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Review

Natural phenanthrenes and their biological activity

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Abstract

The aim of this review is to survey the various naturally occurring phenanthrene compounds that have been isolated from different plants. Only one review has previously been published on this topic. Gorham [Gorham, J., 1989. Stilbenes and phenanthrenes. Meth. Plant Biochem. 1, 159–196] reviewed the structures, biosynthesis, separations and spectroscopy of stilbenes and phenanthrenes.

The present study furnishes an overview of the hydroxy or/and methoxy-substituted 9,10-dihydro/phenanthrenes, methylated, prenylated and other monomeric derivatives, dimeric and trimeric phenanthrenes and their biological activities.

A fairly large number of phenanthrenes have been reported from higher plants, mainly in the Orchidaceae family, in the species *Dendrobium*, *Bulbophyllum*, *Eria*, *Maxillaria*, *Bletilla*, *Coelogyna*, *Cymbidium*, *Ephemerantha* and *Epidendrum*. A few phenanthrenes have been found in the Hepaticae class and Dioscoreaceae, Combretaceae and Betulaceae families. Their distribution correlates strongly with the taxonomic divisions.

These plants have often been used in traditional medicine, and phenanthrenes have therefore been studied for their cytotoxicity, antimicrobial, spasmolytic, anti-inflammatory, antiplatelet aggregation, antiallergic activities and phytotoxicity.

On the basis of 120 references, this review covers the phytochemistry and pharmacology of phenanthrenes, describing 252 compounds. This contribution stems from our work on the medicinal plant *Tamus communis*.

Keywords: Phenanthrenes; Dihydrophenanthrenes; Biological activity; Dimeric phenanthrenes; Phenanthraquinones

Contents

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1. Introduction

The phenanthrenes are a rather uncommon class of aromatic metabolites which are presumably formed by oxidative coupling of the aromatic rings of stilbene precursors. Besides these stilbene derived compounds, phenanthrenes most likely originated from diterpenoid precursors are also included in the present review. A large number of differently substituted phenanthrenes have been reported to occur in plants and have been demonstrated to possess various biological activities.

The phenanthrenes isolated so far may be classified into three major groups: monophenanthrenes, diphenanthrenes and triphenanthrenes. Monophenanthrenes are subdivided according to the number and type of the structural moieties, while diphenanthrenes can be classified by the type of connection of the phenanthrene units. Up to present only one compound of the triphenanthrene group was described.

2. Occurrence of phenanthrenes

A fairly large number of phenanthrenes have been reported from higher plants, mainly in the Orchidaceae family, in 49 species: in particular *Dendrobium*, *Bulbophyllum*, *Eria*, *Maxillaria*, *Bletilla*, *Coelogyna*, *Cymbidium*, *Ephemerantha* and *Epidendrum*. A few phenanthrenes have been found in the Hepaticae class and Dioscoreaceae, Combretaceae and Betulaceae families (Table 1). The phenanthrenes were mainly isolated from the whole plants, but in some cases the cortex, tubers or stems were studied and found to contain such compounds. The greatest number of phenanthrenes has been described from the *Juncus* species, but notable numbers have been isolated from *Bletilla striata* and *Bulbophyllum vaginatum*.

3. Structural characteristics of phenanthrenes

3.1. Monomeric phenanthrenes

Most natural phenanthrenes occur in monomeric form; this group consists of about 210 compounds (Tables 2–9). Of these, almost 100 are only hydroxy- and/or methoxy-substituted, and equally 9,10-dihydro- or dehydro derivatives (Tables 2–5). Their great structural diversity stems from the number and position of their oxygen functions. The hydroxy and methoxy moieties number are between 3 and 6, and can usually be found on C-2, C-3, C-5, C-6 or C-7. Homogeneously substituted phenanthrenes are rare; there are only four such compounds among the trisubstituted phenanthrenes bearing only methoxy functionalities (**2**, **10**, **12** and **20**). Only two of the tetrasubstituted compounds are all-hydroxy-substituted (**29**, **58**) and three are substituted only with methoxy groups [callosumin (**26**), **46**, callosuminin (**57**)]. The structures of two compounds [rotundatin (**40**) and **61**] are unusual as they contain a hydroxy or methoxy group on C-9 or C-10. None of the pentasubstituted compounds bears only hydroxy or only methoxy groups. Interestingly, one compound [plicatol-A (**97**)] contains methoxy functions on both C-9 and C-10. There are only two hexasubstituted monophenanthrenes (**98**, **99**) (Table 5).

Besides hydroxy and methoxy groups, further substituents can be found in monomeric phenanthrenes, such as methyl [stemanthrene A (**104**)], hydroxymethyl (**120**), carboxy (**123**), formyl [dehydroeffusal (**153**)], prenyl [gancaonin U (**154**), sinensol G (**156**)] and vinyl (**123**–**128**) (Table 6). Compounds, substituted with methyl and vinyl groups can be found in *Micrandropsis*, *Sagotia*, *Stemona*, *Juncus* and *Domohinea* species. Euphorbiaceae family can be characterized by the occurrence of a wide range of diterpenes, thus it can be assumed that methyl and oxymethyl-substituted phenanthrenes in *Micrandropsis*, *Sagotia* and *Domohinea* have diterpenoid origin (de Alvarenga et al., 1976). *Juncus* phenanthrenes obviously also derived from a specific biosynthetic pathway. Glycosides are relatively rare: they have been reported only in *Juncus effusus* [effusides I–V. (**157**–**161**)], *Epimedium koreanum* [epimedoicariside A (**162**)], *Dendrobium chrysanthum* [denchryside A (**163**)] and *B. striata* (**164**–**167**). In *Coelogyne ochracea* a carboxy group [ochrolic acid (**168**)], in *Micrandropsis scleroxylon* the uncommon *S*-methyl group [micrandrol C (**169**)], and in *Polysyphonia ferulacea* two bromide groups [polysiphenol (**170**)] are attached to the phenanthrene skeleton. Yamaki et al. (1993a) isolated a novel type of phenanthrene with a spirolactone ring, blespirol (**171**), from *B. striata* (Table 7). The structure was proved by X-ray analysis. In general, unusual substitution is somewhat more likely in 9,10-dihydrophenanthrenes.

Another type of monomeric phenanthrenes is the group of phenanthraquinones; altogether 19 compounds belong in this group (Table 8). They are usually hydroxy, methoxy or methyl-substituted, but in *Cremastra appendiculata* a 2-oxopropyl group (**184**, **185**), in *Spiranthes sinensis* a prenyl group [spiranthoquinone (**186**)], and in *Plectranthus* species a 2-propenyl [plectranthon A, C, D (**187**, **188**, **190**)] or 2-acetoxypropyl group (**189**) can be found in the molecule. Plectanthrones A–D (**187**–**190**) are 1,4-phenanthraquinones, which biogenetically are derived from the diterpenoid type abietanoic precursors. (Alder et al., 1984). In the 1990s, a new bisbibenzyl derivative, shancilin (**246**) was isolated from the tubers of the orchid *Pleione bulbocodioides*, and were two **244** and **245** from *Frullania convoluta*. Guo et al. (2006) isolated an unusual molecule, a bibenzyl-dihydrophenanthrene ether, phoyunnanin D (**247**), from the whole plant of *Pholidota yunnanensis*.

Isolation of monomeric phenanthrenes was carried out in general similarly. Usually, the plant materials are extracted with MeOH, EtOH, $CHCl_3$, Me_2CO or MeOH–$CHCl_3$ (1:1). After concentration *in vacuo*, the residue is extracted successively with Et_2O, EtOAc, $CHCl_3$ or *n*-hexane. Extracts are chromatographed on a silica gel

Table 1
Occurrence of phenanthrenes in plant families

	Latin name	Drug	Compounds	Activity
Berberidaceae	*Epimedium koreanum*		**162**	
Betulaceae	*Alnus maximowiczii*	Herba	**20**	
Combretaceae	*Combretum apiculatum*	Cortex	**27**, **31**, **62**, **65–70**, **76**, **78–80**, **83**, **84**	
	Combretum caffrum	Cortex	**62**, **66**, **67**, **69**, **82**	Antitumour
	Combretum molle	Cortex	**65**, **68–70**, **80**, **84**	
	Combretum psidioides	Cortex	**25**, **56**, **62**, **66**, **71**, **75**, **81**, **82**	
Dioscoreaceae	*Dioscorea batatas*		**53–55**	Antifungal
	Dioscorea bulbifera		**29**, **58**	
	Dioscorea decipiens	Radix	**74**	
	Dioscorea prazeri	Tuber, yam	**69**	
	Dioscorea rotundata	Tuber, yam	**6**, **53**, **56**	Antifungal
	Tamus communis	Radix	**25**, **27**, **28**, **42**, **43**, **47**, **48**, **56**, **85–93**, **182**	Antitumour, antiviral
Euphorbiaceae	*Domohinea perrieri*	Stem	**108–111**, **179**	Cytotoxic
	Micrandropsis scleroxylon	Trunk wood	**100**, **102**, **169**	
	Sagotia racemosa	Trunk wood	**100–103**	
Fabaceae	*Glycyrrhiza uralensis*	Aerial part	**154**, **155**	
Hepaticae	*Frulania convoluta*		**244**, **245**	
	Marchantia polymorpha	Herba	**21**, **22**, **226–228**	
	Plagiochila killarniensis	Aerial part	**8–14**, **23**, **26**	
	Plagiochila oresitropha			
Juncaceae	*Juncus acutus*	Aerial part	**112–128**, **131**, **133–138**, **142**, **146–148**, **152**, **236–241**	Antialgal
	Juncus effusus	Aerial part	**112**, **115–118**, **121–124**, **126–128**, **130**, **132–135**, **139–141**, **143–146**, **149–151**, **153**, **157–161**	
	Juncus roemerianus	Root	**115**, **116**, **129**, **146**	Antimicrobial
Lamiaceae	*Plectranthus* species		**187–190**	
Orchidaceae	*Agrostophyllum callosum*	Whole plant	**3**, **24**, **26**, **31**, **57**, **221**, **222**	
	Agrostophyllum khasiyanum	Whole plant	**221**, **222**	
	Arundina graminifolia	Rhizoma	**202**	
	Bletilla formosana	Whole plant	**41**, **192–201**, **218**	
	Bletilla striata	Tuber	**1**, **2**, **4**, **17**, **46**, **164–167**, **171**, **191–195**, **197**, **207**, **214–216**, **218**, **219**, **229**, **249–252**	Antitumour/antimicrobial
	Bulbophyllum gymnopus	Whole plant	**62**, **75**, **85**, **96**	
	Bulbophyllum leopardium	Whole plant	**51**	
	Bulbophyllum reptans	Whole plant	**1**, **19**, **62**, **75**, **85**, **96**, **214**, **223–225**	
	Bulbophyllum vaginatum	Whole plant	**1**, **19**, **24**, **30**, **36**, **42–44**, **50**, **52**, **61–64**, **75–77**, **233**	
	Cirrhopetalum andersonii	Whole plant	**34**, **45**	
	Cirrhopetalum maculosum		**223**	
	Coelogyne cristata	Whole plant	**73**, **95**	
	Coelogyne elata	Whole plant	**1**	
	Coelogyne flaccida	Whole plant	**31**	
	Coelogyne ochracea	Whole plant	**1**, **168**, **176**, **177**	
	Cremastra appendiculata	Tuber	**18**, **19**, **184**, **185**, **223**, **230**, **231**, **243**	Cytotoxic
	Cymbidium aloifolium	Root	**1**, **24**, **180**, **181**	
	Cymbidium pendulum	Whole plant	**86**, **99**	
	Cypripedium tibeticum		**173**, **178**	
	Dendrobium chrysanthum	Herba	**163**	
	Dendrobium densiflorum	Stems	**4**, **15**, **86**, **173**, **175**	
	Dendrobium loddigesii	Stems	**15**	Antiplatelet aggregation inhibitory
	Dendrobium moniliforme	Stem	**172**, **183**	Anti-inflammatory
	Dendrobium moscatum		**15**	
	Dendrobium nobile	Aerial part	**4**, **172**	Antitumour
	Dendrobium plicatile	Stems	**4**, **15**, **36**, **40**, **43**, **97**, **174**, **213**	
	Dendrobium rotundatum	Whole plant	**40**, **42**, **62**, **75**	
	Dendrobium thyrsiflorum	Stems	**86**, **220**, **242**	Cytotoxic
	Ephemerantha fimbriata		**38**, **50**, **94**	
	Ephemerantha lonchophylla	Stems	**35–37**, **43**, **48**, **172**, **174**	Antiplatelet aggregation inhibitory

Table 1 (*continued*)

	Latin name	Drug	Compounds	Activity
	Epidendrum rigidum	Whole plant	**35**, **94**	Phytotoxic
	Eria carinata	Whole plant	**42**	
	Eria confusa	Whole plant	**85**, **98**	
	Eria flava	Whole plant	**1**, **19**, **37**, **43**, **214**	
	Eria stricta	Whole plant	**42**	
	Eulophia nuda	Tuber	**1**, **32**, **33**, **42**, **43**, **59**, **60**, **86**, **232**	
	Eulophia petersii	Root	**1**, **4**, **16**, **32**, **59**	
	Gymnadenia conopsea	Tuber	**1**, **7**, **194**, **195**, **210**, **211**, **214**, **217**	Antiallergic
	Loroglossum hircinum		**5**, **6**	Antifungal
	Lusia indivisa	Whole plant	**4**, **16**	
	Lusia volucris		**234**	
	Maxillaria densa	Whole plant	**36**, **39**, **42**, **49**, **94**, **96**	Phytotoxic, spasmolytic
	Nidema boothii	Whole plant	**4**, **37**, **43**, **72**, **86**, **174**	Spasmolytic
	Orchis militaris		**3**	Antifungal
	Pholidota yunnanensis	Whole plant	**247**, **248**	NO production inhibitory
	Pleione bulbocodioides		**1**, **4**, **195**, **207**, **246**	
	Scaphyglottis livida	Whole plant	**1**, **43**, **86**	Spasmolytic/aorta dilatatory
	Spiranthes sinensis	Aerial part	**156**, **186**, **202–206**, **208**, **209**, **235**	Cytotoxic
	Thunia alba	Whole plant	**4**, **43**, **86**, **214**, **223**	
Rhodomelaceae	*Polysyphonia ferulacea*		**170**	
Stemonaceae	*Stemona collinsae*		**104–107**	
	Stemona pierrei		**104–107**	
	Stemona tuberosa		**104–107**	

column or on Sephadex LH-20 or subjected to preparative TLC and HPLC. Majumder et al. (1982) developed a special method for the isolation of phenanthrenes. The plant materials were soaked in MeOH for three weeks. The MeOH extract was then drained off, concentrated under reduced pressure, and diluted with H_2O, and the liberated solids were exhaustively extracted with Et_2O. The Et_2O extract was fractionated into acidic and non-acidic fractions with 2 M aqueous NaOH. The aqueous alkaline solution was acidified in the cold with conc. HCl, and the liberated solids were extracted with Et_2O, the extract was washed with H_2O and dried, and the solvent was removed.

3.2. Dimeric phenanthrenes and a triphenanthrene

The nearly 40 dimeric phenanthrenes include 9,10-dihydro- and dehydro derivatives (Tables 10 and 11). The monomers are mostly 1-1′-linked, but 1-3′, 1-8′ and 3-3′ linkages also occur in the natural compounds. The compounds are usually hydroxy and methoxy-substituted. In 2003, DellaGreca et al. isolated five dimeric 9,10-dihydrophenanthrenoids with interesting hepta- or octacyclic structures (**237**–**241**) from the rhizome of *Juncus acutus*. From the stems of *Dendrobium thyrsiflorum*, a derivative of phenanthrene–phenanthraquinone, denthyrsinone (**242**), was obtained (Zhang et al., 2005). Investigation of the tubers of *B. striata* led to the isolation of four unusual *bis*(dihydrophenanthrene)ethers (**249**–**252**), in which phenanthrene monomers are coupled through ether bridge. The structures of blestrin C (**251**) and D (**252**) were confirmed by X-ray analysis (Yamaki et al., 1992) (see Table 11).

The only triphenanthrene (**243**) described so far was isolated from the tubers of an orchidaceous plant, *C. appendiculata* (Xue et al., 2006).

4. Biological activities

4.1. Anticancer effects of phenanthrenes

In 1979, Pettit et al. began a study of cancer cell growth inhibitors present in the African willow tree *Combretum caffrum* which resulted in the isolation and structural determination of a series of active phenanthrenes, dihydrophenanthrenes and stilbenes. The cell growth inhibitory activities of phenanthrenes from *C. caffrum* (**62**, **66**, **69**, **82**) were tested on murine P388 lymphocytic leukaemia cell lines; the IC_{50} values were 2.2, 2.8, 2.6 and 2.0 μg/ml, respectively. A series of publications by other researchers reported similar effects of phenanthrenes (Pettit et al., 1988, and references cited therein).

Lusianthridin (**4**) and denbinobin (**172**) isolated from *Dendrobium nobile* were found to exert cytotoxic effects both *in vitro* and *in vivo*. The significant activities of these compounds on A549 human lung carcinoma [ED_{50}: 7.7 μg/ml (**4**); 1.3 μg/ml (**172**)]; SK-OV-3 human ovary adenocarcinoma [ED_{50}: 9.4 μg/ml (**4**); 3.5 μg/ml (**172**)] and HL-60 human promyelocytic leukaemia [ED_{50}: 9.8 μg/ml (**4**); 0.11 μg/ml (**172**)] cell lines were also demonstrated. Lusianthridin (**4**) appears to be less effective than denbinobin (**172**). Their methylated derivatives did not exhibit activities, suggesting that a free phenolic hydroxy group

Table 2
Trisubstituted dihydro/phenanthrenes with hydroxy- or/and methoxy-substitution

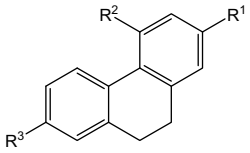
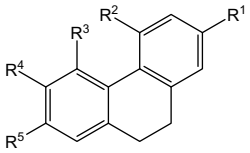
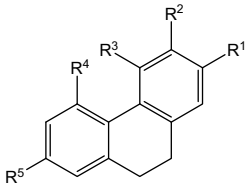
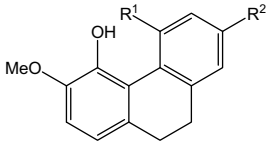
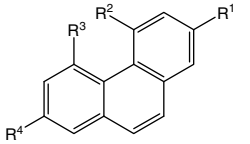
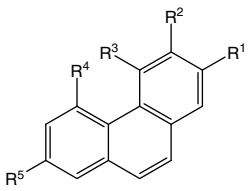
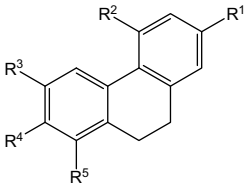
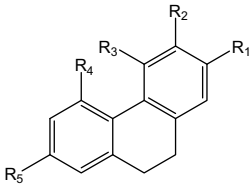
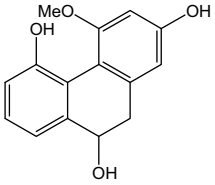
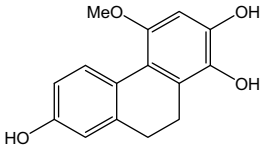
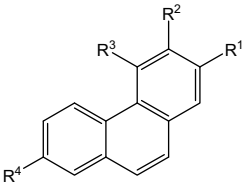
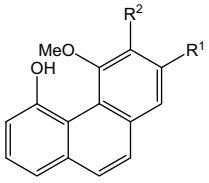
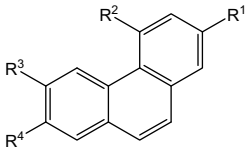
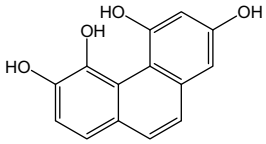
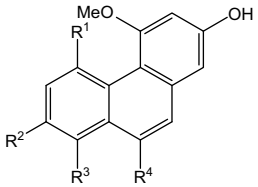
	**1** $R^1 = OH$, $R^2 = OMe$, $R^3 = OH$; coelonin	*B. reptans* (Majumder et al., 1999) *B. striata* (Yamaki et al., 1991) *B. vaginatum* (Leong et al., 1997) *C. aloifolium* (Juneja et al., 1987) *C. elata* (Majumder et al., 1982) *C. ochracea* (Majumder et al., 1982) *E. flava* (Majumder and Banerjee, 1990a) *E. nuda* (Tuchinda et al., 1988) *E. petersii* (Blitzke et al., 2000) *G. conopsea* (Matsuda et al., 2004; Morikawa et al., 2006) *P. bulbocodioides* (Bai et al., 1996) *S. livida* (Estrada et al., 1999a)
	2 $R^1 = OMe$, $R^2 = OMe$, $R^3 = OMe$	*B. striata* (Yamaki et al., 1991)
	3 $R^1 = OMe$, $R^2 = OMe$, $R^3 = OH$; orchinol	*A. callosum* (Majumder et al., 1995, 1996) *O. militaris* (Baller et al., 1957; Fisch et al., 1973)
	4 $R^1 = OMe$, $R^2 = OH$, $R^3 = OH$; lusianthridin	*B. striata* (Takagi et al., 1983) *D. densiflorum* (Fan et al., 2001) *D. nobile* (Lee et al., 1995) *D. plicatile* (Yamaki and Honda, 1996) *E. petersii* (Blitzke et al., 2000) *L. indivisa* (Majumder and Lahiri, 1990d) *N. boothii* (Hernandez-Romero et al., 2004) *P. bulbocodioides* (Bai et al., 1996) *T. alba* (Majumder et al., 1998b)
	**5** $R^1 = OMe$, $R^2 = OMe$, $R^3 = OH$, $R^4 = H$, $R^5 = H$; loroglossol	*L. hircinum* (Fisch et al., 1973)
	6 $R^1 = OH$, $R^2 = OMe$, $R^3 = OH$, $R^4 = H$, $R^5 = H$; hircinol	*L. hircinum* (Fisch et al., 1973) *D. rotundata* (Coxon et al., 1982)
	**7** $R^1 = OMe$, $R^2 = H$, $R^3 = OH$, $R^4 = OH$, $R^5 = H$	*G. conopsea* (Matsuda et al., 2004; Morikawa et al., 2006)
	8 $R^1 = OH$, $R^2 = OMe$, $R^3 = H$, $R^4 = OMe$, $R^5 = H$	*Plagiochila* sp. (Anton et al., 1997) *P. killarniensis* (Rycroft et al., 1999)
	9 $R^1 = OMe$, $R^2 = OMe$, $R^3 = H$, $R^4 = OH$, $R^5 = H$	*Plagiochila* sp. (Anton et al., 1997)
	10 $R^1 = OMe$, $R^2 = OMe$, $R^3 = H$, $R^4 = OMe$, $R^5 = H$	*Plagiochila* sp. (Anton et al., 1997)
	11 $R^1 = OH$, $R^2 = OMe$, $R^3 = H$, $R^4 = H$, $R^5 = OMe$	*Plagiochila* sp. (Anton et al., 1997)
	12 $R^1 = OMe$, $R^2 = OMe$, $R^3 = H$, $R^4 = H$, $R^5 = OMe$	*Plagiochila* sp. (Anton et al., 1997)
	**13** $R^1 = OH$, $R^2 = H$	*Plagiochila* sp. (Anton et al., 1997) *P. killarniensis* (Rycroft et al., 1999)
	14 $R^1 = H$, $R^2 = OMe$	*Plagiochila* sp. (Anton et al., 1997)
	**15** $R^1 = OH$, $R^2 = OMe$, $R^3 = OH$, $R^4 = H$; plicatol-B, moscatin	*D. plicatile* (Honda and Yamaki, 2000) *D. rotundatum* (Majumder and Sen, 1987b; Majumder and Pal, 1992) *D. densiflorum* (Fan et al., 2001) *D. moscatum* (Majumder and Sen, 1987b) *D. loddigesii* (Chen et al., 1994)
	16 $R^1 = OMe$, $R^2 = OH$, $R^3 = H$, $R^4 = OH$; lusianthrin	*E. petersii* (Blitzke et al., 2000) *L. indivisa* (Majumder and Lahiri, 1990d)
	17 $R^1 = OMe$, $R^2 = OMe$, $R^3 = H$, $R^4 = OMe$	*B. striata* (Yamaki et al., 1991)
	18 $R^1 = OH$, $R^2 = OMe$, $R^3 = H$, $R^4 = OMe$	*C. appendiculata* (Xue et al., 2006)
	19 $R^1 = OH$, $R^2 = OMe$, $R^3 = H$, $R^4 = OH$; flavanthrinin	*B. reptans* (Majumder et al., 1999) *B. vaginatum* (Leong et al., 1997) *E. flava* (Majumder and Banerjee, 1990a) *C. appendiculata* (Xue et al., 2006)
	**20** $R^1 = OMe$, $R^2 = OMe$, $R^3 = OMe$, $R^4 = H$, $R^5 = H$	*A. maximowiczii* (Tori et al., 1995)
	21 $R^1 = OMe$, $R^2 = OMe$, $R^3 = H$, $R^4 = H$, $R^5 = OH$	*M. polymorpha* (Adam and Becker, 1994)
	22 $R^1 = OH$, $R^2 = OMe$, $R^3 = H$, $R^4 = H$, $R^5 = OH$	*M. polymorpha* (Adam and Becker, 1994)
	23 $R^1 = OH$, $R^2 = OMe$, $R^3 = H$, $R^4 = OMe$, $R^5 = H$	*Plagiochila* sp. (Anton et al., 1997)

Table 3
Tetrasubstituted dihydro/phenanthrenes with hydroxy- or/and methoxy-substitution

	**24** $R^1 = OH$, $R^2 = OMe$, $R^3 = OMe$, $R^4 = OH$, $R^5 = H$; 6-methoxy-coelonin	*A. callosum* (Majumder et al., 1995, 1996) *B. vaginatum* (Leong et al., 1997) *C. aloifolium* (Juneja et al., 1987)
	25 $R^1 = OMe$, $R^2 = OMe$, $R^3 = OMe$, $R^4 = OH$, $R^5 = H$;	*C. psidioides* (Letcher and Nhamo, 1972b) *T. communis* (Kovács et al., 2007)
	26 $R^1 = OMe$, $R^2 = OMe$, $R^3 = OMe$, $R^4 = OMe$, $R^5 = H$; callosumin	*A. callosum* (Majumder et al., 1996) *Plagiochila* sp. (Anton et al., 1997)
	27 $R^1 = OMe$, $R^2 = OH$, $R^3 = OMe$, $R^4 = OH$, $R^5 = H$	*T. communis* (Aquino et al., 1985a, 1991; Letcher and Nhamo, 1972a) *C. apiculatum* (Letcher and Nhamo, 1971)
	28 $R^1 = OMe$, $R^2 = OH$, $R^3 = OMe$, $R^4 = OMe$, $R^5 = H$	*T. communis* (Aquino et al., 1985a, 1991)
	29 $R^1 = OH$, $R^2 = OH$, $R^3 = OH$, $R^4 = OH$, $R^5 = H$	*D. bulbifera* (Wij and Rangaswami, 1978)
	30 $R^1 = OH$, $R^2 = OMe$, $R^3 = OH$, $R^4 = OH$, $R^5 = H$	*B. vaginatum* (Leong et al., 1999)
	31 $R^1 = OH$, $R^2 = OMe$, $R^3 = OH$, $R^4 = OMe$, $R^5 = H$; callosin	*A. callosum* (Majumder et al., 1995, 1996) *C. flaccida* (Majumder et al., 1995) *C. apiculatum* (Letcher and Nhamo, 1971)
	32 $R^1 = OMe$, $R^2 = OH$, $R^3 = H$, $R^4 = OMe$, $R^5 = OH$; eulophiol	*E. nuda* (Tuchinda et al., 1988) *E. petersii* (Blitzke et al., 2000)
	33 $R^1 = OH$, $R^2 = OMe$, $R^3 = H$, $R^4 = OMe$, $R^5 = OH$	*E. nuda* (Tuchinda et al., 1988)
	**34** $R^1 = R^2 = –O–CH_2–O–$, $R^3 = OH$, $R^4 = H$, $R^5 = OH$; cirrhopetalanthridin	*C. andersonii* (Majumder and Basak, 1991a)
	35 $R^1 = OMe$, $R^2 = OMe$, $R^3 = OH$, $R^4 = H$, $R^5 = OH$; ephemeranthol-A	*E. lonchophylla* (Tezuka et al., 1991) *E. rigidum* (Hernandez-Romero et al., 2005)
	36 $R^1 = OH$, $R^2 = OMe$, $R^3 = OMe$, $R^4 = H$, $R^5 = OH$; erianthridin	*B. vaginatum* (Leong et al., 1997) *D. plicatile* (Yamaki and Honda, 1996) *E. lonchophylla* (Chen et al., 2000; Tezuka et al., 1991) *M. densa* (Estrada et al., 1999b, 2004; Valencia-Islas et al., 2002)
	37 $R^1 = OMe$, $R^2 = OH$, $R^3 = OMe$, $R^4 = H$, $R^5 = OH$; ephemeranthol-B, flavanthridin	*E. lonchophylla* (Tezuka et al., 1991) *E. flava* (Majumder and Banerjee, 1990a) *N. boothii* (Hernandez-Romero et al., 2004)
	38 $R^1 = OH$, $R^2 = OH$, $R^3 = OMe$, $R^4 = OH$, $R^5 = H$; ephemeranthol-C	*E. fimbriata* (Tezuka et al., 1993)
	39 $R^1 = OH$, $R^2 = OMe$, $R^3 = OMe$, $R^4 = OH$, $R^5 = H$	*M. densa* (Estrada et al., 1999b)
	**40** plicatol-C, rotundatin	*D. plicatile* (Honda and Yamaki, 2000) *D. rotundatum* (Majumder and Pal, 1992)
	**41**	*B. formosana* (Lin et al., 2005)
	**42** $R^1 = OH$, $R^2 = OMe$, $R^3 = OMe$, $R^4 = OH$; nudol	*B. vaginatum* (Leong et al., 1997) *D. rotundatum* (Majumder and Pal, 1992) *E. carinata* (Bhandari et al., 1985) *E. stricta* (Bhandari et al., 1985) *E. nuda* (Bhandari et al., 1985; Tuchinda et al., 1988) *M. densa* (Estrada et al., 1999b, 2004) *T. communis* (Réthy et al., 2006)

(*continued on next page*)

Table 3 (*continued*)

	43 R^1 = OMe, R^2 = OH, R^3 = OMe, R^4 = OH;	*B. vaginatum* (Leong et al., 1997) *D. plicatile* (Yamaki and Honda, 1996) *E. flava* (Majumder and Banerjee, 1990a) *E. lonchophylla* (Chen et al., 2000) *E. nuda* (Tuchinda et al., 1988) *N. boothii* (Hernandez-Romero et al., 2004) *S. livida* (Estrada et al., 1999a; Estrada-Soto et al., 2006) *T. alba* (Majumder et al., 1998b) *T. communis* (Réthy et al., 2006)
	44 R^1 = OH, R^2 = OH, R^3 = OMe, R^4 = OH	*B. vaginatum* (Leong et al., 1997, 1999)
	45 $R^1 = R^2$ = –O–CH_2–O–, R^3 = OMe, R^4 = OH, cirrhopetalin	*C. andersonii* (Majumder and Basak, 1990b, 1991a)
	46 R^1 = OMe, R^2 = OMe, R^3 = OMe, R^4 = OMe	*B. striata* (Yamaki et al., 1991)
	47 R^1 = OMe, R^2 = OMe, R^3 = OMe, R^4 = OH;	*T. communis* (Bordat et al., 2006; Réthy et al., 2006)
	48 R^1 = OMe, R^2 = OMe, R^3 = OH, R^4 = OH; TaVIII.	*E. lonchophylla* (Tezuka et al., 1991) *T. communis* (Aquino et al., 1985a,b; Letcher and Wong, 1979; Reisch et al. 1973)
	**49** R^1 = OH, R^2 = OMe	*M. densa* (Estrada et al., 1999b, 2004)
	50 R^1 = OH, R^2 = OH; fimbriol-B	*B. vaginatum* (Leong et al., 1997) *E. fimbriata* (Tezuka et al., 1993)
	51 R^1 = OMe, R^2 = OH; bulbophyllanthrin	*B. leopardium* (Majumder et al., 1985)
	**52** R^1 = OH, R^2 = OMe, R^3 = OMe, R^4 = OH	*B. vaginatum* (Leong et al., 1997)
	53 R^1 = OMe, R^2 = OMe, R^3 = OH, R^4 = OMe; batatasin I	*D. batatas* (Takasugi et al., 1987) *D. rotundata* (de Alvarenga and Gottlieb, 1974)
	54 R^1 = OMe, R^2 = OMe, R^3 = OH, R^4 = OH	*D. batatas* (Takasugi et al., 1987)
	55 R^1 = OH, R^2 = OMe, R^3 = OMe, R^4 = OH	*D. batatas* (Takasugi et al., 1987)
	56 R^1 = OMe, R^2 = OMe, R^3 = OMe, R^4 = OH; TaVI	*C. psidioides* (Letcher and Nhamo, 1972b) *D. rotundata* (Coxon et al., 1982) *T. communis* (Aquino et al., 1985a,b; Kovács et al., 2007; Letcher and Nhamo, 1972a; Reisch et al., 1969, 1973)
	57 R^1 = OMe, R^2 = OMe, R^3 = OMe, R^4 = OMe; callosuminin	*A. callosum* (Majumder et al., 1996)
	**58**	*D. bulbifera* (Wij and Rangaswami, 1978)
	**59** R^1 = H, R^2 = OH, R^3 = OMe, R^4 = H	*E. nuda* (Tuchinda et al., 1988) *E. petersii* (Blitzke et al., 2000)
	60 R^1 = H, R^2 = OMe, R^3 = OH, R^4 = H	*E. nuda* (Tuchinda et al., 1988)
	61 R^1 = OH, R^2 = H, R^3 = H, R^4 = OMe	*B. vaginatum* (Leong et al., 1997)

is essential for inhibitory activity (Lee et al., 1995). Lusianthridin (**4**) isolated from *B. striata* did not exert activity against the leukaemic P388 cell line *in vitro* (Takagi et al., 1983). In contrast, at a dose of 20 μg/kg, lusianthridin (**4**) displayed an antitumour effect, while denbinobin (**172**) was inactive in ICR mice implanted intraperitoneally with 10^6 cells of sarcoma 180 (Takagi et al., 1983).

D. thyrsiflorum has been used in Chinese ethnomedicine. Five phenanthrenes isolated from the stems were assayed against several tumour cell lines by use of the MTT test. Two dimeric phenanthrenes (**220**, **242**) and denthirsinin (**86**) displayed significant cytotoxicity against HeLa, K-562 and MCF-7 cells. The IC_{50} values (μM) on these cell lines were: denthyrsinol (**220**) 9.3, 1.6 and -, denthyrsinone (**242**) 9.9, 6.0 and 3.5, and denthirsinin (**86**) 2.7, 2.3 and 4.8, respectively. Hircinol (**6**) ($IC_{50} > 100$, 6.3 and >100 μM) and moscatin (**15**) ($IC_{50} > 100$, 7.1 and >100 μM) were less effective in killing HeLa and MCF-7 cells than denthyrsinol (**220**). Structure–activity relationship analyses revealed that the dimerization of phenanthrenes is a very important factor for the inhibition of cancer cell growth (Zhang et al., 2005).

Table 4
Pentasubstituted dihydro/phenanthrenes with hydroxy- or/and methoxy-substitution

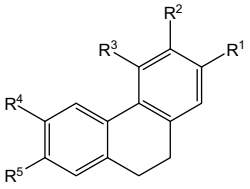
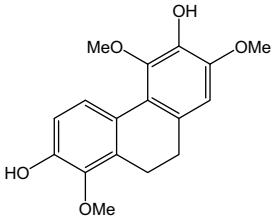
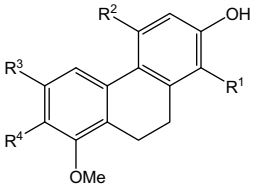
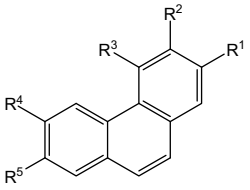
	**62** $R^1 = OH$, $R^2 = OMe$, $R^3 = OMe$, $R^4 = OMe$, $R^5 = OH$	*B. gymnopus* (de Alvarenga et al., 1976; Majumder and Banerjee, 1988b) *B. reptans* (Majumder et al., 1999) *B. vaginatum* (Leong et al., 1997) *C. apiculatum* (Malan and Swinny, 1993) *C. caffrum* (Pettit et al., 1988) *C. psidioides* (Letcher and Nhamo, 1972b) *D. rotundatum* (Majumder and Pal, 1992)
	63 $R^1 = OH$, $R^2 = OH$, $R^3 = OMe$, $R^4 = OMe$, $R^5 = OH$	*B. vaginatum* (Leong et al., 1999)
	64 $R^1 = OH$, $R^2 = OH$, $R^3 = OMe$, $R^4 = OH$, $R^5 = OH$	*B. vaginatum* (Leong et al., 1999)
	65 $R^1 = OMe$, $R^2 = OMe$, $R^3 = OH$, $R^4 = OH$, $R^5 = OH$	*C. apiculatum* (Malan and Swinny, 1993) *C. molle* (Letcher et al., 1972)
	66 $R^1 = OMe$, $R^2 = OMe$, $R^3 = OMe$, $R^4 = OMe$, $R^5 = OH$	*C. apiculatum* (Malan and Swinny, 1993) *C. caffrum* (Pettit et al., 1988) *C. psidioides* (Letcher and Nhamo, 1972b)
	67 $R^1 = OH$, $R^2 = OMe$, $R^3 = OMe$, $R^4 = OMe$, $R^5 = OMe$	*C. apiculatum* (Pettit et al., 1988) *C. caffrum* (Pettit et al., 1988)
	68 $R^1 = OMe$, $R^2 = OMe$, $R^3 = OH$, $R^4 = OMe$, $R^5 = OH$	*C. apiculatum*, (Letcher and Nhamo, 1971; Malan and Swinny, 1993) *C. molle* (Letcher et al., 1972)
	69 $R^1 = OMe$, $R^2 = OMe$, $R^3 = OMe$, $R^4 = OH$, $R^5 = OH$; prazerol	*C. apiculatum* (Malan and Swinny, 1993) *C. caffrum* (Pettit et al., 1988) *C. molle* (Letcher et al., 1972; Malan and Swinny, 1993) *D. prazeri* (Biswas et al., 1988)
	70 $R^1 = OH$, $R^2 = OMe$, $R^3 = OMe$, $R^4 = OH$, $R^5 = OMe$	*C. apiculatum* (Letcher and Nhamo, 1971) *C. molle* (Letcher and Nhamo, 1971; Letcher et al., 1972)
	71 $R^1 = OH$, $R^2 = OMe$, $R^3 = OMe$, $R^4 = OH$, $R^5 = OH$	*C. psidioides* (Letcher and Nhamo, 1972b)
	**72**	*N. boothii* (Hernandez-Romero et al., 2004)
	**73** $R^1 = H$, $R^2 = OH$, $R^3 = OH$, $R^4 = OMe$, coeloginanthridin	*C. cristata* (Majumder et al., 2001)
	74 $R^1 = H$, $R^2 = OMe$, $R^3 = OMe$, $R^4 = OH$	*D. decipiens* (Sunder et al., 1978)
	**75** $R^1 = OH$, $R^2 = OMe$, $R^3 = OMe$, $R^4 = OMe$, $R^5 = OH$	*B. gymnopus* (DellaGreca et al., 1993; Majumder and Banerjee, 1988b) *B. reptans* (Majumder et al., 1999) *B. vaginatum* (Leong et al., 1997) *C. psidioides* (Letcher and Nhamo, 1972b) *D. rotundatum* (Honda and Yamaki, 2000; Majumder and Pal, 1992)
	76 $R^1 = OH$, $R^2 = OH$, $R^3 = OMe$, $R^4 = OMe$, $R^5 = OH$	*B. vaginatum* (Leong et al., 1997, 1999) *C. apiculatum* (Malan and Swinny, 1993)
	77 $R^1 = OH$, $R^2 = OH$, $R^3 = OMe$, $R^4 = OH$, $R^5 = OH$	*B. vaginatum* (Leong et al., 1999)
	78 $R^1 = OMe$, $R^2 = OH$, $R^3 = OMe$, $R^4 = OH$, $R^5 = OH$	*C. apiculatum* (Malan and Swinny, 1993)
	79 $R^1 = OMe$, $R^2 = OH$, $R^3 = OMe$, $R^4 = OMe$, $R^5 = OH$	*C. apiculatum* (Malan and Swinny, 1993)
	80 $R^1 = OMe$, $R^2 = OMe$, $R^3 = OH$, $R_4 = OMe$, $R^5 = OH$	*C. apiculatum* (Malan and Swinny, 1993) *C. molle* (Letcher et al., 1972)
	81 $R^1 = OH$, $R^2 = OMe$, $R^3 = OMe$, $R^4 = OH$, $R^5 = OH$	*C. psidioides* (Letcher and Nhamo, 1972b)
	82 $R^1 = OMe$, $R^2 = OMe$, $R^3 = OMe$, $R^4 = OMe$, $R^5 = OH$	*C. caffrum* (Pettit et al., 1988) *C. psidioides* (Letcher and Nhamo, 1972b)
	83 $R^1 = OH$, $R^2 = OMe$, $R^3 = OMe$, $R^4 = OH$, $R^5 = OMe$	*C. apiculatum* (Letcher and Nhamo, 1971)
	84 $R^1 = OMe$, $R^2 = OMe$, $R^3 = OH$, $R^4 = OH$, $R^5 = OH$	*C. apiculatum* (Letcher and Nhamo, 1971) *C. molle* (Letcher et al., 1972)

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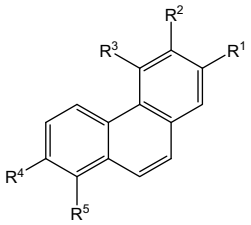
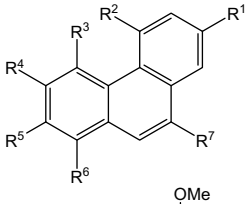
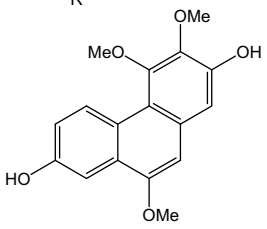
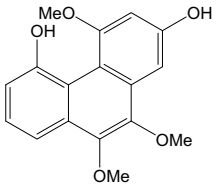
Table 4 (*continued*)

	**85** $R^1 = OH$, $R^2 = OMe$, $R^3 = OMe$, $R^4 = OH$, $R^5 = OMe$; confusarin	*B. gymnopus* (de Alvarenga et al., 1976; Majumder and Banerjee, 1988b) *B. reptans* (Majumder et al., 1999) *E. confusa* (Majumder and Kar, 1987a) *T. communis* (Réthy et al., 2006; Bordat et al., 2006)
	86 $R^1 = OMe$, $R^2 = OH$, $R^3 = OMe$, $R^4 = OH$, $R^5 = OMe$; denthyrsinin	*C. pendulum* (Majumder and Sen, 1991b) *D. densiflorum* (Fan et al., 2001) *D. thyrsiflorum* (Zhang et al., 2005) *E. nuda* (Tuchinda et al., 1988) *N. boothii* (Hernandez-Romero et al., 2004) *S. livida* (Estrada et al., 1999a) *T. alba* (Majumder et al., 1998b) *T. communis* (Réthy et al., 2006; Bordat et al., 2006)
	87 $R^1 = OMe$, $R^2 = OMe$, $R^3 = OMe$, $R^4 = OH$, $R^5 = OMe$;	*T. communis* (Kovács et al., 2007)
	88 $R^1 = OMe$, $R^2 = OMe$, $R^3 = OMe$, $R^4 = R^5 = –O–CH_2–O–$; TaI	*T. communis* (Majumder and Basak, 1991a; Letcher and Wong, 1978)
	89 $R^1 = OMe$, $R^2 = OH$, $R^3 = OMe$, $R^4 = R^5 = –O–CH_2–O–$; TaIV	*T. communis* (Majumder and Basak, 1991a; Letcher and Wong (1979))
	90 $R^1 = OMe$, $R^2 = R^3 = –O–CH_2–O–$, $R^4 = OMe$, $R^5 = OMe$ TaI	*T. communis* (Aquino et al., 1985b, 1991; Reisch et al., 1969, 1970)
	91 $R^1 = OMe$, $R^2 = R^3 = –O–CH_2–O–$, $R^4 = OH$, $R^5 = OMe$; TaIV	*T. communis* (Aquino et al., 1985b, 1991; Letcher and Wong, 1979; Reisch et al., 1969, 1970)
	92 $R_1 = OMe$, $R_2 = OMe$, $R_3 = OMe$, $R_4 = OMe$, $R_5 = OH$; TaV	*T. communis* (Aquino et al., 1985a,b, 1991; Letcher and Wong, 1978; Reisch et al., 1970, 1973)
	93 $R^1 = OMe$, $R^2 = OMe$, $R^3 = OH$, $R^4 = OMe$, $R^5 = OH$; TaIX	*T. communis* (Aquino et al., 1985a,b, 1991; Reisch et al., 1973; Takasugi et al., 1987)
	**94** $R^1 = H$, $R^2 = OH$, $R^3 = OMe$, $R^4 = OMe$, $R^5 = OH$, $R^6 = H$, $R^7 = OMe$; fimbriol-A	*E. fimbriata* (Tezuka et al., 1993) *E. rigidum* (Hernandez-Romero et al., 2005) *M. densa* (Estrada et al., 1999b, 2004)
	95 $R^1 = OH$, $R^2 = OH$, $R^3 = H$, $R^4 = OH$, $R^5 = OMe$, $R^6 = OMe$, $R^7 = H$; coeloginanthrin	*C. cristata* (Majumder et al., 2001)
	**96** gymnopusin	*B. gymnopus* (Majumder and Banerjee, 1988b) *B. reptans* (Majumder et al., 1999) *M. densa* (Estrada et al., 1999b, 2004; Fisch et al., 1973; Valencia-Islas et al., 2002)
	**97** plicatol-A	*D. plicatile* (Honda and Yamaki, 2000)

This was supported by the investigation of mono-, bi-, and triphenanthrenes of *C. appendiculata*. The tuber of this plant has been used in traditional Chinese medicine for the treatment of various cancers. The isolated phenanthrenes (**18**, **19**) were inactive ($IC_{50} > 5$ μg/ml) against all the tested cell lines (A549, A2780, Bel7402, BGC-823, HCT-8, MCF-7 and WISH). Biphenanthrenes (**223**, **231**) and the unusual triphenanthrene (**243**) proved to be active compounds in this investigation (Xue et al., 2006).

Many phenanthrenes have been isolated from petroleum ether and chloroform extracts of the rhizomes of *Tamus communis* through cytotoxic assay guidance. The antitumour effects of eight phenanthrenes and one dihydrophenanthrene were tested on the HeLa cell line by Hohmann et al.; the compounds showed high cytotoxic activities with IC_{50}s of 20.18 (**42**), 6.66 (**43**), 13.85 (**47**), 0.97 (**85**), >20 (**86**), 15.86 (**25**), 12.18 (**56**), 8.52 (**87**) and 3.64 μM (**89**) (Réthy et al., 2006; Kovács et al., 2007).

Aquino et al. studied the cytotoxicities of compounds **27**, **28**, **90**, **92** and **93**, isolated from *T. communis* on CER (chicken embryo-related) and HeLa cells. The HeLa cells were found to be generally more susceptible than the

Table 5
Hexasubstituted dihydro/phenanthrenes with hydroxy- or/and methoxy-substitution

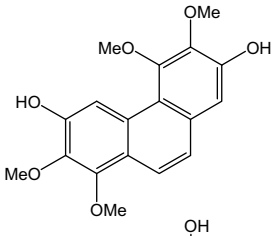
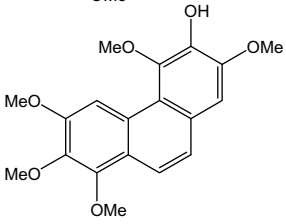
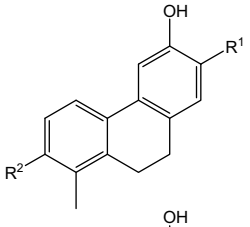
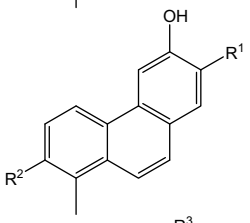
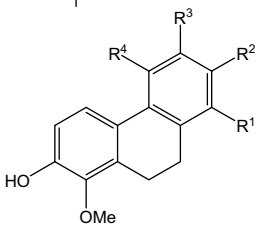
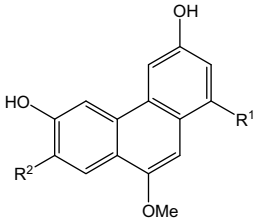
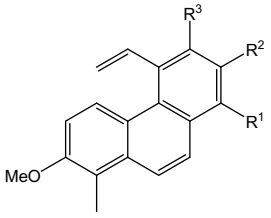
	**98** confusaridin	*E. confusa* (Majumder and Kar, 1987a)
	**99** pendulin	*C. pendulum* (Majumder and Sen, 1991b)

Table 6
Methyl, oxymethyl, vinyl and prenylsubstituted monomeric dihydro/phenanthrenes

	**100** R^1 = Me, R^2 = OH; micrandrol-B	*M. scleroxylon* (de Alvarenga and Gottlieb, 1974) *S. racemosa* (de Alvarenga et al., 1976)
	101 R^1 = OMe, R^2 = Me; micrandrol-F	*S. racemosa* (de Alvarenga et al., 1976)
	**102** R^1 = Me, R^2 = OH; micrandrol-A	*M. scleroxylon* (de Alvarenga and Gottlieb, 1974) *S. racemosa* (de Alvarenga et al., 1976)
	103 R^1 = OMe, R^2 = Me; micrandrol-E	*S. racemosa* (de Alvarenga et al., 1976)
	**104** R^1 = H, R^2 = OH, R^3 = Me, R^4 = OMe; stemanthrene A	*S. collinsae* (Adams et al., 2005) *S. pierrei* (Adams et al., 2005; Kostecki et al., 2004) *S. tuberosa* (Adams et al., 2005)
	105 R^1 = H, R^2 = OMe, R^3 = Me, R^4 = OH; stemanthrene B	*S. collinsae*, (Adams et al., 2005) *S. pierrei* (Adams et al., 2005; Kostecki et al., 2004) *S. tuberosa* (Adams et al., 2005)
	106 R^1 = Me, R^2 = OH, R^3 = Me, R^4 = OMe; stemanthrene C	*S. collinsae* (Adams et al., 2005) *S. pierrei* (Adams et al., 2005; Kostecki et al., 2004) *S. tuberosa* (Adams et al., 2005)
	107 R^1 = Me, R^2 = OH, R^3 = H, R^4 = OMe; stemanthrene D, racemosol	*S. collinsae* (Adams et al., 2005; Pacher et al., 2002) *S. pierrei* (Adams et al., 2005) *S. tuberosa* (Adams et al., 2005)
	**108** R^1 = Me, R^2 = Me **109** R^1 = CH_2OH, R^2 = Me **110** R^1 = Me, R^2 = CH_2OH **111** R^1 = CH_2OH, R^2 = CH_2OH	*D. perrieri* (Long et al., 1997) *D. perrieri* (Long et al., 1997) *D. perrieri* (Long et al., 1997) *D. perrieri* (Long et al., 1997)
	**112** R^1 = OH, R^2 = H, R^3 = Me	*J. acutus* (DellaGreca et al., 2002a, 2004) *J. effusus* (DellaGreca et al., 1993)
	113 R^1 = H, R^2 = OH, R^3 = H	*J. acutus* (DellaGreca et al., 2004)
	114 R^1 = H, R^2 = Me, R^3 = H	*J. acutus* (DellaGreca et al., 2004)

(*continued on next page*)

Table 6 (*continued*)

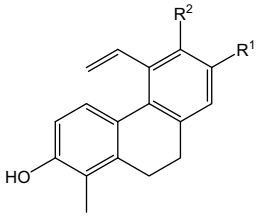
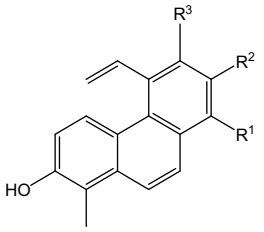
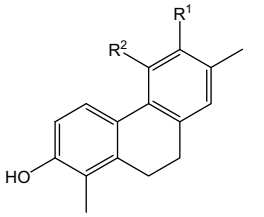
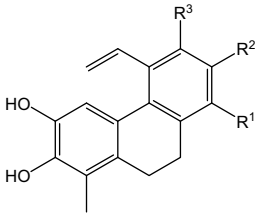
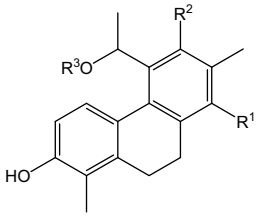
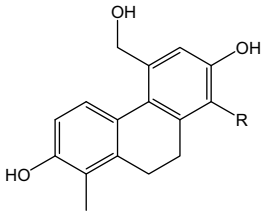
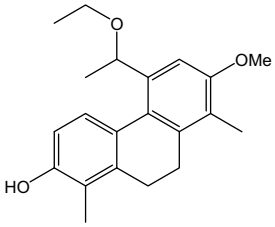
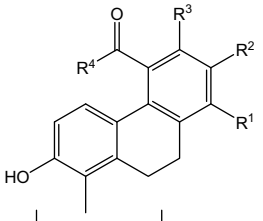
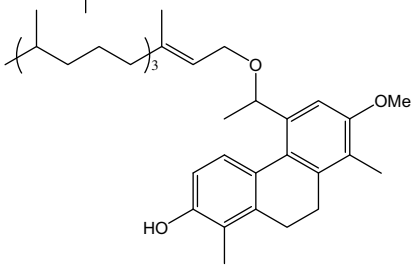
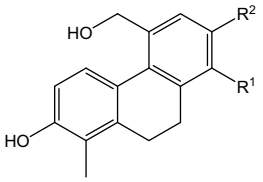
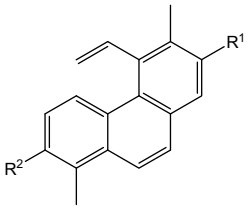
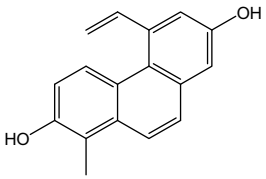
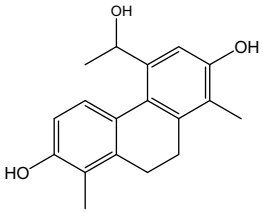
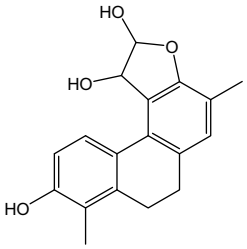
	**115** R^1 = Me, R^2 = H, juncunol	*J. acutus* (DellaGreca et al., 2002a, 2004) *J. effusus* (DellaGreca et al., 1993) *J. roemerianus* (Sarkar et al., 1988)
	116 R^1 = OH, R^2 = Me, juncusol	*J. acutus* (DellaGreca et al., 2002a,b, 2004) *J. effusus* (DellaGreca et al., 1993; Shima et al., 1991) *J. roemerianus* (Chapatwala et al., 1981; Sarkar et al., 1988)
	117 R^1 = Me, R^2 = OH	*J. acutus* (DellaGreca et al., 2004) *J. effusus* (DellaGreca et al., 1993)
	118 R^1 = OH, R^2 = H, effusol	*J. acutus* (DellaGreca et al., 2004) *J. effusus* (DellaGreca et al., 1993; Shima et al., 1991)
	119 R^1 = H, R^2 = Me	*J. acutus* (DellaGreca et al., 2004)
	120 R^1 = OH, R^2 = CH_2OH	*J. acutus* (DellaGreca et al., 2004)
	121 R^1 = CH_2OH, R^2 = H	*J. acutus* (DellaGreca et al., 2004) *J. effusus* (DellaGreca et al., 1997)
	122 R^1 = H, R^2 = CH_2OH	*J. acutus* (DellaGreca et al., 2004) *J. effusus* (DellaGreca et al., 1997)
	**123** R^1 = COOH, R^2 = H, R^3 = H	*J. acutus* (DellaGreca et al., 2004) *J. effusus* (DellaGreca et al., 1993)
	124 R^1 = H, R^2 = COOH, R^3 = H	*J. acutus* (DellaGreca et al., 2004) *J. effusus* (DellaGreca et al., 1993)
	125 R^1 = H, R^2 = H, R^3 = COOH	*J. acutus* (DellaGreca et al., 2004)
	126 R^1 = Me, R^2 = OH, R^3 = H	*J. acutus* (DellaGreca et al., 2002a, 2004) *J. effusus* (DellaGreca et al., 1993)
	127 R^1 = OH, R^2 = H, R^3 = Me	*J. acutus* (DellaGreca et al., 2004) *J. effusus* (DellaGreca et al., 1993)
	128 R^1 = Me, R^2 = OMe, R^3 = H	*J. acutus* (DellaGreca et al., 2002a, 2004) *J. effusus* (DellaGreca et al., 1993)
	**129** R^1 = OH, R^2 = Ac; juncunone	*J. roemerianus* (Sarkar et al., 1988)
	130 R^1 = OH, R_2 = H	*J. effusus* (DellaGreca et al., 1993)
	**131** R^1 = OH, R^2 = H, R^3 = Me	*J. acutus* (DellaGreca et al., 2004)
	132 R^1 = H, R^2 = Me, R^3 = H	*J. effusus* (DellaGreca et al., 1993)
	**133** R^1 = H, R^2 = OH, R^3 = H	*J. acutus* (DellaGreca et al., 2002a, 2004) *J. effusus* (DellaGreca et al., 1993, 1997)
	134 R^1 = H, R^2 = OH, R^3 = Me	*J. acutus* (DellaGreca et al., 2002a, 2004) *J. effusus* (DellaGreca et al., 1993)
	135 R^1 = OH, R^2 = H, R^3 = H	*J. acutus* (DellaGreca et al., 2002a, 2004) *J. effusus* (DellaGreca et al., 1993)
	**136** R = H	*J. acutus* (DellaGreca et al., 2004)
	137 R = Me	*J. acutus* (DellaGreca et al., 2004)

Table 6 (*continued*)

	**138** *J. acutus* (DellaGreca et al., 2002a, 2004)
	**139** $R^1 = H$, $R^2 = Me$, $R^3 = OH$, $R^4 = Me$ *J. effusus* (DellaGreca et al., 1993) **140** $R^1 = Me$, $R^2 = OMe$, $R^3 = H$, $R^4 = H$ *J. effusus* (DellaGreca et al., 1993) **141** $R^1 = H$, $R^2 = Me$, $R^3 = OH$, $R^4 = H$ *J. effusus* (DellaGreca et al., 1993)
	**142** *J. acutus* (DellaGreca et al., 2002a, 2004)
	**143** $R^1 = Me$, $R^2 = OH$ *J. effusus* (DellaGreca et al., 1997) **144** $R^1 = Me$, $R^2 = OMe$ *J. effusus* (DellaGreca et al., 1997) **145** $R^1 = H$, $R^2 = Me$ *J. effusus* (DellaGreca et al., 1997)
	**146** $R^1 = OH$, $R^2 = OH$, dehydrojuncusol *J. effusus* (Shima et al., 1991) *J. roemerianus* (Sarkar et al., 1988) *J. acutus* (DellaGreca et al., 2002a, 2004) **147** $R^1 = H$, $R^2 = OH$ *J. acutus* (DellaGreca et al., 2002a, 2004) **148** $R^1 = OMe$, $R^2 = OMe$ *J. acutus* (DellaGreca et al., 2002a, 2004)
	**149** dehydroeffusol *J. effusus* (Shima et al., 1991)
	**150** *J. effusus* (DellaGreca et al., 1997)
	**151** *J. effusus* (DellaGreca et al., 1997)

(*continued on next page*)

Table 6 (*continued*)

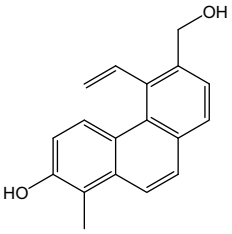
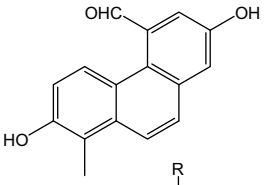
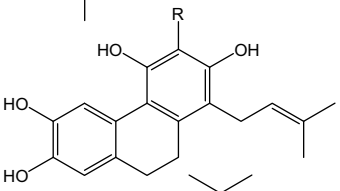
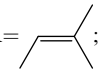
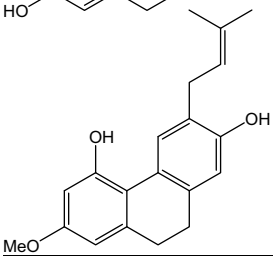
	**152**	*J. acutus* (DellaGreca et al., 2004)
	**153** dehydroeffusal	*J. effusus* (Shima et al., 1991)
	**154** R=  ; gancaonin U	*G. uralensis* (Fukai et al., 1991)
	155 R = H; gancaonin V	*G. uralensis* (Fukai et al., 1991)
	**156** sinensol G	*S. sinensis* (Lin et al., 2001)

Table 7
Miscellaneous monomeric phenanthrene derivatives

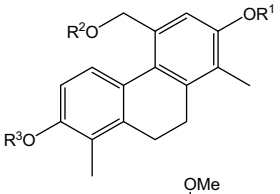
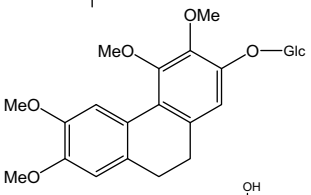
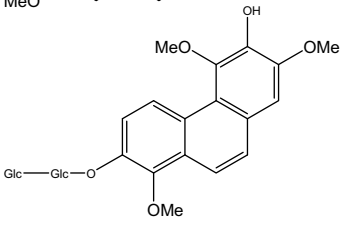
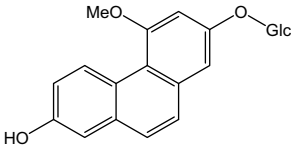
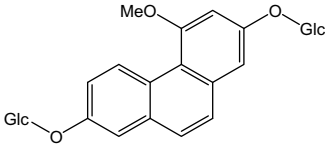
	**157** R^1 = Me, R^2 = Glc, R^3 = H, effuside I	*J. effusus* (DellaGreca et al., 1995)
	158 R^1 = H, R^2 = Glc, R^3 = H, effuside II	*J. effusus* (DellaGreca et al., 1995)
	159 R^1 = Glc, R^2 = H, R^3 = H, effuside III	*J. effusus* (DellaGreca et al., 1995)
	160 R^1 = H, R^2 = H, R^3 = Glc, effuside IV	*J. effusus* (DellaGreca et al., 1995)
	161 R^1 = Me, R^2 = Glc, R^3 = Glc, effuside V	*J. effusus* (DellaGreca et al., 1995)
	**162** epimedoicarisoside A	*E. koreanum* (Li et al., 1995)
	**163** denchryside A	*D. chrysanthum* (Ye et al., 2003)
	**164**	*B. striata* (Yamaki et al., 1993b)
	**165**	*B. striata* (Yamaki et al., 1993b)

Table 7 (*continued*)

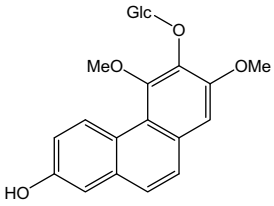
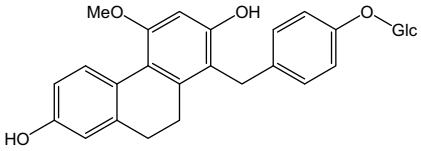
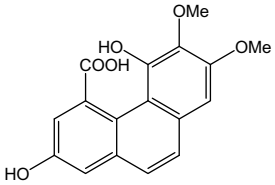
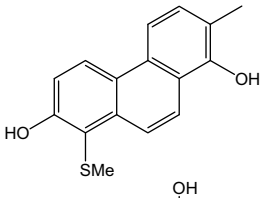
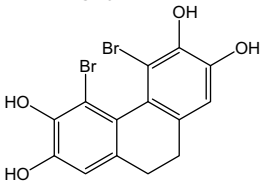
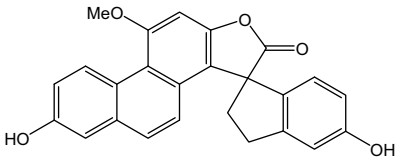
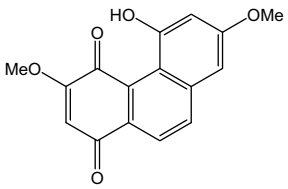
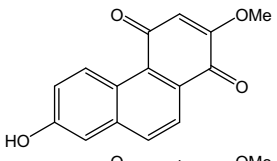
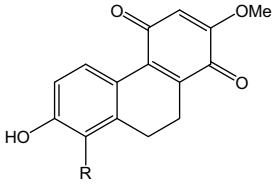
	**166**	*B. striata* (Yamaki et al., 1993b)
	**167**	*B. striata* (Yamaki et al., 1993b)
	**168** ochrolic acid	*C. ochracea* (Anuradha et al., 1994)
	**169** micrandrol C	*M. scleroxylon* (de Alvarenga and Gottlieb, 1974)
	**170** polysiphenol	*P. ferulacea* (Aknin et al., 1992)
	**171** blespirol	*B. striata* (Yamaki et al., 1993a)

Table 8
Phenanthraquinones

	**172** denbinobin	*D. moniliforme* (Lin et al., 2001) *D. nobile* (Lee et al., 1995) *E. lonchophylla* (Chen et al., 2000; Tezuka et al., 1991)
	**173** densiflorol B, cypritibetquinone A	*C. tibeticum* (Liu et al., 2005a) *D. densiflorum* (Fan et al., 2001)
	**174** R = H; ephemeranthoquionone **175** R = OMe; cypripedin	*D. plicatile* (Yamaki and Honda, 1996) *E. lonchophylla* (Tezuka et al., 1991) *N. boothii* (Hernandez-Romero et al., 2004) *D. densiflorum* (Fan et al., 2001)

(*continued on next page*)

Table 8 (*continued*)

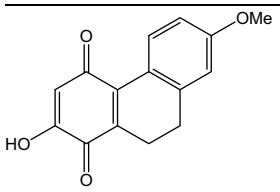
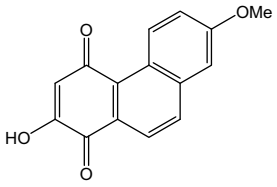
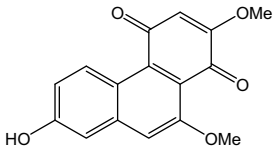
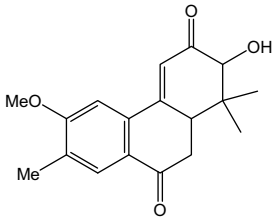
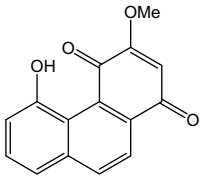
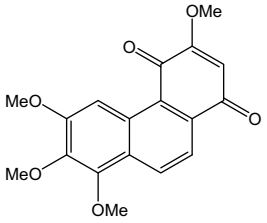
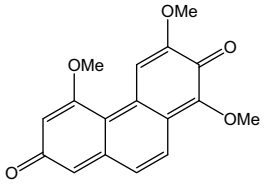
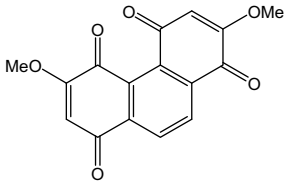
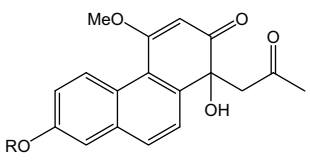
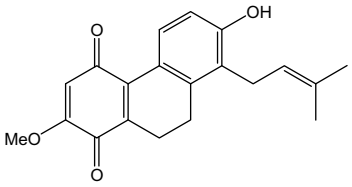
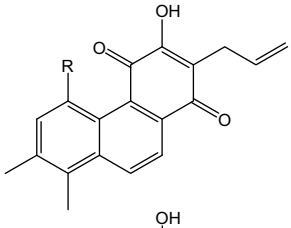
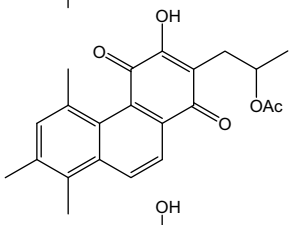
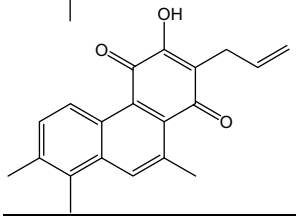
	**176** ochrone A	*C. ochracea* (Bhaskar et al., 1991)
	**177** ochrone B	*C. ochracea* (Bhaskar et al., 1991)
	**178** cypritibetquinone B	*C. tibeticum* (Liu et al., 2005a)
	**179** domohinone	*D. perrieri* (Long et al., 1997)
	**180** cymbinodin A	*C. aloifolium* (Barua et al., 1990)
	**181** cymbinodin B	*C. aloifolium* (Ghosh et al., 1992)
	**182** TaII	*T. communis* (Reisch et al., 1970)
	**183** moniliformin	*D. moniliforme* (Lin et al., 2001)
	**184** R = H **185** R = Me	*C. appendiculata* (Xue et al., 2006) *C. appendiculata* (Xue et al., 2006)

Table 8 (*continued*)

	**186** spiranthoquinone	*S. sinensis* (Tezuka et al., 1990)
	**187** R = Me, plectranthon A **188** R = H, plectranthon C	*Plectranthus* sp. (Alder et al., 1984) *Plectranthus* sp. (Alder et al., 1984)
	**189** plectranthon B	*Plectranthus* sp. (Alder et al., 1984)
	**190** plectranthon D	*Plectranthus* sp. (Alder et al., 1984)

CER cells to the toxic action of these compounds, which were toxic to the cells at concentrations above 4–20 μg/ml, with the exception of **90** (100 μg/ml), the only compound in which hydroxy groups are missing. This is a further indication that free phenolic hydroxy groups are essential for the inhibitory activity (Aquino et al., 1991).

Compounds from *Domohinea perrieri* were screened for *in vitro* cytotoxicity against a number of cancer cell lines. Compounds **108** and **109** were found to demonstrate significant cytotoxic responses against several lines, with some cell-type selectivity. Compound **108** was more active against drug-resistant KB cells, while **109** was active against HT (fibrosarcoma) and U373 (glioma) cell lines. **110**, **111** and **179** were not significantly active against any of the cell lines tested. Compounds with a hydroxymethyl group on C-7 were not active, suggesting that an unsubstituted methyl group on C-7 is important for the activity (Long et al., 1997).

Hydroxybenzyl-phenanthrenes [sinensol A–F (**202**–**206** and **208**)] from *S. sinensis* proved to be active against the MS-G2 cell line and were cytotoxic at 20 μg/ml, but showed no anti-hepatitis B virus e antigen (HBeAg) effect at non-cytotoxic (5 or 10 μg/ml) doses (Lin et al., 2000).

4.2. Antimicrobial effects

The accumulation of phytoalexins in plants is a response to infection by pathogenic fungi. Phytoalexins are utilized by plants to stop the growth of the attacking fungus. Orchid phytoalexins are phenanthrenes and dihydrophenanthrenes, as exemplified by orchinol (**3**) from *Orchis militaris* and hircinol (**6**) from *Loroglossum hircinum*. Their antifungal activities, together with those of loroglossol (**5**), were investigated on *Candida lipolitica* in 1973. Loroglossol was inactive, while orchinol (**3**) (at either 50 or 100 ppm) was considerably more active than hircinol (**6**). Orchinol (**3**) at 100 ppm inhibited the growth of the cells completely for the first 6 days, whereas hircinol (**6**) or the control did so for only 3 days (Fisch et al., 1973).

The tubers of *B. striata* were investigated, because this has been used in traditional medicine in China to treat pneumonorrhagia and pneumonophthisis. The methanol extracts of *B. striata* and lusianthridin (**4**) were mainly active against Gram-positive bacteria, but weakly active against certain fungi. Biphenanthrenes [blestriareneA-C (**214**, **218**, **229**)] were active against the Gram-positive bacteria *Staphylococcus aureus* and *Streptococcus nutans*. Blestriarene B (**218**) exhibited the most potent activity against both test organisms (Yamaki et al., 1989).

The dihydrophenanthrene stemanthrene D (**107**) from *Stemona collinsae* demonstrated a weak activity against the fungi: *Fusarium avenaceum*, *Cladosporium herbarium* and *Pyricularia grisea*, with EC_{50} values >200 μg/ml. The antifungal properties of stemanthrenes A–D (**104**–**107**) from *Stemona pierrei* were also investigated. In this study

Table 9
Monomeric phenanthrenes with hydroxybenzyl substitution

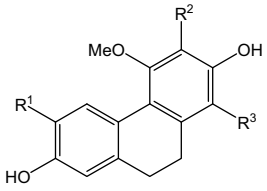
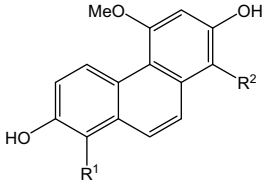
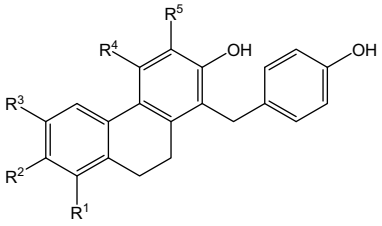
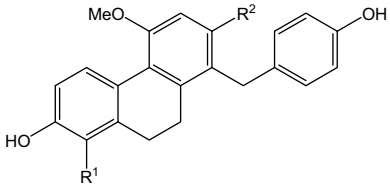
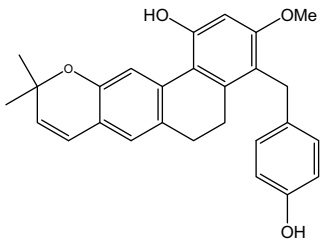
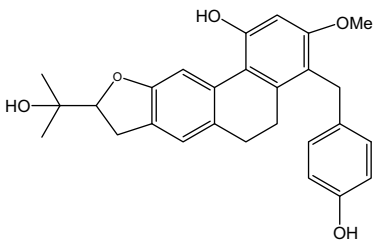
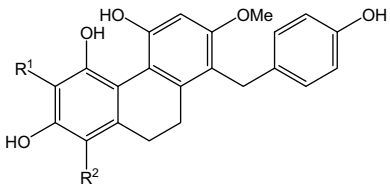
	**191** R^1 = H, R^2 = hydroxybenzyl, R^3 = H	*B. striata* (Yamaki et al., 1990)
	192 R^1 = hydroxybenzyl, R^2 = H, R^3 = hydroxybenzyl	*B. formosana* (Lin et al., 2005) *B. striata* (Yamaki et al., 1990)
	193 R^1 = H, R^2 = hydroxybenzyl, R^3 = hydroxybenzyl	*B. formosana* (Lin et al., 2005) *B. striata* (Bai et al., 1993)
	194 R^1 = H, R^2 = H, R^3 = hydroxybenzyl	*B. formosana* (Lin et al., 2005) *B. striata* (Bai et al., 1993; Yamaki et al., 1990) *G. conopsea* (Matsuda et al., 2004; Morikawa et al., 2006)
	**195** R^1 = H, R^2 = hydroxybenzyl	*B. formosana* (Lin et al., 2005) *B. striata* (Yamaki et al., 1990) *G. conopsea* (Matsuda et al., 2004; Morikawa et al., 2006) *P. bulbocodioides* (Bai et al., 1996)
	196 R^1 = OMe, R^2 = hydroxybenzyl	*B. formosana* (Lin et al., 2005)
	197 R^1 = hydroxybenzyl, R^2 = hydroxybenzyl	*B. formosana* (Lin et al., 2005) *B. striata* (Bai et al., 1991)
	**198** R^1 = H, R^2 = OH, R^3 = hydroxybenzyl, R^4 = OMe, R^5 = hydroxybenzyl	*B. formosana* (Lin et al., 2005)
	199 R^1 = H, R^2 = OMe, R^3 = H, R^4 = OMe, R^5 = H	*B. formosana* (Lin et al., 2005)
	200 R^1 = OMe, R^2 = OH, R^3 = H, R^4 = OMe, R^5 = H	*B. formosana* (Lin et al., 2005)
	201 R^1 = hydroxybenzyl, R^2 = OH, R^3 = H, R^4 = OMe, R^5 = H	*B. formosana* (Lin et al., 2005)
	**202** R_1 = H, R^2 = OMe; arundinaol, sinensol A	*A. graminifolia* (Liu et al., 2005b) *S. sinensis* (Lin et al., 2000)
	203 R^1 =  ; R^2 = OMe; sinensol B	*S. sinensis* (Lin et al., 2000)
	204 R^1 =  ; R^2 = H; sinensol C	*S. sinensis* (Lin et al., 2000)
	**205** sinensol D	*S. sinensis* (Lin et al., 2000)
	**206** sinensol E	*S. sinensis* (Lin et al., 2000)
	**207** R^1 = H, R^2 = H; shancidin	*B. striata* (Takagi et al., 1983) *P. bulbocodioides* (Bai et al., 1996) *S. sinensis* (Lin et al., 2000)
	208 R^1 =  ; R^2 = hydroxybenzyl; sinensol F	
	209 R^1 = hydroxybenzyl, R^2 = hydroxybenzyl; sinensol H	*S. sinensis* (Lin et al., 2001)

Table 9 (*continued*)

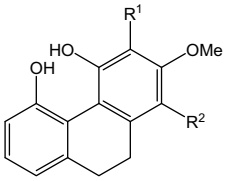
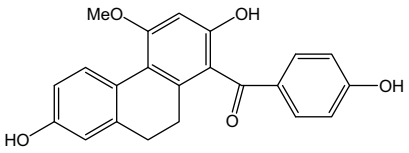
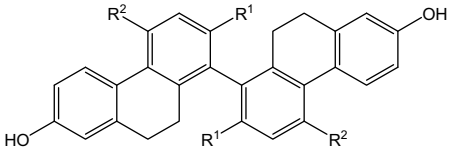
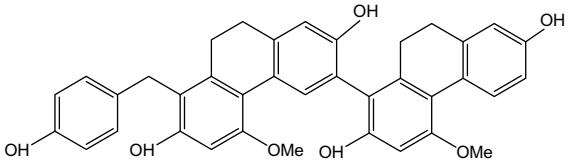
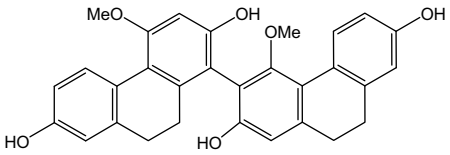
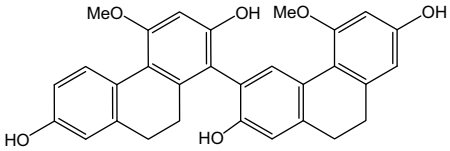
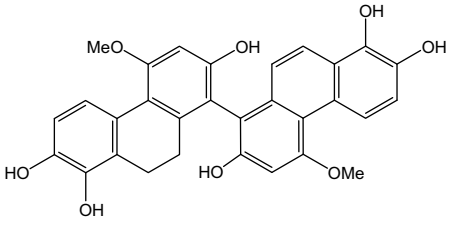
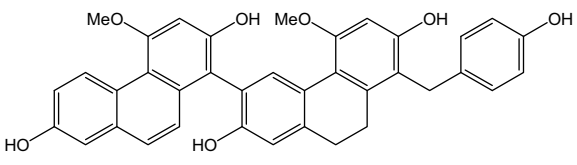
	**210** R^1 = H, R^2 = hydroxybenzyl; gymconopin A	*G. conopsea* (Matsuda et al., 2004; Morikawa et al., 2006)
	211 R^1 = hydroxybenzyl, R^2 = H; gymconopin B	*G. conopsea* (Matsuda et al., 2004; Morikawa et al., 2006)
	**212**	*B. striata* (Bai et al., 1993)

Table 10
Dihydro/phenanthrene dimers and a triphenanthrene

	**213** R^1 = OMe, R^2 = OH **214** R^1 = OH, R^2 = OMe; blestriarene A, flavanthrin	*D. plicatile* (Yamaki and Honda, 1996) *B. reptans* (Majumder et al., 1999) *B. striata* (Yamaki et al., 1989) *E. flava* (Majumder and Banerjee, 1988a, 1990a) *G. conopsea* (Matsuda et al., 2004; Morikawa et al., 2006) *T. alba* (Majumder et al., 1998b)
	**215** blestrianol B	*B. striata* (Bai et al., 1991)
	**216** blestrianol A	*B. striata* (Bai et al., 1991)
	**217** gymconopin C	*G. conopsea* (Matsuda et al., 2004)
	**218** blestriarene B	*B. striata* (Yamaki et al., 1989) *B. formosana* (Lin et al., 2005)
	**219** blestrianol C	*B. striata* (Bai et al., 1991)

(*continued on next page*)

Table 10 (*continued*)

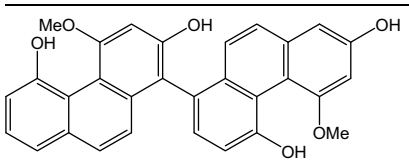
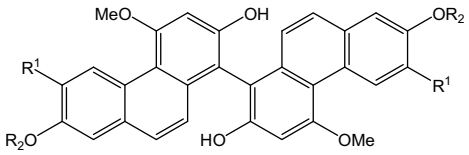
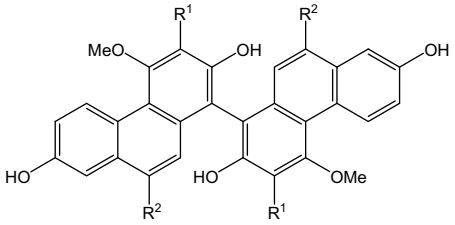
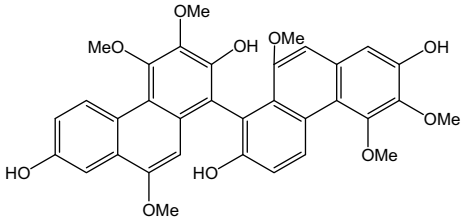
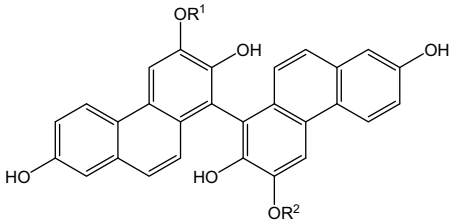
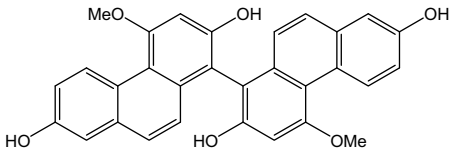
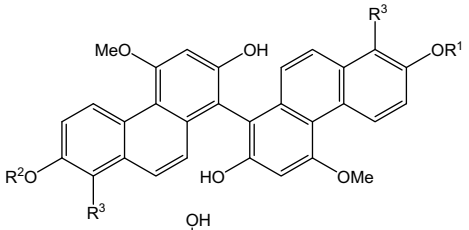
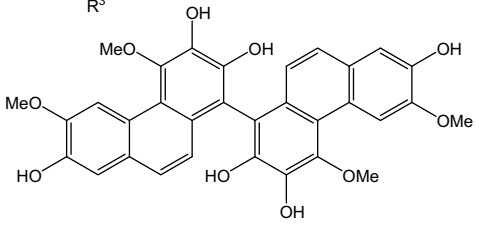
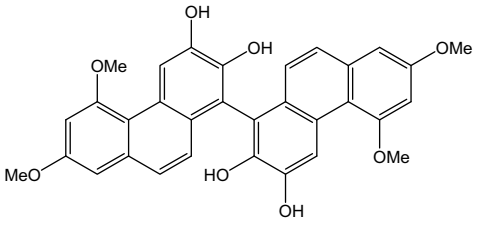
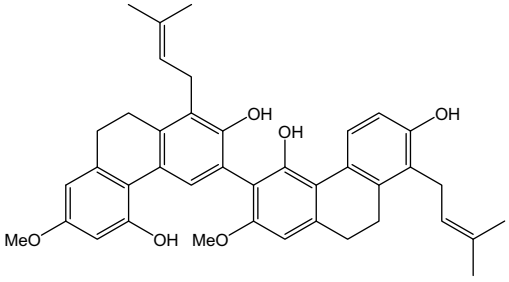
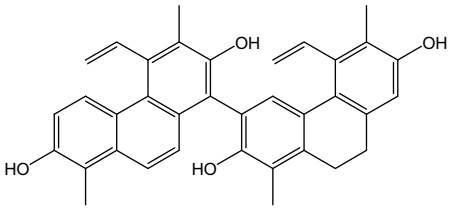
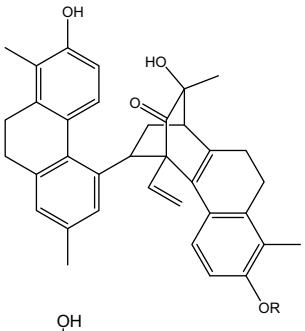
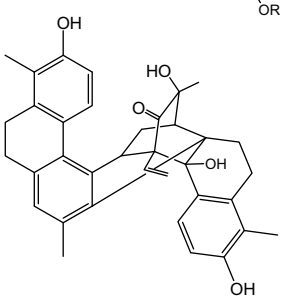
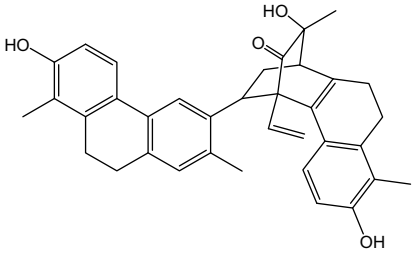
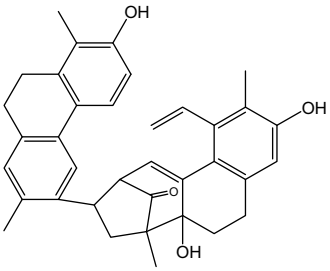
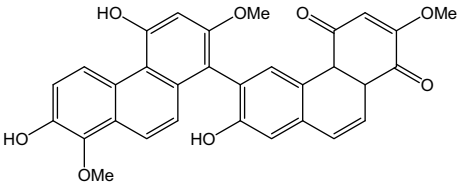
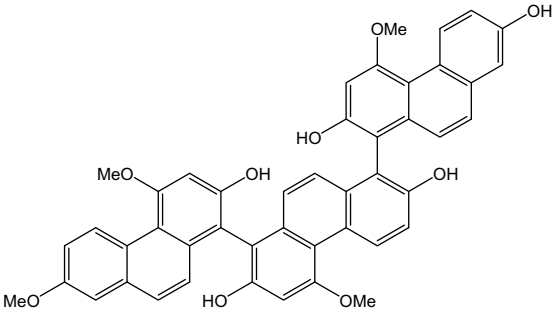
	**220** denthyrsinol	*D. thyrsiflorum* (Zhang et al., 2005)
	**221** R^1 = OMe, R^2 = H; agrostonin **222** R^1 = OH, R^2 = Me; agrostonidin	*A. khasiyanum* (Majumder et al., 1998a) *A. callosum* (Majumder et al., 1998a) *A. khasiyanum* (Majumder et al., 1998a) *A. callosum* (Majumder et al., 1998a)
	**223** R^1 = H, R^2 = H; cirrhopetalanthrin **224** R^1 = OMe, R^2 = OMe; reptanthrin	*C. maculosum* (Majumder et al., 1990e) *B. reptans* (Majumder et al., 1999) *T. alba* (Majumder et al., 1998b) *C. appendiculata* (Xue et al., 2006) *B. reptans* (Majumder et al., 1999)
	**225** isoreptanthrin	*B. reptans* (Majumder et al., 1999)
	**226** R^1 = Me, R^2 = Me **227** R^1 = Me, R^2 = H **228** R^1 = H, R^2 = H	*M. polymorpha* (Adam and Becker, 1994) *M. polymorpha* (Adam and Becker, 1994) *M. polymorpha* (Adam and Becker, 1994)
	**229** blestriarene C	*B. striata* (Yamaki et al., 1989)
	**230** R^1 = Me, R^2 = H, R^3 = H **231** R^1 = Me, R^2 = Me, R^3 = H **232** R^1 = H, R^2 = H, R^3 = OMe	*C. appendiculata* (Xue et al., 2006) *C. appendiculata* (Xue et al., 2006) *E. nuda* (Tuchinda et al., 1988)
	**233**	*B. vaginatum* (Leong and Harrison, 2004)

Table 10 (*continued*)

	**234** volucrin	*L. volucris* (Majumder and Lahiri, 1990c)
	**235** spiranthesol	*S. sinensis* (Tezuka et al., 1990)
	**236**	*J. acutus* (DellaGreca et al., 2003)
	**237** R = H **238** R = Me	*J. acutus* (DellaGreca et al., 2003)
	**239**	*J. acutus* (DellaGreca et al., 2003)
	**240**	*J. acutus* (DellaGreca et al., 2003)

(*continued on next page*)

Table 10 (*continued*)

	**241**	*J. acutus* (DellaGreca et al., 2003)
	**242** denthyrsinone	*D. thyrsiflorum* (Zhang et al., 2005)
	**243**	*C. appendiculata* (Xue et al., 2006)

dihydrophenanthrenes exerted a weak activity, similarly as in previous studies (Kostecki et al., 2004; Pacher et al., 2002).

The microbiological effects of juncusol (**116**) have been tested on several species. *Bacillus* species were inhibited at all concentrations, while *Plannococcus* species were inhibited only at the highest concentration. *Pseudomonas* species, *Mycobacterium smegmatis*, *Enterobacter aerogenes* and *Escherichia coli* were not inhibited at any of the concentrations used (Chapatwala et al., 1981).

The virus replication inhibitory effects of phenanthrenes of *T. communis* (**27**, **28**, **90**, **91**, **92**, **93**) have been tested on RNA enveloped virus: vesicular stomatitis virus (VSV) and human rhinovirus serotype 1B (HRV 1B). The results of the screening revealed marked inhibitory action on plaque formation against VSV (**27**), with an IC_{50} of 9 μg/ml. On HRV, these compounds produced a low decrease in viral multiplication (Aquino et al., 1991).

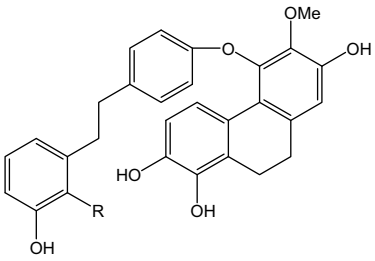
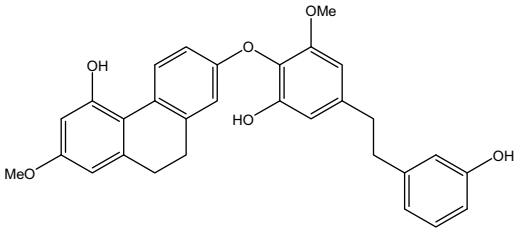
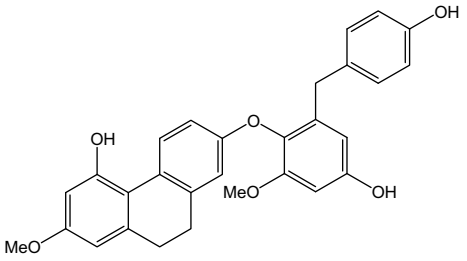
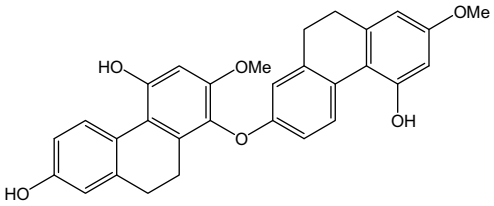
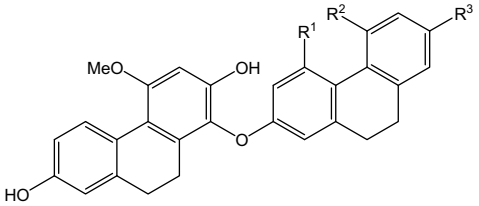
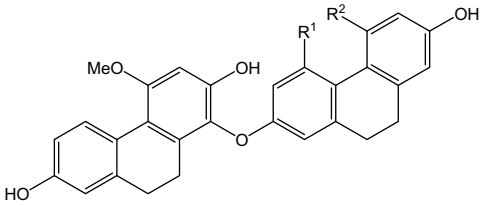
4.3. Spasmolytic effects

Spasmolytic effects have been investigated in case of phenanthrenes isolated from *Scaphyglottis livida*, *Maxillaria densa* and *Nidema boothii*. *S. livida* and *M. densa* are used by indigenous people in the tropical forests of Mexico. The ground herb of *S. livida* is applied to eliminate ectoparasites. The decoction is used for the treatment of stomach aches and to avoid abortion. *M. densa* is utilized for the same purposes.

Estrada et al. investigated the spasmolytic action of compounds of *S. livida* (Estrada et al., 1999a). Bioactivity-guided fractionation of the active extract resulted in the isolation of lusianthridin (**4**), **43** and denthirsinin (**86**). Compound **43** significantly antagonized the histamine-induced contractions of the rat ileum, in contrast with lusianthridin (**4**), and denthirsinin (**86**), which were inactive. The contractions evoked by $BaCl_2$ were inhibited slightly by **43** and denthirsinin (**86**), but lusianthridin (**4**) enhanced the contractions elicited by $BaCl_2$. The relaxatory response elicited by natural products is probably mediated by the neuronal release of NO. Compounds of *S. livida* induced the production of NO in ileal tissue, which in turn provoked relaxation of the ileal muscles by elevating the cyclic GMP content. Later, the vasorelaxing effect of **43** was studied on intact and denuded rat aorta rings. Compound **43** and denthirsinin (**86**) provoked the inhibition of NA-evoked contractions in the endothelium and appeared to induce a dose–response vasorelaxation by more than one mechanism (Estrada et al., 1999a, 2006). Phenanthrenes [erianthridin (**36**), **39**, nudol (**42**), **49** and gymnopusin (**96**)] isolated from *M. densa* provoked a concentration-dependent inhibition of the spontaneous contractions of the rat ileum induced by histamine, $BaCl_2$ and L-NAME. All these compounds antagonized the contractions, but they exerted a weaker smooth muscle relaxant activity than the extract; this could be due to a synergistic effect of the isolated compounds (Estrada et al., 2004).

Bioassay-guided fractionation of the active extract of *E. boothii* led to the identification of a new dihydrophenanthrene (**72**) and numerous known stilbenoids

Table 11
Dihydro/phenanthrenes with unusual structure

	**244** R = H **245** R = OH	*F. convoluta* (Flegel et al., 1999) *F. convoluta* (Flegel et al., 1999)
	**246** shancilin	*P. bulbocodioides* (Bai et al., 1996)
	**247** phoyunnanin D	*P. yunnanensis* (Guo et al., 2006)
	**248** phoyunnanin E	*P. yunnanensis* (Guo et al., 2006)
	**249** R^1 = OMe, R^2 = H, R^3 = OH; blestrin A **250** R^1 = H, R^2 = OH, R^3 = OMe; blestrin B	*B. striata* (Bai et al., 1990) *B. striata* (Bai et al., 1990)
	**251** R^1 = OMe, R^2 = H; blestrin C **252** R^1 = H, R^2 = OMe; blestrin D	*B. striata* (Yamaki et al., 1992) *B. striata* (Yamaki et al., 1992)

[lusianthridin (**4**), flavanthridin (**37**), **43**, denthirsinin (**86**) and **174**]. Denthyrsinin (**86**) and **72** induced noteworthy concentration-dependent inhibition of the spontaneous contractions of the guinea-pig ileum (Hernandez-Romero et al., 2004).

4.4. Antiallergic and anti-inflammatory activities

The tubers of *Gymnadenia conopsea* have been used in traditional Chinese medicine for the treatment of asthma, neurasthenia and chronic hepatitis. The methanolic

extract of the tubers was found to shown an antiallergic effect on the ear passive cutaneous anaphylaxis reaction in mice. Column chromatography of the methanolic extract afforded a fraction which inhibited the antigen-induced release of β-hexosaminidase, a marker of degranulation, in RBL-2H3 cells sensitized with anti-DNP IgE. From the active fraction, numerous phenanthrenes were isolated, but these compounds were not investigated (Matsuda et al., 2004).

Denbinobin (**172**), a phenanthraquinone from *Dendrobium moniliforme*, showed *in vitro* anti-inflammatory activity. This compound, at 1 μM, stimulated with 1 μg/ml of lipopolysaccharide, significantly inhibited the formation of tumour necrosis factor α and prostaglandin E2 in RAW 264.7 and N9 cells (Lin et al., 2001).

Various species from the genus *Stemona* have long been used in traditional Asian medical practices for the treatment of inflammation-related diseases, such as asthma. Phenanthrenes of the *Stemona* species were tested in an *ex vivo* leukotriene biosynthesis inhibition assay, using human neutrophile granulocytes. Stemanthrene A (**104**) and D (**107**) displayed clear activity in a dose-dependent manner, with IC_{50} values of 8.5 μM and 4.8 μM, respectively. Stemanthrene B (**105**) and C (**106**) initially caused very high inhibition (100%) at 25 μM, but because of the degradation of the compounds during storage the activity was lost. The potency of phenanthrenes in this test system suggests that these substances might be the anti-inflammatory and antiasthmathic principles of the *Stemona* species (Adams et al., 2005).

In 2006, four compounds were isolated from the rhizomes of *T. communis* (**47**, **85**, **86** and **92**) and their anti-inflammatory activities were analysed. The activity of **86** was evaluated from the production of prostaglandin PG6KF1-α, induced in keratinocytes by the stimulation of arachidonic acid and calcium ionophore A23187 (Bordat et al., 2006). The compounds showed a significant anti-inflammatory activity at 1 μg/ml, 3 μg/ml and 10 μg/ml with the inhibition percent of the release of PG6KF1-α of 25%, 59% and 90%, respectively.

4.5. Antiplatelet aggregation, phytotoxicity and antialgal activity

Ephemerantha lonchophylla was used in traditional Chinese medicine as a health tonic, to regulate the body fluid balance, and as an antipyretic. An ethanolic extract of the stems of *E. lonchophylla* exhibited antiplatelet aggregation activity. Chen et al. isolated erianthridin (**36**), **43** and denbinobin (**172**) from the stems of this plant. The *in vitro* antiplatelet effects of these compounds were evaluated on washed rabbit platelets against aggregation induced by either thrombin, arachidonic acid (AA), collagen or PAF. At high concentration (100 μg/ml) the isolated compounds displayed significant inhibitory effects against the aggregation caused by AA, collagen and PAF. Further dose–response analyses indicated that inhibition against AA-induced aggregation was effective, erianthridin (**36**) proving to be the most potent compound, with an IC_{50} of about 9 μM, while for **43** IC_{50} was 24 μM. The antiplatelet effects may be due to the inhibition of thromboxane A_2 formation because the platelet aggregation induced by AA or collagen was most readily inhibited (Chen et al., 2000).

Dendrobium loddigesii is used with the same aims as *E. lonchophylla* in China. The active principle, moscatin (**15**), was isolated by using bioassay-guided fractionation by Chen et al. This compound strongly inhibited both AA and collagen-induced platelet aggregation. The antiplatelet effects of this compound may be due to the inhibition of thromboxane A_2 formation (Chen et al., 1994).

The phytotoxicities of compounds obtained from *M. densa* and *Epidendrum rigidum* were examined on *Amaranthus hypochondriacus*. Gymnopusin (**96**) and erianthridin (**36**) from *M. densa* inhibited the radical elongation of *A. hypochondriacus* seedlings, with IC_{50} values of 330 and 58.2 μM, respectively. Both phenanthrene derivatives exhibited moderate cytotoxicity towards all mammalian cells tested (Valencia-Islas et al., 2002). Compounds ephemeranthol-A (**35**) and fimbriol A (**94**) isolated from *E. rigidum* also demonstrated substantial phytotoxicty against *A. hypochondriacus*, with IC_{50} values of 0.12 and 5.9 μM, respectively (Hernandez-Romero et al., 2005).

The antialgal activities of 41 monomeric and 5 dimeric phenanthrenes were investigated against *Selenastrum capricornutum* by DellaGreca et al. in numerous studies. (DellaGreca et al., 1993, 1995, 1997, 2002a,b, 2003). The antialgal activities of the dimeric phenanthrenes were higher than those of the 9,10-dihydrophenanthrenes. As already observed in monomeric 9,10-dihydrophenanthrenes, a reduction of the polarity in related compounds causes a decrease in activity.

5. Conclusions

Numerous phenanthrenes and their derivatives have been found, mainly in higher plants, and their biological activities have been studied. The phenanthrenes are a promising and expanding group of biologically active natural compounds whose potential has not yet been investigated sufficiently throughly, and which have not been exploited by the pharmaceutical industry.

Many phenanthrene-containing plants have been used in traditional medicine throughout the world, but mainly in China, and phytochemical–pharmacological investigations which have resulted in the identification of phenanthrenes as their active principles have provided support for the use of these plants in ethnomedical practice. On the other hand, the mechanisms of action and the structure–activity relationships of these compounds have been reported only rarely and are worthy of future investigations.

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