Plant Cyclopeptides

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Contents

1. Introduction

We define plant cyclopeptides [with the exception of the acyclic compounds lasiodine-A (**1**),[13] sanjoinine-G2 (**2**),[74] astin-J (**216**),[156] asternin-A−C (**217**−**219**),[157] and MCoTI-III (**462**)[320]] as cyclic compounds formed mainly with the peptide bonds of 2−37 protein or non-protein amino acids and discovered in higher plants, mainly L-amino acids. Since cyclolinopeptide A (CLA, type VI, **295**) was isolated and

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Ning-Hua Tan was born in Zunyi, Guizhou, P. R. China, in 1963. After she received her Ph.D. in medicinal chemistry from China Pharmaceutical University with Professor Shou-Xun Zhao and Professor Jun Zhou, she moved to Kunming Institute of Botany, Chinese Academy of Sciences, for postdoctoral research with Professor Jun Zhou in 1993. She has been a professor of phytochemistry and pharmacology at Kunming Institute of Botany since 1998. She went to Germany and the U.S.A. as a visiting scientist in 1996 and 1998. Her research has involved drug discovery, including natural product chemistry, drug screening and design, and new drug research and development, especially the chemistry and biology of plant cyclopeptides, the discovery of natural active compounds, bioassay, computer-aided drug design, and anti-cancer drug research and development. She has investigated plant cyclopeptides for 15 years. She and her group have published over 110 papers and book chapters.

Jun Zhou, born in 1932, graduated from East China College of Chemical Engineering in 1958. Since 1986 he has been a professor of natural products chemistry at Kunming Institute of Botany, Chinese Academy of Sciences. He is also the former director of Kunming Institute of Botany. In 1999 he was elected to be an academician of the Chinese Academy of Sciences. His research focuses on phytochemistry and plant resources, including new and active compound discovery, traditional Chinese medicine research, plant chemotaxonomy, and sustainable utilization. He has found over 400 new compounds from plants. Several bioactive compounds from Chinese officinal plants have been used in traditional Chinese medicine production. He has investigated plant cyclopeptides for 15 years. He has received several important awards, and has published over 200 papers.

determined from *Linum usitatissimum* (linseed oil, Linaceae) in 1959 by Kaufmann and Tobschirbel,[206,207,250,251] about 455 cyclopeptides have been discovered from higher plants during the past half century, belonging to 26 families, 65 genera, and 120 species. In particular, plants of the Caryophyllaceae and Rhamnaceae families commonly contain cyclopeptides. Researchers in Europe, America, Asia, Oceania, and Africa, especially France, Germany, the U.S.A., Japan, China, Australia, Sweden, and Korea, have made important contributions in this field.

On the basis of their structural skeletons and distributions in plants, herein we propose the systematic structural classification of plant cyclopeptides which are divided into two classes, five subclasses, and eight types. During the discovery of plant cyclopeptides, type I attracted more attention in the circle of natural product chemistry from the mid 1960s to the 1980s, type VII attracted more attention from the mid 1970s to the 1990s, and types VI and VIII attracted more attention during the past decade. Particularly, sedative sanjoinine-A (type I, frangufoline, **37**),[74] immunosuppressive cycloleonurinin (type VI, **290**),[248] antitumor RA-VII (type VII, **398**),[265,271] and kalata B1 (type VIII, **424**)[321] with the fascinating structural motif of a cyclic cystine knot have aroused new and important influences in the field of plant cyclopeptides. It is noteworthy that TLC protosite reaction with ninhydrin reagent is a good specific and sensitive chemical detection method for plant cyclopeptides. It can be used effectively not only to detect whether plant extracts contain cyclopeptides but also to guide cyclopeptide separation and purification.[247] Also, cyclotides (type VIII) are gene products verified by experiments[345] and may be plant defense molecules which need more experimental evidence for clarification in the future.[344,346]

Many reviews on the occurrence, isolation, properties, classification, structural determination, synthesis, biosynthesis, bioactivity, and biofunction of cyclopeptides have been published. The main reviews related to cyclopeptide alkaloids are as follows: Warnhoff[1] mainly reviewed the cyclopeptide alkaloids found up to 1970 and their structural determination with 61 references. In 1975 Tschesche and Kaubmann[2] reported the research history, occurrence, isolation, properties, classification, structural determination, bioactivity, and biofunction of cyclopeptide alkaloids with 62 references, especially MS spectra. In 1985 Schmidt et al.[3] mainly described classification, new compounds, structural determination, synthesis, and biosynthesis of cyclopeptide alkaloids with 64 references, particularly focused on synthesis. The same year, Joullie and Nutt[4] mainly reported the occurrence, isolation, properties, classification, structural determination, synthesis, bioactivity, and biofunction of cyclopeptide alkaloids with 94 references, particularly focused on synthesis. In 1998 Gournelis et al.[5] reviewed mainly the classification, structural determination, synthesis, biosynthesis, bioactivity, and physical and spectral data of cyclopeptide alkaloids found up to 1995, especially MS and physical and spectral data. This is the most recent comprehensive review on cyclopeptide alkaloids, with 170 references. In 2004 Joullie and Richard[6] published a minireview, with 45 references, mainly about the synthesis, bioactivity, and biofunction of cyclopeptide alkaloids. The main reviews related to cyclopeptides are as follows: In 1997 and 2004 Tan et al.[7,8] reported the research history, distribution, properties, isolation, classification, chemical detection method, structural determination, bioactivity, and synthesis of 189 and 98 cyclopeptides with 69 and 77 references during 1966−1995 and 1994−2000, respectively, particularly focused on a structural classification proposal and physical and spectral data. In 1997 Itokawa et al.[9] described mainly cyclopeptide alkaloids from *Zizyphus* plants, Rubiaceae-type cyclopeptides from *Rubia* spp., Compositae-type cyclopeptides from *Aster tataricus*, and Caryophyllaceae-type cyclopeptides from caryophyllaceae plants, with 286 references, especially of their own works. The main reviews related to cyclotides are as follows: In 2001 and 2002 Craik et al.[10,11]

briefly reviewed the definition, discovery, classification, structural charateristics, synthesis, biosynthesis, bioactivity, function, and application in drug design of cyclotides during the past decade. In *Natural Product Reports* (1984−2002), Lewis also introduced some new cyclopeptides.[12]

In this review we describe the progress in the chemistry and biology of 455 cyclopeptides discovered from higher plants during 1959−2005 with 347 references.

2. Classification

On the basis of their structural skeletons and distributions in plants, herein we propose the systematic structural classification of plant cyclopeptides which are divided into two classes, five subclasses, and eight types (Figure 1). According to the skeletons, whether formed with amino acid peptide bonds or not, cyclopeptides can be divided into two classes, i.e., heterocyclopeptides and homocyclopeptides. Then on the basis of the number of rings, these classes can be divided into five subclasses, i.e., heteromonocyclopeptides, heterodicyclopeptides, homomonocyclopeptides, homodicyclopeptides, and homopolycyclopeptides. Finally, according to the characteristics of rings and sources, cyclopeptides can be divided into the following eight types. The numbers of cyclopeptides discovered from higher plants up to 2005, which belong to types I, II, III, IV, V, VI, VII, and VIII are 185, 2, 4, 13, 9, 168, 23, and 51, respectively. Among them, types I and VI are the largest two types. These 455 cyclopeptides involve cyclic di- (2), tri- (3), tetra- (4), penta- (5), hexa- (6), hepta- (7), octa- (8), nona- (9), deca- (10), undeca- (11), dodeca- (12), tetradeca- (14), octacosa- (28), nonacosa- (29), traconta- (30), hentriaconta- (31), tetratraconta- (34), and heptatraconta- (37) peptides, respectively.

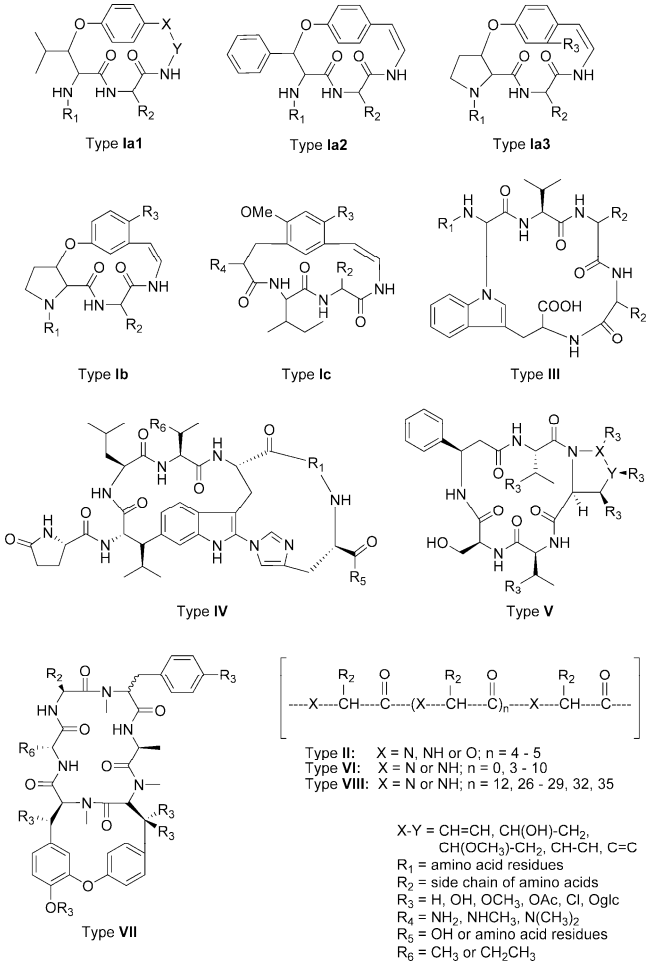
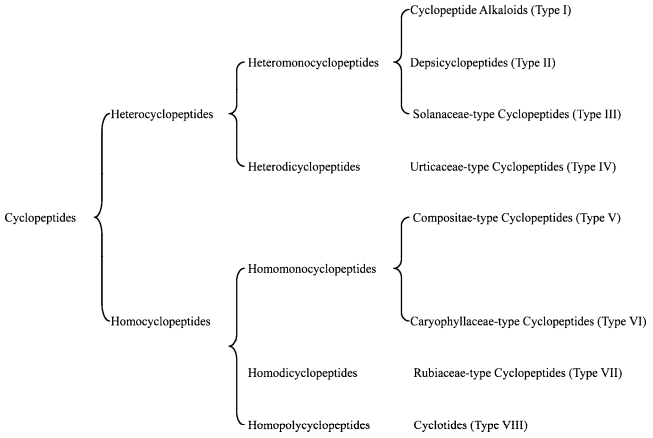


Figure 1. Types of cyclopeptides.



2.1. Heterocyclopeptides

2.1.1. Heteromonocylopeptides

2.1.1.1. Cyclopeptide Alkaloids (Rhamnaceae-Type Cyclopeptides) (Type I). We define cyclopeptide alkaloids[2] [with the exception of lasiodine-A[13] (**1**) and sanjoinine-G2[74] (**2**)] as basic compounds embodying a *p*- or *m*-ansa structure with a 13-, 14-, or 15-membered ring, in which a 10- or 12-membered peptide-type bridge spans the 1, 3 or 1, 4 positions of a benzene ring.[3] Cyclopeptide alkaloids were also called cyclic peptide alkaloids,[3] peptide alkaloids,[1] basic peptides,[1] ansapeptides,[4] and phencyclopeptines.[47] They are principally composed of one styrylaminine moiety, two or three ring-bonded α-amino acid residues, and, or not, one or two side-chain *N*-methyl or *N*,*N*-dimethyl α-amino acid residues. Their basicity is attributable to an N-terminal amino acid residue.[4]

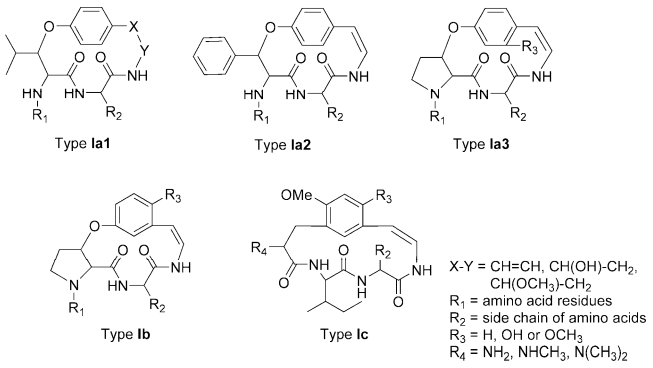


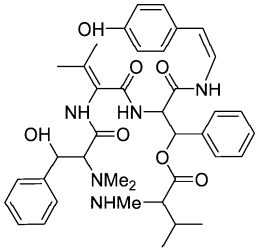
Figure 2. Types of cyclopeptide alkaloids.

Table 1. Summary of Cyclopeptide Alkaloids Isolated from Higher Plants during the Past Half Century

period	type Ia1	type Ia2	type Ia3	type Ia4	type Ib	type Ic	acyclic	total
1960s	14	8	0	2	0	0	1	25
1970s	17	11	16	0	11	12	0	67
1980s	14	4	0	0	21	0	1	40
1990s	10	3	7	0	10	0	0	30
2000s	2	6	6	0	11	0	0	25
total	57	32	29	2	53	12	2	187

The presence of alkaloids in *Ceanothus americanus* (Rhamnaceae), long used in folk medicines, was noted as early as 1884 by Clinch. In the 1920s and 1930s, Clark and Bertho et al. started to explore this field; in particular, the

Table 2. Cyclopeptide Alkaloids (Type I) Isolated from Higher Plants during 1966−2005



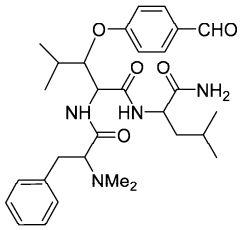
Lasiodine-A (**1**)[1,5,13]

from *Lasiodiscus marmoratus* (Rhamnaceae, leaves).

$C_{39}H_{49}N_5O_7$, MW=699; mp 195, $[\alpha]_D^{20}$ +38° ($CHCl_3$, c 1.0);

IR, UV, PMR, CMR;

hydrogenation, amino acid analysis after hydrolysis, methylation, acetylation.



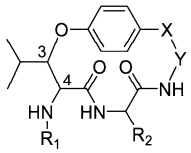
Sanjoinine-G2 (**2**)[5,74,75](Frangufoline-amido-aldehyde)

from *Zizyphus vulgaris* var. *spinosus* (Rhamnaceae, seeds).

$C_{30}H_{42}N_4O_5$; 1.6×10^{-4}%, needles, mp 182, $[\alpha]_D^{26}$ -79.2° ($CHCl_3$, c 0.275);

IR, UV, EI-MS[538(M^+)], PMR, CMR;

alkaline hydrolysis.



Type **Ia1**

No.	Source (family, part)	Cyclopeptide (No.) (synonym)	Structure* R_1	R_2	X – Y	C_3	C_4	Structural and spectral data	Bioactivity	Reference
1	*Canthium anorldianum* (Rubiaceae) (stem barks)	Anorldianine (**3**)	N,N-Me_2Leu	Pro(side chain)	CH=CH			$C_{27}H_{40}N_4O_4$; 1.7×10^{-3}%, pinkish crystals, mp 160; IR, UV, EI-MS[484(M^+)], PMR, CMR, 2D NMR (COSY); elemental analysis.		73
2	*Ceanothus americanus* (Rhamnaceae) (root barks)	Adouetine-X (**4**) (Ceanothamine-B)	N,N-Me_2Leu	Ile(side chain)	CH=CH			$C_{28}H_{44}N_4O_4$; colorless matted needles, mp 279.0-280.5, $[\alpha]_D^{25}$ –370° ($CHCl_3$, c 0.205); IR, UV, EI-MS[500(M^+)], PMR; elemental analysis, hydrogenation, amino acid analysis after hydrolysis, ozonolysis.		1,14,22,36
	(root barks)	Americine (**5**)	N-MeVal	Trp(side chain)	CH=CH			$C_{31}H_{39}N_5O_4$; 1.7×10^{-2}%, mp 135.5-137.0 and 142-182, $[\alpha]_D^{20}$ –198° (CH_3OH, c 0.51); IR, UV, EI-MS[545(M^+)], PMR; elemental analysis, hydrogenation, amino acid analysis after hydrolysis, methylation, ozonolysis.		18
	(root barks)	Ceanothine-A (**6**) (N-Desmethyl-myrianthine -B (**11**)) (N-Desmethyl-frangufoline) (Sanjoinine-B (**56**))	N-MePhe	Ile(side chain) or Leu(side chain)	CH=CH			$C_{30}H_{40}N_4O_4$; colorless matted needles, mp 256-259, $[\alpha]_D$ –256° ($CHCl_3$, c 0.5); IR, UV, EI-MS[520(M^+)], PMR; elemental analysis, hydrogenation, acetylation.		1,5,14
	(root barks)	Ceanothine-B (**7**) (Ceanothine)	N-MePro	Phe(side chain)	CH=CH			$C_{29}H_{36}N_4O_4$; colorless matted needles, mp 238.5-240.5, $[\alpha]_D^{25}$ –293° ($CHCl_3$, c 0.68); IR, UV, EI-MS[504(M^+)], PMR; elemental analysis, hydrogenation, amino acid analysis after hydrolysis, acetylation, ozonolysis.		14-17,48
	(root barks)	Ceanothine-C (**8**)	N-MePro	Ile(side chain) or Leu(side chain)	CH=CH			$C_{26}H_{38}N_4O_4$; colorless matted needles, mp 223-229, $[\alpha]_D^{25}$ –368° ($CHCl_3$, c 1.01); IR, UV, EI-MS[470(M^+)], PMR; elemental analysis, hydrogenation, acetylation.		14,22
	(root barks)	Homoamericine (**9**) (Discarine-I (**18**)) (N-Desmethyl-texensine)	N-MeIle or Leu	Trp(side chain)	CH=CH			$C_{32}H_{41}N_5O_4$; mp 135.5-137 and 142-182; EI-MS[559(M^+)].		5,18
3	*C. integerrimus* (root barks)	N-Methyl-americine (**10**)	N,N-Me_2Val	Trp(side chain)	CH=CH			$C_{32}H_{41}N_5O_4$; mp 233; MS[559(M^+)], PMR; amino acid analysis after hydrolysis.		47,48
4	*C. sanguineus* (root barks)	N-Desmethyl-myrianthine-B (**11**)	N-MePhe	Ile(side chain)	CH=CH			$C_{30}H_{40}N_4O_4$; mp 229; MS[520(M^+)]; amino acid analysis after hydrolysis.		48
5	*Colubrina texensis* (Rhamnaceae) (aerial parts)	Texensine (**12**)	N,N-Me_2Leu	Trp(side chain)	CH=CH			$C_{33}H_{43}N_5O_4$; 5.0×10^{-4}%, mp 249-252, $[\alpha]_D^{25}$ –144° ($CHCl_3$, c 0.50); IR, UV, MS[573(M^-)], PMR; hydrogenation, amino acid analysis after hydrolysis.		29
6	*Discaria americama* (Rhamnaceae) (root barks)	Discarine-M (**13**)	$(CH_3)_2$CHCH=CHCO	*L*-Leu(side chain)	CH=CH	*S*	*S*	$C_{26}H_{37}N_5O_4$; 1.8×10^{-3}%, white amorphous powder, $[\alpha]_D^{20}$ –176.7° (CH_3OH:$CHCl_3$ (1:1), c 0.2); IR, pos. FAB-MS[456(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}HCOSY, HMQC, HMBC, NOESY); elemental analysis, amino acid analysis after hydrolysis, absolute configuration (chiral phase GC).		104
	(root barks)	Discarine-N (**14**) (a stereoisomer of scutianene-C (**41**))	PhCH=CHCO	*L*-β(*R*)-OHPhe(side chain)	CH=CH	*S*	*S*	$C_{32}H_{33}N_3O_5$; 1.8×10^{-3}%, white powder, mp 233-235, $[\alpha]_D^{20}$ +98.1° (CH_3OH:$CHCl_3$ (1:1), c 0.092); IR, pos. FAB-MS[540(M+H)$^+$], PMR, CMR, 2D NMR (DEPT, HMQC, HMBC, NOESY); elemental analysis, amino acid analysis after hydrolysis, absolute configuration (chiral phase GC).		104

Table 2 (Continued)

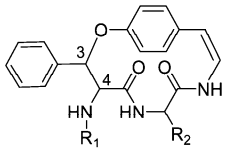
No.	Source (family, part)	Cyclopeptide (No.) (synonym)	Structure* R_1	R_2	X – Y	C_3	C_4	Structural and spectral data	Bioactivity	Reference
7	*D. febrifuga* (barks)	Discarine-F (**15**) (N-Desmethyl-adouetine-X)	N-MeLeu	Ile(side chain)	CH=CH			$C_{27}H_{42}N_4O_4$; mp 264, $[\alpha]_D^{20}$ –191° ($CHCl_3$); IR, UV, EI-MS[486(M)$^+$], PMR.		55
	(root barks)	Discarine-G (**16**)	N,N-Me_2Phe	Ile(side chain)	CH(OH)-CH_2			$C_{31}H_{44}N_4O_5$; mp 257, $[\alpha]_D^{20}$ –366° (CH_3OH, c 1.0); IR, UV, MS[552(M)$^+$], PMR, CMR; acetylation.		5
	(root barks)	Discarine-H (**17**)	N,N-Me_2Leu	Leu(side chain)	CH(OH)-CH_2			$C_{28}H_{46}N_4O_5$; mp 232, $[\alpha]_D^{20}$ –266° (CH_3OH); IR, UV, MS[518(M)$^+$], PMR, CMR; acetylation.		5
	(root barks)	Discarine-I (**18**) (N-Desmethyl-discarine-B)	N-MeIle	Trp(side chain)	CH=CH			$C_{32}H_{41}N_5O_4$; 1.2×10^{-4}%, mp 140, $[\alpha]_D^{25}$ –149° (CH_3OH, c 0.1); IR, UV, EI-MS[559(M)$^+$], PMR, CMR; elemental analysis.		61
	(roots)	Discarine-K (**19**)	N,N-Me_2Ile	Trp(side chain)	CH(OH)-CH_2			$C_{33}H_{45}N_5O_5$; colorless crystals, mp 237, $[\alpha]_D^{20}$ –62° (CH_3OH); IR, UV, MS[591(M)$^+$], PMR, CMR, 2D NMR (COSY-45 technique).		67
	(root barks)	Discarine-L (**20**)	N,N-Me_2Ile	Leu(side chain)	CH(OH)-CH_2			$C_{28}H_{46}N_4O_5$; 1.0×10^{-4}%, amorphous powder, $[\alpha]_D$ –30° (CH_3OH, c 0.5); IR, EI-MS[518(M)$^+$], PMR, CMR, 2D NMR (COSY, DEPT, spin-echo experiments).		83
8	*D. longispina* (roots)	Discarine-A (**21**)	N,N-Me_2Trp	Ile(side chain)	CH=CH			$C_{33}H_{43}N_5O_4$; mp 229-231, $[\alpha]_D$ –282° ($CHCl_3$, c 0.05); IR, UV, MS[573(M$^+$)], PMR, CMR; hydrogenation, amino acid analysis after hydrolysis.	anti-bacteria	5,26,104
	(roots, root barks)	Discarine-B (**22**)	N,N-Me_2Ile	Trp(side chain)	CH=CH			$C_{33}H_{43}N_5O_4$; 1.3×10^{-2}%, mp 235-236, $[\alpha]_D$ –172° ($CHCl_3$, c 0.1); IR, UV, EI-MS[573(M$^+$)], PMR, CMR, 2D NMR (COSY, DEPT, spin decoupling, HETCOSY); elemental analysis, hydrogenation, amino acid analysis after hydrolysis.	anti-bacteria	26,47,48,61 ,87,99,104
	(root barks)	Discarine-E (**23**)	N,N-Me_2Ile	Ile(side chain)	CH=CH			$C_{28}H_{44}N_4O_4$; 3.4×10^{-3}%, mp 270-273, $[\alpha]_D^{25}$ +236° (AcOH, c 0.5); IR, UV, EI-MS[500(M)$^+$], PMR, CMR, 2D NMR (COSY, DEPT, spin decoupling, HETCOSY); elemental analysis.		5,87
9	*D. pubescens*	Pubescine-A (**24**) (stereoisomer of melonovine-A (**30**))	N,N-Me_2Val	*D*-Leu(side chain)	CH=CH	*S*	*S*	$C_{27}H_{42}N_4O_4$; 1.5×10^{-3}%, colorless needles, mp 247-250, $[\alpha]_D^{20}$ –230°(CH_3OH, c 0.076); IR, UV, EI-MS[486(M)$^+$], PMR; amino acid analysis after enzymatic hydrolysis, ozonolysis, configuration (amino acid oxidase).		49
10	*Heisteria nitida* (Olacaceae) (barks)	Anorldianine 27-N oxide (**25**)	N,N-Me_2Leu(N→O)	Pro(side chain)	CH=CH			$C_{27}H_{40}N_4O_5$; 4.1×10^{-3}%; IR, UV, FAB-MS[501(M+H)$^+$], PMR, CMR, 2D NMR (DEPT, HMQC, HMBC); amino acid analysis after hydrolysis.		94
11	*Hovenia dulcis* *H. tomentella* (Rhamnaceae) (root barks)	Hovenine-A (**26**) (N-Desmethyl-frangulanine)	N-MeIle	Leu(side chain)	CH=CH			$C_{27}H_{42}N_4O_4$; 5.0×10^{-3}%, mp 215; IR, MS[486(M)$^+$], PMR; amino acid analysis after hydrolysis, reductive methylation.		30
12	*Lasiodiscus marmoratus* (Rhamnaceae) (leaves)	Lasiodine-B (**27**)	N-MePhe-Pro	Leu(side chain)	CH=CH			$C_{35}H_{47}N_5O_5$; mp 221, $[\alpha]_D^{20}$ –301°($CHCl_3$:CH_3OH (1:1), c 1.0); IR, UV, MS[617(M)$^+$], PMR, CMR; amino acid analysis after hydrolysis, acetylation.		1,5,13
13	*Melochia corchorifolia* (Sterculiaceae) (leaves, woody parts, aerial parts)	Adouetine-Y' (**28**) (Myrianthine-B) (Lotusanine-A) (AM-1)	*L*-N,N-Me_2Phe	*L*-Ile(side chain)	CH=CH	*S*	*S*	$C_{31}H_{42}N_4O_4$; colorless amorphous solids, mp 289.0-290.5, $[\alpha]_D^{20}$ –305°($CHCl_3$); IR, UV, EI-MS[534(M)$^+$], PMR, CMR, 2D NMR (COSY, HMQC, HMBC); hydrogenation, amino acid analysis after hydrolysis, absolute configuration (GC).		1,5,21,35,4 8,63,79,86, 87,92,95,96 ,99,101,104
	(aerial parts)	Melofoline (**29**)	N,N-Me_2-β-OHLeu	CH_2CH_3	CH=CH			$C_{26}H_{40}N_4O_5$; 1.7×10^{-3}%, mp 305-307, $[\alpha]_D^{20}$ –252°($CHCl_3$); IR, MS[488(M)$^+$], PMR; elemental analysis, amino acid analysis after hydrolysis, acetylation.		63
14	*M. tomentosa* (roots)	Melonovine-A (**30**) (Daechuine-S5)	N,N-Me_2Val	Leu(side chain)	CH=CH			$C_{27}H_{42}N_4O_4$; 9.4×10^{-4}%, mp 295, $[\alpha]_D$ –285°($CHCl_3$); IR, MS[486(M)$^+$], PMR; amino acid analysis after hydrolysis.		43,74
	(roots)	Melonovine-B (**31**)	N,N-Me_2Val	Tyr(side chain)	CH=CH			$C_{30}H_{40}N_4O_5$; 6.3×10^{-4}%, mp 200-206; IR, MS[536(M)$^+$], PMR; amino acid analysis after hydrolysis.		43
15	*Myrianthus arboreus* (Urticaceae) (leaves)	Myrianthine-C (**32**)	N,N-Me_2Leu	Val(side chain)	CH=CH			$C_{27}H_{42}N_4O_4$; mp 294, $[\alpha]_D^{20}$ –228°($CHCl_3$, c 1.0); IR, UV, MS[486(M)$^+$], PMR.		1,5,72
16	*Panda oleosa* (Pandaceae) (root barks)	Pandamine (**33**)	N,N-Me_2Ile	Phe(side chain)	CH(OH)-CH_2			$C_{31}H_{44}N_4O_5$; mp 256, $[\alpha]_D$ –103°($CHCl_3$, c 0.5); IR, UV, MS[552(M)$^+$], PMR, CMR; amino acid analysis after hydrolysis, alkaline hydrolysis, acetylation.		1,5
	(root barks)	Pandaminine (**34**)	N,N-Me_2Val	Phe(side chain)	CH(OH)-CH_2			$C_{30}H_{42}N_4O_5$, MW=538; mp 272, $[\alpha]_D$ –117°($CHCl_3$, c 0.5); IR, PMR, CMR; acetylation.		1,5
17	*Plectronia odorata* (Rubiaceae) (aerial parts)	N-Desmethyl-myrianthine-C (**35**)	NMeLeu	Val(side chain)	CH=CH			$C_{26}H_{40}N_4O_4$; amorphous, $[\alpha]_D^{20}$ –103°($CHCl_3$, c 1.0); IR, UV, MS[473(M+H)$^+$], PMR.		72

Table 2 (Continued)

No.	Source (family, part)	Cyclopeptide (No.) (synonym)	Structure* R_1	R_2	X – Y	C_3	C_4	Structural and spectral data	Bioactivity	Reference
18	*Rhamnus frangula* (Rhamnaceae) (barks)	Franganine (**36**) (Daechuine-S4)	*L*-N,N-Me_2Leu	*L*-Leu(side chain)	CH=CH			$C_{28}H_{44}N_4O_4$; colorless needles, mp 248, $[\alpha]_D^{22}$ –302° ($CHCl_3$, c 0.1); IR, UV, EI-MS[500(M^+)], PMR, CMR, 2D NMR (COSY-45, DEPT, spin-echo, 2D-J resolved techniques); hydrogenation, amino acid analysis after hydrolysis, absolute configuration (GC).		1,5,20,21,31,67,74,78,92,99,104
	(barks)	Frangufoline (**37**) (Sanjoinine-A) (Daechuine-S1)	*L*-N,N-Me_2Phe	*L*-Leu(side chain)	CH=CH	*S*	*S*	$C_{31}H_{42}N_4O_4$; colorless needles, mp 244, $[\alpha]_D^{22}$ –299° ($CHCl_3$, c 0.1); IR, UV, EI-MS[534(M^+)], PMR, CMR; hydrogenation, amino acid analysis after hydrolysis.	sedative, anti-bacteria, anti-fungi	1,5,20,21,31,35,39,40,48,50,66,74-76,82,86,88,116
	(barks)	Frangulanine (**38**) (Ceanothamine-A) (Daechuine-S2)	*L*-N,N-Me_2Ile	*L*-Leu(side chain)	CH=CH	*S*	*S*	$C_{28}H_{44}N_4O_4$; colorless matted needles, mp 276-279, $[\alpha]_D$ –293°($CHCl_3$); x-ray, CD, IR, UV, EI-MS[500(M^+)], PMR, CMR; elemental analysis, hydrogenation, amino acid analysis after hydrolysis, methylation.		1,5,14,20,22,26,30,31,36,46,74,104,112
19	*Scutia buxifolia* (Rhamnaceae) (barks)	Scutianine (**39**) (Scutianine-A)	*L*-N,N-Me_2-Phe-*L*-Pro	*L*-Phe(side chain)	CH=CH			$C_{39}H_{47}N_5O_5$; mp 186-187, $[\alpha]_D^{20}$ –399° ($CHCl_3$, c 0.15); IR, UV, MS[665(M^+)], PMR; elemental analysis, hydrogenation, amino acid analysis after hydrolysis, ozonolysis, absolute configuration (GC).		1,5,23,37
	(roots, barks)	Scutianine-B (**40**)	*L*-N,N-Me_2Phe	*L*-Phe(side chain)	CH=CH	*S*	*S*	$C_{34}H_{40}N_4O_4$; mp 248-250, $[\alpha]_D^{20}$ –296° ($CHCl_3$, c 0.1); CD, IR, UV, EI-MS[568(M^+)], PMR; hydrogenation, amino acid analysis after hydrolysis, absolute configuration (GC).	anti-bacteria	5,23,35,43,44,92,95,96,101
	(roots)	Scutianene-C (**41**)	PhCH=CHCO	β-OHPhe(side chain)	CH=CH			$C_{32}H_{33}N_3O_5$, MW=539; mp 232-234, $[\alpha]_D$ +203° ($CHCl_3$:CH_3OH(3:2), c 0.12); IR, UV, MS, PMR; hydrogenation, amino acid analysis after hydrolysis.		37
	(roots, barks)	Scutianine-C (**42**) (Scutianine-D) (Scutianine-E)	*L*-N,N-Me_2Phe	*L*-β-OHPhe(side chain)	CH=CH			$C_{34}H_{40}N_4O_5$; mp 202-204, $[\alpha]_D$ –188° ($CHCl_3$, c 0.15); CD, IR, UV, MS[584(M^+)], PMR, CMR; hydrogenation, amino acid analysis after hydrolysis, acetylation, absolute configuration (GC).		5,35,45,92
	(roots, barks)	Scutianine-D (**43**) (Scutianine-C)	*L*-N,N-Me_2Ile	*L*-Phe(side chain)	CH=CH	*S*	*S*	$C_{31}H_{42}N_4O_4$; mp 255-256, $[\alpha]_D$ -210° ($CHCl_3$, c 0.5); CD, IR, UV, EI-MS[534(M^+)], PMR; hydrogenation, amino acid analysis after hydrolysis, absolute configuration (GC).		5,37,45,82,92,100,101
	(barks)	Scutianine-F (**44**) (N-Desmethyl-scutianine-A)	N-MePhe-Pro	Phe(side chain)	CH=CH			$C_{38}H_{45}N_5O_5$; mp 208, $[\alpha]_D^{20}$ -132° (CH_3OH, c 0.02); IR, UV, EI-MS[651(M^+)], PMR; hydrogenation, amino acid analysis after hydrolysis, methylation.		5,42
	(barks)	Scutianine-G (**45**)	*L*-N,N-Me_2Phe	*D*-β-OHPhe(side chain)	CH=CH			$C_{34}H_{40}N_4O_5$; 3.0×10^{-4}%, mp 162, $[\alpha]_D^{20}$ -112° (CH_3OH, c 0.02); IR, UV, EI-MS[584(M^+)], PMR; amino acid analysis after enzymatic hydrolysis, ozonolysis, absolute configuration (GC).		44,92
	(barks)	Scutianine-H (**46**)	N,N-Me_2Ile	β-OHPhe(side chain)	CH=CH			$C_{31}H_{42}N_4O_5$; 1.0×10^{-3}%, mp 242-243, $[\alpha]_D^{20}$ -223° ($CHCl_3$, c 0.1); IR, UV, EI-MS[550(M^+)], PMR; hydrogenation, amino acid analysis after hydrolysis.		45
	(barks)	Scutianine-J (**47**)	N,N-Me_2β-OHPhe	β-OHPhe(side chain)	CH=CH			$C_{34}H_{40}N_4O_6$; 5.0×10^{-4}%, amorphous; IR, UV, pos. FAB-MS[601(M+H)$^+$], PMR, 2D NMR (COSY); elemental analysis.		85
		Scutianine-K (**48**)	*L*-N,N-Me_2Phe	α-*R*/β-*S*-β-OHPhe(side chain)	CH=CH	*S*	*S*	$C_{34}H_{40}N_4O_5$; 3.5×10^{-4}%, colorless crystals, mp 215-217, $[\alpha]_D^{25}$ –20.9° ($CHCl_3$, c 0.1); pos. FAB-MS[585(M+H)$^+$], PMR, CMR, 2D NMR (COSY, NOESY, DEPT, HETCOR); hydrogenation, amino acid analysis after hydrolysis, absolute configuration (chiral phase GC).		93
20	*Waltheria douradinha* (Sterculiaceae) (root barks, barks)	Waltherine-A (**49**)	N,N-Me_2Leu	Phe(side chain)	CH=CH			$C_{31}H_{42}N_4O_4$; colorless needles, mp 234-235, $[\alpha]_D^{20}$ –229.8° (CH_3OH, c 0.24); EI-MS[534(M^+)], PMR, CMR, 2D NMR (COSY, NOESY, proton noise-decoupled ^{13}C spectroscopy, DEPT, HMQC, HMBC).		95,96
	(root barks, barks)	Waltherine-B (**50**) (a stereoisomer of discarine –A (**21**) and amphibine-A (**52**))	N,N-Me_2Trp	Ile(side chain)	CH=CH			$C_{33}H_{43}N_5O_4$; colorless needles, mp 242-243, $[\alpha]_D^{20}$ –201.8° (CH_3OH, c 0.21), $[\alpha]_D^{20}$ –356.7° ($CHCl_3$, c 0.5); EI-MS[573(M^+)], PMR, CMR, 2D NMR (COSY, NOESY, DEPT, HMQC, HMBC).		95,96
	(barks)	Waltherine-C (**51**)	*L*-N,N-Me_2Trp	*L*-Ala(side chain)	CH=CH	*S*	*S*	$C_{30}H_{37}N_5O_4$; 7.1×10^{-4}%, amorphous powder, $[\alpha]_D$ –182° ($CHCl_3$, c 0.20); pos. FAB-MS[532(M+H)$^+$], PMR, CMR, 2D NMR (^1H-^1H COSY, NOESY, DEPT, HMQC, HMBC); elemental analysis, absolute configuration (chiral phase GC).		96
21	*Zizyphus amphibia* (Rhamnaceae) (stem barks)	Amphibine-A (**52**)	N,N-Me_2Trp	Ile(side chain)	CH=CH			$C_{33}H_{43}N_5O_4$; mp 237-239, $[\alpha]_D^{20}$ –310° (CH_3OH, c 0.021); UV, EI-MS[573(M^+)], PMR; hydrogenation, amino acid analysis after hydrolysis.		5,24,40

Table 2 (Continued)

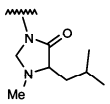
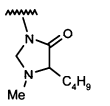
No.	Source (family, part)	Cyclopeptide (No.) (synonym)	Structure* R_1	R_2	X – Y	C_3	C_4	Structural and spectral data	Bioactivity	Reference
22	*Z. lotus* (aerial parts)	Lotusanine-B (**53**)	PhCH=CHCO-Pro	Phe(side chain)	CH=CH	*S*	*S*	$C_{37}H_{40}N_4O_5$; amorphous solids; IR, UV, EI-MS[620(M)$^+$], PMR, CMR, 2D NMR (DEPT).		86
23	*Z. nummularia* (stem barks)	Nummularine-K (**54**) (Discarine-X)	N,N-Me_2Trp	Leu(side chain)	CH=CH			$C_{33}H_{43}N_5O_4$; 2.4×10^{-3}%, mp 235-239, $[\alpha]_D^{20}$ –45° (CH_3OH, c 0.04); IR, UV, EI-MS[573(M)$^+$], PMR, CMR, 2D NMR (COSY); hydrogenation, amino acid analysis after hydrolysis.	anti-bacteria, anti-fungi	3,5,66.76,87
24	*Z. vulgaris* var. *spinosus* (seeds)	Sanjoinenine (**55**)	PhCH=CHCO	Leu(side chain)	CH=CH	*S*	*S*	$C_{29}H_{35}N_5O_4$; 2.2×10^{-4}%, needles, mp 281-282, $[\alpha]_D^{22}$ –272.5° (pyridine, c 1.6); IR, UV, EI-MS[489(M)$^+$], PMR, CMR.		74,75,86
	(seeds)	Sanjoinine-B (**56**) (N-Desmethyl-frangufoline)	N-MePhe	Leu(side chain)	CH=CH			$C_{30}H_{40}N_4O_4$; 5.5×10^{-6}%, needles, mp 212-214; EI-MS[520(M)$^+$], PMR.		5,74,75
	(seeds)	Sanjoinine-D (**57**) (O-Methyl-sanjoinine-G1)	N,N-Me_2Phe	Leu(side chain)	CH(OCH_3)-CH_2			$C_{32}H_{46}N_4O_5$; 4.0×10^{-5}%, needles, mp 256-258, $[\alpha]_D^{26}$ –53.6° ($CHCl_3$, c 0.25); IR, UV, EI-MS[566(M)$^+$], PMR, CMR.		5,74,75
	(seeds)	Sanjoinine-F (**58**)	N,N-Me_2Phe	β-OHLeu(side chain)	CH=CH	*S*	S	$C_{31}H_{42}N_4O_5$; 1.3×10^{-4}%, needles, mp 228-229, $[\alpha]_D^{26}$ –215° ($CHCl_3$, c 0.28); IR, UV, EI-MS[550(M)$^+$], PMR, CMR; hydrogenation, amino acid analysis after hydrolysis, acetylation.		74,75,86
	(seeds)	Sanjoinine-G1 (**59**)	*L*-N,N-Me_2Phe	*L*-Leu(side chain)	CH(*R*-OH)-CH_2	*S*	*S*	$C_{31}H_{44}N_4O_5$; 3.5×10^{-5}%, crystalline powder, mp 236-238, $[\alpha]_D^{20}$ –68.6° ($CHCl_3$, c 0.175); CD, IR, UV, EI-MS[552(M)$^+$], PMR, 2D NMR (^{1}H-^{1}H COSY, decoupling experiments); acid hydrolysis, acetylation, benzoylation, absolute configuration and solution conformation (CD, GC, $^2J_{1H\text{-}1H}$, NOE, total synthesis).		74,90

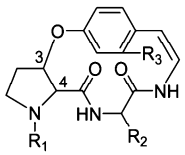


Type **Ia2**

No.	Source (family, part)	Cyclopeptide (No.) (synonym)	Structure* R_1	R_2	C_3	C_4	Structural and spectral data	Bioactivity	Reference
1	*Araliorhamnus vaginatus* (Rhamnaceae) (leaves, stem barks)	Aralionine (**60**) (Aralionine-A)	N,N-Me_2Ile	PhCO			$C_{34}H_{38}N_4O_5$; mp 165-167, $[\alpha]_D^{20}$ +82° (CH_3OH, c 0.2); CD, IR, UV, MS[582(M$^+$)], PMR; hydrogenation, amino acid analysis after hydrolysis, desbenzoylation.		1,2,5
	(leaves, barks)	Aralionine-B (**61**) (AM-2) (N-Desmethyl-adouetine-Y)	*L*-N-MePhe	*L*-Ile(side chain)			$C_{33}H_{38}N_4O_4$; mp 103-105, $[\alpha]_D^{20}$ -73° (CH_3OH, c 0.1); CD, IR, UV, EI-MS[554(M$^+$)], PMR; amino acid analysis after hydrolysis, absolute configuration (GC).		2,5,42,79
	(barks)	Aralionine-C (**62**)	N,N-Me_2Ile	β-OHPhe(side chain)			$C_{34}H_{40}N_4O_5$; mp 95-97, $[\alpha]_D^{20}$ –17° (CH_3OH, c 0.015); IR, UV, EI-MS[584(M$^+$)], PMR; hydrogenation, amino acid analysis after hydrolysis.		42
	(stem barks)	Desbenzoyl-aralionine-A (**63**)	N,N-Me_2Ile	H			$C_{27}H_{34}N_4O_4$; mp 101-104, $[\alpha]_D^{20}$ +100° (CH_3OH, c 0.16); CD, IR, UV, MS[478(M$^+$)], PMR.		5
2	*Canthium euryoides* (Rubiaceae)	Canthiumine (**64**)	N,N-Me_2Phe	Pro(side chain)			$C_{33}H_{36}N_4O_4$; mp 232-233, $[\alpha]_D$ –254° ($CHCl_3$, c 1.0); IR, UV, MS[552(M$^+$)], PMR; hydrogenation, amino acid analysis after hydrolysis.		2,5
3	*Ceanothus americanus* (Rhamnaceae) (root barks)	Adouetine-Y (**65**)	N,N-Me_2Phe	Ile(side chain)			$C_{34}H_{40}N_4O_4$; mp 287-289, $[\alpha]_D$ –213° ($CHCl_3$); IR, UV, EI-MS[568(M$^+$)], PMR; hydrogenation, amino acid analysis after hydrolysis.		1,5,22,99
	(root barks)	Ceanothine-E (**66**)	N,N-Me_2Phe	Leu(side chain)			$C_{34}H_{40}N_4O_4$; mp 238-239, $[\alpha]_D$ –285° ($CHCl_3$); EI-MS[568(M$^+$)]; hydrogenation, amino acid analysis after hydrolysis.		1,22
4	*C. integerrimus* (root barks)	N-Desmethyl-integerrenine (**67**) (a stereoisomer of nummularine-D (**86**))	N-MeIle	Leu(side chain)			$C_{30}H_{40}N_4O_4$; mp 213; MS[520(M$^+$)], PMR; amino acid analysis after hydrolysis.		47
	(root barks)	N-Desmethyl-integerrine (**68**)	N-MeVal	Trp(side chain)			$C_{34}H_{37}N_5O_4$; mp>350; MS[579(M$^+$)], PMR; amino acid analysis after hydrolysis.		5,47
	(root barks)	Deoxo-aralionine-A (**69**) (Deoxy-aralionine-C)	N,N-Me_2Ile	Phe(side chain)			$C_{34}H_{40}N_4O_4$; mp>350; MS[568(M$^+$)], PMR.		5,47
	(roots, root barks)	Integerrenine (**70**)	N,N-Me_2Ile	Leu(side chain)			$C_{31}H_{42}N_4O_4$; mp 278, $[\alpha]_D^{20}$ –228° ($CHCl_3$, c 0.2); CD, IR, UV, MS[534(M$^+$)], PMR; hydrogenation, amino acid analysis after hydrolysis.		1,5,19,40,47,50,94
	(roots)	Integerressine (**71**)	N,N-Me_2Val	Phe(side chain)			$C_{33}H_{38}N_4O_4$; mp 285, $[\alpha]_D^{20}$ –164° ($CHCl_3$, c 0.2); CD, IR, UV, MS[554(M$^+$)], PMR; hydrogenation, amino acid analysis after hydrolysis.		1,5,19,47
	(roots, root barks)	Integerrine (**72**)	N,N-Me_2Val	Trp(side chain)			$C_{35}H_{39}N_5O_4$; mp 258; UV, EI-MS[593(M$^+$)], PMR.		1,19,47
5	*Condalia buxifolia* (Rhamnaceae) (root barks)	Condaline-A (**73**) (a stereoisomer of aralioline-B (**61**))	*L*-N-MePhe	*L*-Ile(side chain)	*R*	*S*	$C_{33}H_{38}N_4O_4$; 9.2×10^{-2}%, needles, mp 115-116, $[\alpha]_D^{25}$ -73° (CH_3OH, c 0.08); IR, pos. LSI-MS[555(M+H)]$^+$, PMR, CMR, 2D NMR (COSY, DEPT, HMQC, HMBC, NOESY); elemental analysis, hydrogenation, amino acid analysis after hydrolysis, absolute configuration (chiral phase GC, NOESY).	anti-bacteria	101

Table 2 (Continued)

No.	Source (family, part)	Cyclopeptide (No.) (synonym)	Structure* R_1	Structure* R_2	C_3	C_4	Structural and spectral data	Bioactivity	Reference
6	*Discaria americana* (Rhamnaceae) (root barks)	Discarene-C (**74**)	$(CH_3)_2CHCH=CHCO$	*L*-Leu(side chain)	*R*	*S*	$C_{29}H_{33}N_3O_4$; 1.7×10^{-3}%, white powder, mp 297, $[\alpha]_D^{20}$ -51.7° (CH_3OH-$CHCl_3$ (1:1), c 0.2); IR, pos. FAB-MS[490(M+H)$^+$], PMR, CMR, 2D NMR (COSY, HMQC, HMBC); amino acid analysis after hydrolysis, absolute configuration (chiral phase GC, NOESY).		99
	(root barks)	Discarene-D (**75**)	$(CH_3)_2CHCH=CHCO$	*L*-Phe(side chain)	*S*	*R*	$C_{32}H_{33}N_3O_4$; 1.2×10^{-3}%, amorphous powder, $[\alpha]_D^{25}$ -176° (CH_3OH-$CHCl_3$ (1:1), c 0.2); IR, pos. FAB-MS[524(M+H)$^+$], PMR, CMR, 2D NMR (COSY, DEPT, HMQC, HMBC, NOESY); amino acid analysis after hydrolysis, absolute configuration (chiral phase GC, NOESY).		99
7	*D. crenata* (leaves, stems)	Crenatine-A (**76**) (Discarine-D)	N,N-Me_2Leu	Phe(side chain)			$C_{34}H_{40}N_4O_4$; 2.9×10^{-3}%, mp 223, $[\alpha]_D^{20}$ –292.58° ($CHCl_3$, c 0.1); IR, UV, EI-MS[568(M)$^+$], PMR.		5,34,99,104
8	*D. febrifuga* (stem barks)	Discarine-C (**77**)	N,N-Me_2Leu	Leu(side chain)			$C_{31}H_{42}N_4O_4$; IR, UV, MS[534(M)$^+$], PMR.		5,99,104
	(barks)	Discarine-F (**78**) (a stereoisomer of myrianthine-A (**80**))	N,N-Me_2Leu	Ile(side chain)			$C_{27}H_{42}N_4O_4$; mp 264, $[\alpha]_D^{20}$ –191° ($CHCl_3$); IR, UV, EI-MS[486(M)$^+$], PMR; elemental analysis.		55
9	*Feretia apondanthera* (Rubiaceae) (leaves)	Feretine (**79**) (N-Desmethyl-adoueti ne-Z)	N-MePhe-Pro	Phe(side chain)			$C_{41}H_{43}N_5O_5$; mp 123, $[\alpha]_D$ –139° (CH_3OH, c 1.0); IR, UV, MS[685(M)$^+$], PMR.		3,5
10	*Myrianthus arboreus* (Urticaceae) (leaves)	Myrianthine-A (**80**)	N,N-Me_2Leu	Ile(side chain)			$C_{31}H_{42}N_4O_4$; mp 286, $[\alpha]_D^{20}$ –263° ($CHCl_3$, c 1.0); IR, UV, MS[534(M)$^+$], PMR.		1,5,99
11	*Paliurus hemsleyanus* (Rhamnaceae) (roots)	Hemsine-C (**81**)	*L*-N,N-Me_2Trp-*L*-Pro	*L*-Leu(side chain)	*S*	*S*	$C_{41}H_{48}N_6O_5$; 1.5×10^{-4}%, $[\alpha]_D^{26}$ –107° (CH_3OH, c 1.0); CD, IR, UV, Pos. FAB-MS[705(M+H)$^+$], PMR, CMR, 2D NMR (COSY, TOCSY, NOESY, HMQC, HMBC).		103
	(roots)	Hemsine-D (**82**)	*L*-N-MeVal	*L*-Ile(side chain)	*S*	*S*	$C_{29}H_{38}N_4O_4$; 5.1×10^{-5}%, $[\alpha]_D^{26}$ –573.3° ($CHCl_3$, c 0.75); CD, IR, UV, pos. FAB-MS[507(M+H)$^+$], PMR, CMR, 2D NMR (COSY, TOCSY, NOESY, HMQC, HMBC).		103
12	*Scutia buxifolia* (Rhamnaceae)	Scutianine-L (**83**) (a stereoisomer of adouetine-Y (**65**))	*L*-N,N-Me_2Phe	*L*-Ile(side chain)			$C_{34}H_{40}N_4O_4$; 2.0×10^{-4}%, colorless crystals, mp 122-123, $[\alpha]_D^{25}$ –72° ($CHCl_3$, c 2.4); pos. FAB-MS[569(M+H)$^+$], PMR, CMR, 2D NMR (COSY, NOESY, DEPT, HETCOR); hydrogenation, amino acid analysis after hydrolysis, absolute configuration (chiral phase GC).		93
13	*Waltherica americana* (Sterculiaceae) (whole plants)	Adouetine-Z (**84**) (Adouetine)	N,N-Me_2Phe-Pro	Phe(side chain)			$C_{42}H_{43}N_5O_5$; mp 140-145, $[\alpha]_D^{20}$ –184° ($CHCl_3$, c 1.0); IR, UV, EI-MS[699(M)$^+$], PMR, CMR; hydrogenation, amino acid analysis after hydrolysis.		1,3,5,50
14	*Zizyphus jujuba* (Rhamnaceae) (stem barks)	Jubanine-C (**85**)	N,N-Me_2Ile-Pro	Phe(side chain)			$C_{39}H_{47}N_5O_5$; 4.6×10^{-4}%, colorless granules, mp 233-235; IR, UV, MS[665(M)$^+$]; amino acid analysis after hydrolysis, partial hydrolysis.		100
15	*Z. nummularia* (root barks, stem barks)	Nummularine-D (**86**) (N-Desmethyl-integer renine)	N-MeIle	Leu(side chain)			$C_{30}H_{40}N_4O_4$; 2.5×10^{-4}%, mp 265-268, $[\alpha]_D^{20}$ –186° ($CHCl_3$, c 0.2); IR, UV, EI-MS[520(M)$^+$], PMR; hydrogenation, acetylation, methylation.		5,40
	(stem barks, root barks)	Nummularine-E (**87**)	N,N-Me_2Thr	Leu(side chain)			$C_{29}H_{38}N_4O_4$; 1.1×10^{-3}%, mp 278-279, $[\alpha]_D^{20}$ +12° (CH_3OH, c 0.02); IR, UV, EI-MS[522(M)$^+$], PMR; hydrogenation, amino acid analysis after hydrolysis, acetylation.		5,40,51
	(stem barks)	Nummularine-G (**88**)		Leu(side chain)			$C_{31}H_{40}N_4O_4$; mp 174-175, $[\alpha]_D^{20}$ –133° (CH_3OH, c 0.085); IR, UV, MS[532(M)$^+$], PMR; hydrogenation, amino acid analysis after hydrolysis.		3,5
	(stem barks)	Nummularine-M (**89**)	N,N-Me_2Ile	Ile(side chain)			$C_{31}H_{42}N_4O_4$; 1.7×10^{-4}%, amorphous powder, mp 263-265, $[\alpha]_D$ -46.66° ($CHCl_3$, c 0.1); IR, UV, MS[534(M)$^+$]; amino acid analysis after hydrolysis.		53
16	*Z. sativa* (barks)	Sativanine-A (**90**)	N,N-Me_2Ile	Val(side chain)			$C_{30}H_{40}N_4O_4$; 9.6×10^{-6}%, mp 80; IR, UV, EI-MS[520 (M)$^+$].		5,46
	(barks)	Sativanine-B (**91**)		Val(side chain)			$C_{30}H_{38}N_4O_4$; 8.4×10^{-6}%, amorphous; IR, UV, EI-MS[518(M)$^+$].		5,46



Type **Ia3**

No.	Source (family, part)	Cyclopeptide (No.) (synonym)	Structure* R_1	Structure* R_2	R_3	C_3	C_4	Structural and spectral data	Reference
1	*Paliurus hemsleyanus* (Rhamnaceae) (roots)	Hemsine-A (**92**)	*L*-N,N-Me_2Trp	*L*-Ile(side chain)	H	*S*	*S*	$C_{32}H_{40}N_5O_4$; 2.9×10^{-4}%, $[\alpha]_D^{26}$ –64.5° (CH_3OH, c 2.0); CD, IR, UV, pos. FAB-MS[558(M+H)$^+$], PMR, CMR, 2D NMR (COSY, TOCSY, HMQC, HMBC); absolute configuration (CD, NMR).	103
	(roots)	Hemsine-B (**93**)	*L*-N,N-Me_2Ile-*L*-Phe	*L*-Ile(side chain)	H	*S*	*S*	$C_{36}H_{49}N_5O_5$; 7.6×10^{-5}%, $[\alpha]_D^{26}$ –124° (CH_3OH, c 1.0); CD, IR, UV, pos. FAB-MS[632(M+H)$^+$], PMR, CMR, 2D NMR (COSY, TOCSY, HMQC, HMBC, NOE); absolute configuration (CD, NMR).	103

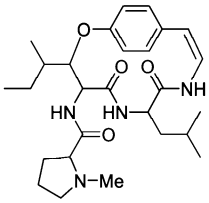
Table 2 (Continued)

No.	Source (family, part)	Cyclopeptide (No.) (synonym)	Structure[a] R_1	R_2	R_3	C_3	C_4	Structural and spectral data	Reference
2	*P. ramosissimus* (roots)	Ramosine-A (**94**)	*L*-N,N-Me_2Ile	*L*-Ile(side chain)	H	*S*	*S*	$C_{27}H_{40}N_4O_4$; 5.2×10^{-5}%, colorless amorphous solids, mp 55-56, $[\alpha]_D^{26}$ –125° (CH_3OH, c 0.76); CD, IR, UV, pos. FAB-MS[485(M+H)$^+$], PMR, CMR, 2D NMR (DEPT, COSY, NOESY, HMQC, HMBC); absolute configuration (CD, NMR).	103
	(roots)	Ramosine-B (**95**) (N-Desmethyl-hemsine-B)	*L*-N-MeIle-*L*-Phe	*L*-Ile(side chain)	H	*S*	*S*	$C_{35}H_{47}N_5O_5$; 4.2×10^{-5}%, $[\alpha]_D^{26}$ –181.5° (CH_3CN, c 2.0); CD, IR, UV, pos. FAB-MS[618(M+H)$^+$], PMR, CMR, 2D NMR (DEPT, COSY,); absolute configuration (CD, NMR).	103
	(roots)	Ramosine-C (**96**)	*L*-N,N-Me_2Phe	*L*-Ile(side chain)	OH	*S*	*S*	$C_{30}H_{38}N_4O_5$; 1.5×10^{-5}%, $[\alpha]_D^{26}$ –39° (CH_3OH, c 1.0); CD, IR, UV, pos. FAB-MS[535(M+H)$^+$], PMR, CMR, 2D NMR (DEPT, COSY, NOE, HMBC); absolute configuration (CD, NMR).	103
3	*Zizyphus amphibia* (Rhamnaceae) (stem barks)	Amphibine-B (**97**)	N,N-Me_2Phe-Ile	Phe(side chain)	H			$C_{39}H_{47}N_5O_5$; amorphous, $[\alpha]_D^{20}$ -181° (CH_3OH, c 0.08); CD, IR, UV, MS[665(M)$^+$], PMR; hydrogenation, amino acid analysis after hydrolysis.	2,5,39,88
	(stem barks)	Amphibine-C (**98**)	N,N-Me_2Leu-Ile	Phe(side chain)	H			$C_{36}H_{49}N_5O_5$; amorphous, $[\alpha]_D^{20}$ -224° (CH_3OH, c 0.075); CD, IR, UV, MS[631(M)$^+$], PMR.	2,5
	(stem barks)	Amphibine-D (**99**)	N,N-Me_2Phe-Ile	Ile(side chain)	H			$C_{36}H_{49}N_5O_5$; amorphous, $[\alpha]_D$ -203° (CH_3OH); CD, IR, UV, EI-MS[631(M)$^+$], PMR, CMR; hydrogenation, amino acid analysis after hydrolysis.	2,5,39,51,75
	(stem barks)	Amphibine-E (**100**)	*L*-N,N-Me_2Leu-*L*-Trp	*L*-Ile(side chain)	H	*S*	*S*	$C_{38}H_{50}N_6O_5$; amorphous, $[\alpha]_D^{20}$ -175° (CH_3OH, c 0.14); CD, IR, UV, CI-MS[671(M+H)$^+$], PMR, CMR.	2,5,39,89
	(stem barks)	Amphibine-F (**101**)	N-MeIle	Phe(side chain)	H			$C_{29}H_{36}N_4O_4$; amorphous powder, $[\alpha]_D^{20}$ -171° ($CHCl_3$, c 0.26); IR, UV, MS[504(M)$^+$], PMR; hydrogenation, amino acid analysis after hydrolysis, methylation.	2,5
	(stem barks)	Amphibine-G (**102**)	N,N-Me_2Trp	Leu(side chain)	H			$C_{32}H_{39}N_5O_4$; mp 182-185, $[\alpha]_D^{20}$ -218° ($CHCl_3$, c 0.24); CD, IR, UV, MS[557(M)$^+$], PMR; hydrogenation, amino acid analysis after hydrolysis.	2,5
4	*Z. hysodrica* (barks)	Hysodricanine-A (**103**)	N,N-Me_2Ile-Phe	Pro(side chain)	H			$C_{35}H_{45}N_5O_5$; mp 93-96, $[\alpha]_D^{20}$ -215° ($CHCl_3$, c 0.05); IR, UV, EI-MS[615(M)$^+$], PMR; hydrogenation, amino acid analysis after hydrolysis.	42,51
5	*Z. lotus* (root barks)	Lotusine-A (**104**)	*L*-N,N-Me_2Phe	*L*-Ile(side chain)	H	*S*	*S*	$C_{30}H_{38}N_4O_4$; $[\alpha]_D$ –215° ($CHCl_3$, c 1.0); CD, IR, UV, MS[518(M)$^+$], PMR, CMR, 2D NMR (COSY, HMQC, HMBC).	80,103
	(root barks)	Lotusine-B (**105**)	N,N-Me_2Leu-Phe	Ile(side chain)	H			$C_{36}H_{49}N_5O_5$; $[\alpha]_D$ –179° ($CHCl_3$, c 0.32); IR, UV, EI-MS[631(M)$^+$], PMR, CMR, 2D NMR (COSY).	84
	(root barks)	Lotusine-C (**106**)	N-MeVal-N-MePhe	Ile(side chain)	H			$C_{35}H_{47}N_5O_5$; $[\alpha]_D$ –168° ($CHCl_3$, c 0.5); IR, UV, EI-MS[617(M)$^+$], PMR, CMR, 2D NMR (COSY, HMQC, HMBC).	84
	(root barks)	Lotusine-D (**107**) (N-Desmethyl-lotusine A)	*L*-N-MePhe	*L*-Ile(side chain)	H	*S*	*S*	$C_{29}H_{36}N_4O_4$; $[\alpha]_D$ –187° ($CHCl_3$, c 0.5); CD, IR, UV, MS[504(M)$^+$], PMR, CMR, 2D NMR (COSY, HMQC, HMBC).	5,80,103
	(root barks)	Lotusine G (**108**)	Val	Ile(side chain)	H			$C_{24}H_{34}N_4O_4$; 1.5×10^{-5}%, $[\alpha]_D$ –142.7° ($CHCl_3$, c 0.5); IR, UV, EI-MS[442(M)$^+$], PMR, CMR, 2D NMR (COSY, HMQC, HMBC).	102
6	*Z. mauritiana* (barks)	Mauritine-A (**109**)	*L*-N,N-Me_2Ala-*L*-Val	*L*-Phe(side chain)	H	*S*	*S*	$C_{32}H_{41}N_5O_5$, MW=575; mp 104, $[\alpha]_D^{20}$ –315° (CH_3OH, c 0.33); x-ray, MS; hydrogenation, amino acid analysis after hydrolysis.	2,5,25,41,42,82,113
	(barks)	Mauritine-B (**110**)	N,N-Me_2Ile-Val	Phe(side chain)	H			$C_{35}H_{47}N_5O_5$, MW=617; amorphous, $[\alpha]_D^{20}$ –151° (CH_3OH, c 0.44); UV, MS; hydrogenation, amino acid analysis after hydrolysis.	2,5,25
	(barks)	Mauritine-C (**111**)	N-MeVal	Phe(side chain)	H			$C_{28}H_{34}N_4O_4$; 1.8×10^{-3}%, amorphous, $[\alpha]_D^{20}$ –224° (CH_3OH, c 0.11); IR, UV, EI-MS[490(M)$^+$], PMR; elemental analysis, hydrogenation, amino acid analysis after hydrolysis, methylation, formylation.	2,5,39,42
	(barks)	Mauritine-D (**112**)	N,N-Me_2Ile-Leu	Ile(side chain)	H			$C_{33}H_{51}N_5O_5$; 6.6×10^{-3}%, amorphous, $[\alpha]_D^{20}$ –259° (CH_3OH, c 0.16); IR, UV, EI-MS[597(M)$^+$], PMR; elemental analysis, hydrogenation, amino acid analysis after hydrolysis, partial hydrolysis.	2,39,42,62,65,88
	(stem barks)	Mauritine-E (**113**)	N,N-Me_2Ala-Val	β-OHPhe(side chain)	H			$C_{32}H_{41}N_5O_6$, MW=591; 2.1×10^{-3}%, amorphous, $[\alpha]_D^{20}$ –243° (CH_3OH, c 0.11); IR, UV, MS, PMR; elemental analysis, hydrogenation, amino acid analysis after hydrolysis.	2,5,39
	(stem barks)	Mauritine-F (**114**) (N-Desmethyl-mauritine-A)	N-MeAla-Val	Phe(side chain)	H			$C_{31}H_{39}N_5O_5$; 1.0×10^{-3}%, mp 222-225, $[\alpha]_D^{20}$ –285° (CH_3OH, c 0.15); IR, UV, EI-MS[561(M)$^+$], PMR; elemental analysis, hydrogenation, amino acid analysis after hydrolysis, methylation.	2,5,39,40
	(barks)	Mauritine-H (**115**)	N,N-Me_2Ala-Leu	Phe(side chain)	H			$C_{33}H_{43}N_5O_5$; mp 212-215, $[\alpha]_D^{20}$ -169° (CH_3OH, c 0.013); IR, UV, EI-MS[589(M)$^+$], PMR; hydrogenation, amino acid analysis after hydrolysis.	42
	(root barks)	Mauritine-J (**116**) (N-Desmethyl-amphibine-E)	*L*-N-MeLeu-*L*-Trp	*L*-Ile(side chain)	H	*S*	*S*	$C_{37}H_{48}N_6O_5$; 2.2×10^{-3}%, amorphous, $[\alpha]_D$ –175.9° (CH_3OH, c 1.0); IR, UV, CI-MS[657(M+H)$^+$], PMR, CMR, 2 D NMR (^{1}H-^{1}H COSY, ^{1}H-^{13}C COSY, HMBC, NOESY); absolute configuration ($[\alpha]_D$).	89
7	*Z. mucronata* (root barks)	Mucronine-J (**117**)	*L*-N,N-Me_2Leu	*L*-Ile(side chain)	H	*S*	*S*	$C_{27}H_{40}N_4O_4$; 1.9×10^{-3}%, colorless amorphous powder, $[\alpha]_D^{21}$ –236° ($CHCl_3$, c 1.0); CD, IR, UV, pos. FAB-MS[485(M+H)$^+$], PMR, CMR, 2 D NMR (^{1}H-^{1}H COSY, J-modulated ^{13}C, HMQC, HMBC, NOE); amino acid analysis after hydrolysis, absolute configuration (NOE, GC), solution conformation (NOE, MM2).	91,103

Table 2 (Continued)

No.	Source (family, part)	Cyclopeptide (No.) (synonym)	Structure* R_1	R_2	R_3	C_3	C_4	Structural and spectral data	Reference
8	*Z. nummularia* (root bakrs, stem barks)	Nummularine-F (**118**)	N,N-Me_2Gly	Ile(side chain)	H			$C_{23}H_{32}N_4O_4$; 5.0×10^{-4}%, mp 120, $[\alpha]_D^{20}$ –204° (CH_3OH, c 0.2); IR, UV, EI-MS[428(M)$^+$], PMR; hydrogenation, amino acid analysis after hydrolysis.	5,40
9	*Z. oenoplia* (stem barks)	Zizyphine-G (**119**)	Ile	Pro(side chain)	H			$C_{24}H_{32}N_4O_4$; mp 130, $[\alpha]_D^{20}$ -185° (CH_3OH, c 0.19); IR, UV, MS[440(M$^+$)], PMR.	5,33
10	*Z. spina-christi* (stem barks)	Spinanine-A (**120**)	Leu	Pro(side chain)	H			$C_{24}H_{32}N_4O_4$; 8.6×10^{-4}%, crystals, mp 175-176, $[\alpha]_D$ -121° (CH_3OH, c 0.1); IR, UV, MS[440(M$^+$)]; amino acid analysis after acid hydrolysis.	77

Type **Ia4**



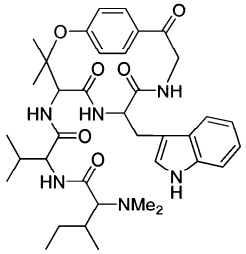
Ceanothine-D (**121**)[1,22]

from *Ceanothus americanus* (Rhamnaceae, root barks).

$C_{26}H_{38}N_4O_4$; mp 227-229, $[\alpha]_D$ –347° ($CHCl_3$);

EI-MS[470(M$^+$)], PMR;

hydrogenation, amino acid analysis after hydrolysis.



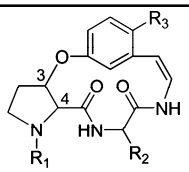
Hymenocardine (**122**)[1,5]

from *Hymenocardia acida* (Euphorbiaceae or Hymenocardiaceae, root barks).

$C_{37}H_{50}N_6O_6$; mp 261, $[\alpha]_D^{20}$ –124° ($CHCl_3$ or $CHCl_3$: CH_3OH (9 : 1), c 1.0);

IR, UV, MS[674(M$^+$)], PMR, CMR;

hydrogenation, alkaline hydrolysis.



Type **Ib**

No.	Source (family, part)	Cyclopeptide (No.) (synonym)	Structure* R_1	R_2	R_3	C_3	C_4	Structural and spectral data	Bioactivity	Reference
1	*Paliurus ramosissimus* (Rhamnaceae) (roots, stems)	Paliurine-A (**123**)	*L*-N,N-Me_2Ile-*L*-Phe	*L*-Ile(side chain)	OCH_3	*S*	*S*	$C_{37}H_{51}N_5O_6$; 9.4×10^{-5}%, amorphous powder, $[\alpha]_D^{26}$ –345° (CH_3OH, c 1.0); CD, IR, UV, pos. FAB-MS[662(M+H)$^+$], PMR, CMR, 2D NMR (COSY-45, HETCOR, NOED, NOESY, HMQC, HMBC); absolute configuration (CD, NMR).		97,98
	(roots, stems)	Paliurine-B (**124**) (N-Desmethyl-paliurine-A)	*L*-N-MeIle-*L*-Phe	*L*-Ile(side chain)	OCH_3	*S*	*S*	$C_{36}H_{49}N_5O_6$; 1.5×10^{-4}%, colorless amorphous solids, mp 111-112, $[\alpha]_D^{26}$ –391.3° (CH_3OH, c 0.76); CD, IR, UV, pos. FAB-MS[648(M+H)$^+$], PMR, CMR, 2D NMR (COSY-45, HETCOR, NOED, NOESY, ROESY, TOCSY, COLOC, HMQC, HMBC); absolute configuration (CD, NMR).		5,97,98
	(roots, stems)	Paliurine-C (**125**)	*L*-N,N-Me_2Phe-*L*-Ile	*L*-Ile(side chain)	OCH_3	*S*	*S*	$C_{37}H_{51}N_5O_6$; 6.4×10^{-5}%, colorless amorphous solids, $[\alpha]_D^{26}$ –311° (CH_3CN, c 1.0); CD, IR, UV, pos. FAB-MS[662(M+H)$^+$], PMR, CMR, 2D NMR (COSY-45); absolute configuration (CD, NMR).		97,98
	(roots)	Paliurine-D (**126**) (N-Desmethyl-paliurine-C)	*L*-N-MePhe-*L*-Ile	*L*-Ile(side chain)	OCH_3	*S*	*S*	$C_{36}H_{49}N_5O_6$; 2.5×10^{-5}%, $[\alpha]_D^{26}$ –164° (CH_3CN, c 1.0); CD, IR, UV, pos. FAB-MS[648(M+H)$^+$], PMR, CMR, 2D NMR (COSY-45, NOED, NOESY, HMQC, HMBC); absolute configuration (CD, NMR).		97
	(roots, stems)	Paliurine-F (**127**)	*L*-N,N-Me_2Leu-*L*-Ile	*L*-Ile(side chain)	OCH_3	*S*	*S*	$C_{34}H_{53}N_5O_6$; 6.1×10^{-5}%, $[\alpha]_D^{26}$ –323° (CH_3CN, c 1.0); CD, IR, UV, pos. FAB-MS[628(M+H)$^+$], PMR, CMR, 2D NMR (COSY-45, NOEs, HMBC); absolute configuration (CD, NMR).		97,98
	(stems)	Paliurine-G (**128**)	*L*-N,N-Me_2Phe-*L*-Val	*L*-Ile(side chain)	OCH_3	*S*	*S*	$C_{36}H_{49}N_5O_6$; 1.7×10^{-4}%, amorphous powder, $[\alpha]_D^{30}$ –335° (CH_3OH, c 0.33); CD, IR, UV, pos. FAB-MS[648(M+H)$^+$], PMR, CMR, 2D NMR (COSY-45, DEPT); absolute configuration (CD, NMR).		98
	(stems)	Paliurine-H (**129**) (N-Desmethyl-paliurine-F)	*L*-N-MeLeu-*L*-Ile	*L*-Ile(side chain)	OCH_3	*S*	*S*	$C_{33}H_{51}N_5O_6$; 1.8×10^{-4}%, amorphous powder, $[\alpha]_D^{30}$ –412° (CH_3OH, c 0.24); CD, IR, UV, pos. FAB-MS[614(M+H)$^+$], PMR, CMR, 2D NMR (COSY-45, DEPT); absolute configuration (CD, NMR).		98
	(stems)	Paliurine-I (**130**)	*L*-N-MeIle-*L*-Leu	*L*-Phe(side chain)	OCH_3	*S*	*S*	$C_{36}H_{49}N_5O_6$; 1.4×10^{-4}%, amorphous powder, $[\alpha]_D^{30}$ –374.3° (CH_3OH, c 1.07); CD, IR, UV, pos. FAB-MS[648(M+H)$^+$], PMR, CMR, 2D NMR (COSY-45, DEPT); absolute configuration (CD, NMR).		98

Table 2 (Continued)

No.	Source (family, part)	Cyclopeptide (No.) (synonym)	Structure* R_1	R_2	R_3	C_3	C_4	Structural and spectral data	Bioactivity	Reference
2	*Sphaeranthus indicus* (Asteraceae) (flowers)	Subfraction-I (**131**)	N,N-Me_2Phe	Pro(side chain)	OCH_3			$C_{30}H_{36}N_4O_5$; mp 75; IR, UV, MS[531(M-H)$^+$].		5
	(flowers)	Subfraction-II (**132**)	Ala	Pro(side chain)	OCH_3			$C_{22}H_{28}N_4O_5$; mp 72; IR, UV, MS[427 (M-H)$^+$].		5
3	*Zizyphus amphibia* (Rhamnaceae) (stem barks)	Amphibine-H (**133**)	N,N-Me_2Ala-Val	Phe(side chain)	OCH_3			$C_{33}H_{43}N_5O_6$; mp 201-205, $[\alpha]_D^{20}$ −570° (CH_3OH, c 0.12); IR, UV, MS[605(M)$^+$], PMR; hydrogenation, amino acid analysis after hydrolysis.	anti-bacteria, anti-fungi	2,5,40,41,66,76,77
4	*Z. jujuba* (stem barks)	Jubanine-A (**134**)	N,N-Me_2Phe-Phe	Ile(side chain)	OCH_3			$C_{40}H_{49}N_5O_6$; 1.6×10^{-3}%, amorphous, $[\alpha]_D^{20}$ −326° (CH_3OH, c 0.12); IR, UV, EI-MS[695(M)$^+$], PMR; hydrogenation, amino acid analysis after hydrolysis.		5,41,77
	(stem barks)	Jubanine-B (**135**)	N,N-Me_2Phe-Phe	Phe(side chain)	OCH_3			$C_{43}H_{47}N_5O_6$; 5.0×10^{-4}%, amorphous, mp 97-100, $[\alpha]_D^{20}$ −218° (CH_3OH, c 0.28); IR, UV, EI-MS[729(M)$^+$], PMR; hydrogenation, amino acid analysis after hydrolysis.		5,41,59
5	*Z. jujuba* var. *inermis* (fruits, stem barks)	Daechucyclopeptide-I (**136**) (Daechuine-S26) (O-Desmethyl-daechuine-S6)	N,N-Me_2Phe	Ile(side chain)	OH			$C_{30}H_{38}N_4O_5$, MW=534; 4.1×10^{-3}%, mp 114.		5,74
	(stem barks)	Daechuine-S3 (**137**)	*L*-N,N-Me_2Ile-*L*-Ile	*L*-Ile(side chain)	OCH_3	*S*	*S*	$C_{34}H_{53}N_5O_6$; 5.9×10^{-4}%, mp 192-194, $[\alpha]_D$ −440°; CD, pos. FAB-MS[628(M+H)$^+$], PMR, CMR, 2D NMR (COSY-45, DEPT).		5,74,98
	(stem barks)	Daechuine-S6 (**138**) (Paliurine-E)	*L*-N,N-Me_2Phe	*L*-Ile(side chain)	OCH_3	*S*	*S*	$C_{31}H_{40}N_4O_5$; 6.2×10^{-4}%, mp 192, $[\alpha]_D$ −393.5°; CD, IR, UV, pos. FAB-MS[549(M+H)$^+$], PMR, CMR, 2D NMR (COSY-45); absolute configuration (CD, NMR).		5,74,97
	(stem barks)	Daechuine-S7 (**139**)	N,N-Me_2Leu	Leu(side chain)	OCH_3			$C_{28}H_{42}N_4O_5$, MW=514; 1.4×10^{-4}%, mp 158, $[\alpha]_D$ −648.3°.		74
	(stem barks)	Daechuine-S8-1 (**140**)	N,N-Me_2Leu-Leu	Leu(side chain)	OCH_3			$C_{33}H_{51}N_5O_6$, MW=613; 1.2×10^{-4}%, mp 185-188, $[\alpha]_D$ −218.2°.		5,74
6	*Z. lotus* (root barks)	Lotusine-E (**141**)	N,N-Me_2Leu-Phe	Ile(side chain)	OH			$C_{36}H_{49}N_5O_6$; $[\alpha]_D$ −106° ($CHCl_3$, c 1.0); IR, UV, EI-MS[647(M)$^+$], PMR, CMR, 2D NMR (COSY, HOHAHA, HMQC, HMBC).		84
	(root barks)	Lotusine-F (**142**) (N-Desmethyl-daechucyclopeptide-I)	N-MePhe	Ile(side chain)	OH			$C_{29}H_{36}N_4O_5$; $[\alpha]_D$ −244° ($CHCl_3$, c 0.5); IR, UV, pos. FAB-MS[521(M+H)$^+$], PMR, CMR, 2D NMR (COSY, HMQC, HMBC).		84
7	*Z. mucronata* (roots)	(**143**)	N,N-Me_2Leu	Ile(side chain)	OCH_3			$C_{28}H_{42}N_4O_5$; 1.0×10^{-3}%, needles, mp 153-154, $[\alpha]_D^{20}$ −418° ($CHCl_3$, c 1.1); UV, EI-MS[514(M)$^+$], PMR, CMR, 2D NMR (TOCSY, FLOCK, ROESY).		81
	(roots)	O-Desmethyl-mucronine-D (**144**)	N,N-Me_2Phe-Leu	Ile(side chain)	OH			$C_{36}H_{49}N_5O_6$; 1.0×10^{-4}%, $[\alpha]_D^{20}$ −191° ($CHCl_3$, c 0.3); UV, EI-MS[647(M)$^+$], PMR, CMR, 2D NMR (TOCSY, FLOCK, ROESY).		81
	(stem barks, roots, root barks)	Mucronine-D (**145**) (Daechuine-S9)	N,N-Me_2Phe-Leu	Ile(side chain)	OCH_3			$C_{37}H_{51}N_5O_6$; 1.7×10^{-4}%, amorphous, mp 115, $[\alpha]_D^{20}$ −487° ($CHCl_3$, c 0.12); CD, IR, UV, EI-MS[661(M)$^+$], PMR, CMR, 2D NMR (TOCSY, FLOCK, ROESY); hydrogenation, amino acid analysis after hydrolysis.		2,5,40,41,46,74,81,91
8	*Z. nummularia* (stem barks, root barks)	Nummularine-A (**146**) (N-Desmethyl-mucronine-D)	N-MePhe-Leu	Ile(side chain)	OCH_3			$C_{36}H_{49}N_5O_6$; mp 235-240, $[\alpha]_D^{20}$ −397° ($CHCl_3$, c 0.2); IR, UV, MS[647(M)$^+$], PMR; hydrogenation, amino acid analysis after hydrolysis, methylation.		2,5,40,41
	(root barks, stem barks)	Nummularine-B (**147**) (Daechuine-S27) (N-Desmethyl-amphibine-H)	N-MeAla-Val	Phe(side chain)	OCH_3			$C_{32}H_{41}N_5O_6$; mp 226-231, $[\alpha]_D^{20}$ −390° ($CHCl_3$, c 0.2); IR, UV, MS[591(M)$^+$], PMR; hydrogenation, amino acid analysis after hydrolysis, methylation, formylation.	anti-bacteria, anti-fungi	2,5,40,41,46,53,62,74,76
	(stem barks, root barks)	Nummularine-C (**148**)	N,N-Me_2Phe	Leu(side chain)	OCH_3			$C_{31}H_{40}N_4O_5$; mp 278-280, $[\alpha]_D^{20}$ −371° ($CHCl_3$, c 0.2); IR, UV, MS[548(M)$^+$], PMR; hydrogenation, amino acid analysis after hydrolysis.		2,5
	(stem barks)	Nummularine-H (**149**) (N-Desmethyl-jubanine-A)	*L*-N-MePhe-*L*-Phe	*L*-Ile(side chain)	OCH_3	*S*	*S*	$C_{39}H_{47}N_5O_6$; amorphous powder, mp 194-196, $[\alpha]_D^{20}$ −343° (CH_3OH, c 0.27); CD, IR, UV, pos. FAB-MS[682(M+H)$^+$], PMR, CMR, 2D NMR (COSY-45, DEPT); hydrogenation, amino acid analysis after hydrolysis, methylation, acetylation.		3,5,98
	(stem barks)	Nummularine-N (**150**)	N,N-Me_2Gly-Val	Phe(side chain)	OCH_3			$C_{31}H_{41}N_5O_6$; 3.0×10^{-4}%, bright colorless crystals, mp 243-245; IR, UV, MS[579(M)$^+$], PMR; amino acid analysis after hydrolysis.		53
	(stem barks, root barks)	Nummularine-O (**151**) (N-Desmethyl-jubanine-B)	N-MePhe-Phe	Phe(side chain)	OCH_3			$C_{42}H_{45}N_5O_6$; 1.8×10^{-4}%, colorless powder, mp 159-161, $[\alpha]_D^{20}$ −239° (CH_3OH, c 0.2); IR, UV, MS[715(M)$^+$], PMR; amino acid analysis after hydrolysis, formylation.		5,59
	(stem barks)	Nummularine-P (**152**)	N-MeAla-Val	Leu(side chain)	OCH_3			$C_{29}H_{43}N_5O_6$; 3.6×10^{-4}%, colorless crystals, mp 143-144; IR, UV, EI-MS[557(M)$^+$], PMR; amino acid analysis after hydrolysis, formylation.		65,71

Table 2 (Continued)

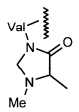
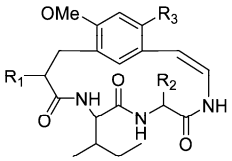
No.	Source (family, part)	Cyclopeptide (No.) (synonym)	Structure* R_1	R_2	R_3	C_3	C_4	Structural and spectral data	Bioactivity	Reference
	(stem barks)	Nummularine-R (**153**) (Daechuine-S10)	N,N-Me_2Trp	Ile(side chain)	OCH_3			$C_{33}H_{41}N_5O_5$; 4.2×10^{-4}%, mp 134-135, $[\alpha]_D$ –381.5°; IR, UV, MS[587(M^+)]; amino acid analysis after hydrolysis, partial hydrolysis.	anti-bacteria, anti-fungi	66,74,76
	(stem barks)	Nummularine-S (**154**)	Leu	Phe(side chain)	OCH_3			$C_{29}H_{36}N_4O_5$; 5.8×10^{-5}%, mp 210-211; IR, UV, EI-MS[520(M^+)]; amino acid analysis after hydrolysis.	anti-bacteria, anti-fungi	70,76
	(barks)	Nummularine-T (**155**)	N-CHO-N-MeAla-Val	Phe(side chain)	OCH_3			$C_{33}H_{41}N_5O_7$; 2.3×10^{-4}%, granules, mp 188-190; IR, UV, MS[619(M^+)], PMR; partial hydrolysis, total hydrolysis, deformylation.		82
9	*Z. oenoplia* (root barks, stem barks)	Zizyphine-A (**156**) (Zizyphine)	N,N-Me_2Ile-Ile	Pro(side chain)	OCH_3			$C_{33}H_{49}N_5O_6$; mp 124-126, $[\alpha]_D^{20}$ -411° ($CHCl_3$, c 0.086); IR, UV, MS[611(M^+)], PMR, CMR; hydrogenation, amino acid analysis after hydrolysis, oxidation.		5,28,38,100
	(stem barks, root barks)	Zizyphine-B (**157**) (Zizyphinine) (N-Desmethyl-zizyphine-A)	N-MeIle-Ile	Pro(side chain)	OCH_3			$C_{32}H_{47}N_5O_6$; amorphous, $[\alpha]_D^{24}$ –457° ($CHCl_3$, c 1.0); IR, UV, EI-MS[597(M^+)]; acetylation.		2,5,38
	(stem barks)	Zizyphine-C (**158**)	N,N-Me_2Phe-Ile	Pro(side chain)	OCH_3			$C_{36}H_{47}N_5O_6$; amorphous, $[\alpha]_D^{20}$ -331±5° ($CHCl_3$, c 0.10), $[\alpha]_D^{20}$ -343±5° (CH_3OH, c 0.10); IR, UV, EI-MS[645(M^+)], PMR; hydrogenation, amino acid analysis after hydrolysis, ozonolysis.		38
	(stem barks)	Zizyphine-F (**159**) (O-Desmethyl-zizyphine-A)	N,N-Me_2Ile-Ile	Pro(side chain)	OH			$C_{32}H_{47}N_5O_6$; mp 235, $[\alpha]_D^{20}$ -277° (CH_3OH, c 0.15); IR, UV, MS[597(M^+)], PMR.		5,33,77
	(stem barks)	Zizyphine-I (**160**)	N,N-Me_2Ile-Phe	Pro(side chain)	OCH_3			$C_{36}H_{47}N_5O_6$; mp 135; IR, UV, MS[645(M^+)], PMR.		5
	(stem barks)	Zizyphine-K (**161**)	N,N-Me_2Ile-Val	Pro(side chain)	OH			$C_{31}H_{45}N_5O_6$; mp 230; IR, UV, MS[583(M^+)], PMR.		5
10	*Z. oenoplia* var. *brunoniana* (roots)	Ziziphine-N (**162**)	*L*-N,N-Me_2Ile-*L*-Leu	*L*-Pro(side chain)	OCH_3	*S*	*S*	$C_{33}H_{49}N_5O_6$; 8.3×10^{-4}%, colorless solids, mp 117-119, $[\alpha]_D^{30}$ –326.6° ($CHCl_3$, c 0.18); IR, UV, EI-MS[612(M+H)$^+$], PMR, CMR, 2D NMR (DEPT, ^{1}H-^{1}H COSY, HMQC, HMBC, NOESY); absolute configuration (NMR).	antiplasmodia, antimycobacteria	105
	(roots)	Ziziphine-O (**163**)	*L*-N-MeIle-*L*-Leu	*L*-Pro(side chain)	OCH_3	*S*	*S*	$C_{32}H_{47}N_5O_6$; 5.6×10^{-4}%, colorless solids, mp 106-108, $[\alpha]_D^{31}$ –380.2° ($CHCl_3$, c 0.15); IR, UV, EI-MS[598(M+H)$^+$], PMR, CMR, 2D NMR (DEPT, ^{1}H-^{1}H COSY, HMQC, HMBC, NOESY); absolute configuration (NMR).		105
	(roots)	Ziziphine-P (**164**)	*L*-N,N-Me_2Ile-*L*-Leu	*L*-Pro(side chain)	OH	*S*	*S*	$C_{32}H_{47}N_5O_6$; 4.8×10^{-4}%, colorless solids, mp 127-129, $[\alpha]_D^{31}$ –385.4° ($CHCl_3$, c 0.15); IR, UV, EI-MS[598(M+H)$^+$], PMR, CMR, 2D NMR (DEPT, COSY, HMQC, HMBC, NOESY); absolute configuration (NMR).		105
	(roots)	Ziziphine-Q (**165**)	*L*-N,N-Me_2Ile-*L*-Val	*L*-Pro(side chain)	OCH_3	*S*	*S*	$C_{32}H_{47}N_5O_6$; 1.9×10^{-4}%, colorless solids, mp 140-142, $[\alpha]_D^{29}$ –345.0° ($CHCl_3$, c 0.16); IR, UV, pos. FAB-MS[598(M+H)$^+$], PMR, CMR, 2D NMR (DEPT, COSY, HMQC, HMBC, NOESY); absolute configuration (NMR).	antiplasmodia, antimycobacteria	105
11	*Z. rugosa* (stem barks)	Rugosanine-A (**166**)	N-CHO-N-MeAla-Val	Leu(side chain)	OCH_3			$C_{30}H_{43}N_5O_7$; 3.8×10^{-4}%, colorless granules, mp 237-240; IR, UV, EI-MS[585(M^+)]; amino acid analysis after hydrolysis, deformylation, methylation.	anti-bacteria, anti-fungi	69,76
	(stem barks)	Rugosanine-B (**167**)	N,N-Me_2Trp	Phe(side chain)	OCH_3			$C_{36}H_{39}N_5O_5$; 5.0×10^{-4}%, colorless granules, mp 216-218; IR, UV, MS[621(M^+)]; amino acid analysis after hydrolysis, partial hydrolysis.	anti-bacteria, anti-fungi	71,76
12	*Z. sativa* (barks)	Sativanine-C (**168**)	N-MeAla-Val	Ile(side chain)	OCH_3			$C_{29}H_{43}N_5O_6$; 3.8×10^{-5}%, mp 113-114; IR, UV, EI-MS[557(M^+)]; amino acid analysis after hydrolysis, formylation.		52
	(barks)	Sativanine-D (**169**)		Ile(side chain)	OCH_3			$C_{30}H_{43}N_5O_6$; 3.4×10^{-5}%, mp 119-121; IR, UV, EI-MS[569(M^+)]; amino acid analysis after hydrolysis.		57
	(barks)	Sativanine-E (**170**)	N,N-Me_2Trp	Leu(side chain)	OCH_3			$C_{33}H_{41}N_5O_5$; 1.2×10^{-4}%, mp 127-128, $[\alpha]_D^{20}$ -99° ($CHCl_3$, c 0.2); IR, UV, EI-MS[587(M^+)], PMR; amino acid analysis after hydrolysis.		56
	(barks)	Sativanine-F (**171**)	N-CHOVal-Val	Phe(side chain)	OCH_3			$C_{34}H_{43}N_5O_7$; 3.5×10^{-5}%, mp 139-141; IR, UV, EI-MS[633(M^+)]; amino acid analysis after hydrolysis.		58
	(barks)	Sativanine-G (**172**)	*L*-N,N-Me_2Ile	*L*-Ile(side chain)	OCH_3	*S*	*S*	$C_{28}H_{42}N_4O_5$; 6.0×10^{-5}%, mp 92, $[\alpha]_D^{26}$ -327.0° (CH_3OH, c 0.85); CD, IR, UV, EI-MS[514(M^+)], PMR, CMR, 2D NMR (COSY-45); amino acid analysis after hydrolysis, absolute configuration (CD, NMR).		54,97
	(barks)	Sativanine-H (**173**)	N,N-Me_2Gly-Val	Leu(side chain)	OCH_3			$C_{29}H_{43}N_5O_6$;		60,71

Table 2 (Continued)

No.	Source (family, part)	Cyclopeptide (No.) (synonym)	Structure* R_1	R_2	R_3	C_3	C_4	Structural and spectral data	Bioactivity	Reference
								mp 191-192; IR, UV, EI-MS[557(M^+)]; amino acid analysis after hydrolysis.		
	(barks)	Sativanine-K (**174**)	N-CHOIle	Ile(side chain)	OCH_3			$C_{27}H_{38}N_4O_6$; 2.7×10^{-3}%, mp 160-162; IR, UV, EI-MS[514(M^+)]; amino acid analysis after hydrolysis.		64
	(stem barks)	Tscheschamine (**175**)	Ile	Phe(side chain)	OCH_3			$C_{29}H_{36}N_4O_5$; 6.2×10^{-3}%, amorphous powder, mp 197-198; IR, UV, EI-MS[520(M^+)], PMR; amino acid analysis after hydrolysis.		68



Type **Ic**

No.	Source (family, part)	Cyclopeptide (No.) (synonym)	Structure* R_1	R_2	R_3	Structural and spectral data	Bioactivity	Reference
1	*Zizyphus abyssinica* (Rhamnaceae) (barks)	Abyssenine-A (**176**) (N-Desmethyl-mucronine-C)	$NHCH_3$	Leu(side chain)	H	$C_{25}H_{38}N_4O_4$; 5.5×10^{-3}%, mp 237-239, $[\alpha]_D^{20}$ +160° ($CHCl_3$, c 0.22), $[\alpha]_D^{20}$ -58° (CH_3OH, c 0.1); CD, IR, UV, EI-MS[458(M^+)], PMR; hydrogenation, amino acid analysis after hydrolysis, methylation, acetylation, oxidation.		32,38,91
	(barks)	Abyssenine-B (**177**)	$NHCH_3$	Ile(side chain)	H	$C_{25}H_{38}N_4O_4$; 4.0×10^{-3}%, mp 229-230, $[\alpha]_D^{20}$ +151° ($CHCl_3$, c 0.16); IR, UV, EI-MS[458(M^+)], PMR; hydrogenation, amino acid analysis after hydrolysis, methylation, acetylation, oxidation.		32,38
	(barks)	Abyssenine-C (**178**) (N-Desmethyl-abyssinine-B)	NH_2	Ile(side chain)	H	$C_{24}H_{36}N_4O_4$; 3.8×10^{-3}%, $[\alpha]_D^{20}$ +144° ($CHCl_3$, c 0.12), $[\alpha]_D^{20}$ -15° (CH_3OH, c 0.13); IR, UV, EI-MS[444(M^+)], PMR; hydrogenation, amino acid analysis after hydrolysis, methylation, acetylation, oxidation.	anti-bacteria, anti-fungi	32
2	*Z. mucronata* (stem barks)	Mucronine-A (**179**)	$N(CH_3)_2$	Phe(side chain)	H	$C_{29}H_{38}N_4O_4$; mp 235, $[\alpha]_D^{20}$ –28.3° ($CHCl_3$, c 0.06); CD, IR, UV, EI-MS[506(M^+)], PMR; elemental analysis, hydrogenation, amino acid analysis after hydrolysis, oxidation.		5,27,32
	(stem barks)	Mucronine-B (**180**) (N-Desmethyl-mucronine-A)	$NHCH_3$	Phe(side chain)	H	$C_{28}H_{36}N_4O_4$; mp 222-224, $[\alpha]_D^{25}$ +175° ($CHCl_3$, c 0.2); CD, IR, UV, EI-MS[492(M^+)], PMR; elemental analysis, hydrogenation, amino acid analysis after hydrolysis, methylation.		5,27,32
	(stem barks)	Mucronine-C (**181**)	$N(CH_3)_2$	Leu(side chain)	H	$C_{26}H_{40}N_4O_4$; mp 257, $[\alpha]_D^{20}$ –39.4° ($CHCl_3$, c 0.09); CD, IR, UV, EI-MS[472(M^+)], PMR; hydrogenation, amino acid analysis after hydrolysis.		5,27,32
	(stem barks)	Mucronine-E (**182**) (4-Methoxy-abyssinine-A)	$NHCH_3$	Leu(side chain)	OCH_3	$C_{26}H_{40}N_4O_5$; 3.8×10^{-3}%, mp 232-234, $[\alpha]_D^{20}$ –89° (CH_3OH, c 0.084); CD, IR, UV, EI-MS[488(M^+)], PMR; hydrogenation, amino acid analysis after hydrolysis, methylation, acetylation, oxidation.		5,32
	(stem barks)	Mucronine-F (**183**) (N-Desmethyl-mucronine-E)	NH_2	Leu(side chain)	OCH_3	$C_{25}H_{38}N_4O_5$; 3.4×10^{-3}%, mp 208-214, $[\alpha]_D^{20}$ +17.4° (CH_3OH, c 0.092); IR, UV, EI-MS[474(M^+)], PMR; hydrogenation, amino acid analysis after hydrolysis, methylation, acetylation, oxidation.	anti-bacteria	5,32
	(stem barks)	Mucronine-G (**184**) (4-Methoxy-abyssinine-C)	NH_2	Ile(side chain)	OCH_3	$C_{25}H_{38}N_4O_5$; 3.8×10^{-4}%, amorphous, $[\alpha]_D^{20}$ –50° (CH_3OH, c 0.084); IR, UV, EI-MS[474(M^+)], PMR; amino acid analysis after hydrolysis, acetylation, oxidation.	anti-bacteria	2,5,32
	(stem barks)	Mucronine-H (**185**) (N-Desmethyl-mucronine-B)	NH_2	Phe(side chain)	H	$C_{27}H_{34}N_4O_4$; 5.1×10^{-4}%, amorphous, $[\alpha]_D^{20}$ +5° (CH_3OH, c 0.1); IR, UV, EI-MS[478(M^+)], PMR; hydrogenation, amino acid analysis after hydrolysis, methylation, acetylation.	anti-bacteria	2,5,32
3	*Z. oenoplia* (stem barks)	Zizyphine-D (**186**)	$NHCH_3$	β-OHIle(side chain)	H	$C_{25}H_{38}N_4O_5$; needles, mp 195, $[\alpha]_D^{20}$ +236±4° ($CHCl_3$, c 0.10), $[\alpha]_D^{20}$ -121±2° (CH_3OH, c 0.1); IR, UV, EI-MS[474(M^+)], PMR, CMR; amino acid analysis after hydrolysis, ozonolysis, acetylation.		5,38
	(stem barks)	Zizyphine-E (**187**) (N-Desmethyl-zizyphine-D)	NH_2	β-OHIle(side chain)	H	$C_{24}H_{36}N_4O_5$; amorphous, $[\alpha]_D^{20}$ +150±2° ($CHCl_3$, c 0.10), $[\alpha]_D^{20}$ -111±2° (CH_3OH, c 0.1); IR, UV, EI-MS[460(M^+)], PMR; acetylation.		38

* Ala, Gly, Ile, OHIle, Leu, OHLeu, Phe, OHPhe, Pro, Thr, Trp, Tyr and Val are the abreviations of the following amino acids: alanine, glycine, isoleucine, hydroxyl isoleucine, leucine, hydroxyl leucine, phenylalanine, hydroxyl phenylalanine, proline, threonine, tryptophan, tyrosine and valine, respectively.

latter isolated pure ceanothine-B (ceanothine, **7**, subtype **Ia1**) from the alkaloid mixtures of *C. americanus* and just determined the correct empirical formula as $C_{29}H_{36}N_4O_4$ in 1933. In 1965 Warnhoff et al.[14] succeeded in isolating ceanothine-B from the alkaloid mixtures of *C. americanus* and proposed the complete structure,[15] which was revised by Klein et al.[16] and Servis et al.[17] in 1968, respectively. The first discovery of the cyclopeptide alkaloids was made in 1963 by Pais et al., who isolated adouetines-X (ceanothamine-B, **4**, subtype **Ia1**), -Y (**65**, subtype **Ia2**), and -Z (adouetine, **84**, subtype **Ia2**) from *Waltheria americana* (Sterculiaceae), without proposing a complete structure, and just reported their structures in 1968.[1] In 1963 Menard et al. isolated zizyphine (zizyphine-A, **156**, subtype **Ib**) from *Zizyphus oenoplia* (Rhamnaceae) and just recognized isoleucine and proline as components. Two years later, Zbiral et al. proposed the complete structure of zizyphine, which was revised by Tschesche et al. in 1973. In 1964 Pais et al. first proposed the term peptide alkaloids and suggested the structure of pandamine (**33**, subtype **Ia1**) isolated from *Panda*

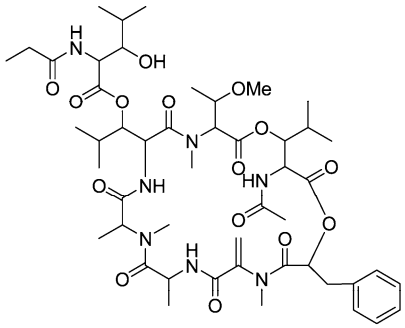
Table 3. Sources of Some Cyclopeptide Alkaloids Isolated from More Higher Plants during the Past Half Century

cyclopeptide alkaloids	family	genus	species	parts	refs
			Type Ia1		
adouetine-X (**4**)	Rhamnaceae	Ceanothus	*Ceanothus americanus*	root barks	14, 22
		Zizyphus	*Zizyphus jujuba* var. *inermis*	root barks	36
	Sterculiaceae	Waltheria	*Waltheria americana*	whole plants	1
ceanothine-B (**7**)	Rhamnaceae	Ceanothus	*Ceanothus americanus*	root barks	14
			C. sanguineus	root barks	48
N-methyl-americine (**10**)	Rhamnaceae	Ceanothus	*Ceanothus integerrimus*	root barks	47
			C. sanguineus	root barks	48
discarine-A (**21**)	Rhamnaceae	Discaria	*Discara americana*	root barks	104
			D. longispina	roots	26
discarine-B (**22**)	Rhamnaceae	Ceanothus	*Ceanothus integerrimus*	root barks	47
			C. sanguineus	root barks	48
		Discaria	*Discara americana*	root barks	99
			D. febrifuga	root barks	61
			D. longispina	roots, root barks	26, 87
discarine-E (**23**)	Rhamnaceae	Discaria	*Discaria febrifuga*	stem barks	5
			D. longispina	root barks	87
hovenine-A (**26**)	Rhamnaceae	Hovenia	*Hovenia dulcis*	root barks	30
			H. tomentella	root barks	30
adouetin-Y′ (**28**)	Euphorbiaceae	Antidesma	*Antidesma montana*	leaves, terminal branches	79
	Rhamnaceae	Ceanothus	*Ceanothus sanguineus*	root barks	48
		Condalia	*Condalia buxifolia*	root barks	101
		Discaria	*Discaria ameriacana*	root barks	99
			D. febrifuga	stem barks	5
			D. longispina	roots, root barks	35, 87
		Zizyphus	*Zizyphus lotus*	aerial parts	86
	Sterculiaceae	Melochia	*Melochia corchorifolia*	leaves, woody parts, aerial parts	1, 21, 63
		Waltheria	*Waltheria americana*	whole plants	1
			W. douradinha	root barks, barks	95, 96
	Urticaceae	Myrianthus	*Myrianthus arboreus*	leaves	1
melonovine-A (**30**)	Rhamnaceae	Zizyphus	*Zizyphus jujuba* var. *inermis*	stem barks	74
	Sterculiaceae	Melochia	*Melochia tomentosa*	roots	43
myranthine-C (**32**)	Rubiaceae	Plectronia	*Plectronia odorata*	aeral parts	72
	Urticaceae	Myrianthus	*Myrianthus arboreus*	leaves	1
franganine (**36**)	Celastraceae	Euonymus	*Eunonymus europeaus*	roots, root barks	31
	Rhamnaceae	Discaria	*Discaria americana*	root barks	99
			D. febrifuga	stem barks, roots	5, 67
		Rhamnus	*Rhamnus frangula*	barks	1, 20
		Zizyphus	*Zizyphus jujuba* var. *inermis*	stem barks	74
			Z. spina-christi	stem barks	5
	Sterculiaceae	Melochia	*Melochia corchorifolia*	leaves, woody parts, aerial parts	1, 21, 78
frangufoline (**37**)	Celastraceae	Euonymus	*Eunonymus europeaus*	leaves	31
	Rhamnaceae	Ceanothus	*Ceanothus sanguineus*	root barks	48
		Discaria	*Discaria febrifuga*	stem barks	5
			D. longispina	roots	35
		Rhamnus	*Rhamnus frangula*	barks	1, 20
		Zizyphus	*Zizyphus jujuba*	stem barks	66
			Z. jujuba var. *inermis*	stem barks	74
			Z. lotus	aerial parts	86
			Z. mauritiana	stem barks	5, 39
			Z. nummularia	root barks, stem barks, barks	40, 66, 82
			Z. oenoplia	stem barks	88
			Z. vulgaris var. *spinosus*	seeds	74
	Sterculiaceae	Melochia	*Melochia corchorifolia*	leaves, woody parts	21
			M. pyramidata	leaves	50
frangulanine (**38**)	Celastraceae	Euonymus	*Eunonymus europeaus*	leaves, stems, roots, root barks	31
	Rhamnaceae	Ceanothus	*Ceanothus americanus*	root barks	14, 22
		Discaria	*Discaria longispina*	roots	26
		Hovenia	*Hovenia dulcis*	root barks	30
			H. tomentella	root barks	30
		Rhamnus	*Rhamnus frangula*	barks	1
		Zizyphus	*Zizyphus jujuba* var. *inermis*	root barks, stem barks	36, 74
			Z. sativa	barks	46
scutianine-B (**40**)	Rhamnaceae	Condalia	*Condalia buxifolia*	root barks	103
		Discaria	*Discaria febrifuga*	stem barks	5
		Scutia	*Scutia buxifolia*	roots, barks	23, 35, 44
	Sterculiaceae	Melochia	*Melochia tomentosa*	roots	43
		Waltheria	*Waltheria douradinha*	root barks, barks	95, 96
scutianine-D (**43**)	Rhamnaceae	Condalia	*Condalia buxifolia*	root barks	101
		Scutia	*Scutia buxifolia*	roots, barks	37, 45
		Zizyphus	*Zizyphus jujuba*	stem barks	100
			Z. nummularia	barks	82
amphibine-A (**52**)	Rhamnaceae	Zizyphus	*Zizyphus amphibia*	stem barks	5, 24
			Z. nummularia	root barks	40
			Z. spina-christi	stem barks	5
nummularine-K (**54**)	Rhamnaceae	Discaria	*Discaria longispina*	root barks	87
		Zizyphus	*Zizyphus nummularia*	stem barks	5
			Z. xylopyra	stem barks	66
sanjoinenine (**55**)	Rhamnaceae	Zizyphus	*Zizyphus lotus*	aerial parts	86
			Z. vulgaris var. *spinosus*	seeds	74
sanjoinine-F (**58**)	Rhamnaceae	Zizyphus	*Zizyphus lotus*	aerial parts	86
			Z. vulgaris var. *spinosus*	seeds	74
			Type Ia2		
aralionine-B (**61**)	Euphorbiaceae	Antidesma	*Antidesma montana*	leaves, terminal branches	79
	Rhamnaceae	Araliorhamnus	*Araliorhamnus vaginatus*	leaves, barks	2, 5, 42
adouetine-Y (**65**)	Rhamnaceae	Ceanothus	*Ceanothus americanus*	root barks	22
		Discaria	*Discaria americana*	root barks	99
	Sterculiaceae	Waltheria	*Waltheria americana*	whole plants	1
integerrenine (**70**)	Olacaceae	Heisteria	*Heisteria nitida*	barks	94
	Rhamnaceae	Ceanothus	*Ceanothus integerrimus*	roots, root barks	19, 47
		Zizyphus	*Zizyphus nummularia*	root barks	40
	Sterculiaceae	Melochia	*Melochia pyramidata*	leaves	50
crenatine-A (**76**)	Rhamnaceae	Discaria	*Discaria americana*	root barks	99
			D. crenata	leaves, stems	34
			D. febrifuga	stem barks	5
discarine-C (**77**)	Rhamnaceae	Discaria	*Discaria americana*	root barks	99
			D. febrifuga	stem barks	5
myrianthine-A (**80**)	Rhamnaceae	Discaria	*Discaria americana*	root barks	99
	Urticaceae	Myrianthus	*Myrianthus arboreus*	leaves	1

Table 3 (Continued)

cyclopeptide alkaloids	family	genus	species	parts	refs
			Type Ia2 (Continued)		
adouetine-Z (**84**)	Rubiaceae	Feretia	*Feretia apodanthera*	leaves	3, 5
	Sterculiaceae	Melochia	*Melochia pyramidata*	leaves	50
		Waltheria	*Waltheria americana*	whole plants	1
nummularine-E (**87**)	Rhamnaceae	Zizyphus	*Zizyphus hysodrica*	barks	51
			Z. nummularia	stem barks, root barks	5, 40
sativanine-A (**90**)	Rhamnaceae	Zizyphus	*Zizyphus sativa*	barks	46
			Z. spina-christi	stem barks	5
			Type Ia3		
amphibine-B (**97**)	Rhamnaceae	Zizyphus	*Zizyphus amphibia*	stem barks	2, 5
			Z. mauritiana	stem barks	5, 39
			Z. oenoplia	stem barks	88
amphibine-D (**99**)	Rhamnaceae	Zizyphus	*Zizyphus amphibia*	stem barks	2, 5
			Z. juazeiro	barks	51
			Z. mauritiana	stem barks	5, 39
			Z. rugosa	barks	51
			Z. rulgaris var. *spinosus*	seeds	75
amphibine-E (**100**)	Rhamnaceae	Zizyphus	*Zizyphus amphibia*	stem barks	2, 5
			Z. mauritiana	root barks	39, 89
			Z. spina-christi	stem barks	5
amphibine-F (**101**)	Rhamnaceae	Zizyphus	*Zizyphus amphibia*	stem barks	2, 5
			Z. mauritiana	stem barks	2, 5
			Z. spina-christi	stem barks	5
hysodricanine-A (**103**)	Rhamnaceae	Zizyphus	*Zizyphus hutchinsonii*	barks	51
			Z. hysodrica	barks	42
lotusine-A (**104**)	Rhamnaceae	Paliurus	*Paliurus ramosissimus*	roots	103
		Zizyphus	*Zizyphus lotus*	root barks	80
lotusine-D (**107**)	Rhamnaceae	Paliurus	*Paliurus ramosissimus*	roots	103
		Zizyphus	*Zizyphus lotus*	root barks	80
mauritine-A (**109**)	Rhamnaceae	Zizyphus	*Zizyphus amphibia*		2
			Z. jujuba	stem barks	41
			Z. mauritiana	barks	25, 42
			Z. nummularia	barks	82
			Z. spina-christi	stem barks	5
mauritine-C (**111**)	Rhamnaceae	Zizyphus	*Zizyphus mauritiana*	barks	39, 42
			Z. nummularia	root barks	5
			Z. spina-christi	stem barks	5
mauritine-D (**112**)	Rhamnaceae	Zizyphus	*Zizyphus mauritiana*	barks	39, 42
			Z. nummularia	stem barks	65
			Z. oenoplia	stem barks	88
			Z. xylopyra	barks	62
mauritine-F (**114**)	Rhamnaceae	Zizyphus	*Zizyphus mauritiana*	stem barks	5, 39
			Z. nummularia	root barks	40
mucronine-J (**117**)	Rhamnaceae	Paliurus	*Paliurus ramosissimus*	roots	103
		Zizyphus	*Zizyphus mucronata*	root barks	91
			Type Ib		
amphibine-H (**133**)	Rhamnaceae	Zizyphus	*Zizyphus amphibia*	stem barks	2, 5
			Z. jujuba	stem barks	41
			Z. nummularia	root barks	40
			Z. spina-christi	stem barks	77
			Z. xylopyra	stem barks	66
jubanine-A (**134**)	Rhamnaceae	Zizyphus	*Zizyphus jujuba*	stem barks	41
			Z. nummularia	root barks	5
			Z. spina-christi	stem barks	77
jubanine-B (**135**)	Rhamnaceae	Zizyphus	*Zizyphus jujuba*	stem barks	41
			Z. nummularia	root barks, stem barks	5, 59
daechuine-S3 (**137**)	Rhamnaceae	Paliurus	*Paliurus ramosissimus*	stems	98
		Zizyphus	*Zizyphus jujuba* var. *inermis*	stem barks	74
daechuine-S6 (**138**)	Rhamnaceae	Paliurus	*Paliurus ramosissimus*	roots	97
		Zizyphus	*Zizyphus jujuba* var. *inermis*	stem barks	74
mucronine-D (**145**)	Rhamnaceae	Zizyphus	*Zizyphus jujuba*	stem barks	41
			Z. jujuba var. *inermis*	stem barks	74
			Z. mucronata	stem barks, roots, root barks	2, 5, 81, 91
			Z. nummularia	root barks	40
			Z. sativa	barks	46
nummularine-A (**146**)	Rhamnaceae	Zizyphus	*Zizyphus jujuba*	stem barks	41
			Z. nummularia	stem barks, root barks	5, 40
nummularine-B (**147**)	Rhamnaceae	Zizyphus	*Zizyphus jujuba*	stem barks	41
			Z. jujuba var. *inermis*	stem barks	74
			Z. nummularia	root barks, stem barks	40, 53
			Z. sativa	barks	46
			Z. xylopyra	barks	62
nummularine-H (**149**)	Rhamnaceae	Paliurus	*Paliurus ramossisimus*	stems	98
		Zizyphus	*Zizyphus nummularia*	stem barks	3, 5
nummularine-P (**152**)	Rhamnaceae	Zizyphus	*Zizyphus nummularia*	stem barks	65
			Z. rugosa	stem barks	71
nummularine-R (**153**)	Rhamnaceae	Zizyphus	*Zizyphus jujuba* var. *inermis*	stem barks	74
			Z. nummularia	stem barks	66
zizyphine-A (**156**)	Rhamnaceae	Zizyphus	*Zizyphus jujuba*	stem barks	100
			Z. oenoplia	root barks, stem barks	5, 28, 38
zizyphine-F (**159**)	Rhamnaceae	Zizyphus	*Zizyphus oenoplia*	stem barks	5, 33
			Z. spina-christi	stem barks	77
sativanine-G (**172**)	Rhamnaceae	Paliurus	*Paliurus ramossisimus*	roots	97
		Zizyphus	*Zizyphus sativa*	barks	54
sativanine-H (**173**)	Rhamnaceae	Zizyphus	*Zizyphus rugosa*	stem barks	71
			Z. sativa	barks	60
			Type Ic		
abyssenine-A (**176**)	Rhamnaceae	Zizyphus	*Zizyphus abyssinica*	barks	32
			Z. mucronata	root barks	91
			Z. oenoplia	stem barks	38
abyssenine-B (**177**)	Rhamnaceae	Zizyphus	*Zizyphus abyssinica*	barks	32
			Z. oenoplia	stem barks	38
mucronine-A (**179**)	Rhamnaceae	Zizyphus	*Zizyphus abyssinica*	barks	32
			Z. mucronata	stem barks	5, 27
mucronine-B (**180**)	Rhamnaceae	Zizyphus	*Zizyphus abyssinica*	barks	32
			Z. mucronata	stem barks	5, 27
mucronine-C (**181**)	Rhamnaceae	Zizyphus	*Zizyphus abyssinica*	barks	32
			Z. mucronata	stem barks	5, 27

Table 4. Depsicyclopeptides (Type II) Isolated from Higher Plants up to 2005



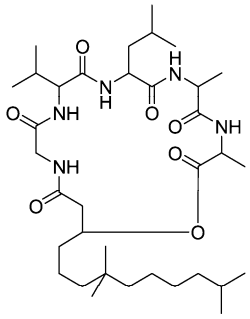
FR900359 (**188**)[137]

from *Ardisia crenata* (Myrsinaceae, whole plants).

$C_{49}H_{75}N_7O_{15}$; 6.9×10^{-4}%;

IR, FAB-MS[1002(M+H)$^+$], PMR, CMR;

reduction, amino acid analysis after hydrolysis, partial hydrolysis, ammonolysis, methanolysis.



Triptotin-L (**189**)[138]

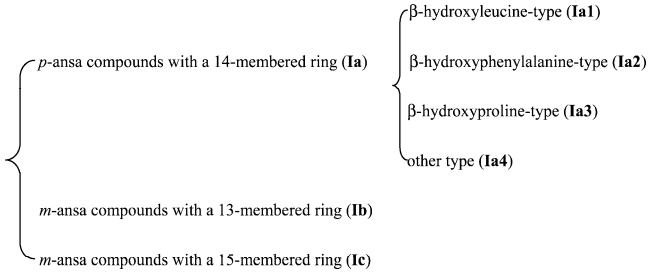
from *Triptergium wilfordii* (Celastraceae, root barks).

$C_{35}H_{63}N_5O_7$; 2.5×10^{-6}%, amorphous powder, $[\alpha]_D^{20}$ -33.5° (CH_3OH, c 0.025);

IR, EI-MS[665(M)$^+$], PMR, CMR, 2D NMR (COSY, TOCSY, HMQC, HMBC, NOESY).

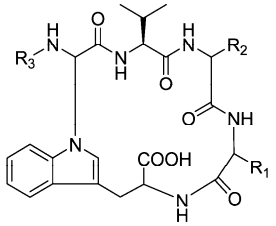
oleosa (Pandaceae), which structure was confirmed in 1966 by them. In 1964 the occurrence of alkaloids in *Scutia buxifolia* (Rhamnaceae) was reported by Wasicky et al., and three years later, Tschesche et al. reported the structure of scutianine-A (scutianine, **39**, subtype **Ia1**) from *S. buxifolia*.[1,2,4] Since then the number of cyclopeptide alkaloids has risen to 185. Workers in Europe, America, Asia, and Africa, especially France, Germany, the U.S.A., and Korea, have made important contributions in this field.

The first classification of cyclopeptide alkaloids was proposed by Pais et al. in 1971, on the basis of the various residues that constituted the molecule.[4] Later, according to the ring size, in 1975 Tschesche et al. divided cyclopeptide alkaloids into three types: **Ia**, **Ib**, and **Ic**, in which type **Ia** includes four subtypes **Ia1**, **Ia2**, **Ia3**, and **Ia4** based on the β-hydroxyl amino acid residue (Figure 2).[2−4] So far about 57, 32, 29, 2, 53, and 12 cyclopeptide alkaloids which belong to types **Ia1**, **Ia2**, **Ia3**, **Ia4**, **Ib**, and **Ic** were isolated respectively. Type **Ia** is the largest type, and the 1970s is the gold period of investigating of it (Table 1). Details of cyclopeptide alkaloids isolated during the past half century are listed in Tables 2 and 3.



2.1.1.2. Depsicyclopeptides (Type II). Up to 2005, only two depsicyclopeptides, FR900359 (**188**) and triptotin-L (**189**), have been isolated from higher plants (Table 4). **188** was isolated from the MeOH extract of the whole plants of *Ardisia crenata* (Myrsinaceae), and its structure was deter-

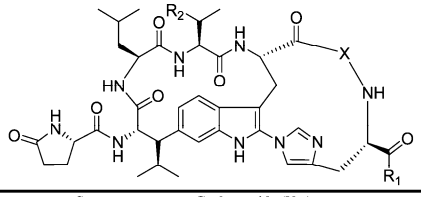
Table 5. Solanaceae-Type Cyclopeptides (Type III) Isolated from Higher Plants up to 2005



No.	Source (family, part)	Cyclopeptide (No.)	Structure* R_1	R_2	R_3	Structural and spectral data	Bioactivity	Reference
1	*Lycium chinense L. barbarm* (Solanaceae) (root barks, stems)	Lyciumin-A (**190**)	*L*-Ser(side chain)	Gly(side chain)	*L*-pyroGlu- *L*-Pro- *L*-Tyr-	$C_{42}H_{49}N_9O_{12}$; 5.6×10^{-3}%, white powder, $[\alpha]_D^{21}$ +10.1° (DMSO, c 0.54); UV, neg. FAB-MS[870(M-H)$^-$], PMR, CMR, 2D NMR (COSY, HOHAHA, NOESY, ROESY); amino acid analysis after acid hydrolysis, partial acid hydrolysis, α-chymotrypsin hydrolysis, proline-specific endopeptidase hydrolysis, dinitrophenyl reaction.	anti-ACE, anti-renin	139,140
	(root barks, stems)	Lyciumin-B (**191**)	*L*-Ser(side chain)	Gly(side chain)	*L*-pyroGlu- *L*-Pro- *L*-Trp-	$C_{44}H_{52}N_{10}O_{11}$; 1.1×10^{-2}%, white powder, $[\alpha]_D^{20}$ -3.5° (DMSO, c 0.74); neg. FAB-MS[895(M-H)$^-$], PMR, CMR, 2D NMR (COSY); amino acid analysis after acid hydrolysis, partial acid hydrolysis, α-chymotrypsin hydrolysis, proline-specific endopeptidase hydrolysis.	anti-ACE, anti-renin	139,140
	(root barks)	Lyciumin-C (**192**)	*L*-Ser(side chain)	*L*-Phe(side chain)	*L*-pyroGlu- *L*-Pro- *L*-Tyr-	$C_{49}H_{57}N_9O_{12}$; 3.9×10^{-3}%, white powder, $[\alpha]_D^{24}$ -11.9° (DMSO, c 0.97); neg. FAB-MS[962(M-H)$^-$], PMR, CMR, 2D NMR (COSY); amino acid analysis after acid hydrolysis, partial acid hydrolysis, α-chymotrypsin hydrolysis, proline-specific endopeptidase hydrolysis.		140
	(root barks)	Lyciumin-D (**193**)	*L*-Ile(side chain)	Gly(side chain)	*L*-pyroGlu- *L*-Pro- *L*-Tyr-	$C_{45}H_{57}N_9O_{11}$; 1.1×10^{-3}%, white powder, $[\alpha]_D^{25}$ -8.4° (DMSO, c 0.45); neg. FAB-MS[898(M-H)$^-$], PMR, CMR, 2D NMR (COSY); amino acid analysis after acid hydrolysis, partial acid hydrolysis, α-chymotrypsin hydrolysis, proline-specific endopeptidase hydrolysis.		140

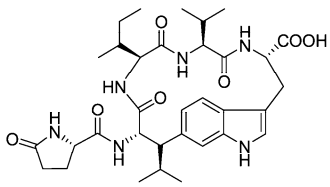
* Gly, Ile, Phe, Pro, pyroGlu, Ser, Trp and Tyr are the abreviations of the following amino acids: glycine, isoleucine, phenylalanine, proline, pyroglutamic acid, serine, tryptophan and tyrosine, respectively.

Table 6. Urticaceae-Type Cyclopeptides (Type IV) Isolated from Higher Plants up to 2005



No.	Source (family, part)	Cyclopeptide (No.)	Structure* X	R_1	R_2	Structural and spectral data	Bioactivity	Reference
1	*Celosia argentea* (Amaranthaceae) (seeds)	Celogentin-A (**194**)	*L*-Arg	OH	CH_3	$C_{45}H_{63}N_{13}O_9$; 2.0×10^{-4}%, colorless solid, $[\alpha]_D^{23}$ -43° (50% CH_3OH, c 0.3); IR, UV, FAB-MS[930(M+H)$^+$], PMR, CMR, 2D NMR (COSY, HOHAHA, HMQC, HMBC, NOESY); amino acid analysis after acid hydrolysis, absolute configuration (chiral HPLC, NOESY).	antimitotic	143
	(seeds)	Celogentin-B (**195**)	*L*-Arg	*L*-His	CH_3	$C_{51}H_{70}N_{16}O_{10}$; 1.0×10^{-4}%, colorless solid, $[\alpha]_D^{23}$ -32° (50% CH_3OH, c 0.5); IR, UV, FAB-MS[1067(M+H)$^+$], PMR, CMR, 2D NMR (COSY, HOHAHA, HMQC, HMBC, NOESY); amino acid analysis after acid hydrolysis, absolute configuration (chiral HPLC).	antimitotic	143
	(seeds)	Celogentin-C (**196**)	*L*-Pro-*L*-Arg	OH	CH_3	$C_{50}H_{70}N_{14}O_{10}$; 1.0×10^{-3}%, colorless solid, $[\alpha]_D^{23}$ -54° (50% CH_3OH, c 0.5); IR, UV, FAB-MS[1027(M+H)$^+$], PMR, CMR, 2D NMR (COSY, HOHAHA, HMQC, HMBC, NOESY); amino acid analysis after acid hydrolysis, absolute configuration (chiral HPLC).	antimitotic	143
	(seeds)	Celogentin-D (**197**)	*L*-Arg	*L*-His-*L*-Lys	CH_3	$C_{57}H_{82}N_{18}O_{11}$; 4.0×10^{-5}%, colorless solid, $[\alpha]_D^{24}$ -33° (50% CH_3OH, c 0.4); IR, UV, FAB-MS[1195(M+H)$^+$], PMR, CMR, 2D NMR (COSY, HOHAHA, HMQC, HMBC, NOESY); amino acid analysis after acid hydrolysis, absolute configuration (chiral HPLC, NOESY).	antimitotic	144
	(seeds)	Celogentin-E (**198**)	*L*-Arg-Gly	*L*-Asp	CH_3	$C_{51}H_{71}N_{15}O_{13}$; 8.0×10^{-4}%, colorless solid, $[\alpha]_D^{22}$ -39° (50% CH_3OH, c 0.5); IR, UV, FAB-MS[1101(M)$^+$], PMR, CMR, 2D NMR (COSY, HOHAHA, HMQC, HMBC, NOESY); amino acid analysis after acid hydrolysis, absolute configuration (chiral HPLC, NOESY).	antimitotic	144
	(seeds)	Celogentin-F (**199**)	*L*-Arg-Gly	*L*-Arg	CH_3	$C_{53}H_{78}N_{18}O_{11}$; 3.0×10^{-3}%, colorless solid, $[\alpha]_D^{22}$ -31° (50% CH_3OH, c 0.5); IR, UV, FAB-MS[1143(M+H)$^+$], PMR, CMR, 2D NMR (COSY, HOHAHA, HMQC, HMBC, NOESY); amino acid analysis after acid hydrolysis, absolute configuration (chiral HPLC).	antimitotic	144
	(seeds)	Celogentin-G (**200**)	*L*-Arg-Gly	OH	CH_2CH_3	$C_{48}H_{68}N_{14}O_{10}$; 7.0×10^{-4}%, colorless solid, $[\alpha]_D^{22}$ -47° (50% CH_3OH, c 1.0); IR, UV, FAB-MS[1001(M+H)$^+$], PMR, CMR, 2D NMR (COSY, HOHAHA, HMQC, HMBC, NOESY); amino acid analysis after acid hydrolysis, absolute configuration (chiral HPLC).	antimitotic	144
	(seeds)	Celogentin-H (**201**)	*L*-Arg-Gly	*L*-Asp	CH_2CH_3	$C_{52}H_{73}N_{15}O_{13}$; 4.0×10^{-4}%, colorless solid, $[\alpha]_D^{22}$ -40° (50% CH_3OH, c 0.5); IR, UV, FAB-MS[1115(M)$^+$], PMR, CMR, 2D NMR (COSY, HOHAHA, HMQC, HMBC, NOESY); amino acid analysis after acid hydrolysis, absolute configuration (chiral HPLC).	antimitotic	144
	(seeds)	Celogentin-J (**202**)	*L*-Arg-Gly	*L*-Arg	CH_2CH_3	$C_{54}H_{80}N_{18}O_{11}$; 3.0×10^{-4}%, colorless solid, $[\alpha]_D^{22}$ -38° (50% CH_3OH, c 0.4); IR, UV, FAB-MS[1157(M+H)$^+$], PMR, CMR, 2D NMR (COSY, HOHAHA, HMQC, HMBC, NOESY); amino acid analysis after acid hydrolysis, absolute configuration (chiral HPLC).	antimitotic	144
2	*C. argentea* (Amaranthaceae) (seeds) *Laportea moroides* (Urticaceae) (leaves, leaf atallus)	Moroidin (**203**)	*L*-Arg-Gly	OH	CH_3	$C_{47}H_{66}N_{14}O_{10}$; 2.0×10^{-3}%, colorless powder, $[\alpha]_D^{24}$ -55° (50% CH_3OH, c 0.3); IR, UV, FAB-MS[987(M+H)$^+$], PMR, CMR, 2D NMR (COSY, DEPT, DQF-COSY, TOCSY, HMQC, HMBC, NOESY); amino acid analysis after acid hydrolysis, partial hydrolysis, trypsin, carboxypeptidase Y, oxidization, absolute configuration (GC, chiral HPLC, NOESY, molecular modeling, molecular dynamics stimulation).	antimitotic	145-147

* Arg, Asp, Gly, His, Lys and Pro are the abreviations of the following amino acids: arginine, aspartic acid, glycine, histidine, lysine and proline, respectively.



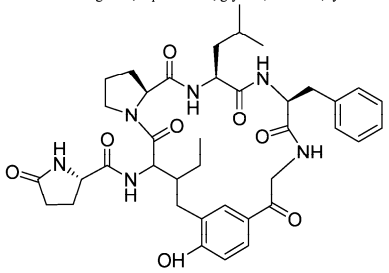
Stephanotic acid (**204**)[148]

from *Stephanotis floribunda* (Asclepiadaceae, stems).

$C_{33}H_{46}N_6O_7$; 1.1×10^{-1}%, mp 250-252, $[\alpha]_D^{25}$ -143° (CH_3OH, c 1.16);

CD, IR, UV, pos. FAB-MS[639(M+H)$^+$], PMR, CMR, 2D NMR (HOHAHA, HMBC, NOESY, ROESY);

amino acid analysis after hydrolysis, methylation, absolute configuration (chiral HPLC, NOE).



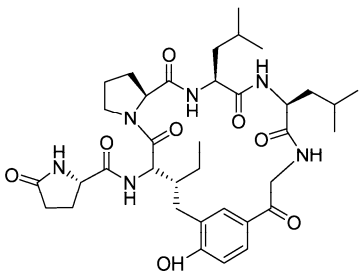
Hibispeptin-A (**205**)[149]

from *Hibiscus syriacus* (Malvaceae, root barks).

$C_{39}H_{50}N_6O_8$; white powder, 1.1×10^{-3}%, $[\alpha]_D$ -38° ($CHCl_3$:CH_3OH (1:1), c 0.21);

IR, UV, FAB-MS[731(M+H)$^+$], PMR, CMR, 2D NMR (DEPT, DQF-COSY, HMQC, HMBC);

amino acid analysis after hydrolysis, absolute configuration (chiral TLC).



Hibispeptin-B (**206**)[150]

from *Hibiscus syriacus* (Malvaceae, root barks).

$C_{36}H_{52}N_6O_8$; white powder, 3.8×10^{-4}%, $[\alpha]_D$ -42.7° ($CHCl_3$:CH_3OH (1:1), c 0.75);

IR, UV, FAB-MS[697(M+H)$^+$], PMR, CMR, 2D NMR (DEPT, DQF-COSY, HMQC, HMBC);

amino acid analysis after hydrolysis, absolute configuration (chiral TLC).

mined by hydrolytic, NMR, and MS studies, which inhibited platelet aggregation in rabbits *in vitro*, decreased the blood pressure, and caused dose-related hypotension in anesthetized normotensive rats. It is cytotoxic to cultured rat fibroblasts and myelocytic leukemia cells. Of particular significance for this depsicyclopeptide is the uncommon

amino acid *N*-methyldehydroalanine found previously in a toxin from the blue-green alga *Microcystis aeruginosa* and the novel amino acid *N*,*O*-dimethylthreonine.[137] **189** was isolated from the EtOH extract of root barks of *Tripterygium wilfordii* (Celastraceae), and its structure was established on the basis of spectroscopic studies, especially 2D NMR techniques.[138]

2.1.1.3. Solanaceae-Type Cyclopeptides (Type III). Up to 2005, only four Solanaceae-type cyclopeptides, lyciumins-A (**190**), -B (**191**), -C (**192**), and -D (**193**), have been isolated from the MeOH extract of *Lycium chinense* (Solanaceae), and their structures were elucidated by a combination of chemical, NMR, and MS studies, which show them to have inhibitory activity on ACE and renin (Table 5). Lyciumins are interesting because of their monocyclic octapeptides containing a novel C−N linkage between tryprophan N_1 and glycine C_α.[139,140] Itokawa and co-workers studied the configuration and conformation of **190** by spectroscopic and computational chemical methods. Results indicated that the major solution form of **190** in pyridine-d_5 has a type II β-turn-like conformation between the Val and Gly residues constituting the cyclic backbone.[141] Schmidt et al. have accomplished the first total synthesis of **190** and **191**.[142]

2.1.2. Heterodicyclopeptides

2.1.2.1. Urticaceae-Type Cyclopeptides (Type IV). Up to 2005, only 13 Urticaceae-type cyclopeptides, celogentins-A (**194**), -B (**195**), -C (**196**), -D (**197**), -E (**198**), -F (**199**), -G (**200**), -H (**201**), and -J (**202**), moroidin (**203**), stephanotic acid (**204**), and hibispeptins-A (**205**) and -B (**206**), have been isolated from higher plants (Table 6). Moroidin (**203**) is the first one of this kind of cyclopeptide, it was isolated from the leaves and leaf atallus of *Laportea moroides* (Urticaceae), and its structure was elucidated by a combination of chemical, NMR, MS, molecular modeling, and molecular dynamics simulation studies. An important feature of **203** is an unusual C−N linkage between tryptophan (C_2) and histidine (N_1) residues which completes its bicyclic structure. Meanwhile, it gave a positive test with chlorine−starch−iodine. It is noteworthy that **203** was also discovered from the MeOH extract of seeds of *Celosia argentea* (Amaranthaeae) and strongly inhibited the polymerization of tubulin, i.e., antimitotic activity, which was more potent than that of colchicine. These results suggested that **203** is a new class of microtubule inhibitor.[145−147] Later, Kobayashi et al.[143,144] found antimitotic celogentins (**194**−**202**) of Urticaceae-type cyclopeptides from the MeOH extract of seeds of *C. argentea*, in which celogentin-C (**196**) was four times more potent than **203** in inhibitory activity. The SAR study indicated that the bicyclic ring system including unusual non-peptide connections among β^s-Leu, Trp, and His residues characteristic of **194**−**203**, ring size, and conformations would be important for their interaction with tubulin. The same group[148] found stephanotic acid (**204**) from the stems of *Stephanotis floribunda* (Asclepiadaceae), which is a monocyclopeptide from cleaving the right-hand ring of **203**. Hibispeptins-A (**205**) and -B (**206**), isolated from the MeOH extract of root barks of *Hibiscus syriacus* (Malvaceae), are moroidin-like cyclopeptides with the unusual non-peptide connection of Ahabpa, and the geometry of the proline amide bond was determined to be *cis*-form, in which only **205** inhibited lipid peroxidation.[149,150]

2.2. Homocyclopeptides

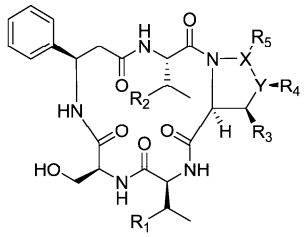
2.2.1. Homomonocyclopeptides

2.2.1.1. Compositae-Type Cyclopeptides (Type V). Up to 2005, only 13 Compositae-type cyclopeptides, astins-A (**207**), -B (**208**), -C (**209**), -D (**210**), -E (**211**), -F (**212**), -G (**213**), -H (**214**), -I (**215**), and -J (**216**) and asternins-A (**217**), -B (**218**), and -C (**219**), have been isolated from higher plants (Table 7). Astin-C (asterin, **209**) is the first one of this kind of cyclopeptide, it was isolated from the roots of *Aster tataricus* (Compositae), and its structure was elucidated on the basis of spectral data coupled with some chemical evidence. It gave positive Beilstein and Dragendorff tests. **207**−**215** are cyclic peptides, and **216**−**219** are acyclic peptides, and the latter may be the artifacts of the former under mild basic conditions. These cyclopeptides have only been found in the roots of *A. tataricus* now. It is noteworthy that Compositae-type cyclopeptides are halogenated cyclic pentapeptides containing one chlorinated proline, *allo*-theronine (*allo*-Thr), β-phenylalanine (β-Phe), α-aminobutyric acid (Abu), and serine (Ser) with one *cis* configuration in the proline peptide bond. Their structures are very similar to that of cyclochlorotine, a toxic principle isolated from *Penicillium islandicum*. Among them, **207**−**209** showed antitumor activity.[151−157]

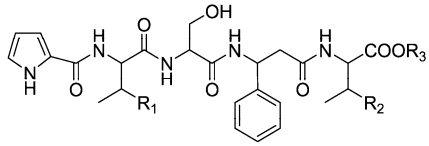
Due to the interesting structures and antitumor activity, the conformations of **207**−**209** and **218**−**219** were studied by X-ray, 2D NMR techniques, molecular mechanics, and molecular dynamics calculations. Results indicated that the conformation of **208** in the solution was homologous to that observed in the solid state; the conformation in solution of **207** possessed a backbone conformation similar to that of **209**; **207** and **209,** with weaker activity than **208**, took different backbone conformations from that of **208**.[158−160] The solution conformation of **218** was characterized as a nonclassic β-turn structure at the ($^\Delta$Pro-Thr-Ser-β-Phe) region with an amphiphilic feature, and that of **219** was more flexible with multiple conformational averaging.[161,162] Itokawa and co-workers investigated the chemical conversion and a hepatic microsomal biotransformation in rats of astins. Results suggested that 1,2-*cis* dichlorinated proline residues of astins-A (**207**), -B (**208**), and -C (**209**) play an important role in the antitumor activity.[163] They also reported that the produced thioastins after replacing the serine amide bonds in **207**−**209** with thioamide bonds showed more promising antitumor activities than their parent compounds.[164] Joullie and co-workers synthesized three important non-protein amino acids of (+)-(*S*)-2-aminobutanoic acid, the methyl ester of L-β-phenylalanine and (−)-(3*S*,4*R*)-dichloro-L-proline, and one tripeptide of *N*-Boc-L-Abu-*O*-Bn-L-Ser-L-β-Phe. Finally, they accomplished the first total synthesis of astin-G (**213**) in 1999.[165−167]

2.2.1.2. Caryophyllaceae-Type Cyclopeptides (Type VI). We define Caryophyllaceae-type cyclopeptides as homomonocyclopeptides formed with the peptide bonds of protein or non-protein α-amino acids, which include cyclic di-, penta-, hexa-, hepta-, octa-, nona-, deca-, undeca-, and dodecapeptides. Cyclolinopeptide A (CLA, **295**) is the first Caryophyllaceae-type cyclopeptide isolated from higher plants. It is a cyclic nonapeptide with potent immunosuppressive activity. It was isolated from the seeds of *Linum usitatissimum* (linseed oil, Linaceae) in 1959 by Kaufmann and Tobschirbel and was subsequently synthesized by Porx et al. in 1966 by classical solution methods. Soon after its

Table 7. Compositae-Type Cyclopeptides (Type V) Isolated from Higher Plants up to 2005



No.	Source (family, part)	Cyclopeptide (No.) (synonym)	Structure						Structural and spectral data	Bioactivity	Reference
			R_1	R_2	R_3	R_4	R_5	X-Y			
1	*Aster tataricus* (Compositae) (roots)	Astin-A (**207**)	H	OH	Cl	Cl	H	CH-CH	$C_{25}H_{33}N_5O_7Cl_2$; colorless needles, mp 192-194, $[\alpha]_D$ -77.0° (CH_3OH, c 0.37); FAB-MS[586$(M)^+$], PMR, CMR, 2D NMR (COSY, HOHAHA, HMQC, HMBC, NOEs); amino acid analysis after acid hydrolysis, absolute configuration (HPLC).	antitumor	151
	(roots)	Astin-B (**208**)	OH	H	Cl	Cl	H	CH-CH	$C_{25}H_{33}N_5O_7Cl_2$; colorless needles, mp 183-185, $[\alpha]_D$ -84.9° (CH_3OH, c 0.31); FAB-MS[586$(M)^+$], PMR, CMR, 2D NMR (COSY, HOHAHA, HMQC, HMBC, NOEs); amino acid analysis after acid hydrolysis, absolute configuration (HPLC).	antitumor	151
	(roots)	Astin-C (**209**) (Asterin)	H	H	Cl	Cl	H	CH-CH	$C_{25}H_{33}N_5O_6Cl_2$; 5.0×10^{-2}%, colorless needles, mp 183-187, $[\alpha]_D^{25}$ -65.4° (CH_3CH_2OH, c 0.11); IR, UV, FD-MS[569$(M-H)^+$], PMR, CMR, 2D NMR (NOEs); amino acid analysis after acid hydrolysis, partial hydrolysis, dechlorination, methanolysis, absolute configuration (HPLC).	antitumor, hepatoxic	151,152
	(roots)	Astin-D (**210**)	H	H	H	H	Cl	C=C	$C_{25}H_{32}N_5O_6Cl$; colorless needles, mp 245 (dec.), $[\alpha]_D$ -86.7° (CH_3OH, c 0.12); IR, UV, FAB-MS[534$(M)^+$], PMR, CMR, 2D NMR (COSY, HOHAHA, HMQC, HMBC, NOEs, NOESYPH); amino acid analysis after acid hydrolysis, absolute configuration (HPLC).		153
	(roots)	Astin-E (**211**)	OH	H	H	H	Cl	C=C	$C_{25}H_{32}N_5O_7Cl$; colorless needles, mp 183-184, $[\alpha]_D$ -109.2° (CH_3OH, c 1.22); IR, FAB-MS[550$(M)^+$], PMR, CMR, 2D NMR (COSY, HOHAHA, HMQC, HMBC, NOEs, NOESYPH); amino acid analysis after acid hydrolysis, absolute configuration (HPLC).		153
	(roots)	Astin-F (**212**)	H	H	Cl	H	H	CH-CH	$C_{25}H_{34}N_5O_6Cl$; 2.0×10^{-3}%, colorless needles, mp 237-239, $[\alpha]_D$ -68.6° (CH_3OH, c 0.54); IR, FAB-MS[536$(M)^+$], PMR, CMR, 2D NMR (COSY, HOHAHA, HMQC, HMBC, NOEs, NOESYPH); amino acid analysis after acid hydrolysis, absolute configuration (HPLC).		154
	(roots)	Astin-G (**213**)	H	H	H	H	H	CH-CH	$C_{25}H_{35}N_5O_6$; 2.0×10^{-3}%, colorless needles, mp 289-291, $[\alpha]_D$ -107.9° (CH_3OH, c 1.14); IR, FAB-MS[502$(M+H)^+$], PMR, CMR, 2D NMR (COSY, HOHAHA, HMQC, HMBC, NOEs, NOESYPH); amino acid analysis after acid hydrolysis, absolute configuration (HPLC).		154
	(roots)	Astin-H (**214**)	H	OH	H	H	Cl	C=C	$C_{25}H_{32}N_5O_7Cl$; 2.0×10^{-4}%, colorless needles, mp 265-266, $[\alpha]_D$ -107.3° (CH_3OH, c 0.11); IR, FAB-MS[550$(M)^+$], PMR, CMR, 2D NMR (COSY, HOHAHA, HMQC, HMBC, NOEs, NOESYPH); amino acid analysis after acid hydrolysis, absolute configuration (HPLC).		154
	(roots)	Astin-I (**215**)	H	H	OH	Cl	H	CH-CH	$C_{25}H_{34}N_5O_7Cl$; 1.5×10^{-4}%, mp 174.1-176.5, $[\alpha]_D$ -78.8° (CH_3OH, c 0.13); IR, FAB-MS[552$(M)^+$], PMR, CMR, 2D NMR (COSY, HOHAHA, HMQC, HMBC, NOEs); amino acid analysis after acid hydrolysis, absolute configuration (HPLC).		155



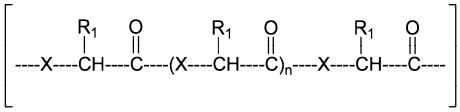
No.	Source (family, part)	Cyclopeptide (No.)	Structure			Structural and spectral data	Reference
			R_1	R_2	R_3		
1	*Aster tataricus* (Compositae) (roots)	Astin-J (**216**)	H	H	H	$C_{25}H_{33}N_5O_7$; 3.0×10^{-3}%, colorless needles, mp 282 (dec.), $[\alpha]_D$ +6.0° (C_5H_5N, c 0.13); IR, UV, FAB-MS[516$(M+H)^+$], PMR, CMR, 2D NMR (COSY, HMQC, HMBC); amino acid analysis after acid hydrolysis, absolute configuration (HPLC).	156
	(roots)	Asternin-A (**217**)	OH	H	H	$C_{25}H_{33}N_5O_8$; amorphous powder, mp 272-274, $[\alpha]_D$ +38.5° (C_5H_5N, c 0.33); IR, UV, FAB-MS[532$(M+H)^+$], PMR, CMR, 2D NMR (COSY, COLOC); elemental analysis, amino acid analysis after acid hydrolysis, enzymatic hydrolysis with α-chymotrypsin, methylation.	157
	(roots)	Asternin-B (**218**)	OH	H	CH_3	$C_{26}H_{33}N_5O_8$; amorphous powder, mp 235-237, $[\alpha]_D$ +3.1° (C_5H_5N, c 0.57); IR, UV, FAB-MS[546$(M+H)^+$], PMR, CMR, 2D NMR (COSY, COLOC); elemental analysis, amino acid analysis after acid hydrolysis, enzymatic hydrolysis with α-chymotrypsin.	157
	(roots)	Asternin-C (**219**)	H	OH	CH_3	$C_{26}H_{33}N_5O_8$; amorphous powder, mp 250-252, $[\alpha]_D$ -4.9° (C_5H_5N, c 0.33); IR, UV, FAB-MS[546$(M+H)^+$], PMR, CMR, 2D NMR (COSY, COLOC, NOESY); elemental analysis, amino acid analysis after acid hydrolysis, enzymatic hydrolysis with α-chymotrypsin.	157

synthesis, it became the object of intensive structural studies.[206,207,250,251] Up to 1989, other Caryophyllaceae-type cyclopeptides such as cleromyrine I (**256**)[184] and labaditin (**284**)[200] were discovered. In total about 168 Caryophyllaceae-type cyclopeptides have been discovered from higher plants during the past half century (Table 8). The 1990s was the gold period of investigation of them. Workers in Asia, Europe, and America, especially Japan, China, and France, made important contributions in this field.

2.2.2. Homodicyclopeptides

2.2.2.1. Rubiaceae-Type Cyclopeptides. Rubiaceae-type cyclopeptides are homodicyclohexapeptides formed with one D-α-alanine (rarely D-α-aminobutyric acid), one *N*-methyl-

Table 8. Caryophyllaceae-Type Cyclopeptides (Type VI) Isolated from Higher Plants during 1959−2005



X = N or NH; n = 0, 3 - 10; R_1 = side chain of amino acids.

No.	Source (family, part)	Cyclopeptide (No.) (synonym)	Structure*	Structural and spectral data	Bioactivity	Reference
1	*Annona cherimola* (Annonaceae) (seeds)	Cherimolacyclopeptide A (**220**)	Cyclo-(*L*-Pro[1]-*L*-Gln[2]-*L*-Thr[3]-Gly[4]-*L*-Met[5]-*L*-Leu[6]-*L*-Pro[7]-*L*-Ile[8])	$C_{38}H_{63}N_9O_{10}S$; 6.2×10[-3]%, colorless solids, mp 192-193, $[\alpha]_D^{22}$ −8.5° (CH_3OH, c 0.9); pos. ESI-qTOF-MS[838(M+H)$^+$], ESI-qTOF MS/MS, PMR, CMR, 2D NMR (COSY, TOCSY, HSQC, HMBC, NOESY); amino acid analysis after acid hydrolysis, absolute configuration (chiral GC), solution conformation (NMR).	cytotoxic	168
	(seeds)	Cherimolacyclopeptide B (**221**)	Cyclo-(*L*-Pro[1]-*L*-Gln[2]-*L*-Thr[3]-Gly[4]-*L*-OMet[5]-*L*-Leu[6]-*L*-Pro[7]-*L*-Ile[8])	$C_{38}H_{63}N_9O_{11}S$; 6.6×10[-3]%, colorless solids, mp 228-229, $[\alpha]_D^{22}$ −8.3° (CH_3OH, c 2.0); pos. ESI-qTOF-MS[854(M+H)$^+$], ESI-qTOF MS/MS, PMR, CMR, 2D NMR (COSY, TOCSY, HSQC, HMBC, NOESY); amino acid analysis after acid hydrolysis, absolute configuration (chiral GC), solution conformation (NMR).	cytotoxic	168
2	*A. glabra* (seeds)	Glabrin A (**222**)	Cyclo-(Pro-Gly-Leu-Val-Ile-Tyr)	$C_{33}H_{50}N_6O_7$; 2.3×10[-2]%, needles, mp 300-303, $[\alpha]_D^{28}$ −195.86° (CH_3OH, c 0.845); IR, UV, pos. FAB-MS[643(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, ^{1}H-^{13}C COSY, COLOC); amino acid analysis after acid hydrolysis.		169
	(seeds)	Glabrin B (**223**)	Cyclo-(Pro-OMet-Val[1]-Ala-Val[2]-Tyr-Gly-Thr)	$C_{38}H_{58}N_8O_{11}S$; 6.0×10[-3]%, needles, mp 205, $[\alpha]_D^{29}$ −76.67° (CH_3OH, c 0.375); IR, UV, pos. FAB-MS[835(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, ^{1}H-^{13}C COSY, COLOC); amino acid analysis after acid hydrolysis.		169
	(seeds)	Glabrin C (**224**)	Cyclo-(Pro-Gly-Tyr-Val[1]-Leu[1]-Ala-Leu[2]-Val[2])	$C_{41}H_{64}N_8O_9$; 1.0×10[-2]%, amorphous powder, mp 153, $[\alpha]_D^{29.0}$ −35.11° (CH_3OH, c 0.235); IR, UV, pos. FAB-MS[813(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, ^{1}H-^{13}C COSY, COLOC).		170
	(seeds)	Glabrin D (**225**)	Cyclo-(Pro[1]-Pro[2]-Val-Tyr-Gly-Pro[3]-Glu)	$C_{36}H_{49}N_7O_{10}$; 5.8×10[-3]%, amorphous powder, mp 219, $[\alpha]_D^{29.1}$ −53.54° (CH_3OH, c 0.551); IR, UV, pos. FAB-MS[739(M)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, ^{1}H-^{13}C COSY, COLOC).		170
3	*A. muricata* (seeds)	Annomuricatin A (**226**)	Cyclo-(Pro-Phe-Val-Ser-Ala-Gly)	$C_{27}H_{38}N_6O_7$; 6.6×10[-3]%, needles, mp 285-287, $[\alpha]_D^{23}$ +11.28° (C_5H_5N, c 0.4); IR, UV, pos. FAB-MS[559(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, ^{1}H-^{13}C COSY, COLOC); amino acid analysis after acid hydrolysis.		171
	(seeds)	Annomuricatin B (**227**)	Cyclo-(Pro-Asn-Ala-Trp-Leu-Gly-Thr)	$C_{35}H_{49}N_9O_9$; 9.0×10[-3]%, needles, mp 213, $[\alpha]_D^{19}$ −37.25° (CH_3OH, c 0.51); IR, UV, pos. FAB-MS[740(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, ^{1}H-^{13}C COSY, COLOC).		172
4	*A. squamosa* (seeds)	Annosquamosin A (**228**)	Cyclo-(Pro-OMet-Thr-Ala-Ile-Val-Gly-Tyr)	$C_{39}H_{60}N_8O_{11}S$; 7.5×10[-3]%, needles, mp 215-216, $[\alpha]_D^{24.3}$ −65.27° (CH_3OH, c 0.429); IR, pos. FAB-MS[849(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, ^{1}H-^{13}C COSY, COLOC); amino acid analysis after acid hydrolysis.		173
	(seeds)	Cyclosquamosin A (**229**)	Cyclo-(*L*-Pro[5]-*L*-Val[6]-*L*-Pro[7]-Gly[1]-*L*-Ser[2]-*L*-Phe[3]-Gly[4])	$C_{31}H_{43}N_7O_8$; 3.0×10[-3]%, colorless powder, $[\alpha]_D^{20}$ −74.7° (CH_3OH, c 0.83); IR, pos. FAB-MS[642(M+H)$^+$], PMR, CMR, 2D NMR (COSY, HOHAHA, HMBC, NOESY); amino acid analysis after acid hydrolysis, absolute configuration (chiral HPLC), solution conformation (phase sensitive NOESY).		174
	(seeds)	Cyclosquamosin B (**230**)	Cyclo-(*L*-Pro-*L*-Pro-*L*-Ile-*L*-Thr-Gly-*L*-Leu-*L*-Met-*L*-Gln)	$C_{38}H_{63}N_9O_{10}S$; 2.0×10[-3]%, colorless powder, $[\alpha]_D^{20}$ −53.8° (CH_3OH, c 0.58); IR, pos. FAB-MS[838(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, HMQC, HMBC, NOESY); amino acid analysis after acid hydrolysis, absolute configuration (chiral HPLC).		174
	(seeds)	Cyclosquamosin C (**231**)	Cyclo-(*L*-Pro-*L*-Pro-*L*-Ile-*L*-Thr-Gly-*L*-Leu-*L*-OMet-*L*-Gln)	$C_{38}H_{63}N_9O_{11}S$; 2.0×10[-2]%, colorless powder, $[\alpha]_D^{20}$ −94.0° (CH_3OH, c 0.10); IR, pos. FAB-MS[854(M+H)$^+$], PMR, CMR; amino acid analysis after acid hydrolysis, reduction, absolute configuration (chiral HPLC).		174
	(seeds)	Cyclosquamosin D (**232**)	Cyclo-(*L*-Pro-Gly-Gly-*L*-Val-*L*-Leu-*L*-Ser-*L*-Tyr-*L*-Tyr)	$C_{41}H_{56}N_8O_{11}$; 8.0×10[-2]%, colorless powder, $[\alpha]_D^{20}$ −36.4° (CH_3OH, c 0.11); IR, UV, pos. FAB-MS[837(M+H)$^+$], PMR; amino acid analysis after acid hydrolysis, enzymatic hydrolysis with α-chymotrypsin and sequence determination, absolute configuration (chiral HPLC).		174
	(seeds)	Cyclosquamosin E (**233**)	Cyclo-(*L*-Pro-Gly-Gly-*L*-Val-*L*-Leu-*L*-Ser-*L*-Tyr-*L*-Tyr-*L*-Tyr)	$C_{50}H_{65}N_9O_{13}$; 2.0×10[-3]%, colorless powder, $[\alpha]_D^{20}$ −10.9° (CH_3OH, c 1.38); IR, UV, pos. FAB-MS[1000(M+H)$^+$], PMR; amino acid analysis after acid hydrolysis, enzymatic hydrolysis with α-chymotrypsin and sequence determination, absolute configuration (chiral HPLC).		174
	(seeds)	Cyclosquamosin F (**234**)	Cyclo-(*L*-Pro-*L*-Ala-*L*-Leu-*L*-Thr-*L*-Thr-*L*-Tyr-Gly-*L*-Ala)	$C_{36}H_{54}N_8O_{11}$; 1.0×10[-3]%, colorless powder, $[\alpha]_D^{20}$ −38.2° (CH_3OH, c 1.11); IR, UV, pos. FAB-MS[775(M+H)$^+$], PMR; amino acid analysis after acid hydrolysis, enzymatic hydrolysis with α-chymotrypsin and sequence determination, absolute configuration (chiral HPLC).		174
	(seeds)	Cyclosquamosin G (**235**)	Cyclo-(*L*-Pro-*L*-Met-*L*-Thr-*L*-Ala-*L*-Ile-*L*-Val-Gly-*L*-Tyr)	$C_{39}H_{60}N_8O_{10}S$; 2.0×10[-3]%, colorless powder, $[\alpha]_D^{20}$ −37.1° (CH_3OH, c 0.14); IR, UV, pos. FAB-MS[833(M+H)$^+$], PMR, CMR; amino acid analysis after acid hydrolysis, absolute configuration (chiral HPLC).		174

Table 8 (Continued)

No.	Source (family, part)	Cyclopeptide (No.) (synonym)	Structure*	Structural and spectral data	Bioactivity	Reference
5	*Arenaria juncea* (Caryophyllaceae) (roots)	Arenarin A (**236**)	Cyclo-(Pro^1-Phe^1-Ser^2-Ser^1-Phe^2-Ile-Pro^2)	$C_{40}H_{53}N_7O_9$; amorphous powder; IR, pos. FAB-MS[782(M+Li)$^+$], PMR, CMR, 2D NMR (DQF-COSY, TOCSY, HMQC, HMBC, NOESY); amino acid analysis after acid hydrolysis.		175
6	*A. oreophila* (whole plants)	Arenariphilin A (**237**)	Cyclo-(Thr-Gly)	$C_6H_{10}N_2O_3$; 2.3×10^{-5}%, amorphous powder, $[\alpha]_D^{25.6}$ +3.33° (CH_3OH, c 0.15); IR, UV, pos. FAB-MS[158(M)$^+$], PMR, CMR.		176
	(whole plants)	Arenariphilin B (**238**)	Cyclo-(Ser^1-Gly-Ser^2-Ile-Phe^1-Phe^2)	$C_{32}H_{42}N_8O_8$; 5.4×10^{-5}%, amorphous powder, $[\alpha]_D^{25.4}$ 0° (CH_3OH, c 0.10); IR, UV, pos. FAB-MS[639(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, TOCSY, HMQC, HMBC, ROESY).		176
7	*Brachystemma calycinum* (Caryophyllaceae) (roots)	Brachystemin A (**239**)	Cyclo-(Pro^1-Phe-Leu-Ala^1-Thr-Pro^2-Ala^2-Gly)	$C_{37}H_{54}N_8O_9$; 6.2×10^{-5}%, white amorphous powder, mp>250, $[\alpha]_D^{21}$ -33.8° (CH_3OH, c 0.20); IR, pos. FAB-MS[755(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, TOCSY, HMBC).		177
	(roots)	Brachystemin B (**240**)	Cyclo-(Pro^1-Ala-Phe-Trp-Asp-Pro^2-Leu-Gly)	$C_{45}H_{57}N_9O_{10}$; 3.1×10^{-5}%, white solids, mp 240-242, $[\alpha]_D^{25}$ -0.004° (CH_3OH, c 0.40); pos. FAB-MS[884(M+H)$^+$], PMR, CMR, 2D NMR (DEPT, ^{1}H-^{1}H COSY, TOCSY, HMBC, ROESY).		177
	(roots)	Brachystemin C (**241**)	Cyclo-(Pro^2-Pro^3-Ile^4-Gly^5- Val^6-Ala^7-Ala^8-Tyr^1)	$C_{38}H_{56}N_8O_9$; 3.8×10^{-5}%, white solids, mp>250, $[\alpha]_D^{25}$ -21.0° (CH_3OH, c 0.25); pos. FAB-MS[769(M+H)$^+$], PMR, CMR, 2D NMR (DEPT, ^{1}H-^{1}H COSY, HMBC); solid conformation (x-ray).		177,178
	(roots)	Brachystemin D (**242**)	Cyclo-(Pro-OMet-Trp-Ile-Gly-Ala-Leu-Asp)	$C_{42}H_{61}N_9O_{11}S$; 3.8×10^{-5}%, white solids, mp 215-217.5, $[\alpha]_D^{28}$ -55.0° (CH_3OH, c 0.15); pos. FAB-MS[899(M)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, HMQC, HMBC).		177
	(roots)	Brachystemin E (**243**)	Cyclo-(Pro^1-Leu-Ile^1-Gly-Pro^2-Ile^2-Trp-Asn)	$C_{45}H_{66}N_{10}O_9$; 4.5×10^{-4}%, crystals, mp 210-211.5, $[\alpha]_D^{25.1}$ -48.5° (CH_3OH, c 0.52); IR, pos. FAB-MS[891(M+H)$^+$], PMR, CMR, 2D NMR (DEPT, ^{1}H-^{1}H COSY, TOCSY, HMQC, HMBC); amino acid analysis after acid hydrolysis, solid conformation (x-ray).		179
8	*Cerastium arcticum* (Caryophyllaceae) (whole plants)	Arcticumin A (**244**)	Cyclo-(Pro-Phe-Ile-Ile-Gly-Ile-Gly)	$C_{36}H_{55}N_7O_7$; 5.2×10^{-4}%; pos. FAB-MS[697(M)$^+$]; amino acid analysis after acid hydrolysis.		180
	(whole plants)	Arcticumin B (**245**)	Cyclo-(Thr-Val-Ser-Val-Gly-Asp-Ser-Glu-Gly)	$C_{33}H_{53}N_9O_{16}$; 3.9×10^{-4}%; pos. FAB-MS[830(M-H)$^+$]; amino acid analysis after acid hydrolysis.		180
	(whole plants)	Arcticumin C (**246**)	Cyclo-(Pro-Phe-Pro-Thr-Gly-Ser-Ser-Gly-Asp)	$C_{37}H_{51}N_9O_{14}$; 4.7×10^{-4}%; pos. FAB-MS[845(M)$^+$]; amino acid analysis after acid hydrolysis.		180
9	*C. regelii* (whole plants)	Regelin A (**247**)	Cyclo-(Pro-Leu-Ser-Gly-Leu-Glu-Val-Phe-Gly-Gly)	$C_{45}H_{68}N_{10}O_{13}$; 4.3×10^{-4}%; pos. FAB-MS[956(M)$^+$]; amino acid analysis after acid hydrolysis.		180
10	*Citrus aurantium* (Rutaceae) (fruit peels)	(**248**)	Cyclo-(*L*-Pro^5-*L*-Ser^6-Gly^1-*L*-Leu^2-*L*-Val^3-*L*-Leu^4)	$C_{27}H_{46}N_8O_7$; 1.1×10^{-2}%, colorless powder, $[\alpha]_D^{23}$ -123.6° (CH_3OH, c 0.23); IR, UV, pos. FAB-MS[567(M+H)$^+$], PMR, CMR, 2D NMR (COSY, HMQC, HMBC); amino acid analysis after acid hydrolysis, absolute configuration (HPLC).		181
	(fruit peels)	(**249**)	Cyclo-(*L*-Pro^6-*L*-Pro^7-*L*-Phe^8-Gly^1-Gly^2-*L*-Leu^3-*L*-Leu^4 -*L*-Leu^5)	$C_{41}H_{62}N_8O_8$; 1.4×10^{-3}%, colorless powder, $[\alpha]_D^{23}$ -109.6° (CH_3OH, c 0.30); IR, UV, pos. FAB-MS[795(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, HMQC, HMBC, NOESY); amino acid analysis after acid hydrolysis, absolute configuration (HPLC).		181
11	*C. medica* var. *sarcodactylis* (fruit peels)	(**250**)	Cyclo-(Gly^1-*L*-Asp^2-*L*-Leu^3-*L*-Val^4-*L*-Thr^5-*L*-Tyr^6-*L*-Ph e^7)	$C_{39}H_{53}N_7O_{11}$; 4.2×10^{-3}%, colorless powder, $[\alpha]_D^{24}$ –22.3° (CH_3OH, c 0.25); IR, UV, pos. FAB-MS[796(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, HMQC, HMBC, NOESY); absolute configuration (HPLC).		182
	(fruit peels)	(**251**)	Cyclo-(*L*-Pro^3-*L*-Trp^4-*L*-Leu^5-*L*-Ile^6-*L*-Ala^7-*L*-Ala^8-Gly ^{1}-*L*-Leu^2)	$C_{42}H_{63}N_9O_8$; 2.1×10^{-3}%, colorless powder, $[\alpha]_D^{24}$ –81.1° (CH_3OH, c 0.15); IR, UV, pos. FAB-MS[822(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, HMQC, HMBC, NOESY); absolute configuration (HPLC).		182
12	*C. sinensis* (fruit peels) *C. natsudaidai* (fruit peels)	Citrusin II (**252**)	Cyclo-(Pro^7-Ala^1-Pro^2-Phe^3-Trp^4-Gly^5-Gly^6)	$C_{37}H_{44}N_8O_7$; 4.0×10^{-4}%, white crystals, mp 213-215, $[\alpha]_D^{22}$ –75.16° (CH_3OH, c 0.15); pos. FAB-MS[713(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY); amino acid analysis after acid hydrolysis.		183
	(fruit peels)	Citrusin III (**253**)	Cyclo-(Pro-Leu-Leu-Pro-Tyr-Gly-Ser)	$C_{36}H_{53}N_7O_9$; 1.3×10^{-3}%, white crystals, mp 160-163, $[\alpha]_D^{22}$ –103.09° (CH_3OH, c 0.14); pos. FAB-MS[728(M+H)$^+$], PMR, CMR; amino acid analysis after acid hydrolysis.		183
	(fruit peels)	Citrusin IV (**254**)	Cyclo-(Pro-Glu-Ala-Glu-Trp-Gly-Glu-Val)	$C_{41}H_{55}N_9O_{14}$; 6.0×10^{-4}%, yellow crystals, mp 220-221, $[\alpha]_D^{22}$ +5.58° (CH_3OH, c 0.05); pos. FAB-MS[898(M+H)$^+$], PMR; amino acid analysis after acid hydrolysis.		183
13	*C. unshiu* (fruit peels)	Citrusin I (**255**)	Cyclo-(Leu^1-Ile^2-Ala^3-Thr^4-Gly^5-Thr^6-Phe^7)	$C_{34}H_{53}N_7O_9$; 7.0×10^{-3}%, white crystals, mp>300, $[\alpha]_D^{22}$ –25.92° (CH_3OH, c 0.03); pos. FAB-MS[704(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY); amino acid analysis after acid hydrolysis.		183

Table 8 (Continued)

No.	Source (family, part)	Cyclopeptide (No.) (synonym)	Structure*	Structural and spectral data	Bioactivity	Reference
14	*Clerodendrum myricoides* (Verbenaceae) (whole plants)	Cleromyrine I (**256**)	Cyclo-(*L*-Pro-*L*-Ile-*L*-Val-*L*-Phe-*L*-Ala-Gly)	$C_{30}H_{44}N_6O_6$; 3.3×10^{-2}%, crystals, mp 159-160, $[\alpha]_D^{25}$ –132° (CH_3OH, c 2.3); EI-MS[584(M)$^+$], PMR, CMR, 2D NMR (DEPT, HOHAHA, ^{13}C-^1H COSY, ROESY); amino acid analysis after acid hydrolysis, hydrogenation, absolute configuration (chiral GC); solution conformation (NMR).		184
15	*Dianthus superbus* (Caryophyllaceae) (whole plants)	Dianthin A (**257**)	Cyclo-(Ala-Tyr-Asn-Phe-Gly-Leu)	$C_{33}H_{43}N_7O_8$; 2.3×10^{-4}%, cubic crystals, mp 205-208, $[\alpha]_D^{25}$ –38.6° (CH_3OH, c 0.290); IR, UV, pos. FAB-MS[666(M+H)$^+$], PMR, CMR, 2D NMR (^1H-^1H COSY, TOCSY, ^1H-^{13}C COSY, COLOC, ROESY).		185
	(whole plants)	Dianthin B (**258**)	Cyclo-(Pro^1-Ile-Phe^2-Phe^1-Pro^2-Gly)	$C_{36}H_{46}N_6O_6$; 4.7×10^{-5}%, amorphous powder, $[\alpha]_D^{25}$ –167.3° (CH_3OH, c 0.263); IR, UV, pos. FAB-MS[659(M+H)$^+$], PMR, CMR, 2D NMR (TOCSY, HMQC, ROESY).		185
		Dianthin C (**259**)	Cyclo-(*L*-Pro^2-Gly^1-*L*-Ile^6-*L*-Val^5-*L*-Tyr^4-*L*-Phe^3)	$C_{36}H_{48}N_6O_7$; 3.3×10^{-3}%, pale yellow powder, $[\alpha]_D^{21}$ –50° (CH_3OH, c 0.17); CD, IR, UV, ESI-MS[677(M+H)$^+$], PMR, CMR, 2D NMR (DEPT, TOCSY, HMQC, HMBC, ROESY), MS/MS; absolute configuration (HPLC) , solution conformation (CD).		186
		Dianthin D (**260**)	Cyclo-(*L*-Pro^4-*L*-Pro^5-*L*-Ile^6-*L*-Phe^7-Gly^1-*L*-Ser^2-*L*-Leu^3)	$C_{36}H_{53}N_7O_8$; 4.8×10^{-4}%, pale yellow powder, $[\alpha]_D^{21}$ –19.6° (CH_3OH, c 0.10); CD, IR, UV, ESI-MS[712(M+H)$^+$], PMR, CMR, 2D NMR (DEPT, TOCSY, HMQC, HMBC, ROESY), MS/MS; absolute configuration (HPLC) , solution conformation (CD).		186
		Dianthin E (**261**)	Cyclo-(*L*-Pro^2-Gly^1-*L*-Val^6-*L*-Phe^5-*L*-Ser^4*L*-Ile^3)	$C_{30}H_{44}N_6O_7$; 2.2×10^{-3}%, pale yellow powder, $[\alpha]_D^{21}$ –30.5° (CH_3OH, c 0.02); CD, IR, UV, ESI-MS[601(M+H)$^+$], PMR, CMR, 2D NMR (DEPT, TOCSY, HMQC, HMBC, ROESY), MS/MS; absolute configuration (HPLC) , solution conformation (CD).	cytotoxic	186
		Dianthin F (**262**)	Cyclo-(*L*-Pro^2-Gly^1-*L*-Phe^5-*L*-Val^4-*L*-Phe^3)	$C_{30}H_{37}N_5O_5$; 4.8×10^{-4}%, pale yellow powder, $[\alpha]_D^{21}$ –16.0° (CH_3OH, c 0.03); CD, IR, UV, ESI-MS[548(M+H)$^+$], PMR, CMR, 2D NMR (DEPT, TOCSY, HMQC, HMBC, ROESY), MS/MS; absolute configuration (HPLC), solution conformation (CD).		186
16	*Drymaria diandra* (Caryophyllaceae) (whole plants)	Drymarin A (**263**)	Cyclo-(Pro^1-Pro^2-Pro^3-Phe^2-Phe^3-Val-Ile-Ala-Phe^1)	$C_{56}H_{73}N_9O_9$; 1.4×10^{-4}%, colorless needles, mp 183-185, $[\alpha]_D^{26}$ –81.5° (CH_3OH, c 0.37); IR, pos. FAB-MS[1017(M+2H)$^+$], PMR, CMR, 2D NMR (^1H-^1H COSY, TOCSY, HMQC, HMBC, ROESY).		187
	(whole plants)	Drymarin B (**264**)	Cyclo-(Pro^1-Phe-Tyr-Pro^2-Gly-Leu)	$C_{36}H_{46}N_8O_7$; 1.1×10^{-2}%, white crystals, mp 199-202, $[\alpha]_D^{25}$ –95.8° (CH_3OH, c 0.49); IR, pos. FAB-MS[675(M+H)$^+$], PMR, CMR, 2D NMR (^1H-^1H COSY, HMQC-TOCSY, HMBC); amino acid analysis after acid hydrolysis.		187
	(whole plants)	(**265**)	Cyclo-(Pro-Pro-Phe-Phe-Val-Ile-Ala-Phe-Leu)	$C_{57}H_{77}N_9O_9$; 2.2×10^{-4}%, white crystals, mp 154-156, $[\alpha]_D^{26}$ –127.7° (CH_3OH, c 0.37); IR, pos. FAB-MS[1033(M+2H)$^+$], PMR, CMR, 2D NMR (^1H-^1H COSY, HMQC-TOCSY, HMBC, ROESY).		188
	(whole plants)	Diandrine A (**266**)	Cyclo-(*L*-Pro^2-*L*-Trp^3-*L*-Pro^4-*L*-Tyr^5-*L*-Phe^6-Gly^1)	$C_{41}H_{43}N_7O_7$; 7.5×10^{-5}%, pale yellow powder, $[\alpha]_D^{26}$ –67.6° (CH_3OH, c 0.14); CD, IR, UV, pos. FAB-MS[748(M+H)$^+$], PMR, CMR, 2D NMR (COSY, TOCSY, HMBC, ROESY); absolute configuration (HPLC); solution conformation (NMR, CD).	antiplatelet	189
	(whole plants)	Diandrine B (**267**)	Cyclo-(*L*-Pro^2-*L*-Leu^3-*L*-Pro^4-*L*-Leu^5-*L*-Trp^6-*L*-Ser^7-*L*-Ser^8-Gly^1)	$C_{41}H_{59}N_9O_{10}$; 4.2×10^{-5}%, pale yellow powder, $[\alpha]_D^{27}$ –66.2° (CH_3OH, c 0.04); CD, IR, UV, pos. FAB-MS[838(M+H)$^+$], PMR, CMR, 2D NMR (TOCSY, HMBC, ROESY); absolute configuration (CD); solution conformation (NMR, CD).		189
	(whole plants)	Diandrine C (**268**)	Cyclo-(*L*-Pro^3-*L*-Tyr^4-*L*-Trp^5-*L*-Pro^6-Gly^1-Gly^2)	$C_{34}H_{39}N_7O_7$; 4.0×10^{-4}%, pale yellow powder, $[\alpha]_D^{26}$ +2.2° (CH_3OH, c 0.19); CD, IR, UV, pos. FAB-MS[658(M+H)$^+$], PMR, CMR, 2D NMR (TOCSY, HMBC, ROESY); absolute configuration (CD); solution conformation (NMR, CD).		189
	(whole plants)	Diandrine D (**269**)	Cyclo-(*L*-Pro^3-*L*-Tyr^4-*L*-Trp^5-*L*-Pro^6-Gly^1-Gly^2)	$C_{34}H_{39}N_7O_7$; 8.5×10^{-5}%, pale yellow powder, $[\alpha]_D^{26}$ +6.8° (CH_3OH, c 0.19); CD, IR, UV, pos. FAB-MS[658(M+H)$^+$], PMR, CMR, 2D NMR (TOCSY, HMBC, ROESY); absolute configuration (CD); solution conformation (NMR, CD).		189
17	*Goniothalamus griffithii* (Annonaceae) (stems)	Grifficyclocin A (**270**)	Cyclo-(Pro^1-Ile-Phe-Pro^2-Pro^3-Gly-Leu-Pro^4)	$C_{43}H_{62}N_8O_8$; 5.0×10^{-4}%, needles, $[\alpha]_D^{20}$ –132° (CH_3OH, c 0.12); IR, UV, pos. FAB-MS[819(M+H)$^+$], PMR, CMR, 2D NMR (^1H-^1H COSY, HMQC-TOCSY, HMBC, ROESY); amino acid analysis after acid hydrolysis.		190
18	*G. leiocarpus* (seeds)	Leiocyclocin A (**271**)	Cyclo-(Pro-Gln-Ile-Gly-Leu-Phe-Ser-Ala)	$C_{39}H_{59}N_9O_{10}$; 9.8×10^{-3}%, needles; pos. FAB-MS[814(M+H)$^+$], PMR, CMR, 2D NMR (HMQC-TOCSY, HMBC); amino acid analysis after acid hydrolysis.		191
	(seeds)	Leiocyclocin B (**272**)	Cyclo-(Pro^1-Pro^3-Ala^2-Pro^2-Trp-Val-Ala^1-Leu)	$C_{43}H_{61}N_9O_8$; 8.8×10^{-3}%, needles; pos. FAB-MS[832(M+H)$^+$], PMR, CMR, 2D NMR (HMQC-TOCSY, HMBC); amino acid analysis after acid hydrolysis.		191
	(seeds)	Leiocyclocin C (**273**)	Cyclo-(Pro^1-Pro^3-Gly^1-Ser-Pro^2-Tyr^2-Gly^2-Tyr^1)	$C_{40}H_{50}N_8O_{11}$; needles; pos. FAB-MS[819(M+H)$^+$], PMR, CMR, 2D NMR (HMQC-TOCSY, HMBC, ROESY).		192
	(seeds)	Leiocyclocin D (**274**)	Cyclo-(Pro^2-Gly^1-Leu-Pro^1-Gly^2-Phe-Tyr)	$C_{38}H_{49}N_7O_8$;		192

Table 8 (Continued)

No.	Source (family, part)	Cyclopeptide (No.) (synonym)	Structure*	Structural and spectral data	Bioactivity	Reference
				4.9×10^{-4}%, amorphous solids; pos. FAB-MS[731(M)$^+$], PMR, CMR, 2D NMR (HMQC-TOCSY, HMBC).		
19	*Jatropha chevalieri* (Euphorbiaceae) (latex)	Chevalierin A (**275**)	Cyclo-(*L*-Pro^3-*L*-Ile^4-*L*-Leu^5-*L*-Ala^6-*L*-Ile^7-*L*-Met^8-Gly^1-*L*-Ile^2)	$C_{39}H_{68}N_8O_8S$; $[\alpha]_D^{22}$ –13° (CH_3OH, c 0.18); pos. LSI-MS[809(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, TOCSY, HOHAHA, *J*-modulated ^{13}C, HMQC, HMBC, ROESY); amino acid analysis after acid hydrolysis, oxidation, absolute configuration (chiral GC), solid-phase synthesis.	antimalarial	193
	(latex)	Chevalierin B (**276**)	Cyclo-(*L*-Pro^3-*L*-Ile^4-*L*-Leu^5-*L*-Ala^6-*L*-Ile^7-*L*-OMet^8-Gly^1-*L*-Ile^2)	$C_{39}H_{68}N_8O_9S$; $[\alpha]_D^{22}$ –11° (CH_3OH, c 0.33); pos. LSI-MS[825(M+H)$^+$], PMR, CMR, 2D NMR (COSY, HOHAHA, HMQC, HMBC); amino acid analysis after acid hydrolysis, absolute configuration (chiral GC), solid-phase synthesis.		193
	(latex)	Chevalierin C (**277**)	Cyclo-(*L*-Tyr^1-*L*-Thr^2-*L*-Ile^3-*L*-Phe^4-*L*-Asp^5-*L*-Ile^6-*L*-Phe^7-Gly^8-*L*-Ala^9)	$C_{52}H_{69}N_9O_{13}$; $[\alpha]_D^{22}$ –114° (CH_3OH, c 0.33); pos. LSI-MS[1028(M+H)$^+$], PMR, CMR, 2D NMR (COSY, TOCSY, HMQC, HMBC, ROESY); amino acid analysis after acid hydrolysis, absolute configuration (chiral GC), solid-phase synthesis.		193
20	*J. curcas* (latex)	Curcacycline A (**278**)	Cyclo-(Gly^1-Leu^2-Leu^3-Gly^4-Thr^5-Val^6-Leu^7-Leu^8)	$C_{37}H_{66}N_8O_9$; pos. FAB-MS[767(M+H)$^+$], PMR, 2D NMR (HOHAHA, ROESY); amino acid analysis after acid hydrolysis.	immunomodulating and inhibiting human T-cells proliferation	194
	(latex)	Curcacycline B (**279**)	Cyclo-(*L*-Pro^4-*L*-Ile^5-*L*-Leu^6-*L*-Leu^7-Gly^8-*L*-Ile^9-*L*-Leu^1-Gly^2-*L*-Ser^3)	$C_{42}H_{73}N_9O_{10}$; pos. LSI-MS[864(M+H)$^+$], PMR, CMR, 2D NMR (COSY, TOCSY, *J*-modulated ^{13}C, HMQC, HMBC, ROESY); amino acid analysis after acid hydrolysis, absolute configuration (chiral GC).	enhancing rotamase activity of human cyclophilin B	195
21	*J. gossypifolia* (latex)	Cyclogossine A (**280**)	Cyclo-(*L*-Leu^1-*L*-Ala^2-*L*-Thr^3-*L*-Trp^4-*L*-Leu^5-Gly^6-*L*-Val^7)	$C_{37}H_{56}N_8O_8$; pos. FAB-MS[741(M+H)$^+$], PMR, 2D NMR (TOCSY, ROESY); amino acid analysis after acid hydrolysis, absolute configuration (chiral GC).		196
	(latex)	Cyclogossine B (**281**)	Cyclo-(Gly^1-Gly^2-*L*-Trp^3-*L*-Leu^4-*L*-Ala^5-*L*-Ala^6-*L*-Ile^7-*L*-Leu^8)	$C_{39}H_{59}N_9O_8$; colorless amorphous solids, $[\alpha]_D^{22}$ –9° (CH_3OH, c 0.1); pos. LSI-MS[782(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, HOHAHA, *J*-modulated ^{13}C, HMQC, HMBC, ROESY); amino acid analysis after acid hydrolysis, absolute configuration (chiral GC).		197
22	*J. mahafalensis* (latex)	Mahafacyclin A (**282**)	Cyclo-(Gly^1-*L*-Thr^2-*L*-Ile^3-*L*-Leu^4-Gly^5-*L*-Val^6-*L*-Phe^7)	$C_{34}H_{57}N_7O_8$; pos. LSI-MS[688(M+H)$^+$], PMR, CMR, 2D NMR (COSY, TOCSY, *J*-modulated ^{13}C, HMQC, HMBC, ROESY); amino acid analysis after acid hydrolysis, absolute configuration (chiral GC); solution conformation (NMR).	antimalarial	198
	(latex)	Mahafacyclin B (**283**)	Cyclo-(Gly^1-*L*-Thr^2-*L*-Phe^3-*L*-Phe^4-Gly^5-*L*-Phe^6-*L*-Phe^7)	$C_{44}H_{49}N_7O_8$; pos. LSI-MS[804(M+H)$^+$], PMR, CMR, 2D NMR (COSY, TOCSY, *J*-modulated ^{13}C, HMQC, HMBC, ROESY); amino acid analysis after acid hydrolysis, absolute configuration (chiral GC); solution conformation (NMR), solid-phase synthesis.	antimalarial	199
23	*J. multifida* (latex)	Labaditin (**284**)	Cyclo-(Ala^1-Gly^7-Val^8-Trp^2-Thr^{10}-Val^5-Trp^6-Gly^9-Thr^3-Ile^4)	$C_{53}H_{74}N_{12}O_{12}$; pos. FAB-MS[1071(M+H)$^+$], PMR, 2D NMR (COSY, NOESY); amino acid analysis after acid hydrolysis.	immunomodulating	200
24	*J. podagrica* (latex)	Podacyclin A (**285**)	Cyclo-(Gly^1-*L*-Leu^2-*L*-Leu^3-Gly^4-*L*-Ala^5-*L*-Val^6-*L*-Trp^7-*L*-Ala^8-Gly^9)	$C_{40}H_{60}N_{10}O_9$; pos. FAB-MS[825(M+H)$^+$], PMR, 2D NMR (HOHAHA, ROESY); amino acid analysis after acid hydrolysis, absolute configuration (chiral GC).		201
	(latex)	Podacyclin B (**286**)	Cyclo-(*L*-Phe^1-*L*-Ala^2-Gly^3-*L*-Thr^4-*L*-Ile^5-*L*-Phe^6-Gly^7)	$C_{35}H_{47}N_7O_8$; pos. FAB-MS[694(M+H)$^+$], PMR, 2D NMR (HOHAHA, ROESY); amino acid analysis after acid hydrolysis, absolute configuration (chiral GC).		201
25	*J. pohliana* ssp. *molissima* (latex)	Pohlianin A (**287**)	Cyclo-(*L*-Pro^2-*L*-Leu^3-Gly^4-*L*-Val^5-*L*-Leu^6-*L*-Leu^7-*L*-Tyr^1)	$C_{39}H_{61}N_7O_8$; $[\alpha]_D^{22}$ –122° (CH_3OH, c 0.20); pos. LSI-MS[756(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, TOCSY, *J*-modulated ^{13}C, HMQC, HMBC, ROESY); amino acid analysis after acid hydrolysis, absolute configuration (chiral GC); solution conformation (NMR).	antimalarial	202
	(latex)	Pohlianin B (**288**)	Cyclo-(*L*-Pro^2-*L*-Leu^3-Gly^4-*L*-Leu^5-*L*-Leu^6-*L*-Leu^7-*L*-Tyr^1)	$C_{40}H_{63}N_7O_8$; $[\alpha]_D^{22}$ –120° (CH_3OH, c 0.20); pos. LSI-MS[770(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, TOCSY, *J*-modulated ^{13}C, HMQC, HMBC, ROESY); amino acid analysis after acid hydrolysis, absolute configuration (chiral GC).	antimalarial	202
	(latex)	Pohlianin C (**289**)	Cyclo-(Gly^1-Gly^2-*L*-Thr^3-*L*-Ile^4-*L*-Ile^5-*L*-Phe^6-Gly^7-*L*-Phe^8)	$C_{40}H_{56}N_8O_9$; $[\alpha]_D^{22}$ –38° (CH_3OH, c 0.20); pos. LSI-MS[793(M+H)$^+$], PMR, CMR, 2D NMR (COSY, TOCSY, HMQC, HMBC, ROESY); amino acid analysis after acid hydrolysis, absolute configuration (chiral GC), solution conformation (NMR).	antimalarial	202
26	*Leonurus artemisia* *L. sibiricus* (Labiatae) (fruits) *L. heterophyllus* (fruits)	Cycloleonurinin (**290**)	Cyclo-(*L*-Pro^2-*L*-Pro^3-*L*-Tyr^1-*L*-Tyr^2-*L*-Thr^1-*L*-Pro^4-*L*-Ala-Gly-*L*-Pro^1-*L*-Thr^2-*L*-Gln-*L*-Tyr^3)	$C_{65}H_{85}N_{13}O_{18}$; 8.0×10^{-3}%, white powder, mp 222-225, $[\alpha]_D$ –28.8° (CH_3OH, c 0.79); IR, UV, pos. FAB-MS[1336(M+H)$^+$], FAB MS/MS, PMR, CMR, 2D NMR (DEPT, ^{1}H-^{1}H COSY, ^{13}C-^{1}H COSY, ^{13}C-^{1}H long-range COSY, NOESY); elemental analysis, amino acid analysis after acid hydrolysis, enzymatic hydrolysis with α-chymotrypsin, absolute configuration (amino acid oxidase), solution conformation (NMR).	immunosuppressive	203,204,248
27	*L. heterophyllus* (fruits)	Cycloleonuripeptide A (**291**)	Cyclo-(*L*-Pro^2-*L*-Pro^3-*L*-Pro^4-*L*-Tyr^5-*L*-Pro^6-*L*-Pro^7-*L*-Met^8-*L*-Ile^9-Gly^1)	$C_{47}H_{67}N_9O_{10}S$; 3.5×10^{-3}%, colorless needles, mp 216-218, $[\alpha]_D$ –175.0° (CH_3OH, c 0.36); IR, pos. FAB-MS[950(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, HMQC, NOESY); amino acid analysis after acid hydrolysis, absolute configuration (HPLC), solution conformation (NMR).		204,249

Table 8 (Continued)

No.	Source (family, part)	Cyclopeptide (No.) (synonym)	Structure*	Structural and spectral data	Bioactivity	Reference
	(fruits)	Cycloleonuripeptide B (**292**)	Cyclo-(*L*-Pro^2-*L*-Pro^3-*L*-Pro^4-*L*-Tyr^5-*L*-Pro^6-*L*-Pro^7-*L*-OMet^8-*L*-Ile^9-Gly^1)	$C_{47}H_{67}N_9O_{11}S$; 2.0×10^{-3}%, colorless powder, $[\alpha]_D$ –153.6° (CH_3OH, c 0.98); IR, UV, pos. FAB-MS[966(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, HMQC, NOESY); amino acid analysis after acid hydrolysis, absolute configuration (HPLC), solution conformation (NMR).	cytotoxic	204,249
	(fruits)	Cycloleonuripeptide C (**293**)	Cyclo-(*L*-Pro^2-*L*-Pro^3-*L*-Pro^4-*L*-Tyr^5-*L*-Pro^6-*L*-Pro^7-*L*-OMet^8-*L*-Ile^9-Gly^1)	$C_{47}H_{67}N_9O_{11}S$; 1.2×10^{-3}%, colorless powder, $[\alpha]_D$ –170.5° (CH_3OH, c 0.60); IR, UV, pos. FAB-MS[966(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, HMQC, NOESY); amino acid analysis after acid hydrolysis, absolute configuration (HPLC), solution conformation (NMR).	cytotoxic	204,249
	(fruits)	Cycloleonuripeptide D (**294**)	Cyclo-(*L*-Pro^2-*L*-Pro^3-*L*-Pro^4-*L*-Tyr^5-*L*-Phe^6-*L*-Gln^7-*L*-Thr^8-*L*-Pro^9-*L*-Ile^{10}-*L*-Ser^1)	$C_{56}H_{77}N_{11}O_{14}$; 2.0×10^{-3}%, colorless needles, mp 200-202, $[\alpha]_D$ –99.0° (CH_3OH, c 0.21); IR, UV, pos. FAB-MS[1128(M+H)$^+$], ESI MS/MS, PMR, CMR, 2D NMR (HOHAHA, DQF-COSY, HMQC, NOESY); amino acid analysis after acid hydrolysis, enzymatic hydrolysis with α-chymotrypsin, methylation, absolute configuration (HPLC); solid conformation (x-ray).	inhibiting cyclooxygenase	205
28	*Linum usitatissimum* (Linaceae) (seeds)	Cyclolinopeptide A (**295**)	Cyclo-(*L*-Pro^1-*L*-Pro^2-*L*-Phe^3-*L*-Phe^4-*L*-Leu^5-*L*-Ile^6-*L*-Ile^7-*L*-Leu^8-*L*-Val^9)	$C_{57}H_{88}N_9O_9$; 7.0×10^{-3}%, colorless needles, mp 243, $[\alpha]_D$ –111.1° (CH_3OH, c 0.23); IR, UV, pos. FAB-MS[1040(M+H)$^+$]; amino acid analysis after acid hydrolysis, solution and solid conformation (NMR, x-ray).	immunosuppressive	206,207,250,251
	(seeds)	Cyclolinopeptide B (**296**)	Cyclo-(*L*-Pro^1-*L*-Pro^2-*L*-Phe^3-*L*-Phe^4-*L*-Val^5-*L*-Ile^6-*L*-Met^7-*L*-Leu^8-*L*-Ile^9)	$C_{56}H_{83}N_9O_9S$; 4.0×10^{-4}%, colorless powder, $[\alpha]_D$ –104.1° (CH_3OH, c 0.20); IR, UV, pos. FAB-MS[1058(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, HMQC, HMBC, ROESY); amino acid analysis after acid hydrolysis, absolute configuration (HPLC), solution conformation (NMR).	immunosuppressive	206,251
	(seeds)	Cyclolinopeptide C (**297**)	Cyclo-(*L*-Pro^1-*L*-Pro^2-*L*-Phe^3-*L*-Phe^4-*L*-Val^5-*L*-Ile^6-*L*-OMet^7-*L*-Leu^8-*L*-Ile^9)	$C_{56}H_{83}N_9O_{10}S$; 3.0×10^{-3}%, colorless powder, $[\alpha]_D$ –109.7° (CH_3OH, c 0.21); IR, UV, pos. FAB-MS[1074(M+H)$^+$], PMR, CMR, 2D NMR (COSY, HMQC, HMBC, ROESY); amino acid analysis after acid hydrolysis, reduction, absolute configuration (HPLC).		206
	(seeds)	Cyclolinopeptide D (**298**)	Cyclo-(*L*-Pro^1-*L*-Phe^2-*L*-Phe^3-*L*-Trp^4-*L*-Ile^5-*L*-OMet^6-*L*-Leu^7-*L*-Leu^8)	$C_{57}H_{77}N_9O_9S$; 1.2×10^{-3}%, colorless powder, $[\alpha]_D$ –75.0° (CH_3OH, c 0.20); IR, UV, pos. FAB-MS[1064(M+H)$^+$], PMR, CMR, 2D NMR (HMBC, NOE); amino acid analysis after acid hydrolysis, reduction, absolute configuration (HPLC).		206
	(seeds)	Cyclolinopeptide E (**299**)	Cyclo-(*L*-Pro^1-*L*-Leu^2-*L*-Phe^3-*L*-Ile^4-*L*-OMet^5-*L*-Leu^6-*L*-Val^7-*L*-Phe^8)	$C_{51}H_{76}N_8O_9S$; 2.0×10^{-4}%, colorless powder, $[\alpha]_D$ –75.5° (CH_3OH, c 0.20); IR, UV, pos. FAB-MS[977(M+H)$^+$], PMR, CMR, 2D NMR (HMBC, NOE); amino acid analysis after acid hydrolysis, reduction, absolute configuration (HPLC).	immunosuppressive	206
	(seeds)	Cyclolinopeptide F (**300**)	Cyclo-(*L*-Pro^1-*L*-Phe^2-*L*-Phe^3-*L*-Trp^4-*L*-Val^5-*L*-OMet^6-*L*-Leu^7-*L*-OMet^8)	$C_{55}H_{73}N_9O_{10}S_2$; 8.0×10^{-4}%, colorless powder, $[\alpha]_D$ –71.4° (CH_3OH, c 0.21); IR, UV, pos. FAB-MS[1084(M+H)$^+$], PMR, CMR, 2D NMR (HMBC, NOE); amino acid analysis after acid hydrolysis, reduction, absolute configuration (HPLC).		207
	(seeds)	Cyclolinopeptide G (**301**)	Cyclo-(*L*-Pro^1-*L*-Phe^2-*L*-Phe^3-*L*-Trp^4-*L*-Ile^5-*L*-OMet^6-*L*-Leu^7-*L*-OMet^8)	$C_{56}H_{75}N_9O_{10}S_2$; 2.4×10^{-3}%, colorless powder, $[\alpha]_D$ –66.6° (CH_3OH, c 0.20); IR, UV, pos. FAB-MS[1098(M+H)$^+$], PMR, CMR, 2D NMR (HMBC, NOE); amino acid analysis after acid hydrolysis, reduction, absolute configuration (HPLC).		207
	(seeds)	Cyclolinopeptide H (**302**)	Cyclo-(*L*-Pro^1-*L*-Phe^2-*L*-Phe^3-*L*-Trp^4-*L*-Ile^5-*L*-OMet^6-*L*-Leu^7-*L*-Met^8)	$C_{56}H_{73}N_9O_9S_2$; 2.0×10^{-4}%, colorless powder, $[\alpha]_D$ –87.7° (CH_3OH, c 0.15); IR, UV, pos. FAB-MS[1082(M+H)$^+$], PMR, CMR, 2D NMR (HMBC, NOE); amino acid analysis after acid hydrolysis, reduction, absolute configuration (HPLC).		207
	(seeds)	Cyclolinopeptide I (**303**)	Cyclo-(*L*-Pro^1-*L*-Phe^2-*L*-Phe^3-*L*-Trp^4-*L*-Val^5-*L*-Met^6-*L*-Leu^7-*L*-OMet^8)	$C_{55}H_{73}N_9O_9S_2$; 7.0×10^{-5}%, colorless powder, $[\alpha]_D$ –60.6° (CH_3OH, c 0.20); IR, UV, pos. FAB-MS[1068(M+H)$^+$], PMR, CMR, 2D NMR (HMBC, NOE); amino acid analysis after acid hydrolysis, reduction, absolute configuration (HPLC).		207
29	*Microtoena prainiana* (Labiatae) (stems)	Microtoenin A (**304**)	Cyclo-(*L*-Pro^1-*L*-Val^1-*L*-Ala-*L*-Phe-*L*-Pro^2-*L*-Val^2-*L*-Leu-*L*-Tyr)	$C_{47}H_{66}N_8O_9$; 2.6×10^{-4}%, white amorphous powder, mp 280-282, $[\alpha]_D^{20}$ –104.8° (CH_3OH, c 0.23); IR, UV, ESI-MS[887(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, TOCSY, HSQC, HMBC, NOESY), MS/MS; amino acid analysis after acid hydrolysis, absolute configuration (HPLC).		208
	(stems)	Microtoenin B (**305**)	Cyclo-(*L*-Pro-*L*-Val-*L*-Phe^2-*L*-Phe^1-*L*-Ala^2-*L*-Ala^1-Gly-*L*-Phe^3)	$C_{45}H_{58}N_8O_8$; 1.4×10^{-4}%, white amorphous powder, mp 288-290, $[\alpha]_D^{20}$ –68.3° (CH_3OH, c 0.12); IR, UV, ESI-MS[859(M+Na)$^+$], PMR, CMR, 2D NMR (TOCSY, HSQC, HMBC, NOESY), MS/MS; amino acid analysis after acid hydrolysis, absolute configuration (HPLC).		208
	(stems)	Microtoenin C (**306**)	Cyclo-(*L*-Pro^1-*L*-Ile-*L*-Pro^3-*L*-Leu-*L*-Pro^2-*L*-Phe-*L*-Asn-*L*-Tyr)	$C_{49}H_{67}N_9O_{10}$; 2.6×10^{-4}%, white amorphous powder, mp 256-258, $[\alpha]_D^{20}$ –93.8° (CH_3OH, c 0.13); IR, UV, ESI-MS[964(M+Na)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, TOCSY, HSQC, HMBC, NOESY), MS/MS; amino acid analysis after acid hydrolysis, absolute configuration (HPLC).		208
30	*Panax notoginseng* (Araliaceae) (roots)	(**307**)	Cyclo-(Leu-Thr)	$C_{10}H_{18}N_2O_3$; needles, mp 280-282; pos. FAB-MS[215(M+H)$^+$], PMR, CMR.		209
	(roots)	(**308**)	Cyclo-(Leu-Ile)	$C_{12}H_{22}N_2O_2$; pos. FAB-MS[227(M+H)$^+$], PMR, CMR, 2D NMR (DEPT, COSY, HMQC, HMBC).		209
	(roots)	(**309**)	Cyclo-(Leu-Val)	$C_{11}H_{20}N_2O_2$; pos. FAB-MS[213(M+H)$^+$], PMR, CMR, 2D NMR (DEPT, COSY, HMQC, HMBC).		209
	(roots)	(**310**)	Cyclo-(Ile-Val)	$C_{11}H_{20}N_2O_2$;		209

Table 8 (Continued)

No.	Source (family, part)	Cyclopeptide (No.) (synonym)	Structure*	Structural and spectral data	Bioactivity	Reference
				pos. FAB-MS[213(M+H)$^+$], PMR, CMR, 2D NMR (DEPT, COSY, HMQC, HMBC).		
	(roots)	(**311**)	Cyclo-(Leu-Ser)	$C_9H_{16}N_2O_3$; needles, mp 240-242; IR, pos. FAB-MS[201(M+H)$^+$], PMR, CMR, 2D NMR (DEPT, COSY, HMQC, HMBC).		209
	(roots)	(**312**)	Cyclo-(Leu-Tyr)	$C_{15}H_{20}N_2O_3$; needles, mp 260-262; IR, UV, pos. FAB-MS[279(M+3H)$^+$], PMR, CMR, 2D NMR (DEPT, COSY, HMQC, HMBC).		209
	(roots)	(**313**)	Cyclo-(Pro-Val)	$C_{10}H_{16}N_2O_2$; needles, mp 145-147; IR, pos. FAB-MS[197(M+H)$^+$], PMR, CMR.		209
	(roots)	(**314**)	Cyclo-(Pro-Ala)	$C_8H_{12}N_2O_2$; needles, mp 170-172; IR, pos. FAB-MS[169(M+H)$^+$], PMR, CMR.		209
	(roots)	(**315**)	Cyclo-(Phe-Tyr)	$C_{18}H_{18}N_2O_3$; needles, mp 291-293; IR, UV, pos. FAB-MS[310(M)$^+$], PMR, CMR.		209
	(roots)	(**316**)	Cyclo-(Phe-Ala)	$C_{12}H_{14}N_2O_2$; pos. FAB-MS[218(M)$^+$], PMR, CMR, 2D NMR (DEPT, COSY, HMQC, HMBC).		209
31	*Phytolacca polyandra* (Phytolaccaceae) (roots)	(**317**)	Cyclo-(Pro-Tyr)	$C_{14}H_{16}N_2O_3$; 1.4×10^{-5}%, white powder; IR, pos. FAB-MS[261(M+H)$^+$], PMR, CMR, 2D NMR (COSY, HMBC).		210
32	*Polycarpon prostratum* (Caryophyllaceae) (whole plants)	Polycarponin A (**318**)	Cyclo-(Pro^2-Pro^1-Gly-Phe^1-Phe^2-Ala^1-Ile^1-Ala^2-Ile^2)	$C_{48}H_{67}N_9O_9$; colorless needles; IR, pos. FAB-MS[914(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, HMQC, HMBC).		211
	(whole plants)	Polycarponin B (**319**)	Cyclo-(Pro-Gly^1-Ile-Val^1-Leu^1-Val^2-Gly^2-Leu^2)	$C_{37}H_{64}N_8O_8$; 3.0×10^{-4}%, colorless needles, mp 182-184, $[\alpha]_D^{26}$ −87.9° (CH_3OH, c 0.44); IR, pos. FAB-MS[749(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, HMQC, HMBC).		212
	(whole plants)	Polycarponin C (**320**)	Cyclo-(Pro^1-Thr-Leu^1-Pro^2-Pro^3-Val-Leu^2-Phe)	$C_{45}H_{68}N_8O_9$; 1.0×10^{-3}%, colorless needles, mp 183-186, $[\alpha]_D^{25}$ −124.8° (CH_3OH, c 0.57); IR, pos. FAB-MS[865(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, HMBC, NOESY); amino acid analysis after acid hydrolysis.		212
33	*Psammosilene tunicoides* (Caryophyllaceae) (roots)	(**321**)	Cyclo-(Ala-Ala)	$C_6H_{10}N_2O_2$; 6.8×10^{-5}%, colorless needles, mp 206-208; IR, EI-MS[142(M)$^+$], PMR, CMR.		213
	(roots) *Panax notoginseng* (Araliaceae) (roots)	(**322**)	Cyclo-(Ala-Val)	$C_8H_{14}N_2O_2$; 4.8×10^{-5}%, colorless needles, mp 177-179; IR, EI-MS[170(M)$^+$], PMR, CMR.		209,213
	(roots) *Panax notoginseng* (Araliaceae) (roots) *Phytolacca polyandra* (Phytolaccaceae) (roots)	(**323**)	Cyclo-(Ala-Leu)	$C_9H_{16}N_2O_2$; pos. FAB-MS[185(M+H)$^+$], PMR, CMR, 2D NMR (DEPT, ^{1}H-^{1}H COSY, ^{13}C-^{1}H COSY, HMBC).		208,210,213
	(roots) *Panax notoginseng* (Araliaceae) (roots) *Phytolacca polyandra* (Phytolaccaceae) (roots)	(**324**)	Cyclo-(Ala-Ile)	$C_9H_{16}N_2O_2$; pos. FAB-MS[185(M+H)$^+$], PMR, CMR, 2D NMR (DEPT, ^{1}H-^{1}H COSY, ^{13}C-^{1}H COSY, HMBC).		209,210,213
	(roots)	Psammosilenin A (**325**)	Cyclo-(Pro^1-Phe^1-Pro^2-Phe^2-Phe^3-Ala-Pro^3-Leu)	$C_{51}H_{64}N_8O_8$; 4.0×10^{-5}%, white powder, $[\alpha]_D^{24}$ −108.14° (CH_3OH, c 0.39); IR, pos. FAB-MS[917(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, HMQC, HMBC).		214
	(roots)	Psammosilenin B (**326**)	Cyclo-(Pro^1-Gly-Phe^1-Val-Pro^2-Phe^2-Thr-Ile)	$C_{45}H_{62}N_8O_9$; 2.4×10^{-5}%, white powder, $[\alpha]_D^{24}$ −73.6° (CH_3OH, c 0.023); IR, pos. FAB-MS[859(M+H)$^+$], PMR, CMR, 2D NMR (TOCSY, DQF-COSY, HMQC, ROESY).		214
34	*Pseudostellaria heterophylla* (Caryophyllaceae) (roots)	Heterophyllin A (**327**)	Cyclo-(Pro-Val-Ile^1-Phe-Gly-Ile^2-Thr)	$C_{37}H_{57}N_7O_8$; 1.5×10^{-3}%, needles, mp 225-227, $[\alpha]_D^{19}$ −70.0° (CH_3OH, c 0.1); IR, UV, neg. FAB-MS[726(M-H)$^-$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, ^{13}C-^{1}H COSY, ^{1}H-^{1}H relayed COSY, ^{13}C-^{1}H relayed COSY, COLOC); amino acid analysis after acid hydrolysis, enzymatic hydrolysis with α-chymotrypsin and sequence determination.		215
	(roots)	Heterophyllin B (**328**)	Cyclo-(Pro^1-Pro^2-Pro^3-Ile-Phe-Gly^1-Gly^2-Leu)	$C_{40}H_{58}N_8O_8$; 4.9×10^{-3}%, needles, mp 234.5-236.5, $[\alpha]_D^{18}$ −130.0° (CH_3OH, c 0.1); IR, UV, neg. FAB-MS[777(M-H)$^-$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, ^{13}C-^{1}H COSY, ^{1}H-^{1}H relayed COSY, ^{13}C-^{1}H relayed COSY, COLOC); amino acid analysis after acid hydrolysis, enzymatic hydrolysis with α-chymotrypsin and sequence determination.		215
	(roots)	Heterophyllin C (**329**)	Cyclo-(Pro^1-Ile^3-Ile^1-Pro^2-Ile^2-Leu-Gly)	$C_{36}H_{61}N_7O_7$, MW=703.		216
	(roots)	Heterophyllin J (**330**)	Cyclo-(Pro^3-Val^4-Tyr^5- Ala^1-Gly^2)	$C_{24}H_{33}N_5O_6$; yellow amorphous powder; neg. FAB-MS[486(M-H)$^-$], PMR, CMR, 2D NMR (DEPT, ^{1}H-^{1}H COSY, HMQC, HMBC, ROESY).		217
	(roots) *Stellaria yunnanensis* (Caryophyllaceae) (roots)	Pseudostellarin A (**331**)	Cyclo-(*L*-Pro-*L*-Tyr-*L*-Leu-*L*-Ala-Gly)	$C_{25}H_{35}N_5O_6$; 2.5×10^{-3}%, colorless needles, mp 151-153, $[\alpha]_D$ −118.7° (CH_3OH, c 0.92); IR, UV, pos. FAB-MS[502(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, HMQC, HMBC, NOESYPH); amino acid analysis after acid hydrolysis, absolute configuration (HPLC), solution conformation (NMR).	inhibiting tyrosinase	218,236,252
	(roots)	Pseudostellarin B (**332**)	Cyclo-(*L*-Pro^1-*L*-Pro^2-*L*-Phe-Gly^1-*L*-Ile-Gly^2-Gly^3-Gly^4)	$C_{33}H_{46}N_8O_8$; 6.0×10^{-3}%, colorless needles, mp 167-169, $[\alpha]_D$ −54.5° (CH_3OH, c 0.32); IR, UV, pos. FAB-MS[683(M+H)$^+$], ESI MS/MS, PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, HMQC, NOESYPH); amino acid analysis after acid hydrolysis, enzymatic	inhibiting tyrosinase	218

Table 8 (Continued)

No.	Source (family, part)	Cyclopeptide (No.) (synonym)	Structure*	Structural and spectral data	Bioactivity	Reference
				hydrolysis with α-chymotrypsin, absolute configuration (HPLC).		
	(roots)	Pseudostellarin C (**333**)	Cyclo-(*L*-Pro^1-*L*-Ser-*L*-Pro^2-*L*-Phe-*L*-Leu^2-Gly-*L*-Thr-*L*-Leu^1)	$C_{40}H_{60}N_8O_{10}$; 4.5×10^{-3}%, colorless needles, mp 185-187, $[\alpha]_D$ −39.1° (CH_3OH, c 0.52); IR, UV, pos. FAB-MS[813(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, HMQC, HMBC, NOESYPH); amino acid analysis after acid hydrolysis, absolute configuration (HPLC).	inhibiting tyrosinase and melanogenesis	218
	(roots)	Pseudostellarin D (**334**)	Cyclo-(*L*-Pro^4-*L*-Leu^5-*L*-Ile^6-*L*-Leu^7-Gly^1-*L*-Tyr^2-Gly^3)	$C_{36}H_{55}N_7O_8$; 4.0×10^{-3}%, colorless needles, mp 177-179, $[\alpha]_D$ −64.8° (CH_3OH, c 0.54); IR, UV, pos. FAB-MS[714(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, HMQC, HMBC, NOESYPH); amino acid analysis after acid hydrolysis, absolute configuration (HPLC), solution and solid conformation (NMR, x-ray).	inhibiting tyrosinase	219,253
	(roots)	Pseudostellarin E (**335**)	Cyclo-(*L*-Pro-*L*-Pro-*L*-Leu-Gly-*L*-Pro-*L*-Val-*L*-Ile-*L*-Phe-Gly)	$C_{45}H_{67}N_9O_9$; 8.5×10^{-3}%, colorless needles, mp 168-170, $[\alpha]_D$ −112.1° (CH_3OH, c 0.33); IR, UV, pos. FAB-MS[878(M+H)$^+$], ESI MS/MS; amino acid analysis after acid hydrolysis, enzymatic hydrolysis with α-chymotrypsin, absolute configuration (HPLC).	inhibiting tyrosinase	219
	(roots)	Pseudostellarin F (**336**)	Cyclo-(*L*-Pro^1-*L*-Pro^2-*L*-Leu^2-*L*-Ser-Gly^1-Gly^2-*L*-Tyr-*L*-Leu^1)	$C_{38}H_{56}N_8O_{10}$; 1.3×10^{-3}%, colorless needles, mp 169-171, $[\alpha]_D$ −58.9° (CH_3OH, c 0.98); IR, UV, pos. FAB-MS[785(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, HMQC, HMBC, NOESYPH); amino acid analysis after acid hydrolysis, absolute configuration (HPLC).	inhibiting tyrosinase	219
	(roots)	Pseudostellarin G (**337**)	Cyclo-(*L*-Pro^1-*L*-Phe^1-*L*-Ser-*L*-Phe^2-Gly-*L*-Pro^2-*L*-Leu-*L*-Ala)	$C_{42}H_{56}N_8O_9$, MW=816; 1.0×10^{-3}%, colorless needles, mp 265 (dec.), $[\alpha]_D$ −57.7° (CH_3OH, c 0.78); PMR, CMR, 2D NMR (DQF-COSY, HOHAHA, HMQC, HMBC, ROESY); amino acid analysis after acid hydrolysis, absolute configuration (HPLC).	inhibiting tyrosinase and melanogenesis	220
	(roots)	Pseudostellarin H (**338**)	Cyclo-(*L*-Pro^1-*L*-Thr^2-*L*-Pro^2-*L*-Leu-*L*-Phe^1-*L*-Phe^2-Gly-*L*-Thr^1)	$C_{44}H_{60}N_8O_{10}$; 6.0×10^{-5}%, colorless needles, mp 171-172, $[\alpha]_D$ −51.9° (CH_3OH, c 0.11); IR, pos. FAB-MS[861(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, HOHAHA, HMQC, HMBC, NOESYPH); amino acid analysis after acid hydrolysis, absolute configuration (HPLC).	inhibiting tyrosinase	221
35	*Schizandra chinensis* (Schizandraceae) (fruits)	(**339**)	Cyclo-(Pro-Leu)	$C_{11}H_{18}N_2O_2$; 3.9×10^{-4}%, needles, mp 155-156, $[\alpha]_D^{11.7}$ −71.25° ($CHCl_3$, c 0.4); IR, EI-MS[210(M)$^+$], PMR, CMR.		222
	(fruits)	(**340**)	Cyclo-(Pro-Phe)	$C_{14}H_{16}N_2O_2$; 2.6×10^{-4}%, white powder, mp 138.5-139, $[\alpha]_D^{11.6}$ −192.59° ($CHCl_3$, c 0.135); IR, EI-MS[244(M)$^+$], PMR, CMR.	Ca^{2+} antagonism	222
	(fruits)	(**341**)	Cyclo-(Phe-Leu)	$C_{15}H_{20}N_2O_2$; 2.2×10^{-4}%, white powder, mp 261-263, $[\alpha]_D^{25}$ +21.0° (CH_3OH, c 0.6); IR, EI-MS[260(M)$^+$], PMR, CMR.		222
	(fruits) *Panax notoginseng* (Araliaceae) (roots)	(**342**)	Cyclo-(Phe-Val)	$C_{14}H_{18}N_2O_2$, MW=246; mixture; comparison with synthetic mixture in HPLC, EI.		209,222
	(fruits)	(**343**)	Cyclo-(Phe-Ile)	$C_{15}H_{20}N_2O_2$, MW=260; mixture; comparison with synthetic mixture in HPLC, EI.		222
	(fruits)	(**344**)	Cyclo-(Phe-Phe)	$C_{18}H_{18}N_2O_2$, MW=294; mixture; comparison with synthetic mixture in HPLC, EI.		222
36	*Schnabelia oligophylla* (Labitacae) (whole plants)	Schnabepeptide (**345**)	Cyclo-(Pro-*L*-Val-Pro-*L*-Ser-Gly-*L*-Ile-*L*-Val-*D*-Trp)	$C_{42}H_{61}N_9O_9$; 2.4×10^{-3}%, white amorphous powder, mp 208-210, $[\alpha]_D^{25}$ −120° (CH_3OH, c 0.43); IR, pos. FAB-MS[836(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, HMQC, HMBC, NOESY); amino acid analysis after acid hydrolysis, absolute configuration (chiral HPLC).	immunosuppressive	223
37	*Silene szechuensis* (Caryophyllaceae) (roots)	Silenin A (**346**)	Cyclo-(Pro^1-Leu^1-Ser-Phe-Pro^2-Tyr-Leu^2-Val)	$C_{48}H_{68}N_8O_{10}$; 6.3×10^{-4}%, white needles, mp 264-266, $[\alpha]_D^{20}$ −68.94° (C_5H_5N, c 0.359); IR, pos. FAB-MS[918(M+2H)$^+$], PMR, CMR, 2D NMR (DEPT, ^{1}H-^{1}H COSY, ^{1}H-^{13}C COSY, TOCSY, COLOC); amino acid analysis after acid hydrolysis.		224
	(roots)	Silenin B (**347**)	Cyclo-(Pro^1-Leu^2-Pro^2-Phe^2-Pro^3-Phe^1-Leu^1-Ala)	$C_{48}H_{66}N_8O_8$; 3.6×10^{-3}%, white amorphous powder, $[\alpha]_D^{20}$ −131.33° ($CHCl_3$, c 0.316); IR, pos. FAB-MS[883(M+H)$^+$], PMR, CMR, 2D NMR (DEPT, ^{1}H-^{1}H COSY, ^{1}H-^{13}C COSY, TOCSY, COLOC); amino acid analysis after acid hydrolysis.		224
	(roots)	Silenin C (**348**)	Cyclo-(Pro^1-Gly-Phe^2-Tyr^2-Pro^2-Tyr^1-Ala-Phe^1)	$C_{51}H_{58}N_8O_{10}$; 9.2×10^{-4}%, white amorphous powder, $[\alpha]_D^{20}$ −81.82° (CH_3OH, c 0.330); IR, pos. FAB-MS[943(M+H)$^+$], PMR, CMR, 2D NMR (DEPT, ^{1}H-^{1}H COSY, ^{1}H-^{13}C COSY, TOCSY, COLOC); amino acid analysis after acid hydrolysis.		224
38	*Stellaria crassipes* (Caryophyllaceae) (whole plants)	Crassipin B (**349**)	Cyclo-(Leu-Gly-Phe-Gly-Gly-Tyr-Ala)	$C_{33}H_{43}N_7O_8$; 7.5×10^{-4}%, pos. FAB-MS[665(M)$^+$]; amino acid analysis after acid hydrolysis.		180
39	*S. delavayi* (roots)	Stelladelin A (**350**)	Cyclo-(Pro-Pro-Pro-Leu^2-Leu^1-Gly^2-Pro-Pro-Tyr^1-Tyr^2-Gly^1)	$C_{59}H_{81}N_{11}O_{13}$; 9.0×10^{-4}%, amorphous powder, $[\alpha]_D^{19}$ −15.9° (CH_3OH, c 0.561); IR, UV, pos. FAB-MS[1152(M+H)$^+$], PMR, CMR, 2D NMR (TOCSY, DQF-COSY, HMQC, HMBC, NOESY); amino acid analysis after acid hydrolysis, enzymatic hydrolysis with α-chymotrypsin and sequence determination.		225
	(roots)	Stelladelin B (**351**)	Cyclo-(Pro^2-Pro^1-Ala-Tyr-Asp-Leu-Gly-Ile)	$C_{40}H_{58}N_8O_{11}$; 5.0×10^{-4}%, amorphous powder, $[\alpha]_D^{19}$ −81.4° (CH_3OH, c		225

Table 8 (Continued)

No.	Source (family, part)	Cyclopeptide (No.) (synonym)	Structure*	Structural and spectral data	Bioactivity	Reference
				0.842); IR, UV, pos. FAB-MS[827(M+H)$^+$], PMR, CMR, 2D NMR (TOCSY, DQF-COSY, HMQC, HMBC, NOESY); amino acid analysis after acid hydrolysis.		
	(roots)	Stelladelin C (**352**)	Cyclo-(Pro^3-Tyr^2-Pro^2-Pro^1-Phe-Tyr^1-Ser-Val)	$C_{50}H_{62}N_8O_{11}$; 5.0×10^{-6}%, amorphous powder, $[\alpha]_D^{21}$ –65.1° (C_5H_5N, c 0.515); IR, UV, pos. FAB-MS[951(M+H)$^+$], PMR, CMR, 2D NMR (TOCSY, DQF-COSY, HMQC, HMBC, ROESY); amino acid analysis after acid hydrolysis.		225
	(roots)	Stelladelin D (**353**)	Cyclo-(Pro^1-Ser-Pro^3-Tyr-Phe-Pro^2-Ala^2-Ala^1-Ile-Gly-Val)	$C_{55}H_{77}N_{11}O_{13}$; 1.5×10^{-6}%, amorphous powder; IR, pos. FAB-MS[1101(M+2H)$^+$], PMR, CMR, 2D NMR (TOCSY, DQF-COSY, HMQC, HMBC, NOESY); amino acid analysis after acid hydrolysis.		226
	(roots)	Delavayin A (**354**)	Cyclo-(Gly^1-*L*-Ser^2-*L*-γ-OH Ile^3-*L*-Phe^4-*L*-Phe^5-*L*-Ala^6)	$C_{32}H_{42}N_6O_8$; 1.1×10^{-6}%, colorless powder, $[\alpha]_D$ +17.2° (CH_3OH, c 0.19); IR, pos. FAB-MS[661(M+Na)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, HOHAHA, HMQC, HMBC, ROESY); amino acid analysis after acid hydrolysis, absolute configuration (HPLC).		227
	(roots)	Delavayin B (**355**)	Cyclo-(Gly^1-*L*-Ser^2-*L*-Ile^3-*L*-Phe^4-*L*-Phe^5-*L*-Ala^6)	$C_{32}H_{42}N_6O_7$; 3.5×10^{-6}%, colorless powder, $[\alpha]_D$ +6.0° (CH_3OH, c 0.20); IR, pos. FAB-MS[645(M+Na)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, HOHAHA, HMQC, HMBC, ROESY); amino acid analysis after acid hydrolysis, absolute configuration (HPLC).		227
	(roots)	Delavayin C (**356**)	Cyclo-(*L*-Pro^5-*L*-Val^6-*L*-Pro^7-Gly^1-*L*-Tyr^2-*L*-Tyr^3-*L*-Try^4)	$C_{44}H_{53}N_7O_{10}$; 4.0×10^{-5}%, colorless powder, $[\alpha]_D$ –52.4° (CH_3OH, c 0.08); IR, pos. FAB-MS[840(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, HOHAHA, HMQC, HMBC, ROESY); amino acid analysis after acid hydrolysis, absolute configuration (HPLC).		227
40	*S. dichotoma* var. *lanceolata* (roots)	Stellaria cyclopeptide (**357**)	Cyclo-(Tyr-Gly-Gly-Ala-Ala-Val)	$C_{24}H_{34}N_6O_7$; white needles, mp>300, $[\alpha]_D^{20}$ +0.151° (C_5H_5N, c 1.0); IR, UV, MS[518(M)$^+$], PMR, CMR, 2D NMR (^{13}C-^{1}H COSY); elemental analysis, amino acid analysis after acid hydrolysis.		228
	(roots)	Dichotomin A (**358**)	Cyclo-(Gly^1-*L*-Thr^2-*L*-Phe^3-*L*-Leu^4-*L*-Tyr^5-*L*-Val^6)	$C_{35}H_{48}N_6O_8$; 7.0×10^{-3}%, colorless needles, mp 179-180, $[\alpha]_D$ +14.0° (CH_3OH, c 0.10); IR, UV, pos. FAB-MS[681(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, HMQC, HMBC, ROESY); amino acid analysis after acid hydrolysis, absolute configuration (HPLC), solid conformation (x-ray).	cytotoxic	229
	(roots)	Dichotomin B (**359**)	Cyclo-(Gly^1-*L*-Thr^2-*L*-Phe^3-*L*-Leu^4-*L*-Tyr^5-*L*-Thr^6)	$C_{34}H_{46}N_6O_9$; 4.0×10^{-6}%, colorless powder, $[\alpha]_D$ +16.0° (CH_3OH, c 0.10); IR, UV, pos. FAB-MS[683(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, HMQC, HMBC, ROESY); amino acid analysis after acid hydrolysis, absolute configuration (HPLC).	cytotoxic	229
	(roots)	Dichotomin C (**360**)	Cyclo-(Gly^1-*L*-Thr^2-*L*-Phe^3-*L*-Leu^4-*L*-Tyr^3-*L*-Ala^5)	$C_{33}H_{44}N_6O_8$; 3.0×10^{-3}%, colorless powder, $[\alpha]_D$ +34.0° (CH_3OH, c 0.10); IR, UV, pos. FAB-MS[653(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, ^{1}H-^{13}C COSY, COLOC, NOE); amino acid analysis after acid hydrolysis, absolute configuration (HPLC).	cytotoxic	229
	(roots)	Dichotomin D (**361**)	Cyclo-(Gly^1-*L*-Val^2-Gly^3-*L*-Phe^4-*L*-Tyr^5-*L*-Ile^6)	$C_{33}H_{44}N_6O_7$; 1.2×10^{-3}%, colorless needles, mp 156-158, $[\alpha]_D$ –21.4° (CH_3OH, c 0.10); IR, UV, pos. FAB-MS[637(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, HMQC, HMBC, NOESY); amino acid analysis after acid hydrolysis, absolute configuration (HPLC).	inhibiting cyclooxygenase	229
	(roots)	Dichotomin E (**362**)	Cyclo-(Gly^1-*L*-Tyr^2-*L*-Ala^3-*L*-Phe^4-*L*-Ala^5)	$C_{26}H_{31}N_5O_6$; 2.0×10^{-4}%, colorless powder, $[\alpha]_D$ –66.7° (CH_3OH, c 0.11); IR, UV, pos. FAB-MS[510(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, HMQC, HMBC); amino acid analysis after acid hydrolysis, absolute configuration (HPLC).	cytotoxic	229
	(roots)	Dichotomin F (**363**)	Cyclo-(*L*-Pro-*L*-Tyr-*L*-Phe-*L*-Val-*L*-Leu-*L*-Pro-*L*-Ser-*L*-Val-*L*-Tyr)	$C_{56}H_{75}N_9O_{12}$; 3.0×10^{-4}%, colorless needles, mp 150-151, $[\alpha]_D$ –85.1° (CH_3OH, c 0.23); IR, UV, pos. FAB-MS[1066(M+H)$^+$], ESI MS/MS; amino acid analysis after acid hydrolysis, enzymatic hydrolysis with α-chymotrypsin and sequence determination, absolute configuration (HPLC).	inhibiting cyclooxygenase	230
	(roots)	Dichotomin G (**364**)	Cyclo-(*L*-Pro^2-*L*-Leu^3-*L*-Pro^4-*L*-Ile^5-*L*-Pro^6-*L*-Pro^7-*L*-Phe^8-*L*-Tyr^9-*L*-Ser^1)	$C_{53}H_{73}N_9O_{11}$; 6.0×10^{-4}%, colorless powder, $[\alpha]_D$ –100.5° (CH_3OH, c 0.76); IR, pos. FAB-MS[1012(M+H)$^+$], ESI MS/MS, PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, HMQC, HMBC, ROESY); amino acid analysis after acid hydrolysis, enzymatic hydrolysis with α-chymotrypsin, absolute configuration (HPLC).	inhibiting cyclooxygenase	230
	(roots)	Dichotomin H (**365**)	Cyclo-(*L*-Pro^2-*L*-Thr^3-*L*-Phe^4-*L*-Tyr^5-*L*-Pro^6-*L*-Leu^7-*L*-Ile^8-*L*-Ala^1)	$C_{47}H_{66}N_8O_{10}$; 1.0×10^{-4}%, colorless powder, $[\alpha]_D$ –77.5° (CH_3OH, c 0.93); IR, UV, pos. FAB-MS[903(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, HOHAHA, HMQC, HMBC, ROESY); amino acid analysis after acid hydrolysis, absolute configuration (HPLC).	cytotoxic	231
	(roots)	Dichotomin I (**366**)	Cyclo-(*L*-Pro^2-*L*-Thr^3-*L*-Phe^4-*L*-Tyr^5-*L*-Pro^6-*L*-Leu^7-*L*-Ile^8-*L*-Val^1)	$C_{49}H_{70}N_8O_{10}$; 5.0×10^{-4}%, colorless powder, $[\alpha]_D$ –99.6° (CH_3OH, c 0.54); IR, UV, pos. FAB-MS[931(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, HOHAHA, HMQC, HMBC, ROESY); amino acid analysis after acid hydrolysis, absolute configuration (HPLC).	cytotoxic	231
41	*S. yunnanensis* (roots)	Stellarin A (**367**)	Cyclo-(Pro^1-Phe-Pro^2-Gly^2-Tyr-Gly^3-Gly^1)	$C_{34}H_{41}N_7O_8$; 2.0×10^{-2}%, amorphous powder, $[\alpha]_D^{19}$ -11.4° (CH_3OH, c 0.696); IR, UV, pos. FAB-MS[676(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, DQF-COSY, TOCSY, HMQC, HMBC, NOESY); amino acid analysis after acid hydrolysis, enzymatic hydrolysis with α-chymotrypsin and sequence determination.		232
	(roots)	Stellarin B (**368**)	Cyclo-(Gly-Ser-δ-HO Ile-Phe-Phe-Ala)	$C_{32}H_{42}N_6O_8$;		233

Table 8 (Continued)

No.	Source (family, part)	Cyclopeptide (No.) (synonym)	Structure*	Structural and spectral data	Bioactivity	Reference
				3.7×10^{-4}%, amorphous powder, $[\alpha]_D^{19}$ +15° (CH_3OH, c 0.153); IR, UV, pos. FAB-MS[639(M+H)$^+$], PMR, CMR, 2D NMR (DEPT, ^{1}H-^{1}H COSY, ^{1}H-^{13}C COSY, TOCSY, HMBC, NOESY); amino acid analysis after acid hydrolysis.		
	(roots)	Stellarin C (**369**)	Cyclo-(Gly-Ser-δ-HO Ile-Phe-Phe-Ser)	$C_{32}H_{42}N_6O_9$; 4.7×10^{-4}%, amorphous powder, $[\alpha]_D^{19}$ −12.29° (CH_3OH, c 0.143); IR, UV, pos. FAB-MS[655(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, TOSY, HMQC, HMBC, NOESY); amino acid analysis after acid hydrolysis.		233
	(roots)	Stellarin D (**370**)	Cyclo-(Pro^1-Gly-Tyr-Leu-Phe-Pro^2-Ile)	$C_{42}H_{57}N_7O_8$; 4.9×10^{-4}%, amorphous powder, $[\alpha]_D^{15}$ −38.3° (CH_3OH, c 0.183); IR, UV, pos. FAB-MS[788(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, TOCSY, DQF-COSY, HMQC, HMBC, NOESY); amino acid analysis after acid hydrolysis.		234
	(roots)	Stellarin E (**371**)	Cyclo-(Pro-Tyr-Ile-Ala-Ala-Gly-Ile)	$C_{34}H_{51}N_7O_8$; 5.7×10^{-4}%, amorphous powder, $[\alpha]_D^{19}$ −116.8° (CH_3OH, c 0.143); IR, UV, pos. FAB-MS[686(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, TOCSY, DQF-COSY, HMQC, HMBC, NOESY); amino acid analysis after acid hydrolysis.		234
	(roots)	Stellarin F (**372**)	Cyclo-(Pro^1-Gly^1-Ala-Gly^2-Ser-Pro^2-Trp-Phe)	$C_{40}H_{49}N_9O_9$; 1.1×10^{-3}%, amorphous powder, $[\alpha]_D^{16}$ −64.6° (CH_3OH, c 0.542); IR, UV, pos. FAB-MS[800(M+H)$^+$], PMR, CMR, 2D NMR (TOCSY, DQF-COSY, HMQC, HMBC, NOESY); amino acid analysis after acid hydrolysis, enzymatic hydrolysis with α-chymotrypsin and sequence determination.		235
	(roots)	Stellarin G (**373**)	Cyclo-(Gly-Ala-Tyr-Leu-Ala)	$C_{23}H_{33}N_5O_6$; 2.0×10^{-4}%, amorphous powder, $[\alpha]_D^{17}$ −60.0° (CH_3OH, c 0.05); IR, UV, pos. FAB-MS[476(M+H)$^+$], PMR, CMR, 2D NMR (TOCSY, NOESY).		235
	(roots)	Stellarin H (**374**)	Cyclo-(Pro^1-Pro^2-Tyr-Ser^2-Phe-Ser^1-Leu^2-Val-Leu^1)	$C_{51}H_{73}N_9O_{12}$; 2.7×10^{-4}%, amorphous powder, $[\alpha]_D^{17}$ −89.2° (CH_3OH, c 0.033); IR, UV, pos. FAB-MS[1004(M+H)$^+$], PMR, CMR, 2D NMR (TOCSY, DQF-COSY, HMQC, HMBC, NOESY); amino acid analysis after acid hydrolysis.		236
	(roots)	Yunnanin A (**375**)	Cyclo-(*L*-Pro^3-*L*-Phe^4-*L*-Pro^5-Gly^6-*L*-Tyr^7-Gly^1-Gly^2)	$C_{34}H_{41}N_7O_8$; 2.0×10^{-3}%, colorless needles, mp 197-199 (dec.), $[\alpha]_D$ −21.1° (CH_3OH, c 0.56); IR, UV, pos. FAB-MS[676(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, HMQC, HMBC, ROESY); amino acid analysis after acid hydrolysis, absolute configuration (HPLC), solution and solid conformation (NMR, x-ray), solid-phase synthesis.	cytotoxic	237,238,254,258
	(roots)	Yunnanin B (**376**)	Cyclo-(Gly^1-*L*-Ser^2-*L*-δ-HO Ile^3-*L*-Phe^4-*L*-Phe^5-*L*-Ala^6)	$C_{32}H_{42}N_6O_8$; 4.0×10^{-3}%, colorless needles, mp 151-153, $[\alpha]_D$ +12.5° (CH_3OH, c 1.70); IR, pos. FAB-MS[639(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, HMQC, HMBC, ROESY); amino acid analysis after acid hydrolysis, absolute configuration (HPLC).	cytotoxic	237,238
	(roots)	Yunnanin C (**377**)	Cyclo-(*L*-Pro^7-Gly^1-*L*-Ile^2-Gly^3-*L*-Phe^4-*L*-Tyr^5-*L*-Ser^6)	$C_{36}H_{47}N_7O_9$; 4.3×10^{-4}%, colorless needles, mp 255, $[\alpha]_D$ −48.1° (CH_3OH, c 0.21); IR, UV, pos. FAB-MS[722(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, HOHAHA, HMQC, HMBC, ROESY); amino acid analysis after acid hydrolysis, absolute configuration (HPLC), solid-phase synthesis.	cytotoxic	238,258
	(roots)	Yunnanin D (**378**)	Cyclo-(*L*-Pro^7-Gly^1-*L*-Ile^2-*L*-Ser^3-*L*-Phe^4-*L*-Arg^5-*L*-Phe^6)	$C_{40}H_{56}N_{10}O_9$; 2.3×10^{-3}%, colorless powder, $[\alpha]_D$ −20.0° (CH_3OH, c 0.60); IR, pos. FAB-MS[805(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, HOHAHA, HMQC, HMBC, ROESY); amino acid analysis after acid hydrolysis, absolute configuration (HPLC).	cytotoxic	239
	(roots)	Yunnanin E (**379**)	Cyclo-(Gly^1-*L*-Ser^2-*L*-δ-OH Ile^3-*L*-Phe^4-*L*-Phe^5-*L*-Ser^6)	$C_{32}H_{42}N_6O_9$; 6.7×10^{-3}%, colorless powder, $[\alpha]_D$ −9.6° (CH_3OH, c 0.25); IR, pos. FAB-MS[677(M+Na)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, HOHAHA, HMQC, HMBC, ROESY); amino acid analysis after acid hydrolysis, absolute configuration (HPLC).		239
	(roots)	Yunnanin F (**380**)	Cyclo-(*L*-Pro^6-*L*-Ser^7-*L*-Ser^8-Gly^1-*L*-Val^2-*L*-Thr^3-*L*-Trp^4-*L*-Tyr^5)	$C_{42}H_{53}N_9O_{12}$; 2.3×10^{-4}%, colorless powder, $[\alpha]_D$ −56.5° (CH_3OH, c 0.29); IR, UV, pos. FAB-MS[878(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, HMQC, HMBC, ROESY); amino acid analysis after acid hydrolysis, absolute configuration (HPLC).		239
42	*Vaccaria segetalis* (Caryophyllaceae) (seeds)	Segetalin A (**381**) (Vaccarin D)	Cyclo-(*L*-Pro-*L*-Val^2-*L*-Trp-*L*-Ala-Gly-*L*-Val^1)	$C_{31}H_{43}N_7O_6$; 2.0×10^{-2}%, colorless needles, mp 183-185, $[\alpha]_D$ −73.4° (CH_3OH, c 0.41); IR, UV, pos. FAB-MS[610(M+H)$^-$], ESI MS/MS, PMR, CMR, 2D NMR (COSY, HMQC, HMBC); amino acid analysis after acid hydrolysis, enzymatic hydrolysis with α-chymotrypsin, thionation, absolute configuration (HPLC), solution and solid conformation (NMR, x-ray), solid-phase synthesis.	estrogen-like activity	240,242,243,255,259,261
	(seeds)	Segetalin B (**382**) (Vaccarin A)	Cyclo-(Gly^1-*L*-Val^2-*L*-Ala^3-*L*-Trp^4-*L*-Ala^5)	$C_{24}H_{32}N_6O_5$; 4.0×10^{-3}%, colorless needles, mp 153-155, $[\alpha]_D$ −32.4° (C_5H_5N, c 0.41); IR, UV, pos. FAB-MS[485(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, HMQC, HMBC, ROESY); amino acid analysis after acid hydrolysis, thionation, absolute configuration (HPLC), solution conformation (NMR), solid-phase synthesis.	estrogen-like activity	241,243,260,261
	(seeds)	Segetalin C (**383**)	Cyclo-(*L*-Pro^7-Gly^1-*L*-Leu^2-*L*-His^3-*L*-Phe^4-*L*-Ala^5-*L*-Phe^6)	$C_{40}H_{51}N_9O_7$; 4.0×10^{-4}%, colorless needles, mp 172-175, $[\alpha]_D$ −23.2° (CH_3OH , c 0.42); IR, UV, pos. FAB-MS[770(M+H)$^+$], PMR, CMR, 2D NMR		241

Table 8 (Continued)

No.	Source (family, part)	Cyclopeptide (No.) (synonym)	Structure*	Structural and spectral data	Bioactivity	Reference
				(HMQC, HMBC, NOESY); amino acid analysis after acid hydrolysis, absolute configuration (HPLC).		
	(seeds)	Segetalin D (**384**) (Vaccarin B)	Cyclo-(*L*-Pro^7-Gly^1-*L*-Leu^2-*L*-Ser^3-*L*-Phe^4-*L*-Ala^5-*L*-Phe^6)	$C_{37}H_{46}N_7O_8$; 4.0×10^{-3}%, colorless needles, mp 165-167, $[\alpha]_D$ +13.7° (CH_3OH, c 0.41); IR, UV, pos. FAB-MS[720(M+H)$^+$], PMR, CMR, 2D NMR (PFG-HMBC); amino acid analysis after acid hydrolysis, absolute configuration (HPLC), solution conformation (NMR).		241,256
	(seeds)	Segetalin E (**385**) (Vaccarin C)	Cyclo-(*L*-Pro^7-Gly^1-*L*-Tyr^2-*L*-Val^3-*L*-Pro^4-*L*-Leu^5-*L*-Trp^6)	$C_{43}H_{56}N_8O_8$; 4.0×10^{-3}%, needles, mp 166-168, $[\alpha]_D$ −59° (CH_3OH, c 0.4); IR, UV, pos. FAB-MS[813(M+H)$^+$], PMR, CMR, 2D NMR (HMQC, PFG-HMBC, HMBC, ROESY); amino acid analysis after acid hydrolysis, absolute configuration (HPLC), solution conformation (NMR).	cytotoxic	244,256
	(seeds)	Segetalin G (**386**)	Cyclo-(Gly^1-*L*-Val^2-*L*-Lys^3-*L*-Tyr^4-*L*-Ala^5)	$C_{25}H_{38}N_6O_6$; 1.1×10^{-3}%, colorless powder, $[\alpha]_D$ −89.0° (CH_3OH, c 0.4); IR, pos. FAB-MS[519(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, HMQC, HMBC, ROESY); amino acid analysis after acid hydrolysis, absolute configuration (HPLC), solid-phase synthesis.	estrogen-like activity	245,260
	(seeds)	Segetalin H (**387**)	Cyclo-(Gly^1-*L*-Tyr^2-*L*-Arg^3-*L*-Phe^4-*L*-Ser^5)	$C_{29}H_{38}N_8O_7$; 1.8×10^{-3}%, colorless powder, $[\alpha]_D$ −79.0° (CH_3OH, c 0.4); IR, pos. FAB-MS[611(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, HMQC, HMBC, ROESY); amino acid analysis after acid hydrolysis, absolute configuration (HPLC).	estrogen-like activity	245

* Ala, Arg, Asn, Asp, Gln, Glu, Gly, His, Ile, OHIle, Leu, Lys, Met, OMet, Phe, Pro, Ser, Thr, Trp, Tyr and Val are the abreviations of the following amino acids: alanine, arginine, asparagine, aspartic adid, glutamine, glutamic acid, glycine, histidine, isoleucine, hydroxyl isoleucine, leucine, lysine, methionine, S-oxomethionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine, respectively.

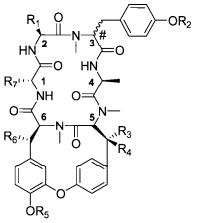
L-α-alanine, three modified *N*-methyl-L-α-tyrosines (rarely one modified *N*-methyl-D-tyrosine), and one other protein L-α-amino acid. The most unusual feature is a 14-membered ring formed by oxidative coupling of the phenolic oxygen of one tyrosine with a carbon ortho to the phenolic hydroxyl group of an adjacent tyrosine with a *cis* peptide bond, and the 14-membered ring was fused to the 18-membered cylic hexapeptide ring. Even with a *cis* peptide bond, the molecular models indicated that the 14-membered ring, which also contains a paracyclophane and a metacyclophane ring system, possesses some angle strain and very little flexibility. Bouvardin (**388**) and deoxybouvardin (**389**) are the first two Rubiaceae-type cyclopeptides, which were isolated and identified from the stems, leaves, and flowers of *Bouvardia ternifolia* (Rubiaceae) in 1977. **388** and **389** gave a positive test with chlorine-*o*-toluidine reagent.[262] Later, RAs were found from *Rubia cordifolia* and *R. akane* (Rubiaceae), in which RA-XII (**403**), -XIII (**404**), -XIV (**405**), -XV (**406**), and -XVI (**407**) are cyclopeptide glucosides discovered in higher plants for the first time.[269] RA-dimer A (**410**) is a dimer.[275] Rubiaceae-type cyclopeptides possess a promising antitumor activity, and the major active principle RA-VII (**398**) was reported to have undergone phase I clinical trials at the NCI as an anticancer drug in Japan in 1990s, whose therapeutic ratio was 400.[9] The distribution and quantitative variations of RA-V (deoxybouvardin, **389**) and **398** in *Rubia* and related species were investigated by means of HPLC.[276] Up to 2005, 23 Rubiaceae-type cyclopeptides were isolated from higher plants (Table 9). Rubiaceae-type cyclopeptides have attracted much attention for their potent antitumor activity *in vitro* and *in vivo* coupled with their characteristic bicyclic structure incorporating the isodityrosine moiety. Workers in Asia, America, and Europe, especially Japan and the U.S.A., have made important contributions in this field.

2.2.3. Homopolycyclopeptides

2.2.3.1. Cyclotides (Violaceae-Type Cyclopeptides). Cyclotides (*cyclo*pep*tides*)[322] [with the exception of SFTI-1 (**461**)[331] and MCoTI-III (**462**)[320]] are plant disulfide-rich macrocyclic proteins with 28−37 amino acids (Table 10), which not only contain a unique amide head to tail cyclized peptide backbone but also incorporate a cyclic cystine knot (CCK). The CCK is a fascinating structural motif in which a small embedded ring formed by two disulfide bonds and their connecting back-bond segments is threaded by a third disulfide bond, which produces a unique protein fold that is topologically complex and has exceptional resistance to enzymatic breakdown and high chemical stability.[322,339] Cyclotides were also called macrocyclic peptides,[10] circular proteins,[10] cyclic mini-proteins,[10] and cyclic proteins.[322] The first cyclotide to be structurally characterized was kalata B1 (**424**), a 29-residue cyclopeptide from the tropical African plant *Oldenlandia affinis* with uterotonic activity. **424** had been discovered in 1970 as the active agent in a native medicine used by women in Africa to accelerate labor and childbirth. The medicine was prepared by boiling the plant to make a tea, which was orally ingested during labor. At that time, although the structure had not been determined, the fact that it was cyclic had been described. In 1995 its structure was finally determined.[10,321] In 1993−1994 other cyclotides such as circulins A and B (**411** and **412**),[315] cyclopsychotride A (**433**),[324] and violapeptide I (**442**)[326] were discovered. Since then about 50 cyclotides have been discovered from higher plants up to 2005 (Table 10). Workers in Oceania, Europe, and America, especially Australia, the U.S.A., and Sweden, have made important contributions in this field.

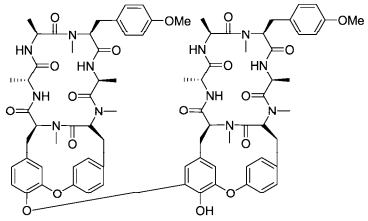
Fifty cyclotides have been isolated from 8 genera and 12 plants in the Cucurbitaceae, Rubiaceae, and Violaceae families now. About 20 protein amino acids were found in cyclotides. They occur in aerial parts, stems, barks, roots, seeds, and whole plants. Their yield varies from (1×10^{-4})% to 1% and depends not only upon the plant source but also upon the method of isolation (Table 10). With LC-MS analysis Craik and co-workers investigated the expression patterns of cyclotides in different plant parts of *Viola hederacea*, the native Australian violet, and various other *Viola* species (Violaceae). All *Viola* species and tissue types of *V. hederacea* examined contained complex mixtures of cyclotides, with individual profiles differing significantly. This study revealed at least 57 novel cyclotides present in *V. hederacea*. Although these species only constitute a comparatively small part of the genus *Viola*, expression of cyclotides can probably be regarded as a common theme in the genus.[328]

Table 9. Rubiaceae-Type Cyclopeptides (Type VII) Isolated from Higher Plants up to 2005



No.	Source (family, part)	Cyclopeptide (No.) (synonym)	Structure* R_1	R_2	R_3	R_4	R_5	R_6	R_7	#	Structural and spectral data	Bioactivity	Reference
1	*Bouvardia ternifolia* (Rubiaceae) (stems, leaves, flowers)	Bouvardin (**388**)	CH_3	CH_3	H	OH	H	H	CH_3	*L*	$C_{40}H_{48}N_6O_{10}$; 1.0×10^{-3}%, colorless needles, mp 254-255, $[\alpha]_D^{25}$ −181° ($CHCl_3$, c 1.0); MS[772(M)$^+$], PMR, CMR; elemental analysis, amino acid analysis after acid hydrolysis, methylation, absolute configuration ($[(\alpha]_D$), solid conformation (x-ray).	antitumor	262,263
	(stems, leaves, flowers) *Rubia cordifolia* (Rubiaceae) (roots) *R. akane* (roots) (stems, leaves, flowers)	Deoxybouvardin (**389**) (RA-V)	CH_3	CH_3	H	H	H	H	CH_3	*L*	$C_{40}H_{48}N_6O_9$; 4.8×10^{-4}%, colorless powder, mp 237-240, $[\alpha]_D^{25}$ −138° ($CHCl_3$, c 0.7); IR, UV, MS[756(M)$^+$], PMR, CMR; elemental analysis, amino acid analysis after acid hydrolysis, acetylation, methylation, absolute configuration ($[(\alpha]_{Me}$), solid conformation (x-ray).	antitumor	262,263,265,277
		6-*O*-Methylbouvardin (**390**)	CH_3	CH_3	H	OH	CH_3	H	CH_3	*L*	$C_{41}H_{50}N_6O_{10}$, MW=786; colorless plates, mp 244-247, $[\alpha]_D^{24}$ −191° ($CHCl_3$, c 1.0); PMR, CMR.	antitumor	263
2	*Rubia cordifolia* (Rubiaceae) (roots)	RA-I (**391**)	CH_2OH	CH_3	H	H	H	H	CH_3	*L*	$C_{40}H_{48}N_6O_{10}$; 1.9×10^{-4}%, colorless powder, mp 284 (dec.), $[\alpha]_D^{21}$ −216° ($CHCl_3$-CH_3OH (9:1), c 0.08); IR, MS[772(M)$^+$], PMR, CMR; methylation.	antitumor	264
	(roots)	RA-II (**392**)	CH_3	H	H	H	CH_3	H	CH_3	*L*	$C_{39}H_{46}N_6O_9$; 1.3×10^{-4}%, colorless needles, mp 261 (dec.), $[\alpha]_D^{28}$ −201° ($CHCl_3$, c 0.1); IR, MS[742(M)$^+$], PMR, CMR.	antitumor	264
	(roots)	RA-III (**393**)	CH_2OH	CH_3	H	H	CH_3	H	CH_3	*L*	$C_{41}H_{50}N_6O_{10}$; 1.4×10^{-4}%, colorless needles, mp>300, $[\alpha]_D^{28}$ −199° ($CHCl_3$, c 0.1); IR, UV, MS[786(M)$^+$], PMR, CMR; elemental analysis, amino acid analysis after acid hydrolysis, acetylation.	antitumor	264
	(roots)	RAI-III (**394**)	CH_2OH	CH_3	H	H	CH_3	H	CH_3	*L*	$C_{41}H_{50}N_6O_{10}$; colorless needles, mp 209-211, $[\alpha]_D$ −38.3° ($CHCl_3$, c 0.12); MS[786(M)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, ^{13}C-^{1}H COSY, HMBC, NOESYPH); amino acid analysis after acid hydrolysis, absolute configuration ($[(\alpha]_D$), solution conformation (NMR).	antitumor	267
	(roots)	RA-IV (**395**)	CH_3	CH_3	H	H	CH_3	OH	CH_3	*L*	$C_{40}H_{48}N_6O_{10}$; 4.5×10^{-5}%, colorless powder, mp 247-255, $[\alpha]_D^{21}$ −126° ($CHCl_3$, c 0.07); IR, UV, MS[772(M)$^+$], PMR, CMR; elemental analysis, oxidation.	antitumor	264
	(roots)	RA-VI (**396**)	CH_2OH	CH_3	H	H	CH_3	H	CH_3	*D*	$C_{41}H_{50}N_6O_{10}$; 6.8×10^{-5}%, colorless needles, mp 219-220, $[\alpha]_D$ −118.6° ($CHCl_3$, c 0.68); MS[786(M)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, ^{13}C-^{1}H COSY, HMBC, NOESYPH); amino acid analysis after acid hydrolysis, methylation, absolute configuration ($[(\alpha]_D$), solution and solid conformation (NMR, x-ray).	antitumor	266
	(roots)	RAI-VI (**397**)	CH_2OH	CH_3	H	H	CH_3	H	CH_3	*D*	$C_{41}H_{50}N_6O_{10}$; colorless needles, mp 200-202, $[\alpha]_D$ −129.4° ($CHCl_3$, c 0.17); MS[786(M)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, ^{13}C-^{1}H COSY, HMBC, NOESYPH); solution conformation (NMR).	antitumor	267
	(roots) *R. akane* (roots)	RA-VII (**398**)	CH_3	CH_3	H	H	CH_3	H	CH_3	*L*	$C_{41}H_{50}N_6O_{9}$; 8.0×10^{-3}%, colorless needles, mp>300, $[\alpha]_D^{21}$ −229° ($CHCl_3$, c 0.1); CD, IR, UV, MS[770(M)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, ^{13}C-^{1}H COSY, COLOC, HOHAHA, NOESY); amino acid analysis after acid hydrolysis, hydrogenolysis, methylation, solution conformation (CD).	antitumor	265,277,278
	(roots)	RA-VIII (**399**)	$CHOHCH_3$	CH_3	H	H	CH_3	H	CH_3	*L*	$C_{42}H_{52}N_6O_{10}$; 4.5×10^{-4}%, colorless needles, mp 267-269, $[\alpha]_D$ −159.5° ($CHCl_3$, c 0.39); MS[800(M)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, ^{13}C-^{1}H COSY, HOHAHA, HMBC, NOESYPH); amino acid analysis after acid hydrolysis, methylation, absolute configuration ($[(\alpha]_D$), solution conformation (NMR).	antitumor	266
	(roots)	RA-IX (**400**)	pyroGlu (side chain)	CH_3	H	H	CH_3	H	CH_3	*L*	$C_{41}H_{50}N_6O_{10}$; 2.0×10^{-4}%, colorless needles, mp 242-243, $[\alpha]_D^{20}$ −158.1° ($CHCl_3$, c 0.94); IR, UV, MS[811(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, ^{13}C-^{1}H COSY, COLOC, NOESYPH); amino acid analysis after acid hydrolysis, absolute configuration, solution conformation (NMR).	cytotoxic	268
	(roots)	RA-X (**401**)	CH_2CH_2COOH	CH_3	H	H	CH_3	H	CH_3	*L*	$C_{43}H_{54}N_6O_{12}$; 5.0×10^{-4}%, colorless needles, mp 254.5-255.5, $[\alpha]_D^{26}$ −205.4° ($CHCl_3$:CH_3OH (1:1), c 1.43); IR, UV, MS[829(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, ^{13}C-^{1}H COSY, COLOC, NOESYPH); amino acid analysis after acid hydrolysis, methylation, absolute configuration, solution conformation (NMR).	antitumor	268
	(roots)	RA-XI (**402**)	CH_2CH_2COOH	CH_3	H	H	H	H	CH_3	*L*	$C_{42}H_{50}N_6O_{11}$; colorless needles, mp 255.5, $[\alpha]_D$ −235.8° (CH_3OH, c 0.24); IR, UV, MS[815(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, ^{13}C-^{1}H COSY, COLOC); methylation.	antitumor	269
	(roots) *R. yunnanensis* (roots)	RA-XII (**403**) (RY-1, RY-3)	CH_3	CH_3	H	H	glc	H	CH_3	*L*	$C_{48}H_{58}N_6O_{14}$; amorphous powder, mp 252-255, $[\alpha]_D$ −270.0° (CH_3OH, c 0.2); IR, UV, MS[919(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, ^{13}C-^{1}H COSY, COLOC); acid hydrolysis, enzymatic hydrolysis with β-D-glucosidase.	antitumor	269,272,274
	(roots)	RA-XIII (**404**)	CH_2CH_2COOH	CH_3	H	H	glc	H	CH_3	*L*	$C_{48}H_{56}N_6O_{14}$; amorphous powder, mp 273-276, $[\alpha]_D$ −109.3° (CH_3OH, c 0.08); IR, UV, MS[999(M+Na)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, ^{13}C-^{1}H COSY, COLOC); acid hydrolysis, methylation.	antitumor	269
	(roots)	RA-XIV (**405**)	pyroGlu (side chain)	CH_3	H	H	glc	H	CH_3	*L*	$C_{48}H_{56}N_6O_{15}$; colorless powder, mp 264-267, $[\alpha]_D$ −257.8° (CH_3OH, c 0.26); IR, UV, MS[959(M+H)$^+$], PMR, CMR, 2D NMR (^{1}H-^{1}H COSY, ^{13}C-^{1}H COSY, COLOC); acid hydrolysis.		269
	(roots)	RA-XV (**406**)	CH_3	CH_3	H	H	6-OAc-glc	H	CH_3	*L*	$C_{48}H_{56}N_6O_{15}$; 1.1×10^{-4}%, needles, mp 218-220, $[\alpha]_D$ −202.4° (CH_3OH, c 0.2); IR, UV, FAB-MS[961(M+H)$^+$], PMR, CMR; acetylation.	antitumor	270
	(roots)	RA-XVI (**407**)	CH_3	CH_3	H	H	glc	OAc	CH_3	*L*	$C_{48}H_{58}N_6O_{16}$; 3.6×10^{-4}%, needles, mp 220 (dec.), $[\alpha]_D$ −179.7° (CH_3OH, c 0.06); IR, UV, FAB-MS[977(M+H)$^+$], PMR, CMR; acetylation.	antitumor	270
	(roots)	RA-XVII (**408**)	CH_3	CH_3	H	H	H	H	CH_2CH_3	*L*	$C_{41}H_{50}N_6O_9$; 4.8×10^{-3}%, amorphous powder, $[\alpha]_D^{24}$ −194° ($CHCl_3$, c 0.01); ESI-MS[771(M+H)$^+$], PMR, 2D NMR (^{1}H-^{1}H COSY, NOESY); solution conformation (NMR), synthesis.	antitumor	271
3	*R. yunnanensis* (roots)	RY-2 (**409**)	CH_2OH	CH_3	H	H	glc	H	CH_3	*L*	$C_{48}H_{58}N_6O_{15}$, MW=934; PMR, CMR, 2D NMR (TOCSY, HMQC, HMBC, ROESY).		273,274

* pyroGlu and glc are the abreviations of pyroglutamic acid and β-D-glucose.



RA-dimer A (**410**)[275]

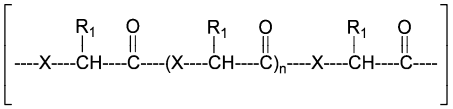
from *Rubia cordifolia* (Rubiaceae, roots).

$C_{80}H_{94}N_{12}O_{16}$; 5.0×10^{-6}%, amorphous powder, $[\alpha]_D^{25}$ −247° ($CHCl_3$, c 0.09);

IR, pos. FAB-MS[1511(M+H)$^+$], PMR, CMR, 2D NMR (DQF-COSY, HMQC, HMBC, NOESY);

synthesis.

Table 10. Cyclotides (Type VIII) Isolated from Higher Plants up to 2005



X = N or NH; n = 12, 26 - 29, 32, 35; R_1= side chain of amino acids.

No.	Source (family, part)	Cyclopeptide (No.) (synonym)	Structure*	Structural and spectral data	Bioactivity	Reference
1	*Chassalia parvifolia* (Rubiaceae) (stems)	Circulin A (**411**)	Cyclo-(C^{I}GESC^{II}VWIPC^{III}ISAALGC^{IV}SC^{V}KNKVC^{VI}YRNGIP)	30 amino acids, net charge (+2); UV, pos. FAB-MS[3153(M+H)$^+$]; amino acid analysis after acid hydrolysis, enzymatic hydrolysis with endoproteinase Lys-C and Glu-C, Edman sequencing, reduction and alkylation, partial acid hydrolysis, solution conformation (NMR).	anti-HIV, antimicrobial, cytotoxic	315,316,332,346
	(stems)	Circulin B (**412**)	Cyclo-(C^{I}GESC^{II}VFIPC^{III}ISTLLGC^{IV}SC^{V}KNKVC^{VI}YRNGVIP)	31 amino acids, net charge (+2); pos. FAB-MS[3284(M+H)$^+$]; amino acid analysis after acid hydrolysis, enzymatic hydrolysis with endoproteinase Arg-C, Edman sequencing, reduction and alkylation, partial acid hydrolysis, synthesis.	anti-HIV, haemolytic, antimicrobial, cytotoxic	315,316,342,343,346
	(stems)	Circulin C (**413**)	Cyclo-(C^{I}GESC^{II}VWIPC^{III}ITSVAGC^{IV}SC^{V}KSKVC^{VI}YRNGIP)	30 amino acids, net charge (+2); 2.7×10^{-2}%, amorphous white solids; pos. FAB-MS[3102(M+H)$^+$]; amino acid analysis after acid hydrolysis, enzymatic hydrolysis with endoproteinase Arg-C, Edman sequencing, reduction and alkylation.	anti-HIV	317
	(stems)	Circulin D (**414**)	Cyclo-(C^{I}GFSC^{II}VWIPC^{III}VTSIFNC^{IV}KC^{V}ENKVC^{VI}YHDKIP)	30 amino acids, net charge (0); 2.2×10^{-2}%; pos. FAB-MS[3397(M+H)$^+$]; amino acid analysis after acid hydrolysis, enzymatic hydrolysis with endoproteinase Arg-C, Edman sequencing, reduction and alkylation.	anti-HIV	317
	(stems)	Circulin E (**415**)	Cyclo-(C^{I}GESC^{II}VWIPC^{III}LTDVFNC^{IV}KC^{V}ENKVC^{VI}YHDKIP)	30 amino acids, net charge (0); 1.7×10^{-2}%; pos. FAB-MS[3396(M+H)$^+$]; amino acid analysis after acid hydrolysis, enzymatic hydrolysis with endoproteinase Arg-C, Edman sequencing, reduction and alkylation.	anti-HIV	317
	(stems)	Circulin F (**416**)	Cyclo-(C^{I}GESC^{II}VWIPC^{III}ISAAIGC^{IV}SC^{V}KNKVC^{VI}YRAIP)	29 amino acids, net charge (+2); 1.7×10^{-2}%; pos. FAB-MS[3053(M+H)$^+$]; amino acid analysis after acid hydrolysis, enzymatic hydrolysis with endoproteinase Arg-C, Edman sequencing, reduction and alkylation.	anti-HIV	317
2	*Hybanthus parviflorus* (Violaceae) (aerial parts)	Hypa A (**417**)	Cyclo-(C^{I}AESC^{II}VYIPC^{III}TITALLGC^{IV}SC^{V}KNKVC^{VI}YNGIP)	30 amino acids; 6.5×10^{-4}%; MW=3143, MS/MS; amino acid analysis after acid hydrolysis, enzymatic hydrolysis with trypsin and endoproteinase Glu-C, Edman sequencing, reduction and alkylation.		318
3	*Leonia cymosa* (Violaceae) (barks)	Cycloviolin A (**418**)	Cyclo-(C^{I}GESC^{II}VFIPC^{III}ISAAIGC^{IV}SC^{V}KNKVC^{VI}YRNGVIP)	31 amino acids, net charge (+2); 1.8×10^{-3}%; pos. FAB-MS[3213(M+H)$^+$]; amino acid analysis after acid hydrolysis, enzymatic hydrolysis with endoproteinase Glu-C, Edman sequencing, reduction and alkylation.	anti-HIV	319
	(barks)	Cycloviolin B (**419**)	Cyclo-(C^{I}GESC^{II}YVLPC^{III}FTVGC^{IV}TC^{V}TSSQC^{VI}FKNGTA)	28 amino acids, net charge (0); 1.1×10^{-3}%; pos. FAB-MS[2887(M+H)$^+$]; amino acid analysis after acid hydrolysis, enzymatic hydrolysis with endoproteinase Glu-C, Edman sequencing, reduction and alkylation.	anti-HIV	319
	(barks)	Cycloviolin C (**420**)	Cyclo-(C^{I}GESC^{II}VFIPC^{III}LTTVAGC^{IV}SC^{V}KNKVC^{VI}YRNGIP)	30 amino acids, net charge (+2); 6.8×10^{-4}%; pos. FAB-MS[3145(M+H)$^+$]; amino acid analysis after acid hydrolysis, enzymatic hydrolysis with endoproteinase Glu-C, Edman sequencing, reduction and alkylation.	anti-HIV	319
	(barks)	Cycloviolin D (**421**)	Cyclo-(C^{I}GESC^{II}VFIPC^{III}ISAAIGC^{IV}SC^{V}KNKVC^{VI}YRNGFP)	30 amino acids, net charge (+2); 7.9×10^{-4}%; pos. FAB-MS[3149(M+H)$^+$]; amino acid analysis after acid hydrolysis, enzymatic hydrolysis with endoproteinase Glu-C, Edman sequencing, reduction and alkylation.	anti-HIV	319
4	*Momordica cochinchinensis* (Cucurbitaceae) (seeds)	MCoTI-I (**422**)	Cyclo-(C^{I}PKILQRC^{II}RRDSDC^{III}PGAC^{IV}IC^{V}RGNGYC^{VI}GSGSDGGV)	34 amino acids; MW=3480; amino acid analysis after acid hydrolysis, enzymatic hydrolysis with endoproteinase Lys-C, Edman sequencing, reduction and alkylation.	inhibiting trypsin	320
	(seeds)	MCoTI-II (**423**)	Cyclo-(C^{I}PKILKKC^{II}RRDSDC^{III}PGAC^{IV}IC^{V}RGNGYC^{VI}GSGSDGGV)	34 amino acids, net charge (+3); MW=3453; amino acid analysis after acid hydrolysis, enzymatic hydrolysis with endoproteinase Lys-C and Asp-N, Edman sequencing, reduction and alkylation, solution conformation (NMR).	inhibiting trypsin	320,333,334
5	*Oldenlandia affinis* (Rubiaceae) (aerial parts)	Kalata B1 (**424**)	Cyclo-(C^{I}GETC^{II}VGGTC^{III}NTPGC^{IV}TC^{V}SWPVC^{VI}TRNGLPV)	29 amino acids, net charge (0); MW=2892, PMR, 2D NMR (DQF-COSY, HOHAHA, NOESY); amino acid analysis after acid hydrolysis, enzymatic hydrolysis with trypsin and protease *Staphylococcus aureus* V8, Edman sequencing, reduction and alkylation, solution conformation (NMR), synthesis, biosynthesis.	uterotonic, cardiotoxic, haemolytic, insecticidal, antimicrobial, cytotoxic	321,335-338,343,345,346
		Kalata B2 (**425**)	Cyclo-(C^{I}GETC^{II}FGGTC^{III}NTPGC^{IV}SC^{V}TWPIC^{VI}TRDGLPV)	29 amino acids.		322
		Kalata B3 (**426**)	Cyclo-(C^{I}GETC^{II}FGGTC^{III}NTPGC^{IV}TC^{V}DPWPIC^{VI}TRDGLPT)	30 amino acids.		322
		Kalata B4 (**427**)	Cyclo-(C^{I}GETC^{II}VGGTC^{III}NTPGC^{IV}TC^{V}SWPVC^{VI}TRDGLPV)	29 amino acids.		322
		Kalata B5 (**428**)	Cyclo-(C^{I}GESC^{II}VYIPC^{III}ISGVIGC^{IV}SC^{V}TDKVC^{VI}YLNGTP)	30 amino acids.		322
	(aerial parts)	Kalata B6 (**429**)	Cyclo-(C^{I}GETC^{II}FGGTC^{III}NTPGC^{IV}SC^{V}SSWPIC^{VI}TRNGLPT)	30 amino acids.		345
	(aerial parts)	Kalata B7 (**430**)	Cyclo-(C^{I}GETC^{II}TLGTC^{III}YTQGC^{IV}TC^{V}SWPIC^{VI}KRNGLPV)	29 amino acids.		345
		Kalata S (**431**)	Cyclo-(C^{I}GETC^{II}VGGTC^{III}NTPGC^{IV}SC^{V}SWPVC^{VI}TRNGLPV)	29 amino acids.		322
6	*Palicourea condensata* (Rubiaceae) (barks)	Palicourein (**432**)	Cyclo-(C^{I}GETC^{II}RVIPVC^{III}TYSAALGC^{IV}TC^{V}DDRSDGLC^{VI}KRNGDPTF)	37 amino acids, net charge (-1); 1.0%, white powder, $[\alpha]_D$ -68.1 (CH_3OH, c 0.79); UV, MW=3904; amino acid analysis after acid hydrolysis, enzymatic hydrolysis with endoproteinase Lys-C, Edman sequencing, reduction and alkylation, solution conformation (NMR).	anti-HIV	323,340

Table 10 (Continued)

No.	Source (family, part)	Cyclopeptide (No.) (synonym)	Structure*	Structural and spectral data	Bioactivity	Reference
7	*Psychotria longipes* (Rubiaceae) (whole plants)	Cyclopsychotride A (**433**)	Cyclo-(**C**^{I}GES**C**^{II}VFIP**C**^{III}TVTALLG**C**^{IV}S**C**^{V}KSKV**C**^{VI}YKNSIP)	31 amino acids, net charge (+2); $C_{139}H_{222}N_{35}O_{41}S_6$; 2.0×10^{-3}%; CD, pos. FAB-MS [3229(M+H)$^+$]; amino acid analysis after acid hydrolysis, partial acid hydrolysis, enzymatic hydrolysis with endoproteinase Glu-C, Edman sequencing, absolute configuration (Marfey's reagent), synthesis.	inhibiting neurotensin binding, stimulating intracellular Ca^{2+}, antimicrobial, cytotoxic	324,342,344,346
8	*Viola arvensis* (Violaceae) (aerial parts) *V. tricolor* (aerial parts)	Vary peptide A (**434**) (Varv A)	Cyclo-(**C**^{I}GET**C**^{II}VGGT**C**^{III}NTPG**C**^{IV}S**C**^{V}SWPV**C**^{VI}TRNGLPV)	29 amino acids, net charge (0); 1.2×10^{-4}%; MW=2879; amino acid analysis after acid hydrolysis, enzymatic hydrolysis with endoproteinase Glu-C, Edman sequencing, reduction and alkylation.	cytotoxic	325,330,347
	(aerial parts)	Vary peptide B (**435**) (Varv B)	Cyclo-(**C**^{I}GET**C**^{II}FGGT**C**^{III}NTPG**C**^{IV}S**C**^{V}DPWPM**C**^{VI}SRNGLPV)	30 amino acids, net charge (-1); 4.0×10^{-4}%; MW=3087; amino acid analysis after acid hydrolysis, enzymatic hydrolysis with endoproteinase Glu-C, Edman sequencing, reduction and alkylation.		326
	(aerial parts)	Vary peptide C (**436**) (Varv C)	Cyclo-(**C**^{I}GET**C**^{II}VGGT**C**^{III}NTPG**C**^{IV}S**C**^{V}SWPV**C**^{VI}TRNGVPI)	29 amino acids, net charge (0); 2.7×10^{-3}%; MW=2878; amino acid analysis after acid hydrolysis, enzymatic hydrolysis with endoproteinase Glu-C, Edman sequencing, reduction and alkylation.		326
	(aerial parts)	Vary peptide D (**437**) (Varv D)	Cyclo-(**C**^{I}GET**C**^{II}VGGS**C**^{III}NTPG**C**^{IV}S**C**^{V}SWPV**C**^{VI}TRNGLPI)	29 amino acids, net charge (0); 4.1×10^{-3}%; MW=2879; amino acid analysis after acid hydrolysis, enzymatic hydrolysis with endoproteinase Glu-C, Edman sequencing, reduction and alkylation.		326
	(aerial parts) *V. odorata* *V. tricolor* (aerial parts)	Vary peptide E (**438**) (Cycloviolacin O12) (Varv E)	Cyclo-(**C**^{I}GET**C**^{II}VGGT**C**^{III}NTPG**C**^{IV}S**C**^{V}SWPV**C**^{VI}TRNGLPI)	29 amino acids, net charge (0); 4.3×10^{-3}%; MW=2894; amino acid analysis after acid hydrolysis, enzymatic hydrolysis with endoproteinase Glu-C, Edman sequencing, reduction and alkylation.	cytotoxic	322,326,330
	(aerial parts)	Vary peptide F (**439**) (Varv F)	Cyclo-(**C**^{I}GET**C**^{II}TLGT**C**^{III}YTAG**C**^{IV}S**C**^{V}SWPV**C**^{VI}TRNGVPI)	29 amino acids, net charge (0); 3.6×10^{-3}%; MW=2956; amino acid analysis after acid hydrolysis, enzymatic hydrolysis with endoproteinase Glu-C, Edman sequencing, reduction and alkylation.	cytotoxic	326,347
	(aerial parts)	Vary peptide G (**440**) (Varv G)	Cyclo-(**C**^{I}GET**C**^{II}FGGT**C**^{III}NTPG**C**^{IV}S**C**^{V}DPWPV**C**^{VI}SRNGVPV)	30 amino acids, net charge (-1); 1.8×10^{-3}%; MW=3023; amino acid analysis after acid hydrolysis, enzymatic hydrolysis with endoproteinase Glu-C, Edman sequencing, reduction and alkylation.		326
	(aerial parts)	Vary peptide H (**441**) (Varv H)	Cyclo-(**C**^{I}GET**C**^{II}FGGT**C**^{III}NTPG**C**^{IV}S**C**^{V}ETWPV**C**^{VI}SRNGLPV)	30 amino acids, net charge (-1); 2.1×10^{-3}%; MW=3053; amino acid analysis after acid hydrolysis with trypsin and endoproteinase Glu-C, Edman sequencing, reduction and alkylation.		326
		Violapeptide I (**442**)	Cyclo-(**C**^{I}GET**C**^{II}VGGT**C**^{III}NTPG**C**^{IV}S**C**^{V}SRPV**C**^{VI}TRNGLPV)	29 amino acids.	haemolytic	326
9	*V. cotyledon* (acrial parts)	Vico A (**443**)	Cyclo-(**C**^{I}AES**C**^{II}VYIP**C**^{III}FTGIAG**C**^{IV}S**C**^{V}KNKV**C**^{VI}YYNGSIP)	31 amino acids; MW=3271; MS/MS; amino acid analysis after acid hydrolysis, enzymatic hydrolysis with trypsin and endoproteinase Glu-C, Edman sequencing, reduction and alkylation, aminoethylation, acetylation.		327
	(aerial parts)	Vico B (**444**)	Cyclo-(**C**^{I}AES**C**^{II}VYIP**C**^{III}ITGIAG**C**^{IV}S**C**^{V}KNKV**C**^{VI}YYNGSIP)	31 amino acids; MW=3237; MS/MS; amino acid analysis after acid hydrolysis, enzymatic hydrolysis with trypsin and endoproteinase Glu-C, Edman sequencing, reduction and alkylation, aminoethylation, acetylation.		327
10	*V. hederaceae* (roots)	Cycloviolacin H1 (**445**)	Cyclo-(**C**^{I}GES**C**^{II}VYIP**C**^{III}LTSAIG**C**^{IV}S**C**^{V}KSKV**C**^{VI}YRNGIP)	30 amino acids.		322
		Vhr1 (**446**)	Cyclo-(**C**^{I}AES**C**^{II}VWIP**C**^{III}TVTALLG**C**^{IV}S**C**^{V}SNKV**C**^{VI}YNGIP)	30 amino acids; amino acid analysis after acid hydrolysis, enzymatic hydrolysis with endoproteinase Glu-C, Edman sequencing, reduction and alkylation, solution conformation (NMR).		328
11	*V. odorata*	Cycloviolacin O1 (**447**)	Cyclo-(**C**^{I}AES**C**^{II}VYIP**C**^{III}TVTALLG**C**^{IV}S**C**^{V}SNRV**C**^{VI}YNGIP)	30 amino acids, net charge (0); MW=3116; amino acid analysis after acid hydrolysis, enzymatic hydrolysis with endoproteinase Glu-C, Edman sequencing, reduction and alkylation, solution conformation (NMR).		322,337
		Cycloviolacin O2 (**448**)	Cyclo-(**C**^{I}GES**C**^{II}VWIP**C**^{III}ISSAIG**C**^{IV}S**C**^{V}KSKV**C**^{VI}YRNGIP)	30 amino acids, net charge (+2); MW=3141.	cytotoxic	322,347
		Cycloviolacin O3 (**449**)	Cyclo-(**C**^{I}GES**C**^{II}VWIP**C**^{III}LTSAIG**C**^{IV}S**C**^{V}KSKV**C**^{VI}YRNGIP)	30 amino acids.		322
		Cycloviolacin O4 (**450**)	Cyclo-(**C**^{I}GES**C**^{II}VWIP**C**^{III}ISSAIG**C**^{IV}S**C**^{V}KNKV**C**^{VI}YRNGIP)	30 amino acids.		322
		Cycloviolacin O5 (**451**)	Cyclo-(**C**^{I}GES**C**^{II}VWIP**C**^{III}ISSAVG**C**^{IV}S**C**^{V}KNKV**C**^{VI}YKNGTP)	30 amino acids.		322
		Cycloviolacin O6 (**452**)	Cyclo-(**C**^{I}GES**C**^{II}VWIP**C**^{III}ISAAVG**C**^{IV}S**C**^{V}KSKV**C**^{VI}YKNGTLP)	31 amino acids.		322
		Cycloviolacin O7 (**453**)	Cyclo-(**C**^{I}GES**C**^{II}VWIP**C**^{III}TITALAG**C**^{IV}K**C**^{V}KSKV**C**^{VI}YNSIP)	30 amino acids.		322
		Cycloviolacin O8 (**454**)	Cyclo-(**C**^{I}ES**C**^{II}VWIP**C**^{III}ISSVVG**C**^{IV}S**C**^{V}KSKV**C**^{VI}YKNGTLP)	30 amino acids.		322
		Cycloviolacin O9 (**455**)	Cyclo-(**C**^{I}GES**C**^{II}VWIP**C**^{III}LTSAVG**C**^{IV}S**C**^{V}KSKV**C**^{VI}YRNGIP)	30 amino acids.		322
		Cycloviolacin O10 (**456**)	Cyclo-(**C**^{I}GES**C**^{II}VYIP**C**^{III}LTSAVG**C**^{IV}S**C**^{V}KSKV**C**^{VI}YRNGIP)	30 amino acids.		322
		Cycloviolacin O11 (**457**)	Cyclo-(**C**^{I}GES**C**^{II}VWIP**C**^{III}ISAVVG**C**^{IV}S**C**^{V}KSKV**C**^{VI}YKNGTLP)	31 amino acids.		322
	(aerial parts)	Vodo M (**458**)	Cyclo-(**C**^{I}GES**C**^{II}FTGK**C**^{III}YTVQ**C**^{IV}S**C**^{V}SWPV**C**^{VI}TRNGAPI)	29 amino acids; ESI-MS [3077(M)$^+$], MS/MS; amino acid analysis after acid hydrolysis, enzymatic hydrolysis with endoproteinase Glu-C, Edman sequencing, reduction and alkylation.		329
	(aerial parts)	Vodo N (**459**)	Cyclo-(**C**^{I}GET**C**^{II}TLGK**C**^{III}YTAG**C**^{IV}S**C**^{V}SWPV**C**^{VI}YRNGLPV)	29 amino acids; ESI-MS [3048(M)$^+$], MS/MS; amino acid analysis after acid hydrolysis, enzymatic hydrolysis with endoproteinase Glu-C, Edman sequencing, reduction and alkylation.		329
12	*V. tricolor* (aerial parts)	Vitri A (**460**)	Cyclo-(**C**^{I}GES**C**^{II}VWIP**C**^{III}ITSAIG**C**^{IV}S**C**^{V}KSKV**C**^{VI}YRNGIP)	30 amino acids, net charge (+2); 1.2×10^{-4}%;	cytotoxic	330

Table 10 (Continued)

No.	Source (family, part)	Cyclopeptide (No.) (synonym)	Structure*	Structural and spectral data	Bioactivity	Reference
				MW=3152; amino acid analysis after acid hydrolysis, enzymatic hydrolysis with endoproteinase Glu-C, Edman sequencing, reduction and alkylation.		
13	*Helianthus annus* (Compositae) (seeds)	SFTI-1 (**461**)	Cyclo-(**C^{VII}**TKSIPPI**C^{VIII}**FPDGR)	14 amino acids; MW=1513; amino acid analysis after acid hydrolysis, enzymatic hydrolysis with endoproteinase Lys-C, Edman sequencing, reduction and alkylation, solution conformation (NMR), solid conformation (x-ray).	inhibiting trypsin, cathepsin G, elastase, chymotrypsin, thrombin	331,341
	Momordica cochinchinensis (Cucurbitaceae) (seeds)	MCoTI-III (**462**)	CPRILKKCRRDSDCPGECICKENGYCGERA	30 amino acids; MW=3379; amino acid analysis after acid hydrolysis, enzymatic hydrolysis with pyroglutamyl aminopeptidase, Edman sequencing, reduction and alkylation.	inhibiting trypsin	320

* A, R, N, D, C, Q, E, G, H, I, L, K, M, F, P, S, T, W, Y and V are the abreviations of the following amino acids: alanine, arginine, asparagine, aspartic adid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine, respectively. Four disulfide bonds are formed between **C^{I}-C^{IV}**, **C^{II}-C^{V}**, **C^{III}-C^{VI}** for cyclotides **411-460** and **C^{VII}-C^{VIII}** for cyclotide **461**.

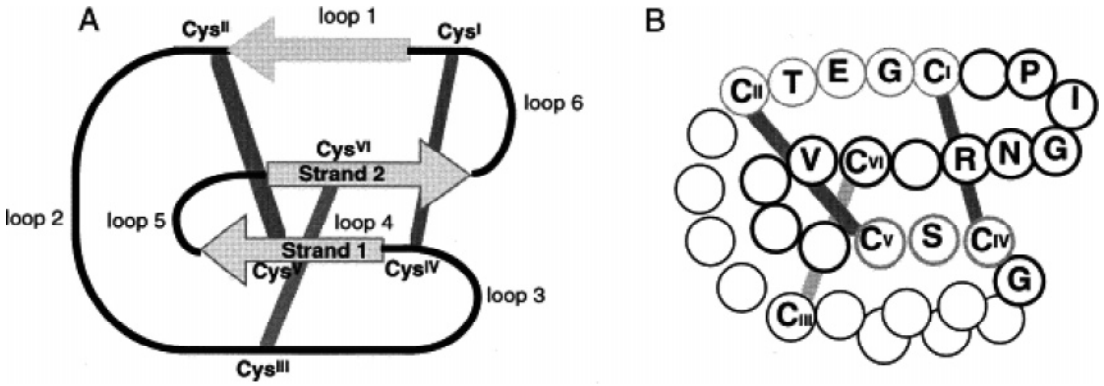


Figure 3. Structural features of cyclotides.[322] (A) Schematic representation of the cyclic cystine knot motif showing the arrangement of the connected disulfide bonds and the general topology of the knot. The backbone regions between successive Cys residues are labeled loops 1−6. The β-strands which form a β-hairpin are labeled strands 1 and 2. The third strand, shown in lighter shading, is often distorted. (B) Summary of the conserved and variable residues in the known cyclotides. Conserved residues are indicated by their one-letter code, and in some cases they may be replaced by highly homologous residues. For example, the Thr adjacent to Cys II is a Ser in the bracelet cyclotides, and the Ile in loop 6 is often replaced by a Leu. Residues which make up the embedded ring are shown as shaded circles. Blank circles indicate variable residues.

Cyclotides can be divided into the following four subfamilies (Table 10).[337] The conservation of loop spacings in the cyclotides is $C^{I}X_{3-6}C^{II}X_{4-5}C^{III}X_{3-7}C^{IV}X_{1}C^{V}X_{4-7}C^{VI}X_{5-8}$, in which loops 1 and 4 are absolutely conserved, and within the Bracelet and Moebius cyclotides there is a high degree of conservation in loop sizes (Table 10).[11] Figure 3 summarizes the structural features (cystine knot, turns, and sheet) common to the cyclotides and highlights regions of conserved sequence.[322]

- Bracelet----------circulin A-F (**411-416**), Hypa (**417**), cycloviolin A-D (**418-421**), kalata B5 (**428**), palicourein (**432**), cyclopsychotride A (**433**), Vico A-B (**443-444**), cycloviolacin H1 (**445**), Vhr1 (**446**), cycloviolacin O1-O11 (**447-457**), Vitri A (**460**)
- Moebius----------kalata B1-B4 (**424-427**), kalata B6-B7 (**429-430**), kalata S (**431**), vary peptide A-I (**434-442**), Vodo M-N (**458-459**)
- Trypsin inbibitor----MCoTI-I-II (**422-423**)
- Others----------SFTI-1 (**461**)

3. Distribution and Chemotaxonomy

Up till now, 455 cyclopeptides have been found in 26 families, 65 genera, and 120 species; in particular, plants of the Caryophyllaceae and Rhamnaceae families commonly contain cyclopeptides. These 26 families include Amaranthaceae, Annonaceae, Araliaceae, Asclepiadaceae, Asteraceae, Caryophyllaceae, Celastraceae, Compositae, Cucurbitaceae, Euphorbiaceae, Labiatae, Linaceae, Malvaceae, Myrsinaceae, Olacaceae, Pandaceae, Phytolaccaceae, Rhamnaceae, Rubiaceae, Rutaceae, Schizandraceae, Solanaceae, Sterculiaceae, Urticaceae, Verbenaceae, and Violaceae.

3.1. Distribution of Cyclopeptide Alkaloids

185 cyclopeptide alkaloids have been found in 9 families, 23 genera, and 52 species. They are particularly common in plants of the family Rhamnaceae, especially the genus *Zizyphus*, but they have also been found in plants of the families Asteraceae, Celastraceae, Euphorbiaceae, Olacaceae, Pandaceae, Rubiaceae, Sterculiaceae, and Urticaceae (Table 11). They occur almost in all plant parts, including barks, root barks, stem barks, roots, stems, leaves, terminal branches, woody parts, aerial parts, flowers, fruits, seeds, and whole plants, most commonly in barks, root barks, and stem barks (Tables 2 and 3). Their yield varies from (1×10^{-6})% to (1×10^{-2})% and depends not only upon the plant source but also upon the method of isolation (Table 2).

3.2. Distribution of Caryophyllaceae-Type Cyclopeptides

168 Caryophyllaceae-type cyclopeptides have been found in 10 families, 23 genera, and 43 species. They are

Table 11. Distribution of Cyclopeptide Alkaloids Isolated from Higher Plants during the Past Half Century

				cyclopeptide						
no.	family	genus	species	type **Ia1**	type **Ia2**	type **Ia3**	type **Ia4**	type **Ib**	type **Ic**	acyclic
1	Asteraceae	Sphaeranthus	*Sphaeranthus indicus*					131, 132		
2	Celastraceae	Euonymus	*Euonymus europeaus*	36, 37, 38						
3	Euphorbiaceae	Antidesma	*Antidesma montana*	28	61					
		Hymenocardia	*Hymenocardia acida*				122			
4	Olacaceae	Heisteria	*Heisteria nitida*	25	70					
5	Pandaceae	Panda	*Panda oleosa*	33, 34						
6	Rhamnaceae	Araliorhamnus	*Araliorhamnus vaginatus*		60, 61, 62, 63					
		Ceanothus	*Ceanothus americanus*	4, 5, 6, 7, 8, 9, 38	65, 66		121			
			C. integerrimus	10, 22	67, 68, 69, 70, 71, 72					
			C. sanguineus	7, 10, 11, 22, 28, 37						
		Colubrina	*Colubrina texensis*	12						
		Condalia	*Condalia buxifolia*	28, 40, 43	73					
		Discaria	*Discaria americana*	13, 14, 21, 22, 28, 36	65, 74, 75, 76, 77, 80					
			D. crenata		76					
			D. febrifuga	15, 16, 17, 18, 19, 20, 22, 23, 28, 36, 37, 40	76, 77, 78					
			D. longispina	21, 22, 23, 28, 37, 38, 54						
			D. pubescens	24						
		Hovenia	*Hovenia dulcis*	26, 38						
			H. tomentella	26, 38						
		Lasiodiscus	*Lasiodiscus marmoratus*	27						1
		Paliurus	*Paliurus hemsleyanus*		81, 82	92, 93				
			P. ramosissimus			94, 95, 96, 104, 107, 117		123, 124, 125, 126, 127, 128, 129, 130, 137, 138, 149, 172		
		Rhamnus	*Rhamnus frangula*	36, 37, 38						
		Scutia	*Scutia buxifolia*	39, 40, 41, 42, 43, 44, 45, 46, 47, 48	83					
		Zizyphus	*Zizyphus abyssinica*						176, 177, 178, 179, 180, 181	
			Z. amphibia	52		97, 98, 99, 100, 101, 102, 109		133		
			Z. hutchinsonii			103				
			Z. hysodrica		87	103				
			Z. juazeiro			99				
			Z. jujuba	37, 43	85	109		133, 134, 135, 145, 146, 147, 156		
			Z. jujuba var. *inermis*	4, 30, 36, 37, 38				136, 137, 138, 139, 140, 145, 147, 153		
			Z. lotus	28, 37, 53, 55, 58		104, 105, 106, 107, 108		141, 142		
			Z. mauritiana	37		97, 99, 100, 101, 109, 110, 111, 112, 113, 114, 115, 116				
			Z. mucronata			117		143, 144, 145	176, 179, 180, 181, 182, 183, 184, 185	
			Z. nummularia	37, 43, 52, 54	70, 86, 87, 88, 89	109, 111, 112, 114, 118		133, 134, 135, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155		
			Z. oenoplia	37		97, 112, 119		156, 157, 158, 159, 160, 161, 162, 163, 164, 165	176, 177, 186, 187	
			Z. rugosa			99		152, 166, 167, 173		
			Z. sativa	38	90, 91			145, 147, 168, 169, 170, 171, 172, 173, 174, 175		
			Z. spina-christi	36, 52	90	100, 101, 109, 111, 120		133, 134, 159		
			Z. vulgaris var. *spinosus*	37, 55, 56, 57, 58, 59		99				2
			Z. xylopyra	54		112		133, 147		
7	Rubiaceae	Canthium	*Canthium anorldianum*	3						
			C. euryoides		64					
		Feretia	*Feretia apondanthera*		79, 84					
		Plectronia	*Plectronia odorata*	32, 35						
8	Sterculiaceae	Melochia	*Melochia corchorifolia*	28, 29, 36, 37						
			M. pyramidata	37	70, 84					
			M. tomentosa	30, 31, 40						
		Waltheria	*Waltheria americana*	4, 28	65, 84					
			W. douradinha	28, 40, 49, 50, 51						
9	Urticaceae	Myrianthus	*Myrianthus arboreus*	28, 32	80					

particularly common in plants of the family Caryophyllaceae, but they have also been found in plants of the families Annonaceae, Araliaceae, Euphorbiaceae, Labiatae, Linaceae, Phytolaccaceae, Rutaceae, Schizandraceae, and Verbenaceae. They occur mainly in roots, seeds, and whole plants but rarely in latex, fruit peels, fruits, and stems. Their yield varies from (1×10^{-5})% to (1×10^{-2})% and depends not only upon the plant source but also upon the method of isolation (Table 8).

3.3. Chemotaxonomy of Cyclopeptide Alkaloids

Only a few papers involved the chemotaxonomic considerations of cyclopeptide alkaloids.[31,47,70]

Table 12. Amino Acids in Cyclopeptide Alkaloids

no.	β-hydroxyl amino acids	ring bond amino acids	intermediate amino acids	basic end amino acids
1	β-hydroxyl isoleucine (β-OHIle)	alanine (Ala)	isoleucine (Ile)	alanine (Ala)
2	β-hydroxyl leucine (β-OHLeu)	glycine (Gly)	leucine (Leu)	*N*-methyl alanine (*N*-MeAla)
3	β-hydroxyl phenylalanine (β-OHPhe)	isoleucine (Ile)	phenylalanine (Phe)	*N*,*N*-dimethyl alanine (*N*,*N*-Me_2Ala)
4	β-hydroxyl proline (β-OHPro)	β-hydroxyl isoleucine (β-OHIle)	*N*-methyl phenylalanine (*N*-MePhe)	*N*-aldehyde-*N*-methyl alanine (*N*-CHO-*N*-MeAla)
5	β-hydroxyl valine (β-OHVal)	leucine (Leu)	proline (Pro)	*N*,*N*-dimethyl glycine (*N*,*N*-Me_2Gly)
6		β-hydroxyl leucine (β-OHLeu)	tryptophan (Trp)	isoleucine (Ile)
7		phenylalanine (Phe)	valine (Val)	*N*-methyl isoleucine (*N*-MeIle)
8		β-hydroxyl phenylalanine (β-OHPhe)		*N*,*N*-dimethyl isoleucine (*N*,*N*-Me_2Ile)
9		proline (Pro)		*N*-aldehyde isoleucine (*N*-CHOIle)
10		tryptophan (Trp)		leucine (Leu)
11		tyrosine (Tyr)		*N*-methyl leucine (*N*-MeLeu)
12		valine (Val)		*N*,*N*-dimethyl leucine (*N*,*N*-Me_2Leu)
13				*N*-oxo-*N*,*N*-dimethyl leucine (*N*,*N*-Me_2Leu(N→O))
14				*N*,*N*-dimethyl β-hydroxyl leucine (*N*,*N*-Me_2β-OHLeu)
15				*N*-methyl phenylalanine (*N*-MePhe)
16				*N*,*N*-dimethyl phenylalanine (*N*,*N*-Me_2Phe)
17				*N*,*N*-dimethyl β-hydroxyl phenylalanine (*N*,*N*-Me_2β-OHPhe)
18				*N*-methyl proline (*N*-MePro)
19				*N*,*N*-dimethyl threonine (*N*,*N*-Me_2Thr)
20				*N*,*N*-dimethyl tryptophan (*N*,*N*-Me_2Trp)
21				valine (Val)
22				*N*-methyl valine (*N*-MeVal)
23				*N*,*N*-dimethyl valine (*N*,*N*-Me_2Val)
24				*N*-aldehyde valine (*N*-CHOVal)

3.4. Chemotaxonomy of Caryophyllaceae-Type Cyclopeptides

Only a few papers involved the chemotaxonomic considerations of Caryophyllaceae-type cyclopeptides. On the basis of the chemical studies of Caryophyllaceae plants, we found cyclopeptides are present in the three subfamilies of Caryophyllaceae: Paronychioideae Vierh., Alsinoideae Vierh., and Silenoideae A. Br., rich in Alsinoideae Vierh. Thus, we thought cyclopeptides are characteristic components of Caryophyllaceae plants, which can be used as a marker of secondary metabolites for Caryophyllaceae plants.[180,246]

4. Chemical and Physical Properties

4.1. Chemical and Physical Properties of Cyclopeptide Alkaloids

Cyclopeptide alkaloids generally crystallize easily. The melting points are mostly over 200 °C. Most of them are levorotatory. Cyclopeptide alkaloids are rather weak bases and sparingly soluble in water but readily so in alcohols, $CHCl_3$, and some other organic solvents (Table 2).[2]

About 34 amino acids are found in cyclopeptide alkaloids, including 5 β-hydroxyl amino acids, 12 ring bond amino acids, 7 intermediate amino acids, and 24 basic end amino acids, which usually belong to the L-amino acids. Ring bond amino acids are usually common amino acids and rarely β-hydroxyl amino acids. Intermediate amino acids are usually common amino acids and rarely *N*-methyl amino acids. Basic end amino acids are often mono- or dimethylated and sometime are common amino acids, *N*-aldehyde, or *N*-oxo amino acids (Table 12).

4.2. Chemical and Physical Properties of Caryophyllaceae-Type Cyclopeptides

Caryophyllaceae-type cyclopeptides are generally crystals or powders. The melting points are mostly around 200 °C. Most of them are levorotatory. Caryophyllaceae-type cyclopeptides are sparingly soluble in water but readily so in DMSO, C_5H_5N, CH_3OH, $CHCl_3$, and some other organic solvents (Table 8).

About 23 amino acids are found in Caryophyllaceae-type cyclopeptides, including 19 protein α-amino acids and 4 non-protein α-amino acids, which usually belong to the L-amino acids. Protein α-amino acids include alanine, arginine, asparagine, aspartic acid, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. Non-protein α-amino acids include γ-hydroxyl isoleucine, δ-hydroxyl isoleucine, *S*-oxomethionine, and D-tryptophan (Table 8).

5. Chemical Detection Methods

5.1. Chemical Detection Methods of Cyclopeptide Alkaloids

The following reagents or methods were used to detect cyclopeptide alkaloids nonspecifically: a fluorescent indicator,[14,81,94,104] 10% or 30% aqueous sulfuric acid,[14,102,104] vanillin−sulfuric acid reagent,[94] anisaldehyde−H_2SO_4 reagent,[105] diazo reagent,[43] cerium(IV) reagent,[81] Mayer's reagent,[73] and Dragendorff's reagent;[20,55,58,64,69,77,80−82,85−87,89,91,94,100,104,105] Dragendorff's reagent was the most common one.

5.2. Chemical Detection Methods of Caryophyllaceae-Type Cyclopeptides

The following reagents or methods were used to detect Caryophyllaceae-type cyclopeptides: UV at 254 nm,[200] vanillin−sulfuric acid reagent,[200] chlorine-*o*-toluidine reagent,[168,193−199,201,202] Dragendorff's reagent,[203,205,206,219,221,227,229,230,238,241,245] and TLC protosite reaction with ninhydrin reagent;[176,177,179,180,209,210,217,247] TLC protosite reaction with ninhydrin reagent was the most specific one.

Since we accidentally isolated heterophyllins A and B (**327** and **328**) from the roots of *Pseudostellaria heterophylla* in 1991 and published their structures determined by chemical, spectral, and enzymatic methods in 1993,[215] we have been looking for a specific and sensitive TLC detection method for plant cyclopeptides. Although some reagents or methods have been used to detect plant cyclopeptides in the literature, such as chlorine-*o*-toluidine reagent and Dragendorff's reagent, there have not been any special TLC chemical methods for detecting plant cyclopeptides. Because there are no free amino groups (NH or NH_2) in structures of most cyclopeptides, they cannot react with ninhydrin reagent.

Later, we gradually established a special chemical detection method for plant cyclopeptides and reported it in 2000.[247] This method is a new TLC protosite reaction with ninhydrin reagent. By this method, 73 cyclopeptides were isolated by our group, and their structures were elucidated from 17 plants which belong to 5 families and 14 genera, from dicyclopeptides to undecacyclopeptides, including 68 new ones. After application of this method for the past 10 years, we have found that it is a good specific and sensitive chemical detection method for plant cyclopeptides. It can be used effectively not only to detect whether plant extracts contain cyclopeptides but also to guide cyclopeptide separation and purification.

The details of this new method are as follows: The sample was dotted at one corner of each of two identical 25 mm × 50 mm silica gel G plates (plates 1 and 2), and these plates were developed with $CHCl_3-CH_3OH$ (8.5:1.5 or 9:1). After removal of the solvent, plate 2 was hung in a sealed glass vessel with about 1 mL of concentrated HCl and hydrolyzed in a drying incubator (110 °C) for 1−2 h. After it was cooled for a few minutes, plate 2 was taken out, and the HCl was volatilized with a ventilator. Then plates 1 (nonhydrolyzed plate) and 2 (hydrolyzed plate) were sprayed with 0.2% ninhydrin−acetone reagent and colored after heating with a drier for several minutes. The above-mentioned process was repeated once more. If there are some purplish red spots in most cases and/or yellow spots in a few cases for plate 2, but there are no spots in the same locations on plate 1, this indicates that the detected samples contain cyclopeptides.[247]

6. Extraction and Isolation

6.1. Extraction and Isolation of Cyclopeptide Alkaloids

The dried ground plants are sometimes treated with a dilute basic solution (10% aqueous ammonia or 1% aqueous sodium carbonate) and then extracted with an organic solvent such as ether. Conversely, they may be treated directly with a solvent such as methanol or ethanol. The resulting solution is acidified with 0.4 N sulfuric acid or 2 N chlorhydric acid to pH 1.5. The acidified mixture is shaken with ether, then basified with 20% aqueous sodium hydroxide or aqueous ammonia to pH 9−10, and extracted with chloroform, ether, or benzene. In some instances, the dried material is simply heated with benzene-concentrated aqueous ammonia−methanol (100:1:1). The bases are usually separated from the extracts by treatment with 5% aqueous citric acid.[2,4,14,26,47]

Further purification and separation of the individual bases are accomplished by standard chromatographic methods including preparative TLC, CC, centrifugal partition chromatography, semipreparative HPLC, HPLC, and recrystallization. Chromatographic separations may be effected on alumina or, more commonly, on silica gel columns using solvents such as chloroform, acetone, ethyl acetate, dioxane, acetonitrile, and ether as well as chloroform−methanol mixtures. Fractions may be detected with an ultraviolet light source.[2,4,14,26,47,97]

6.2. Extraction and Isolation of Caryophyllaceae-Type Cyclopeptides

The dried ground plants are treated directly with a solvent such as CH_3OH or EtOH, and the extracts are partitioned with $CHCl_3$, EtOAc, or *n*-BuOH. Then the fractions are repeatedly chromatographed on a silica gel ($CHCl_3-CH_3OH$, EtOAc−CH_3OH, petrol−$CHCl_3-CH_3OH$), Diaion HP-20 (CH_3OH-H_2O), Sephadex LH-20 (CH_3OH-H_2O), and/or HPLC or MPLC on an ODS or C_{18} (CH_3OH-H_2O, CH_3CN-H_2O) column. If the plant materials are seeds or fruits, the materials are usually defatted with petrol, *n*-hexane, or cyclohexane at first. If the plant materials are latex, the materials are dissolved in water and then extracted with EtOAc.[168,173,174,202,205,215,229]

6.3. Extraction and Isolation of Cyclotides

The dried ground plants are treated with a solvent such as $CHCl_3-CH_3OH$ (1:1) or CH_3OH, and the extracts are partitioned in H_2O with *n*-BuOH. Then the fractions are fractionated by gel permeation on Sephadex LH-20 (CH_3OH, CH_3OH-H_2O), centrifugal partition chromatography (H_2O-*n*-BuOH−HOAc−EtOH, 10:8:1:1), vacuum−liquid chromatography (CH_3OH-H_2O), or HPLC on a C_{18} (CH_3CN-H_2O) column.[315,317,319,323]

Claeson et al. have developed a fractionation protocol for cyclotide separation from plants, which efficiently dereplicates most ubiquitous plant constituents and enables isolation of a highly purified polypeptide fraction from plant biomass.[325] The protocol is as follows: The dried ground plants were first defatted with CH_2Cl_2 and then treated with a solvent such as $EtOH-H_2O$ (1:1). The acidified extract was filtered through polyamide gel to remove tannins before being partitioned between H_2O and *n*-BuOH. The *n*-BuOH fractions were fractionated by gel filtration on Sephadex G-10 for removal of low-molecular-weight components, solid-phase extraction on RP-18 silica for removal of salts and polysaccharides, ion exchange chromatography, Sephadex LH-20 (CH_3OH-H_2O), and HPLC on a C_{18} (CH_3CN-H_2O) column for final purification. On the basis of this protocol, Hypa A (**417**),[318] vary peptides A−H (**434**−**441**),[325,326] vico A and B (**443** and **444**),[327] vodo M and N (**458** and **459**),[329] and vitri A (**460**)[330] were isolated by the group.

7. Structural Elucidation

7.1. Structural Elucidation of Cyclopeptide Alkaloids

Structures of cyclopeptide alkaloids have been determined by chemical degradation reactions and spectroscopic methods. Chemical degradation reactions include elemental analysis, oxidization, acetylation, methylation, formylation, hydrogenation, and amino acid analysis after acid or alkaline hydrolysis with PC, TLC, GC, LC, and MS. Spectral methods include IR, UV, NMR, MS, CD, and X-ray diffraction. MS and amino acid analysis after hydrolysis are particularly informative.[2,4,18,22,26]

7.1.1. Chemical Degradation

Acid hydrolysis is the most commonly used method for amino acid determination. Hydrolysis is often carried out after reduction or ozonolysis of the styrylamine functionality. Direct acidic hydrolysis has been used also. Alkaline hydrolysis has been used to ascertain the tryptophan content in cyclopeptide alkaloids and the substituents on the aromatic ring of the aryl ether moiety. Amino acid components have also been determined quantitatively directly by PC, TLC,

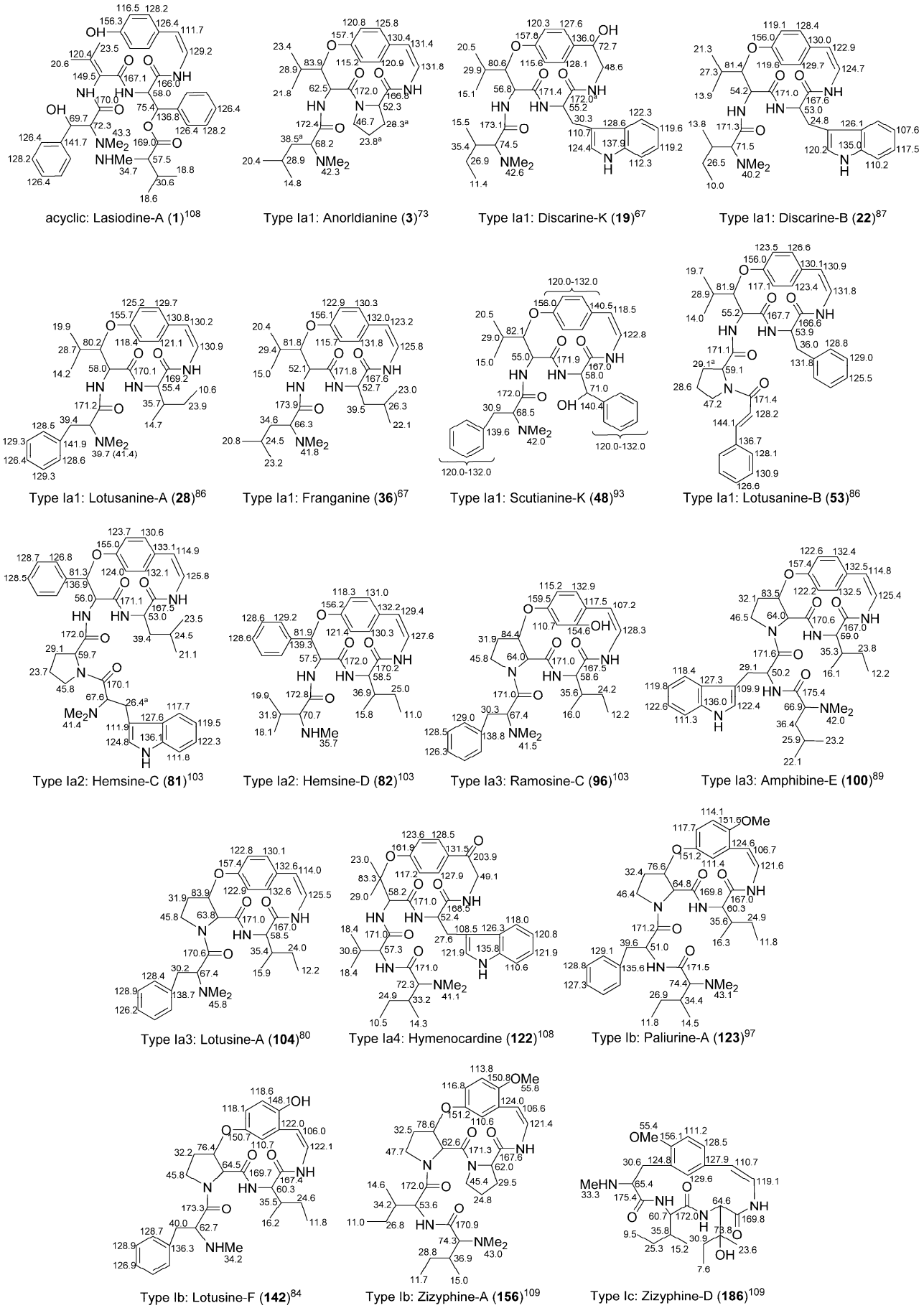


Figure 4. ^{13}C NMR data of some cyclopeptide alkaloids. [a] Data were corrected by us.

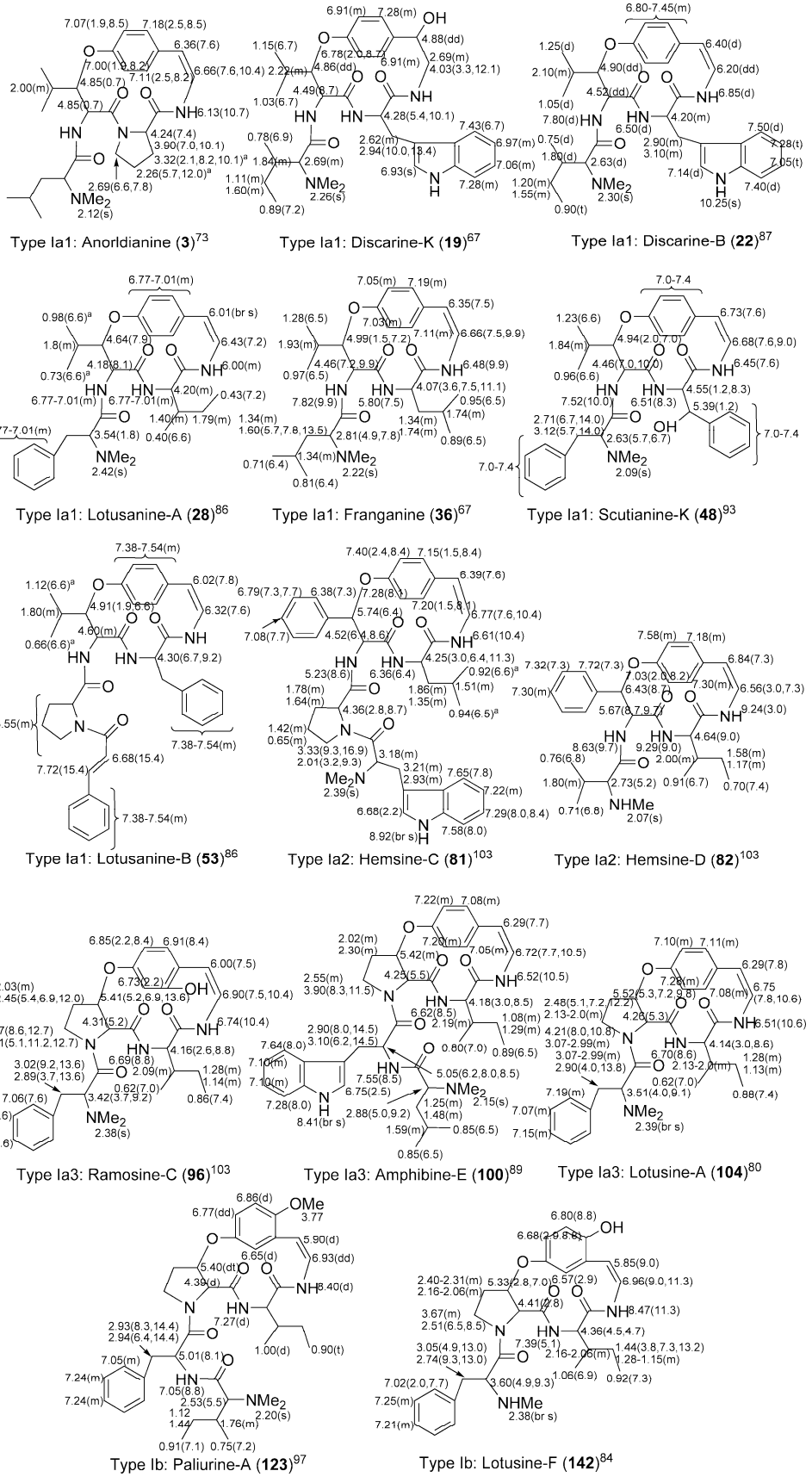


Figure 5. ^{1}H NMR data of some cyclopeptide alkaloids. [a] Data were corrected by us.

HPLC, and MS or as their derivatives by GC. Partial hydrolysis with 6 N H_2SO_4 or HCl−HOAc−H_2O (1:1:1) has been used to obtain the intact macrocycle.[4,82,100]

7.1.2. UV

The UV spectra of type **Ia** cyclopeptide alkaloids exhibit only an end absorption with shoulders at 250 and 270 nm

because the conjugation was reduced because in the macrocycle the *p*-orbitals of the aryloxy and enamide chromophores cannot overlap to any extent and each group must therefore absorb independently. The UV spectra of type **Ib** and **Ic** cyclopeptide alkaloids exhibit the maximum absorptions of the aryloxyenamide chromophore at 210, 270, and/or 320 nm. Lasiodine-A (**1**), one acyclopeptide alkaloid, exhibits the maximum absorption of the aryloxyenamide chromophore at 280 nm. Of the other UV absorbing groups found in cyclopeptide alkaloids, a tryptophan moiety is revealed by the maxima in the 220, 270, and 290 nm region.[1,2,4,18,26,32,33,38,40,41,46,54,55,59,66,84,97,103]

7.1.3. IR

The IR spectra of cyclopeptide alkaloids exhibit the typical bands for NH (3285−3400 cm^{-1}), methoxyl (2830 cm^{-1}), *N*-methyl (2780−2790 cm^{-1}), amide (1690−1630 cm^{-1}), double bond (1625 cm^{-1}), and phenol ether (1230−1240 cm^{-1}) groups.[2,23,32,42,54,55,59,97,103]

7.1.4. CD

The CD measurements on **Ia1** reveal a weak positive band at 285 nm and a strong negative one at 237 nm, while those on **Ib** reveal a weak positive one at 232 nm and strong negative ones at 324, 276, 254, and 218 nm[2,23] and those on **Ic** reveal a strong positive one at 228 nm and a strong negative one at 206 nm.[32,97,98,103]

7.1.5. NMR

NMR started to be used for structure elucidations of cyclopeptide alkaloids in the 1970s and was widely applied in the 1990s. Now about one-third of cyclopeptide alkaloids have NMR data available which show H and C atom signal characteristics of a styrylaminine moiety, a β-hydroxyl amino acid residue, a ring bond α-amino acid residue, an intermediate α-amino acid residue, and a basic end α-amino acid residue.[61,67,73,80,81,83,84,86,87,89,91,93,95−98,103,106−110] ^{13}C NMR and ^{1}H NMR data of some cyclopeptide alkaloids are given in Figures 4 and 5.

7.1.6. MS

MS with the electron impact mean has been used more extensively than any other method for structural determination of cyclopeptide alkaloids. Many cyclopeptide alkaloids have been identified and characterized solely by MS. High-resolution MS readily gives the elemental composition. The fragmentation patterns as follows depend on the β-hydroxy amino acid present in cyclopeptide alkaloids.[4]

The structures of **Ia1** and **Ia2** cyclopeptide alkaloids can largely be determined by their MS data. With the earlier investigations on the mass spectra of cyclopeptide alkaloids as guides, Fehlhaber used high-resolution mass spectroscopy to formulate the general breakdown pattern (Figure 6) of the **Ia1** and **Ia2** cyclopeptide alkaloids in 1968.[1,2]

The base peak of the MS is the ion **a**, which results from the facile splitting of the $C_\alpha-CO$ bond of the basic end α-amino acid residue. The fragment **b**, formed by cleaving the side chain of the basic end α-amino acid residue, decomposes thermally to ions **c** and **d**. The ring may open via the scission at the $C_\alpha-C_\beta$ and $C_\alpha-CO$ bonds of the β-hydroxyl amino acid residue and the CO−NH bond of the β-hydroxyl amino acid residue and the ring bond α-amino acid residue, which leads to ions **e**, **f, h**, and **i**. The fragment **g**, formed by the scission of the $C_\alpha-CO$ bond of the basic end α-amino acid residue, decomposes to ions **j**, **k**, **l**, and **m**. Therefore, the separate building units of cyclopeptide alkaloids are recognizable as follows: ion **a** represents the end α-amino acid residue, ion **m** represents the β-hydroxyl amino acid residue, ion **i** represents the styrylamine unit, and the typical amino fragment ($\mathbf{H}_2N^+{=}CH-R''$) represents the ring α-amino acid residue. Fragmentation of cyclopeptide alkaloids with a proline residue, another amino acid residue in the basic end α-amino acid residue, and a nonprotein amino acid residue in the ring bond amino acid residue brings about a variation shown in Figure 6. However, the positions of the substituents on the aromatic ring cannot be determined nor can leucine be distinguished from isoleucine.[2,34,47,87]

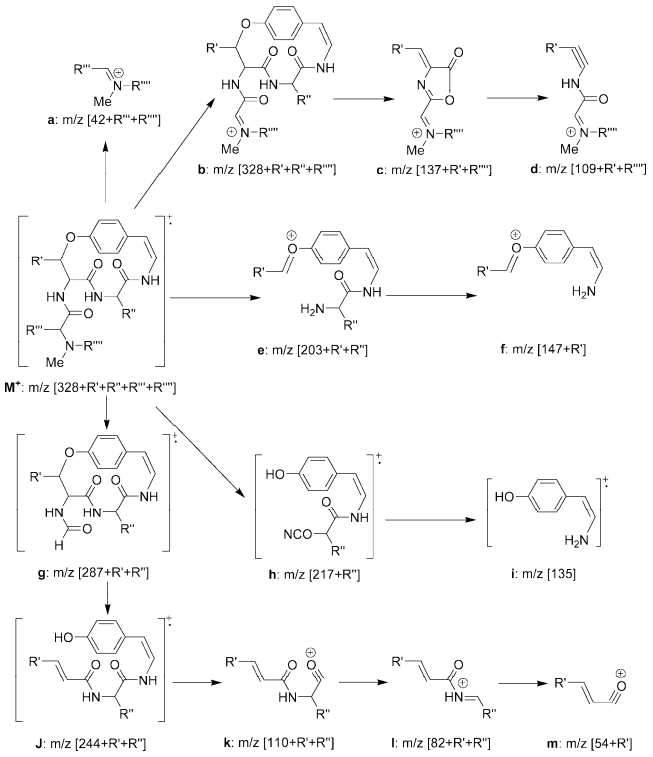


Figure 6. Mass spectrometric fragmentation patterns of types **Ia1** and **Ia2**.

The MS fragmentation patterns of **Ia3** cyclopeptide alkaloids are summarized in Figure 7. In addition to ions **a**, **b**, and **h**, which are the same as those for **Ia1** and **Ia2** (Figure 6), there are some special ions **n**−**t** due to the presence of the β-hydroxyl proline residue in the ring system, which prevents the normal scission at the $C_\alpha-C_\beta$ bond of the β-hydroxyl amino acid residue. The ions **n**−**s** establish the structure of the ring system, and the ion **t** identifies the basic end α-amino acid residue and the β-hydroxyl proline residue.[2]

The MS fragmentation patterns of **Ib** cyclopeptide alkaloids are largely analogous to those of **Ia3**.[2,6,56]

In the MS of **Ic** cyclopeptide alkaloids in which the basic nitrogen carries two methyl groups, the base peak is usually the molecular peak. The primary fragmentation is a α scission at the basic nitrogen to generate isocyanic acid and the radical ion. Further stepwise degradation of the peptide fraction leads to ions which permit the sequence of both ring bond α-amino acids.[2]

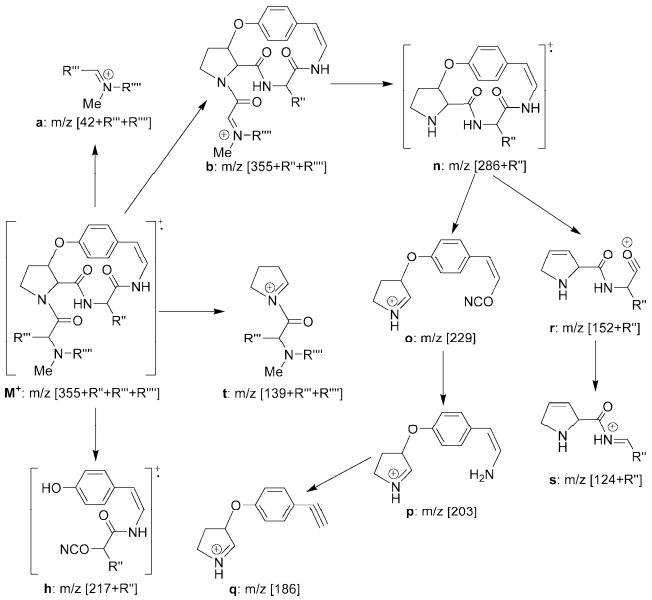


Figure 7. Mass spectrometric fragmentation patterns of type **Ia3**.

7.2. Structural Elucidation of Caryophyllaceae-Type Cyclopeptides

Structures of Caryophyllaceae-type cyclopeptides have been determined by chemical, enzymatic, and spectral methods. Chemical methods include mainly amino acid analysis after acid hydrolysis, rarely elemental analysis, thionation, hydrogenation, and reduction. Enzymatic methods include hydrolysis with α-chymotrypsin and sequence determination by the Edman sequencing method and MS/MS, and oxidation with amino acid oxidases. Spectral methods include IR, UV, NMR, MS, CD, and X-ray diffraction. NMR is particularly informative (Table 8).[168,173,174,189,199,203−206,215,218,219,225,229,230,232,235,240]

7.2.1. Strategies of Structural Elucidation

There are no standard protocols leading to structural elucidation of Caryophyllaceae-type cyclopeptides. On the basis of works by us and the literature, we proposed the following strategies for the structure determination dealing with the planar structure, configuration, and conformation of Caryophyllaceae-type cyclopeptides on the basis of chemical, enzymatic, and spectral methods, which can be used as a guide for assigning an isolated compound to be one Caryophyllaceae-type cyclopeptide.[7,8]

7.2.1.1. Planar Structure. *A. Composition of Amino Acid Residues.* At first take ^{1}H NMR and ^{13}C NMR spectra in C_5D_5N, DMSO-d_5, or CD_3OD, that are more important for the next structure elucidation. If the compound can provide one set of sharp ^{1}H and ^{13}C signals in a suitable solvent and at suitable temperature and other conditions, the composition can be determined using 2D NMR techniques including DEPT, ^{1}H−^{1}H COSY, DQF−COSY, ^{1}H−^{1}H relayed, TOCSY, HOHAHA, ^{1}H−^{13}C COSY, ^{1}H−^{13}C relayed, *J*-modulated ^{13}C, HMQC, HSQC, HMQC−TOCSY, COLOC, HMBC, PFG−HMBC, and so on. Sometimes cyclopeptides can give broad ^{1}H and ^{13}C signals under certain experimental conditions because more conformers exit in solution. In this case the composition can be measured by amino acid analysis with standard methods after total acid hydrolysis, which can give a definite confirmation to the results of NMR data.

B. Sequence of Amino Acid Residues. If the composition can be deduced from NMR data, the sequence of amino acid residues can be determined by 2D NMR techniques including COLOC, ^{1}H−^{13}C relayed, HMBC, NOEs, NOESY, ROESY, NOESYPH, and so on. If the ^{1}H and ^{13}C signals are broadened, the sequence of amino acid residues can be determined by sequence analysis after enzymatic hydrolysis with α-chymotrypsin and ESI-qTOF, FAB, or ESI MS/MS techniques with or without enzymatic hydrolysis with α-chymotrypsin.

C. Planar Structure. MS can give the molecular weight, molecular formula, and important fragmentation peaks, usually by positive or negative FAB, positive ESI-qTOF, positive LSI, and EI-MS means. Finally, the planar structure of the cyclopeptide can be elucidated by the combination of the above-mentioned evidence.

7.2.2.2. Configuration. The configuration can be determined by chiral GC, chiral HPLC, and enzymatic oxidation (see section 8.1.2).

7.2.2.3. Conformation. The conformation can be investigated by NMR, CD, a computational chemical method, and X-ray diffraction (see section 8.2.2).

7.2.2. NMR

Most papers on Caryophyllaceae-type cyclopeptides also reported their NMR data, which show ^{1}H and ^{13}C atom signal characteristics of 19 protein α-amino acids and 4 non-protein α-amino acids (see section 4.2). The ^{13}C NMR and ^{1}H NMR data of these α-amino acid residues picked up from some Caryophyllaceae-type cyclopeptides are given in Figures 8 and 9.

7.3. Structural Elucidation of Cyclotides

Because of the exceptional resistance to enzymatic breakdown and high chemical stability of the cyclic backbone and CCK motif of cyclotides, their structures have been determined by sequence analyses after enzymatic hydrolysis of the reduced and alkylated derivatives or partial acidic hydrolysis. The detailed methods include amino acid analyses, proteinase digestion of PEC derivatives after reduction and alkylation, partial acid hydrolysis, N-terminal Edman degradation, FAB-MS, ESI-MS, or MALDI-TOF MS analyses, MS/MS, and 2D NMR (DQF−COSY, HOHAHA, NOESY).[315−330]

Recently Goransson et al. have developed a strategy for analysis of cyclotide total-expression profiles of *Viola* cyclotides (*V. arvensis*, *V. biflora*, *V. cotyledon*, *V. odorata*, *V. riviniana*, *V. tricolor*) with LC-MS and tandem MS sequencing of intercysteine loops after introduction of charges and cleavage sites by aminoethylation. All were found to express notably complex mixtures, with single species containing >50 cyclotides.[327]

8. Configuration and Conformation Study

8.1. Configuration Study

8.1.1. Configuration Study of Cyclopeptide Alkaloids

The configuration of cyclopeptide alkaloids has been studied by chemical conversions, enzymic oxidation, and spectroscopic methods. Chemical conversions of amino acids into diastereomeric derivatives and subsequent identification by amino acid analysis, GC, and GLC have been used

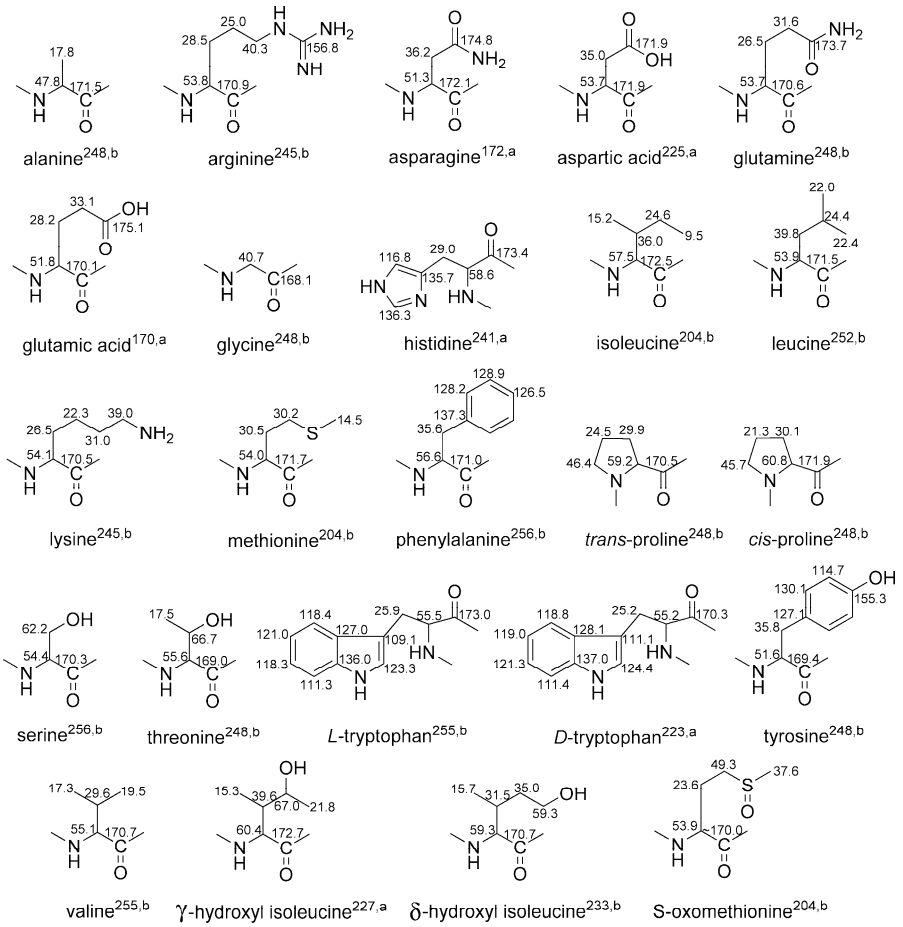


Figure 8. ^{13}C NMR data of amino acid residues picked up from some Caryophyllaceae-type cyclopeptides. [a] In C_5D_5N. [b] In DMSO-d_5.

successfully to determine the chirality of amino acids. Enzymic oxidation with amino acid oxidase is one of the useful methods too.[44,49] Spectral methods include NMR, CD, and X-ray diffraction. Chiral GC and NMR are particularly informative.

Amino acids in cyclopeptide alkaloids generally occur in the L-form (Table 2).[2,112,113] In 1972 Sierra et al. showed that the β-hydroxyleucine, from which the aryl ether function in **Ia1** is constructed, is present in the L-*erythro* (3*S*/4*S*)-form with ^1H NMR, GC, amino acid oxidase, and X-ray analysis.[4,111,112] The characteristic feature of **Ia3** and **Ib** is the *trans* (3*S*/4*S*)-β-hydroxyproline as a constituent of the 14- or 13-membered ring system.[4,97,98,113] Chemical conversion of amino acids into diastereomeric derivatives and subsequent identification by GLC have been used successfully to determine the chirality of *N*,*N*-dimethylamino acids.[4]

The configurations of the ring bond α-amino acid residue, the basic end α-amino acid residue, and the β-hydroxyl amino acid residue of waltherine-C (**51**) were determined to be L-(*S*)-Ala, L-(*S*)-*N*,*N*-Me_2Trp, and L-*erythro*-(3*S*/4*S*)-β-OHLeu;[96] those of sanjoinine-G1 (**59**) were determined to be L-(*S*)-Leu, L-(*S*)-*N*,*N*-Me_2Phe, and L-*erythro*-(3*S*/4*S*)-β-OHPhe;[90] those of scutianine-L (**83**) were determined to be L-(*S*)-Ile, L-(*S*)-*N*,*N*-Me_2Phe, and L-*erythro*-(3*S*/4*S*)-β-OHPhe;[93] those of mucronine-J (**117**) were determined to be L-(*S*)-Ile, L-(*S*)-*N*,*N*-Me_2Leu, and *trans*-(3*S*/4*S*)-β-OHPro;[91] those of paliurine-A (**123**) were determined to be L-(*S*)-Ile, L-(*S*)-*N*,*N*-Me_2Ile-L-(*S*)-Phe, and *trans*-(3*S*/4*S*)-β-OHPro;[97] and those of paliurine-G (**128**) were determined to be L-(*S*)-Ile, L-(*S*)-*N*,*N*-Me_2Phe-L-(*S*)-Val, and *trans*-(3*S*/4*S*)-β-OHPro[98] by chiral GC, ^1H NMR, COSY, NOESY, and CD.

Exceptions are lasiodine-A (**1**) with the ring bond α-amino acid of D-β-OHPhe,[2] pubescine-A (**24**) with the ring bond α-amino acid of D-Leu,[49] scutianine-G (**45**) with the ring bond α-amino acid of D-β-OHPhe,[44,92] scutianine-K (**48**) with the ring bond α-amino acid residue of D-*threo*-(α*R*/β*S*)-β-OHPhe,[93] condaline-A (**73**) with the β-hydroxyl amino acid residue of L-*threo*-(3*S*/4*S*)-β-OHPhe,[101] and discarene-C (**74**) and -D (**75**) with the β-hydroxyl amino acid residues of L-*threo*-(3*S*/4*S*)-β-OHPhe and D-*threo*-(3*S*/4*S*)-β-OHPhe.[99]

8.1.2. Configuration Study of Caryophyllaceae-Type Cyclopeptides

The configurations of Caryophyllaceae-type cyclopeptides have been studied mainly by chiral GC, chiral HPLC, and enzymatic oxidation.

Chiral GC. The amino acids in the hydrolysate after total acidic hydrolysis were converted into the propyl or butyl esters of their *N*-trifluoroacetyl derivatives. These esters were analyzed by GC on a chiral capillary column, and their retention times were compared with those of standards.[168,184,193,195−199,201,202]

Chiral HPLC. The amino acids in the hydrolysate after total acidic hydrolysis were analyzed by HPLC on a chiral column,[174] or the derivatives of the acid hydrolysate were analyzed by treating with Marfey's reagent, and their retention times were compared with those of standards.[181,182,189,204−207,218−221,227,229−231,238−241,244,245]

Enzymatic Oxidation: amino acid oxidase.[203]

Amino acids in Caryophyllaceae-type cyclopeptides generally occur in the L-form (Table 8). The only exception is schnabepeptide (**345**) containing D-Trp.[223]

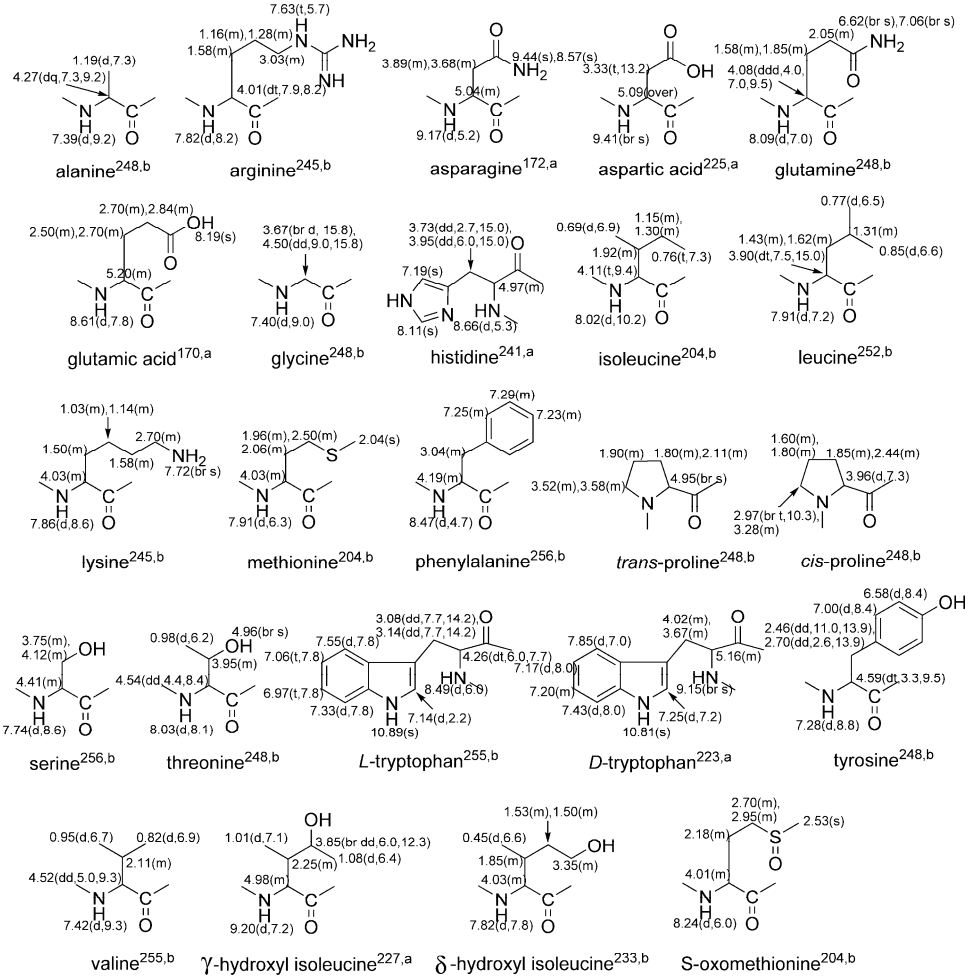


Figure 9. ^{1}H NMR data of amino acid residues picked up from some Caryophyllaceae-type cyclopeptides. [a]In C_5D_5N. [b]In DMSO-d_5.

8.2. Conformation Study

8.2.1. Conformation Study of Cyclopeptide Alkaloids

Conformational studies of cyclopeptide alkaloids have aroused great interest because the restricted molecular mobility of these compounds severely limits the numbers of possible conformers. Their conformations have been investigated by a variety of physicochemical techniques such as NMR and X-ray diffraction.[3]

NMR spectroscopy supplied the first clues to the simultaneous existence of several conformations in solution. Integerrenine (**70**) and adouetine-Z (**84**) exist as mixtures of two conformers in trifluoroacetic acid and CCl_4 solution, respectively. A detailed study has been made of the conformations of discarine-B (**22**), frangulanine (**38**), and paliurine-B (**124**).[3,4,106,107,114]

The **Ia** cyclopeptide alkaloid structures of mauritine-A (**109**) and *N*,*N*,*N*-trimethylfrangulanine methiodide have been confirmed by X-ray analyses. In both, all of the amino acids were found to be of L-configuration, with the amide bonds having a *trans*-geometry. Ring strain in the 14-membered macrocycles was clearly evident in the crystlals. In frangulanine (**38**) the L-*erythro*-(3*S*/4*S*)-stereochemistry of hydroxyleucine was confirmed, the benzene ring and neighboring double bond are twisted as much as 73°, and the conformation of the peptide units is of the β-pleated sheets structure. X-ray diffraction showed **38** to have largely the same conformation whether in crystal form or in solution. In **109** the benzene ring in the central ring system is slightly bent and the attached atoms are considerably out of the benzene plane. A pronounced deviation from coplanarity is apparent in the styrylamide system, preventing π-orbital overlap. The *trans*-stereochemistry of β-hydroxyproline was clearly established.[3,4,112,113]

8.2.2. Conformation Study of Caryophyllaceae-Type Cyclopeptides

Conformational studies of Caryophyllaceae-type cyclopeptides have aroused great interest because these cyclopeptides exhibit a wide range of biological activities. The cyclopeptide backbone is generally considered to be quite flexible with more conformers. But higher plants tend to be rich in proline (Pro) residues, which results in formation of some turns, which are often stabilized by intramolecular hydrogen bonds. So the backbone is constrained and the presence of Pro residues leads to a number of possible stable conformations due to *cis*−*trans* isomerization of a Pro amide bond, which makes the conformational studies in solution or crystals possible.[174] Their conformations have been investigated by a variety of physicochemical techniques such as NMR, CD, computational chemical methods, and X-ray diffraction.

Solution Conformation. Cherimolacyclopeptide A (**220**) is one cyclic octapeptide. Its 3D solution structure was determined by NMR (NOESY) and molecular modeling, and it was characterized by the presence of two β turns and a new type of β-bulge.[168] Diandrines A (**266**), C (**268**), and D (**269**) are cyclic hexapeptides, and diandrine B (**267**) is one

cyclic octapeptide. In **266** the amide bonds of both Pro residues adopted a *cis* geometry and a type IV β turn formed between Phe[6] and Trp[3], as determined by NMR (ROESY), CD, and molecular modeling. In **267** the amide bonds of both Pro residues adopted a *trans* geometry, and it had an L_{+2} helix conformation by NMR and CD. It is more interesting that **268** and **269** are stable conformational isomers. Among them, the amide bonds of both Pro residues adopted a *trans* geometry, and they had a β-pleated sheet conformation by NMR and CD.[189] Mahafacyclin A (**282**) is one cyclic heptapeptide without Pro residues. The solution conformation was shown to have β-bulge characteristics by NMR (ROESY).[198] Segetalin B (**382**) is one cyclic pentapeptide without Pro residues. The solution conformation was shown to have a type II β turn between Trp[4] and Ala[5], and none of the five amide protons was involved in intramolecular hydrogen bondings by NMR (ROESY) and using stimulated annealing calculations.[241] Cycloleonurinin (**290**) is one cyclic dodecapeptide. The solution conformation was examined by NMR methods (ROESY), distance geometry calculations, and restrained energy minimization from NMR data. The backbone structure consisted of two β turns: a type VI β turn at Pro[2]-Pro[3] and a type I β turn at Pro[4]-Ala. In addition to two transannular 4→1 backbone hydrogen bonds between Tyr[2]-NH and Pro[3]-CO and between Thr[1]-NH and Tyr[1]-CO, γ turns between Thr[2]-NH and Tyr[1]-CO and between Ala-NH and Thr[1]-OH were observed. Pro[1], Pro[2], and Pro[4] residues adopted a *trans* geometry, but the Pro[3] residue adopted a *cis* one.[248] Cycloleonuripeptides A−C (**291**−**293**) are cyclic nonapeptides with five Pro residues with Pro-Pro and Pro-Pro-Pro sequences. It is more interesting that **292** and **293** are stable conformational isomers. Their 3D structures were determined by distance geometry calculations and restrained energy minimizations from NMR data (ROESY). Their backbone structures consisted of two β turns: a type VI β turn at Pro[3]-Pro[4] and a type I β turn at Pro[7]-Met[8] or OMet[8]. In addition to a transannular 4→1 backbone hydrogen bond between Tyr[5]-NH and Pro[2]-CO, two intramolecular hydrogen bonds between Gly[1]-NH and Pro[6]-CO and between Ile[9]-NH and Pro[6]-CO, which constructed a β-bulge conformation, were observed. The Pro[1], Pro[2], Pro[3], and Pro[5] residues adopted a *trans* geometry, but the Pro[4] residue adopted a *cis* one.[249] Pseudostellarin A (**331**) is one cyclic pentapeptide. Its conformational studies were performed by NMR (ROESY) and computational chemical evidences, and it was characterized by the presence of one transannular hydrogen bond between Gly and Leu, one β turn, and one γ turn.[252] Segetalins D and E (**384** and **385**) are cyclic hepapeptides. Their conformational studies were performed by NMR (ROESY) and computational methods. Each had two β turns: a type II β turn at Pro[7]-Gly[1] and a type I β turn at Phe[4]-Ala[5] for **384**, and a type II β turn at Pro[7]-Gly[1] and a type VI β turn at Val[3]-Pro[4] for **385**, respectively. In addition, each had three intramolecular hydrogen bonds, which constructed a classical β-bulge motif.[256]

Solid Conformation. Brachystemin C (**241**) is one cyclic octapeptide. The stereochemistry was clarified by an X-ray crystallographic study. The cyclic octapeptide backbone contained three β turns. Two of them are type I β turns, and one is a type III β turn (right-handed 3_{10} helix). There were intermolecular hydrogen bonds between the cyclopeptide and the solvent molecules which maintained the steady spatial arrangement in the crystal.[178] Cycloleonuripeptide D (**294**) is one cyclic decapeptide with three successive Pro residues. The solid state conformation was clarified by an X-ray diffraction study. The cyclic decapeptide backbone contained two β turns: one type I β turn at Pro[9]-Ile[10] and one III β turn at Pro[4]-Tyr[5]. A transannular 4→1 backbone hydrogen bond between Ser[1]-NH and Thr[8]-CO, and a 5→1 hydrogen bond between Phe[6]-NH and Pro[2]-CO encompassing Pro[3]-Pro[4]-Tyr[5], in which the peptide linkage between the two Pro residues was shown to be in the *cis* conformation, were observed.[205] Dichotomin A (**358**) is one cyclic hexapeptide without Pro residues. Single-crystal X-ray analysis was conducted. The cyclic hexapeptide backbone contained two β turns: one type I β turn at Phe[3]-Leu[4] without a transannular intramolecular hydrogen bond and one type II β turn at Val[6]-Gly[1] with the intramolecular hydrogen bond between Thr[2]-NH and Tyr[5]-CO. Additionally, a side chain−main chain interaction was observed between the backbone NH group of Leu[4] and the side chain oxygen of Thr[2].[229]

Solution and Solid State Conformations. Cyclolinopeptides A and B (**295** and **296**) are cyclic nonapeptides. Their solid state and solution conformations were examined by X-ray, NMR, and distance geometry calculations by several groups. The solid conformation of **295** by X-ray was characterized by the presence of five intramolecular hydrogen bonds and four turns (a type III β turn, a type I β turn, an inverse γ turn, and an α turn). The amide bonds except the Pro[1]-Pro[2] bond had *trans* geometry. The conformation in the solid state of **295** was similar to those in the solution state of **295** and **296**.[250,251] Pseudostellarin D (**334**) is one cyclic heptapeptide. The solid and solution conformations were examined by X-ray and NMR (ROESY). The solid conformation of **334** possessed a type II β turn between Leu[7] and Gly[1], a type I β turn between Pro[4] and Leu[5], one transannular 4→1 hydrogen bond between Ile[6]-NH and Gly[3]-CO, and two bifurcated hydrogen bonds between Tyr[2]-NH and Ile[6]-CO and between Gly[3]-NH and Ile[6]-CO, forming a classical β-bulge. The amide bonds had *trans* geometry. The conformation in the solution state of **334** was homologous to that in the solid state.[253] Yunnanin A (**375**) is one cyclic heptapeptide. The solid and solution conformations were examined by X-ray, NMR (ROESY), and Monte Carlo (MC) and restrained molecular dynamics (MD) calculations. The solid conformation of **375** possessed three intramolucular hydrogen bonds forming one type II β turn, one type II′ β turn, and a classical β-bulge unit with all *trans* amide bonds. The conformation in the solution state of **375** was homologous to that in the solid state.[254] Segetalin A (**381**) is one cyclic hexapeptide. The solid and solution conformations were examined by X-ray, NMR (ROESY), and computational chemical evidence. The solid conformation of **381** was characterized by two β turns (a type I β turn and a type VI β turn), fixed by two transannular hydrogen bonds formed between Gly and Val[2]. On the other hand, in solution, the molecule was shown to have two β turns (a type II β turn and a type VI β turn). Results demonstrated that **381** took different backbone conformations in solid and solution states.[255]

8.2.3. Conformational Study of Rubiaceae-Type Cyclopeptides

Usually Rubiaceae-type cyclopeptides have more conformers in solution, which are produced by the isomerization about one or more *N*-methyl amide bonds and which make their NMR spectra more complicated and difficult for ^{1}H

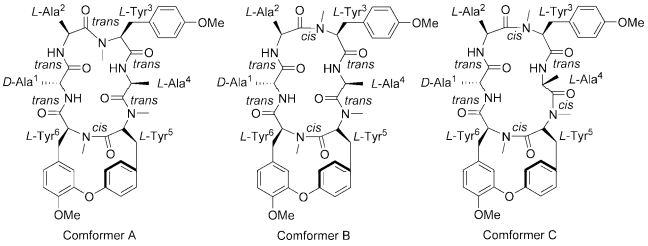


Figure 10. Molecular structures of three different conformers, A, B, and C, of RA-VII (**398**) in DMSO-d_6.

and ^{13}C signal assignments and solution conformational study.

The ^1H NMR spectrum of RA-VII (**398**) suggested the presence of two stable conformational states in $CDCl_3$, i.e., conformers A and B, and of three different conformers, A, B, and C, in a polar solvent, e.g., in DMSO-d_6. The conformational analysis of **398** in solution states was conducted by spectroscopic (NMR and CD) and computational chemical methods (molecular dynamics and molecular mechanics calculations). The predominant conformer, A, exhibited a typical type II β turn with a *trans* peptide bond at L-Ala^2 and L-Tyr^3 by stabilization of the intramolecular hydrogen bond between D-Ala^1-CO and L-Ala^4-NH, which is similar to the crystal structure analyzed by X-ray diffraction. Conformer B exhibited a type IV β turn with a *cis* peptide bond at L-Ala^2 and L-Tyr^3. Conformer C adopted three *cis* peptide bonds at L-Ala^2 and L-Tyr^3, L-Ala^4 and L-Tyr^5, and L-Tyr^5 and L-Tyr^6. Thus, conformers A, B, and C of **398** are *trans*−*cis* isomers about the L-Ala^2 and L-Tyr^3, L-Ala^4 and L-Tyr^5, and L-Tyr^5 and L-Tyr^6 peptide bonds (Figure 10).[277,278] The LiCl complexed solution conformation of **398** closely resembles the X-ray structure conformation.[279]

The solid conformational analysis of RA-V (deoxybouvardin, **389**) indicated that **389** can be divided into two structurally distinct moieties: one, the more characteristic moiety, is a highly strained 14-membered ring consisting of a diaryl ether, L-Tyr^5, and L-Tyr^6, and the other is 18-membered ring which forms an antiparallel β-pleated sheet with a type II β turn at L-Ala^2 and L-Tyr^3. Two weak intramolecular hydrogen bonds between D-Ala^1-CO and L-Ala^4-NH and between D-Ala^1-NH and L-Ala^4-CO stabilize this β turn.[277]

The solid conformation of bouvardin (**388**) was studied by X-ray diffraction. It contained a *cis* peptide bond in the 14-membered ring and had a weak intramolecular hydrogen bond between D-Ala^1-CO and L-Ala^4-NH.[255] **388**, deoxybouvardin (**389**), and 6-*O*-methylbouvardin (**390**) were observed to be two conformers (85:15) in $CHCl_3$, in which the barrier is about 20 kcal/mol. The major conformation of **388** in solution is the same as that in the crystal.[263]

By the conformational analysis of RA-VI (**396**) in its crystalline state using the X-ray diffractometric technique, **396** was shown to have, in its solid state, a type V β turn structure at the residues L-Ser^2 and D-Tyr^3, while other RAs have type II β turns. In a solution of $CDCl_3$, **396** was shown to exist only as conformer A and RA-VIII (**398**) was shown to exist as conformers A, B, and C. A combination of 2D NMR and NOE relationships showed that the amino acids constituting the β turn of **396** are L-Ser^2 and D-Tyr^3 and those of **398** are L-Thr^2 and L-Tyr^3.[266]

More interestingly, RAI-III (**394**) and -VI (**397**) are conformational isomers of RA-III (**393**) and -VI (**396**), respectively. By the conformational analysis of **394** and **397** using spectroscopic and computational chemical methods, they were shown to have γ turn structures at L-Ser^2, D-Tyr^3, and L-Ala^4, which were stabilized by a hydrogen bond between L-Ser^2-OH and L-Ala^1-CO.[267]

The NMR spectroscopic data indicated that RA-IX (**400**) has a single stable conformational state in solution, i.e., a type II β turn at L-pyroGlu^2 and L-Tyr^3, which was considered to be due to the constrained structure of the five-membered ring of the pyroGlu^2 residue. But RA-X (**401**) has two conformational states (85:15) in $CDCl_3$.[268]

8.2.4. Conformational Study of Cyclotides

Using 2D NMR and distance-restrained simulated annealing, the three-dimensional solution structure of kalata B1 (**424**) has been determined. Results indicated that **424** was composed mainly of β-strands connected by tight turns, forming regions of β-sheets, except in the case of one section which forms a longer, less structured loop. The tertiary fold, together with the disulfides that form a sulfur core, produces a striking and unusual surface in which the majority of the hydrophobic residues form a solvent-exposed patch. The hydrophobic side of **424** is flanked by two diametrically opposed and opposite-charged residues. Three disulfide bonding patterns are C^I-C^{IV}, C^{II}-C^V, and C^{III}-C^{VI}. Its cyclic peptide backbone is folded back onto itself and braced with disulfide pairs across diagonally opposed β-strands. This structure involves the third disulfide bond of C^{III}-C^{VI} threading through the eight amino acid loop formed by the other two disulfide bonds of C^I-C^{IV} and C^{II}-C^V and the peptide fragments connecting them (CCK motif).[321] Later, Volkman and co-workers proposed different three disulfide bonding patterns of C^I-C^{VI}, C^{II}-C^V, and C^{III}-C^{IV} based on 2D NMR, a laddered arrangement.[335] Recently, Craik and co-workers provided more evidence in favor of the originally proposed knotted topology with oxidative refolding and reductive unfolding,[336] using 2D NMR[337] and disulfide analysis.[338]

The three-dimensional solution structure of circulin A (**411**) was determined using 2D NMR (TOCSY, NOESY). **411** adopted a compact structure consisting of β-turns and a distorted segment of triple-stranded β-sheets and contained a CCK motif.[332]

The solution structure of MCoTI-II (**423**) was determined using 2D NMR (TOCSY, NOESY) and simulated annealing calculations. **423** consisted of a small β-sheet, several turns, and a CCK motif.[333,334]

The three-dimensional solution structure of palicourein (**432**), the largest known cyclotide, was determined using 2D NMR (TOCSY, NOESY) and simulated annealing calculations. The structural data showed that an increase in size of a loop did not perturb the core fold. **432** contained a CCK motif also.[340]

The solution structure of vhr1 (**446**) was determined using 2D NMR (COSY, TOCSY, NOESY) combined with simulated annealing calculations. Results indicated that **446** contained a CCK motif also.[328]

The three-dimensional structure of cycloviolacin O1 (**447**), determined by 2D NMR and distance-restrained simulated annealing, is compact and contains a number of β-turns, three β-strands arranged in a triple-stranded β-sheet, a short helical segment, and a network of disulfide bonds which form a CCK motif.[322,337]

The solid structure of SFTI-1 (**461**) was determined by X-ray diffraction. Its structure formed two antiparallel β-strands connected at the reactive site end by an extended

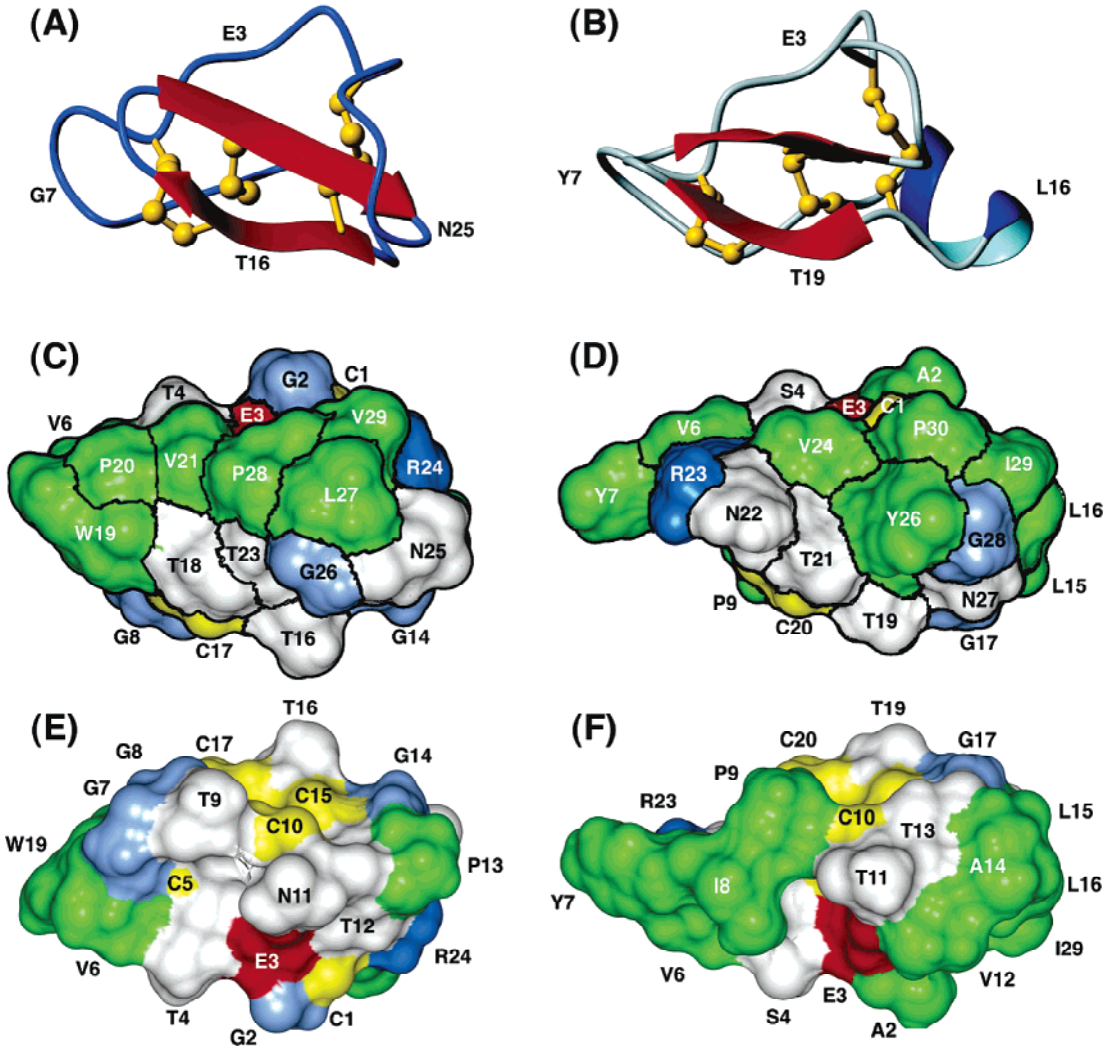


Figure 11. Structures of representative cyclotides kalata B1 (**424**, Moebius) and cycloviolacin O1 (**447**, Bracelet). Parts A and B show the orientation used to view the surfaces of **424** (C) and **447** (D), respectively. The surface of individual residues is colored based on their properties, with green, blue, yellow, white, red, and purple representing hydrophobic, glycine, cysteine, hydrophilic, negative, and positive residues, respectively. From parts C and D it is clear that a major hydrophobic patch involving loops 2, 5, and 6 is present in **424** and **447**. In contrast, on the other face of the molecules (shown in parts E and F, respectively, for **424** and **447**), there are clearly differences in the surface nature, with **447** incorporating an additional hydrophobic patch because of the hydrophobic nature of the extended loop 3. E and F are rotated 180° in relation to C and D.[337]

loop region and connected by a hairpin turn at the opposite end. These strands were constrained by the single disulfide bond (between C^{VII} and C^{VIII}), dividing **461** into a nine-residue loop region (the "reactive loop") and a five-residue turn (the "cyclic loop"). There is a sharp turn in the peptide chain at −N-Ile-Pro-CO− with *cis* conformation. There were three intramolecular main-chain hydrogen bonds stabilizing the backbone. **461** showed clear parallels with the trypsin-reactive loop region of the Bowman−Birk inhibitor family of inhibitors in amino acid sequence, conformation, and mechanism of inhibition, but it differed from this family in size and its cyclic nature.[331] Its solution structure is similar to the crystal structure of **461** in complex with trypsin.[341]

Figure 11 presents the structures of the representative cyclotides kalata B1 (**424**, Moebius) and cycloviolacin O1 (**447**, Bracelet).[337]

9. Synthesis

9.1. Synthesis of Cyclopeptide Alkaloids

During the past three decades, synthesis of cyclopeptide alkaloids has been paid more attention because of the importance of their structures, biological activities and functions, and sources. Schmidt[3] and Joullie[4,6] have reviewed the synthesis of cyclopeptide alkaloids. Compared with the cases of types **Ib** and **Ic**, synthesis of type **Ia** cyclopeptide alkaloids is more difficult as a result of the rigid structure in the 14-membered ring with two *s-trans* amide groups. The primary synthetic challenges that must be overcome in such an endeavor are formation of the alkyl−aryl ether, introduction of unsaturation, and macrocyclization.[6] Pioneering works of synthetic chemistry related to cyclopeptide alkaloids were carried out by the Pais[122] and Rapoport[123] groups in the 1970s. Later, the Schmidt,[124−128] Joullie,[129−132] Lipshutz,[133] Han,[134] and Zhu[135,136] groups made great contributions to the field, especially the Schmidt group.

The Schmidt group discovered that activation of a carboxyl group as a pentafluorophenyl ester is particularly efficient for the desired macrolactamization. On the basis of this methodology, they accomplished the first total synthesis of types **Ia**, **Ib**, and **Ic** cyclopeptide alkaloids or dihydrocyclopeptide alkaloids (Figure 12): **Ia**, dihydrozizyphine-G[124] and frangulanine (**38**);[128] **Ib**, dihydrozizyphine-A,[125] dihydrozizy-

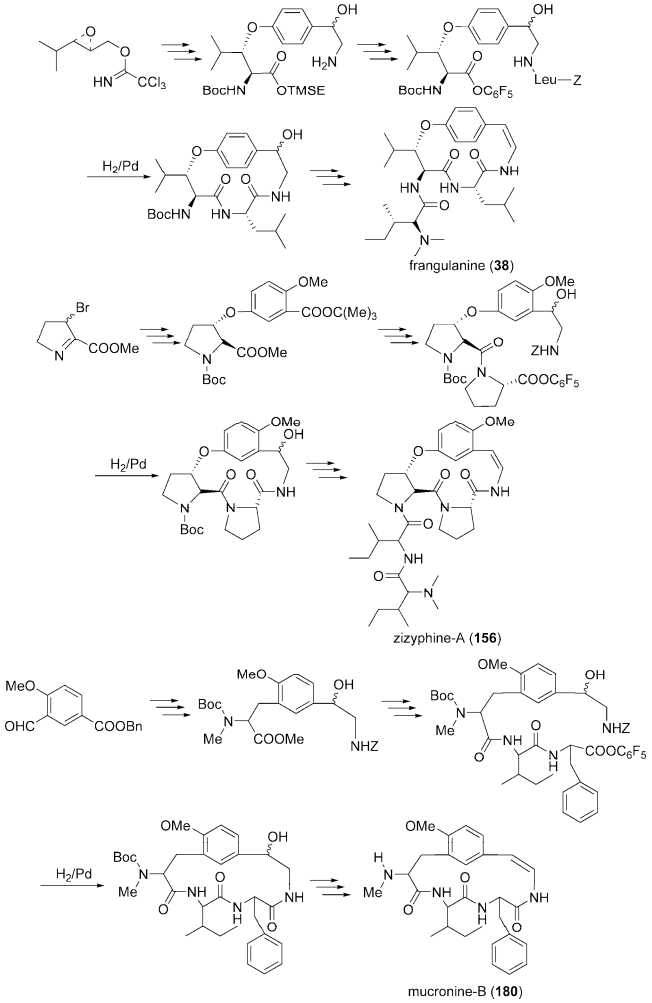


Figure 12. Summary of the Schmidt syntheses of frangulanine (**38**), zizyphine-A (**156**), and mucronine-B (**180**).

phine-B,[125] and zizyphine-A (**156**);[126] **Ic**, mucronine-B (**180**).[127]

Upon the basis of a similar macrolactamization strategy to that of the Schmidt group, the Joullie group accomplished the total syntheses of type **Ia** cyclopeptide alkaloids or dihydrocyclopeptide alkaloids (Figure 13), dihydromauritine-A,[129] frangufoline (**37**),[131] sanjoinine-G1 (**59**),[132] sanjoinine G1 C-11 epimer,[132] and nummularine-F (**118**),[130] in which **59** was synthesized by the Han group at first in 1995.[134]

The Zhu group developed the macrocyclization protocol featuring a key intramolecular S_NAr reaction. On the basis of this methodology, they accomplished the total syntheses of type **Ia** cyclopeptide alkaloids (Figure 14): sanjoinine-G1 (**59**)[136] and mauritine-A (**109**).[135]

9.2. Synthesis of Caryophyllaceae-Type Cyclopeptides

Only a few publications dealt with the synthesis of Caryophyllaceae-type cyclopeptides by SPPS methods. To confirm the proposed sequence of chevalierins A−C (**275**−**277**) and mahafacyclin B (**283**) and to make available sufficient amounts of these cyclopeptides for bioassays, in which **275** and **283** showed antimalarial activity (IC_{50} = 8.9 and 2.2 μM), Auvin-Guette and co-workers synthesized these four cyclopeptides by a solid-phase technique with the glycine residue in the C-terminal position to prevent racemization in the cyclization. The cyclization step was ac-

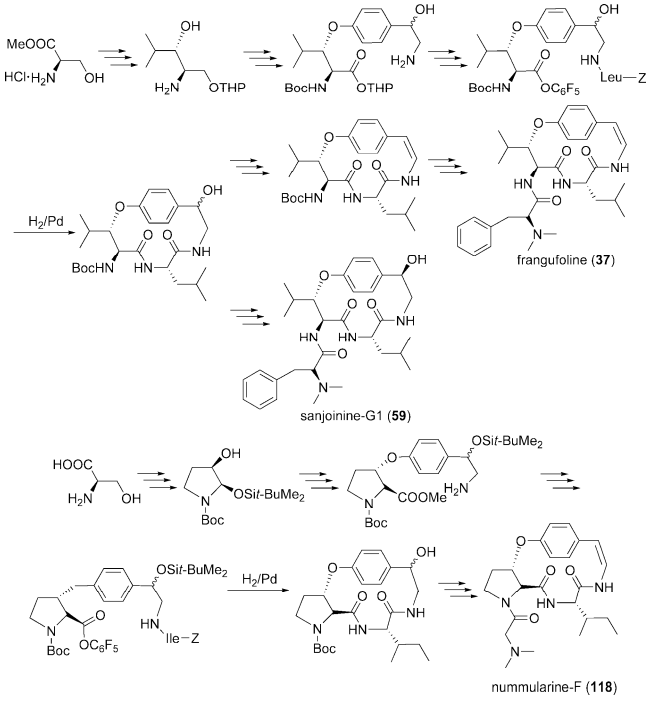


Figure 13. Summary of the Joullie syntheses of frangufoline (**37**), sanjoinine-G1 (**59**), and nummularine-F (**118**).

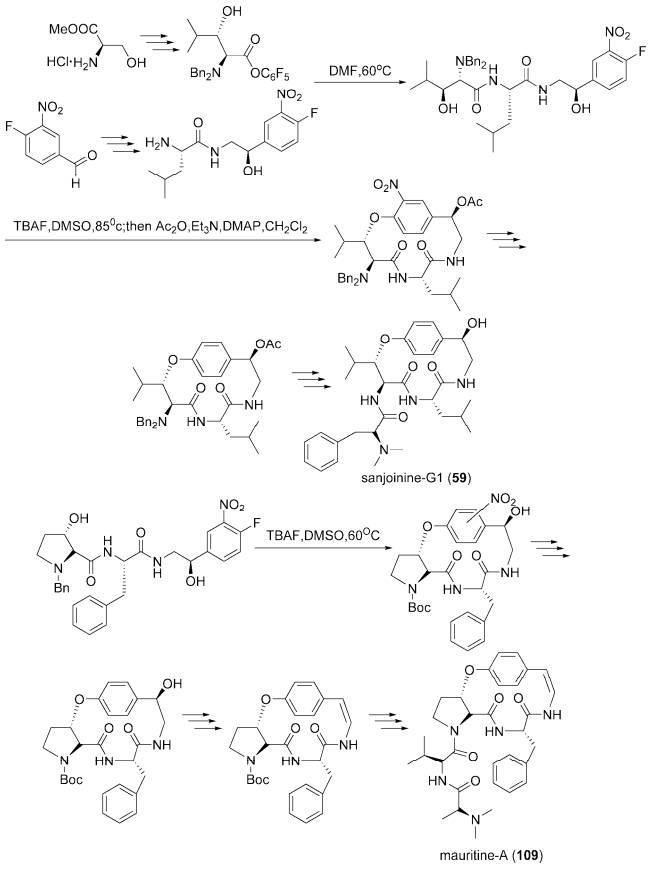


Figure 14. Summary of the Zhu syntheses of sanjoinine-G1 (**59**) and mauritine-A (**109**).

complished in DMF under high dilution conditions (10^{-3} M) with 1.5 equiv of HBTU and 10 equiv of Net_3.[193,199] Poojary et al. synthesized pseudostellarin G (**337**) using the *p*-nitrophenyl ester method for cyclization. The synthetic **337** showed antibacterial, anti-inflammatory, and anthelmintic acitivities.[257] Gomez-Paloma and co-workers synthesized

yunnanins A (**375**) and C (**377**) with antitumor activity, using a combination of solid and solution techniques with the Fmoc/*t*-Bu chemistry and a 2-chlorotrityl chloride resin as solid support. The cyclization reaction was allowed to proceed in solution using HATU and DIEA in CH_2Cl_2. Interestingly, the synthetic cyclopeptides, although found to be chemically identical with their natural counterparts, did not display antitumor activity.[258] Sonnet et al. synthesized segetalins A (**381**), B (**382**), and G (**386**) with estrogen-like activity, using standard automated continuous-flow SPPS methods with the alanine or glycine residues in the C-terminal position. DPPA in acetonitrile gave the best results for the ring closures without epimerization.[259,260] Itokawa and co-workers provided four derivatives of thionation of **381** and **382** with Lawesson's reagent. Results indicated that only thiosegetalin A2 took the similar solution conformation to that of parent **381** and showed estrogen-like activity.[261]

9.3. Synthesis of Rubiaceae-Type Cyclopeptides

The molecular architecture and interesting biological activity made Rubiaceae-type cyclopeptides attractive synthetic targets. Realizing that ring closure of the 18-membered macrocycle at D-Ala[1] and L-Tyr[6] was relatively easy, all synthetic efforts had thus far concentrated on synthesis of the key subunit, L,L-*N*,*N*-dimethylcycloisodityrosine, which relied on formation of the biaryl ether bond. The Inoue,[280,281] Boger,[282−285] and Zhu[286] groups have made great contributions to the synthesis of Rubiaceae-type cyclopeptides.

The Inoue group accomplished the first total synthesis of deoxybouvardin (**389**) and RA-VII (**398**) in low yields. The first step was an intramolecular oxidative coupling reaction of two phenolic parts of a L-tyrosyl-L-tyrosyl derivative with TTN, which was crucial to the synthesis and afforded a highly strained 14-membered ring system. The subsequent coupling with a tetrapeptide followed by ring closure at D-Ala[1] and L-Tyr[6] with DCC led to **398**. Selective demethylation of **398** with $AlCl_3$ afforded **389** (Figure 15).[280,281]

Later, The Boger group accomplished the synthesis of bouvardin (**388**), deoxybouvardin (**389**), and RA-VII (**398**) based on the intramolecular Ullmann reaction with NaH and $CuBr-SMe_2$ as the key macrocyclization reaction in the preparation of the elusive 14-membered cycloisodityrosine subunit. Subsequent coupling with a tetrapeptide and macrocyclization at D-Ala[1] and L-Tyr[6] provided **398**. Selective demethylation of **398** with BBr_3 afforded **389**.[282−284] Then the authors indicated that their past 14-membered intermediates possessed the unnatural (9*R*,12*S*)-stereochemistry and that their conversion to **388**, **389**, and **398** required reepimerization of the Cα of L-Tyr[6] to the natural (*S*)-configuration. They synthesized two 14-membered intermediates: natural (9*S*,12*S*)-cycloisodityrosine derivatives and unnatural (9*R*,12*S*)-diastereomers. This approach developed by the Zhu group[286] was based on an intramolecular S_NAr reaction for formation of the key biaryl ether with 14-membered ring macrocyclization with NaH and included the documentation of a facile C9 base-catalyzed epimerization within the natural 9*S* series.[285] But the syntheses of **388**, **389**, and **398** had not been reported by them.

The Zhu group accomplished the synthesis of RA-VII (**398**) in which the conditions were much milder and the yield was much higher than those of Inoue's and Boger's works. This method was based on an intramolecular S_NAr-based cycloetherification reaction to form the key ring-closure step for construction of the illusive 14-membered *m*,*p*-cyclophane

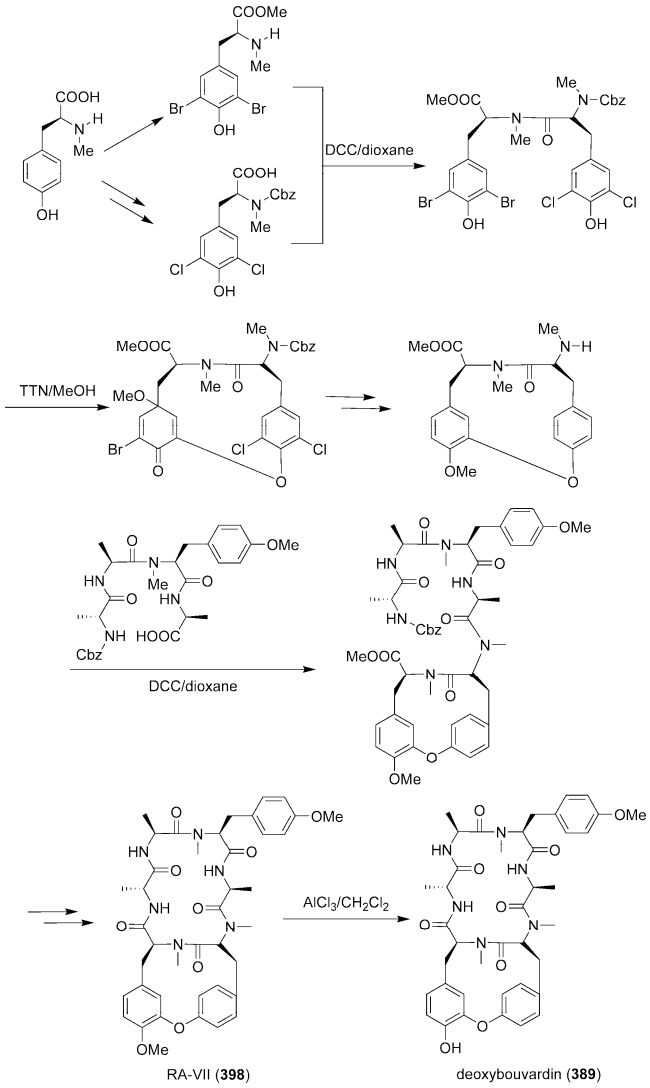


Figure 15. Summary of the Inoue syntheses of deoxybouvardin (**389**) and RA-VII (**398**).

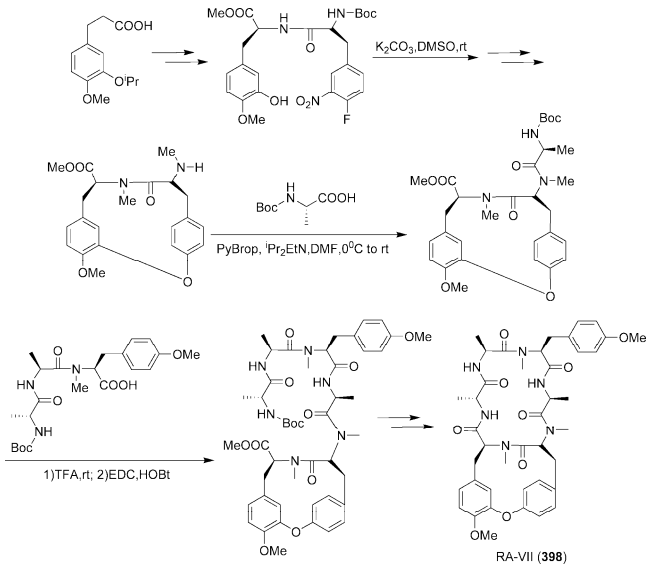


Figure 16. Summary of the Zhu synthesis of RA-VII (**398**).

with K_2CO_3. Subsequent coupling with a L-*N*-Boc-Ala and a tripeptide and macrocyclization at D-Ala[1] and L-Tyr[6] provided **398** (Figure 16).[286]

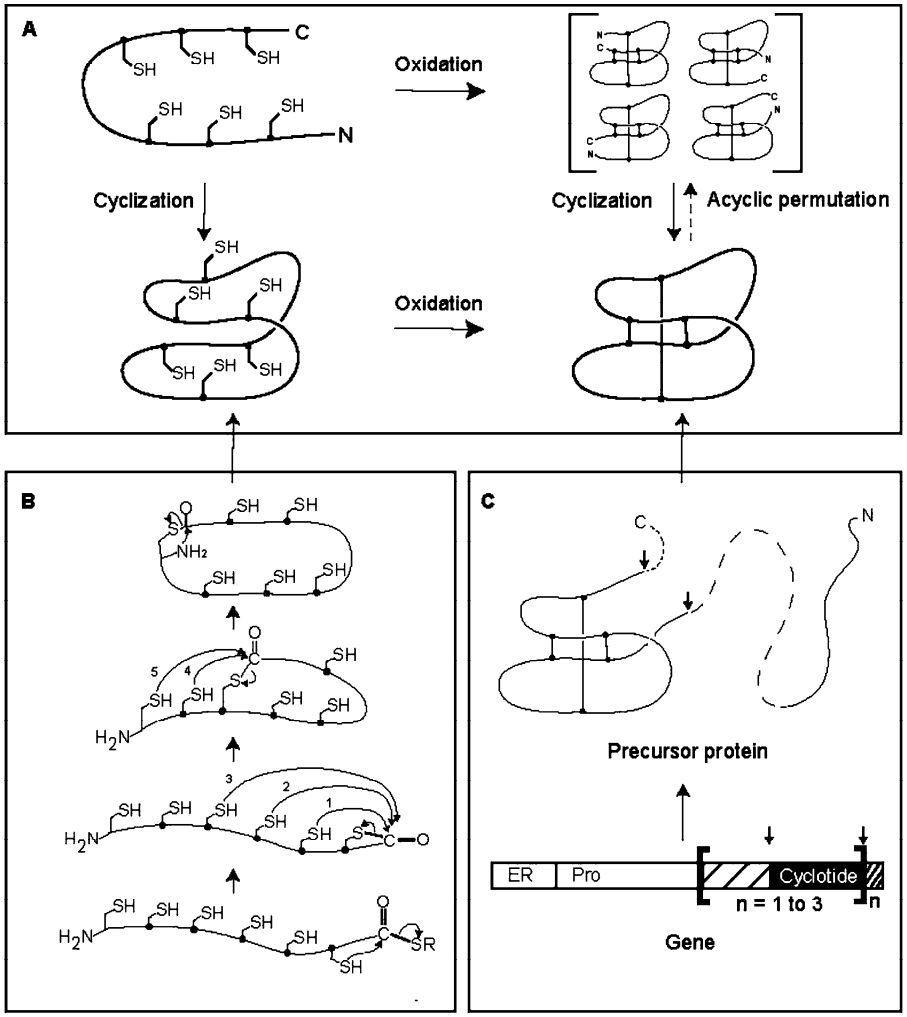


Figure 17. Pathways for the production of cyclotides.[11] (A) Two general synthetic strategies for cyclotides involve either oxidation followed by cyclization, or cyclization followed by oxidation. The concept of acyclic permutation is also shown in the top right-hand region of the panel, with the four acyclic permutants that can form a cystine knot illustrated.[343] (B) This section shows the synthetic approach to cyclization by the thia zip mechanism. Facile thioester/thiol exchange allows serial thioester ring expansion and is indicated with arrows labeled 1−5. The final step involves an S,N-acyl migration to form a cyclic product.[342] (C) The biosynthetic pathway to native cyclotides has been reported. A schematic representation of the cyclotide gene structure is shown at the bottom of the panel. The ER signal peptide is followed by a prodomain. This domain is followed by an N-terminal (N−T) repeat fragment (wide hashed area) that precedes the cyclotide domain. A small C-terminal tail follows the cyclotide domain (close hashed area). Some genes contain multiple copies of the N−T repeat and mature domains. A schematic representation of a precursor protein with a single mature domain is shown above the gene structure. The mature domain is shown as a solid line with disulfide bonds formed, and the N−T repeat fragment and the C-terminal tail are dashed to correspond to the hashing in the gene structure. The linear multidomain precursor protein is cleaved and ligated to give mature cyclotides. The ligation sites required to produce the mature domain are indicated with small arrows.[345]

9.4. Synthesis of Cyclotides

Investigation of the synthesis and folding of cyclotides is somewhat more challenging because of their cyclic nature with three disulfide bonds, i.e., the CCK motif.

The Craik group has synthesized kalata B1 (**424**) using two separate methods, one of which involved formation of the disulfide bonds prior to cyclization and one of which involved cyclization prior to formation of the disulfide bonds. The latter was the preferred strategy (Figure 17A).[11,343]

The Tam group has synthesized circulin B (**412**) and cyclopsychotride A (**433**) using the thia zip mechanism for cyclization (Figure 17B).[11,342]

10. Biosynthesis

10.1. Biosynthesis of Cyclopeptide Alkaloids

Types **Ia** and **Ib** of cyclopeptide alkaloids may be formed biogenetically from a tripeptide containing two dehydroamino acids by addition of a phenolic group to the double bond of one of the latter. This assumption is supported by the isolation from *Lasiodiscus marmoratus* (Rhamnaceae) of a linear alkaloid, lasiodine-A (**1**, Table 2), which was shown to have both a free phenolic group and a dehydroamino acid unit. Biogenesis of **Ic** cyclopeptide alkaloids may involve a *m*-phenylenedialanine precursor or the corresponding dehydro compound (Figure 18).[3] In 1993 Baig et al. provided the preliminary experimental results of tetrapeptide precursors by callus of *Ceanothus americanus*.[115]

10.2. Biosynthesis of Cyclotides

Cyclotides may be gene products derived from the processing of a larger precursor protein, whose sequence is encoded by DNA. Anderson and co-workers have isolated a cDNA clone that encodes the cyclotide kalata B1 (**424**) as well as three other clones for related cyclotides from the African plant *Oldenlandia affinis*. The cDNA clones encode

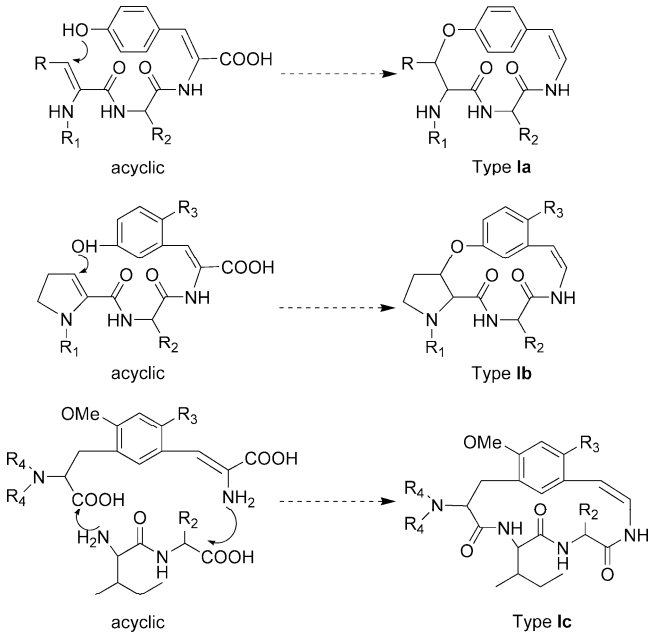


Figure 18. Possible biosynthetic pathway of cyclopeptide alkaloids.

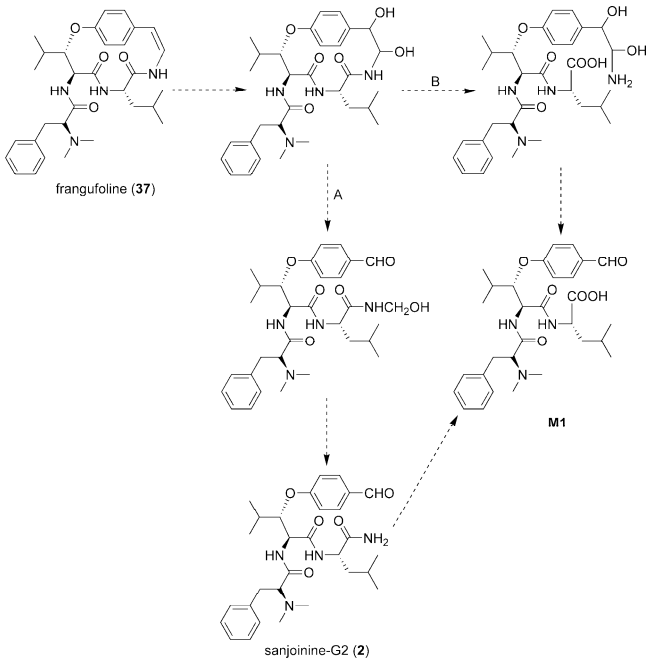


Figure 19. Possible mechanism for the ring cleavage of frangufoline (**37**).

prepropeptides with a 20-aa signal sequence, an N-terminal prosequence of 46−68 amino acids, and one, two, or three cyclotide domains separated by regions of about 25 aa. The corresponding cyclotides have been isolated from plant material, indicating that the cyclotide domains are excised and cyclized from all four predicted precursor proteins. The exact processing site is likely to lie on the N-terminal side of the strongly conserved GlyLeuPro or SerLeuPro sequence that flanks both sides of the cyclotide domain (Figure 17C).[11,345]

11. Biological Activity and Biological Functions

11.1. Biological Activity

11.1.1. Biological Activity of Cyclopeptide Alkaloids

Although some cyclopeptide alkaloids showed antibacterial, antifungal, antiplasmodial, antimycobacterial, sedative, and immunostimulant activities (Table 2), there have not been any potential cyclopeptide alkaloids for new drug research and development. It is noteworthy that discarine-A (**21**),[104] discarine-B (**22**),[104] frangufoline (**37**),[76] scutianine-B (**40**),[101] nummularine-K (**54**),[76] condaline-A (**73**),[101] amphibine-H (**133**),[76] nummularine-B (**147**),[76] nummularine-R (**153**),[76] nummularine-S (**154**),[76] rugosanine-A (**166**),[76] rugosanine-B (**167**),[76] abyssenine-C (**178**),[32] mucronine-F (**183**),[32] mucronine-G (**184**),[32] and mucronine-H (**185**)[32] showed antibacterial activity; **37**,[76] **54**,[76] **133**,[76] **147**,[76] **153**,[76] **154**,[76] **166**,[76] **167**,[76] and **178**[32] showed antifungal activity; Ziziphine-N (**162**)[105] and -Q (**165**)[105] showed antiplasmodial and antimycobacterial activity; and **37** (sanjoinine-A) showed strong sedative activity by measuring the hexobarbital-induced sleeping time.[74] Naturally occurring **37** and sanjoinine-G2 (**2**), along with synthetically derived sanjoinine AH-1 and sanjoinine A dialdehyde, were reported to be effective inhibitors of calmodulin-induced activation of Ca^{2+} ATPase, which was found to correlate well with their sedative properties. In addition, sanjoinine D (**57**) was shown to act as an inhibitor of calmoduolin-induced activation of phophodiesterase.[6] But studies by Lee and co-workers have shown that nummularine-H (**149**) could shorten the mexthohexital-induced sleeping time instead of prolonging for paliurine-A (**123**) and paliurine-F (**127**),[98] and **123**, paliurine-B (**124**), paliurine-C (**125**), paliurine-D (**126**), **127**, and sativanine-G (**172**) possessed immunostimulant activity.[97]

Han and co-workers[116] reported that frangufoline (**37**), a sedative **Ia1** cyclopeptide alkaloid, was converted to a linear compound sanjoinine-G2 (**2**) via unusual enamide cleavage under mild acidic conditions (2 N HCl, 55 °C, 10 h). Air oxidation of the vinylic double bond followed by the liberation of formaldehyde is proposed for a possible mechanism for the ring cleavage (Figure 19, A). One year later, Han and co-workers[117] reported that **37** was found to be rapidly converted, via an enzymatic process, *in vitro* and *in vivo* in rodents to **M1**, which was also formed by acid treatment of **37**.[116] They thought the enamide bond is the site being cleaved and proposed a possible mechanism for the conversion, in which oxidation of the vinyl group and enzyme-catalyzed hydrolysis of the adjacent amide bond, possibly by a B-esterase-like enzyme, proceed in a concerted manner (Figure 19, B).

11.1.2. Biological Activity of Caryophyllaceae-Type Cyclopeptides

It has been reported that some Caryophyllaceae-type cyclopeptides showed interesting biological activities including cytotoxic, antiplatelet, antimalarial, immunomodulating, immunosuppressive, Ca^{2+} antagonistic, inhibiting cyclooxgenase and tyrosinase, enhancing rotamase, and estrogen-like activity (Table 8). It is noteworthy that cherimolacyclopeptides A and B (**220** and **221**),[168] dianthin E (**261**),[186] cycloleonuripeptides B and C (**292** and **293**),[204] dichotomins A−C (**358**−**360**), E (**362**), H (**365**), and I (**366**),[229,231] yunnanins A−D (**375**−**378**),[238,239] and segetalin E (**385**)[338] showed cell growth inhibitory activity against tumoral KB or P-388 cells. Only diandrine A (**266**) showed a selective inhibitory effect on collagen-induced platelet aggregation.[189] Chevalierin A (**275**),[193] mahafacyclins A and B (**282** and **283**),[198,199] and pohlianins A−C (**287**−**289**)[202] showed antimalarial activity. Curcacyline A (**278**)[194] and labaditin

Table 13. Activity Summary of Rubiaceae-Type Cyclopeptides

cyclopeptide	PS test (T/C)	B1 test (T/C)	KB cell ([a]ED_{50}, [b]IC_{50}) (μg/mL)	P388 cell (IC_{50}, μg/mL)
bouvardin (**388**)[262]	135−217% at 0.02−2.0 mg/kg	134−152% at 0.12−2.0 mg/kg	4.3×10^{-7} [a]	
deoxybouvardin (**389**)[262]	142−216% at 0.04−2.0 mg/kg	133−175% at 0.25−8.0 mg/kg	1.9×10^{-8} [a]	
6-*O*-methylbouvardin (**390**)[263]	134% at 1.0 mg/kg			
RA-I (**391**)[264]	169.3% at 10 mg/kg			
RA-II (**392**)[264]	142.2% at 10 mg/kg			
RA-III (**393**)[264,266]	179.4% at 2.0 mg/kg		4.0×10^{-3} [b]	1.2×10^{-2}
RAI−III (**394**)[267]			7.4×10^{-1} [b]	1.4×10^{-1}
RA-IV (**395**)[264]	149.0% at 10 mg/kg			
RA-V (deoxybouvardin, **389**)[264]	187.4% at 10 mg/kg			
RA-VI (**396**)[266]			1.2[b]	3.5
RA-VII (**398**)[264,266]	173.6% at 4.0 mg/kg		1.8×10^{-3} [b]	1.4×10^{-3}
RA-VIII (**399**)[266]			6.7×10^{-2} [b]	3.1×10^{-2}
RA-IX (**400**)[268]	105.3% at 15 mg/kg		3.0×10^{-1} [b]	3.7×10^{-1}
RA-X (**401**)[268]	126.3−159.7% at 1.5−15 mg/kg		1.5×10^{-1} [b]	1.8×10^{-1}
RA-XI (**402**)[269]				5.2
RA-XII (**403**)[269]				4.6×10^{-2}
RA-XIII (**404**)[269]				6.3
RA-XIV (**405**)[269]				>10
RA-XV (**406**)[270]				4.5×10^{-1}
RA-XVI (**407**)[270]				1.5
RA-XVII (**408**)[271]				2.8×10^{-2}
RA-dimer A (**410**)[275]				2.6×10^{-1}

(**284**)[200] showed inhibition of the classical pathway activity of human complement, but cyclolinopeptides A and B (**295** and **296**) and E (**299**)[206,207] and schnabepeptide (**345**)[223] showed immunosuppressive activity. Only **340** showed Ca^{2+} antagonistic activity.[222] Cycloleonuripeptide D (**294**)[205] and dichotomins D, F, and G (**361**, **363**, and **364**)[229,230] showed inhibition of cyclooxgensase activity. Only pseudostellarins A−H (**331**−**338**)[218−221] showed inhibition of tyrosinase activity. Only curcacycline B (**279**) showed enhancing rotamase activity of human cyclophilin B.[195] Only segetalins A and B (**381** and **382**) and G and H (**386** and **387**) showed estrogen-like activity *in vivo*.[240,243,245] The most potentially active Caryophyllaceae-type cyclopeptide is cycloleonurinin (**290**). It showed a potent immunosuppressive effect on the mitogen (concanavalin A)-induced response of human peripheral blood lymphocytes (IC_{50}: 28 ng/mL). The IC_{50} in this system of a well-known immunosuppressive agent, cyclosporine A, was shown to be 3 ng/mL, which is comparable to that of **290**. Meantime, **290** may not be lymphocytotoxic but rather only inhibitory toward DNA synthesis.[248]

11.1.3. Biological Activity of Rubiaceae-Type Cyclopeptides

Rubiaceae-type cyclopeptides showed potent antitumor activities against various experimental murine tumors *in vivo* and cultured cells *in vitro* (Table 13). The major active principle RA-VII (**398**) was reported to have undergone phase I clinical trials as an anticancer drug in Japan in the 1990s.[271] The sodium salt of RA-X (**401**), containing glutamic acid at residue 2,[268] and RA-XII (**403**), with a glucosyl moiety at residue 5,[269] showed water solubility and were recently nominated as antitumor principles. Studies on a spectrum of experimental tumors in mice revealed that **398** amd RA-V (**389**) exhibited significant activity against leukemias and ascites tumors, P-388, L1210, B-16 melanoma and solid tumors, colon 38, Lewis lung carcinoma, and Ehrlich carcinoma.[287] Metabolites of **398** and **401** were studied by hepatic microsomal biotransformation in rats and in the bile juice of rabbits to which these drugs were administered intravascularly. Results indicated that the hydroxylation and demethylation reactions *in vivo* are considered to be a bioinactivation process, especially specific N-demethylation of L-Tyr[3] and O-demethylation and hydroxylation at the aromatic rings of L-Tyr[3] and L-Tyr[5].[288]

Bouvardin (**388**) inhibited protein synthesis[288] in intact eukaryotic cells and cell-free systems. Results indicated that **388** acted at the level of the 80S ribosome in a site somehow involved with the interaction of EF1 and EF2. It inhibited EF1-dependent binding of aminoacyl-tRNA and EF2-dependent translocation of peptidyl-tRNA, but it did not affect the nonenzymic translocation since this reaction does not require EF2. The site of the 80S ribosome involved in the interaction with **388** appeared to be independent from the cycloheximide and crytopleurine binding sites since yeast mutants resistant to cycloheximide or cryptopleurine were sensitive to **388**.[290] RA-VII (**398**) completely inhibited *in vitro* protein synthesis in rabbit reticulocyte lysates at a concentration of 5 μM, with an IC_{50} of 80 nM. Unlike **388**, **398** had no effect upon aminoacyl-tRNA binding, but it inhibited the peptidyltransferase step. No effect of **398** upon translocation had been observed. Results indicated that **398** also interacted directly with 80S ribosomes.[291] Experiments indicated that in the presence of rat liver ribosomes the ^1H NMR signals of RA-XII (**403**) tended to broaden. This is considered to correlate with bind formation between **403** and ribosome in a fast exchange process, preferentially of the major conformer.[292]

Various studies of the SAR in the RAs and their derivatives indicated that the ring systems;[277,293,295,296,302,306,312] substitutions in the β-positions of L-Ala[2],[297,300,301] L-Tyr[5],[310] and L-Tyr[6];[264] substitutions in the *o*-positions of L-Tyr[3],[299,307] and L-Tyr[6];[294,299] substitutions in the α-position of L-Tyr[6].[309] substitutions in the N-positions of amino acid residues;[266,277,283,284,298,304,305] the conformations;[266,277,297] the configuration;[311] and thionation[303,308] could increase or decrease the antitumor activities of Rubiaceae-type cyclopeptides, in which particularly a 14-membered ring, a type II β turn with a *cis* peptide bond at L-Ala[2] and L-Tyr[3], and *o*-OMe substitution of L-Tyr[3] play more important roles in their antitumor activities *in vitro* and *in vivo*.[9,277,299,313,314]

11.1.4. Biological Activity of Cyclotides

Cyclotides displayed an interesting range of biological activities, i.e., anti-HIV (**411**−**416**, [315,317] **418**−**421**,[319] **432**[323]), inhibiting neurotensin binding (**433**[324]), inhibiting trypsin (**422** and **423**,[320] **461**[331]), uterotonic (**424**[321]), haemolytic (**412**,[343] **424**,[343] **442**[326]), antimicrobial (**411** and **412**,[346] **424**,[346] **433**[344,346]), insecticidal (**424**[345]), cytotoxic (**411** and **412**,[346] **424**,[346] **433**,[346] **434**,[330,347] **438**,[330] **439**,[347] **448**,[347] **460**[330]), and

cardiotoxic (**424**[321]) activities. These activities lend to their potential as leads for drug development. Of perhaps greater interest is their potential application as stable peptide-based templates for the presentation of a diverse range of introduced bioactivities.[11] Two major strategies are currently being used to exploit the favorable characteristics of the CCK framework of the cyclotides in drug design applications. The first involves conferring the advantages of a circular backbone onto linear proteins that have pharmaceutically important bioactivities. The second involves the grafting of small peptide epitopes onto a generic CCK framework to introduce a desired bioactivity to the stable scaffold. Both strategies have been exemplified in recent patent applications.[11]

11.2. Biological Functions

11.2.1. Biological Functions of Cyclopeptide Alkaloids

The effect of frangulanine (**38**) on mitochondrial swelling has been investigated. **38** induced mitochondrial swelling in 0.15 M KCl solution at a 6.5 μM concentration. The cyclopeptide alkaloid showed ion selectivity on the induction of mitochondrial swelling. Mitochondria underwent swelling in 0.15 M KCl or RbCl solution but not in either NaCl or LiCl solution. The ion selectivity might be caused by the formation of a complex with K^+ or Rb^+, which would act as an ionophore in the mitochondrial inner membranes in a manner similar to that for valinomycin. Such a complex could have biological significance in plants, perhaps being involved in absorption of nutrients from the soil, especially alkali metals.[4,119] In another study by Rapoport and co-workers, ceanothine-B (**7**) exhibited binding with Mg^{2+}, Ca^{2+}, and Li^+ but not Na^+. Therefore, cyclopeptide alkaloids may function as ionophores in plants.[121]

Andreo and Vallejos discovered that discarine-B (**22**) is a specific inhibitor of energy transfer in spinach chloroplasts while discarine-A (**21**) behaves as a mixed-type inhibitor.[118] Four years later, they reported the further works of photophosphorylation in isolated spinach chloroplasts, which was inhibited by 21 cyclopeptide alkaloids. Scutianine-A (**39**), adouetine-Z (**84**), amphibines-B (**97**), -C (**98**), and -D (**99**), and zizyphines-A (**156**) and -B (**157**) inhibited the coupled but not the uncoupled electron transport. The other alkaloids stimulated nonphosphorylating electron flow, behaving like uncouplers. Lasiodine-A (**1**), aralionine-A (**60**), and mucronine-B (**180**) were the strongest inhibitors and uncouplers. **1** stimulated by several times the light-induced proton uptake by chloroplasts. All of the cyclopeptide alkaloids assayed inhibited photophosporylation. Some of them specifically affected ATP synthesis while others behaved like uncouplers. Cyclopeptide alkaloids may become useful tools in the study of energy conservation in chloroplasts. The sensitivity of the photosynthetic energy conservation machinery to cyclopeptide alkaloids may be related to their still unknown biological role in plants.[4,120]

11.2.2. Biological Functions of Cyclotides

Recent reports have shown that cyclotides act as insecticidal[345] and antimicrobial agents,[344,346] implying a role in the plant's defense system. On the basis of tissue-specific expression of cyclotides in *Viola* species, Craik and coworkers proposed that cyclotides might be regarded as a new family of plant defense peptides.[328] On the basis of the observation of haemolytic activity for kalata B1 (**424**) and circulin B (**412**), the same group proposed that the natural function of these molecules might involve a defense mechanism for the plants.[343]

12. Perspectives and Concluding Remarks

In this review, we have systematically described the progress in the chemistry and biology of cyclopeptides discovered from higher plants during the past 120 years, especially the recent half century. Since Clinch noted the presence of alkaloids in *Ceanothus americanus* (Rhamnaceae) in 1884 and Kaufmann et al. isolated cyclolinopeptide A (CLA, **295**) from *Linum usitatissimum* (linseed oil, Linaceae) and determined its structure in 1959, exploration of plant cyclopeptides by human beings has not stopped. It is noteworthy that some important discoveries and breakthroughs on plant cyclopeptides have been acquired during the past decade. On the basis of the recent known understanding of plant cyclopeptides, we preliminarily infer that cyclotides (type VIII) with 28−37 amino acids are gene products and other cyclopeptides (types I, II, III, IV, V, VI, and VII) may be not gene products. The sequence of cyclotides is encoded by DNA, and thus, we think that cyclotides may be the preliminary metabolites in plants which are derived from the processing of a larger precursor protein. Other types of cyclopeptides with 2−14 amino acids may be synthesized through a multienzyme pathway *in vivo*, which may be the secondary metabolites in plants. We believe that some significant accomplishments in the study of both the chemistry and biology of cyclopeptides from higher plants will continue to be made, especially new cyclopeptide discoveries. Despite this fact, important biological functions, potential biological activity, efficient synthesis methods, and further configuration and conformation studies of plant cyclopeptides remain to be valuably explored in the future. Just recently, Craik said that "there is no end in sight" in the field of plant cyclopeptides.

13. Acknowledgments

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14. Abbreviations

ACE	angiotensin-converting enzyme
Ahabpa	2-amino-3-(2-hydroxy-5-aminoacetylbenzyl)pentanoic acid
ATP	adenosine triphosphate
ATPase	adenosine triphosphatase
B1 test	B16 melanotic melanoma test
Bn	benzyl
Boc	*t*-butyloxycarbonyl
CC	column chromatography
CD	circular dichroism
DCC	*N*,*N*-dicyclohexylcarbodiimide
DIEA	diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DPPA	diphenylphosporyl azide
GC	gas chromatography
GLC	gas liquid chromatography

HATU	*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate
HBTU	*O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate
HPLC	high pressure liquid chromatography
IR	infrared spectroscopy
LC	liquid chromatography
MS	mass spectroscopy
Net_3	triethylamine
NMR	nuclear magnetic resonance spectroscopy
OSi-*t*-$BuMe_2$	((1,1-dimethylethyl)dimethylsilyl)oxyl
OTHP	tetrahydropyran-2-yloxyl
OTMSE	$Me_3SiCH_2CH_2O$
PC	paper chromatography
PEC	*S*-(*β*-4-pyridylethyl) cysteine
PS test	P388 lymphocytic leukemia test
SAR	structure−activity relationship
S_NAr	nucleophilic aromatic substitution
SPPS	solid-phase peptide synthesis
T/C	test/control
TBAF	tetrabutylammonium fluoride
TLC	thin-layer chromatography
TTN	thallium(III) trinitrate
UV	ultraviolet spectroscopy
Z	benzyloxycarbonyl

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