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Synthesis of Phosphonodipeptide Conjugates of Ursolic Acid and Their Homologs

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ABSTRACT: *To prepare novel derivatives of naturally bioactive 3β-hydroxy-urs-12-en-28-oic acid (ursolic acid) with unusual properties and broad spectrum of activities, a number of chemical reactions were conducted. First, a variety of α-aminophosphonates were prepared by a series of reactions involving the three-component Mannich type reaction as a key step. Second, an array of phosphonodipeptides and their homologs was synthesized through multistep reactions including condensation of phthalic anhydride with glycine or β-alanine, chlorination of N-blocked amino acids, coupling of acid chloride with α-aminophosphonates and sequential hydrazinolysis. Finally, new classes of phosphonodipeptide conjugates of ursolic acid and their homologs were obtained by condensation of 3β-acetoxy-urs-12-en-28-oyl chloride with phosphonodipeptides and their homologs*. © 2008 Wiley Periodicals, Inc. Heteroatom Chem 19:55–65, 2008; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20396

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INTRODUCTION

Ursolic acid (UA) **1** (Fig. 1), a pentacyclic triterpene compound, naturally occurs in a large variety of vegetarian foods, medicinal herbs, and plants [1]. This terpenoid compound has attracted considerable interest owing to its significant biological activities and promising clinical application as chemotherapeutic and chemopreventive agent (anti-inflammation [2], antimicrobial activity [3–5], as well as inhibition of mutagenesis in bacteria [6]). Moreover, ursolic derivatives, especially dicarboxylic acid hemiesters, exhibit antihuman immunodeficiency virus type 1 (anti-HIV-1) activity, though slight toxicity is observed [7–9]. These new derivatives are assumed to be responsible for inhibition of HIV-1 protease dimerization [10]. Some ursolic derivatives also demonstrate anticancer activity. Indeed, UA and its derivatives display cytotoxic dose-dependent activity by inhibiting the growth of implanted ascetic tumor cells in vivo [11]. The cytotoxic potential of UA has also been found by inhibition of B16 cell growth (mouse melanoma cell lines) [12]. It can also be a potential candidate in treatment or prevention of skin cancer and a new promising anticancer agent in treatment of melanoma by apoptosis induction [13]. It is obviously a potent inhibitor of MCF-7 in the light of both cytostatic and cytotoxic activity [14].

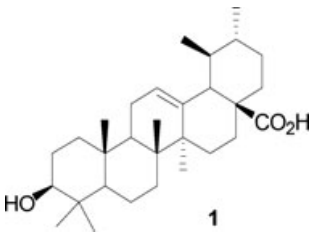


FIGURE 1 Structure of ursolic acid (UA).

However, the literature review reveals that only limited synthetic analogues have been reported for the purpose of bioactivity evaluation. A number of new derivatives are still needed for extensive investigation to establish structure-activity correlation. Our previous work demonstrated that acylation of ursolic acid at C-3 position and glycosylation at C-28 position could yield important compounds with anti-HT29 (human colon cancer cell) and anti-HIV activities [15]. More recent study revealed that α-aminophosphonates conjugates of ursolic acid (Fig. 2) possessed good anti-HIV activity with 20% inhibition at 10^{-4} M (R = *p*-MeOPh). These phosphorus-containing compounds proved to be good HIV-1 entry inhibitor capable of inhibiting CD4-gp120 interaction. Moreover, the derivatives of α-aminophosphonic acid conjugates are expected to improve the biological activity [16]. These exciting results prompted us to continue our synthesis of more derivatives of ursolic acid through the introduction of bioactive subunit-α-aminophosphonic acid.

It is well known that phosphonopeptides, as mimetics of naturally occurring peptides, have emerged as an important aspect in bioorganic and medicinal chemistry due to their unique biological activities [17]. Phosphonopeptides have been shown to be transition state analogs of the scissile amide bond, so they are of great interest in development of enzyme inhibitors [18–20] and haptens for the production of catalytic antibodies possessing esterase activities [21,22]. Some amino phosphonodipeptides and phosphono-oligopeptides have been used as antibacterial, anticancer, and antibiotic agents [23–25].

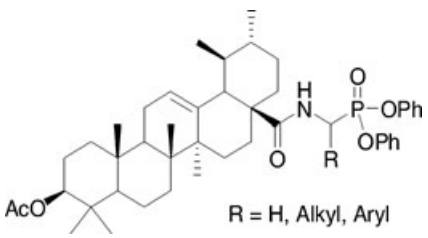


FIGURE 2 Structures of the reported compounds.

Some derivatives of pyrimidinyl or purinyl phosphonic acid demonstrate antiviral activity with a broad spectrum of activities against retrovirus and DNA virus by inhibiting DNA polymerase [26,27]. In the past decade, numerous studies have been published regarding the synthesis of phosphonopeptides with α-aminophosphonic acid in the C-terminal position for the purpose of evaluation of their properties related to metabolic process [26–31].

On the basis of our previous work, we designed and synthesized a number of novel phosphonodipeptide conjugates of UA and their homologs to examine their biological activity.

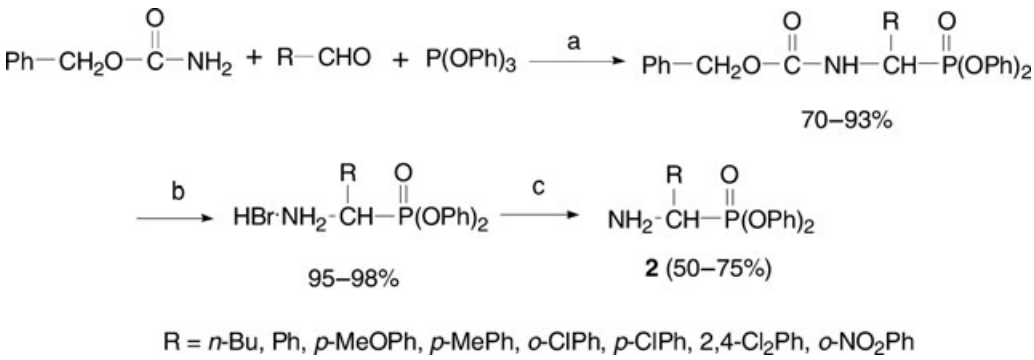
To facilitate synthesis of phosphorus-containing conjugates of ursolic acid, carboxylic acid moiety was first converted to acyl chloride. Coupling of acyl chloride with phosphonodipeptides, which were obtained by condensation of α-aminophosphonates with N-protected amino acid chlorides and sequential hydrazinolysis, provided desired conjugates. The biological activity evaluation of the synthesized compounds is in progress.

RESULTS AND DISCUSSION

A variety of N-protected α-aminophosphonates were prepared in good to excellent yields (70–93%) through the one-pot three-component reaction according to the literature [32]. The three components (benzyl carbomate, aldehyde, triphenylphosphite) were used in equal molar ratios. It was found that slight excess of aldehyde (1.1–1.3 equivalent) would improve the yield of the expected product, whereas the higher reaction temperature and longer reaction time would not affect the result of the reaction. For the aliphatic aldehydes, the yields were generally lower compared to that of aromatic aldehydes. It was noticed that the products derived from aromatic aldehyde could precipitate immediately at room temperature after the reaction was complete, whereas precipitation of the product from aliphatic aldehyde usually required harsh conditions such as cooling (–10°C) and storage in freezer overnight.

The ammonium hydrobromides were sequentially obtained after deprotection with a solution of hydrobromide in acetic acid at room temperature in a short time (0.5–2 h) [32]. Use of excessive hydrobromide (>2 equiv.) would speed up the reaction and gave nearly quantitative yield of the products (95%–98%).

Transformation of ammonium bromides into free amine was carried out in alternative ways. Free ammonia and triethylamine were chosen in this case, respectively. Neutralization by free ammonia was performed in large-scale preparation.



SCHEME 1 Reagents and conditions: (a) AcOH, 80°C–85°C, 2 h; (b) HBr/AcOH, rt, 2 h; (c) NEt_3/THF.

To facilitate the small-scale reaction, triethylamine was preferentially used to saponify the corresponding salt even though completion of the reaction required a little longer time. Thus, the desired α-aminophosphonates were obtained by treating hydrobromide derivatives with triethylamine (>3 equiv.) in anhydrous THF. Filtration of salt and following evaporation of low-boiling point substances under reduced pressure resulted in free amines (**2**) as sticky oils in 50%–75% yields (Scheme 1). Without further purification, the obtained α-aminophosphonates **2** were then dissolved in anhydrous THF and used as such in the next step.

Synthesis of phosphonodipeptides began with condensation of phthalic anhydride with amino acids at high temperature (≥180°C) under solvent-free condition. It should be noted that both of the reactants should be well ground and mixed evenly to ensure entire transformation of starting materials into the product **3** [33,34]. To complete the reaction, vigorous stirring was necessary after the solid mixture melted into dark brown liquid. The pure white crystal was obtained in nearly quantitative yield by recrystallization from water.

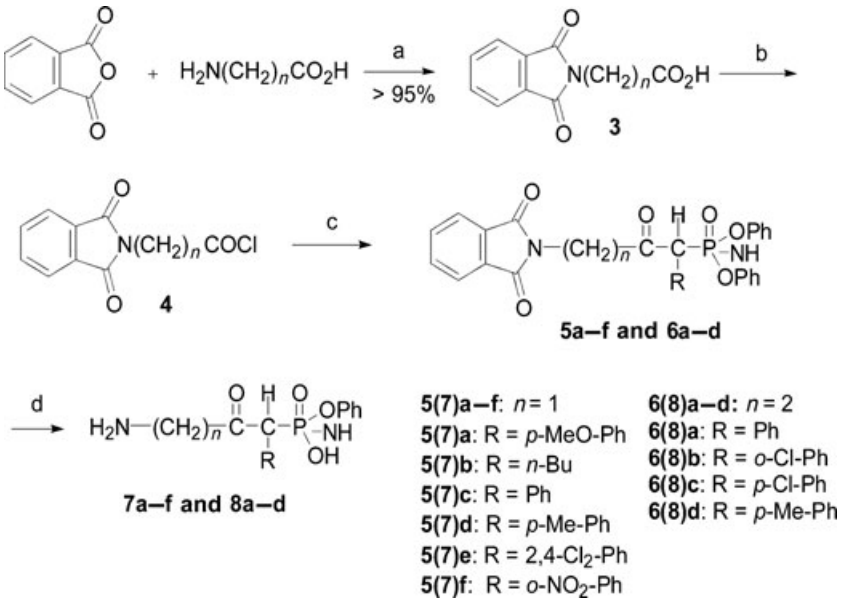
Chlorination of N-protected amino acids by thionyl chloride was achieved under solvent-free condition at 60°C. The excess of thionyl chloride was removed at 55°C. It was found that higher temperature would cause partial decomposition of the product. The crude acid chloride generated was used immediately after dissolution in anhydrous THF.

The coupling of acid chloride **4** [35] with α-aminophosphonates **2** proceeded smoothly on ice-bath in the presence of triethylamine. The pure products **5a–f** and **6a–d** were obtained in 36%–68% yields after recrystallization from a mixture of dichloromethane/diethyl ether. The structures of **5a–f** and **6a–d** were elucidated by spectroscopic methods.

Phosphonodipeptides **7a–f** and homologs **8a–d** were obtained after deprotection of **5a–f** and **6a–d** by hydrazinolysis in absolute ethanol overnight at room temperature (Scheme 2). The reaction usually ended up with some white precipitate. It should be noted that the complete removal of precipitate required repetitive filtration of the reaction mixture (four times). The filtrate was subject to concentration under reduced pressure at low temperature (≤55°C). Interestingly, it was found that in all cases one of the phosphonate phenyl groups was lost. It just met our requirement, and consequently, it facilitated our synthesis of target molecules bearing terminal phosphonic acid. Thus, all of compounds **7a–f** and **8a–d** obtained from hydrazinolysis were directly used in the next step without further purification.

The starting material **9** (3β-acetoxy-urs-12-en-28-oic acid) was quantitatively obtained by treatment of ursolic acid with an excess of acetic anhydride in pyridine in the presence of DMAP as catalyst [36,37]. Further reaction of compound **9** with excessive thionyl chloride under free-solvent condition at 65°C afforded acid chloride **10**, which was slightly different from the method reported in the literature [38]. The excess thionyl chloride was removed under reduced pressure and inert atmosphere. It was noteworthy that removal of thionyl chloride should be performed at 50°C–60°C; higher temperature would lead to decomposition. The crude sticky product was thus obtained and subject to evaporation on high vacuum (oil pump). The brown solid furnished was used without further purification.

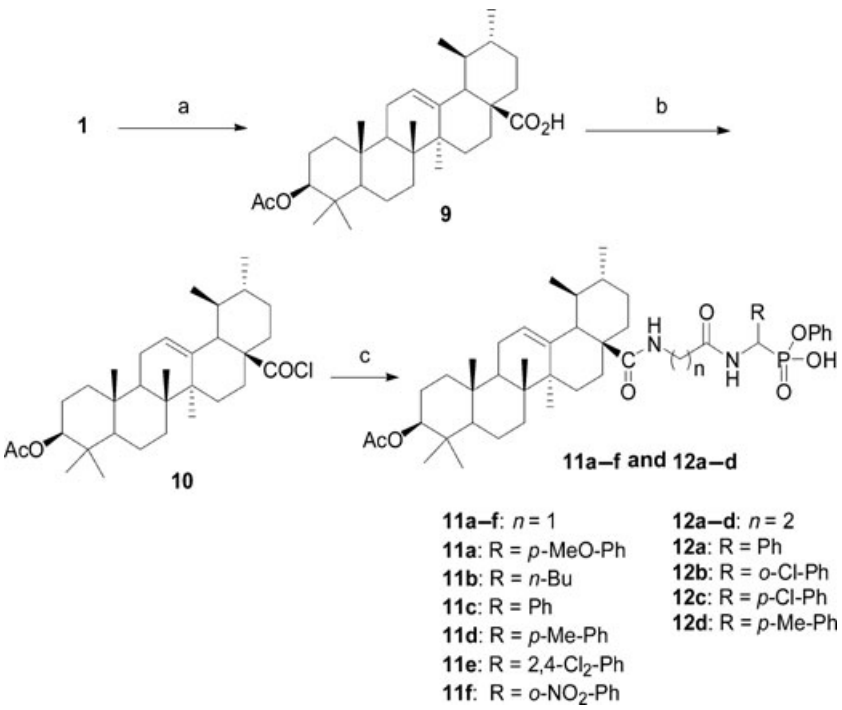
Condensation of phosphonodipeptides **7a–f** and their homologs **8a–d** with acid chloride **10** was carried out in anhydrous THF in the presence of triethylamine under nitrogen atmosphere. Upon completion of the reaction, the crude mixture was subject to preparative thin layer chromatography after routine work-up. The pure products **11a–f** and **12a–d** were obtained as sticky oil with 8%–24%



SCHEME 2 Reagents and conditions: (a) 185°C–200°C, 15 min; (b) $SOCl_2$, 60°C, 3 h; (c) **2**, NEt_3/THF, 0°C, 15 min; rt, overnight; (d) NH_2–NH_2·H_2O, EtOH, rt, 16 h.

yields. Some more polar byproducts were observed and the structures were unidentified (Scheme 3). The low yield of desired products and the complication of the reaction were presumably attributed to interference of the phosphonic acid.

Compounds **11a–f** and **12a–d** were characterized by ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, FT-IR, and microanalysis. The ^{1}H and ^{31}P NMR spectral data suggested that all of **11a–f** and **12a–d** consisted of diastereoisomers. For example, the ^{31}P NMR spectrum



SCHEME 3 Reagents and conditions: (a) Ac_2O, DMAP, pyridine, rt, 2.5 h; (b) $SOCl_2$, 65°C, 5 h; (c) **7a–f** and **8a–d**, NEt_3/THF, 0°C, 0.5 h; rt, overnight.

of **11c** showed two overlapped peaks (18.18 and 18.04), suggesting the existence of an equimolar mixture of diastereoisomers. In corresponding ^{1}H NMR spectrum, the signals at 5.23 and 5.24 ppm representing H-12 moiety appeared as two broad single peaks, confirming the presence of diastereoisomers.

In summary, a series of α-aminophosphonates were prepared in a convenient method in good yields; a variety of phosphonodipeptides and homologs were also obtained in moderate to good yields through multistep reactions; the introduction of phosphonodipeptides and their homologs to ursolic acid at C-28 was achieved, affording new classes of phosphonodipeptide conjugates of ursolic acid and their homologs. The bioassays such as anti-HT29 (human colon cancer cell line) and anti-HIV are in progress.

EXPERIMENTAL

Reagents and solvents were purchased from commercial sources and used without further purification unless stated otherwise. Ursolic acid was purchased from Aldrich-Sigma Co. (L'isle d'Abeau, 38297 Saint Quentin Fallavier, France) Tetrahydrofuran was dried over sodium before use. Thionyl chloride and triethylamine were freshly distilled before use. Ethanol was dried by refluxing with magnesium and iodine. Melting points (mp) were determined with a Kofler bench and were uncorrected. The ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on a Bruker AC-P300 instrument. All spectra were recorded in $CDCl_3$; tetramethylsilane (TMS) was used as an internal standard for ^{1}H NMR, and 85% phosphoric acid (H_3PO_4) was used as an external standard for ^{31}P NMR spectroscopy. IR (KBr) was preformed on Avatar 360 FT-IR instrument. Elemental analyses were carried out on a Yanaco MT-3 instrument. Analytical thin layer chromatography (TLC) was performed on Merck silica gel 60F_{254} precoated plates. The preparative thin layer chromatography was made using silica gel H (10–40 μm) containing F_{254} as coating. All reactions involving air- or water-sensitive compounds were routinely conducted under nitrogen atmosphere.

General Procedure for the Preparation of N-Benzyloxycarbonyl-diphenyl-α-aminophosphonates

To a 100-mL three-necked flask, triphenylphosphite (31.0 g, 0.1 mol), aldehyde (0.12 mol), benzylcarbomate (15.3 g, 0.1 mol), and acetic acid (15 mL) were added. The mixture was stirred at room temperature for 1 h, then warmed to 80°C–85°C and continued for another 2 h. The reaction solution was subjected to evaporation under reduced pressure to remove low-boiling point substances. The anhydrous methanol (50 mL) was added. The resulting mixture was cooled to –10°C for 3 h, affording a large amount of white precipitate. The following filtration and washing with anhydrous methanol (2 × 50 mL) and subsequent drying on vacuum gave desired white powder in 70%–93% yields.

General Procedure for the Preparation of Diphenyl-α-aminophosphonates Hydrobromides

To a flask containing *N*-benzyloxycarbonyl-diphenyl-α-aminophosphonates (0.01 mol), a solution of HBr in AcOH (25 mL, 30%) was added. The mixture was stirred at room temperature for 2 h. When evolution of bubbles stopped, excess HBr and solvent were subsequently removed by distillation under reduced pressure. The residue was washed with diethyl ether (30 mL), producing white solid. Further filtration and washing with diethyl ether yielded white powder. The spectral data of all known products are in accordance with that reported in the literature.

*General Procedure for the Preparation of Diphenyl-α-aminophosphonates (**2**)*

To a suspension of diphenyl-α-aminophosphonates hydrobromide (0.25 mmol) in 20 mL, anhydrous THF was added dropwise 0.3 mL of triethylamine. The mixture was kept stirring for about 3 h at room temperature. The precipitate was then filtered off, and the solvent was evaporated under reduced pressure. The resulting sticky product was used as such without further purification.

*Synthesis of 1,3-Dihydro-1,3-dioxo-2H-isoindole-2-acetic Acid (**3**)*

To a 100-mL flask, phthalic anhydride (7.5 g, 0.051 mol) and well-ground glycine (3.75 g, 0.050 mol) were sequentially added. The mixture was then warmed up to 185°C; the solid began to collapse and became brown liquid gradually. After about 15 min, the mixture became homogeneous solution. The reaction was allowed to continue with stirring at that temperature for another 5 min, followed by exposure to air until the solution solidified completely at ambient temperature. The resulting white solid was recrystallized from 100 mL of water, affording 10.12 g of colorless crystal. Yield 98.7%. mp 191°C–192°C (lit. [33,34], mp 192°C, yield 97%).

Compound 1,3-dihydro-1,3-dioxo-2*H*-isoindole-2-propanoic acid was prepared in a similar manner with 98.4% yield, mp 153°C–154°C (lit. [33,34], mp 152°C–153°C).

*Preparation of Phthalimidoacetyl Chloride (**4**)*

To a 100-mL three-necked flask, phthalimidoacetic acid (9.21 g, 0.045 mol) and thionyl chloride (15 mL) were added in a sequence. The reaction mixture was then warmed up to 60°C and stirred for about 3 h. The excess thionyl chloride was evaporated under reduced pressure. Petroleum ether (30 mL) was subsequently added and stirred, resulting in precipitation of white solid. After filtration, the crude solid was recrystallized from a mixture of benzene and petroleum ether, affording pale yellow crystal. Yield 81.6%, mp 82°C–84°C (lit. [35], mp 83°C–85°C).

Phthalimidopropionyl chloride was prepared by a similar manner and used immediately in the next reaction. Yield 82.8%, mp 106°C–107°C (lit. [35], mp 107.5°C–108°C).

*General Procedure for the Synthesis of N-Blocked Phosphonodipeptides (**5a–f**) and Homologs (**6a–d**)*

A prepared solution of acid chloride **4** in THF (30 mL) was added dropwise to an ice-cooled solution of α-aminophosphonates **2** (1 equiv.) and triethylamine (1.1 equiv.) in methylene chloride (30 mL) over 15 min. The solution was then stirred at ambient temperature overnight. After removal of ammonium chloride by filtration, the solution was concentrated on a rotavapor. The resulting residue was dissolved in methylene chloride (40 mL), washed with water, dried over sodium sulfate, followed by filtration and evaporation. The obtained residue was then crystallized from a mixture of methylene chloride/diethyl ether (1/5, v/v), affording white powder. Pure products **5a–f** and **6a–d** were obtained by recrystallization from the same solvents.

*Diphenyl(N-phthalimidomethylcarbonyl)aminomethyl(p-methoxyphenyl) Phosphonate (**5a**).* Yield 57%; mp 224°C–226°C; IR (KBr) (cm^{-1}): 3274, 1775, 1719, 1515, 1488; ^{1}H NMR ($CDCl_3$) δ: 3.83 (s, 3H, CH_3O), 4.08 (d, 2H, $^2J_{H-H} = 16.35$ Hz, NCH_2), 5.91 (dd, 1H, $^3J_{H-H} = 9.76$ Hz, $^2J_{P-H} = 21.48$ Hz, CHP), 6.65–7.89 (m, 18H, H_{arom}), 8.54 (d, 1H, $^3J_{H-H} = 9.76$ Hz, NH); ^{13}C NMR ($CDCl_3$) δ: 49.5 (CH_2), 51.7, (CH), 55.8 (CH_3), 114.8, 120.8, 121.2, 123.8, 125.6, 126.0, 129.9, 130.4, 132.6, 134.4, 150.5, 160.2 (C—O—CH_3), 166.5 (C=O), 168.0 (NH—C=O); ^{31}P NMR ($CDCl_3$) δ: 14.83.

*Diphenyl(N-phthalimidomethylcarbonyl)aminomethyl(n-butyl) Phosphonate (**5b**).* Yield 48%; mp 156°C–158°C; IR (KBr) (cm^{-1}): 3278, 1775, 1723, 1488; ^{1}H NMR ($CDCl_3$) δ: 0.93 (t, 3H, $^3J_{H-H} = 7.26$ Hz, CH_3), 1.32–1.47 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.50–1.72 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.83–1.98 (m, 2H, $CH_2CH_2CH_2CH_3$), 4.25 (m, 2H, CH_2C=O), 4.85 (t q, 1H, $^3J_{H-H} = 3.22$ Hz, $^3J_{H-H} = 6.58$ Hz, $^2J_{P-H} = 17.02$ Hz, CHP), 7.03 (br s, 1H, NH), 7.12–7.90 (m, 14H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ: 14.2 (CH_3), 19.3 (CH_2), 33.4, 40.6, 45.2 (CH), 47.3 (CH_2), 115.9, 119.4, 121.0, 123.6, 125.8, 129.6, 130.2, 132.5, 134.3, 150.4, 157.7 (O—C), 167.3 (C=O), 168.2 (NH—C=O); ^{31}P NMR ($CDCl_3$) δ: 18.09.

*Diphenyl(N-phthalimidomethylcarbonyl)aminomethylphenyl Phosphonate (**5c**).* Yield 55%; mp 216°C–218°C; IR (KBr) (cm^{-1}): 3298, 1776, 1723, 1488; ^{1}H NMR ($CDCl_3$) δ: 4.09 (d, 2H, $^2J_{H-H} = 16.65$ Hz, NCH_2), 5.95 (dd, 1H, $^3J_{H-H} = 9.75$ Hz, $^2J_{P-H} = 21.72$ Hz, CHP), 6.61–7.89 (m, 19H, H_{arom}), 8.53 (dd, 1H, $^3J_{P-H} = 2.86$ Hz, $^3J_{H-H} = 9.75$ Hz, NH); ^{13}C NMR ($CDCl_3$) δ: 49.8 (CH_2), 51.9 (CH), 116.0, 121.0, 123.6, 125.9, 129.1, 129.8, 130.2, 132.4, 134.3, 150.5, 168.3 (O—C), 170.2 (C=O), 174.6 (NH—C=O); ^{31}P NMR ($CDCl_3$) δ: 14.71.

*Diphenyl(N-phthalimidomethylcarbonyl)aminomethyl(p-tolyl) Phosphonate (**5d**).* Yield 68%; mp 213°C–215°C; IR (KBr) (cm^{-1}): 3273, 1777, 1725, 1488; ^{1}H NMR ($CDCl_3$) δ: 2.28 (s, 3H, CH_3), 4.03 (d, 2H, $^2J_{H-H} = 16.54$ Hz, CH_2C=O), 5.82 (dd, 1H, $^3J_{H-H} = 9.70$ Hz, $^2J_{P-H} = 21.40$ Hz, CHP), 6.60–7.81 (m, 18H, H_{arom}), 8.98 (dd, 1H, $^3J_{P-H} = 3.01$ Hz, $^3J_{H-H} = 9.70$ Hz, NH); ^{13}C NMR ($CDCl_3$) δ: 21.7 (CH_3), 48.0 (CH_2), 52.1 (CH), 120.9, 121.4, 123.9, 125.6, 126.1, 129.1, 129.9, 130.6, 131.1, 132.7, 134.4, 139.0, 150.6 (O—C), 166.8 (C=O), 168.0 (NH—C=O); ^{31}P NMR ($CDCl_3$) δ: 14.75.

*Diphenyl(N-phthalimidomethylcarbonyl)aminomethyl(2,4-dichorophenyl) Phosphonate (**5e**).* Yield 50%; mp 229°C–231°C; IR (KBr) (cm^{-1}): 3271, 1779, 1724, 1488; ^{1}H NMR ($CDCl_3$) δ: 4.08 (d, 2H, $^2J_{H-H} = 16.53$ Hz, CH_2C=O), 6.39 (dd, 1H, $^3J_{H-H} = 9.30$ Hz, $^2J_{P-H} = 22.72$ Hz, CHP), 6.73–8.00 (m, 17H, H_{arom}), 8.53 (dd, 1H, $^3J_{P-H} = 4.02$ Hz, $^3J_{H-H} = 9.30$ Hz, NH); ^{13}C NMR ($CDCl_3$) δ: 40.1 (CH_2), 48.2 (CH), 115.9, 119.4, 120.4, 121.1, 123.6, 125.9, 126.3, 129.6, 130.1, 130.6, 131.5, 132.5, 134.4, 150.3 (O—C), 157.7, 167.0, 168.0 (C=O), 172.4 (NH—C=O); ^{31}P NMR ($CDCl_3$) δ: 22.72.

*Diphenyl(N-phthalimidomethylcarbonyl)aminomethyl(o-nitrophenyl)phosphonate (**5f**).* Yield 36%;

mp 186°C–188°C; IR (KBr) (cm^{-1}): 3279, 1775, 1722, 1532, 1488; ^1H NMR ($CDCl_3$) δ: 4.22 (d, 2H, $^2J_{H-H} = 16.76$ Hz, $CH_2C{=}O$), 7.48–7.68 (m, hidden in aromatic protons' peaks, 1H, CHP), 6.77–8.02 (m, 18H, H_{arom}), 8.38 (dd, 1H, $^3J_{P-H} = 2.88$ Hz, $^3J_{H-H} = 9.44$ Hz, NH); ^{13}C NMR ($CDCl_3$) δ: 40.1 (CH), 46.1, (CH_2), 120.4, 120.9, 123.8, 126.3, 129.9, 130.4, 132.3, 134.6, 150.2, 167.5 (C=O), 168.3 (NH—C=O); ^{31}P NMR ($CDCl_3$) δ: 13.24.

*Diphenyl(N-phthalimidoethylcarbonyl)aminomethylphenyl Phosphonate (***6a***).* Yield 60%; mp 168°C–170°C; IR (KBr) (cm^{-1}): 3299, 1773, 1722, 1489; ^1H NMR ($CDCl_3$) δ: 2.57–2.64 (m, 2H, $CH_2C{=}O$), 3.94 (t, 2H, $^3J_{H-H} = 7.28$ Hz, NCH_2), 5.95 (dd, 1H, $^3J_{H-H} = 9.88$ Hz, $^2J_{P-H} = 20.80$ Hz, CHP), 6.76–7.79 (m, 19H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ: 34.0 (CH_2), 49.8 (CH_2), 51.9 (CH), 116.0, 121.0, 123.6, 125.9, 129.1, 129.8, 130.2, 132.4, 134.3, 150.5, 168.3 (O—C), 170.2 (C=O), 174.6 (NH—C=O); ^{31}P NMR ($CDCl_3$) δ: 14.32.

*Diphenyl(N-phthalimidoethylcarbonyl)aminomethyl-(o-chlorophenyl)Phosphonate (***6b***).* Yield 44%; mp 174°C–176°C; IR (KBr) (cm^{-1}): 3341, 1775, 1716, 1490; ^1H NMR ($CDCl_3$) δ: 2.50–2.56 (m, 2H, $CH_2C{=}O$), 3.82–3.88 (m, 2H, NCH_2), 5.82 (dd, 1H, $^3J_{H-H} = 9.76$ Hz, $^2J_{P-H} = 21.81$ Hz, CHP), 6.70–7.75 (m, 18H, H_{arom}), 8.85 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ: 34.4 (CH_2), 49.1 (CH_2), 51.3 (CH), 120.6, 123.6, 125.8, 126.0, 129.4, 129.6, 130.3, 132.3, 133.0, 134.3, 150.6, 168.3 (C=O), 170.0 (NH—C=O); ^{31}P NMR ($CDCl_3$) δ: 13.73.

*Diphenyl(N-phthalimidoethylcarbonyl)aminomethyl(p-chlorophenyl) Phosphonate (***6c***).* Yield 37%; mp 196°C–198°C; IR (KBr) (cm^{-1}): 3278, 1780, 1717, 1489; ^1H NMR ($CDCl_3$) δ: 2.44–2.53 (m, 2H, $CH_2C{=}O$), 3.78–3.87 (m, 2H, NCH_2), 6.48 (dd, 1H, $^3J_{H-H} = 9.43$ Hz, $^2J_{P-H} = 22.28$ Hz, CHP), 6.68–7.78 (m, 18H, H_{arom}), 7.97 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ: 33.8 (CH_2), 34.6 (CH_2), 48.4 (CH), 116.0, 120.3, 120.9, 123.5, 125.6, 126.0, 129.4, 129.6, 130.1, 132.3, 134.4, 150.5, 157.7 (O—C), 168.3 (C=O), 170.3, 175.3 (NH—C=O); ^{31}P NMR ($CDCl_3$) δ: 13.80.

*Diphenyl(N-phthalimidoethylcarbonyl)aminomethyl-(p-tolyl)Phosphonate (***6d***).* Yield 55%; mp 158°C–160°C; IR (KBr) (cm^{-1}): 3333, 1775, 1717, 1489; ^1H NMR ($CDCl_3$) δ: 2.33 (s, 3H, CH_3), 2.60 (m, 2H, $CH_2C{=}O$), 3.94 (t, 2H, $^3J_{H-H} = 7.26$ Hz, NCH_2), 5.92 (dd, 1H, $^3J_{H-H} = 9.59$ Hz, $^2J_{P-H} = 21.77$ Hz, CHP), 6.75–7.78 (m, 18H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ: 21.0, 34.1 (CH_2), 45.9 (CH_2), 51.4 (CH), 115.3, 120.5, 123.3, 125.6, 128.5, 129.6, 130.6, 131.9, 134.2, 138.6, 150.3, 156.9 (O—C), 168.4 (C=O), 170.5 (NH—C=O); ^{31}P NMR ($CDCl_3$) δ: 14.56.

*General Procedure for the Synthesis of Phosphonodipeptides (***7a–f***) and Homologs (***8a–d***)*

N-Blocked phosphonodipeptide **5a–f** or homologs **6a–d** (0.2 mmol) in anhydrous ethanol (5 mL) were treated with hydrazine monohydrate (0.1 mL) under nitrogen atmosphere at room temperature overnight. The reaction ended up with some white precipitate. After removal of the precipitate, the filtrate was concentrated on the rotavapor. After most of solvent was removed, anhydrous THF (10 mL) was subsequently added. The mixture was evaporated again on the rotavapor (≤55°C), followed by evaporation on vacuum (oil pump), resulting in a colorless sticky liquid. The obtained free amines were used in the next reaction without further purification.

*Synthesis of 3β-Acetoxy-urs-12-en-28-oic Acid (***9***)*

To a 50-mL flask, ursolic acid (0.1 g, 0.22 mmol), pyridine (10 mL), acetic anhydride (2 mL), and DMAP (0.027 g, 0.22 mmol) were added. The mixture was kept stirring at room temperature under nitrogen for 2.5 h, then ground ice was added to the solution with stirring. After the ice dissolved completely, the mixture was then extracted with methylene chloride (20 mL, 3 × 15 mL). The extracted organic phase was combined and washed with water (5 × 20 mL). The separated organic layer was further dried over anhydrous sodium sulfate for 2 h, followed by filtration and evaporation under reduced pressure. The residue was subject to azeotropic evaporation with toluene (20 mL) on the rotavapor. After repetition of addition and evaporation of toluene (four times), the pale powder was obtained. Recrystallization of crude solid from ethyl acetate/hexane (1/6, v/v) afforded a white solid with 97% yield, mp 289°C–290°C (lit. [36,37], mp 288°C–289°C).

*Synthesis of 3β-Acetoxy-urs-12-en-28-oyl Chloride (***10***)*

To a 10-mL flask, compound **9** (43 mg, 0.086 mmol) and freshly distilled thionyl chloride (2 mL) were added. The reaction was warmed to 65°C and kept stirring for about 5 h. The excess thionyl chloride was then removed under reduced pressure at 50°C–60°C. Further evaporation on vacuum (oil pump) provided a brown semisolid. The crude solid was used in the next reaction without further purification.

*General Procedure for the Preparation of Phosphonodipeptide Conjugates of Ursolic Acid (**11a–f**) and Homologs (**12a–d**)*

To a 25-mL flask containing a solution of phosphonodipeptides **7a–f** or homologs **8a–d** (0.2 mmol) in anhydrous THF (10 mL), triethylamine (0.3 mL) and a newly prepared solution of acid chloride **10** (1 equiv.) in anhydrous THF (5 mL) over 10 min at 0°C were sequentially added. After completion of addition, the reaction was allowed to continue at 0°C for 0.5 h and then at room temperature overnight. The precipitate was filtered off, and the filtrate was concentrated on the rotavapor. The residue was dissolved in dichloromethane (3 mL), and subsequently separated by preparative thin layer chromatography (25×25 cm^2) using a mixture of ethyl acetate/hexane (1/1, v/v) as eluent. The desired fraction ($R_f = 0.2$–0.3) was collected and eluted with acetone. The solvent was then evaporated under reduced pressure, yielding the products **11a–f** and **12a–d** as sticky oils. Yellow solid was obtained after standing for a couple of days.

*Phenyl[(N-3β-acetoxy-urs-12-en-28-oyl)(aminomethylcarbonyl)(aminomethyl-p-methoxyphenyl)] Phosphonate (**11a**).* Yield 24%; Pale yellow solid; mp 127°C–129°C; IR (KBr) (cm^{-1}): 3393, 2929, 1735, 1518, 1243, 1024; ^{1}H NMR ($CDCl_3$) δ: 0.56–1.98 (m, 43H, parent structure of ursolic acid unless otherwise indicated), 2.05 (s, 3H, $CH_3C{=}O$), 3.42–3.74 (m, 1H, CH in 18), 3.80 (s, 3H, CH_3O), 3.70–4.10 (m, 2H, CH_2N), 4.45–4.52 (m, 1H, CH in 3), 5.35 and 5.39 (m, 1H,=CH), 5.62 (dd, 1H, $^3J_{H-H} = 9.65$ Hz, $^2J_{P-H} = 20.34$ Hz, CHP), 6.65 and 6.70 (t, 1H, N<u>H</u>CH_2, $^3J_{H-H} = 4.8$ Hz), 6.84–7.41 (m, 9H, H_{arom}), 7.89 and 7.96 (dd, 1H, $^3J_{H-H} = 9.64$ Hz, $^3J_{P-H} = 3.60$ Hz, N<u>H</u>CH); ^{13}C NMR ($CDCl_3$) δ: 15.9, 16.5, 16.8, 17.1, 17.6, 18.5, 21.7, 23.6, 23.7, 23.9, 28.2, 28.4, 30.1, 31.2, 32.1, 37.1, 38.0, 38.6, 39.3, 39.7, 39.9, 40.1, 42.6, 47.8, 48.1, 53.9, 54.2 (C-18), 55.6 (C-5), 64.9 (O–<u>C</u>H_3), 81.2 (C-3), 114.5, 120.8, 120.9, 125.5 (C-12), 126.7, 129.9, 130.1, 139.4 (C-13), 150.8, 160.0, 169.0 (O–<u>C</u>=O), 171.4 (NH–C=O), 178.9, 179.4 (C-28); ^{31}P NMR ($CDCl_3$) δ: 18.30 and 18.42. Anal. calcd for $C_{48}H_{67}N_2O_8P{\cdot}H_2O$: C, 67.90; H, 8.19; N, 3.30. Found: C, 67.78; H, 8.05; N, 3.18.

*Phenyl[(N-3β-acetoxy-urs-12-en-28-oyl)(aminomethylcarbonyl)(aminomethyl-N-butyl)] Phosphonate (**11b**).* Yield 16%; pale yellow solid; mp 102°C–103°C; IR (KBr) (cm^{-1}): 3395, 2925, 1737, 1656, 1245, 1028; ^{1}H NMR ($CDCl_3$) δ: 0.59–1.97 (m, 52H, $CH_2CH_2CH_2CH_3$ + parent structure of ursolic acid unless otherwise indicated), 1.97 (s, 3H, $CH_3C{=}O$), 3.51 (d, 1H,$^3J_{H-H} = 9.36$ Hz, CH in 18), 3.45–4.04 (m, 2H, $CH_2C{=}O$), 4.06–4.17 (m, 1H, CHP), 4.41 (dd, overlapped, 1H, $^3J_{H-H} = 8.04$, 6.55 Hz, CH in 3), 5.33 (m, 1H, CH=C), 6.64 and 6.66 (t, 1H, N<u>H</u>CH_2, $^3J_{H-H} = 4.13$ Hz), 7.09–7.28 (m, 5H, H_{arom}), 8.37 and 8.65 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ: 14.0, 15.8, 16.0, 16.8, 17.1, 17.6, 18.5, 21.7, 23.6, 23.7, 23.8, 28.1, 28.4, 29.7, 31.2, 32.1, 37.2, 38.0, 38.7, 39.4, 39.9, 40.1, 42.6, 47.8, 48.6, 54.2(C-18), 55.6 (C-5), 81.1 (C-3), 120.8, 125.3 (C-12), 126.1, 126.6, 130.0, 139.4 (C-13), 141.5, 150.8, 169.4 (O–<u>C</u>=O), 171.4 (NH–C=O), 179.1 (C-28); ^{31}P NMR ($CDCl_3$) δ: 21.74 and 21.92. Anal. calcd for $C_{45}H_{69}N_2O_7P{\cdot}1/2H_2O$: C, 68.41; H, 8.95; N, 3.55. Found: C, 68.38; H, 9.34; N, 3.63.

*Phenyl[(N-3β-acetoxy-urs-12-en-28-oyl)(aminomethylcarbonyl)(aminomethylphenyl)] Phosphonate (**11c**).* Yield 15%; pale yellow solid; mp 141°C–143°C; IR (KBr) (cm^{-1}): 3391, 2928, 1735, 1695, 1653, 1244, 1027; ^{1}H NMR ($CDCl_3$) δ: 0.57–1.96 (m, 42H, parent structure of ursolic acid unless otherwise indicated), 1.98 (s, 3H, CH_3), 3.50 (d, 1H, $^3J_{H-H} = 9.86$ Hz, CH in 18), 3.62–4.09 (m, 2H, CH_2N), 4.42 (m, 1H, CH in 3), 5.23 and 5.24 (m, 1H,=CH), 5.59 (dd, 1H, $^3J_{H-H} = 9.44$ Hz, $^2J_{P-H} = 19.72$ Hz, CHP), 6.56 and 6.58 (br s, 1H, NH), 6.89–7.37 (m, 10H, H_{arom}), 7.81 and 7.84 (br s, 1H, N<u>H</u>CH), 8.63 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ: 15.9, 16.5, 16.8, 17.1, 17.6, 18.5, 21.7, 23.6, 23.7, 23.9, 25.2, 28.2, 28.4, 30.1, 30.7, 31.2, 32.1, 37.1, 37.3, 38.0, 38.7, 39.3, 39.7, 39.9, 40.1, 42.6, 47.8, 48.1, 53.8, 54.2 (C-18), 55.5 (C-5), 81.2 (C-3), 120.8, 120.9, 125.5 (C-12), 126.6, 128.6, 129.1, 130.1, 134.7, 139.5 (C-13), 150.7, 169.1 (O–<u>C</u>=O), 171.4 (NH–C=O), 179.0, 179.5 (C-28); ^{31}P NMR ($CDCl_3$) δ: 18.04 and 18.18. Anal. calcd for $C_{47}H_{65}N_2O_7P{\cdot}1/2H_2O$: C, 69.68; H, 8.22; N, 3.46. Found: C, 69.75; H, 8.50; N, 3.16.

*Phenyl[(N-3β-acetoxy-urs-12-en-28-oyl)(aminomethylcarbonyl)(aminomethyl-p-tolyl)] Phosphonate (**11d**).* Yield 20%; pale yellow solid; mp 121°C–123°C; IR (KBr) (cm^{-1}): 3251, 2933, 1708, 1646, 1590, 1254, 1043; ^{1}H NMR ($CDCl_3$) δ: 0.57–1.95 (m, 43H, parent structure of ursolic acid unless otherwise indicated), 1.97 (s, 3H, $CH_3C{=}O$), 2.25 (s, 3H, CH_3), 3.47 (d, 1H, $^3J_{H-H} = 10.86$ Hz, CH in 18), 3.73–4.01 (m, 2H, $CH_2C{=}O$), 4.40 (m, 1H, CH in 3), 5.27 and 5.31 (m, 1H, =CH), 5.56 (dd, 1H, $^3J_{H-H} = 9.58$ Hz, $^2J_{P-H} = 17.12$ Hz, CHP), 6.57 and 6.62 (br s, 1H, N<u>H</u>CH_2), 7.03–7.28 (m, 9H, H_{arom}), 7.90 and 7.95 (d, 1H, $^3J_{H-H} = 9.57$ Hz, N<u>H</u>CH), 8.36 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ: 15.9, 16.5, 16.8, 17.1, 17.6, 18.5, 21.6, 21.7, 23.1, 23.6, 23.7, 25.2, 28.2, 28.4, 30.1, 31.2, 32.3, 37.1, 37.3, 38.0,

38.6, 39.3, 39.7, 39.9, 40.0, 42.6, 47.8, 48.1, 53.8, 54.0 (C-18), 55.5 (C-5), 81.2 (C-3), 120.8, 121.0, 125.5 (C-12), 126.7, 128.5, 129.8, 130.1, 131.6, 139.4 (C-13), 150.8, 169.0 (O—C=O), 171.4 (NH—C=O), 179.0, 179.4 (C-28); ^{31}P NMR ($CDCl_3$) δ: 18.35 and 18.53. Anal. calcd for $C_{48}H_{67}N_2O_7P{\cdot}3H_2O$: C, 66.34; H, 8.47; N, 3.22. Found: C, 66.47; H, 8.69; N, 3.64.

*Phenyl[(N-3β-acetoxy-urs-12-en-28-oyl)(aminomethylcarbonyl)(aminomethyl-2,4-dichlorophenyl)] Phosphonate (***11e***).* Yield 14%; pale yellow solid; mp 138°C–140°C; IR (KBr) (cm^{-1}): 3375, 2923, 1737, 1660, 1369, 1244, 1024; ^{1}H-NMR ($CDCl_3$) δ: 0.59–1.92 (m, 43H, parent structure of ursolic acid unless otherwise indicated), 1.94 (s, 3H, CH_3C=O), 3.43 (d, 1H, $^3J_{H-H} = 9.36$ Hz, CH in 18), 3.50–3.96 (m, 2H, CH_2C=O), 4.36 (m, 1H, CH in 3), 5.28 (m, 1H, CH=C), 6.10 (dd, 1H, $^3J_{H-H} = 7.88$ Hz, $^2J_{P-H} = 22.86$ Hz, CHP), 6.60 and 6.91 (br s, 1H, N<u>H</u>CH_2), 7.08–7.40 (m, 8H, H_{arom}), 7.67 and 7.80 (br s, 1H, N<u>H</u>CH), 8.59 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ: 16.0, 16.5, 16.8, 17.1, 17.4, 17.7, 18.5, 21.6, 21.7, 23.6, 23.7, 23.9, 25.4, 26.0, 28.1, 28.4, 30.7, 31.2, 32.1, 33.0, 37.1, 37.4, 38.0, 38.7, 39.3, 39.5, 39.9, 40.1, 42.6, 43.1, 47.8, 48.1, 48.6, 53.9, 54.2 (C-18), 55.6 (C-5), 81.1 (C-3), 120.8, 120.9, 125.7 (C-12), 126.1, 127.9, 129.9, 130.7, 132.1, 135.2, 139.4 (C-13), 141.5, 150.8, 154.3, 169.0 (O—C=O), 171.4 (NH—C=O), 174.6, 179.5 (C-28); ^{31}P NMR ($CDCl_3$) δ: 16.86 and 16.98. Anal. calcd for $C_{47}H_{63}Cl_2N_2O_7P$: C, 64.89; H, 7.30; N, 3.22. Found: C, 64.94; H, 7.24; N, 2.91.

*Phenyl[(N-3β-acetoxy-urs-12-en-28-oyl)(aminomethylcarbonyl)(aminomethyl-o-nitro phenyl)] Phosphonate (***11f***).* Yield 12%; yellow solid; mp 143°C–145°C; IR (KBr) (cm^{-1}): 3372, 2930, 1733, 1696, 1652, 1534, 1243, 1024; ^{1}H NMR ($CDCl_3$) δ: 0.60–1.94 (m, 43H, parent structure of ursolic acid unless otherwise indicated), 1.97 (s, 3H, CH_3C=O), 3.55–4.15 (m, 3H, H-18, CH_2C=O), 4.41 (d t, overlapped, 1H, $^3J_{H-H} = 6.24$, 6.05 Hz, CH in 3), 5.30 (m, 1H, CH=C), 6.70 and 6.78 (dd, 1H, $^3J_{H-H} = 6.08$ Hz, $^2J_{P-H} = 20.56$ Hz, CHP), 6.90 and 6.93 (br s, 1H, N<u>H</u>CH_2) 7.01–7.99 (m, 9H, H_{arom}), 8.06 (br s, 1H, N<u>H</u>CH); ^{13}C NMR ($CDCl_3$) δ: 15.9, 16.3, 16.9, 17.1, 17.6, 18.5, 21.7, 23.7, 23.9, 25.2, 28.1, 28.4, 30.1, 31.2, 32.9, 37.1, 37.4, 38.0, 38.6, 39.3, 39.7, 39.9, 40.0, 42.6, 47.8, 48.1, 53.9, 54.2 (C-18), 55.6 (C-5), 66.2, 81.2 (C-3), 120.4, 120.9, 125.8 (C-12), 126.7, 129.3, 133.9, 130.1, 139.4 (C-13), 148.7, 150.6, 169.3 (O—C=O), 171.4 (NH—C=O), 179.4 (C-28); ^{31}P NMR ($CDCl_3$) δ: 16.30 and 16.97. Anal. calcd for $C_{47}H_{64}N_3O_9P{\cdot}2H_2O$: C, 64.00; H, 7.77; N, 4.76. Found: C, 64.05; H, 7.97; N, 4.52.

*Phenyl[(N-3β-acetoxy-urs-12-en-28-oyl)(aminoethylcarbonyl)(aminomethylphenyl)] Phosphonate (***12a***).* Yield 18%; pale yellow solid; mp 105°C–107°C; IR (KBr) (cm^{-1}): 3380, 2918, 1737, 1695, 1654, 1248, 1028; ^{1}H NMR ($CDCl_3$) δ: 0.59–1.96 (m, 43H, parent structure of ursolic acid unless otherwise indicated), 1.98 (s, 3H, CH_3C=O), 3.04–3.46 (m, 2H, CH_2C=O), 3.49 (m, 1H, H-18), 3.51–3.92 (m, 2H, CH_2N), 4.37 and 4.40 (t, 1H, $^3J_{H-H} = 3.56$ Hz, H-3), 5.09 and 5.14 (m, 1H,=CH), 5.61 and 5.68 (dd, 1H, $^3J_{H-H} = 7.34$ Hz, $^2J_{P-H} = 13.36$ Hz, CHP), 6.37 and 6.48 (t, 1H, $^3J_{H-H} = 6.02$ Hz, N<u>H</u>CH_2 minor isomer), 7.04–7.44 (m, 11H, H_{arom}, NHCH); ^{13}C NMR ($CDCl_3$) δ: 15.9, 16.5, 17.1, 17.5, 18.5, 21.6, 21.7, 23.6, 23.9, 25.1, 28.1, 28.4, 30.1, 30.7, 31.2, 32.3, 33.0, 35.6, 37.1, 37.5, 37.6, 38.0, 38.6, 39.3, 39.9, 40.0, 42.6, 47.8, 48.0, 53.8, 54.0 (C-18), 55.6 (C-5), 65.0, 66.3, 81.3 (C-3), 115.7, 120.8, 125.6 (C-12), 126.3, 128.7, 129.2, 130.1, 134.8, 139.2 (C-13), 150.7, 169.1 (O—C=O), 171.5 (NH—C=O), 178.7 (C-28); ^{31}P NMR ($CDCl_3$) δ: 18.69 and 18.76. Anal. calcd for $C_{48}H_{67}N_2O_7P$: C, 70.74; H, 8.29; N, 3.44. Found: C, 70.50; H, 8.30; N, 3.39.

*Phenyl[(N-3β-acetoxy-urs-12-en-28-oyl)(aminoethylcarbonyl)(aminomethyl-o-chlorophenyl)] Phosphonate (***12b***).* Yield 16%; pale yellow solid; mp 119°C–121°C; IR (KBr) (cm^{-1}): 3385, 2927, 1734, 1656, 1243, 1022; ^{1}H NMR ($CDCl_3$) δ: 0.66–1.96 (m, 43H, parent structure of ursolic acid unless otherwise indicated), 1.97 (s, 3H, CH_3C=O), 3.02–3.58 (m, 2H, CH_2C=O), 3.59 (d, 1H, $^3J_{H-H} = 9.86$ Hz, H-18), 3.60–4.14 (m, 4H, N–CH_2–CH_2), 4.40 (m, 1H, H-3), 5.09 and 5.12 (m, 1H, H-12), 5.42 and 5.66 (dd, 1H, $^3J_{H-H} = 9.44$ Hz, $^2J_{P-H} = 22.26$ Hz, CHP), 6.33 and 6.48 (br s, 1H, N<u>H</u>CH_2), 7.08–7.38 (m, 9H, H_{arom}), 7.50 (br s, 1H, NHCH) 8.98 and 9.06 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ: 15.9, 16.4, 17.1, 17.5, 18.5, 21.6, 21.7, 23.6, 23.9, 25.1, 28.1, 28.4, 29.7, 30.1, 30.7, 31.1, 31.3, 33.0, 35.6, 35.8, 37.1, 37.6, 38.0, 38.6, 39.3, 39.9, 42.7, 47.8, 48.0, 53.2, 53.9, 54.0 (C-18), 55.6 (C-5), 65.0, 81.3 (C-3), 115.8, 120.8, 125.6 (C-12), 120.8, 125.8, 126.3, 129.3, 130.2, 139.4 (C-13), 150.7, 163.7 (O—C=O), 171.4 (NH—C=O), 178.6 (C-28); ^{31}P NMR ($CDCl_3$) δ: 17.98 and 21.52. Anal. calcd for $C_{48}H_{66}ClN_2O_7P{\cdot}3H_2O$: C, 63.81; H, 8.03; N, 3.10. Found: C, 63.85; H, 8.26; N, 3.57.

*Phenyl[(N-3β-acetoxy-urs-12-en-28-oyl)(aminoethylcarbonyl)(aminomethyl-p-chlorophenyl)]Phosphonate (***12c***).* Yield 11%; pale yellow solid; mp 125°C–127°C; IR (KBr) (cm^{-1}): 3400, 2926, 1735, 1657, 1534, 1243, 1026; ^{1}H NMR ($CDCl_3$) δ: 0.65–1.95 (m, 43H, parent structure of ursolic acid unless otherwise indicated), 1.96 (s, 3H, CH_2C=O), 3.06–3.45

(m, 2H, $CH_2C{=}O$), 3.56 (m, 1H, H-18), 3.60–3.90 (m, 2H, NCH_2), 4.43 (m, 1H, H-3), 5.02 and 5.15 (m, 1H, H-12), 6.16 and 6.23 (dd, 1H, $^3J_{H-H} = 8.42$ Hz, $^2J_{P-H} = 19.75$ Hz, CHP, minor isomer), 6.31 and 6.51 (br s, 1H, $N\underline{H}CH_2$), 7.08–7.52 (m, 9H, H_{arom}), 7.55 (br s, 1H, $N\underline{H}CH$, minor isomer), 8.92 and 9.04 (br s, 1H,OH); ^{13}C NMR ($CDCl_3$) δ: 15.9, 16.3, 17.1, 17.3, 17.5, 18.5, 21.6, 21.7, 23.6, 23.7, 23.9, 25.1, 28.2, 28.4, 29.7, 30.1, 30.7, 31.1, 31.3, 32.1, 33.0, 35.3, 35.4, 37.1, 37.6, 38.1, 38.6, 39.3, 39.9, 42.6, 47.8, 48.0, 53.2, 53.8, 54.2 (C-18), 55.6 (C-5), 62.0, 65.0, 81.3 (C-3), 120.8, 125.7 (C-12), 126.4, 126.5, 127.6, 129.9, 130.1, 133.3, 133.5, 134.4, 134.6, 139.0, 139.4 (C-13), 150.7, 168.7 (O—$\underline{C}$=O), 171.4 (NH—C=O), 178.6 (C-28); ^{31}P NMR ($CDCl_3$) δ: 18.12 and 18.15. Anal. calcd for $C_{48}H_{66}ClN_2O_7P{\cdot}1/2H_2O$: C, 67.15; H, 7.88; N, 3.26. Found: C, 67.24; H, 7.83; N, 3.28.

*Phenyl[(N-3β-acetoxy-urs-12-en-28-oyl)(aminoethylcarbonyl)(aminomethyl-p-tolyl)] Phosphonate (***12d***).* Yield 8%; pale yellow solid; mp 126°C–128°C; IR (KBr) (cm^{-1}): 3400, 2922, 1736, 1647, 1243, 1026; ^1H NMR ($CDCl_3$) δ: 0.58–1.96 (m, 43H, parent structure of ursolic acid unless otherwise indicated), 1.97 (s, 3H, $CH_3C{=}O$), 2.10 (s, 3H, CH_3), 3.03–4.20 (m, 5H, H-18, $CH_2C{=}O$, NCH_2), 4.41 (m, 1H, H-3), 5.12 and 5.19 (m, 1H, H-12), 5.60 and 5.70 (dd, 1H, $^3J_{H-H} = 9.88$ Hz, $^2J_{P-H} = 22.65$ Hz, CHP), 6.38 and 6.52 (t, 1H, $^3J_{H-H} = 9.88$ Hz, $NHCH_2$), 7.06–7.31 (m, 10H, H_{arom}, $NHCH_2$), 8.90 and 9.34 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ: 15.8, 16.4, 17.1, 17.3, 17.5, 18.5, 21.6, 21.7, 23.6, 23.9, 25.1, 28.2, 28.4, 29.7, 30.1, 30.7, 31.1, 31.3, 32.3, 33.0, 35.3, 35.4, 37.1, 37.6, 38.0, 38.6, 39.2, 39.9, 42.6, 47.8, 48.0, 54.0 (C-18), 55.5 (C-5), 64.9, 81.3 (C-3), 115.8, 120.9, 125.6 (C-12), 126.3, 128.6, 129.9, 130.1, 131.8, 138.6, 139.0, 139.3 (C-13), 150.9, 168.7 (O—C=O), 171.4 (NH—C=O), 178.6 (C-28); ^{31}P NMR ($CDCl_3$) δ: 18.75 and 22.21. Anal. calcd for $C_{49}H_{69}N_2O_7P{\cdot}3/2H_2O$: C, 65.97; H, 8.52; N, 3.14. Found: C, 66.07; H, 8.59; N, 3.56.

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