Chapter 6

Pro-Drugs

INTRODUCTION

A pro-drug is a chemically modified inert precursor of the drug that on biotransformation liberates the pharmacologically active parent compound. A pro-drug is also called as pro-agent, bio-reversible derivative, or latentiated drug. The design of pro-drug approach is also called as drug latentiation.

Ideal Properties

The ideal properties of pro-drugs are as follows:

- Drug and the carrier linkage must be cleared in vivo.
- It should not have intrinsic pharmacologic activity.
- It should rapidly transform, chemically or enzymatically, into the active form where desired
- The metabolic fragments, apart from the active drug, should be nontoxic.

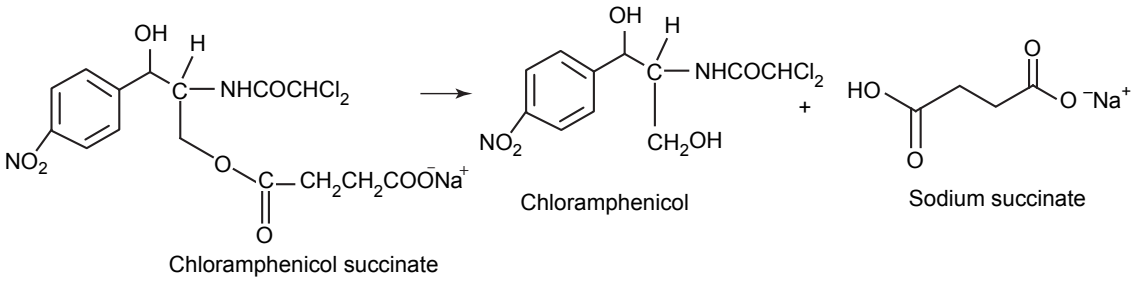
CLASSIFICATION OF PRO-DRUG

Depending on the constitution, lipophilicity, and method of bioactivation, pro-drugs are classified into two categories.

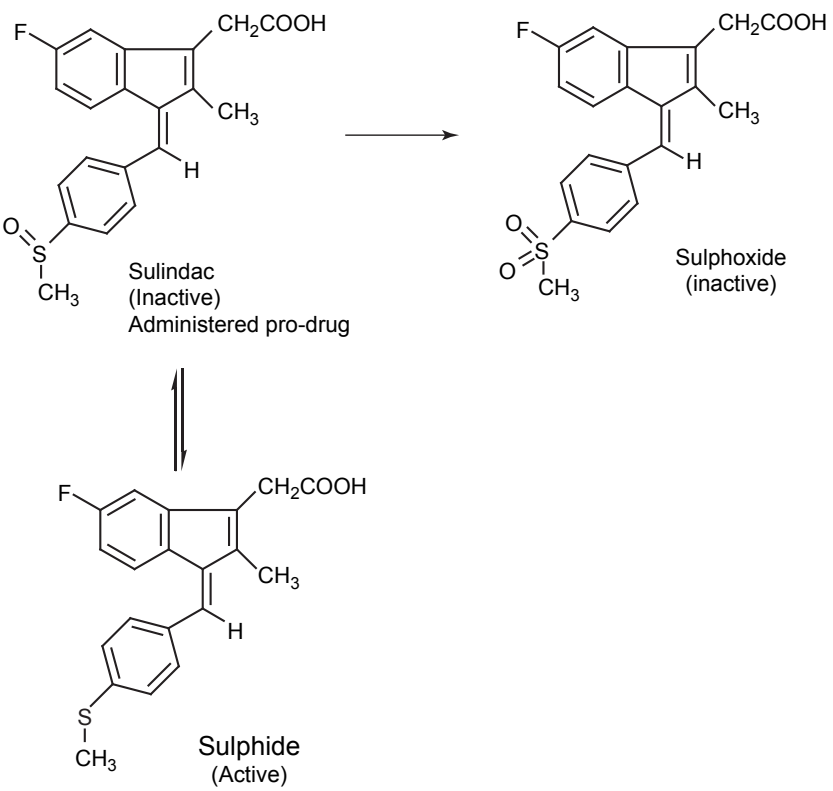
1. Carrier-linked pro-drugs
2. Bio-precursors

Carrier-linked pro-drug or simple pro-drugs: They are generally esters or amides. Carrier-linked pro-drugs are the ones where the active drug is covalently linked to an inert carrier or transport moiety. Such pro-drugs modify the lipophilicity due to the attached carrier. The active drug is released by hydrolytic cleavage, either chemically or enzymatically.

Examples:



Bioprecursors: They are inert molecules obtained by a chemical modification of the active drugs, but do not contain a carrier. For example, nonsterodial anti-inflammatory drug, sulindac, is inactive as sulphoxide and must be reduced metabolically to active sulphide.



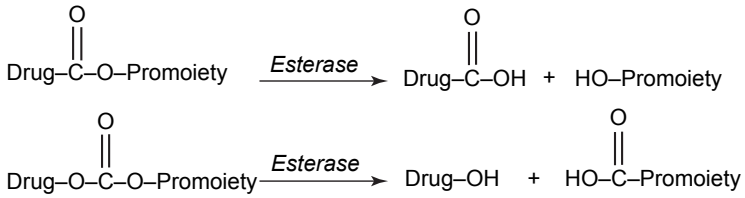
Pro-drugs are also classified according to the functional group. They are

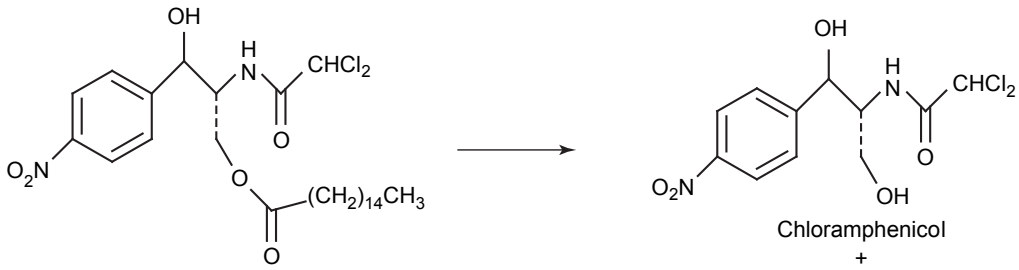
- Carboxylic acids and alcohols
- Amines
- Azo linkages
- Carbonyl compounds

Carboxylic acid and alcohols: Pro-drugs of carboxylic acid and alcohol functionalities can be prepared by conversion to esters. The esters can be easily hydrolyzed by *esterase* enzymes (e.g. lipase, ester hydrolase, cholesterol esterase, acetyl cholinesterase, and carboxy peptidase) present in plasma and other tissues to give active drug.

Example:

(i)





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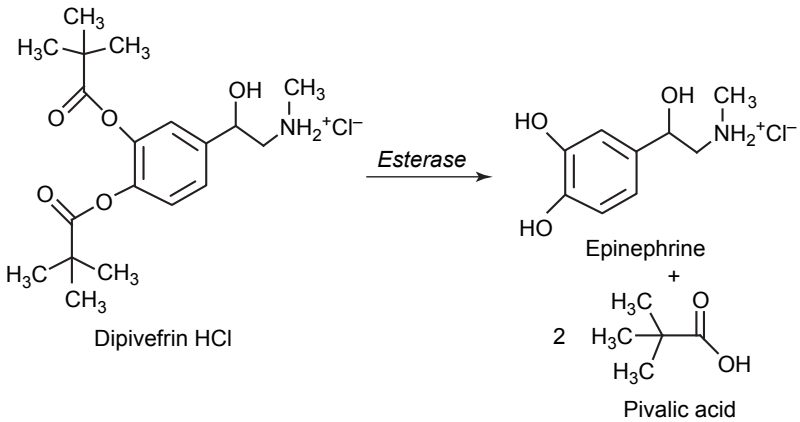
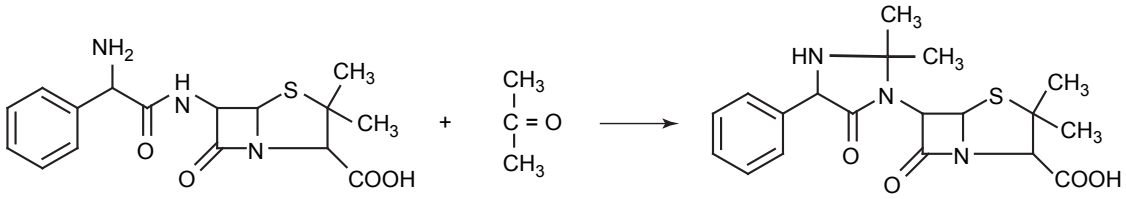
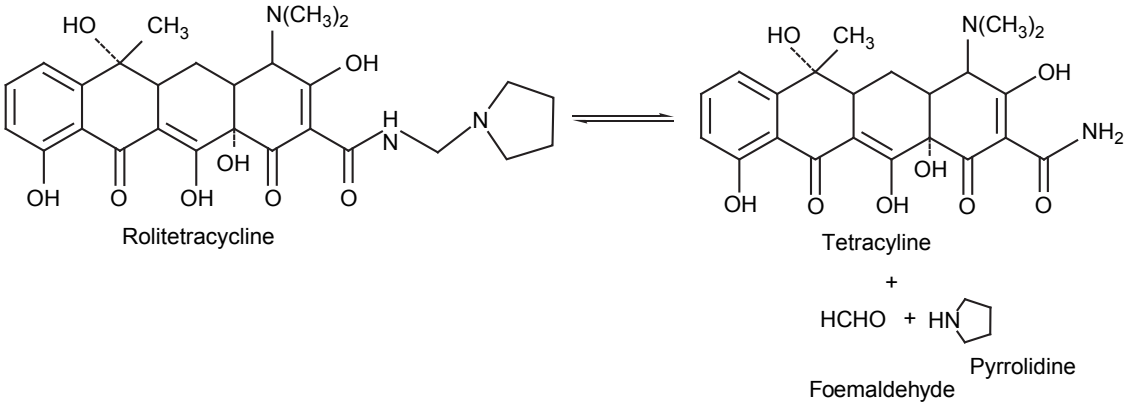


Amines: Due to the high stablility and lack of *amidase* enzyme necessary for hydrolysis, the conversion of amines to amide as a pro-drug is not been used for most of the drugs. A more common approach adopted is to use Mannich bases as pro-drug form of amines.



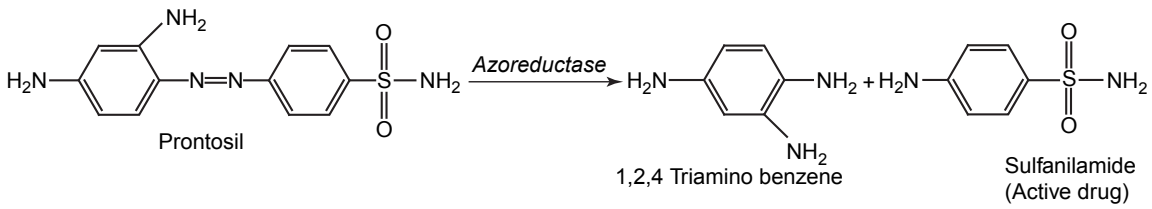
Hetacillin is a pro-drug form of ampicillin in which amide nitrogen and α amino functionalities have been allowed to react with acetone to give a Mannich base (imidazolidine ring system). This leads to decrease in the basicity and increase in the lipophilicity and absorption.



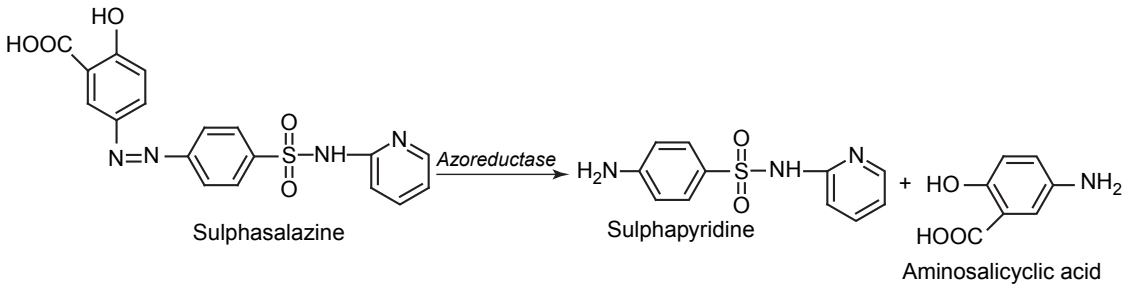
The basic pyrrolidine nitrogen increases water solubility of the parent drug rolitetracycline. The Mannich base hydrolyzes completely and rapidly in aqueous media to give the active tetracycline.

Azo linkage: Pro-drugs of amines are occasionally prepared by incorporating them in to an azo linkage. By the action of *azo reductase* the amino compounds are released in vivo.

- Prontosil drug is inactive in vitro, but it is active in vivo since it is converted to sulphanilamide by *azo reductase* enzymes.

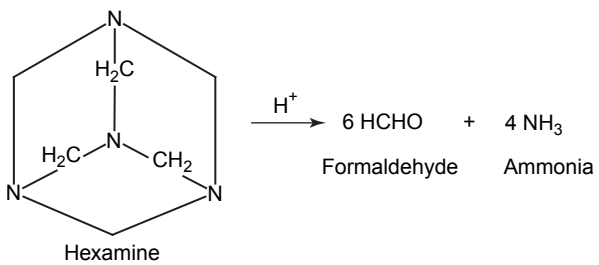


- Sulphasalazine by the action of *azo reductase* releases the amino salicylic acid and sulphapyridine. The generation of anti-inflammatory salicyclic acid prior to absorption prevents the systemic absorption of the agents and enhances the concentration of it in active site.



Carbonyl moiety: Conversion of carbonyl functionalities, such as aldehyde and ketone, to pro-drug have not been found wide clinical use. They are converted into derivatives in which the sp^2 carbonyl carbon is converted as sp^3 hybridized carbon attached to hetero-atoms. These pro-drugs are re-converted to carbonyl compound by hydrolysis.

For example, hexamine releases formaldehyde in the urine (acidic P^H), which acts as an antibacterial agent.



The differences between bioprecursors and carrier prodrugs are given in Table 6.1.

Table 6.1 Differences between bioprecursors and carrier prodrugs.

Characteristic	Carrier Pro-drugs	Bioprecursors
Constitution	Active principles + Carrier group	No carrier group
Bioactivation	Hydrolytic	Oxidative or reductive
Catalysis	Chemical or enzymic	Only enzymatic
Lipophilicity	Strongly modified	Slightly modified

APPLICATIONS OF PRO-DRUG

The aim of pro-drug development is, in most cases, to solve specific pharmaceutic or pharmacological and pharmacokinetic problems. The main objectives of pro-drug are as follows:

- Improvement of taste.
- Improvement of odour.
- Enhancement of bioavailability.
- Improvement of stability and solubility properties.
- Decreased toxicity and adverse reactions.
- Increased site specificity.
- Increased duration of pharmacological actions.
- Drug absorption, distribution, metabolism, and excretion affect pharmacokinectis.

Improvement of Taste

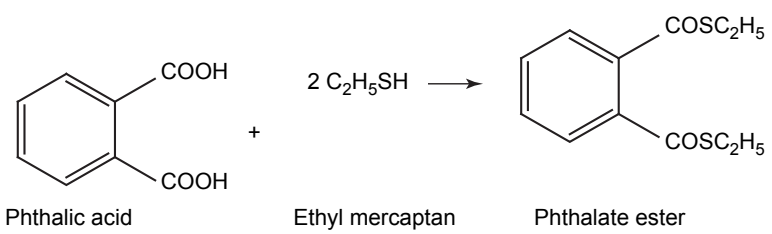
One of the reasons for poor patient compliance particularly in case of children is the bitterness, acidity, or causticity of the drug. Two approaches are adopted to overcome the bad taste of drug. The first is reduction of drug solubility in saliva and the other is to lower the affinity of drug towards taste receptors, thus, masking the bitterness. Some examples of drugs with improved taste are given in Table 6.2.

Table 6.2 Drugs with improved taste.

Parent drug	Pro-drug with improved taste
Chloramphenicol	Palmitate ester
Clindamycin	Palmitate ester
Sulfisoxazole	Acetyl ester
Erythromycin	Estolate

Improvement of Odour

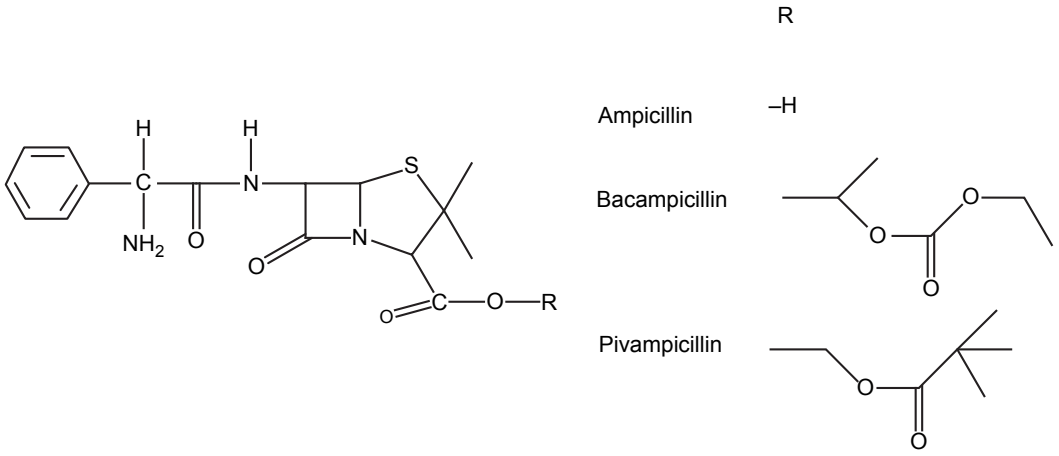
The odour of a compound depends on its vapour pressure; a liquid with high vapour will have a strong odour. For example, ethyl mercaptan is a foul smelling liquid used in the treatment of leprosy. This is converted to phthalate ester, a diethyl dithioisophthalate that has higher boiling point and is odourless.



Enhancement of Bio-Availability (Lipophilicity)

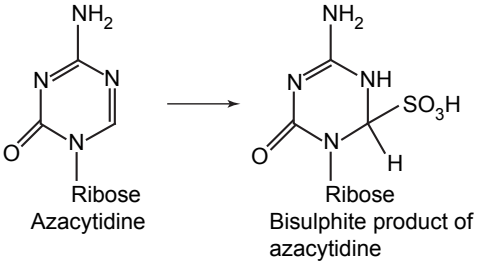
Due to the presence of an amino group in the side chain, Ampicillin possesses low lipophilicity and is only 30%–40% absorbed when taken by oral route. Altering the polarity of this antibiotic, by esterifying the

free carboxyl group results in compounds that are completely absorbed, that is, with greater bio-availability than the parent ampicillin.



Improvement of Stability and Solubility

Stability: To improve their stability, prodrug approach is a good technique. Several drugs may decompose in their shelf life or in the gastro intestinal tract (GIT) when used orally. An antineoplastic drug, Azacytidine, hydrolyse readily in acidic pH, but the bisulphite prodrug of it is more stable.

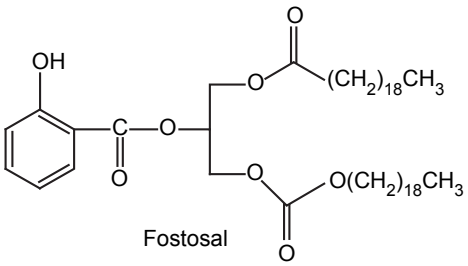


Solubility: Hydrophilic or water-soluble drugs are needed when parenteral or ophthalmic formulation of such agents is desired. Drugs with hydroxyl functional group can be converted to their hydrophilic form through the use of half ester such as hemi-glutarate or hemi-phthalates, the other half of this acid carries sodium, potassium, or amine salts, and renders the moiety more soluble.

Parent drug	Pro-drug with enchanced hydrophilicity
Tocophenols	Sodium succinate ester
Metronidazole	Amino acid esters

Decreased Toxicity and Adverse Reactions

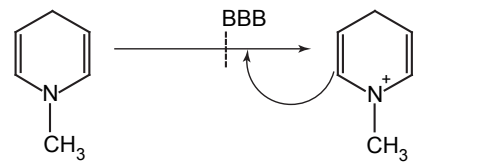
Carboxylic acids and phenols are sometimes too toxic to be employed as such in clinical practice. Ester prodrugs of the acidic nonsteroidal anti-inflammatory drugs are devoid of gastric ulcerogenic activity and is considered as one of the responsible factors for the adverse reaction of these drugs.



Fostosal

Site-Specific Drug Delivery

Many pro-drugs could be so prepared that they will be delivered to a specific site, thus reducing the toxicity to other organs. The dihydropyridine/pyridinium redox chemical delivery system is very useful for the brain.

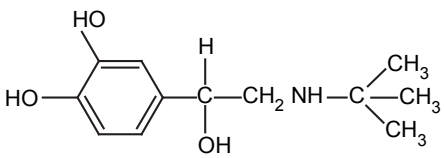


Dihydropyridine (Lipophilic)

Pyridinium system (Hydrophilic)

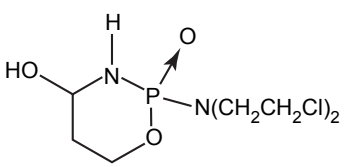
Increased duration of action

The pro-drug di-*p*-toluate ester of *N*-*t*butyl noradrenaline provides a longer duration of bronchodilator activity than the parent drug. The pro-drug is preferentially distributed into the lung tissues rather than into the plasma or the heart, so that the bronchodilator effect is exerted.



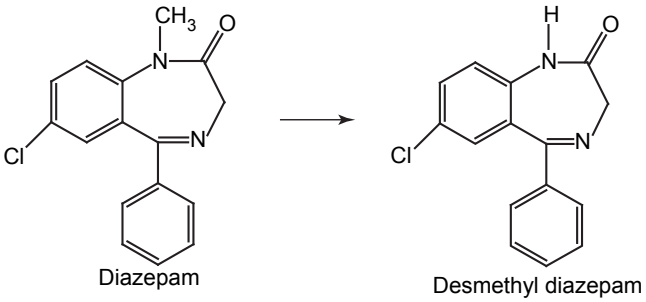
Bio-Precursor Prodrug

Bio-precursor pro-drug does not contain a carrier or a promoiety, but rather contains a latent functionality that is metabolically or chemically transformed into active drug molecule. The types of activation involves phase I, such as oxidation, reduction, phosphorylation, or chemical activation.

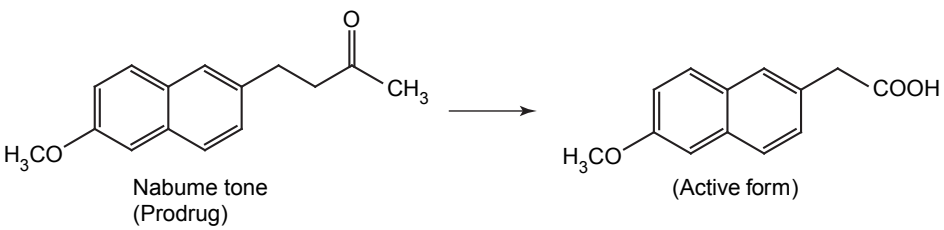


Bio-activation: Hydroxylation of cyclophosphamide followed by the metabolite decomposition converts the pro-drug into the cytotoxic phosphoxamide mustard.

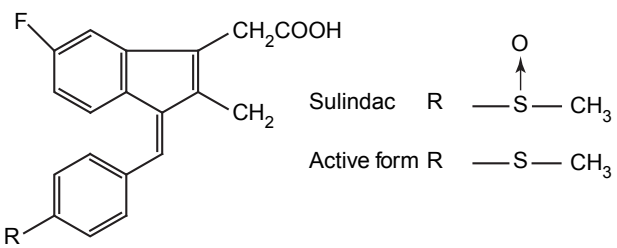
N-dealkylation: Many drugs are transformed into their active metabolite form by ***N***-dealkylation



Oxidation: The prodrug nabumetone in which the formyl group formed is oxidized into a carboxylate group and generating the active drug.



Reduction: The nonsteroidal anti-inflammatory drug sulindac is reduced in vivo to the active form.



PROBABLE QUESTIONS

1. Describe the various approaches of lead discovery.
2. What are the different types of receptors existing? Describe them with suitable examples.
3. What are the different forces involved in drug receptors interaction? Explain any two of them.
4. Explain the various factors affecting the drug-receptor interaction.
5. Write in detail about computer aided drug design (CADD).
6. Define QSAR and explain about Hansch analysis and Free-Wilson analsysis.

7. Write in detail about the steps involved in the QSAR studies.
8. Write a note on the following.
   (a) Comparative Molecular Field Analysis (CoMFA) (b) Comparative Molecular Similarity Indices Analysis (CoMSIA)
9. What is combinatorial chemistry? Write its application in the drug discovery.
10. Write a note on combinatorial synthesis on solid phase.
11. What is pro-drug? Write their classification based on the functional group.
12. What are the advantages of pro-drugs? Explain with suitable examples.
13. Write a note on bioprecursor prodrug

SUGGESTED READINGS

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