TROPANE ALKALOIDS: AN OVERVIEW[a]

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Summary

Tropane alkaloids are a group of secondary metabolites containing a 8-azabicyclo[3.2.1]octane nucleus skeleton as a key structural element. They have hallucinogenic features and are active on Central Nervous System. Some of them, such as atropine and scopolamine, are used in medicine as antimuscarinic drugs. Tropane alkaloids are abundant above all in Solanaceae and Erythroxylaceae, where they are the most important alkaloids, but they were extracted also from other families of higher plants, e.g. Proteaceae, Euphorbiaceae, Rhizophoraceae, Convolvulaceae, Cruciferae and Moraceae. All these secondary metabolites, containing the tropane core as main structure, have as a common biosynthetic origin the amino acid L-ornitine. This compound, after several biosynthetic steps, is converted in hygrine, from which α-tropine, β-tropine, ecgonine and cuscohygrine origin and constitute the bases for the biosynthesis of all the tropane alkaloids known. The diffuse presence of tropane alkaloids among higher plants, can support the idea that they can be considered as a chemical link among different families of plants.

Keyword: Chemotaxonomy, Tropane Alkaloids, Atropine, Scopolamine.

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Introduction

Chemotaxonomy, or chemosystematics, is the attempt to classify plants according to the differences in their biochemical features. Recently, it becomes more evidently the importance of a chemosystematic approach in chemical and/or pharmacological studies on biologically active plants.
One of the most fascinating field of research is constituted by plants containing compounds active on Central Nervous System and, among them by plants containing alkaloids. In this paper we attempt to consider a link between tropane alkaloids pharmacological activity and their distribution in different families of higher plants.
All tropane alkaloids contain the 8-azabicyclo[3.2.1]octane nucleus skeleton as key structural element (Fig.1).

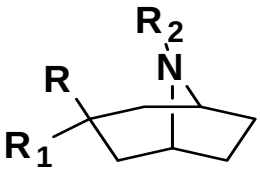

Figure 1. *8-azabicyclo [3,2,1]octane nucleus.*

Since tropane alkaloids have a quite simple chemical structure and are easy to be extract, they have been identified not only in Solanaceae and Erythroxylaceae, where they are the most abundant alkaloids, but also in other families, e. g. Proteaceae, Euphorbiaceae, Rhizophoraceae, Convolvulaceae, Cruciferae and Moraceae (1).
Plants containing tropane alkaloids have been medicinally used for centuries for their different pharmacological activities. Among the most important alkaloids, while cocaine (**1**) acts as an anaesthetic and a sympathomimetic, classical tropane alkaloids, as atropine (**2**) and scopolamine (**3**), are parasympatholytic; in fact, they act as competitive antagonists, by blocking the action of acetylcholine at parasympathetic sites in smooth muscle, secretory glands and CNS. For this reason, they are classified as antimuscarinic drugs. But it is also important to remind the hallucinogenic characteristics of some tropane alkaloids extract above all from the Solanaceus genera *Brugmansia* and *Datura*. In fact, in most native American cultures, along with medicinal plants, these plants play a central role in therapeutic rites based on "magical plants", which are seen as intermediaries between the human world and that of supernatural forces (2).

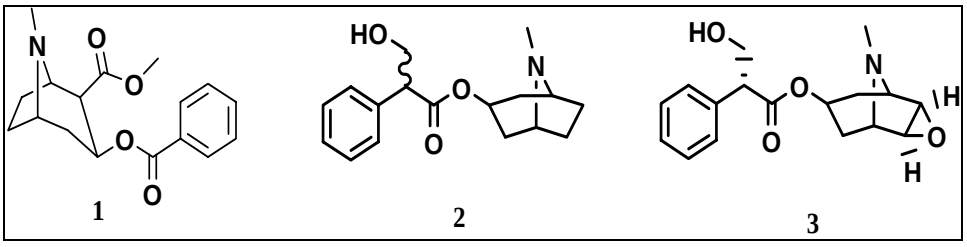

Figure 2. *Cocaine (**1**); (+/-)-hyoscyamine or atropine (**2**); hyoscine or scopolamine (**3**).*

In this paper we present an overview on the chemotaxonomy of plant families containing tropane alkaloids and on their biological activities.

Results

Solanaceae

Solanaceae is the family where tropane alkaloids are really abundant. This family is usually divided by botanists in different subfamilies and tribes, characterized by chemical differences in their composition. (1).

In the subfamily Solanoideae, the tribe Datureae, and specifically *Datura* and *Brugmansia* genera, contains the greatest range of tropane alkaloids. Tha aerial parts of *Datura* genus contain above all hyoscyamine (**2**) but also scopolamine (**3**), littorine (**4**) and the base 6β-(2-methylbutanoyloxy)tropan-3α-ol (**5**), while the roots yeald valtropine, a tropane alkaloid common in *Duboisia* species (3).

Recently, polyhydroxylated tropane alkaloids have been reported in *Datura* species: in the leaves of *Datura wrightii* Regel and in tubers of *Solanum* spp., calystegine A_3 (1β,2α,3β-trihydroxynortropane) (**6**) and calystegine B_2 (1β,2α,3β,4α-tetrahydroxynortropane) (**7)** have been found, while calystegines C_1 (1β,2β,3β,4β,6β-pentahydroxynortropane) (**8**) and C_2 (1β,2α,3β,4α,6β-pentahydroxynortropane) (**9**) have been isolated from *Duboisia leichhardtii* F. Muell. (3).

The aerial parts of some species belonging to *Brugmansia* genus contain scopolamine (**3**) and/or hyoscyamine (**2**) as principal alkaloids, with smaller amounts of derivatives of these bases (10), while the roots contain in addition a large number of esters formed from dihydroxytropane and teloidine (**10**) (9).

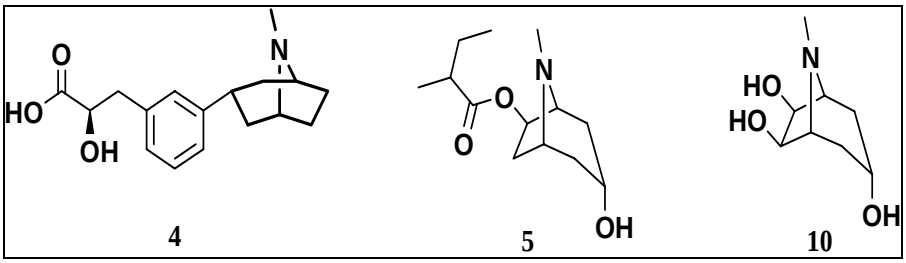

Figure 3. *Littorine (**4**); 6β-(2-methylbutanoyloxy)tropan-3α-ol (**5**); teloidine (**10**).*

The genus *Solandra*, (tribe Solandreae) contains atropine (**2**) and/or hyoscyamine (**3**) and their nor-derivatives as principal alkaloids (4).

Atropa belladonna L. (tribe Solaneae) contains hyoscyamine (**2**) as the principal alkaloid but also scopolamine (**3**), apoatropine (**11**), hyoscyamine (**2**) and scopolamine *N*-oxides (5). Leaves of *A. belladonna* and of *Hyosciamus* spp. contain also a few quantity of calystegines A_3 (**6**), B_1 (**12**) and B_2 (**7**). Hyoscyamine (**2**) and tigloidine (**13**) have been found in some species of the minor genera *Latua* and *Acristus*. Tigloidine (3β-tigloyloxytropane) and 3α-tigloyloxytropane were isolated as root alkaloids (6-7). Some secotropane alkaloids have been isolated, as major alkaloids, from the roots and have been subsequently identified as (+)-physoperuvine (**14**), racemic physoperuvine and (+)-*N*,*N*-dimethyl-physoperuvinium salt (8). Extracts from leaves and roots contain 3β-acetoxytropane and *N*-methylpyrrolidinylhygrine (two isomers), but also 3β-tigloyloxytropane (**15**), hygrine (**16**), physoperuvine (**14**), tropine (**17**) and cuscohygrine (**18**) (9). Roots of *Physalis alkekengi* L. yielded tigloidine (**13**), 3α-tigloyloxytropane (**15**), cuscohygrine (**18**), the hygrine dimer phygrine and some unidentified bases. Calystegines A_3 (**6**), B_2 (**7**), A_5 (1β,3β,4α-trihydroxynortropane) (**19**) and B_3 (1β,2β,3β,4α-tetrahydroxynortropane) (**20**) were extracted from the roots of *Physalis alkekengi* L.(9), while from *Licyum chinense* Mill. calystegines C_2 (**9**), B_4 (**21**), A_7 (**22**) and N-methylcalystegines were isolated (10).

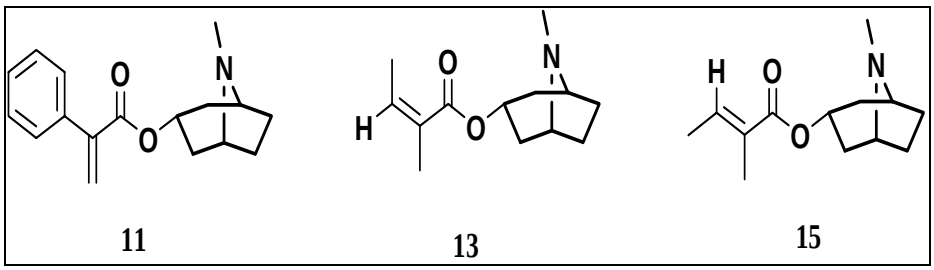

Figure 4. *Apoatropine (**11**); tigloidine (**13**); tigloyloxytropane (**15**).*

The large genus *Solanum* does not contains the usual tropane alkaloids (11): calystegine A_3 (**6**) has been found along with calystegine B_2 (**7**) in the leaves of some *Solanum* species, including *S. tuberosum* L., *S. dulcamara* L., *S. melongena* L. and in herbarium fragments of *S. kwebense* N. E. Br. ex C. H. Wright from Southern Africa (12).
In conclusion, calystegines are located in *A. belladonna* (all parts but mainly upper leaves), *Mandragora officinarum* L. (likewise, mainly spring leaves), *Scopolia carniolica* Jacq. (spring leaves and flowers), *Hyoscyamus niger* L. (traces in all plant parts) and *Solanum tuberosum* L. (sprouts only). Specifically, *Hyoscyamus niger* L. contains also an alkaloid with a bridgehead aminogroup, calystegine N_1 (**23**) (13).
For many centuries *Mandragora* roots have been considered very important as folk medicines. The former *Mandragora officinalis* Mill. comprises two distinct species, *M. autumnalis* Bertol. and *M. vernalis* Bertol., which contain hyoscyamine (**2**), scopolamine (**3**), cuscohygrine (**18**), apoatropine (**11**), 3α-tigloyloxytropane (**15**) and 3,6-ditigloyloxytropane. The roots contain small quantities of cuscohygrine (**18**), pseudotropine (**24**), tropine (**17**) and hyoscyamine (**2**). *Withania somnifera* Dunal likewise contains cuscohygrine (**18**) and 3α-tigloyloxytropane (**15**), but also tropine (**17**) and pseudotropine (**24**) (14). The main base from the roots of *Cyphomandra betacea* Cav. is N,N′-bis-(4-dimethylaminobutyl)-hexamide. Other bases included tropinone (**25**), cuscohygrine (**18**), hyoscyamine (**2**), tigloidine (**13**), tropine (**17**) and pseudotropine (**24**) (5).

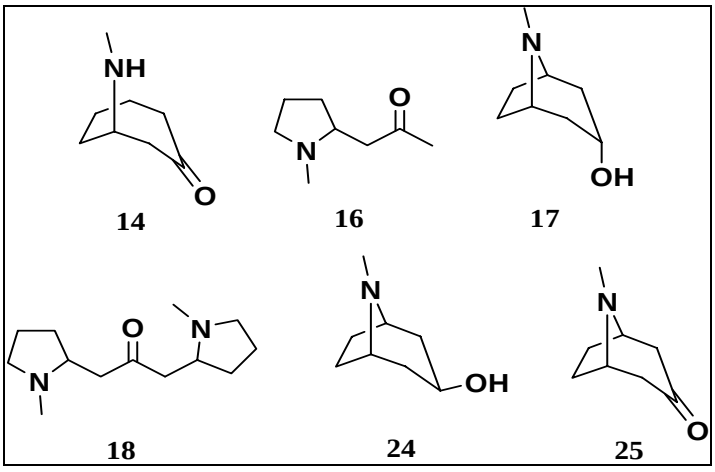

Figure 5. *Physoperuvine (**14**); hygrine (**16**); tropine (**17**); cuscohygrine (**18**); pseudotropine (**24**); tropinone (**25**).*

N-oxides were found in *Scopolia* spp. and *Hyoscyamus* spp. (tribe Hyoscyameae) (6) which, along with *Physochlaina* spp. and *Przewalskia* spp., contain hyoscyamine (**2**) as the major alkaloid with some scopolamine (**3**) derivatives (5, 6).
To the subfamily Cestroideae belong the tribes Anthocercideae, Nicandreae, and Salpiglossidae.
The tribe Anthocercideae includes seven genera, *Duboisia*, *Anthocercis*, *Cyphanthera*, *Anthotroche*, *Symonanthus*, *Grammosolen* and *Crenidium*.
Among *Duboisia* genus, *Duboisia myoporoides* L. Br. contains scopolamine (**3**) (15), the dominant alkaloid in a variety collected North of Gosford, NSW Australia, or hyoscyamine (**2**), the major alkaloid in a variety South of Gosford. In a region known as Acacia Plateau near Killarney, Queensland, Australia, a third variety was discovered in which nicotine (**26**) and anabasine (**27**) are the dominant alkaloids (16). *Duboisia leichhardtii* F. Muell and *D. myoporoides* R. Br. contain hyoscyamine (**2**) and scopolamine (**3**) as the most important tropane alkaloid (17), but from the first one was isolated calystegine C_2 (**9**), too. In *Duboisia arenitensis* Craven the alkaloid content is less than the other species and the most important are scopolamine (**3**) and hyoscyamine (**2**).
Anthocercis spp. contain either hyoscyamine (**2**) or scopolamine (**3**) as predominant alkaloids, frequently accompanied by their respective *apo*- and *nor*-derivatives. Among this genus, *Anthocercis littorea* Endl. contains mainly littorine (**4**) and meteloidine (**28**) (18) but also some mono- and ditigloyl esters of teloidine (**10**) (19); *Anthocercis viscosa* R. Br. and *A. fasciculata* F. Muell. contain hyoscyamine (**2**) (18); *Cyphanthera anthocercidea* Haegi (=*Anthocercis frondosa*) yelds scopolamine (**3**) and hyoscyamine (**2**), but chiefly nicotine (**26**) (20).
Among *Cyphanthera* genus, *Cyphanthera albicans* Miers (=*Anthocercis albicans*) affords butyryl esters of tropine and 6β-hydroxytropine. The alkaloids of *Cyphanthera odgersii* Haegi and *Cyphanthera tasmanica* Miers were found to be consistent with other known *Cyphanthera* species (11).
Three species belonging to *Anthotroche* genus, *A. myoporoides* C. A. Gardner, *A. pannosa* Endl. and *A. walcottii* F. Muell., contain hyoscyamine (**2**), norhyoscyamine (**29**), apoatropine (**11**) and scopolamine (**3**) (20).
Among *Symonanthus* genus (two species), the roots of *Symonanthus aromaticus* Haegi contain mono- and ditigloyl esters like *Datura* species and both aerial parts and roots have scopolamine (**3**) and its derivative aposcopolamine (**30**), as the main alkaloids (11).

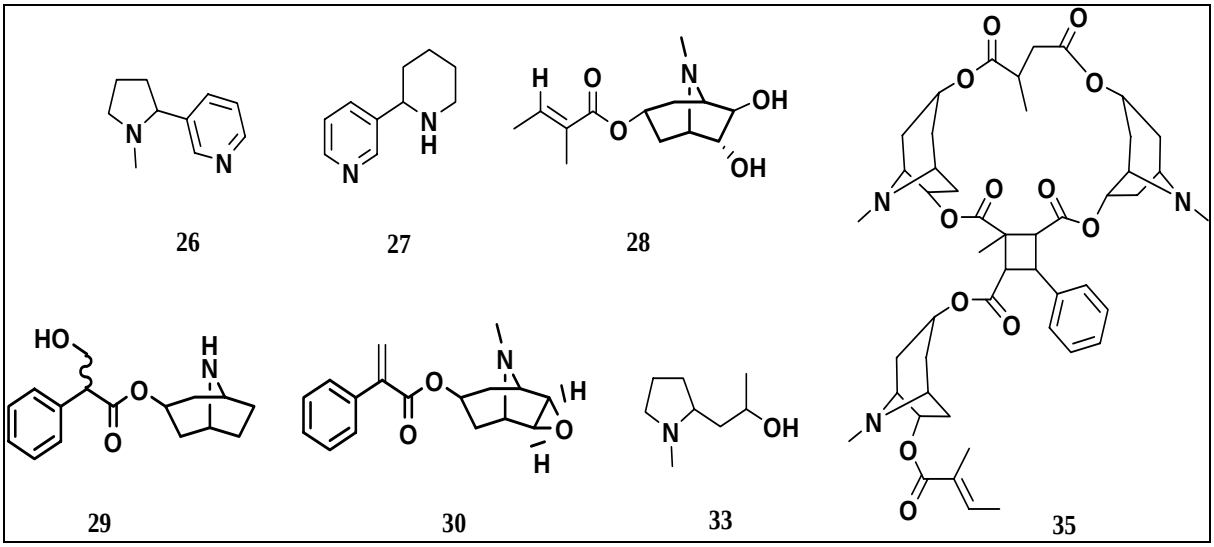

Figure 6. *Nicotine (**26**); anabasine (**27**); meteloidine (**28**); norhyoscyamine (**29**); aposcopolamine (**30**); hygroline (**33**); grahamine (**35**).*

The genus *Grammosolen* (two species) appears most closely related chemically to *Cyphanthera* and *Anthotroche* (11).
The genus *Crenidium* has a single species, *C. spinescens* Haegi, where hyoscyamine (**2**) is the predominant alkaloid, but are present also anabasine (**27**) with ursolic acid (**31**). *Anthocercis ilicifolia* Hook possesses a similar alkaloid spectrum to that of *A. littorea* Endl. *Anthocercis genistoides* Miers shows meteloidine (**28**) as the major alkaloid (11).
Esters of tropic acid (**32**) are not found in the tribe *Nicandrae*. However, tropine (**17**) was isolated from the roots of *Nicandra* species (21).
Schizanthus pinnatus Ruiz (tribe Salpiglossidae) contains tropane-derivate as schizanthines A and B which are 6β-senecioyloxytropan-3β-ol esters of dibasic mesaconic acid (A is a diester of 6-senecioyloxytropine, B is a mixed ester of 6-senecioyloxytropine and ethanol) (22). The root alkaloids of *S. hookeri* Lodd. are tropine (**17**), a pair of diastereoisomeric hygrolines (**33**) and the alkaloids 3α-senecioyloxytropan-6β-ol and 6β-angeloyloxytropan-3α-ol (22). *Schizanthus litoralis* Phil. contains hydroxytropane esters, hygrolines (**33**), the tropane diester of itaconic acid (**34**) and the alkaloids 6β-senecioyloxy-tropan-3α-methylmesaconate, 6β-cinnamoyloxytropan-3α-methylmesaconate, 6β-senecioyl-oxytropan-3α-ol, *cis*- and *trans*-N-(4-hydroxyphenyl)-ferulamides (23) but also 3α-senecioyloxytropan-6β-ol, (−)-hygroline and (+)-pseudohygroline, which had already been reported present in *S. pinnatus* Ruiz (24). Schizanthines C, D, E, and a trimeric tropane alkaloid occur in *S. grahamii* Borrer ex Baker (25). Grahamine (**35**) contains a cyclobutane ring substituted by three carboxyl groups and is formed from cinnamoyltropine and mesaconic acid (**36**).

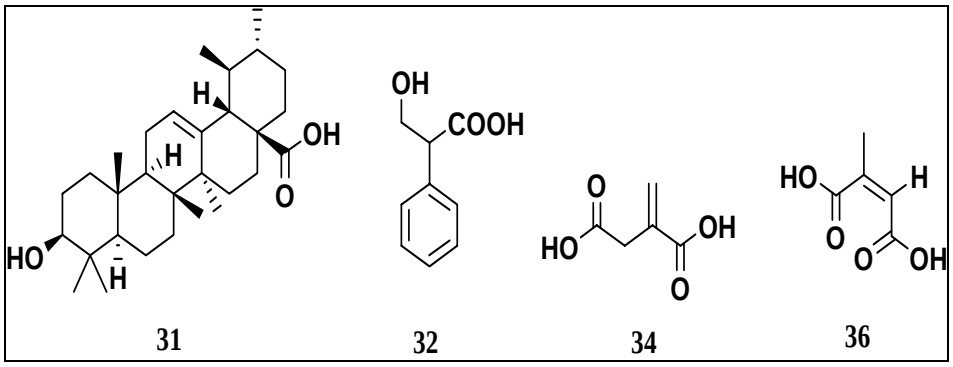

Figure 7. *Ursolic acid (**31**); tropic acid (**32**); itaconic acid (**34**); mesaconic acid (**36**).*

Erythroxylaceae

The genus *Erythroxylum* contains about 200 species. *Erythroxylum argentinum* O. E. Schulz, *E. cataractarum* Spruce ex Peyr, *E. cumanense* Kunth, *E. glaucum* O. E. Schulz, *E. mamacoca* Mart. and *E. shatona* Macbride contain total alkaloids in the range 0.06–0.20% compared with all species from the sections *Macrocalyx*, *Rhabdophyllum* and *Leptogramme* save one, which were lower in alkaloid content (0.002–0.04%) (11). In the six *Erythroxylum* spp. of *Archerythroxylum*, benzoic and phenylacetic acids form esters with alkamines, principally tropan-3-ols, tropan-3,6-diols and their derivatives. 3β-Benzoyloxytropane is the most frequently occurring alkaloid, together with nortropacocaine (3β-benzoyloxynortropane) extracted from *E. mamacoca* Mart.. Dihydrocuscohygrine and cuscohygrine (**18**) are present in some species. Cuscohygrine (**18**) as the main alkaloid of *E. cataractarum* Spruce ex Peyr is unique in the genus.

Tropacocaine (**37**) is extracted from *E. ulei* O. E. Schulz (section *Leptogramme*), *E. mamacoca* Mart. and *E. argentinum* O. E. Schulz (section *Archerythroxylon*), but not in the sections *Marcrocalyx* and *Rhabdophyllum* (11). Dihydrocuscohygrine and cuscohygrine (**18**) are also found in the cultivated cocaine producing species, *E. coca* Lam. and *E. novogranatense* Morris, and its variety *truxillense*. Cocaine (**1**) and the *cis* and *trans* isomers of cinnamoyl cocaine (**38**) is contained in *E. coca* Lam. and *E. novogranatense* Morris var. *truxillense* (26). A series (α, β, γ, δ, ε) of dimeric methylecgonine (methyl ester of ecgonine, the basic moiety of cocaine) esters of truxillic acid (1,3-diphenylcyclobutane-2,4-dicarboxylic acids, dimers of cinnamic acid) was identified in Bolivian coca leaf and α-truxilline (**39**) and β-truxilline were the most abundant (27). A new alkaloid, 1-hydroxytropacocaine, was discovered in *E. novogranatense* Morris var. *novogranatense* and var. *truxillense* (28). The base 6β-benzoyloxytropan-3α-ol occurs in both *E. cumanense* Kunth and *E. glaucum* O. E. Schulz (both section *Archerythroxylum*). Trimethoxybenzoyl esters are found in the roots of *E. cumanense* Kunth. *Erythroxylum macrocarpum* O. E. Schulz and *E. sideroxyloides* Lam. of the section *Packylobus* contain a similar range of alkaloids consisting mainly of benzoyl esters of tropan-3α-ol, tropan-3β-ol and tropan-3α,6β-diol together with their *nor*-derivatives. Three alkaloids have been found, 3α-benzoyloxytropan-6β-ol (from *E. sideroxyloides* Lam.), 3α-benzoyloxynortropane and 3β-benzoyloxynortropan-6β-ol (both species) (29). The root barks of *E. pervillei* Baill. and *E. hypericifolium* Lam. contain the bases 3α-(3-hyroxyphenylacetoxy)-tropane, (+)-3α-phenylacetoxytropan-6β-ol, 6β-acetoxy-3α-phenylacetoxytro-pane, 3α-phenylacetoxytropan-6β,7β-diol, 3α-phenylacetoxynortropane and 3α-phenylacetoxytropane (29). Important to be noted are also the alkaloids 3α-cinnamoyloxytropan-6β-ol isolated as the (+) base from leaves of *Knightia* spp. (30). This is the first pseudotropane ester to be found in *Erythroxylum hypericifolium* Lam. The benzoyl analogue is widely distributed in *Erythroxylum* spp. The alkaloids 3α-cinnamoyloxytropane, 3α,6β-dicinnamoyloxytropane (analogous to the dibenzoyl ester found in *E. cuneatum* Kurz (31)), 3-cinnamoyloxytropan-6-ol (stereochemistry not established), 6β-acetoxy-3α-cinnamoyloxytropane and 6-phenylacetoxytropan-3-ol are found in *Crossostylis* spp. (32), together with cinnamate tropane dimers and esters of truxillic acid (33). These were identified as 3,3′-truxilloyloxy-6′-acetoxyditropane, 3,3′-truxilloyl-6hydroxy-6′-acetoxyditropane and 3,3′-truxilloyloxy-6′-hydroxyditropane. As in root bark, in the stem bark of *E. hypericifolium* Lam. predominate esters of phenylacetic acid: 3α-phenylacetoxynortropan-6β-ol, the main alkaloid, 6β-acetoxy-3α-benzoyloxytropane, 3-acetoxy-6-phenylacetoxytropane and hygrine (**16**) (34). *Erythroxylum zambesiacum* N. Robson (section *Melanocladus*) likewise has a complex mixture of root bark alkaloids. The most important are 3α-(3,4,5-trimethyoxybenzoyloxy)-nortropane, 3α-(3,4,5-trimethoxybenzoyloxy)-tropan-6β-ol, 3α-(3,4,5-trimethoxybenzoyloxy)-nortropan-6β-ol, 6β-benzoyloxytropan-3α,7β-diol, 6β-benzoyloxy-3α-(3,4,5-trimethoxycinnamoyloxy)-tropan-7β-ol, and 7β-acetoxy-6β-benzoyloxy-3α-(3,4,5-trimethoxy-cinnamoyloxy)-tropane. Other minor bases identified include 3α-(3,4,5-trimethoxybenzoyloxy)-tropane, 3α-(3,4,5-trimethoxycinnamoyloxy)-tropane, 3α-phenylacetoxytropan-6β-ol, 3α-(3,4,5-trimethoxybenzoyloxy)tropan-6β,7β-diol, 6β-benzoyloxytropan-3α-ol, and 6β-benzoyloxy-3α-(3,4,5-trimethoxycinnaomoyloxy)tropane (35). The main alkaloid of *E. zambesiacum* N. Robson is 3α-(3′,4′,5′-trimethoxybenzoyl)-oxytropane, followed by three new alkaloids characterized as 6β-benzoyloxytropan-3-one, 6-isovaleryloxytropan-3-ol and 3-(2-methyl butyryloxy)-6,7-diol (36). Other dimeric tropane alkaloids, although in very low yield (ca 0.003%), have been isolated from *E. moonii* Hochr.: moniine A **(40**) and mooniine B (**41**) (37). They are diesters of tropine and nortropine with carboxylic dibasic acids presumably resulting from tropic acid biogenesis. With the exception of tropyl esters, the tropane alkaloid spectrum of the genus *Erythroxylum* is remarkably similar to that of the Solanaceae (12, 38). *Erythroxylum australe* F. Muell (section *Coelocarpus*) contains tigloyl esters of meteloidine (**28**), 3α-tigloyloxytropan-6β-ol, 3α-tigloyloxynortropan-6β-ol and an unknown base which was tentatively identified as 7-hydroxy-6-tigloyloxynortropan-3-yl, 2-hydroxy-3-phenylpropionate. 2-

Hydroxy-3-phenyl-propionic acid, closely related to tropic acid and a component of the solanaceous alkaloid littorine (**4**), is a further link (besides meteloidine (**28**)) with the family *Solanceae* (39). *Erythroxylum zeylanicum* O. E. Schulz contains three tropane alkaloids: erythrozeylanines A [1R,3R,5S,6R-6-acetoxy-3-(3',4',5'-trimethoxybenzoyloxy)-tropane], B [cis-3β-(cinnamoyloxy)-tropane], and C [cis-6β-acetoxy-3α-(cinnamoyloxy)-tropane], and others already found in other *Erythroxylum* species (40).
Calystegines were identified in the genus *Erythroxylum*, too. *Erythroxylum novogranatense* Morris var. *novogranatense* contained 0.2% total calystegines in dry leaves. Forty-six *Erythroxylum* herbarium species, consisting mostly of leaf tissue, were analysed for calystegines, and 38 were found positive. Calystegines A_3 (**6**) and B_2 (**7**) were the major calystegines in most species. The simultaneous occurrence of calystegines, cocaine (**1**), other alkaloids of a 3α-hydroxy- or 3β-hydroxytropane structure and nicotine (**26**), supports the concept of common biosynthetic steps of these alkaloids in *Erythroxylum* (41). Finally, recently, pervilleine A (**42**), a novel tropane alkaloid, was extracted from *Erythroxylum pervillei* Baill. (42).

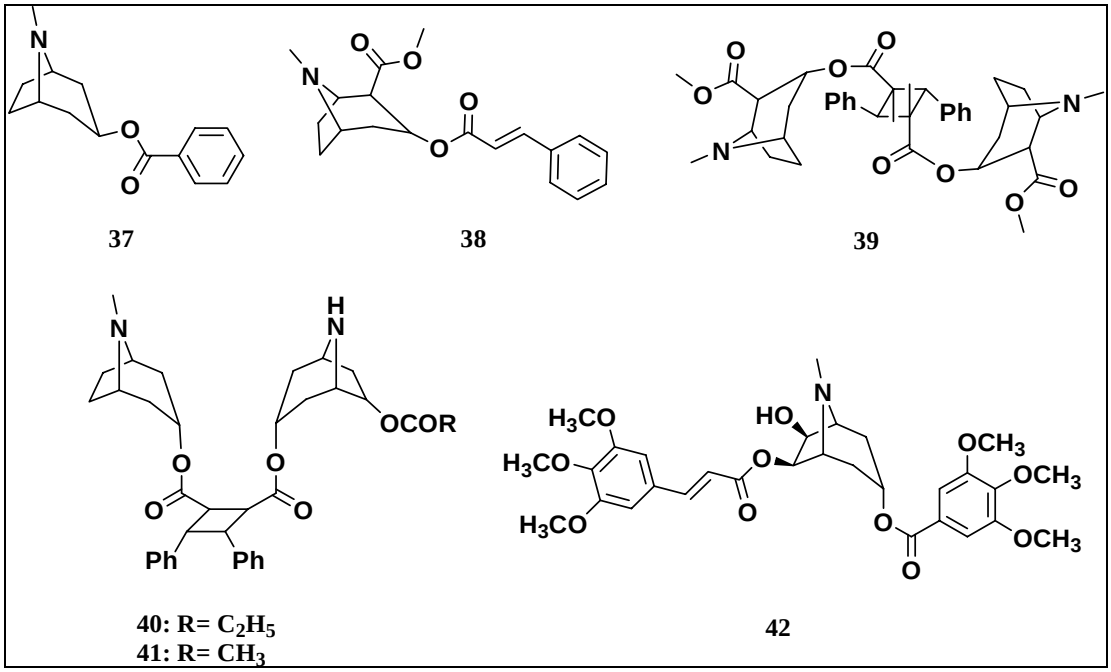

Figure 8. *Tropacocaine (**37**); cinnamoyl-cocaine (**38**); α-truxilline (**39**); mooniine A (**40**); mooniine B (**41**); pervilleine A (**42**).*

Proteaceae

Bellandena montana R. Br. afforded the first alkaloid from the *Proteaceae*, bellendine (**43**), an unusual tropane alkaloid (43). Similar alkaloids, such as darlingine (**44**), a pyranotropane base, were isolated from *Darlingia darlingiana* L. A. S. Johnson. (44) *D. ferruginea* J. F. Bailey contains darlingine (**44**), ferruginine (**45**), ferrugine (**46**) and 3α-benzoyloxy-2α-hydroxybenzyltropine (45). *Bellendena montana* R. Br. contains bellendine (**43**), isobellendine (**47**) and darlingine (**44**) (46). Alkaloids of a 2-benzyltropine type were obtained from genus *Knightia*, *K. deplanchei* Vieill ex Brongn. & Gris and *K. strobilina* R. Br. (47).

D-strobiline (**48**) is the main alkaloid of *K. strobilina* R. Br., together with 3α-cinnamoyloxytropan-6β-ol, 3α-acetoxy-2α-acetoxybenzyltropane (acetylknightionl) (**49**), 3α-acetoxy-2α-benzyltropan-6β-ol (knightoline) (**50**), 6β-benzoyloxytropan-3α-ol (**51**), 2α-hydroxybenzyl-3α-acetoxytropane (knightinol) (**52**), dihydrostrobiline (**53**) (33), strobamine B (**54**), chalcostrobamine (**55**), strobolamine (**56**), knightalbinol (**57**) and knightolamine (**58**) (30). *Agastachys odorata* R. Br. contains 6β-acetoxy-3α-tigloyloxytropane and 3α-(*p*-hydroxybenzoyloxy)-trop-6-ene, the first naturally occurring tropene base (45).

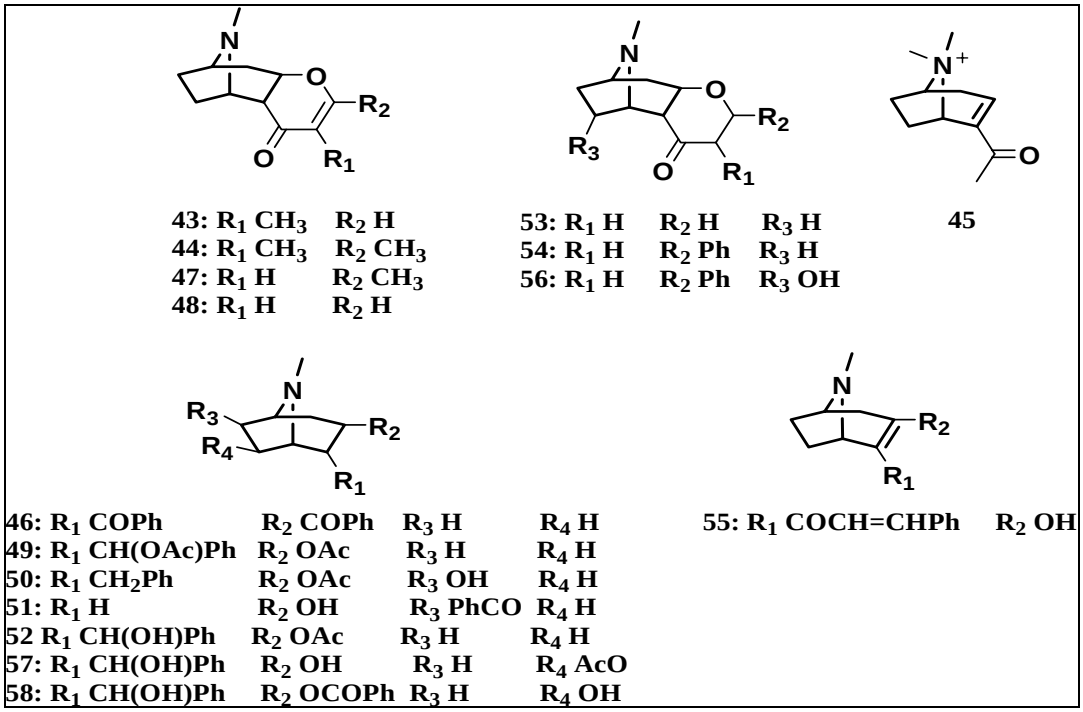

Figure 9. *Bellendine (**43**); darlingine (**44**); ferruginine (**45**); ferrugine (**46**); isobellendine (**47**); strobiline (**48**); acetylknightinol (**49**); knightoline (**50**); 6β-benzoyloxytropan-3α-ol (**51**); knightinol (**52**); dihydrostrobiline (**53**); strobamine (**54**); chalcostrobamine (**55**); strobolamine (**56**); knightalbinol (**57**); knightolamine (**58**).*

Euphorbiaceae

In this family, tropane alkaloids are isolated just from *Peripentadenia mearsii* (C.T.White) L. S. Sm. They are tropacocaine (**37**) (3β-benzoyloxytropane), 3α-acetoxy-6β-hydroxytropane and 2α-benzoyloxy-3β-hydroxytropane (48).

Rhizophoraceae

This family contains some dithiolane esters: brugine (tropine 1,2-dithiolane-3-carboxylate) (**59**) was obtained from *Bruguiera sexangula* Poir., while *B. exaristata* Ding Hou contains other tropine esters of acetic, propionic, *n*-butyric, isobutyric, isovaleric and benzoic acids (49).

Brugine (**59**) has been also found in *Crossostylis* spp. (*C. biflora* Forst., *C. multiflora* Brongn. & Gris and *C. sebertii* Brongn. & Gris) along with tropine (**17**), 3α-benzoyl-oxytropane and two esters of tropine, tropine cinnamate (**60**) and ferulate (**61**) (32). Of *Crossostylis* species, *C. Sebertii* (Pancher) Pierre Arbuste contains the tropane alkaloids tropan-3α-yl cinnamate and tropan-3α-yl benzoate; *C. multiflora* Brongn. & Gris contains tropan-3α-yl-ferulate, 3α-tropanol and brugine (**59**) and *C. biflora* J. R. Forst. & G. Forst. contains hygrine (**16**) and tropanone (50).

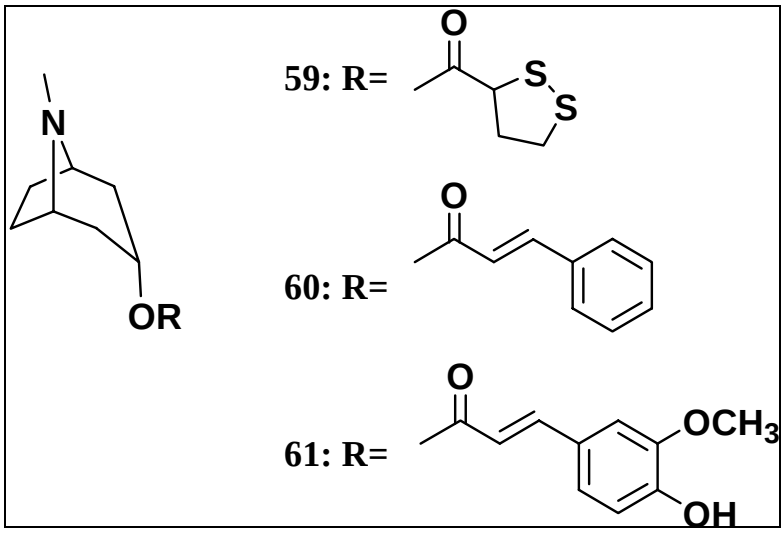

Figure 10. *Brugine (**59**); tropine cinnamate (**60**); tropine ferulate (**61**).*

Convolvulaceae

One-hundred twenty-nine convolvulaceous species belonging to 29 genera (all 12 tribes), revealed the occurrence of one to six polyhydroxy alkaloids of the nortropane type (calystegines) in 62 species belonging to 22 genera of all tribes except the unique parasitic *Cuscuteae*. Specifically, the tetrahydroxylated alkaloids B_2 (**7**) and calystegine B_1 (**12**) are the most frequent compounds (90% and 68%) followed by the trihydroxynortropane A_3 (**6**) (38%) and the pentahydroxylated congener C_1 (**8**) (26%) (51). Calystegines A_5 (**19**), B_3 (**20)**, and B_5 (**62**), isolated also in *Scopolia japonica* Maxim. (*Solanaceae*) (52), displayed a minor frequency, ranging from 16% to 20%. Calystegine A_6 (**63**), characterized by the lack of a hydroxy group at C-3, has been only discovered in *Stictocardia mojangensis* (51).

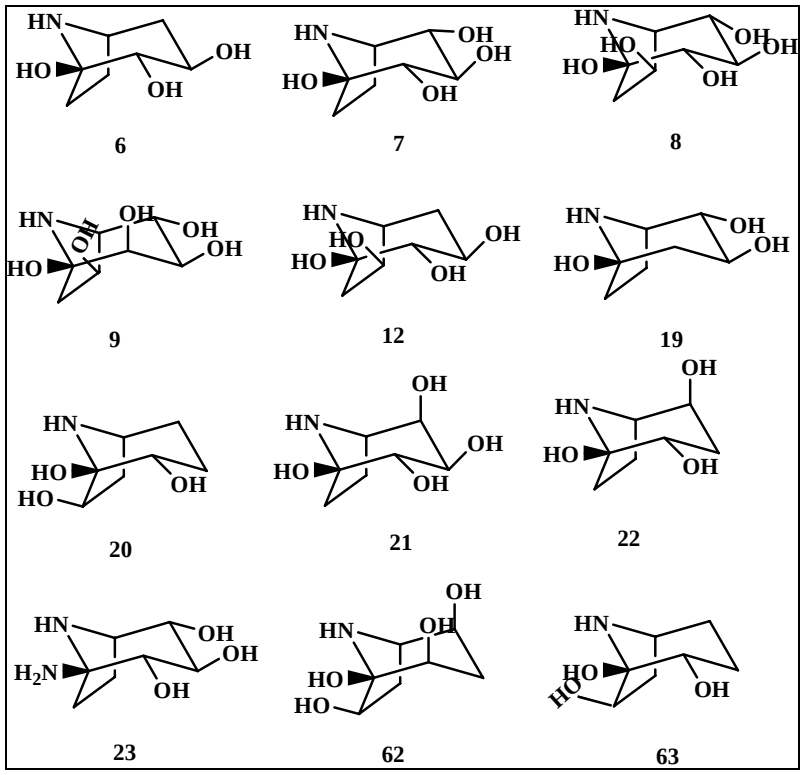

Figure 11. *Calystegines: A_3 (**6**); B_2 (**7**); C_1 (**8**); C_2 (**9**); B_1 (**12**); A_5 (**19**); B_3 (**20**); B_4 (**21**); A_7 (**22**); N_1 (**23**); B_5 (**62**); A_6 (**63**).*

Convolvine (**64**) and convolamine (**65**), a nortropan-3α-yl veratrate and its N-methyl derivate, respectively, have been isolated from *Convolvulus lineatus* L. and *C. pseudocantabricus* Schrenk, together with closely related alkaloids having a veratroyl or a vanilloyl moiety as the acyl component. Convolvine (**64**) and convolamine (**65**) were extracted also from *C. krauseanus* Regel & Schmalh and *C. subhirsutus* L. Moreover, *C. krauseanus* Regel & Schmalh and *C. subhirsutus* L. contain a series of tropine esters with methoxy substituted benzoic acids of tropane alkaloids which include convolvine (3α-veratroyloxynortropane), convolidine (3α-vanilloyloxynortropane) (53,54), confoline (3α-veratroyl-*N*-formylnortropine) (55) and convolamine-*N*-oxide (56). Recently, from the aerial part of *C. subhirsutus L.* has been extracted a new tropane alkaloid, the confolidine ((±)3a-vanillyl-N-formylnortropane), too. *Evolvulus sericeus* Sw. likewise contains convoline, convolamine (**65**) and convolidine. From *E. elliptilimba* Merr. & Chun and *E. hainanesis* Merr., *Erycibe* species, erycibelline (2β,7β-dihydroxynortropane) (**66**) and baogongten C (**67**) have been isolated (57). Baotongten A, (2β-hydroxy-6β-acetoxynortropane) and baogongten B have been isolated from *Erycibe obtusifolia* Benth. The roots of *Convolvulus arvensis* L. and transformed root cultures of *Calystegia sepium* R. Br. contain calystegine (calystegin) B_1 (1β,2α,3β,6α-tetrahydroxynortropane) (**12**), calystegine B_2 (1β,2α,3β,4α-tetrahydroxynortropane) (**7**) and calystegine A_3 (1β,2α,3β-trihydroxynortropane) (**6**) (58). From roots of *C. sepium* R. Br. also calystegines A_1, A_2 and A_4 (59) hae been isolated. The roots of *C. siculus* L. contain consiculine (**68**), a tropan-3α-ol esters, and merresectine B (**69**), while roots of *C. sabatius* Viv. ssp. *mauritanicus* contain consiculine (**68**) and consabatine (2'-deoxyconsiculine) (**70**). Finally from roots of *Convolvulus sabatius* Viv. ssp. *sabatius* are extracted 3α-[1,4-dihydroxy-3-(3-methyl-but-2-enyl)-cyclohex-2-enecarboxy]tropane (4'-dihydroconsabatine) (**71**) (60).
Recently, the β-isomer of phyllalbine was found *C. cneorum L.*, whose epigeal vegetative parts contain also the 3β-vanilloyloxytropane, named concneorine (**72**) (61).

From *Merremia Dissecta* Hallier F. and *M. guerichii* A. Meeuse were isolated four novel 3α-acyloxytropanes, merresectines A–D: 3α-(4-methoxybenzoyloxy)-nortropane (merresectine A) (**73**), 3α-kurameroyloxytropane (merresectine B) (**69**), 3α-nervogenoyloxytropane (merresectine C) (**74**) and 3α-[4-(β-D-glucopyranosyloxy)-3-methoxy-5-(3-methyl-2-butenyl)benzoyloxy]tropane (β-D-glucoside of merresectine D (**75**) (**76**). Moreover, the novel 3α,6β-di-(4-methoxybenzoyloxy)-tropane (merredissine) (**77**) has been isolated from *M. dissecta* Hallier F. The 4-β-D-glucoside (**78**) of merresectine E (**79**) has been identified in six *Merremia* species (60).

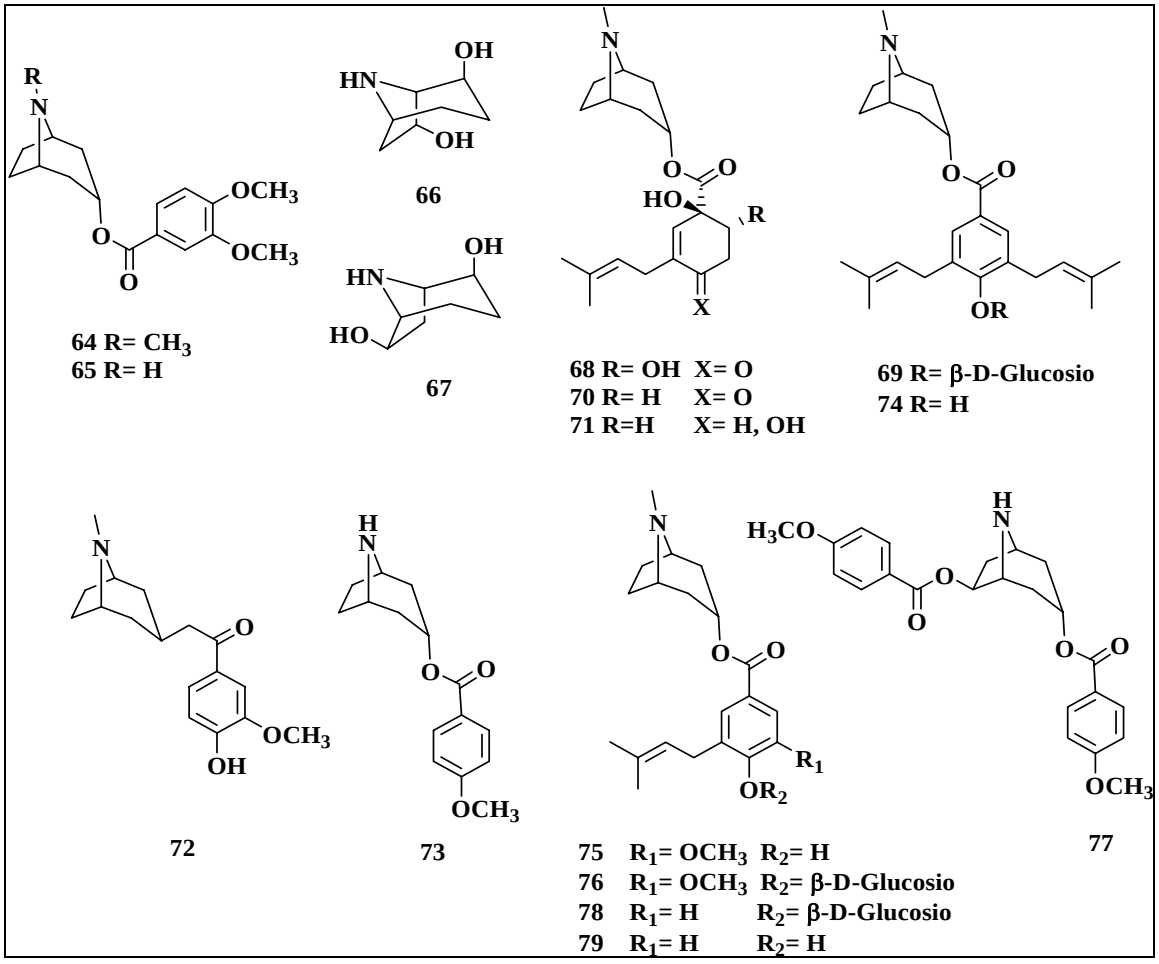

Figure 12. *Convolvine (**64**); convolamine (**65**); erycibelline (**66**); baogongten C (**67**); consiculine (**68**); merresectine B (**69**); consabatine (**70**); 4'-dihydroconsabatine (**71**); concneorine (**72**); merresectine A (**73**); merresectine C (**74**); merresectine D (**75**); merresectine D β-D-glucoside (**76**); merredissine (**77**); merresectine E β-D-glucoside (**78**); merresectine E (**79**).*

Crucifereae

Brassicaceae or Cruciferae contain a novel group of hydroxylated nortropane alkaloids, some calystegines, above all calystegine A and the 3-hydroxybenzoate ester of tropine and cochlearine (**80**). The last one is the first tropane alkaloid identified in *Cochlearia officinalis* L. and *Cochlearia arctica* Schlecht (60).

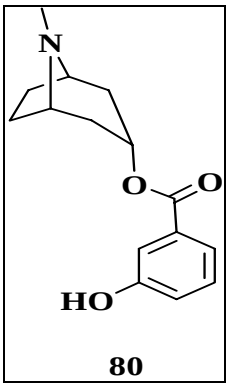

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Figure 13. *Cochlearine (**80**).*

In most genus *Cochlearia* tropine (**17**), the alcohol moiety of cochlearine (**80**) and pseudotropine (**24)** were found in minor concentration.
Calystegines were found in high concentrations in *Cochlearia officinalis* L. tissues. However, it contains calystegine A_5 (**19**) as the major compound, while calystegines A_3 (**6**) and B_2 (**7**) dominate in *Solanaceae*, calystegines B_1 (**12**) and B_2 (**7**) in *Convolvulaceae* and calystegines A_3 (**6**) and B_2 (**7**) in *Erythroxylaceae* (60).

Moraceae

Among this family, *Morus alba* L. is important to be remembered for its contents of tropan alkaloids. Specifically, from its root bark the penthydroxylated nortropane calystegine C_1 (**8**) (61), was isolated, while fruits contain calystegines A_8 and A_9 (62).

Pharmacology of Tropane Alkaloids

Cocaine (**1**), first isolated from the leaves of Peruvian *Erythroxylum coca* Lam. in 1860, shows local anaesthetic properties, stimulates the Central Nervous System and improves physical endurance. In fact, it is both a stimulant of the Central Nervous System and an appetite suppressant. Specifically, it is a dopamine reuptake inhibitor. It gives a feeling to what has been described as a euphoric sense of happiness and increased energy. It is most often used recreationally for this effect. Because of the way it affects the mesolimbic reward pathway, cocaine (**1**) is addictive. Nevertheless, cocaine (**1**) is still used in medicine as a topical anesthetic, even in children, specifically in eye, nose and throat surgery (63).

Atropine (**2**) lowers the “rest and digest” activity of muscle and glands regulated by Parasympathetic Nervous System. For this reason, it is used topically as a cycloplegic, to temporarily paralyze the accomodation reflex, and as a midriatic, to dilate the pupils. In fact, it blocks the contraction of the circular papillary sphincter muscle which is normally stimulated by acetylcholine release, thereby allowing the radial papillary dilator muscle to contract and dilate pupil. Injections of atropine are used in the treatment of bradycardia, asystole and pulseless electrical activity (PEA) in cardiac arrest. These effects take place because the main action of the vagus nerve of the parasympathetic system on the heart is to slow it down. Atropine (**2**) blocks such action and therefore may speed up the heart rate.

It is also useful in treating first degree of heart block, second degree of heart block Mobitz Type 1 and third degree heart block, too, with a high Purkinje or AV-nodal escape rhythm. Moreover, this comound acting on Parasympathetic Nervous System, inhibits salivary, sweat and mucus gland. This can be useful in treating hyperhydrosis and can prevent the death rattle of dying patients. Finally, by blocking the action of acetylcholine at muscarinic receptors, atropine also serves as an antidote for poisoning by organophosphate insecticides and nerve gases (64). Finally, hyoscyamine, the laevogyrate isomer of atropine (**2**), is used to provide symptomatic relief to various gastrointestinal disorders including spasm, peptic ulcers, irritable bowel syndrome, pancreatitis, colic and cystitis. It is also been used to control some of the symptoms of Parkinson's disease as well as for the control of respiratory secretions in end of life care (65).

Scopolamine (**3**), also known as hyoscine, is used in medicine (in form of scopolamine hydrobromide,) for its depressant activity on the Central Nervous System, though it can cause delirium in the presence of pain, midrysis and cycloplegia. Combined with morphine, it produces amnesia and a tranquilized state known as twilight sleep. It is used in ophthalmogy to deliberately cause cycloplegia and mydriasis for diagnostic purposes and in the treatment of iridocyclitis. In otholaryngology, it has been used to dry the upper airway prior to use medical instrumentation on the airway. Scopolamine (**3**) is also an antiemetic, an antivertigo and an antispasmodic and can be used in the pre-anestetic sedation, as an antiarrhithmic during anesthesia and for the prevention of motion sickness. Some times ago it was also used in obstetrics, but now it is considered dangerous in this field (66). In October 2006 researchers at US National Institute of Mental Health found that scopolamine **(3)** reduces symptoms of depression within a few days and the improvement lasted for at least a week after switching to a placebo (67).

Nicotine (**26**) effects on the cardiovascular system are mediated by sympathetic neural stimulation associated with an increase in the levels of circulating catecholamines. Nicotine (**26**) causes sympathetic stimulation through central and peripheral mechanisms. Central Nervous System mediated mechanisms include activation of peripheral chemoreceptors, particularly the carotid chemoreceptor, and direct effects on the brain stem and spinal cord. Peripheral mechanisms include release of catecholamines from the adrenal glands and vascular nerve endings (68). These effects of nicotine (**26**) result in an acute increase in heart rate and blood pressure when it is delivered via cigarette smoking, chewing gum, nasal spray or intravenous infusion. Nicotine (**26**) differentially affects blood flow to different organs, causing vasoconstriction in some vascular beds (eg. skin) and vasodilatation in others (eg. skeletal muscle). Cutaneous vasoconstriction results in a decrease in the fingertip temperature (69). Nicotine (**26**) induces vasoconstriction in coronary arteries, as evidenced by a lack of increased blood flow in response to increased oxygen demand and by direct observation, specifically in atherosclerotic arteries. Coronary vasoconstriction appears to be mediated by catecholamines and can be abolished by the α-adrenergic blocker phentolamine (70).

Calystegines (**Fig.11**) are selective glycosidase inhibitors and could be applied as pharmaceutical compounds for diabetic patients (71).

Tigloidine (**13**) seems to be a substitute for atropine (**2**) (72), so it could be a potential anti-Parkinson agent (73); moreover, it could be used in the symptomatic treatment of spastic paraplegia (74) and in extrapyramidal syndromes (Huntington's chorea) (75).

Phyllalbine acts as central and peripheral sympathomimetic (76).

Finally, because of its structural similarity with the well known (-)-hyoscyamine and (-)-cocaine (**1**), pervilleine A (**42**) shows cholinergic and adrenergic activities (77). Moreover, recent studies attest that pervilleine A (**42**) is an inhibitor of P-glycoprotein, a protein of drug efflux associated with a poor response to cancer chemotherapy, and should be further evaluated for clinical utility (42).

Discussion

Looking at the chemical structure of the tropane alkaloids, it is possible to note that all compounds are caracterized by the presence of the tropanic core and it has been proposed a possible common biosynthetic pathway, starting from the amino acid L-ornitine. After several biosynthetic steps, this compound is converted to hygrine, from which α-tropine, β-tropine, ecgonine and cuscohygrine origin (Fig. 14) and act as the bases for the biosynthesis of all the tropane alkaloids known.

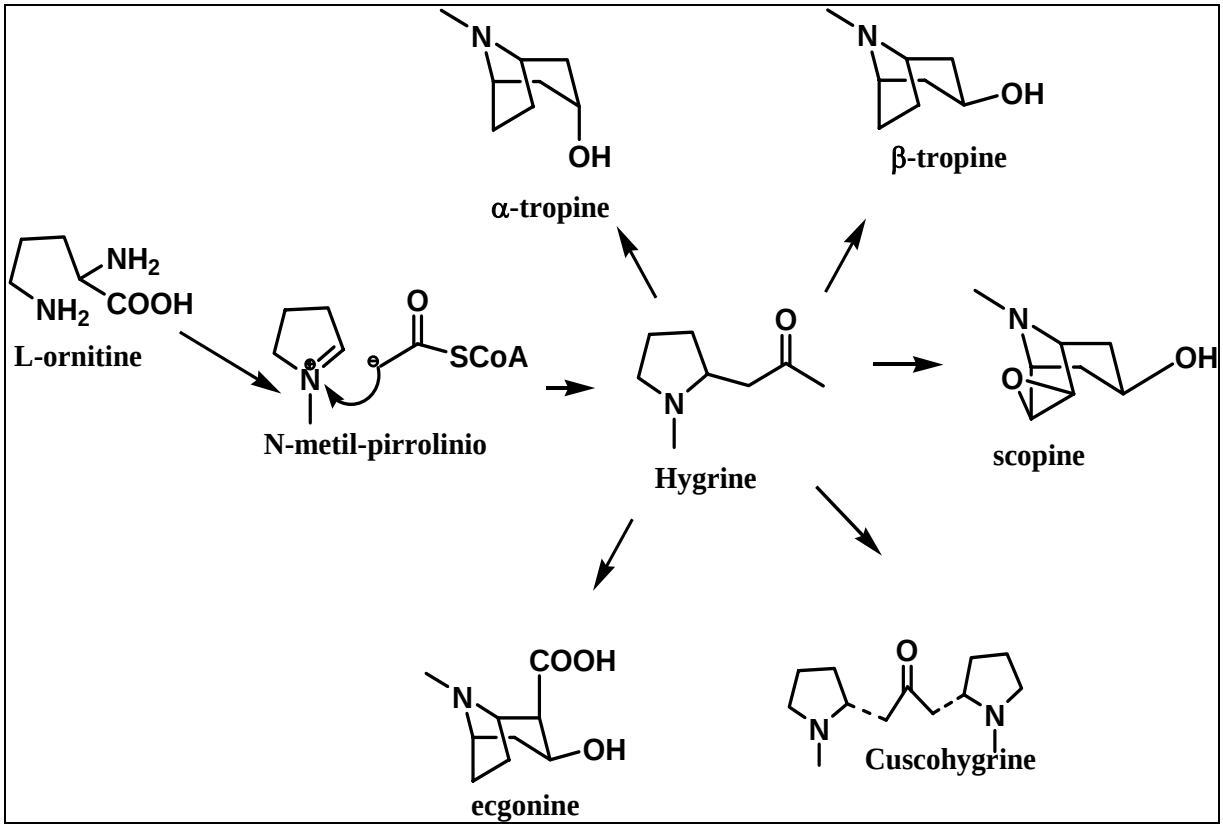

Figure 14. *Biosynthesis of tropane alkaloids from L-ornitine.*

Conclusion

Chemical and biological resemblances among different families of higher plants containing tropane alkaloids support the modern botanic classification of Solanaceae and Convolvulaceae in the order of Solanales and of Euphorbiaceae and Rhizophoraceae in the group of Malpighiales (**Fig.15**) (78).

Now, in fact, Solanaceae and Convolvulaceae are considered "sisters" because of their morphology and their plastidial DNA (79-84). In a similar way, Euphorbiaceae and Rhizophoraceae are now considered members of Malpighiales (83-86).
In addiction, the recent botanic classification considers Brassicaceae (Brassicales), Moraceae (Rosales) and Malpighiales members of the same larger group Roside (**Fig.15**) (78). This is to support, again, that biosynthesis of similar secondary metabolites can be related to a common phylogenetic origin.

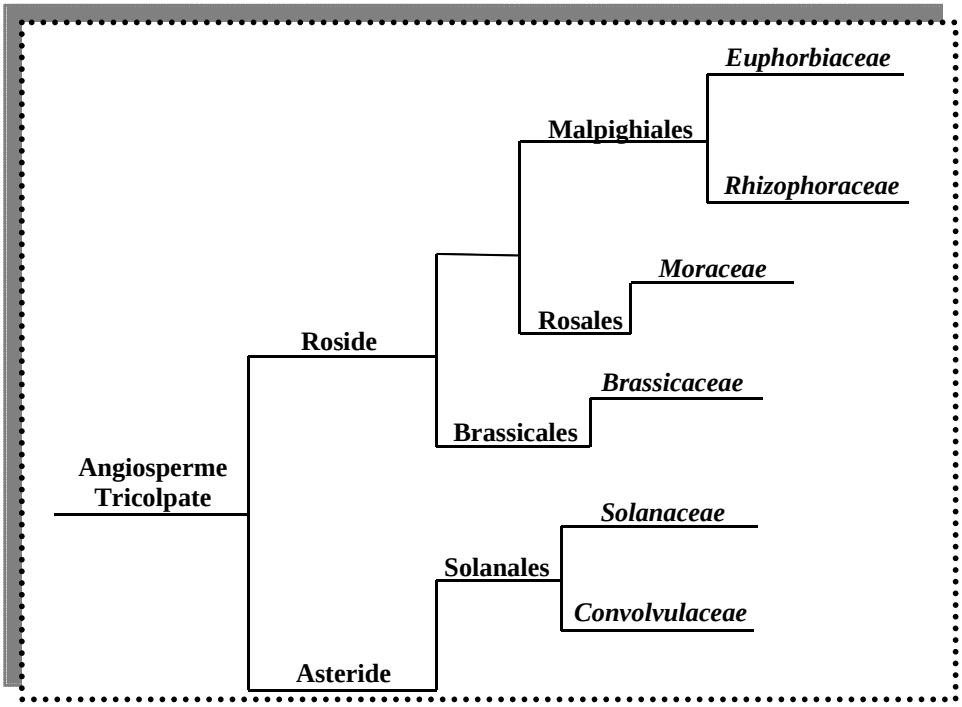

Figure 15. *Simple cladogramme of the families of higher plant containing tropane alkaloids.*

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