Concepts of Alkaloids from Natural Sources

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By

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and Nafisa Aijaz Ahmed

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We, the authors, would first like to express our profound gratitude to the Almighty, the epitome of wisdom and knowledge, for granting us the opportunity to undertake this endeavor.

Although this book is a joint effort of Dr. Rukhsana, Prof. Areej, and Ms. Nafisa, it stands as a heartfelt tribute from two devoted students to their mentor and inspiration, Dr. Rukhsana. This book is a reflection and interpretation of the knowledge we gained from her during our graduation and post-graduation studies. We extend our deepest gratitude to her for guiding us through this process; her contributions have turned this work into a valuable resource for students and researchers in the fields of pharmacy and life sciences.

We lovingly dedicate this book to all our family members—parents, partners, and dear children—whose unwavering support made this accomplishment possible. You have been the driving force behind the successful completion of this book, and we are deeply thankful for your belief in us and for never giving up on us.

In addition, we dedicate this work to our lifelong friends, who, knowingly or unknowingly, taught us the power of words and stood by us when we needed those much-needed tea breaks.

Lastly, we hope that this book will serve as a source of inspiration and motivation to young minds, aiding them in their lifelong learning journey.

Thank you all.

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PREFACE

Pharmacognosy is the study of crude drugs obtained from natural sources like plants, animals, fungi. With the aid of science, we have gone a long way, and there are numerous ongoing advancements taking place in every field of life sciences to find the most potent drug showing no toxicity. In a same vein, pharmacognosy has been developed by researchers, and numerous novel phytochemicals to be used as nutraceuticals and medications are coming to light. Pharmacist, botanist or agriculturalist can appreciate the significance of having a thorough understanding of these phytochemicals isolated from the crude medicinal plants.

A simple conversation on books in pharmacognosy during the academic session gave rise to the idea for this book specifically which would entice learning in experts, researchers, and students in the field of pharmacy and life sciences.

Concepts of Alkaloids from Natural Sources is a book on natural products and pharmacognosy, explaining a few important alkaloids obtained from various natural sources. To make things easier to grasp, straightforward language and tabular structures are used whenever possible. Details about alkaloids derived from natural sources are included in this book. The writers have worked hard to compile the most recent data and arrange it logically as per their significance and applications. There are important phytochemical structures organized in appropriate manner for better correlation of their pharmacological action. The information regarding marine pharmaceuticals that may be found in this book makes it distinctive. There is also an explanation of drugs derived from different marine sources, such as marine algae and fungi. The authors also have introduced a unique chapter emphasizing about repurposing of alkaloids reinstating the future prospects and applications of these novel molecules in the field of drug discovery. It is sincere effort made by the fellow pharmacognosists to disseminate the essential information about the alkaloids for all the learners and researchers in the field of pharmacy and life science who wish to unfold the mysteries of these magical natural chemicals.

FOREWORD

The journey of Prof. Areej and me towards graduation from pharmacy school began in 2005, sparked by their encounter with the inspiring Professor Dr. Rukhsana. Over the years, the bond between us grew stronger, nurtured by Dr. Rukhsana's engaging and unforgettable lectures. Her teaching style created vivid experiences that made students feel at one with nature, leaving a lasting impression. Dr. Rukhsana has always been a role model we deeply admire.

Working with Dr. Rukhsana has been a pleasure, as she embodies genuine honesty and a fun-loving spirit. A national award winner and the author of numerous reference books and research articles, Dr. Rukhsana's contributions to natural drug discovery are truly remarkable. Her dedication and expertise have greatly influenced the field and inspired many, including us.

As longtime friends, we are thrilled to have collaborated on this book. What began as a shared dream has now become a reality, and we are delighted by how our relationship, which started with us as instructors and students, has evolved into a lifelong friendship. This book is a testament to that bond and to our mutual admiration for Dr. Rukhsana.

As a friend of Prof. Areej, I am overjoyed that she approached me with the idea for this book, which honors Dr. Rukhsana, our cherished professor, inspiration, and role model. Prof. Areej is a dedicated and hardworking individual. Her determination, even in the face of challenges, ensures she successfully completes any task she undertakes. Her positive attitude transforms the impossible into the possible. The famous quote, "I might not be there with you, but I am always there for you," perfectly encapsulates the foundation of our friendship. I would like to take this opportunity to thank Prof. Areej for always being by my side.

The goal of this book is to disseminate information in a straightforward manner, much like how our lecturer made complex topics easy to understand for us. We hope this book serves as a valuable resource and continues the legacy of clear, impactful teaching inspired by Dr. Rukhsana.

Sincerely,
Nafisa.

INTRODUCTORY NOTE

A comprehensive guide to the world of alkaloids and their medicinal sources, spanning plants, animals, and marine organisms. It is designed to serve as a valuable resource for students, learners, and researchers pursuing degrees in Pharmacy, Botany, and Agriculture. The book delves into the occurrence, diversity, properties, extraction, isolation, identification, classification, and general applications of therapeutically active alkaloids.

Key features of the book include:

- **Occurrence and Diversity:** Detailed descriptions of where various alkaloids are found in nature, highlighting the vast diversity of these compounds.
- **Properties and Applications:** Insights into the chemical properties of alkaloids and their applications as lead molecules in pharmacology.
- **Extraction and Isolation:** Methods for extracting and isolating alkaloids from different sources, ensuring readers understand practical applications.
- **Classification:** A thorough classification system for alkaloids, aiding in the systematic study and understanding of these compounds.
- **Detailed Plant Examples:** Each major class of alkaloids is illustrated with examples from at least three to four plants. These examples cover:
  - **Pharmacognosy:** The study of the physical, chemical, biochemical, and biological properties of drugs, drug substances, or potential drugs of natural origin.
  - **Phytochemistry:** The chemistry of plants and plant processes, detailing the specific chemical compounds found in plants.
  - **Applications and Future Prospects:** Current uses of these alkaloids and potential future applications in medicine and pharmacology.

Additionally, the book covers significant plant alkaloidal analogues and their applications, providing insights into the repurposing of pharmacologically significant alkaloids into novel drug delivery systems.

This aspect emphasizes the innovative approaches being explored to enhance the efficacy and delivery of these compounds.

The book's straightforward explanation style, supplemented with phytochemical structures, flowcharts, diagrams, and tables, makes it an excellent choice for both notes and reference material. It is particularly suited for pharmacy and life science students, guiding them in their foundational research into alkaloids and their natural sources.

For researchers, the book serves as a robust literature backbone, supporting work on active plant metabolites and their potential repurposing as lead molecules. By providing detailed examples and practical applications, the book facilitates deeper exploration and innovation in the field of natural product research.

This compendium stands as a testament to the importance of alkaloids in modern medicine and offers a detailed roadmap for future research and application in the therapeutic landscape.

CHAPTER 1

INTRODUCTION TO ALKALOIDS

History

In 1819, the term alkaloid was named by a German scientist **Carl Friedrich Wilhelm Meissner** and was derived from the combination of Latin and Greek languages, which meant "alkali-like."

In 1804, the German chemist Friedrich Sertürner initiated the search for alkaloids. Sertürner isolated "morphium," now known as morphine, from the opium poppy capsule, naming it after Morpheus, the Greek god of dreams. (Michael W,1998)

Another milestone in alkaloid chemistry was achieved by the German chemist Albert Ladenburg in 1886 when he successfully synthesized coniine. Ladenburg accomplished this by reacting 2-methylpyridine with acetaldehyde, followed by reducing the resulting 2-propenyl pyridine with sodium to produce coniine. (Vafa Amirkia et.al, 2014)

Alkaloids from various plants have been utilized for centuries as medications, ranging from mild stimulants like caffeine to poisons such as coniine from hemlock. (John E., 1981)

Definition

Alkaloids defined as organic compounds are obtained from natural origin such as plant or animal sources, and are basic in nature, having “N”, nitrogen in heterocyclic ring structure. The basicity is due to the presence of “Nitrogen” in the heterocyclic ring structure, which is marked by physiological and pharmacological actions. (C. K. Kokate, 2007)

Nomenclature

It can be named in multiple formats; the commonly used nomenclature includes ending the alkaloid's name with a **suffix "ine"** for example:

-Reserp**(ine)** is an antihypertensive obtained from the roots of *Rauwolfia Serpentina.*

-Morph**(ine)** is a narcotic analgesic obtained from the poppy capsule of *Papaver somniferum.*

-Caffe**(ine)** is a CNS stimulant obtained from the beans of *Coffea arabica* and leaves of *Thea sinensis*. Quin**(ine)** is an antimalarial obtained from the bark of the cinchona tree, *Cinchona calisaya*.

-Vincrist**(ine)** and Vinblast**(ine)** obtained from the leaves of *Catharanthus roseus*.

Some alkaloids are named based on reference to **genus or species** of the plant for example

-*Atropa belladonna,* here the alkaloid Atropine, an antimuscarinic agent, is derived from the genus name Atropa.

-*Erythroxylon coca,* here the alkaloid Cocaine, a CNS stimulant is derived from the species named Coca.

Some alkaloids are named based on the **Family** from which they are obtained for example

-Papaverine used as a smooth muscle relaxant obtained from *Papaver somniferum* that belongs to the family Papaveraceae.

Some alkaloids are named based on the **scientist** responsible for their discoveries eg;

-Pelletierine used to treat tapeworm infections, obtained from *Sedum alpestre* and *Sedum annuum.* It was named after Pelletier the scientist who discovered it.

Some alkaloids are named based on the **physiological action** e.g.

-Emetine is an emetic obtained from the plant of *Cephaelis ipecacuanha.*

-Morphine is a narcotic analgesic(narcosis) obtained from the poppy capsule of *Papaver somniferum.*

Some alkaloids are termed based on the **physical properties** they display eg;

-Hygrine is an antimalarial obtained from the leaves of *Erythroxylum coca* that is hygroscopic in nature. (David. S, 1998)

Prefix	**Action**	**Name of Alkaloid**	**Uses**
Nor-	N-demethylation or N-demethoxylation	Norpseudoephedrine	appetite suppressant
Apo-	Dehydration	Apomorphine	treatment of episodes in Parkinson disease
Iso-, pseudo-, neo-, & epi-	Isomerism	(–)-ergotamine & (+)-ergotamine (–)-Quinine & (+)-Quinine, also known as quinidine	Antimigraine antimalarial & antiarrhythmic
Suffix	**Action**	**Name of Alkaloid**	**Uses**
-dine	Isomerism	Quinidine & Cinchonidine	antiarrhythmic & antimalarial
-ine	Less potency	Ergotaminine	antimigraine

Table: 1.1: Identification based on Prefixes and Suffixes

Occurrence

Research has confirmed that about 20% of plant species, including marine algae, contain alkaloids, which are mainly used by plants to defend themselves against herbivores and pathogens. In plants, alkaloids are

typically found in three forms: free-state, N-oxide, or as salts. Some animal sources also contain alkaloids, such as toxic secretions present in fire ants, ladybugs, and toads. Additionally, certain insects use plant alkaloids as attractants or pheromones to initiate pollination.

Plant families that show an abundance of alkaloids include Apocynaceae, Rubiaceae, Solanaceae, and Papaveracea. On the other hand, plant families free from alkaloids include Rosaceae and Labiatae. (Tadeusz A, 2015).

Distribution and occurrence of alkaloids have been confirmed in various parts of plants, viz;

-Roots of Rauwolfia, Ipecac, Belladonna

-Bark of Cinchona, Kurchi

-Leaves of Vinca, Datura, Vasaka

-Stem of Ephedra

-Seeds of *Nux vomica*, Cocoa, Colchicum

-Flowers of Artemisia

-Fruits or capsules of Opium.

Physical Properties

The below mentioned physical properties are observed in most of the alkaloids:

1. **Colour:** Colourless
   - Exception: Berberine-yellow colour, Bethanidine-red colour, Sanguinarine-Copper red colour.
2. **State:** Solid and crystalline
   - Exception: nicotine-volatile liquid used as pesticides
   - Pilocarpine: non-volatile liquid used to treat dry mouth
3. **Solubility:** Alkaloids as salt form are soluble in water and insoluble in organic solvents. “with” Alkaloids are insoluble in water but soluble in organic solvents. Alkaloidal salt forms, on the Alkaloid bases and their salts forms show solubility in alcohol.
   - Exception: Caffeine, Ephedrine, Pilocarpine are alkaloidal bases soluble in warm water.

- Colchicine soluble in alkaline water, quaternary amine alkaloids are water soluble.
- Quinine monosulphate is the salt form insoluble in water.

4. **Isomerization:** Isomers are compounds with the same empirical formula but different structural arrangements. Many alkaloids feature an asymmetric carbon atom in their ring structure, resulting in optical activity and isomerism. These differences in structure lead to variations in pharmacological properties among isomers. For example, l-Ephedrine is 3.5 times more active as a CNS stimulant than d-Ephedrine. Similarly, l-Ergotamine is 3-4 times more effective as an antimigraine agent compared to d-Ergotamine. Additionally, the levo isomer of quinine is used as an antimalarial, while its dextro isomer, quinidine, is used as an antiarrhythmic. (Trease E.C et.al, 2009)

Chemical Properties

1. Chemically, alkaloids consist of carbon, hydrogen, and nitrogen, and in most cases, oxygen as part of their basic ring structure.
2. **Basicity:** Alkaloids are basic in nature due to the presence of nitrogen in their heterocyclic ring structure. Typically, they contain one nitrogen atom, but certain substances like ergotamine may contain up to five nitrogen atoms. The nitrogen in alkaloids can be present as a primary amine (RNH2), secondary amine (R2NH), or tertiary amine (R3N). The order of basicity is as follows: R2NH > RNH2 > R3N.
3. Most alkaloids, like all bases, form crystalline salts with acids such as hydrochloric acid, sulfuric acid, citric acid, and tartaric acid.
4. When alkaloids react with phosphotungstic acid, phosphomolybdic acid, picric acid, potassium mercuric iodide, and tannic acid, they yield insoluble precipitates known as double salts. (Trease E.C et.al, 2009)

General Method of Extraction

Alkaloids generally occur as mixtures of alkaloidal salts with inert materials such as tannins, proteins, fats, resins, and pigments, which complicates their separation and purification and typically results in very low yields. Therefore, extraction methods often utilize hot Soxhlet extraction with successive solvents and repeated basification, acidification, and separation using organic solvents to achieve better separation of pure alkaloids. The

extracted alkaloids can be further purified using techniques such as silica gel column chromatography, thin-layer chromatography, Sephadex LH-20, and recrystallization. –Vinod D, 2008)

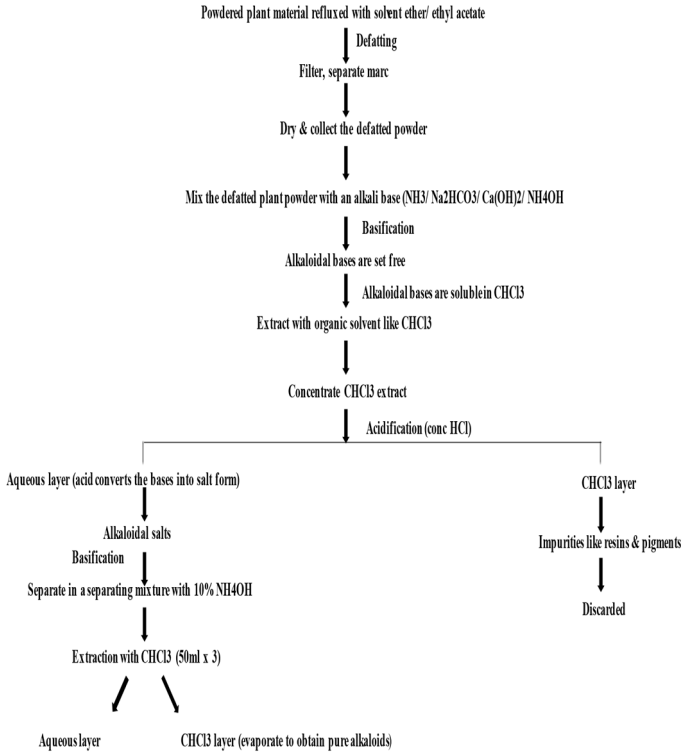


Fig. 1.1: Stass Otto Method

Separation & Purification of individual alkaloids

1. **Fractional precipitation crystallization**: Some alkaloidal derivatives can be converted to their pure form by forming oxalate, tartrate, and picrate salts. (JI Yubin et.al, 2014)
2. **Gradient pH extraction:** Alkaloids exhibit varying degrees of basicity, and changes in pH allow their conversion into salt forms, which can then be solubilized and separated using various solvents. To extract alkaloids from plant powder, the powder can initially be

acidified by mixing it with 2% tartaric acid to achieve a low pH. The pH is then gradually increased, depending on the basicity of the alkaloids. At each step of pH increment, different organic solvents can be used to separate the pure alkaloids.

3. **Chromatographic techniques:** Chromatographic techniques are highly appropriate for the separation of complex mixtures, including alkaloids. Alkaloids can be further purified from their crude extract by separation on a column chromatograph. This process involves using an appropriate adsorbent, such as silica gel, alumina, or Sephadex, and employing solvent elution with regular monitoring of eluents by thin-layer chromatography (TLC). Pooling together TLC-homogeneous eluents and subsequent crystallization will yield pure alkaloids. High-performance liquid chromatography (HPLC) can also be used to better quantify and purify pure alkaloidal samples. (Vinod Borde et.al, 2014)

Sr. No.	Test	Reagent content	Observation
1	Dragendorff's	Potassium bismuth iodide solution	Brick red ppt
2	Mayer's	Potassium mercuric iodide solution	Cream/ off white ppt
3	Wagner's	Iodine & Potassium iodide solution	Reddish-purple ppt
4	Hager's	Saturated sodium picrate solution	Bright yellow ppt

Table 1.2: General Confirmatory Test for Alkaloids

Classification

Alkaloids are indeed a diverse group of compounds with various pharmacological, botanical, and biochemical properties. They can be classified in several ways:

1. **Biosynthetic Classification**: Alkaloids can be classified based on the precursors utilized by plants to synthesize them. This

classification sheds light on the biochemical pathways involved in alkaloid biosynthesis.
2. **Pharmacological Classification**: Alkaloids can be categorized based on their pharmacological activities. This classification helps in understanding the therapeutic properties and potential applications of alkaloids in medicine.
3. **Taxonomic Classification**: Alkaloids can also be classified based on the taxonomy of the plants from which they are obtained. This classification provides insights into the distribution of alkaloids across different plant families and genera.

Each classification system offers valuable insights into the diverse nature and properties of alkaloids, contributing to our understanding of these compounds in various fields such as pharmacology, botany, and biochemistry. (Heinrich. M et.al, 2021)

General Classification

A comprehensive overview of the different types of alkaloids:

I. **True Alkaloids**: These alkaloids contain nitrogen in a heterocyclic ring and are derived from amino acids. They are highly reactive and form water-soluble salts. True alkaloids are biologically active, often occurring in crystalline form and conjugating with acids to form salts. They are typically bitter and solid, with the exception of nicotine, which is a brown liquid. Common amino acids such as l-phenylalanine, l-tyrosine, l-ornithine, l-histidine, and l-lysine serve as main sources for true alkaloids. Naturally occurring true alkaloids include cocaine, morphine, and quinine.

II. **Protoalkaloids**: Protoalkaloids are a minor group of alkaloids structurally composed of simple compounds. They contain nitrogen atoms derived from amino acids but not part of the heterocyclic ring system. Main precursors of protoalkaloids include l-tryptophan and l-tyrosine. Examples of protoalkaloids include yohimbine, mescaline, and hordenine, which find applications in disorders such as mental illness, pain, and neuralgia.

III. **Pseudoalkaloids:** Unlike protoalkaloids and true alkaloids, pseudoalkaloids are not directly derived from amino acids but relate to amino acid pathways. They are derived from precursors through amination or transamination reactions, which can include non-amino acid precursors such as phenylalanine or acetate. Common examples of pseudoalkaloids are capsaicin, caffeine, and ephedrine. It's worth noting that true and protoalkaloids

are obtained from amino acids, whereas pseudoalkaloids have more diverse origins. (Britannica. T, 2023)

Chemical Classification

The chemical classification of alkaloids based on the presence of heterocyclic rings and their chemical nature is indeed significant. Alkaloids are broadly categorized into heterocyclic compounds and non-heterocyclic compounds.

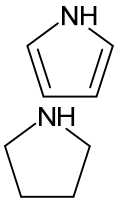
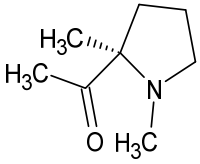
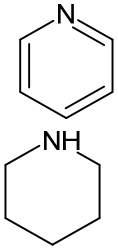
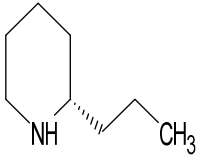
1. Heterocyclic Alkaloids: Also known as typical alkaloids, these compounds contain nitrogen (N) within their heterocyclic ring structures. They are further classified into mononuclear and polynuclear alkaloids.

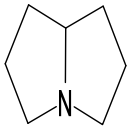
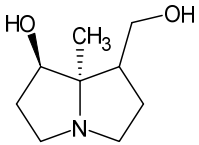
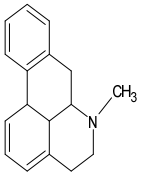
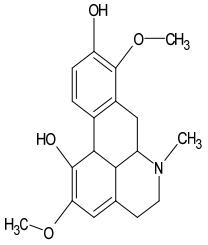
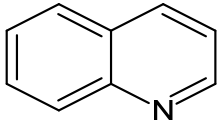
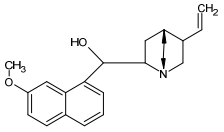
- **Mononuclear Alkaloids**: These alkaloids contain a single heterocyclic ring with nitrogen (N) atoms. Examples include nicotine, caffeine, and morphine.
- **Polynuclear Alkaloids**: These alkaloids contain multiple fused heterocyclic rings with nitrogen (N) atoms. Examples include quinine, ergotamine, and reserpine.

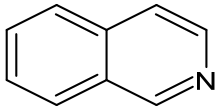
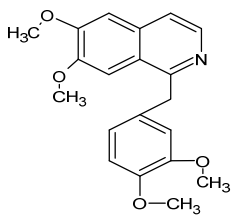
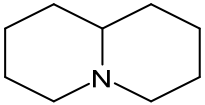
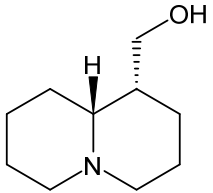
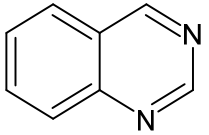
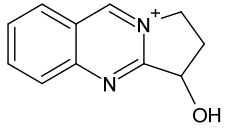
2. Non-Heterocyclic Alkaloids: Also known as atypical alkaloids, these compounds contain nitrogen (N) within their aliphatic chains rather than within heterocyclic ring structures. Examples include the tropane alkaloids such as atropine and scopolamine.

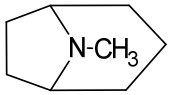
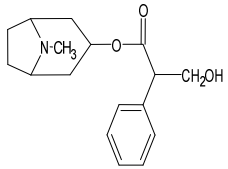
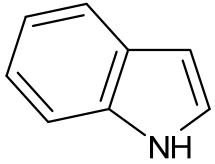
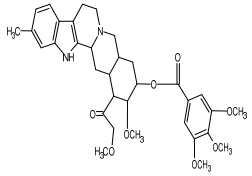
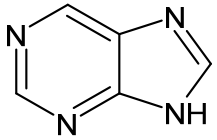
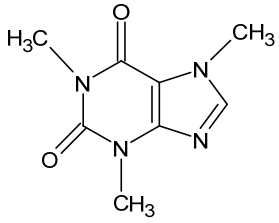
This chemical classification provides valuable insights into the structural diversity of alkaloids, helping to understand their properties and functions in various biological systems.

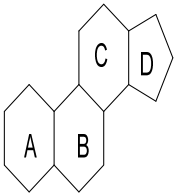
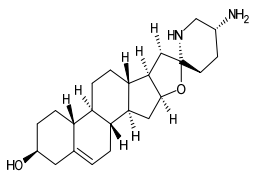
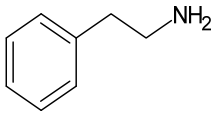
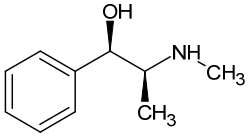
Examples are depicted in the table below:

Heterocyclic/Typical alkaloids			
Mononuclear Alkaloids		**Polynuclear Alkaloids**	
Mononuclear Alkaloids			
Type	**Basic Chemical ring**	**Example**	**Structure**
Pyrrole and Pyrrolidine alkaloids		Hygrine	
Pyridine and piperidine alkaloids		Arecoline Lobeline Coniine	 Coniine

Pyrrolizidine alkaloids		Retronecine	
Aporphine		Boldine	
Polynuclear Alkaloids			
Type	**Basic Chemical ring**	**Example**	**Structure**
Quinoline alkaloids		Quinine	

Isoquinoline alkaloids		Papaverine Emetine	 Papaverine
Norlupinane alkaloids		Lupinine	
Quinazoline alkaloids		Vasicine	

Tropane alkaloids		Atropine and Hyoscine	 Atropine
Indole alkaloids		Reserpine Vincristine	 Reserpine
Purine alkaloids		Caffeine	

Steroidal Alkaloids		Solasodine	
Non heterocyclic/Atypical alkaloids			
Type	**Basic Chemical ring**	**Example**	**Structure**
Amino alkaloid		Ephedrine Mescaline	 Ephedrine

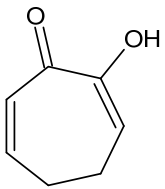
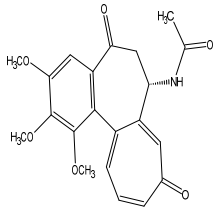
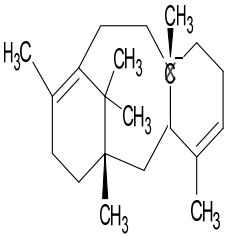
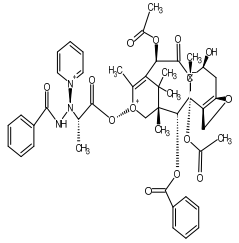
Tropolone		Colchicine	
Modified diterpenes		Taxol	

Table 1.3: Hetero cyclic alkaloids

Few of the important classes are described below:

a. Tropane alkaloid: Tropane alkaloids, as the name suggests, contain a tropane (C4N skeleton) nucleus. These compounds are primarily found in the Solanaceae family and are derived from ornithine and acetoacetate. Pyrrolines serve as the precursors for tropane alkaloids. Most of these alkaloids exhibit a variety of hydroxylation patterns, appearing as mono-, di-, or tri-hydroxy propane derivatives.

Notable examples of tropane alkaloids include cocaine, atropine, and scopolamine, along with their various derivatives.

b. Pyrrolizidine alkaloids:

The pyrrolizidine nucleus is a distinctive feature of pyrrolizidine alkaloids. These compounds are commonly found in the Asteraceae and Fabaceae families. They predominantly occur as N-oxides, though they often lose this functional group during the isolation process. Pyrrolizidine alkaloids are known for their hepatotoxic properties.

c. Piperidine alkaloids:

Piperidine alkaloids are characterized by the presence of a piperidine nucleus. One of the key features of true piperidine alkaloids is the C5N nucleus in the monocyclic compounds. These alkaloids often have a distinctive odour and pungent taste, which is attributed to piperine. The first alkaloid ever extracted was coniine, a piperidine alkaloid, as noted in historical records. Piperidine alkaloids occur naturally in both poisonous and non-poisonous plants. Examples of poisonous plants containing piperidine alkaloids include hemlock (*Conium maculatum L.*) and the opium poppy (*Papaver somniferum L., Papaveraceae*). Non-poisonous plants containing these alkaloids include black pepper (*Piper nigrum L., Piperaceae*), *Psilocaulon absimile* (Aizoaceae), and *Petrosimonia monandra*. Lobeline, another significant piperidine alkaloid, is obtained from the genus Lobelia, including *Lobelia inflata*, also known as Indian tobacco.

d. Quinolines alkaloids: Quinoline alkaloids are characterized by the presence of a quinoline nucleus, a structure that is often obtained from cinchona plants. Many of these alkaloids, particularly the heteroaromatic quinolines, are also extracted from marine sources. Examples include 4,8-quinolinediol from cephalopods and 2-heptyl-4-hydroxyquinoline from