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

Andreas Berger · Karin Valant-Vetschera · Johann Schinnerl · Lothar Brecker

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**Abstract** The species-rich genus *Palicourea* (Rubiaceae: *Palicoureae*) 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, monoterpenoidoindole, i.e., tryptamine-irido-alkaloids of various structural types including javaniside, alstrostine 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** Palicoureaceae · Alkaloid classification · Biosynthesis · Chemosystematics · Chemodiversity

**Abbreviations**
- CrSTR *Catharanthus roseus* strictosidine synthase
- IA Indole alkaloid
- INMT Indolethylamine N-methyltransferase
- MIA Monoterpenoidoindole alkaloid
- OpSTR *Ophiorrhiza pumila* strictosidine synthase
- PSR Pictet-Spengler reaction
- RsSTR *Rauvolfia serpentina* strictosidine synthase
- SLS Secologanin synthase
- SmGD *Strychnos mellodora* 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
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; Mungan 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 secoiridoid 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 (Koehbach 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](image-url) 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
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. Delprête & 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 (Palicoureeae)

| 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 |
| Monoterpane-indole alkaloids (see "Monoterpane-indole alkaloids" section) | 65 | 36 | 73.5 |
| Tryptamine-secologanin alkaloids (see "Tryptamine-secologanin alkaloids" section) | 55 | 33 | 67.3 |
| Stricosidine and related glucosides | 25 | 28 | 57.1 |
| Stricosamide and related glucosides | 4 | 11 | 22.4 |
| Correantosides and correantines | 11 | 2 | 4.1 |
| Stricosidine-derived aglycones | 7 | 9 | 18.4 |
| Stricosamide-derived aglycones | 4 | 5 | 10.2 |
| Javaniside | 1 | 1 | 2.0 |
| Alstrostines | 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 chimonanthine and calycanthine as well as related oligomers are well-known constituents of the sweetshrub family (Caly- canthaceae). 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, chimonanthine and calycanthine appear widespread, but oligomers are much rarer with trimers, tetrarmers 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 calycanthine and its isomer chimonanthine 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 calycanthine and chimonanthine 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. chimonanthine) 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...
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 chimonanthine 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 chimonanthine to calycanthine under acidic conditions and therefore questioned if calycanthines 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 chimonanthine 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
acid or tetrahydronorharman-1-one are known. Their structures are enumerated in Berger et al. (2021).

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.

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

**Monoterpenoid 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 alstrostines (Scheme 11) as examples for compounds with a 1:2 ratio in this genus.

**Scheme 3** Follow up reactions of the chimonanthine core observed under acidic conditions. The ring system opens leading to calycanthine and iso-calycanthine 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.

**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.
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 carbone 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 rubiaceous *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 rubiaceous 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 secologanic- 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), alastrostines and javaniside (see "Tryptamine-secologanic 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-secologanic alkaloids found in *Palicourea* species are reported to possess a 3αH 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 3αH orientation starting from strictosidine, except were indicated otherwise. However, analogous steps towards the few derivatives with 3βH 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-secologanic alkaloids**

**Strictosidine and related glucosides**

The occurrence of tryptamine-secologanic 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.
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) 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 \( \beta \)-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 glycosides. 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 suerrensis* (Donn. Sm.) Borhidi (Berger et al. 2017). They possess a unique N-4→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 glycosidic 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 coryae* (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
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.

Correantosides and correantines differ in the mode of azepane formation and substitution pattern. It is hypothesized that correantosides 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 the carboxyl group (C-22) with N-1 resulting in correantosides (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 unspecified β-glucosidase, correantone A is formed (Achenbach et al. 1995). After

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**Scheme 7** Proposed biosynthesis of strictosamide (pathway a), correantosides (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 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. Nβ-methyl-21-β-hydroxy-mayumbine and akagerine are referenced in the text and are shown in a box; both are not found in *Palicourea*.
incubation of dolichantoside with SGD from *Rauvolfia serpentina*, 3-isocorreantine A is formed (Gerasimenko 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\textsubscript{b}-methyl-21-\textbeta-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 apocynaceous *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 \textbeta-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 antirhine and 10-hydroxy antirhine N-oxide, were isolated from *Palicourea prunifolia* (Kunth) Steyerm. (Faria et al. 2010; Kato et al. 2012). 10-Hydroxy isodeppeaninol is related to deppeaninol which was isolated from the rubiaceous *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 antirhine is related to antirhine, which was first isolated from the rubiaceous *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 (Guirimand 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 *Ophiirrhiza 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-oxopruinfoline 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 ophiorine may also act as precursor.
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).

**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 isodepepanol. 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

**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 heteroyohimbine to oxindole alkaloids. This involves...
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.

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.
Alstrostines

Alstrostines 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 alstrostine A, dehydro-rudgeifoline and iso-alstrostine 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 alstrostines 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 alstrostine derivatives (Scheme 11).

**Scheme 11** Proposed biosynthetic route to alstrostine and iso-alstrostine 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-alstrostine (a) or alstrostine (b) skeleton in a Mannich type reaction mechanism (Kornpointner et al. 2020).
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; Panjikar 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 aminal formation (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...
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 rubiaceous *Hedyotis diffusa* Willd. (Zhang and Luo 2008) and from the apocynaceous *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 re-glucosylation) 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.
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