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Novel imidazo[1,2-*c*]pyrimidine base-modified nucleosides: synthesis and antiviral evaluation

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Abstract—The preparation of a series of novel 6-(β-D-ribofuranosyl)-2-alkyl/aryl-6*H*-imidazo[1,2-*c*]pyrimidin-5-one nucleosides and the 2-nitrile nucleosides, 6-(β-D-ribofuranosyl)-5-oxo-5,6-dihydro-imidazo[1,2-*c*]pyrimidine-2-carbonitrile and 2*R* and 2*S* isomers of 6-(β-D-ribofuranosyl)-5-oxo-2,3,5,6-tetrahydro-imidazo[1,2-*c*]pyrimidine-2-carbonitrile, is described using two synthetic approaches. The nucleoside mimetics described were evaluated against a wide range of viral types and strains in cell culture. With the exception of one nucleoside, which displayed anti-CMV activity at toxic concentrations, none of the compounds showed antiviral activity most likely due to a lack of substrate recognition by viral and/or cellular nucleoside kinases.

1. Introduction

Base-modified nucleosides and nucleotides have demonstrated an important impact in various fields.[1] Their biological properties have found application as antiviral tools against herpes simplex virus (HSV), varicella-zoster virus (VZV), cytomegalovirus, hepatitis B virus and human immunodeficiency virus (HIV),[2] in the evaluation and study of DNA damage[3] and DNA base-to-base interactions,[4] as well as in antisense and DNA probe technology.[5,6] Bicyclic pyrimidine nucleosides have shown considerable potential as antiviral agents.[7] Of particular interest are the imidazo-,[8,9] oxazolo-[10] and thieno-[11] fused pyrimidine base-modified nucleosides (**1**–**4**), which have demonstrated antiviral and antileukemic activity in vitro (Fig. 1).

A study of the molecular structure of the 3,N^4-ethenocytidine nucleoside (**1**)[12] indicated a spatial outline and binding area comparable with adenosine with an *anti*-conformation about the glycosyl bond.[13] The oxazolo- and thieno-fused pyrimidine nucleosides (**3**) and (**4**) were also shown to be substrates for adenosine kinase,[10,11]

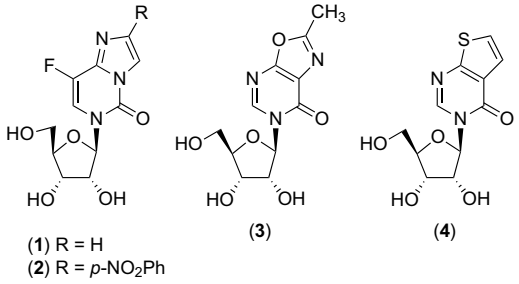

Figure 1. Base modified nucleosides with antiviral and antileukemic activity in vitro.

further supporting the similarity of these base-modified nucleosides to the naturally occurring purine nucleosides rather than the naturally occurring pyrimidine nucleosides.

The demonstrated potential of these base-modified nucleosides led us to prepare a series of ribofuranosyl-imidazo[1,2-*c*]pyrimidine base-modified nucleosides with both hydrophobic and hydrophilic functional groups for broad antiviral screening. The target compounds were the 2-substituted 6-(β-D-ribofuranosyl)-6*H*-imidazo[1,2-*c*]pyrimidin-5-one nucleosides (I) and 2-substituted 6-(β-D-ribofuranosyl)-2,6-dihydro-3*H*-imidazo[1,2-*c*]pyrimidin-5-one nucleosides (II) (Fig. 2).

Keywords: Imidazo[1,2-*c*]pyrimidine-5-one; Imidazo[1,2-*c*]pyrimidine-2-carbonitrile; Base-modified nucleosides; Antiviral activity.
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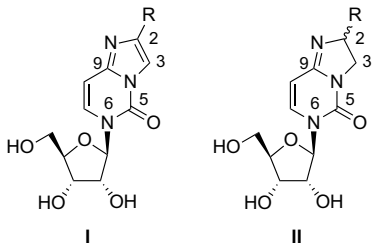


Figure 2. Target imidazo[1,2-*c*]pyrimidine base-modified nucleosides.

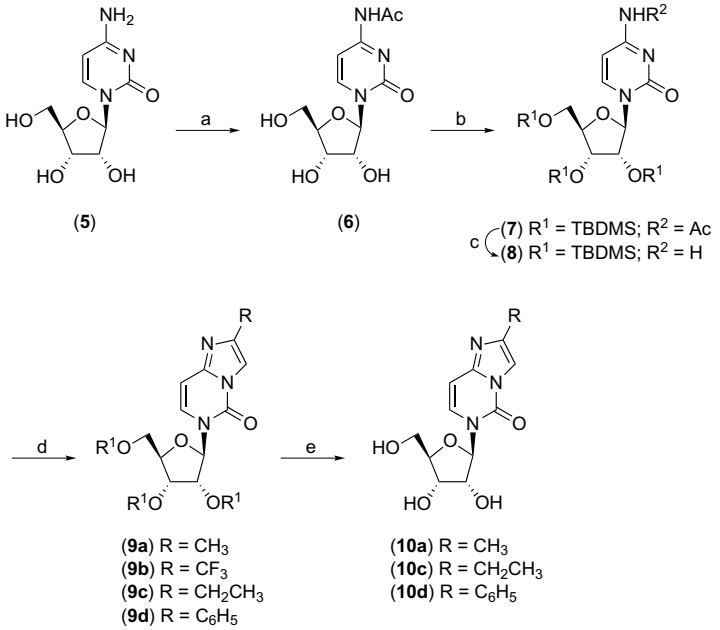
2. Results and discussion

The synthesis of the imidazo[1,2-*c*]pyrimidine base-modified nucleosides started from cytidine (**5**), which was selectively *N*-acetylated to give (**6**), according to the procedure of Watanabe and Fox.[14] This procedure was very facile and suitable for a scale-up reaction, which involved filtration of the residues to give the pure product in high yield (95%) (Scheme 1).

The 2′-, 3′- and 5′-hydroxy groups were then protected with *tert*-butyldimethylsilyl (TBDMS) groups (**7**) using standard methodology,[15] followed by deprotection of the C-4 cytidine amino group by reaction with methanolic ammonia, to give the key intermediate, 2′,3′,5′-tri-*O*-*tert*-butyldimethylsilyl-cytidine[15] (**8**) (Scheme 1). The cyclisation of the ribofuranosyl-imidazo[1,2-*c*]pyrimidine base-modified nucleosides containing a hydrophobic functional group, involved a modification of the procedure described by Mansour et al.[8] Reaction of **8** with 2 equiv of the appropriate α-haloketone with an equal amount of sodium bicarbonate as the base in refluxing methanol for 1–4 days gave the cyclised compounds (**9a**–**d**) in low to moderate yields (Scheme 1). The use of two molecular equivalent of the α-haloketone was required for the reaction to proceed, with 1 equiv of α-haloketone leading to very unsatisfactory yields. The addition of base was found to be essential to quench the hydrobromic acid generated during the reaction, when the reaction was performed without base (according to the literature methodology[8]) decomposition, presumably glycosidic cleavage, was found to occur as observed by thin layer chromatography.

Preparation of the trifluoromethyl derivative (**9b**) proved problematic with a very low yield (8%) of product obtained as a result of incomplete reaction and difficulties in purification. Desilylation was found to occur on columning of crude **9b**, and in addition to the required product, 10% of the 5′-deprotected product was also obtained. The optimum conditions for deprotection of **9a**,**c** and **9d** were found to be TFA–H_2O 9:1 v/v,[16] even though the reaction was found to be slow (5 days) under these conditions, the products were obtained cleanly with good yields recorded for **10a**,**c** and **10d**.

Introduction of a hydrophilic nitrile moiety was of interest as the available lone pair on the nitrogen may act as a proton acceptor for possible hydrogen bonding with the corresponding nucleos(t)ide. Cyclisation of the silyl protected cytidine (**8**) to give the required carbonitrile substituted bicyclic imidazo[1,2-*c*]pyrimidine nucleoside followed the methodology described by Khana et al.[17] for the preparation of imidazolines. Accordingly, 2′,3′,5′-tri-*O*-*tert*-butyldimethylsilyl-cytidine (**8**) was treated with 3 molecular equivalents of 2-chloroacrylonitrile and Hunig's base (diisopropylethylamine) and the reaction heated under reflux overnight. After column chromatography racemic silyl protected 6-



Scheme 1. Reagents and conditions: (a) Ac_2O, EtOH, reflux, 5 h, 95%; (b) TBDMSCl, imidazole, DMF, overnight, 90%; (c) NH_3/MeOH, overnight, 92% (d) $H_3C(O)CH_2Cl$ (**9a**), $RC(O)CH_2Br$ (**9b**, R = CF_3; **9c**, R = Et; **9d**, R = Ph), MeOH, $NaHCO_3$, 4 Å molecular sieves, reflux, 1–4 days, 8–49%; (e) TFA–H_2O (9:1 v/v), 5 days, 73–95%.

(β-D-ribofuranosyl)-5-oxo-2,3,5,6-tetrahydro-imidazo-[1,2-*c*]pyrimidine-2-carbonitrile (**11**) was obtained in good yield. Again this methodology was found to be very suitable to scale-up with the reaction performed on a 10 g scale. Deprotection using the previously described method of TFA–H_2O 9:1 v/v, gave the 2*R* and 2*S* isomers of **12**; the isomers were present in equal amounts and were separable by column chromatography (Scheme 2).

Aromatisation of silyl protected 6-(β-D-ribofuranosyl)-5-oxo-2,3,5,6-tetrahydro-imidazo[1,2-*c*]pyrimidine-2-carbonitrile (**11**) was achieved by dehydrogenation using 10% palladium on activated carbon in refluxing cumene overnight. The silyl protected 6-(β-D-ribofuranosyl)-5-oxo-5,6-dihydro-imidazo[1,2-*c*]pyrimidine-2-carbonitrile (**13**) was obtained in good yield when the reaction was performed on a small scale (0.2 g); however, on increasing the scale of the reaction lower yields were obtained (55% for 1.0 g, 34% for 9.5 g) with incomplete reaction in addition to decomposition observed. Treatment of **13** with TFA–H_2O 9:1 v/v resulted in desilylation to give the desired product 6-(β-D-ribofuranosyl)-5-oxo-5,6-dihydro-imidazo[1,2-*c*]pyrimidine-2-carbonitrile (**14**).

The imidazo[1,2-*c*]pyrimidine nucleosides displayed characteristic signals for the imidazole CH(H-3/C-3) and the quaternary carbons (C2 and C9) (Table 1). Assignment of the 2*R* and 2*S* isomers of **12** was not possible by NMR and the compounds were also unsuitable for X-ray crystallography.

Reduction of the nitrile moiety of nucleoside (**13**) was of interest to generate the methyl amino substitutent as a handle for further derivatisation. The reduction involved hydrogenation with 10% Pd/C as the catalyst at 40 psi (Parr hydrogenator) overnight. The initial hydrogenation included the addition of 1.25 M HCl in methanol, which was necessary to protonate the amino group formed, thus avoiding poisoning of the catalyst. However the addition of acid resulted in cleavage of the 5′-silyl protecting group with 2-aminomethyl-6-(2,3-di-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)-5-oxo-5,6-dihydro-imidazo[1,2-*c*]pyrimidine-5-one (**15**) obtained as the sole product in 37% yield, shortening the time of the hydrogenation reaction resulted in incomplete reaction with starting material recovered. Hydrogenation in the absence of acid led to the required product (**16**) in a very low yield of 16% with 24% of the starting material recovered (Scheme 3).

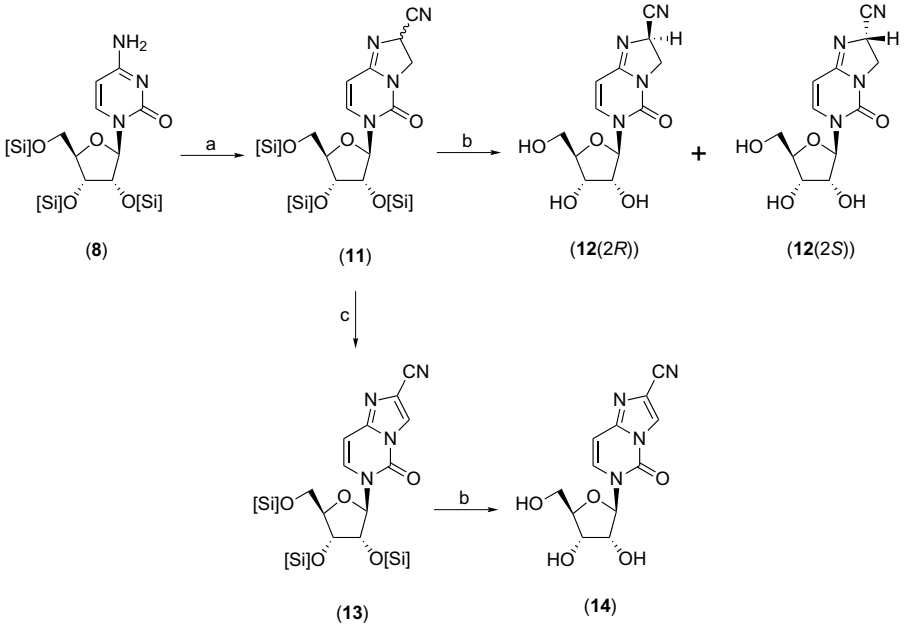
Table 1. Selective NMR data for 1′-(2-substituted-6*H*-imidazo[1,2-*c*]pyrimidin-5-one)-β-D-ribofuranosides **10**, **12** and **14**

Compound	H-3	C-2	C-3	C-9
10a[a]	7.67, s	145.85	135.02	146.20
10c[a]	7.71, s	145.88	135.57	146.16
10d[b]	8.38, s	144.20	129.20	145.25
14[a]	8.45, s	118.24	123.25	148.21
12 (isomer 1)[a]	4.18, m	119.55	50.22	149.29
12 (isomer 2)[a]	4.16, m	119.69	50.28	149.36

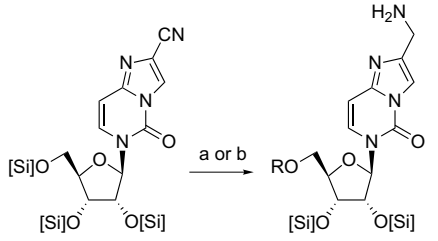
[a] CD_3OD.
[b] DMSO-d_6.

3. Conclusions

Only the aminomethyl nucleoside **16** displayed activity, with EC_{50} values against cytomegalovirus of 7.3 μM (AD-169 strain) and 8.9 μM (Davis strain) recorded (cf. ganciclovir 5.1 and 4.7 M against AD-169 and Davis strains, respectively), however this was at toxic concentrations (CC_{50} 9.6 μM, MCC 20 M), therefore compound **16** cannot be considered as an antiviral. None of



Scheme 2. Reagents and conditions: (a) 2-chloroacrylonitrile, Et(^{i}Pr)$_2$N, THF, reflux, overnight, 86% (b) TFA–H_2O (9:1 v/v), 5 days, **12** 55%, **14** 54%; (c) NH_3/MeOH, overnight, 92%. [Si] = ^{t}BuMe$_2$Si.



Scheme 3. Reagents and conditions: (a) Pd/C, H_2, MeOH, 1.25 M HCl, overnight, 37% (b) Pd/C, H_2, MeOH, overnight, 16%. [Si] = ^{t}BuMe$_2$Si.

the other compounds included in the antiviral evaluations (i.e. **10a**,**c**,**d**, **11**, **12** (2*R*), **12** (2*S*), **13** and **14**) were inhibitory to DNA or RNA viruses (see list in Section 4) in cell culture at subtoxic concentrations. Most likely, the cellular ribonucleoside kinases such as adenosine kinase and uridine/cytidine kinase do not recognise the test compounds as efficient substrates for phosphorylation. This may be due to the nature of the modifications made in the base-part of the molecules as well as the presence of silyl groups in the sugar part of some of the molecules (i.e. **11**, **13**). Also, none of the RNA viruses included in this study encode for a ribonucleoside kinase, and the DNA viruses that were subject of this study (i.e. HSV, VZV) encode for 2′-deoxyribonucleoside kinases that do not (efficiently) recognise ribonucleosides as a substrate. Thus, the test compounds may not be activated (phosphorylated) in the virus-infected cell cultures, explaining the lack of antiviral efficacy.

4. Experimental

4.1. Chemistry

Unless stated otherwise, starting materials were obtained from commercial sources and were used without further purification. All reactions were performed in anhydrous conditions in an atmosphere of nitrogen. ^{1}H and ^{13}C NMR spectra were recorded with a Brucker Avance DPX300 spectrometer operating at 300 and 75 MHz, with Me_4Si as internal standard. Mass spectra were determined by the EPSRC mass spectrometry centre (Swansea, UK). Microanalyses were determined by Medac Ltd (Surrey, UK). Flash column chromatography was performed with silica gel 60 (230–400 mesh) (Merck) and TLC was carried out on precoated silica plates (kiesel gel 60 F_{254}, BDH). Melting points were determined on an electrothermal instrument and are uncorrected. Infrared spectra were recorded using NaCl discs on a Perkin–Elmer 1600 series (FTIR) spectrometer. Hydrogenation was performed using a Parr hydrogenator.

4.1.1. General procedure for the synthesis of 6-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)-2-alkyl/aryl-6*H*-imidazo[1,2-*c*]pyrimidin-5-one nucleosides (9). To a solution of 2′,3′,5′-tri-*O*-*tert*-butyldimethylsilyl-cytidine[15] (**8**) (1.0 mmol) in anhydrous methanol (10 mL) was added sodium bicarbonate (2.0 mmol), the α-haloketone (2.0 mmol) and 4 Å molecular sieves and the reaction refluxed overnight, continuing for a maximum of 4 days. The reaction mixture was concentrated under reduced pressure, diluted with CH_2Cl_2 (100 mL) and washed with water (2 × 50 mL). The organic layer was dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography.

4.1.2. 6-(2,3,5-Tri-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)-2-methyl-6*H*-imidazo[1,2-*c*]pyrimidin-5-one (9a). Purification by flash column chromatography (petroleum ether–EtOAc 96:4 v/v) gave the product **9a** as an orange syrup. Yield: 49%, TLC system: petroleum ether–EtOAc 4:1 v/v, R_F: 0.32. ^{1}H NMR ($CDCl_3$) δ 7.75 (d, $J_{7,8}$ = 7.9 Hz, 1H, H-7), 7.41 (s, 1H, H-3), 6.46 (d, $J_{8,7}$ = 7.9 Hz, 1H, H-8), 6.11 (d, $J_{1',2'}$ = 3.5 Hz, 1H, H-1′), 4.11 (m, 3H, H-2′, H-3′, H-4′), 3.98 (dd, $J_{5',4'}$ = 1.7 Hz, $J_{5'a,5'b}$ = 11.5 Hz, 1H, H-5′), 3.13 (dd, $J_{5',4'}$ = 1.8 Hz, $J_{5'a,5'b}$ = 11.5 Hz, 1H, H-5′), 2.32 (s, 3H, CH_3), 0.94 (s, 9H, $C(CH_3)_3$), 0.88 (s, 9H, $C(CH_3)_3$), 0.83 (s, 9H, $C(CH_3)_3$), 0.12 (s, 6H, $Si(CH_3)_2$), 0.04 (s, 6H, $Si(CH_3)_2$), 0.00 (s, 6H, $Si(CH_3)_2$). ^{13}C NMR ($CDCl_3$): δ 145.98 (C, C-9), 145.01 (C, C-2), 142.77 (C=O, C-5), 127.67 (CH, C-3), 109.46 (CH, C-7), 98.76 (CH, C-8), 89.65 (CH, C-1′), 85.19 (CH, C-2′), 76.86 (CH, C-3′), 71.42 (CH, C-4′), 62.38 (CH_2, C-5′), 26.42, 26.25, 26.14 (CH_3, $C(CH_3)_3$), 18.87, 18.49, 18.33 (C, $C(CH_3)_3$), 14.51 (CH_3, Me), −3.85, −4.25, −4.39, −4.43, −5.01, −5.12 (CH_3, $Si(CH_3)_2$). HRMS (ES+) for $C_{30}H_{58}N_3O_5Si_3$ $(M + H)^+$: calcd 624.3684; found, 624.3680.

4.1.3. 6-(2,3,5-Tri-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)-2-trifluoromethyl-6*H*-imidazo[1,2-*c*]pyrimidin-5-one (9b). Purification by flash column chromatography (petroleum ether–EtOAc 96:4 v/v) gave the product **9b** as an orange syrup. Yield: 8%, TLC system: petroleum ether–EtOAc 1:1 v/v, R_F: 0.72. ^{1}H NMR ($CDCl_3$) δ 8.11 (s, 1H, H-3), 8.04 (d, $J_{7,8}$ = 8.1 Hz, 1H, H-7), 6.66 (d, $J_{8,7}$ = 8.1 Hz, 1H, H-8), 6.18 (d, $J_{1',2'}$ = 3.5 Hz, 1H, H-1′), 4.15 (m, 3H, H-2′, H-3′, H-4′), 4.07 (dd, $J_{5',4'}$ = 1.4 Hz, $J_{5'a,5'b}$ = 11.3 Hz, 1H, H-5′), 3.85 (dd, $J_{5',4'}$ = 1.4 Hz, $J_{5'a,5'b}$ = 11.3 Hz, 1H, H-5′), 1.03 (s, 9H, $C(CH_3)_3$), 0.97 (s, 9H, $C(CH_3)_3$), 0.93 (s, 9H, $C(CH_3)_3$), 0.14 (s, 6H, $Si(CH_3)_2$), 0.13 (s, 6H, $Si(CH_3)_2$), 0.12 (s, 6H, $Si(CH_3)_2$). ^{13}C NMR ($CDCl_3$): δ 144.70 (C, C-9), 144.37 (C=O, C-5), 134.75 (C, C-2), 134.34 (C, CF_3), 128.51 (CH, C-3), 111.53 (CH, C-7), 97.86 (CH, C-8), 88.62 (CH, C-1′), 83.97 (CH, C-2′), 75.52 (CH, C-3′), 69.86 (CH, C-4′), 60.82 (CH_2, C-5′), 24.98, 24.79, 24.67 (CH_3, $C(CH_3)_3$), 17.46, 17.05, 16.89 (C, $C(CH_3)_3$), −5.27, −5.69, −5.83, −5.88, −6.42, −6.59 (CH_3, $Si(CH_3)_2$). ^{19}F NMR ($CDCl_3$): δ −64.31 (CF_3). LRMS (ES) m/z 700.9 $(M+Na)^+$.

4.1.4. 6-(2,3,5-Tri-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)-2-ethyl-6*H*-imidazo[1,2-*c*]pyrimidin-5-one (9c). Purification by flash column chromatography (petroleum ether–EtOAc 1:1 v/v) gave the product **9c** as an

orange syrup. Yield: 46%, TLC system: petroleum ether–EtOAc 1:1 v/v, R_F: 0.80. ^{1}H NMR ($CDCl_3$) δ 7.77 (d, $J_{7,8} = 7.9$ Hz, 1H, H-7), 7.41 (s, 1H, H-3), 6.47 (d, $J_{8,7} = 7.9$ Hz, 1H, H-8), 6.08 (d, $J_{1',2'} = 2.7$ Hz, 1H, H-1′), 4.09 (m, 3H, H-2′, H-3′, H-4′), 3.98 (dd, $J = 1.7$ Hz, $J_{5'a,5'b} = 11.7$ Hz, 1H, H-5′), 3.74 (dd, $J = 0.8$ Hz, $J_{5'a,5'b} = 11.8$ Hz, 1H, H-5′), 2.68 (q, $J = 7.5$ Hz, 2H, CH_2), 1.26 (t, $J = 7.5$ Hz, 3H, CH_3), 0.87 (m, 27H, 3×C(CH_3)$_3$), 0.07 (m, 18H, 3×Si(CH_3)$_2$). ^{13}C NMR ($CDCl_3$): δ 149.08 (C=O, C-5), 146.12 (C, C-9), 145.07 (C, C-2), 127.64 (CH, C-3), 108.40 (CH, C-7), 98.87 (CH, C-8), 89.85 (CH, C-1′), 84.97 (CH, C-2′), 76.90 (CH, C-3′), 71.19 (CH, C-4′), 62.21 (CH_2, C-5′), 26.44, 26.26, 26.17 (CH_3, C(CH_3)$_3$), 22.39 (CH_2, CH_2CH_3), 18.89, 18.50, 18.36 (C, C(CH_3)$_3$), 13.38 (CH_3, CH_2-CH_3), −3.81, −4.18, −4.41, −4.45, −4.99, −5.13 (CH_3, Si(CH_3)$_2$). HRMS (ES+) for $C_{31}H_{60}N_3O_5Si_3$ $(M+H)^+$: calcd 638.3841; found, 638.3847. Anal. for $C_{31}H_{59}N_3O_5Si_3 \cdot 1.2H_2O$: calcd C, 56.44%, H, 9.01%, N, 6.37%; found: C, 56.29%, H, 8.87%, N, 6.31%.

4.1.5. 6-(2,3,5-Tri-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)-2-phenyl-6*H*-imidazo[1,2-*c*]pyrimidin-5-one (9d). Purification by flash column chromatography (petroleum ether–EtOAc 95:5 v/v) gave the product **9d** as a yellow syrup. Yield: 36%, TLC system: petroleum ether–EtOAc 9:1 v/v, R_F: 0.34. ^{1}H NMR ($CDCl_3$) δ 8.00 (s, 1H, H-3), 7.89 (m, 2H, Ph), 7.41 (m, 3H, Ph), 7.29 (d, $J_{7,8} = 7.4$ Hz, 1H, H-7), 6.61 (d, $J_{8,7} = 7.5$ Hz, 1H, H-8), 6.13 (d, $J_{1',2'} = 3.4$ Hz, 1H, H-1′), 4.14 (m, 3H, H-2′, H-3′, H-4′), 4.02 (dd, $J = 1.7$ Hz, $J_{5'a,5'b} = 11.7$ Hz, 1H, H-5′), 3.77 (dd, $J = 0.9$ Hz, $J_{5'a,5'b} = 11.8$ Hz, 1H, H-5′), 1.33 (m, 27H, 3×C(CH_3)$_3$), 0.14 (m, 18H, 3×Si(CH_3)$_2$). ^{13}C NMR ($CDCl_3$): δ 160.00 (C=O, C-5), 146.18 (C, C-9), 145.07 (C, C-2), 133.29 (C, Ph), 129.20 (CH, Ph), 128.57 (CH, Ph), 128.28 (CH, C-3), 126.21 (CH, Ph), 108.27 (CH, C-7), 99.09 (CH, C-8), 89.94 (CH, C-1′), 85.18 (CH, C-2′), 76.98 (CH, C-3′), 71.31 (CH, C-4′), 62.30 (CH_2, C-5′), 26.47, 26.28, 26.18 (CH_3, C(CH_3)$_3$), 18.93, 18.53, 18.38 (C, C(CH_3)$_3$), −3.78, −4.18, −4.36, −4.42, −4.96, −5.11 (CH_3, Si(CH_3)$_2$). HRMS (ES+) for $C_{35}H_{60}N_3O_5Si_3$ $(M+H)^+$: calcd 686.3841; found, 686.3833.

4.2. General procedure for desilylation

To a solution of the 2′,3′,5′-tri-*O*-*tert*-butyldimethylsilylnucleoside (1.0 mmol) in CH_2Cl_2 (7 mL) was added TFA–H_2O 9:1 v/v (7 mL) and the reaction stirred at room temperature overnight. Additional TFA–H_2O 9:1 v/v (7 mL) was then added and the reaction stirred for a further 4 days. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with water (2×50 mL). The organic layer was dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography.

4.2.1. 6-(β-D-Ribofuranosyl)-2-methyl-6*H*-imidazo[1,2-*c*]-pyrimidin-5-one (10a). Desilylation of **9a** using the general method described gave crude **10a**, which was purified by flash column chromatography ($CHCl_3$–MeOH, 92:8 v/v) to give the product **10a** as a colourless syrup. Yield: 95%, TLC system: $CHCl_3$–MeOH 9:1 v/v, R_F: 0.13. ^{1}H NMR (CD_3OD) δ 8.24 (d, $J_{7,8} = 7.9$ Hz, 1H, H-7), 7.67 (s, 1H, H-3), 6.75 (d, $J_{8,7} = 7.9$ Hz, 1H, H-8), 6.13 (d, $J_{1',2'} = 4.1$ Hz, 1H, H-1′), 4.30 (dd, $J_{2',1'} = 4.2$ Hz, $J_{2',3'} = 9.2$ Hz, 1H, H-2′), 4.24 (dd, $J_{3',4'} = 5.1$ Hz, $J_{3',2'} = 9.2$ Hz, 1H, H-3′), 4.12 (dd, $J_{4',5'} = 2.6$ Hz, $J_{4',3'} = 5.1$ Hz, 1H, H-4′), 3.93 (dd, $J_{5',4'} = 2.6$ Hz, $J_{5'a,5'b} = 12.3$ Hz, 1H, H-5′), 3.81 (dd, $J_{5',4'} = 2.8$ Hz, $J_{5'a,5'b} = 12.3$ Hz, 1H, H-5′), 2.41 (s, 3H, CH_3). ^{13}C NMR (CD_3OD): δ 146.20 (C, C-9), 145.85 (C, C-2), 138.38 (C=O, C-5), 135.02 (CH, C-3), 111.59 (CH, C-7), 95.68 (CH, C-8), 92.45 (CH, C-1′), 87.20 (CH, C-2′), 76.84 (CH, C-3′), 71.40 (CH, C-4′), 62.31 CH_2, C-5′), 12.22 (CH_3, Me). HRMS (ES+) for $C_{12}H_{16}N_3O_5$ $(M+H)^+$: calcd 282.1090; found, 282.1087.

4.2.2. 6-(β-D-Ribofuranosyl)-2-ethyl-6*H*-imidazo[1,2-*c*]-pyrimidin-5-one (10c). Desilylation of **9c** using the general method described gave crude **10c** which was purified by flash column chromatography ($CHCl_3$–MeOH, 92:8 v/v) to give the product **10c** as a colourless syrup. Yield: 89%, TLC system: $CHCl_3$–MeOH 9:1 v/v, R_F: 0.10. ^{1}H NMR (CD_3OD) δ 8.30 (d, $J_{7,8} = 7.9$ Hz, 1H, H-7), 7.71 (s, 1H, H-3), 6.78 (d, $J_{8,7} = 7.9$ Hz, 1H, H-8), 6.14 (d, $J_{1',2'} = 4.1$ Hz, 1H, H-1′), 4.31 (dd, $J_{2',1'} = 4.2$ Hz, $J_{2',3'} = 9.2$ Hz, 1H, H-2′), 4.25 (Ψt, $J_{3',4'} = 5.1$ Hz, $J_{3',2'} = 9.2$ Hz, 1H, H-3′), 4.12 (dd, $J_{4',5'} = 2.5$ Hz, $J_{4',3'} = 5.1$ Hz, 1H, H-4′), 3.94 (dd, $J_{5',4'} = 2.5$ Hz, $J_{5'a,5'b} = 12.3$ Hz, 1H, H-5′), 3.82 (dd, $J_{5',4'} = 2.7$ Hz, $J_{5'a,5'b} = 12.3$ Hz, 1H, H-5′), 2.80 (q, $J = 7.5$ Hz, 2H, CH_2), 1.35 (t, $J = 7.5$ Hz, 3H, CH_3). ^{13}C NMR (CD_3OD): δ 146.16 (C, C-9), 145.88 (C, C-2), 143.83 (C=O, C-5), 135.57 (CH, C-3), 110.73 (CH, C-7), 95.47 (CH, C-8), 92.56 (CH, C-1′), 87.24 (CH, C-2′), 76.93 (CH, C-3′), 71.37 (CH, C-4′), 62.28 (CH_2, C-5′), 21.05 (CH_2, CH_2CH_3), 13.44 (CH_3, CH_2CH_3). HRMS (ES+) for $C_{13}H_{18}N_3O_5$ $(M+H)^+$: calcd 296.1246; found, 296.1244.

4.2.3. 6-(β-D-Ribofuranosyl)-2-phenyl-6*H*-imidazo[1,2-*c*]-pyrimidin-5-one (10d). Desilylation of **9d** using the general method described gave crude **10d**, which was purified by flash column chromatography ($CHCl_3$–MeOH, 92:8 v/v) to give the product **10d** as a white solid. Yield: 73%, mp: 250 °C (decomp), TLC system: $CHCl_3$–MeOH 9:1 v/v, R_F: 0.28. ^{1}H NMR (DMSO-d_6) δ 8.38 (s, 1H, H-3), 8.00 (d, $J = 7.3$ Hz, 1H, Ph), 7.83 (d, $J_{7,8} = 7.9$ Hz, 1H, H-7), 7.43 (m, 2H, Ph), 7.33 (m, 2H, Ph), 6.79 (d, $J_{8,7} = 7.9$ Hz, 1H, H-8), 6.09 (d, $J_{1',2'} = 5.5$ Hz, 1H, H-1′), 5.50 (br s, 1H, H5′-OH, ex), 5.22 (br s, 1H, H2′-OH or H3′-OH, ex), 5.20 (br s, 1H, H2′-OH or H3′-OH, ex), 4.17 (d, $J_{2',1'} = 5.2$ Hz, 1H, H-2′), 4.06 (m, 1H, H-4′), 3.95 (dd, $J_{3',4'} = 2.9$ Hz, $J_{3',2'} = 6.2$ Hz, 1H, H-3′), 3.66 (dd, $J_{5'a,5'b} = 11.8$ Hz, 2H, H-5′). ^{13}C NMR (DMSO-d_6): δ 146.04 (C=O, C-5), 145.25 (C, C-9), 144.20 (C, Ph), 132.97 (C, Ph), 129.21 (CH, C-3), 129.10 (2×CH, Ph), 128.39 (CH, Ph), 125.85 (2×CH, Ph), 108.79 (CH, C-7), 98.60 (CH, C-8), 89.04 (CH, C-1′), 85.59 (CH, C-2′), 74.44 (CH, C-3′), 70.29 (CH, C-4′), 61.12 (CH_2, C-5′).

HRMS (ES+) for $C_{17}H_{18}N_3O_5$ $(M+H)^+$: calcd 344.1246; found, 344.1250.

4.2.4. 6-(2,3,5-Tri-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)-5-oxo-2,3,5,6-tetrahydro-imidazo[1,2-*c*]pyrimidine-2-carbonitrile) (11). To a solution of 2′,3′,5′-tri-*O*-*tert*-butyldimethylsilyl-cytidine[15] (**8**) (10.0 g, 17.06 mmol) in anhydrous THF (50 mL) was added 2-chloroacrylonitrile (2.04 mL, 25.6 mmol) and diisopropylethylamine (4.46 mL, 25.6 mmol). The reaction was heated under reflux for 6 h, then additional 2-chloroacrylonitrile (2.04 mL, 25.6 mmol) and diisopropylethylamine (4.46 mL, 25.6 mmol) were added, and the reaction was heated under reflux overnight. The reaction mixture was concentrated under reduced pressure and the resulting crude residue purified by flash column chromatography (petroleum ether–EtOAc 3:1 v/v) to give the product **11** as an orange syrup. Diastereomeric ratio 2(*R*):2(*S*) 1:1. Yield: 9.50 g (87%), TLC system: petroleum ether–EtOAc 1:1 v/v, R_F: 0.80. ^{1}H NMR ($CDCl_3$) δ 7.81 (d, $J_{7,8} = 8.2$ Hz, 1/2H, H-7), 7.78 (d, $J_{7,8} = 8.2$ Hz, 1/2H, H-7), 5.87 (d, $J_{1',2'} = 3.6$ Hz, 1/2H, H-1′), 5.86 (d, $J_{1',2'} = 3.1$ Hz, 1/2H, H-1′), 5.80 (d, $J_{8,7} = 8.1$ Hz, 1/2H, H-8), 5.79 (d, $J_{8,7} = 8.2$ Hz, 1/2H, H-8), 5.04 (m, 1H, H-2′), 4.22 (m, 2H, H-3′, H-4′), 4.11 (m, 3H, H-2 and H-3), 4.05 (m, 1H, H-5′), 3.79 (m, 1H, H-5′), 0.95 (m, 27H, $3\times C(CH_3)_3$), 0.14 (m, 18H, $3\times Si(CH_3)_2$). ^{13}C NMR ($CDCl_3$): δ 167.63, 167.55 (C, C-9), 157.60, 157.52 (C=O, C-5), 148.09, 148.01 (CH, C-7), 128.51, 128.42 (C, CN), 105.61, 105.52 (CH, C-8), 98.69, 98.43 (CH, H-1′), 94.55, 94.33 (CH, C-4′), 86.06, 85.87 (CH, C-2′), 81.08, 80.72 (CH, C-3′), 71.99, 71.73 (CH_2, C-3), 63.81, 63.76 (CH, C-2), 58.12 (CH_2, C-5′), 35.95, 35.76, 35.68 (CH_3, $C(CH_3)_3$), 28.42, 28.02, 27.91 (C, $C(CH_3)_3$), 5.78, 5.66, 5.38, 5.24, 5.14, 5.11, 4.54, 4.39, 4.36 (CH_3, $Si(CH_3)_2$). HRMS (ES+) for $C_{30}H_{57}N_4O_5Si_3$ $(M+H)^+$: calcd 637.3637; found, 637.3629. IR (NaCl): 2330.0 (CN), 1698.2 (C=O), 1650.1 (C=C/C=N) cm^{-1}.

4.2.5. 2(*R*) and 2(*S*) Diastereoisomers of 6-(β-D-ribofuranosyl)-5-oxo-2,3,5,6-tetrahydro-imidazo[1,2-*c*]pyrimidine-2-carbonitrile (12). Desilylation of **11** using the general method described gave crude **12**, which was purified by flash column chromatography ($CHCl_3$–MeOH, 9:1 v/v) to give the products, **12** (2*R*) and **12** (2*S*), as white syrups. Yield: isomer 1, 28%, isomer 2, 28%, TLC system: $CHCl_3$–MeOH 9:1 v/v, R_F: 0.14 and 0.25. ^{1}H NMR (CD_3OD) isomer 1 δ 8.04 (d, $J_{7,8} = 8.0$ Hz, 1H, H-7), 5.96 (d, $J_{8,7} = 8.0$ Hz, 1H, H-8), 5.88 (d, $J_{1',2'} = 4.3$ Hz, 1H, H-1′), 5.25 (m, 1H, H-2′), 4.35 (m, 1H, H-4′), 4.25 (m, 1H, H-3′), 4.18 (m, 2H, H-3), 4.03 (m, 1H, H-2), 3.85 (dd, $J_{5',4'} = 2.4$ Hz, $J_{5'a,5'b} = 12.2$ Hz, 1H, H-5′), 3.75 (dd, $J_{5',4'} = 2.6$ Hz, $J_{5'a,5'b} = 12.2$ Hz, 1H, H-5′). ^{13}C NMR (CD_3OD): δ 160.70 (C, C-9), 149.29 (C=O, C-5), 143.43 (CH, C-7), 119.55 (C, CN), 94.94 (CH, C-8), 91.28 (CH, C-1′), 86.85 (CH, C-2′), 76.14 (CH, C-3′), 71.58 (CH, C-4′), 62.49 (CH_2, C-5′), 52.85 (CH, C-2), 50.26 (CH_2, C-3).^{1}H NMR (CD_3OD) isomer 2 δ 7.98 (d, $J_{7,8} = 7.9$ Hz, 1H, H-7), 5.94 (d, $J_{8,7} = 7.9$ Hz, 1H, H-8), 5.88 (d, $J_{1',2'} = 4.0$ Hz, 1H, H-1′), 5.24 (m, 1H, H-2′), 4.34 (m, 1H, H-4′), 4.25 (m, 1H, H-3′), 4.16 (m, 2H, H-3), 4.02 (m, 1H, H-2), 3.85 (dd, $J_{5',4'} = 2.4$ Hz, $J_{5'a,5'b} = 12.2$ Hz, 1H, H-5′), 3.74 (dd, $J_{5',4'} = 2.8$ Hz, $J_{5'a,5'b} = 12.2$ Hz, 1H, H-5′). ^{13}C NMR (CD_3OD): δ 160.70 (C, C-9), 149.36 (C=O, C-5), 143.09 (CH, C-7), 119.69 (C, CN), 95.19 (CH, C-8), 91.29 (CH, C-1′), 86.81 (CH, C-2′), 76.06 (CH, C-3′), 71.58 (CH, C-4′), 62.54 (CH_2, C-5′), 53.22 (CH, C-2), 50.28 (CH_2, C-3). HRMS (ES+) for $C_{12}H_{15}N_4O_5$ $(M+H)^+$: calcd 295.1042; found, 295.1049.

4.2.6. 6-(2,3,5-Tri-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)-5-oxo-5,6-dihydro-imidazo[1,2-*c*]pyrimidine-2-carbonitrile (13). To a solution of 2′,3′,5′-tri-*O*-*tert*-butyldimethylsilyl-1′-(5-oxo-2,3,5,6-tetrahydro-imidazo[1,2-*c*]-pyrimidine-2-carbonitrile)-β-D-ribofuranoside (**11**) (0.20 g, 0.31 mmol) in cumene (5.0 mL) was added 10% palladium on activated carbon (20 mg) and the reaction heated under reflux overnight. The reaction mixture was diluted with CH_2Cl_2/MeOH (25 mL 1:1 v/v) and this suspension filtered through a bed of Celite. The filtrate was collected, concentrated under reduced pressure and the resulting crude residue purified by flash column chromatography (petroleum ether–EtOAc 9:1 v/v) to give the product **13** as an orange foamy solid. Yield: 0.17 g (85%), mp: 50–52 °C, TLC system: $CHCl_3$–MeOH 9:1 v/v, R_F: 0.80. ^{1}H NMR ($CDCl_3$) δ 8.17 (s, 1H, H-3), 7.97 (d, $J_{7,8} = 8.1$ Hz, 1H, H-7), 6.53 (d, $J_{8,7} = 8.1$ Hz, 1H, H-8), 6.07 (d, $J_{1',2'} = 3.7$ Hz, 1H, H-1′), 4.11 (m, 3H, H-2′, H-3′, H-4′), 3.96 (m, 1H, H-5′), 3.74 (m, 1H, H-5′), 0.88 (m, 27H, $3\times C(CH_3)_3$), 0.11 (m, 18H, $3\times Si(CH_3)_2$). ^{13}C NMR ($CDCl_3$): δ 146.11 (C, C-9), 145.20 (C=O, C-5), 130.59 (CH, C-3), 121.15 (CH, C-7), 118.31 (C, C-2), 114.27 (C, CN), 98.75 (CH, C-8), 90.07 (CH, C-1′), 85.63 (CH, C-2′), 76.98 (CH, C-3′), 71.43 (CH, C-4′), 62.36 (CH_2, C-5′), 26.46, 26.24, 26.10 (CH_3, $C(CH_3)_3$), 18.92, 18.49, 18.33 (C, $C(CH_3)_3$), −3.82, −4.28, −4.34, −4.40, −4.94, −5.11 (CH_3, $Si(CH_3)_2$). Anal. for $C_{30}H_{54}N_4O_5Si_3$ calcd C, 56.74%, H, 8.57%, N, 8.82%; found: C, 56.95%, H, 8.54%, N, 8.57%. LRMS (ES) m/z 657.7 $(M+Na)^+$. IR (NaCl): 2240.0 (C≡N), 1729.9 (C=O), 1632.5 (C=C/C=N) cm^{-1}.

4.2.7. 6-(β-D-Ribofuranosyl)-5-oxo-5,6-dihydro-imidazo-[1,2-*c*]pyrimidine-2-carbonitrile (14). Desilylation of **13** using the general method described gave crude **14**, which was purified by flash column chromatography ($CHCl_3$–MeOH, 94:6 v/v) to give **14** as a crispy white solid. Yield: 25 mg (54%), mp: 98–100 °C, TLC system: $CHCl_3$–MeOH 9:1 v/v, R_F: 0.29. ^{1}H NMR (CD_3OD) δ 8.45 (s, 1H, H-3), 7.98 (d, $J_{7,8} = 8.1$ Hz, 1H, H-7), 6.59 (d, $J_{8,7} = 8.1$ Hz, 1H, H-8), 6.07 (d, $J_{1',2'} = 4.5$ Hz, 1H, H-1′), 4.21 (dd, $J_{2',1'} = 4.8$ Hz, $J_{2',3'} = 9.6$ Hz, 1H, H-2′), 4.15 (dd, $J_{3',4'} = 4.9$ Hz, $J_{3',2'} = 9.7$ Hz, 1H, H-3′), 4.02 (m, 1H, H-4′), 3.83 (dd, $J_{5',4'} = 2.4$ Hz, $J_{5'a,5'b} = 12.2$ Hz, 1H, H-5′), 3.71 (dd, $J_{5',4'} = 2.8$ Hz, $J_{5'a,5'b} = 12.2$ Hz, 1H, H-5′). ^{13}C NMR (CD_3OD): δ 148.21 (C, C-9), 146.21 (C=O, C-5), 133.22 (CH, C-3), 123.25 (CH, C-7), 118.24 (C, C-2), 115.19 (C, CN), 98.91 (CH, C-8), 92.03 (CH, C-1′), 87.19 (CH, C-2′), 76.70 (CH, C-3′), 71.68 (CH, C-4′), 62.54 (CH_2, C-5′). HRMS (ES+) for $C_{12}H_{13}N_4O_5$ $(M+H)^+$: calcd 293.0886; found, 293.0879.

4.2.8. 2-Aminomethyl-6-(2,3-di-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)-5-oxo-5,6-dihydro-imidazo[1,2-*c*]pyrimidine-5-one (15). To a solution of **13** (0.26 g, 0.41 mmol) in methanol (3 mL) was added 10% Pd on activiated carbon (32 mg) and 1.25 M HCl in methanol (0.33 mL), and the reaction mixture hydrogenated at 40 psi overnight. Water was added to quench the reaction, which was then filtered through Celite and the filtrate concentrated under reduced pressure to give a yellow precipitate. Purification by flash column chromatography (CH_2Cl_2–MeOH, 93:7 v/v) gave the product **15** as a pale yellow syrup. Yield: 80 mg (37%), TLC system: $CHCl_3$–MeOH 9:1 v/v, R_F: 0.25. ^{1}H NMR ($CDCl_3$) δ 7.62 (d, $J_{7,8} = 7.9$ Hz, 1H, H-7), 7.58 (s, 1H, H-3), 6.55 (d, $J_{8,7} = 7.9$ Hz, 1H, H-8), 5.85 (d, $J_{1',2'} = 5.3$ Hz, 1H, H-1′), 5.30 (br s, 3H, 5′-OH, NH_2, ex), 4.50 (dd, $J_{2',1'} = 5.2$ Hz, $J_{2',3'} = 7.9$ Hz, 1H, H-2′), 4.23 (dd, $J_{3',4'} = 3.2$ Hz, $J_{3',2'} = 7.9$ Hz, 1H, H-3′), 4.11 (d, $J_{4',3'} = 3.1$ Hz, 1H, H-4′), 3.94 (m, 3H, H-5′(1) and CH_2), 3.75 (dd, $J_{5',4'} = 2.0$ Hz, $J_{5'a,5'b} = 12.2$ Hz, 1H, H-5′), 0.90 (s, 9H, $C(CH_3)_3$), 0.83 (s, 9H, $C(CH_3)_3$), 0.08 (s, 6H, $Si(CH_3)_2$), 0.00 (s, 6H, $Si(CH_3)_2$). ^{13}C NMR ($CDCl_3$): δ 145.94 (C, C-9), 145.78 (C=O, C-5), 138.42 (C, C-2), 130.36 (CH, C-3), 109.01 (CH, C-7), 99.04 (CH, C-8), 93.04 (CH, C-1′), 86.65 (CH, C-2′), 74.97 (CH, C-3′), 72.32 (CH, C-4′), 61.74 (CH_2, C-5′), 40.34 (CH_2, CH_2NH_2), 26.25, 26.15 (CH_3, $C(CH_3)_3$), 18.48, 18.29 (C, $C(CH_3)_3$), −4.02, −4.27, −4.37, −4.54 (CH_3, $Si(CH_3)_2$). HRMS (ES+) for $C_{24}H_{45}N_4O_5Si_2$ $(M+H)^+$: calcd 525.2928; found, 525.2925.

4.2.9. 2-Aminomethyl-6-(2,3,5-tri-*O*-*tert*-butyldimethylsilyl-β-D-ribofuranosyl)-5-oxo-5,6-dihydro-imidazo[1,2-*c*]-pyrimidine-5-one (16). To a solution of **13** (0.16 g, 0.26 mmol) in methanol (3 mL) was added 10% Pd on activiated carbon (20 mg) and the reaction mixture hydrogenated at 40 psi overnight. Water was added to quench the reaction, which was then filtered through Celite and the filtrate concentrated under reduced pressure to give a yellow precipitate. Purification by flash column chromatography (CH_2Cl_2–MeOH, 96:4 v/v) gave the product **16** as a colourless syrup. Yield: 20 mg (16%), TLC system: $CHCl_3$–MeOH 9:1 v/v, R_F: 0.50. ^{1}H NMR ($CDCl_3$) δ 7.78 (d, $J_{7,8} = 7.9$ Hz, 1H, H-7), 7.60 (s, 1H, H-3), 6.48 (d, $J_{8,7} = 7.9$ Hz, 1H, H-8), 6.10 (d, $J_{1',2'} = 3.4$ Hz, 1H, H-1′), 4.12 (m, 3H, H-2′, H-3′, H-4′), 3.98 (dd, $J_{5',4'} = 1.8$ Hz, $J_{5'a,5'b} = 11.8$ Hz, 1H, H-5′), 3.75 (dd, $J_{5',4'} = 1.5$ Hz, $J_{5'a,5'b} = 11.8$ Hz, 1H, H-5′), 2.00 (br s, 2H, NH_2, ex), 0.93 (s, 9H, $C(CH_3)_3$), 0.88 (s, 9H, $C(CH_3)_3$), 0.83 (s, 9H, $C(CH_3)_3$), 0.12 (s, 6H, $Si(CH_3)_2$), 0.11 (s, 6H, $Si(CH_3)_2$), 0.05 (s, 6H, $Si(CH_3)_2$). ^{13}C NMR ($CDCl_3$): δ 146.11 (C, C-9), 145.47 (C=O, C-5), 145.05 (C, C-2), 128.05 (CH, C-3), 110.24 (CH, C-7), 98.94 (CH, C-8), 89.79 (CH, C-1′), 85.20 (CH, C-2′), 76.89 (CH, C-3′), 71.39 (CH, C-4′), 62.36 (CH_2, C-5′), 46.76 (CH_2, CH_2 NH_2), 26.45, 26.27, 26.17 (CH_3, $C(CH_3)_3$), 18.91, 18.52, 18.36 (C, $C(CH_3)_3$), −3.81, −4.20, −4.37, −4.41, −4.99, −5.10 (CH_3, $Si(CH_3)_2$). HRMS (ES+) for $C_{30}H_{59}$ N_4 O_5 Si_3 $(M+H)^+$: calcd 639.3793; found, 639.3789.

5. Virology

5.1. Experiments with virus-infected cell cultures

The antiviral assays were based on an inhibition of virus-induced cytopathicity in either human embryonic skin muscle (E_6SM) cells, HeLa cells, simian Vero cells, or human embryonic lung (HEL) cell cultures, following previously established procedures.[18–21] Briefly, confluent cell cultures in microtiter trays were inoculated with 100 $CCID_{50}$ of virus, 1 $CCID_{50}$ being the virus dose required to infect 50% of the cell cultures. After a 1 h virus adsorption period, residual virus was removed, and the cell cultures were incubated in the presence of varying concentrations (400, 200, 100,... μg/mL) of the test compounds. Viral cytopathicity was recorded as soon as it reached completion in the control virus-infected cell cultures. The following viruses were included in the study: herpes simplex virus type 1 (HSV-1, strain KOS), HSV-2 (strain G), a thymidine kinase (TK)-deficient HSV-1 strain (HSV-1/TK$_-$ ACV^r), vaccinia virus and vesicular stomatitis virus (VSV) in E_6SM cell cultures, cytomegalovirus (strain AD169 and Davis), varicella-zoster virus (strains YS and OKA) and TK-deficient VZV (strains 07/1 and YS/R) in HEL cell cultures, vesicular stomatitis virus, Coxsackie virus B4 and respiratory syncytial virus (RSV) in HeLa cell cultures, and parainfluenza-3 virus, reovirus-1, Sindbis virus, Coxsackie virus B4 and Punta Toro virus in Vero cell cultures.

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