Supporting Information for

Spacer optimization of new conjugates for a melanoma-selective delivery approach

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Experimental

Synthesis of the vinyl ethers precursors (11a-d).

2-[2-(vinyloxy)ethoxy]ethyl-4-toluenesulfonate (9). In a mortar, K_2CO_3 (11 g) was wet with diethyleneglycol monovinyl ether (3 g, 22.70 mmol) and TsCl (6.492 g, 34.05 mmol) was added and the mixture was grinded with a pestle for 10 minutes. KOH (3.184 g, 56.75 mmol) was added and the mixture was grinded with a mortar for 3 minutes. Et_2O (50 mL) was added and the mixture was filtered. The solid was rinsed with DCM (2 x 25 mL), the filtrates were combined and concentrated *in vacuo*. After column chromatography on silica gel (EtOAc-cyclohexane, 25-75, v-v) the pure product was obtained as a colourless fragrant oil (4.906 g, 75%). R_f 0.31 (EtOAc-cyclohexane, 25-75, v-v); ^{1}H NMR: δ2.45 (3H, s, ArC*H*$_3$), 3.64-3.79 (6H, m, OC*H*$_2$C*H*$_2$O, OC*H*$_2$CH$_2$OTs), 4.01 (1H, dd, *J* 7.1, 2.1, H *'trans'* to O), 4.15 (1H, dd, *J* 14.0, 2.1, H *'cis'* to O), 4.18 (2H, t, *J* 5.3, OCH$_2$C*H*$_2$OTs), 6.46 (1H, dd, *J* 14.0, 7.1, H$_2$C=C*H*), 7.34 (2H, d, *J* 8.2, 2 x Ar*H* *'o'* to CH$_3$), 7.80 (2H, d, *J* 8.2, 2 x Ar*H* *'m'* to CH$_3$); ^{13}C NMR: δ21.7 (Ar*C*H$_3$), 67.2 (O*C*H$_2$CH$_2$O), 68.8, 69.8 (OCH$_2$*C*H$_2$O, O*C*H$_2$CH$_2$OTs), 69.3 (OCH$_2$*C*H$_2$OTs), 86.9 (H$_2$*C*=CH), 128.1 (2 x Ar*C*H *'m'* to CH$_3$), 129.9 (2 x Ar*C*H *'o'* to CH$_3$), 133.0 (Ar*C*SO$_2$O), 144.9 (Ar*C*CH$_3$), 151.7 (H$_2$C=*C*H).

General procedure for the preparation of oligoethyleneglycol monobenzoates (10c-d)

To a solution of dry oligoethyleneglycol, DIPEA (1 equivalent) and DMAP (0.05 equivalents) in anhydrous DCM (10 mL / mmol) was added a solution of BzCl (0.6 equivalents) in anhydrous DCM (1.5 mL / mmol). The mixture was stirred for 16 h at rt, poured into DCM (12 mL / mmol) then washed with 2% aq. Na_2CO_3 (12 mL / mmol) and water (12 mL / mmol). The aqueous layers were combined and extracted with DCM (5 mL / mmol). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*.

2-{2-[2-(2-hydroxyethoxy)ethoxy]ethoxy}ethyl benzoate (10c). Prepared from tetraethylene glycol (10 g, 20.59 mmol). After column chromatography on silica gel (EtOAc-DCM-EtOH, 70-26-4, v-v-v)

the pure product was obtained as a colourless oil (3.115 g, 81%). R_f 0.28 (EtOAc-DCM-EtOH, 70-26-4, v-v-v); ^{1}H NMR: δ2.47 (1H, br s, O*H*), 3.57-3.75 (12H, m, HOC*H*$_2$C*H*$_2$O, 2 x OC*H*$_2$C*H*$_2$O), 3.84 (2H, t, *J* 5.2, OC*H*$_2$CH$_2$OBz), 4.49 (2H, t, *J* 5.2, OCH$_2$C*H*$_2$OBz), 7.39-7.48 (2H, m, 2 x Ar*H* *'m'* to COO), 7.52-7.60 (1H, m, Ar*H* *'p'* to COO), 8.03-8.10 (2H, m, 2 x Ar*H* *'o'* to COO); ^{13}C NMR: δ61.7 (HO*C*H$_2$CH$_2$O), 64.2 (OCH$_2$*C*H$_2$OBz), 69.3 (O*C*H$_2$CH$_2$OBz), 70.4-70.7 (2 x O*C*H$_2$*C*H$_2$O), 72.5 (HOCH$_2$*C*H$_2$O), 128.3 (2 x Ar*C*H *'m'* to COO), 129.7 (2 x Ar*C*H *'o'* to COO), 130.1 (Ar*C*COO), 133.0 (Ar*C*H *'p'* to COO), 166.6 (*C*OO).

23-hydroxy-3,6,9,12,15,18,21-heptaoxatricos-1-yl benzoate (10c). Prepared from octaethylene glycol (2.486 g, 6.71 mmol). After column chromatography on silica gel (DCM-EtOH, 93-7, v-v) the pure product was obtained as a colourless oil (1.477 g, 46%). R_f 0.32 (DCM-EtOH, 93-7, v-v); ^{1}H NMR: δ2.56 (1H, br s, O*H*), 3.58-3.72 (28H, m, HOC*H*$_2$C*H*$_2$O, 6 x OC*H*$_2$C*H*$_2$O), 3.83 (2H, t, *J* 5.2, OC*H*$_2$CH$_2$OBz), 4.47 (2H, t, *J* 5.2, OCH$_2$C*H*$_2$OBz), 7.39-7.47 (2H, m, 2 x Ar*H* *'m'* to COO), 7.52-7.60 (1H, m, Ar*H* *'p'* to COO), 8.03-8.08 (2H, m, 2 x Ar*H* *'o'* to COO); ^{13}C NMR: δ61.6 (HO*C*H$_2$CH$_2$O), 64.1 (OCH$_2$*C*H$_2$OBz), 69.2 (O*C*H$_2$CH$_2$OBz), 70.3-70.6 (2 x O*C*H$_2$*C*H$_2$O), 72.5 (HOCH$_2$*C*H$_2$O), 128.3 (2 x Ar*C*H *'m'* to COO), 129.6 (2 x Ar*C*H *'o'* to COO), 130.1 (Ar*C*COO), 133.0 (Ar*C*H *'p'* to COO), 166.5 (*C*OO).

2-(vinyloxy)ethyl acetate (11a). To a solution of ethyleneglycol monovinyl ether (2 g, 22.70 mmol), pyridine (2.75 mL, 34.05 mmol) and DMAP (0.277 g, 3.27 mmol) in anhydrous DCM (60 mL) was added Ac$_2$O (3.2 mL, 34.05 mmol). The mixture was stirred for 1 h 30 at rt then poured into a mixture of water (100 mL) and sat. aq. NaHCO$_3$ (100 mL) which was extracted with DCM (40 mL then 2 x 100 mL). The organic layers were combined, dried over MgSO$_4$ and concentrated *in vacuo*. After column chromatography on silica gel (EtOAc-cyclohexane, 10-90, v-v) the pure product (**11a**) was obtained as a colourless oil (2.658 g, 90%). R_f 0.28 (EtOAc-cyclohexane, 10-90, v-v); ^{1}H NMR: δ11.40 (3H, s, OCOC*H*$_3$), 3.88 (2H, t, *J* 5.2, OC*H*$_2$CH$_2$OCO), 4.05 (1H, dd, *J* 7.2, 2.0, H *'trans'* to O), 4.20 (1H, dd, *J* 14.1, 2.0, H *'cis'* to O), 4.31 (2H, t, *J* 5.2, OCH$_2$C*H*$_2$OCO), 6.49 (1H, dd, *J* 14.1, 7.2, H$_2$C=C*H*); ^{13}C

NMR: δ 20.9 (CH_3), 62.7 (OCH_2CH_2OCO), 65.8 (OCH_2CH_2OCO), 87.1 (H_2C=CH), 151.4 (H_2C=CH), 170.9 ($OCOCH_3$).

2-[(1-méthyl)vinyloxy]ethyl benzoate (11b). This compound was prepared according to the literature procedure.[17]

General procedure for the preparation of compounds (11c-d)

To a solution of the relevant oligoethyleneglycol monobenzoate (**10c-d**) in anhydrous THF (20 mL / mmol) was added NaH (60% in mineral oil, 2 equivalents) and the mixture was stirred for 45 minutes at rt and a solution of the sulfonate (**9**) (1.3 equivalents) in anhydrous THF (4 mL / mmol) was added and the mixture was stirred for 20 h at reflux then poured into DCM (70 mL / mmol) and washed with water (2 x 30 mL / mmol). The combined aqueous layers were extracted with DCM (15 mL / mmol), the organic layers were combined and washed with brine (2 x 30 mL / mmol), dried over $MgSO_4$ and concentrated *in vacuo*.

3,6,9,12,15,18-hexaoxaicos-19-en-1-yl benzoate (11c). Prepared from 2-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy)ethyl benzoate (2.233 g, 7.49 mmol). After column chromatography on silica gel (DCM-EtOH, 96-4, v-v) the pure product (**11c**) and its free alcohol analogue were obtained as colourless fragrant oils (1.203 g, 39% and 1.304 g, 56%). The latter was converted into (**11c**) with a quantitative benzoylation, leading to a combined yield of 95%. R_f 0.31 (DCM-EtOH, 96-4, v-v); ^{1}H NMR: δ 3.61-3.86 (22H, m, 5 x OCH_2CH_2O, OCH_2CH_2OBz), 4.00 (1H, dd, *J* 7.2, 2.1, H *'trans'* to O), 4.17 (1H, dd, *J* 14.2, 2.1, H *'cis'* to O), 4.47 (2H, t, *J* 5.2, OCH_2CH_2OTs), 6.49 (1H, dd, *J* 14.2, 7.2, H_2C=CH), 7.39-7.48 (2H, m, 2 x ArH *'m'* to COO), 7.52-7.61 (1H, m, ArH *'p'* to COO), 8.03-8.09 (2H, m, 2 x ArH *'o'* to COO);); ^{13}C NMR: δ 64.2 (OCH_2CH_2OBz), 67.2 (H_2C=$CHOCH_2CH_2O$), 69.2, 69.6 (H_2C=$CHOCH_2CH_2O$, OCH_2CH_2OBz), 70.6-70.7 (5 x OCH_2CH_2), 86.6 (H_2C=CH), 128.4 (2 x ArCH *'m'* to COO), 129.7 (2 x ArCH *'o'* to COO), 130.1 (ArCCOO), 133.0 (ArCH *'p'* to COO), 151.8 (H_2C=CH), 166.5 (ArCOO).

3,6,9,12,15,18,21,24,27,30-decaoxadotriacont-31-en-1-yl benzoate (11d). Prepared from 23-hydroxy-3,6,9,12,15,18,21-heptaoxatricos-1-yl benzoate (1.477 g, 3.11 mmol). After column chromatography on silica gel (DCM-EtOH, 93-7, v-v) the pure product (**11d**) and its free alcohol analogue were obtained as colourless fragrant oils (0.260 g, 14% and 0.318 g, 21%). The latter was converted into (**9d**) with a quantitative benzoylation, leading to a combined yield of 35%. R_f 0.29 (DCM-EtOH, 93-7, v-v); ^{1}H NMR: δ3.62-3.86 (38H, m, 9 x OC*H*$_2$C*H*$_2$O, OC*H*$_2$CH$_2$OBz), 3.94 (1H, dd, *J* 7.2, 2.1, H *'trans'* to O), 4.18 (1H, dd, *J* 14.2, 2.1, H *'cis'* to O), 4.48 (2H, t, *J* 5.2, OCH$_2$C*H*$_2$OTs), 6.50 (1H, dd, *J* 14.2, 7.2, H$_2$C=C*H*), 7.39-7.47 (2H, m, 2 x Ar*H* *'m'* to COO), 7.51-7.60 (1H, m, Ar*H* *'p'* to COO), 8.03-8.07 (2H, m, 2 x Ar*H* *'o'* to COO);); ^{13}C NMR: δ64.1 (OCH$_2$*C*H$_2$OBz), 67.2 (H$_2$C=CHO*C*H$_2$CH$_2$O), 69.2, 69.6 (H$_2$C=CHOCH$_2$*C*H$_2$O, O*C*H$_2$CH$_2$OBz), 70.6-70.7 (5 x O*C*H$_2$*C*H$_2$), 86.2 (H$_2$*C*=CH), 128.3 (2 x Ar*C*H *'m'* to COO), 129.7 (2 x Ar*C*H *'o'* to COO), 130.1 (Ar*C*COO), 133.0 (Ar*C*H *'p'* to COO), 157.7 (H$_2$C=*C*H), 166.5 (Ar*C*OO).

General procedure for the preparation of compounds (12a-d)

To a solution of (**6**) and camphorsulfonic acid (0.04 equivalents) in anhydrous THF (10 mL / mmol) was added a solution of the corresponding vinyl ether (**9a-d**) in anhydrous THF (5 mL / mmol). The mixture was stirred for different time for different times at rt then poured into a mixture of water (30 mL / mmol (**6**)) and sat. aq. NaHCO$_3$ (15 mL / mmol (**6**)) which was extracted with DCM (3 x 15 mL / mmol). The organic layers were combined, dried over MgSO$_4$ and concentrated *in vacuo*.

3'-*O*-{1-[2-(acetyloxy)ethoxy]ethyl}-5-iodo-5'-*O*-triisopropylsilyl-2'-deoxyuridine (12a). Prepared from (**6**) (1.5 g, 2.94 mmol) and vinyl ether (**11a**) (1.147 g, 8.82 mmol). Reaction time: 5 h. After column chromatography on silica gel (EtOAc-cyclohexane, 35-65, v-v) the pure product (**12a**) was obtained as a white solid (1.859 g, 99%). Mp 96-98 °C; R_f 0.24 (EtOAc-cyclohexane, 35-65, v-v); ^{1}H NMR: δ1.09-1.29 (21H, m, 3 x ^{i}Pr), 1.35 (3H, d, *J* 5.0, O[CHC*H*$_3$]O), 2.03-2.13 (4H, m, H-2', OCOC*H*$_3$), 2.43-2.54 (1H, m, H-2'), 3.61-3.92 (4H, m, H-5', OC*H*$_2$CH$_2$OCO), 3.96-4.25 (3H, m, H-4',

OCH_2CH_2OCO), 4.44-4.51 (1H, m, H-3'), 4.85 (1H, q, *J* = 5.0, O[C*H*CH_3]O), 6.18-6.25 (1H, m, H-1'), 8.04 (1H, s, H-6), 8.36 (1H, br s, N*H*); ^{13}C NMR: δ 12.0 (Si[*C*H(CH_3)$_2$]$_3$), 18.2 (Si[CH(*C*H_3)$_2$]$_3$), 20.0 (O[CH*C*H_3]O), 41.0 (C-2'), 62.2, 63.5, 63.7 (C-5', O*C*H_2*C*H_2OCO), 68.7 (C-5), 74.9 (C-3'), 85.7 (C-1'), 86.2 ($C_{4'}$), 99.2 (O[*C*HCH$_3$]O), 144.1 (C-6), 150.1 (C-2 *C*=O), 160.1 (C-4 *C*=O), 171.0 (O*C*OCH$_3$); *m/z* (ESI) 639.05 [M - H]$^-$.

3'-*O*-(1-(2-(benzoyloxy)ethoxy)-1-méthylethyl)-5-iodo-5'-*O*-triisopropylsilyl-2'-deoxyuridine (12b). Prepared from (**6**) (1.5 g, 2.94 mmol) and vinyl ether (**11b**) (1.818 g, 8.82 mmol). Reaction time: 4 h. After column chromatography on silica gel (EtOAc-cyclohexane, 35-65, v-v) the pure product (**10a**) was obtained as a white foam (0.851 g, 40%). R_f 0.31 (EtOAc-cyclohexane, 35-65, v-v); ^{1}H NMR: δ 1.03-1.25 (21H, m, 3 x ^{i}Pr), 1.37 (6H, s, O[C(C*H*$_3$)$_2$]O), 2.00-2.08 (1H, m, H-2'), 2.38-2.48 (1H, m, H-2'), 3.73-3.86 (4H, m, H-5', OC*H*$_2$CH$_2$OCO), 4.06-4.08 (1H, m, H-4'), 4.40-4.53 (3H, m, H-3', OCH_2CH_2OCO), 6.21 (dd, 1H, *J* 7.8, 5.1, H-1'), 7.35-7.42 (2H, m, 2 x Ar*H* *'m'* to COO), 7.49-7.53 (1H, m, Ar*H* *'p'* to COO), 7.94 (1H, s, H-6), 7.97-8.01 (2H, m, 2 x Ar*H* *'o'* to COO), 9.81 (1H, br s, N*H*); ^{13}C NMR: δ 11.9 (Si[*C*H(CH_3)$_2$]$_3$), 18.1 (Si[CH(*C*H_3)$_2$]$_3$), 25.4-25.7 (O[C(*C*H_3)$_2$]O, 40.5 (C-2'), 59.6 (O*C*H_2CH$_2$OCO), 63.4 (C-5'), 64.2 (OCH_2*C*H_2OCO), 68.7 (C-5), 71.1 (C-3'), 85.8 (C-1'), 87.0 (C-4'), 101.2 (O[*C*(CH_3)$_2$]O), 128.4 (2 x Ar*C*H *'m'* to COO), 129.6 (2 x Ar*C*H *'o'* to COO), 130.0 (Ar*C*COO), 133.1 (Ar*C*H *'p'* to COO), 144.1 (C-6), 150.2 (C-2 *C*=O), 160.2 (C-4 *C*=O), 166.5 (O*C*OPh).

5-iodo-3'-*O*-(1-methyl-21-oxo-21-phenyl-2,5,8,11,14,17,20-heptaoxahenicos-1-yl)-5'-*O*-triisopropylsilyl-2'-deoxyuridine (12c). Prepared from (**6**) (1.411 g, 2.92 mmol) and vinyl ether (**11c**) (1.710 g, 4.15 mmol). Reaction time: 18 h. After column chromatography on silica gel (EtOAc-DCM, 65-35, v-v) the pure product (**12c**) was obtained as a light yellow oil (2.358 g, 92%). R_f 0.27 (EtOAc-DCM, 65-35, v-v); ^{1}H NMR: δ 1.06-1.25 (21H, m, 3 x ^{i}Pr), 1.32 (3H, d, *J* 5.0, O[CHC*H*$_3$]O), 1.91-2.16 (1H, m, H-2'), 2.38-2.55 (1H, m, H-2'), 3.55-3.74 (20H, m, 5 x OC*H*$_2$C*H*$_2$O), 3.83 (2H, t, *J* 5.2, OC*H*$_2$CH$_2$OCOPh), 3.83-4.14 (3H, m, H-4', H-5'), 4.39-4.45 (1H, m, H-3'), 4.47 (2H, t, *J* 5.2,

OCH_2CH_2OCOPh), 4.82 (1H, q, *J* = 5.0, O[C*H*CH_3]O), 6.20 (dd, 1H, *J* 8.1, 5.7, H-1'), 7.38-7.47 (2H, m, 2 x Ar*H* *'m'* to COO), 7.51-7.60 (1H, m, Ar*H* *'p'* to COO), 8.01-8.08 (3H, m, H-6, 2 x Ar*H* *'p'* to COO), 8.74 (1H, br s, N*H*); ^{13}C NMR: δ 11.9 (Si[*C*H(CH_3)$_2$]$_3$), 18.1 (Si[CH(*C*H_3)$_2$]$_3$), 20.0 (O[CH*C*H_3]O), 39.2 (C-2'), 63.3 (C-5'), 63.7 (O[CHCH$_3$]O*C*H_2), 64.2 (OCH_2CH_2OCOPh), 68.6 (C-5), 69.2 (OCH_2CH_2OCOPh), 70.5-70.7 (O[CHCH$_3$]OCH_2*C*H_2, 4 x O*C*H_2*C*H_2O), 74.7 (C-3'), 85.6 (C-1'), 86.0 (C-4'), 99.3 (O[*C*HCH$_3$]O), 128.3 (2 x Ar*C*H *'m'* to COO), 129.7 (2 x Ar*C*H *'o'* to COO), 130.1 (Ar*C*COO), 133.0 (Ar*C*H *'p'* to COO), 144.0 (C-6), 150.0 (C-2 *C*=O), 160.1 (C-4 *C*=O), 166.5 (O*C*OPh).

5-iodo-3'-*O*-(1-methyl-33-oxo-33-phényl-2,5,8,11,14,17,20,23,26,29,32-undecaoxadotritriacont-1-yl)-5'-*O*-triisopropylsilyl-2'-deoxyuridine (12d). Prepared from (**6**) (0.500 g, 0.98 mmol) and vinyl ether (**11d**) (0.633 g, 1.08 mmol). Reaction time: 20 h. After column chromatography on silica gel (EtOAc-DCM-EtOH, 80-20-5, v-v-v) the pure product (**12d**) was obtained as a light yellow oil (0.595 g, 55%). R_f 0.31 (EtOAc-DCM-EtOH, 80-20-5, v-v-v); ^{1}H NMR: δ 1.08-1.29 (21H, m, 3 x ^{i}Pr), 1.31 (3H, d, *J* 5.0, O[CHC*H*$_3$]O), 1.92-2.17 (1H, m, H-2'), 2.39-2.56 (1H, m, H-2'), 3.53-3.79 (36H, m, 9 x O*C*H_2*C*H_2O), 3.81-4.14 (5H, m, H-4', H-5', O*C*H_2CH$_2$OCOPh), 4.47 (2H, t, *J* 5.3, OCH_2CH_2OCOPh), 4.83 (1H, q, *J* 5.0, O[C*H*CH_3]O), 6.20 (dd, 1H, *J* 8.0, 5.8, H-1'), 7.36-7.49 (2H, m, 2 x Ar*H* *'m'* to COO), 7.52-7.60 (1H, m, Ar*H* *'p'* to COO), 8.02-8.09 (3H, m, H-6, 2H, m, 2 x Ar*H* *'o'* to COO), 8.61 (1H, br s, N*H*); ^{13}C NMR: δ 11.9 (Si[*C*H(CH_3)$_2$]$_3$), 18.2 (Si[CH(*C*H_3)$_2$]$_3$), 20.0 (O[CH*C*H_3]O), 39.6 (C-2'), 63.3 (C-5'), 63.7 (O[CHCH$_3$]O*C*H_2), 64.2 (OCH_2CH_2OCOPh), 68.6 (C-5), 69.2 (OCH_2CH_2OCOPh), 70.5-70.7 (O[CHCH$_3$]OCH_2*C*H_2, 8 x O*C*H_2*C*H_2O), 74.8 (C-3'), 85.7 (C-1'), 86.0 (C-4'), 99.4 (O[*C*HCH$_3$]O), 128.4 (2 x Ar*C*H *'m'* to COO), 129.6 (2 x Ar*C*H *'o'* to COO), 130.1 (Ar*C*COO), 133.0 (Ar*C*H *'p'* to COO), 144.1 (C-6), 150.1 (C-2 *C*=O), 160.0 (C-4 *C*=O), 166.6 (O*C*OPh).

General procedure for the preparation of compounds (13a-d)

To a solution of (**12a-d**) in anhydrous EtOH (20 mL / mmol) was added LiOH (1.5 equivalents). The mixture was stirred for different times at rt then poured into a mixture of 5% aq. Na_2CO_3 (80 mL / mmol) and sat. aq. NaCl (30 mL / mmol) which was extracted with DCM (4 x 30 mL / mmol). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*.

3'-*O*-[1-(2-hydroxyethoxy)ethyl]-5-iodo-5'-*O*-triisopropylsilyl-2'-deoxyuridine (13a). Prepared from (**12a**) (1.959 g, 2.94 mmol). Reaction time: 1 h. After column chromatography on silica gel (EtOAc-cyclohexane, 80-20, v-v) the pure product (**11a**) was obtained as a colourless caramel (1.630 g, 93%). R_f 0.29 (EtOAc-cyclohexane, 80-20, v-v); ^{1}H NMR: δ 1.06-1.19 (21H, m, 3 x ^{i}Pr), 1.37 (3H, d, *J* 5.0, O[CHC*H*$_3$]O), 1.93-2.13 (2H, H-2', O*H*), 2.43-2.63 (1H, m, H-2'), 3.52-3.76 (2H, m, OC*H*$_2$CH$_2$OCO), 3.71-3.75 (2H, m, OCH$_2$C*H*$_2$OCO), 3.82-3.98 (2H, m, H-5'), 3.95-4.15 (1H, m, H-4'), 4.43-4.55 (1H, m, H-3'), 4.87 (1H, q, *J* = 5.0, O[C*H*CH$_3$]O), 6.18-6.25 (1H, m, H-1'), 8.04 (1H, s, H-6), 8.63 (1H, br s, N*H*); ^{13}C NMR: δ 12.0 (Si[*C*H(CH$_3$)$_2$]$_3$), 18.2 (Si[CH(*C*H$_3$)$_2$]$_3$), 20.1 (O[CH*C*H$_3$]O), 39.6 (C-2'), 61.9 (OCH$_2$*C*H$_2$OCO), 63.5 (C-5'), 66.0 (O*C*H$_2$CH$_2$OCO), 68.7 (C-5), 75.3 (C-3'), 86.1 (C-1'), 86.5 (C-4'), 99.4 (O[*C*HCH$_3$]O), 144.2 (C-6), 150.1 (C-2 *C*=O), 160.0 (C-4 *C*=O); *m/z* (ESI) 596.98 [M - H]$^-$.

3'-*O*-[1-(2-hydroxyethoxy)-1-methylethyl]-5-iodo-5'-*O*-triisopropylsilyl-2'-deoxyuridine (13b). Prepared from (**12b**) (0.851 g, 1.19 mmol). Reaction time: 4 h. After column chromatography on silica gel (EtOAc-cyclohexane, 70-30, v-v) the pure product (**11a**) was obtained as a white foam (0.632 g, 87%). R_f 0.31 (EtOAc-cyclohexane, 70-30, v-v); ^{1}H NMR: δ 1.09-1.29 (21H, m, 3 x ^{i}Pr), 1.39 (6H, s, O[C(C*H*$_3$)$_2$]O), 1.95 (1H, t, *J* 5.9, O*H*), 2.00-2.09 (1H, m, H-2'), 2.40-2.49 (1H, m, H-2'), 3.55 (2H, t, *J* 5.2, OC*H*$_2$CH$_2$OH), 3.68-3.76 (2H, m, OCH$_2$C*H*$_2$OH), 3.84-4.01 (2H, m, H-5'), 4.02-4.11 (1H, m, H-4'), 4.56 (1H, d, *J* 5.9, H-3'), 6.24 (dd, 1H, *J* 8.8, 4.9, H-1'), 8.06 (1H, s, H-6), 8.44 (1H, br s, N*H*); ^{13}C NMR: δ 12.0 (Si[*C*H(CH$_3$)$_2$]$_3$), 18.2 (Si[CH(*C*H$_3$)$_2$]$_3$), 25.7, 25.8 (O[C(*C*H$_3$)$_2$]O), 40.7 (C-2'), 62.1

(OCH_2CH_2OH), 62.6 (OCH_2CH_2OH), 63.7 (C-5'), 68.7 (C-5), 71.4 (C-3'), 86.1 (C-1'), 87.2 (C-4'), 101.2 ($O[C(CH_3)_2]O$), 144.3 (C-6), 150.2 (C-2 *C*=O), 160.1 (C-4 *C*=O).

3'-*O*-(19-hydroxy-1-methyl-2,5,8,11,14,17-hexaoxanonadec-1-yl)- 5-iodo-5'-*O*-triisopropylsilyl-2'-deoxyuridine (13c). Prepared from (**12c**) (1.477 g, 1.60 mmol). Reaction time: 3 h. After column chromatography on silica gel (DCM-EtOH, 92-8, v-v) the pure product (**11c**) was obtained as a colourless oil (1.294 g, 99%). R_f 0.32 (DCM-EtOH, 92-8, v-v); ^{1}H NMR: δ 1.07-1.28 (21H, m, 3 x ^{i}Pr), 1.31 (3H, d, *J* 5.0, $O[CHCH_3]O$), 1.93-2.19 (1H, m, H-2'), 2.41-2.60 (1H, m, H-2'), 2.78 (1H, t, *J* 5.7, O*H*), 3.60-3.73 (24H, m, 6 x OCH_2CH_2O), 3.83-3.97 (2H, m, H-5'), 3.99-4.14 (1H, m, H-4'), 4.38-4.52 (1H, m, H-3'), 4.82 (1H, q, *J* = 5.0, $O[CHCH_3]O$), 6.20 (dd, 1H, *J* 8.3, 5.7, H-1'), 8.04 (1H, s, H-6), 8.59 (1H, br s, N*H*); ^{13}C NMR: δ 11.9 ($Si[CH(CH_3)_2]_3$), 18.2 ($Si[CH(CH_3)_2]_3$), 20.0 ($O[CHCH_3]O$), 39.6 (C-2'), 61.7 ($O[CHCH_3]OCH_2$), 63.9 (C-5'), 68.7 (C-5), 70.3 (OCH_2CH_2OH), 70.5-70.7 ($O[CHCH_3]OCH_2CH_2$, 4 x OCH_2CH_2O), 72.6 (OCH_2CH_2OH), 74.8 (C-3'), 85.6 (C-1'), 86.1 (C-4'), 99.4 ($O[CHCH_3]O$), 144.1 (C-6), 150.0 (C-2 *C*=O), 160.2 (C-4 *C*=O).

3'-*O*-(31-hydroxy-1-methyl-2,5,8,11,14,17,20,23,26,29-decaoxahentriacont-1-yl)-5-iodo-5'-*O*-triisopropylsilyl-2'-deoxyuridine (13d). Prepared from (**12d**) (590 mg, 0.54 mmol). Reaction time: 3 h. After column chromatography on silica gel (DCM-EtOH, 90-10, v-v) the pure product (**11d**) was obtained as a colourless oil (0.423 g, 79%). R_f 0.29 (DCM-EtOH, 90-10, v-v); ^{1}H NMR: δ 1.05-1.26 (21H, m, 3 x ^{i}Pr), 1.32 (3H, d, *J* 5.0, $O[CHCH_3]O$), 1.92-2.17 (1H, m, H-2'), 2.40-2.58 (1H, m, H-2'), 2.52 (1H, t, *J* 5.7, O*H*), 3.60-3.73 (40H, m, 10 x OCH_2CH_2O), 3.81-3.95 (2H, m, H-5'), 3.97-4.16 (1H, m, H-4'), 4.34-4.50 (1H, m, H-3'), 4.84 (1H, q, *J* = 5.0, $O[CHCH_3]O$), 6.21 (dd, 1H, *J* 8.3, 5.7, H-1'), 8.03 (1H, s, H-6), 8.75 (1H, br s, N*H*); ^{13}C NMR: δ 11.9 ($Si[CH(CH_3)_2]_3$), 18.2 ($Si[CH(CH_3)_2]_3$), 20.0 ($O[CHCH_3]O$), 39.7 (C-2'), 61.7 ($O[CHCH_3]OCH_2$), 63.9 (C-5'), 68.7 (C-5), 70.4 (OCH_2CH_2OH), 70.5-70.7 ($O[CHCH_3]OCH_2CH_2$, 8 x OCH_2CH_2O), 72.7 (OCH_2CH_2OH), 74.8 (C-3'), 85.7 (C-1'), 86.1 (C-4'), 99.4 ($O[CHCH_3]O$), 144.1 (C-6), 150.1 (C-2 *C*=O), 160.2 (C-4 *C*=O).

General procedure for the preparation of compounds (14a-d)

To a solution of (**13a-d**) and DIPEA (2.5 equivalents) in anhydrous DCM (12 mL / mmol) was added MsCl (1.2 equivalents). The mixture was stirred for 1 h at rt then poured into a mixture of water (110 mL / mmol) and sat. aq. NaCl (15 mL / mmol) which was extracted with DCM (3 x 40 mL / mmol). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*.

5-iodo-3'-*O*-{1-[2-(methylsulfonyloxy)ethoxy]ethyl}-5'-*O*-triisopropylsilyl-2'-deoxyuridine (14a). Prepared from (**13a**) (1.630 g, 2.72 mmol). After column chromatography on silica gel (EtOAc-cyclohexane, 65-35, v-v) the pure product (**14a**) was obtained as a white foam (1.639 g, 89%). R_f 0.29 (EtOAc-cyclohexane, 65-35, v-v); ^{1}H NMR: δ 1.09-1.26 (21H, m, 3 x ^{i}Pr), 1.36 (3H, d, *J* 5.0, O[CHC*H*$_3$]O), 2.02-2.14 (1H, m, H-2'), 2.39-2.48 (1H, m, H-2'), 3.04 (3H, s, OSO_2CH_3), 3.67-4.15 (5H, m, H-4', H-5', $OCH_2CH_2OSO_2$), 4.32-4.38 (2H, m, $OCH_2CH_2OSO_2$), 4.43-4.50 (1H, m, H-3'), 4.86 (1H, q, *J* = 5.0, O[C*H*CH$_3$]O), 6.20 (1H, dd, *J* = 7.9, 5.2, H-1'), 8.03 (1H, s, H-6), 8.36 (1H, br s, N*H*); ^{13}C NMR: δ 12.0 (Si[*C*H(CH$_3$)$_2$]$_3$), 18.2 (Si[CH(*C*H$_3$)$_2$]$_3$), 20.0 (O[CH*C*H$_3$]O), 37.7 (OSO_2CH_3), 39.3, 39.8 (C-2'), 62.3 (C-5'), 63.4 ($OCH_2CH_2OSO_2$), 68.9, 69.0 (C-5, $OCH_2CH_2OSO_2$), 75.3 (C-3'), 85.7 (C-1'), 86.2 (C-4'), 99.4 (O[*C*HCH$_3$]O), 144.1 (C-6), 150.2 (C-2 *C*=O), 160.2 (C-4 *C*=O); *m/z* (ESI) 675.02 [M - H]$^-$.

5-iodo-3'-*O*-(1-methyl-1-{2-[(methylsulfonyl)oxy]ethoxy}ethyl)-5'-*O*-triisopropylsilyl-2'-deoxyuridine (14b). Prepared from (**13b**) (0.632 g, 1.03 mmol). After column chromatography on silica gel (EtOAc-cyclohexane, 60-40, v-v) the pure product (**14b**) was obtained as a white foam (0.629 g, 88%). R_f 0.34 (EtOAc-cyclohexane, 60-40, v-v); ^{1}H NMR: δ 1.09-1.29 (21H, m, 3 x ^{i}Pr), 1.39 (6H, s, O[C(C*H*$_3$)$_2$]O), 1.99-2.13 (1H, m, H-2'), 2.34-2.44 (1H, m, H-2'), 3.02 (3H, s, OSO_2CH_3), 3.55 (2H, t, *J* 5.1, OCH_2CH_2OMs), 3.83-3.95 (2H, m, H-5'), 3.99-4.00 (1H, m, H-4'), 4.32 (2H, t, *J* 5.1, OCH_2CH_2OMs), 4.56 (1H, d, *J* 6.2, H-3'), 6.23 (dd, 1H, *J* 8.9, 4.8, H-1'), 8.04 (1H, s, H-6), 8.44 (1H, br s, N*H*); ^{13}C NMR: δ 12.0 (Si[*C*H(CH$_3$)$_2$]$_3$), 18.2 (Si[CH(*C*H$_3$)$_2$]$_3$), 25.5, 25.7 (O[C(*C*H$_3$)$_2$]O), 37.5

(OSO_2CH_3), 40.5 (C-2'), 59.5 (OCH_2CH_2OMs), 63.5 (C-5'), 68.8 (C-5), 69.2 (OCH_2CH_2OMs), 71.4 (C-3'), 85.9 (C-1'), 87.0 (C-4'), 101.4 (O[$C(CH_3)_2$]O), 144.1 (C-6), 150.3 (C-2 *C*=O), 160.2 (C-4 *C*=O).

3'-*O*-(1-methyl-21,21-dioxo-2,5,8,11,14,17,20-heptaoxa-21-thiadocos-1-yl)-5-iodo-5'-*O*-triisopropylsilyl-2'-deoxyuridine (14c). Prepared from (**13c**) (0.950 g, 1.16 mmol). After column chromatography on silica gel (EtOAc) the pure product (**14c**) was obtained as a light yellow oil (0.681 g, 65%). R_f 0.27 (EtOAc); ^{1}H NMR: δ 1.05-1.24 (21H, m, 3 x ^{i}Pr), 1.32 (3H, d, *J* 5.0, O[CHCH_3]O), 1.93-2.18 (1H, m, H-2'), 2.37-2.55 (1H, m, H-2'), 3.08 (3H, s, OSO_2CH_3), 3.54-3.72 (20H, m, 5 x OCH_2CH_2O), 3.76 (2H, t, *J* 5.3, OCH_2CH_2OMs), 3.82-3.96 (2H, m, H-5'), 4.01-4.16 (1H, m, H-4'), 4.38 (2H, t, *J* 5.3, OCH_2CH_2OMs), 4.42-4.51 (1H, m, H-3'), 4.82 (1H, q, *J* = 5.0, O[C*H*CH_3]O), 6.20 (dd, 1H, *J* 8.1, 5.8, H-1'), 8.04 (1H, s, H-6), 8.51 (1H, br s, N*H*); ^{13}C NMR: δ 11.9 (Si[*C*H(CH_3)$_2$]$_3$), 18.2 (Si[CH(*C*H_3)$_2$]$_3$), 20.0 (O[CH*C*H_3]O), 37.8 (OSO_2CH_3), 39.6 (C-2'), 63.4 (C-5'), 63.7 (O[CHCH$_3$]O*C*H_2CH_2), 68.6 (C-5), 69.0 (OCH_2CH_2OMs), 69.4 (OCH_2CH_2OMs), 70.5-70.6 (O[CHCH$_3$]OCH_2CH_2, 4 x OCH_2CH_2O), 74.8 (C-3'), 85.6 (C-1'), 86.1 (C-4'), 99.4 (O[*C*HCH$_3$]O), 144.1 (C-6), 150.0 (C-2 *C*=O), 160.1 (C-4 *C*=O).

5-iodo-3'-*O*-(1-methyl-33,33-dioxo-2,5,8,11,14,17,20,23,26,29,32-undecaoxa-33-thiatetra triacont -1-yl)-5'-*O*-triisopropylsilyl-2'-deoxyuridine (14d). Prepared from (**13d**) (0.150 g, 0.15 mmol). After column chromatography on silica gel (EtOAc-DCM-EtOH, 46-46-8, v-v-v) the pure product (**14d**) was obtained as a light yellow oil (0.141 g, 87%). R_f 0.35 (EtOAc-DCM-EtOH, 46-46-8, v-v-v); ^{1}H NMR: δ 1.04-1.26 (21H, m, 3 x ^{i}Pr), 1.33 (3H, d, *J* 5.0, O[CHCH_3]O), 1.91-2.21 (1H, m, H-2'), 2.36-2.57 (1H, m, H-2'), 3.11 (3H, s, OSO_2CH_3), 3.52-3.75 (36H, m, 9 x OCH_2CH_2O), 3.78 (2H, t, *J* 5.2, OCH_2CH_2OMs), 3.80-3.94 (2H, m, H-5'), 4.01-4.16 (1H, m, H-4'), 4.40 (2H, t, *J* 5.2, OCH_2CH_2OMs), 4.44-4.53 (1H, m, H-3'), 4.86 (1H, q, *J* = 5.0, O[C*H*CH_3]O), 6.21 (dd, 1H, *J* 8.1, 5.8, H-1'), 8.03 (1H, s, H-6), 8.55 (1H, br s, N*H*); ^{13}C NMR: δ 11.9 (Si[*C*H(CH_3)$_2$]$_3$), 18.2 (Si[CH(*C*H_3)$_2$]$_3$), 20.0 (O[CH*C*H_3]O), 37.8 (OSO_2CH_3), 39.6 (C-2'), 63.3 (C-5'), 63.8 (O[CHCH$_3$]OCH_2CH_2), 68.6 (C-5),

69.1 (OCH_2CH_2OMs), 69.4 (OCH_2CH_2OMs), 70.5-70.6 ($O[CHCH_3]OCH_2CH_2$, 8 x OCH_2CH_2O), 74.7 (C-3'), 85.6 (C-1'), 86.0 (C-4'), 99.4 ($O[CHCH_3]O$), 144.1 (C-6), 150.0 (C-2 *C*=O), 160.1 (C-4 *C*=O).

General procedure for the preparation of compounds (15a-d)

To a solution of (**14a-d**) in anhydrous MeCN (20 mL / mmol) was added secondary amine (**5**) (1.5 equivalents). The mixture was stirred for different times at different temperatures (see details below) then poured into sat. aq. $NaHCO_3$ (160 mL / mmol) and extracted with DCM (3 x 50 mL / mmol). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*.

3'-*O*-(1-{2-[ethyl(2-{[(6-iodoquinoxalin-2-yl)carbonyl]amino}ethyl)amino]ethoxy}ethyl)-5-iodo-5'-*O*-triisopropylsilyl-2'-deoxyuridine (15a). Prepared from (**14a**) (1.244 g, 1.84 mmol). Time of reaction: 88 h, temperature: 55 °C. After column chromatography on silica gel (EtOAc-EOH-NH_4OH, 95-5-0.5, v-v-v) the pure product (**15a**) was obtained as a light brown foam (0.265 g, 15%). R_f 0.29 (EtOAc-EOH-NH_4OH, 95-5-0.5, v-v-v); ^{1}H NMR: δ 1.08-1.16 (24H, m, 3 x ^{i}Pr, NCH_2CH_3), 1.30 (3H, d, *J* 5.0, $O[CHCH_3]O$), 1.96-2.04 (1H, m, H-2'), 2.39-2.44 (1H, m, H-2'), 2.65-2.82 (6H, m, 3 x NCH_2), 3.51-3.85 (4H, m, OCH_2CH_2N, NCH_2CH_2NH), 3.87-3.98 (2H, m, H-5'), 4.04-4.10 (1H, m, H-4'), 4.38-4.44 (1H, m, H-3'), 4.78 (1H, q, *J* = 5.0, $O[CHCH_3]O$), 6.17 (1H, q, *J* = 7.8, 5.2, H-1'), 7.80 (1H, d, *J* 8.8, Ar*H* *'m'* to I), 7.96-8.09 (2H, m, H-6, Ar*H* *'o'* to I), 8.38 (1H, br s, ArCON*H*), 8.60 (d, 1H, *J* 1.8, Ar*H* *'o'* to I), 9.63 (1H, s, Ar*H* *'o'* to CONH); ^{13}C NMR: δ 12.0 ($Si[CH(CH_3)_2]_3$, NCH_2CH_3), 18.3 ($Si[CH(CH_3)_2]_3$), 20.2 ($O[CHCH_3]O$), 37.5 (NCH_2CH_2NH), 39.7 (C-2'), 48.7 (NCH_2CH_3), 52.9, 53.2 (OCH_2CH_2N, NCH_2CH_2NH), 63.1, 63.5 (C-5', OCH_2CH_2N), 68.7 (C-5), 75.0 (C-3'), 85.8 (C-1'), 86.4 (C-4'), 98.2 (Ar*C*I), 99.5 ($O[CHCH_3]O$), 130.8 (Ar*C*H *'m'* to I), 138.7 (Ar*C*H *'β'* to N), 139.6 (Ar*C* *'p'* to I), 139.9 (Ar*C*H *'o'* to I), 144.1 (C-6), 144.2, 144.5 (Ar*C*CONH, Ar*C* *'m'* to I), 144.8 (Ar*C*H *'o'* to CONH), 149.9 (C-2 C=O), 160.0 (C-4 C=O), 163.2 (Ar*C*ONH).

3'-*O*-(1-{2-[ethyl(2-{[(6-iodoquinoxalin-2-yl)carbonyl]amino}ethyl)amino]ethoxy}-1-methylethyl)-5-iodo-5'-*O*-triisopropylsilyl-2'-deoxyuridine (15b). Prepared from (**14b**) (0.629 g, 0.91

mmol). Time of reaction: 96 h, temperature: 50 °C. After column chromatography on silica gel (EtOAc-EOH-NH_4OH, 96-4-0.5, v-v-v) the pure product (**15b**) was obtained as a light brown foam (0.134 g, 15%). R_f 0.30 (EtOAc-EOH-NH_4OH, 95-5-0.5, v-v-v); ^{1}H NMR: δ 1.09-1.29 (24H, m, 3 x ^{i}Pr, NCH_2CH_3), 1.33 (6H, s, $O[C(CH_3)_2]O$), 1.93-2.00 (1H, m, H-2'), 2.31-2.40 (1H, m, H-2'), 2.60-2.79 (6H, m, 3 x NCH_2), 3.47-3.61 (4H, m, OCH_2CH_2N, NCH_2CH_2NH), 3.80-3.98 (2H, m, H-5'), 4.07-4.08 (1H, m, H-4'), 4.54 (1H, d, *J* 5.7, H-3'), 6.22 (1H, q, *J* = 8.7, 5.1, H-1'), 7.82 (1H, d, *J* 8.8, Ar*H 'm'* to I), 8.03 (1H, s, H-6), 8.09 (1H, dd, *J* 8.8, 1.9, Ar*H 'o'* to I), 8.35 (1H, br s, ArCON*H*), 8.62 (d, 1H, *J* 1.9, Ar*H 'o'* to I), 9.65 (1H, s, Ar*H 'o'* to CONH); ^{13}C NMR: δ 12.0 ($Si[CH(CH_3)_2]_3$), 12.3 (NCH_2CH_3), 18.3 ($Si[CH(CH_3)_2]_3$), 25.6, 25.9 ($O[C(CH_3)_2]O$), 37.5 (NCH_2CH_2NH), 40.8 (C-2'), 48.8 (NCH_2CH_3), 53.1, 53.4 (OCH_2CH_2N, NCH_2CH_2NH), 60.1 (OCH_2CH_2N), 63.7 (C-5'), 68.7 (C-5), 71.1 (C-3'), 85.9 (C-1'), 87.3 (C-4'), 98.1 (Ar*C*I), 101.1 ($O[C(CH_3)_2]O$), 130.8 (Ar*C*H *'m'* to I), 138.7 (Ar*C*H *'β'* to N), 139.6 (Ar*C 'p'* to I), 139.9 (Ar*C*H *'o'* to I), 144.2 (C-6), 144.2, 144.5 (Ar*C*CONH, Ar*C 'm'* to I), 144.8 (Ar*C*H *'o'* to CONH), 150.0 (C-2 C=O), 160.0 (C-4 C=O), 163.0 (Ar*C*ONH).

3'-*O*-[20-ethyl-24-(6-iodoquinoxalin-2-yl)-1-methyl-24-oxo-2,5,8,11,14,17-hexaoxa-20,23-diazatetracos-1-yl]-5-iodo-5'-*O*-triisopropylsilyl-2'-deoxyuridine (15c). Prepared from (**14c**) (0.442 g, 0.49 mmol). Time of reaction: 90 h, temperature : 60 °C. After column chromatography on silica gel (DCM-EtOH-NH_4OH, 92-8-0.5) the pure product (**15c**) was obtained as a brown caramel (0.170 g, 30%). R_f 0.29 (DCM-EtOH-NH_4OH, 92-8-0.5); ^{1}H NMR: δ 0.96-1.25 (24H, m, 3 x ^{i}Pr, NCH_2CH_3), 1.28 (3H, d, *J* 5.0, $O[CHCH_3]O$), 1.86-2.11 (1H, m, H-2'), 2.35-2.50 (1H, m, H-2'), 2.60-2.80 (6H, m, 3 x NCH_2), 3.32-3.67 (24H, m, 5 x OCH_2CH_2O, OCH_2CH_2N, NCH_2CH_2NH), 3.78-4.10 (3H, m, H-4', H-5'), 4.37-4.46 (1H, m, H-3'), 4.78 (1H, q, *J* = 5.0, $O[CHCH_3]O$), 6.20 (1H, dd, *J* = 8.0, 5.8, H-1'), 7.78 (1H, d, *J* 8.8, Ar*H 'm'* to I), 7.97 (1H, s, H-6), 8.03 (1H, dd, *J* 8.8, 1.9, Ar*H 'o'* to I), 8.40 (1H, br s, ArCON*H*), 8.56 (d, 1H, *J* 1.9, Ar*H 'o'* to I), 9.61 (1H, s, Ar*H 'o'* to CONH); ^{13}C NMR: δ 11.7 ($Si[CH(CH_3)_2]_3$), 17.3 (NCH_2CH_3), 18.2 ($Si[CH(CH_3)_2]_3$), 20.0 ($O[CHCH_3]O$), 37.5 (NCH_2CH_2NH), 39.6 (C-2'), 48.5 (NCH_2CH_3), 52.8, 52.9 (OCH_2CH_2N, NCH_2CH_2NH), 63.3 (C-5'), 63.7 (OCH_2CH_2N),

68.7 (C-5), 68.6-68.8 (O[CHCH$_3$]OCH$_2$*C*H$_2$, O*C*H$_2$CH$_2$N, 4 x O*C*H$_2$*C*H$_2$O), 75.0 (C-3'), 85.5 (C-1'), 86.1 (C-4'), 98.0 (Ar*C*I), 99.4 (O[*C*HCH$_3$]O), 130.9 (Ar*C*H *'m'* to I), 138.6 (Ar*C*H *'β'* to N), 139.6 (Ar*C* *'p'* to I), 139.7 (Ar*C*H *'o'* to I), 144.0 (C-6), 144.2, 144.3 (Ar*C*CONH, Ar*C* *'m'* to I), 144.7 (Ar*C*H *'o'* to CONH), 150.0 (C-2 C=O), 160.2 (C-4 C=O), 163.0 (Ar*C*ONH).

3'-*O*-[32-ethyl-36-(6-iodoquinoxalin-2-yl)-1-methyl-36-oxo-2,5,8,11,14,17,20,23,26,29-decaoxa-32,35-diazahexatriacont-1-yl]-5-iodo-5'-*O*-triisopropylsilyl-2'-deoxyuridine (15d). Prepared from (**14d**) (0.141 g, 0.13 mmol). Time of reaction: 70 h, temperature : 70 °C. After column chromatography on silica gel (EtOAc-DCM-EtOH-NH$_4$OH, 20-67-13-0.5) the pure product (**15d**) was obtained as a brown caramel (0.022 g, 12%). R_f 0.28 (EtOAc-DCM-EtOH-NH$_4$OH, 20-67-13-0.5); ^{1}H NMR: δ 0.94-1.27 (24H, m, 3 x ^{i}Pr, NCH$_2$C*H$_3$*), 1.30 (3H, d, *J* 5.0, O[CHC*H$_3$*]O), 1.84-2.13 (1H, m, H-2'), 2.34-2.52 (1H, m, H-2'), 2.62-2.82 (6H, m, 3 x NC*H$_2$*), 3.31-3.65 (40H, m, 9 x OC*H$_2$C*H$_2$O, OC*H$_2$*CH$_2$N, NCH$_2$C*H$_2$*NH), 3.76-4.12 (3H, m, H-4', H-5'), 4.35-4.46 (1H, m, H-3'), 4.81 (1H, q, *J* = 5.0, O[C*H*CH$_3$]O), 6.22 (1H, dd, *J* = 7.8, 5.9, H-1'), 7.79 (1H, d, *J* 8.9, Ar*H* *'m'* to I), 7.96 (1H, s, H-6), 8.04 (1H, dd, *J* 8.9, 1.8, Ar*H* *'o'* to I), 8.42 (1H, br s, ArCON*H*), 8.58 (d, 1H, *J* 1.8, Ar*H* *'o'* to I), 9.62 (1H, s, Ar*H* *'o'* to CONH); ^{13}C NMR: δ 11.9 (Si[*C*H(CH$_3$)$_2$]$_3$), 17.3 (NCH$_2$*C*H$_3$), 18.2 (Si[CH(*C*H$_3$)$_2$]$_3$), 20.1 (O[CH*C*H$_3$]O), 37.4 (NCH$_2$*C*H$_2$NH), 39.6 (C-2'), 48.5 (N*C*H$_2$CH$_3$), 52.6, 52.7 (OCH$_2$*C*H$_2$N, N*C*H$_2$CH$_2$NH), 63.3 (C-5'), 63.7 (O*C*H$_2$CH$_2$N), 68.6 (C-5), 69.9-71.1 (O[CHCH$_3$]OCH$_2$*C*H$_2$, O*C*H$_2$CH$_2$N, 8 x O*C*H$_2$*C*H$_2$O), 74.9 (C-3'), 85.5 (C-1'), 86.0 (C-4'), 97.9 (Ar*C*I), 99.3 (O[*C*HCH$_3$]O), 130.8 (Ar*C*H *'m'* to I), 138.6 (Ar*C*H *'β'* to N), 139.6 (Ar*C* *'p'* to I), 139.7 (Ar*C*H *'o'* to I), 144.0 (C-6), 144.2, 144.3 (Ar*C*CONH, Ar*C* *'m'* to I), 144.8 (Ar*C*H *'o'* to CONH), 150.1 (C-2 C=O), 160.2 (C-4 C=O), 163.0 (Ar*C*ONH).

Synthesis of the tertiary amine precursors (18-19).

***tert*-butyl 2-bromoethylcarbamate (16).** To a stirred solution of bromoethylamine bromhydrate (4 g, 19.52 mmol) and DIPEA (9.8 mL, 56.04 mmol) in anhydrous DCM (100 mL) was added Boc$_2$O (4.26 g, 19.52 mmol). The mixture was stirred for 15 h at rt and concentrated *in vacuo* to give a white solid.

Et_2O (100 mL) was added and the suspension was filtered. The white solid was rinsed with Et_2O (2 x 20 mL), the filtrates were combined and concentrated *in vacuo* to give a clear oil. After column chromatography on silica gel (EtOAc-cyclohexane, 20-80, v-v) the pure product (**14**) was obtained as a colourless oil (1.971 g, 45%). R_f 0.32 (EtOAc-cyclohexane, 20-80, v-v); ^{1}H NMR: δ 1.45 (9H, s, ^{t}Bu), 3.41-3.57 (4H, m, BrC*H*$_2$C*H*$_2$NH), 5.29 (1H, br s, N*H*); ^{13}C NMR: δ 28.5 (C[*C*H$_3$]$_3$), 33.0 (Br*C*H$_2$), 42.5 (*C*H$_2$NH), 80.0 (*C*[CH$_3$]$_3$), 155.7 (*C*ONH).

***tert*-butyl 2-[ethyl-(2-{[(6-iodoquinoxalin-2-yl)carbonyl]amino}ethyl)amino]ethylcarbamate (17).** To a suspension of secondary amine (**5**) (500 mg, 1.35 mmol) in anhydrous MeCN (10 mL) was added (**16**) (908 mg, 4.05 mmol). The mixture was stirred for 96 h at rt then poured into 5% aq. Na_2CO_3 which was extracted with DCM (3 x 20 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo* to give a dark oil. After column chromatography on silica gel (EtOAc-cyclohexane-NEt_3, 90-10-2, v-v-v) the pure product (**17**) was obtained as a brown oil (370 mg, 53%). R_f 0.30 (EtOAc-cyclohexane-NEt_3, 90-10-2, v-v-v); ^{1}H NMR: δ 0.99 (3H, t, *J* 6.8, NCH$_2$C*H*$_3$), 1.28 (9H, s, ^{t}Bu), 2.51-2.62 (4H, m, NC*H*$_2$CH$_3$, NC*H*$_2$CH$_2$NH), 2.66 (2H, t, *J* 5.9, ArCONHCH$_2$C*H*$_2$), 3.13 (2H, q, *J* 6.1, NCH$_2$C*H*$_2$NH), 4.03 (q, 2H, *J* 5.9, ArCONHC*H*$_2$CH$_2$), 5.24 (1H, br s, N*H*CO^{t}Bu), 7.78 (1H, d, *J* 8.8, ArC*H* *'m'* to I), 7.97 (1H, dd, *J* 8.8, 1.2, ArC*H* *'o'* to I), 8.26 (1H, t, *J* 5.0, ArCON*H*), 8.50 (1H, d, *J* 1.2, ArC*H* *'o'* to I), 9.55 (1H, s, ArC*H* *'o'* to CONH); ^{13}C NMR: δ 11.9 (NCH$_2$*C*H$_3$), 28.3 (C[*C*H$_3$]$_3$), 37.3 (ArCONH*C*H$_2$), 38.8 (NCH$_2$*C*H$_2$NHCO^{t}Bu), 47.6 (N*C*H$_2$CH$_3$), 52.5 (N*C*H$_2$CH$_2$NHCO^{t}Bu), 53.0 (ArCONHCH$_2$*C*H$_2$), 79.1 (*C*[CH$_3$]$_3$), 98.0 (Ar*C*I), 130.8 (Ar*C*H *'m'* to I), 138.4 (Ar*C*H *'β'* to N), 139.4 (Ar*C* *'p'* to I), 139.6 (Ar*C*H *'o'* to I), 143.9 (Ar*C*CONH), 144.3 (Ar*C* *'m'* to I), 144.6 (Ar*C*H *'o'* to CONH), 156.0 (NH*C*O^{t}Bu), 162.8 (Ar*C*ONH).

***N*-{2-[ethyl(2-aminoethyl)amino]ethyl}-6-iodoquinoxaline-2-carboxamide (18).** To a solution of (**17**) (370 mg, 0.72 mmol) in anhydrous DCM (7.4 mL) was added TFA (3.7 mL). The mixture was stirred for 1 h 30 at rt then poured into 5% aq. Na_2CO_3. Layers were separated and the aqueous layer was extracted with DCM (2 x 60 mL). The organic layers were combined, dried over $MgSO_4$ and

concentrated *in vacuo* to give an orange semi-solid (285 mg, 96%). This crude product was used for the next step without further purification. ^{1}H NMR: δ 1.08 (3H, t, *J* 7.1, NCH$_2$C*H*$_3$), 1.68 (2H, br s, N*H*$_2$), 2.57-2.83 (8H, m, 3 x NC*H*$_2$, C*H*$_2$NH$_2$), 3.58 (2H, q, *J* 5.8, ArCONHC*H*$_2$CH$_2$), 7.79 (1H, d, *J* 8.9, ArC*H* *'m'* to I), 8.06 (1H, dd, *J* 8.9, 1.9, ArC*H* *'o'* to I), 8.48 (1H, br s, ArCON*H*), 8.60 (1H, d, *J* 1.9, ArC*H* *'o'* to I), 9.64 (1H, s, ArC*H* *'o'* to CONH); ^{13}C NMR: δ 11.8 (NCH$_2$*C*H$_3$), 37.4 (ArCONH*C*H$_2$), 39.8 (NCH$_2$*C*H$_2$NH$_2$), 47.5 (N*C*H$_2$CH$_3$), 52.3 (ArCONHCH$_2$*C*H$_2$), 56.4 (N*C*H$_2$CH$_2$NH$_2$), 98.0 (Ar*C*I), 130.6 (Ar*C*H *'m'* to I), 138.4 (Ar*C*H *'β'* to N), 139.4 (Ar*C* *'p'* to I), 139.6 (Ar*C*H *'o'* to I), 144.0, 144.3 (Ar*C*CONH, Ar*C* *'m'* to I), 144.5 (Ar*C*H *'o'* to CONH), 162.8 (Ar*C*ONH).

***N*-{2-[ethyl(2-hydroxyethyl)amino]ethyl}-6-iodoquinoxaline-2-carboxamide (19).** To a suspension of secondary amine (**5**) (200 mg, 0.54 mmol) in anhydrous MeCN (4 mL) were added DIPEA (65 µL, 0.65 mmol) and 2-bromoethanol (46 µL, 0.65 mmol). The mixture was stirred for 48 h at reflux then poured into 5% aq. Na$_2$CO$_3$ and extracted with DCM (3 x 15 mL). The organic layers were combined, dried over MgSO$_4$ and concentrated *in vacuo* to give a dark oil. After column chromatography on silica gel (EtOAc-EtOH-NH$_4$OH, 90-10-1, v-v-v) the pure product (**19**) was obtained as a thick brown oil (138 mg, 62%). R_f 0.22 (EtOAc-EtOH-NH$_4$OH, 90-10-1, v-v-v); ^{1}H NMR: δ 1.08 (3H, t, *J* 6.8, NCH$_2$C*H*$_3$), 2.04 (1H, br s, O*H*), 2.67-2.82 (6H, m, 3 x NC*H*$_2$), 3.60-3.66 (4H, m, NHC*H*$_2$CH$_2$N, C*H*$_2$OH), 7.82 (1H, d, *J* 8.8, ArC*H* *'m'* to I), 8.07 (1H, dd, *J* = 8.8, 1.5, ArC*H* *'o'* to I), 8.28 (1H, br s, N*H*), 8.61 (1H, d, *J* 1.5, ArC*H* *'o'* to I), 9.63 (1H, s, ArC*H* *'o'* to CONH); ^{13}C NMR: δ 11.9 (NCH$_2$*C*H$_3$), 37.6 (CONH*C*H$_2$), 47.7 (N*C*H$_2$CH$_3$), 52.6 (NHCH$_2$*C*H$_2$N), 55.7 (N*C*H$_2$CH$_2$OH), 59.2 (*C*H$_2$OH), 98.2 (Ar*C*I), 130.8 (Ar*C*H *'m'* to I), 138.6 (Ar*C*H *'β'* to N), 139.5 (Ar*C* *'p'* to I), 139.9 (Ar*C*H *'o'* to I), 143.9 (Ar*C*CONH), 144.5 (Ar*C* *'m'* to I), 144.6 (Ar*C*H *'o'* to CONH), 163.1 (Ar*C*ONH); *m/z* (ESI) 415.10 [M+H]$^{+}$.

Metabolic Stability

Table S1 Metabolic profile of conjugates (**1**) [a]

S9 Liver fraction		Liver microsomes	
Retention time (min)	Relative amount (%)	Retention time (min)	Relative amount (%)
15.4	0.6	15.4	0.5
16.0	14.7	16.0	15.1
16.7	5.0	16.7	5.0
17.5	16.7	17.5	19.5
17.9	59.8	17.9	55.9
20.1	1.4	20.1	1.9

[a] Conjugate (500 µM) was incubated at 37°C for 4h.