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The efficient synthesis of 2-arylpyrimidine acyclic nucleoside phosphonates using Liebeskind–Srogl cross-coupling reaction

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ABSTRACT

A series of novel acyclic nucleoside phosphonates with various aryls attached to the C-2 position of the pyrimidine moiety has been prepared using the Liebeskind–Srogl cross-coupling protocol. The reactions of highly functionalised 2-(methylsulfanyl)pyrimidines with various arylboronic acids were studied and optimised.

1. Introduction

Acyclic nucleoside phosphonates (ANPs) are nucleotide analogues containing a stable phosphonomethyl moiety. ANPs possess a broad spectrum of biological activities, e.g., antiviral, cytostatic and antiprotozoal.[1] The most pronounced is their antiviral activity against retroviruses and DNA viruses and they are currently used as successful drugs against HIV, HBV and herpes viral infections. The choice of a heterocyclic base of antivirally active ANPs is limited, with the exception of cytosine, to purine derivatives (adenine, 2,6-diaminopurine and guanine).[2] A second generation of ANPs is derived from 2,4-diamino-6-hydroxy- (e.g., compounds **1a** and **2**, Fig. 1) and 2-amino-4,6-dihydroxypyrimidine (e.g., compound **1b**, Fig. 1), bearing the (phosphonomethoxy)alkyl side chain attached to the oxygen atom at the C-6 position of the pyrimidine ring.[3] These compounds mimic purine acyclic nucleoside phosphonates[4] and are recognised by HIV-1 reverse transcriptase as purine nucleotides.[5] The antiviral activities of pyrimidine ANPs closely resemble the activities of the parent purine derivatives.

Cross-coupling reactions of heteroaromatics with various organometallic reagents are widely used in drug design for modifications of purine[6] and pyrimidine[7] bases of biologically active compounds. Mild reaction conditions, high selectivity, and the broad availability of reaction partners offer a powerful tool for organic synthesis. The Liebeskind–Srogl[8] cross-coupling of thioorganics with arylboronic acids extends the versatility of the Suzuki–Miyaura[9] and Stille[10] cross-coupling reactions. The Liebeskind–Srogl cross-coupling methodology comprises a Pd-catalysed and copper(I)-mediated reactions of thioethers with arylboronic acids under the base-free conditions. This methodology has also been successfully applied to various hetarylthioether reactions[11] and selective reactions of functionalized 2-(methylsulfanyl)pyrimidinones.[12]

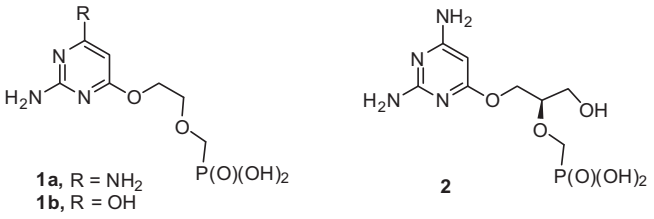

Fig. 1. Examples of the second generation of ANPs.

Herein, we report on the efficient synthesis of 2-arylpyrimidine acyclic nucleoside phosphonates using the Liebeskind–Srogl cross-coupling protocol. The reactions of highly functionalised 2-(methylsulfanyl)pyrimidines with various arylboronic acids were optimized and two series of novel acyclic nucleoside phosphonates were prepared.

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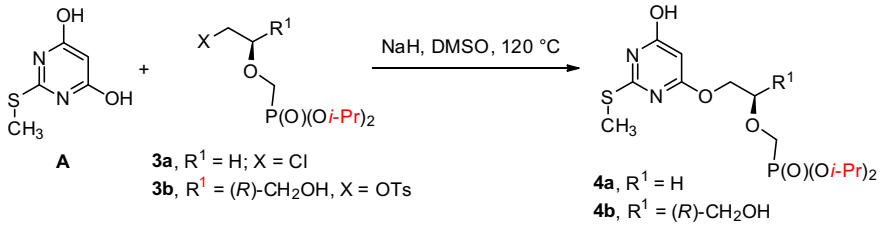
2. Results and discussion

2.1. Chemistry

Starting 2-(methylsulfanyl)pyrimidine derivatives **4a** and **4b** bearing the 2-(phosphonomethoxy)ethoxy (PMEO) and (*R*)-3-hydroxy-2-(phosphonomethoxy)propoxy (HPMPO) side chain, respectively, were readily prepared by an alkylation of commercially available 4,6-dihydroxy-2-(methylsulfanyl)pyrimidine (**A**) with the phosphonate-bearing building blocks **3a** and **3b** according to the previously described procedure (Scheme 1).[13]

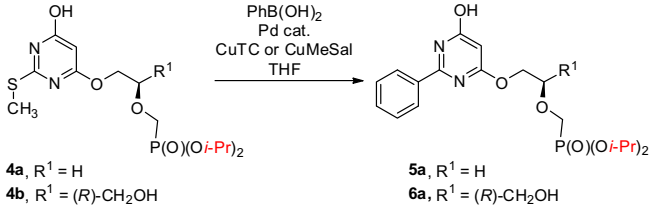


Scheme 1. Synthesis of the starting ANPs bearing 2-(methylsulfanyl) group.

Phenylboronic acid and protected phosphonate **4a** were chosen as model compounds for the optimisation study of the Liebeskind–Srogl cross-coupling reaction (Scheme 2) and the influence of various catalytic systems was studied (entries 1–5, Table 1). Reactions of the compound **4a** with phenylboronic acid using various Pd catalysts in the presence of copper(I) thiophene-2-carboxylate (CuTC, 1.5 equiv) afforded the product **5a** in 52–60% yields in 48 h (entries 1,4 and 5, Table 1). An increased loading of the CuTC (2.2 equiv) under otherwise identical reaction conditions did not improve the yield of **5a** (entry 2, Table 1). On the other hand, the conversion of **4a** to **5a** under catalysis with $Pd(PPh_3)_4$ in the presence of copper(I) 3-methylsalicylate (CuMeSal, 2.2 equiv) was nearly quantitative (98%) in only 24 h (entry 3, Table 1), whilst a lower ratio of CuMeSal is not sufficient to afford satisfactory yields.[12] From the results it can clearly be seen that the crucial role is played by the organocopper(I) salt used in the cross-coupling reactions.

As expected, the reaction of the more functionalized compound **4b** with phenylboronic acid using $Pd(PPh_3)_4$ in the presence of CuTC (1.5 equiv) gave lower yield (23%) of the product **5b** (entry 6, Table 1), compared to the analogous reaction of derivative **4a** (53% of **5a**, entry 1, Table 1).

To improve the yields, the influence of microwave heating on the Liebeskind–Srogl reaction[14] of compound **4b** using a $Pd(PPh_3)_4$/CuTC catalytic system was studied next (Table 1). The results show that the microwave-assisted reactions afforded only slightly higher yields of the product **5b** (entries 7 and 8, Table 1) compared to the conventional heating (entry 1, Table 1), however, the reaction times were significantly decreased (30 and 60 min compared to 48 h). Not even prolonged reaction times (3 h) of the MW-assisted reactions improved the yields dramatically.



Scheme 2. Optimisation of the reaction of **4a** and **4b** with phenylboronic acid.

Finally, we studied the influence of $Zn(OAc)_2$, which has been reported as an essential additive in some cases of the Liebeskind–Srogl cross-coupling.[11a] In our case, the addition of $Zn(OAc)_2$ (1.2 equiv) significantly lowered the yields of the product **5b** under both conventional heating (entry 9, Table 1) and MW irradiation (entry 10, Table 1). Complex mixtures of products were formed in both cases apparently owing to the instability of the starting material and/or the product under the reaction conditions.

In analogy to compounds **5a**, the best yield of the coupled product **5b** (86%) was obtained by the conventional reaction of the starting compound **4b** under the catalysis with the $Pd(PPh_3)_4$/CuMeSal system (entry 11, Table 1).

To summarize the optimisation, the best results of the cross-coupling of 2-(methylsulfanyl)pyrimidines **4a** and **4b** with phenylboronic acid were achieved with a $Pd(PPh_3)_4$ (5%) in the presence of CuMeSal (2.2 equiv) as metal co-factor.

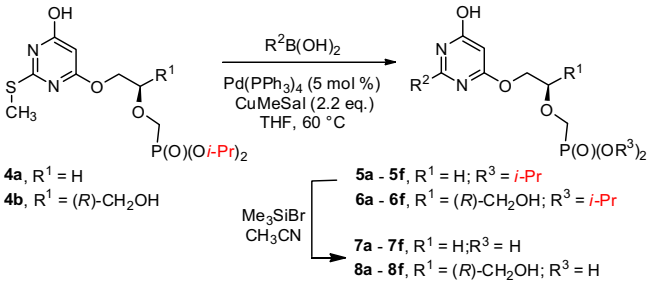
Subsequently, we have decided to exploit our optimised reaction conditions of the Liebeskind–Srogl cross-coupling protocol for the synthesis of the acyclic nucleoside phosphonates with

Table 1
Optimisation of the Liebeskind–Srogl cross-coupling reaction of compounds **4a** and **4b** with phenylboronic acid (Scheme 2)

Entry	Compd	R^2	Pd catalyst	Cu (I) salt	Reaction conditions	Time	Yield[a] (%) of **5a**/**6a**
1	**4a**	Ph	$Pd(PPh_3)_4$, 5%	CuTC[b] (1.5 equiv)	60 °C[d]	48 h	53
2	**4a**	Ph	$Pd(PPh_3)_4$, 5%	CuTC (2.2 equiv)	60 °C[d]	48 h	54
3	**4a**	Ph	$Pd(PPh_3)_4$, 5%	CuMeSal[c] (2.2 equiv)	60 °C[d]	24 h	98
4	**4a**	Ph	$Pd(PPh_3)_2Cl_2$, 5%	CuTC (1.5 equiv)	60 °C[d]	48 h	52
5	**4a**	Ph	$Pd_2(dba)_3$, 4%, Ph_3P 20%	CuTC (1.5 equiv)	60 °C[d]	48 h	60
6	**4b**	Ph	$Pd(PPh_3)_4$, 5%	CuTC (1.5 equiv)	65 °C[d]	48 h	23
7	**4b**	Ph	$Pd(PPh_3)_4$, 5%	CuTC (1.5 equiv)	100 °C[e]	30 min	54
8	**4b**	Ph	$Pd(PPh_3)_4$, 5%	CuTC (1.5 equiv)	100 °C[e]	60 min	62
9	**4b**	Ph	$Pd(PPh_3)_4$, 5%	CuTC (1.5 equiv)	65 °C[d,f]	8 h	27
10	**4b**	Ph	$Pd(PPh_3)_4$, 5%	CuTC (1.5 equiv)	100 °C[e,f]	30 min	34
11	**4b**	Ph	$Pd(PPh_3)_4$, 5%	CuMeSal (2.2 equiv)	60 °C[d]	24 h	86

[a] Yield were determined by HPLC.
[b] CuTC (copper(I) thiophene-2-carboxylate).
[c] CuMeSal (copper(I) 3-methylsalicylate).
[d] Conventional heating.
[e] Microwave irradiation.
[f] Addition of $Zn(OAc)_2$ (1.2 equiv).

substituted aryls attached to the pyrimidine moiety at the C-2 position. We have attempted to elucidate the influence of either electron withdrawing or electron donating substituents at the C-4 position of the phenylboronic acid on the reactivity and the yields of 2-arylpyrimidine ANPs. Thus, compounds **4a** and **4b** reacted under the optimised conditions ($Pd(PPh_3)_4$ (5%), CuMeSal (2.2 equiv)) with a number of 4-substituted phenylboronic acids giving the desired pyrimidine ANPs with PMEO and HPMPO side chains, compounds **5a**–**f** and **6a**–**f**, respectively (Scheme 3, Table 2). The best isolated yields (89% for **5a** and 75% for **6a**) were obtained with the unsubstituted phenylboronic acid (entries 1 and 7, Table 2). All other coupled products **5b**–**f** and **6b**–**f** were obtained in moderate to good yields (41–65%) and no significant effect of the C-4 substituent of the phenylboronic acid on the reaction yields of the cross-coupling reaction was observed.



Scheme 3. Liebeskind–Srogl cross-coupling of **4a** and **4b** with arylboronic acids and formation of the free phosphonic acids **7** and **8**.

Table 2
Synthesis of 2-arylpyrimidine ANPs **5** and **6** via Liebeskind–Srogl reaction (Scheme 3)

Entry	R^1	R^2	Product	Time (h)	Yield[a] (%)
1	H	Phenyl	**5a**	24	89
2	H	4′-F–phenyl	**5b**	24	64
3	H	4′-CH_3O–phenyl	**5c**	24	57
4	H	4′-NO_2–phenyl	**5d**	24	56
5	H	4′-CF_3–phenyl	**5e**	24	50
6	H	4′-OH–phenyl	**5f**	24	41
7	(*R*)-CH_2OH	Phenyl	**6a**	24	75
8	(*R*)-CH_2OH	4′-F–phenyl	**6b**	24	54
9	(*R*)-CH_2OH	4′-CH_3O–phenyl	**6c**	24	60
10	(*R*)-CH_2OH	4′-NO_2–phenyl	**6d**	24	41
11	(*R*)-CH_2OH	4′-CF_3–phenyl	**6e**	24	65
12	(*R*)-CH_2OH	4′-OH–phenyl	**6f**	24	63

[a] Isolated yield.

The above synthetic protocol has also been applied to the synthesis of 2-heteroaryl pyrimidines. Unfortunately, the reactions of compounds **4a** and **4b** with 2-furyl-, 3-pyridyl- and 4-pyridylboronic acids were unsuccessful and an analogous treatment of 2-(sulfanylmethyl)pyrimidines with heteroaryl stannanes failed as well. Attempts with elevated temperature, or with the described[11a] addition of $Zn(OAc)_2$ only led to the complex reaction mixtures.

Eventually, the compounds **5a**–**f** and **6a**–**f** were converted to the desired final products **7a**–**f** and **8a**–**f**, respectively, by the standard transesterification reaction with bromotrimethylsilane (TMSBr) and subsequent hydrolytic cleavage of the corresponding silylester phosphonates (Scheme 3, Table 3).

2.2. Biological evaluation

The compounds **7a**–**f** and **8a**–**f** were tested for their in vitro inhibition of cell growth in mouse leukaemia L1210 cells, human T-lymphoblastoid CCRF-CEM cell line, human promyelocytic leukaemia HL-60 cells and human cervix carcinoma HeLa S3 cells (Dr. I. Votruba, IOCB, Prague) but none of the compounds exhibited considerable cytostatic activity or cytotoxicity. None of the prepared derivatives displayed any significant inhibitory activity against the viruses so far tested (HCMV, VZV, HCV).

Table 3
Formation of the free phosphonic acids **7** and **8** (Scheme 3)

Entry	R^1	R^2	Product	Time (h)	Yield[a] (%)
1	H	Phenyl	**7a**	16	79
2	H	4′-F–phenyl	**7b**	16	67
3	H	4′-CH_3O–phenyl	**7c**	16	61
4	H	4′-NO_2–phenyl	**7d**	16	77
5	H	4′-CF_3–phenyl	**7e**	16	82
6	H	4′-OH–phenyl	**7f**	16	79
7	(*R*)-CH_2OH	Phenyl	**8a**	16	66
8	(*R*)-CH_2OH	4′-F–phenyl	**8b**	16	76
9	(*R*)-CH_2OH	4′-CH_3O–phenyl	**8c**	16	81
10	(*R*)-CH_2OH	4′-NO_2–phenyl	**8d**	16	71
11	(*R*)-CH_2OH	4′-CF_3–phenyl	**8e**	16	90
12	(*R*)-CH_2OH	4′-OH–phenyl	**8f**	16	76

[a] Isolated yield.

3. Conclusions

A series of 12 new 2-(4-substituted-aryl)pyrimidine acyclic nucleoside phosphonates with PMEO and HPMPO side chains was prepared using the Liebeskind–Srogl cross-coupling protocol as the key synthetic step. The reaction conditions of the cross-coupling were optimised and $Pd(PPh_3)_4$ (5%)/CuMeSal (2.2 equiv) catalytic system was found to give the best yields. As for the arylboronic acids, the best yields of the 2-arylpyrimidines were obtained by the coupling with unsubstituted phenylboronic acid. No significant influence of the substituent at the C-4 position of the phenylboronic acid on the reaction course was observed. The presence of the functional groups of ANPs is well tolerated under the reaction conditions. Analogous reactions with hetarylboronic acids or heteroaryl stannanes failed. None of the final free phosphonic acids **7a**–**f** and **8a**–**f** displayed any cytostatic or antiviral activity.

4. Experimental section

4.1. General methods

Solvents were dried by standard procedures. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone under argon. Melting points were determined on a Büchi Melting Point B-545 apparatus and are uncorrected. TLC was performed on plates of Kieselgel 60 F_{254} (Merck) in 5% MeOH in $CHCl_3$ (solvent system A) or in 10% MeOH in $CHCl_3$ (solvent system B). ^1H and ^{13}C NMR spectra were recorded on Bruker Avance 500 (500 MHz for ^1H and 125.8 MHz for ^{13}C) and Bruker Avance 400 (^1H at 400, ^{13}C at 100.6 MHz) spectrometers in $CDCl_3$, DMSO-d_6, or D_2O. Chemical shifts (in ppm, δ scale) were referenced to TMS (for ^1H NMR spectra in $CDCl_3$) and/or to the solvent signal ($CDCl_3$ δ=7.26 ppm for ^1H NMR and δ=77.0 ppm for ^{13}C NMR; DMSO-d_6 for ^1H NMR δ=2.5 ppm and for ^{13}C δ=39.7). Chemical shifts in D_2O were referenced to 1,4-dioxane for ^1H NMR δ=3.75 and for ^{13}C NMR δ=67.19. Mass spectra were measured on a ZAB-EQ (VG Analytical) spectrometer using FAB (ionization by Xe, accelerating voltage 8 kV, glycerol matrix) or on a LCQ classic spectrometer using electrospray ionization (ESI). Elemental microanalysis was performed using a PE 2400 Series II CHNS/O Analyzer (Perkin Elmer, USA). IR spectra were recorded on an FTIR spectrometer Bruker IFS 55 (Equinox) in $CHCl_3$. Preparative HPLC purification was performed on a column packed with 10 μm C18 reversed phase (Luna), 250 mm×21 mm using linear gradient of MeOH (0–100%) in H_2O. Flash

chromatography was performed on ISCO combi flash Companion (prepacked silicagel columns).

It is important to note that ^{13}C NMR signals of the pyrimidine carbons of 4-hydroxypyrimidine derivatives were usually not observed most probably because of the tautomer exchange reaction (amide–iminol) of intermediate rate on the NMR time scale. In some cases, the carbon atom C-6 could be detected in the 2D-H, C-HMBC spectra, where the three-bond correlations from the side chain were observed. The structure of the compounds is confirmed by HRMS analysis.

*4.1.1. 6-{2-[(Diisopropoxyphosphoryl)methoxy]ethoxy}-4-hydroxy-2-methylsulfanylpyrimidine (**4a**).* 4,6-Dihydroxy-2-(methylsulfanyl)pyrimidine (6.00 g, 38.2 mmol) in DMSO (200 mL) was treated with NaH (60% dispersion in mineral oil, 1.42 g, 35.5 mmol) and the reaction mixture was heated at 60 °C under argon atmosphere for 30 min. 2-[(Diisopropoxyphosphoryl)methoxy]ethyl chloride (9.6 g, 36.2 mmol) in DMSO (20 mL) was added dropwise (30 min) and the resulting mixture was heated at 120 °C for 8 h. The mixture was cooled to room temperature, poured into ice cold water (250 mL) and the product was extracted with $CHCl_3$ (3×100 mL) and dried over $MgSO_4$. Flash chromatography afforded **4a** as a colourless oil (5.00 g, 34%), R_f 0.35 (A). ^1H NMR (DMSO-d_6): 12.32 (br s, 1H, OH), 5.39 (br s, 1H, H-5), 4.59 (d, $J_{CH,CH3}$=6.2, $J_{CH,P}$=7.8, 2H, CHipr.), 4.33 (m, 2H, H-1′), 3.80 (m, 2H, H-2′), 3.79 (d, $J_{CH2,P}$=8.3, 2H, CH_2P), 2.47 (s, 3H, SCH_3), 1.24 (d, $J_{CH3,CH}$=6.0, 6H) and 1.22 (d, $J_{CH3,CH}$=6.0, 6H, CH_3ipr.). ^{13}C NMR (DMSO-d_6): 169.2 (C-4), 86.1 (C-5), 70.7 (d, $J_{2,P}$=11.9, C-2′), 70.4 (d, $J_{C,O,P}$=6.3, CHipr.), 65.8 (C-1′), 65.0 (d, $J_{C,P}$=164.5, CH_2P), 24.0 (d, $J_{CH3,P}$=3.6) and 23.9 (d, $J_{CH3,P}$=4.4, CH_3ipr.), 13.1 (SCH_3). MS (ESI): *m*/*z* (%)=403 (100) $[M+Na]^+$. HRMS (FAB) for $C_{14}H_{26}N_2O_6PS$ $[MH]^+$ calcd: 381.1249, found 381.1265.

*4.1.2. 6-(2R)-{2-[(Diisopropoxyphosphoryl)methoxy]-3-hydroxypropoxy}-4-hydroxy-2-methylsulfanylpyrimidine (**4b**).* 4,6-Dihydroxy-2-(methylsulfanyl)pyrimidine (3.55 g, 22.6 mmol) in DMSO (50 mL) was treated with NaH (60% dispersion in mineral oil, 544 mg, 13.6 mmol) and the reaction mixture was heated at 60 °C under argon atmosphere for 30 min (*R*)-2-[(Diisopropoxyphosphoryl) methoxy]-3-hydroxypropyl-1-*p*-toluenesulfonate (4.8 g, 11.3 mmol) in DMSO (10 mL) was added dropwise (30 min) and the resulting mixture was heated at 120 °C for 48 h. The mixture was cooled to room temperature, poured into ice cold water (100 mL) and the product was extracted with $CHCl_3$ (3×100 mL) and dried over $MgSO_4$. Flash chromatography afforded **4b** as a colourless oil (2 g, 43%), R_f 0.36 (B). ^1H NMR ($CDCl_3$): 13.37 (br s, 1H, NH), 5.50 (s, 1H, H-5), 4.71–4.84 (m, 2H, CHipr.), 4.33–4.39 (m, 2H, H-1′), 4.06 (dd, J_{gem}=14.0, $J_{H,C,P}$=7.6, 1H, PCHa), 3.80–3.88 (m, 3H, PCHb, H-2′, H-3′a), 3.68 (dd, J_{gem}=12.3, $J_{3'b-2'}$=5.7, 1H, H-3′b), 2.56 (s, 3H, SCH_3), 1.35 (d, $J_{CH3,CH}$=6.1, 6H) and 1.33 (d, J_{CH3-CH}=6.0, 6H, CH_3ipr.). ^{13}C NMR ($CDCl_3$): 169.2 (C-6), 167.1 (C-4), 163.1 (C-2), 88.0 (C-5), 81.8 (d, $J_{2'-P}$=8.3, C-2′), 71.9 (d, J_{C-O-P}=6.7) and 71.4 (d, J_{C-O-P}=6.9, CHipr.), 66.5 (C-1′), 65.4 (d, J_{C-P}=169.0, PCH_2), 61.7 (C-3′), 23.8–24.1 (m, CH_3ipr.), 13.2 (SCH_3). MS (ESI): *m*/*z* (%)=433.1 (100) $[M+Na]^+$. HRMS (ESI) for $C_{15}H_{28}O_7N_2PS$ calcd: 411.1349; found: 411.1350.

4.2. Liebeskind–Srogl cross-coupling reaction. General procedure

A mixture of compound **4a** or **4b** (0.3 mmol), arylboronic acid (1.75 equiv, 0.525 mmol), CuMeSal (2.2 equiv, 6.66 mmol, 141 mg) and $Pd(PPh_3)_4$ (5%, 0.015 mmol, 17 mg) in dry THF under argon atmosphere was heated at 60 °C until complete absorption of the starting material (TLC). The solvent was removed in vacuo and the residue was dissolved in ethylacetate (50 mL) and washed with saturated $NaHCO_3$ (25 mL), saturated aqueous EDTA (25 mL) and finally with brine (20 mL). The organic layer was dried over $MgSO_4$, evaporated in vacuo and the residue was purified by flash chromatography (0–7% MeOH in $CHCl_3$).

*4.2.1. 6-{2-[(Diisopropoxyphosphoryl)methoxy]ethoxy}-4-hydroxy-2-phenylpyrimidine (**5a**).* White solid (320 mg, 89%), R_f 0.46 (A), mp 69 °C (recryst from EtOAc/light petroleum). ^1H NMR (DMSO-d_6): 12.43 (br s, 1H, OH), 8.18 (m, 2H) and 7.55 (m, 3H, arom.), 5.63 (s, 1H, H-5), 4.59 (m, 2H, CHipr.), 4.44 (m, 2H, H-1′), 3.86 (m, 2H, H-2′), 3.82 (d, $J_{H,P}$=8.3, 2H, PCH_2), 1.23 (d, J=6.2, 6H) and 1.22 (d, J=6.2, 6H, CH_3ipr.). ^{13}C NMR (DMSO-d_6): 169.5 (C-4), 131.6 (C-4″), 128.5 (C-3″), 127.7 (C-2″), 88.7 (C-5), 70.4 (d, J=11.8, C-2′), 70.0 (d, J=6.4, CHipr.), 65.4 (C-1′), 64.7 (d, J=164.4, PCH_2), 23.7 (d, J=3.8) and 23.5 (d, J=4.5, CH_3ipr.). MS (ESI): *m*/*z* (%)=411.2 (100) $[M+H]^+$; 433.2 (80) $[M+Na]^+$. HRMS (ESI) for $C_{19}H_{27}O_6N_2NaP$ calcd: 433.1499; found 433.1499.

*4.2.2. 6-{2-[(Diisopropoxyphosphoryl)methoxy]ethoxy}-4-hydroxy-2-(4-fluorophenyl)pyrimidine (**5b**).* White solid (360 mg, 64%), R_f 0.48 (A). ^1H NMR (500 MHz, DMSO-d_6): 8.25 (m, 2H, H-2″), 7.36 (m, 2H, H-3″), 5.66 (br s, 1H, H-5), 4.58 (d, $J_{H-C-O-P}$=7.8, $J_{CH,CH3}$=6.2, 2H, CHipr.), 4.44 (m, 2H, H-1′), 3.86 (m, 2H, H-2′), 3.81 (d, $J_{H,P}$=8.3, 2H, PCH_2), 1.22 and 1.21 (2× d, $J_{CH3,CH}$=6.2, 2× 6H, CH_3ipr.). ^{13}C NMR (125.8 MHz, DMSO-d_6): 164.5 (d, $J_{4'',F}$=249.8, C-4″), 130.6 (d, $J_{2'',F}$=9.1, C-2″), 129.8 (C-1″), 115.9 (d, $J_{3'',F}$=21.8, C-3″), 88.8 (C-5), 70.7 (d, $J_{2',P}$=11.9, C-2′), 70.4 (d, J_{C-O-P}=6.4, CHipr.), 65.7 (C-1′), 65.0 (d, $J_{C,P}$=164.5, PCH_2), 24.0 (d, $J_{C,P}$=3.7) and 23.9 (d, $J_{C,P}$=4.5, CH_3ipr.). MS (ESI): *m*/*z* (%)=429.1 (100) $[M+H]^+$, 451 (17) $[M+Na]^+$. HRMS (ESI) calcd for $C_{19}H_{27}O_6N_2FP$ $[M+H]^+$ 429.1585; found 429.1585.

*4.2.3. 6-{2-[(Diisopropoxyphosphoryl)methoxy]ethoxy}-4-hydroxy-2-(4-methoxyphenyl)pyrimidine (**5c**).* White solid (332 mg, 57%), R_f 0.54 (A). ^1H NMR (500 MHz, DMSO-d_6): 12.42 (br s, 1H, OH), 8.16 (m, 2H, H-2″), 7.06 (m, 2H, H-3″), 5.52 (br s, 1H, H-5), 4.59 (dh, $J_{H,C,O,P}$=7.8, $J_{CH,CH3}$=6.2, 2H, CHipr.), 4.40 (m, 2H, H-1′), 3.85 (m, 2H, H-2′), 3.84 (s, 3H, OCH_3), 3.81 (d, $J_{H,C,P}$=8.3, 2H, PCH_2), 1.23 and 1.22 (2× d, $J_{CH3,CH}$=6.2, 2× 6H, CH_3ipr.). ^{13}C NMR (125.8 MHz, DMSO-d_6): 169.7 (C-4), 162.4 (C-4″), 160.3 (C-2), 132.5 (C-1″), 129.9 (C-2″), 114.2 (C-3″), 88.5 (C-5), 70.8 (d, $J_{C,O,P}$=6.3, CHipr.), 65.7 (C-1′), 65.0 (d, $J_{C,P}$=164.5, PCH_2), 55.7 (OCH_3), 24.0 (d, $J_{C,P}$=3.4) and 23.9 (d, $J_{C,P}$=4.4, CH_3ipr.). MS (ESI): *m*/*z* (%)=441 (100) $[M+H]^+$, 463.2 (35) $[M+Na]^+$. HRMS (ESI) calcd for $C_{20}H_{30}O_7N_2P$ $[M+H]^+$ 441.1785, found 441.1785.

*4.2.4. 6-{2-[(Diisopropoxyphosphoryl)methoxy]ethoxy}-4-hydroxy-2-(4-nitrophenyl)pyrimidine (**5d**).* Yellowish solid (334 mg, 56%), R_f 0.45 (A). ^1H NMR (500 MHz, DMSO-d_6): 12.30 (br s, 1H, OH), 8.47 (m, 2H, H-2″), 8.35 (m, 2H, H-3″), 5.90 (br s, 1H, H-5), 4.58 (dh, $J_{H,C,O,P}$=7.8, $J_{CH,CH3}$=6.2, 2H, CHipr.), 4.52 (m, 2H, H-1′), 3.88 (m, 2H, H-2′), 3.82 (d, $J_{H,C,P}$=8.3, 2H, PCH_2), 1.22 and 1.21 (2× d, $J_{CH3,CH}$=6.2, 6H, CH_3ipr.). ^{13}C NMR (125.8 MHz, DMSO-d_6): 170.5 (C-4), 159.6 (C-2), 149.2 (C-4″), 141.5 (C-1″), 129.3 (C-2″), 123.9 (C-3″), 89.3 (C-5), 70.7 (d, $J_{2',P}$=11.9, C-2′), 70.4 (d, $J_{C,O,P}$=6.3, CHipr.), 65.7 (C-1′), 65.0 (d, $J_{C,P}$=164.3, PCH_2), 24.0 (d, $J_{C,P}$=3.6) and 23.9 (d, $J_{C,P}$=4.4, CH_3ipr.). MS (ESI): *m*/*z* (%)=456 (100) $[M+H]^+$, 478 (44) $[M+Na]^+$. HRMS (ESI) calcd for $C_{19}H_{27}O_8N_3P$ $[M+H]^+$ 456.1530; found 456.1529.

*4.2.5. 6-{2-[(Diisopropoxyphosphoryl)methoxy]ethoxy}-4-hydroxy-2-(4-trifluorophenyl)pyrimidine (**5e**).* White solid (312 mg, 50%), R_f 0.56 (A). ^1H NMR (500 MHz, DMSO-d_6): 12.34 (br s, 1H, OH), 8.42 (m, 2H, H-2″), 7.89 (m, 2H, H-3″), 5.82 (br s, 1H, H-5), 4.58 (dh, $J_{H,C,O,P}$=7.7, $J_{CH,CH3}$=6.2, 2H, CHipr.), 4.49 (m, 2H, H-1′), 3.87 (m, 2H, H-2′), 3.82 (d, $J_{H,C,P}$=8.3, 2H, PCH_2), 1.22 and 1.21 (2× d, $J_{CH3,CH}$=6.2, 2× 6H, CH_3ipr.). ^{13}C NMR (125.8 MHz, DMSO-d_6): 170.3 (C-4), 159.0 (C-2), 138.7 (C-1″), 131.2 (q, $J_{4'',F}$=31.7, C-4″), 128.8 (C-2″), 125.7 (q, $J_{3'',F}$=3.8, C-3″), 124.2 (q, $J_{C,F}$=272.3, CF_3), 89.3 (C-5), 70.7 (d,

$J_{2',P}$=11.9, C-2′), 70.3 (d, $J_{C,O,P}$=6.4, CHipr.), 65.7 (C-1′), 65.0 (d, $J_{C,P}$=164.4, PCH_2), 24.0 (d, $J_{C,P}$=3.8) and 23.9 (d, $J_{C,P}$=4.5, CH_3ipr.). MS (ESI): *m/z* (%)=479 (100) $[M+H]^+$, 501 (34) $[M+Na]^+$. HRMS (ESI) calcd for $C_{20}H_{27}O_6N_2F_3P$ $[M+H]^+$ 479.1553; found 479.1553.

*4.2.6. 6-{2-[(Diisopropoxyphosphoryl)methoxy]ethoxy}-4-hydroxy-2-(4-hydroxyphenyl)pyrimidine (**5f**).* White solid (231 mg, 41%), R_f 0.24 (A). ^{1}H NMR (500 MHz, DMSO-d_6): 10.29 (br s, 1H, OH), 8.04 (m, 2H, H-2″), 6.86 (m, 2H, H-3″), 5.46 (br s, 1H, H-5), 4.58 (dh, $J_{H,C,O,P}$=7.7, $J_{CH,CH3}$=6.2, 2H, CHipr.), 4.39 (m, 2H, H-1′), 3.84 (m, 2H, H-2′), 3.80 (d, $J_{H,C,P}$=8.3, 2H, PCH_2), 1.22 and 1.21 (2× d, $J_{CH3,CH}$=6.2, 2× 6H, CH_3ipr.). ^{13}C NMR (125.8 MHz, DMSO-d_6): 169.7 (C-4), 161.3 (C-4″), 157.7 (C-2), 130.1 (C-2″), 123.2 (C-1″), 115.7 (C-3″), 88.3 (C-5), 70.3 (d, $J_{2',P}$=12.0, C-2′), 70.6 (d, $J_{C,O,P}$=6.4, CHipr.), 65.8 (C-1′), 65.1 (d, *J*=164.4, PCH_2), 24.1 (d, $J_{C,P}$=3.8) and 23.9 (d, $J_{C,P}$=4.5, CH_3ipr.). MS (ESI): *m/z* (%)=427 (40) $[M+H]^+$, 449.1 (100) $[M+Na]^+$. HRMS (ESI) calcd for $C_{19}H_{27}N_2O_7P$ $[M+H]^+$ 427.1629; found 427.1630.

*4.2.7. 6-(2R)-{2-[(Diisopropoxyphosphoryl)methoxy]-3-hydroxypropoxy}-4-hydroxy-2-phenylpyrimidine (**6a**).* Colourless oil (75%), R_f 0.40 (B). ^{1}H NMR ($CDCl_3$): 13.23 (br s, 1H, OH), 8.23 (m, 2H, H-2″), 7.52–7.61 (m, 3H, H-3″, H-4″), 5.74 (s, 1H, H-5), 4.70–4.83 (m, 2H, CHipr.), 4.43–4.49 (m, 2H, H-1′), 4.09 (dd, J_{gem}=14.1, $J_{H,P}$=7.5, 1H, PCHa), 3.91 (m, 1H, H-2′), 3.86 (dd, J_{gem}=14.1, $J_{H,P}$=8.3, 1H, PCHb), 3.86 (m, 1H, H-3′a), 3.73 (dd, J_{gem}=12.3, $J_{3'b,2'}$=6.0, 1H, H-3′b), 1.34 (d, 6H) and 1.33 (d, $J_{CH3,CH}$=6.2, 6H, CH_3ipr.). ^{13}C NMR ($CDCl_3$): 170.0 (C-6), 167.0 (C-4), 157.2 (C-2), 132.5 (C-4″), 131.3 (C-1″), 128.9 (C-3″), 127.9 (C-2″), 90.8 (C-5), 81.9 (d, $J_{2',P}$=8.2, C-2′), 71.9 (d, $J_{C,P}$=6.6) and 71.4 (d, $J_{C,P}$=6.8, CHipr.), 65.5 (C-1′), 65.4 (d, $J_{C,P}$=168.9, PCH_2), 61.8 (C-3′), 23.9–24.1 (m, CH_3ipr.). MS (ESI): *m/z* (%)=441.1 (15) $[M+H]^+$; 463.2 (100) $[M+Na]^+$. HRMS (ESI) for $C_{20}H_{29}O_7N_2NaP$ calcd: 463.1605; found 463.1603.

*4.2.8. 6-(2R)-{2-[(Diisopropoxyphosphoryl)methoxy]-3-hydroxypropoxy}-4-hydroxy-2-(4-fluorophenyl)pyrimidine (**6b**).* White solid (319 mg, 54%), R_f 0.40 (B). ^{1}H NMR (500 MHz, DMSO-d_6): 12.33 (br s, 1H, OH), 8.26 (m, 2H, H-2″), 7.36 (m, 2H, H-3″), 5.66 (br s, 1H, H-5), 4.85 (br s, 1H, OH-3′), 4.55–4.62 (m, 2H, CHipr.), 4.50 (dd, J_{gem}=11.4, $J_{1'a,2'}$=3.4, 1H, H-1′a), 4.31 (dd, J_{gem}=11.4, $J_{1'b,\ 2'}$=5.9, 1H, H-1′b), 3.86–3.95 (m, 2H, PCH_2), 3.78 (m, 1H, H-2′), 3.54–3.60 (m, 2H, H-3′), 1.20–1.23 (m, 12H, CH_3ipr.). ^{13}C NMR (125.8 MHz, DMSO-d_6): 170.0 (C-4), 164.4 (d, $J_{4'',F}$=249.7, C-4″), 130.7 (d, $J_{2'',F}$=9.1, C-2″), 130.3 (C-1″), 115.9 (d, $J_{3'',F}$=21.9, C-3″), 88.8 (C-5), 80.3 (d, $J_{2',P}$=11.5, C-2′), 70.3–70.4 (m, CHipr.), 66.1 (C-1′), 64.0 (d, $J_{C,P}$=165.0, PCH_2), 59.9 (C-3′), 23.8–24.0 (CH_3ipr.). MS (ESI): *m/z* (%)=459 (98) $[M+H]^+$, 481 (100) $[M+Na]^+$. HRMS (ESI) calcd for $C_{20}H_{29}O_7N_2FP$ $[M+H]^+$ 459.16909; found 459.16920.

*4.2.9. 6-(2R)-{2-[(Diisopropoxyphosphoryl)methoxy]-3-hydroxypropoxy}-4-hydroxy-2-(4-methoxy)pyrimidine (**6c**).* White solid (363 mg, 60%), R_f 0.45 (B). ^{1}H NMR (600 MHz, DMSO-d_6): 12.35 (br s, 1H, OH), 8.16 (m, 2H, H-2″), 7.06 (m, 2H, H-3″), 5.52 (br s, 1H, H-5), 4.86 (br s, 1H, OH-3′), 4.55–4.63 (m, 2H, CHipr.), 4.46 (dd, J_{gem}=11.4, $J_{1'a,2'}$=3.6, 1H, H-1′a), 4.27 (dd, J_{gem}=11.4, $J_{1'b,2'}$=6.0, 1H, H-1′b), 3.88–3.95 (m, 2H, PCH_2), 3.83 (s, 3H, OCH_3), 3.77 (m, 1H, H-2′), 3.54–3.59 (m, 2H, H-3′), 1.20–1.23 (m, 12H, CH_3ipr.). ^{13}C NMR (151 MHz, DMSO-d_6): 169.8 (C-4), 162.5 (C-4″), 157.8 (C-2), 129.9 (C-2″), 125.1 (C-1″), 114.3 (C-3″), 88.5 (C-5), 80.4 (d, $J_{2',P}$=11.4, C-2′), 70.4–70.45 (m, CHipr.), 66.1 (C-1′), 64.0 (d, $J_{C,P}$=164.6, PCH_2), 60.0 (C-3′), 55.7 (OCH_3), 23.9–24.1 (m, CH_3ipr.). MS (ESI): *m/z* (%)=471.1 (100) $[M+H]^+$, 493.1 (96) $[M+Na]^+$. HRMS (ESI) calcd for $C_{21}H_{32}O_8N_2P$ $[M+H]^+$ 471.1891; found 471.1893.

*4.2.10. 6-(2R)-{2-[(Diisopropoxyphosphoryl)methoxy]-3-hydroxypropoxy}-4-hydroxy-2-(4-nitrophenyl)pyrimidine (**6d**).* White solid (255 mg, 41%), R_f 0.40 (B). ^{1}H NMR (500 MHz, DMSO-d_6): 12.33 (br s, 1H, OH), 8.48 (m, 2H, H-2″), 8.36 (m, 2H, H-3″), 5.90 (br s, 1H, H-5), 4.88 (br s, 1H, OH-3′), 4.54–4.61 (m, 3H, CHipr., H-1′a), 4.38 (dd, J_{gem}=11.4, $J_{1'b,2'}$=5.9, 1H, H-1′b), 3.86–3.96 (m, 2H, PCH_2), 3.80 (m, 1H, H-2′), 3.55–3.62 (m, 2H, H-3′), 1.19–1.22 (m, 12H, CH_3ipr.). ^{13}C NMR (125.8 MHz, DMSO-d_6): 170.6 (C-4), 149.2 (C-4″), 141.2 (C-1″), 129.3 (C-2″), 123.9 (C-3″), 89.4 (C-5), 80.3 (d, $J_{2',P}$=11.3, C-2′), 70.3–70.4 (m, CHipr.), 66.0 (C-1′), 64.0 (d, $J_{C,P}$=164.7, PCH_2), 59.9 (C-3′), 23.83–24.01 (m, CH_3ipr.). MS (ESI): *m/z* (%)=486.01 (100) $[M+H]^+$, 508.08 (89) $[M+Na]^+$. HRMS (ESI) calcd for $C_{20}H_{29}O_9N_3P$ $[M+H]^+$ 486.16359; found 486.16380.

*4.2.11. 6-(2R)-{2-[(Diisopropoxyphosphoryl)methoxy]-3-hydroxypropoxy}-4-hydroxy-2-(4-trifluorophenyl)pyrimidine (**6e**).* White solid (424 mg, 65%), R_f 0.47 (B). ^{1}H NMR (600 MHz, DMSO-d_6): 12.36 (br s, 1H, OH), 8.42 (m, 2H, H-2″), 7.89 (m, 2H, H-3″), 5.82 (br s, 1H, H-5), 4.88 (br s, 1H, OH-3′), 4.54–4.60 (m, 3H, CHipr, H-1′a), 4.36 (dd, J_{gem}=11.4, $J_{1'b,2'}$=5.9, 1H, H-1′b), 3.86–3.95 (m, 2H, PCH_2), 3.79 (m, 1H, H-2′), 3.55–3.60 (m, 2H, H-3′), 1.19–1.22 (m, 12H, CH_3ipr.). ^{13}C NMR (151 MHz, DMSO-d_6): 170.5 (C-4), 159.2 (C-2), 138.8 (C-1″), 131.3 (q, $J_{4'',F}$=31.8, H-4″), 128.9 (C-2″), 125.7 (q, $J_{3'',F}$=3.7, C-3″), 124.3 (q, $J_{C,F}$=272.1, CF_3), 89.3 (C-5), 80.3 (d, $J_{2',P}$=11.5, C-2′), 70.3–70.4 (m, CHipr.), 66.0 (C-1′), 64.0 (d, $J_{C,P}$=164.8, PCH_2), 59.9 (C-3′), 23.8–24.1 (m, CH_3ipr.). MS (ESI): *m/z* (%)=507.2 (100) $[M-H]^-$. HRMS (ESI) calcd for $C_{21}H_{27}O_7N_2F_3P$ $[M-H]^-$ 507.15135; found 507.15079.

*4.2.12. 6-(2R)-{2-[(Diisopropoxyphosphoryl)methoxy]-3-hydroxypropoxy}-4-hydroxy-2-(4-hydroxyphenyl)pyrimidine (**6f**).* White solid (369 mg, 63%), R_f 0.28 (B). ^{1}H NMR (500 MHz, DMSO-d_6): 12.26 and 10.29 (2× br s, 2× OH), 8.05 (m, 2H, H-2″), 6.86 (m, 2H, H-3″), 5.46 (br s, 1H, H-5), 4.85 (br s, 1H, OH-3′), 4.55–4.62 (m, 2H, CHipr.), 44.4 (dd, J_{gem}=11.4, $J_{1'a,2'}$=3.7, 1H, H-1′a), 4.26 (dd, J_{gem}=11.4, $J_{1'b,2'}$=5.8, 1H, H-1′b), 3.87–3.95 (m, 2H, PCH_2), 3.76 (m, 1H, H-2′), 3.54–3.58 (m, 2H, H-3′), 1.20–1.24 (m, 12H, CH_3ipr.). ^{13}C NMR (125.8 MHz, DMSO-d_6): 169.7 (C-4), 161.3 (C-4″), 158.5 (C-2), 130.1 (C-2″), 123.0 (C-1″), 115.6 (C-3″), 88.2 (C-5), 80.4 (d, $J_{2',P}$=11.4, C-2′), 70.4–70.5 (m, CHipr.), 66.0 (C-1′), 64.0 (d, $J_{C,P}$=164.6, PCH_2), 60.0 (C-3′), 23.8–24.0 (m, CH_3ipr.). MS (ESI): *m/z* (%)=455.2 (100) $[M-H]^-$. HRMS (ESI) calcd for $C_{20}H_{29}N_2O_8P$ $[M-H]^-$ 455.1589; found 455.1587.

4.3. Deprotection of diisopropyl esters 5 and 6 to free phosphonic acids 7 and 8. General procedure

Diisopropyl ester **5** or **6** (0.5 mmol) in CH_3CN (20 mL) was treated with Me_3SiBr (2 mL) at room temperature overnight. Volatiles were evaporated under reduced pressure and the residue was codistilled with water. The crude product was purified by preparative HPLC (linear gradient 20–100% of aqueous MeOH) or on Dowex 1× 2 (acetate form): after application of the aqueous solution of the crude product, alkalized by several drops of aqueous ammonia onto the column, it was washed with water until the UV absorption dropped. The column was then eluted with a 0.5 M of dilute acetic and subsequently with formic acid (1 M). The UV absorbing eluate was evaporated and the residue was evaporated several times codistilled with water to remove the formic acid and crystallized.

*4.3.1. 4-Hydroxy-2-phenyl-6-[2-(phosphonomethoxy)ethoxy]pyrimidine (**7a**).* White solid (125 mg, 79%), mp 236–238 °C (recryst from H_2O/EtOH); IR (KBr): 3300 (NH), 2700, 2300 (P–OH), 3080, 3038 (=CH), 1677, 1660 (C=O), 1611, 1595, 1502, 1444 (ring). ^{1}H NMR (DMSO-d_6): 8.17 (m, 2H) and 7.50–7.58 (m, 3H, Ph), 5.66 (s, 1H, H-5), 4.39 (m, 2H, H-1′), 3.85 (m, 2H, H-2′), 3.63 (d, *J*=8.7, 2H, PCH_2). ^{13}C NMR (DMSO-d_6): 169.9 (C-4), 166.6 (C-6), 158.7 (C-2), 133.2

(C-1″), 132.0 (C-4″), 128.9 (C-3″), 128.1 (C-2″), 89.0 (C-5), 70.6 (d, $J_{2',P}$=11.1, C-2′), 66.9 (d, $J_{C,P}$=160.0, PCH_2), 66.2 (C-1′). MS (ESI): *m*/*z* (%)=325 (48) $[M-H]^-$, 347 $[M-2H+Na]^-$. HRMS (ESI) for $C_{13}H_{14}O_6N_2P$ calcd: 325.0595; found 325.0595. For $C_{13}H_{15}N_2O_6P$ (326.07) calcd: C 47.86, H 4.63, N 8.59, P 9.49; found: C 47.72, H 4.63, N 8.51, P 9.44.

*4.3.2. 4-Hydroxy-2-(4-fluorophenyl)-6-[2-(phosphonomethoxy)ethoxy]pyrimidine (**7b**).* White solid (434 mg, 77%), mp 225–227 °C (recryst from H_2O/EtOH); IR (KBr): 3285 (NH), 2800–2000 (P–OH), 3083, 3050 (=CH), 1653, 1578 (C=O), 1616, 1513, 1406, 1327 (ring). ^{1}H NMR (DMSO-d_6): 8.25 (m, 2H) and 7.35 (m, 2H, Ph), 5.69 (s, 1H, H-5), 4.40 (m, 2H, H-1′), 3.85 (m, 2H, H-2′), 3.63 (d, *J*=8.7, 2H, PCH_2). ^{13}C NMR (DMSO-d_6): 170.0 (C-4), 167.1 (C-6), 164.5 (d, $J_{4'',F}$=249.8, C-4″), 158.2 (C-2), 130.7 (d, $J_{2'',F}$=9.1, C-2″), 130.2 (C-1″), 115.9 (d, $J_{3'',F}$=22.0, C-3″), 88.8 (C-5), 70.6 (d, $J_{2',P}$=11.3, C-2′), 66.9 (d, $J_{C,P}$=160.8, PCH_2), 66.2 (C-1′). MS (ESI): *m*/*z* (%)=343.1 (100) $[M-H]^-$. HRMS (ESI^-) for $C_{13}H_{13}N_2O_6FP$ calcd: 343.0501; found 343.0502.

*4.3.3. 4-Hydroxy-2-(4-methoxyphenyl)-6-[2-(phosphonomethoxy) ethoxy]pyrimidine (**7c**).* White solid (145 mg, 61%), mp 142–144 °C (recryst from H_2O/EtOH); IR (KBr): 3436, 3279 (NH), 2848 (CH_3), 1655, 1627 (C=O), 1605, 1593, 1518, 1411 (ring). ^{1}H NMR (DMSO-d_6): 8.15 (m, 2H, H-2″), 7.06 (m, 2H, H-3″), 5.55 (s, 1H, H-5), 4.64 (m, 2H, H-1′), 3.84 (m, 2H, H-2′), 3.84 (s, 3H, CH_3), 3.62 (d, $J_{P,C}$=8.7, 2H, PCH_2). ^{13}C NMR (DMSO-d_6): 169.7 (C-4), 166.0 (C-6), 162.5 (C-4″), 157.8 (C-2), 129.9 (C-2″), 124.9 (C-1″), 114.3 (C-3″), 88.4 (C-5), 70.6 (d, $J_{2',P}$=11.2, C-2′), 66.9 (d, $J_{C,P}$=160.5, PCH_2), 66.1 (C-1′), 55.7 (CH_3). MS (ESI): *m*/*z* (%)=355.1 (100) $[M-H]^-$. HRMS (ESI^-) for $C_{14}H_{16}N_2O_7P$ calcd: 355.0701; found 355.0702.

*4.3.4. 4-Hydroxy-2-(4-nitrophenyl)-6-[2-(phosphonomethoxy)ethoxy]pyrimidine (**7d**).* Pale orange solid (185 mg, 77%), mp 224–226 °C (recryst from H_2O/EtOH); IR (KBr): 3240, 3100, 3000 (NH), 2800–2000, (P–OH), 1668, (C=O), 1522, 1354, 1345 ($-NO_2$), 1582, 1554, 1433, 1392 (ring). ^{1}H NMR (DMSO-d_6): 8.43 (m, 2H, H-2″), 8.31 (m, 2H, H-3″), 5.92 (s, 1H, H-5), 4.44 (m, 2H, H-1′), 3.86 (m, 2H, H-2′), 3.59 (d, *J*=9.0, 2H, PCH_2). ^{13}C NMR (DMSO-d_6): 170.5 (C-4), 169.5 (C-6), 159.1 (C-2), 149.1 (C-4″), 141.2 (C-1″), 129.3 (C-2″), 123.9 (C-3″), 89.3 (C-5), 70.3 (d, $J_{2',P}$=10.0, C-2′), 67.5 (d, $J_{C,P}$=162.5, PCH_2), 66.2 (C-1′). MS (ESI): *m*/*z* (%)=370.1 (100) $[M-H]^-$. HRMS (ESI^-) for $C_{13}H_{13}N_3O_8P$ calcd: 370.0446; found 370.0445.

*4.3.5. 4-Hydroxy-2-(4-trifluorophenyl)-6-[2-(phosphonomethoxy) ethoxy]pyrimidine (**7e**).* White solid (191 mg, 82%), mp 236–238 °C (recryst from H_2O); IR (KBr): 3427, 3240, 3063 (NH, OH), 2800–2000, (P–OH), 1683, 1662 (C=O), 1602, 1520, 1403, 1268, 852 (ring). ^{1}H NMR (DMSO-d_6): 8.40 (m, 2H, H-2″), 7.87 (m, 2H, H-3″), 5.84 (s, 1H, H-5), 4.44 (m, 2H, H-1′), 3.86 (m, 2H, H-2′), 3.63 (m, 2H, PCH_2). ^{13}C NMR (DMSO-d_6): 170.3 (C-4), 168.4 (C-6), 159.0 (C-2), 138.5 (C-1″), 131.3 (q, $J_{4'',F}$=31.9, C-4″), 128.9 (C-2″), 125.7 (q, $J_{3'',F}$=3.8, C-3″), 124.2 (q, $J_{C,F}$=272.4, CF_3), 89.3 (C-5), 70.5 (d, $J_{2',P}$=10.1, C-2′), 67.0 (d, $J_{C,P}$=165.4, PCH_2), 66.2 (C-1′). MS (ESI): *m*/*z* (%)=393.1 (100) $[M-H]^-$. HRMS (ESI^-) for $C_{14}H_{13}N_2O_6F_3P$ calcd: 393.0469; found 393.0468.

*4.3.6. 4-Hydroxy-2-(4-hydroxyphenyl)-6-[2-(phosphonomethoxy) ethoxy]pyrimidine (**7f**).* White solid (135 mg, 79%), mp 156–158 °C (recryst from H_2O); IR (KBr): 3492, 3432, 3102 (NH, OH), 2800–2000, (P–OH), 1565, 1439 (C=O), 1611, 1595, 1518, 1419 (ring). ^{1}H NMR (DMSO-d_6): 8.05 (m, 2H, H-2″), 6.86 (m, 2H, H-3″), 5.49 (s, 1H, H-5), 4.35 (m, 2H, H-1′), 3.83 (m, 2H, H-2′), 3.62 (d, *J*=8.7, 2H, PCH_2). ^{13}C NMR (DMSO-d_6): 169.7 (C-4), 165.7 (C-6), 161.3 (C-4″), 157.7 (C-2), 130.1 (C-2″), 123.1 (C-1″), 115.6 (C-3″), 88.1 (C-5), 70.7 (d, $J_{2',P}$=11.3, C-2′), 66.9 (d, $J_{C,P}$=160.5, PCH_2), 66.1 (C-1′). MS (ESI): *m*/*z* (%)=341.1 (100) $[M-H]^-$. HRMS (ESI^-) for $C_{13}H_{14}N_2O_7P$ calcd: 341.0544; found 341.0545.

*4.3.7. 4-Hydroxy-2-phenyl-6-(2R)-[2-(phosphonomethoxy)-3-hydroxypropoxy]pyrimidine (**8a**).* Freeze dried, white solid (139 mg, 66%), mp 105–109 °C (recryst from H_2O); IR (KBr): 3421, 3287 (NH, OH), 2800–2000 (P–OH), 3071 (=CH), 1654 (C=O), 1605, 1595, 1502, 1446 (ring). ^{1}H NMR (D_2O): 7.76 (m, 2H) and 7.59 (m, 1H) and 7.48 (m, 2H, Ph), 5.64 (s, 1H, H-5), 4.28 (dd, $J_{1'a,2'}$=4.1, J_{gem}=11.0, 1H, H-1′a), 4.21 (dd, $J_{1'b-2'}$=5.5, J_{gem}=11.0, 1H, H-1′b), 3.77–4.00 (m, 5H, H-2′, H-3′, PCH_2). ^{13}C NMR (D_2O): 171.3 (C-4), 168.1 (C-6), 158.9 (C-2), 133.9 (C-4″), 131.3 (C-1″), 130.1 (C-3″), 128.7 (C-2″), 90.3 (C-5), 81.1 (d, $J_{2',P}$=11.58, C-2′), 67.9 (C-1′), 66.3 (d, $J_{C,P}$=139.9, PCH_2), 61.4 (C-3′). MS (ESI): *m*/*z* (%)=355.1 (100) $[M-H]^-$. HRMS (ESI^-) for $C_{14}H_{16}N_2O_7P$ calcd: 355.0701; found 355.0700. $[\alpha]_D^{25}$ −5.0 (*c* 0.141, DMSO).

*4.3.8. 4-Hydroxy-2-(4-fluorophenyl)-6-(2R)-[2-(phosphonomethoxy)-3-hydroxypropoxy]pyrimidine (**8b**).* White solid (186 mg, 76%), mp 196–197 °C (recryst from H_2O); IR (KBr): 3557 (OH), 3459, 3417, 3150, (NH, OH), 2800–2000 (P–OH), 1651, 1566 (C=O), 1608, 1511, 1403, 1324 (ring). ^{1}H NMR (DMSO-d_6): 8.26 (m, 2H, H-2″), 7.35 (m, 2H, H-3″), 5.68 (s, 1H, H-5), 4.41 (dd, 1H, J_{gem}=11.3, $J_{1'a,2'}$=4.1, 1H, H-1′a), 4.30 (dd, 1H, J_{gem}=11.2, $J_{1'b-2'}$=5.6, 2H, H-1′b), 3.68–3.78 (m, 3H, CH_2P, H-2′), 3.54–3.59 (m, 2H, H-3′). ^{13}C NMR (DMSO-d_6): 170.0 (C-4), 167.1 (C-6), 164.4 (d, $J_{4'',F}$=249.6, C-4″), 158.3 (C-2), 130.7 (d, $J_{2'',F}$=9.0, C-2″), 130.3 (C-1″), 115.9 (d, $J_{3'',F}$=21.9, C-3″), 88.8 (C-5), 80.3 (d, $J_{2',P}$=9.6, C-2′), 66.3 (C-1′), 66.0 (d, $J_{C,P}$=160.4, PCH_2), 60.2 (C-3′). MS (ESI): *m*/*z* (%)=373.2 (100) $[M-H]^-$. HRMS (ESI^-) for $C_{14}H_{15}N_2O_7FP$ calcd: 373.0606; found 373.0607. $[\alpha]_D^{25}$ −1.1 (*c* 0.234, DMSO).

*4.3.9. 4-Hydroxy-2-(4-methoxyphenyl)-6-(2R)-[2-(phosphonomethoxy)-3-hydroxypropoxy]pyrimidine (**8c**).* White solid (220 mg, 81%), mp 197–199 °C (recryst from H_2O/EtOH); IR (KBr): 3516 (OH), 3419, 3220 (NH, OH), 2843 (CH_3), 1640, 1561 (C=O), 1609, 1592, 1517, 1411 (ring). ^{1}H NMR (DMSO-d_6): 8.16 (m, 2H, H-2″), 7.06 (m, 2H, H-3″), 5.54 (s, 1H, H-5), 4.39 (dd, 1H, J_{gem}=11.2, $J_{1'a,2'}$=4.2, 1H, H-1′a), 4.27 (dd, 1H, J_{gem}=11.2, $J_{1'b,2'}$=5.6, 1H, H-1′b), 3.83 (s, 3H, OCH_3), 3.69–3.78 (m, 3H, CH_2P, H-2′), 3.56 (d, 2H, $J_{3',2'}$=5.3 H-3′). ^{13}C NMR (DMSO-d_6): 169.8 (C-4), 166.1 (C-6), 162.5 (C-4″), 157.8 (C-2), 129.9 (C-2″), 125.0 (C-1″), 114.3 (C-3″), 88.5 (C-5), 80.4 (d, $J_{2',P}$=9.8, C-2′), 66.3 (C-1′), 65.9 (d, $J_{C,P}$=160.9, PCH_2), 60.2 (C-3′), 55.7 (OCH_3). MS (ESI): *m*/*z* (%)=385.2 (100) $[M-H]^-$. HRMS (ESI^-) for $C_{15}H_{18}N_2O_8P$ calcd: 385.0806; found 385.0806. $[\alpha]_D^{25}$ −3.3 (*c* 0.275, DMSO).

*4.3.10. 4-Hydroxy-2-(4-nitrophenyl)-6-(2R)-[2-(phosphonomethoxy)-3-hydroxypropoxy]pyrimidine (**8d**).* White solid (130 mg, 71%), dec 237 °C (recryst from H_2O/EtOH); IR (KBr): 3433, 3252 (NH, OH), 1670, 1650 (C=O), 1524, 1350 ($-NO_2$), 1615, 1501, 1400, 1110 (ring). ^{1}H NMR (DMSO-d_6): 8.48 (m, 2H, H-2″), 7.35 (m, 2H, H-3″), 5.93 (s, 1H, H-5), 4.49 (dd, 1H, J_{gem}=11.2, $J_{1'a,2'}$=4.2, 1H, H-1′a), 4.38 (dd, 1H, J_{gem}=11.2, $J_{1'b,2'}$=5.6, 1H, H-1′b), 3.70–3.81 (m, 3H, CH_2P, H-2′), 3.55–3.61 (m, 2H, H-3′). ^{13}C NMR (DMSO-d_6): 170.6 (C-4), 169.4 (C-6), 159.2 (C-2), 149.2 (C-4″), 141.2 (C-1″), 129.4 (C-2″), 123.9 (C-3″), 89.4 (C-5), 80.3 (d, $J_{2',P}$=9.7, C-2′), 66.3 (C-1′), 65.9 (d, $J_{C,P}$=160.6, PCH_2), 60.1 (C-3′). MS (ESI): *m*/*z* (%)=400.1 (100) $[M-H]^-$. HRMS (ESI^-) for $C_{14}H_{15}N_3O_9P$ calcd: 400.0551; found 400.0551. $[\alpha]_D^{25}$ −1.5 (*c* 0.374, DMSO).

*4.3.11. 4-Hydroxy-2-(4-trifluorophenyl)-6-(2R)-[2-(phosphonomethoxy)-3-hydroxypropoxy]pyrimidine (**8e**).* White solid (297 mg, 90%), mp 158–159 °C (recryst from H_2O/EtOH); IR (KBr): 3386, 3230, 3080 (NH, OH, H_2O), 2800–2000, (P–OH), 1672 (C=O), 1601, 1572, 1595, 1520, 1404 (ring). ^{1}H NMR (DMSO-d_6): 8.41 (m, 2H,

H-2″), 7.88 (m, 2H, H-3″), 5.84 (s, 1H, H-5), 4.46 (dd, 1H, J_{gem}=11.1, $J_{1'a,2'}$=4.1, 2H, H-1′a), 4.35 (dd, 1H, J_{gem}=11.2, $J_{1'b,2'}$=5.6, 2H, H-1′b), 3.70–3.79 (m, 3H, CH_2P, H-2′), 3.55–3.60 (m, 2H, H-3′). ^{13}C NMR (DMSO-d_6): 170.4 (C-4), 168.5 (C-6), 159.0 (C-2), 138.6 (C-1″), 131.3 (q, $J_{4'',F}$=31.8, C-4″), 128.9 (C-2″), 125.8 (q, $J_{3'',F}$=3.7, C-3″), 124.3 (q, $J_{C,F}$=272.3, CF_3), 89.4 (C-5), 80.3 (d, $J_{2',P}$=9.7, C-2′), 66.3 (C-1′), 66.0 (d, $J_{C,P}$=161.2, PCH_2), 60.1 (C-3′). MS (ESI): *m*/*z* (%)=423.1 (100) $[M-H]^-$. HRMS (ESI^-) for $C_{15}H_{15}N_2O_7F_3P$ calcd: 423.0575; found 423.0573. $[\alpha]_D^{25}$ −1.1 (*c* 0.242, DMSO).

*4.3.12. 4-Hydroxy-2-(4-hydroxyphenyl)-6-(2R)-[2-(phosphonomethoxy)-3-hydroxypropoxy]pyrimidine (**8f**).* Pale orange solid (216 mg, 76%), mp 121–122 °C (recryst from H_2O/EtOH); IR (KBr): 3386, 3104 (NH, OH), 2800–2000, (P–OH), 1695, 1648 (C=O), 1610, 1596, 1518, 1420, 1320 (ring). ^1H NMR (DMSO-d_6): 8.05 (m, 2H, H-2″), 6.88 (m, 2H, H-3″), 5.49 (s, 1H, H-5), 4.37 (dd, 1H, J_{gem}=11.2, $J_{1'a-2'}$=4.2, 2H, H-1′a), 4.25 (dd, 1H, J_{gem}=11.2, $J_{1'b,2'}$=5.6, 2H, H-1′b), 3.69–3.78 (m, 2H, CH_2P, H-2′), 3.56 (d, 2H, $J_{3',2'}$=5.3, H-3′). ^{13}C NMR (DMSO-d_6): 169.8 (C-4), 165.8 (C-6), 161.4 (C-4″), 157.8 (C-2), 130.1 (C-2″), 123.0 (C-1″), 115.7 (C-3″), 88.2 (C-5), 80.3 (d, $J_{2',P}$=10.0, C-2′), 66.3 (C-1′), 65.8 (d, $J_{C,P}$=160.6, PCH_2), 60.2 (C-3′). MS (ESI): *m*/*z* (%)=371.2 (100) $[M-H]^-$. HRMS (ESI^-) for $C_{14}H_{16}N_2O_8P$ calcd: 371.0650; found 371.0650. $[\alpha]_D^{25}$ −1.3 (*c* 0.285, DMSO).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.07.040. These data include MOL files and InChiKeys of the most important compounds described in this article.

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