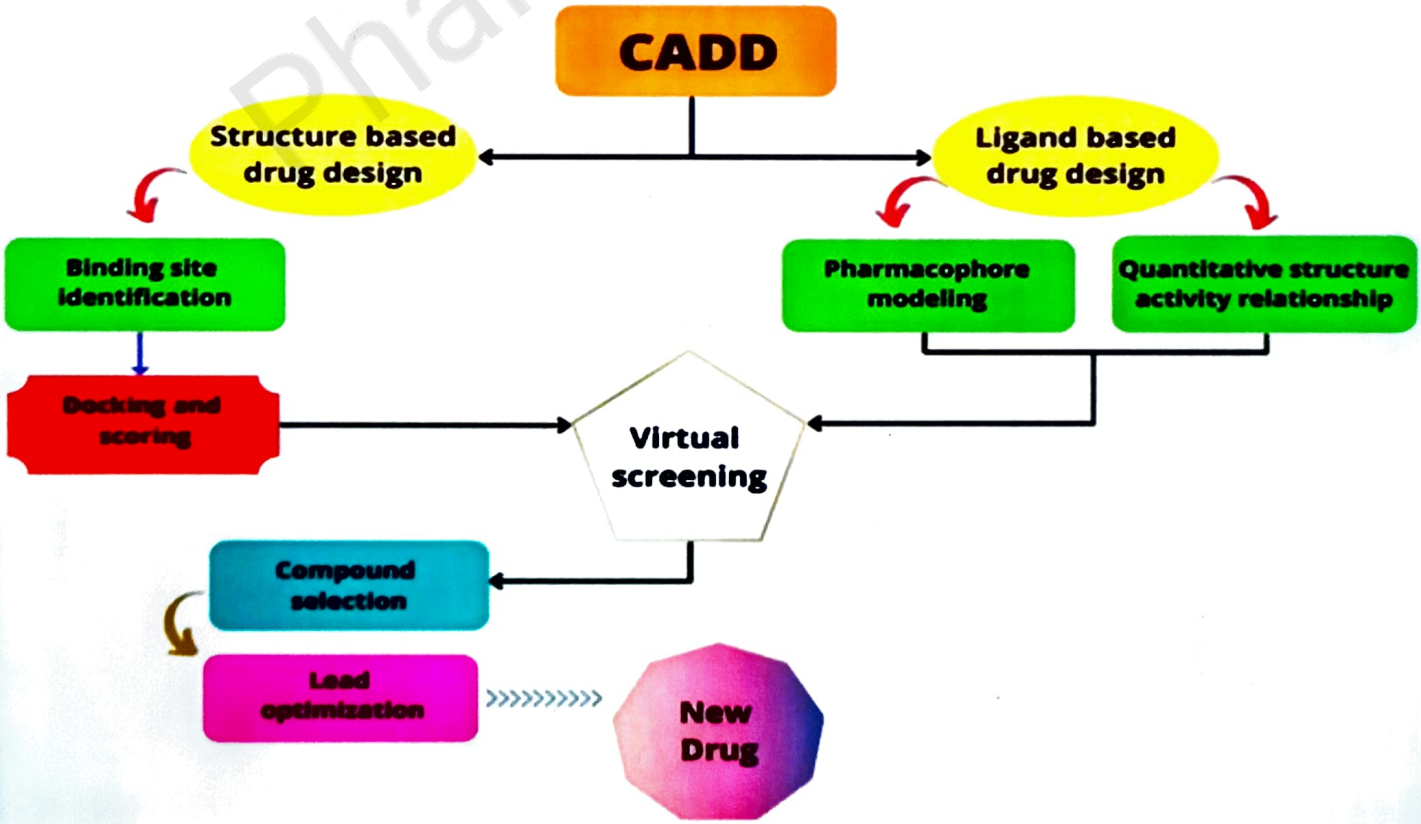
UNIT-I

Introduction to drug discovery and development

Points to be covered in this topic

- ❑ INTRODUCTION
- ❑ STAGES OF DRUG DISCOVERY
- ❑ STAGES OF DRUG DEVELOPMENT
- ❑ LEAD DISCOVERY
- ❑ ANALOG BASED DRUG DESIGN



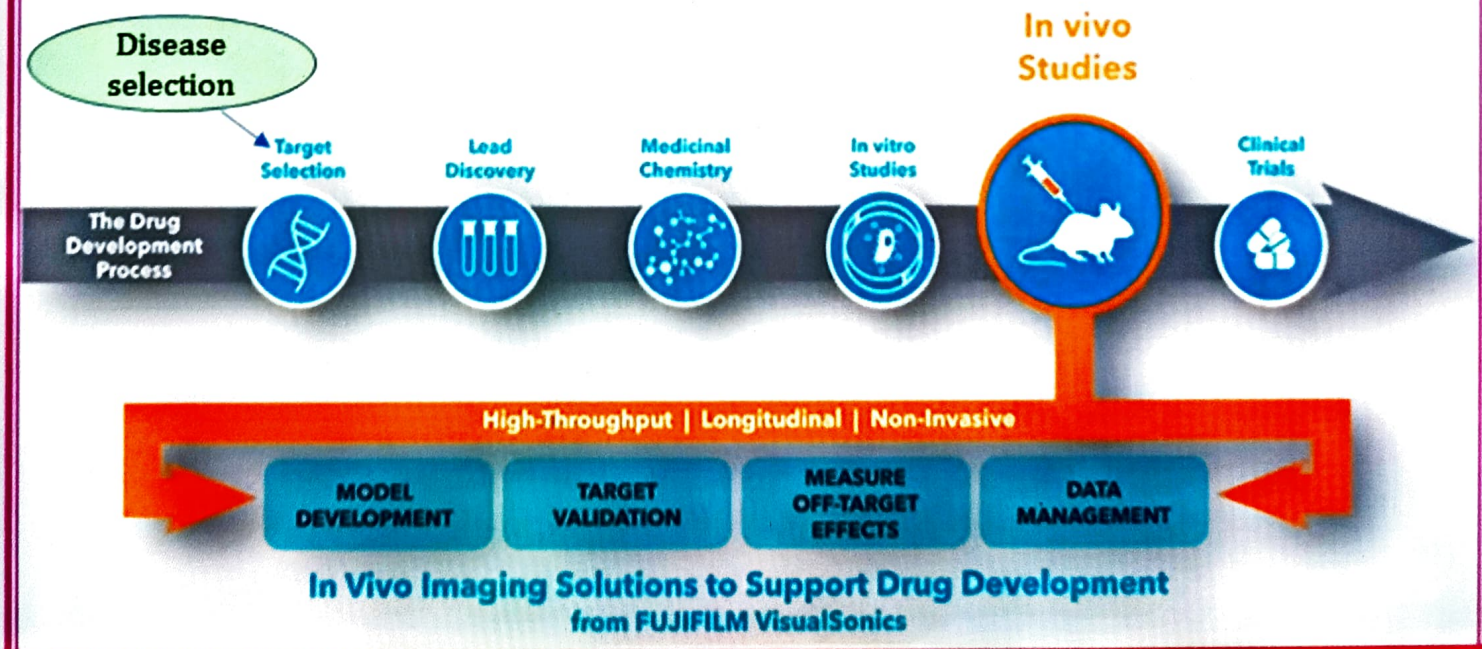
❑ INTRODUCTION

- Drug discovery involves **identification of the compound** which have the potential to be converted into a therapeutic product.
- Drug discovery is the **initial phase characterized by a search for appropriate targets** or effects and **identification of small molecules** or biologics that selectively modulate those targets.
- Drug discovery and development is **complex, time consuming, costly process which carries commercial risk.**
- Discovering and developing **new treatments for diseases and other medical conditions is a lengthy and expensive process**. Millions of dollars and years of work is involved in getting a therapeutic product manufactured, tested, approved and marketed for use of patients.
- Drug discovery and development **are broadly divided into two category**.

a) **Preclinical evaluation:-** This step **validates the safety and biological activity of a therapeutic compound** through in vitro and animal studies.

b) **Clinical trials:-** It follow preclinical studies and are designed to determine the safe and most effective dosages, route of administration, efficacy (how well the therapeutic compound works) and patient outcomes.

❑ STAGES OF DRUG DISCOVERY



❖ Disease selection:- It is important to concentrate on disease where there is a need for new drugs.

❖ Drug target identification

- Once a therapeutic area has been identified, the next stage is to identify a suitable drug target (e.g.. receptor, enzyme or nucleic acid).
- To understanding of which, bio macromolecules are involved in a particular disease state is also important.

➢ Discovery of drug targets

- If a drug or a poison produces a biological effect, there must be a molecular target for that agent in the body.
- Many early drugs such as the analgesic morphine are a natural product derived from plants, and interact with a molecular target in the human body.

➢ Specificity and selectivity of target between species

- The more selective a drug is for its target, the less chance that it will interact with different targets and have undesirable side effects.

➢ Specificity and selectivity of target within the body

- Selectivity is also important for drugs acting on targets within the body. These inhibitors should ideally interact with a specific kind of receptor rather than a variety of different receptors. For example, receptor agonists and antagonists.

➢ Targeting drugs to specific organ and tissues

- Targeting drugs against specific receptor subtypes often allow drugs to be targeted against specific organs or against specific area of the brain.

❖ Lead discovery:-

- Once the therapeutic target has been identified, scientists must then find one or more leads **(e.g.,**
- **chemical compounds or molecules)** that interact with the therapeutic target so as to induce the desired therapeutic effects, e.g., through antiviral or antibacterial activity.

❖ Medicinal chemistry:-

- It prepare or select appropriate compounds for biological evaluation that, if found to be active, could serve as lead compounds.
- They then evaluate the structure-activity relationships (SAR) of analogous compounds with regard to their in vitro and in vivo efficacy and safety.

❖ In vitro studies:-

- In vitro tests do not involve live animals. Instead, specific tissues, cells, or enzymes are used.
- Enzyme inhibitors can be treated on the pure enzyme in solution.
- For example, HIV protease has been cloned and expressed in the bacterium E. coli.
- A variety of experiments can be carried out on this enzyme to determine whether the enzyme inhibitor is competitive or non-competitive, and to determine IC50 values.

❖ In vitro studies:-

- In vivo test on animals often involve inducing a clinical condition in the animal to produce observable symptoms.
- The animal is then treated to see whether the drug alleviates the problem by eliminating the observable symptoms.
- For example, the developments of non-steroidal anti-inflammatory drugs were carried out by inducing inflammation on test animals, then testing drugs to see whether they relived the inflammation.

❑ STAGES OF DRUG DEVELOPMENT

- Drug discovery normally refers to the process of taking a compound that has been identified through the steps necessary to bring it to market.

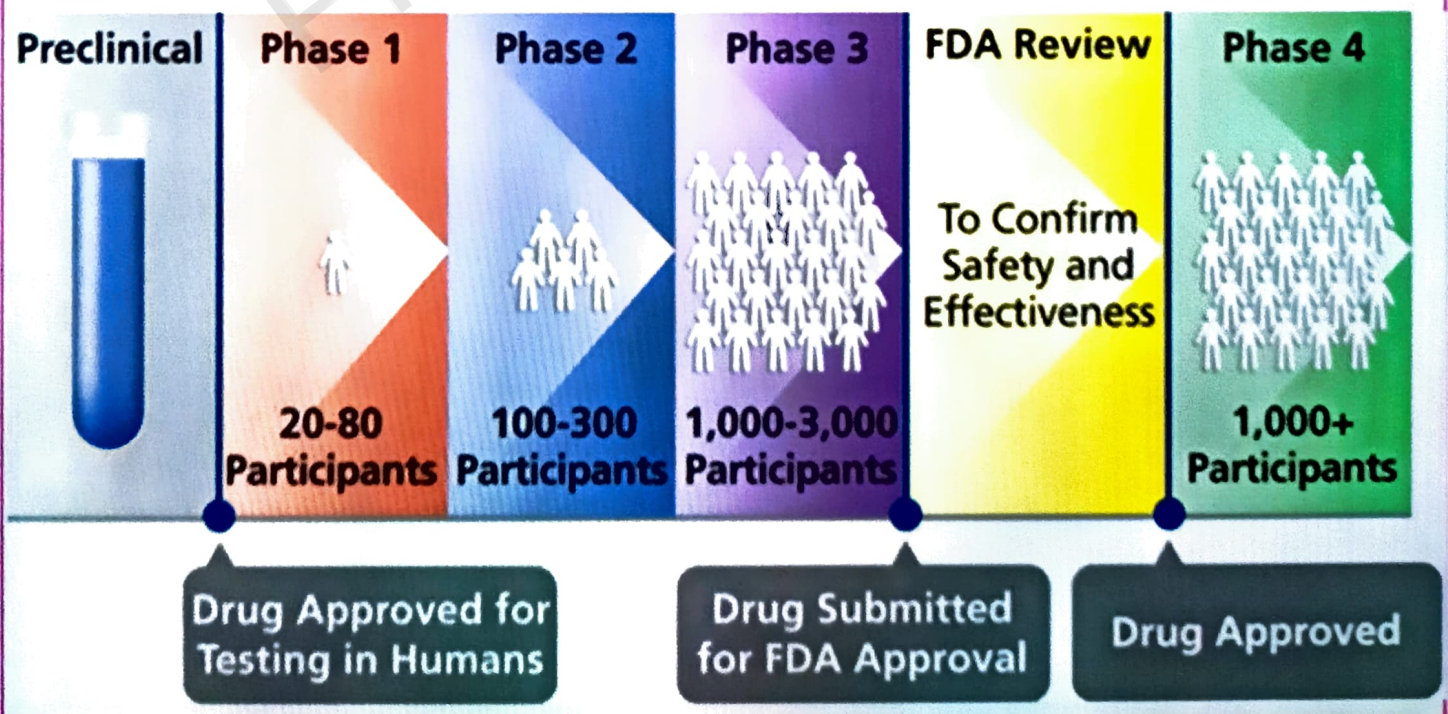
❖ Preclinical trials:-

- Preclinical development is the stage of research between drug discovery and clinical development, which typically includes:

- Development of synthetic process that will enable the **compound to be manufactured in reproducible purity on large** (multi kilogram) **scale.**
- Development of a formulation, in most cases **a solution or suspension** of the drug that can be **administered to animals in toxicity tests** and a **solution or suspension or pill** that can be **administered to humans in clinical trials.**
- Toxicity testing in animals under **conditions prescribed by the regulatory authorities** in the region where the clinical trials will occur (the FDA in the US; the European Medicines Agency in Europe; the Japanese Ministry of Health and Welfare in Japan).
- Following toxicity studies, **gaining permission from the regulatory authorities to administer the drug to human.** In the US, such permission is obtained through the submission of the FDA of an Investigational New Drug (IND) application which summarizes the discovery and preclinical development research done to date.

❖ Clinical trials:-

- Clinical trials are used to **determine whether new biomedical or behavioural interventions are safe, efficacious, and effective.**
- Clinical development is normally **conducted in three phases (Phase I-III) prior to applying for regulatory approval to market the drug:**



- **Phase I:** Clinical trials test a new biomedical **intervention in a small group of people (e.g., 20- 80)** for the first time **to evaluate safety (e.g., to determine a safe dosage range, and to identify side effects).**
- **Phase II:** Clinical trials study the biomedical or behavioral **intervention in a larger group of people (several hundred) to determine efficacy and to further evaluate its safety.**
- **Phase III:** Studies investigate the efficacy of the biomedical or behavioral **intervention in large groups of human subjects (from several hundred to several thousand)** by comparing the intervention to other standard or experimental **interventions as well as to monitor adverse effects,** and to collect information that will allow the **intervention to be used safely.**
- **Phase IV:** Studies are conducted after the intervention has been marketed. These studies are designed to **monitor effectiveness of the approved intervention** in the general population and **to collect information about any adverse effects.**

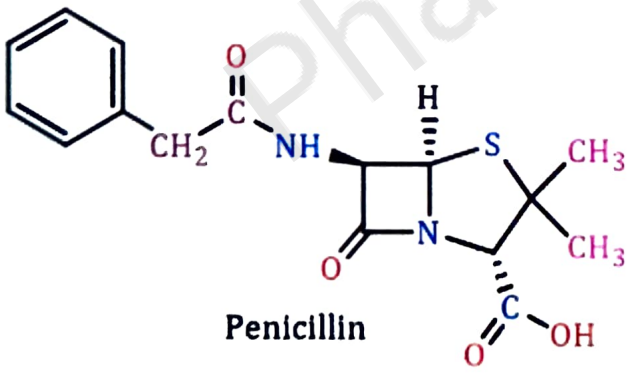
❑ LEAD DISCOVERY

- Once a target & a testing system has been chosen, the next is **to find a "Lead Compound" which shows the desired pharmaceutical activity.**
- A lead compound is generally defined as a new chemical entity that could potentially be **developed into a new drug by optimizing its beneficial effects and minimizing its side effects.**
- Lead compounds are typically used as **starting points in the drug design to give new drug entities.**
- Drug Design strategies can be used to improve the **compound's pharmacodynamics and pharmacokinetic properties.**
- It is the process of **chemical modification of lead molecules** and their subsequent characterization in order to obtain drug-like compounds.
- The developed leads are characterized by **in vitro and in vivo biological activities, physicochemical properties, pharmacokinetic and toxicological properties.**

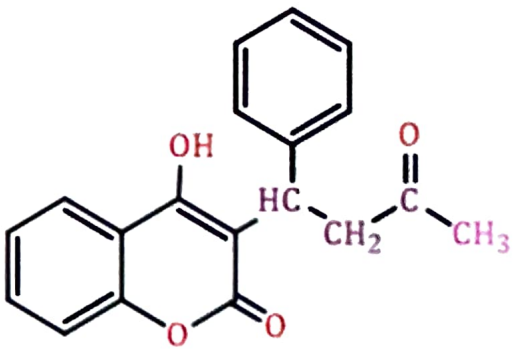
- **Lead optimization** includes selection of **ligand libraries, and then making chemical modifications to molecules and characterize** them with suitable properties to **become a drug.**
- Lead optimization includes **identification of pharmacophores, optimization of functional groups, structural activity relationship studies, and homologation**

❖ Serendipitous drug discovery:-

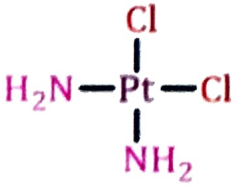
- It is **also called lead discovery without a lead** (Finding something new while looking for something else), **accidental or unexpected drug discovery is called serendipitous drug discovery.**
- **Penicillin discovery**- Staphylococcus culture contaminated with mold
- **Warfarin discovery**- Cattles fed with clover hay
- **Nitrous oxide discovery as anaesthetics** (nitrogen fillings released NO_2)
- **Cisplatin discovery**- Effects of electric field on E. coli growth (Platinum conducting fields)
- **Saccharin discovery**
- **Lithium discovery**



Penicillin



Warfarin



Cisplatin

Saccharin

Li

Lithium

❖ Rational approaches to lead discovery based on traditional medicine:-

- Rational approaches have **become the major route of lead discovery.**
- The first step is **to identify the cause of disease state.**

➢ Many diseases arise from:

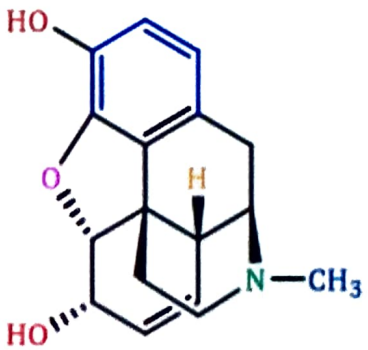
- **Imbalance of particular chemicals in the body.**
- **Invasion of foreign organism.**
- **Abnormal cell growth.**

➢ The effect of imbalance can be corrected by:-

- Antagonism or agonism of a receptor.
- Inhibition of particular enzyme
- Inhibition of enzymes of foreign organism.
- Interference with biosynthesis of DNA.
- Inhibition of abnormal cell growth.
- Lead compound were obtained from the following sources.

i. Plant:-

- **Morphine** is a pain medication of the **opiate family** that is found naturally in a number of plants and animals.
- **In 1805, morphine was first isolated from opium** by **Serturner (German pharmacist)**
- **Schaumann first identified and recognized** the presence of a **quaternary carbon atom in the morphine** molecule, in the field of drug design of narcotic analgesics.
- Intensive research further led to the **evolution of Pethidine (meperidine)** which incidentally **combines both the properties of morphine and atropine.**

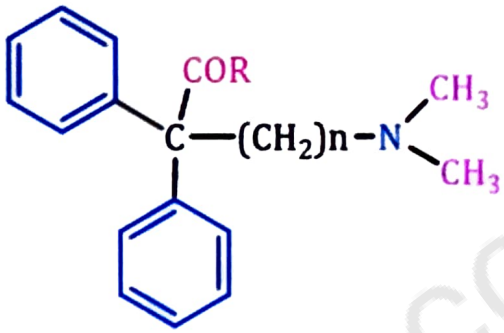


Morphine

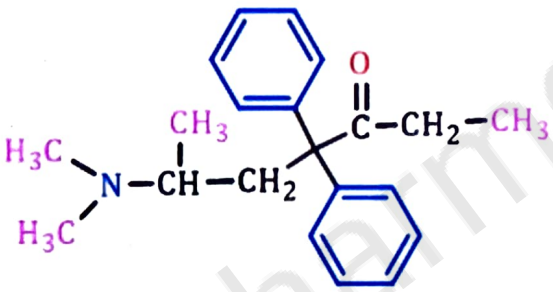
Pethidine

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

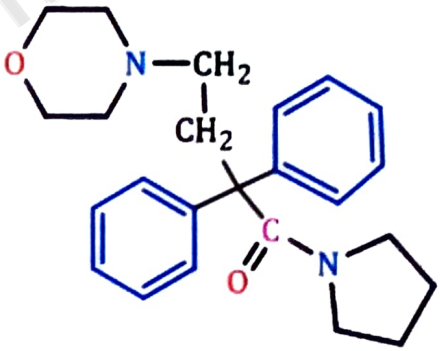
- Where, **Ar is aromatic ring** and **X is basic side chain and carbonyl function in the form of ester, ketone or an amide**. Later on general formula is modified as follows:



- Successfully **led to the development** of the following **three narcotics:-**

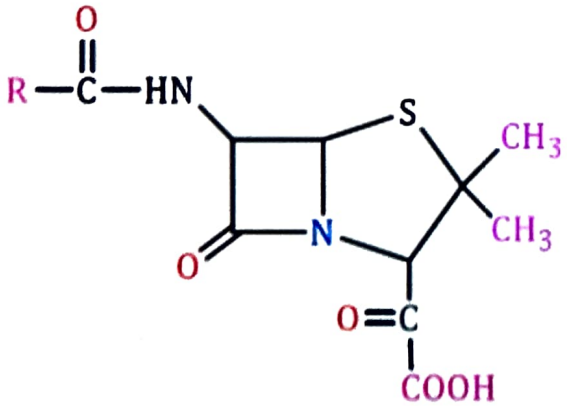


Methadone

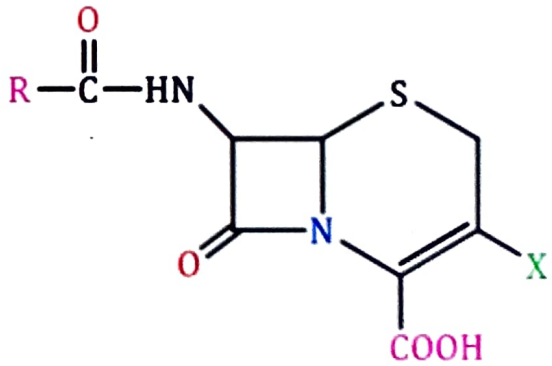


Dextromoramid

ii. Microbes:- Most of **antibiotics as lead are obtained from microbes** as follows:-

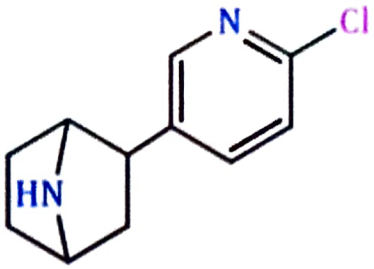


Penicillin



Cephalosporin

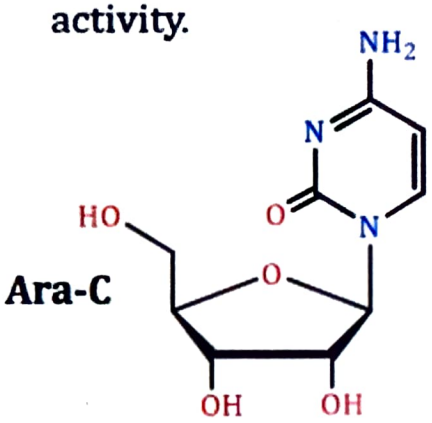
iii. Animals:- Epibatidine is obtained from frog skin



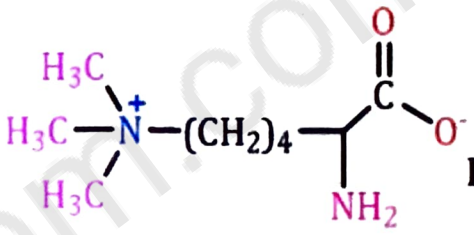
Epibatidine

iv. Marine:-

- **Laminine** is obtained from ***Laminaria angustata***, it is having hypotensive activity.
- **Ara-C** is obtained from *Caribben sponge*, which is having anticancer activity.



Ara-C



Laminine

- **2-cyno, 4,5-dibromoprole** is obtained from **Agelaoriods**, it is having antimicrobial activity.

2-cyno,4,5- dibromoprole

- **Aeroplysinine** is obtained from ***asparagopsis taxiformis,*** having antimicrobial

Aeroplysinine

❖ Random screening

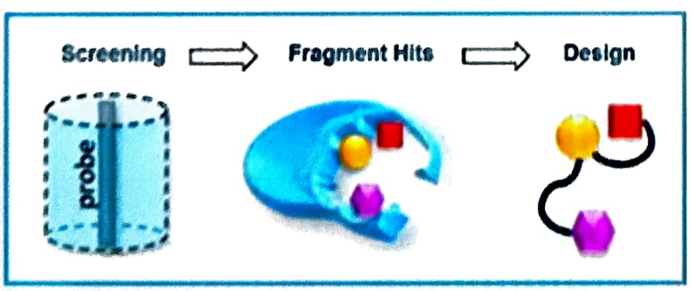
- Screening refers to the exercise to conducting a **biological assay on a large collection of compounds to identify those compounds** that have the desired activity.
- Initially, these compounds may **bind weakly to the target** and are known as the hits. **Hit can be considered as predecessor to leads.**
- It includes **screening of all new chemical** entities obtained from natural source or synthetic chemical libraries for multiple targets.
- This method requires huge cost and time, but **new structures with unexpected and unknown activity** can be explored.
- This type of screening is applicable when the receptor is unknown, and the availability of High Throughput Screening (HTS), **large ligand libraries could be screened.**
- **Examples** for drugs discovered through random screening - streptomycin, tetracycline.

➢ Fragment based screening:-

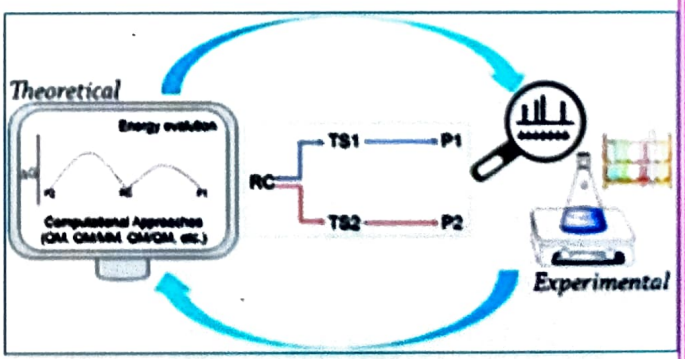
- To identify simple molecules (fragments) possessing typically modest **affinity for a target, with the intent of connecting two or more of these fragments** to create a useful lead compound. **EXAMPLE** (X-ray crystallography or NMR spectrometry)

➢ Computational approaches:-

- The structure of several known ligands, computational approaches may be **used to design potential lead compounds.**
- The screening of organisms **became very popular after the discovery of penicillin.**



Fragment based screening



Computational approaches

❖ Non- Random screening

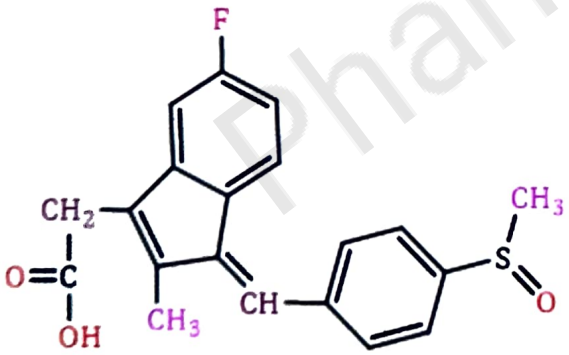
- This method of screening is also called targeted or **focused screening, is also called narrow approach or more focussed screening.** This type of screening is applicable to compounds **which are uncovered in random screening.**
- The molecules with structural similarity are screened for the selected target, **which increases the chance or development of successful drug-like molecules.**

❖ Discovery of drug through drug metabolism:-

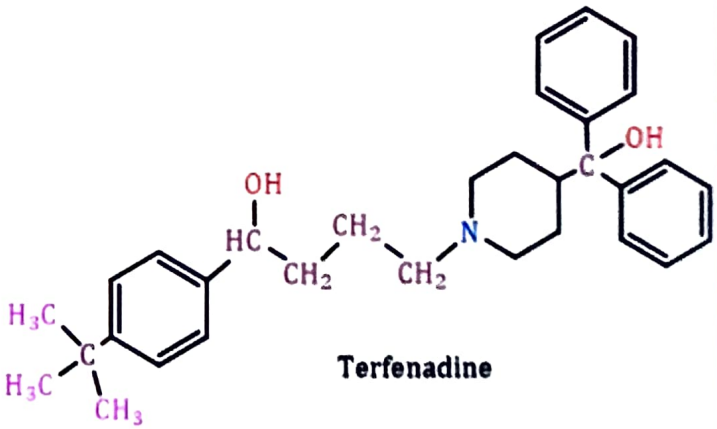
- During drug metabolism studies, metabolites (drug degradation products generated in vivo) **that are isolated are screened to determine** if the activity observed is derived from the drug candidate or from a metabolite.

➢ Examples:-

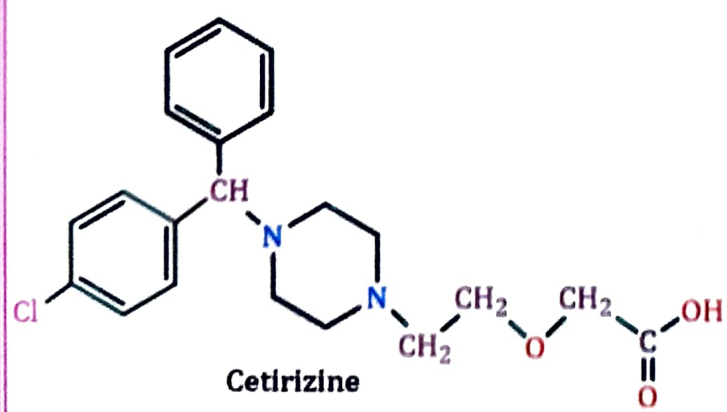
- **Sulindac sulfide** is the **active metabolite of Sulindac,** which exhibits **anti-inflammatory activity, Terfenadine** was found to be **cardiotoxic,** when its metabolism is inhibited by **certain antifungal drugs.**
- **Fexofenadine is the metabolite of terfenadine,** which is a safer drug, does not exhibit drug interactions



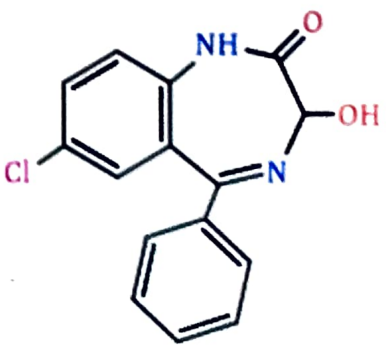
Sulindac



Terfenadine



Cetirizine



Oxazepam

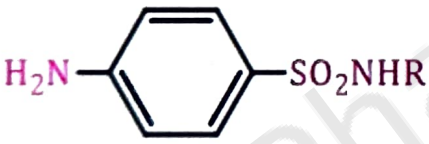
- Cetirizine is the metabolite of Hydroxyzine, **discovered from metabolic studies**
- Oxazepam is the metabolite of Diazepam, **discovered from metabolic studies.**

❖ Discovery of drug through clinical observation:-

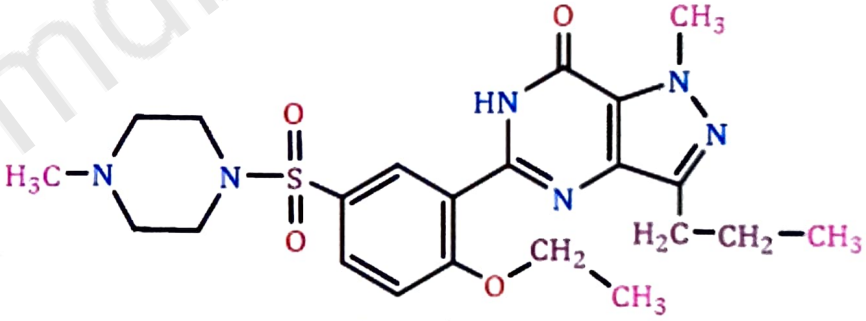
- Sometimes a drug candidate during clinical trials will exhibit **more than one pharmacological activity, that is, it may produce a side effect**. This compound, then, can be **used as a lead for the secondary activity.**

➢ Examples:-

- Sulpha drug **sulphathiazole used specifically for treating typhoid, lowered blood glucose drastically.** This led to the development of sulfonylureas as oral hypoglycaemic agents
- **Sildenafil designed as antianginal drug possess adverse effect as penile erection,** which led to relaunch the drug in treatment of erectile dysfunction, which was a blockbuster drug.

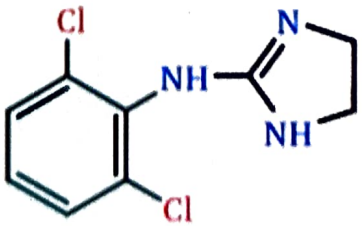


Sulfa drug



Sildenafil

- Clonidine was discovered as a **nasal decongestant, the adverse effect of it is sedation and lowering of blood pressure.** Further studies on it led to development this drug as a antihypertensive drug.



Clonidine

❑ ANALOG BASED DRUG DESIGN

- Analog design is defined as the modification of a drug molecule or of any bioactive compound in order to prepare a new molecule showing chemical or biological similarity with the original model compound.

❖ Objective of analog based drug design:-

- Analogue based drug design modifies the chemical structure of the lead compound having desirable pharmacological property with minimizing the adverse effects, and enhance the drug-likeness features such as physicochemical properties that could result in a better therapeutic agent.
- Analogues in pharmacological study design aims to understand the biological or pathophysiological phenomenon of disease.

❖ Bioisosterism:-

- **Isosteres are** defined as those compounds or functional groups of atoms that have same number and arrangement of electrons is called as Isosteres.
- **Bioisosteres are** the compounds or groups that possess nearly equal molecular shape, mass, volume, having approximately same electronic distribution, exhibit similar physical properties **such as** hydrophobicity, and having similar physical and chemical properties eliciting a similar pharmacological effect.
- **This term** coined by Harries L. Friedman and extended by Alfred Burger.

❖ Classification of bioisosteres:- There are two types of isosteres:

- Classical isosteres
- Non-classical isosteres

1. **Classical Bioisosteres:-** They have similarities of shape and electronic configuration of atoms, groups and molecules which they replace. Various examples are as follows:-

a) **Univalent or monovalent atoms:-**

F,H OH, NH F, OH, NH or CH_3 for H SH, OH Cl, Br, CF_3

b) Bivalent or Divalent atoms and groups

—CH=S— —CH=O— —CH=NH C=CH—

$-CH_2-$ —NH— —O— —S—

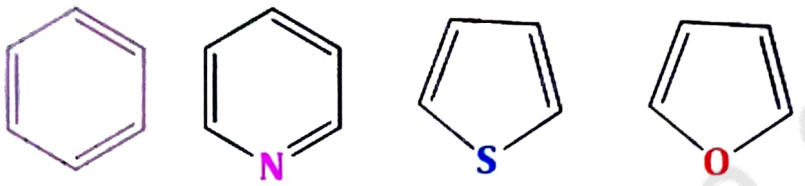
c) Trivalent atoms and groups

—CH= —N= —P= —As=

d) Tetravalent atoms and group

$=N^{+}=$ =C= $=P^{+}=$ $=As^{+}=$

e) Ring equivalents



2. Non-classical Bioisosteres:- They **do not obey the stearic and electronic definition** of classical isosteres.

- Non-classical bioisosteres are **functional groups with dissimilar valence electronic configuration.**

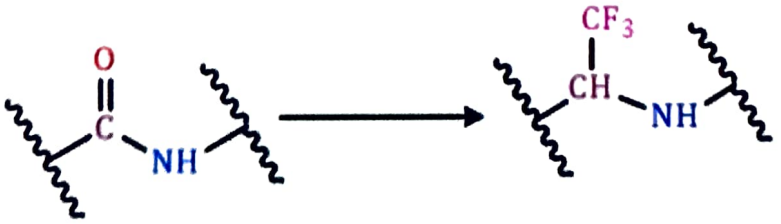
a) Carboxyl (COOH) bioisosteres

$—SO_2NH_2$ —CONHOH $—SO_2OH$ —CONHCN

b) Hydroxyl (OH) bioisosteres

$—CH_2OH$ $—NHCONH_2$ $—NHSO_2CH_3$ —NHCN

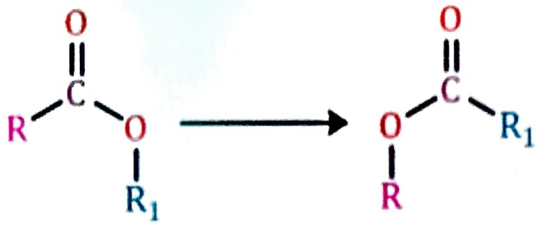
c) Amide ($CONH_2$) bioisosteres



d) Halogen isosterism

Cl CN CF_3

e) **Retroisosterism**

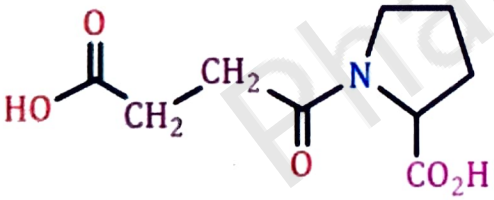


❖ Bioisosteric replacement strategies

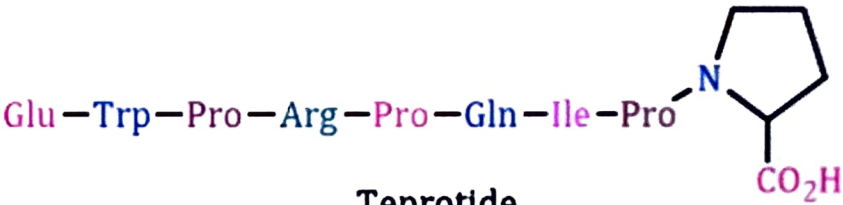
- Isosteric modification involves **the replacement of an atom, or group of atoms, in a molecule** by another group with similar electronic and steric configuration.
- Two molecules or molecular fragments **containing an identical number and arrangement of electrons** should have similar properties are termed as isosteres, **e.g. CO, N_2, CO_2, N_2O, CH_2N_2, CH_2=CO and CH_4.**

➢ CASE STUDY I:- The design of captopril

- The design of ACE inhibitors demonstrates how it is **possible to design drugs for a protein** target in a rational manner, even if the **structure of the target has not been determined.**
- First of all, it was assumed that the **active site contained the zinc ion and arginine group.** Succinyl proline was chosen, since proline is present on the terminus of teprotide (a known inhibitor of ACE).

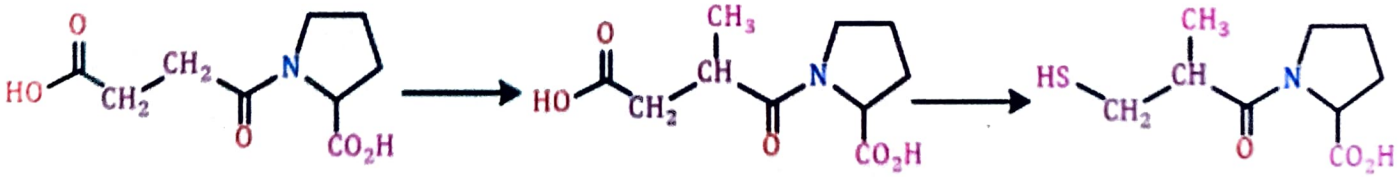


Succinyl proline



Teprotide

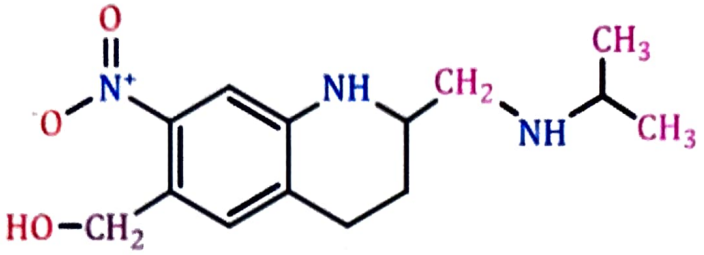
- The next step was to introduce a better group the **carboxylate ion to interact with zinc, and it was discovered that a thiol group led to increased activity.** This resulted in captopril, which was the first non-peptide ACE inhibitor to become commercially available



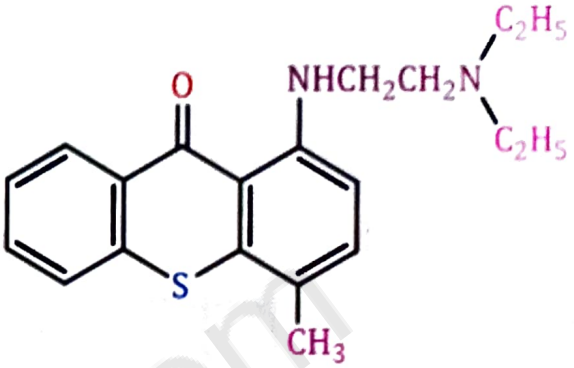
Development of captopril

➢ CASE STUDY II:- The design of Oxamniquine

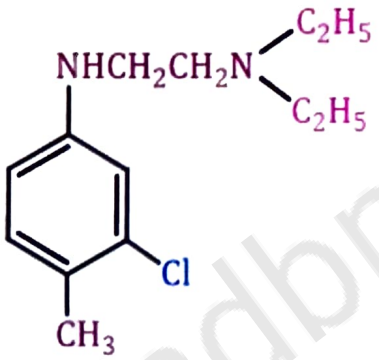
- The first stage in the **development of oxamniquine was to find a lead compound,** and so a study was made of compounds that were against the parasite. The tricyclic structure lucanthone was chosen.
- It was **decided to simplify the structure** to see whether the tricyclic system was really necessary. This gave **a compound called mirasan.**



oxamniquine

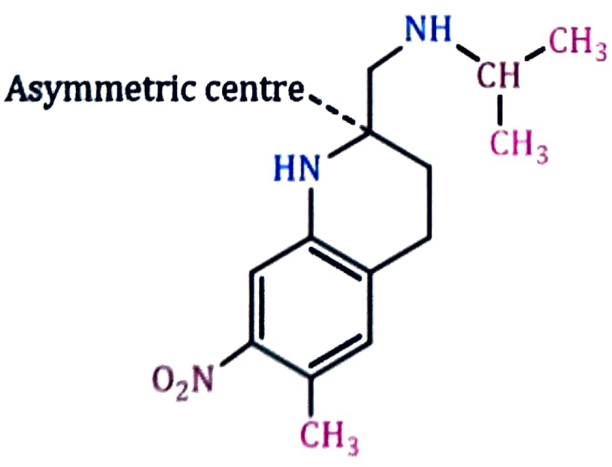


Lucanthone

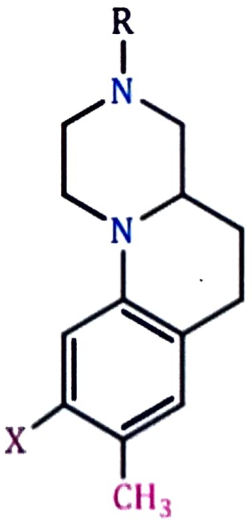


Mirasan

- The optimum structure based on these results was structure (1). It has one asymmetric center and, as one might expect, **the activity was must greater in one enantiomer than it was in the other.**



1



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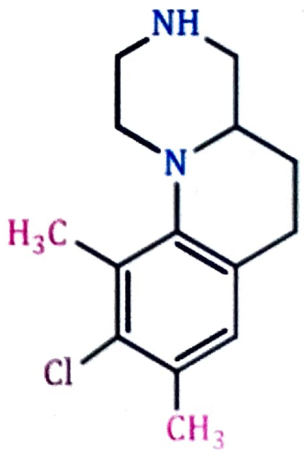


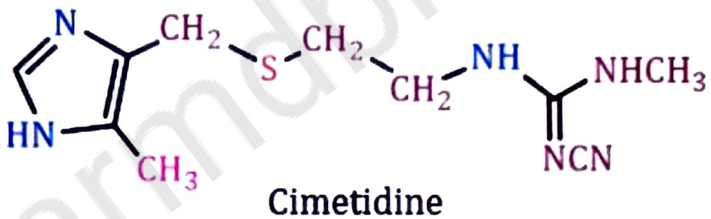
3

The optimum structure (1) and the tricyclic structure (2) and (3)

- The tricyclic structures (2) was also constructed. However, some conflicting **results were obtained compared with the previous results for structures (1).**
- Adding a further methyl group to the aromatic ring to give structure (3) with **increased activity. The resulting increase in activity suggests that a better fitting conformation is obtained for the binding site.**
- Compound (3) was **three times more active** than structure (1). However, structure (1) was chosen rather than 3 based on preliminary toxicity results, as well as the fact that it was cheaper to synthesize.
- The methyl group on (1) was **replaced by a hydroxyl methylene group to give oxamniquine.** The drug was put on the market in 1975.

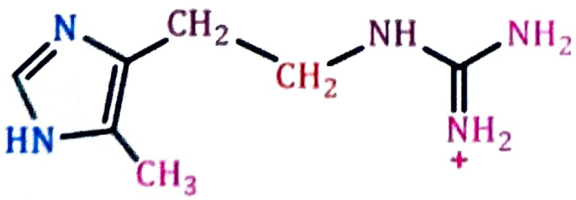
➢ CASE STUDY III: Design of cimetidine

- Cimetidine was **developed by utilizing various lead modification methods** to uncover the first Histamine H, receptor antagonist and an entirely new class drugs.

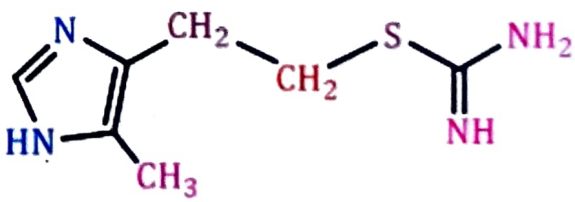


Cimetidine

- The first lead compound, **N-alpha guanylhistamine was very weakly active** as an inhibitor of histamine stimulation. Later it was found to be **a partial agonist, not an antagonist.** A more potent isosteres, isothiourea was synthesized.

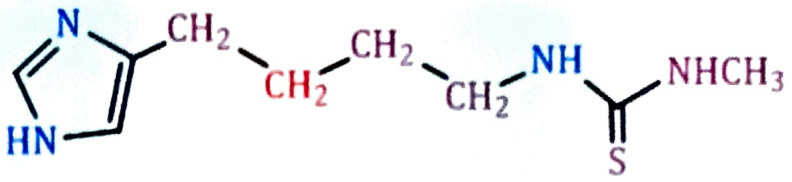


N-alpha guany lhistamine



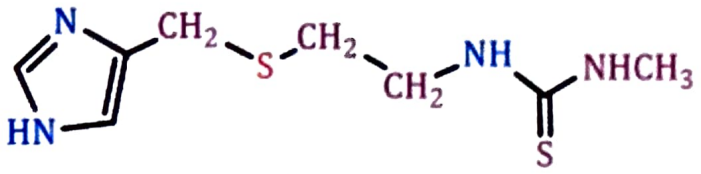
Isothiourea isostere

- A purely competitive antagonist was given by homologation of the side chain. No agonist effects were observed. When **methylation and further homologation on the thiourea nitrogen were carried out; the n-methyl analog called burimamide.**



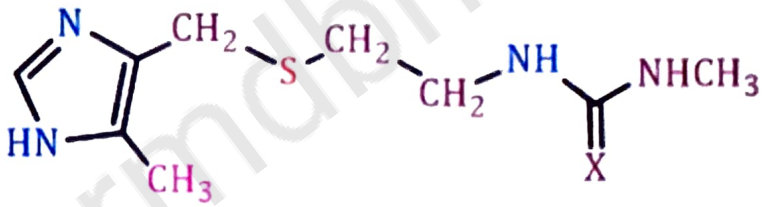
Burimamide

- Thiaburimamide was **developed which is about three times more potent** as a histamine H_2 receptor antagonist in vitro than burimamide.



Thiaburimamide

- cyanoguanidine (X-N-CN; cimetidine, Tagamet) and nitroguanidine (X=N-NO,) were synthesized. They both **were potent H, receptor antagonists, comparable in potency to metiamide,** but without granulocytopenia (cimetidine was slightly more potent than, X=NO).



✓ **Urea (X=O), guanidine (X=NH), cyanoguanidine (X-N-CN; cimetidine) and nitroguanidine (X=N-NO) analogs**

- Cimetidine was **first marketed in the United Kingdom in1976;** therefore, it took **12 years from initiation of the H, receptor antagonist program to commercialization.**
- After the introduction of cimetidine to the US drug market, **three other H_2 receptor antagonists were approved, ranitidine (Zantac, Glaxo Laboratories), which rapidly became the largest selling drug worldwide, famotidine and Nizatidine.**