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•Review•

Recent advances on the structural modification of parthenolide and its derivatives as anticancer agents

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[ABSTRACT] Parthenolide (PTL) is a sesquiterpene lactone derived from medicinal plant feverfew (*Tanacetum parthenium*). Recent studies have demonstrated that it has multiple pharmacological activities, especially in the treatment of various hematological and solid cancers. The superior anticancer activity of PTL suggests that it has the potential to be a first-line drug. However, due to the limited physical and chemical properties, as well as bioavailability, structural modification strategies are strongly recommended to improve the anticancer activity. This review describes representative PTL derivatives obtained by different modification strategies, which are reported to exert antiproliferative activities superior to the parent compound PTL. Furthermore, we also summarize their basic mechanisms on cancer-related signaling pathways, so as to explain the potential and characteristics of PTL and its derivatives in cancer therapy.

[KEY WORDS] Parthenolide; Derivatives; Structural modification; Anticancer mechanisms
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Introduction

Natural products play a key role in discovering new scaffolds with diverse biological activities that can be directly used [1, 2]. Sesquiterpenes are the most common secondary metabolites derived from plants, and their medicinal values have been confirmed by a large number of basic researches and clinical applications. Previous studies indicated that sesquiterpenes and their derivatives show great therapeutic potential in multiple cancers, and often act as drug candidates in clinical trials to replace conventional chemotherapeutics [3-5]. Parthenolide (PTL) is a germacrane-type sesquiterpene lactone originally purified from the aerial parts of feverfew (*Tanacetum parthenium*). After extraction optimization by Végh *et al*., it can be harvested in large quantities from flower heads (0.604 %) [6, 7]. Although the total synthesis strategy of PTL has been reported, the yield is always unsatisfactory. Therefore, PTL has become one of attractive raw materials [8, 9].

PTL has plent of pharmacological activities, such as antinociception [10], antiinflammation [11], antioxidation [12], as well as antibacterial [13], antiviral [14], antiprotozoan [15], and anticancer effects (Fig. 1) [16, 17]. According to previous investigations, PTL and its derivatives exhibited strong antiproliferative activity against various cancer cell lines including leukemia [18], lung cancer [19], colorectal cancer [20], liver cancer [21], prostate cancer [22], melanoma [23], and osteosarcoma [24]. Furthermore, the combined use of PTL and other types of drugs display great therapeutic potential in overcoming durg resistance of cancer cells and enhancing drug lethality. These encouraging findings promote researchers to conduct more preclinical studies [25].

PTL is confirmed to have a narrow therapeutic window with poor bioavailability. In order to meet the requirements toward druggability and toxicological properties, it is necessary to make structural modifications to develop a series of novel prodrugs. Dimethylamino-PTL (DMAPT) is an effective hydrophilic derivative that have successfully undergone phase I clinical trial in the United Kingdom and primarily used for the treatment of acute myeloid leukemia, acute lymphoblastic leukemia and other types of blood or lymph cancers [26-28]. Although this trial was discontinued in 2017 because of the unknown therapy line and limited indications, this result encourages researchers to comprehensively modify the scaffold and fragment of PTL to discover more suitable drugs.

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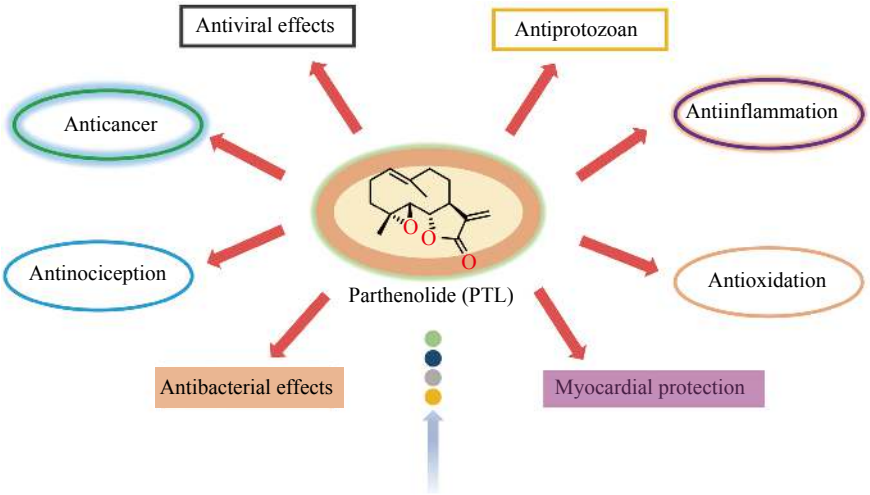


Fig. 1 The identified biological activities of PTL

In this review, we summarized all feasible modification strategies related to PTL, focusing on derivatives with superior anticancer effects reported in the past two decades. Furthermore, we discussed their pharmacological progress in anticancer mechanisms, which may provide guidance for further investigation and development of PTL.

Derivatizations of PTL Scaffold

Structure characteristics such as the C1-C10 double bond, gemmarane scaffold and unsaturated lactone make PTL easy to be modified. Previous studies indicated that the C14 methyl group was easily converted to hydroxy group under the catalysis of selenium dioxide/tert-butyl hydroperoxide or P450 enzyme, which may yield another sesquiterpene lactone, melampomagnolide B (MMB, 2, Fig. 2), a component isolated from *Magnolia grandiflora* [29, 30]. As for the C1-C10 double bond, the addition of *m*-chloroperoxybenzoic acid introduced an epoxy bond to afford product **3**, while 254 nm UV light changed the state of the double bond from the (*E*) configuration to the (*Z*) configuration, and then gave *cis*-geometric isomer product **4** [31]. By contrast, the C11-C13 double bond can be selectively catalyzed by some specific catalysts, followed by harvesting 11,13-dihydroparthenolide (**5**) [31].

Another modification strategy of PTL is to change the reaction conditions, so as to promote electrophilic transannular cyclization/rearrangement. It is reported that natural product micheliolide (MCL, **6**), an excellent PKM2 activator, was prepared with high yield (90%) by adding p-toluenesulfonic acid in dichloromethane [32], or yielded **7** in the presence of strong acid without using methanol as the solvent [33, 34]. Interestingly, PTL was easily converted to a mixture of **5** and **8**−**10** in acidic environment when methanol was selected as the reaction solvent [31, 35].

The development and utilization of natural products requires the reproducibility of chemical methods, the effectiveness of synthetic strategies, satisfactory yield, and the maintenance of pharmacological activities [36, 37]. Various PTL scaffolds have been reported. However, limited by the above factors, the current researches still focus on MMB and MCL. In this review, we divided the existing compounds into three catergories, namely C14 modification, C13 modification and electrophilic transannular cyclization/rearrangment, according to their coorespoding synthetic strategies. To emphasize the contribution of these structural modification, the representative derivatives were demonstrated in detail, while their mechanisms of action and pharmacological activities were discussed.

C-14 Modification of PTL

All the derivatives modified at the C14 position are obtained through the reaction of MMB with the corresponding compounds, and MMB is generated by the allylic oxidation of PTL.

Esterified derivatives modified at the C14 position

Based on base catalysis, the hydroxyl group of MMB forms an ester bond with corresponding carboxylic acid or acid chloride to generate a series of esterified derivatives (Fig. 3). In JANG's work, six carbamate derivatives were designed through reacting *p*-nitrophenoxycarbonyl ester of MMB with various amino compounds to evaluate their anticancer effects against sixty human cancer cell lines. Derivatives **11**−**17** were evaluated as effective NF-*κ*B inhibitors and JNK activators, which reduced glutathione levels, leading to reactive oxygen species-mediated (ROS-mediated) mitochondrial endogenous apoptosis in CCRF-CEM, HOP-92, MDA-MB-435, RXF 393 and MDA-MB-468 cells [38]. Based on the potential biological evaluation results of carbamate derivatives and satisfactory results in *in vitro* screening, Penthala *et al*. synthesized MMB-triazole carbamate intermediate **18.** Product **18** was further optimized to improve chain length and substituents on benzene ring, and the representative derivative **19** was selected among eleven different derivatives and showed submicromolar half inhibitory activities in K-562, HCT-116 and OVCAR-3 cells. In addition, mechanism

studies indicated that **19** strongly reduced the activation of NF-*κ*B and prevented NF-*κ*B-DNA binding [39]. To increase the content of esterified derivatives, Tyagi and his coworkers introduced a series of aromatic fragments through chemoenzymatic synthesis on C-14 modification. Although this strategy brought unpredictable cytotoxicity, it greatly enriched the types of PTL derivatives. It should be noted that derivatives **20**−**22** exhibited moderate potential against M9-

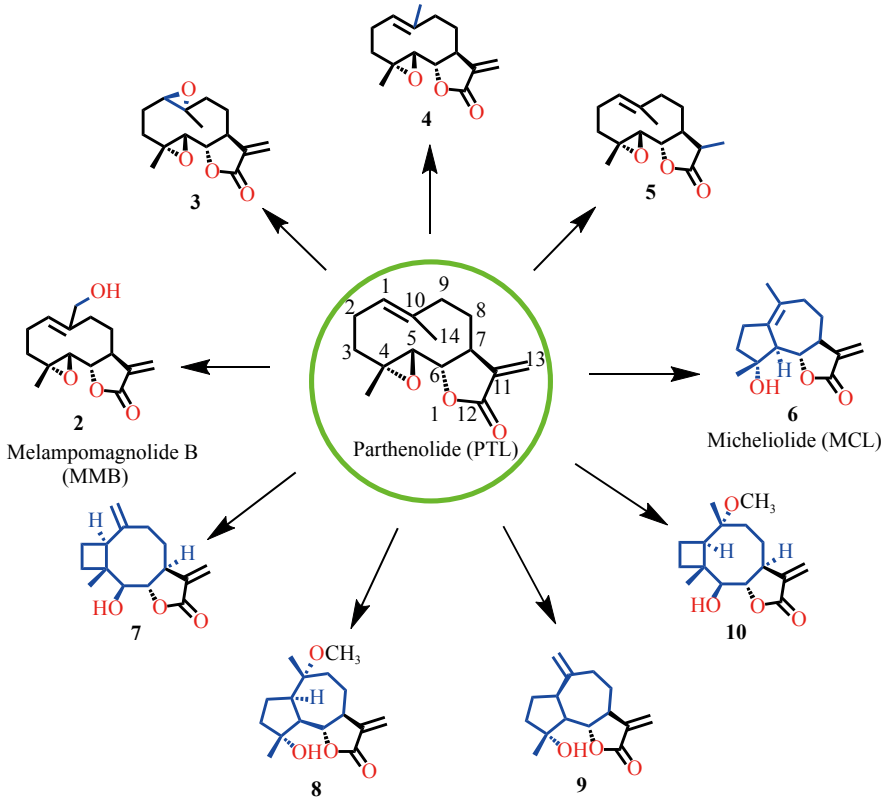
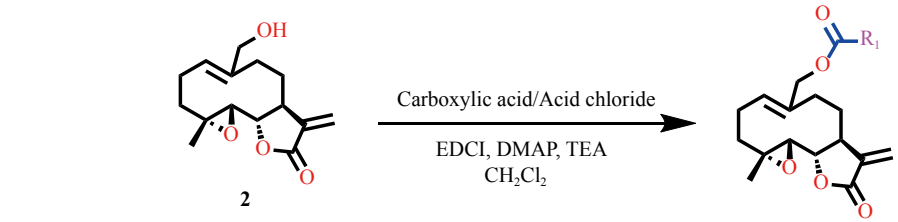


Fig. 2 The reported PTL scaffold derivatives 2−10



R_1=

11
IC_{50}^{a} = 0.68 μmol·L^{-1}
IC_{50}^{b} = 1.45 μmol·L^{-1}
IC_{50}^{c} = 0.46 μmol·L^{-1}
IC_{50}^{d} = 1.20 μmol·L^{-1}
IC_{50}^{e} = 0.57 μmol·L^{-1}

12
IC_{50}^{a} = 2.49 μmol·L^{-1}
IC_{50}^{b} = 2.25 μmol·L^{-1}
IC_{50}^{c} = 6.56 μmol·L^{-1}
IC_{50}^{d} = 4.08 μmol·L^{-1}
IC_{50}^{e} = 2.30 μmol·L^{-1}

13
IC_{50}^{a} = 2.65 μmol·L^{-1}
IC_{50}^{b} = 2.25 μmol·L^{-1}
IC_{50}^{c} = 6.01 μmol·L^{-1}
IC_{50}^{d} = 2.22 μmol·L^{-1}
IC_{50}^{e} = 3.22 μmol·L^{-1}

14
IC_{50}^{a} = 3.03 μmol·L^{-1}
IC_{50}^{b} = 2.30 μmol·L^{-1}
IC_{50}^{c} = 5.89 μmol·L^{-1}
IC_{50}^{d} = 3.00 μmol·L^{-1}
IC_{50}^{e} = 3.26 μmol·L^{-1}

15
IC_{50}^{a} = 0.62 μmol·L^{-1}
IC_{50}^{b} = 0.65 μmol·L^{-1}
IC_{50}^{c} = 2.24 μmol·L^{-1}
IC_{50}^{d} = 0.90 μmol·L^{-1}
IC_{50}^{e} = 1.29 μmol·L^{-1}

16

17

18

19
IC_{50}^{f} = 0.37 μmol·L^{-1}
IC_{50}^{g} = 0.24 μmol·L^{-1}
IC_{50}^{h} = 0.28 μmol·L^{-1}

20
IC_{50}^{i} = 3.8 μmol·L^{-1}

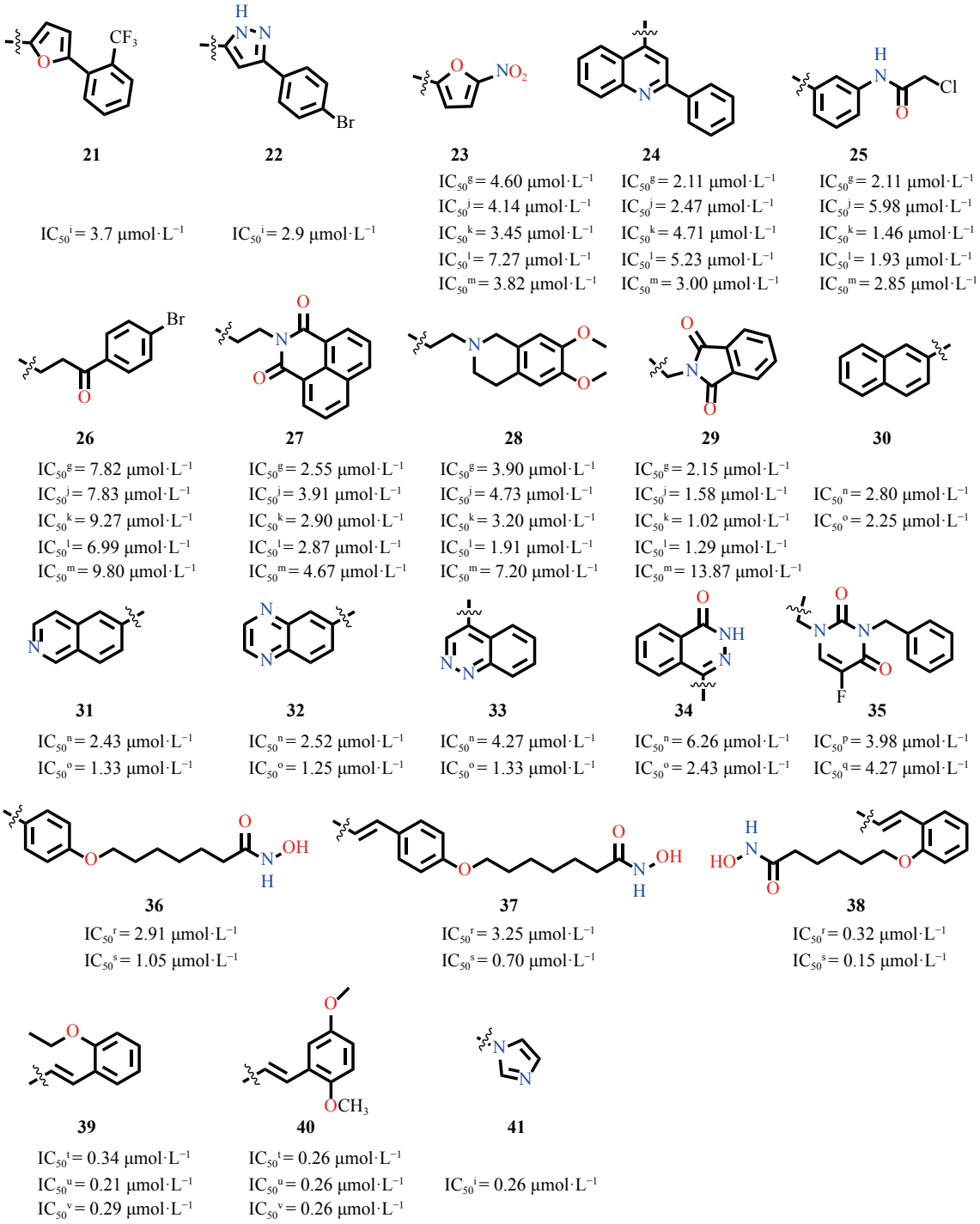


Fig. 3 Esterified derivatives 11−41 modified at the C14 position. IC_{50}^{a}: CCRF-CEM, IC_{50}^{b}: HOP-92, IC_{50}^{c}: MDA-MB-435, IC_{50}^{d}: RXF 393, IC_{50}^{e}: MDA-MB-468, IC_{50}^{f}: K-562, IC_{50}^{g}: HCT-116, IC_{50}^{h}: OVCAR-3, IC_{50}^{i}: M9-ENL1, IC_{50}^{j}: U87MG, IC_{50}^{k}: HepG2, IC_{50}^{l}: BGC823, IC_{50}^{m}: PC9, IC_{50}^{n}: HT29, IC_{50}^{o}: SW480, IC_{50}^{p}: Bel-7402, IC_{50}^{q}: Bel-7402/5-FU, IC_{50}^{r}: HL-60, IC_{50}^{s}: HL-60/ADR, IC_{50}^{t}: MDA-MB-231, IC_{50}^{u}: SUM-159, and IC_{50}^{v}: MCF-7

ENL1 cells, without adverse reactions on healthy blood cells at therapeutic doses [40]. ZENG *et al*. supplied another thirty-five kinds of aromatic fragments, where the most active derivatives **23**−**29** acted as both NF-*κ*B and STAT3 inhibitors, and exerted excellent cytotoxicity against HCT116, U87MG, HepG2, BGC823 and PC9 cell lines [41]. To harvest more attractive derivatives, a series of activators targeting PKM2 were designed by LIU *et al*., obtaining the representative derivatives **30**−**34** with good cytotoxic activity against HT29 and SW480 cells.

Drug resistance of cancer cells often occurs after long-term treatment of a single chemotherapeutic agent. Multi-tar-

get therapy can overcome this problem, such as splicing the active fragments of different drugs into a structure. To treat 5-FU resistant tumors, DING *et al*. conjugated PTL and 5-FU analogs to obtain a variety of derivatives, where the most promising product **35** exerted highly potent inhibitory activity against Bel-7402 and Bel-7402/5-FU cell lines by reducing MDR1, ABCC1 and ABCG2, while the accumulation of intracellular drug **35** led to apoptosis through the mitochondrial pathway [42]. Based on the dual target strategy, GE and coworkers reported PTL-SAHA derivatives, the representative hybrids **36**–**38** showed excellent activity in HL-60 and HL-60/ADR cell lines, and promoted cell apoptosis by decreasing the expression of HDAC1, HDAC6 and ABCC1 [43]. To overcome acquired drug resistance in triple-negative breast cancer patients, a series of cinnamic acid fragments were developed, where derivatives **39** and **40** had antiproliferative activity more than ten times higher than PTL, blocking G_1 phase and inducing apoptosis *via* the mitochondrial pathway in MDA-MB-231, SUM-159 and MCF-7 cells [44].

Although the reported PTL ester derivatives show promising therapeutic potential, the metabolic stability of ester bonds *in vivo* is an inherent and non-negligible risk. To assess the metabolic characteristics of these compounds, product **41** was orally or intravenously injected in BALB/c mice to evaluate for its bioavailability. It was demonstrated that the absolute plasma bioavailability of **41** (45.5% ± 2%) was much higher than that of starting compound **3** (6.7% ± 0.8%), which indicated that the ester derivatives of PTL may be used as clinical candidates [45].

O-alkylation derivatives modified at the C14 position

Introducing alkyl groups on alcoholic hydroxyl groups can improve the pharmacokinetics properties of derivatives (Fig. 4). Tyagi *et al*. inserted carbenoids into O–H bond, using rhodium as the catalyst. Among the synthesized derivatives, products **42** and **43** exhibited slightly low micromolar activity in M9-ENL1 cells and AML01 specimens [40]. Based on the promising anticancer potential shown by ether derivatives, in Alwaseem's working, the same strategy was appied to design derivatives **44**–**48** with high cytotoxicity against Jurkat, JeKo-1 and HeLa cells [29]. YANG *et al*. used silver oxide as the catalyst and corresponding alkyl halides to carry out the alkylation reaction, and the representative derivatives **49** and **50** were prepared, exhiting excellent activity against KG1a and HL-60 cells [46].

Triazole derivatives modified at the C14 position

Adding $CuSO_4$ and sodium ascorbate to promote the Click reaction is a commonly construction method to yield new compounds. In the presence of diphenyl azidophosphate and 1,8-diazabicyclo[5.4.0]undec-7-ene, MMB is converted to azide product **51** (Fig. 5) through Mitsunobu reaction, which provides a new strategy for designing triazole PTL derivatives. DING and coworkers first reported plentiful

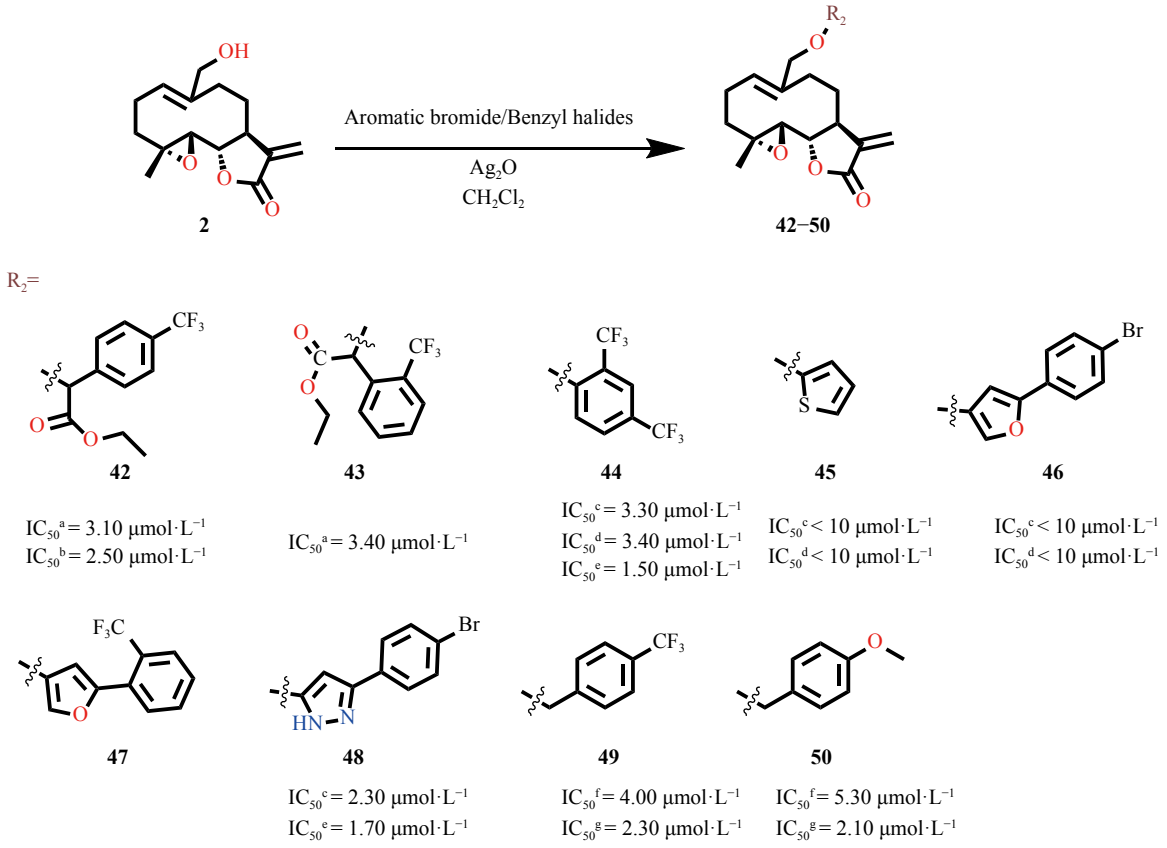


Fig. 4 O-alkylation derivatives 42–50 modified at the C14 position. IC_{50}^a: M9-ENL1, IC_{50}^b: AML01 specimen, IC_{50}^c: Jurkat, IC_{50}^d: JeKo-1, IC_{50}^e: HeLa, IC_{50}^f: KG1a, and IC_{50}^g: HL-60

triazole derivatives, but the antiproliferative activity of azide derivatives **52**−**54** were not fully improved compared with the stating compound PTL against Bel-7402 and Bel-7402/5-FU cells [42]. To get more derivatives with potent anticancer effects, Janganati *et al*. synthesized 22 triazole derivatives, where **55**−**61** showed superior cytotoxicity in most of 60 cancer cell lines [47].

Aldehyde and carboxylic acid derivatives modified at the C14 position

In ZHANG's working, MMB is further oxidized to generate aldehyde product **62** (Fig. 6) *via* Dess-Martin oxidation reaction, before reaction with 2-aminobenzenethiol to obtain product **63** or oxidation by sodium hypochlorite to afford carboxylic acid product **69**, which then react with corresponding amine-based and ester-based compounds to provide additional derivatives **70**−**72** or **73** and **74** [46, 48]. To investigate the SAR between the substituents of semicarbazides or thiosemicarbazides, JIA *et al*. synthesized 21 derivatives by refluxing semicarbazide or thiosemicarbazide fragments with derivative **62** under acetic acid conditions. Derivatives **64**−**68** exhibited superior antiproliferative activity in HCT116, U87-MG, HepG2, BGC823, and PC9 cells, as well as MC38-bearing mice [49].

C-13 Modification of PTL

Heck coupled derivatives modified at the C13 position

Pnthala *et al*. initially synthesized E-olefinic coupled derivatives by utilizing Heck reaction. In brief, under the catalysis of palladium (II), PTL was coupled with appropriate iodo-aromatic or iodo-heteroaromatic compounds in the presence of di-isopropylethyl-amine to prepare derivatives **75**−**81** (Fig. 7), which were considered to regulate cell cycle and affect the growth of multiple cancer cells [50]. In LIU's working, the antiproliferative activity of heterocycle derivatives **82** and **83** were superior to that of **84** and **85** in HT29 and SW480 cells, and theses activities were eventually confirmed to be independent of the interaction between the ligand and PKM2 [48].

Michael addition derivatives modified at the C13 position

Michael addition reaction of α-methylene-γ-lactone with nucleophilic amino or sulfhydryl occur in the presence of metal or organic catalyst in alkaline condition [51]. To improve the solubility and safety of PTL, a dimethylamino product **86** (Fig. 8) was synthesized to cater for clincial demand [27]. Based on this finding, Neelakantan and coworkers developed a series of linear or cyclic PTL amine derivatives,

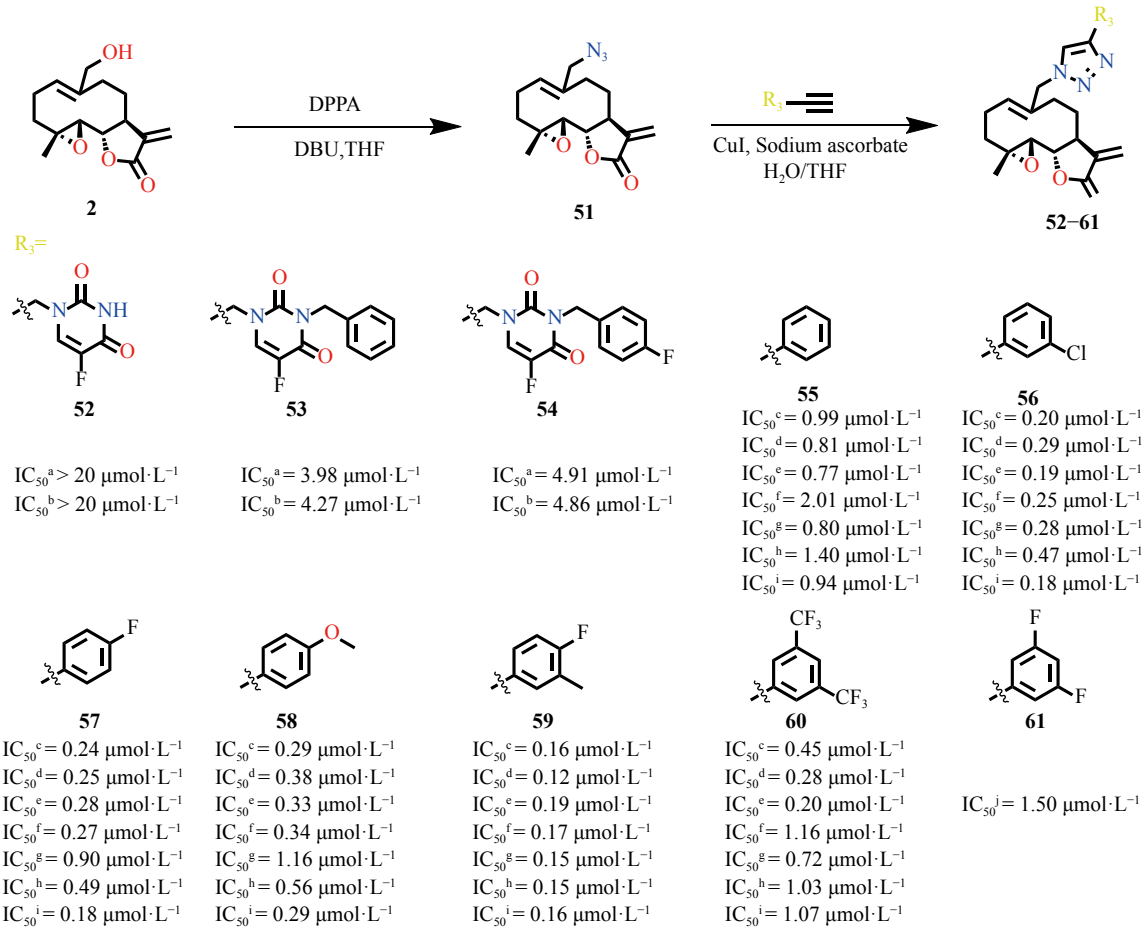


Fig. 5 Triazole derivatives 51−61 modified at the C14 position. IC_{50}^{a}: Bel-7402, IC_{50}^{b}: Bel-7402/5-FU, IC_{50}^{c}: CCRF-CEM, IC_{50}^{d}: NCI-H522, IC_{50}^{e}: HCT-15, IC_{50}^{f}: SF-539, IC_{50}^{g}: LOX IMVI, IC_{50}^{h}: OVCAR-3, IC_{50}^{i}: ACHN, and IC_{50}^{j}: M9-ENL1

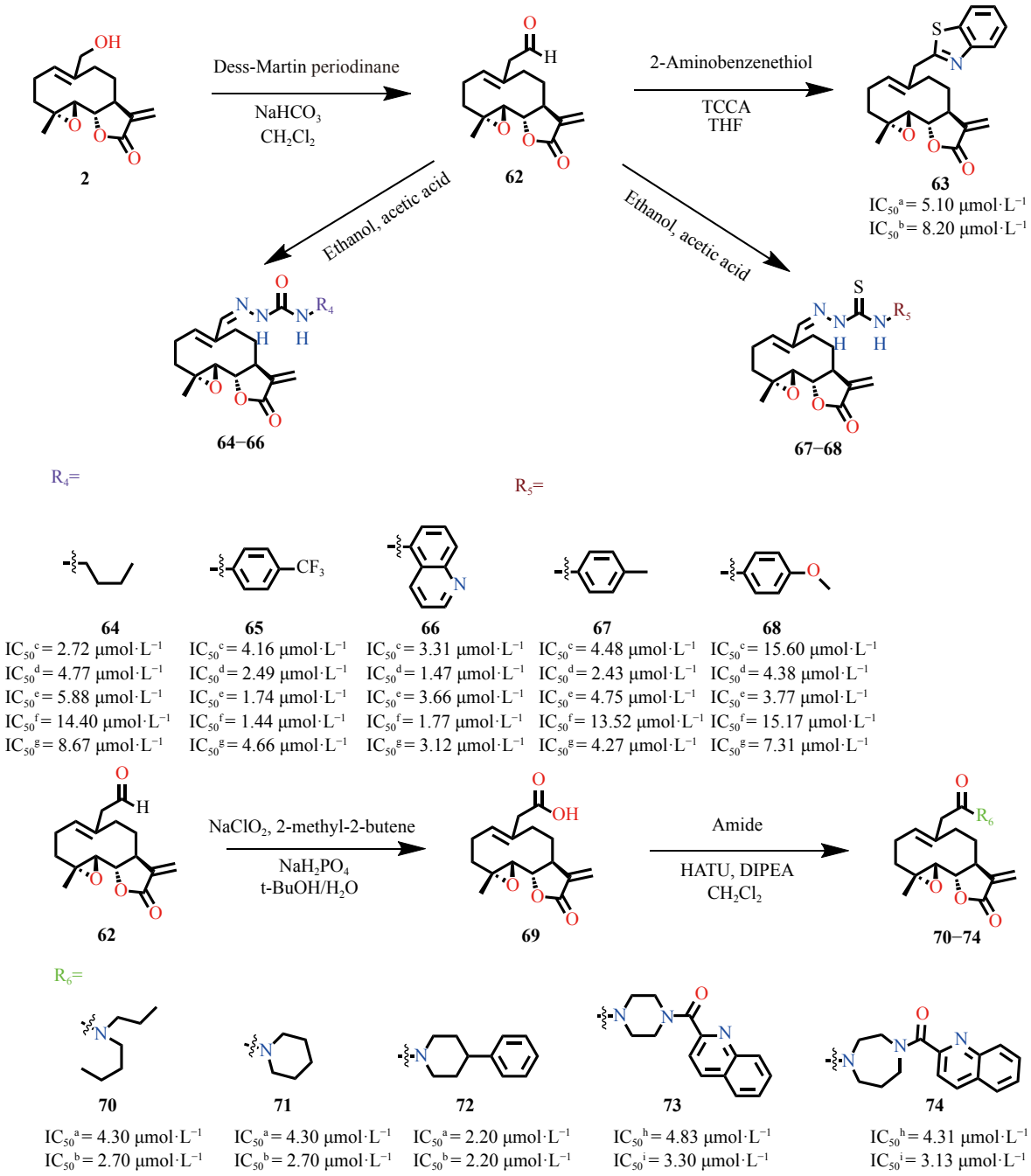


Fig. 6 Aldehyde derivatives 62−68 and carboxylic acid derivatives 69−74 modified at the C14 position. IC_{50}^{a}: KG1a, IC_{50}^{b}: HL-60, IC_{50}^{c}: HCT116, IC_{50}^{d}: U87-MG, IC_{50}^{e}: HepG2, IC_{50}^{f}: BGC823, IC_{50}^{g}: PC9, IC_{50}^{h}: HT29, and IC_{50}^{i}: SW480

where derivatives **87**−**89** exhibited good anti-leukemia activity with low ID_{50} values aganist primary AML cells from patients [34]. To diversify the types of amine derivatives, Crooks *et al*. prepared derivatives **90**−**97** by introducing several nucleophilic primary and secondary amine fragments, which was complemented in Moumou's research [52, 53]. In a mechanism study of C13 modified derivatives, Janganati *et al*. reported derivatives **98** and **99**, and their further studies showed that amino derivatives modified at the C13 position regulated G_2/M cell cycle progression in *Xenopus* oocyte maturation [54]. Taleghani *et al*. introduced cytarabine and melphalan into *α*-methylene-*γ*-lactone to obtain parthabine **100** and parthalan **101**. Derivatives **100** and **101** overcame the loss of anticancer effects caused by the addition of azamichael, while showing significant cytotoxicity against CHO, HepG2, LNcaP, and MCF-7 cells. The cytotoxicity caused by these two derivatives was thought to be associated with inhibiting the transcription of major genes involved in the proliferation, inflammation and anti-apoptosis and depleting glutathione levels in cancer cells [55, 56]. LI *et al*. screened the library of amino derivatives by determining pKa, cLogD, cLogP, and TPSA. In addition, the stability of these compounds

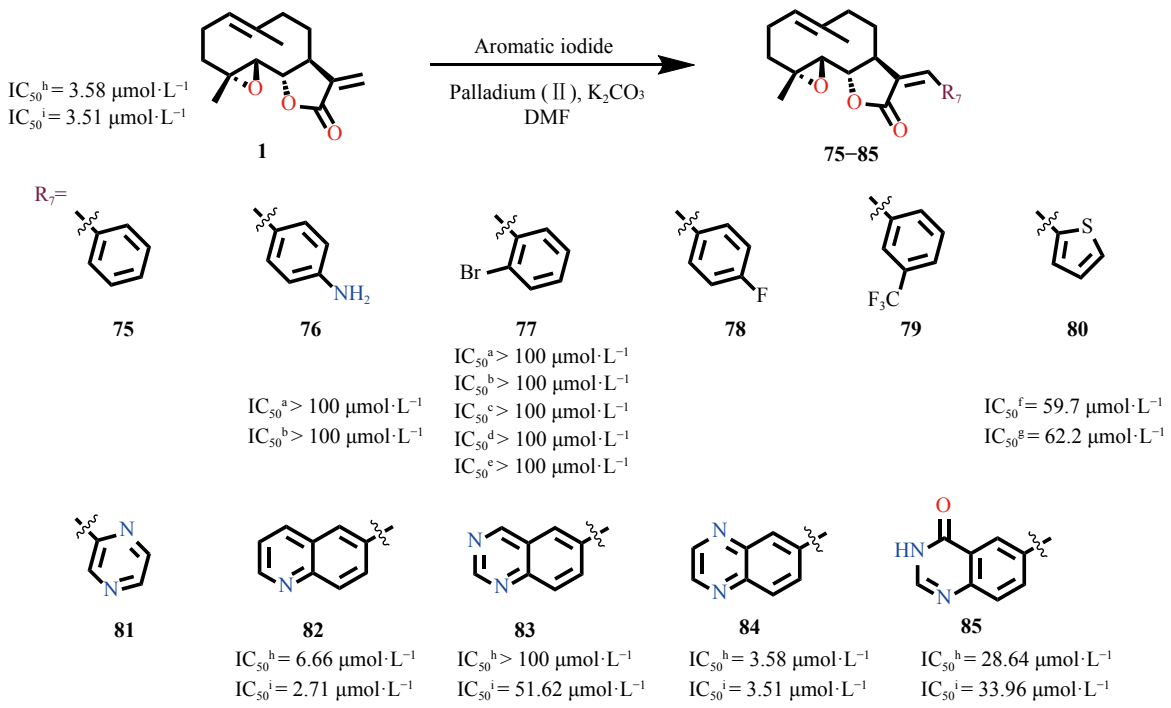


Fig. 7 Heck coupled derivatives 75−85 modified at the C13 position. IC_{50}^{a}: MOLT-4, IC_{50}^{b}: PC-3, IC_{50}^{c}: CCRF-CEM, IC_{50}^{d}: HL-60, IC_{50}^{e}: RPMI-8226, IC_{50}^{f}: NCI-H522, IC_{50}^{g}: SF-539, IC_{50}^{h}: HT29, and IC_{50}^{i}: SW480

in solution, microsomes and hepatocytes, as well as Caco-2 permeability were evaluated, and product **102** was picked out as the most promising prodrug [57]. Sulfhydryl groups have the ability to add to unsaturated double bonds. DING and coworkers prepared several PTL dithiocarbamate ester derivatives, and demonstrated that the antiproliferative mechanism of derivatives **103**−**105** was activation of p38 and JNK by inhibited total and phosphorylated ERK1/2. Furthermore, compound **105** extended the lifespan of a patient-derived xenograft model mice, without significant toxicity [58].

Electrophilic Transannular Cyclization/rearrangment of MCL Derivatives

MCL derivatives substituted at 4-hydroxyl

Previous studies indicated that PTL was converted to MCL (**6**) with high yield (90%) [32, 59]. MA *et al*. synthesized a series of etherified and esterified MCL derivatives at the C4 position (Fig. 9), and found that only derivatives **106**−**108** maintained stronger antiproliferative activity than the parent compound against AML cell lines HL-60, HL-60 and KG-1a, which suggested that the C4 hydroxyl group of MCL might not be a suitable position for structural modification [60].

MCL derivatives modified at the C9 position

To explore more suitable substitution sites, ZENG and coworkers reported a large number of derivatives modified at the C9 position, where the representative derivatives **109**−**125** (Fig. 10) were evaluated in HCT116, U87MG, HepG2, BGC823 and PC9 cells by MTT assay [41].

MCL derivatives modified at the C14 and C2 positions

To overcome the obstacles of late-stage derivatization caused by MCL, P450-mediated chemoenzymatic synthesis was conducted to develop novel derivatives substituted on the C2, C4, and C14 positions. Ackun-Farmmer *et al*. reported a series of novel derivatives substituted at the C2 and C14 positions, and found that the cytotoxicity of most derivatives **126**−**129** and **133**−**134** (Fig. 11) increased more than two-fold than that of MCL [61]. In Alwaseem's report, they screened the enzymes with high selectivity and catalytic efficiency from more than 800 P450 variants for subsequent modification, and **130**−**132** and **135**−**136** were selected from 34 derivatives with ID_{50} values far less than 20 μmol·L^{-1} against various of leukemia cells, as well as patient specimens [62]. Although there were some reports concerning the Heck derivatives of MCL, these derivatives were not listed because of the unideal antiproliferative activity.

The Structure-activity Relationship (SAR) of PTL

Researchers conducted numerous studies to improve the water solubility, metabolic stability and anticancer effects of PTL. To briefly illustrate these contributions, we summarized the SAR of PTL. As shown in Fig. 12, the specific modification positions and associated anticancer effects are highlighted. The changed sites of PTL can be roughly divided into four categories. First, the C11-C13 double bond is identified as the core part. Apart from modifying PTL as a prodrug, modification at the C13 position may destroy the double bond, which will be detrimental to antiproliferative activity. As Heck addition at this position results in a complete loss of activity of the products, Michael addition appears to be more beneficial. Moreover, bioactivity data indicated that Michael addition products obtained by introducing short aliphatic chains are almost superior to those harvested by introducing

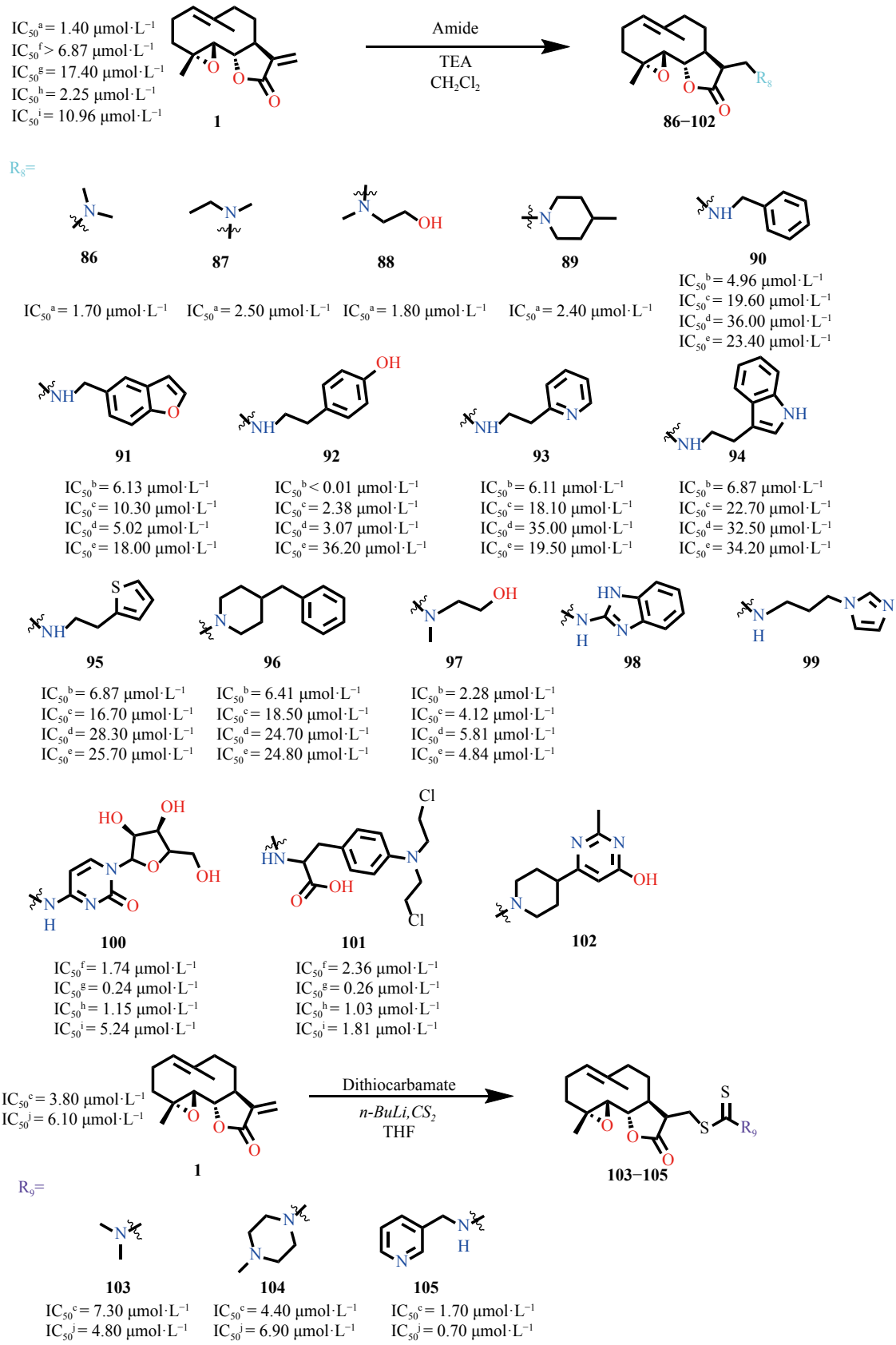


Fig. 8 Michael addition derivatives 86−105 modified at the C13 position. IC_{50}^{a}: AML cells from patients, IC_{50}^{b}: CCRF-CEM, IC_{50}^{c}: HL-60, IC_{50}^{d}: K-562, IC_{50}^{e}: MOLT-4, IC_{50}^{f}: CHO, IC_{50}^{g}: Hep G2, IC_{50}^{h}: LNcaP, IC_{50}^{i}: MCF-7, and IC_{50}^{j}: KG1a

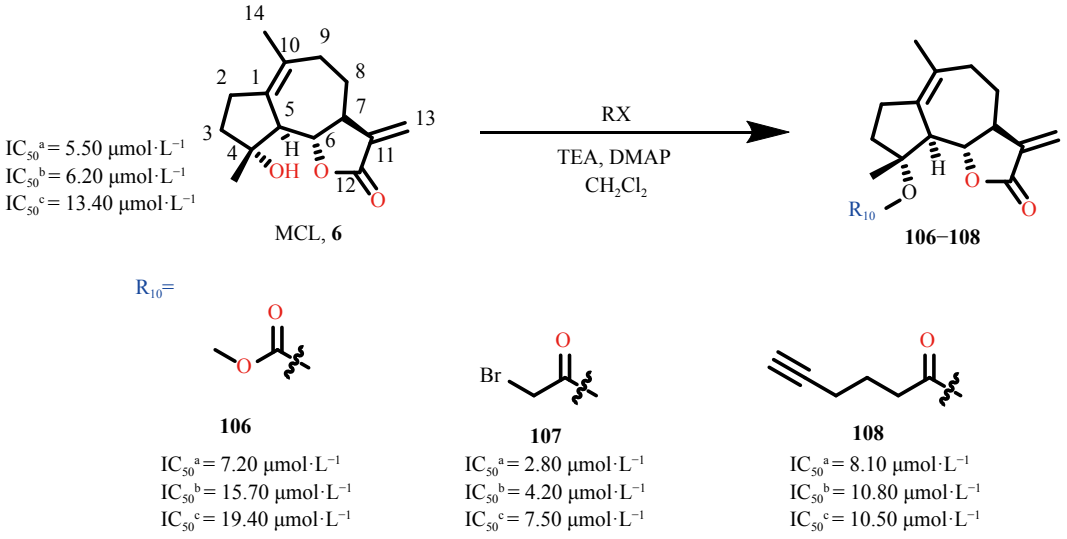


Fig. 9 MCL derivatives 106−108 substituted at 4-hydroxyl. IC_{50}^{a}: HL-60, IC_{50}^{b}: HL-60/A, and IC_{50}^{c}: KG-1a

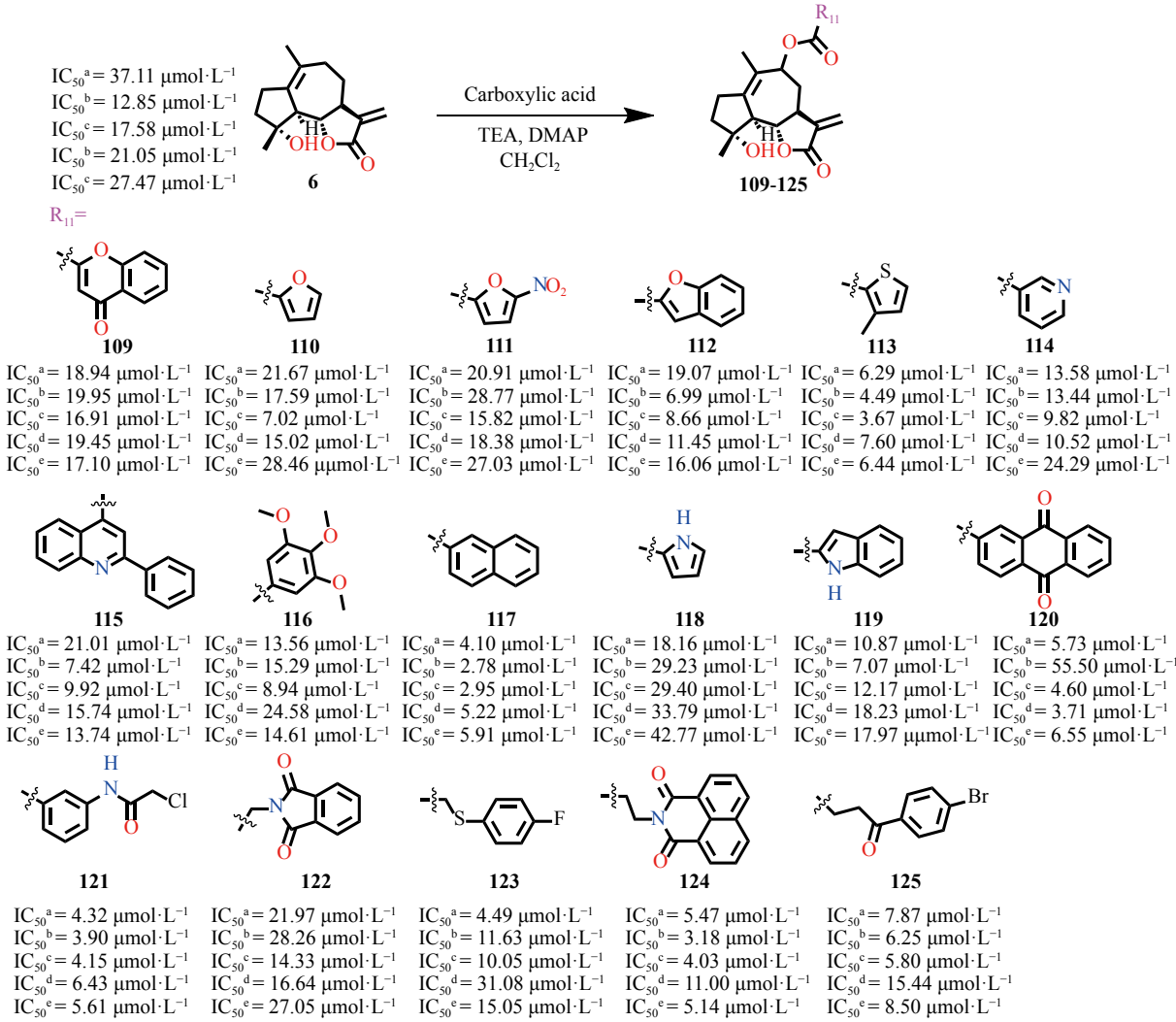


Fig. 10 MCL derivatives 109−125 modified at the C9 position. IC_{50}^{a}: HCT116, IC_{50}^{b}: U87MG, IC_{50}^{c}: HepG2, IC_{50}^{d}: BGC823, and IC_{50}^{e}: PC9

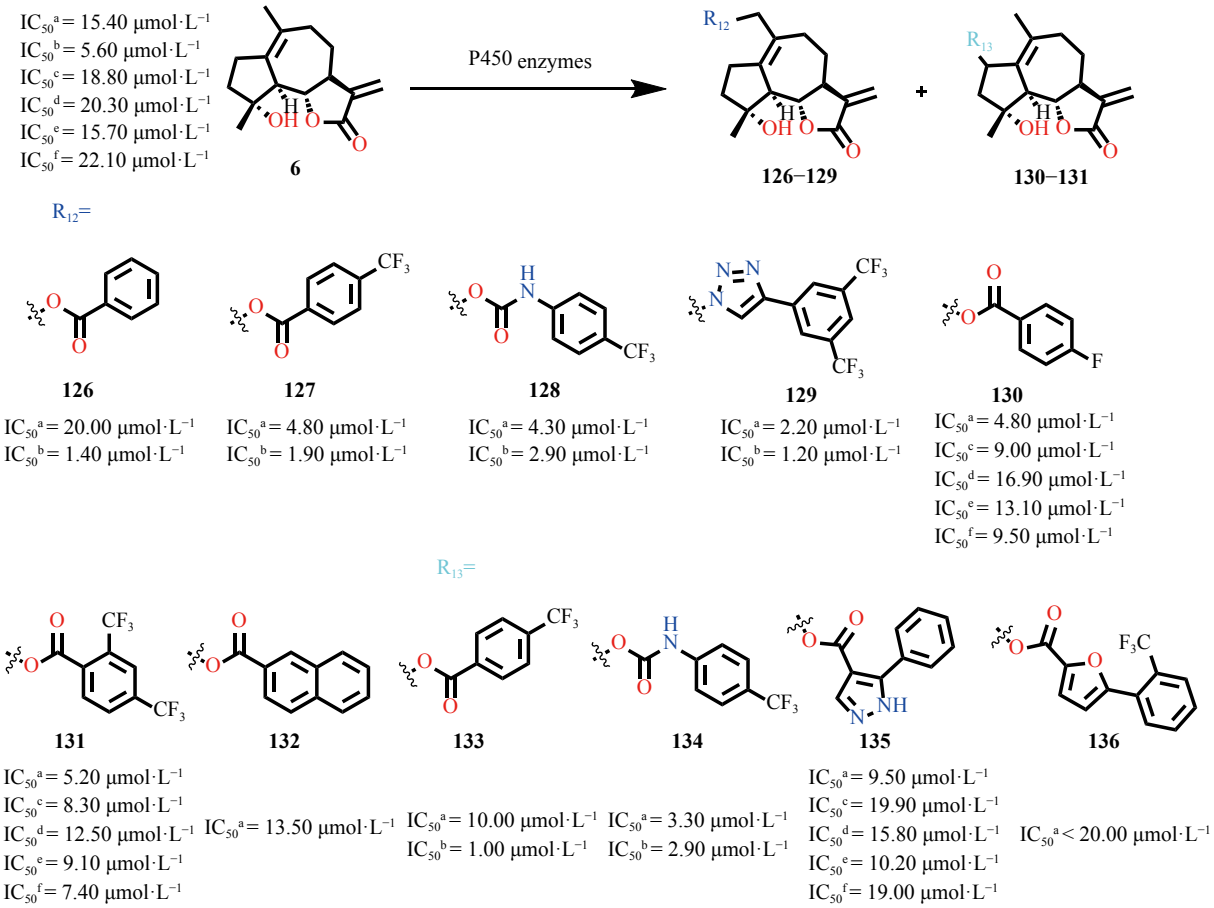


Fig. 11 MCL derivatives 126−136 modified at the C14 and C2 positions. IC_{50}^{a}: M9-ENL1, IC_{50}^{b}: MV-411, IC_{50}^{c}: AML01 specimen, IC_{50}^{d}: AML02 specimen, IC_{50}^{e}: AML03 specimen, and IC_{50}^{f}: AML04 specimen

long aliphatic, aromatic or heterocyclic chains [50, 58, 63]. Second, modification at the C14 position is an optional derivation strategy. Whether introducing rigid or flexible groups at this site, most of products including esterified, etherified, azide and carboxylic acid derivatives are reported to have strong anticancer activity. It should be noted that introduction of strong electron-withdrawing groups, especially halogens such as bromine and fluorine, enhances the cytotoxicity of the derivatives [46, 48]. Third, the change of the C1-C10 double bond greatly enrichs PTL derivative library. However, the effect of such a modification strategy on antiproliferative activity is unclear [48, 53, 64]. Finally, the effect of modifying the C4-C5 epoxy bond is uncertain, as the antiproliferative activity of these derivatives synthesized *via* this route varied in different cancer cells.

The ten-membered ring of PTL can be rearranged to generate a novel derivative (MCL) when attacked by protons. In order to further illustrate the potential of this derivative, we comprehensively described the SAR of MCL. The C11-C13 double bond of MCL is indispensable, and all the derivatives modified at the C13 position do not contribute to anticancer effects [65]. The C4 hydroxyl group of MCL has been extensively modified, including exploring different condensation reactions, changing chain lengths and introducing different monocyclic and heterocyclic fragments. However, modifications on this position are not recommended due to a low yield and poor antiproliferative activity of the products [41]. Modifications at the C2, C9 and C14 positions can be achieved through P450-mediated chemoenzymatic synthesis. For modification at the C9 position, only ester synthesis reaction is covered, while introduction of a benzene ring and electron-withdrawing groups generally lead to an increase in the antiproliferative activity of the product [41]. For products modified at the C2 and C14 positions, most of these products have stronger cytotoxicity than MCL, amd preparation of fluorine-containing aromatic derivatives is the best choice to improve the activity [61, 62].

Anticancer Mechanisms of PTL and Its Derivatives

As an important active ingredient in feverfew, PTL exerts anticancer effects through a variety of pharmacological mechanisms. However, these complex anticancer mechanisms are not conducive to the subsequent development. To achieve precision anticaner therapy, appropriate structural modification strategies are required based on the existing targets, and one of the common approach is to introduce more potent fragments [66]. Given the previous summary of PTL as an anticancer agent [67], we categorized the recently reported targets of PTL and its derivatives related to anticancer effects, and discussed the underlying mechanisms of these targets, so

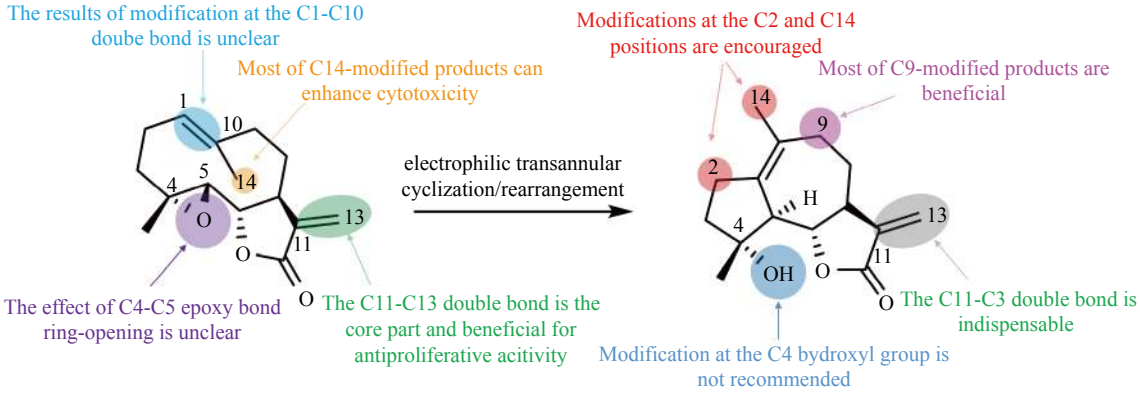


Fig. 12 The major structure-activity relationship of PTL and MCL. Left: PTL and Right: MCL

as to provide guidance for further research of PTL.

Tubulin carboxypeptidase inhibitor

The homeostasis of tubulin is the basis of multiple cellular functions including division, mitosis, and signal transduction [68]. Tubulin homeostasis is regulated by tubulin carboxypeptidase (TCP) and tubulin tyrosine ligase (TTI) [69]. Tubulin inhibitors are able to interfere the structure and dynamics of cytoskeleton, disrupt mitotic spindles formation, and block cell cycle to induce cell apoptosis [70]. In 2007, PTL was identified as a powerful TCP inhibitor that reduced the abnormal tubulin accumulation, which was proved to be independent of NF-κB expression [71, 72]. The synthesis of PTL analogs indicated that the epoxidation of C4-C5 was the crucial factor to maintain the inhibitory activity of TCP [59], which was further confirmed by mass spectrometry to form PTL-tubulin covalent adducts to block tubulin detyrosinylation and indirectly reduce polymerization-competent pool [73].

TrxR inhibitor

As an important part of thioredoxin system, thioredoxin reductase (TrxR) plays a key role in regulating redox signaling pathways and maintaining intracellular redox homeostasis [74]. TrxR is considered as a crucial factor in cancer adaptation and development and overexpressed in nearly all types of cancers [75]. Several TrxR inhibitors have been reported to treat redox-sensitive cancers [76-78]. Previous studies indicated that PTL promoted the modification of surface protein thiols and inhibited the production of thiols [79, 80]. In recent years, PTL has been demonstrated to selectively inhibit selenocysteine residues in TrxR1, leading to the sensitization of HeLa cells without altering thiol homeostasis [81]. In addition, chemical modification methods confirmed that unsaturated lactone ring is a vital reactive group for PTL and its derivatives **39** and **40** to maintain thiol reactivity [44, 82].

JAK inhibitor

For PTL, inhibition of the STAT3 signaling pathway is attributed to JAK targeting [83]. The activation of the JAK/STAT3 axis contributes to the establishment and metastasis of cancer [84]. PTL was confirmed by mass spectrometry as a covalent JAK inhibitor that bound to the FERM-SH2 domains (Cys178, Cys243, and Cys480) of JAK to induce cell apoptosis in human hepatocellular carcinoma cells [21, 85].

EGFR inhibitor

EGFR is a crucial driving factor in tumorigenesis [86]. PTL was discovered to affect EGFR by stimulating the generation of superoxide anion and ROS [87]. Furthermore, inhibition of EGFR by PTL and its Heck products **75**−**81** suppressed the PI3K/AKT and MEK/ERK signaling pathways, while some of them exhibited strong antiproliferative properties against H1975 xenograft tumor [50, 88]. In addition, the protocol for preparing paclitaxel and PTL co-loaded EGFR-targeted delivery system was shown to have higher intracellular delivery capacity and could be used for the treatment of paclitaxel-resistant A549-T24 cells [89].

PKM2 activator

Previous studies suggested that targeting energy metabolism is a promising strategy for cancer therapy [90]. PKM2 activator was demonstrated to change the metabolic state from aerobic glycolysis to oxidative phosphorylation, while preventing the translocation of PKM2 dimers to the nucleus to inhibit the expression of transcription factors associated with proliferation and metastasis [91, 92]. PTL and its derivative MCL were identified as the first class of covalent activators, which effectively inhibited the nucleus translocation of PKM2 and suppressed the PKM2-STAT3 signaling pathway against glioblastoma multiforme by covalent binding on C424 of PKM2 [30, 93]. Based on the relationship between PTL and PKM2, Liu and coworkers developed a series of heterocycle derivatives **30**−**34** and **73**−**74**, and demonstrated that introduction of heterocycle fragments, especially quinoline at the C14 position enhanced the interaction of the derivatives and PKM2 through SAR study, and the optimal derivative showed strong inhibitory effect against HT29 xenograft tumor [48].

NF-κB inhibitor

The NF-κB signaling pathway is demonstrated to change the expression and transformation of angiogenic and tumorigenic chemokines to promote the proliferation, metastasis and drug resistance of cancer cells [94-96]. The role of PTL and its soluble derivative as NF-κB inhibitors were discussed in previous studies [67, 97]. Thus, in this review, we simply emphasized the recent advances. PTL was subsequently revealed to disrupt the interaction of NF-κB and β-catenin, leading to the activation of β-catenin, reducing osteoclast precursors adhesion and diffusion, and decreasing the survival of mature osteoclasts [95, 98]. PTL was demonstrated to inhibit angiogenesis through suppressing the NF-κB/AP-1/VEGF signaling

pathway to attenuate the growth of Eca109 xenograft [99]. In addition, MCL, PTL derivatives **11**−**17**, **19** and **23**−**29** were also reported to inhibit NF-κB activity [38, 39, 41].

Other mechanisms associated with anticancer effects

Other important anticancer mechanisms of PTL and its derivatives are illustrated in Table 1.

Table 1 The reported anticancer targets and mechanisms of PTL and its derivatives

Compd.	Cell lines	Mechanisms of action	Ref.
PTL	HeLa; U2OS; CHL-1	TCP ↓	[71, 73]
PTL, **39**, **40**	Granta-519; HeLa; HepG2; HL-60; SUM-159; MCF-7	Thiols ↓; TrxR1 ↓	[44, 81]
PTL	MDA-MB-231; and Du 145	JAK1↓; JAK2 ↓; STAT3 ↓	[21, 83-85]
PTL, **75**−**81**	H1975; PC-9; HCC829; A549; A549-T24	EGFR ↓; PI3K/AKT ↓; MEK/ERK ↓	[50, 87-89]
PTL	GLC-82; H1650; and H1299	BRAF ↓; MAPK/Erk ↓; c-Myc ↓	[100]
MCL, PTL, **30**−**34**, **73**−**74**	HL-60; KG-1a; U87; U118; C6; SW480; HT29	PKM2 tetramer ↑; PKM2 dimier ↓; STAT3 ↓; c-Caspase 3 ↑; c-PARP ↑	[30, 48]
PTL, MCL, **11**−**17**, **19**, **23**−**29**, **55**−**61**, **86**	4T1-BT2; Mat-LyLu; Eca109; KYSE-510; HCT116; U87MG	NF-κB ↓; β-catenin ↑; AP-1 ↓; VEGF ↓; JNK ↑	[38, 39, 47, 96, 98, 99, 101, 102]
PTL	SW620	E-cadherin ↑; vimentin ↓; Snail ↓; COX-2 ↓; MMP-2 ↓; MMP-9 ↓	[103]
PTL, **86**	SGC-7901/DDP; Hep3B; SK-Hep1; HBL-100; MDA-MB-231	STAT3 ↓, TRAIL-R1/2 ↑	[21, 97, 104]
PTL	HBL-100; MDA-MB-436	JNK ↑; XIAP ↓; c-XIAP ↓	[105, 106]
PTL, **20**, **21**	THP-1	Hsp72 ↓	[107]
PTL	MCF-7	EFL-α-1 ↓; vimentin ↓	[108]
PTL	HEK293T; HCT116; SW480	USP7 ↓; Wnt ↓; β-catenin ↓	[109]
PTL	Jurkat	TCR ↓; p-Erk1/2 ↓; p-p53 ↓	[110]
PTL, MCL	-	UGT1A1 ↓	[111]
PTL	MV4-11	DNMT1 ↓	[112]
PTL	A549; H1299	PI3K ↓; Akt ↓; p-FOXO3α↓	[113]

Conclusions

Sesquiterpene lactones belong to a large class of secondary metabolites with diverse structures and extensive bioactivities [114]. As most of these compounds contain a critical α-methylene-γ-butyrolactone pharmacophore, they can form covalent bond with cancer-associated reductases in organisms. As a candidate for anticancer drugs, PTL exerts strong anticancer effects in multiple cancer cells [115]. Previous studies indicated that PTL is a potent agent that can both increase intracellular ROS levels, deplete glutathione to enhance the sensitivity of cancer cells and activate the above-mentioned apoptosis- and necrosis-associated signaling pathway to exert anticancer effects [116-118]. PTL is demonstrated to be a pan inhibitor that may act on a variety of signaling pathways, which means that it is difficult to selectively kill cancer cells (HT29 and SW480 cells) and normal cells (NCM-460 cells) [48, 103]. Futhermore, PTL has a narrow therapeutic window, with poor water solubility and undesirable metabolic stability, which restrict the efficient application and development of PTL [119].

Sructural modification is an effective strategy to improve the targeting and selectivity of drugs [120]. On the one hand, the highly reactive ten-membered ring scaffold, the C1=C10 double bond, and unsaturated lactone provide good modification conditions for PTL. On the other hand, for sites that are difficult to react with, chemoenzymatic synthesis is frequently used to transform PTL into other special derivatives. For example, P450 variant II-C5 or P450 variant FL#46 were frequently used to obtain derivatives modified at the C-9 and C14 positions, respectively [40, 121]. In the current review, we summarized the relationship between PTL and anticancer effects through a systematic derivation strategy based on modification sites, which may help researchers to find the most promising compound from a broad categories of PTL derivatives. These findings will promote the biological and pharmacodynamic evaluation of PTL [48].

In conclusion, this article summarize the derivatization strategies of PTL in past two decades, and describe the representative derivatives with significant anticancer activity obtained through different modification methods. In order to further explore the significance of natural products as anticancer drugs, we discuss their pharmacodynamic mechanisms based on the existing investigations of PTL and its derivatives. With the gradual deepening of preclinical researches, PTL and its derivatives exhibit low exposure and poor PK characteristics *in vivo*. In the future, it will also be a challenge to solve their drug properties through structural modification.

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