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Discovery of ursolic acid prodrug (NX-201): Pharmacokinetics and in vivo antitumor effects in PANC-1 pancreatic cancer

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ABSTRACT

The aim of our study was to develop ursolic acid (UA) prodrugs in order to overcome UA's weakness, which has an extremely low bioavailability. UA-medoxomil (NX-201), one of our UA prodrugs, showed an improved bioavailability about 200 times better than UA in rodent model. According to in vivo test performed with PANC-1 xenograft SCID mouse model, tumor growth rate decreased dose-dependently and 100 mg/kg dose of NX-201 had an anticancer effect comparable to gemcitabine. Most of all the combination of NX-201 (50 mg/kg, po, daily) and gemcitabine (40 mg/kg, iv, 2 times per week) even reduced tumor size after three weeks.

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Natural products have been used for curing and preventing disease since long before, and medicinal chemists have contributed to the mankind by utilizing certain natural products as lead compounds in order to develop more effective and less toxic drug candidates. Among many natural products, pentacyclic triterpene series¹ have more diverse and interesting pharmacological activities, and various studies related to these activities have been frequently conducted. Recently ursolic acid (UA, 3 β -hydroxy-urs-12-ene-28-oic acid, Fig. 1.) has been proved to have many biological activities suggesting that it could be developed as a drug candidate for various intractable diseases.

UA, which is a natural compound of ursane-type pentacyclic triterpenic acid, is present in many plants and can be supplied as a single compound. In view of new drug development, UA became known to have various pharmacological effects; hepatoprotective, immunomodulatory, anti-inflammatory, kidneyprotective, antidiabetic, anti-muscle atrophy, antibacterial, antiviral against HCV, HSV and HPV, anti-*trypanosoma cruzi* for Chagas disease, and anticancer.² Among them the anticancer effect has been drawing the most attention and consequently, the numerous studies related to mode of action and therapeutic method of UA as an anticancer drug have proceeded. UA has been known for STAT-3 inhibitor³ which suppresses the proliferation of various cancer cell types. Until now several STAT-3 inhibitors⁴ including UA have been

developed but it is not yet potent enough to undergo clinical trials. However it has been reported that combination of UA and prescribed anticancer drugs such as cisplatin and paclitaxel, which is commercially available, would create a synergetic effects in reducing tumor growth rate.⁵ Furthermore, there are also reports⁶ that UA can act as a potent anticancer agent for some cancers which are resistant to currently available anticancer drug, for example gemcitabine-resistant pancreatic cancer.

Pancreatic cancer is known as one of the most fatal cancers. Gemcitabine has been used as a standard chemotherapy, but 5-year survival rate is about 9% and attempts for the development of new drug have been much less compared to other intractable cancers such as lung cancer whose 5-year survival rate is now up to 22%. Therefore developing more efficient and less toxic pharmacotherapy for pancreatic cancer should be given priority in this field.

According to Lie's research, in vivo test was carried out with utilizing human pancreatic gemcitabine-resistant cancer cell lines such as PANC-1, MIA and PaCA-2 on nude mouse xenograft model. The test was conducted for two weeks with UA 100 mg/kg and 200 mg/kg by ip injection. The result showed that tumor growth rate decreased strikingly dose-dependently. Unfortunately, UA has a serious physicochemical disadvantage resulting in an extremely low bioavailability, which obstructs oral administration of UA. For that reason injectable formulation or chemical modification of UA capable of showing more effectiveness have been regarded as alternatives in many ways. For example injectable

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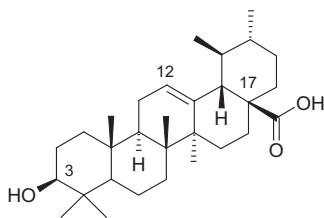


Figure 1. Structure of ursolic acid (UA).

UA liposome (UAL) was reported in terms of clinical phase 1 trial.⁷ In spite of low toxicity and usefulness of UA, new derivatization of UA inevitably increases the risk of consumption of time and cost in the long process of confirmation of safety and efficacy.^{8,9} Therefore, our research team put a great effort on developing an oral UA prodrug which results in better PK profile and can be expected to be safe comparable to UA itself.

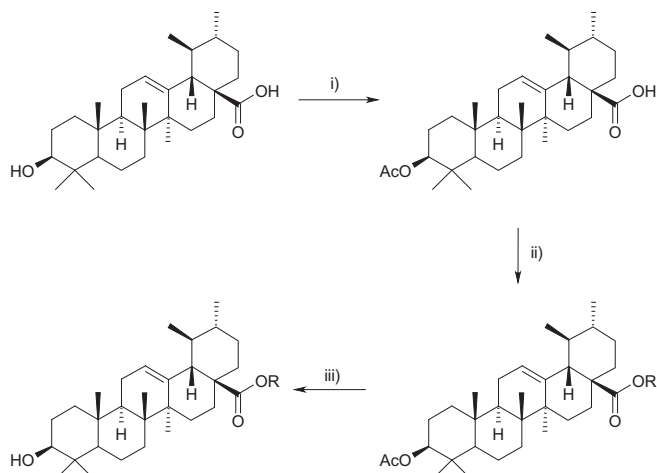
As shown in Figure 1, chemical structure of UA is very rigid, and has an alcohol group located on C-3, a double bond on C-12 and an unusual tertiary carboxylic acid on C-17. Since UA's pK_a is 5.29, UA

might be absorbed through intestine after oral administration, however, we found that no absorption has occurred through PK test. Our team designed ester type prodrugs to enhance oral absorption rates by increasing lipophilicity of carboxylic acid on C-17. Several well-known promoieties of prodrugs which have been proved to be safe and easily biodegradable after orally taken, were introduced into UA.

Synthetic process of UA prodrugs shown in Scheme 1 consisted of 3 steps. After protection of hydroxyl group on C-3 with acetyl group, carboxylic acid on C-17 was transformed to several esters of promoieties, and finally deprotection of hydroxyl group was performed to offer UA prodrugs. As for protection of C-3 alcohol, acetyl group was more suitable in the aspect of separation and purification of final products, compared to TBDMS, THP. Selective deacetylation of C-3 in final step was important to achieve high purity, so the acidic condition was favorable because of lability of C-17 ester under the basic condition. UA having 99% purity was used as a starting material, and all final products showed over 98% in HPLC purity.

Among the synthesized four derivatives in Table 1, UA-medoxomil (NX-201),¹⁰ shown in Figure 2, was preferentially applied to in vivo PK and efficacy tests for the following two reasons. First, NX-201 has relatively good physicochemical properties, for example, crystallinity and stability, which allow easier purification in large scale. Second, medoxomil promoiety has been researched profoundly in terms of the bioconversion mechanism and toxicity in many cases including olmesartan medoxomil, even though all four derivatives would be considered as orally administrated prodrugs¹¹ that is rapidly and completely metabolized to UA in gastrointestinal mucosa, portal blood and liver before it comes into systemic circulation. Prodrug compounds other than NX-201 is currently followed up to evaluate their potential as a drug in parallel with NX-201 in our research team.

As a result PK study shown in Table 2, bioavailability (F) of NX-201 was proved to be over 200 times better than that of UA and



Scheme 1. Synthesis of UA prodrugs. Reagent and conditions: (i) acetic anhydride, pyridine, DMAP cat., THF; (ii) K_2CO_3 , RX (RX = 1-(acetoxyethyl)-bromide (axetil); 4-chloromethyl-5-methyl-2-oxo-1,2-dioxolane (medoxomil); 1-chloromethyl pivalate (pivoxetil); 1-chloroethyl cyclohexyl carbonate (hexetil)), KI, acetone; (iii) p-TsOH, CH_2Cl_2 , MeOH.

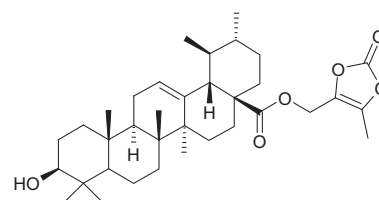


Figure 2. Structure of UA-medoxomil (NX-201).

Table 1

UA prodrugs: structure, purification method, yield

Compound	Structure of promoiety ($-CO_2R$ in Scheme 1)	Purification method	Total yield (%)
UA-axetil		Column chromatography	22
UA-medoxomil		Crystallization	47
UA-pivoxetil		Column chromatography	21
UA-hexetil		Column chromatography	25

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