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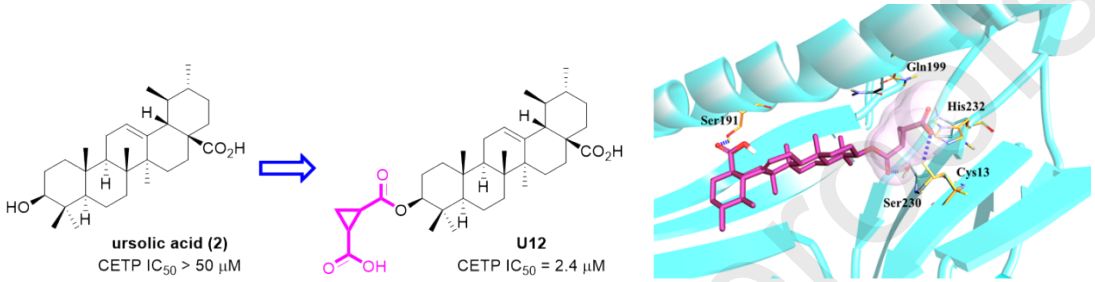

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Synthesis, biological evaluation and SAR studies of ursolic acid 3β-ester derivatives as novel CETP inhibitors

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ABSTRACT

Cholesteryl ester transfer protein (CETP) is an attractive therapeutic target for the prevention and treatment of cardiovascular diseases by lowering low-density lipoprotein cholesterol levels as well as raising high-density lipoprotein cholesterol levels in human plasma. Herein, a series of ursolic acid 3β-ester derivatives were designed, synthesized and evaluated for the CETP inhibiting activities. Among these compounds, the most active compound is **U12** with an IC_{50} value of 2.4 μM in enzymatic assay. The docking studies showed that the possible hydrogen bond interactions between the carboxyl groups at both ends of the molecule skeleton and several polar residues (such as Ser191, Cys13 and Ser230) in the active site region of CETP could significantly enhance the inhibition activity. This study provides structural insight of the interactions between these pentacyclic triterpenoid 3β-ester derivatives and CETP protein for the further modification and optimization.

Cardiovascular diseases (CVDs) are identified as the leading cause of death in low-income and middle-income countries.[1] Epidemiological studies confirmed that lowering low-density lipoprotein cholesterol (LDL-C) levels as well as raising high-density lipoprotein cholesterol (HDL-C) levels in human plasma appeared as a promising treatment strategy for cardiovascular events.[2] Cholesteryl ester transfer protein (CETP) is a crucial modulator of plasma lipoproteins that promotes the migration of cholesteryl esters from high density lipoprotein (HDL) to low-density lipoprotein (LDL) and very-low-density lipoproteins (VLDL).[3] The growing experimental and clinical studies have suggested that a high CETP concentration is associated with an increased risk of CVDs by raising proatherogenic LDL-C and lowering atheroprotective HDL-C.[4] This suggests that CETP inhibition could be a promising approach for the prevention and treatment of CVDs. In the past two decades, several CETP inhibitors with different structural scaffolds have been identified, and four of them have been evaluated in large scale, randomized cardiovascular clinical outcome trials.[5] While the trials with torcetrapib, dalcetrapib and evacetrapib with the purpose of reducing CVDs risk have been unsuccessful, treatment with anacetrapib shows significant benefit for major coronary events.[6] However, as the manufacturers of anacetrapib recently decided to suspend development of the drug,[6d] the future of CETP inhibition as a potential therapeutic option for reducing major cardiovascular events is currently uncertain.[7] Therefore, the discovery of effective and safe CETP inhibitors with different structural scaffolds has been an important area of pharmaceutical research due to the association of CETP activity with the risk of CVDs.

Pentacyclic triterpenoids (PTs), a group of widespread natural products that exhibiting similar structures to cholesterol and cholesteryl esters (CE), were observed to possess hypolipidemic activity more than thirty years ago.[8] In China, ursolic acid (**2**) as the main triterpene ingredients from *Fructus Ligustri Lucidi* has been marketed as an OTC drug (trade name Taizhi'an capsule) for the treatment of hyperlipidemia.[9] Many studies have indicated that sustained treatment with the plant extracts containing pentacyclic triterpene compounds could cause a significant decrease in TC, TG and LDL-C levels, and increase in HDL-C levels.[10] However, the biological mechanism of hypolipidemic activity of PTs is still under investigation.[10] As part of our ongoing research to find novel CETP inhibitors, we have designed and synthesized a series of oleanolic acid (**1**) 3β-ester derivatives, some of them displayed moderate inhibiting human CETP activity with IC_{50}s less than 10 μM.[11] The most potent compound **20** with an IC_{50} value of 2.3 μM (Figure 1) showed robust potential to regulate the lipid profile both in ap2-CETPTg mice and high-fat fed guinea pig models, meanwhile it exhibited an excellent pharmacokinetic profile without changes on the systolic blood pressure in guinea pigs.[11] Additionally, Chang and

co-v ited linking the PTs scaffolds and the active fragment from Torcetrapib through fragment-based drug design approaches.[12] In this manuscript, we have designed and synthesized a series of ursolic acid 3β-ester derivatives **U1-U15** and explored them as novel CETP inhibitors. In *vitro* screening assay showed that the most active compound was **U12** with an IC_{50} value of 2.4 μM (Figure 1). The molecular docking studies were carried out to investigate the mode of interaction of these compounds and their structure-activity relationship (SAR), which revealed that these pentacyclic triterpene 3β-ester derivatives might bind at the active site and interact with Cys13, Ser191, Gln199, Ser230 and His232 present in the binding site. The molecular docking demonstrated excellent co-relations with the experimental findings.

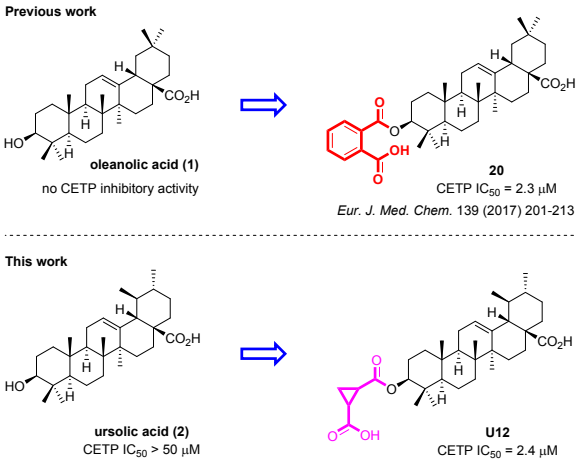
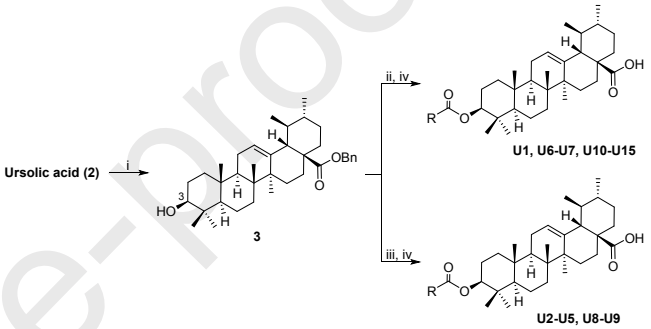


Figure 1. Discovery of pentacyclic triterpene 3β-ester derivatives as novel CETP inhibitors.

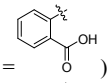
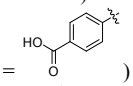
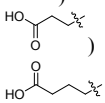
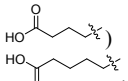
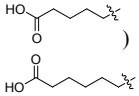
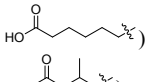
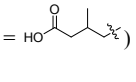
The general synthetic route for the target compounds **U1-U15** is shown in Scheme 1. A typical condensation method was embraced by treating **2** with benzyl chloride and K_2CO_3 in DMF to provide benzyl ester **3**. Then, esterification of the 3β-hydroxyl group of **3** with corresponding anhydrides in anhydrous pyridine, followed by debenzylation with H_2 over Pd/C in THF to give the desired compounds **U1**, **U6-U7** and **U10-U15** in 41-93% yields for two steps. Similarly, the product **3** was reacted with various carboxylic acid compounds in the present of DCC and DMAP, followed by debenzylation with H_2 over Pd/C in THF to afford the target products **U2-U5** and **U8-U9** in 35-85% yields for two steps. The structures of all synthesized compounds were established by spectroscopic data *i.e.* ^{1}H NMR, ^{13}C NMR and ESI Mass spectrometry.

All the target compounds were evaluated for their lipid-regulating effect by *in vitro* CETP enzymatic inhibition assay, and the results are summarized in Table 1. The initial screening was carried out at a concentration of 10 μM for each compound, and compounds that displayed >30% inhibition at 10 μM were further evaluated for their IC_{50}s. We found that compounds **U1** and **U2** with the phthalic acid monoester or isophthalic acid monoester moiety displayed moderate inhibition of CETP with IC_{50} values 5.5 μM and 3.3 μM, respectively. However, a significant loss of inhibitory potency was observed for compound **U3**, which having terephthalic acid monoester moiety. Further comparison of **U2** with **U4** (% inhibition at 10 μM = 22.7%) and **U5** (% inhibition at 10 μM = 11.2%) revealed that carboxyl group on the skeleton chain was essential to enhance the inhibitory activity. Moreover, the compounds **U6-U11** with carboxyl group at the end of the alkyl chain contributed significantly to our understanding of the linker region on the potency of inhibitory activity. Among them, succinic acid moderate inhibitory effect toward CETP with an IC_{50} of 10.9 μM and 3.2 μM, respectively, while adipi acid monoester **U8** and heptane diacid monoester **U9** have hardly any inhibitory potency. Compared with **U7**, due to the steric hindrance of methyl group, **U10** and **U11** with glutaric acid monoester moiety showed a complete loss in inhibitory potency against CETP. Quite unexpectedly, 1,2-cyclopropanedicarboxylic acid monoester **U12** showed the most potent CETP inhibitory activity; its IC_{50} reached 2.4 μM. Similarly, the existence of branched methyl group of **U13** caused a complete loss in inhibitory potency. It is regrettable that 1,2-cyclopentanedicarboxylic acid monoester **U14** and 1,2-cyclohexanedicarboxylic acid monoester **U15** also have no CETP inhibitory activities. Through a series of further comparisons (**U2** vs **U3**, **U7** vs **U8**, **U7** vs **U11**, and **U12** vs **U13**), we concluded that the carboxyl group at the end of skeleton chain and the length of skeleton chain are both key factors to maintain the inhibitory potency against CETP. Overall, **U12** emerged as the most potent compound in this series, with an IC_{50} value of 2.4 μM in the in *vitro* enzymatic assay.



Scheme 1. Synthesis of the target compounds **U1-U15**. Reaction conditions: (i) BnBr, K_2CO_3, DMF, r.t.; (ii) anhydrides, DMAP, pyridine, reflux; (iii) carboxylic acids, DCC, DMAP, DCM, reflux; (iv) H_2, 10% Pd/C, THF, r.t.

Table 1. Screening assay of ursolic acid 3β-ester derivatives as novel CETP inhibitors in vitro. [a]

Compd.	In vitro CETP inhibitory activity	
	% Inhibition at 10 μM	IC_{50} (μM)
U1 (R^1 = )	47.9	5.5 ± 1.0 [d]
U2 (R^1 = )	61.8	3.3 ± 0.5 [d]
U3 (R^1 = )	24.5	/ [e]
U4 (R^1 = )	22.7	/
U5 (R^1 = )	11.2	/
U6 (R^1 = )	42.8	10.9 ± 1.3 [d]
U7 (R^1 = )	55.1	3.2 ± 0.8 [d]
U8 (R^1 = )	23.3	/
U9 (R^1 = )	11.1	/
U10 (R^1 = )	1.1	/

U11 (R^1 =)		
U12 (R^1 =)	53.2	2.4 ± 0.37 [d]
U13 (R^1 =)	9.0	/
U14 (R^1 =)	0	/
U15 (R^1 =)	1.5	/
Anacetrapib [f]	88.4	0.036 ± 0.004 [c]

[a] The initial screening was carried out at a concentration of 10 μM for each compound and IC_{50}s were measured for compounds that displayed >30% inhibition of CETP. [b] The value of % inhibition at 10 μM is the mean of more than two independent assays. [c] The IC_{50} value was expressed as the mean ± SEM of two separate tests. [d] The IC_{50} value was expressed as the mean ± SEM of three separate tests. [e] "/" means that no experiment was conducted. [f] The reference drug.

Molecular docking studies were carried out to explore the mode of interaction of these novel CETP inhibitors with PTs scaffolds and their SAR. Here we applied Glide-docking module of Schrödinger software (Maestro v9.0, Schrödinger 2009, LLC, NEW YORK, NY) for docking studies. The crystal structure of CE in complex with CETP (PDB ID: 2OBD) was retrieved from the protein data bank.[3] In our previous research,[11] we hypothesized that PTs might be substrate analogue inhibitors of CETP, and designed a series of oleanolic acid (**1**) 3β-ester derivatives, which mimicking the protein-ligand interactions between the active site and CE scaffold. Among them, compound **20** (IC_{50} = 2.3 μM) was identified as a potent CETP inhibitor, which could regulate the lipid profile both in ap2-CETPTg mice and high-fat fed guinea pig models. Therefore, compound **20** was first selected for docking studies, and the binding mode was depicted in Figure 2. We found that **20** almost occupied the binding position of the endogenous ligand CE in the active site. Besides, the hydrogen bond interaction between **20** and Ser191 was observed (Figure 2a). Interestingly, the carboxyl group on the benzene ring of **20** was observed to stretch itself into a hydrophilic pocket, which was consisted by four polar residues Cys13, Gln199, Ser230 and His232 (Figure 2b). Recent studies also showed that it might be possible to incorporate some hydrophilic groups that interact with Ser230, His232, or Gln199, which located at the interior of the inhibitor binding pocket, to improve compound solubility while maintaining binding affinities.[13] Therefore, we concluded that the carboxyl groups at the end of molecular scaffold of **20** could form crucial hydrogen bond interactions with several polar residues in the active site region of CETP, which might contribute significantly to its inhibitory activity.

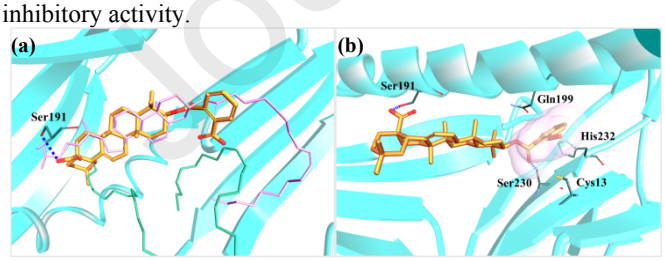


Figure 2. (a) Alignment of docking conformation of compound **20** (orange) and the crystal conformation of CE (pink). (b) Proposed binding mode of compound **20** (orange) with CETP. Residues involved in interactions are shown as blackish green sticks. The blue dash line indicates hydrogen bond interaction. Light pink shadow region indicates a hydrophilic pocket, which was consisted by Cys13, Gln199, Ser230 and His232.

Next, several ursolic acid 3β-ester derivatives were selected to further investigate the mode of interaction with CETP protein. ed a similar binding mode to CETP protein. The docked view of **U12** showed that it almost occupied the binding position, and got the key hydrogen bond interactions with Ser191 and Ser230 (Figure 3a). Moreover, the carboxyl group from 1,2-cyclopropanedicarboxylic acid moiety of **U12** was also observed to stretch itself into the hydrophilic pocket, therefore the compounds **U12** and **20** showed similar activities of IC_{50} values of 2.4 and 2.3 μM, respectively. We reasoned that the hydrogen bond interactions involving Ser191 and Ser230 might explain the SAR observed in other ursolic acid 3β-ester derivatives as CETP inhibitors. For example, docking of glutaric acid monoester **U7** into the active site of CETP showed the similar combination, and two hydrogen bond interactions between **U7** and Ser191, Cys13 were observed (Figure 3b). In contrast, the dimethy moiety of **U11** (Figure 3c) and the cyclohexyl moiety of **U15** (Figure 3d) created steric hindrance, which losing the interactions with Ser191, Cys13 and Ser230, and resulted in a complete loss in activity.

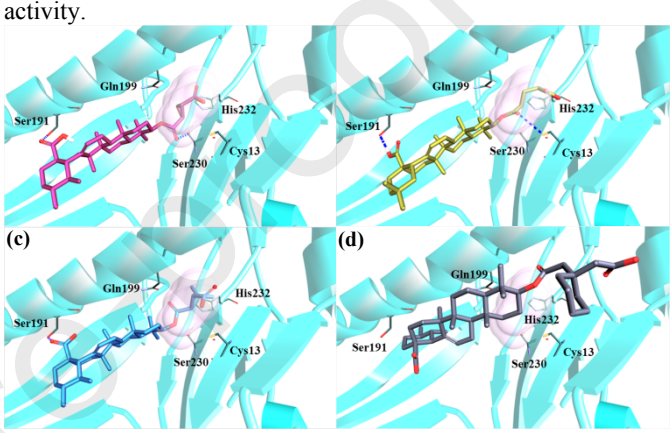


Figure 3. The binding modes of compounds **U12** (pink), **U7** (bright green), **U11** (blue) and **U15** (gray) are presented. The active site residues involved in interactions are depicted in blackish green sticks. The blue dash line indicates hydrogen bond interaction. Light pink shadow region indicates a hydrophilic pocket.

To further validate our docking model, a series of pentacyclic triterpenoid derivatives including oleanolic acid 3β-ester derivatives[11] and ursolic acid 3β-ester derivatives were docked into the active site of CETP protein, and the relationship between the docking scores produced by several scoring functions and the known inhibition ratios of CETP at 10 μM of these docked compounds was computed. The docking scores are depicted in Supporting Information (SI) Table 1, and the relationship is shown in SI Figure 1. LigScore2, XP-Score, and PMF-Score provided better correlations than the other scoring functions (SI Figure 1a), however, which were not able to satisfactorily predict the binding affinities for ligands bound to the target protein. From their docking results in the active site of CETP, we found that the carboxyl groups of some docked compounds could not form the hydrogen bond interactions with the hydrophilic pocket. Thus, we reasoned that the conformation of polar residues in the hydrophilic pocket changed in the ligand-binding process, and the computation directly on unaltered crystal structure was not suitable for the investigation of above hydrogen bond interactions. In order to introduce some flexibility into the docking process, the induced-fit docking protocol of Schrödinger was used. Induce-fit docking aims to improve the docking of ligands in which it is believed that the receptor adjusts significantly to the presence of the ligand.[14] By performing a constrained minimization of the receptor following by initial Glide docking and redocking the ligands, better receptor structures for each ligand can be obtained. With this method, molecular docking of compound **U12** into the active site of CETP showed that the polar residues (Cys13, Ser230 and His232) in the hydrophilic

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hydrogen bond interactions after the ligand binding to the receptor (Figure 4). With this new conformation, the relationship between the binding scores produced by XP-Score, PMF-Score and LigScore2 and the known inhibition ratios of these docked compounds was recomputed. The docking results showed that the relationship between inhibition ratios and binding scores was significantly increased (SI Figure 1b), which indicated that the new docking model might be more suitable to predict the inhibitory activity of these triterpenoid derivatives against CETP. Furthermore, the hydrogen bond interactions between carboxyl groups at both ends of the molecule skeleton and several polar residues (such as Ser191, Cys13 and Ser230) in the active site region of CETP are the key factor to maintain the inhibitory activity of these triterpenoid derivatives.

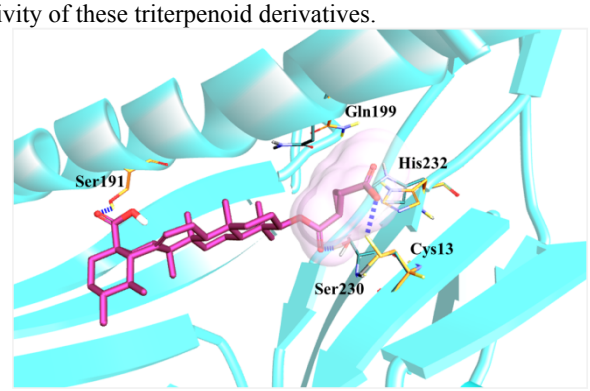
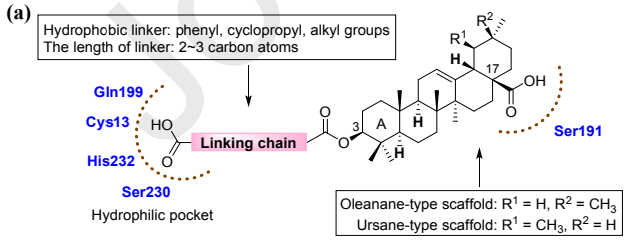


Figure 4. The conformation transitions in the induced-fit docking study of compound **12** to the active site of CETP protein. The polar residues in the hydrophilic pocket (residues displayed in blackish green stick style) would turn toward the ligand molecule to form the hydrogen bond interactions (residues displayed in yellow stick style).

Combined with our previous research results,[11] the whole SAR of these 3β-ester derivatives of PTs has been summarized in Figure 5a. A good CETP inhibiting activity may be attributed to the presence of carboxyl groups at opposite ends on the molecular scaffold, which could form the hydrogen bond interactions with the polar residues (such as Ser191, Cys13 and Ser230) in the active site of CETP protein. The hydrophobic linking chains at C-3 position of molecular skeleton could be aryl and alkyl groups; the length of carbon chains prefers 2~3 carbon atoms. In addition, oleanane-type and ursane-type scaffolds might be more suitable to fit the active pocket of CETP than other pentacyclic scaffolds. As outlined above, through the superimposed binding modes of five active compounds (Figure 5b), we can clearly observed that all these conformations have very similar binding interactions in the binding pocket except for minor differences.



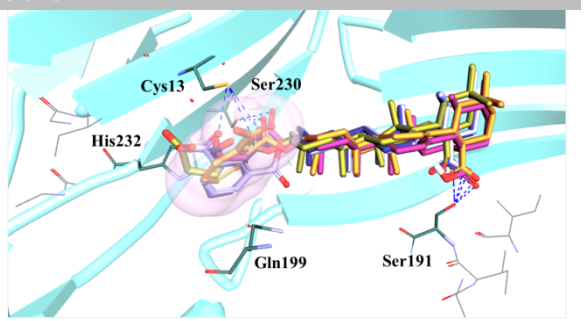


Figure 5. (a) SAR for 3β-ester derivatives of PTs as CETP inhibitors. (b) The superimposed binding modes of active compounds **20** (orange), **U1** (dark blue), **U2** (purple), **U7** (bright green) and **U12** (pink) are presented. The active site residues involved in interactions are depicted in blackish green sticks. The blue dash line indicates hydrogen bond interaction. Light pink shadow region indicates a hydrophilic pocket.

In summary, a series of ursolic acid 3β-ester derivatives were designed, synthesized and evaluated for the CETP inhibiting activities. In *vitro* screening assay showed that 5 out of 15 compounds displayed moderate inhibiting human CETP activity; the most active compound was **U12** with an IC_{50} value of 2.4 μM. The docking studies showed that the possible hydrogen bond interactions between the carboxyl groups at both ends of these triterpenoid 3β-ester derivatives and several polar residues (such as Ser191, Cys13 and Ser230) in the active site region of CETP could significantly enhance the inhibition activity, which gave us a direction for further lead optimization. We believe that ursolic acid 3β-ester derivative **U12** may serve as a lead compound for the design of more effective and safe CETP inhibitors.

Acknowledgments

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Supplementary Material

Supplementary material associated with this article can be found in the online version, at http://dx.doi.org/xxxxx.

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Highlights

A series of ursolic acid 3β-ester derivatives were synthesized and evaluated for the CETP inhibiting activities.

In *vitro* screening assay showed that the most active compound was **U12** with an IC_{50} value of 2.4 μM.

The molecular docking studies were carried out to investigate the structure-activity relationships of these pentacyclic triterpene 3β-ester derivatives.