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Review Article

A Review of Endiandric Acid Analogues

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ABSTRACT
The genus *Beilschmiedia* and *Endiandra* belonging to Lauraceae family have been used as folk medicines in treating uterine tumors, rheumatism, pulmonary diseases, dysentery and headache. This report briefly the current information and update on isolated endiandric acid analogues and their pharmacological studies. The informations on both genus were gathered via internet using scientific databases such as Google Scholar, MedlinePlus, Pubmed, SciFinder, Scopus and Web of Science. A literature survey shows that both genus are mainly known for their endiandric acid analogues with antiapoptotic proteins, which emphasize the existence of various potential leads to develop new anticancer agents. Modern pharmacology studies have also demonstrated that their phytochemicals possess wide pharmacological activities, which are anti-inflammatory, cytotoxic, antibacterial, antiplasmodial and antitubercular activities.

Keywords: Endiandric acid, *Beilschmiedia*, *Endiandra*, Phytochemistry, Pharmacology

INTRODUCTION

The World Health Organization (WHO) estimated that 80% of the populations of the developing countries rely on traditional medicines, mostly plant-based drugs, for their primary health care need. Also, modern pharmacopoeia still contains at least 25% drugs derived from plants while many others are synthetic analogues built on prototype compounds isolated from plants[1]. Medicinal plants have traditionally occupied an important position in the socio-cultural spiritual and medicinal arena of rural and tribal lives in the world. Ayurveda, a system of herbal medicine in India, Sri Lanka and South-East Asia have more than 8000 plant remedies. China has demonstrated the best use of traditional medicine in providing the health care. It has pharmacologically validated and improved many traditional herbal medicines and eventually integrated them in formal health care system[2-4]. Many secondary metabolites of plant are commercially important and find use in a number of pharmaceuticals. Plants can provide biologically active molecules and lead structures for the development of modified derivatives with enhanced activity. In some cases, the crude extracts of medicinal plants may be used as medicaments. On the other hand, the isolation and identification of the active principles and elucidation of the mechanism of action of a drug are of paramount importance. The scientific study of traditional medicines, derivatization of drugs through bioprospecting and systematic conservation of the concerned medicinal plants are thus of great importance[5-6]. The Lauraceae family is by far the largest family of the order Laurales with about 50 genera and over 2000 species distributed throughout tropical to subtropical latitudes especially Southeast Asia and tropical America. In Malaysia, it is known as '*medang*' or '*tejur*' and contribute about 213 species from 16 genera[7-8]. *Beilschmiedia* is a pantropical genus of about 287 species most commonly represented in tropical regions of Asia and Africa. Most of the species grow in tropical climates but few of them are native to temperate regions. They are widespread in tropical Asia, Africa, Australia, New Zealand, Central and South America. Economically most of *Beilschmiedia* species is used most as timber for example *B. roxburghiana* is used to build houses and tea boxes in Bhutan. The genus comprises trees and rarely shrubs and is usually distinguished from other genera of the Lauraceae by the following characteristics: paniculate or racemose inflorescences that are not strictly cymose at the terminal division, bisexual and trimerous flowers with six equal to subequal tepals, six to nine fertile stamens representing the outer two or three whorls, two-celled anthers and fruits lacking cupules[9-10]. The genus produces several classes of compounds such as terpenoids, endiandric acid derivatives, essential oils, fatty acids, epoxyfuranoid lignans, flavonoids and alkaloids. Some of these compounds are reported to exhibit antioxidant, antibacterial, antimalarial and antituberculosis activities[11-15]. The available literature and information show that several *Beilschmiedia* species have traditionally been used as medicine in different parts of the world. Some species of this genus are used as herb such as the bark of *B. sphaerocarpa* is used to cure pustule in Indochina[16]. The leaves of *B. tonkinensis* is used to make medicine for

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easing the pain, inflammation and broken bone[17]. In Cameroon, *B. anacardiodes* stem bark is used to cure uterine tumors, rubella, female genital infections, and rheumatisms[18]. Besides, the fruits of *B. manii*, *B. gabonensis*, and *B. zenkeri* are used as appetite stimulants and also as spices. In addition, *B. manii* is used in traditional medicine in Africa for the treatment of dysentery and headache, and also as appetite stimulant[19]. In Peninsular Malaysia, a decoction of bark of *B. pahangensis* is used as a drink after childbirth and also for stomachache and diarrhea[20]. In addition, the leaves of *B. tonkinensis* are used by Indonesians and Malays to make poultices for application to broken bones[20]. The leaf of *B. acuta* and *B. obscura* has been used to treat cancer and gastrointestinal infections in Cameroon[21-22]. The wood of *B. madang* and the bark of *B. cryptocaryoides* are used traditionally for antimalarial preparation. The bark decoction of *B. tawa* is used for treating wound, colds and stomachaches[23]. The genus *Endiandra* comprises about 100 species distributed in tropical parts of South East Asia, Australia, and the Western Pacific Ocean. Economically, species of *Endiandra* is an important source of woods. In Australia, the species produce woods that are utilized by local people. The people recognized the species as Walnut, such as Rose Walnut (*E. cowleyana*), Brown Walnut (*E. glauca*), Pink Walnut (*E. sieberi*) and Queensland Walnut (*E. palmerstonii*). Among those species, Queensland Walnut has produced the best quality of wood, used mainly in high quality furniture production. Other Walnuts produce large logs used for furniture, panelling and wood flooring[24-25]. Taxonomically, *Endiandra* consists of over 100 species which can be recognized by these characters: paniculate inflorescence in which the ultimate cyme not strictly oppposite, bisexual flowers, stamens 3 (rarely 2 or more than 3) with 2 locules of anthers, and fruits free on receptacles. *Endiandra* is grouped together with the genus *Beilschmiedia* Nees, *Potameia* Thouars, *Cryptocarya* R.Br. and *Triadodaphne* Kosterm based on the inflorescence type of *Cryptocaryeae* tribe[26]. Vegetatively, *Endiandra* is very close to *Beilschmiedia* which consists of about 250 species and has pantropical distribution. The two genera can only be separated by observing flowering specimens. Typical flowers of *Endiandra* have 3 stamens, whereas *Beilschmiedia* has 9 stamens. Therefore, it is rather difficult to determine the correct genus without a flowering specimen[27-29]. However, no traditional uses have been reported from this genus. This review summarizes the updated and comprehensive information concerning the isolated endiandric acid analogues and their pharmacology from *Beilschmiedia* and *Endiandra* species together with the possible trend and scope for further research on both species in the future.

Phytochemicals Studies

Detailed and extensive phytochemical investigations are necessary to understand the pharmacological activity of the species, as well as the mechanisms of action and for quality control purposes. Chemical investigations of the different species of genus *Beilschmiedia* and *Endiandra* have led to the isolation and identification of several endiandric acid derivatives. All isolated endiandric acid analogues and their chemical structures are presented in Table 1 and Figure 1, respectively. Endiandric acids are a rare class of secondary tetracyclic metabolites generally encountered in *Beilschmiedia* and *Endiandra* species. Endiandric acids have been isolated frequently as racemates from the species of *Beilschmiedia*. It is the result of the series of consecutive nonenzymatic cyclizations (8πe, 6πe and Diels-Alder) of a polyunsaturated fatty acid precursor[30]. To date, there are only nine species which include *B. oligandra*, *B. tooram*, *B. obtusifolia*, *B. fulva*, *B. erythrophloia*, *B. anacardioides*, *B. tsangii*, *B. cryptocaryoides* and an unknown Gabonese species were reported to produce endiandric acids, most of which were published in the past three years[31-39]. Several *Beilschmiedia* species were reported to contain new endiandric acid analogues. In 1994, Banfield et al.[20] reported the presence of endiandric acids A-C (**22-24**) from the leaves of *B. obtusifolia* and *B. tooram*. Phytochemical investigation of the root of *B. erythrophloia* led to the isolation of two new endiandric acid analogs, endiandric acids I-J (**27-28**)[32]. A year later, seven new endiandric acid analogues, erythrophloins A-F (**34-39**) and beilcyclone A (**17**) were isolated from the roots of the same species[33]. Besides, four new beilschmiedic acid derivatives, cryptobeilic acids A-D (**18-21**) have been isolated from the bark of *B. cryptocaryoides* collected from Madagascar. These compounds were all isolated as racemic mixtures and represent the first report on chemical constituents of this plant[39]. Chouna et al.[13,34-35] had successfully isolated eight new endiandric acid derivatives from the stem bark of *B. anacardioides* which are beilschmiedic acids A-G (**1-7**) and beilschmiedin (**16**). In addition, Huang et al.[36-37] reported the presence of six new endiandric acid analogues, endiandric acids K-L (**29-30**), endiandramides A-B (**32-33**) and tsangibeilins A-B (**72-73**) from the roots of *B. tsangii*. They also managed to isolate another new compounds, tsangibeilin C-D (**74-75**), tricyclotsangibeilin (**76**) and endiandric acid M (**31**) from the same species. High-throughput natural product chemistry methods have facilitated the isolation of eight new beilschmiedic acids; beilschmiedic acids H-O (**8-15**) from the leaves of a Gabonese species of *Beilschmiedia*[38]. In another study, chemical investigations of *B. ferruginea* leaves and flowers extracts have led to the isolation of eleven new tetracyclic endiandric acid analogues which are isolated as racemic mixtures, named ferrugineic acids A-K (**40-50**). They all retained the characteristics of endiandric acid tetracyclic carbon skeleton as exemplified by tsangibeilins A-B (**72-73**) and endiandramides A-B (**32-33**)[36, 40].

From a phytochemical point of view, only three *Endiandra* species which are *E. introrsa*, *E. anthropophagorum* and *E. kingiana*, have been studied for their phytochemicals, which led to the isolation of endiandric acid analogues. St. Black and his group, was thoroughly investigated the leaves of the Australian plant *E. introrsa*, leading to the discovery of a series of cyclic polyketides, endiandric acids A-D (**22-25**)[26,30]. More recently, the chemical investigation of the dichloromethane extract from the roots of *E. anthropophagorum* resulted in the isolation of

cyclobutane lignan[41-42]. Leverrier et al.[43] had successfully isolated fourteen analogs, named kingianins A-N (**58**-**71**) by bioguided fractionation of the bark of *E. kingiana*. Three years later, from the same species, another series of new natural pentacyclic polyketides were isolated by Azmi et al.[44]. The compounds were characterized as kingianins A-L (**58**-**69**), isolated from the methanolic extract of the bark of this species. In addition, endiandric acid M (**31**) and tsangibeilin B (**73**) were also isolated from this species.

Table 1: Endiandric acid analogues isolated from *Beilschmiedia* and *Endiandra* species

Compounds		
Beilschmiedic acid A (1)	*B. anacardioides* Robyns & R.Wilczek	Stem bark [30, 31]
	B. gabonese Meisn	Leaves [32]
Beilschmiedic acid B (2)	*B. anacardioides* Robyns & R.Wilczek	Stem bark [30]
Beilschmiedic acid C (3)	*B. anacardioides* Robyns & R.Wilczek	Stem bark [30, 31]
	B. Gabonese Meisn	Leaves [32]
Beilschmiedic acid D (4)	*B. anacardioides* Robyns & R.Wilczek	Stem bark [33]
Beilschmiedic acid E (5)	*B. anacardioides* Robyns & R.Wilczek	Stem bark [33]
Beilschmiedic acid F (6)	*B. anacardioides* Robyns & R.Wilczek	Stem bark [31]
Beilschmiedic acid G (7)	*B. anacardioides* Robyns & R.Wilczek	Stem bark [31]
Beilschmiedic acid H (8)	*B. gabonese* Meisn	Leaves [32]
Beilschmiedic acid I (9)	*B. gabonese* Meisn	Leaves [32]
Beilschmiedic acid J (10)	*B. gabonese* Meisn	Leaves [32]
Beilschmiedic acid K (11)	*B. gabonese* Meisn	Leaves [32]
Beilschmiedic acid L (12)	*B. gabonese* Meisn	Leaves [32]
Beilschmiedic acid M (13)	*B. gabonese* Meisn	Leaves [32]
Beilschmiedic acid N (14)	*B. gabonese* Meisn	Leaves [32]
Beilschmiedic acid O (15)	*B. gabonese* Meisn	Leaves [32]
Beilschmiedin (16)	*B. anacardioides* Robyns & R.Wilczek	Stem bark [33]
Beilcyclone A (17)	*B. erythrophloia* Hayata	Roots [34]
Cryptobeilic acid A (18)	*B. cryptocaryoides* Kosterm	Bark [35]
Cryptobeilic acid B (19)	*B. cryptocaryoides* Kosterm	Bark [35]
Cryptobeilic acid C (20)	*B. cryptocaryoides* Kosterm	Bark [35]
Cryptobeilic acid D (21)	*B. cryptocaryoides* Kosterm	Bark [35]
Endiandric acid A (22)	*B. obtusifolia* F.Muell	Leaves [36]
	E. introrsa C.T.White	Leaves [36]
Endiandric acid B (23)	*B. tooram* B.Hyland	Leaves [36]
	E. introrsa C.T.White	Leaves [36]
Endiandric acid C (24)	*B. tooram* B.Hyland	Leaves [36]
	E. introrsa C.T.White	Leaves [36]
Endiandric acid D (25)	*E. introrsa* C.T.White	Leaves [36]
Endiandric acid H (26)	*B. fulva* Robyns & R.Wilczek	Stem [37]
Endiandric acid I (27)	*B. erythrophloia* Hayata	Roots [38]
Endiandric acid J (28)	*B. erythrophloia* Hayata	Roots [38]
Endiandric acid K (29)	*B. tsangii* Merr.	Roots [39]
Endiandric acid L (30)	*B. tsangii* Merr.	Roots [39]
Endiandric acid M (31)	*B. tsangii* Merr.	Roots [40]
	E. kingiana Gamble	Bark [41]
Endiandramide A (32)	*B. tsangii* Merr.	Roots [39]
Endiandramide B (33)	*B. tsangii* Merr.	Roots [39]
Erythrophloin A (34)	*B. erythrophloia* Hayata	Roots [34]
Erythrophloin B (35)	*B. erythrophloia* Hayata	Roots [34]
Erythrophloin C (36)	*B. erythrophloia* Hayata	Roots [34]
Erythrophloin D (37)	*B. erythrophloia* Hayata	Roots [34]
Erythrophloin E (38)	*B. erythrophloia* Hayata	Roots [34]
Erythrophloin F (39)	*B. erythrophloia* Hayata	Roots [34]
Ferrugineic acid A (40)	*B. ferruginea* H.Liu	Leaves/flower [43]
Ferrugineic acid B (41)	*B. ferruginea* H.Liu	Leaves/flower [43]
Ferrugineic acid C (42)	*B. ferruginea* H.Liu	Leaves/flower [43]
Ferrugineic acid D (43)	*B. ferruginea* H.Liu	Leaves/flower [43]
Ferrugineic acid E (44)	*B. ferruginea* H.Liu	Leaves/flower [43]
Ferrugineic acid F (45)	*B. ferruginea* H.Liu	Leaves/flower [43]
Ferrugineic acid G (46)	*B. ferruginea* H.Liu	Leaves/flower [43]

Table 1: Endiandric acid analogues isolated from *Beilschmiedia* and *Endiandra* species

Compounds		
Ferrugineic acid H (47)	*B. ferruginea* H.Liu	Leaves/flower [43]
Ferrugineic acid I (48)	*B. ferruginea* H.Liu	Leaves/flower [43]
Ferrugineic acid J (49)	*B. ferruginea* H.Liu	Leaves/flower [43]
Ferrugineic acid K (50)	*B. ferruginea* H.Liu	Leaves/flower [43]
Kingianic acid A (51)	*E. kingiana* Gamble	Bark [44]
Kingianic acid B (52)	*E. kingiana* Gamble	Bark [44]
Kingianic acid C (53)	*E. kingiana* Gamble	Bark [44]
Kingianic acid D (54)	*E. kingiana* Gamble	Bark [44]
Kingianic acid E (55)	*E. kingiana* Gamble	Bark [44]
Kingianic acid F (56)	*E. kingiana* Gamble	Bark [44]
Kingianic acid G (57)	*E. kingiana* Gamble	Bark [44]
Kingianin acid A (58)	*E. kingiana* Gamble	Trunk bark [45]
Kingianin acid B (59)	*E. kingiana* Gamble	Trunk bark [45]
Kingianin acid C (60)	*E. kingiana* Gamble	Trunk bark [45]
Kingianin acid D (61)	*E. kingiana* Gamble	Trunk bark [45]
Kingianin acid E (62)	*E. kingiana* Gamble	Trunk bark [45]
Kingianin acid F (63)	*E. kingiana* Gamble	Trunk bark [45]
Kingianin acid G (64)	*E. kingiana* Gamble	Trunk bark [45]
Kingianin acid H (65)	*E. kingiana* Gamble	Trunk bark [45]
Kingianin acid I (66)	*E. kingiana* Gamble	Trunk bark [45]
Kingianin acid J (67)	*E. kingiana* Gamble	Trunk bark [45]
Kingianin acid K (68)	*E. kingiana* Gamble	Trunk bark [45]
Kingianin acid L (69)	*E. kingiana* Gamble	Trunk bark [45]
Kingianin acid M (70)	*E. kingiana* Gamble	Trunk bark [45]
Kingianin acid N (71)	*E. kingiana* Gamble	Trunk bark [45]
Tsangibeilin A (72)	*B. tsangii* Merr.	Roots [39]
Tsangibeilin B (73)	*B. tsangii* Merr.	Roots [39]
	B. cryptocaryoides Kosterm	Bark [35]
	E. kingiana Gamble	Bark [44]
Tsangibeilin C (74)	*B. tsangii* Merr.	Roots [40]
Tsangibeilin D (75)	*B. tsangii* Merr.	Roots [40]
Tricyclotsangibeilin (76)	*B. tsangii* Merr.	Roots [40]

Pharmacological Studies

Endiandric acids and their close derivatives, beilschmiedic acids, are the most characteristic type of natural products isolated from *Beilschmiedia* and *Endiandra* species. They were found to exhibit various biological activities, such as anti-inflammatory, antibacterial, cytotoxicity, antiplasmodial, anticancer and antitubercular activities, as listed in Table 2.

Anticancer activity.

The antiapoptotic proteins Bcl-2, Bcl-xL, Bcl-w, Mcl-1, and A1, members of the Bcl-2 family, have become attractive molecular targets for cancer treatment. The discovery of dual inhibitors acting on Bcl-xL and Mcl-1 could play a significant role in cancer treatment. Apart from that, Apel et al.40 had investigated the anticancer activity of isolated endiandric acid from *B. ferruginea*, ferrugineic acid A-K (**40**-**50**) against antiapoptotic proteins Bcl-xL and Mcl-1 by using a fluorescence polarization assay. Ferrugineic acid B (**41**), C (**42**) and J (**49**) were proved to be significantly exhibited binding affinity for both antiapoptotic proteins, Bcl-xL. Meanwhile, ferrugineic acid D (**43**) showed only a strong inhibiting activity for antiapoptotic protein, Mcl-1. Considering the weak binding affinity for Mcl-1 of other tested compounds, it could be postulated that the length of the saturated carbon side chain (preferentially five or seven CH_2 groups) associated with a terminal 4-hydroxyphenyl ring, play a crucial role for Bcl-xL and Mcl-1 binding affinities. Leverrier et al.[45] have screened 1476 extracts prepared from approximately 700 Malaysian plants to search for new potent inhibitors of the protein Bcl-xL. The bark extract of *E. kingiana* was selected for its high potency as a modulating agent between Bcl-xL and Bak, which motivated its chemical investigation, and successfully reported the isolation, structural elucidation and biogenetic hypothesis of kingianin A (**58**). The binding affinity of the racemic mixtures of kingianic acid A-L (**58**-**71**) were screened by evaluation on Bcl-xL by competition against the fluorescent-tagged BH3 domain of the protein Bak. The biological study indicated that the (-)-enantiomers of kingianin acids G-L (**64**-**69**) have the most potent binding affinity for the protein Bcl-xL with *Ki* ranging from 1.0 to 12.0 µM. These results concluded that the presence of two acidic, or one acidic and one *N*-ethylacetamide side chains, and their spatial position are essential for a significant binding affinity for Bcl-xL[43]. Azmi et al.[44] screened kingianic acids A (**51**), C (**53**), kingianic acids E-G (**55**-**57**), endiandric acid M (**31**) and

tsangibeilin B (**73**) against the anti-apoptotic proteins Bcl-xL and Mcl-1 assays based on the interaction of fluorescein-labeled peptides. No binding was detected for Bcl-xL and only weak binding affinity for Mcl-1 (25%–30% inhibition at 20 μM and ≥ 75% at 100 μM) were obtained with compounds (**53**), (**56**) and (**73**).

Table 2: Pharmacological studies of endiandric acid analogues from *Beilschmiedia* and *Endiandra* species

Biological activities/ Compounds	Description/Control
Antitubercular	
Erythrophloin C (36)	Showed significant activity against *Mycobacterium tuberculosis* H37Rv showing MIC of 50 μg/mL. Control: ethambutol (MIC of 6.25 μg/mL) [33]
Anti-inflammatory	
Endiandric acid K (29)	Exhibited moderate iNOS inhibitory activity with IC_{50} of 58.21 ± 0.19 μM at a concentration of 100 μM.
Endiandric acid L (30)	Exhibited moderate iNOS inhibitory activity with IC_{50} of 39.56 ± 2.30 μM at a concentration of 100 μM.
Endiandramide A (32)	Exhibited potent iNOS inhibitory activity with IC_{50} of 9.59 μM at a concentration of 100 μM.
Endiandramide B (33)	Exhibited potent iNOS inhibitory activity with IC_{50} of 16.40 μM at a concentration of 100 μM.
Tsangibeilin A (72)	Exhibited moderate iNOS inhibitory activity with IC_{50} of 49.59 ± 0.64 μM at a concentration of 100 μM.
Tsangibeilin B (73)	Exhibited moderate iNOS inhibitory activity with IC_{50} of 42.30 ± 1.06 μM at a concentration of 100 μM. Control: aminoguanidine (IC_{50} of 26.55 ± 0.48 μM) and N^{ω}-nitro-L-arginine (IC_{50} of 152.46 ± 10.53 μM) [36]
Endiandric acid M (31)	Exhibited moderate iNOS inhibitory activity with IC_{50} of 31.70 μM at a concentration of 100 μM. Control: aminoguanidine (IC_{50} of 26.55 ± 0.48 μM) and N^{ω}-nitro-L-arginine (IC_{50} of 152.46 ± 10.53 μM) [37]
Antibacterial	
Beilschmiedic acid A (1)	Demonstrated weak activity against *Bacillus subtilis* (MIC of 181.6 μM), *Micrococcus luteus* (MIC of 173.6 μM) and *Streptococcus faecalis* (MIC of 363.3 μM). Control: ampicillin (MIC of 89.5 μM - *Bacillus subtilis*), (MIC of 5.58 μM - *Micrococcus luteus*), (MIC of 11.1 μM - *Streptococcus faecalis*) [12] Moderate activity against *Staphylococcus aureus* with MIC of 10 μg/mL. Control: vancomycin (MIC of 2 μg/mL) [38] Demonstrated weak activity against *Bacillus subtilis* (MIC of 181.6 μM), *Micrococcus luteus* (MIC of 173.6 μM) and *Streptococcus faecalis* (MIC of 363.3 μM). Control: ampicillin (MIC of 89.5 μM - *Bacillus subtilis*), (MIC of 5.58 μM - *Micrococcus luteus*), (MIC of 11.1 μM - *Streptococcus faecalis*) [34]
Beilschmiedic acid B (2)	Demonstrated moderate activity against *Bacillus subtilis* (MIC of 11.3 μM), *Micrococcus luteus* (MIC of 347.2 μM) and *Streptococcus faecalis* (MIC of 45.3 μM) [12] Demonstrated moderate activity against *Bacillus subtilis* (MIC of 11.3 μM) and *Streptococcus faecalis* (MIC of 45.3 μM) and weak activity against *Micrococcus luteus* (MIC of 347.2 μM) [34]
Beilschmiedic acid C (3)	Demonstrated strong activity against *Bacillus subtilis* (MIC of 5.6 μM), *Micrococcus luteus* (MIC of <0.7 μM) and *Streptococcus faecalis* (MIC of 22.7 μM) [38] Displayed no activity against *Staphylococcus aureus* at the highest dose (30 μM) [38]
Beilschmiedic acid H (8)	Displayed no activity against *Staphylococcus aureus* at the highest dose (30 μM).
Beilschmiedic acid I (9)	Moderate activity against *Staphylococcus aureus* with MIC of 12 μg/mL.
Beilschmiedic acid K (11)	Moderate activity against *Staphylococcus aureus* with MIC of 11 μg/mL.
Beilschmiedic acid L (12)	Moderate activity against *Staphylococcus aureus* with MIC of 11 μg/mL.
Beilschmiedic acid M (13)	Moderate activity against *Staphylococcus aureus* with MIC of 12 μg/mL.
Beilschmiedic acid N (14)	Moderate activity against *Staphylococcus aureus* with MIC of 13 μg/mL.
Beilschmiedic acid O (15)	Moderate activity against *Staphylococcus aureus* with MIC of 13 μg/mL. Control: vancomycin (MIC of 2 μg/mL) [38]
Cryptobeilic acid A (18)	Displayed moderate activity against *Escherichia coli* with MIC of 10 μM and weak activity against *Acinetobacter calcoaceticus*, *Pseudonamas stutzeri* and *Serratia plymuthica* (MIC of >50 μM each).
Cryptobeilic acid B (19)	Displayed moderate activity against *Escherichia coli* and *Acinetobacter calcoaceticus* (MIC of 20 μM), *Pseudonamas stutzeri* (MIC of 10 μM) and weak activity against *Serratia plymuthica* (MIC of >50 μM each).

Table 2: Pharmacological studies of endiandric acid analogues from *Beilschmiedia* and *Endiandra* species

Biological activities/ Compounds	Description/Control
Cryptobeilic acid C (20)	Displayed weak activity against *Escherichia coli*, *Acinetobacter calcoaceticus*, *Pseudonamas stutzeri* and *Serratia plymuthica* (MIC of >50 μM each).
Cryptobeilic acid D (21)	Displayed weak activity against *Escherichia coli* (MIC of 50 μM), *Acinetobacter calcoaceticus*, *Pseudonamas stutzeri* and *Serratia plymuthica* (MIC of >50 μM each).
Tsangibeilin B (73)	Displayed weak activity against *Escherichia coli* (MIC of 50 μM), *Acinetobacter calcoaceticus*, *Pseudonamas stutzeri* and *Serratia plymuthica* (MIC of >50 μM each). Control: difloxacin and ampicillin (MIC of 5 μM - *Escherichia coli* and *Acinetobacter calcoaceticus*) and (MIC of 20 μM - *Pseudonamas stutzeri*) [39]
Cytotoxicity	
Beilschmiedic acid A (1)	Moderate activity against NCI-H460 cell with IC_{50} of 6.1 μM.
Beilschmiedic acid C (2)	Displayed no activity against NCI-H460 cell at the highest dose (30 μM).
Beilschmiedic acid H (8)	Displayed no activity against NCI-H460 cell at the highest dose (30 μM).
Beilschmiedic acid I (9)	Moderate activity against NCI-H460 cell with IC_{50} of 5.5 μM.
Beilschmiedic acid K (11)	Moderate activity against NCI-H460 cell with IC_{50} of 5.9 μM.
Beilschmiedic acid L (12)	Moderate activity against NCI-H460 cell with IC_{50} of 4.4 μM.
Beilschmiedic acid M (13)	Moderate activity against NCI-H460 cell with IC_{50} of 8.7 μM.
Beilschmiedic acid N (14)	Weak activity against NCI-H460 cell with IC_{50} of 19.0 μM.
Beilschmiedic acid O (15)	Displayed no activity against NCI-H460 cell at the highest dose (30 μM). Control: camptothecin (IC_{50} of 0.003 μM) [38]
Cryptobeilic acid A (18)	Demonstrated weak activity against the L6 cell line (cell line derived from rat skeletal myoblasts) with IC_{50} of 59.5 μM.
Cryptobeilic acid B (19)	Demonstrated weak activity against the L6 cell line with IC_{50} of 20.4 μM.
Cryptobeilic acid C (20)	Demonstrated weak activity against the L6 cell line with IC_{50} of 59.3 μM.
Cryptobeilic acid D (21)	Demonstrated weak activity against the L6 cell line with IC_{50} of 61.0 μM. Control: podophyllotoxin (MIC of 0.008 μM) [39]
Ferrugineic acid A-K (40-50)	All compounds were devoid of cytotoxicity against HCT-116 (human colorectal carcinoma) and K562 (human leukemia) cancer cell lines tested at concentrations up to 50 μM [40]
Kingianic acid A (51)	Displayed strong activity against HT-29 (IC_{50} of 35.0 ± 0.2 μM), moderate acyivity against A549 (IC_{50} of 85.4 ± 0.2 μM) and weak activity against PC3 (IC_{50} of >100 μM) cell lines.
Kingianic acid C (53)	Displayed weak activity against HT-29 (IC_{50} of >100 μM) and PC3 (IC_{50} of >100 μM) cell lines and moderate activity against A549 (IC_{50} of 85.3 ± 0.2 μM) cell line.
Kingianic acid E (55)	Displayed strong activity against HT-29 (IC_{50} of 17.1 ± 0.1 μM) and A549 (IC_{50} of 15.4 ± 0.2 μM) and moderate activity against PC3 (IC_{50} of 77.2 ± 0.2 μM) cell lines.
Endiandric acid M (31)	Displayed weak activity against HT-29, PC3 and A549 (IC_{50} of >100 μM each) cell lines. Control: cisplatin (IC_{50} of 70.3 ± 1.1 μM - HT29), (IC_{50} of 36.2 ± 1.4 μM - A549) and (IC_{50} of 44.5 ± 7.7 μM - PC3) [44]
Tsangibeilin B (73)	Demonstrated weak activity against the L6 cell line with IC_{50} of 21.5 μM [39] Displayed strong activity against A549 (IC_{50} of 38.1 ± 0.1 μM) and weak activity against HT-29 and PC3 (IC_{50} of >100 μM each) cell lines [44]
Antiplasmodial	
Cryptobeilic acid A (18)	Displayed weak activity against *Plasmodium falciparum* strain NF54 with IC_{50} of 17.7 μM.
Cryptobeilic acid B (19)	Displayed moderate activity against *Plasmodium falciparum* strain NF54 with IC_{50} of 5.35 μM.
Cryptobeilic acid C (20)	Displayed weak activity against *Plasmodium falciparum* strain NF54 with IC_{50} of 14.0 μM.
Cryptobeilic acid D (21)	Displayed weak activity against *Plasmodium falciparum* strain NF54 with IC_{50} of 10.8 μM.
Tsangibeilin B (73)	Displayed moderate activity against *Plasmodium falciparum* strain NF54 with IC_{50} of 8.2 μM [39]
Anticancer	
Ferrugineic acid A (40)	Exhibited weak inhibiting activities of the antiapoptotic proteins, Bcl-xL (percentage at 100 μM = 22%; K_i = >100 μM).
Ferrugineic acid B (41)	Exhibited strong inhibiting activities of the antiapoptotic proteins, Bcl-xL (percentage at 100 μM = 60%; K_i = 19.2 μM) and Mcl-1 (percentage at 100 μM = 85%; K_i = 14.0 μM).

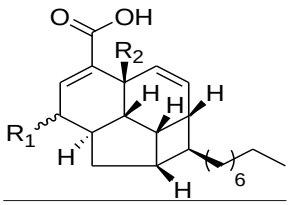
Table 2: Pharmacological studies of endiandric acid analogues from *Beilschmiedia* and *Endiandra* species

Biological activities/ Compounds	Description/Control
Ferrugineic acid C (42)	Exhibited strong inhibiting activities of the antiapoptotic proteins, Bcl-xL (percentage at 100 μM = 93%; K_i = 12.6 μM) and Mcl-1 (percentage at 100 μM = 82%; K_i = 13.0 μM).
Ferrugineic acid D (43)	Showed significant binding affinity for antiapoptotic protein, Mcl-1 (percentage at 100 μM = 82%; K_i = 5.2 μM).
Ferrugineic acid J (49)	Exhibited strong inhibiting activities of the antiapoptotic proteins, Bcl-xL (percentage at 100 μM = 58%; K_i = 19.4 μM) and Mcl-1 (percentage at 100 μM = 81%; K_i = 5.9 μM).
Ferrugineic acid K (50)	Exhibited weak inhibiting activities of the antiapoptotic proteins, Bcl-xL (percentage at 100 μM = 22%; K_i = >100 μM).
	Control: U-Bak (K_i = 0.012 ± 0.001 μM), U-Bid (K_i = 0.016 ± 0.002 μM) [40]
Kingianin acid A (58)	Exhibited weak inhibiting activities of the antiapoptotic proteins, Bcl-xL (K_i = 213 ± 53 μM : racemix mixture/ K_i = 60 ± 1.5 μM : (-)-enantiomer).
Kingianin acid B-E (59-62)	Exhibited weak inhibiting activities of the antiapoptotic proteins, Bcl-xL (K_i = >300 μM : racemix mixture).
Kingianin acid F (63)	Exhibited weak inhibiting activities of the antiapoptotic proteins, Bcl-xL (K_i = 231 ± 47 μM : racemix mixture).
Kingianin acid G (64)	Exhibited strong inhibiting activities of the antiapoptotic proteins, Bcl-xL (K_i = 2 ± 0 μM : racemix mixture/ K_i = 1.0 ± 0.2 μM : (-)-enantiomer/ K_i = 5 ± 1 μM : (+)-enantiomer).
Kingianin acid H (65)	Exhibited potent inhibiting activities of the antiapoptotic proteins, Bcl-xL (K_i = 18 ± 7 μM : racemix mixture/ K_i = 4.0 ± 0.4 μM : (-)-enantiomer/ K_i = 27.0 ± 0.6 μM : (+)-enantiomer).
Kingianin acid I (66)	Exhibited potent inhibiting activities of the antiapoptotic proteins, Bcl-xL (K_i = 18 ± 3 μM : racemix mixture/ K_i = 12.0 ± 1.1 μM : (-)-enantiomer/ K_i = 16.0 ± 2.2 μM : (+)-enantiomer).
Kingianin acid J (67)	Exhibited potent inhibiting activities of the antiapoptotic proteins, Bcl-xL (K_i = 29 ± 6 μM : racemix mixture/ K_i = 9.0 ± 0.2 μM : (-)-enantiomer/ K_i = 25.0 ± 3.2 μM : (+)-enantiomer).
Kingianin acid K (68)	Exhibited weak inhibiting activities of the antiapoptotic proteins, Bcl-xL (K_i = 80 ± 36 μM : racemix mixture/ K_i = 6.0 ± 0.1 μM : (-)-enantiomer/ K_i = 112 ± 15 μM : (+)-enantiomer).
Kingianin acid L (69)	Exhibited potent inhibiting activities of the antiapoptotic proteins, Bcl-xL (K_i = 36 ± 11 μM : racemix mixture/ K_i = 4.0 ± 0.1 μM : (-)-enantiomer/ K_i = 71 ± 10 μM : (+)-enantiomer).
Kingianin acid M (70)	Exhibited weak inhibiting activities of the antiapoptotic proteins, Bcl-xL (K_i = >300 μM : racemix mixture).
Kingianin acid N (71)	Exhibited weak inhibiting activities of the antiapoptotic proteins, Bcl-xL (K_i = 177 ± 9 μM : racemix mixture) [43]
Endiandric acid M (31)	Exhibited moderate inhibiting activities of the antiapoptotic proteins, Bcl-xL (percentage at 100 μM = 10% ± 0.5) and Mcl-1 (percentage at 100 μM = 39% ± 0.9 μM).
Kingianic acid A (51)	Exhibited weak inhibiting activities of the antiapoptotic proteins, Bcl-xL (percentage at 100 μM = 21% ± 1.8) and Mcl-1 (percentage at 100 μM = 36% ± 2.3 μM).
Kingianic acid C (53)	Exhibited weak inhibiting activities of the antiapoptotic proteins, Bcl-xL (percentage at 100 μM = 25% ± 1.7) and Mcl-1 (percentage at 100 μM = 75% ± 1.1 μM).
Kingianic acid E (55)	Exhibited strong inhibiting activities of the antiapoptotic proteins, Bcl-xL (percentage at 100 μM = 1% ± 0.8) and strong activity on Mcl-1 (percentage at 100 μM = 8% ± 5.5 μM).
Kingianic acid F (56)	Exhibited weak inhibiting activities of the antiapoptotic proteins, Bcl-xL (percentage at 100 μM = 22% ± 2.9) and Mcl-1 (percentage at 100 μM = 80% ± 0.7 μM).
Kingianic acid G (57)	Exhibited moderate inhibiting activities of the antiapoptotic proteins, Bcl-xL (percentage at 100 μM = 19% ± 1.6) and Mcl-1 (percentage at 100 μM = 47% ± 2.9 μM).
Tsangibeilin B (73)	Exhibited weak inhibiting activities of the antiapoptotic proteins, Bcl-xL (percentage at 100 μM = 26% ± 2.5) and Mcl-1 (percentage at 100 μM = 81% ± 2.4 μM).
	Control: U-Bak (K_i = 12 ± 1 μM), U-Bid (K_i = 16 ± 2 μM) [44]

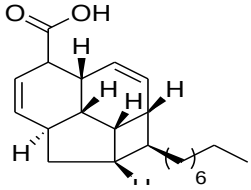
Anti-inflammatory activity.

Huang et al.[36] also studied the anti-inflammatory activity of several compounds isolated from *B. tsangii*. They found that endiandramide A-B (**32**-**33**) exhibited significant iNOS inhibitory activity against RAW 264.7 cells at the concentration range of 0.1-100 μM. A year later, they reported moderate iNOS inhibitory activity for endiandric acid M (**31**). They also suggested that endiandramide B (**33**) and endiandric acids K-M (**29**-**31**) with the same skeleton but with different substituents at C-8, exhibited ascending degrees of iNOS inhibitory activity in the order: endiandramide B (**33**) (16.40 μM) > endiandric acid M

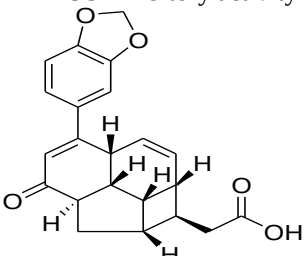
(**31**) (31.70 μM) > endiandric acid L (**30**) (39.56 μM) > endiandric acid K (**29**) (58.21 μM). This suggests that the iNOS potency of the substituent at C-8 could be arranged as *N*-isobutylamido group > an α,β-unsaturated carboxylic acid group > a carboxylic acid group. Endiandric acid M (**31**), with four fewer methylenes than endiandric acid L (**30**), showed stronger potency than endiandric acid L (**30**). This also suggests that fewer methylenes in the alkyl side of endiandric acid analogues result in greater potency of iNOS inhibitory activity[37].



(**1**) R_1 = β-OH ; R_2 = H
(**2**) R_1 = β-OH ; R_2 = OH
(**3**) R_1 = α-OH ; R_2 = H
(**4**) R_1 = H ; R_2 = H



(**5**)



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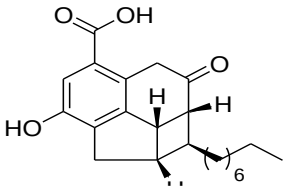
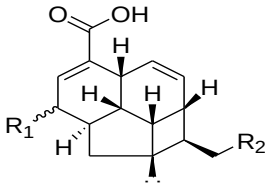
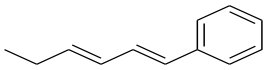
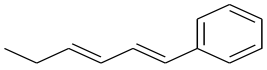


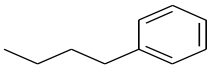
(**7**)

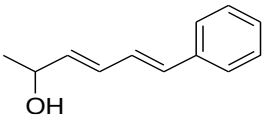


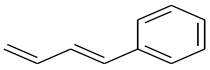
R_1 R_2

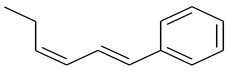
(**8**) α-OH 

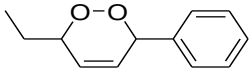
(**9**) β-OH 

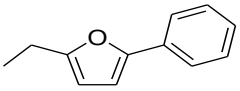
(**10**) H 

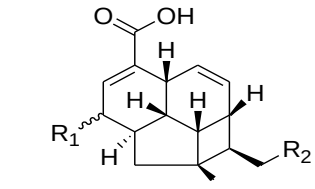
(**11**) α-OH 

(**12**) α-OH 

(**13**) α-OH 

(**14**) α-OH 

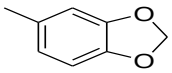
(**15**) α-OH 



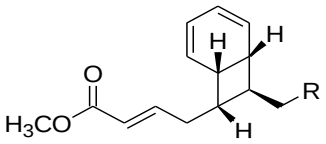
R_1 R_2

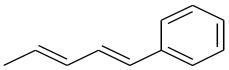
(**18**) β-OH $(CH_2)_6CH_3$

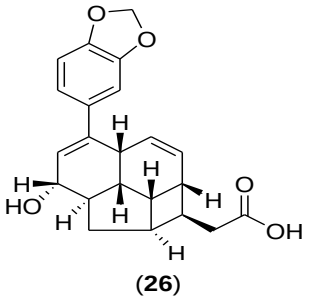
(**19**) α-OH $(CH_2)_6CH_3$

(**20**) C=O 

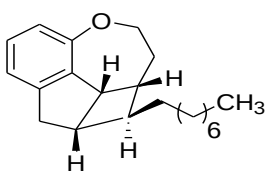
(**21**) H $(CH_2)_6CH_3$



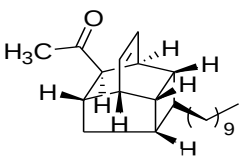
(**25**) R = 



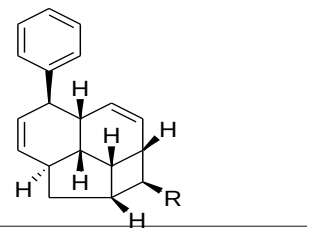
(**26**)



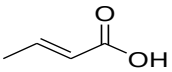
(**16**)

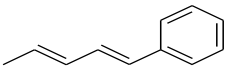


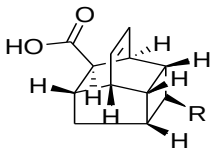
(17)

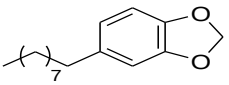


(**22**) R = $(CH_2)COOH$

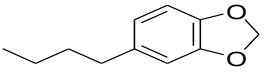
(**23**) R = 

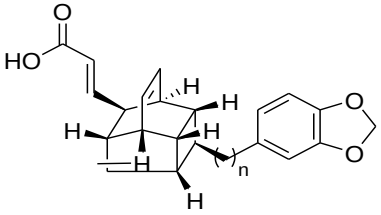
(**24**) R = 



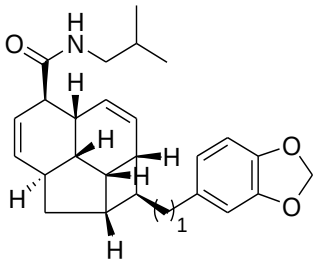
(**27**) R = 

(**28**) R = $(CH_2)_8CH_3$

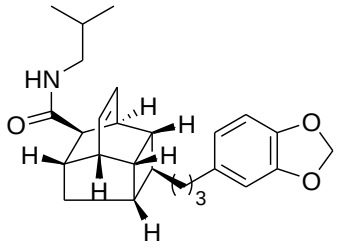
(**29**) R = 



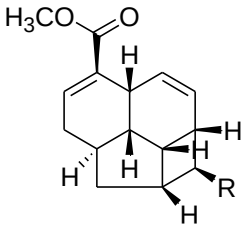
(**30**) n = 5
(**31**) n = 1

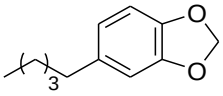


(**32**)

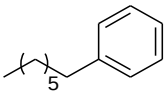


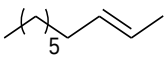
(**33**)

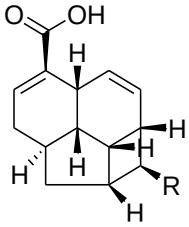


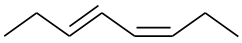
(**34**) R = 

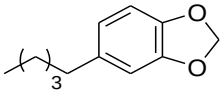
(**35**) R = $(CH_2)_8CH_3$

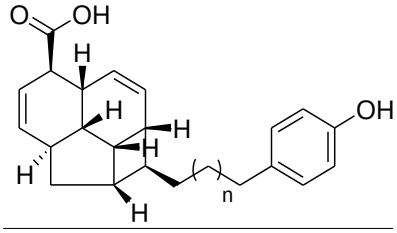
(**36**) R = 

(**37**) R = 

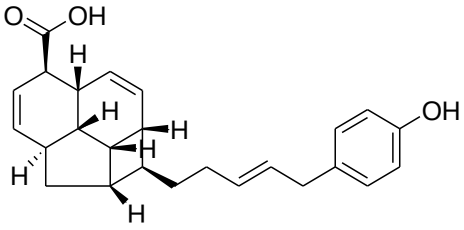


(**38**) R = 

(**39**) R = 



(**40**) R = R_1 = OH; R_2 = H ; n = 0
(**41**) R = R_1 = OH; R_2 = H ; n = 3
(**42**) R = R_1 = OH; R_2 = H ; n = 5
(**43**) R = R_1 = OH; R_2 = OH ; n = 0



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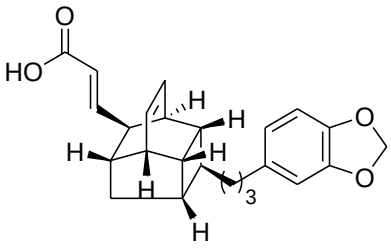

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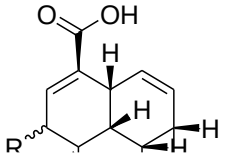
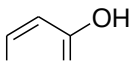
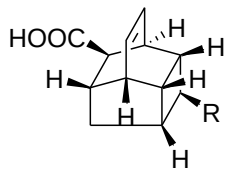
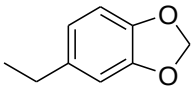
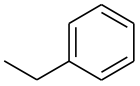


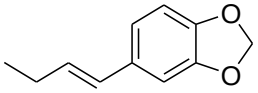


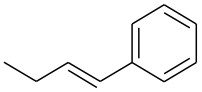
(**45**) R = α-OH
(**46**) R = β-OH
(**47**) R = C=O

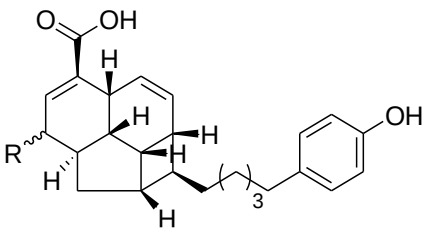


(**51**) R = 

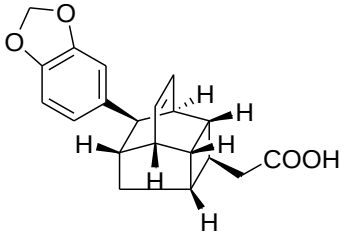
(**52**) R = 

(**53**) R = 

(**54**) R = 



(**48**) R = α-OH
(**49**) R = β-OH



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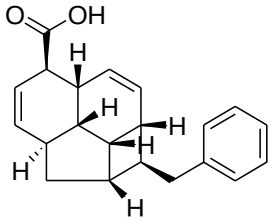

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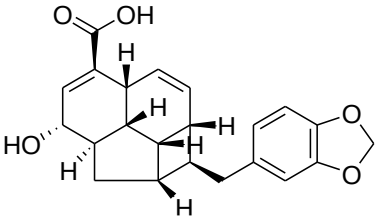

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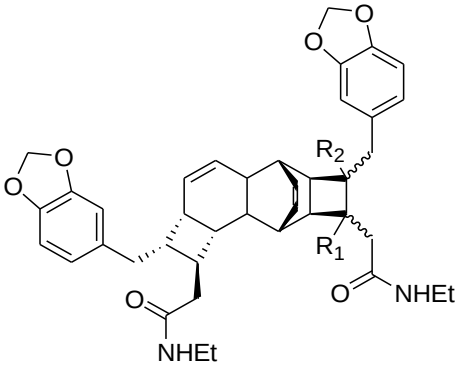
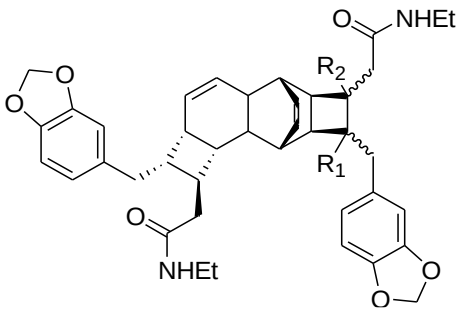
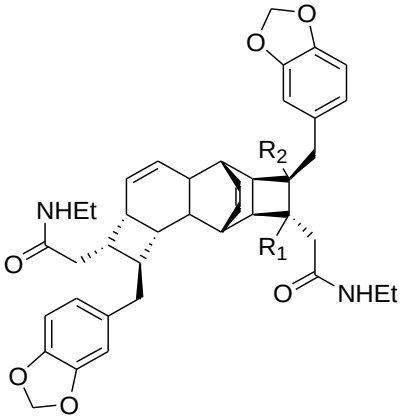


(**58**) R_1 = β-H ; R_2 = α-H
(**59**) R_1 = α-H ; R_2 = β-H



(**60**) R_1 = β-H ; R_2 = α-H
(**61**) R_1 = α-H ; R_2 = β-H



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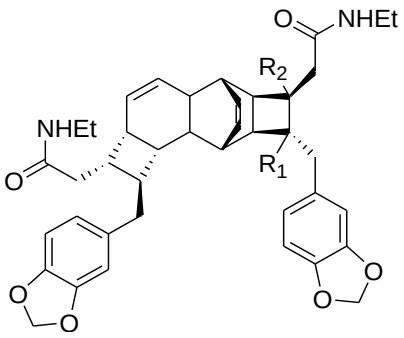

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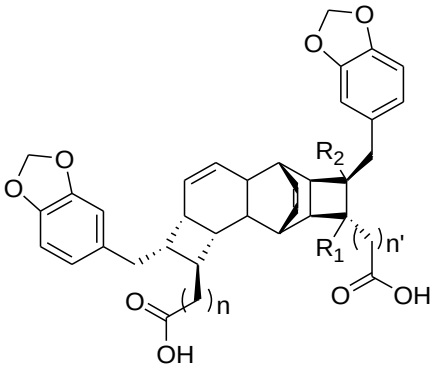
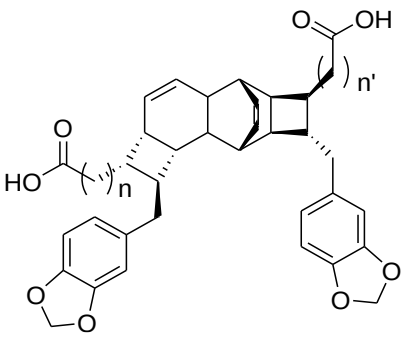
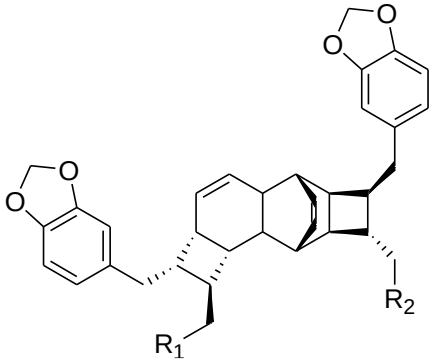


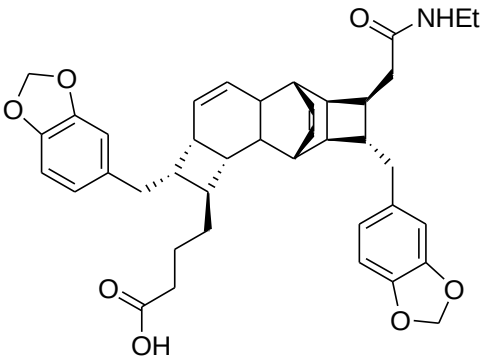
(**64**) n = 1 ; n′ = 3
(**65**) n = n′ = 3



(**66**) n = 3 ; n′ = 1
(**67**) n = n′ = 3



(**68**) R_1 = CONHEt ; R_2 = CH_2CH_2COOH
(**69**) R_1 = CH_2CH_2COOH ; R_2 = CONHEt



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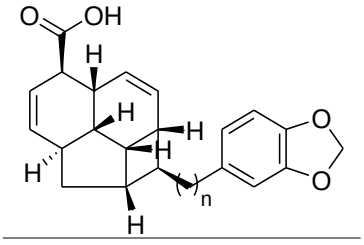
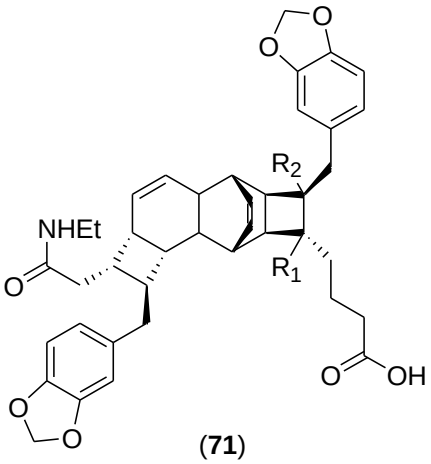
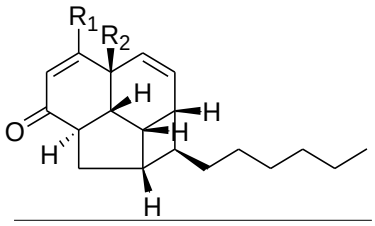


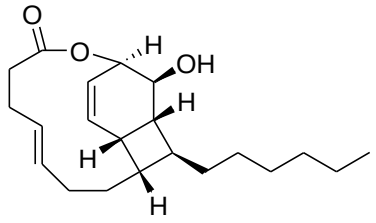
(**72**) n = 3
(**73**) n = 1



(**71**)



(**74**) R_1 = COOH ; R_2 = H
(**75**) R_1 = R_2 = OH



(**76**)

Figure 1. Endiandric acid structures from *Beilschmiedia* and *Endiandra* species

Cytotoxicity activity.

Williams et al.[38] screened the isolated endiandric acids for their *in vitro* cytotoxicity activity against NCI-H460 (large cell lung carcinoma), PC-3 (prostate adenocarcinoma) and M14 (amelanotic melanoma cell) lines using an MTT-based assay. They managed to find moderate activity of beilschmiedic acid L (**12**), I (**9**) and K (**11**) against NCI-H460 cell lines with IC_{50} values of 4.4, 5.5 and 5.9 µM, respectively. In another study, Talontsi et al.[39] isolated cryptobeilic acid B (**19**), together with tsangibeilin B (**73**), but found to have weak *in vitro* cytotoxic activity against the L6 cell line. Kingianic acids A (**51**), C (53), E (**55**), endiandric acid M (**31**) and tsangibeilin B (**73**) were screened by Azmi et al.[44] for cytotoxic activity against A549 (lung adenocarcinoma epithelial), HT29 (colorectal adenocarcinoma) and PC3 (prostate adenocarcinoma) cell lines. Kingianic acid E (**55**), showed moderate cytotoxic activity against A549 and HT-29 cell lines with IC_{50} of 15.36 ± 0.19 µM and 17.10 ± 0.11 µM, respectively. The other compounds showed very weak or devoid of A549 cytotoxic activity against the cancer cell lines tested. The results concluded that some synthetic tetracyclic endiandric acids were not active on prostate adenocarcinoma cancer cells (PC3), but significantly active on lung carcinoma cells.

Antibacterial activity.

Talontsi et al.[39] and co-worker identified cryptobeilic acids A-D (**18**-**21**) and subjected to antibacterial activity and showed that compound (**18**) gave moderate activity against *Escherichia coli* (MIC of 10 µM), while compound (**19**) active against *Escherichia coli*, *Acinetobacter*

calcoaceticus (MIC of 20 µM) and *Pseudonamas stutzeri* (MIC of 10 µM). In another study, Chouna et al. [34] reported that beilschmiedic acid C (**3**) demonstrated the best activity against *Bacillus subtilis* and *Micrococcus luteus* with MIC of 89.5, 5.58 and 11.1 µM, respectively. Antibacterial activity on endiandric acid derivatives was further studied by Williams et al.[38] and successfully observed that beilschmiedic acid A (**1**), K (**11**) and L (**12**) gave moderate activity against clinical isolate of methicillin-resistant *Staphylococcus aureus* with MIC values of 10-11 µM.

Antitubercular activity.

The study of antitubercular activity, Yang et al.[33] have determined the activity among the isolated endiandric acid analogues, beilcyclone A (**1**), endiandramide A-B (**32**-**33**) and erythrophloin A-F (**34**-**39**). They verified that erythrophloin C (**36**) showed significant activity against *Mycobacterium tuberculosis* H37Rv (MIC of 50 µg/mL), comparable to ethambutol (MIC of 6.25 µg/mL). Compound (**36**) has a phenyl group, with no other substitution in the side chain moiety, that could be responsible for the activity.

Antiplasmodial activity.

Talontsi et al.[39] studied the antiplasmodial activity of the isolated endiandric acid derivatives from *B. cryptocaryoides*. All of the tested compounds (**18**-**21**, **73**) exhibited antiplasmodial activity against the erythrocytic stages of chloroquine-resistant *Plasmodium falciparum* strain NF54, with cryptobeilic acid B (**19**) showing the best potency, followed by tsangibeilin B (**73**) and cryptobeilic acid D (**21**) at the concentration of 10 µg/mL.

CONCLUSION

The pharmacological studies conducted on endiandric acid analogues isolated from *Beilschmiedia* and *Endiandra* species indicate the immense potential in the treatment of cancer. However, the diverse pharmacological activities of the analogues and isolated phytochemicals have only been assayed in *in vitro* tests using laboratory animals, and the results obtained may not necessarily be those observed in humans. While there are gaps in the studies conducted so far, which need to be bridged in order to exploit the full medicinal potential of *Beilschmiedia* and *Endiandra* species, it is still very clear that this family of plants with an already tremendous widespread and with an extraordinary potential for the future. Further research, clinical trials and product development can strengthen the *Beilschmiedia* and *Endiandra* species as an important part of our biodiversity to respect and sustainably use for generations to come.

ACKNOWLEDGEMENTS

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