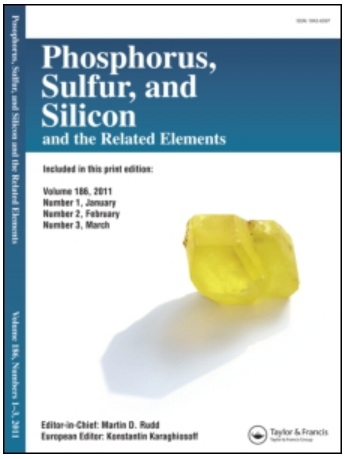

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Synthesis of the Novel Phosphoramidate Derivatives of Chrysin

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SYNTHESIS OF THE NOVEL PHOSPHORAMIDATE DERIVATIVES OF CHRYSIN

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A novel type of phosphoramidate derivatives of chrysin were synthesized by a facile phosphorylation reaction. The structures of all the newly synthesized chrysin derivatives were confirmed by ESI MS, HR MS, NMR, and IR.

Keywords 5,7-Dihydroxyflavone; phosphoramidates; phosphorylation

INTRODUCTION

5,7-Dihydroxyflavone (chrysin), extensively distributed in plants, has been reported to have many biological activities, including antioxidant, antibacterial, anticancer, anti-inflammatory, anti-allergenic, and anxiolytic antivities.[1–6] 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 previously published articles.[7,8] The introduction of a phosphate group essentially changes the physical and chemical properties of the parent molecule, resulting in changes to the polarization and intermolecular bonding characteristics of that molecule.[9–11] Moreover, phosphates and phosphoramidates were widely used as pro-drug moieties to enhance water solubility and have proven to be exceedingly important agents for anticancer and antiviral therapy.[12–17]

Given the importance of this functional group to these properties and potential biological activities, arylalkoxy-amino acid phosphorochloridates are coupled with chrysin to provide the target compounds, aryl phosphoramidates of chrysin, in order to change the physical and chemical properties of the parent molecule and enhance its bio-availability. A novel type of phosphoramidate derivatives of chrysin was synthesized by a facile phosphorylated reaction (Scheme 1) for the first time. The structures of all the newly synthesized chrysin derivatives were elucidated by ESI MS, HR MS, NMR, and IR.

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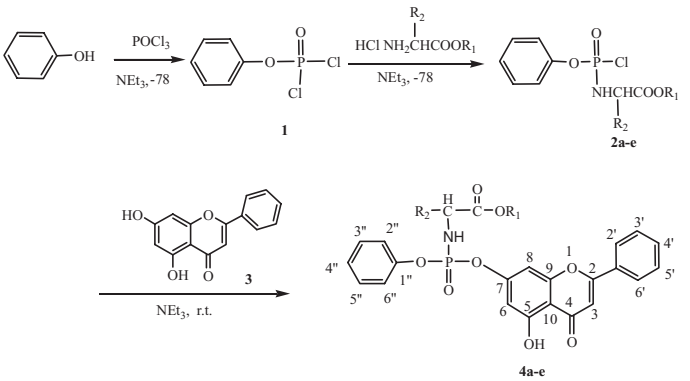

2, 4	a	b	C	d	e
R_1	C_2H_5	CH_3	C_2H_5	CH_3	C_2H_5
R_2	CH_3	$CH_2CH(CH_3)_2$	$CH_2CH(CH_3)_2$	H	H

Scheme 1 Synthesis of phosphoramidates of chrysin.

RESULTS AND DISCUSSION

In the synthesis of phosphoramidate derivatives of chrysin **(4)** (Scheme 1), phenol was first reacted with phosphorus oxychloride at low temperature in the presence of triethylamine to give phenyl dichlorophosphates **(1)**. Then phenyl dichlorophosphates **(1)** were coupled to different *L*-amino acid ester hydrochloride salts to achieve phenyl aminophosphorochloridates **(2)**, which were not further purified by chromatography. Chrysin **(3)** was reacted with phenyl aminophosphorochloridates **(2)** in THF to form phosphoramidate derivatives of chrysin **(4)** in the presence of triethylamine at room temperature. The structures of all the newly synthesized chrysin derivatives were confirmed by ESI MS, HR MS, NMR, and IR.

Phenyl aminophosphorochloridates **(2)** could react at two different reaction positions (7-OH and 5-OH) of chrysin **(3)**. The results showed that the phosphorylation occurred chemselectively only at the 7-OH of chrysin and not at 5-OH. This conclusion was confirmed by the ^{13}C NMR of compound **4d**. For example, ^{13}C NMR of compound **4d** showed that the signals from 7-C at δ 155.83 ($J = 6.3$), 6-C at δ 104.01 ($J = 6.4$), and 8-C at δ 99.36 ($J = 4.6$) were split into doublets by the single phosphorus atom nearby, respectively. Whereas, the singles from 5-C at δ 162.17 and 10-C at δ 108.43 were not split, and only a singlet was observed. These facts explain that the phosphorylation proceeds chemselectively favoring attack at 7-OH of chrysin. The reason why the phosphorylation occurred at the 7-OH of chrysin may be due to the hydrogen bonding of 5-OH group with the carbonyl group.

Due to the stereochemistry at the chiral phosphorus center, the products **4a–4c** were isolated as mixtures of diastereoisomers, which were not easily separated by column chromatography, but are readily distinguished by ^{31}P NMR. These diastereoisomers displayed

two closely spaced signals by ^{31}P NMR (e.g., **4a**, δ −2.98, −3.00). Moreover, the presence of phosphate diastereoisomers was also apparent in the ^{1}H NMR and ^{13}C NMR spectra.

EXPERIMENTAL

All experiments involving water-sensitive compounds were conducted under scrupulously dry conditions. The solvents were dried by appropriate methods. IR spectra were recorded on a Shimadazu IR-408. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on a Bruker Avance DPX spectrometer operating at 400.13, 100.61, and 161.98 MHz, respectively, with ^{13}C and ^{31}P spectra being recorded proton-decoupled. All NMR spectra were recorded in $CDCl_3$ at room temperature (20°C ± 3°C). ^{1}H and ^{13}C chemical shifts are quoted in parts per million downfield from TMS. ^{31}P chemical shifts are quoted in parts per million relative to an external 85% H_3PO_4 standard. *J* values refer to coupling constants, and signal splitting patterns are described as singlet (s), broad singlet (bs), doublet (d), triplet (t), quartet (q), multiplet (m), or combinations thereof. TLC was performed on silica gel plates and preparative chromatograph on columns of silica gel (200–300 mesh). HR MS were recorded on Q-Tof Micro.

General Procedure for the Synthesis of Phosphoramidates of Chrysin

A solution of phenol (50.0 g, 0.53 mol) in phosphorus oxychloride (48.7 mL, 0.53 mol) and anhydrous diethylether (200 mL) was stirred at −78°C. Anhydrous triethylamine (76 mL, 0.54 mol) was added dropwise to this solution for 30 min. The reaction mixture was then allowed to warm up to room temperature and stirred for 16 h. The precipitated triethylamine hydrochloride salt was filtered off, and the filtrate was evaporated to dryness under reduced pressure. The crude product of phosphorodichloridate **(1)** was obtained as a clear liquid.[18]

Phosphodichloridate **(1)** (1.05 g, 5.0 mmol) and the appropriate amino acid esters hydrochloric salt (5.0 mmol) were suspended in anhydrous dichloromethane. Anhydrous triethylamine was added dropwise at −78°C during 1 h, and then the reaction was left to warm to room temperature. After 5 h, the solvent was removed under reduced pressure, and the residue was washed with anhydrous ether and was filtered. The filtrate was evaporated to dryness under reduced pressure. The crude phosphochloridate **(2)** was obtained and used without further purification by the chromatography.[18]

Anhydrous triethylamine was added dropwise to a solution of the appropriate phosphorochloridate **(2)** (0.02–0.03 mol) and chrysin **(3)** (2.54 g, 0.01 mol) in anhydrous tetrahydrofuran at room temperature, and the reaction mixture was stirred for 6–10 h. The precipitated triethylamine hydrochloride salt was filtered off, and the filtrate was evaporated to dryness under reduced pressure. The crude product **(4)** was purified by column chromatography on silica gel (CH_2Cl_2/ CH_3OH = 1:10).

Compound 4a ($C_{26}H_{24}NO_8P$). Yield (56%); mp 157–158°C. ^{1}H NMR (400.13 MHz, $CDCl_3$) δ: 12.74, 12.73 (s, 1H, 5-H), 7.88–7.86 (m, 2H, 2′,6′-H), 7.57–7.49 (m, 3H, C-3′, 4′, 5′), 7.38–7.18 (m, 5H, H-2″, 3″, 4″, 5″, 6″), 7.05 (s, 1H, 8-H), 6.71 (s, 1H, 3-H), 6.66, 6.63 (d, 1H, J = 2.0, 6-H), 4.20–4.11 (m, 3H, $OC\underline{H}_2$, $C\underline{H}$-NH), 4.09–4.03 (m, 1H, NH), 1.43, 1.42 (d, 3H, J = 2.2, $C\underline{H}_3$-CH), 1.27–1.23 (m, 3H, $OCH_2C\underline{H}_3$). ^{13}C NMR (100.61 MHz, $CDCl_3$) δ: 182.74 (C-4), 173.01 (d, J = 8.0, C=O), 164.67, 164.65 (C-2), 162.15, 162.12 (C-5), 157.02 (C-9), 156.01, 155.93 (d, J = 6.5, C-7), 150.41, 150.34

(d, J = 6.2, C-1″), 132.15 (C-3′, 5′), 130.87 (C-1′), 129.83 (C-3″, 5″), 129.14 (C-4′), 126.40 (C-2′, 6′), 125.39 (C-4″), 120.18, 120.13 (d, J = 4.7, C-2″, 6″), 108.34 (C-10), 106.03 (C-3), 104.05, 104.00 (d, J = 3.7, C-6), 99.37, 99.28 (d, J = 4.6, C-8). 61.79, 61.77 (OCH_2), 50.49 (CH-NH), 21.00 (CH_3), 14.07 ($OCH_2\underline{C}H_3$). ^{31}P NMR ($CDCl_3$) δ: −2.98, −3.00. IR(KBr) ν_{max}(cm^{-1}): 1257 (P=O), 3200 (NH). ESI MS *m/z*: 532 [M + Na]$^+$. A molecular formula of $C_{26}H_{24}NO_8P$ was determined from the molecular ion peak at 510.1318 *m/z* [M + H]$^+$ (calc. 510.1318 for $C_{26}H_{24}NO_8PH$) obtained by HR MS.

Compound 4b ($C_{28}H_{28}NO_8P$). Yield (59%); mp 149–150°C. ^{1}H NMR (400.13 MHz, $CDCl_3$) δ: 12.77 (s, 1H, 5-H), 7.83 (d, 2H, J = 7.4, 2′, 6′-H), 7.52–7.45 (m, 3H, C-3′, 4′, 5′), 7.37–7.27 (m, 4H, H-2″, 3″, 5″, 6″), 7.20–7.16 (m, 1H, H-4″), 7.05 (s, 1H, 8-H), 6.70 (s, 1H, 3-H), 6.67, 6.62 (d, 1H, J = 2.0, 6-H), 4.38–4.33 (m, 1H, NH), 4.14–4.08 (m, 1H, NH−C$\underline{H}$), 3.68, 3.65 (s, 3H, OCH_3), 1.73–1.65 (m, 1H, C$\underline{H}$-$(CH_3)_2$), 1.65–1.52 (m, 2H, C$\underline{H_2}$−CH−$(CH_3)_2$), 0.90, 0.88 (d, 6H, J = 3.7, CH-(C$\underline{H_3}$)$_2$). ^{13}C NMR (100.61 MHz, $CDCl_3$) δ: 182.69, 182.69 (C-4), 173.75, 173.69 (d, J = 4.0, C=O), 164.56, 164.54 (C-2), 162.05, 162.02 (C-5), 156.93 (C-9), 156.09, 156.04 (d, J = 3.7, C-7), 150.49, 150.43 (C-1″), 132.12 (C-3′, 5′), 130.73 (C-1′), 129.75, 129.80 (C-3″, 5″), 129.09 (C-4′), 126.32 (C-2′, 6′), 125.30 (C-4″), 120.18, 120.09 (d, J = 5.0, C-2″, 6″), 108.21 (C-10), 105.90 (C-3), 104.02, 103.95 (C-6), 99.34, 99.27 (d, J = 4.5, C-8), 53.38, 53.35 (NH-CH), 52.33, 52.28 (OCH_3), 43.57, 43.51 (d, J = 1.3, $\underline{C}H_2$-CH-$(CH_3)_2$), 24.35, 24.28 ($\underline{C}$H-$(CH_3)_2$), 22.68, 21.75 (CH−($\underline{C}H_3$)$_2$). ^{31}P NMR ($CDCl_3$) δ: −2.23, −2.41. IR(KBr) ν_{max}(cm^{-1}): 1253(P=O), 3184(NH). ESI MS: *m/z*: 538[M + H]$^+$, 1097[2M + Na]$^+$. A molecular formula of $C_{28}H_{28}NO_8P$ was determined from the molecular ion peak at 538.1639 *m/z* [M + H]$^+$ (calc.538.1631 for $C_{28}H_{28}NO_8PH$) obtained by HR MS.

Compound 4c ($C_{29}H_{30}NO_8P$). Yield (54%); mp 129–130°C. ^{1}H NMR (400.13 MHz, $CDCl_3$) δ: 12.71, 12.71 (s, 1H, 5-H), 7.83 (d, 2H, J = 7.0, 2′, 6′-H), 7.52–7.45 (m, 3H, C-3′, 4′, 5′), 7.36–7.27 (m, 4H, 3″, 2″, 5″, 6″-H), 7.20–7.18 (m, 1H, 4″-H), 7.05 (d, 1H, J = 1.36, 8-H), 6.70 (s, 1H, 3-H), 6.67, 6.63 (d, 1H, J = 1.68, 6-H), 4.30 (d, 1H, J = 3.7, N$\underline{H}$), 4.15–4.08 (m, 3H, NH−C$\underline{H}$, OCH_2), 1.59–1.53 (m, 2H, C$\underline{H_2}$−CH−$(CH_3)_2$), 1.26–1.19 (m, 3H, $OCH_2\underline{C}H_3$), 0.91, 0.89 (d, 6H, J = 4.0, CH-(C$\underline{H_3}$)$_2$). ^{13}C NMR (100.61 MHz, $CDCl_3$) δ: 182.7 (C-4), 173.3, 173.2 (d, J = 4.1, C=O), 164.5 (C-2), 162.1, 162.0 (C-5), 156.9(C-9), 156.1 (d, J = 6, C-7), 150.5 (d, J = 1.7, C-1″), 132.1 (C-3′, 5′), 130.8 (C-1′), 129.8, 129.7 (C-3″, 5″), 129.1 (C-4′), 126.3 (C-2′, 6′), 125.3 (C-4″), 120.2, 120.1 (d, J = 5.0, C-2″, 6″), 108.2 (C-10), 105.9 (C-3), 104.1, 103.1 (d, J = 3.4, C-6), 99.4, 99.3 (d, J = 4.5, C-8), 61.4, 61.5 (OCH_2), 53.5, 53.4 (NH−CH), 43.7, 43.6 ($\underline{C}H_2$−CH−$(CH_3)_2$), 24.4, 24.3 ($\underline{C}$H−$(CH_3)_2$), 22.7, 21.8 (C−CH−($\underline{C}H_3$)$_2$). ^{31}P NMR ($CDCl_3$) δ: −2.16, −2.34. IR(KBr) ν_{max}(cm^{-1}): 1252 (P=O), 3188 (NH). ESI MS m/z: 574 [M + Na]$^+$, 1125 [2M + Na]$^+$. A molecular formula of $C_{28}H_{28}NO_8P$ was determined from the molecular ion peak at 552.1782 *m/z* [M + H]$^+$ (calc. 552.1787 for $C_{29}H_{30}NO_8PH$) obtained by HR MS.

Compound 4d ($C_{24}H_{20}NO_8P$). Yield (58%); mp 156–157°C. ^{1}H NMR (400.13 MHz, $CDCl_3$) δ: 12.75 (s, 1H, 5-H), 7.88–7.86 (m, 2H, 2′, 6′-H), 7.56–7.50 (m, 3H, C-3′, 4′, 5′), 7.39–7.26 (m, 4H, H-2″, 3″, 5″, 6″), 7.23–7.19 (m, 1H, H-4″), 7.06, 7.06 (d d, 1H, J = 2.1, J = 1.0, 8-H), 6.71 (s, 1H, 3-H), 6.66, 6.65 (d d, 1H, J = 2.0, J = 0.6, 6-H), 3.92 (d, 2H, J = 9.8, C$\underline{H_2}$-NH), 3.75 (s, 3H, OCH_3). ^{13}C NMR (100.61 MHz, $CDCl_3$) δ: 182.76 (C-4), 170.40 (d, J = 9.0, C=O), 164.71 (C-2), 162.17 (C-5), 157.05 (C-9), 155.83 (d, J = 6.3, C-7), 150.28 (d, J = 7.0, C-1″), 132.19 (C-3′, 5′), 130.84 (C-1′), 129.91 (C-2″, 6″), 129.16 (C-4′), 126.42 (C-2′, 6′), 125.51 (C-4″), 120.14 (d, J = 4.7, C-3″, 5″), 108.43 (C-10), 106.04 (C-3), 104.01 (d, J = 6.4, C-6), 99.36 (d, J = 4.6, C-8). 52.65 (OCH_3), 42.98

(CH_2-NH). ^{31}P NMR ($CDCl_3$) δ: -2.77. IR(KBr) ν_{max}(cm^{-1}): 1252 (P=O), 3220 (NH). ESI MS: *m/z*: 504.0$[M + Na]^+$. A molecular formula of $C_{24}H_{20}NO_8P$ was determined from the molecular ion peak at 482.1008 *m/z* $[M + H]^+$ (calc. 482.1005 for $C_{24}H_{20}NO_8PH$) obtained by HR MS.

Compound 4e ($C_{25}H_{22}NO_8P$). Yield (56%); mp 139–140°C. ^{1}H NMR (400.13 MHz, $CDCl_3$) δ: 12.75 (s, 1H, 5-H), 7.88 (d, 2H, $J = 6.9$, 2′, 6′-H), 7.57–7.51 (m, 3H, H-3′, 4′, 5′), 7.39–7.19 (m, 4H, H-2″, 3″, 5″, 6″), 7.07 (d, 1H, $J = 0.92$, 8-H), 6.72 (s, 1H, 3-H), 6.66 (s, 1H, 6-H), 4.24–4.19 (m, 1H, CH_2—NH), 4.09 (d, 2H, $J = 6.7$, CH_2—NH), 3.89 (d d, 2H, $J = 9.2$, 5.7, OCH_2), 1.27 (t, 3H, $J = 7.2$, CH_3). ^{13}C NMR (100.61 MHz, $CDCl_3$) δ: 182.77 (C-4), 170.00 (d, $J = 7.9$, C=O), 164.73 (C-2), 162.21 (C-5), 157.08 (C-9), 155.95 (d, $J = 6.1$, C-7), 132.19 (C-3′, 5′), 130.90 (C-1′), 129.80 (C-2″, 6″), 129.17 (C-4′), 126.43 (C-2′, 6′), 125.49 (C-4″), 120.15 (d, $J = 5.0$, C-3″, 5″), 108.46 (C-10), 106.08 (C-3), 104.02 (d, $J = 6.6$, C-6), 99.36 (d, $J = 4.6$, C-8), 61.93 (OCH_2), 43.13 (CH_2-NH), 14.12 (CH_3). ^{31}P NMR ($CDCl_3$) δ: −2.42. IR(KBr) ν_{max}(cm^{-1}): 1252 (P=O), 3194 (NH). ESI MS: *m/z*: 496 $[M + H]^+$, 518 $[M + Na]^+$. A molecular formula of $C_{25}H_{22}NO_8P$ was determined from the molecular ion peak at 496.1163 *m/z* $[M + H]^+$ (calc. 496.1161 for $C_{25}H_{22}NO_8PH$) obtained by HR MS.

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