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Plant alkaloids of the polymethyleneamine series

L N Rogoza, N F Salakhutdinov, G A Tolstikov

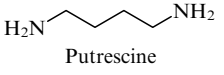
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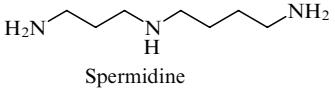
Abstract. The published data on the structures and biological activities of the plant alkaloids of the biogenic polymethyleneamine series, *viz*., putrescine (1,4-diaminobutane), spermidine (1,8-diamino-4-azaoctane), and spermine (1,12-diamino-4,9-diazadodecane), are considered and systematised. The structures and biological activities of some synthetic analogues of these alkaloids are also presented. The bibliography includes 84 references.

I. Introduction

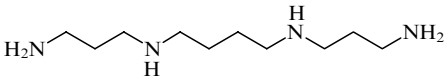
The biogenic polymethylenepolyamines putrescine, spermidine and spermine have been identified in detectable amounts in all living cells.



Putrescine



Spermidine



Spermine

These are natural amino acid metabolites in plants and animals [1, 2] and are involved in many biological processes.[1, 3] Valuable biological activities of biogenic polymethyleneamines gave impetus to the development of methods for their synthesis and the synthesis of their analogues.†

The natural polyamines occur as free aliphatic bases and structural elements of alkaloids commonly referred to as secondary metabolites.

This review is devoted to plant alkaloids with putrescine, spermidine or spermine fragments as their constituents. They play an essential role in different stages of plant development (flowering, fruit ripening, ageing, *etc*.). as well as in miscellaneous interactions of plants with the environment.[4, 5] Depending on the nature of the parent polyamine, the alkaloids can be divided into three groups, *viz*., putrescine-borne polyamines, spermidine-borne polyamines and spermine-borne polyamines. Each of these groups is represented by both cyclic and linear compounds. A special group of alkaloids includes lactams.

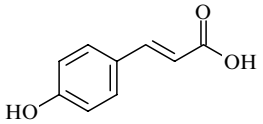
The present review covers the literature published in 1992 – 2003 dealing with the description of methods for the isolation of this group of alkaloids from plants, determination of their structures and biological activities and structural modification aimed at the design of targeted-action medicines. References to previous publications are given where necessary.

It is common practice that trivial names of natural compounds derive from the names of plants they are isolated from. Some linear polymethyleneamine derivatives have no such names and the substitutive nomenclature is used where putrescine, spermidine or spermine are taken as parent compounds and the locants of the nitrogen atoms indicate their positions in the chain.

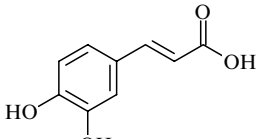
II. Linear polymethyleneamine alkaloids

Linear alkaloids containing spermine, spermidine, putrescine or guanidinoputrescine fragments are represented by amides of various carboxylic acids (*N*-acylpolyamines). As a rule, these compounds contain only one polyamine constituent. The only exception is alkaloid tenuilobine isolated from plants of the *Oncinotis* genus (Apocynaceae), with contains both spermine and spermidine fragments.

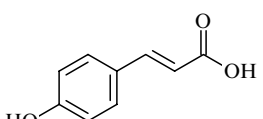
The carboxylic acids most commonly found in linear spermine and spermidine derivatives include cinnamic acid and its derivatives, *e.g*., *p*-coumaric (*p*-hydroxycinnamic), caffeic (3,4-dihydroxycinnamic), ferulic (4-hydroxy-3-methoxycinnamic), 3,4-dimethoxycinnamic and, less frequently, dihydrocinnamic acids.



p-Coumaric acid



Caffeic acid



Ferulic acid

† Since recently, synthetic polymethyleneamine derivatives are considered as promising antitumour and antiinfectious agents.[1]

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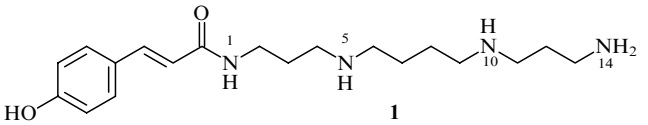
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Uspekhi Khimii **74** (4) 411 – 427 (2005); translated by R L Birnova

Some alkaloids contain benzoic and hexadecanedioic acids as carboxylic acid components. In addition to the foregoing carboxylic acids, linear putrescine derivatives contain aliphatic acids and carboxy derivatives of flavaglines,[6] cyclopenta[*bc*]benzopyrans (aglaines and aglaforbesines) and benzo[*b*]oxepins (forbaglines).

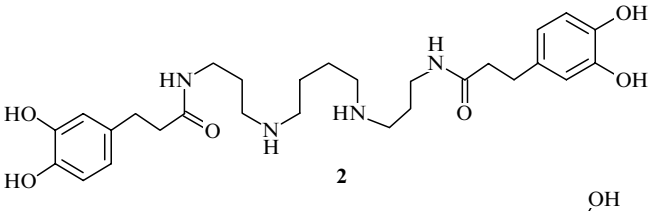
Cinnamamides are present in many higher plants.[7,8] They were found in the reproductive organs (anthers) as the main structural components of pollen and in some other parts of the plants. Their presence is associated with responses of plants to pathogenic factors, *e.g.*, viral or fungal infections.[9]

1. Linear spermine derivatives

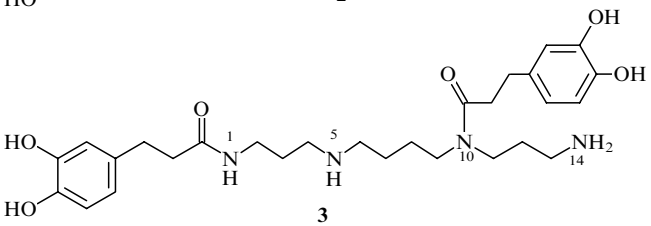
Linear spermine derivatives are few in number. 1-(*N*-*p*-Coumaroyl)spermine (**1**) is the simplest representative of natural spermine amides.[10] Kukoamines A (**2**) and B (**3**) isolated from the root bark of *Lycium chinense* also belong to this group. These compounds contain dihydrocaffeic acid fragments.[11]



1



2



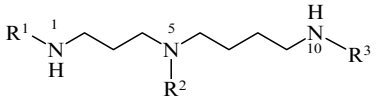
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2. Linear spermidine derivatives

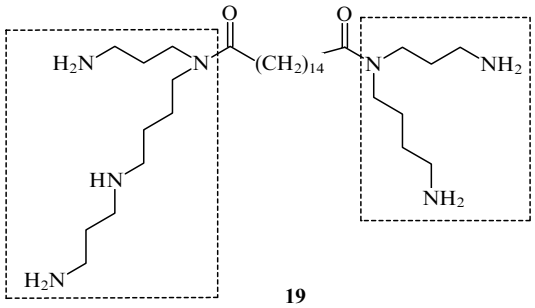
Linear spermidine derivatives include mono- (**4**–**6**), di- (**7**–**10**) and triacyl (**11**–**18**) derivatives of cinnamic acids.[7,9,10,12–15] Some spermidine amides isolated from plants are listed in Table 1. The monoamide **4** and its synthetic isomer (compound **5**) differing in the position of the central nitrogen atom in the chain result from acylation of the primary amino group. Diamides include compounds with all possible combinations of pairwise substitutions, *viz*., N^1 and N^5; N^1 and N^{10}; N^5 and N^{10}. In these compounds, fragments of the same acid (compounds **7**–**9**) or of different acids (compound **10**) serve as the substituents. Trisubstituted spermidine derivatives are the most numerous; in this case, too, the role of substituents is played by the same acid (compounds **11**–**13**) or two different acids (compounds **14**–**17**). The alkaloid **18** is the only spermidine alkaloid containing three different acyl substituents (coumaric, caffeic and ferulic acid fragments).

In addition to fragments of cinnamic acids, some linear spermidine derivatives contain fragments of other acids. Thus 5-*N*-benzoylspermidine (**6**)[12] (monoamide) and tenuilobine (**19**) (diamide), were isolated from the leaves of *Oncinotis tenuiloba* Stapf (Apocynaceae).[16] Compound **19** represents a diamide of hexadecanedioic acid and contains one spermine and one spermidine fragment. This was also isolated from the Central Asian plant *Salsola subaphylla*[17] and was named subaphylline.

Table 1. Linear alkaloids derived from spermidine.



Alkaloid	R^1	R^2	R^3	Plant source	Ref.
Monosubstituted derivatives					
4	*p*-coumaroyl	H	H	–	10
5	H	H	*p*-coumaroyl	synthetic	10
6	H	benzoyl	H	*Oncinotis tenuiloba* Stapf	12
Disubstituted derivatives					
7	*p*-coumaroyl	*p*-coumaroyl	H	*Pterocarya fraxinifolia*, *Aphelandra tetragona*, *A. chamissoniana*	13, 14
8	*p*-coumaroyl	H	*p*-coumaroyl	*A. tetragona*, *A. chamissoniana*	14
9	feruloyl	feruloyl	H	*Betula verrucosa*	13
10	caffeyl	H	feruloyl	*Corylus avellana*	13
Trisubstituted derivatives					
11	*p*-coumaroyl	*p*-coumaroyl	*p*-coumaroyl	*Quercus dentata*, *Q. alba*, *A. tetragona*, *A. chamissoniana*	7, 9, 14
12	caffeyl	caffeyl	caffeyl	*Q. dentata*, *Q. alba*	7, 9
13	feruloyl	feruloyl	feruloyl	*Hippeastrum* hortorum	15
14	*p*-coumaroyl	*p*-coumaroyl	caffeyl	*Q. dentata*	7, 13
15	*p*-coumaroyl	caffeyl	*p*-coumaroyl	*Q. alba*	9
16	*p*-coumaroyl	caffeyl	caffeyl	*Q. dentata*	7
17	feruloyl	caffeyl	caffeyl	*Q. dentata*	13
18	*p*-coumaroyl	caffeyl	feruloyl	*Q. dentata*	13



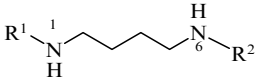
19

3. Linear putrescine derivatives

A characteristic feature of mono- and diacyl putrescine derivatives is diversity of substituents. Putrescine mono- and diamides isolated from plants are listed in Table 2.[5,6,18–27]

The aminoamides **20**, **21** and the diamides **22**–**25** contain 'standard' fragments of cinnamic, ferulic, coumaric and benzoic acids. The alkaloid **24** is known under two names, *viz*., pyramidatine (being isolated from *Aglaia pyramidata* Hance, syn. *Aglaia*

Table 2. Linear alkaloids derived from putrescine.



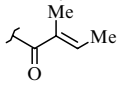
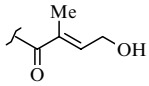
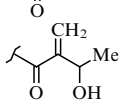
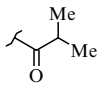
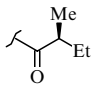
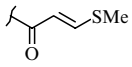
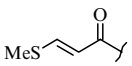
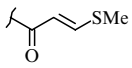
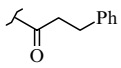
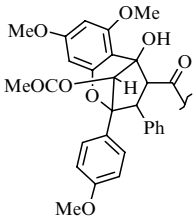
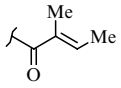
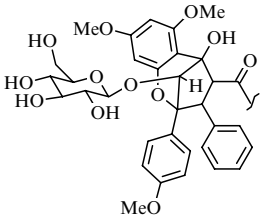
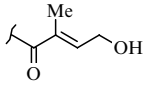
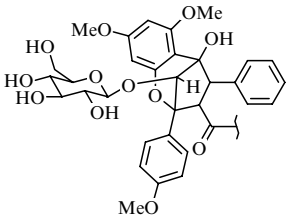
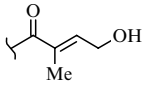
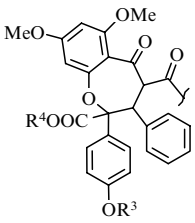
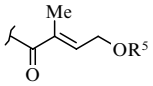
Alkaloid	Trivial name	R^1	R^2	Plant source	Ref.
20	–	*p*-coumaroyl	H	*Hordeum vulgare*	5
21	–	feruloyl	H	*H. vulgare*	5
22	–	feruloyl	feruloyl	cereals, maize	18, 19
23	–	*p*-coumaroyl	feruloyl	cereals, maize	18, 19
24	haplamidine (pyramidatine)	cinnamoyl	benzoyl	*Haplophyllum latifolium* (*Aglaia pyramidata* Hance)	20 6, 21
25	haplamide	benzoyl	benzoyl	*H. latifolium*	22
26	grandiamide B	cinnamoyl		*Agl. grandis* Korth.	21, 23
27	dasyclamide	cinnamoyl		*Agl. dasyclada*	24
28	grandiamide C	cinnamoyl		*Agl. grandis* Korth.	21, 23
29	secopirifirine	cinnamoyl		*Agl. gracilis* A.C.Smith	21, 25
30	(+)-secoodorine	cinnamoyl		*Agl. gracilis* A.C.Smith	21, 25
31	aglaithioduline			*Agl. edulis* A.Gray, *Agl. leptantha* Miq.	21, 26, 27
32	aglaithioduline			*Agl. edulis* A.Gray, *Agl. leptantha* Miq.	21, 26, 27
33	edulimide [a]	cinnamoyl		*Agl. edulis* (synonym *Agl. pirifera* Hance)	6
34	grandiamide A			*Agl. grandis* Korth.	21, 23
35	bisamide of the aglaine type [b]			*Agl. dasyclada*	24
36	bisamide of the aglaine type [b]			*Agl. dasyclada*	24

Table 2 (continued).

Alkaloid	Trivial name	R^1	R^2	Plant source	Ref.
37, **38**	bisamide of the forbagline type [b]			*Agl. dasyclada*	24

37: $R^3 = R^4 = R^5 = H$;
38: $R^3 = R^4 = Me$; R^5 = glucosyl.

[a] Edulimide is a triamide with an additional Ac substituent at N^6. [b] The names for structure types are indicated.

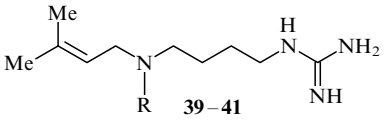
silvestris) [6, 21] and haplamidine (being isolated from *Haplophyllum latifolium*).[20] It is noteworthy that haplamide (**25**) (putrescine dibenzoate) was isolated from the same plant.[22]

Putrescine diamides containing various aromatic and aliphatic acids were identified in plants of the *Aglaia* genus (Meliaceae). This genus comprises 130 dioecious arboreal and shrub species occurring predominantly in tropical and subtropical climatic zones. Depending on the structures of the substituents R^1 and R^2, these compounds are categorised into two types. One of them includes compounds **26**–**30**,[21, 23–25] which contain cinnamic acid or its derivatives as the substituent R^1 as well as two sulfur-containing methylthioacrylic acid diamides [21, 26] [aglaithioduline (**31**) and aglaidithioduline (**32**)] and edulimide (**33**).[21, 26] The latter contains an acetyl group at the nitrogen atom as a third substituent and is the only representative of dihydrocinnamic acid imides in this group of compounds. Compounds containing aglaine (**34**, **35**), aglaforbesine (**36**) and forbagline (**37**, **38**) are related to the second type of diamides.[21, 23, 24] Diamides of the former type are accumulated predominantly in plant leaves, while structurally more complex amides are usually present in the bark.

The presence, in the same plant species, of different types of amides, which occurs quite often, suggests close biogenetic relationships between them. Thus the ability of dasyclamide **27** to be converted into diamides **35**–**38** upon cycloaddition with flavonoids suggests its role as a biosynthetic precursor of these compounds.[24]

4. Linear guanidinoputrescine derivatives

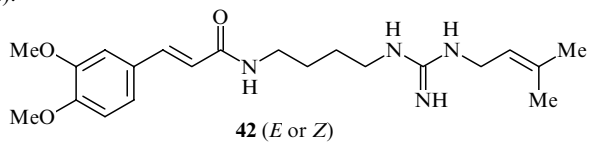
Guanidinoputrescine, which is most likely formed upon enzymatic decarboxylation of arginine, undergoes further transformations. Sphaerophysine (**39**), the first guanidinoputrescine derivative with a simple structure, was isolated from the Central Asian plants *Sphaerophysa salsula* and *Smirnovia turkestana*.[28] Sphaerophysine acetate and malonate, named smirnovine (**40**) and smirnovinine (**41**),[29] were also isolated from *Smirnovia turkestana*.



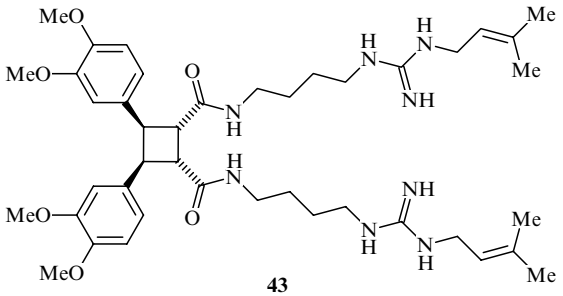
39–**41**

R = H (**39**), C(O)Me (**40**), $C(O)CH_2CO_2H$ (**41**).

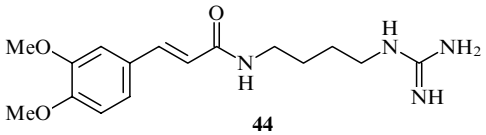
More complex guanidinoputrescine derivatives containing a 3,4-dimethoxycinnamic acid fragment were found in the Venezuelian plant *Verbesina caracasana* Fries. One of them, *viz*., caracasanamide (**42**), was isolated as a mixture of *E*- and *Z*-forms.[30, 31] The second compound, *viz*., caracasanediamide (**43**), represents a cyclobutane-type dimer of caracasanamide **42** [31, 32] and yet another is 1-(3,4-dimethoxycinnamoylamino)-4-guanidinobutane (**44**).[33]



42 (*E* or *Z*)

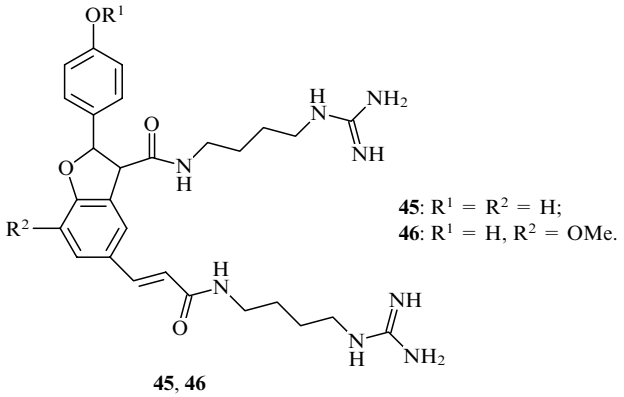


43



44

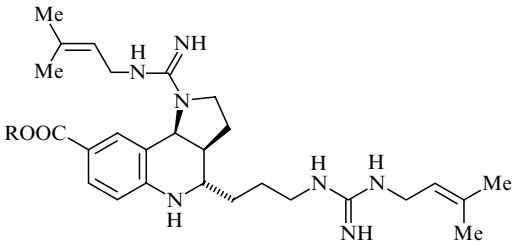
The alkaloids (+)-hordatines A (**45**) and B (**46**), which contain a benzofuran core with two guanidinoputrescine residues as substituents, were isolated from barley (*Hordeum vulgare* L.) sprouts.[34]



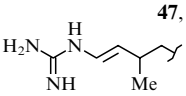
45: $R^1 = R^2 = H$;
46: $R^1 = H$, $R^2 = OMe$.

45, **46**

Martinellinic acid (**47**) and its ester, martinelline (**48**), isolated from the roots of the tropical liana *Martinella iquitosensis* have even more complex structures.[35] They contain a pyrroloquinoline backbone and several guanidino groups including a guanidinoputrescine group.



47, **48**

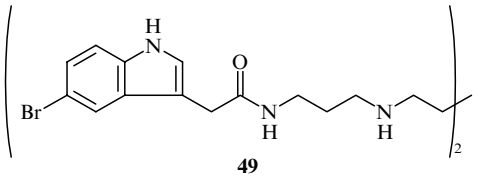
R = H (**47**),  (**48**).

Of special note is the fact that no natural compounds with such a backbones have been reported hitherto.

5. Biological activities of linear alkaloids

Linear alkaloids manifest diverse kinds of biological activities. Thus the hypotensive activity kukoamine A (**2**) gave an impetus to the synthesis and assay of all of its regioisomers as potential hypotensive drugs.[36] Besides, this compound causes mixed-type inhibition of trypanothione reductase (K_i = 1.8 μmol litre^{-1} and K_{ii} = 13 μmol litre^{-1}), a unique specific enzyme of protozoan parasites (trypanosomes, Leischmania). It is of note that kukoamine A has no effect on the human enzyme endowed with a similar protective function.

Synthetic mono- and diacyl, analogues kukoamine A based on spermine and spermidine also inhibit trypanothione reductase, however, with much lesser efficiency (K_i = 11–607 μmol litre^{-1}).[37] Studies of inhibiting activities of a panel of kukoamine A-based inhibitors prepared by solid-phase combinatorial chemical synthesis have shown that the highest inhibiting activity is manifested by bis(5-bromoindol-3-ylacetyl)spermine (compound **49**) (K_i = 0.076 μmol litre^{-1}).[38]

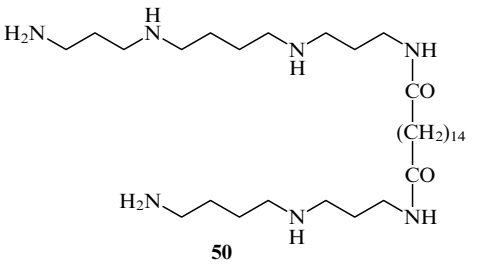


49

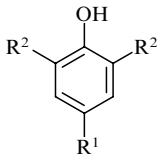
The monosubstituted alkaloids 1-(*N*-*p*-coumaroyl)spermine (**1**) and 1-(*N*-*p*-coumaroyl)spermidine (**4**) cause reversible dose-dependent inhibition of neuromuscular synapses in insects (IC_{50} = 70 and 60–200 μmol litre^{-1}, respectively), which opens a way to a better understanding of their role as a means of chemical self-protection of plants against pests. Structural analogues of these alkaloids, *viz*., polyamines isolated from the toxins of *Nephila* spiders, produce irreversible blocking effects (IC_{50} = 0.1 μmol litre^{-1}).[10]

The triamides **11**, **12** and **15** manifest fungicidal activities: they inhibit mycelial growth in the pathogenic fungus *Pyrenophora avenae* affecting oats leaves and protect barley seedlings against mildew.[9]

Among synthetic derivatives of tenuilobine **19**, isotenuilobin (**50**)[39] and the aromatic derivatives **51**–**55** are worthy of note.[39] The structural similarity of tenuilobine **19** to spider and wasp toxins widely known as potent inhibitors of CNS glutamate



50



51–**55**

51: R^1 = Bu^t, R^2 = $(CH_2)_2C(O)N[(CH_2)_3NH_2](CH_2)_4NH_2$;
52: R^1 = Bu^t, R^2 = $(CH_2)_2C(O)N[(CH_2)_3NH_2](CH_2)_4NH(CH_2)_3NH_2$;
53: R^1 = Bu^t, R^2 = $(CH_2)_2C(O)NH(CH_2)_3NH(CH_2)_4NH_2$;
54: R^1 = R^2 = $(CH_2)_2C(O)N[(CH_2)_3NH_2](CH_2)_4NH_2$;
55: R^1 = R^2 = $(CH_2)_2C(O)N[(CH_2)_3NH_2](CH_2)_4NH(CH_2)_3NH_2$.

receptors provided a rationale for their biological testing as candidate inhibitors of ionotropic glutamate receptors. These studies are currently under way.[40]

Presumably symmetrical and non-symmetrical tenuilobine derivatives of hexadecanedioic acid and spermidine, spermine and their shorter-chain analogues inhibit polyamine transport. At present, methods for the synthesis of these compounds are developed and investigations into their ability to control polyamine metabolism are underway.[41]

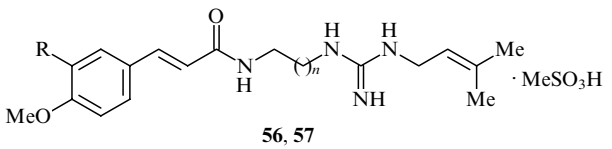
Some disubstituted putrescines also possess biological activity. Thus compounds **22** and **23** cause reversible inhibition of α-glucosidase,‡ which is involved in carbohydrate catabolism. Studies on structure–activity relationships have shown that inhibiting activities of these compounds are determined by the presence of a hydroxy group in the aromatic ring.[25]

Non-cytotoxic concentrations of the sulfur-containing bisamides aglaithioduline (**31**) and aglaidithioduline (**32**) have little effect on the herpes simplex virus (types 1 and 2);[26] pyramidatine (**24**) manifests antileukemic activity *in vivo*.[42]

The identification of sphaerophysine (**39**) and the discovery of its hypotensive activity were of great consequence for the therapy of a hypertonic disease, being the first demonstration of high potential of guanidinoputrescine derivatives as efficient hypotensive drugs. Sphaerophysine benzoate§ is successfully used in the therapy of hypertony and as a labour-stimulating agent in obstetrical-gynecological practice.[43] Smirnovine (**40**) also possesses hypotensive activity.[45]

Worthy of notice are water-soluble guanidinoputrescine derivatives caracasanamide (**42**, *Z*-form) and caracasanediamide (**43**) endowed with hypotensive properties. Caracasanamide (**42**) can be used in the therapy of moderate arterial hypertension; its therapeutic effect is commensurate with those of reserpine and papaverine. Caracasanediamide (**43**) exceeds compound **42** in hypotensive and antihypertensive activities and has no adverse side effects (*e.g*., reflexive tachycardia or low cardiac inotropism) manifested by the majority of antihypertensive and vasodilating agents.[31]

Candidates for hypotensive drugs were aslo found among synthetic derivatives of compound **44** containing a modified diaminoalkane chain or a modified acyl moiety.[33] The derivative **56** containing an (*E*)-*p*-methoxycinnamic acid fragment produces a stronger hypotensive effect than compound **44**. The number of methylene groups in the diaminoalkyl chains of compounds of the type **57** does not influence their therapeutic activity. In pharma-



56, **57**

56: R = H, *n* = 3; **57**: R = OMe, *n* = 1–5.

‡ In the past decade, α-glucosidase inhibitors have been widely used as peroral hypoglycemic drugs in the therapy of diabetes, but a search for novel, safer inhibitors remains a topical task.

§ At present, sphaerophysine benzoate has no wide application.[44]

cological doses, all these compounds produced hypotensive and slightly positive inotropic effects devoid of substantial chronotropic and respiratory effects.

Hordatines A (**45**) and B (**46**) possess fungicide activities.[34]

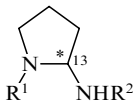
There is evidence that the sap of two tropical liana species (of the genus *Martinella* Bignoniaceae), *viz*., *M. iquitosensis* A.Sampaio and *M. obovata* (HBK) Bureau et K.Schum, is used by representatives of thirteen different ethnolinguistic groups in nine countries of South America as a folk remedy against various eye diseases. Some native tribes residing in the Amazonian Region of Peru extract this sap from the root bark of *M. obovata*. One or two drops of such potion immediately eliminate inflammation in the eye infected by a parasitic microorganism (or a group of microorganisms, including Gram-positive and Gram-negative bacteria). Studies have shown that this effect is provided by martinellinic acid (**47**) and martinelline (**48**), the only natural non-peptide antagonists of B_1- and B_2-receptors of bradykinin (BK). It is noteworthy that martinelline (**48**) exceeds martinellinic acid (**47**) in activity. Thus, the sap from the root bark of *M. obovata* possess antiinflammatory and analgesic effects. Martinelline (**48**) is an antagonist of histaminergic, α-adrenergic and muscarinic receptors, manifests moderate antibiotic activity and has little or no cytotoxic or lytic effect with respect to red blood cells. Such a happy combination of antiinflammatory, analgesic and antimicrobial actions makes this compound a valuable tool in the treatment of conjunctivitis.[35]

III. Cyclic polymethyleneamine alkaloids

Yet another important class of polyamine alkaloids comprises cyclic compounds with polyamine backbones. These compounds can be divided into two main subtypes, *viz*., cycloputrescine derivatives (2-aminopyrrolidines) and macrocyclic (8–22-membered) lactams containing biogenic bases (mostly spermine and spermidine). Putrescine, spermidine and spermine are present in the ring systems either as a whole molecule or as a part thereof.

1. Cycloputrescine derivatives

Cycloputrescine derivatives are represented by pyrrolidine bisamide alkaloids, which rarely occur in nature and contain a 2-aminopyrrolidine group. By present, pyrrolidine bisamides have been identified only in plants of the *Aglaia* genus (Meliaceae). Some aminopyrrolidine bisamides isolated from these plants are listed in Table 3.



Depending on the structures of their substituents R^1 and R^2, all aminopyrrolidine bisamides are divided into two types. Compounds **58**–**65** have simple structures and contain various carboxylic acid fragments as substituents R^1 and R^2. In structurally more complex bisamides, the role of the substituent R^2 is played by carboxylic acids, while that of substituent R^1 is played by structural fragments, of the aglaine (**66**–**69**), aglaforbesine (**70**, **71**), forbagline (**72**, **73**), tapsakine (**74**) or tapoxepin types (**75**). Such complex bisamides are related to flavaglines and represent typical secondary metabolites of 30 investigated species of the genus *Aglaia*.[6] Presumably, the flavagline molecule consists of a flavonoid and a fragment of cinnamic acid. Flavaglines are represented by three structural types, *viz*., cyclopenta[*b*]benzofurans (rocaglamides,[49] aglaroxin A, pannelline), cyclopenta[*bc*]benzopyrans (aglaines, aglaforbesines, tapsakins) and benzo[*b*]oxepins (forbaglines, tapoxepins). The latter two types are related to polyamine derivatives. Possible biogenetic relationships between different types of flavaglines and putative mechanisms of their formation have been discussed. [48].

As a rule, the same plant species produces different types of bisamides. Different compositions of linear and cyclic bisamides in plants of the same species is interpreted as a 'survival strategy' preventing the adaptation of herbivores and microorganisms to the common chemical profile of the plant.[27] The presence of different forms of bisamides in the same plant species suggests close biogenetic relationships between them. Cycloaddition of the pyrrolidine bisamide odorine (**58**) to a flavonoid affords aglaines

Table 3. Aminopyrrolidine bisamides from plants of the genus *Aglaia* (Meliaceae).

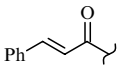
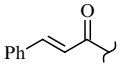
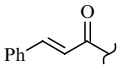
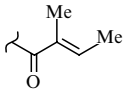
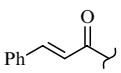
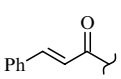
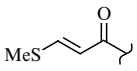
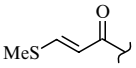
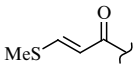
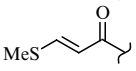
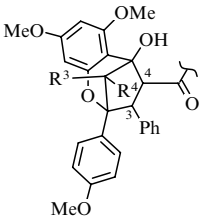
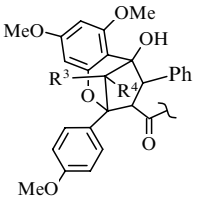
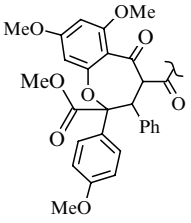
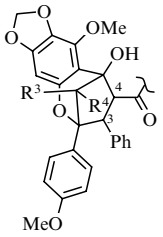
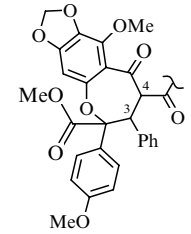
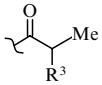
Alkaloid	Name	R^1	R^2	Plant source	Ref.
58	odorine		C(O)Bu^s	*Aglaia odorata* Lour, *Agl. elaeagnoidea*, *Agl. argentea* Blume, *Agl. forbesii* King, *Agl. elliptica* Blume (synonym *Agl. harmsiana* Perkins)	6
59	odorine		C(O)C(Me)(Et)OH	*Agl. odorata* Lour, *Agl. elaeagnoidea*	6
60	dehydroodorine			*Agl. tomentosa*, *Agl. formosana*	6, 46
61	piriferine		C(O)CMe$_2$OH	*Agl. edulis* (synonym *Agl. pirifera* Hance), *Agl. elaeagnoidea*	6
62	piriferinol		C(O)Pr^i	*Agl. elaeagnoidea*	6
63	agleptin		C(O)Bn	*Agl. leptantha* Miq.	27
64	isoagleptin	BnC(O)		*Agl. leptantha* Miq.	27
65	leptantine			*Agl. leptantha* Miq.	27

Table 3 (continued).

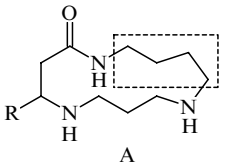
Alkaloid	Name	R^1	R^2	Plant source	Ref.
	aglaines		C(O)Bu^s	*Agl. argentea* Blume	47
66	A				
67	B				
68	C				
		A: R^3 = OAc, R^4 = H; H-3β, H-4α, 13*S* B: R^3 = H, R^4 = OH; H-3β, H-4α, 13*S* C: R^3 = H, R^4 = OH; H-3α, H-4β, 13*S*			
69	deacetylaglaine A	R^3 = OH, R^4 = H; H-3β, H-4α, 13*S*		*Agl. gracilis*	25
	aglaforbesines		C(O)Bu^s	*Agl. forbesii*	47
70	A				
71	B				
		A: R^3 = OH, R^4 = H; 13*R*; B: R^3 = H, R^4 = OH; 13*R*			
	forbaglines		C(O)Bu^s	*Agl. forbesii*	47
72	A				
73	B				
		13*R* (A), 13*S* (B)			
74	tapsakines			*Agl. edulis*	48
		R^3 = H, R^4 = OH, R^5 = Me; H-3β, H-4α, 13*S* (A); 13*R* (B); R^3 = OH, R^4 = H, R^5 = Me; H-3β, H-4α, 13*S*; R^3 = H, R^4 = OH, R^5 = Et; H-3α, H-4β, 13*S*; R^3 = H, R^4 = OCOMe, R^5 = Me; H-3α, H-4β, 13*S*; R^3–R^4 = O, R^5 = Me; H-3α, H-4β, 13*S*; R^3–R^4 = O, R^5 = Me; H-3β, H-4α, 13*S*			
75	tapoxepines			*Agl. edulis*	48
		R^3 = Me; H-3α, H-4β; 13*S* (A); 13*R* (B); R^3 = Et; H-3α, H-4β, 13*S*; R^3 = Me; H-3β, H-4α; 13*S* (A); 13*R* (B)			

A, B and C (**66**–**68**) as well as agloforbesines A and B (**70** and **71**).[47] Simultaneous presence of pyrrolidine bisamides and the corresponding linear analogues [*e.g.*, odorine (**58**) and secoodorine (**30**),[25] pirifirine (**61**) and secopirifirine (**29**),[25] agleptine (**63**), isoagleptine (**64**), leptantine (**65**) and aglaithioduline (**31**) or aglaidithioduline (**32**)],[27] in the same plant species prompts a conclusion that all alkaloids containing a 2-aminopyrrolidine fragment have a biogenetic linear putrescine bisamide precursor;[25] its cyclisation is effected by an enzymatic system of its own.[21]

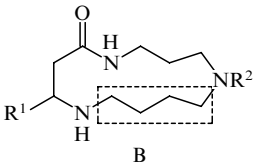
2. Cyclic spermidine alkaloids

a. 13-Membered cyclic spermidine alkaloids

Palustrine (**76**), the first alkaloid in this series, was isolated from marsh horsetail *Equisetum palustre* L. in 1936.[50] The asymmetry of spermidine structure enables the formation of two types of cyclic alkaloids, *viz.*, type A (compounds **76**–**84**) and type B (compounds **85**–**98**).[51]



A

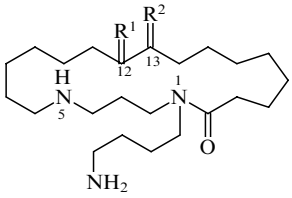


B

Both types of alkaloids occur in plants (Table 4). Mayfoline (**98**) belonging to the B-type alkaloid contains a hydroxy substituent at the secondary nitrogen atom of the spermidine chain; this feature has been observed for the first time in this type of a compound. Plants containing this kind of an alkaloid may contain its analogue the *N*-hydroxy group in which is replaced by the *N*-acetyl group.[8]

b. Spermidine alkaloids isolated from various species of plants of the genera *Oncinotis*, *Lunaria* and *Codonocarpus*

Polyamine alkaloids present in plants of the genus *Oncinotis* (Apocynaceae) are classified into two groups, *viz.*, linear and macrocyclic. All macrocyclic keto lactams contain a 16-membered hydrocarbon chain linked to the neighbouring nitrogen atoms of spermidine. Depending on the mode of attachment of the chain to spermidine, one can distinguish monocyclic inandenines (com-



Inandenines, inandeninols

R^1 = O or OH, H; R^2 = H_2;
R^1 = H_2; R^2 = O or OH, H.

Table 4. 13-Membered spermidine macrocyclic lactam alkaloids.

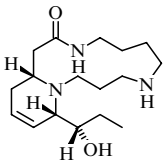
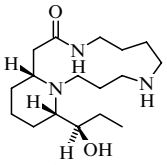
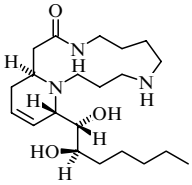
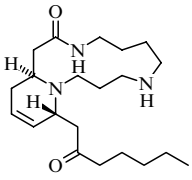
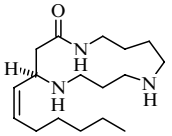
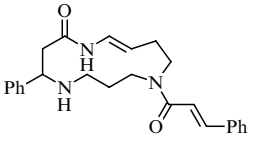
Alkaloid	Name	Structure	Plant source	Ref.
Type A				
76	palustrine		*Equisetum palustre* L.	50
77	dihydropalustrine		*E. palustre* L.	52
78	cannabisativine		*Cannabis sativa* L. (roots, leaves)	53
79	anhydrocannabisativine		*C. sativa* L. (roots, leaves)	53
80	(−)-(4*R*)-dihydroisomyricoidine		synthetic	51
81	periphylline (*trans*-cinnamoyl)		*Peripterygia marginata* (Baill.) Loes.	54

Table 4 (continued).

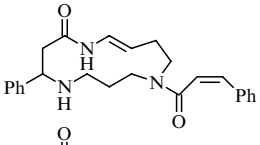
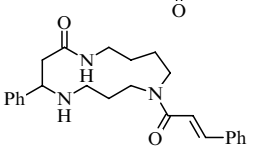
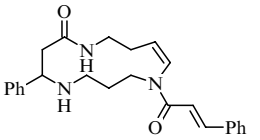
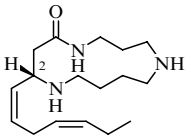
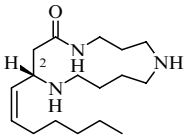
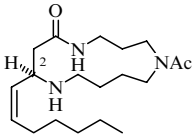
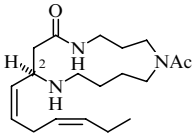
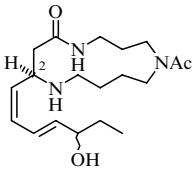
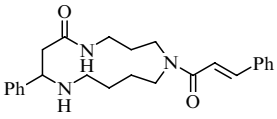
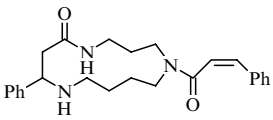
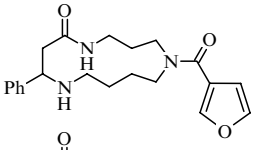
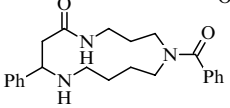
Alkaloid	Name	Structure	Plant source	Ref.
Type A				
82	isoperiphylline (*cis*- cinnamoyl)		*P. marginata* (Baill.) Loes.	54
83	(+)-(*S*)-dihydro-periphylline (*trans*-cinnamoyl)		*P. marginata* (Baill.) Loes.	54
84	neoperiphylline (*trans*-cinnamoyl)		*P. marginata* (Baill.) Loes.	54
Type B				
85	(+)-(2*S*)-myricoidine		*Clerodendrum myricoides* Vatke (Verbenaceae)	55
86	(+)-(2*S*)-dihydro-myricoidine		*C. myricoides* Vatke, *Maytenus loeseneri* Urb. (Celastraceae)	51, 55
87	(+)-(2*R*)-loesenerine		*M. loeseneri* Urb.	55
88	(+)-(2*R*)-17,18-dide-hydroloesenerine		*M. loeseneri* Urb.	55
89	(+)-(2*R*)-16,17-dide-hydroloesenerin-18-ol		*M. loeseneri* Urb.	55
90	celacinnine (*trans*-cinnamoyl)		*M. arbutifolia* (*M. serrata*) (Hochst., ex A.Rich) R.Wilczek (Celastraceae) (branches); *Tripterygium wilfordii* Hook (Celastraceae) (roots); *M. heterophylla* (bark), *Pleurostulia africana* (leaves)	8, 56
91	celallocinnine (*cis*-cinnamoyl)		*M. arbutifolia* (Hochst., ex A.Rich) R.Wilczek (Celastraceae) (branches)	56
92	celafurine		*T. wilfordii* Hook (Celastraceae) (roots)	56
93	celabensine		*M. mossambicensis* (Klotzsch) Blakelock var. *mossambicensis*; *T. wilfordii* Hook (Celastraceae) (roots)	56, 57

Table 4 (continued).

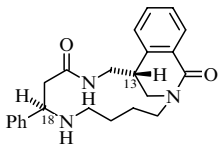
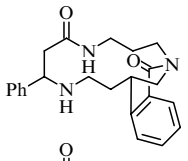
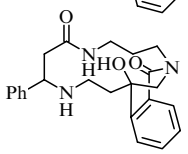
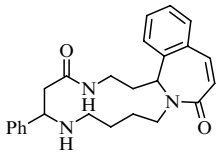
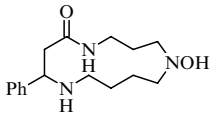
Alkaloid	Name	Structure	Plant source	Ref.
Type B				
94	(+)-(18*S*,13*R*)-cyclocelabensine		*M. mossambicensis* (Klotzsch) Blakelock var. *mossambicensis*	57
95	(+)-isocyclocelabensine		*M. mossambicensis* (Klotzsch) Blakelock var. *mossambicensis*	57
96	(+)-hydroxyisocyclocelabensine		*M. mossambicensis* (Klotzsch) Blakelock var. *mossambicensis*	57
97	pleurostiline		*P. africana* (leaves)	8
98	mayfoline		*M. buxifolia* (superterrestrial parts)	8

Table 5. Spermidine alkaloids from plants of the genus *Oncinotis* (Apocynaceae).

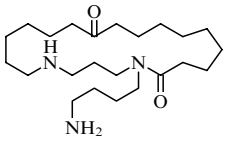
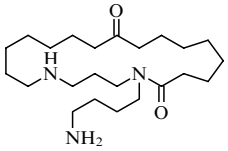
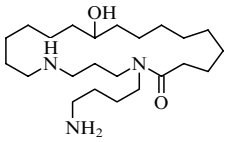
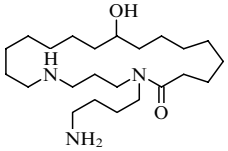
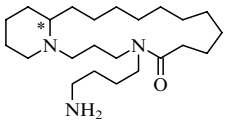
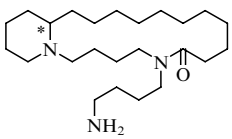
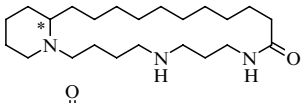
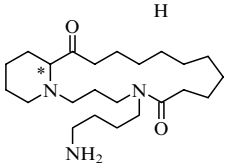
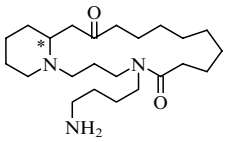
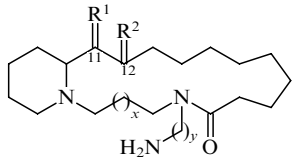
Alkaloid	Name	Structure	Plant source	Ref.
99	inandenin-12-one		*Oncinotis tenuiloba* Stapf *O. inandensis* Wood et Evans, *O. nitida* Benth.	58 59
100	inandenin-13-one		*O. inandensis* Wood et Evans, *O. nitida* Benth. *O. tenuiloba* Stapf	59 58
101	inandenin-12-ol		*O. tenuiloba* Stapf *O. nigra* Pich.	58 59
102	inandenin-13-ol		*O. tenuiloba* Stapf *O. nigra* Pich.	58 59
103	(−)-oncinotine		*O. nitida* Benth.	59
104	(−)-neooncinotine		*O. nitida* Benth.	59

Table 5 (continued).

Alkaloid	Name	Structure	Plant source	Ref.
105	(−)-isooncinotine		*O. nitida* Benth.	59
106	oncinotin-11-one		*O. tenuiloba* Stapf	59
107	oncinotin-12-one		*O. tenuiloba* Stapf	59

pounds **99**–**102**, Table 5),[58, 59] bicyclic oncinotines (compounds **103**–**107**, Table 5)[59] and linear tenuilobine (**19**).

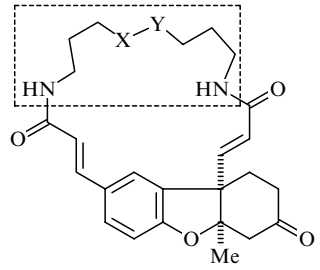


Oncinotines

$R^1 = O, R^2 = H_2$; $R^1 = H_2, R^2 = O$;
$x = 1, y = 4$; $x = 2, y = 3$.

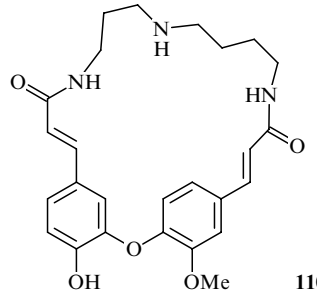
The specific content of an alkaloid in a plant depends on the species and the organ from which it was isolated. Thus the stem bark of the Nigerian species *O. nitida* Benth. predominantly contains oncinotine (**103**) and its isomers, *viz*., neooncinotine (**104**) and isooncinotine (**105**). Inandenines were found in this plant in only minor amounts and were isolated as a non-separable mixture of isomers. In contrast, leaves of *O. inandensis* Wood et Evans and *O. tenuiloba* are rich in inandenines. The concentration of inandeninols, *i.e*., the secondary alcohols formed upon reduction of the keto groups of inandenines, in these plant species is very small. However, in the leaves of *O. nigra* Pich. these compounds are present as major components.[58, 59]

Lunarine (**108**) isolated from *Lunaria annua*[60] differs from lunaridine (**109**) which is present in *L. biennis* and *L. rediviva*[8]



108, **109**

108: X = NH, Y = CH_2;
109: X = CH_2, Y = NH.



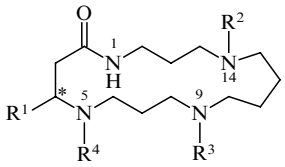
110

simultaneously with lunarine, in the mode of attachment of spermidine. Codonocarpine (**110**) was isolated from the bark of *Codonocarpus attenuatus* (Phytolaccaceae).[8]

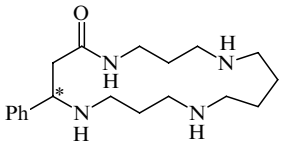
3. Cyclic spermine alkaloids

a. 17-Membered cyclic spermine alkaloids

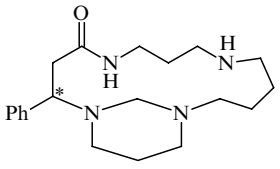
Compounds containing spermine and carboxylic acids constitute a large group of cyclic polyamine alkaloids. 17-Membered cyclic spermine alkaloids form a special group. Depending on the nature of the carboxylic acid and the substituents at the nitrogen atoms of the 17-membered macrocycle, these alkaloids are divided into two groups, *viz*., alkaloids from *Verbascum* (Scrophulariaceae), *Incarvillea sinensis*, *Clerodendrum buchneri* (Verbenaceae) (group A, compounds **111**–**128**, Table 6)[61–67] and budmunchiamines from plants of the *Albizia* genus (group B, compounds **129**–**148**, Table 7).[68–72]



The 17-membered ringes of the group A alkaloids contain fragments of dihydrocinnamic acid or its 4-methoxy derivative and spermine ($R^3 = R^4 = H$, compounds **111**–**121**) or its cyclic analogue (R^3–$R^4 = -CH_2-$, compounds **122**–**128**). The structures of (−)-protoverbine (**111**) and (+)-protomethine (**122**) are typical basic structures.



111

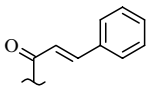
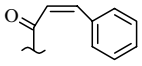
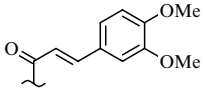
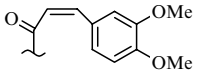
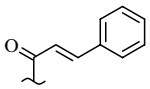
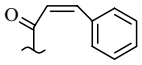
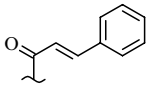
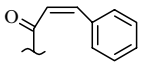
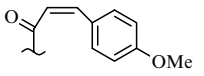
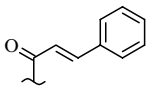
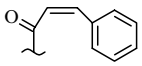
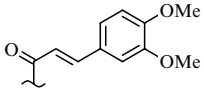
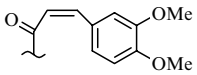
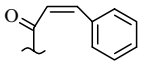
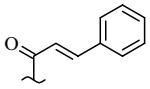


122

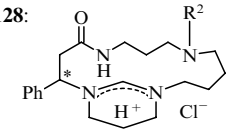
The alkaloids protoverbine **111** and (+)-protomethine (**122**) are thought to be putative biogenetic precursors of a large class of spermine alkaloids. Thus, compound **111** is a hypothetical precursor of verbacine (**112**) and verballocine (**113**), while compound **122** is a precursor of (+)-verbamethine (**123**) and (+)-isoverbamethine (**124**).[61] Compounds **112** and **113** are often considered as biogenetic precusors of their *N*-acetylated derivatives verbascenine (**118**) and verballoscenine (**119**). Simultaneous isolation of all the four compounds provides supporting evidence in favour of this hypothesis.[66]

Fragments of cinnamic, 4-methoxycinnamic, 3,4-dimethoxycinnamic (*E*- or *Z*-forms), acetic and formic acids are typical

Table 6. Spermidine alkaloids from plants of the genus *Verbascum* (Scrophulariaceae), *Incarvillea sinensis* and *Clerodendrum buchneri* (Verbenacae).

Alkaloid	Name	R^1	R^2	R^3	R^4	Plant source	Ref.
111	(−)-protoverbine	Ph	H	H	H	*Verbascum pseudonobile* Stoj. et Stef.	61
112	(−)-verbacine (*E*)	Ph		H	H	*V. pseudonobile* Stoj. et Stef.	61, 62
113	(−)-verballocine (*Z*)	Ph		H	H	*Incarvillea sinensis*	63
114	(−)-(*S*)-verbasitrine (*E*)	Ph		H	H	*V. pseudonobile* Stoj. et Stef.	64
115	(−)-(*S*)-isoverbasitrine (*Z*)	Ph		H	H	*V. pseudonobile* Stoj. et Stef.	64
116	verbamedine (*E*)	Ph		CHO	H	*V. pseudonobile* Stoj. et Stef.	65
117	isoverbamedine (*Z*)	Ph		CHO	H	*V. pseudonobile* Stoj. et Stef.	65
118	verbascenine (*E*)	Ph		Ac	H	*V. phoeniceum* L., *V. nigrum* L., *V. pseudonobile* Stoj. et Stef.	62
119	verballoscenine (*Z*)	Ph		Ac	H	*V. phoeniceum* L.	66
120	buchnerine	4-$MeOC_6H_4$	H	H	H	*Clerodendrum buchneri*	67
121	*N*-(*Z*)-*p*-methoxycinnamoylbuchnerine	4-$MeOC_6H_4$		H	H	*C. buchneri*	67
122	(+)-protomethine	Ph	H	$-CH_2-$		*V. pseudonobile* Stoj. et Stef.	61
123	(+)-verbamethine (*E*)	Ph		$-CH_2-$		*V. pseudonobile* Stoj. et Stef.	61
124	(+)-isoverbamethine (incasine C) (*Z*)	Ph		$-CH_2-$		*V. pseudonobile* Stoj. et Stef., *I. sinensis*	65
125	(+)-(*S*)-verbametrine (*E*)	Ph		$-CH_2-$		*V. pseudonobile* Stoj. et Stef.	64
126	(+)-(*S*)-isoverbametrine (*Z*)	Ph		$-CH_2-$		*V. pseudonobile* Stoj. et Stef.	64
127	incasine B′ (or verdoline) (*Z*) (see [a])	Ph		$-CH_3^+-$		*V. pseudonobile* Stoj. et Stef.	65
128	incasine B (or isoverdoline) (*E*)	Ph		$-CH_3^+-$		*I. sinensis*	63

[a] The structures of compounds **127** and **128**:



substituents at the nitrogen atoms in the macrocycles of the type A alkaloids. Alkaloids containing cinnamic and 3,4-dimethoxycinnamic acid fragments as substituents R^2 usually form *E*/*Z*-isomeric pairs, *e.g.*, **112**/**113**, **114**/**115**, **116**/**117**, **118**/**119**, **123**/**124**, **125**/**126**, **127**/**128** (see Table 6). The (*E*)-verbamedine/(*Z*)-isoverbamedine and (*E*)-verbacine/(*Z*)-verballocine alkaloid pairs are

Table 7. Spermine alkaloids from plants of the genus *Albizia*.

Alkaloid	Name	R^1	R^2	R^3	R^4	Plant source	Ref.
129	budmunchiamine A	$C_{11}H_{23}$-n	Me	Me	Me	*Albizia amara*, *Alb. gummifera*	68, 69
130	budmunchiamine B	C_9H_{19}-n	Me	Me	Me	*Alb. amara*	68
131	budmunchiamine C	$C_{13}H_{27}$-n	Me	Me	Me	*Alb. amara*	68
132	6,′ξ-hydroxybudmunchiamine C	n-$C_5H_{10}CH(OH)C_7H_{15}$-n	Me	Me	Me	*Alb. schimperana*	70
133	budmunchiamine D	n-$C_9H_{18}C(O)C_3H_7$-n	Me	Me	Me	*Alb. amara*	68
134	budmunchiamine E	n-$C_8H_{16}C(O)C_4H_9$-n	Me	Me	Me	*Alb. amara*	68
135	budmunchiamine F	$C_{11}H_{23}$-n	Me	Me	H	*Alb. amara*	68
136	budmunchiamine G	$C_{13}H_{27}$-n	Me	Me	H	*Alb. amara*, *Alb. gummifera*	68, 69
137	budmunchiamine H	n-$C_9H_{18}C(O)C_3H_7$-n	Me	Me	H	*Alb. amara*	68
138	budmunchiamine I	n-$C_8H_{16}C(O)C_4H_9$-n	Me	Me	H	*Alb. amara*	68
139	budmunchiamine K	$C_{15}H_{31}$-n	Me	Me	Me	*Alb. gummifera*	69
140	5-normethylbudmunchiamine K	$C_{15}H_{31}$-n	Me	Me	H	*Alb. schimperana*	70
141	9-normethylbudmunchiamine K	$C_{15}H_{31}$-n	Me	H	Me	*Alb. gummifera*	69
142	14-normethylbudmunchiamine K	$C_{15}H_{31}$-n	H	Me	Me	*Alb. schimperana*	70
143	6′ξ-hydroxybudmunchiamine K	n-$C_5H_{10}CH(OH)C_9H_{19}$-n	Me	Me	Me	*Alb. gummifera*	60
144	6′ξ-hydroxy-5-nor-methylbudmunchiamine K	n-$C_5H_{10}CH(OH)C_9H_{19}$-n	Me	Me	H	*Alb. schimperana*	70
145	budmunchiamine L1	$C_{16}H_{33}$-n	H	H	H	*Alb. lebbek*	71
146	budmunchiamine L2	$C_{14}H_{29}$-n	H	H	H	*Alb. lebbek*	71
147	budmunchiamine L4	$C_{13}H_{27}$-n	H	H	H	*Alb. adinocephala*	72
148	budmunchiamine L5	$C_{15}H_{31}$-n	H	H	H	*Alb. adinocephala*	72

the major components of *Verbascum pseudonobile* Stoj. et Stef. (Scrophulariaceae), while the (*E*)-verbacitrine/(*Z*)-isoverbacitrine pair was isolated from this plant species in only minor amounts.[65] Incasines B and B′ isolated from *Incarvillea sinensis* were also found in *V. pseudonobile*. The (*E*)-verbamedine/(*Z*)-isoverbamedine pair was structurally identical to incasines A and A′, although in the authors' opinion[65] the structures of the latter were not established unambiguously.

The *E*:*Z* ratio of the isomeric pairs of alkaloids containing cinnamic acid fragments (**112**:**113** and **123**:**124**) is 5:4, that of the alkaloids containing a 3,4-dimethoxycinnamic substituent (**114**:**115** and **125**:**126**) is 1:9. Similar ratios were obtained after irradiation of these alkaloids with visible or UV light (λ = 365 nm). It was thus concluded that *Z*-isomers represent photoisomerisation products of the corresponding *E*-isomers formed in intact plant tissues under the influence of solar irradiation.[64]

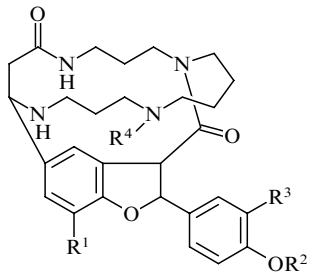
The 17-membered rings of the group B alkaloids, *viz*., budmunchiamines, isolated from plants of the genus *Albizia*, contain spermine and various fatty acid fragments (R^1CH_2COOH) [$R^1 = C_nH_{2n+1}$, where $n \geqslant 9$, or $R^1 = C_mH_{2m}C(O)C_pH_{2p+1}$, where $m + p = 13$], the major part of the alkyl chains of the fatty acids (substituent R^1) is not incorporated into the macrocycle. The classification of budmunchiamines (from A to L) is based on the length of the side alkyl chain (R^1) and the degree of methylation of the nitrogen atoms in the macrocycle.

The lengths of the side alkyl chains of the alkaloids of the same series are constant; within the series, the differences reflect different degrees of methylation of the nitrogen atoms in the macrocycle or the presence of hydroxy groups in the side chain R as, *e.g.*, in budmunchiamines C and K. Budmunchiamines L are an exception: all the four nitrogen atoms in the macrocycles in these alkaloids are non-methylated and differ from one another only in the length of the alkyl side chain.

Budmunchiamines are largely isolated from legumes (Leguminosae) and different species of mimosa (Mimosoidae): from seeds of *Albizia amara* Bolv. and an Indian plant (*Alb. lebbek* Benth.), from the stem skins of the Kenyan species *Alb. gummifera* (J.F.Gmel.) C.A.Sm. and *Alb. schimperana* Oliv. and from the stem bark (budmunchiamines L4 and L5) and leaves (budmunchiamines L5) of the Panamanian plant *Alb. adinocephala* (J.D.Sm.) Britton et Rose ex Record.

b. Spermine bimacrocyclic alkaloids of the aphelandrine type

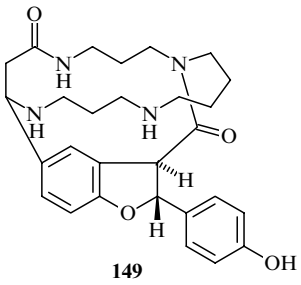
Spermine alkaloids of the aphelandrine type were isolated from the roots of plants of three families, *viz*., Acanthaceae, Scrophulariaceae and Ephedraceae. These alkaloids contain two macrocycles one of which is identical to the 17-membered lactam ring of the aforementioned group A spermine alkaloids, whereas the other (13-membered) macrocycle contains a fragment of the highly substituted dihydrobenzofuran core. Aphelandrine type alkaloids can also be regarded as compounds the spermine component in which is acylated by two fragments of *p*-coumaric acid.



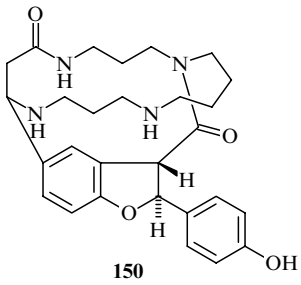
Alkaloids of the aphelandrine type

R^1 = H, OMe; R^2 = H, Me; R^3 = H, OMe; R^4 = H, OH, OAc.

Plants of the genus *Aphelandra* (Acanthaceae) occur on the territory extending from the south of Mexico to the north of Argentina and are represented by nearly 165 species. The roots of some representatives of this genus (*A. tetragona, A. squarrosa, A. sinclairiana, A. pepeparodii, A. aurantiaca, A. chamissoniana, A. fuscopunctata*) contain the bicyclic spermine alkaloid (+)-aphelandrine (**149**) and its diastereoisomer (−)-oranthine (**150**) (syn. ephedradine A).

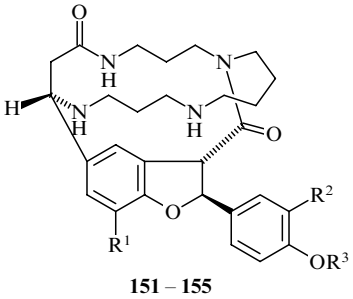


149



150

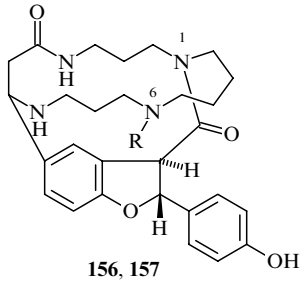
Aphelandrine was also isolated from *Encephalosphaera lasiandra* also belonging to this family; oranthine was isolated from *Chaenorhinum minus*, *Schweinfurthia papilioacea* (Scrophulariaceae) and *Ephedra* (Ephedraceae). The alkaloid (−)-*O*-methyloranthine (**151**) was found in *C. minus* and *C. villosum* (Scrophulariaceae); (−)-epioranthine (**152**) was found in *S. papilioacea* (Scrophulariaceae). Representatives of yet another group of alkaloids structurally similar to aphelandrine, *viz*., (−)-ephedradines B, C and D (compounds **153**–**155**), were found in *Ephedra* (Ephedraceae).[73, 74]



151–**155**

151: $R^1 = R^2 = H$, $R^3 = Me$;
152: $R^1 = R^2 = R^3 = H$;
153: $R^1 = R^3 = H$, $R^2 = OMe$;
154: $R^1 = H$, $R^2 = OMe$, $R^3 = Me$;
155: $R^1 = OMe$, $R^2 = R^3 = H$.

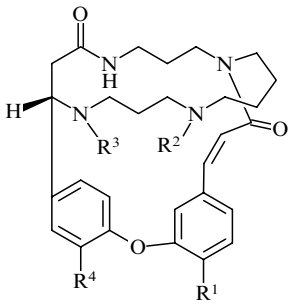
The isolation of (+)-*N*(6)-hydroxyaphelandrines (**156**) and (+)-*N*(6)-acetoxyaphelandrine (**157**) from the roots of *A. fuscopunctata* confirmed that macrocyclic spermine alkaloids are typical of the genus *Aphelandra*.[73] However, in the upper (superterranean) parts and in cell cultures of *A. tetragona* and *A. sinclairiana,* this type of alkaloid was not found.[74]



156, **157**

156: R = OH;
157: R = OAc.

Besides oranthine and ephedradines B and C, the roots of some plants of the family Scrophulariaceae contain a variety of other macrocyclic spermine alkaloids. Thus chaenorine (**158**) and chaenorpine (**159**) were isolated from the plant *C. minus,* while 18-*O*-methylchaenorpine (**160**) was isolated from *A. tetragona*. The alkaloids **158**–**160** are structurally similar to the aphelandrine alkaloids **149**–**157**.[75, 76]

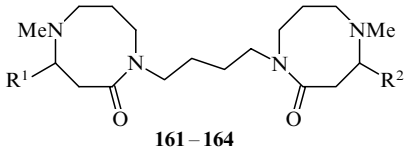


158–**160**

158: $R^1 = H$, $R^2 = Ac$, $R^3 = H$, $R^4 = OMe$;
159: $R^1 = OH$, $R^2 = R^3 = R^4 = H$;
160: $R^1 = OMe$, $R^2 = R^3 = R^4 = H$.

c. Spermine alkaloids from *Homalium* plants

The group of homaline alkaloids comprises four spermine derivatives, *viz*., homaline (**161**), hopromine (**162**), hopromінol (**163**) and hopromalinol (**164**), isolated from the leaves of plants of the genus *Homalium* and *Homalium pronyense* Guillaum (Flacourtiaceae) growing in the rainforests of New Caledonia.[77, 78]



161–**164**

161: $R^1 = R^2 = (S)$-Ph;
162: $R^1 = n\text{-}C_5H_{11}$, $R^2 = n\text{-}C_7H_{15}$;
163: $R^1 = n\text{-}C_5H_{11}$, $R^2 = CH_2CH(OH)C_5H_{11}\text{-}n$;
164: $R^1 = Ph$, $R^2 = CH_2CH(OH)C_5H_{11}\text{-}n$.

4. Biological activities of cyclic alkaloids

In the past decade, plants of the genus *Aglaia* (Meliaceae) attracted keen attention as a novel source of unique natural compounds, primarily because of unusually high insecticidal activities of their lipophilic extracts. Non-nitrogenous flavaglines with a cyclopenta[*b*]benzofuran backbone manifest especially high insecticidal and antiproliferative activities;[49] their hypothetical biosynthetic intermediates are polyamine-containing tapsakines devoid of insecticidal activity.[48]

Some bisamide alkaloids isolated from plants of the genus *Aglaia*, *e.g*., dehydroodorine (**60**), manifest cytotoxic activity.[46] The spermidine alkaloid lunarine (**108**) causes time-dependent inhibition of trypanthione reductase (presumably, this reaction is accompanied by the binding of the enzyme to one of the double bonds in the lunarine macrocycle).[79]

The arboreal plant *Alb. gummifera* (J.F.Gmel.) C.A.Sm. is widely used in the folk medicine of Kenya. Its bark possesses pronounced antipyretic properties and is a popular remedy against cold, dermatosis, gonorrhea, malaria, gastric pains (as aqueous extract) and wound contamination (as powder).[69] Yet another Kenyan plant, *Alb. schimperana* Oliv., is used for the treatment of bacterial and parasite-borne infections (pneumonias, infected injuries, malaria) and as a component of antipyretic and analgesic drugs.[70] The species *Alb. julibrissin* is a component of a patented herbal mix for regulation of the level of female hormones. The therapeutic activity of budmunchiamines is usually associated with their physiological effect on the human nervous system.[80]

Wide application of plants of the genus *Albizia* in folk medicine has given strong impetus to their comprehensive studies. It was found that budmunchiamines isolated from these plants

manifest different types of biological activity. A mixture of budmunchiamines A–C (compounds **129**–**131**) (4 : 1 : 1) has non-specific cytotoxic and antibacterial (*Salmonella typhimurium* TM677) effects; besides, it prevents platelet aggregation and transformation of human lymphocytes and inhibits cyclooxygenase activity.[81]

Budmunchiamines L4 (**147**) and L5 (**148**) induce moderate inhibition of plasmepsin II,¶ a specific enzyme of the malaria pathogen *Plasmodium falciparum* (IC_{50} = 14 and 15 μmol litre^{-1}, respectively).[72] The currently observed increase in the gravity of the disease and its abundance due to appearance of novel drug- and insecticide-resistant parasites and mosquitos makes the development of newer treatment strategies and novel antimalarial drugs with enhanced properties and new in principle mechanisms of action a central task. This situation is further aggravated by the lack of efficient vaccines and the ambiguity of results of some clinical trials of novel antimalarial drugs.

Budmunchiamines **129**, **132** and **139**–**144** isolated from the Kenyan plants *Alb. gummifera* and *Alb. schimperana* possess antibacterial and cytotoxic properties.[69] Their antibacterial activities were tested in experiments with two Gram-positive (*Bacillus subtilis* and *Staphylococcus aureus*) and two Gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) bacteria; chloramphenicol was used as a standard. Cytotoxicity studies were carried out on sea shrimp larvae. It was found that the biological activities of budmunchiamines strongly depend on two factors, *viz.*, the presence of hydroxy groups in the side alkyl chain R^1 and the degree of methylation of the nitrogen atoms in the macrocycle. A decrease in the degree of methylation of nitrogen atoms (from three to two groups) has no effect on the antibacterial activity, but causes significant reduction of the cytotoxic activity. Both antibacterial and cytotoxic activities decrease significantly, if the side alkyl chain R^1 contains hydroxy groups.[69] The decrease in antibacterial and cytotoxic activities of budmunchiamines A–I (**129**–**138**) in the presence of carbonyl groups in their side chains provide conclusive evidence in favour of this assumption.[68]

Budmunchiamine A (**129**) was examined for the ability to control the activity of calcium receptors, which are extremely sensitive to even minor changes in Ca^{2+} concentrations. It was found that compound **129** inhibits the effect of the extracellular Ca^{2+} ion on the cell containing the Ca^{2+} receptor. This finding led the authors to conclude[82] that budmunchiamine A is a helpful tool in structure–activity studies.

Ephedradines extracted from plant roots are used as essential components of the Oriental antiperspirant composition 'maokon'. Pharmacological studies have shown that this preparation exhibits antitussive and antiallergic properties.[83] Intravenous injection of ephedradine dihydrochlorides or -bromides to mice produces a hypotensive effect.[84]

* * *

The data presented in this review demonstrate the extreme structural diversity of plant polymethyleneamine alkaloids. Many of them showed high activity in pharmacological tests (Table 8) and proved to be promising models in comprehensive structure–activity studies. The wealth of literature data on various biological activities of polymethyleneamine alkaloids and the abundant experience in their synthesis open up broad opportunities for the development of novel, highly efficient drugs.

¶ Plasmepsin II is a representative of the plasmepsin family and plays a crucial role in the survival and proliferation of enzymes. It is extensively studied and readily available and is thereby used as a target of choice for screening a library of natural products.

Table 8. Biological activities of plant source alkaloids of the polymethyleneamine series.

Type of biological activity	Alkaloids	
	natural	synthetic analogues
Antagonists of histaminergic, α-adrenergic and muscarinic receptors	**48**	
Antibacterial	**129**–**132**, **139**–**144**	
Antiherpetic	**31**, **32**	
Antileukemic	**24**	
Hypotensive	**2**, **39**, **40**, **42**, **43**, **153**–**155**	**56**
Inhibitor of:		
α-glucosidase	**22**, **23**	
calcium receptor	**129**	
bradykinin (BK) B_1 and B_2 receptors	**47**, **48**	
trypanothione reductase	**108**	**49**
plasmepsin II	**147**, **148**	
cyclooxygenase	**129**–**131**	
Neurotoxic	**1**, **4**, **19**	
Labour-stimulating	**39**	
Fungicidal	**11**, **12**, **15**	
Cytotoxic	**60**, **129**–**132**, **139**–**144**	

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