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Abstract

Cyclopeptide alkaloids are macrocyclic compounds, the ring system of which consists of a hydroxystyrylamine moiety, an amino acid and a β-hydroxy amino acid, and which is substituted with one or two additional units. This review covers scientific literature published since 2006 until today. In the past decade, 39 new cyclopeptide alkaloids have been reported. In addition, absolute or relative configurations of known compounds have been established. New sources of known compounds are listed: Plant families from which cyclopeptide alkaloids have been obtained during the past decade include the Acanthaceae, Malvaceae, Phyllanthaceae and Rubiaceae**.** Some development concerning total synthesis of cyclopeptide alkaloids are discussed. Finally, a critical overview is given of various biological activities that have been reported, i.e. on the central nervous system (CNS), antimicrobial activity and others.

Keywords

Classification; new structures 2006-2016; sources; total synthesis; biological activities

Introduction

Cyclopeptide alkaloids are macrocyclic compounds, the ring system of which consists of a hydroxystyrylamine moiety, an amino acid and a β-hydroxy amino acid. This ring is substituted with one or two additional units. Although they occur in various plant families, they are most widely distributed in the Rhamnaceae family, notably the genus *Ziziphus* (although sometimes the spelling *Zizyphus* is applied, in this review *Ziziphus* is used throughout). Over the years they have been covered in various reviews because of their intriguing chemical and biological properties. In 1997 a review on cyclopeptide alkaloids was published covering the literature from January 1985 to December 1995 (Gournelis et al. 1997). About ten years later, a review on plant cyclopeptides, including cyclopeptide alkaloids, was published covering the literature up to 2005 (Tan and Zhou 2006). El-Seedi et al. (2007) published a review on cyclopeptide alkaloids covering the literature from 1995 till 2005. A chapter was devoted to cyclopeptide alkaloids from higher plants in the book series "The Alkaloids", covering the literature up to 2008, by Morel et al. (2009). Since then, no comprehensive review on the cyclopeptide alkaloids has been published anymore. In view of the limited accessibility of book chapters, the present review was conceived in order to cover new findings and developments since 2005, i.e. covering the literature published from 2006 until now (last SciFinder® access on 27 September 2016).

Classification

The cyclopeptide alkaloids *sensu stricto* contain a 13-, 14- or sometimes 15-membered macrocyclic ring (Gournelis et al. 1997; Joullié and Richard 2004). In the 13-membered ring compounds, this macrocyclic ring is closed through an ether bridge in the *m*-position of the styrylamine unit, whereas in the 14-membered ring compounds the ring is closed in the *p*-position. As exemplified for 13-membered ring compounds in Fig. 1, cyclopeptide alkaloids typically contain four building blocks (A, B, C and D) and in particular series of compounds a fifth building block E is present between A and B. "A" is a basic terminal amino acid, usually with a primary, monomethylated or dimethylated amino group; "B" is a β-hydroxy amino acid; "C" is an amino acid taking part in the macrocyclic ring; "D" is the hydroxystyrylamine unit; and "E" (if present) is an amino acid. In this way the macrocyclic ring contains two amide bonds and one ether linkage. According to the size of the macrocyclic ring (13- or 14-membered) and the number of building blocks (4 or 5), cyclopeptide alkaloids can be classified as belonging to the 4(13), 5(13), 4(14) or 5(14) type. The 14-membered ring class is the largest one, and

the 4(14) and 5(14) groups are subdivided according to the nature of the β-hydroxy amino acid (building block B). In this way, the 4(14) group has been subdivided into the frangulanine type (in which the β-hydroxy amino acid is leucine), the integerrine type (phenylalanine) and the amphibine-F type (proline). Similarly, the 5(14) group has been subdivided into the scutianine-A type (leucine or phenylalanine) and the amphibine-B type (proline). Accordingly, the 4(13) and 5(13) groups, with proline as β-hydroxy amino acid, are classified as the nummularine-C type and the ziziphine-A type, respectively. The 15-membered ring compounds are rather rare, and do not follow the general scheme of Fig. 1. For instance, the macrocyclic ring of mucronine-A (Fig. 2) consists of a hydroxystyrylamine unit and 3 amino acids. The basic amino acid (building block A), in this case with a dimethylamino group, is also part of the ring system. Mucronine-A is the prototype of the 4(15) class of cyclopeptide alkaloids.

The 14-membered cyclopeptide alkaloids have also been categorized according to the macrocyclic ring (El-Seedi et al., 2005), substructure 1 covering the frangulanine, intergerrine and scutianine-A type; substructure 2 covering the pandamine and hymenocardine type (see below); substructure 3 being a unique substructure represented by anorldianine; substructure 4 covering the amphibine-F type with proline; and substructure 5 covering the amphibine-B and –F type alkaloids without proline.

In addition to the cyclopeptide alkaloids *sensu stricto*, also linear peptide alkaloids, in which the macrocyclic ring system is broken, and neutral compounds, in which the basic amino acid (building block A) is missing, can be distinguished (Gournelis et al. 1997). Some particular features of the neutral cyclopeptide alkaloids are discussed below in section 3.5. Although Tan and Zhou (2006) have proposed a classification system of plant cyclopeptides in which the cyclopeptide alkaloids (type I) are subdivided as types Ia1, Ia2, Ia3, Ib and Ic, in this review the classification system described above used in the previous reviews by Gournelis et al. (1997) and El-Seedi et al. (2007) was applied.

Structures of new compounds

Cyclopeptide alkaloids of the 4(13) type (nummularine-C type)

Since 2006, a total of 7 new cyclopeptide alkaloids of the 4(13) type have been reported, more in particular belonging to the nummularine-C type with proline as the β-hydroxy amino acid (building block B) (Table 1). Sativanine-N and sativanine-O were obtained from stem bark of *Ziziphus sativa* Gaertn (Singh et al. 2006). Sativanine-N (**1**) contains isoleucine both as ring-bound amino acid

(building block C) and as basic terminal amino acid (building block A) with an unsubstituted primary amino group. In sativanine-O (**2**), 2 phenylalanine units are present instead, still with a primary amino group. From root bark and bark of *Ziziphus xylopyrus* (Retz.) Willd. (although originally referred to a *Zizyphus xylopyra*) 4 cyclopeptide alkaloids of the same type have been reported, all of them containing a phenylalanine unit as ring-bound amino acid (building block C). The basic terminal amino acid (building block A) is *N*,*N*-dimethyl-leucine in xylopyrine-A (**3**), *N,N*-dimethyl-phenylalanine in xylopyrine-B (**4**), *N,N*-dimethylvaline in xylopyrine-D (**5**), and valine in xylopyrine-E (**6**) (Singh et al. 2007a; Pandey et al. 2008a). A cyclopepeptide related to xylopyrine-B, in which the A-unit is *N*-methyl-phenylalanine, was isolated from bark of *Ziziphus jujuba* Mill. and named jubanine-E (**7**), together with the known compound nummularine-K (Pandey et al. 2008a; 2008d). The same compound was obtained from *Ziziphus joazeiro* Mart. and named joazerine, in addition to the known compound nummularine-M (Singh et al. 2012a, 2012b).

Cyclopeptide alkaloids of the 5(13) type (ziziphine-A type)

In the same time frame, also 7 new cyclopeptide alkaloids of the 5(13) type, more in particular of the ziziphine-A type, again charcacterised by proline as the β-hydroxy amino acid (building block B), have been described (Table 2). Sativanine-M isolated from *Ziziphus sativa* bark contains isoleucine as building block C (ring-bound amino acid), valine as additional building block E, and an alanine derivative as basic terminal amino acid (building block A), i.e. *N*-formyl, *N*-methyl-alanine (**8**). Also nummularine-P was reported (Pandey et al. 2008b). Five jubanines (F – J) (**9** – **13**) belonging to the same type have been obtained from roots of *Ziziphus jujuba*, in addition to the known compounds nummularine-B, daechuine-S3 and mucronine-K (Kang et al. 2015). They all have isoleucine or valine as building blocks C or E in various combinations, and *N*-methyl- or *N,N*-dimethyl-alanine as basic terminal amino acid. Finally, mauritine-M (**14**) was reported from the root of *Ziziphus mauritiana* Lam. (Panseeta et al. 2011). Mauritine-M contains *N*-methyl-leucine, proline, isoleucine and tryptophane as building blocks A, B, C and E, respectively (D being the hydroxystyrylamine unit).

Cyclopeptide alkaloids of the 4(14) type (integerrine and frangulanine type)

In addition to the xylopyrines discussed above, belonging to the 4(13) class, some other new xylopyrines have been isolated from root bark or bark of the same species (*Ziziphus xylopyrus*), showing a 4(14) structure, i.e. xylopyrines-C, -F, -G and –H (**15** – **18**), together with scutianine-C, nummularine-P, sativanine-H, franganine, frangufoline, amphibine-D and mauritine-A (Rai et al.,

2008; Singh et al. 2008a; Pandey et al. 2008c; Pandey et al. 2012). They all belong to the integerrine type, containing phenylalanine as building block B (Table 3). The basic terminal amino acid (unit A) is derived from phenylalanine, leucine or isoleucine, in which the amino-group can be primary, mono-methylated or methylated and formylated. It should be noted that because of the formyl substitution, the nitrogren atom loses its basic properties. Xylopyrine-F was also reported as rugosanine-C from stem bark of *Ziziphus rugosa* Lam., in addition to nummularine-K, -M, -N, sativanine-C, mauritine-A, -D, and amphibine-B (Singh et al. 2008; Singh et al. 2013). Together with mauritine-L (**19**) from the root of *Ziziphus mauritiana* altogether 5 new 4(14) type alkaloids of the integerrine type were identified since 2006. In addition, one new 4(14) cyclopeptide alkaloid of the frangulanine type, characterised by leucine as building block B, i.e. chamaedrine (**20**), was obtained from roots of *Melochia chamaedrys* A. St. Hill in addition to adouetine-X, frangufoline, scutianine-B and -C (Dias at al. 2007). The genus *Melochia* is now classified in the Malvaceae family (Emile et al. 2007, Michalet et al. 2008).

Cyclopeptide alkaloids of the 5(14) type

Only one new cyclopeptide alkaloid belonging to the scutianine-A type (with leucine or phenylalanine as the β-hydroxy amino acid unit (building block B) has been reported since 2006, i.e. oxyphylline-A (**21**) from stem bark or *Ziziphus oxyphylla* Edgew. (Table 4), together with nummularine-R (Inayat-Ur-Rahman et al. 2007). The terminal basic amino acid (unit A) is *N,N*-dimethyl-phenylalanine, the additional intermediary amino acid (unit E) proline. In addition to sativanine-K, one 5(14)-type cyclopeptide alkaloid has been isolated from root bark of *Ziziphus mauritiana*, i.e. mauritine-K (**22**), in which the β-hydroxy amino acid unit (building block B) is proline (amphibine-B type), the basic terminal amino acid leucine (unit A), the ring-bound amino acid (unit C) as well as the additional amino acid (unit E) leucine (Singh et al. 2007b). Six new cyclopeptide alkaloids (**23** – **28**) belonging to the same amphibine-B type have been isolated from stems of *Ziziphus apetala* Hook. f. in addition to the known compounds mauritine-A and mauritine-F (Han et al. 2011). Apetaline-A (**23**) and –B (**24**) consist of phenylalanine as the β-hydroxy amino acid (building block B) and the ring-bound amino acid (unit C), valine as additional amino acid (unit E), and an unusual terminal unit (A), i.e. 2-(hydroxylimino)-propanoic acid (which can be considered as an alanine derivative) in apetaline-A, and an imidizolidine-4-one structure (formed by bridging one methyl of *N,N*-dimethyl-alanine and the N-atom of the preceding valine unit) in apetaline-B. Another new compound was identified as epimauritine-A (**25**), being the C-34 epimer of mauritine-A (C-34 is the chiral carbon of the terminal alanine moiety). In addition, also epimauritine-A *N*-oxide (**26**) and mauritine-A *N*-oxide (**27**) were

obtained. Apetaline-C (**28**) is similar to (epi)mauritine-A, but contains *N*-formyl, *N*-methylamine-alanine as terminal amino acid; the absolute configuration at C-34 could not be determined.

Recently three new cyclopeptide alkaloids have been obtained from root bark of *Hymenocardia acida* Tul. (Phyllanthaceae) (Tuenter et al. 2016). In addition to the known major compound hymenocardine, also hymenocardine *N*-oxide (**29**), hymenocardinol (**30**) and hymenocardine-H (**31**) were obtained. These cyclopeptide alkaloids do not contain the usual hydroxystyrylamine building block, but rather a *p*-hydroxyphenylethylamine unit: The –CH=CH– moiety is replaced by a –CH(OH)-CH_2– group in hymenocardinol (**30**). Hymenocardinol can be considered as the reduced analogue of hymenocardine, possessing a hydroxyl- instead of a keto-functionality. Whereas hymenocardine and hymenocardinol consist of *N,N*-dimethyl-isoleucine, valine, tryptophane and valine as building blocks A, B, C and E, respectively, the new cyclopeptide alkaloid hymenocardine-H consist of *N,N*-dimethyl-isoleucine, leucine, histidine and isoleucine as building blocks A, B, C and E, respectively. Because of the presence of histidine, an unusual amino acid in cyclopeptide alkaloids, the name hymenocardine-H (**31**) was adopted for this compound.

3.5. Neutral cyclopeptide alkaloids

Neutral cyclopeptide alkaloids follow the same structural pattern as the other cyclopeptide alkaloids, but the terminal basic amino acid known as building block A (Fig. 1) is replaced by a substituent that does not contain a nitrogen atom (or that is not derived from an amino acid), e.g. an acyl group. It should be noted that the absence of the nitrogen atom in this substituent is a less ambiguous criterion than the absence of basic properties, since *N*-formylation destroys its basic character. Nevertheless, *N*-formyl containing cyclopeptide alkaloids as described above should not be classified as “neutral cyclopeptide alkaloids” in order not to create confusion. Because the number of neutral cyclopeptide alkaloids is still rather small, there has been no particular need to distinguish subtypes, but obviously also here the same distinction between 13-, 14- and 15-membered ring types consisting of 4 or 5 building blocks (depending on the presence or absence of unit E) can be made. Two new neutral cyclopeptide alkaloids have been reported from the root of *Ziziphus oxyphylla* Edgew., i.e. oxyphylline-B (**32**) and oxyphylline-C (**33**) (Table 5), together with oxyphylline-D, nummularine-C and -R (Kaleem et al. 2012). Oxyphylline-B consists of proline, isoleucine and valine as building blocks B, C and E, respectively; oxyphylline-C of phenylalanine, proline and again phenyl-alanine, respectively. In both compounds the “neutral” or rather nitrogen-lacking moiety is a cinnamoyl group. It should be noted that a compound obtained from *Ziziphus oxyphylla* that was

named oxyphylline-D had already been reported before from *Sphaeranthus indicus* L. (Nisar et al. 2010). Also hemsine-A was reported from *Z. oxyphylla* (Choudhary et al. 2011).

In amaiouine (**34**), isolated from leaves of *Amaioua guianensis* Aubl. (Rubiaceae), units B, C and E are phenylalanine, phenylalanine and proline, respectively, in which the proline-*N* is again substituted with a cinnamoyl residue (Laurindo de Oliveira et al. 2009). Compounds **32** – **34** can therefore be considered as 5(14) neutral cyclopeptide alkaloids. Four new neutral cyclopeptide alkaloids of the 4(14) type have been isolated from root bark of *Scutia buxifolia* Reiss. (Rhamnaceae) (Maldaner et al. 2011), in addition to the known compounds scutianine-B, -C, -D and -E. Scutianene-E (**35**) and two of its diastereoisomers 3,4,28-*tris*-*epi*-scutianene-E (**36**) and 28-*epi*-scutianene-E (**37**) consist of β-hydroxy-phenylalanine as ring-bound amino acid (building block C), and leucine as building block B. A cinnamoyl moiety is directly attached to *N*-atom of the β-hydroxy-leucine unit. Similarly, in scutianene-L (**38**) isoleucine is the ring-bound amino acid (unit C), whereas the β-hydroxy-amino acid (unit B) is phenylalanine, the *N*-atom of which is substituted with a cinnamoyl group. A related 4(14) type compound, justicianene-A, was obtained from whole plant of *Justicia procumbens* L. (Acanthaceae), but interestingly a tyrosine moiety is present instead of a hydroxystyrylamine unit (Jin et al. 2015). This adds evidence to the hypothesis that the hydroxystyrylamine unit is biogenetically derived from tyrosine (Gournelis et al. 1997).

There may be some controversy whether or not these neutral cyclopeptides should be considered as alkaloids, since they are missing the peptidogenic amino acid with a mono- or dimethylated amino group exhibiting basic properties (unless in the case of formyl-substitution). However, many alkaloids devoid of a basic nitrogen are known, such as colchicine or piperine, and similarly also the neutral compounds discussed above could be termed “cyclopeptide alkaloids”. Until 2011 only 8 neutral cyclopeptide alkaloids had been reported: Scutianene-C (= scutianene-D), discarenes-C and –D, discarines-M and –N, lotusanine-B, sanjoinenine and amaiouine (Maldaner et al. 2011). In the meantime oxyphyllines-B and –C, scutianene-E and its 2 isomers, scutianene-L and justitiacene-A have been added to this list, bringing the total to 15 representatives. All of them contain a 14-membered macrocyclic ring. Remarkably, all recently isolated neutral cyclopeptide alkaloids as listed in Table 5 contained a cinnamoyl moiety as the *N*-acyl group. It has been proposed by Maldaner et al. (2011) to use the ending *ine* for cyclopeptide alkaloids *sensu stricto*, and to use *ene* for neutral compounds.

Distribution of cyclopeptide alkaloids

This review paper confirms that the Rhamnaceae family and especially the genus *Ziziphus* is by far the most important source of cyclopeptide alkaloids. Other plant families from which cyclopeptide alkaloids have been obtained during the past decade include the Acanthaceae, Malvaceae, Phyllanthaceae and Rubiaceae. The presence of the cyclopeptide alkaloids frangulanine and melonovine-A in *Christiana africana* DC. supported the reclassification of the genus *Christiana* from Tiliaceae to Malvaceae (Michalet et al. 2008). Recently UPLC/QTOF MS combined with an informatics platform was applied for the rapid characterisation of Ziziphi Spinosae Semen, the dried seeds of *Ziziphus jujuba* Mill. var. *spinosa* (Bunge) Hu ex H.F.Chou, and to distinguish it from its adulterant Ziziphi Mauritianae Semen (Zhang et al. 2016). With regard to cyclopeptide alkaloids, only ramosine-A, sanjoinine-A and lotusine-B were detected in Ziziphi Spinosae Semen, whereas a much wider range was present in Ziziphi Mauritianae Semen, including amphibine-D, lotusanine-A, lotusine-B, ramosine-A, sanjoinenine, sanjoinine-A, -B, -D, -F, G1 and its 11-epimer, and -G2. Daechuine S10 has been obtained from roots of *Z. jujuba* Mill. var. *spinosa* (Meng et al. 2013).

Configurational studies and total synthesis

For some cyclopeptide alkaloids originally reported before 2006, the relative or absolute configuration has been investigated more recently. The relative configuration of oxyphylline-D, nummularin-C and –R was reported by Nisar et al. (2010). Single crystal X-ray diffraction of the 13-membered ring compound nummularine-B methiodide revealed all-*S* configurations of the amino acid residues (Panseeta et al. 2011). The absolute configuration of franganine, isolated from root bark of *Discaria americana* Gillies & Hook. (Rhamnaceae), was established by NMR spectroscopy and X-ray diffraction analysis of tri-N-methylfranganine methiodide (Caro et al. 2012). The absolute configuration of discarine-C, -D and myrianthine-A, three cyclopeptide alkaloids originally obtained from *Discaria febrifuga*, was determined by a combination of NMR studies, chiral gas chromatography, and comparison of NMR data with those of synthetic tripeptides (Mostardeiro et al. 2013).

Because of their diverse biological properties (see below), the cyclopeptide alkaloids and non-natural analogues have been of considerable interest to synthetic organic chemists. A two-step

synthesis of *p*-cyclophanes (such as the 14-membered ring cyclopeptide alkaloids) by the combined use of a Ugi four-component reaction (Ugi-4CR) and an intramolecular S_NAr-based macrocyclisation reaction has been reported as a sequence allowing the introduction of at least 4 points of diversity (Cristau et al. 2006). De Greef et al. (2006) have developed a flexible two-step route to macrocyclic ansapeptoids and peptides, in which the core structure is synthesised by a combination of a Ugi four-component reaction with bifunctional building blocks to form the dipeptoid part, followed by a suitable macrocyclisation reaction. The synthesis of cyclopeptide alkaloids starting from amino acids as building blocks and using copper(I) catalysis to install the key structural elements was discussed by Evano (2008). The total synthesis of the cyclopeptide alkaloids paliurine-E and –F, ziziphine-N and –Q, abyssenine-A and mucronine-E was reported, involving an intramolecular amidation of vinyl iodide, which allowed to address simultaneously two synthetic challenges associated with cyclopeptide alkaloids: The formation of the enamide and macrocyclisation (cycloenamidation reaction). Physical, spectroscopic and spectrometric characteristics of synthetic (-)-paliurine-F and mucronine-E corresponded in all respects to those reported for the natural products, thereby establishing their relative and absolute configurations (Toumi et al. 2007; 2008a; 2008b; 2009). The total synthesis of abyssenine-B and mucronine-E was also reported by Wang et al. (2007) using a CuI/N,N-dimethylglycine-catalyzed coupling reaction of vinyl iodides with amides as the key step. The configuration of natural abyssenine-B and mucronine-E could tentatively be assigned as *S,S,S*. The total synthesis of ziziphine-N was also reported using a Mitsunobu reaction, followed by installation of the enamide part and ring closure (He et al. 2007). More recently Cu-mediated enamide formation in the total synthesis of complex peptide natural products was reviewed by Kuranaga et al. (2014).

Biological activity

Activity on the Central Nervous System (CNS), analgesic and anti-inflammatory activity

As pointed out in previous reviews, many cyclopeptide alkaloids exert activity on the Central Nervous System (CNS) (Gouleris et al. 1997; El-Seedi et al. 2007). The cyclopeptide alkaloid fraction from Ziziphi Spinosi Semen, defined as the dried seed of *Ziziphus jujuba* Mill. var. *spinosa* (Rhamnaceae), and traditionally used as a tranquiliser, analgesic and anticonvulsant, was found to enhance pentobarbital-induced sleeping behaviour in mice after oral administration. It was suggested that the enhancement of Cl^- influx by the cyclopeptide alkaloid fraction may play an important role in the

potentiation of pentobarbital-induced sleeping behaviour (Ma et al. 2008). The observed effects were comparable to those of muscimol used as a positive control. The cyclopeptide alkaloid fraction was prepared using a common liquid/liquid partition scheme for isolation of alkaloids, but unfortunately it was not phytochemically characterised. The same alkaloid fraction also showed anxiolytic effects: it increased the time spent on the open arms and the number of open arm entries in the elevated plus-maze test. Significant effects were obtained at a dose of 8.0 mg/kg, whereas diazepam used as a positive control was administered at a dose of 2.0 mg/kg. In addition the cyclopeptide alkaloid fraction increased the number of head-dips in the hole-board test (significant effect at 8.0 mg/kg), and increased the percentage of centre zone ambulatory time in the open-field box (significant effect at 2.0 mg/kg), again vs. diazepam active at a dose of 0.5 and 2.0 mg/kg, respectively. However, in contrast to diazepam, it did not affect locomotor activity, and it did not influence grip force. The cyclopeptide alkaloid fraction was found to increase Cl^- influx and to over-express γ-subunits of $GABA_A$ receptors in cultured cerebellar granule cells (Han et al. 2008).

The cyclopeptide alkaloid fraction, prepared using a common liquid/liquid partition scheme for isolation of alkaloids from leaves of *Ziziphus nummularia*, was evaluated after oral administration for its analgesic activity in the acetic acid induced writhing, tail flick and hot plate tests; and for its anti-inflammatory activity against rat paw oedema, mouse peritonitis and cotton pellet granuloma. Although it was mentioned that the presence of cyclopeptide alkaloids was confirmed by identification tests, TLC and GC-MS analysis, there is no information on the composition of the extract. Anti-oedematogenic and anti-nociceptive effects were observed (Goyal et al. 2013). In the anti-oedematogenic assays significant effects were observed in a dose range of 10-30 mg/kg vs. indomethacine used as a positive control at 10 mg/kg. Analgesic activity in the acetic acid-induced writhing test was observed in the same dose range vs. aspirin as a positive control at 100 mg/kg. In addition, analgesic effects were also observed in the tail flick and hot plate tests, used to evaluate centrally acting analgesics, vs. morphine at 5 mg/kg as a positive control. However, in an acute toxicity study, the LD_{50} value was established as 200 mg/kg, leaving a rather narrow therapeutic range.

The potential antinociceptive effect of six (4)14-membered cyclopeptide alkaloids, all belonging to the frangulanine-type, was investigated in mice using the tail-flick test as a simple pain model. Test compounds were administered intrathecally into the spinal column (Trevisan et al. 2009). Obviously results obtained after intrathecal administration cannot be compared to those observed after oral administration as in the studies mentioned above. Franganine and adouetine-X showed antinociceptive effects; adouetine-X also exhibited a pronounced analgesic effect in a chronic neuropathic pain model in mice, but unfortunately no positive control was used. Adouetine-X was able to decrease the activities of Ca^{2+}-ATPase and Na^+/K^+-ATPase *in vitro*.

Five cyclopeptide alkaloids isolated from *Ziziphus oxyphylla*, including oxyphylline-B, -C, -D, nummularin-C and –R were evaluated in the acetic acid induced writhing and formalin induced flinching behaviour tests after intraperitoneal administration. Especially oxyphylline-B and nummularin-R showed activity. Significant activities were already observed at a dose of 2.5 mg/kg, vs. diclofenac used as a positive control at 10 mg/kg. It was concluded that the peripheral analgesia was strongly augmented by their central effects (Kaleem et al. 2013).

In summary, it appears that there is increasing evidence for the CNS activities of particular cyclopeptide alkaloids at realistic doses. In view of the limited number of cyclopeptide alkaloids evaluated for their effects on the CNS, it has not been possible yet to establish clear structure-activity relationships.

It has been reported that traditional practitioners of Indian medicine extract the stem part of *Ziziphus jujuba* by a crude pyrolysis method and use the oil in the treatment of pain. A prototype pyrolyser was applied to simulate this traditional method. FTIR and GC-MS analysis of the extracted oily substance obtained by both the traditional as the simulated process revealed the presence of various cyclic, nitrogenous, long chain and heterocyclic compounds, which were believed to be the pyrolysates of various cyclopeptide alkaloids present in the stem of *Ziziphus jujuba* (Shanmugavasan et al. 2011).

6.2. Antimicrobial activity

Mauritine-K, isolated from *Ziziphus mauritiana* Lam., exhibited antifungal activity (inhibition of spore germination) against some plant pathogenic fungi such as *Botrytis cinerea* at doses ranging from 200 to 1000 µg/ml, but since no positive control was used it is difficult to evaluate these results. Sativanine-K on the other hand was not active (Singh et al. 2007b). Bioassay-guided fractionation of a leaf extract of *Melochia odorata* L.f. (Malvaceae) resulted in the isolation of frangulanine, which showed moderate antifungal activity against *Candida albicans* and *Saccharomyces cerevisiae.* The minimal amount of frangulanine needed to inhibit fungal growth on a TLC plate was 25 and 50 µg, respectively, compared to 2.5 and 5.0 µg for ketoconazole, respectively (Emile et al. 2007).

Mauritine-L, –M, nummularine-H, -B and hemsine-A exhibited antiplasmodial activity against *Plasmodium falciparum* strain K1 with IC_{50} values ranging from 3.7 to 10.3 µM, whereas dihydroartemisinin used as a positive control exhibited an IC_{50} value of 4.2 nM (Panseeta et al. 2011). Hymenocardine, its *N*-oxide, hymenocardine-H and hymenocardinol obtained from *Hymenocardia acida* showed antiplasmodial activity (strain K1) in a concentration range from 12.2 to 27.9 µM, vs. chloroquine used as a positive control with an IC_{50} value of 0.2 µM. However, only moderate

cytotoxicities were observed against human lung fibroblasts (MRC-5 cells), yiealding favourable selectivity indices (Tuenter et al. 2016).

Mauritine-M and nummularine-H showed antimycobacterial activity against *Mycobacterium tuberculosis* with MIC values of 72.8 and 4.5 µM, respectively, whereas the standard drugs isoniazid and kanamycin sulfate showed MIC values of 0.4 and 4.2 µM, respectively. No cytotoxicity controls were carried out, therefore the selectivity cannot be evaluated (Panseeta et al. 2011). The synthetic cyclopeptide alkaloids paliurine-E and –F, ziziphine-N and –Q, abyssenine-A and mucronine-E were evaluated for cytotoxicity against the human HT1080 tumoural cell line, and for antibacterial activity against a methicillin-resistant strain of *Staphylococcus aureus*, *Bacillus anthracis* and *Escherichia coli*. No significant antibacterial activity was observed, whereas paliurine-F, abyssenine-A and mucronine-E were moderately cytotoxic, displaying IC_{50} values of 0.82, 1.03 and 0.68 mM, respectively. No positive controls were used (Toumi et al. 2009).

Again, as mentioned above for the CNS activity, the number of cyclopeptide alkaloids evaluated for their antimicrobial effects still is too low to allow the establishment of clear structure-activity relationships. Nevertheless, it appears that the cyclopeptide alkaloids as a class can be considered as a promising source of new antimicrobial lead compounds, especially against some fungi, mycobacteria or protozoa, with favourable selectivity indices, in the absence of obvious cytotoxicity.

Other activities

Three cyclopeptide alkaloids isolated from *Ziziphus oxyphylla* Edgew., nummularine-C, -R and hemsine-A showed inhibition of α-glucosidase and anti-glycation activities, which may support local antidiabetic use. With regard to α-glucosidase inhibition, all compounds were more active than 1-deoxynojirimycin, used as a positive control. Hemsine-A was more active as anti-glycation agent than rutine, used as a positive control in this assay (bovine serum albumin – methyl glyoxal assay) (Choudhary et al. 2011). Oxyphylline-D, nummularin-C and –R from the same species were found to be active as *in vitro* inhibitors of urease, catalysing the production of ammonia and carbon dioxide from urea, which plays a role in various pathologies. All test compounds were more active than thiourea used as a positive control (Kaleem et al. 2013). Oxyphylline-B, -C, -D, nummularine-C and –R showed *in vitro* antioxidative (radical scavenging) potential (Kaleem et al. 2015).

For all biological activities, it should be noted that publications dealing with extracts, e.g. *Ziziphus* extracts, were only included in this review if at least the presence of cyclopeptide alkaloids

had been confirmed. Reports dealing with biological activities of completely uncharacterised extracts were not included in this review.

Conclusions

Although the number of cyclopeptide alkaloids is gradually increasing, it remains a relatively small class of natural products. All cyclopeptide alkaloids identified in the past decade follow the same structural patterns as outlined before. Remarkably, from the 39 compounds reported for the first time from nature in this time frame, 8 belong to the class of neutral cyclopeptide alkaloids, bringing the total of representative of this group to 15. It is proposed to use the wording "neutral cyclopeptide alkaloid" only for those compounds containing a side that does not contain a nitrogen atom (or that is not derived from an amino acid), e.g. an acyl group. Indeed, the absence of the nitrogen atom in this substituent is a less ambiguous criterion than the absence of basic properties, since *N*-formylation of an amino-acid derived moiety results in loss of the basic character, but the latter compounds should not be considered as neutral cyclopeptide alkaloids. By analogy with the differentiation between 4(13), 5(13), 4(14) and 5(14) cyclopeptide alkaloids, it is proposed to distinguish two types of neutral cyclopeptide alkaloids, i.e. the 4(14) and the 5(14) type, in which the *N*-acyl moiety is considered as the 4^{th} resp. the 5^{th} building block.

When reviewing the literature it becomes obvious that on many occasions the relative or absolute configuration of all chiral centers has not been determined yet. This remains a challenge for future chemical and spectroscopic work. A second observation is that relatively few compounds have pharmacologically been investigated, and that even fewer compounds have been the subject of systematic investigations to establish structure-activity relationships. Small libraries of cyclopeptide alkaloids should be constructed (by isolation of synthetically) in order to fill this gap.

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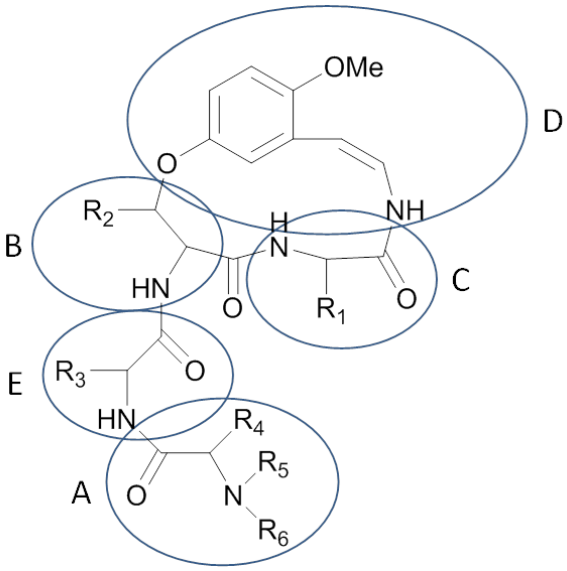


Fig. 1. General structure of 13-membered cyclopeptide alkaloids

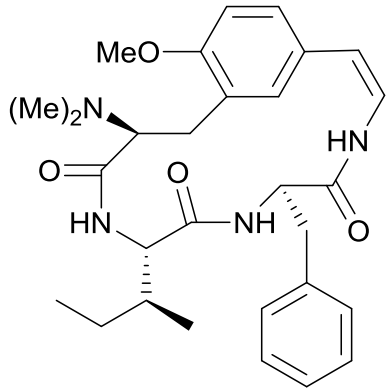
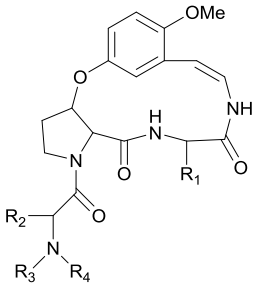


Fig. 2. Mucronine-A, a 15-membered cyclopeptide alkaloid

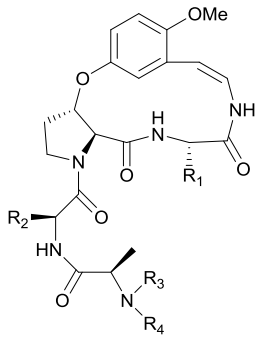
Table 1. 4(13) Cyclopeptide alkaloids (nummularine-C type)

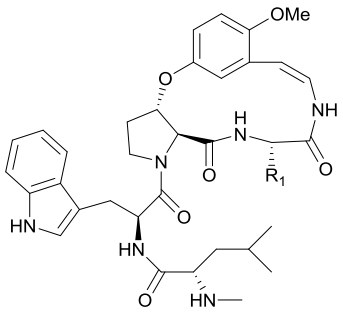


1 Sativanine-N	$R_1 = R_2$	$CH(CH_3)CH_2CH_3$	$R_3 = R4$	H
2 Sativanine-O	$R_1 = R_2$	Benzyl	$R_3 = R_4$	H
3 Xylopyrine-A	R_1	Benzyl	$R_3 = R_4$	CH_3
	R_2	$CH_2CH(CH_3)_2$		
4 Xylopyrine-B	$R_1 = R_2$	Benzyl	$R_3 = R_4$	CH_3
5 Xylopyrine-D	R_1	Benzyl	$R_3 = R_4$	CH_3
	R_2	$CH(CH_3)_2$		
6 Xylopyrine-E	R_1	Benzyl	$R_3 = R_4$	H
	R_2	$CH(CH_3)_2$		
7 Jubanine-E	$R_1 = R_2$	Benzyl	R_3	CH_3
			R_4	H

No.	Name	Plant origin	Family	Chem. formula	M_r	Reference
1	Sativanine-N	*Ziziphus sativa* Gaertn.	Rhamnaceae	$C_{26}H_{38}N_4O_5$	486	Singh et al. 2006
2	Sativanine-O			$C_{32}H_{34}N_4O_5$	554	
3	Xylopyrine-A	*Ziziphus xylopyrus* (Retz.) Willd.	Rhamnaceae	$C_{31}H_{40}N_4O_5$	548	Singh et al. 2007a
4	Xylopyrine-B			$C_{34}H_{38}N_4O_5$	582	Pandey et al. 2008a
5	Xylopyrine-D			$C_{30}H_{38}N_4O_5$	534	
6	Xylopyrine-E			$C_{28}H_{34}N_4O_5$	506	
7	Jubanine-E	*Ziziphus jujuba* Mill.	Rhamnaceae	$C_{33}H_{36}N_4O_5$	568	Pandey et al. 2008a
7	Joazerine (= Jubanine-E)	*Ziziphus joazeiro* Mart.	Rhamnaceae	$C_{33}H_{36}N_4O_5$	568	Singh et al. 2012a

Table 2. 5(13) Cyclopeptide alkaloids (ziziphine-A type)





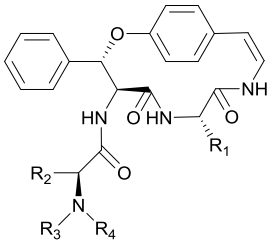
8 Sativanine-M	R_1	$CH(CH_3)CH_2CH_3$	R_3	CH_3
	R_2	$CH(CH_3)_2$	R_4	CHO
14 Mauritine-M	R_1	$CH(CH_3)CH_2CH_3$		

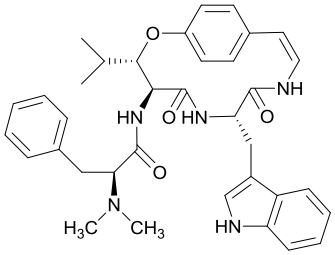
(**8**: no relative configurations assigned)

9 Jubanine-F	$R_1 = R_2$	$CH(CH_3)_2$	R_3	CH_3
			R_4	H
10 Jubanine-G	R_1	$CH(CH_3)_2$	R_3	CH_3
	R_2	$CH(CH_3)CH_2CH_3$	R_4	H
11 Jubanine-H	$R_1 = R_2$	$CH(CH_3)CH_2CH_3$	R_3	CH_3
			R_4	H
12 Jubanine-I	R_1	$CH(CH_3)CH_2CH_3$	$R_3 = R_4$	CH_3
	R_2	$CH(CH_3)_2$		
13 Jubanine-J	$R_1 = R_2$	$CH(CH_3)CH_2CH_3$	$R_3 = R_4$	CH_3

No.	Name	Plant origin	Family	Chem. formula	M_r	Reference
8	Sativanine-M	*Ziziphus sativa* Gaertn.	Rhamnaceae	$C_{30}H_{43}N_5O_7$	585	Pandey et al. 2008b
9	Jubanine-F	*Ziziphus jujuba* Mill.	Rhamnaceae	$C_{28}H_{41}N_5O_6$	543	Kang et al. 2015
10	Jubanine-G			$C_{29}H_{43}N_5O_6$	557	
11	Jubanine-H			$C_{30}H_{45}N_5O_6$	571	
12	Jubanine-I			$C_{30}H_{45}N_5O_6$	571	
13	Jubanine-J			$C_{31}H_{47}N_5O_6$	585	
14	Mauritine-M	*Ziziphus mauritiana* Lam.	Rhamnaceae	$C_{38}H_{50}N_6O_6$	686	Panseeta et al. 2011

Table 3. 4(14) Cyclopeptide alkaloids (integerrine- and frangulanine-type)





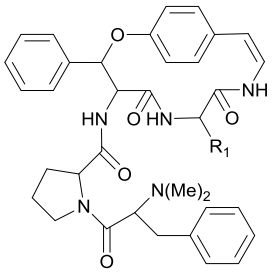
15 Xylopyrine-C	$R_1 = R_2$	Benzyl	R_3	CH_3
			R_4	H
16 Xylopyrine-F	$R_1 = R_2$	$CH_2CH(CH_3)_2$	$R_3 = R_4$	H
17 Xylopyrine-G	R_1	Benzyl	R_3	CH_3
	R_2	$CH_2CH(CH_3)_2$	R_4	CHO
18 Xylopyrine-H	R_1	Benzyl	R_3	CH_3
	R_2	$CH(CH_3)_2$	R_4	H
19 Mauritine-L	$R_1 = R_2$	$CH(CH_3)CH_2CH_3$	R_3	CH_3
			R_4	H

20 Chamaedrine

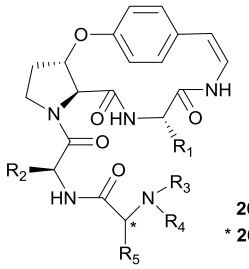
(**15 - 18**: no relative configurations assigned)

No.	Name	Plant origin	Family	Chem. formula	M_r	Reference
15	Xylopyrine-C	*Ziziphus xylopyrus* (Retz.) Willd.	Rhamnaceae	$C_{36}H_{36}N_4O_4$	588	Singh et al. 2008a
16	Xylopyrine-F			$C_{29}H_{38}N_4O_4$	506	Pandey et al. 2008c
17	Xylopyrine-G			$C_{34}H_{38}N_4O_5$	582	Pandey et al. 2012
18	Xylopyrine-H			$C_{32}H_{36}N_4O_4$	540	
16	Rugosanine-C (= xylopyrine-F)	*Ziziphus rugosa* Lam.	Rhamnaceae	$C_{29}H_{36}N_4O_4$	506	Singh et al. 2013
19	Mauritine-L	*Ziziphus mauritiana* Lam.	Rhamnaceae	$C_{30}H_{40}N_4O_4$	520	Panseeta et al. 2011
20	Chamaedrine	*Melochia chamaedrys* A. St.Hill.	Malvaceae	$C_{36}H_{41}N_5O_4$	607	Dias et al. 2007

Table 4. 5(14) Cyclopeptide alkaloids



21 Oxyphylline-A R_1 1-OH-Benzyl

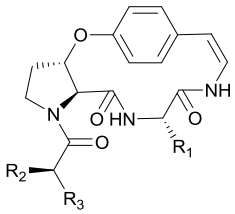


22 Mauritine-K $R_1 = R_2 = R_5$ $CH(CH_3)CH_2CH_3$; $R_3 = R_4$ H

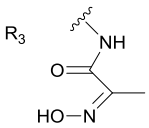
26, **27** N-oxide

* **26**: *R* **27**: *S*

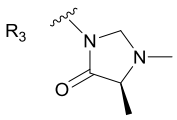
(**22**: no relative configurations assigned)



23 Apetaline-A R_1 Benzyl; R_2 $CH(CH_3)_2$



24 Apetaline-B R_1 Benzyl; R_2 $CH(CH_3)_2$



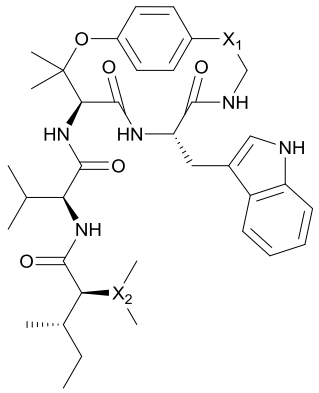
25 Epimauritine-A

26 Epimauritine-A N-oxide

27 Mauritine-A N-oxide

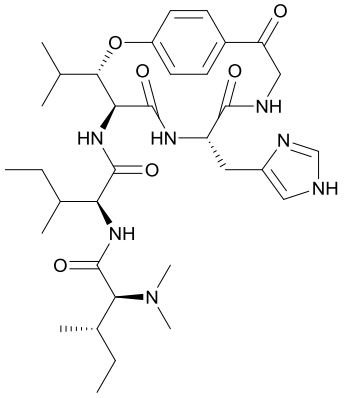
R_1 Benzyl; R_2 $CH(CH_3)_2$; $R_3 = R_4 = R_5$ CH_3

28 Apetaline-C R_1 Benzyl; R_2 $CH(CH_3)_2$; $R_3 = R_5$ CH_3; R_4 CHO



29 Hymenocardine N-oxide X_1 C=O X_2 N^+-O^-

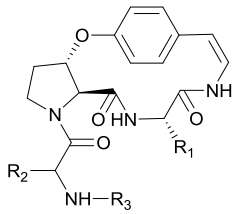
30 Hymenocardinol X_1 CH-OH X_2 N



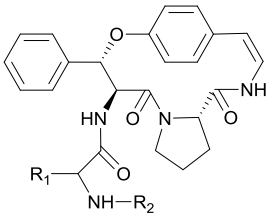
31 Hymenocardine-H

No.	Name	Plant origin	Family	Chem. formula	M_r	Reference
21	Oxyphylline-A	*Ziziphus oxyphylla* Edgew.	Rhamnaceae	$C_{42}H_{45}N_5O_6$	715	Inayat-Ur-Rahman et al. 2007
22	Mauritine-K	*Ziziphus mauritiana* Lam.	Rhamnaceae	$C_{31}H_{47}N_5O_5$	569	Singh et al. 2007b
23	Apetaline-A	*Ziziphus apetala* Hook. f.	Rhamnaceae	$C_{30}H_{35}N_5O_6$	561	Han et al. 2011
24	Apetaline-B			$C_{32}H_{39}N_5O_5$	573	
25	Epimauritine-A			$C_{32}H_{41}N_5O_5$	575	
26	Epimauritine-A N-oxide			$C_{32}H_{41}N_5O_6$	591	
27	Mauritine-A N-oxide			$C_{32}H_{41}N_5O_6$	591	
28	Apetaline-C			$C_{32}H_{39}N_5O_6$	589	
29	Hymenocardine N-oxide	*Hymenocardia acida* Tul.	Phyllanthaceae	$C_{37}H_{50}N_6O_7$	690	Tuenter et al. 2016
30	Hymenocardinol			$C_{37}H_{52}N_6O_6$	676	
31	Hymenocardine-H			$C_{34}H_{51}N_7O_6$	653	

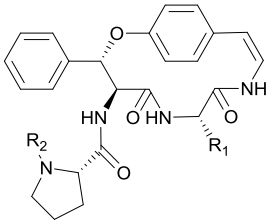
Table 5. Neutral cyclopeptides



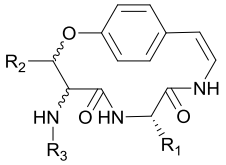
32 Oxyphylline-B R_1 $CH(CH_3)CH_2CH_3$
R_2 $CH(CH_3)_2$
R_3 Cinnamoyl



33 Oxyphylline-C R_1 Benzyl
R_2 Cinnamoyl



34 Amaouine R_1 Benzyl
R_2 Cinnamoyl

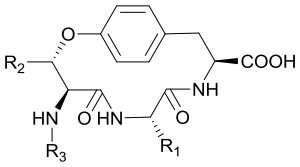


35 Scutianene-E R_1 1-OH-Benzyl (*L-threo*)
R_2 $CH(CH_3)_2$ (*L-erythro*)
R_3 Cinnamoyl

36 3,4,28-*tris-epi*-Scutianene R_1 1-OH-Benzyl (*L-erythro*)
R_2 $CH(CH_3)_2$ (*D-erythro*)
R_3 Cinnamoyl

37 28-*epi*-Scutianene R_1 1-OH-Benzyl (*L-erythro*)
R_2 $CH(CH_3)_2$ (*L-erythro*)
R_3 Cinnamoyl

38 Scutianene-L R_1 $CH(CH_3)CH_2CH_3$
R_2 Benzyl (*D-threo*)
R_3 Cinnamoyl



39 Justicianene-A R_1 Benzyl
R_2 $CH(CH_3)_2$
R_3 Cinnamoyl

No.	Name	Plant origin	Family	Chem. formula	M_r	Reference
32	Oxyphylline-B	*Ziziphus oxyphylla* Edgew.	Rhamnaceae	$C_{33}H_{40}N_4O_5$	572	Kaleem et al. 2012
33	Oxyphylline-C			$C_{40}H_{38}N_4O_5$	654	
34	Amaiouine	*Amaioua guianensis* Aubl.	Rubiaceae	$C_{40}H_{38}N_4O_5$	654	Laurindo de Oliveira et al. 2009
35	Scutianene-E	*Scutia buxifolia* Reiss.	Rhamnaceae	$C_{32}H_{33}N_3O_5$	539	Maldaner et al. 2011
36	3,4,28-*tris-epi*-Scutianene-E			$C_{32}H_{33}N_3O_5$	539	
37	28-*epi*-Scutianene-E			$C_{32}H_{33}N_3O_5$	539	
38	Scutianene-L			$C_{32}H_{32}N_3O_4$	523	
39	Justicianene-A	*Justicia procumbens* L.	Acanthaceae	$C_{33}H_{36}N_3O_6$	570	Jin et al. 2015