

BIFUNCTIONAL ACYCLIC NUCLEOSIDE PHOSPHONATES.**1. SYMMETRICAL 1,3-BIS[(PHOSPHONOMETHOXY)PROPAN-2-YL] DERIVATIVES OF PURINES AND PYRIMIDINES**

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Dedicated to Professor Jaroslav Podlaha on the occasion of his 70th birthday.

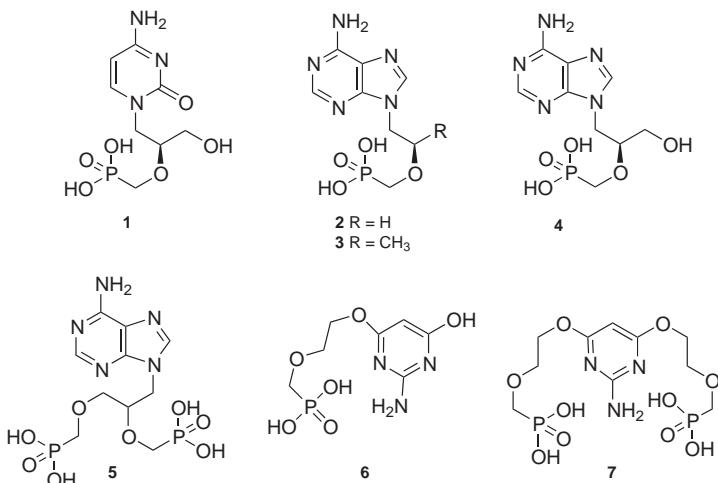
We report here a general method for the synthesis of new symmetrical bis-phosphonates of acyclic nucleosides. 1,3-Bis[(diisopropoxypyrophosphoryl)methoxy] derivatives of purine and pyrimidine bases were prepared by their reaction with 1,3-bis[(diisopropoxypyrophosphoryl)methoxy]propan-2-yl tosylate. Cytosine, uracil and thymine provided regiospecifically N^1 -isomers. This alkylation regiospecificity applies to several other tosylates of primary and secondary alcohols as well. 6-Chloropurine and 2-amino-6-chloropurine were alkylated in N^9 position. Resulting bis-phosphonates were converted to the respective free phosphonic acids and tested for antiviral and cytostatic activity. Despite the fact that no biological activity was found so far, the outcome of this work can serve as a useful tool in synthesis of novel groups of acyclic nucleoside phosphonates (ANPs).

Keywords: Acyclic nucleotide analogues; Acyclic nucleoside phosphonates; ANP; Purines; Pyrimidines; Phosphonomethyl ethers; Biphosphonates; Antivirals.

Acyclic nucleoside phosphonates (ANP) deserve proper attention owing to their significant biological activity. This is particularly important, though by no means limited to the suppression of DNA virus and/or retrovirus replication. Three compounds (each of them representing one of the structural classes with diverse substituents at the β -position of the alkyl chains) were approved and marketed: cidofovir, Vistide® with a wide range of anti-DNA virus activity and the candidate for smallpox chemotherapy in case of its criminal artificial outbreak; adefovir, aimed at the therapeutic use in hepatitis B, specifically for lamivudine-resistant mutants of the HBV, and tenofovir, a very successful drug used in the HAART combination of AIDS therapy. While the first drug mentioned is used for infusion, the oral forms

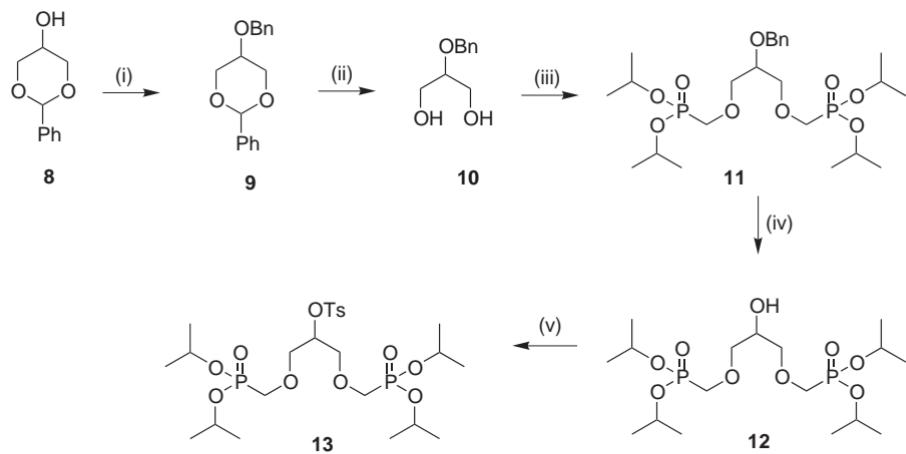
of the other two ANPs with increased intestinal absorption contain pro-drugs of the above active principles: adefovir dipivoxil (Hepsera®) and tenofovir disoproxil fumarate (Viread®, Truvada®), respectively. Once transported into the cell, the liberated ANP undergo metabolic transformation to the α -modified triphosphate analogues – the active antimetabolites. These dNTP analogues then inhibit the DNA synthesis de novo acting as chain terminators (**2** and **3**) or as alternative substrates/inhibitors **1** capable of limited incorporation which is followed by appropriate consequences. There are two recent reviews on the synthetic methods, mechanism of action, metabolic transformations and biological effects of ANP^{1,2}.

Phosphonomethyl ether group is one of the characteristic features of the pharmacophore in biologically active ANP. To our knowledge, there are only two compounds described in the literature which bear two such groups in the molecule: the asymmetric 3-phosphonomethyl ether (**5**) of HPMPA, 9-[3-hydroxy-2-(phosphonomethoxy)propyl]adenine³ (**4**), and 2-amino-4,6-bis[2-(phosphonomethoxy)ethoxy]pyrimidine (**7**), a symmetrical ANP from the novel class of “ring-open” compounds⁴. While compound **5** is devoid of any antiviral activity in contrast to its parent compound, the antiviral activity demonstrated by the parent pyrimidine derivative **6** remains preserved following the introduction of an additional 2-phosphonomethyl group in **7**. Obviously, high polarity itself is not hindrance for the membrane transport of the compound into the cell as is the charge distribution in the molecule. Therefore, we decided to synthesize and study biological activity and other properties of the simplest symmetrical 1,3-bis-



(phosphonomethyl)ether derived from glycerol whose secondary hydroxy function is replaced by heterocyclic base residue bound at its N¹ (pyrimidine) or N⁹ (purine) position. Formally, these compounds could be also taken for double PME (2-(phosphonomethoxy)ethyl) molecules. In addition to their potential biological activity, these compounds might be interesting objects for physico-chemical investigation: due to the repulsion of negatively charged groups, their conformation should depend on proximate pH of their aqueous solutions.

The synthesis of the bis-phosphonate alkylating agent proceeded as depicted in Scheme 1. 2-(Benzylxy)propane-1,3-diol (**10**) can be synthesized by known methods⁵⁻⁷, however, we used an alternative approach. 2-Phenyl-1,3-dioxan-5-ol (**8**) was prepared by the known procedure⁸ and purified by crystallization from cyclohexane. It was subsequently converted to its *O*-benzyl derivative **9**. The benzylidene protecting group was removed by acid-catalyzed hydrolysis (Dowex 50X8, H⁺ form) to provide 2-(benzylxy)propane-1,3-diol (**10**). This intermediate was further alkylated with (diisopropoxypyrophosphoryl)methyl tosylate to form compound **11**. It was subsequently hydrogenated and the thus obtained intermediate **12** was under standard conditions finally converted to 1,3-bis[(diisopropoxypyrophosphoryl)methoxy]propan-2-yl tosylate (**13**).

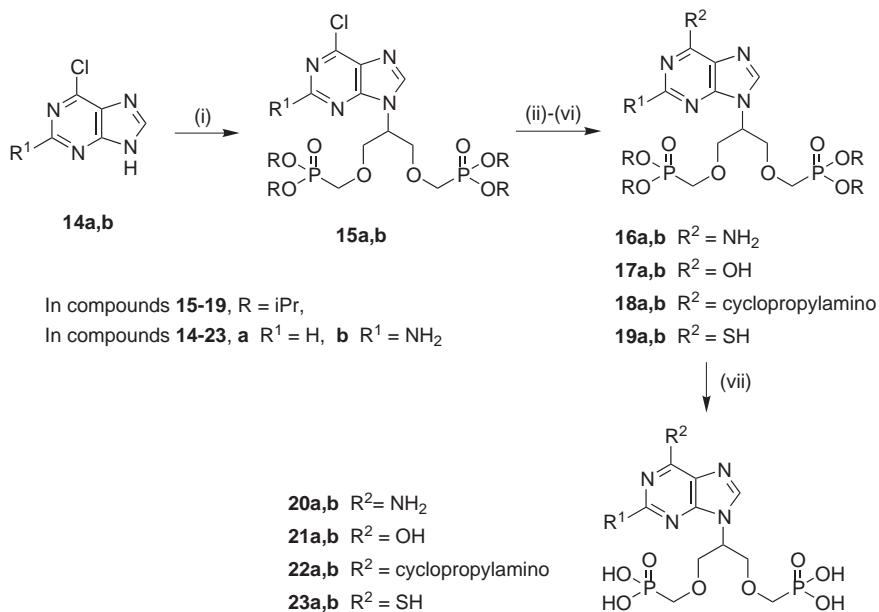


(i) NaH, BnBr, THF; (ii) Dowex 50X8 (H⁺ form), 80% MeOH, reflux; (iii) TsOCH₂P(O)(O*i*Pr)₂, NaH, DMF, 0 °C; (iv) H₂/10% Pd/C, MeOH, HCl, r.t.; (v) TsCl, Et₃N, DMAP, CH₂Cl₂, 0 °C

SCHEME 1
Synthesis of bis-phosphonate alkylating agent

Alkylation of nucleobases with compound **13** was performed under standard conditions (0.5 equivalent of Cs_2CO_3 , DMF, heating). Alkylation of purines is depicted in Scheme 2. The reaction of 6-chloropurine **14a** and 2-amino-6-chloropurine **14b** proceeded at N^9 position of the ring to give compounds **15a** and **15b** only. Essentially no N^7 -regioisomer formation was observed.

The intermediates **15** were further converted to other base-modified phosphonates: thus, adenine **16a** and 2,6-diaminopurine **16b** derivatives were prepared by the ammonolysis with methanolic ammonia; hypoxanthine derivative **17b** was obtained in reaction of **16a** with 3-methylbutyl nitrite in 80% acetic acid while acid hydrolysis of **15b** led to guanine derivative **17b**. Replacement of chlorine atom in the 6-chloro derivatives **15** by sulfanyl group in compounds **19a** and **19b** was achieved by the reaction with thiourea. We have also prepared the 6-(cyclopropylamino) derivatives



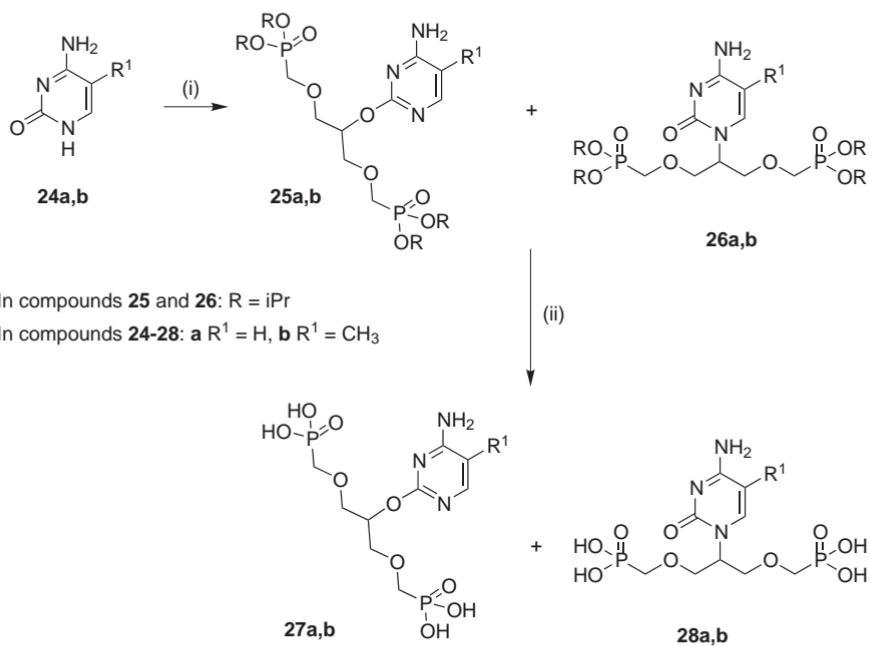
(i) **8**, Cs_2CO_3 , DMF, 90°C ; (ii) for compounds **16**, methanolic ammonia, 100°C ; (iii) for **17a**: **16a**, 3-methylbutyl nitrite, 80% CH_3COOH , r.t.; (iv) for **17b**: **16b**, 80% CH_3COOH , r.t.; (v) for **18**: cyclopropylamine, dioxane, reflux; (vi) for **19**: thiourea, ethanol, reflux; (vii) for **20-23**: TMSBr in acetonitrile, r.t.

SCHEME 2
Alkylation of purine bases

18a and **18b** by reaction of tetraester **15a** and **15b** with cyclopropylamine in dioxane because cyclopropylamino group possesses very interesting feature. It is catabolized in the cells to 6-oxo derivative. 2-Amino-6-(cyclopropylamino)purines can therefore serve as guanine prodrugs^{9,10}.

Subsequent deprotection of compounds **16–19** with bromotrimethylsilane in acetonitrile followed by hydrolysis yielded the corresponding free bis-phosphonic acids **20–23** that were ultimately purified as deionized crude materials by ion exchange chromatography.

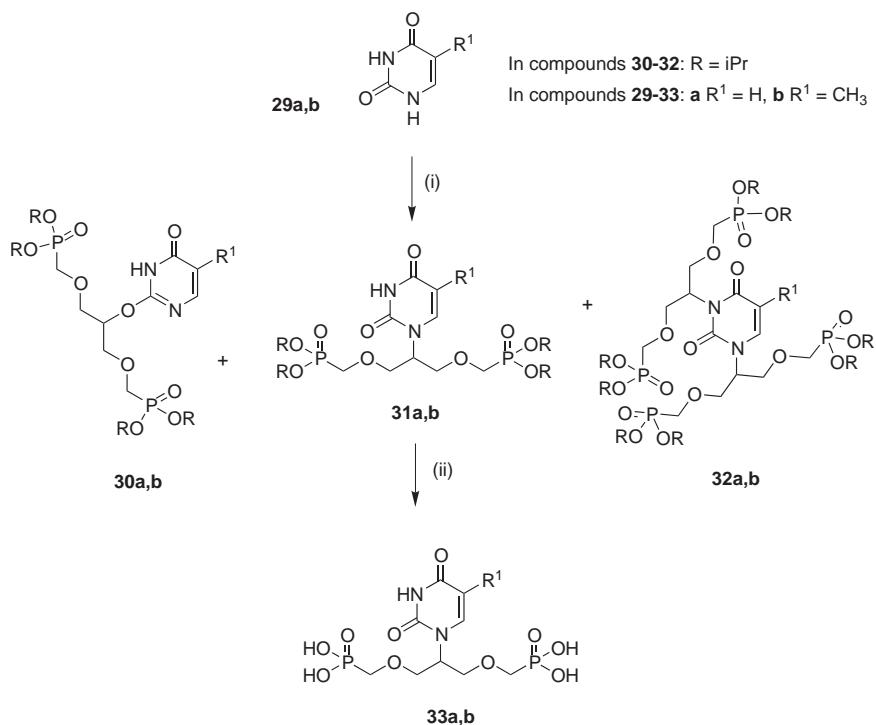
The reaction of cytosine and 5-methylcytosine derivatives **24a** and **24b** with intermediate **13** under the above conditions afforded a mixture of *O*²-regioisomer (**25**; yield 7%), and *N*¹-regioisomer (**26**; yield 14%), which were further converted to the corresponding free bis-phosphonic acids **27** and **28** as shown in Scheme 3. *O*²- and *N*¹-isomers in the pyrimidine series can be readily distinguished by ¹³C NMR spectroscopy. The phosphonate-bearing three-carbon chain linked via its position 2 to oxygen shows δ_{CH} 72 ppm while in that bound to N δ_{CH} 54 ppm (cf. Experimental).



(i) **13**, Cs_2CO_3 , DMF, 90 °C; (ii) TMSBr in acetonitrile, r.t.

SCHEME 3
 Alkylation of cytosine derivatives

Scheme 4 shows the course of alkylation of uracil **29a** and thymine **29b** with synthon **13** under standard conditions. Of the three products formed in both cases (*O*²-**30**, *N*¹-**31** and bis-*N*¹,*N*³-isomer **32**) the *N*¹-isomer **31** was always the major product. It was isolated in about 15% yield while the *O*²-isomer and bis-*N*¹,*N*³-substituted compound were obtained only in 1.1 and 0.5% yields, respectively. The subsequent deprotection of tetraester **31** with bromotrimethylsilane in acetonitrile followed by hydrolysis yielded mesoforms of the corresponding free phosphonic acids **33** that were isolated from the deionized product by ion exchange chromatography. Bis-*N*¹,*N*³ derivative **32** was identified using ¹H NMR spectroscopy by the absence of the signal of NH group. In ¹³C NMR, the residue bound to pyrimidine base provides two signals with $\delta_{C,H}$ 50 and 40 ppm for *N*¹ and *N*³, respectively. This also clearly indicates a double substitution of the pyrimidine ring.



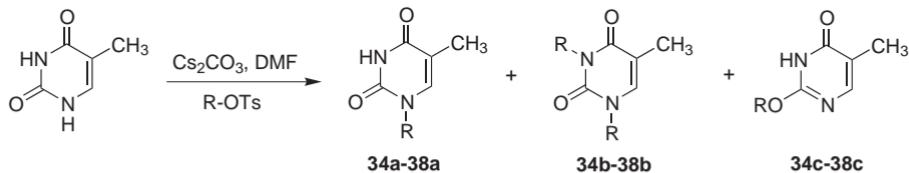
(i) **13**, Cs₂CO₃, DMF, 90 °C; (ii) TMSBr in acetonitrile, r.t.

SCHEME 4
Alkylation of uracil and thymine

Our results are therefore in agreement with the known fact that N^1 position of the thymine and uracil ring is the preferred alkylation target under given conditions^{11,12}. Bis- N^1,N^3 - and O -isomer are our minor products. N^3 -Isomer, that is preferentially formed in alkylation of uridine and thymidine, is not formed in our case at all¹³. To verify the general validity of this phenomenon we have briefly examined the regiospecificity of alkylations of thymine with the tosyl derivatives of various primary and secondary alcohols (Scheme 5). The results summarized in Table I clearly demonstrate that – under the reaction conditions used – the major product of the reaction is the N^1 -isomer both with the primary and secondary tosylates.

All tosylates of primary alcohols (No. 1, 2, and 3) provide mixtures of N^1 and bis- N^1,N^3 derivatives in the ratio ca. 3:1. When tosylate of secondary alcohol is used (No. 4), N^1 derivative is preferentially formed. Also, the reaction with “bis-phosphonate precursor” (No. 5) gives the same result. In all these cases O derivative is formed as minor product.

It should be also considered that, while the nucleosidations are mainly $SN1$ reactions, the mechanism of alkylation by tosylates is evidently $SN2$. Though the advantage of the 4- O -alkyl protection 4-methoxypyrimidin-2(1*H*)-ones) of uracil, thymine and related pyrimidines, which are generally used for such transformations, consists in improved yields of alkylations due to good solubility of the alkylation substrates, the above finding on the regiospecificity of the alkylation reaction of free pyrimidine bases in DMF in the presence of cesium carbonate could be useful in those cases where the corresponding 4-methoxypyrimidin-2(1*H*)-ones are not accessible at all or with difficulties only, as it can be, e.g., in the case of minute reaction scales (labeled compounds) or with bases sensitive to the reaction conditions required for the 4-methoxypyrimidin-2(1*H*)-one preparation. To control the reaction it is advisable to perform it at mild temperature and with a small excess of the reagent only, to avoid the formation of the bis-alkylated product.

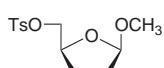
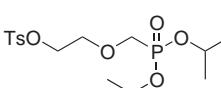
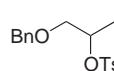


SCHEME 5
Alkylation of thymine with primary and secondary alkyl tosylates

Biological Activity

Biological activity of the bis-phosphonates both in the purine and pyrimidine series is limited by their high polarity. They are inactive both in the antiviral assays of DNA viruses, RNA viruses and retroviruses, specifically against hepatitis B and C viruses and against HIV, against herpesviruses (HSV-1 and HSV-2, VZV and CMV) and RNA virus models of human patho-

TABLE I
Yields of alkylations of thymine with primary and secondary alkyl tosylates

No.	Tosylates	<i>N</i> ¹ -derivative	Bis- <i>N</i> ¹ , <i>N</i> ³ -derivative	<i>O</i> -derivative
1		39%	10%	1%
	34	34a	34b	34c
2		31%	10%	1%
	35	35a	35b	35c
3		32%	10%	1%
	36	36a	36b	36c
4		25%	<4%	1%
	37	37a	37b	37c
5		23%	<1%	1%
	38	38a	38b	38c

gens. Nor was there any activity observed on any of the four human transformed cell lines tested. Nonetheless, the data are not considered to be conclusive, since some tests are still in progress. Also, it is necessary to convert at least some of the compounds presented in this paper to their lipophilic derivatives, e.g. to mono- or diesters with long-chain aliphatic alcohols to enhance their transport across the cellular membrane. This study is currently being carried out.

Conclusion

In conclusion, we have developed a general method for the synthesis of symmetrical bifunctional phosphonates of acyclic nucleoside as a novel group of ANP. Selected purine and pyrimidine derivatives were prepared and characterized. On this occasion we have discovered that uracil and thymine are alkylated by tosylates of primary and secondary alcohols regiospecifically in the position N¹.

EXPERIMENTAL

Materials and Methods

Unless otherwise stated, solvents were evaporated at 40 °C/2 kPa, and compounds were dried at 2 kPa over P₂O₅. Melting points were determined on a Büchi melting point apparatus. NMR spectra were measured on an FT NMR spectrometer Varian Unity 500 (¹H at 500 MHz and ¹³C at 125.7 MHz frequency). Chemical shifts are given in ppm (δ-scale), coupling constants (J) in Hz. Mass spectra were measured on a ZAB-EQ (Micromass, Manchester, U.K.) spectrometer using FAB (ionization by Xe, accelerating voltage 8 kV, glycerol matrix) or using EI (electron energy 70 eV). UV spectra (λ in nm) were taken on a Beckman DU-65 spectrophotometer in methanol solution. Elemental analyses were carried out on a Perkin-Elmer CHN Analyser 2400, Series II Sys (Perkin-Elmer, Norwolk, CT, U.S.A.). Chemicals were purchased from Sigma-Aldrich (Prague, Czech Republic). Dimethylformamide and acetonitrile were distilled from P₂O₅ and stored over molecular sieves (4 Å). Tetrahydrofuran was distilled with CaH₂ and stored over molecular sieves (4 Å).

2-Phenyl-1,3-dioxan-5-ol (**8**)

Concentrated H₂SO₄ (3 drops) was added to a solution of glycerol (113 g, 1227 mmol) and benzaldehyde (100 g, 942 mmol) in toluene (450 ml). The mixture was refluxed in modified Dean-Stark apparatus for 4 h (88% of water separated). The reaction mixture was then cooled to room temperature and the solvent was evaporated. The residue was dissolved in ether (500 ml) and washed three times with water (500 ml). The organic layer was dried over anhydrous MgSO₄, filtered and evaporated. Crystallization from *n*-hexane provided compound **8** as a white solid (yield 92 g, 55%). M.p. 61.9–63.3 °C. For C₁₀H₁₂O₃ (180.2) calculated: 66.65% C, 6.71% H; found: 66.44% C, 6.63% H. FAB MS: 181.1 (MH⁺) (100).

¹H NMR (500 MHz, DMSO-*d*₆ + DAc): 7.40–7.30 (m, 10 H, arom.); 5.53 and 5.41 (2 × s, 2 × 1 H, 2 × O-CH₂O); 5.24 and 5.01 (2 × d, 2 × 1 H, *J* = 2 × 5.2, 2 × OH); 4.13 (dd, 2 H, *J* = 5.1 and 11.0, O-CH₂); 3.48 (t, 2 H, *J* = 10.6 and 10.6, O-CH₂); 4.04 (dd, 2 H, *J* = 1.5 and 11.8, O-CH₂); 3.95 (dd, 2 H, *J* = 1.2 and 11.8, O-CH₂); 3.72 (tq, 1 H, *J* = 3 × 5.2 and 2 × 10.3, O-CH_{ax}); 3.50 (m, 1 H, O-CH_{eq}). ¹³C NMR (125.7 MHz, DMSO-*d*₆ + DAc): 139.25; 138.57; 129.01; 128.92; 128.35 (2 C); 128.28 (2 C); 126.60 (2 C); 126.54 (2 C); 100.64 and 100.60 (2 × O-CH₂O); 72.02 (2 C, O-CH₂); 71.76 (2 C, O-CH₂); 62.76 and 60.57 (O-CH).

5-(Benzylxyloxy)-2-phenyl-1,3-dioxane (9)

Under argon atmosphere 2-phenyl-1,3-dioxan-5-ol (90 g, 499 mmol) was added at 0 °C to a suspension of NaH (20 g of 60% suspension in mineral oil, 499 mmol, prewashed with *n*-hexane) in dry THF (550 ml). The reaction mixture was then cooled to -10 °C and benzyl bromide (94 g, 549 mmol) in THF (200 ml) was added dropwise during 1 h. The mixture was stirred for 30 min at -10 °C and at room temperature overnight under argon. When the reaction was complete (TLC), methanolic ammonia (30 ml) was added. After stirring the solution for 1 h, the solvent was evaporated. The residue was dissolved in chloroform (500 ml) and washed with water (500 ml). The organic layer was dried with anhydrous MgSO₄, filtered and evaporated to yield crude product **9**, which was used without further purification.

2-(Benzylxyloxy)propane-1,3-diol (10)

A solution of crude **9** in 80% methanol (500 ml) was refluxed with Dowex 50X8 in H⁺ form (10 g) for 4 h. The resin was filtered off, the solution neutralized with aqueous ammonia and the solvent was evaporated. The crude product was purified by silica gel column chromatography, using chloroform–methanol gradient 0–5%, to yield 74 g (80%) of pure **10** as colorless solid. M.p. 38.1–39.6 °C. For C₁₀H₁₄O₃ (182.2) calculated: 65.91% C, 7.74% H; found: 65.87% C, 7.68% H. MS (EI), *m/z*: 182.2 (M⁺). ¹H NMR (500 MHz, DMSO-*d*₆): 7.34 (m, 5 H, arom.); 4.61 (s, 2 H, CH₂-benzyl); 4.58 (t, 2 H, OH, *J*_{OH,CH₂} = 5.6); 3.52 (dt, 2 H, *J*_{CH₂,CH} ~ *J*_{CH₂,OH} = 5.4, O-CH₂); 3.45 (dt, 2 H, *J*_{gem} = 11.2, O-CH₂); 3.38 (q, 2 H, *J* = 5.2, O-CH). ¹³C NMR (125.7 MHz, DMSO-*d*₆): 139.47; 128.27 (2 C); 127.61 (2 C); 127.35; 81.12 (O-CH); 70.96 (CH₂-O-Ph); 61.05 (O-CH₂).

2-(Benzylxyloxy)-1,3-bis[(diisopropoxyphosphoryl)methoxy]propane (11)

A solution of **10** (20 g, 110 mmol) in dry DMF (50 ml) was added dropwise at 0 °C to a stirred suspension of NaH (11 g of 60% suspension in mineral oil, 274 mmol, prewashed with *n*-hexane) in dry DMF (450 ml) under a CaCl₂ protecting tube. (Diisopropoxyphosphoryl)methyl tosylate (88 g, 252 mmol) was added dropwise and the mixture was stirred with a mechanical stirrer at room temperature for 8 h. The reaction mixture was neutralized with 4.5 M HCl in DMF, the solvent evaporated, the residue was co-evaporated with toluene, dissolved in ethyl acetate (300 ml) and washed three times with water (300 ml). The organic layer was dried with anhydrous MgSO₄ and evaporated. The residue was purified by silica gel column chromatography, using chloroform–methanol gradient 0–3%, to yield 37 g (65%) of pure **11** as yellowish oil. For C₂₄H₄₄O₉P₂ (538.6) calculated: 53.52% C, 8.23% H, 11.50% P; found: 53.23% C, 8.39% H, 11.75% P. FAB MS: 539.2 (M⁺) (40). ¹H NMR (500 MHz, CDCl₃): 7.37–7.30 (m, 5 H, arom.); 4.74 (m, 4 H, CH-iPr, *J*_{H,P} = 7.7, *J*_{vic} = 6.2); 4.69 (s, 2 H, CH₂-O-Ph); 3.78 (tt, 1 H, *J*_{1',2'} = 5.7 and 4.8, H-1'); 3.78 and 3.72 (2 × dd, 2 × 2 H, *J*_{gem} =

13.9, $J_{\text{H,P}} = 8.3$, H-3'); 3.68 (dd, 2 H, $J_{\text{gem}} = 10.3$, $J_{2'a,1'} = 5.7$, H-2'a); 3.72 (dd, 2 H, $J_{\text{gem}} = 10.3$, $J_{2'b,1'} = 4.8$, H-2'b); 1.34, 1.32 and 1.30 (3 \times d, 24 H, $J_{\text{vic}} = 6.2$, CH₃-iPr). ¹³C NMR (125.7 MHz, CDCl₃): 128.29; 127.71; 127.55; 76.94 (CH-1'); 73.31 (d, $J_{\text{C,P}} = 11.0$, CH₂-2'); 72.25 (CH₂-benzyl); 70.97 (d, $J_{\text{C,P}} = 7.0$, CH-iPr); 66.36 (d, $J_{\text{C,P}} = 167.0$, CH₂-3'); 24.10 and 24.09 (d, $J_{\text{C,P}} = 4.0$, CH₃-iPr).

1,3-Bis[(diisopropoxyphosphoryl)methoxy]propan-2-ol (12)

Palladium on activated charcoal (10% Pd, 1 g) and concentrated HCl (1 ml) were added to a solution of **11** (34 g, 63 mmol) in methanol (300 ml). The reaction mixture was hydrogenated at atmospheric pressure and room temperature overnight. The catalyst was filtered off through a Celite pad, the filtrate was neutralized with Et₃N and evaporated to give crude product **12**, which was directly used in the subsequent reaction. FAB MS: 449.1 (MH⁺) (60). ¹H NMR (500 MHz, DMSO-*d*₆): 4.93 (bs, 1 H, OH); 4.59 (tt, 1 H, $J_{1',2'} = 7.4$ and 4.5, H-1'); 4.50 (m, 4 H, CH-iPr); 3.78 and 3.76 (2 \times dd, 2 \times 2 H, $J_{\text{gem}} = 13.8$, $J_{\text{H,P}} = 8.1$, H-3'); 3.48 (dd, 2 H, $J_{\text{gem}} = 10.0$, $J_{2'a,1'} = 7.6$, H-2'a); 3.43 (dd, 2 H, $J_{\text{gem}} = 10.0$, $J_{2'b,1'} = 4.8$, H-2'b); 1.24, 1.23 and 1.21 (3 \times d, 24 H, $J_{\text{vic}} = 6.2$, CH₃-iPr). ¹³C NMR (125.7 MHz, DMSO-*d*₆): 74.55 (d, $J_{\text{C,P}} = 10.7$, CH₂-2'); 70.26 (d, $J_{\text{C,P}} = 6.4$, CH-iPr); 68.47 (CH-1'); 65.56 (d, $J_{\text{C,P}} = 164.6$, CH₂-3'); 24.01 and 23.90 (d, $J_{\text{C,P}} = 4.0$, CH₃-iPr).

1,3-Bis[(diisopropoxyphosphoryl)methoxy]propan-2-yl Tosylate (13)

A mixture of crude **12**, 4-(dimethylamino)pyridine (0.7 g) and Et₃N (8 g) in dry dichloromethane (200 ml) was stirred at 0 °C with a CaCl₂ protecting tube. Tosyl chloride (15 g) in dichloromethane (100 ml) was added dropwise. The mixture was stirred at 0 °C for 1 h and then kept in refrigerator overnight. The organic solution was diluted with ice water (300 ml) and the layers separated. The organic layer was dried with anhydrous MgSO₄, filtered and evaporated in vacuo. The residue was purified by column chromatography on silica gel, using chloroform-methanol gradient 0-2%, to yield 30 g (78%) of pure **13** as yellowish oil. For C₂₄H₄₄O₁₁P₂S (602.6) calculated: 47.83% C, 7.36% H, 10.28% P, 5.32% S; found: 47.50% C, 7.38% H, 10.53% P, 5.57% S. FAB MS: 602.9 (MH⁺) (75). ¹H NMR (500 MHz, DMSO-*d*₆): 7.80 and 7.46 (d, 2 \times 2 H, arom); 4.70 (tt, 1 H, $J_{1',2'} = 7.4$ and 4.5, H-1'); 4.56 (m, 4 H, CH-iPr); 3.79 and 3.75 (2 \times dd, 2 \times 2 H, $J_{\text{gem}} = 13.8$, $J_{\text{H,P}} = 8.1$, H-3'); 3.67 (dd, 2 H, $J_{\text{gem}} = 10.3$, $J_{2'a,1'} = 7.4$, H-2'a); 3.64 (dd, 2 H, $J_{\text{gem}} = 10.3$, $J_{2'b,1'} = 4.5$, H-2'b); 2.41 (s, 3 H, CH₃-tosyl); 1.23, 1.22 and 1.21 (3 \times d, 24 H, $J_{\text{vic}} = 6.2$, CH₃-iPr). ¹³C NMR (125.7 MHz, DMSO-*d*₆): 144.94; 133.48; 130.18 (2 C); 127.79 (2 C); 79.32 (CH-1'); 70.93 (d, $J_{\text{C,P}} = 10.2$, CH₂-2'); 70.37 (d, $J_{\text{C,P}} = 5.9$, CH-iPr); 65.40 (d, $J_{\text{C,P}} = 164.1$, CH₂-3'); 23.97 and 23.85 (d, $J_{\text{C,P}} = 3.6$, CH₃-iPr); 21.27 (CH₃).

General Procedure for Alkylation of Nucleobases with Compound **13**

A solution of an appropriate nucleobase (**14a**, **14b**; **24a**, **24b**; **29a**, **29b**; 7-10 mmol) in dry DMF (50 ml) was treated with Cs₂CO₃ (0.5 equiv.) at room temperature under a CaCl₂ protecting tube for 1 h. The reaction mixture was then heated at 60 °C and synthon **13** (1.0 equiv.) was added. The mixture was then stirred at 90 °C for 24 h. Solvent was taken down and the residue was co-evaporated with toluene. The residue in chloroform was filtered through a Celite pad, evaporated and purified on a silica gel column in chloroform-methanol.

9-{1,3-Bis[(diisopropoxypyrophosphoryl)methoxy]propan-2-yl}-6-chloro-9H-purine (15a). Column chromatography (silica gel, chloroform-methanol gradient 0-6%) afforded the product as yellowish oil (yield 25%). FAB MS: 585.9 (MH⁺) (70). ¹H NMR (500 MHz, DMSO-*d*₆): 8.79 (s, 1 H, H-2); 8.76 (s, 1 H, H-8); 5.14 (tt, 1 H, *J*_{1',2'} = 8.1 and 4.3, H-1'); 4.41 (m, 4 H, CH-iPr); 4.16 (dd, 2 H, *J*_{gem} = 10.5, *J*_{2'a,1'} = 8.1, H-2'a); 3.95 (dd, 2 H, *J*_{gem} = 10.5, *J*_{2'b,1'} = 4.3, H-2'b); 3.80 and 3.73 (2 × dd, 2 × 2 H, *J*_{gem} = 14.0, *J*_{H,P} = 8.3, H-3'); 1.13, 1.12, 1.10 and 1.05 (4 × d, 24 H, *J*_{vic} = 6.2, CH₃-iPr). ¹³C NMR (125.7 MHz, DMSO-*d*₆): 152.35 (CH-2); 151.59 (C-6); 149.20 (C-4); 146.76 (CH-8); 130.99 (C-5); 70.45 (d, *J*_{C,P} = 11, CH₂-2'); 70.30 and 70.26 (d, *J*_{C,P} = 6, CH-iPr); 64.98 (d, *J*_{C,P} = 164.0, CH₂-3'); 54.85 (CH-1'); 23.87, 23.75, 23.64 and 23.62 (d, *J*_{C,P} = 4.0, CH₃-iPr).

9-{1,3-Bis[(diisopropoxypyrophosphoryl)methoxy]propan-2-yl}-6-chloro-9H-purin-2-amine (15b). Column chromatography (silica gel, chloroform-methanol gradient 0-6%) afforded the product as yellowish foam (yield 30%). FAB MS: 600.5 (MH⁺) (100). ¹H NMR (500 MHz, DMSO-*d*₆): 8.17 (s, 1 H, H-8); 6.88 (bs, 2 H, NH₂); 4.80 (tt, 1 H, *J*_{1',2'} = 7.9 and 4.4, H-1'); 4.46 (m, 4 H, CH-iPr); 4.05 (dd, 2 H, *J*_{gem} = 10.3, *J*_{2'a,1'} = 7.9, H-2'a); 3.87 (dd, 2 H, *J*_{gem} = 10.3, *J*_{2'b,1'} = 4.4, H-2'b); 3.79 and 3.72 (2 × dd, 2 × 2 H, *J*_{gem} = 13.9, *J*_{H,P} = 8.2, H-3'); 1.10, 1.09, 1.07 and 1.06 (4 × d, 24 H, *J*_{vic} = 6.2, CH₃-iPr). ¹³C NMR (125.7 MHz, DMSO-*d*₆): 159.81 (C-2); 154.49 (C-6); 149.44 (C-4); 142.17 (CH-8); 123.43 (C-5); 70.67 (d, *J*_{C,P} = 12, CH₂-2'); 70.38 and 70.27 (d, *J*_{C,P} = 6, CH-iPr); 65.05 (d, *J*_{C,P} = 164.0, CH₂-3'); 53.70 (CH-1'); 23.87, 23.82, 23.75 and 23.70 (d, *J*_{C,P} = 4.0, CH₃-iPr).

2-({[1,3-Bis(diisopropoxypyrophosphoryl)methoxy]propan-2-yl}oxy)pyrimidin-4-amine (25a). Column chromatography (silica gel, chloroform-methanol gradient 0-12%) afforded the product as yellowish oil (7%). FAB MS: 542.4 (MH⁺) (40). ¹H NMR (500 MHz, DMSO-*d*₆): 7.83 (d, 1 H, *J*_{H6,H5} = 5.8, H-6); 6.82 (bs, 2 H, NH₂); 6.06 (d, 1 H, *J*_{H5,H6} = 5.8, H-5); 5.28 (tt, 1 H, *J*_{1',2'} = 8.2 and 4.8, H-1'); 4.58 (m, 4 H, CH-iPr); 3.78 (dd, 2 H, *J*_{gem} = 13.9, *J*_{2'a,1'} = 8.2, H-2'a); 3.74 (dd, 2 H, *J*_{gem} = 13.9, *J*_{2'b,1'} = 4.8, H-2'b); 3.71 and 3.70 (2 × dd, 2 × 2 H, *J*_{gem} = 13.9, *J*_{H,P} = 8.5, H-3'); 1.22, 1.21, 1.20 and 1.19 (4 × d, 24 H, *J*_{vic} = 6.2, CH₃-iPr). ¹³C NMR (100.6 MHz, DMSO-*d*₆): 165.60 (C-4); 164.38 (C-2); 156.29 (C-6); 99.69 (C-5); 72.40 (CH-1'); 71.55 (d, *J*_{C,P} = 11.7, CH₂-2'); 70.46 and 70.35 (d, *J*_{C,P} = 6.3, CH-iPr); 65.48 (d, *J*_{C,P} = 164.1, CH₂-3'); 23.96, 23.94, 23.85 and 23.81 (d, *J*_{C,P} = 4.0, CH₃-iPr).

4-Amino-1-{{[1,3-bis(diisopropoxypyrophosphoryl)methoxy]propan-2-yl}pyrimidin-2(1H)-one (26a). Column chromatography (silica gel, chloroform-methanol gradient 0-12%) afforded the product as yellowish oil (14%). FAB MS: 542.3 (MH⁺) (40). ¹H NMR (500 MHz, DMSO-*d*₆): 7.53 (d, 1 H, *J*_{H6,H5} = 7.3, H-6); 6.97 (bs, 2 H, NH₂); 5.63 (d, 1 H, *J*_{H5,H6} = 7.3, H-5); 4.70 (tt, 1 H, *J*_{1',2'} = 7.4 and 4.8, H-1'); 4.54 (m, 4 H, CH-iPr); 3.84 (dd, 2 H, *J*_{gem} = 10.5, *J*_{2'a,1'} = 7.4, H-2'a); 3.68 (dd, 2 H, *J*_{gem} = 10.5, *J*_{2'b,1'} = 4.8, H-2'b); 3.75 and 3.70 (2 × dd, 2 × 2 H, *J*_{gem} = 14.0, *J*_{H,P} = 8.2, H-3'); 1.22, 1.21, 1.20 and 1.19 (4 × d, 24 H, *J*_{vic} = 6.1, CH₃-iPr). ¹³C NMR (100.6 MHz, DMSO-*d*₆): 165.54 (C-4); 155.93 (C-2); 142.70 (C-6); 93.32 (C-5); 70.67 (d, *J*_{C,P} = 11.2, CH₂-2'); 70.37 and 70.46 (d, *J*_{C,P} = 6.3, CH-iPr); 65.00 (d, *J*_{C,P} = 163.6, CH₂-3'); 54.50 (CH-1'); 23.96, 23.94, 23.86 and 23.81 (d, *J*_{C,P} = 4.3, CH₃-iPr).

2-({[1,3-Bis(diisopropoxypyrophosphoryl)methoxy]propan-2-yl}oxy)-5-methylpyrimidin-4-amine (25b). Column chromatography (silica gel, chloroform-methanol gradient 0-12% afforded the product as yellowish oil (7%). FAB MS: 556.0 (MH⁺) (100). ¹H NMR (500 MHz, DMSO-*d*₆): 7.74 (q, 1 H, *J*_{H6,CH₃} = 1.0, H-6); 6.65 (bs, 1 H, NH₂); 5.36 (tt, 1 H, *J*_{1',2'} = 8.2 and 4.9, H-1'); 4.56 (m, 4 H, CH-iPr); 3.78 (dd, 2 H, *J*_{gem} = 13.9, *J*_{2'a,1'} = 8.2, H-2'a); 3.73 (dd, 2 H, *J*_{gem} = 13.9, *J*_{2'b,1'} = 4.9, H-2'b); 3.53 and 3.49 (2 × dd, 2 × 2 H, *J*_{gem} = 12.8, *J*_{H,P} = 8.4, H-3'); 1.80 (d, 3 H, *J*_{CH₃,H₆} = 1.0, CH₃); 1.22, 1.21, 1.20 and 1.19 (4 × d, 24 H, *J*_{vic} = 6.1, CH₃-iPr). ¹³C NMR

(100.6 MHz, DMSO-*d*₆): 164.33 (C-4); 163.10 (C-2); 154.91 (C-6); 107.02 (C-5); 72.31 (CH-1'); 71.61 (d, *J*_{C,P} = 11.7, CH₂-2'); 70.36 and 70.30 (d, *J*_{C,P} = 6.3, CH-iPr); 65.48 (d, *J*_{C,P} = 164.5, CH₂-3'); 23.86, 23.85, 23.83 and 23.81 (d, *J*_{C,P} = 4.2, CH₃-iPr); 13.13 (CH₃).

4-Amino-1-{{[1,3-bis(diisopropoxypyrophoryl)methoxy]propan-2-yl}-5-methylpyrimidin-2(1H)-one (26b). Column chromatography (silica gel, chloroform-methanol gradient 0-15%) afforded the product as yellowish oil (14%). FAB MS: 556.1 (MH⁺) (100). ¹H NMR (500 MHz, DMSO-*d*₆): 7.43 (q, 1 H, *J*_{H6,CH3} = 1.0, H-6); 6.87 (bs, 2 H, NH₂); 4.80 (tt, 1 H, *J*_{1',2'} = 7.7 and 4.8, H-1'); 4.53 (m, 4 H, CH-iPr); 3.84 (dd, 2 H, *J*_{gem} = 10.5, *J*_{2'a,1'} = 7.7, H-2'a); 3.68 (dd, 2 H, *J*_{gem} = 10.5, *J*_{2'b,1'} = 4.8, H-2'b); 3.75 and 3.70 (2 × dd, 2 × 2 H, *J*_{gem} = 13.9, *J*_{H,P} = 8.5, H-3'); 1.82 (d, 3 H, *J*_{CH3,H6} = 1.0, CH₃); 1.21, 1.20, 1.19 and 1.18 (4 × d, 24 H, *J*_{vic} = 6.1, CH₃-iPr). ¹³C NMR (100.6 MHz, DMSO-*d*₆): 164.78 (C-4); 155.55 (C-2); 142.70 (C-6); 100.66 (C-5); 70.65 (d, *J*_{C,P} = 11.2, CH₂-2'); 70.47 and 70.46 (d, *J*_{C,P} = 6.3, CH-iPr); 64.98 (d, *J*_{C,P} = 164.1, CH₂-3'); 53.88 (CH-1'); 24.01, 23.98, 23.86 and 23.82 (d, *J*_{C,P} = 4.1, CH₃-iPr); 13.35 (CH₃).

2-{{[1,3-Bis(diisopropoxypyrophoryl)methoxy]propan-2-yl}oxy}pyrimidin-4(3H)-one (30a). Column chromatography (silica gel, chloroform-methanol gradient 0-10%) afforded the product as yellowish oil (1%). FAB MS: 543.2 (MH⁺) (60). ¹H NMR (500 MHz, DMSO-*d*₆): 7.75 (d, 1 H, *J*_{H6,H5} = 8.0, H-6); 5.64 (d, 1 H, *J*_{H5,H6} = 8.0, H-5); 5.01 (tt, 1 H, *J*_{1',2'} = 8.1 and 4.5, H-1'); 4.55 (m, 4 H, CH-iPr); 3.78 (dd, 2 H, *J*_{gem} = 10.7, *J*_{2'a,1'} = 8.1, H-2'a); 3.74 (dd, 2 H, *J*_{gem} = 10.7, *J*_{2'b,1'} = 4.5, H-2'b); 3.72 and 3.70 (2 × dd, 2 × 2 H, *J*_{gem} = 14.0, *J*_{H,P} = 8.3, H-3'); 1.22, 1.21, 1.20 and 1.19 (4 × d, 24 H, *J*_{vic} = 6.2, CH₃-iPr). ¹³C NMR (100.6 MHz, DMSO-*d*₆): 163.40 (C-4); 162.46 (C-2); 155.32 (C-6); 106.19 (C-5); 72.62 (CH-1'); 71.25 (d, *J*_{C,P} = 12.00, CH₂-2'); 70.44 and 70.31 (d, *J*_{C,P} = 6.0, CH-iPr); 65.42 (d, *J*_{C,P} = 164.0, CH₂-3'); 23.95, 23.93, 23.86 and 23.89 (d, *J*_{C,P} = 4.1, CH₃-iPr).

1-{{[1,3-Bis(diisopropoxypyrophoryl)methoxy]propan-2-yl}pyrimidine-2,4(1H,3H)-dione (31a). Column chromatography (silica gel, chloroform-methanol gradient 0-8%) afforded the product as yellowish oil. Crystallization from ethyl acetate/petroleum ether gave white solid (12%). FAB MS: 543.2 (MH⁺) (65). ¹H NMR (500 MHz, DMSO-*d*₆): 11.28 (bs, 1 H, NH); 7.64 (d, 1 H, *J*_{H6,H5} = 8.0, H-6); 5.56 (d, 1 H, *J*_{H5,H6} = 8.0, H-5); 4.80 (tt, 1 H, *J*_{1',2'} = 8.1 and 4.5, H-1'); 4.57 (m, 4 H, CH-iPr); 3.86 (dd, 2 H, *J*_{gem} = 10.7, *J*_{2'a,1'} = 8.1, H-2'a); 3.78 (dd, 2 H, *J*_{gem} = 10.7, *J*_{2'b,1'} = 4.5, H-2'b); 3.74 and 3.70 (2 × dd, 2 × 2 H, *J*_{gem} = 14.0, *J*_{H,P} = 8.3, H-3'); 1.22, 1.21, 1.20 and 1.19 (3 × d, 24 H, *J*_{vic} = 6.2, CH₃-iPr). ¹³C NMR (100.6 MHz, DMSO-*d*₆): 163.29 (C-4); 151.46 (C-2); 143.13 (C-6); 101.11 (C-5); 70.42 (d, *J*_{C,P} = 12.00, CH₂-2'); 70.40 and 70.21 (d, *J*_{C,P} = 6.0, CH-iPr); 64.98 (d, *J*_{C,P} = 164.0, CH₂-3'); 54.12 (CH-1'); 23.95, 23.93, 23.85 and 23.89 (d, *J*_{C,P} = 4.1, CH₃-iPr).

1,3-Bis{{[1,3-bis(diisopropoxypyrophoryl)methoxy]propan-2-yl}pyrimidine-2,4(1H,3H)-dione (32a). Column chromatography (silica gel, chloroform-methanol gradient 0-4%) afforded the product as yellowish oil (0.5%). FAB MS: 973.2 (MH⁺) (45). ¹H NMR (500 MHz, DMSO-*d*₆): 8.28 (d, 1 H, *J*_{H6,H5} = 5.7, H-6); 6.52 (d, 1 H, *J*_{H5,H6} = 5.7, H-5); 5.42 and 5.34 (tt, 1 H, *J*_{1',2'} = 6.1 and 5.0, H-1'); 4.57 (m, 4 H, CH-iPr); 3.87 and 3.85 (dd, 2 H, *J*_{gem} = 10.1, *J*_{2'a,1'} = 6.1, H-2'a); 3.78 and 3.76 (dd, 2 H, *J*_{gem} = 10.7, *J*_{2'b,1'} = 5.0, H-2'b); 3.48 and 3.43 (4 × dd, 4 × 2 H, *J*_{gem} = 14.0, *J*_{H,P} = 8.4, H-3'); 1.22, 1.21, 1.20 and 1.19 (8 × d, 48 H, *J*_{vic} = 6.2, CH₃-iPr). ¹³C NMR (100.6 MHz, DMSO-*d*₆): 163.26 (C-4); 151.97 (C-2); 143.65 (C-6); 101.15 (C-5); 70.23 and 70.19 (d, *J*_{C,P} = 12.00, CH₂-2'); 70.41 and 70.21 (d, *J*_{C,P} = 6.3, 4 × CH-iPr); 64.83 and 64.79 (d, *J*_{C,P} = 164.6, CH₂-3'); 53.11 and 45.46 (CH-1'); 23.95, 23.93, 23.91 and 23.89 (d, *J*_{C,P} = 4.1, CH₃-iPr).

2-{{[1,3-Bis(diisopropoxypyrophoryl)methoxy]propan-2-yl}oxy}-5-methylpyrimidin-4(3H)-one (30b). Column chromatography (silica gel, in chloroform-methanol gradient 0-9%) afforded

the product as yellowish oil (1.1%). FAB MS: 557.1 (MH^+) (60). ^1H NMR (500 MHz, $\text{DMSO}-d_6$): 7.53 (q, 1 H, $J_{\text{H}6,\text{CH}3} = 1.0$, H-6); 4.90 (tt, 1 H, $J_{1',2'} = 8.2$ and 4.6, H-1'); 4.53 (m, 4 H, CH-iPr); 3.85 (dd, 2 H, $J_{\text{gem}} = 10.7$, $J_{2'\text{a},1'} = 8.2$, H-2'a); 3.71 (dd, 2 H, $J_{\text{gem}} = 10.7$, $J_{2'\text{b},1'} = 4.6$, H-2'b); 3.72 and 3.70 ($2 \times \text{dd}$, 2×2 H, $J_{\text{gem}} = 14.0$, $J_{\text{H,P}} = 8.2$, H-3'); 1.82 (d, 3 H, $J_{\text{CH}3,\text{H}6} = 1.0$, CH_3); 1.22, 1.21, 1.20 and 1.19 ($4 \times \text{d}$, 24 H, $J_{\text{vic}} = 6.2$, $\text{CH}_3\text{-iPr}$). ^{13}C NMR (100.6 MHz, $\text{DMSO}-d_6$): 163.91 (C-4); 162.46 (C-2); 139.01 (C-6); 108.19 (C-5); 71.62 (CH-1'); 70.45 (d, $J_{\text{C,P}} = 12.00$, $\text{CH}_2\text{-2'}$); 70.38 and 70.31 (d, $J_{\text{C,P}} = 6.0$, CH-iPr); 65.22 (d, $J_{\text{C,P}} = 164.0$, $\text{CH}_2\text{-3'}$); 23.95, 23.93, 23.85 and 23.89 (d, $J_{\text{C,P}} = 4.1$, $\text{CH}_3\text{-iPr}$).

1-*{[1,3-Bis(diisopropoxypyrophoryl)methoxy]propan-2-yl}-5-methylpyrimidine-2,4(1H,3H)-dione (31b).*

Column chromatography (silica gel, chloroform-methanol gradient 0-7%) afforded the product as yellowish oil (12%). FAB MS: 557.0 (MH^+) (65). ^1H NMR (500 MHz, $\text{DMSO}-d_6$): 11.20 (bs, 1 H, NH); 7.52 (q, 1 H, $J_{\text{H}6,\text{CH}3} = 1.0$, H-6); 4.80 (tt, 1 H, $J_{1',2'} = 8.3$ and 4.6, H-1'); 4.53 (m, 4 H, CH-iPr); 3.86 (dd, 2 H, $J_{\text{gem}} = 10.5$, $J_{2'\text{a},1'} = 8.3$, H-2'a); 3.69 (dd, 2 H, $J_{\text{gem}} = 10.5$, $J_{2'\text{b},1'} = 4.6$, H-2'b); 3.77 and 3.72 ($2 \times \text{dd}$, 2×2 H, $J_{\text{gem}} = 14.0$, $J_{\text{H,P}} = 8.3$, H-3'); 1.82 (d, 3 H, $J_{\text{CH}3,\text{H}6} = 1.0$, CH_3); 1.22, 1.21, 1.20 and 1.19 ($4 \times \text{d}$, 24 H, $J_{\text{vic}} = 6.1$, $\text{CH}_3\text{-iPr}$). ^{13}C NMR (100.6 MHz, $\text{DMSO}-d_6$): 163.89 (C-4); 151.46 (C-2); 138.72 (C-6); 108.63 (C-5); 70.41 (d, $J_{\text{C,P}} = 11.2$, $\text{CH}_2\text{-2'}$); 70.38 and 70.09 (d, $J_{\text{C,P}} = 6.4$, CH-iPr); 64.95 (d, $J_{\text{C,P}} = 164.1$, $\text{CH}_2\text{-3'}$); 53.74 (CH-1'); 23.95, 23.90, 23.86 and 23.85 (d, $J_{\text{C,P}} = 4.1$, $\text{CH}_3\text{-iPr}$); 23.76 (CH₃).

1,3-Bis{[1,3-bis(diisopropoxypyrophoryl)methoxy]propan-2-yl}-5-methylpyrimidine-2,4(1H,3H)-dione (32b).

Column chromatography (silica gel, chloroform-methanol gradient 0-4%) afforded the product as yellowish oil (0.5%). FAB MS: 987.2 (MH^+) (45). ^1H NMR (500 MHz, $\text{DMSO}-d_6$): 7.43 (q, 1 H, $J_{\text{H}6,\text{CH}3} = 1.0$, H-6); 5.40 and 5.31 (tt, 1 H, $J_{1',2'} = 6.1$ and 5.0, H-1'); 4.56 (m, 4 H, CH-iPr); 3.87 and 3.85 (dd, 2 H, $J_{\text{gem}} = 10.1$, $J_{2'\text{a},1'} = 6.1$, H-2'a); 3.78 and 3.72 (dd, 2 H, $J_{\text{gem}} = 10.7$, $J_{2'\text{b},1'} = 5.0$, H-2'b); 3.48 and 3.43 ($4 \times \text{dd}$, 4×2 H, $J_{\text{gem}} = 14.0$, $J_{\text{H,P}} = 8.4$, H-3'); 1.81 (d, 3 H, $J_{\text{CH}3,\text{H}6} = 1.0$, CH_3); 1.22, 1.21, 1.20 and 1.19 ($8 \times \text{d}$, 48 H, $J_{\text{vic}} = 6.2$, $\text{CH}_3\text{-iPr}$). ^{13}C NMR (100.6 MHz, $\text{DMSO}-d_6$): 163.91 (C-4); 151.45 (C-2); 139.23 (C-6); 108.15 (C-5); 70.23 and 70.19 (d, $J_{\text{C,P}} = 12.00$, $\text{CH}_2\text{-2'}$); 70.41 and 70.21 (d, $J_{\text{C,P}} = 6.3$, $4 \times \text{CH-iPr}$); 64.83 and 64.56 (d, $J_{\text{C,P}} = 164.6$, $\text{CH}_2\text{-3'}$); 51.17 and 43.56 (CH-1'); 23.95, 23.93, 23.91 and 23.89 (d, $J_{\text{C,P}} = 4.1$, $\text{CH}_3\text{-iPr}$).

9-{1,3-Bis[(diisopropoxypyrophoryl)methoxy]propan-2-yl}-9*H*-purine-6-amine (16a)

A solution of **15a** (940 mg, 1.6 mmol) in methanolic ammonia (50 ml) was stirred and heated (100 °C) in an autoclave for 3 days. The solvent was evaporated and the residue was purified by column chromatography on silica gel with chloroform-methanol gradient 0-6% to yield the product as yellowish oil (80%). FAB MS: 566.5 (MH^+) (100). ^1H NMR (500 MHz, $\text{DMSO}-d_6$): 8.16 (s, 1 H, H-2); 8.11 (s, 1 H, H-8); 7.20 (bs, 2 H, NH_2); 4.93 (tt, 1 H, $J_{1',2'} = 7.4$ and 4.7, H-1'); 4.45 (m, 4 H, CH-iPr); 4.09 (dd, 2 H, $J_{\text{gem}} = 10.3$, $J_{2'\text{a},1'} = 7.4$, H-2'a); 3.90 (dd, 2 H, $J_{\text{gem}} = 10.3$, $J_{2'\text{b},1'} = 4.7$, H-2'b); 3.79 and 3.72 ($2 \times \text{dd}$, 2×2 H, $J_{\text{gem}} = 13.9$, $J_{\text{H,P}} = 8.2$, H-3'); 1.15, 1.13, 1.10 and 1.09 ($4 \times \text{d}$, 24 H, $J_{\text{vic}} = 6.2$, $\text{CH}_3\text{-iPr}$). ^{13}C NMR (125.7 MHz, $\text{DMSO}-d_6$): 156.15 (C-6); 152.36 (CH-2); 149.82 (C-4); 139.99 (CH-8); 118.88 (C-5); 70.95 (d, $J_{\text{C,P}} = 12$, $\text{CH}_2\text{-2'}$); 70.36 and 70.35 (d, $J_{\text{C,P}} = 6.3$, CH-iPr); 65.02 (d, $J_{\text{C,P}} = 163.6$, $\text{CH}_2\text{-3'}$); 53.64 (CH-1'); 23.89, 23.85, 23.78 and 23.72 (d, $J_{\text{C,P}} = 3.7$, $\text{CH}_3\text{-iPr}$).

9-{1,3-Bis[(diisopropoxypyrophoryl)methoxy]propan-2-yl}-9*H*-purine-2,6-diamine (16b)

A solution of **15b** (980 mg, 1.6 mmol) in methanolic ammonia (50 ml) was stirred and heated (100 °C) in an autoclave for 3 days. The solvent was evaporated and the residue was

purified by column chromatography on silica gel with chloroform-methanol gradient 0–10% to yield the product as yellowish foam (70%). FAB MS: 581.3 (MH^+) (100). ^1H NMR (500 MHz, $\text{DMSO-}d_6$): 7.73 (s, 1 H, H-8); 6.63 (bs, 2 H, $\text{NH}_2\text{-C}_6$); 5.71 (bs, 2 H, $\text{NH}_2\text{-C}_2$); 4.68 (tt, 1 H, $J_{1',2'} = 7.3$ and 4.8, H-1'); 4.50 (m, 4 H, CH-iPr); 4.00 (dd, 2 H, $J_{\text{gem}} = 10.3$, $J_{2'a,1'} = 7.3$, H-2'a); 3.84 (dd, 2 H, $J_{\text{gem}} = 10.3$, $J_{2'b,1'} = 4.8$, H-2'b); 3.78 and 3.72 (2 \times dd, 2 \times 2 H, $J_{\text{gem}} = 13.9$, $J_{\text{H,P}} = 8.3$, H-3'); 1.19, 1.17, 1.15 and 1.14 (4 \times d, 24 H, $J_{\text{vic}} = 6.2$, $\text{CH}_3\text{-iPr}$). ^{13}C NMR (125.7 MHz, $\text{DMSO-}d_6$): 160.26 (C-2); 156.26 (C-6); 152.01 (C-4); 136.38 (CH-8); 113.24 (C-5); 71.12 (d, $J_{\text{C,P}} = 12$, $\text{CH}_2\text{-2'}$); 70.43 and 70.40 (d, $J_{\text{C,P}} = 6$, CH-iPr); 65.10 (d, $J_{\text{C,P}} = 164.0$, $\text{CH}_2\text{-3'}$); 23.95, 23.81, 23.74 and 23.79 (d, $J_{\text{C,P}} = 4.0$, $\text{CH}_3\text{-iPr}$); 52.79 (CH-1').

9-{1,3-Bis[(diisopropoxyphosphoryl)methoxy]propan-2-yl}-1*H*-purin-6(9*H*)-one (17a)

3-Methylbutyl nitrite (10 equiv.) was added to a solution of compound **16a** (450 mg, 0.8 mmol) in 80% acetic acid (20 ml) and the mixture was stirred at room temperature overnight and then at 70 °C for 2 h. After evaporation of volatiles the residue was codistilled with water and purified by column chromatography on silica gel with chloroform-methanol gradient 0–12% to yield the product as yellowish foam (77%). FAB MS: 567.4 (MH^+) (100). ^1H NMR (500 MHz, $\text{DMSO-}d_6$): 12.25 (bs, 1 H, NH); 8.13 (s, 1 H, H-2); 8.04 (s, 1 H, H-8); 4.92 (tt, 1 H, $J_{1',2'} = 7.8$ and 4.3, H-1'); 4.46 (m, 4 H, $J_{\text{H,P}} = 7.8$, $J_{\text{vic}} = 6.2$, CH-iPr); 4.06 (dd, 2 H, $J_{\text{gem}} = 10.4$, $J_{2'a,1'} = 7.8$, H-2'a); 3.88 (dd, 2 H, $J_{\text{gem}} = 10.4$, $J_{2'b,1'} = 4.3$, H-2'b); 3.79 and 3.73 (2 \times dd, 2 \times 2 H, $J_{\text{gem}} = 13.9$, $J_{\text{H,P}} = 8.3$, H-3'); 1.17, 1.16, 1.15 and 1.13 (4 \times d, 24 H, $J_{\text{vic}} = 6.2$, $\text{CH}_3\text{-iPr}$). ^{13}C NMR (100.6 MHz, $\text{DMSO-}d_6$): 156.80 (C-6); 148.70 (C-4); 145.47 (CH-2); 139.41 (CH-8); 124.03 (C-5); 71.00 (d, $J_{\text{C,P}} = 11.2$, $\text{CH}_2\text{-2'}$); 70.38 and 70.35 (d, $J_{\text{C,P}} = 6.3$, CH-iPr); 65.02 (d, $J_{\text{C,P}} = 164.1$, $\text{CH}_2\text{-3'}$); 54.02 (CH-1'); 23.89, 23.87, 23.78 and 23.72 (d, $J_{\text{C,P}} = 4.0$, $\text{CH}_3\text{-iPr}$).

2-Amino-9-{1,3-bis[(diisopropoxyphosphoryl)methoxy]propan-2-yl}-1*H*-purin-6(9*H*)-one (17b)

A solution of **15b** (620 mg, 1.0 mmol) in 80% acetic acid (20 ml) was refluxed for 6 h. The solvent and excess of acetic acid was then evaporated. The residue was co-evaporated with toluene and ethanol and purified by column chromatography on silica gel chloroform-methanol gradient 0–15% to yield the product as yellowish foam (75%). FAB MS: 582.4 (MH^+) (100). ^1H NMR (500 MHz, $\text{DMSO-}d_6$): 10.56 (bs, 1 H, NH); 7.73 (s, 1 H, H-8); 6.42 (bs, 2 H, NH_2); 4.66 (tt, 1 H, $J_{1',2'} = 7.4$, 4.7, H-1'); 4.50 (m, 4 H, $J_{\text{H,P}} = 7.7$, $J_{\text{vic}} = 6.2$, CH-iPr); 3.97 (dd, 2 H, $J_{\text{gem}} = 10.3$, $J_{2'a,1'} = 7.4$, H-2'a); 3.82 (dd, 2 H, $J_{\text{gem}} = 10.3$, $J_{2'b,1'} = 4.7$, H-2'b); 3.78 and 3.72 (2 \times dd, 2 \times 2 H, $J_{\text{gem}} = 13.9$, $J_{\text{H,P}} = 8.3$, H-3'); 1.19, 1.17, 1.15 and 1.14 (4 \times d, 24 H, $J_{\text{vic}} = 6.2$, $\text{CH}_3\text{-iPr}$). ^{13}C NMR (100.6 MHz, $\text{DMSO-}d_6$): 156.96 (C-6); 153.56 (C-2); 151.45 (C-4); 136.28 (CH-8); 116.54 (C-5); 71.11 (d, $J_{\text{C,P}} = 12$, $\text{CH}_2\text{-2'}$); 70.44 and 70.40 (d, $J_{\text{C,P}} = 6.0$, CH-iPr); 65.10 (d, $J_{\text{C,P}} = 164.0$, $\text{CH}_2\text{-3'}$); 53.07 (CH-1'); 23.93, 23.89, 23.78 and 23.76 (d, $J_{\text{C,P}} = 4.0$, $\text{CH}_3\text{-iPr}$).

9-{1,3-Bis[(diisopropoxyphosphoryl)methoxy]propan-2-yl}-*N*-cyclopropyl-9*H*-purin-6-amine (18a)

A solution of **15a** (430 mg, 0.7 mmol) and cyclopropylamine (7 equiv.) in dioxane (15 ml) was refluxed for 7 h. The solvent and excess of amine were then evaporated to dryness and codistilled with toluene. The residue was purified by column chromatography on silica gel

with chloroform-methanol gradient 0–6% to yield yellowish oil (84%). FAB MS: 606.3 (MH^+) (100). ^1H NMR (500 MHz, $\text{DMSO}-d_6$): 8.21 (s, 1 H, H-2); 8.16 (s, 1 H, H-8); 7.85 (bs, 1 H, NH); 4.95 (tt, 1 H, $J_{1',2'} = 7.8$ and 4.5, H-1'); 4.45 (m, 4 H, CH-iPr); 4.09 (dd, 2 H, $J_{\text{gem}} = 10.4$, $J_{2'a,1'} = 7.8$, H-2'a); 3.90 (dd, 2 H, $J_{\text{gem}} = 10.4$, $J_{2'b,1'} = 4.6$, H-2'b); 3.79 and 3.72 ($2 \times$ dd, 2 \times 2 H, $J_{\text{gem}} = 13.9$, $J_{\text{H,P}} = 8.2$, H-3'); 3.04 (bm, 1 H, CH-cyclopropyl); 1.16, 1.15, 1.12 and 1.10 ($4 \times$ d, 24 H, $J_{\text{vic}} = 6.2$, $\text{CH}_3\text{-iPr}$); 0.71 and 0.59 ($2 \times$ m, $2 \times$ 2 H, $\text{CH}_2\text{-cyclopropyl}$). ^{13}C NMR (125.7 MHz, $\text{DMSO}-d_6$): 155.75 (C-6); 152.27 (CH-2); 149.61 (C-4); 139.84 (CH-8); 119.26 (C-5); 70.94 (d, $J_{\text{C,P}} = 12$, $\text{CH}_2\text{-2'}$); 70.37 and 70.32 (d, $J_{\text{C,P}} = 6$, CH-iPr); 65.01 (d, $J_{\text{C,P}} = 164$, $\text{CH}_2\text{-3'}$); 53.61 (CH-1'); 23.88, 23.81, 23.73 and 23.71 (d, $J_{\text{C,P}} = 4$, $\text{CH}_3\text{-iPr}$ and CH-cyclopropyl); 6.56 ($\text{CH}_2\text{-cyclopropyl}$).

**9-{1,3-Bis[(diisopropoxyphosphoryl)methoxy]propan-2-yl}- N^6 -cyclopropyl-
9H-purine-2,6-diamine (18b)**

A solution of **15b** (490 mg, 0.8 mmol) and cyclopropylamine (7 equiv.) in dioxane (15 ml) was refluxed for 7 h and worked up as described for compound **18a**. Purification by silica gel chromatography yielded yellowish oil (75%). FAB MS: 621.5 (MH^+) (100). ^1H NMR (500 MHz, $\text{DMSO}-d_6$): 7.73 (s, 1 H, H-8); 7.60 (bs, 1 H, NH); 5.79 (bs, 2 H, NH_2); 4.70 (tt, 1 H, $J_{1',2'} = 7.3$ and 4.6, H-1'); 4.48 (m, 4 H, CH-iPr); 4.00 (dd, 2 H, $J_{\text{gem}} = 10.3$, $J_{2'a,1'} = 7.3$, H-2'a); 3.84 (dd, 2 H, $J_{\text{gem}} = 10.3$, $J_{2'b,1'} = 4.6$, H-2'b); 3.78 and 3.72 ($2 \times$ dd, 2 \times 2 H, $J_{\text{gem}} = 13.9$, $J_{\text{H,P}} = 8.3$, H-3'); 3.05 (bm, 1 H, CH-cyclopropyl); 1.18, 1.16, 1.14 and 1.13 ($4 \times$ d, 24 H, $J_{\text{vic}} = 6.1$, $\text{CH}_3\text{-iPr}$); 0.65 and 0.57 ($2 \times$ m, $2 \times$ 2 H, $\text{CH}_2\text{-cyclopropyl}$). ^{13}C NMR (125.7 MHz, $\text{DMSO}-d_6$): 160.19 (C-2); 150.07 (C-6); 149.92 (C-4); 136.14 (CH-8); 113.51 (C-5); 71.12 (d, $J_{\text{C,P}} = 11.7$, $\text{CH}_2\text{-2'}$); 70.42 and 70.39 (d, $J_{\text{C,P}} = 6.3$, CH-iPr); 65.10 (d, $J_{\text{C,P}} = 163.6$, $\text{CH}_2\text{-3'}$); 52.74 (CH-1'); 23.94, 23.92, 23.88 and 23.80 (d, $J_{\text{C,P}} = 3.9$, $\text{CH}_3\text{-iPr}$ and CH-cyclopropyl); 6.56 ($\text{CH}_2\text{-cyclopropyl}$).

**9-{1,3-Bis[(diisopropoxyphosphoryl)methoxy]propan-2-yl}-
1H-purine-6(9H)-thione (19a)**

A solution of compound **15a** (350 mg, 0.6 mmol) and thiourea (3 equiv.) in ethanol (20 ml) was refluxed for 3 h, cooled and made alkaline with triethylamine. The mixture was evaporated, refluxed with chloroform, and filtered while hot. The filtrate was evaporated and purified on of silica gel column with chloroform-methanol gradient 0–10% to yield the product as yellowish foam (52%). FAB MS: 583.0 (MH^+) (80). ^1H NMR (500 MHz, $\text{DMSO}-d_6$): 13.70 (bs, 1 H, NH); 8.33 (s, 1 H, H-2); 8.32 (s, 1 H, H-8); 4.95 (tt, 1 H, $J_{1',2'} = 7.8$ and 4.3, H-1'); 4.45 (m, 4 H, $J_{\text{H,P}} = 7.8$, $J_{\text{vic}} = 6.2$, CH-iPr); 4.07 (dd, 2 H, $J_{\text{gem}} = 10.5$, $J_{2'a,1'} = 7.8$, H-2'a); 3.90 (dd, 2 H, $J_{\text{gem}} = 10.5$, $J_{2'b,1'} = 4.3$, H-2'b); 3.79 and 3.73 ($2 \times$ dd, 2 \times 2 H, $J_{\text{gem}} = 13.9$, $J_{\text{H,P}} = 8.3$, H-3'); 1.19, 1.15, 1.11 and 1.10 ($4 \times$ d, 24 H, $J_{\text{vic}} = 6.2$, $\text{CH}_3\text{-iPr}$). ^{13}C NMR (100.6 MHz, $\text{DMSO}-d_6$): 176.12 (C-6); 144.94 (CH-2); 144.49 (C-4); 142.06 (CH-8); 135.11 (C-5); 70.80 (d, $J_{\text{C,P}} = 11.7$, $\text{CH}_2\text{-2'}$); 70.36 and 70.30 (d, $J_{\text{C,P}} = 6.3$, CH-iPr); 65.10 (d, $J_{\text{C,P}} = 164.1$, $\text{CH}_2\text{-3'}$); 54.21 (CH-1'); 23.89, 23.88, 23.79 and 23.73 (d, $J_{\text{C,P}} = 4.0$, $\text{CH}_3\text{-iPr}$).

**2-Amino-9-{1,3-Bis[(diisopropoxyphosphoryl)methoxy]propan-2-yl}-
1H-purine-6(9H)-thione (19b)**

A solution of compound **15b** (360 mg, 0.6 mmol) and thiourea (3 equiv.) in ethanol (20 ml) was refluxed for 3 h and worked up as described for compound **19a**. Purification by silica

gel chromatography yielded yellowish oil (60%). FAB MS: 598.0 (MH^+) (100). 1H NMR (500 MHz, $DMSO-d_6$): 11.70 (bs, 1 H, NH); 7.93 (s, 1 H, H-8); 6.80 (bs, 2 H, NH_2); 4.67 (tt, 1 H, $J_{1',2'} = 7.8$ and 4.3, H-1'); 4.48 (m, 4 H, $J_{H,P} = 7.8$, $J_{vic} = 6.2$, CH-iPr); 3.99 (dd, 2 H, $J_{gem} = 10.4$, $J_{2'a,1'} = 7.8$, H-2'a); 3.84 (dd, 2 H, $J_{gem} = 10.4$, $J_{2'b,1'} = 4.3$, H-2'b); 3.78 and 3.72 (2 \times dd, 2 \times 2 H, $J_{gem} = 13.9$, $J_{H,P} = 8.3$, H-3'); 1.18, 1.16, 1.14 and 1.13 (4 \times d, 24 H, $J_{vic} = 6.2$, CH_3 -iPr). ^{13}C NMR (100.6 MHz, $DMSO-d_6$): 175.07 (C-6); 152.99 (C-2); 148.20 (C-4); 139.33 (CH-8); 128.28 (C-5); 70.89 (d, $J_{C,P} = 11.7$, CH_2 -2'); 70.42 and 70.40 (d, $J_{C,P} = 6.3$, CH-iPr); 65.10 (d, $J_{C,P} = 164.1$, CH_2 -3'); 53.28 (CH-1'); 23.92, 23.91, 23.82 and 23.76 (d, $J_{C,P} = 4.1$, CH_3 -iPr).

General Procedure for Preparation of Free Phosphonic Acids

The starting [1,3-bis(diisopropoxyphosphoryl)methoxy]propan-2-yl derivative (**16–19**, **25**, **26** and **31**, 1 mmol, co-distilled with acetonitrile), acetonitrile (20 ml) and $BrSiMe_3$ (3 ml) were stirred at room temperature overnight. After evaporation and co-distillation with acetonitrile, the residue was treated with water and aqueous ammonia. The mixture was evaporated to dryness, and the residue dissolved in water was applied onto a column of Dowex 50X8 in H^+ form and washed with water. Elution with water and evaporation in vacuo afforded the product as the free phosphonic acid (**20–23**, **27**, **28** and **33**).

*9-[1,3-Bis(phosphonomethoxy)propan-2-yl]-9H-purin-6-amine (**20a**).* White solid (yield 70%), m.p. 256–257 °C (dec.). For $C_{10}H_{17}N_5O_8P_2\cdot H_2O$ (415.2) calculated: 28.93% C, 4.61% H, 16.87% N, 14.92% P; found: 29.14% C, 4.44% H, 16.71% N, 15.01% P. FAB MS: 398.3 (MH^+) (100). 1H NMR (500 MHz, D_2O + NaOD, ref_{dioxane} = 3.75): 8.48 (s, 1 H, H-8); 8.23 (s, 1 H, H-2); 5.04 (tt, 1 H, $J_{1',2'} = 7.4$ and 4.4, H-1'); 4.13 (dd, 2 H, $J_{gem} = 11.0$, $J_{2'a,1'} = 7.4$, H-2'a); 4.04 (dd, 2 H, $J_{gem} = 11.0$, $J_{2'b,1'} = 4.4$, H-2'b); 3.47 and 3.45 (2 \times dd, 2 \times 2 H, $J_{gem} = 12.6$, $J_{H,P} = 8.5$, H-3'). ^{13}C NMR (125.7 MHz, D_2O + NaOD, ref_{dioxane} = 69.3): 158.31 (C-6); 155.17 (CH-2); 152.00 (C-4); 144.86 (CH-8); 121.12 (C-5); 73.73 (d, $J_{C,P} = 10$, CH_2 -2'); 72.12 (d, $J_{C,P} = 150$, CH_2 -3'); 57.48 (CH-1'). UV: (0.01 M HCl) $\lambda_{max} = 259$ ($\epsilon_{max} = 14302$); (H_2O) $\lambda_{max} = 260$ ($\epsilon_{max} = 13756$); (0.01 M NaOH) $\lambda_{max} = 261$ ($\epsilon_{max} = 13837$).

*9-[1,3-Bis(phosphonomethoxy)propan-2-yl]-9H-purine-2,6-diamine (**20b**).* White solid (yield 65%), m.p. 237–238 °C (dec.). For $C_{10}H_{18}N_6O_8P_2\cdot 1/2H_2O$ (421.2) calculated: 28.51% C, 4.55% H, 19.95% N, 14.71% P; found: 28.55% C, 4.58% H, 19.70% N, 14.81% P. FAB MS: 413.1 (MH^+) (90). 1H NMR (40 MHz, D_2O , ref_{dioxane} = 3.75): 8.17 (s, 1 H, H-8); 4.84 (tt, 1 H, $J_{1',2'} = 7.2$ and 4.6, H-1'); 4.04 (dd, 2 H, $J_{gem} = 11.0$, $J_{2'a,1'} = 7.2$, H-2'a); 3.98 (dd, 2 H, $J_{gem} = 11.0$, $J_{2'b,1'} = 4.6$, H-2'b); 3.49 and 3.44 (2 \times dd, 2 \times 2 H, $J_{gem} = 13.7$, $J_{H,P} = 8.6$, H-3'). ^{13}C NMR (125.7 MHz, D_2O , ref_{dioxane} = 69.3): 156.28 (C-2); 155.17 (C-6); 151.55 (C-4); 139.52 (CH-8); 112.93 (C-5); 71.22 (d, $J_{C,P} = 10.8$, CH_2 -2'); 69.56 (d, $J_{C,P} = 149.9$, CH_2 -3'); 54.03 (CH-1'). UV: (0.01 M HCl) $\lambda_{max} = 288$ ($\epsilon_{max} = 9070$); (H_2O) $\lambda_{max} = 282$ ($\epsilon_{max} = 8807$); (0.01 M NaOH) $\lambda_{max} = 281$ ($\epsilon_{max} = 10059$).

*9-[1,3-Bis(phosphonomethoxy)propan-2-yl]-1H-purin-6(9H)-one (**21a**).* White solid (72%), m.p. 107–109 °C (dec.). For $C_{10}H_{16}N_4O_9P_2\cdot 3/2H_2O$ (425.2) calculated: 28.25% C, 4.50% H, 13.18% N, 14.57% P; found: 28.46% C, 4.45% H, 13.23% N, 14.71% P. FAB MS: 399.2 (MH^+) (10). 1H NMR (500 MHz, D_2O , ref_{dioxane} = 3.75): 8.32 (s, 1 H, H-8); 8.14 (s, 1 H, H-2); 4.99 (tt, 1 H, $J_{1',2'} = 7.3$ and 4.6, H-1'); 4.09 (dd, 2 H, $J_{gem} = 11.0$, $J_{2'a,1'} = 7.3$, H-2'a); 4.02 (dd, 2 H, $J_{gem} = 11.0$, $J_{2'b,1'} = 4.6$, H-2'b); 3.46 and 3.43 (2 \times dd, 2 \times 2 H, $J_{gem} = 12.7$, $J_{H,P} = 8.6$, H-3'). ^{13}C NMR (125.7 MHz, D_2O , ref_{dioxane} = 69.3): 165.59 (C-6); 151.68 (C-4); 149.84 (CH-2); 140.46 (CH-8); 123.08 (C-5); 71.15 (d, $J_{C,P} = 10.3$, CH_2 -2'); 69.45 (d, $J_{C,P} = 149.9$,

$\text{CH}_2\text{-}3')$; 54.70 (CH-1'). UV: (0.01 M HCl) $\lambda_{\text{max}} = 250$ ($\epsilon_{\text{max}} = 9797$); (H_2O) $\lambda_{\text{max}} = 249$ ($\epsilon_{\text{max}} = 9555$); (0.01 M NaOH) $\lambda_{\text{max}} = 254$ ($\epsilon_{\text{max}} = 10080$).

2-Amino-9-[1,3-bis(phosphonomethoxy)propan-2-yl]-1H-purin-6(9H)-one (21b). White solid (yield 74%), m.p. 220–221 °C (dec.). For $\text{C}_{10}\text{H}_{17}\text{N}_5\text{O}_9\text{P}_2\cdot 1/2\text{H}_2\text{O}$ (422.2) calculated: 28.45% C, 4.30% H, 16.59% N, 14.67% P; found: 28.73% C, 4.55% H, 16.68% N, 14.79% P. FAB MS: 414.1 (MH^+) (90). ^1H NMR (500 MHz, D_2O , ref_{dioxane} = 3.75): 8.98 (s, 1 H, H-8); 5.14 (tt, 1 H, $J_{1',2'} = 6.5$ and 4.0, H-1'); 4.21 (dd, 2 H, $J_{\text{gem}} = 11.0$, $J_{2'a,1'} = 6.5$, H-2'a); 4.08 (dd, 2 H, $J_{\text{gem}} = 11.0$, $J_{2'b,1'} = 4.0$, H-2'b); 3.47 and 3.45 (2 \times dd, 2 \times 2 H, $J_{\text{gem}} = 13.4$, $J_{\text{H,P}} = 8.8$, H-3'). ^{13}C NMR (125.7 MHz, D_2O , ref_{dioxane} = 69.3): 155.17 (C-6); 155.28 (C-2); 150.25 (C-4); 137.34 (CH-8); 107.44 (C-5); 70.16 (d, $J_{\text{C,P}} = 12.2$, $\text{CH}_2\text{-}2'$); 66.76 (d, $J_{\text{C,P}} = 157.7$, $\text{CH}_2\text{-}3'$); 55.31 (CH-1'). UV: (0.01 M HCl) $\lambda_{\text{max}} = 255$ ($\epsilon_{\text{max}} = 11352$); (H_2O) $\lambda_{\text{max}} = 251$ ($\epsilon_{\text{max}} = 11635$); (0.01 M NaOH) $\lambda_{\text{max}} = 267$ ($\epsilon_{\text{max}} = 10464$).

9-[1,3-Bis(phosphonomethoxy)propan-2-yl]-N-cyclopropyl-9H-purin-6-amine (22a). Yellowish hygroscopic solid (yield 69%), m.p. 142–144 °C (dec.). For $\text{C}_{13}\text{H}_{21}\text{N}_5\text{O}_8\text{P}_2\cdot \text{H}_2\text{O}$ (455.3) calculated: 34.29% C, 5.09% H, 15.38% N, 13.61% P; found: 34.52% C, 5.25% H, 15.29% N, 13.72% P. FAB MS: 438.0 (MH^+) (80). ^1H NMR (500 MHz, D_2O , ref_{dioxane} = 3.75): 8.55 and 8.46 (2 \times s, 2 \times 1 H, H-2 and H-8); 5.16 (tt, 1 H, $J_{1',2'} = 7.3$ and 4.3, H-1'); 4.18 (dd, 2 H, $J_{\text{gem}} = 11.0$, $J_{2'a,1'} = 7.3$, H-2'a); 4.06 (dd, 2 H, $J_{\text{gem}} = 11.0$, $J_{2'b,1'} = 4.3$, H-2'b); 3.70 and 3.65 (2 \times dd, 2 \times 2 H, $J_{\text{gem}} = 13.4$, $J_{\text{H,P}} = 8.7$, H-3'); 2.89 (bm, 1 H, CH-cyclopropyl); 1.09 and 0.88 (2 \times m, 2 \times 2 H, $\text{CH}_2\text{-cyclopropyl}$). ^{13}C NMR (125.7 MHz, D_2O , ref_{dioxane} = 69.3): 152.66 (C-6); 150.49 (C-4); 146.66 (CH-2 and CH-8); 120.95 (C-5); 73.55 (d, $J_{\text{C,P}} = 12$, $\text{CH}_2\text{-}2'$); 69.50 (d, $J_{\text{C,P}} = 158$, $\text{CH}_2\text{-}3'$); 57.69 (CH-1'); 25.45 (CH-cyclopropyl); 9.35 ($\text{CH}_2\text{-cyclopropyl}$). UV: (0.01 M HCl) $\lambda_{\text{max}} = 268$ ($\epsilon_{\text{max}} = 17655$); (H_2O) $\lambda_{\text{max}} = 269$ ($\epsilon_{\text{max}} = 16\,968$); (0.01 M NaOH) $\lambda_{\text{max}} = 271$ ($\epsilon_{\text{max}} = 18301$).

9-[1,3-Bis(phosphonomethoxy)propan-2-yl]-N⁶-cyclopropyl-9H-purine-2,6-diamine (22b). White solid (60%), m.p. 164–166 °C (dec.). For $\text{C}_{13}\text{H}_{22}\text{N}_6\text{O}_8\text{P}_2\cdot \text{H}_2\text{O}$ (470.3) calculated: 33.20% C, 5.14% H, 17.87% N, 13.17% P; found: 33.18% C, 5.24% H, 17.57% N, 13.32% P. FAB MS: 453.3 (MH^+) (100). ^1H NMR (500 MHz, D_2O , ref_{dioxane} = 3.75): 8.21 (s, 1 H, H-8); 4.92 (tt, 1 H, $J_{1',2'} = 7.3$ and 4.1, H-1'); 4.10 (dd, 2 H, $J_{\text{gem}} = 11.0$, $J_{2'a,1'} = 7.3$, H-2'a); 4.00 (dd, 2 H, $J_{\text{gem}} = 11.0$, $J_{2'b,1'} = 4.1$, H-2'b); 3.71 and 3.65 (2 \times dd, 2 \times 2 H, $J_{\text{gem}} = 13.3$, $J_{\text{H,P}} = 8.7$, H-3'); 2.82 (bm, 1 H, CH-cyclopropyl); 1.03 and 0.83 (2 \times m, 2 \times 2 H, $\text{CH}_2\text{-cyclopropyl}$). ^{13}C NMR (125.7 MHz, D_2O , ref_{dioxane} = 69.3): 157.40 (C-2); 152.59 (C-6); 150.52 (C-4); 140.95 (CH-8); 114.35 (C-5); 70.77 (d, $J_{\text{C,P}} = 12.2$, $\text{CH}_2\text{-}2'$); 66.88 (d, $J_{\text{C,P}} = 157.2$, $\text{CH}_2\text{-}3'$); 54.50 (CH-1'); 22.71 (CH-cyclopropyl); 6.75 ($\text{CH}_2\text{-cyclopropyl}$). UV: (0.01 M HCl) $\lambda_{\text{max}} = 294$ ($\epsilon_{\text{max}} = 12\,584.6$); (H_2O) $\lambda_{\text{max}} = 291$ ($\epsilon_{\text{max}} = 12\,059.4$); (0.01 M NaOH) $\lambda_{\text{max}} = 284$ ($\epsilon_{\text{max}} = 14\,119.8$).

9-[1,3-Bis(phosphonomethoxy)-2-propyl]-1H-purine-6(9H)-thione (23a). Yellow solid (84%), m.p. 109–110 °C (dec.). For $\text{C}_{10}\text{H}_{16}\text{N}_4\text{O}_8\text{P}_2\text{S}\cdot 3/2\text{H}_2\text{O}$ (441.3) calculated: 27.22% C, 4.34% H, 12.70% N, 14.04% P, 7.27% S; found: 27.44% C, 4.18% H, 12.41% N, 14.15% P, 7.42% S. FAB MS: 415.0 (MH^+) (10). ^1H NMR (500 MHz, D_2O , ref_{dioxane} = 3.75): 8.46 (s, 1 H, H-8); 8.30 (s, 1 H, H-2); 5.02 (tt, 1 H, $J_{1',2'} = 7.2$ and 4.5, H-1'); 4.10 (dd, 2 H, $J_{\text{gem}} = 11.0$, $J_{2'a,1'} = 7.2$, H-2'a); 4.03 (dd, 2 H, $J_{\text{gem}} = 11.0$, $J_{2'b,1'} = 4.5$, H-2'b); 3.47 and 3.43 (2 \times dd, 2 \times 2 H, $J_{\text{gem}} = 12.8$, $J_{\text{H,P}} = 8.5$, H-3'). ^{13}C NMR (125.7 MHz, D_2O , ref_{dioxane} = 69.3): 177.16 (C-6); 150.77 (CH-2); 146.17 (C-4); 142.37 (CH-8); 135.26 (C-5); 71.03 (d, $J_{\text{C,P}} = 10.2$, $\text{CH}_2\text{-}2'$); 69.45 (d, $J_{\text{C,P}} = 149.9$, $\text{CH}_2\text{-}3'$); 54.58 (CH-1'). UV: (0.01 M HCl) $\lambda_{\text{max}} = 323$ ($\epsilon_{\text{max}} = 18927$); (H_2O) $\lambda_{\text{max}} = 322$ ($\epsilon_{\text{max}} = 20321$); (0.01 M NaOH) $\lambda_{\text{max}} = 310$ ($\epsilon_{\text{max}} = 18099$).

2-Amino-9-[1,3-bis(phosphonomethoxy)propan-2-yl]-1H-purine-6(9H)-thione (23b). Yellowish solid (91%), m.p. 183–184 °C (dec.). For $\text{C}_{10}\text{H}_{17}\text{N}_5\text{O}_8\text{P}_2\text{S}\cdot 3/2\text{H}_2\text{O}$ (456.3) calculated: 26.32% C,

4.42% H, 15.35% N, 13.58% P, 7.03% S; found: 26.08% C, 4.35% H, 15.19% N, 13.62% P, 7.23% S. FAB MS: 430.0 (MH^+) (40). 1H NMR (500 MHz, D_2O , ref_{dioxane} = 3.75): 9.15 (s, 1 H, H-8); 5.09 (tt, 1 H, $J_{1',2'} = 6.5$ and 4.0, H-1'); 4.16 (dd, 2 H, $J_{gem} = 11.0$, $J_{2'a,1'} = 6.7$, H-2'a); 4.03 (dd, 2 H, $J_{gem} = 11.0$, $J_{2'b,1'} = 4.0$, H-2'b); 3.72 and 3.685 ($2 \times$ dd, 2 \times 2 H, $J_{gem} = 13.3$, $J_{H,P} = 8.8$, H-3'). ^{13}C NMR (125.7 MHz, D_2O , ref_{dioxane} = 69.3): 174.72 (C-6); 154.69 (C-2); 146.31 (C-4); 139.96 (CH-8); 119.97 (C-5); 70.16 (d, $J_{C,P} = 12.2$, CH₂-2'); 67.00 (d, $J_{C,P} = 157.2$, CH₂-3'); 55.28 (CH-1'). UV: (0.01 M HCl) $\lambda_{max} = 345$ ($\epsilon_{max} = 19008$); (H_2O) $\lambda_{max} = 341$ ($\epsilon_{max} = 22280.6$); (0.01 M NaOH) $\lambda_{max} = 319$ ($\epsilon_{max} = 17654.8$).

2-{{1,3-Bis(phosphonomethoxy)propan-2-yl}oxy}pyrimidin-4-amine (27a). White hygroscopic solid (80%), m.p. 118–119 °C (dec.). For $C_9H_{17}N_3O_9P_2 \cdot H_2O$ (391.2) calculated: 27.63% C, 4.90% H, 10.74% N, 15.83% P; found: 27.50% C, 5.10% H, 10.54% N, 15.95% P. FAB MS: 374.1 (MH^+) (30). 1H NMR (500 MHz, D_2O , ref_{dioxane} = 3.75): 7.83 (d, 1 H, $J_{H6,H5} = 7.2$, H-6); 6.43 (d, 1 H, $J_{H5,H6} = 7.2$, H-5); 5.68 (tt, 1 H, $J_{1',2'} = 6.0$ and 4.0, H-1'); 3.96 (dd, 2 H, $J_{gem} = 11.8$, $J_{2'a,1'} = 6.0$, H-2'a); 3.93 (dd, 2 H, $J_{gem} = 11.8$, $J_{2'b,1'} = 4.0$, H-2'b); 3.83 and 3.74 ($2 \times$ dd, 2 \times 2 H, $J_{gem} = 13.6$, $J_{H,P} = 8.6$, H-3'). ^{13}C NMR (125.7 MHz, D_2O , ref_{dioxane} = 69.3): 166.45 (C-2); 157.68 (C-4); 142.93 (C-6); 100.07 (C-5); 76.33 (CH-1'); 70.66 (d, $J_{C,P} = 11.2$, CH₂-2'); 66.70 (d, $J_{C,P} = 157.7$, CH₂-3'). UV: (0.01 M HCl) $\lambda_{max} = 259$ ($\epsilon_{max} = 8282$); (H_2O) $\lambda_{max} = 260$ ($\epsilon_{max} = 8181$); (0.01 M NaOH) $\lambda_{max} = 271$ ($\epsilon_{max} = 6969$).

4-Amino-1-{{1,3-bis(phosphonomethoxy)propan-2-yl}pyrimidin-2(1H)-one (27b). White solid (70%), m.p. 130–131 °C (dec.). For $C_9H_{17}N_3O_9P_2 \cdot H_2O$ (391.2) calculated: 27.63% C, 4.90% H, 10.74% N, 15.84% P; found: 27.80% C, 5.12% H, 10.60% N, 15.92% P. FAB MS: 374.1 (MH^+) (30). 1H NMR (500 MHz, D_2O , ref_{dioxane} = 3.75): 8.08 (d, 1 H, $J_{H6,H5} = 7.8$, H-6); 6.20 (d, 1 H, $J_{H5,H6} = 7.2$, H-5); 5.02 (tt, 1 H, $J_{1',2'} = 7.2$ and 4.2, H-1'); 3.99 (dd, 2 H, $J_{gem} = 11.2$, $J_{2'a,1'} = 7.2$, H-2'a); 3.52 (dd, 2 H, $J_{gem} = 11.2$, $J_{2'b,1'} = 4.2$, H-2'b); 3.68 and 3.64 ($2 \times$ dd, 2 \times 2 H, $J_{gem} = 13.4$, $J_{H,P} = 8.8$, H-3'). ^{13}C NMR (125.7 MHz, D_2O , ref_{dioxane} = 69.3): 158.94 (C-4); 149.41 (C-2); 147.53 (C-6); 94.61 (C-5); 69.83 (d, $J_{C,P} = 12.2$, CH₂-2'); 66.82 (d, $J_{C,P} = 157.7$, CH₂-3'); 52.96 (CH-1'). UV: (0.01 M HCl) $\lambda_{max} = 282$ ($\epsilon_{max} = 15473$); (H_2O) $\lambda_{max} = 280$ ($\epsilon_{max} = 10484$); (0.01 M NaOH) $\lambda_{max} = 274$ ($\epsilon_{max} = 8201$).

2-{{1,3-Bis(phosphonomethoxy)propan-2-yl}oxy}-5-methylpyrimidin-4-amine (28a). White hygroscopic solid (75%), m.p. 154–155 °C (dec.). For $C_{10}H_{19}N_3O_9P_2 \cdot H_2O$ (405.2) calculated: 29.64% C, 5.22% H, 10.37% N, 15.29% P; found: 29.42% C, 5.32% H, 10.46% N, 15.17% P. FAB MS: 388.2 (MH^+) (100). 1H NMR (500 MHz, D_2O , ref_{dioxane} = 3.75): 7.77 (q, $J_{H6,CH_3} = 1.0$, 1 H, H-6); 6.34 (tt, 1 H, $J_{1',2'} = 6.2$ and 4.9, H-1'); 3.86 (dd, 2 H, $J_{gem} = 10.5$, $J_{2'a,1'} = 6.2$, H-2'a); 3.83 (dd, 2 H, $J_{gem} = 10.5$, $J_{2'b,1'} = 4.9$, H-2'b); 3.53 and 3.49 ($2 \times$ dd, 2 \times 2 H, $J_{gem} = 12.8$, $J_{H,P} = 8.4$, H-3'); 2.10 (d, $J_{CH_3,H_6} = 1.0$, 3 H, CH₃). ^{13}C NMR (125.7 MHz, D_2O , ref_{dioxane} = 69.3): 164.99 (C-2); 164.68 (C-4); 154.55 (C-6); 108.92 (C-5); 74.29 (CH-1'); 71.61 (d, $J_{C,P} = 11.2$, CH₂-2'); 69.70 (d, $J_{C,P} = 150.4$, CH₂-3'); 12.14 (CH₃). UV: (0.01 M HCl) $\lambda_{max} = 264$ ($\epsilon_{max} = 7918$); (H_2O) $\lambda_{max} = 264$ ($\epsilon_{max} = 8100$); (0.01 M NaOH) $\lambda_{max} = 275$ ($\epsilon_{max} = 7009$).

4-Amino-1-{{1,3-bis(phosphonomethoxy)propan-2-yl}5-methylpyrimidin-2(1H)-one (28b). White solid (80%), m.p. 124–126 °C (dec.). For $C_{10}H_{19}N_3O_9P_2 \cdot H_2O$ (405.2) calculated: 29.64% C, 5.22% H, 10.37% N, 15.29% P; found: 29.38% C, 5.30% H, 10.54% N, 15.27% P. FAB MS: 388.3 (MH^+) (100). 1H NMR (500 MHz, D_2O , ref_{dioxane} = 3.75): 7.70 (q, $J_{H6,CH_3} = 1.0$, 1 H, H-6); 5.06 (tt, 1 H, $J_{1',2'} = 7.3$ and 4.3 H-1'); 3.87 (dd, 2 H, $J_{gem} = 11.2$, $J_{2'a,1'} = 7.3$, H-2'a); 3.52 (dd, 2 H, $J_{gem} = 11.2$, $J_{2'b,1'} = 4.3$, H-2'b); 3.50 and 3.49 ($2 \times$ dd, 2 \times 2 H, $J_{gem} = 12.8$, $J_{H,P} = 8.4$, H-3'); 1.99 (d, $J_{CH_3,H_6} = 1.0$, 3 H, CH₃). ^{13}C NMR (125.7 MHz, D_2O , ref_{dioxane} = 69.3): 160.29 (C-4); 156.50 (C-2); 138.93 (C-6); 104.53 (C-5); 71.25 (d, $J_{C,P} = 10.2$, CH₂-2');

69.49 (d, $J_{C,P} = 148.9$, $\text{CH}_2\text{-}3'$); 53.96 ($\text{CH-1}'$); 12.14 (CH_3). UV: (0.01 M HCl) $\lambda_{\max} = 289$ ($\epsilon_{\max} = 14241$); (H_2O) $\lambda_{\max} = 288$ ($\epsilon_{\max} = 9837$); (0.01 M NaOH) $\lambda_{\max} = 280$ ($\epsilon_{\max} = 7898$).

1-[1,3-Bis(phosphonomethoxy)propan-2-yl]pyrimidine-2,4(1H,3H)-dione (33a). White solid (80%), m.p. 105–106 °C (dec.). For $\text{C}_9\text{H}_{16}\text{N}_2\text{O}_{10}\text{P}_2\text{H}_2\text{O}$ (392.2) calculated: 27.56% C, 4.63% H, 7.14% N, 15.80% P; found: 27.30% C, 4.58% H, 6.98% N, 15.53% P. FAB MS: 375.0 (MH^+) (10). ^1H NMR (500 MHz, $\text{D}_2\text{O} + \text{NaOD}$, $\text{ref}_{\text{dioxane}} = 3.75$): 7.55 (d, 1 H, $J_{\text{H}6,\text{H}5} = 7.5$, H-6); 5.82 (d, 1 H, $J_{\text{H}5,\text{H}6} = 7.5$, H-5); 5.03 (tt, 1 H, $J_{1',2'} = 7.3$ and 5.1, H-1'); 3.87 (dd, 2 H, $J_{\text{gem}} = 11.0$, $J_{2'\text{a},1'} = 7.3$, H-2'a); 3.84 (dd, 2 H, $J_{\text{gem}} = 11.0$, $J_{2'\text{b},1'} = 5.1$, H-2'b); 3.47 and 3.44 (2 \times dd, 2 \times 2 H, $J_{\text{gem}} = 12.7$, $J_{\text{H},\text{P}} = 8.5$, H-3'). ^{13}C NMR (125.7 MHz, $\text{D}_2\text{O} + \text{NaOD}$, $\text{ref}_{\text{dioxane}} = 69.3$): 162.64 (C-4); 155.60 (C-2); 144.96 (C-6); 104.38 (C-5); 73.07 (d, $J_{\text{C,P}} = 10.7$, $\text{CH}_2\text{-}2'$); 71.45 (d, $J_{\text{C,P}} = 149.9$, $\text{CH}_2\text{-}3'$); 56.93 (CH-1'). UV: (0.01 M HCl) $\lambda_{\max} = 266$ ($\epsilon_{\max} = 8484$); (H_2O) $\lambda_{\max} = 264$ ($\epsilon_{\max} = 8161$); (0.01 M NaOH) $\lambda_{\max} = 265$ ($\epsilon_{\max} = 8444$).

1-[1,3-Bis(phosphonomethoxy)propan-2-yl]-5-methylpyrimidine-2,4(1H,3H)-dione (33b). Yellowish solid (80%), m.p. 96–97 °C (dec.). For $\text{C}_{10}\text{H}_{18}\text{N}_2\text{O}_{10}\text{P}_2\text{H}_2\text{O}$ (406.2) calculated: 29.57% C, 4.96% H, 6.90% N, 15.25% P; found: 29.30% C, 4.72% H, 6.85% N, 15.59% P. FAB MS: 389.0 (MH^+) (10). ^1H NMR (500 MHz, $\text{D}_2\text{O} + \text{NaOD}$, $\text{ref}_{\text{dioxane}} = 3.75$): 7.77 (q, 1 H, $J_{\text{H}6,\text{CH}3} = 1.0$, H-6); 5.14 (tt, 1 H, $J_{1',2'} = 7.3$ and 5.1, H-1'); 3.96 (dd, 2 H, $J_{\text{gem}} = 11.0$, $J_{2'\text{a},1'} = 7.3$, H-2'a); 3.84 (dd, 2 H, $J_{\text{gem}} = 11.0$, $J_{2'\text{b},1'} = 5.1$, H-2'b); 3.47 and 3.44 (2 \times dd, 2 \times 2 H, $J_{\text{gem}} = 12.7$, $J_{\text{H},\text{P}} = 8.6$, H-3'); 1.19 (d, 3 H, $J_{\text{CH}3,\text{H}6} = 6.1$, CH_3). ^{13}C NMR (125.7 MHz, $\text{D}_2\text{O} + \text{NaOD}$, $\text{ref}_{\text{dioxane}} = 69.3$): 156.80 (C-4); 154.90 (C-2); 139.46 (C-6); 111.34 (C-5); 70.57 (d, $J_{\text{C,P}} = 11.2$, $\text{CH}_2\text{-}2'$); 69.34 (d, $J_{\text{C,P}} = 149.9$, $\text{CH}_2\text{-}3'$); 54.90 (CH-1'); 12.08 (CH_3). UV: (0.01 M HCl) $\lambda_{\max} = 270$ ($\epsilon_{\max} = 8444$); (H_2O) $\lambda_{\max} = 271$ ($\epsilon_{\max} = 8150$); (0.01 M NaOH) $\lambda_{\max} = 271$ ($\epsilon_{\max} = 8320$).

General Procedure for Alkylation of Thymine with Primary and Secondary Alkyl Tosylates (34–39)

A solution of thymine (0.5 g) in dry DMF (20 ml) was treated with Cs_2CO_3 (0.5 equiv.) at room temperature under a CaCl_2 protecting tube for 1 h. The reaction mixture was then heated at 60 °C and synthon (34–39, 1.0 equiv.) was added. The mixture was then stirred at 90 °C for 24 h. Solvent was taken down and the residue was co-evaporated with toluene. The residue in chloroform was filtered through a Celite pad, evaporated and purified on a preparative thin layer chromatography (silica gel).

5-Methyl-1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]pyrimidine-2,4(1H,3H)-dione (34a). Preparative TLC (chloroform–8% methanol) afforded the product as white solid (39%). FAB MS: 241.09 (MH^+) (65). ^1H NMR (500 MHz, $\text{DMSO-}d_6$): 11.30 (bs, 1 H, NH); 7.45 (q, 1 H, $J_{\text{H}6,\text{CH}3} = 1.0$, H-6); 4.28 (m, 1 H, H-2'); 3.99 (dd, 1 H, $J_{3\text{a}',2'} = 8.7$ and 6.6, H-3a'); 3.79 (dd, 1 H, $J_{1\text{a}',2'} = 14.0$ and 4.3, H-1a'); 3.72 (dd, 1 H, $J_{1\text{b}',2'} = 14.0$ and 6.6, H-1b'); 3.66 (dd, 1 H, $J_{3\text{b}',2'} = 8.7$ and 5.6, H-3b'); 2.01 (d, 3 H, $J_{\text{CH}3,\text{H}6} = 1.0$, CH_3); 1.32 and 1.24 (2 \times s, 3 H, CH_3). ^{13}C NMR (100.6 MHz, $\text{DMSO-}d_6$): 164.44 (C-4); 151.36 (C-2); 142.42 (C-6); 109.00 (CH-iPr); 108.27 (C-5); 73.57 (C-2'); 66.13 (C-3'); 49.54 (C-1'); 26.68 and 25.35 (CH_3 -iPr); 12.11 (CH_3).

5-Methyl-1,3-bis[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]pyrimidine-2,4(1H,3H)-dione (34b). Preparative TLC (hexane–ethyl acetate 1:1) afforded the product as yellowish oil (10%). FAB MS: 355.12 (MH^+) (45). ^1H NMR (500 MHz, $\text{DMSO-}d_6$): 8.13 (q, 1 H, $J_{\text{H}6,\text{CH}3} = 1.0$, H-6); 4.40 (m, 1 H, H-2'); 4.29 (dd, 1 H, $J_{1\text{a}',2'} = 11.2$ and 1.6, H-1a'); 4.22 (dd, 1 H, $J_{1\text{b}',2'} = 11.2$ and 2.3, H-1b'); 4.07 and 4.06 (dd, 1 H, $J_{3\text{a}',2'} = 8.4$ and 6.6, H-3a'); 3.79 and 3.73 (dd, 1 H, $J_{3\text{b}',2'} = 8.4$ and 6.2, H-3b'); 2.01 (d, 3 H, $J_{\text{CH}3,\text{H}6} = 1.0$, CH_3); 1.34, 1.29 and 1.28 (s, 12 H, CH_3). ^{13}C NMR (100.6 MHz, $\text{DMSO-}d_6$): 168.65 (C-4); 162.93 (C-2); 157.78 (C-6); 110.93

(C-5); 109.03 and 108.96 (CH-iPr); 73.47 (2 C, C-2'); 67.65 and 66.61 (C-3'); 65.94 and 65.61 (C-1'); 26.82, 26.68, 25.55 and 11.58 (CH₃).

2-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methoxy]-5-methylpyrimidin-4(3H)-one (34c). Preparative TLC (chloroform-10% methanol) afforded the product as yellowish oil (1%). FAB MS: 241.11 (MH⁺) (45). ¹H NMR (500 MHz, DMSO-*d*₆): 7.65 (q, 1 H, *J*_{H6,CH3} = 1.0, H-6); 4.28 (m, 1 H, H-2'); 3.86 (dd, 1 H, *J*_{3a',2'} = 8.7 and 6.6, H-3a'); 4.25 (dd, 1 H, *J*_{1a',2'} = 14.0 and 4.3, H-1a'); 3.72 (dd, 1 H, *J*_{1b',2'} = 14.0 and 6.6, H-1b'); 3.66 (dd, 1 H, *J*_{3b',2'} = 8.7 and 5.6, H-3b'); 1.95 (d, 3 H, *J*_{CH3,H6} = 1.0, CH₃); 1.32 and 1.24 (2 × s, 3 H, CH₃). ¹³C NMR (100.6 MHz, DMSO-*d*₆): 164.44 (C-4); 151.36 (C-2); 142.42 (C-6); 109.00 (CH-iPr); 108.27 (C-5); 73.57 (C-2'); 70.21 (C-1'); 66.13 (C-3'); 26.68 and 25.35 (CH₃-iPr); 12.11 (CH₃).

1-[(Tetrahydro-4-methoxy-2,2-dimethylfuro[3,4-d][1,3]dioxol-6-yl)methyl]-5-methylpyrimidine-2,4(1H,3H)-dione (35a). Preparative TLC (chloroform-8% methanol) afforded the product as white solid (31%). FAB MS: 313.35 (MH⁺) (65). ¹H NMR (500 MHz, DMSO-*d*₆): 11.34 (bs, 1 H, NH); 7.51 (q, 1 H, *J*_{H6,CH3} = 1.0, H-6); 4.95 (s, 1 H, H-1'); 4.72 (bd, 1 H, *J*_{3',4'} = 1.0 and *J*_{3',2'} = 6.0, H-3'); 4.62 (d, 1 H, *J*_{2',3'} = 6.0, H-2'); 4.32 (bt, 1 H, *J*_{4',3'} = 1.0 and *J*_{4',5'} = 7.3, H-4'); 3.87 (dd, 1 H, *J*_{5a',4'} = 13.9 and 7.6, H-5a'); 3.55 (dd, 1 H, *J*_{5b',4'} = 13.9 and 7.2, H-5b'); 3.28 (s, 3 H, OCH₃); 1.75 (d, 3 H, *J*_{CH3,H6} = 1.2, CH₃); 1.36 and 1.24 (2 × s, 3 H, CH₃). ¹³C NMR (100.6 MHz, DMSO-*d*₆): 164.35 (C-4); 151.21 (C-2); 141.93 (C-6); 111.89 (CH-iPr); 109.35 (C-1'); 108.79 (C-5); 84.76 (C-4'); 83.69 (C-2'); 81.31 (C-3'); 55.09 (OCH₃); 50.25 (C-5'); 26.44 and 24.91 (iPr); 12.11 (CH₃).

1,3-Bis[(tetrahydro-4-methoxy-2,2-dimethylfuro[3,4-d][1,3]dioxol-6-yl)methyl]-5-methylpyrimidine-2,4(1H,3H)-dione (35b). Preparative TLC (hexane-ethyl acetate 1:1) afforded the product as colorless oil (10%). FAB MS: 499.32 (MH⁺) (65). ¹H NMR (500 MHz, DMSO-*d*₆): 7.62 (q, 1 H, *J*_{H6,CH3} = 1.0, H-6); 4.95 and 4.94 (2 × s, 1 H, H-1'); 4.74 and 4.68 (2 × bd, 1 H, *J*_{3',4'} = 1.0, H-3'); 4.63 and 4.60 (2 × d, 1 H, *J*_{2',3'} = 6.0, H-2'); 4.37 and 4.23 (2 × dd, 1 H, *J*_{4',5'} = 7.3, 4.8 and 9.6, H-4'); 4.07 and 3.96 (2 × dd, 1 H, *J*_{5a',4'} = 9.6 and 7.6, H-5a'); 3.65 and 3.48 (2 × dd, 1 H, *J*_{5b',4'} = 7.2 and 4.8, *J*_{gem} = 13.9 and 13.0, H-5b'); 3.28 and 3.27 (2 × s, 3 H, OCH₃); 1.75 (d, 3 H, *J*_{CH3,H6} = 1.2, CH₃); 1.36, 1.33, 1.24, and 1.20 (4 × s, 6 H, CH₃). ¹³C NMR (100.6 MHz, DMSO-*d*₆): 163.30 (C-4); 151.44 (C-2); 140.95 (C-6); 111.85 and 111.69 (CH-iPr); 109.49 (C-5); 108.06 and 108.85 (C-1'); 84.88 and 84.75 (C-4'); 83.52 and 83.51 (C-2'); 81.84 and 81.34 (C-3'); 55.16 and 54.71 (OCH₃); 51.39 and 43.41 (C-5'); 26.47, 26.43, 24.92 and 24.91 (iPr); 12.72 (CH₃).

2-[(Tetrahydro-4-methoxy-2,2-dimethylfuro[3,4-d][1,3]dioxol-6-yl)methoxy]-5-methylpyrimidin-4(3H)-one (35c). Preparative TLC (chloroform-8% methanol) afforded the product as colorless oil (1%). FAB MS: 313.21 (MH⁺) (35). ¹H NMR (500 MHz, DMSO-*d*₆): 7.51 (q, 1 H, *J*_{H6,CH3} = 1.0, H-6); 4.98 (s, 1 H, H-1'); 4.74 (bd, 1 H, *J*_{3',4'} = 1.0 and *J*_{3',2'} = 6.0, H-3'); 4.62 (d, 1 H, *J*_{2',3'} = 6.0, H-2'); 4.35 (bt, 1 H, *J*_{4',3'} = 1.0 and *J*_{4',5'} = 7.3, H-4'); 3.85 (dd, 1 H, *J*_{5a',4'} = 13.9 and 7.6, H-5a'); 3.65 (dd, 1 H, *J*_{5b',4'} = 13.9 and 7.2, H-5b'); 3.25 (s, 3 H, OCH₃); 1.75 (d, 3 H, *J*_{CH3,H6} = 1.2, CH₃); 1.36 and 1.24 (2 × s, 3 H, CH₃). ¹³C NMR (100.6 MHz, DMSO-*d*₆): 164.35 (C-4); 151.21 (C-2); 141.93 (C-6); 111.89 (CH-iPr); 109.35 (C-1'); 108.79 (C-5); 84.76 (C-4'); 83.69 (C-2'); 81.31 (C-3'); 71.13 (C-5'); 55.09 (OCH₃); 26.44 and 24.91 (iPr); 12.11 (CH₃).

1-((Bis(diisopropoxy)phosphoryl)methoxyethyl)-5-methylpyrimidine-2,4(1H,3H)-dione (36a). Preparative TLC (chloroform-10% methanol) afforded the product as white solid (32%). FAB MS: 349.25 (MH⁺) (65). ¹H NMR (500 MHz, DMSO-*d*₆): 11.25 (bs, 1 H, NH); 7.43 (q, 1 H, *J*_{H6,CH3} = 1.0, H-6); 4.55 (m, 2 H, CH-iPr); 3.81 (t, 2 H, H-1'); 3.76 (d, 2 H, *J* = 8.4, H-3'); 3.68 (t, 2 H, *J* = 5.0, H-2'); 1.75 (d, 3 H, *J*_{CH3,H6} = 1.2, CH₃); 1.21 and 1.19 (2 × d, 6 H, *J* = 6.2, CH₃).

CH_3 . ^{13}C NMR (100.6 MHz, $\text{DMSO}-d_6$): 164.49 (C-4); 151.05 (C-2); 142.25 (C-6); 108.04 (C-5); 70.34 (2 C, $J = 6.4$, CH-iPr); 70.14 (d, $J = 11.7$, C-2'); 64.84 (d, $J = 164.1$, C-3'); 46.97 (C-1'); 23.97, 26.43, 23.83 and 23.25 (iPr); 12.15 (CH_3).

1,3-Bis({bis[(diisopropoxy)phosphoryl]methoxy}ethyl)-5-methylpyrimidine-2,4(1H,3H)-dione (36b). Preparative TLC (chloroform-10% methanol) afforded the product as colorless oil (10%). FAB MS: 571.23 (MH^+) (45). ^1H NMR (500 MHz, $\text{DMSO}-d_6$): 7.51 (q, 1 H, $J_{\text{H6,CH3}} = 1.0$, H-6); 4.55 (m, 2 H, CH-iPr); 4.07 and 3.81 (2 \times t, 2 H, $J = 6.0$ and 5.0, H-1'); 3.76 and 3.74 (2 \times d, 2 H, $J = 8.4$, H-3'); 3.72 and 3.68 (2 \times t, 2 H, $J = 6.0$ and 5.0, H-2'); 1.75 (d, 3 H, $J_{\text{CH3,H6}} = 1.2$, CH_3); 1.22, 1.21, 1.20 and 1.19 (4 \times d, 6 H, $J = 6.1$, CH_3). ^{13}C NMR (100.6 MHz, $\text{DMSO}-d_6$): 163.26 (C-4); 150.99 (C-2); 141.02 (C-6); 107.24 (C-5); 70.34 (4 C, CH-iPr , $J = 6.3$); 70.00 and 68.97 (d, $J = 12.2$, C-2'); 64.83 and 64.68 (d, $J = 164.6$, C-3'); 48.11 and 39.46 (C-1'); 23.97, 23.94, 23.83 and 23.80 (iPr); 12.75 (CH_3).

2-({Bis[(diisopropoxy)phosphoryl]methoxy}ethoxy)-5-methylpyrimidin-4(3H)-one (36c). Preparative TLC (chloroform-10% methanol) afforded the product as yellowish oil (1%). FAB MS: 349.12 (MH^+) (25). ^1H NMR (500 MHz, $\text{DMSO}-d_6$): 7.43 (q, 1 H, $J_{\text{H6,CH3}} = 1.0$, H-6); 4.55 (m, 2 H, CH-iPr); 3.79 (t, 2 H, H-1'); 3.75 (d, 2 H, $J = 8.4$, H-3'); 3.66 (t, 2 H, $J = 5.0$, H-2'); 1.75 (d, 3 H, $J_{\text{CH3,H6}} = 1.2$, CH_3); 1.21 and 1.19 (2 \times d, 6 H, $J = 6.2$, CH_3). ^{13}C NMR (100.6 MHz, $\text{DMSO}-d_6$): 164.49 (C-4); 151.05 (C-2); 142.25 (C-6); 108.04 (C-5); 70.34 (2 C, $J = 6.4$, CH-iPr); 70.14 (d, $J = 11.7$, C-2'); 65.13 (C-1'); 64.84 (d, $J = 164.1$, C-3'); 23.97, 26.43, 23.83, 23.54 (iPr); 12.15 (CH_3).

1-[1-(Benzylxy)propan-2-yl]-5-methylpyrimidine-2,4(1H,3H)-dione (37a). Preparative TLC (chloroform-5% methanol) afforded the product as white solid (25%). FAB MS: 275.21 (MH^+) (65). ^1H NMR (500 MHz, $\text{DMSO}-d_6$): 11.20 (bs, 1 H, NH); 7.54 (q, 1 H, $J_{\text{H6,CH3}} = 1.0$, H-6); 7.30-7.24 (m, 5 H, arom.); 4.75 (m, 1 H, H-1'); 4.50 and 4.42 (2 \times d, 2 H, $J = 12.2$, BnOCH_2); 3.62 and 3.51 (2 \times dd, 2 H, $J = 10.5$ and 8.2, 10.5 and 4.6, OCH_2); 1.75 (d, 3 H, $J_{\text{CH3,H6}} = 1.2$, CH_3); 1.21 (d, 3 H, $J = 7.1$, CH_3). ^{13}C NMR (100.6 MHz, $\text{DMSO}-d_6$): 163.95 (C-4); 151.29 (C-2); 138.30 (C); 138.12 (C-6); 128.45 (2 C); 127.69 (C); 127.58 (2 C); 108.83 (C-5); 71.98 and 71.94 (OCH_2); 49.89 (C-1'); 15.66 (CH_3); 12.27 (CH_3).

1,3-Bis[1-(benzylxy)propan-2-yl]-5-methylpyrimidine-2,4(1H,3H)-dione (37b). Preparative TLC (hexane-ethyl acetate 7:3) afforded the product as white solid (3.5%). FAB MS: 423.52 (MH^+) (45). ^1H NMR (500 MHz, $\text{DMSO}-d_6$): 7.59 (q, 1 H, $J_{\text{H6,CH3}} = 1.0$, H-6); 7.30-7.24 (m, 10 H, arom.); 5.20 and 4.81 (m, 1 H, H-1'); 4.48, 4.45, 4.40 and 4.37 (4 \times d, 4 H, $J = 12.2$, BnOCH_2); 3.93 and 3.64 (2 \times dd, 2 H, $J = 9.5$ and 8.2, 9.5 and 6.1, OCH_2); 3.62 and 3.35 (2 \times dd, 2 H, $J = 10.5$ and 8.2, 10.5 and 4.8, OCH_2); 1.75 (d, 3 H, $J_{\text{CH3,H6}} = 1.2$, CH_3); 1.30 and 1.21 (d, 3 H, $J = 7.1$, CH_3). ^{13}C NMR (100.6 MHz, $\text{DMSO}-d_6$): 163.95 (C-4); 151.29 (C-2); 138.61 (C); 136.84 (C-6); 136.52, 138.26, 129.66, 129.33 and 128.35 (4 C); 127.64 (2 C); 127.52 (2 C); 127.58 (2 C); 109.0 (C-5); 71.98, 71.90, 70.92, 70.54 (OCH_2); 50.94 and 50.90 (C-1'); 15.58, 14.71 and 12.97 (CH_3).

2-[1-(Benzylxy)propan-2-yloxy]-5-methylpyrimidin-4(3H)-one (37c). Preparative TLC (chloroform-5% methanol) afforded the product as white solid (1%). FAB MS: 275.31 (MH^+) (55). ^1H NMR (500 MHz, $\text{DMSO}-d_6$): 7.54 (q, 1 H, $J_{\text{H6,CH3}} = 1.0$, H-6); 7.30-7.24 (m, 5 H, arom.); 4.75 (m, 1 H, H-1'); 4.52 and 4.42 (2 \times d, 2 H, $J = 12.2$, BnOCH_2); 3.61 and 3.51 (2 \times dd, 2 H, $J = 10.5$ and 8.2, 10.5 and 4.6, OCH_2); 1.75 (d, 3 H, $J_{\text{CH3,H6}} = 1.2$, CH_3); 1.21 (d, 3 H, $J = 7.1$, CH_3). ^{13}C NMR (100.6 MHz, $\text{DMSO}-d_6$): 163.95 (C-4); 151.29 (C-2); 138.30 (C); 138.12 (C-6); 128.45 (2 C); 127.69 (C); 127.58 (2 C); 108.83 (C-5); 71.98 and 71.94 (OCH_2); 65.85 (C-1'); 15.66 (CH_3); 12.27 (CH_3).

5-Methyl-1-(2-phenyl-1,3-dioxan-5-yl)pyrimidine-2,4(1H,3H)-dione (38a). Preparative TLC (hexane-ethyl acetate 7:3) afforded the product as white solid (23%). FAB MS: 335.12 (MH^+) (65). ^1H NMR (500 MHz, DMSO- d_6): 11.38 (bs, 1 H, NH); 8.16 (q, 1 H, $J_{\text{H}6,\text{CH}3} = 1.0$, H-6); 7.42–7.24 (m, 5 H, arom.); 5.73 (s, 1 H, O-CH-O); 4.42 and 4.25 (bd, 4 H, $J_{\text{gem}} = 12.6$, H-2', 2''); 4.37 (bt, 1 H, $J_{\text{CH},\text{CH}2} = 2.0$ H-1'); 1.80 (d, 3 H, $J_{\text{CH}3,\text{H}6} = 1.2$, CH₃). ^{13}C NMR (100.6 MHz, DMSO- d_6): 163.95 (C-4); 151.29 (C-2); 139.37 (C-6); 138.19; 129.28; 128.51 (2 C); 126.25 (2 C); 108.28 (C-5); 101.04 (O-CH-O); 68.86 (2 C, C-2', 2''); 47.53 (C-1'); 12.73 (CH₃).

5-Methyl-1,3-bis(2-phenyl-1,3-dioxan-5-yl)pyrimidine-2,4(1H,3H)-dione (38b). Preparative TLC (hexane-ethyl acetate 7:3) afforded the product as white solid (1%). FAB MS: 451.23 (MH^+) (45). ^1H NMR (500 MHz, DMSO- d_6): 8.16 (q, 1 H, $J_{\text{H}6,\text{CH}3} = 1.0$, H-6); 7.50–7.30 (m, 10 H, arom.); 5.67 and 5.66 (s, 1 H, O-CH-O); 5.10 and 4.90 (pent, 2 H, $J_{\text{CH},\text{CH}2} = 1.6$, H-1'); 4.28 (m, 8 H, H-2', 2''); 2.10 (d, 3 H, $J_{\text{CH}3,\text{H}6} = 1.2$, CH₃). ^{13}C NMR (100.6 MHz, DMSO- d_6): 168.36 (C-4); 162.55 (C-2); 157.99 (C-6); 138.68; 138.60, 128.96; 128.84, 128.22 (2 C); 128.18 (2 C); 126.31 (2 C); 126.18 (2 C); 111.29 (C-5); 100.32 and 100.13 (O-CH-O); 68.54 and 68.38 (2 C, C-2', 2''); 68.17 and 67.88 (C-1'); 11.68 (CH₃).

2-(2-Phenyl-1,3-dioxan-5-yloxy)-5-methylpyrimidin-4(3H)-one (38c). Preparative TLC (hexane-ethyl acetate 7:3) afforded the product as colorless oil (1%). FABMS: 335.13 (MH^+) (45). ^1H NMR (500 MHz, DMSO- d_6): 8.16 (q, 1 H, $J_{\text{H}6,\text{CH}3} = 1.0$, H-6); 7.42–7.24 (m, 5 H, arom.); 5.69 (s, 1 H, O-CH-O); 4.37 (bt, 1 H, $J_{\text{CH},\text{CH}2} = 2.0$ H-1'); 4.32 and 4.25 (bd, 4 H, $J_{\text{gem}} = 12.6$, H-2', 2''); 1.80 (d, 3 H, $J_{\text{CH}3,\text{H}6} = 1.2$, CH₃). ^{13}C NMR (100.6 MHz, DMSO- d_6): 163.95 (C-4); 151.29 (C-2); 139.37 (C-6); 138.19; 129.28; 128.51 (2 C); 126.25 (2 C); 108.28 (C-5); 101.04 (O-CH-O); 69.12 (C-1'); 68.86 (2 C, C-2', 2''); 12.73 (CH₃).

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