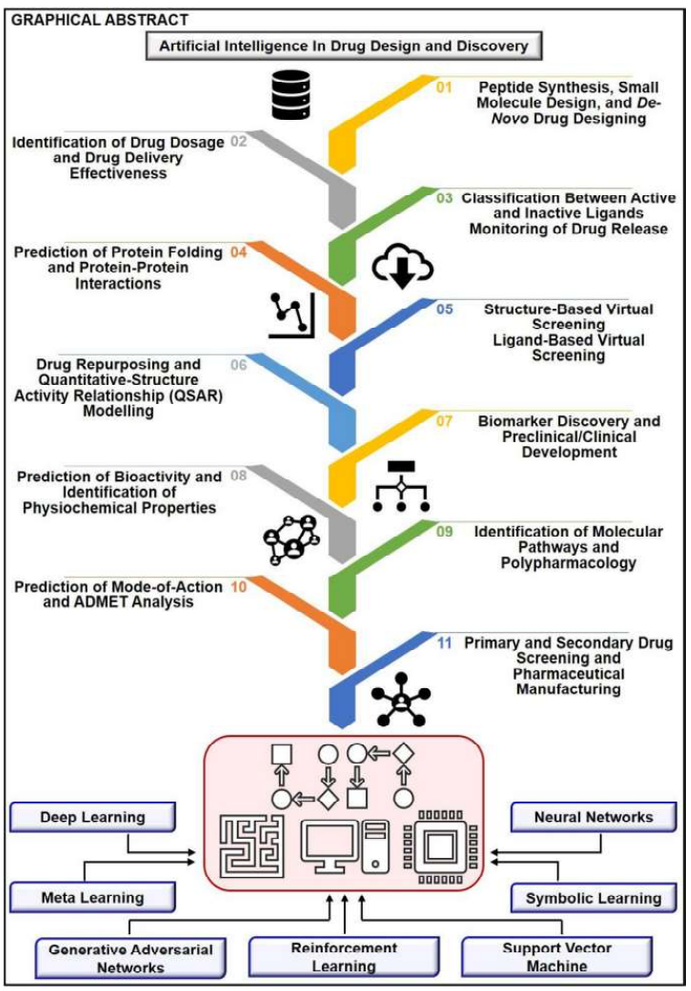

Fig. 1.2 *Artificial Intelligence in Drug Design and Discovery*

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1.2.1 Procedures Followed in Drug Design

Developing a new drug and bringing to market is an exceptionally effort taking process. Identifying a potential compound and its development into a drug is a very tedious process. The major steps include preclinical development, clinical development and regulatory approval. Below is a schematic representation of processing a drug.

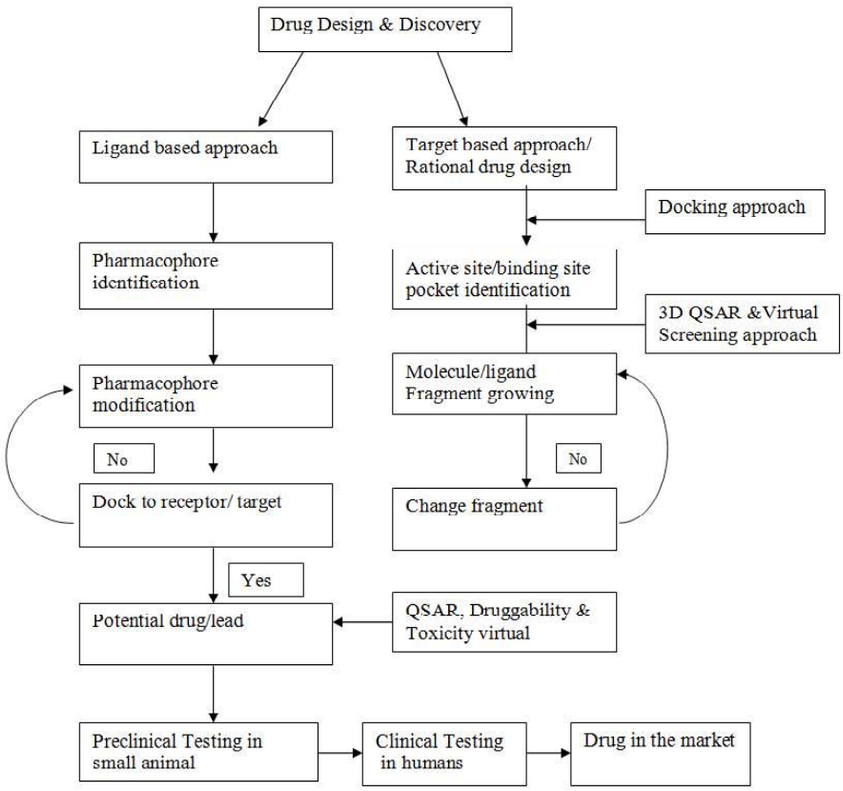

Fig. 1.3 *Processing a Drug*

1.2.2 Concept: Lead Compound, Lead Modification, Prodrugs and Soft Drugs

In discovery of drugs lead compounds are those chemical structures that have pharmacological activity likely to be used as therapeutic but they may require some sub-optimal structure modification to fit better to the target site. A lead compound is a chemical molecule with pharmacological or biological action that is likely to be therapeutically beneficial but has a poor structure that has to be modified to fit better to the target; lead medications have the potential to be followed by back-up compounds. Lead optimization is needed to maximise the interactions with the active site off selected drug targets to increase selectivity. Bioinformatics have played a major role in lead identification and optimization. Once lead compound is identified it is followed by its optimization make it a candidate drug. Synthetic changes are made to adjust ADMET properties of the compound.

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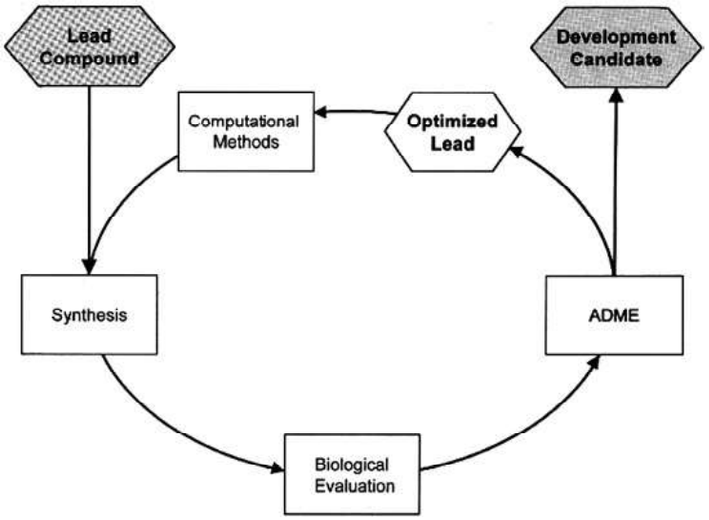

Fig. 1.4 *Lead Compound and Lead Modification*

Lead modifications that are done to process a compound are as follows:

- Identification of active part, i.e., pharmacophore
- Functional group modifications ,i.e., replacement of functional group
- Homologation, i.e., lengthning of carbon side chain from methyl to pentyl to nonyl increases the pharmacological effect whereas further lengthening results in sudden decline in potency.
- Soft drugs are still often confused with prodrugs because they both require metabolic transformations; however, they are conceptual opposites, whereas, prodrugs are pharmacologically inactive and are converted by a predictable mechanism to the active drug, soft drugs are active therapeutic agents as such and are designed to undergo a predictable and controllable metabolic deactivation after exerting their desired therapeutic effect.

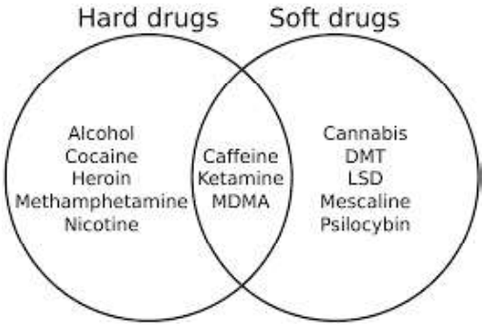

Fig. 1.5 *Examples of Hard Drugs and Soft Drugs*

Check Your Progress

1. Which two countries have shown some evidences of therapeutic use of plant concoctions?
2. Define lead compounds.
3. Name any two soft drugs.

1.3 STRUCTURE ACTIVITY RELATIONSHIP (SAR)

NOTES

In 1868, Crum-Brown and Fraser suspected that the quaternary ammonium character of curare, the name for a variety of South American quaternary alkaloid poisons that cause muscle paralysis known since the sixteenth century, when they were used on arrowheads, may be responsible for its muscular paralytic properties (It blocks the action of the excitatory neurotransmitter acetylcholine at muscle receptors.). From these studies, they concluded that the physiological action of a molecule was function of its chemical constitution. Richardson noted that the hypnotic activity of aliphatic alcohols was a function of their MW. These observations were the basis for the future focus by medicinal chemists on SARs. Drugs can be classified as being structurally specific or structurally nonspecific. Structurally specific drugs act at particular sites, such as a receptor or enzyme. Their activity and potency are very susceptible to changes in chemical structure; molecules with similar biological activities tend to have common structural features. Structurally nonspecific drugs does not have specific action site and have reduced potency. Similar biological activities may occur with different types of structures. Examples of these drugs are sedatives, anesthetics, hypnotics and many antiseptics and disinfectants. Even though only a part of the molecule may be associated with its activity, there is a multitude of molecular modifications that could be made. The hallmark of SAR studies is the synthesis of numerous analogs of the lead compound and their testing to determine the effect of structure on potency for a particular activity.

1.4 FACTORS AFFECTING BIOACTIVITY

There are multiple factors that influence the bioactivity of the drug. These factors may have favourable or adverse effects on human body.

1.4.1 Resonance

Resonance refers to the state of molecule when it has delocalised set of electrons and hence; it has more than one structure to explain its existence. Drug complexes that exhibit resonance will have its bioactivity reduced or enhanced by adjacent functional groups.

Example– Penicillin V has better bioavailability then Penicillin G as ether oxygen on Penicillin V is electron donating group and donates electrons via resonance whereas it is absent in Penicillin G.

1.4.2 Inductive Effect

Inductive effect is the ability of a compound to donate or withdraw electrons from adjacent atoms or functional groups. As inductive effect affects the acidity or basicity of a chemical species which can lead to enhanced or reduced action of the drug. For example in case of Penicillin V have better availability because it has electron withdrawing effect.

1.4.3 Isosterism

The term 'isosterism' is used to define the molecules or ions which have same number of atoms and valence electrons. Nitrogen, carbon monoxide and the cyanide ion are isosteric molecules; their electronic Lewis structures are identical.

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:N:::N: :C:::O: :C:::N:

In general, isosteric molecules have the same shape. This is a consequence of their identical electron arrangements.

When this term is used in field of medicinal chemistry it is referred as bio-isosterism.

1.4.4 Bio-Isosterism

The term 'bioisosterism' was given by Harris L. Friedman and further explain by Alfred Burger. Bioisosteres are compounds that have similar physical or chemical properties and have related molecular shapes following which they must produce similar biological properties.

- In 1919, Langmuir gave the concept of isosterism.
- In 1925, Grimm proposed hydride displacement law.
- Later, Erlenmeyer broaden the concept of bioisosteres as atom science or molecules which were considered to have identical electron arrangement.

Bioisosteric modifications can have the following effects on a compound:

- Structural changes like size shape polar eyes ability and hydrogen bonding can be affected.
- Receptor interactions
- Pharmacokinetics
- Metabolism

1.4.5 Spatial Considerations

Spatial consideration refers to any kind of change in stereospecificity that will affect its activity. The two kind of isomers are as follows:

- **Optical isomers**: Enantiomers with the same physical properties. For example, (R)-(+)-Thalidomide is a sedative whereas (S)-(-)-Thalidomide is a teratogen.
- **Geometric isomers**: Enantiomers with the different physical properties. For example, cisplatin is an effective anti-cancer drug, whereas transplantin is not effective at all.

Check Your Progress

4. Who gave the term 'bioisosterism'?
5. What is inductive effect?
6. Write the two types of isomers with examples of each.

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1.5 THEORIES OF DRUG ACTIVITY

In recent times, many theories were proposed to observe the physiological response of a drug when it interacts with its target in human body. These theories were developed and overtime it was concluded that the action of drug is determined by the rate of drug receptor combination rather than the percentage of drug receptor interaction. The theories suggested are described below.

1.5.1 Occupancy Theory

This theory was proposed by Gaddam and Clark which stated that intensity of the pharmacological effects is directly proportional to the number of receptors occupied by the drug. The drug reacts only till it is combined with the receptor. Once, it gets dissociated the response stops. This theory was not able to justify the agonists that don't produce maximum response. Also, it doesn't talk about partial agonists and inverse agonists.

To further relate this theory with partial agonist; Ariens and Stephenson modified it. They explain that interaction of drug with receptor can be done in the following two steps:

1. Formation of complex between drug and receptor which was termed as affinity
2. Initiation of responds, i.e., biological effects of the drug which Ariens called intrinsic activity whereas Stephenson termed it as efficacy

When this theory was proposed initially by Gaddam and Clark they assumed efficacy as constant. Hence, the modified occupancy theory was able to explain the response of partial agonists and inverse agonists. But still the modified version couldn't explain that why different types of drugs respond in different ways even when occupying same receptor.

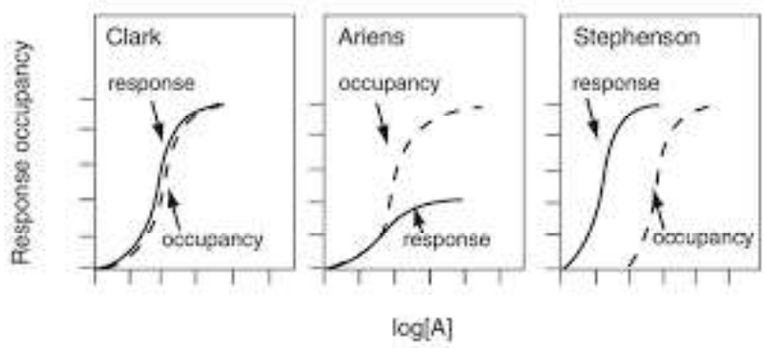

Fig. 1.6 *Occupancy Theory*

1.5.2 Rate Theory

This theory was developed as an alternative for occupancy theory by Paton. It stated that activation of receptors is proportional to the total number of interactions of the drug with its receptor per unit time. According to this theory, the range for which receptor gets occupied determines whether a molecule is an agonists, agonists

and inverse agonists.

- In case of agonists; the rate of association and dissociation will be fast.
- In case of antagonists; the rate of association will be fast, and dissociation will be slow.
- In case of partial agonists; the rate of dissociation will be intermediate.

The occupancy and rate theory coincides when a reaction is at equilibrium state. Again, same as occupancy theory, rate theory was also not able to justify why different types of drugs respond in different ways even when occupying same receptor.

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1.5.3 Induced Fit Theory

Originally, this theory was proposed by Koshland for the interaction of substrates with enzymes but it could also be used to understand the interaction between drug and receptor. This theory stated that to combine with drug it is not necessary that the confirmation of the receptor should be appropriate. When drug advances toward receptors, some conformational changes are observed which orients the necessary binding sites. This conformational change is responsible for biological response. The receptor (enzyme) was reported as elastic and can retain its shape once the drug dissociates. It isn't necessary that receptor will undergo conformational change rather the drug may also have the following conformational changes:

- Agonists induces conformational change and gives response.
- Antagonists doesn't induce conformational change and hence no response.
- Partial agonists induces partial conformational change and gives partial response.

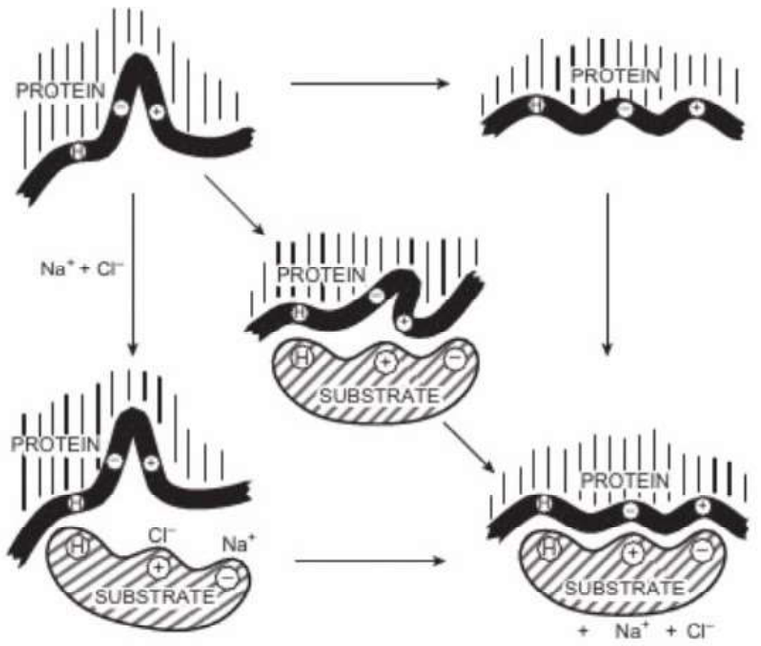

Fig. 1.7 *Schematic of the induced-fit theory. Koshland, Jr., D. E., and Neet, K. E., Annu. Rev. Biochem., Vol. 37, 1968. Annual Review of Biochemistry by Annual Reviews. Reproduced with permission of Annual Reviews via Copyright Clearance Center, 2013*

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Check Your Progress

7. Who proposed occupancy theory?
8. Which theory was developed as an alternate for occupancy theory?
9. What relationship can be studied by induced fit theory?

1.6 QUANTITATIVE STRUCTURE ACTIVITY RELATIONSHIP (QSAR)

Quantitative structure activity relationship is a computational method for drug modelling that reveals the relationship between biological activities and structural properties of prospective chemical compound for a drug. It has become one of the key tool in discovery of novel drugs but it has its own limitations.

Structural properties refer to physicochemical properties that are as follows:

- Lipophilicity
- Partition coefficient
- Electronic ionization constants
- Steric, shelton and surface activity parameters
- Redox potentials

Biological activities refer to pharmacokinetics properties that are as follows:

- Absorption
- Distribution
- Metabolism
- Excretion
- Toxicity

1.6.1 History and Development of QSAR

Let us study the history of QSAR in detail.

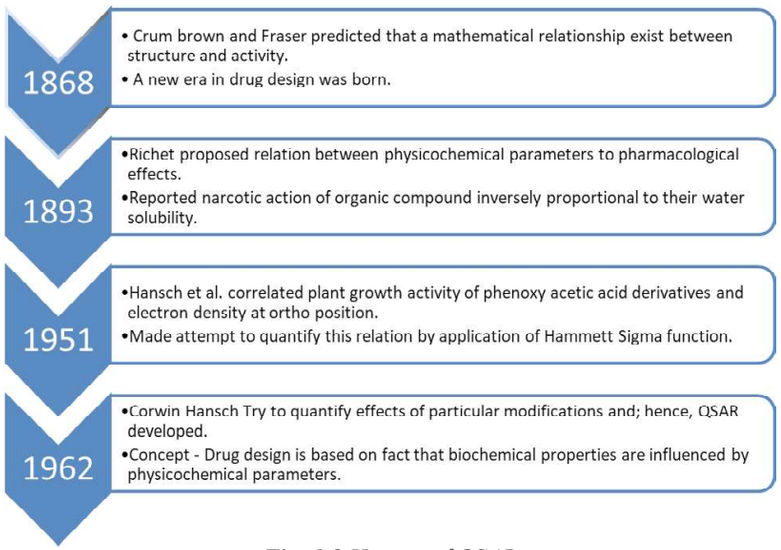

Fig. 1.8 *History of QSAR*

Objectives of QSAR

Some of the common objectives of QSAR are as follows:

- Diagnosis of mechanism
- Prediction of activity
- Optimization of activity
- Reduction and replacement of animals

Steps involved in a QSAR study

Follow the given steps in a QSAR study:

1. Select a series of biologically active analogues with their biological activity.
2. Calculate various physicochemical parameters.
3. Determine correlation matrix between various physicochemical parameters and biological activity.
4. Generate QSAR equation. Prediction of biological activity.

Fig. 1.9 *Steps involved in a QSAR Study*

1.7 CONCEPTS OF DRUG RECEPTORS

In 1905, John Langley proposed that so-called receptive substances in the body could accept either a stimulating compound, which would cause a biological response, or a non-stimulating compound, which would prevent a biological response. Receptor sites usually take the form of pockets, grooves or other cavities in the surface of certain proteins and glycoproteins in the living organism.

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1.7.1 Elementary Treatment of Drug Receptor Interactions

Let us study various drug receptor interactions.

- **Ligand:** It is any molecule which attaches selectively to particular receptor.
- **Affinity:** It is the capability of drug to bind to the receptor and form receptor complex.
- **Intrinsic activity:** It is the ability of the drug to trigger the pharmacological response after forming complex

Check Your Progress

10. Define QSAR.
11. What is the first step in a QSAR study?
12. What do you understand by a ligand?

1.8 PHYSICOCHEMICAL PARAMETERS

Let us study various physicochemical parameters in detail.

1.8.1 Lipophilicity

Hansch proposed that like resonance and inductive effect lipophilicity should be linearly related to biological activity. Lipophilicity refers to the affinity of a drug for a lipid surrounding. It has become one of the critical parameters in developing drugs. A compound with good lipophilicity can be suitable candidate for lipid-based formulations. Correlation reported by Richet, Overton and Meyer between the lipid solubility and biological activity made Hansch conclude it as an important factor.

As a measure of lipophilicity, Hansch Proposed partition coefficient, P.

$$P = \frac{Compound\ (oct)}{Compound\ (aq)(1-\alpha)}$$

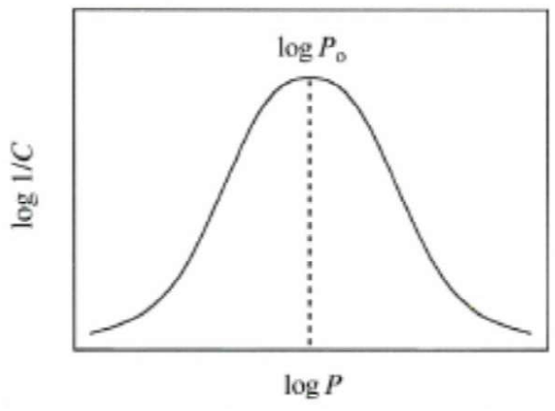

Fig. 1.10 *Effect of log P on Biological Response*

(P is the partition coefficient, and C is the concentration of the compound required to produce a standard biological effect. Log P o is the optimal log P for biological activity.)

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1.8.2 Partition Coefficient

As a measure of lipophilicity, Hansch proposed partition coefficient, P.

$$P = \frac{Compound\ \ (oct)}{Compound\ \ (aq)\,(1-\alpha)}$$

It is affected by factors, such as:

- pH
- Surfactant
- Complexation
- Cosolvents

1.8.3 Electronic Ionization Constants

It is the ratio of products and reactants raised to appropriate stoichiometric powers or the ratio between the product of concentration and reactant. The degree of ionization (pKa) of a drug is a unique physicochemical property that controls its ionization state when in solution. If the drug's pKa is the same as the pH of the solution it is dissolved in, then 50% of the drug exists ionized and 50% exists nonionized.

1.8.4 Steric, Shelton and Surface Activity Parameters

Surfactant is defined as a material that can reduce the surface tension of water at very low concentration.

Surface active agents affect the drug absorption which depends on the following:

- Chemical nature of a surfactant
- Concentration of a surfactant
- Effect of a surfactant on biological membrane and the micelle formation

In lower concentration of a surfactant enhanced the rate of absorption because amphiphilies reduce the surface tension and better absorption. On the other hand, in higher concentration of surfactant, the rate of absorption is reduced.

Some of the common applications are as follows:

- Antihelmentic activity of hexylresorcinol
- Bactericidal activity of cationic quaternary ammonium compounds
- Bactericidal activity of aliphatic alcohols
- Disinfectant action of phenol and cresol
- Bile salt solutions of approximately physiological concentration greatly enhance the dissolution rate of poorly water soluble drugs like grasiofulvin, hexestrol by micellar solubilization effect.

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1.8.5 Redox Potentials

It is the tendency of compound to donate or receive electrons. For example, riboflavin with redox potential of -0.185 V shows its effect on human body whereas dichlororiboflavin with redox potential of -0.095 V can't be used as a therapeutic.

1.9 ANALYTICAL ANALYSIS

Let us study two analysis, namely Free-Wilson analysis and Hansch analysis and their relationship with each other in detail.

1.9.1 Free-Wilson Analysis

The Free–Wilson approach depends upon the structure-activity method and is comprised of the various structural fragments which contribute to biological activity. Equation below represents the Free– Wilson approach.

$$BA = + \sum_j ajXj + \mu$$

The presence and absence of a structural feature is denoted by indicator variables. It is found that substituent effects are cumulative and constant toward the de novo approach.

In equation above- BA stands for biological activity;

Xj stands for the j-th substituent, which carries the value of 1 if present and 0 if absent.

The contribution of the j-th substituent to biological activity is represented by aj.

The summation of all activity contributions at each position must equal zero.

This method has the following advantages:

- Such analysis can be conducted to obtain quantitative biological data.
- Physicochemical constants are not required.

This method has the following limitations:

- Nonlinear dependency of activity on substituent properties
- Intramolecular interactions between the substituents are not handled very well
- Extrapolation to substituents outside the study is not feasible
- To explain small number of compounds a very large count of variables is required

1.9.2 Hansch Analysis

Corwin Hansch, the father of QSAR, contributed Hansch analysis by reporting the quantitative correlation between the physicochemical substituent and biological activity of compounds.

The main features of the Hansch group are as follows:

- Hydrophobic substituent constant ð was developed and have similarity with the Hammett equation:

  log P (R- X) = log P (R-H) + π (X)

  P(R-X) and P(R-H) are partition coefficients of R-X and R-H, with R-X indicating a structure derived from R-H by replacing H atom by substituent X; π (X) is the hydrophobic substituent constant, to be defined as the lipophilicity contribution of substituent X to lipophilicity when replacing H by X.

- The multiparameter approach to QSAR can be shown as:

  log (BA) = a log P + bσ + cE_s + d

  The given equation exemplifies a correlation with the three parameters log P, σ, and E_s.

1.9.3 Relationships between Free-Wilson and Hansch Analysis

The Hansch analysis and Free–Wilson analysis have similarities and thus a further approach is based on the contribution of activities on their theoretical consistency and the numerical equivalencies. This is approach is termed the mixed approach and is represented by equation:

$$\log (1 / C) = \sum_i ai + \sum_i ci\varphi i + constant$$

Where, ai = denotes the contribution for each i-th substituent

φi = any physicochemical property of a substituent Xi

Molar refractivity plays a significant role as determinant of modulating ability. On the other hand, molecular weight is a ubiquitous parameter in cross-resistance profiles in case of multidrug-resistance phenomena.

1.10 LD-50 AND ED-50 (MATHEMATICAL DERIVATIONS OF EQUATIONS EXCLUDED)

LD-50 refers to quantity of drug that proof to be lethal dose of toxin. It is the value dosage of substance that is required to kill 50% of test population. This factor is generally used as an indicator for drug toxicity. The test was created by J.W. Trevan in 1927. Limitation of using this factor in approving a drug toxicity is the variability in result due to variation in genetic characteristic of sample population, environmental factors and mode of administration.

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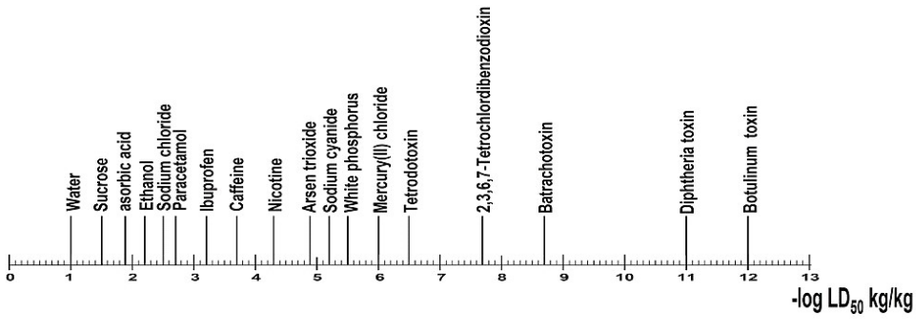

Fig. 1.11 *Poison Scale*

ED-50 refers to quantity of drug required to achieve 50% of desired result in 50% of population. Calculation of 50% desired result is done using dose response curve. It is one of the important factors which are reported to regulatory authorities when a drug is sent for getting approved.

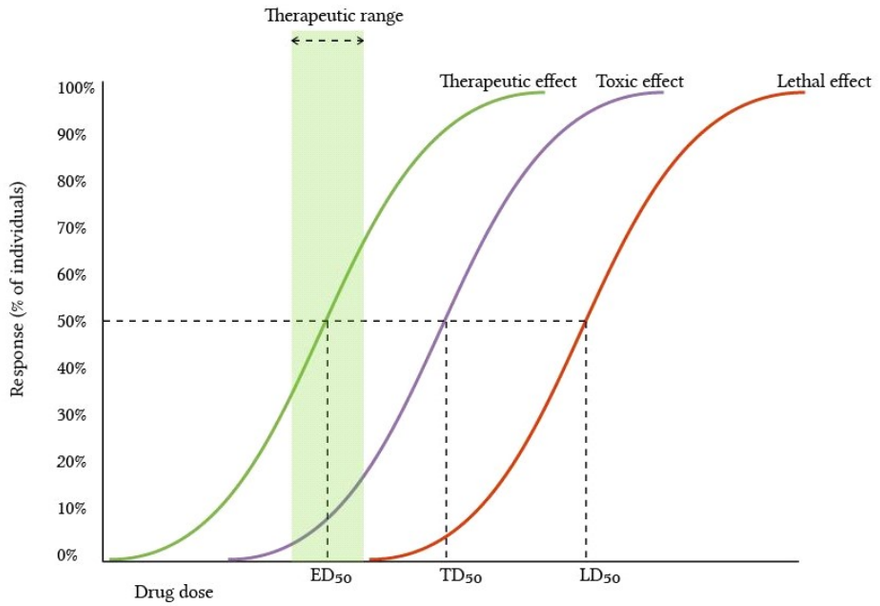

Fig. 1.12 *Effects of LD-50 and ED-50*

Check Your Progress

13. Write the equation representing the Free–Wilson approach.
14. Who is known as the father of QSAR?
15. What does LD-50 refer to?

1.11 ANSWERS TO 'CHECK YOUR PROGRESS'

1. The historical records of countries like China and India have some evidences of therapeutic use of plant concoctions.

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2. A lead compound is a chemical molecule with pharmacological or biological action that is likely to be therapeutically beneficial but has a poor structure that has to be modified to fit better to the target.
3. Cannibis and DMT are the two soft drugs.
4. The term 'bioisosterism' was given by Harris L. Friedman and further explain by Alfred Burger.
5. Inductive effect is the ability of a compound to donate or withdraw electrons from adjacent atoms or functional groups.
6. Optical isomers: These are enantiomers with the same physical properties. For example, (R)-(+)-Thalidomide is a sedative whereas (S)-(-)-Thalidomide is a teratogen.

   Geometric isomers: These are enantiomers with the different physical properties. For example, cisplatin is an effective anti-cancer drug whereas transplantin is not effective at all.
7. This theory was proposed by Gaddam and Clark which stated that intensity of the pharmacological effects is directly proportional to the number of receptors occupied by the drug.
8. Rate theory was developed as an alternative for occupancy theory by Paton.
9. Induced fit theory was proposed by Koshland for the interaction of substrates with enzymes but it could also be used to understand the interaction between drug and receptor.
10. Quantitative structure activity relationship is a computational method for drug modelling that reveals the relationship between biological activities and structural properties of prospective chemical compound for a drug.
11. The first step involves the selection of a series of biologically active analogues with their biological activity.
12. It is any molecule which attaches selectively to particular receptor.
13. The equation below represents the Free–Wilson approach:

    $BA = \sum_j ajXj + \mu$
14. Corwin Hansch is known as the father of QSAR.
15. LD-50 refers to quantity of drug that proof to be lethal dose of toxin.

1.12 SUMMARY

- Drug designing projects have always been the biggest challenge for the pharmaceutical companies. The probable statistics suggest that human body has about 35000 open reading frames in its genome which generate approx. 500,000 proteins.
- In 1928 the accidental discovery of penicillin by Alexander Fleming vasaki achievement. Thereafter a new era of pharmaceuticals started.
- The major steps include in drug design preclinical development, clinical development and regulatory approval.

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- Bioinformatics have played a major role in lead identification and optimization.
- Prodrugs are pharmacologically inactive and are converted by a predictable mechanism to the active drug.
- Soft drugs are active therapeutic agents as such and are designed to undergo a predictable and controllable metabolic deactivation after exerting their desired therapeutic effect.
- Factors that influence the bioactivity of the drug are resonance, inductive effect, isosterism, bio-isosterism and spatial considerations.
- Occupancy theory was proposed by Gaddam and Clark which stated that intensity of the pharmacological effects is directly proportional to the number of receptors occupied by the drug.
- Rate theory was developed as an alternative for occupancy theory by Paton. It stated that activation of receptors is proportional to the total number of interactions of the drug with its receptor per unit time.
- Induced fit theory was proposed by Koshland and stated that to combine with drug it is not necessary that the confirmation of the receptor should be appropriate.
- Quantitative structure activity relationship is a computational method for drug modelling that reveals the relationship between biological activities and structural properties of prospective chemical compound for a drug.
- Receptor sites usually take the form of pockets, grooves or other cavities in the surface of certain proteins and glycoproteins in the living organism.
- Lipophilicity refers to the affinity of a drug for a lipid surrounding. It has become one of the critical parameters in developing drugs.
- As a measure of lipophilicity, Hansch proposed partition coefficient, P.

$$P = \frac{Compound\ (oct)}{Compound\ (aq)\ (1 - \alpha)}$$

- Surfactant is defined as a material that can reduce the surface tension of water at very low concentration.
- Redox potentials refer to the tendency of compound to donate or receive electrons.
- The Free–Wilson approach depends upon the structure-activity method and is comprised of the various structural fragments which contribute to biological activity.
- Corwin Hansch, the father of QSAR, contributed Hansch analysis by reporting the quantitative correlation between the physicochemical substituent and biological activity of compounds.
- LD-50 refers to quantity of drug that proof to be lethal dose of toxin. It is the value dosage of substance that is required to kill 50% of test population.
- ED-50 refers to quantity of drug required to achieve 50% of desired result in 50% of population.

1.13 KEY TERMS

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- **Drug:** It is a chemical substance that causes a change in an organism's physiology or psychology when consumed.
- **Lead Compound:** It refers to a small molecule having pharmacological or biochemical features that suggest that it can be used for drug development.
- **Prodrug:** It is a medication or compound that, after administration, is metabolized into a pharmacologically active drug.
- **Soft Drug:** It is a drug that is easily metabolized by the body into inactive, nontoxic metabolites.
- **Isosterism:** This term refers to the molecules or ions which have same number of atoms and valence electrons.
- **Quantitative Structure Activity Relationships (QSAR):** The term refers to mathematical relationships that connect chemical structure and pharmacological activity in a quantitative manner for a series of compounds.
- **Lipophilocity:** The term refers to the capacity of a chemical substance to dissolve in fats, oils, lipids, and non-polar solvents.
- **Free-Wilson Analysis:** In correlations with biological activity, it is a regression technique that uses the presence or absence of substituents or groups as the only molecular descriptors.
- **Hansh Analysis:** It is the study of the quantitative link between the biological activity of a series of compounds and their physicochemical substituents or global factors representing hydrophobic, electronic, steric, and other effects.
- **Toxicity:** It refers to the quantity of a compound which when administered can harm the body.

1.14 SELF-ASSESSMENT QUESTIONS AND EXERCISES

Short-Answer Questions

1. Differentiate between lead compound and lead modification.
2. How does a soft drug become active?
3. What are the effects of the bioisosteric modifications on a compound?
4. Write a short note on physicochemical parameters.
5. How does redox potential affect human body?

Long-Answer Questions

1. Analyse the procedures followed in drug design in detail.
2. Discuss the factors affecting bioactivity.
3. Explain various theories of drug activity with examples.

4. Give the detailed account of the history and development of QSAR.
5. Evaluate the relationships between Free-Wilson and Hansch analysis.

NOTES

1.15 FURTHER READING

Lednicer, D. 2015. *Antineoplastic Drugs: Organic Syntheses*. Germany: Wiley.

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UNIT 2 PHARMACOKINETICS AND PHARMACODYNAMICS

Structure

2.0 INTRODUCTION

For investigating disposition profiles and pharmacological efficacy off drugs in body, pharmacokinetics and pharmacodynamics have become the important factors in Pharmaceutical industry. The purpose of pharmacokinetics is to study ADME processes of drugs. The data interpretation using these factors helps us to know that how a drug would react when enters and administered in human body. Pharmacodynamics places specific accentuation on portion reaction connections, that is, the connections between drug fixation and impact. It materialized following the emergence of formalized drug medications during clinical trials. After the introduction how the foreign material reacts with the internal body environment and what are the responses made by the body metabolism; this is called pharmacokinetics. The compound of interest may be from any stream, varying from pharmaceutical drugs, pesticides, antibiotics, stimulants, food additives, and even cosmetics. How an organism is affecting the drug entered due to its body, is the basis of Pharmacokinetics. This unit will introduce the concepts of drug absorption, disposition, and elimination using pharmacokinetics. It will discuss the pharmacodynamics along with the elementary treatment of enzyme stimulation. In addition, it will describe the significance of drug metabolism in medicinal chemistry.

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2.1 OBJECTIVES

After going through this unit you will be able to:

- Explain pharmacokinetics and pharmacodynamics
- Discuss the process of enzyme stimulation, drug absorption and drug disposition
- Describe the process of drug inhibition
- Discuss therapeutical applications of pharmacokinetics
- Analyse the uses of pharmacokinetics in drug development process
- Evaluate the uses of drug metabolism in medicinal chemistry

2.2 PHARMACOKINETICS

It is a branch of pharmacology dedicated to determine the fate of substances administered to a living organism. The way in which the body affects a specific xenobiotic/chemical after administration through the mechanisms of absorption and distribution, as well as the metabolic changes of the substance in the body and the effects and routes of excretion of the metabolites of the drug can be studied in pharmacokinetics. Let us study the terms related to pharmacokinetics

2.2.1 Introduction to Drug Absorption, Disposition, Elimination using Pharmacokinetics

Let us study the given terms in detail.

Drug absorption

Drug absorption in pharmacokinetics is concerned with the journey of foreign drug particles in the living body. The drug absorption in our body takes place through two basic routes:

- Oral drug delivery
- Intravenous drug delivery

The classification of the route of the Drug Administration is based on the location. Moreover, the further classification may also be based on the site of Drug Action. It may be classified into the following pathways:

- Topical or local action
- Enteral action
- Parenteral action

Some other ways of drug delivery transfer involve:

- Intravenous
- Intramuscular
- Enteral
- Inhalation

Among these pathways, Inhalation is the best route of delivery into our body. Intravascular administration lacks to involve the process of drug absorption. One of the major factors that determine the route is the type of drug needed. For example:

- Capsules or tablets in oral administration
- Solution in intravenous administration

Role of drug absorption

Drug absorption may be defined as the study of observing the flow of drugs after being introduced into the body, from its pharmaceutical form into the bloodstream.

The basic and primary step involved in drug absorption is'dissolution'. Dissolution can be defined as the process of conversion of the compound into its soluble form. The process of Dissolution is inevitably important because it is the basis of determining its bioavailability and therapeutic effectiveness.There is a term given to the group of foreign drugs or compounds introduced into the living body for their action, these foreign chemical particles are commonly referred to as 'xenobiotics'. Based on the researches and calculations the formula for the Absorption rate constant is defined as:

ARC = Absorption rate/amount of drug remained to be absorbed and the formula for finding the bioavailability of a drug

BA = Amount of drug absorbed/drug dose

The most important aspect in the field of pharmacokinetics is Drug Absorption. It is considered the basic principle of pharmacokinetic studies. According to the pharmaceutical perspective, Drug Absorption is responsible for the transportation of the drug from its unmetabolized form to its metabolized form. Many factors too affect the process of Drug Absorption in the study of pharmacokinetics. It includes:

- Drug specific factors
- Patient-specific factors

Drug disposition

Drug disposition is the area of pharmacology specifically clinical pharmacology. It deals with the fate of a drug. It is the knowledge used for deciding the fate of a drug. The entry and exit of drug delivery and concentration change are described under drug disposition. There are basic processes of drug disposition. They are:

- Drug absorption
- Drug distribution
- Drug metabolism
- Drug excretion

Based on the definition and terms the four basic phases have been given an abbreviated term as ADME. In the pre-clinical and clinical spheres of pharmaceuticals, the concept of drug disposition plays an evitable role in predicting various pharmakinetical parameters. They are:

- Drug interaction
- Drug potential

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- Drug evaluation
- Pharmacokinetic variability

These parameters are very important in deciding the clinical trials through the application of drug disposition.

Drug distribution

Drug distribution is the phase of pharmacokinetics which is a branch of pharmacology. It helps in highlighting the reversible pathway of a drug from one site to other inside our body. After a drug enters the human body for action, the steps of drug disposition begin. The drug enters into the blood circulation by the name of drug absorption. After this step, it gets distributed into different body parts and tissues. This mixing of the drug into the body fluid, this step is called drug distribution.

Based on the drug type and chemistry of our body tissues the dosage of the drug is different for our different body organs and tissues. The basis of this difference is that drug remains in different organs types for a different period.

According to Pascuzzo, several factors are affecting the process of drug distribution inside our bodies. Some of them are as follows:

- **Physical volume of an organism:** When any drug enters the body fluid it acts as a solute for the body fluid for the body tissues acting as a solvent. The chemical nature of the drug is directly specified to the body's differentiation type.
- **Removal Rate:** It is calculated by the proportion of the drug that is removed from circulation by each organ after the drug has been delivered to the organ by the circulating blood supply.
- **Degree to which drug binds with plasma proteins or tissues:** A drug and plasma protein binding condition is rarely specific. The situation is completely labile and reversible.

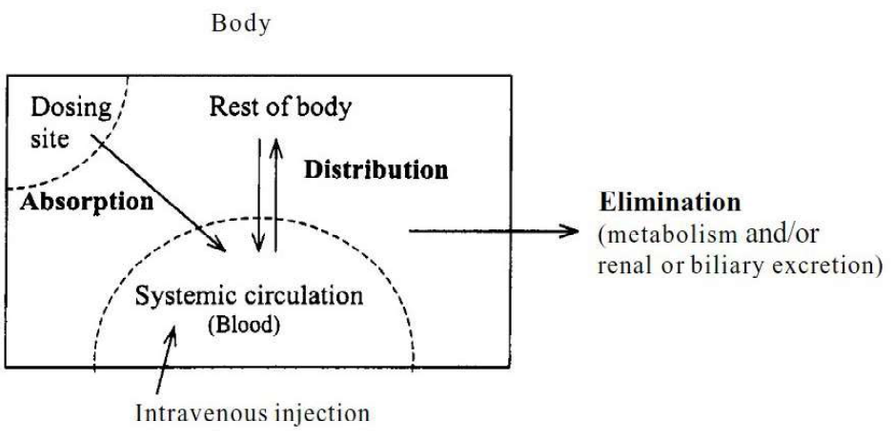

Fig. 2.1 *Drug Distribution*

2.2.2 Important Pharmacokinetic Parameters in Defining Drug Disposition and in Therapeutics

The pharmacokinetic characteristics can be quantitatively expressed by its parameters, such as:

- Elimination rate constant (K)
- Half-life (t 1/2)
- Apparent volume of distribution (Vd)
- Total clearance rate (CL)

Pharmacokinetic information is required to optimize the pharmacodynamic response. The primary pharmacokinetic disposition parameter is clearance. Knowledge of this value and its major constituent parts, i.e. fractional renal and hepatic elimination, allows the clinician to prescribe the correct dosage regimen to obtain a mean therapeutic concentration and to predict the effects of various disease states. The other primary disposition parameter, volume of distribution at steady-state, may also vary with changes in physiologic and pathologic conditions. Both clearance and volume of distribution as well as the correlation of concentration measurements with pharmacodynamics would be expected to vary with changes in plasma protein binding.

2.2.3 Uses of Pharmacokinetics in Drug Development Process

The uses of pharmacokinetics (PK) in drug discovery are to:

- Support the optimisation of the absorption, distribution, metabolism and excretion (ADME) properties of lead compounds.
- Attain a clinical candidate which achieves a concentration-time profile in the body that is adequate for the desired efficacy and safety profile.

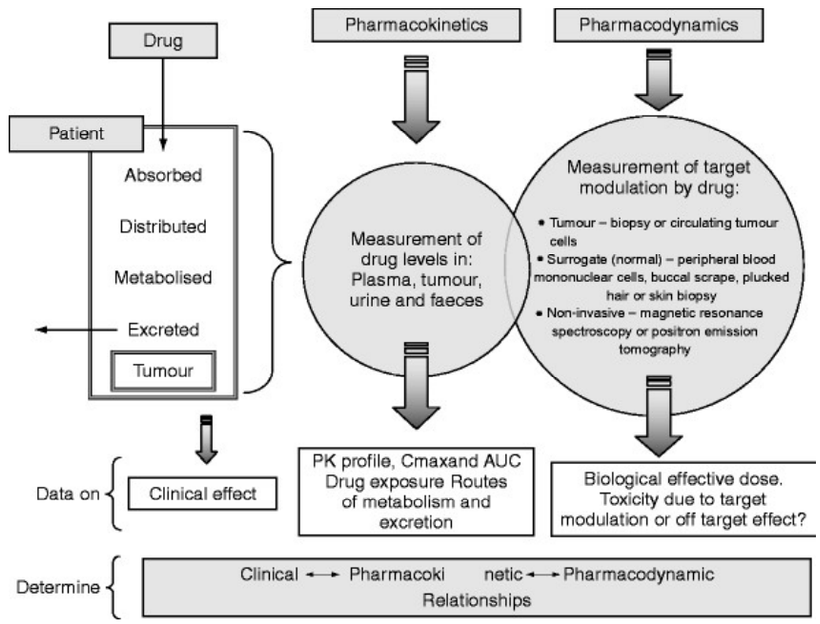

Fig. 2.2 *Drug Development Process*

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Check Your Progress

1. List the two pathways of drug absorption in our body.
2. What is drug absorption?
3. What are the basic processes of drug disposition?

2.3 PHARMACODYNAMICS

The study of the biochemical and physiologic effects of medications is known as pharmacodynamics, especially pharmaceutical drugs. In other words, it is the study of how a drug affects an organism.

2.3.1 Elementary Treatment of Enzyme Stimulation

Taking one drug can speed up the metabolism of another. Animal experiments show that this is a result of the drug's ability to induce the synthesis of drug metabolizing enzymes in liver microsomes. This effect is of great importance in pharmacological and toxicological studies in animals, and recent studies suggest that it may explain the changes in therapeutic response observed in some patients when multiple drugs are administered simultaneously. Environmental substances such as the pesticides chlordane and DDT have been shown to stimulate drug-metabolizing enzymes in the liver of animals, but the significance of these observations in humans is unknown. Drugs that stimulate drug metabolism also increase the hydroxylation of testosterone, estradiol, progesterone and cortisol by enzymes in the liver microsomes. Further studies are needed to establish the physiological significance of this drug interaction in steroid metabolism.

One drug may potentiate and prolong its pharmacological action by inhibiting the metabolism of another. This effect is well documented in animals, but a recent report suggests it may be important in humans as well. For example, the action of coumarin anticoagulants may be enhanced by the administration of certain drugs that inhibit metabolism. Monoamine oxidase inhibitors block the metabolism of certain sympathomimetic amines that can cause serious side effects. Thus, hypertensive crises were observed in patients treated with monoamine oxidase inhibitors who ate cheese with a high tyramine content.

2.3.2 Enzyme Inhibition

Enzyme inhibitors are molecules that disrupt the normal pathway between enzymes and substrates. Enzyme inhibitors can be either competitive or non-competitive, depending on the mechanism of action.

Types of enzyme inhibition

Enzymes Inhibitors prevent the formation of enzyme substrate complexes and therefore prevent the formation of products. Inhibition of enzymes can be either reversible or irreversible, depending on the particular effect of the inhibitor used.

Normal enzyme reaction

In a normal reaction, the substrate binds to the enzyme (via the active site) to form an enzyme-substrate complex. The shape and properties of the substrate and active site are complementary, leading to enzyme substrate specificity. When binding occurs, the active site undergoes a conformational change to optimally interact with the substrate (induced adaptation). This change in conformation destabilizes the chemical bonds in the substrate and reduces the activation energy. As a result of enzymatic interactions, the substrate is converted to product at an accelerated rate.

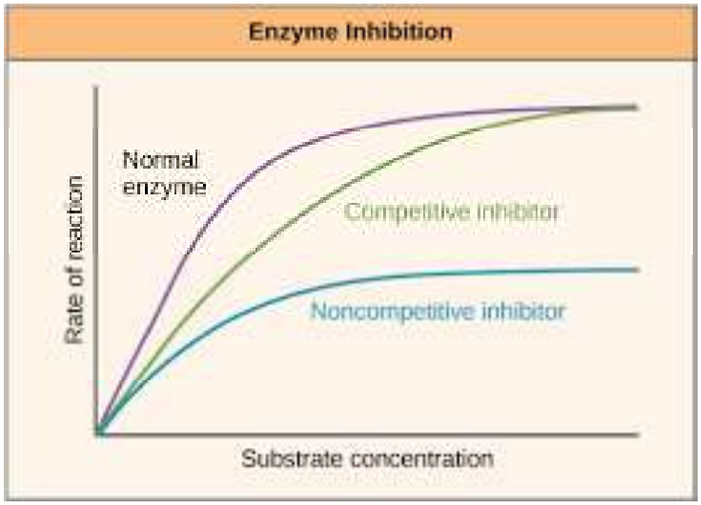

Fig. 2.3 *Enzyme Inhibition*

Competitive inhibition

In competitive inhibition, molecules other than the substrate bind to the active site of the enzyme. Molecules (inhibitors) are structurally and chemically similar to substrates (and thus can bind to the active center). Competitive inhibitors block the active center and thus prevent substrate binding Inhibitors compete with the substrate, so increasing the substrate concentration can reduce its effectiveness.

Non-competitive inhibition

In non-competitive inhibition, the molecule binds to a site other than the active site (allosteric site). Inhibitor binding to the allosteric center causes a conformational change in the active center of the enzyme. As a result of this change, the active center and substrate no longer share specificity. This means that the substrate cannot bind. Inhibitors do not compete directly with the substrate, so increasing substrate levels cannot diminish the effectiveness of the inhibitor.

2.3.3 Sulphonamides

A sulfate-related group of antibiotics used to treat bacterial and some fungal infections. Examples of sulfonamides are sulfadiazine, sulfamethizole (trade name: Thiosulfil Forte), sulfamethoxazole (gantanol), sulfasalazine (azulfidin), sulfisoxazole (gantricin), and three sulfonamides. Various high concentration combinations of

sulfa drugs kill bacteria and fungi by destroying cell metabolism. They were the pre-miracle remedies for penicillin and are still used today. Treatment of urinary tract infections is one of the most common uses because sulfonamides concentrate in the urine before they are excreted.

Sulfonamides can have potentially dangerous interactions with prescription and over-the-counter medications (including PABA sunscreens) and are not suitable for patients with certain health conditions. Many people are allergic to sulfonamides. Before taking sulfonamides, make sure your doctor knows about the other medications you are taking, drug allergies, and your complete medical history.

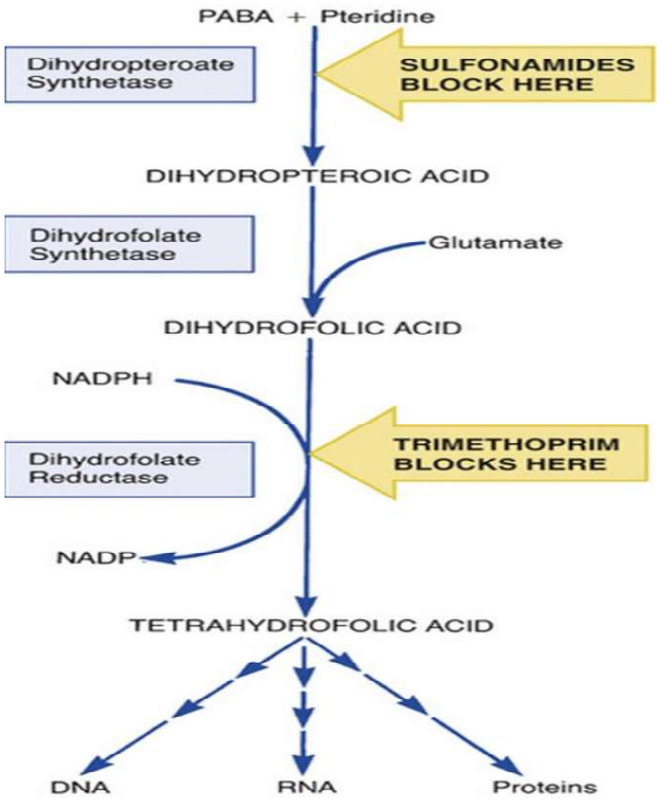

Fig. 2.4 *Sulphonamides*

2.3.4 Membrane Active Drugs

There are antibiotics that disorder the cytoplasmic membrane, which leads to the escape of intracellular components, especially small molecules. The result is a quick killing effect. Such groups can be classified as macrocyclic polypeptides. Strictly speaking, these bacterial products are not proteins. This is because some amino acids have a d-configuration and others are never found in proteins. For example, á, ã-diaminobutyric acid (DAB).

Tyrotricin, first tested in 1944, was obtained from Bacillus Brevis. It is actually a mixture of polypeptides, two of which, tyrocidine and gramicidin, have been crystallized and sequenced. They are two large groups of cyclic peptide antibiotics called tyrosidine. Their effectiveness is primarily against Gram-positive bacteria. Due to toxicity such as B. Erythrocyte lysis, application is limited to topical

application and throat tablets when administered systemically. Another group of cyclic peptide antibiotics developed by several strains of

Bacillus polymixa is polymyxin. They contain a ring portion of 7 amino acids with high DAB content and a side chain ending in a methylalkanoic acid chain with a length of 8-10 carbon atoms. Polymyxin B, consisting of B | Polymyxin E consisting of B2 (aerosporin) and colistin and E2 are clinically interesting because they are somewhat less toxic than most others in this group. Polymyxin is more effective against Gram-negative bacteria, even toxic Pseudomonas aeruginosa, which is highly resistant to most other antibiotics.

The mechanism of action initially involves binding to the plasma membrane. In Gram-negative bacteria, the drug may need to break first or somehow cross this barrier, as it is protected by a unique structure that includes the adventitia. As a result, the integrity of the membrane is destroyed and phosphate leakage is caused.

Check Your Progress

4. Define pharmacodynamics.
5. What is the use of a sulfate-related group of antibiotics?
6. Why are macrocyclic polypeptides not proteins?

2.4 DRUG METABOLISM

Drugs can be metabolized by the following processes:

- oxidation
- reduction
- hydrolysis
- hydration
- conjugation
- condensation
- isomerization

The purpose is to promote drug elimination. Enzymes involved in metabolism are found in many tissues, but are generally more concentrated in the liver. The rate of drug metabolism varies from patient to patient. Some patients metabolize the drug so quickly that therapeutically effective blood and tissue levels are not achieved. In others, metabolism is so slow that it is toxic at normal doses. The individual metabolic rate of a drug is affected by genetic factors, coexisting diseases (especially chronic liver disease and progressive heart failure), and drug interactions (especially those that induce or inhibit metabolism).

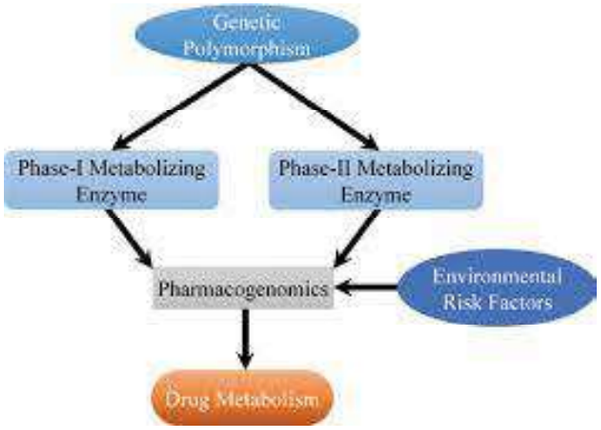

Fig. 2.5 *Drug Metabolism*

2.4.1 Xenobiotics

Xenobiotic is a term used to describe chemicals that are not life-threatening to animals, such as plant ingredients, pharmaceuticals, pesticides, cosmetics, fragrances, fragrances, food additives, industrial chemicals, and environmental pollutants. It is estimated that humans are exposed to 13 million xenobiotic substances in their lifetime.

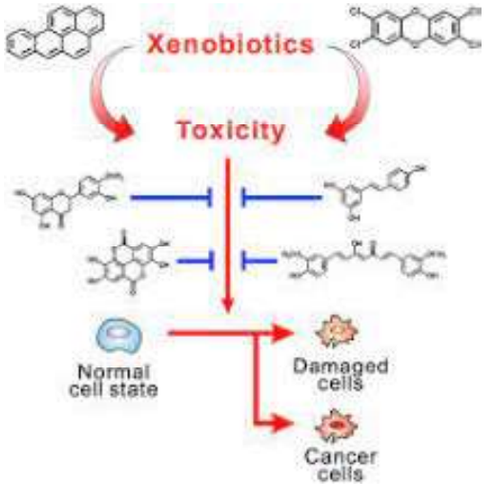

Fig. 2.6 *Xenobiotics*

2.4.2 Biotransformation

Drug biotransformation involves the conversion of lipophilic/hydrophobic drug (to enter cells) into hydrophilic metabolites.

Advantages

Some of the advantages of biotransformation are as follows:

- Termination of drug action - (decreases toxicity)
- Reduced lipophilicity.
- Renal/biliary excretion increases (decreases renal reabs)

Absorbed drugs

Some of the changes are as follows:

- Metabolic changes by enzymes (microsomal, cytoplasmic, mitochondrial)
- Spontaneous molecular rearrangement – Hofmann elimination, i.e., elimination reaction of amine
- Excreted unchanged (highly polar drugs) - aminoglycosides, methotrexate, neostigmine

Consequences

Some of the consequences are as follows:

- Drug inactivation. i.e., inactive or less active propranolol, pentobarbitone, morphine, chloramphenicol, paracetamol, ibuprofen, lignocaine
- Active drug to active metabolite- active metabolite effect is due to parent drug and its active metabolite

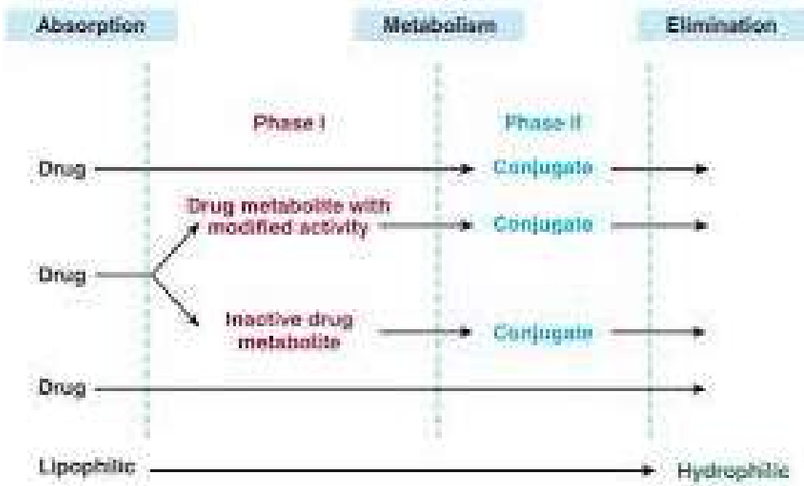

Fig. 2.7 Biotransformation

2.4.3 Significance of Drug Metabolism in Medicinal Chemistry

Drug metabolism involves the enzymatic conversion of therapeutically important chemical species to a new molecule inside the human body. The process may result in pharmacologically active, inactive, or toxic metabolite. Drug metabolic process involves two phases, the occurrence of which may vary from compound to compound.

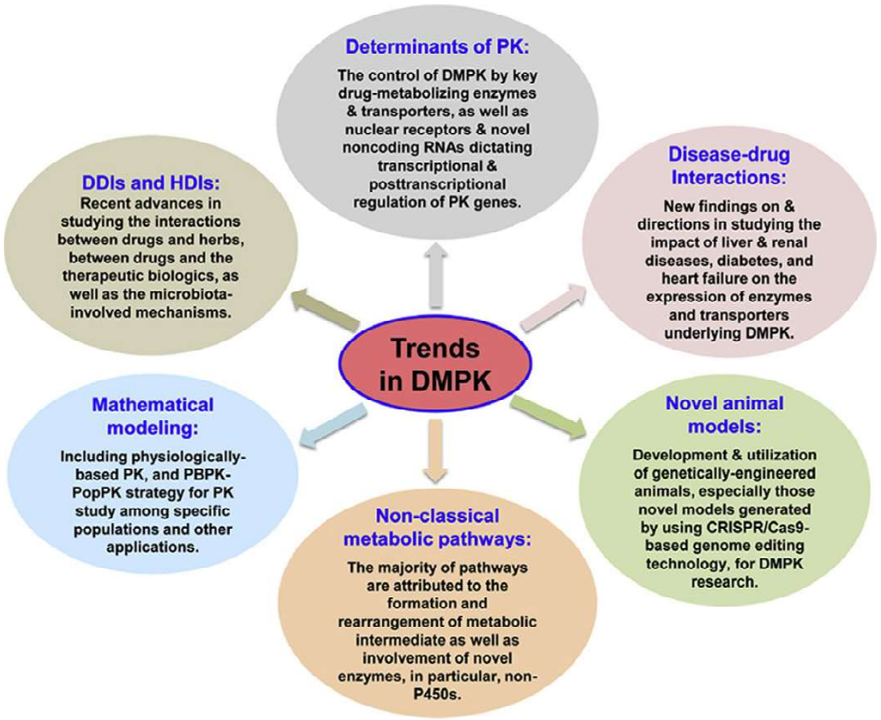

Fig. 2.8 *Trends in Drug Metabolism and Pharmacokinetic (DMPK)*

Check Your Progress

7. Write any two ways to metabolize drugs.
8. Define the term 'xenobiotic'.
9. What is Hofmann elimination?

2.5 ANSWERS TO 'CHECK YOUR PROGRESS'

1. The drug absorption in our body takes place through two basic routes:
   - Oral drug delivery
   - Intravenous drug delivery
2. Drug absorption may be defined as the study of observing the flow of drugs after being introduced into the body, from its pharmaceutical form into the bloodstream.
3. The basic processes of drug disposition are:
   - Drug absorption
   - Drug distribution
   - Drug metabolism
   - Drug excretion
4. The study of the biochemical and physiologic effects of medications is known as pharmacodynamics (especially pharmaceutical drugs).

NOTES

5. A sulfate-related group of antibiotics used to treat bacterial and some fungal infections.
6. This is because some amino acids have a d-configuration and others are never found in proteins. For example, á, ã-diaminobutyric acid (DAB).
7. Drugs can be metabolized by oxidation, reduction, hydrolysis, hydration, conjugation, condensation and isomerization. (Write any two.)
8. Xenobiotic is a term used to describe chemicals that are not life-threatening to animals, such as plant ingredients, pharmaceuticals, pesticides, cosmetics, fragrances, fragrances, food additives, industrial chemicals, and environmental pollutants.
9. Hofmann elimination involves the elimination reaction of amine.

2.6 SUMMARY

- Pharmacokinetics is a branch of pharmacology dedicated to determine the fate of substances administered to a living organism.
- Drug absorption in pharmacokinetics is concerned with the journey of foreign drug particles in the living body.
- Inhalation is the best route of delivery into our body.
- Drug absorption may be defined as the study of observing the flow of drugs after being introduced into the body, from its pharmaceutical form into the bloodstream.
- The basic and primary step involved in drug absorption is 'dissolution'.
- The most important aspect in the field of pharmacokinetics is Drug Absorption.
- Drug disposition is the area of pharmacology specifically clinical pharmacology.
- Drug distribution is the phase of pharmacokinetics which is a branch of pharmacology. It helps in highlighting the reversible pathway of a drug from one site to other inside our body.
- Drugs that stimulate drug metabolism also increase the hydroxylation of testosterone, estradiol, progesterone and cortisol by enzymes in the liver microsomes.
- Enzyme inhibitors are molecules that disrupt the normal pathway between enzymes and substrates.
- Enzymes Inhibitors prevent the formation of enzyme substrate complexes and therefore prevent the formation of products.
- A sulfate-related group of antibiotics used to treat bacterial and some fungal infections.
- They are two large groups of cyclic peptide antibiotics called tyrosidine. Their effectiveness is primarily against Gram-positive bacteria.
- Drugs can be metabolized by the following processes oxidation, reduction, hydrolysis, hydration, conjugation, condensation and isomerization.

- Xenobiotic is a term used to describe chemicals that are not life-threatening to animals, such as plant ingredients, pharmaceuticals, pesticides, cosmetics, fragrances and fragrances.
- Drug biotransformation involves the conversion of lipophilic/hydrophobic drug (to enter cells) into hydrophilic metabolites.
- Drug metabolism involves the enzymatic conversion of therapeutically important chemical species to a new molecule inside the human body.

2.7 KEY TERMS

- **Pharmacokinetics:** It is a branch of pharmacology dedicated to determine the fate of substances administered to a living organism.
- **Drug Absorption:** It is a pharmacokinetic parameter that refers to the way a drug is absorbed from a pharmaceutical formulation into the bloodstream.
- **Drug Metabolism:** It is the term used to describe the biotransformation of pharmaceutical substances in the body so that they can be eliminated more easily.
- **Drug Distribution:** It is a branch of pharmacokinetics which describes the reversible transfer of a drug from one location to another within the body.
- **Drug Excretion:** It is the removal of drugs from the body, either as a metabolite or unchanged drug.
- **Pharmacodynamics:** It is the study of the biochemical and physiologic effects of drugs.
- **Enzyme:** It is a biological molecule that catalyses' a chemical reaction or causes a chemical change in another substance.
- **Enzyme Stimulation:** The enzyme induction effect is the ability of numerous foods or drugs to stimulate the production of drug-metabolizing enzymes in the liver, which may result in increased metabolism of the administered drug as well as other related or even unrelated drugs.
- **Enzyme Inhibition:** It refers to a decrease in enzyme-related processes, enzyme production, or enzyme activity.
- **Sulphonamides:** These are one of the oldest broad-spectrum antimicrobial agents that work by competitively inhibiting bacterial metabolic enzymes needed for bacterial function.
- **Xenobiotics:** These are chemical substances not normally present in the environment of living organisms.
- **Biotransformation:** It means chemical alteration of chemicals such as nutrients, amino acids, toxins, and drugs in the body.

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2.8 SELF-ASSESSMENT QUESTIONS AND EXERCISES

Short-Answer Questions

1. What are the roles of drug absorption?
2. What are the factors affecting the process of drug distribution inside our bodies?
3. How is pharmacokinetics (PK) used in drug discovery?
4. Write a short note on drug disposition.
5. Mention the advantages of biotransformation and its consequences.

Long-Answer Questions

1. Discuss and illustrate pharmacokinetic parameters in defining drug disposition.
2. Explain the different phases of drug disposition.
3. Analyse the broad-spectrum role of pharmacodynamics in the medical industry.
4. Evaluate the mechanism of enzymatic action of drug metabolism inside our body.
5. Describe the process of biotransformation. Also, discuss the factors affecting it.

2.9 FURTHER READING

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UNIT 3 ANTINEOPLASTIC AGENTS AND CARDIOVASCULAR DRUGS

NOTES

Structure

3.0 INTRODUCTION

Antineoplastic agents are drugs used for the treatment of cancer, malignancy, tumour, carcinoma, sarcoma, leukemia, or neoplasm (Greek, neo = new, plasm = formation). Neoplasm is a term used to describe a category of disorders produced by a combination of causes, including chemical substances and radiant light. Cancer is a disease in which cells divide abnormally and uncontrollably, resulting in tumours and invasion of normal organs. Cancer cells frequently break from the main tumour

and travel through the lymphatic system to distant organ locations, where they divide and create secondary tumours (metastasis).

A basic understanding of cardiovascular physiology is key to the comprehension of the conditions and pharmacologic mechanisms. The treatment of patients with inherent or nonheritable cardiac illness remains a crucial challenge for physicians accountable of those usually precarious patients. Cardiovascular drugs are used to treat various heart disease (cardiovascular diseases). These drugs particularly affect blood vessels and heart. This unit will discuss antineoplastic agents and cardiovascular drugs and their synthesis. In addition, it will explain the role of these agents in treatment of cancer along with the recent development in field of antineoplastic and cardiovascular drugs. Moreover, it will introduce carcinolytic antibiotics and mitotic inhibitors. It will also describe the hormones and natural products along with arteriolar dilators.

3.1 OBJECTIVES

After going through this unit, you will be able to:

- Explain the antineoplastic agents and cardiovascular drugs
- Describe the synthesis of antineoplastic and cardiovascular drugs
- Evaluate the effects of cancer chemotherapy
- Anaylse the synthesis of cardiovascular drugs and diseases
- Discuss the recent development in field of antineoplastic and cardiovascular drugs

3.2 ANTINEOPLASTIC AGENTS: INTRODUCTION

The term 'neoplastic' means cancer cells. Antineoplastic agents are a class of medications that are mostly used to treat cancer. In the 1940s, the first antineoplastic medicines were created from either synthetic chemicals or natural botanicals. Antineoplastic agents are categorised based on where they come from and how they function to kill cancer cells.

3.2.1 Cancer Chemotherapy

Many types of cancer can be treated by chemotherapy. It uses one or more anti-cancer drug for the treatment. It may be given with a curative intent, which almost always involves combinations of drugs, or it may aim to prolong life or to reduce symptoms. Cancer medicines have emerged from conscientious efforts to optimize the medical specialty of agents that displayed cytotoxic activity. They also act as agents designed to interfere with recognized organic chemistry pathways promoting growth, or moving the neoplasm cell microenvironment as well as vasculature of the neoplasm and immune cells. Ensuing sections can contend with every category of metastatic tumor agents. Cancer treatment once administered as a dose or doses at intervals seeks to maximize the therapeutic magnitude

relation between neoplasm effects and harmful effects on the host. Therapy may be administered to specific compartments, for instance, the intrathecal area, to assure distribution to neoplasm cells sequestered therein compartment.

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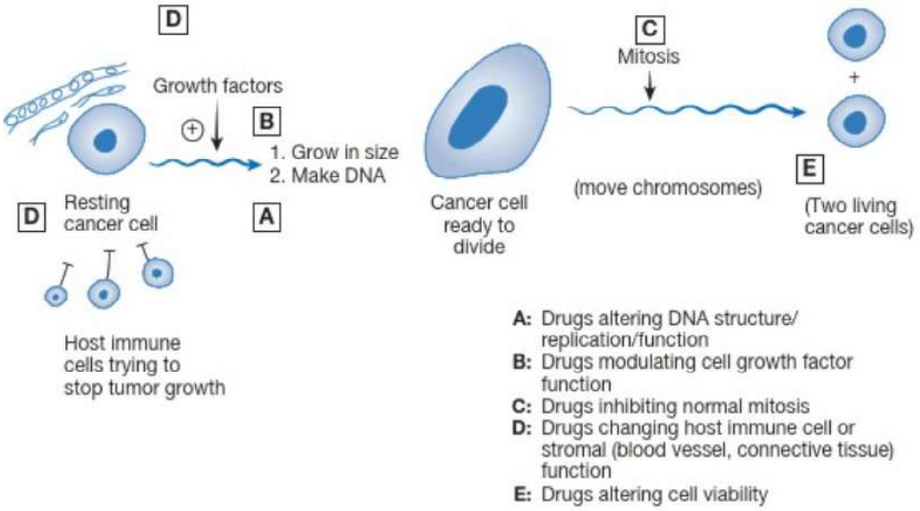

Fig. 3.1 *Pathophysiology of Cancer*

3.2.2 Special Problems

We need to know that why cancer medicines work at first place. However, after a few sessions of doses, these cancer drugs stop working or never work. The possible causes of these problems are as follows:

- **Classic (1940s–1990s) view:** Every exposure to a helpful antineoplastic drug treatment kills a relentless fraction of 'susceptible' cells till all cancer cells units are killed or remaining cells area unit 'dormant' or area unit eliminated by the system.
- **Modern view:** Medicines that kill cancer cells in preference to traditional cells act on processes active in cancer cells as a result of mutations; the medicine area unit preferentially acts deadly to growth cells within the context of these mutations by activating death programs in growth cells, similar or the image of 'physiologic' death pathways active in traditional organism growth or perform prosperou cancer medicine area unit so 'synthetically' deadly with neoplastic cell mutations
- Cancer cells not possessing artificial deadly mutations are not killed by the drug, and can be defiance against the drug.
- Tumors have the following alternative potential ways to resist drug action:
  - o Pump out or do not admit drug to cross the cell membrane.
  - o Metabolize the drug to inactive metabolites.
  - o Exist as a heterogeneous population of cells with and while not artificial deadly mutations.
- Tumors can lack mechanisms to activate host immunity even when drug action.

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3.2.3 Role of Alkylating Agents and Antimetabolites in Treatment of Cancer

The origin of chemotherapy as a therapeutic agent is constructed on the inspiration of organic chemistry warfare. The synthesis of mustard agent in 1854 and its ulterior use throughout war I highlighted its gastrointestinal and myelosuppressive toxicity. After swapping out the sulfide cluster in favor of an amino group, chlormethine (mechlorethamine) became the primary evaluated chemotherapeutical agent of the trendy age. It became the example medication for alkylating agents. An impressive variety of cytotoxic compounds whose antineoplastic activity is due to their reactions with deoxyribonucleic acid is studied within the clinic. Several of those comprise medication that presently type a part of the mixtures would not treat growth malady. This account includes solely a restricted variety of alkylating agents since this space has been well coated elsewhere.

Alkylating agents directly damage the DNA via DNA intra- and inter-strand covalent crosslinking, preventing the cells from reproducing. Generally, they are cell cycle– dependent, however, not cell cycle phase-specific. Bone marrow suppression, as well as leucopenia, neutropenia, lymphopenia, anemia, and thrombopenia, may be a common adverse event of all alkylating agents. Alternative, common adverse events embody endocrine toxicity/failure, carcinogenicity, and nausea and regurgitation. All alkylating agents can potentially cause therapy-related myeloid neoplasms (t-MN), as well as acute granulocytic leukemia (AML) and myelodysplastic syndromes (MDSs) that typically occur five to seven years following treatment and involve abnormalities of chromosome 5 and/or 7.

The different types of alkylating agents based on the chemical structures are as follows:

- **Nitrogen mustard:** cyclophosphamide, ifosfamide, chlorambucil, melphalan, bendamustine and mechlorethamine
- **Nitrosourea:** streptozocin, carmustine (BCNU)and lomustine (CCNU)
- **Triazine:** dacarbazine and temozolomide
- **Alkyl sulfonate:** busulfan
- **Ethylenimine:** thiotepa
- **Platinum agents:** cisplatin, carboplatin and oxaliplatin

Drug delivery is a significant issue in drug development. For instance, several medication are not absorbed once administered orally, whereas others could also be metabolized thus quickly they will never reach effective concentrations at the crucial site. Additionally to analysis to cope with such issues, there has been some work dedicated to the other scenario: developing medication that is required to be metabolized close to the location of action. Such medications are usually observed as prodrugs. The associate antineoplastic agent, apaziquone is an example of a prodrug. Apaziquone is an artificial analogue of the antineoplastic fermentation product antibiotic drug. The drug is reduced to active metabolites in hypoxic locations like the interiors of tumors. The compound has been extensively tested for treating bladder cancer. The condensation of the substituted

benzoquinone with the aminoalkane from ethyl radical -acetoacetate results in pyrroloquinone. The reaction is envisioned by the displacement of Br within the benzoquinone by the aminoalkane chemical element. This then transforms the benzoquinone itself to enamine; and then adds to the freshly fashioned facet chain and closes the ring. The treatment of that intermediate with dichlorodicyanoquinone (DDQ) oxidizes the methoxymethyl cluster on the pyrrole to the corresponding organic compound. The reaction of this last intermediate with ylide from Emmons chemical agent and triethylamine results in the spinoff with a long facet chain. The presence of atomic number 3 chloride within the reaction medium enforces the tendency to make a trans-aliphatic compound. The treatment of this last intermediate with diisobutylaluminum binary compound reduces each esters to alcohols. The displacement of the benzoquinone methoxyl by aziridine could involve associate degree addition– expulsion reaction. Regardless of the mechanism, the reaction affords apaziquone.

Antimetabolites are chemotherapy medications that are structurally associated with fundamental metabolites found within the body. They act as a substrate in replacement of an actual matter that will be utilized in fundamental metabolism. As such, cell replication and growth is suppressed to prevent proliferation of cancer cells. This happens through substrate competition for enzyme-binding sites or incorporation directly into deoxyribonucleic acid or ribonucleic acid. Antimetabolites are cell cycle– dependent and late G1/S phase-specific, with major effects on the processes concerned in deoxyribonucleic acid replication. The foremost categories of antimetabolites are pyrimidine and purine analogs and antifolates. Pyrimidine analogs and purine analogs are structures that mimic deoxyribonucleic acid, however, are changed slightly by substitution of an H with a halogen or an O with a sulfur or arabinose sugar with ribose/deoxyribose. The hypomethylating agents (HMAs) azacitidine and decitabine are cytosine analogs that target the catalyst DNA methyltransferase (DNMT). The process by which cells proliferate needs a set of chemical compounds that is necessary for the synthesis of latest very important cell constituents, such as nucleic acids. An alternate approach for by selection wiping out cancerous cells while not harming traditional tissues involves administering the alleged false substrates for the compounds commonly used for building new deoxyribonucleic acid and/or polymer. False substrate could be a general term grasp compounds whose chemical structure is getting ready to that of the compound that is commonly used for a few endogenous organic chemistry method. If the chemical structure of the mimic is shut enough to it of the authentic substrate, it will be accepted by the enzymes concerned within the method. The false substrate cannot, however, substitute - operationally and so brings the method to a halt. The cell, so denied the authentic product, merely expires. Note, however, that antimetabolite cancer chemotherapy, in common with that using alkylating agent, also relies for preferential effect on cancer cells on the significantly more rapid turnover of malignant cells over that of normal cells. Several of the facet effects from administering these medication square measure because of operation of an equivalent method on traditional cells.

3.2.4 Carcinolytic Antibiotics

The majority of cancer chemotherapeutical agents are introduced by microorganisms. Antibiotics, such as actinomycin D, anthracyclines, and the anthracenones are approved as antitumor agents. Waksman and Woodruff discovered and introduced the primary antitumour antibiotic 'actinomycin D' from actinomyces antibioticus in 1940 that was extremely toxic to animals, whereas it absolutely was well-tried to be effective in some childhood tumors subsequently. This was the onset of utilizing antibiotics in cancer chemotherapy and from this point numerous antibiotics either natural or artificial are used for the treatment of cancer.

Anticancer antibiotics comprise completely different classes that do not seem to be much similar in their structures. A summarized classification is described in Table 3.1.

Table 3.1 *Classification of Anticancer Antibiotics*

Group	Example(s)
Aromatic polyketides (anthracyclines)	daunorubicin, doxorubicin (adriamycin), epirubicin, pirarubicin, idarubicin, valrubicin, amrubicin
Glycopeptides	bleomycin, phleomycin
Non-ribosomal peptides	actinomycin D (dactinomycin)
Mitosanes	mitomycin C
Enediynes	calicheamicin
Indolocarbazoles	rebeccamycin
Epothilones	ixabepilone
Other agents	mithramycin

Aromatic polyketides (anthracyclines)

Bacteria, fungi and a few plants are able to turn out aromatic polyketides. These compounds possess a novel polycyclic aromatic structure that distinguishes them from alternative polyketides. Soil actinomycetes, specifically actinomycete are the center of the many analysis programs because of their ability to provide a large range of bioactive elements. Actinomycetes are capable of synthetizing aromatic polyketides by utilising polyketide synthases enzymes. These enzymes turn successive decarboxylative condensation between the starter and extender units and supply â-ketone intermediate that bears region-specific reduction, aromatization or cyclization hence, resulting in the polycyclic aromatic structures that undergo alternative enzymatic changes later on leading to biologically active elements. Aromatic polyketides are also called anthracyclines because of the presence of a tetracyclic bearing an anthraquinone chemical group in their aglycone moiety. Antracyclines are effective inhibitors of topoisomerase II and they also are ready to attach to polymer. Necessary antitumor agents, such as daunorubicin and its spinoff antibiotic drug (adriamycin) are the members of this category of antibiotics.

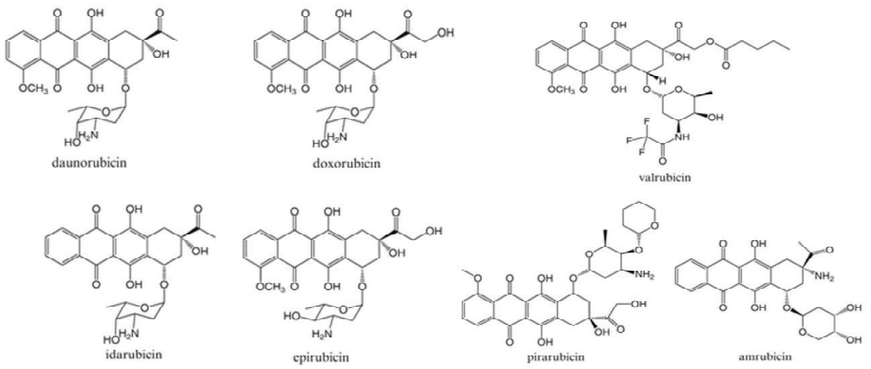


Fig. 3.2 *Structures of Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Valrubicin, Pirarubicin and Amrubicin*

Glycopeptides (bleomycins)

This category of antibiotics that was at first recognized in some species of streptomyces consists of glycosylated oligopeptide derivatives that possess uncommon amino acids in their structures. Bleomycins (e.g., bleomycin A2) might bind to deoxyribonucleic acid and ribonucleic acid, and consequently cause breakage in their structures. They are additionally capable of inhibiting t-RNA, and it is found that their oxidative function requires a metal ion.

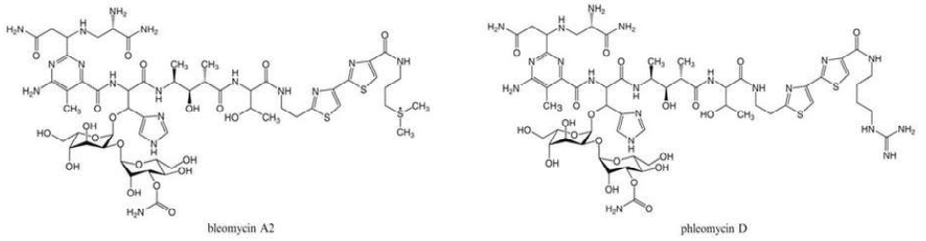


Fig. 3.3 *Structures of Bleomycin A2 and Phleomycin D*

Non-ribosomal peptides

Non-ribosomal peptide synthases are the key enzymes within the synthesis of non-ribosomal peptides. These peptides have additional diversity compared to the ribosomal peptides. The non-ribosomal peptides, actinomycins, comprise a series of chromopeptide antibiotics that are structurally connected. They enclose numerous amino acids in their structures. Actinomycin D (dactinomycin), an inhibitor of RNA polymerase, owns the name of being the member of those primal anti-tumor antibiotics discovered in 1940s from actinomyces antibiotics.

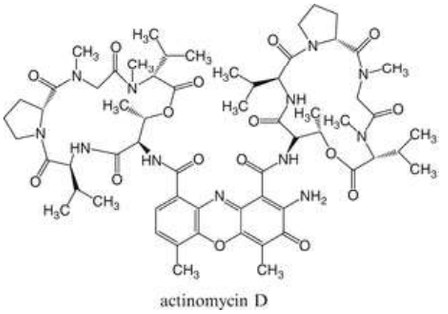


Fig. 3.4 *Structure of Actinomycin D*

Mitosanes

Mitosanes were discovered within the late 1950s from Streptotnyces caespitosus and bear a definite four-ringed structure, which has an aziridine ring, saturation at carbons 9 and 9a, and eventually the quinone oxidation state. Once turning into their active forms, this cluster of antitumor antibiotics attaches to deoxyribonucleic acid just like alkylating agents. Mitomycin C is beyond question an impressive member of this category of anti-tumor that stops cellular division and protein synthesis. Mitomycin is employed as a section of antitumor medical aid programme in the treatment of adenocarcinomas of the cervix, stomach, exocrine gland and respiratory organ. Toxicity to the heart, liver, lung, excretory organ and also the bone marrow has been related to the utilization of mitomycin.

Enediynes

Enediynes contain an unsaturated core with 2 aliphatic compound groups conjugated to a double bond, during a nine- or ten-membered ring. They are originated from polyphenols that are converted into the ultimate structure through a series of reactions, creating the ultimate enediynes capable of intercalating to deoxyribonucleic acid resulting in cleavage. Enediynes were discovered within the 1980s. They are provided by numerous natural sources. Some enediynes are isolated from a spread of microorganisms like streptomyces and actinomycetes. Calicheamicin (Mylotarg) and a polymer by-product of neocarzinostatin (SMANCS) are employed in cancer therapy.

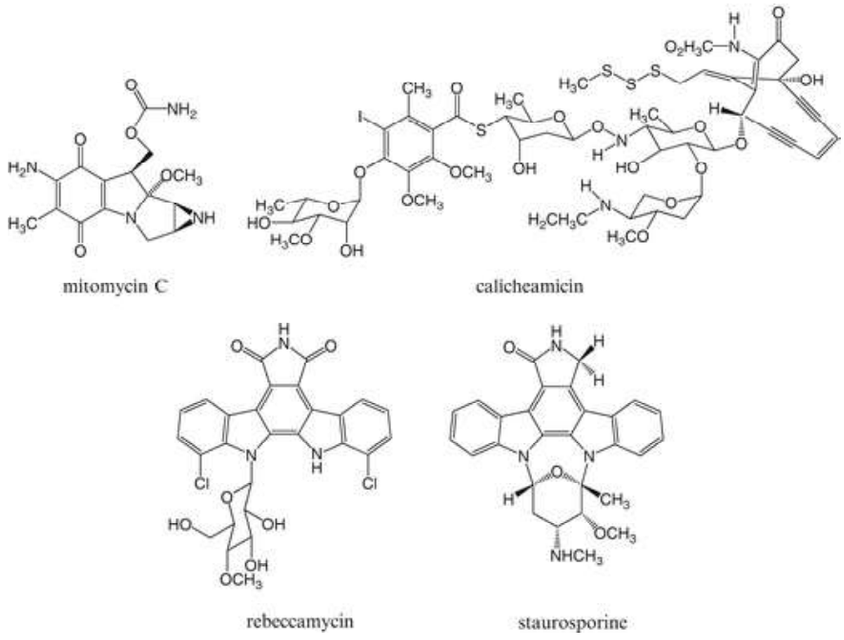


Fig. 3.5 *Structures of Mitomycin C, Calicheamicin, Rebeccamycin and Staurosporine*

Indolocarbazoles

An indole unit, amalgamated to at least one of the aromatic hydrocarbon rings of a carbazole, constructs the core of indocarbazole antitumor antibiotics. Considering the variability within the structure of those cluster of anti-neoplastic agents, totally

different complicated mechanisms are attributed to their anti-tumor activity as well as Topoisomerase I (TOPO I) poisoning, protein kinase C (PKC), protein kinase A (PKA), CDK1/cyclin B, and CDK5/p25 inhibition. A juncture is that the antitumor property depends to the sugar moiety. It has been recommended that biological targeting and property may well be effectively improved in indolocarbazoles by a very little modification in numerous elements of their chemical structures.

Epothilones

The discovery of epothilones goes back to 1987, once some strains of myxo-bacterium like Sorangium cellulosum were found to provide these polyketide macrolide lactones that possessed antifungal activity. Epothilones appear to demonstrate similarities with taxanes in their mechanism of anti-tumor activity furthermore as their facet effects. These 16-membered ring macrolides are microtubule-stabilizing agents.

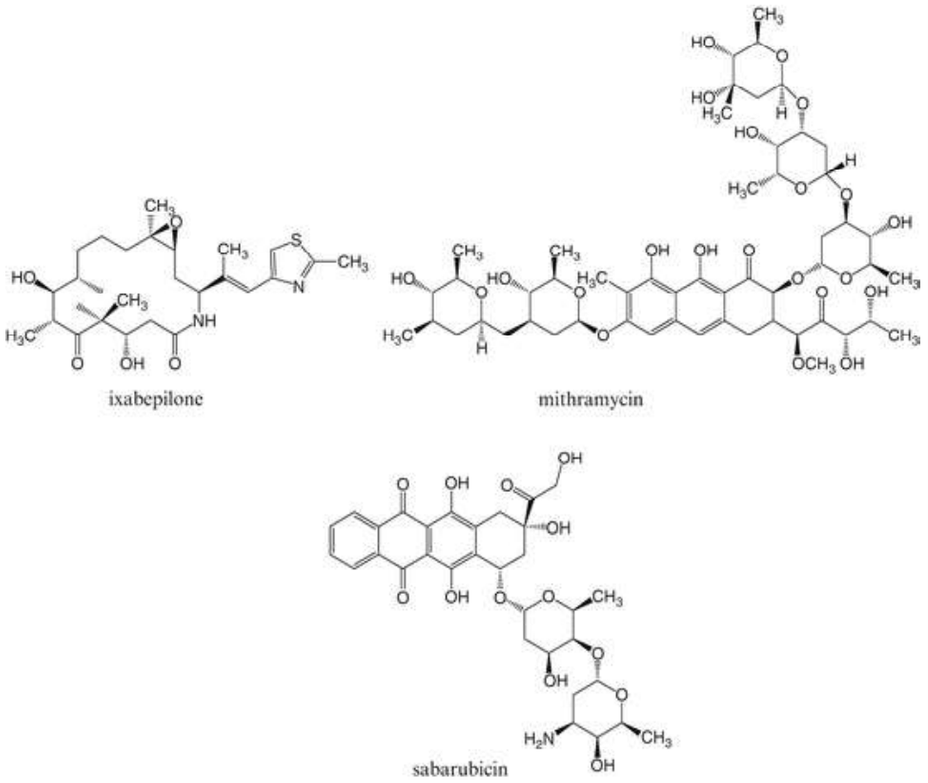


Fig. 3.6 *Structures of Ixabepilone, Mithramycin and Sabarubicin*

3.2.5 Mitotic Inhibitors

Drugs that inhibit mitosis, or cell division are called mitotic inhibitors. These drugs disrupt microtubules, which are structures that pull the chromosomes apart when a cell divides. Mitosis is the part of the cell cycle once replicated deoxyribonucleic acid condenses into chromosomes, each of that consists of a deoxyribonucleic acid helix with one template deoxyribonucleic acid strand and one recently synthesized deoxyribonucleic acid strand throughout the previous S phase. The

chromosomes are still joined at the centromere. Microtubules are macromolecule structures that link every centromere to a centrosome, leads to the movement away from the centromere and into new offspring cells. Throughout the mid-20th century, screening programs searching for medication that will block neoplastic cell growth discovered that various natural product drugs typically used as a defense mechanism against incursive cells in their microenvironments might disrupt the method of cell division in cancer cells, and many of those have tested clinically helpful. Microtubule directed agents embrace the drug's core structure isolated from or synthesized from precursors in plants (vinca alkaloids, taxanes), marine organisms (eribulin), and bacterium (epothilones). These agents disrupt body movement throughout cell division.

A sizeable cluster of compounds with wide variable chemical structures owe their antineoplastic activity to the inhibition of the chemical process of tubulin for building microtubules. Most of those medicine bind to tubulin and therefore inactivate the substance. The end point of that method could comprise inhibition of the creation of new blood vessels in solid tumors or halting the expansion of ovarian cancer cells.

Check Your Progress

1. What are antineoplastic agents?
2. Mention the ways in which tumors resist drug action.
3. Name one prodrug.

3.3 SYNTHESIS OF CHEMOTHERAPEUTIC DRUGS

Chemotherapeutic drugs destroy fast-growing cells in the body and are used to treat cancer. They belong to a class of medications called cytotoxic agents. Many chemotherapy drug resistance mechanisms include efflux, inactivation of drug, alteration of drug targets, and cell death inhibition. A particular efflux pathway involves the tumor producing a substance known as p-glycoprotein, which essentially removes the drug from the tumor cell. Let us study the synthesis of some of the common chemotherapeutic drugs in detail.

3.3.1 Mechlorethamin

Mechlorethamine, bis-(2-chloroethyl)methylamine, is made by reacting methylamine with ethylene oxide, forming bis-(2-hydroxyethyl)methylamine, which upon reaction with thionyl chloride turns into the desired mechlorethamine.

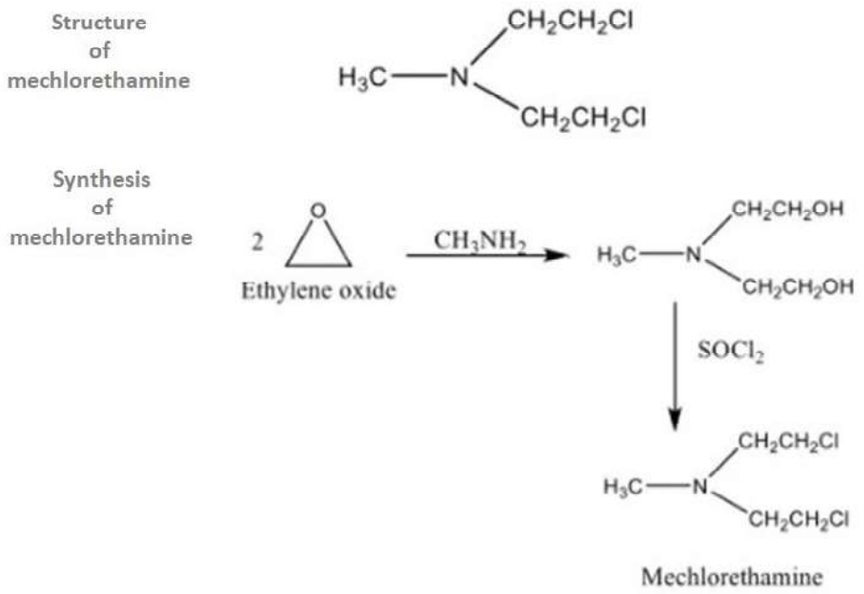


Fig. 3.7 *Synthesis of Mechlorethamine*

3.3.2 Cyclophosphamide

Cyclophosphamide is one of the best known and widely used antineoplastic agents. The drug comprises 'C' in a large number of multidrug for treating cancer. One of the several schemes for preparing this compound starts with the condensation of aminoalcohol (1) with phosphorus oxychloride to afford the oxazaphosphorine derivative (2) through stepwise displacement of halogens in phosphorus oxychloride by the base and alkoxide group in (1). The still reactive chlorine in that product is then displaced with 2-chloroethylamine (3). The same reagent is then used to add a second chloroethyl function. This brief sequence affords cyclophosphamide (5).

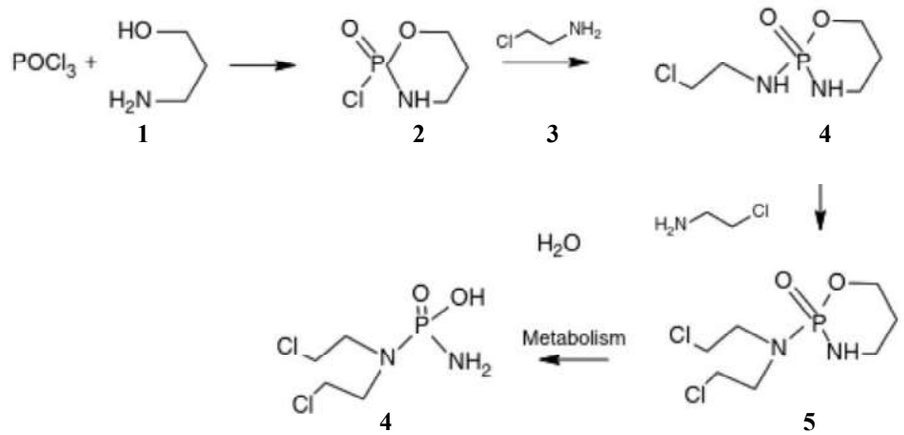


Fig. 3.8 *Synthesis of Cyclophosphamide*

3.3.3 Melphalan

Bis-2-chloroethylamine mustard is linked to l-phenylalanine. Melphalan enters the cells primarily via energy-dependent high-affinity l-amino acid transporter (high

extracellular concentration of leucine or other amino acid competitively inhibits cellular uptake of melphalan). Glutathione conjugation is an important detoxification mechanism; inactive metabolites include monohydroxymelphalan and dihydroxymelphalan.

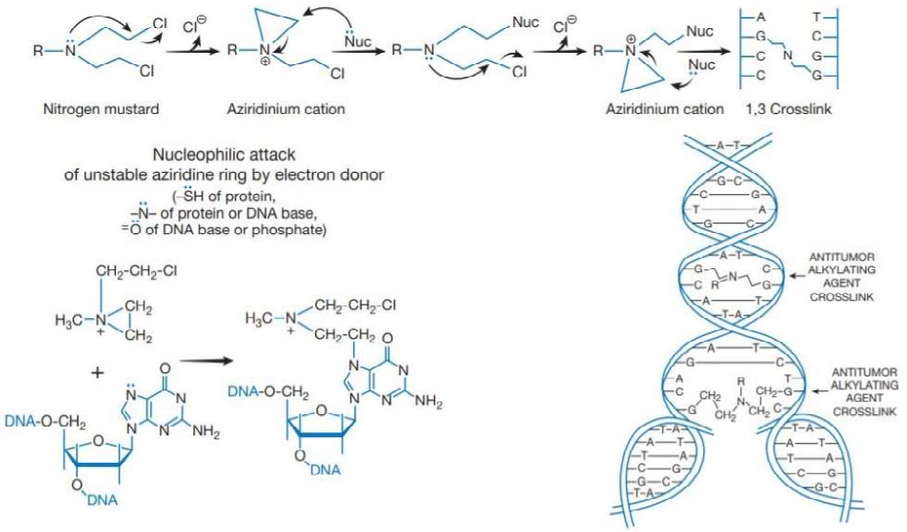
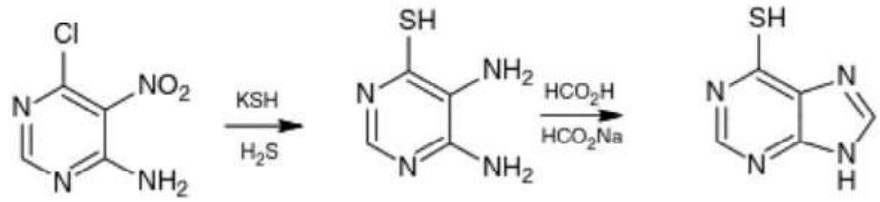


Fig. 3.9 *Mechanism of Action of DNA Alkylation by Nitrogen Mustards*

3.3.4 6-Mercaptopurine

Synthesis of 6-mercaptopurine starts with nucleophilic aromatic displacement of chlorine in the highly substituted pyrimidine (1) with potassium sulfide in the presence of hydrogen sulfide gas. The nitro group is apparently reduced to an amine under those conditions. The reaction of the product (2) with formic acid in the presence of sodium formate closes the fused ring to afford the purine 6-mercaptopurine (3).



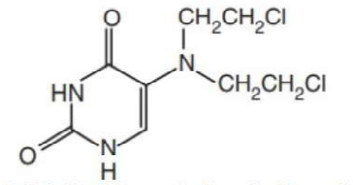
(1) **(2)** **(3)**

Fig. 3.10 *Synthesis of 6-Mercaptopurine*

3.3.5 Uracil Mustards

It is an off-white crystalline, odourless powder. It is soluble in water or alcohol. It is used for the treatment of prostate cancer.

Uracil Mustard



5-[Bis(2-chloro ethyl)amino] uracil

Synthesis

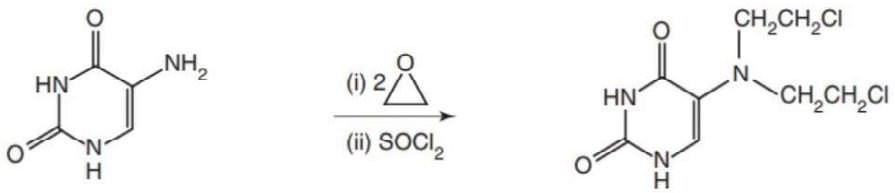


Fig. 3.11 *Synthesis of Uracil Mustard*

Check Your Progress

4. How is mechlorethamine obtained?
5. Write the physical properties of uracil mustard.

3.4 RECENT DEVELOPMENT IN CANCER CHEMOTHERAPY

Cancer is one amongst the foremost predominant diseases inflicting death within the world. Since numerous side effects are often reported from this therapy and chemo-preventive anticancer medicine, there is a growing trend towards new drug discovery, particularly from natural origins. So as to facilitate antineoplastic drug discovery and development, new ways must be thought of to get simpler or new lead compounds from natural sources. On the other hand, not solely ancient screening of meditative plants, marine alga or alternative natural sources look necessary to seek out effective compounds with lower toxicity and better activity, however additionally new approaches during this space concerning new aspects of 'reverse pharmacognosy' ought to be in addition to high output screening, virtual screening and in-silico databases to market antineoplastic drug discovery. In fact, if chemistry data and high-throughput screening are combined, identification of various selective active compounds would be doable.

Creating a link between ancient knowledge and rapid screening systems will be a productive action to discover novel antineoplastic agents. As an example, a cell-based high output screening methodology was reported to be applied as a contemporary bio-sensor that by selection detected caspase-mediated cell death on the premise of the fluorescence resonance energy transfer (FRET) technique.

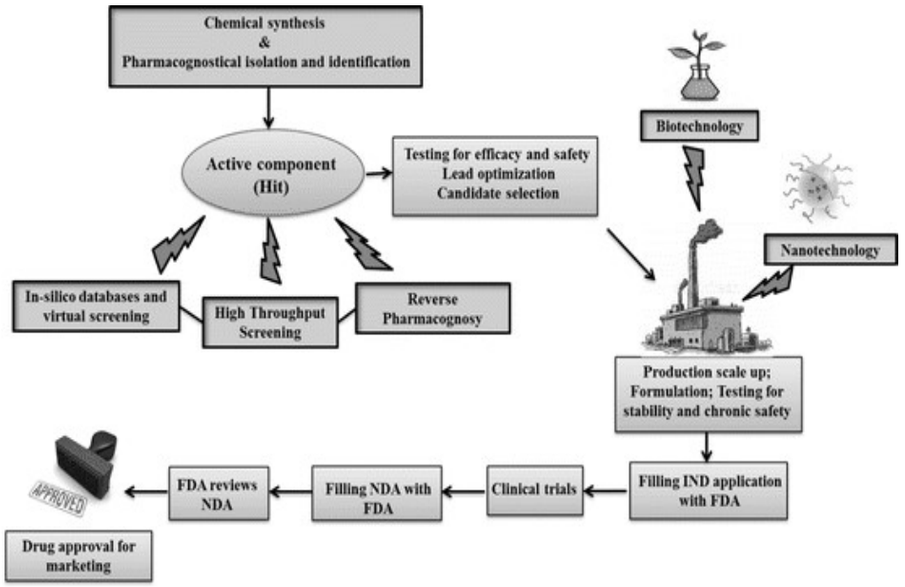


Fig. 3.12 *Various Novel Approaches in Promoting Anticancer Drug Discovery from Natural Origin*

Finding new targets is the main goal in drug discovery of cancer. Moreover, nanoparticles show an excellent promise within the treatment of a large vary of diseases because of their flexibility in structure, composition and properties. Nanoparticle-targeting antineoplastic medicine are more thought of recently due to biodegradability, biocompatibility, surface modification, stability, wonderful pharmacokinetic management and suitableness for entrapping a large range of therapeutic agents, however, considerations on the potential toxicity of all nano-compounds still stay. On the opposite aspect, since antineoplastic therapy agents are in the main cytotoxic and hydrophobic compounds, they have to be adequately diluted for slow infusion into the body. To enhance and deal with the constraints and disadvantages of standard therapy, nanotechnology and biocompatible compound nanoparticles are developed as a major output of contemporary science.

3.5 HORMONE AND NATURAL PRODUCTS

Hormone therapy is used to treat cancers that can be caused by hormones. It slows or stops the growth of cancer cells. The use of sex hormones and their antagonists is claimed to have begun close to the turn of the nineteenth century with the observation of 3 cases of advanced carcinoma where removal of women's ovaries had good effects on their tumors. The ovaries are currently best-known to be one amongst the principal sources of estrogens. In a very similar vein, a study reported a serious improvement in cancer of the prostate when the testes were removed, a source of androgens. Additional developments within the field anticipated advances in reproductive physiology and within the chemistry and organic chemistry of the sex hormones. Analysis within the known estrogen receptors; this was followed by the development of assays for those receptors. Those tests discovered that the majority reproductive organ tissues within the

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feminine are endowed with receptors for estrogens. Estrogens, analysis showed, can cause receptor-positive cancers to proliferate. Antiestrogens, like tamoxifen, were found to bind to estrogen receptors and diminish current estrogen levels. This drug and a number of other estrogen antagonists are still used extensively for treating estrogen receptor positive breast cancer.

Cancer is a major issue worldwide, and is the most typical or second most typical reason behind death in several countries. Complementary and alternative medicine (CAM) is reported to be utilized by concerning 40% of all cancer patients. Patients usually do not suppose these approaches to cure their unwellness, however, chiefly use them to alleviate pain, boost their immune system, or to regulate treatment-related aspect effects.

Complementary oncologic therapies are classified as various medical systems (e.g., homeopathy and ancient Chinese medicine), biologically based mostly medicines (e.g., herbs, vitamins and food), artful practices (e.g., massage), energy drugs (e.g., reiki), and mind-body practices (e.g., yoga and meditation). Ancient healthful herbs as a subcategory of CAM modalities for cancer are helpful in cancer through many ways—by delaying or hiding sickness onset by obstructing a number of the molecular alterations within the process of cancer formation, preventing the event or metastasis of cancer, rising quality of life, and reducing adverse effects because of standard cancer treatments together with chemotherapeutical agents and radiation therapy.

Some of the common natural products having anticancer properties are as follows:

- *Allium sativum L.* (Garlic)
- *Boswellia* species
- *Commiphora mukul Engl.* (Guggul)
- *Coriandrum sativum L.* (Coriander)
- *Descureania Sophia L.* (Flixweed)
- *Iris germanica L.* (Iris)
- *Linum usitatissimum L.* (Flax)
- *Matricaria recutita L.* (Chamomile)
- *Plantago* species
- *Portulaca oleracea L.* (Purslane)
- *Solanum nigrum L.* (Black Nightshade)
- *Urtica dioica L.* (Stinging Nettle)
- *Viola odorata L.* (Sweet Violet)
- *Zingiber officinale Roscoe* (Ginger)

Check Your Progress

6. Which drug is used to diminish estrogen levels?
7. Name any two natural products having anticancer properties.

NOTES

3.6 CARDIOVASCULAR DRUGS: INTRODUCTION

The drugs that affect the function of the heart and blood vessels are called cardiovascular drugs. These drugs accounts for the major use in medicine.

3.6.1 Cardiovascular Diseases

Cardiovascular diseases (CVDs) could be a general term for conditions affecting the heart or blood vessels. It has related to a build-up of fatty deposits within the arteries (atherosclerosis) and an inflated risk of blood clots. It can even be related to injury to arteries in organs like the brain, heart, kidneys and eyes. CVD is one in every of the most causes of death and disability, however it can be prevented by leading a healthy style.

Types of CVDs

There are many kinds of CVDs. Four common types are as follows:

(i) **Coronary heart condition**

Coronary heart condition occurs when the flow of oxygen-rich blood to the heart muscle is blocked or reduced.

This puts an inflated strain on the heart, and may lead to:

- **Angina**: It involves hurting caused by restricted blood flow to the heart muscle.
- **Heart attacks**: It occurs when the blood flow to the heart muscle is suddenly blocked
- **Heart failure**: It occurs when the heart is unable to pump blood round the body properly.

(ii) **Strokes and transient ischemic attacks (TIAs)**

A stroke occurs when the blood provided to a part of the brain is interrupted, which may cause brain injury and probably death. A transient ischemic attack (also known as a transient ischemic attack or 'mini-stroke') is comparable; however the blood flow to the brain quickly discontinues. The main symptoms of a stroke or transient ischemic attack may be remembered with the word 'fast' that stands for:

- **Face**: The face might have drooped on one side, the person is also be unable to smile, or their mouth or eye might have dropped.
- **Arms**: The person might not be able to raise his/her arms and keep them there due to arm weakness or numbness in one arm.
- **Speech**: The speech can also be slurred or confused, or a person is unable to speak in the least.
- **Time**: It is the time to dial 999 now if you see any of those signs or symptoms.

(iii) Peripheral blood vessel sickness

Peripheral blood vessel sickness occurs when there is a blockage within the arteries to the limbs, typically the legs. This can cause dull or cramping leg pain that is worse once walking and gets higher with rest hair loss on the legs and feet symptom or weakness within the legs, persistent ulcers (open sores) on the feet and legs.

(iv) Aortic sickness

Aortic diseases are a bunch of conditions affecting the arterial blood vessel. This is often the biggest vessel within the body that carries blood from the heart to the remainder of the body. One among most typical aortal diseases is an aneurism, wherever the arterial blood vessel becomes weakened and bulges outward. This does not typically have any symptoms, however there is a probability it may burst and cause grave harm.

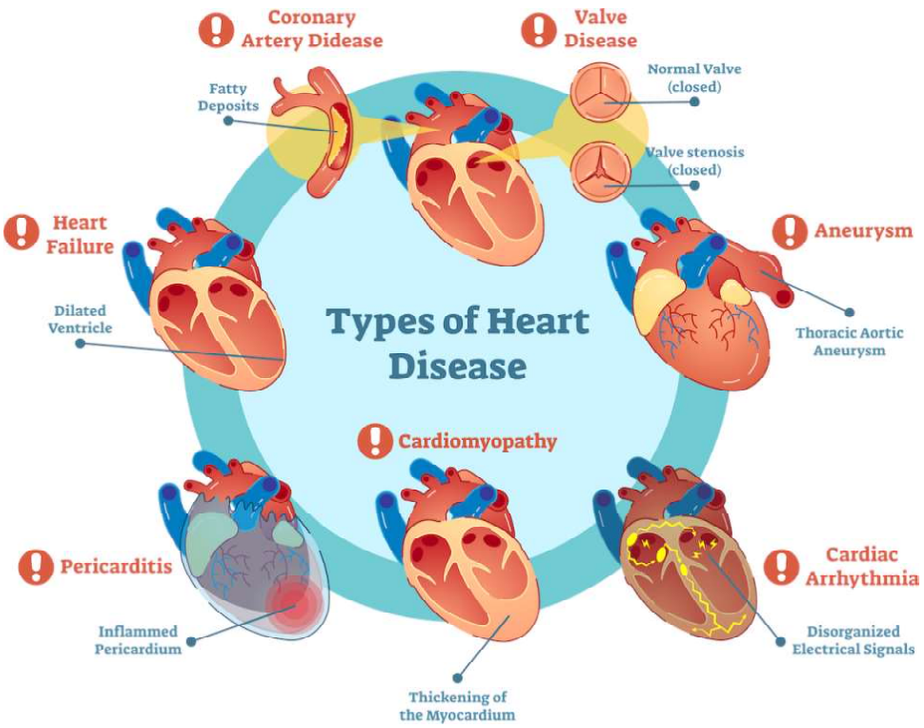

Fig. 3.13 *Types of Cardiovascular Diseases*

Causes of CVDs

The exact reason behind CVDs is not clear; however, there are a lot of factors which may increase risk of its occurrence. These are known as 'risk factors'. The additional risk factors a person gets, the larger your possibilities of developing CVDs. The most common risk factors for CVD are as follows:

- High blood pressure
- Smoking
- High cholesterol
- Diabetes

- Inactivity
- Obesity
- Family history of CVD
- Ethnic background

Other risk factors

Other factors that have an effect on your risk of developing CVDs include:

- **Age**: CVDs are most common among people over 50 years and the risk of developing them increases with the age.
- **Gender:** Men are probable to develop CVD at an earlier age than women.
- **Diet**: An unhealthy diet will result in high cholesterol and high blood pressure.
- **Alcohol**: Excessive alcohol consumption can even increase cholesterol and blood pressure levels, and contribute to weight gain.

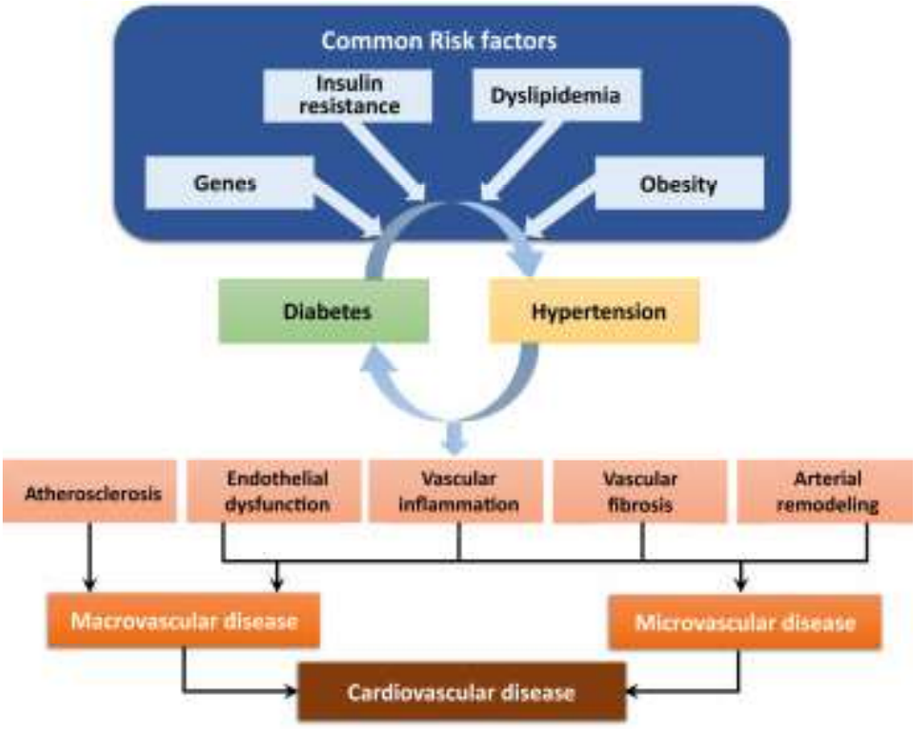

Fig. 3.14 *Common Risk Factors Leading to Cardiovascular Disorders*

Prevention of CVDs

A healthy style will lower your risk of CVDs. If a person already has a CVD, staying as healthy as potential will scale back the possibilities of it obtaining worse. The ways that reduce the CVD risk are as follows:

- Stop smoking.
- Have a balanced diet.
- Exercise frequently.

- Maintain a healthy weight.
- Cut down on alcohol.

If you have got a very high risk of developing CVD, your doctor might advocate taking medication to scale back your risk. Medications that will be counseled include statins to lower blood cholesterol levels, low-dose aspirin to forestall blood clots, and tablets to reduce blood pressure.

Check Your Progress

8. What are the types of VCDs?
9. When does coronary heart condition occur?
10. What does the word 'fast' stand for?

3.7 DRUG INHIBITORS OF PERIPHERAL SYMPATHETIC FUNCTION

Sympatholytic medicine can potentially block this sympathetic adrenergic system at 3 different levels. First, peripheral sympatholytic medicine like alpha-adrenergic receptor and beta-adrenergic receptor antagonists block the influence of norepinephrine at the effector organ (heart or blood vessel). Second, there are ganglionic blockers that block impulse transmission at the sympathetic ganglia. Third, there are medicines that block sympathetic activity inside the brain. These are referred to as centrally acting sympatholytic medicine.

Therapeutic indications

Centrally acting á2-adrenoceptor agonists are utilized in the treatment of cardiovascular disease. However, they are not thought of first-line medical care in massive half due to side effects that are related to their actions inside the brain. They're sometimes administered together with a diuretic drug to stop fluid accumulation that will increase blood volume and compromises the pressure level lowering impact of the medicine. Fluid accumulation may also cause puffiness. Centrally acting á2-adrenoceptor agonists are effective in hypertensive patients with nephritic illness, they do not compromise nephritic perform.

Specific medicine

Several totally different centrally acting á2-adrenoceptor agonists for clinical use are as follows:

- clonidine
- guanabenz
- guanfacine
- á-methyldopa

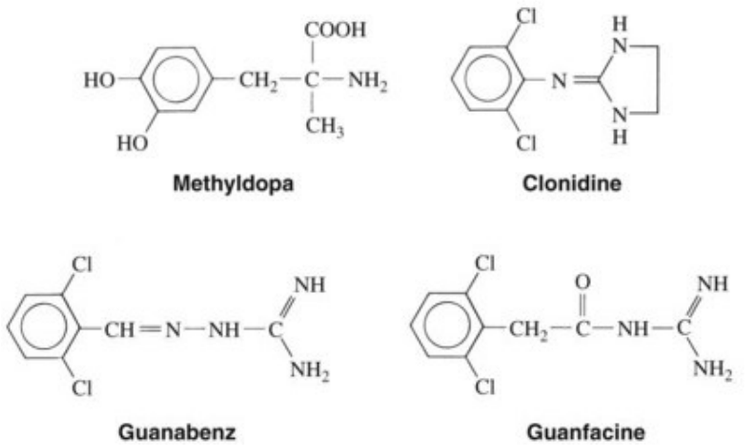

Fig. 3.15 *Structures of Methyldopa, Clonidine, Guanabenz and Guanfacine*

Clonidine, guanabenz and guanfacine are structurally connected compounds and have similar medicinal drug profiles. á-methyldopa may be a structural analog of dihydroxyphenylalanine and functions as a prodrug. Once administration, α-methyldopa is converted to á-methynorepinephrine, that then is agonist within the medulla to decrease sympathetic outflow.

Side effects and contraindications

- Side effects of centrally acting α2-adrenoceptor agonists embody sedation, dryness and nasal mucosa, cardiac arrhythmia (because of enhanced cranial nerve stimulation of the cardiac pacemaker likewise as sympathetic withdrawal), hypotension, and impotence.
- Constipation, nausea and gastric upset are related to the sympatholytic effects of those medicine. Fluid retention and puffiness is additionally a retardant with chronic therapy; thus, synchronic medical care with a diuretic drug is important.
- Abrupt discontinuance of antihypertensive will cause rebound cardiovascular disease, which results from excessive sympathetic activity.

3.8 CENTRAL INTERVENTION OF CARDIOVASCULAR OUTPUT

Normal cardiovascular performance needs delicate leveling of the many complicated biochemical processes. Situation of those processes might cause cardiac muscle dysfunction or end in structural cardiopathy. A range of altered sign systems might contribute to the progression of cardiac muscle dysfunction. Cardiovascular performance is mirrored within the blood pressure and flow rate (mean blood flow), that successively are addicted to four factors: preload, after load, cavity ability, and vital sign.

Although several aspects of cardiovascular performance are well preserved at rest in older adults, aging has necessary effects on vessel performance throughout exercise. The decline in aerobic capability with age in people with no proof of disorder is referable partially to peripheral factors, like enhanced body fat, reduced muscle mass, and a decline in O_2 extraction with age.

The maximum pulse rate attained throughout exercise decreases step by step with age in humans, a truth renowned by cosmopolitan posters unremarkably seen in exercise facilities. Apparently, this decrease is not laid low with physical conditioning as a result of its present in each inactive and fit people. Many mechanisms are concerned within the reduction in most vital sign throughout exercise in aging. One mechanism involves a decrease within the sensitivity of the aging cardiac muscle to sympathetic stimulation.

Normally, the sympathetic nervous system becomes activated throughout exercise, and releases catecholamines (noradrenaline and adrenaline) to act on â-adrenergic receptors within the heart. This â-adrenergic stimulation ends up in a rise in pulse rate and augments the force of contraction of the guts. However, it is well established that the responsiveness of the heart stimulation declines with age. This can be thought to flow from to high current levels of vasoconstrictive that are present in older adults. These high levels of catecholamines in older adults arise from a decrease in plasma clearance of vasoconstrictive and a rise within the event of catecholamines from numerous organ systems into the circulation in older adults. Chronic exposure to high levels of catecholamines might desensitize parts of the â-adrenergic receptor signal cascade within the aging heart and limit the increase in pulse rate throughout exercise. A further mechanism that's thought to limit the maximum pulse rate in exercise is that the decrease within the total population of sinoatrial nodal pacemaker cells within the aging heart. This decrease within the range of pacemaker cells might impair the response of the heart to sympathetic stimulation throughout exercise.

3.8.1 Direct Acting Arteriolar Dilators

Arterial dilator medication is usually used to treat systemic and pulmonary high blood pressure, coronary failure and angina. They reduce blood pressure by decreasing systemic vascular resistance. This edges patients in coronary failure by reducing the afterload on the heart ventricle, which reinforces stroke volume and flow and results in secondary decreases in chamber preload and blood vessel pressures. Heart disease patients have the benefit of arterial dilators, by reducing afterload on the heart; vasodilators decrease the oxygen demand of the heart, and thereby improve the oxygen supply/demand quantitative relation. Oxygen demand is reduced chamber bodily cavity wall stress is reduced once artery pressure is minimized. Some vasodilators also can reverse or stop blood vessel vasospasm (transient contraction of arteries), which may precipitate anginose attacks.

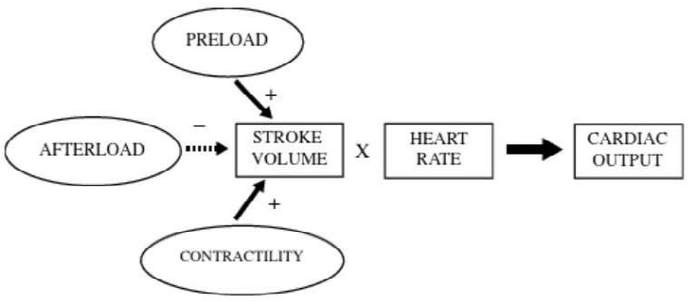

Fig. 3.16 *Preload, Contractility, and Afterload Each Impact Cardiac Output via their Effects on Stroke Volume*

Vasodilator medication is classified based on their site of action (arterial versus venous) or by mechanism of action. Some medication primarily dilate resistance vessels (arterial dilators; e.g., hydralazine), whereas others primarily have an effect on venous capacitance vessels (venous dilators; e.g., nitroglycerine). Most dilator medication, however, have mixed arterial and venous dilator properties (mixed dilators; e.g., alpha receptor antagonists, angiotensin catalyst inhibitors).

It is a lot of common, however, to classify dilator medication based on their primary mechanism of action. The figure below depicts necessary mechanistic categories of dilator medication.

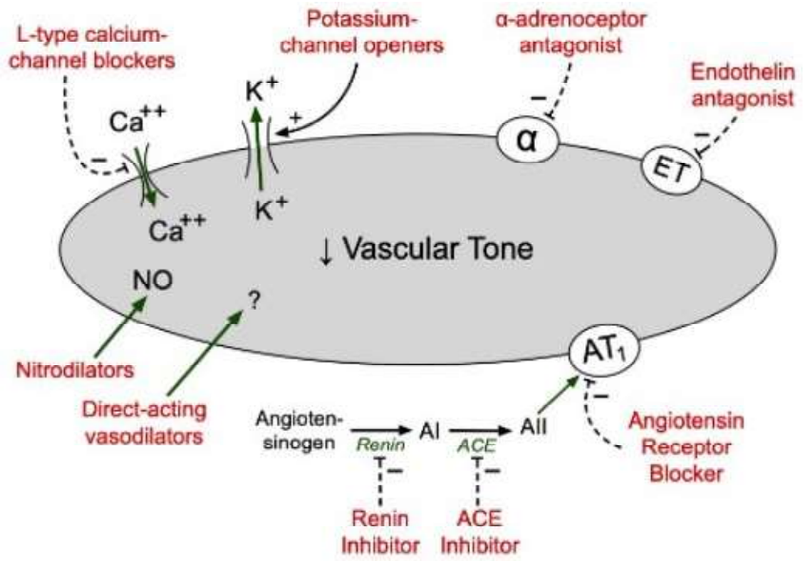

Fig. 3.17 *Schematic Representation of Mechanistic Categories of Dilator Medication*

These categories of medicine, furthermore as different categories that produce vasodilation, are as follows:

- Alpha-adrenoceptor antagonists (alpha-blockers)
- Angiotensin converting enzyme (ACE) inhibitors
- Angiotensin receptor blockers (ARBs)
- Beta2-adrenoceptor agonists (â2-agonists)
- Calcium-channel blockers (CCBs)
- Centrally acting sympatholytics
- Direct acting vasodilators
- Endothelin receptor antagonists
- Ganglionic blockers
- Nitrodilators
- Phosphodiesterase inhibitors
- Potassium-channel openers
- Renin inhibitors

Vasodilators are used to treat high blood pressure, coronary failure and angina; but, some vasodilators are higher suited than others for these indications. Some vasodilators that act totally on resistance vessels (arterial dilators) are used for high blood pressure, and coronary failure, and angina; but, reflex internal organ stimulation makes some arterial dilators unsuitable for angina.

Side-effects of vasodilators

There are 3 potential drawbacks within the use of vasodilators:

- Systemic dilatation and blood pressure reduction will cause a baroreceptor-mediated reflex stimulation of the heart (increased pulse rate and inotropy). This will increase oxygen demand that is undesirable if the patient additionally has arterial blood vessel illness.
- Vasodilators will impair traditional baroreceptor-mediated reflex constriction once an individual stands up, which may cause hypotension and syncope upon standing.
- Vasodilators will cause nephritic retention of Na and water that will increase blood volume and flow and thereby compensates for the reduced systemic vascular resistance.

Check Your Progress

11. What are vasodilators?
12. Which three compounds are structurally connected and have similar medicinal drug profiles?
13. What is the use of arterial dilators?

3.9 SYNTHESIS OF CARDIOVASCULAR DRUGS

Cardiovascular medications are the common name of compounds used to treat completely different heart disorders (such as congestive coronary failure, angina, or arrhythmia) or diseases of the system (e.g., hypertension). Coronary failure is acute (sudden left-ventricular insufficiency and as a consequence respiratory organ failure without hypertrophy of heart muscle), counteractive (no respiratory organ failure however hypertrophy of heart muscle), or thoroughgoing (no additional compensation of the heart muscle even if there's hypertrophy). Coronary failure is influenced by completely different categories of medicine, as well as nitrates, Ca^{2+} antagonists, â-blockers, digitalis, ACE inhibitors, phosphodiesterase inhibitors, etc.

3.9.1 Amyl Nitrate

Amyl nitrite, like other alkyl nitrites, reacts with carbanions to give oximes. Amyl nitrites are also useful as reagents in a modification of the Sandmeyer reaction. The reaction of the alkyl nitrite with an aromatic amine in a halogenated solvent produces a radical aromatic species, this then frees a halogen atom from the solvent.

For the synthesis of aryl iodides diiodomethane is used, whereas bromoform is the solvent of choice for the synthesis of aryl bromides.

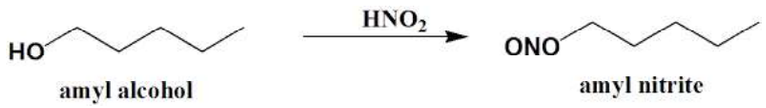

Fig. 3.18 *Synthesis of Amyl Nitrite*

3.9.2 Sorbitrate

Isosorbide dinitrate is converted to the active nitric oxide to activate guanylate cyclase. This activation increases levels of cyclic guanosine 3',5'-monophosphate (cGMP). cGMP activates protein kinases and causes a series of phosphorylation reactions which leads to dephosphorylation of myosin light chains of smooth muscle fibres. Finally there is a release of calcium ions which causes smooth muscle relaxation and vasodilation.

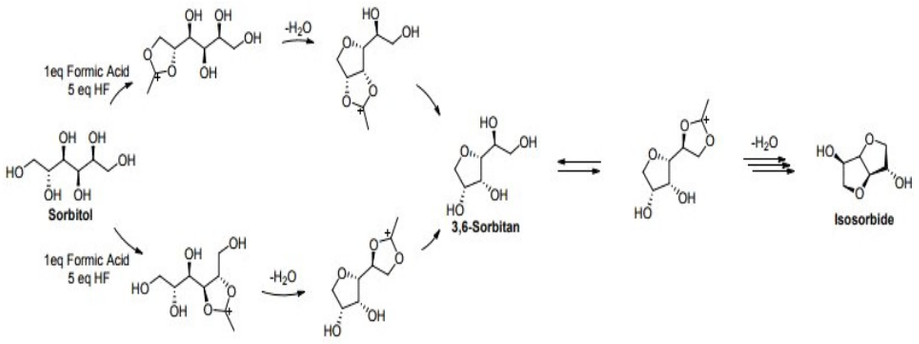

Fig. 3.19 *Synthesis of Sorbitrate*

3.9.3 Diltiazem

The synthesis of diltiazem can be obtained by oxidizing N-(N,N-dimethylethanamine)-4-aminophenol and adding 3-mercaptopropionic acid via a Michael reaction.

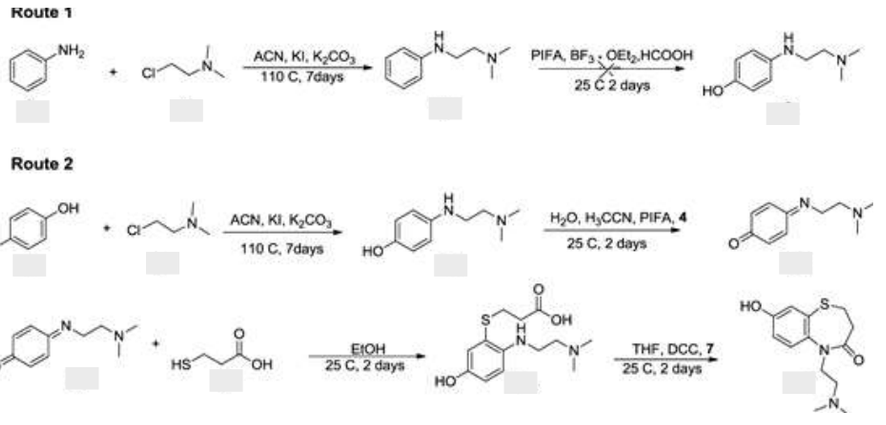

Fig. 3.20 *Synthesis of Diltiazem*

3.9.4 Quinidine

Quinidine is an optical isomer of quinine, originally extracted from the bark of the Cinchona tree and similar plant species. Quinidine is the d-isomer of quinine. Quinidine is a Class 1A agent that increases the action potential duration and the effective refractory period. It also reduces the force of contraction of the heart and possesses anticholinergic activity.

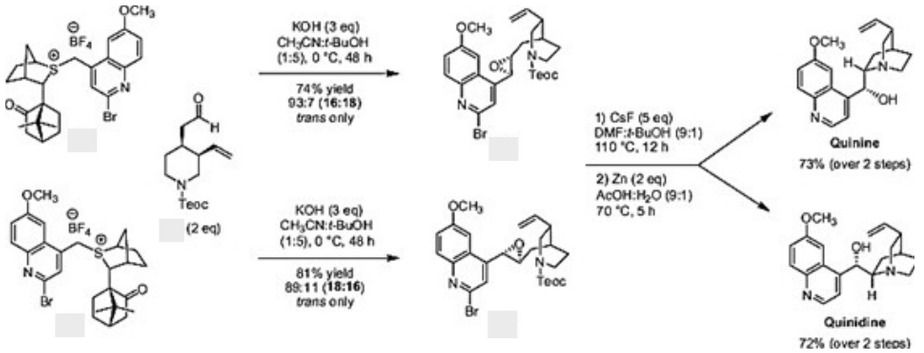

Fig. 3.21 *Synthesis of Quinidine*

3.9.5 Veropamil

5-[(3,4-dimethoxyphenethyl)methylamino]-2-(3,4 dimethoxyphenyl) isopropylvaleronitrile, is synthesized by a scheme using 3,4-dimethoxyphenyl-acetonitrile as the initial substance. The synthesis of the final product is accomplished by alkylating 2-(3.4-dimethoxyphenyl)-3-methylbutyronitrile with N-[2-(3,4-dimethoxyphenyl)-ethyl]-N-3-(chloropropyl)-N-methylamine. The initial 2-(3.4-dimethoxyphenyl)-3-methylbutyronitrile is synthesized by alkylating 3,4-dimethoxyphenylacetonitrile with isopropyl chloride in the presence of sodium amide. The alkylating agent, N-[2-(3,4-dimethoxyphenyl)-ethyl]-N-3-(chloropropyl)-N-methylamine, is also synthesized from 3,4 dimethoxyphenylacetonitrile followed by reduction into 3,4-dimethoxyphenylethylamine, with subsequent methylation into N-methyl-N-3,4-dimethoxyphenylethylamine. Next, the resulting N-[2-(3,4-dimethoxyphenyl)-ethyl]-N-methylamine is alkylated by 1-chloro-3-bromopropane into the desired N-[2-(3,4-dimethoxyphenyl)-ethyl]-N-3-(chloropropyl)-N-methylamine, which is alkylated by 2-(3.4-dimethoxyphenyl)-3-methylbutyronitrile to give the final product, verapamil.

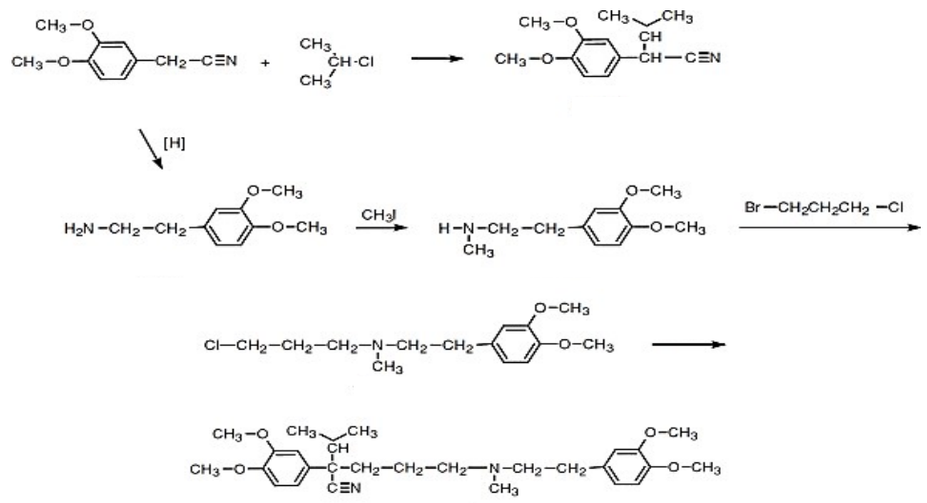

Fig. 3.22 Synthesis of Veropamil

3.9.6 Methyldopa

Methyldopa, (-)-3-(3,4-dihydroxyphenyl)-2-methylalanine, is synthesized by a few methods that are only slightly different. The first method is from 3,4-dimethoxyphenylacetone, which undergoes a Strecker–Zelinski reaction using potassium cyanide and ammonium carbonate, to give 4-methyl-4-(3,4-dimethoxybenzyl-hydantoine, which is further hydrolyzed in the presence of barium hydroxide to give (±)-3-(3,4-dimethoxyphenyl)-2-methylalanine (22.3.4). This undergoes acetylation at the amino group, and the racemic mixture is then separated using (-)-1-phenylethylamine. The isolated isomer is hydrolyzed using hydrobromic acid, which simultaneously removes the methoxy- and acetyl groups to give the desired (-)-3-(3,4-dihydroxyphenyl)-2-methylalanine.

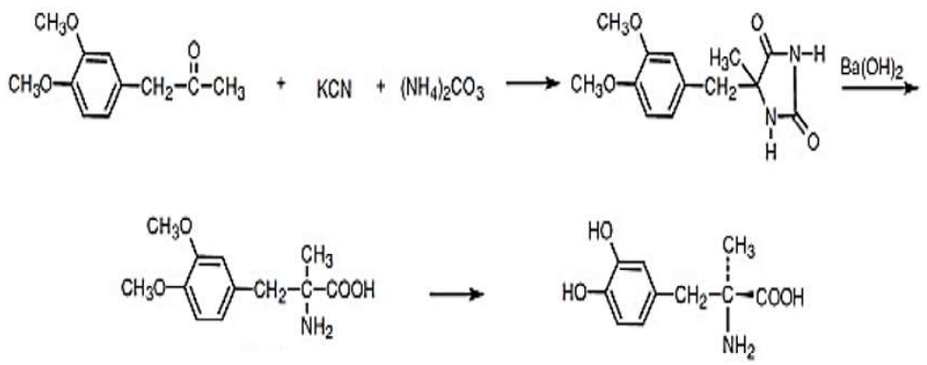

Fig. 3.23 Synthesis of Methyldopa

3.9.7 Atenolol

Atenelol is a beta – adrenergic blocking agent that blocks the effects of adrenergic chemicals, for example, adrenaline or epinephrine, released by nerves of sympathetic nervous system. One of the important function of beta- adrenergic

nerves is to stimulate the heart muscle to beat more rapidly. By blocking the stimulation by these nerves, atenelol reduces the heart rate and is useful in treating abnormally rapid heart rhythm. Atenelol also reduces the force of contraction of heart muscle and lowers the blood pressure. It is useful in treating angina.

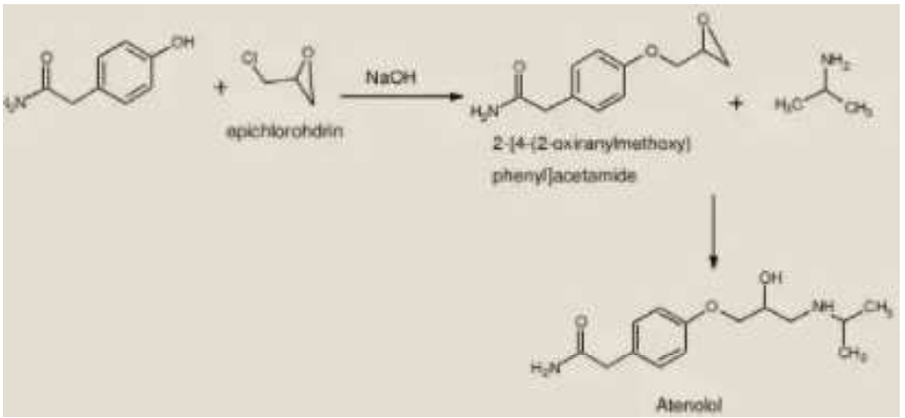

Fig. 3.24 *Synthesis of Atenolol*

3.9.8 Oxprenolol

Oxprenolol is a beta blocker. In addition, it has been found to act as an antagonist of the serotonin.

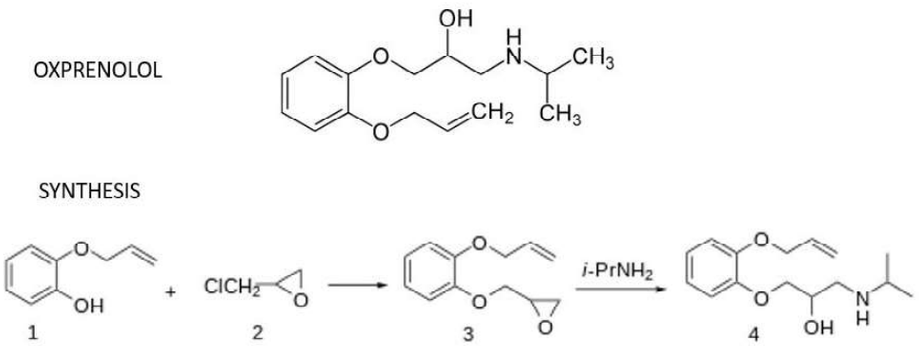

Fig. 3.25 *Synthesis of Oxprenolol*

Check Your Progress

14. What happens when amyl nitrite reacts with carbanions?
15. Name the reaction involves in the synthesis of diltiazem.
16. Write the name of the optical isomer of quinine.

3.10 ANSWERS TO 'CHECK YOUR PROGRESS'

1. Antineoplastic agents are a class of medications that are mostly used to treat cancer.

2. Tumors have the following alternative potential ways to resist drug action:
   - Pump out or do not admit drug to cross the cell membrane.
   - Metabolize the drug to inactive metabolites.
   - Exist as a heterogeneous population of cells with and while not artificial deadly mutations.
3. Apaziquone is an example of a prodrug.
4. Mechlorethamine, bis-(2-chloroethyl)methylamine, is made by reacting methylamine with ethylene oxide, forming bis-(2-hydroxyethyl)methylamine, which upon reaction with thionyl chloride turns into the desired mechlorethamine.
5. It is an off-white crystalline, odourless powder. It is soluble in water or alcohol.
6. Antiestrogens, like tamoxifen, were found to bind to estrogen receptors and diminish current estrogen levels.
7. The two common natural products having anticancer properties *Allium sativum* L. (Garlic) and *Boswellia* species. (Write any given in the unit.)
8. The four common types of VCDs are coronary heart condition, strokes and transient ischemic attacks (TIAs), peripheral blood vessel sickness and aortic sickness.
9. Coronary heart condition occurs when the flow of oxygen-rich blood to the heart muscle is blocked or reduced.
10. The word 'fast' stands for face, arm, speech and time.
11. Vasodilators are drugs that are involved on the relaxation or widening of blood vessels and thereby maintaining or reducing blood pressure.
12. Clonidine, guanabenz and guanfacine are structurally connected compounds and have similar medicinal drug profiles.
13. Arterial dilator medication is usually used to treat systemic and pulmonary high blood pressure, coronary failure and angina.
14. Amyl nitrite, like other alkyl nitrites, reacts with carbanions to give oximes.
15. The synthesis of diltiazem can be obtained by oxidizing N-(N,N-dimethylethanamine)-4-aminophenol and adding 3-mercaptopropionic acid via a Michael reaction.
16. Quinidine is an optical isomer of quinine.

3.11 SUMMARY

- The term 'neoplastic' means cancer cells. Antineoplastic agents are a class of medications that are mostly used to treat cancer.
- Many types of cancer can be treated by chemotherapy. It uses one or more anti-cancer drug for the treatment.

NOTES

- The synthesis of mustard agent in 1854 and its ulterior use throughout war I highlighted its gastrointestinal and myelosuppressive toxicity.
- Alkylating agents directly damage the DNA via DNA intra- and inter-strand covalent crosslinking, preventing the cells from reproducing.
- The different types of alkylating agents based on the chemical structures are nitrogen mustard, nitrosourea, triazine, alkyl sulfonate, ethylenimine and platinum agents.
- Antimetabolites are chemotherapy medications that are structurally associated with fundamental metabolites found within the body.
- Pyrimidine analogs and purine analogs are structures that mimic deoxyribonucleic acid, however, are changed slightly by substitution of an H with a halogen or an O with a sulfur or arabinose sugar with ribose/ deoxyribose.
- Antibiotics, such as actinomycin D, anthracyclines, and the anthracenones are approved as antitumor agents.
- Bacteria, fungi and a few plants are able to turn out aromatic polyketides.
- Aromatic polyketides are also called anthracyclines because of the presence of a tetracyclic bearing an anthraquinone chemical group in their aglycone moiety.
- Non-ribosomal peptide synthases are the key enzymes within the synthesis of non-ribosomal peptides.
- Drugs that inhibit mitosis, or cell division are called mitotic inhibitors.
- Chemotherapeutic drugs destroy fast-growing cells in the body and are used to treat cancer.
- Some of the common chemotherapeutic drugs are mechlorethamin, cyclophosphamide, melphalan, 6-mercaptopurine and uracil mustards.
- The four common types of VCDs are coronary heart condition, strokes and transient ischemic attacks (TIAs), peripheral blood vessel sickness and aortic sickness.
- Factors responsible for VCDs are alcohol, age, high blood pressure, obesity, diet, gender, etc.
- Cardiovascular medications are the common name of compounds used to treat completely different heart disorders (such as congestive coronary failure, angina, or arrhythmia) or diseases of the system (e.g., hypertension).
- Coronary failure is influenced by drugs such as amyl nitrate, sorbitrate, diltiazem, quinidine, veropamil, methyldopa, atenolol and oxprenolol.

3.12 KEY TERMS

- **Antineoplastic Agents**: They refer to the drugs that block the formation of neoplasms (growths that may become cancer).

- **Chemotherapy:** It refers to the treatment of disease using chemical substances, especially the treatment of cancer by cytotoxic and other drugs.
- **Alkylating Agents**: They are compounds that work by adding an alkyl group to the guanine base of the DNA molecule, preventing the strands of the double helix from linking as they should.
- **Antimetabolites:** These substances interfere with the normal metabolic processes within cells, typically by combining with enzymes.
- **Mitotic Inhibitors:** These drugs inhibit mitosis, or cell division by disrupting microtubules, which are structures that pull the chromosomes apart when a cell divides.
- **Antagonist Drugs:** These substances that stop the action or result of another substance.
- **Adrenergic Receptors:** These are a category of G protein-coupled receptors that are targets of the many catecholamines like norepinephrine (noradrenaline) and epinephrine (adrenaline) made by the body.
- **Cardiovascular Diseases (CVDs):** These diseases refer to conditions that involve narrowed or blocked blood vessels that can lead to a heart attack, chest pain (angina) or stroke.
- **Arteriolar Dilators:** These substances preferentially dilate arterioles.

3.13 SELF-ASSESSMENT QUESTIONS AND EXERCISES

Short-Answer Questions

1. What are the challenges faced during the development of chemotherapy drugs?
2. Mention the causes of cardiovascular diseases.
3. Enlist all the natural products which can effectively help in reducing symptoms of cancer.
4. What are the mechanistic categories of dilator medication?
5. What are the ways to reduce the risk of cardiovascular diseases?

Long-Answer Questions

1. Give a detailed account of mitotic inhibitors.
2. Explain the recent developments that have been done to provide better health care to cancer patients.
3. Analyse the role of alkylating agents in treatment of cancer.
4. Discuss and illustrate the synthesis of any three antineoplastic agents.

3.14 FURTHER READING

Lednicer, D. 2015. *Antineoplastic Drugs: Organic Syntheses*. Germany: Wiley.

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UNIT 4 ANTIINFECTIVE DRUGS AND PSYCHOACTIVE DRUGS

NOTES

Structure

NOTES

4.0 INTRODUCTION

Antiinfectives are medications that stop and treat infections; they're very important to the health and well-being of society. Usually helping the body's defenses, this wide selection of medicines has been developed to manage infections caused by microorganism, viruses, and parasites. The clinical course of any infection relies on the interaction between the infectious agent and a complex set of host defenses.

Prior to starting antiinfectives medical care, specimens for culture and sensitivity testing ought to be obtained. The exceptions to the current care are septic patients, in whom prompt antiinfectives medical care shouldn't be delayed if culture specimens can't be obtained in a very timely manner, as a result of early administration of antibiotics in infection has shown to reduce mortality. Empiric antiinfectives medical care choice relies on the seemingly pathogens for the location or kind of infection; the patient's medical, medication, and social history; previous antibiotic use; and local condition patterns.

The pharmacological treatment of psychiatric disorders has created speedy progress since the 1950s. Psychoactive medication are among the foremost wide used pharmacological agents worldwide and their range has enhanced exponentially. These developments have occurred in spite of the extremely advanced clinical characteristics of psychiatric disorders and also the absence of biological anchors for their diagnosing. Each of these limitations are a consequence of the very fact that the pathophysiological basis of most psychiatric disorders has not yet been de defined. A role for genetic factors within the pathologic process of the many of the main psychiatric syndromes is well established. The arrival of recent molecular techniques has led to an intensive hunt for susceptibility genes, eûorts that have yielded intriguing leads however no deûnitive ûndings. This unit will explain synthesis of different antiinfective and psychotic drugs Also, it will describe mode of action of drugs. In addition, it will also analyse the recent developments in pharmaceutical industry.

4.1 OBJECTIVES

After going through this unit, you will be able to:

- Explain the local antiinfective drugs
- Discuss synthesis of different antiinfective and psychotic drugs
- Describe the mode of action of drugs
- Analyse the recent developments in pharmaceutical industry

4.2 LOCAL ANTIINFECTIVE DRUGS: INTRODUCTION

The first thought in choosing antimicrobial medical care is whether or not an antiinfectives agent is really required. The medical diagnosis ought to indicate

whether or not the cause needs treatment with an antiinfectives drug or whether or not the infection is self-limiting and can resolve while not antiinfectives therapy. For self-limiting infections, supportive treatment and symptom management are suggested. If potential, antiinfectives use ought to be restricted to extremely suspicious, empiric, and definitive diagnoses of infection to avoid toxicity and therefore the development of antiinfectives resistance.

4.2.1 General Mode of Action

Antiinfective agents act on invasive organisms in many alternative ways as mentioned medical care.

Table 4.1 *Drugs and their Modes of Action*

Drug	**Mode of Action**
Penicillins	Interfere with the biosynthesis of the pathogen cell wall
Sulfonamides	Inhibit invading organisms from using substances essential to their growth and development
Antimycobacterial	
Trimethoprim-Sulfamethoxazole	
Aminoglycosides	Interfere with steps involves in protein synthesis thereby rendering cell division non-functional
Macrolides	
Chloramphenicol	
Fluoroquinolones	Interfere with DNA synthesis leading to inability to divide and ultimately, cell death
Antifungals	Alteration of cell membrane permeability leading to leakage of essential cellular components and cell death
Antiprotozoals	
Other antibiotics	

4.3 SYNTHESIS OF ANTIINFECTIVE DRUGS

Let us study the process of synthesis of antiinfective drugs in detail.

4.3.1 Sulphonamides

Sulfonamide molecular structure is comparable to p-Amino benzoic acid (PABA) that is required in bacterium organisms as a substrate of the catalyst dihydro pteroate synthetase for the synthesis of characid Hydro folic acid (THF). Folic acid - synthesized from PABA, pteridine and salt. All sulfonamides are analogs of PABA. All antibacterial medicines are bacteriostatic.

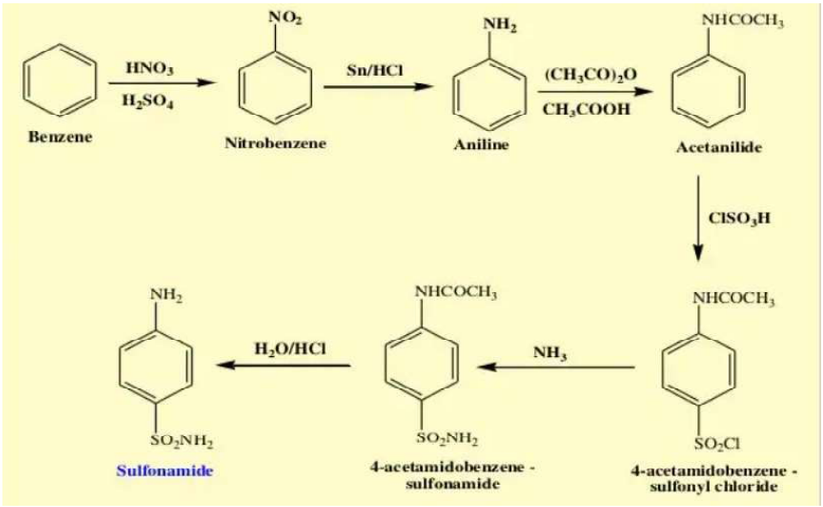

Fig. 4.1 *Synthesis of Sulphonamides*

4.3.2 Furazolidone

Furazolidone, 3-(5-nitrofurfuryliden) amino-2-oxazolidinone, is synthesized from 2-hydroazinoethanol, which is reacted with diethyloxalate to make 3-amino-2-oxazolidone. Reacting this with benzaldehyde gives the corresponding hydrazone. Purifying the resulting product and then reacting it with 5-nitrofurfurol gives furazolidone.

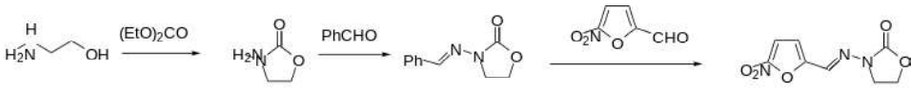

Fig. 4.2 *Synthesis of Furazolidone*

4.3.3 Nalidixic Acid

Nalidixic acid, 1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthiridin-3-carboxylic acid, is synthesized by the following scheme. In the first stage, the reaction of 2-amino-6-methylpyridine and diethyl ethoxymethylenemalonate forms the substituted product, which when heated cyclizes to ethyl ester of 4-hydroxy -7-methyl-1,8-napthiridin-3-carboxylic acid. Hydrolyzing the resulting product with a base gives the corresponding acid. Alkylating this with ethyl iodide in the presence of potassium hydroxide gives nalidixic acid.

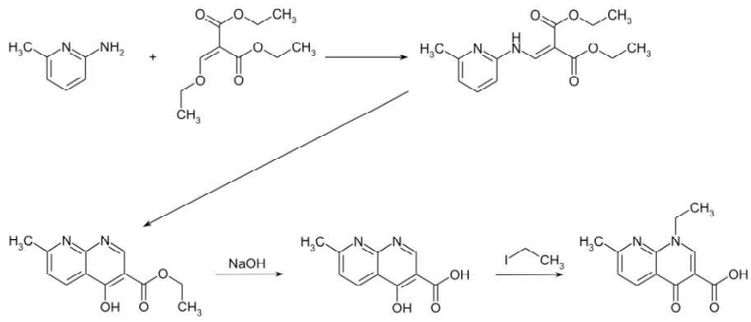

Fig. 4.3 *Synthesis of Nalidixic Acid*

4.3.4 Ciprofloxacin

Ciproûoxacin coordination compound is yellow, crystalline in nature, slightly absorbent powder, soluble in water, slightly soluble in methyl alcohol, very slightly soluble in ethyl alcohol, however insoluble in ketone, ester, and dichloromethane. It is very effective for the treatment of urinary tract infection, prostatitis, and for acute diarrhoeic sickness caused by E. coli, Shigella, Salmonella and Campylobacter.

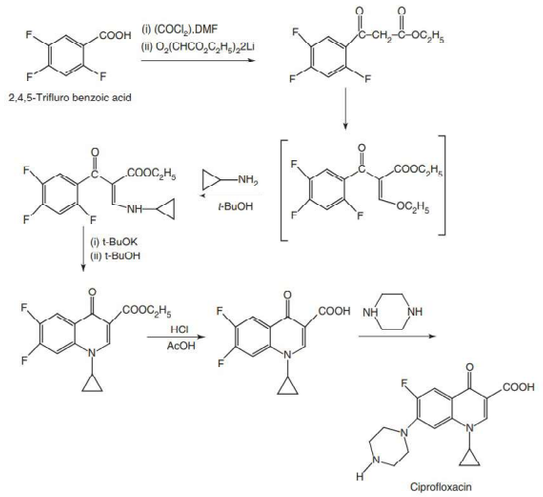

Fig. 4.4 *Synthesis of Ciproûoxacin*

4.3.5 Norfloxacin

The method of synthesis is basically the same as that suggested for synthesizing nalidixic and oxolinic acids. Reacting 3-chloro-4-fluoroaniline and ethyl ethoxymethylenmalonate gives the substitution product, which upon heating in diphenyl ester cyclizes into ethyl ester of 6-fluoro-7-chloro-1,4-dihydro-3-quinolin-4-on-carboxylic acid. Direct treatment of the product with ethyl iodide in the presence of triethylamine and subsequent hydrolysis with a base gives 1-ethyl-6-fluoro-7-chloro-1,4-dihydro-3-quinolin-4-on-carboxylic acid. Reacting this with piperazine gives norfloxacin.

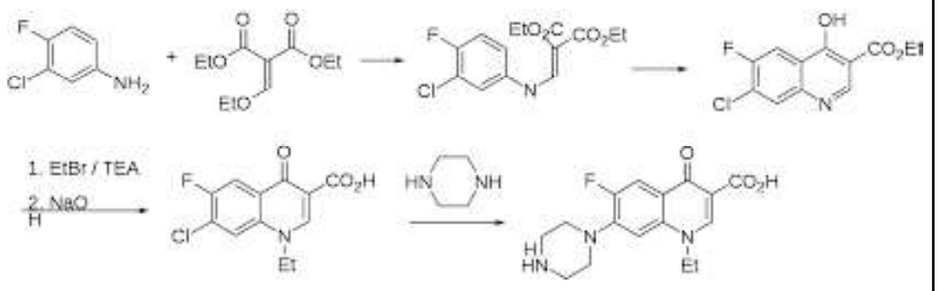

Fig. 4.5 *Synthesis of Norfloxacin*

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4.3.6 Dapsone

Dapsone, 4,42 -diaminodiphenylsulfone, is synthesized from either 4-chloronitrobenzene or from the sodium salt of 4-acetamidobenzenesulfonic acid. Reacting 4-chloronitrobenzene with sodium sulfide gives 4,42 -dinitrodiphenylthioester, and oxidation of the sulfur atom in this compound using potassium dichromate in sulfuric acid gives 4,42 -dinitrodiphenylsulfone. Reduction of the nitro group in the resulting compound using tin dichloride in hydrochloric acid makes the desired dapsone.

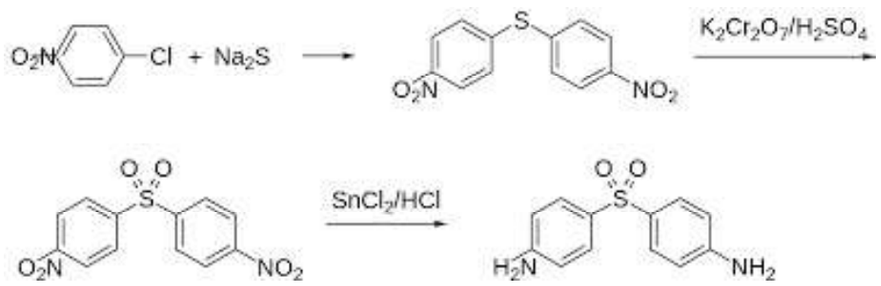

Fig. 4.6 *Synthesis of Dapsone*

4.3.7 Amino Salicylic Acid

The synthesis of 5-aminosalicylic acid from the Kolbe-Schmidt reaction involves three steps. First, sodium p-aminophenol is obtained from the reaction of p-aminophenol and sodium hydroxide. Second, carboxylation of sodium p-aminophenol with CO_2 follows. Finally, 5-aminosalicylic acid is obtained after acid washing.

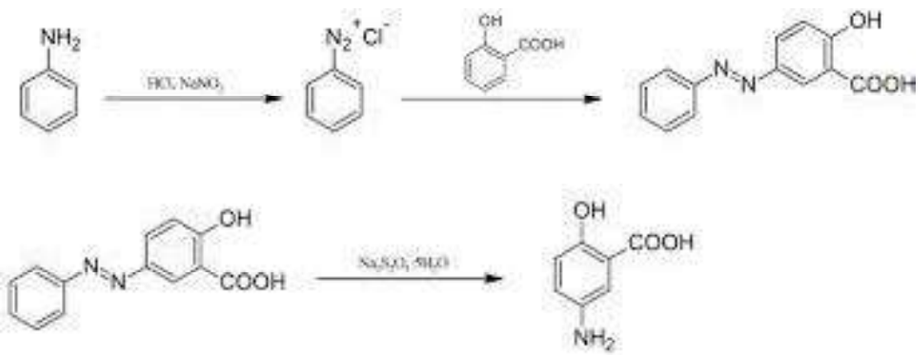

Fig. 4.7 *Synthesis of Amino Salicylic Acid*

4.3.8 Isoniazid

The antimicrobial activity of INH is selective for mycobacteria, likely due to its ability to inhibit mycolic acid synthesis, which interferes with cell wall synthesis, thereby producing a bactericidal effect.

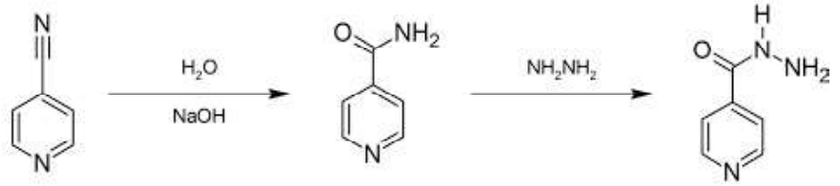

Fig. 4.8 *Synthesis of Isoniazid*

4.3.9 Ethionamide

Ethionamide, 2-(ethyl)isonicotinthioamide, a derivative of isonicotinic acid, is synthesized by the following scheme. Diethyl oxalate is condensated with methylethylketone in the presence of sodium ethoxide to form the ethyl ester of propi-onylpyruvic acid. Condensation of this with cyanoacetamide results in heterocyclization, to form 3-cyano-4-carboethoxy-6-ethyl-2-pyridone, which is hydrolyzed with hydrochloric acid to give 4-carboxy-6-ethyl-2-pyridone. Reacting this with a mixture of phosphorous oxychloride and pentachloride gives 6-ethyl-2-chloroisonicotinic acid chloride, which is subsequently treated with ethyl alcohol to obtain the ethyl ester of 6-ethyl-2-chloroisonicotinic acid. Reducing this with hydrogen over a palladium catalyst removes the chlorine atom at position 2 of the pyridine ring, giving the ethyl ester of 6-ethylisonicotinic acid. Interacting this with ammonia, followed by dehydration of the resulting amide of 6-ethylisonicotinic acid using phosphorous pentoxide gives the nitrile of 6-ethylisonicotinic acid. Finally, reacting this with hydrogen sulfide gives ethionamide.

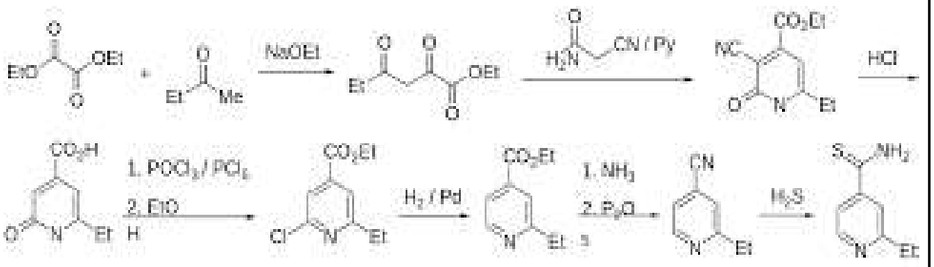

Fig. 4.9 *Synthesis of Ethionamide*

4.3.10 Ethambutol

Ethambutol, (±)-N, N2 -ethylenbis-(2-aminobutan-1-ol), is synthesized in several different ways. According to one of them, nitropropane undergoes oxymethylation using formaldehyde, and the nitro group in the resulting 2-nitrobutanol is reduced by hydrogen to an amino group, making racemic (±) 2-aminobutanol. l (+) tartaric acid is used to separate (+) 2-aminobutanol. Reacting this with 1, 2-dichloroethane in the presence of sodium hydroxide gives ethambutol.

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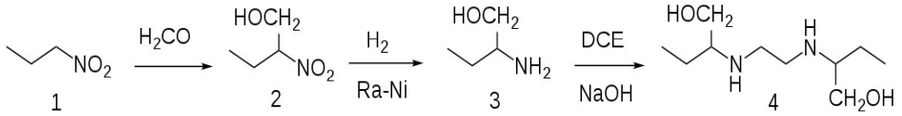

***Fig. 4.10** Synthesis of Ethambutol*

4.3.11 Fluconazole

The Friedel-Crafts condensation of 1,3-di (I) with chloroacetyl chloride (II) by means of $AlCl_3$ yields alpha-chloro-2,4-difluoroacetophenone (III), which is treated with 1,2,4- (IV) and triethylamine in refluxing ethyl acetate giving alpha-(1H-12,4-triazol-1-yl)-2,4-diftuoroacetophenone (V). The reaction of (V) with trimethylsulfoxonium iodide (VI) by means of NaOH in toluene affords 1-[2-(2,4-di fluorophenyl)-2,3-epoxypropyl]- (VII), which is finally treated again with 1,2,4-triazole (IV) and K_2CO_3 in hot DMF.

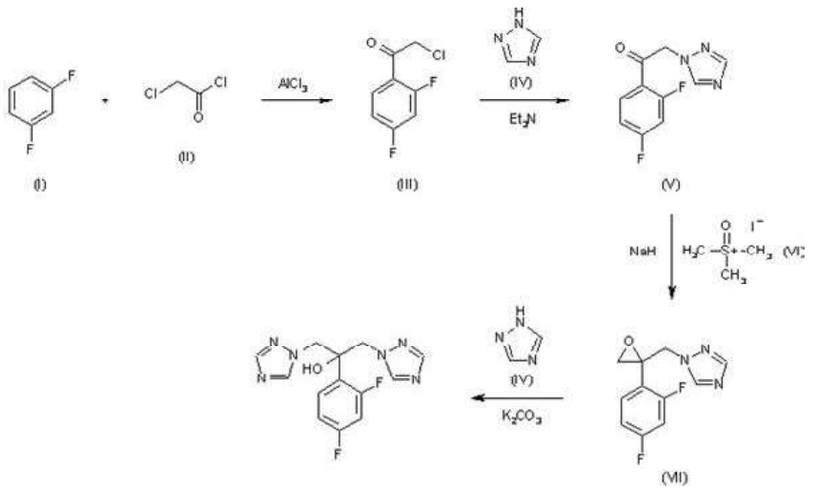

***Fig. 4.11** Synthesis of Fluconazole*

4.3.12 Econozole

For synthesis of econazole nitrate, imidazole is coupled with brominated 2,4-dichloroaceto -phenone and the resultant ketone is oxidized with sodium borohydride to the corresponding alcohol. This product is coupled with 2,4-dichlorotoluene by means of sodium hydridein hexamethylphosphoramide before being extracted with nitric acid to give econazole nitrate.

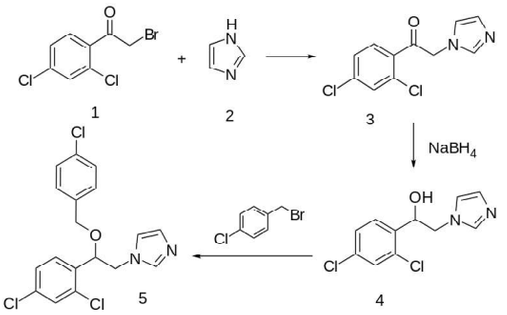

***Fig. 4.12** Synthesis of Econozole*

4.3.13 Griseofulvin

The first step in the biosynthesis of griseofulvin by P. griseofulvin is the synthesis of the 14-carbon poly-â-keto chain by a type I iterative polyketide synthase (PKS) via iterative addition of 6 malonyl-CoA to an acyl-CoA starter unit. The 14-carbon poly-â-keto chain undergoes cyclization/aromatization, using cyclase/aromatase, respectively, through a Claisen and aldol condensation to form the benzophenone intermediate. The benzophenone intermediate is then methylated via S-adenosyl methionine (SAM) twice to yield griseophenone C. The griseophenone C is then halogenated at the activated site ortho to the phenol group on the left aromatic ring to form griseophenone B. The halogenated species then undergoes a single phenolic oxidation in both rings forming the two oxygen diradical species. The right oxygen radical shifts alpha to the carbonyl via resonance allowing for a stereospecific radical coupling by the oxygen radical on the left ring forming a tetrahydrofuranone species.The newly formed grisan skeleton with a spiro center is then O-methylated by SAM to generate dehydrogriseofulvin. Ultimately, a stereoselective reduction of the olefin on dehydrogriseofulvin by NADPH affords griseofulvin.

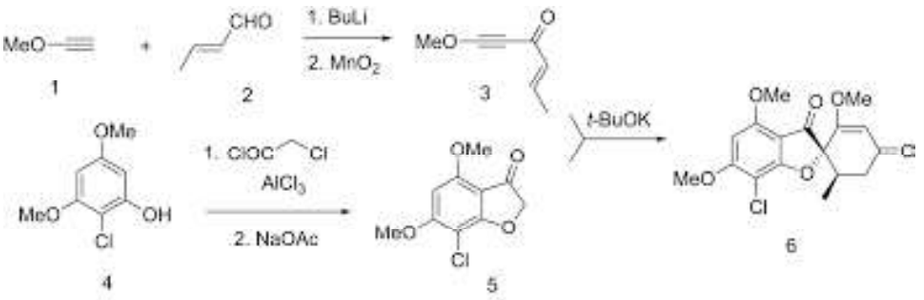

Fig. 4.13 *Synthesis of Griseofulvin*

4.3.14 Chloroquine

Chloroquine, 7-chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline, is made by reacting 4,7-dichloroquinoline with 4-diethylamino-1-methylbutylamine at 180 °C.

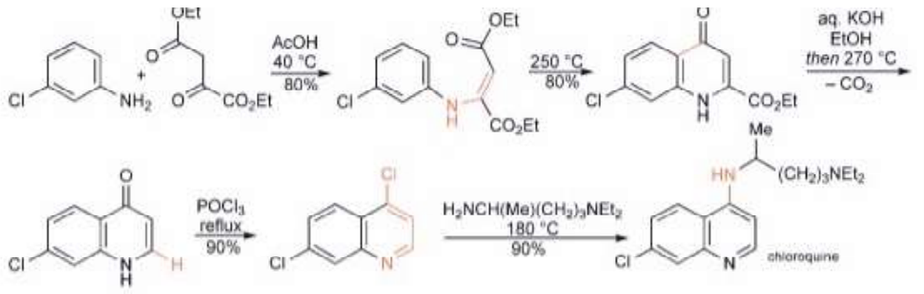

Fig. 4.14 *Synthesis of Chloroquine*

Check Your Progress

1. How does aminoglycoside act on invasive organisms?
2. Write the molecular formula of nalidixic acid.
3. Which antiinfective drug is used to treat acute diarrhoeic sickness caused by E. coli, Shigella?

4.4 PSYCHOACTIVE DRUGS-THE CHEMOTHERAPY OF MIND: INTRODUCTION

Whether drugs are an art or science could seem an outdated, if not naive, discussion at the dawn of the 21st century. This impression is bolstered by the in depth basis of recent drugs in bioscience. Powerful diagnostic technology has boundlessly exaggerated the exactness of diagnosing, and evidence-based prescription is speedily turning into a hallowed cornerstone of medicine. Yet, one has to look no more than pharmacotherapy so as to comprehend how tenuous the scientiûc roots of our discipline still are. This can be significantly true of the pharmacotherapy of psychiatric disorders but is by no means suggesting being restricted to the present. Let us study neurotransmitters, CNS depressants and general anaesthetics in detail.

4.4.1 Neurotransmitters

Neurotransmitters are chemical substances that relay, amplify, and modulate signals between one nerve cell and another or between a nerve cell and another cell. Typically, neurotransmitters are packaged into vesicles that cluster below the membrane on the presynaptic side of a conjugation and are discharged into the junction cleft, wherever they bind to receptors within the membrane on the postsynaptic cell. Release of neurotransmitters sometimes follows arrival of a nerve impulse at the conjugation however might follow stratified electrical potentials. Low level "baseline" unharness can also occur without electrical stimulation. Figure 4.15 shows the different types of neurotransmitters.

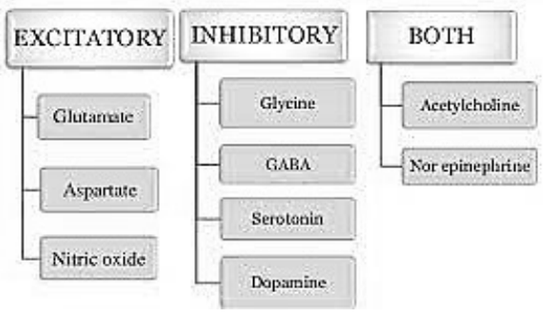

Fig. 4.15 *Types of Neurotransmitters*

The first neurotransmitter to be discovered was a small molecule known as acetylcholine. It plays a significant role within the peripheral nervous system,

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wherever it's discharged by motor neurons and neurons of the involuntary nervous system. It additionally plays a very important role within the central nervous system in maintaining cognitive function. Injury to the cholinergic neurons of the central nervous system is related to Alzheimer illness.

Glutamate is the primary stimulative transmitter within the central nervous system. Conversely, a serious repressive transmitter is its derivative ã-aminobutyric acid (GABA), whereas another repressive neurotransmitter is the organic compound known as glycine that is principally found within the spinal cord. Many neuromodulators, like dopamine, are monoamines. There are many monoamine neurotransmitter pathways within the brain, and this neurochemical is concerned in several functions, as well as motor control, reward and reinforcement and motivation.

Noradrenaline (or norepinephrine) is another aminoalkane and is primary neurotransmitter within the sympathetic nervous system wherever it works on the activity of various organs within the body to regulate blood pressure, heart rate, liver function and plenty of different functions. Neurons that use 5-hydroxytryptamine (another monoamine) project to numerous components of the nervous system. As a result, serotonin is involved in functions like sleep, memory, appetite, mood et al. It additionally produced within the gastrointestinal tract in response to food. Histamine, the last of the main monoamines, plays a job in metabolism, temperature management, control numerous hormones, and regulate the sleep-wake cycle, amongst different functions.

Neurotransmitters regulate many necessary functions, including:

- Heart rate
- Breathing
- Sleep cycles
- Digestion
- Mood
- Concentration
- Appetite
- Muscle movement

4.4.2 CNS Depressants

There are several CNS depressants, and most act on the brain. They have an effect on the neurochemical gamma-aminobutyric acid (GABA). Neurotransmitters are brain chemicals that facilitate communication between brain cells. GABA works by decreasing brain activity. Though completely different categories of CNS depressants add distinctive ways in which, ultimately it is their ability to extend GABA activity that produces a drowsy or calming result. Despite these helpful effects for individuals affected by anxiety or sleep disorders, barbiturates and benzodiazepines are often addictive and should be used solely as prescribed.

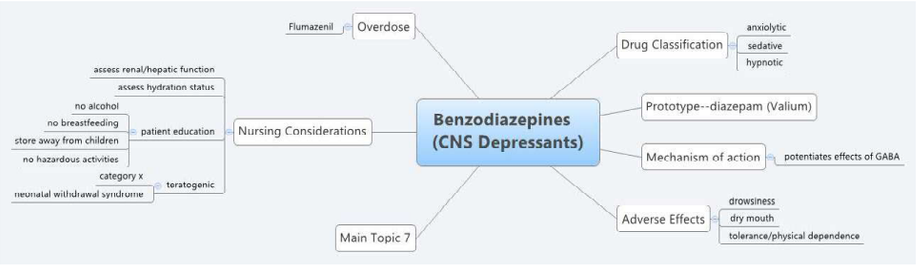

Fig. 4.16 *Benzodiazepines – CNS Depressants*

CNS depressants mustn't be combined with any medication or substance that causes drowsiness, together with prescription pain medicines, bound over-the-counter cold and allergic reaction medications, or alcohol. If combined, they'll slow respiration, or slow both the heart and respiration, which might be fatal.

Discontinuing prolonged use of high doses of CNS depressants will result in withdrawal. As they work by decelerating the brains activity, a possible consequence of abuse is that when one stops taking a CNS depressant, the brains activity will rebound to the purpose that seizures will occur. Somebody considering ending their use of a CNS depressant, or who has stopped and is suffering withdrawal, ought to speak with a doctor and get medical treatment.

In addition to medical direction, guidance in an in-patient or out-patient setting will facilitate those who are overcoming addiction to CNS depressants. For instance, cognitive-behavioral medical care has been used with success to assist people in treatment for abuse of benzodiazepines. This kind of medical care focuses on modifying a patients thinking, expectations and behaviours, whereas at the same time increasing their skills for handling numerous life stressors.

Often the abuse of CNS depressants happens in conjunction with the abuse of another substance or drug, like alcohol or hard drug. In these cases of polydrug abuse, the treatment approach ought to address the multiple addictions.

4.4.3 General Anaesthetics

General anesthesia could be a combination of medicines that place you in a very sleep-like state before a surgery or different process. After general anaesthesia, you do not feel pain as a result of you are fully unconscious. General anaesthesia sometimes uses a mixture of intravenous medication and inhaled gasses (anesthetics). General anesthesia is over simply being asleep, although it'll probably feel that way to you. However, the anesthetised brain does not reply to pain signals or reflexes. An anesthesiologist could be a specially trained doctor who makes a speciality of anaesthesia. Whereas you are under anaesthesia, the medical specialist monitors your body's very important functions and manages your respiration.

Risks and side effects

You might feel a little drowsy when you wake up from the anesthesia. Other common side effects from the medicine are as follows:

- Nausea and vomiting
- Dry mouth

- Sore throat
- Hoarse voice
- Sleepiness
- Shivering
- Muscle aches
- Itching
- Confusion, especially in older people

4.4.4 Mode of Action of Hypnotics and Sedatives

Hypnotics are believed to exert their effect on the brain by interacting with receptors for the neurotransmitter GABA. Their effect at these receptors enhances the action of GABA as an inhibitory neurotransmitter and results in a depression of brain activity.

Benzodiazepines

Some of the common effects of benzodiazepines are as follows:

- Increase frequency of opening of Cl- channels induced by GABA (GABA facilitatory action)
- Increase binding of GABA to GABAA receptor

Barbiturates

Some of the common effects of barbiturates are as follows:

- Increase duration of opening of Cl- channels induced by GABA (GABA facilitatory action) at high concentration
- Can directly increase Cl- conductance through Cl- channels (GABA mimetic action)
- Inhibit Ca dependent release of neurotransmitters
- Depress glutamate induced neuronal depolarization through AMPA receptor
- Depress voltage sensitive Na+ & K+ channels

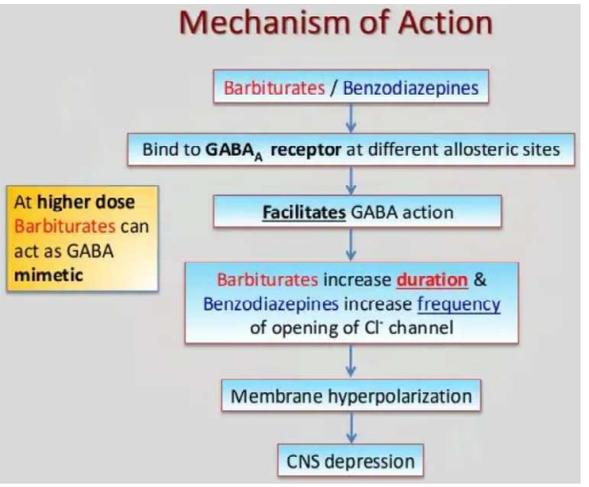

Fig. 4.17 *Mechanism of Action of Hypnotics*

Sedatives are central nervous system depressants and vary wide in their efficiency. They are typically within the variety of a pill or liquid. Although sedatives are used wide for their healthful properties, abuse of sedatives may end up in dependence and addiction.

Uses of sedatives

Sedatives are accustomed treat varied conditions; a number of common examples include anxiety, tension, seizures, panic disorders and sleep disorders. Most sedatives that are used for recreational functions are entertained from medical use.

Effects of sedatives

The effects of sedatives will last anywhere from a few of hours to quite a day. Generally, sedatives cause physical depression, muscular relaxation and sedation; because of the varied kinds of sedatives, there's a spread of alternative effects counting on that substance has been taken. Sedatives depress most body functions, so that they greatly impact the flexibility to drive, operate machinery and participate in tasks requiring muscle coordination. A person who is under the influence of a sedative, particularly if together with another drug, never ne'er drive. Here are some effects of sedatives:

- Feeling of relaxation
- Reduced anxiety
- Lowered inhibitions
- Reduced intensity of physical sensations
- Lightheadedness
- Drowsiness
- Slurred speech
- Slowed pulse rate
- Muscle incoordination
- Reduced dexterity
- Impaired learning throughout period the sedative is active
- Interruptions in memory
- Sometimes surprising self-contradictory side effects occur, for example, anxiety, nightmares and hostility

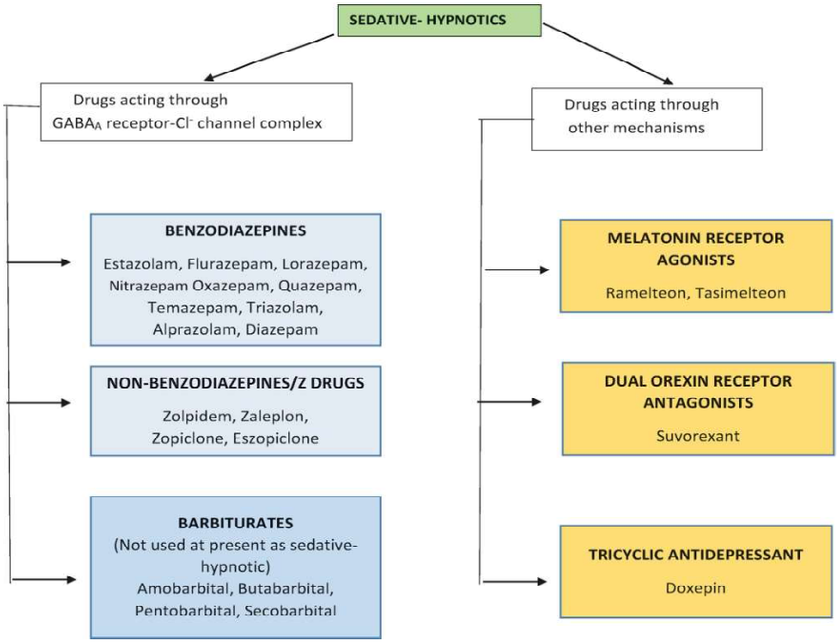

Fig. 4.18 *Sedative— Hypnotics*

Check Your Progress

4. What are the effects of benzodiazepines?
5. What are sedatives?
6. Name two melatonin receptor agonists.

4.5 ANTI-ANXIETY DRUGS

Some anti-anxiety medicines are designed to be taken on a short-term basis, while other medicines are prescribed for longer periods. Depending on your symptoms, you may need medicine to treat your physical symptoms, as well as your psychological ones. If you are considering taking medication for generalised anxiety disorder (GAD), your general practitioner (GP) should discuss the different options with you in detail before you start a course of treatment, including:

- Different types of medication
- Length of treatment
- Side effects and possible interactions with other medicines

Types of medication to treat anxiety, such as:

- Antidepressants
- Beta-blockers
- Low doses of antipsychotics

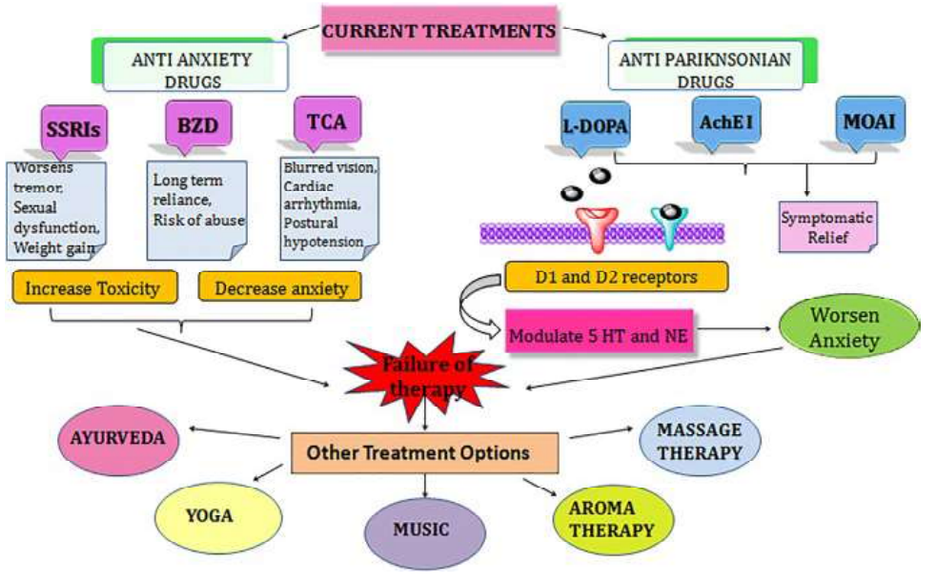

Fig. 4.19 *Types of Medication*

4.5.1 Benzodiazipines

Benzodiazepines represent a heterogenous cluster of medication that are increasing in variety as new compounds are endlessly developed, and that they are being seen with increasing frequency in rhetorical and drug police investigation programmes as medicine of abuse in recent years. They're clinically vital as medications to treat conditions like anxiety and sleep disorder. Benzodiazepines act on human gamma-aminobutyric acid A (GABA-A) receptors, as positive allosteric modulators to extend affinity of gamma aminobutyric acid binding and enhance the response. Overall, they perform as central nervous system depressants, and are artificial substances with modifications that impact their specific medicine properties. they have been used clinically since the 1960s with the introduction of chlordiazepoxide, for treatment of seizures and as sedatives and anxiolytics. Risks related to misuse of most benzodiazepines embrace acutely increasing risk of fatal respiratory overdose once taken with alternative sedating agents, and inveterately causing speedy tolerance and dependence with associated withdrawal on halt of use which will precipitate agitation, psychosis, convulsions and death.

Physical and chemical description

The general structure of a benzodiazepine molecule is that the presence of an amalgamated diazepine ring and a benzene. Nearly all clinically necessary benzodiazepines have an extra phenyl ring on that substitutions, or variations in side chains will occur to change features like efficiency, period of action, and pathway and rate of metabolism and elimination. The prototypical classical benzodiazepine is diazepam, a 1,4-benzodiazepine, thus named for the position of the N atoms within the central, seven sided diazepine ring.

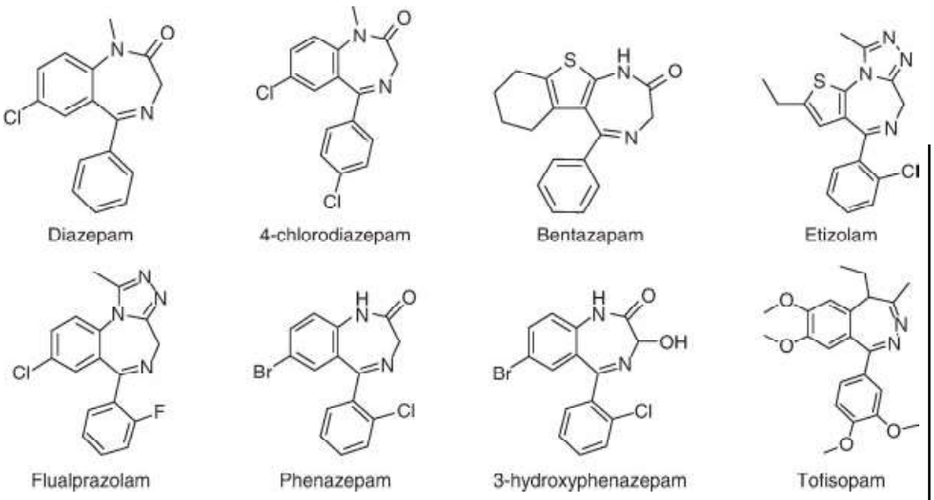

Fig. 4.20 *Chemical Structure of Benzodiazepines*

Pharmacokinetics

The pharmacology of benzodiazepines will vary considerably between the various medicine at intervals this category, as their structural variations greatly have an effect on pace of peripheral distribution, pathways of metabolism, and production of active metabolites. Most benzodiazepines are extremely protein bound, highly lipid soluble, and poorly filtered by the kidneys leading to primarily hepatic metabolism and elimination. They're ready to passively diffuse into the central nervous system to bind to target receptors.

Pharmacodynamics

The majority of benzodiazepines are pharmacologically active at the $GABA_A$ receptors within the central nervous system that contain both an á and a ã subunits. They cause a modification within the receptor position that promotes binding of gamma aminobutyric acid, and enhance its effects due to the main repressive neurochemical. On their own, benzodiazepines cannot open gamma aminobutyric acid channels even at high doses, requiring the neurochemical to be present. The prevalence of use of novel benzodiazepines isn't included in nationwide representative surveys. Thus it will solely be calculable from variety of various proxy measures, as well as population surveys, forensic seizures of drugs, screening for drivers comprehended beneath the influence, clinical displays to health care and post mortem investigations.

4.5.2 Buspirone

Buspirone causes a complex cascade of events in 5-HT system: at first impact at somatodendritic receptor causes decrease in 5-HT release but effects relieved by postsynaptic receptor agonism; chronic treatment (>2 weeks) leads to come to normal of 5-HT somatic cell firing and release. Combined with direct postsynaptic result could cause overall increase in 5-HT activity.

Elimination half-life is brief (three hours) thus needs multiple daily dosing. Slow release type has effective half-life of 9 hours. Active substance 1-pyramidyl

NOTES

piperazine (1-PP, an, antagonist) could contribute to buspirone's effect. Buspirone is used for GAD particularly if associated symptoms of depression. It doesn't seem to be as effective as BDZS and take longer to act. So, of very little use for acute anxiety

Mechanism of synthesis

Alkylation of 1-(2-pyrimidyl)piperazine (**1**) with 3-chloro-1-cyanopropane (**2**, 4-chlorobutyronitrile) gives **3**, which is reduced either by hydrogenation over Raney nickel catalyst, or with LAH. The resulting 1° amine (**4**) from the previous step is then reacted with 3,3-tetramethyleneglutaric anhydride (**5)**, 8-Oxaspiro [4.5]decane-7,9-dione) in order to yield buspirone (**6**).

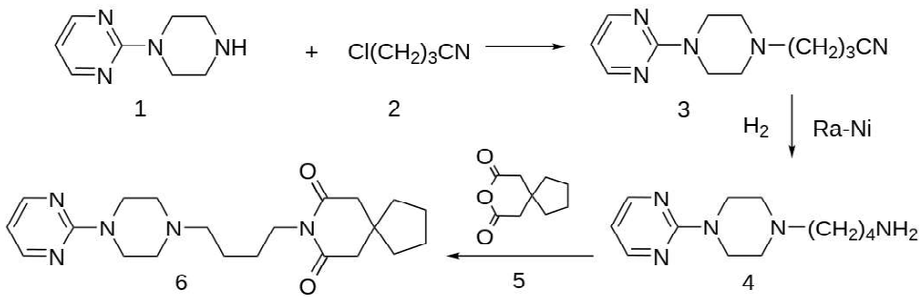

Fig. 4.21 *Synthesis of Buspirone*

Adverse effects

Some of the adverse effects of buspirone are as follows:

- Nausea, dizziness, headache
- No proof of a withdrawal syndrome
- No interaction with alcohol

Check Your Progress

7. Name any one antiparkinsonian drug.
8. How does benzodiazepine act on humans?

4.6 NEUROCHEMISTRY OF MENTAL DISEASES

Exciting analysis on the neurochemistry of psychiatric and neurologic disorders is being conducted by neurobiology researchers from a diversity of backgrounds. This analysis ranges from studies at the cellular and molecular level through studies on laboratory models and investigations on potential biomarkers in body fluids and postmortem brain tissue.

Illnesses below investigation embody mental sicknesses like mood and anxiety disorders, psychosis and variety of medicine disorders during which subjects show psychiatrical symptoms (e.g., Alzheimer's, stroke, induration, motor disorders, and eating disorders). Comorbidity, the presence of quite one disorder in a personal,

is usually a retardant once learning psychiatric and neurologic disorders. Many researchers are investigation the relationships not solely between psychiatrical and medicine disorders, however conjointly between disorders and conditions like cardiovascular disease and addictions. Many researchers are specializing in the importance of neuroglia and glia-neuron interactions in brain function/dysfunction.

Many of those studies aim to spot the potential causes and ways in which to stop the disorders, furthermore as increase the understanding of the mechanisms concerned in current treatments and develop better medication for future medical care.

Techniques used include the following techniques:

- Gas chromatography
- High pressure liquid chromatography
- Mass spectrometry
- Magnetic resonanace spectroscopy
- In vivo microdialysis
- Voltammetric techniques
- Pharmacokinetics
- Gene arrays
- Receptor binding techniques
- Rt-Pcr
- Histochemistry
- Immunoassays
- Animal models
- Enzyme assays
- Drug development
- Drug metabolism
- Deep sequencing and bioinformatics
- Autoradiography

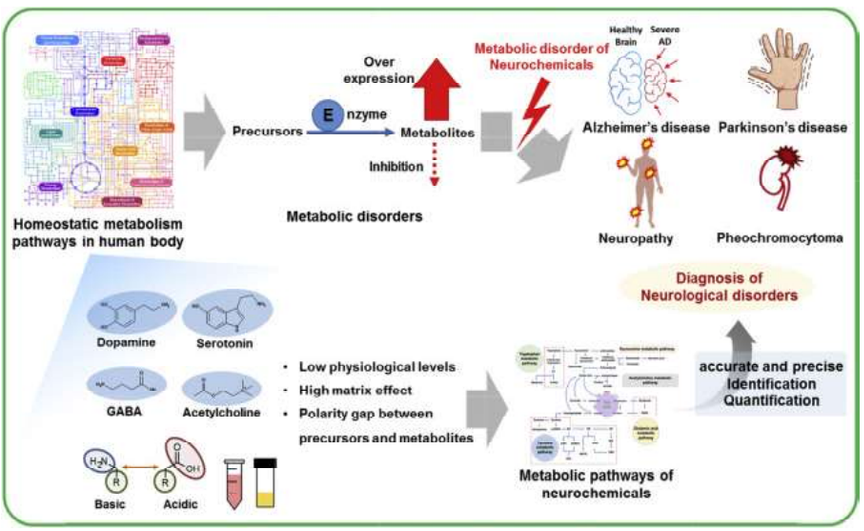

Fig. 4.22 *Neurochemical Profiling*

4.7 ANTIPSYCHOTIC DRUGS-THE NEUROLEPTICS

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Neuroleptics, also called antipsychotic medications, are medications that block dopamine receptors within the system. They're principally prescribed to manage mental diseases, like schizophrenic psychosis and major affective disorder, likewise as psychosis. Psychosis describes loss of touch with reality, with specific symptoms like problem concentrating, delirious, and engaging in movements without a purpose (i.e., psychomotor activity). There are 2 categories of antipsychotic drugs: the 'typical', additionally called 'first-generation', medication and also the additional usually prescribed 'atypical', or 'second- generation', drugs. First-generation neuroleptics are any classified as high or low efficiency, supported the quantity of the drug needed to attenuate the symptoms. Common high-potency, first-generation neuroleptics include neuroleptic drug, trifluoperazine and fluphenazine. Common low-potency, first-generation neuroleptics embody thioridazine, chlorpromazine and thiothixene. Among second-generation medications, clozapine, olanzapine, paliperidone, and risperidone are the foremost frequently prescribed. However, there are some limitation of antipsycotic drugs (Refer Figure 4.23).

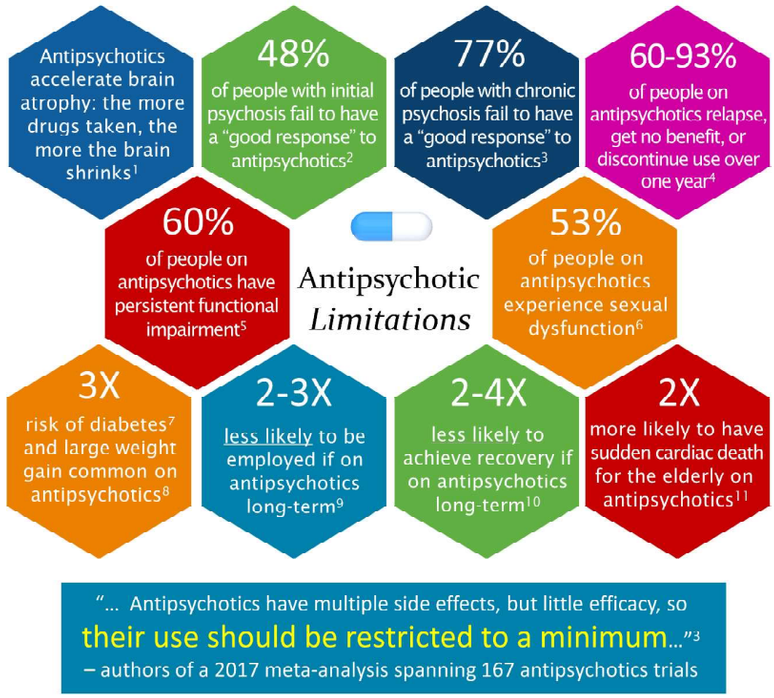

Fig. 4.23 *Limitations of Antipsycotic*

4.7.1 Antidepressants

The first effective medicinal drug agents of the trendy era were discovered accidentally within the late 1950s, which are as follows:

- **Iproniazid (monoamine oxidase inhibitor, MAOI):** It was originally developed as an antitubercular drug.

- **Imipramine (tricyclic):** It was originally developed as an antipsychotic drug analogue. (1957) MAOIs and tricyclics have the common property of interacting with aminoalkane systems (DA, NA, 5-HT).

Monoamine hypothesis of depression

The monoamine hypothesis was originally projected within the 1960s supported the actions of medication (reserpine determined to cause depression and antidepressants to alleviate depression). Some of the points regarding the hypothesis are as follows:

- Schildkraut—proposed catecholamines (NA, DA) to be functionally deficient in depression and elevated in activity in mania.
- Ashcroft—proposed indolamines (5-HT) to be functionally deficient in depression. This led to the event of 5-HT-selective medicine within the 1970s leading to the selective 5-hydroxytryptamine re-uptake inhibitors (SSRIs).
- It's been a lot of changed over succeeding decades, with the main target moving from neurochemical turnover, through receptor regulation, to intracellular changes.
- A current formulation proposes that a standard mechanism of medicinal drug action is to extend 5-HT neurotransmission by fixing receptor sensitivity.
- For instance, chronic 5-HT re-uptake blockade with SSRIs leads to down-regulation of 5-HT1A receptors on the cell bodies of serotonergic neurones within the brain stem, therefore disabling feedback, restoring cell firing rate leading to enhanced junction 5HT.

The action of antidepressants on aminoalkane neurotransmission doesn't by itself mean that these systems area unit abnormal in depression.

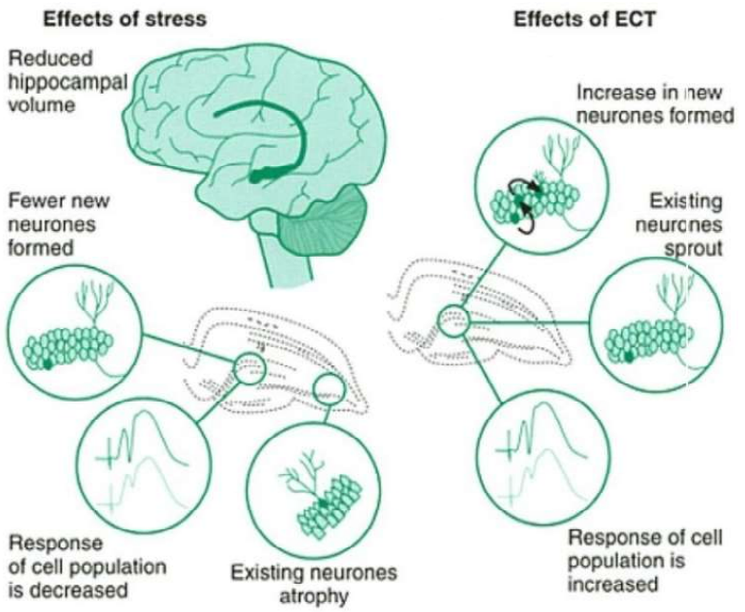

Fig. 4.24 *Reciprocal Effect of Stress and Electroconvulsive Therapy*

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The main evidence is summarised below.

Serotonin (5-HT)

- Reduced 5-HT metabolites within the liquid body substance of sufferers, and in brain tissue post-mortem
- Inflated platelet/brain 5-HT2 receptors
- Downregulation/reduced numbers of postsynaptic 5-HT1A receptors (neuroendocrine studies: prolactin response to tryptophan infusion; buspirone-induced hypothermia; positron emission tomography (PET) studies of brain 5-HT1A receptor binding)
- Relapse of depression elicited by tryptophan depletion in SSRI-treated and sober recovered depressed patients

Noradrenaline (NA)

- Reduced levels of the Na matter MHPG within the excretion of depressed subjects
- Attainable postsynaptic $\alpha 2$ downregulation (neuroendocrine studies: abnormal endocrine response to clonidine; insulin-induced hypoglycaemia)
- Attenuated responses to β-receptor agonists in depression
- Relapse of depression elicited by á-methyl paratyrosine (NA synthesis inhibitor) in patients treated with Na re-uptake inhibitors

Dopamine (DA)

- Enhanced D2 receptor numbers in some PET studies of depressed patients
- Mood elevating effects of DA-releasing psychostimulants
- Potential antipsychotic-induced depression (high dose—postsynaptic DA receptor blockade). Attainable neuroleptic drug antidepressant activity (low dose—presynaptic DA autoreceptor blockade)
- Presymptomatic studies systematically implicate DA systems in neural basis of reward (related to anhedonia)

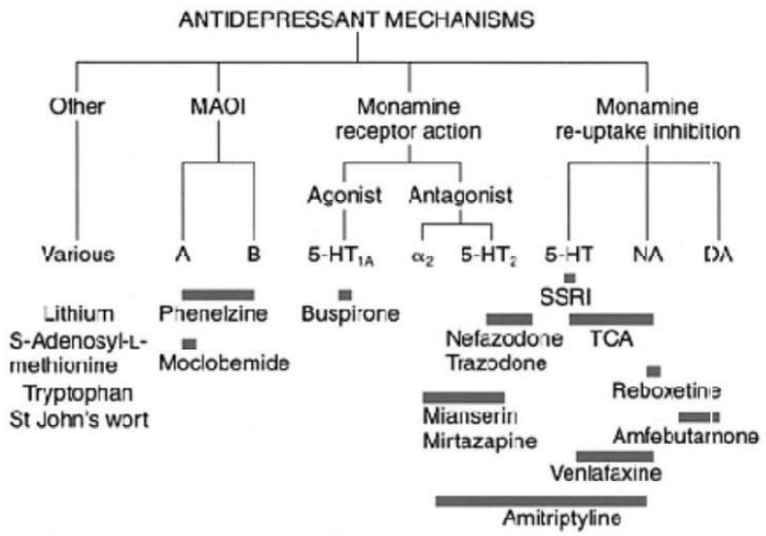

Fig. 4.25 *Acute Pharmacology of Some Antidepressants*

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4.7.2 Butyrophenones

Butyrophenones are a class of pharmaceutical drugs derived from butyrophenone.

Some of the examples of butyrophenones are as follows:

- Haloperidol, the most widely-used drug in this class
- Droperidol, often used for neuroleptanalgesic anesthesia and sedation in intensive-care treatment
- Benperidol, the most potent commonly-used antipsychotic (~ 200 times more potent as chlorpromazine)
- Triperidol, a highly-potent antipsychotic (100 times more potent than chlorpromazine)
- Melperone, a weakly-potent antipsychotic, in Europe commonly used for treatment of insomnia, confusional states, psychomotor agitation, and delirium, in particular, in geriatric patients
- Lenperone
- Domperidone, an dopamine-antagonist antiemetic, derived further from butyrophenone (not being a butyrophenone itself)

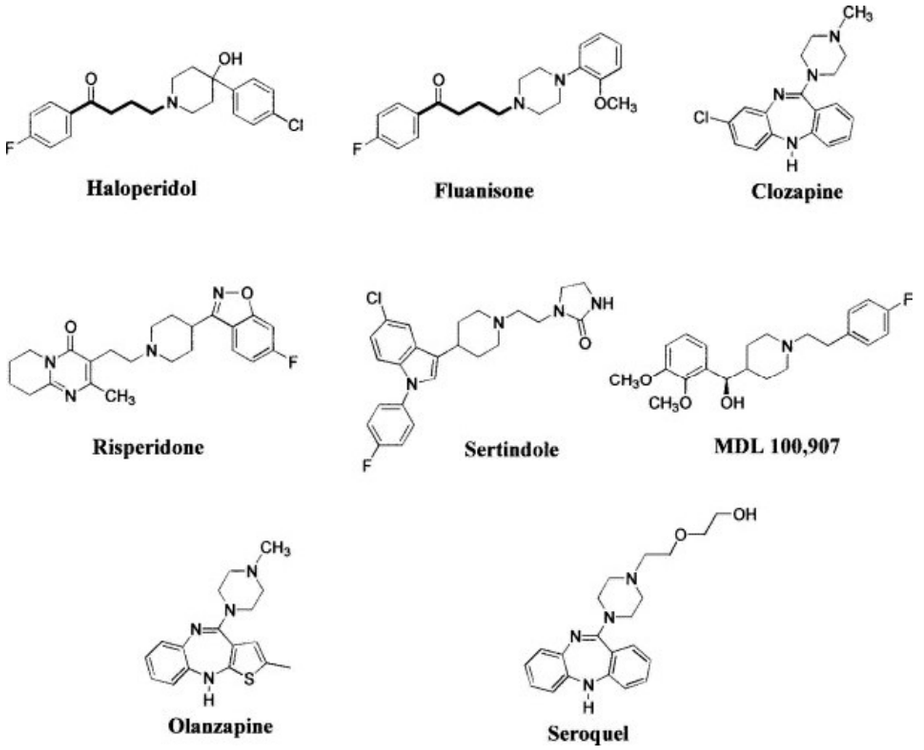


Fig. 4.26 *Structures of Butyrophenones*

4.7.3 Stereochemical Aspects of Psychotropic Drugs

Stereoisomers are used as tools to research the role of spatial (3-dimensional) features in organic compound and activity effects of mind-bending medication. Studies using enantiomers (optical isomers), geometrical isomers and semi-rigid

molecules have shown that spatial options play a job in effects of antidepressant, antipsychotic, antiparkinsonian, and antianxiety medication, yet as stimulants and psychotomimetic. An understanding of the role of spatial features in effects of psychotropic medication would possibly aid in reducing their side effects and in enhancing their therapeutic efficacy.

- Optimal neuroleptic activity drug need rings which are planar.
- Neuroleptic receptors need geometry like phenothiazine type molecule.
- If all three rings have 6 atoms and middle ring deviates from planarity that molecule exhibit antidepressant properties.

4.7.4 Serendipity and Drug Development

Serendipity is one in all the various factors that may contribute to drug discovery. It's played a role within the discovery of prototype psychotropic medication that led to trendy pharmacologic treatment in psychiatry. It's additionally played a job within the discovery of many medication that have had an effect on the event of psychological medicine, 'Serendipity' in drug discovery implies the finding of 1 factor while trying to find something else. This was the case in six of the twelve lucky discoveries, i.e., aniline purple, penicillin, acid diethylamide, meprobamate, chlorpromazine, and imipramine, within the case of 3 medication, i.e., potassium bromide, chloral hydrate, and lithium, the invention was lucky as a result of an totally false explanation led to correct empirical results; and just in case of 2 others, i.e., iproniazid and sildenafil, as a result of valuable indications were found for these medication that weren't at the start those wanted. The invention of one of the twelve medication, chlordiazepoxide, was sheer luck.

Check Your Progress

9. What are antipsychotic medications?
10. Write any two second-generation medication.
11. Where are butyrophenones derived from?

4.8 SYNTHESIS OF ANTIPSYCHOTIC DRUGS

Let us study the process of synthesis of different antipsychotic drugs in detail.

4.8.1 Diazepam

Synthesis of diazepam is shown in the given figure as (1) 2-amino-5-chlorobenzophenone; (2) glycine ethyl ester; (3) 7-chloro-1,3 dihydro-5-phenyl 2H-1, 4-benzodiazepin-2-one; (4) diazepam is obtained.

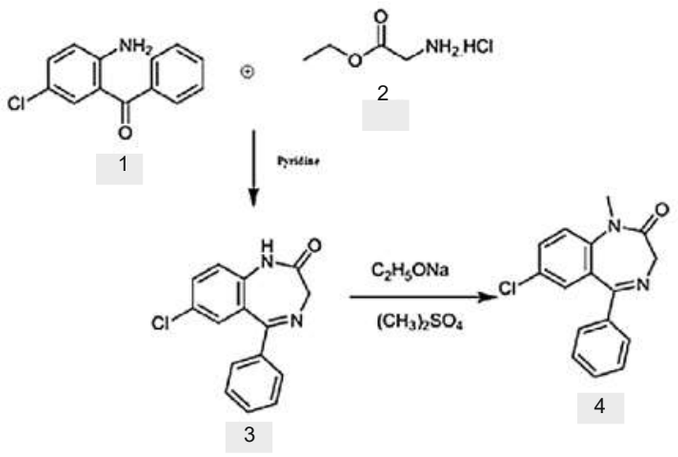


Fig. 4.27 *Synthesis of Diazepam*

4.8.2 Oxazepam

6-chloro-2-xhloromethyl-4-phenylquinazolin-3-oxide is treated with sodium hydroxide to give 7-chloro-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-on-4-oxide. The formed compound undergoes acetoxylation reaction of the 3rd position of the benzodiazepine ring by using acetic anhydride, and which reminiscent the Polonovski reaction to produce 7-chloro-1,3-dihydro-3-acetoxy-5-phenyl-2H-benzodiazepin-2-one. Hydrolysis of the latter formed compound gives oxazepam.

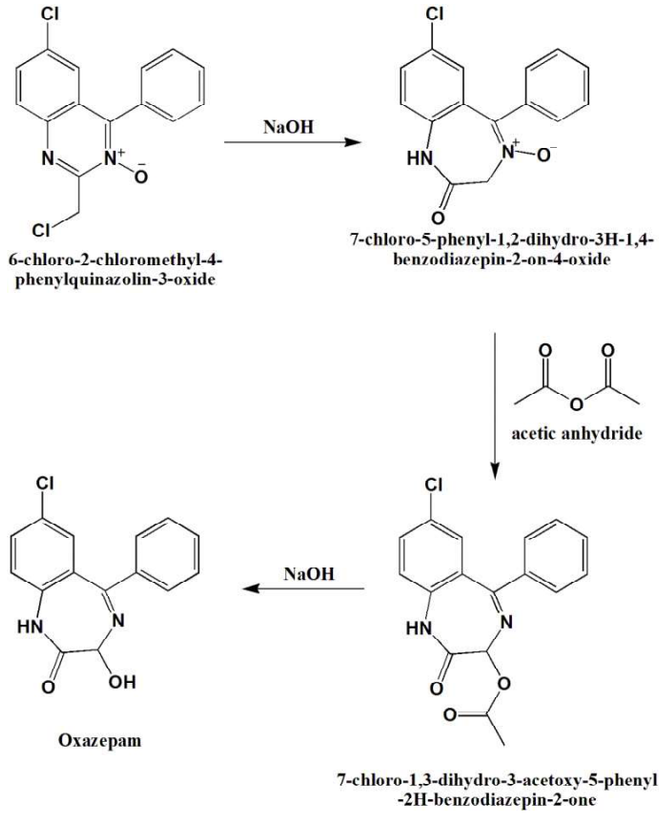


Fig. 4.28 *Synthesis of Oxazepam*

4.8.3 Clonazepan

2-chloro-2'nitrobenzophenone is reduced to 2-chloro-2'-aminobenzophenone by hydrogen over Raney nickel. The amino group of the above formed compound is amidated by 2-bromoacetyl bromide to produce bromoacetamide. Bromoacetamide is coverted into aminoacetamide by reaction with ammonia. On reaction with pyridine, the above formed compound cycled into 5-(2-chlorophenyl)-2,3-dihydro-1H-1,4-benzodiazepine-2-one. Upon nitration, clonazepam is synthesised.

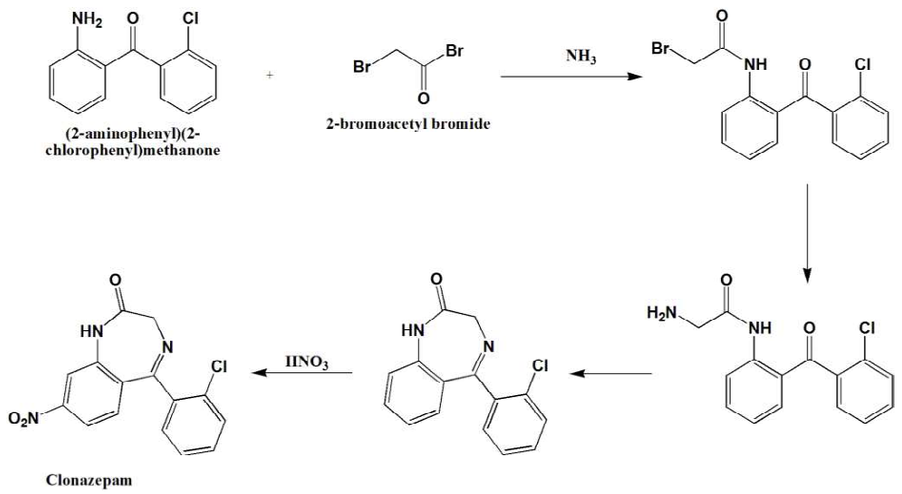


Fig. 4.29 *Synthesis of Chlonazepam*

4.8.4 Alprazolam

Alprazolam, 8-chloro-1-methyl-6-phenyl-4H-s-triazolo[4,3-a] [1,4] benzodiazepine, is a chemical analog of triazolam that differs by the absence of a chlorine atom in the o-position of the 6-phenyl ring. The same scheme that was used to make triazolam can be used to make alprazolam, with the exception that it begins with 2-amino-5-chlorobenzophenone. However, a non-standard way of making alprazolam has been suggested, which comes from 2,6-dichloro-4-phenylquinoline, the reaction of which with hydrazine gives 6-chloro-2-hydrazino-4-phenylquinoline. Boiling this with triethyl orthoacetate in xylene leads to the heterocyclization into a triazole derivative. The resulting product undergoes oxidative cleavage using sodium periodate and ruthenium dioxide in an acetone–water system to give 2-[4-(32 -methyl-1,2,4-triazolo)]-5-chlorobenzophenone. Oxymethylation of the last using formaldehyde and subsequent substitution of the resulting hydroxyl group by phosphorous tribromide, gives 2-[4-(32 -methyl-52 -bromomethyl-1,2,4-triazolo)]-5-chlorobenzophenone. Substitution of the bromine atom with an amino group using ammonia and the spontaneous, intermolecular heterocyclization following that reaction gives alprazolam.

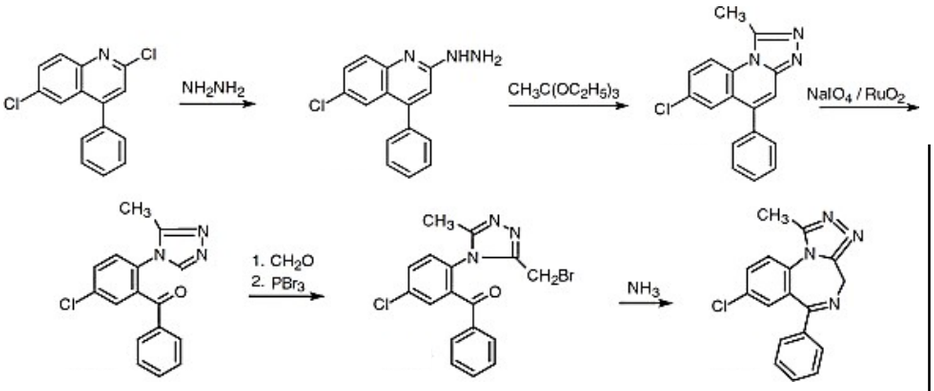
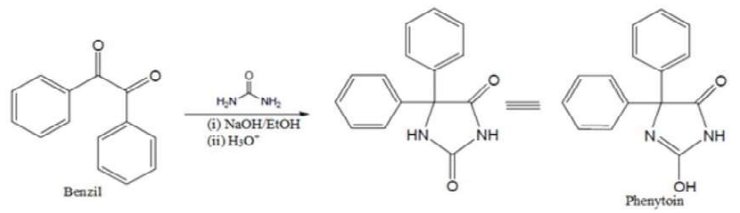


Fig. 4.30 *Synthesis of Alprazolam*

4.8.5 Phenytoin

Phenytoin (5,5'-dipenylimidazolidine-2,4-dione) is the prime example of anticonvulsant agent. According to reported procedure, it is synthesized by condensation of benzil and urea in presence of base (30% w/v NaOH) using ethanol as solvent which itself acts as CNS stimulant.

Reaction:



Mechanism:

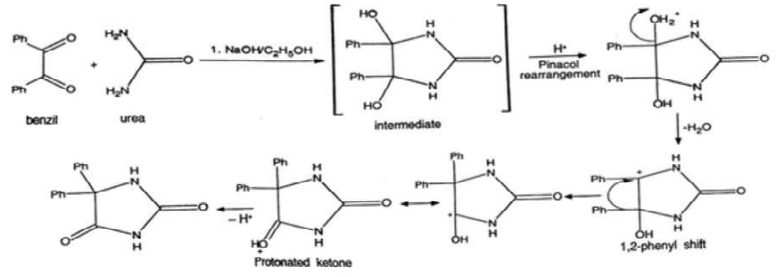


Fig. 4.31 *Synthesis of Phenytoin*

4.8.6 Ethosuximide

Ethosuximide, 3-ethyl-3-methypyrrolidine-2,5-dione (4) is synthesized from methylethylketone and cyanoacetic ester, which are condensed in Knoevanagel reaction conditions. Then hydrogen cyanide is added to the resulting product (1). After acidic hydrolysis and decarboxylation of synthesized dinitrile (2), 2-methyl-2-ethylsuccinic acid (3) is formed. Reacting this product with ammonia gives the diammonium salt, and heterocyclization into the ethosuximide (4) takes place during subsequent heating.

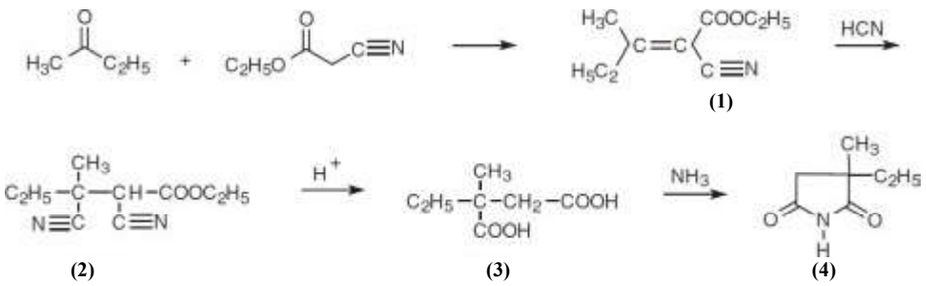


Fig. 4.32 *Synthesis of Ethosuximide*

4.8.7 Trimethadione

Trimethadione, 3,5,5-trimethyloxazolidine-2,4-dione (2), is synthesized by methylating 5,5-trimethyloxazolidine-2,4-dione (1) with dimethylsulfate. Starting 5,5-trimethyloxazolidine-2,4-dione (1) is in turn synthesized by the cyclocondensation of the ester of 2-hydroxyisobutyric acid with urea.

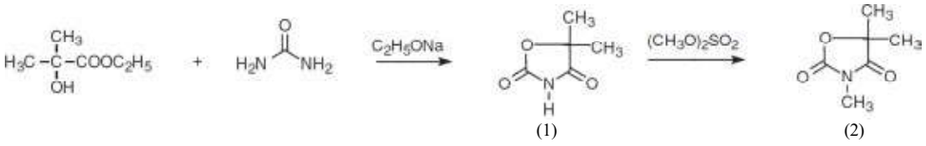


Fig. 4.33 *Synthesis of Trimethadione*

4.8.8 Barbiturates

Barbiturates primarily act on GABA: benzodiazepin receptor Cl^- channel complex and potentiate GABA ergic inhibitory action by increasing the lifetime of Cl^- channel opening induced by GABA.

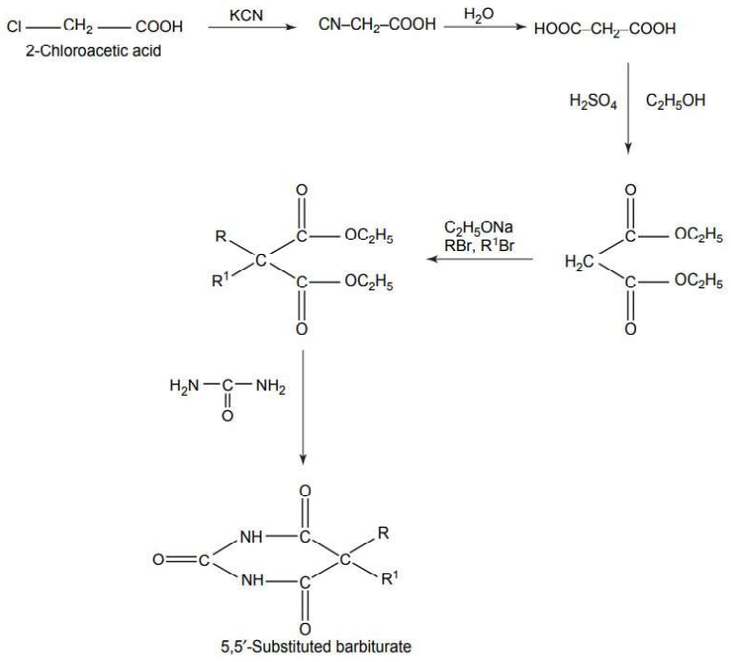


Fig. 4.34 *Synthesis of Barbiturates*

4.8.9 Thiopental Sodium

Thiopental is synthesized by the alkylation of ethylmalonic ester with 2-bromopentane in the presence of sodium ethoxide. The product ethyl-(1-methylbutyl) malonic ester undergoes heterocyclization with thiourea using sodium ethoxide as its base.

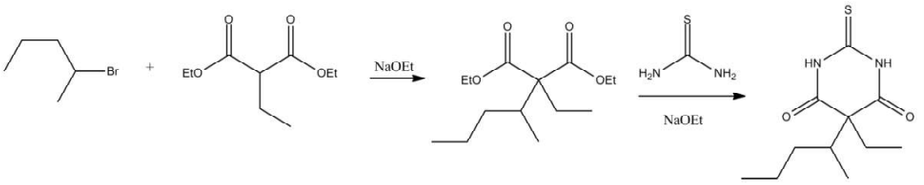


Fig. 4.35 *Synthesis of Thiopental Sodium*

4.8.10 Glutethimide

Glutethimide, 2-ethyl-2-phenylgutarimide, is synthesized by addition of 2-phenylbutyronitrile to the methylacrylate (Michael reaction), and the subsequent alkaline hydrolysis of the nitrile group in the obtained compound into an amide group, and the subsequent acidic cyclization of the product into the desired glutethimide.

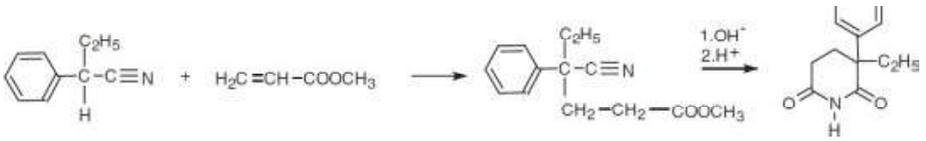


Fig. 4.36 *Synthesis of Thiopental Sodium*

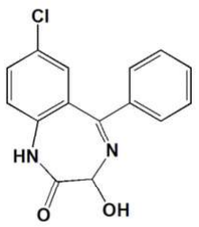
Check Your Progress

12. What happens when 6-chloro-2-xhloromethyl-4-phenylquinazolin-3-oxide is treated with sodium hydroxide?
13. Give the structural formula of oxazepam.
14. Which base is used in the synthesis of phenytoin?

4.9 ANSWERS TO 'CHECK YOUR PROGRESS'

1. Aminoglycosides interfere with steps involves in protein synthesis thereby rendering cell division non-functional.
2. The molecular formula of nalidixic acid is 1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthiridin-3-carboxylic acid.
3. Ciproûoxacin is used to treat acute diarrhoeic sickness caused by E. coli, Shigella.
4. Benzodiazepines increase frequency of opening of Cl- channels induced by GABA (GABA facilitatory action) and increase binding of GABA to GABAA receptor.

5. Sedatives are central nervous system depressants and vary wide in their efficiency. They're typically within the variety of a pill or liquid.
6. The two melatonin receptor agonists are ramelteon and tasimelteon.
7. L-Dopa is an example of antiparkinsonian drug.
8. Benzodiazepines act on human gamma-aminobutyric acid A (GABA-A) receptors, as positive allosteric modulators to extend affinity of gamma aminobutyric acid binding and enhance the response.
9. Neuroleptics, additionally called antipsychotic medications, are medications that block dopamine receptors within the system.
10. Among second-generation medications, clozapine, olanzapine, paliperidone, and risperidone are the foremost frequently prescribed. (Write any two.)
11. Butyrophenones are a class of pharmaceutical drugs derived from butyrophenone.
12. 6-chloro-2-xhloromethyl-4-phenylquinazolin-3-oxide is treated with sodium hydroxide to give 7-chloro-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-on-4-oxide.
13. The structural formula of oxazepam is:



14. NaOH is used in the synthesis of phenytoin.

4.10 SUMMARY

- Antiinfectives are medications that stop and treat infections; they're very important to the health and well-being of society.
- Some of the common antiinfective drugs are sulphonamides, furazolidone, nalidixic acid, ciprofloxacin, norfloxacin, dapsone, amino salicylic acid, isoniazid, ethionamide, ethambutol, fluconazole, econozole, griseofulvin, and chloroquine.
- Neurotransmitters are chemical substances that relay, amplify, and modulate signals between one nerve cell and another or between a nerve cell and another cell.
- There are several CNS depressants, and most act on the brain. They have an effect on the neurochemical gamma-aminobutyric acid (GABA).
- General anesthesia could be a combination of medicines that place you in a very sleep-like state before a surgery or different process.

- Hypnotics are believed to exert their effect on the brain by interacting with receptors for the neurotransmitter GABA.
- Sedatives are central nervous system depressants and vary wide in their efficiency.
- Benzodiazepines act on human gamma-aminobutyric acid A (GABA-A) receptors, as positive allosteric modulators to extend affinity of gamma aminobutyric acid binding and enhance the response.
- Neuroleptics, additionally called antipsychotic medications, are medications that block dopamine receptors within the system.
- Butyrophenones are a class of pharmaceutical drugs derived from butyrophenone.
- Stereoisomers are used as tools to research the role of spatial (3-dimensional) features in organic compound and activity effects of mind-bending medication.
- Serendipity is one in all the various factors that may contribute to drug discovery. It's played a role within the discovery of prototype psychotropic medication that led to trendy pharmacologic treatment in psychiatry.
- Some of the antipsychotic drugs are diazepam, oxazepam, chlonazepam, alprazolam, phenytoin, ethosuximide, trimethadione, barbiturates, thiopental sodium and glutethimide.

4.11 KEY TERMS

- **Antiinfective Drugs:** These drugs refer to either an antibiotic (or antibacterial), an antifungal or an antiviral agent, as well as the sulfonamides.
- **Psychoactive Drugs:** These drugs refer to the class of drugs that effect thinking, perception, emotion and other psychological processes.
- **Hypnotics:** These drugs are commonly known as sleeping pills. These are a class of psychoactive drugs whose main function is to induce sleep and to treat insomnia.
- **Sedatives:** These drugs are also known as tranquillizers. They affect directly the central nervous system and decelerate its activity, reducing irritability or excitement.
- **Antipsychotic Drugs:** These drugs are also known as neuroleptics. They refer to a class of psychotropic medication that is mainly used to manage psychosis including delusions, hallucinations, paranoia or disordered thought.
- **Hydrolysis:** It is a chemical reaction in which a molecule of water breaks one or more chemical bonds. The term is used broadly for substitution, elimination, and solvation reactions in which water is the nucleophile.

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4.12 SELF-ASSESSMENT QUESTIONS AND EXERCISES

Short-Answer Questions

1. What are the major cause of anxiety?
2. How is furazolidone sysnthesised?
3. Why are CNS depressants considered fatal?
4. What are the categories of antipsychotic drugs?
5. Write a short note on stereochemical aspects of psychotropic drugs.

Long-Answer Questions

1. Give a detailed account of mode of action of antiinfective drugs.
2. Discuss and illustrate the preparation of chloroquine.
3. Explain the mechanism of synthesis of phenytoin.
4. Analyse the effects of neuromodulators on the human nervous system.
5. 'All antibacterial medicines are bacteriostatic.' Justify the given statement.

4.13 FURTHER READING

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UNIT 5 ANTIBIOTICS

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Structure

5.0 INTRODUCTION

The term 'antibiotic' was coined by Selman Waksman who worked at Rutgers University. Simultaneously, Albert Schatz and Elizabeth Bugie discovered the antibiotic named streptomycin. According to Waksman's definition, an antibiotic could be a chemical substance that is made by microorganisms which have the capability, in dilute solution, to inhibit the growth of, and even destroy, different microorganisms. Scientists were able to develop artificial compounds that had antibiotic properties. Though some scientists together with Waksman powerfully resisted the misuse of the term 'antibiotic', the definition was nonetheless modified to incorporate artificial antibiotics. This unit will discuss the process of cell wall biosynthesis and synthesis of various antibiotics. In addition, it will explain the structures of inhibitors and β-lactam rings. Also, it will describe antibiotics that inhibit protein synthesis.

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5.1 OBJECTIVES

After going through this unit, you will be able to

- Discuss different types of antibiotics
- Explain the process of cell wall biosynthesis
- Describe inhibitors and β-lactam rings
- Discuss different antibiotics that inhibit protein synthesis
- Analyse the synthesis of some antibiotics

5.2 ANTIBIOTICS

Antibiotics are often outlined as molecules that either kill or inhibit growth of microorganisms. Since the practical application of antibiotics is to cure infections in humans, a necessary property of an antibiotic must be selectivity. Therefore an antibiotic is currently wide outlined as a chemical substance that inhibits growth of microorganisms by selection and causes minimum harm to the host cells. This definition continues to be very restrictive owing to the term 'microorganism'. Most scientists would not take into account viruses as microorganisms, however, there are antiviral medication in the market, and they operate by mechanisms almost like that of antibiotics. Whenever, a layperson talks regarding utilising an antibiotic to cure a viral infection, the learned or expertise indicates that antibiotics cure solely infections caused by microorganisms and not viral infections. However, it is to be noted that this is often a matter of definition. If antibiotics are outlined to incorporate antiviral medication, then they are often utilised to cure viral infections additionally.

5.2.1 History of Antibiotics

Ever since it was verified by Robert Koch and Louis Pasteur within the late nineteenth century that diseases are often caused by germs, scientists are checking out ways to kill these disease-causing germs. One thriving approach developed by Louis Pasteur was to use harmless bacterium to cure diseases caused by harmful microorganisms. Nowadays we are able to justify these observations. The harmless microorganisms most likely made antibiotics that killed the infecting disease-causing microorganism. Another approach was to use chemicals to kill microorganisms, giving rise to the method known as chemotherapy. This was started by a bacteriologist, Paul Ehrlich who understood that the primary step of the therapy should be binding of the chemical to the bacterium. This led to the testing of dyes as bactericide agents and it was seen that they could bind microorganisms. While testing various dyes, in 1904, he found a dye that would cure mice infected with trypanosomes. He named the dye, trypan red. It was the primary chemotherapeutical agent discovered.

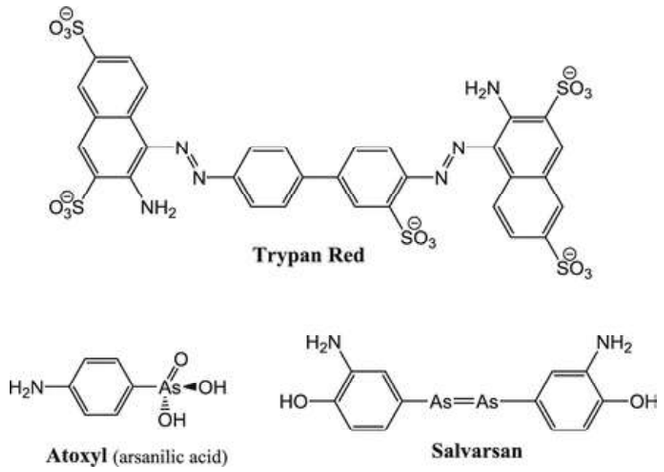

Fig. 5.1 *Some Early Chemotherapeutic (Antibiotic) Agents*

Discovery of modern antibiotics

Alexander Fleming discovered an antibiotic, penicillin. He was awarded the Nobel Prize for his discovery. However, penicillin was not the primary antibiotic to be discovered. The Greeks were noted to use extracts of Dryopteris filix-mas to treat worm infestations. In the 16th century, the extract of the bark was employed in Republic of Peru, Bolivia, and Republic of Ecuador to treat malaria. The active part of the extract was later shown to be quinine which was majorly present in the market antimalarial till the 1940s once antimalarial became a lot of widespread drug of selection. However, antimalarial drugs continues to be used for the treatment of protozoal infections.

Discovery of lysozyme

In 1920, Fleming had discovered the antibiotic, lysozyme, a naturally occurring substance present in human tears. Lysozyme kills microorganisms by lysing (breaking) their cells walls. This causes microorganisms' cells burst open. Fleming delineated the results of his experiment as, 'A thick opaque suspension of a microorganism can be fully cleared during a few seconds by the fraction of a drop of human tears or albumen.' However, lysozyme is not popularly referred to as an antibiotic as a result of being a protein, it could not be used for treating patients.

Discovery of penicillin

In 1928, Fleming created his second bactericide discovery, penicillin. The majority have heard a story regarding the invention of the antibiotic. Fleming detected that in one amongst the previous plates (petri dishes) left within the laboratory, colonies of the bacterium staphylococci (that causes skin diseases) had lysed, most likely owing to a contaminating light-green mildew growing in an adjacent space of the plate. This led to the discovery of penicillin. By extracting the substance from cultures of the mildew, he was able to demonstrate its bactericide activity not solely on plates but also once to infected mice. Fleming named this substance that killed microorganisms 'penicillin' after the fungus genus mildew from which it was obtained.

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It is to be noted that this serendipity in no way diminishes the credit that goes to Fleming. In 1945, Nobel winner Fleming gave the statement, 'My solely advantage is that I did not neglect the observation and that I pursued the topic as a bacteriologist.'

5.2.2 Properties of a Perfect Antibiotic

A perfect antibiotic must have the following properties besides having the ability to kill microorganisms:

- **Selectivity**: It should kill or inhibit the infecting organism, however, it causes minimum damage to the host cells.
- **Water solubility**: It should be soluble in water to an adequate extent to smoothen its transportation through body fluids to the infected sites. Some antibiotics are poorly soluble in water; but, some solubility is crucial for effectiveness.
- **Few side effects**: Side reactions of the antibiotic ought to be minimum. These reactions embody potential allergies and negative interaction with food or different medication that the patient is also taking.
- **Stability**: It includes shelf stability and bio-stability. The antibiotic must have an extended period of time to be economically helpful. It must be stable at room temperature; but, there are several antibiotics that are required to be kept in a refrigerator. Once taken by a patient, the antibiotic must stay unmoved within the body fluids for enough time to be able to perform its function. Foreign molecules within the body can eventually be either degraded (usually within the liver) or excreted along with the body waste. For the best antibiotic, both these processes ought to be slow. However, fast excretion is really a desired property for treating urinary tract infections since a high concentration of the drug is achieved within the body waste.
- **Low cost**: The price of producing of the antibiotic must be low enough for patients to be able to afford it.
- **Slow resistance development**: Microorganisms have developed resistance to most antibiotics. A perfect antibiotic is the one to that develops resistance at a slow rate. This can rely not solely on the characteristics of the antibiotic, however, on its frequency of use.

5.2.3 Classification of Antibiotics

Antibiotics can be classified on the basis of the targets within the microorganism cell that causes growth inhibition. Consequently, there are six major categories of antibiotics:

- Antibiotics that inhibit microorganism cell wall synthesis
- Antibiotics that disrupt the cytomembrane
- Antibiotics that inhibit the synthesis of vital metabolites
- Antibiotics that inhibit DNA synthesis (replication)
- Antibiotics that inhibit RNA synthesis (transcription)
- Antibiotics that inhibit protein synthesis (translation)

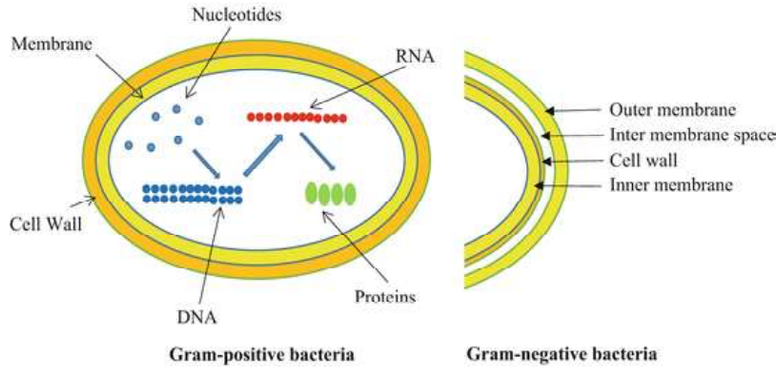

Fig. 5.2 *Targets for Antibiotics*

Bacteriostatic and bactericidal antibiotics

The classification of antibiotics are based on the growth and survival of the bacterium. The antibiotics that kill microorganisms are known as bactericidal, for example, penicillin and the that stop the growth of microorganisms, however, do not kill them are known as bacteriostatic, for example, chloramphenicol.

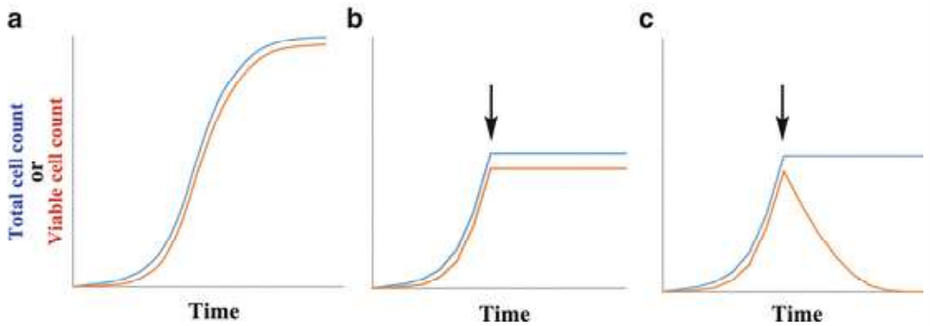

Fig 5.3 *Hypothetical growth curves for bacteria (a) in the Absence of Bacteriostatic (b) Presence of Bacteriostatic (c) Bactericidal Antibiotics (The* arrows *indicate the time of addition of the antibiotic.)*

Check Your Progress

1. Who coined the term 'antibiotic'?
2. Which approach was developed by Louis Pasteur?
3. Name the naturally occurring substance present in human tears.

5.3 CELL WALL BIOSYNTHESIS

Biosynthesis of the cell wall takes place in three stages. The process starts within the cytoplasm (Stage 1) and is followed by reactions within the membrane (Stage 2). The product then crosses the membrane and final reactions come within the cell wall (Stage 3). There are many enzymes that are required to catalyse these reactions.

Let us study the process in detail.

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Stage 1: The cytosolic phase of synthesis

The cytosolic phase is also considered to begin from fructose-6-phosphate, that receives an amino from the standard amino group donor, glutamine to create 2-glucosamine-6-phosphate (Step 1), and then it is then isomerized to 2-glucosamine-1-phosphate (Step 2) which later acetylated to make N-acetyl glucosamine-phosphate (Step 3).

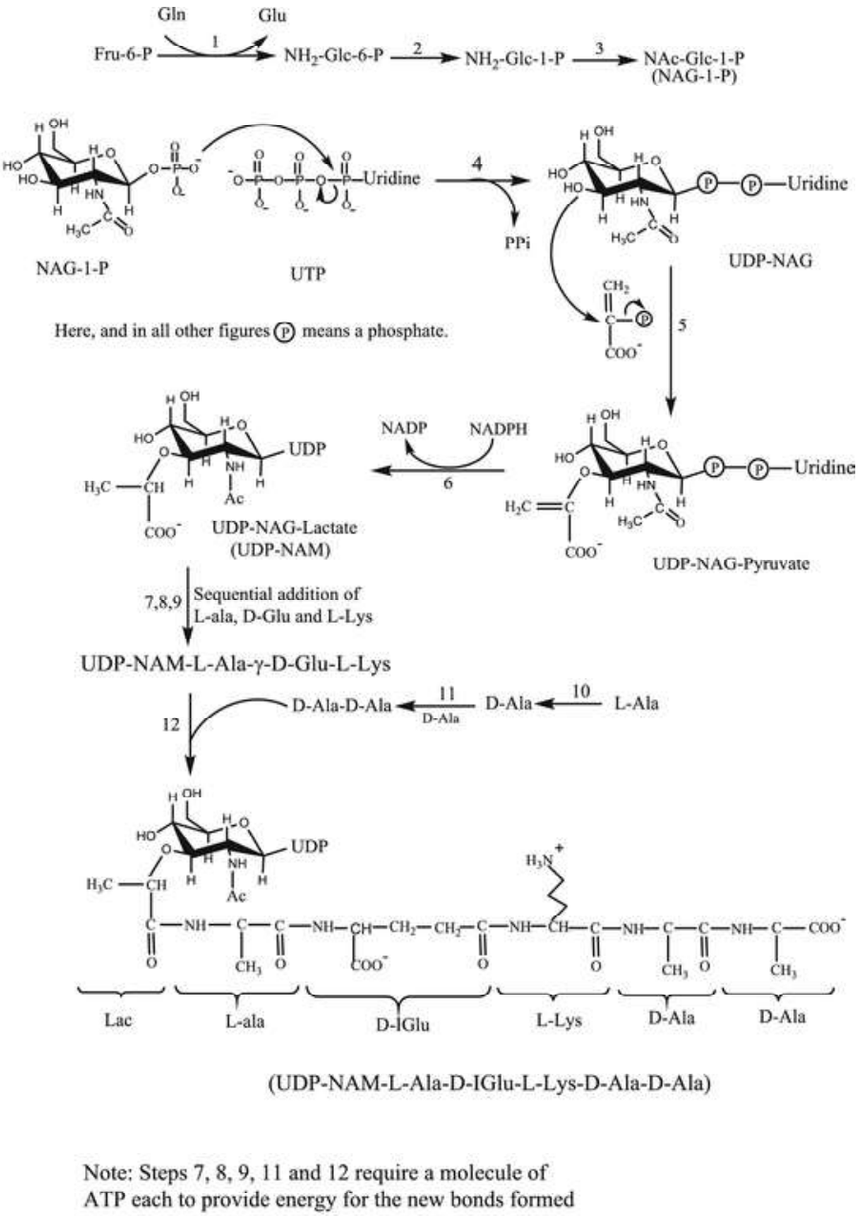

Fig. 5.4 *Reactions in the Cytosolic Phase of Cell Wall Synthesis*

The enzymes catalyzing the twelve steps in the above scheme are as follows:

- Glucosamine-6-phosphate synthase (or, l-glutamine:d-fructose-6-phosphate amidotransferase)
- Glucosamine mutase

- Glucosamine-1-phosphate acetyltransferase
- UDP-NAG Synthase (or, UDP-GlcNAc pyrophosphorylase)
- Phosphoenolpyruvate transferase (UDP-GlcNAc enolpyruvyl transferase, or MurA)
- UDP-NAG-enolpyruvate reductase (MurB)
- MurC
- MurD
- MurE
- Alanine racemase
- d-Ala-d-Ala synthetase (d-Ala-d-Ala ligase)
- MurF

Stage 2: The membrane phase of synthesis

The reactions occur within the cytosol, whereas the cell wall is found on the opposite side of the membrane. The product of these reactions are polar and need to be transported through the membrane that includes a hydrophobic interior. Polar compounds cannot enter or cross the lipid bilayer of the membrane due to the hydrophobic surroundings. A membrane carrier is required to bring a polar compound into the membrane wherever the subsequent phase of cell wall synthesis takes place. The membrane carrier used is undecaprenyl phosphate (C55-P), a 55 carbon lipid that consists of the five carbon units, isoprene repeated eleven (undeca) times. As a result of the long fifty-five carbon hydrophobic chain, it is soluble within the membrane and is ready to bring polar products through the membrane. It forms phospho anhydride linkage to P-NAM-pentapeptide (Step 1). The reaction takes place at the interphase of the membrane and the cytoplasm.

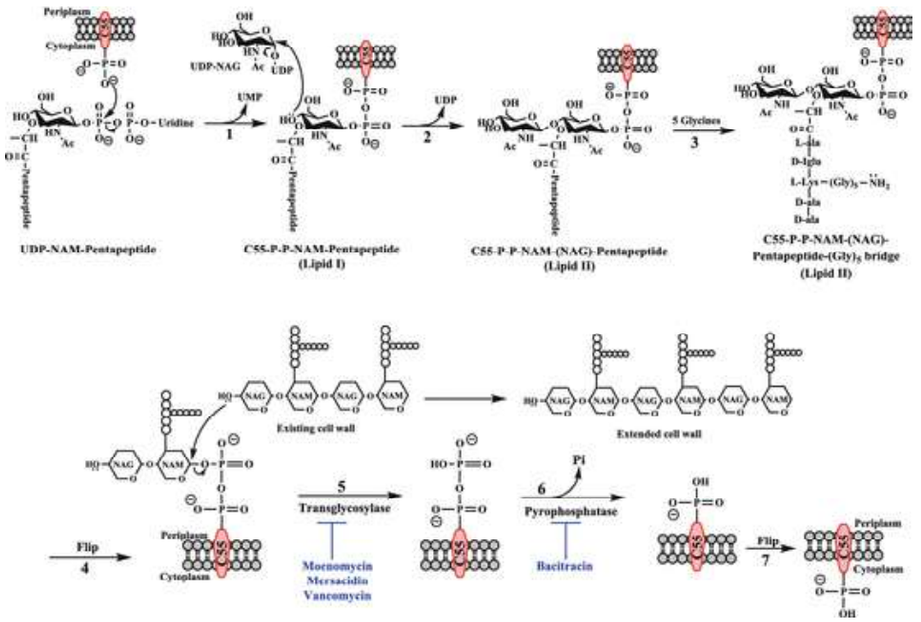

Fig 5.5 *Membrane and Cell Wall Phases of Cell Wall Synthesis*

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Stage 3: The cell wall phase of synthesis

The final step in process is the cross-linking of the peptidoglycan strands by transpeptidation. The cross-linking is very important because it makes the cell wall sturdy and rigid.

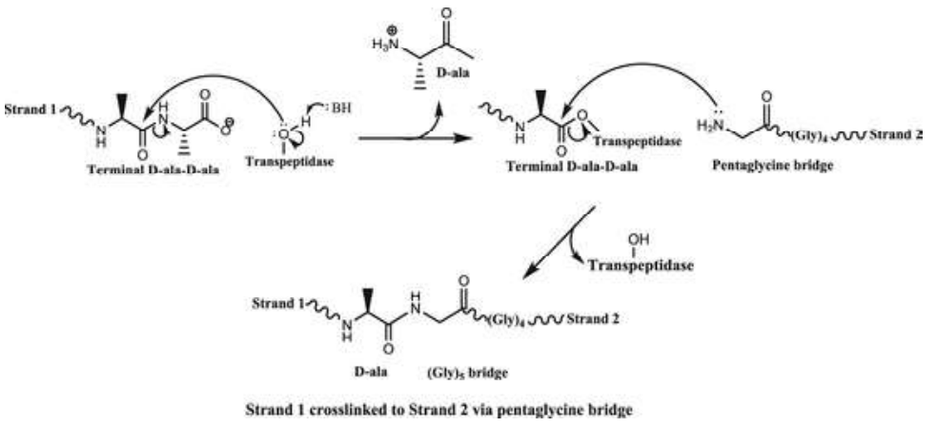

Fig 5.6 *Cell Wall Phase of Cell Wall Synthesis: Peptidoglycan Cross-inking by Transpeptidase*

5.3.1 Inhibitors

Antibiotics that inhibit cell wall biosynthesis are called inhibitors. There are different inhibitors that target each phase of the cell wall biosynthesis. Let them study in detail.

Antibiotics targeting the cytosolic phase of synthesis

- **Fosfomycin**

It is an effective antibiotic because it functions as a suicide inhibitor of MurA enzyme. The mechanisms of the reaction are catalyzed by the enzyme with the natural substrates, UDP-NAG and PEP and reactions of the enzyme with fosfomycin are shown in figures below, respectively.

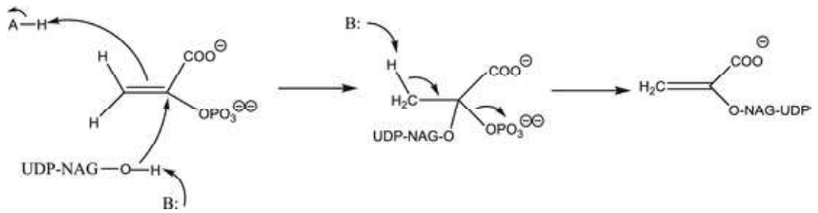

Fig 5.7 *Reaction between UDP-NAG and PEP Catalyzed by Pyruvyl Transferase*

The B: and A–H are basic and acidic amino acids, respectively at the active site.

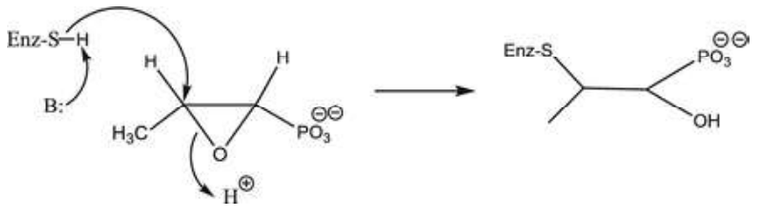

Fig 5.8 Mechanism based (suicide) Inactivation of Pyruvyl Transferase by Fosfomycin

The SH group belongs to a cysteine residue at the active site of the enzyme.

• D-Cycloserine

It is also known as oxamycin. It is an antibiotic that inhibits two enzymes in the cytoplasmic phase of bacterial cell wall synthesis. Resistance development against d -Cycloserine can be seen by increasing the expression of the enzyme alanine racemase or the enzyme D-ala-D-ala synthetase or both.

Antibiotics targeting the cell wall phase of synthesis

• Penicillin

It is used to treat a variety of bacterial infections, such as infection of the throat, ear, nasal sinuses, respiratory tract, skin and soft tissue, and sexually transmitted diseases, for example, Syphilis. We have already discussed about it in detail in this unit.

• Cephalosporin

It was originally derived from the fungus Acremonium (previously known as Cephalosporium). It was discovered in 1945. It is used to treat infections caused by bacteria susceptible to this particular form of antibiotic.

Antibiotics targeting the membrane phase of synthesis

Bacitracin, named after a patient, Treacy, is a peptide antibiotic produced by some strains of Bacillus licheniformis and Bacillus subtilis. It inhibits the cell wall formation in Gram-positive as well as some Gram-negative bacteria.

The antibiotics that inhibit transglycosylation reaction are as follows:

• Moenomycin

It belongs to a family of phosphoglycolipid antibiotics. It targets bacterial peptidoglycan glycosyltransferases, inhibiting cell wall formation, which results in the death of the cell.

• Lantibiotics: Mersacidin

Lantibiotics are a class of poly cyclic peptide antibiotics, containing the characteristic thioether amino acids lanthionine or methyllanthionine, and the unsaturated amino acids dehydroalanine and 2-aminoisobutyric acid. Mersacidin is a tetracyclic lantibiotic with antibacterial activity against Gram-positive pathogens.

• Vancomycin

It is used to treat severe bacterial infections in hospitalized patients. It is effective against infections of the respiratory tract (for example, pneumonia), urinary tract, skin and soft tissues, bones and joints, heart, blood and others.

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- **Teixobactin**

It is a peptide-like secondary metabolite produced by some species of bacteria. It kills some Gram-positive bacteria.

5.3.2 β-Lactam Rings

A traditional template for antibiotics is the â-lactam ring, and many novel entities are produced by varying the attached appendages. Thiadiazole, a â-lactam derivative, was active against Gram-negative bacteria and showed an activity against Gram-positive organisms including Staphylococcus aureus.

Resistance to β-lactam antibiotics

Some bacteria are naturally resistant to certain antibiotics (known as intrinsic resistance), while others develop resistance to the antibiotics (known as acquired resistance).

Intrinsic resistance

To inhibit cell wall synthesis, the antibiotic drug needs to first approach the cell wall. The cell wall of Gram-positive bacterium is accessible to the drug than that of the cell wall of Gram-negative bacterium. The drug must be first transported through the outer membrane. However, the outer membrane does not act as a selective barrier. Hydrophobic antibiotics such as macrolides will get diffused through the hydrophobic lipid bilayer of the outer membrane, whereas tiny hydrophilic antibiotics withstand the porin channels that are present within the outer membrane.

Acquired resistance

The three ways by which bacteria can acquire resistance to â-lactams are as follows:

- By decreasing permeability of the drug into the cell
- By developing mutations in the target protein (PBP) to decrease binding affinity to the drug
- By acquiring gene for â-lactamase enzyme which can degrade the drug

β-lactamase: An enzyme that inactivates β-lactam drugs

Resistance is developed quickly to any or all of antibiotics. The foremost effective mechanism of developing resistance to antibiotic is by producing an enzyme that inactivates the drug. Since it breaks down β-lactams, the enzyme is termed as β-lactamase (aka penillinase) that hydrolyzes the 4-membered ring, thereby inactivating the antibiotic. Owing to the low penetration of β-lactams into Gram-negative bacterium, it had been found that solely a small quantity of â-lactamase enzyme might confer a high level of resistance. In contrast, Gram-positive bacterium need a far higher quantity of the enzyme.

Mechanism of action of β-lactamases

The structure of â-lactamase enzymes leads water enter the active site when the acyl group bond is created between the â-lactamase and penicillin. This leads to a

fast chemical reaction of the acyl group bond, releasing the antibiotic drug with the hydrolyzed lactam ring. The stability of a complex is additionally expressed by its half life ($t_{1/2}$), i.e., the time taken for 1/2 the complex to be hydrolyzed. The $t_{1/2}$ of transpeptidase-penicillin complex is ~90 min, that is over 106 times longer than the $t_{1/2}$ (~4 ms) for the â-lactamase-penicillin complex. This implies that the latter is hydrolyzed quite 1,000,000 times quicker than the former. Note that half lifetime of 90 minutes is incredibly high compared to usual doubling times of most bacterium and therefore the antibiotic drug effectively stops growth of cells. Cephalosporins and carbapenems also are hydrolyzed within the same approach.

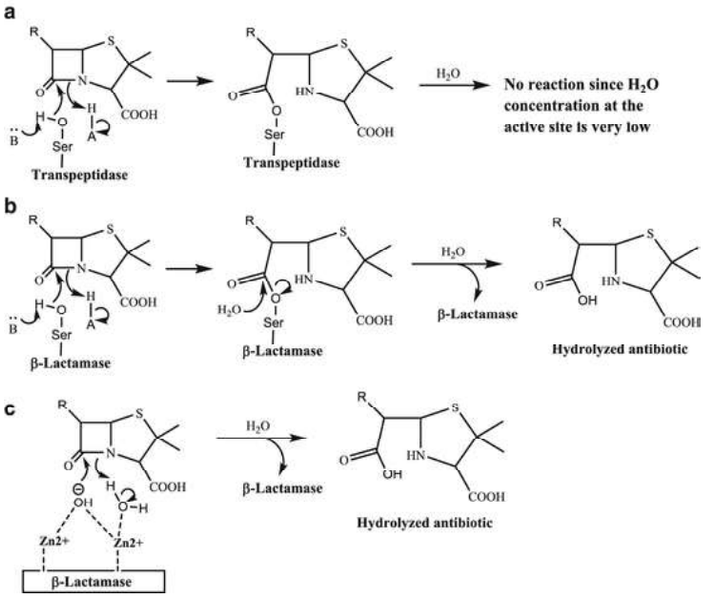

Fig 5.9 *Reactions of* β*-lactams (a) Transpeptidase, (b) Serine* β*-lactamase and (c) Metallo-*β*-lactamase*

(All interactions between the Zn and the enzyme are not shown.)

β-Lactamase inhibitors

A big discovery within the field of antibiotics was that of tiny molecules that operate as mechanism primarily (suicide) inhibitors of β-lactamases. These compounds are used along with the antibiotics to stop the destruction of the antibiotic by the β-lactamase enzyme. There are 3 inhibitors that became clinically successful:

- Clavulanic acid
- Sulbactam
- Tazobactam

Clavulanic acid is an enol ether lactam, whereas Sulbactam and Tazobactam are sulfonyl derivatives of β-lactam. It is the concern of microorganisms get immune to carbapenems by virtue of secretion of metallo-β-lactamase.

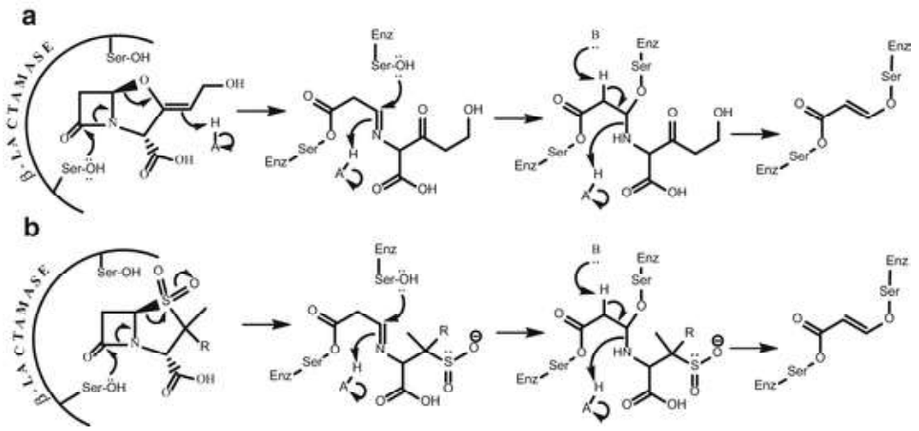

Fig 5.10 *Suicide Inhibitors of â-Lactamase. Reactions of (a) Clavulanic Acid and (b) Sulbactam (R = methyl) and Tazobactam (R = triazole) with â-Lactamase Enzyme*

(The base, B: and the acid, A–H represent various basic and acidic amino acids, respectively at the active site of the enzyme.)

Metallo-β-lactamases inhibitors

Several inhibitors of metallo-â-lactamases are being studied. Carbapenem resistance in Bacteroides fragilis is present because of the secretion of a metallo-β-lactamase that hydrolyzes the antibiotic. Biphenyl tetrazoles (BPTs) are a structural category of potent competitive inhibitors of metallo-beta-lactamase known through screening and utilised molecular modeling of the enzyme structure. The compound was shown to inhibit the metallo-â-lactamase in vitro and regenerate imipenem-resistant B. fragilis from resistant to sensitive.

Unusual β-lactams

Some of the unusual β-lactams are as follows:

- Monobactam
- Carbapenems

Check Your Progress

4. Where does the process of cell wall biosynthesis start?
5. Why is fosfomycin considered an effective antibiotic?
6. Name one β-lactam derivative.
7. What are biphenyl tetrazoles?

5.4 ANTIBIOTICS INHIBITING PROTEIN SYNTHESIS

To protein synthesis to take place, first the mRNA has to be made. So inhibitors of RNA synthesis will also have a secondary effect on protein synthesis. Each of the steps in the process of protein synthesis can be potential targets for antibiotics

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development, and there are many such antibiotics already known. Antibiotics can function by inhibiting any of the steps of translation and thus reduce speed of the growth of bacteria. Most inhibitors of protein synthesis are bacteriostatic and therefore proper protein synthesis can resume once the antibiotic is removed. Thus the effect of these antibiotics is to prevent growth of the bacteria. However, aminoglycosides, which are also inhibitors of protein synthesis, are bactericidal. Antibiotics can inhibit protein synthesis by targeting either the 30S subunit, such as spectinomycin, tetracycline, and the aminoglycosides kanamycin and streptomycin, or to the 50S subunit, such as clindamycin, chloramphenicol, linezolid, and the macrolides erythromycin, clarithromycin, azithromycin and tylosin.

Some of the common antibiotics that inhibit protein synthesis are as follows:

Puromycin

It is an antibiotic obtained from Streptomyces alboniger. It is a non-selective antibiotic that interferes in protein synthesis in both prokaryotes and eukaryotes and therefore has no clinical use due to toxic effects in the host. However, it is used in research, especially cell culture research. Puromycin is an aminonucleoside antibiotic containing a 32 -amino-N,N-dimethyladenosine linked by an amide bond to O-methyltyrosine. It also causes membrane damage. The truncated protein prematurely released by puromycin can be incorporated in the membrane thus creating channels in it making the membranes leaky.

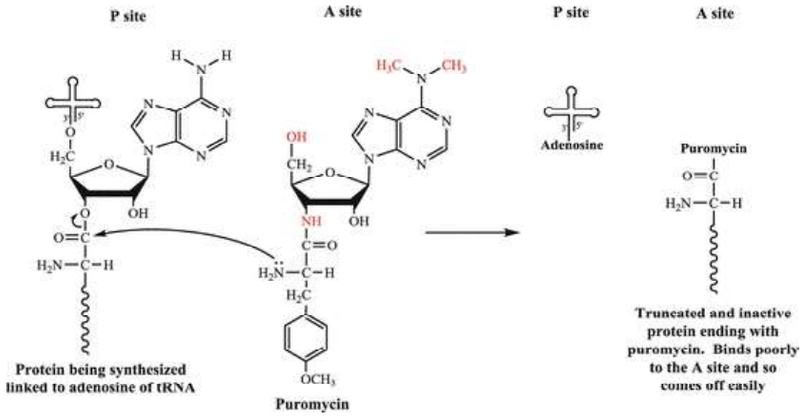

Fig. 5.11 *Mechanism of Action of Puromycin*

Aminoglycosides

The first aminoglycoside, streptomycin, was discovered in 1943 by Selman Waksman, Albert Schatz, and Elizabeth Bugie at Rutgers University from the soil bacteria, Streptomyces griseus. Streptomycin has a streptidine ring, while kanamycin, gentamycin, and neomycin have streptamine rings. Amikacin is a semisynthetic derivative of kanamycin designed to prevent resistance development to the antibiotic.

Tetracyclines

Chlorotetracycline was discovered as a yellow antibiotic from Streptomyces aurofaciens and was then named aureomycin which was later renamed as

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chlorotetracycline. Later the first semisynthetic antibiotic, tetracycline was made by the catalytic hydrogenation of chlorotetracycline. Tetracyclines are active against a wide range of infections with minimal side effects. Tetracyclines, except minocycline, are known to bind to food and chelate metal ions such as calcium, magnesium, aluminum and iron, which prevents their absorption from the digestive system and thereofre should not be administered with food.

Chloramphenicol

Chloramphenicol, previously known as chloromycetin, was the first broad spectrum antibiotic developed and was isolated from a soil bacteria, Streptomyces venezuela. It can be easily synthesized and is available at a very low cost, which is one of the main advantages of the antibiotic. It has a very broad range of activities against most bacteria including anaerobes. The major advantage of the drug is that it can easily penetrate all tissues including the cerebrospinal fluid (CSF) and therefore can be used to treat meningitis. It is also one of the very few antibiotics that can enter human cells and therefore can be used against intracellular bacteria. However, in spite of the many advantages of the drug, chloramphenicol is not used in the USA due to its side effects including aplastic anemia, which can sometimes be fatal.

MLS group of antibiotics

The MLS group of antibiotics consists of the following:

- Macrolides
- Lincosamides
- Streptogramins

Oxazolidinones

A few new antibiotics have been discovered in the last few decades; most new antibiotics have been the derivatives of the existing ones. The only truly novel agent to be introduced in the last 20 years is the oxazolidinone linezolid, which was discovered in the 1990s and approved for clinical use in 2000. Oxazolidinones have been known since the 1950s as monoamine oxidase inhibitors. Their antibiotic property with a new mechanism of action was first reported in 1987. Although other oxazolidinones have been studied, linezolid is the most clinically useful oxazolidinone antibiotic.

Protein synthesis antibiotics with unusual mechanisms of action

- Thermorubin
- Fusidic Acid
- Mupirocin

Peptide deformylase inhibitors: Actinonin

Since peptidyl deformylase is a unique target, it holds great promise for developing effective antibiotics. Since there is no such antibiotic already in use, it can be expected that there is no resistance gene already prevalent in nature.

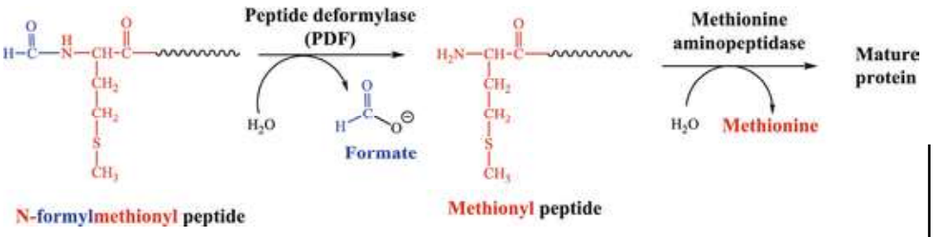

Fig. 5.12 *Potential Targets for Development of New Antibiotics*

Methionine aminopeptidase inhibitors

Methionine aminopeptidase is present not just in bacteria but in all life forms. In fact eukaryotes including humans express two MetAP enzymes, MetAP1 and MetAP2, which are required for cell proliferation, tissue repair, and protein degradation. Cells can still survive if one of these genes is deleted. Since the single gene present in prokaryotes is essential for their survival, this can be an effective target for new antibiotic development. In humans MetAP2 has been shown to be involved in endothelial cell proliferation and thus is a potential target for anticancer drug development. MetAP-2 was identified as the target of the antiangiogenic natural product fumagillin and its drug candidate analog, TNP-470. Although originally developed as anticancer agents, methionine aminopeptidase (MetAP2) inhibitors were also found to cause weight reduction.

Check Your Progress

8. How is puromycin obtained?
9. Name the first broad spectrum antibiotic.
10. What does the MLS group of antibiotics consist of?

5.5 SYNTHESIS OF ANTIBIOTICS

Let us discuss the synthesis of different antibiotics in detail.

5.5.1 Penicillin G

Penicillin G is a penicillin beta-lactam antibiotic used in the treatment of bacterial infections caused by susceptible, usually Gram-positive organisms. The name 'penicillin' can either refer to several variants of penicillin available, or to the group of antibiotics derived from the penicillins. Penicillin G has in vitro activity against Gram-positive and Gram-negative aerobic and anaerobic bacteria. The bactericidal activity of penicillin G results from the inhibition of cell wall synthesis and is mediated through penicillin G binding to penicillin binding proteins (PBPs). Penicillin G is stable against hydrolysis by a variety of beta-lactamases, including penicillinases, and cephalosporinases and extended spectrum beta-lactamases.

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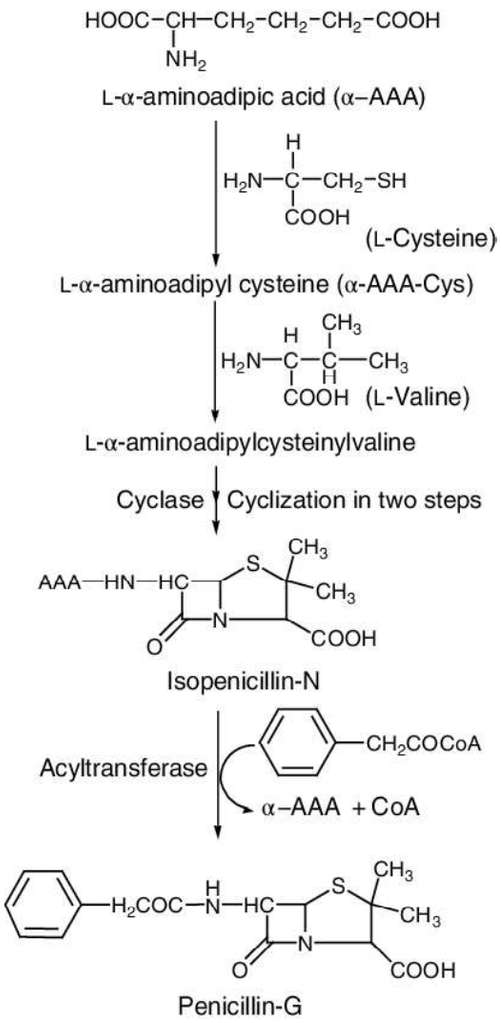

Fig. 5.13 *Synthesis of Penicillin G*

5.5.2 Penicillin V

Penicillin V is a white, odourless, crystalline powder which is slightly bitter in taste and soluble in water. It is more resistant to inactivation by gastric juice than penicillin G and better absorbed from the gastrointestinal (GI) tract. Equivalent oral doses provide two or ûve times greater plasma concentration than penicillin G. Penicillin V is given to treat 'trench mouth'. It is useful in the treatment of streptococcal pharyngitis, pneumonia, arthritis, meningitis, and endocarditis caused by S. pyrogenes.

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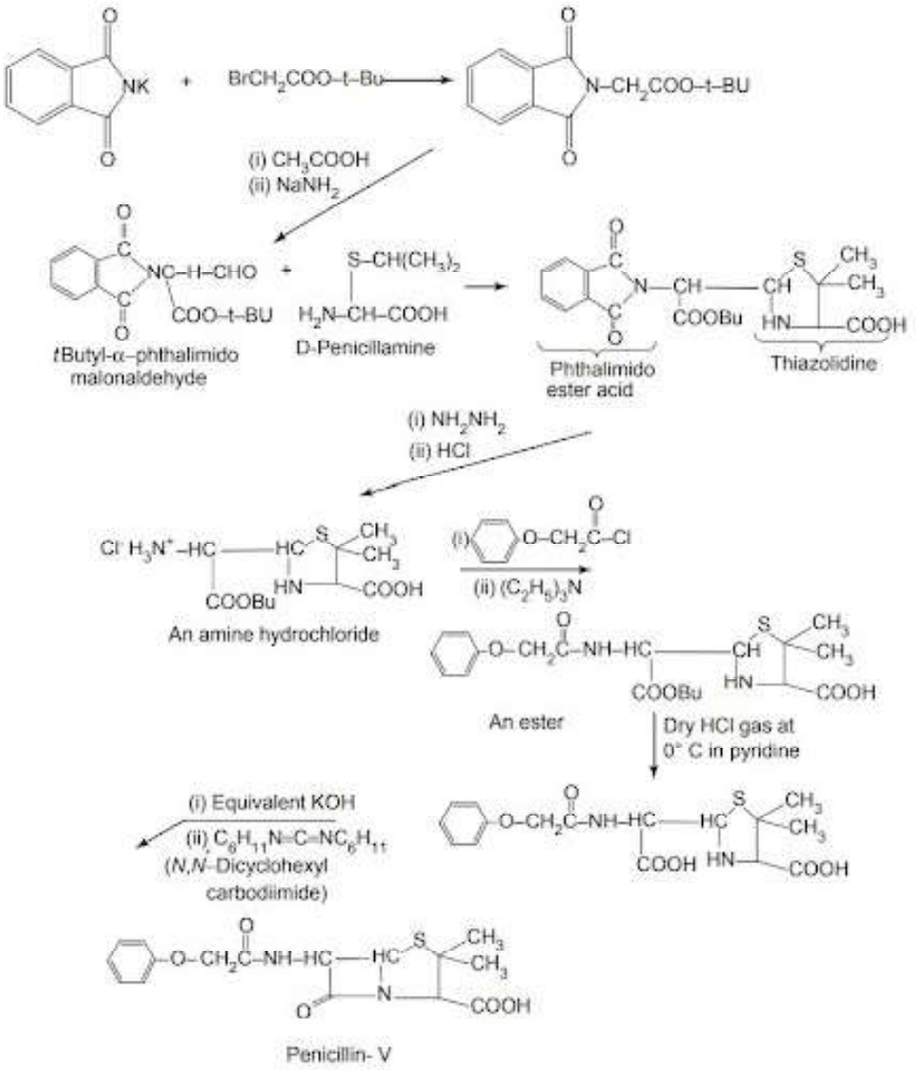

Fig. 5.14 *Synthesis of Penicillin V*

5.5.3 Ampicillin

Ampicillin is a penicillin beta-lactam antibiotic used in the treatment of bacterial infections caused by susceptible, usually Gram-positive organisms**.** By binding to specific penicillin-binding proteins (PBPs) located inside the bacterial cell wall, ampicillin inhibits the third and last stage of bacterial cell wall synthesis. Cell lysis is then mediated by bacterial cell wall autolytic enzymes such as autolysins; it is possible that ampicillin interferes with an autolysin inhibitor.

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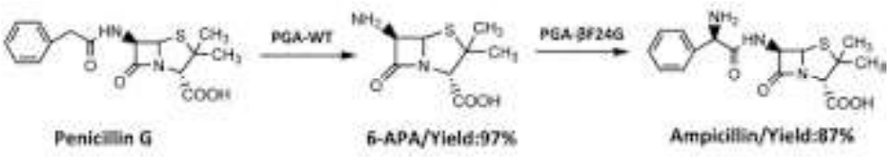

Fig 5.15 *Synthesis of Ampicillin*

5.5.4 Amoxicillin

Amoxicillin (α-amino-p-hydroxybenzyl penicillin, or AMOX) is a semisynthetic derivative of penicillin with a structure similar to ampicillin but with better absorption when taken by mouth, thus yielding higher concentrations in blood and in urine. Amoxicillin attaches to the cell wall of susceptible bacteria and results in their death. It also is a bactericidal compound. It is effective against streptococci, pneumococci, enterococci, Haemophilus influenzae, Escherichia coli, Proteus mirabilis, Neisseria meningitidis, Neisseria gonorrhoeae, Shigella, Chlamydia trachomatis, Salmonella, Borrelia burgdorferi and Helicobacter pylori. As a derivative of ampicillin, amoxicillin is a member of the penicillin family and like penicillins, it is a β-lactam antibiotic.

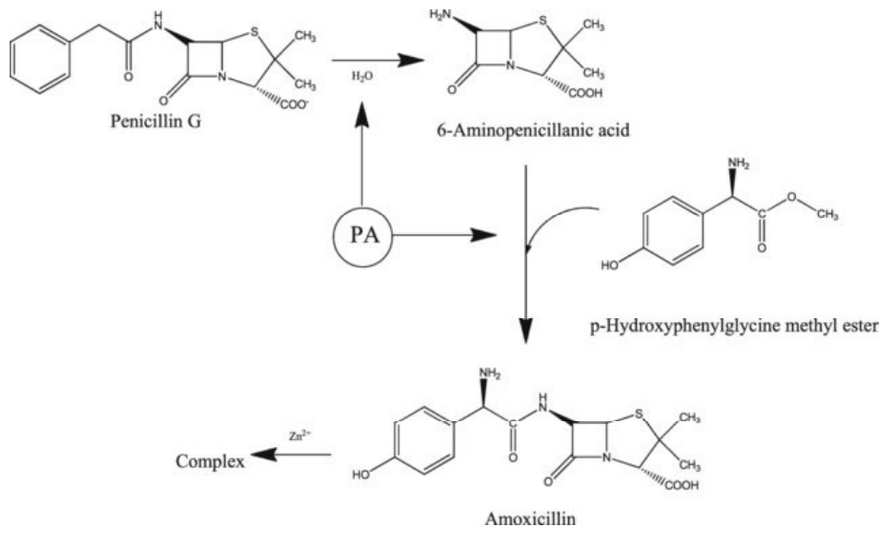

Fig 5.16 *Synthesis of Amoxicillin*

Amoxicillin is also synthesised from the reaction of p-hydroxyphenyl glycine methyl ester (PHPGME) and 6-aminopenicillanic acid (6-APA). There are two side reactions: PHPGME hydrolysis to p-hydroxyphenyl glycine (PHPG) and amoxicillin hydrolysis to 6-APA and PHPG.

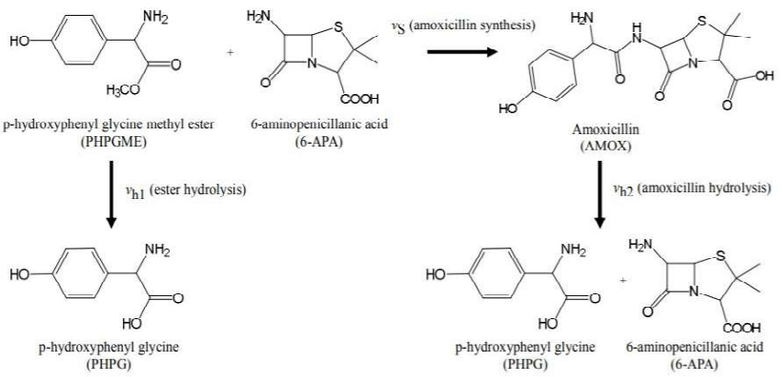

Fig 5.17 *Synthesis of Amoxicillin*

5.5.5 Chloramphenicol

Chloramphenicol is a broad spectrum antibiotic introduced into clinical practice in 1948. It causes serious and fatal aplastic anemia and is now used rarely and reserved for severe, life-threatening infections for which other antibiotics are not available.

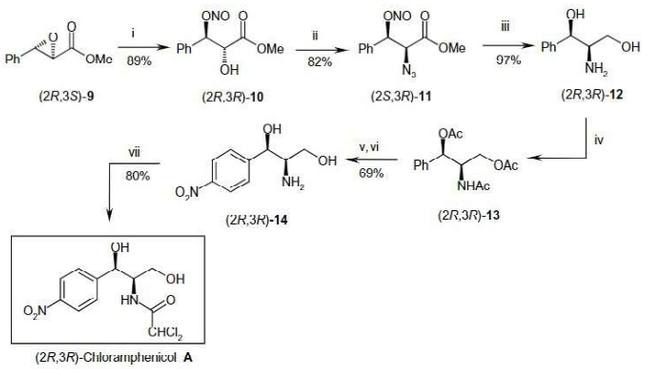

Fig. 5.18 *Synthesis of Chloramphenicol, Reagents and Conditions: (i) NaNO2, AcOH, H2O, 0°C to rt, 2 h; (ii) DPPA, DEAD, PPh3, THF, 0°C to rt, 12 h; (iii) 10% Pd–C, MeOH,1 atm, rt, 12 h; (iv) Ac2O, DMAP, pyridine; (v) HNO3,H2SO4,20°C to rt, 1.5 h; (vi) aqueous 5% HCl, 90°C; (vii) Cl2CHCOOCH3,90°C, 1 h.1746J. Boruwa et al./ Tetrahedron Letters 46 (2005) 1743–1746*

5.5.6 Cephalosporin

Cephalosporin biosynthesis proceeds from ä-(á-aminoadipyl)-l-cysteinyl-d-valine to isopenicillin N. At the next stage, penicillin N is produced by the transformation of the l-á-AAA side chain into the d-form by the action of a labile racemase. After ring expansion to deacetoxycephalosporin C by the expandase reaction, hydroxylation via a dioxygenase to deacetylcephalosporin C occurs. The acetylation of cephalosporin C by an acetyl-CoA-dependent transferase is the end point of the pathway in fungi.

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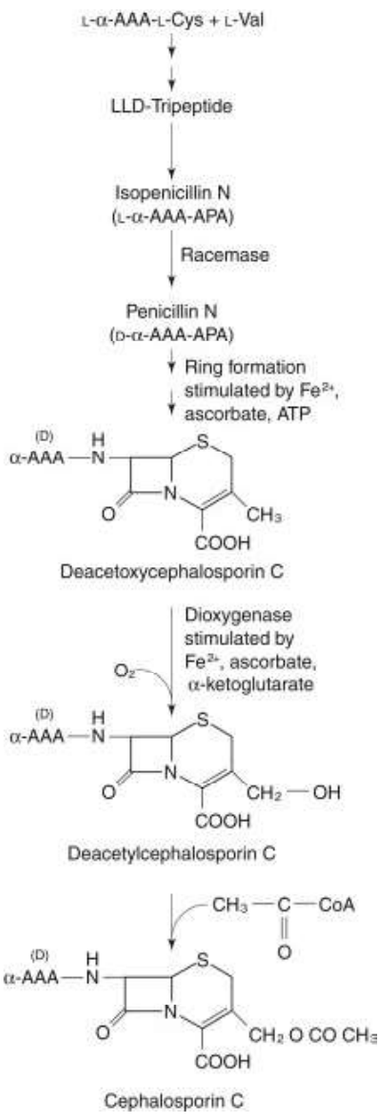

Fig 5.19 *Biosynthesis of cephalosporin C by Cephalosporium Acremonium*

5.5.7 Tetracycline

The starting point for the synthesis was the enantiomerically-pure ester 2, prepared by fermentation of benzoic acid (1) to the 1,2-dihydrodiol, followed by epoxidation, rearrangement and silylation. Acylation of 3 with 2 gave the ketone 4, which on exposure to LiOTf underwent a very interesting and diastereoselective carbon-carbon bond forming reaction to give, after selective desilylation with TFA, the alcohol 5. The authors speculate that this reaction is proceeding by initial SN2′epoxide opening by the N, followed by ylide formation and 2,3-rearrangement. The alcohol 5 was the common intermediate for both syntheses. For the deoxy series, 5 was carried on to the enone 6. Conjugate addition of the anion 7 proceeded with remarkable diastereoselectivity, to give, after intramolecular acylation and deprotection, doxycycline (9).

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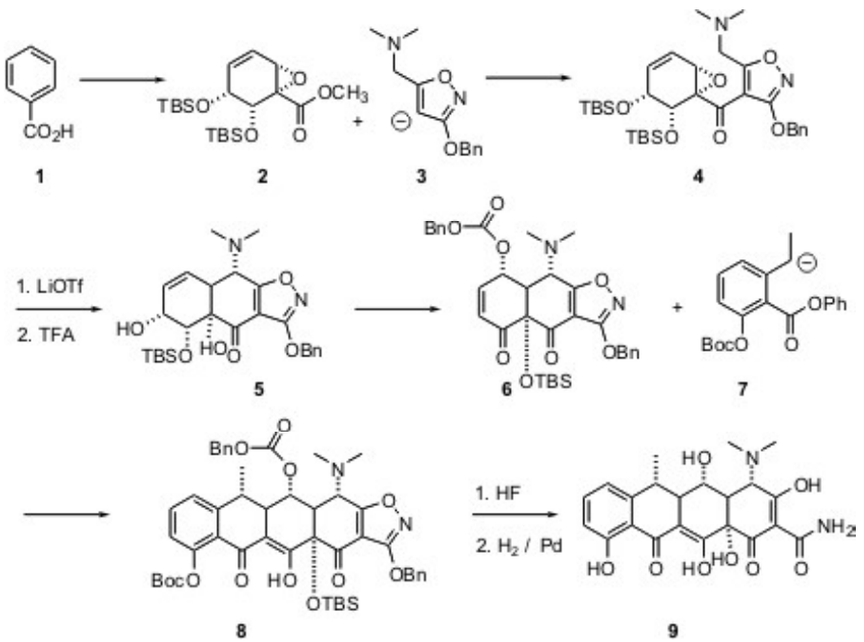

Fig 5.20 *Scheme 1 – Synthesis of Tetracycline*

It is the total synthesis of the more highly oxygenated (-)-tetracycline (16). To this end, the alcohol 5 was carried on to the enone 10. Opening of the cyclobutane 11 to the o-quinone methide was followed by Diels-Alder cycloaddition to 10 delivered the endo adduct 12. Deprotection and oxidation of 12 gave 13, which was further oxidized to the sulfoxide. Elimination of the sulfoxide gave the naphthalene derivative 14, which underwent spontaneous oxidation to 15. Reductive deprotection then gave tetracycline (16).

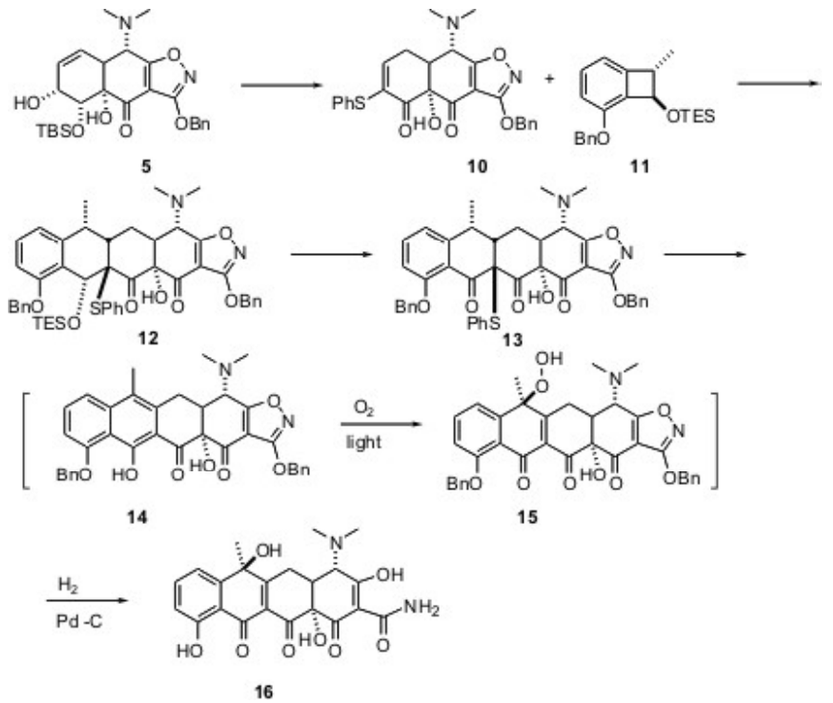

Fig 5.21 *Scheme 2–Synthesis of Tetracycline*

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5.5.8 Streptomycin

Streptomycin is produced by the bacteria Streptomyces griseus. It consists of aminocyclitol (streptidine), 6-deoxyhexose (streptose), and N-methyl-L-glucosamine moieties, which are formed by independent biosynthetic pathways. All of them are derivated from D-Glucose. Experiments on streptomycin biosynthesis in S. griseus have revealed that over 29 genes are involved in the pathway.

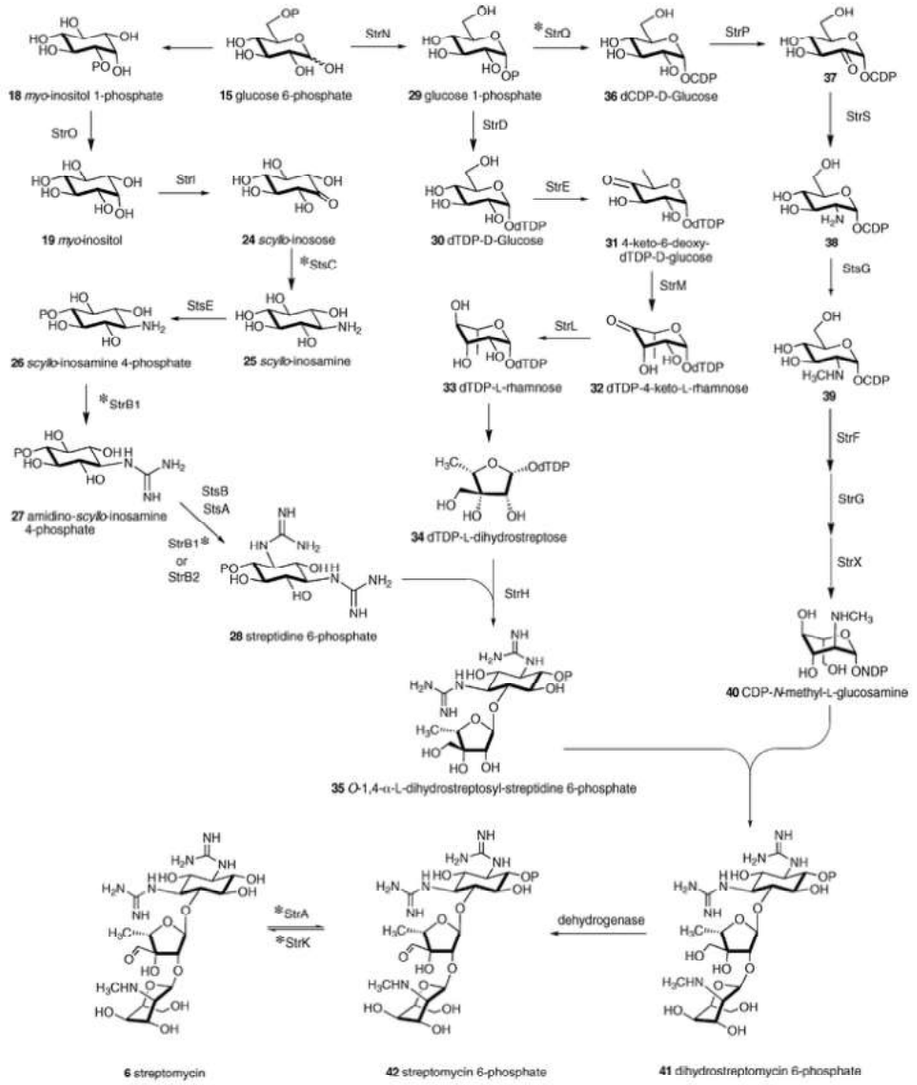

Fig 5.22 *Synthesis of Streptomycin*

Check Your Progress

11. What is the use of penicillin G?
12. Write the composition of streptomycin.
13. Name one derivative of D-Glucose.

5.6 ANSWERS TO 'CHECK YOUR PROGRESS'

NOTES

1. The term 'antibiotic' was coined by Selman Waksman who worked at Rutgers University.
2. One thriving approach developed by Louis Pasteur was to use harmless bacterium to cure diseases caused by harmful microorganism.
3. In 1920, Fleming had discovered the antibiotic, lysozyme, a naturally occurring substance present in human tears.
4. The process starts within the cytoplasm (Stage 1) and is followed by reactions within the membrane.
5. Fosfomycin is an effective antibiotic because it functions as a suicide inhibitor of MurA enzyme.
6. Thiadiazole, a â-lactam derivative, was active against Gram-negative bacteria and showed activity against Gram-positive organisms including Staphylococcus aureus.
7. Biphenyl tetrazoles (BPTs) are a structural category of potent competitive inhibitors of metallo-beta-lactamase known through screening and utilised molecular modeling of the enzyme structure.
8. Puromycin is an antibiotic obtained from Streptomyces alboniger.
9. Chloramphenicol, which was previously known as chloromycetin was the first broad spectrum antibiotic developed and was isolated from Streptomyces venezuela, a soil bacteria.
10. The MLS group of antibiotics consist of macrolides, lincosamides and streptogramins.
11. Penicillin G is a penicillin beta-lactam antibiotic used in the treatment of bacterial infections caused by susceptible, usually Gram-positive, organisms.
12. Streptomycin consists of aminocyclitol (streptidine), 6-deoxyhexose (streptose), and N-methyl-L-glucosamine moieties, which are formed by independent biosynthetic pathways.
13. Aminocyclitol (streptidine), 6-deoxyhexose (streptose), and N-methyl-L-glucosamine moieties are derivatives of D-Glucose.

5.7 SUMMARY

- The term 'antibiotic' was coined by Selman Waksman, who worked at Rutgers University. Simultaneously, Albert Schatz and Elizabeth Bugie discovered the antibiotic streptomycin.
- Antibiotics are often outlined as molecules that either kill or inhibit growth of microorganisms. Since the practical application of antibiotics is to cure infections in humans, a necessary property of an antibiotic must be selectivity.
- Penicillin was the primary scientifically studied antibiotic. However, it was not the primary recorded use of antibiotic. The Greeks were noted to use extracts of Dryopteris filix-mas to treat worm infestations.

NOTES

- Alexander Fleming, performing at St. Mary's Hospital in London is wide attributable for the invention of penicillin antibiotic.
- One thriving approach developed by Louis Pasteur was to use harmless bacterium to cure diseases caused by harmful microorganisms.
- Another approach was to use chemicals to kill microorganisms, giving rise to the method known as chemotherapy.
- In 1920, Fleming had discovered the antibiotic, lysozyme, a naturally occurring substance present in human tears.
- The classification of antibiotics are based on the growth and survival of the bacterium.
- Biosynthesis of the cell wall takes place in three stages, namely cytosolic phase of synthesis, membrane phase of synthesis and cell wall phase of synthesis.
- Antibiotics that inhibit cell wall biosynthesis are called inhibitors.
- Antibiotics targeting the cytosolic phase of synthesis are fosfomycin, and D-Cycloserine.
- Antibiotics targeting the cell wall phase of synthesis are penicillin and cephalosporin.
- Antibiotics that inhibit transglycosylation reaction are Moenomycin, Lantibiotics: Mersacidin Vancomycin and Teixobactin.
- Some bacteria are naturally resistant to certain antibiotics (known as intrinsic resistance), while others develop resistance to the antibiotics (known as acquired resistance).
- The structure of â-lactamase enzymes leads water enter the active site when the acyl group bond is created between the â-lactamase and penicillin.
- Some of the common antibiotics that inhibit protein synthesis are Puromycin, Aminoglycosides, Tetracyclines, Chloramphenicol, Oxazolidinones, etc.
- Penicillin G is a penicillin beta-lactam antibiotic used in the treatment of bacterial infections caused by susceptible, usually Gram-positive organisms.
- Penicillin V is a white, odourless, crystalline powder which is slightly bitter in taste and soluble in water.
- Ampicillin is a penicillin beta-lactam antibiotic used in the treatment of bacterial infections caused by susceptible, usually Gram-positive organisms.
- Amoxicillin (á-amino-p-hydroxybenzyl penicillin, or AMOX) is a semisynthetic derivative of penicillin with a structure similar to ampicillin but with better absorption when taken by mouth, thus yielding higher concentrations in blood and in urine.
- Chloramphenicol is a broad spectrum antibiotic causes serious and fatal aplastic anemia.
- Cephalosporin biosynthesis proceeds from ä-(á-aminoadipyl)-l-cysteinyl-d-valine to isopenicillin N. At the next stage, penicillin N is produced by the

transformation of the l-á-AAA side chain into the d-form by the action of a labile racemase.

- The starting point for the synthesis was the enantiomerically-pure ester 2, prepared by fermentation of benzoic acid (1) to the 1,2-dihydrodiol, followed by epoxidation, rearrangement and silylation.
- Streptomycin is produced by the bacteria Streptomyces griseus. It consists of aminocyclitol (streptidine), 6-deoxyhexose (streptose), and N-methyl-L-glucosamine moieties.

NOTES

5.8 KEY TERMS

- **Biosynthesis:** It is a multi-step, enzyme-catalyzed process in which compounds are used to synthesize macromolecules inside the living cells.
- **Inhibitors:** These are the substances/antibodies that prevent chemical reaction.
- **Lysozyme:** It is an enzyme which catalyses the destruction of the cell walls of certain bacteria, and occurs notably in tears and egg white.
- **Antibiotic:** It is an antimicrobial substance that is active against bacteria.
- **β-lactam Ring:** It is a lactam consists of four members. It is a cyclic amide and part of the core structure of several antibiotic families, such as penicillins, cephalosporins and carbapenems.
- **Peptidoglycan:** It is a substance that forms the cell walls of many bacteria, consisting of glycosaminoglycan chains interlinked with short peptides.
- **Resistance:** It refers to the ability of germs, such as bacteria and fungi to defeat the drugs designed to kill them.

5.9 SELF-ASSESSMENT QUESTIONS AND EXERCISES

Short-Answer Questions

1. What are the major functions of β-lactam rings?
2. Mention all the stages involved in cell wall biosynthesis.
3. Which antibiotics inhibit transglycosylation reaction?
4. What are the six major categories of antibiotics?

Long-Answer Questions

1. Discuss and illustrate the synthesis of penicillin G.
2. Write a short note on discovery of modern antibiotics.
3. Enlist the targets of antibiotics. Give a diagrammatic explanation for each case.
4. Explain the mechanism of action of puromycin.
5. Discuss the properties of a perfect antiobiotic.

5.10 FURTHER READING

NOTES

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