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Lead tetraacetate mediated one pot oxidative cleavage and acetylation reaction: An approach to apio and homologated apio pyrimidine nucleosides and their anticancer activity

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An efficient and versatile strategy of general applicability towards apio and homologated apio pyrimidines has been delineated. The methodology portrays tosylation followed by *in situ* cyclization and one pot oxidative cleavage and acetylation by $Pb(OAc)_4$ as the key steps. The methodology has been applied to D-ribose and D-mannose derivatives to achieve asymmetric synthesis of apio and homologated apio pyrimidine nucleosides.

Introduction

A variety of nucleoside analogues have been synthesized with renewed exigency which enrich the antiviral and/or anticancer spectrum and amend the pharmacological properties of the parent compounds.[1] However, drug resistance, several side effects and toxicity have resulted in the limitation of clinical use of these agents. As a consequence, an incessant exploration and development of structurally new, expedient and novel nucleoside derivatives with prodigious bioactivity profile has been enduring since past decades. This has ensued in tremendous progress in the field of nucleosides with special prevalence in their asymmetric synthesis. Therefore, it is imperative that development of pioneering methodologies for the synthesis of potent nucleoside analogues is a prolific approach. Several structural modifications in both the sugar ring as well as the nucleobase have been reported in order to develop promising therapeutic agents.[2] Apionucleoside is one of such sugar ring modified nucleoside, in which the hydroxymethyl side chain is shifted from the 4′ position to the 3′ position (Figure 1). This class of nucleosides has enticed much attention owing to stabilization of the glycosyl bond under acidic condition, metabolic resistance to adenosine deaminase and influential biological activity.[3] For instance, apio 2′, 3′-dideoxyadenosine (apio-ddA) **4** has been reported to show potent anti-HIV activity comparable to that of the parent 2′, 3′-dideoxyadenosine (ddA) **3** and better stability against glycosidic bond hydrolysis than that of ddA.[4] Similarly, apio-analogues of neplanocin and aristeromycin have also been described as selective A_3 adenosine receptor agonists.[5]

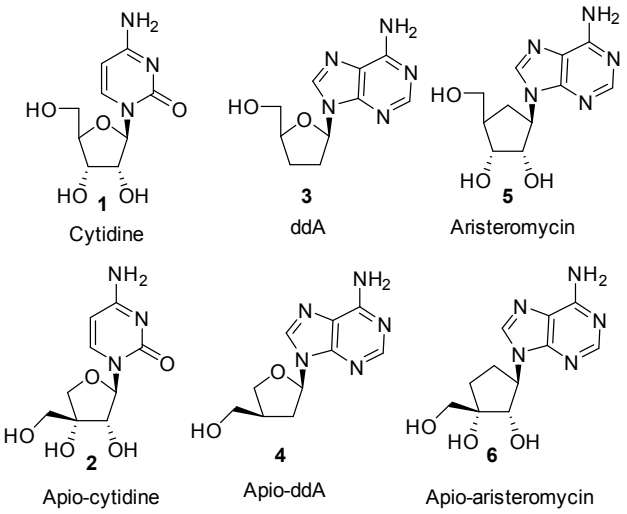

Fig. 1 Representative nucleosides and their apio analogues.

In homologated nucleosides, the incorporation of a single bond between the nucleobase and the sugar helps the nucleoside for free rotation, which may provide a better edifice to persuade maximum favorable interactions in the binding sites. Hence, the synthesis of homologated-apio nucleosides is of great interest which might combine the properties of both apionucleosides and homologated nucleosides. While a few number of synthetic routes for D-apiofuranose and its derivatives have been published,[6] most of these procedures suffer from multistep synthesis with low overall yield, lack of selectivity and less cost-effective etc.

Owing to the above intricacies and our continuing research interest in development of novel synthetic methodologies towards potent modified nucleoside templates, we thought to devise an improved, efficient and stereoselective route to D-apio and homologated-apio nucleosides and wish to report our exploratory

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results here in. Our retrosynthetic strategy towards the target nucleosides is as shown in figure 2. We contemplated that, both the apio pyrimidine and homologated apio pyrimidine derivatives would be obtained from a common diol intermediate **8**. The D-apio pyrimidine analogue was prophesied to be synthesized from D-apiofuranoacetate **7** *via* Vorbrüggen condensation[7] and deprotection. The key apioacetate **7** and homologated apio alcohol **11** were envisaged to be derived from the common diol intermediate **8** *via* oxidative cleavage, acetylation and oxidative cleavage, reduction respectively. Further, the diol **8** was predicted to be synthesized from lactol **9** by tosylation and *in situ* tetrahydrofuran formation followed by dihydroxylation sequentially and the lactol **9** can be prepared from D-ribose **10** by the reported procedure.[8]

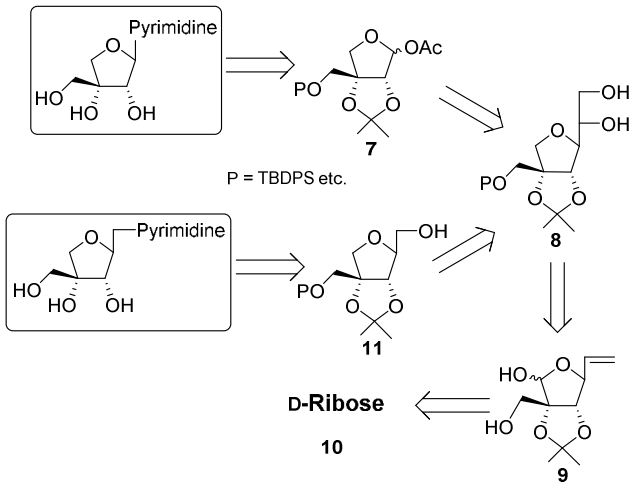
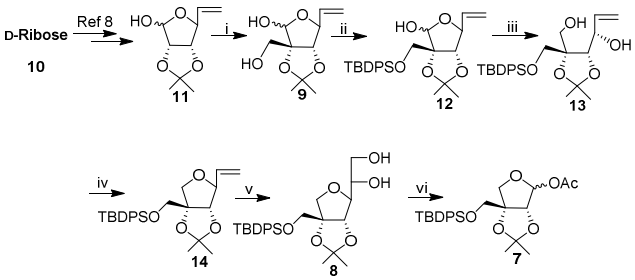


Fig. 2 Retrosynthetic strategy of target nucleosides.

Results and discussion

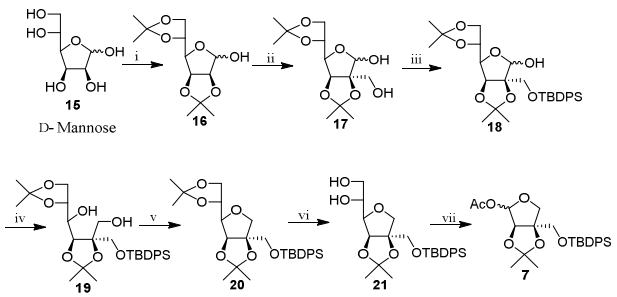
In order to execute the aforementioned retrosynthetic strategy outlined in figure 2, a general and unified approach for the key apio acetate **7** was commenced as shown in scheme 1. The lactol **11** which was readily prepared from D-ribose by the reported procedure,[8] underwent stereoselective hydroxymethylation using 37% aqueous formaldehyde in methanol to yield hydoxymethylated compound **9** which established the apio frame work. The hydroxymethylated compound **9** was subjected to selective primary hydroxyl group protection by TBDPSCl to give *tert*-butyldiphenylsilyl ether **12** in very good yield. The compound **12** upon reduction with sodium borohydride in methanol formed the diol **13** and subsequent exposure of the diol **13** to *p*-tolunesulfonylchloride in dry pyridine at room temperature furnished the desired olefin **14** by primary alcohol tosylation and *in situ* tetrahydrofuran formation.[9] Dihydroxylation of olefin derivative **14** by OsO_4 and NMO exhibited the diol **8** in good yield.[10] The key acetate **7** was achieved from the diol **8** by treatment of excess lead tetraacetate in EtOAc at room temperature.



Reagents and conditions: (i) 37% aq. HCHO, K_2CO_3, MeOH, reflux, 36 h, 91%; (ii)TBDPSCl, Et_3N, DMAP, CH_2Cl_2, 15 h, 90%; (iii) $NaBH_4$, MeOH, 0 °C-RT, 1 h, 95%; (iv) TsCl, Py, rt, overnight, 87%; (v) OsO_4, NMO, Acetone:H_2O, 8 h, 91%; (vi) $Pb(OAc)_4$, EtOAc, rt, 20 h, 72%.

Scheme 1 Synthesis of the key apio acetate from D- ribose

The versatility of the above mentioned methodology was examined on D-mannose derived lactol **18** and the key acetate **7** was prepared with quantitative yield in relatively shorter steps than that from D-ribose as shown in the scheme 2. Initially D-mannose **15** was converted to di-acetonide **16** by treating with molecular iodine in acetone.[11] The hydroxymethylation was accomplished on compound **16** with 37% HCHO aqueous solution in methanol to afford compound **17** in a stereoselective manner.[12] The selective protection of the primary hydroxyl group of the compound **17** by TBDPSCl delivered the *tert*-butyldiphenylsilyl ether derivative 18. $NaBH_4$ reduction of compound **18** gave the diol **19** which on tosylation and in situ cyclization furnished the desired lactol **20**. Deprotection of primary acetonide group in compound **20** was accomplished selectively by 60% acetic acid to produce the diol **21** in good yield.[13] The diol **21** upon treatment with excess $Pb(OAc)_4$ in ethyl acetate afforded the acetate **7** in good yield.

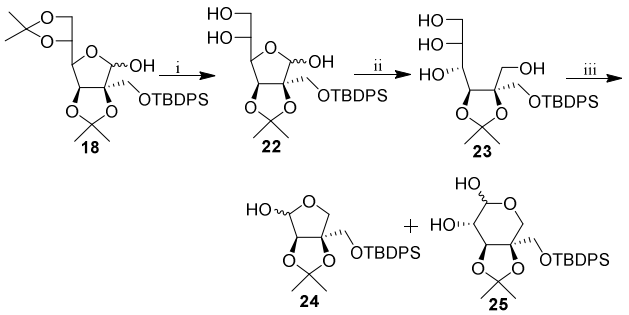


Reagents and conditions: (i) I_2, acetone, rt, 24 h, 88%; (ii) aq. HCHO, K_2CO_3, MeOH, reflux, 36 h, 86%; (iii) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, 15 h, 90%; (iv) $NaBH_4$, MeOH, rt, 1 h, 94%; (v) TsCl, Py, rt, overnight, 92%; (vi) 60% AcOH, rt, 6 h, 81%; (vii) $Pb(OAc)_4$, EtOAc, rt, 24 h, 72%

Scheme 2 Synthesis of the key apio acetate from D- Mannose

The efficacy of the present methodology towards the synthesis of the D-apiofuranose over the reported [6d-f] procedure was appraised by endeavoring the same sequence of reaction conditions to the D-mannose derivative **18** (Scheme 3). The selective hydrolysis of 5,6-acetonide of **18** in the presence of the 2,3-acetonide was achieved with 60% acetic acid or 0.8% H_2SO_4 in MeOH to give the triol **22**. On the contrary to the reported method,

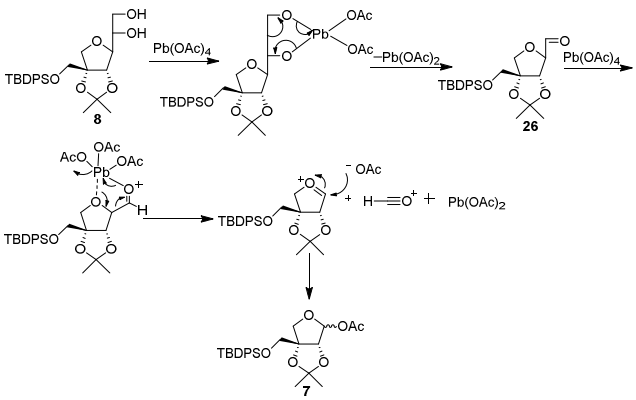
the $NaBH_4$ reduction of the triol **22** followed by oxidative cleavage using sodium metaperiodate provided the compounds **24** and **25**. The formation of the major product **25** may be elucidated as it endures the faster cleavage of one primary and one secondary hydroxyl group than the cleavage of both secondary hydroxyl groups to form **24**. Therefore, by considering the above fact, present methodology has been proven to be more dynamic and proficient for the synthesis of D-apiofuranoacetate**.**



Reagents and Condition: (i) 60% AcOH, rt, 24 h, 84%; (ii) $NaBH_4$, MeOH, rt, 4 h, 91%; (iii) $NaIO_4$, CH_2Cl_2, H_2O, 0 °C to rt, 2 h, 36% for **24** and 49% for **25**

Scheme 3 Synthesis of D-apiose **24** and **25**

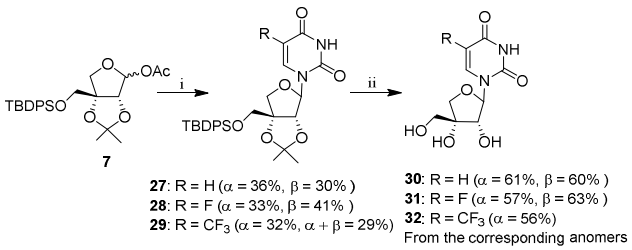
The direct formation of acetate from vicinal diol on furanose sugar frameworks has not been explored yet. However, a few reports are available on thio sugar derivatives[14] where the oxidative cleavage of diol to aldehyde, oxidation of the aldehyde to acid and oxidative decarboxylation of acid were described as the presumable mechanistic pathway. In general, the oxidation of aldehyde to corresponding acid by $Pb(OAc)_4$ is not accustomed, rather it can produce acid by oxidative cleavage of α-hydroxycarbonyl compounds.[15] During the transformation of vicinal diol to apioacetate using lead tetraacetate, the intermediate apioaldehyde **26** was isolated and characterized, and after a longer duration, it was converted to the apioacetate directly without forming any corresponding acid derivative.



Scheme 4 Proposed mechanism for acetate formation

Hence the plausible mechanism for the conversion of apioacetate from vicinal diol using $Pb(OAc)_4$ has been explicated as shown in scheme 4.

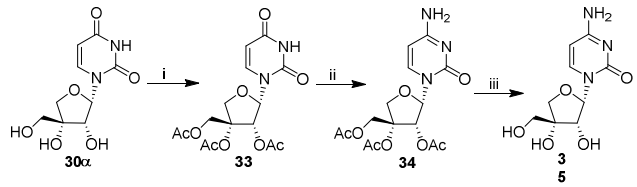
The synthesized apio acetates were used for nucleobase condensation under Vorbrüggen condition.[7] Condensation of glycosyl donor **7** with silylated pyrimidine bases (uracil, 5-F uracil, trifluorothymine) in presence of TMSOTf afforded the corresponding condensed products **27** to **29** as their (α & β) anomers. The TBDPS deprotection[16] of **27** to **29** by tetrabutyl ammonium fluoride (TBAF) followed by acetonide deprotection using 3N HCl provided the nucleosides **30** to **32** respectively (scheme 5).



Reagents and conditions: (i) HMDS, $(NH_4)_2SO_4$, nucleobase, DCE, TMSOTf; (ii) (a) TBAF, THF, rt, 1 h; (b) 3N HCl, rt.

Scheme 5 Synthesis of apio pyrimidine nucleosides

The major α anomer of uracil derivative **30** was transformed to the cytosine derivative **35** as shown in scheme 6.[17] Treatment of **30** with acetic anhydride in pyridine gave the triacetate **33** which was rehabilitated to the triazole adduct by treating with $POCl_3$ and 1,2,4-triazole in the presence of triethylamine. Subsequently, the triazole derivative was converted to the cytosine derivative **34** by treatment of ammonium hydroxide in 1,4-dioxane. Removal of the acetate groups by methanolic ammonia produced the final cytosine derivative **35**.



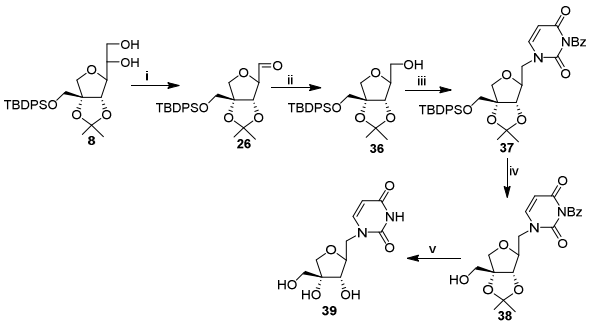
Reagents and conditions: (i) Ac_2O, Py, rt, overnight; (ii) $POCl_3$,1,2,4-Triazole, Et_3N, 24 h, NH_4OH, rt,15 h; (iii) methanolic NH_3, rt, overnight, 50% for 3 steps.

Scheme 6 Conversion of uracil derivative **30α** to cytosine derivative **35**

All the synthesized compounds were thoroughly characterized by ^1H NMR, ^{13}C NMR, ^{19}F NMR, HRMS, IR and UV spectroscopy and the spectral data of compounds **30** and **35** were compared with the reported literature.[18]

The synthesis of homologated-apio pyrimidine by employing this methodology was also successfully accomplished (Scheme 7). The oxidative cleavage of the diol **8** by leadtetraacetate at 0 °C furnished the aldehyde **26**, which upon reduction with sodium borohydride produced the key alcohol **36**.[19] The condensation of alcohol **36** with N^3-benzoyluracil under Mitsunobu condition afforded the uracil derivative **37**.[17a] Treatment of **37** with methanolic ammonia followed by desilylation produced the

compound **38**. The acetonide deprotection of compound **38** with 3N HCl furnished the final uracil nucleoside **39**.



Reagents and conditions: (i) $Pb(OAc)_4$, EtOAc, 0 °C, 10 min, 87%; (ii) $NaBH_4$, MeOH, rt,1 h, 92%; (iii) N^3-benzoyluracil, DIAD, PPh_3, THF, 16 h; (iv)TBAF, THF, rt, 1 h, 62% (for 2 steps); (v) (a) NH_3/ MeOH, rt; (b) 3N HCl, rt, overnight, 58%.

Scheme 7 Synthesis of homologated apio pyrimidine nucleoside

Anticancer activity study

Anticancer activity of the compound **30α**, **31β**, **35** and **39** were tested in breast cancer cell line MCF7 using standard MTT cell viability assay. MCF7 cells were treated with different concentration of the compounds for 48 hours and measured the growth inhibition effect. Results demonstrated that, these compounds do not have anticancer activity as compared to the 5-fluoro-uracil (5-FU). For example, 5-FU inhibits 50% growth of MCF (IC_{50}) at 7.57 ± 1.21 µM whereas IC_{50} for these compounds are >100 µM.

Conclusions

In summary, an efficient, general and effective synthetic route to apio and homologated apio pyrimidine nucleosides has been described. The methodology involves tosylation followed by *in situ* cyclization and one pot oxidative cleavage and acetylation by $Pb(OAc)_4$ as the key steps. To the best of our knowledge, apio and homologated apio nucleosides synthesized here are the first example accomplishing lead tetraacetate mediated one pot oxidative cleavage and *in situ* acetylation on D-furanose templates. The pyrimidine nucleoside derivatives have been synthesized successfully starting from both D-ribose and D-mannose. However, compounds **30α**, **31β**, **35** and **39** did not show significant anticancer activity. The present methodology has been found to be more competent for the synthesis of D-apiofuranose frameworks and also offers ample opportunity for the synthesis of several apio, homologated and truncated nucleoside analogues for therapeutic profiling.

Experimental Section

General Information

All reagents and solvents were purchased from commercial suppliers and used without purification, unless otherwise stated. All moisture and air-sensitive reactions were performed under argon atmosphere with dry and freshly distilled solvents at anhydrous condition. Reactions were monitored by analytical thin-layer chromatography (TLC) on aluminum precoated Merck silica gel plates (EM-60-F254) and spots visualized by exposure to UV lamp and/or charring solution (*p*-anisaldehyde) followed by heating. Solvents were removed in a rotary evaporator under reduced pressure. Column chromatography was generally performed on silica gel (100-200 mesh) and the elution was done with hexane & ethyl acetate and dichloromethane & methanol mixtures. The reported yields are for the isolated compounds. Melting points were recorded in Buchi M-560 instrument and are uncorrected. ^{1}H NMR (400 MHz), proton decoupled ^{13}C NMR (100 MHz) and proton decoupled ^{19}F NMR (376.5 MHz) were recorded on a Bruker Avance 400 spectrometer. Samples were generally prepared in $CDCl_3$ and chemical shifts are expressed in parts per million (δ) scale using tetramethylsilane (Me_4Si) as internal standard (for ^{1}HNMR) and the central line of $CDCl_3$ (for ^{13}C NMR). Coupling constants (*J*), whenever discernible, have been reported in hertz (Hz). The standard abbreviations s, d, t, q, m, br s refer to singlet, doublet, triplet, quartet, multiplet and broad singlet respectively. High resolution mass spectra (HRMS) were recorded on +ESI mode with Q-TOF Micromass spectrometer. UV spectra were recorded on a Perkin Elmer Lambda-35 UV/vis spectrometer IR spectra were recorded in a range 4000-600 cm^{-1} with Bruker Tensor 27 (FT-IR) spectrometer on NaCl plates or in KBr.

(1*S*)-1-((5*S*)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-en-1-ol (13). To a cooled (0 °C) stirred solution of **12** (4.6 g, 10.12 mmol) in methanol (50 ml) was added portion wise $NaBH_4$ (0.77 g, 20.22 mmol) and the resulting reaction mixture was allowed to stir at room temperature for 1 hour. The reaction mixture was neutralized with acetic acid and evaporated under reduced pressure. The residue was partitioned by EtOAc (80 ml) and water (60 ml), the aqueous layer was extracted using EtOAc (3 x 100 ml). The combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4. After evaporation of solvent, the crud residue was purified through a silica gel column chromatography [Hexane/ EtOAc (10:1)] to afford the diol **13** (4.4 g, 95%) as a colorless solid: R_f 0.48 [hexanes/EtOAc (4:1)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.08 (s, 9H), 1.31 (s, 3H), 1.43 (s, 3H), 2.43 (br s, 1H), 3.61 (br s, 1H), 3.79 (s, 2H), 3.83 to 3.87 (m, 3H), 4.33 to 4.36 (m, 1H), 5.23 (td, 1H, *J* = 1.6 Hz, 10.4 Hz), 5.42 (td, 1H, *J* = 1.2 Hz, 17.2 Hz), 5.93-6.01 (m, 1H), 7.37-7.44 (m, 6H), 7.69-7.73 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 19.4, 26.5, 27.1, 28.6, 62.2, 66.5, 70.1, 81.7, 84.7, 108.5, 116.3, 128.0, 128.1, 130.1, 132.7, 133.0, 135.8, 136.1, 137.8; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{26}H_{36}O_5SiNa$ 479.2230; found 479.2227.

***tert*-butyl(((3a*S*,6a*S*)-2,2-dimethyl-6-vinyldihydrofuro[3,4-*d*][1,3]dioxol-3a(4*H*)-yl)methoxy) diphenylsilane (14).** To a stirred solution of compound **13** (4.4 g, 9.64 mmol) in pyridine (30 ml) at 0 °C was added *p*-tolune sulfonyl chloride (4.6 g, 24.1 mmol). Then the reaction mixture was stirred at room temperature for overnight. Pyridine was co-evaporated with toluene (2 x 15 ml) and the residue was diluted with water (50 ml) and ethyl acetate (70 ml). The aqueous phase was extracted using ethyl acetate (3 x 80 ml). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. Removal of solvent followed by

column chromatography [Hexane/ EtOAc (25:1)] of the crud product on silica gel yielded the compound **14** (3.7 g, 87 %) as a colorless liquid: R_f 0.55 [hexanes/EtOAc (9:1)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.06 (s, 9H), 1.37 (s, 3H), 1.54 (s, 3H), 3.66 (d, 1H, *J* = 10.8 Hz) 3.78 (d, 1H, *J* = 10.8 Hz), 3.90 (q, 2H, *J* = 10 Hz, 17.6 Hz), 4.49 (d, 1H, *J* = 1.2 Hz), 4.57-4.59 (m, 1H), 5.16 (td, 1H, *J* = 1.6 Hz, 10.8 Hz), 5.30 (td, 1H, *J* = 1.6 Hz, 17.2 Hz), 5.74-5.83 (m, 1H), 7.36-7.43 (m, 6H), 7.65-7.78 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 19.5, 27.0, 28.1, 65.3, 74.6, 86.0, 87.0, 93.3, 113.7, 116.7, 128.0, 130.0, 130.1, 133.0, 133.2, 135.8, 135.9 ; HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{26}H_{34}O_4SiNa$ 461.2124; found 461.2122.

(1*S*)-1-((3a*S*,6a*S*)-6a-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)ethane-1,2-diol (8). To a suspension of **14** (4 g, 9.12 mmol) in 100 ml acetone/water (3:1) was added *N*-methylmorpholine *N*-oxide (1.6 g, 13.7 mmol) and OsO_4 (2.5 % in ^{t}BuOH, 4 ml) successfully. The reaction mixture was stirred at room temperature for 8 h. The mixture was treated with 40% aqueous $NaHSO_3$ (10 ml) and the resulting solution was stirred for another 30 min. Acidified with saturated NH_4Cl aqueous solution and extracted with EtOAc (4 x 80 ml). The combined organic extracts were dried over anhydrous $NaSO_4$ and solvent was evaporated. The residue was purified by silica gel column chromatography [Hexane/ EtOAc (3:1)] to afford the diol **8** (3.95 g, 91 %) as a colour less fluid: R_f 0.4 [hexanes/EtOAc (1.5:1)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.07 (s, 9H), 1.36 (d, 3H, *J* = 7.6 Hz), 1.51 (d, 3H, *J* = 3.6), 3.00 (br d, 2H), 3.63-3.75 (m, 4H), 3.82-3.88 (m, 2H), 3.92-4.00 (m, 2H), 4.66 (dd, 1H, *J* = 1.6 Hz, 2.4 Hz), 7.36-7.43 (m, 6H), 7.67-7.70 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 19.4, 27.0, 27.9, 28.0, 28.2, 28.3, 63.7, 63.9, 65.1, 65.3, 70.3, 71.0, 75.0, 75.4,84.4, 85.9, 86.6, 92.9, 93.3, 114.1, 114.3, 127.9, 130.0, 130.1, 132.9, 135.8, 135.9; HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{26}H_{36}O_6SiNa$ 495.2179; found 495.2181.

(3a*R*,6a*S*)-6a-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl acetate (7). To an ice-cooled solution of **8** (1 g, 2.12 mmol) in EtOAc (40 mL) was added excess of $Pb(OAc)_4$ (4.95 g, 11.2 mmol) at 0 °C and the reaction mixture was stirred for overnight at rt. The reaction mixture was filtered with celite and the filtrate was diluted with EtOAc (50 ml). The filtrate was washed with saturated aqueous $NaHCO_3$ solution (20 ml), aqueous layer was extracted using EtOAc (3 x 50 ml), dried over anhydrous $NaSO_4$, and evaporated. The residue was purified by silica gel column chromatography [hexane/ethyl acetate, (12:1)] to give **7** (0.72 g, 72 %) as colour less thick liquid: R_f 0.6 [hexanes/EtOAc (4:1)]; IR (film, ν_{max} in cm^{-1}) 3071, 3050, 2991, 2934, 2891, 2859, 1739, 1468, 1428, 1219; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.09 (s, 9H), 1.34 (s, 3H), 1.48 (s, 3H), 2.02 (s, 3H), 3.80 (q, 2H, *J* = 10.4 Hz), 4.03 (d, 1H, *J* = 10 Hz), 4.16 (d, 1H, *J* = 10 Hz), 4.63 (s, 1H), 6.19 (s, 1H), 7.38-7.46 (m, 6H), 7.66-7.69 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 19.5, 21.3, 27.0, 27.9, 28.1, 64.6, 75.7, 86.9, 92.2, 102.3, 114.1, 128.0, 128.1, 130.2, 132.9, 135.8, 135.9, 169.9; ; HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{26}H_{34}O_6SiNa$ 493.2022; found 493.2025.

***tert*-butyl(((3a*S*,6a*S*)-6-(2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-3a-yl)methoxy)diphenylsilane (20).** To a cooled (0 °C) and stirred solution of **19** (10 g, 18.8 mmol) in pyridine (70 mL) was added *p*-toluenesulfonyl chloride (10.8 g, 56.6 mmol). Stirring was continued overnight at ambient temperature. The solvent was co-evaporated with tolune (2 x 30 ml), and the residue was dissolved ethyl acetate (100 ml) and washed with water (150 ml). The aqueous layer was extracted using EtOAc (2 x 180 ml), combined organic layer was dried over anhydrous Na_2SO_4 and solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography using hexane and ethyl acetate as eluents [hexane/ethyl acetate, (25:1)] to give the compound **20** (8.9 g, 92 %) as colourless liquid. R_f 0.5 [hexanes/EtOAc (9:1)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.07 (s, 9H), 1.28 (s, 3H), 1.39 (s, 3H), 1.45 (d, 6H, *J* = 5.6 Hz), 3.61 (dd, 1H, *J* = 3.2 Hz, 8 Hz), 3.77 (d, 2H, *J* = 4.4 Hz), 3.83 (d, 1H, *J* = 10 Hz), 3.90 (d, 1H, *J* = 10 Hz), 4.06-4.13 (m, 2H), 4.39-4.44 (m, 1H), 4.64 (d, 1H, *J* = 3.2 Hz), 7.37-7.46 (m, 6H), 7.64-7.67 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 19.4, 25.5, 26.9, 27.1, 27.4, 27.5, 65.2, 67.1, 73.5, 75.6, 83.9, 92.7, 109.3, 113.3, 128.0, 128.1, 130.2, 132.9, 135.7, 135.8 ; HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{29}H_{40}O_6SiNa$ 535.2492; found 535.2466.

1-((3a*S*,6a*S*)-6a-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)ethane-1,2-diol (21). To a solution of **20** (8.9 g, 17.4 mmol) in 60 % aqueous AcOH (80 ml) was stirred at room temperature for 6 h. The reaction mixture was evaporated under reduced pressure, and the resulting residue was purified by silica gel column chromatography [hexane/EtOAc, (2.5:1)] to give the diol **21** (6.7 g, 81%) as a thick liquid. R_f 0.35 [hexanes/EtOAc (1:1)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.07 (s, 9H), 1.30 (s, 3H), 1.48 (s, 3H), 2.17 (br s, 1H), 2.77 (br s, 1H), 3.61 (dd, 1H, *J* = 3.2 Hz, 7.6 Hz), 3.74-3.81 (m, 4H), 3.86 (dd, 1H, *J* = 3.2 Hz, 11.2 Hz), 3.92 (d, 1H, *J* = 10 Hz), 4.07 (s, 1H), 4.66 (d, 1H, *J* = 3.2 Hz), 7.37-7.46 (m, 6H), 7.64-7.67 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 19.4, 26.9, 27.1, 27.6, 64.9, 65.2, 70.5, 75.4, 83.1, 84.3, 92.8, 113.5, 128.0, 128.1, 130.2, 132.9, 135.7, 135.8, 135.9; HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{26}H_{36}O_6$ SiNa 495.2179; found 495.2138.

1-((3a*S*,6a*S*)-6a-(((*tert*-butyldiphenylsilyl)oxy)methyl)-6-hydroxy 2,2dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)ethane-1,2-diol (22). A solution of **18** (7.5 g, 14.2 mmol) in 60% aqueous AcOH (60 ml) was stirred at room temperature for 24 h and the reaction mixture was evaporated. The resulting residue was purified by silica gel column chromatography [hexane/ethyl acetate (2:1)] to give the triol **22** (5.8 g, 84%) as diastereomeric mixtures as colourless liquid. R_f 0.45 [hexane/EtOAc (1:1)]; HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{26}H_{36}O_7$ SiNa 511.2128; found 511.2131.

(1*R*)-1-((4*S*,5*S*)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propane-1,2,3-triol (23). To a stirred solution of triol **22** (4.5 g, 9.2 mmol) in MeOH (50 ml) was added, cautiously in several portions, excess of sodium borohydride (1.58 g, 41.8 mmol) at 0 °C and the reaction mixture was stirred at room temperature for 4 h. It was neutralized with acetic acid and evaporated to dryness. The mixture was partitioned between EtOAc (60 ml) and water (50 ml) and the organic layer was extracted by EtOAc (4 X 60 ml), dried over anhydrous Na_2SO_4 and evaporated. The resulting residue was purified by silica gel column chromatography [hexane:EtOAc, (1.5:1)] to give **23** (4.1 g, 91%) as a color less syrup: R_f 0.56 [hexane/EtOAc (1:2)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.06 (s, 9H), 1.35 (s, 3H), 1.49 (s, 3H), 3.02 (br s, 3H, exchanged with D_2O), 3.67-3.82 (m, 8H), 3.94 (d, 1H, *J* = 6.8 Hz), 4.42 (s, 1H), 7.38-7.44 (m, 6H), 7.66-7.68 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 19.4, 26.7, 27.0, 28.0, 63.4, 64.1, 66.8, 69.9, 73.0, 83.9, 108.5, 128.0, 130.1, 130.2, 132.7, 135.8, 135.9; HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{26}H_{38}O_7SiNa$ 513.2285; found 513.2280.

(3a*R*,6a*S*)-6a-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-ol (24) and (3a*S*,7*S*,7a*S*)-3a-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,2-dimethyltetrahydro-4*H*-[1,3]dioxolo[4,5-c]pyran-6,7-diol (25) To the stirred suspension of **23** (3 g, 6.1 mmol) in methylene chloride (30 ml), an aqueous solution of of $NaIO_4$ (3.27 g, 15.3 mmol) was added dropwise at 0 °C and the reaction was stirred for 2 hours at rt. After addition of water (40 ml), the aqueous phase was extracted with methylene chloride (3 x 50 ml). The combine organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give the crud product. It was then purified by silica gel column chromatography using hexane and ethyl acetate as eluent to give the lactols **24** and **25**.

Data for Compound (**24**): Colourless oil, (0.94 g, 36%); R_f 0.6 [hexane/EtOAc (3:1)] ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.08 (s, 9H), 1.29 (s, 3H), 1.47 (s, 3H), 3.13 (d, 1H, *J* = 6.4 Hz), 3.80 (d, 2H, *J* = 1.6 Hz), 3.96 (d, 1H, *J* = 10 Hz), 4.16 (d, 1H, *J* = 10 Hz), 4.43 (s, 1H), 5.39 (d, 1H, *J* = 6.4 Hz), 7.38-7.45 (m, 6H), 7.66-7.69 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 19.4, 27.0, 27.1, 27.4, 27.8, 65.0, 65.7, 70.6, 74.3, 81.8, 87.6, 91.5, 91.7, 98.4, 102.0, 113.5, 114.5, 127.9, 128.1, 130.2, 132.6, 135.7, 135.8, 135.9, 136.0; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{24}H_{32}O_5SiNa$ 451.1917; found 451.1915.

Data for Compound (**25**): Colourless oil, (1.37 g, 49%); R_f 0.5 [hexane/EtOAc (2:1)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.08 (s, 9H), 1.32 (s, 3H), 1.46 (s, 3H), 3.60 (d, 1H, *J* = 12.4 Hz), 3.66-3.74 (m, 3H), 3.84 (d, 1H, *J* = 12.4Hz), 3.98 (td, 1H, *J* = 2.4 Hz, 8.4 Hz), 4.06 (d, 1H, *J* = 10 Hz), 4.40 (d, 1H, *J* = 2.8 Hz), 4.97 (dd,1H, *J* = 2.0 Hz, 10 Hz), 7.37-7.47 (m, 6H), 7.67-7.73 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 19.3, 26.7, 26.8, 27.0, 28.0, 28.3, 62.5, 66.5, 68.1, 68.2, 78.7, 78.9, 92.0, 94.4, 109.9, 128.1, 130.3, 132.1, 132.4, 135.8, 136.1; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{25}H_{34}O_6SiNa$ 481.2022; found 481.2022.

General method for pyrimidine nucleobase condensation to apio acetate: (**27-29**) Corresponding nucleobase (2 equiv.), ammonium sulfate (0.5 equiv.) and HMDS (50 ml) were refluxed at 160 °C under inert and dry conditions for overnight. The solvent was evaporated under high vacuum. The resulting solid was re-dissolved in 1,2-dichloroethane (30 ml), cooled to 0 °C and stirred at inert condition. To the stirring mixture, was added a solution of apio acetate 7 (1 equiv.) in 1,2- dichloroethane (20 ml) and TMSOTf (2 equiv.) dropwise. The Mixture was stirred for 30 minutes at 0 °C, for 1 h at rt, and then heated 80 °C for 8 h. After completion (TLC) the mixture was cooled, diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$ solution. The organic layer was dried with Na_2SO_4 and evaporated under reduced pressure. The crud product was subjected to silica gel column chromatography (hexane/ EtOAc) to give corresponding pure pyrimidine nucleoside derivatives.

1-((3a*R*,6a*S*)-6a-(((tert-butyldiphenylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)pyrimidine-2,4(1*H*,3*H*)-dione (27α). Colourless liquid, (0.35 g, 36%); R_f 0.6 [hexane/EtOAc (1:1)] ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.10 (s, 9H), 1.18 (s, 3H), 1.46 (s, 3H), 3.79 (s, 2H), 3.97 (d, 1H, *J* = 10 Hz), 4.05 (d, 1H, *J* = 10.4 Hz), 4.63 (d, 1H, *J* = 2.8 Hz), 5.70 (dd, 1H, *J* = 2.4 Hz, 8.4 Hz), 5.85 (d, 1H, *J* = 2.8 Hz), 7.40-7.47 (m, 6H), 7.61-7.69 (m, 5H), 8.43 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 19.4, 26.6, 27.1, 27.4, 65.0, 73.7, 81.5, 85.9, 91.4, 101.0, 114.1, 128.1, 128.2, 130.3, 130.4, 132.6, 135.9, 141.8, 150.0, 163.1.

1-((3a*R*,6a*S*)-6a-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)pyrimidine-2,4(1*H*,3*H*)-dione (27β). Colourless liquid, (0.29 g, 30%); R_f 0.5 [hexane/EtOAc (1:1)] ^{1} H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.02 (s, 9H), 1.36 (s, 3H), 1.54 (s, 3H), 3.78 (q, 2H, *J* = 10.8 Hz), 4.17 (d, 1H, *J* = 10 Hz), 4.24 (d, 1H, *J* = 10.4Hz), 4.88 (d, 1H, *J* = 0.8 Hz), 5.58 (dd, 1H, *J* = 2.4 Hz, 8 Hz), 5.76 (d, 1H, *J* = 1.2 Hz), 7.30(d, 1H, *J* = 8.4Hz), 7.36-7.46 (m, 7H), 7.59-7.61 (m, 4H), 8.22 (br s, 1H).

1-((3aR,6aS)-6a-(((tert-butyldiphenylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-5-fluoropyrimidine-2,4(1H,3H)-dione (28α). Colourless liquid, (0.15 g, 33%); R_f 0.65 [hexane/EtOAc (1.5:1)] ^{1} H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.10 (s, 9H), 1.18 (s, 3H), 1.48 (s, 3H), 3.79 (s, 2H), 3.97 (d, 1H, *J* = 10 Hz), 4.06 (d, 1H, *J* = 10 Hz), 4.61 (d, 1H, *J* = 2.8 Hz), 5.84 (dd, 1H, *J* = 2 Hz, 8 Hz), 7.39-7.47 (m, 6H), 7.64-7.71 (m, 5H), 9.23 (d, 1H, *J* = 4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 19.4, 26.6, 27.1, 27.4, 64.9, 73.8, 81.4, 85.8, 91.3, 114.2, 126.3, 126.6, 128.1, 128.2, 130.3, 130.4, 132.5, 135.8, 138.7, 141.0, 148.8, 156.9, 157.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -167.1(s).

1-((3a*R*,6a*S*)-6a-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-5-fluoropyrimidine-2,4(1*H*,3*H*)-dione (28β). Colourless liquid, (0.19 g, 41%); R_f 0.55 [hexane/EtOAc (1.5:1)] ^{1} H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.01 (s, 9H), 1.35 (s, 3H), 1.53 (s, 3H), 3.76 (q, 2H, *J* = 10.4 Hz), 4.19 (s, 1H), 4.89 (d, 1H, *J* = 0.8 Hz), 5.70 (s, 1H), 7.36-7.42 (m, 8H), 7.58-7.60 (m, 4H), 8.45 (d, 1H, *J* = 3.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 19.3, 26.9, 27.1, 28.1, 28.3, 64.0, 88.0, 91.9, 95.2, 114.9, 123.8, 124.1, 128.2, 130.4, 132.4, 135.7, 135.9, 148.7, 156.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -165.1(s); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{28}H_{33}FN_2O_6SiNa$ 563.1990; found 563.1989.

1-((3a*R*,6a*S*)-6a-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-5-(trifluoromethyl)pyrimidine-2,4(1*H*,3*H*)-dione (29α). Colorless liquid, (0.16 g, 32%); R_f 0.45 [hexane/EtOAc (2:1)] ^{1} H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.10 (s, 9H), 1.17 (s, 3H), 1.45 (s, 3H), 3.79 (s, 2H), 4.01 (d, 1H, *J* = 10 Hz), 4.10 (d, 1H, *J* = 10 Hz), 4.59 (d, 1H, *J* = 3.2 Hz), 5.89 (d, 1H, *J* = 2.8 Hz), 7.40-7.48 (m, 6H), 7.63-7.69 (m, 4H), 8.11 (d, 1H, *J* = 0.4 Hz) 8.25 (br s, 1H) ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 19.4, 26.6, 27.1, 64.8, 73.8, 81.2, 85.9, 91.5, 114.4, 128.2, 130.4, 130.5, 132.5, 135.8, 143.2, 148.8, 158.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -63.6(s); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{29}H_{33}F_3N_2O_6SiNa$ 613.1958; found 613.1957.

General procedure for synthesis of 30-32

To a solution of nucleoside derivatives (**27**-**29**) in THF was added TBAF solution (1.3 equiv.) at 0 °C and the reaction was allowed to stir at room temperature for 1 h. Solvent was removed, the residue was dissolved in EtOAc and washed with water and the aqueous layer was extracted using EtOAc dried and evaporated under reduced pressure to give the crud desilylated products. To the crud residue was added 3 N hydrochloric acid (8 ml) and the mixture stirred at room temperature for overnight. The mixture was neutralized with aqueous NH_3 solution, and then carefully evaporated under reduced pressure. The mixture was subjected to silica gel column chromatography (CH_2Cl_2/ MeOH) to afford the final nucleoside derivatives **30**-**32** respectively.

1-((3*R*,4*R*)-3,4-dihydroxy-4-(hydroxymethyl)tetrahydrofuran-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione (30α). Colorless liquid, (0.05 g, 61%) R_f 0.5 [CH_2Cl_2/ MeOH (4:1)]; UV (MeOH) λ_{max} 260 nm; ^{1}H NMR (400 MHz,CD_3OD) δ (ppm) 3.58 (s, 2H), 3.91 (d, 1H, *J* = 9.6 Hz), 3.99 (d, 1H, J = 9.6 Hz) 4.31 (d, 1H, *J* = 6.0 Hz), 5.64 (d, 1H, *J* = 8 Hz), 6.11 (d, 1H, J = 6.0 Hz), 7.83 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ (ppm) 65.0, 72.6, 74.8, 79.9, 87.7, 101.1, 144.9, 152.7, 166.7; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_9H_{12}N_2O_6Na$ 267.0593; found 267.0594.

1-((3*R*,4*R*)-3,4-dihydroxy-4-(hydroxymethyl)tetrahydrofuran-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione (30β).Colorless solid, (0.04 g, 60%) R_f 0.45 [CH_2Cl_2/ MeOH (4:1)]; mp 193−195 °C; UV (MeOH) λ_{max} 261 nm; ^{1}H NMR (400 MHz,CD_3OD) δ (ppm) 3.58 (q, 2H, *J* = 11.2 Hz), 3.88 (d, 1H, *J* = 10Hz), 4.31 (t, 2H, *J* = 9.6 Hz, 8 Hz), 5.75 (d, 1H, *J* = 8 Hz), 5.92 (d, 1H, *J* = 7.2 Hz), 7.66 (d, 1H, *J* = 8Hz); ^{13}C NMR (100 MHz, CD_3OD) δ (ppm) 64.3, 72.6, 76.5, 79.7, 91.8, 103.4, 143.2, 152.8, 166.2; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for C_9H_1 N_2O_6Na 267.0593; found 267.0594.

1-((3*R*,4*R*)-3,4-dihydroxy-4-(hydroxymethyl)tetrahydrofuran-2-yl)-5-fluoropyrimidine-2,4(1*H*,3*H*)-dione (31α). Colourless floppy solid, (0.05 g, 57%) R_f 0.55 [CH_2Cl_2/ MeOH (4:1)]; UV (MeOH) λ_{max} 268 nm; ^{1}H NMR (400 MHz, CD_3OD) δ (ppm) 3.57 (s, 2H), 3.89 (d, 1H, *J* = 9.6 Hz), 4.01 (d, 1H, *J* = 9.6 Hz) 4.34 (d, 1H, *J* = 6.0 Hz), 6.10 (dd, 1H, *J* = 1.6 Hz, 6.4 Hz), 8.00 (d, 1H, *J* = 7.2 Hz); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_9H_{11}FN_2O_6Na$ 285.0499; found 285.0500.

1-((3*R*,4*R*)-3,4-dihydroxy-4-(hydroxymethyl)tetrahydrofuran-2-yl)-5-fluoropyrimidine-2,4(1*H*,3*H*)-dione (31β). Hygroscopic white solid, (0.05 g, 63%) R_f 0.5 [CH_2Cl_2/ MeOH (4:1)]; UV (MeOH) λ_{max} 268 nm; ^{1}H NMR (400 MHz,CD_3OD) δ (ppm) 3.56 (q, 2H, *J* = 11.2 Hz), 3.87 (d, 1H, *J* = 9.6 Hz), 4.21 (d, 1H, *J* = 7.2 Hz), 4.31(d, 1H, *J* = 9.6 Hz), 5.93 (dd, 1H, *J* = 1.2 Hz, 7.6 Hz), 7.88 (d, 1H, *J* = 6.8 Hz) ^{13}C NMR (100 MHz, CD_3OD) δ (ppm) 64.3, 75.7, 76.4, 79.6, 91.5, 126.5, 126.9, 145.5; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_9H_{11}FN_2O_6$ Na 285.0499; found 285.0500.

1-((3*R*,4*R*)-3,4-dihydroxy-4-(hydroxymethyl)tetrahydrofuran-2-yl)-5 (trifluoromethyl)pyrimidine-2,4(1*H*,3*H*)-dione (32). Colourless thick liquid, (0.03 g, 56%) R_f 0.5 [CH_2Cl_2/ MeOH (5:1)]; UV (MeOH) λ_{max} 261 nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 3.85 (q, 2H, *J* = 9.6 Hz), 4.28 (t, 1H, *J* = 6.0 Hz), 5.02 (br s, 1 H), 5.11 (s, H), 5.72 (d, 1H, *J* = 6 Hz), 6.06 (d, 1H, *J* = 6.4 Hz), 8.44 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 62.3, 70.2, 73.6, 78.1, 85.3, 101.5(q), 115.7, 144.9, 149.9,159.0;HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{10}H_{11}F_3N_2O_6$ Na 335.0467; found 335.0464.

4-amino-1-((3*R*,4*R*)-3,4-dihydroxy-4-(hydroxymethyl)tetrahydrofuran-2-yl)pyrimidin-2(1*H*)-one (35). Compound **30α** (0.17 g, 0.7 mmol) was dissolved in pyridine (10 ml) followed by dropwise addition of acetic anhydride (5 ml, excess) and the mixture was stirred at room temperature for overnight under N_2 atmosphere. The mixture was quenched by saturated sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was dried over $NaSO_4$, filtered, and evaporated. The residue was purified with silica gel column chromatography [hexane:EtOAc, (2:8)] to give the triacetate **33** as a thick liquid.

To a suspension of 1,2,4-triazole (0.4 g, 5.8 mmol) in anhydrous CH_3CN (20 ml) was added $POCl_3$ (0.6 ml) slowly at 0 °C and the mixture was stirred at room temperature for 5 min. Et_3N (1.35 ml) and a solution of the triacetate **33** in CH_3CN (10 ml) was added to the above mixture slowly at 0 °C and the mixture was stirred at rt for 24 h. After completion of reaction, more Et_3N (3.5 ml) was added followed by quenching with addition of little amount of water and the mixture was stirred for 10 min. After the mixture was evaporated, the residue was used for the next step without further purification. The triazole derivative was dissolved in dioxane (10 ml) and excess aqueous ammonia (10 ml) and the mixture was stirred at rt for 15 h in a closed condition. After completion of reaction, the mixture was evaporated. The residue was dissolved in methanolic ammonia (10 ml) and the mixture was stirred at room temperature for another overnight. The solvent was evaporated and the residue was purified by silica gel column chromatography [CH_2Cl_2: MeOH, (8:2)] to give the thick liquid, which was triturated to give **35** (0.086 g, 50 %) as a white solid: R_f 0.5 [CH_2Cl_2/ MeOH (2:1)]; mp 206-208 °C; UV (MeOH) λ_{max} 274 nm; ^{1}H NMR (400 MHz,CD_3OD) δ (ppm) 3.60 (s, 2H), 3.94 (d, 1H, *J* = 9.6 Hz), 4.02 (d, 1H, *J* = 9.6 Hz) 4.32 (d, 1H, *J* = 5.6 Hz), 5.95 (d, 1H, *J* = 7.2 Hz), 6.14 (d, 1H, *J* = 5.6 Hz), 7.87 (d, 1H, *J* = 7.6Hz); ^{13}C NMR (100 MHz, CD_3OD) δ (ppm) 65.0, 72.6, 74.9, 80.1, 88.6, 145.9 ; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_9H_{13}N_3O_5$ 266.0753 found 266.0757.

(3a*S*,6a*S*)-6a-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxole-4-carbaldehyde (26).To an ice-cooled (0 °C) solution of **8** (1 g, 2.12 mmol) in ethyl acetate (25 ml) was added $Pb(OAc)_4$ (1.12 g, 12.3 mmol) and the reaction mixture was stirred for 10 min at same temperature. The reaction mixture was filtered, the filtrate was diluted with EtOAc (30 ml), and the organic layer was washed with saturated aqueous $NaHCO_3$ solution (2 x 50 ml), dried over anhydrous $NaSO_4$, and evaporated. The residue was purified by silica gel flash column chromatography (hexane/ethyl acetate, 9:1) to give the aldehyde **26** (0.81 g, 87%) as a colourless liquid: R_f 0.55 [hexanes/EtOAc (2:1)]; IR (film, ν_{max} in cm^{-1}) 2987, 2934, 2860, 1727, 1467, 1428, 1376, 1247, 1214;^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.03 (s, 9H), 1.33 (s, 3H), 1.51 (s, 3H), 3.63 (d, 1H, *J* = 10.4 Hz), 3.71 (d, 1H, *J* = 10.4 Hz), 3.98 (d, 1H, *J* = 10 Hz), 4.05 (d, 1H, *J* = 10.4 Hz), 4.46 (s, 1H), 4.89 (d, 1H, *J* = 0.8 Hz), 7.37-7.44 (m, 7H), 7.61-7.64 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 19.3, 27.0, 27.1, 27.8, 28.0, 64.6, 75.8, 84.0, 90.1, 92.6, 114.2, 128.0, 130.2, 132.7, 132.8, 135.8, 135.7, 201.2.

((3a*S*,6a*S*)-6a-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methanol (36). To a stirred solution of aldehyde **26** (0.8 g, 1.81mmol) in MeOH (15 ml) was carefully added sodium borohydride (0.137 g, 3.62 mmol) in several portions at 0 °C, and the reaction mixture was stirred for 1 h at room temperature and neutralized with glacial AcOH. After the removal of the solvent, the mixture was partitioned between EtOAc (60 ml) and brine (50 ml). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated. The resulting residue was purified by silica gel column chromatography [hexane/ethylacetate, (3.5:1)] to give **36** as colourless liquid (0.74 g, 92%): R_f 0.5 [hexane/EtOAc (2:1)]; IR (film, ν_{max} in cm^{-1}) 3458, 2986, 2934, 2861, 1468, 1428, 1375, 1247, 1214; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.07 (s, 9H), 1.37 (s, 3H), 1.53 (s, 3H), 3.62 (d, 2H, *J* = 5.6 Hz), 3.68 (d, 1H, *J* = 10 Hz), 3.96 (d, 1H, *J* = 10Hz), 4.15 (dt, 1H, *J* = 2 Hz, 5.6 Hz), 4.49 (d, 1H, *J* = 2 Hz), 7.36-7.45 (m, 6H), 7.66-7.69 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 19.4, 27.0, 28.0, 28.2, 61.8, 65.0, 74.5, 84.0, 86.1, 93.0, 114.2, 128.0, 130.1, 132.9, 135.8, 135.9; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{25}H_{34}O_5SiNa$ 465.2073; found 465.2073.

3-benzoyl-1-(((6a*R*)-6a-(hydroxymethyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl)pyrimidine-2,4(1H,3H)-dione (38). A solution of DIAD (0.8 ml, 4.06 mmol) in dry THF (10 ml) was added slowly to the suspension of **36** (0.8 g, 1.8 mmol), PPh_3 (1.12 g, 4.27 mmol), and N^3 - benzoyluracil (0.72 g, 3.3 mmol) in anhydrous THF (8 ml) at 0 °C and the reaction mixture was stirred at the same temperature for 30 min and then at room temperature for 16 h. The solvent was removed under the reduced pressure, and the residue was purified by silica gel column chromatography [(hexane: EtOAc, (4:1)] to afford **37** (0.91 g) as yellowish liquid. To the compound **37** in THF was added TBAF solution (2.1 ml, 1M in THF) at 0 °C and the reaction was allowed to stir at room temperature for 1 h. Solvent was removed, the residue was purified by silica gel column chromatography [(hexane: EtOAc, (1:1)] to give **38** (0.45 g, 62% for two steps) as colourless liquid: R_f 0.55 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.40 (s, 3H), 1.53 (s, 3H), 2.09 (s, 1H), 3.66 (d, 1H, *J* = 11.6 Hz), 3.78 (d, 1H, *J* = 11.6 Hz), 3.85-3.93 (m, 4H), 4.34-4.37 (m, 1H), 4.49 (d, 1H, *J* = 1.6 Hz), 5.83 (d, 1H, *J* = 8.0 Hz), 7.30 (d, 1H, *J* = 8 Hz), 7.51 (t, 2H, *J* = 7.6 Hz), 7.65-7.69 (m, 1H), 7.95 (dd, 2H, *J* = 0.8 Hz, 8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 19.8, 35.6, 46.5, 55.5, 56.7, 64.5, 74.5, 86.3, 101.3, 107.4, 116.7, 122.3, 134.4, 140.8.

1-(((4*R*)-3,4-dihydroxy-4-(hydroxymethyl)tetrahydrofuran-2-yl)methyl)pyrimidine-2,4(1*H*,3*H*)-dione (39). The compound **38** (0.23 g, 0.57 mmol) in saturated methanoilc ammonia (7 ml) was stirred at room temperature for 4 h. The solvent was evaporated and the residue was purified by silica gel column chromatography [(hexane/EtOAc, (3:7)] to give the debenzoylated compound (0.16 g) as a thick liquid. To the debenzoylated compound was added 3 N hydrochloric acid (10 ml) and the mixture stirred at room temperature for overnight. The mixture was neutralized with aqueous NH_3 solution, and then carefully evaporated under reduced pressure. The residue was subjected to silica gel column chromatography [(CH_2Cl_2: MeOH, (7:1)] to afford the final nucleoside derivative **39** (0.085 g, 58%) as floppy solid: R_f 0.5 [(CH_2Cl_2: MeOH, (2:1)]; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 3.23-3.30 (m, 2H), 3.50 (d, 1H, *J* = 9.6 Hz), 3.62 (q, 2H, *J* = 8.0.Hz), 3.78 (dt, 1H, *J* = 3.2 Hz, 8.0 Hz), 3.87(d, 1H, *J* = 9.2 Hz), 4.04(dd, 1H, *J* = 3.2 Hz, 14 Hz), 4.51 (s, 1H), 4.87 (t, 1H, *J*= 5.6 Hz), 5.04 (d, 1H, *J* = 6.8Hz), 5.50(d, 1H, *J* = 8.0 Hz), 7.39 (br s, 2H), 7.53 (d, 1H, *J* = 8.0 Hz), ^{13}C NMR (100 MHz, DMSO- d_6) δ (ppm) 49.6, 62.5, 72.9, 73.9, 78.4, 78.9, 79.5, 100.3, 146.5, 150.9, 163.7; HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{10}H_{14}N_2O_6SiNa$ 281.0750 found 281.0750.

Effect of the compounds (30α, 31β, 35, 39) in growth of breast cancer cell line

The *in vitro* cytotoxic effects of the compounds were measured in human breast cancer cell line MCF7 using standard 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Cells were cultured in DMEM media containing 10% fetal bovine serum according to the American Type Culture Collection instructions. Cells were maintained at 37 °C and 5% CO_2 in a humidified incubator. MCF7 cells ($5x10^3$/per well of 96 well plate) were seeded one day prior and then were treated with these compounds (0-100 μM) for 48 hours. DMSO (0.05% v/v) treated cells were considered as a control. At the end of incubation, 850 μM of MTT was added in each well and incubated further for 4 hours in the CO_2 incubator. Then, MTT containing medium was replaced with 150 μl of MTT solvent (4 mM HCl, 0.1% NP-40 in isopropanol) and further incubated for 15 minutes at room temperature. Finally the absorbance at 595 nm were measured in Elisa plate reader (Thermo Fisher Multiskan 80). The data were acquired from three independent cell passages and the IC_{50} values were calculated from the plot of cell viability *vs* concentration of complexes.

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Notes and references

1 (a) L. P. Jordheim, D. Durantel, F. Zoulim and C. Dumontet, *Nat. Rev. Drug Discov*. 2013, **12**, 447. (b) G. Romeo, U. Chiacchio, A. Corsaro and P. Merino, *Chem. Rev.* 2010, **110**, 3337. (c) O. Arjona, A. M. Gomez, J. C. Lopez and J. Plumet, *Chem. Rev*. 2007, **107**, 1919. (d) C. M. Galmarini, *Electron. J: Oncol.* 2002, **1**, 22. (e) C. R. Wagner, V. V. Iyer and E. J. McIntee, *Med. Res. Rev.* 2000, **20**, 417. (f) X. Tan, C. K. Chu and F. D. Boudinot, *Adv. Drug Delivery Rev.* 1999, **39**, 117. (g) G. J. Koomen, *Recl. Trav. Chim. Pays- Bas* 1993, **112**, 51. (h) C. Perigaud, G. Gosselin and J. L. Imbach, *Nucleosides Nucleotides* 1992, **11**, 903. (i) D. M. Huryn and M. Okabe, *Chem. Rev.* 1992, **92**, 1745.

2 (a) O. Sari, V. Roy and L. A. Agrofoglio, In *Chemical Synthesis of Nucleoside Analogues*; John Wiley & Sons, Inc.: 2013, p 49. (b) Q. Wu and C. Simons, *Synthesis* 2004, **10**, 1533. (c) E. Ichikawa and K. Kato, *Synthesis* 2002, **1**, 1. (d) E. Ichikawa and K. Kato, *Curr. Med. Chem.* 2001, **8**, 385. (e) M. Meldgaard and J. Wengel, *J. Chem. Soc., Perkin Trans. 1* 2000, **21**, 3539. (f) E. S. H. El Ashry and N. Rashed, *Curr. Org. Chem.* 2000, **4**, 609. (g) H. Gao and A. K. Mitra, *Synthesis* 2000, **3**, 329. (h) C. Meier, *Synlett* 1998, **3**, 233.

3 (a) T. B. Sells and V. Nair, *Tetrahedron Lett*. 1993, **34**, 3527. (b) V. Nair and Z. Nuesca, *J. Am. Chem. Soc*. 1992, **114**, 7951.

4 Y. Terao, M. Akamatsu and K. Achiwa, *Chem. Pharm. Bull.* 1991, **39**, 823.

5 J. A. Lee, H. R. Moon, H. O. Kim, K. R. Kim, K. M. Lee, B. T. Kim, K. J. Hwang, M. W. Chun, K. A. Jacobson and L. S. Jeong, *J. Org. Chem.* 2005, **70**, 5006.

6 (a) K. S. Toti, M. Derudas, F. Pertusati, D. Sinnaeve, F. V. Broeck, L. Margamuljana, J. C. Martins, P. Herdewijn, J. Balzarini, C. McGuigan and S. V. Calenbergh, *J. Org. Chem*. 2014, **79**, 5097. (b) M. Koos, J. Micova, B. Steiner and Alfoldi, J. *Tetrahedron Lett.* 2002, **43**, 5405. (c) I. Burger, B. V. Burger, C. F. Albrecht, H. S. C. Spie and, P. Sandor, *Phytochemistry* 1998, **49**, 2087. (d) R. J. Nachman, M. Honel, T. M. Williams, R. C. Halaska and H. S. Mosher, *J. Org. Chem*. 1986, **51**, 4802. (e) M. Koos and H. S. Mosher, *Carbohydr. Res*. 1986, **146**, 335. (f) P. T. Ho, *Can. J. Chem*. 1979, **57**, 381. (g) D. T. Williams and J. K. N. Jones, *Can. J. Chem*. 1964, **42**, 67. (h) R. Schaffer, *J. Am. Chem. Soc*. 1959, **81**, 5452.

7 (a) Y. Song, H. Ding, Y. Dou, R. Yang, Q. Sun, Q. Xiao and Y. Ju, *Synthesis* 2011, **9**, 1442. (b) I. M. Lagoja, S. Pochet, V. Boudou, R. Little, E. Lescrinier, J. Rozenski and P. Herdewijn, *J. Org. Chem.* 2003, **68**, 1867. Other references there in.

8 (a) A. Panda, S. Das and S. Pal, *Carbohydr. Res*. 2014, **398**, 13. (b) H. R. Moon, H. O. Kim, K. M. Lee, M. W. Chun, J. H. Kim and L. S. Jeong, *Org. Lett*. 2002, **4**, 3501.

9 (a) D. Canals, D. Mormeneo, G. Fabrias, A. Llebaria, J. Casas and A. Delgado, *Bioorg. Med. Chem*. 2009, **17**, 235. (b) R. J. B. H. N. Van den Berg, T. J. Boltje, C. P. Verhagen, R.E. J. N.

Litjens, G. A. Van der Marel and H. S. Overkleeft, *J. Org. Chem.* 2006, **71**, 836.
10 (a) R. Alibes, P. Bayon, P. March, M. Figueredo, J. Font and G. Marjanet, *Org. Lett.* 2006, **8**, 1617. (b) G. Mehta, N. Mohal and S. Lakshminath, *Tetrahedron Lett*. 2000, **41**, 3505.
11 (a) J. Liu, Y. Liu, X. Zhang, C. Zhang, Y. Gao, L. L. Wang and Y. Du, *J. Org. Chem*. 2012, **77**, 9718. (b) P. Ghosal and A. K. Shaw, *J. Org. Chem.* 2012, **77**, 7627.
12 G. V. Ramana and B. V. Rao, *Tetrahedron Lett*. 2003, **44**, 5103.
13 (a) L. S. Jeong, S. A. Choe, P. Gunaga, H. O. Kim, H. W. Lee, S. K. Lee, D. K. Tosh, A. Patel, K. K. Palaniappan, Z. G. Gao, K. A. Jacobson and H. R. Moon, *J. Med. Chem*. 2007, **50**, 3159. (b) L. S. Jeong, H. W. Lee, K. A. Jacobson, H. O. Kim, , D. H. Shin, J. A. Lee, Z. G. Gao, C. Lu, H. T. Duong, P. Gunaga, S. K. Lee, D. Z. Jin, M. W. Chun and H. R. Moon, *J. Med. Chem.* 2006, **49**, 273.
14 (a) L. S. Jeong, S. Pal, S. A. Choe, W. J. Choi, K. A. Jacobson, Z. G. Gao, A. M. Klutz, X. Hou, H. O. Kim, H. W. Lee, D. K. Tosh and H. R. Moon, *J. Med. Chem*. 2008, **51**, 6609. (b) P. Gunaga, H. O. Kim, H. W. Lee, D. K. Tosh, J. S. Ryu, S. Choi and L. S. Jeong, *Org. Lett.* 2006, **8**, 4267.
15 (a) I. Carrera, M. C. Brovetto, J. C. Ramos, G. A. Seoane, *Tetrahedron Lett*. 2009, **50**, 5399. (b) A. D. Lebsack, L. E. Overman and R. J. Valentekovich, *J. Am. Chem. Soc.* 2001**,** **123**, 4851.
16 W. J. Choi, Y. J. Ko, G. Chandra, H. W. Lee, H. O. Kim, H. J. Koh, H. R. Moon, Y. H. Jung and L. S. Jeong, *Tetrahedron* 2012, **68**, 1253.
17 (a) W. J. Choi, H. J. Chung, G. Chandra, V. Alexander, L. X. Zhao, H. W. Lee, A. Nayak, M. S. Majik, H. O. Kim, J. H. Kim, Y. B. Lee, C. H. Ahn, S. K. Lee and L. S. Jeong, *J. Med. Chem*. 2012, **55**, 4521. (b) L. S. Jeong, D. K. Tosh, W. J. Choi, S. K. Lee, Y. J. Kang, S. Choi, J. H. Lee, H. Lee, H. W. Lee and O. K. Hea, *J. Med. Chem*. 2009, **52**, 5303. (c) L. S. Jeong, L. X. Zhao, W. J. Choi, S. Pal, Y. H. Park, S. K. Lee, M. W. Chun, Y. B. Lee, C. H. Ahn and H. R. Moon, *Nucleosides Nucleotides Nucleic Acids* 2007, **26**, 713.
18 (a) F. Hammerschmidt, E. Ohler, J. P. Polsterer, E. Zbiral, J. Balzarini and E. DeClercq, *Liebigs Ann*. 1955, 551. (b) D. K. Parikh and R. R. Watson, *J. Med. Chem*. 1978, **21**, 706.
19 H. W. Lee, H. O. Kim, W. J. Choi, S. Choi, J. H. Lee, S. Park, L. Yoo, K. A. Jacobson and L. S. Jeong, *Bioorg. Med. Chem*. 2010, **18**, 7015.