# Biologically active diterpenes containing a gem-dimethylcyclopropane subunit: An intriguing source of PKC modulators


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REVIEW

# Biologically active diterpenes containing a *gem*-dimethylcyclopropane subunit: An intriguing source of PKC modulators

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María Jesús Durán-Peña,[a] José Manuel Botubol Ares,[a] Isidro G. Collado[a*] and Rosario Hernández-Galán[a*]

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The biological activity of tigliane, lathyrane, ingenane, casbane, jatropholane and premyrsinane diterpenoids which contain the *gem*-dimethylcyclopropyl unit, is described. Particular attention is given to their anti-viral, anti-microbial and cytotoxic activity. In the main text there are 132 references covering the literature from 1973-2013. The electronic supplementary information contains tables listing 424 of these diterpenoids, their occurrence and biological activity together with the references.



## 1 Introduction

The study of the biological substrate-target interactions of proteins with organic molecules of low molecular weight including Natural Products (NPs), has led to the identification of the role of these proteins in several important biological processes. This field of research has attracted great interest in recent years because it facilitates the study of complex cellular mechanisms, many of which have led to the recognition and identification of important biological targets.[1]

The Natural Products include those containing a *gem*-dimethylcyclopropane subunit, some of which are considered to be of great interest for the discovery of new NP-based drugs due to their wide range of biological activity and structural diversity. Some of these compounds are currently under study in preclinical or clinical trials or have already been approved for the treatment of certain disease.[2]

This three-membered carbocycle is found in various types of compounds, particularly terpenoids, and have been isolated from a large variety of organisms like plants, some fungi and marine organisms such as soft corals and insects.

Natural Products with a *gem*-dimethylcyclopropane unit are mainly terpenoids and this carbocycle forms part of their basic skeleton.

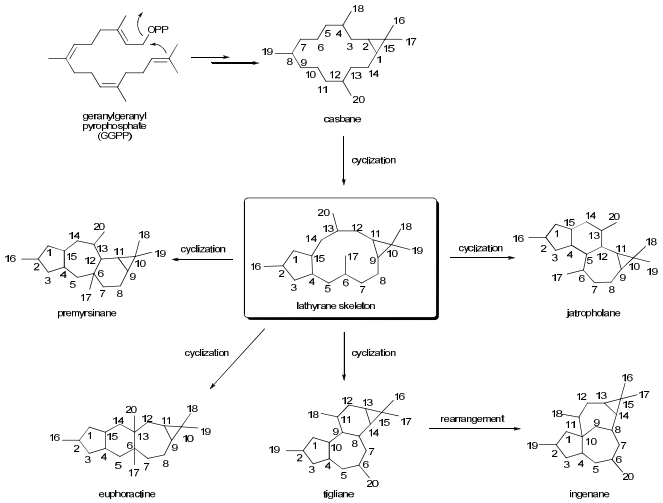
Tables listing the known natural products of these structural types, the species from which they were isolated, their biological activities and references are available in the Electronic Supplementary Information (ESI)†

## 2 Diterpenoids with a *gem*-dimethylcyclopropyl unit

A large number of diterpenes contain a *gem*-dimethylcyclopropane ring. These diterpenes have a wide variety of carbon skeleta, derived from the cation casbane. They include tiglianes, lathyranes, ingenanes, casbanes, premyrsinanes and jatropholanes. They are mostly present in species of the Euphorbiaceae. These plants are of great interest in the search for new drugs based on Natural Products because of the wide variety of pharmacological properties which they have and the great diversity of compounds with high structural variability that they produce.[1,3]

These polycyclic diterpenes, occurring widely in the Euphorbiaceae, can be formed by intramolecular cyclization of casbane.[4] Despite the recent advances in the understanding of the biosynthesis of many types of natural products, the specific enzymes responsible for building this strained three member ring have only been identified in a few cases and many mechanistic details remain unclear.[5]

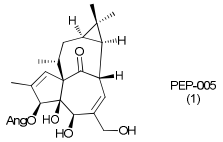
A number of enzymes in the terpenoid synthase family that catalyze cyclopropane formation have also been biochemically and mechanistically characterized recently, specially those responsible for the production of the bicyclic plant monoterpenes as carene or sabinene synthase.[5] However the reported data on the biosynthesis and enzymatic formation of cyclopropane ring in diterpenes are sparse. At least one diterpene synthase, casbene synthase, has been shown to cyclize geranylgeranyl pyrophosphate (GGPP) into casbene, which seem to be the key biosynthetic precursor of the lathyrane skeleton, an intermediate to jatropholane, tigliane, or premyrsinane which retain the cyclopropane ring in their final structures.[5-9]




This enzyme seems to follow a mechanism where cleavage of the allylic pyrophosphate moiety of GGPP, by a divalent metal ion, leads to an allylic carbocation that through alkylation and deprotonation generates the cyclopropane moiety in casbane skeleton.[6-9]

The ring strain present in the *gem*-dimethylcyclopropane moiety look like responsible for the biological activities of these compounds, many of them are potent alkylation agents. However, no many reports about biological relevance of this subunit have been published. For more detailed information about biosynthesis and biological activity of this interesting subunit, the reader is directed to a recent excellent review.[5]

Tiglianes and ingenanes, together with daphnanes are referred to as phorboids and are known for being proinflammatory agents and tumor promoters which behave as protein kinase C (PKC) activators. Proof of the pharmacological relevance of this group of compounds is the FDA's approval in January 2012 of 3-*O*-angeloylingenol (PEP-005, Picato ®, Leo Pharma) for the treatment of actinic keratosis, a precancerous skin condition.[1]

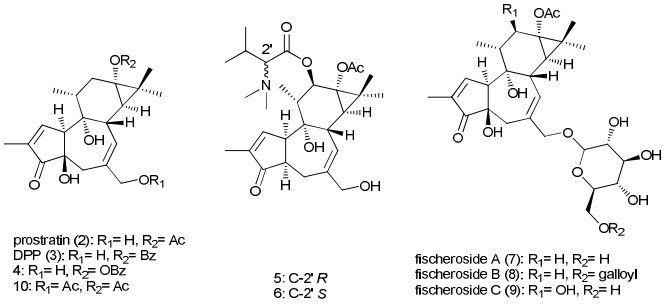



### 2.1 Tiglianes†

Protein Kinase Cs (PKCs) are involved in many physiological functions and certain NPs, such as phorbol esters, have proved to be important activators of these proteins. Certain phorbol esters can activate PKCs, but after an incubation period they decrease its regulatory activity. The activating capacity of PKCs is responsible for the wide variety of biological activities reported for this group of compounds such as platelet aggregation,[10] cell differentiation,[11,12] metabolic activity,[13-15] irritant,[16] tumor-promotion,[17,18] anti-HIV-1,[19,20] cytotoxicity[21] and as a molluscicide.[22]

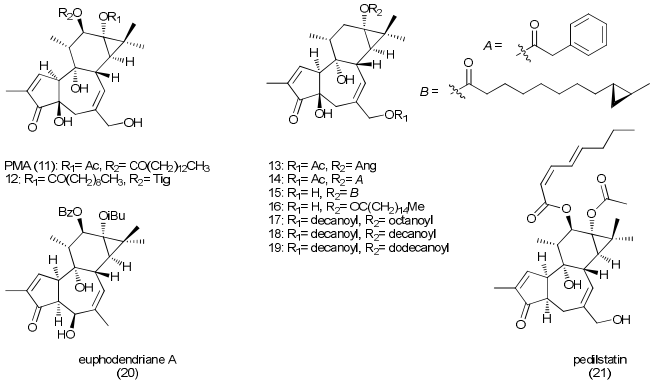
#### 2.1.1 Anti-HIV activity

12-Deoxyphorbols such as prostratin (13-*O*-acetyl-12-deoxyphorbol (**2**)) are a subclass of PKC activators since, unlike other phorbol esters, these do not induce tumor formation. Prostratin (**2**) has been found in *Euphorbia* species.[23,24] Recently, it has been shown that prostratin is a PKC activator that is potentially useful in the treatment of HIV as it affects viral reservoirs in $CD4^+$ T-cells with a latent infection.[25] DPP (**3**) induces HIV-1 gene expression in latently infected cells at concentrations of 20-40 times lower than prostratin.[26] Considering that the only structural difference between prostratin (**2**) and DPP (**3**) is the nature of the ester group bonded to the C-13 carbon, it is easy to associate the activity of the 12-deoxyphorbol skeleton with other phorbol esters such as 13-*O*-benzoyl-12-deoxyphorbol (**4**) which have exhibited the same type of behaviour in other studies.[27,28] Epimers **5** and **6** are potent PKC activators.[29] Fischerosides A-C (**7-9**), tiglianes that carry a glycoside group on the C-20 carbon, have a mild inhibitory effect on the HIV-1 virus. Fischeroside C (**9**) had an $EC_{50}$ value of 0.02 μM and a therapeutic index of 17.50, while prostratin (**2**) and 13,20-*O*-diacetyl-12-deoxyphorbol (**10**) were significantly more active.[30]



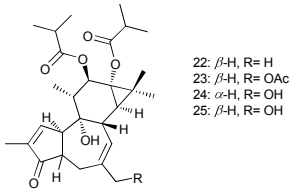

### 2.1.2 Cytotoxic activity

Important protein kinase C (PKC) activators, which show great potential as HIV-1 activators, were isolated from different species of the *Euphorbia* genus. PMA (or TPA, **11**) is used extensively as a molecular biological research tool. It is known to stimulate the kinase activity of PKC and antagonize HIV-1 latency efficiently.[17,31,32] Compounds **12-19** displayed cytotoxicity on human cancer cell lines.[33-36] Euphodendriane A (**20**) and pedilstatin (**21**) are cancer cell growth inhibitors.[37,38]



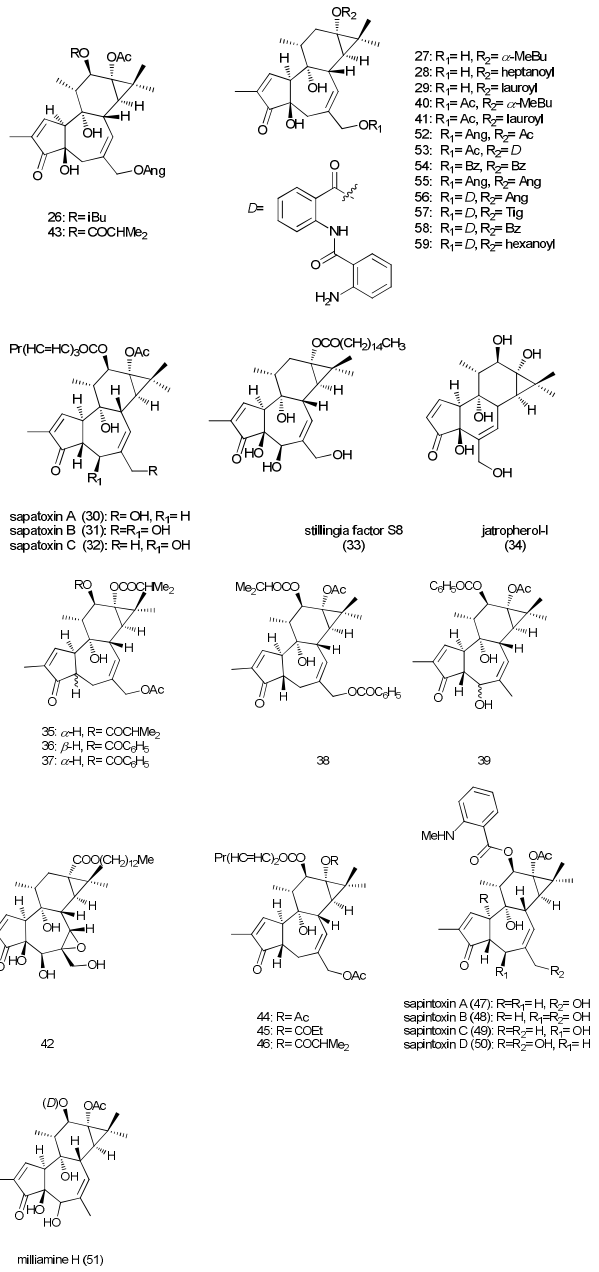

### 2.1.3 Inhibitory activity on the mitochondrial respiratory chain

Compounds **22-25** were active when evaluated for their inhibition of NADH oxidase activity in submitochondrial particles from beef heart. All of them are described as NADH oxidase inhibitors, **22** being the strongest inhibitor of NADH oxidase activity with an $IC_{50}$ value of 2.60 mM.[39]




### 2.1.4 Toxic activity

It is known that ingestion of certain members of the Euphorbiaceae by animals reduces their performance, contaminates milk, decreases reproduction and can even cause death.[40] This toxicity is associated with phorbol esters such as PMA (**11**). The phorbols known to be toxic **26-33** are also highly irritant.[41] Jatropherol-I (**34**) was highly toxic to silkworm larvae,[42,43] moreover compounds **35-51** acted as irritants.[44-50] On the other hand, compounds **52-59** exhibit molluscicidal activity against the snail, *Biomphalaria glabrata.* This snail the major intermediate host for *Schistosoma mansoni*, one of the important schistosomes infecting man.[21,51]



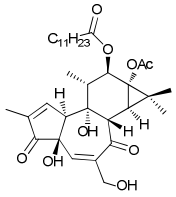

### 2.1.5 Tumor promotion activity

PMA (**11**) is a known protein kinase C activator that promotes tumors.[52-54] The esters, **35-39** also display tumor-promoting activity.[47] Phorbol esters do not induce tumors on their own but rather promote their growth by continuous exposure to certain levels of these esters.[38]

In contrast to this ability to activate tumor growth, many malignant cells have been observed entering apoptosis in response to PKC activation by phorbol esters. PKC activity displacement is attributed to its role in the activation of different metabolic pathways, its cellular localization, phosphorylation, interaction with other molecules and accessibility to various substrates.[55,56]

### 2.1.6 Other activities

Prostratin (**2**) exhibited analgesic and sedative effects in preliminary pharmacological assays carried out with mice.[22] Fischeroside B (**8**) provided significant protection against the oxidative stress caused by *t*-butylhydroperoxide by inhibiting the generation of reactive oxygen species and increasing glutathione levels in HepG2 cells.[57] Trigowiin A (**60**) exhibited antiviral activity against the Chikungunya virus.[58]

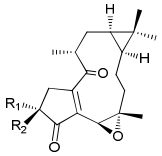


trigowiin A (60)

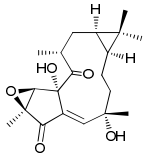
## 2.2 Lathyranes†

### 2.2.1 Antimicrobial activity

Diterpenes **61-63** exhibited antibacterial activity against *Bacillus subtilis* and *Staphylococcus aureus*.[59-61]



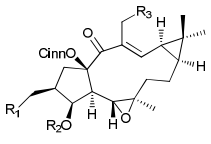
61: $R_1$= OH, $R_2$= Me
62: $R_1$= Me, $R_2$= OH



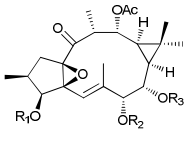
japodagrin (63)

### 2.2.2 Antiviral activity

Latilagascenes A-C (**64-66**), E (**67**) and jolkinol B (**68**) decreased immediate-early (IE) antigen expression of the human cytomegalovirus (CMV). These antiviral compounds also act as anti-tumour compounds towards certain forms of cancers that are associated with human CMV.[62] On the other hand, the HIV/AIDS field is gaining momentum with the goal of finding a functional cure for HIV infection by utilizing strategies that specifically reactivate the latent viral reservoir in combination with the Highly Active Antiretroviral Therapy (HAART). The virus HIV can be destroyed by HAART when it is active.[63] Compounds **69** and **70** were able to reactivate HIV-1 latency. Results with **69** strongly suggest that it reactivates HIV-1 through a PKC-dependent pathway.[30] Compound **70** induced cell-cycle arrest and HIV-1-LTR promoter activation and could be a novel lead compound for the development of therapies against HIV-1 latency.[64]



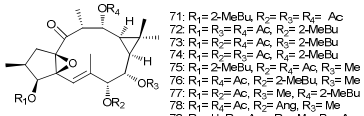
64: $R_1$= OAc, $R_2$= $R_3$= H
65: $R_1$= OH, $R_2$= $R_3$= H
66: $R_1$= OAc, $R_2$= Ac, $R_3$= H
67: $R_1$= OBz, $R_2$= H, $R_3$= OH
jolkinol B (68): $R_1$= $R_2$= $R_3$= H



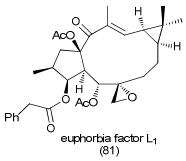
69: $R_1$= Ac, $R_2$= H, $R_3$= Tig
70: $R_1$= Bz, $R_2$= Ac, $R_3$= Me

### 2.2.3 Cytotoxic activity

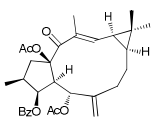
Latilagascene B (**65**) showed anti-tumour activity against gastric carcinoma cells.[65] The diterpenoid esters **71-80** exhibited important cytotoxic activity.[66,67] Euphorbia factors $L_1$ (**81**), $L_3$ (**82**) and japodagrol (**83**) exhibited *in vitro* anticancer activity.[68,69]



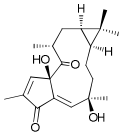
71: $R_1$= 2-MeBu, $R_2$= $R_3$= $R_4$= Ac
72: $R_1$= $R_3$= $R_4$= Ac, $R_2$= 2-MeBu
73: $R_1$= $R_2$= $R_4$= Ac, $R_3$= 2-MeBu
74: $R_1$= $R_2$= $R_3$= Ac, $R_4$= 2-MeBu
75: $R_1$= 2-MeBu, $R_2$= $R_4$= Ac, $R_3$= Me
76: $R_1$= $R_4$= Ac, $R_2$= 2-MeBu, $R_3$= Me
77: $R_1$= $R_2$= Ac, $R_3$= Me, $R_4$= 2-MeBu
78: $R_1$= $R_4$= Ac, $R_2$= Ang, $R_3$= Me
79: $R_1$= H, $R_2$= Ang, $R_3$= Me, $R_4$= Ac
80: $R_1$= $R_4$= Ac, $R_2$= H, $R_3$= Me



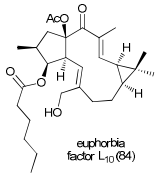
euphorbia factor $L_1$ (81)



euphorbia factor $L_3$ (82)



japodagrol (83)



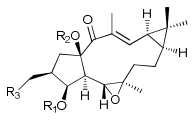
euphorbia factor $L_{10}$ (84)

### 2.2.4 Modulation of multidrug resistance

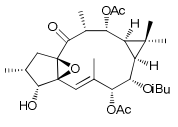
P-glycoprotein (P-gp) is a multidrug transporter which is overexpressed in cancer cell plasma membranes as an efflux pump conferring cellular resistance to anticancer chemotherapy. Latilagascene B (**65**) was found to be an effective P-gp inhibitor and it is an inhibitor of multidrug resistance by tumor cells. It proved highly efficient in inhibiting rhodamine 123 efflux of the human MDR1 gene from transfected mouse lymphoma cells when compared to the untreated cells or the positive control verapamil.[70,71] Euphorbia factor $L_{10}$ (**84**) also inhibited the transport activity of this protein, exhibiting a higher level of activity than that of the specific and potent P-gp inhibitor cyclosporin A.[72]

### 2.2.5 Other activities

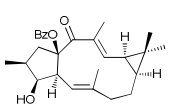
Latilagascenes A-C (**64-66**) and jolkinol B (**68**) are antitumor promoters and diminished the IE antigen expression of cytomegalovirus (CMV).[60] Besides, latilagascenes C (**66**) and D (**85**) exhibited high antineoplastic activity.[63] Lathyrane **69** has recently been patented as a promoter of stem cell proliferation in mouse brain.[73] Lathyrane **79** was particularly active as a prostaglandin $E_2$ inhibitor[74] and lathyrane **86** is a potent active ingredient in rabbit basilar and carotid arteries at resting tension.[75] Finally, lathyranes **87-91** showed significant vascular-relaxing activity.[76]



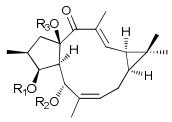
85: $R_1$= H, $R_2$= Cinn, $R_3$= OBz
87: $R_1$=$R_2$= Bz, $R_3$= H
88: $R_1$= Bz, $R_2$= $R_3$= H



86



89

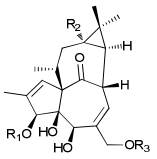


90: $R_1$= Cinn, $R_2$=$R_3$=H
91: $R_1$= $R_3$= H, $R_2$= Cinn

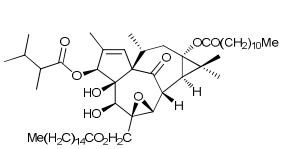
## 2.3 Ingenanes†

### 2.3.1 Cytotoxic activity

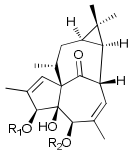
PEP-005 (**1**) is a PKC activator exhibiting topical antitumor activity against human cancer cell lines in mice and against actinic keratosis in humans. PEP-005 also appears to have antileukemic effects, inducing apoptosis in leukemia cell lines and primary acute myeloid leukemia blasts.[77] The related compound PEP-008 (**92**) is a novel PKC-activating drug that arrests growth with senescence characteristics in solid cell lines derived from a variety of tissue types. This compound may therefore have therapeutic potential in a subset of breast cancer, colon cancer and melanoma tumors.[78] Euphorbia factor $L_5$ (**93**) acts as a cocarcinogen on the back skin in mice.[79] Kansuiphorin A-D (**94-97**) and **98-102** were cytotoxic against various cancer cell lines.[34-35,80-83]



PEP-008 (92): $R_1$= Ang, $R_2$= H, $R_3$= Ac
euphorbia factor $L_5$ (93): $R_1$= $CO(CH_2)_{14}CH_3$, $R_2$= $R_3$= H
kansuiphorin A (94): $R_1$= 2,3-dimethylbutanoyl, $R_2$= dodecanoyl, $R_3$= hexadecanoyl
98: $R_1$= CO(CH=CH)(CH=CH)$(CH_2)_4CH_3$, $R_2$= $R_3$= H (*E*) (*Z*)
99: $R_1$= $R_2$= Bz, $R_3$= H
100: $R_1$= 2,3-dimethylbutanoyl, $R_2$= dodecanoyl, $R_3$= H
101: $R_1$= Bz, $R_2$= octanoyl, $R_3$= H
102: $R_1$= 2,3-dimethylbutanoyl, $R_2$= octanoyl, $R_3$= H



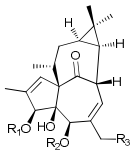
kansuiphorin B (95)



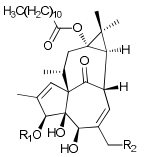
kansuiphorin C (96): $R_1$= Ac, $R_2$= Bz
kansuiphorin D (97): $R_1$= Bz, $R_2$= Ac

### 2.3.2 Effects on cell division

Results showed that esters **98** and **103-112** significantly inhibited cell division (0.5 μg/ml of each compound led to a reduction of cell division above 75%). Amongst these, **110** and **111** significantly prevented cell cleavage. It should be noted that inhibitory activity was weaker in compounds with an acyl residue at position 13. Besides, compound **113** was tested and showed some activity (10 μg/ml of this compound led to a 60% reduction in cell division).[84,85]



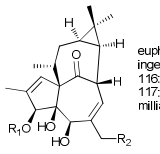
103: $R_1$= CO(CH=CH)(CH=CH)$(CH_2)_4CH_3$, $R_2$= H, $R_3$= OAc (*E*) (*Z*)
104: $R_1$= H, $R_2$= H, $R_3$= OCO(CH=CH)(CH=CH)$(CH_2)_4$Me (*E*) (*E*)
105: $R_1$= H, $R_2$= H, $R_3$= OCO(CH=CH)(CH=CH)$(CH_2)_4$Me (*E*) (*Z*)
106: $R_1$= CO(CH=CH)(CH=CH)$(CH_2)_4$Me, $R_2$= COMe, $R_3$= OH (*E*) (*Z*)
107: $R_1$= CO(CH=CH)(CH=CH)$(CH_2)_4$Me, $R_2$= H, $R_3$= OAc (*E*) (*E*)
108: $R_1$= H, $R_2$= H, $R_3$= $OCO(CH_2)_6$Me
109: $R_1$= H, $R_2$= CO(CH=CH)(CH=CH)$(CH_2)_4$Me, $R_3$= OH (*E*) (*E*)
110: $R_1$= CO(CH=CH)(CH=CH)$(CH_2)_4CH_3$, $R_2$= H, $R_3$= H (*E*) (*E*)
111: $R_1$= CO(CH=CH)(CH=CH)$(CH_2)_4CH_3$, $R_2$= H, $R_3$= H (*E*) (*Z*)
112: $R_1$= CO(CH=CH)(CH=CH)$(CH_2)_4CH_3$, $R_2$= H, $R_3$= OH (*E*) (*Z*)



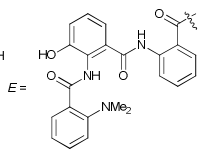
113: $R_1$= Bz, $R_2$= OH

### 2.3.3 Irritant activity

PEP-005 (**1**), euphorbia factor $L_5$ (**93**) and compounds **114-118**, exhibit irritant activity.[86-90]



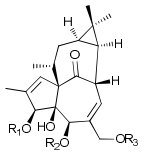
euphorbia factor $L_6$ (114): $R_1$= $CO(CH_2)_{13}$Me, $R_2$= OH
ingenol (115): $R_1$=H, $R_2$= OH
116: $R_1$= COC(Me)=CHMe, $R_2$= H
117: $R_1$= H, $R_2$= octanoyl
milliamine C (118): $R_1$= *E*, $R_2$= OH



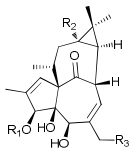
*E* =

### 2.3.4 Pesticidal activity

Ingenol esters **112** and **119-122** exhibited antinematodal activity against the pine-wood nematode *Bursaphelenchus xylophilus*. This nematode is the causal agent of pine wilt disease, one of the most damaging pest problems to be found in forests.[83,91-94]

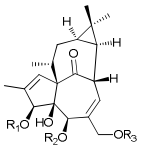


119: $R_1$= CO(CH=CH)(CH=CH)$(CH_2)_4CH_3$, $R_2$= H, $R_3$= Ac (*E*) (*Z*)
120: $R_1$= H, $R_2$= CO(CH=CH)(CH=CH)$(CH_2)_4CH_3$, $R_3$= Ac (*E*) (*Z*)

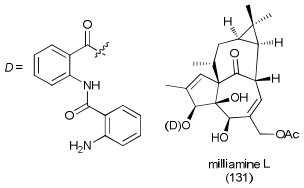


121: $R_1$= 2,3-dimethylbutanoyl, $R_2$= dodecanoyloxy, $R_3$= OH
DBDI (122): $R_1$= 2,3-dimethylbutanoyl, $R_2$= decanoyloxy, $R_3$= OH

Compounds **123-131** exhibited molluscicidal activity. Amongst these milliamine L (**131**), proved to be one of the most potent molluscicidal substances discovered to date under laboratory conditions.[95-97]

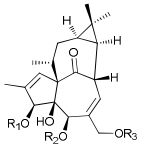


123: $R_1$= *D*, $R_2$= Ac, $R_3$= Ang
124: $R_1$= *D*, $R_2$= Ang, $R_3$= Ac
125: $R_1$= Ac, $R_2$= *D*, $R_3$= Ang
126: $R_1$= Ac, $R_2$= Ang, $R_3$= *D*
127: $R_1$= Ac, $R_2$= *D*, $R_3$= Ac
128: $R_1$= *D*, $R_2$= Ac, $R_3$= Ac
129: $R_1$= *D*, $R_2$= H, $R_3$= Ac
130: $R_1$= Ac, $R_2$= H, $R_3$= *D*



*D* =

milliamine L (131)



132: $R_1$= COEt, $R_2$= H, $R_3$= 2-MeBu
133: $R_1$= H, $R_2$= H, $R_3$= $COCHMe_2$
134: $R_1$= COEt, $R_2$= H, $R_3$= $COCHMe_2$
135: $R_1$= $COCHMe_2$, $R_2$= H, $R_3$= $COCHMe_2$
136: $R_1$= Ac, $R_2$= Ac, $R_3$= Ac
137: $R_1$= H, $R_2$= H, $R_3$= 2-MeBu
138: $R_1$= COEt, $R_2$= COEt, $R_3$= $COCHMe_2$
139: $R_1$= Ac, $R_2$= H, $R_3$= Ang
140: $R_1$= Ang, $R_2$= H, $R_3$= Ac
141: $R_1$= Ang, $R_2$=OAc, $R_3$=OAc

Compounds **98** and **100** showed insecticidal activity.[98] Results suggest that both compounds could be used directly as natural pesticides or as lead ingredients for the control of brown plant hopper and two-spotted spider mite.[81] Ingenol-3,20-diesters **132-138** showed weak piscicidal activity.[99]

### 2.3.5 Tumor-promoting activity

Biological investigations revealed that euphorbia factor $L_5$ (**93**) and compounds **139** and **140** are tumor promoters.[100,101]

### 2.3.6 Other activities

Kansuiphorin A (**94**) showed antiviral activity and it is suggested that this compound prevents viral pneumonia in mice.[102] DBDI (**122**) inhibits degranulation in rat basophilic leukemia cells and results suggest that DBDI may have

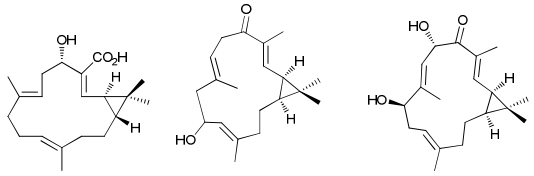
therapeutic potential for allergic diseases[103] and finally, compound **141** exhibits antiangiogenic activity.[104]

## 2.4 Casbanes†

Diterpenes with casbane skeletons are rarely found in plants. However, some have been isolated from plants of the *Euphorbia* genus.[105-109]

### 2.4.1 Antimicrobial activity

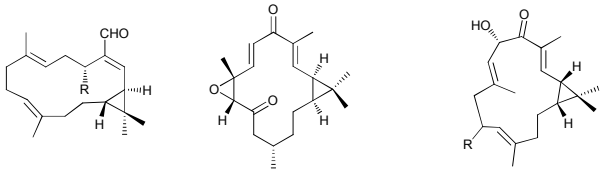
Yuexiandajisu A (**142**) and 10-hydroxydepressin (**143**) exhibited antibacterial activity.[110] Additionally, casbene **144** had an antimicrobial effect on planktonic forms and the biofilm arising from some bacteria and yeasts.[111]



yuexiandajisu A (142) | 10-hydroxydepressin (143) | 144

### 2.4.2 Cytotoxic activity

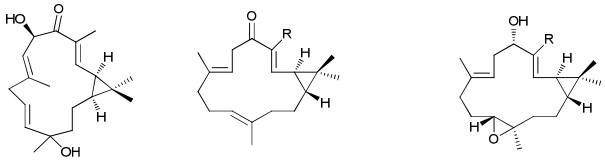
10-Hydroxydepressin (**143**) and casbenes **145-154** were cytotoxic against cancer cell lines.[106,109,112-115]



pekinenal (145): R= OH
pekinenin F (146): R= H

microclavatin (147)

148: R= =O
agrostistachin (149): R= β-OH



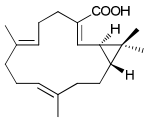
agroskerin (150)

pekinenin A (151): R= $CH_2OH$
pekinenin C (152): R= CHO

pekinenin D (153): R= CHO
pekinenin E (154): R= COOH

### 2.4.3 Other activities

Yuexiandajisu B (**155**) inhibited the proliferation of B lymphocytes.[108]

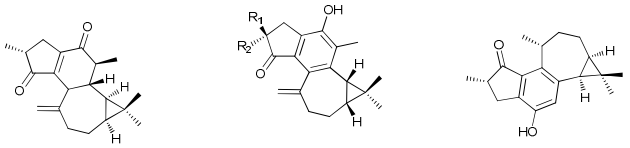


yuexiandajisu B (155)

## 2.5 Jatropholanes†

### 2.5.1 Antimicrobial activity

Sikkimenoid (**156**) demonstrated inhibitory activity against the microorganisms *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, and *Staphylococcus epidermidis*.[116]



sikkimenoid B (156)

jatropholone A (157): $R_1$= Me, $R_2$= H,
158: $R_1$= Me, $R_2$= OH
jatropholone B (159): $R_1$= H, $R_2$= Me,
160: $R_1$= OH, $R_2$= Me

falodone (161)

Malaria is one of the most common parasitic infections worldwide. *Plasmodium falciparum*, a protozoan parasite, is the most prevalent strain in Africa and also the most fatal.[117] Jatropholone A (**157**) and the compound **158** showed antiplasmodial activity against *Plasmodium falciparum*.[118]

### 2.5.2 Cytotoxic activity

Jatropholones A (**157**) and B (**159**) exhibited antitumor activity.[119,120] Compound **160** was mildly cytotoxic against Vero cells.[121] Moreover, falodone (**161**) strongly inhibited the proliferation of the A-549 human cancer cell line.[122]

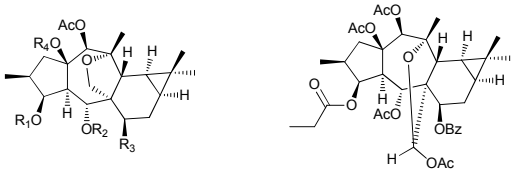
### 2.5.3 Gastroprotective activity

Jatropholones A (**157**) and B (**159**) showed biological activity as gastroprotectors. Compound **157** was less active than compound **159** in preventing the appearance of gastric ulcers but both reduced gastric lesions.[118]

## 2.6 Premyrsinanes†

### 2.6.1 Modulation of multidrug resistance

Premyrsinanes **162-165,** isolated from *Euphorbia falcata,* act with a mild to very strong synergy with doxorubicin against the MDR mouse lymphoma cell line.[123,124]

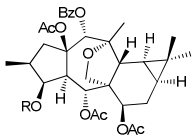


162: $R_1$= *n*-hexanoyl, $R_2$=$R_3$=$R_4$= H
163: $R_1$= propanoyl, $R_2$= Ac, $R_3$= OBz, $R_4$= Ac
164: $R_1$= isobutanoyl, $R_2$= H, $R_3$= OBz, $R_4$= Ac

165

### 2.6.2 Neuroprotective activity

Euphorbiaproliferins I (**166**) and J (**167**) exhibited neuroprotective effects.[125]




euphorbiaproliferin I (166): R= propanoyl
euphorbiaproliferin J (167): R= butanoyl

## 2.7 Euphoractine group†

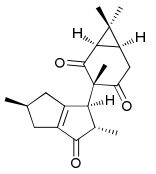
Euphoractines are Natural Products that contain the rare 5-6-7-3 fused diterpene core which had been obtained from a lathyrane skeleton by chemical cyclization.[126] The listed euphoractines showed no biological activities.[127-130]

## 2.8 Other diterpenes†

Other compounds with a *gem*-dimethylcyclopropane in the structures have been isolated from many different sources. However, their structures do not belong to the above groups and were therefore placed together in this sub-group.

### 2.8.1 Antimicrobial activity

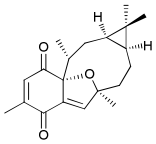
Riolozatrione (**168**) acts as an antibiotic against *Staphyloccocus aureus*.[131]




riolozatrione (168)

### 2.8.2 Cytotoxic activity

The cytotoxicity of multifidone (**169**) was measured against the cancerous cell lines TPH-1, HL-60, A-375 and A-549.[132]




multifidone (169)

## 3 Conclusions and future outlook

In summary, this comprehensive review covered the isolation of diterpenes containing this *gem*-dimethylcarbocycle and whose biological activities are enhanced. The *gem*-dimethylcyclopropane ring remains intact in the biogenetic route leading to a large variety of secondary metabolites in many organisms. In fact, in these natural products the dimethylcyclopropyl unit remains as opposed to an isopropyl unit. This suggests the vital importance of this subunit in nature. Biological research on these *gem*-dimethylcyclopropane derivates has lent credence to the use of some plants in traditional medicine. Furthermore, the secondary metabolism of these plants and of a group of microorganisms, fungi or soft corals, revealed new activities for those compounds.

The study of the structure-activity relationship of these compounds has gained momentum in recent years, especially with the study of interactions with proteins kinase C and it is to be expected that this trend will continue in the years to come.

On the other hand, the massive genome sequencing projects of different type of organisms will lead to discover and identify new cyclopropane-ring containing natural products and their biosynthetic gene cluster, which it will help to unveil new terpene synthases and additional mechanism for *gem*-dimethylcyclopropane ring formation.

We anticipate that this substantial number of diterpenoids containing the *gem*-dimethylcyclopropane ring could be used in the study of in vivo protein-NPs interactions with the aim of designing new drugs. A deeper study of these biological interactions will reveal the role of this intriguing ring in the pathway of the modulation of diverse proteins kinase C and it will allow to modulate them. The occurrence of a wide range of diterpenoids with this feature or even derivatized products that have resulted biologically active supports the biological potential of these structures. This is the main reason why they should deserve more attention. Therefore, these metabolites and those to be isolated in the future as well as related compounds offer scope for development as potential therapeutic agents.

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### Notes and references

[a] Department of Organic Chemistry, Faculty of Science, University of Cádiz, Polígono Río San Pedro s/n, 11510, Puerto Real (Cádiz), Spain.
* Corresponding authors

† Electronic Supplementary Information (ESI) available: [tables listing the known natural products of these structural types, the species from which they were isolated, their biological activity and the bibliographical reference]. See DOI: 10.1039/b000000x/

**Keywords** Bioactivity, euphorbiaceae, phorboid, terpenes, protein kinase C.

**Abbreviations**

| | |
|---|---|
| 2-MeBu | 2-methylbutanoyl |
| Ang | Angelate |
| Anth | Anthranoyl |
| Bz | Benzoyl |
| Cinn | Cinnamoyl |
| EBV | Epstein-Barr virus |
| HIV-1-LTR | Human Immunodeficiency Virus-1- Long Terminal Repeats |
| PKC | Protein kinase C |
| PMA | Phorbol Myristate Acetate |
| Tig | Tigliate |
| TPA | Tetradecanoyl Phorbol Acetate |

1 B. R. Stockwell, *Nature,* 2004, **432**, 846-854.
2 A. Vasas, D. Redei, D. Csupor, J. Molnar and J. Hohmann, *Eur. J. Org. Chem.*, 2012, 27, 5115-5130.
3 Q.-W. Shi, X.-H. Su and H. Kiyota, *Chem. Rev.*, 2008, **108**, 4295-4327.

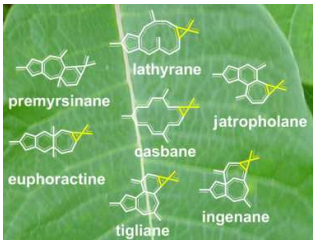
4 W.-W. Tao, J.-A. Duan, Y.-P. Tang, N.-Y. Yang, J.-P. Li and Y.-F. Qian, *Phytochemistry,* 2013, **94**, 249-253.
5 C. J. Thibodeaux, W. Chang and H. Liu, *Chemical Reviews,* 2012, **112**, 1681-1709.
6 M. T. Dueber, W. Adolf and C. A. West, *Plant Physiol.*, 1978, **62**, 598-603.
7 C. J. D.Mau and C. A. West, *Proc. Nat. Acad. Sci.*, 1994, **91**, 8497-501.
8 K-X. Huang, Q-L. Huang and A.I. Scott, *Arch. Biochem. Biophys.*, 1998, **352**, 144-152.
9 J. Kirby, M. Nishimoto, J. G. Park, S. T. Withers, F. Nowroozi, D. Behrendt, E. J. G Rutledge, J. L. Fortman, H. E. Johnson, J. V. Anderson and J. D. Keasling, *Phytochemistry*, 2010, **71**, 1466-1473.
10 M. Wigler, D. DeFeo and I. B. Weinstein, *Cancer Res.*, 1978, **38**, 1434-1437
11 V. Kinzel, J. Richards, K. Goerttler, H. Loehrke, G. Fürstenberger and F. Marks, *IARC Sci. Publ.*, 1984, **56**, 253-264.
12 I. B. Weinstein, L.-S. Lee, P. B. Fisher, A. Mufson and H. Yamasaki, *J. Supramol. Struct.*, 1979, **12**, 195-208.
13 D. T. Chu and D. K. Granner, *J. Biol. Chem.*, 1986, **261**, 16848-16853.
14 S. L. Poccote and R. W. Holz, *J. Biol. Chem.*, 1986, **261**, 1873-1877.
15 U. Testa, M. Titeux, F. Louache, P. Thomopoulos and H. Rochant, *Cancer Res.*, 1984, **44**, 4981-4986.
16 A. D. Kinghorn, *J. Nat. Prod.*, 1979, **42**, 112-115.
17 G. W. J. Olivier, M. G. Rowan, S. K. Branch, M. F. Mahon and K. C. Molloy, *J. Chem. Soc., Perkin Trans. 1*, 1992, 1831-1835.
18 P. P. Roux, B. A. Ballif, R. Anjum, S. P. Gygi and J. Blenis, *Proc. Natl. Acad. Sci. USA*, 2004, **101**, 13489-13494.
19 K. R. Gustafson, J. H. Cardellina, J. B. McMahon, R. J. Gulakowski, J. Ishitoya, Z. Szallasi, N. E. Lewin, P. M. Blumberg, O. S. Weislow, J. A. Beutler, *J. Med. Chem.*, 1992, **35**, 1978-1986.
20 J. Rullas, M. Bermejo, J. García-Pérez, M. Beltán, N. González, M. Hezareh, S. J. Brown and J. Alcamí, *Antivir. Ther.*, 2004, **9**, 545-554.
21 P. M. Blumberg and Z. Szallasi, PCT Int Appl WO 9427593 A1 19941208, 1994.
22 I. B. Baloch, M. K. Baloch and A. K. Baloch, *Planta Med.*, 2010, **76**, 809-814.
23 Q.-G. Ma, W.-Z. Liu, X.-Y. Wu, T.-X. Zhou and G.-W. Qin, *Phytochemistry*, 1997, **44**, 663-666.
24 Y.-X. Sun and J.-C. Liu, *Chem. Biodiversity*, 2011, **8**, 1205-1214.
25 J. Kulkosky, D. M. Culnan, J. Roman, G. Dornadula, M. Schnell, M. R. Boyd and R. J. Pomerantz, *Blood*, 2001, **98**, 3006-3015.
26 S. Bocklandt, P. M. Blumberg and D. H. Hamer, *Antiviral Res.*, 2003, **59**, 89-98.
27 G. Brooks, N. A. Morrice, C. Ellis, A. Aitken, A. T. Evans and F. J. Evans, *Toxicon*, 1987, **25**, 1229-1233.
28 N. Márquez, M. A. Calzado, G. Sánchez-Duffhues, M. Pérez, A. Minassi, A. Pagani, G. Appendino, L. Diaz, M. A. Muñoz-Fernández and E. Muñoz, *Biochem. Pharmacol.*, 2008, **75**, 1370-1380.
29 A. Pagani, C. Navarrete, B. L. Fiebich, E. Muñoz and G. Appendino, *J. Nat. Prod.*, 2010, **73**, 447-451.
30 L.-L. Pan, P.-L. Fang and X.-J. Zhang, *J. Nat. Prod.*, 2011, **74**, 1508-1512.
31 L. Ávila, M. Perez, G. Sanchez-Duffhues, R. Hernández-Galán, E. Muñoz, F. Cabezas, W. Quinones, F. Torres and F. Echeverri, *Phytochemistry*, 2010, **71**, 243-248.
32 N. Rudra, N. Singh and M. Gupta, *J. Biosci.*, 1996, **21**, 477-485.
33 I. B. Baloch, M. K. Baloch and Q. N. Saqib, *Eur. J. Med. Chem.*, 2008, **43**, 274-281.
34 M. O. Fatope, L. Zeng, J. E. Ohayaga, G. Shi and J. L. McLaughlin, *J. Med. Chem.*, 1996, **39**, 1005-1008.
35 S. M. Kupchan, I. Uchida, A. R. Branfman, R. G. Jr. Dailey and B. Y. Fei, *Science*, 1976, **191**, 571-572.
36 Y.-B. Wang, P. Ji, H.-B. Wang and G.-W. Qin, *Zhongguo Tianran Yaowu*, 2010, **8**, 94-96.
37 I. S. Aljancic, M. Pesic, S. M. Milosavjevic, N. M. Todorovic, M. Jadranin, G. Milosavljevic, D. Povrenovic, J. Bankovic, N. Tanic, I. D. Markovic, S. Ruzdijic, V. E. Vajs and V. V. Tesevic, *J. Nat. Prod.*, 2011, **74**, 1613-1620.
38 G. R. Pettit, S. Ducki, R. Tan, R. S. Gardella, J. B. McMahon, M. R. Boyd, G. R. III Pettit, P. M. Blumberg, N. E. Lewin, D. L. Doubek, L. P. Tackett and M. D. Williams, *J. Nat. Prod.*, 2002, **65**, 1262-1265.
39 L. Betancur-Galvis, E. Palomares, J. A. Marco and E. Estornell, *J. Ethnopharm.*, 2003, **85**, 279-282.
40 G. Goel, H. P. S. Makkar, G. Francis and K. Becker, *Int. J. Toxicol.,* 2007, **26**, 279-288.
41 W. Adolf and E. Hecker, *Tetrahedron Lett.*, 1980, **21**, 2887-2890.
42 L. Jing, Y. Fang, X. Ying, H. Wenxing, X. Meng, M. N. Syed and C. Fang, *J. Appl. Entomol.*, 2005, **129**, 98-104.
43 L. Jing, Y. Fang, X. Ying, H. Wenxing, X. Meng, M. N. Syed and C. Fang, *Nongyaoxue Xuebao,* 2005, **7**, 29-34.
44 F. J. Evans, *Toxicon*, 1978, **16**, 51-57.
45 G. Falsone and A. E. G. Crea, *Liebigs Ann. Chem.*, 1979, **8**, 1116-1121.
46 A. Marston and E. Hecker, *Planta Med.*, 1984, **50**, 319-322.
47 S. E. Taylor, M. A. Garfur, A. K. Choudhury and F. J. Evans, *Experientia*, 1981, **37**, 681-682.
48 S. E. Taylor, M. Edwards, E. Williamson and F. J. Evans, *J. Pharm. Pharmacol.*, 1981, **33**, 54.
49 S. M. Zayed, M. Farghaly, S. M. Soliman, H. Gotta, B. Sorg and E. Hecker, *J. Cancer Res. Clin.,* 2001, **127**, 40-47.
50 S. Zayed, A. Hafez, W. Adolf and E. Hecker, *Experientia*, 1977, **33**, 1554-1555.
51 A. E. Lockyer, J. N. Spinks, A. J. Walker, R. A. Kane, L. R. Noble, D. Rollinson, E. Dias-Neto and C. S. Jones, *Dev. Comp. Immunol.*, 2007, **31**, 763-782.
52 W. L. Jr. Lowe, M. A. Yorek, C. W. Karpen, R. M. Teasdale, J. G. Hovis, B. Albrecht and C. Prokopiou, *Mol. Endocrinol.*, 1992, **6**, 741-752.
53 E. G. Puszkin and M. B. Zucker, *Nature: New biology*, 1973, **245**, 277-280.
54 L. G. Rao and T. M. Murray, *Calcif. Tissue Int.*, 1989, **45**, 354-359.
55 C. Brodie and P. M. Blumberg, *Apoptosis*, 2003, **8**, 19-27.
56 A. M. González-Guerrico, J. Meshki, L. Xiao, F. Benavides, C. J. Conti, M. G. Kazanietz, *Biochem. Mol. Biol.,* 2005, **38**, 639-645.
57 S. Oidovsambuu, C. Y. Kim, K. Kang, B. Dulamjav, T. Jigjidsuren and C. W. Nho, *Planta Med.*, 2013, **79**, 116-122.

58 M. Bourjout, L. Delang, N. Van H. Nguyen, J. Neyts, F. Guéritte, P. Leyssen and M. Litaudon, *J. Nat. Prod.*, 2012, **75**, 2183-2187.
59 O. O. Aiyelaagbe, K. Adesogan, O. Ekundayo and J. B. Gloer, *Phytochemistry*, 2007, **68**, 2420-2425.
60 R. K. Devappa , H. P. S. Makkar and K. Becker, *J. Am. Oil Chem. Soc.*, 2011, **88**, 301-322.
61 G. Schmeda-Hirschmann, F. Tsichritzis and J. Jakupovic, *Phytochemistry*, 1992, **31**, 1731-1735.
62 R. Pusztai, M.-J. U. Ferreira, N. Duarte, H. Engi and J. Molnar, *Anticancer Res.*, 2007, **27**, 201-206.
63 S. Budhiraja and A. P. Rice, *Future Virology,* 2013, **8**, 649-659.
64 M. Daoubi, N. Marquez, N. Mazoir, A. Benharref; R. Hernández-Galán, E. Muñoz and I. G. Collado, *Bioorg. Med. Chem.*, 2007, **15**, 4577-4584.
65 H. Lage, N. Duarte, C. Coburger, A. Hilgeroth and M.-J. U. Ferreira, *Phytomedicine*, 2010, **17**, 441-448.
66 I. B. Baloch, M. K. Baloch and Q. N. Saqib, *Planta Med.*, 2006, **72**, 830-834.
67 V. Ravikanth, V. L. N. Reddy, A. V. Reddy, K. Ravinder, T. P. Rao, T. S. Ram, K. A. Kumar, D. P. Vamanarao and Y. Venkateswarlu, *Chem. Pharm. Bull.*, 2003, **51**, 431-434.
68 S. B. Sanni, H. Behm, P. T. Beurskens, E. Y. Adesogan and J. I. Durodola, *J. Chem. Crystallogr.*, 1988, **18**, 575-582.
69 J.-Y. Zhang, C. Zhang, H.-B. Chen, L.-W. Fu, Y.-W. Tao, X.-Q. Zheng, Z.-M. Cao, Y.-F. Zhong and L.-H. Yu, *J. Med. Plants Res.*, 2010, **4**, 335-338.
70 N. Duarte, N. Gyemant, P. M. Abreu, J. Molnar and M.-J. U. Ferreira, *Planta Med.*, 2006, **72**, 162-168.
71 O. Wesolowska, J. Wisniewski, N. Duarte, M.-J. U. Ferreira and K. Michalak, *Anticancer Res.*, 2007, **27**, 4127-4134.
72 G. Appendino, C. Della porta, G. Conseil, O. Sterner, E. Mercalli, C. Dumontet and A. Di Pietro, *J. Nat. Prod.*, 2003, **66**, 140-142.
73 C. Castro-González, R. Hernández-Galán, A. J. Macías-Sánchez, F. Echeverri, N. Geribaldi-Doldan, A. Aguilera-Díaz, J. Domnguez-Riscart, A. Castillo-Domínguez and M. Murillo-Carretero, PCT Int. Appl., 2013, WO 2013057337 A2 20130425.
74 V. Ravikanth, V. L. N. Reddy, T. Prabhakar, P. V. Diwan, S. Ramakrishna and Y. Venkateswarlu, *Phytochemistry*, 2002, **59**, 331-335.
75 F. J. Miranda, J. A. Alabadi, M. Orti, J. M. Centeno, M. Pinon, A. Yuste, J. F. Sanz-Cervera, J. A. Marco and E. Alborch, *J. Pharm. Pharmacol.*, 1998, **50**, 237-241.
76 Y. Tian, W. Xu, C. Zhu, S. Lin, Y. Li, L. Xiong, S. Wang, L. Wang, Y. Yang, Y. Guo, H. Sun, X. Wang and J. Shi, *J. Nat. Prod*., 2011, **74**, 1221-1229.
77 P. Hampson, K. Wang and J. M. Lord, *Drugs Fut.,* 2005, **30**, 1003-1005.
78 S. A. Mason, S.-J. Cozzi, C. J. Pierce, S. J. Pavey, P. G. Parsons and G. M. Boyle, *Invest. New Drugs*, 2010, **28**, 575-586.
79 W. Adolf and E. Hecker, *Z. Krebsforsch. Klin. O.,* 1975, **84**, 325-344.
80 Z.-Q. Lu, M. Yang, J.-Q. Zhang, G.-T. Chen, H.-L. Huang, S.-H. Guan, C. Ma, X. Liu and D.-A. Guo, *Phytochemistry*, 2008, **69**, 812-819.
81 D. J. Pan, C. Q. Hu, J. J. Chang, T. T. Y. Lee, Y. P. Chen, H. Y. Hsu, D. R. McPhail, A. T. McPhail and K. H. Lee, *Phytochemistry*, 1991, **30**, 1018-1020.
82 Y.-B. Wang, Y.-Y. Li, H.-B. Wang and G.-W. Qin, *Zhongguo Tianran Yaowu*, 2007, **5**, 182-185.
83 T. S. Wu, Y. M. Lin, M. Haruna, D. J. Pan, T. Shingu, Y. P. Chen, H. Y. Hsu, T. Nakano and K. H. Lee, *J. Nat. Prod*., 1991, **54**, 823-829.
84 L.-Y.Wang, N.-L. Wang, X.-S. Yao, S. Miyata and S. Kitanaka, *Chem. Pharm. Bull.*, 2003, **51**, 935-941.
85 L.-Y.Wang, N.-L. Wang, X.-S. Yao, S. Miyata and S. Kitanaka, *J. Nat. Prod.*, 2002, **65**, 1246-1251.
86 W. Adolf and E. Hecker, Z. *Krebsforsch. Klin. O.*, 1975, **84**, 325-344
87 J. Hohmann, F. Evanics, L. Berta and T. Bartok, *Planta Med*., 2000, **66**, 291-294.
88 A. R. Jassbi, *Phytochemistry*, 2006, **67**, 1977-1984.
89 A. M. Rizk, F. M. Hammouda, M. M. El-Missiry, H. M. Radwan and F. J. Evans, *Phytochemistry*, 1985, **24**, 1605-1606.
90 D. Uemura, and Y. Hirata, *Tetrahedron Lett.,* 1973, **11**, 881-884.
91 W. Ye, R. W. Giblin-Davis, *J. Parasitol.,* 2013, **99**, 803-815.
92 J. Shi, Z. Li, T. Nitoda, M. Izumi, H. Kanzaki, N. Baba, K. Kawazu and S. Nakajima, *Z. Naturforsch., J. Biosci.,* 2008, **63**, 59-65.
93 Q.-W. Shi, X.-H. Su, H. Kiyota, *Chem. Rev.*, 2008, **108**, 4295-4327.
94 J.-X. Shi, Z.-X. Li, T. Nitoda, M. Izumi, H. Kanzaki, N. Baba, K. Kawazu and S. Nakajima, *Biosci., Biotechnol., Biochem.*, 2007, *71*, 1086-1089.
95 I. B. Baloch, M. K. Baloch and A. K. Baloch, *Eur. J. Med. Chem.,* 2009, **44**, 3188-3194.
96 B. A. Nascimento and C. L. Zani, *Phytochem. Anal.,* 1999, **10**, 93-96.
97 C. L. Zani, A. Marston, M. Hamburger and K. Hostettmann, *Phytochemistry*, 1993, **34**, 89-95.
98 Q. L. Dang, Y. H. Choi, G. J. Choi, K. S. Jang, M. S. Park, N.-J. Park, C. H. Lira, H. Kim, L. H. Ngoc and J.-C. Kim, *J. Asia Pacific Entomol.,* 2010, **13**, 51-54.
99 M. Hirota, H. Ohigashi, Y. Oki and K. Koshimizu, *Agric. Biol. Chem.,* 1980, **44**, 1351-1356.
100 I. B. Baloch, M. K. Baloch and Z. N. Saqib, *Helv. Chim. Acta.*, 2005, **88**, 3145-3150.
101 R. R. Upadhyay, M. Ansarin, M. H. Zarintan and P. Shakui. *Experientia*, 1976, **32**, 1196-1197.
102 W. Zheng, *Zhongcaoyao*, 2004, **35**, 65-68.
103 S. Nunomura, S. Kitanaka and C. Ra, *Biol. Pharm. Bull.*, 2006, **29**, 286-290.
104 X.-L. Li, Y. Li, S.-F. Wang, Y.-L. Zhao, K.-C. Liu, X.-M. Wang and Y.-P. Yang, *J. Nat. Prod.*, 2009, **72**, 1001-1005.
105 Y. Bai, Y.-P. Yang and Y. Ye, *Tetrahedron Lett.*, 2006, **47**, 6637-6640.
106 H. Chen and Z. J. Jia, Indian *J. Chem. Sect. B: Org. Chem. Incl. Med. Chem.*, 1996, **35B**, 1308-1310.
107 Y.-H. Choi, J. M. Pezzuto, A. D. Kinghorn and N. R. Farnsworth, *J. Nat. Prod*., 1988, **51**, 110-116.
108 Y. Kashman, M. W. Bernart, M. Tischler, J. H. Cardellina and M. R. Boyd, *J. Nat. Prod*., 1994, **57**, 426-430.
109 Z.-H. Xu, J. Sun, R.-S. Xu and G.-W. Qin, *Phytochemistry*, 1998, **49**, 149-151.
110 Y. Li, M. Carbone, R. M. Vitale, P. Amodeo, F. Castelluccio, G. Sicilia, E. Mollo, M. Nappo, G. Cimino, Y. W. Guo and M. Gavagnin, *J. Nat. Prod.*, 2010, **73**, 133-138.

111 V. A. Carneiro, H. Silva dos Santos, F. V. S. Arruda, P. N. Bandeira, M. R. J. R. Albuquerque, M. O. Pereira, M. Henriques, B. S. Cavada and E. H. Teixeira, *Molecules,* 2011, **16**, 190-201.
112 Y. H. Choi, J. Kim, J. M. Pezzuto, A. D. Kinghorn, N. R. Farnsworth, H. Lotter and H. Wagner, *Tetrahedron Lett.,* 1986, **27**, 5795-5798.
113 Q.-L. Liang, C.-C. Dai, J.-H. Jiang, Y.-P. Tang and J.-A. Duan, *Fitoterapia*, 2009, **80**, 514-517.
114 F.-G. Shao, R. Bu, C. Zhang, C.-J. Chen, J. Huang and J.-H. Wang, *J. Asian Nat. Prod. Res.,* 2011, **13**, 805-810.
115 C.-X. Zhang, S.-J. Yan, G.-W. Zhang, W.-G. Lu, J.-Y. Su, L.-M. Zeng, L.-Q. Gu, X.-P. Yang and Y.-J. Lian, *J. Nat. Prod.,* 2005, **68**, 1087-1089.
116 Y.-F. Yang, J.-Q. Liu, L. Shi, Z.-R. Li and M.-H. Qiu, *Nat. Prod. Bioprospect.,* 2013, **3**, 99-102.
117 S. A. Pawluk, K. J. Wilby and M. H. H. Ensom, *Clinical Pharmacokinetics*, 2013, **52**, 153-167.
118 S. Sutthivaiyakit, W. Mongkolvisut, S. Prabpai and P. Kongsaeree, *J. Nat. Prod*., 2009, **72**, 2024-2027.
119 M. Pertino, G. Schmeda-Hirschmann, J. A. Rodriguez and C. Theoduloz, *Planta Med*., 2007, **73**, 1095-1100.
120 K. K. Purushothaman, S. Chandrasekharan, A. F. Cameron, J. D. Connolly, C. Labbe, A. Maltz and D. S. Rycroft, *Tetrahedron Lett.,* 1979, **20**, 979-980.
121 S. Sutthivaiyakit, W. Mongkolvisut, S. Prabpai and P. Kongsaeree, *J. Nat. Prod*., 2009, **72**, 2024-2027.
122 A. Falodun, Q. Sheng-Xiang, G. Parkinson and S. Gibbons, *Pharm. Chem. J*., 2012, **45**, 636-639.
123 Sulyok, A. Vasas, D. Redei, P. Forgo, Z. Kele, G. Pinke and J. Hohmann, *Tetrahedron*, 2011, **67**, 7289-7293.
124 A. Vasas, E. Sulyok, A. Martins, D. Redei, P. Forgo, Z. Kele, I. Zupko, J. Molnar, G. Pinke and J. Hohmann, *Tetrahedron*, 2012, **68**, 1280-1285.
125 J. Xu, Y. Guo, C. Xie, Y. Li, J. Gao, T. Zhang, W. Hou, L. Fang and L. Gui, *J. Nat. Prod*., 2011, **74**, 2224-2230.
126 W. Adolf and E. Hecker, *Tetrahedron Lett.*, 1970, 2241-2244.
127 J. Shi and Z. Jia, *Phytochemistry*, 1995, **38**, 1445-1447.
128 L. Barboni, P. Gariboldi, E. Torregiani, G. Appendino, B. Gabetta, G. Zini and E. Bombardelli, *Phytochemistry*, 1993, **33**, 1553.
129 J. Shi, Z. Jia and L. Yang, *Phytochemistry*, 1992, **32**, 208-210.
130 A. Vasas, J. Hohmann, P. Forgo and P. Szabo, *Tetrahedron*, 2004, **60**, 5025-5030.
131 W. H. Watson, V. Zabel and X. A. Dominguez, *Acta Crystallographic. Sect. B: Struct. Sci.,* 1982, **B38**, 689-691.
132 B. Das, K. R. Reddy, B. Ravikanth, T. V. Raju, B. Sridhar, P. U. Khan and T. V. Rao, *Bioorg. Med. Chem. Lett.,* 2009, **19**, 77-79.




This review with more than 200 references describes the diterpenes containing the *gem*-dimethylcyclopropane subunit isolated from natural sources with a special emphasis in its intringuing biological activities as source of PKC modulators.