ROLE OF NATURAL PRODUCTS IN DRUG DISCOVERY AND DEVELOPMENT

Dr. Sama Venkatesh

M. Pharm, PhD, PG Dip IPR

G. Pulla Reddy College of Pharmacy,

Mehdipatanam, Hyderabad- 500 028

E Mail: venkateshsama@rediffmail.com

India is rich heritage of Medicinal plants particularly with the great Himalayas and Western ghats of Nilgiris Land mark of Ayurveda

Nature: **A primitive state of existence, untouched and uninfluenced by civilization or artificiality.**

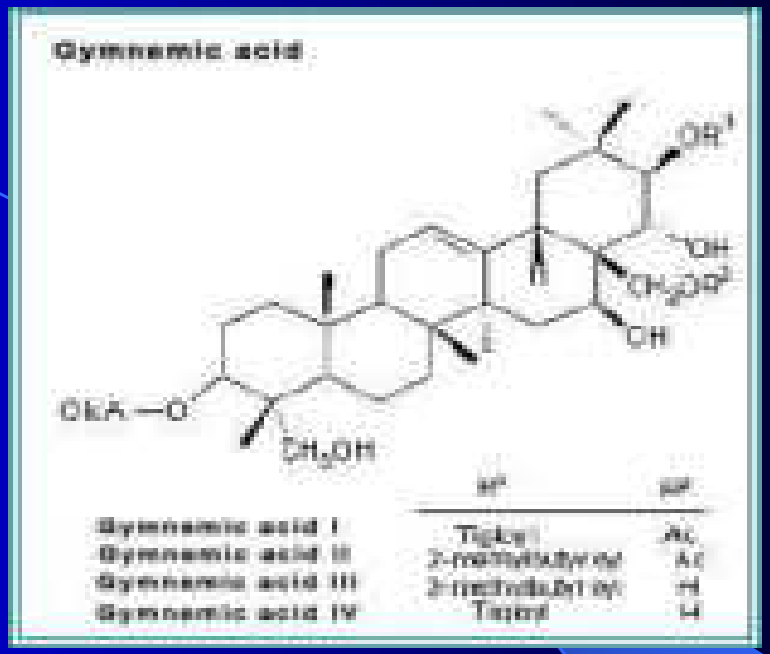
Natural product: A chemical substance produced by a living organism. A term used commonly in reference to chemical substances found in nature that have distinctive pharmacological effects.

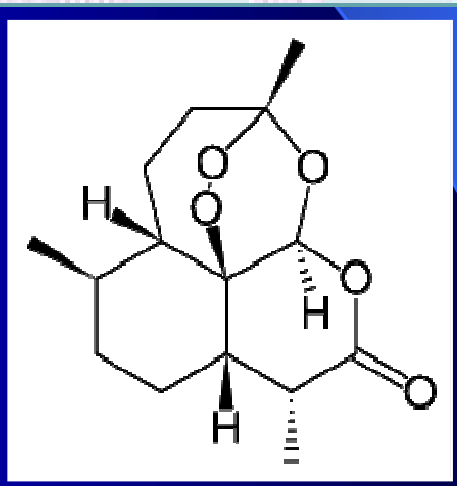
Drug: A chemical substance that affects the processes of the mind or body

Discovery: Exposure to view. Finding out or ascertaining something previously unknown or unrecognized

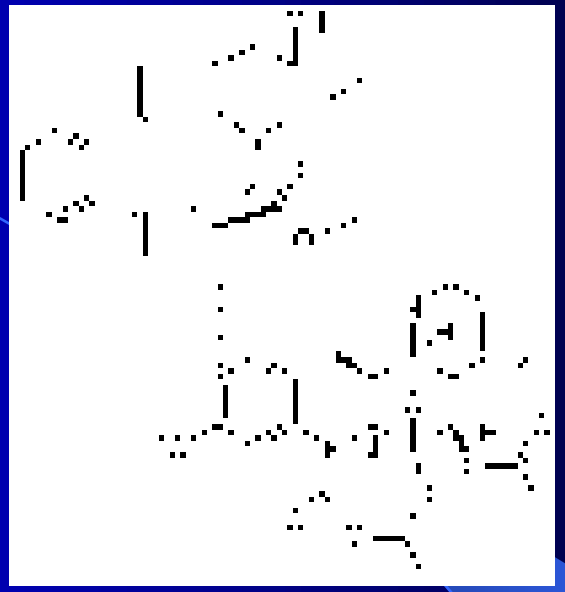
Facts about the Natural products

- Natural products serve as a major source of **new drug Leads** – 520 new drugs (1983 - 1994) – 39 % were natural products.
- Half of the **20 top selling drugs** in 1999 – lead molecules of natural sources.
- New discoveries of potent anti-cancer, anti-malarial, anti-diabetics in plants(eg.- Taxol, Artemesinin, Camptothecin) rekindled interest in Natural products and Traditional Medicines.
- Natural products bear evidence to the value of **modern economy**
- **Chemical complexity** of natural products serve as an advantage for the discovery of candidate products and their derivatives.



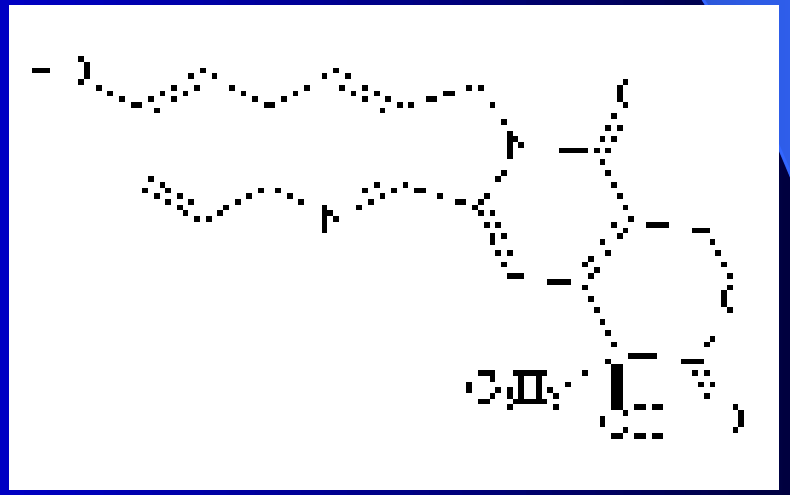


ARTEMISININ



VINCRISTINE

CAMPTOTHECIN



TRADITIONAL SYSTEMS OF MEDICINE(TSM): Ayurveda, Siddha, Unani & Homoeopathy

- Play a crucial role in health care and the only affordable treatment for people in the developing countries.
- Practicing and existing from ancient days and found to be proven in preserving the health of human beings.
- Less side effects.
- Long history of safety.
- Available in remote communities.
- 80% of world population depends on TSM for Primary Health Care.
- No. of medicinal plants being used world wide – 52,885

Past scenario:

- **19th century**- All medicines are derived from Natural sources only.
- Knowledge of pharmaceuticals and medicines are documented in **Materia Medica.**
- **Pharmacology:** The action of drug.
- **Pharmacognosy**: All aspects of drugs with less emphasis on action.
- 1970-1980: Investigation of Natural products as sources of novel human therapeutics reached its peak in the **western Pharmaceutical industry.**
- **Medicinal chemistry was in dormant stage**.
- Late 19th century- Complex organic compounds are synthesized , some of which are having therapeutic activity

Decreased Emphasis

- Introduction of **High throughput screening**
- Move from natural product extract libraries towards "**Screening friendly**"synthetic chemical libraries.
- **Combinatorial chemistry**- Drug like screening libraries of wide chemical diversity
- Advances in **molecular biology, cellular biology** and **genomic leads** increased molecular targets and decreased drug discovery timelines.

Today drug discovery environment calls for rapid screening, hit identification and hit-to-lead development.

Extract screening, bioassay guided isolation, structure elucidation are age old and time consuming

Drug Discovery

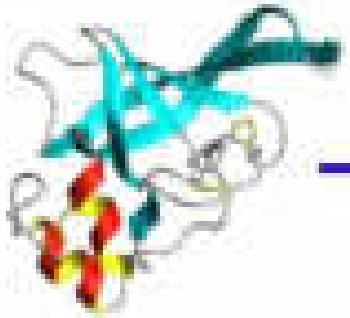
- Identification of a disease and therapeutic target of interest.
- Methodology and assay development.
- Lead identification and characterization in vitro.
- Formulation, animal pharmacology studies.
- Pharmacokinetic and safety studies in animals
- Phase I and Phase II clinical studies in humans
- Advances made in several disciplines of science and technology, pharmacy and medicine, computer engineering etc., during the past decade has speeded up and economized new drug discovery process.

- Drug discovery and development is a **risky, expensive** and protracted process and is the first in the pre-clinical phase of drug development.
- Once potential drug entity is identified, discovered or designed and synthesized, it undergoes extensive testing in the laboratory and in animals to assess its biological activity and safety
- The cost of drug discovery and drug development is increased all the time, but there is a decrease in the number of new medicine introduced to the world market.
- Efforts in synthetic chemistry- High throughput chemistry, combinatorial chemistry- Not satisfactory.
- **Lack of new synthetic moieties**.
- Scientists are in search of new molecules, new complexes and lead molecules.

Drug Discovery & Development Process

Discovery

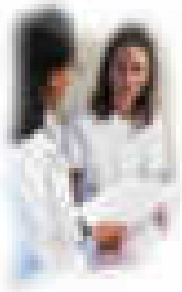
Disease



Identify a protein involved in disease (target)

Find a molecule effective against the target

Preclinical testing



Human clinical trials

Approval by regulatory authorities

Drug on the market

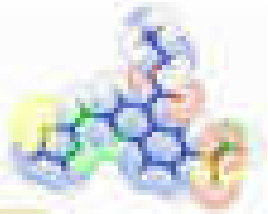
Development

The whole process takes 10 – 15 years and costs ~1 billion USD !

Cheminformatics in the Drug Discovery

Target identification

Lead finding



Lead optimization

Chemical Genomics

Bioinformatics

Genomics
Proteomics
Systems biology
Pathway analysis

Cheminformatics

Molecular databases
Combinatorial chemistry
HTS screening support
Data mining
Virtual screening
Property Calculation

QSAR
In silico ADME
Toxicity alerting
Bioisosteric design

Marketed drugs identified by CADD/Rational drug design

- **Captopril (Capoten®, Bristol Myers-Squibb) :** angiotensin-converting enzyme (ACE) inhibitor.
- **Dorzolamide (Trusopt®, Merck):** carbonic anhydrase inhibitor
- **Saquinavir (Invirase®, Hoffmann-La Roche):** HIV-1 Protease inhibitor
- **Zanamivir (Relenza®, Gilead Sciences):** Neuraminidase (NA)
- **Aliskiren (Tekturna®, Novartis):** Renin inhibitor
- **Boceprevir (Schering-Plough):** NS3-NS4A serine protease in Hepatitis C virus (HCV) inhibitor.
- **LY-517717 (Lilly/Protherics):** factor Xa serine protease inhibitor, an important target in the blood coagulation cascade.
- **NVP-AUY922 (Novartis):** HSP90 inhibitor

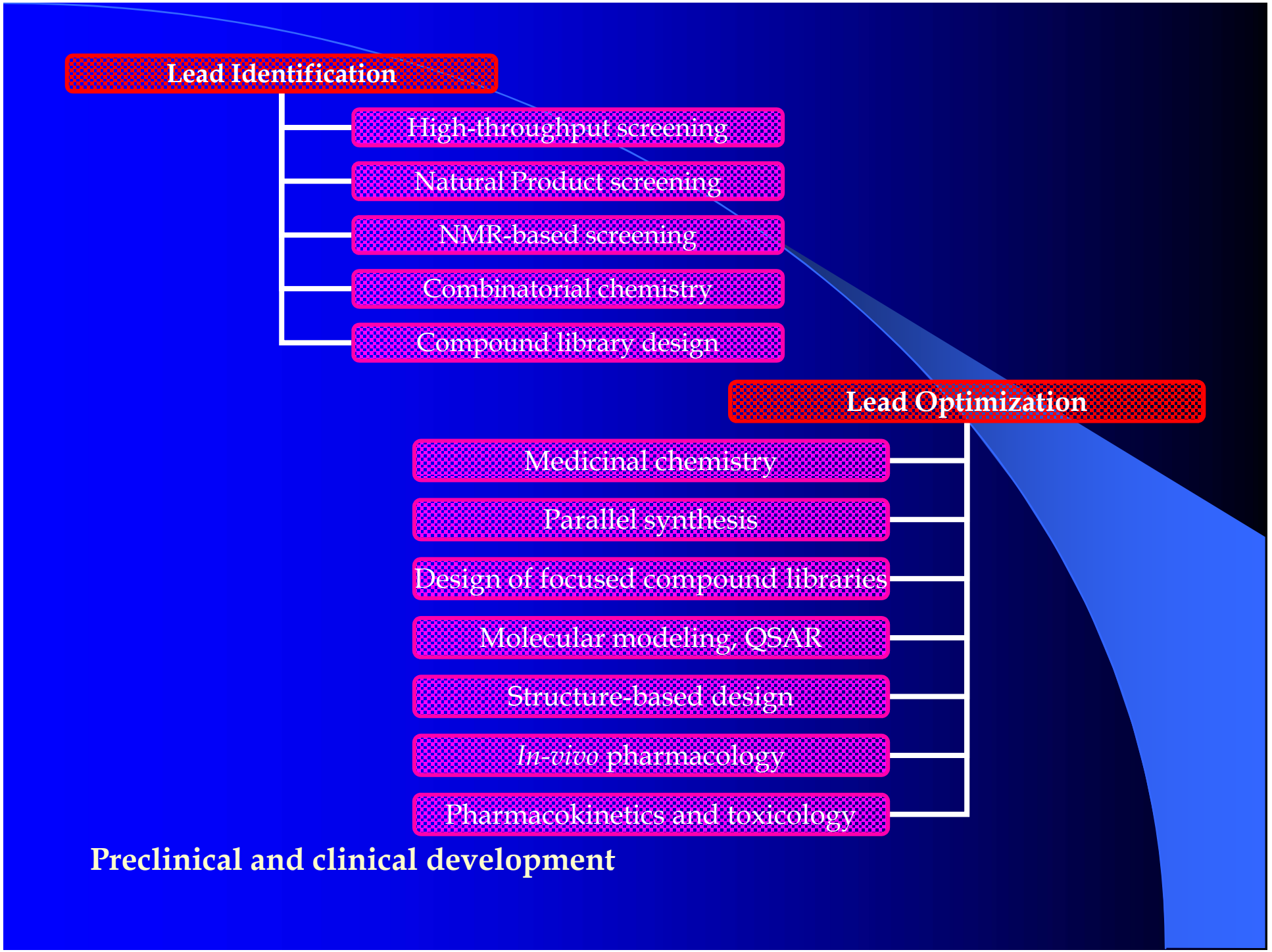
- Development of new medicines is complex, time consuming and very expensive.

– Success rate in getting from an initial compound to an approved and commercially available product is very low.

– < 2% of new compounds investigated may show suitable biological activity

– Modification of an existing drug can yield as little as 1% suitable Compounds

– < 10% of these compounds result in successful human clinical trials and reaches the market place


Lead Identification
High-throughput screening
Natural Product screening
NMR-based screening
Combinatorial chemistry
Compound library design
Lead Optimization
Medicinal chemistry
Parallel synthesis
Design of focused compound libraries
Molecular modeling, QSAR
Structure-based design
In-vivo pharmacology
Pharmacokinetics and toxicology
Preclinical and clinical development

Natural Products

- Structural diversity provided by natural product.
- Natural products have drug like properties- They can be absorbed and they are easily metabolized.
- Bioactive natural products occurs along with number of homologies and give structure activity information.
- Natural products typically have a greater number of chiral centers and increased steric complexity than either synthetic drugs or combinatorial libraries
- Lead compounds found from screening of natural products can be optimized by traditional medicinal chemistry or by application of combinatorial approaches.
- Number of MNC world wide rein back to natural products research in search of new medicines for suffering human kind.

The isolation of many bioactive products from natural sources has led to the systematic screening of plant and animal extracts for activity.

- About 25 percent of modern prescription drugs contain compounds derived from higher plants.
- 80% of the world's population uses drugs exclusively from natural sources.
- 35% of drugs contain 'principles' (key structure elements) of natural origin.
- It has been estimated that of 122 drug of plant- derived natural products used worldwide from a total of 94 species.
- 72% can be traced to the original ethnobotanical uses that have been documented for their plant of origin.

Approaches to the choice of plants and other organisms

- Random screening
- Selection of specific taxonomic groups, such as families or genera
- A chemotaxonomic approach in which restricted classes of secondary metabolites, such as alkaloids etc
- An information-managed approach, which involves the target collection of species selected by database surveillance, and
- Selection by an ethnomedical approach (e.g., by investigating remedies used in traditional medicine by 'shamans' or medicine men or women).

Value of Natural drug products

- Natural products provide a number of extremely useful drugs that are difficult, if not impossible, to produce commercially by synthetic means

  Ex: Opium alkaloids, Ergot alkaloids, Cardio tonics

- Natural sources supply basic compounds that may be modified slightly to render them more effective or less toxic.

  Ex: Morphine molecule.

- The third role of natural products is their utility as prototypes or models for synthetic drugs possessing physiologic activities similar to the originals.

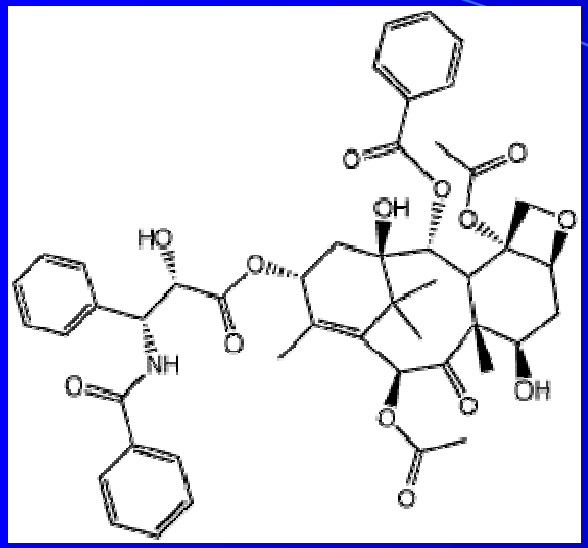
  ex: Procaine and similar local anesthetics.

- Some natural compounds that demonstrate little or no activity themselves but which can be modified by chemical or biological methods to produce potent drugs not easily obtained by other methods.

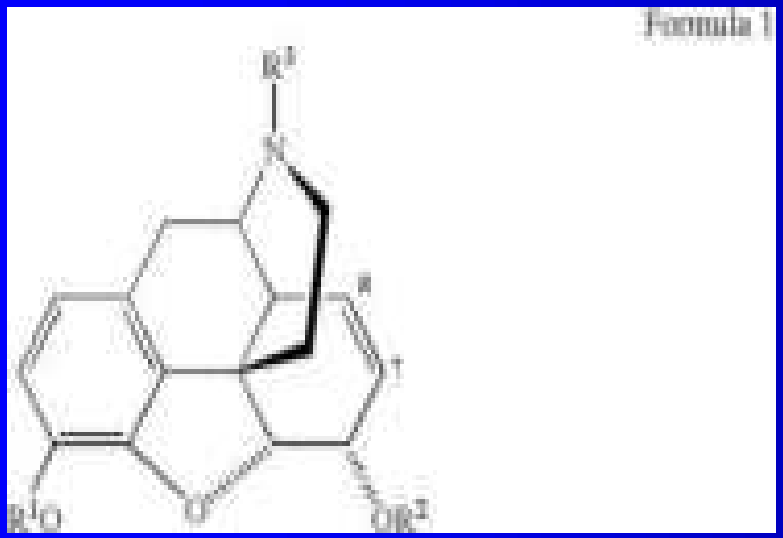
Ex. Taxol synthesized from Baccatin III.; Cartciosteroids from Stigmosterol

Examples of Natural products

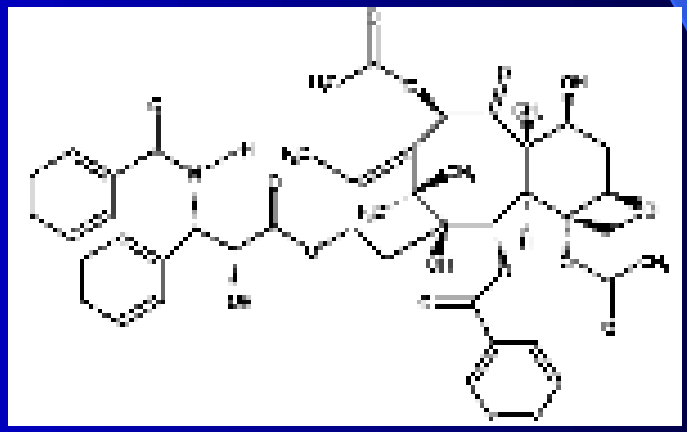
SOURCES	CHEMICAL COMPOUND	ACTIVITY
Plant kingdom	(i)Paclitaxel (ii)Artemisinin	Anticancer agent Antimalarial agent
Microbial world	(i)Lovastatin (ii)Ciclosporin	Hypolipidemic agent Immuno suppresent
Marine world	Bryostatin, Curacin A, eleutherobin	Antitumour agent
Animal sources	Epibatidine (Ecuadorian poison frog)	Analgesic
Venoms and toxins	Teprotide (Brazilian viper)	Antihypertensive agent



TAXOL

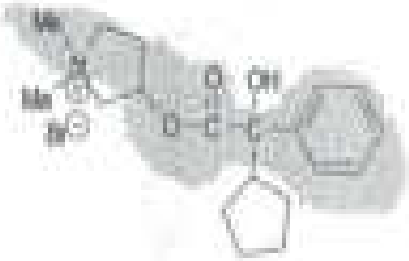
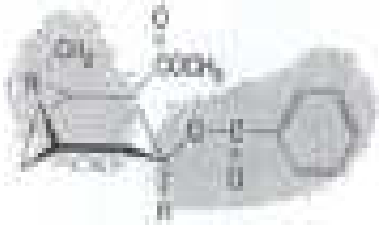
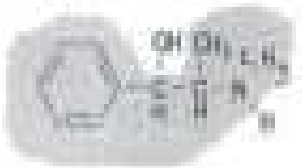
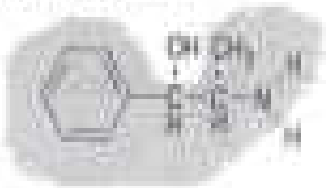


MORPHINE

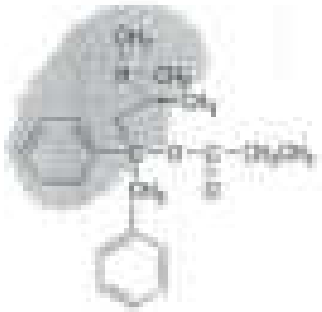
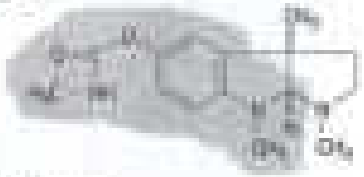
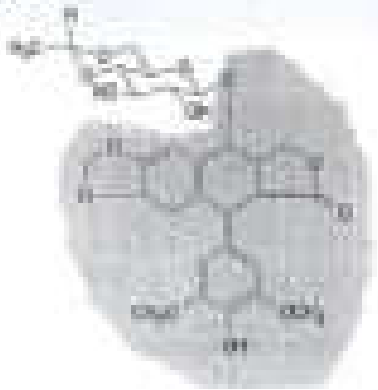


PACLITAXEL

Examples of Plant Drugs Serving as Prototypes or Models for Other Medicinals

Natural (Activity)	Closely Related Semisynthetic	Prototype-Derived Synthetic
Atropine (Anticholinergic) 	Homatropine 	Glycopyrrolate 
Cocaine (local anesthetic) 		Procaine 
Ephedrine (adrenomimetic) 	Phenylpropanolamine 	Tetrahydrozoline 

Examples of Plant Drugs Serving as Prototypes or Models for Other Medicines—(Continued)

Natural (Activity)	Closely Related Semisynthetic	Prototype-Derived Synthetic
Morphine (narcotic analgesic) 	Hydromorphone 	Propoxyphene 
Physostigmine (cholinergic) 	—	Neostigmine 
Podophyllotoxin (antineoplastic) 	Etoposide 	—

How new medicines are discovered

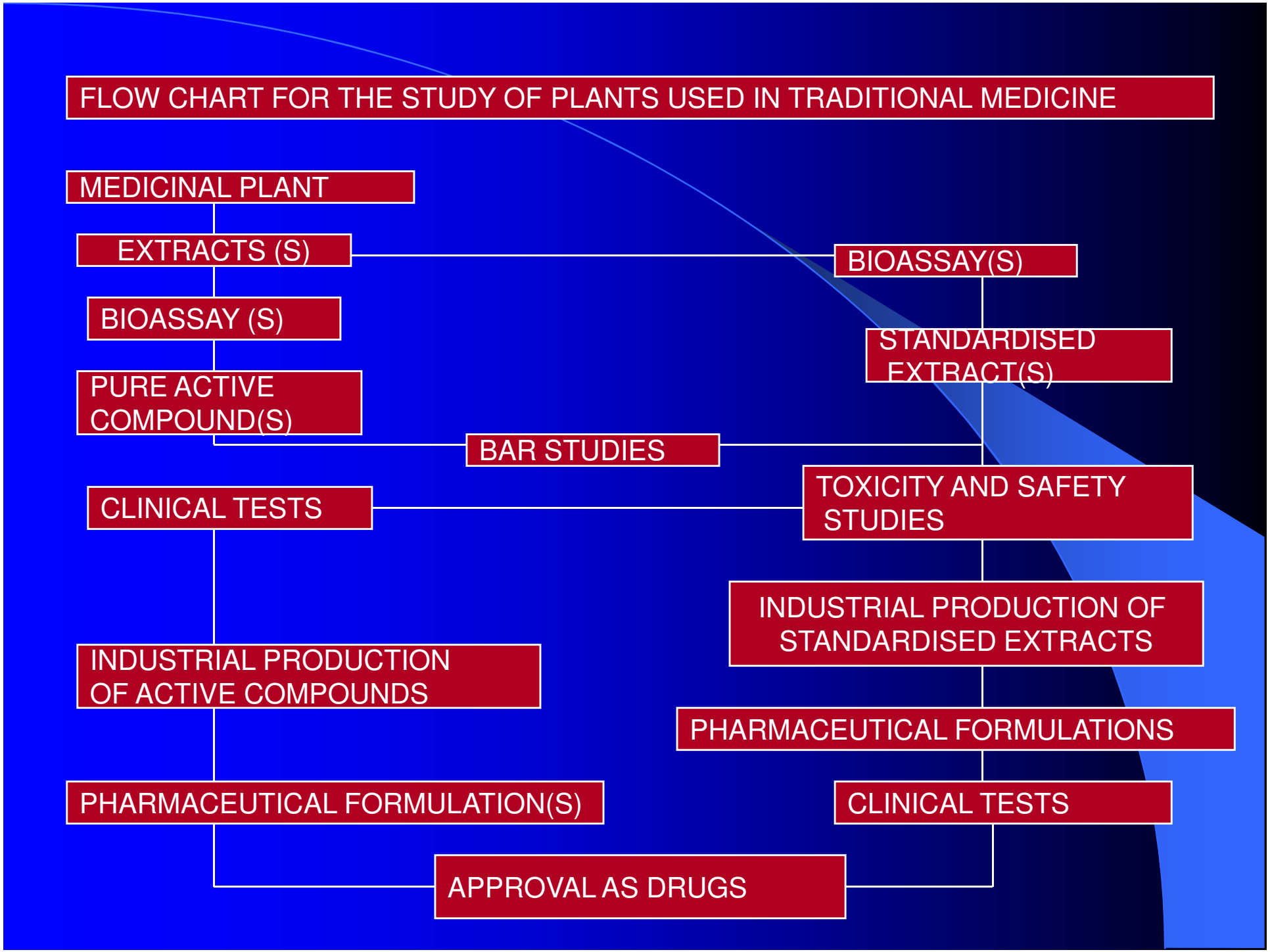
- Traditional approach- Trial and error

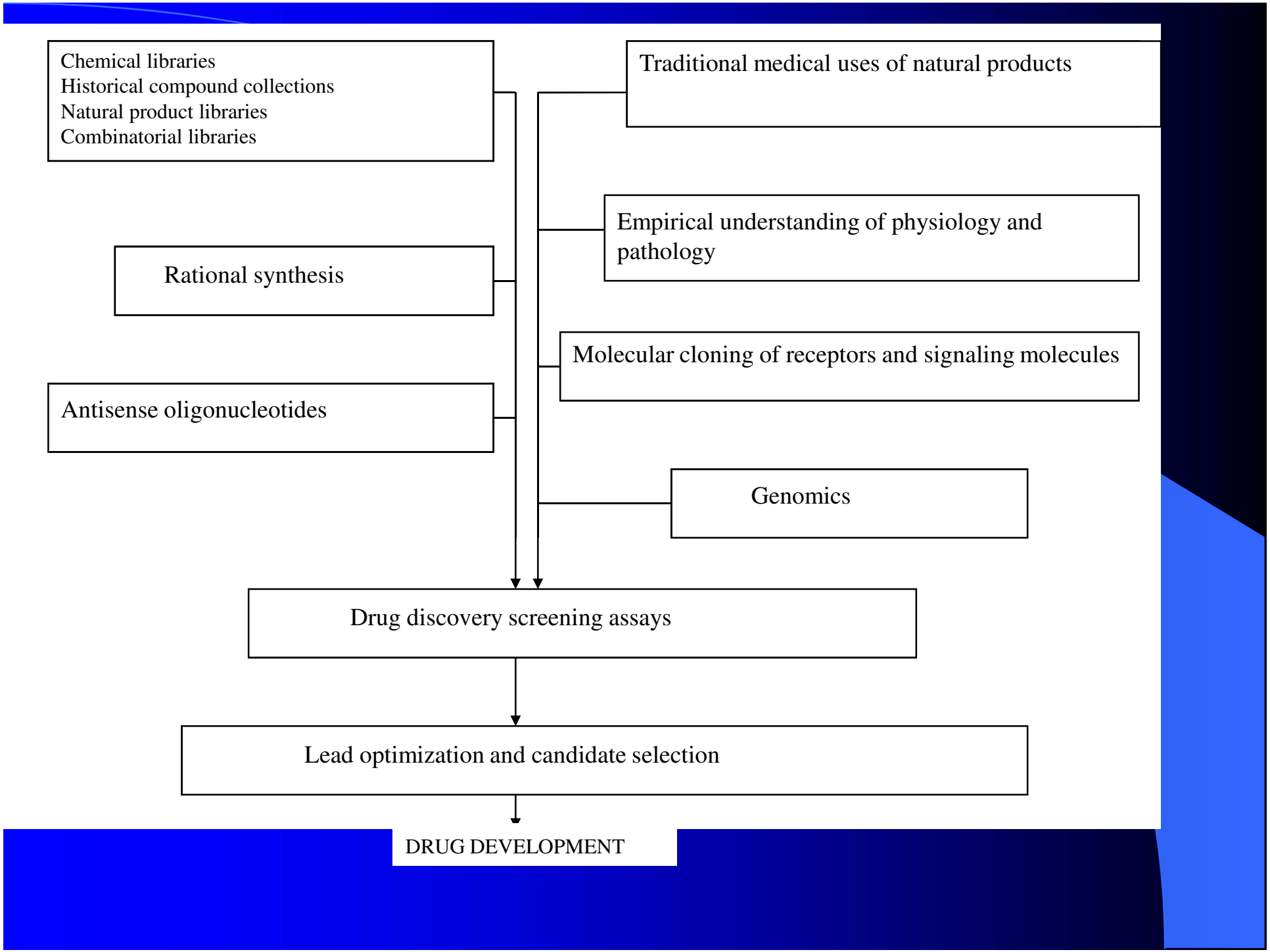
Morphine, quinine and ephedrine

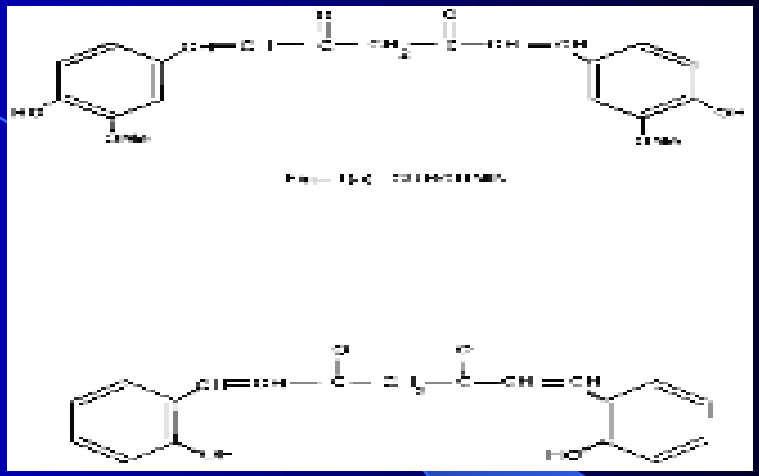
- Empirical approach- Understanding the relevant physiological process and often develops a therapeutic agent from natural lead.

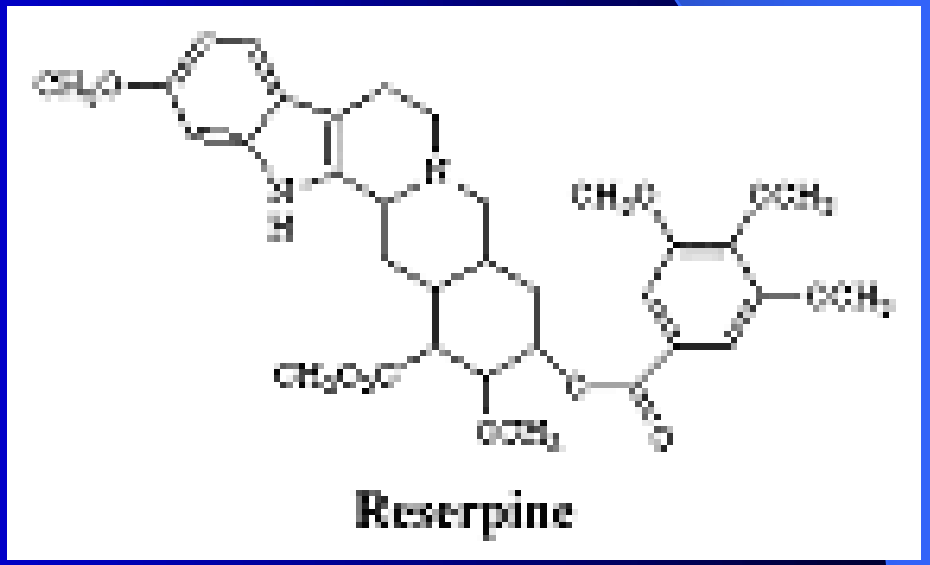
Eg: Tubocurarine, propranolol, Cimetidine and the histamine H_2 receptor antagonists.

- Molecular approach: Understanding of a molecular targets for the medicinal agent. Major drug discovery is based on the molecular approach.
- Rational drug design using computer aided techniques.
- Antisense approach- Manipulation of targets.
- Pragmatic approach for random screening(Currently dominate drug discovery activity)


FLOW CHART FOR THE STUDY OF PLANTS USED IN TRADITIONAL MEDICINE
MEDICINAL PLANT
EXTRACTS (S)
BIOASSAY (S)
PURE ACTIVE COMPOUND(S)
CLINICAL TESTS
INDUSTRIAL PRODUCTION OF ACTIVE COMPOUNDS
PHARMACEUTICAL FORMULATION(S)
APPROVAL AS DRUGS
BAR STUDIES
BIOASSAY(S)
STANDARDISED EXTRACT(S)
TOXICITY AND SAFETY STUDIES
INDUSTRIAL PRODUCTION OF STANDARDISED EXTRACTS
PHARMACEUTICAL FORMULATIONS
CLINICAL TESTS


Chemical libraries
Historical compound collections
Natural product libraries
Combinatorial libraries
Traditional medical uses of natural products
Empirical understanding of physiology and pathology
Rational synthesis
Molecular cloning of receptors and signaling molecules
Antisense oligonucleotides
Genomics
Drug discovery screening assays
Lead optimization and candidate selection
DRUG DEVELOPMENT




Reserpine

LEAD OPTIMIZATION

What is Lead

- Shows the way to destination by preceding or accompanying them.
- Optimization – make the best or most effective use of recourses.
- Lead is more than a compound active in the primary screening.
- Lead is starting point either it may be pharmacologically or biochemically inspired.
- Lead selection do not vary significantly from one therapeutic area to another.
- Selection of wrong lead compound can lead to months and sometimes years of fruit less effort.
- Selection of lead is the maturity of the therapeutic area and criteria established for clinical candidate selection
- Time frame from chemist discovery programme to first clinical studies could be minimum 5 years

LEAD COMPOUND

A *lead compound* is:

– "a compound from a series of related compounds that has some of a desired biological activity. This molecule can be characterised, and modified to produce another molecule with a better profile of wanted properties to unwanted side effects"

A *lead compound* is a first foothold on the drug discovery ladder.

It takes much more effort to make a *lead compound into a drug candidate*

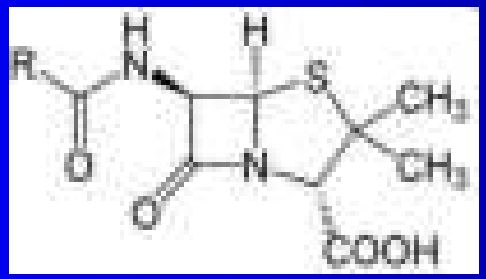
PROPERTIES OF LEAD COMPOUND

- A lead compound possesses the desired biological activity, but is typically un-optimized.
- An ideal lead should be easily synthesized.
- It should be of low molecular weight and have a partition coefficient (logP) to afford reasonable bioavailability.
- It should also have structural features that can be modified to alter its physical properties to adjust ADME parameters such as solubility.
- The closer a lead compound is to the ideal properties of the final drug, the better the lead is.
- A drug compound is just a lead that has been optimized sufficiently to be used for its intended purpose…to treat a disease in the human or animal that has it.

IDENTIFICATION OF LEAD COMPOUNDS

Lead compounds may be identified by chance:

e.g. Penicillin (antibiotic) – discovered by Fleming (and others).

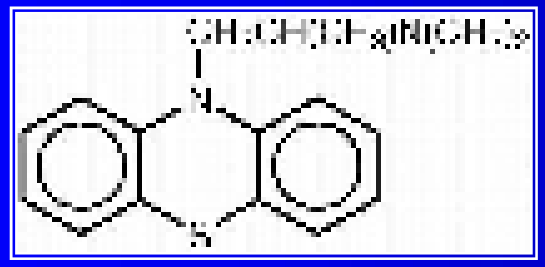


Pencillin-antibiotic

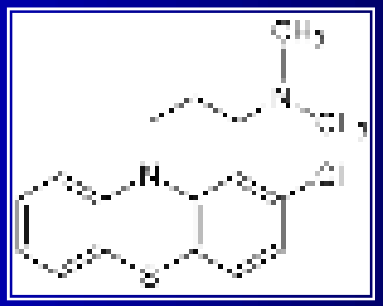
Some drugs in the clinic have been found to have side effects. Structures can be modified to reduce the primary indication and optimize side effects.

e.g., Chlorpromazine (antipsychotic-tranquilizers).

Phenothiazines were being developed as antihistamines, but the French navy surgeon Laborit noticed the relaxed nature of patients about to undergo the knife.



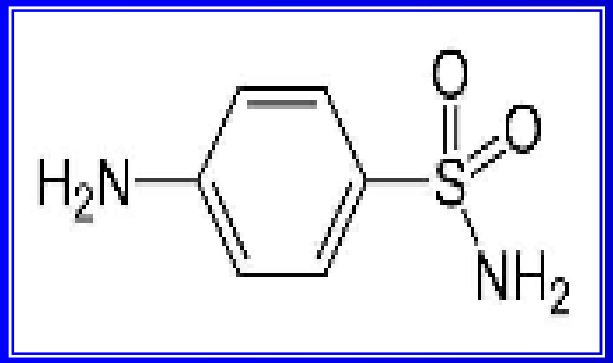
Promethazine



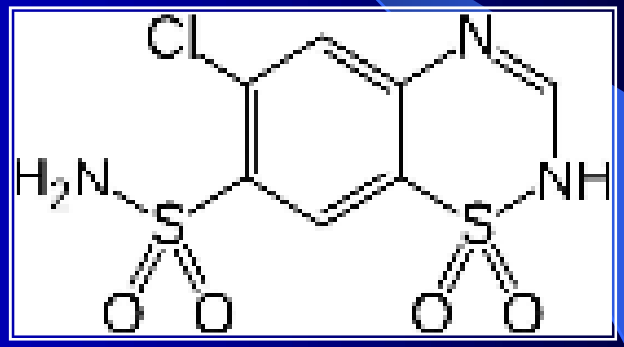
Chlorpromazine

Chlorothiazide (diuretic):

Sulphanilamide, the active metabolite of an early class of antibiotics had diuretic side effects.

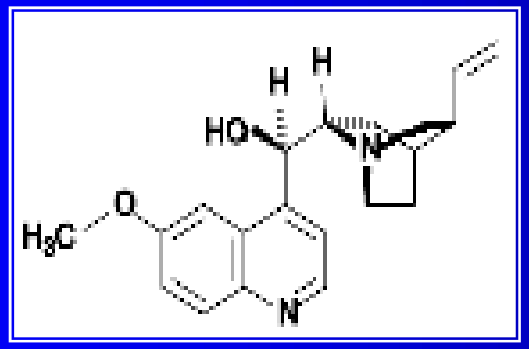


Sulphnilamide



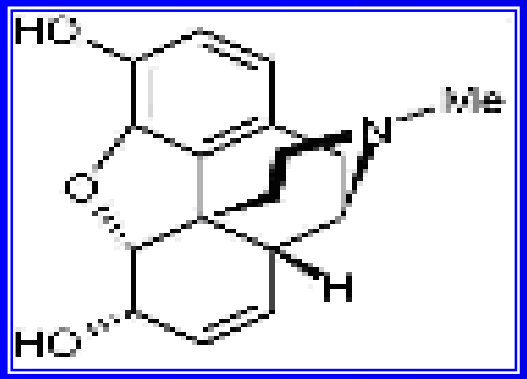
Chlorthiazide

Lead compounds have been identified by isolation of active ingredients of folklore / traditional remedies, e.g.:

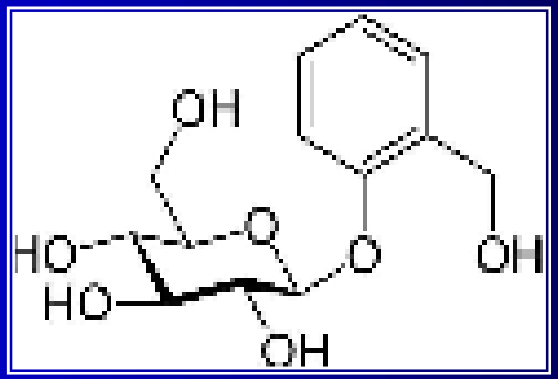


Quinine
Cinchona bark- anti-malarial

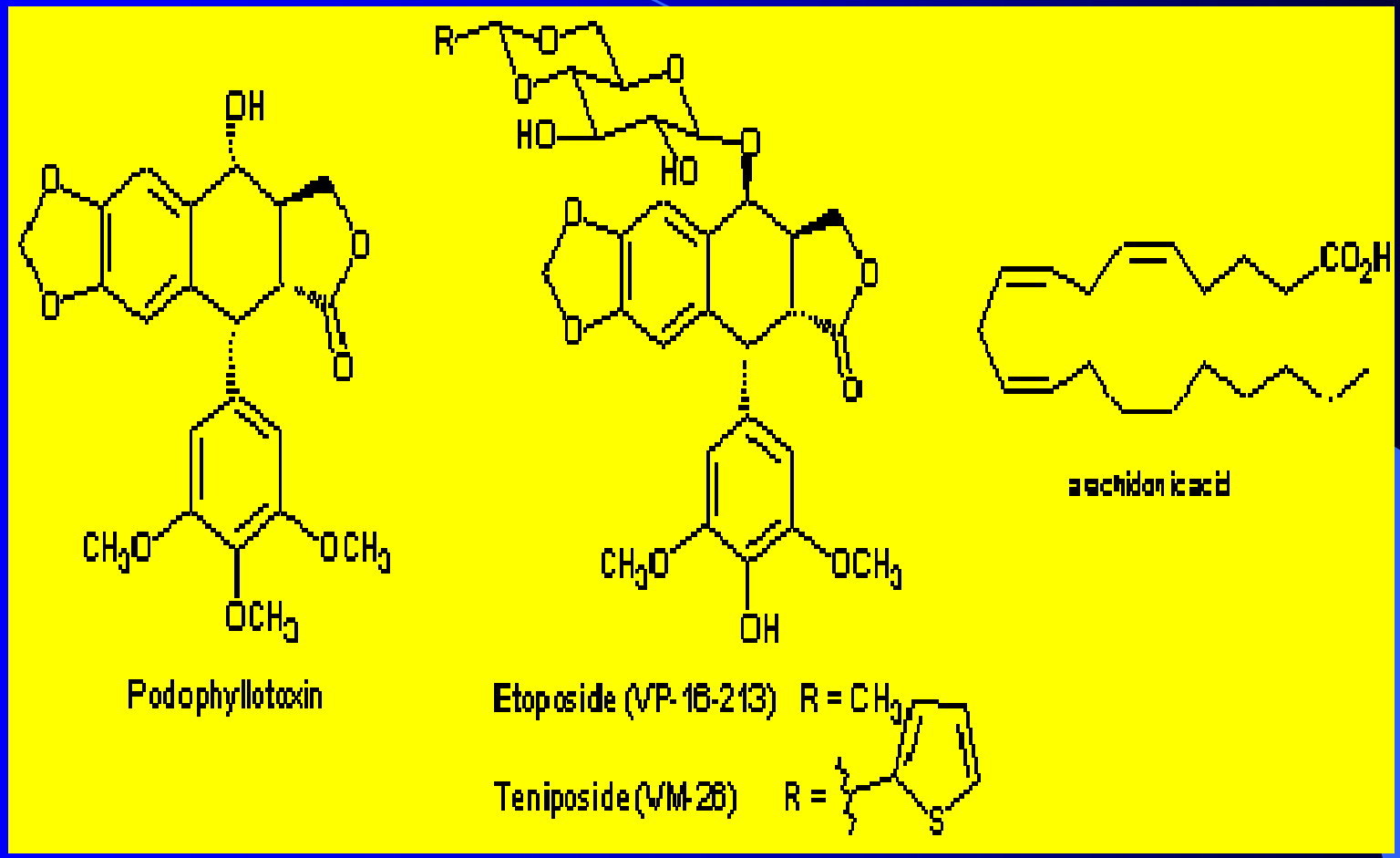
Colchicin
Crocus- gout



Morphine
Poppy- Analgesic



Salicin
Willow bark-Analgesic & antipyretic


OH
O
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CH3O
OCH3
OCH3
Podophyllotoxin
R
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HO
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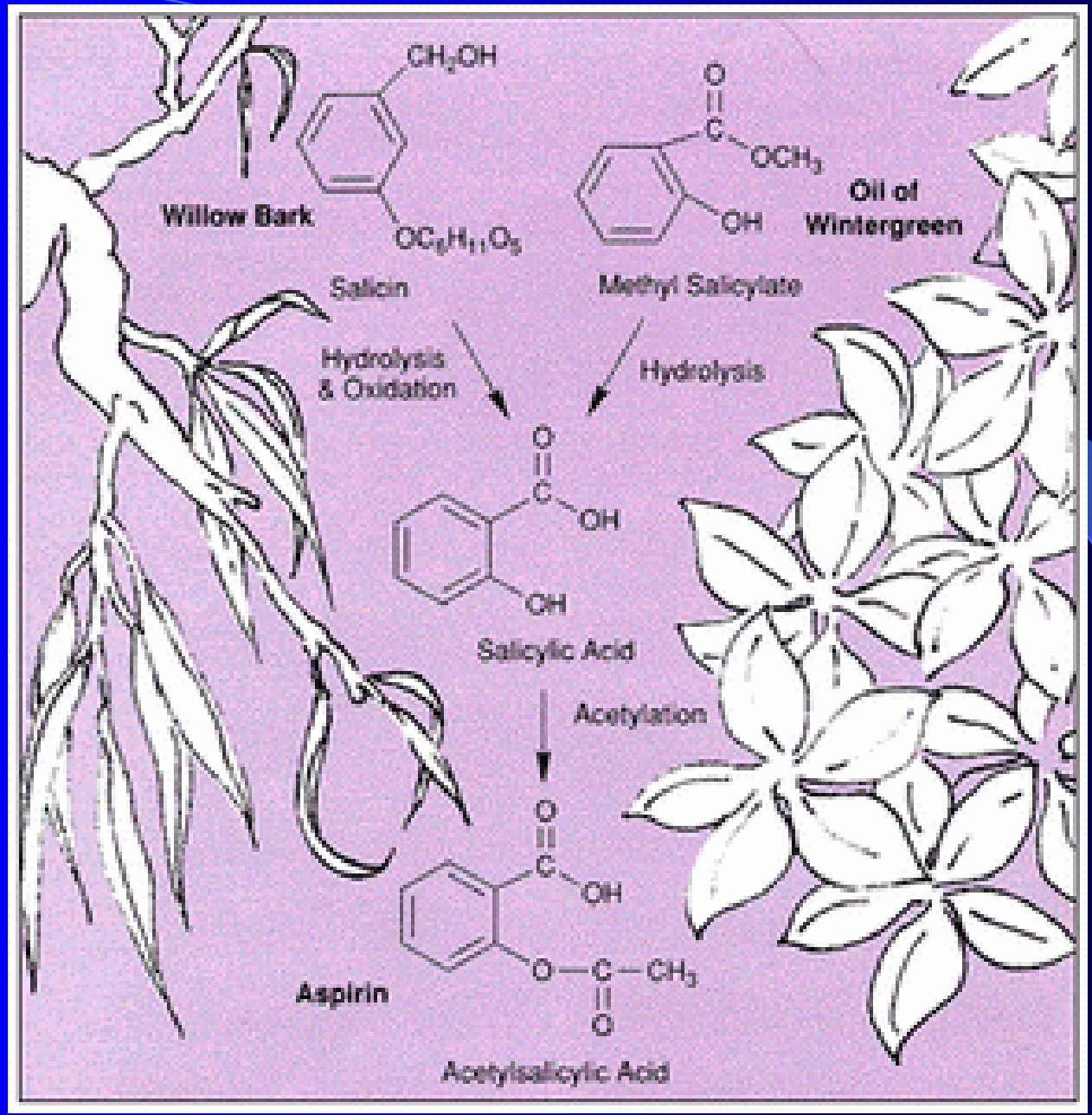
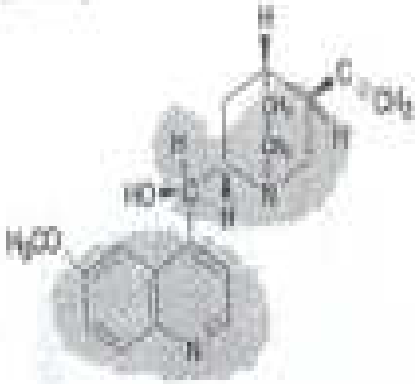
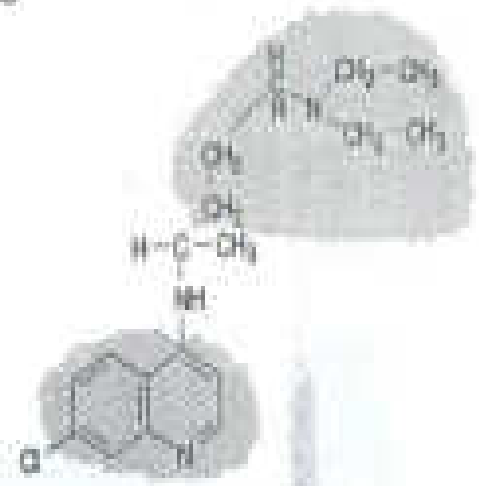
CH3O
OCH3
OH
Etoposide (VP-16-213) R = CH3
Teniposide (VM-26) R =
S
CO2H
arachidonic acid


Willow Bark
Salicin
Oil of Wintergreen
Methyl Salicylate
Hydrolysis & Oxidation
Hydrolysis
Salicylic Acid
Acetylation
Aspirin
Acetylsalicylic Acid

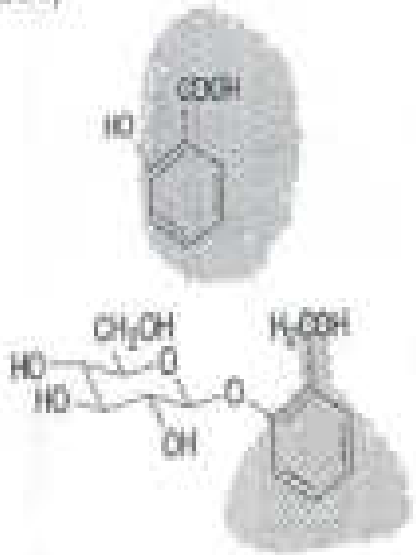
Quinine
(antimalarial)



Chloroquine



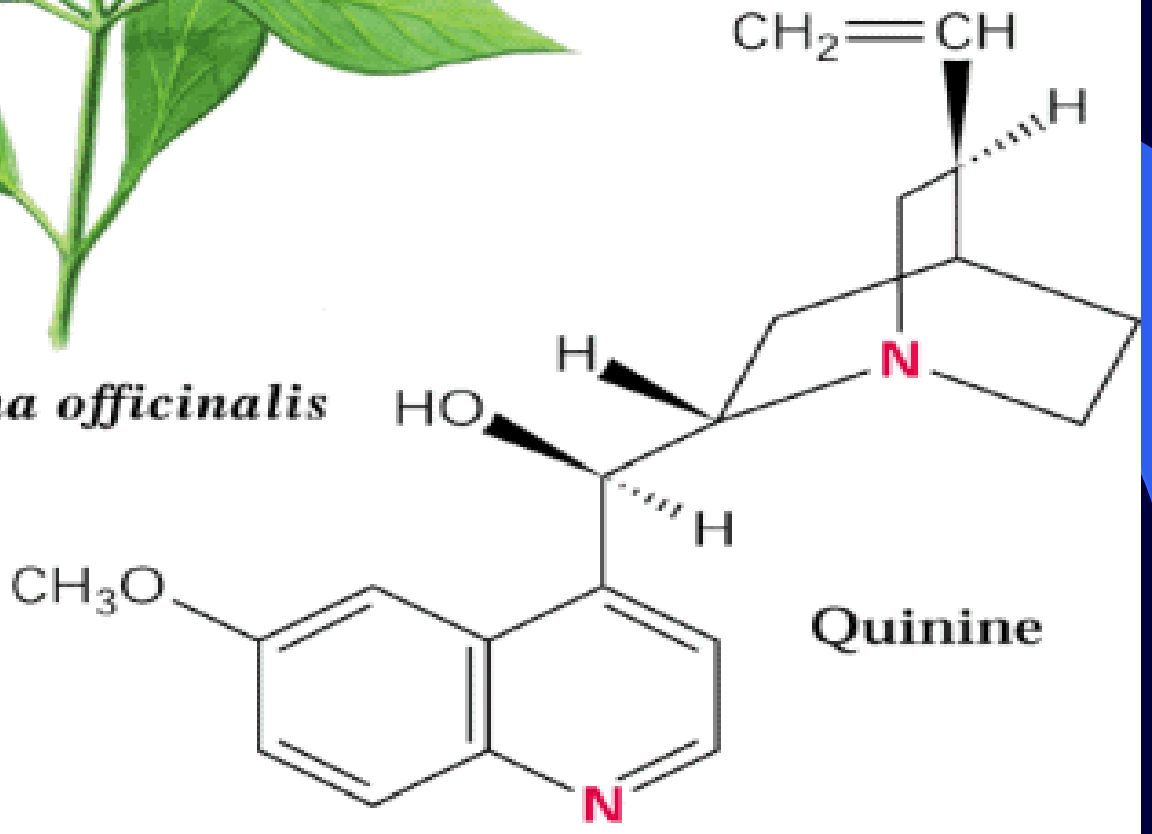
Salicin and Salicylic Acid
(Analgesic)



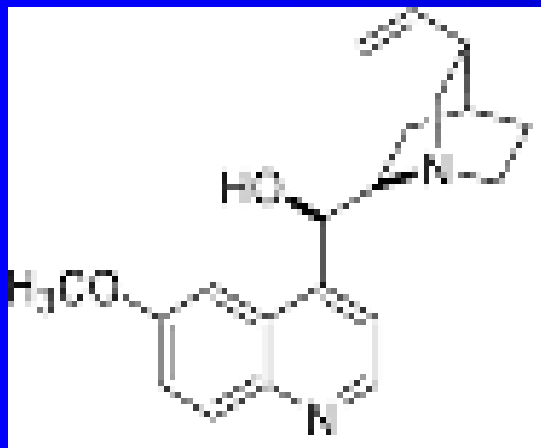
Aspirin

Ibuprofen

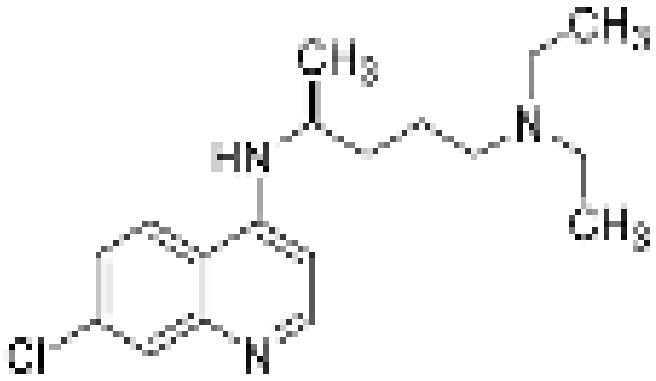
Cinchona officinalis



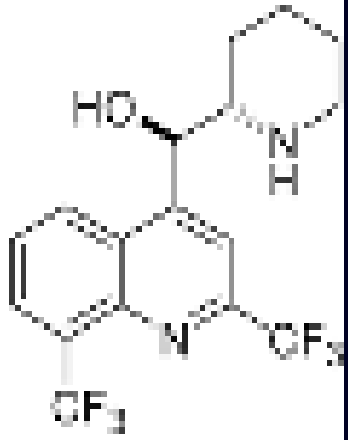
Quinine



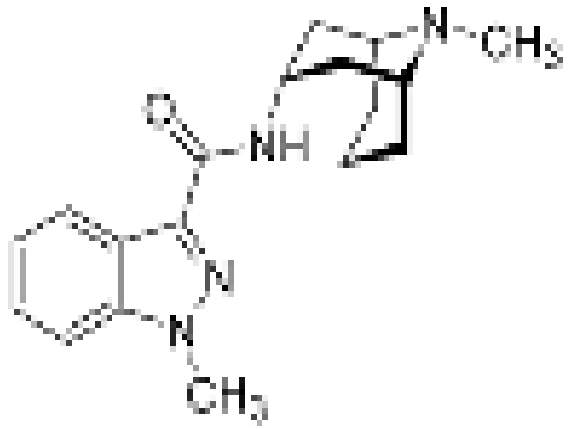
Quinine



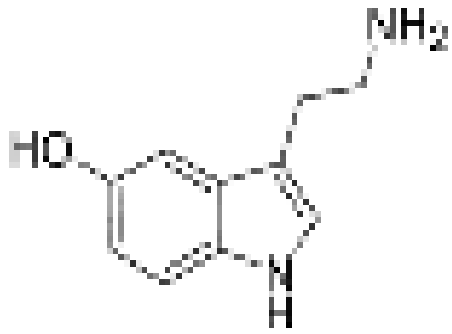
Chloroquine



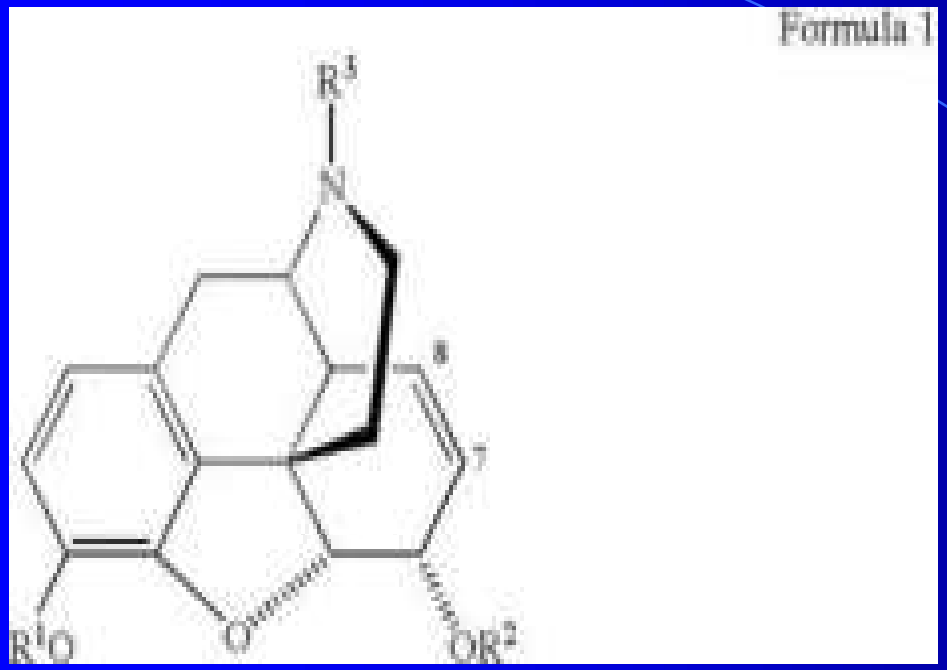
Mefloquine



Granisetron

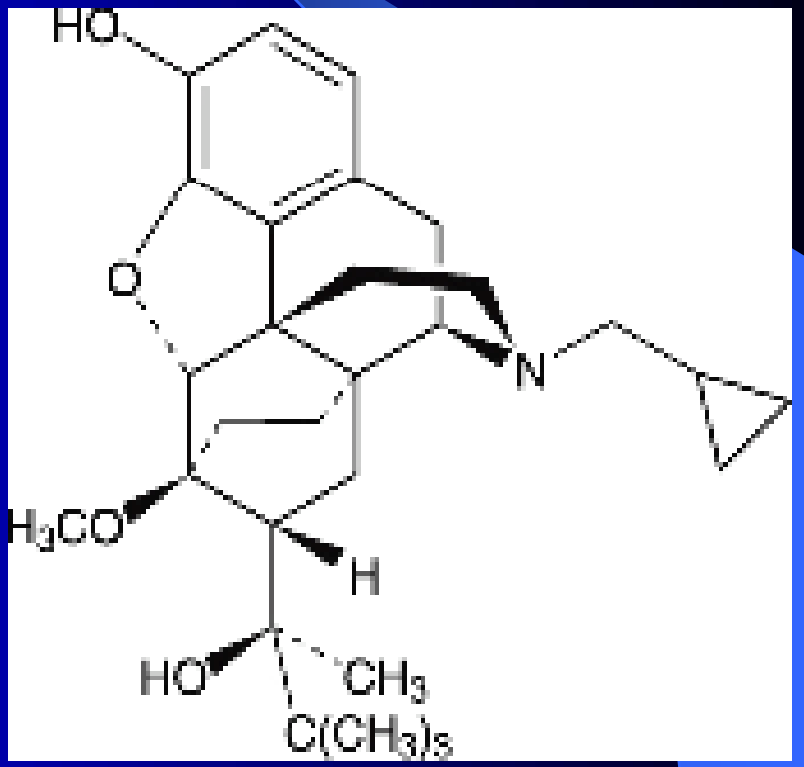


5-HT
Serotonin



MORPHINE

BUPRENORPHINE

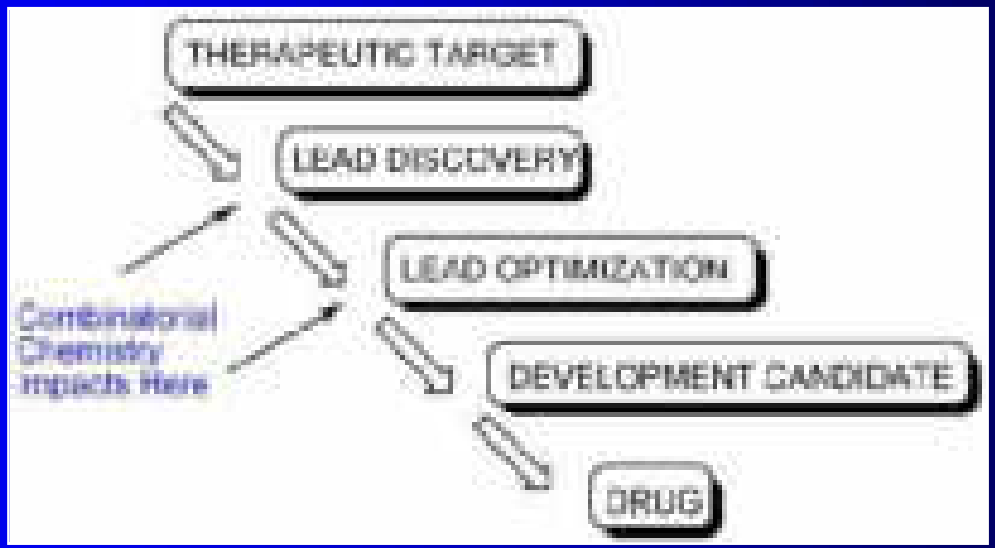


COMBINATORIAL CHEMISTRY

(*"combinatorial"*: of, relating to, or involving combinations)

Definition: the synthesis of chemical compounds as ensembles (libraries) and the screening of those libraries for compounds with desirable properties

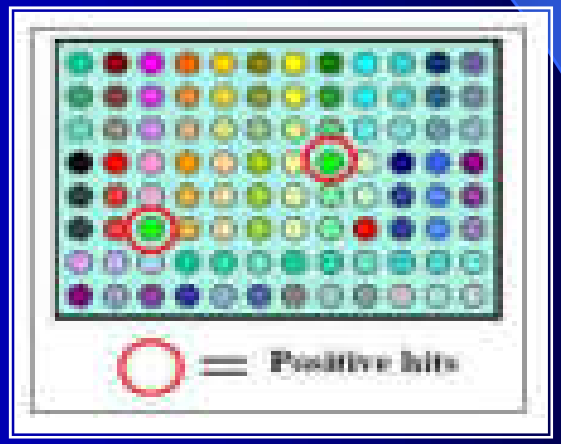
The aim of combinatorial chemistry ("CombiChem") is the generation of (large) numbers of compounds very quickly.



HIGH-THROUGHPUT SCREENING

'High-throughput' screening (HTS) assays have become widely used for affording new leads.

In this process, large numbers of crude extracts from organisms can be simultaneously evaluated in a cell- or noncell-based format, usually utilizing multi-well microtiter plates.



COMPOUND LIBRARIES

A 'compound library' is a collection of compounds, just as we use 'library' for a collection of books. The variety (diversity) of compounds may be:

– small and very limited diversity (e.g. departmental library),

– big but relatively limited diversity (e.g. University academic library),

– big and diverse (e.g. city library).

Compound libraries from past projects are kept and may be screened for the biological activity you are looking for in a new project.

New compounds may also be made "in-house" but nowadays specialist chemical companies are often contracted to simply make NCEs (new chemical entities) for big pharmaceutical companies.

Conclusion

- Globally, there is positive trend in favor of traditional and integrative health sciences both in research and practice. There are common approaches to drug discovery including use of chemical biology, serendipity, chemical synthesis, combinatorial chemistry and genomics. However, the innovative approaches involve ethanopharmcology, holistic, systems biology and personalized medicine.
- Safety remains the most important starting point and the efficacy becomes a matter of validation.
- A golden triangle consisting of Traditional Knowledge, Modern Medicine and Modern Science with systems orientation will converge to form an innovative discovery engine for newer, safer, affordable and effective therapies.

Thank you