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Evolution in Medicinal Chemistry of Ursolic Acid Derivatives as Anticancer Agents

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Abstract

Currently, there is a renewed interest in common dietaries and plant-based traditional medicines for the prevention and treatment of cancer. In the search for potential anticancer agents from natural sources, ursolic acid (UA), a pentacyclic triterpenoid widely found in various medicinal herbs and fruits, exhibits powerful biological effects including its attractive anticancer activity against various types of cancer cells. However, the limited solubility, rapid metabolism and poor bioavailability of UA restricted its further clinical applications. In the past decade, with substantial progress toward the development of new chemical entities for the treatment of cancer, numerous UA derivatives have been designed and prepared to overcome its disadvantages. Despite extensive effort, discovery of effective UA derivatives has so far met with only limited success. This review summarizes the current status of the structural diversity and evolution in medicinal chemistry of UA analogues and provides a detailed discussion of future direction for further research in the chemical modifications of UA.

Keywords

Natural products; ursolic acid derivatives; anticancer agents; drug discovery; chemical biology

INTRODUCTION

Throughout the ages, natural products have served and continue to serve as an unparalleled source to develop novel effective therapeutic agents for the treatment of a wide spectrum of diseases [1,2]. In the plant kingdom, triterpenoids represent a broad family of widespread

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CONFLICT OF INTEREST
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natural compounds containing more than 20,000 members [3,4]. Among them, pentacyclic triterpenes have emerged as a unique group of triterpenoid natural products with distinct biological properties as demonstrated by promising results in preclinical and clinical studies [5,6]. Ursolic acid (UA, 3β-hydroxy-12-urs-12-ene-28-oic acid, Figure **1**) as a hydroxy pentacyclic triterpene acid, is a constituent of certain medicinal herbs and the main component of wax-like protective coatings of various fruits including apples, pears, olives, prunes, cranberries and figs [7]. UA possesses considerable pharmacological effects including hepatoprotective [8,9], immunomodulatory [10], anti-inflammatory [11,12], antidiabetic [13], antibacterial [14,15], antiviral [16,17], antiulcer [18] and anticancer activities [19]. Recently, UA has been attracting a rising attention for its multifunctional anticancer activities [19,20]. Moreover, as an integral part of the human diet, UA is implicated in protection and prevention against human cancers [21,22].

Accumulating mechanistic studies indicate that the anticancer effect of UA is attributed to its ability to induce cancer cell apoptosis, prevent tumorigenesis, and inhibit cancer cell proliferation. UA triggers autophagy, cell cycle arrest, and apoptosis in different cancer cell lines through several signaling pathways [19], including NF-κB [23], STAT3 [24,25], and TRAIL [26]. For instance, UA has demonstrated to block the NF-κB pathway through suppression of p65 phosphorylation, leading to down-regulation of the expression of several downstream oncogenes such as Bcl2 and Bcl-XL [23]. Nevertheless, the precise molecular mechanisms of UA involved in apoptosis induction and proliferation inhibition in cancer remains to be elucidated [19]. The associated signaling pathways may be substantially different in various cancer cell lines, and partial signaling pathways may be regulated successively or simultaneously and synergized to contribute to UA treatment [27]. Further mechanistic elucidations and pathway signaling investigations are imperative to identify novel targets and provide useful insights into the molecular basis for the beneficial effects produced by UA and the relevant drug discovery of new chemical entities.

Despite its significant profiles of safety and efficacy in cancer treatment, its limited solubility, rapid metabolism and poor bioavailability of UA resulted in low therapeutic potential and restricted its further clinical applications [28]. Due to its naturally abundant supply from common sources and inexpensive availability, UA could be used as an attractive starting point for further structural modifications [29]. This article seeks to review the evolution in medicinal chemistry of UA derivatives to improve anticancer activity for preclinical development. Based on structural properties, we clustered most of reported UA analogues into two categories: 1) modifications on the positions of C-3/C-28, C-11, C-17 and C-28; and 2) modifications on C-2/C-3 positions and ring A.

MODIFICATONS ON THE POSITIONS OF C-3/C-28, C-11, C-17 AND C-28

Over the past decade, numerous attempts have been made to develop more potent UA derivatives. Daneshtalab and co-workers [30] isolated UA and five triterpenes from apple peels. They found that UA was present in the largest quantity (76% in crude triterpenes, 17 g from 27 kg of fresh apples). After that, a series of UA analogues were prepared with the modifications on the C-3, C-11, C-17 and C-28 positions [30]. As shown in Figure **2**, 3β-amino derivative **2**exhibited 20-fold more potent than 3α-formin cytotoxicity on all tested

cancer cell lines, indicating that the configuration at C-3 is a critical factor on the antiproliferative activity. Similarly, UA analogues with β-oriented hydrogen-bond forming groups at C-3 displayed more potent inhibition than their α-counterparts. All these results reinforced the notion of the important role of the configurations. Compound **3** bearing a hydroxymethyl group at C-17 displayed no activity, suggesting that the carbonyl group at C-17 is essential for the potency. In addition, introduction of an additional oxo moiety at C-11 position (compound **4**) is intolerable. Notably, introduction of amino alkyl groups at C-28 position (compound **5**) resulted in significant improvement of cytotoxicity. Despite the lack of detailed mechanistic and pharmacological studies, the general structure-activity relationship (SAR) described in this work served as the basis for further structural modifications on UA.

Following upon the initial findings discussed above, several research groups reported their drug discovery efforts and several interesting UA analogues have been discovered to show good *in vitro* anticancer activity. Meng et al. [31] prepared a series of UA derivatives (Figure **3**) in order to investigate which positions are important for the activity. In consistent with the previous results, they also found that introduction of a substituted acetyl group at C-3 hydroxyl group together with amino alkyl moiety at C-28 could significantly enhance the anticancer activity [31]. The UA derivatives with acetyl group at C-3 exhibited more potent antiproliferative effects than unsubstituted analogues. To further explore the benefit of the modifications at the C-3 and C-28 positions, they designed, synthesized and biologically evaluated another series of UA derivatives featured with UA-amino acid conjugates or related amino alcohol moieties [32]. The preliminary SAR studies also suggested that both the 3-*O*-acetyl moiety and a 28-amido group appeared to be essential for improving anticancer activity. Meanwhile, UA derivatives with free hydroxyl moiety at the C-28 amide branched side chain displayed similar inhibitory activity to those compounds without the hydroxyl group on the amide side chain, indicating that a hydroxyl group at the C-28 amide branched side chain has little influence on the antiproliferative activity. Taken together, the general SAR from their work suggested that 1) acetylation of C-3 position and formation of an amide by coupling with an amino alcohol acetate or amino acid methyl ester at C-28 position resulted in UA derivatives showing enhanced anticancer activity; 2) the C-3 free hydroxyl may decrease anticancer effects, while the free hydroxyl at C-28 amide side chain may retain the activity; and 3) too many branched alkyl side chains at C-28 amide chain could decrease anticancer effects. The preliminary antiproliferative mechanisms of these UA–amino alcohol conjugates were also explored. It was found that compounds **7** and **8** inhibited cell growth via the induction of apoptosis and cell cycle arrest at the S phase. Further comparison studies of UA derivatives by acetylated and butylated at the C-3 position demonstrated that acetylated compounds exhibited higher antiproliferative effects[33].

Shao et al. made a similar effort along these lines and synthesized another series of UA derivatives (Figure **4**) by modifying at C-3 and C-28 positions [34]. Slight enhancement of anticancer activity was achieved by the introduction of an acetyl group at the C-3 position together with that of alkylamino and/or piperidine moieties at the C-28 position. Their SAR studies also revealed that 1) compounds with disubstituted amide displayed higher potency than those monosubstituted ones; and 2) the piperazine derivatives showed relatively lower

potency than the piperidine analogues. Compound **10** induced cell apoptosis accompanied by cell cycle progression arrest at the S phase and the activation of caspase-3. However, this compound only demonstrated a slight reduction in tumor growth in hepatocellular carcinoma xenografts in nude mice even at a high dose of 150 mg/kg.

The increasing studies support that the ester functionality at C-3 and acid moiety at C-17 are essential, while a hydrogen donor group at either C-3 position and/or C-28 position is favorable for the anticancer activity. Based upon available SAR information, Guo and his co-workers identified a novel derivative [3β-acetoxy-urs-12-en-28-oyl]-1-monoglyceride (**11**, Figure **4**), which displayed significant anticancer effects without apparent cytotoxicity to human normal gastric cell line GES-1 [35]. Compound **11** was found to significantly induce apoptosis of BGC-823 cells by regulating the mitochondrial signaling pathway. Further extensive mechanism studies revealed that the activity of caspase-3 was up-regulated, while the expressions of Bcl-2 and Survivin were down-regulated. Intriguingly, compound **11** at 6.0 mg/kg exerted more efficacious antitumor effects than Taxol without apparent toxicity in nude mice bearing gastric tumor xenografts. The significant *in vivo* efficacy of this molecule may be attributed to its enhanced membrane permeability and favorable prodrug-like pharmaceutical properties.

Lin et al. also prepared and evaluated twenty-three new UA derivatives [36]. Several compounds exhibited significant anticancer effects against NTUB1 cells. Compound **12** (Figure **5**) with the succinyl moiety at C-3 position or compound **13** with an isopropyl ester at C-28 position displayed significantly improved antiproliferative activity likely owing to their enhanced cell permeability of ester prodrug forms. Interestingly, these compounds mediated through generation of reactive oxygen species (ROS), inducing inhibition of tubulin polymerization, cell cycle arrest at G2/M and G1, and apoptosis. Chen et al. prepared a series of furoxan-based nitric oxide (NO)-donating UA analogues and the most potent NO-drug hybrid **14** exhibited significantly improved anticancer activity against HepG2 cells, providing a promising direction for further investigation [37].

Accumulating evidence in drug discovery and the previous observations from the structural modification on UA revealed that the incorporation of a piperazine moiety might provide unexpected biological enhancement [34,38]. In order to search for UA derivatives with higher anticancer activities, Yang et al. designed and synthesized a series of UA derivatives with an additional acyl piperazine moiety on C-28 position (Figure **6**) [39]. They found that retaining the polar group at C-3 while incorporating a certain acyl piperazine motif at C-28 could significantly enhance anticancer activity against breast cancer and gastric cancer cell lines. Compound **15** was found to induce a higher cancer cell apoptosis ratio.

Despite numerous efforts on the chemical modifications of UA at the C-3 and C-28 position, no systematical SAR studies were pursued to explore the role of electronic properties. To this end, Guo et al. synthesized a series of novel UA derivatives with distinct electronic property at these two interesting positions [40]. They divided these newly designed UA analogues into two groups, namely negatively charged group and positively charged group. The extensive SAR investigation revealed that the positively charged group exhibited more potent cytotoxicity. The improvement of the lipophilicity appeared to strengthen the

anticancer activity. Among them, the representative compound **16** (Figure **6**) not only displayed potent anticancer activity and the ability to induce the apoptosis, but also exhibited reasonable oil/water partition coefficient and enhanced aqueous solubility.

Inspired by such advantages mentioned above, Bhat et al. designed and synthesized a focused library of UA-triazolyl based congeners at C-28 position by utilizing click chemistry protocol in order to develop more effective anticancer agents (Figure **7**) [41]. Intriguingly, most of these newly designed UA analogues demonstrated remarkable antiproliferative effects against all the tested cancer cell lines while exhibiting low toxicity to normal cells. The extensive SAR studies revealed that UA-triazolyl derivatives (**17**-**19**) with *o*-bromo, *o*-chloro or *o*-methoxy substitution at aromatic ring possessed highly potent anticancer activity with IC_{50} values less than 0.1 μM against MCF-7 (breast) and THP-1 (leukemia) cancer cell lines. It is worthy to note that the scaffold of this series has a 3-oxo functionality in the A ring, indicating that appropriate modifications on the A ring appear to be tolerable for anticancer activity enhancement. Further constructions with diverse functionality at the A-ring may open new doors to provide unique chemical entities with a promising pharmacological profile.

MODIFICATIONS ON THE C-2 POSITION

As discussed above, considerable structural modifications on UA performed so far are primarily on the hydroxyl group at C-3 position and on the carboxylic acid group at C-28 position. Esters and amides are the most common semisynthetic analogues and some derivatives exhibit significantly improved anticancer effects. In view of the above discussion, it is noteworthy to mention that the major advancement in triterpenoid research over the past decade was the synthesis of 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid (**CDDO**, Figure **8**) [42]. This oleanolic acid (**OA**) derivative, and its C-28 methyl ester (**CDDO-Me**) as well as its C-28 imidazole (**CDDO-Im**) showed significantly improved anti-inflammatory and antitumor activities. The enhanced effects are attributed to the 1-en-3-one and 9-en-12-one functionalities in the ring A and ring C, respectively. Inspired by the success of **CDDO** analogues in human clinical trials for cancer therapy, similar effort has been made on UA modifications since both UA and OA share a similar triterpenoid template. Interestingly, derivatives of UA substituted with cyano or trifluoromethyl group at the C-2 position in ring A containing the 1-en-3-one functionality also exhibited higher IC_{50} values than UA methyl ester (Table **1**) [43]. On the other hand, C-2 cyano or trifluoromethyl analogues (compounds **20** and **21**) also demonstrated higher potency than C-2 iodo-substituted compound (**22**).

To modify the A ring of UA, Lin et al. developed a promising compound **23** (Figure **9**) with *seco*-structures [36]. This compound was prepared from UA by oxidation, lactonization and ring-opening reaction. Despite only two-fold enhancement in cytotoxicity against NTUB1 cells, this kind of scaffold provides a new skeleton with potential for further explorations.

Jing et al. prepared a series of new *N*-acylimidazoles and *N*-alkylimidazoles of UA derivatives with an α,β-unsaturated ketone and found that most of these compounds exhibited significantly enhanced anticancer activity [44]. These novel UA derivatives

(**24**-**26**, Table **2**) displayed improved anticancer activity with IC_{50} values ranging from 1.9 to 7.3 μ M. The introduction of the *N*-alkyl heterocyclic motif in the ring A conjugated with an α,β-unsaturated ketone provides a better Michael acceptor and allows potential interaction with certain target proteins. Compound **26** arrests cell cycle in G1 phase and induces apoptosis in AsPC-1 cells by up-regulating p53, $p21^{waf1}$ and NOXA. UA derivatives with an α,β-unsaturated ketone conjugated with an heterocyclic moiety present a new scaffold for further drug discovery in cancer treatment.

CONCLUSIONS AND PERSPECTIVES

Natural products continue to serve as an invaluable source of molecular diversity for drug discovery. In the past two decades, UA, a widespread occurrence throughout the plant kingdom, has attracted considerable interest due to its biological potential as an antiviral, anti-inflammatory, antioxidant, or anticancer agent. Its most prominent function is anticancer effect because accumulating studies have demonstrated that UA is capable of regulating cell cycle, autophagy, and apoptosis in various malignant cancer cells, including breast, leukemia, lung, endometrial, and melanoma cancers [45]. In a phase I clinical and pharmacokinetic study to evaluate its pharmacokinetics, tolerance and safety, UA was proven to be extremely safe [46]. Despite its great profile of safety and efficacy, UA has not been adopted widely into clinical practice due to limited aqueous solubility, short plasma half-life, and low bioavailability. Therefore, a variety of UA derivatives with diversified modifications have been designed and synthesized in the search of more effective and orally bioavailable UA-based chemotherapeutic agents for cancer therapy.

This review summarizes the current progress in medicinal chemistry of UA analogues (Table **3**) as potential anticancer agents, which may serve as an important reference for further research on structural optimization, SAR and molecular biology studies of UA and other triterpenoid acids. The accumulated results on the structural variability and their anticancer effects against various malignant cancer cells have established some meaningful SAR which is depicted in Figure **10**. By critical examination of all reported UA analogues with modifications either at the positions of C-3/C-28, C-11, C-17 and C-28 or at C-2/C-3 positions of ring A, most of UA derivatives appeared to be active *in vitro* against various cancer cell lines but unfortunately, did not exhibit satisfactory potency and efficacy *in vivo*. These findings warrant more comprehensive SAR study and further development of UA derivatives with enhanced druggability through alternative drug design strategies [47]. To advance UA and its analogues as a viable cancer therapy, there remain several issues and new directions on which we can take action. (1) From the above literature survey, modifications on the ring A may significantly increase efficacy of UA. Compared to the modifications at C3, C17 and C28 positions, which have already received tremendous attention in the past decade, ring A/C-based diverse construction is relatively less explored and may be a more effective strategy to yield highly potent UA derivatives [48]. More extensive synthetic efforts and efficient methodologies are needed due to the challenges in structural diversifications on the ring A/C. To this end, our previous work on the concise synthesis of novel oridonin A-ring structural diversification with the success to yield superior diterpenoids may provide some useful and efficient synthetic strategies [49-52]. (2) To increase the efficiency in terms of structural modifications, and especially the efficacy in

animal models, the synthesis and extensive pharmacological evaluation of a larger library of UA derivatives are imperative to establish useful criteria for the further drug design and development. However, in most of the reported studies, only individual compounds of each series were tested *in vitro* against limited cancer cell lines [53] or *in vivo* in selected cancer models. Therefore, a more extensive investigation of UA derivatives using comprehensive cancer panel assays may provide a more detailed SAR. (3) Aqueous insolubility is one of the key restricting factors limiting clinical potential of many chemotherapeutic drugs. Although some of the UA analogues demonstrated potent effects *in vitro*, they are insoluble in aqueous media with poor efficacy *in vivo* [54]. More attention should be paid to enhance the aqueous solubility of UA analogues during structural modifications of UA by incorporation of hydrophilic fragments or moieties. One of the potential approaches to access better UA derivatives with improved aqueous solubility may take advantage of our published strategies by generating *O*-alkylamino-tethered derivatives, capable of having more favorable physicochemical properties [55-57]. Beneficial effects of making glucosides widely used in pharmaceutical industry may be another viable approach for the enhancement of solubility [58,59]. (4) Drug delivery systems are well known to improve aqueous solubility and bioavailability of many clinically used anticancer drugs [60,61]. Such delivery strategies may also prove useful for some potent UA derivatives to further improve their hydrophilicity and oral bioavailability. Formulations containing liposomes, cyclodextrin complexes, micelles, colloids and nanoparticles may be designed and generated to overcome such difficulties in clinical application of UA derivatives [62,63]. In addition, nanoparticulate drug delivery systems may provide unique approaches for cancer therapy [64,65]. The intelligently designed nanoparticles loaded with UA derivatives may enable targeting tumor cells passively or actively by enhanced permeation and retention (EPR) effect or by utilizing molecular targeting moieties. (5) Prodrug strategy has been developed to improve bioavailability of many conventional drugs [66]. By intelligent design, UA may be modified to be inactive in the gastrointestinal tract to avoid first-pass effect but active in tumor tissues after the targeted release of parent compound from the prodrug forms. (6) In most of the aforementioned literatures, the mechanisms of UA derivatives with respect to the activity enhancement in cancers are not in depth [67,68]. Many researchers have revealed that UA can inhibit cell proliferation, cause cell cycle arrest, induce apoptosis, as well as induce intracellular ROS formation in different cancer cell lines through several signaling pathways. However, the detailed action modes and potential novel targets of the UA derivatives remain to be unraveled. Once the exact targets of UA are identified, structure-based and fragment-based drug design can be applied in the refined structural modifications [69]. (7) Some natural products have been successfully used as potent adjunct drug to conventional chemotherapy although they are lack of efficacy as a single agent at low concentrations [70]. Combinations of UA derivatives with other conventional chemotherapeutic agents may offer the possibility of not only lowering their effective doses and thereby reducing unwanted adverse effects, but also acquiring unexpected attractive pharmacological properties as anticancer agents.

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ABBREVIATIONS USED

UA	ursolic acid
NF-κB	nuclear factor-κB
STAT3	signal transducer and activator of transcription 3
TRAIL	tumor necrosis factor (TNF)-related apoptosis inducing ligand
Bcl2	B-cell lymphoma-2
Bcl-XL	B-cell lymphoma-extra large
SAR	structure-activity relationship
ROS	reactive oxygen species
NO	nitric oxide
OA	oleanolic acid
CDDO	2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid
NOXA	phorbol-12-myristate-13-acetate-induced protein 1
EPR	enhanced permeation and retention

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Highlights

- Recent developments on medicinal aspects of UA analogues were discussed.
- Significant bioactive compounds as anticancer agents were documented.
- Relevant SAR studies and potential mechanisms were summarized.
- Future direction for further UA-based drug discovery was elaborated.

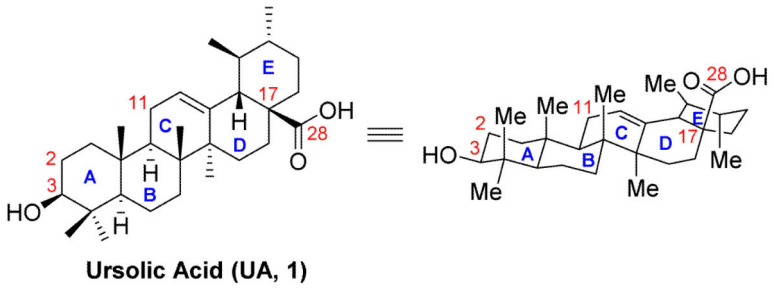


Figure 1.
Structure of ursolic acid (UA, 3β-hydroxy-12-urs-12-ene-28-oic acid, **1**).

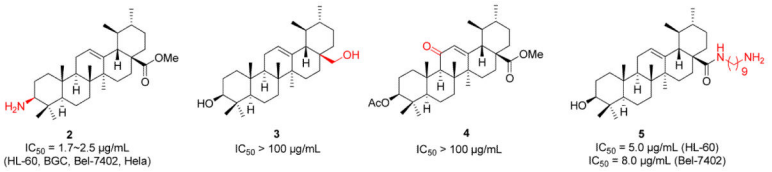


Figure 2.
Daneshtalab's work on UA derivatives.

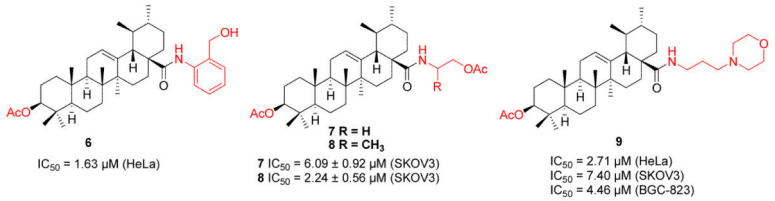


Figure 3.
Meng's work on UA derivatives.

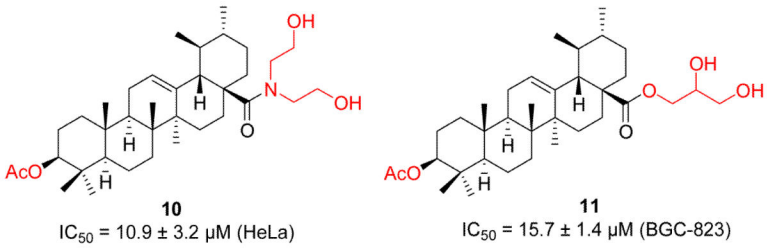


Figure 4.
Shao's and Guo's work on UA derivatives.

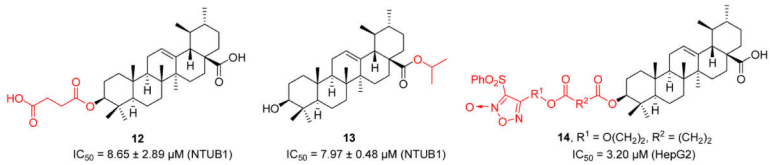


Figure 5.
Lin's and Chen's work on UA derivatives.

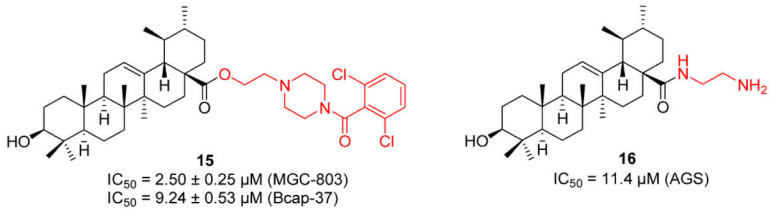


Figure 6.
Yang's and Guo's work on UA derivatives.

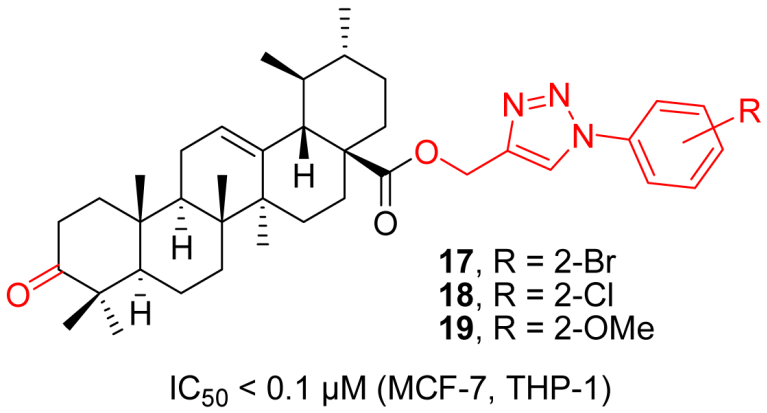


Figure 7.
Bhat's work on UA derivatives.

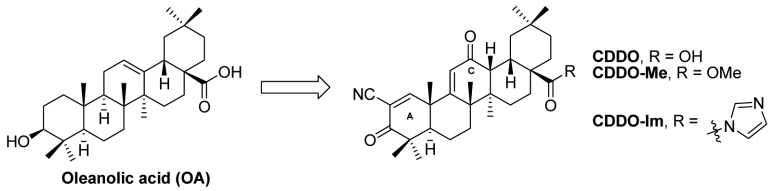
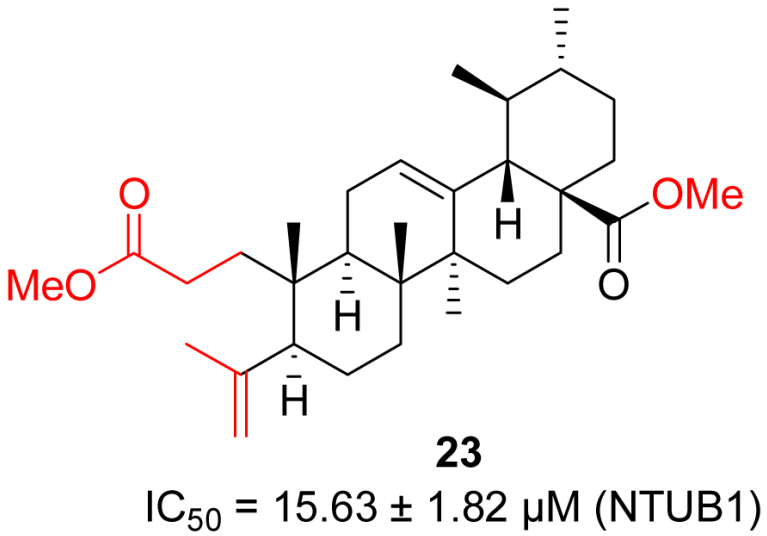


Figure 8.

The chemical structures of oleanolic acid (**OA**) and its derivatives (**CDDO**, **CDDO-Me** and **CDDO-Im**).



23

IC_{50} = 15.63 ± 1.82 μM (NTUB1)

Figure 9.
Lin's work on UA derivatives.

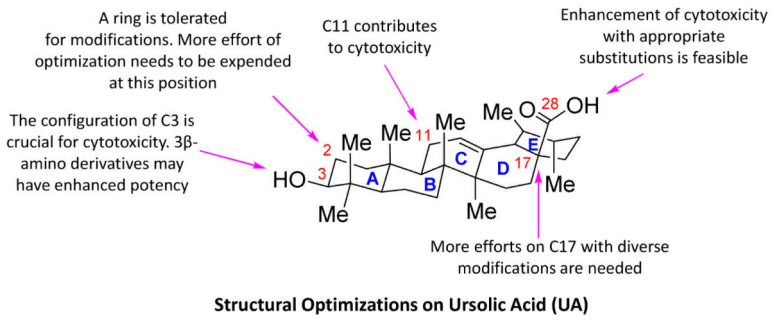
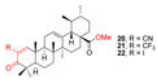


Figure 10.

Graphical depiction of the general SAR for cell cytotoxicity based on available biological results of UA derivatives.

Table 1

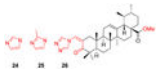
The IC_{50} μM) of UA derivatives (Safe's work)



Compd	235JB-V	KU7	Panc-1	Panc-28
CDDO-Me	0.03	0.12	0.27	0.29
UA methyl ester	6.13	8.95	11.75	10.58
20	0.17	0.30	0.53	0.97
21	0.17	0.47	0.65	1.13
22	4.90	6.02	6.91	13.49

Table 2

Cytotoxicity (μM) of UA heterocyclic derivatives (Jing's work)



Compd	AsPC-1	PANC-1	MIA PaCa-2	HepG2	MCF7	A549	PC-3
UA	12.6	14.9	10.4	15.0	12.3	11.4	20.8
24	5.8	5.1	7.3	2.0	5.3	5.6	6.8
25	2.1	5.6	5.6	4.0	2.2	5.3	3.5
26	1.9	3.5	4.0	3.2	2.3	4.9	3.0

Table 3

Summary of *in vitro* and *in vivo* studies with representative UA derivatives against various cancer cell lines.

Compd	*In vitro* anti-proliferation (IC_{50})	*In vivo* study	Potential molecular mechanisms	Ref.
2	2.0 μg/mL(HL-60) 2.5 μg/mL(BGC) 1.7 μg/mL (Bel-7402) 2.4 μg/mL (Hela)	-[a]	-	[30]
5	5.0 μg/mL(HL-60) 30.0 μg/mL(BGC) 8.0 μg/mL (MDA-MB-435)	-	-	[30]
6	1.63 μM (Hela)	-	-	[31]
8	2.24 μM (SKOV3)	-	Induce apoptosis; block cell cycle in S phase (Hela cells)	[32]
9	2.71 μM (Hela) 7.40 μM (SKOV3) 4.46 μM (BGC-823)	-	-	[33]
10	20.25 μM (HepG2) 15.52 μM (BGC-823) 13.24 μM (SH-SY5Y) 10.87 μM (Hela) 38.06 μM (HELF)	H22 xenografts in Kunming mice (50, 100, 150 mg/kg, i.p.)	Induce apoptosis; arrest cell cycle progression at the S phase in HepG2 cells; up-regulation of caspase-3	[34]
11	18.43 μM (HT-29) 27.46 μM (HepG2) 15.66 μM (BGC-823)	BGC-823 cells xenograft nude mice (6.0 mg/kg, 30 mg/kg, i.v.)	Induce apoptosis via the mitochondrial signaling pathway; up-regulation of caspase-3, down-regulation of Survivin and Bcl-2 (BGC-823 cells)	[35]
13	7.97 μM (NTUB1)	-	G2/M and G1 cell cycle arrest; enhancement of ROS; inhibition of tubulin polymerization (NTUB1 cells)	[36]
14	3.20 μM (HepG2)	-	-	[37]
15	2.50 μM (MGC-803) 9.24 μM (Bcap-37)	-	Induce cell apoptosis in MGC-803 cells	[39]
16	11.4 μM (AGC) 21.3 μM (HepG2) 14.3 μM (HT-29) < 10 μM (PC-3)	-	Induce cell apoptosis in AGC cells	[40]
18	<0.1μM (A-549, MCF-7, THP-1) 0.3 μM (HCT-116)	-	-	[41]
20	0.17 μM (235JB-V) 0.30 μM (KU7) 0.53 μM (Panc-1) 0.97 μM (Panc-28)	-	-	[43]
23	15.63 μM (NTUB1)	-	G2/M and G1 cell cycle arrest; enhancement of ROS; inhibition of tubulin polymerization (NTUB1 cells)	[36]
26	1.9 μM (AsPC-1) 3.5 μM (PANC-1) 4.0 μM (MIA PaCa-2) 3.2 μM (HepG2) 2.3 μM (MCF7) 4.9 μM (A549) 3.0 μM (PC-3)	-	Arrest cell cycle in G1 phase and induce apoptosis in AsPc-1 cells, up-regulation of P53, $P21^{waf1}$ and NOXA proteins	[44]

[a] Not available.