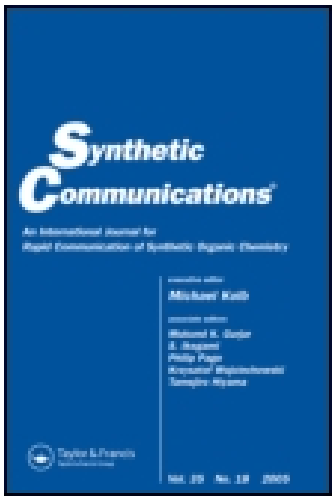

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SYNTHESIS OF N-PHOSPHOPEPTIDES COUPLED BY DICHLOROTRIPHENYLPHOSPHORANE

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SYNTHESIS OF N-PHOSPHOPEPTIDES COUPLED BY DICHLOROTRIPHENYL-PHOSPHORANE

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ABSTRACT

Coupling of N-phosphoamino acids **2** and amino acid methyl esters by dichlorotriphenylphosphorane **3** produced N-phosphopeptide methyl esters **5**, which were sequentially hydrolyzed in triethylamine or dilute NaOH aqueous solution. The target products N-phosphodipeptides **6** were obtained in reasonable yields and high purity after isolation using extraction method. The convenient and efficient approach could be generally used for synthesis of polypeptides.

Derivatives of N-phosphopeptides are of pharmaceutical and biologically active interest.[1–4] They are continuing to be increasingly important as mechanistic probes for proteases,[5] potent inhibitors of peptidases as tetrahedral transition-state or high-energy intermediate analogs,[6] useful tools for

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the investigation of phosphorylation, or as important posttranslational modification of peptides and proteins.[7]

In order to decipher the role of many phosphopeptides and explore their biological activities, a facile method to acqurie multi-gram quantities of phosphopeptides is in high demand. In general, N-(dialkoxyphosphoryl)peptides were prepared by phosphorylating the peptides obtained by the deprotection of N-protected peptides such as N-Boc-peptides.[4] However, N-(dialkoxyphosphoryl)amino acids have hardly been used for the synthesis of N-(dialkoxyphosphoryl)peptides, probably because it is difficult to synthesize and purify them. Fortunately, an efficient method to prepare highly pure and large quantities of N-phosphoamino acids has been developed in our lab.[8]

Furthermore, it has been proved that the phosphinic carboxylic mixed anhydride method had the superiority in peptide synthesis[9] than the mixed carboxylic anhydride method for the faster coupling rate, more regiospecificity in nucleophilic attack and more thermal stability to disproportionation. Hence, the methodology of N-phosphopeptide synthesis starting from N-phosphoamino acid and using dichlorotriphenylphosphorane **3** as the coupling reagent was investigated.

RESULTS AND DISCUSSION

Synthesis of N-(Diisopropyloxyphosphoryl)dipeptide Methyl Esters 5 (N-DIPP-dipeptide Methyl Esters)

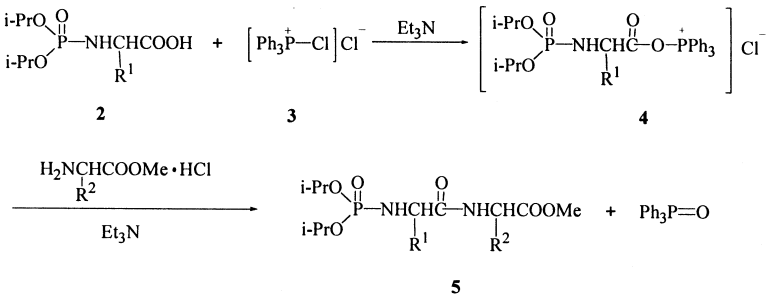
Dichlorotriphenylphosphorane **3**, which was assigned to the ionised form according to ^{31}P NMR spectrum ($\delta_P = 61.1$ ppm), is either commercially available or can readily be prepared by the reaction of triphenylphosphine with hexachloroethane without any undesirable phosphorus by-product (**Scheme 1**).[10]

3

Scheme 1. Synthetic Pathway of Dichlorotriphenylphosphorane **3**.

1.5 equivalents of in-situ generated dichlorotriphenylphosphorane **3** was added to 1 equivalent of N-(diisopropyloxyphosphoryl)amino acid **2** (N-DIPP-amino acid **2**), amino acid methyl ester and triethylamine (Et_3N) in CH_2Cl_2 at room temperature. The mixture was stirred for 1 h,

and compound **2** and amino acid ester almost transferred into N-DIPP-dipeptide methyl ester **5** in quantitative amount (indicated by the single signal at about ^{31}P NMR 6.8 ppm of compound **5**) (**Scheme 2**). The activation mechanism was proposed that dichlorotriphenylphosphorane **3** phosphorylated N-DIPP-amino acid **2** to give the phosphinic carboxylic mixed anhydride **4**, followed by the nucleophilic attack of amino acid methyl ester resulting into the formation of peptide bond.[11] Excessive dichlorotriphenylphosphorane **3** would consume the remnant water to guarantee the anhydrous environment and make the coupling reaction complete. Moreover, it would not bring in further by-products because **3** can react with H_2O to form triphenylphosphine oxide, which is the same as the product yielded in coupling reaction.



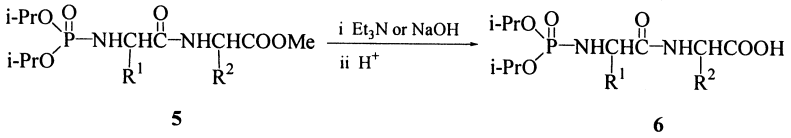
2 **3** **4** **5**

Scheme 2. Synthetic Pathway of N-DIPP-dipeptide Methyl Esters **5**.

Hydrolysis of N-DIPP-dipeptide Methyl Esters 5

In order to avoid the side reactions on N-protecting group DIPP (diisopropyloxyphosphoryl), triethylamine, as a weak base, was the first choice to catalyze the hydrolysis of compound **5** (**Scheme 3**).[12] Yet it was only efficient for the hydrolysis of compound **5a**, **5b** and **5c**. Hydrolysis of compound **5d**, **5e**, **5f**, however, was completed in a stronger base, dilute NaOH aqueous solution, with a longer time as shown in **Table 1**. **Table 1** shows that the only difference between **5a**, **5b**, and **5d**, **5e**, **5f** lies in the side chain of the amino acid residue on C-terminal. And the nuance between compound **5c** and **5e** is the addition of phenyl on the side-chain of the first amino acid residue. These show that the hydrolysis reaction is strongly dependent upon the dual side-chains.

The hydrolysis reaction was carried out in aqueous-organic mixed solvents to facilitate the tracing of reaction process by ^{31}P NMR techniques. N-DIPP-dipeptide methyl esters **5** are organic soluble species, while the



5 6

Scheme 3. Synthetic Pathway of N-DIPP-dipeptides **6**.

Table 1. Hydrolysis of N-DIPP-dipeptide Methyl Esters **5**

Final Poduct **6**	R^1	R^2	Base	Time (h)	Overall Yield (%)
DIPP-Phe-Gly **a**	$-CH_2$-Ph	-H	Et_3N	3.5	85.2
DIPP-Phe-Ala **b**	$-CH_2$-Ph	$-CH_3$	Et_3N	3.5	60.7
DIPP-Ala-Phe **c**	$-CH_3$	$-CH_2$-Ph	Et_3N	3.5	60.0
DIPP-Phe-Leu **d**	$-CH_2$-Ph	$-CH_2$-Pr^1	NaOH (0.17 N)	7.0	80.3
DIPP-Phe-Phe **e**	$-CH_2$-Ph	$-CH_2$-Ph	NaOH (0.17 N)	7.0	75.8
DIPP-Phe-Val **f**	$-CH_2$-Ph	-Pr^1	NaOH (0.65 N)	9.0	88.2

basic hydrolyzed products **6** are the corresponding salts which are aqueous soluble. As the hydrolysis proceeding the signal at about ^{31}P NMR 6.8 ppm of compound **5** in organic phase decreased. At the end point there was no compound **5** left, therefore no ^{31}P NMR signal of compound **5** could be detected in the organic phase. Whilst triphenylphosphine oxide was imprisoned in organic phase (the signal at about ^{31}P NMR 28.0 ppm of $Ph_3P=O$ only existed in the organic phase). So the major impurity was removed completely. Dichlorotriphenylphosphorane **3** gives cleaner reactions due to the high sensitivity towards the atmosphere and the exclusive resultant triphenylphosphine oxide. Hence after eliminating the main impurity $Ph_3P=O$, we got highly pure N-phosphodipeptides **6a–f** using simple extraction workup.

The purity and structure of compounds **6a–f** were determined by ^{1}H NMR, ^{13}C NMR, ^{31}P NMR and ESI-MS methods. Each target product gave only one ^{31}P NMR signal implying that no racemization occurred during this peptide bond formation.[13] These highly optical pure N-DIPP-dipeptides **6a–f** could be used for elongation of N-phosphopeptides or/and test for biological activities.

In conclusion, dichlorotriphenylphosphorane **3** is an effective coupling reagent for synthesis of N-phosphopeptides. The present method enables us to obtain N-phosphopeptides on a large-scale and highly pure production because of its availability, convenience and low racemization. Further, the N-phosphopeptides could be deprotected under acid conditions[14] to yield the corresponding peptides. Thus the convenient and efficient approach could be also applied for the synthesis of polypeptides.

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EXPERIMENTAL

General Procedure

All glassware was dried in an oven for at least 3 h at 120°C prior to use. Air sensitive materials were transferred under a nitrogen atmosphere. Dichloromethane and triethylamine were dried over P_2O_5 and CaH_2 respectively. ^1H MNR and ^{13}C NMR spectra were recorded on Bruker AM 500 spectrometer. TMS ($\delta = 0.0$) and $CDCl_3$ ($\delta = 77.0$ ppm) were references for ^1H and ^{13}C NMR spectra respectively. ^{13}C NMR spectra were all taken under ^1H decoupled and ^{31}P coupled conditions. ^{31}P NMR spectra were taken on Bruker AC 200 spectrometer at 81 MHz under ^1H decoupled conditions. ^{31}P NMR chemical shifts are reported in ppm downfield (+) or upfield (−) from external 85% H_3PO_4 as reference. Mass spectra were conducted on Bruker Esquire-LC mass spectrometer in positive and negative ion mode.

Synthesis of Diisopropyl Phosphite (DIPPH) **1**

The starting material DIPPH **1** was prepared according to the published procedure.[15] Yield: 75%. ^{31}P NMR: 4.4 ppm.

Synthesis of N-(Diisopropyloxyphosphoryl)amino Acids **2**

N-DIPP-amino acid **2** was synthesized by adding diisopropyl phosphite **1** to an aqueous-organic mixture containing the amino acid, water, carbon tetrachloride, triethylamine and ethanol, well stirring the mixture at 0–20°C for a few hours, and quenching the reaction by acidification.[8] Yields: DIPP-Ala, 89%; DIPP-Phe, 93%. ^{31}P NMR: 7.1, 6.9 ppm respectively.

Synthesis of Dichlorotriphenylphosphorane **3**

According to literature,[10] under a nitrogen atmosphere, 2 mmol triphenylphosphine in 3 mL dry CH_2Cl_2 was added dropwise to a stirred 2 mmol hexachloroethane in 3 mL dry CH_2Cl_2 in an ice-water bath. After five minutes, the bath was removed. The reaction was stirred continuously for 1 h at room temperature, then dichlorotriphenylphosphorane **3** was produced. Yield: 90% (by ^{31}P NMR spectral integral). ^{31}P NMR: 61.1 ppm.

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Synthesis of N-(Diisopropyloxyphosphoryl)dipeptide Methyl Esters **5**

Under a nitrogen atmosphere, 1.2 mmol dichlorotriphenylphosphorane **3** in CH_2Cl_2 was added dropwise to a stirred dry CH_2Cl_2 (5 mL) solution of 0.8 mmol N-(diisopropyloxyphosphoryl)amino acid **2**, 0.8 mmol amino acid methyl ester and 350 μL dry Et_3N at room temperature. Extra addition of adequate Et_3N was followed after half an hour. The stirring was continued for 1 h. After the removal of solvent the resultant residue was dissolved in 15 mL ethyl acetate, then followed by the filtration of residue triethylamine hydrochloride. The filtrate was washed with 4 mL 1 mol/L citric acid, 4 mL saturated NaCl solution, 4 mL 5% $NaHCO_3$ solution, and 4 mL H_2O.

Synthesis of N-(Diisopropyloxyphosphoryl)dipeptides **6**

Method A: The above filtrate by ethyl acetate was evaporated to dryness. A mixture of 3.5 mL Et_3N and 3.5 mL H_2O was added to the resulting residue containing N-(diisopropyloxyphosphoryl)dipeptide methyl ester **5** and stirred at 40°C for 3.5 h. The water layer was washed with Et_3N (3×4 mL) followed by addition of 1.5 equivalents NaOH. The mixture was stirred for ten minutes, then washed with CH_2Cl_2 (3×5 mL) and acidified to pH 3 with 1 mol/L HCl in an ice-water bath. The nepheloid solution was extracted with ethyl acetate (3×15 mL). The organic layer was washed with water, brine and dried over anhydrous $MgSO_4$. Removal of the solvent afforded the pure products **6a–c** as white solid.

Spectral data for compounds **6a–c**

N-DIPP-Phe-Gly 6a, yield: 85.2%. ^{31}P NMR (81.0 MHz, AcOEt), δ (ppm): 6.95. ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 1.09–1.25 (m, 12H, ($P(OCH(C\underline{H}_3)_2)_2$), 2.97–3.11 (m, 2H, $C\underline{H}_2Ph$), 3.78–3.83 (m, 2H, $C\underline{H}_2COOH$), 4.04–4.16 (br, 1H, CO-NH), 4.19 (q, $J = 5.7$ Hz, $^3J_{P\text{-}H} = 18.6$ Hz, 1H, $C\underline{H}CH_2Ph$), 4.27–4.38 (m, 2H, $P(OC\underline{H}(CH_3)_2)_2$), 7.18–7.29 (m, 6H, P-NH, Ph). ^{13}C NMR (125 MHz, $CDCl_3$), δ (ppm): 23.52 (br, $OCH(C\underline{H}_3)_2$), 40.30 (d, $^3J_{P\text{-}C} = 5.0$ Hz, $\underline{C}H_2Ph$), 41.49 ($\underline{C}H_2COOH$), 56.78 ($\underline{C}HCH_2Ph$), 71.07 (q, $^2J_{P\text{-}C} = 6.1$ Hz, $P(O\underline{C}H(CH_3)_2)_2$), 126.80–136.53 (Ph), 172.23 (COOH), 172.40 (d, $^3J_{P\text{-}C} = 4.4$ Hz, CO-NH). Positive-ion ESI-MS (m/z): 387.1 $(M + H)^+$. Negative-ion ESI-MS (m/z): 385.1 $(M\text{-}H)^-$.

N-DIPP-Phe-Ala 6b, yield: 60.7%. ^{31}P NMR (81.0 MHz, AcOEt), δ (ppm): 7.21. ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 1.12 (d, $J = 6.0$ Hz, 3H, $CHC\underline{H}_3$), 1.15–1.31 (m, 12H, ($P(OCH(C\underline{H}_3)_2)_2$), 3.01–3.08 (m, 2H, $C\underline{H}_2Ph$), 3.74 (t, 1H, $C\underline{H}CH_3$), 4.06 (br, 1H, CO-NH), 4.28–4.41 (m, 2H

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(P(OCH(CH$_3$)$_2$)$_2$), 4.41–4.54 (m, 1H, CHCH$_2$Ph), 7.19–7.48 (m, 6H, P-NH, Ph). ^{13}C NMR (125 MHz, CDCl$_3$), δ (ppm): 18.13 (CHCH$_3$), 23.51–23.60 (m, (P(OCH(CH$_3$)$_2$)$_2$), 39.59 (d, $^3J_{P\text{-}C} = 5.5$ Hz, CH$_2$Ph), 48.14 (CHCOOH), 56.54 (CHCO-NH), 72.00 (q, $^2J_{P\text{-}C} = 5.8$ Hz, (P(OCH(CH$_3$)$_2$)$_2$), 126.83–136.25 (Ph), 171.99 (d, $^3J_{P\text{-}C} = 4.4$ Hz, CO-NH), 175.16 (COOH). Positive-ion ESI-MS (m/z): 401 $(M+H)^+$. Negative-ion ESI-MS (m/z): 399 $(M\text{-}H)^-$.

N-DIPP-Ala-Phe 6c, yield: 60.0%. ^{31}P NMR (81.0 MHz, AcOEt), δ (ppm): 6.85. ^{1}H NMR (500 MHz, CDCl$_3$), δ (ppm): 1.21 (d, J = 4.5 Hz, 3H, CHCH$_3$, 1.26–1.30 (m, 12H, (P(OCH(CH$_3$)$_2$)$_2$), 2.93 (d, J = 7.5 Hz, 2H, CH$_2$Ph), 4.54 (m, 1H, CHCOOH), 4.54 (br, 1H, CO-NH), 4.58–4.61 (m, 2H, (P(OCH(CH$_3$)$_2$)$_2$), 4.80 (m, 1H, CHCH$_3$), 7.19–7.26 (m, 6H, P-NH, Ph). ^{13}C NMR (125 MHz, CDCl$_3$), δ (ppm): 20.67 (CHCH$_3$), 23.57–23.73 ((P(OCH(CH$_3$)$_2$)$_2$), 37.45 (CH$_2$Ph), 51.42 (CHCOOH), 53.27 (CHCH$_3$), 72.06 (q, $^2J_{P\text{-}C} = 5.3$ Hz, (P(OCH(CH$_3$)$_2$)$_2$), 126.77–136.55 (Ph), 173.12 (d, $^3J_{P\text{-}C} = 5.5$ Hz, CO-NH), 174.20 (COOH). Positive-ion ESI-MS (m/z): 401 $(M+H)^+$. Negative-ion ESI-MS (m/z): 399 $(M\text{-}H)^-$.

Method B: The above filtrate by ethyl ecetate was evaporated to dryness. A mixture of 6 mL NaOH aqueous solution (0.17 mol/L for **6d** and **6e**, 0.65 mol/L for **6f**) and 3 mL CH_2Cl_2 was added to the resulting residue containing N-(diisopropyloxyphosphoryl)dipeptide methyl ester **5** and stirred at room temperature for 7 h. The water layer was washed with CH_2Cl_2 (3×4 mL). The following isolation procedure was the same as that of method A.

Spectral data for compounds **6d–f**.

N-DIPP-Phe-Leu 6d, yield: 80.3%. ^{31}P NMR (81.0 MHz, AcOEt), δ (ppm): 7.28. ^{1}H NMR (500 MHz, CDCl$_3$), δ (ppm): 0.89 (q, J = 6.5, 16.5 Hz, 6H, CH$_2$CH(CH$_3$)$_2$), 1.13–1.25 (m, 12H, P(OCH(CH$_3$)$_2$)$_2$), 1.44–1.55 (m, 2H, CH$_2$CH(CH$_3$)$_2$), 1.59–1.64 (m, 1H, CH$_2$CH(CH$_3$)$_2$), 3.00–3.15 (m, 2H, CH$_2$Ph), 3.58 (t, 1H, CHCOOH), 4.07 (br, 1H, CO-NH), 4.32–4.43 (m, 2H, P(OCH(CH$_3$)$_2$)$_2$), 4.59 (q, J = 7.8 Hz, $^3J_{P\text{-}H} = 13.8$ Hz, 1H, CHCH$_2$pH), 7.19–7.38 (m, 6H, P-NH, Ph). ^{13}C NMR (125 MHz, CDCl$_3$), δ (ppm): 22.29, 22.65 (CH$_2$CH(CH$_3$)$_2$), 23.50–23.65 (P(OCH(CH$_3$)$_2$)$_2$), 24.52 (CH$_2$CH(CH$_3$)$_2$), 39.30 (d, $^3J_{P\text{-}C} = 4.5$ Hz, CH$_2$Ph), 41.51 (CH$_2$CH(CH$_3$)$_2$), 50.83 (CHCOOH), 56.62 (CHCH$_2$Ph), 71.92–72.13 (q, $^2J_{P\text{-}C} = 5.9$ Hz, P(OCH(CH$_3$)$_2$)$_2$), 126.84–136.26 (Ph), 171.85 (d, $^3J_{P\text{-}C} = 5.4$ Hz, CO-NH), 175.26 (COOH). Positive-ion ESI-MS (m/z): 443.3 $(M+H)^+$. Negative-ion ESI-MS (m/z): 441.3 $(M\text{-}H)^-$.

N-DIPP-Phe-Phe 6e, yield: 75.8%. ^{31}P NMR (81.0 MHz, AcOEt), δ (ppm): 6.93. ^{1}H NMR (500 MHz, CDCl$_3$), δ (ppm): 1.03–1.23 (m, 12H, (P(OCH(CH$_3$)$_2$)$_2$), 2.89–3.07 (m, 4H, 2(CH$_2$Ph)), 3.83 (t, J = 10.8 Hz, 1H,

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CHCOOH), 3.99 (br, 1H, CO-NH), 4.26–4.38 (m, 2H, (P(OCH(CH$_3$)$_2$)$_2$), 4.79 (q, J = 6.5 Hz, ^{3}J$_{P\text{-}C}$ = 12.5 Hz, 1H, CHCO-NH), 7.07–7.39 (m, 11H, P-NH, 2Ph). ^{13}C NMR (125 MHz, CDCl$_3$), δ (ppm): 23.45–23.54 ((P(OCH(CH$_3$)$_2$)$_2$), 37.52 (PhCH$_2$CHCOOH), 39.51 (d, ^{3}J$_{P\text{-}C}$ = 4.9 Hz, PhCH$_2$CHCONH), 53.46 (CHCOOH), 56.83 (CHCONH), 71.00 (q, ^{2}J$_{P\text{-}C}$ = 6.1 Hz, (P(OCH(CH$_3$)$_2$)$_2$), 126.69–126.48 (2 Ph), 172.06 (d, ^{3}J$_{P\text{-}C}$ = 5.1 Hz, CO-NH), 173.70 (COOH). Positive-ion ESI-MS (m/z): 477 (M + H)$^+$. Negative-ion ESI-MS (m/z): 475 (M-H)$^-$.

N-DIPP-Phe-Valf 6f, yield: 88.2%. ^{31} P NMR (81.0 MHz, AcOEt), δ (ppm): 6.89. ^{1}H NMR (500 MHz, CDCl$_3$), δ (ppm): 0.86 (dd, J = 7.0, 14.0 Hz, 6H, CHCH(CH$_3$)$_2$), 1.08–1.19 (m, 12H, (P(OCH(CH$_3$)$_2$)$_2$), 2.13–2.18 (m, 1H, CHCH(CH$_3$)$_2$), 2.96–3.04 (m, 2H, CH$_2$Ph), 4.10 (m, 1H, CHCOOH), 4.12 (br, 1H, CO-NH), 4.18–4.37 (m, 2H, (P(OCH(CH$_3$)$_2$)$_2$), 4.45 (q, J = 5.0 Hz, ^{3}J$_{P\text{-}H}$ = 8.5 Hz, 1H, CHCH$_2$Ph), 7.12–7.40 (m, 6H, P-NH, Ph). ^{13}C NMR (125 MHz, CDCl$_3$), δ (ppm): 17.72, 18.53 (CHCH(CH$_3$)$_2$), 23.35–23.46 ((P(OCH(CH$_3$)$_2$)$_2$), 30.92 (CHCH(CH$_3$)$_2$), 39.67 (d, ^{3}J$_{P\text{-}C}$ = 5.1 Hz, CH$_2$Ph), 56.58 (CHCOOH), 57.34 (CHCH$_2$Ph), 71.64 (q, ^{2}J$_{P\text{-}C}$ = 5.8 Hz, (P(OCH(CH$_3$)$_2$)$_2$), 126.59– 136.41 (Ph), 172.85 (d, ^{3}J$_{P\text{-}C}$ = 4.3 Hz, CO-NH), 174.96 (COOH). Positive-ion ESI-MS (m/z): 429 (M + H)$^+$. Negative-ion ESI-MS (m/z): 427 (M-H)$^-$.

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