

## Progress in structure, synthesis and biological activity of natural cephalotane diterpenoids

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### ABSTRACT

The *Cephalotaxus* genus is well-known owing to the numerous complex, biologically relevant natural products that can be obtained from its constituent species. The successful identification of various *Cephalotaxus* alkaloids and natural, structurally diverse cephalotane diterpenoids that exhibit antitumor activities and excellent pharmacological properties has encouraged the discovery of previously undescribed compounds from this genus. The present review summarizes the different strategies for the total synthesis of cephalotane diterpenoids as well as their diverse chemical structures, antitumor activities, structure–activity relationships (SARs), and biosynthetic pathways.

### 1. Introduction

The *Cephalotaxus* genus, which is distributed in China, India, Japan, Korea, Laos, Myanmar, Thailand and Vietnam, is the only member of the Cephalotaxaceae family composed of 11 species (Perard-Viret et al., 2017). However, as Traditional Chinese Medicine, some of the species have been considered as endangered, for the interference of human activities and a long-periodic development of seed or a low regeneration rate in the wild (Man et al., 2012; Abdelkafi et al., 2012). Various compounds have been discovered from these species, including alkaloids (Paudler et al., 1963; Powell et al., 1974; Morita et al., 2000a, 2002b; Wang et al., 2004; Takano et al., 1996; Ni et al., 2016a, b; Loc et al., 2017), essential oil (Moirangthem et al., 2015; Cisowski et al., 2005; Zhang et al., 2012), lignans (Liu et al., 2008a, 2008b; Zhang et al., 2014a; He et al., 2012; Yoon et al., 2007), phenylpropanoids (Liu et al., 2008c), terpenoids (Ahmed et al., 2008; Xu et al., 2011; Chen et al., 2017; Politi et al., 2003; Zeng et al., 2015; Zhang et al., 2014), and flavonoids (Bae et al., 2007; Ren et al., 2018; Xiao et al., 2019). Notably, these compounds show antitumor (Wang et al., 2004), antiviral (Kang et al., 1981; Kim et al., 2019), antioxidant (Zeng et al., 2012), antimicrobial (Moirangthem et al., 2014), antibacterial (Moirangthem et al.,

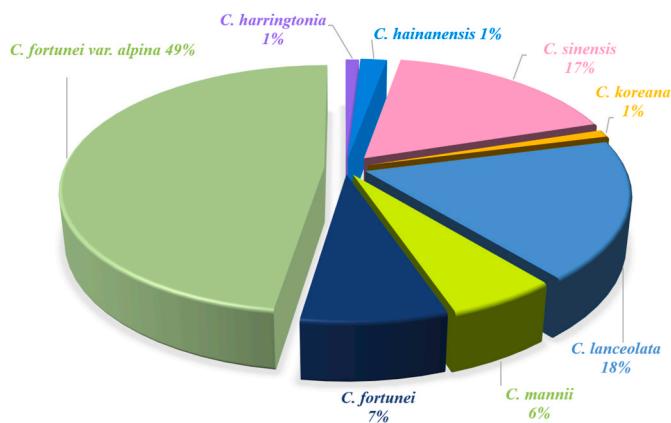
2012), anti-inflammatory (Feng et al., 2019), and antihyperglycemic activities (Ren et al., 2018; Li et al., 2007), and have been used as parasiticides (Kim et al., 1998) and for plant growth inhibition (Buta et al., 1978; Sasse et al., 1982).

*Cephalotaxus* alkaloids have attracted the attention of phytochemists due to their excellent anticancer activities. For example, homoharringtonine was listed as one of the 47 most commonly used anti-cancer drugs approved by the former Ministry of Health of China in the 1990s (Zhang et al., 2019). Thus, homoharringtonine and harringtonine have been applied clinically for the treatment of acute non lymphocytic leukemia, myelodysplastic syndrome (MDS), chronic myeloid leukemia and polycythemia vera in China. Furthermore, homoharringtonine was approved by the United States Food and Drug Administration (FDA) in 2012 to cure chronic- or accelerated-phase myeloid leukemia (Abdelkafi et al., 2012). Cephalotane diterpenoids are another major class of compounds within the *Cephalotaxus* genus and have been gaining increasing attention, especially in recent years, due to their unique and complicated carbon skeletons and their remarkable antitumor activities. This review presents a summary of the chemical structure classification, total synthesis, antitumor activity, and structure–activity relationships (SARs) of cephalotane diterpenoids, as well as their biosynthetic

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**Fig. 1.** Distributions of reported cephalotane diterpenoids in the different species of the *Cephalotaxus* genus.

pathways.

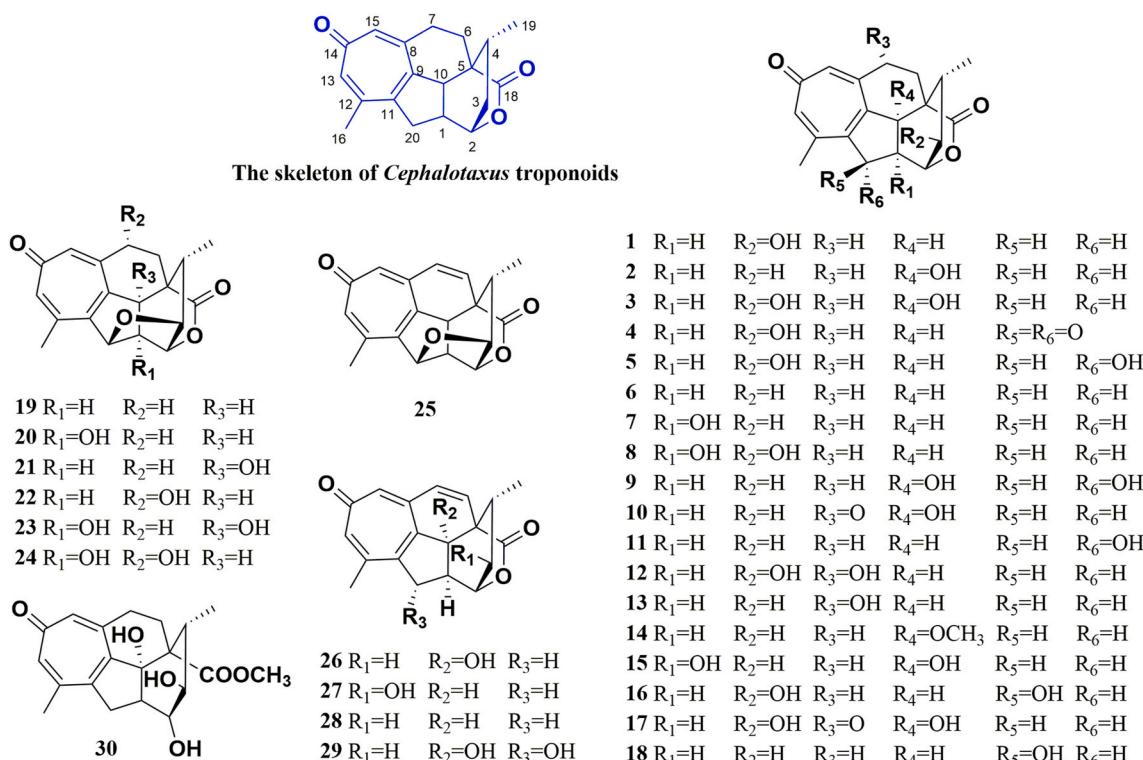
## 2. Structure classification of *Cephalotaxus* diterpenoids

Previous phytochemical investigations have led to the isolation of 73 cephalotane-type diterpenoids from the *Cephalotaxus* genus, which were classified into five structural types: *Cephalotaxus* troponoids (C19), cephalotane-type diterpenoids (C20), 17-nor-cephalotane-type diterpenoids (C19), A-ring-contracted cephalotane-type norditerpenoids (C19, C18), and cephalotane dimers. Cephalotane diterpenoids have been reported in seven species *Cephalotaxus harringtonia* (Knight ex J. Forbes) K. Koch (Cephalotaxaceae), *C. hainanensis* H.L.Li, *C. sinensis* (Rehder & E.H. Wilson) H.L.Li, *C. koreana* Nakai, *C. lanceolata* K.M.Feng ex W.C.Cheng, L.K.Fu & C.Y.Cheng, *C. mannii* Hook. f., *C. fortunei* Hook. and one variety *C. fortunei* var. *alpina* H.L.Li of the *Cephalotaxus* genus. The distributions of these species are shown in Fig. 1.

The *Cephalotaxus* troponoids represent a rare class of C19

norditerpenoids described with an intriguing architecture featured by a highly rigid tetracyclic carbon scaffold including a tropone, oxygenated groups like a lactone, a tetrahydrofuran ring or alcohols, and two methyl groups at C-4 and C-12 (Fig. 2). In 1978, Buta et al. reported the first troponoid, harringtonolide (19), from the seeds of *C. harringtonia* (Buta et al., 1978), harringtonolide (19) was also isolated from *C. hainanensis* and called hainanolide by Sun et al. (1979), who also later discovered it in *C. fortunei* (Sun et al., 1981). Hainanolidol (1) was also discovered by Sun et al., in 1979 (Sun et al., 1979), and its structure elucidation was completed a few years later. Fortunolides A (2) and B (20) were isolated in 1999 by Du et al. from the stems and needles of *C. fortunei* var. *alpina* (Du et al., 1999), but the absolute configuration of 2 was established by Yue's group 20 years later (Ge et al., 2019). Yoon et al. isolated 11-hydroxyhainanolidol from the aerial parts of *C. koreana* Nakai in 2007 (Yoon et al., 2007), however, the originally proposed structure was revised to that of 3 in 2017 by Yue's group (Zhao et al., 2017). These five *Cephalotaxus* troponoids were the only ones reported before 2012. Compound 30 is the only one with an open lactone between the C-18 and C-2 positions. By now, there have been 30 *Cephalotaxus* troponoids reported from the abovementioned seven species and one variety of the *Cephalotaxus* genus. It is worth noting that the majority of cephalotane diterpenoids were isolated from *Cephalotaxus* species in recent years.

Cephalotane-type diterpenoids feature an intact C20 carbon skeleton, and most of them possess a lactone moiety between the C-14 and C-17 positions (Fig. 3). Mannolides A-C (41–43) featuring an intact C20 carbon skeleton were isolated from *C. mannii* in 2016 for the first time by Yue's group (Ni et al., 2016a, b). A new cephalotane-type diterpenoid glucoside from *C. sinensis* named cephaphinenoside A (39) was reported by Hua et al., in 2019, which was the first cephalotane diterpenoid glycoside to be discovered and is the only one known to date (Zhao et al., 2019). Additionally, cephafortunoids A-D (40, 48, 49, 37) were obtained from the branches and leaves of *C. fortunei* var. *alpina* by Hua's group. Cephafortunoids A and B were the first *Cephalotaxus* troponoid diterpenoids found to possess a complete C20 scaffold and exhibit the migration of their 17-CH<sub>3</sub> moieties to the C-15 or C-13 positions,



**Fig. 2.** Structures of *Cephalotaxus* troponoids (C19).

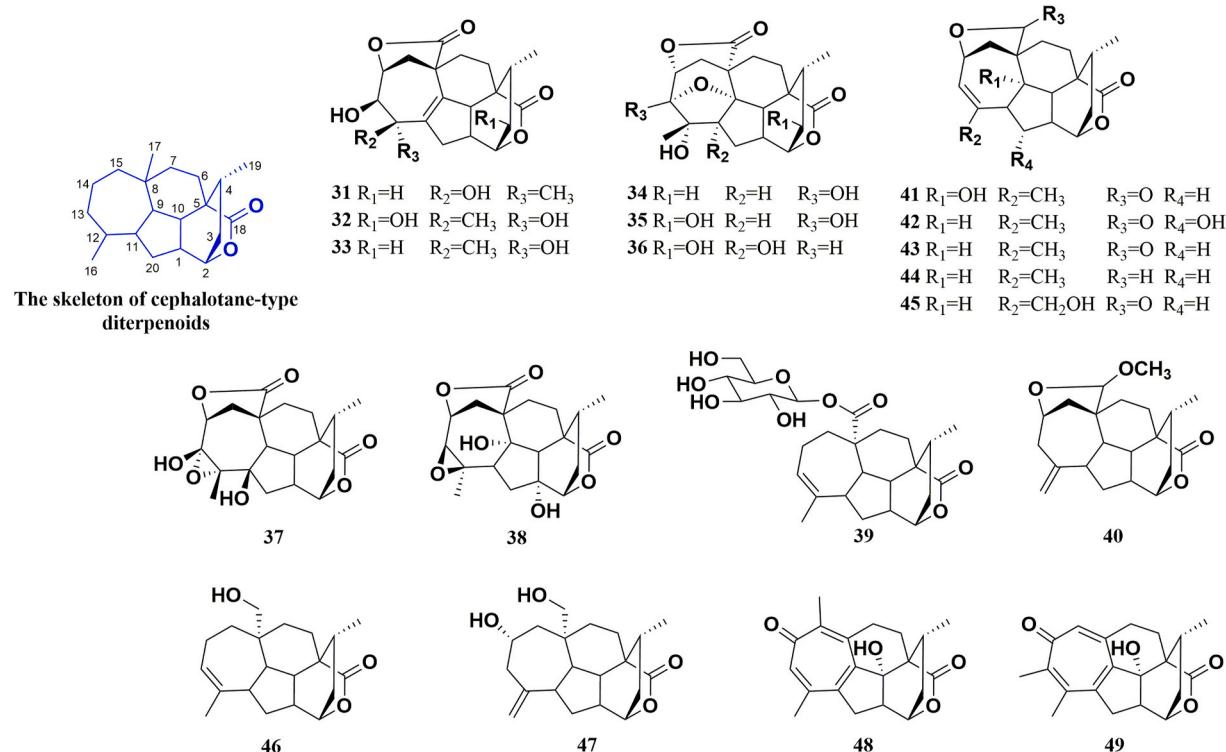


Fig. 3. Structures of cephalotane-type diterpenoids (C20).

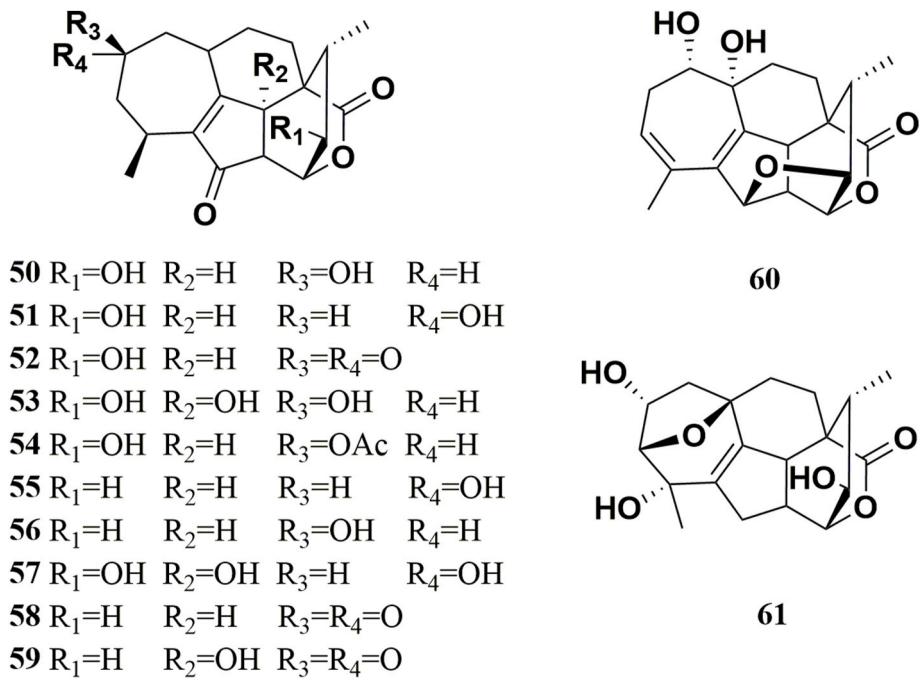


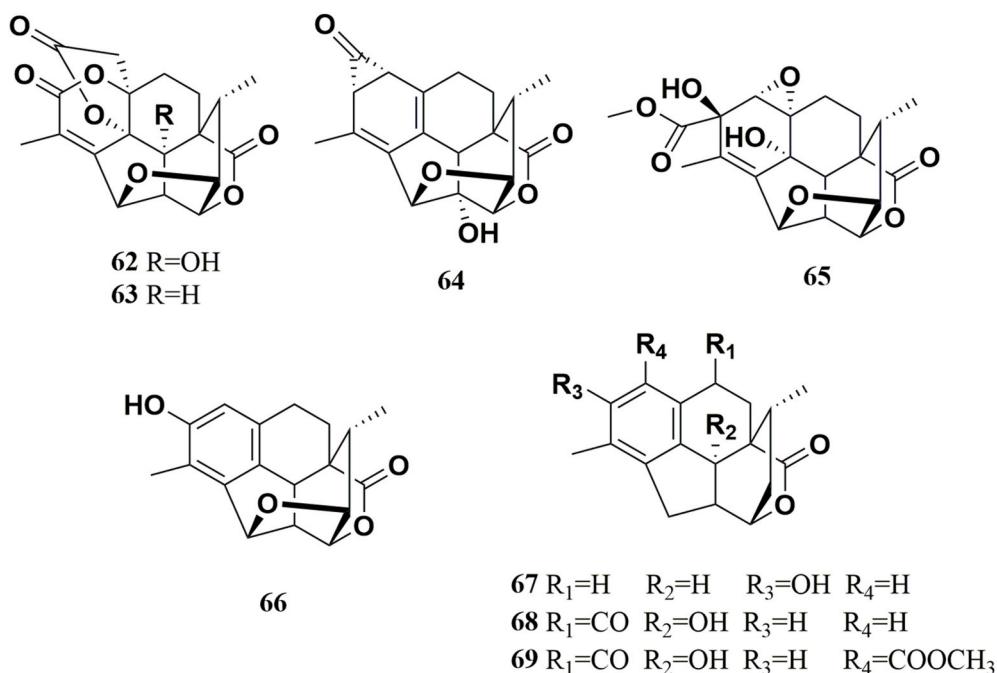
Fig. 4. Structures of 17-nor-cephalotane-type diterpenoids (C19).

respectively (Li et al., 2020).

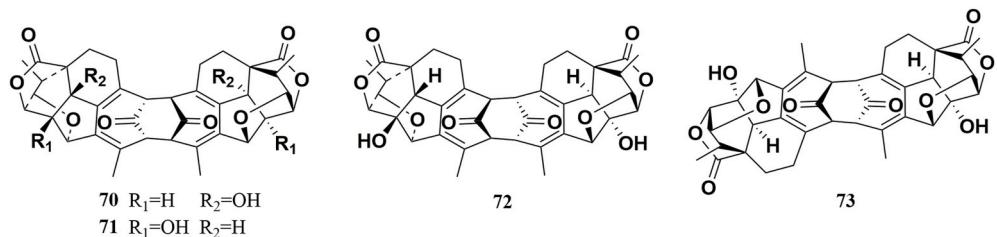
17-nor-Cephalotane-type diterpenoids were derived from *Cephalotaxus* troponoids through the reduction of the tropone ring (Fig. 4). Lanceolatin G (**50**) was isolated from the branches and leaves of *C. lanceolata* as the first member of 17-nor-cephalotane-type diterpenoids in 2014 by Zhang et al. (He et al., 2015). Fortalpinoids K-Q (**60–61**, **55–59**) are 17-nor-cephalotane-type diterpenoids that were obtained from the seeds of *C. fortunei* var. *alpina* by Yue's group in 2019

(Ge et al., 2019). This was the first discovery of fortalpinoid L (**61**), which possesses an 8-oxabicyclo [3.2.1]oct-2-ene moiety.

Four previously undescribed A-ring-contracted norditerpenoids named cephalotanins A (**62**) and B (**63**) with new skeletal norditerpenoid trilactones, cephalotanin C (**64**) with a new bicyclo [4.1.0]hepta-2,4-dien-7-one moiety and cephalotanin D (**65**) were obtained from the leaves of *C. sinensis* in 2016 by Yue's group (Fan et al., 2017). Cephanolides A-D (**66–69**) were also isolated from *C. sinensis* in 2017 by



**Fig. 5.** Structures of A-ring-contracted cephalotane-type norditerpenoids (C19, C18).



**Fig. 6.** Structures of C19-norditerpenoid dimers.

Yue's group; among them, cephalolides A-C (**66–68**) were the first examples of A-ring-contracted cephalotane-type dinorditerpenoids, and cephalolide D (**69**) was a norditerpenoid with similar structure (Xu et al., 2016) (Fig. 5).

Recently, new progress has been made in the discovery of cephalotane diterpenoids. Yue's group reported four C19-norditerpenoid dimers (Fig. 6) firstly from the seeds of *C. fortunei* var. *alpina* in 2021: cephalodiones A-D (**70–73**), which shared a unique tricyclo [6.4.1.12,7] tetradeca-3,5,9,11-tetraene-13,14-dione core that was capped on both ends with rigid, multicyclic ring systems in either a C2-symmetrically or asymmetrically (Ge et al., 2021). The process through which all the aforementioned cephalotane diterpenoids were discovered is shown in Fig. 7.

### 3. Total synthesis of cephalotane diterpenoids

Due to their intriguing, complex structures and outstanding biological activities, numerous organic chemists have set about developing total syntheses of these components. Harringtonolide (**19**), the first troponoid to be discovered from *Cephalotaxus*, attracted particular attention. The incipient synthetic study toward **19** was conducted by Xue et al. and involved a semi-synthesis from the parent compound hainanololidol (**1**) that proceeded through pseudobenzylidic oxidation with lead tetraacetate (Xue et al., 1982). To date, six alternative strategies for **19** have been proposed (Fig. 8), which include those developed by Mander (1998, 2007) (Frey et al., 1998a; 1998b; 2000; Zhang et al., 1998; Rogers et al., 1999; Mander et al., 2003; O'Sullivan et al., 2007),

Huang (2004) (Zhang et al., 1996; Lu et al., 1997; Yang et al., 1997a, 1997b; Yu et al., 1999, 2000; Li et al., 2002, 2004), Nay (2012) (Abdelkafi et al., 2011a, 2011b, 2013a, 2013b), Tang (2013) (Zhang et al., 2013), and Zhai (2016) (Zhang et al., 2016). The total synthesis of **19** and the attempts at building of its core structure that occurred before 2012 have been summarized by Nay (Abdelkafi et al., 2012). Here, we will focus on the researches conducted on cephalotane diterpenoids after 2012.

#### 3.1. Total synthesis of hainanololidol (**1**) and harringtonolide (**19**)

Tang's group revealed a [5 + 2] cycloaddition reaction as the crucial step for constructing the core structure of **19** (Fig. S1) (Zhang et al., 2013). The total synthesis of **19** was achieved via two stereoselective [3, 3]-sigmatropic rearrangements, an oxidopyrylium-based [5 + 2] cycloaddition to form the tetracyclic carbon frame, an anionic ring opening of the ether bridge derived from the [5 + 2] cycloaddition, and the construction of a tropone unit through a series of reactions: [4 + 2] cycloaddition, Kornblum-DeLaMare rearrangement, and then double elimination. Notably, this previously undescribed synthetic approach for **19** can be easily modified to obtain other *Cephalotaxus* norditerpenoids and diverse derivatives.

Additionally, Zhai's group has developed a previously undescribed and clear method for the first enantioselective total synthesis of (+)-**19** (Fig. S2) (Zhang et al., 2016). The key conversions included an asymmetric transfer hydrogenation, an intramolecular Diels-Alder reaction, selective functionalization of the olefin with an acetylenic group, a

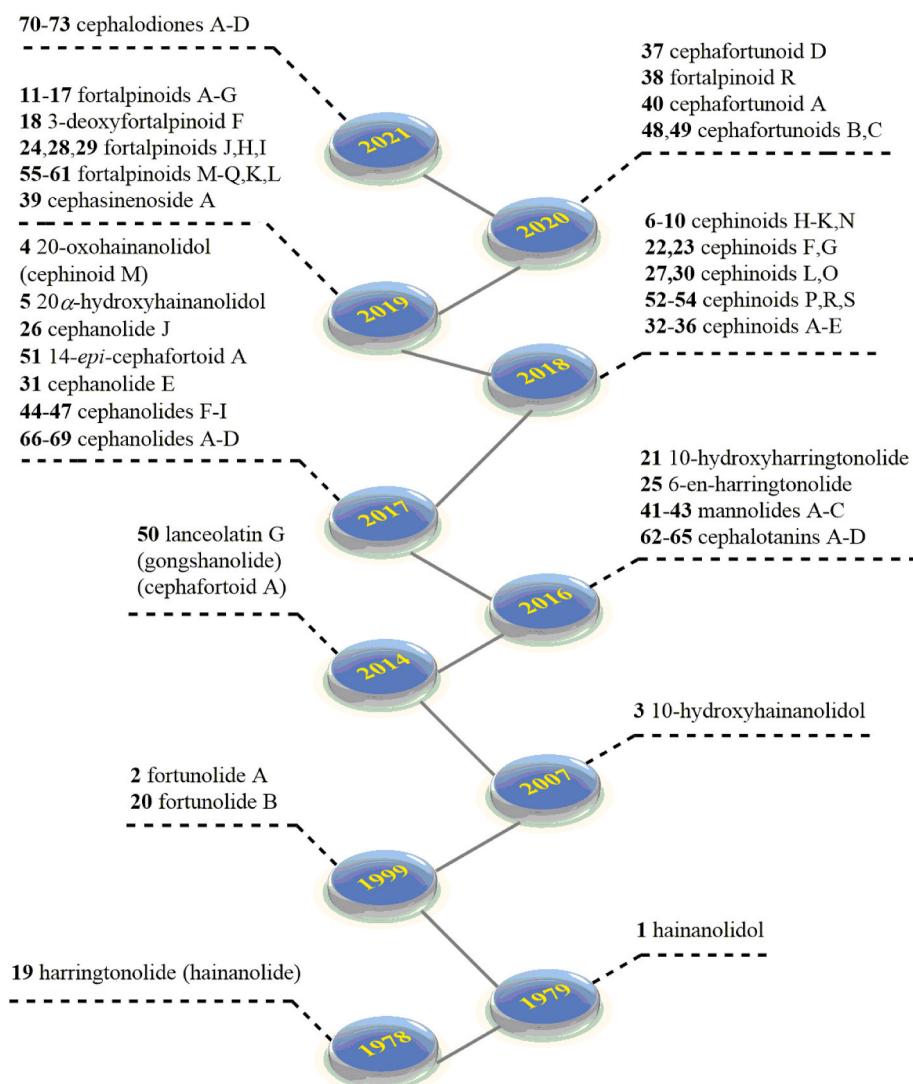


Fig. 7. Discovery process of cephalotane diterpenoids.

rhodium-complex-catalyzed intramolecular [3 + 2] cycloaddition, and the formation of the tropone unit via a silyl enol ether. This challenging procedure was extremely efficient in forging asymmetric **19**.

### 3.2. The total synthesis of cephalolides A, B, C, and D (**66–69**)

Cephalolide A (**66**) is an A-ring-contracted cephalotane-type nor-diterpenoid. Recently, the first asymmetric total synthesis of **66** has been successfully realized by Gao through a convergent approach (Fig. S3) (Zhang et al., 2020). The contiguous chiral centers in the C ring were precisely constructed with a commercial chiral enone as the starting ingredient. The central A-B-C-ring unit was constructed through an intramolecular Prins cyclization followed by a remote hydroxyl-group-directed hydrogenation that gave the hexahydro-fluorenol frame. The D-E-F-ring unit was efficiently built by a series of ring-forming reactions: lactonization, cation-mediated etherification, and Friedel-Crafts cyclization. Ultimately, after 15 steps **66** was achieved.

In addition, syntheses of cephalolides B (**67**) and C (**68**) were developed; these two compounds were obtained from *C. sinensis* and possess a rarely encountered aromatic benzen ring different from that of **19**. The first chemical syntheses of these cephalolides were realized by Zhao and co-workers and began with 5-bromo-2-methylanisole (Fig. S4), which efficiently forms the 6-5-6 *cis*-fused tricyclic ring

systems of *Cephalotaxus* diterpenoids via a palladium-catalyzed cascade cyclization reaction (Xu et al., 2018). Furthermore, a subsequent late-stage regioselective sp<sup>3</sup> C-H bond oxidation reaction was crucial for oxygenating the C-10 and C-7 positions.

Recently, Sarpong et al. reported total syntheses of **66–69** that were based on retrosynthesis and guided by chemical network analysis (Haider et al., 2021). In this study, **69** was firstly achieved through chemical synthesis, and the synthetic approaches towards **66–68** were different from those listed above. According to the retrosynthesis (Fig. S5), a commercially available indanone was selected as the starting material. The core framework of the cephalolides was rapidly built by an iterative C(sp<sup>2</sup>)-C(sp<sup>3</sup>) cross-coupling reaction, followed by an enol ether/intramolecular inverse-demand Diels-Alder reaction. Moreover, a late-stage oxygenation strategy served as a useful tool in these strategies, particularly for **66** and **67**.

### 3.3. Synthesis of the harringtonolide (**19**) core structure

Several intermediates (Fig. 9) were also synthesized through the efficient retrosynthetic analysis of **19** by organic chemists. The synthesis strategies reported since 2012 for two important intermediates contributing to the total synthesis of cephalotane diterpenoids are summarized here.

A promising intermediate for the synthesis of **19** has been reported

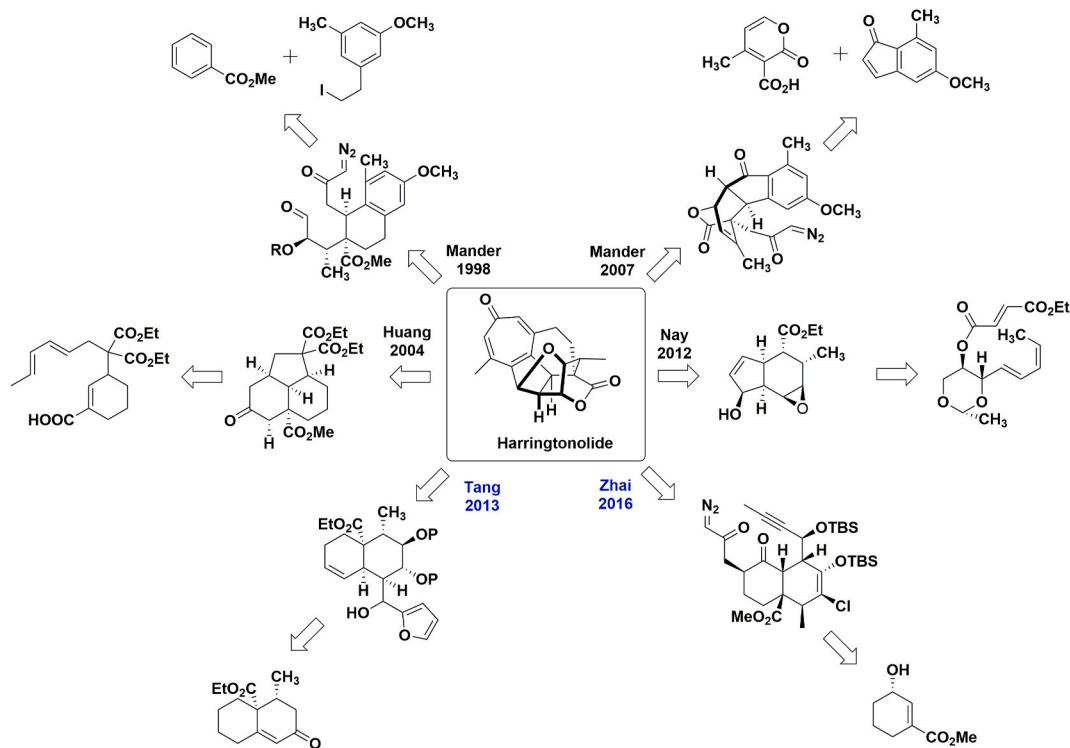


Fig. 8. Six synthetic strategies reported for harringtonolide (19).

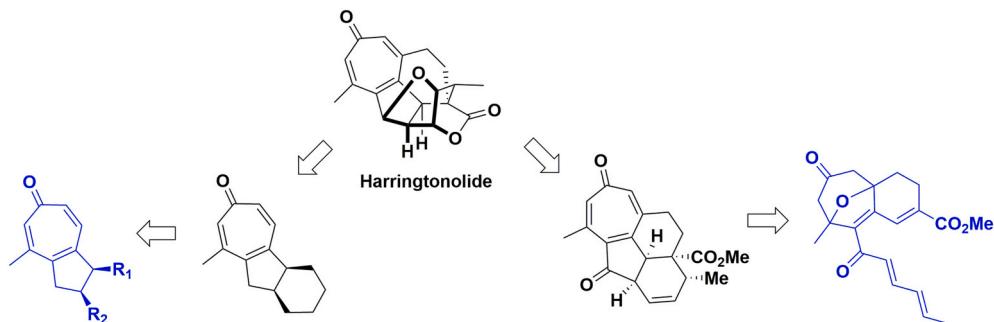
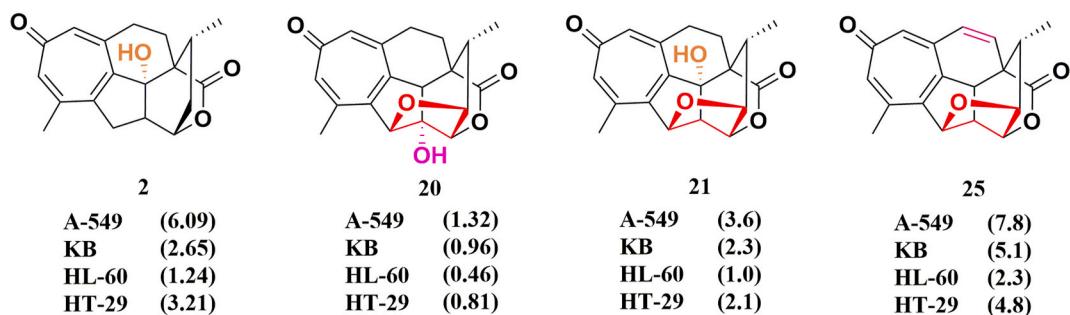


Fig. 9. Two core structures toward 19.

Fig. 10. Cytotoxicity of compounds 2, 20, 21, and 25 against A-549, KB, HL-60 and HT-29 cells (IC<sub>50</sub> in  $\mu\text{M}$ ).

by Zhai's group (Fig. S6), which has an oxo-bridged 7/6-bicyclic unit that is realized through a [4 + 3] cycloaddition reaction (Ma et al., 2014). Furthermore, Yuan's group exploited a potent and one-pot process to provide enantiomerically pure 2,3-dihydroazulen-6(1H)-ones through organocatalyzed Michael reaction and selective oxidative dearomatizations (Fig. S7), which is the tricyclic framework of

*Cephalotaxus* norditerpenes (Zheng et al., 2016). However, the enantioselective total synthesis of **19** through a one-pot protocol has not yet been achieved.

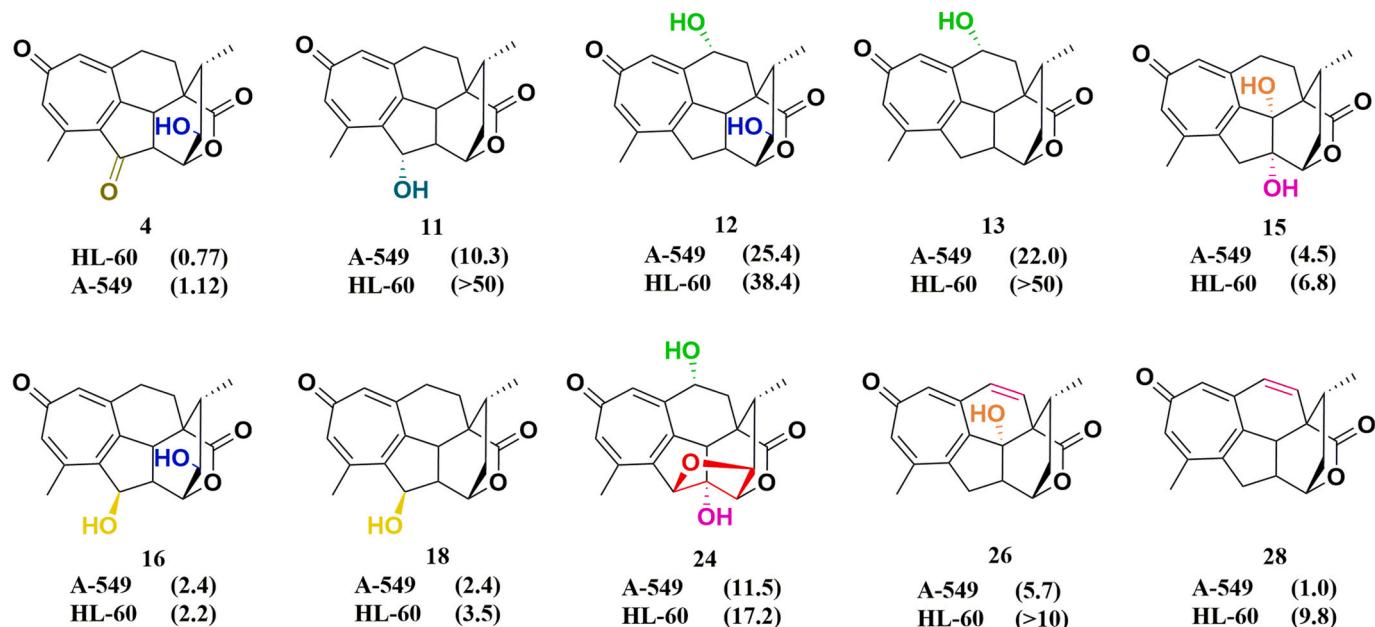


Fig. 11. Cytotoxicity of some *Cephalotaxus* troponoids against A-549 and HL-60 cell lines (IC<sub>50</sub> in μM).

#### 4. Antitumor activity and SARs

Cephalotane diterpenoids have reportedly inhibited plant growth (Buta et al., 1978) and exhibited antiviral (Kang et al., 1981), anti-inflammatory (Ni et al., 2018), and antitumor activities (Ge et al., 2019; Zhao et al., 2017; He et al., 2015; Ni et al., 2016a, b; Fan et al., 2017; Xu et al., 2016). The antitumor activities are primarily focused on in this section, and the antitumor SARs are briefly discussed.

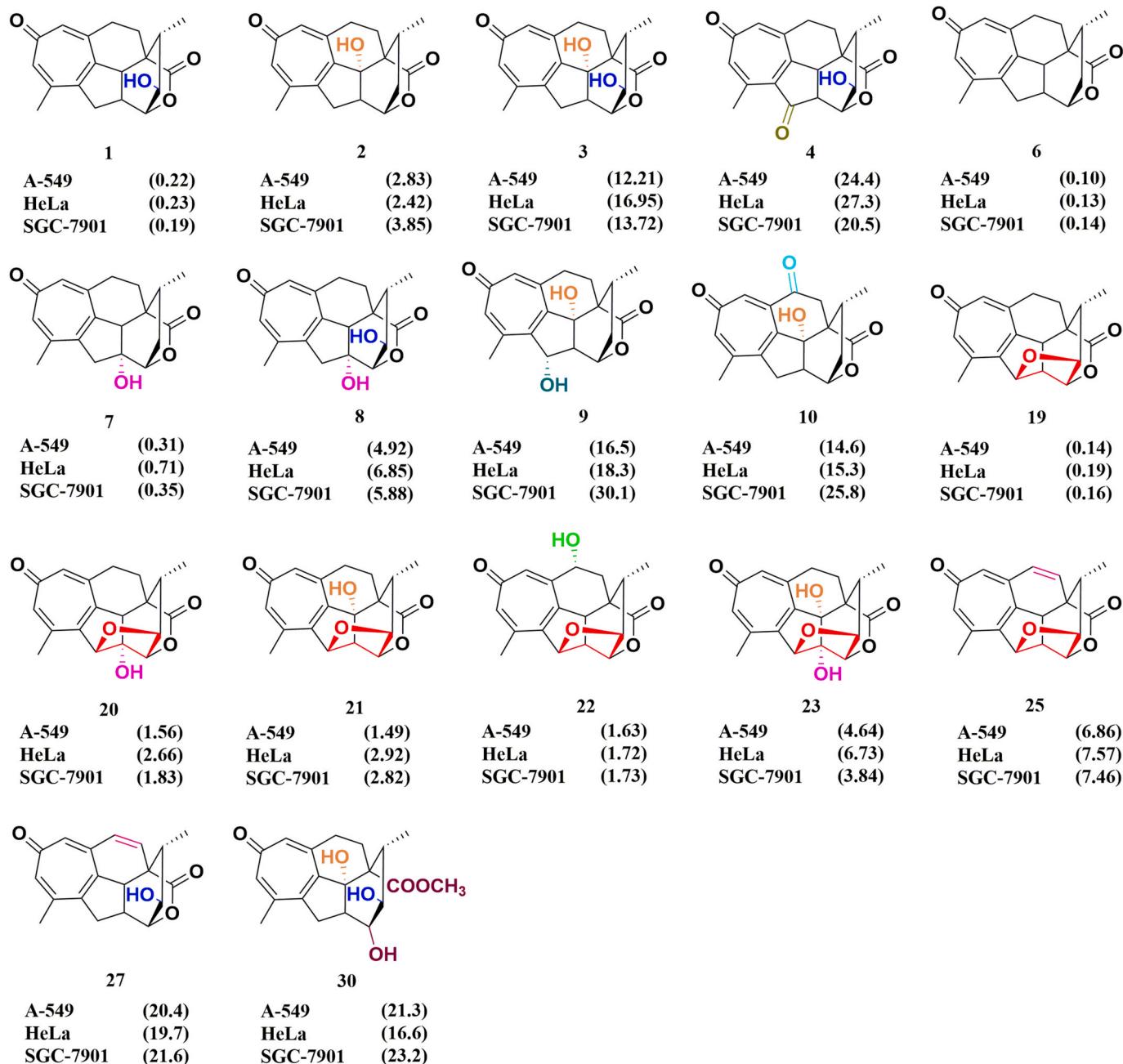
Fortunolides A (2) and B (20) as well as cephanolides A-J (26, 31, 44–47, 66–69) were assessed against human lung adenocarcinoma cells (A-549), human oral epithelial carcinoma cells (KB), human promyelocytic leukemia cells (HL-60), and human colorectal cancer cells (HT-29) (Xu et al., 2016). The results revealed compounds 2 and 20 exhibited remarkable cytotoxic activities towards these cell lines with IC<sub>50</sub> values as follows: 6.093 ± 3.535 (A-549), 2.652 ± 0.345 (KB), 1.243 ± 0.104 (HL-60), and 3.215 ± 0.057 (HT-29) for 2 and 1.326 ± 0.300 (A-549), 0.964 ± 0.008 (KB), 0.464 ± 0.032 (HL-60), 0.817 ± 0.165 μM (HT-29) for 20. In contrast, the other compounds showed no cytotoxic activity against these four cell lines, indicating that the tropone motif is vital for such activity. 10-Hydroxyharringtonolide (21), 6-en-harringtonolide (25), and mannolides A-C (41–43) were also tested for their cytotoxicity against A-549, KB, HL-60, and HT-29, and the results (Fan et al., 2017) revealed that 21 and 25 show remarkable cytotoxic activities towards these cell lines; the IC<sub>50</sub> values are as follows: 3.683 ± 0.947 (A-549), 2.325 ± 0.040 (KB), 1.038 ± 0.002 (HL-60), and 2.108 ± 0.108 (HT-29) for 21 and 7.804 ± 3.797 (A-549), 5.115 ± 0.148 (KB), 2.319 ± 0.247 (HL-60), and 4.890 ± 0.622 μM (HT-29) for 25, which indicated that a Δ<sup>6</sup> double bond adjacent to the tropone unit might be what weakens these activities (Fig. 10). Compounds 41–43 without the tropone moiety were inactive.

10-Hydroxyhainanololidol (3), 20-oxohainanololidol (4), 20-α-hydroxyhainanololidol (5), cephafortoid A (50), and 14-*epi*-cephafortoid A (51) were evaluated for their cytotoxicity against the HL-60 and A-549 cells (Zhao et al., 2017), revealing that compound 4 showed remarkable activities against the HL-60 and A-549 cells with IC<sub>50</sub> values of 0.77 ± 0.05 and 1.129 ± 0.057 μM, respectively (Fig. 11). Fortalpinoids A-Q (11–17, 24, 28, 29, 55–61), 3-deoxyfortalpinoid F (18), and cephanolide J (26) were also tested against the A-549 and HL-60 cell lines; among them, compounds 15, 16, 18, 26, and 28 exhibited remarkable cytotoxicity against these two cell lines (Ge et al., 2019). It was also discovered that

compounds 55–61 were inactive due to their lack of the tropone ring. Substituting the C-1 and/or C-3 positions (these are far from the tropone ring) of 16 and 18 with a hydroxy group slightly impacted the activities of these compounds. In addition, introducing a β-OH moiety at the C-20 position of the same compounds did not affect their activities; however, introducing an α-OH unit or methoxy groups at the C-7, C-10, or C-20 positions of 14, 24, 26, and 29, which are close to their tropone motifs, significantly reduced the cytotoxicities of these compounds. Moreover, the presence of a carbonyl moiety at a position adjacent to the tropone unit (C-7) forcefully weakens the activities against A-549, HeLa, SGC-7901 cells, which is observed for 1 and 4, as well as 10 and 2 (Fig. 11).

Hainanololidol (1), fortunolide A (2), 10-hydroxyhainanololidol (3), cephinoid M (4), cephinoids A-S (6–10, 22, 23, 27, 30, 52–54, 32–36), harringtonolide (19), fortunolide B (20), 10-hydroxyharringtonolide (21), 6-en-harringtonolide (25), gongshanolide (50), and cephalotanin C (64) were evaluated against human cervical carcinoma cells (HeLa), human gastric cancer cells (SGC-7901), and A-549 (Ni et al., 2018). The results showed that 1, 6, 7, and 19 presented excellent inhibitory effects while compounds 32–36, 50, 52–54, and 64 were inactive. This suggests that the tropone motif is required for these activities. The Δ<sup>6</sup> double bond or a carbonyl moiety at positions adjacent to the tropone unit (C-7 or C-20) reduced the activities, as was demonstrated in compounds 4, 10, 25, and 27. Compound 30 was the least potent among the tested compounds, with a mean IC<sub>50</sub> value of 20 μM, which implied that the six-membered lactone moiety was also significant for these activities. However, the furan ring between the C-3 and C-20 positions has no obvious effect, as shown in 6 and 19 (Fig. 12). Meanwhile, the inhibitory activity of these compounds towards the signal pathway of the nuclear factor kappa-B (NF-κB) and towards nitric oxide (NO) production were assayed (Ge et al., 2021).

Harringtonolide (19) was tested against KB cells and exhibited an IC<sub>50</sub> value of 43 nM (Evanno et al., 2008). Harringtonolide (19) and gongshanolide (50) were evaluated against A-549, human colorectal (HCT-116), and human hepatocellular carcinoma (HepG2) cells (He et al., 2012), where 19 showed significant inhibition of all three with IC<sub>50</sub> values of 12.84, 0.17 and 0.63 μM respectively. However, 50 was inactive due to its lack of the tropone motif. Furthermore, cepha-sinenoside A (39) was evaluated against HL-60 leukemia cell lines and demonstrated a GI<sub>50</sub> value of 7.17 ± 1.03 μM. Interestingly, it was active



**Fig. 12.** Cytotoxicity of some *Cephalotaxus* troponoids against A-549, HeLa, and SGC-7901 cell lines ( $IC_{50}$  in  $\mu M$ ).

despite not possessing the tropone motif. This could be due to the glycosyl group changing the lipid/water distribution coefficient, thus affecting the activity (Fig. 13) (Zhao et al., 2019).

Hainanolidol (1), fortunolide A (2), cephinoid H (6), cephinoid I (7), cephinoid K (9), fortalpinoid E (15), fortalpinoid J (24), cephafortoid A (50), 14-*epi*-cephafortoid A (51), cephalolide E (31), and cephafortinoids A-D (48, 49, 37, 38) were evaluated for their cytotoxicity against HL-60, human acute monocytic leukemia (THP-1), human breast cancer (MDA-MB-231), and human prostate cancer (PC-3) cells. The introduction of one more methyl groups at the C-13 or C-15 positions of the tropone rings of 48 and 49 led to their inactivity, revealing that structural alteration of the tropone ring will apparently affect these activities (Li et al., 2020).

The potent antitumor activities of cephalotane diterpenoids against Lewis lung carcinoma cells, Walker-256 tumor cells, osteosarcoma S-180 cells, leukemic L-1210 cells, leukemic L-615 cells, K-562 leukemia

cells, and P-388 leukemia cells were also reported (Sun et al., 1979; Zhou et al., 2011).

From the above discussion, we may reasonably arrive at the following conclusions (Fig. 14): 1) The complete tropone ring was a requirement for the cytotoxic activity (pink section), as cephalotane diterpenoids without this functional group were inactive; 2) The six-membered lactone moiety was also meaningful for cytotoxic activities (orange section), which is demonstrated by the changes in activity upon its opening; 3) The existence of a  $\Delta^6$  double bond or a carbonyl moiety at positions adjacent to the tropone unit (C-7 or C-20) led to decreased activities (purple section), but this may be selective only towards specific cell lines; 4) The  $\beta$ -oriented 3,20-ether bridge slightly impacted activities (red section); 5) Substitution with  $\alpha$ -OH moiety or methoxy groups at the C-7, C-10, or C-20 positions nearby the tropone motif notably weakens the antitumor activities (green section), whereas the presence of a  $\beta$ -OH unit at the C-20 position and/or a hydroxy group at

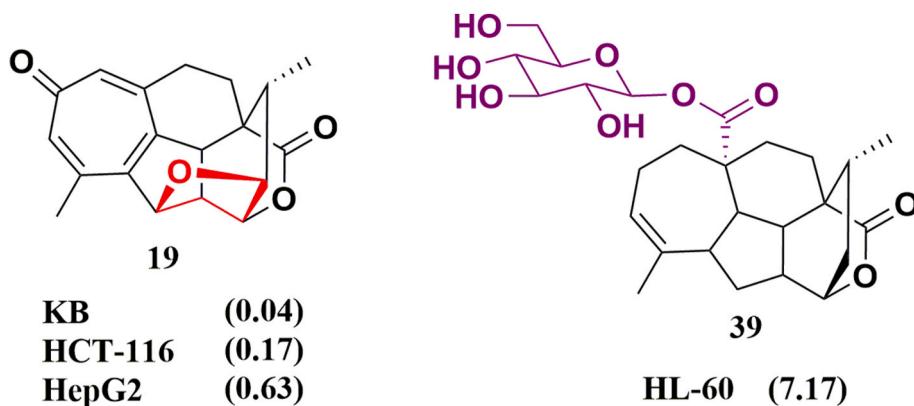
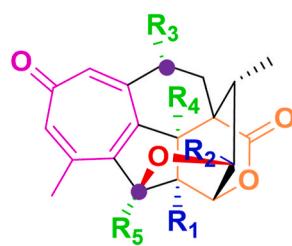


Fig. 13. Cytotoxicity of **19** against KB, A-549, HCT-116, and HepG2 cell lines ( $IC_{50}$  in  $\mu M$ ) and cytotoxicity of **39** against HL-60 cell lines ( $GI_{50}$  in  $\mu M$ ).



- Pink:** tropone ring is essential
- Orange:** lactone ring is also important
- Green:** R=OH or OCH<sub>3</sub>, substitution is disfavored
- Blue:** R=OH, substitution has no obvious effect
- Purple:** conjugated C-7 or C-20 keto group or  $\Delta^6$  double bond is disfavored
- Red:** 3,20-ether bridge has no obvious effect

Glycosyl group may affect the activity though the structure lacking tropone motif;  
Structural variation in the tropone ring will dramatically impact the cytotoxic activities.

Fig. 14. Brief summary of the antitumor structure–activity relationships (SARs) of cephalotane diterpenoids.

the C-1 and/or C-3 positions (which are not near the tropone ring) exerts no clear influence on the activities (blue section); 6) The activities were inversely proportional to the number of hydroxyl substitutions in the cephalotane diterpenoids; 7) The glycosyl group may change the lipid/water distribution coefficient of cephalotane diterpenoids lacking the tropone motif, thus affecting their activities; 8) Structural alteration of the tropone ring, such as the introduction of a methyl group, apparently affects the cytotoxic activities of cephalotane diterpenoids.

##### 5. Biosynthetic pathways of *Cephalotaxus* diterpenoids

The biogenesis of *Cephalotaxus* diterpenoids is attractive due to their characteristic, multicyclic structures and rare distribution. With more and more *Cephalotaxus* diterpenoids found in plants, it was discovered that the troponoid framework unique to the *Cephalotaxus* genus is obviously derived from the cephalotane-type scaffold; specifically, upon the loss of its C-17 position via oxidative decarboxylation. A biosynthetic pathway was postulated that described the troponoids as being derived from pimaranes; however, the absence of real, co-occurring compounds featuring the carbon scaffold of this theoretical the principal intermediate made this proposition less credible (Abdelkafi et al., 2012). The biosynthetic pathways below (Fig. 15), which propose labdane or geranylgeranyl pyrophosphate as precursors, are more convincing (Ni et al., 2016a; b, 2018). Proposed biosynthetic routes for formation of cephalotanins A-D (62–65) and cephafortunoids A-D (66–69) are described as well (Li et al., 2020; Fan et al., 2017; Xu et al., 2016).

##### 6. Conclusion

Based on the literature, chemical structures, total synthesis,

pharmacological effects, SAR and biosyntheses of *Cephalotaxus* diterpenoids were discussed in this review paper. As illuminated in the review, natural cephalotane diterpenoids have become a research hotspot for natural products and organic synthesis chemistry. The *Cephalotaxus* genus is considered a potent resource for discovering and identifying previously undescribed cephalotane diterpenoids. Cephalotane diterpenoids have been reported with excellent antitumor activities. However, although most of these studies were conducted as in vitro assays, little information on the action mechanism has been reported. Furthermore, no in vivo animal studies or clinical trials have been carried out to assess the treatment effects of cephalotane diterpenoids. Further investigations into the antitumor activity of these compounds should be carried out, which could include finding suitable targets to probe the mechanism. Moreover, further investigations should be performed on other species of this genus to enrich the compound library of cephalotane diterpenoids. We hope this review can provide useful information to those who are interested in cephalotane diterpenoids.

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##### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

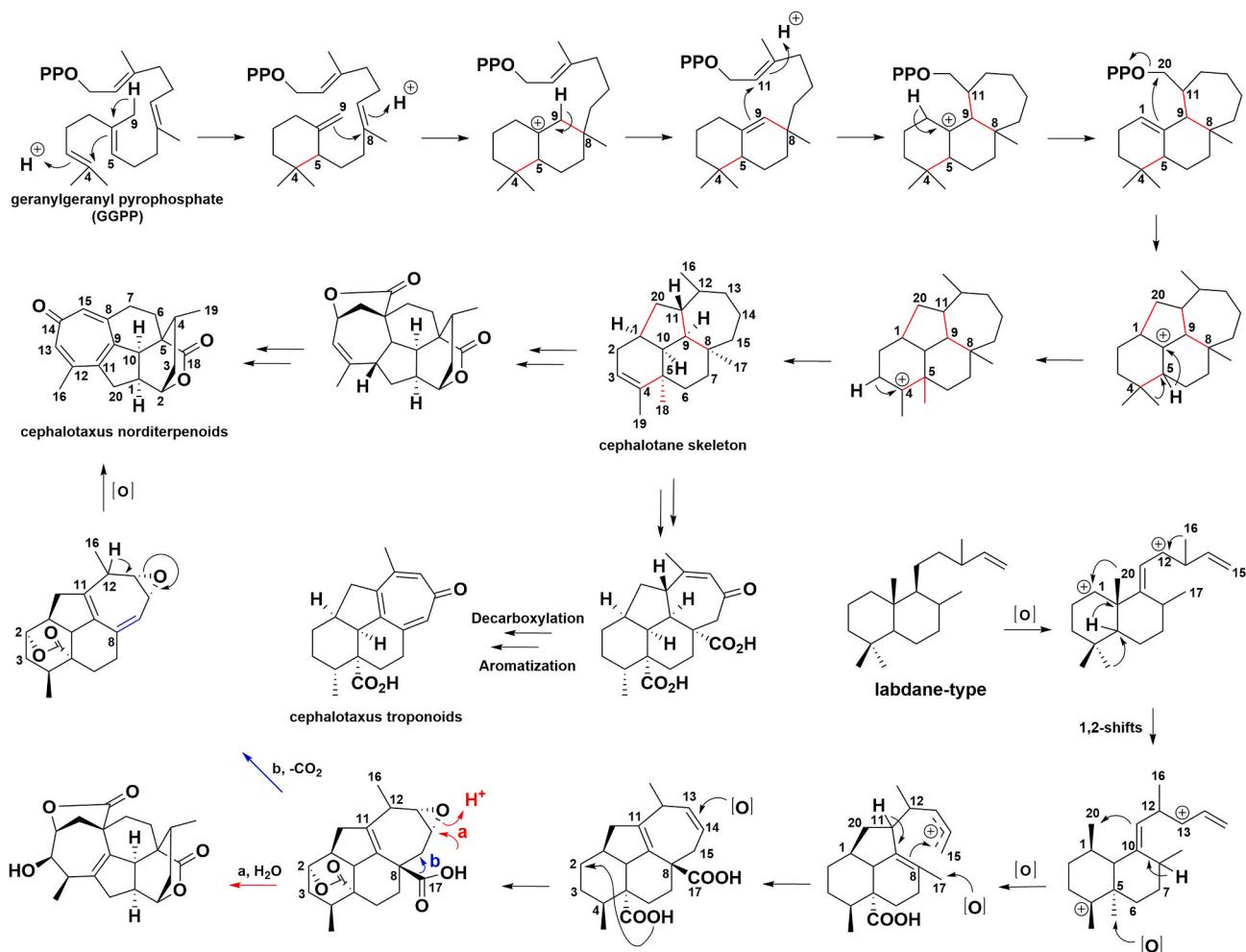


Fig. 15. Plausible biosynthetic pathways of cephalotane diterpenoids.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.phytochem.2021.112939>.

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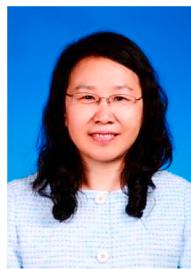
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