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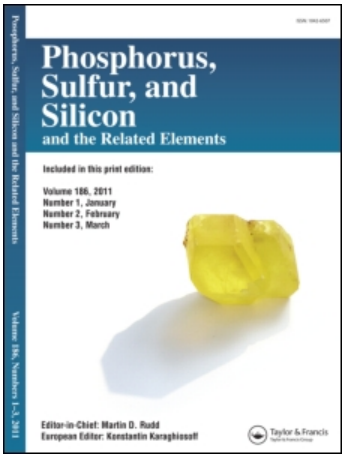


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# Synthesis of Phosphoryl Amino Acids Chrysin Esters

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# Synthesis of Phosphoryl Amino Acids Chrysin Esters

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*The N-phosphoryl amino acids are coupled with chrysin to form phosphoryl amino acids chrysin esters. Five of its new analogs have been synthesized. The structures of all the newly synthesized chrysin derivatives were confirmed by ESI-MS, NMR and IR.*

**Keywords** 5,7-dihydroxyflavone; *N*-phosphoamino acids; phosphoryl amino acids chrysin esters

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## INTRODUCTION

Chrysin, 5,7-dihydroxyflavone, extensively distributed in plants,was reported to have many biological activities, including antioxidant,[1] antibacterial,[2] anticancery,[3] anti-inflammatory,[4] antiallergic,[5] and anxiolytic[6] antivities. Though chrysin has extensively pharmaceutical values in clinics, there are still some flaws to confine its pharmaceutical application, for example, low solubility. Efforts to improve the biological activity of chrysin have led to the development of its derivatives by appropriate modification of chrysin as mentioned in some published papers. Ester and amides of phosphoric acid play a vital role in many biological process and could be hydrolyzed into the parents compound in living organism. The studies from C.B. Xue, H. Fu, and C.X. Lin indicate that *N*-phosphoamino acids are important to explain some living phenomena and probe into living origin, e.g., N-phospho-$\alpha$-amino

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acids could self-activated to give N-phosphoryl peptides, N-phospho-$\alpha$-amino acid esters, ester-exchanged products on phosphorus, and an intramolecular phosphoryl group migration from nitrogen to oxygen, which suggest that N-phosphoamino acids might be prebiotic precursors of oligopeptides. At the same time, they have application foreground in the fields of biology technology, medicine and so on.[7–9] Within the pharmaceutical industry, phosphate esters are often used as prodrugs to increase the water solubility and hence bio-availability of the agent.[10] In the work described in this article, *N*-phosphoamino acids were introduced to modification of crysin. The *N*-phosphated amino acids are coupled with chrysin to form phosphoryl amino acids chrysin esters. Five chrysin new analogs were synthesized. The structures of all the newly synthesized chrysin derivatives were elucidated by ESI-MS (Scheme 2), NMR, and IR.

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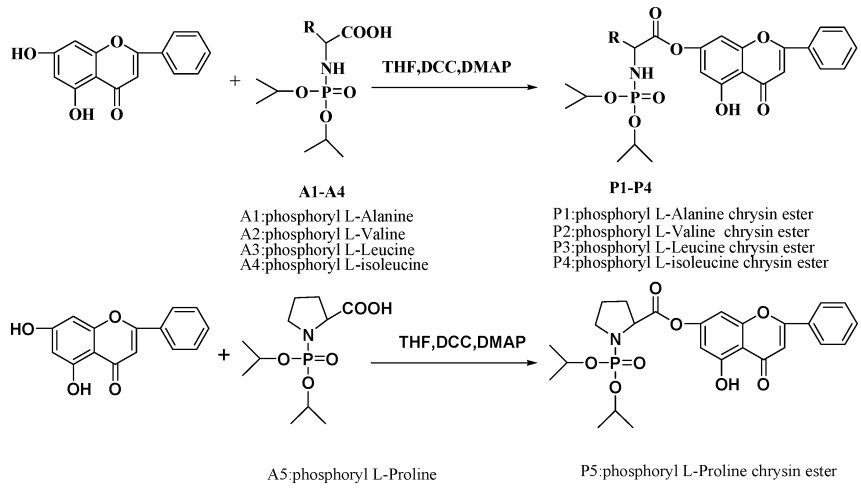
## EXPERIMENTAL

IR spectra were recorded on a Shimadazuir-408 1H and $^{31}$P NMR spectra were on a Bruker-DTX-400. Chemical shifts are expressed in parts per million positive values downfield form internal TMS ($^{1}$H) and externa 85% $H_3PO_4$($^{31}$P). Coupling constants are expressed in Hertz. TLC was performed on silica gel plates and preparative chromatograph on columns of silica gel (200–300 mesh). MS were recorded on Bruker Esquire-3000.




**SCHEME 1**

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## Compound P1. $C_{24}H_{28}NO_8P$

0.5404 g chrysin and 0.5398 g N-phosphoryl L-Alanine were added to a solution of 40 ml THF. The mixture was stirred until chrysin was dissolved and then a solution of DCC and DMAP (0.5936 g DCC + 0.0530 g DMAP) was added with vigorous stirring in ice-water bath. The reaction proceeded for 12 h at 5–10°C. The solution was removed by distillation. The product was further purified by column chromatography (ethyl acetate:petroleum ether:ethanol = 50:40:1). The yield of yellow product is 62%. m.p. 155–156°C. $^1$H NMR (400 MHz, DMSO) $\delta$: 8.10 (d, 2H, $J = 7.40$, 2′-H, 6′-H), 7.62 (m, 3H, 3′-H, 4′-H, 5′-H), 7.13 (s, 1H, 3-H), 7.09 (d, 1H, $J = 1.1$, 6-H), 6.60 (s, 1H, $J = 1.2$, 8-H), 4.51 (m, 2H, 2‴-H), 4.05 (m, 1H, 2″-H), 2.53 (1H, N-H), 1.47 (m, 3H, 1″-H), 1.28 (m, 12H, 1‴-H). $^{13}$C NMR $\delta$: 182.82 (s, 1C, 4-C), 172.21 (s, 1C, 3″-C), 164.57 (s, 1C, 5-C), 160.88 (s, 1C, 2-C), 156.69 (s, 1C, 9-C), 156.22 (s, 1C, 7-C), 132.80 (s, 1C, 1′-C), 130.63 (s, 2C, 3′-C, 5′-C), 129.57 (s, 1C, 4′-C), 126.83 (d, 2C, $J = 98$,2′-C, 6′-C), 108.66 (s, 1C, 10-C), 106.11 (s, 1C, 6-C), 105.31 (s, 1C, 3-C), 101.84 (s, 1C, 8-C), 70.34 (m, 1C, 2‴-C), 50.68 (s, C, 2″-C), 23.89 (d, 1C, $J = 17.6$, 1‴-C), 19.67 (d, 1C, $J = 26.4$, 1″-C). $^{31}$P NMR (400 MHz, D2O): $\delta$: 6.243. ESI-MS/MS: m/z: 490[M + H]$^+$, 978 [2M], 1001 [2M + Na]$^+$. IR 1265 (PO). A molecular formula of $C_{24}H_{28}NO_8P$ was determined from the molecular ion peak at 490.1639.1130 m/z [M+H]$^+$ (calcd. 490.1631 for $C_{24}H_{28}NO_8P$ ) obtained by ESIQ-TOF.

## Compound P2. $C_{26}H_{32}NO_8P$

0.4678 g chrysin and 0.5895 g phosphoryl L-valine was added to a solution of 40 ml THF. The mixture was stirred until chrysin was dissolved and then a solution of DCC and DMAP (0.5216 g DCC + 0.0568 g DMAP) was added dropwise with vigorous stirring in ice-water bath. The reaction proceeded for 12 h at 5–10°C. The solution was removed by distillation. The product was further purified by column chromatography (ethyl acetate:petroleum ester:ethanol = 50:40:1). The yield of yellow product is 60%. m.p. 176–178. $^1$H NMR (400 MHz, DMSO): $\delta$: 8.14 (d, 2H, $J = 7.20$, 2′-H, 6′-H), 7.62 (m, 3H, 3′-H, 4′-H, 5′-H), 7.16 (s, 1H, 3-H), 7.09 (d, 1H, $J = 0.8$, 6-H), 6.60 (s, 1H, 8-H), 4.49 (m, 2H, 2‴-H), 3.67 (m, 1H, 3″-H), 2.52 (1H, N-H), 2.13 (m, 1H, 2″-H), 1.24 (m, 12H, 1‴-H), 1.03 (m, 6H, 1″-H). $^{13}$C NMR $\delta$:182.84 (s, 1C, 4-C), 171.30 (s, 1C, 4″-C), 164.57 (s, 1C, 5-C), 160.87 (s, 1C, 2-C), 156.73 (s, 1C, 9-C), 155.93 (s, 1C, 7-C), 132.82 (s, 1C, 1′-C), 130.63 (s, 2C, 3′-C, 5′-C), 129.55 (s, 1C, 4′-C), 126.99 (d, 2C, $J = 98$, 2′-C, 6′-C), 108.72 (s, 1C, 10-C), 106.13 (s, 1C, 6-C), 105.12 (s, 1C, 3-C), 101.82 (s, 1C, 8-C), 70.45 (d, 1C, $J = 55.6$, 2‴-C), 60.91 (s, 1C, 3″-C), 31.53 (s, 1C, 2″-C), 19.05 (d, 1C, $J = 27$,

1″-C).$^{31}$P NMR (400 MHz, D2O): $\delta$ 7.01. ESI-MS/MS: m/z: 518 $[M+H]^+$, 1057 $[2M+Na]^+$. IR 1266 (PO). A molecular formula of $C_{26}H_{32}NO_8P$ was determined from the molecular ion peak at 518.1940 m/z $[M+H]^+$ (calcd. 518.1944 for $C_{26}H_{32}NO_8P$) obtained by ESI-Q-TOF.

## Compound P3. $C_{27}H_{34}NO_8P$

0.6202 g chrysin and 0.6649 g phosphoryl L-leucine was added to a solution 40 ml THF. The mixture was stirred until chrysin was dissolved and then a solution of DCC and DMAP (0.5665 g DCC + 0.0593 g DMAP) was added dropwise with vigorous stirring in ice-water bath. The reaction proceed for 12 h at 5–10°C. The solution was removed by distillation. The product was futher purified by comumn chromatography (ethyl acetate:petroleum ether:ethanol = 50:40:1).The yield of yellow productis 64%. m.p. 157–159. $^1$H NMR(400 MHz, DMSO) $\delta$: 8.13 (d, 2H, $J = 7.20$, 2′-H, 6′-H), 7.62 (m, 3H, 3′-H, 4′-H, 5′-H), 7.14 (s, 1H, 3-H), 7.10 (d, 1H,$J = 0.8$, 6-H), 6.63 (d, 1H, $J = 1.78$, 8-H), 4.48 (m, 2H, 2‴-H), 3.91 (m, 1H, 4″-H), 2.52 (1H, N-H), 1.85 (m, 1H, 2″-H), 1.68 (m, 2H, 3″-H), 1.21 (m, 12H, 1‴-H), 0.92 (m, 6H, 1″-H). $^{13}$C NMR $\delta$: 182.93 (s, 1C, 4-C), 172.34 (s, 1C, 5″-C), 164.63 (s, 1C, 5-C), 160.96 (s, 1C, 2-C), 156.81 (s, 1C, 9-C), 155.19 (s, 1C, 7-C), 132.90 (s, 1C, 1′-C), 130.73 (s, 2C, 3′-C, 5′-C), 129.65 (s, 1C, 4′-C), 127.07 (s, 2C, 2′-C, 6′-C), 108.79 (s, 1C, 10-C), 106.22 (s, 1C, 6-C), 105.32 (s, 1C, 3-C), 101.93 (s, 1C, 8-C), 70.45 (m, 1C, ,2‴-C), 53.35 (s, 1C, 4″-C), 42.00 (d, 1C, $J = 31.20$, 3″-C), 24.20 (d, 1C, $J = 167.6$, 1‴-C) 23.19 (s, 2C, 1″-C), 21.74 (s, 1C, 2″-C). $^{31}$P NMR (400 MHz, D2O) $\delta$: 6.899 ... ESI-MS/MS: m/z: 532 $[M+H]^+$. IR 1267 (PO). A molecular formula of $C_{27}H_{34}NO_8P$ was determined from the molecular ion peak at 532.2104 m/z $[M+H]^+$ (calc. 532.2100 for $C_{27}H_{34}NO_8P$) obtained by ESI-Q-TOF.

## Compound P4. $C_{27}H_{34}NO_8P$

0.5035 g chrysin and 0.6487 g phosphoryl L-isoleucine was added to a solution 40 ml THF. The mixture was stirred until chrysin was dissolved and then a solution of DCC and DMAP (0.5665 g DCC + 0.0435 g DMAP) was added dropwise with vigorous stirring in ice-water bath. The reaction proceed for 12 h at 5–10°C. The solution was removed by distillation. The product was further purified by column chromatography (ethyl acetate:petroleum ether:ethanol = 50:40:1). The yield of yellow product is 63%. m.p. 158–160. $^1$H NMR (400 MHz, DMSO): $\delta$: 8.14 (m, 2H, 2′-H, 6′-H), 7.63 (m, 3H, 3′-H, 4′-H5′-H), 7.16 (s, 1H, 3-H), 7.09 (d, 1H, $J = 1.98$, 6-H), 6.60 (d, 1H, $J = 1.97$, 8-H), 4.49 (m, 2H, 2‴-H), 3.73 (m, 1H, 4″-H), 2.52 (1H, N-H), 1.89 (m, 1H, 3″-H), 1.62 (m,

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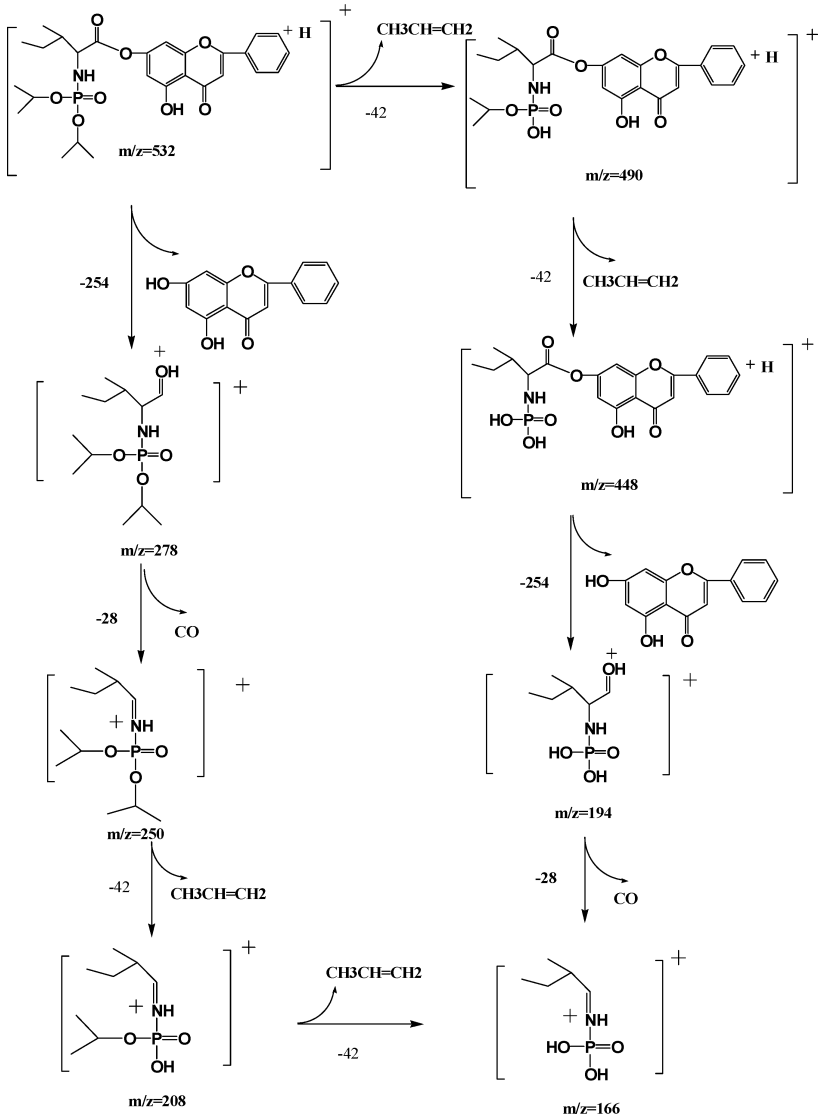
2H, 2″-H), 1.26 (m, 12H, 1‴-H), 1.00 (m, 3H, 6″-H), 0.92 (m, 3H, 1″-H). $^{13}$C NMR $\delta$: 182.84 (s, 1C, 4-C), 171.26 (s, 1C, 5″-C), 164.57 (s, 1C, 5-C), 160.87 (s, 1C, 2-C), 156.74 (s, 1C, 9-C), 155.90 (s, 1C, 7-C), 132.82 (s, 1C, 1′-C), 130.62 (s, 2C, 3′-C, 5′-C), 129.55 (s, 1C, 4′-C), 127.00 (s, 2C,




**SCHEME 2** Positive ion ESI mass spectral fragmentation pathway of protonated compound P4.

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2′-C, 6′-C), 108.72 (s, 1C, 10-C), 106.13 (s, 1C, 6-C), 105.15 (s, 1C, 3-C), 101.81 (s, 1C, 8-C), 70.39 (m, 1C, 2‴-C), 59.53 (s, 1C, 4″-C), 37.86 (d, 1C, $J = 31.20$, 3″-C), 24.97 (s, 1C, 2″-C) , 23.89 (d, 1C, $J = 18.4$, 1‴-C), 15.69 (s, 1C, 6″-C), 11.20 (s, 1C, 1″-C). $^{1}$P NMR (400MHz, $D_2O$) $\delta$: 4.59 $\delta$: 7.30. ESI-MS/MS: m/z: 532 $[M+H]^+$, 1062 $[2M]^+$. IR 1267 (PO). A molecular formula of $C_{27}H_{34}NO_8P$ was determined from the molecular ion peak at 532.2103 m/z $[M+H]^+$ (calcd. 532.2100 for $C_{27}H_{34}NO_8P$) obtained by ESI-Q-TOF.

## Compound P5. $C_{26}H_{30}NO_8P$

0.4715 chrysin and 0.4335 g phosphoryl L-isoleucine was added to a solution 40 ml THF. The mixture was stirred until chrysin was dissolved and then a solution of DCC and DMAP (0.4821 g DCC + 0.0439 g DMAP) was added dropwise with vigorous stirring in ice-water bath. The reaction proceed for 12 h at 5–10°C. The solution was removed by distillation. The product was futher purified by comumn chromatography (ethyl acetate:petroleum ether:ethanol = 50:40:1). The yield of yellow product is 63%. m.p. 163–164°C. $^{1}$H NMR (400 MHz, DMSO): 8.12 (m, 2H, 6′-H, 2′-H), 7.63 (m, 3H, 3′-H, 5′-H, 4′-H), 7.14 (s. 1H, 3-H), 7.12 (d, 1H, $J = 1.92$, 6-H), 6.67 (d, 1H, $J = 1.92$, 8-H), 4.50 (m, 2H, 2‴-H), 4.39 (d, 1H, $J = 4.28$, 4″-H), 3.19 (m, 2H, 1″-H), 2.26 (m, 2H, 3″-H), 1.95 (m, 2H, 2″-H), 1.26 (m, 12H, 1‴-H). $^{13}$C NMR $\delta$:182.94 (s, 1C, 4-C), 172.35 (s, 1C, 5″-C), 164.63 (s, 1C, 5-C), 160.96 (s, 1C, 2-C), 156.76 (s, 1C, 9-C), 156.22 (s, 1C, 7-C), 132.89 (s, 1C, 1′-C), 130.72 (s, 2C, 3′-C, 5′-C), 129.65 (s, 2C, 2′-C, 6′-C), 126.93 (s, 1C, 4′-C), 108.76 (s, 1C, 10-C),106.19 (s, 1C, 6-C), 105.46 (s, 1C, 3-C), 102.01 (s, 1C, 8-C), 70.37 (m, 1C, 2‴-C), 60.60 (d, 1C, $J = 27.2$ 4″-C), 47.22 (s, 1C, 1″-C), 31.26 (d, 1C, $J = 32.40$, 3″-C), 25.64 (d, 1C, $J = 33.6$, 2″-C), 23.95 (m, 1C, 1‴-C). $^{31}$P NMR (400 MHz, D2O) $\delta$: 4.59. ESI-MS/MS: m/z: 516$[M+H]^+$. IR 1267 (PO). A molecular formula of $C_{17}H_{27}Cl_2N_2O_3P$ was determined from the molecular ion peak at 516.1792 m/z $[M+H]^+$ (calc. 516.1787 for $C_{17}H_{27}Cl_2N_2O_3P$) obtained by ESI-Q-TOF.

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