Alkaloids Derived from Tyrosine: Modified Benzyltetrahydroisoquinoline Alkaloids

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Abstract

Secondary metabolites are produced by plants in response to biotic or abiotic interactions with their environment and confer protection through a variety of antimicrobial, pesticidal, and pharmacological properties. Alkaloids are a class of plant secondary metabolites that traditionally have been classified as basic compounds derived from amino acids that contain one or more heterocyclic nitrogen atom. About 20 % of plant species accumulate alkaloids, which are mostly derived from amino acids, e.g., phenylalanine, tyrosine, tryptophan, and lysine. The alkaloids are popular for their medicinal importance. The pharmaceutically important representatives of secondary metabolites are mostly alkaloids derived from tyrosine. In this chapter, we summarized the prior information, basic knowledge about the alkaloids, origin, physicochemical properties, uses, classification, biosynthetic reactions, and distribution of tyrosine-derived alkaloids especially opium alkaloids and their biosynthetic pathways in plants. We have also reviewed different web resources related to alkaloids and secondary metabolic pathway databases such as KEGG.

Keywords

Anticancer • antimalarial • classification of alkaloids • isoquinoline alkaloids • KEGG • tyrosine alkaloid biosynthesis

Abbreviations

BIA	Benzylisoquinoline alkaloids
CNMT	(S)-coclaurine-*N*-methyltransferase
Cor	Codeinone reductase
CYP	Cytochrome P
DOPA	Dihydroxy phenylalanine
KEGG	Kyoto Encyclopedia of Genes and Genomes
M6G	Morphine-6-glucuronide
NCS	(S)-norcoclaurine synthase
OMT	(R,S)-reticuline 7-*O*-methyltransferase
SalR	Salutaridine reductase

SDR	Short-chain dehydrogenase/reductase
tyrDC	Tyrosine decarboxylase
UGT2B7	UDP-Glucuronosyltransferase-2B7

1 Introduction

Plants produce a vast array of secondary metabolites in response to biotic or abiotic interactions with their environment, which impart flavor, color, and fragrance and confer protection through a variety of antimicrobial, pesticidal, and pharmacological properties. About 20 % of plant species accumulate alkaloids, which are mostly derived from amino acids, e.g., Phe, Tyr, Trp, and Lys. In addition, the monoterpenoid indole alkaloids, which form a large class of complex compounds, are derived from tryptophan and terpenoid precursors [1]. They are assumed to play indispensable roles for the survival of plants producing these metabolites as defense compounds against pathogenic organisms or predators and allelopathic metabolites for competing with other plants. These are natural products of non-peptidic origin containing nitrogen that have had the major impact throughout history on the economic, medical, political, and social affairs of humans. In fact, they are the skeleton framework of about 60 % of the modern drugs, such as atropine for tropicamide, quinine for chloroquine, and cocaine for procaine and tetracaine, that are available today. Thus, there has been a resurgence in the screening of plant extracts for pharmacological activities as part of industrial drug development programs in recent years.

Their basic character is reflected in the name derived from alkaline which means basic. The ease with which they can be extracted from plants, fungi, or insects where they occur naturally coupled with their sometimes profound biological effects on human have made them a very early focus of systematics chemical research. Given the commercial value of the alkaloids, the processes and genes involved in their biosynthesis and secretion are attractive targets for genetic engineering. In the course of studying the biosynthesis of these metabolites at biochemical, genomic, and systematic level, life scientists recently listed the following questions: (a) to what extent is the genomic pathways conserved among different species? (b) is there a minimal set of pathways that are required by all organisms? (c) how are organisms related in terms of the distance between pathways rather than at the level of DNA sequence similarity? At the core of such questions lies the identification of pathways in different organisms. So in a way pathway knowledge in public databases enables us to examine how individual metabolites are connected via chemical reactions and what genes are implicated in those processes. Given the commercial value of the alkaloids and the processes and genes involved in their biosynthesis and secretion which are attractive targets for genetic engineering, very little is known about how plants synthesize these substances and so far little is known about how the synthesis is regulated at the genetic level. Moreover,

owing to the cost of sequencing and their relatively large size, the full genome sequences of only a few plants are currently available. Recent progress in the many plant sequencing projects; there is an imperative need to integrate functional genomics data to obtain a more comprehensive system-biology view of the results. Besides, biochemical pathway maps composed of genes, proteins, and metabolites are powerful tools around which one can compile the biological context of functional genomics datasets. Several metabolic pathway databases are available to facilitate our understanding of transcriptome and metabolome data such as KEGG (http://www.genome.ad.jp/kegg), MetaCyc (http://metacyc.org), AraCyc (http://www.arabidopsis.org/tools/aracyc), BioCyc (http://biocyc.org), and Reactome (http://reactome.org), but the pathways and reactions involved in alkaloid biosynthesis are not well represented and the information contained in these databases does not meet the unique data requirements for plant researchers, especially those involved in plant alkaloid metabolism studies. Alkaloids have an enormous structural and biosynthetic diversity, and these are identified and quantified using a wide range of technology platforms. In this chapter, alkaloid structure, classification, biosynthesis, and function and their role in disease therapy like malaria and cancer have been covered.

1.1 Natural Product

A natural product is a chemical compound or substance produced by a living organism found in nature that usually has a pharmacological or biological activity for use in pharmaceutical drug discovery and drug design. Not all natural products can be fully synthesized, and many natural products have very complex structures that are too difficult and expensive on an industrial scale such as penicillin, morphine, paclitaxel, and vincristine. To avoid side effects of many nonnatural and synthetic drugs, active molecules derived from secondary metabolites are harvested through medicinal plants. Figure 15.1 represents the synthesis of natural products derived from plants. Prior reports describe the biosynthesis of different natural medicinal products [2].

2 Secondary Metabolites

Because of their sessile way of life, plants have developed a rich arsenal of chemicals, encompassing some 200,000 known compounds [2]. These metabolites participate in all kinds of biotic and abiotic interactions with the environment, predominantly with regard to defense against herbivores and pathogens, and are considered "secondary metabolites" because they are not involved in the primary processes of growth and development [3, 4]. They have traditionally been of interest only due to their pronounced and various physiological activities in animals and humans [5]. They are low molecular weight organic compounds that possess

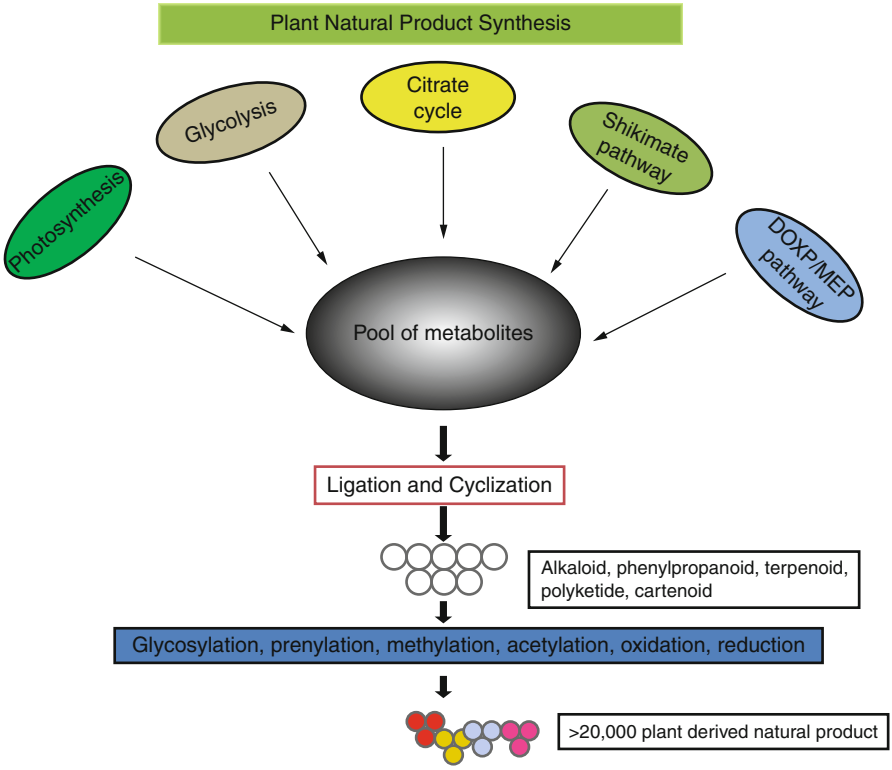


Fig. 15.1 Synthesis of natural products derived from plants

interesting biological activities and fine applications, such as pharmaceuticals, insecticides, dyes, flavors, and fragrances. Higher plants produce a wide variety of secondary metabolites, including more than 25,000 terpenoids, about 8,000 phenolic compounds, and about 12,000 alkaloids [6]. One of the most conspicuous features of secondary metabolites is that they are often restricted to individual species or related groups of species, rather than being broadly distributed in the plant kingdom. Figure 15.2 represents the biosynthetic relationships of major groups of secondary compounds.

2.1 Classification of Secondary Metabolites

Most of the secondary metabolites of interest belong to the following categories. These categories are broad categories which classify secondary metabolites based on their biosynthetic origin.

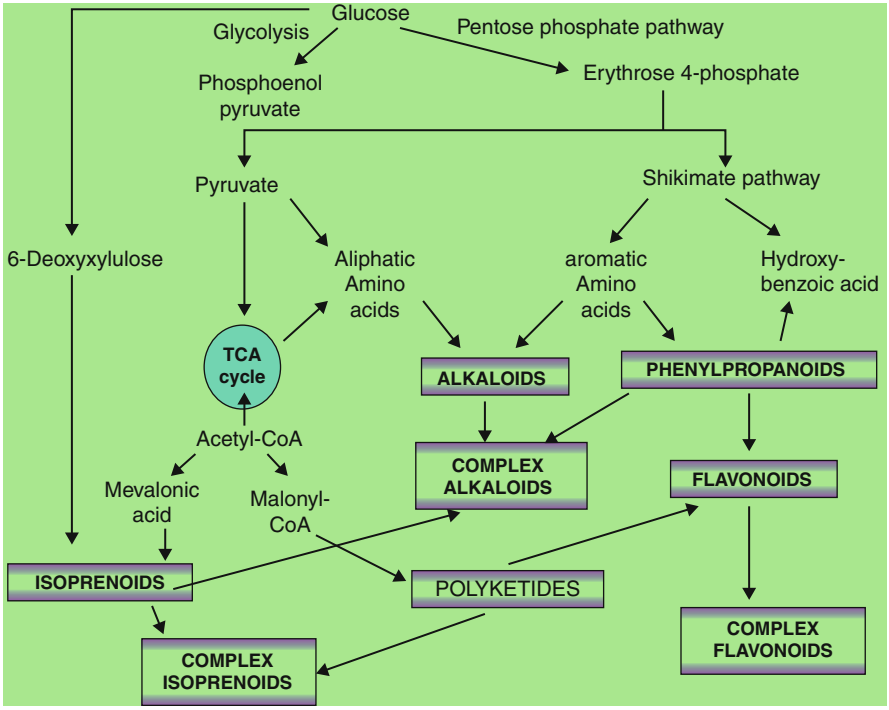


Fig. 15.2 Biosynthetic relationships of major groups of secondary compounds

Alkaloids (derived from amino acids):
- Hyoscyamine, present in *Datura stramonium*
- Atropine, present in *Atropa belladonna*
- Cocaine, present in *Erythroxylon coca*
- Codeine and morphine, present in *Papaver somniferum*

Terpenoids (come from semiterpene oligomerization):
- Azadirachtin, present in seeds of *Azadirachta indica* (neem)
- Artemisinin, present in *Artemisia annua*
- Tetrahydrocannabinol, present in *Cannabis sativa*

Steroids (terpenes with a particular ring structure)
Glycosides (heavily modified sugar molecules)
Phenols
Phenazines

3 Alkaloids

Alkaloids are a class of secondary plant metabolites that traditionally have been classified as basic compounds derived from amino acids that contain one or

more heterocyclic nitrogen atom. Although this definition holds for most known alkaloids recently, any *N*-containing secondary compound is considered an alkaloid if it cannot readily be classified otherwise – i.e., not an amine, cyanogenic glycoside, glucosinolate, etc. The original definition for alkaloids is pharmacologically active, *N*-containing basic compounds of plant origin. Ergot alkaloids are toxins and important pharmaceuticals and have been identified in two orders of fungi and three families of higher plants [7]. The most important producers are fungi of the genera Claviceps, Penicillium, and Aspergillus (all belonging to the Ascomycota). Chemically, ergot alkaloids are characterized by the presence of a tetracyclic ergoline ring and can be divided into three classes according to their structural features, i.e., amide or peptide-like amide derivatives of D-lysergic acid and the clavine alkaloids. Significant progress has been achieved on the molecular biological and biochemical investigations of ergot alkaloid biosynthesis in the last decade. By gene cloning and genome mining, gene clusters for ergot alkaloid biosynthesis have been identified in at least 8 different ascomycete species. The functions of most structure genes have been assigned to reaction steps in the biosynthesis of ergot alkaloids by gene inactivation experiments or biochemical characterization of the overproduced proteins. An overview of the studies related to the biosynthesis of alkaloids has been published [8]. Several biologically active alkaloids (1–4, 6), including a new quinazoline-6-carboxylic acid (1), were isolated from the medicinal plant Zanthoxylum rhetsa, an evergreen tree, native to subtropical areas [9]. Whereas the pharmacological properties of the plant extract and single constituents have been widely tested, we now show that all of the metabolites have anti-algal activities, all but 6 are antibacterial, and 6 and the reduction product 5 (derived from 4) are also antifungal. A detailed account on the biological activities of structurally diverse secondary metabolites from marine sponges having 2-aminoimidazole, glycociamidine, and/or 2-thiohydantoin ring functions has been analyzed by Kumar et al. [10].

4 Classification of Alkaloids

The alkaloids, as an important and enormously large conglomerate of naturally occurring nitrogen-containing plant substances having very specific as well as most diversified pharmacological properties, may be classified in a number of modes and means. Hegnauer [11] conveniently classified alkaloids into six important groups, corresponding to the six amino acids legitimately considered as the starting points for their biosynthesis, such as anthranilic acid, histidine, lysine, ornithine phenylalanine, and tryptophan. Price [12] further took a leading clue from the earlier observation and considered in details the alkaloids present in one of the families (Rutaceae) and logically placed them in the following *nine* chemical-structural categories, namely,

acridines, amides, amines, benzylisoquinolines, canthinones, imidazoles, indolquinazolines, furoquinolines, and quinazolines. Another school of thought classifies alkaloids in the following *four* heads, namely:

(a) *Biosynthetic Classification* – In this particular instance, the significance solely lies to the precursor from which the alkaloids in question are produced in the plant biosynthetically. Therefore, it is quite convenient and also logical to group together all alkaloids having been derived from the same precursor but possessing different taxonomic distribution and pharmacological activities.

Examples

1. Indole alkaloids derived from tryptophan
2. Piperidine alkaloids derived from lysine
3. Pyrrolidine alkaloids derived from ornithine
4. Phenylethylamine alkaloids derived from tyrosine
5. Imidazole alkaloids derived from histidine

(b) *Chemical Classification* – It is probably the most widely accepted and common mode of classification of **alkaloids** for which the main criterion is the presence of the basic heterocyclic nucleus (i.e., the **chemical entity**).

Examples

1. Pyrrolidine alkaloids (e.g., hygrine)
2. Piperidine alkaloids (e.g., lobeline)
3. Pyrrolizidine alkaloids (e.g., senecionine)
4. Tropane alkaloids (e.g., atropine)
5. Quinoline alkaloids (e.g., quinine)
6. Isoquinoline alkaloids (e.g., morphine)
7. Aporphine alkaloids (e.g., boldine)
8. Indole alkaloids (e.g., ergometrine)
9. Imidazole alkaloids (e.g., pilocarpine)
10. Diazocin alkaloids (e.g., lupanine)
11. Purine alkaloids (e.g., caffeine)
12. Steroidal alkaloids (e.g., solanidine)
13. Amino alkaloids (e.g., ephedrine)
14. Diterpene alkaloids (e.g., aconitine)

(c) *Pharmacological Classification* – Interestingly, the **alkaloids** exhibit a broad range of pharmacological characteristics. This method is also used as a strong basis for the general classification of the wide spectrum of alkaloids derived from the plant kingdom, such as analgesics, cardiovascular drugs, CNS stimulants and depressants, dilation of pupil of eye, mydriatics, anticholinergics,

sympathomimetics, antimalarials, and purgatives. However, such a classification is not quite common and broadly known.

Examples

1. Morphine as narcotic analgesic
2. Quinine as antimalarial
3. Strychnine as reflex excitability
4. Lobeline as respiratory stimulant
5. Boldine as choleretics and laxatives
6. Aconitine as neuralgia as an external agent in neuralgia and rheumatism
7. Pilocarpine as antiglaucoma agent and miotic
8. Ergonovine as oxytocic
9. Ephedrine as bronchodilator
10. Narceine as analgesic (narcotic) and antitussive

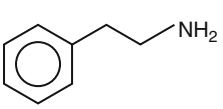
(d) *Taxonomic Classification* – This particular classification essentially deals with the "Taxon," i.e., the taxonomic category. The most common *taxa* are the genus, subgenus, species, subspecies, and variety. Therefore, the taxonomic classification encompasses the plethora of alkaloids exclusively based on their respective distribution in a variety of plant families, sometimes also referred to as the "natural order." A few typical examples of plant families and the various species associated with them are stated below, namely:

1. *Cannabinaceous Alkaloids:* e.g., *Cannabis sativa* Linn. (Hemp, Marijuana)
2. *Rubiaceous Alkaloids:* e.g., *Cinchona Sp*. (Quinine), *Mitragyna speciosa* Korth (Katum, Kratum, Kutum), *Pausinystalia johimbe* (K. Schum) (Yohimbe)
3. *Solanaceous Alkaloids:* e.g., *Atropa belladona* L. (Deadly Nightshade, Belladona), *Brunfelsia uniflorus* (Pohl) D. Don (Manaca, Manacan), *Capsicum annuum* L. (Sweet Peppers, Paprika), *Datura candida* (Pers.) Saff. (Borrachero, Floripondio), *Duboisia myoporoides* R. Br. (Corkwood Tree, Pituri), *Hyoscyamus niger* L. (Henbane, Henblain, Jusquaime), *Mandragora officinarum* L. (Mandrake, Loveapple), *Nicotiana glauca* R. Grah. (Tree Tobacco), *Seopolia carniolica* Jacq. (Scopolia), *Solanum dulcamara* L. (Bittersweet, Bitter Nightshade, Felonwood), *Withania somniferum* (L.) Dunal (Ashwagandha), etc.

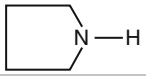
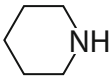
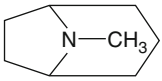
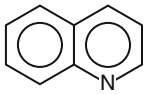
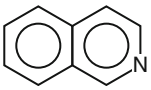
Invariably, they are grouped together according to the name of the *genus* wherein they belong to, such as coca, cinchona, and ephedra. Some "phytochemists" have even gone a step further and classified the alkaloids based on their chemotaxonomic classification.

In the recent past, the alkaloids have been divided into *two* major categories based on the analogy that one contains a *non-heterocyclic nucleus* while the other has the *heterocyclic nucleus*. These two classes of alkaloids shall be discussed briefly as under:

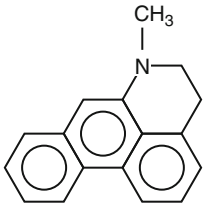
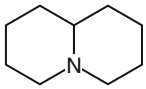
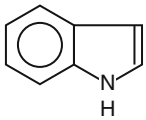
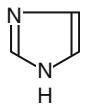
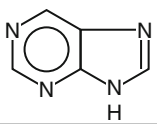
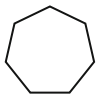
(a) *Non-heterocyclic Alkaloids* – A few typical alkaloids having a non-heterocyclic nucleus are enumerated below with other related information:

S.No.	Basic ring structure	Alkaloid	Botanical origin	Family
1	Phenylethylamine 	Ephedrine	*Ephedra vulgaris*	Gnetaceae
		Hordenine	*Hordeum vulgare*	Graminae
		Capsaicin	*Capsicum annuum*	Solanaceae
		Mescaline	*Laphophora williamsii*	Cactaceae
		Narceine	*Papaver somniferum*	Papaveraceae

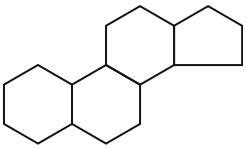
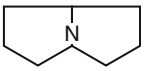
(b) *Heterocyclic Alkaloids* – A large number of specific alkaloids possessing heterocyclic nucleus are stated below with other related information

S.No.	Basic ring structure	Alkaloid	Botanical origin	Family
1	Pyrrolidine 	Hygrine	*Erythroxylon coca*	Erythroxylaceae
		Stachydrine	*Stachys tuberifera*	Labiatae
2	Pyridine 	Arecoline	*Areca catchu*	Palmaceae
		Ricinine	*Ricinus communis*	Euphorbiaceae
		Trigenelline	*Trigonella foenumgraecum*	Leguminosae
3	Piperidine 	Connine	*Conium maculatum*	Umbelliferae
		Lobeline	*Lobelia inflata*	Lobeliaceae
		Pelletierine	*Punica granatum*	Punicaceae
4	Tropane [piperidine-pyrrolidine(*N*-methyl)] 	Atropine	*Atropa belladona*	Solanaceae
		Cocaine	*Datura stramonium*	Solanaceae
		Hyoscyamine	*Erythroxylon coca*	Erythroxylaceae
			Atropa belladona	Solanaceae
5	Quinoline 	Quinine, Quinidine	*Cinchona officinalis*	Rubiaceae
		Cuspareine	*Cusparia trifoliata*	Rutaceae
6	Isoquinoline 	Papaverine	*Papaver somniferum*	Papaveraceae
		Berberine	*Hydrastis canadensis*	Berberidaceae
		Emetine	*Uragoga ipecacuanha*	Rubiaceae
		Corydaline	*Corydalis aurea*	Fumariaceae
			Corydalis solida	Fumariaceae
		Tubocurarine	*Chondodendron tomentosum*	Menispermaceae

(*continued*)

S.No.	Basic ring structure	Alkaloid	Botanical origin	Family
7	Aporphine Isoquinoline Phenanthrene 	Boldine	*Peumus boldus*	Monimiaceae
8	Norlupinane 	Sparteine	*Lupinus luteus*, *Lupinus niger*, *Cytisus scoparius*, *Anagyris foetida*	Leguminosae
		Lupinine	*Lupinus luteus*	Leguminosae
			Anabasis aphylla	Chenopodiaceae
9	Indole (benzopyrrole) 	Ergotamine, Ergometrine	*Claviceps purpurea*	Hypocreales
		Physostigmine	*Physostigma venenosum*	Leguminosae
		Reserpine	*Rauwolfia serpentina*	Apocynaceae
		Yohimbine	*Coryanthe johimbe*	Rubiaceae
			Rauwolfia serpentina	Apocynaceae
		Vinblastine	*Vinca rosea*	Apocynaceae
		Strychnine	*Strychnos nux-vomica*	Loganiaceae
10	Imidazole (glyoxaline) 	Pilocarpine	*Pilocarpus jaborandi*	Rutaceae
11	Purine (pyrimidine-imidazole) 	Caffeine	*Thea sinensis*	Ternstroemiaceae
			Camellia sinensis	
			Coffea arabica	Rubiaceae
			Theobroma cacao	Sterculiaceae
12	Tropolone 	Colchicine	*Colchicum autumnale*	Liliaceae

(*continued*)

S.No.	Basic ring structure	Alkaloid	Botanical origin	Family
13	Steroid 	Conessine	*Holarrhena antidysenterica*	Apocynaceae
		Funtumine	*Funtumia latifolia*	Apocynaceae
		Solanidine	*Solanum spp.*	Solanaceae
		Veratramine	*Veratrum grandiflorum, Veratrum viride*	Liliaceae
14	Terpenoid (diterpene)	Aconine	*Aconitum napellus*	Ranunculaceae
		Aconitine (Glycoside)	*Aconitum napellus*	Ranunculaceae
		Atisine	*Aconitum heterophyllum, Aconitum anthora*	Ranunculaceae
		Lycoetonine	*Aconitum lycoctonum*	Ranunculaceae
15	Pyrrolizidine 	Senecionine	*Senecio vulgaris*	Compositae
		Seneciphylline	*Senecio platyphyllus*	Compositae

It is pertinent to mention that the enormous volume of authentic information accumulated so far with regard to the isolation of alkaloids from a variety of plant species and their subsequent characterization by the help of latest analytical techniques they may be classified as follows:

(a) Alkaloids derived from amination reactions
1. Acetate-derived alkaloids
2. Phenylalanine-derived alkaloids
3. Terpenoid alkaloids
4. Steroidal alkaloids

(b) Alkaloids derived from anthranilic acid
1. Quinazoline alkaloids
2. Quinoline alkaloids
3. Acridine alkaloids

(c) Alkaloids derived from histidine
Imidazole alkaloids

(d) Alkaloids derived from lysine
1. Piperidine alkaloids
2. Quinolizidine alkaloids
3. Indolizidine alkaloids

(e) Alkaloids derived from nicotinic acid
Pyridine alkaloids

(f) Alkaloids derived from ornithine

1. Pyrrolidine alkaloids
2. Tropane alkaloids
3. Pyrrolizidine alkaloids

(g) Alkaloids derived from tyrosine

1. Phenylethylamine alkaloids
2. Simple tetrahydroisoquinoline alkaloids
3. Modified benzyl tetrahydroisoquinoline alkaloids

(h) Alkaloids derived from tryptophan

1. Simple indole alkaloids
2. Simple b-carboline alkaloids
3. Terpenoid indole alkaloids
4. Quinoline alkaloids
5. Pyrroloindole alkaloids
6. Ergot alkaloids (Table 15.1)

Table 15.1 Distribution of pathways according to alkaloids

S.No.	Pathway name	Alkaloids
1	Alkaloidal amines biosynthesis	Dopamine, colchicine, ephedrine, methaphetamine
2	Tropane alkaloid Biosynthesis	Scopolamine, nicotine, hygrine, calystegines B1, calystegines B2, spermidine, spermine, cocaine, tropinone, littorine, tropine
3	Quinoline alkaloid biosynthesis	Quinine, quinidine
4	Indole alkalod biosynthesis	Tryptamine, sarpagine, ajmaline, vinblastine, vindoline, catharanthine, serpentine, tetrahydro alstonine, ajmalicine
5	Quinolizidine alkaloid biosynthesis	Cadaverine, (+)-P- coumaroylepilupinine/lupinine, (−)-13a-tigloyloxymutiflorine/lupanine
6	Purine alkaloid biosynthesis	Xanthine, 1,3,7-trimethylxanthine(caffeine), 3,7-dimethylxanthine(theobromine), 1,3-dimethylxanthine (theophylline)
7	Steroidal alkaoid biosynthesis	Solanine, chaconine, solasodine
8	Isoquinoline alkaloid biosynthesis	Dopamine, sanguinarine, morphine, laudanine, berbamunine, guatteguaumerine, 2′-Norberbamunine, 10-hydroxychelerythrine, macarpine, (S)canadine, berberine, 7,8-dihydroberberine, thebaine, methopapaverberbine, macrantaline, narcotolinediol, narcotinediol, narcotoline, noscapine
9	Pyrrolizidine alkaloid biosynthesis	Senecionine *N*-oxide
10	Pyridine-piperidine alkaloid biosynthesis	Cadaverine, lupinate, L-pipecolate, *N*-methyl pelletierine, anapheline, anatabine, nicotine, nornicotine, *N*-formylnornicotine, nicotyrine, myosrnine, cotinine, tropinone, *N*-methyl pelletierine, anapheline, anatalline, anabasine

5 Biosynthesis of Alkaloids

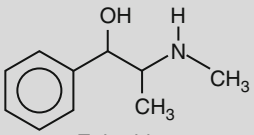
Alkaloids derived from tyrosine include phenylethylamine alkaloids, simple tetrahydroisoquinoline alkaloids, and modified benzyl tetrahydroisoquinoline alkaloids. The chemistry of Erythrina and related alkaloids from 1996 to mid-2009 has been reviewed, with a particular focus on the preparation of Erythrina alkaloids possessing an aromatic "D" ring [13].

Phenylethylamine Alkaloids

The important alkaloids belonging to this category are, namely, **ephedrine**, **hordenine**, **mescaline**, and **narceine**.

Ephedrine

It occurs in *Ephedra vulgaris* Hook. F. (*E. gerardiana* Wall), *Ephedra sinica* Stapf. (1–3 %), and *Ephedra equisetina* Bunge (2 %) belonging to the natural order *Gentaceae* and several other Ephedra species. Besides, it is also found in the roots of *Aconitum napellus* L. (*Ranunculaceae*) (Aconite, Monkshood, Blue Rocket); and *Ephedra nevadensis* S. Wats. (*Ephedraceae*) (Mormon Tea, Nevada Jointfir).

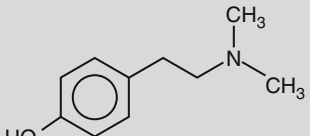


Ephedrine

α-[1-(Methylamino)-ethyl] benzene-methanol; ($C_{10}H_{15}NO$)

Hordenine

It is obtained from the plant of *Lophophora williamsii* (Lamaire) Coult. (*Catctaceae*) (Peyote) and *Selenicereus grandiflorus* Britt and Rose (*Coctaceae*) (Night Blooming Cereus).



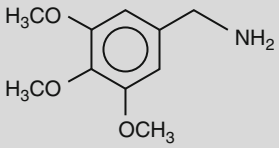
Hordenine

4-[2-Dimethylamino) ethyl] phenol; ($C_{10}H_{15}NO$)

It is very soluble in chloroform, ethanol, and ether; 7 g dissolves in 1 L of water; practically insoluble in petroleum ether; and sparingly soluble in benzene, xylene and toluene.

Mescaline

It is obtained from *Peyote* (Mescal Buttons) the flowering heads of *Lophophora williamsii* (Lemaire) Coult. (*Coctaceae*) and the cactus *Trichocereus pachanoi* Britton and Rose (*Cactaceae*) (Achuma, San Pedro Aguacolli).



Mescaline

3, 4, 5-Trimethoxybenzeneethanamine; ($C_{11}H_{17}NO_3$)

5.1 Pyrrolizidine Alkaloids

The system of pyrrolizidine alkaloids has proven to be a powerful system for studying the evolution of a biosynthetic pathway in plant secondary metabolism. Pyrrolizidine alkaloids are typical plant secondary products produced by the plant as a defense against herbivores. The first specific enzyme, homospermidine synthase, has been shown to have evolved by duplication of the gene encoding deoxyhypusine synthase, which is involved in primary metabolism. Despite the identical function of the homospermidine synthase for pyrrolizidine alkaloid biosynthesis in the various plant lineages, this gene duplication has occurred several times independently during angiosperm evolution. After duplication, these gene copies diverged with respect to gene function and regulation. In the diverse plant lineages producing pyrrolizidine alkaloids, homospermidine synthase has been shown to be expressed in a variety of tissues, suggesting that the regulatory elements were recruited individually after the duplication of the structural gene [14].

Pyrrolizidine alkaloids are one of the best-studied examples of a plant's defense system that has been recruited by several insect lineages for their own chemical defense. In each case, this recruitment requires sophisticated mechanisms of adaptations, e.g., efficient excretion, transport, suppression of toxification, or detoxification. Here, we briefly summarize the detoxification mechanism known for pyrrolizidine alkaloids and focus on pyrrolizidine alkaloid *N*-oxidation as one of the mechanisms allowing insects to accumulate the sequestered toxins in an inactivated protoxic form. Recent research into the evolution of pyrrolizidine alkaloid *N*-oxygenases of adapted arctiid moths (Lepidoptera) has shown that this enzyme originated by the duplication of a gene encoding a flavin-dependent monooxygenase of unknown function early in the arctiid lineage. The available

data suggest several similarities in the molecular evolution of this adaptation strategy of insects to the mechanisms described previously for the evolution of the respective pathway in plants [15].

5.2 Isoquinoline Alkaloids

Isoquinoline alkaloids are tyrosine-derived plant alkaloids with an isoquinoline skeleton. Among them, benzylisoquinoline alkaloids form an important group with potent pharmacological activity, including analgesic compounds of morphine and codeine and antiinfective agents of berberine, palmatine, and magnoflorine. Biosynthesis of isoquinoline alkaloids proceeds via decarboxylation of tyrosine or DOPA to yield dopamine, which together with 4-hydroxyphenylacetaldehyde, an aldehyde derived from tyrosine, is converted to reticuline, an important precursor of various benzylisoquinoline alkaloids.

5.3 Isoquinoline Alkaloid Biosynthesis

Isoquinoline alkaloid biosynthesis is one of the well-characterized pathways in the secondary metabolism of plant cells which comprises some of the most important drugs for therapy and euphoria (e.g., morphine and its chemical derivatives, papaverine, berberine, dimeric bisbenzylisoquinolines).

The benzylisoquinoline alkaloid class includes several important medicinal compounds such as analgesic morphine, codeine, papaverine, berberine, tubocurarine, and antimicrobial sanguinarine. Enzymes involved in the biosynthesis of at least two tetrahydrobenzylisoquinoline alkaloids, the benzophenanthridine alkaloid sanguinarine and the bisbenzylisoquinoline alkaloid berbamunine, have been reported. The branch point that differentiates the biosynthetic pathway from that which leads to (S)-reticuline-derived benzylisoquinoline alkaloids is shown to be (S)-*N*-methylcoclaurine. All benzylisoquinoline alkaloids share a common biosynthetic origin beginning with a lattice of decarboxylations, ortho-hydroxylations, and deaminations that convert L-tyrosine into both dopamine and 4-hydroxyphenylacetaldehyde. Dopamine and 4-hydroxyphenylacetaldehyde condense to form the trihydroxylated (S)-reticuline which is a key branch-point intermediate in the biosynthesis of most benzylisoquinoline alkaloids, including those with a morphinan (e.g., morphine), benzophenanthridine (e.g., sanguinarine), or protoberberine (e.g., berberine) nucleus and are found mainly in species of the Papaveraceae, Monimiaceae, Ranunculaceae, Berberidaceae, and Menispermaceae. (S)-Reticuline is clearly one of the most versatile molecules in plant secondary metabolism. Five enzymes of alkaloid formation are reported: (R,S)-3-hydroxy-*N*-methylcoclaurine 4-*O*-methyltransferase central to the biosynthesis of tetrahydroisoquinoline-derived alkaloids, the berberine bridge

enzyme of the sanguinarine pathway, (R,S)-reticuline 7-*O*-methyltransferase specific to laudanosine formation, and salutaridinol 7-*O*-acetyltransferase and codeinone reductase, which lead to morphine. The conversion of (S)-reticuline to (S)-scoulerine via the berberine bridge enzyme (BBE) represents the first committed step in benzophenanthridine and protoberberine alkaloid biosynthesis. Plant *O*-methyltransferases: molecular analysis, common signature and classification have been studied by Ibrahim et al. [16].

Morphine and codeine are members of the large and diverse group of benzylisoquinoline alkaloids, of which morphine and sanguinarine share a common biosynthetic pathway, beginning with the condensation of two L-Tyr derivatives to produce the central precursor (S)-norcoclaurine yields (S)-reticuline, the last common intermediate in the biosynthesis of both sanguinarine and morphine. Berberine bridge enzyme (BBE) catalyzes the conversion of (S)-reticuline to (S)-scoulerine, the first committed step in the sanguinarine pathway. Alternatively, (S)-reticuline can be isomerized to its (R)-epimer as the first step in the formation of morphine. Since the pathway from tyrosine to (S)-reticuline is also known at the enzyme level, the conversion of L-tyrosine to macarpine involves a total of 19 enzymes which are now at least partially characterized.

The isoquinoline pathway's enzyme orthologs in other plants showed that genes of methyltransferase family such as (R,S)-reticuline 7-*O*-methyltransferase, coclaurine 4′-*O*-methyltransferase, (S)-norcoclaurine 6-*O*-methyltrasferase, columbamine *O*-methyltransferase, coclaurine *N*-methyltransferase, putrescine *N*-methyltransferase responsible for the production of reticuline, coclaurine, norcoclaurine, columbaine have been reported from *Papaver somniferum, Coptis japonica, Thalictrum flavum, Thalictrum tuberosum, Coffea liberica, Coffea arabica, Coffea canephora, Nicotiana tabacum, Solanum tuberosum, Datura stramonium, Hyoscyamus niger*, and *Atropa belladonna.* Pathway contains information of about four alkaloids such as dopamine, colchicine, ephedrine, and methamphetamine and identified two missing links.

Eschscholzia californica produces various types of isoquinoline alkaloids. The structural diversity of these chemicals is often due to cytochrome P450 (P450) activities. Members of the CYP719A subfamily, which are found only in isoquinoline alkaloid-producing plant species, catalyze methylenedioxy bridge-forming reactions. In this study, four kinds of CYP719A genes from *E. californica* have been characterized. These four cDNAs encoded amino acid sequences that were highly homologous to *Coptis japonica* CYP719A1 and *E. californica* CYP719A2 and CYP719A3, which suggested that these gene products may be involved in isoquinoline alkaloid biosynthesis in *E. californica*, especially in methylenedioxy bridge-forming reactions. Expression analysis of these genes showed that two genes (CYP719A9 and CYP719A11) were preferentially expressed in plant leaf, where pavine-type alkaloids accumulate, whereas the other two showed higher expression in the root than in other tissues [17] (Fig. 15.3, Tables 15.2–15.5).

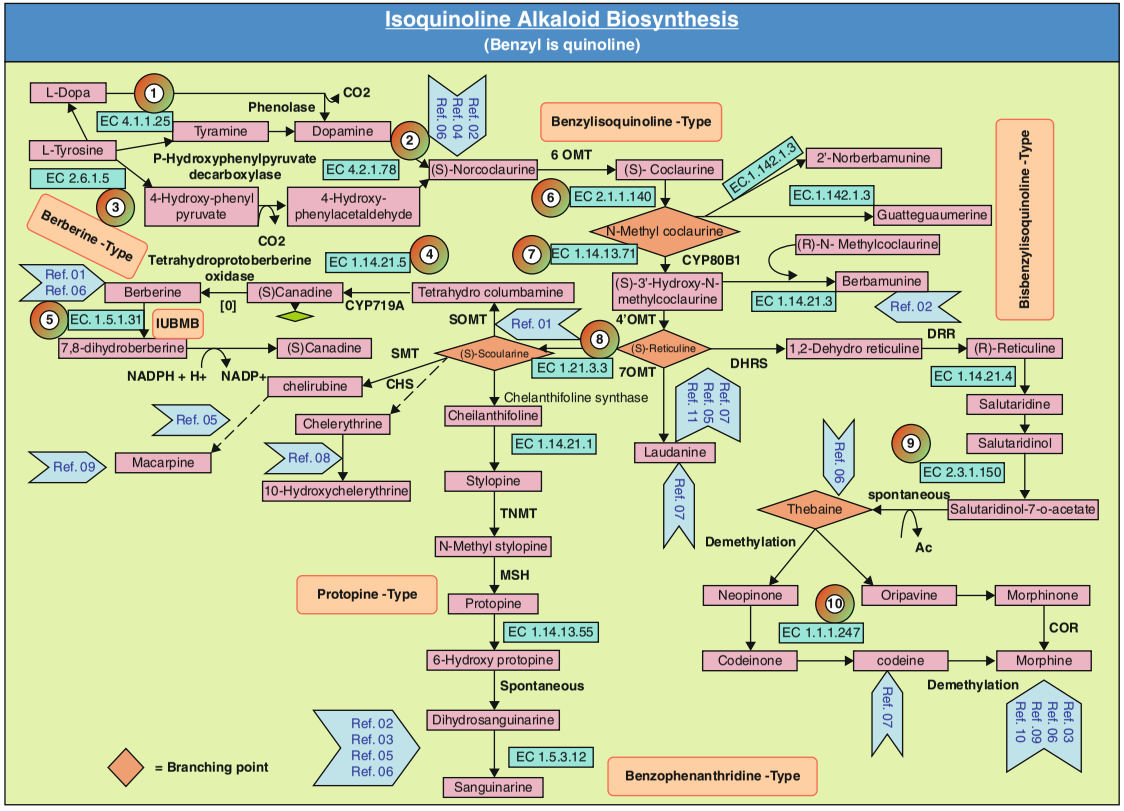
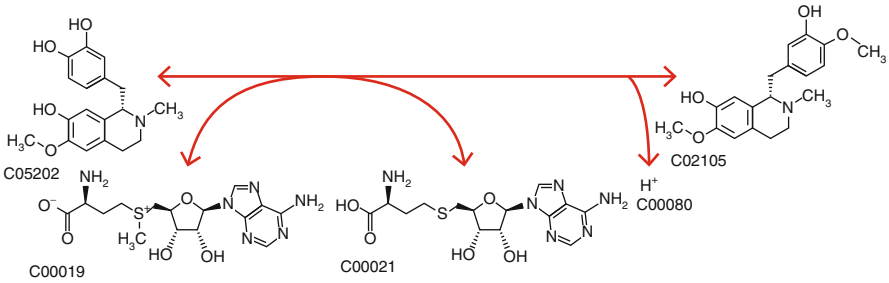


Fig. 15.3 Isoquinoline alkaloid biosynthesis pathway represented in DbAlBioPath database (Available at intranet, CSIR-CIMAP, Lucknow, India)

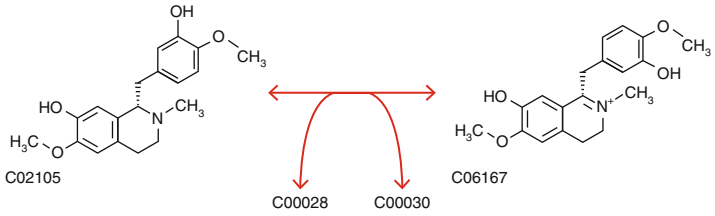
Table 15.2 Details of KEGG pathway and enzyme name and equation catalyzed by the enzyme during the biosynthesis of isoquinoline alkaloids

KEGG reaction entry	R03832
Name	S-adenosyl-L-methionine:3′-hydroxy-*N*-methyl-(S)-coclaurine 4′-*O*-methyltransferase
Definition	S-adenosyl-L-methionine + 3′-hydroxy-*N*-methyl-(S)-coclaurine < = > S-adenosyl-L-homocysteine + (S)-reticuline + H+
Equation	C00019 + C05202 < = > C00021 + C02105 + C00080



Enzyme	2.1.1.116; 3′-hydroxy-*N*-methyl-(S)-coclaurine 4′-O-methyltransferase; transferases
Pathway	Isoquinoline alkaloid biosynthesis (rn00950)
Orthology	K13386; 3′-hydroxy-*N*-methyl-(S)-coclaurine 4′-O-methyltransferase [EC:2.1.1.116]

KEGG reaction entry	R03833
Definition	(S)-reticuline + acceptor < = > 1,2-dehydroreticuline + reduced acceptor
Equation	C02105 + C00028 < = > C06167 + C00030

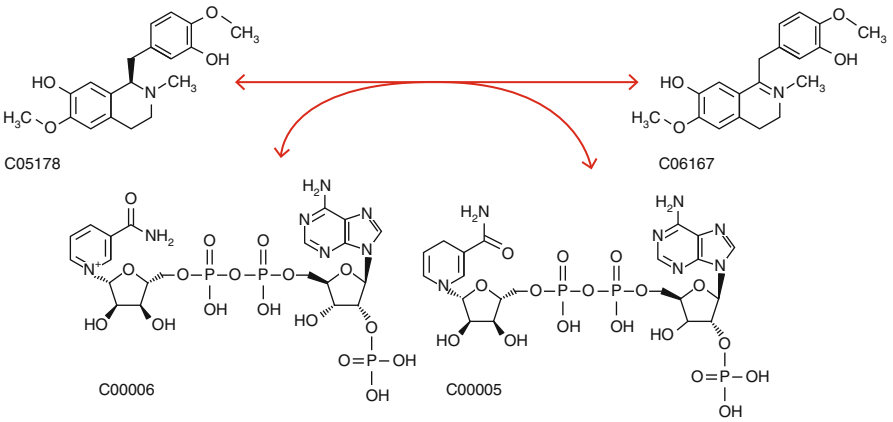


Enzyme	1.5.-.-; Oxidoreductases; acting on the CH-NH group of donors
Pathway	Isoquinoline alkaloid biosynthesis
	Metabolic pathways
	Biosynthesis of secondary metabolites

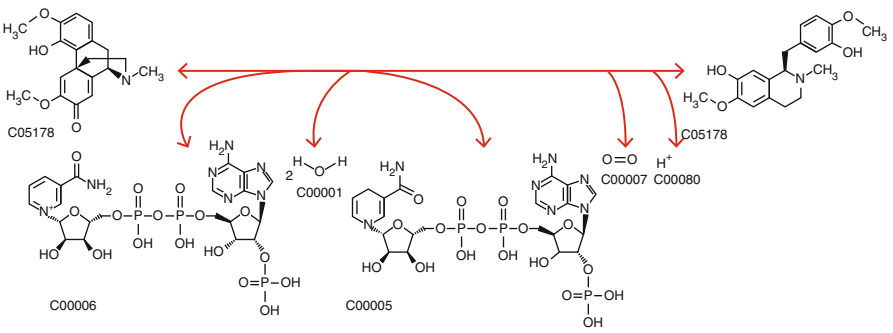
KEGG reaction entry	R04695
Name	(R)-reticuline:NADP + oxidoreductase
Definition	(R)-reticuline + NADP + <= > 1,2-dehydroreticuline + NADPH
Equation	C05178 + C00006 < = > C06167 + C00005

(*continued*)

Table 15.2 (continued)



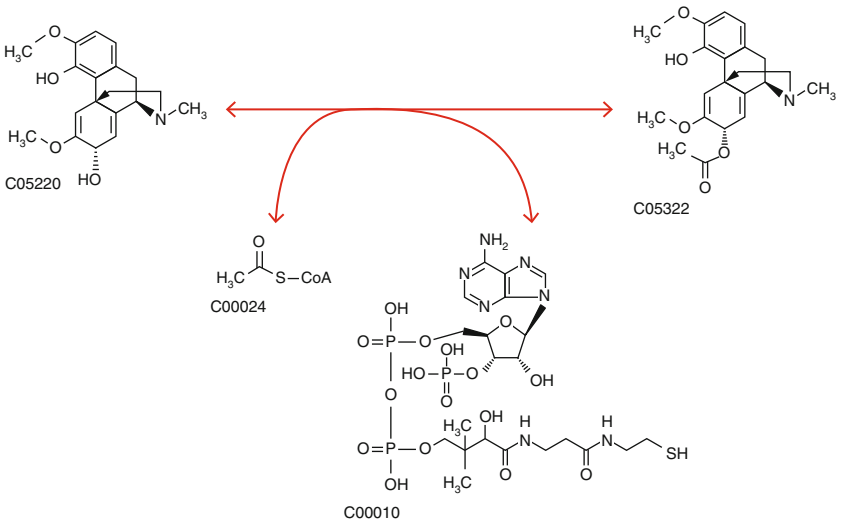
Enzyme	1.5.1.27; 1,2-dehydroreticulinium reductase (NADPH); 1,2-dehydroreticulinium ion reductase
Pathway	Isoquinoline alkaloid biosynthesis
KEGG reaction entry	R04696
Name	(R)-reticuline, NADPH:oxygen oxidoreductase (C-C phenol-coupling)
Definition	Salutaridine + NADP+ + 2 H2O < = > (R)-reticuline + NADPH + oxygen + H+
Equation	C05179 + C00006 + 2 C00001 < = > C05178 + C00005 + C00007 + C00080



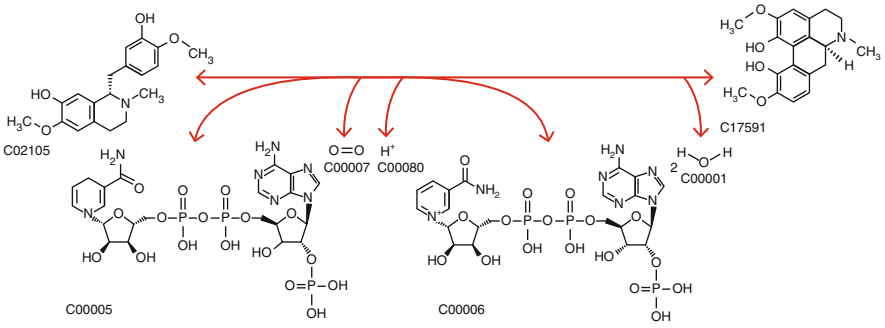
Enzyme	1.14.21.4; salutaridine synthase; (R)-reticuline oxidase (C-C phenol-coupling) (oxidoreductases)
Pathway	Isoquinoline alkaloid biosynthesis
Orthology	Cytochrome P450, family 719, subfamily B, polypeptide 1 (salutaridine synthase) [EC:1.14.21.4] (K13391)
KEGG reaction entry	R04723
Name	Acetyl-CoA:salutaridinol 7-*O*-acetyltransferase
Definition	Acetyl-CoA + 5,6,8,14-Tetradehydro-3,6-dimethoxy-17-methyl-morphinan-4,7-diol < = > CoA + 7-*O*-acetylsalutaridinol
Equation	C00024 + C05220 < = > C00010 + C05322

(*continued*)

Table 15.2 (continued)



Enzyme	2.3.1.150; Salutaridinol 7-*O*-acetyltransferase; class: transferases; acyltransferases
Pathway	Isoquinoline alkaloid biosynthesis
Orthology	Salutaridinol 7-*O*-acetyltransferase [EC:2.3.1.150] (K13393)
Enzyme	Spontaneous (following salutaridinol 7-*O*-acetyltransferase [2.3.1.150] reaction)
Pathway	Isoquinoline alkaloid biosynthesis
KEGG reaction entry	R08790
Name	(S)-reticuline,NADPH:oxygen oxidoreductase (C-C phenol-coupling)
Definition	(S)-Reticuline + NADPH + Oxygen + H + <=> (S)-Corytuberine + NADP+ + 2 H2O
Equation	C02105 + C00005 + C00007 + C00080 <=> C17591 + C00006 + 2 C00001

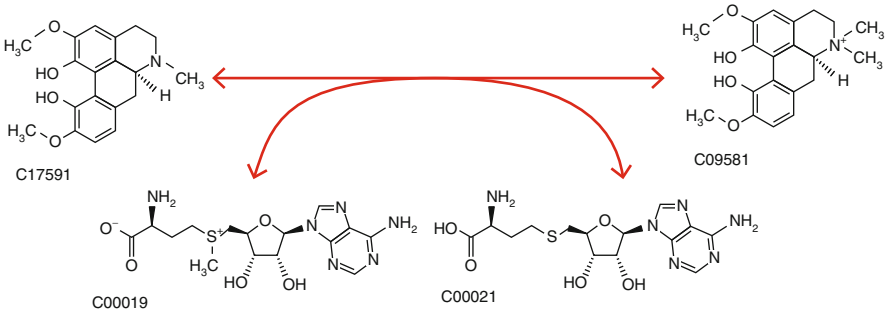


Comment	CYP80G2
Enzyme	1.14.21.-; Oxidoreductases

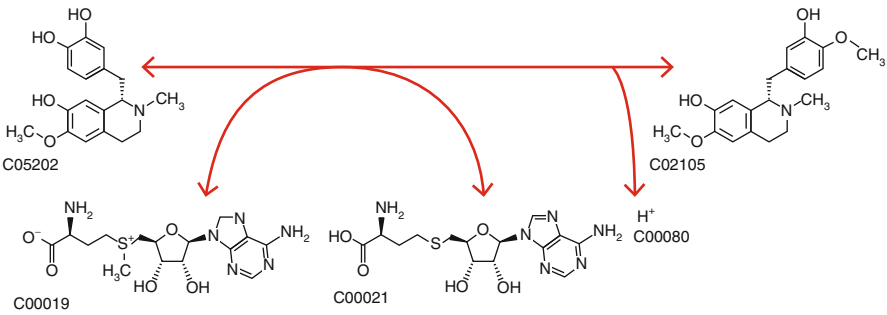
(*continued*)

Table 15.2 (continued)

Pathway	Isoquinoline alkaloid biosynthesis (rn00950)
Orthology	K13389; cytochrome P450, family 80, subfamily G, polypeptide 2 (corytuberine synthase) [EC:1.14.21.-]
KEGG reaction entry	R08791
Name	S-adenosyl-L-methionine:(S)-corytuberine N-methyltransferase
Definition	(S)-corytuberine + S-adenosyl-L-methionine < = > magnoflorine + S-adenosyl-L-homocysteine
Equation	C17591 + C00019 < = > C09581 + C00021



Comment	coclaurine *N*-methyltransferase
Enzyme	2.1.1.-
Pathway	Isoquinoline alkaloid biosynthesis (rn00950)
KEGG reaction entry	R03832
Name	S-adenosyl-L-methionine:3′-hydroxy-*N*-methyl-(S)-coclaurine 4′-O-methyltransferase
Definition	S-adenosyl-L-methionine + 3′-Hydroxy-*N*-methyl-(S)-coclaurine < = > S-adenosyl-L-homocysteine + (S)-reticuline + H+
Equation	C00019 + C05202 < = > C00021 + C02105 + C00080



Enzyme	2.1.1.116; 3′-hydroxy-*N*-methyl-(S)-coclaurine 4′-O-methyltransferase; transferases
Pathway	Isoquinoline alkaloid biosynthesis (rn00950)
Orthology	K13386; 3′-hydroxy-*N*-methyl-(S)-coclaurine 4′-O-methyltransferase [EC:2.1.1.116]

Table 15.3 The distribution of pathways in DbAlBioPath based on the number of alkaloids, enzymes, reactions, reactions with missing annotation and branching points

Pathways	Alkaloids	Total number of alkaloids	Total number of enzymes	Number of reactions	Reaction with missing annotations
Isoquinoline alkaloid biosynthesis	Dopamine, sanguinarine, morphine, laudanine, berbamunine, guatteguaumerine, 2′-norberbamunine, 10-hydroxychelerythrin, macarpine, (S)canadine, berberine, 7,8-dihydroberberine, thebaine, methopapaverberbine, macrantaline, narcotolinediol, narcotinediol, narcotoline, noscapine	19	32	>52	2

Table 15.4 Predicted orthologs of isoquinoline alkaloid biosynthesis pathway enzymes (benzylisoquinoline) in other plants

S.No.	*Plants*	E1	E2	E3	E4	E5	E6	E7	E8	E9	E10	E11	E12	E13	E14	E15
1	*Berberis stolonifera*	+		+											+	+
2	*Coptis japonica var. dissecta*	+						+	+		+					+
3	*Papaver somniferum*	+	+	+	+		+	+	+		+		+	+		+
4	*Eschscholzia californica*	+		+						+	+			+	+	+
5	*Coptis chinensis*	+														+
6	*Vitis vinifera*	+	+	+		+	+		+		+		+			+
7	*Thalictrum flavum subsp. glaucum*	+		+			+		+		+					+
8	*Catharanthus roseus*	+	+				+								+	
9	*Arabidopsis thaliana*	+	+	+		+	+		+		+		+			+
10	*Pastinaca sativa*	+														+
11	*Oryza sativa Japonica Group*	+	+	+		+	+	+	+		+		+			+
12	*Oryza sativa Indica group*	+		+		+	+	+	+		+		+			+

Note: "+" refers presence of homolog

Table 15.5 Details of enzymes detected for orthologs in other plants related to isoquinoline alkaloid biosynthesis pathway

S.No.	Enzyme code	Enzymes	Genes	Organism
1	E1	Berbamunine synthase	CYP, gfh, TT7, IMT, tht	*Berberis stolonifera*
2	E2	Salutaridinol 7-*O*-acetyltransferase	MAT, SALAT, ACT, AAT, Pun, BEAT, DAT, catf, hct, HQT, AsHHT	*Vitis vinifera*
3	E3	Reticuline oxidase	BBE, CBDAS	*Berberis stolonifera*
4	E4	Salutaridine synthase	Not reported	*Papaver somniferum*
5	E5	Tyrosine transaminase	SUR, TAT, naat, CORi	*Arabidopsis thaliana*
6	E6	Tyrosine decarboxylase	eli5, TYDC, AADC, PAAS, tyrDC	*Arabidopsis thaliana*
7	E7	(S)-norcoclaurine synthase	NCS, betv, PR10, picg	*Papaver somniferum*
8	E8	(S)-coclaurine-*N*-methyltransferase	CNMT	*Thalictrum flavum subsp. glaucum*
9	E9	(S)-stylopine synthase	Not reported	*Eschscholzia californica*
10	E10	(S)-canadine synthase	CYP, EcCYP	*Thalictrum flavum subsp. glaucum*
11	E11	Berberine reductase	Not reported	*Corydalis cava*
12	E12	Codeinone reductase	Cor, PKR, AKR	*Papaver somniferum*
13	E13	Dihydrobenzophenanthridine oxidase	Not reported	*Eschschoizia californica*
14	E14	Protopine 6-monooxygenase	Not reported	*Chelidonium majus*
15	E15	*N*-methylcoclaurine 3′-monooxygenase	CYP, IMT, Hf1	*Eschscholzia californica*

6 Intermediates of Morphine Biosynthetic Pathway

Poppies (Papaver somniferum, Papaveraceae) have long been used as medicinal plants, food plants, and drugs of abuse. Morphine alkaloids are found in many members of the genus Papaver, but codeine and morphine are only found in *P. somniferum*. Another species, Papaver bracteatum contains thebaine. Morphine alkaloids are derived from (−)- or (R)-reticuline by series of reactions involving an oxidative coupling reaction. Radioactive labelling experiments have established the series of reactions from thebaine to codeine to morphine. The most important compound from a biosynthetic

point of view is (+)-reticuline. This alkaloid is a precursor of several other groups of alkaloids. (+)- or (S)-reticuline is converted to (−)- or (R)-reticuline, which is, in turn, a major precursor of another alkaloid group. For morphinan alkaloid biosynthesis, (S)-reticuline undergoes an inversion of stereochemistry to (R)-reticuline (an isoquinoline alkaloid) catalyzed by (R,S)-reticuline 7-*O*-methyltransferase (OMT), a member of the short-chain dehydrogenase/reductase (SDR) protein family. (S)-reticuline formed in the poppy plant is converted by means of 1,2-dehydroreticuline to (R)-reticuline, which in turn is then transformed into morphine. cDNAs have been isolated for all of the enzymes leading to (S)-reticuline, as well as those involved in the conversion of (R)-reticuline to salutaridine-7-*O*-acetate. Recently, the short-chain dehydrogenase/reductase (SDR) implicated in morphine biosynthesis was cloned from Papaver somniferum. The biosynthetic pathways and the participating enzymes or cDNAs are characterized only for a few selected members, whereas the biosynthesis of the majority of the compounds is still largely unknown [18].

The benzylisoquinoline alkaloids (BIA) comprise a large and diverse group of nitrogen-containing secondary metabolites with about 2,500 compounds identified in plants. BIA biosynthesis begins with the condensation of the tyrosine-derived precursors dopamine and *p*-hydroxyphenylacetaldehyde to (S)-norcoclaurine. Subsequent regiospecific *O*- and *N*-methylations and aromatic ring hydroxylation lead to (S)-reticuline, which is the central intermediate for almost all BIAs. For morphinan alkaloid biosynthesis, (S)-reticuline undergoes an inversion of stereochemistry to (R)-reticuline, followed by C-C phenol coupling catalyzed by a unique cytochrome P450-dependent monooxygenase to yield salutaridine. The cDNA sequence of enzymes leading to (S)-reticuline, as well as those involved in the conversion of (R)-reticuline to salutaridine-7-*O*-acetate is already characterized. The inversion of (S)-reticuline to (R)-reticuline represent the important steps in morphine biosynthesis. Wound induced transcript accumulation in Papaver reveals a novel wound inducible EST (NCBI DbEST: GO238757) showing homology with (R,S)-reticuline 7-*O*-methyltransferase (ID:Q6WUC2) isolated from Papaver somniferum. Researchers compared the substrate binding homology of this novel wound inducible (R,S)-reticuline 7-*O*-methyltransferase (7-OMT) using template of P. somniferum (Q6WUC2; gb|AAQ01668) as experimental control. Homology modeling with 70 % identity and 85 % similarity with the catalytic site of template protein, i.e., (Q6WUC2) short-chain dehydrogenase/reductase (SDR), showed docking energy −69.9 and −75.8 kcal/mol with (S)-reticuline (CID:439653) and (R)-reticuline (CID:440586), respectively, which are comparable with experimental control binding site interaction energies. Docking of S- and R-reticuline into the active site revealed eight amino acids, namely, (F(5), E(18), W(24), C(47), F(44), P(45), C(46), and I(47), presumably responsible for the high substrate specificity of (R,S)-reticuline 7-*O*-methyltransferase.

The concept of phenolic oxidative coupling is a crucial theme in modifying the basic benzyltetrahydroisoquinoline skeleton to many other types of alkaloid. Tetrandrine and tubocurarine represent the coupling of two benzyltetrahydroisoquinoline molecules by ether bridges, but this form of coupling is perhaps less frequent than that involving carbon–carbon bonding between aromatic rings. The principal opium alkaloids **morphine**, **codeine**, and **thebaine** are derived from this

type of coupling, though the subsequent reduction of one aromatic ring to some extent disguises their benzyltetrahydroisoquinoline origins. (*R*)-**Reticuline** is firmly established as the precursor of these morphinan alkaloids. (*R*)-Reticuline is the substrate for one-electron oxidations via the phenol group in each ring, giving the diradical. Coupling *ortho* to the phenol group in the tetrahydroisoquinoline, and *para* to the phenol in the benzyl substituent, then yields the dienone **salutaridine**, found as a minor alkaloid constituent in the opium poppy *Papaver somniferum* (Papaveraceae). The alkaloid **thebaine** is obtained by way of **salutaridinol**, formed from salutaridine by stereospecific reduction of the carbonyl group. Ring closure to form the ether linkage in thebaine would be the result of nucleophilic attack of the phenol group on to the dienol system and subsequent displacement of the hydroxyl. This cyclization step can be demonstrated chemically by treatment of salutaridinol with acid. Subsequent reactions involve conversion of thebaine into **morphine** by way of **codeine**, a process which modifies the oxidation state of the diene ring, but most significantly removes two *O*-methyl groups. One is present as an enol ether, removal generating **neopinone**, which gives **codeinone** and then codeine by allylic isomerization and reduction, respectively. The last step, demethylation of the phenol ether codeine to the phenol morphine, is the type of reaction only achievable in the laboratory by the use of powerful and reactive demethylating agents, e.g., HBr or BBr3. Because of the other functional groups present, chemical conversion of codeine into morphine is not usually a satisfactory process. However, the enzyme-mediated conversion in *P. somniferum* proceeds smoothly and efficiently. The enzymic demethylations of both the enol ether and the phenol ether probably involve initial hydroxylation followed by the loss of the methyl groups as formaldehyde.

The involvement of these *O*-demethylation reactions is rather unusual; secondary metabolic pathways tend to increase the complexity of the product by adding methyls rather than removing them. In this pathway, it is convenient to view the methyl groups in reticuline as protecting groups, which reduce the possible coupling modes available during the oxidative coupling process, and these groups are then removed towards the end of the synthetic sequence. There is also some evidence that the later stages of the pathway are modified in some strains of opium poppy. In such strains, thebaine is converted by way of **oripavine** and **morphinone**, this pathway removing the phenolic *O*-methyl before that of the enol ether, i.e., carrying out the same steps but in a different order. The enzymic transformation of thebaine into morphine and the conversion of (*R*)-reticuline into salutaridinol have also been observed in mammalian tissues, giving strong evidence that the trace amounts of morphine and related alkaloids which can sometimes be found in mammals are actually of endogenous origin rather than dietary. Detection of substrate binding motifs for morphine biosynthetic pathway intermediates has been done by Sonal Mishra et al. [19].

A minor constituent of *P. somniferum* is the aporphine alkaloid **isoboldine**. Other species of poppy, e.g., *Papaver orientale* and *P. pseudoorientale*, are known to synthesize aporphine alkaloids as principal constituents rather than morphinan structures. (*S*)-Isoboldine is readily appreciated to be the product of oxidative coupling of (*S*)-**reticuline**, coupling *ortho* to the phenol group in the tetrahydroisoquinoline and *para* to the phenol of the benzyl substituent. Some

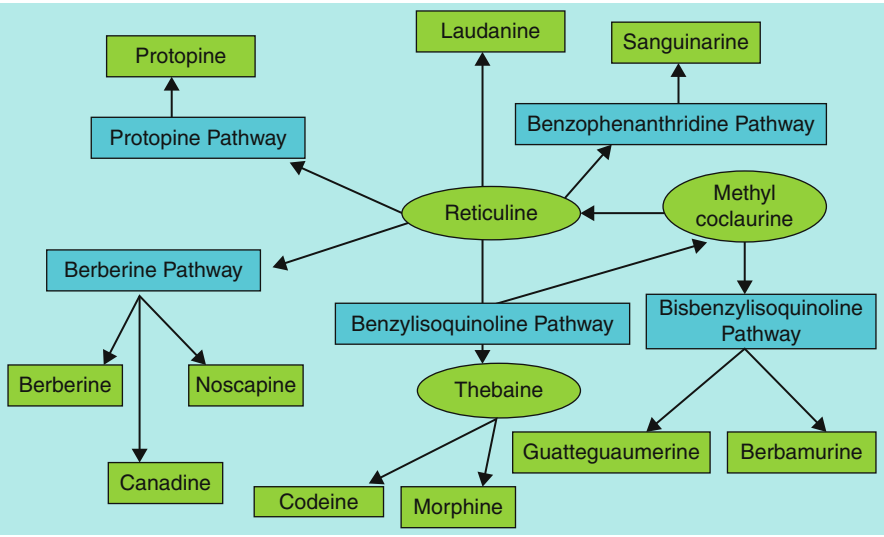


Fig. 15.4 Flowchart representing the branching points and links to different pathways in isoquinoline biosynthesis pathways

structures, e.g., **isothebaine** from *P. orientale*, are not as easily rationalized. (*S*)-**Orientaline** is a precursor of isothebaine (Fig. 15.4). This benzyltetrahydroisoquinoline, with a different methylation pattern to reticuline, is able to participate in oxidative coupling, but inspection of the structures indicates a phenol group is lost in the transformation. The pathway involves an unexpected rearrangement process, however. Thus, oxidative coupling *ortho–para* to the phenol groups gives a dienone **orientalinone** (compare the structure of salutaridine). After reduction of the carbonyl group, a rearrangement occurs, restoring aromaticity and expelling the hydroxyl (originally a phenol group) to produce **isothebaine**. This type of rearrangement, for which good chemical analogies are available, is a feature of many other alkaloid biosynthetic pathways and occurs because normal keto–enol tautomerism is not possible for rearomatization when coupling involves positions already substituted. The process is fully borne out by experimental evidence, including the subsequent isolation of orientalinone and orientalinol from *P. orientale*.

Stephanine from *Stephania* species (Menispermaceae) is analogous to isothebaine and shares a similar pathway, though from (*R*)-**orientaline**. The different substitution pattern in stephanine compared to isothebaine is a consequence of the intermediate dienol suffering migration of the alkyl rather than aryl group. **Aristolochic acid** is a novel modified aporphine containing a nitro group and is produced from stephanine by oxidative reactions leading to ring cleavage. Aristolochic acid is present in many species of *Aristolochia* (Aristolochiaceae) used in traditional medicine, e.g., snake root *A. serpentina*. However, because aristolochic acid is now known to be nephrotoxic and to cause acute kidney failure, the use of *Aristolochia* species in herbal medicines, especially Chinese remedies, has been banned in several countries.

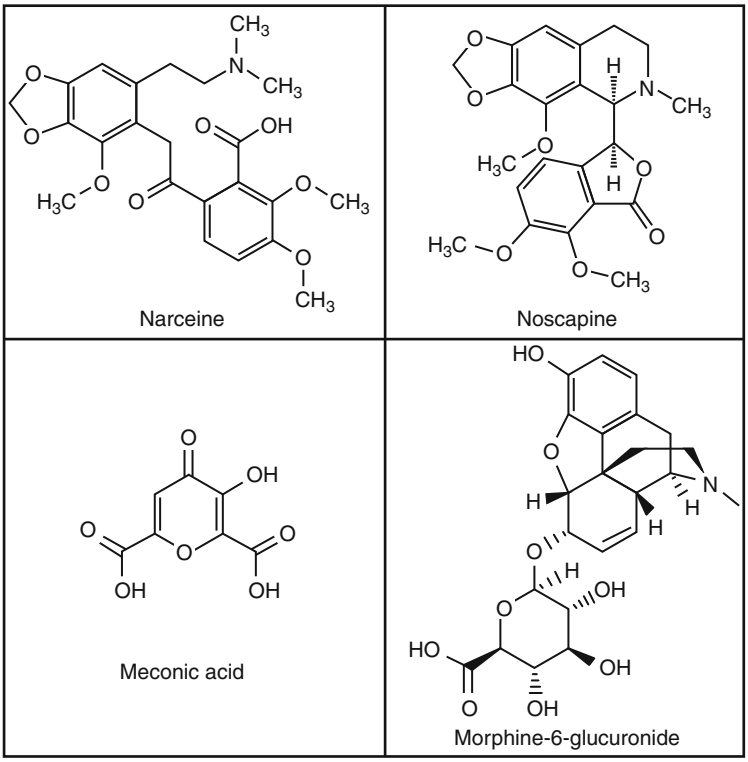


Fig. 15.5 Chemical structure of opium alkaloids

The alkaloid **berberine** is found in many members of the Berberidaceae (e.g., *Berberis*, *Mahonia*), the Ranunculaceae (e.g., *Hydrastis*), and other families. Berberine has antiamoebic, antibacterial, and antiinflammatory properties, and plants containing berberine have long been used in traditional medicine. Its tetracyclic skeleton is derived from a benzyltetrahydroisoquinoline system with the incorporation of an extra carbon atom, supplied from *S*-adenosylmethionine via an *N*-methyl group. This extraskeletal carbon is known as a "berberine bridge." Formation of the berberine bridge is readily rationalized as an oxidative process in which the *N*-methyl group is oxidized to an iminium ion, and a cyclization to the aromatic ring occurs by virtue of the phenolic group.

The oxidative cyclization process is analogous to the formation of a methylenedioxy group, while the mechanism of cyclization is exactly the same as that invoked in the formation of a tetrahydroisoquinoline ring, i.e., a Mannich-like reaction. The product from the enzymic transformation of (*S*)-**reticuline** is the protoberberine alkaloid (*S*)-**scoulerine**, the berberine bridge enzyme requiring molecular oxygen as oxidant and releasing H_2O_2 as by-product. Its role in the cyclization reaction completed, the phenol group in scoulerine is then methylated,

and **tetrahydrocolumbamine** is oxidized further to give the quaternary isoquinoline system in **columbamine**. This appears to involve two separate oxidation steps, both requiring molecular oxygen, though H_2O_2 and H_2O are produced in the successive processes. The mechanistic sequence through an iminium ion has been suggested to account for these observations. Finally, **berberine** is produced by transformation of the *ortho*-methoxyphenol to a methylenedioxy group, via the O^2-, NADPH-, and cytochrome P450-dependent enzyme. The protoberberine skeleton of scoulerine may be subjected to further modifications. Cleavage of the heterocyclic ring systems adjacent to the nitrogen atom as shown give rise to new skeletal types: protopine, e.g., **protopine** from *Chelidonium majus* (Papaveraceae); phthalideisoquinoline, e.g., **hydrastine** from *Hydrastis canadensis* (Ranunculaceae); and benzophenanthridine, e.g., **chelidonine**, also from *Chelidonium majus*. The non-heterocyclic system seen in the opium alkaloid **narceine** from *Papaver somniferum* can be visualized as the result of cleavage of two of these bonds (Fig. 15.5). Some alkaloids of the phthalide type are medicinally important. **Noscapine** is one of the opium alkaloids, and although it lacks any analgesic activity, it is an effective cough suppressant (Fig. 15.5). **Hydrastine** is beneficial as a traditional remedy in the control of uterine bleeding. *Hydrastis* also contains berberine, indicating the close biosynthetic relationship of the two types of alkaloid. **Bicuculline** from species of *Corydalis* and *Dicentra* (Fumariaceae) and its quaternary methiodide have been identified as potent GABA (γ-aminobutyric acid) antagonists and have found widespread application as pharmacological probes for convulsants acting at GABA neuroreceptors. Figure 15.4 represents the branching points and links to different pathways in isoquinoline biosynthesis pathways.

6.1 The Opium Alkaloids

More than 12,000 alkaloids are known in plants, mostly used as medicine with a world market value of about 4 billion US$. Opium poppy, *Papaver somniferum*, is the most important economic source of morphinane alkaloids such as morphine, codeine, thebaine, narcotine, and papaverine that are exploited by the pharmaceutical industry as analgesics, antitussives, and antispasmodics. Opium is the air-dried milky exudates, or latex, obtained by incising the unripe capsules of the opium poppy *Papaver somniferum* (Papaveraceae). The plant is an annual herb with large solitary flowers, of white, pink, or dull red-purple color. For opium production, the ripening capsules, which are just changing color from blue-green to yellow, are carefully incised with a knife to open the latex tubes, but not to cut through to the interior of the capsule. These latex tubes open into one another, so it is not necessary to incise them all. Cuts are made transversely or longitudinally according to custom. The initially white milky latex quickly oozes out but rapidly turns brown and coagulates. This material, the raw opium, is then removed early the following morning, being scraped off and moulded into balls or blocks. Typically, these are wrapped in poppy leaves and shade-dried. The blocks may be dusted with various plant materials to prevent cohering. Fresh opium is pale to dark brown and plastic,

but it becomes hard and brittle when stored. Crude opium has been used as an analgesic and sleep inducer (narcotic) and for the treatment of coughs. Opium has traditionally been smoked for pleasure, but habitual use develops a craving for the drug followed by addiction. An unpleasant abstinence syndrome is experienced if the drug is withdrawn [20].

The six opium alkaloids which occur naturally in the largest amounts are morphine, narcotine, codeine, thebaine, papaverine, and narceine. Of these, three are phenanthrene alkaloids and are under international control; these are morphine, codeine, and thebaine. They are all three used in the drug industry, thebaine usually for conversion into some derivative which is more useful medically. Of the other three, not under international control, narcotine and narceine have scarcely any medical or other uses. Consequently, the four economically significant alkaloids of opium are morphine, codeine, thebaine, and papaverine. About twenty other alkaloids exist in opium, but they have little or no significance medically or economically up to the present time. The relative proportions of the different alkaloids vary greatly, however, in different kinds of opium and certainly also in different varieties of the poppy. All varieties, however, belong to one species of poppy, *P. somniferum*. Figure 15.6 represents the biosynthesis of opium alkaloids.

In modern medicine, only the purified opium alkaloids and their derivatives are commonly employed. Although the ripe poppy capsule can contain up to 0.5 % total alkaloids, opium represents a much concentrated form and up to 25 % of its mass is composed of alkaloids. Of the many (>40) alkaloids identified, some six represent almost all of the total alkaloid content. Actual amounts vary widely, e.g., morphine (4–21 %), codeine (0.8–2.5 %), thebaine (0.5–2.0 %), papaverine (0.5–2.5 %), noscapine (narcotine) (4–8 %), and narceine (0.1–2 %). A typical commercial sample of opium would probably have a morphine content of about 12 %. Powdered opium is standardized to contain 10 % of anhydrous morphine, usually by dilution with an approved diluent, e.g., lactose or cocoa husk powder. The alkaloids are largely combined in salt form with meconic acid, opium containing some 3–5 % of this material. Meconic acid is invariably found in opium but, apart from its presence in other Papaver species, has not been detected elsewhere. It gives a deep red-colored complex with ferric chloride, and this has thus been used as a rapid and reasonably specific test for opium. Of the main opium alkaloids, only morphine and narceine display acidic properties, as well as the basic properties due to the tertiary amine. Narceine has a carboxylic acid function, while morphine is acidic due to its phenolic hydroxyl. This acidity can be exploited for the preferential extraction of these alkaloids (principally morphine) from an organic solvent by partitioning with aqueous base (Table 15.6).

6.1.1 Morphine

Morphine is the main alkaloid of opium both in amount and in medical importance (UNODC-Bulletin on Narcotics). The expression of the morphine content of opium as a percentage depends in part on the moisture content. When the government

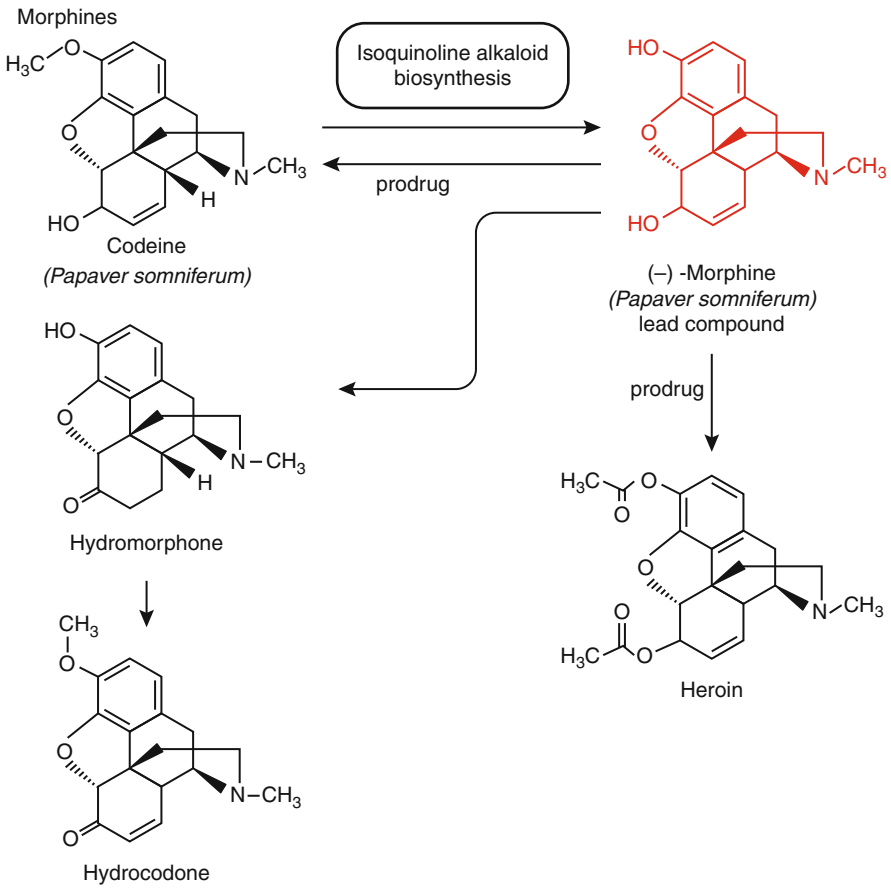


Fig. 15.6 Biosynthesis of opium alkaloids

purchases the opium as soon as practicable after it is collected, the moisture content is then usually about 30 percent (%). Commercial opium usually has around 15–10 % moisture. Opium apparently dry at ordinary temperatures still retains considerable moisture, usually about 6 % which can be driven off at about 103° centigrade. Normal, unadulterated opium of any type, in the air-dry condition, usually has between 8 and 19 % of morphine. The principal commercial opiums generally have approximately the following morphine contents: Yugoslavia 15 %, Turkey 13 %, Iran 11 %, and India 11 %. The quantity of morphine produced by poppy plants in the form of opium depends on two factors: the percentage of morphine in the opium and the quantity of opium produced. The latter factor in turn depends in part on whether each capsule is bled several times, or once only. In Turkey, Yugoslavia, Greece, and Bulgaria, it is customary to bleed each capsule only once, but in most other opium-producing

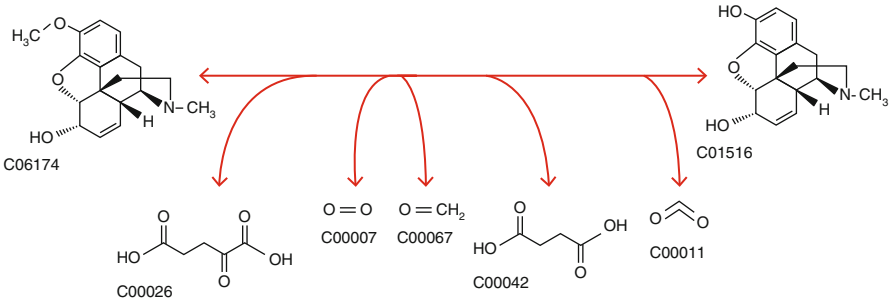
Table 15.6 Representation of chemical category and component of opium alkaloids

Chemical category	Opium components
Alkaloids	16-Hydroxythebaine, berberine, canadine, codamine, coptisine, coreximine, cycloartenol, cycloartenone, cyclolaudenol, dehydroreticuline, dihydrosanguinarine, glaucine, isoboldine, isocorypalmine, laudanidine, magnoflorine, narceine, narceinone, norlaudanosoline, norsanguinarine, oripavine, oxysanguinarine, palaudine, papaverrubine B (*O*-methyl-porphyroxine), papaverrubine C (epiporphyroxine), reticuline, salutaridine (sinoacutine), sanguinarine, scoulerine, somniferine, stepholidine
Morphine group (phenanthrenes, opioids)	Codeine, morphine, narcotoline, neopine, perparin, papaverrubine D (porphyroxine), pseudocodeine, pseudomorphine, thebaine
Isoquinolines	Cotarnine, eupaverine, hydrocotarnine, laudanosine, laudanine, noscapine (narcotine), papaverine, papaveraldine, xanthaline
Protopine group	α-Allocryptopine, α-fagarine, corycavamine, corycavine, cryptopine, protopine
Tetrahydroprotoberberine group	Corydaline, corybulbine, isocorybulbine, capaurine
Aporphine group	Dicentrine, glaucine, corytuberine, cularine, corydine, isocorydine, bulbocapnine
Phtalide-isoquinolines	Adulmine, bicuculline, bicucine, corlumine
α-Naphthaphenanthridines	Chelidonine, β-homochelidonoine, chelerythrine, sanguinarine
Other components	Meconic acid

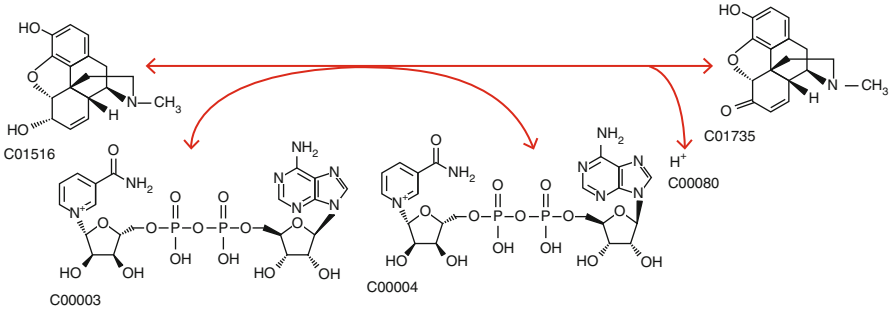
countries, the capsules are incised repeatedly, often four or five times on different days, until they will yield no more latex.

The quantity of latex falls off rapidly with later incisions, and so does the morphine content, as was shown by Annett in India (1). Usually, all the opium so obtained is mixed together. This is probably the chief reason for the lower morphine content of Iranian and Indian opiums as compared with Turkish and Yugoslav opiums, although it must also be recognized that there are low-yielding and high-yielding strains of the poppy, one or the other of which may predominate in a given district. Samples of opium assaying some 15 % morphine from Japan, Indochina, and Afghanistan, as well as from Turkey, Greece, and Yugoslavia, have been examined by the Secretariat. Afghanistan at one time exported two grades of opium, one of about 15 % morphine and the other about 10 %. The morphine content of dry capsule-chaff is about 0.25–0.5 % when not washed out by rain. Here again there are low-yielding and high-yielding varieties, but proper agricultural selection of poppies for morphine production means taking into account not only the percentage yield of morphine but also the total weight of the capsule-chaff produced per hectare, the poppy seed production per hectare, and other factors. Morphine is used to manufacture apomorphine (not subject to the conventions), codeine, ethylmorphine, beta-4-morpholinylethylmorphine, benzylmorphine, diacetylmorphine, dihydromorphine, hydromorphone (dihydromorphinone), metopon, morphine-*N*-oxide, desomorphine (dihydrodesoxymorphine), and *N*-allyl-normorphine.

KEGG reaction entry	R09402
Name	Codeine, 2-oxoglutarate:oxygen oxidoreductase (3-*O*-demethylating)
Definition	Codeine + 2-oxoglutarate + oxygen < = > morphine + formaldehyde + succinate + CO2
Equation	C06174 + C00026 + C00007 < = > C01516 + C00067 + C00042 + C00011



Enzyme	1.14.11.32; codeine 3-*O*-demethylase; codeine *O*-demethylase; CODM; oxidoreductases; codeine,2-oxoglutarate:oxygen oxidoreductase (3-*O*-demethylating)
Pathway	Isoquinoline alkaloid biosynthesis (rn00950)
KEGG reaction Entry	R03591
Name	Morphine: NAD + 6-oxidoreductase
Definition	Morphine + NAD + < = > morphinone + NADH + H+
Equation	C01516 + C00003 < = > C01735 + C00004 + C00080



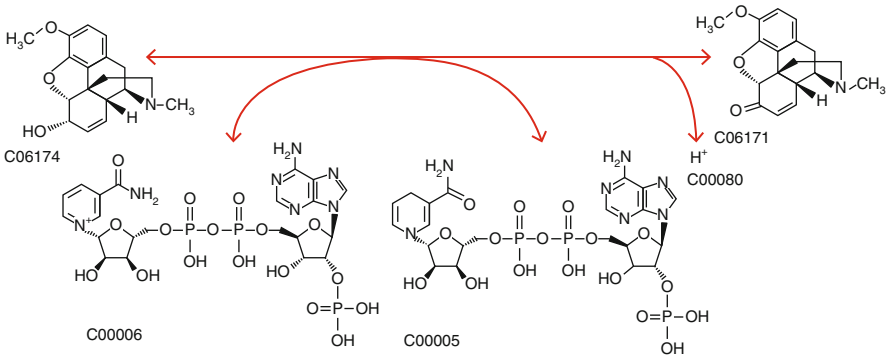
Enzyme	1.1.1.218; Morphine 6-dehydrogenase; naloxone reductase; reductase, naloxone; oxidoreductases
Pathway	Isoquinoline alkaloid biosynthesis (rn00950)

6.1.2 Codeine

The codeine content of opium is related inversely to the morphine content but only in a general way. The codeine content is closely related to the type of opium produced in a given district or even in some cases in an entire country. The opiums of the principal exporting countries have approximately the following percentages

of codeine: Yugoslavia 1.25 %, Turkey 1.25 %, Iran 3.4 %, and India 3.0 %. The manufacturer's statistics do not ordinarily show all the codeine obtained from opium. Some of its coprecipitates with the morphine, and there is no necessity of purifying the morphine completely on its codeine content, especially if it is to be used to manufacture more codeine. Codeine is used to manufacture dihydrocodeine and acetyldihydrocodeine and may also be used to manufacture the drugs ordinarily made by conversion of thebaine.

KEGG reaction entry	R05124
Name	Codeine: NADP + oxidoreductase
Definition	Codeine + NADP + < = > codeinone + NADPH + H+
Equation	C06174 + C00006 < = > C06171 + C00005 + C00080

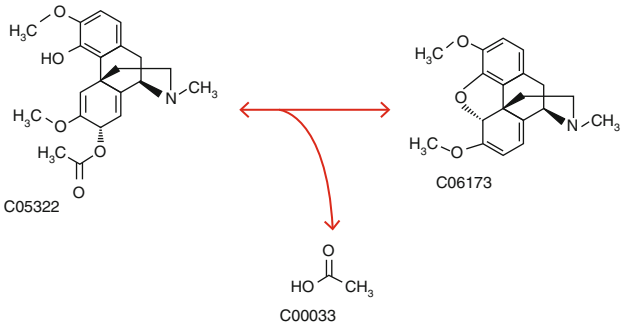


Enzyme	1.1.1.247; Codeinone reductase (NADPH); oxidoreductases; codeine-NADP + oxidoreductase
Pathway	Isoquinoline alkaloid biosynthesis (rn00950)

6.1.3 Thebaine

The Secretariat is currently engaged in a survey, the most extensive ever attempted in this field, of opium samples from different regions for their thebaine and papaverine percentages. As yet, it is premature for general conclusions. However, the highest thebaine percentages found (nearly 5 %) were in some samples from Indochina, which at the same time had virtually no papaverine. Both thebaine and papaverine have been higher in the most Iranian samples run. Papaverine is low in some Afghan and Indian opiums. Thebaine is the most poisonous opium alkaloid and is scarcely used medically. It is even omitted from some of the preparations of mixed opium alkaloids which are used as soluble substitutes for opium. However, it is converted into several other narcotics which have medical use: hydrocodone (dihydrocodeinone), acetyldihydrocodeinone, and oxycodone (dihydrohydroxy-codeinone). Papaverine has a considerable medical use, so much so that supplies available from opium have sometimes run short. It is then manufactured synthetically.

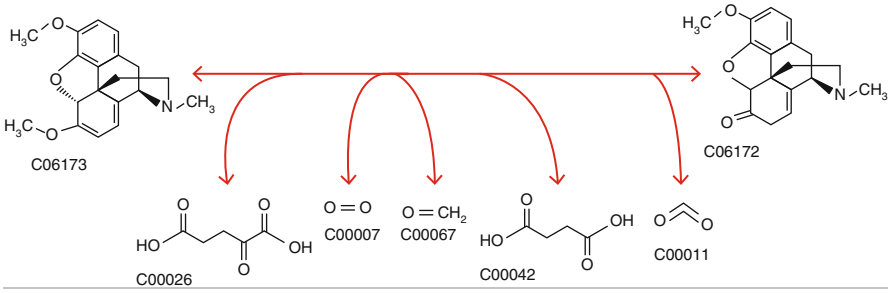
KEGG reaction entry	R04769
Definition	7-*O*-Acetylsalutaridinol < = > thebaine + acetate
Equation	C05322 < = > C06173 + C00033



Enzyme	Spontaneous (following salutaridinol 7-*O*-acetyltransferase [2.3.1.150] reaction)
Pathway	Isoquinoline alkaloid biosynthesis

Thebaine converted into **morphine** by way of **codeine**, a process which modifies the oxidation state of the diene ring, but most significantly removes two *O*-methyl groups. One is present as an enol ether, removal generating **neopinone**, which gives **codeinone**.

KEGG reaction entry	R05126
Name	Thebaine,2-oxoglutarate:oxygen oxidoreductase (6-*O*-demethylating)
Definition	Thebaine + 2-oxoglutarate + oxygen < = > neopinone + formaldehyde + succinate + CO_2
Equation	C06173 + C00026 + C00007 < = > C06172 + C00067 + C00042 + C00011



Enzyme	1.14.11.31; Thebaine 6-*O*-demethylase; T6ODM; oxidoreductases; thebaine,2-oxoglutarate:oxygen oxidoreductase (6-*O*-demethylating)
Pathway	Isoquinoline alkaloid biosynthesis (rn00950), metabolic pathways (rn01100), biosynthesis of secondary metabolites (rn01110)
KEGG reaction entry	R05125

(*continued*)

Definition	Codeinone < = > neopinone
Equation	C06171 < = > C06172

C06171 C06172

Pathway	Isoquinoline alkaloid biosynthesis (rn00950)

6.2 Papaverine

Papaverine is a benzylisoquinoline alkaloid and is structurally very different from the morphine, codeine, and thebaine group of alkaloids (morphinans). It has little or no analgesic or hypnotic properties put possesses spasmolytic and vasodilator activity. It has been used in some expectorant preparations and in the treatment of gastrointestinal spasms, but its efficacy was not substantiated. It is sometimes used as an effective treatment for male impotence, being administered by direct injection to achieve an erection of the penis.

Papaverine is an opium alkaloid antispasmodic drug, used primarily in the treatment of visceral spasm, vasospasm (especially those involving the heart and the brain), and occasionally in the treatment of erectile dysfunction. While it is found in the opium poppy, papaverine differs in both structure and pharmacological action from the analgesic (morphine-related) opium alkaloids (opioids). Papaverine is approved to treat spasms of the gastrointestinal tract, bile ducts, and ureter and for use as a cerebral and coronary vasodilator in subarachnoid hemorrhage (combined with balloon angioplasty) and coronary artery bypass surgery. Papaverine may also be used as a smooth muscle relaxant in microsurgery where it is applied directly to blood vessels.

Papaverine is used as an erectile dysfunction drug. Papaverine, when injected in penile tissue, causes direct smooth muscle relaxation and consequent filling of the corpus cavernosum with blood, resulting in erection. It is also commonly used in cryopreservation of blood vessels along with the other glycosaminoglycans and protein suspensions. It functions as a vasodilator during cryopreservation when used in conjunction with verapamil, phentolamine, nifedipine, tolazoline, or nitroprusside. Papaverine is also being investigated as a topical growth factor in tissue expansion with some success.

6.2.1 Narceine

Narceine is an opium alkaloid produced by the *Papaver somniferum* (opium poppy) plant. It is a bitter, crystalline compound with narcotic effects and was formerly used as a substitute for morphine (Fig. 15.5).

6.2.2 Noscapine

Noscapine was first isolated and characterized in the chemical breakdown and properties in 1817 under the denomination of "Narcotine" by Pierre Robiquet, a French chemist in Paris. Noscapine's antitussive effects appear to be primarily mediated by its sigma receptor agonist activity. Noscapine is currently under investigation for use in the treatment of several cancers and hypoxic ischemia in stroke patients. Noscapine can survive the manufacturing processes of heroin and can be found in street heroin.

Noscapine is a member of the phthalideisoquinoline alkaloids and provides a further structural variant in the opium alkaloids. Noscapine has good antitussive and cough suppressant activity comparable to that of codeine, but no analgesic or narcotic action. Its original name "narcotine" was changed to reflect this lack of narcotic action. Despite many years of use as a cough suppressant, the finding that noscapine may have teratogenic properties (i.e., may deform a fetus) has resulted in noscapine preparations being deleted. In recent studies, antitumour activity has been noted from noscapine, which binds to tubulin as do podophyllotoxin and colchicine, thus arresting cells in mitosis. The chemotherapeutic potential of this orally effective agent merits further evaluation. Noscapine (also known as narcotine, nectodon, nospen, anarcotine, and (archaic) opiane) is a benzylisoquinoline alkaloid from plants of the Papaveraceae family, without significant painkilling properties. This agent is primarily used for its antitussive (cough-suppressing) effects. It has also been shown to have anticancer activity (Fig. 15.5).

7 Other Compounds

7.1 Meconic Acid

Meconic acid, also known as acidum meconicum and poppy acid, is a chemical substance found in certain plants of the Papaveraceae family (poppy) such as Papaver somniferum (opium poppy) and Papaver bracteatum. Meconic acid constitutes about 5 % of opium and can be used as an analytical marker for the presence of opium. Meconic acid has erroneously been described as a mild narcotic, but it has little or no physiological activity, and is not used medicinally. Meconic acid forms salts with alkaloids and metals. These salts as well as meconic acid esters are called meconates. Meconic acid was first isolated by Friedrich Sertürner in 1805 (Fig. 15.5).

7.2 Morphine-6-Glucuronide

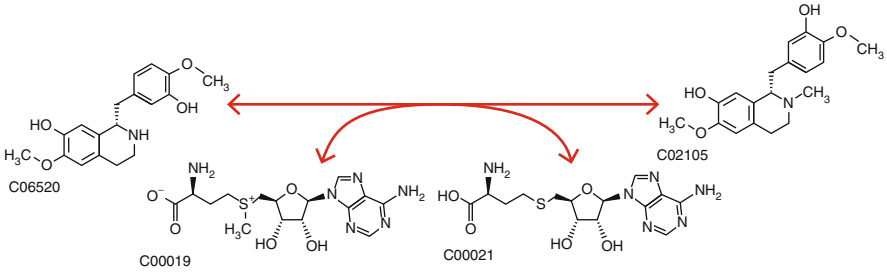
Morphine-6-glucuronide (M6G) is a major active metabolite of morphine and as such is the molecule responsible for much of the pain-relieving effects of morphine (and thus heroin). M6G is formed from morphine by the enzyme

UDP-glucuronosyltransferase-2B7 (UGT2B7). M6G can accumulate to toxic levels in kidney failure. The opioid receptor subtype 3 appears to be activated (agonized) by morphine-6β-glucuronide but not morphine itself. This finding is also true of certain heroin metabolites (6-MAM) but not morphine proper. This analgesic activity of M6G (in animals) was first noted by Yoshimura (Fig. 15.5).

7.3 Narcotoline

Narcotoline is an opiate alkaloid chemically related to noscapine. It binds to the same receptors in the brain as noscapine to act as an antitussive and has also been used in tissue culture media. It can be obtained from the opium poppy, Papaver somniferum. It is present at much higher levels in culinary strains (cultivars) of *P. somniferum* used for poppy seed production than in high-morphine pharmaceutical strains used for opium production.

KEGG reaction entry	R05211
Name	S-adenosyl-L-methionine:(RS)-1-benzyl-1,2,3,4-tetrahydroisoquinolie *N*-methyltransferase
Definition	S-adenosyl-L-methionine + (S)-norreticuline < = > S-adenosyl-L-homocysteine + (S)-reticuline
Equation	C00019 + C06520 < = > C00021 + C02105



Enzyme	2.1.1.115; (RS)-1-benzyl-1,2,3,4-tetrahydroisoquinoline *N*-methyltransferase; norreticuline *N*-methyltransferase; transferases
Pathway	Isoquinoline alkaloid biosynthesis (rn00950)

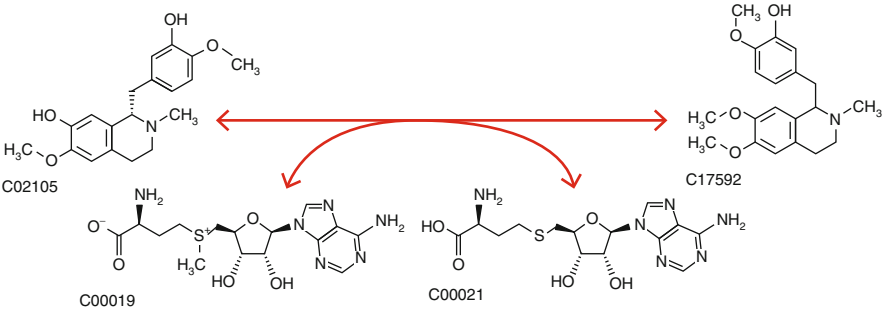
7.4 Pseudomorphine

Pseudomorphine (also known as oxydimorphine or dehydromorphine) is a natural dimerization product of the morphine molecule in tandem and thus a common impurity in morphine concentrations. It was first described by Pelletier in 1835. This compound may be synthesized by the oxidative coupling of morphine by potassium ferricyanide.

7.5 Laudanosine

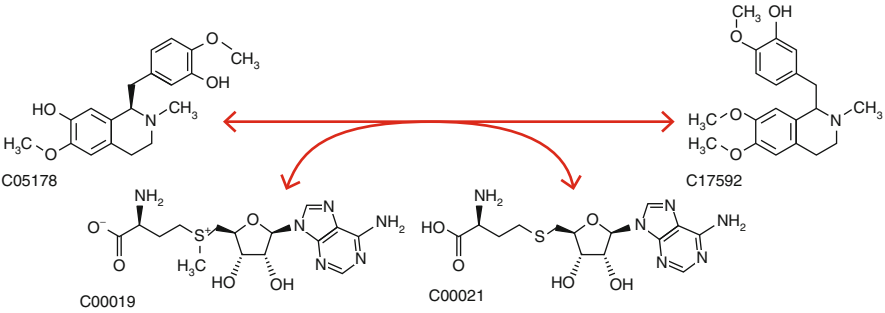
Laudanosine or *N*-methyltetrahydropapaverine is a recognized metabolite of atracurium and cisatracurium. Laudanosine decreases the seizure threshold, and thus, it can induce seizures if present at sufficient threshold concentrations; however, such concentrations are unlikely to be produced consequent to chemodegradable metabolism of clinically administered doses of cisatracurium or atracurium. Laudanosine also occurs naturally in minute amounts (0.1 %) in opium, from which it was first isolated in 1871. Partial dehydrogenation of laudanosine will lead to papaverine, the alkaloid found in the opium poppy plant (Papaver somniferum). Laudanosine is a benzyltetrahydroisoquinoline alkaloid. It has been shown to interact with GABA receptors, opioid receptors, and nicotinic acetylcholine receptors, but not benzodiazepinergic or muscarinic receptors which are also involved in epilepsy and other types of seizures.

KEGG reaction entry	R08787
Name	S-adenosyl-L-methionine:(S)-reticuline methyltransferase 7-O-methyltransferase
Definition	(S)-reticuline + S-Adenosyl-L-methionine < = > laudanine + S-adenosyl-L-homocysteine
Equation	C02105 + C00019 < = > C17592 + C00021



Comment	(R,S)-reticuline 7-*O*-methyltransferase
Enzyme	2.1.1.-
Pathway	Isoquinoline alkaloid biosynthesis (rn00950)
Orthology	(R,S)-reticuline 7-*O*-methyltransferase [EC:2.1.1.-]
KEGG reaction entry	R08788
Name	S-adenosyl-L-methionine:(R)-reticuline methyltransferase 7-*O*-methyltransferase
Definition	(R)-reticuline + S-adenosyl-L-methionine < = > Laudanine + S-adenosyl-L-homocysteine
Equation	C05178 + C00019 < = > C17592 + C00021

(*continued*)



Comment	(R,S)-reticuline 7-*O*-methyltransferase
Enzyme	2.1.1.-
Pathway	Isoquinoline alkaloid biosynthesis (rn00950)
Orthology	(R,S)-reticuline 7-*O*-methyltransferase [EC:2.1.1.-]

7.6 Berberine

Berberine is a quaternary ammonium salt from the protoberberine group of isoquinoline alkaloids. It is found in such plants as Berberis (e.g., Berberis aquifolium (Oregon grape), Berberis vulgaris(Barberry), and Berberis aristata (Tree Turmeric)),Hydrastis canadensis (Goldenseal), Phellodendron amurense (Amur Cork Tree, Huang Bai, Huang Po, Po Mu) and Coptis chinensis (Chinese Goldthread, Huang-Lian, Huang-Lien), and Tinospora cordifolia, and to a smaller extent in Argemone mexicana (Prickly Poppy) and Eschscholzia californica (Californian Poppy). Berberine is usually found in the roots, rhizomes, stems, and bark. Berberine is strongly yellow colored, which is why in earlier times Berberis species were used to dye wool, leather, and wood. Wool is still today dyed with berberine in northern India. Under ultraviolet light, berberine shows a strong yellow fluorescence. Because of this, it is used in histology for staining heparin in mast cells. As a natural dye, berberine has a Colour Index (CI) of 75160.

As a traditional medicine or dietary supplement, berberine has shown some activity against fungal infections, Candida albicans, yeast, parasites, and bacterial/viral infections. Berberine seems to exert synergistic effects with fluconazole even in drug-resistant Candida albicans infections. Some research has been undertaken into possible use against MRSA infection. Berberine is considered antibiotic. When applied in vitro and in combination with methoxyhydnocarpin, an inhibitor of multidrug resistance pumps, berberine inhibits growth of Staphylococcus aureus and Microcystis aeruginosa, a toxic cyanobacterium. Berberine is a component of some eye drop formulations. There is some evidence it is useful in the treatment of trachoma, and it has been a standard treatment for leishmaniasis. Berberine prevents and suppresses proinflammatory cytokines, E-selectin,

and genes, and increases adiponectin expression which partly explains its versatile health effects. Berberine is a nucleic acid-binding isoquinolone alkaloid with wide potential therapeutic properties. Berberine is produced by transformation of the *ortho*-methoxyphenol to a methylenedioxy group, via the O_2^-, $NADPH^-$, and cytochrome P450-dependent enzyme.

7.7 Sanguinarine

Sanguinarine is a quaternary ammonium salt from the group of benzylisoquinoline alkaloids. It is extracted from some plants, including bloodroot (Sanguinaria canadensis), Mexican prickly poppy Argemone mexicana, Chelidonium majus and Macleaya cordata. It is also found in the root, stem and leaves of the opium poppy but not in the capsule. Sanguinarine is a toxin that kills animal cells through its action on the Na^+-K^+ -ATPase transmembrane protein. Epidemic dropsy is a disease that results from ingesting sanguinarine. If applied to the skin, sanguinarine kills cells and may destroy tissue. In turn, the bleeding wound may produce a massive scab, called an eschar. For this reason, sanguinarine is termed an escharotic. In plants, sanguinarine is synthesized from dihydrosanguinarine through the action of dihydrobenzophenanthridine oxidase (EC 1.5.3.12).

7.8 Coptisine

Coptisine is an alkaloid found in Chinese goldthread (Coptis chinensis). Famous for the bitter taste that it produces, it is used in Chinese herbal medicine along with the related compound berberine for treating digestive disorders caused by bacterial infections. It is also found in Greater Celandine and has also been detected in opium. Coptisine has been found to reversibly inhibit Monoamine oxidase A in mice, pointing to a potential role as a natural antidepressant. However, this may also imply a hazard for those taking other medications or with a natural functional disorder in Monoamine oxidase A. Coptisine was found to be toxic to larval brine shrimp and a variety of human cell lines, potentially implying a therapeutic effect on cancer or alternatively a generally toxic character. The same authors illustrate a four-step process to produce Coptisine from Berberine.

7.9 Cycloartenol

Cycloartenol is an important type of stanol found in plants. The biosynthesis of cycloartenol starts from the triterpenoid squalene. It is the first precursor in the biosynthesis of other stanols and sterols, referred to as phytostanols and phytosterols in photosynthetic organisms and plants. The identities and distribution of phytostanols and phytosterols is characteristic of a plant species. One notable product of cycloartenol biosynthesis is the triterpenoid lanosterol.

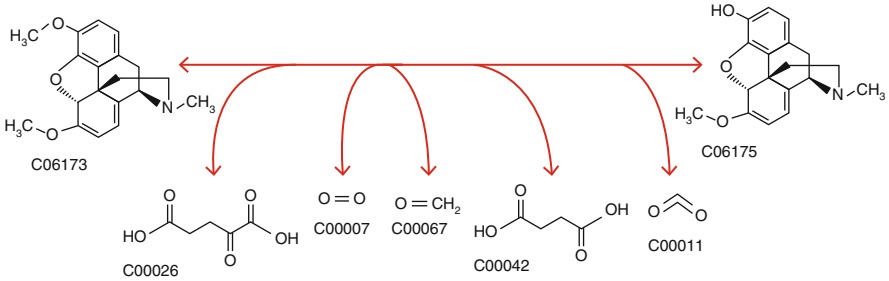
7.10 Glaucine

Glaucine is an alkaloid found in several different plant species such as Glaucium flavum, Glaucium oxylobum, Croton lechleri and Corydalis yanhusuo. It has bronchodilator and antiinflammatory effects, acting as a PDE4 inhibitor and calcium channel blocker, and is used medically as an antitussive in some countries. Glaucine may produce side effects such as sedation, fatigue, and a hallucinogenic effect characterized by colorful visual images, and has recently been detected as a novel recreational drug.

7.11 Oripavine

Oripavine is an opiate and the major metabolite of thebaine. It is the parent compound from which a series of semisynthetic opioids are derived, which includes the compounds etorphine and buprenorphine. Although its analgesic potency is comparable to morphine, it is not used clinically due to its severe toxicity and low therapeutic index. Oripavine possesses an analgesic potency comparable to morphine; however, it is not clinically useful due to severe toxicity and low therapeutic index. In both mice and rats, toxic doses caused tonic-clonic seizures followed by death, similar to thebaine. Oripavine has a potential for dependence which is significantly greater than that of thebaine but slightly less than that of morphine.

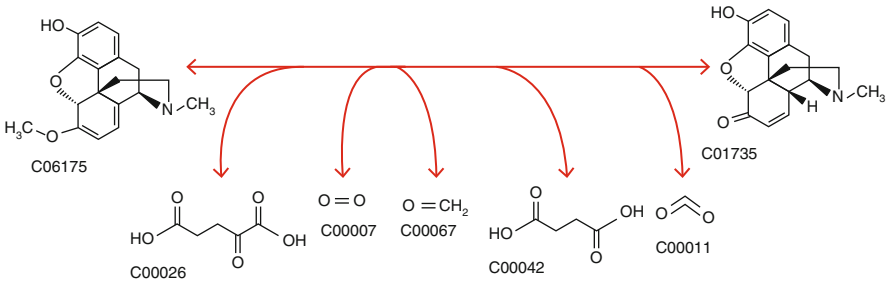
KEGG reaction entry	R05127
Name	thebaine,2-oxoglutarate:oxygen oxidoreductase (3-*O*-demethylating)
Definition	Thebaine + 2-oxoglutarate + oxygen < = > oripavine + formaldehyde + succinate + CO2
Equation	C06173 + C00026 + C00007 < = > C06175 + C00067 + C00042 + C00011



Enzyme	1.14.11.32; codeine 3-*O*-demethylase; codeine *O*-demethylase; CODM; oxidoreductases; codeine,2-oxoglutarate:oxygen oxidoreductase (3-*O*-demethylating)
Pathway	Isoquinoline alkaloid biosynthesis (rn00950)
KEGG Reaction Entry	R03698
Name	Oripavine,2-oxoglutarate:oxygen oxidoreductase (6-*O*-demethylating)
Definition	Oripavine + 2-oxoglutarate + oxygen < = > morphinone + formaldehyde + succinate + CO2

(*continued*)

Equation	C06175 + C00026 + C00007 < = > C01735 + C00067 + C00042 + C00011

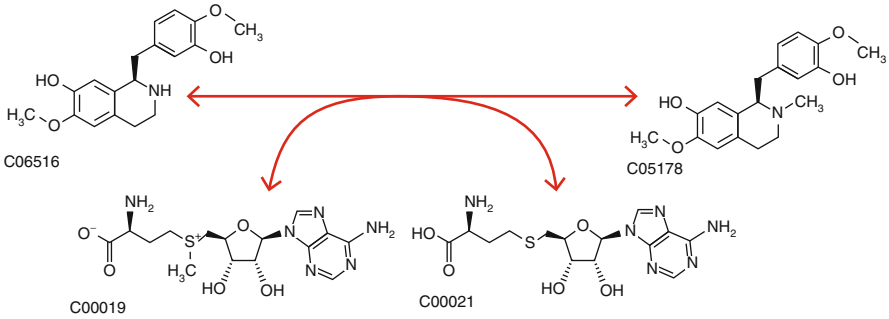


Enzyme	1.14.11.31; thebaine 6-*O*-demethylase; T6ODM; oxidoreductases
Pathway	Isoquinoline alkaloid biosynthesis (rn00950)

7.12 Reticuline

Reticuline is a chemical compound that can be found in Lindera aggregata. It is also one of the alkaloids found in opium. Metabolism showed that 3′-hydroxy-*N*-methyl-(S)-coclaurine 4′-*O*-methyltransferase uses *S*-adenosyl methionine and 3′-hydroxy-*N*-methyl-(S)-coclaurine to produce S-adenosylhomocysteine and (S)-reticuline. Reticuline oxidase uses (S)-reticuline and O_2 to produce (S)-scoulerine and H_2O_2. Salutaridine synthase uses (R)-reticuline, NADPH, H^+, and O_2 to produce salutaridine, $NADP^+$, and H_2O. 1,2-dehydroreticulinium reductase (NADPH) uses (R)-reticuline and NADP + to produce 1,2-dehydroreticulinium, NADPH, and H^+.

KEGG Reaction Entry	R05216
Name	S-adenosyl-L-methionine:(RS)-1-benzyl-1,2,3,4-tetrahydroisoquinolie *N*-methyltransferase
Definition	S-adenosyl-L-methionine + (R)-Norreticuline < = > S-adenosyl-L-homocysteine + (R)-reticuline
Equation	C00019 + C06516 < = > C00021 + C05178



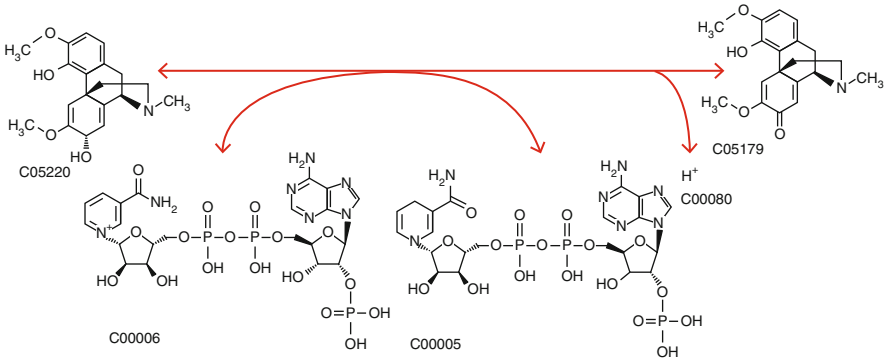
(*continued*)

Enzyme	2.1.1.115; (RS)-1-benzyl-1,2,3,4-tetrahydroisoquinoline N-methyltransferase; norreticuline N-methyltransferase; transferases
Pathway	Isoquinoline alkaloid biosynthesis (rn00950)

7.13 Salutaridine

Salutaridine is an alkaloid that is present in the morphinan alkaloid pathway of opium poppy. Its precursor is the alkaloid (R)-reticuline. (R)-reticuline is converted to salutaridine by the enzyme salutaridine synthase. Salutaridine is converted to salutaridinol by the enzyme salutaridine reductase (SalR), with the reduction of NADPH to $NADP^+$.

KEGG Reaction Entry	R04697
Name	Salutaridinol: NADP + 7-oxidoreductase
Definition	5,6,8,14-Tetradehydro-3,6-dimethoxy-17-methyl-morphinan-4,7-diol + NADP + < = > salutaridine + NADPH + H+
Equation	C05220 + C00006 < = > C05179 + C00005 + C00080



1.1.1.248; Salutaridine reductase (NADPH); oxidoreductases

Isoquinoline alkaloid biosynthesis (rn00950)

Salutaridine reductase (NADPH) [EC:1.1.1.248] (K13392)

7.14 Sanguinarine

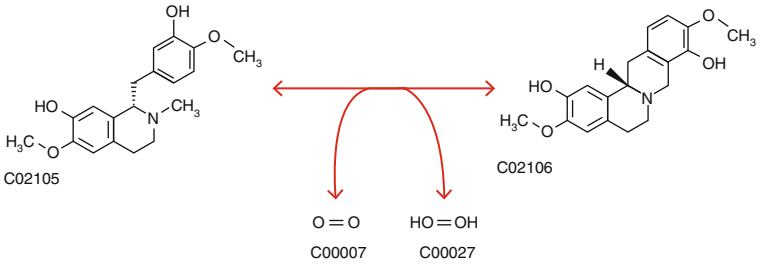
Sanguinarine is a quaternary ammonium salt from the group of benzylisoquinoline alkaloids. It is extracted from some plants, including bloodroot (Sanguinaria canadensis), Mexican prickly poppy Argemone mexicana, Chelidonium majus, and Macleaya cordata. It is also found in the root, stem, and leaves of the opium poppy but not in the capsule. Sanguinarine is a toxin that kills animal cells through its action on the Na^+-K^+-ATPase transmembrane protein. Epidemic dropsy is a disease that results from ingesting sanguinarine. If applied to the skin,

sanguinarine kills cells and may destroy tissue. In turn, the bleeding wound may produce a massive scab, called an eschar. For this reason, sanguinarine is termed an escharotic. In plants, sanguinarine is synthesized from dihydrosanguinarine through the action of Dihydrobenzophenanthridine oxidase (EC 1.5.3.12).

7.15 Scoulerine

Scoulerine, also known as discretamine and aequaline, is an alkaloid found in the opium poppy, Croton flavens, and certain plants in the Erythrina genus. Studies show that scoulerine is an antagonist at the α2-adrenoceptor, α1D-adrenoceptor, and 5-HT receptor. It has also been found to be a GABAA receptor agonist.

KEGG reaction entry	R03831
Name	(S)-reticuline:oxygen oxidoreductase (methylene-bridge-forming)
Definition	(S)-reticuline + oxygen < = > (S)-scoulerine + hydrogen peroxide
Equation	C02105 + C00007 < = > C02106 + C00027



Enzyme	1.21.3.3; Reticuline oxidase; BBE; berberine bridge enzyme; berberine-bridge-forming enzyme; tetrahydroprotoberberine synthase; oxidoreductases
Pathway	Isoquinoline alkaloid biosynthesis (rn00950)
Orthology	Reticuline oxidase [EC:1.21.3.3]

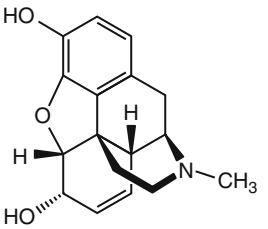
7.16 Stepholidine

(−)-Stepholidine is a naturally occurring chemical compound found in the herb Stephania intermedia. Stepholidine is a dual D2 receptor antagonist and D1 receptor agonist, and has shown antipsychotic activity in animal studies.

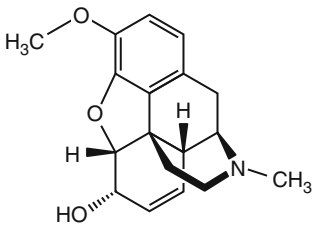
7.17 Structure and Properties of Alkaloids

The different types of alkaloids have different structures and thus have different properties. The structures and properties of alkaloids have been represented in Table 15.7 and 15.8

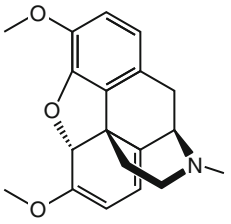
Table 15.7 Comparison of the properties of different opium alkaloids



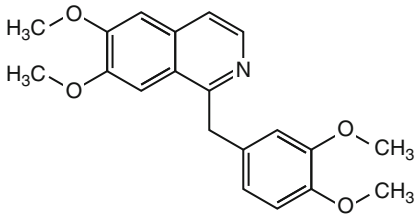
Morphine	
Bioavailability	~25 % (Oral); 100 % (IV)
Protein binding	30–40 %
Metabolism	Hepatic, 90 %
Half-life	2–3 h
Excretion	Renal 90 %, biliary 10 %
CAS number	57-27-2, 64-31-3, 52-26-6
PubChem	CID 5288826
DrugBank	DB00295
ChemSpider	4450907
KEGG	D08233
ChEBI	CHEBI:17303
ChEMBL	CHEMBL70
Formula	$C_{17}H_{19}NO_3$
Mol. mass	285.34



Codeine	
Bioavailability	~90 % Oral
Metabolism	Hepatic, via CYP2D6 (cytochrome P450 2D6)
Half-life	2.5–3 h
CAS number	76-57-3
PubChem	CID 5284371
DrugBank	APRD00120
ChemSpider	4447447
KEGG	C06174
ChEBI	CHEBI:16714
ChEMBL	CHEMBL485
Formula	$C_{18}H_{21}NO_3$
Mol. mass	299.364 g/mol



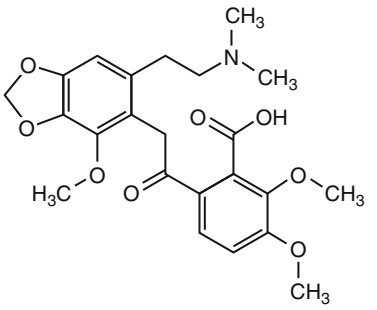
Thebaine	
CAS number	115-37-7
PubChem	5324289
ChemSpider	4481822, 4479543
KEGG	C06173
ChEBI	CHEBI:9519
ChEMBL	CHEMBL403893
Molecular formula	$C_{19}H_{21}NO_3$
Molar mass	311.37 g mol^{-1}
Metabolism	*O*-demethylation



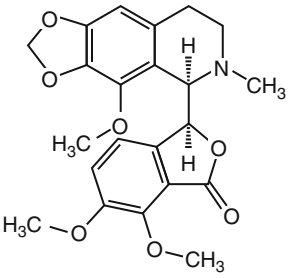
Papaverine	
Bioavailability	80 %
Protein binding	~90 %
Metabolism	Hepatic
Half-life	1.5–2 h
Excretion	Renal
CAS number	58-74-2, 61-25-6
PubChem	CID 4680
DrugBank	APRD00628
ChemSpider	4518
KEGG	D07425
ChEMBL	CHEMBL19224
Formula	$C_{20}H_{21}NO_4$
Mol. mass	339.385 g/mol

(*continued*)

Table 15.7 (continued)



Narceine	
CAS number	131-28-2
PubChem	8564
Molecular formula	$C_{23}H_{27}NO_8$
Molar mass	445.46 g mol^{-1}

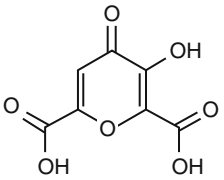


Noscapine	
Bioavailability	~30 %
Half-life	1.5 to 4 h (mean 2.5)
CAS number	128-62-1
PubChem	CID 275196
KEGG	D01036[Y]
ChEMBL	CHEMBL364713[Y]
Synonyms	Narcotine
Formula	$C_{22}H_{23}NO_7$
Mol. mass	413.421

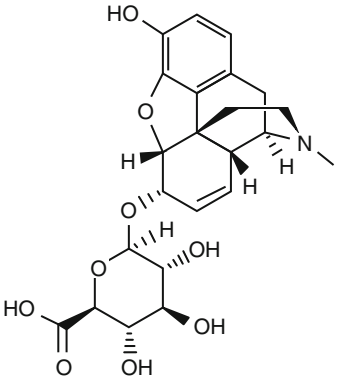
8 Use of Alkaloids in Medicine

Natural compounds, mostly from plants, have been the mainstay of traditional medicine for thousands of years [21]. They have also been the source of lead compounds for modern medicine, but the extent of mining of natural compounds for such leads decreased during the second half of the twentieth century. The advantage of natural compounds for the development of drugs derives from their innate affinity for biological receptors. Natural compounds have provided the best antimalarials known to date. Recent surveys have identified many extracts of various organisms (mostly plants) as having anti-plasmodial activity. Huge libraries of fractionated natural compounds have been screened with impressive hit rates. Importantly, many cases are known where the crude biological extract is more efficient pharmacologically than the most active purified compound from this extract. This could be due to synergism with other compounds present in the extract, which as such have no pharmacological activity. Indeed, such compounds are best screened by cell-based assay where all potential targets in the cell are probed and possible synergies identified. Traditional medicine uses crude extracts. These have often been shown to provide many concoctions that deal better with the overall disease condition than with the causative agent itself. Traditional medicines are used by ~80 % of Africans as a first response to ailment. Many of the traditional medicines have demonstrable anti-plasmodial activities. It is suggested that rigorous evaluation of traditional medicines involving controlled clinical trials in

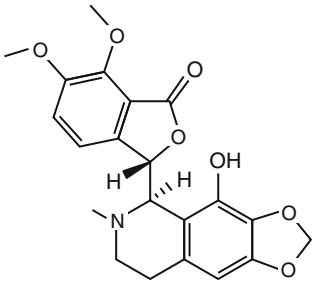
Table 15.8 Details of compounds similar to opium alkaloids



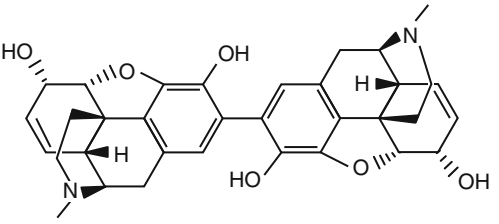
Meconic acid	
CAS number	497-59-6
PubChem	5351448
Molecular formula	$C_7H_4O_7$
Molar mass	200.10



Morphine-6-glucuronide	
CAS number	20290-10-2
PubChem	5360621
ChemSpider	4514548
ChEMBL	CHEMBL1330
Molecular formula	$C_{23}H_{27}NO_9$
Molar mass	461.46 g/mol



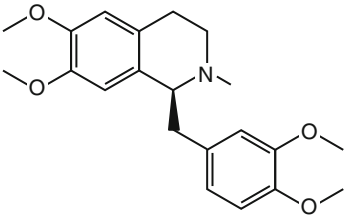
Narcotoline	
CAS number	521-40-4
PubChem	442330
Molecular formula	$C_{21}H_{21}NO_7$
Molar mass	399.39 g mol^{-1}



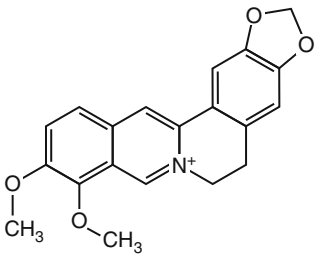
Pseudomorphine	
Abbreviations	2,2′-bimorphine
CAS number	125-24-6
PubChem	234570
ChemSpider	4590027
Molecular formula	$C_{34}H_{36}N_2O_6$
Molar mass	568.66 g mol^{-1}

(*continued*)

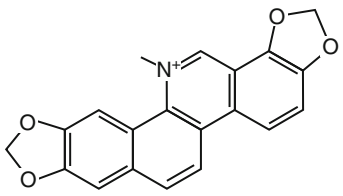
Table 15.8 (continued)



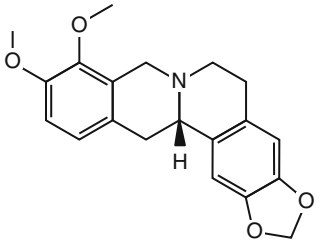
Laudanosine	
CAS number	2688-77-9
PubChem	73397
Molecular formula	$C_{21}H_{27}NO_4$
Molar mass	357.44 g mol^{-1}
Melting point	89 °C



Berberine	
CAS number	633-66-9
PubChem	2353
ChemSpider	2263
DrugBank	DB04115
ChEBI	CHEBI:16118
ChEMBL	CHEMBL12089
Molecular formula	$C_{20}H_{18}NO_4$
Molar mass	336.36122 g/mol



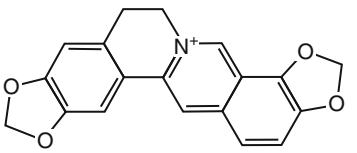
Sanguinarine	
CAS number	2447-54-3
PubChem	CID 5154
ChemSpider	4970
ChEBI	CHEBI:17183
ChEMBL	CHEMBL417799
Formula	$C_{20}H_{14}NO_4$
Mol. mass	332.09



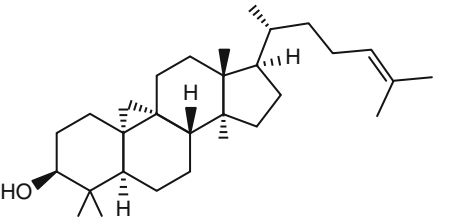
Canadine	
CAS number	522-97-4
PubChem	21171
ChemSpider	19910
ChEMBL	CHEMBL490533
Molecular formula	$C_{20}H_{21}NO_4$
Molar mass	339.38504

(*continued*)

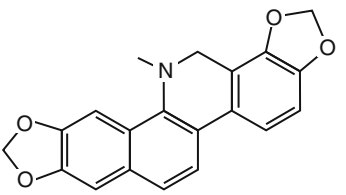
Table 15.8 (continued)



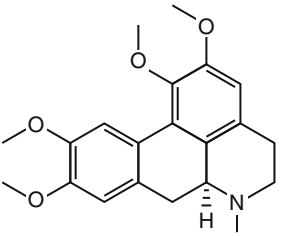
Coptisine	
CAS number	3486-66-6
PubChem	72322
ChemSpider	65268
ChEMBL	CHEMBL362071
Molecular formula	$C_{19}H_{14}NO_4$
Molar mass	320.319



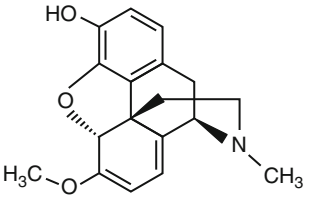
Cycloartenol	
CAS number	469-38-5
PubChem	92110
ChemSpider	16788581
Molecular formula	$C_{30}H_{50}O$
Molar mass	426.72 g/mol



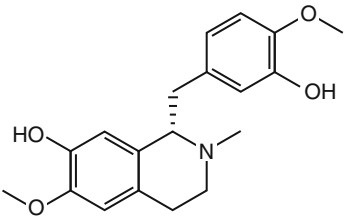
Dihydrosanguinarine	
CAS number	3606-45-9
PubChem	124069
Molecular formula	$C_{20}H_{15}NO_4$
Molar mass	333.34 g mol^{-1}



Glaucine	
CAS number	475-81-0, 5630-11-5
PubChem	CID 16754
ChEMBL	CHEMBL228082
Formula	$C_{21}H_{25}NO_4$
Mol. mass	355.428 g/mol



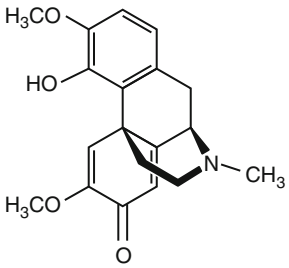
Oripavine	
CAS number	467-04-9
PubChem	5462306
ChemSpider	4575366
KEGG	C06175
ChEMBL	CHEMBL437602
Molecular formula	$C_{18}H_{19}NO_3$
Molar mass	297.35 g mol^{-1}



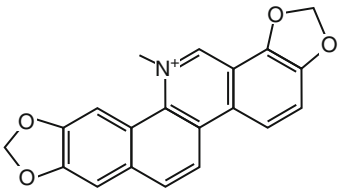
Reticuline	
CAS number	485-19-8
PubChem	439653
ChEMBL	CHEMBL401501
Molecular formula	$C_{19}H_{23}NO_4$
Molar mass	329.39 g/mol

(*continued*)

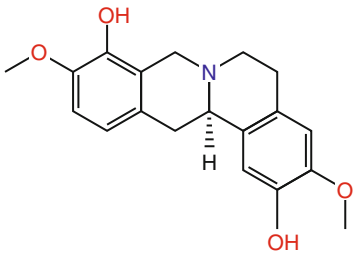
Table 15.8 (continued)



Salutaridine	
CAS number	1936-18-1
PubChem	5408233
ChEMBL	CHEMBL404097
Molecular formula	$C_{19}H_{21}NO_4$
Molar mass	327.37 g mol^{-1}



Sanguinarine	
CAS number	2447-54-3
PubChem	CID 5154
ChemSpider	4970
ChEBI	CHEBI:17183
ChEMBL	CHEMBL417799
Formula	$C_{20}H_{14}NO_4$
Mol. mass	332.09



Scoulerine	
CAS number	605-34-5
PubChem	439654
ChemSpider	388725
ChEBI	CHEBI:17129
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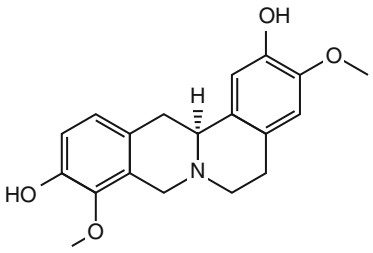
Molecular formula	$C_{19}H_{21}NO_4$
Molar mass	327.37 g/mol



(−)-Stepholidine	
CAS number	16562-13-3
PubChem	5290
ChEMBL	CHEMBL487387
Molecular formula	$C_{19}H_{21}NO_4$
Molar mass	327.374 g/mol

parallel with agronomical development for more reproducible levels of active compounds could improve the availability of drugs at an acceptable cost and a source of income in malaria endemic countries [21].

8.1 Antimalarial Properties of Alkaloids

Developing countries suffering from various infectious diseases like HIV, tuberculosis, and malaria. Among these diseases, malaria is the major killer of humans, and approximately 300–500 million clinical cases and one million deaths per year

caused world wide due to malaria [22]. Four Plasmodium species (*P. vivax, P. ovale, P. malariae, and P. falciparum*) are responsible for human malaria. Out of these, *P. falciparum* species causes most fatal form of malaria. This parasite has a plastid-like organelle called as apicoplast. Resistance to known antimalarial and the lack of an effective vaccine has created an urgent need to discover new biologically active compounds.

Natural compounds as a source for antimalarial drugs. Research on natural compounds has already contributed to the discovery of new antimalarial drugs. Atovaquone, artemisinin, and its semisynthetic derivatives, as well as clindamycin, erythromycin, azithromycine, chlortetracycline, tetracycline, oxytetracycline, and doxycycline, are noteworthy examples of the varied contribution of natural products for the development of effective antimalarial drugs, particularly valuable for the treatment of chloroquine-resistant parasites. Several comprehensive reviews on the antimalarial potency of plant products derived from ethnic medicine were published in the last decade. The quality of the data used in these reviews differs, and in earlier reports the chemical structure of the purified compound was not known and toxicity tests were not performed. However, in many cases, good activity and selectivity were observed. Most importantly, several compounds containing unique structural composition have been isolated and characterized. It is therefore not surprising that natural compounds dominate the recent malaria patent literature [21]. Although many compounds cannot be further developed for reasons mentioned above, the discovered lead compounds provide valuable bioactive scaffolds which could be further adjusted by semisynthetic approaches to obtain effective antimalarials.

Living organisms, especially plants, provide an innumerable number of molecules with potential for the treatment of many serious diseases. The current chapter attempts to give an overview on the potential of such plant-derived natural products as antiprotozoal leads and/or drugs [23]. Many plant species are used in traditional medicines of malarious countries, and a relatively few number of these have been investigated for evaluation of their antimalarial effect. Still lower is the number of those that have had the active natural compounds isolated and the toxicity determined [24]. Indole alkaloids are one of the important class of marine-derived secondary metabolites, with wide occurrence among variety of marine sources such as sponges, tunicates, algae, worms, and microorganisms and have been extensively studied for their biological activities. Among this chemical family, a sponge-derived bis-indole alkaloid fascaplysin (1) exhibited broad range of bioactivities including antibacterial, antifungal, antiviral, anti-HIV-1-RTase, p56 tyrosine kinase inhibition, antimalarial, anti-angiogenic, antiproliferative activity against numerous cancer cell lines, specific inhibition of cyclin-dependent kinase-4 (IC(50) 350 nM) and action as a DNA intercalator [25].

The possible anti-plasmodial compounds from leaf, stem, root, and flower extracts of Ocimum canum (*O. canum*), *Ocimum sanctum* (*O. sanctum*), and *Ocimum basilicum* (*O. basilicum*) have been analyzed by Inbaneson et al. [35]. The leaf extract of O. sanctum showed excellent anti-plasmodial activity ($IC_{(50)}$ 35.58 μg/mL) followed by leaf extract of O. basilicum ($IC_{(50)}$ 43.81 μg/mL).

The in vitro anti-plasmodial activity might be due to the presence of alkaloids, glycosides, flavonoids, phenols, saponins, triterpenoids, proteins, resins, steroids, and tannins in the ethanolic extracts of tested plants. Thirty bioactive compounds belonging to a variety of chemical classes such as spermine and isoquinoline alkaloids, glycosylflavones, phenylethanoid glycosides, ecdysteroids, quercetin arabinofuranosides, clerodane-type diterpenoids, sipandinolid, galloylquercetin derivatives, gallates, oleamide, and mangiferin derivatives [26]. Bioassay-guided fractionation of the MeOH extract from the stem bark of Neonauclea purpurea used in traditional medicine resulted in the isolation of 2 indole alkaloids, cadambine (1) and alpha-dihydrocadambine (2), as well as a quinolic compound, 2,6-dimethoxy-1,4-benzoquinone (3). Antimalarial activity evaluation showed that compounds 2 and 3 exhibited mild in vitro antimalarial activity against *Plasmodium falciparum*, [27].

Two new indole alkaloids, bisnicalaterine D (1), consisting of an eburnane and a corynanthe type of skeletons, and nicalaterine A (2) were isolated from the bark of Hunteria zeylanica. Their structures were elucidated by various spectroscopic data such as NMR and CD spectra. A series of bisnicalaterines and nicalaterine A showed potent anti-plasmodial activity against *P. falciparum* 3D7 [28].

8.2 Anticancer Properties of Alkaloids

Several methods exist for the treatment of cancer in modern medicine. These include chemotherapy, radiotherapy, and surgery; most cancer chemotherapeutants severely affect the host normal cells. Hence, the use of natural products now has been contemplated of exceptional value in the control of cancer. Plant-derived natural products such as flavonoids, terpenes, and alkaloids have received considerable attention in recent years due to their diverse pharmacological properties including cytotoxic and cancer chemopreventive effects.

The antioxidant and anticancer evaluation of Scindapsus officinalis (Roxb.) Schott fruits has been attempted to investigate its antitumor activity [29]. The collection and authentication of the plant material, mainly fruits, and their various extractions were done. Identification of plant's active constituents by preliminary phytochemical screening was carried out. An *in vitro* cytotoxic assay using the brine shrimp lethality assay with brine shrimp eggs (Artemia salina) at a dose of 1–10 μg/ml with the fruit extract was performed.

Increasing recurrence of mammalian tumors and severe side effects of chemotherapeutic agents reduce the clinical efficacy of a large variety of anticancer agents that are currently being used. Vinca alkaloid and their derivatives, alone and in combination with therapeutic agents, have been used for a long time for the treatment of various types of cancers. Polyphenols form one of the most important and extensively used classes of plant-derived therapeutics for cancer prevention or chemotherapy. The present chapter highlights a plethora of studies focused on the antineoplastic properties of plant-derived chemicals, such as vinca alkaloids, saponins, and flavonoids [30].

Nature is the main source of compounds for pharmaceutical purposes, either by providing the natural organic chemical compounds of interest or as a source of inspiration for the design of new drugs. The known antiinflammatory and anticancer agents belong to a great diversity of structural skeletons since inflammatory and cancer processes involve many different biological targets. Their origins extend to plants, fungi, bacteria, and marine organisms, besides those produced by semisynthesis and total synthesis. The tasks of the organic chemist are the screening, the structure assignment, and the semi and total syntheses of active molecules. The active compounds are organized by their biosynthetic origins as terpenoids; macrolides, polyketides, and ansamycins; phenolics; alkaloids; peptides; glycoconjugates; other compounds; and food compounds [31]. The isolation of the vinca alkaloids, vinblastine, and vincristine. Paclitaxel (Taxol®, **3**) from the bark of the Pacific Yew, *Taxus brevifolia* Nutt. Camptothecin, isolated from the Chinese ornamental tree *Camptotheca acuminate* Decne (Nyssaceae), Topotecan and irinotecan are semisynthetic derivatives of camptothecin and are used for the treatment of ovarian and small cell lung cancers, and colo-rectal cancers, respectively [32]. Epipodophyllotoxin is an isomer of podophyllotoxin which was isolated as the active antitumor agent from the roots of *Podophyllum* species, *Podophyllum peltatum* Linnaeus and *Podophyllum emodi* Wallich (Berberidaceae) [33]. Etoposide and teniposide are two semisynthetic derivatives of epipodophyllotoxin and are used in the treatment of lymphomas and bronchial and testicular cancers [34]. Homoharringtonine, isolated from the Chinese tree *Cephalotaxus harringtonia* var. *drupacea* (Sieb and Zucc.).

9 Conclusion

In this chapter, we studied and analyzed the various biosynthetic routes involved in biosynthesis of alkaloids especially tyrosine-derived alkaloids. The plant alkaloids have been known to have important medicinal values and provided the medicines for the treatments of cancer, malaria, tuberculosis, etc. Keeping in mind the therapeutic importance, there is an urgent need to investigate their biosynthesis at the level of enzyme and gene.

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Web Resources

Alkaloids. www.friedli.com/herbs/phytochem/alkaloids/alkaloid1.html
KEGG: Kyoto Encyclopedia of Genes and Genomes. www.genome.jp/kegg/
Plant Alkaloids – Wayne's Word. http://waynesword.palomar.edu/ww0703.htm
Wikipedia-Alkaloid. http://en.wikipedia.org/wiki/Alkaloid/