Alkaloid diversification in the genus *Palicourea* (Rubiaceae: Palicoureeae) viewed from a (retro-)biogenetic perspective

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Abstract The species-rich genus *Palicourea* (Rubiaceae: Palicoureeae) is source of an intriguing diversity of alkaloids derived from tryptamine and its precursor tryptophan. So far simple tryptamine analogues, polypyrroloindoline, β -carboline, and, most importantly, monoterpene-indole, i.e., tryptamine-iridoid alkaloids of various structural types including javanaside, alstroline and strictosidine derivatives have been identified. Here the diverse alkaloids that numerous studies have found in the genus are examined and organized according to their structures and biosynthetic groups. Using a parsimony-based approach that follows the concept of retro-biogenesis usually applied in synthetic chemistry, possible biosynthetic pathways are proposed and important steps and relationships between these alkaloids are highlighted. Understanding alkaloid diversification is of importance in studying the ecological significance and evolution of biosynthetic capabilities of the genus *Palicourea*, and should stimulate future investigations on the biochemical and genetic background.

Keywords Palicoureeae · Alkaloid classification · Biosynthesis · Chemosystematics · Chemodiversity

Abbreviations

CrSTR	<i>Catharanthus roseus</i> strictosidine synthase
IA	Indole alkaloid
INMT	Indolethylamine <i>N</i> -methyltransferase
MIA	Monoterpene-indole alkaloid
OpSTR	<i>Ophiorrhiza pumila</i> strictosidine synthase
PSR	Pictet-Spengler reaction
RsSTR	<i>Rauvolfia serpentina</i> strictosidine synthase
SLS	Secologanin synthase
SmGD	<i>Strychnos mellodora</i> glucosidase
STR	Strictosidine synthase
T5H	Tryptamine 5-hydroxylase
TDC	Tryptophan decarboxylase
SGD	Strictosidine β -glucosidase

Introduction

Many plant families and genera show an exceptional diversity of specialized plant metabolites playing important roles in biotic interactions as well as the adaptation to abiotic factors. This structural diversity results from a variety of biosynthetic pathway genes and biosynthetic enzymes through coordinated biosynthesis and metabolic channeling (Jørgensen et al. 2005; Weng et al. 2012). However, the

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expression of biosynthetic genes is modulated by environmental factors, and some genes may not be expressed for which Lewinsohn and Gijzen (2009) have coined the term “silent metabolism”. Knowledge about accumulation patterns and biosynthetic relationships are among the crucial principles when studying the ecological importance and evolution of plant metabolites, and for understanding the use of plants in traditional medicine. Furthermore, they are essential tools or prerequisites for optimized and sustainable production of phytotherapeutics and plant metabolites, and can help to find new leads in drug discovery. Hence, an inventory of specialized plant metabolites and their classification based upon phylogenetic and biosynthetic relationships are of fundamental importance, as exemplified by numerous chemotaxonomic studies at the generic level (e.g. Crockett and Robson 2011; Kinoshita 2014; Muangrom et al. 2021; Muellner et al. 2005; Tundis et al. 2014) or at higher-level taxonomic groups (e.g. do Nascimento Rocha et al. 2015; Jirschitzka et al. 2012; Wink 2013).

Ideally, the plant group under study is taxonomically well settled, its chemical features are known from a representative range of taxa, and the biosynthetic background is characterized by genetic and enzymatic studies. However, the knowledge of biosynthetic sequences is at the most limited to single species or compounds, being mostly of commercial or medicinal interest, and then transferred to closely related taxa. A possible way to infer biosynthetic pathways in previously unstudied species is to apply a parsimony-based approach based on the retro-biosynthetic concept, which is usually applied to design multistep enzyme catalyzed transformations. Briefly, retro-biosynthesis starts from a desired target molecule and ‘walks’ backwards to known intermediates and simple precursors using as few and reasonable (bio-)chemical transformations as possible (see below; Bachmann 2010; Hadadi and Hatzimanikatis 2015). The concept of retro-biosynthesis is presented in more detail in the section “[Biosynthetic classification of *Palicourea* alkaloids](#)”.

Alkaloids are a structurally diverse and important group of specialized metabolites showing manifold biological activities, and more than 21,000 plant-derived compounds have been identified to date (Cordell et al. 2001). There have been a number of different definitions for this structurally

inhomogeneous group of compounds since alkaloids were first described more than two centuries ago (Meissner 1819). Nowadays, alkaloids are commonly defined as natural products containing one or more nitrogen atoms originating from an amino acid. However, numerous exceptions are known and make the definition somewhat ambiguous.

Due to the lack of such an unambiguous, uniform and generally accepted structural definition, alkaloids are variously and tentatively differentiated based on their chemical structure, origin, biogenesis and/or pharmacological effect. In order to make at least some basic divisions into subgroups, the division in “protoalkaloids” and “true alkaloids” — as used by Aniszewski (2015) — is followed here. Being aware that the groups are not always unambiguous, the nitrogen in “protoalkaloids” is not part of a heterocycle. In contrast in “true alkaloids” representing the bulk of all known compounds, the amino acid-derived nitrogen is located in a heterocycle (e.g. Aniszewski 2015).

One of the largest and structurally most diverse groups of “true alkaloids” are monoterpene-indole alkaloids (MIA) with way more than 5,100 derivatives (Cordell et al. 2001). The group includes countless important drugs and other bioactive compounds such as vincristine from *Catharanthus roseus* L. (Apocynaceae), strychnine from *Strychnos* spp. (Loganiaceae) or quinine from *Cinchona* spp. (Rubiaceae) therefore creating a huge impact on human health and society. MIA are formed by a stereospecific strictosidine synthase (STR)-catalyzed Pictet-Spengler reaction (PSR) between the amine function of tryptamine and the aldehyde function of secologanin, a seco-iridoid derived from the non-mevalonate terpene biosynthesis (e.g. Aniszewski 2015; O'Connor and Maresh 2006). These compounds may thus be classified as tryptamine-iridoid alkaloids, a term that reflects their biosynthetic origin better than MIA (see below).

Taxonomy of the genus *Palicourea*

Species of the genus *Palicourea* (Rubiaceae: Palicoureeae) have been reported as rich sources of structurally diverse alkaloids indicative of varied biosynthetic capabilities (e.g. Achenbach et al. 1995; Berger et al. 2012, 2015, 2017; Kornpointner et al. 2020; Lopes et al. 2004; Paul et al. 2003). Cyclotides (Koebach et al. 2013), polyphenols, flavonoids

(Berger et al. 2016) and iridoids (Berger 2012; Lopes et al. 2004) furthermore highlight the chemical diversity of *Palicourea* species. Whilst each genus of tribe Palicoureeae appears to have its own characteristic alkaloid content (Berger et al. 2021), a number of different alkaloid classes were found in *Palicourea*. It therefore is more diverse than the other genera of the tribe, each of which containing a single class of alkaloids. Hence, the genus is a candidate for a more in-depth analysis of diversification and possible biosynthetic relationships of alkaloids occurring in closely related species.

The genus *Palicourea* (Fig. 1) consists of more than 800 species and is a member of the speciose *Psychotria* alliance comprising the sister tribes Palicoureeae and Psychotrieae with more than 3,100 species.

Recent DNA-phylogenetic studies and a re-evaluation of morphological characters have radically challenged the traditional circumscription of *Psychotria*, the largest genus of the alliance, and one of the largest genera of flowering plants. It was shown that *Psychotria*, in its traditional circumscription, is not monophyletic, and that numerous species once accommodated in the genus actually belong to other lineages (e.g. Nepokroeff et al. 1999; Razafimandimbison et al. 2014; Robbrecht and Manen 2006). Consequently, views shifted towards a narrower concept of *Psychotria* and Psychotrieae that peaked in the establishment of the sister tribe Palicoureeae and the transfer of hundreds of species of *Psychotria* subg. *Heteropsychotria* to *Palicourea* (e.g. Berger 2017, 2018; Delprete & Lachenaud 2018; Taylor and

Fig. 1 Species of *Palicourea* show a remarkable morphological and chemical diversity. **A:** *Palicourea acuminata* (Benth.) Borhidi; **B:** *Palicourea adusta* Standl.; **C:** *Palicourea glomerulata* (Donn. Sm.) Borhidi; **D:** *Palicourea hoffmannseggiana*

(Roem. & Schult.) Borhidi; **E:** *Palicourea padifolia* (Humb. & Bonpl. ex Roem. & Schult.) C.M. Taylor & Lorence; **F:** *Palicourea winkleri* Borhidi. Photographs: A. Berger

Hollowell 2016; Taylor et al. 2010; Taylor 2015a, 2015b, 2017, 2018, 2019a, 2019b). The new generic concepts within *Palicoureeae* and *Psychotrieae* are now widely accepted in floristic and systematic literature (e.g. Borhidi 2019; Kiehn and Berger 2020; Taylor 2014). Thus, most secondary metabolites previously reported from *Psychotria* were actually isolated from species now assigned to *Palicourea*, which needs to be considered when interpreting chemical characters for both genera (Berger et al. 2021).

Palicourea alkaloids

A total of 78 phytochemical studies were retrieved, and a revised taxonomic classification shows that these studies refer to 49 species of *Palicourea* as currently circumscribed (see Berger et al. 2021). Briefly, eight “protoalkaloids” were reported from three species, and 86 “true alkaloids”, derived from the amino acid tryptophan and the related tryptamine, were reported from 43 species. Six further species lack reports on alkaloids and instead accumulate other compound classes such as flavonoids, iridoids and triterpenoids. These data show that indole alkaloids—possessing an indole or indoline moiety—characterize the genus *Palicourea*.

In view of a lack of a phylogeny with sufficient taxon-sampling in *Palicourea*, the observed alkaloid diversification cannot be interpreted in a phylogenetic way. Furthermore, only a limited number of species was placed in sections based on in-depth morphological studies (e.g. Delprete & Lachenaud 2018; Taylor and Hollowell 2016; Taylor et al. 2010; Taylor 2015a, 2015b, 2017, 2018, 2019a, 2019b). Thus, it would be premature to associate the observed alkaloid diversification with intrageneric taxonomy, although some promising patterns have emerged. Instead, a classification of *Palicourea* alkaloids is recommended, which derives from structural features and possible biosynthetic relationships proposed by the parsimony-based retro-biosynthetic concept. This classification approach is non-biased by taxonomy and allows defining possible chemical characters, which could be tested and mapped on future phylogenies.

Biosynthetic classification of *Palicourea* alkaloids

The biosynthesis of monoterpene-indole alkaloids has been studied in a variety of species and several enzymatic key-steps have been identified and investigated (e.g. Barleben et al. 2007; El-Sayed and Verpoorte 2007; Geerlings et al. 2000; O'Connor and Maresh 2006). These are in particular: (1) Decarboxylation of the amino acid tryptophan to tryptamine via the enzyme tryptophan decarboxylase (TDC); (2) Formation of secologanin in the non-mevalonate monoterpene pathway; (3) Subsequent STR catalyzed condensation of tryptamine and secologanin to strictosidine, the key intermediate in the monoterpene-indole alkaloid synthesis; (4) Deglucosylation of strictosidine by a strictosidine β -glucosidase (SGD) forming reactive derivatives which undergo spontaneous or enzyme-catalyzed conversions. The latter reaction is considered the key-step for further downstream modifications towards more complex alkaloids. Likewise, all these steps take part in creating the characteristic chemical diversity found in the genus *Palicourea* (see also Berger et al. 2021).

Using these key-steps as a basic framework, the present study reviews the known biosynthetic reactions and proposes a series of chemically and biologically reasonable biochemical transformations i.e. pathways leading to the major classes of *Palicourea* alkaloids. These proposals are based on a retro-biosynthetic approach, which is applied here to infer pathways leading to the isolated major groups of alkaloids. Such studies of possible precursors based on a final metabolic product have been used for decades to make proposals for indole alkaloid biosynthesis (e.g. Scott 1970).

Within the last decade retro(-bio)-synthesis is increasingly used as a molecular pathway design method in synthetic (bio-)chemistry. The method starts from a target molecule and ‘walks’ backwards to infer simple precursors. In creating these pathways known (bio-)chemical transformations are used (Bachmann 2010; Hadadi and Hatzimanikatis 2015). Originally, this synthetic concept was developed for the design of multistep chemical or enzyme-catalyzed syntheses. Therefore, the most common application of retrobiosynthesis is the *de novo* design of pathways leading to new and/or high-value chemicals (Birmingham et al. 2014; de Souza et al. 2017; Firth et al. 2016; Green and Turner 2016; Hadadi and

Hatzimanikatis 2015). This retro-biosynthetic approach used for synthetic approaches is recently finding its way into the investigation of multistep metabolisms occurring in nature and supports the proposals of biosynthetic pathways *in planta* (Romek et al. 2015).

The biosynthetic routes deduced by this method involve minimal reaction steps, which are biologically and chemically sound. As such, the proposed reaction schemes follow the biological principle of parsimony, which assumes that the simplest of competing explanations or pathways is most likely to be correct due to strong optimizing evolutionary selection (Bordbar et al. 2014; Ye and Doak 2009). Still, it has to be noted that there is a certain risk of over-simplification, since the “simplest” reactions are not always represented in nature, and organisms sometimes follow unexpected routes to achieve a product.

Based upon these considerations, structural and (retro-)biosynthetic alkaloid groups are delineated for the genus *Palicourea* and Table 1 highlights these. In the following sections, all types of alkaloids are

enumerated, putative pathways are proposed and discussed in relation to known biosynthetic steps. In the proposed reaction schemes, retro-biosynthetic steps are not illustrated by common reaction arrows starting from the reactants and going to the products [→]. Rather, the possible reaction step is represented by a retrosynthetic analysis arrow [⇐], which starts from the product and leads to a possible simpler precursor molecule. Therewith the basic reaction type, putative reaction mechanism or possible type of enzyme can be added.

Palicourea indole alkaloid groups

Simple indole alkaloids

This group is composed of alkaloids derived directly from tryptamine without condensation reactions with building blocks from other biosynthetic pathways. Thus, they are termed ‘simple’ indole alkaloids (IA), which stands in contrast to more complex structures

Table 1 (Retro-)biosynthetic alkaloid groups and numbers of respective compounds found in species of the genus *Palicourea* (Palicoureaeae)

Alkaloid groups	Alkaloids	Spp.	% of studied spp.*
No alkaloids	–	6	12.2
Protoalkaloids**	8	3	6.1
Simple indole alkaloids (see “Simple indole alkaloids” section)	21	15	30.6
Tryptamine analogues	6	5	10.2
Polypyrroloindoline alkaloids	15	10	20.4
β-Carbolines (see “β-Carbolines” section)	4	7	14.3
Monoterpene-indole alkaloids (see “Monoterpene-indole alkaloids” section)	65	36	73.5
Tryptamine-secologanin alkaloids (see “Tryptamine-secologanin alkaloids” section)	55	33	67.3
Strictosidine and related glucosides	25	28	57.1
Strictosamide and related glucosides	4	11	22.4
Correantoides and correantines	11	2	4.1
Strictosidine-derived aglycones	7	9	18.4
Strictosamide-derived aglycones	4	5	10.2
Javaniside	1	1	2.0
Alstroines	3	1	2.0
Tryptamine-loganin alkaloids (see “Tryptamine-loganin alkaloids” section)	10	4	8.2

Species, their alkaloids, and corresponding literature data is shown in Berger et al. (2021). Note that species may contain compounds classified in several groups

* Total number of species (spp.) studied: 49

** See Aniszewski (2015)

that are formed by the incorporation of other moieties, primarily iridoids. According to the mode of cyclisation and the number of monomers involved, simple IA can be divided into two subgroups. The first comprises tryptamine analogues as well as dimers, which are likely formed from these monomers. In the second subgroup all tryptamine-derived dimeric and oligomeric structures with quaternary carbon stereocenters are included and they are termed polypyrroloindoline alkaloids. Numerous simple indole alkaloids have been isolated from species of *Palicourea*. The respective structures and their plant origins are enumerated in Berger et al. (2021), and their biosynthesis is discussed below.

Tryptamine analogues

This group includes the structurally simplest alkaloids found in *Palicourea* species, which are related to tryptamine as putative precursor. *N*-Methyltryptamine (Naves 2014) or bufotenine (5-hydroxy *N,N*-dimethyltryptamine; Ribeiro et al. 2016), the hallucinogenic principle of cane toad skin (*Rhinella marina* (Linnaeus, 1758), Bufonidae) can be mentioned as typical members of this group. Interestingly, both are related to the well-known hallucinogenic *N,N*-dimethyltryptamine (DMT), one of few alkaloid still known from the genus *Psychotria*, but that has not yet been isolated from a species of *Palicourea*. Structures of the respective alkaloids known from *Palicourea*-species are enumerated in Berger et al. (2021).

Single or double *N*-methylation of tryptamine is catalyzed by the *S*-adenosyl-*L*-methionine-dependent enzyme indolethylamine-*N*-methyltransferase (INMT; Chu et al. 2014; Mulvena and Slaytor 1983). A similar biosynthetic route towards bufotenine is proposed here by double *N*-methylation from the widespread serotonin, which is formed from tryptamine by the enzyme tryptamine 5-hydroxylase (T5H; Kang et al. 2008). Bufotenine was isolated together with two of its dimers possessing a biphenyl core structure otherwise known only from the below-mentioned polypyrroloindoline alkaloids. A similar mode of reaction is proposed here for the biosynthesis of brachybotryne (Scheme 1).

Polypyrroloindoline alkaloids

Polypyrroloindoline alkaloids also known as cyclotryptamines, hexahydropyrrolo indole alkaloids or *cis*-pyrrolidino[2,3-*b*]indoline alkaloids, are dimers and oligomers, which have emerged from tryptamine monomers. They consist of two or more units which are connected by quaternary carbon stereocenters which can lead to a great diversity of different stereoisomers (Scheme 2). The dimers chimonanthe and calycanthe as well as related oligomers are well-known constituents of the sweetshrub family (Calycanthaceae). They have received considerable attention due to their broad range of biological activities including antifungal, antiviral, antibacterial, analgesic and cytotoxic activities (Jamison et al. 2017; Ruiz-Sanchis et al. 2011; Steven and Overman 2007). In *Palicourea*, chimonanthe and calycanthe appear widespread, but oligomers are much rarer with trimers, tetramers and pentamers being already known (Berger et al. 2021).

Robinson and Teuber (1954) proposed a biosynthetic route of polypyrroloindoline dimers, which was largely confirmed in Calycanthaceae by feeding studies with the radioactively labeled precursors [3-¹⁴C]tryptophan (Schütte and Maier 1965), [1'-¹⁴C]tryptophan (O'Donovan and Keogh 1966), [2'-¹⁴C, 2-³H]tryptophan, [2'-¹⁴C, 2-³H]tryptamine and *N*-[methyl-¹⁴C]methyltryptamine (Kirby et al. 1969). All were incorporated into calycanthe and its isomer chimonanthe in good yield establishing that tryptophan, tryptamine and *N*-methyltryptamine act as precursors. In addition, the 2-³H label was retained, which allowed excluding a biosynthetic route involving a 2-oxindole. Such an oxidative coupling of two monomers has been widely used in the synthesis of calycanthe and chimonanthe derivatives (Ruiz-Sanchis et al. 2011; Schmidt and Movassaghi 2008; Steven and Overman 2007). A similar reaction was suggested as a possible biosynthetic route (Sun et al. 2014), but this is not in accordance with the above-mentioned experimental data.

Subsequently, oligomers may be formed from the dimeric 3a,3a'-bispyrrolidino[2,3-*b*]indoline (i.e. chimonanthe) core by adding further *cis*-pyrrolidino[2,3-*b*]-indoline units at *peri*-benzoid positions leading to diaryl substituted quaternary carbon stereocenters. As a possible mode of reaction, involvement of indolenine radicals via single electron oxidation of

Scheme 1 (a) Biosynthesis of serotonin from tryptophan (Kang et al. 2008) and N-methylation resulting in bufotenine. (b) Proposed radical dimerization of bufotenine to brachybotryne, two alkaloids found in *Palicourea gracilenta* (Müll. Arg.) Delprete & J.H. Kirkbr. The decisive step is the formation of the

radical intermediate stage, illustrated here by a homolytic cleavage of the C–H bond. It is not clear whether the reaction is induced photochemically (light) or chemically (radicals). TDC: Tryptophan decarboxylase; T5H: tryptamine 5-hydroxylase; INMT: indolethylamine-N-methyltransferase

N-methyltryptamine was suggested (Steven and Overman 2007). The intermediate C-3a or C-7 radicals may couple at either of the corresponding C-3a' or C-7' positions of another N-methyltryptamine unit forming the typical linkage of oligomeric polypyrroloindoline alkaloids via bis-3-[2-(methylamino)ethyl] indoline intermediates (Scheme 2). Based on the position of the C-3a–C-3a' linkage and the resulting chimonanthe core as either “terminal” or “internal”, different structural groups are differentiated in oligomers (Jamison et al. 2017).

Furthermore, Kirby et al. (1969) demonstrated the spontaneous conversion of chimonanthe to calycanthe under acidic conditions and therefore questioned if calycanthes really occur in nature or are artifacts derived from acid/base extraction (Steven and Overman 2007). In conclusion, feeding studies with labeled precursors have established that the biosynthesis of chimonanthe starts from tryptophan and proceeds via the intermediates tryptamine and N-methyltryptamine as shown in Scheme 3.

β-Carbolines

Alkaloids with a tricyclic pyrido(3,4-*b*)indole skeleton are generally called β-carbolines. Depending on the

saturation of ring C, they are divided in β-carboline, dihydro-β-carboline and tetrahydro-β-carboline alkaloids. The present chapter is focused on structurally ‘simple’ β-carbolines that are devoid of additional fused-ring systems and other major modifications (Allen and Holmstedt 1980). In turn MIAs with a β-carboline core showing a formal terpenoid C₁ substituent, belong to a different biosynthetic group and have a different numbering of the positions, which is derived from that of strictosidine. These compounds are discussed in the section “Monoterpene-indole alkaloids”. For general details to numbering of indole alkaloids see Le Men and Taylor (1965).

β-Carbolines are frequently C₁-methylated and such compounds belong to the so-called harmala alkaloids. They are named after their first known source, the well-known African rue (*Peganum harmala* L.; Nitrariaceae), but are also found in *Banisteriopsis caapi* (Spruce ex Griseb.) C.V. Morton (Malpighiaceae) and other plants of ethnobotanical importance. These compounds act as reversible monoamine oxidase inhibitors targeting the MAO-A isoform and are thus of pharmacological interest (Wang et al. 2010). Within the genus *Palicourea*, harman and derivatives such as harman-3-carboxylic

Scheme 2 Proposed biosynthetic routes to polypyrroloindoline alkaloids (Jamison 2017; Schütte and Maier 1965; Steven and Overman 2007). Accordingly, the *N*-methylation of tryptamine is shown here as an introductory step. However, there are no indications that this *N*-methylation can be ruled out at a later stage in the reaction sequence. Shown are the *N*-methyl indolenine radicals in position 3 and 7, likely generated by single electron oxidation of *N*-methyltryptamine monomers. The unpaired electron is located at the bond-forming position in order to provide a better overview for the reactions to the dimers / oligomers. These radicals are possible precursors for 3,3'- and

3,7'-dimerization, as well as for 3,7'-polymerization, respectively. These three different dimerizations represent the key steps in the reaction cascades. The basic structure of the resulting dimer is decided in each case. Following addition would lead to chimonanthine and to precursor for synthesis of hodgkinsine and respective further oligomers. In chimonanthine and hodgkinsine all chiral centers possibly forming different diastereomers are indicated with asterisks. Some bonds are indicated in bold for better recognition in the different structures. INMT: indolethylamine-*N*-methyltransferase

acid or tetrahydronorharman-1-one are known. Their structures are enumerated in Berger et al. (2021).

Biosynthesis of harmala alkaloids was shown to involve a PSR with the ketone function of pyruvic acid

Scheme 3 Follow up reactions of the chimonanthe core observed under acidic conditions. The ring system opens leading to calycanthe and iso-calycanthe cores via two different modes of cyclization indicated as ‘a’ and ‘b’ (Kirby et al. 1969;

Steven and Overman 2007). Both pathways are suggested to occur during isolation procedures. Some bonds are indicated in bold for better recognition of the different structures

and subsequent oxidation and dehydrogenation reactions (Rommelspacher et al. 2012). This pathway was studied in plants by feeding radioactively labeled precursors to *Elaeagnus angustifolia* L. (Elaeagnaceae) and *Passiflora edulis* Sims (Passifloraceae; Herbert and Mann 1982). A PSR of tryptamine with pyruvic acid leads to a 1-methyl-tetrahydro- β -carboline-1-carboxylic acid intermediate, which is oxidatively decarboxylated to harmalan (Herbert and Mann 1982; Scheme 4). A corresponding enzyme is not yet known, but the first step of the reaction may be catalyzed by STR or a related Pictet-Spenglerase. These enzymes are discussed below in the section “Monoterpene-indole alkaloids”.

Monoterpene-indole alkaloids

Numerous monoterpene-indole alkaloids have been isolated from species of *Palicourea* and the respective structures and source-plants are enumerated in Berger et al. (2021). The basic biosynthetic steps towards tryptamine and secologanin are well established (e.g. O’Connor and Maresh 2006) and the key role of STR towards strictosidine as one key intermediate has already been addressed before. This enzyme catalyzes

the stereospecific Pictet-Spengler reaction (PSR) between the amine function and the pyrrole moiety of tryptamine and the aldehyde function of secologanin (Scheme 5). Apart from the resulting tryptamine-secologanin i.e. monoterpene-indole alkaloids like strictosidine, several tryptamine-loganin alkaloids have also been described (see “Strictosamide and related glucosides” section and Scheme 12). They most probably derive from a PSR between tryptamine and an oxidized loganin moiety and are differentiated here, but corresponding enzymes remain unknown. All products resulting from these PSRs bear a tricyclic tetrahydro- β -carboline core (compare also “ β -Carbolines” section). It represents the basic structure of all tryptamine-iridoid alkaloids and acts as the key intermediate in the biosynthesis of a large number of further derived natural products, which are the result of subsequent reactions and rearrangements (O’Connor and Maresh 2006). With few exceptions, in *Palicourea* all tryptamine-iridoid alkaloids show a tryptamine to iridoid ratio of 1:1. However, see bahienoside (Scheme 6) and alstroines (Scheme 11) as examples for compounds with a 1:2 ratio in this genus.

Scheme 4 Biosynthesis of harmala group β -carboline alkaloids starting from tryptamine according to Herbert and Mann (1982). Key step is a Pictet-Spengler type reaction of tryptamine with the keto function of pyruvic acid

Scheme 5 Strictosidine synthase catalyzed biosynthesis of strictosidine via a stereospecific Pictet-Spengler reaction. The central tetrahydro- β -carboline core in strictosidine is indicated in bold. STR: strictosidine synthase

In synthetic chemistry, a variety of aldehydes can be used for a PSR leading to the tetrahydro- β -carboline core (e.g. Sudžuković et al. 2016). Even biocatalyzed reactions with STR have been applied to synthesize carboline structures (e.g. Pressnitz et al. 2018). However, *in planta* corresponding enzymes usually have a high rate of substrate specificity. The enzyme STR is one of the most-studied Pictet-Spenglerases and was characterized from the apocynaceous *Catharanthus roseus* (CrSTR) and *Rauvolfia serpentina* (L.) Benth. ex Kurz (RsSTR), as well as from the rubiaceaceous *Ophiorrhiza pumila* Champ. ex Benth. (OpSTR). CrSTR and RsSTR share 82% sequence identity and both tolerate a variety of substituted tryptamine analogues, but only minor changes of the aldehyde are accepted (Bernhardt et al. 2010; Ma et al. 2006; McCoy et al. 2006; Treimer and Zenk 1979).

By contrast, the rubiaceaceous OpSTR has a low sequence identity to its apocynaceous homologs CrSTR (54%) and RsSTR (60%) and differs by also accepting a range of simple aldehydes (Bernhardt et al. 2010). Due to common ancestry within Rubiaceae, STR from species of *Palicourea* is closer related to OpSTR than to CrSTR and RsSTR, which suggests a comparable degree of substrate promiscuity. It is therefore possible that STR from *Palicourea* spp. is capable of catalyzing both, the biosynthesis of secologanin- and loganin-derived tryptamine-iridoid alkaloids. Likewise, the enzyme is also a conceivable candidate for the biosynthesis of β -carboline alkaloids (see " β -Carbolines" section), alstroines and javanins (see "Tryptamine-secologanin alkaloids"

section). Hence, it appears promising to characterize STR from *Palicourea* in the future.

It should also be mentioned that the vast majority of tryptamine-secologanin alkaloids found in *Palicourea* species are reported to possess a $3\alpha\text{H}$ orientation (see Berger et al. 2021). This can be attributed to the dynamic stereoselectivity of STR during the Pictet-Spengler reaction leading to strictosidine and the resulting follow up products. Hence, the assumed reaction steps are shown here for the $3\alpha\text{H}$ orientation starting from strictosidine, except were indicated otherwise. However, analogous steps towards the few derivatives with $3\beta\text{H}$ orientation are also possible starting from the C3-epimer of strictosidine, vincoside, which remains unknown in the genus *Palicourea*. It cannot be ruled out that there are species that exclusively form such epimers by activity of another Pictet-Spenglerase with 3β stereoselectivity. However, the discovery of such a "vincoside synthase" appears unlikely given all the time and effort invested by numerous research groups into the study of MIA biosynthesis in *Catharanthus*, *Rauvolfia* and other genera.

Tryptamine-secologanin alkaloids

Strictosidine and related glucosides

The occurrence of tryptamine-secologanin MIA structurally similar to strictosidine was reported from many species of *Palicourea* and appears to prevail in the genus (see Berger et al. 2021). They feature only minor structural modifications, which do not lead to rearrangements or other pronounced reorganizations

Scheme 6 Strictosidine synthase-catalyzed biosynthesis of strictosidine and derivatives from tryptamine and secologanin. The Pictet-Spengler reaction, which leads to strictosidine, can be seen as a key step in this reaction cascade. Only 5-carboxy strictosidine and desoxycordifoline are probable exceptions. So far, there is no evidence for a decarboxylation of one of the two

in the core moieties of the molecules. Variations found within these alkaloids include 1) Saponification of the carboxylic ester of the iridoid moiety leading to e.g. strictosidinic acid. 2) Presence of functional groups on the tryptamine core like 5-carboxystrictosidine. 3)

compounds. However, this reaction cannot be ruled out, and is therefore given here as a possible pathway. Furthermore, note the formation of an additional ring system in ophiorines; the bond formation is indicated by an arrow in the precursor lyaloside. TDC: tryptophan decarboxylase; STR: strictosidine synthase

Various *N*-alkylations in position 4 such as in palicoside or bahienoside which incorporates a second secologanin unit. 4) Dehydration of the C-ring to gain an aromatic β -carboline core like in lyaloside. 5) Modifications of the glucoside moiety resulting in di-

and oligosaccharides or their cinnamic acid esters such as present in the various cinnamoyl lyalosides.

Interestingly, most derivatives of strictosidine retain the glucose moiety. This is remarkable because *Palicourea* species create chemical diversity by omitting strictosidine β -glucosidase, otherwise considered the gateway to tryptamine-iridoid alkaloid diversity (O'Connor and Maresh 2006). Hence, it is hypothesized here that the maintenance of the characteristic glucose residue might be caused by a downregulated or outright inoperative SGD activity in a couple of *Palicourea* species channeling the biosynthesis towards other pathways.

The presence of a carboxyl group at C-5 is a rare structural feature found in 5-carboxystrictosidine and desoxycordifoline. A probable origin of the carboxyl group could be a direct condensation of tryptophan with secologanin in a PSR leading to 5-carboxystrictosidine. It was shown that CrSTR (see above) does not accept tryptophan as substrate (Treimer and Zenk 1979), but it remains unknown if a corresponding STR from the genus *Palicourea* would catalyze such a condensation. Carboxylation of strictosidine would represent an alternative route, but such a reaction appears unlikely, as corresponding carboxylases are rare and restricted to carbon fixation. The biosynthetic pathways putatively leading to strictosidine, 5-carboxystrictosidine and other derivatives are shown in Scheme 6.

Another interesting structure is found in ophiorines (A and B), first reported from and named after the genus *Ophiorrhiza* (Rubiaceae; Aimi et al. 1985). Within *Palicourea*, ophiorines are exclusively known from *Palicourea suerrensii* (Donn. Sm.) Borhidi (Berger et al. 2017). They possess a unique N -4 $\rightarrow$ C-17 linkage creating an additional heterocycle by formal alkylation of N -4. However, they retain their glucose moiety and the carboxyl group from the iridoid function. According to their (positively charged) quaternary ammonium cation and negatively charged carboxyl group, these are classified as betaine-type tryptamine-iridoid alkaloids. A possible biosynthetic pathway starting from strictosidinic and lyalosidic acid via a cyclisation of the double bond of secologanin and the amine function of the tryptamine moiety is proposed in Scheme 6.

Strictosamide and related glucosides

Strictosamide is a glucoside featuring a pentacyclic core and a lactam ring. It is found in several species of *Palicourea* such as in *Palicourea acuminata* (Benth.) Borhidi (Berger et al. 2017; see Berger et al. 2021 for a full enumeration). The conversion of strictosidine to strictosamide is regarded as the first step in camptothecin biosynthesis in both, *Ophiorrhiza pumila* and *Camptotheca acuminata* Decne. (Nyssaceae), as demonstrated by feeding studies with radioactively labeled precursors (Hutchinson et al. 1974, 1979; O'Connor and Maresh 2006). The conversion of strictosidine to strictosamide requires the loss of a methyl ester at C-22, and, in contrast to the formation of correantosides and correantines, no N -4 alkylation. As earlier described by Hutchinson et al. (1974), it is proposed that strictosidinic acid acts as the direct precursor, which could form strictosamide by an intramolecular cyclization (Scheme 7a). More specifically, a lactam is formed between the secondary amine and the carboxyl group derived from secologanin, which forms strictosamide upon elimination of water. To date, however, no respective enzymes are known for this lactam formation.

Correantosides and correantines

Correantosides and the related correantines differ from other MIA by incorporating an azepane moiety, which is derived by an intramolecular cyclization between N -1 and the iridoid framework as well as an epimerisation of position 3 (Scheme 7b, 7c). Whilst correantines are aglycones, correantosides still bear the glucose moiety and the exocyclic ethylene group originating from secologanin. So far, correantines and correantosides appear to be a rare feature within *Palicourea*, hitherto known only from *Psychotria stachyoides* Benth. (Pimenta et al. 2010a, 2010b, 2011) and *Palicourea corraeae* (Dwyer & M.V. Hayden) Borhidi (Achenbach et al. 1995). The respective structures found in these species are shown in Berger et al. (2021).

The formation of both, correantosides and correantines appears to require an N -4 methylation, which acts as an amine protecting group. This blocks the reaction of this specific amine function with either the aldehyde/enol tautomeric group at C-17 or C-21, as well as with the carboxyl function, which would both

Scheme 7 Proposed biosynthesis of strictosamide (pathway **a**), correantiosides (pathway **b**) and correantines (pathway **c**) starting from strictosidine. A direct lactamisation is likely in pathway (**a**). However, a saponification to strictosidinic acid cannot be excluded, from which strictosamide is then formed by a ring closure to the lactam ring. In pathways (**b**) and (**c**) either

lead to a presumably sterically and thermodynamically favored hexacyclic ring system. In addition, all these isolated alkaloids with an azepane moiety show an epimerization at position 3. Vincoside, the *C*-3 epimer of strictosidine is likely not the precursor, at least in *Palicourea*, since an isolation of this compound has hitherto not been described from this genus. Instead, a *C*-3 epimerization of dolichantoside (4-*N*-β-methyl strictosidine) to isodolichantoside seems rather more likely, as the latter compound has already been isolated from two species of the genus (see Berger et al. 2021). To date, however, there are no studies on the course of this isomerization in a natural environment.

Correantiosides and correantines differ in the mode of azepane formation and substitution pattern. It is hypothesized that correantiosides are formed from isodolichantoside by saponification of the methyl ester. This leads to the not yet isolated *C*-3 epimer of palicoside, which can undergo a lactam formation of

saponification or deglucosylation leads to the respective products. Some bonds are indicated in bold (black or red) for better recognition and identification of the different structures. *N*₆-methyl-21-β-hydroxy-mayumbine and akagerine are referenced in the text and are shown in a box; both are not found in *Palicourea*

the carboxyl group (*C*-22) with *N*-1 resulting in correantiosides (Scheme 7b). Within this reaction sequence the glucoside and the exocyclic vinyl moiety are retained. By contrast, the related correantines could originate from the deglucosylation product of isodolichantoside, leading to a different structure incorporating part of the exocyclic vinyl moiety and retaining the carboxyl group (Scheme 7c). The corresponding linkages are *C*-18→*N*-1 and *C*-20→*O* (of the secologanin ring). A similar reaction leading to alkaloids with an azepane moiety was proposed for compounds isolated from *Strychnos johnsonii* Hutch. & M.B. Moss (Massiot et al. 1987).

Various studies on the *in vitro* enzymatic deglucosylation of strictosidine and derivatives indicate that subsequent rearrangements of the aglycone are spontaneous, substrate driven and affected by enzymes and experimental setup. After deglucosylation of isodolichantoside with an unspecific β-glucosidase, correantine A is formed (Achenbach et al. 1995). After

incubation of dolichantoside with SGD from *Rauvolfia serpentina*, 3-isocorrealine A is formed (Gerashenko et al. 2002). By contrast, incubation of dolichantoside with three glucosidases isolated from *Catharanthus roseus*, *Strychnos mellodora* S. Moore (SmGD) and sweet almonds (*Prunus dulcis* (Mill.) D.A. Webb; Rosaceae) gave *N*₆-methyl-21- β -hydroxy-mayumbine, a hetero-yohimbine quaternary alkaloid. After incubation of palicoside with SmGD, two conversion products were formed, and one was identified as akagerine (Brandt et al. 2001). Again this demonstrates the formation of an azepane moiety from a strictosidine backbone.

Strictosidine-derived aglycones

Deglucosylation of strictosidine by a dedicated SGD leads to a reactive species that subsequently undergoes a spontaneous conversion leading to various structural types. Hence, this reaction is considered to be the key-step initiating downstream modifications towards more complex alkaloids (Smith et al. 1968; see also O'Connor and Maresh 2006). From *Palicourea* species some strictosidine-derived aglycones have been isolated, which are likely early products of this metabolic process (Scheme 8). The respective compounds are enumerated in Berger et al. (2021).

One of these aglycones is (*E/Z*)-vallesiachotamine, which was first discovered in the apocynaceae *Vallesia glabra* (Cav.) Link (Djerassi et al. 1966, as *V. dichotoma* Ruiz & Pav.), and later found to be quite common in *Palicourea* as well as in other Rubiaceae. *In planta* the deglucosylation of strictosidine leads to a reactive intermediate that undergoes spontaneous cyclization leading to vallesiachotamine (O'Connor and Maresh 2006). The same reaction was also demonstrated in 22 strains belonging to 21 species of bacteria cultivated in a minimal medium spiked with strictosidine (Shen et al. 1998). These results demonstrate that an unspecific β -glucosidase is sufficient for vallesiachotamine formation. A possible biosynthesis of vallesiachotamine and related strictosidine-derived aglycones is shown in Scheme 8.

The structurally related lagamboside was first described from *Palicourea acuminata* (Berger et al. 2012) and appears to be of rather restricted occurrence. Beside large amounts of the widespread strictosamide, the aglycones 10-hydroxy isodeppeaninol, 10-hydroxy antirrhine and 10-hydroxy antirrhine *N*-

oxide, were isolated from *Palicourea prunifolia* (Kunth) Steyerl. (Faria et al. 2010; Kato et al. 2012). 10-Hydroxy isodeppeaninol is related to deppeaninol which was isolated from the rubiaceae *Deppea blumenaviensis* (K. Schum.) Lorence (Kan-Fan et al. 1995). A similar open chain was found in tetrahydroakagerine isolated from *Strychnos johnsonii* Hutch. & M.B. Moss (Massiot et al. 1987). In contrast 10-hydroxy antirrhine is related to antirrhine, which was first isolated from the rubiaceae *Antirhea putaminosa* (F. Muell.) F. Muell. (Johns et al. 1967), but is also known from *Strychnos johnsonii* (Massiot et al. 1987).

Besides forming a key biosynthetic intermediate in the downstream modification of strictosidine, the deglucosylation reaction was suggested to be involved in plant defense against herbivores (Gurimand et al. 2010). Upon disruption of the cell tissue, the strictosidine pool reacts with the dedicated SGD releasing a reactive aldehyde intermediate, in a similar way as the famous “mustard oil bomb” myrosinase–glucosinolate defense system in Brassicaceae. Hence the active principle was suggested not to be a selective, non-covalent binding to a receptor leading to symptoms of intoxication, but rather non-specific reactions with various functional groups capable of protein cross-linking and precipitation.

Strictosamide-derived aglycones

In addition to strictosidine, strictosamide is also known to act as a precursor of various alkaloids with a pronounced reorganization of the iridoid moiety as found in *Camptotheca acuminata* and *Ophiorrhiza pumila*. Likewise, it is here considered as a precursor for the biosynthesis of the below-mentioned alkaloids. Strictosamide is deglucosylated, probably by the enzyme SGD, which supposedly leads to a reactive dialdehyde intermediate, as demonstrated for strictosidine (e.g. O'Connor and Maresh 2006).

In *Palicourea prunifolia* strictosamide as well as the putatively strictosamide-derived aglycones prunifoleine and 14-oxoprufoleine were found in addition to some of the above mentioned strictosidine-derived aglycones (Faria et al. 2010; Kato et al. 2012). The two prunifoleines are characterized by their unusual ring formation (Scheme 9) and their co-occurrence with strictosamide makes its deglucosylated form a probable precursor. However, deglucosylated strictosidine or an ophiorrhine may also act as precursor.

Scheme 8 Possible biosynthesis of strictosidine-derived aglycones after strictosidine β -glucosidase catalyzed deglucosylation. All subsequent reactions are based on the reactive intermediate and lead to a quite large structural variability: An en-amine formation (a) would lead to a yet undescribed intermediate, which is a possible precursor for (*E/Z*)-vallesiachotamine after an epimerization, and lagamboside after a *N*-

glucosylation and reduction. Furthermore, a saponification and decarboxylation (b) followed by reduction of the aldehyde and oxidation at position 10 would lead to 10-hydroxy isodeppeanol. In two consecutive follow up reactions 10-hydroxy antirhine and 10-hydroxy antirhine *N*-oxide can be generated by cyclisation and following *N*-oxidation; SGD: strictosidine β -glucosidase

Furthermore, angustine was isolated from *Palicourea didymocarpos* (A. Rich.) Griseb. (Paul et al. 2003; as *Psychotria bahiensis* DC.). Angustine-type alkaloids are aglycones and possess a pyridine instead of a dihydropyran ring, and likely derive from strictosamide after deglucosylation (Scheme 9). It is worth mentioning that the oxo-derivative naucletine was found in *Psychotria suterella* Müll. Arg. (van de Santos et al. 2001). Angustine-type alkaloids appear to be widespread and are also known from *Mitragyna*, *Nauclea*, *Strychnos* and *Uncaria* within the Gentianales (Hotellier et al. 1975; Phillipson et al. 1974). In these species, angustine or naucletine are accompanied by strictosamide, which supports that it is a precursor for both. Structures of all further strictosamide-derived aglycones from *Palicourea* species are shown in Berger et al. (2021).

Javaniside

Javaniside is a MIA first reported from *Alangium javanicum* (Blume) Wangerin (Cornaceae; Ma and Hecht 2004) and was recently isolated from *Palicourea luxurians* (Rusby) Borhidi. It represents the only spirocyclic oxindole alkaloid reported from the genus *Palicourea* (Scheme 10, Kornpointner et al. 2020; see also Berger et al. 2021). Alkaloids with a spiro structure, i.e., two cycles fused at a central carbon, are compounds with various bioactivities, and are well-known from species of the genus *Uncaria* (Rubiaceae; e.g. Muhammad et al. 2001; Wang et al. 2011). Kornpointner et al. (2020) proposed two possible cyclisation reactions related to a Pictet-Spengler type reaction probably catalyzed by STR. A direct oxidation leads to the spiro-oxindole moieties in an earlier step of the biosynthesis. Another possibility of javaniside biosynthesis is an oxidation, which proceeds analogously to the conversion of heteroyohimbines to oxindole alkaloids. This involves

Scheme 9 Proposed biosynthesis of strictosamide-derived aglycones. Here the reactive intermediate from the glucoside cleavage is the key structure for further reactions: A pyridine formation and dehydrogenation can lead to angustine. Alternatively, prunifoleine and 14-oxoprunifoleine might derive in a cascade of reactions starting from deglucosylated strictosamide. This cascade includes a saponification of the amide followed by decarboxylation of the resulting β -keto acid. The resulting aldehyde, which is here shown as enol, is subject to enamine formation, while the second aldehyde is reduced to an alcohol

rearrangement and oxidation at a later step in biosynthesis (Saxton 2009; Stavrinides et al. 2016). Since both proposed reaction mechanisms can be traced back to tryptamine and secologanin, javaniside may be viewed in the broadest sense as strictosidine-related glucoside. Due to the unique spiro structure, it is here treated in a distinct group.

function, which further reacts to the double bond of the enamine in an addition. Furthermore, there is dehydrogenation and associated aromatization, which is comparable to the conversion of 5-carboxy strictosidine to desoxycordifoline. The sequence of these steps is not clear, and hence no further possible intermediates are shown here. Furthermore, it cannot be excluded that a similar reaction cascade starting from deglucosylated strictosidine or an alternative reaction sequence starting from ophiorines would (also) lead to prunifoleine and 14-oxoprunifoleine; SGD: strictosidine β -glucosidase

Javaniside belongs to the class of 2-oxindole alkaloids. The biosynthesis as well as synthesis of other representatives of this compound class is well studied (see e.g. Lopes et al. 2019; Martin et al. 1991). Therefore, similar work is necessary to investigate the proposed javaniside biosynthesis in *Palicourea* in the context of the general 2-oxindole alkaloids biosynthetic pathways.

Scheme 10 Proposed biosynthesis of javanide starting from tryptamine which reacts with secologanin in a Pictet-Spengler type reaction, and upon oxidation forms a spiro-type compound.

The basics of the mechanism go back to Bailey (1987). Further saponification and lactam formation results in javanide (Kornpointner et al. 2020); STR: strictosidine synthase

Scheme 11 Proposed biosynthetic route to alstroetine and iso-alstroetine type structures. Starting from tryptamine a cyclization and oxidation leads to an alline-type intermediate. A following enamine formation with two secologanin units leads to quasi symmetrical follow up product. Depending on the

position of a protonation on one of the enamine moieties a spontaneously cyclization leads to the iso-alstroetine (a) or alstroetine (b) skeleton in a Mannich type reaction mechanism (Kornpointner et al. 2020)

Alstroetines

Alstroetines are a group of MIA possessing an unusual hexahydropyrrolo indole core and a tryptamine to secologanin ratio of 1:2. These compounds were first isolated and described from *Alstonia rostrata* C.E.C. Fisch. (Apocynaceae; Cai et al. 2011) and subsequently found in a single species of *Chassalia* and *Rudgea*, both from tribe Palicoureeae (Schinnerl et al. 2012). The derivatives alstroetine A, dehydro-rudgeifoline and iso-alstroetine A were recently isolated from *Palicourea luxurians* (Kornpointner et al. 2020), which represents the first record for the genus *Palicourea*. The reports from three single species out of three genera indicate that alstroetines are uncommon and of scattered occurrence in the tribe (see also Berger et al. 2021).

Cai et al. (2011) proposed a biosynthetic route involving the condensation of a cyclized tryptamine

and two units of secologanin leading to the reported tetracyclic system. In an additional analysis inspired by two newly described derivatives, Kornpointner et al. (2020) proposed a refined biosynthetic route in which tryptamine is cyclized to a tricyclic alline-type molecule similar to the core structures found in polypyrroloindoline alkaloids (see “Polypyrroloindoline alkaloids” section). Subsequently, the two secondary amine functions can react with the respective aldehyde functions of two secologanin units forming enamines. Finally, two possibilities of acid-catalyzed cyclization reactions lead to various alstroetine derivatives (Scheme 11).

Tryptamine-loganin alkaloids

Contrary to the above-mentioned secologanin-derived tryptamine-iridoid alkaloids, a related group features a loganin instead of the common secologanin moiety

Scheme 12 Proposed biosynthesis of loganin-derived tryptamine-iridoid alkaloids. Here, two quasi parallel biosynthetic pathways are formulated, which are shown one above the other, and which differ in the elimination of water. This dehydration is assumed here to be an early point in biosynthesis, when deoxygeniposide is being formed from loganin. However, such an elimination can also be assumed in further steps, which are not shown here for reasons of clarity. Any epimerization in brachycerine and palicroceaine (indicated with a box) cannot be

conclusively explained and should be the aim of future investigations. The same applies to the possible epimerization at C-21 in the biosynthesis of croceaine A and psychollatine. This epimerization requires de- and re-glucosylation of the epimeric acetal. In the case of amination (brachycerine to palicroceaine), formaldehyde is specified as a formal reagent. The additional carbon probably originates from methionine followed by oxidation, comparable the biosynthesis of berberine (Amann et al. 1986)

(Scheme 12). So far, such tryptamine-loganin alkaloids have been reported from four species of *Palicourea*, which are enumerated in Berger et al. (2021). Following Gregianini et al. (2004), it is likewise hypothesized that these are formed by the condensation of tryptamine and an oxidized loganin derivative. The reaction is probably catalyzed by STR or a related Pictet-Spenglerase, which is expected to show a similar degree of substrate promiscuity as reported for the only characterized rubiaceous STR accepting a number of different aldehydes (see "Monoterpene-indole alkaloids" section).

Cleavage of loganin to secologanin is catalyzed by the enzyme secologanin synthase (SLS; De Luca et al. 2014; O'Connor and Maresh 2006; Panjekar et al. 2012; Yamamoto et al. 2000). The formation of secologanin is considered a bottleneck in tryptamine-iridoid alkaloid formation (Oudin et al. 2007) and may be hampered by downregulation of SLS or a detrimental mutation. The resulting lack of secologanin and concomitant presence of loganin may channel the biosynthesis towards loganin-derived alkaloids. Two possible and nearly identical biosynthetic sequences

are discussed here, but corresponding enzymes catalyzing these steps are not yet known.

Firstly, loganin might be oxidized to 10-hydroxyloganin, a compound already known from three species of Rubiaceae (Mitova et al. 2002). A subsequent follow up oxidation of the hydroxyl leads to an aldehyde, which is required for a PSR (Bernhardt et al. 2010; O'Connor and Maresh 2006). The corresponding aldehyde is not yet known from nature, but it might be an intermediate condensed with tryptamine to form brachycerine, as shown in Scheme 12. However, the simultaneous isomerization of four chiral centers required for the reaction requires further investigations. Palicroceaine is likely a follow-up product after an amination (Berger et al. 2015). An inverted stereochemistry is reported from four of the five loganin-derived chiral centers in each of these two compounds (indicated in a box in Scheme 12). It remains unclear whether an epimerization or a biosynthesis of an enantiomer of loganin can be made responsible for these inversions.

Secondly, an alternative route from loganin starting with an elimination at position 7 to form

Scheme 13 Sequential decarboxylation and stepwise *N*-methylation as possible key steps in channeling tryptophan and tryptamine towards various alkaloid biosynthetic pathways in

Palicourea species. STR: strictosidine synthase; TDC: tryptophan decarboxylase; INMT: indolethylamine-*N*-methyltransferase

deoxygeniposide is feasible. Upon hydroxylation at position 10, geniposide might be formed. The biosynthetic conversion of loganin to geniposide in Rubiaceae was proposed by Inouye et al. (1972) using feeding experiments with labeled precursors. Further oxidation could lead to the corresponding aldehyde 10-dehydrogeniposide. The compound was already described from the rubiaceae *Hedyotis diffusa* Willd. (Zhang and Luo 2008) and from the apocynaceae *Cerbera manghas* L., where it was found together with loganin (Yamauchi et al. 1990). Condensation of tryptamine with 10-dehydrogeniposide could finally lead to croceaine A and psychollatine, depending on absolute configuration at C-3. It has to be emphasized that absolute configuration at C-21 is reported to be

inverted between 10-dehydrogeniposide and croceaine A as well as psychollatine. Such inversion can be caused by an epimerization (de- and reglucosylation) of this position. Dehydrogenation of both compounds would lead to croceaine B.

Conclusion and outlook

The present review highlights confirmed biosynthetic, as well as postulated biogenetic steps in the genus *Palicourea* leading to various tryptamine-derived monoterpene-indole alkaloids with different core structures. The assumed steps are formulated applying a parsimony-based retro-biosynthetic approach, and a

resulting series of bio-(retro)-synthetic schemes are proposed that guide through the unique blend of *Palicourea* alkaloids in a biosynthetic context. A major dichotomy is found between alkaloids, which directly derive from tryptamine, and alkaloids that derive from a condensation of tryptamine and other building blocks, in particular with the seco-iridoid secologanin. Most of these monoterpene-indole alkaloids retain their glucose moieties, which sets the genus apart from Apocynaceae and other groups in which such glucosides are, at the most, only found as precursors for a variety of aglycones. Conspicuously, *Palicourea* alkaloids differ in the degree of *N*-methylation, *N*-alkylation or amide formation, which may block various cyclisation reactions at the nitrogen atom originating from the primary amine in tryptamine. Hence, *N*-methylation is here proposed as a critical step in channeling the biosynthesis towards one of these routes (Scheme 13). Likewise, the ratio of tryptamine to iridoid building blocks are of importance with 1:0 represented in simple indole alkaloids, whereas 1:1 is realized in most MIA with few exceptions of 1:2.

To date, it remains unclear why *Palicourea* differs chemically from other genera within the alkaloid-rich order Gentianales, but a lack, malfunction or down-regulation of respective biosynthetic enzymes may be involved. Variances in compartmentation and subcellular transport, which was shown to be crucial in the formation of complex alkaloids in *Catharanthus roseus*, may also be of importance (Payne et al. 2017). It is hoped that the present considerations encourage further investigations within *Palicourea* and other taxa and that some of the proposed biosynthetic schemes will be tested in the future applying genetic, enzymatic, and molecular approaches.

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Declarations

Conflicts of interest The author declare that they have no conflict of interest.

Consent to participate All authors consented to participate in the work.

Consent for publication All authors consented the publication of the work.

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