The application of phosphoramidate ProTide technology to acyclovir confers anti-HIV inhibition

Supporting Information

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Chemistry

General. Anhydrous solvents were bought from Aldrich and used without further purification. Reactions were monitored with analytical TLC on silica gel 60-F254 precoated aluminium plates and visualised under UV (254 nm) and/or with ^{31}P-NMR spectra. Column chromatography was performed on silica gel (35-70 μM). Proton (^{1}H), carbon (^{13}C), phosphorus (^{31}P) and fluorine (^{19}F) NMR spectra were recorded on a Bruker Avance 500 spectrometer at 25 °C. Spectra were auto-calibrated to the deuterated solvent peak and all ^{13}C-NMR, ^{31}P-NMR and ^{19}F-NMR were proton-decoupled.

Analytical and semi-preparative HPLC were conducted by Varian Prostar (LC Work Station-Varian prostar 335 LC detector) using Varian Polaris C18-A (10 μM) as an analytic column and Varian Polaris C18-A (10 μM) as a semi-preparative column.

High resolution mass spectra was performed as a service by Birmingham University and by Cardiff University, using electrospray (ES).

CHN microanalysis were performed as a service by the School of Pharmacy at the University of London and by MEDAC Ltd, Surrey.

Synthesis of 4-fluorophenyldichlorophosphate [27].

Prepared according to standard procedure A, using **25** (1.83 g, 16.34 mmol) in dry diethyl ether (30 mL), $POCl_3$ (1.50 mL, 16.34 mmol) and dry TEA (2.28 mL, 16.34 mmol). After ^{31}P NMR, the solvent was removed under reduced pressure and the residue was triturated with dry diethyl ether. The precipitate was filtered, and the organic phase was removed under reduced pressure to give an oil (79%, 2.94 g). ^{31}P-NMR ($CDCl_3$, 202 MHz): δ 4.18. ^{19}F-NMR ($CDCl_3$, 471 MHz): δ -114.28, -114.29. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.33-7.27 (2H, m, Ph), 7.17-7.11 (2H, m, Ph).

Synthesis of 1-naphthyl(methoxy-L-alaninyl)-phosphorochloridate [46].

Prepared according to standard procedure B, **26** (2.00 g, 7.66 mmol), L-alanine methyl ester hydrochloride **30** (1.07 g, 7.66 mmol), anhydrous TEA (2.14 mL, 15.32 mmol) in anhydrous DCM (45 mL). The reaction mixture was stirred at -78 ^{o}C for 1 h, then at room temperature for 2 h. The crude was purified by column

chromatography eluting with ethyl acetate/hexane = 60/40 to give an oil (61%, 1.54 g). ^{31}P-NMR ($CDCl_3$, 202 MHz): δ 8.14, 7.88. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 8.01-7.35 (7H, m, Naph), 4.33-4.27 (1H, m, NH), 4.26-4.20 (1H, m, C*H*NH), 3.74, 3.69 (3H, 2s, COOCH_3), 1.50-1.46 (3H, m, CHCH_3).

Synthesis of 1-naphthyl(ethoxy-L-alaninyl)-phosphorochloridate [47].

Prepared according to standard procedure B, **26** (2.09 g, 8.00 mmol), L-alanine ethyl ester hydrochloride **31** (1.23 g, 8.00 mmol), anhydrous TEA (2.23 mL, 16.00 mmol) in anhydrous DCM (50 mL). The reaction mixture was stirred at -78 ^{o}C for 30 min, then at room temperature for 1 h. The crude was purified by column chromatography eluting with ethyl acetate/hexane = 60/40 to give an oil (63%, 1.71 g). ^{31}P-NMR ($CDCl_3$, 202 MHz): δ 8.23, 7.91. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 8.12-8.09 (1H, m, H-8 Naph), 7.90-7.88 (1H, m, H-6 Naph), 7.76-7.75 (1H, m, H-2 Naph), 7.64-7.44 (4H, m, Naph), 4.34-4.22 (3H, m, C*H*CH_3, COOC$H_2$$CH_3$), 4.17-4.13 (1H, m, COOC$H_2$$CH_3$), 1.59-1.55 (3H, m, CHC$H_3$), 1.37-1.27 (3H, m, $COOCH_2C$$H_3$).

Synthesis of 1-naphthyl-(*tert*-butoxy-L-alaninyl)-phosphorochloridate [48].

Prepared according to standard procedure B, **26** (1.44 g, 5.51 mmol), L-alanine *tert*-butyl ester hydrochloride **32** (1.00 g, 5.51 mmol), anhydrous TEA (1.53 mL, 11.00 mmol) in anhydrous DCM (40 mL). The reaction mixture was stirred at -78 ^{o}C for 30 min, then at room temperature for 30 min. The crude was purified by column chromatography eluting with ethyl acetate/hexane = 70/30 to give an oil (64%, 1.31g). ^{31}P-NMR ($CDCl_3$, 202 MHz): δ 8.40, 8.05. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 8.13-8.09 (1H, m, H-8 Naph), 7.90-7.89 (1H, m, H-6 Naph), 7.76-7.75 (1H, m, H-2 Naph), 7.64-7.55 (3H, m, Naph), 7.48-7.44 (1H, m, Naph), 4.45-4.32 (1H, m, C*H*CH_3), 1.55-1.51 (9H, m, C(CH_3)$_3$), 1.30-1.27 (3H, m, CHCH_3).

Synthesis of 1-naphthyl-(*iso*-propoxy-L-alaninyl)-phosphorochloridate [49].

Prepared according to standard procedure B, **26** (3.81 g, 14.61 mmol), L-alanine *iso*-propyl ester hydrochloride **33** (3.81 g, 14.61 mmol), anhydrous TEA (4.07 mL, 29.22 mmol) in anhydrous DCM (100 mL). The reaction mixture was stirred at -78 ^{o}C for 30 min, then at room temperature for 1 h. The crude was purified by

column chromatography eluting with ethyl acetate/hexane = 70/30 to give an oil (72%, 5.20 g). ^{31}P-NMR ($CDCl_3$, 202 MHz): δ 8.26, 7.90. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 8.12-8.09 (1H, m, H-8 Naph), 7.90-7.88 (1H, m, H-6 Naph), 7.76-7.75 (1H, m, H-2 Naph), 7.64-7.45 (4H, m, Naph), 5.16-5.07 (1H, m, COOC*H*$(CH_3)_2$), 4.45-4.22 (1H, m, C*H*CH_3), 1.58-1.53 (3H, m, CHC*H*$_3$), 1.33-1.27 (6H, m, COOCH(C*H*$_3)_2$).

Synthesis of phenyl-(methoxy-L-alaninyl)-phosphorochloridate [50].

Prepared according to standard procedure B, from **28** (2.24 mL, 15.00 mmol), L-alanine methyl ester hydrochloride **30** (2.09 g, 15.00 mmol), anhydrous TEA (4.20 mL, 30.00 mmol) and anhydrous DCM (80 mL). The reaction mixture was stirred at -78 ^{o}C for 30 min, then at room temperature for 2.5 h. The crude was purified by column chromatography eluting with ethyl acetate/hexane = 60/40 to give an oil (81%, 3.35 g). ^{31}P-NMR ($CDCl_3$, 202 MHz): δ 7.95, 7.66. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.32-7.15 (5H, m, PhO), 4.42-4.34 (1H, m, NH), 4.17-4.08 (2H, m, C*H*NH), 3.72, 3.70 (3H, 2s, COOC*H*$_3$), 1.45-1.43 (3H, m, CHC*H*$_3$).

Synthesis of phenyl-(benzoxy-L-alaninyl)-phosphorochloridate [51].

Prepared according to standard procedure B, using **28** (0.30 mL, 2.00 mmol), L-alanine benzyl ester hydrochloride **29** (0.43 g, 2.00 mmol), anhydrous TEA (0.56 mL, 4.00 mmol) in anhydrous DCM (15 mL). The reaction mixture was stirred at -78 ^{o}C for 1 h, then at room temperature for 3.5 h. The crude was obtained as an oil (87%, 0.62 g). ^{31}P-NMR ($CDCl_3$, 202 MHz): δ 7.86, 7.52. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.33-7.28 (10H, m, PhO, OCH_2P*h*), 5.15-5.13 (2H, m, OC*H*$_2$Ph), 4.18-4.13 (1H, m, C*H*NH), 1.46-1.44 (3H, m, CHC*H*$_3$).

Synthesis of phenyl-(*iso*-propoxy-L-alaninyl)-phosphorochloridate [52].

Prepared according to standard procedure B, from **28** (2.00 mL, 13.85 mmol), L-alanine isopropyl ester hydrochloride **33** (2.24 g, 13.85 mmol), anhydrous TEA (3.73 mL, 26.77 mmol) and anhydrous DCM (50 mL). The reaction mixture was stirred at -78 ^{o}C for 30 min, then at room temperature for 2 h. The crude was obtained as an oil (96%, 3.94 g). ^{31}P-NMR ($CDCl_3$, 202 MHz): δ 8.13, 7.75. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.47-7.16 (5H, m, PhO), 5.18-4.98 (1H, m, COOC*H*),

4.41, 4.33 (1H, 2bs, N*H*CH), 4.21-4.09 (1H, m, NHC*H*), 1.53, 1.51 (3H, 2d, J = 2.30, CHCH_3), 1.35-1.27 (6H, m, COOCH(CH_3)$_2$).

Synthesis of 4-fluoro-phenyl-(benzoxy-L-alaninyl)-phosphorochloridate [53].
Prepared according to standard procedure B, using **27** (1.50 mL, 6.55 mmol), L-alanine benzyl ester tosylate **29** (2.30 g, 6.55 mmol), anhydrous TEA (1.82 mL, 13.10 mmol) in anhydrous DCM (40 mL). The reaction mixture was stirred at -78 ^{o}C for 30 min, then at room temperature for 3 h. The crude was purified by column chromatography eluting with ethyl acetate/petroleum ether = 70/30 to give an oil (72%, 1.75 g). ^{31}P-NMR ($CDCl_3$, 202 MHz): δ 8.34, 8.02. ^{19}F-NMR ($CDCl_3$, 471 MHz): δ -116.29 (d, J = 3.10), -116.33 (d, J = 2.90). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.43-7.33 (5H, m, Ph), 7.26-7.20 (2H, m, Ph), 7.09-7.04 (2H, m, Ph), 5.24, 5.23 (2H, 2s, OCH_2Ph), 4.37 (1H, bs, CHN*H*), 4.32-4.20 (1H, m, C*H*NH), 1.55 (3H, d, J = 5.00, CHCH_3), 1.54 (3H, d, J = 4.60, CHCH_3).

Synthesis of phenyl-(benzoxy-D-alaninyl)-phosphorochloridate [54].
Prepared according to standard procedure B, using **28** (1.06 mL, 7.11 mmol), D-alanine benzyl ester tosylate **34** (2.50 g, 7.11 mmol), anhydrous TEA (1.98 mL, 14.23 mmol) in anhydrous DCM (50 mL). The reaction mixture was stirred at -78 ^{o}C for 1 h, then at room temperature for 3.5 h. The crude was purified by column chromatography eluting with ethyl acetate/hexane = 70/30 to give an oil (84%, 2.11 g). ^{31}P-NMR ($CDCl_3$, 202 MHz): δ 7.86, 7.49. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.47-7.22 (10H, m, PhO, OCH$_2$*Ph*), 5.25-5.23 (2H, 2s, OCH_2Ph), 4.32-4.20 (1H, m, C*H*NH), 1.56 (1.5H, d, J = 3.30, CHCH_3 of one diastereoisomer), 1.54 (1.5H, d, J = 2.90, CHCH_3 of one diastereoisomer).

Synthesis of 1-naphthyl(benzoxy-dimethylglycinyl)-phosphorochloridate [55].
Prepared according to the standard procedure B, using **26** (1.53 g, 5.88 mmol) and dimethylglycine benzyl ester tosylate **35** (2.15 g, 5.88 mmol), anhydrous TEA (4.59 mL, 32.94 mmol) and anhydrous DCM (50 mL). The reaction mixture was stirred at -78 ^{o}C for 30 min, then at room temperature for 2 h. The crude product was obtained as an oil (33%, 0.80 g). ^{31}P-NMR ($CDCl_3$, 202 MHz): δ 5.78. ^{1}H-

NMR ($CDCl_3$, 500 MHz): δ 8.03-7.28 (12H, m, Naph, OCH_2*Ph*), 5.16 (2H, s, OCH_2Ph), 1.76, 1.70 (6H, 2s, $C(CH_3)_2$).

Synthesis of phenyl-(benzoxy-dimethylglycinyl)-phosphorochloridate [56].
Prepared according to the standard procedure B, using **28** (2.45 mL, 16.40 mmol) and dimethylglycine benzyl ester tosylate **35** (6.00 g, 16.4 mmol), anhydrous TEA (4.58 mL, 33.00 mmol) and anhydrous DCM (150 mL). The reaction mixture was stirred at -78 °C for 30 min, then at room temperature for 1 h. The crude was purified by column chromatography eluting with ethyl acetate/petroleum ether = 70/30 to give an oil (90%, 5.50 g). ^{31}P NMR ($CDCl_3$, 202 MHz): δ 5.43. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.41-7.23 (10H, m, PhO, OCH_2*Ph*), 5.24 (2H, s, OCH_2Ph), 4.70-4.68 (1H, bs, NH), 1.74, 1.72 (6H, 2s, $C(CH_3)_2$).

Synthesis of phenyl-(benzoxy-L-phenylalaninyl)-phosphorochloridate [57].
Prepared according to standard procedure B, from **28** (1.28 mL, 8.57 mmol), L-phenylalanine benzyl ester hydrochloride **36** (2.50 g, 8.57 mmol), anhydrous TEA (2.40 mL, 17.13 mmol) and anhydrous DCM (80 mL). The reaction mixture was stirred at -78 °C for 30 min, then at room temperature for 2 h. The crude was purified by column chromatography eluting with ethyl acetate/hexane = 60/40 to give an oil (58%, 2.15 g). ^{31}P-NMR ($CDCl_3$, 202 MHz): δ 7.80, 7.77. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.32-6.91 (15H, m, PhO, $CHCH_2$*Ph*, OCH_2*Ph*), 5.08-5.07 (2H, m, OCH_2Ph), 4.46-4.33 (1H, m, C*H*NH), 3.12-3.01 (2H, m, $CHCH_2$Ph).

Synthesis of phenyl-(benzoxy-L-valinyl) phosphorochloridate [58].
Prepared according to standard procedure B, from **28** (0.91 mL, 6.13 mmol), L-valine benzyl ester tosylate **36** (2.33 g, 6.13 mmol), anhydrous TEA (1.71 mL, 12.26 mmol) and anhydrous DCM (50 mL). The reaction mixture was stirred at -78 °C for 30 min, then at room temperature for 1 h. The crude was purified by column chromatography eluting with ethyl acetate/petroleum ether = 70/30 to give an oil (77%, 1.80 g). ^{31}P NMR ($CDCl_3$, 202 MHz): δ 9.37, 8.89. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.42-7.23 (10H, m, PhO, OCH_2*Ph*), 5.24-5.23 (2H, m, OCH_2Ph), 4.08-3.96 (1H, m, NHC*H*), 2.24-2.17 (1H, m, C*H*$(CH_3)_2$), 1.05-1.01 (3H, m, $CH(CH_3)_2$), 0.94-0.91 (3H, m, $CH(CH_3)_2$).

Synthesis of 1-naphthyl-(methoxy-L-valinyl) phosphorochloridate [59].

Prepared according to the standard procedure B, using **26** (4.33 g, 16.60 mmol), L-valine methyl ester hydrochloride **38** (2.78 g, 16.60 mmol), anhydrous TEA (4.63 mL, 33.20 mmol) and anhydrous DCM (110 mL). The reaction mixture was stirred at -78 ^{o}C for 30 min, the reaction was stirred at room temperature for 2 h. The crude was purified by column chromatography eluting with ethyl acetate/petroleum ether = 70/30 to give an oil (52%, 3.10 g). ^{31}P-NMR ($CDCl_3$, 202 MHz): δ 9.67, 9.26. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 8.12-7.44 (7H, m, Naph), 4.30-4.22 (1H, m, N*H*CH), 4.10-4.07 (1H, m, NHC*H*), 3.81, 3.77 (3H, 2s, $COOCH_3$), 2.24-2.18 (1H, m, C*H*$(CH_3)_2$), 1.08-0.95 (6H, m, CH(C*H*$_3)_2$).

Synthesis of 1-naphthyl-(ethoxy-L-valinyl) phosphorochloridate [60].

Prepared according to the standard procedure B, using **26** (3.60 g, 13.76 mmol), L-valine ethyl ester hydrochloride **39** (2.50 g, 13.76 mmol), anhydrous TEA (3.84 mL, 13.76 mmol) and anhydrous DCM (92 mL). The reaction mixture was stirred at -78 ^{o}C for 30 min, then at room temperature for 2 h. The crude was purified by column chromatography eluting with ethyl acetate/petroleum ether = 70/30 to give an oil (67%, 3.40 g). ^{31}P-NMR ($CDCl_3$, 202 MHz): δ 9.84, 9.38. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 8.14-7.43 (7H, m, Naph), 4.41-4.35 (1H, m, N*H*CH), 4.30-4.20 (2H, m, C*H*$_2$CH$_3$), 4.09-4.03 (1H, m, NHC*H*), 2.24-2.17 (1H, m, C*H*$(CH_3)_2$), 1.35-1.32 (3H, m, CH$_2$C*H*$_3$), 1.08-0.96 (6H, m, CH(C*H*$_3)_2$).

Synthesis of 1-naphthyl-(methoxy-D-valinyl) phosphorochloridate [61].

Prepared according to standard procedure B, using **26** (3.97 g, 14.90 mmol), D-valine methyl ester hydrochloride **40** (2.53 g, 14.90 mmol), anhydrous TEA (4.13 mL, 29.80 mmol) and anhydrous DCM (98 mL). The reaction mixture was stirred at -78 ºC for 30 min, then at room temperature for 2 h. The crude was purified by column chromatography eluting with ethyl acetate/petroleum ether = 70/30 to give an oil (77%, 4.06 g). ^{31}P-NMR ($CDCl_3$, 202 MHz): δ 9.94, 9.30. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 8.13-7.43 (7H, m, Naph), 4.40-4.34 (1H, m, N*H*CH), 4.17-4.06 (1H, m, NHC*H*), 3.81-3.77 (3H, 2s, $COOCH_3$), 2.23-2.16 (1H, m, C*H*$(CH_3)_2$), 1.07-0.95 (6H, m, CH(C*H*$_3)_2$).

Synthesis of phenyl-(benzoxy-L-leucinyl) phosphorochloridate [62].

Prepared according to standard procedure B, using **28** (0.91 mL, 6.13 mmol), L-leucine benzyl ester tosylate **41** (2.41 g, 6.13 mmol), anhydrous TEA (1.71 mL, 12.26 mmol) and anhydrous DCM (50 mL). The reaction mixture was stirred at -78 ºC for 30 min, then at room temperature for 1 h. The crude was purified by column chromatography eluting with ethyl acetate/petroleum ether = 70/30 to give an oil (93%, 2.25 g). ^{31}P NMR ($CDCl_3$, 202 MHz): δ 8.34, 8.10. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.43-7.22 (10H, m, PhO, OCH_2*Ph*), 5.27-5.09 (2H, m, OCH_2Ph), 4.21-4.11 (1H, m, NHC*H*), 1.90-1.75 (1H, m, $CHCH_2CH(CH_3)_2$), 1.71-1.59 (2H, m, $CH_2CH(CH_3)_2$, $CHCH_2CH(CH_3)_2$), 0.98-0.95 (6H, m, CH_3).

Synthesis of phenyl-(benzoxy-L-isoleucinyl) phosphorochloridate [63].

Prepared according to standard procedure B, using **28** (0.91 mL, 6.13 mmol), L-isoleucine benzyl ester tosylate **42** (2.41 g, 6.13 mmol), anhydrous TEA (1.71 mL, 12.26 mmol) and anhydrous DCM (50 mL). The reaction mixture was stirred at -78 ºC for 30 min, then at room temperature for 1 h. The crude was purified by column chromatography eluting with ethyl acetate/petroleum ether = 70/30 to give an oil (99%, 2.41 g). ^{31}P NMR ($CDCl_3$, 202 MHz): δ 9.01, 8.61. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.45-7.22 (10H, m, PhO, OCH_2*Ph*), 5.27-5.19 (2H, m, OCH_2Ph), 4.11-4.00 (1H, m, NHC*H*), 1.52-1.40 (1H, m, NHCHC*H*, 1.25-1.16 (2H, m, $CHCH(CH_3)CH_2CH_3$), 0.94-0.75 (6H, m, CH_3).

Synthesis of phenyl-(benzoxy-L-prolinyl) phosphorochloridate [64].

Prepared according to standard procedure B, using **28** (3.09 mL, 20.68 mmol), L-proline benzyl ester hydrochloride **43** (5.00 g, 20.68 mmol), anhydrous TEA (5.76 mL, 41.36 mmol) and anhydrous DCM (100 mL). The reaction mixture was stirred at -78 ºC for 30 min, then at room temperature for 1 h. The crude product was obtained as an oil (quantitative, 7.85 g). ^{31}P NMR ($CDCl_3$, 202 MHz): δ 7.78, 7.72. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.40-7.19 (10H, m, PhO, OCH_2*Ph*), 5.25-5.15 (2H, m, OCH_2Ph), 4.58-4.55 (0.5H, m, NC*H* of one diastereoisomer), 4.49-4.45 (0.5H, m, NC*H*, of one diastereoisomer), 3.64-3.45 (2H, m, NCH_2CH_2), 2.31-2.21 (1H, m, $NCHCH_2CH_2CH_2$), 2.18-2.10 (1H, m, $NCHCH_2CH_2CH_2$), 2.09-1.92 (2H, m, $NCHCH_2CH_2CH_2$).

Synthesis of phenyl-(benzoxy-glicinyl) phosphorochloridate [65].

Prepared according to standard procedure B, using **28** (2.21 mL, 14.81 mmol), glycine benzyl ester hydrochloride **44** (5.00 g, 14.81 mmol), anhydrous TEA (4.20 mL, 30.00 mmol) and anhydrous DCM (100 mL). The reaction mixture was stirred at -78 ºC for 30 min, then at room temperature for 1 h. The crude was purified by column chromatography eluting with ethyl acetate/petroleum ether = 70/30 to give an oil (90%, 4.50 g). ^{31}P NMR ($CDCl_3$, 202 MHz): δ 8.75. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.45-7.24 (10H, m, PhO, OCH_2*Ph*), 5.26 (2H, s, OCH_2Ph), 4.27-4.26 (1H, bs, NH), 4.04-3.91 (2H, m, $NHCH_2$).

Synthesis of N^2-DMF-acyclovir-[1-naphthyl(methoxy-L-alaninyl)] phosphate [68].

Prepared according to Standard Procedure C, from **66** (0.40 g, 1.43 mmol) in anhydrous THF (15 mL), ^{t}BuMgCl (1.0 M THF solution, 2.86 mL, 2.86 mmol), **46** (1.41 g, 4.32 mmol) in anhydrous THF (10 mL) and the reaction mixture was stirred at room temperature overnight. The residue was purified by column chromatography gradient elution of DCM/MeOH = 96/4 then 94/6, to give a white solid (35%, 0.43 g). ^{31}P-NMR (MeOD, 202 MHz): δ 3.76, 3.53. ^{1}H-NMR (MeOD, 500 MHz): δ 8.41 (1H, s, $NCHN(CH_3)_2$), 8.01-7.95 (1H, m, H-8 Naph), 7.79-7.78 (1H, m, H-6 Naph), 7.73-7.71 (1H, m, H-2 Naph), 7.55, 7.53 (1H, 2s, H-8), 7.43-7.39 (2H, m, Naph), 7.33-7.18 (2H, m, Naph), 5.38, 5.36 (2H, 2s, H-1'), 4.20-4.13 (2H, m, H-5'), 3.89-3.82 (1H, m, $CHCH_3$), 3.72-3.66 (2H, m, H), 3.48, 3.45 (3H, 2s, $COOCH_3$), 2.94, 2.90 (6H, 2s, $N(CH_3)_2$) 1.18-1.14 (3H, m, $CHCH_3$).

Synthesis of N^2-DMF-acyclovir-[1-naphthyl(ethoxy-L-alaninly)] phosphate [69].

Prepared according to Standard Procedure C, from **66** (0.40 g, 1.43 mmol) in anhydrous THF (15 mL), ^{t}BuMgCl (1.0 M THF solution, 2.86 mL, 2.86 mmol), **47** (1.46 g, 4.32 mmol) in anhydrous THF (10 mL) and the reaction mixture was stirred at room temperature overnight. The residue was purified by column chromatography gradient elution of DCM/MeOH = 98/2 then 96/4, to give a white solid (51%, 0.39 g). ^{31}P-NMR (MeOD, 202 MHz): δ 4.13, 4.05. ^{1}H-NMR

(MeOD, 500 MHz): δ 8.60, 8.59 (1H, 2s, NC*H*N(CH_3)$_2$), 8.28-7.35 (8H, m, H-8, Naph), 5.52, 5.50 (2H, 2s, H-1'), 4.34-4.25 (2H, m, H-5'), 4.11-3.81 (5H, m, C*H*CH_3+OC*H*$_2$$CH_3$, H-4'), 3.11-3.05 (6H, m, NCHN(C*H*$_3$)$_2$), 1.33-1.29 (3H, m, CHC*H*$_3$), 1.11-1.07 (3H, m, OCH_2C*H*$_3$).

Synthesis of N_2-DMF-acyclovir-[1-naphthyl(*tert*-butoxy-L-alaninyl)] phosphate [70].

Prepared according to Standard Procedure C, from **66** (0.40 g, 1.43 mmol) in anhydrous THF (15 mL), ^{t}BuMgCl (1.0 M THF solution, 2.86 mL, 2.86 mmol), **48** (1.60 g, 4.32 mmol) in anhydrous THF (10 mL) and the reaction mixture was stirred at room temperature overnight. The residue was purified by column chromatography gradient elution of DCM/MeOH = 98/2 then 97/3, to give a white solid (72%, 0.63 g). ^{31}P-NMR (MeOD, 202 MHz): δ 4.22, 4.19. ^{1}H-NMR (MeOD, 500 MHz): δ 8.59, 8.58 (1H, 2s, NC*H*N(CH_3)$_2$), 8.30-8.29 (1H, m, H-8 Naph), 7.94-7.34 (7H, m, H-8, Naph), 5.51, 5.49 (2H, 2s, H-1'), 4.32-4.27 (2H, m, H-5'), 3.90-3.87 (1H, m, C*H*CH_3), 3.85-3.81 (2H, m, H-4'), 3.11, 3.10 (3H, 2s, N(CH_3)$_2$), 3.07, 3.06 (3H, 2s, N(CH_3)$_2$), 1.42-1.27 (9H, m, C(C*H*$_3$)$_3$), 1.21-1.18 (3H, m, CHC*H*$_3$).

Synthesis of N_2-DMF-acyclovir-[1-naphthyl(*iso*-propoxy-L-alaninyl)] phosphate [71].

Prepared according to Standard Procedure C, from **66** (0.40 g, 1.43 mmol) in anhydrous THF (15 mL), ^{t}BuMgCl (1.0 M THF solution, 2.86 mL, 2.86 mmol), **49** (1.54 g, 4.32 mmol) in anhydrous THF (10 mL) and the reaction mixture was stirred at room temperature overnight. The residue was purified by column chromatography gradient elution of DCM/MeOH = 98/2 then 97/3, to give a white solid (73%, 0.63 g). ^{31}P-NMR (MeOD, 202 MHz): δ 4.13, 4.04. ^{1}H-NMR (MeOD, 500 MHz): δ 8.53, 8.52 (1H, 2s, NC*H*N(CH_3)$_2$), 8.29-8.26 (1H, m, H-8 Naph), 8.16-8.11 (1H, m, Naph), 7.95-7.31 (6H, m, H-8, Naph), 5.47, 5.45 (2H, 2s, H-1'), 4.96-4.77 (1H, m, C*H*(CH_3)$_2$), 4.32-4.21 (2H, m, H-5'), 4.00-3.94 (1H, m, C*H*CH_3), 3.82-3.77 (2H, m, H-4'), 3.07, 3.06 (3H, 2s, N(CH_3)$_2$), 3.02, 3.02 (3H, 2s, N(CH_3)$_2$), 1.36-1.26 (3H, m, CHC*H*$_3$), 1.10, 1.07 (6H, 2d, CH(C*H*$_3$)$_2$).

Synthesis of N^2-DMF-acyclovir-[1-phenyl-(methoxy-L-alaninyl)] phosphate [72].

Prepared according to Standard Procedure C, from **66** (0.40 g, 1.43 mmol) in anhydrous THF (15 mL), ^{t}BuMgCl (1.0 M THF solution, 2.86 mL, 2.86 mmol), **50** (1.20 g, 4.32 mmol) in anhydrous THF (10 mL) and the reaction mixture was stirred at room temperature overnight. The residue was purified by column chromatography gradient elution of DCM/MeOH = 96/4 then 94/6, to give a white solid (36%, 0.27 g). ^{31}P-NMR (MeOD, 202 MHz): δ 3.76, 3.53. ^{1}H-NMR (MeOD, 500 MHz): δ 8.60 (1H, s, NC*H*N$(CH_3)_2$), 7.88, 7.86 (1H, 2s, H-8), 7.27-7.04 (3H, m, PhO), 6.97-6.90 (2H, m, PhO), 5.47, 5.45 (2H, 2s, H-1'), 4.15-4.12 (1H, m, H-5' of one diastereoisomer), 4.10-4.07 (1H, m, H-5' of one diastereoisomer), 3.85-3.78 (1H, m, C*H*CH_3), 3.74-3.66 (2H, m, H-4'), 3.58, 3.57 (3H, 2s, $COOCH_3$), 3.05, 3.01 (6H, 2s, N$(CH_3)_2$), 1.15-1.14 (3H, s, CHC*H*$_3$).

Synthesis of N^2-DMF-acyclovir-[1-phenyl-(benzoxy-L-alaninyl)] phosphate [73].

Prepared according to Standard Procedure C, from **66** (0.40 g, 1.43 mmol) in anhydrous THF (15 mL), ^{t}BuMgCl (1.0 M THF solution, 2.86 mL, 2.86 mmol), **51** (1.53 g, 4.32 mmol) in anhydrous THF (10 mL) and the reaction mixture was stirred at room temperature overnight. The residue was purified by column chromatography eluting with DCM/MeOH = 95/5, to give a white solid (44%, 0.38 g). ^{31}P-NMR (MeOD, 202 MHz): δ 3.84, 3.47. ^{1}H-NMR (MeOD, 500 MHz): δ 8.54 (1H, s, NC*H*N$(CH_3)_2$), 7.80, 7.77 (1H, 2s, H-8), 7.26-7.14 (7H, m, PhO, OCH_2*Ph*), 7.05-7.00 (3H, m, PhO, OCH_2*Ph*), 5.41, 5.38 (2H, 2s, H-1'), 5.01, 4.99 (2H, 2s, OC*H*$_2$Ph), 4.08-4.05 (1H, m, H-5' of one diastereoisomer), 4.04-4.00 (1H, m, H-5' of one diastereoisomer), 3.86-3.81 (1H, m, C*H*CH_3), 3.66-3.61 (2H, m, H-4'), 3.03, 3.02 (3H, 2s, N$(CH_3)_2$), 2.97 (3H, s, N$(CH_3)_2$), 1.22-1.18 (3H, m, CHC*H*$_3$).

Synthesis of N^2-DMF-acyclovir-[1-phenyl-(isopropoxy-L-alaninyl)] phosphate [74].

Prepared according to Standard Procedure C, from **66** (0.40 g, 1.43 mmol) in anhydrous THF (15 mL), ^{t}BuMgCl (1.0 M THF solution, 2.86 mL, 2.86 mmol),

52 (1.31 g, 4.28 mmol) in anhydrous THF (10 mL) and the reaction mixture was stirred at room temperature overnight. The residue was purified by column chromatography gradient elution of DCM/MeOH = 98/2 then 97/3 then 96/4, to give a white solid (59%, 0.54 g). ^{31}P-NMR (MeOD, 202 MHz): δ 3.88, 3.65. ^{1}H-NMR (MeOD, 500 MHz): δ 8.72 (1H, s, NC*H*N$(CH_3)_2$), 7.96, 7.94 (1H, 2s, H-8), 7.36-7.32 (2H, m, PhO), 7.20-7.17 (3H, m, PhO), 5.59, 5.57 (2H, 2s, H-1'), 5.08-4.92 (1H, m, COOC*H*$(CH_3)_2$), 4.29-4.19 (2H, m, H-5'), 3.91-3.80 (3H, m, C*H*CH_3, H-4'), 3.21, 3.14 (6H, 2s, N(C*H*$_3)_2$,), 1.41-1.01 (9H, m, COOCH(C*H*$_3)_2$, CHC*H*$_3$).

Synthesis of N^2-DMF-acyclovir-[1-*p*-fluoro-phenyl-(benzoxy-L-alaninyl)] phosphate [75].

Prepared according to Standard Procedure C, from **66** (0.40 g, 1.43 mmol) in anhydrous THF (15 mL), ^{t}BuMgCl (1.0 M THF solution, 2.86 mL, 2.86 mmol), **53** (1.60 g, 4.28 mmol) in anhydrous THF (10 mL) and the reaction mixture was stirred at room temperature overnight. The residue was purified by column chromatography gradient elution of DCM/MeOH = 98/2 then 95/5, to give a white solid (52%, 0.88 g). ^{31}P-NMR (MeOD, 202 MHz): δ 4.08, 3.76. ^{19}F-NMR ($CDCl_3$, 471 MHz): δ -120.16 (d, J = 2.30), -120.18 (d, J = 2.30). ^{1}H-NMR (MeOD, 500 MHz): δ 8.71 (1H, s, NC*H*N$(CH_3)_2$), 7.97, 7.94 (1H, 2s, H-8), 7.40-7.28 (6H, m, Ph), 7.22-7.11 (3H, m, PhO), 5.60-5.50 (2H, m, H-1'), 5.19-5.06 (2H, m, OC*H*$_2$Ph), 4.20-4.15 (2H, m, H-5'), 3.99-3.95 (1H, m, C*H*CH_3), 3.80-3.75 (2H, m, H-4'), 3.19, 3.17, 3.12 (6H, 3s, N(C*H*$_3)_2$), 1.36-1.28 (3H, m, CHC*H*$_3$).

Synthesis of N^2-DMF-acyclovir-[1-phenyl-(benzoxy-D-alaninyl)] phosphate [76].

Prepared according to Standard Procedure C, from **66** (0.40 g, 1.43 mmol) in anhydrous THF (15 mL), ^{t}BuMgCl (1.0 M THF solution, 2.86 mL, 2.86 mmol), **54** (1.51 g, 4.32 mmol) in anhydrous THF (10 mL) and the reaction mixture was stirred at room temperature overnight. The residue was purified by column chromatography eluting with DCM/MeOH = 95/5, to give a white solid (57%, 0.49 g). ^{31}P-NMR (MeOD, 202 MHz): δ 3.84, 3.46. ^{1}H-NMR (MeOD, 500 MHz): δ 8.70 (1H, s, NC*H*N$(CH_3)_2$), 7.95, 7.92 (1H, 2s, H-8), 7.43-7.09 (10H, m, PhO,

OCH_2*Ph*), 5.55, 5.52 (2H, 2s, H-1'), 5.18-5.06 (2H, m, OC*H*$_2$Ph), 4.22-4.09 (2H, m, H-5'), 4.03-3.94 (1H, m, C*H*CH_3), 3.82-3.74 (2H, m, H-4'), 3.18-3.11 (6H, m, N(C*H*$_3)_2$), 1.36-1.26 (3H, m, CHC*H*$_3$).

Synthesis of N^2-DMF-acyclovir-[1-naphthyl(benzoxy-dimethylglycinyl)] phosphate [77].

Prepared according to Standard Procedure C, from **66** (0.20 g, 0.72 mmol) in anhydrous THF (10 mL), ^{t}BuMgCl (1.0 M THF solution, 0.86 mL, 0.86 mmol), **55** (0.80 g, 1.92 mmol) and the mixture reaction was stirred at room temperature overnight. Then ^{t}BuMgCl (1.0 M THF solution, 0.58 mL, 0.58 mmol), was added, and after 3 h the solution was concentrated. The residue was purified by column chromatography eluting with DCM/MeOH = 93/7, to give a white solid (35%, 0.17 g). ^{31}P-NMR (MeOD, 202 MHz): δ 2.55. ^{1}H-NMR (MeOD, 500 MHz): δ 8.59 (1H, s, NC*H*N(CH$_3)_2$), 8.15 (1H, d, *J* = 7.90 Hz, H-8 Naph), 7.88 (1H, s, H-6 Naph), 7.86 (1H, s, H-8), 7.67 (1H, d, *J* = 8.20 Hz, H-2 Naph), 7.55-7.26 (9H, m, Naph, OCH_2*Ph*), 5.48 (2H, s, H-1'), 5.17-5.08 (2H, m, OC*H*$_2$Ph), 4.28-4.17 (2H, m, H-5'), 3.79-3.70 (2H, m, H-4'), 3.09, 3.07 (6H, 2s, CHN(C*H*$_3)_2$), 1.51, 1.49 (6H, 2s, NHC(C*H*$_3)_2$). ^{13}C-NMR (MeOD, 125 MHz): δ 27.46 (d, J_{C-P} = 4.80, NHC(*C*H$_3)_2$), 27.71 (d, J_{C-P} = 6.90, NHC(*C*H$_3)_2$), 35.30, 41.41 (2s, N(*C*H$_3)_2$), 58.08 (*C*(CH$_3)_2$), 67.20 (d, J_{C-P} = 5.70, C-5'), 68.23 (O*C*H$_2$Ph), 69.43 (d, J_{C-P} = 7.30, C-4'), 73.67 (C-1'), 116.31, 117.37 120.33, 122.95 125.77, 126.47, 127.30, 127.70, 127.89, 128.48, 128.82, 129.29, 129.55, 130.89 (C-5, C-2 Naph, C-3 Naph, C-4 Naph, C-5 Naph, C-6 Naph, C-7 Naph, C-8 Naph, C-8a Naph, OCH_2*Ph*), 136.25, 137.33 (C-4a Naph, 'ipso' OCH_2*Ph*), 140.61 (C-8), 148.08, 148.14 ('ipso' Naph, C-4), 152.45 (C-2), 159.37 (C-6), 159.85 (*C*HN(CH$_3)_2$) 176.56 (d, J_{C-P} = 3.30, *C*OOCH$_2$Ph). EI MS= 662.2499 (M+H). Anal. Calcd for $C_{32}H_{36}N_7O_7P \cdot H_2O$: C, 56.55; H, 5.64; N, 14.43. Found: C, 56.86; H, 5.05; N, 13.93.

Synthesis of N^2-DMF-acyclovir-[1-phenyl-(benzoxy-dimethylglicinyl)] phosphate [78].

Prepared according to standard procedure C, from **66** (0.50 g, 1.78 mmol) in anhydrous THF (20 mL), ^{t}ButMgCl (1.0 M THF solution, 3.70 mL, 3.70 mmol),

56 (2.01 g, 5.34 mmol), in anhydrous THF (10 mL) and the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue was purified by column chromatography, gradient elution of DCM/MeOH = 98/2, then 96/4 to give a white solid (93%, 1.02 g). ^{31}P NMR (MeOD, 202 MHz): δ 2.17. ^{1}H NMR (MeOD, 500 MHz): δ 8.69 (1H, s, NC*H*N(CH$_3$)$_2$), 7.91 (1H, s, H-8), 7.40-7.25 (7H, m, PhO, OCH$_2$*Ph*), 7.17-7.15 (3H, m, PhO, OCH$_2$*Ph*), 5.53 (2H, s, H-1'), 5.19-5.06 (2H, m, OC*H*$_2$Ph), 4.18-4.12 (2H, m, H-5'), 3.77-370 (2H, m, H-4'), 3.18 (3H, s, N(CH$_3$)$_2$), 3.12 (3H, s, N(CH$_3$)$_2$), 1.48, 1.47 (6H, 2s, C(CH$_3$)$_2$). ^{13}C NMR (MeOD, 126 MHz): δ 27.42 (d, J_{C-P} = 4.70, CH$_3$), 27.58 (d, J_{C-P} = 6.60, CH$_3$), 35.38 (NCHN(*C*H$_3$)$_2$), 41.51 (NCHN(*C*H$_3$)$_2$), 57.98 (*C*(CH$_3$)$_2$), 67.02 (d, J_{C-P} = 5.60, C-5'), 68.20 (O*C*H$_2$Ph), 69.43 (d, J_{C-P} = 7.40, C-4'), 73.69 (C-1'), 120.35, 121.47, 121.51, 125.99, 129.31, 129.58, 130.68 (C-5, PhO, OCH$_2$*Ph*), 137.36 ('ipso' OCH$_2$*Ph*), 140.62 (C-8), 152.28, 152.33 (2s, C-4), 159.37 (C-2), 159.90 (N*C*HN(CH$_3$)$_2$), 176.51 (d, J_{C-P} = 3.70, *C*OOCH$_2$Ph). EI MS= 612.2316 (M+H). Anal. Calcd for C$_{28}$H$_{34}$N$_7$O$_7$P·0.5H$_2$O: C, 54.19; H, 5.68; N, 15.80. Found: C, 54.16; H, 5.61; N, 15.70.

Synthesis of N^2-DMF-acyclovir-[1-phenyl-(benzoxy-L-phenylalaninyl)] phosphate [79].

Prepared according to Standard Procedure C, from **66** (0.40 g, 1.43 mmol) in anhydrous THF (15 mL), ^{t}BuMgCl (1.0 M THF solution, 2.86 mL, 2.86 mmol), **57** (1.25 g, 2.88 mmol) in anhydrous THF (10 mL) and the reaction mixture was stirred at room temperature overnight. The residue was purified by column chromatography gradient elution of DCM/MeOH = 98/2 then 95/5, to give a white solid (60%, 0.58 g). ^{31}P-NMR (MeOD, 202 MHz): δ 3.39, 3.36. ^{1}H-NMR (MeOD, 500 MHz): δ 8.48, 8.47 (1H, 2s, NC*H*N(CH$_3$)$_2$), 7.74, 7.73 (1H, 2s, H-8), 7.19-6.86 (15H, m, PhO, COOCH$_2$*Ph*, CHCH$_2$*Ph*), 5.33, 5.32 (2H, 2s, H-1'), 4.95-4.90 (2H, m, COOC*H*$_2$Ph), 4.03-3.96 (1H, m, C*H*CH$_2$Ph), 3.91-3.86 (0.5H, m, H-5' of one diastereoisomer), 3.81-3.67 (1.5H, m, H-5'), 3.54-3.48 (2H, m, H-4'), 2.96-2.87 (7H, m, N(C*H*$_3$)$_2$, CHC*H*$_2$Ph of one diastereoisomer), 2.76-2.71 (1H, m, CHC*H*$_2$Ph of one diastereoisomer).

Synthesis of N^2-DMF-acyclovir-[1-phenyl-(benzoxy-L-valinyl)] phosphate [80].

Prepared according to Standard Procedure C, from **66** (0.40 g, 1.43 mmol) in anhydrous THF (20 mL), ^{t}BuMgCl (1.0 M THF solution, 2.86 mL, 2.86 mmol), **58** (1.63 g, 4.29 mmol) in anhydrous THF (10 mL) and the reaction mixture was stirred at room temperature overnight. The residue was purified by column chromatography gradient elution of DCM/MeOH = 98/2 then 96/4 then 94/6, to give a white solid (57%, 0.51 g). ^{31}P NMR (MeOD, 202 MHz): δ 4.52, 4.18. ^{1}H NMR (MeOD, 500 MHz): δ 8.68 (1H, s, NC*H*N$(CH_3)_2$), 8.03, 7.97 (1H, 2s, H-8), 7.38-7.11 (10H, m, PhO, OCH_2*Ph*), 5.52, 5.50 (2H, 2s, H-1'), 5.10, 5.03 (2H, 2s, OCH_2Ph), 4.16 (2H, s, H-5'), 3.76-3.64 (3H, m, NHC*H*, H-4'), 3.15, 3.10 (6H, 2s, N$(CH_3)_2$), 2.03-1.99 (0.5H, m, C*H*$(CH_3)_2$ of one diastereoisomer), 1.93-1.91 (0.5H, m, C*H*$(CH_3)_2$ of one diastereoisomer), 0.86-0.84 (6H, m, CH$(CH_3)_2$).

Synthesis of N^2-DMF-acyclovir-[1-naphthyl-(methoxy-L-valinyl)] phosphate [81].

Prepared according to standard procedure C, from **66** (0.50 g, 1.78 mmol) in anhydrous THF (16 mL), ^{t}BuMgCl (1.0M THF solution, 3.56 mL, 3.56 mmol), **59** (0.90 g, 2.53 mmol) in anhydrous THF (16 mL) and the reaction mixture was stirred at room temperature overnight. The residue was purified by column chromatography, gradient elution of DCM/MeOH = 98/2, then 96/4, then 95/5, to give a white solid (42%, 0.45 g). ^{31}P-NMR (MeOD, 202MHz): δ 4.89, 4.85. ^{1}H-NMR (MeOD, 500MHz): δ 8.59 (1H, s, NC*H*N$(CH_3)_2$), 8.15-8.13 (1H, m, Naph), 7.91 (1H, bs, H-8), 7.88-7.86 (1H, m, Naph), 7.69-7.67 (1H, m, Naph), 7.54-7.52 (2H, m, Naph), 7.44-7.36 (2H, m, Naph,), 5.52, 5.51 (2H, 2s, H-1'), 4.33-4.27 (2H, m, H-5'), 3.84-3.83 (2H, m, H-4'), 3.71-3.67 (1H, m, NHC*H*), 3.37, 3.33 (3H, 2s, $COOCH_3$), 3.10, 3.06 (6H, 2s, N$(CH_3)_2$), 2.00-1.96 (1H, m, C*H*$(CH_3)_2$), 0.89-0.84 (6H, m, CH$(CH_3)_2$). EI MS= 600.2349 (M+H).

Synthesis of N^2-DMF-acyclovir-[1-naphthyl-(ethoxy-L-valinyl)] phosphate [82].

Prepared according to Standard Procedure C, from **66** (0.50 g, 1.78 mmol) in anhydrous THF (16 mL), ^{t}BuMgCl (1.0 M THF solution, 3.56 mL, 3.56 mmol), **60** (1.96 g, 5.34 mmol) in anhydrous THF (16 mL) and the reaction mixture was

stirred at room temperature overnight. The residue was purified by column chromatography gradient elution of DCM/MeOH = 98/2 then 96/4 then 95/5, to give a white solid (88%, 0.94 g). ^{31}P-NMR (MeOD, 202MHz): δ 5.07, 4.88. ^{1}H-NMR (MeOD, 500MHz): δ 8.51 (1H, s, NC*H*N$(CH_3)_2$), 8.14-8.12 (1H, m, Naph), 7.91 (1H, bs, H-8), 7.85-7.83 (1H, m, Naph), 7.66-7.64 (1H, m, Naph), 7.51-7.49 (2H, m, Naph), 7.47-7.40 (2H, m, Naph), 5.49 (2H, s, H-1'), 4.31-4.28 (2H, m, H-5'), 4.06-3.96 (2H, m, C*H*$_2$CH$_3$), 3.83-3.80 (2H, m, H-4'), 3.74-3.66 (1H, m, NHC*H*), 3.06, 3.01 (6H, 2s, N$(CH_3)_2$), 2.02-1.96 (1H, m, C*H*$(CH_3)_2$), 1.17-1.12 (3H, m, CH_2C*H*$_3$), 0.89-0.84 (6H, m, CH(C*H*$_3)_2$).

Synthesis of N^2-DMF-acyclovir-[1-naphthyl-(methoxy-D-valinyl)] phosphate [83].

Prepared according to Standard Procedure C, from **66** (0.50 g, 1.78 mmol) in anhydrous THF (16 mL), ^{t}BuMgCl (1.0 M THF solution, 3.56 mL, 3.56 mmol), **61** (0.90 g, 2.53 mmol) in anhydrous THF (16 mL) and the reaction mixture was stirred at room temperature overnight. The residue was purified by column chromatography gradient elution of DCM/MeOH = 98/2 then 96/4 then 95/5, to give a white solid (31%, 0.33 g). ^{31}P-NMR (MeOD, 202MHz): δ 4.86, 4.81. ^{1}H-NMR (MeOD, 500MHz): δ 8.54 (1H, s, NC*H*N$(CH_3)_2$), 8.15-8.12 (1H, m, Naph), 7.94 (1H, bs, H-8), 7.87-7.85 (1H, m, Naph), 7.68-7.66 (1H, m, Naph), 7.53-7.51 (2H, m, Naph), 7.46-7.41 (2H, m, Naph), 5.49, 5.48 (2H, 2s, H-1'), 4.31-4.26 (2H, m, H-5'), 3.83-3.81 (2H, m, H-4'), 3.74-3.67 (1H, m, NHC*H*), 3.56 (3H, bs, $COOCH_3$), 3.07, 3.04 (6H, 2s, N$(CH_3)_2$), 2.00-1.95 (1H, m, C*H*$(CH_3)_2$), 0.88-0.81 (6H, m, CH(C*H*$_3)_2$).

Synthesis of N^2-DMF-acyclovir-[1-Phenyl-(Benzoxy-L-leucinyl)] phosphate [84].

Prepared according to Standard Procedure C, from **66** (0.40 g, 1.43 mmol) in anhydrous THF (20 mL), ^{t}BuMgCl (1.0 M THF solution, 2.86 mL, 2.86 mmol), **62** (2.25 g, 5.68 mmol) in anhydrous THF (10 mL) and the reaction mixture was stirred at room temperature overnight. The residue was purified by column chromatography gradient elution of DCM/MeOH = 98/2 then 96/4 then 95/5, to give a white solid (65%, 0.59 g). ^{31}P NMR (MeOD, 202 MHz): δ 4.10, 3.57. ^{1}H NMR (MeOD, 500 MHz): δ 8.69 (1H, s, NC*H*N$(CH_3)_2$), 7.95, 7.93 (1H, 2s, H-8),

7.44-6.98 (10H, m, PhO, OCH_2*Ph*), 5.56-5.49 (2H, m, H-1'), 5.12-5.11 (2H, m, OCH_2Ph), 4.21-4.07 (2H, m, H-5'), 3.99-3.83 (1H, m, NHC*H*), 3.76-3.74 (2H, m, H-5'), 3.17-3.16 (3H, m, $N(CH_3)_2$), 3.11 (3H, s, $N(CH_3)_2$), 1.70-1.61 (1H, m, $CHCH_2CH(CH_3)_2$), 1.54-1.40 (2H, m, $CHCH_2CH(CH_3)_2$), 0.91-0.76 (6H, m, $CHCH_2CH(CH_3)_2$).

Synthesis of N^2-DMF-Acyclovir-[1-phenyl-(benzoxy-L-isoleucinyl)] phosphate [85].

Prepared according to Standard Procedure C, from **66** (0.49 g, 1.75 mmol) in anhydrous THF (20 mL), ^{t}BuMgCl (1.0 M THF solution, 2.86 mL, 2.86 mmol), **63** (2.41 g, 6.09 mmol) in anhydrous THF (10 mL) and the reaction mixture was stirred at room temperature overnight. After this period ^{t}BuMgCl (1.0 M THF solution, 2.00 mL, 2.00 mmol) and the reaction mixture was stirred at room temperature for 6 h. The residue was purified by column chromatography gradient elution of DCM/MeOH = 98/2 then 96/4 then 95/5, to give a white solid (45%, 0.50 g). ^{31}P NMR (MeOD, 202 MHz): δ 4.44, 4.05. ^{1}H NMR (MeOD, 500 MHz): δ 8.69 (1H, s, $NCHN(CH_3)_2$), 7.98-7.97 (1H, m, H-8), 7.33-7.16 (10H, m, PhO, OCH_2*Ph*), 5.53-5.52 (2H, 2s, H-1'), 5.14-5.06 (2H, m, OCH_2Ph), 4.20-4.11 (2H, m, H-5'), 3.83-3.65 (3H, m, NHC*H*, H-4'), 3.15-3.10 (6H, 2s, $N(CH_3)_2$), 1.78-1.71 (1H, m, $CHCH(CH_3)CH_2CH_3$), 1.52-1.36 (1H, m, $CH(CH_3)CH_2CH_3$), 1.16-1.07 (1H, m, $CH(CH_3)CH_2CH_3$), 0.86-0.80 (6H, m, $CH(CH_3)CH_2CH_3$).

Synthesis of N^2-DMF-Acyclovir-[1-Phenyl-(Benzoxy-L-prolinyl)] phosphate [86].

To a suspension of **66** (1.00 g, 3.57 mmol) in a 3/2 mixture of THF/pyridine (50 mL), were added a solution of **64** (4.07 g, 10.71 mmol) in anhydrous THF (10 mL) and NMI (0.85 mL, 10.70 mmol) and the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure. The residue was purified by column chromatography, gradient elution of DCM/MeOH = 98/2, then 97/3, then 96/4, to give a white solid (16%, 0.35 g). ^{31}P NMR (MeOD, 202 MHz): δ 1.73. ^{1}H NMR (MeOD, 500 MHz): δ 8.68 (1H, s, $NCHN(CH_3)_2$), 7.94 (1H, s, H-8), 7.38-7.26 (7H, m, PhO, OCH_2*Ph*), 7.19-7.13 (3H, m, PhO, OCH_2*Ph*), 5.60-5.50 (2H, m, H-1'), 5.16-5.08 (2H, m, OCH_2Ph), 4.31-4.22 (2H, m, H-5', NC*H*), 4.19-4.14 (1H, m, H-5'), 3.79-3.78 (2H, m, H-4'),

3.27-3.19 (2H, m, CHNCH_2), 3.17, 3.10 (6H, 2s, N(CH_3)$_2$), 2.15-2.07 (1H, m, NCHCH_2), 1.98-1.91 (1H, m, NCHCH_2), 1.89-1.73 (2H, m, NCHCH$_2$CH_2). ^{13}C NMR (MeOD, 126 MHz): δ 26.18 (d, J_{C-P} = 8.90, NCHCH$_2$*C*H$_2$CH$_2$), 32.19 (d, J_{C-P} = 9.10, NCH*C*H$_2$), 35.36, 41.49 (2s, NCHN(*C*H$_3$)$_2$), 48.09 (d, J_{C-P} = 4.50, NCHCH$_2$CH$_2$*C*H$_2$), 62.17 (d, J_{C-P} = 7.00, N*C*H), 67.08 (d, J_{C-P} = 5.00, C-5'), 67.99 (O*C*H$_2$Ph), 69.49 (d, J_{C-P} = 7.20, C-4'), 73.73 (C-1'), 120.38, 121.17, 121.21, 126.18, 129.34, 129.60, 130.87 (C-5, PhO, OCH$_2$*Ph*), 137.26 ('ipso' OCH$_2$*Ph*), 140.68 (C-8), 152.03 (d, J_{C-P} = 6.50, C-4), 159.41 (C-2), 159.55 (N*C*HN(CH$_3$)$_2$), 160.23 (C-6), 174.84 (*C*OOCH$_2$Ph). EI MS= 624.2338 (M+H). Anal. Calcd for $C_{29}H_{34}N_7O_7P \cdot H_2O$: C, 54.29; H, 5.66, N, 15.28. Found: C, 54.63; H, 5.44; N, 15.23.

Synthesis of N^2-DMF-acyclovir-[1-phenyl-(benzoxy-glicinyl)] phosphate [87].

To a suspension of **66** (1.00 g, 3.57 mmol) in a 3/2 mixture of THF/pyridine (50 mL), were added a solution of **65** (3.64 g, 10.70 mmol) in anhydrous THF (10 mL) and NMI (0.85 ml, 10.70 mmol) and the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure. The residue was purified by column chromatography, gradient elution of DCM/MeOH (98/2, then 97/3, then 96/4, then 95/5) to give a white solid (81%, 1.69 g). ^{31}P NMR (MeOD, 202 MHz): δ 4.78. ^{1}H NMR (MeOD, 500 MHz): δ 8.70 (1H, s, NC*H*N(CH$_3$)$_2$), 7.92 (1H, s, H-8), 7.39-7.28 (7H, m, PhO, OCH$_2$*Ph*), 7.20-7.15 (3H, m, PhO, OCH$_2$*Ph*), 5.53 (2H, s, H-1'), 5.16 (2H, s, OCH_2Ph), 4.29-4.17 (2H, m, H-5'), 3.80-3.74 (4H, m, H-4', NHCH_2), 3.17, 3.11 (6H, 2s, N(CH$_3$)$_2$).

Synthesis of acyclovir-[1-naphthyl(*n*-propoxy-L-alaninyl)] phosphate [3].

A solution of **67** (0.78 g, 1.20 mmol) in n-propanol (28 mL) was stirred under reflux for 18 h. The solvent was then removed under reduced pressure and the residue was purified by column chromatography eluting with DCM/MeOH = 95/5, to give a white solid (3%, 0.020g). ^{31}P-NMR (DMSO, 202 MHz): δ 4.09, 4.01. ^{1}H-NMR (DMSO, 500 MHz): δ 10.68 (1H, bs, NH), 8.16-8.12 (1H, m, H-8 Naph), 8.01-7.99 (1H, m, H-6 Naph), 7.86, 7.85 (1H, 2s, H-8), 7.79-7.50 (5H, m, Naph), 6.55 (2H, bs, NH$_2$), 6.20-6.14 (1H, m, N*H*CH), 5.41, 5.40 (2H, 2s, H-1'),

4.22-4.17 (2H, m, H-5'), 4.00-3.93 (3H, m, C*H*CH_3, OC*H*$_2CH_2CH_3$), 3.77-3.74 (2H, m, H-4'), 1.61-1.50 (2H, m, $OCH_2CH_2CH_2CH_3$), 1.31-1.27 (3H, m, $CHCH_3$), 0.90-0.84 (3H, m, $OCH_2CH_2CH_3$). ^{13}C-NMR (DMSO, 125 MHz): δ 10.07 ($CH_3CH_2CH_2$), 19.68 (d, J_{C-P} = 8.77, $CHCH_3$), 19.75 (d, J_{C-P} = 6.94, $CHCH_3$), 21.36, 21.39 (2s, $CH_3CH_2CH_2$), 49.81, 49.89 (2s, $CHCH_3$), 65.11, 65.14 (2s, C-5'), 65.86, 65.90 (2s, $COOCH_2CH_2CH_3$), 67.57, 67.63 (2s, C-4'), 71.84 (C-1'), 114.76, 116.48, 121.45, 121.51, 124.08, 125.64, 125.99, 126.04, 126.17, 126.24, 126.61, 127.64, 127.96, 128.32 (C-5, C-2 Naph, C-3 Naph, C-4 Naph, C-5 Naph, C-6 Naph, C-7 Naph, C-8 Naph, C-8a Naph), 134.21 (C-4a Naph), 137.57 (C-8), 146.46, 146.51 ('ipso' Naph), 151.36 (C-4), 153.88 (C-2), 156.73 (C-6), 173.15 (d, J_{C-P} = 4.84, $COOCH_2CH_2CH_3$), 173.33 (d, J_{C-P} = 3.83, $COOCH_2CH_2CH_3$). EI MS= 567.1721 (M+Na). HPLC = H_2O/AcCN from 100/0 to 0/100 in 60 min = retention time 20.63, 20.83 min.

Synthesis of acyclovir-[1-naphthyl(methoxy-L-alaninyl)] phosphate [4].

A solution of **68** (0.41 g, 0.72 mmol) in 2-propanol (15 mL) was stirred under reflux for 72 h. The solvent was then removed under reduced pressure and the residue was purified by column chromatography gradient elution of DCM/MeOH = 98/2 then 96/4 then 92/8. The product was purified by preparative TLC (gradient elution of DCM/MeOH = 98/2 then 96/4 then 95/5) then by preparative reverse phase HPLC (gradient elution of H_2O/CH_3CN= from 100/0 to 0/100 in 45 min) to give a white solid (7%, 0.028 g). ^{31}P-NMR (MeOD, 202 MHz): δ 4.07, 4.05. ^{1}H-NMR (MeOD, 500 MHz): δ 8.14-8.12 (1H, m, H-8 Naph), 7.88-7.87 (1H, m, H-6 Naph), 7.82, 7.81 (1H, 2s, H-8), 7.71-7.70 (1H, m, H-2 Naph), 7.56-7.51 (2H, m, H-5 Naph, H-7 Naph), 7.45-7.39 (2H, m, H-3 Naph, H-4 Naph), 5.44, 5.42 (2H, 2s, H-1'), 4.30-4.28 (1H, m, H-5' of one diastereoisomer), 4.27-4.24 (1H, m, H-5' of one diastereoisomer), 4.06-3.98 (1H, m, C*H*CH_3), 3.84-3.82 (1H, m, H-4' of one diastereoisomer), 3.80-3.79 (1H, m, H-4' of one diastereoisomer), 3.63, 3.59 (3H, 2s, COOC*H*$_3$), 1.34-1.30 (3H, m, $CHCH_3$). ^{13}C-NMR (MeOD, 125 MHz): δ 20.38 (d, J_{C-P} = 7.30, $CHCH_3$), 20.50 (d, J_{C-P} = 6.50, $CHCH_3$), 51.59 ($CHCH_3$), 52.67, 52.76 (2s, $COOCH_3$), 67.24 (d, J_{C-P} = 5.6, C-5'), 67.31 (d, J_{C-P} = 5.1, C-5'), 69.39 (d, J_{C-P} = 7.4, C-4'), 69.47 (d, J_{C-P} = 7.6, C-4'), 73.68 (C-1'), 116.23, 116.25, 116.28, 117.56, 122.69, 122.74, 125.90, 126.51,

127.42, 127.44, 127.75, 127.89, 127.94, 128.81, 128.83 (C-5, C-2 Naph, C-3 Naph, C-4 Naph, C-5 Naph, C-6 Naph, C-7 Naph, C-8 Naph, C-8a Naph), 136.26 (C-4a Naph), 139.69 (C-8), 148.00, 148.06 ('ipso' Naph), 153.38 (C-4), 155.80 (C-2), 159.57 (C-6), 175.47 (d, J_{C-P} = 5.20, *C*OOCH$_3$), 175.60 (d, J_{C-P} = 4.40, *C*OOCH$_3$). EI MS = 539.1410 (M+Na). Anal. Calcd for $C_{22}H_{25}N_6O_7P{\cdot}2H_2O$: C, 47.87; H, 5.29; N, 15.21. Found: C, 48.23; H, 4.80; N, 15.30.

Synthesis of acyclovir-[1-naphthyl(ethoxy-L-alaninyl)] phosphate [5].

A solution of **69** (0.38 g, 0.72 mmol) in 2-propanol (15 mL) was stirred under reflux for 45 h. After this period the solvent was removed under reduced pressure and the residue was purified by column chromatography, gradient elution of DCM/MeOH = 98/2 then 96/4 then 94/6. The product was purified by preparative TLC (gradient elution of DCM/MeOH = 98/2 then 96/4 then 92/8) to give a white solid (18%, 0.07 g). ^{31}P-NMR (MeOD, 202 MHz): δ 4.10. ^{1}H-NMR (MeOD, 500 MHz): δ 8.16-8.11 (1H, m, H-8 Naph), 7.89-7.87 (1H, m, H-6 Naph), 7.82, 7.80 (1H, 2s, H-8), 7.70 (1H, d, H-2 Naph), 7.58-7.51 (2H, m, Naph), 7.47-7.39 (2H, m, Naph), 5.44, 5.42 (2H, 2s, H-1'), 4.36-4.22 (2H, m, H-5'), 4.16-3.94 (3H, m, C*H*CH$_3$, COOC*H*$_2$CH$_3$), 3.86-3.76 (2H, m, H-4'), 1.35, 1.31 (3H, 2dd, *J* = 7.10, 1.00, CHC*H*$_3$), 1.21 (3H, t, *J* = 7.1, COOCH$_2$C*H*$_3$), 1.17 (3H, t, *J* = 7.1, COOCH$_2$C*H*$_3$). ^{13}C-NMR (MeOD, 125 MHz): δ 14.39, 14.43 (2s, COOCH$_2$*C*H$_3$), 20.41 (d, J_{C-P} = 7.30, CH*C*H$_3$), 20.54 (d, J_{C-P} = 6.50, CH*C*H$_3$), 51.70 (*C*HCH$_3$), 62.31, 62.39 (2s, COO*C*H$_2$CH$_3$), 67.24 (d, J_{C-P} = 6.00, C-5'), 67.28 (d, J_{C-P} = 6.30, C-5'), 69.39 (d, J_{C-P} = 7.30, C-4'), 69.48 (d, J_{C-P} = 7.50, C-4'), 73.68 (C-1'), 116.25, 116.27, 117.58, 122.70, 122.77, 125.90, 126.52, 127.41, 127.43, 127.75, 127.90, 127.95, 128.81 128.83 (C-5, C-2 Naph, C-3 Naph, C-4 Naph, C-5 Naph, C-6 Naph, C-7 Naph, C-8 Naph, C-8a Naph), 136.27 (C-4a Naph), 139.71 (C-8), 148.01, 148.07 (2s, 'ipso' Naph), 153.39 (C-4), 155.66 (C-2), 159.38 (C-6), 175.03 (d, J_{C-P} = 5.10, *C*OOCH$_2$CH$_3$), 175.16 (d, J_{C-P} = 4.40, *C*OOCH$_2$CH$_3$). EI MS = 553.1580 (M+Na). Anal. Calcd for $C_{23}H_{27}N_6O_7P$: C, 52.08; H, 5.13; N, 15.84. Found: C, 51.99; H, 5.15; N, 16.01.

Synthesis of acyclovir-[1-naphthyl(*tert*-butoxy-L-alaninyl)] phosphate [6].

A solution of **70** (0.63 g, 1.03 mmol) in 2-propanol (25 mL) was stirred under reflux for 50 h. After this period the solvent was removed under reduced pressure and the residue was purified by column chromatography, gradient elution of DCM/MeOH = 98/2 then 96/4 then 94/6. The product was purified by preparative TLC (gradient elution of DCM/MeOH = 98/2 then 96/4 then 92/8) to give a white solid (18%, 0.10 g). ^{31}P-NMR (MeOD, 202 MHz): δ 4.25, 4.20. ^{1}H-NMR (MeOD, 500 MHz): δ 8.15-8.12 (1H, m, H-8 Naph), 7.89-7.83 (1H, m, H-6 Naph), 7.81, 7.79 (1H, 2s, H-8), 7.67 (1H, s, H-2 Naph) 7.57-7.49 (2H, m, Naph), 7.47-7.35 (2H, m, Naph), 5.42, 5.40 (2H, 2s, H-1'), 4.30-4.24 (2H, m, H-5'), 3.95-3.85 (1H, m, C*H*CH_3), 3.82-3.79 (2H, m, H-4'), 1.42, 1.37 (9H, 2s, C(C*H*$_3$)$_3$), 1.32 (1.5H, d, *J* = 7.1, CHC*H*$_3$ of one diastereoisomer), 1.30 (1.5H, d, *J* = 6.6, CHC*H*$_3$ of one diastereoisomer). ^{13}C-NMR (MeOD, 125 MHz): δ 20.58 (d, J_{C-P} = 7.30, CH*C*H$_3$), 20.73 (d, J_{C-P} = 6.60, CH*C*H$_3$), 28.18, 28.23 (2s, C(*C*H$_3$)$_3$), 52.30 (*C*HCH$_3$), 67.24 (d, J_{C-P} = 5.60, C-5'), 67.28 (d, J_{C-P} = 5.00, C-5'), 69.38 (d, J_{C-P} = 6.90, C-4'), 69.49 (d, J_{C-P} = 7.50, C-4'), 73.71 (C-1'), 82.63, 82.74 (2s, *C*(CH$_3$)$_3$), 116.25, 116.27, 116.32, 117.55, 122.73, 122.83, 125.90, 126.51, 126.52, 127.40, 127.41, 127.74, 127.89, 127.94 128.83 (C-5, C-2 Naph, C-3 Naph, C-4 Naph, C-5 Naph, C-6 Naph, C-7 Naph, C-8 Naph, C-8a Naph), 136.26 (C-4a Naph), 139.70 (C-8), 148.07 ('ipso' Naph), 153.35 (C-4), 155.66 (C-2), 159.42 (C-6), 174.38, 174.45 (2s, *C*OOCH$_3$). EI MS = 581.1893 (M+Na). HPLC = H_2O/AcCN from 100/0 to 0/100 in 20 min = retention time 13.59 min; H_2O/MeOH 40/60 isocratic = retention time 18.85 min, 21.16 min.

Synthesis of acyclovir-[1-naphthyl(isopropoxy-L-alaninyl)] phosphate [7].

A solution of **71** (0.50 g, 0.83 mmol) in 2-propanol (25 mL) was stirred under reflux for 40 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography, gradient elution of DCM/MeOH = 96/4 then 94/6. The product was purified by preparative TLC (gradient elution of DCM/MeOH = 98/2 then 96/4 then 92/8) to give a white solid (2%, 0.010 g). ^{31}P-NMR (MeOD, 202 MHz): δ 4.15. ^{1}H-NMR (MeOD, 500 MHz): δ 8.18-8.12 (1H, m, H-8 Naph), 7.92-7.86 (1H, m, H-6 Naph), 7.81, 7.79 (1H, 2s, H-8), 7.72-7.70 (1H, m, H-2 Naph) 7.58-7.52 (2H, m, Naph), 7.48-7.39 (2H, m, Naph), 5.47-5.41 (2H, m, H-1'), 5.00-4.90 (1H, m, C*H*(CH$_3$)$_2$), 4.38-4.20 (2H, m, H-5'), 4.00-3.96

(1H, m, C*H*CH_3), 3.86-3.75 (2H, m, H-4'), 1.35 (3H, dd, J = 7.10, J = 0.90, CHC*H*$_3$), 1.22 (3H, d, J = 2.70, CH(C*H*$_3$)$_2$), 1.21 (3H, d, J = 2.70, CH(C*H*$_3$)$_2$). ^{13}C-NMR (MeOD, 125 MHz): δ 20.40 (d, J_{C-P} = 6.30, CH*C*H_3), 20.56 (d, J_{C-P} = 6.60, CH*C*H_3), 21.86, 21.95 (2s, CH(*C*H_3)$_2$), 51.82 (*C*HCH_3), 67.23 (d, J_{C-P} = 5.60, C-5'), 67.28 (d, J_{C-P} = 6.30, C-5'), 69.37 (d, J_{C-P} = 7.30, C-4'), 69.50 (C-4'), 70.14, 70.22 (2s, *C*H(CH_3)$_2$), 73.67 (C-1'), 116.24, 116.27, 122.71, 122.80, 125.91, 126.51, 127.40, 127.42, 127.75, 127.95, 128.84 (C-5, C-2 Naph, C-3 Naph, C-4 Naph, C-5 Naph, C-6 Naph, C-7 Naph, C-8 Naph, C-8a Naph), 136.28 (C-4a Naph), 139.67 (C-8), 148.05 ('ipso' Naph), 153.39 (C-4), 155.71 (C-2), 159.42 (C-6), 174.62 (d, J_{C-P} = 4.60, *C*OOCH(CH_3)$_2$), 174.73 (d, J_{C-P} = 5.00, *C*OOCH(CH_3)$_2$). EI MS = 567.1741 (M+Na).

Synthesis of acyclovir-[1-phenyl-(methoxy-L-alaninyl)] phosphate [8].

A solution of **72** (0.27 g, 0.52 mmol) in 2-propanol (10 mL) was stirred under reflux for 40 h. The solvent was then removed under reduced pressure and the residue was purified by column chromatography eluting with DCM/MeOH = 95/5. The product was purified by preparative TLC (gradient elution of DCM/MeOH = 95/5 then 94/6 then 92/8) to give a white solid (13%, 0.032 g). ^{31}P-NMR (MeOD, 202 MHz): δ 3.72, 3.55. ^{1}H-NMR (MeOD, 500 MHz): δ 7.87-7.85 (1H, 2s, H-8), 7.36-7.33 (2H, m, PhO), 7.20-7.16 (3H, m, PhO), 5.50, 5.47 (2H, 2s, H-1'), 4.27-4.17 (2H, m, H-5'), 3.97-3.90 (1H, m, C*H*CH_3), 3.84-3.78 (2H, m, H-4'), 3.69, 3.67 (3H, 2s, COOC*H*$_3$), 1.35-1.31 (3H, m, CHC*H*$_3$). ^{13}C-NMR (MeOD, 125 MHz): δ 20.36 (d, J_{C-P} = 7.00, CH*C*H_3) 20.44 (d, J_{C-P} = 6.40, CH*C*H_3), 51.45, 51.52 (2s, *C*HCH_3), 52.72, 52.77 (2s, COO*C*H_3), 67.01 (d, J_{C-P} = 5.30, C-5'), 67.11 (d, J_{C-P} = 5.30, C-5'), 69.43 (d, J_{C-P} = 5.30, C-4'), 69.48 (d, J_{C-P} = 5.30, C-4'), 73.68 (C-1'), 117.52, 121.10, 121.14, 121.32, 121.40, 121.42, 121.44, 121.45, 121.54, 121.58, 123.89, 126.07, 130.10, 130.25, 130.71 (C-5, PhO), 139.79 (C-8), 152.18 (d, J_{C-P} = 2.04, C-4), 152.23 (d, J_{C-P} = 2.80, C-4), 155.69 (C-2), 159.41 (C-6), 175.46 (d, J_{C-P} = 5.40, *C*OOCH_3), 175.58 (d, J_{C-P} = 4.90, *C*OOCH_3). EI MS = 489.1267 (M+Na). HPLC = H_2O/AcCN from 100/0 to 0/100 in 20 min = retention time 9.71 min; H_2O/MeOH 40/60 isocratic = retention time 5.56 min, 5.72 min.

Synthesis of acyclovir-[1-phenyl-(benzoxy-L-alaninyl)] phosphate [9].

A solution of **73** (0.38 g, 0.63 mmol) in 2-propanol (15 mL) was stirred under reflux for 40 h. The solvent was then removed under reduced pressure and the residue was purified by column chromatography gradient elution of DCM/MeOH = 95/5 then 90/10. The product was purified by preparative TLC (gradient elution of DCM/MeOH = 96/4 then 94/6) to give a white solid (14%, 0.048 g). ^{31}P-NMR (MeOD, 202 MHz): δ 3.80, 3.50. ^{1}H-NMR (MeOD, 500 MHz): δ 7.74-7.71 (1H, 2s, H-8), 7.23-7.14 (7H, m, PhO, OCH_2*Ph*), 7.06-7.01 (3H, m, PhO, OCH_2*Ph*), 5.32, 5.29 (2H, 2s, H-1'), 5.00-4.99 (2H, 2s, OCH_2Ph), 4.04-3.99 (2H, m, H-5'), 3.89-3.82 (1H, m, $CHCH_3$), 3.62-3.59 (2H, m, H-4'), 1.22, 1.21 (3H, 2d, $CHCH_3$). ^{13}C-NMR (MeOD, 125 MHz): δ 20.34 (d, J_{C-P} = 7.63, $CHCH_3$), 20.43 (d, J_{C-P} = 6.34, $CHCH_3$), 51.61, 51.73 (2s, $CHCH_3$), 67.01 (d, J_{C-P} = 5.30, C-5'), 67.10 (d, J_{C-P} = 5.46, C-5'), 67.97, 67.98 (2s, OCH_2Ph), 69.39 (d, J_{C-P} = 3.90, C-4'), 69.45 (d, J_{C-P} = 3.90, C-4'), 73.76 (C-1'), 117.30, 121.39, 121.43, 121.47, 121.51, 126.08, 126.10, 129.19, 129.33, 129.36, 129.53, 129.58, 129.61, 130.19, 130.73 (C-5, PhO, OCH_2*Ph*), 137.27 ('ipso' OCH_2P*h*), 139.75 (C-8), 152.11, 152.17 (2s, C-4), 155.73 (C-2), 159.32 (C-6), 174.77 (d, J_{C-P} = 5.20, $COOCH_2$Ph), 174.91 (d, J_{C-P} = 4.60, $COOCH_2$Ph). EI MS= 565.1581 (M+Na). Anal. Calcd for $C_{24}H_{27}N_6O_7P$: C, 53.14; H, 5.02; N, 15.49. Found: C, 53.01; H, 4.90; N, 15.10.

Synthesis of acyclovir-[1-phenyl-(isopropoxy-L-alaninyl)] phosphate [10].

A solution of **74** (0.53 g, 0.98 mmol) in 2-propanol (18 mL) was stirred under reflux for 72 h. The solvent was then removed under reduced pressure and the residue was purified by column chromatography with DCM/MeOH = 95/5. The residue was tritured with water and the precipitate filtered to give a white solid (7%, 0.035 g). ^{31}P-NMR (MeOD, 202 MHz): δ 3.80, 3.65. ^{1}H-NMR (MeOD, 500 MHz): δ 7.86, 7.84 (1H, 2s, H-8), 7.36-7.33 (2H, m, PhO), 7.20-7.17 (3H, m, PhO), 5.50, 5.47 (2H, 2s, H-1'), 5.00-4.94 (1H, m, $COOCH(CH_3)_2$), 4.29-4.16 (2H, m, H-5'), 3.92-3.86 (1H, m, $CHCH_3$), 3.84-3.79 (2H, m, H-4'), 1.34 (1.5H, d, *J* = 7.10, $CHCH_3$ of one diastereoisomer), 1.31 (1.5H, d, *J* = 6.70, $CHCH_3$ of one diastereoisomer), 1.25-1.22 (6H, m, $COOCH(CH_3)_2$).^{13}C-NMR (MeOD, 125 MHz): δ 20.39 (d, J_{C-P} = 7.00, $CHCH_3$), 20.52 (d, J_{C-P} = 6.40, $CHCH_3$), 21.89 ($CH(CH_3)_2$), 21.96 (d, J_{C-P} = 3.00, $CH(CH_3)_2$), 51.68, 51.77 (2s, $CHCH_3$), 67.01

(d, J_{C-P} = 5.60, C-5'), 67.08 (d, J_{C-P} = 5.50, C-5'), 69.40 (d, J_{C-P} = 6.10, C-4'), 69.46 (d, J_{C-P} = 6.20, C-4'), 70.13, 70.17 (2s, COO*C*H(CH_3)$_2$), 73.67 (C-1'), 117.54 (C-5), 121.42 (d, J_{C-P} = 4.90, PhO), 121.47 (d, J_{C-P} = 4.80, PhO), 126.07 (d, J_{C-P} = 2.40, PhO), 130.72 (C-5, PhO), 139.75 (C-8), 152.20 (d, J_{C-P} = 4.30, C-4), 152.26 (d, J_{C-P} = 4.20, C-4), 153.44 ('ipso' Ph), 155.71 (C-2), 159.41 (C-6), 174.55 (d, J_{C-P} = 5.50, *C*OOCH(CH_3)$_2$), 174.69 (d, J_{C-P} = 5.00, *C*OOCH(CH_3)$_2$). EI MS= 517.1588 (M+Na). HPLC = H_2O/AcCN from 100/0 to 0/100 in 20 min = retention time 11.27 min; H_2O/MeOH 40/60 isocratic = retention time 7.40 min.

Synthesis of acyclovir-[1-p-fluoro-phenyl-(benzoxy-L-alaninyl)] phosphate [11].

A solution of **75** (0.46 g, 0.73 mmol) in 2-propanol (20 mL) was stirred under reflux for 24 h. The solvent was then removed under reduced pressure and the residue was purified by column chromatography with DCM/MeOH = 95/5 to give a white solid (16%, 0.068 g). ^{31}P-NMR (MeOD, 202 MHz): δ 4.02, 3.78. ^{19}F-NMR ($CDCl_3$, 471 MHz): δ -120.20, -120.22. ^{1}H-NMR (MeOD, 500 MHz): δ 7.84, 7.81 (1H, 2s, H-8), 7.39-7.29 (5H, m, Ph), 7.19-7.11 (2H, m, Ph), 7.06-7.02 (2H, m, Ph), 5.47, 5.44 (2H, 2s, H-1'), 5.15, 5.14 (2H, 2s, OC*H*$_2$Ph), 4.21-4.11 (2H, m, H-5'), 4.01-3.96 (1H, m, C*H*CH_3), 3.79-3.71 (2H, m, H-4'), 1.37 (1.5H, d, *J* = 7.1, CHC*H*$_3$ of one diastereoisomer), 1.34 (1.5H, d, *J* = 7.2, CHC*H*$_3$ of one diastereoisomer). ^{13}C-NMR (MeOD, 125 MHz): δ 20.30 (d, J_{C-P} = 7.10, CH*C*H$_3$) 20.40 (d, J_{C-P} = 6.50, CH*C*H$_3$), 51.60, 51.72 (2s, *C*HCH$_3$), 67.04 (d, J_{C-P} = 5.50, C-5'), 67.12 (d, J_{C-P} = 5.50, C-5'), 67.97 (O*C*H$_2$Ph), 69.32 (d, J_{C-P} = 4.00, C-4'), 69.38 (d, J_{C-P} = 4.10, C-4'), 73.76 (C-1'), 116.96, 117.15, 117.55, 122.99, 123.04, 123.06, 123.07, 123.10, 123.14, 128.00, 128.27, 129.35, 129.36, 129.38, 129.57, 129.60, (C-5, PhO, OCH$_2$*Ph*), 137.28 ('ipso' OCH$_2$*Ph*), 139.74 (C-8), 153.41 (C-4), 155.71 (C-2), 159.42 (C-6), 160.15, 162.09 (F-*Ph*), 174.71 (d, J_{C-P} = 5.20, *C*OOCH$_2$Ph), 174.83 (d, J_{C-P} = 4.60, *C*OOCH$_2$Ph). EI MS= 583.1479 (M+Na). Anal. Calcd for $C_{24}H_{26}FN_6O_7P \cdot H_2O$: C, 49.83; H, 4.88; N, 14.53. Found: C, 49.96; H, 4.57; N, 14.38.

Synthesis of acyclovir-[1-phenyl-(benzoxy-D-alaninyl)] phosphate [12].

A solution of **76** (0.48 g, 0.80 mmol) in 2-propanol (20 mL) was stirred under reflux for 48 h. The solvent was then removed under reduced pressure and the residue was purified by column chromatography gradient elution of DCM/MeOH = 96/4 then 94/6 to give a white solid (25%, 0.11 g).^{31}P-NMR (MeOD, 202 MHz): δ 3.80, 3.50. ^{1}H-NMR (MeOD, 500 MHz): δ 7.83, 7.80 (1H, 2s, H-8), 7.38-7.25 (7H, m, PhO, OCH_2*Ph*), 7.19-7.11 (3H, m, PhO, OCH_2*Ph*), 5.44, 5.41 (2H, 2s, H-1'), 5.13, 5.12 (2H, 2s, OCH_2Ph), 4.20-4.10 (2H, m, H-5'), 4.02-3.95 (1H, m, $CHCH_3$), 3.76-3.69 (2H, m, H-4'), 1.35 (3H, d, J = 7.20, $CHCH_3$), 1.32 (3H, d, J = 7.20, $CHCH_3$). ^{13}C-NMR (MeOD, 125 MHz): δ 20.34 (d, J_{C-P} = 6.80, $CHCH_3$) 20.43 (d, J_{C-P} = 6.60, $CHCH_3$), 51.60, 51.73 (2s, $CHCH_3$), 67.01 (d, J_{C-P} = 5.50, C-5'), 67.10 (d, J_{C-P} = 5.40, C-5'), 67.97, 67.98 (2s, OCH_2Ph), 69.34 (d, J_{C-P} = 3.70, C-4'), 69.40 (d, J_{C-P} = 3.70, C-4'), 73.69 (C-1'), 117.55, 121.39, 121.43, 121.48, 121.51, 126.10, 126.23, 129.33, 129.36, 129.57, 129.60, 130.29, 130.59, 130.73 (C-5, PhO, OCH_2*Ph*), 137.29, 137.59 (2s, 'ipso' OCH_2*Ph*), 139.75 (C-8), 152.13, 152.17 (2s, C-4), 155.68 (C-2), 159.46 (C-6), 174.76 (d, J_{C-P} = 5.00, $COOCH_2$Ph), 174.91 (d, J_{C-P} = 4.60, $COOCH_2$Ph). EI MS= 565.1571 (M+Na). Anal. Calcd for $C_{24}H_{27}N_6O_7P{\cdot}H_2O$: C, 51.43; H, 5.22; N, 14.99. Found: C, 51.90; H, 5.03; N, 14.67.

Synthesis of acyclovir-[1-naphthyl(benzoxy-dimethylglycinyl)] phosphate [13].

A solution of **77** (0.17 g, 0.26 mmol) in 2-propanol (10 mL) was stirred under reflux for 96 h. The solvent was then removed under reduced pressure and the residue was purified by column chromatography eluting with DCM/MeOH = 96/4. The product was purified by preparative TLC (gradient elution of DCM/MeOH = 98/2 then 96/4) to give a white solid (23%, 0.037 g). ^{31}P-NMR (MeOD, 202 MHz): δ 2.52. ^{1}H-NMR (MeOD, 500 MHz): δ 8.20-8.13 (1H, m, H-8 Naph), 7.87 (1H, dd, *J* = 6.20, 3.20 Hz, H-6 Naph), 7.76 (1H, s, H-8), 7.68 (1H, d, *J* = 8.20 Hz, H-2 Naph), 7.55-7.49 (2H, m, Naph, OCH_2*Ph*), 7.46-7.25 (7H, m, Naph, OCH_2*Ph*), 5.38 (2H, s, H-1'), 5.16-5.08 (2H, m, OCH_2Ph), 4.20-4.17 (2H, m, H-5'), 3.71-3.69 (2H, m, H-4'), 1.52, 1.50 (6H, 2s, $NHC(CH_3)_2$). ^{13}C-NMR (MeOD, 125 MHz): δ 27.45 (d, J_{C-P} = 4.60, CH_3), 27.72 (d, J_{C-P} = 6.80, CH_3), 58.10 ($C(CH_3)_2$), 67.21 (d, J_{C-P} = 5.70, C-5'), 68.25 (OCH_2Ph), 69.48 (d, J_{C-P} =

7.50, C-4'), 73.61 (C-1'), 116.34, 117.55, 122.97, 125.76, 126.50, 127.30, 127.68, 127.93, 128.78, 129.26, 129.31, 129.54 (C-5, C-2 Naph, C-3 Naph, C-4 Naph, C-5 Naph, C-6 Naph, C-7 Naph, C-8 Naph, C-8a Naph, OCH_2*Ph*), 136.26, 137.32 (C-4a Naph, 'ipso' OCH_2*Ph*), 139.69 (C-8), 148.09, 148.15 ('ipso' Naph, C-4), 155.62 (C-2), 159.36 (C-6), 176.59 (d, J_{C-P} = 3.60, *C*$OOCH_2$Ph). EI MS= 607.2048 (M+Na). Anal. Calcd for $C_{29}H_{31}N_6O_7P \cdot H_2O$: C, 55.77; H, 5.33; N, 13.46. Found: C, 55.83; H, 5.15; N, 12.92.

Synthesis of acyclovir [1-phenyl-(benzoxy-dimethylglicinyl)] phosphate [14].
A solution of **78** (1.02 g, 1.65 mmol) in 2-propanol (50 mL) was stirred under reflux for 2 days. The solvent was then removed under reduced pressure and the residue was purified by column chromatography, gradient elution of DCM/MeOH (98/2, then 96/4, then 94/6). The residue was then triturated with ether, filtered and washed with water to give a white solid (14%, 0.13 g). ^{31}P NMR (MeOD, 202 MHz): δ 2.13. ^{1}H NMR (MeOD, 500 MHz): δ 7.81 (1H, s, H-8), 7.39-7.29 (7H, m, PhO, OCH_2*Ph*), 7.25-7.14 (3H, m, PhO, OCH_2*Ph*), 5.43 (2H, s, H-1'), 5.17-5.09 (2H, m, O*C*H_2Ph), 4.15-4.12 (2H, m, H-5'), 3.74-3.69 (4H, m, H-4'), 1.49 (6H, s, C(CH_3)$_2$). ^{13}C NMR (MeOD, 126 MHz): δ 27.37 (d, J_{C-P} = 4.80, C(*C*H_3)$_2$), 27.57 (d, J_{C-P} = 6.60, C(*C*H_3)$_2$), 57.99 (*C*(CH$_3$)$_2$), 67.01 (d, J_{C-P} = 5.70, C-5'), 68.22 (O*C*H_2Ph), 69.46 (d, J_{C-P} = 7.50, C-4'), 73.61 (C-1'), 117.52, 121.34, 121.38, 121.47, 121.51, 125.96, 129.06, 129.14, 129.29, 129.34, 129.52, 129.56, 130.06, 130.66 (C-5, PhO, OCH_2*Ph*), 137.36 ('ipso' OCH_2*Ph*), 139.74 (C-8), 152.31 (d, J_{C-P} = 7.30, C-4), 155.68 (C-2), 176.54 (d, J_{C-P} = 3.80, *C*$OOCH_2$Ph). EI MS= 557.1891 (M+H). HPLC = H_2O/AcCN from 100/0 to 0/100 in 30 min = retention time 16.37 min; H_2O/MeOH 100/0 to 20/80 in 5 min, 20/80 isocratic 10 min, then to 0/100 in 10 min = retention time 18.19 min.

Synthesis of acyclovir-[1-phenyl-(benzoxy-L-phenylalaninyl)] phosphate [15].
A solution of **79** (0.49 g, 0.73 mmol) in 2-propanol (20 mL) was stirred under reflux for 64 h. The solvent was then removed under reduced pressure and the residue was purified by column chromatography eluting with DCM/MeOH = 95/5. The product was purified by preparative TLC (gradient elution of

DCM/MeOH = 98/2 then 96/4) to give a white solid (14%, 0.054 g). ^{31}P-NMR (MeOD, 202 MHz): δ 3.41, 3.31.

^{1}H-NMR (MeOD, 500 MHz): δ 7.65-7.64 (1H, 2s, H-8), 7.19-6.87 (15H, m, PhO, $COOCH_2$*Ph*, $CHCH_2$*Ph*), 5.25, 5.24 (2H, 2s, H-1'), 4.98-4.95 (2H, m, $COOCH_2$Ph), 4.06-3.97 (1H, m, $CHCH_3$), 3.89-3.84 (0.5H, m, H-5' of one diastereoisomer), 3.80-3.64 (1.5H, m, H-5'), 3.48 (2H, bs, H-4'), 2.97-2.90 (1H, m, $CHCH_2$Ph of one diastereoisomer), 2.78-2.73 (1H, m, $CHCH_2$Ph of one diastereoisomer). ^{13}C-NMR (MeOD, 125 MHz): δ 40.91 (d, J_{C-P} = 7.20, $CHCH_2$Ph), 40.96 (d, J_{C-P} = 6.80, $CHCH_2$Ph), 57.77, 57.91 (2s, $CHCH_2$Ph), 66.87 (C-5'), 68.02, 68.03 (2s, $COOCH_2$Ph), 69.25, 69.32 (2s, C-4'), 73.64 (C-1'), 117.55, 121.30, 121.34, 121.37, 121.41, 126.00, 127.93, 129.37, 129.52, 129.54, 129.57, 130.62, 130.65, 130.68 (C-5, PhO, OCH_2*Ph*, $CHCH_2$*Ph*), 137.03, 138.02, 138.08 ('ipso' $CHCH_2$*Ph*, 'ipso' OCH_2*Ph*), 139.73 (C-8), 152.08 (C-4), 155.65 (C-2), 159.41 (C-6), 173.85 ($COOCH_2$Ph). EI MS= 641.1886 (M+Na). HPLC = H_2O/AcCN from 100/0 to 0/100 in 20 min = retention time 14.56 min; H_2O/MeOH 40/60 isocratic = retention time 22.52, 24.61 min.

Synthesis of acyclovir-[1-phenyl-(benzoxy-L-valinyl)] phosphate [16].

A solution of **80** (0.51 g, 0.81 mmol) in 2-propanol (20 mL) was stirred under reflux for 2 days. The solvent was then removed under reduced pressure and the residue was purified by column chromatography, gradient elution of DCM/MeOH (98/2 then 96/4 then 94/6) to give a white solid which was further purified by preparative reverse phase HPLC (gradient elution of H_20/CH_3CN from 100/0 to 0/100 in 30 min) to give a white solid (8%, 0.037 g). ^{31}P NMR (MeOD, 202 MHz): δ 4.51, 4.27. ^{1}H NMR (MeOD, 500 MHz): δ 7.82-7.80 (1H, 2s, H-8), 7.37-7.30 (7H, m, PhO, OCH_2*Ph*), 7.19-7.14 (3H, m, PhO, OCH_2*Ph*), 5.45-5.43 (2H, 2s, H-1'), 5.14-5.13 (2H, m, OCH_2Ph), 4.16-4.14 (2H, m, H-5'), 3.74-3.66 (3H, m, H-4', NHC*H*), 2.05-2.01 (1H, m, NHCHC*H*), 0.91-0.85 (6H, m, $CH(CH_3)_2$). ^{13}C NMR (MeOD, 126 MHz): δ 18.15, 18.31 (2s, $CH(CH_3)_2$), 33.07 (d, J_{C-P} = 7.20, $CH(CH_3)_2$) 33.25 (d, J_{C-P} = 6.90, $CH(CH_3)_2$), 61.93, 61.97 (2s, NHCH), 67.05 (d, J_{C-P} = 5.60, C-5'), 67.13 (d, J_{C-P} = 5.80, C-5'), 67.82 (OCH_2Ph), 69.36 (d, J_{C-P} = 4.70, C-4'), 69.42 (d, J_{C-P} = 4.80, C-4'), 73.63 (s, C-1'), 117.56, 121.34, 121.38, 121.48, 121.51, 126.00, 126.07, 129.39, 129.41, 129.56, 129.57, 129.62,

130.69 (C-5, PhO, OCH_2*Ph*), 137.23 ('ipso' OCH_2*Ph*), 139.71 (C-8), 152.22 (d, J_{C-P} = 4.80, C-4), 152.28 (d, J_{C-P} = 4.70, C-4), 155.68 (C-2), 159.41 (C-6), 173.95 (d, J_{C-P} = 3.50, *C*$OOCH_2$Ph), 174.08 (d, J_{C-P} = 3.10, *C*$OOCH_2$Ph). EI MS= 593.1895 (M+Na). HPLC = H_2O/AcCN from 100/0 to 0/100 in 30 min = retention time 17.29 min; H_2O/MeOH 100/0 to 20/80 in 5 min, 20/80 isocratic 10 min, then to 0/100 in 10 min = retention time 20.09, 20.47 min.

Synthesis of acyclovir-[1-naphthyl-(methoxy-L-valinyl)] phosphate [17].

A suspension of **81** (0.45 g, 0.75 mmol) in 2-propanol (25 mL) was stirred under reflux for 72 h. The solvent was then removed under reduced pressure and the residue was purified by column chromatography, gradient elution of DCM/MeOH (98/2, then 96/4, then 95/5). The product was further purified by preparative TLC, gradient elution of DCM/MeOH (98/2, then 96/4, then 95/5) to give a white solid (6%, 0.030 g). ^{31}P-NMR (MeOD, 202MHz): δ 4.89, 4.84. ^{1}H-NMR (MeOD, 500MHz): δ 8.17-8.11 (1H, m, H-8 Naph), 7.91-7.87 (1H, m, H-6 Naph), 7.82 (1H, bs, H-8), 7.71-7.70 (1H, m, H-2 Naph), 7.58-7.52 (2H, m, Naph), 7.49-7.39 (2H, m, Naph), 5.50 (1H, s, H-1'), 4.29-4.26 (2H, m, H-5'), 3.81-3.79 (2H, m, H-4'), 3.74-3.71 (1H, m, NHC*H*), 3.59, 3.58 (3H, 2s, $COOCH_3$), 2.03-1.98 (1H, m, C*H*$(CH_3)_2$), 0.92-0.85 (6H, m, CH(C*H*$_3)_2$). ^{13}C-NMR (MeOD, 125MHz): δ 18.22, 18.31, 19.46, 19.48 (4s, CH(*C*$H_3)_2$), 33.21, 33.27 (2s, *C*H$(CH_3)_2$), 52.37, 52.42 (2s, COO*C*H_3), 61.92 (s, NH*C*H), 67.27 (d, J_{C-P} = 5.50, C-5'), 67.38 (d, J_{C-P} = 5.70, C-5'), 69.39 (d, J_{C-P} = 7.30, C-4'), 69.56 (d, J_{C-P} = 7.30, C-4'), 73.71 (C-1'), 116.18, 116.21, 122.73, 122.80, 125.87, 126.34, 126.51, 126.52, 127.07, 127.41, 127.74, 127.90, 128.82 (C-5, C-2 Naph, C-3 Naph, C-4 Naph, C-5 Naph, C-6 Naph, C-7 Naph, C-8 Naph, C-8a Naph), 136.28 (C4a Naph), 139.71 (C-8), 148.01, 148.07 ('ipso' Naph, C-4), 155.67 (C-2), 159.31 (C-6), 174.63, 174.65 (2s, *C*OOMe). EI MS= 545.1906 (M+H). HPLC = H_2O/AcCN from 100/0 to 0/100 in 20 min = retention time 19.31 min.

Synthesis of acyclovir-[1-naphthyl-(ethoxy-L-valinyl)] phosphate [18].

A solution of **82** (0.96 g, 1.56 mmol) in 2-propanol (45 mL) was stirred under reflux for 72 h. The solvent was then removed under reduced pressure and the residue was purified by column chromatography, gradient elution of DCM/MeOH (98/2, then 96/4, then 95/5). The product was further purified by preparative TLC,

gradient elution of DCM/MeOH (98/2, then 96/4, then 94/6) to give a white solid (10%, 0.084 g). ^{31}P-NMR (MeOD, 202MHz): δ 4.97, 4.87. ^{1}H-NMR (MeOD, 500MHz): δ 8.19-8.10 (1H, m, Naph), 7.81, 7.80 (1H, 2s, H-8), 7.89-7.87 (1H, m, Naph) 7.71-7.69 (1H, m, Naph), 7.58-7.51 (2H, m, Naph), 7.48-7.38 (2H, m, Naph), 5.50 (1H, s, H-1'), 4.31-4.26 (2H, m, H-5'), 4.09-3.97 (2H, m, C*H*$_2$CH$_3$), 3.82-3.79 (2H, m, H-4'), 3.73-3.71 (1H, m, NHC*H*), 2.04-1.98 (1H, m, C*H*(CH$_3$)$_2$), 1.20-1.15 (3H, m, CH$_2$C*H*$_3$), 0.93-0.87 (6H, m, CH(C*H*$_3$)$_2$). ^{13}C-NMR (MeOD, 125MHz): δ 14.45, 14.48 (2s, CH$_2$*C*H$_3$), 18.23, 18.30, 19.45, 19.48 (4s, CH(*C*H$_3$)$_2$), 33.07 (d, J_{C-P} = 7.30 *C*H(CH$_3$)$_2$), 33.27 (d, J_{C-P} = 7.10 *C*H(CH$_3$)$_2$), 61.96, 61.98 (2s, *C*H$_2$CH$_3$), 62.12, 62.16 (2s, NH*C*H), 67.27 (d, J_{C-P} = 5.6, C-5'), 67.40 (d, J_{C-P} = 5.70, C-5'), 69.39 (d, J_{C-P} = 7.20, C-4'), 69.51 (d, J_{C-P} = 7.60, C-4'), 73.66, 73.70 (2s, C-1'), 116.17, 116.19, 116.23, 116.25, 117.53, 117.59, 122.75, 122.83, 125.87, 126.50, 127.39, 127.74, 127.90, 127.93, 127.95, 128.81, 128.82 (C-5, C-2 Naph, C-3 Naph, C-4 Naph, C-5 Naph, C-6 Naph, C-7 Naph, C-8 Naph, C-8a Naph), 136.27 (C4a Naph), 139.70 (C-8), 148.04 (d, J_{C-P} = 2.10, C-4), 148.10 (d, J_{C-P} = 2.10, C-4), 155.64, 155.67 (2s, C-2), 159.36 (C-6), 174.17 (d, J_{C-P} = 3.10, *C*OOEt), 174.17 (d, J_{C-P} = 2.90, *C*OOEt). EI MS= 559.2056 (M+H). HPLC = H$_2$O/AcCN from 100/0 to 0/100 in 20 min = retention time 16.77 min.

Synthesis of acyclovir-[1-naphthyl-(methoxy-D-valinyl)] phosphate [19].

A solution of **83** (0.33 g, 0.55 mmol) in 2-propanol (20 mL) was stirred under reflux for 72 h. The solvent was then removed under reduced pressure and the residue was purified by column chromatography, gradient elution of DCM/MeOH = 98/2, then 96/4, then 95/5. The product was further purified by preparative TLC, gradient elution of DCM/MeOH = 98/2, then 96/4, then 94/6 to give a white solid (14%, 0.040 g). ^{31}P-NMR (MeOD, 202MHz): δ 4.90, 4.85. ^{1}H-NMR (MeOD, 500MHz): δ 8.19-8.07 (1H, m, Naph), 7.90-7.85 (1H, m, Naph), 7.83 (1H, bs, H-8), 7.70-7.68 (1H, m, Naph), 7.57-7.50 (2H, m, Naph), 7.48-7.37 (2H, m, Naph), 5.50 (1H, s, H-1'), 4.29-4.26 (2H, m, H-5'), 3.81-3.79 (2H, m, H-4'), 3.74-3.71 (1H, m, NHC*H*), 3.58, 3.57 (3H, 2s, COOCH$_3$), 2.03-1.97 (1H, m, C*H*(CH$_3$)$_2$), 0.91-0.85 (6H, m, CH(C*H*$_3$)$_2$). ^{13}C-NMR (MeOD, 125MHz): δ 18.23, 18.32, 19.47, 19.49 (4s, CH(*C*H$_3$)$_2$), 33.21, 33.27 (2s, *C*H(CH$_3$)$_2$), 52.39, 52.44 (2s, COOCH$_3$), 61.92 (NH*C*H), 67.29 (d, J_{C-P} = 5.50, C-5'), 67.41 (d, J_{C-P} = 5.60, C-5'), 69.43 (d, J_{C-P} = 7.30, C-4'), 69.54 (d, J_{C-P} = 7.20, C-4'), 73.75 (C-1'), 116.18,

116.21, 122.72, 122.79, 125.88, 126.51, 126.52, 127.41, 127.74, 127.89, 127.94, 128.80, 128.83, (C-5, C-2 Naph, C-3 Naph, C-4 Naph, C-5 Naph, C-6 Naph, C-7 Naph, C-8 Naph, C-8a Naph), 136.26 (C4a Naph), 139.73 (C-8), 148.00, 148.06 ('ipso' Naph, C-4), 155.67 (C-2), 159.32 (C-6), 174.64, 174.66 (2s, *C*OOMe). EI MS= 545.1902 (M+H). HPLC = H_2O/AcCN from 100/0 to 0/100 in 20 min = retention time 15.85 min.

Synthesis of acyclovir-[1-phenyl-(benzoxy-L-leucinyl)] phosphate [20].

A solution of **84** (0.59 g, 0.93 mmol) in 2-propanol (20 mL) was stirred under reflux for 2 days. The solvent was then removed under reduced pressure and the residue was purified by column chromatography gradient elution of DCM/MeOH = 98/2 then 96/4 then 94/6. The product was purified by preparative reverse phase HPLC (gradient elution of H_20/CH_3CN from 100/0 to 0/100 in 30 min) to give a white solid (8%, 0.042 g). ^{31}P NMR (MeOD, 202 MHz): δ 4.05, 3.60. ^{1}H NMR (MeOD, 500 MHz): δ 7.82, 7.79 (1H, 2s, H-8), 7.38-7.37 (7H, m, PhO, OCH_2*Ph*), 7.19-7.15 (3H, m, PhO, OCH_2*Ph*), 5.45, 5.42 (2H, 2s, H-1'), 5.12, 5.13 (2H, 2s, OCH_2Ph), 4.16-4.07 (2H, m, H-5'), 3.95-3.88 (1H, m, NHC*H*) 3.74-3.71 (2H, m, H-4'), 1.73-1.66 (0.5H, m, $CH_2CH(CH_3)_2$ of one diastereoisomer), 1.62-1.46 (2.5H, m, $CH_2CH(CH_3)_2$ of one diastereoisomer, $CH_2CH(CH_3)_2$), 0.91-0.80 (6H, m, $CH_2CH(CH_3)_2$). ^{13}C NMR (MeOD, 126 MHz): δ 21.75, 22.01, 23.12, 23.20 (4s, $CH_2CH(CH_3)_2$), (2s, CH_3), 25.40, 25.55 (2s, $CH(CH_3)_2$), 43.84 (d, J_{C-P} = 7.80, $CH_2CH(CH_3)_2$), 44.05 (d, J_{C-P} = 7.40, $CH_2CH(CH_3)_2$), 54.48, 54.70 (2s, NHCH), 67.03 (d, J_{C-P} = 1.80, C-5'), 67.07 (d, J_{C-P} = 1.80, C-5'), 67.87, 67.89 (2s, OCH_2Ph), 69.35 (d, J_{C-P} = 2.20, C-4'), 69.41 (d, J_{C-P} = 2.40, C-4'), 73.64 (s, C-1'), 117.54, 121.26, 121.30, 121.51, 121.54, 125.99, 126.09, 129.36, 129.38, 129.47, 129.57, 129.59, 130.69, 130.71 (C-5, PhO, OCH_2*Ph*), 137.27 ('ipso' OCH_2*Ph*), 139.70, 139.74 (2s, C-8), 152.22 (d, J_{C-P} = 2.10, C-4), 152.27 (d, J_{C-P} = 2.10, C-4), 155.66 (C-2), 159.37, 159.38 (2s, C-6), 174.85 (d, J_{C-P} = 2.80, $COOCH_2$Ph), 175.09 (d, J_{C-P} = 2.60, $COOCH_2$Ph). EI MS= 607.2051 (M+Na). Anal. Calcd for $C_{27}H_{33}N_6O_7P \cdot H_2O$: C, 53.82; H, 5.85; N, 13.95. Found: C, 54.16; H, 5.62; N, 13.67.

Synthesis of acyclovir-[1-phenyl-(benzoxy-L-isoleucinyl)] phosphate [21].

A solution of **85** (0.50 g, 0.78 mmol) in 2-propanol (20 mL) was stirred under reflux for 3 days. The solvent was then removed under reduced pressure and the residue was purified by column chromatography, gradient elution of DCM/MeOH = 98/2, then 96/4, then 94/6. The product was purified by preparative reverse phase HPLC (gradient elution of H_20/CH_3CN from 100/0 to 0/100 in 30 min) to give a white solid (3%, 0.015 g). ^{31}P NMR (MeOD, 202 MHz): δ 4.42, 4.13. ^{1}H NMR (MeOD, 500 MHz): δ 7.82-7.80 (1H, 2s, H-8), 7.39-7.30 (7H, m, PhO, OCH_2*Ph*), 7.19-7.14 (3H, m, PhO, OCH_2*Ph*), 5.45-5.44 (2H, 2s, H-1'), 5.16-5.09 (2H, m, OCH_2Ph), 4.17-4.12 (2H, m, H-5'), 3.79-3.77 (1H, m, NHC*H*), 3.75-3.73 (2H, m, H-4'), 1.78-1.72 (1H, m, NHCHC*H*), 1.49-1.39 (1H, m, $CHCH_2CH_3$), 1.19-1.08 (1H, m, $CHCH_2CH_3$), 0.88-0.80 (6H, m, $CH(CH_3)CH_2CH_3$). ^{13}C NMR (MeOD, 126 MHz): δ 11.52, 11.55, 15.84, 15.88 (4s, $CH(CH_3)CH_2CH_3$), 25.80, 25.90 (2s, $CH(CH_3)CH_2CH_3$), 39.86 (d, J_{C-P} = 6.90, $CH(CH_3)CH_2CH_3$), 40.01 (d, J_{C-P} = 6.70, $CH(CH_3)CH_2(CH_3)$, 60.72, 60.86 (2s, NH*C*H), 67.05 (d, J_{C-P} = 4.00, C-5'), 67.10 (d, J_{C-P} = 5.00, C-5'), 67.81 (OCH_2Ph), 69.36 (d, J_{C-P} = 5.20, C-4'), 69.42 (d, J_{C-P} = 5.50, C-4'), 73.63, 73.65 (2s, C-1'), 117.54, 121.32, 121.36, 121.50, 121.54, 126.00, 126.08, 129.40, 129.41, 129.55, 129.57, 129.65, 129.66, 130.68, 130.69 (C-5, PhO, OCH_2*Ph*), 137.21 ('ipso' OCH_2*Ph*), 139.72 (C-8), 152.22 (d, J_{C-P} = 1.60, C-4), 152.27 (d, J_{C-P} = 1.60, C-4), 155.67 (C-2), 159.38 (C-6), 173.91 (d, J_{C-P} = 3.00, $COOCH_2$Ph), 174.07 (d, J_{C-P} = 3.00, $COOCH_2$Ph). EI MS= 607.2044 (M+Na). HPLC = H_2O/AcCN from 100/0 to 0/100 in 20 min = retention time 15.00 min.

Synthesis of acyclovir-[1-phenyl-(benzoxy-L-prolinyl)] phosphate [22].

A solution of **86** (0.35 g, 0.56 mmol) in 2-propanol (20 mL) was stirred under reflux for 2 days. The solvent was then removed under reduced pressure and the residue was purified by column chromatography gradient elution of DCM/MeOH (98/2, then 96/4, then 94/6). The product was purified by preparative reverse phase HPLC (gradient eluition of H_20/MeOH from 100/0 to 20/80 in 5 min, isocratic 20/80 for 10 min, from 20/80 to 0/100 in 10 min, isocratic 0/100 for 5 min) to give a white solid as a pure diastereoisomer (4%, 0.020 g). ^{31}P NMR (MeOD, 202 MHz): δ 1.68. ^{1}H NMR (MeOD, 500 MHz): δ 7.84 (1H, m H-8), 7.38-7.27 (7H, m, PhO, OCH_2*Ph*), 7.22-7.12 (3H, m, PhO, OCH_2*Ph*), 5.49-5.44

(2H, m, H-1'), 5.17-5.11 (2H, m, OC*H*$_2$Ph), 4.32-4.21 (2H, m, NCH, H-5'), 4.18-4.10 (1H, m, H-5'), 3.80-3.71 (2H, m, H-4'), 3.31-3.22 (2H, m, CHNC*H*$_2$), 2.15-2.11 (1H, m, CH_2NCHC*H*$_2$$CH_2$), 1.99-197 (1H, m, CH_2NCHC*H*$_2$$CH_2$), 1.91-1.76 (2H, m, CH_2NCHCH_2*CH*$_2$). ^{13}C NMR (MeOD, 126 MHz): δ 26.18 (d, J_{C-P} = 8.90, $NCHCH_2$*C*H_2), 32.20 (d, J_{C-P} = 9.10, NCH*C*H_2), 48.12 (d, J_{C-P} = 4.60, CHN*C*H_2), 62.17 (d, J_{C-P} = 7.00, N*C*H), 67.08 (d, J_{C-P} = 5.00, C-5'), 68.03 (O*C*H_2Ph), 69.46 (d, J_{C-P} = 7.40, C-4'), 73.66 (C-1'), 117.60, 121.18, 121.22, 126.16, 129.36, 129.40, 129.59, 130.85 (C-5, PhO, OCH_2*Ph*), 137.25 ('ipso' OCH_2*Ph*), 139.75 (C-8), 152.05 (d, J_{C-P} = 6.70, C-4), 155.74 (C-2), 159.50 (C-6), 174.84 (*C*$OOCH_2$Ph). EI MS= 569.1917 (M+H). HPLC = H_2O/AcCN from 100/0 to 0/100 in 30 min = retention time 16.57 min; H_2O/MeOH 100/0 to 20/80 in 5 min, 20/80 isocratic 10 min, then to 0/100 in 10 min = retention time 19.07 min.

Synthesis of acyclovir-[1-phenyl-(benzoxy-glicinyl)] phosphate [23].

A solution of **87** (1.69 g, 2.89 mmol) in 2-propanol (60 mL) was stirred under reflux for 2 days. The solvent was then removed under reduced pressure and the residue was purified by column chromatography gradient elution of DCM/MeOH = 98/2, then 96/4, then 94/6. The product was purified by preparative reverse phase HPLC (gradient elution of H_20/MetOH from 100/0 to 20/80 in 5 min, isocratic 20/80 for 10 min, from 20/80 to 0/100 in 10 min, isocratic 0/100 for 5 min) to give a white solid (2%, 0.031 g). ^{31}P NMR (MeOD, 202 MHz): δ 4.77. ^{1}H NMR (MeOD, 500 MHz): δ 7.81 (1H, s, H-8), 7.37-7.31 (7H, m, PhO, OCH_2*Ph*), 7.18-7.16 (3H, m, PhO, OCH_2*Ph*), 5.44 (2H, s, H-1'), 5.17 (2H, s, OC*H*$_2$Ph), 4.26-4.16 (2H, m, H-5'), 3.80 (1H, s, NHC*H*$_2$), 3.77-3.76 (3H, m, H-4', NHC*H*$_2$). ^{13}C NMR (MeOD, 126 MHz): δ 43.91 ($NHCH_2$), 67.11 (d, J_{C-P} = 5.40, C-5'), 67.95 (O*C*H_2Ph), 69.37 (d, J_{C-P} = 7.40, C-4'), 73.66 (C-1'), 117.57, 121.43, 121.47, 126.10, 129.37, 129.43, 129.58, 130.73 (C-5, PhO, OCH_2*Ph*), 137.23 ('ipso' OCH_2*Ph*), 139.74 (C-8), 152.31 (d, J_{C-P} = 6.00, C-4), 155.67 (C-2), 159.39 (C-6), 172.31 (d, J_{C-P} = 4.90, *C*$OOCH_2$Ph). EI MS= 529.1617 (M+H). Anal. Calcd for $C_{23}H_{25}N_6O_7P{\cdot}H_2O$: C, 50.55; H, 4.98; N, 15.38. Found: C, 50.97; H, 4.73; N, 15.31.

Enzymatic Procedure: compounds **6**, **9**, **10**, **17** and **19** (5 mg) were dissolved in d_6-acetone (0.15 mL) and Trizma buffer (0.30 mL) and a ^{31}P-NMR was recorded (**Fig. 3-7**, starting material). Then a solution of carboxypeptidase Y (0.1 mg) in Trizma buffer (0.15 mL) was added and a ^{31}P-NMR esperiment was performed recording the experiment every 15 min. For compounds **10** and **17** additional enzyme (0.1 mg) was added after 46 h and 24 h respectively.

Stability Studies:

Human Serum: compound **9** (5 mg) was dissolved in DMSO (50 μL) and D_2O (150 μL) and human serum (300 μL) was added and a ^{31}P-NMR esperiment was performed at 37 ^{o}C recording the experiment every 20 min;

pH = 1 buffer: compound **9** (5 mg) was dissolved in MeOD (0.1 mL) and pH = 1 buffer (prepared from equals part of 0.2M HCl and 0.2M KCl) (0.5 mL) was added and a ^{31}P-NMR esperiment was performed at 37 ^{o}C recording the experiment every 23 min.

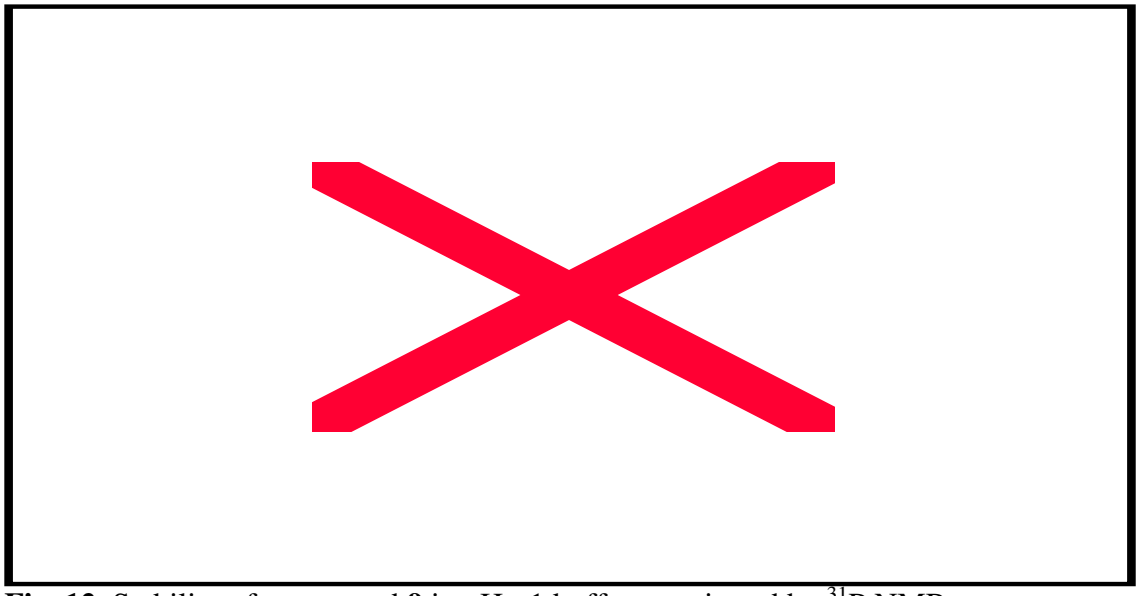

Fig. **12**. Stability of compound **9** in pH =1 buffer, monitored by ^{31}P NMR.

Molecular Modelling: All molecular modelling studies were performed on a MacPro dual 2.66GHz Xeon running Ubuntu 8 using Molecular Operating Environment (MOE) 2008.10 and FlexX (Biosolveit FlexX 3; BiosolveIT GmbH An der Ziegelei 75, 53757 Sankt Augustin, Germany; http://www.biosolveit.de/flexx).

Hydrogen atoms were added to the crystal structure (PDB code: 1KPF) and minimised with MOE until a gradient of 0.05 Kcal mol-1 Å-1 was reached, using the MMFF94x forcefield. The partial charges were automatically calculated. Docking experiments were carried out using the MOE GUI of FlexX implemented in MOE. Acyclovir analogues were built in MOE and minimised before the docking.