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Jatrophane and rearranged jatrophane-type diterpenes: biogenesis, structure, isolation, biological activity and SARs (1984–2019)

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Abstract Diterpene compounds specially macrocyclic ones comprising jatrophane, lathyrane, terracinolide, ingenane, pepluane, paraliane, and segetane skeletons occurring in plants of the Euphorbiaceae family are of considerable interest in the context of natural product drug discovery programs. They possess diverse complex skeletons and a broad spectrum of therapeutically relevant biological activities including anti-inflammatory, anti-chikungunya virus, anti-HIV, cytotoxic, and multidrug resistance-reversing activities as well as curative effects on thrombotic diseases. Among macrocyclic diterpenes of *Euphorbia*, the discovery of jatrophane and modified jatrophane diterpenes with a wide range of structurally unique polyoxygenated polycyclic derivatives and as a new class of powerful inhibitors of P-glycoprotein has opened new frontiers for research studies on this genus. In this review, an attempt has been made to give in-depth coverage of the articles on the naturally occurring jatrophanes and rearranged jatrophane-type diterpenes isolated from species belonging to the Euphorbiaceae family published from 1984 to March 2019, with emphasis on the biogenesis, isolation methods, structure, biological activity, and structure–activity relationship.

Keywords Natural products · Euphorbia · Jatrophane diterpenes · Rearranged Jatrophanes · Chromatography · Multidrug resistance

Abbreviations

ABCB1	ATB-Binding Cassette Sub-Family B Member 1
Bel-7402	Hepatoma cell line
BGC-823	Human gastric carcinoma cell line
Caov-4	Ovarian cancer cell line
CBS	Casbene synthase
CC	Column chromatography
CHIK	Chikungunya virus
CNS	Central nervous system
COLO320	Colon adenocarcinoma cell line
CsA	Cyclosporine A
DCCC	Droplet countercurrent chromatography
EC_{50}	Half maximal effective concentration
FAR	Fluorescence activity ratio

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FICi	Fractional inhibitory concentration index
FIX	Fractional inhibitory index
GGPP	Geranylgeranyl pyrophosphate
GI_{50}	concentration of the anti-cancer drug that inhibits the growth of cancer cells By 50%
GIRK	G protein-coupled inwardly rectifying potassium
GTP	Guanosine triphosphate
HAART	Highly active antiretroviral therapy
HEK293	Human embryonic kidney cell line
Hela	Human cervical carcinoma cells
HPLC	High-performance liquid chromatography
IC_{50}	Half maximal inhibitory concentration
ID_{50}	Median infectious dose
LC_{50}	Median lethal dose
LPS	Lipopolysaccharide
MCF-7	Breast cancer cell line
MDA-MB-231	Breast tumor cells
MDR	Multidrug resistance
MFS	Major facilitator superfamily
MIC_{80}	Minimum inhibitory concentration (For 80%)
MPLC	Medium pressure liquid chromatography
MRP	Multidrug resistance protein
MTB	Methyl-tert-butyl ether
MTT	3-(4,5-Dimethylthiazol-2-Yl)-2,5-diphenyltetrazolium bromide
NADH	Nicotinamide adenine dinucleotide factor
NCI-H460	Non-small cell lung carcinoma cell line
NF-κB	Nuclear factor
NGF	Nerve growth factor
NP	Normal phase
OVCAR-3	Ovarian carcinoma cell line
PE	Petroleum ether
P-gp	P-glycoprotein
PKC	Protein kinase C
PTX	Paclitaxel
RP	Reverse phase
RR	Relative resistance
Rho123	Rhodamine-123
SAR	Structure activity relationship
SGC-7901	Human gastric carcinoma cell line
SF-268	Glioblastoma brain cell line
SFV	Semliki forest virus
SI	Seletivity index
SINV	Sindbis virus
SNP	Single nucleotide polymorphism
TLC	Thin layer chromatography
TQ	Tariquidar
Trk	Tropomyosin receptor kinase
VLC	Vacuum liquid chromatography

Introduction

Natural products are comprised of a large number of structurally complex molecules, the structural diversity of which sometimes far exceeds the abilities of chemists and their equipment within the laboratories. In addition to the fascinating diverse structures, many natural compounds possess intriguing biological properties. Building blocks of natural origin are being used as a plentiful source of lead compounds for drug discovery. Euphorbiaceae family composed of five subfamilies, 49 tribes, 317 genera, and about 8000 species, is one of the biggest families with probably the highest species richness in many habitats (Webster 1986). Exposure to a large range of habitats predisposed *Euphorbia* species to unavoidable high mutation loads caused by stressful habitats. The presence of environmental stimuli had necessitated the development of rich storage of defensive secondary metabolites (Mwine and Van Damme 2011). The botanical name "Euphorbia" derives from the Greek "Euphorbius" in honour to the physician of Mauritania, who is assumed to have used in his treatment a certain plant (*Euphorbia resinifera*) with a milky latex (Appendino and Szallasi 1997). Moreover, this plant family is known also as "spurge" derived from the Latin "expurgare", which means "to cleanse" referring to the early traditional application of these plants as purgative medication (Burkill 1994). Euphorbiaceae species had played an important role in traditional ethnomedicine as mentioned in the Greek and Roman medical literature for the treatment of toothache, to remove warts, as purgatives, and in asthma and bronchial catarrh (Lawant and Winthagen 2002). They are also part of different herbal remedies used in traditional Chinese medicines and ayurvedic medicine for similar indications (Kapoor 2017; Liang et al.

2009). Over the last decades, several Euphorbiaceae constituents have successfully been employed in clinical trials or applied as lead structures for the development of novel drugs. Species of this family are prolific producers of unique diterpenoids (Singla and Kamla 1990) of great biomedical relevance (Evans and Taylor 1983), the promising biological properties of which have attracted interests of phytochemists to the isolation of Euphorbiaceae constituents. One of the largest chemical classes isolated from the milky latices of Euphorbiaceae species is macrocyclic diterpenes based on jatrophane, lathyrane, terracinolide, ingenane, pepluane, paraliane, and segetane skeletons, many of which show interesting pharmacological properties. When 'jatrophone', the first jatrophane-type diterpene, isolated by Kupchan and co-workers in 1970 from *Jatropha gossypiifolia* L. as a natural product with significant antiproliferative effects against human tumor cell lines, the biological and chemical interest in the jatrophane structures greatly increased (Kupchan et al. 1970). Modified jatrophanes consist of "segetanes", "paralianes", "pepluanes", and "terracinolides". "Euphoractanes" being occasionally considered as modified jatrophanes or modified lathyrane skeletons, were a black box for decades and there was no biosynthesis or chemical conversion evidence to support or oppose different biogenesis proposals. In this regard, the recently published article by Wang et al. (2019) has mentioned the proposal suggested by Haiming et al. (2008) in which it had been claimed that euphoractane skeletons come from macrocyclic jatrophanes. Subsequently, Wang et al. in 2019 have certainly demonstrated that euphoractane skeletons are obtained by the treatment of lathyrane-type diterpene (Euphorbia Factor L1) with $BF_3.ET_2O$ in ethyl acetate at room temperature and it has confirmed the biogenesis relationship between the euphoractanes and lathyranes by chemical conversion method for the first time. Hereupon, euphoractanes are not considered as modified jatrophane skeletons (Wang et al. 2019). Vasas and Hohmann (2014) have published a worthwhile review article of the represented papers on all diterpenoids isolated from *Euphorbia* between 2008 and 2012, parts of which include jatrophane and modified jatrophane diterpenes (Vasas and Hohmann 2014). Moreover, another comprehensive review article has been published by Shi et al. (2008) of the papers written on the chemical and pharmacological aspects of the plants in genus *Euphorbia* over the past few decades (Shi et al. 2008). Meanwhile, the vacancy of a review article intensely focusing on jatrophane diterpenes was sensated. Therefore, this present review article has been aimed at giving in depth coverage of the papers published from 1984 to March 2019 particularly on the jatrophanes and rearranged jatrophane-type diterpenes, with emphasis on their biogenesis, isolation, structure, biological activity and structure activity relationship.

Biogenesis

As demonstrated in Fig. 1, two mechanistically different biogenetic pathways are possible for the biosynthesis of diterpenes, leading either to the phytanes such as abietanes, kauranes, atisanes, etc. or to the casbene derived diterpenes including casbanes, jatrophanes, tiglianes, etc. (Appendino et al. 2000).

Casbene is considered as a precursor for different macrocyclic and polycyclic diterpenes including those of the jatrophane-, casbane-, lathyrane-, tigliane-, ingenane- and daphnane- type (Breitmaier 2006).

Biosynthesis of casbene derived diterpenes, commences from GGPP; the diphosphate group is cleaved from GGPP affording requisite delocalized cation, which interacts with the C-(14, 15) terminal double bond and transformed to cembrene intermediate with C-15 tertiary carbocation undergoing additional cyclization and rearrangements to form a diversity of the carbon skeletons outlined in Fig. 2 (Breitmaier 2006; Nakano et al. 2012; Rinner 2015; Robinson and West 1970). Finally, the cyclopropane ring is formed via a nonclassical carbocation (a corner-protonated cyclopropane) by proton loss of cembrene intermediate, delivering casbene. The whole sequence is catalyzed by a single enzyme, called casbene synthase (E1) (Fig. 3) (Dewick 2002; Kirby et al. 2010). A second ring closure between C-6 and C-10 delivers the precursor of natural products of the lathyrane family and a third ring closure between C-5 and C-14 affords the tigliane skeleton an intermediate in the hypothetical biogenetic route toward phorbol (Kinghorn et al. 2011).

From casbene, the biosynthetic route to macrocyclic and polycyclic diterpenoids is poorly understood but is thought to proceed through intermediates

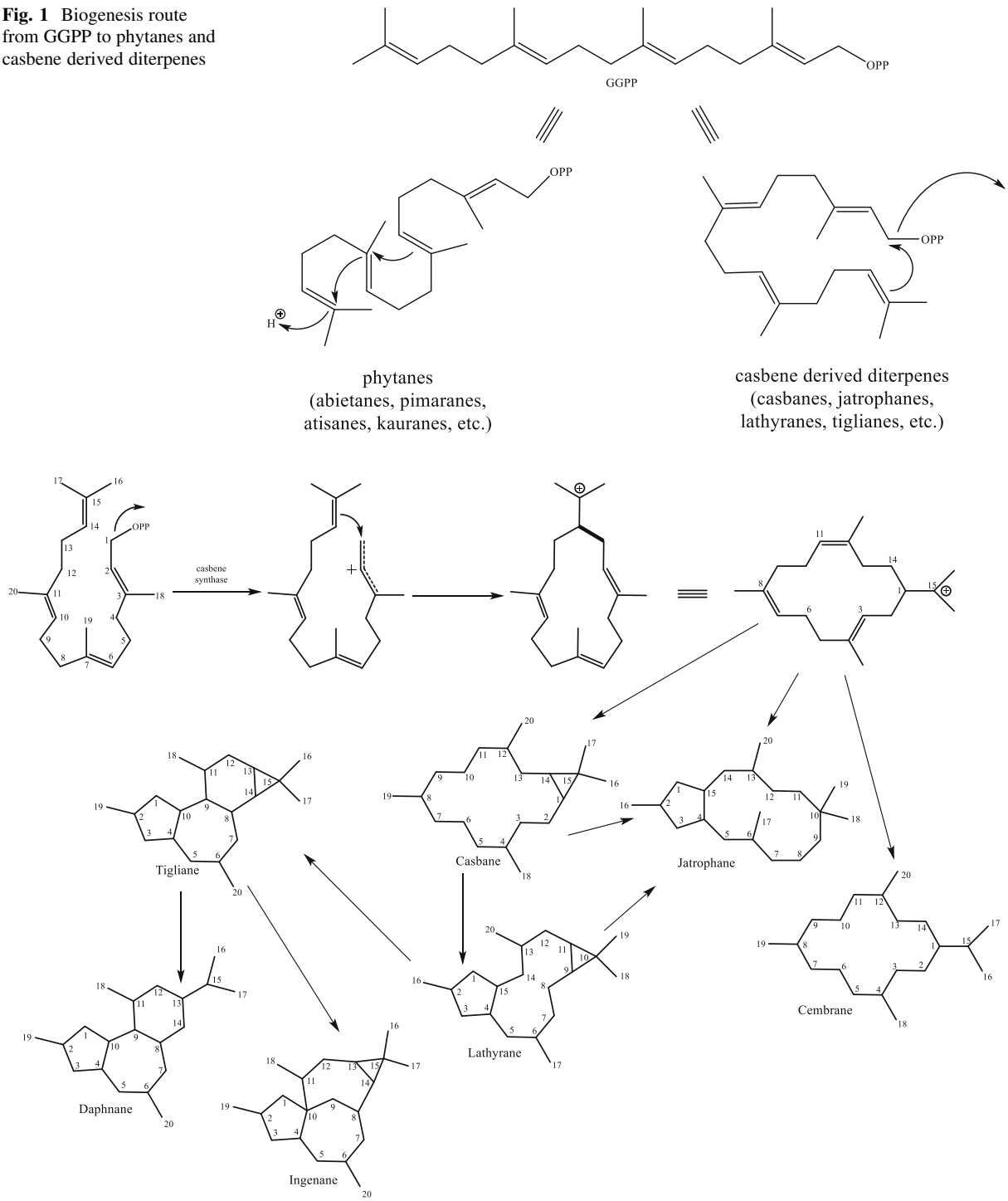


Fig. 1 Biogenesis route from GGPP to phytanes and casbene derived diterpenes

Fig. 2 Biogenesis route of macrocyclic and polycaclic derived from Casbene

such as jolkinol C via cytochrome P450-catalyzed oxidations and possibly a short-chain alcohol dehydrogenase (ADH) (Fig. 4). This cyclization requires the activity of two CYP450s to form an intermediate '6-hydroxy-5,9-diketocasbene' including one of the

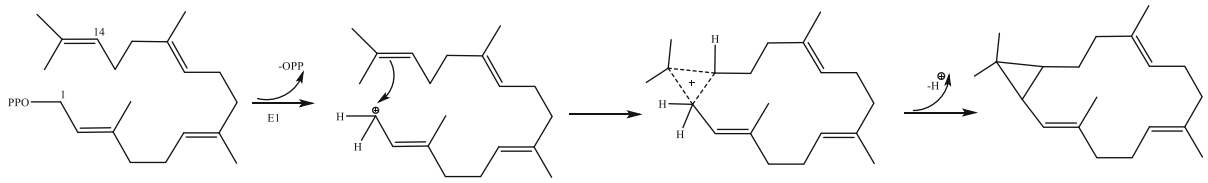


Fig. 3 Sequence of transforming the cembrene to casbene

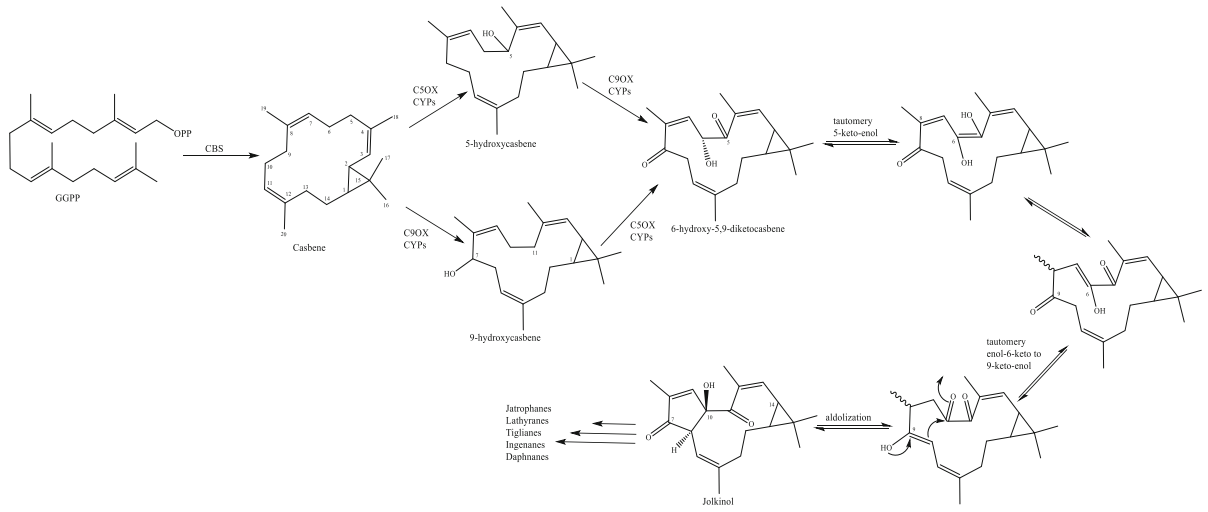


Fig. 4 Proposed pathway for the production of macrocyclic diterpenes in detail

tautomers (9-hydroxy-5,6-diketocabene) may undergo aldolization (King et al. 2016).

Jatrophanes and cyclojatrophanes

Three different biogenetic mechanisms for the formation of the jatrophane framework have already been reported (Fig. 2). Jatrophane is a bicyclic pentadecane skeleton (Fig. 5) without the cyclopropane ring (Evans and Taylor 1983) which is biosynthesized either directly from above mentioned cembrene cation

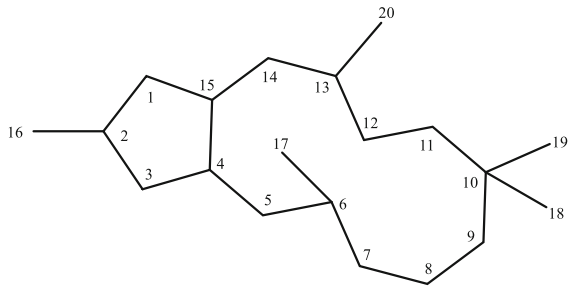


Fig. 5 Jatrophane skeleton

through Wagner-Meerwein rearrangements or through the more likely casbene pathway. In the biosynthesis of jatrophane from casbene rout, casbene precursor is formed first, followed by the opening of the cyclopropane ring, and then closure of the five-membered ring between C-6 and C-10 to form jatrophane core (Fig. 2) (Adolf and Hecker 1977; Lanzotti 2013). According to a different point of view, jatrophanes may be derived from lathyranes by cyclopropane ring being opened (Appendino 2016; Lanzotti 2013).

Final closure of the five-membered ring between C-6 and C-10 would accomplish the biogenetic route toward the jatrophane skeleton. Further functionalization leads to a huge class of natural products with different oxygenation states and stereochemical features. Only a few explanations concerning the biosynthesis of natural products, which are considered to arise from the jatrophane skeleton, have been reported.

In a study reported by Pattenden and Smithies (1996) the mechanism of cyclopropane ring opening in casbene was investigated. Using several radical-mediated reactions with casbene, they found a number of products which are in agreement with compounds

found as metabolites, such as those from the cembrane family. The detailed mechanism, however, is not yet clear. The participation of a "casbene synthetase", which needs a divalent cation such as magnesium, is also discussed in the biosynthetic pathway of casbene (Dueber et al. 1978).

The skeleton-type 1 (15 → 14) abeo-jatrophane with 6/12 membered ring system differs from the jatrophane skeleton with 5/12 membered ring system in the migration of C-15 in its original place C-1–C-15 single bond in jatrophane parent framework to another position. C-1 position remained unchanged and is connected to C-14 in the final structure instead of C-15 in parent structure, leads to conversion of the five-member ring to a six-member ring. The numbering of the structure is also retained unchanged in the new abeo scaffold. Marco et al. reported a pinacol-type rearrangement [13-14] α-ketol (pinacolic) of an oxidized jatrophane in positions 14 and 15 to explain these five to six-member ring extension (Fig. 6) (Marco et al. 1998).

Another class of jatrophanes is 12,17-cyclojatrophanes with 5/8/8 membered ring system. A proposed biogenetic pathway for the rare 12,17-cyclojatrophanes has been illustrated in Fig. 7. It appears that Jatrophanes (119–122) are biogenetically interrelated. In this regards, the 11,12-epoxidation of a favorable Δ6(17), Δ11-jatrophane precursor results in epoxiwelwitschene whose epoxide ring can undergo a nucleophilic attack in two different ways. Epoxy ring-opening by the 15-hydroxyl group nucleophilic attack causes the formation of a tetrahydrofuran ring, leading to welwitschene (route b) with 12,17-cyclojatrophane structure. In a second way, the attack by the 6(17)-exomethylene gives rise to a 12,17-transannular cyclization (route a). This 12,17-cyclojatrophane intermediate would then subsequently go through dehydration at C-11. Epoxidation of the resulting double bond and oxidation at C-2 affords salicifoline which is another rare structural feature of euphowelwitschine A and has been isolated from *Euphorbia salicifolia* to date (route c) (Hohmann et al. 2001b). Euphowelwitschines A and B supposed to be formed via epoxide ring-opening by the free hydroxyl at C-15 (route d) (Fig. 7) (Reis et al. 2015). This 12,15-ether bridge is not common in macrocyclic jatrophanes; the only compounds that have such functionality were isolated exclusively from *Euphorbia helioscopia* (Kosemura et al. 1985; Lu et al. 2008; Yamamura et al. 1989).

Another type of cyclojatrophane is 9,13-cyclojatrophane with an architecturally novel (5.9.5) tricyclic framework named jatrophatrione. It was isolated from the chloroform extract of *Jatropha macrorhiza* roots. It was recognized by the University of Arizona team as a tumor-inhibitory agent being particularly active toward the P-388 (3PS) lymphocytic leukemia assay (Torrance et al. 1976). An isomeric compound, citlalitrione, has subsequently been reported from *Jatropha dioica* (Villarreal et al. 1988), but its bioactivity has not been evaluated. Jatrophatrione may be derived in nature from the bicyclic precursor illustrated its formation through the biosynthetic route of casbene origin as discussed before (Fig. 8) (Torrance et al. 1976).

Further functionalization leads to a huge class of natural products with different oxygenation states and stereochemical features. Jatrophane diterpenes occur generally in form of polyesters. They are mainly polyacylated derivatives whose number of ester moieties is ranging between three (guyonianin E) (Hegazy et al. 2010) and eight (esulatin H) (Vasas et al. 2011). The acyl residues are frequently acetyl, propionyl, butanoyl, isobutanoyl, 2-methylbutanoyl, angeloyl, tigloyl, benzoyl, nicotinoyl, or rarely cinnamoyl. Depending on their substitution, jatrophanes may

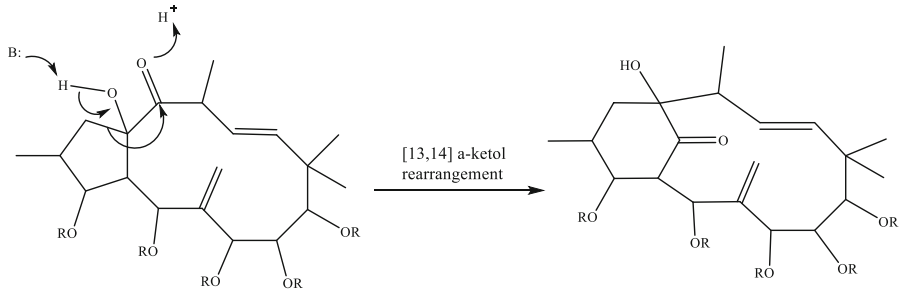


Fig. 6 Pinacol-type rearrangement of a jatrophane to 1(15 → 14) abeo-jatrophane skeleton

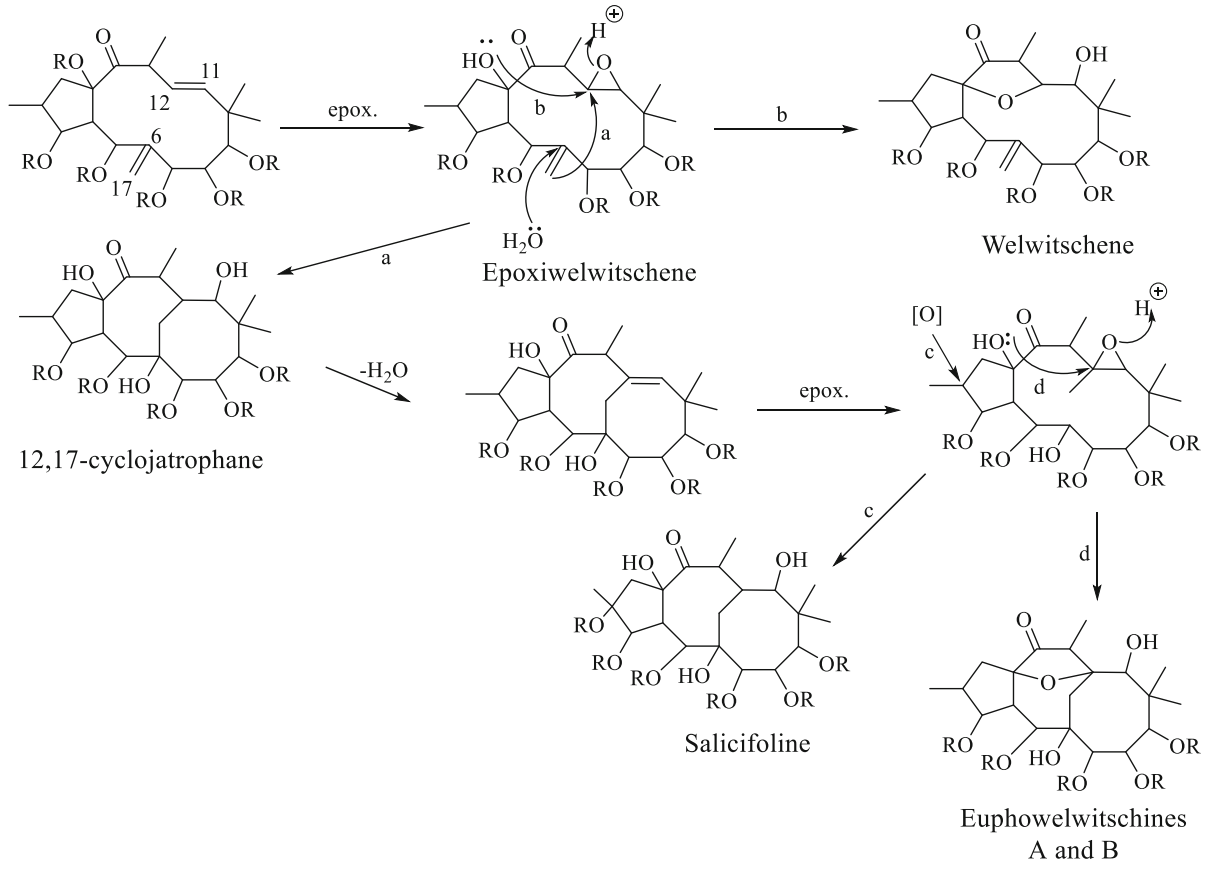


Fig. 7 Proposed biogenetic pathway for 12,17-cyclojatrophanes

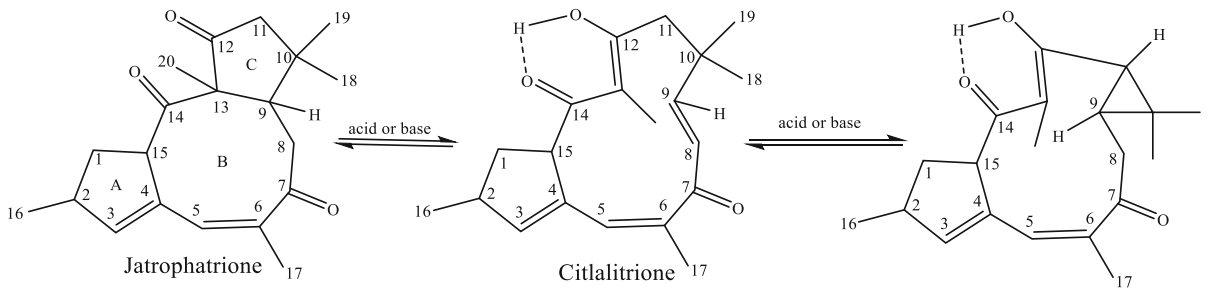


Fig. 8 Proposed biogenetic pathway for 9,13-cyclojatrophanes

have 5 to 10 chiral centers and since the configuration of the carbons is variable, jatrophanes do not form a stereochemically homogeneous series. Other structural variabilities arised from the number and position of the double bonds, the nature and number of oxygen functions (hydroxy, keto, epoxy, ether or ester groups) and the configuration of the diterpene core.

Segetane diterpenoids

The segetane diterpenoids are the main constituents of *Euphorbia segetalis* (Jakupovic et al. 1998a), a species that the name of the entire skeletal class had originated from it. Segetanes had been isolated from *E. peplus* (Wan et al. 2016a) and *E. portlandica* (Madureira et al. 2006) and *E. paralias* grown in Turkey (Öksüz et al. 1997), Spain (Jakupovic et al. 1998c), Egypt

(Abdelgaleil et al. 2001), and Italy (Barile and Lanzotti 2007). They are characterized by a modified jatrophane skeleton comprising a bicyclo [4.3.1] undecane ring system which could have up to nine chiral centers.

Segetane originates from an appropriate jatrophane skeleton through cyclization steps that occurred on the unprecedented tricyclic skeleton found for pre-segetanin as a possible intermediate supposed by Jakupovic (Jakupovic et al. 1998a) (Fig. 9). In general, segetanes can be derived from an epoxidized jatrophane in Δ6(17). Extant vinyl alcohol is followed by a complete cycle expansion which can be illustrated by an enzymatic epoxidation Δ6(17) followed by an acid-catalyzed opening of this epoxide ring (Fig. 9).

Unlike the aforementioned biosynthesis proposed by Barile et al. (2007) and previously by Jakupovic et al. (1998a, b, c) that the segetane tetracyclic skeleton was formed by a two-steps cyclization of jatrophane derivative, Wan et al. (2016b) found that an intermediate with four double bonds is a precursor of segetanes. Through this biosynthetic pathway, the intermediate bearing four double bonds is formed by an elimination reaction on a proper jatrophane; after that this intermediate can be transformed into a segetane via a Diels–Alder reaction in the presence of a Lewis base and/or a Lewis acid (Fig. 10). The study of the generalization of this reaction proved that the presence of a carbonyl at C-9 and lack of substitution at C-8 are indispensable to the formation of a segetane skeleton from a jatrophane skeleton (Wan et al. 2016b).

Pepluane and paraliane

Both pepluane and paraliane diterpenes are based on a fused tetracyclic core originated from further rearrangements of an proper jatrophane (Fig. 11) (Jakupovic et al. 1998c). The paraliane skeletones isolated for the first time from *Euphorbia paralias* in 1998 are rare 5/6/5/5 tetracyclic systems, probably formed through a transannular ring-closing reaction of the jatrophane diterpene (a jatropha-6(l7),12-diene) resulting in a 5/6/5/5-ring system. This hypothesis is supported by the fact that jatrophanes are systematically co-isolated (Zhou et al. 2016). The introduction of primary alcohol on gem-dimethyl followed by a complete cycle expansion results in the formation of the peplus skeleton (5/6/5/6). The acetylated vicinal diol (C-8 and C-9) found in all known pepluans, can be explained by an enzymatic epoxidation in Δ8(9) followed by an opening of the epoxide as shown in Fig. 11 (Hohmann et al. 1999a; Jakupovic et al. 1998c).

Terracinolide diterpenes

Terracinolide is another diterpene skeleton based on a modified jatrophane skeleton. These compounds display a 17-ethyl bis-homojatrophane (C_{22}) framework, a skeleton previously found in *E. terracina* diterpenes (Marco et al. 1996), that gave the name to the entire skeletal class. The terracinolide skeleton bearing an additional two-carbon segment bound to C-17 in the framework of a δ-lactone ring. This attachment of a two-carbon fragment to C-17 could arise from the opening of a 5,17-epoxide by nucleophilic attack on a C_2 unit (acetate or malonate) followed by cyclization with a proximate hydroxyl group to give a δ-lactone ring (Marco et al. 1997) (Fig. 12).

Structures of isolated compounds

A tremendous number of jatrophane diterpenoids including twelve-membered ring jatrophanes, 5/8/8 fused ring systems, rearranged polycyclic jatrophanes, and terracinolides have been isolated and reported from 1984 to 2019 which are arranged in order of chemical structure in Table 1.

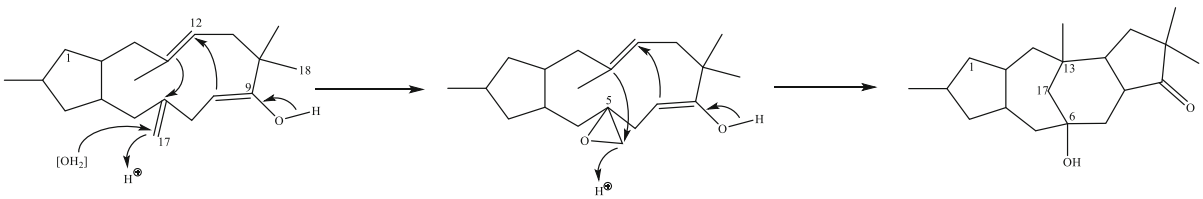


Fig. 9 First proposed biogenesis route for segetane diterpenoids

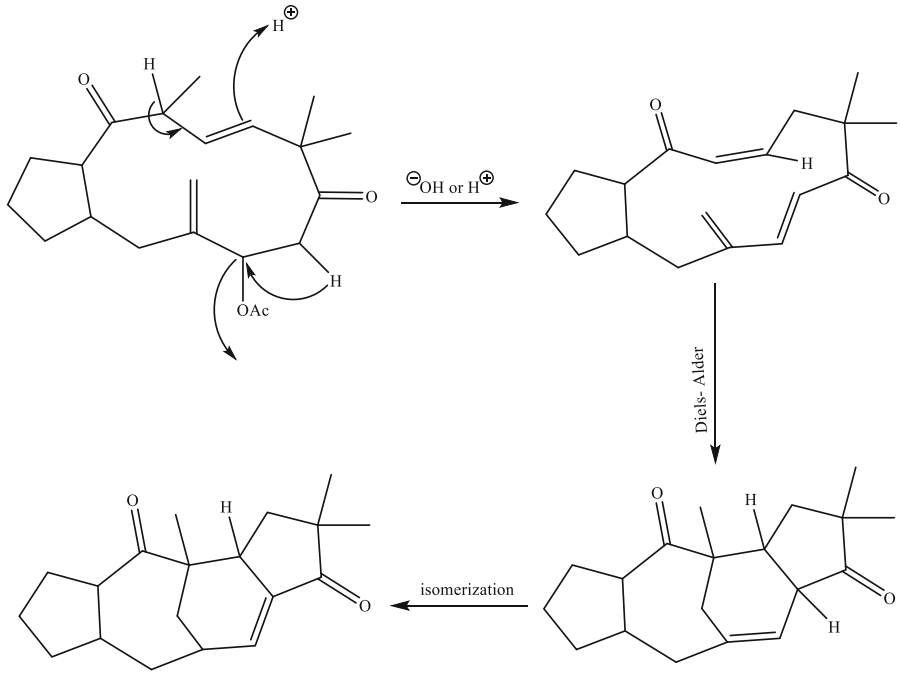


Fig. 10 Second proposed biogenesis route for segetane diterpenoids

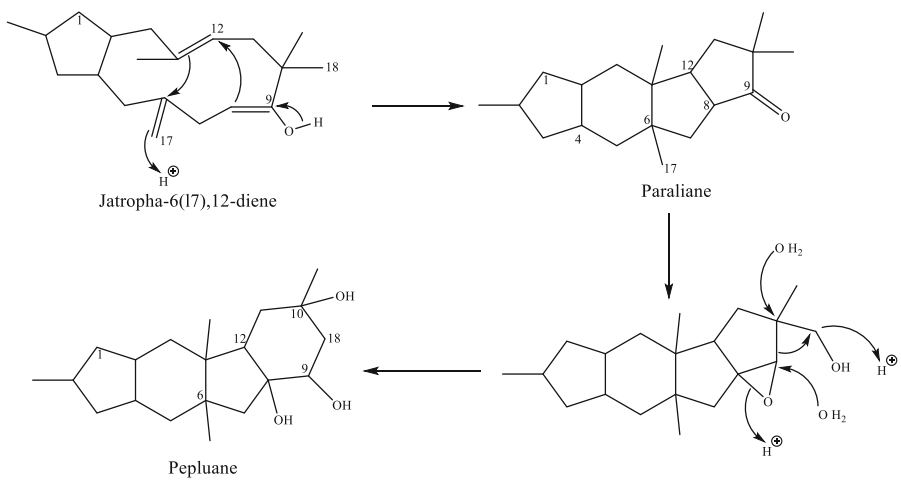


Fig. 11 Biogenesis route of Pepluane and paraliane diterpenoids

It is worth mentioning that the flexibility of the twelve-membered ring can adopt two main conformations: *endo*- and *exo*-type depending on the spatial orientation of the 6,17 *exo*-methylene group (Appendino et al. 1998; Jakupovic et al. 1998b, c; Marco et al. 1998). It is also reported that the conformational option depends on the acylation pattern on the jatrophane core (Corea et al. 2005a; Esposito et al. 2016; Günther et al. 1998). Diagnostic spectral features to discriminate between the two conformations are the $^{3}J_{4,5}$ value and spatial close NOESY correlations (Appendino et al. 1998; Corea et al. 2005a; Jakupovic et al. 1998c). The large $^{3}J_{4,5}$ = 9–11 Hz coupling and the existence of a diagnostic NOESY cross-peak between H-5 and H-17, due to the perpendicular orientation of the exomethylene group to the mean plane of the macrocycle would advocate for a perpendicular *endo*-type conformation whereas small $^{3}J_{4,5}$ = 0–4 Hz coupling and interactions between H-4/H-7 and H-5/H-8 along with no interaction between H-5 or H-7 and the exomethylenic H-17 could indicate a parallel *exo*-type

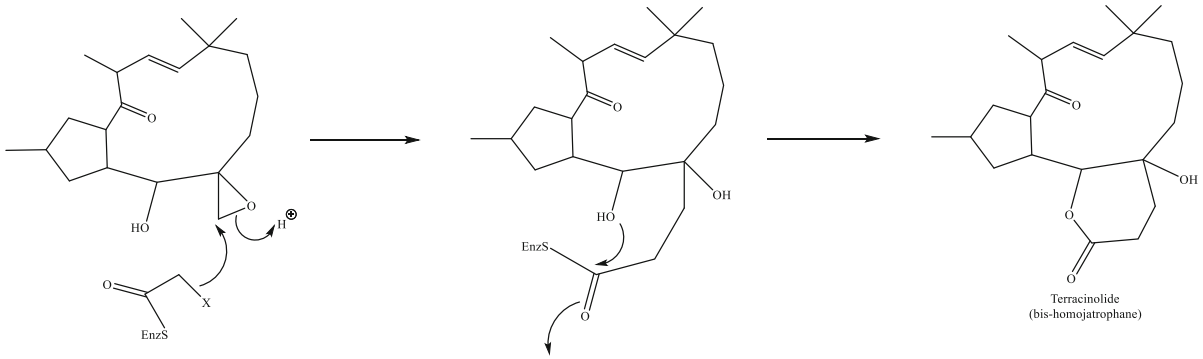


Fig. 12 Biogenesis of terracinolides by incorporation of a C_2 unit (from acetate or malonate) into jatrophane precursor

conformation (Appendino et al. 1998;Jakupovic et al. 1998a, b, c; Marco et al. 1998). For jatrophanes, conformational flexibility was reported to be important for P-gp modulation, since molecules with the macrocyclic jatrophane-type twelve-membered ring scaffold were generally found to be more active than the 5/8/8 fused ring systems like welwitschines A and B. Similar observations were also found for rearranged polycyclic jatrophanes like segetane, paraliane and pepluane skeletons showing a lower P-gp modulatory efficiency when compared to molecules with the macrocyclic jatrophane-type scaffold (Ferreira et al. 2014; Reis et al. 2012).

Isolation of diterpenes

Diterpenes are generally isolated from various *Euphorbia* species by similar protocols. All parts of the plants may accumulate diterpenoids. The roots, leaves, stems, fruits, seeds and the whole plant are equally studied. Furthermore, *Euphorbia* plants are known to produce white irritant latex-containing different metabolites such as macrocyclic diterpenoids (Nothias-Scaglia et al. 2014, 2015a, c) and hence, it is commonly investigated as well (Fattorusso et al. 2002; Shi et al. 2008; Vasas and Hohmann 2014). In general, extraction of the plant materials performs at room temperature by maceration. The extracts are evaporated at reduced pressure at 40 °C. Since the plants produce complex mixtures of structurally-related analogues whose core is the same and are differed from each other by the substitution pattern, then their isolation requires a multistep separation protocol. Mustafa Ghanadian and coworkers developed a five-step method for isolation and purification of macrocyclic diterpenes in nine *Euphorbia* species. The sample preparation includes: (A) the percolation or maceration of powdered plant material with CH_2Cl_2:-acetone (2:1) at room temperature, (B) extract is suspended in MeOH:H2O (75:25) after concentration and subjected to vacuum filtration using a porcelain Buchner funnel with a vacuum pump and a large glass funnel filter with fritted sintered glass disc containing RP-18 adsorbent or silica gel pregnated with paraffin (15%), eluting with MeOH:H2O (75:25) as solvent, (C) the defatted fraction which is rich in diterpenoids and free from dark green chlorophylls and fats, is concentrated and loaded on the gravity silica gel column using mixtures comprising hexane: EtOAc of increasing polarity, D) resultant fractions being rich in macrocyclic diterpenoids are selected based on primary ^{1}H-NMR analysis and are subjected to Sephadex LH-20 eluting by hexane:acetone:MeOH (30:10:60) to remove remaining chlorophyll and unwanted materials and to gain crude diterpenoidal subfraction. The concentrated fractions are screened by TLC using hexane:acetone (6:4) and (7:3) as mobile phases. TLCs are Sprayed by concentrated serium sulphate 1% in sulfuric acid 10% followed by heating at 105 °C for the visualization of the polyester diterpene spots visulalized in dark brown color spots with Rf values of 0.2–0.7. E) Fractions which are rich in diterpenes are subjected on silica prep HPLC column (20 × 250 mm, 5 µm) using hexane:EtOAc in stepwise gradient solvent system (90:10; 85:15; 80:20; 75:25; 70:30) as final purification (Ayatollahi et al. 2010a, b, Ghanadian et al. 2013, 2015; Zolfaghari et al. 2016).

Table 1 Isolated jatrophane diterpenoids

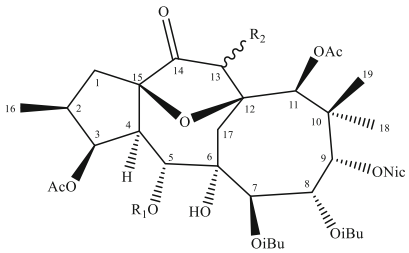
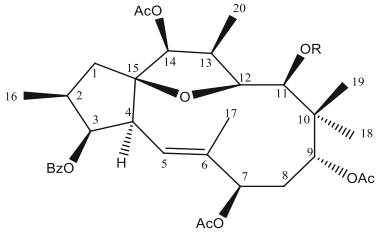
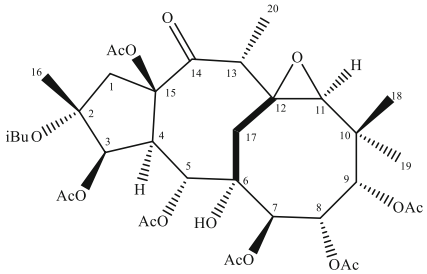
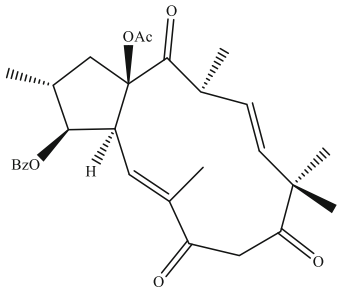
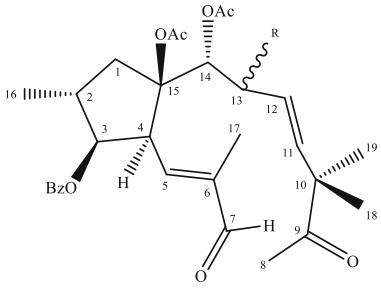
Isolated compound	Substitute (Common name)	Plant	References
	1. R_1 = Ac, R_2 = α-CH_3 (euphowelwitschine A) 2. R_1 = H, R_2 = β-CH_3 (euphowelwitschine B)	*E. welwitschii*	Reis et al. (2015)
	3. R = H 4. R = Ac	*E. helioscopia*	Lu et al. (2008)
	5. (salicifoline)	*E. salicifolia*	Hohmann et al. (2001b)
	6. (helioscopianoid G)	*E. helioscopia*	Mai et al. (2018b)
	7. (heliojatrone B)	*E. helioscopia*	Mai et al. (2018a)
	8. R = β-CH_3 (secoheliosphane A) 9. R = α-CH_3 (secoheliosphane B)	*E. helioscopia*	Mai et al. (2017b)

Table 1 continued

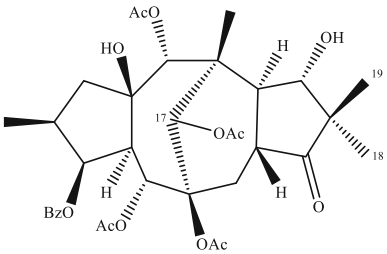
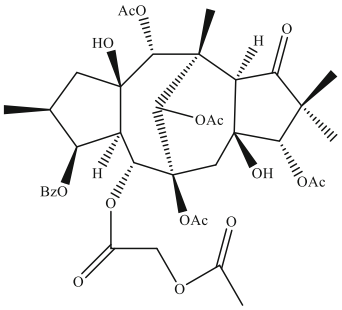
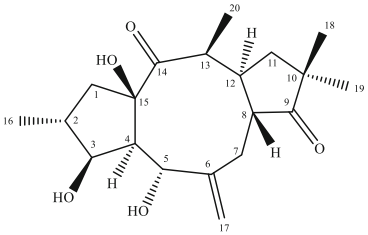
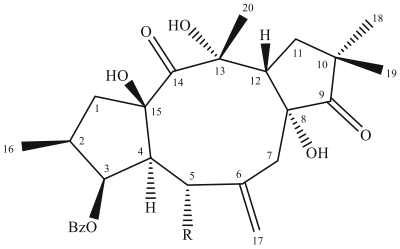
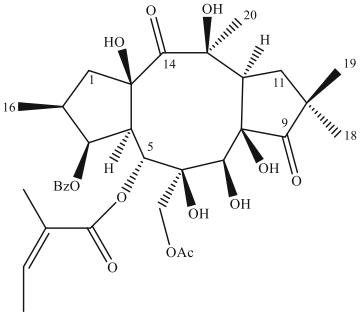
Isolated compound	Substitute (Common name)	Plant	References
	10. (segetanin A)	*E. paralias*	Barile and Lanzotti (2007)
	11. (segetanin B)	*E. paralias*	Barile and Lanzotti (2007)
	12.	*E. helioscopia*	Li et al. (2018a)
	13. R = diMeBuO (euphorbesulin A) 14. R = OBz (euphorbesulin B) 15. R = OAc (euphorbesulin C)	*E. esula*	Zhou et al. (2016)
	16. (pre-segetanin)	*E. paralias*	Barile and Lanzotti (2007)

Table 1 continued

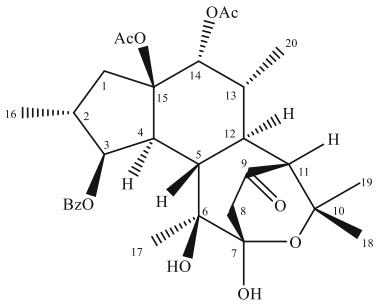
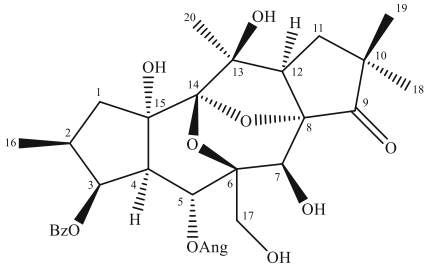
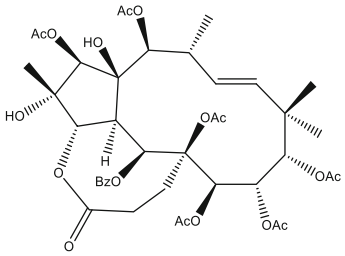
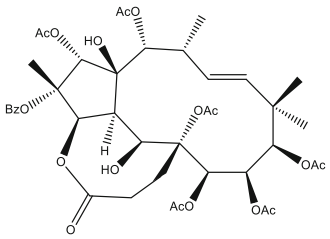
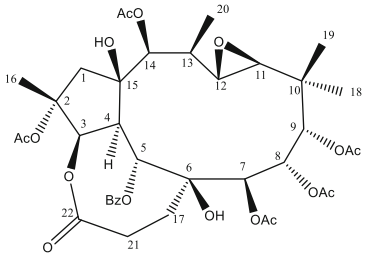
Isolated compound	Substitute (Common name)	Plant	References
	17. (secoheliospholane A)	*E. helioscopia*	Mai et al. (2017b)
	18.	*E. segetalis*	Jakupovic et al. (1998a)
	19. (sororianolide A)	*E. sororia*	Huang and Aisa (2010b)
	20. (sororianolide C)	*E. sororia*	Huang and Aisa (2010b)
	21. (guyonianin F)	*E. guyoniana*	Hegazy et al. (2010)

Table 1 continued

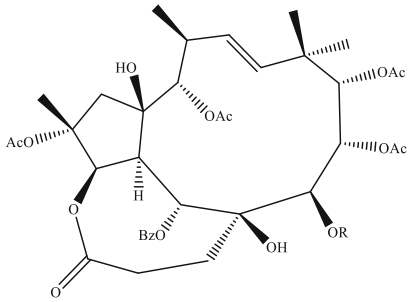
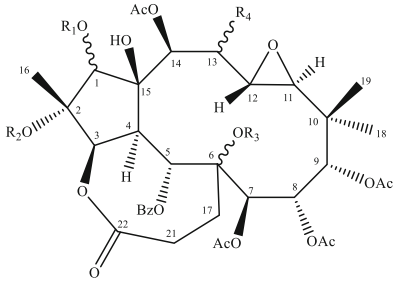
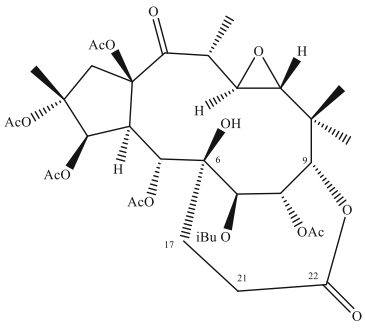
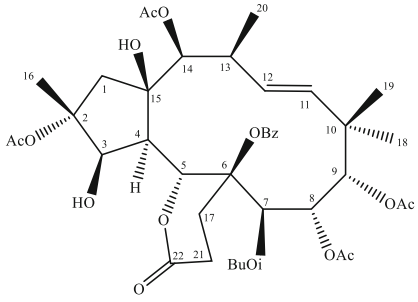
Isolated compound	Substitute (Common name)	Plant	References
	22. R = iBu (isoterracinolide A) 23. R = Pr (isoterracinolide B)	*E. terracina*	Marco et al. (1999b)
	24. R_1 = β-Ac, R_2 = Ac, R_3 = β-H, R_4 = β-CH_3	*E. sororia*	Hu et al. (2018)
	25. R_1 = α-Ac, R_2 = H, R_3 = α-Ac, R_4 = α-CH_3 (sororianolide B)	*E. sororia*	Huang and Aisa (2010b)
	26. (salicinolide)	*E. salicifolia*	Hohmann et al. (2001b)
	27.	*E. sororia*	Hu et al. (2018)

Table 1 continued

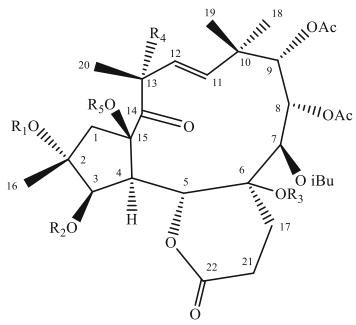
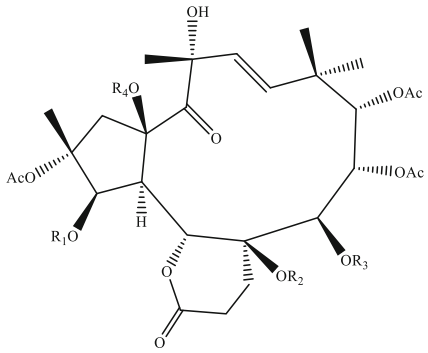
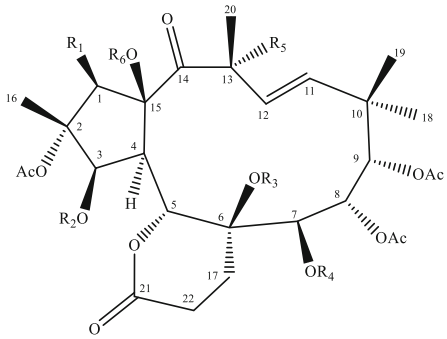
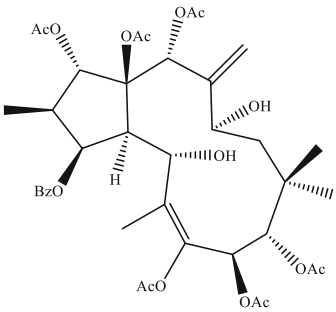
Isolated compound	Substitute (Common name)	Plant	References
	28. R_1 = Ac, R_2 = Ac, R_3 = Ac, R_4 = OH, R_5 = H (13α-hydroxyterracinolide G)	*E. dendroides*	Esposito et al. (2016)
	29. R_1 = Ac, R_2 = Ac, R_3 = Ac, R_4 = OH, R_5 = Ac		
	30. R_1 = Ac, R_2 = Ac, R_3 = iBu, R_4 = H, R_5 = H		
	31. R_1 = Ac, R_2 = H, R_3 = Ac, R_4 = H, R_5 = Ac		
	32. R_1 = Ac, R_2 = Ac, R_3 = iBu, R_4 = H, R_5 = H (terracinolide J)	*E. dendroides*	Corea et al. (2003b)
	33. R_1 = H, R_2 = Ac, R_3 = Ac, R_4 = H, R_5 = Ac (terracinolide K)		
	34. R_1 = H, R_2 = Ac, R_3 = iBu, R_4 = H, R_5 = Ac (terracinolide L)		
	35. R_1 = Ac, R_2 = iBu, R_3 = iBu, R_4 = Ac (13α-OH terracinolide F)	*E. dendroides*	Corea et al. (2003b)
	36. R_1 = Ac, R_2 = Ac, R_3 = iBu, R_4 = H	*E. terracina*	Marco et al. (1999b)
	37. R_1 = Ac, R_2 = Bz, R_3 = iBu, R_4 = H		
	38. R_1 = H, R_2 = Ac, R_3 = iBu, R_4 = Ac (terracinolide C)	*E. terracina*	Marco et al. (1997)
	39. R_1 = Ac, R_2 = Bz, R_3 = Ac, R_4 = Ac (terracinolide D)		
	40. R_1 = Ac, R_2 = Bz, R_3 = Pr, R_4 = Ac (terracinolide E)		
	41. R_1 = Ac, R_2 = iBu, R_3 = iBu, R_4 = Ac (terracinolide F)		
	42. R_1 = Ac, R_2 = Ac, R_3 = iBu, R_4 = H (terracinolide G)		
	43. R_1 = Ac, R_2 = Bz, R_3 = iBu, R_4 = Ac (terracinolide A)	*E. terracina*	Marco et al. (1996)
	44. R_1 = Ac, R_2 = Ac, R_3 = iBu, R_4 = Ac (terracinolide B)		
	45. R_1 = H, R_2 = H, R_3 = iBu, R_4 = iBu, R_5 = H, R_6 = Ac (terracinolide H)	*E. segetalis*	Jakupovic et al. (1998a)
	46. R_1 = OAc, R_2 = Ac, R_3 = Ac, R_4 = iBu, R_5 = H, R_6 = H (terracinolide I)		
	47. R_1 = H, R_2 = Ac, R_3 = Ac, R_4 = iBu, R_5 = OH, R_6 = Ac (13α-hydroxyterracinolide B)		
	48. R_1 = OAc, R_2 = Ac, R_3 = Ac, R_4 = iBu, R_5 = OH, R_6 = H (13α-hydroxyterracinolide I)		
	49.	*Pedilanthus tithymaloides*	Zhu et al. (2016)

Table 1 continued

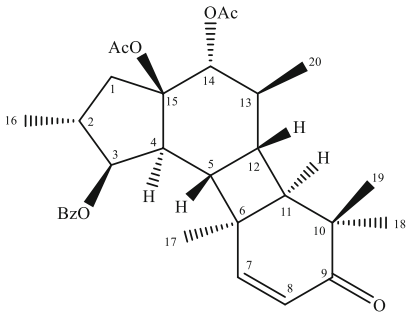
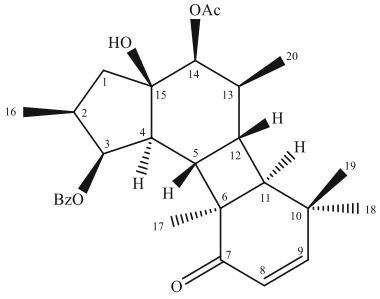
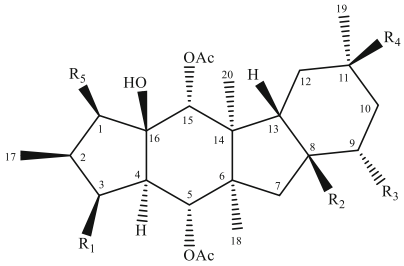
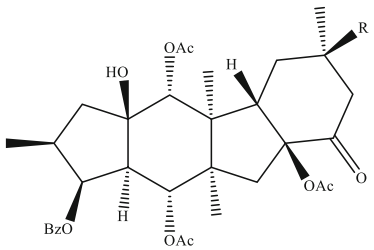
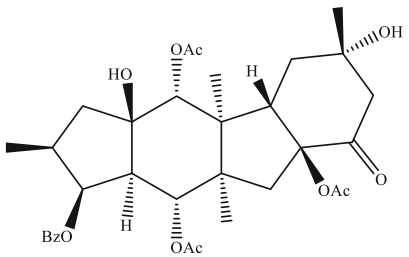
Isolated compound	Substitute (Common name)	Plant	References
	50. (heliosterpenoid A)	*E. helioscopia*	Mai et al. (2017a)
	51. (heliosterpenoid B)	*E. helioscopia*	Mai et al. (2017a)
	52. R_1 = OBz, R_2 = OAc, R_3 = OH, R_4 = OH, R_5 = H (pepluanol A) 53. R_1 = OBz, R_2 = OH, R_3 = OAc, R_4 = OH, R_5 = H (pepluanol B) 54. R_1 = OH, R_2 = OAc, R_3 = OAc, R_4 = OH, R_5 = H (pepluanol C) 55. R_1 = OBz, R_2 = OAc, R_3 = OAc, R_4 = OH, R_5 = OAc (pepluanol D)	*E. peplus*	Wan et al. (2016a)
	56. R = OH (pepluanol E)	*E. peplus*	Wan et al. (2016a)
	57. R = OAc (pepluanone)	*E. peplus*	Corea et al. (2005b)
	58. (pepluanol F)	*E. peplus*	Wan et al. (2016a)

Table 1 continued

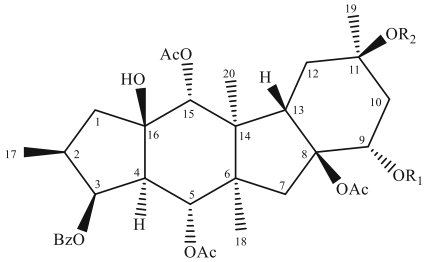
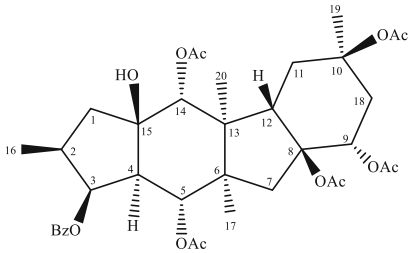
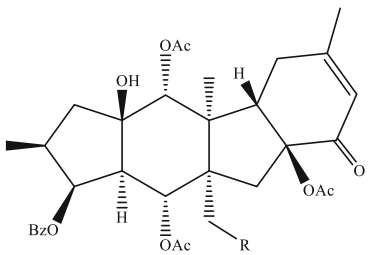
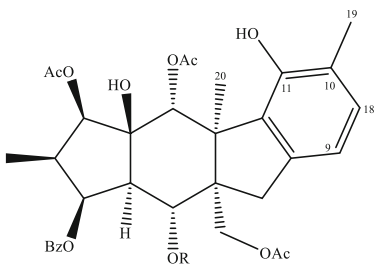
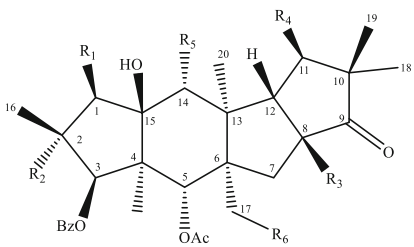
Isolated compound	Substitute (Common name)	Plant	References
	59. R_1 = H, R_2 = Ac	*E. peplus*	Hohmann et al. (2000a)
	60. R_1 = Ac, R_2 = H	*E. peplus*	Hohmann et al. (1999a)
	61.	*E. peplus*	Jakupovic et al. (1998b)
	62. R = H (pepluanol G) 63. R = OAc (pepluanol H)	*E. peplus*	Wan et al. (2016a)
	64. R = H (pepluene)	*E. paralias*	Barile et al. (2007)
	65. R = Ac	*E. segetalis*	Jakupovic et al. (1998a)
	66. R_1 = H, R_2 = H, R_3 = OH, R_4 = H, R_5 = OAc, R_6 = H (paralianone A)	*E. peplus*	Wan et al. (2016a)
	67. R_1 = H, R_2 = H, R_3 = OAc, R_4 = H, R_5 = OAc, R_6 = OAc (paralianone B)		
	68. R_1 = H, R_2 = H, R_3 = H, R_4 = H, R_5 = OAc, R_6 = H (paralianone C)		
	69. R_1 = H, R_2 = H, R_3 = H, R_4 = H, R_5 ==O, R_6 = H (paralianone D)		
	70. R_1 = H, R_2 = H, R_3 = H, R_4 = H, R_5 ==O, R_6 = Ac (euphorbesulin O)	*E. esula*	Zhou et al. (2016)
	71. R_1 = OAc, R_2 = H, R_3 = H, R_4 = OH, R_5 = OAc, R_6 = Ac (paralianone)	*E. paralias*	Barile et al. (2007)
	72. R_1 = H, R_2 = H, R_3 = OAc, R_4 = H, R_5 = OAc, R_6 = H	*E. paralias*	Jakupovic et al. (1998c)
	73. R_1 = OAc, R_2 = H, R_3 = OAc, R_4 = H, R_5 = OAc, R_6 = H	*E. segetalis*	Jakupovic et al. (1998a)
	74. R_1 = OAc, R_2 = H, R_3 = H, R_4 = H, R_5 = OAc, R_6 = H		

Table 1 continued

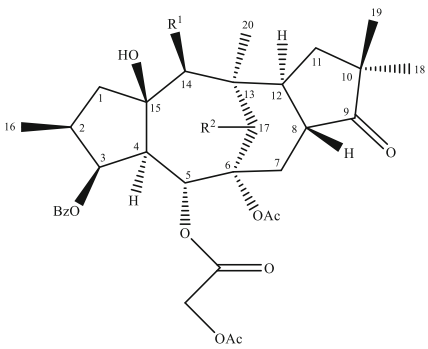
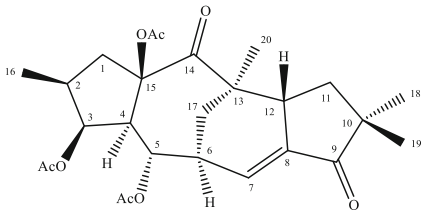
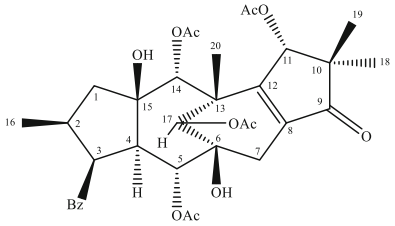
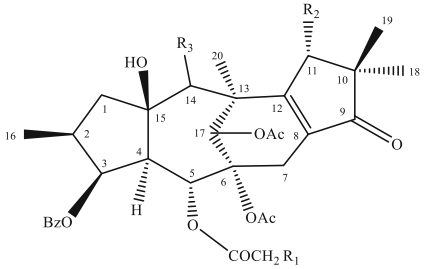
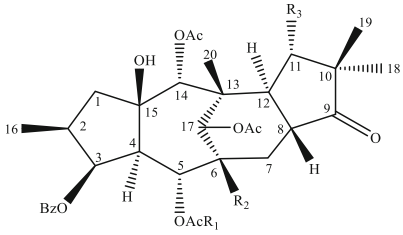
Isolated compound	Substitute (Common name)	Plant	References
	75. R_1 = H, R_2 = OAc, R_3 = H, R_4 = H, R_5 = OAc, R_6 = H 76. R_1 = OAc, R_2 = H, R_3 = H, R_4 = H, R_5 = OAc, R_6 = OAc		
	77. R_1 = β-OAc, R_2 = H	*E. taurinensis*	Rédei et al. (2018)
	78.	*E. peplus*	Wan et al. (2016a)
	79. (euphoportlandol A)	*E. portlandica*	Madureira et al. (2006)
	80. R_1 = H, R_2 = OAc, R_3 = β-OAc (segetane A) 81. R_1 = OAc, R_2 = H, R_3 = α-OAc (segetane B)	*E. paralias*	Abdelgaleil et al. (2001)
	82. R_1 = OAc, R_2 = OAc, R_3 = H 83. R_1 = OAc, R_2 = OAc, R_3 = OAc 84. R_1 = OH, R_2 = OAc, R_3 = H	*E. segetalis*	Jakupovic et al. (1998a)
	85. R_1 = H, R_2 = OH, R_3 = OAc (euphoportlandol B)	*E. portlandica*	Madureira et al. (2006)

Table 1 continued

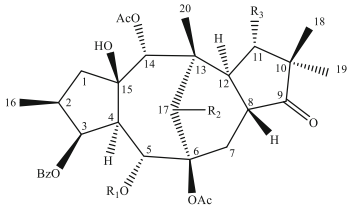
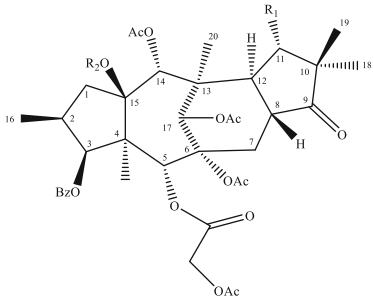
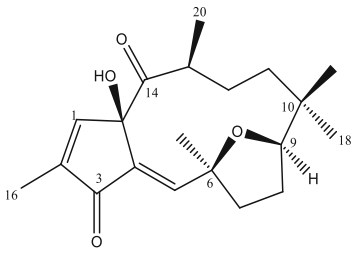
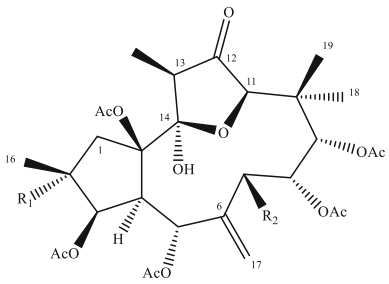
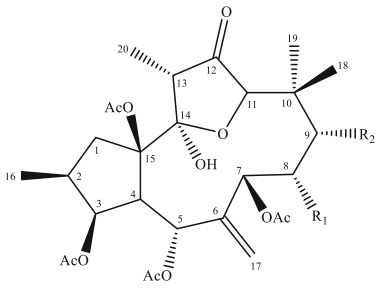
Isolated compound	Substitute (Common name)	Plant	References
	86. R_1 = AcOAc, R_2 = H, R_3 = OAc 87. R_1 = Ac, R_2 = OAc, R_3 = OAc	*E. paralias*	Jakupovic et al. (1998c)
	88. R_1 = R_2 = H (paralinone A) 89. R_1 = OAc, R_2 = H (paralinone B)	*E. paralias*	Öksüz et al. (1997)
	90. (japodagrone)	*J. podagrica*	Aiyelaagbe et al. (2007)
	91. R_1 = H, R_2 = OAc 92. R_1 = OAc, R_2 = OiBu (esulatin C)	*E. esula* *E. esula*	Liu et al. (2002) Hohmann et al. (1997)
	93. R_1 = ONic, R_2 = OAc 94. R_1 = OAc, R_2 = ONic 95. R_1 = OBz, R_2 = OAc (kansuinin A)	*E. kansui* *E. kansui*	Jin-Jun et al. (2017) Wang et al. (2002)

Table 1 continued

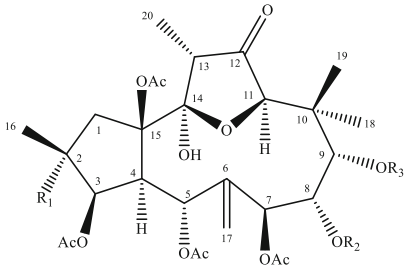
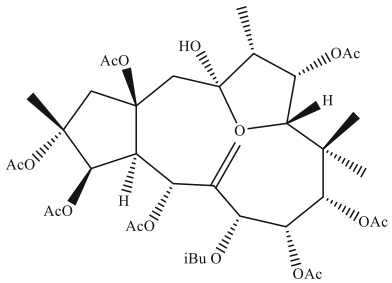
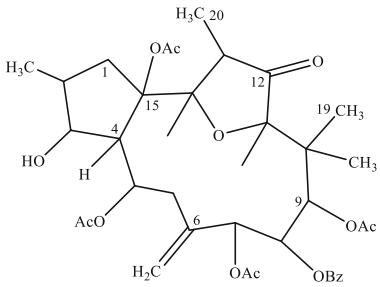
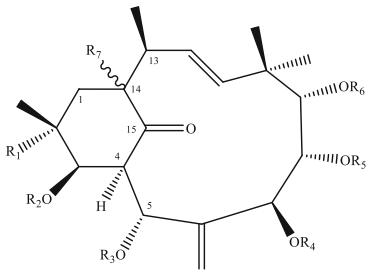
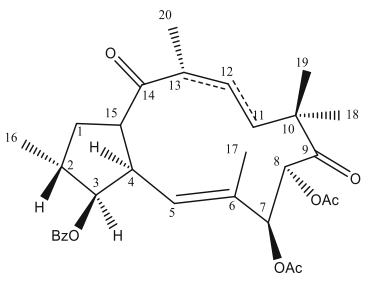
Isolated compound	Substitute (Common name)	Plant	References
	96. R_1 = OH, R_2 = Bz, R_3 = Ac (kansuinin H) 97. R_1 = H, R_2 = Bz, R_3 = Nic (kansuinin D) 98. R_1 = H, R_2 = MeBu, R_3 = Ac (kansuinin J)	*E. kansui* *E. kansui*	Pan et al. (2004) Guo et al. (2010)
	99. (esulatin H)	*E. esula*	Vasas et al. (2011)
	100. (esulol A)	*E. esula*	Sekine et al. (1998)
	101. R_1 = H, R_2 = H, R_3 = MeBu, R_4 = iBu, R_5 = MeBu, 102. R_6 = H, R_7 = 14β-OH 103. R_1 = OH, R_2 = Ac, R_3 = iBu, R_4 = Bz, R_5 = Ac, R_6 = Ac, R_7 = 14β-OH (abeodendroidin F) 104. R_1 = OH, R_2 = Ac, R_3 = iBu, R_4 = Bz, R_5 = Ac, R_6 = Ac, R_7 = 14α-OH (epiabeodendroidin F)	*E. terracina* *E. dendroides* 	Marco et al. (1998) Corea et al. (2003b)
	104. $\Delta_{11,12}$ (euphoscopin M) 105. $\Delta_{12,13}$ (euphoscopin N)	*E. helioscopia*	Barile et al. (2008a)

Table 1 continued

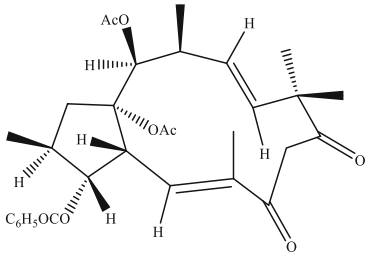
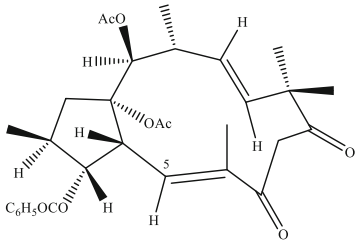
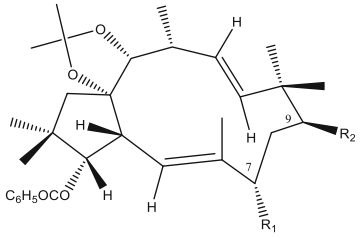
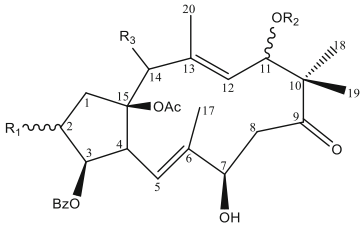
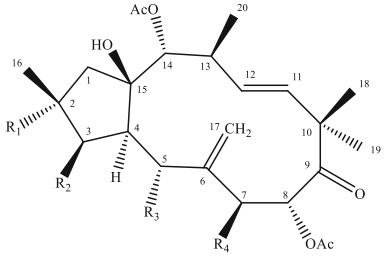
Isolated compound	Substitute (Common name)	Plant	References
	106. (euphoscopin D)	*E. helioscopia*	Yamamura et al. (1989)
	107. (epieuphoscopin D)	*E. helioscopia*	Yamamura et al. (1989)
	108. $R_1 = R_2 = Ac$ 109. $R_1 = R_2 = H$ 110. $R_1 = COC_6H_4Br\text{-}p$, $R_2 = H$ 111. $R_1 = Ac$, $R_2 = H$ 112. $R_1 = H$, $R_2 = Ac$ 113. $R_1 = OAc$, $R_2 = =O$	*E. helioscopia*	Yamamura et al. (1989)
	114. $R_1 = \beta\text{-}CH_3$, $R_2 = \alpha\text{-}H$, $R_3 = = O$ (euphoheliosnoid D)	*E. helioscopia*	Zhang and Guo (2006)
	115. $R_1 = \alpha\text{-}CH_3$, $R_2 = \beta$ -H, $R_3 = \alpha\text{-}OAc$ (euphoheliosnoid C)	*E. helioscopia*	Zhang and Guo (2005)
	116. $R_1 = OAc$, $R_2 = OBz$, $R_3 = OH$, $R_4 = OAc$	*E. glomerulans*	Hasan et al. (2019)
	117. $R_1 = OH$, $R_2 = OBz$, $R_3 = OH$, $R_4 = OBz$		
	118. $R_1 = OAc$, $R_2 = OH.$, $R_3 = OBz$, $R_4 = OAc$	*E. exigua*	Rédei et al. (2015)

Table 1 continued

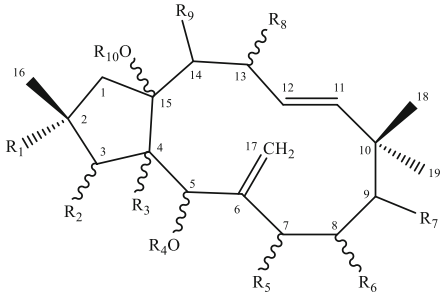
Isolated compound	Substitute (Common name)	Plant	References
	119. R_1 = OAc, R_2 = β-OBz, R_3 = α-H, R_4 = α-H, R_5 = β-OAc, R_6 = α-OAc, R_7 = = O, R_8 = β-CH_3, R_9 = α-OAc, R_{10} = β-H	*E. exigua*	Rédei et al. (2015)
	120. R_1 = OH, R_2 = β-OBz, R_3 = α-H, R_4 = α-H, R_5 = β-OBz, R_6 = α-OAc, R_7 = = O, R_8 = β-CH_3, R_9 = α-OAc, R_{10} = β-H		
	121. R_1 = OAc, R_2 = β-OH, R_3 = α-H, R_4 = α-Bz, R_5 = β-OAc, R_6 = α-OAc, R_7 = = O, R_8 = β-CH_3, R_9 = α-OAc, R_{10} = β-H	*E. exigua*	Rédei et al. (2015)
	122. R_1 = H, R_2 = α-OBz, R_3 = α-OH, R_4 = α-Ac, R_5 = H, R_6 = α-OAc, R_7 = = O, R_8 = α-CH_3, R_9 = = O, R_{10} = β-Ac (euphopubescenol)	*E. pubescens*	Valente et al. (2004b)
	123. R_1 = H, R_2 = β-OBz, R_3 = α-OH, R_4 = α-Ac, R_5 = H, R_6 = β-OAc, R_7 = = O, R_8 = α-CH_3, R_9 = = O, R_{10} = β-Ac (pubescenol)	*E. pubescens*	Valente et al. (2004c)
	124. R_1 = H, R_2 = β-OBz, R_3 = α-H, R_4 = α-Ac, R_5 = β-OAc, R_6 = α-H, R_7 = = O, R_8 = β-CH_3, R_9 = = O, R_{10} = β-H	*E. mongolica*	Rédei et al. (2012)
	125. R_1 = H, R_2 = β-OBz, R_3 = α-H, R_4 = α-Ac, R_5 = β-Pr, R_6 = α-OAc, R_7 = = O, R_8 = β-CH_3, R_9 = = O, R_{10} = β-H		
	126. R_1 = H, R_2 = β-OBz, R_3 = α-H, R_4 = α-Ac, R_5 = β-OBu, R_6 = α-OAc, R_7 = = O, R_8 = β-CH_3, R_9 = = O, R_{10} = β-H		
	127. R_1 = H, R_2 = β-OBz, R_3 = α-H, R_4 = α-Ac, R_5 = β-iBu, R_6 = α-OAc, R_7 = = O, R_8 = β-CH_3, R_9 = = O, R_{10} = β-H		
	128. R_1 = α-OBz, R_2 = β-OAc, R_3 = α-H, R_4 = α-Ac, R_5 = β-OAc, R_6 = H, R_7 = = O, R_8 = α-CH_3, R_9 = = O, R_{10} = β-Ac (esulatin I)	*E. esula*	Vasas et al. (2011)
	129. R_1 = α-H, R_2 = β-OAc, R_3 = α-H, R_4 = α-Ac, R_5 = β-OiBu, R_6 = H, R_7 = = O, R_8 = α-CH_3, R_9 = = O, R_{10} = β-Ac (esulatin J)		
	130. R_1 = α-H, R_2 = β-OAc, R_3 = α-H, R_4 = α-Bz, R_5 = β-OAc, R_6 = α-OAc, R_7 = = O, R_8 = β-CH_3, R_9 = = O, R_{10} = β-Ac	*E. bungei*	Shokoohinia et al. (2011)
	131. R_1 = α-H, R_2 = β-OAc, R_3 = α-H, R_4 = α-Bz, R_5 = β-OBz, R_6 = α-OAc, R_7 = = O, R_8 = β-CH_3, R_9 = = O, R_{10} = β-Ac		
	132. R_1 = α-ONic, R_2 = β-OAc, R_3 = α-H, R_4 = α-Ac, R_5 = β-OAc, R_6 = H, R_7 = α-ONic, R_8 = α-CH_3, R_9 = = O, R_{10} = β-Ac (esulatin K)	*E. esula*	Vasas et al. (2011)
	133. R_1 = α-OAc, R_2 = β-OAc, R_3 = α-H, R_4 = α-Ac, R_5 = β-OiBu, R_6 = H, R_7 = α-ONic, R_8 = α-CH_3, R_9 = = O, R_{10} = β-Ac (esulatin L)		
	134. R_1 = α-H, R_2 = β-OAc, R_3 = α-H, R_4 = α-Ac, R_5 = β-OiBu, R_6 = H, R_7 = α-ONic, R_8 = α-CH_3, R_9 = = O, R_{10} = β-Ac (esulatin M)		
	135. R_1 = α-OAc, R_2 = β-OBz, R_3 = α-H, R_4 = α-Ac, R_5 = β-OiBu, R_6 = α-OAc, R_7 = α-ONic, R_8 = β-CH_3, R_9 = β-OAc, R_{10} = β-H (euphopeplin A)	*E. peplus*	Zhi-Qin et al. (2010)
	136. R_1 = α-OiBu, R_2 = β-OBz, R_3 = α-H, R_4 = α-H, R_5 = β-OAc, R_6 = α-OAc, R_7 = α-OAc, R_8 = α-CH_3, R_9 = β-OH, R_{10} = α-Ac	*E. sororia*	Huang and Aisa (2010a)
	137. R_1 = α-OiBu, R_2 = β-OBAc, R_3 = α-H, R_4 = α-iBu, R_5 = β-OiBu, R_6 = α-OAc,		

Table 1 continued

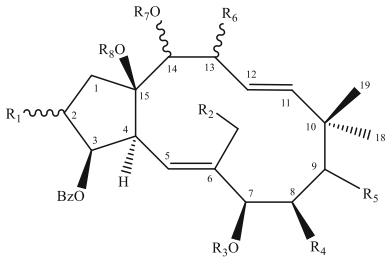
Isolated compound	Substitute (Common name)	Plant	References
	R_7 = α-OAc, R_8 = α-CH_3, R_9 = β-OBz, R_{10} = α-H		
	138. R_1 = α-OiBu, R_2 = α-ONic, R_3 = β-H, R_4 = β-Ac, R_5 = α-OAc, R_6 = α-OAc, R_7 = α-OAc, R_8 = α-CH_3, R_9 = = O, R_{10} = β-Ac	*E. sororia*	Huang and Aisa (2010a)
	139. R_1 = α-OiBu, R_2 = α-ONic, R_3 = β-H, R_4 = β-Ac, R_5 = α-OiBu, R_6 = α-OAc, R_7 = α-OAc, R_8 = α-CH_3, R_9 = = O, R_{10} = β-Ac		
	140. R_1 = α-OiBu, R_2 = α-OBz, R_3 = β-H, R_4 = β-Ac, R_5 = α-OiBu, R_6 = α-OAc, R_7 = α-OAc, R_8 = α-CH_3, R_9 = = O, R_{10} = β-Ac		
	141. R_1 = α-OiBu, R_2 = α-ONic, R_3 = β-H, R_4 = β-Ac, R_5 = α-OAc, R_6 = α-OAc, R_7 = α-OAc, R_8 = α-CH_3, R_9 = = O, R_{10} = β-Ac		
	142. R_1 = α-OBz, R_2 = β-OAc, R_3 = α-H, R_4 = α-Ac, R_5 = β-OBz, R_6 = α-OAc, R_7 = α-OAc, R_8 = β-CH_3, R_9 = = O, R_{10} = β-Ac (euphotuckeyanol)	*E. tuckeyana*	Duarte et al. (2008)
	143. R_1 = α-H, R_2 = β-OAc, R_3 = α-H, R_4 = α-Ac, R_5 = β-OMeBu, R_6 = α-OAc, R_7 = = O, R_8 = β-CH_3, R_9 = β-OBz, R_{10} = β-H (tuckeyanol A)	*E. tuckeyana*	Duarte et al. (2008)
	144. R_1 = α-H, R_2 = β-OAc, R_3 = α-H, R_4 = α-Ac, R_5 = β-OiBu, R_6 = α-OAc, R_7 = = O, R_8 = β-CH_3, R_9 = β-OBz, R_{10} = β-H (tuckeyanol B)		
	145. R_1 = α-ONic, R_2 = β-OAc, R_3 = α-H, R_4 = α-Bz, R_5 = β-OAc, R_6 = α-OAc, R_7 = α-OAc, R_8 = β-CH_3, R_9 = = O, R_{10} = β-Ac (guyonianin C)	*E. guyoniana*	El-Bassuony (2007)
	146. R_1 = α-H, R_2 = β-OBz, R_3 = α-H, R_4 = α-Ac, R_5 = H, R_6 = H, R_7 = α-OAc, R_8 = β-CH_3, R_9 = = O, R_{10} = β-Ac (guyonianin D)		
	147. R_1 = α-ONic, R_2 = β-OAc, R_3 = α-H, R_4 = α-Bz, R_5 = β-OAc, R_6 = α-OAc, R_7 = α-OAc, R_8 = β-CH_3, R_9 = = O, R_{10} = β-H (guyonianin A)	*E. guyoniana*	Ahmed et al. (2006)
	148. R_1 = α-H, R_2 = β-OBz, R_3 = α-H, R_4 = α-Ac, R_5 = H, R_6 = H, R_7 = = O, R_8 = β-CH_3, R_9 = = O, R_{10} = β-Ac (guyonianin B)		
	149. R_1 = α-OAc, R_2 = β-OAc, R_3 = α-H, R_4 = α-MeBu, R_5 = β-OiBu, R_6 = α-OAc, R_7 = α-OAc, R_8 = β-CH_3, R_9 = β-OBz, R_{10} = β-H	*E. sororia*	Hu et al. (2018)
	150. R_1 = α-OiBu, R_2 = β-OAc, R_3 = α-H, R_4 = α-Bz, R_5 = β-OiBu, R_6 = α-OAc, R_7 = α-OAc, R_8 = β-CH_3, R_9 = β-OH, R_{10} = β-H		
	151. R_1 = β-CH_3, R_2 = H, R_3 = Tig, R_4 = H, R_5 = α-OAc, R_6 = β-CH_3, R_7 = β-Ac, R_8 = H	*E. dulcis*	Kusz et al. (2018)
	152. R_1 = β-CH_3, R_2 = H, R_3 = Tig, R_4 = OAc, R_5 = α-OAc, R_6 = β-CH_3, R_7 = β-Ac, R_8 = H		
	153. R_1 = β-CH_3, R_2 = H, R_3 = Tig, R_4 = OAc, R_5 = α-OAc, R_6 = β-CH_3, R_7 = β-Tig, R_8 = H		
	154. R_1 = β-CH_3, R_2 = H, R_3 = H, R_4 = OAc, R_5 = α-OAc, R_6 = β-CH_3, R_7 = β-Tig, R_8 = H		
	155. R_1 = β-CH_3, R_2 = H, R_3 = H, R_4 = OAc, R_5 = α-OAc, R_6 = β-CH_3, R_7 = β-Ac, R_8 = H		
	156. R_1 = β-CH_3, R_2 = H, R_3 = Ac, R_4 = OH, R_5 = α-OAc, R_6 = β-CH_3, R_7 = β-Ac, R_8 = H		
	157. R_1 = β-CH_3, R_2 = H, R_3 = Ac, R_4 = OH, R_5 = α-OH, R_6 = β-CH_3, R_7 = β-Ac, R_8 = H		

Table 1 continued

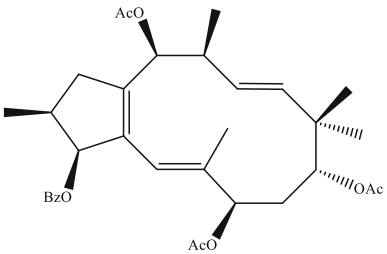
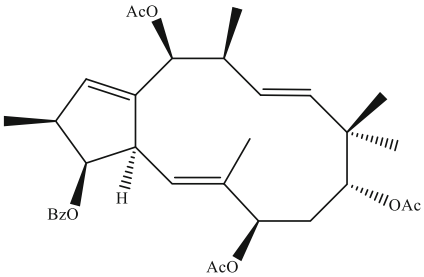
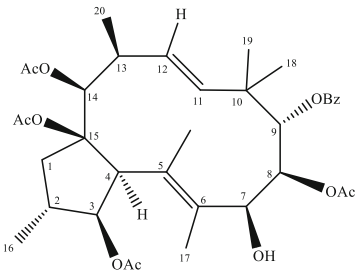
Isolated compound	Substitute (Common name)	Plant	References
	158. R_1 = β-CH_3, R_2 = H, R_3 = H, R_4 = OH, R_5 = α-OH, R_6 = β-CH_3, R_7 = β-Ac, R_8 = H		
	159. R_1 = β-CH_3, R_2 = H, R_3 = Ac, R_4 = OAc, R_5 = α-OH, R_6 = β-CH_3, R_7 = β-H, R_8 = Ac		
	160. R_1 = β-CH_3, R_2 = H, R_3 = Ac, R_4 = H, R_5 = = O, R_6 = α-CH_3, R_7 = β-Ac, R_8 = Ac (euphornin N)	*E. helioscopia*	Geng et al. (2010)
	161. R_1 = α-CH_3, R_2 = H, R_3 = Ac, R_4 = H, R_5 = α-OAc, R_6 = β-CH_3, R_7 = α-Ac, R_8 = Ac (euphornin L)	*E. helioscopia*	Tao et al. (2008)
	162. R_1 = β-CH_3, R_2 = H, R_3 = H, R_4 = H, R_5 = α-OH, R_6 = β-CH_3, R_7 = β-Ac, R_8 = H	*E. helioscopia*	Lu et al. (2008)
	163. R_1 = β-CH_3, R_2 = H, R_3 = Ac, R_4 = H, R_5 = α-OH, R_6 = β-CH_3, R_7 = β-Ac, R_8 = H		
	164. R_1 = α-CH_3, R_2 = OH, R_3 = Ac, R_4 = H, R_5 = α-OAc, R_6 = β-CH_3, R_7 = β-Ac, R_8 = H		
	165. R_1 = α-CH_3, R_2 = H, R_3 = Ac, R_4 = H, R_5 = α-OAc, R_6 = β-CH_3, R_7 = β-Ac, R_8 = H		
	166. R_1 = α-CH_3, R_2 = OH, R_3 = Bz, R_4 = H, R_5 = = O, R_6 = α-CH_3, R_7 = α-Ac, R_8 = Ac		
	167. R_1 = α-CH_3, R_2 = H, R_3 = Bz, R_4 = H, R_5 = = O, R_6 = α-CH_3, R_7 = α-Ac, R_8 = Ac		
	168. R_1 = α-CH_3, R_2 = H, R_3 = H, R_4 = OAc, R_5 = α-OAc, R_6 = β-CH_3, R_7 = β-Ac, R_8 = Ac	*E. serrulata*	Hohmann et al. (2002)
	169.	*E. helioscopia*	Li et al. (2018a)
	170.	*E. helioscopia*	Li et al. (2018a)
	171.	*E. gaditana*	Flores-Giubi et al. (2017)

Table 1 continued

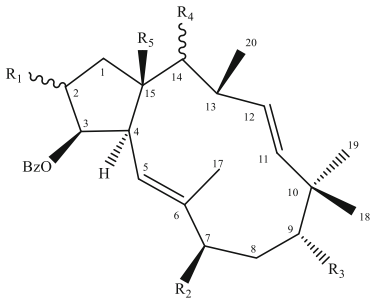
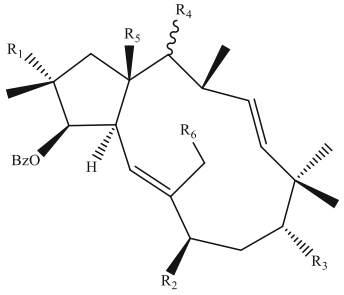
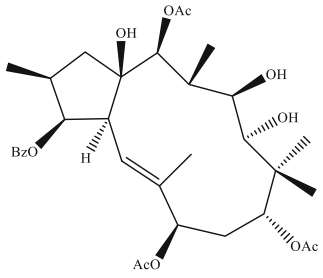
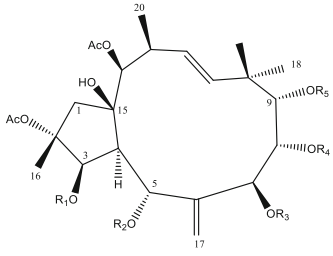
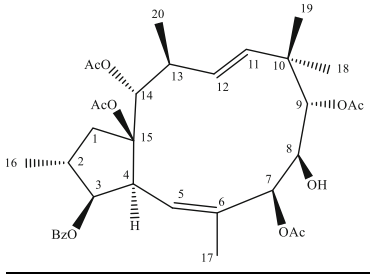
Isolated compound	Substitute (Common name)	Plant	References
	172. R_1 = α-CH_3, R_2 = OH, R_3 = = O, R_4 = α-OAc, R_5 = OH (helioscopianoid A) 173. R_1 = α-CH_3, R_2 = OH, R_3 = OAc, R_4 = α-OAc, R_5 = OAc (helioscopianoid B) 174. R_1 = β-CH_3, R_2 = OAc, R_3 = = O, R_4 = α-OAc, R_5 = OAc (helioscopianoid N) 175. R_1 = β-CH_3, R_2 = OH, R_3 = = O, R_4 = α-OAc, R_5 = OAc (helioscopianoid O) 176. R_1 = β-CH_3, R_2 = = O, R_3 = OAc, R_4 = = O, R_5 = OAc (helioscopianoid P)	*E. helioscopia*	Mai et al. (2018b)
	177. R_1 = OH, R_2 = OAc, R_3 = OAc, R_4 = β-OAc, R_5 = OH, R_6 = H (helioscopianoid C) 178. R_1 = H, R_2 = = O, R_3 = = O, R_4 = α-OAc, R_5 = OAc, R_6 = H (helioscopianoid D) 179. R_1 = H, R_2 = OAc, R_3 = = O, R_4 = β-OAc, R_5 = OH, R_6 = OH (helioscopianoid E)	*E. helioscopia*	Mai et al. (2018b)
	180. (helioscopianoid F)	*E. helioscopia*	Mai et al. (2018b)
	181. R_1 = Bz, R_2 = Ac, R_3 = Ac, R_4 = Ac, R_5 = Nic, (pepluanin A) 182. R_1 = Bz, R_2 = Ac, R_3 = MeBu, R_4 = H, R_5 = Nic, (pepluanin B) 183. R_1 = Ac, R_2 = iBu, R_3 = Bz, R_4 = Ac, R_5 = Ac, (pepluanin C)	*E. peplus*	Corea et al. (2004a)
	184. (euphosquamosin A)	*E. squamosa*	Rawal et al. (2014)

Table 1 continued

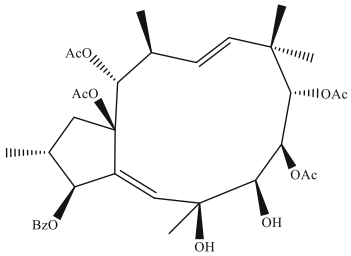
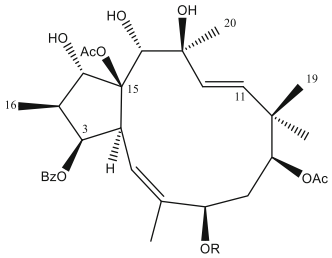
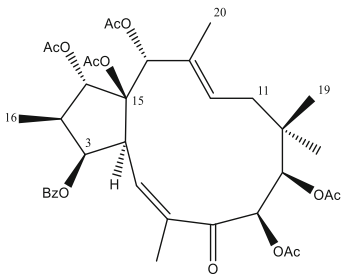
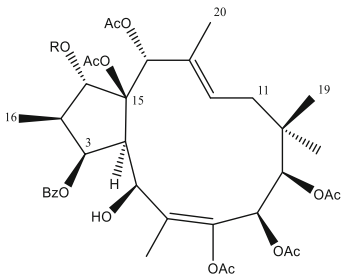
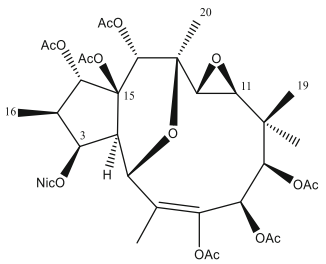
Isolated compound	Substitute (Common name)	Plant	References
	185. (euphosquamosin B)	*E. squamosa*	Rawal et al. (2014)
	186. R = Bz 187. R = H	*Pedilanthus tithymaloides*	Mongkolvisut and Sutthivaiyakit (2007)
	188.	*Pedilanthus tithymaloides*	Mongkolvisut and Sutthivaiyakit (2007)
	189. R = H 190. R = Ac	*Pedilanthus tithymaloides*	Mongkolvisut and Sutthivaiyakit (2007)
	191.	*Pedilanthus tithymaloides*	Mongkolvisut and Sutthivaiyakit (2007)

Table 1 continued

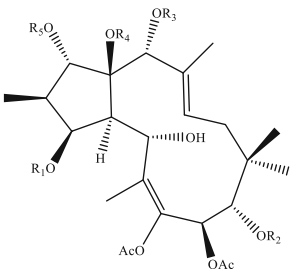
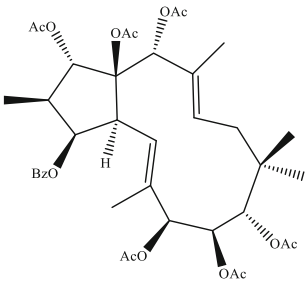
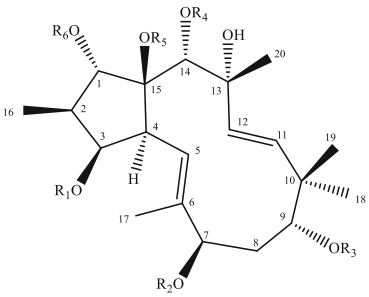
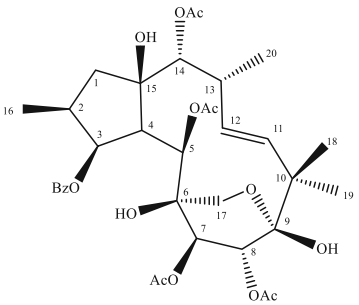
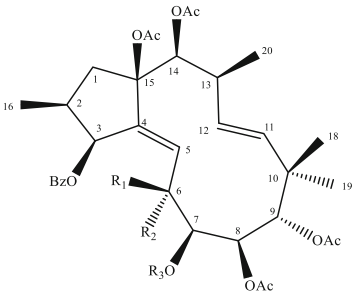
Isolated compound	Substitute (Common name)	Plant	References
	192. R_1 = Nic, R_2 = Ac, R_3 = Ac, R_4 = Ac, R5 = Ac	*Pedilanthus tithymaloides*	Zhu et al. (2016)
	193.	*Pedilanthus tithymaloides*	Zhu et al. (2016)
	194. R_1 = Bz, R_2 = Ac, R_3 = Ac, R_4 = H, R_5 = Ac, R_6 = H 195. R_1 = Bz, R_2 = H, R_3 = Ac, R_4 = Bz, R_5 = Ac, R_6 = H 196. R_1 = Bz, R_2 = Bz, R_3 = Ac, R_4 = H, R_5 = H, R_6 = H	*Pedilanthus tithymaloides*	Zhu et al. (2016)
	197. (jatrohemiketal)	*E. amygdaloides*	Nothias-Scaglia et al. (2015b)
	198. R_1 = CH_3, R_2 = OH, R_3 = Ac	*E. platyphyllos*	Hohmann et al. (2003a)
	199. R_1 = CH_3, R_2 = OH, R_3 = Ac 200. R_1 = CH_3, R_2 = OH, R_3 = Bz	*E. serrulata*	Hohmann et al. (2002)

Table 1 continued

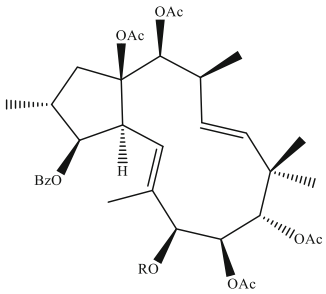
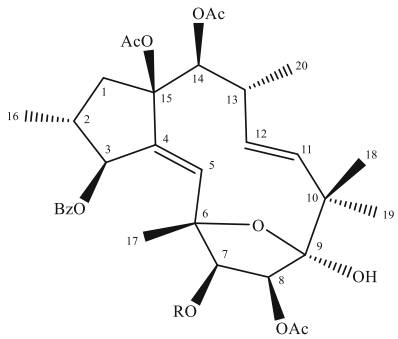
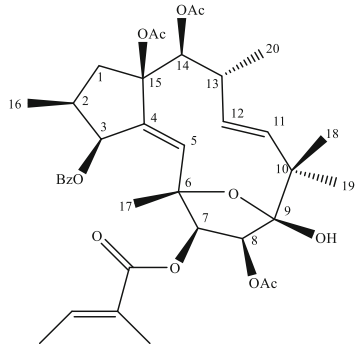
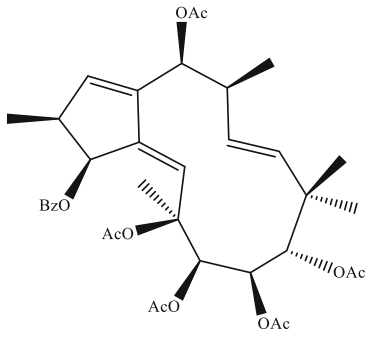
Isolated compound	Substitute (Common name)	Plant	References
	201. R = Ac	*E. platyphyllos*	Hohmann et al. (2003a)
	202. R = Bz	*E. platyphyllos*	Hohmann et al. (2003a)
	203.  203. R=	*E. serrulata*	Redei et al. (2003)
	204. (serrulatin A)	*E. serrulata*	Hohmann et al. (2000b)
	205.	*E. serrulata*	Redei et al. (2003)
	206.	*Pedilanthus tithymaloides*	Zhu et al. (2016)

Table 1 continued

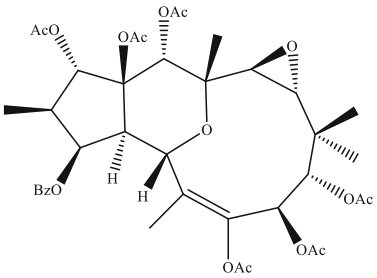
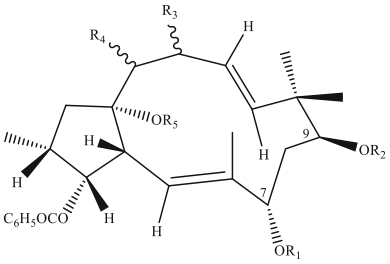
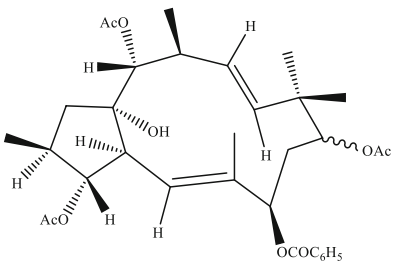
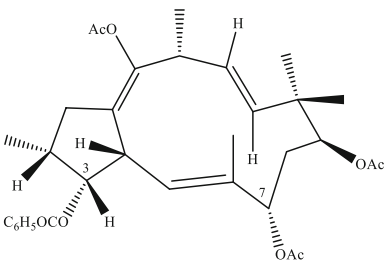
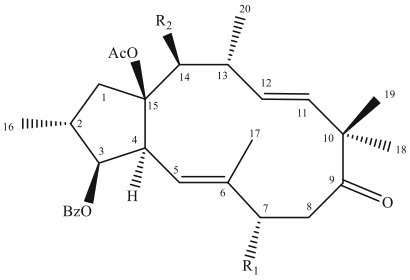
Isolated compound	Substitute (Common name)	Plant	References
			
	207. R_1 = H, R_2 = H, R_3 = β-CH_3, R_4 = β-OAc, R_5 = H 208. R_1 = Ac, R_2 = Ac, R_3 = α-CH_3, R_4 = α-OAc, R_5 = H (euphornin) 209. R_1 = H, R_2 = H, R_3 = α-CH_3, R_4 = α-OH, R_5 = H 210. R_1 = H, R_2 = Ac, R_3 = α-CH_3, R_4 = α-OAc, R_5 = H (euphornin A) 211. R_1 = Ac, R_2 = H, R_3 = α-CH_3, R_4 = α-OAc, R_5 = H (euphornin B) 212. R_1 = Ac, R_2 = Ac, R_3 = α-CH_3, R_4 = α-OAc, R_5 = Ac (euphornin D)	*E. helioscopia*	Yamamura et al. (1989)
	213.	*E. helioscopia*	Yamamura et al. (1989)
	214. (euphornin E)	*E. helioscopia*	Yamamura et al. (1989)
	215. R_1 = OBu, R_2 = OAc 216. R_1 = OMeBu, R_2 = OAc 217. R_1 = OSal, R_2 = OAc	*E. helioscopia*	Li et al. (2018a)

Table 1 continued

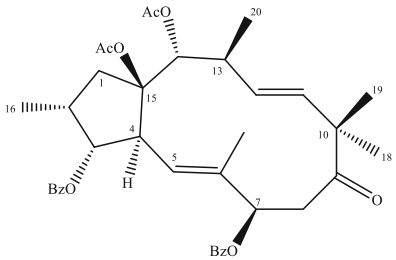
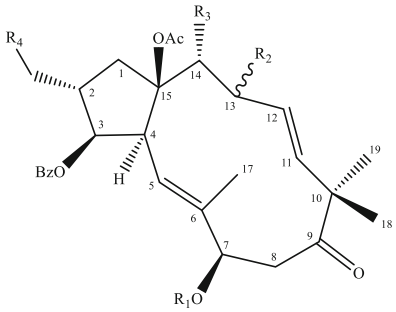
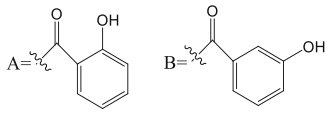
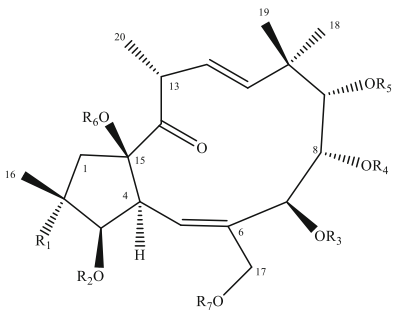
Isolated compound	Substitute (Common name)	Plant	References
	218.	*E. lunulata*	Liu et al. (2014)
	219. R_1 = H, R_2 = β-CH_3, R_3 = OAc, R_4 = H (2-epi-euphornin I)	*E. helioscopia*	Mai et al. (2017b)
	220. R_1 = H, R_2 = α-CH_3, R_3 = OAc, R_4 = H (helioscopianoid H)	*E. helioscopia*	Mai et al. (2018b)
	221. R_1 = 2″-methylbutanoyl, R_2 = α-CH_3, R_3 = OAc, R_4 = H (helioscopianoid I)		
	222. R_1 = A, R_2 = α-CH_3, R_3 = OAc, R_4 = H (helioscopianoid J)		
	223. R_1 = B, R_2 = α-CH_3, R_3 = OAc, R_4 = H (helioscopianoid K)		
	224. R_1 = Bz, R_2 = α-CH_3, R_3 = OAc, R_4 = OH (helioscopianoid L)		
			
	225. R_1 = H, R_2 = Pr, R_3 = Ac, R_4 = iBu, R_5 = Bz, R_6 = Nic, R_7 = H (euphodendrophane H)	*E. dendroides*	Jadranin et al. (2013)
	226. R_1 = H, R_2 = Pr, R_3 = Ac, R_4 = iBu, R_5 = Nic, R_6 = Nic, R_7 = H (euphodendrophane I)		
	227. R_1 = H, R_2 = Pr, R_3 = Ac, R_4 = iBu, R_5 = iBu, R_6 = Nic, R_7 = H (euphodendrophane J)		
	228. R_1 = H, R_2 = iBu, R_3 = Ac, R_4 = iBu, R_5 = Bz, R_6 = Nic, $_{R7}$ = H (euphodendrophane K)		
	229. R_1 = H, R_2 = iBu, R_3 = Ac, R_4 = iBu, R_5 = Nic, R_6 = Nic, R_7 = H (euphodendrophane L)		
	230. R_1 = H, R_2 = iBu, R_3 = Ac, R_4 = Ac, R_5 = Nic, R_6 = Ac, R_7 = H (euphodendrophane M)		
	231. R_1 = H, R_2 = Ac, R_3 = Ac, R_4 = iBu, R_5 = Ac, R_6 = Nic, R_7 = H (euphodendrophane N)		
	232. R_1 = OAc, R_2 = iBu, R_3 = Ac, R_4 = iBu, R_5 = Ac, R_6 = Nic, R_7 = H (euphodendrophane O)		
	233. R_1 = OAc, R_2 = iBu, R_3 = Nic, R_4 = iBu, R_5 = Ac, R_6 = Nic, R_7 = H (euphodendrophane P)		
	234. R_1 = OAc, R_2 = Pr, R_3 = iBu, R_4 = Ac, R_5 = Nic, R_6 = Ac, R_7 = Ac (euphodendrophane Q)		
	235. R_1 = OAc, R_2 = Ac, R_3 = iBu, R_4 = Nic, R_5 = Nic, R_6 = Ac, R_7 = Ac (euphodendrophane R)		

Table 1 continued

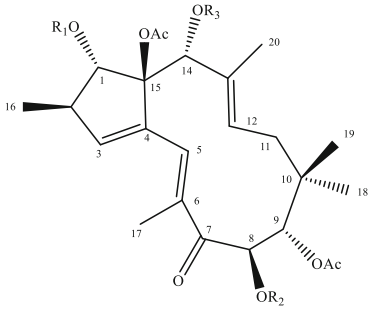
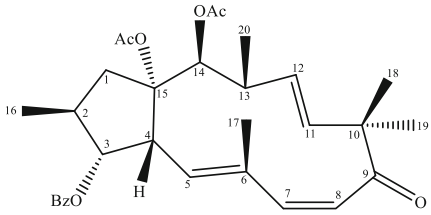
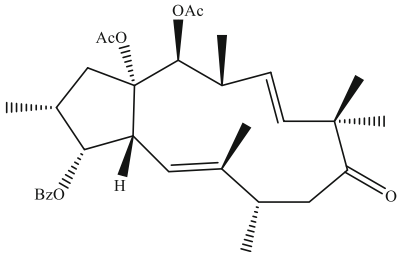
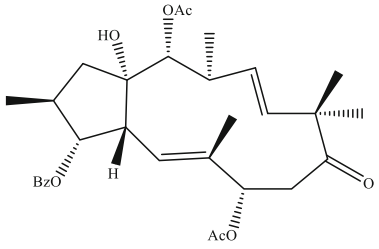
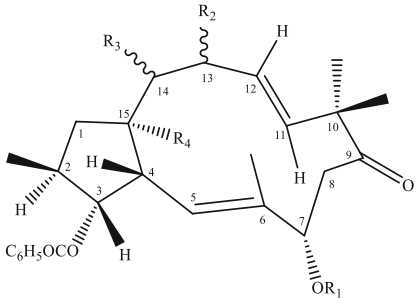
Isolated compound	Substitute (Common name)	Plant	References
	236. R_1 = OAc, R_2 = Ac, R_3 = iBu, R_4 = Ac, R_5 = Bz, R_6 = Ac, R_7 = Ac (euphodendrophane S)		
	237. R_1 = OAc, R_2 = Ac, R_3 = iBu, R_4 = Ac, R_5 = Nic, R_6 = Ac, R_7 = Ac (euphodendrophane F)	*E. dendroides*	Aljancic et al. (2011)
	238. R_1 = Ac, R_2 = Ac, R_3 = Ac	*Pedilanthus tithymaloides*	Zhu et al. (2016)
	239. (euphorbiapene A)	*E. helioscopia*	Chen et al. (2014)
	240. (euphorbiapene B)	*E. helioscopia*	Chen et al. (2014)
	241. (euphorbiapene C)	*E. helioscopia*	Chen et al. (2014)
	242. R_1 = H, R_2 = β-CH_3, R_3 = β-OAc, R_4 = OAc (euphoscopin A) 243. R_1 = COC_6H_4Br-p, R_2 = β-CH_3, R_3 = β-OAc, R_4 = OAc 244. R_1 = Ac, R_2 = β-CH_3, R_3 = β-OAc, R_4 = OAc (euphoscopin B) 245. R_1 = COC_6H_5, R_2 = β-CH_3, R_3 = β-OAc, R_4 = OAc (euphoscopin C) 246. R_1 = H, R_2 = β-CH_3, R_3 = β-OAc, R_4 = OH (euphoscopin G) 247. R_1 = Ac, R_2 = β-CH_3, R_3 = β-OAc, R_4 = OAc (euphoscopin H)	*E. helioscopia*	Yamamura et al. (1989)

Table 1 continued

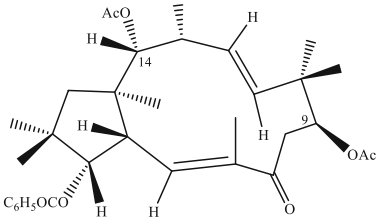
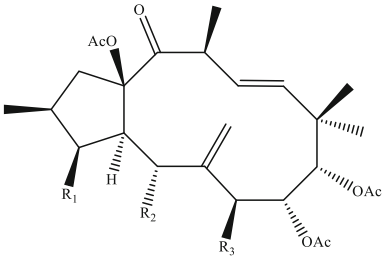
Isolated compound	Substitute (Common name)	Plant	References
	248. R_1 = Ac, R_2 = β-CH_3, R_3 = β-OH, R_4 = OAc (euphoscopin K)		
	249. R_1 = H, R_2 = β-CH_3, R_3 = β-OH, R_4 = OAc (euphoscopin I)		
	250. R_1 = Ac, R_2 = β-CH_3, R_3 = β-OH, R_4 = OAc (euphoscopin J)		
	251. R_1 = $SiMe_2Bu$, R_2 = β-CH_3, R_3 = β-OH, R_4 = OH		
	252. R_1 = H, R_2 = β-CH_3, R_3 = β-OAc, R_4 = OAc (epieuphoscopin A)		
	253. R_1 = $BuMe_2Si$, R_2 = β-CH_3, R_3 = β-OAc, R_4 = OAc		
	254. R_1 = Ac, R_2 = β-CH_3, R_3 = β-OAc, R_4 = OAc (epieuphoscopin B)		
	255. R_1 = H, R_2 = α-CH_3, R_3 = α-OAc, R_4 = OH (euphornin F)		
	256. R_1 = Ac, R_2 = α-CH_3, R_3 = α-OAc, R_4 = OH (euphornin G)		
	257. R_1 = Ac, R_2 = α-CH_3, R_3 = α-OH, R_4 = OH		
	258. R_1 = Bu^tMe_2Si, R_2 = α-CH_3, R_3 = α-OH, R_4 = OH		
	259. R_1 = Ac, R_2 = α-CH_3, R_3 = β-OAc, R_4 = OAc (euphornin H)		
	260. R_1 = Ac, R_2 = α-CH_3, R_3 = β-OAc, R_4 = OH (euphornin I)		
	261. R_1 = H, R_2 = α-CH_3, R_3 = α-OH, R_4 = OBu^tMe_2Si		
	262. R_1 = Ac, R_2 = β-CH_3, R_3 = β-OAc, R_4 = OAc (euphornin J)		
	263. R_1 = H, R_2 = β-CH_3, R_3 = β-OAc, R_4 = OAc (euphornin K)		
	264. R_1 = Bu^tMe_2Si, R_2 = β-CH_3, R_3 = β-OH, R_4 = OH		
	265. (euphornin C)	*E. helioscopia*	Yamamura et al. (1989)
	266. R_1 = OBz, R_2 = OAc, R_3 = OBz	*E. glomerulans*	Hasan et al. (2019)

Table 1 continued

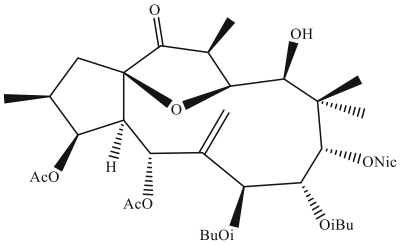
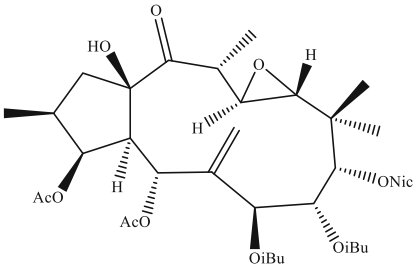
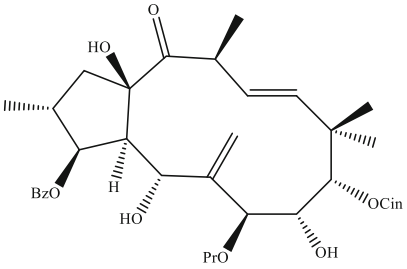
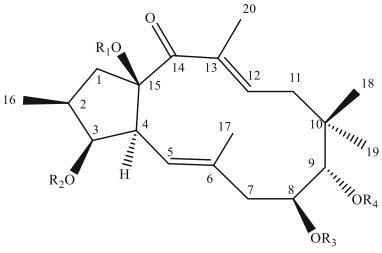
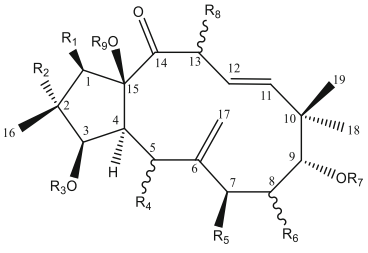
Isolated compound	Substitute (Common name)	Plant	References
	267. (welwitschene)	*E. welwitschii*	Reis et al. (2015)
	268. (epoxywelwitschene)	*E. welwitschii*	Reis et al. (2015)
	269.	*E. exigua*	Rédei et al. (2015)
	270. $R_1 = R_2 = R_4 = Ac$, $R_3 = Bz$ (pubescene A) 271. $R_1 = R_2 = R_4 = Ac$, $R_3 = Bu$ (pubescene B) 272. $R_1 = H$, $R_2 = R_4 = Ac$, $R_3 = Bz$ (pubescene C)	*E. pubescens*	Valente et al. (2003)
	273. $R_1 = H$, $R_2 = OAc$, $R_3 = OPr$, $R_4 = \alpha$-Ac, $R_5 = OiBu$, $R_6 = \alpha$-OAc, $R_7 = Nic$, $R_8 = \alpha$-CH_3, $R_9 = OH$ (nicaeenin B) 274. $R_1 = H$, $R_2 = ONic$, $R_3 = OiBu$, $R_4 = \alpha$-OAc, $R_5 = OiBu$, $R_6 = \alpha$-OAc, $R_7 = Ac$, $R_8 = \alpha$-CH_3, $R_9 = OH$ (nicaeenin C) 275. $R_1 = H$, $R_2 = ONic$, $R_3 = OPr$, $R_4 = \alpha$-OAc, $R_5 = OiBu$, $R_6 = \alpha$-H, $R_7 = Nic$, $R_8 = \alpha$-CH_3, $R_9 = OH$ (nicaeenin D)	*E. nicaeensis*	Krstić et al. (2018)
	276. $R_1 = H$, $R_2 = H$, $R_3 = OPr$, $R_4 = \alpha$-OAc, $R_5 = OAc$, $R_6 = \alpha$-H, $R_7 = Nic$, $R_8 = \alpha$-CH_3, $R_9 = OAc$ (nicaeenin E) 277. $R_1 = H$, $R_2 = H$, $R_3 = OPr$, $R_4 = \alpha$-OAc, $R_5 = OAc$, $R_6 = \alpha$-H, $R_7 = Nic$, $R_8 = \alpha$-CH_3, $R_9 = OAc$ (nicaeenin F) 278. $R_1 = H$, $R_2 = H$, $R_3 = OPr$, $R_4 = \alpha$-OAc, $R_5 = OiBu$, $R_6 = \alpha$-ONic, $R_7 = Ac$, $R_8 = \alpha$-CH_3, $R_9 = OH$ (nicaeenin G)	*E. nicaeensis*	Krstić et al. (2018)

Table 1 continued

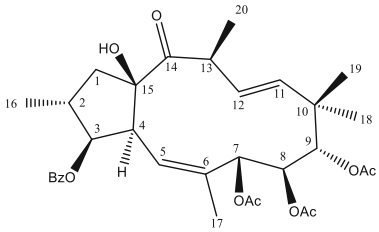
Isolated compound	Substitute (Common name)	Plant	References
	279. R_1 = H, R_2 = H, R_3 = OCin, R_4 = α-OAc, R_5 = H, R_6 = α-H, R_7 = Ac, R_8 = β-CH_3, R_9 = OH	*E. taurinensis*	Rédei et al. (2018)
	280. R_1 = H, R_2 = OiBu, R_3 = OAc, R_4 = β-OH, R_5 = OAc, R_6 = β-OAc, R_7 = Bz, R_8 = β-CH_3, R_9 = OH (guyonianin G)	*E. guyoniana*	Kúsz et al. (2016)
	281. R_1 = H, R_2 = OiBu, R_3 = OAc, R_4 = β-OH, R_5 = OiBu, R_6 = β-OAc, R_7 = Bz, R_8 = β-CH_3, R_9 = OH (guyonianin H)		
	282. R_1 = H, R_2 = H, R_3 = OAc, R_4 = α-OBz, R_5 = OAc, R_6 = α-OAc, R_7 = Ac, R_8 = β-CH_3, R_9 = OH (euphorbesulin D)	*E. esula*	Zhou et al. (2016)
	283. R_1 = H, R_2 = H, R_3 = OBz, R_4 = α-OAc, R_5 = OAc, R_6 = α-OAc, R_7 = Ac, R_8 = β-CH_3, R_9 = OAc (euphorbesulin E)		
	284. R_1 = H, R_2 = H, R_3 = OAc, R_4 = α-OAc, R_5 = OAc, R_6 = α-OAc, R_7 = Ac, R_8 = β-CH_3, R_9 = OAc (euphorbesulin F)		
	285. R_1 = H, R_2 = H, R_3 = OAc, R_4 = α-OBz, R_5 = OBz, R_6 = α-OAc, R_7 = Ac, R_8 = β-CH_3, R_9 = OAc (euphorbesulin G)		
	286. R_1 = H, R_2 = H, R_3 = OAc, R_4 = α-OAc, R_5 = OBz, R_6 = α-OAc, R_7 = Ac, R_8 = β-CH_3, R_9 = $HOCH_2$ CO_2 (euphorbesulin H)		
	287. R_1 = H, R_2 = H, R_3 = OAc, R_4 = α-OBz, R_5 = OAc, R_6 = α-OAc, R_7 = Ac, R_8 = β-CH_3, R_9 = OAc (euphorbesulin I)		
	288. R_1 = H, R_2 = H, R_3 = OAc, R_4 = α-OAc, R_5 = OBz, R_6 = α-OH, R_7 = Ac, R_8 = β-CH_3, R_9 = OAc (euphorbesulin J)		
	289. R_1 = H, R_2 = OAc, R_3 = OAc, R_4 = α-OBz, R_5 = OAc, R_6 = α-OAc, R_7 = Ac, R_8 = β-CH_3, R_9 = OAc (euphorbesulin K)		
	290. R_1 = H, R_2 = OAc, R_3 = OBz, R_4 = α-OAc, R_5 = OAc, R_6 = α-OAc, R_7 = Ac, R_8 = β-CH_3, R_9 = OAc (euphorbesulin L)		
	291. R_1 = H, R_2 = OH, R_3 = OBz, R_4 = α-OAc, R_5 = OBz, R_6 = α-OAc, R_7 = Ac, R_8 = β-CH_3, R_9 = OAc (euphorbesulin M)		
	292. R_1 = OH, R_2 = OH, R_3 = OBz, R_4 = α-OBz, R_5 = OBz, R_6 = α-OAc, R_7 = Ac, R_8 = β-CH_3, R_9 = OAc (euphorbesulin N)		
	293. (euphomelliferine)	*E. mellifera*	Valente et al. (2012)

Table 1 continued

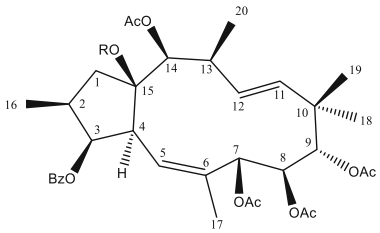
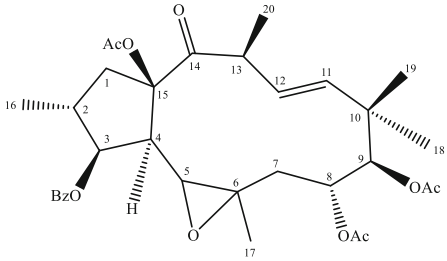
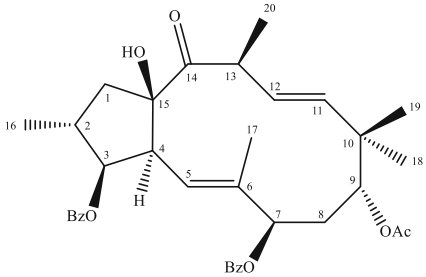
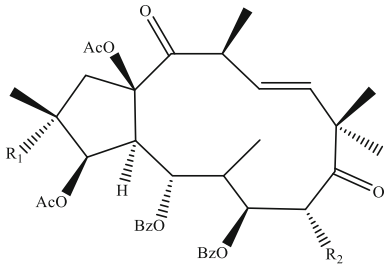
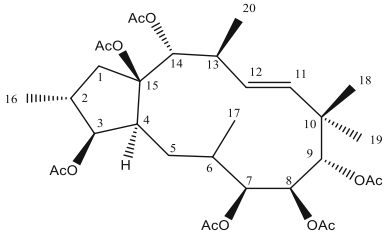
Isolated compound	Substitute (Common name)	Plant	References
	294. R = Ac (euphomelliferene A) 295. R = H (euphomelliferene B)	*E. mellifera*	Valente et al. (2012)
	296.	*E. connata*	Shadi et al. (2015)
	297. (Pubescene D)	*E. pubescens*	Valente et al. (2004a)
	298. $R_1 = R_2 = OH$ (esulone A) 299. $R_1 = OH$, $R_2 = OAc$ (esulone B)	*E. esula*	Manners and Wong (1985)
	300. (euphopubescene)	*E. pubescens*	Valente et al. (2004b)

Table 1 continued

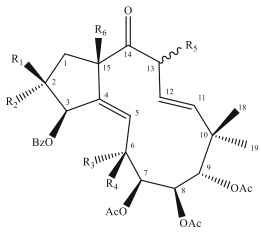
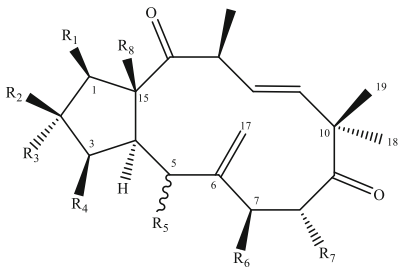
Isolated compound	Substitute (Common name)	Plant	References
	301. R_1 = CH_3, R_2 = OH, R_3 = CH_3, R_4 = OAc, R_5 = β-CH_3, R_6 = OAc	*E. serrulata*	Hohmann et al. (2002)
	302. R_1 = H, R_2 = CH_3, R_3 = CH_3, R_4 = OH, R_5 = β-CH_3, R_6 = OAc		
	303. R_1 = CH_3, R_2 = OAc, R_3 = OH, R_4 = CH_3, R_5 = β-CH_3, R_6 = OH	*E. serrulata*	Redei et al. (2003)
	304. R_1 = CH_3, R_2 = OAc, R_3 = OAc, R_4 = CH_3, R_5 = β-CH_3, R_6 = OAc		
	305. R_1 = H, R_2 = CH_3, R_3 = CH_3, R_4 = OAc, R_5 = α-CH_3, R_6 = OAc		
	306. R_1 = CH_3, R_2 = H, R_3 = CH_3, R_4 = OAc, R_5 = α-CH_3, R_6 = OAc (serrulatin B)	*E. serrulata*	Hohmann et al. (2000b)
	307. R_1 = H, R_2 = CH_3, R_3 = H, R_4 = OBz, R_5 = α-OAc, R_6 = OAc, R_7 = OAc, R_8 = OAc	*E. glomerulans*	Hasan et al. (2019)
	308. R_1 = H, R_2 = CH_3, R_3 = H, R_4 = OAc, R_5 = α-OBz, R_6 = OAc, R_7 = OH, R_8 = OAc		
	309. R_1 = H, R_2 = CH_3, R_3 = H, R_4 = OBz, R_5 = α-OAc, R_6 = OAc, R_7 = OH, R_8 = OAc		
	310. R_1 = H, R_2 = CH_3, R_3 = H, R_4 = OAc, R_5 = α-OBz, R_6 = OAc, R_7 = H, R_8 = OAc		
	311. R_1 = H, R_2 = CH_3, R_3 = H, R_4 = OBz, R_5 = α- OAc, R_6 = OAc, R_7 = H, R_8 = OAc		
	312. R_1 = H, R_2 = CH_3, R_3 = OH, R_4 = OBz, R_5 = α-OAc, R_6 = OBz, R_7 = OAc, R_8 = OH		
	313. R_1 = H, R_2 = CH_3, R_3 = H, R_4 = OBz, R_5 = α- OAc, R_6 = OBz, R_7 = OH, R_8 = OAc		
	314. R_1 = H, R_2 = CH_3, R_3 = OH, R_4 = OBz, R_5 = α-OAc, R_6 = OAc, R_7 = OiBu, R_8 = OH		
	315. R_1 = H, R_2 = CH_3, R_3 = OAc, R_4 = OBz, R_5 = α-OAc, R_6 = OAc, R_7 = OiBu, R_8 = OH		
	316. R_1 = H, R_2 = CH_3, R_3 = OAc, R_4 = OBz, R_5 = α-OAc, R_6 = OiBu, R_7 = OAc, R_8 = OH		
	317. R_1 = H, R_2 = CH_3, R_3 = H, R_4 = OBz, R_5 = α-OAc, R_6 = OAc, R_7 = OH, R_8 = OH		
	318. R_1 = H, R_2 = CH_3, R_3 = H, R_4 = OAc, R_5 = α- OBz, R_6 = OAc, R_7 = OBz, R_8 = OAc		
	319. R_1 = H, R_2 = CH_3, R_3 = H, R_4 = OBz, R_5 = α-OAc, R_6 = OBz, R_7 = OAc, R_8 = OAc		
	320. R_1 = H, R_2 = CH_3, R_3 = H, R_4 = $CH_3COCH_2CO_2$, R_5 = α-OAc, R_6 = OBz, R_7 = OAc, R_8 = OH		
	321. R_1 = H, R_2 = H, R_3 = CH_3, R_4 = OBz, R_5 = α-OAc, R_6 = H, R_7 = H, R_8 = OH	*E. helioscopia*	Li et al. (2018a)
	322. R_1 = H, R_2 = CH_3, R_3 = H, R_4 = OH, R_5 = β-OBz, R_6 = H, R_7 = H, R_8 = OAc	*E. sororia*	Hu et al. (2018)
	323. R_1 = OH, R_2 = CH_3, R_3 = OH, R_4 = OAc, R_5 = α-OBz, R_6 = OBz, R_7 = OH, R_8 = OAc (kanesulone A)	*E. kansui*	Lee et al. (2016)
	324. R_1 = OAc, R_2 = CH_3, R_3 = OH, R_4 = OAc, R_5 = α-OBz, R_6 = OBz, R_7 = OAc, R_8 = OH (kanesulone B)		
	325. R_1 = Tig	*E. characias*	Seip and Hecker (1984)
	326. R_1 = Bz		

Table 1 continued

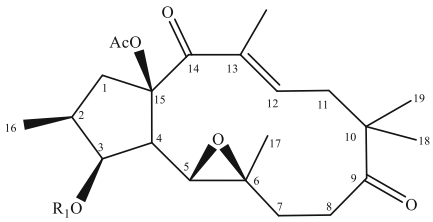
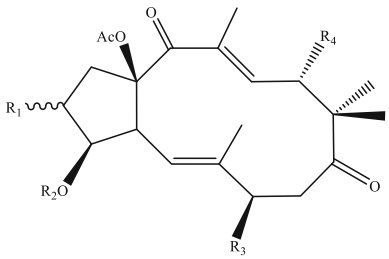
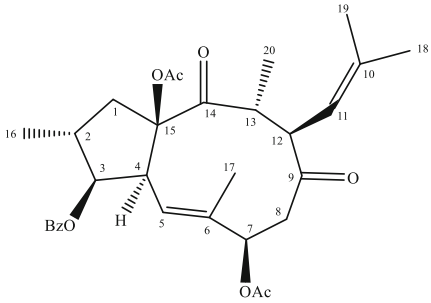
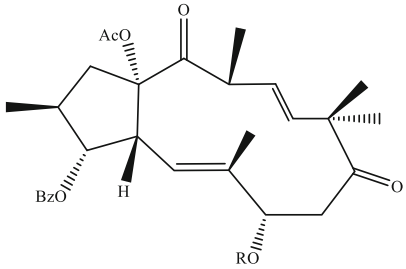
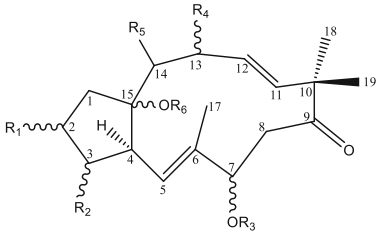
Isolated compound	Substitute (Common name)	Plant	References
	327. R_1 = β-H, R_2 = Pr, R_3 = H, R_4 = H	*E. characias*	Seip and Hecker (1984)
	328. R_1 = α-CH_3, R_2 = Bz, R_3 = OH, R_4 = OH (helioscopianoid Q)	*E. helioscopia*	Mai et al. (2018b)
	329. (heliojatrone A)	*E. helioscopia*	Mai et al. (2018a)
	330. R = Bz (euphorbiapene D)	*E. helioscopia*	Chen et al. (2014)
	331. R_1 = β-CH_3, R_2 = α-C_6H_5OCO, R_3 = H, R_4 = β-CH_3, R_5 = = O, R_6 = α-Ac (euphoscopin E) 332. R_1 = β-CH_3, R_2 = α-C_6H_5OCO, R_3 = Ac, R_4 = β-CH_3, R_5 = = O, R_6 = α-Ac (euphoscopin F) 333. R_1 = β-CH_3, R_2 = α-C_6H_5OCO, R_3 = $SiMe_2Bu$, R_4 = β-CH_3, R_5 = = O, R_6 = α-Ac 334. R_1 = β-CH_3, R_2 = α-C_6H_5OCO, R_3 = $SiMe_2Bu$, R_4 = α-CH_3, R_5 = = O, R_6 = α-H 335. R_1 = β-CH_3, R_2 = α-C_6H_5OCO, R_3 = Ac, R_4 = α-CH_3, R_5 = = O, R_6 = α-Ac (epieuphoscopin F)	*E. helioscopia*	Yamamura et al. (1989)

Table 1 continued

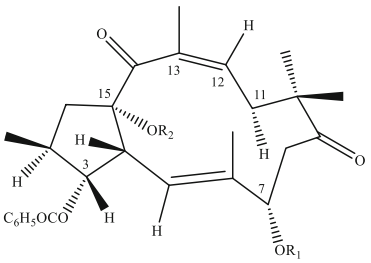
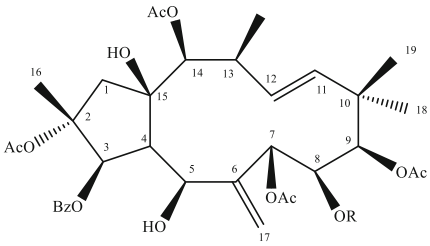
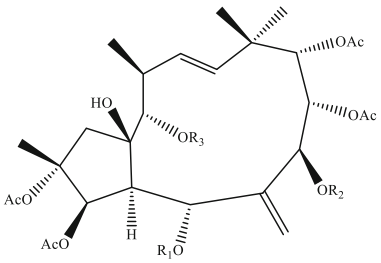
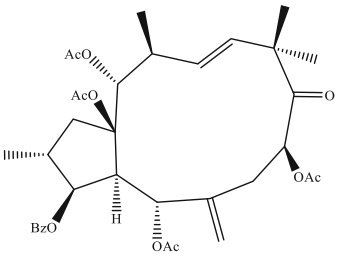
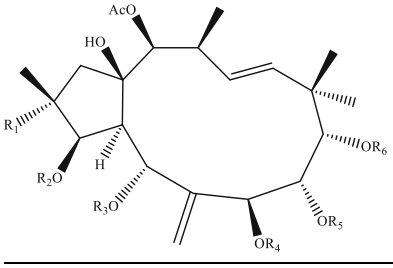
Isolated compound	Substitute (Common name)	Plant	References
	336. R_1 = β-CH_3, R_2 = α-C_6H_5OCO, R_3 = $SiMe_2Bu$, R_4 = β-CH_3, R_5 = = O, R_6 = α-H		
	337. R_1 = α-CH_3, R_2 = β-OBz, R_3 = β-Nic, R_4 = α-CH_3, R_5 = α-OAc, R_6 = β-Ac (euphoheliosnoid A)	*E. heliosc opia*	Zhang and Guo (2005)
	338. R_1 = β-CH_3, R_2 = β-OBz, R_3 = β-Nic, R_4 = α-CH_3, R_5 = α-OAc, R_6 = β-Ac (euphoheliosnoid B)		
	339. R_1 = H, R_2 = Ac (euphoscopin L)	*E. helioscopia*	Yamamura et al. (1989)
	340. R_1 = $SiMe_2Bu$, R_2 = H		
	341. R_1 = Ac, R_2 = Ac		
	342. R = But	*E. osyridea*	Ghanadian et al. (2015)
	343. R = Prop		
	344. R = Ac		
	345. R_1 = Bz, R_2 = iBu, R_3 = Ac	*E. sororia*	Lu et al. (2014)
	346. R_1 = Bz, R_2 = iBu, R_3 = Bz (ES2)		
	347. R_1 = iBu, R_2 = iBu, R_3 = Bz		
	348. R_1 = iBu, R_2 = Pr, R_3 = Bz		
	349. R_1 = Pr, R_2 = iBu, R_3 = Bz		
	350. (euphosquamosin C)	*E. squamosa*	Rawal et al. (2014)
	351. R_1 = OAc, R_2 = Bz, R_3 = Ac, R_4 = Ac, R_5 = Ac, R_6 = Ac	*E. peplus*	Jakupovic et al. (1998b)
	352. R_1 = OAc, R_2 = Bz, R_3 = Ac, R_4 = iBu, R_5 = H, R_6 = Nic		
	353. R_1 = OAc, R_2 = Bz, R_3 = Ac, R_4 = iBu, R_5 = H, R_6 = Ac		
	354. R_1 = OAc, R_2 = Bz, R_3 = Ac, R_4 = Ac, R_5 = H, R_6 = Nic		

Table 1 continued

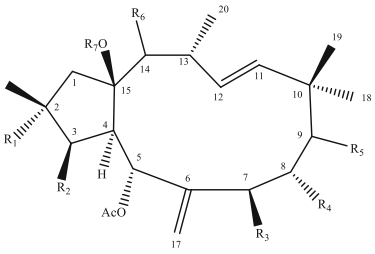
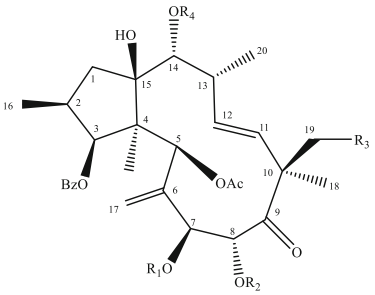
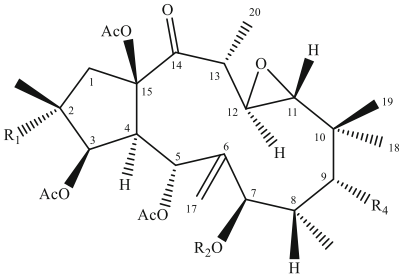
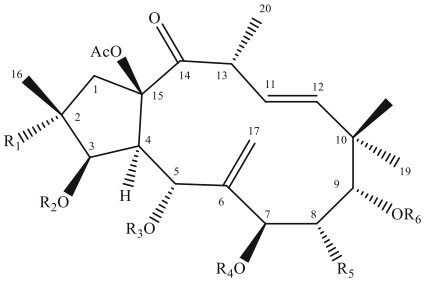
Isolated compound	Substitute (Common name)	Plant	References
	355. R_1 = OAc, R_2 = Bz, R_3 = Ac, R_4 = Ac, R_5 = H, R_6 = Ac		
	356. R_1 = H, R_2 = H, R_3 = Mebu, R_4 = iBu, R_5 = Mebu, R_6 = H	*E. segetalis*	Jakupovic et al. (1998a)
	357. R_1 = H, R_2 = OBz, R_3 = OAc, R_4 = OAc, R_5 = = O, R_6 = α-OAc, R_7 = H	*E. semiperfoliata*	Appendino et al. (1998)
	358. R_1 = H, R_2 = OBz, R_3 = OAc, R_4 = OiBu, R_5 = = O, R_6 = α-OAc, R_7 = H		
	359. R_1 = H, R_2 = OBz, R_3 = OAc, R_4 = OH, R_5 = = O, R_6 = α-OH, R_7 = H		
	360. R_1 = H, R_2 = OBz, R_3 = OAc, R_4 = OAc, R_5 = = O, R_6 = α-OH, R_7 = H		
	361. R_1 = H, R_2 = OBz, R_3 = OAc, R_4 = OH, R_5 = = O, R_6 = α-OAc, R_7 = H		
	362. R_1 = H, R_2 = OBz, R_3 = OAc, R_4 = H, R_5 = = O, R_6 = α-OAc, R_7 = H		
	363. R_1 = OAc, R_2 = $PhO_2CH_2CO_2C$, R_3 = OiBu, R_4 = OAc, R_5 = α-OAc, R_6 = = O, R_7 = H	*E. segetalis*	Jakupovic et al. (1998a)
	364. R_1 = H, R_2 = OBz, R_3 = H, R_4 = H, R_5 = = O, R_6 = α-OAc, R_7 = H (guyonianin E)	*E. guyoniana*	Hegazy et al. (2010)
	365. R_1 = H, R_2 = Ac, R_3 = H, R_4 = H	*E. amygdaloides*	Nothias-Scaglia et al. (2015b)
	366. R_1 = Ac, R_2 = H, R_3 = OH, R_4 = Ac		
	367. R_1 = Ac, R_2 = iBu, R_3 = H, R_4 = H	*E. amygdaloides*	Nothias-Scaglia et al. (2014)
	368. R_1 = Ac, R_2 = MeBu, R_3 = H, R_4 = H		
	369. R_1 = H, R_2 = Ac, R_3 = OBz, R_4 = OBz (kansuinin F)	*E. kansui*	Pan et al. (2004)
	370. R_1 = H, R_2 = Ac, R_3 = H, R_4 = ONic (kansuinin G)		
	371. R_1 = H, R_2 = Ac, R_3 = OBz, R_4 = ONic (kansuinin E)		
	372. R_1 = OAc, R_2 = iBu, R_3 = OiBu, R_4 = OAc	*E. salicifolia*	Hohmann et al. (2001a)
	373. R_1 = OAc, R_2 = Ac, R_3 = OiBu, R_4 = OAc		
	374. R_1 = OAc, R_2 = iBu, R_3 = OAc, R_4 = OAc (esulatin A)	*E. esula*	Hohmann et al. (1997)
	375. R_1 = H, R_2 = Bz, R_3 = Ac, R_4 = Ac, R_5 = OAc, R_6 = Ac	*E. mongolica*	Hohmann et al. (2003b)
	376. R_1 = H, R_2 = Ac, R_3 = Bz, R_4 = Ac, R_5 = OAc, R_6 = Ac		
	377. R_1 = OAc, R_2 = Ac, R_3 = Ac, R_4 = Bz, R_5 = OAc, R_6 = Ac	*E. turczaninowii*	Liu and Tan (2001)
	378. R_1 = H, R_2 = Ac, R_3 = Ac, R_4 = Bz, R_5 = OAc, R_6 = Ac		
	379. R_1 = OBz, R_2 = Ac, R_3 = Ac, R_4 = Ac, R_5 = OAc, R_6 = Ac		
	380. R_1 = OAc, R_2 = Bz, R_3 = Ac, R_4 = iBu, R_5 = OAc, R_6 = Nic	*E. peplus*	Hohmann et al. (2000a)
	381. R_1 = H, R_2 = Ac, R_3 = Ac, R_4 = Ac, R_5 = H, R_6 = Nic	*E. peplus*	Hohmann et al. (1999b)

Table 1 continued

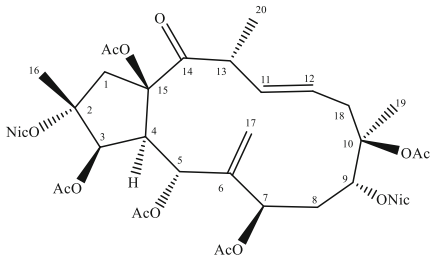
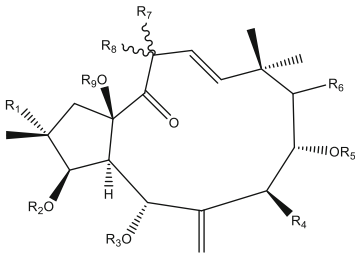
Isolated compound	Substitute (Common name)	Plant	References
	382. R_1 = OAc, R_2 = Ac, R_3 = Ac, R_4 = Ac, R_5 = H, R_6 = Ac (esulatin D)	*E. esula*	Günther et al. (1998)
	383. (euphosalicin)	*E. salicifolia*	Hohmann et al. (2001a)
	384. R_1 = H, R_2 = Ac, R_3 = Ac, R_4 = OAng, R_5 = Ang, R_6 = α-ONic, R_7 = β-CH_3, R_8 = α-OH, R_9 = H (amygdaloidin A)	*E. amygdaloides*	Corea et al. (2005a)
	385. R_1 = H, R_2 = Ang, R_3 = H, R_4 = OAng, R_5 = Ac, R_6 = α-ONic, R_7 = β-CH_3, R_8 = α-OH, R_9 = H (amygdaloidin B)		
	386. R_1 = H, R_2 = Hydrp, R_3 = H, R_4 = OAng, R_5 = Ac, R_6 = α-ONic, R_7 = β-CH_3, R_8 = α-OH, R_9 = H (amygdaloidin C)		
	387. R_1 = H, R_2 = Ang, R_3 = H, R_4 = OAng, R_5 = Ac, R_6 = α-OAc, R_7 = β-CH_3, R_8 = α-OH, R_9 = H (amygdaloidin D)		
	388. R_1 = H, R_2 = Ang, R_3 = Ac, R_4 = OHydrp, R_5 = Ac, R_6 = α-OAc, R_7 = β-CH_3, R_8 = α-OH, R_9 = H (amygdaloidin E)		
	389. R_1 = H, R_2 = Ang, R_3 = Ac, R_4 = OH, R_5 = Hydrp, R_6 = α-OAc, R_7 = β-CH_3, R_8 = α-OH, R_9 = H (amygdaloidin G)		
	390. R_1 = H, R_2 = Hydrp, R_3 = Ac, R_4 = OH, R_5 = Ang, R_6 = α-OAc, R_7 = β-CH_3, R_8 = α-OH, R_9 = H (amygdaloidin H)		
	391. R_1 = H, R_2 = Ac, R_3 = Hydrp, R_4 = OH, R_5 = Ang, R_6 = α-OAc, R_7 = β-CH_3, R_8 = α-OH, R_9 = H (amygdaloidin I)		
	392. R_1 = H, R_2 = Hydrp, R_3 = Ac, R_4 = OAng, R_5 = H, R_6 = α-OAc, R_7 = β-CH_3, R_8 = α-OH, R_9 = H (amygdaloidin J)		
	393. R_1 = H, R_2 = Ac, R_3 = Hydrp, R_4 = OAng, R_5 = H, R_6 = α-OAc, R_7 = β-CH_3, R_8 = α-OH, R_9 = H (amygdaloidin K)		
	394. R_1 = H, R_2 = Ang, R_3 = Ac, R_4 = OHydrp, R_5 = H, R_6 = α-OAc, R_7 = β-CH_3, R_8 = α-OH, R_9 = H (amygdaloidin L)		
	395. R_1 = H, R_2 = Ang, R_3 = H, R_4 = OHydrp, R_5 = Ac, R_6 = α-OAc, R_7 = β-CH_3, R_8 = α-OH, R_9 = Ac (amygdaloidin F)		
	396. R_1 = H, R_2 = Pr, R_3 = Ac, R_4 = OiBu, R_5 = Ac, R_6 = α-ONic, R_7 = α-CH_3, R_8 = H, R_9 = H (euphodendrophane A)	*E. dendroides*	Aljancic et al. (2011)
	397. R_1 = H, R_2 = iBu, R_3 = Ac, R_4 = OiBu, R_5 = Ac, R_6 = α-ONic, R_7 = α-CH_3, R_8 = H, R_9 = H (euphodendrophane B)		
	398. R_1 = H, R_2 = Pr, R_3 = Ac, R_4 = OiBu, R_5 = Ac, R_6 = α-ONic, R_7 = α-CH_3, R_8 = H, R_9 = Ac (euphodendrophane C)		
	399. R_1 = H, R_2 = iBu, R_3 = Ac, R_4 = OAc, R_5 = Bz, R_6 = α-OAc, R_7 = α-CH_3, R_8 = H, R_9 = H (euphodendrophane D)		

Table 1 continued

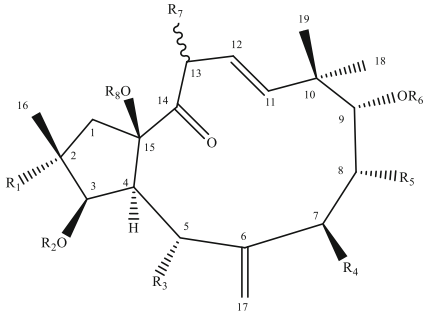
Isolated compound	Substitute (Common name)	Plant	References
	400. R_1 = H, R_2 = Pr, R_3 = Ac, R_4 = OiBu, R_5 = Bz, R_6 = α-OAc, R_7 = α-CH_3, R_8 = H, R_9 = H (euphodendrophane E)		
	401. R_1 = OH, R_2 = Bz, R_3 = Ac, R_4 = H, R_5 = Ac, R_6 = α-ONic, R_7 = β-CH_3, R_8 = H, R_9 = Ac (euphocharacin A)	*E. characias*	Corea et al. (2004b)
	402. R_1 = OH, R_2 = Bz, R_3 = Ac, R_4 = H, R_5 = Ac, R_6 = α-ONic, R_7 = β-CH_3, R_8 = H, R_9 = H (euphocharacin B)		
	403. R_1 = OH, R_2 = Bz, R_3 = Ac, R_4 = H, R_5 = Ac, R_6 = α-OBz, R_7 = β-CH_3, R_8 = H, R_9 = H (euphocharacin C)		
	404. R_1 = OH, R_2 = MeBu, R_3 = Ac, R_4 = H, R_5 = Ac, R_6 = α-ONic, R_7 = β-CH_3, R_8 = H, R_9 = Ac (euphocharacin D)		
	405. R_1 = H, R_2 = Bz, R_3 = Ac, R_4 = H, R_5 = Ac, R_6 = α-ONic, R_7 = β-CH_3, R_8 = H, R_9 = H (euphocharacin E)		
	406. R_1 = H, R_2 = Bz, R_3 = Ac, R_4 = H, R_5 = Ac, R_6 = α-ONic, R_7 = β-CH_3, R_8 = H, R_9 = Ac (euphocharacin F)		
	407. R_1 = H, R_2 = iBu, R_3 = Ac, R_4 = H, R_5 = Ac, R_6 = α-ONic, R_7 = β-CH_3, R_8 = H, R_9 = H (euphocharacin G)		
	408. R_1 = H, R_2 = iBu, R_3 = Ac, R_4 = H, R_5 = Ac, R_6 = α-ONic, R_7 = β-CH_3, R_8 = H, R_9 = Ac (euphocharacin H)		
	409. R_1 = H, R_2 = Pr, R_3 = Ac, R_4 = H, R_5 = Ac, R_6 = α-ONic, R_7 = β-CH_3, R_8 = H, R_9 = Ac (euphocharacin I)		
	410. R_1 = H, R_2 = Ac, R_3 = Ac, R_4 = H, R_5 = Ac, R_6 = α-ONic, R_7 = β-CH_3, R_8 = H, R_9 = Ac (euphocharacin J)		
	411. R_1 = H, R_2 = iBu, R_3 = H, R_4 = H, R_5 = Ac, R_6 = α-ONic, R_7 = β-CH_3, R_8 = H, R_9 = Ac (euphocharacin K)		
	412. R_1 = OH, R_2 = Bz, R_3 = H, R_4 = H, R_5 = Ac, R_6 = α-ONic, R_7 = β-CH_3, R_8 = H, R_9 = Ac (euphocharacin L)		
	413. R_1 = H, R_2 = Ac, R_3 = Ac, R_4 = OiBu, R_5 = Ac, R_6 = = O, R_7 = β-CH_3, R_8 = H, R_9 = Ac	*E. terracina*	Marco et al. (1998)
	414. R_1 = OH, R_2 = Ac, R_3 = OAc, R_4 = H, R_5 = H, R_6 = Nic, R_7 = α-CH_3, R_8 = Ac (nicaeenin A)	*E. nicaeensis*	Krstić et al. (2018)
	415. R_1 = H, R_2 = Ac, R_3 = OAc, R_4 = OAc, R_5 = H, R_6 = Ac, R_7 = β-CH_3, R_8 = Ac (pepluanin D)	*E. peplus*	Corea et al. (2004a)
	416. R_1 = OAc, R_2 = Bz, R_3 = OiBu, R_4 = OAc, R_5 = OH, R_6 = Nic, R_7 = β-CH_3, R_8 = H (pepluanin E)		
	417. R_1 = OAc, R_2 = H, R_3 = OiBu, R_4 = OBz, R_5 = OAc, R_6 = Ac, R_7 = β-CH_3, R_8 = H (euphodendroidin A)	*E. dendroides*	Corea et al. (2003a)
	418. R_1 = OAc, R_2 = H, R_3 = OMeBu, R_4 = OBz, R_5 = OAc, R_6 = Ac, R_7 = β-CH_3, R_8 = H (euphodendroidin B)		
	419. R_1 = OAc, R_2 = H, R_3 = ONic, R_4 = OBz, R_5 = OAc, R_6 = Ac, R_7 = β-CH_3, R_8 = H (euphodendroidin C)		

Table 1 continued

Isolated compound	Substitute (Common name)	Plant	References
	420. R_1 = H, R_2 = H, R_3 = OiBu, R_4 = OBz, R_5 = OAc, R_6 = Ac, R_7 = β-CH_3, R_8 = H (euphodendroidin D)		
	421. R_1 = H, R_2 = Ac, R_3 = OiBu, R_4 = OBz, R_5 = OAc, R_6 = Ac, R_7 = β-CH_3, R_8 = H (euphodendroidin E)		
	422. R_1 = OH, R_2 = Ac, R_3 = OiBu, R_4 = OBz, R_5 = OAc, R_6 = Ac, R_7 = β-CH_3, R_8 = H (euphodendroidin F)		
	423. R_1 = OAc, R_2 = Nic, R_3 = OAc, R_4 = OiBu, R_5 = OAc, R_6 = Ac, R_7 = β-CH_3, R_8 = H (euphodendroidin G)		
	424. R_1 = H, R_2 = Bz, R_3 = OAc, R_4 = OiBu, R_5 = OAc, R_6 = Ac, R_7 = β-CH_3, R_8 = H (euphodendroidin H)		
	425. R_1 = OMB(2-MethylButyrate), R_2 = H, R_3 = OMB, R_4 = OAc, R_5 = OAc, R_6 = Ac, R_7 = β-CH_3, R_8 = H	*E. obtusifolia*	Marco et al. (1999a)
	426. R_1 = OiBu, R_2 = H, R_3 = OMB, R_4 = OAc, R_5 = OAc, R_6 = Ac, R_7 = β-CH_3, R_8 = H		
	427. R_1 = ONic, R_2 = H, R_3 = OMB, R_4 = OAc, R_5 = OAc, R_6 = Ac, R_7 = β-CH_3, R_8 = H		
	428. R_1 = OMB, R_2 = H, R_3 = OMB, R_4 = OiBu, R_5 = OAc, R_6 = Ac, R_7 = β-CH_3, R_8 = H		
	429. R_1 = OAc, R_2 = H, R_3 = OMB, R_4 = OiBu, R_5 = OAc, R_6 = Ac, R_7 = β-CH_3, R_8 = H		
	430. R_1 = OMB, R_2 = MB, R_3 = OH, R_4 = OAc, R_5 = OBz, R_6 = Ac, R_7 = β-CH_3, R_8 = H		
	431. R_1 = OMB, R_2 = MB, R_3 = OH, R_4 = OiBu, R_5 = OAc, R_6 = Ac, R_7 = β-CH_3, R_8 = H		
	432. R_1 = ONic, R_2 = Ac, R_3 = OiBu, R_4 = OAc, R_5 = OAc, R_6 = Nic, R_7 = β-CH_3, R_8 = Ac (euphodendroidin I)	*E. dendroides*	Corea et al. (2003a)
	433. R_1 = H, R_2 = H, R_3 = OMeBu, R_4 = OMeBu, R_5 = OMeBu, R_6 = H, R_7 = β-CH_3, R_8 = H	*E. terracina*	Marco et al. (1998)
	434. R_1 = H, R_2 = H, R_3 = OiBu, R_4 = OiBu, R_5 = OiBu, R_6 = H, R_7 = β-CH_3, R_8 = H		
	435. R_1 = H, R_2 = H, R_3 = OMeBu, R_4 = OMeBu, R_5 = OiBu, R_6 = H, R_7 = β-CH_3, R_8 = H		
	436. R_1 = H, R_2 = H, R_3 = OiBu, R_4 = OiBu, R_5 = OMeBu, R_6 = H, R_7 = β-CH_3, R_8 = H		
	437. R_1 = H, R_2 = Ac, R_3 = OH, R_4 = OiBu, R_5 = OMeBu, R_6 = H, R_7 = β-CH_3, R_8 = H		
	438. R_1 = H, R_2 = H, R_3 = OiBu, R_4 = OiBu, R_5 = OMeBu, R_6 = H, R_7 = β-CH_3, R_8 = H		
	439. R_1 = H, R_2 = H, R_3 = OMeBu, R_4 = OiBu, R_5 = OMeBu, R_6 = H, R_7 = β-CH_3, R_8 = H		
	440. R_1 = OAc, R_2 = Ac, R_3 = OiBu, R_4 = OiBu, R_5 = OAc, R_6 = Ac, R_7 = β-CH_3, R_8 = H		
	441. R_1 = OAc, R_2 = Ac, R_3 = OBz, R_4 = OiBu, R_5 = OAc, R_6 = Ac, R_7 = β-CH_3, R_8 = H		
	442. R_1 = OAc, R_2 = $BzOCH_2CO$, R_3 = OAc, R_4 = OiBu, R_5 = OAc, R_6 = Ac, R_7 = β-CH_3, R_8 = H		
	443. R_1 = OAc, R_2 = Ac, R_3 = Ac, R_4 = OAc, R_5 = H, R_6 = Nic, R_7 = α-CH_3, R_8 = Ac	*E. peplus* *E. segetalis*	Jakupovic et al. (1998b)

Table 1 continued

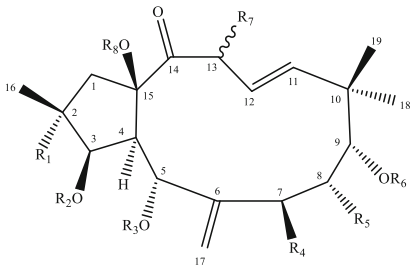
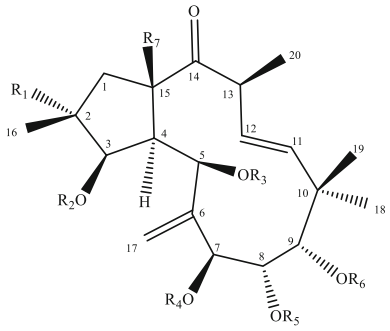
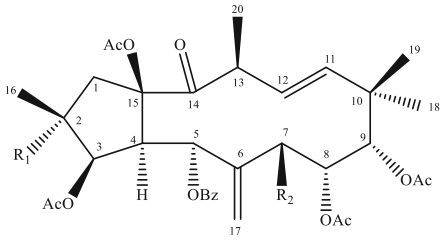
Isolated compound	Substitute (Common name)	Plant	References
	444. R_1 = OAc, R_2 = $COCH_2CO_2Ph$, R_3 = Ac, R_4 = OiBu, R_5 = OAc, R_6 = Ac, R_7 = β-CH_3, R_8 = H		Jakupovic et al. (1998a)
	445. R_1 = H, R_2 = H, R_3 = iBu, R_4 = OiBu, R_5 = OiBu, R_6 = H, R_7 = β-CH_3, R_8 = H		
	446. R_1 = H, R_2 = H, R_3 = MeBu, R_4 = OiBu, R_5 = OMeBu, R_6 = H, R_7 = β-CH_3, R_8 = H		
	447. R_1 = H, R_2 = H, R_3 = iBu, R_4 = OiBu, R_5 = OMeBu, R_6 = H, R_7 = β-CH_3, R_8 = H		
	448. R_1 = H, R_2 = Cin, R_3 = Ac, R_4 = H, R_5 = H, R_6 = Cin, R_7 = β-CH_3, R_8 = H		
	449. R_1 = OAc, R_2 = Ac, R_3 = Ac, R_4 = Ac, R_5 = H, R_6 = Ac, R_7 = OAc	*E. semiperfoliata*	Nothias et al. (2017)
	450. R_1 = OAc, R_2 = Ac, R_3 = Ac, R_4 = Ac, R_5 = Ac, R_6 = Ac, R_7 = OAc		
	451. R_1 = OH, R_2 = Ac, R_3 = Bz, R_4 = Nic, R_5 = Ac, R_6 = H, R_7 = CH_3 (euphodendroidin P)	*E. dendroides*	Esposito et al. (2017)
	452. R_1 = ONic, R_2 = Ac, R_3 = Ac, R_4 = Bz, R_5 = Ac, R_6 = H, R_7 = CH_3 (euphodendroidin Q)		
	453. R_1 = ONic, R_2 = Ac, R_3 = Ac, R_4 = Bz, R_5 = Ac, R_6 = Ac, R_7 = CH_3 (euphodendroidin R)		
	454. R_1 = ONic, R_2 = Ac, R_3 = Ac, R_4 = iBu, R_5 = Ac, R_6 = Ac, R_7 = CH_3 (euphodendroidin S)		
	455. R_1 = ONic, R_2 = Ac, R_3 = iBu, R_4 = Bz, R_5 = Ac, R_6 = H, R_7 = CH_3 (euphodendroidin T)		
	456. R_1 = OH, R_2 = Bz, R_3 = H, R_4 = Bz, R_5 = Ac, R_6 = Ac, R_7 = OH (euphodendroidin J)	*E. dendroides*	Esposito et al. (2016)
	457. R_1 = OAc, R_2 = iBu, R_3 = iBu, R_4 = Bz, R_5 = Ac, R_6 = Ac, R_7 = OH (euphodendroidin K)		
	458. R_1 = OAc, R_2 = Ac, R_3 = iBu, R_4 = Bz, R_5 = Ac, R_6 = Ac, R_7 = OH (euphodendroidin L)		
	459. R_1 = OAc, R_2 = Bz, R_3 = iBu, R_4 = iBu, R_5 = Ac, R_6 = Ac, R_7 = OH (euphodendroidin M)		
	460. R_1 = OAc, R_2 = H, R_3 = Bz, R_4 = Bz, R_5 = Ac, R_6 = Ac, R_7 = OH (euphodendroidin N)		
	461. R_1 = OAc, R_2 = H, R_3 = Bz, R_4 = Bz, R_5 = H, R_6 = Ac, R_7 = OH (euphodendroidin O)		
	462. R_1 = OAc, R_2 = Ac, R_3 = Ac, R_4 = iBu, R_5 = Ac, R_6 = Ac, R_7 = OH		
	463. R_1 = H, R_2 = AcO (altotibetin A)	*E.altotibetic*	Li et al. (2003)
	464. R_1 = H, R_2 = PrCOO (altotibetin B)		
	465. R_1 = OH, R_2 = AcO (altotibetin C)		
	466. R_1 = OH, R_2 = PrCOO (altotibetin D)		

Table 1 continued

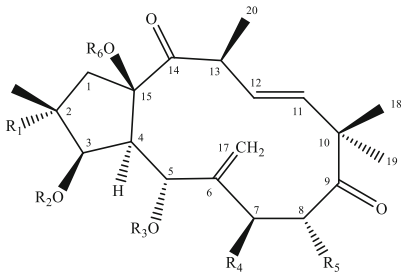
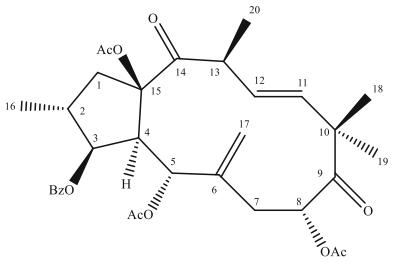
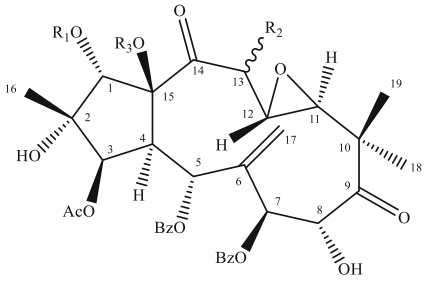
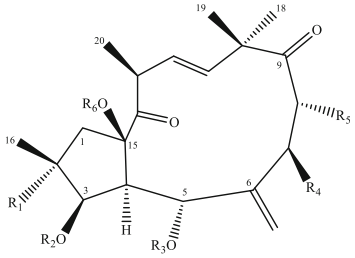
Isolated compound	Substitute (Common name)	Plant	References
	467. R_1 = H, R_2 = Bz, R_3 = α-Ac, R_4 = OAc, R_5 = OAc, R_6 = H	*E. mongolica*	Hohmann et al. (2003b)
	468. R_1 = H, R_2 = Ac, R_3 = α-Ac, R_4 = OBz, R_5 = OAc, R_6 = Ac	*E. turczaninowii*	Liu and Tan (2001)
	469. R_1 = H, R_2 = Ac, R_3 = α-Ac, R_4 = OAc, R_5 = OAc, R_6 = Ac		
	470. R_1 = OAc, R_2 = Ac, R_3 = α-Ac, R_4 = OAc, R_5 = H, R_6 = Ac (esulatin B)	*E. esula*	Hohmann et al. (1997)
	471. R_1 = H, R_2 = Pr, R_3 = α-Bz, R_4 = OiBu, R_5 = OH, R_6 = H (enukokurin)	*E. lateriflora*	Fakunle et al. (1989)
	472. R_1 = H, R_2 = iBu, R_3 = β-H, R_4 = H, R_5 = H, R_6 = Ac	*E. characias*	Seip and Hecker (1984)
	473. R_1 = H, R_2 = Tig, R_3 = β-H, R_4 = H, R_5 = H, R_6 = Ac		
	477. R_1 = OAc, R_2 = Ac, R_3 = β-Ac, R_4 = H, R_5 = Bz, R_6 = Nic		
	475. R_1 = OAc, R_2 = Ac, R_3 = β-Ac, R_4 = H, R_5 = Tig, R_6 = Nic		
	476.	*E. hyberna*	Ferreira et al. (2002)
	477. R_1 = H, R_2 = β-CH_3, R_3 = Ac (kansuinin B)	*E. kansui*	Wang et al. (2002)
	478. R_1 = Ac, R_2 = β-CH_3, R_3 = H (kansuinin C)		
	479. R_1 = Ac, R_2 = α-CH_3, R_3 = H	*E. esula*	Liu et al. (2002)
	480. R_1 = OH, R_2 = Bz, R_3 = H, R_4 = OAc, R_5 = OBz, R_6 = Ac (cyparissin A)	*E. cyparissias*	Lanzotti et al. (2015)
	481. R_1 = OH, R_2 = Bz, R_3 = Ac, R_4 = OAc, R_5 = OBz, R_6 = H (cyparissin B)		
	482. R_1 = H, R_2 = Ac, R_3 = Ac, R_4 = Pr, R_5 = OAc, R_6 = Ac	*E. sororia*	Lu et al. (2014)
	483. R_1 = ONic, R_2 = iVal (isoValeryl), R_3 = Ac, R_4 = H, R_5 = H, R_6 = H (euphodendrophane G)	*E. dendroides*	Jadranin et al. (2013)

Table 1 continued

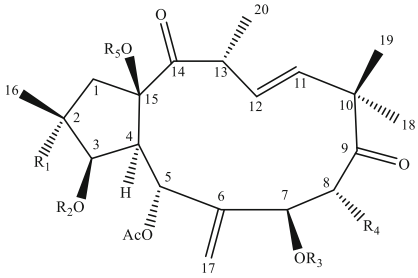
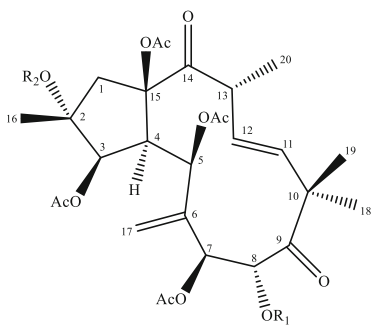
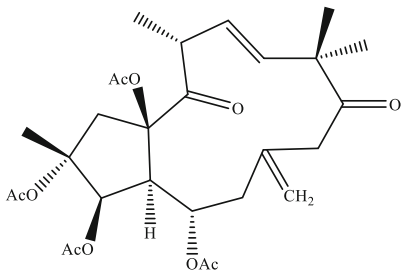
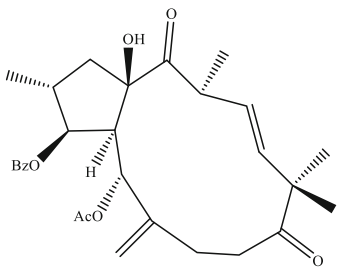
Isolated compound	Substitute (Common name)	Plant	References
	484. R_1 = OAc, R_2 = Ac, R_3 = Ac, R_4 = OBz, R_5 = Ac	*E. paralias*	Jakupovic et al. (1998c)
	485. R_1 = OAc, R_2 = Ac, R_3 = Ac, R_4 = OiBu, R_5 = Ac		
	486. R_1 = OAc, R_2 = Ac, R_3 = Ac, R_4 = OMeBu, R_5 = Ac		
	487. R_1 = OAc, R_2 = Ac, R_3 = Ac, R_4 = OAng, R_5 = Ac		
	488. R_1 = OAc, R_2 = Ac, R_3 = Ac, R_4 = OAc, R_5 = Ac (SJ-23b)		
	489. R_1 = H, R_2 = Ac, R_3 = Ac, R_4 = OiBu, R_5 = Ac		
	490. R_1 = OAc, R_2 = Ac, R_3 = Ac, R_4 = H, R_5 = Ac	*E. hyberna*	Appendino et al. (2002)
	491. R_1 = ONic, R_2 = Ac, R_3 = Ac, R_4 = OAc, R_5 = Ac		
	492. R_1 = OAc, R_2 = Ac, R_3 = iBu, R_4 = OAc, R_5 = Ac		
	493. R_1 = OAc, R_2 = Ac, R_3 = Ac, R_4 = OTigl, R_5 = Ac	*E. semiperfoliata*	Appendino et al. (1998)
	494. R_1 = ONic, R_2 = Ac, R_3 = Ac, R_4 = OAc, R_5 = Ac		
	495. R_1 = OAc, R_2 = Ac, R_3 = Bz, R_4 = OAc, R_5 = Ac		
	496. R_1 = OAc, R_2 = Ac, R_3 = iBu, R_4 = OAc, R_5 = Ac		
	497. R_1 = OBz, R_2 = Ac, R_3 = Ac, R_4 = OAc, R_5 = Ac		
	498. R_1 = OAc, R_2 = Ac, R_3 = Ac, R_4 = OH, R_5 = Ac		
	499. R_1 = OAc, R_2 = Ac, R_3 = iBu, R_4 = H, R_5 = Ac		
	500. R_1 = Ac, R_2 = H	*E. amygdaloides*	Nothias-Scaglia et al. (2014)
	501. R_1 = iBu, R_2 = H		
	502. R_1 = Tig, R_2 = H		
	503. R_1 = Bz, R_2 = H		
	504. (esulatin E)	*E. esula*	Günther et al. (1998)

Table 1 continued

Isolated compound	Substitute (Common name)	Plant	References
	505. (helioscopianoid M)	*E. helioscopia*	Mai et al. (2018b)

Andrea Vasas and coworkers also developed a three-step sample for the screening of macrocyclic diterpenes in 33 Euphorbiaceae species. The sample preparation includes the percolation of powdered plant material with MeOH at room temperature. After concentration, water is added to the extract and it is subjected to solvent–solvent partitioning with $CHCl_3$. The organic phase is subjected to polyamide-6 column chromatography with a MeOH:H_2O gradient system (1:3, 3:1, 4:1 and 1:0) as eluent. The concentrated fractions are monitored by TLC (Fig. 1), with the use of $CHCl_3$:Me_2CO (19:1) and cyclohexane:EtOAc:EtOH (60:30:1) as mobile phases. Spraying with concentrated sulfuric acid, followed by heating at 105 °C, is used for visualization of the diterpene spots which are appeared in black or dark brown color or rarely blue spots with Rf values of 0.2–0.8. The fraction eluted with MeOH (60%) are enriched in the diterpene esters, with a mixture of MeOH:H_2O (4:1) rich in triterpenes and fats, and fractions obtained from MeOH (100%) contained large amounts of chlorophyll (Vasas et al. 2012). For final purification, repeated column chromatography separations, using different adsorbents have been applied as is reported in supplementary file.

Biological activities and SAR studies

Antineoplastic activity

Liu and Tan (2001) evaluated five new (377–379, 467, and 468) along with one known 497 jatrophane diterpenoids from *E. turczaninowii* in mouse ear inflammation assay and in cytotoxicity test against the mouse melanoma B16 cell line. Results showed that all the six exhibited no irritant activity (ID_{50}^{24-} > 100 μg/ear) in a mouse ear inflammation model and also no significant cytotoxicity when evaluated against the B16 melanoma cell line ($IC_{50} > 5$ μg/mL) (Liu and Tan 2001).

Liu et al. (2002) investigated the cytotoxicity of two new macrocyclic jatrophanes (91 and 479) of *E. esula* by the standard MTT test for the tumor cell lines mouse melanoma B16, human epidermoid KB, human hepatoma SMMC, human gastric adenocarcinoma BGC, and leukemia HL-60 (vinblastine was used as positive control with IC_{50} being 2.44, 3.23, 2.78, 1.47, and 1.32 μg/mL, respectively). The results indicated that 479 was cytotoxic to B16 with $IC_{50} = 1.81$ μg/mL. The irritant activity assay indicated that both 91 and 479 are inactive in a mouse ear inflammation model ($ID_{502}^{4} >$ 100 μg/ear) (Liu et al. 2002).

Wang et al. (2002) isolated three jatrophanes kansuinins A (95), B (477), and C (478) from *E. kansui* and tested their effects on the division of isolated cells from the early Xenopus laevis embryo to investigate the cell growth inhibition. The results showed that 95 and 478 did not inhibit cell division of the isolated cells. However, treatment of cells with 10, 50 and 200 μg/mL kansuinin B (477) structure of which was very similar to that of 95 resulted in cleavage arrest in 57%, 87%, and 98% of cells, respectively. Concerning observations, among these three jatrophanes (95, 477, and 478) only kansuinin B (477) showed remarkable activity, resulting in 87% cleavage arrest at 50 μg/mL (Wang et al. 2002).

Miglietta et al. (2003) isolated known jatrophanes (362, 358, and 357) from *E. semiperfoliata*. To discover more desirable biological analogues with

mechanisms similar to that of paclitaxel, they focused on the action of these compounds on tubulin function, both in the assembly of purified tubulin and in living cells. These jatrophanes did not interfere with GTP-induced tubulin assembly in contrast to the other microtubule-interacting drugs; instead, they induced the formation of tubulin polymers rapidly in the absence of other promoters. Besides, jatrophane polymerization products were destabilized and disassembled by calcium ions unlike those of paclitaxel (Schiff and Horwitz 1980). In addition, no irregular tubulin polymerization products were formed. In this regard, jatrophanes interact with the tubulin differently from paclitaxel and their biological activity cannot be caused by suppression of microtubule dynamics, which is the target of many microtubule-interacting agents. At a cellular level, jatrophanes reorganize microtubules without inducing microtubule bundling in contrast to the common tubulin-polymerizing agents. These results depicted that jatrophane polyesters from *E. semiperfoliata* can represent a new type of active tubulin-interacting pharmacophores (Miglietta et al. 2003).

Betancur-Galvis et al. (2003) evaluated the antitumor activity of seven macrocyclic jatrophanes (425–431) of *E. obtusifolia* by nicotinamide adenine dinucleotide factor (NADH) oxidase activity assay. The results depicted that all (425–431) inhibited NADH oxidase activity, with IC_{50} values ranging from 5.1 ± 0.2 μM for 371 to 13.9 ± 1.8 μM for 366. The performing SAR studies showed that 344, the strongest inhibitor, displayed an isobutyrate group at C-7 leading to an IC_{50} value of 6.3 μM. Less active compounds (426 and 427) had an acetoxy group at C-7. Even 429 with an isobutyrate group at C-7 and an acetoxy group at C-2 showed a reduction in NADH oxidase inhibitory. Accordingly, it was proposed that the presence of acetoxy groups at C-2 and C-7 reduces the inhibitory effect on the NADH oxidase activity. The suggested mechanism was associated with the inhibition of the mitochondrial electron transport chain that arose from the breakdown of the transmembrane mitochondrial potential, resulting in early apoptosis (Betancur-Galvis et al. 2003).

Valente et al. (2003) evaluated pubescenes A (270), B (271), and C (271) of *E. pubescens* for their in vitro effect on the growth of three human cancer cell lines: MCF-7(breast), NCI-H460 (lung), and SF-268 (CNS) as well as their capacity to interfere with the proliferation of human peripheral blood lymphocytes. The compounds did not show any inhibitory activity on in vitro growth of the human cancer cell lines even at a concentration as high as 50 μM. They even had not any suppressor effects against the in vitro proliferation of human lymphocytes to phytohaemagglutinin even when tested at 100 μM (Valente et al. 2003).

Valente et al. (2004a, b, c) evaluated jatrophanes euphopubescenol (122) and euphopubescene (300) of *E. pubescens* for their ability to inhibit the in vitro growth of three human tumor cell lines: MCF-7, NCI-H460, and SF-268. They inhibited both MCF-7 and NCI-H460 cell lines with GI_{50} values ranging between 40.9 μM and 95.3 μM but were not effective on the SF-268 cell line (Valente et al. 2004b).

Valente et al. (2004a, b, c) isolated a new jatrophane diterpene, pubescenol (123) from *E. pubescens* evaluated for its ability to inhibit the in vitro growth of MCF-7, NCI-H460, and SF-268 cell lines. Results showed that 123 is a moderate growth inhibitor for all mentioned cell lines (GI_{50} = 69.04 ± 4.59, 55.56 ± 3.95, and 75.16 ± 6.54, respectively) (Valente et al. 2004c).

Lu et al. (2008) isolated four new jatrophane-type diterpenoids (3, 162, 164 and 166) together with 16 known compounds from *E. helioscopia*. All the compounds were evaluated for their cytotoxicity against human cervical carcinoma cells (HeLa) and breast tumor cells (MDA-MB-231) among which only euphornin (208) was found to have inhibitory activity for the HeLa and MDA-MB-231 cells (IC_{50} = 3.1 and 13.4 μM, respectively). All other jatrophanes were inactive ($IC_{50} > 10$ μM) on both cell lines (Lu et al. 2008).

Hegazy et al. (2010) isolated two new jatrophanes guyonianins E (364) and F (21) along with a known jatrophane diterpene (362) from methylenechloride/methanol extract of the aerial parts of *E. guyoniana*. Compound 362 showed significant activity (IC_{50} = 35 μM) while new compounds 364 and 21 had a moderate activity (IC_{50} = 70 and 100 μM, respectively) against human embryonic kidney 293 (HEK293) cells (Hegazy et al. 2010).

Wang et al. (2012) isolated two jatrophanes, kansuinin A (95) and kansuinin B (477), by cytotoxic assay guided multistep separation on the dichloromethane extract of the roots of *E. kansui*. These diterpenoids were evaluated in vitro for their

cytotoxicity effect in hepatoma cell lines (Bel-7402 and Bel-7402/5FU) and human gastric carcinoma cell lines (BGC-823 and SGC-7901) and displayed no antiproliferative effects (Wang et al. 2012).

Liu et al. (2014) isolated a new jatrophane-type diterpenoid (218) from the whole plant of *E. lunulata* Bge. The in vitro antiproliferative activities against MCF-7 and non-small cell lung carcinoma (NCI-H460) cell lines for this compound were evaluated. The results showed moderate cytotoxic activities for both cell lines with the IC_{50} values ranging from 32.1 to 58.2 μM (Liu et al. 2014).

Ghanadian et al. (2015) isolated three new diterpenes (342–344) from *E. osyridea* and analyzed their cytotoxicity by performing MTT, annexin V-FITC, and PI staining assays against Caov-4 and OVCAR-3 ovarian cancer cell lines. The results showed that 131–133 inhibit cell proliferation through apoptosis in both Caov-4 and OVCAR-3 cells. Compounds 342 and 343 illustrated more significant inhibitory effects with IC_{50} values of 38.81 ± 3.30 and 42.59 ± 4.50 μM on the OVCAR-3 cell line, and 46.27 ± 3.86 and 36.48 ± 3.18 μM on the Caov-4 cell line. Compound 344 showed moderate cytotoxicity with IC_{50} values of 75.65 ± 2.56 and 85.86 ± 6.75 μM against OVCAR-3, and Caov-4 cell lines, respectively. Doxorubicin as the standard drug suppressed the ovarian cancer cells, with IC_{50} values of 0.33 ± 0.09 and 0.84 ± 0.19 on OVCAR-3 and Caov-4 cells, respectively (Ghanadian et al. 2015).

Shadi et al. (2015) isolated jatrophane 296 from *E. connata* and evaluated its cytotoxicity using MTT assay against two MCF-7 and MDA-MB 469 human breast cancer cell lines. It showed weak cytotoxicity with IC_{50} values of 55.67 ± 7.09 μM against MDA-MB and moderate cytotoxicity with IC_{50} values of 24.33 ± 3.21 μM against MCF-7 cell line (Shadi et al. 2015).

Bahmani et al. (2017) evaluated cytotoxicity and the molecular mechanism of apoptosis induced by the novel 'jatropha-6(17),11E-diene' class derivatives (342–344) previously extracted from *E. osyridea* on Caov-4 and OVCAR-3 ovarian cancer cell lines. 133 showed the lowest activity against Caov-4 and OVCAR-3 ovarian cell lines ($IC_{50} = 85.86 \pm 6.75$ and 75.65 ± 2.56 μM, respectively). 343 showed stronger cytotoxic effects ($IC_{50} = 36.48 \pm 3.18$ and 42.59 ± 4.50 μM) than 133 ($IC_{50} = 46.27 \pm 3.86$ and 38.81 ± 3.30 μM) upon which it seems that benzoyl moiety occupying position 3 and C-8 occupation with propyl group in Euph B have critical effects in the potency of this jatrophane (Pešić et al. 2011). Apoptosis evaluation showed 342–344 increase induction of both early and late apoptosis ($P < 0.01$). Mitochondrial membrane potential ($\Delta\Psi m$), ROS production, and caspase 3 and 9 activation were also evaluated which were all increased by these compounds in treated cells. According to these observations, 342 and 343 displayed significant inhibitory effects on OVCAR-3 and Caov-4 proliferation and induction of apoptosis. Induced ROS production in Caov-4 and OVCAR-3 was evaluated 2.6 and 4.4 for 131; and 4.7 and 9.9 fold/control for 343, respectively. In this regard, ROS overproduction and trigger of caspase activation might be the potential mechanism of these compounds interposing apoptosis in the ovarian cancer cells by mitochondria or pro-oxidant activity of ionizable groups of 342 and 343 (Bahmani et al. 2017).

MDR reversing activity

In chemotherapy, P-gp is a membrane protein that confers upon cells the ability to resist lethal doses of certain cytotoxic drugs by pumping them out of the cells leading to a reduction of their cytotoxic or antiproliferation effects (Barile et al. 2008b). The presence of P-gp transport proteins in the microorganism membrane makes also challenge the treatment of the infectious diseases, as they cause a mechanism of multidrug resistance (MDR) developed during treatment, by pumping out anti-infectious drugs (Schnabel and Hiersemann 2009; Schnabel et al. 2010; Shukla et al. 1999; Sutherland and Polley 2011). The emergence of cancer MDR has been pointed out as one of the major barriers to successful chemotherapy. The most well-known mode of resistance has been associated with P-gp (ATB-binding cassette sub-family B member 1 (ABCB1)/P-gp), the first human ABC transporter to be described. The overexpression of ABCB1 results in reduced intracellular concentration of drugs to levels leading to treatment failure, causing also cross-resistance or cross-sensitivity to other drugs (Gottesman et al. 2002). To enhance the efficacy of chemotherapy, several approaches have been proposed to circumvent MDR. Developing the molecules that are able to impair the drug efflux mediated by ABCB1 as well as the development of collateral

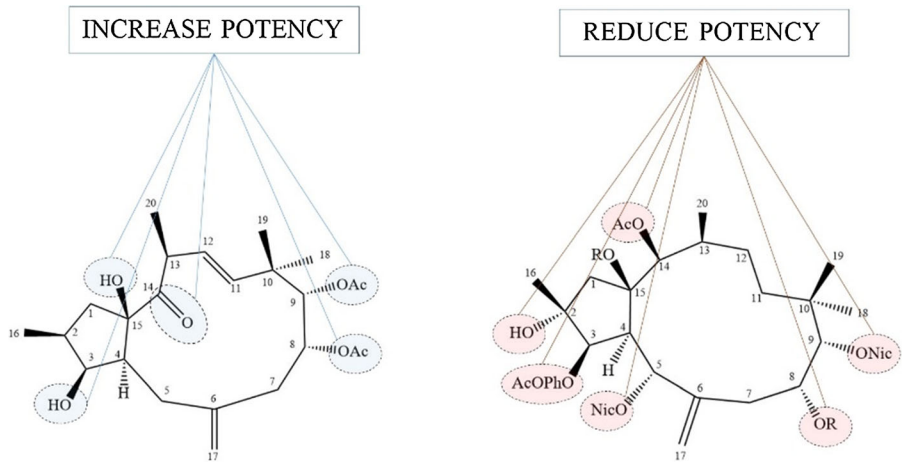


Fig. 13 Key pharmacophoric elements for the anti-MDR activity of P-gp

sensitivity agents lay among the most promising strategies (Callaghan et al. 2014; Szakács et al. 2014). Therefore, potent and selective P-gp inhibitors are potential targeted agents to combat chemotherapy drug resistance. In drug discovery programs for cancer MDR, a large number of compounds have been investigated (Eid et al. 2015; Palmeira et al. 2012; Wu et al. 2011) among which the polyoxygenated jatrophane and lathyrane-type macrocyclic diterpenes from *Euphorbia* species have shown potential anti-MDR activities, by ABCB1 modulation and/or by selective targeting of MDR cancer cells (Corea et al. 2009; Vasas and Hohmann 2014; Vieira et al. 2014).

Ferreira et al. (2014) in a review article provided a summary (2001–2013) of anticancer compounds from *Euphorbia* and *Momordica* species comprising diterpenes, triterpenes, and phenolic derivatives, particularly for their P-gp inhibition ability (Ferreira et al. 2014). In another study, Amaral et al. (2016) prepared a mini-review focusing on the property of MDR cancer cells (proliferation, apoptotic mechanism, efflux pumps) affected by bioactive compounds.

A set of over seventy jatrophanes and modified jatrophanes have been specifically investigated by Corea et al. (2009) for their MDR reversing potential (Corea et al. 2009). This wide analysis let the authors attribute the MDR reversal activity of these compounds to the key pharmacophoric elements as follows (Fig. 13):

Hohmann and others have isolated 22 jatrophane polyesters from *Euphorbia* genera reported in several articles over the period of 2001 to 2003, three of which (375, 376, and 467) were from *E. mongolica;* 168, 199, 200, 301, 302, and 305 from *E. serrulata;* 374 (esulatin A), 382 (esulatin D), 470 (esulatin B) from *E. esula;* 381, 351, 354, 352, and 353 from *E. peplus* (Hohmann et al. 2002); a novel diterpene polyester named euphosalicin (383) and finally two new jatrophanes (26 and 372) from *E. salicifolia* (Hohmann et al. 2001a). These compounds were investigated for the reversal of MDR in L5178 mouse lymphoma cells using the rhodamine 123 (Rho123) exclusion test. 375, 376, and 467 displayed a significant effect on inhibiting the efflux-pump activity of multidrug-resistant L5178 mouse lymphoma cells as compared with that of the positive control 'verapamil' (FAR = 13.14 at 23 μM) in the range of 11.2–112 μM as expressed by the FAR increasing at higher concentrations (FAR = 12.29, 2.60, 2.79 at 11.2 μM and FAR = 22.92, 18.02, 29.29 at 112 μM) (Hohmann et al. 2003b). 381, 354, and 352 also displayed strong activity (FAR = 71.98–78.88) compared with that of the positive control 'verapamil' (FAR = 8.27); while 374, 382, 470, and 372 revealed weak potency. 302 and 353 had low effect on the drug accumulation at higher concentrations than at lower ones; in these cases, the increased membrane permeability could be responsible for the toxic effect that resulted in enhanced Rho123 diffusion out of the treated cells due to a membrane disintegration (Hohmann et al. 2002). The novel diterpene polyester 383 displayed considerable potency in inhibiting the efflux-pump activity of MDR

P-gp in mouse lymphoma cells (FAR = 22.46 at 2 μg/mL) being even stronger than the positive control 'verapamil' (FAR = 8.49 at 2 μg/mL) (Hohmann et al. 2001a). Comparison of the pairs (302 and 305), (374 and 372), and (354 and 352) differing only in the lipophilicity of one of the substituents (OH, OAc, OiBu) demonstrated an increase in the MDR modifier effect. These data supported the conclusion that the effect on drug accumulation in drug-resistant cells is proportional to the hydrophobicity. Surprisingly, other structurally related pairs of compounds such as (374 and 381), with 2-OAc and 2-H and with 9-OAc and 9-ONic substitutions, respectively, and (351 and 353) differing only in the esterification at C-7-C-9 (7-OAc/7-OiBu, 8-OAc/8-OH, and 9-OAc/9-ONic) exerted very different effects in the modulation of the MDR of mouse lymphoma cells (Hohmann et al. 2002). This observation has been explained by the high flexibility of the macrocyclic ring of the jatrophane skeleton (Appendino et al. 1998).

Corea et al. isolated ten closely related jatrophanes from *E. dendroides*, nine of which were new, euphodendroidins A-I (417–424, and 432) and one was known (444) (Corea et al. 2003a). In another research Corea et al. isolated five new jatrophanes (pepluanins A-E (181–183, 415, and 416)) together with two known analogues (355 and 443) from *E. peplus* (Corea et al. 2004a) and twelve new diterpenes named euphocharacins A-L (401–412) from *E. characias* (Corea et al. 2004b). The inhibitory activity of all compounds was assayed in Pgp-mediated daunomycin transport efflux. Euphodendroidin D (420) (Corea et al. 2003a) and pepluanin A (181) (Corea et al. 2004a) together with euphocharacins C (403) and I (409) was found to be highly potent inhibitors since they were almost twofold more efficient than 'cyclosporin A', the golden standard of P-gp modulators. Thus, the following sequence in efficiency at C-3 may now be proposed as: propionyl > benzoyl > acetyl, isobutyryl. Another positive role was played by the benzoyl at C-9 (euphocharacin C (403), 123%) which was better than nicotinyl in euphocharacin B (402) (72%). However, they went beyond the southwestern fragment of the molecule (C-2/C-5) binding by performing SAR studies on pepluanins A-E (181–183, 415, and 416) and underlined the importance of the substitution on other carbons of the medium-sized ring C-8, C-9, C14, and C-15 in modulating the activity. Observations showed this series of seven jatrophane diterpenes (pepluanins A-E, 355, and 443) highlighting the importance of an acetoxyl at C-8 (by comparison to a free hydroxyl), and of a free hydroxyl at C-15. Moreover, a carbonyl at C-14 and acetoxyl at C-9 were also favorable substitutions.

Corea et al. (2003a, b) isolated 10 terracinolides from *E. dendroides*, four of which (terracinolides J-L (32–34) and 13α-OH terracinolide F (35)) were novel and two other, (abeodendroidin F (102) and epiabeodendroidin F (103)) were new (Corea et al. 2003b). The inhibitory effect of P-gp mediated daunomycin efflux by these compounds was evaluated relative to cyclosporine A (CsA) by monitoring intracellular drug accumulation. Terracinolide H (45) displayed significant inhibition, even more potent (138 ± 27%) than cyclosporin A (CsA). SAR studies demonstrated that the revertant activity of terracinolides and abeojatrophanes was strongly affected by the presence of a free hydroxyl group, with the following ranking of position: 3 > 15 > 13 > 2 (Corea et al. 2003b).

Valente et al. (2004) isolated pubescenes A-D (270–272, and 297) from *E. pubescens* and evaluated them for MDR reversing activity on L5178 mouse lymphoma cells. Tested compounds displayed strong activity in the cells by inhibiting the efflux-pump activity mediated by P-gp. Among all, pubescene A (270) (FAR = 79.78 in 32 μM) and D (297) (FAR = 111.00 in 32 μM) exhibited the highest effects in reversing MDR compared with the positive control 'verapamil'. The highest lipophilicity of pubescene A (270) due to the presence of four ester groups can be suggested for its strong activity. Another important structural feature was the presence of the benzoyl group as a sterically expansive group at C-7. Moreover, the higher activity of pubescene D (297) compared with 272 was due to a different configuration of the stereocenter at C-2 bearing an α-oriented Methyl-16 (Valente et al. 2004a).

Ferreira et al. (2005) isolated rearranged jatrophanes (270–272, 297, 122, 300, and 123) from *E. pubescens*. They evaluated the ability of pubescene A (270), pubescene B (271), pubescene C (272), and pubescene D (297) as MDR modulators on L5178 mouse lymphoma cells, most of which were able to enhance the Rho123 accumulation of human MDR1-gene-transfected mouse lymphoma cells. Euphopubescenol (122), euphopubescene (300), and pubescenol (123) were examined for the reversal of MDR

on the human breast cancer MDA-MB-231(HTB-26) cell line by flow cytometry. The tested compounds did not show significant toxicity (FAR = 0.9, 0.8; 0.9, 0.7; 1.0, 0.7 at 5 and 20 μM, respectively) on MDA-MB-231 cells since their ID_{50} values were higher than those of the DMSO control (FAR = 0.8). Moreover, they were tested on MRP; carboxyfluorescein (BCECF-AM) served as a substrate for MRP-mediated drug efflux and its accumulation in the MDA-MB-231 breast cancer cells was measured at 5 and 20 μM respectively; Some compounds i.e. 270, 297, 122, 300, and 123 showed a remarkable MRP-specific increase in fluorescence activity (11.5, 3.9, 12.7, 4.4, and 5.8 at 20 μM) comparing to the positive control 'indomethacine' (FAR = 1.5 at 27.9 μM) (FERREIRA et al. 2005).

Buey et al. (2005) evaluated the interactions of microtubules with a number of compounds consist of jatrophanes described as stabilizing agents, to understand which ones have the capability to stabilize microtubules and mimic the activity of paclitaxel/docetaxel. Most of them including lonafarnib, dicumarol, lutein, and jatrophanes did not show any stabilizing effect on microtubules. Jatrophanes 362, 358, and 357 have not able to induce assembly at concentrations as high as 60 μM guanosine triphosphate (GTP)-tubulin and 66 μM ligand, as checked by centrifugation and electron microscopy. Overall, jatrophanes indicated no ability of induction or modulation in vitro microtubule assembly or displacement of a fluorescent taxoid (Flutax-2) from its binding site, suggesting that the microtubule-stabilizing activity of these compounds, if any, arises from interactions with other factors regulating cellular microtubule polymer mass rather than by direct binding to microtubules (Buey et al. 2005).

Engi et al. (2007) isolated nine diterpenes from *E. esula* (compounds 374 and 470), *E. peplus* (compounds 351 and 352), and *E. serrulata* (compounds 305, 302, and 168). Their MDR-reversal effects on a human colon (COLO320) cancer cell line, as well as the synergistic capacity of these compounds, were investigated. 305, 302, and 168 were found to be very strong inhibitors (FAR > 2.00 at 40 μg/mL). For 305 the effect was almost the same at the two concentrations (FAR = 2.05 at 4 μg/mL and FAR = 2.03 at 40 μg/mL), meaning that both of the applied concentrations were in the saturation zone. 374, 470, 351, and 352 were moderately effective (0.59 < FAR < 1.7). Moreover, the synergistic capacity of these compounds in combination with 'epirubicin' was examined and 302 proved to be the most active, exhibiting a synergistic interaction (FIX = 0.25) with 'epirubicin'. In contrast, 352 and 168 did not enhance the antiproliferative effect of the anticancer drug when applied in combination with the COLO320 cell line. Comparing the efficacies of 305 and 302, it can be presumed that the presence of a hydroxy group instead of peracylation is favourable as it concerns the antiproliferative activity in combination with 'epirubicin' (Engi et al. 2007).

Barile et al. (2008a, b) isolated new jatrophanes: euphoscopin M (104) and euphoscopin N (105) together with three other known analogues: euphoscopin C (245), euphornin (208), and epieuphoscopin B (254) from *E. helioscopia*. The biological activities of 104, 105, 245, 208, and 254 were monitored through their ability to inhibit P-gp-mediated mitoxantrone efflux leading to drug accumulation, measured by flow cytometry. All tested compounds exhibited concentration-dependent inhibition of mitoxantrone efflux. The concentration dependence analysis indicated that 254 with IC_{50} value of 1.71 ± 0.83 μM is twice as potent as the reference inhibitor 'cyclosporin A' (IC_{50}: 3.37 ± 1.39 μM). In contrast, 208 is much less efficient with IC_{50} value of 8.46 ± 3.51 μM. Finally, the remaining compounds 104, 105, and 245 with IC_{50} values of 3.78 ± 2.18, 3.47 ± 1.88, and 3.58 ± 1.78 μM, respectively appeared similar in activity to 'cyclosporin A' (Barile et al. 2008a). Comparing jatrophanes of *E. helioscopia* with those from other *Euphorbia* species (Corea et al. 2003a, b, 2004a, b), three main structure–activity relationships was deduced: (1) a marked, fivefold positive effect on P-gp inhibition played by a carbonyl versus an OAc group at position 9 when comparing 254 and 208; (2) a twofold positive effect of an OAc versus an OBz substituent at position 7 when comparing 254 and 245; (3) a neutral effect of having the double bond at either 11–12 or 12–13 positions in 105 and 104 (Barile et al. 2008a).

Duarte et al. (2008) isolated tuckeyanols A (143), B (144), and euphotuckeyanol (142) from *E. tuckeyana*. They tested them for P-gp modulating properties on human MDR1 gene-transfected and parental L5178 mouse lymphoma cell lines. Moreover, their combinations with the cytostatic anticancer drug 'epirubicine' were tested in order to obtain evidence as to

additive or synergistic interactions. Tuckeyanols A (143), B (144), and euphotuckeyanol (142) showed strong activity (FAR = 39.8, 25.0, and 81.0 at 4 μM, respectively) compared to 'verapamil' (FAR = 13.7 at 10 μM). SAR studies on euphotuckeyanol (142) with the highest activity (FAR = 81.0 at 4.0 μg/mL) showed that 142 with seven ester residues has the highest values of logP (6.7), molecular weight (818), and the highest number of hydrogen bond acceptor groups (15 H-bond acceptors), all of which considered by several authors, as important requirements to P-gp modulation (Robert and Jarry 2003; Wiese and Pajeva 2001). Based on the spatial orientation of the SP2 terminal methylene group at C-6, analouge 142 showed endo-type conformation (NOESY correlation of exo-methylen H-17 with 5-H (β)) (Jakupovic et al. 1998b, c; Marco et al. 1998) versus tuckeyanols A (143) and B (144) with exo-type conformation (Duarte et al. 2008) which may also be an important factor in MDR modulation. Concerning all these factors, it is difficult to explain which of them has the most relevant role for the high MDR-reversal activity. Duarte et al. observed that tested compounds exhibited a synergistic interaction with 'epirubicine' on the studied cell line (fractional inhibitory index (FIX) = 0.07–0.25) among which, the most effective compound was euphotuckeyanol (142), expressing a low FIX (0.07 and 0.08, respectively) in the checkerboard experiments (Duarte et al. 2008).

Pešic et al. (2011) investigated the inhibitory effect of two previously isolated jatrophanes from *E. dendroides*: euphodendrophane A (396) and euphodendrophane B (397) on the growth of the sensitive non-small cell lung carcinoma (NSCLC) cell line (NCI-H460) and its resistant counterpart (NCI-H460/R). They further examined the potential of Euph A and B on mdr1 mRNA expression (Pešić et al. 2011). Both jatrophanes were more efficacious at P-gp inhibition than 'verapamil'. The development of synthetic jatrophanes based on their natural skeleton revealed that the presence of a lipophilic aromatic substituent at C-3 enhances the P-gp inhibitory activity compared to that of 'verapamil' (Schnabel et al. 2010). Although Euph A and B possess the smaller benzoyl residue at C-3, it does not influence their effect on P-gp inhibition which even overcomes the effect of 'verapamil'. Earlier findings highlighted the positive role of the free hydroxyl group at C-5 and acetyl group at C-8 being present in Euph A and B (Corea et al. 2009). Both jatrophanes significantly reduced the level of mdr1 expression in (NCI-H460) sensitive cells, suggesting that they could not induce the development of resistance in spite of PTX which is a P-gp substrate. For the resistant cells, PTX decreased the expression of mdr1, while both jatrophanes did not significantly influence the expression level. Observed inhibitory effect of Euph A and B on P-gp synthesis in sensitive cell line and P-gp activity in resistant cell lines could be considered as their application as adjuvant therapy in both sensitive and resistant malignancies. Pešic et al. had shown earlier that the resistant NCIH460/R cell line displays cross-resistance to paclitaxel, vinblastine, doxorubicin, epirubicin, and etoposide (Pesic et al. 2006) so they were interested in the investigation of the simultaneous combinations of Euph A/B and PTX on the MDR cancer cell lines. Importantly in this study, both Euph A and B enhanced the growth inhibition of PTX in a concentration-dependent manner. In this regard, all combinations used in the course of treatments of resistant NCIH460/R cells induced a strong synergistic effect. This research demonstrated that Euph A and B have the potential to reverse PTX resistance. Moreover, it was showed that the synergism between Euph A/B and PTX is partly due to their mutual effect on microtubule assembly (Pešić et al. 2011).

Vasas et al. (2011) isolated esulatins A-E (374, 470, 92, 382, and 504) and H-M (99, 128, 129, and 132–134) from *E. esula*. They were evaluated for their antiproliferative activity against a set of human adherent cell lines of gynecological origin (HeLa (cervix adenocarcinoma), Ishikawa (endometrial adenocarcinoma), and MCF-7 (breast epithelial adenocarcinoma)) using the MTT test and 'cisplatin' as positive control (Vasas et al. 2011). Moreover, Vasas et al. tested MDR-reversing activity of the compounds on L5178 mouse lymphoma cells, using a standard functional assay with Rho123. It was investigated that esulatins J (129), A (374), and E (504) were the most effective compounds against all cell lines; especially esulatin J (129) exhibited high cell growth inhibitory activity on Ishikawa (98.4% at 30 μg/mL) and MCF7 (81.4% at 30 μg/mL) cells. Esulatin I (128) and esulatin B (470) displayed marked inhibitory effects on MCF7 (60.1% and 43.3% at 30 μg/mL). SAR studies demonstrated that the most potent compounds, esulatins I, J, B and E (128, 129, 470, and 504) are tetra- or penta- esters of jatrophane polyols, which

contain a keto group at C-9. Moreover, esulatin A (374), containing an epoxy group at C-11–C-12, found also to be effective against all three cell lines. All tested compounds differed significantly in the inhibition of the efflux pump activity of P-gp in tumor cells. Within the compounds investigated, esulatin J (129) (FAR = 52.5 at 40 μg/mL) and esulatin M (134) (FAR = 119.9 at 40 μg/mL) were found to be the most powerful inhibitors of efflux pump activity. Their efficacy was 25-fold higher than that of positive control 'verapamil' (FAR = 23.2 at 10 μg/mL); thus, both 185 and 188 appeared to be promising leads for drug development to overcome the MDR of cancer cells (Vasas et al. 2011).

Aljancic et al. (2011) investigated the sensitivity of NCI-H460/R cells to another anticancer chemotherapeutic agent, doxorubicin, in the presence of six new jatrophanes, euphodendrophanes A-F (396–400, and 237) from *E. dendroides*. Moreover, the synergistic effect between these jatrophanes and the 'paclitaxel' was reported for the first time. They also investigated the effects of 396 and 397 on Rho123 accumulation in NCI-H460/R cells and compared the results with that of untreated resistant NCI-H460/R cells by the FAR. Rho123 accumulation was about twofold higher in untreated NCI-H460 cells compared to NCI-H460/R cells. A significantly higher accumulation of Rho123 in the NCI-H460/R cell line was obtained with 396 and 397, compared to that of 'verapamil'. This observation had been elucidated by the positive role of certain pharmacophoric elements in the activities of jatrophanes against P-gp (Corea et al. 2009), like a free hydroxy group at C-5 or an acetate group at C-8, which are both present in 396 and 397. NCI-H460/R cells were exposed to combinations of 1, 2.5, and 5 μM of 396 and 397 with 0.05-5 μM doxorubicin and paclitaxel and sensitivity were assessed using an SRB assay. The IC_{50} value for paclitaxel decreased in combination with 396, demonstrating 3-, 19-, and 38-fold reversal activity for the aforementioned concentrations, respectively. An even more considerable effect was also obtained for 397, exhibiting 11-, 25-, and 60-fold reversal activity. There were no significant differences in reversal activity at concentration levels of 2.5 and 5 μM between 396 and 397 and 'verapamil'. Both jatrophanes at 5 μM decreased the IC_{50} values of doxorubicin significantly, showing a similar reversal potential to 'verapamil'. These results pointed to the potential of 396 and 397 to reverse paclitaxel and doxorubicin resistance in the MDR cancer cell line used (Aljancic et al. 2011).

Valente et al. (2012) isolated three new jatrophanes euphomelliferine (293), euphomelliferenes A (294) and B (295) along with two known jatrophanes 306 and 302 from *E. mellifera*. 293–295 and 302 were investigated for their P-gp modulating effects on human MDR1-gene transfected mouse lymphoma cells (L5178Y MDR) and on human colon adenocarcinoma cells (COLO320) using 'verapamil' as a positive control. These compounds were also evaluated for their activity as apoptosis inducers using the annexinV/propidium iodide assay. 294 showed the highest P-gp modulating activity on both cell lines (FAR = 23.1 and 5.5 at 20 μM on L5178Y MDR and COLO320, respectively). But a much lower activity was observed in 295 (FAR = 1.6 and 2.8 at 20 μM) having an OH group at C-15. However, when comparing the effects of 293 (FAR = 12.1 and 5.1 at 20 μM) and 295 differing in the type of function at C-14, the presence of a carbonyl group at this position improves the activity, as for 293. The different location of one of the double bonds and the substitution at C-6 also influenced the efflux pump activity, as demonstrated by the FAR values of 293 and 302 (FAR = 10.1 and 3 at 20 μM) on the two cell lines. Contrarily, the configuration at C-2 did not seem to play a significant role in MDR modulatory activity (Valente et al. 2004a). It was concluded that the differences in the observed modulating effects between the two MDR cell lines may be associated with different levels of P-gp expression, which were lower in COLO320 cells according to immunohistological studies (Engi et al. 2006). Moreover, none of the tested compounds were able to induce significant apoptosis and cell death (Valente et al. 2012).

Rédei et al. (2012) isolated four novel (124–127) and one known (326) diterpenes from *E. mongolica* being evaluated for MDR reversing activity against human MDR gene-transfected L5178 mouse lymphoma cells via the intracellular accumulation of Rho123. Tested compounds displayed a significant inhibitory effect compared to 'verapamil'. SAR studies demonstrated that the differences in the substitution at positions C-7 and C-8 influences the ability to enhance intracellular drug accumulation by comparison of the structures 124–127 and the MDR-modifying activity (FAR = 6.23, 16.36, 66.97 and 37.12 at 2 μg/mL respectively). The MDR-modifying activity

exhibited a definite increase with the size of the acyl group at C-7 in the following sequence: acetyl < propanoyl < n-butanoyl < isobutanoyl. 484 unsubstituted at C-7 and C-8, had a potency similar to that of 170 (FAR = 6.3 at 2 μg/mL). Within this jatrophanes, 126 appeared to be the most powerful P-gp inhibitor (Rédei et al. 2012).

Reis et al. (2012) tested MDR reversal potential of jatrophanes pubescene A (270), pubescene C (272), pubescene D (297), euphopubescenol (122), euphopubescene (300), pepluanin D (415), tuckeyanol A (143), and tuckeyanol B (144) and a rearranged polycyclic jatrophane derivative "1β,5α,14α,17α-tetraacetoxy-3β-benzoyloxy-15β-hydroxy-9-oxo-paraliane" on COLO320 MDR cells by rhodamine-123 exclusion assay and verapamil was applied as positive control. Both compounds had MDR reversal activity at 2 μM and 20 μM, respectively. Regarding physicochemical properties of compounds, it was showed that the presence of an aromatic moiety in the molecule is important for an increased P-gp affinity. An additional hydrogen bond acceptor connected to the oxygen at C-15 is also important, particularly in the jatrophane scaffold.

Podolski-Renic et al. (2013) evaluated euphodendrophane H (225) and euphodendrophane S (236) which had been previously isolated from *E. dendroides* (Jadranin et al. 2013) on cancer cell growth in three human MDR cancer cell lines: NCI-H460/R, colorectal carcinoma DLD1-TxR, and glioma U87-TxR by the sulforhodamine B assay (SRB) and their chemo-sensitizing effects in MDR cancer cell lines. 225 and 236 exerted the best inhibitory effect in non-small cell lung carcinoma (NSCLC) cell lines: NCI-H460 and NCI-H460/R. However, the IC_{50} values for 225 differed between sensitive NCI-H460 and resistant NCI-H460/R cells (6 μM and 15 μM, respectively). Colorectal carcinoma cell lines (DLD1 and DLD1-TxR), as well as the glioma cell lines (U87 and U87-TxR), showed considerably lower sensitivity to the two jatrophanes. These results recapitulated those obtained in the previous study (Aljancic et al. 2011) and indicated the potential of Euph H (225) and Euph S (236) for NSCLC treatment. 225 significantly sensitized NCI-H460/R and DLD1-TxR cells to Paclitaxel (PTX), similar to paclitaxel, R ± verapamil (Dex-VER), and tariquidar (TQ); while 236 demonstrated the moderate chemo-sensitizing effect. These observations were in agreement with stronger anti-P-gp activity obtained with 225 in NCI-H460/R and DLD1-TxR. All tested P-gp inhibitors had similar potential for the reversion of PTX resistance. In addition, Dex-VER and TQ showed significantly lower reversal potential in U87-TxR cells as it was expected from single nucleotide polymorphism (SNP) analysis. In conclusion, it was confirmed that jatrophanes stimulate purified tubulin assembly in vitro by this assumption that the mutual effect of PTX and new jatrophanes on microtubule assembly leads to cycle arrest at G2/M phase and partly contributes to Euph H/S and PTX combined effects (Podolski-Renić et al. 2013).

Thirteen new jatrophanes, euphodendrophane G-S (483, and 225-236), and three known compounds (euphodendrophane A (396), euphodendrophane B (397), euphodendrophane F (237)) were isolated from *E. dendroides* by Jadranin et al. (2013) (Jadranin et al. 2013). The P-gp inhibiting activities of 157–169 had been assessed on previously characterized P-gp overexpressing MDR cancer cell lines: NCI-H460/R, colorectal carcinoma DLD1-TxR, and glioma U87-TxR (Pesic et al. 2006; Podolski-Renić et al. 2011). The most promising compounds were euphodendrophane H and K (225 and 228), which completely blocked the P-gp pump and demonstrated higher activity than Dex-VER and TQ. However, the effects of 227, 222, and 236 were noteworthy as they had also achieved the complete blockage of P-gp in colorectal MDR cancer cells and exceeded the Dex-VER activity (Jadranin et al. 2013). SAR studies showed no obvious difference in the activity of jatrophanes with 6, 17 exo- (483, and 225–229, 396, and 397), and those with 5, 6 endo- double bond (234–237). This could be in accordance with the previous findings that said modifications in connectivity made less change in activity than the oxygenation pattern (Corea et al. 2003b). The activity was strongly affected by the OBz group at the positions C-8 and C-9 for jatrophanes with exo- and endo- double bonds, respectively. Wide range of compounds with the same exo- jatrophane skeleton (Corea et al. 2003a) emphasized the importance of free hydroxyl group at C-3 as well as substitution on C-2 and C-5. These conclusions were extended to modified jatrophanes as well (Jadranin et al. 2013).

Lu et al. (2014) isolated six new jatrophanes (345–349, and 482) from *E. sororia*. Compounds (345–349, and 482) were evaluated for their capacity

to inhibit in vitro growth of two human mammary adenocarcinoma (MCF-7) and lung adenocarcinoma (A549) cell lines using a sulforodamine B (SRB) assay. All the compounds were inactive (IC_{50} > 10 μm) for the two human cancer cell lines. Compounds (345–349, and 482) were tested for their MDR-reversing activity on KBv200 cells by monitoring the intracellular accumulation of Rho123. Compound 346 was found to be a highly potent inhibitor of efflux pump activity of P-gp in the cancer cells since it was more efficient at 10 μM than the standard modulator 'verapamil' (Lu et al. 2014).

Lanzotti et al. (2015) isolated cyparissins A and B (480 and 481) from *E. cyparissias* and evaluated their ability to inhibit P-gp-mediated MDR and their cytotoxic activity against two human ovarian cancer cell lines, A2780 WT and A2780 ADR. Weak P-gp inhibition was exhibited by 480 and 481 with IC_{50} of 8.55 ± 3.21 μM and 8.72 ± 3.45, respectively comparing to cyclosporine A (CsA) (IC_{50} of 3.37 ± 1.39 μM) (Lanzotti et al. 2015). This finding is in agreement with previous SAR studies on jatrophane diterpenes indicating that the presence of both acylation at C-3 and hydroxylation or acylation at C-5 is detrimental for P-gp reversal activity (Corea et al. 2009) and a keto group at C-9 is rather an important feature for cytotoxicity (Vasas et al. 2011). In another study, Barile and Lanzotti isolated presegetanin 16 as well as segetanin A and B (10 and 11), along with four known segetanes (86-89) from *E. paralias*. The cytotoxicity and the anti-MDR activity of all compounds were also tested on human ovarian cancer cells A2780. In a range of concentrations between 0.1 to 10,000 nM, none of the tested compounds showed significant activity as compared to controls (Barile and Lanzotti 2007).

Rédei et al. (2015) isolated two new (118 and 269) and one known, isoterracinolide B (23), jatrophanes from *E. exigua*. P-gp modulatory activities of the compounds on human MDR gene-transfected L5178 mouse lymphoma cells were investigated. In agreement with their earlier published studies, the nature of the substituent at C(7) influences the ability of jatrophane to enhance intracellular drug accumulation and subsequent MDR reversing activities. It was observed that the activity of 118 and 269 is proportional to the lipophilicity and the size of the ester group at C(7). 269 with two aromatic ester groups was the most lipophilic molecule so it showed maximum activity (FAR = 35.59) at 8 μg/mL concentration. 23 displayed similar maximum activity (FAR = 36.09) at 80 mg/ml. Moreover, both compounds had a propanoyl group at C(7), in contrast to the 7-O-acetyl substituted compound 118, which had the lowest activity (FAR = 25.97) (Rédei et al. 2015).

Reis et al. (2015) isolated a rare class of 12,17-cyclojatrophanes, (euphowelwitschine A (1), euphowelwitschine B (2), welwitschene (267), epoxywelwitschene (268)) from *E. welwitschii*. Potential selective antiproliferative activity of the compounds was evaluated against parental gastric (EPG85-257) and pancreatic (EPP-181) human cancer cells. Their drug-selected counterparts resistant to novantrone (RN) and to daunorubicin (RDB), was also evaluated using the SRB assay (Reis et al. 2014). MDR-selective activity was calculated through the relative resistance ratio (RR = IC_{50} (resistant)/IC_{50} (parental)). RR < 1 indicates that the compound kills MDR cells more effectively than parental cells, but if RR < 0.5, then a collateral sensitivity effect would be taking place. Anti-proliferative selectivity against the resistant gastric cell line EPG85-257RDB was shown by welwitschene (267) (IC_{50} = 17.2 ± 1.6 μM, RR = 0.6) and epoxywelwitschene (268) (IC_{50} = 3.6 ± 0.3 μM, RR = 0.1), with the latter showing a collateral sensitivity effect. For the pancreatic cell lines, an MDR-selective anti-proliferative effect was observed only for 268 against EPP85-181RN (IC_{50} = 21.3 ± 2.5 μM, RR = 0.7) and against EPP85-181RDB (IC_{50} = 18.2 ± 3.1 μM, RR = 0.6). It was concluded that epoxywelwitschene (268) can be regarded as a potential MDR reverser (Reis et al. 2015).

Zhu et al. (2016) isolated 13 jatrophanes (238, 192, 49, 193, 206, 194–196, and 186–190) from *Pedilanthus tithymaloides* eight of which (238, 192, 49, 193, 206, and 194–196) were new. Among them, 186–190 had enough yield to design derivatives with different substituents and functions to investigate SAR related to the MDR. Zhu and his coworkers prepared a total of 22 new derivatives through esterification, hydrolysis, or epoxidation modifications. The library containing 35 compounds representing two groups of jatrophanes (I and II) with the presence of 8-OAc or 8-methylene to screen for P-gp dependent MDR modulators. A flow cytometry-based Rho123 effluxion assay was done; the high expressions of P-gp in adriamycin resistant human hepatocellular carcinoma cell line HepG2

(HepG2/ADR) and adriamycin resistant human breast adenocarcinoma cell line MCF-7 (MCF-7/ADR) were first validated by Western blot. '(1S,2R,3S,4S,7R,9R,13R,14R,15R)-9,15-Diacetoxy-1-tosyl-3,7-dibenzyloxy-13,14-dihydroxy jatropha-5E,11E-diene' obtained from reaction with tosyl chloride and '(1S,2R,3S,4S,7R,9R,13R,14R,15R)-1,9,15-triacetoxy-3,7-dibenzoyloxy-13,14-dihydroxy-jatropha-5E,11E-diene' prepared by acetylation and '(1S,2S,3S,4S,7R,9R,13R,14R,15S)-9,15-fiacetoxy-3,7-dibenzoyloxy-1,13,14-trihydroxyjatropha-5E-ene' obtained by treating the solution of 222 with 10% Pd/C under H_2 were all identified as potent MDR modulators with greater chemoreversal ability and less cytotoxicity than the third-generation drug 'tariquidar' (TQ). SAR studies showed that increasing the lipophilicity of this class of P-gp inhibitors is beneficial to MDR reversal activity; saturated ring A was essential, while the presence of free hydroxyls on C1–C15–C14–C13 fragment had little influence on the activity. In addition, the formation of a rare C5–O–C13 bridge would increase the activity, while epoxidation of Δ^{12} is detrimental to the activity (Zhu et al. 2016).

Reis et al. (2016) screened jatrophanes euphowelwitschine A (1), euphowelwitschine B (2), welwitschene (267), epoxywelwitschene (268) and esulatin M (134) for MDR resistance activity through a combination of Rho123 efflux and chemoreversal assays on adriamycin resistant human hepatocellular carcinoma cell line HepG2 (HepG2/ADR) and adriamycin resistant human mammary adenocarcinoma cell line MCF-7 (MCF-7/ADR). 1, 267, 268, and 134 showed to be able to revert the MDR phenotype, at 20 μM, being two-fold (1 and 134) and three-fold (267 and 268) more effective than 'verapamil' (FAR = 12.5 at 20 μM) (Reis et al. 2016). In assays on EPG85-257RNOV cells which have been done previously, 268 caused a 4.5-fold increase of total apoptosis and 134 showed a 2.6-fold increase. Furthermore, both showed a similar effect causing apoptosis in about 2.5 fold for EPG85-257RDB cells (Reis et al. 2015). The compounds 268 and 134 appear particularly interesting, due to their dual activity: as ABCB1 modulators and MDR-selective anti-proliferative compounds. SAR results that high conformational flexibility of the twelve-membered ring of jatrophanes 267, 268, and 134 favored ABCB1 modulation, in contrast to the 5/8/8 fused ring system of euphowelwitschines A (1) and B (2) (Reis et al. 2016).

Mai et al. (2017a, b) isolated heliosterpenoids A and B (50 and 51) with a novel 5/6/4/6-fused tetracyclic ring skeleton, from *E. helioscopia*. Their potency for P-gp (ABCB1) inhibitory was evaluated using an adriamycin (ADM)-resistant human breast adenocarcinoma cell line (MCF-7/ADR) (Barile et al. 2008a). Similar inhibitory activity was seen for both compared to CsA (IC_{50} = 0.49 μM) with IC_{50} values of 1.28 μM and 1.02 μM, respectively. Moreover, the cytotoxicity of 50 and 51 was also tested against five human cancer lines (MDA-MB-231, A549, Hela, U118MFG and RKO) by MTT assay. Adriamycin was used as a positive control (IC_{50} = 0.31 μM) (Lu et al. 2008). 50 displayed moderate cytotoxicity against MDA-MB-231 cell lines with IC_{50} value of 24.7 μM. Both 50 and 51 demonstrated to be new structural potent inhibitors of P-gp (ABCB1) (Mai et al. 2017a).

Hu et al. (2018) isolated five new (149, 150, 322, 27, and 24) and ten known (22, 345–349, 482, 413, 441, and 140) jatrophanes from *E. sororia*. The cytotoxicity and anti-MDR activity of all these compounds were evaluated in a parental DOX-sensitive MCF-7 cell line and its DOX-selected derivative P-gp overexpressing MCF-7/ADR cells by the MTT method. 149 displayed significant MDR reversal activity (IC_{50} = 2.65 ± 0.33 μM) in comparison to the other compounds with a low EC_{50} value (92.68 ± 18.28 nM) in the MCF-7/ADR cell lines overexpressing P-gp. The remarkable advantages of 149 are its high survival potency toward normal cell line HEK293 (IC_{50} = 98.20 ± 1.59 μM) as well as its high therapeutic index (ratio of IC_{50} toward HEK293 to EC_{50} for reversing DOX resistance = 1059.56). The results of the Western blot analysis demonstrated that the MDR reversal activity induced by 149 was not due to the inhibition of P-gp expression. The Dixon plot analysis was used to elucidate the type of inhibition. The competitive relationship between the inhibitor and substrate, gave rise to passage of the linear regression line through the origin as it was previously reported (Iseki et al. 1999; Wang et al. 2000). The regression lines of 149 and 'verapamil' coincide with the origin indicating that both were competitive inhibitors of P-gp-mediated DOX transport, which was in accordance with the Lineweaver–Burk analysis. Besides, kinetic characterization revealed that 149

(Ki = 0.49–0.50 μM) possessed a high binding affinity to the DOX recognition site of P-gp with about 5.84- to 5.88-fold lower Ki values than the average Ki of 'verapamil'. In this regard, 149 was proven to significantly inhibit DOX transport, increase intracellular DOX concentration, and finally resensitize MCF-7/ADR to DOX. They further found that fourfold more of 'verapamil', compared with 149, is needed to completely restore the DOX accumulation in the MCF-7/ADR cells to the level of the parental MCF-7 cells. Based on SAR study, the activity order of the ester groups at C-5 is 2-methylbutanoyloxy > benzoyloxy > propionyloxy > isobutanoyloxy. Moreover, the presence of an aromatic ester group (benzoyl) at C-14 might increase the modulation potency in comparison to a substituent group of carbonyl or acetoxyl (Hu et al. 2018).

Fang et al. (2018) isolated ES2 (346) from *E. sororia*. They focused on in vitro and in vivo investigation of MDR reversal activity of 346, as well as elucidation of its underlying mechanisms. The antiproliferative activity of 346 on ABCB1-overexpressing cells (KBv200, MCF-7/ADR, and A549/T) and their parental cells (KB, MCF-7 and A549) were very weak at up to 30 M; therefore, the study was performed at a maximum concentration of 10 M. 346 considerably increased the sensitivity of KBv200 and MCF-7/ADR), but not their parental cells, to chemotherapeutic drugs (NVB, PTX, and DOX) which are substrates of ABCB1 at concentration as low as 0.3 M; moreover, the reversal effect of 346 was more potent than 'verapamil' at 10 M in both cell lines. These results indicated that 346 can increase the sensitivity of ABCB1- mediated MDR cells to chemotherapeutic agents. The reversal ability of 346 was mainly due to the inhibition of the efflux function of ABCB1 transporter; thus, it increased the intracellular accumulation of chemotherapeutic agents displaying anti-proliferative effects on drug-resistant cells. The drug-efflux function of ABCB1 utilizes energy from ATP hydrolysis, so the rate of ATP hydrolysis is directly proportional to the transport activity of ABCB1. 346 stimulated ABCB1 ATPase activity in a concentration-dependent manner although it had no inhibitory impact on verapamil-stimulated ABCB1 ATPase activity; therefore 346 might have direct interaction with ABCB1, which may be different from 'verapamil'. Besides, 346 had no effect on downregulating the protein level of ABCB1. These results and docking analysis together confirmed 346 induced ABCB1 malfunction may be caused by directly binding to it. These findings suggest the application of 346 in combination with chemotherapeutic agents for cancer treatment (Fang et al. 2018).

Krstic et al. (2018) isolated seven new jatrophanes: nicaeenins A-G (414, and 273–278) together with eight known: euphodendrophanes A-C (396–398), F (237), N (231), O (232), Q (234), and S (236) from *E. nicaeensis*. Their P-gp inhibitory potency was evaluated in two MDR cancer cells (NCI-H460/R and DLD1-TxR). The most potent P-gp inhibitors were 277 with FAR = 4.52 ± 0.02 and 5.89 ± 0.04 along with 278 with FAR = 5.02 ± 0.02 and 4.39 ± 0.03 in two mentioned MDR cancer cells lines. 278 also chemosensitized NCI-H460/R cells to DOX stronger than Dex-verapamil due to prolonged effect of P-gp inhibition that remained for seventy-two hours while the effectiveness of 277 was similar to Dex- verapamil. This indicated that the maintenance of the activity against P-gp for a longer period is contributed to the increased reversal potential of jatrophanes. Previous SAR study had shown that two groups of jatrophanes with exo-methylene 6,17 double bond (Jadranin et al. 2013) that lack oxygenation at C-2 and with identical structures except for the substitution at C-8, had a favorable effect on P-gp inhibition (Corea et al. 2003a) upon substitution of OBz at C-8 with ONic, OiBu or OAc. Therefore, it can be demonstrated that 277 and 278 possessing OAc and ONic at C-8 respectively, have moderate but the best potential for P-gp inhibition among tested jatrophanes from *E. nicaeensis* (Krstić et al. 2018).

Mai et al. (2018) isolated two jatrophanes heliojatrones A and B (329 and 7) with a unique trans bicycle (8.3.0) tridecane core, from EtOH extract of the whole plant of *E. helioscopia*. The inhibitory effect of P-gp mediated ADM efflux by these compounds was evaluated in MCF-7/ADM Cells and cyclosporine A (CsA) was used as positive control (Zhao et al. 2015). Compound 7 (IC_{50} = 0.58 ± 0.05 μM) showed a remarkable P-gp inhibitory activity in a concentration-dependent manner similar to P-gp inhibitory activity of CsA (0.84 ± 0.03 μM) while weak P-gp inhibitory activities were observed for 329 (12.03 ± 4.14 μM). Therefore compound 7 can be considered as a new structural template for the development of potential MDR reversal agents (Mai et al. 2018a).

Li et al. (2018) isolated euphornin (208) from *E. helioscopia* in a large amount. Alkaline hydrolysis of 208 using potassium carbonate afforded the main product monodeacetyleuphornin whose structural modification at 14-OH with acyl chlorides yielded 7 alkyl acylated derivatives euphornoate A-G and 14 aryl acylated derivatives euphornoate H-U led to a mini library of 21 acylated jatrophane derivatives for expanded SAR studies of MDR modulators (Li et al. 2018b). All compounds were tested for their MDR reversal activities in K562/ADR cell using the MTT method to ensure these compounds were non-cytotoxic at tested concentrations (2 μM and 20 μM). It was seen that the inhibition ratios of all compounds were less than 50% at 2 μM and only two compounds (euphornoate B and euphornoate C) displayed cytotoxic (inhibition ratios were more than 50%) at 20 μM; Thus, euphornoate B and euphornoate C were not examined for their MDR reversal activity at 20 μM. The reversal fold values (RF = ratio of IC_{50} of adriamycin (ADR) alone to IC_{50} of ADR in presence of 2 or 20 μM sample) were used in evaluating the MDR reversal activity and Verapamil as a positive control. All compounds displayed favorable activities with the RF values over tenfold; over half of them (euphornoate E and euphornoate J, euphornoate K and euphornoates M-U) showed reversal ability greater than verapamil. The reversal activities significantly increased at 20 μM. The RF values of 11 compounds (euphornoates D-F, euphornoate H, euphornoates M–O, euphornoate Q, euphornoate R, euphornoate T, euphornoate U) were over 100 fold even over 400 fold as the most active (euphornoate U) one, and reversal activities of all compounds were greater than the positive control. Previous SAR studies confirmed that substitutions of the "southwestern" fragment (C-2, C-3, and C-5) of jatrophanes, as well as the presence of free hydroxyl at C-15 are important for the activity (Corea et al. 2003a, b). Recently, Zhu et al. (2016) have established the significance of acylation of the free hydroxyl at C-14 as it increases the activity. Therefore, it was aimed to explore different substitutions for expanded SAR studies relative to C-14. Based upon these investigations, the introduction of acyl groups bearing 4 carbons showed the most potent activities at 20 μM in alkyl acylated derivatives, for example, euphornoate D (with crotonoyl group) and euphornoate E (with isobutyryl group) exhibited RF values of 393 and 141 respectively. Overall, the MDR reversal activities were better for the aryl acylated derivatives, than the alkyl acylated derivatives at 2 μM. However, attaching electron withdrawing groups on the aromatic ring, such as nitryl and trifluoromethyl, decreased the activity (euphornoate K and euphornoate L), while electron donating groups, such as methyl and methoxyl, increased the activity (euphornoates M-Q), and the activity of ortho-substituting compound (euphornoate N) was higher than meta- and para-substituting compounds (euphornoate M and euphornoate O). Moreover, introducing of an aromatic heterocyclic ring considerably enhanced the activity, as compounds euphornoate T (2-thiophenecarbonyl group) and euphornoate U (2-furoyl group) displayed RF values of 324 and 424 fold respectively. The current SAR studies demonstrated that introduction of an alkyl acyl group bearing 4 carbons at C-14 or an aryl acyl group with electron-donating groups is desirable for the activity and several compounds with RF values over 300 fold at 20 μM (euphornoate D, euphornoate N, euphornoate R, euphornoate T, euphornoate U) were thought to be promising MDR modulators. This is in agreement with previous SAR studies confirmed the importance of acylation of free hydroxyl at C-14 as it increases the activity (Zhu et al. 2016).

Mai et al. (2018a, b) isolated 17 new jatrophanes, helioscopianoids A–Q (172, 173, 177–180, 6, 220–224, 505, 174–176, and 328), together with eight known, euphornin L (161), euphornin (208), euphornin D (212), euphoscopin F (332), euphoscopin E (331), euphoscopin C (245), euphoscopin B (244), and euphoheliosnoid D (114) from *E. helioscopia.* P-gp inhibitory effects of helioscopianoids A–Q were evaluated in an adriamycin (ADM)-resistant human breast adenocarcinoma cell line (MCF-7/ADR) where cyclosporin A (CsA) was used as the positive control. Neuroprotective effects were also investigated against serum deprivation-induced and rotenone-induced PC12 cell damage. 220 and 176 enhanced the accumulation of ADM in MCF-7/ADR cells by relatively threefold at a concentration of 20 μM. Besides, 220 could reduce rotenone-induced PC12 cell damage, and 173, 220, and 224 displayed neuroprotective activities against serum deprivation-induced PC12 cell damage. SAR studies and corresponding P-gp inhibitory effects demonstrated that the presence of different acyl groups or carbonyl groups at C-7 in the same jatrophane core, especially the butanoyl group instead

of the hydroxy group at C-7, plays a significant role in their activity (Mai et al. 2018b).

Rédei et al. (2018) isolated novel segetane diterpenoid 77, new jatrophane compound 279, along with two other known compounds, segetane 88 and jatrophane 448 from *E. taurinensis*. The evaluation of the cytotoxic and MDR-reversing activities of them was conducted using flow cytometry measuring the retention of R123 by ABCB1 (P-gp) in MDR mouse T-lymphoma cells overexpressing the ABCB1 protein and MTT assay. None of the compounds displayed cytotoxic activity on the sensitive parent and resistant MDR cells while all inhibited the ABCB1 MDR efflux pump of the resistant mouse T-lymphoma cells in comparison to 'verapamil', suggesting that they could be used as potential resistance modifiers. Segetane 70 indicated the most potent ABCB1-modulating effect at 20 μM (FAR = 44.44) as the first report of the biological activity of segetane-type diterpene (Rédei et al. 2018).

Hasan et al. (2019) isolated 17 new (116, 117, 266, and 307–320) and five known jatrophane diterpenoids (131, 376, 375, 467, and 124) from *E. glomerulans*. The MDR-reversing activity and cytotoxicity of the new jatrophanes were assessed in the MCF-7 cells and P-gp overexpressing MCF-7/ADR cells using the MTT method. The results demonstrated that these compounds displayed different chemoreversal activities and significantly decreased cytotoxicity. Especially, 314 with IC_{50} value of 5.0 ± 0.8 μM and 315 with IC_{50} value of 5.2 ± 2.0 μM afforded MDR reversal activities with RF (reversal fold) values of 12.9 and 12.3 at 10 μM, respectively, which was as superior as that of 'verapamil' (RF = 13.7, IC_{50} value of 4.7 ± 0.6 μM). Because the structurally homogeneous skeletons of (307–309) and (310–320) are different only in the substitution pattern, performing SAR studies was possible. The presence of an isobutanoyloxy moiety at C-8 rather than at C-7 had a positive effect on the modulation of drug accumulation in the MCF-7/ADR cells by comparing the substituents and RF values of 314, 315, and 316. Furthermore, with the comparison of the biological results of 307, 309, and 311 to those of 308, 310, and 318, it was demonstrated that favorable following trend in activity at C-8 is: benzoyloxy group > H ≈ hydroxy group (Hasan et al. 2019).

Antiviral activity

Remy and Litaudon (2019) have published a review on anti-CHIKV activity of eighty diterpenoids covering the years 2011 to 2019. Twenty-five jatrophanes have been investigated for their ability to inhibit viral replication. Existence of an acetyl group at position 2 within the 9,14-dioxojatropha-dienes and the 2-methylbutyryl group in the 9-oxojatropha-dienes series, proved to be deleterious for anti-CHIKV activity. Furthermore, the C-8 substitution influences the activity of jatrophanes (tiglyloxy > benzoyloxy > acetyloxy ≈ isobutyryloxy) (Remy and Litaudon 2019).

Esposito et al. (2016) isolated six new jatrophane esters including euphodendroidins J-O (456–461) from the *E. dendroides*. The assessment of the antiviral activity of these compounds was performed in a virus-cell-based assay for the Chikungunya (CHIK) virus. 460 and 461 showed moderate antimetabolic effects on Vero cells (Esposito et al. 2016).

Nothias-Scaglia et al. (2014) evaluated the anti-CHIKV capacity of six new (367, 368, and 500–503) together with six known (488, 493, 484, and 359–361) jatrophanes from *E. amygdaloides*. The compounds were classified into two groups A and B. Group A (500–503, 488, 359, and 493) were the esters of '9,14-dioxojatropha-6(17),11E-diene' and group B (367, 368, and 484, 360, 361) were those of '9-oxojatropha-6(17),11E-diene'. The selective antiviral activity was investigated against CHIK virus with two additional members of the genus alphavirus (Sindbis virus (SINV) and Semliki Forest virus (SFV)) and two members of the genus Lentivirus, i.e. human immunodeficiency virus (HIV)-1 and HIV-2 viruses. Regarding the antiviral activity against alphaviruses, 502 and to a lesser extent 503 were found to be potent selective inhibitors of CHIKV replication (half = maximal effective concentration (EC_{50}) = 0.76 ± 0.14 μM, selectivity index (SI) = 208, and EC_{50} = 4.3 ± 0.2 μM, SI = 29, respectively). 502 also exhibited moderate anti-SINV activity, while 360, 367, and 368 showed a significant, albeit weak, antiviral activity on the replication of SINV and SFV. Concerning the activity of group A compounds, since 359 and 493 were weakly active, it could be concluded that the presence of an acetyl group at position 2 might be detrimental for anti-CHIKV activity (cf. 502 vs. 359, and 503 vs. 493). The

influence of the C-8 substitution as shown by the comparison of anti-CHIKV activities of (500–502 and 488, 359, 493) was the other substantial chemical feature. In this regard, the following sequence inefficiency at C-8 was proposed: tiglyloxy > benzoyloxy > acetyloxy ≈ isobutyryloxy. Only 360 and 367 of group B showed significant anti-CHIKV activities (EC_{50} = 19.5 ± 3.6 μM, SI = 7.8; EC_{50} = 21.0 ± 3.4 μM, SI = 2.8, respectively). These results proved that the acetyl group plays an equivalent role as an isobutyryl substituent at C-8 in the anti-CHIKV activity. Contrarily, since 368 was much less active, it was deduced that the 2-methylbutyryl group might be detrimental for this activity. In virus-cell-based assay for HIV, only 502 showed a strong selective antiviral effect on HIV-1 and HIV-2 virus replication, with IC_{50} = 0.34 ± 0.05 μM, SI > 96 and IC_{50} = 0.043 ± 0.005 μM, SI > 751, respectively. 503, 488, 359, and 360 displayed moderate antiviral activity against HIV-2 (Nothias-Scaglia et al. 2014).

Bedoya et al. (2009) investigated the anti-HIV activity of SJ-23b (488) previously isolated from *E. hyberna* (Appendino et al. 2002) to identify the potent natural or synthetic PKC agonists lacking tumor promoter and cellular proliferative activities for treatment of HIV-1 latency in combination with HAART (highly active antiretroviral therapy). Although 'prostratin' a non-tumorogenic phorbol ester, is a favorable lead compound to antagonize HIV-1 latency, the high concentrations required may prevent its clinical use. SJ-23b with at least one order of magnitude more potent than 'prostratin' internalized the HIV-1 receptors (CD4, CXCR4, and CCR5) and prevented de novo viral infection in human primary T cells at the nanomolar range. Due to their mechanisms of action, short cycles of treatment with these small molecules inducing HIV reactivation combined with HAART, could contribute to a decrease in viral reservoirs. Concerning this investigation, SJ-23b can be considered as an adjuvant therapy agent to target latent reservoirs for patients on HAART (Bedoya et al. 2009).

Abdelgaleil et al. (2001) isolated two new segetanes named segetanes A (80) and B (81) along with five jatrophanes (484-487 and 489) and four segetanes (84, 85, 88, and 89) and two paralianes (72 and 73), which had previously been isolated from the same plant collected in Turkey (Öksüz et al. 1997) and Spain (Jakupovic et al. 1998c), and from *Euphorbia segetalis* (Jakupovic et al. 1998a). Antiviral activity against HIV-1 replication was tested on the inhibition of virus-induced cytopathicity in MT-4 cells. 88 and 485, 487, and 489 showed weak activities in a range of EC_{50} = 40–79 μg/mL and compound 72 showed a moderate antiviral activity (EC50 = 14 mg/ml) (Abdelgaleil et al. 2001).

Mai et al. (2017a, b) isolated secoheliosphanes A (8) and B (9) and secoheliospholane A (17) together with 2-epieuphornin I (219) and euphoscopin A (242) from *E. helioscopia*. Antiviral activity of all isolated compounds was evaluated against the herpes simplex virus 1 (HSV-1) using Vero cells (Lv et al. 2016). 'Acyclovir' (ACV) was used as the positive control, with IC_{50} values of 0.41 μM. Among all, 9 displayed moderate activity against HSV-1 with IC_{50} value of 6.41 μM. The bioassay data demonstrated that seco-jatrophane skeleton (8, 9, and 17) has stronger antiviral activity against HSV-1 than its precursor (242) possessing jatrophane skeleton (Mai et al. 2017b).

Esposito et al. (2016) isolated six new jatrophanes: euphodendroidins J (456), K (457), L (458), M (459), N (460), and O (461) together with nine known diterpenoids: euphodendroidins A (417), B (418), E (421), and F (422), 13α-hydroxyterracinolides G and B (28 and 47), and terracinolides J and C (32 and 38) from *E. dendroides*. The antiviral activity of all compounds was conducted in a virus-cell-based assay for the CHIK virus. 32 displayed anti-CHIKV activity with EC_{50} values of 15.0 ± 3.8 μM and showed a remarkable anti-metabolic effect only at concentrations of 36 ± 3.1 μM, allowing the calculation of selectivity index (SI) of 2.4 (Esposito et al. 2017).

Antifungal activity

Rawal et al. (2014) isolated euphosquamosins A-C (184, 185, and 350) along with guyonianin B (148) and Deacetylserrulatin B and euphoscopin C (245) from *E. squamosa* and evaluated their ability to inhibit drug efflux by multidrug transporters of Candida albicans. Deacetylserrulatin B and euphosquamosin C (350) strongly inhibited the drug-efflux activity of the primary ABC-transporter CaCdr1p, an effect that was translated into increased sensitivity to fluconazole. These compounds were transported by CaCdr1p, as shown by observation of an 11- to 14-fold cross-

resistance of yeast growth, and could also inhibit the secondary major facilitator superfamily (MFS)-transporter CaMdr1p. In contrast, euphosquamosin A (184) was selective for CaCdr1p, possibly as a result of a different binding mode. Taken together, these observations suggested the jatrophane diterpenes be a new class of potent inhibitors of multidrug transporters critical for drug resistance in pathogenic yeasts (Rawal et al. 2014).

Nim et al. (2016) investigated the jatrophanes euphopubescenol (122), euphomelliferene A (294), euphomelliferene B (295), and euphomelliferine (293) for their inhibitory effect on drug efflux activity of *Candida albicans* CaCdr1p and CaMdr1p multidrug transporters overexpressed in a Saccharomyces cerevisiae strain. Their inhibitory potency was evaluated through a functional assay of Nile Red accumulation monitored by flow cytometry. A chemosensitization assay, using the checkerboard method, was also utilized to evaluate their type of interaction with fluconazole. In the transport assay, most compounds were found to suppress both transporters as shown by relative resistance indices close to unity. In contrast, 122 and 294 were selective for CaMdr1p and CaCdr1p, respectively. Moreover, when used in combination with fluconazole, 295 and 293 exhibited strong synergistic interactions (fractional inhibitory concentration index (FICi) = 0.071) against the yeast strain overexpressing CaMdr1p by a 13-fold decrement of the minimum inhibitory concentration for 80% (MIC_{80}) of the antifungal agent. Both compounds were also able to reduce the effective concentration of this antifungal agent by 4- to eightfold against an azole-resistant clinical isolate of *Candida albicans* (Nim et al. 2016).

Esposito et al. (2017) isolated twenty-nine jatrophanes from *E. semiperfoliata* (501, 502, 367, 488, 493, 484, 360, 368, 361, and 359) and *E. dendroides* (28, 47, 32, 38, 421, 422, 417, 457–461, 451–455, and 462) five of which (451–455), were new (Esposito et al. 2017). The ability of these compounds to modulate drug efflux by multidrug transporters of *Candida albicans* was assessed in *Saccharomyces cerevisiae* strain overexpressing either CaCdr1p or CaMdr1p. Cytotoxicity of active compounds on a *C. albicans* MDR strain evaluated in the second bioassay along with their ability to sensitize yeast growth through synergistic interaction with fluconazole. 462 was selective for CaCdr1p and induced a strong Nile Red (NR) accumulation (92%) through inhibition of CaCdr1p mediated efflux, whereas 367 was selective for CaMdr1p, with a 74% NR accumulation. In contrast, 28 and 418 were found to accumulate the Nile Red (NR) mediated by the two multidrug transporters, at 8–-64% for CaCdr1p and 79–65% for CaMdr1p. The ability of the 367, 28, 462, and 418 showed potent inhibition of the MDR transporters Cdr1p and Mdr1p to sensitize yeast growth through the antifungal agent fluconazole was evaluated by the checkerboard method (White et al. 1996). Regarding these results, 367, 28, 462, and 418 displayed high fractional inhibitory index (FICI) values ($\geq$ 1 μM), revealing that, despite their ability to inhibit *C. albicans* MDR transporters expressed in yeast strains, they were not able to induce sensitization to fluconazole for *C. albicans*-resistant strain growth. However, some jatrophanes were found to be selective or dual inhibitors against the yeast MDR transporters CaCdr1p and CaMdr1p, but only deacetylserrulatin B and 350 obtained from *E. squamosa* and 295 and 293 isolated from *E. mellifera* were able to sensitize the *C. albicans* MDR strain to fluconazole (Nim et al. 2016; Rawal et al. 2014). Even with structural similarity of mentioned jatrophanes with the latter substance, none of them exhibited a similar biological activity; therefore, the ability of inhibitors to sensitize yeast growth to the antifungal activity of fluconazole is mainly dependent on the nature, number, and position of functional groups on the macrocyclic core. To apply SAR study, the chemical space of diterpenoids, was classified into A to D groups (group A: esters of '9,14-dioxojatropha-6(17),11E-diene' (501–503, 488, 359, and 493), group B: esters of '9-oxojatropha-6(17),11E-diene' (360, 367, 484, and 360), group C: esters of '14-oxojatropha-6(17),11E-diene' (28, 47, 32, 38, 421, 422, 417, 457–461, 451–455, and 462), and group D: esters of '17-bishomojatrophane' (28–31)). The potency and selectivity of compounds are sensitive to the substitution pattern on the jatrophane skeleton. Hydrophobicity and an electron acceptor moiety are essential factors for the recognition of diterpenes with P-gp multidrug transporters in human cancer cell lines (Ferreira et al. 2011). But according to the results of 84.9% of the data set variance (PC1: 50.4%, PC2: 24.5%, and PC3: 10.0%) it was demonstrated that the modulation of CaMdr1p and CaCdr1p multidrug transporters in *S. cerevisiae* by 462, 28, 367, and 418 could not be affected by the

hydrophobicity or by other chemical properties used in this PCA analysis. It was instead concluded that difference in acylation pattern between 367 with 361 and 484 from group B, appears to play an important role for a strong inhibition of the CaMdr1p multidrug transporter. An isobutyrate group at C-8 in 367, instead of an acetoxy group or hydroxy group in 360 and 484, respectively. Moreover, the comparison of 418 with 417 and 460 from group C showed that the presence of a methylbutyrate group at C-5, instead of either an isobutyrate group or a benzoate group, respectively, had a significant contribution to the inhibition of CaCdr1p activity. Besides, since 29 was much less active than 28, it was indicated that the acetoxy group at C-15 was detrimental for inhibiting drug-efflux activities of both CaCdr1p and CaMdr1p transporters. Regarding complex conformational behavior of jatrophanes depending on their esterification pattern (Esposito et al. 2016; Günther et al. 1998), it was deduced that the modulation of CaMdr1p and CaCdr1p multidrug transporters by jatrophanes could rely on their conformational characteristics. In conclusion, 30 and 28 from group C and 417, 418, and 421 from group D were shown to be promising candidates for the development of P-gp modulators to tackle MDR human cancer cell lines. These results also demonstrated that macrocyclic diterpenoids, which are able to reverse the MDR of cancer cell lines overexpressing P-gp transporters, have not necessarily the ability of chemosensitizing *C. albicans* MDR strains (CaCDR1 and CaMDR1), revealing a possibly different binding mode (Esposito et al. 2017).

Anti-inflammatory activity

The Nitric Oxide (NO) produced by iNOS in macrophages is involved in various inflammatory diseases and therefore inhibitors of NO production may have potential therapeutic value as anti-inflammatory agents.

Barile et al. (2008a, b) evaluated in vivo anti-inflammatory potential of a set of over sixty structurally-homogeneous diterpenes belonging to the rare classes of pepluane and paraliane. The results showed the importance of functionality and structure of the D-ring for the activity and its possible involvement in the inhibition of NF-κB activation as follows (Fig. 14) (Barile et al. 2008b):

Lee et al. (2016) isolated two new jatrophanes: kanesulones A (323) and B (324) together with six known jatrophanes: kansuinin A (95), B (477), D (97), E (371), H (96), and esulone A (298) from *E. kansui*. The inhibition of NO production was tested in lipopolysaccharide (LPS)-stimulated RAW 264.7 cells, with 'aminoguanidine' as the positive control (IC50 = 18.7 μM). It was demonstrated that all

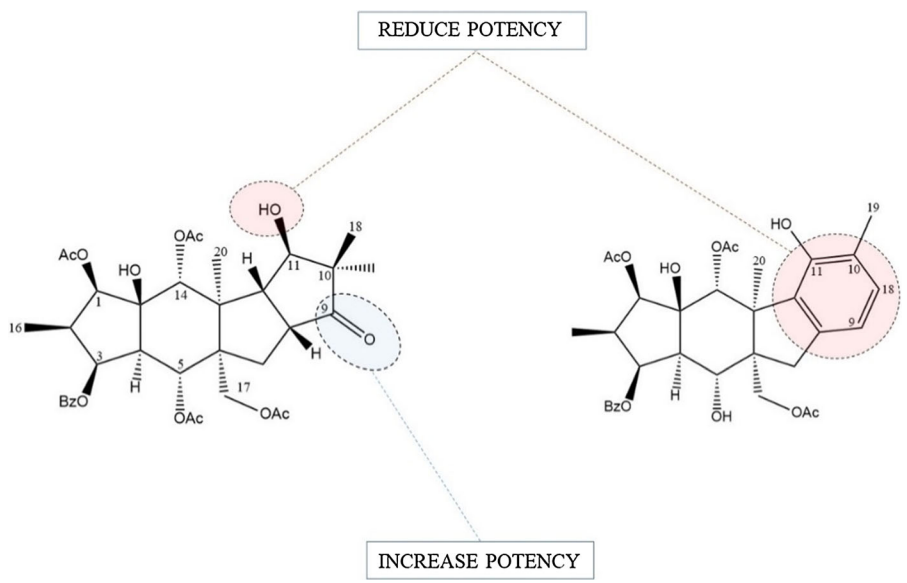


Fig. 14 Key pharmacophoric elements for the anti-inflammatory activity

compounds exhibited inhibitory effects on LPS-induced NO production which possessed lipophilic substituents such as benzoyl, nicotinoyl and decadienoyl moieties with IC_{50} values ranging from 0.7 to 46.5 μM in RAW 264.7 macrophages (Lee et al. 2016).

Wan et al. (2016a, b) isolated paralianones A-D (66–69) and pepluanols A-H (52–56, 58, 62, and 63), along with five known compounds 72 (Jakupovic et al. 1998b), 59 (Hohmann et al. 1999a), 60 (Hohmann et al. 2000a), 61 (Hohmann et al. 1999b), and pepluanone (57) (Corea et al. 2005b), from *E. peplus*.The isolated compounds were tested for inhibitory activity on LPS-stimulated NO production in RAW264.7 macrophage cell line. Compounds 68, 69, 62, 72, and 61 displayed inhibitory effects on NO inhibition, with IC_{50} values of 33.7, 38.3, 36.6, 29.9, and 37.1 μM, respectively. In addition, none of the test compounds displayed any obvious cytotoxicity to RAW264.7 cells (Wan et al. 2016a).

Chen et al. (2014) isolated new compounds 239–241, and 330 along with five known analogues: 332, 247, 337, 245, and 256 from *E. helioscopia*. The inhibitory activity of the compounds was investigated on LPS-induced NO production in murine microglial BV-2 cells. All tested diterpenes exhibited inhibitory effects on LPS-induced NO production. 330 and five aforementioned known analogues inhibited LPS-induced NO production dose-dependently with IC_{50} values of 41.9, 25.5, 17.5, 45.2, 20.9, and 27.3 μM, respectively. 239, 241, 337, and 256 showed moderate inhibitory effects while 247 and 245 showed weak activity (IC_{50} values > 100 μM). All the assayed compounds had no considerable cytotoxicity to the BV-2 cells at their effective concentration for the inhibition of NO production in MTT assay. It could be deduced that these bioactive diterpenes, especially 330 and 332 with strong NO inhibitory activities, might be considered as impressive agents in various inflammatory diseases (Chen et al. 2014).

Barile and Lanzotti (2007) isolated two new diterpenes, paralianone (71) and pepluene (64) together with two known analogues (76 and 65) from *Euphorbia paralias*. The ability of the isolated compounds as an anti-inflammatory agent on LPS-stimulated NO production in RAW264.7 macrophage cell line. Compound 76 showed the highest anti-inflammatory activity comparable to those recently discovered for pepluanone (57). Comparison of the activity of paralianes (71 and 76) and pepluanes (64 and 65) demonstrated the crucial role of a carbonyl on D-ring and negative effects when D-ring is hydroxylated or aromatic (Barile et al. 2007).

Corea (2005) isolated a new diterpene, pepluanone (57) together with a known pepluane diterpene (61) (Hohmann et al. 1999a; Jakupovic et al. 1998b) from *Euphorbia peplus* L. The ability of pepluanone (57) as an anti-inflammatory agent on LPS-stimulated NO production in RAW264.7 macrophage cell line. The results showed that pepluanone inhibited in a concentration-dependent manner, without cytotoxicity, both LPS-induced NO and PGE2 productions. It was also able to inhibit TNF-R mRNA expression. The mechanism by which pepluanone inhibits iNOS, COX-2, and TNF-R mRNA involves the suppression of NF-κB activation. Comparison of high in vivo efficiency of pepluanone and the absence of notable in vivo activity for compound 61 highlighted the importance of functionality at C-9 (a ketone in pepluanone and an acetoxyl in compound 61 (Corea et al. 2005b).

Anti-arrhythmic effect

In heart muscle, G protein-coupled inwardly rectifying potassium (GIRK) channels are responsible for K^+-fluxes and membrane repolarisation and/or hyperpolarisation. These ion channels selectively expressed in the cardiac atrium are not present in the ventricle. Electrical remodeling of atrial heart muscle during chronic atrial fibrillation may result in a constitutively active form of the GIRK channel, which may indeed lead to a better understanding of the important role this channel plays in said disease. Kúsz et al. (2016) investigated electrophysiological effects of guyonianin G (280) and H (281), together with four jatrophanes 326, 302, 372, and 5 previously isolated from *E. mongolica* (Rédei et al. 2012), *E. serrulata* (Hohmann et al. 2002), and *E. salicifolia* (Hohmann et al. 2001a, b) on stable transfected HEK–GIRK1/4 (Kir3.4) cell lines (Kúsz et al. 2016). It was demonstrated that jatrophanes could be new inhibitors with high potency for atrial GIRK channels for the first time. The most significant dose-dependent inhibitory effects on GIRK channel were displayed by guyonianin G (280) and H (281). Guyonianin G (280) had the highest blocking activity (70% at 10 μM), while the inhibition of GIRK current by guyonianin H (281) at 10 μM was 48%. 484 also inhibited the GIRK current

with similar activity to guyonianin H (44% at 10 μM). Besides, this substance illustrated a quick effect occurred immediately after the application. Low blocking activity was observed in diterpenes 302 and 372 while 5 did not represent any remarkable effect (Kúsz et al. 2016). Selective inhibition of the GIRK channel might lead to develope a promising class of new antiarrhythmic drugs (Dobrev et al. 2005; Hashimoto et al. 2006; Kobayashi and Ikeda 2006).

Kusz et al. (2018) isolated nine new (151–159) and two known (euphomelliferene B (295), euphornin (208)) jatrophanes from *E. dulcis*. The electrophysiological effects of 151, 152, 159, 295, and 208 were assayed in the HEK-hERG cell line. In order to find effective natural agents for the treatment of atrial fibrillation, the selectivity of their GIRK blocking effect on stable transfected HEKGIRK1/4 (Kir3.1/3.4) and HEK-hERG (Kv11.1) cell lines in two concentrations (1 and 10 μM) was examined. Almost all of the diterpenoids showed remarkable blocking activity on GIRK channels at 10 μM concentration (60.8–88.7%) and displayed considerable inhibitory effects even at 1 μM concentration. None of the tested jatrophanes interfered with the function of hERG proteins. Therefore, jatrophane diterpenoids might be suggested as a group of potential lead compounds for novel therapeutic agents against atrial fibrillation (Kusz et al. 2018).

Antibacterial activity

Japodagrone (90) which had previously been isolated from *Jatropha podagrica* was investigated for its antibacterial activities on *staphylococcus aureus* (ATCC29213), *bacillus subtilis* (ATCC6051), *escherichia coli* (ATCC25922), and *pseudomonas aeruginosa* (ATCC 27853) by Aiyelaagbe et al. (2007). Streptomycin and gentamycin (20 μg/disk) were used as positive controls. It was observed that japodagrone (90) only showed activity against *Bacillus subtilis* (ATCC6051), giving a zone of 12 mm at 20 μg/disk. This compound was presumed to be responsible for some of the antibacterial activity exhibited by extracts of this plant (Aiyelaagbe et al. 2007).

Neuroprotective effect

Pan et al. (2004) isolated kansuinines F (369), G (370), and H (96) together with four known jatrophanes: kansuinines D (97), E (371), A (95), and '3β,5α,7β,15β-tetraacetoxy-9α-nicotinoyloxy jatropha-6(17)-11E-dien-14-one' from *E. kansui*. The ability of different kansuinins to activate tropomyosin receptor kinase (Trk) A and Trk B signaling was tested by determining the survival effects of these compounds on fibroblasts expressing Trk A and Trk B. The survival of these cells is solely dependent on nerve growth factor (NGF) and BDNF (a member of the neurotrophin family related to NGF) treatment and they would normally die in the absence of NGF and BDNF. NGF had been the best candidate for its neuroprotective effects in the animal models of neurodegenerative diseases. The ability of small molecules like kansuinins which mimic or induce NGF activity was investigated for the treatment of Alzheimer. Kansuinin E (371) showed a particular effect on the survival of TrkA fibroblasts compared with TrkB cells with an ED_{50} value of 0.23 μg/mL. In contrast, kansuinins A (95), D (97), and F (369) enhanced the survival of both Trk A- and Trk B-expressing fibroblasts (Pan et al. 2004).

Antithrombotic activity

Activated protein kinase C (PKC) phosphorylates and regulates downstream substrates that can lead to platelet activation, secretion, and aggregation, which are indeed important for thrombus formation. Therefore PKC plays an outstanding role in the occurrence of thrombotic diseases. Several tumor-promoting *Euphorbia* diterpenes are known to act as direct activators of PKC, but many types of such diterpenes have not been studied as platelet stimulators yet. Tsai et al. (2016) studied esulatins B and I (470 and 128) previously obtained from *E. esula* for their effects on PKC activation and platelet stimulation. These compounds did not induce platelet aggregation at a concentration as high as 10 μM. Furthermore, these compounds which were inactive in the platelet aggregation assay failed to induce platelet secretion but the mentioned research suggests that platelets appear to be a useful model for screening PKC activators of natural origin or their chemical derivatives (Tsai et al. 2016).

Antimalarial activity

Zhou et al. (2016) isolated 14 new diterpenoids, named euphorbesulins A-O (13–15, 282–292, and 70). These euphorbesulins included presegetane (13–15) and jatrophanes (282–292) and one paraliane (70). Tested jatrophanes (13–23) isolated from *E. esula* for antimalarial effects against chloroquine-resistant *plasmodium falciparum* strain Dd2 using a SYBR-Green assay with artemisinin as the positive control. Euphorbesulin G (285) exhibited low nanomolar antimalarial activity ($IC_{50} = 0.12 \pm 0.04$), while the rest showed only moderate to no antimalarial activity ($IC_{50} > 5$) (Zhou et al. 2016).

Mongkolvisut and Sutthivaiyakit (2007) isolated six new poly-O-acylated jatrophanes (186–191) from the *Pedilanthus tithymaloides*. Their biological activities including antimalarial effects against *plasmodium falciparum* K1 strain as well as antitubercular effects against *mycobacterium tuberculosis* H37 Ra were investigated. 186 and 188–190 were found to be active against *P. falciparum* with IC_{50} values of 3.4–4.4 μg/mL; whereas, 187 was inactive at 10 μg/mL. Considering the anti-mycobacterial activity, 186 was the most active while 187–190 have shown moderate to mild activity. An additional anti-fungal assay was applied on 186, 187, and 190 against *Candida albicans* at 50 μg/mL, none of which was active (Mongkolvisut and Sutthivaiyakit 2007).

Lipid-lowering agent

Li et al. (2018a, b) isolated 33 jatrophanes, seven of which (215–217, 321, 12, 169, and 170) were new and others were known compounds identified as euphoscopin A-D (242, 244, 245, and 106), euphoheliosnoid A (337), euphoscopin E–F (331 and 332), euphorbiapene D (330), euphoscopin J (250), euphorbiapene A (239), epieuphoscopin A and B (252 and 254), epieuphoscopin D (107), epieuphoscopin F (335), euphornin L (161), euphorbiapene C (241), euphornin (208), euphornin A (210), euphornin C and D (265 and 212), euphornin H and I (259 and 260), euphornin G (258), euphornin J and K (262 and 263), euphorbiapene B (240), euphoheliosnoid B (338) from *E. helioscopia*. This mini-library of jatrophanes was established to screen hit or lead compounds possessing lipid-lowering activity. LDL-uptake screening assay showed that most of them improved LDL-uptake rate in HepG2 cells, with 239, 161, and 212 displaying superior effects. It was further found that these three compounds could enhance LDLR protein level in HepG2 cells dose-dependently. SAR studies demonstrated that the type of substitution at C-9 is essential for the activity, as replacing carbonyl with acetoxy group considerably increased the activity of 259 vs. 212. However, different substitutions at C-7 look to be less effective on the activity, as compounds (215–217), (242, 244, 245, 106, and 337) and (208, 210, and 265) displayed similar results. 239 with a long conjugated fragment from C-5 to the carbonyl exhibited significantly increased activity. Besides, large steric hindrance between C-14 and C-15 is unpleasant for the activity, as 208, 210, and 265 displayed weak activities although they all have an acetoxy group at C-9. The presence of a carbonyl or an acetoxy group at C-14 also did not influence activity (242 vs. 331, 244 v.s 332, 245 vs. 330). Furthermore, similar activities were seen for 244 vs. 262, 245 vs. 240, 337 vs. 338, 252 vs. 260, and 241 vs. 256 demonstrating that configuration at C-2 was not important for the activity, same being true for configuration at C-13 as the results of 242 vs. 252, 106 vs. 107, 259 vs. 262 had been shown this matter. Among all, 161 showed a notable lowering effect in serum CHOL and LDL-C levels while it was less effective on HDL-C level and body weight in vivo (Li et al. 2018a).

Conclusion

Jatrophanes isolated from *Euphorbia* species and their polycyclic rearranged derivatives with a wide chemical structural diversity have been mentioned recently as privileged bio-resources for the development of potential drugs (Jassbi 2006; Kirby et al. 2010). Jatrophanes and modified jatrophanes have exhibited a large number of biological activities, such as being inhibitors of CaCdr1p and/or CaMdr1p efflux pumps in *Candida albicans* (Esposito et al. 2017), modulators of P-glycoprotein (P-gp) exhibiting reverse multidrug resistance (MDR) (Corea et al. 2003a; Hohmann et al. 2002), paclitaxel-like microtubule interacting activity (Miglietta et al. 2003), moderate cytotoxic agents against a variety of cancer cells (Hegazy et al. 2010; Lanzotti et al. 2015), and promising synergistic agents increasing the anticancer activity on resistant cells in

combination with anticancer drugs (Pešić et al. 2011). The most studied biological activity of them is the MDR reversing activity in cancer cells overexpressing P-gp. Jatropha-5,12-diene inhibitors of the drug efflux transporters ABCB1 P-gp and ABCG2 have been developed (Reis et al. 2016). SAR studies provide invaluable information on the key pharmacophoric elements of these compounds. Furthermore, they give the possibility to evaluate the efficacy of different ester groups on each position of the jatrophane macrolides requiring no costly, time-consuming labor-intensive synthesis or semisynthetic modifications. These findings coupled with conformational flexibility of twelve-membered jatrophane core have suggested that conformational flexibility is determinant for P-gp modulation, and in MDR activity, they are generally more active than the rearranged polycyclic ones (Ferreira et al. 2014; Reis et al. 2012). Besides, the hydrophobicity along with the substitutions of the "southwestern" fragment (C-2, C-3, and C-5) are also critical factors for the activity of jatrophane-type diterpenes (Corea et al. 2004a). Jatrophanes exhibit also anti-inflammatory activities (Chen et al. 2014; Lee et al. 2016). They have also been reported for in vitro antiviral activity against human immunodeficiency (Bedoya et al. 2009) and Chikungunya viruses (Nothias-Scaglia et al. 2014). It had been proposed that short cycles of treatment with these small molecules inducing HIV reactivation combined with highly active antiretroviral therapy (HAART), could contribute to a decrease of viral reservoirs (Bedoya et al. 2009; Nothias-Scaglia et al. 2014). Jatrophanes like pubescenol and pubescene D showed considerable antiproliferative activity against human tumor cell lines MCF-7, NCI-H460, and SF-268 (Valente et al. 2004a, c). Thus, more clinical trials and structural analysis will be required in the future to evaluate the clinical benefits of these recently discovered compounds.

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