

Naturally occurring aristolactams, aristolochic acids and dioxoaporphines and their biological activities

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Aristolactams, having a phenanthrene chromophore are a small group of compounds mainly found in the Aristolochiaceae together with the aristolochic acids and 4,5-dioxoaporphines. In this report, these three important classes of natural products are reviewed and classified on the basis of their oxygenation pattern. In addition the biological activities of these compounds and their general chemistry are discussed.

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1 Introduction

Aristolactams, having a phenanthrene chromophore are a small group of compounds mainly found in the Aristolochiaceae together with the aristolochic acids and 4,5-dioxoaporphines.^{1,2} They have also been reported from plants of the Annonaceae, Monimimaceae, Menispermaceae and Piperaceae.³ Hutchinson observed that the Aristolochiaceae were the most closely related family to the Menispermaceae on the basis of the similarity of their stem structure.⁴ As a part of our ongoing research programme on the isolation and identification of potentially useful compounds from *Piper* species, we have isolated several

aristolactams and 4,5-dioxoaporphines from *P. wightii*, *P. argyrophyllum*, *P. schmidtii*, *P. acutisleginum*, and *P. betel*.^{5,6} Even though the aristolochic acids and aristolactams are non-basic, they are nevertheless classified as aporphinoids since their skeletons bear a distinct similarity to that of the aporphines. The structural relationship between these two groups of natural products suggests that aristolochic acids are derived from aristolactams rather than directly from quaternary aporphine alkaloids.

An alcoholic extract of *Aristolochia indica*, commonly known as “Indian birthwort” and which is reputedly used in Indian folk medicine as an emmenagogue and as an abortifacient, was found to show reproducible tumour inhibitory activity against the adenocarcinoma 755-test system in mice.⁷ Aristolochic acid A **80** was characterized as the main tumour inhibitory principle.⁸

The current interest in aristolochic acids and similar compounds as immunostimulants and anticancer agents means that new compounds in this class may be useful for further development as pharmaceuticals.⁹

Little is known about the biosynthesis of aristolactams. They are, however, biogenetically related to aporphine alkaloids from

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Virinder S. Parmar was born in Allahabad (India) in 1948 and received his PhD degree in Chemistry from the University of Delhi in 1978. He was appointed lecturer at St Stephen's College of the University of Delhi in 1970. After two years of postdoctoral studies at Cornell University (USA) and the University of Basel (Switzerland), Dr Parmar joined the Department of Chemistry, University of Delhi as a Reader (Associate Professor) in 1984, where he has been full Professor since 1994. His research interests are biocatalytic reactions, nanotechnology, synthetic organic chemistry, polymer chemistry and natural products chemistry. He has handled nearly two dozen research projects sponsored by Indian and international funding agencies, covering investigations of both a fundamental and applied nature, in collaboration with twenty research groups worldwide. He has organized six international conferences/symposia in different frontier areas of science. He has been a visiting scientist/visiting Professor at different institutions, i.e. Massachusetts Institute of Technology (MIT), Harvard University, Polytechnic University (New York) and the University of Massachusetts Lowell (USA), Imperial College of Science, Technology and Medicine and the University of Warwick (UK), the University of Basel (Switzerland) and Odense University (Denmark). He has authored more than 225 scientific publications and has supervised the research work of a large number of PhD (32) and MPhil (14) students, in addition to that of 16 postdoctoral fellows. He has widely traveled and delivered invited/plenary lectures at 55 symposia/conferences and 208 research seminars at 161 institutions in 22 countries. He has been a member of the IUPAC Organic and Biomolecular Chemistry Division's sub-committee on Biomolecular Chemistry and has also been on the editorial board of many scientific journals. Recently, he has been honored with the Chemical Research Society of India's Medal for his contributions to the chemical sciences.



Virinder S. Parmar

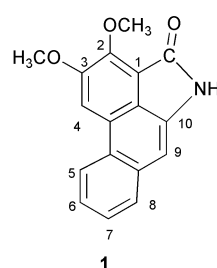
which they are probably derived.¹⁰ The isolation of 4-hydroxy-, 5-oxo- and 4,5-dioxoaporphines from plants of the Aristolochiaceae, Menispermaceae, Papaveraceae and Piperaceae¹¹⁻¹³ has led to the idea that 4,5-dioxoaporphines might arise by the oxidation of aporphines and may function as intermediates in the biosynthesis of aristolactams, which in turn are the precursors for aristolochic acids. In fact, conversion of a 4,5-dioxoaporphine into an aristolactam takes place *in vitro* and is regarded as a benzylic acid rearrangement, followed by loss of a carbon atom. The biogenetic relationship among the three alkaloids is also evident from the considerable similarity in their skeletons.

Bentley¹⁴⁻¹⁶ has reviewed the occurrence of aristolactams, aristolochic acids and 4,5-dioxoaporphines on an annual basis. In this report, we have reviewed these three important classes of natural products isolated between 1982 and June 2003 and classified them on the basis of their oxygenation pattern. In addition we discuss the biological activities of these compounds and their general chemistry.

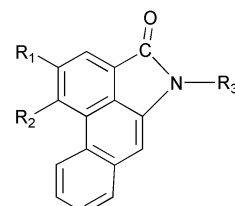
2 Aristolactams

Aristolactam-type alkaloids are not confined to the Aristolochiaceae. Aristolactams II **5** and BII **7** occur in *Stephania cepharantha* (Menispermaceae)¹¹ and were later found in *Schefferomitra subaequalis* (Annonaceae).¹⁷ The occurrence of aristolactams in these families is of taxonomic significance and supports the view that the Aristolochiales are related to the Magnoliales and Ranunculales.¹⁸

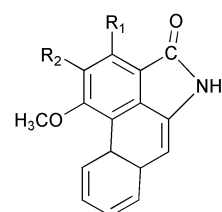
Priestap isolated seven aristolactams from *A. argentina*, of which aristolactams Ia **19**, III **20**, IIIa **21**, AIa **23** and AIIIa **25** were new.¹⁰



1



- 2 R₁=OH; R₂=OCH₃; R₃=H
 5 R₁+R₂=-OCH₂O-; R₃=H
 6 R₁+R₂=-OCH₂O-; R₃=glucosyl
 7 R₁=R₂=OCH₃; R₃=H
 8 R₁=OCOCH₃; R₂=OCH₃; R₃=COCH₃
 9 R₁=OCH₃; R₂=OH; R₃=CH₃
 10 R₁=OCH₃; R₂=OH; R₃=H
 11 R₁=OH; R₂=OCH₃; R₃=CH₃
 12 R₁=OH; R₂=OCH₃; R₃=H
 39 R₁=OH; R₂=R₃=OCH₃

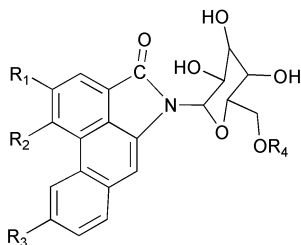


- 3 R₁=CH₂OH; R₂=OCH₃
 4 R₁=OH; R₂=COOH

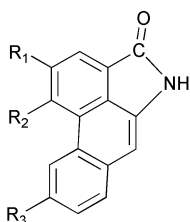
A number of compounds (aristolactams), possibly having postcoital antifertility activity, were isolated from *A. indica*.¹⁹ Mahmood *et al.* reported the isolation of new aristolactams,

Table 1 ^1H NMR Chemical shift values of key protons of piperolactam A and aristolactam FI

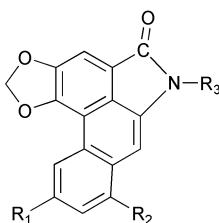
Compound	H-2	H-5	H-6	H-7	H-8	H-9	OMe
Piperolactam A ²⁴	7.66s	9.12d	7.58m	7.58m	7.95d	7.10s	4.02
Aristolactam FI ²¹	8.09s	9.45dd	7.65td	7.65td	7.92dd	7.48s	4.05



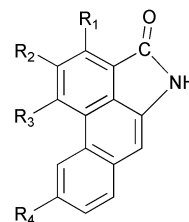
- 13 $\text{R}_1=\text{R}_2=\text{OCH}_3$; $\text{R}_3=\text{OH}$; $\text{R}_4=\text{H}$
 14 $\text{R}_1=\text{R}_2=\text{OCH}_3$; $\text{R}_3=\text{OH}$; $\text{R}_4=\text{OHC}_6\text{H}_4\text{CH}_2\text{CHCO}$
 15 $\text{R}_1=\text{R}_2=\text{R}_3=\text{OH}$; $\text{R}_4=\text{H}$
 16 $\text{R}_1=\text{R}_2=\text{R}_3=\text{OCH}_3$; $\text{R}_4=\text{H}$



- 17 $\text{R}_1=\text{OCH}_3$; $\text{R}_2=\text{R}_4=\text{OH}$; $\text{R}_3=\text{H}$
 23 $\text{R}_1=\text{OH}$; $\text{R}_2=\text{OCH}_3$; $\text{R}_3=\text{H}$; $\text{R}_4=\text{OH}$
 24 $\text{R}_1=\text{OH}$; $\text{R}_2=\text{R}_3=\text{OCH}_3$; $\text{R}_4=\text{H}$
 25 $\text{R}_1=\text{R}_3=\text{OH}$; $\text{R}_2=\text{OCH}_3$; $\text{R}_4=\text{H}$
 26 $\text{R}_1=\text{R}_2=\text{R}_3=\text{OCH}_3$; $\text{R}_4=\text{H}$
 34 $\text{R}_1=\text{OH}$; $\text{R}_2=\text{R}_4=\text{OCH}_3$; $\text{R}_3=\text{H}$
 35 $\text{R}_1=\text{R}_2=\text{OCH}_3$; $\text{R}_3=\text{OH}$; $\text{R}_4=\text{H}$
 36 $\text{R}_1=\text{R}_4=\text{OCH}_3$; $\text{R}_2=\text{OH}$; $\text{R}_3=\text{H}$
 43 $\text{R}_1=\text{R}_2=\text{R}_4=\text{OCH}_3$; $\text{R}_3=\text{H}$
 44 $\text{R}_1=\text{R}_2=\text{OCH}_3$; $\text{R}_3=\text{H}$; $\text{R}_4=\text{OH}$



- 18 $\text{R}_1=\text{R}_3=\text{H}$; $\text{R}_2=\text{OCH}_3$
 19 $\text{R}_1=\text{R}_3=\text{H}$; $\text{R}_2=\text{OH}$
 20 $\text{R}_1=\text{OCH}_3$; $\text{R}_2=\text{R}_3=\text{H}$
 21 $\text{R}_1=\text{OH}$; $\text{R}_2=\text{R}_3=\text{H}$
 22 $\text{R}_1=\text{R}_2=\text{OCH}_3$;
 $\text{R}_3=\text{OHC}_6\text{H}_4\text{CH}_2\text{CHCO-glucosyl}$
 29 $\text{R}_1=\text{OH}$; $\text{R}_2=\text{H}$; $\text{R}_3=\text{glucosyl}$
 32 $\text{R}_1=\text{H}$; $\text{R}_2=\text{OCH}_3$; $\text{R}_3=\text{glucosyl}$
 45 $\text{R}_1=\text{R}_2=\text{OCH}_3$; $\text{R}_3=\text{H}$
 46 $\text{R}_1=\text{O-glucosyl}$; $\text{R}_2=\text{OCH}_3$; $\text{R}_3=\text{glucosyl}$



- 27 $\text{R}_1=\text{CH}_2\text{OH}$; $\text{R}_2=\text{R}_3=\text{R}_4=\text{OCH}_3$
 28 $\text{R}_1=\text{CH}_2\text{OH}$; $\text{R}_2=\text{OH}$; $\text{R}_3=\text{R}_4=\text{OCH}_3$
 30 $\text{R}_1=\text{COOH}$; $\text{R}_2=\text{OH}$; $\text{R}_3=\text{R}_4=\text{OCH}_3$
 31 $\text{R}_1=\text{R}_3=\text{OCH}_3$; $\text{R}_2=\text{OH}$; $\text{R}_4=\text{H}$
 33 $\text{R}_1=\text{CH}_2\text{OH}$; $\text{R}_2=\text{R}_4=\text{OH}$; $\text{R}_3=\text{OCH}_3$
 40 $\text{R}_1=\text{OH}$; $\text{R}_2=\text{R}_3=\text{OCH}_3$; $\text{R}_4=\text{H}$
 41 $\text{R}_1=\text{R}_2=\text{R}_3=\text{OCH}_3$; $\text{R}_4=\text{H}$
 42 $\text{R}_1=\text{R}_2=\text{OCH}_3$; $\text{R}_3=\text{OH}$; $\text{R}_4=\text{H}$
 55 $\text{R}_1=\text{R}_2=\text{R}_3=\text{OCH}_3$; $\text{R}_4=\text{OH}$

methoxy-2-carboxylic acid derivatives, respectively, rather than the 3-hydroxymethyl and the 2-hydroxy-4-methoxy-3-carboxylic acid structures which were suggested previously.

The isolation of cepharanone B 7, aristolactam AII 2, piperolactam A 10 and B 40 from *Piper longum* was the first report of the isolation of aristolactams from the family Piperaceae.²⁴ Later, several aristolactams were isolated from the genus *Piper*.²⁵⁻²⁸ The isolation of 10-amino-4-hydroxy-2,3-dimethoxyphenanthrene-1-carboxylic acid lactam (piperolactam D) 42 from *P. acutisleginum*²⁹ in our laboratory led to the revision of the structures of piperolactam B 40 and piperolactam D 42. Piperolactam B has been found to be the 2-hydroxy- and piperolactam D to be the 4-hydroxy isomer, rather than the 4-hydroxy- and 2-hydroxy derivatives, respectively. The same structure has been assigned to piperolactam A (10) isolated from *P. longum*²⁴ and to aristolactam FI isolated from *Pararistolochia flos-avis*.²¹ However, there is a significant difference in the mps and the ^1H NMR spectral data of these two compounds (Table 1); the mp of piperolactam A is 303–306 °C²⁴ and that of aristolactam FI has been reported as 271–273 °C.²¹

In vitro cytotoxicity of aristolactam Ia 19 and aristolochic acid I 80, isolated from the roots of *A. longa* against P-388 lymphocytic leukaemia and N S C L C N 6 (bronchial epidermoid carcinoma of human origin) was observed.³⁰ These compounds also showed antibacterial activity against *Escherichia coli*, *Pseudomonas aeruginosa*, *Streptococcus faecalis*, *Staphylococcus aureus* and *Staphylococcus epidermidis*.³⁰

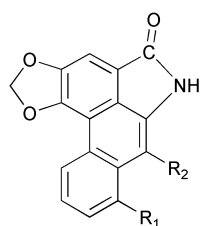
Neurological disorders, especially Parkinson's disease have been treated by the administration of the aristolactam, taliscanine 43 to the affected patient.³¹ The biological activities of aristolochic acid, aristolactam, *N*-methyl aristolactam and aristolactam- β -D-glucoside have been evaluated towards Erlich ascities carcinoma cells in Swiss albino mice.³² These studies showed that the cytotoxic activity is in the order aristolochic acid > aristolactam- β -D-glucoside > aristolactam > *N*-methylaristolactam.

Aristolactam BII 7 and sauristolactam 12 were isolated for the first time from the genus *Saururus*.³³ Houghton and Ogutveren⁹ isolated three novel aristolactams from *A. auricularia*, namely 9-methoxyaristolactam I 52, 9-methoxyaristolactam II 37 and 9-methoxyaristolactam IV 57.

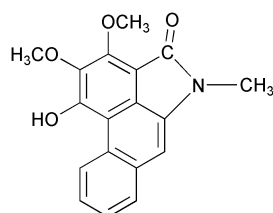
A new alkaloid velutinam 44 has been isolated from *Goniothalamus velutinus*.³⁴ Bioassays of this compound showed that it is selectively active against gram positive bacteria and it is quite cytotoxic against Hela (human cervical carcinoma) and murine leukaemia LI210 cell lines.³⁴

viz. enterocarpam I 48 and enterocarpam II 34 from *Orophea enterocarpa*.²⁰ Two novel aristolactams, aristolactam FI 10 and FII 31 have been isolated along with aristolactam I 18 and AII 2 from *Pararistolochia flos-avis*.²¹ Aristolactam AII 2 showed cytotoxicity against PS and KB cells in culture at ED₅₀ 3.2 and 2.1 g ml⁻¹, respectively.²¹ Aristolactam F II (or goniopedaline 31) was the first 2-oxygenated as well as the first 2,3,4-trioxygenated aristolactam.²¹

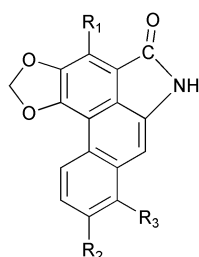
Four new aristolactams *viz.* CII, CIII, DII and DIII were isolated from *A. argentina*.²² Later on, Talapatra *et al.*²³ revised the structures of aristolactam CII 3, CIII 27, DII 4, and DIII 30 to the 2-hydroxymethyl derivatives and the 3-hydroxy-4-



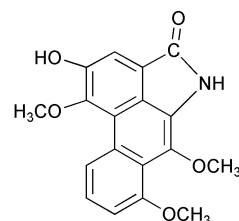
37 R₁=H; R₂=OCH₃
 49 R₁=OCH₃; R₂=OC₂H₅
 50 R₁=OCH₃; R₂=OH



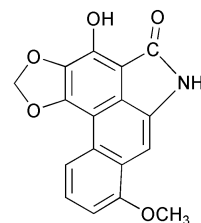
38



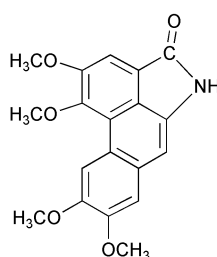
47 R₁=H; R₂=OCH₃; R₃=OH
 52 R₁=OH; R₂=H; R₃=OCH₃



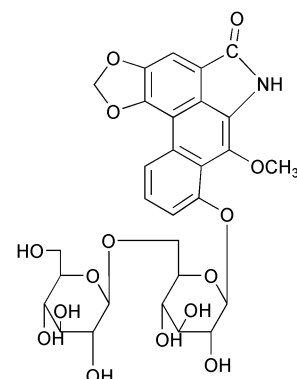
48



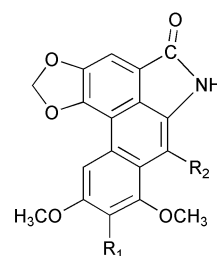
51



53



54



56 R₁=H; R₂=OCH₃
 57 R₁=OCH₃; R₂=H

A new acylated glycoside, aristolactam *N*-(6'-*trans-p*-coumaroyl)- β -D-glucopyranoside **22**, isolated from the roots of *A. contorta*, showed significant antibacterial activity against gram positive bacteria.³⁵

Hong *et al.*³⁶ isolated two new aristolactams, cepharanone A *N*- β -D-glucoside **6** and 2-hydroxy-8-methoxycepharanone A **51**. Aristolactam I **18**, aristolactam III **20**, aristolactam AII **2**, cepharanone A **5**, aristolactam AIII **24**, aristolactam-*N*- β -D-glucoside **32** and aristolactam C *N*- β -D-glucoside **29** were subjected to cytotoxicity and antiplatelet aggregation evaluation. Most of them showed significant cytotoxicity in the KB, P-388, A-549, HT-29 and HL-60 test systems.³⁷ The first report of the isolation of an aristolactam from the *Asarum* genus came from *Asarum petelotii*.³⁸ Stiboroba *et al.*³⁹ reported the analysis of the DNA adducts formed from aristolactam I **18** and II **5**, which are the final metabolites from carcinogenic aristolochic acids *in vivo* after their oxidation by microsomal cytochrome P450 and horseradish peroxidase *in vitro*. Recently, Wang *et al.*⁴⁰ described the hypertensive effect of the chloroform fraction of the extract of *Saururus chinensis*. One of the constituents of the chloroform fraction was found to be cepharanone B **7**. Aristolactam III **20** has been reported to exhibit cytotoxic activity against three kinds of human cancer cell lines (A-549, SK-MEL-2 and SK-OV-3).⁴¹ Zhang *et al.*,⁴² Yu *et al.*⁴³ and Hu *et al.*⁴⁴ reported the isolation of aristolactams *viz.* griffithinam, uvarilactam and goniofithine from *Goniothalamus griffithi* and *Uvaria microcarpa*, respectively. These three aristolactams were found to have the same structure, *i.e.* **36**. Cepharanone B **7**, taliscanine **43**, aristolactam AII **2** and velutinum **44** showed *in vitro* antimalarial activity with IC₅₀ values of 7.51–11.01 μ g mL⁻¹.⁴⁵

Various naturally occurring aristolactams have been classified into four categories on the basis of their oxygenation pattern *viz.* dioxygenated (Table 2), trioxygenated (Table 3), tetraoxygenated (Table 4) and penta-oxygenated aristolactams (Table 5).

2.1 Chemistry of aristolactams

Aristolactams can be synthesized by the general synthetic methodology used by Couture *et al.*¹¹³ The synthesis starts with halogeno-*N*-(diphenylphosphino)lmethyl benzamide derivatives **58**. These can be synthesized by the reaction of differently substituted 2-halogenobenzoic acid or benzaldehyde and phosphorylated amine in the presence of DCC and dimethylaminopyridine.¹¹⁴ Compounds **58** when exposed to potassium bis(trimethylsilyl)amide (2 eq.), followed by acidic treatment give the phosphorylated lactams **59**. Then, a Horner reaction with the appropriate bromobenzaldehyde gives the arylmethylenoisindolinones **60**. The arylmethylenoisindolinones on reaction with tributyltin hydride and AIBN then afford the various aristolactams **61**.

3 Aristolochic acids

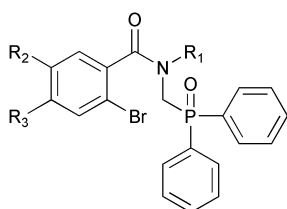
All aristolochic acid derivatives in *Aristolochia* species have a methylenedioxy group on ring A. However, 3-hydroxy-4-methoxy-10-nitrophenanthrene-1-carboxylic acid methyl ester has the possibility to be a species marker, which is useful to characterize the species.²⁸

Table 2 Dioxygenated aristolactams

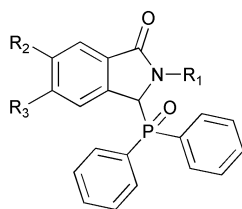
Compound isolated	Source	Reference(s)	Colloquial name and folk medicinal use
10-Amino-2,4-dimethoxy-phenanthrene-1-carboxylic acid lactam 1 Aristolactam AII 2	<i>Goniothalamus griffithii</i>	46	
	<i>Annona cacans</i>	47	
	<i>Aristolochia baetica</i>	48	Emmenagogue, in cancer
	<i>A. chamissonis</i>	49	Debility
	<i>A. contorta</i>	50	Pipe vine- cancer
	<i>A. cucurbitifolia</i>	51,52	Anodyne, antiphlogistic, expectorant, antiasthmatic
	<i>A. foveolata</i>	53	
	<i>A. heterophylla</i>	54,55	Expectorant, antitussive, analgesic, antiasthmatic
	<i>A. indica</i>	19	Indian birthwort- cardiotonic, diuretic, anti-inflammatory
	<i>A. kaempferi</i>	56,57	Asthma, cough, piles
	<i>A. kankauensis</i>	37	Expectorant, antitussive, analgesic, antiasthmatic
	<i>A. liukiensis</i>	58	Antiphlogistic, detoxicant, anodyne
	<i>A. mollissima</i>	59,60	Xun gu feng- analgesic, anti-inflammatory, antimalarial
	<i>A. triangularis</i>	61	Antifertility, diaphoretic, diuretic
	<i>Fissistigma balansae</i>	63	Anti-inflammatory, cancer, rheumatism
	<i>F. glaucescens</i>	62	
	<i>Goniothalamus cheliensis</i>	64	
	<i>G. griffithii</i>	42	Cytotoxic against human cancer
	<i>G. sesquipedalis</i>	23	
	<i>G. tenuifolius</i>	45	
	<i>Houttuynia cordata</i>	65,66	Yakmomil- diuretic, suppurative gonorrhoea, urethritis, stomach cancer
	<i>Monocyclanthus vignei</i>	67	
	<i>Pararistolochia flos-avis</i>	21	
	<i>Piper boehmeriaefolium</i>	25	
	<i>P. hamiltonii</i>	25	Jangli paan
	<i>P. longum</i>	24	Long pepper- asthma, jaundice, diarrhoea, paralysis, cholera, hepatitis, apoplexy, beri-beri
	<i>Saururus chinensis</i>	68	
<i>Uvaria microcarpa</i>	43		
Aristolactam CII 3	<i>Aristolochia argentina</i>	22	Chharuga- antiseptic, diaphoretic, diuretic, emmenagogue
Aristolactam DII 4	<i>A. triangularis</i>	61	
	<i>Aristolochia argentina</i>	23,69	
Cepharanone A 5 (aristolactam II)	<i>A. liukiensis</i>	70	
	<i>Aristolochia argentina</i>	10	
	<i>A. auricularia</i>	9	
	<i>A. cucurbitifolia</i>	51,52	
	<i>A. kaempferi</i>	56,57	
	<i>A. kankauensis</i>	37	
	<i>A. zollingeriana</i>	71	Pain killer
	<i>Aristolochia tubiflora</i>	72	
	<i>Piper boehmeriaefolium</i>	73	
	<i>Schefferomitra subaequalis</i>	17	
Cepharanone A <i>N</i> - β -D-glucoside 6	<i>Stephania cepharantha</i>	11	
	<i>Aristolochia cinnabarina</i>	36,74	
	<i>A. contorta</i>	50	
	<i>A. foveolata</i>	53	
Cepharanone B 7 (aristolactam BII)	<i>A. heterophylla</i>	54,55	
	<i>A. mollissima</i>	75	
	<i>Annona cacans</i>	47	
	<i>Aristolochia acutifolia</i>	76	
	<i>A. baetica</i>	48	
	<i>A. cucurbitifolia</i>	51,52	
	<i>A. heterophylla</i>	55	
	<i>A. kaempferi</i>	57	
	<i>A. liukiensis</i>	58	
	<i>A. triangularis</i>	61	
	<i>Fissistigma balansae</i>	63	
	<i>F. glaucescens</i>	62	
	<i>Goniothalamus andersonii</i>	77	
	<i>G. griffithii</i>	42	
	<i>G. malayanus</i>	78	
	<i>G. tenuifolius</i>	45	
	<i>G. velutinus</i>	34,79	Headache, food poisoning
	<i>Houttuynia cordata</i>	65,80,81	
	<i>Mezzettia umbellata</i>	82	
	<i>Piper attenuatum</i>	25	Dysuria, fever, gonorrhoea
<i>P. augustum</i>	83		
<i>P. boehmeriaefolium</i>	25,73		
<i>P. chiadoense</i>	84		
<i>P. longum</i>	24,25		
<i>P. tuberculatum</i>	85	Stomach ache	
<i>P. wightii</i>	86		

Table 2 (Contd.)

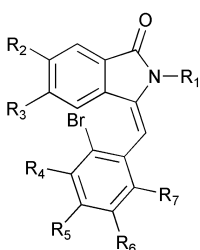
Compound isolated	Source	Reference(s)	Colloquial name and folk medicinal use
	<i>Saururus cernuus</i>	33	Lizard tail, swamp fly
	<i>S. chinensis</i>	40	Chinese lizard tail, water dragon
	<i>Schefferomitra subaequalis</i>	17	
	<i>Stephania cepharantha</i>	11	
	<i>Uvaria hamiltonii</i>	87	
	<i>U. microcarpa</i>	43	
<i>N,O</i> -Diacetylristolactam 8	<i>Goniothalamus sesquipedalis</i>	23	
4-Hydroxy-3-methoxy- <i>N</i> -methyl aristolactam 9 (<i>N</i> -methyl piperolactam A)	<i>Aristolochia chamissonii</i>	49	
Piperolactam A 10 (aristolactam FI)	<i>Piper ribesioides</i>	27	<i>Ta khaan</i> - carminative, dropsy, swelling
	<i>Aristolochia cucurbitifolia</i>	51	
	<i>A. heterophylla</i>	54,55	
	<i>A. kaempferi</i>	57	
	<i>Fissistigma balansae</i>	63	
	<i>F. glaucescens</i>	62	
	<i>F. oldhamii</i>	63	
	<i>Houttuynia cordata</i>	65,66	
	<i>Oxymitra velutina</i>	88	
	<i>Pararistolochia flos-avis</i>	21	
	<i>Piper argyrophyllum</i>	89	
	<i>P. attenuatum</i>	25	
	<i>P. boehmerifolium</i>	25	
	<i>P. hamiltonii</i>	25	
	<i>P. longum</i>	24,25	
	<i>P. wightii</i>	86	
Piperolactam S 11	<i>Piper puberulum</i>	28	
Sauristolactam 12	<i>Saururus cernuus</i>	33	



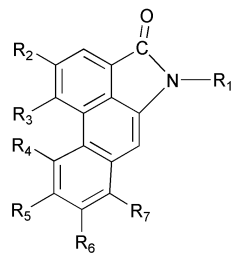
58



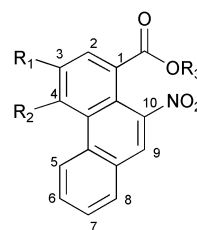
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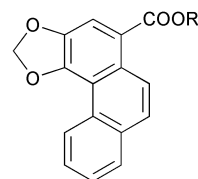
60



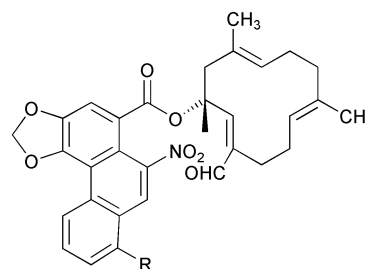
61



- 62** R₁=R₂=OCH₃; R₃=CH₃
65 R₁+R₂=OCH₂O; R₃=H
70 R₁=OH; R₂=OCH₃; R₃=CH₃
71 R₁+R₂=-OCH₂O-; R₃=CH₃
72 R₁+R₂=-OCH₂O-;
R₃=NH.CH(CH₃).COOCH₃
73 R₁+R₂=-OCH₂O-; R₃=Na



- 63** R = Me
64 R = H



- 66** R = H
88 R = OCH₃

Aristolochic acid obtained from *A. indica* disrupted nidation in mice when administered on day one of the pregnancy.¹¹⁵ The aristolochic acid **I 80** is a direct mutagen in *Salmonella typhimurium*,¹¹⁶ *Drosophilla*¹¹⁷ and it is carcinogenic in the rat.¹¹⁸ 2-(Phenanthro [3,4-*d*]-1,3-dioxole-6-nitro-5-carboxamido)-propanoic acid methyl ester **72** and aristolochic acid IV **102** (first time in free form) were isolated from *A. longa*.¹¹⁹ The antitumour agents aristolochin **111** and its methyl ester **112** were obtained from *A. manushuriensis*.¹²⁰ Aristolochic acid **A 80** showed herbicidal activity against *Chenopodium album*, *Amaranthus reproflexus*, *Lindemia pyxidaria* and *Setaria viridis* but it was not phytotoxic to corn and soybeans.¹²¹

The acute toxic effects of aristolochic acid **A 80** were observed in rats and mice. Oral or intravenous administration of high doses was followed by death from acute renal failure within 15 days.¹²² Aristolochic acid **A 80** also showed antifertility activity in mice.¹²³ The aristolochic acids **I 80** and **II 65**, the two main ingredients of the carcinogenic plant are metabolized to a reactive intermediate which binds covalently to DNA *in vitro* and *in vivo*.¹²⁴

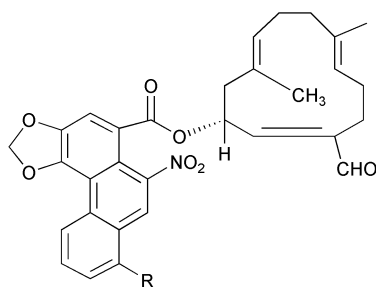
Pezzuto *et al.*¹²⁵ evaluated the mutagenic cytostatic potential of aristolochic acid and several of its derivatives and found that the phenanthrene ring substituents in addition to the NO₂ group at position 10 serve important roles for biological

Table 3 Trioxxygenated aristolactams

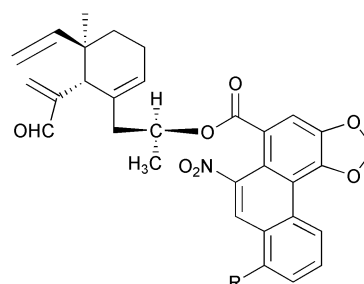
Compound isolated	Source	Reference(s)	Colloquial name and folk medicinal use	
10-Amino-1-carboxy-3,4-dimethoxy-6-hydroxy-phenanthrene lactam <i>N</i> - β -D-glucopyranoside 13	<i>Aristolochia constricta</i>	90	<i>Saragez</i> - analgesic, anticancer, antimalarial, anti-inflammatory	
10-Amino-1-carboxy-3,4-dimethoxy-6-hydroxy-phenanthrene lactam <i>N</i> - β -D-(6'- <i>trans-p</i> -coumaroyl)-glucopyranoside 14	<i>Aristolochia constricta</i>	90		
10-Amino-1-carboxy-3,4,6-trihydroxyphenanthrene lactam- <i>N</i> - β -D-glucopyranoside 15	<i>Aristolochia constricta</i>	90		
10-Amino-1-carboxy-3,4,6-trimethoxyphenanthrenelactam- <i>N</i> - β -D-glucopyranoside 16	<i>Aristolochia constricta</i>	90		
10-Amino-4,8-dihydroxy-3-methoxyphenanthrene-1-carboxylic acid lactam 17	<i>Goniothalamus cheliensis</i>	91		
Aristolactam I 18	<i>Aristolochia auricularia</i>	9		
	<i>A. baetica</i>	92		
	<i>A. bracteata</i>	93	<i>Bracteated birthwort</i> - purgative, antidote, used in snake bite, insecticide, anodyne	
	<i>A. brevipes</i>	94	Toothache	
	<i>A. chilensis</i>	95	Emmenagogue	
	<i>A. contorta</i>	50		
	<i>A. cucurbitifolia</i>	51,52		
	<i>A. elegans</i>	71		
	<i>A. foveolata</i>	53		
	<i>A. heterophylla</i>	55		
	<i>A. indica</i>	19		
	<i>A. kankauensis</i>	37		
	<i>A. mollissima</i>	96		
	<i>A. ponticum</i>	97		
	<i>A. zollingeriana</i>	98		
	<i>Aristolochia tubiflora</i>	72		
	<i>Asarum maximum</i>	99		
	<i>Pararistolochia flos-avis</i>	21		
	Aristolactam Ia 19	<i>Aristolochia argentina</i>	10	
		<i>A. longa</i>	30	
<i>A. triangularis</i>		61		
Aristolactam III 20	<i>Aristolochia argentina</i>	10		
	<i>A. auricularia</i>	9		
	<i>A. baetica</i>	48		
	<i>A. kankauensis</i>	37		
	<i>A. ponticum</i>	97		
	<i>Asiasarum spp.</i>	41		
Aristolactam IIIa 21	<i>Aristolochia argentina</i>	10		
	<i>A. baetica</i>	48,92		
	<i>A. cucurbitifolia</i>	51		
	<i>A. heterophylla</i>	54,55		
	<i>A. kaempferi</i>	56,57		
	<i>A. manshuriensis</i>	100		
Aristolactam <i>N</i> -(6'- <i>trans-p</i> -coumaroyl)- β -D-glucopyranoside 22	<i>Aristolochia contorta</i>	35		
Aristolactam A Ia 23	<i>Aristolochia argentina</i>	10		
	<i>A. triangularis</i>	61		
	<i>Uvaria grandiflora</i>	101	Sudorfic (causing sweat), cough, flatulence	
	<i>U. microcarpa</i>	43		
	<i>Aristolochia baetica</i>	48		
Aristolactam A III 24	<i>A. heterophylla</i>	54,55		
	<i>A. kaempferi</i>	57		
	<i>A. kankauensis</i>	37		
	<i>A. liukuensis</i>	58		
	<i>Goniothalamus borneensis</i>	102	Mosquito repellent	
	<i>Uvaria hamiltonii</i>	86		
	<i>Aristolochia argentina</i>	10		
	<i>A. heterophylla</i>	54,55		
	<i>A. kaempferi</i>	56,57		
	<i>A. mollissima</i>	59		
Aristolactam A IIIa 25	<i>A. triangularis</i>	61		
	<i>Fissistigma balansae</i>	63		
	<i>Goniothalamus cheliensis</i>	64		
	<i>Aristolochia argentina</i>	10		
	<i>A. kankauensis</i>	37		
	<i>Fissistigma balansae</i>	63		
	<i>F. glaucescens</i>	62,74		
	<i>F. oldhamii</i>	63		
Aristolactam B III 26	<i>Aristolochia argentina</i>	22		
	<i>Aristolochia heterophylla</i>	55,103		
	<i>Aristolochia cinnabarina</i>	36		
	<i>A. contorta</i>	50		
	<i>A. cucurbitifolia</i>	52		
Aristolactam C III 27	<i>A. foveolata</i>	53		
Aristolactam C IV 28				
Aristolactam C <i>N</i> - β -D-glucoside 29				

Table 3 (Contd.)

Compound isolated	Source	Reference(s)	Colloquial name and folk medicinal use
	<i>A. heterophylla</i>	55	
	<i>A. kaempferi</i>	57	
	<i>A. kankauensis</i>	37	
	<i>A. mollissima</i>	59	
	<i>A. rotunda</i>	104	Cancer, depurative
Aristolactam D III 30	<i>Aristolochia argentina</i>	22,69	
Aristolactam FII 31 (goniopetaline)	<i>Fissistigma oldhamii</i>	63	
	<i>Goniothalamus sesquipetalis</i>	22	
	<i>Pararistolochia flos-avis</i>	21	
	<i>Uvaria hamiltonii</i>	86	
Aristolactam-N-β-D-glucoside 32	<i>Aristolochia cinnabarina</i>	74,105	
	<i>A. clematidis</i>	106	<i>Upright birthwort</i> - cancer, depurative, menstrual trouble, leg ulcer, wound, tumour
	<i>A. contorta</i>	35	
	<i>A. heterophylla</i>	54,55	
	<i>A. indica</i>	19	
	<i>A. kaempferi</i>	57	
	<i>A. kankauensis</i>	37	
	<i>A. mollissima</i>	59,75	
	<i>A. rotunda</i>	104	
	<i>A. zollingeriana</i>	98	
Aristolukine A 33	<i>Aristolochia kaempferi</i>	56,57	
	<i>A. mollissima</i>	59	
Enterocarpam II 34	<i>Orophea enterocarpa</i>	20	
Goniothalactam 35	<i>Fissistigma balansae</i>	63	
	<i>F. glaucescens</i>	62	
	<i>Goniothalamus borneensis</i>	102	
Griffithinam/goniofithine/uvarilactam 36	<i>Goniothalamus cheliensis</i>	91	
	<i>G. griffithii</i>	42,44	
	<i>Uvaria hamiltonii</i>	87	
	<i>U. microcarpa</i>	43	
9-Methoxyaristolactam II 37	<i>Aristolochia auricularia</i>	9	
N-Methyl-10-amino-4-hydroxy-2,3-dimethoxyphenanthrene-1-carboxylic acid lactam 38	<i>Piper augustum</i>	81	
Piperolactam S 39	<i>Piper kadsura</i>	107	
	<i>P. puberullum</i>	108	Diarrhoea, fever, filariasis, inflammation, wound, boil
Piperolactam B 40	<i>Piper acutisleginum</i>	29	
	<i>P. argyrophyllum</i>	89	
	<i>P. boehimeriaefolium</i>	25	
	<i>P. longum</i>	24,25	
Piperolactam C 41	<i>Fissistigma balansae</i>	63	
	<i>Piper argyrophyllum</i>	89	
	<i>P. boehimeriaefolium</i>	25	
	<i>P. longum</i>	25	
	<i>P. wightii</i>	86	
	<i>Uvaria hamiltonii</i>	87	
Piperolactam D 42	<i>Piper acutisleginum</i>	29	
	<i>P. argyrophyllum</i>	89	
	<i>P. attenuatum</i>	26	
	<i>P. boehimeriaefolium</i>	26	
	<i>P. bogotense</i>	109	
Taliscanine 43 (aristolactam BI)	<i>Aristolochia taliscana</i>	31	
	<i>Goniothalamus griffithii</i>	42	
	<i>G. sesquipetalis</i>	23	
	<i>G. tenuifolius</i>	45	
	<i>Oxymitra velutina</i>	88	
	<i>Uvaria microcarpa</i>	43	
Velutinam 44	<i>Fissistigma oldhamii</i>	63	
	<i>Goniothalamus griffithii</i>	42	
	<i>G. tenuifolius</i>	45	
	<i>G. velutinus</i>	34	



67 R = H
89 R = OCH₃



68 R = H
90 R = OCH₃

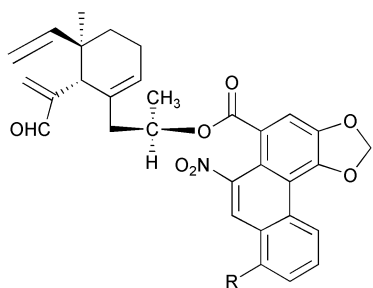
Table 4 Tetraoxygenated aristolactams

Compound isolated	Source	Reference(s)
Aristolactam IV 45	<i>Aristolochia argentina</i>	10
	<i>A. mollissima</i>	96
Aristolamide- <i>N</i> -hexoside 46	<i>Aristolochia contorta</i>	110
	<i>A. debilis</i> ^a	111
Cepharanone C 47	<i>Uvaria grandiflora</i>	101
Enterocarpam I 48	<i>Aristolochia cucurbitifolia</i>	51
	<i>Fissistigma oldhamii</i>	63
9-Ethoxyaristolactam 49	<i>Orophea enterocarpa</i>	20
9-Hydroxyaristolactam I 50	<i>Aristolochia mollissima</i>	112
	<i>Aristolochia brevipes</i>	94
	<i>Aristolochia tubiflora</i>	72
2-Hydroxy-8-methoxy-cepharanone A 51	<i>Aristolochia cinnabarina</i>	36,74
9-Methoxyaristolactam I 52	<i>Aristolochia auricularia</i>	9
	<i>A. cucurbitifolia</i>	51,52
	<i>A. heterophylla</i>	55
	<i>A. kaempferi</i>	57
	<i>A. kankauensis</i>	37
	<i>A. mollissima</i>	59,60
	<i>A. ponticum</i>	97
Norcepharanone 53	<i>Goniothalamus griffithii</i>	42
8-[(6- <i>O</i> -β-D-Glycopyranosyl-β-D-glucopyranosyl)oxy]-9-methoxyaristolactam II 54 (triangularine B)	<i>Aristolochia triangularis</i>	61
Stigmalactam 55	<i>Fissistigma oldhamii</i>	63

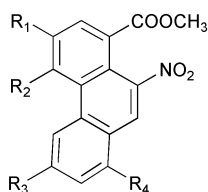
^a Chinese fairy vine- antitumour, sore throat, stomach pain, snake bite.

Table 5 Penta-oxygenated aristolactams

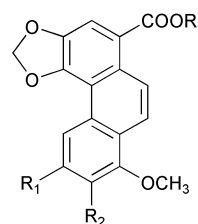
Compound isolated	Source	Reference(s)
7-Methoxyaristolactam IV 56	<i>Asarum maximum</i>	99
	<i>A. petelotii</i>	38
9-Methoxyaristolactam IV 57	<i>Aristolochia auricularia</i>	9
	<i>A. cucurbitifolia</i>	51



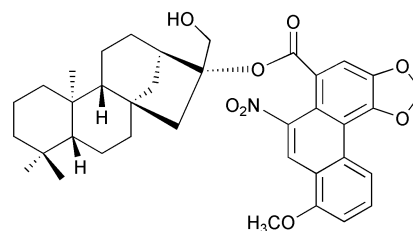
69 R = H
91 R = OCH₃



74 R₁=R₃=OH; R₂=OCH₃, R₄=H
75 R₁=R₂=OCH₃; R₃=OH, R₄=H
76 R₁=OH; R₂=R₄=OCH₃; R₃=H
77 R₁=R₂=R₄=OCH₃; R₃=H



78 R=R₁=R₂=H
94 R=Me; R₁=R₂=H
98 R=H; R₁=Oglc; R₂=H
99 R=R₁=H; R₂=OH
100 R=Me; R₁=H; R₂=OMe
101 R=R₂=H; R₁=OH
115 R=Na; R₁=Oglc; R₂=H
119 R=Na; R₁=H; R₂=OH

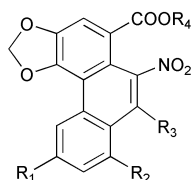


79

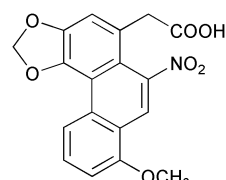
potential. A methanol extract of the dried stem bark of *Cocculus triolobus* showed significant phytotoxic activities towards seeds of *Echinochloa crus-galli* (barnyard grass), *Brassica juncea* (leaf mustard) and *Cucumis sativus* (cucumber). Aristolochic acid A **80** was found to be the active principle.¹²⁶

Metabolites of *A. albida* showed antifeedant activity against tobacco cutworm larvae. Crude methanolic extract of *A. albida* and aristolochic acid A **80** showed strong antifeedant activity, while 6-hydroxyaristolochic acid A **104** showed moderate activity. Aristolactam and aristolic acid did not demonstrate

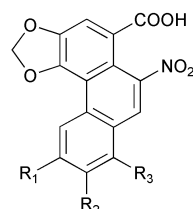
any antifeedant activity. Methyl aristolochate and methyl 6-hydroxyaristolochate (prepared by the diazomethane treatment of the corresponding acid) showed significantly lower activities compared to the parent acids. Thus a free carboxylic acid group in close proximity to a nitro group in the aristolochic acid ring is important for antifeedant activity.¹²⁷ *A. macrophylla* is a major host of the pipevine swallowtail butterfly, *Baltus philenor*. The female butterfly uses a synergistic mixture of



- 80 R₁=R₃=R₄=H; R₂=OCH₃
 81 R₁=R₃=H; R₂=OCH₃; R₄=CH₃
 82 R₁=R₃=R₄=H; R₂=OH
 83 R₁=R₃=H; R₂=OH; R₄=CH₃
 84 R₁=OCH₃; R₂=R₃=R₄=H
 85 R₁=OCH₃; R₂=R₃=H; R₄=CH₃
 86 R₁=OH; R₂=R₃=R₄=H
 87 R₁=O-glucosyl; R₂=R₃=R₄=H
 93 R₁=R₂=R₄=H; R₃=OCH₃
 95 R₁=R₃=H; R₂=OCH₃; R₄=Na
 96 R₁=OCH₃; R₂=R₃=H; R₄=Na
 97 R₁=OH; R₂=R₃=H; R₄=Na
 103 R₁=R₂=OCH₃; R₃=H; R₄=CH₃
 116 R₁=OH; R₂=OCH₃; R₃=H; R₄=Na



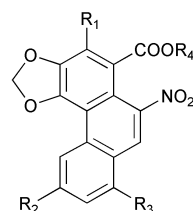
92



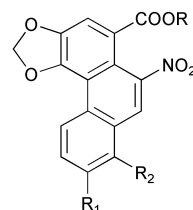
- 102 R₁=R₃=OCH₃; R₂=H
 104 R₁=OH; R₃=OCH₃; R₂=H
 105 R₁=OH; R₂=H; R₃=OCH₃
 106 R₁=OH; R₂=OCH₃; R₃=H
 108 R₁=H; R₂=OH; R₃=OCH₃
 110 R₁=H; R₂=OCH₃; R₃=OH
 111 R₁=O-glucosyl; R₂=H; R₃=OCH₃
 114 R₁=H; R₂=R₃=OCH₃

inositols, acids and lipids as oviposition cues in recognizing the plant on contact. The acids isolated from the alcoholic extract of fresh foliage were identified as aristolochic acid I **80** and II **65**.¹²⁸ Wu *et al.*³⁷ isolated five new aristolochic acids from *A. kankauensis*, named as ariskanins A–E **62,74–77**. The ariskanins A–E, aristolochic acid I **80**, aristolochic acid II **65**, 3-hydroxy-4-methoxy-10-nitrophenanthrene-1-carboxylic acid methyl ester **70**, aristolochic acid C **86**, methyl ester of the aristolochic acid II **71**, aristolactam AIII **24**, aristolactam III **20**, aristolactam II **5**, aristolactam *N*-β-D-glucoside **32**, aristolactam C *N*-β-D-glucoside **29** and aristolactam I **18** were subjected to cytotoxicity and antiplatelet aggregation evaluation. Most of them showed significant cytotoxicity in KB (human epidermoid carcinoma), P-388 (mouse lymphocytic leukaemia), A-549 (lung adenocarcinoma), HT-29 (colon adenocarcinoma) and HL-60 (human leukaemia) test systems.³⁷ Aristolochic acid I **80** exhibited the most potent inhibition of the growth of HT-29 cells. On the other hand, **62,74–77**, 3-hydroxy-4-methoxy-10-nitrophenanthrene-1-carboxylic acid methyl ester **70** and aristolactam AIII **24** at 100 μg mL⁻¹ showed 45–100% inhibition of the rabbit platelet aggregation induced by arachidonic acid (100 μM), collagen (10 μg mL⁻¹) and platelet activation factor (2 μg mL⁻¹), respectively.³⁷

Aristolochic acid IV **102**, isolated from *A. rigida*, exhibited a direct weak mutagenic activity in the Ames test.¹²⁹ It has been reported by Denson *et al.*¹³⁰ that general anaesthetics inhibit Ca²⁺ activated potassium (BK) channels at clinically relevant concentrations. These anaesthetics produce their effect on BK channels by disrupting the phospholipase A₂ (PLA₂)-arachidonic acid signal transduction pathway. The PLA₂ inhibitors, quinacrine (1 M), aristolochic acid I **80** (250 μM) and octadecyl benzoylacrylic acid (7 μM) inhibited BK channels by 61, 47 and 30%, respectively. Detection of DNA adducts formed by aristolochic acid in renal tissue from patients with Chinese herbal nephropathy have been reported by Schmeiser *et al.*^{131,132} Aristoloside **111** has been suggested to be one of the active components of Gmt (Guan mu-tong), a plant material known to have a marked anticancer potential.¹³³ Denitroaristolochic acids are not very common in Aristolochiaceae. Wu *et al.*¹³⁴ isolated seven denitroaristolochic acids, *i.e.* aristolic acid **78**, methyl aristolate **94**, aristofolin A **98**, aristofolin B **99**, aristofolin C **100**, aristofolin D **101** and sodium aristofolin A **115** from *A. cucurbitifolia*. Some of these compounds, **78, 94, 98, 99, 115**, were also isolated later from other species *viz.* *A. elegans*, *A. heterophylla* and *A. kaempferi*. Apart from these reports, there are only three other publications describing the isolation of denitroaristolochic acids, *i.e.* aristofolin E⁵⁷ **63**, aristolic acid II¹⁰⁰ **64** and sodium 7-hydroxy-8-methoxyaristolate⁵¹ **119**. Various naturally occurring aristolochic acids are listed in Tables 6–8.



- 107 R₁=OH; R₂=R₄=H; R₃=OCH₃
 112 R₁=H; R₂=O-glucosyl;
 R₃=OCH₃; R₄=CH₃
 113 R₁=H; R₂=R₃=OCH₃; R₄=CH₃



- 109 R=CH₃; R₁=R₂=OCH₃
 117 R=Na; R₁=R₂=OCH₃
 118 R=Na; R₁=OH; R₂=OCH₃

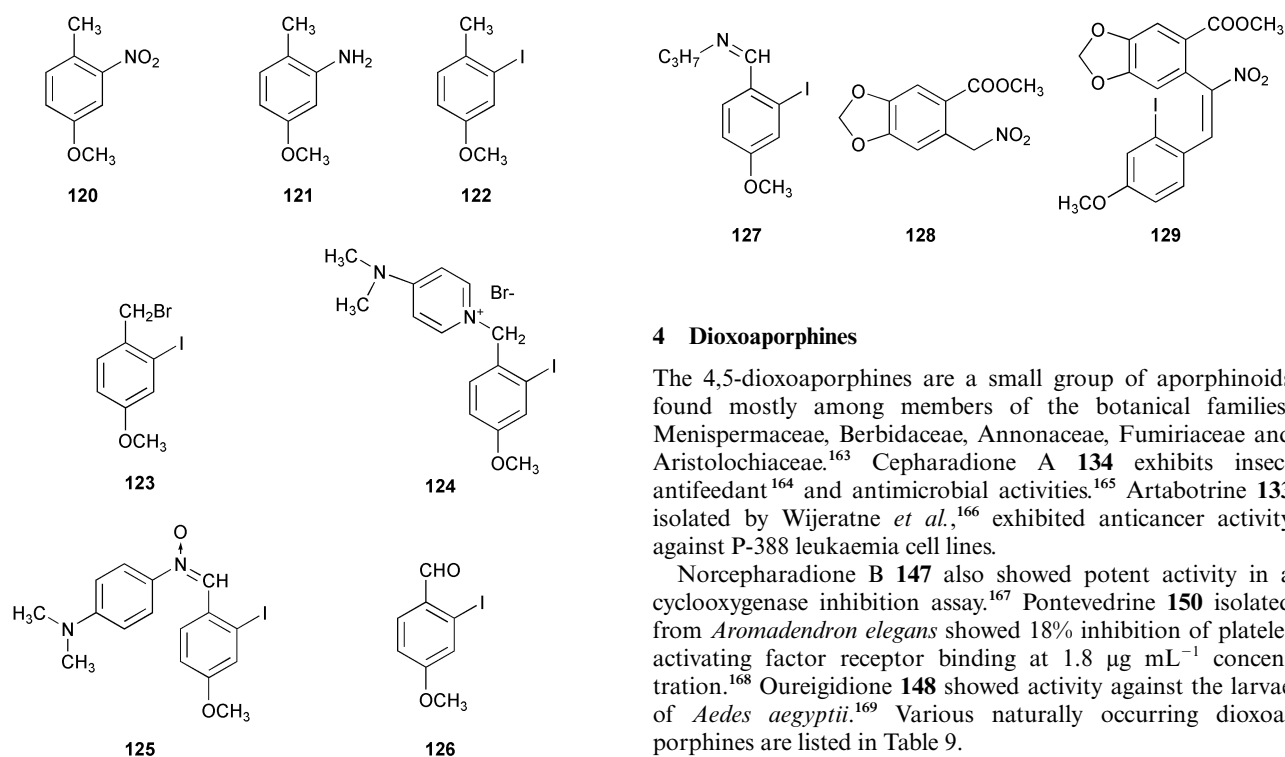
3.1 Chemistry of aristolochic acids and their esters

The methyl esters of aristolochic acids can be synthesized by following the strategy proposed by Kupchan *et al.*¹⁶⁰ 2-Nitro-4-methoxytoluene **120** on reduction with platinum oxide gives 2-amino-4-methoxytoluene **121**.¹⁶⁰ This is then converted into 2-iodo-4-methoxytoluene **122** by the method of Roberts and Smiles.¹⁶¹ This compound was converted to the unstable 2-iodo-4-methoxybenzyl bromide **123** by the use of *N*-bromosuccinimide. Conversion of the benzyl bromide **123** into 1-(2-iodo-4-methoxybenzyl)pyridinium bromide **124** was effected by dissolving it in dry benzene containing 4-dimethylaminopyridine. Compound **124** was in turn converted into 2-iodo-4-methoxyphenyl-*N*-*p*-dimethylaminophenyl nitrene **125** on treatment with 5% sodium hydroxide. Hydrolysis of this product in 6 N sulfuric acid afforded 2-iodo-4-methoxybenzaldehyde **126**. The synthetic precursor of ring A of the desired phenanthrene derivative, *i.e.* the compounds **128**,¹⁶² on condensation with **127** (the Schiff's base of **126**) in glacial acetic acid gave the 2-carbomethoxy-4,5-methylenedioxy-2'-iodo-4'-methoxy-*α*-nitro-*cis*-stilbene **129**. Photolysis of this product afforded aristolochic acid III methyl ester **85**.

Table 6 Dioxygenated aristolochic acids

Compound isolated	Source	Reference(s)
Ariskanin A 62 (aristolochic acid BII methyl ester)	<i>Aristolochia kankauensis</i>	37
Aristofolin E 63	<i>A. manshuriensis</i>	135
Aristolochic acid II 64	<i>Aristolochia kaempferi</i>	57
Aristolochic acid II 65 (aristolochic acid BII)	<i>Aristolochia manshuriensis</i>	100
	<i>Aristolochia argentina</i>	69
	<i>A. auricularia</i>	9
	<i>A. baetica</i>	48,92
	<i>A. cinnabarina</i>	36,105,136
	<i>A. clematitis</i>	106
	<i>A. contorta</i>	137
	<i>A. debilis</i>	20,111,138
	<i>A. heterophylla</i>	55
	<i>A. kaempferi</i>	56
	<i>A. kankauensis</i>	37
	<i>A. liukuensis</i>	70
	<i>A. longa</i> ^a	119
	<i>A. manshuriensis</i>	100,135,139
	<i>A. mollissima</i>	59
	<i>A. ponticum</i>	97
	<i>Aristolochia tubiflora</i>	72
	<i>Battus polydamas</i>	140
Aristoloterpenate II 66	<i>Aristolochia heterophylla</i>	55,139
	<i>A. mollissima</i>	59
Aristoloterpenate IV 67	<i>Aristolochia heterophylla</i>	55,141
	<i>A. mollissima</i>	59
Aristophyllide C 68	<i>Aristolochia heterophylla</i>	55,142
Aristophyllide D 69	<i>Aristolochia heterophylla</i>	55,142
3-Hydroxy-4-methoxy-10-nitrophenanthrene-1-carboxylic acid methyl ester 70	<i>Aristolochia auricularia</i>	9
	<i>A. kankauensis</i>	37
	<i>A. liukuensis</i>	57
	<i>A. zollingeriana</i>	71
Methyl ester of aristolochic acid II 71	<i>Aristolochia argentina</i>	143
	<i>A. cucurbitifolia</i>	51
	<i>A. heterophylla</i>	55
	<i>A. kaempferi</i>	57
	<i>A. kankauensis</i>	37
2-Phenanthro-[3,4- <i>d</i>]-1,3-dioxole-6-nitro-5-carboxamidopropanoic acid methyl ester 72	<i>Aristolochia longa</i>	119
Sodium aristolochate II 73	<i>Aristolochia cucurbitifolia</i>	51
	<i>A. heterophylla</i>	55
	<i>A. kaempferi</i>	57,144
	<i>A. zollingeriana</i>	98

^a Used in treatment of cancer, sclerosis, uterus tumour, nose cancer.



4 Dioxoaporphines

The 4,5-dioxoaporphines are a small group of aporphinoids found mostly among members of the botanical families: Menispermaceae, Berbidaceae, Annonaceae, Fumiriaceae and Aristolochiaceae.¹⁶³ Cepharadione A **134** exhibits insect antifeedant¹⁶⁴ and antimicrobial activities.¹⁶⁵ Artabotrone **133** isolated by Wijeratne *et al.*¹⁶⁶ exhibited anticancer activity against P-388 leukaemia cell lines.

Norcepharadione B **147** also showed potent activity in a cyclooxygenase inhibition assay.¹⁶⁷ Pontevedrine **150** isolated from *Aromadendron elegans* showed 18% inhibition of platelet activating factor receptor binding at 1.8 $\mu\text{g mL}^{-1}$ concentration.¹⁶⁸ Oureigidione **148** showed activity against the larvae of *Aedes aegyptii*.¹⁶⁹ Various naturally occurring dioxoaporphines are listed in Table 9.

Table 7 Trioxxygenated aristolochic acids

Compound isolated	Source	Reference(s)
Ariskanin B 74	<i>Aristolochia kankauensis</i>	37
Ariskanin C 75	<i>Aristolochia kankauensis</i>	37
Ariskanin D 76	<i>Aristolochia kankauensis</i>	37
Ariskanin E 77	<i>Aristolochia kankauensis</i>	37
Aristolich acid 78	<i>Aristolochia cucurbitifolia</i>	51,52,134
	<i>A. elegans</i>	71
	<i>A. heterophylla</i>	54,55
	<i>A. kaempferi</i>	56,57
Aristolin 79	<i>Aristolochia elegans</i>	145
Aristolochic acid A 80 (aristolochic acid I)	<i>Aristolochia argentina</i>	69
	<i>A. auricularia</i>	9
	<i>A. baetica</i>	48,92
	<i>A. bracteata</i>	103,146
	<i>A. chilensis</i>	95
	<i>A. cinnabarina</i>	36,105,136
	<i>A. clematitis</i>	106
	<i>A. contorta</i>	103,137,147,148
	<i>A. cucurbitifolia</i>	51,52
	<i>A. debilis</i>	137
	<i>A. elegans</i>	71
	<i>A. fangchi</i>	149
	<i>A. heterophylla</i>	103,149
	<i>A. indica</i>	19,115
	<i>A. kaempferi</i>	56,57,144
	<i>A. kankauensis</i>	37
	<i>A. kunmingensis</i>	150
	<i>A. kwangsinensis</i>	149
	<i>A. liukuensis</i>	58,70
	<i>A. longa</i>	30,119
	<i>A. manshuriensis</i>	100,135,151
	<i>A. mauroorum</i>	152
	<i>A. mollissima</i>	59,75,96,153,154
	<i>A. moupinensis</i>	149
	<i>A. ponticum</i>	97
	<i>A. versicolor</i>	123,155
	<i>Aristolochin cinabaria</i>	156
	<i>Aristolochia tubiflora</i>	72
	<i>Asarum canadense</i> ^a	157
	<i>A. caudatum</i>	157
	<i>Battus polydamas</i>	140
	<i>Coculus triolobus</i>	126
Aristolochic acid I methyl ester 81	<i>Aristolochia argentina</i>	140
	<i>A. cucurbitifolia</i>	51
	<i>A. debilis</i>	111
	<i>A. indica</i>	19
	<i>A. kaempferi</i>	57
	<i>A. mollissima</i>	75
	<i>A. versicolor</i>	155
Aristolochic acid Ia 82	<i>Aristolochia argentina</i>	69,143
	<i>A. chilensis</i>	94
Aristolochic acid Ia methyl ester 83	<i>Aristolochia kaempferi</i>	57
Aristolochic acid III 84 (6-methoxyaristolochic acid C)	<i>Aristolochia argentina</i>	69
	<i>A. auricularia</i>	9
	<i>A. brevipes</i>	94
	<i>A. cinnabarina</i>	105
	<i>A. debilis</i>	111,138
	<i>A. kankauensis</i>	37
Aristolochic acid III methyl ester 85	<i>Aristolochia cucurbitifolia</i>	51
	<i>A. kaempferi</i>	57
	<i>A. longa</i>	119
Aristolochic acid IIIa 86 (aristolochic acid C)	<i>Aristolochia argentina</i>	69
	<i>A. cinnabarina</i>	36,105,136
	<i>A. contorta</i>	110
	<i>A. cucurbitifolia</i>	51
	<i>A. debilis</i>	138
	<i>A. heterophylla</i>	54,55
	<i>A. kaempferi</i>	56,144
	<i>A. kankauensis</i>	37
	<i>A. manshuriensis</i>	100,135
	<i>A. mollissima</i>	75
	<i>Aristolochia tubiflora</i>	72
	<i>Battus polydamas</i>	140
Aristolochic acid IIIa 6-O-β-D-glucoside 87	<i>Aristolochia baetica</i>	48
	<i>A. cinnabarina</i>	36,136
Aristoloterpenate I 88	<i>Aristolochia heterophylla</i>	55,141
	<i>A. kaempferi</i>	57
	<i>A. mollissima</i>	59,158

Table 7 (Contd.)

Compound isolated	Source	Reference(s)
Aristoloterpenate III 89	<i>Aristolochia cucurbitifolia</i>	51
	<i>A. heterophylla</i>	55,141
	<i>A. kaempferi</i>	57
	<i>A. mollissima</i>	58
Aristophyllide A 90	<i>Aristolochia heterophylla</i>	41,55
	<i>A. mollissima</i>	59
Aristophyllide B 91	<i>Aristolochia heterophylla</i>	55,142
Debilic acid 92	<i>Aristolochia tubiflora</i>	72
9-Methoxyaristolochic acid II 93	<i>Aristolochia ponticum</i>	97
Methyl aristolate 94	<i>Aristolochia cucurbitifolia</i>	52,134
	<i>A. heterophylla</i>	53,54
	<i>A. kaempferi</i>	57
	<i>Uvaria hamiltonii</i>	87
Sodium aristolochate I 95 (aristolochate I)	<i>Aristolochia cucurbitifolia</i>	51,52
	<i>A. elegans</i>	71
	<i>A. foveolata</i>	53
	<i>A. heterophylla</i>	54,55
	<i>A. kaempferi</i>	56,57,144
	<i>A. zollingeriana</i>	97
Sodium aristolochate III 96	<i>Aristolochia cucurbitifolia</i>	51
Sodium aristolochate C 97 (sodium aristolochate IIIa)	<i>Aristolochia foveolata</i>	53
	<i>A. heterophylla</i>	54,55
	<i>A. kaempferi</i>	57
	<i>A. zollingeriana</i>	98

^a *Indian ginger*- analgesic, contraceptive, diuretic, sedative, antidote.

Table 8 Tetraoxygenated aristolochic acids

Compound isolated	Source	Reference(s)	
Aristofolin A 98	<i>Aristolochia cucurbitifolia</i>	52,134	
	<i>A. kaempferi</i>	56,144	
Aristofolin B 99	<i>Aristolochia cucurbitifolia</i>	42,134	
	<i>A. heterophylla</i>	54,55	
	<i>A. kaempferi</i>	56	
	<i>Aristolochia cucurbitifolia</i>	52,134	
Aristofolin C 100	<i>Aristolochia cucurbitifolia</i>	52,134	
Aristofolin D 101	<i>Aristolochia cucurbitifolia</i>	52,134	
Aristolochic acid IV 102 (6-methoxyaristolochic acid)	<i>Aristolochia argentina</i>	69	
	<i>A. auricularia</i>	9	
	<i>A. cucurbitifolia</i>	52	
	<i>A. debilis</i>	111	
	<i>A. kankauensis</i>	37	
	<i>A. longa</i>	119	
	<i>A. manshuriensis</i>	100,135	
	<i>A. rigida</i>	129	
	Aristolochic acid IV methyl ester 103	<i>Aristolochia cucurbitifolia</i>	51,52
		<i>A. kaempferi</i>	57
Aristolochic acid D II 104 (aristolochic acid IVa)	<i>A. kankauensis</i>	37	
	<i>Aristolochia cucurbitifolia</i>	52	
	<i>A. debilis</i>	137	
	<i>A. heterophylla</i>	54,55	
	<i>A. indica</i>	19	
	<i>A. kaempferi</i>	56,143	
	<i>A. kankauensis</i>	37	
	<i>A. manshuriensis</i>	100,135,139,151	
	<i>A. mollissima</i>	59,75,96,153	
	<i>A. triangularis</i>	61	
6,7-Dimethoxy-3,4-methylenedioxy-10-nitro-1-phenanthroic acid 105 (aristolochic acid V)	<i>Battus polydamas</i>	140	
	<i>Aristolochia argentina</i>	69	
6-Hydroxy-7-methoxy-3,4-methylenedioxy-10-nitro-1-phenanthroic acid 106 (aristolochic acid Va)	<i>Aristolochia argentina</i>	69	
2-Hydroxy-8-methoxy-3,4-methylenedioxy-10-nitro-1-phenanthroic acid 107 (aristolochic acid VIa)	<i>Aristolochia argentina</i>	69	
7-Hydroxy-8-methoxy-3,4-methylenedioxy-10-nitro-1-phenanthroic acid 108 (aristolochic acid VIIa)	<i>Aristolochia argentina</i>	69	
	<i>A. contorta</i>	111	
	<i>A. cucurbitifolia</i>	52	
	<i>A. heterophylla</i>	54	
	<i>Aristolochia tubiflora</i>	72	
	<i>Aristolochia cucurbitifolia</i>	52	
	<i>A. liukiensis</i>	70	
	<i>A. moupinensis</i>	159	
	<i>A. versicolor</i>	123,155	
	Aristolochic acid VII methyl ester 109	<i>Aristolochia contorta</i>	147
<i>A. debilis</i>		137	
Aristolochic acid E 110	<i>Aristolochia contorta</i>	147	
	<i>A. debilis</i>	137	

Table 8 (Contd.)

Compound isolated	Source	Reference(s)
Aristolochin 111 (aristoloside)	<i>Aristolochia argentina</i>	69
	<i>A. cinnabarina</i>	36,105,136
	<i>A. manshuriensis</i>	120,151
Aristolochin methyl ester 112	<i>Aristolochia manshuriensis</i>	120
6-Methoxyaristolochic acid methyl ester 113	<i>Aristolochia brevipes</i>	94
	<i>A. fangchi</i>	159
	<i>A. kankauensis</i>	37
7-Methoxyaristolochic acid A 114	<i>Aristolochia contorta</i>	110
Sodium aristofolin A 115	<i>Aristolochia cucurbitifolia</i>	52,134
	<i>A. heterophylla</i>	54
Sodium aristolochate IVA 116	<i>Aristolochia cucurbitifolia</i>	51
	<i>A. heterophylla</i>	55
	<i>A. kaempferi</i>	57
Sodium aristolochate VII 117	<i>A. zollingeriana</i>	98
	<i>Aristolochia baetica</i>	48
	<i>A. heterophylla</i>	55
Sodium 7-hydroxyaristolochate A 118	<i>Aristolochia cucurbitifolia</i>	51,52
	<i>A. foveolata</i>	53
	<i>A. heterophylla</i>	55
Sodium 7-hydroxy-8-methoxyaristololate 119	<i>Aristolochia cucurbitifolia</i>	51

Table 9 Dioxoaporphines

Compound isolated	Source	Reference(s)
Aristolodione 130	<i>Aristolochia chilensis</i>	170
	<i>A. heterophylla</i>	54
	<i>A. kaempferi</i>	57
Aristolukine B 131	<i>Aristolochia heterophylla</i>	54
	<i>A. kaempferi</i>	56,57
	<i>A. mollissima</i>	59
Aristolukine C 132	<i>Aristolochia kaempferi</i>	57
Artabotrine 133 (<i>N</i> -methoxynorcepharadione A)	<i>Artabotrys stenopetalus</i> ^a	171
	<i>A. zeylanicus</i>	166,172
Cepharadione A 134	<i>Aristolochia chilensis</i>	170
	<i>A. cucurbitifolia</i>	51,52
	<i>A. foveolata</i>	53
	<i>A. heterophylla</i>	54,55
	<i>A. indica</i>	19,173
	<i>A. kaempferi</i>	56,57
	<i>A. kankauensis</i>	37
	<i>A. mollissima</i>	59,60
	<i>A. triangularis</i>	61
	<i>A. zollingeriana</i>	98
	<i>Piper acutisleginum</i>	5,174
	<i>P. argyrophyllum</i>	89
	<i>P. attenuatum</i>	25
	<i>P. augustum</i>	83
	<i>P. auritum</i> ^b	5,175
	<i>P. betel</i> ^c	5,174
	<i>P. boehmerifolium</i>	25
	<i>P. bogotense</i>	109
	<i>P. divaricatum</i>	23,176
	<i>P. hamiltonii</i>	25
	<i>P. longum</i>	24,25
	<i>P. manausense</i>	177
	<i>P. methysticum</i>	178
<i>P. pedicellosum</i>	5,174	
<i>P. sanctum</i>	5,10	
<i>P. thomsoni</i>	174	
<i>P. wightii</i>	85	
<i>Stephania cepharantha</i>	11	
<i>S. sasaki</i>	179	
Cepharadione B 135	<i>Houttuynia cordata</i>	66,80
	<i>Piper argyrophyllum</i>	89
	<i>P. attenuatum</i>	25
	<i>P. auritum</i>	10,175
	<i>P. boehmerifolium</i>	25
	<i>P. hamiltonii</i>	25
	<i>P. longum</i>	24,25
	<i>P. sanctum</i>	10
	<i>P. schmidtii</i>	5
	<i>P. wightii</i>	86
7-Chloro-6-demethylcepharadione B 136	<i>Stephania cepharantha</i>	11
	<i>Houttuynia cordata</i>	80
	<i>Telitoxicum krukovii</i>	180

Table 9 (Contd.)

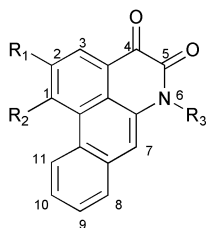
Compound isolated	Source	Reference(s)
1-Desmethoxy-4,5-dioxodehydorasimilobine 137	<i>Monocyclanthus vignei</i>	67
1,2-Dimethoxy-4,5-dioxo-6a,7-dehydroaporphine 138	<i>Piper aborescens</i>	181
4,5-Dioxodehydroasimilobin 139	<i>Aristolochia chilensis</i>	170
	<i>A. contorta</i>	182
	<i>A. cucurbitifolia</i>	51,52
	<i>A. heterophylla</i>	54,55
	<i>A. indica</i>	10
	<i>A. kaempferi</i>	56,57
	<i>A. mollissima</i>	59
	<i>A. triangularis</i>	8,61
	<i>Goniiothalamus cheliensis</i>	64
	<i>Monocyclanthus vignei</i>	67
	<i>Piper longum</i>	24
	<i>Telotoxicum glaziovii</i>	183
	<i>Uvaria microcarpa</i>	43
4,5-Dioxodehydrocrebanine 140	<i>Stephania sasakii</i>	184
Griffithdione 141	<i>Goniiothalamus griffithii</i>	43,185
Labecappolydione 142	<i>Polyalthia cauliflora</i>	186
3-Methoxycepharadione B 143	<i>Mitrephora maingayi</i>	187
8-Methoxyoureigidione 144	<i>Artabotrys zeylanicus</i>	172
Noraristolodione 145 (2-hydroxy-1-methoxy-4,5-dioxo-6,7-dehydroaporphine)	<i>Aristolochia indica</i>	173
	<i>A. liukiensis</i>	58
	<i>Fissistigma balansae</i>	63
	<i>F. glaucescens</i>	62
	<i>Piper attenuatum</i>	25
	<i>P. boehmerifolium</i>	25
	<i>P. longum</i>	24,25
Norcepharadione A 146	<i>Ammonia hayesii</i>	188
	<i>Oncodostigma monosperma</i>	189,190,191
	<i>Stephania cepharanta</i>	192
	<i>Unonopsis pacifica</i>	193
Norcepharadione B 147	<i>Fissistigma balansae</i>	63
	<i>F. glaucescens</i>	62
	<i>Goniiothalamus tenuifolius</i>	42
	<i>Guatteria ouregou</i>	194
	<i>Houttuynia cordata</i>	65,66
	<i>Oxymitra velutina</i>	88
	<i>Piper attenuatum</i>	25
	<i>P. boehmerifolium</i>	25
	<i>P. hamiltonii</i>	25
	<i>P. longum</i>	24,25
	<i>Telotoxicum krukovii</i>	180
Oureigidione 148	<i>Artabotrys zeylanicus</i>	172
	<i>Goniiothalamus malayanus</i>	77
	<i>G. velutinus</i>	78
	<i>Guatteria ouregou</i>	194
	<i>Monocyclanthus manigayi</i>	187
	<i>Telotoxicum glaziovii</i>	183
Piperadione 149	<i>Piper attenuatum</i>	25
	<i>P. hamiltonii</i>	25
	<i>P. longum</i>	24,25
Pontevedrine 150	<i>Aristolochia elegans</i>	172,195
	<i>Glaucium flavum</i>	196
	<i>Platycapnos spicata</i>	197
	<i>Sarcocapnos enneaphylla</i>	198
	<i>S. saetabensis</i>	199
Triangularine A 151	<i>Aristolochia triangularis</i>	61
1,2,3-Trimethoxy-4,5-dioxo-6a,7-dehydroaporphine 152	<i>Piper aborescens</i>	181
	<i>Pseuduvaria macrophylla</i>	200
Tuberosinone 153	<i>Aristolochia cinnabarina</i>	36,105
	<i>A. kaempferi</i>	57
	<i>A. tuberosa</i> ^d	201,202
	<i>Aristolochin cinabaria</i>	156
Tuberosinone-N-β-D-glucoside 154	<i>Aristolochia cinnabarina</i>	36,105
	<i>A. tuberosa</i>	201,202
	<i>Aristolochin cinabaria</i>	156

^a Leaves used in treatment of enlarged spleen. ^b Headache, stomach ache. ^c Antiseptic, astringent, asthma, dysentery. ^d Tuberculosis, sore throat, snake bite.

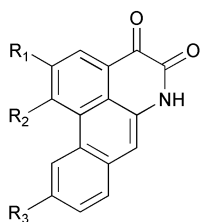
4.1 Chemistry of dioxoaporphines

The preformed biaryl compound **155**, used in the synthesis of dioxoaporphines, on reaction with oxalyl chloride and tin

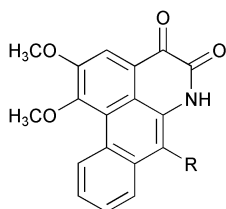
chloride affords the phenanthrylamide **156**. Friedel–Crafts acylation of this with thionyl chloride/aluminium chloride affords the desired 4,5-dioxoaporphines **158** through the intermediate formation of the cyclic precursor **157**.²⁰³



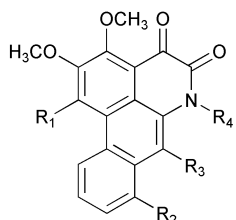
- 130 $R_1=OH$; $R_2=OCH_3$; $R_3=CH_3$
 133 $R_1+R_2=-OCH_2O-$; $R_3=OCH_3$
 134 $R_1+R_2=-OCH_2O-$; $R_3=CH_3$
 135 $R_1=R_2=OCH_3$; $R_3=CH_3$
 137 $R_1=OH$; $R_2=R_3=H$
 139 $R_1=OH$; $R_2=OCH_3$; $R_3=CH_3$
 145 $R_1=OH$; $R_2=OCH_3$; $R_3=H$
 146 $R_1+R_2=-OCH_2O-$; $R_3=H$
 147 $R_1=R_2=OCH_3$; $R_3=H$
 149 $R_1=OH$; $R_2=OCH_3$; $R_3=CH_3$



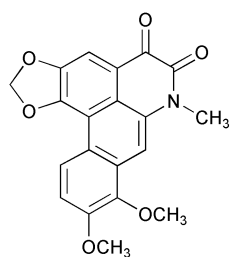
- 131 $R_1=OH$; $R_2=OCH_3$; $R_3=OH$
 132 $R_1=OH$; $R_2=OCH_3$; $R_3=OCH_3$
 151 $R_1=OCH_3$; $R_2=R_3=OH$



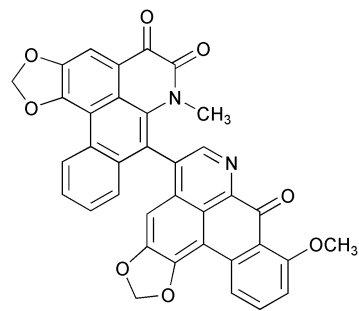
- 136 $R=Cl$
 141 $R=CH_3$



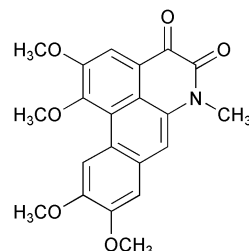
- 138 $R_1=R_2=H$; $R_3=R_4=CH_3$
 143 $R_1=OCH_3$; $R_2=R_3=H$; $R_4=CH_3$
 144 $R_1=R_2=OCH_3$; $R_3=R_4=H$
 148 $R_1=OCH_3$; $R_2=R_3=R_4=H$
 152 $R_1=OCH_3$; $R_2=R_3=H$; $R_4=CH_3$



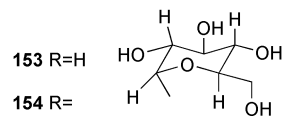
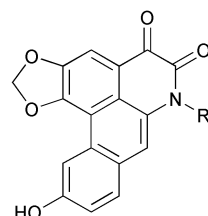
140



142

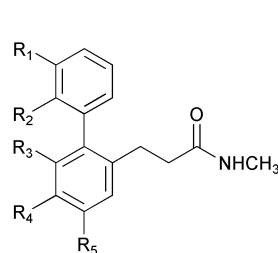


150

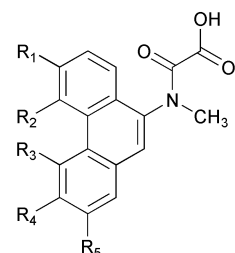


153 $R=H$

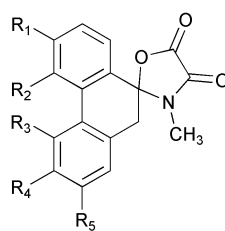
154 $R=$



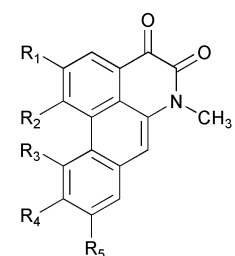
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5 Acknowledgements

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