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Mini review on Cyclic Polyketides from *Beilschmiedia* and *Endiandra* Species (Lauraceae): Chemical Structures, Biological Activities and Biosynthesis

Nur Amirah Saad[1], Mohamad Nurul Azmi[1*] and Pinus Jumaryatno[2]
[1]School of Chemical Sciences, Universiti Sains Malaysia, Pulau Pinang, 11800, Malaysia
[2]Department of Pharmacy, Faculty of Mathematics and Natural Sciences, Universitas Islam Indonesia, Yogyakarta, 55584, Indonesia
*Corresponding author (e-mail: mnazmi@usm.my)

The genus *Beilschmiedia* and *Endiandra* which are belong to the Lauraceae family, has been used extensively in traditional treatment. A rare class of tetracyclic and pentacyclic metabolites (i.e endiandric acids and the kingianin series) have been isolated and found specifically in these *Beilschmiedia* and *Endiandra* species. This current mini review is an update from the years 2000 – 2022 on phytochemical studies and biological activities together with the biosynthesis of the secondary metabolites from both genera. Previous literature reported that the chemical compounds from these two genera possess good biological activities such as anti-allergic, anti-asthmatic, anti-inflammatory, anti-bacterial, anti-tuberculosis, anti-plasmodial, anti-diabetic and anti-proliferative. The literatures and reference for this manuscript were obtained from various sources including SciFinder®, Reaxys®, ScienceDirect®, PubMed Central®, NIH National Library of Medicine, Google Scholar and The Plant List®. This review provides the update regarding the chemical structures, biological activities and biosynthesis of cyclic polyketides specifically in *Beilschmiedia* and *Endiandra* genera.

Key words: Lauraceae; *Beilschmiedia*; *Endiandra*; Cyclic polyketides; Endiandric acids; Kingianins

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The *Beilschmiedia* and *Endiandra* are the genera which are belongs to Lauraceae family and locally known as *Medang* or *Tejur* [1]. The *Beilschmiedia* plants are mostly trees that grow up from 25 m to 35 m tall and it is the one of the largest pantropical genera in the Lauraceae family [1-2]. According to The Plant List Database, 287 names of this genus are accepted, and the remaining are either synonyms or unresolved names [1-2]. The *Beilschmiedia* species mostly grow in tropical climates, but a few are still native to the temperate regions. They are widely found in tropical Asia, Africa, Australia, New Zealand, Central America, Caribbean and South America [3]. In Southeast Asia, *Beilschmiedia* can typically be found in Vietnam, Myanmar, Thailand, Cambodia, Indonesia, Philippines, Malaysia and various islands such as Sumatra and Java [1]. The local people use this genus to treat stomach ache, digestive disorder and dysentery [1]. Meanwhile, *Endiandra* is a genus of evergreen trees in the Lauraceae or Laurel family. Over 125 species in this genus can be found in Southeast Asia, the Pacific region, and Australia [1,4-5]. Recently, only three species i.e *E. introrsa* [6-9], *E. anthropophagorum* [10-11] and *E. kingiana* [12-16], have been studied for their phytochemicals and this genus was reported to be used as a timber [1].

In scientific point of view, these two genera have been identified to contain polyketides in the form of endiandric acids and kingianins. Endiandric acids and kingianins are a unique type of polyketide found in this family and it is derived from late stage electrocyclization of polyenes. This class of compounds was reported to have interesting biological activities. Since *Endiandra* and *Beilschmiedia* plants are rare, there is limited research on them that has been published. Thus, the aim of this review is to provide an overview of chemical and pharmacological studies of cyclic polyketides including their biosynthesis isolated from *Beilschmiedia* and *Endiandra* genera from year 2000-2022. In this mini review, an extensive analysis and comparison of literatures were obtained from various sources including SciFinder®, Reaxys®, ScienceDirect®, PubMed Central®, NIH National Library of Medicine, Google Scholar and The Plant List®. has been employed.

Cyclic Polyketides: Endiandric Acids and Kingianins

Endiandric acids are formed exclusively by the *Beilschmiedia* and *Endiandra* species which have a distinctive tetracyclic carbon skeleton. Type A, type B, and type B′ (Figure 1) are three primary skeletal

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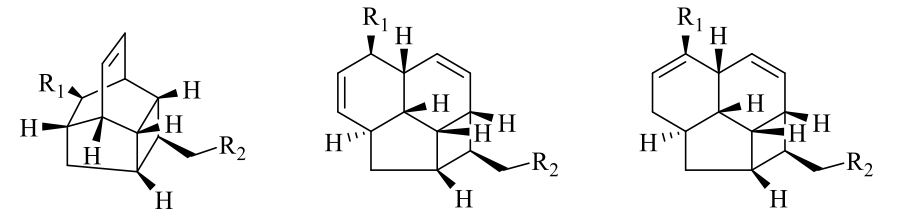


Figure 1. Endiandric acids main skeleton.

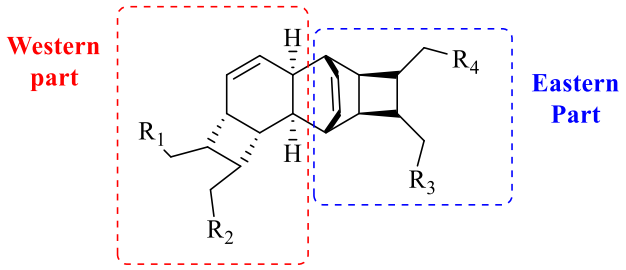


Figure 2. Kingianin pentacyclic skeleton.

groups of these cyclic polyketides, which have eight chiral centers and normally isolated as a racemic mixture [αD] = 0°. Generally, these endiandric acids contain two cyclohexane, one cyclopentane, and one cyclobutane rings, and are commonly substituted with a phenyl ring and a carboxylic acid chain.

The isolated kingianin is an optically inactive compound in the form of a white powder or amorphous solid. A pentacyclic carbon skeleton (bicyclo[4.2.0] backbone), as shown in Figure 2, is a common feature of kingianins. Generally, the main skeleton of kingianins consists of 16 carbons of a pentacyclic moiety, including four *cis*-configured olefinic carbons. The remaining substituents are *N*-ethyl acetamide, butyric acid, and an acetic acid chain with two methylenedioxyphenyl groups. The position of the four substituents at C-1, C-8, C-1' and C-8' distinguishes them from each other. Two of the substituents were methylenedioxyphenyl groups, which were deduced from the absorption bands at λ_{max} 289 nm and 240 nm in the UV spectrum and confirmed by NMR analyses.

Cyclic Polyketides & Biological Activities

The first polyketides identified from a Lauraceae species are endiandric acids A-C (**1-3**) isolated from *E. Introrsa* [6-9]. The same compounds were also isolated from *B. oligandra* by Banfield *et al*. [17]. In addition, the first biological activity studies on endiandric acid were reported by Eder's group in 2004. They isolated endiandric acid H (**4**) from *B. fulva* and patented it for the treatment of allergic diseases, asthmatic diseases, inflammatory accompanying symptoms of asthma and diseases that can be treated by inhibition of c-Maf and NFAT [18]. Recent reports showed that endiandric acids possess various biological activities, such as anti-bacterial [19-21], anti-plasmodial [22], anti-tubercular [23], iNOS inhibitory activity [24] and cytotoxic properties [22,24].

Both species are extensively study since 2009. In 2009, eight endiandric acid derivatives namely beilschmiedic acids A-G (**5-11**) and beilschmiedin (**12**), were isolated from the bark of *B. anacardioides* [19-21]. Anti-bacterial activity of compounds **5-7** was tested *in vitro* against five microbe strains. In comparison to the reference antibiotic ampicillin (MICs value below 90.0 µM), compound **7** exhibited the greatest potency against *Bacillus subtilis*, *Micrococcus luteus*, and *Streptococcus faecalis* (MICs value < 23.0 µM) [20]. This result indicating its significant potential as a new antibacterial agent against the gram-positive bacteria. Yang *et al*. were able to isolate nine endiandric acid analogues from *B. erythrophloia* [23,25] including beilcyclone A (**13**), endiandric acids I-J (**14-15**) and erythrophloins A-F (**16-21**). Among them, erythrophloin C (**18**) showed antitubercular activity against *Mycobacterium tuberculosis* H37Rv (MIC values of 50 µg/mL) and also significantly inhibited P-388 murine lymphocytic leukemia cells [23]. Huang *et al*. used a methanolic extract from the root of *B. tsangii* to screen for anti-inflammatory effects using an inducible nitric oxide synthase (iNOS) assay. The study reported potent inhibition of NO production, with no cytotoxicity against RAW 264.7 cells. Tsangibeilins A-D (**22-23** and **29-30**), endiandramides A (**24**) and B (**28**), and endiandric acids K-M (**25-27**) were isolated from the extract using a bioassay-guided fractionation technique. With IC_{50} values of 9.59 and

16.40 μM, compounds **24** and **28** were reported to have a significant iNOS inhibitory action [24,26].

Williams and co-workers published a series of endiandric acid analogues named beilschmiedic acids H-O (**31**-**38**), as well as known compounds, beilschmiedic acids A and C (**5** and **7**), that were isolated from a *Gabonese B.* species [27]. The compounds were then tested against NCI-H460 human lung cancer cells and a clinical isolate of methicillin-resistant Staphylococcus aureus (MRSA 108) for their cytotoxic and anti-bacterial activity. Based on this screening, only compound **5** demonstrated significant activity in the NCI-H460 human cancer cell line assay, with an IC_{50} value of 6.1 μM and showed strong anti-bacterial activity against *S. aureus* with an IC_{50} value of 10.0 μM [27]. Talonsti *et al*. isolated four beilschmiedic acids from the bark of *E. cryptocaryoides*, namely cryptobeilic acids A-D (**39**-**42**) and tsangibeilin B (**23**) [22]. These compounds showed moderate anti-plasmodial activity against the chloroquino-resistant *Plasmodium falciparum* strain NF54 and anti-bacterial activities against *Escherichia coli*, *Acinetobacter calcoaceticus* and *Pseudomonas stutzeri*. A rapid NMR-based screening on ethyl acetate (EtOAc) extracts of *Beilschmiedia* and *Endiandra* species revealed eleven tetracyclic endiandric acids named ferrugineic acid A-K (**43**-**53**). These polyketides were isolated from *B. ferruginea* and assayed for Bcl-xL and Mcl-1 binding affinities. Based on the results, ferrugineic acid B (**44**), ferrugineic acid C (**45**) and ferrugineic acid J (**52**) exhibited a significant binding affinity for both anti-apoptotic proteins Bcl-xL with the K_i value of 19.2 μM, 12.6 μM and 19.4 μM respectively. While the K_i values for Mcl-1 were 14.0 μM, 13.0 μM and 5.2 μM, respectively. However, ferrugineic acid D (**46**) only showed significant inhibiting activity for Mcl-1 with a K_i value of 5.9 μM [28].

In 2011, a novel polyketide series possessing a [4.2.0] bicyclic main skeleton named kingianins A-N (**54**-**67**) was reported by Leverrier and co-workers [12,13]. These compounds were only isolated from *E. kingiana* and hence were extensively studied for Bcl-xL binding affinity. These studies were evaluated by comparing against a fluorescently labelled reference compound (fluorescence tagged BH3 domain of the protein Bak Neosystem), as described by Qian *et al.* [29]. The laevorotatory enantiomers revealed more potent binding affinity against Bcl-xL with K_i in the range of 1.0 to 12 μM. In addition, an earlier study by Azmi *et al.* (2014) reported seven new tetracyclic endiandric acid analogues, i.e., kingianic acids A-G (**68**-**74**), endiandric acid M (**27**) and tsangibeilin B(**23**) which were isolated from the methanol crude extract of *Endiandra kingiana*'s bark [16]. Subsequently, all the compounds were assayed for Bcl-xL and Mcl-1 binding affinities and cytotoxic activity upon various cancer cell lines. Consequently, kingianic acid E (**72**) showed moderate cytotoxic activity against human colorectal adenocarcinoma (HT-29) and lung adenocarcinoma epithelial (A549) cell lines with IC_{50} values ranging from 15 to 17 μM. However, kingianic acid C (**70**), kingianic acid F (**73**) and tsangibeilin B (**23**) only exhibited weak binding affinity towards the anti-apoptotic protein Mcl-1 [16].

Moreover, three new pentacyclic kingianins were isolated as racemic mixtures in 2015, i.e., kingianins O-Q (**75**-**77**) [15]. In continuation, the compounds kingianins A-Q were then screened for Mcl-1 binding affinity [15]. The assays were compared to the interaction of fluorescein-labelled peptides in Mcl-1. The study showed that kingianin G (**60**), kingianin H (**61**), kingianin J (**63)** and kingianin K (**64**) exhibited similar binding affinities with their respective (+)-counterparts. In addition, kingianin G (**60**), kingianin H (**61**), kingianin J (**63)** exhibited the most potent binding affinities to the protein Mcl-1 with K_i values between 2 and 4 μM, while (−)- and (+)-kingianin K (**64**) and kingianin L (**65**) were less active ($13 < K_i < 17$ μM). Structure-activity relationship study showed that the potency is sensitive to the substitution pattern on the pentacyclic core [15]. Recently, Azmi *et al*. studied the *in vitro* α-glucosidase inhibition activity and molecular docking on four major compounds isolated from the methanol extract of *E. kingiana* bark. These were kingianic acid A (**68**), tsangibeilin B (**23**), kingianin A (**54**) and kingianin F (**59**). Among them, kingianin A and kingianin F showed good inhibition activity towards α-glucosidase with IC_{50} value of 11.9 ± 2.0 μM and 19.7 ± 1.5 μM, respectively. Molecular docking study revealed that both compounds were bound into the active site of the *N*-terminal of MGAM and thus agreed with the α-glucosidase inhibition activity results [14].

A summary of cyclic polyketides found in *Beilschmiedia* and *Endiandra* species are listed in Table 1 and Figure 3 (from 2000 – 2022). A total of 77 cyclic polyketide compounds were managing to be isolated and elucidated from both genera.

Table 1. List of polyketides isolated from *Beilschmiedia* and *Endiandra* species

Name of Polyketides	Name of Plants	Biological activity			Ref.
		Assay	Target	Results	
Endiandric acid A (**1**)	*E. introrsa*, *B. oligandra*	–	–	–	[6-9,17]
Endiandric acid B (**2**)	*E. introrsa*, *B. erythrophloia*	–	–	–	[6-9, 23,25]
Endiandric acid C (**3**)	*E. introrsa*	–	–	–	[36]
Endiandric acid H (**4**)	*B. fulva*	Anti-allergic Anti-asthmatic Anti-inflammatory	–	–	[18]
Beilschmiedic acid A (**5**)	*B. anacardioides*, *B. sp (*Gabonese species)	Anti-bacterial	*Bacillus subtilis*, *Micrococcus luteus*, *Streptococcus faecalis*	15 μM 12 μM 14 μM	[20]
		Cytotoxic activity	Large cell lung carcinoma (NCI-H460)	6.1 μM	[27]
Beilschmiedic acid B (**6**)	*B. anacardioides*	Anti-bacterial	*Bacillus subtilis*, *Micrococcus luteus*, *Streptococcus faecalis*	16 μM 15 μM 15 μM	[20]
Beilschmiedic acid C (**7**)	*B. anacardioides*, *B. sp* (Gabonese species)	Cytotoxic activity	Large cell lung carcinoma (NCI-H460)	Not active	[27]
	B. anacardioides	Anti-bacterial	*Bacillus subtilis*, *Micrococcus luteus*, *Streptococcus faecalis*	13 μM 30 μM 18 μM	[20]
Beilschmiedic acid D (**8**)	*B. anacardioides*	–	–	–	[20-21]
Beilschmiedic acid E (**9**)	*B. anacardioides*	–	–	–	[20-21]
Beilschmiedic acid F (**10**)	*B. anacardioides*	–	–	–	[20-21]
Beilschmiedic acid G (**11**)	*B. anacardioides*	–	–	–	[20-21]
Beilschmiedin (**12**)	*B. anacardioides*	–	–	–	[20-21]
Beilcyclone A (**13**)	*B. erythrophloia*	–	–	–	[23]
Endiandric acid I (**14**)	*B. tsangii*	–	–	–	[25]
Endiandric acid J (**15**)	*B. tsangii*	–	–	–	[25]
Erythrophloin A (**16**)	*B. erythrophloia*	–	–	–	[23]
Erythrophloin B (**17**)	*B. erythrophloia*	–	–	–	[23]
Erythrophloin C (**18**)	*B. erythrophloia*	Anti-tuberculosis	*Mycobacterium tuberculosis* H37Rv	50 μg/mL	[23]
Erythrophloin D (**19**)	*B. erythrophloia*	–	–	–	[23]
Erythrophloin E (**20**)	*B. erythrophloia*	–	–	–	[23]
Erythrophloin F (**21**)	*B. erythrophloia*	–	–	–	[23]
Tsangibeilin A (**22**)	*B. tsangii*	Anti-inflammatory	RAW 264.7 cell	49.59 ± 0.64 μM	[24]
Tsangibeilin B (**23**)	*B. tsangii*	Anti-inflammatory	RAW 264.7 cell	42.30 ± 1.06 μM	[24]
	B. cryptocaryoides,	Cytotoxic activity	L6 cell lines	21.5 μM	[22]
		Anti-bacterial	*Escheria coli* 6r3, *Acinetobacter calcoaceticus* DSM 586, *Pseudonamas stutzeri* A1501, *Serratia plymuthica* C48	50 μg/mL >50 μg/mL >50 μg/mL >50 μg/mL	
		Anti-plasmodial	Chloroquine-resistant *Plasmodium falciparum* strain NF54	8.2. μM	
	E. kingiana	Bcl-xL/Bak binding affinity	Bcl-xL/Bak	26% ± 2.5 @ 100 μM	[16]
		Mcl-1/Bid binding affinity	Mcl-1/Bid	81% ± 2.4 @ 100 μM	
		Cytotoxicity activity	HT-29 A549 PC3	>100 μM 38.1 ± 0.1 μM >100 μM	
		Anti-diabetic	α-glucosidase	97.4 ± 0.6 μM	[14]
Endiandramide A (**24**)	*B. tsangii*	–	–	–	[24, 26]
Endiandric acid K (**25**)	*B. tsangii*	Anti-inflammatory	RAW 264.7 cell	58.21 μM	

Endiandric acid L (**26**)	*B. tsangii*	Anti-inflammatory	RAW 264.7 cell	39.56 μM	
Endiandric acid M (**27**)	*B. tsangii*	Anti-inflammatory	RAW 264.7 cell	31.70 μM	[24, 26]
	E. kingiana	Bcl-xL/Bak binding affinity	Bcl-xL/Bak	10% ± 0.5 @ 100 μM	[16]
		Mcl-1/Bid binding affinity	Mcl-1/Bid	39% ± 0.9 @ 100 μM	[16]
			HT-29 A549 PC3	>100 μM >100 μM >100 μM	[16]
Endiandramide B (**28**)	*B. tsangii*	Anti-inflammatory	RAW 264.7 cell	16.40 μM	[24, 26]
Tsangibeilin C (**29**)	*B. tsangii*	–	–	–	
Tsangibeilin D (**30**)	*B. tsangii*	–	–	–	
Beilschmiedic acid H (**31**)	*B. sp* (Gabonese species)	Cytotoxic activity	Large cell lung carcinoma (NCI-H460)	Not active	[27]
		Anti-bacterial	Methicillin-resistant *Staphylococcus aureus* (MRSA 108)	Not active	
Beilschmiedic acid I (**32**)	*B. sp* (Gabonese species)	Cytotoxic activity	Large cell lung carcinoma (NCI-H460)	5.5 μM	[27]
		Anti-bacterial	Methicillin-resistant *Staphylococcus aureus* (MRSA 108)	12 μg/mL	
Beilschmiedic acid J (**33**)	*B. sp* (Gabonese species)	-	-	-	[27]
Beilschmiedic acid K (**34**)	*B. sp* (Gabonese species)	Cytotoxic activity	Large cell lung carcinoma (NCI-H460)	5.9 μM	[27]
		Anti-bacterial	Methicillin-resistant *Staphylococcus aureus* (MRSA 108)	11 μg/mL	
Beilschmiedic acid L (**35**)	*B. sp* (Gabonese species)	Cytotoxic activity	Large cell lung carcinoma (NCI-H460)	4.4 μM	[27]
		Anti-bacterial	Methicillin-resistant *Staphylococcus aureus* (MRSA 108)	11 μg/mL	
Beilschmiedic acid M (**36**)	*B. sp* (Gabonese species)	Cytotoxic activity	Large cell lung carcinoma (NCI-H460)	8.7 μM	[27]
		Anti-bacterial	Methicillin-resistant *Staphylococcus aureus* (MRSA 108)	12 μg/mL	
Beilschmiedic acid N (**37**)	*B. sp* (Gabonese species)	Cytotoxic activity	Large cell lung carcinoma (NCI-H460)	19 μM	[27]
		Anti-bacterial	Methicillin-resistant *Staphylococcus aureus* (MRSA 108)	13 μg/mL	
Beilschmiedic acid O (**38**)	*B. sp* (Gabonese species)	Cytotoxic activity	Large cell lung carcinoma (NCI-H460)	Not active	[27]
		Anti-bacterial	Methicillin-resistant *Staphylococcus aureus* (MRSA 108)	13 μg/mL	
Cryptobeilic acid A (**39**)	*B. cryptocaryoides*	Cytotoxic activity	L6 cell lines	59.5 μM	[22]
		Anti-bacterial	*Escheria coli* 6r3, *Acinetobacter calcoaceticus* DSM 586, *Pseudonamas stutzeri* A1501, *Serratia plymuthica* C48	10 μg/mL >50 μg/mL 50 μg/mL >50 μg/mL	
		Anti-plasmodial	Chloroquine-resistant *Plasmodium falciparum* strain NF54	17.7 μM	
Cryptobeilic acid B (**40**)	*B. cryptocaryoides*	Cytotoxic activity	L6 cell lines	20.4 μM	[22]
		Anti-bacterial	*Escheria coli* 6r3, *Acinetobacter calcoaceticus* DSM 586, *Pseudonamas stutzeri* A1501, *Serratia plymuthica* C48	20 μg/mL 20 μg/mL 10 μg/mL >50 μg/mL	
		Anti-plasmodial	Chloroquine-resistant *Plasmodium falciparum* strain NF54	5.35 μM	
Cryptobeilic acid C (**41**)	*B. cryptocaryoides*	Cytotoxic activity	L6 cell lines	59.3 μM	[22]
		Anti-bacterial	*Escheria coli* 6r3, *Acinetobacter calcoaceticus* DSM 586,	>50 μg/mL >50 μg/mL	

			Pseudonamas stutzeri A1501, *Serratia plymuthica* C48	>50 μg/mL >50 μg/mL	
		Anti-plasmodial	Chloroquine-resistant *Plasmodium falciparum* strain NF54	14.0 μM	
Cryptobeilic acid D (**42**)	*B. cryptocaryoides*	Cytotoxic activity	L6 cell lines	61.0 μM	[22]
		Anti-bacterial	*Escheria coli* 6r3, *Acinetobacter calcoaceticus* DSM 586, *Pseudonamas stutzeri* A1501, *Serratia plymuthica* C48	50 μg/mL >50 μg/mL >50 μg/mL >50 μg/mL	
		Anti-plasmodial	Chloroquine-resistant *Plasmodium falciparum* strain NF54	10.8 μM	
Ferrugineic acid A (**43**)	*B. ferruginea*	Bcl-xL/Bak binding affinity	Protein Bcl-xL	22% ± 2 @ 100 μM	[28]
		Mcl-1/Bid binding affinity	Protein Mcl-1	0% @ 100 μM	
Ferrugineic acid B (**44**)	*B. ferruginea*	Bcl-xL/Bak binding affinity	Protein Bcl-xL	60% ± 6 @ 100 μM	[28]
		Mcl-1/Bid binding affinity	Protein Mcl-1	85% ± 2 @ 100 μM	
Ferrugineic acid C (**45**)	*B. ferruginea*	Bcl-xL/Bak binding affinity	Protein Bcl-xL	93% ± 3 @ 100 μM	[28]
		Mcl-1/Bid binding affinity	Protein Mcl-1	82% ± 2 @ 100 μM	
Ferrugineic acid D (**46**)	*B. ferruginea*	Bcl-xL/Bak binding affinity	Protein Bcl-xL	39% ± 3 @ 100 μM	[28]
		Mcl-1/Bid binding affinity	Protein Mcl-1	82% ± 2 @ 100 μM	
Ferrugineic acid E (**47**)	*B. ferruginea*	Bcl-xL/Bak binding affinity	Protein Bcl-xL	20% ± 1 @ 100 μM	[28]
		Mcl-1/Bid binding affinity	Protein Mcl-1	14% ± 3 @ 100 μM	
Ferrugineic acid F (**48**)	*B. ferruginea*	Bcl-xL/Bak binding affinity	Protein Bcl-xL	7% ± 1 @ 100 μM	[28]
		Mcl-1/Bid binding affinity	Protein Mcl-1	0% @ 100 μM	
Ferrugineic acid G (**49**)	*B. ferruginea*	Bcl-xL/Bak binding affinity	Protein Bcl-xL	17% ± 1 @ 100 μM	[28]
		Mcl-1/Bid binding affinity	Protein Mcl-1	3% ± 1 @ 100 μM	
Ferrugineic acid H (**50**)	*B. ferruginea*	–	–	–	
Ferrugineic acid I (**51**)	*B. ferruginea*	Bcl-xL/Bak binding affinity	Protein Bcl-xL	35% ± 1 @ 100 μM	[28]
		Mcl-1/Bid binding affinity	Protein Mcl-1	7% ± 2 @ 100 μM	
Ferrugineic acid J (**52**)	*B. ferruginea*	Bcl-xL/Bak binding affinity	Protein Bcl-xL	58% ± 7 @ 100 μM	[28]
		Mcl-1/Bid binding affinity	Protein Mcl-1	81% ± 3 @ 100 μM	
Ferrugineic acid K (**53**)	*B. ferruginea*	Bcl-xL/Bak binding affinity	Protein Bcl-xL	22% ± 3 @ 100 μM	[28]
		Mcl-1/Bid binding affinity	Protein Mcl-1	0% @ 100 μM	
Kingianin A (**54**)	*E. kingiana*	Bcl-xL/Bak binding affinity	Protein Bcl-xL	213 ± 53	[12]
		Mcl-1/Bid binding affinity	Protein Mcl-1	>33	[15]
		Anti-diabetic	α-glucosidase	11.9 ± 2.0 μM	[14]
Kingianin B (**55**)	*E. kingiana*	Bcl-xL/Bak binding affinity	Bcl-xL/Bak	>300	[12]
		Mcl-1/Bid binding affinity	Protein Mcl-1	>33	[15]
Kingianin C (**56**)	*E. kingiana*	Bcl-xL/Bak binding affinity	Bcl-xL/Bak	>300	[12]
		Mcl-1/Bid binding affinity	Protein Mcl-1	>33	[15]
Kingianin D (**57**)	*E. kingiana*	Bcl-xL/Bak binding affinity	Bcl-xL/Bak	>300	[12]
		Mcl-1/Bid binding affinity	Protein Mcl-1	>33	[15]

Kingianin E (**58**)	*E. kingiana*	Bcl-xL/Bak binding affinity	Bcl-xL/Bak	>300	[12]
		Mcl-1/Bid binding affinity	Protein Mcl-1	>33	[15]
Kingianin F (**59**)	*E. kingiana*	Bcl-xL/Bak binding affinity	Bcl-xL/Bak	231 ± 47	[12]
		Mcl-1/Bid binding affinity	Mcl-1/Bid	>33	[15]
		Anti-diabetic	α-glucosidase	19.7 ± 1.5 μM	[14]
Kingianin G (**60**)	*E. kingiana*	Bcl-xL/Bak binding affinity	Bcl-xL/Bak	2 ± 0	[12]
Kingianin H (**61**)	*E. kingiana*	Bcl-xL/Bak binding affinity	Bcl-xL/Bak	18 ± 7	[12]
Kingianin I (**62**)	*E. kingiana*	Bcl-xL/Bak binding affinity	Bcl-xL/Bak	18 ± 3	[12]
Kingianin J (**63**)	*E. kingiana*	Bcl-xL/Bak binding affinity	Bcl-xL/Bak	29 ± 6	[12]
Kingianin K (**64**)	*E. kingiana*	Bcl-xL/Bak binding affinity	Bcl-xL/Bak	80 ± 36	[12]
Kingianin L (**65**)	*E. kingiana*	Bcl-xL/Bak binding affinity	Bcl-xL/Bak	36 ± 11	[12]
Kingianin M (**66**)	*E. kingiana*	Bcl-xL/Bak binding affinity	Bcl-xL/Bak	236 ± 34	[12]
		Mcl-1/Bid binding affinity	Protein Mcl-1	>33	[15]
Kingianin N (**67**)	*E. kingiana*	Bcl-xL/Bak binding affinity	Bcl-xL/Bak	177 ± 9	[12]
		Mcl-1/Bid binding affinity	Protein Mcl-1	19 ± 7	[15]
Kingianic acid A (**68**)	*E. kingiana*	Bcl-xL/Bak binding affinity	Bcl-xL/Bak	21% ± 1.8 @ 100 μM	[16]
		Mcl-1/Bid binding affinity	Mcl-1/Bid	36% ± 2.3 @ 100 μM	[16]
		Cytotoxicity activity	HT-29 A549 PC3	35.0 ± 0.2 μM 85.4 ± 0.2 μM >100 μM	[16]
Kingianic acid B (**69**)	*E. kingiana*	–	–	–	[16]
Kingianic acid C (**70**)	*E. kingiana*	Bcl-xL/Bak binding affinity	Bcl-xL/Bak	25% ± 1.7 @ 100 μM	[16]
		Mcl-1/Bid binding affinity	Mcl-1/Bid	75% ± 1.1 @ 100 μM	[16]
		Cytotoxicity activity	HT-29 A549 PC3	>100 μM 85.3 ± 0.2 μM >100 μM	[16]
Kingianic acid D (**71**)	*E. kingiana*	–	–	–	[16]
Kingianic acid E (**72**)	*E. kingiana*	Bcl-xL/Bak binding affinity	Bcl-xL/Bak	1% ± 0.8 @ 100 μM	[16]
		Mcl-1/Bid binding affinity	Mcl-1/Bid	8% ± 5.5 @ 100 μM	[16]
		Cytotoxicity activity	HT-29 A549 PC3	17.1 ± 0.1 μM 15.4 ± 0.2 μM 77.2 ± 0.2 μM	[16]
Kingianic acid F (**73**)	*E. kingiana*	Bcl-xL/Bak binding affinity	Bcl-xL/Bak	22% ± 2.9 @ 100 μM	[16]
		Mcl-1/Bid binding affinity	Mcl-1/Bid	80% ± 0.7 @ 100 μM	[16]
Kingianic acid G (**74**)	*E. kingiana*	Bcl-xL/Bak binding affinity	Bcl-xL/Bak	19% ± 1.6 @ 100 μM	[16]
		Mcl-1/Bid binding affinity	Mcl-1/Bid	47% ± 2.9 @ 100 μM	[16]
Kingianin O (**75**)	*E. kingiana*	Mcl-1/Bid binding affinity	Mcl-1/Bid	>33	[15]
Kingianin P (**76**)	*E. kingiana*	Mcl-1/Bid binding affinity	Mcl-1/Bid	30 ± 1	[15]
Kingianin Q (**77**)	*E. kingiana*	Mcl-1/Bid binding affinity	Mcl-1/Bid	>33	[15]

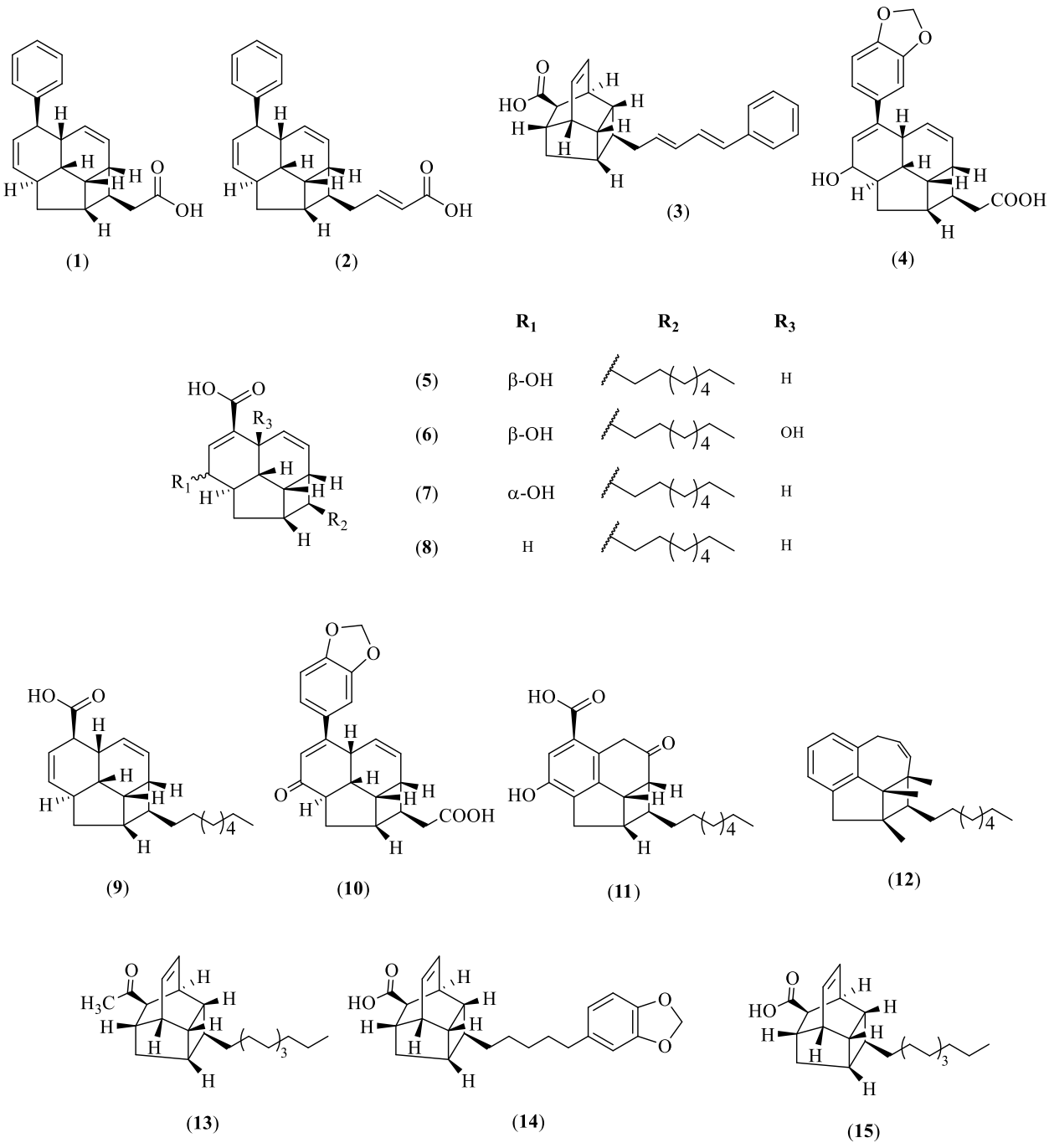
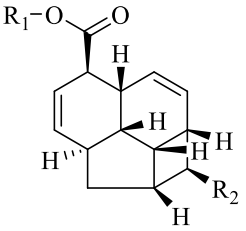


Figure 3. Polyketides isolated from *Beilschmiedia* and *Endiandra* species



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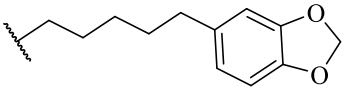
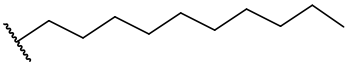
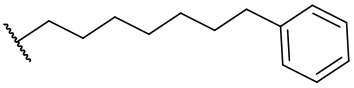
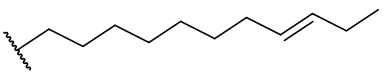
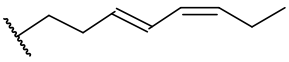
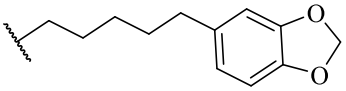
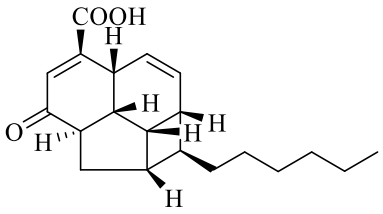
(**16**)	CH_3	
(**17**)	CH_3	
(**18**)	CH_3	
(**19**)	CH_3	
(**20**)	H	
(**21**)	H	



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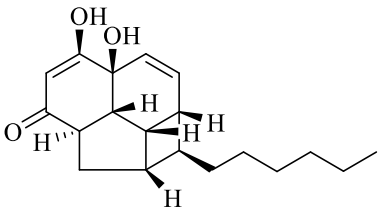

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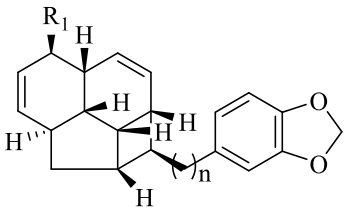
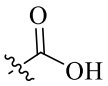
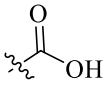
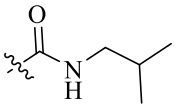
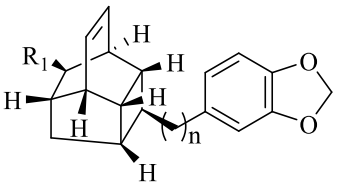


	R_1	n
(**22**)		3
(**23**)		1
(**24**)		1



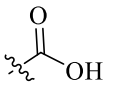
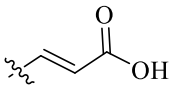
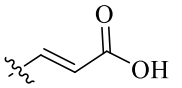
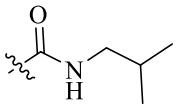
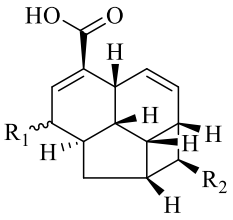
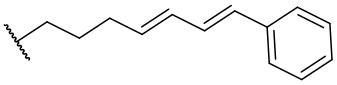
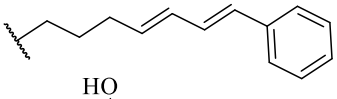
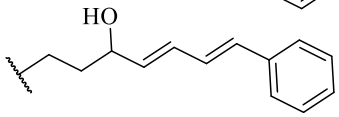
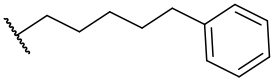
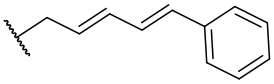
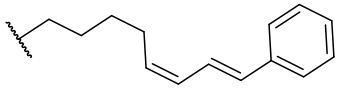
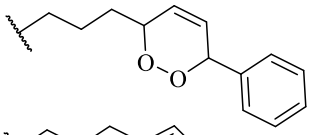
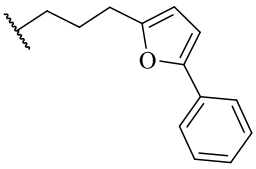
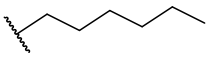
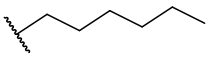
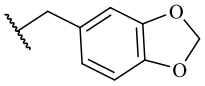
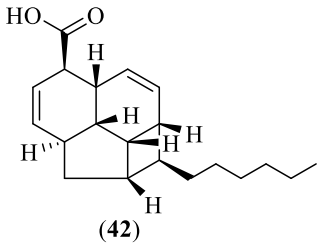
	R_1	n
(**25**)		3
(**26**)		5
(**27**)		1
(**28**)		3

Figure 3. Polyketides isolated from *Beilschmiedia* and *Endiandra* species (con't)



	R_1	R_2
(**31**)	α-OH	
(**32**)	β-OH	
(**33**)	H	
(**34**)	α-OH	
(**35**)	α-OH	
(**36**)	α-OH	
(**37**)	α-OH	
(**38**)	α-OH	
(**39**)	β-OH	
(**40**)	α-OH	
(**41**)	=O	



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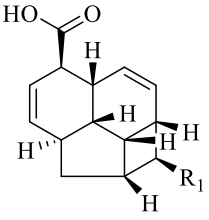
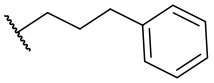
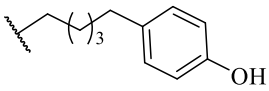
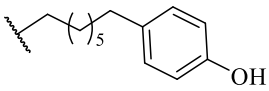
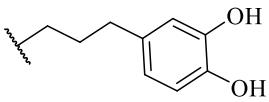
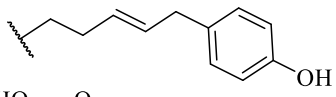
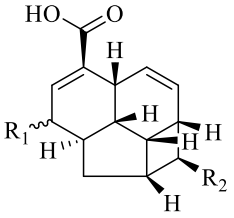
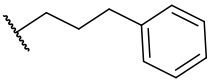
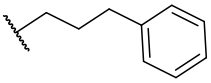
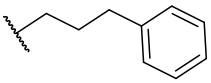
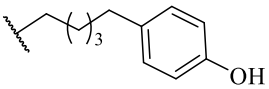
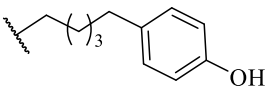
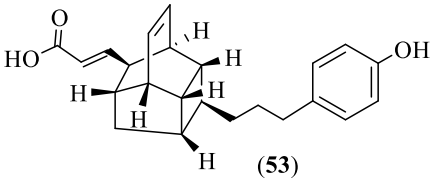


	R_1
(**43**)	
(**44**)	
(**45**)	
(**46**)	
(**47**)	

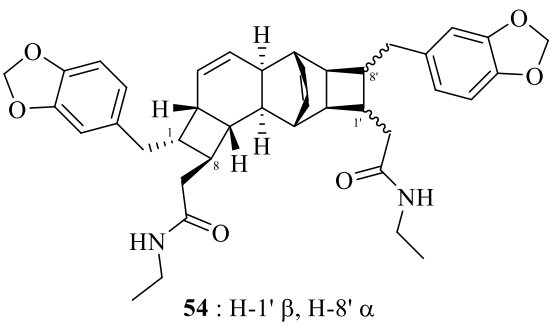


	R_1	R_2
(**48**)	α-OH	
(**49**)	β-OH	
(**50**)	=O	
(**51**)	α-OH	
(**52**)	β-OH	

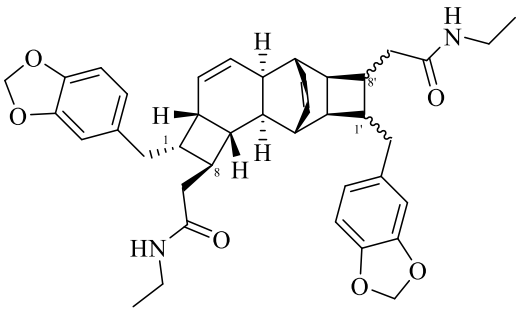


(**53**)

Figure 3. Polyketides isolated from *Beilschmiedia* and *Endiandra* species (con't)



54 : H-1' β, H-8' α
55 : H-1' α, H-8' β



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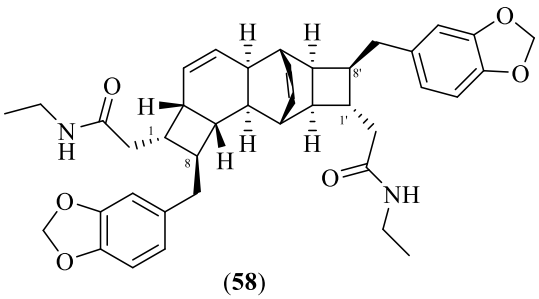
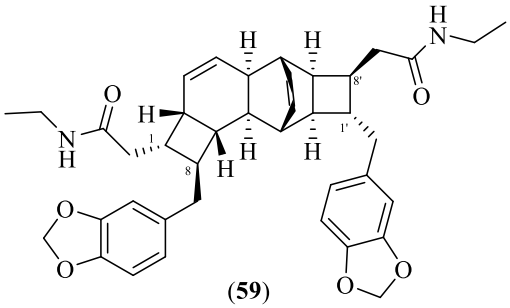
57 : H-1' α, H-8' β



(**58**)



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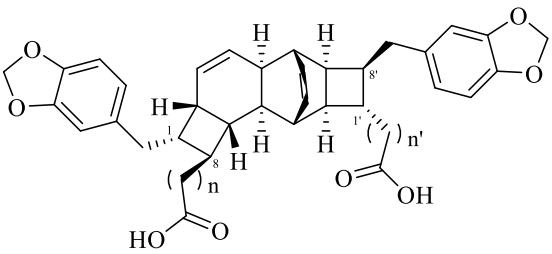
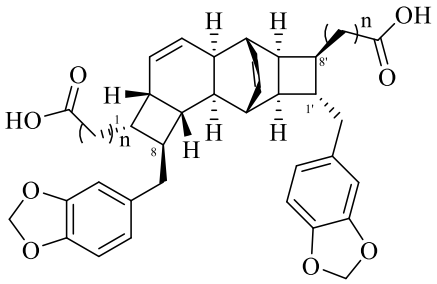
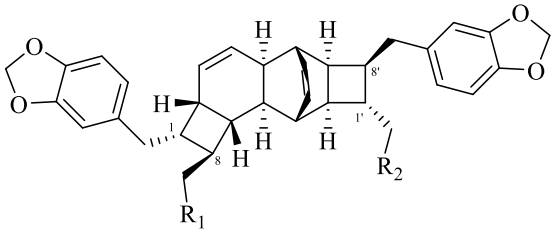


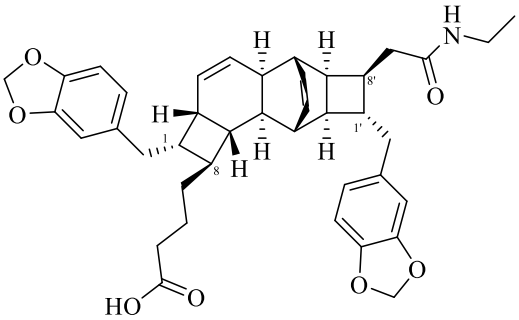
60 : n = 1, n' = 3
61 : n, n' = 3



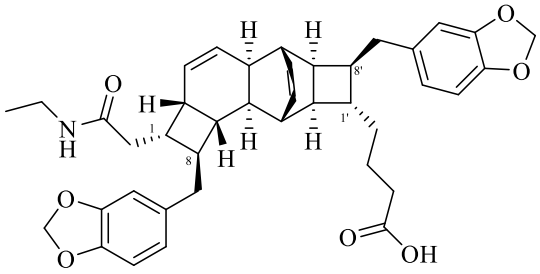
62 : n = 3, n' = 1
63 : n, n' = 3



64 : R_1 = CONHEt, R_2 = CH_2CH_2COOH
65 : R_1 = CH_2CH_2COOH, R_2 = CONHEt



(**66**)



(**67**)

Figure 3. Polyketides isolated from *Beilschmiedia* and *Endiandra* species (con't)

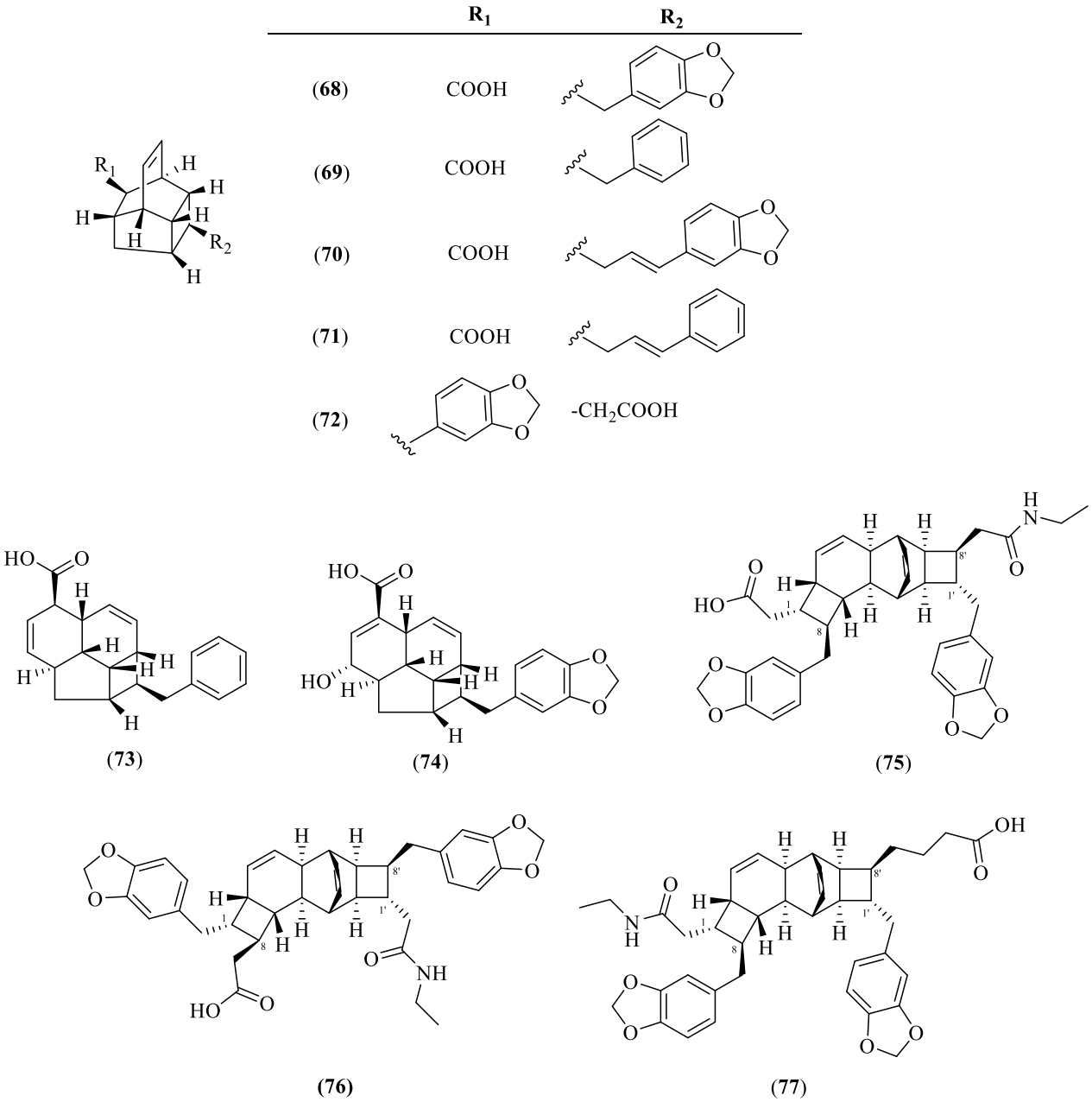


Figure 3. Polyketides isolated from *Beilschmiedia* and *Endiandra* species (con't)

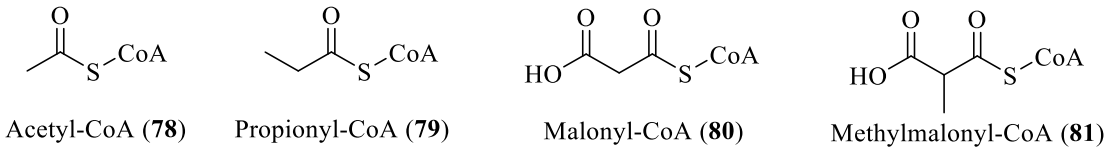
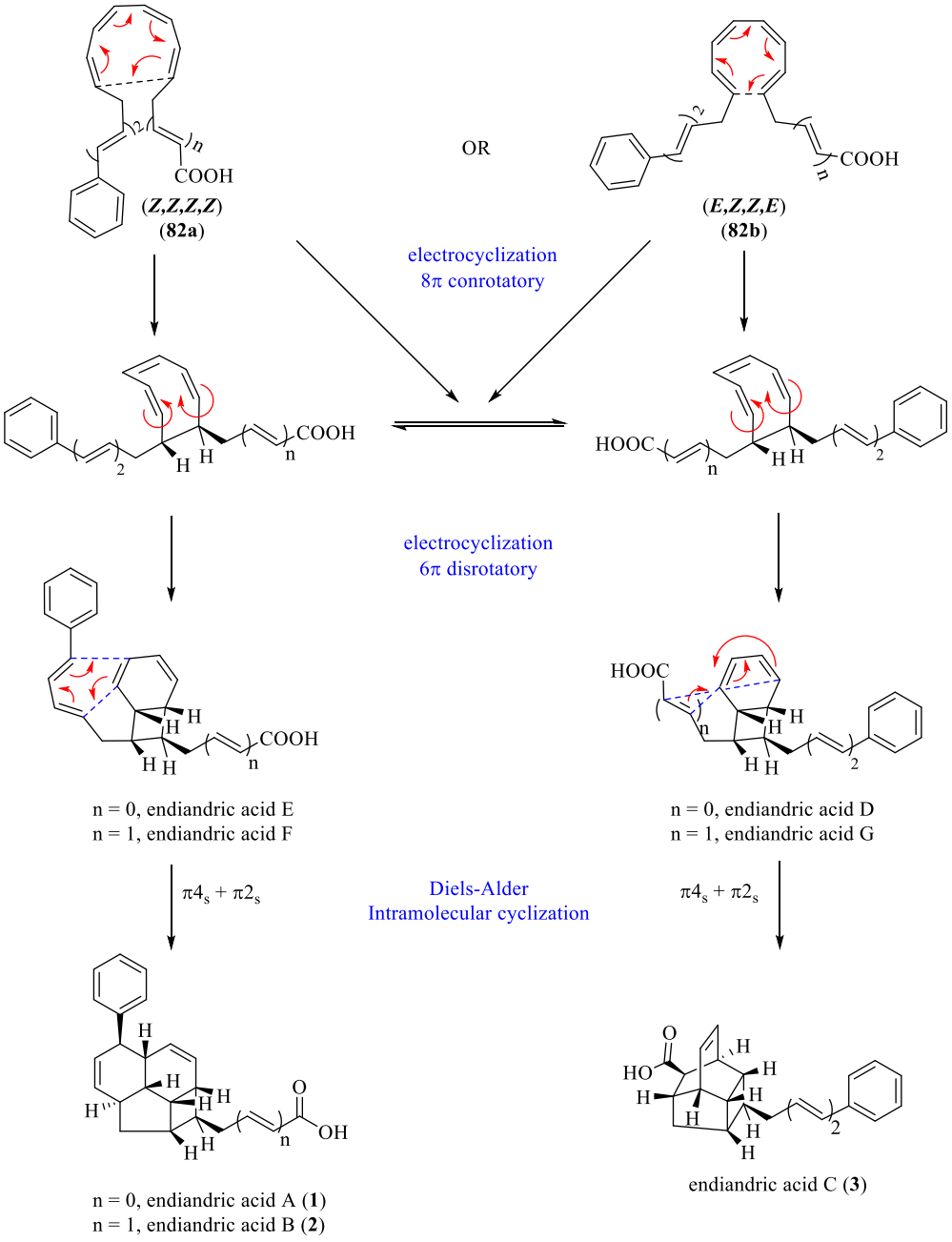


Figure 4. Polyketides synthase extender unit

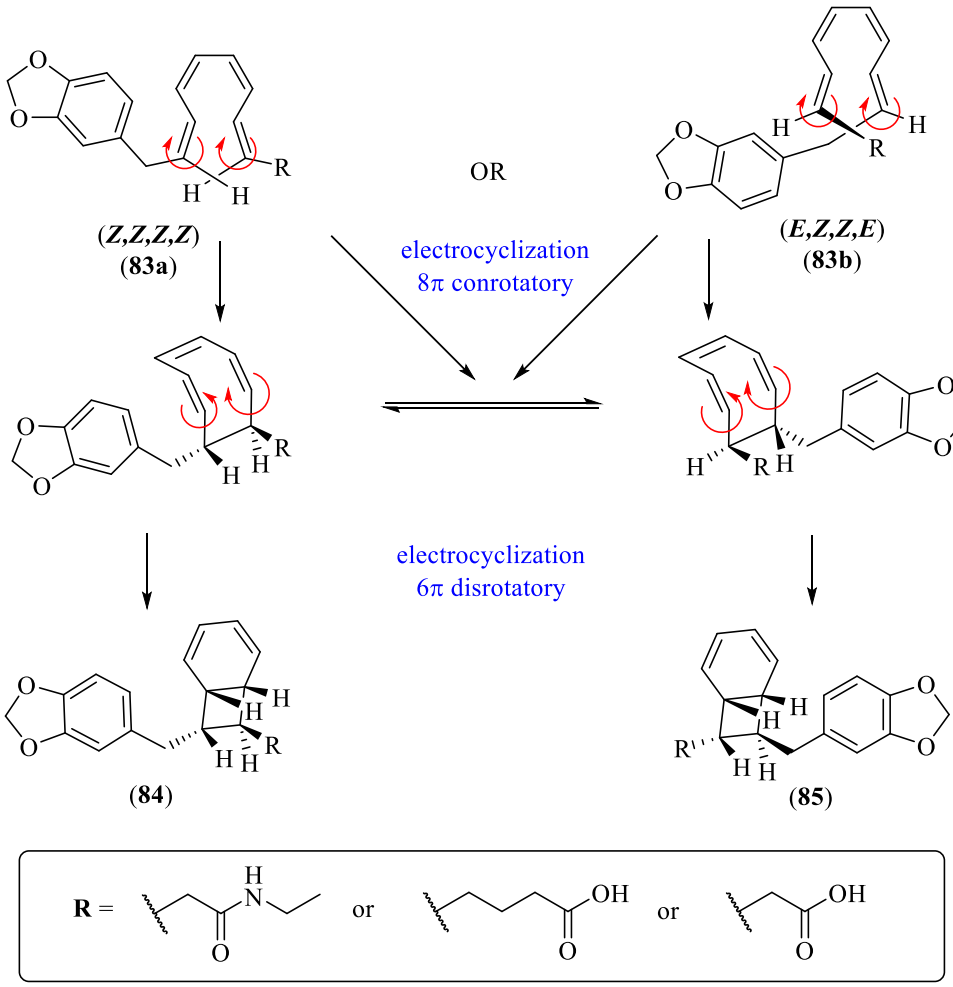
The biosynthesis of polyketides begins with the condensation of the starter unit i.e typically acetyl-CoA (**78**) / propionyl-CoA (**79**) and with an extender unit (commonly malonyl-CoA (**80**) or methylmalonyl-CoA (**81**)), followed by decarboxylative condensation unit (Claisen condensation) (Figure 4). The polyketide chains produced by minimal polyketide synthases (PKSs) and often derivatized and modified into bio-active natural products [30-33].

Endiandric acids which are polycyclic compounds, generally possess eight asymmetric centres.

It occurs as a racemic mixture rather than enantiomeric form. This is a rather unusual observation for naturally occurring compounds resulting from both shikimate and acetate pathways [34]. This observation led Black *et al*. to propose a hypothetical "biogenesis" pathway for these compounds from achiral precursors by a series of non-enzymatic electrocyclization [35-37]. Black's hypothesis suggests a cascade of reactions, the 8π–6π electrocyclic cascade and it is probably the most elegant and classical display of the power of electrocyclization reactions in nature [39-40]. Based on this biomimetic hypothesis, Nicolaou *et al*. and his team reported a total synthesis of endiandric acid A and its analogues [38-39]. It is specifically proposed that these polycyclics are formed from phenyl polyenes, which contain a central conjugated tetraene unit. For the formation of endiandric acid type B such as endiandric acids A (**1**) and B (**2**), which are all-*cis*-isomers (**82a**), or the *trans*-,*cis*-,*cis*-,*trans*-isomer (**82b**), the polyenes undergone two continuous non-enzymatic electrocyclization reactions which are 8π conrotatory and 6π disrotatory, to form intermediate precursors of endiandric acids E and F. In conclusion, the example of biosynthesis for both type A and type B endiandric acid is basically through conrotatory 8π electron cyclization, disrotatory 6π electron cyclization and Diels-Alder intramolecular cyclization. These conversions are shown in Scheme 1.



Scheme 1. Biosynthesis of endiandric acids A, B, and C



Scheme 2. Biogenetic hypothesis of monomers of kingianins

Kingianins are unique, complex and stereochemically rich pentacyclic core which are specifically isolated from the bark of *E. kingiana*. This compound was the first kingianin reported and it is a dimer of bicyclo[4.2.0]octadiene. In the beginning, Litaudon proposed a biosynthesis pathway involving spontaneous Diels-Alder dimerization [12-13]. Based on these observation and hypothesis above, the biogenesis of kingianins involves a series of electrocyclization from an achiral precursor (Scheme 2). The polyketide **83** might lead to a phenyl propylene unit with a central conjugated tetraene. The 8π conrotatory electrocyclization of the all-*cis* tetraene **83a** or the *trans, cis,cis,trans* isomer **83b**, followed by a 6π disrotatory electrocyclization would lead to bicyclo **84** and **85**. Finally, an intermolecular Diels-Alder (4π*s* + 2π*s*) cycloaddition would provide kingianins. Sharma et al. reported the biomimetic synthesis of the monomer based on the electrocyclization strategy, but all attempts to induce thermal dimerization was failed [43]. Recent publications reported that a radical cation Diels-Alder (RCDA) dimerization could explain the formation of the kingianins in nature. The first total synthesis of kingianin A (**45**) was reported by Lim and Parker [44-45]. Their synthetic approach centred on a novel intramolecular radical cation activated Diels-Alder (RCDA) cycloaddition of a tethered bicyclo[4.2.0]octadienyl monomer. At the same time, Drew et al. reported total syntheses of the kingianin A (**45**), D (**48**) and F (**50**) employing the same approach [46]. Both groups employed the Ledwith-Weits salt to initiate the electron transfer reaction. These are the evidence that kingianins are cyclized with non-spontaneous Diels-Alder cyclization.

The kingianin skeleton could generated from non-spontaneous Diels-Alder reaction between two bicyclo[4.2.0]octa-2,4-diene. The cyclization process could explain the formation of racemic mixtures of kingianin compounds as shown in Figure 5. The relative configuration of the pentacyclic carbon skeleton is identical for all kingianins, but the substituents located on the cyclobutane of each monomer are systematically in an *anti*-configuration. The all *cis* configuration at the ring conjugations is due to a series of electrocyclizations involved in their biogenesis. The *anti*-configuration of the cyclobutane rings may be explained by the last step of their biogenesis. The two monomers are indeed in parallel plane during the Diels-Alder reaction. An *anti*-

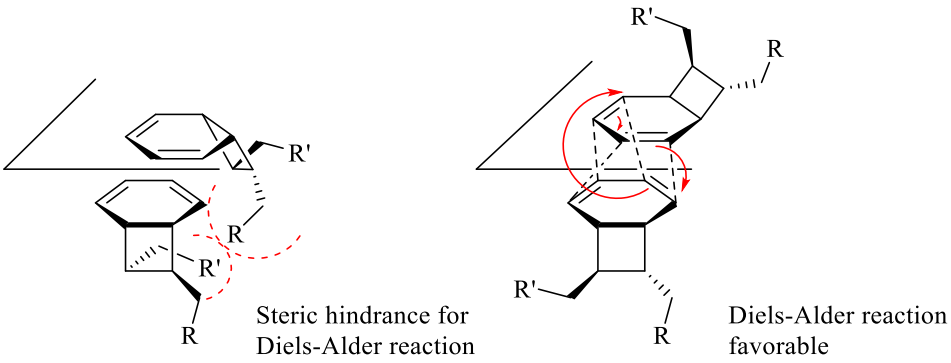


Figure 5. Possible steric hindrance in the intermolecular cyclization

orientation of the two cyclobutanes with respect to the reaction plane could be more sterically favorable (Figure 5). As a conclusion a tandem 8π conrotatory and disrotatory 6π electrocyclization of all *cis* tetraene or *trans*-, *cis*-, *cis*-, *trans*-, yielded the monomer of kingianin; the sequence closely resembled the endiandric acid electrocyclization cascade. Then, an intermolecular Diels-Alder (4πs + 2πs) cycloaddition would be result in kingianin A [47].

CONCLUSION

The phytochemical investigation of *Beilschmiedia* and *Endiandra* species resulted in the isolation of cyclic polyketides which are endiandric acids and kingianins series. It was proven that endiandric acids and kingianins are major secondary metabolites for both genera. Some species were found to possess medical properties and used to treat ailments such as anti-allergic, anti-asthmatic, anti-inflammatory, anti-bacterial, anti-tuberculosis, anti-plasmodial, anti-diabetic and anti-proliferative. The endiandric acids and kingianins are biosynthesized through both shikimate and acetate pathways, which finally enters the 8π–6π electrocyclic cascade reaction followed by Diels-Alder cycloaddition. However, it was still lacking in *in vivo* studies to prove the biological activities. Further research and clinical test can strengthen the properties of chemical constituents isolated in *Beilschmiedia* and *Endiandra* species.

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CONFLICT OF INTEREST

We declare that there is no conflict of interest.

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