Aryl phosphoramidates of 5-phospho erythronohydroxamic acid, a new class of potent trypanocidal compounds

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Experimental procedures and spectral data for all intermediates and the final compounds not described in the main text.

(10) *N*-2,4-dimethoxybenzyloxy-2,3-*O*-isopropylidene erythrono carboxamide[1]

$AlMe_3$ solution 2 M in hexanes (6 ml, 12 mmol) was added dropwise with a syringe into a cooled solution (-78 °C) of 2,3-isopropylidene erythrono lactone (1.58 g, 10 mmol); 2,4-dimethoxybenzyl hydroxylamine **8** (2.2 g, 12 mmol) in DCM (100 ml). The solution was warmed to room temperature and stirred 12 hours, followed by the addition of more erythrono lactone (100 mg) and further stirring for 2 hours. The mixture was poured into a vigorously stirred solution of $NaHCO_3$ sat. The white precipitate of the biphasic suspension was filtered off and washed with MeOH. The aqueous phase was further extracted with DCM (2×20 ml). The collected organic fractions were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by crystallization from a mixture of Hexane/EtOAc (4:1). White crystals, 1.69 g, (50%). ^{1}HNMR (500 MHz, $CDCl_3$) δ: 1.37 (s, 3H, $C(C\underline{H}_3)_2$); 1.44 (s, 3H, $C(C\underline{H}_3)_2$); 3.32 (dd, 1H, J_1=4.6 Hz, J_2=10.1 Hz, CH*H*OH); 3.67-3.72 (m, 1H, CHC*H*HOH); 3.81-3.84 (m, 1H, $CH_2O\underline{H}$); 3.85 (s, 3H, $OC\underline{H}_3$); 3.86 (s, 3H, $OC\underline{H}_3$); 4.56 (dt, 1H, J_1=4.7 Hz, J_2=7.6 Hz, C*H*CH_2OH); 4.69 (d, 1H, *J*=7.6 Hz, COC*H*CH); 4.97 (AB system, 2H, *J*=11.2 Hz, Ar-$C\underline{H}_2$O); 6.50-6.52 (m, 2H, Ar*H*); 7.27-7.29 (m, 1H, Ar*H*); 8.93 (s, 1H, N*H*). ^{13}CNMR (125 MHz, $CDCl_3$) δ: 24.36 ($C(\underline{C}H_3)_2$); 26.65 ($C(\underline{C}H_3)_2$); 55.46 55.59 ($O\underline{C}H_3$), 61.39 ($\underline{C}H_2OH$); 73.59 (Ar-$\underline{C}H_2O$); 76.53 ($\underline{C}HCH_2OH$); 76.78 (CO$\underline{C}$HCH); 98.61 (Ar$\underline{C}$H); 104.19 (Ar$\underline{C}$H); 110.18 ($\underline{C}(CH_3)_2$); 115.49 (Ar$\underline{C}$-CH_2); 132.88 (Ar$\underline{C}$H); 159.49 (Ar$\underline{C}$-OCH_3); 161.95 (Ar$\underline{C}$-OCH_3); 167.12 (HN$\underline{C}$OCH). LCMS (ES+): m/z 151.08 ($[C_9H_{11}O_2]^+$, 100%), 341.17 ($[M+H]^+$, 80%); 525.27 (90%), Rt 2.8 min.

(12c) (4-methyl)phenyl phosphorodichloridate

The title compound was synthesised according to the general procedure A, from *p*-cresol (1 g, 9.25 mmol), phosphorous oxychloride (0.855 ml, 9.25 mmolo), TEA (1.30 ml, 9.25 mmol) and diethyl ether (30 ml). Yellowish oil, 1.98 g (95%). ^{1}HNMR (500 MHz, $CDCl_3$) δ: 2.26 (d, 3H, *J*=1.98 Hz, Ar-$C\underline{H}_3$); 7.03-7.12 (m, 4H, Ar*H*). ^{13}CNMR (125 MHz, $CDCl_3$) δ: 20.82, 20.87 (Ar-$\underline{C}H_3$); 120.16, 120.26, 120.31, 120.52 (Ar$\underline{C}$H); 130.52, 130.72, 130.74, 130.96 (Ar$\underline{C}$H); 137.12, 137.14 (Ar$\underline{C}$-CH_3); 147.58, 147.68 (Ar$\underline{C}$-OP). ^{31}PNMR (121 MHz, $CDCl_3$) δ: 3.91.

(12d) (4-methoxy)phenyl phosphorodichloridate

The title compound was synthesised according to the general procedure B from 4-(methoxy)phenol (1.15 g, 9.25 mmol), phosphorous oxychloride (0.855 ml, 9.25 mmol), TEA (1.3 ml, 9.25 mmol) and diethyl ether (30 ml). Yellowish liquid, 2.23 g (quant.). ^{1}HNMR (500 MHz, $CDCl_3$) δ: 3.82 (s, 3H, $OC\underline{H}_3$); 6.93 (dd, 2H, J_1=0.92 Hz, J_2=9.26 Hz, Ar*H*); 7.23 (dd, 2H, J_1=2.32 Hz, J_2=7.26 Hz, Ar*H*). ^{13}CNMR (125 MHz, $CDCl_3$) δ: 55.62, 55.70 ($O\underline{C}H_3$); 115.09, 115.10 (Ar$\underline{C}$H); 121.56, 121.60 (Ar$\underline{C}$H); 143.15, 143.24 (Ar$\underline{C}$-OCH_3); 158.21, 158.23 (Ar$\underline{C}$-OP). ^{31}PNMR (121 MHz, $CDCl_3$) δ: 4.57.

(12e) (2,3-dimethyl)phenyl phosphorodichloridate

The title compound was synthesised according to the general procedure A from phosphorous oxychloride (170 μl, 1.85 mmol), 2,3-dimethylphenol (226 mg, 1.85 mmol), TEA (270 μl, 1.94 mmol) and Et_2O (5.5 ml). Yellowish oil, 380 mg (86%). ^{1}NMR (500 MHz, $CDCl_3$) δ: 2.16 (s, 3H, 1 of Ar-C*H*$_3$); 2.21 (s, 3H, Ar-C*H*$_3$); 6.95 (m, 2H, Ar*H*); 7.12-7.14 (m, 1H, Ar*H*). ^{31}PNMR (121 MHz, $CDCl_3$) δ: 3.32.

(13b) Phenyl (methoxyglycinyl)phosphorochloridate

The title compound was synthesised following the general procedure A using glycine methyl ester hydrochloride (163 mg, 1.3 mmol), phenyl phosphorodichloridate (232 μl, 1.56 mmol), TEA (380 μl, 2.73 mmol) and DCM (5 ml). Colourless oil, 426 mg (~quant.) ^{31}PNMR (121 MHz, $CDCl_3$) δ: 8.78.

(13d) Phenyl (ethoxy-L-alaninyl)phosphorochloridate

The title compound was synthesised according to the general procedure B using phenyl phosphorodichloridate (0.53 ml, 3.58 mmol), L-alanine ethyl ester hydrochloride (500 mg, 3.25 mmol), TEA (0.95 ml, 6.82 mmol) and DCM (10 ml). Yellowish/orange grease, 1.14 g, (~quant.) ^{1}HNMR (500 MHz, $CDCl_3$) δ: 1.27-1.32 (m, 3H, OCH_2C*H*$_3$); 1.49-1.52 (m, 3H, CHC*H*$_3$); 4.11-4.23 (m, 1H, C*H*CH_3); 4.20-4.27 (m, 2H, OC*H*$_2CH_3$); 4.49-4.57 (m, 1H, N*H*); 7.23-7.27 (m, 3H, Ar*H*); 7.35-7.39 (m, 2H, Ar*H*). ^{31}PNMR (121 MHz, $CDCl_3$) δ: 8.17, 7.79.

(13e) Phenyl (methoxy-L-valinyl)phosphorochloridate

The title compound was synthesised according to the general procedure B from L-valine methyl ester hydrochloride (500 mg, 2.98 mmol), phenyl phosphorochloridate (0.49 ml, 3.28 mmol), TEA (0.87 ml, 6.26 mmol) and DCM (12 ml). Colourless oil, 1.29 g, (~quant.). ^{1}HNMR (500 MHz, $CDCl_3$) δ: 0.87 (dd, 3H, J_1=6.7 Hz, J_2=6.9 Hz, 1 of CH(C*H*$_3$)$_2$); 0.95 (dd, 3H, J_1=6.8 Hz, J_2=12.8 Hz, 1 of CH(C*H*$_3$)$_2$); 2.05-2.13 (m, 1H, C*H*$(CH_3)_2$); 3.71 (d, 3H, 7.81 Hz, OC*H*$_3$); 3.83-3.85 (m, 1H, NHC*H*$CH(CH_3)_2$); 4.05-4.14 (m, 1H, N*H*); 7.15-7.32 (m, 5H, Ar*H*). ^{13}CNMR (125 MHz, $CDCl_3$) δ: 17.29, 17.36, 18.90, 19.01 (CH(*C*H$_3$)$_2$); 32.06, 32.12, 32.14, 32.19 (*C*H$(CH_3)_2$); 52.49, 52.53 (O*C*H$_3$); 59.79, 60.50 (NH*C*H); 120.49, 120.53, 120.54, 120.58, 120.62 (Ar*C*H); 126.02, 127.18 (Ar*C*H); 129.62, 129.94, 130.30, 130.32 (Ar*C*H); 149.73, 149.86 (Ar*C*-OP); 172.10, 172.13, 172.42 (*C*O_2Me). ^{31}PNMR (121 MHz, $CDCl_3$) δ: 9.42, 8.95.

(13f) Phenyl (ethoxy-L-vanilyl)phosphorochloridate

The title compound was synthesised according to the general procedure B phenyl phosphorodichloridate (491 μl, 3.30 mmol), L-valine ethyl ester hydrochloride (500 mg, 2.75 mmol), TEA (803 μl, 5.77 mmol) and DCM (10 ml). Colourless oil, 1.105 (quant.). ^{31}PNMR (121 MHz, $CDCl_3$) δ: 9.46, 8.96.

(13g) Phenyl (*tert*-butoxy-L-valinyl)phosphorochloridate

The title compound was synthesised according to the general procedure B from phenyl phosphorodichloridate (232 μl, 1.56 mmol), L-valine *tert*-butyl ester hydrochloride (273 mg, 1.3 mmol), TEA (380 μl, 2.73 mmol) and DCM (5 ml). Colourless oil, 633 mg (~quant.) ^{31}PNMR (121 MHz, $CDCl_3$) δ: 9.69, 9.27.

(13h) (4-methyl)phenyl (methoxy-L-alaninyl)phosphorochloridate

The title compounds was prepared according to the general procedure B from (4-methyl)phenyl phoshporodichloridate **12c** (900 mg, 4 mmol), Ala-OMe hydrochloride (280 mg, 2 mmol), TEA (700 μl, 5 mmol) and DCM (15 ml). Yellowish oil; 0.95 g (81%). ^{31}PNMR (121 MHz, $CDCl_3$) δ: 8.11, 7.72

(13i) (4-methyl)phenyl (ethoxy-L-alaninyl)phosphorochloridate

The title compound was synthesised following the general procedure B, using (4-methyl)phenyl phosphorodichloridate **12c** (1 g, 4.44 mmol), L-alanine ethyl ester hydrochloride (569 mg, 3.70 mmol), TEA (1.08 ml, 7.77 mmol) and DCM (15 ml). Colourless oil, 1.35 g (99%). ^{1}HNMR (500 MHz, $CDCl_3$) δ: 1.33 (dt, 3H, J_1=6.7 Hz, J_2=7.1 Hz, $CH_2C\underline{H}_3$); 1.52-1.55 (m, 3H, $CHC\underline{H}_3$); 2.36 (s, 3H, Ar-$C\underline{H}_3$); 4.13-4.23 (m, 1H, $C\underline{H}CH_3$); 4.27 (dq, J_1=7.1 Hz, J_2=8.9 Hz, $C\underline{H}_2CH_3$); 7.10-7.23 (m, 4H, Ar$\underline{H}$). ^{13}CNMR (125 MHz, $CDCl_3$) δ: 14.14 ($CH_2\underline{C}H_3$); 20.62, 20.66, 20.69, 20.83 ($CH\underline{C}H_3$ + Ar-$\underline{C}H_3$); 50.43, 50.75 ($\underline{C}HCH_3$); 61.99, 62.07 ($O\underline{C}H_2CH_3$); 120.23, 120.27, 120.32 (Ar$\underline{C}$H); 130.17, 130.40 (Ar$\underline{C}$H); 135.79 (Ar$\underline{C}$-CH_3); 147.53 (Ar$\underline{C}$-OP). ^{31}PNMR (121 MHz, $CDCl_3$) δ: 8.19, 7.80.

(13j) (4-methyl)phenyl (ethoxy-L-alaninyl)phosphorochloridate

The title compound was prepared according to the general procedure B starting from (4-methyl)phenyl phosphorodichloridate **12c** (805 mg, 3.58 mmol), L-valine methyl ester hydrochloride (500 mg, 2.98 mmol), TEA (0.87 ml, 2.26 mmol) and DCM (10 ml). Yellowish oil, 1.04 g (quant.) ^{1}HNMR (500 MHz, $CDCl_3$) δ: 0.87 (dd, 3H, J_1=6.9 Hz, J_2=7.7 Hz, $CH(C\underline{H}_3)_2$); 0.95 (dd, 3H, J_1=6.8 Hz, J_2=11.7 Hz, $CH(C\underline{H}_3)_2$); 2.04-2.12 (m, 1H, $C\underline{H}(CH_3)_2$); 2.26 (s, 3H, Ar-$C\underline{H}_3$); 3.70 (d, 3H, J=7.55 Hz, $OC\underline{H}_3$); 3.81-3.93 (m, 1H, $NHC\underline{H}(CH_3)_2$); 4.10-4.19 (m, 1H, N$\underline{H}$); 7.05-7.11 (m, 4H, Ar$\underline{H}$). ^{13}CNMR (125 MHz, $CDCl_3$) δ: 17.31, 17.37, 18.91, 19.02 ($CH(\underline{C}H_3)_2$); 20.82 (Ar-$\underline{C}H_3$); 32.05, 32.10, 32.13, 32.18 ($\underline{C}H(CH_3)_2$); 52.47, 52.51 ($OC\underline{H}_3$); 59.78, 60.48 ($NH\underline{C}H(CH_3)_2$); 120.18, 120.23, 120.24, 120.28 (Ar$\underline{C}$H); 130.03, 130.37 (Ar$\underline{C}$H); 135.73 (Ar$\underline{C}$-CH_3); 147.48, 147.55, 147.61, 147.68 (Ar$\underline{C}$-OP); 172.15, 172.18, 172.44, 172.47 ($\underline{C}O_2Me$). ^{31}PNMR (121 MHz, $CDCl_3$) δ: 9.64, 9.15.

(13l) (4-methyl)phenyl (ethoxy-L-valinyl)phosphorochloridate (AKA GFRII-48)

The title compound was synthesised according to the general procedure B, using toluyl phosphorodichloridate **12c** (770 mg, 3.42 mmol), L-valine ethyl ester hydrochloride (500 mg, 2.75 mmol), TEA (803 μl, 5.77 mmol) and DCM (10 ml). Colourless oil, 1.03 g (93%). ^{31}PNMR (121 MHz, $CDCl_3$) δ: 9.63, 9.16.

(13m) (4-methoxy)phenyl (methoxy-L-alaninyl)phosphorochloridate

The title compound was synthesised according to the general procedure B from (4-methyl)phenyl phosphorodichloridate **12c** (1.04 g, 4.29 mmol), L-alanine methyl ester hydrochloride (500 mg, 3.58 mmol), TEA (1.1 ml, 7.88 mmol) and DCM (15 ml). Yellow oil, 1.43 g (~quant.). ^{31}PNMR (121 MHz, $CDCl_3$) δ: 8.67, 8.33.

(13n) (4-methoxy)phenyl-(ethoxy-L-valinyl)phosphorochloridate

The title compounds was synthesised according to the general procedure B using (4-methoxy)phenyl phosphorodichloridate **12d** (361 mg, 1.50 mmol), L-valine ethyl ester hydrochloride (226 mg, 1.25 mmol), TEA (365 μl, 2.62 mmol) and DCM (5 ml). ^{31}PNMR (121 MHz, $CDCl_3$) δ: 9.57, 10.2

(13o) (2,3-dimethyl)phenyl (methoxy-L-alanyl)phosphorochloridate

The title compounds was synthesised according to the general procedure B using (2,3-dimethyl)phenyl phosphorodichloridate **12e** (361 mg, 1.51 mmol), L-alanine methyl ester hydrochloride (175 mg, 1.26 mmol), TEA (368 μl, 2.65 mmol) and DCM (5 ml). Yellowish oil, 362 mg (94%). ^{31}PNMR (121 MHz, $CDCl_3$) δ: 7.75, 7.41.

(13p) (2,3-dimethyl)phenyl (ethoxy-L-valinyl)phosphorochloridate

The title compounds was synthesised according to the general procedure B using (2,3-dimethyl)phenyl phosphorodichloridate **12e** (380 mg, 1.59 mmol), L-valine ethyl ester hydrochloride (240 mg, 1.32 mmol), TEA (386 μl, 2.77 mmol) and DCM (5 ml). Yellowish oil, 513 mg (quant.). ^{31}PNMR (121 MHz, $CDCl_3$) δ: 9.24, 8.79.

(13q) (2,3-dimethyl)phenyl (*tert*-butoxyl-L-valinyl)phosphorochloridate

The title compounds was synthesised according to the general procedure B using (2,3-dimethyl)phenyl phosphorodichloridate **12e** (320 mg, 1.34 mmol), L-valine *tert*-butyl ester hydrochloride (235 mg, 1.12 mmol), TEA (327 μl, 2.35 mmol) and DCM (5 ml). Yellowish oil, 423 mg (quant.) ^{1}NMR (500 MHz, $CDCl_3$) δ: 0.86-0.90 (m, 3H, CH(C$\underline{H}_3$)$_2$), 0.96 (t, J=6.9 Hz, 3H, CH(C$\underline{H}_3$)$_2$), 1.41, 1.43 (2s, 9H, C(C$\underline{H}_3$)$_3$), 2.08-2.09 (m, 1H, C$\underline{H}$(CH$_3$)$_2$), 2.14 (s, 3H, Ar-C$\underline{H}_3$), 2.22 (sm 3H, Ar-C$\underline{H}_3$), 2.89 (bs, 1H, N$\underline{H}$), 3.69-3.82 (m, 1H, NHC$\underline{H}$), 6.95-7.02 (m, 2H, Ar-$\underline{H}$), 7.17-7.22 (m, 1H, Ar-$\underline{H}$). ^{13}CNMR (125 MHz, $CDCl_3$) δ: 12.8 (Ar-$\underline{C}$H$_3$), 15.30 (Ar-$\underline{C}$H$_3$), 17.28, 17.49 (CH($\underline{C}$H$_3$)$_2$), 18.89, 18.92 (CH($\underline{C}$H$_3$)$_2$), 20.21 (Ar-$\underline{C}$H$_3$), 28.01 (C($\underline{C}$H$_3$)$_2$), 32.09, 32.15, 32.22, 32.28 ($\underline{C}$H(CH$_3$)$_2$), 60.13, 60.97 (NH$\underline{C}$H), 82.50, 85.62 ($\underline{C}$(CH$_3$)$_3$), 118.10, 118.13 (Ar-$\underline{C}$H), 126.26, 126.27, 126.29 (Ar-$\underline{C}$H), 127.30(Ar-$\underline{C}$H), 127.86, 127.92, 127.97, 128.02 (Ar-$\underline{C}$-CH$_3$), 139.06, 139.09 (Ar-$\underline{C}$-CH$_3$), 148.30, 148.36, 148.43, 148.50 (Ar-$\underline{C}$-O), 170.64, 170.68, 171.05, 171.08 ($\underline{C}$O$_2$^{t}Bu). ^{31}PNMR (121 MHz, $CDCl_3$) δ: 9.69, 9.16.

(14b) *N*-2,4-dimethoxybenzyloxy-2,3-*O*-isopropylidene erythrono carboxamide-4-[phenyl (methyloxyglycinyl)phosphoramidate]

The title compound was synthesised following the general procedure C using phenyl-(methoxy-glycinyl) phosphorochloridate **13a** (426 mg, 1.61 mmol), N-2,4-dimethoxybenzyloxy-2,3-O-isopropylidene erythronocarboxamide **10** (200 mg, 0.58 mmol), NMI (186 µl, 2.34 mmol) and DCM (10 ml). Colourless oil, 41 mg (12%). ^{1}NMR (500 MHz, $CDCl_3$) δ: 1.25, 1.27 (2s, 3H, 1 of $C(C\underline{H}_3)_2$); 1.33, 1.40 (2s, 3H, $C(C\underline{H}_3)_2$); 3.63 (m, 4H, $CO_2C\underline{H}_3$ + $N\underline{H}CH_2$); 3.71-3.75 (m, 8H, 2 × $OC\underline{H}_3$ + $NHC\underline{H}_2$); 4.04-4.18 (m, 1H, C*H*HOP); 4.33-4.43 (m, 1H, CH*H*OP); 4.83-4.88 (m, 2H, Ar-$C\underline{H}_2$); 6.37-6.40 (m, 2H, Ar*H*); 7.04-7.07 (m, 1H, Ar*H*); 7.11-7.15 (m, 2, Ar*H*); 7.17-7.23 (m, 3H, Ar*H*); 8.83, 9.03 (2s, 1H, ON*H*). ^{31}PNMR (121 MHz, $CDCl_3$) δ: 3.44, 2.87. LCMS (ES+): m/z 568.22 ($[M+H]^+$, 100%); Rt 3.3 min., (purity 88.4% by UV trace).

(14d) *N*-2,4-dimethoxybenzyloxy-2,3-*O*-isopropylidene erythrono carboxamide-4-[phenyl (ethoxyalaninyl) phosphoramidate]

The title compound was synthesised according to the general procedure C using phenyl-valOEt phosphorochloridate **13d** (341 mg, 1.17 mmol), N-2,4-dimethoxybenzyloxy-2,3-O-isopropylidene-erythronocarboxamide **10** (200 mg, 0.58 mmol), NMI (186 µl, 2.34 mmol) and DCM (10 ml). Yellowish sticky oil, 212 mg (61%). ^{1}HNMR (500 MHz, $CDCl_3$) δ: 1.24 (dt, 3H, J_1=7.3 Hz, J_2=14.7 Hz, $OCH_2C\underline{H}_3$); 1.28-1.48 (m, 9H, $CHC\underline{H}_3$ + $C(C\underline{H}_3)_2$); 3.80-3.83 (m, 7H, 2 × $OC\underline{H}_3$ + $NHC\underline{H}CH_3$); 4.02-4.07 (m, 1H, CH*H*OP); 4.10-4.16 (m, 2H, $OC\underline{H}_2CH_3$); 4.42-4.50 (m, 1H, C*H*HOP); 4.57-4.68 (m, 2H, C*H*C*H*OP); 4.89-4.96 (m, 2H, Ar-$C\underline{H}_2$); 6.46 (d, 2H, *J*=7.13 Hz, Ar*H*); 7.11-7.14 (m, 1H, Ar*H*); 7.21-7.20 (m, 2H, Ar*H*); 7.29-7.25 (m, 3H, Ar*H*); 8.89, 9.14 (2s, 1H, N*H*). ^{13}CNMR (125 MHz, $CDCl_3$) δ: 14.11, 14.13 ($OCH_2C\underline{H}_3$); 20.90, 20.94, 21.01, 21.05 ($CHC\underline{H}_3$); 24.48, 24.64, 26.53, 26.68 ($C(\underline{C}H_3)_2$); 50.17, 50.26 ($NH\underline{C}HCH_3$); 55.41, 55.50, 55.52 ($O\underline{C}H_3$); 61.38, 61.41 ($O\underline{C}H_2CH_3$); 65.01, 65.05, 65.20, 65.25 ($\underline{C}H_2OP$); 73.53, 73.55 (Ar-$\underline{C}H_2$); 74.90, 75.33 ($\underline{C}HCH_2OP$); 76.08, 76.12, 76.15, 76.18 (C(O)$\underline{C}$HCH); 98.51 (Ar$\underline{C}$H); 104.11, 104.13 (Ar$\underline{C}$H); 110.51, 110.56 ($\underline{C}(CH_3)_2$); 115.75, 115.79 (Ar$\underline{C}$-CH_2); 120.21, 120.35, 120.39, 120.43 (Ar$\underline{C}$H); 124.69, 124.73 (Ar$\underline{C}$H); 129.51, 132.79, 132.82 (Ar$\underline{C}$H); 150.72, 150.77, 150.83, 150.88 (Ar$\underline{C}$-OP); 159.36 (Ar$\underline{C}$-OCH_3), 161.74, 161.77 (Ar$\underline{C}$-OCH_3); 165.72, 165.79 (HN$\underline{C}$(O)CH); 173.43, 173.49, 173.81, 173.87 ($\underline{C}O_2Et$). ^{31}PNMR (121 MHz, $CDCl_3$) δ: 2.66, 2.15. LCMS (ES+): m/z 614.24 ($[M+NH_4]^+$, 100%); m/z 597.24 ($[M+H]^+$, 15%); Rt 3.3 min., (purity 96.3% by UV trace).

(14e) *N*-2,4-dimethoxybenzyloxy-2,3-*O*-isopropylidene erythrono carboxamide-4-[phenyl (methoxyvalinyl) phosphoramidate]

The title compound was synthesised following the general procedure C using phenyl val-OMe phosphorochloridate **13e** (448 mg, 1.46 mmol), *N*-2,4-dimethoxybenzyloxy-2,3-*O*-isopropylidene erythronocarboxamide **10** (250 mg, 0.73 mmol), NMI (232 µl, 2.93 mmol) and DCM (10 ml). Colourless oil, 191 mg (43%). ^{1}NMR (500 MHz, $CDCl_3$) δ: 0.65-0.88 (m, 6H, $CH(C\underline{H}_3)_2$); 1.24-1.40 (m, 6H, $C(C\underline{H}_3)_2$); 1.90-2.01 (m, 1H, $C\underline{H}(CH_3)_2$); 3.58-3.63 (m, 3H, $CO_2C\underline{H}_3$); 3.72-3.83 (m, 7H, 2 × $OC\underline{H}_3$ + $NHC\underline{H}CH(CH_3)_2$); 4.05-4.21 (m, 1H, CH*H*OP); 4.35-4.41 (m, 1H, C*H*HOP); 4.48-4.59 (m, 2H, C(O)C*H*C*H*); 4.83-4.90 (m, 2H, Ar-$C\underline{H}_2O$); 6.35-6.40 (m, 2H, Ar*H*); 7.03-7.04 (m, 1H, Ar*H*); 7.13-7.25

(m, 5H, Ar*H*); 8.74, 9.09 (2s, 0.5H, ON*H*). ^{31}PNMR (121 MHz, $CDCl_3$) δ: 3.50, 2.99. LCMS (ES+): m/z 628.26 ($[M+NH_4]^+$, 100%); m/z 611.26 ($[M+H]^+$, 75%); Rt 3.6 min., (purity 89.4% by UV trace).

(14f) *N*-2,4-dimethoxybenzyloxy-2,3-*O*-isopropylidene erythrono carboxamide-4-[phenyl (ethoxyvalinyl) phosphoramidate]

The title compound was prepared following the general procedure C using phenyl Val-OEt phosphorochloridate **13f** (375 mg, 1.17 mmol), *N*-2,4-dimethoxybenzyloxy-2,3-*O*-isopropylidene erythronocarboxamide **10** (200 mg, 0.585 mol), NMI (186 μl, 2.34 mmol) and DCM (10 ml). Colourless sticky oil, 222 mg (61%). ^{1}HNMR (500 MHz, $CDCl_3$) δ: 0.78 (dd, 3.5H, J_1=6.86 Hz, J_2=29.86 Hz, $CH(CH_3)_2$); 0.94 (dd, 2.5H, J_1=6.87 Hz, J_2=27.09 Hz, $CH(CH_3)_2$); 1.25 (t, 3H, J=7.14 Hz, OCH_2CH_3); 1.35 (d, 3H, J=19.49 Hz, $C(CH_3)_2$); 1.45 (d, 3H, J=40.20 Hz, $C(CH_3)_2$); 2.01-2.09 (m, 1H, $CH(CH_3)_2$); 3.63-3.69 (m, 1H, NHCH); 3.79-3.84 (m, 7H, 2 × OCH_3 + $CHCH(CH_3)_2$); 4.10-4.19 (m, 3H, OCH_2CH_3 + CHCHOP); 4.47-4.49 (m, 1H, CHHOP); 4.58-4.69 (m, 2H, $CHCHCH_2OP$); 4.91-4.99 (m, 2H, Ar-CH_2); 6.46-6.49 (m, 2H, Ar*H*); 7.11 (t, 1H, J=8.8 9Hz, Ar*H*); 7.21-7.32 (m, 5H, Ar*H*); 8.84, 9.20 (2bs, 1H, ON*H*). ^{13}CNMR (125 MHz, $CDCl_3$) δ: 14.20 (CH_2CH_3); 16.93, 17.37 ($CH(CH_3)_2$); 18.80, 18.85 ($CH(CH_3)$); 24.46, 24.65 ($C(CH_3)_2$); 26.50, 26.65 ($C(CH_3)_2$); 31.89, 31.94, 32.25, 32.30 ($CH(CH_3)_2$); 55.42, 55.48, 55.52 (OCH_3); 59.80, 59.85 ($NHCHCH(CH_3)_2$); 61.05, 61.16 (OCH_2CH_3); 65.18, 65.23 (CH_2OP); 73.49, 73.56 (Ar-CH_2O); 74.90, 75.36 ($CHCH_2OP$); 76.18, 76.25 (C(O)CHCH); 98.47, 98.51 (ArCH); 104.06, 104.11 (ArCH); 110.48, 110.52 ($(CH_3)_2$); 115.81, 115.87 (Ar-CH_2); 120.32, 120.36, 120.50, 120.54 (ArCH); 124.62, 124.69 (ArCH), 129.45, 129.48 (ArCH); 132.80, 132.82 (ArCH); 150.86, 150.91 (Ar-OP); 159.36, 159.41 (Ar-OCH_3); 161.70, 161.77 (Ar-OCH_3); 165.91, 165.41 (HN(O)CH); 172.51, 172.55, 173.11, 172.14 (CO_2Et). ^{31}PNMR (121 MHz, $CDCl_3$) δ: 3.61, 3.08. LCMS (ES+): m/z 625.30 ($[M+H]^+$, 100%); Rt 3.7 min., (purity 93.3% by UV trace).

(14g) *N*-2,4-dimethoxybenzyloxy-2,3-*O*-isopropylidene erythrono carboxamide-4-[phenyl (*tert*-butoxyvalinyl) phosphoramidate]

The title compound was prepared following the general procedure C using phenyl val-O*t*Bu phosphorochloridate **13g** (407 mg, 1.17 mmol), 2,4-dimethoxybenzyl erythronohydroxamate **10** (200 mg, 0.58 mmol), NMI (186 μl, 2.34 mmol) and DCM (10 ml). Colourless sticky oil, 181 mg (47%). ^{1}NMR (500 MHz, $CDCl_3$) δ: 0.78 (dd, 3.5H, J_1=6.8 Hz, J_2=24.3 Hz, $CH(CH_3)_2$); 0.94 (dd, 2.5H, J_1=6.8 Hz, J_2=31.1 Hz, $CH(CH_3)_2$); 1.35 (d, 3H, J=15.9 Hz, $C(CH_3)_2$); 1.46 (d, 3H, J=28.1 Hz, $C(CH_3)_2$); 1.99-2.08 (m, 1H, $CH(CH_3)_2$); 3.62 (m, 1H, PN*H*); 3.73-3.80 (m, 1H, NHCHCH); 3.80-3.87 (m, 6H, 2 × OCH_3); 4.12-4.18 (m, 1H, CHHOP); 4.46-4.52 (m, 1H, CHHOP); 4.56-4.69 (m, 2H, C(O)CHCH); 4.91-4.99 (m, 2H, Ar-CH_2); 6.45-6.49 (m, 2H, Ar*H*); 7.10-7.14 (m, 1H, Ar*H*); 7.22-7.27 (m, 2H, Ar*H*); 8.85, 9.21 (2s, 1H, ON*H*). ^{13}CNMR (125 MHz, $CDCl_3$) δ: 16.85, 17.37, 18.77, 18.83 ($CH(CH_3)_2$); 24.51, 24.73, 26.79 ($C(CH_3)_2$); 28.03 ($C(CH_3)_3$); 32.04, 32.38 ($CH(CH_3)_2$); 55.43, 55.49, 55.54 (OCH_3); 60.18, 60.24, (NHCHCH); 65.22, 65. 27, 65.30 (CH_2OP); 73.46, 73.59 (Ar-CH_2O); 74.97, 75.42 ($CHCH_2OP$); 76.21, 76.27 (C(O)CHCH); 81.8, 81.71 ($C(CH_3)_3$); 98.47, 98.53 (ArCH); 104.08, 104.12 (ArCH); 110.51, 110.54 ($C(CH_3)_2$); 115.82, 115.90 (Ar-CH_2O); 120.34, 120.37, 120.57, 120.61 (ArCH); 124.66 (ArCH); 129.45, 129.49 (ArCH); 132.86, 132.79 (ArCH); 150.96 (Ar-OP); 159.37 (Ar-OCH_3); 161.76 (Ar-OCH_3); 165.95 (HN(O)CH); 203.75 (CO_2tBu). ^{31}PNMR (121 MHz, $CDCl_3$) δ: 3.91, 3.23. LCMS (ES+): m/z 670.29 ($[M+NH_4]^+$, 100%); 653.29 ($[M+H]^+$, 20%); Rt 3.9 min., (purity 75% by UV trace).

(14h) *N*-2,4-dimethoxybenzyloxy-2,3-*O*-isopropylidene erythrono carboxamide-4-[(4-methyl)phenyl (methoxyalaninyl) phosphoramidate]

This was synthesised according to the general procedure C using *N*-2,4-dimethoxybenzyloxy-2,3-*O*-isopropylidene erythronocarboxamide **10** (200 mg, 0.585 mmol); (4-methyl)phenyl (methoxy-L-alaninyl) phosphorochloridate **13h** (426 mg, 1.46 mmol); NMI (187 μl, 2.34 mmol) and DCM (15 ml). Colourless oil, 126 mg, 36%. ^{1}HNMR (500 MHz, $CDCl_3$) δ: 1.21-1.41 (m, 9H, CHC*H*$_3$ + C(C*H*$_3$)$_2$); 2.17 (d, 3H, *J*=2.44 Hz, Ar-C*H*$_3$); 3.61 (m, 3H, CO_2C*H*$_3$); 3.74-3.76 (m, 6H, 2 × Ar-OC*H*$_3$); 3.91-4.07 (m, 2H, C*H*CH_3 + CHCH*H*OP); 4.33-4.42 (m, 1H, CHC*H*HOP); 4.49-4.59 (m, 2H, COC*H*C*H*CH_2OP); 4.83-4.89 (m, 2H, Ar-C*H*$_2$); 6.38-6.41 (m, 2H, Ar*H*); 6.97-7.02 (m, 4H, Ar*H*); 7.19-7.21 (m, 1H, Ar*H*); 8.76, 8.99 (2s, 1Hm ON*H*CO). ^{13}CNMR (125 MHz, $CDCl_3$) δ: 20.72 (CH*C*H_3); 21.03 (Ar-*C*H_3); 24.50, 24.66 (C(*C*H_3)$_2$); 26.53 (C(*C*H_3)$_2$); 50.13, 50.21 (*C*HCH_3); 52.37 (CO_2*C*H_3); 55.42, 55.53 (Ar-O*C*H_3); 64.96, 65.16 (*C*H_2OP); 73.59 (O-*C*H_2-Ar); 74.93, 75.39 (CHC*H*CH_2OP); 76.17, 76.22 (CHCHCH_2OP); 98.55 (Ar*C*H); 104.15 (Ar*C*H); 110.5 (*C*(CH_3)$_2$); 115.77 (Ar*C*-CH_2O); 120.07, 120.13 (Ar*C*H); 129.98 (Ar*C*H); 132.82 (Ar*C*H); 134.21 (Ar*C*-CH_3); 148.47, 148.53, 148.6 (Ar*C*-OP); 159.38 (Ar*C*-OCH_3); 161.75 (Ar*C*-OCH_3); 165.72, 165.83 (HN*C*OCH); 173.93, 174.33 (*C*O_2Me).^{31}PNMR (121 MHz, $CDCl_3$) δ: 2.73, 2.25. LCMS (ES+): m/z 597.23 ([M+H]$^+$, 100%), Rt 3.42 min.

(14i) *N*-2,4-dimethoxybenzyloxy-2,3-*O*-isopropylidene erythrono carboxamide -4-[(4-methyl)phenyl (ethoxyalaninyl) phosphoramidate]

The compound was synthesised following the general procedure C using toluyl-Ala-OEt phosphorochloridate **13i** (214 mg, 0.70 mml), *N*-2,4-dimethoxybenzyloxy-2,3-*O*-isopropylidene erythronocarboxamide **10** (200 mg, 0.58 mmol), NMI (233 μl, 2.93 mmol) and DCM (10 ml). Colourless sticky oil, 93 mg (26%). ^{1}HNMR (500 MHz, $CDCl_3$) δ: 1.25 (dt, 3H, J_1=7.09 Hz, J_2=7.10 Hz, CH_2C*H*$_3$); 1.29-1.49 (m, 9H, C(C*H*$_3$)$_2$ + CHC*H*$_3$); 2.29 (d, 3H, *J*=1,65 Hz, Ar-C*H*$_3$); 3,81-3,81 (m, 7H, 2 × OC*H*$_3$ + C*H*CH_3); 4.04-4.18 (m, 3H, OC*H*$_2$$CH_3$ + CH*H*OP); 4.42-4.51 (m, 1H, C*H*HOP); 4.57-4.69 (m, 2H, C(O)C*H*C*H*CH_2OP); 4.90-4.97 (m, 2H, Ar-C*H*$_2$); 6.46-6.49 (m, 2H, Ar*H*); 7.06-7.19 (m, 4H, Ar*H*); 7.28 (t, 1H, *J*=5.06 Hz, Ar*H*); 8.88, 9.12 (2s, 1H, N*H*). ^{13}CNMR (125 MHz, $CDCl_3$) δ: 14.13 (CH_2*C*H_3); 20.72, 20.73 (Ar-*C*H_3); 20.97, 21.00, 21.06, 21.09 (CH*C*H_3); 24.49, 24.65 (C(*C*H_3)$_2$); 26.65, 26.69 (C(*C*H_3)$_2$); 50.17, 50.26 (*C*HCH_3); 55.41, 55.51, 55.53 (Ar-O*C*H_3); 61.37, 61.41 (O*C*$H_2$$CH_3$); 65.00, 65.04, 65.16, 65.20 (C*H*$_2$OP); 73.56 (Ar-*C*H_2O); 74.93, 75.35 (*C*HCH_2OP); 76.11, 76.16, 76.17, 76.22 (C(O)*C*HCH); 98.46, 98.52, 98.57 (Ar*C*H); 103.86, 103.89, 104.10, 104.13 (Ar*C*H); 110.51, 110.56 (*C*(CH_3)$_2$); 115.77, 115.82 (Ar*C*-CH_2); 120.04, 120.08, 120.10, 120.14 (Ar*C*H); 132.80, 132.83 (Ar*C*); 134.19, 134.21 (Ar*C*-CH_3); 148.48, 148.54, 148.60, 148.65 (Ar*C*-OP); 159.38, 159.41 (Ar*C*-OCH_3); 161.10, 161.78 (Ar*C*-OCH_3); 165.72, 165.78 (HN*C*(O)CH); 173.48, 173.54, 173.86, 173.92 (*C*O_2Et). ^{31}PNMR (121 MHz, $CDCl_3$) δ: 2.83, 2.34. LCMS (ES+): m/z 611.21 ([M+H]$^+$, 100%); Rt 3.7 min.

(14i) GFRII-107 *N*-2,4-dimethoxybenzyloxy-2,3-*O*-isopropylidene erythrono carboxamide-4-[(4-methyl)phenyl (methoxyalaninyl) phosphoramidate]

The title compound was synthesised according to the general procedure C, using toluyl-Val-OMe phosphorochloridate **13j** (375 mg, 1.17 mmol), *N*-2,4-dimethoxybenzyloxy-2,3-*O*-isopropylidene erythronocarboxamide **10** (250 mg, 0.73 mmol), NMI (350 μl, 4.39 mmol) and DCM (10ml).

Colourless sticky oil, 47 mg (10%). ^{1}HNMR (500 MHz, $CDCl_3$) δ: 0.70 (dd, 3H, J_1=6.9 Hz, J_2=32.3 Hz, CH(C*H*$_3$)$_2$); 0.79-0.87 (m, 3H, CH(C*H*$_3$)$_2$); 1.21-1.40 (m, 6H, C(C*H*$_3$)$_2$); 1.90-2.00 (m, 1H, C*H*(CH$_3$)$_2$); 2.21 (s, 3H, Ar-C*H*$_3$); 3.58, 3.59 (2s, 3H, CO_2C*H*$_3$); 3.72, 3.73, 3.74, 3.75 (4s, 6H, 2 × Ar-OC*H*$_3$); 4.03-4.09 (m, 1H, NHC*H*(CH$_3$)$_2$); 4.35-4.39 (m, 1H, C*H*HOP); 4.47-4.61 (m, 3H, C*H*C*H*CH*H*OP); 4.82-4.89 (m, 2H, Ar-C*H*$_2$O); 6.37-6.41 (m, 2H, Ar*H*); 6.96-7.02 (m, 4H, Ar*H*); 7.16-7.22 (m, 1H, Ar*H*); 8.77, 9.10 (2s, 1H N*H*). ^{13}CNMR (125 MHz, $CDCl_3$) δ: 17.06, 17.43 (CH(*C*H$_3$)$_2$); 18.84, 18.87 (CH(*C*H$_3$)$_2$); 20.73, 20.75 (Ar-*C*H$_3$); 24.46, 24.65 (C(*C*H$_3$)$_2$); 26.48, 26.65 (C(*C*H$_3$)$_2$); 31.62, 31.92 (*C*H(CH$_3$)$_2$); 55.42, 55.49, 55.54 (O*C*H$_3$); 59.82, 59.87 (*C*HCH(CH$_3$)$_2$); 65.15, 65.19 (CH*C*H$_2$OP); 73.50, 73.57 (Ar-*C*H$_2$O); 74.91, 75.36 (*C*HCH$_2$OP); 76.19, 76.26 (C(O)*C*HCH); 98.48, 98.51, 98.58 (Ar*C*H); 104.07, 104.12 (Ar*C*H); 110.46, 110.51 (*C*(CH$_3$)$_2$); 115.82, 115.88 (Ar*C*-CH$_2$); 120.05, 120.09, 120.12, 120.19 (Ar*C*H); 129.91 (Ar*C*H); 132.80, 132.82 (Ar*C*H); 134.13, 134.17 (Ar*C*-CH$_3$); 148.61, 148.64, 148.66, 148.69 (Ar*C*-OP); 159.36, 159.41 (Ar*C*-OCH$_3$); 161.70, 161.77 (Ar*C*-OCH$_3$); 165.98, 166.00 (HN*C*OCH); 173.08, 173.11, 173.66, 173.69 (*C*O$_2$Me). ^{31}PNMR (121 MHz, $CDCl_3$) δ: 3.67, 3.19. LCMS (ES+): m/z 625.27 ([M+H]$^+$, 100%); Rt 3.7 min.

(14l) *N*-2,4-dimethoxybenzyloxy-2,3-*O*-isopropylidene erythrono carboxamide-4-[(4-methyl)phenyl (ethoxyvaliniyl) phosphoramidate]

The title compound was synthesised following the general procedure C using toluyl-Val-OEt phosphorochloridate **13l** (390 mg, 1.17 mmol), *N*-2,4-dimethoxybenzyloxy-2,3-*O*-isopropylidene erythronocarboxamide **10** (200 mg, 0.58 mmol), NMI (186 μl, 2.34 mmol) and DCM (10 ml). Colourless sticky oil, 94 mg (25%). ^{1}HNMR (500 MHz, $CDCl_3$) δ: 0.71 (dd, 3.5H, J_1=6.9 Hz, J_2= 33.14 Hz, CH(C*H*$_3$)$_2$); 0.85 (dd, 2.5H, J_1=6.9 Hz, J_2= 33.14 Hz, CH(C*H*$_3$)$_2$); 1.16 (t, 3H, *J*=7.13 Hz, OCH$_2$C*H*$_3$); 1.26 (d, 3H, *J*=18.48 Hz, C(C*H*$_3$)$_2$); 1.36 (d, 3H, *J*=35.64 Hz, C(C*H*$_3$)$_2$); 1.93-1.99 (m, 1H, C*H*(CH$_3$)$_2$); 2.21 (s, 3H, Ar-C*H*$_3$); 3.73-3.76 (m, 7H, 2 × OC*H*$_3$ + NHC*H*CH); 4.02-4.10 (m, 3H, OC*H*$_2$CH$_3$ + CH*H*OP); 4.36-4.40 (m, 1H, C*H*HOP); 4.49-4.61 (m, 2H, C*H*C*H*CH$_2$OP); 4.82-4.97 (m, 2H, Ar-C*H*$_2$O); 6.37-6.39 (m, 2H, Ar*H*); 6.99 (AB system, 4H, J_1=8.6 Hz, J_2=10.9 Hz, Ar*H*); 7.12-7.23 (m, 1H, Ar*H*); 8.74, 9.08 (2s, 1H, N*H*). ^{13}CNMR (125 MHz, $CDCl_3$) δ: 14.21 (OCH$_2$*C*H$_3$); 17.00, 18.83 (CH(*C*H$_3$)$_2$); 24.67, 26.68 (C(*C*H$_3$)$_2$); 31.95 (Ar-*C*H$_3$); 55.38, 55.50 (O*C*H$_3$); 59.79, 59.84 (*C*HCH(CH$_3$)$_2$); 61.04, 61.16 (O*C*H$_2$CH$_3$); 65.15 (*C*H$_2$OP); 73.50 (Ar-*C*H$_2$O); 75.38 (*C*HCH$_2$OP); 76.20 (C(O)*C*HCH); 98.48 (Ar*C*H); 103.89, 104.06 (Ar*C*H), 110.51 (*C*(CH$_3$)$_2$); 115.9 (Ar*C*-CH$_2$O); 118.96 (Ar*C*H); 120.10, 120.18, 120.21 (Ar*C*H); 129.89, 130.57 (Ar*C*H); 132.79 (Ar*C*); 134.15 (Ar*C*); 148.73 (Ar*C*-OP); 159.36 (Ar*C*-OCH$_3$); 161.70 (Ar*C*-OCH$_3$); 165.89 (HN*C*(O)CH); 173.15, 173.38 (CO$_2$Et). ^{31}PNMR (121 MHz, $CDCl_3$) δ: 3.79, 3.26. LCMS (ES+): m/z 639.32([M+H]$^+$, 100%); Rt 3.8 min., (purity 80% by UV trace).

(14m) *N*-2,4-dimethoxybenzyloxy-2,3-*O*-isopropylidene erythrono carboxamide-4-[(4-methoxy)phenyl (methoxyalaninyl)phosphoramidate]

The title compound was synthesised following the general procedure C using (4-methoxy)phenyl Ala-OMe phosphorochloridate **13m** (360 mg, 1.17 mmol), *N*-2,4-dimethoxybenzyloxy-2,3-*O*-isopropylidene-erythronocarboxamide **10** (200 mg, 0,58 mmol), NMI (186 μl, 2.34 mmol) and DCM (10 ml). Colourless sticky oil, 103 mg (28%). ^{1}NMR (500 MHz, $CDCl_3$) δ: 1.27-1.49 (m, 9H, CHC*H*$_3$ + C(C*H*$_3$)$_2$); 3.68, 3.83 (m, 12H, 4 × OC*H*$_3$); 4.01-4.14 (m, 2H, NHC*H*CH$_3$ + CH*H*OP); 4.39-4.49 (m, 1H, C*H*HOP); 4.56-4.68 (m, 2H, C*H*C*H*CH$_2$OP); 4.86-4.96 (m, 2H, Ar-CH$_2$O); 6.46-6.48 (m, 2H, Ar*H*); 6.77-6.83 (m, 2H, Ar*H*); 7.11-7.13 (m, 2H, Ar*H*); 7.23-7.27 (m, 1H, Ar*H*); 8.91, 9.14 (2s, 1H, ON*H*).

^{31}PNMR (121 MHz, $CDCl_3$) δ: 3.06, 2.60. LCMS (ES+): m/z 630.29 ($[M+NH_4]^+$, 100%); m/z 613.29 ($[M+H]^+$, 10%); Rt 3.4 min., (purity 89.6% by UV trace).

(14n) *N*-2,4-dimethoxybenzyloxy-2,3-*O*-isopropylidene erythrono carboxamide-4-[(2,3-dimethyl)phenyl (ethyloxyvalinyl)phosphoramidate]

The compound was synthesized according to the general procedure C from the phosphorodichloridate **13n** (222 mg, 0.63 mmol), 2,4-dimethoxybenzyl-2,3-O-isopropylidene erythrono hydroxamate **10** (180 mg, 0.53 mmol), NMI (167 µl, 2.11 mmol) in DCM (3 ml). Colorless oil, 40 mg (12%). ^{1}NMR (500 MHz, $CDCl_3$) δ: 0.75-0.98 (m, 6H, $CH(C\underline{H}_3)_2$), 1.254, 1.257 (2t, J=7.1 Hz, 3H, $CH_2C\underline{H}_3$), 1.33, 1.37 (2s, 3H, 1 of $O_2C(C\underline{H}_3)_2$), 1.43, 1.49 (2s, 3H, 1 of $O_2C(C\underline{H}_3)_2$), 2.01, 2.09 (m, 1H, $C\underline{H}(CH_3)_2$), 3.61-3.69 (m, 1H, $HNC\underline{H}CO_2Et$), 3.76-3.87 (m, 9H, 3 × $OC\underline{H}_3$), 4.11-4.13 (m, 2H, $OC\underline{H}_2CH_3$ + $CH\underline{H}OP$), 4.44-4.48 (m, 3H, $C\underline{H}C\underline{H}C\underline{H}HOP$), 4.91-4.99(m, 2H, Ar-$C\underline{H}_2O$), 6.47-6.79 (m, 4H, Ar$\underline{H}$), 6.77-6.79 (m, 2H, Ar$\underline{H}$), 7.13-7.15 (m, 2H, Ar$\underline{H}$), 7.25-7.32 (m, 3H, Ar$\underline{H}$), 8.86, 9.24 (2s, 1H, ON$\underline{H}$CO). ^{13}CNMR (125 MHz, $CDCl_3$) δ: 14.22 ($OCH_2\underline{C}H_3$), 16.94, 17.40 ($CH(\underline{C}H_3)_2$), 18.82 ($CH(\underline{C}H_3)_2$), 24.47, 24.67 ($O_2C(\underline{C}H_3)_2$), 26.53, 26.65 ($O_2C(\underline{C}H_3)_2$), 31.91, 31.96, 32.35 ($\underline{C}H(CH_3)_2$), 55.40, 55.48, 55.53, 55.58 ($O\underline{C}H_3$), 59.79, 59.84 ($NH\underline{C}HCO_2Et$), 61.04, 61.17 ($O\underline{C}H_2CH_3$), 65.09, 65.14 ($\underline{C}H_2OP$), 73.50, 73.57 (Ar-$\underline{C}H_2ONH$), 74.92, 75.38 ($CHC\underline{H}CH_2OP$), 76.20, 76.26 ($CO\underline{C}HCH$), 98.46, 98.52, 98.58 (Ar$\underline{C}$H), 103.89, 104.06, 104.11 (Ar$\underline{C}$H), 110.47, 110.50 ($O_2\underline{C}H(CH_2)_3$), 114.37, 115.81, 115.88 (Ar$\underline{C}$-CH_2), 121.24, 121.28, 121.38, 121.42 (Ar$\underline{C}$H), 131.75, 132.82 (Ar$\underline{C}$H), 144.46, 144.51 (Ar$\underline{C}$), 156.46 (Ar$\underline{C}$-OCH_3), 159.13, 159.37, 159.41 (Ar$\underline{C}$-OCH_3), 161.11, 161.71, 161.77 (Ar$\underline{C}$-OCH_3), 165.91, 166.07 (HN$\underline{C}$O), 172.60 ($\underline{C}O_2Et$). ^{31}PNMR (121 MHz, $CDCl_3$) δ: 3.58, 4.09. LCMS (ES+): m/z 655 ($[M+H]^+$, 80%); m/z 673 ($[M+NH_4]^+$, 100%); Rt 4.7 min.

(14o) *N*-2,4-dimethoxybenzyloxy-2,3-*O*-isopropylidene erythrono carboxamide-4-[(2,3-dimethyl)phenyl (methyloxyalaninyl)phosphoramidate]

The title compound was synthesised following the general procedure C using (2,3-dimethyl)phenyl-(methoxy-alanilyl) phosphorochloridate **13o** (362 mg, 1.18 mmol), *N*-2,4-dimethoxybenzyloxy-2,3-*O*-isopropylidene-erythronocarboxamide **10** (337 mg, 0.98 mmol), NMI (311 µl, 3.92 mmol) and DCM (6 ml). Colourless oil, 28 mg (~5%). ^{1}NMR (500 MHz, $CDCl_3$) δ: 1.18-1.40 (m, 9H, $C(C\underline{H}_3)_2$ + $CHC\underline{H}_3$); 2.09 (d, 3H, *J*=8.82 Hz, 1 of Ar-$C\underline{H}_3$); 2.17-2.19 (m, 3H, 1 of Ar$C\underline{H}_3$); 3.61-3.64 (m, 3H, $COC\underline{H}_3$); 3.65-3.77 (m, 7H, 2 × $OC\underline{H}_3$ + $PN\underline{H}$); 3.96-4.09 (m, 1H, $NHC\underline{H}$); 4.34-4.42 (m, 2H, $C(O)C\underline{H}C\underline{H}$); 4.80-4.88 (m, 2H, Ar-$C\underline{H}_3$); 6.37-6.41 (m, 2H, Ar$\underline{H}$); 6.84-6.87 (m, 1H, Ar$\underline{H}$); 6.90-6.97 (m, 1H, Ar$\underline{H}$); 7.09-7.14 (m, 1H, Ar$\underline{H}$); 7.16-7.20 (m, 1H, Ar$\underline{H}$); 8.79, 9.05 (2s, 1H, ON$\underline{H}$). ^{13}CNMR (125 MHz, $CDCl_3$) δ: 12.44, 12.53 (Ar-$\underline{C}H_3$); 20.18, 20.23 (Ar-$\underline{C}H_3$); 20.87, 20.92, 21.11 ($CH\underline{C}H_3$); 24.50, 24.68, 26.58, 26.71 ($C(\underline{C}H_3)_2$); 49.95, 50.13, 50.27 ($\underline{C}HCH_3$); 52.35, 52.42 ($CO_2\underline{C}H_3$); 55.42, 55.49, 55.52 ($ArO\underline{C}H_3$); 65.05, 65.08, 65.12 ($\underline{C}H_2OP$); 73.56, 73.59 (Ar-$\underline{C}H_2O$); 74.92, 75.45 ($\underline{C}HCH_2OP$); 76.11, 76.18, 76.24 ($C(O)\underline{C}H$); 98.52 (Ar$\underline{C}$H); 104.08, 104.11 (Ar$\underline{C}$H); 110.51, 110.54 ($\underline{C}(CH_3)_2$); 115.75, 115.83 (Ar$\underline{C}$-CH_2O); 117.61, 117.70 (Ar$\underline{C}$-CH_3); 125.88, 126.06, 126.12 (Ar$\underline{C}$H); 132.80 (Ar$\underline{C}$H); 138.50 (Ar$\underline{C}$-CH_3); 149.04, 149.11, 149.17, 149.24 (Ar$\underline{C}$-OP); 159.37, 159.41 (Ar$\underline{C}$-OCH_3); 161.78 (Ar$\underline{C}$-OCH_3); 165.76, 165.85 (HN$\underline{C}$(O)); 174.00, 174.06, 174.48, 174.53 ($\underline{C}O_2Me$). ^{31}PNMR (121 MHz, $CDCl_3$) δ: 2.90, 2.20. LCMS (ES+): m/z 611.23 ($[M+H]^+$, 100%); Rt 3.6 min., (purity 82% by UV trace).

(14p) *N*-2,4-dimethoxybenzyloxy-2,3-*O*-isopropylidene erythrono carboxamide-4-[(2,3-dimethyl)phenyl (ethyloxyvalinyl)phosphoramidate

The title compound was prepared following the general procedure C using (*O*-2,3-dimethyl)phenyl-(ethoxy-valinyl) **13p** phosphorochloridate (460 mg, 1.32 mmol), *N*-2,4-dimethoxybenzyloxy-2,3-*O*-isopropylidene-erythronocarboxamide **10** (375 mg, 1.10 mmol), NMI (374 μl, 4.40 mmol) and DCM (7 ml). Colourless oil, 131 mg, (18%) purest fraction; 293 mg (41%) less pure fraction. ^{1}NMR (500 MHz, $CDCl_3$) δ: 0.80 (dd, 3H, *J*1=6.8 Hz, *J*2=29.7 Hz, 1 of $CH(C\underline{H_3})_2$); 0.97 (dd, 3H, *J*1=6.8 Hz, *J*2=26.1 Hz, 1 of $CH(C\underline{H_3})_2$); 1.26 (dt, 3H, *J*1=1.23 Hz, *J*2=7.14 Hz, $OCH_2C\underline{H_3}$); 1.35 (d, 3H, *J*=13.8 Hz, 1 of $C(C\underline{H_3})_2$); 1.47 (d, 3H, *J*=13.9 Hz, 1 of $C(C\underline{H_3})_2$); 2.02-2.11 (m, 1H, $C\underline{H}(CH_3)_2$); 2.19 (d, 3H, *J*=15.3 Hz, 1 of Ar-$C\underline{H_3}$); 2.26 (d, 3H, *J*=3.0 Hz, 1 of Ar-$C\underline{H_3}$); 3.63-3.72 (m, 1H, NHC*H*); 3.81-3.89 (m, 7H, 2 × $OC\underline{H_3}$ + PN*H*); 4.11-4.19 (m, 3H, $OC\underline{H_2}CH_3$ + CH*H*OP); 4.44 (m, 1H, C*H*HOP); 4.56-4.70 (m, 2H, C(O)C*H*C*H*); 4.89-4.98 (m, 2H, Ar-$C\underline{H_2}$); 6.45-6.52 (m, 2H, Ar*H*); 6.93 (d, 1H, *J*=7.6 Ar*H*); 7.00 (dt, 1H, *J*1=2.2 Hz, *J*2=7.8 Hz; Ar*H*); 7.26-7.31 (m, 1H, Ar*H*); 8.86, 9.19 (2s, 1H, ON*H*). ^{13}CNMR (125 MHz, $CDCl_3$) δ: 12.43, 12.53 (Ar-$\underline{C}H_3$); 14.19 ($OCH_2\underline{C}H_3$); 17.03, 17.47, 18.77, 18.80 ($CH(\underline{C}H_3)_2$); 20.12 (Ar-$\underline{C}H_3$); 24.49, 24.69, 26.56, 26.69 ($C(\underline{C}H_3)_2$); 31.92, 31.97, 32.37, 32.42 ($\underline{C}H(CH_3)_2$); 55.39, 55.46, 55.50, 55.53 ($O\underline{C}H_3$); 59.79, 59.93 (NH$\underline{C}$H); 60.99, 61.11 ($O\underline{C}H_2CH_3$); 65.07, 65.12, 65.31 ($CH\underline{C}H_2OP$); 73.46, 73.55 (Ar-CH_2O); 74.96, 75.47 ($\underline{C}HCH_2OP$); 76.21, 76.25 (C(O)$\underline{C}$H); 98.48, 98.62 (Ar$\underline{C}$H); 103.97, 104.10, 104.16 (Ar$\underline{C}$H); 110.47, 110.48 ($\underline{C}(CH_3)_2$); 115.87, 115.97 (Ar$\underline{C}$-CH_2O); 117.60, 117.84 (Ar$\underline{C}$H); 125.82, 126.02 (Ar$\underline{C}$H); 127.94, 131.68 (Ar$\underline{C}$-CH_3) ; 132.73, 132.76 (Ar$\underline{C}$H); 138.36, 138.41 (Ar$\underline{C}$-CH_3); 149.27, 149.33 (Ar$\underline{C}$-OP); 159.35, 159.42 (Ar$\underline{C}$-OCH_3); 161.69, 161.77 (Ar$\underline{C}$-OCH_3); 165.78, 166.01 (HN$\underline{C}$(O)); 172.54, 173.22 ($\underline{C}O_2Et$). ^{31}PNMR (121 MHz, $CDCl_3$) δ: 3.99, 3.26. LCMS (ES+): m/z 653.29 ($[M+H]^+$, 100%); Rt 3.9 min., (purity 94.1% by UV trace).

(14q) *N*-2,4-dimethoxybenzyloxy-2,3-*O*-isopropylidene erythrono carboxamide-4-[(2,3-dimethyl)phenyl (*tert*-butyloxyvalinyl)phosphoramidate

The compound was synthesized according to the general procedure C from **13q** (264 mg, 0.70 mmol), *N*-2,4-dimethoxybenzyloxy-2,3-*O*-isopropylidene-erythronocarboxamide **10** (200 mg, 0.58 mmol), NMI (185 μl, 2.34 mmol) in DCM (4 ml). Colorless oil, 73 mg (18%). ^{1}NMR (500 MHz, $CDCl_3$) δ: 0.77 (dd, 3H, J_1=6.8 Hz, J_2=28.3 Hz, 1 of $CH(C\underline{H_3})_2$), 0.96 (dd, 3H, J_1=6.8 Hz, J_2= 28.3 Hz, 1 of $CH(C\underline{H_3})_2$), 1.33, 1.35 (2s, 3H, 1 of $C(C\underline{H_3})_2$), 1.43-1.46 (m, 12H, $C(C\underline{H_3})_3$ + 1 of $CH(C\underline{H_3})_2$), 2.00-2.09 (m, 1H, $C\underline{H}(CH_3)_2$), 2.17, 2.20 (2s, 3H, Ar-$C\underline{H_3}$), 2.24, 2.25 (2s, 3H, Ar-$C\underline{H_3}$), 3.60-3.67 (m, 1H, NHC*H*CO_2), 3.75-3.85 (m, 7H, 2 × $OC\underline{H_3}$), 4.03-4.08 (m, 1H, N*H*CH), 4.35-4.59 (m, 3H, C*H*C*H*$C\underline{H_2}$OP), 4.79-4.89 (m, 2H, $C\underline{H_2}$OAr), 6.36-6.41 (m, 2H, Ar*H*), 6.81-6.84 (m, 1H, Ar*H*), 6.90 (dt, 1H, J_1=3.0 Hz, J_2=7.9 Hz, Ar*H*), 7.13 (t, 1H, J=8.4 Hz, Ar*H*), 7.17-7.22 (m, 1H, Ar*H*), 8.79, 8.91 (2s, 1H, ON*H*CO). ^{13}CNMR (125 MHz, $CDCl_3$) ™: 12.52, 12.59 ($CH(\underline{C}H_3)_2$), 16.87 (Ar-$\underline{C}H_3$), 18.73, 18.82 ($CH(\underline{C}H_3)_2$), 20.17 (Ar-$\underline{C}H_3$), 24.50, 24.76 ($O_2C(\underline{C}H_3)_2$), 26.60, 26.81 ($O_2C(\underline{C}H_3)_2$), 28.00 ($C(\underline{C}H_3)_3$), 31.97, 32.02, 32.45, 32.49 ($CH\underline{C}H(CH_3)_2$), 55.39, 55.44 ($O\underline{C}H_3$), 55.50, 55.57 ($O\underline{C}H_3$), 60.10, 60.28 (NH$\underline{C}HCO_2$), 65.06, 65.09, 65.28, 65.32 ($CH\underline{C}H_2OP$), 73.41, 73.56 (Ar-$\underline{C}H_2O$), 74.95, 75.49 ($\underline{C}HCH_2OP$), 76.17, 76.25, 76.31 ($\underline{C}HCHCH_2OP$), 81.52, 81.66 ($\underline{C}(CH_3)_3$), 98.41, 98.48, 98.58 (Ar$\underline{C}$H), 104.03, 104.08 (Ar$\underline{C}$H), 110.48, 110.49 ($O_2\underline{C}(CH_3)_2$), 115.81, 115.91 (Ar$\underline{C}$-CH_3), 117.60, 117.96 (Ar$\underline{C}$H), 125.81, 126.00, 126.02 (Ar$\underline{C}$-CH_3), 132.75, 132.82, 132.86 (Ar$\underline{C}$H), 138.35, 138.41 (Ar$\underline{C}$-CH_3), 149.27, 149.33 (Ar$\underline{C}$-OP), 159.33, 159.40 (Ar$\underline{C}$-OCH_3), 161.65, 161.73 (Ar$\underline{C}$-OCH_3), 165.75, 165.94 (HN$\underline{C}$OCH),

171.71, 172.33, 172.36 ($\underline{C}O_2{}^tBu$). ^{31}PNMR (121 MHz, $CDCl_3$) δ: 3.50, 4.34. LCMS (ES+): m/z 681 ($[M+H]^+$, 100%); m/z 698 ($[M+NH_4]^+$, 100%); Rt 5.8 min

(15f) 2,3-*O*-isopropylidene erythronocarboxamide-4-[phenyl (ethoxyvalinyl) phosphoramidate]

The title compound was synthesised following the general procedure D from **14f** (180 mg, 0.29 mmol), TFA (30 µl) and DCM (4 ml). Orange foam, 65 mg (47%). ^{1}HNMR (500 MHz, $CDCl_3$) δ: 0.86 (dd, 6H, J_1=6.75 Hz, J_2=12.65 Hz, CH(C$\underline{H}_3$)$_2$); 1.23 (t, 3H, J=7.0 Hz, OCH$_2$C$\underline{H}_3$); 1.34 (s, 3H, C(CH$_3$)$_2$); 1.48 (s, 3H, C(C$\underline{H}_3$)$_2$); 1.99-2.06 (m, 1H, C$\underline{H}$(CH$_3$)$_2$); 3.81-3.85 (m, 1H, NHC$\underline{H}$CH); 4.09-4.11 (m, 3H, OC$\underline{H}_2$CH$_3$ + CH$\underline{H}$OP); 4.19-4.25 (m, 2H, C$\underline{H}$HOP + N$\underline{H}$CH); 4.51-4.57 (m, 1H, C$\underline{H}$CH$_2$OP); 4.75 (d, 1H, J=7.02 Hz, C(O)C$\underline{H}$CH); 7.13 (t, 1H, J=7.22 Hz, Ar$\underline{H}$); 7.22 (d, 2H, J=7.22 Hz, Ar$\underline{H}$); 7.29 (t, 2H, J=7.29 Hz, Ar$\underline{H}$); 9.27, 9.48 (2bs, 1H, ON$\underline{H}$). ^{13}CNMR (125 MHz, $CDCl_3$) δ: 14.14 (CH$_2\underline{C}$H$_3$); 17.23, 18.87 (CH($\underline{C}$H$_3$)$_2$); 24.48, 26.49 (C($\underline{C}$H$_3$)$_2$); 31.94, 31.99 ($\underline{C}$H(CH$_3$)$_2$); 60.02 (NH$\underline{C}$HCH); 61.42 (O$\underline{C}$H$_2$CH$_3$); 64.88, 64.92 (CH$\underline{C}$H$_2$OP); 74.99 ($\underline{C}$HCH$_2$OP); 75.81, 75.89 (C(O)$\underline{C}$HCH); 110.55 ($\underline{C}$(CH$_3$)$_2$); 120.39, 120.43 (Ar$\underline{C}$H); 125.00 (Ar$\underline{C}$H); 129.57 (Ar$\underline{C}$H); 150.59, 150.65 (Ar$\underline{C}$-OP); 166.38 (HN$\underline{C}$(O)); 172.82, 173.49 ($\underline{C}$O$_2$Et). ^{31}PNMR (121 MHz, $CDCl_3$) δ: 3.02, 2.92. LCMS (ES+): m/z 475.24 ($[M+H]^+$, 100%); Rt 3.2 min., (purity 94% by UV); HRMS: Found 475.1829; $C_{20}H_{32}N_2O_9P$ [M+H$^+$] requires 475.1840.

(15g) 2,3-*O*-isopropylidene erythronocarboxamide-4-[phenyl (*tert*-butoxyvalinyl)phosphoramidate]

The title compound was synthesised following the general procedure D from **14g** (181 mg, 0.28 mmol), TFA (50 µl) and DCM (5 ml). White foam, 74 mg (53%). ^{1}NMR (500 MHz, $CDCl_3$) δ: 0.87-0.97 (m, 6H, CH(C$\underline{H}_3$)$_2$); 1.38 (d, 3H, J=8.53 Hz, 1 of C(C$\underline{H}_3$)$_2$); 1.46 (d, 9H, J=9.06 Hz, C(C$\underline{H}_3$)$_3$); 1.53 (d, 3H, J=16.0 Hz, 1 of C(C$\underline{H}_3$)$_2$); 2.03-2.10 (m, 1H, C$\underline{H}$(CH$_3$)$_2$); 3.70-3.97 (m, 2H, N$\underline{H}$C$\underline{H}$); 4.17-4.46 (m, 2H, C$\underline{H}_2$OP); 4.58-4.61 (m, 1H, C$\underline{H}$CH$_2$OP); 4.79 (dd, 1H, J_1=1.89 Hz, J_2=7.96 Hz, C(O)C$\underline{H}$CH); 7.15-.19 (m, 1H, Ar$\underline{H}$); 7.22-7.26 (m, 2H, Ar$\underline{H}$); 7.30-7.35 (m, 2H, Ar$\underline{H}$); 8.84 (bs, 1H, ON$\underline{H}$). ^{13}CNMR (125 MHz, $CDCl_3$) δ: 16.95, 18.90 (CH($\underline{C}$H$_3$)$_2$); 24.41, 26.42 (C($\underline{C}$H$_3$)$_2$); 28.00 (C($\underline{C}$H$_3$)$_3$); 32.17 (CH($\underline{C}$H$_3$)$_2$); 60.36 (NH$\underline{C}$H); 67.19 ($\underline{C}$H$_2$OP); 74.51, 75.75 ($\underline{C}$HCH$_2$OP); 75.84, 76.05 (C(O)$\underline{C}$HCH); 81.42 ($\underline{C}$(CH$_3$)$_3$); 110.45 ($\underline{C}$(CH$_3$)$_2$); 120.27 (Ar$\underline{C}$H); 125.03 (Ar$\underline{C}$H); 129.66 (Ar$\underline{C}$H); 133.36 (Ar$\underline{C}$H); 143.63 (Ar$\underline{C}$); 165.39 (HN$\underline{C}$(O)); 203.36 ($\underline{C}$O$_2$*t*Bu). ^{31}PNMR (121 MHz, $CDCl_3$) δ: 3.57, 3.51. LCMS (ES+): m/z 466.34 ($[M+H]^+$, 100%); Rt 5.4 min., (purity 90% by UV); HRMS: Found 503.2155; $C_{22}H_{36}N_2O_9P$ [M+H$^+$] requires 503.2153.

(15h) 2,3-*O*-isopropylidene erythronocarboxamide-4-[(4-methyl)phenyl (methoxyalaninyl)phosphoramidate]

The title compound was synthesised following the general procedure D from **14h** (90 mg, 0.15 mmol), TFA (20 µl) in DCM (2 ml). The title compound was obtained as yellowish foam. 27 mg (40%). ^{1}HNMR (500 MHz, MeOD) δ: 1.32-1.40 (m, 6H, CHC$\underline{H}_3$ + 1 of C(C$\underline{H}_3$)$_2$); 1.55, 1.57 (2s, 3H, 1 of C(C$\underline{H}_3$)$_2$); 2.33 (s, 3H, Ar-C$\underline{H}_3$); 3.70 (s, 3H, CO$_2$C$\underline{H}_3$); 3.96-4.01 (m, 1H, NHC$\underline{H}$CH$_3$); 4.07-4.11 (m, 1H, CHCH$\underline{H}$OP); 4.31-4.41 (m, 1H, CHC$\underline{H}$HOP); 4.60-4.73 (m, 2H, COC$\underline{H}$C$\underline{H}$CH$_2$OP); 7.11-7.18 (m, 4H, Ar$\underline{H}$). ^{13}CNMR (125 MHz, $CDCl_3$) δ: 20.49 (Ar-$\underline{C}$H$_3$); 20.68, 20.72 (CH$\underline{C}$H$_3$); 24.17, 24.52 (C($\underline{C}$H$_3$)$_2$);

26.11, 26.55 (C($\underline{C}H_3)_2$); 49.86, 50.19 ($\underline{C}HCH_3$); 52.58 ($CO_2\underline{C}H_3$); 64.91, 65.22 (CH$\underline{C}H_2$OP); 74.35 (CH$\underline{C}HCH_2$OP); 75.85, 76.06 ($\underline{C}HCHCH_2$OP); 110.38, 110.60 ($\underline{C}(CH_3)_2$); 119.81 120.03 (Ar$\underline{C}$H); 130.06, 130.20 (Ar$\underline{C}$H); 134.62 (Ar$\underline{C}$-CH_3), 148.21 (Ar$\underline{C}$-OP); 160.71 (NH$\underline{C}$OCH); 173.98 ($\underline{C}O_2$Me). ^{31}PNMR (121 MHz, $CDCl_3$) δ: 2.20. LCMS (ES+): m/z 447.15 ([M+H]$^+$, 100%), Rt 2.8 min, (purity >95% by UV)

(15i) 2,3-*O*-isopropylidene erythronocarboxamide-4-[(4-methyl)phenyl (ethoxyalaninyl)phosphoramidate]

The title compound was synthesised according to the general procedure D from compound **14i** (93 mg, 0.152 mmol), TFA (15 μl) and DCM (2 ml). Orange foam 42 mg, (60%). ^{1}HNMR (500 MHz, $CDCl_3$) δ: 1.17-1.27 (m, 6H, $OCH_2C\underline{H}_3$ + $CHC\underline{H}_3$); 1.29 (s, 3H, C(C$\underline{H}_3)_2$); 1.43 (d, 3H, *J*=3.76 Hz, C(C$\underline{H}_3)_2$); 2.23 (d, 3H, *J*=7.24 Hz, Ar-C$\underline{H}_3$); 3.78-3.89 (m, 2H, CH$\underline{H}$OP + C$\underline{H}CH_3$); 3.99-4.16 (m, 3H, OC$\underline{H}_2CH_3$ + C$\underline{H}$HOP); 4.33 (bs, 0.5H, NH); 4.48-4.53 (m, 1H, C$\underline{H}CH_2$OP); 4.69 (dd, 1H, J_1=5.54 Hz, J_2=7.4 Hz, C(O)C$\underline{H}$CH); 7.00-7.05 (m, 4H, Ar$\underline{H}$); 8.75, 9.02 (2bs, 1H, ON$\underline{H}$C(O). ^{13}CNMR (125 MHz, $CDCl_3$) δ: 14.06, 14.09 ($\underline{C}H_3CH_2$); 20.69, 20.72 (Ar-$\underline{C}H_3$); 20.93, 20.99 (CH$\underline{C}H_3$); 24.38, 24.52 (C($\underline{C}H_3)_2$); 26.26, 26.66 (C($\underline{C}H_3)_2$); 50.01, 50.31 ($\underline{C}HCH_3$); 61.73, 61.84 ($\underline{C}H_2CH_3$); 64.75, 65.17 (CH$\underline{C}H_2$OP); 74.68, 75.65 (CH$\underline{C}HCH_2$OP); 77.22, 77.77 ($\underline{C}HCHCH_2$OP); 110.48, 110.52 ($\underline{C}(CH_3)_2$); 119.87, 119.91, 120.02, 120.06 (Ar-$\underline{C}$H); 130.11, 130.16 (Ar$\underline{C}$H); 134.64, 134. 69 (Ar$\underline{C}$-CH_3); 148.27 (Ar-$\underline{C}$OP), 166.00 (NH$\underline{C}$OCH); 173.67 ($\underline{C}$OOEt). ^{31}PNMR (121 MHz, $CDCl_3$) δ: 2.90, 2.51. LCMS (ES+): m/z 461.21 ([M+H]$^+$, 100%); Rt 3.1 min., (purity ~94% by UV trace); HRMS: Found 461.1671; $C_{19}H_{30}N_2O_9P$ [M+H$^+$] requires 461.1683.

(15j) 2,3-*O*-isopropylidene erythronocarboxamide-4-[(4-methyl)phenyl (methoxyvalinyl)phoshoramidate]

The title compound was prepared following the general procedure D from **14j** (47 mg, 0.075 mmol), TFA (15 μl) and DCM (2 ml). White foam, 19 mg (53%). ^{1}HNMR (500 MHz, $CDCl_3$) δ: 0.76-0.87 (m, 6H, CH(C$\underline{H}_3)_2$); 1.27 (s, 3H, C(C$\underline{H}_3)_2$); 1.44 (s, 3H, C(C$\underline{H}_3)_2$); 1.95-2.01 (m, 1H, C$\underline{H}(CH_3)_2$); 2.23, 2.22 (2s, 3H, Ar-$\underline{C}H_3$); 3.62, 3.65 (2s, 3H, $CO_2C\underline{H}_3$); 3.84 (dd, 1H, J_1=2.4 Hz, J_2=9.7 Hz, C$\underline{H}$CH($CH_3)_2$); 4.09-4.28 (m, 2H, C$\underline{H}_2$OP); 4.48-4.53 (m, 1H, C$\underline{H}CH_2$OP); 4.66-4.69 (m, 1H, C(O)C$\underline{H}$CH); 7.01-7.02 (m, 4H, Ar$\underline{H}$); 8.91 (bs, 1H, ON$\underline{H}$). ^{13}CNMR (125 MHz, $CDCl_3$) δ: 17.16, 17.26 (CH($\underline{C}H_3)_2$); 18.94, 20.75 (CH($\underline{C}H_3)_2$); 24.47, 24.51 (C($\underline{C}H_3)_2$); 26.34, 26.62 (C($\underline{C}H_3)_2$); 32.00, 32.04, 32.15, 32.19 ($\underline{C}$H($CH_3)_2$); 52.29, 52.41 ($CO_2\underline{C}H_3$); 59.78, 59.92 (HN$\underline{C}$HCH($CH_3)_2$); 64.81, 64.85 ($\underline{C}H_2$OP); 74.75, 75.47 ($\underline{C}HCH_2$OP); 75.81, 75.89, 76.00, 76.07 (C(O)$\underline{C}$HCH); 110.50, 110.56 ($\underline{C}(CH_3)_2$); 119.92, 119.95, 120.00, 120.04 (Ar$\underline{C}$H); 130.07 (Ar$\underline{C}$H); 134.56 (Ar$\underline{C}$-CH_3); 148.43, 148.48 (Ar$\underline{C}$-OP); 166.04 (HN$\underline{C}$(O)CH); 174.47, 174.50 ($\underline{C}O_2$Me). ^{31}PNMR (121 MHz, $CDCl_3$) δ: 3.72, 3.65. LCMS (ES+): m/z 475.19 ([M+H]$^+$, 100%); Rt 3.2 min; HRMS: Found 475.1849; $C_{20}H_{32}N_2O_9P$ [M+H$^+$] requires 475.1840.

(15l) 2,3-*O*-isopropylidene erythronocarboxamide-4-[(4-methyl)phenyl (ethoxyvalinyl)phosphoramidate]

The title compound was prepared following the general procedure D from **14l** (61 mg, 0.095 mmol), TFA (30 μl) and DCM (2 ml). Purified by preparative HPLC. White foam, 31 mg (66%).

^{1}HNMR (500 MHz, $CDCl_3$) δ: 0.6-0.97 (m, 6H, CH(C*H*$_3$)$_2$); 1.28 (q, 3H, *J*=7.15 Hz, C*H*$_3$CH$_2$O); 1.38 (d, 3H, *J*=3.90 Hz, C(C*H*$_3$)$_2$); 1.53 (d, 3H, *J*=2.41 Hz, C(C*H*$_3$)$_2$); 2.05-2.11 (m, 1H, C*H*(CH$_3$)$_2$); 2.32 (d, 3H, *J*=4.61 Hz, Ar-C*H*$_3$); 3.77-3.83 (m, 1H, NHC*H*CH); 3.89-3.93 (m, 1H, CH*H*OP); 4.13-4.41 (m, 4H, OC*H*$_2$CH$_3$ + C*H*HOP + N*H*); 4.57-4.62 (m, 1H, C*H*CH$_2$OP); 4.78 (dd, 1H, J_1=1.89 Hz, J_2=7.44, C(O)C*H*CH); 7.11 (d, 4H, *J*=5.61 Hz, Ar*H*); 8.90 (bs, 1H, ON*H*). ^{13}CNMR (125 MHz, $CDCl_3$) δ: 14.16 (OCH$_2$*C*H$_3$); 17.12, 18.94 (CH(*C*H$_3$)$_2$); 20.75 (Ar-*C*H$_3$); 24.48, 26.33, 26.62 (C(*C*H$_3$)$_2$); 32.09, 32,16, 32.21 (*C*H(CH$_3$)$_2$); 59.72, 59.92 (NH*C*HCH); 61.49, 61.64 (O*C*H$_2$CH$_3$); 64.72, 65.42 (*C*H$_2$OP); 74.78, 75.58 (*C*HCH$_2$OP); 75.89, 76.03 (C(O)*C*HCH); 110.46, 110.57 (*C*(CH$_3$)$_2$); 119.93, 119.97, 120.00, 120.04 (Ar*C*H); 130.07 (Ar*C*H); 134.56 (Ar*C*-CH$_3$); 145.44 (Ar*C*-OP); 165.95, 166.01 (HN*C*(O)CH), 174.13 (*C*O$_2$Et). ^{31}PNMR (121 MHz, $CDCl_3$) δ: 3.79, 3.76. LCMS (ES+): m/z 489.24 ([M+H]$^+$, 100%); Rt 3.2 min., (purity 92.6% by UV trace); HRMS: Found 489.1977; $C_{21}H_{34}N_2O_9P$ [M+H$^+$] requires 489.1996.

(15m) 2,3-*O*-isopropylidene erythronocarboxamide-4-[(4-methoxy)phenyl (methoxyalaninyl)phosphoramidate]

The title compound was synthesised according to the general procedure D from **14m** (100 mg, 0.16 mmol), TFA (40 μl) and DCM (5 ml). Orange foam, 38 mg (50%). ^{1}NMR (500 MHz, $CDCl_3$) δ: 1.25-1.31 (m, 6H, CHC*H*$_3$ + 1 of C(C*H*$_3$)$_2$); 1.44 (d, 3H, *J*=9.13 Hz, 1 of C(C*H*$_3$)$_2$); 3.65 (d, 3H, *J*=4.01 Hz, OC*H*$_3$); 3.69 (d, 3H, *J*=1.07 Hz, OC*H*$_3$); 3.89-3.97 (m, 1H, NHC*H*CH$_3$); 3.99-4.05 (m, 1H; CH*H*OP); 4.07-4.11 (m, 0.5H, PN*H*); 4.15 -4.22 (m, 1H, C*H*HOP); 4.48-4.54 (m, 1H, C*H*CH$_2$OP); 4.68 (t, 1H, *J*=7.4 Hz, C(O)C*H*CH); 6.74-6.76 (m, 2H, Ar*H*); 7.04-7.08 (m, 2H, Ar*H*); 8.38 (bs, 1H, O*H*); 8.97, 9.07 (2s, 1H, ON*H*). ^{13}CNMR (125 MHz, $CDCl_3$) δ: 20.91, 20.93, 20.65, 20.96 (CH*C*H$_3$); 24.54, 24.59, 26.42, 26.68 (C(*C*H$_3$)$_2$); 50.06, 50.24, 50.25 (NH*C*HCH$_3$); 52.60, 52.65 (CO$_2$*C*H$_3$); 55.61 (Ar-O*C*H$_3$); 64.92, 64.96, 65.35, 65.39 (CH*C*H$_2$OP); 74.80, 75.38 (*C*HCH$_2$OP); 75.79,75.87, 75.98, 76.05 (C(O)*C*HCH); 110.59, 110.62 (*C*(CH$_3$)$_2$); 114.57 (Ar*C*H); 121.09, 121.13, 121.23, 121.26 (Ar*C*H); 144.02, 144.08, 144.12, 144.18 (Ar*C*-OP); 156.66, 156.70 (Ar*C*-OCH$_3$); 165.90, 165.94 (HN*C*(O)); 174.24, 174.29, 174.94, 174.99 (*C*O$_2$Me). ^{31}PNMR (121 MHz, $CDCl_3$) δ: 3.17, 3.02. LCMS (ES+): m/z 463.18 ([M+H]$^+$, 100%); Rt 2.9 min., (purity 97.2% by UV trace); HRMS: Found 463.1476; $C_{18}H_{28}N_2O_9P$ [M+H$^+$] requires 463.1476.

(15n) 2,3-*O*-isopropylidene erythronocarboxamide-4-[(4-methoxy)phenyl (ethoxylvalinyl)phosphoramidate]

The title compound was synthesised according to the general procedure D using using [*N*-(2,4-dimethoxybezyloxy)-2,3-*O*-isopropylidene erythronocarboxamide] [(4-methoxyphenyl) methoxy-alinyl)]phosphate (40 mg, 0.06 mmol), TFA (30 μl) and DCM (3 ml). Slightly orange foam, 14 mg (37%). ^{1}NMR (500 MHz, $CDCl_3$) δ: 0.77-0.82 (m, 6H, CH(C*H*$_3$)$_2$), 1.16-1.23 (m, 3H, CH$_2$C*H*$_3$), 1.29 (s, 3H, 1 of O$_2$C(C*H*$_3$)$_2$), 1.44 (s, 3H, 1 of O$_2$C(C*H*$_3$)$_2$), 1.96-2.01 (m, 1H, C*H*(CH$_3$)$_2$), 3.74 (s, 3H, OC*H*$_3$), 3.75-3.83 (m, 2H, NHC*H*CO$_2$Et + CH*H*OP), 4.04-4.31 (m, 4H, C*H*$_2$CH$_3$ + C*H*HOP + N*H*), 4.48-4.53 (m, 1H, CHC*H*CH$_2$OP), 4.67-4.70 (m, 1H, C*H*CHCH$_2$OP), 6.73-6.76 (m, 2H, Ar*H*), 7.06-7.08 (m, 2H, Ar*H*), 8.85, 8.85 (2 sb, 1H, ON*H*CO). ^{13}CNMR (125 MHz, $CDCl_3$) δ: 14.16 (CH$_2$*C*H$_3$), 17.10, 17.15 (CH(*C*H$_3$)$_2$), 18.94 (CH(*C*H$_3$)$_2$), 24.48 (O$_2$C(*C*H$_3$)$_2$), 26.36, 26.63 (O$_2$C(*C*H$_3$)$_2$), 32.07, 32.18 (*C*H(CH$_3$)$_2$), 55.63 (O*C*H$_3$), 59.73, 59.93 (NH*C*HCO$_2$Et), 61.49, 61.63 (O*C*H$_2$CH$_3$), 64.73, 64.78, 65.40, 65.45 (CH*C*H$_2$OP), 74.77, 75.56 (*C*HCH$_2$OP), 75.81, 75.90 (*C*HCHCH$_2$OP), 110.47, 110.58 (O$_2$*C*(CH$_3$)$_2$), 114.54 (Ar*C*H), 121.16, 121.20, 121.23 (Ar*C*H), 144.25 (Ar*C*-OP), 156.66 (Ar*C*-OCH$_3$), 166.02 (HN*C*OCH), 174.10,

174.14 (CO_2Et). ^{31}PNMR (121 MHz, $CDCl_3$) δ: 3.92, 4.07. LCMS (ES+): m/z 505.21 ([M+H]$^+$, 100%); Rt 3.9 min. Purity 80% UV trace; HRMS: Found 505.1961; $C_{21}H_{34}N_2O_9P$ [M+H$^+$] requires 505.1946.

(15o) 2,3-*O*-isopropylidene erythronocarboxamide-4-[(2,3-dimethyl)phenyl (methoxyalaninyl)phosphate]

The title compound was synthesised according to the general procedure D from **14o** (28 mg, 0.046 mmol), TFA (10 μl) and DCM (2 ml). Yellowish very hygroscopic foam, 16 mg (75%). ^{1}NMR (500 MHz, $CDCl_3$) δ: 1.19-1.29 (m, 6H, CHC*H*$_3$ + 1 of C(C*H*$_3$)$_2$); 1.39, 1.44 (2s, 3H, 1 of C(C*H*$_3$)$_2$); 2.08 (s, 3H, Ar-C*H*$_3$); 2.18 (d, 3H, *J*=6.09 Hz, 1 of Ar-C*H*$_3$); 3.60-3.65 (2s, 3H, CO_2C*H*$_3$); 3.79-4.20 (m, 4H, C*H*$_2$OP + C*H*CH_3 + PN*H*); 4.35-4.49 (m, 1H, C*H*CH_2O_P); 4.68 (d, 1H, *J*=7.35 Hz, C(O)C*H*); 6.85-6.87 (m, 1H, Ar*H*); 6.93 (t, 1H, *J*=7.7 hz, Ar*H*); 7.13 (dd, 1H, J_1=7.5 Hz, J_2=20.8 Hz, Ar*H*); 8.96, 9.55 (2bs, 1H, N*H*). ^{13}CNMR (125 MHz, $CDCl_3$) δ: 12.30, 12.42 (Ar-*C*H_3); 20.15 (Ar-*C*H_3); 20.61, 20.78 (CH*C*H_3); 24.12, 24.43, 26.08, 26.32 (C(*C*H_3)$_2$); 49.93, 50.19 (*C*HCH_3); 52.55, 52.60 (CO_2*C*H_3); 64.72, 65.19 (*C*H_2OP); 74.28, 74.89 (*C*HCH_2OP); 75.76, 75.99 (C(O)*C*HCH); 110.35, 110.54 (*C*(CH$_3$)$_2$); 117.12, 117.54 (Ar*C*-CH_3); 125.96, 126.23, 126.38, 126.50 (Ar*C*H); 138.64 (Ar*C*-CH_3); 148.85, 148.87 (Ar*C*-OP); 166.23, 166.36 (HN*C*(O)); 174.01, 174.05 (*C*O_2Me). ^{31}PNMR (121 MHz, $CDCl_3$) δ: 1.87. LCMS (ES+): m/z 461.17 ([M+H]$^+$, 100%); Rt 3.2 min., (purity 93% by UV); HRMS: Found 461.1697; $C_{19}H_{30}N_2O_9P$ [M+H$^+$] requires 461.1683.

(15p) 2,3-*O*-isopropylidene erythronocarboxamide-4-[(2,3-dimethyl)phenyl (ethoxyvalinyl)phosphoramidate]

The title compound was synthesised according to the general procedure D from intermediate **14p** (131 mg, 0.20 mmol), TFA (50 μl) and DCM (5 ml). Slightly orange hygroscopic foam, 60 mg (59%). ^{1}NMR (500 MHz, $CDCl_3$) δ: 0.77-0.87 (m, 6H, CH(C*H*$_3$)$_2$); 1.17 (dt, 3H, J_1=1.73 Hz, J_2=7.14 Hz, OCH_2C*H*$_3$); 1.28 (d, 3H, *J*=1.21 Hz, 1 of C(C*H*$_3$)$_2$); 1.43 (d, 3H, *J*=13.99 Hz, 1 of C(C*H*$_3$)$_2$); 1.97-2.03 (m, 1H, C*H*(CH$_3$)$_2$); 2.11 (d, 3H, *J*=9.08 Hz, 1 of Ar-C*H*$_3$); 2.18 (d, 3H, *J*=1.99 Hz, Ar-C*H*$_3$); 3.68-3.82 (m, 1H, NHC*H*); 3.89-4.42 (m, 5H, OC*H*$_2$$CH_3$ + C*H*$_2$OP +N*H*); 4.47-4.51 (m, 1H, C*H*CH_2OP); 4.67 (dd, 1H, J_1=7.63 Hz, J_2=9.81 Hz, C(O)C*H*); 6.87 (t, 1H, *J*=6.0 Hz, Ar*H*); 6.91-6.96 (m, 1H, Ar*H*); 7.11 (t, 1H, *J*=7.3 Hz, Ar*H*); 9.04, 9.09(2bs, 1H, ON*H*). ^{13}CNMR (125 MHz, $CDCl_3$) δ: 12.44, 12.51 (Ar-*C*H_3); 14.14, 14.16 (OCH_2*C*H_3); 17.17, 17.20, 18.84, 18.91 (CH(*C*H_3)$_2$); 20.17 (Ar-*C*H_3); 24.45, 24.53, 26.35, 26.55 (C(*C*H_3)$_2$); 31.97, 32.02, 32.21, 32.26 (*C*H(CH$_3$)$_2$); 59.72, 59.98 (NH*C*H); 61.44, 61.53 (OH_2CH_3); 64.82, 64.87, 65.52, 65.56 (*C*H_2OP); 74.65, 75.40 (*C*HCH_2OP); 72.82, 75.90, 76.02, 76.09 (C(O)*C*H); 110.52, 110.55 (*C*(CH$_3$)$_2$); 117.40, 117.53, 117.55 (Ar*C*H); 125.94, 126.00, 126.31, 126.34 (Ar*C*H); 127.67, 127.72, 127.87, 127.92 (Ar*C*-CH_3); 138.61, 138.64 (Ar*C*-CH_3); 148.95, 149.01, 149.07 (Ar*C*-OP); 166.27 (HN*C*(O)); 173.05, 173.08, 173.90, 173.93 (*C*O_2Et). ^{31}PNMR (121 MHz, $CDCl_3$) δ: 3.72, 3.61. ^{31}PNMR (121 MHz, $CDCl_3$) δ: 3.99, 3.26. LCMS (ES+): m/z 503.23 ([M+H]$^+$, 100%); Rt 3.4 min., (purity >90% by UV trace); HRMS: Found 503.2146; $C_{22}H_{26}N_2O_9P$ [M+H$^+$] requires 503.2153.

(15q) 2,3-*O*-isopropylidene erythronocarboxamide-4-[(2,3-dimethyl)phenyl (*tert*-butoxyvalinyl)phosphoramidate]

The title compound was synthesised according to the general procedure D from **14q** (73 mg, 0.11 mmol), TFA (40 μl) and DCM (4 ml). Slightly orange foam, 35 mg (62%). ^{1}NMR (500 MHz, $CDCl_3$) δ: 0.85-1.01 (m, 6H, $CH(C\underline{H}_3)_2$), 1.37-1.56 (m, 15H, $C(C\underline{H}_3)_3$ + $O_2C(C\underline{H}_3)_2$), 2.03-2.05 (m, 1H, $C\underline{H}(CH_3)_2$), 2.20, 2.22 (2s, 3H, Ar-$C\underline{H}_3$), 2.27, 2.28 (2s, 3H, Ar-$C\underline{H}_3$), 3.73-3.90 (m, 2H, $HNC\underline{H}CO_2$ + $CH\underline{H}OP$), 4.29-4.45 (m, 2H, $N\underline{H}$ + $C\underline{H}HOP$), 4.59-4.60 (m, 1H, $CHC\underline{H}CH_2OP$), 4.78-4.79 (m, 1H, $C\underline{H}CH$), 6.94-6.98 (m, 1H, Ar$\underline{H}$), 7.00-7.07 (m, 1H, Ar$\underline{H}$), 7.17-7.18 (m, 1H, Ar$\underline{H}$), 8.84 (bs, 1H, HON$\underline{H}$). ^{13}CNMR (125 MHz, $CDCl_3$) δ: 12.52, 12,55 ($CH(\underline{C}H_3)_2$), 14.14 (Ar-$\underline{C}H_3$), 17.07, 17.16 ($CH(\underline{C}H_2)_3$), 20.17 (Ar-$\underline{C}H_3$), 24.50, 24.54 ($O_2C(\underline{C}H_3)_2$), 26.46, 26.62 ($O_2C(\underline{C}H_3)_2$), 27.99 ($C(\underline{C}H_3)_3$), 32.09, 32.14, 32.33, 32.38 ($\underline{C}H(CH_3)_2$), 60.04, 60.37 ($NH\underline{C}HCO$), 64.70, 64.75, 65.36, 65.42 ($CH\underline{C}H_2OP$), 74.73, 75.53 ($\underline{C}HCH_2OP$), 75.81, 75.90, 76.07, 76.14 ($\underline{C}HCHCH_2OP$), 82.21, 82.34 ($\underline{C}(CH_3)_3$), 110.48, 110.59 ($O_2\underline{C}(CH_3)_2$), 117.49, 117.60 (Ar$\underline{C}$H), 125.93, 125.96, 126.32 (Ar$\underline{C}$-CH_3), 127.80, 127.91, 127.96 (Ar$\underline{C}$H), 138.58, 138.64 (Ar$\underline{C}$-CH_3), 149.02, 149.07, 149.13 (Ar$\underline{C}$-OP), 166.04 ($NH\underline{C}O$), 173.09, 173.13 ($\underline{C}O_2{}^{t}Bu$). ^{31}PNMR (121 MHz, $CDCl_3$) δ: 4.07, 3.85. LCMS (ES+): m/z 531.22 ($[M+H]^+$, 100%); Rt 4.7 min. Purity >95% UV trace; HRMS: Found 531.2448; $C_{24}H_{40}N_2O_9P$ $[M+H^+]$ requires 531.2466.

References

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