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Design, synthesis, antiviral and cytostatic activity of ω-(1*H*-1,2,3-triazol-1-yl)(polyhydroxy)alkylphosphonates as acyclic nucleotide analogues

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ABSTRACT

The efficient synthesis of a new series of polyhydroxylated dibenzyl ω-(1*H*-1,2,3-triazol-1-yl)alkylphosphonates as acyclic nucleotide analogues is described starting from dibenzyl ω-azido-(polyhydroxy)alkylphosphonates and selected alkynes under microwave irradiation. Selected *O*,*O*-dibenzylphosphonate acyclonucleotides were transformed into the respective phosphonic acids. All compounds were evaluated in vitro for activity against a broad variety of DNA and RNA viruses and for cytostatic activity against murine leukemia L1210, human T-lymphocyte CEM and human cervix carcinoma HeLa cells. Compound (1*S*,2*S*)-**16b** exhibited antiviral activity against Influenza A H3N2 subtype (EC_{50} = 20 μM—visual CPE score; EC_{50} = 18 μM—MTS method; MCC >100 μM, CC_{50} >100 μM) in Madin Darby canine kidney cell cultures (MDCK), and (1*S*,2*S*)-**16k** was active against vesicular stomatitis virus and respiratory syncytial virus in HeLa cells (EC_{50} = 9 and 12 μM, respectively). Moreover, compound (1*R*,2*S*)-**16l** showed activity against both herpes simplex viruses (HSV-1, HSV-2) in HEL cell cultures (EC_{50} = 2.9 and 4 μM, respectively) and feline herpes virus in CRFK cells (EC_{50} = 4 μM) but at the same time it exhibited cytotoxicity toward uninfected cell (MCC ⩾ 4 μM). Several other compounds have been found to inhibit proliferation of L1210, CEM as well as HeLa cells with IC_{50} in the 4–50 μM range. Among them compounds (1*S*,2*S*)- and (1*R*,2*S*)-**16l** were the most active (IC_{50} in the 4–7 μM range).

1. Introduction

Infectious diseases caused by different microorganisms such as bacteria, fungi and viruses, are still a problem of human civilization. Among all pathogenic microorganisms viruses are notorious, the most active and probably the most dangerous because they penetrate into cells, evolve rapidly and interfere with the genetic material of the host. Despite current achievements in the development of antiviral drugs,[1,2] there is still a need for new compounds with an unique mechanism of action and limited side-effects.

The successful search for acyclic nucleoside analogues started when acyclovir [9-(2-hydroxyethoxymethyl)guanine] was described as an antiherpesvirus agent.[3] Soon after, a few other acyclic nucleoside or acyclic nucleoside phosphonate analogues became available as antiviral compounds, namely, ganciclovir, cidofovir, tenofovir, adefovir, etc.[4,5]

Attempts to improve the solubility of compounds in aqueous media resulted in synthesis of hydroxylated analogues of nucleosides such as ganciclovir as well as other nucleoside mimetics shown on Figure 1.[4,6–14] The interest in investigation of hydroxylated nucleosides has also been stimulated by a previous discovery of extreme potency of the naturally accessible D-eritadenine **2**,[7,8] which acts as an inhibitor of *S*-adenosyl-L-homocysteine hydrolase (SAHH). This enzyme has earlier been shown to be an attractive target for poxviruses, (−)RNA viruses such as paramyxovirus and rhabdovirus, and (±)RNA viruses such as reovirus.[15,16] Consequently, (2′*S*)-9-(2′,3′-dihydroxypropyl)adenine **3**[10] and other N(9)-substituted adenines and guanines possessing polyhydroxyalkyl chains have been obtained (Fig. 1).

Among various structural modifications of nucleosides/nucleotides 1,2,3-triazole analogues have been of special interest. The applicability of a 1,2,3-triazole ring as a replacement of sugar[17–19] or nucleobase moieties[17,19–21] as well as an additional linker between a phosphonoalkyl unit and a nucleobase has been widely explored[22–28] including our achievements.[29–35] Recently, several

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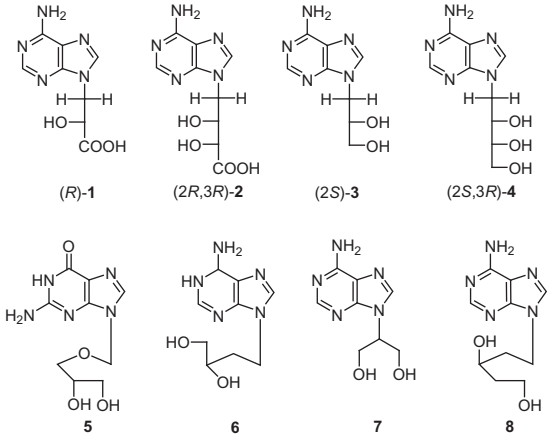


Figure 1. Examples of hydroxylated nucleoside analogues.

acyclic 1,2,3-triazolyl analogues of nucleosides/nucleotides with nucleobases attached via the methylene group at the C4 in the 1,2,3-triazole moiety have been obtained and some of them showed promising biological activity (Fig. 2). While (1,2,3-triazol-1-yl)nucleosides **9**–**11** were found to be inactive against selected viruses,[22,23] the phosphonomethyl-**12** ($n = 1$; B = Thy, Ade) and phosphonoethyl(1,2,3-triazoles) **12** ($n = 2$; R = Thy, Ura) showed moderate activity against hepatitis C virus (HCV).[25] Recently, we succeeded in the synthesis of 1-(3-phosphonopropyl)-1,2,3-triazole **13** substituted with benzoylbenzuracil via a methylene linker which exhibited activity against herpes simplex virus-1 (KOS), herpes simplex virus-2 (G) and feline herpes virus.[33] Moreover, the 1-(3-amino-3-phosphonopropyl)-1,2,3-triazole analogue (*R*)-**14** having 3-acetylindole as a modified nucleobase showed moderate activity toward vesicular stomatitis virus.[35]

In continuation of our research program towards 1,2,3-triazole nucleoside analogues,[14–21] and taking into account the known biological activity of hydroxylated nucleoside analogues as well as the antiviral activity of **13** and **14** and the cytostatic properties of **15**, 1,2,3-triazoles **16** and **17** possessing dibenzyloxyphosphono(polyhydroxy)alkyl residues have been designed (Fig. 3). We assumed that incorporation of additional hydroxyl groups into an alkyl side-chain would assure better solubility and perhaps improve biological activity of 1,2,3-triazoles **16** and **17** in comparison with

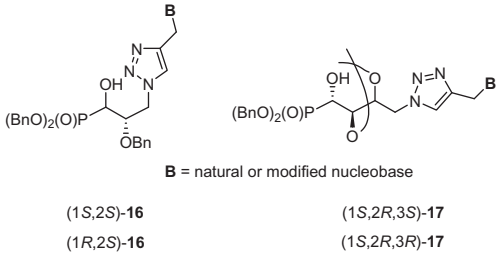


Figure 3. Structures of the designed nucleotide phosphonate analogues **16** and **17**.

analogous compounds having unfunctionalised aliphatic moieties.[33]

2. Results and discussion

2.1. Chemistry

Enantiomerically pure (1*R*,2*S*)- and (1*S*,2*S*)-azidophosphonates **18** were obtained from L-ascorbic acid,[36,37] whereas for the synthesis of (1*S*,2*R*,3*S*)- and (1*S*,2*R*,3*R*)-azidophosphonates **19**[38] tartaric acid and L-isoascorbic acid were used, respectively, as a source of chirality.

The 1,2,3-triazoles (1*R*,2*S*)- and (1*S*,2*S*)-**16** were synthesised by the 1,3-dipolar cycloaddition of the corresponding (1*R*,2*S*)- and (1*S*,2*S*)-azidophosphonates **18** with *N*-propargyl nucleobases **20** (N^9-propargyladenine **20a**,[23] N^1-propargylthymine **20b**,[23] N^1-propargyluracil **20c**,[39] N^4-acetyl-N^1-propargylcytosine **20d**[40]) and several propargylated nucleobase mimetics **20** (N^1-propargyl-6-azauracil **20e**,[41] 3-acetyl-*N*-propargylindole **20f**,[42] N^1-propargyltheobromine **20g**,[43,44] N^7-propargyltheophylline **20h**,[45] 8-chloro-N^7-propargyltheophylline **20i**,[46] *N*-propargyl-2-pyridone **20j**,[47] N^3-benzoyl-N^1-propargyluracil **20k**[33,48] and N^3-benzoyl-N^1-propargylquinazolin-2,4-dione **20l**[33]).

According to a standard protocol the regioselective formation of respective 1,4-disubstituted 1,2,3-triazoles was secured by the 1,3-dipolar cycloaddition of azides with terminal alkynes in the presence of a catalytic amount of Cu(I) at room temperature.[49,50] However, under these conditions more than 3 days were required to complete the reaction of (1*S*,2*S*)- and (1*R*,2*S*)-azidophosphonates **18** with *N*-propargyl nucleobases **20**. To accelerate the reaction

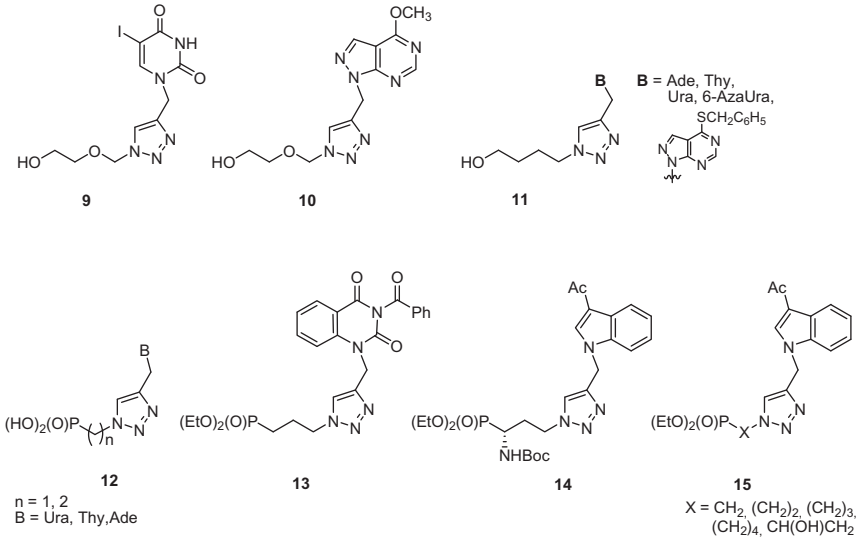
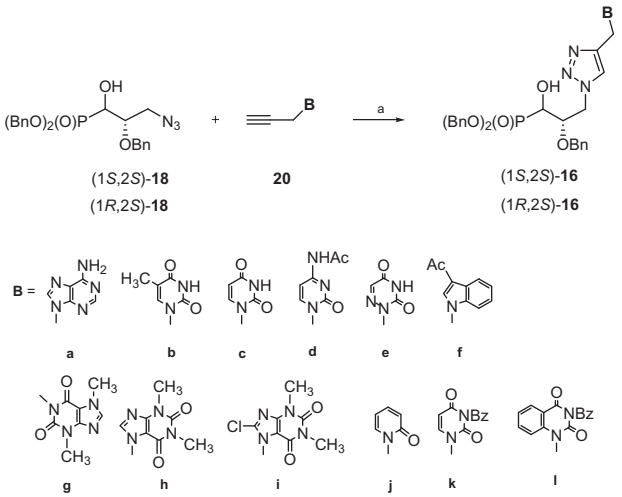


Figure 2. Examples of known 1,2,3-triazolyl analogues of nucleosides/nucleotides.



Scheme 1. Reagents and conditions: (a) $CuSO_4 \times 5H_2O$ (0.05 equiv), sodium ascorbate (0.1 equiv), H_2O·EtOH (1:1), MW, 40–45 °C, 20 min.

the 1,3-dipolar cycloaddition was performed under microwave irradiation. Under these conditions the full conversion of azidophosphonates **18** into 1,2,3-triazoles **16** was observed at 40–45 °C within 20 min (Scheme 1).

In a similar way, employing (1*S*,2*R*,3*S*)- and (1*S*,2*R*,3*R*)-azidophosphonates **19** the corresponding 1,2,3-triazoles (1*S*,2*R*,3*S*)- and (1*S*,2*R*,3*R*)-**17** were successfully obtained (Scheme 2).

The compounds (1*R*,2*S*)- and (1*S*,2*S*)-**16** as well as (1*S*,2*R*,3*S*)- and (1*S*,2*R*,3*R*)-**17** were obtained in good yields after purification by column chromatography on silica gel.

Selected dibenzyl phosphonates (1*S*,2*S*)-**16** were subjected to hydrogenation in the presence of 10% Pd–C in aqueous methanol[37] to give the respective phosphonic acids **21** in good yields (Scheme 3).

Structures of all new compounds were confirmed on the basis of ^1H, ^{13}C, ^{31}P NMR and IR spectra data as well as by elemental analysis.

2.2. Antiviral activity and cytotoxicity evaluation

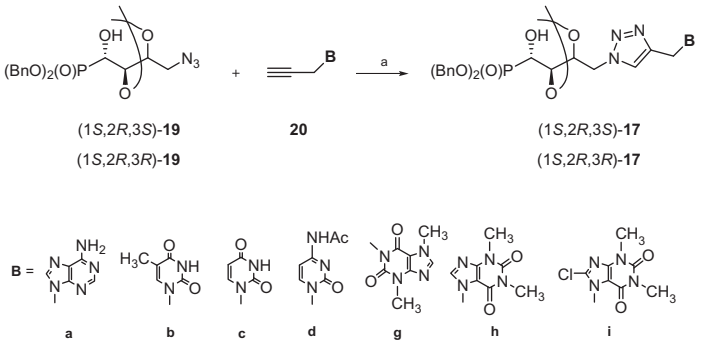
All the synthesised phosphonates (1*R*,2*S*)- and (1*S*,2*S*)-**16** and (1*S*,2*R*,3*S*)- and (1*S*,2*R*,3*R*)-**17** as well as the phosphonic acids (1*S*,2*S*)-**21b** and (1*S*,2*S*)-**21k** were evaluated for their antiviral activities against a wide variety of DNA and RNA viruses, using the following cell-based assays: (a) human embryonic lung (HEL) cells: herpes simplex virus-1 (KOS), herpes simplex virus-2 (G), herpes simplex virus-1 (TK ACV^r KOS), vaccinia virus and vesicular stomatitis virus, cytomegalovirus (AD-169 strain and Davis strain), varicella-zoster virus (TK$^+$ VZV strain OKA and TK$^-$ VZV strain 07-1); (b) CEM cell cultures: human immunodeficiency virus [HIV-1 and HIV-2]; (c): Vero cell cultures: para-influenza-3 virus, reovirus-1, Sindbis virus, Coxsackie virus B4, Punta Toro virus; (d) HeLa cell cultures: vesicular stomatitis virus, Coxsackie virus B4 and respiratory syncytial virus (RSV); (e) Crandell-Rees Feline Kidney (CRFK) cell cultures: feline corona virus (FIPV) and feline herpes virus (FHV); (f) Madin Darby Canine Kidney (MDCK) cell cultures: influenza A virus H1N1 subtype (A/PR/8), influenza A virus H3N2 subtype (A/HK/7/87) and influenza B virus (B/HK/5/72). Ganciclovir, cidofovir, acyclovir, brivudin, (*S*)-9-(2,3-dihydroxypropyl)adenine [(*S*)-DHPA], *Hippeastrum* hybrid agglutinin (HHA), *Urtica dioica* agglutinin (UDA), dextran sulfate (molecular weight 5000, DS-5000), ribavirin, oseltamivir carboxylate, amantadine and rimantadine were used as the reference compounds. The antiviral activity was expressed as the EC_{50}: the compound concentration required to reduce virus plaque formation (VZV) by 50% or to reduce virus-induced cytopathogenicity by 50% (other viruses).

The cytotoxicity of the tested compounds toward the uninfected host cells was defined as the minimum cytotoxic concentration (MCC) that causes a microscopically detectable alteration of normal cell morphology. The 50% cytotoxic concentration (CC_{50}), causing a 50% decrease in cell viability was determined using a colorimetric 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2*H*-tetrazolium (MTS) assay system.

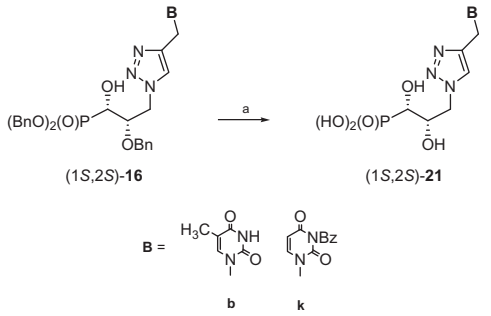
It was established that compound (1*S*,2*S*)-**16b** containing a 1,2,3-triazole moiety substituted at C4′ with thymine exhibited antiviral activity against Influenza A H3N2 subtype (EC_{50} = 20 μM by visual CPE score; EC_{50} = 18 μM by MTS score; MCC >100 μM, CC_{50} >100 μM) in Madin Darby canine kidney cells (MDCK). On the other hand, compound (1*S*,2*S*)-**16k** with N^3-benzoyluracil showed antiviral activity against vesicular stomatitis virus (EC_{50} = 9 μM) and respiratory syncytial virus (EC_{50} = 12 μM) in HeLa cells which favourably compares with the data for ribavirin (EC_{50} = 17 and 5 μM, respectively). Moreover, compound (1*R*,2*S*)-**16l** containing the N^3-benzoylbenzuracil moiety showed activity against both herpes simplex viruses (HSV-1, HSV-2) in HEL cell cultures (EC_{50} = 2.9 and 4 μM, respectively) and feline herpes virus in CRFK cells (EC_{50} = 4 μM) but at the same time it exhibited cytotoxicity toward uninfected cell cultures (MCC ⩾ 4 μM). Moreover, compound (1*S*,2*S*)-**16e** was slightly active against both TK$^+$ VZV and TK VZV strains (EC_{50} = 63.7 and 70 μM, respectively), whereas (1*S*,2*R*,3*R*)-**17i** showed activity against the TK$^+$ VZV strain only (EC_{50} = 55.7 μM).

2.3. Evaluation of cytostatic activity

The cytostatic activity of the tested compounds was defined as the 50% cytostatic inhibitory concentration (IC_{50}), causing a 50% decrease in cell proliferation and was determined against murine



Scheme 2. Reagents and conditions: (a) $CuSO_4 \times 5H_2O$ (0.05 equiv), sodium ascorbate (0.1 equiv), H_2O·EtOH (1:1), MW, 40–45 °C, 20 min.



Scheme 3. Reagents and conditions: (a) H_2, 10% Pd–C, MeOH·H_2O, 24 h.

leukaemia L1210, human lymphocyte CEM and human cervix carcinoma HeLa cells.

The inhibitory effect of the series of dibenzyl (1*H*-1,2,3-triazol-1-yl)alkylphosphonates against the proliferation of murine leukemia (L1210), human T-lymphocyte (CEM) and human cervix carcinoma cells (HeLa) are shown in Table 1. Several compounds were endowed with a cytostatic activity at compound concentrations below 50 μM [i.e., (1*S*,2*S*)-**16i–l** and (1*R*,2*S*)-**16f–l**] toward tested tumor cell lines, namely, L1210,CEM and HeLa. Among all tested compounds, 1,2-dihydroxypropylphosphonates (1*S*,2*S*)- and (1*R*,2*S*)-**16l**, both having N^3-benzoylbenzuracil as a modified nucleobase, were the most potent and showed cytostatic activity between 4 and 7 μM toward the tested tumor cell lines (Table 1).

2.3.1. Structure–activity relationship studies

As far as cytostatic properties are considered, within a series of hydroxylated (1,2,3-triazol-1-yl)nucleotide analogues **16** and **17**, compounds **16** containing three-carbon phosphonoalkyl chain are more cytostatic toward the tested tumor cell lines when compared with four-carbon phosphonates **17** having the same nucleobases (**16a** vs **17a**, **16c** vs **17c**, **16d** vs **17d**, **16g** vs **17g**, **16i** vs **17i**). Moreover, the configurations at stereogenic centres have slight or negligible impact on the cytostatic properties of (1,2,3-triazol-1-yl)nucleotides [(1*S*,2*S*)-**16** vs (1*R*,2*S*)-**16** and (1*S*,2*R*,3*S*)-**17** vs (1*S*,2*R*,3*R*)-**17**)]. Among the series of 1,2-dihydroxypropylphosphonates **16**, both stereoisomers substituted with the N^3-benzoylbenzuracil moiety [(1*S*,2*S*)-**16l** and (1*R*,2*S*)-**16l**] were the most potent to inhibit the proliferation of L1210, CEM as well as HeLa cells, whereas their N^3-benzoyluracil counterparts (1*S*,2*S*)-**16k** and (1*R*,2*S*)-**16k** showed significantly lower inhibitory activity. The removal of the N^3-benzoyl group from uracil resulted in complete loss of activity for (1*S*,2*S*)-**16c** and further decrease in potency for (1*R*,2*S*)-**16c**. Functionalisation of the alkyl chains in the analogues equipped with the N^3-benzoylbenzuracil moiety significantly improved cytostatic activity of 1-hydroxy-2-benzyloxypropylphosphonates (1*S*,2*S*)-**16l** and (1*R*,2*S*)-**16l** when compared with the slightly active 1-hydroxypropyl- and 2-hydroxypropylphosphonates[33] and the inactive propylphosphonate **13**.[33] As could be expected highly polar phosphonic acid (1*S*,2*S*)-**21k** showed no cytostatic activity while much more lipophilic *O*,*O*-dibenzyl ester (1*S*,2*S*)-**16k** was moderately active.

Analogous structure–antiviral activity relationship studies on a series of (1,2,3-triazol-1-yl)nucleotide analogues **16** and **17** were performed. Thus, 1-hydroxy-2-benzyloxypropylphosphonate (1*R*,2*S*)-**16l**, which contains a N^3-benzoylbenzyuracil residue, showed promising antiviral activity against herpes simplex viruses (HSV-1, HSV-2) in HEL cell cultures (EC_{50} = 2.9 and 4 μM, respectively) and feline herpes virus in CRFK cells (EC_{50} = 4 μM), whereas its N^3-benzoyluracil and uracil analogues (1*R*,2*S*)-**16k** and (1*R*,2*S*)-**16c**, respectively, appeared inactive. This trend well correlates with our previous observations on structurally analogous (1,2,3-triazol-1-yl)nucleotides having an unsubstituted phosphonopropyl chain, since compound **13** was the most active against HSV-1, HSV-2 (EC_{50} = 17 μM) and against feline herpes virus (EC_{50} = 24 μM).[33] Furthermore, the stereochemistry of the aliphatic chain substituted with hydroxyl groups is essential for activity since analogue (1*S*,2*S*)-**16l** showed no activity. On the other hand, the significant activity toward vesicular stomatitis virus and respiratory syncytial virus in HeLa cell cultures was observed for compound (1*S*,2*S*)-**16k** containing an N^3-benzoyluracil unit (EC_{50} = 9 and 12 μM, respectively) since analogous compounds (1*S*,2*S*)-**16l** (B = N^3-benzoylbenzuracil) and (1*S*,2*S*)-**16c** (B = uracil) were inactive against these viruses. Again, stereochemistry of an aliphatic fragment appeared important and resulted in lack of activity for (1*R*,2*S*)-**16k**.

Table 1
Inhibitory effect of tested compounds against the proliferation of murine leukemia (L1210), human T-lymphocyte (CEM) and human cervix carcinoma cells (HeLa)

Compound	Nucleobase (B)	IC_{50}[a] (μM)		
		CEM	L1210	HeLa
(1*S*,2*S*)-**16a**	Adenine	78 ± 15	66 ± 6.4	81 ± 21
(1*S*,2*S*)-**16b**	Thymine	>200	>200	>200
(1*S*,2*S*)-**16c**	Uracil	>200	>200	>200
(1*S*,2*S*)-**16d**	N^4-Acetylcytosine	169 ± 9.9	153 ± 35	>200
(1*S*,2*S*)-**16e**	6-Azauracil	71 ± 11	78 ± 7.8	64 ± 18
(1*S*,2*S*)-**16f**	3-Acetylindole	>200	>200	>200
(1*S*,2*S*)-**16g**	Theobromine	82 ± 0.7	71 ± 8.5	78 ± 17
(1*S*,2*S*)-**16h**	Theophylline	71 ± 0.7	71 ± 9.2	79 ± 0.7
(1*S*,2*S*)-**16i**	8-Chlorotheophylline	27 ± 2.1	70 ± 42	>200
(1*S*,2*S*)-**16j**	2-Pyridon	90 ± 0.7	63 ± 22	45 ± 2.1
(1*S*,2*S*)-**16k**	N^3-Benzoyluracil	21 ± 2	26 ± 12	76 ± 21
(1*S*,2*S*)-**16l**	N^3-Benzoylbenzuracil	4.7 ± 0.6	4.1 ± 1.8	7.1 ± 4.3
(1*S*,2*S*)-**21b**	Thymine	>200	>200	>200
(1*S*,2*S*)-**21k**	N^3-Benzoyluracil	>200	>200	>200
(1*R*,2*S*)-**16a**	Adenine	76 ± 11	46 ± 40	80 ± 6.4
(1*R*,2*S*)-**16b**	Thymine	83 ± 2.8	85 ± 9.9	64 ± 25
(1*R*,2*S*)-**16c**	Uracil	91 ± 6.4	86 ± 18	66 ± 12
(1*R*,2*S*)-**16d**	N^4-Acetylcytosine	82 ± 3.5	96 ± 11	160 ± 57
(1*R*,2*S*)-**16e**	6-Azauracil	81 ± 2.8	71 ± 13	122 ± 35
(1*R*,2*S*)-**16f**	3-Acetylindole	16 ± 3.5	15 ± 4.2	13 ± 2.8
(1*R*,2*S*)-**16g**	Theobromine	68 ± 6.4	58 ± 15	76 ± 9.2
(1*R*,2*S*)-**16h**	Theophylline	72 ± 9.9	56 ± 13	83 ± 9.9
(1*R*,2*S*)-**16i**	8-Chlorotheophylline	25 ± 1.4	22 ± 0.7	86 ± 4.2
(1*R*,2*S*)-**16j**	2-Pyridon	101 ± 6.4	76 ± 2.8	28 ± 19
(1*R*,2*S*)-**16k**	N^3-Benzoyluracil	21 ± 1	21 ± 1	57 ± 33
(1*R*,2*S*)-**16l**	N^3-Benzoylbenzuracil	4.7 ± 0.1	4.7 ± 0.3	5.1 ± 3.2
(1*S*,2*R*,3*S*)-**17a**	Adenine	>200	>200	>200
(1*S*,2*R*,3*S*)-**17b**	Thymine	>200	139 ± 46	107 ± 37
(1*S*,2*R*,3*S*)-**17c**	Uracil	>200	>200	118 ± 16
(1*S*,2*R*,3*S*)-**17d**	N^4-Acetylcytosine	>200	>200	>200
(1*S*,2*R*,3*S*)-**17g**	Theobromine	142 ± 40	145 ± 0	>200
(1*S*,2*R*,3*S*)-**17i**	8-Chlorotheophylline	>200	>200	>200
(1*S*,2*R*,3*R*)-**17a**	Adenine	140 ± 49	98 ± 3.5	⩾167
(1*S*,2*R*,3*R*)-**17b**	Thymine	>200	122 ± 21	⩾200
(1*S*,2*R*,3*R*)-**17c**	Uracil	>200	>200	>200
(1*S*,2*R*,3*R*)-**17d**	N^4-Acetylcytosine	>200	>200	>200
(1*S*,2*R*,3*R*)-**17g**	Theobromine	115 ± 4.2	86 ± 2.1	>200
(1*S*,2*R*,3*R*)-**17h**	Theophylline	>200	>200	>200
(1*S*,2*R*,3*R*)-**17i**	8-Chlorotheophylline	51 ± 1.4	58 ± 9.9	85 ± 3.5
5-Fluorouracil		18 ± 5	0.33 ± 0.17	0.54 ± 0.12

[a] 50% Inhibitory concentration or compound concentration required to inhibit tumor cell proliferation by 50%.

3. Conclusions

Dibenzyl ω-(1*H*-1,2,3-triazol-1-yl)alkylphosphonates (1*S*,2*S*)- and (1*R*,2*S*)-**16** as well as (1*S*,2*R*,3*S*)-**17** and (1*S*,2*R*,3*R*)-**17** were efficiently synthesised as acyclic nucleotide analogues. The phosphonic acids (1*S*,2*S*)-**21b** and (1*S*,2*S*)-**21k** were synthesised from *O*,*O*-dibenzylphosphonate acyclonucleotides (1*S*,2*S*)-**16b** and (1*S*,2*S*)-**16k** by hydrogenolysis. All synthesised esters and acids

were tested in vitro for activity against a broad variety of DNA and RNA viruses and for cytostatic activity against murine leukemia L1210, human T-lymphocyte CEM and human cervix carcinoma HeLa cells. Antiviral activity against Influenza A H3N2 subtype (EC_{50} = 20 μM—visual CPE score; EC_{50} = 18 μM—MTS; MCC >100 μM, CC_{50} >100 μM) in Madin Darby canine kidney cell cultures (MDCK) has been observed for phosphonate (1*S*,2*S*)-**16b**, whereas (1*S*,2*S*)-**16k** was found active against vesicular stomatitis virus and respiratory syncytial virus in HeLa cell cultures (EC_{50} = 9 and 12 μM, respectively). Compounds (1*S*,2*S*)-**16i–l** and (1*R*,2*S*)-**16f–l** inhibited proliferation of L1210, CEM as well as HeLa cells with IC_{50}'s in the 4–50 μM range. Especially, (1*S*,2*S*)- and (1*R*,2*S*)-**16l** consistently inhibited tumor cell proliferation in the lower micromolar range (IC_{50} = 4–7 μM), irrespective of the nature of the tumor cell line.

4. Experimental section

^{1}H NMR were taken in $CDCl_3$ or CD_3OD on the following spectrometers: Varian Mercury-300 and Bruker Avance III (600 MHz) with TMS as an internal standard; chemical shifts δ in ppm with respect to TMS; coupling constants *J* in Hz. ^{13}C NMR spectra were recorded for $CDCl_3$,CD_3OD or DMSO-d_6 solutions on a Varian Mercury-300 and Bruker Avance III (600 MHz) spectrometer at 75.5 and 150.5 MHz, respectively. ^{31}P NMR spectra were taken in $CDCl_3$ or CD_3OD on Varian Mercury-300 and Bruker Avance III at 121.5 and 242 MHz.

IR spectral data were measured on an Infinity MI-60 FT-IR spectrometer. Melting points were determined on a Boetius apparatus and are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory of this Faculty on a Perkin Elmer PE 2400 CHNS analyzer. Polarimetric measurements were conducted on an Optical Activity PolAAr 3001 apparatus.

The following adsorbents were used: column chromatography, Merck silica gel 60 (70–230 mesh); analytical TLC, Merck TLC plastic sheets silica gel 60 F_{254}. TLC plates were developed in chloroformmethanol solvent systems. Visualization of the spots was effected with iodine vapours. All solvents were purified by methods described in the literature.

All microwave irradiation experiments were carried out in a microwave reactor Plazmartonika RM 800. The reaction carried out in 50 mL-glass vials.

4.1. General procedure for the preparation of 1,2,3-triazoles

To a solution of azidophosphonate (1.00 mmol) in EtOH (1 mL) and H_2O (1 mL) were added $CuSO_4 \times 5H_2O$ (0.05 mmol), sodium ascorbate (0.10 mmol) and alkynes (1.00 mmol). The suspension was microwave irradiated in the microwave reactor (Plazmatronika RM 800, 800 W) at 40–45 °C for 20 min. After cooling the solvent was removed by vacuum evaporation. The residue was suspended in chloroform (5 mL) and filtered through a layer of Celite. The solution was concentrated in vacuo and the crude product was purified on a silica gel column with chloroform–methanol mixtures (50:1, 20:1 or 10:1, v/v) to give the desired 1,2,3-triazoles.

4.2.1. (1*S*,2*S*)-Dibenzyl 3-{4-[(6-aminopurin-9-yl)methyl-1*H*-1,2,3-triazol-1-yl]}-2-benzyloxy-1-hydroxypropylphosphonate (1*S*,2*S*)-16a

Yield: 86%; white powder [chromatographed on a silica gel column with chloroform–methanol (50:1, 20:1, 10:1, v/v)]; $[\alpha]_D^{20}$ 25.6 (*c* 1.15 in DMSO); mp: <200 °C; IR (KBr): ν = 3389, 2984, 2872, 1643, 1604, 1245, 1025, 749, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.25 (s, 1H, HC5′), 7.86 (s, 1H), 7.64 (s, 1H), 7.30–7.22 (m, 10H, H_{aromat}), 7.19–7.11 (m, 3H, H_{aromat}), 7.06–6.98 (m, 2H, H_{aromat}), 6.16 (br s, 2H, NH_2), 5.37 (AB, *J* = 15.3 Hz, 1H, C*H*$_a$H$_b$-Ade), 5.32 (AB, *J* = 15.3 Hz, 1H, CH$_a$*H*$_b$-Ade), 5.03 (d, *J* = 7.8 Hz, 4H, 2×POCH$_2$Ph), 4.61 (dd, *J* = 14.1 Hz, *J* = 5.1 Hz, 1H, H-3a), 4.54 (d, *J* = 10.8 Hz, 1H, OC*H*$_a$H$_b$Ph), 4.47 (dd, *J* = 14.1 Hz, *J* = 7.2 Hz, 1H, H-3b), 4.25 (dddd, *J* = 7.8 Hz, *J* = 7.2 Hz, *J* = 5.1 Hz, *J* = 3.0 Hz, 1H, H-2), 4.15 (d, *J* = 10.8 Hz, 1H, OCH$_a$*H*$_b$Ph), 3.96 (dd, *J* = 11.1 Hz, *J* = 3.0 Hz, 1H, H-1), 2.16 (br s, 1H, OH); ^{13}C NMR (151 Hz, DMSO-d_6): δ = 156.4, 153.0, 149.8, 143.0, 141.0, 137.9, 137.1 (d, *J* = 6.2 Hz, C_{ipso}), 137.0 (d, *J* = 6.2 Hz, C_{ipso}), 129.3, 129.0, 128.9, 128.8, 128.7, 128.4, 128.3, 128.2, 128.1, 127.5, 125.1, 119.1, 78.7 (d, *J* = 3.3 Hz, C-2), 73.0, 68.0 (d, *J* = 6.5 Hz, POC), 67.8 (d, *J* = 162.2 Hz, PC), 67.3 (d, *J* = 6.5 Hz, POC), 50.9 (d, *J* = 10.0 Hz, C-3), 38.4; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 23.49 ppm. Anal. Calcd for $C_{32}H_{33}N_8O_5P$: C, 59.99; H, 5.19; N, 17.49. Found: C, 60.12; H, 5.19; N, 17.21.

4.2.2. (1*S*,2*S*)-Dibenzyl 2-benzyloxy-3-{4-[(5-methyl-2,4-dioxopyrimidin-1-yl)methyl]-1*H*-1,2,3-triazol-1-yl}-1-hydroxypropylphosphonate (1*S*,2*S*)-16b

Yield: 76%; white powder [chromatographed on a silica gel column with chloroform–methanol (50:1, 20:1, 10:1, v/v)]; $[\alpha]_D^{20}$ 11.8 (*c* 0.77 in $CHCl_3$); mp: 145–147 °C; IR (KBr): ν = 3290, 3031, 2827, 1682, 1604, 1220, 1023, 754, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.77 (br s, 1H, NH), 7.70 (s, 1H, HC5′), 7.33–7.27 (m, 11H, 10H$_{aromat}$, 1H, CH_3C=C*H*), 7.23–7.18 (m, 3H, H_{aromat}), 7.12–7.07 (m, 2H, H_{aromat}), 5.09–4.97 (m, 4H, 2×POCH$_2$Ph), 4.89 (AB, *J* = 14.4 Hz, 1H, C*H*$_a$H$_b$-Thy), 4.83 (AB, *J* = 14.4 Hz, 1H, CH$_a$*H*$_b$-Thy), 4.58 (d, *J* = 10.8 Hz, 1H, OC*H*$_a$H$_b$Ph), 4.57 (dd, *J* = 13.8 Hz, *J* = 5.7 Hz, 1H, H-3a), 4.49 (dd, *J* = 13.8 Hz, *J* = 7.5 Hz, 1H, H-3b), 4.32–4.24 (m, 1H, H-2), 4.19 (d, *J* = 10.8 Hz, 1H, OCH$_a$*H*$_b$Ph), 3.90 (dd, *J* = 12.0 Hz, *J* = 2.1 Hz, 1H, H-1), 3.80 (br s, 1H, OH), 1.83 (s, 3H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 164.5, 151.2, 141.9, 140.1, 136.9, 135.9 (d, *J* = 5.7 Hz, C_{ipso}), 135.8 (d, *J* = 5.7 Hz, C_{ipso}), 128.7, 128.6, 128.5, 128.3, 128.2, 128.2, 128.1, 127.9, 125.5, 111.3, 75.5, 73.9, 68.8 (d, *J* = 7.2 Hz, POC), 68.4 (d, *J* = 7.2 Hz, POC), 68.3 (d, *J* = 162.6 Hz, PC), 50.8 (d, *J* = 10.1 Hz, C-3), 43.0, 12.6; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 22.85 ppm. Anal. Calcd for $C_{32}H_{34}N_5O_7P$: C, 60.85; H, 5.43; N, 11.09. Found: C, 60.96; H, 5.20; N, 11.30.

4.2.3. (1*S*,2*S*)-Dibenzyl 2-benzyloxy-3-{4-[(3,4-dihydro-2,4-dioxopyrimidin-1-yl)methyl]-1*H*-1,2,3-triazol-1-yl}-1-hydroxypropylphosphonate (1*S*,2*S*)-16c

Yield: 74%; white solid [chromatographed on a silica gel column with chloroform–methanol (50:1, 20:1, 10:1, v/v) and appropriate fractions were crystallized from methanol diethyl ether mixture]; $[\alpha]_D^{20}$ 34.1 (*c* 1.50 in DMSO); mp: 178–180 °C; IR (KBr): ν = 3251, 2931, 2830, 1706, 1242, 1023, 750, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.43 (s, 1H, NH), 7.68 (s, 1H, HC5′), 7.40 (d, *J* = 8.1 Hz, 1H, *H*C=CH), 7.33–7.27 (m, 10H, H_{aromat}), 7.22–7.19 (m, 3H, H_{aromat}), 7.10–7.07 (m, 2H, H_{aromat}), 5.64 (d, *J* = 8.1 Hz, 1H, *H*C=CH), 5.10–5.01 (m, 4H, 2 × POCH$_2$Ph), 4.94 (AB, *J* = 14.1 Hz, 1H, C*H*$_a$H$_b$-Ura), 4.90 (AB, *J* = 14.1 Hz, 1H, CH$_a$*H*$_b$-Ura), 4.59 (d, *J* = 11.1 Hz, 1H, OC*H*$_a$H$_b$Ph), 4.57 (dd, *J* = 13.8 Hz, *J* = 5.1 Hz, 1H, H-3a), 4.48 (dd, *J* = 13.8 Hz, *J* = 6.6 Hz, 1H, H-3b), 4.30–4.23 (m, 1H, H-2), 4.19 (d, *J* = 11.1 Hz, 1H, OCH$_a$*H*$_b$Ph), 3.90 (brd, *J* = 8.1 Hz, 1H, H-1), 3.40 (br s, 1H, OH); ^{13}C NMR (151 MHz, DMSO-d_6): δ = 164.1 (s, C=O), 151.2 (s, C=O), 145.8, 142.8, 138.1, 137.2 (d, *J* = 6.2 Hz, C_{ipso}), 137.1 (d, *J* = 6.2 Hz, C_{ipso}), 128.9, 128.9, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 125.1, 101.7, 78.7 (d, *J* = 2.8 Hz, C-2), 73.0, 67.9 (d, *J* = 6.7 Hz, POC), 67.8 (d, *J* = 162.2 Hz, PC), 67.3 (d, *J* = 6.7 Hz, POC), 50.8 (d, *J* = 9.9 Hz, C-3), 42.8; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 22.98 ppm. Anal. Calcd for $C_{31}H_{32}N_5O_7P$: C, 60.29; H, 5.22; N, 11.34. Found: C, 60.06; H, 5.03; N, 11.37.

4.2.4. (1*S*,2*S*)-Dibenzyl 3-{4-[(N^4-acetylamino-2-oxopyrimidin-1-yl)methyl]-1*H*-1,2,3-triazol-1-yl}-2-benzyloxy-1-hydroxypropylphosphonate (1*S*,2*S*)-16d

Yield: 78%; white solid [crystallized from methanol–diethyl ether mixture]; $[\alpha]_D^{20}$ 0.8 (*c* 1.41 in $CHCl_3$); mp: 168–171 °C; IR (KBr): ν = 3276, 3033, 2837, 1720, 1660, 1220, 1025, 796, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 10.22 (br s, 1H, NH), 8.23 (s, 1H, HC5′), 7.82 (d, *J* = 7.5 Hz, 1H, *H*C═CH), 7.51 (d, *J* = 7.5 Hz, 1H, *H*C═CH), 7.32–7.22 (m, 10H, H_{aromat}), 7.18–7.07 (m, 5H, H_{aromat}), 5.18–4.97 (m, 6H, 2 × $POCH_2Ph$, CH_2-Cyt), 4.85–4.75 (m, 2H, H-3a, H-3b), 4.48 (d, *J* = 11.1 Hz, 1H, OCH_aH_bPh), 4.35–4.28 (m, 1H, H-2), 4.23 (d, *J* = 11.1 Hz, 1H, OCH_aH_bPh), 3.99 (dd, *J* = 12.0 Hz, *J* = 2.4 Hz, 1H, H-1), 3.47 (br s, 1H, OH), 2.14 (s, 3H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 171.4, 162.7, 155.6, 148.5, 141.4, 137.3, 136.1 (d, *J* = 5.4 Hz, C_{ipso}), 135.9 (d, *J* = 5.7 Hz, C_{ipso}), 128.7, 128.6, 128.2, 128.1, 128.0, 127.8, 127.7, 126.9, 97.1, 77.5, 73.6, 68.8 (d, *J* = 6.9 Hz, POC), 68.7 (d, *J* = 162.6 Hz, PC), 68.5 (d, *J* = 6.9 Hz, POC), 50.1 (d, *J* = 11.1 Hz), 44.9, 24.6; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 23.63 ppm. Anal. Calcd for $C_{33}H_{35}N_6O_7P$: C, 60.18; H, 5.36; N, 12.76. Found: C, 60.00; H, 5.13; N, 12.91.

4.2.5. (1*S*,2*S*)-Dibenzyl 2-benzyloxy-3-{4-[(3,5-dioxo-1,2,4-triazin-2-yl)methyl]-1*H*-1,2,3-triazol-1-yl}-1-hydroxypropylphosphonate (1*S*,2*S*)-16e

Yield: 93%; white powder [chromatographed on a silica gel column with chloroform–methanol (50:1, 20:1, 10:1, v/v)]; $[\alpha]_D^{20}$ 20.3 (*c* 1.15 in $CHCl_3$); mp: 68–70 °C; IR (KBr): ν = 3262, 3033, 2908, 1730, 1673, 1216, 1022, 769, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 11.07 (br s, 1H, NH), 7.67 (s, 1H, HC5′), 7.35–7.25 (m, 11H, 10H_{aromat}, 1H, *H*C═N), 7.21–7.14 (m, 3H, H_{aromat}), 7.07–7.03 (m, 2H, H_{aromat}), 5.13–5.07 (m, 6H, 2 × $POCH_2Ph$, CH_2), 4.57 (dd, *J* = 13.8 Hz, *J* = 6.0 Hz, 1H, H-3a), 4.52 (d, *J* = 10.5 Hz, 1H, OCH_aH_bPh), 4.50 (dd, *J* = 13.8 Hz, *J* = 8.1 Hz, 1H, H-3b), 4.33–4.26 (m, 1H, H-2), 4.12 (d, *J* = 10.5 Hz, 1H, OCH_aH_bPh), 3.92 (dd, *J* = 11.1 Hz, *J* = 2.1 Hz, 1H, H-1), 3.07 (br s, 1H, OH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 155.6, 149.5, 141.5, 136.9, 135.8 (d, *J* = 5.7 Hz, C_{ipso}), 135.6 (d, *J* = 5.7 Hz, C_{ipso}), 134.8, 128.6, 128.6, 128.3, 128.2, 128.1, 128.0, 127.9, 125.7, 77.5, 73.9, 68.9 (d, *J* = 7.2 Hz, POC), 68.4 (d, *J* = 7.2 Hz, POC), 68.3 (d, *J* = 162.6 Hz, PC), 50.7, 34.6; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 23.34 ppm. Anal. Calcd for $C_{30}H_{31}N_6O_7P$: C, 58.25; H, 5.05; N, 13.59. Found: C, 58.21; H, 4.82; N, 13.36.

4.2.6. (1*S*,2*S*)-Dibenzyl 3-{4-[(3-acetyl-1*H*-indol-1-yl)methyl]-1*H*-1,2,3-triazol-1-yl}-2-benzyloxy-1-hydroxypropylphosphonate (1*S*,2*S*)-16f

Yield: 82%; white powder [chromatographed on a silica gel column with chloroform–methanol (50:1, 20:1, 10:1, v/v)]; $[\alpha]_D^{20}$ 3.7 (*c* 1.08 in $CHCl_3$); mp: 163–165 °C; IR (KBr): ν = 3148, 3063, 3031, 2881, 1645, 1216, 1014, 739, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.83–8.34 (m, 1H), 7.79 (s, 1H, HC5′), 7.35–7.11 (m, 17H, H_{aromat}), 6.98–6.94 (m, 2H, H_{aromat}), 5.36 (s, 2H, CH_2), 5.06–4.95 (m, 5H, 2 × $POCH_2Ph$, OH), 4.53 (dd, *J* = 13.8 Hz, *J* = 4.8 Hz, 1H, H-3a), 4.48 (d, *J* = 10.8 Hz, 1H, OCH_aH_bPh), 3.80 (dd, *J* = 13.8 Hz, *J* = 7.5 Hz, 1H, H-3b), 4.93 (dddd, *J* = 8.1 Hz, *J* = 7.5 Hz, *J* = 4.8 Hz, *J* = 3.3 Hz, 1H, H-2), 4.06 (d, *J* = 10.8 Hz, 1H, OCH_aH_bPh), 3.87 (dd, *J* = 11.1 Hz, *J* = 3.3 Hz, 1H, H-1), 2.45 (s, 3H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 193.1, 142.8, 136.7, 136.4, 135.8 (d, *J* = 6.0 Hz, C_{ipso}), 135.6 (d, *J* = 6.0 Hz, C_{ipso}), 134.8, 128.6, 128.4, 128.2, 128.1, 128.0, 126.4, 123.7, 123.6, 122.8, 122.7, 117.5, 109.8, 77.4, 74.0, 68.7 (d, *J* = 7.0 Hz, POC), 68.4 (d, *J* = 7.0 Hz, POC), 68.3 (d, *J* = 162.0 Hz, PC), 51.0 (d, *J* = 11.1 Hz, C-3), 42.4, 27.7; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 22.74 ppm. Anal. Calcd for $C_{37}H_{37}N_4O_6P$: C, 66.86; H, 5.61; N, 8.43. Found: C, 67.02; H, 5.91; N, 8.27.

4.2.7. (1*S*,2*S*)-Dibenzyl 2-benzyloxy-3-{4-[(3,7-dimethyl-2,6-dioxopurin-1-yl)methyl]-1*H*-1,2,3-triazol-1-yl}-1-hydroxypropylphosphonate (1*S*,2*S*)-16g

Yield: 86%; yellow pale oil [chromatographed on a silica gel column with chloroform–methanol (50:1, 20:1, 10:1, v/v)]; $[\alpha]_D^{20}$ 10.8 (*c* 1.95 in $CHCl_3$); IR (film): = 3267, 3011, 2931, 2893, 1707, 1663, 1253, 1024, 753, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.60 (s, 1H, HC5′), 7.42 (s, 1H), 7.34–7.12 (m, 15H, H_{aromat}), 5.28 (s, 2H, CH_2), 5.09–4.96 (m, 4H, 2 × $POCH_2Ph$), 4.56 (dd, *J* = 13.8 Hz, *J* = 5.4 Hz, 1H, H-3a), 4.55 (d, *J* = 10.2 Hz, 1H, OCH_aH_bPh), 4.42 (dd, *J* = 13.8 Hz, *J* = 6.3 Hz, 1H, H-3b), 4.24–4.12 (m, 1H, H-2), 4.21 (d, *J* = 10.2 Hz, 1H, OCH_aH_bPh), 3.93 (s, 3H, CH_3), 3.87 (dd, *J* = 11.4 Hz, *J* = 2.4 Hz, 1H, H-1), 3.52 (s, 3H, CH_3), 2.93 (br s, 1H, OH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 154.6, 151.1, 148.6, 143.4, 141.8, 137.0, 135.9 (d, *J* = 6.0 Hz, C_{ipso}), 135.8 (d, *J* = 6.0 Hz, C_{ipso}), 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 124.9, 107.8, 77.5, 74.0, 68.5 (d, *J* = 7.2 Hz, POC), 68.4 (d, *J* = 162.0 Hz, PC), 68.2 (d, *J* = 7.2 Hz, POC), 50.5 (d, *J* = 12.3 Hz, C-3), 31.6, 33.7, 29.9; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 22.96 ppm. Anal. Calcd for $C_{34}H_{36}N_7O_7P$: C, 59.56; H, 5.29; N, 14.30. Found: C, 59.28; H, 5.42; N, 14.44.

4.2.8. (1*S*,2*S*)-Dibenzyl 2-benzyloxy-3-{4-[(1,3-dimethyl-2,6-dioxopurin-7-yl)methyl]-1*H*-1,2,3-triazol-1-yl}-1-hydroxypropylphosphonate (1*S*,2*S*)-16h

Yield: 95%; white powder [chromatographed on a silica gel column with chloroform–methanol (50:1, 20:1, 10:1, v/v)]; $[\alpha]_D^{20}$ 2.0 (*c* 0.95 in $CHCl_3$); mp: 167–169 °C; IR (KBr): ν = 3362, 3242, 3140, 2951, 2883, 1705, 1659, 1219, 1018, 745, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.78 (s, 1H, HC5′), 7.77 (s, 1H), 7.35–7.05 (m, 15H, H_{aromat}), 5.53 (AB, *J* = 15.0 Hz, 1H, CH_aH_b), 5.49 (AB, *J* = 15.0 Hz, 1H, CH_aH_b), 5.09–4.97 (m, 4H, 2 × $POCH_2Ph$), 4.56 (d, *J* = 10.8 Hz, 1H, OCH_aH_bPh), 4.55 (dd, *J* = 13.8 Hz, *J* = 5.4 Hz, 1H, H-3a), 4.46 (dd, *J* = 13.8 Hz, *J* = 6.6 Hz, 1H, H-3b), 4.27 (dddd, *J* = 8.4 Hz, *J* = 6.6 Hz, *J* = 5.4 Hz, *J* = 2.4 Hz, 1H, H-2), 4.19 (d, *J* = 10.8 Hz, 1H, OCH_aH_bPh), 3.84 (dd, *J* = 12.0 Hz, *J* = 2.4 Hz, 1H, H-1), 3.55 (s, 3H, CH_3), 3.35 (s, 3H, CH_3), 2.97 (br s, 1H, OH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 155.2, 151.4, 148.7, 141.9, 141.4, 138.8, 135.8 (d, *J* = 5.7 Hz, C_{ipso}), 135.7 (d, *J* = 5.7 Hz, C_{ipso}), 128.6, 128.6, 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 125.1, 106.4, 77.4 (d, *J* = 2.3 Hz, C-2), 74.0, 68.6 (d, *J* = 7.0 Hz, POC), 68.5 (d, *J* = 7.0 Hz, POC), 68.3 (d, *J* = 162.2 Hz, PC), 50.9 (d, *J* = 12.1 Hz, C-3), 41.5, 29.9, 28.1; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 22.86 ppm. Anal. Calcd for $C_{34}H_{36}N_7O_7P$: C, 59.56; H, 5.29; N, 14.30. Found: C, 59.71; H, 4.97; N, 14.15.

4.2.9. (1*S*,2*S*)-Dibenzyl 2-benzyloxy-3-{4-[(8-chloro-1,3-dimethyl-2,6-dioxopurin-7-yl)methyl]-1*H*-1,2,3-triazol-1-yl}-1-hydroxypropylphosphonate (1*S*,2*S*)-16i

Yield: 91%; white powder [chromatographed on a silica gel column with chloroform–methanol (50:1, 20:1, 10:1, v/v)]; $[\alpha]_D^{20}$ 3.8 (*c* 1.05 in $CHCl_3$); mp: 163–165 °C; IR (KBr): ν = 3302, 3011, 2953, 2893, 1706, 1668, 1216, 1045, 753, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.74 (s, 1H, HC5′), 7.34–7.06 (m, 15H, H_{aromat}), 5.58 (AB, *J* = 15.3 Hz, 1H, CH_aH_b), 5.57 (AB, *J* = 15.3 Hz, 1H, CH_aH_b), 5.09–4.96 (m, 4H, 2×$POCH_2Ph$), 4.57 (d, *J* = 10.8 Hz, 1H, OCH_aH_b Ph), 4.55 (dd, *J* = 14.1 Hz, *J* = 5.7 Hz, 1H, H-3a), 4.45 (dd, *J* = 14.1 Hz, *J* = 7.5 Hz, 1H, H-3b), 4.32–4.24 (m, 1H, H-2), 4.17 (d, *J* = 10.8 Hz, 1H, OCH_aH_bPh), 3.84 (br d, *J* = 12.0 Hz, 1H, H-1), 3.51 (s, 3H, CH_3), 3.39 (s, 3H, CH_3), 2.80 (br s, 1H, OH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 154.2, 151.0, 147.0, 141.3, 138.8, 138.7, 135.6 (d, *J* = 5.7 Hz, C_{ipso}), 135.5 (d, *J* = 5.7 Hz, C_{ipso}), 128.4, 128.0, 127.9, 127.8, 127.7, 125.1, 107.2, 77.2 (s, C-2), 73.8; 68.6 (d, *J* = 7.1 Hz, POC), 68.4 (d, *J* = 7.1 Hz, POC), 68.0 (d, *J* = 163.4 Hz, PC), 50.8 (d, *J* = 10.6 Hz, C-3), 40.8, 29.8, 28.0; ^{31}P NMR (121.5 MHz,

$CDCl_3$): δ = 22.73 ppm. Anal. Calcd for $C_{34}H_{35}ClN_7O_7P$: C, 56.71; H, 4.90; N, 13.62. Found: C, 56.48; H, 5.12; N, 13.81.

4.2.10. (1*S*,2*S*)-Dibenzyl 2-benzyloxy-1-hydroxy-3-{4-[(2-oxopyridin-1-yl)methyl]-1*H*-1,2,3-triazol-1-yl}propylphosphonate (1*S*,2*S*)-16j

Yield: 96%; brown oil [chromatographed on a silica gel column with chloroform–methanol (50:1, 20:1, 10:1, v/v)]; $[\alpha]_D^{20}$ 9.2 (*c* 0.90 in $CHCl_3$); IR (film): ν = 3067, 3007, 2913, 2894, 1658, 1217, 1025, 754, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.72 (s, 1H, HC5′), 7.55 (dd, *J* = 6.3 Hz, *J* = 1.3 Hz, 1H, H_{aromat}), 7.35–7.09 (m, 16H, H_{aromat}), 7.52 (d, *J* = 9.0 Hz, 1H, H_{aromat}), 6.15 (dt, *J* = 8.1 Hz, *J* = 1.3 Hz, 1H, H_{aromat}), 5.14 (AB, *J* = 14.4 Hz, 1H, CH_aH_b), 5.13 (AB, *J* = 14.4 Hz, 1H, CH_aH_b), 5.09–4.98 (m, 4H, 2 × $POCH_2Ph$), 4.56 (dd, *J* = 13.8 Hz, *J* = 5.4 Hz, 1H, H-3a), 4.52 (d, *J* = 10.8 Hz, 1H, OCH_aH_bPh), 4.43 (dd, *J* = 13.8 Hz, *J* = 9.0 Hz, 1H, H-3b), 4.27 (ddd, *J* = 9.0 Hz, *J* = 5.4 Hz, *J* = 2.7 Hz, 1H, H-2), 4.20 (d, *J* = 10.8 Hz, 1H, OCH_aH_bPh), 3.84 (ddd, *J* = 11.4 Hz, *J* = 9.0 Hz, *J* = 2.7 Hz, 1H), 3.40 (dd, *J* = 9.0 Hz, *J* = 6.6 Hz, 1H, H-1); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 162.2, 142.3, 139.3, 137.7, 136.8, 135.8 (d, *J* = 5.7 Hz, C_{ipso}), 135.7 (d, *J* = 5.7 Hz, C_{ipso}), 128.5, 128.5, 128.4, 128.4, 128.2, 128.1, 128.0, 127.9, 125.4, 106.2, 77.3 (d, *J* = 4.9 Hz, C-2), 73.9, 68.4 (d, *J* = 7.2 Hz, POC), 68.1 (d, *J* = 162.9 Hz, PC), 68.0 (d, *J* = 7.2 Hz, POC), 50.5 (d, *J* = 11.4 Hz, C-3), 44.3; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 22.96 ppm. Anal. Calcd for $C_{32}H_{33}N_4O_6P$: C, 63.99; H, 5.54; N, 9.33. Found: C, 64.26; H, 5.81; N, 9.11.

4.2.11. (1*S*,2*S*)-Dibenzyl 2-benzyloxy-3-{4-[(3-benzoyl-2,4-dioxopyrimidin-1-yl)methyl]-1*H*-1,2,3-triazol-1-yl}-1-hydroxypropylphosphonate (1*S*,2*S*)-16k

Yield: 77%; white powder [chromatographed on a silica gel column with chloroform–methanol (50:1, 20:1, 10:1, v/v)]; $[\alpha]_D^{20}$ 16.4 (*c* 1.10 in $CHCl_3$); mp: 113–114 °C; IR (KBr): ν = 3418, 3088, 2924, 1748, 1704, 1663, 1235, 1021, 739, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.89–7.86 (m, 1H, H_{aromat}), 7.87 (d, *J* = 8.0 Hz, 1H, *H*C=CH), 7.63–7.55 (m, 2H, H_{aromat}), 7.58 (s, 1H, HC5′), 7.47–7.40 (m, 2H, H_{aromat}), 7.33–7.26 (m, 11H, H_{aromat}), 7.23–7.20 (m, 3H, H_{aromat}), 7.10–7.07 (m, 2H, H_{aromat}), 5.76 (d, *J* = 8.0 Hz, 1H, *H*C=CH), 5.08–5.00 (m, 4H, 2 × $POCH_2Ph$), 4.92 (s, 2H, CH_2), 4.57 (dd, *J* = 14.0 Hz, *J* = 5.2 Hz, 1H, H-3a), 4.58 (d, *J* = 10.9 Hz, 1H, OCH_aH_bPh), 4.45 (dd, *J* = 14.0 Hz, *J* = 7.2 Hz, 1H, H-3b), 4.28–4.20 (m, 1H, H-2), 4.19 (d, *J* = 10.9 Hz, 1H, OCH_aH_bPh), 3.88 (dd, *J* = 11.1 Hz, *J* = 3.2 Hz, 1H, H-1), 3.10 (br s, 1H, OH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 168.4 (s, C=O), 162.1 (s, C=O), 149.5 (s, C=O), 143.8, 136.5, 135.6 (d, *J* = 5.7 Hz, C_{ipso}), 135.5 (d, *J* = 5.7 Hz, C_{ipso}), 135.0, 131.2, 130,2, 129.0, 128.6, 128.5, 128.5, 128.3, 128.1, 128.0, 125.1, 102.3, 74.0, 68.6 (d, *J* = 7.0 Hz, POC), 68.3 (d, *J* = 7.0 Hz, POC), 68.2 (d, *J* = 161.9 Hz, PC), 50.7 (d, *J* = 10.4 Hz, C-3), 43.2;^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 22.20 ppm. Anal. Calcd for $C_{38}H_{36}N_5O_8P$: C, 63.24; H, 5.03; N, 9.70. Found: C, 62.97; H, 4.88; N, 10.02.

4.2.12. (1*S*,2*S*)-Dibenzyl 2-benzyloxy-3-{4-[(3-benzoyl-2,4-dioxoquinazolin-1-yl)methyl]-1*H*-1,2,3-triazol-1-yl}-1-hydroxypropylphosphonate (1*S*,2*S*)-16l

Yield: 82%; white solid [chromatographed on a silica gel column with chloroform–methanol (50:1, 20:1, 10:1, v/v)]; $[\alpha]_D^{20}$ −6.4 (*c* 3.85 in $CHCl_3$); mp: 136–138 °C; IR (KBr): ν = 3430, 3269, 3032, 2957, 2894, 1750, 1702, 1664, 1607, 1480, 1390, 1249, 755, 673 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.18 (dd, *J* = 7.9 Hz, *J* = 1.6 Hz, 1H), 7.95–7.91 (m, 2H, 2 × *o*-CH), 7.85 (br d, *J* = 8.4 Hz, 1H), 7.73 (ddd, *J* = 7.9 Hz, *J* = 7.0 Hz, *J* = 1.6 Hz, 1H), 7.66–7.60 (m, 1H, *p*-CH), 7.59 (s, 1H, *H*C5′), 7.49–7.43 (m, 2H, 2 × *m*-CH), 7.34–7.25 (m, 11H), 7.20–7.13 (m, 3H), 7.03–7.00 (m, 2H), 5.36 (AB, J_{AB} = 15.9 Hz, 1H, CH_aH_b), 5.34 (AB, J_{AB} = 15.9 Hz, 1H, CH_aH_b), 5.08–4.96 (m, 4H, 2 × $POCH_2Ph$), 4.54 (d, *J* = 10.9 Hz, 1H, OCH_aH_bPh), 4.53 (dd, *J* = 14.3 Hz, *J* = 5.3 Hz, 1H, H-3b), 4.40 (dd, *J* = 14.3 Hz, *J* = 7.4 Hz, 1H, H-3b), 4.14–4.06 (m, 1H, H-2), 4.12 (d, *J* = 10.9 Hz, 1H, OCH_aH_bPh), 3.86 (dd, *J* = 11.2 Hz, *J* = 2.9 Hz, 1H, H-1), 3.00 (br s, 1H, OH); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 168.6 (s, C=O); 161.1 (s, C=O); 149.5 (s, C=O); 142.4 (s, HC=C); 140.3; 136.7; 136.2; 135.9 (d, *J* = 5.6 Hz, C_{ipso}), 135.8 (d, *J* = 5.6 Hz, C_{ipso}), 135.1, 131.7, 130,5, 129.2, 128.9, 128.7, 128.7, 128.6, 128.4, 128.2, 128.2, 128.1, 125.1, 123.8, 115.6, 115.2, 77.0 (d, *J* = 1.3 Hz), 74.1, 68.6 (d, *J* = 7.2 Hz, POC), 68.4 (d, *J* = 161.9 Hz, PC), 68.3 (d, *J* = 7.2 Hz, POC), 50.9 (d, *J* = 11.7 Hz, C-3), 38.9; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 22.09 ppm. Anal. Calcd for $C_{42}H_{38}N_5O_8P$: C, 65.36; H, 4.96; N, 9.07. Found: C, 65.63; H, 5.18; N, 9.02.

4.2.13. (1*R*,2*S*)-Dibenzyl 3-{4-[(6-aminopurin-9-yl)methyl-1*H*-1,2,3-triazol-1-yl]}-2-benzyloxy-1-hydroxypropylphosphonate (1*R*,2*S*)-16a

Yield: 70%; white powder [chromatographed on a silica gel column with chloroform–methanol (50:1, 20:1, 10:1, v/v)]; $[\alpha]_D^{20}$ 20.0 (*c* 0.68 in DMSO); mp: 85–88 °C; IR (KBr): ν = 3408, 3289, 3115, 2924, 2888, 1668, 1600, 1244, 1020, 754, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.32 (s, 1H), 8.00 (s, 1H), 7.67 (s, 1H), 7.32–7.22 (m, 10H, H_{aromat}), 7.21–7.13 (m, 3H, H_{aromat}), 7.02–6.98 (m, 2H, H_{aromat}), 6.16 (br s, 2H, NH_2), 5.41 (s, 2H, CH_2-Ade), 5.09–4.96 (m, 4H, 2 × $POCH_2Ph$), 4.70 (dd, *J* = 14.7 Hz, *J* = 3.9 Hz, 1H, H-3a), 4.64 (dd, *J* = 14.7 Hz, *J* = 5.4 Hz, 1H, H-3b), 4.39 (AB, *J* = 11.4 Hz, 1H, OCH_aH_bPh), 4.27 (AB, *J* = 11.4 Hz, 1H, OCH_aH_bPh), 4.11 (dddd, *J* = 8.4 Hz, *J* = 6.0 Hz, *J* = 5.4 Hz, *J* = 3.9 Hz, 1H, H-2), 3.99 (dd, *J* = 8.4 Hz, *J* = 6.0 Hz, 1H, H-1), 2.06 (br s, 1H, OH); ^{13}C NMR (151 Hz, DMSO-d_6): δ = 156.5, 153.0, 149.8, 142.9; 141.0, 138.6, 137.8 (d, *J* = 6.4 Hz, C_{ipso}), 137.6 (d, *J* = 6.4 Hz, C_{ipso}), 129.3, 128.8, 128.6, 128.6, 128.5, 128.4, 128.2, 128.1, 127.9, 127.5, 125.1, 119.1, 78.7 (d, *J* = 10.8 Hz, C-3), 71.7; 68.0 (d, *J* = 4.7 Hz, POC), 67.3 (d, *J* = 4.7 Hz, POC), 67.1 (d, *J* = 161.8 Hz, PC), 40.6, 38.4; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 24.32 ppm. Anal. Calcd for $C_{32}H_{33}N_8O_5P \times H_2O$: C, 58.35; H, 5.36; N, 17.01. Found: C, 58.38; H, 5.14; N, 17.06.

4.2.14. (1*R*,2*S*)-Dibenzyl 2-benzyloxy-3-{4-[(5-methyl-2,4-dioxopyrimidin-1-yl)methyl]-1*H*-1,2,3-triazol-1-yl}-1-hydroxypropylphosphonate (1*R*,2*S*)-16b

Yield: 76%; white powder [chromatographed on a silica gel column with chloroform–methanol (50:1, 20:1, 10:1, v/v)]; $[\alpha]_D^{20}$ 5.3 (*c* 1.20 in $CHCl_3$); mp: 72–74 °C; IR (KBr): ν = 3277, 3061, 2927, 2855, 1680, 1216, 1012, 739, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 9.51 (s, 1H, NH), 7.79 (s, 1H, HC5′), 7.39–7.22 (m, 11H, 10 × H_{aromat}, 1H × CH_3C=C*H*), 7.22–7.17 (m, 3H, H_{aromat}), 7.09–7.05 (m, 2H, H_{aromat}), 5.02 (dd, *J* = 12.3 Hz, *J* = 8.1 Hz, 4H, 2 × $POCH_2Ph$), 4.91 (AB, *J* = 14.7 Hz, 1H, CH_aH_b-Thy), 4.86 (AB, *J* = 14.7 Hz, 1H, CH_aH_b-Thy), 4.79 (dd, *J* = 14.4 Hz, *J* = 3.0 Hz, 1H, H-3a), 4.58 (dd, *J* = 14.4 Hz, *J* = 6.3 Hz, 1H, H-3b), 4.50 (br s, 1H, OH), 4.38 (AB, *J* = 10.8 Hz, 1H, OCH_aH_bPh), 4.33 (AB, *J* = 10.8 Hz, 1H, OCH_aH_bPh), 4.15 (dddd, *J* = 8.1 Hz, *J* = 6.3 Hz, *J* = 6.0 Hz, *J* = 3.0 Hz, 1H, H-2), 4.20 (dd, *J* = 8.4 Hz, *J* = 6.0 Hz, 1H, H-1), 1.87 (s, 3H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 164.7, 151.2, 141.7, 140.3, 136.7, 135.9 (d, *J* = 7.5 Hz, C_{ipso}), 135.8 (d, *J* = 7.5 Hz, C_{ipso}), 128.6, 128.6, 128.5, 128.3, 128.2, 128.2, 128.1, 128.1, 128.0, 125.6, 111.2, 77.4, 72.6, 68.5 (d, *J* = 7.1 Hz, POC), 68.4 (d, *J* = 7.1 Hz, POC), 67.6 (d, *J* = 160.3 Hz, PC), 50.2 (d, *J* = 7.4 Hz), 43.0, 12.5; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 22.85 ppm. Anal. Calcd for $C_{32}H_{34}N_5O_7P$: C, 60.85; H, 5.43; N, 11.09. Found: C, 61.06; H, 5.23; N, 11.22.

4.2.15. (1*R*,2*S*)-Dibenzyl 2-benzyloxy-3-{4-[(2,4-dioxopyrimidin-1-yl)methyl]-1*H*-1,2,3-triazol-1-yl}-1-hydroxypropylphosphonate (1*R*,2*S*)-16c

Yield: 92%; white powder [chromatographed on a silica gel column with chloroform–methanol (50:1, 20:1, 10:1, v/v)]; $[\alpha]_D^{20}$ 6.3

(*c* 1.23 in $CHCl_3$); mp: 73–75 °C; IR (KBr): ν = 3241, 3033, 2891, 2826, 1680, 1214, 1029, 750, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 9.48 (s, 1H, NH), 7.76 (s, 1H, HC5′), 7.47 (d, *J* = 7.7 Hz, 1H, *HC*=CH), 7.31–7.23 (m, 10H, H_{aromat}), 7.22–7.18 (m, 3H, H_{aromat}), 7.10–7.05 (m, 2H, H_{aromat}), 5.66 (d, *J* = 7.7 Hz, 1H, *HC*=CH), 5.04 (dd, *J* = 11.4 Hz, *J* = 8.1 Hz, 4H, 2 × $POCH_2Ph$), 4.98 (AB, *J* = 14.4 Hz, 1H, C$H_a$$H_b$-Ura), 4.88 (AB, *J* = 14.4 Hz, 1H, CH_aH_b-Ura), 4.79 (dd, *J* = 14.4 Hz, *J* = 3.0 Hz, 1H, H-3a), 4.61 (dd, *J* = 14.4 Hz, *J* = 6.9 Hz, 1H, H-3b), 4.41 (d, *J* = 11.1 Hz, 1H, OC$H_a$$H_b$Ph), 4.33 (d, *J* = 11.1 Hz, 1H, OCH_aH_bPh), 4.41 (dddd, *J* = 8.7 Hz, *J* = 6.9 Hz, *J* = 6.0 Hz, *J* = 3.0 Hz, 1H, H-2), 4.00 (dd, *J* = 8.7 Hz, *J* = 6.0 Hz, 1H, H-1), 1.88 (br s, 1H, OH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 164.2 (s, C=O), 151.1 (s, C=O), 144.5, 141.5, 136.7, 135.9 (d, *J* = 6.6 Hz, C_{ipso}), 135.8 (d, *J* = 6.6 Hz, C_{ipso}), 128.8, 128.7, 128.6, 128.4, 128.3, 128.2, 128.2, 128.1, 125.7, 102.7, 77.4, 72.7, 68.7 (d, *J* = 7.0 Hz, POC), 68.7 (d, *J* = 7.0 Hz, POC), 67.5 (d, *J* = 147.4 Hz, PC), 50.3 (d, *J* = 7.4 Hz, C-3), 43.2; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 23.40 ppm. Anal. Calcd for $C_{31}H_{32}N_5O_7P$: C, 60.29; H, 5.22; N, 11.34. Found: C, 60.56; H, 5.14; N, 11.58.

4.2.16. (1*R*,2*S*)-Dibenzyl 3-{4-[(*N*^{4}-acetylamino-2-oxopyrimidin-1-yl)methyl]-1*H*-1,2,3-triazol-1-yl}-2-benzyloxy-1-hydroxypropylphosphonate (1*R*,2*S*)-16d

Yield: 75%; white powder [chromatographed on a silica gel column with chloroform–methanol (50:1, 20:1, 10:1, v/v)]; $[\alpha]_D^{20}$ +20.1 (*c* 0.96 in $CHCl_3$); mp: 82–84 °C; IR (KBr): ν = 3256, 3033, 2937, 2854, 1720, 1660, 1222, 1025, 744, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 10.96 (br s, 1H, NH), 8.88 (s, 1H, HC5′), 8.05 (d, *J* = 6.9 Hz, 1H, *HC*=CH), 7.44 (d, *J* = 6.9 Hz, 1H, *HC*=CH), 7.33–7.08 (m, 15H, H_{aromat}), 5.41 (d, *J* = 14.4 Hz, 1H, C$H_a$$H_b$-Cyt), 5.08–4.80 (m, 5H, 2 × $POCH_2Ph$, H-3a), 4.89 (d, *J* = 14.4 Hz, 1H, CH_aH_b-Cyt), 4.76 (dd, *J* = 14.4 Hz, *J* = 8.7 Hz, 1H, H-3b), 4.73 (AB, *J* = 10.8 Hz, 1H, OC$H_a$$H_b$Ph), 4.39 (AB, *J* = 10.8 Hz, 1H, OCH_aH_bPh), 4.10 (dddd, *J* = 9.3 Hz, *J* = 8.7 Hz, *J* = 3.3 Hz, *J* = 2.7 Hz, 1H, H-2), 3.93 (br d, *J* = 9.3 Hz, 1H, H-1), 3.07 (br s, 1H, OH), 2.18 (s, 3H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 171.4, 162.9, 155.6, 149.1, 141.3, 137.0, 136.0 (d, *J* = 5.4 Hz, C_{ipso}), 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.0, 97.0, 77.4, 72.3, 68.5 (d, *J* = 4.3 Hz, POC), 68.4 (d, *J* = 4.3 Hz, POC), 66.9 (d, *J* = 161.2 Hz, PC), 48.9, 44.6, 24.9; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 27.48 ppm. Anal. Calcd for $C_{33}H_{35}N_6O_7P$: C, 60.18; H, 5.36; N, 12.76. Found: C, 59.87; H, 5.44; N, 12.82.

4.2.17. (1*R*,2*S*)-Dibenzyl 2-benzyloxy-3-{4-[(3,5-dioxo-1,2,4-triazin-2-yl)methyl]-1*H*-1,2,3-triazol-1-yl}-1-hydroxypropylphosphonate (1*R*,2*S*)-16e

Yield: 91%; colorless oil [chromatographed on a silica gel column with chloroform–methanol (50:1, 20:1, 10:1, v/v)]; $[\alpha]_D^{20}$ 2.3 (*c* 1.42 in $CHCl_3$); IR (film): ν = 3242, 3033, 2907, 1730, 1673, 1241, 998, 740, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 11.41 (br s, 1H, NH), 7.68 (s, 1H, HC5'), 7.31 (s, 1H, HC=N), 7.29–7.21 (m, 10H, H_{aromat}), 7.20–7.16 (m, 3H, H_{aromat}), 7.09–7.03 (m, 2H, H_{aromat}), 5.13 (AB, *J* = 14.7 Hz, 1H, C$H_a$$H_b$), 5.10 (AB, *J* = 14.7 Hz, 1H, CH_aH_b), 5.06–4.98 (m, 4H, 2 × $POCH_2Ph$), 4.71 (dd, *J* = 14.4 Hz, *J* = 3.3 Hz, 1H, H-3a), 4.60 (dd, *J* = 14.4 Hz, *J* = 6.3 Hz, 1H, H-3b), 4.39 (d, *J* = 11.1 Hz, 1H, OC$H_a$$H_b$Ph), 4.27 (d, *J* = 11.1 Hz, 1H, OCH_aH_bPh), 4.14 (dddd, *J* = 9.3 Hz, *J* = 6.3 Hz, *J* = 6.3 Hz, *J* = 3.3 Hz, 1H, H-2), 4.01 (dd, *J* = 8.4 Hz, *J* = 6.3 Hz, 1H, H-1), 3.00 (br s, 1H, OH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 155.7, 149.3, 141.3, 136.8, 135.9 (d, *J* = 5.7 Hz, C_{ipso}), 135.8 (d, *J* = 5.7 Hz, C_{ipso}), 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 125.7, 77.4, 72.7, 68.7 (d, *J* = 6.9 Hz, POC), 68.5 (d, *J* = 6.9 Hz, POC), 67.7 (d, *J* = 162.9 Hz, PC), 50.4, 34.7; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 24.40 ppm. Anal. Calcd for $C_{30}H_{31}N_6O_7P$: C, 58.25; H, 5.05; N, 13.59. Found: C, 58.52; H, 5.08; N, 13.67.

4.2.18. (1*R*,2*S*)-Dibenzyl 3-{4-[(3-acetyl-1*H*-indol-1-yl)methyl]-1*H*-1,2,3-triazol-1-yl}-2-benzyloxy-1-hydroxypropylphosphonate (1*R*,2*S*)-16f

Yield: 91%; white powder [chromatographed on a silica gel column with chloroform–methanol (50:1, 20:1, 10:1, v/v)]; $[\alpha]_D^{20}$ +7.7 (*c* 1.09 in $CHCl_3$); mp: 133–135 °C; IR (KBr): ν = 3224, 3033, 2891, 1643, 1231, 1012, 749, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.40–8.36 (m, 1H), 7.81 (s, 1H, HC5′), 7.37–7.11 (m, 17H, H_{aromat}), 6.96–6.93 (m, 2H, H_{aromat}), 5.39 (s, 2H, CH_2), 5.30–4.96 (m, 4H, 2 × $POCH_2Ph$), 4.66 (dd, *J* = 14.5 Hz, *J* = 3.4 Hz, 1H, H-3a), 4.53 (dd, *J* = 14.5 Hz, *J* = 6.7 Hz, 1H, H-3b), 4.35 (d, *J* = 11.1 Hz, 1H, OC$H_a$$H_b$Ph), 4.14 (d, *J* = 11.1 Hz, 1H, OCH_aH_bPh), 4.12–4.06 (m, 2H, H-2, OH), 3.93 (dd, *J* = 8.9 Hz, *J* = 5.4 Hz, 1H, H-1), 2.47 (s, 3H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 193.2, 142.4, 136.6, 136.4, 135.7 (d, *J* = 5.7 Hz, C_{ipso}), 135.6 (d, *J* = 5.7 Hz, C_{ipso}), 135.0, 128.5, 128.3, 128.0, 127.9, 127.8, 126.4, 123.9, 123.5, 122.7, 122.6, 117.3, 109.8, 77.8, 72.0, 68.5 (d, *J* = 6.8 Hz, POC), 68.4 (d, *J* = 6.8 Hz, POC), 67.6 (d, *J* = 161.8 Hz, PC), 50.5, 42.3, 27.6; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 23.68 ppm. Anal. Calcd for $C_{37}H_{37}N_4O_6P$: C, 66.86; H, 5.61; N, 8.43. Found: C, 66.73; H, 5.49; N, 8.53.

4.2.19. (1*R*,2*S*)-Dibenzyl 2-benzyloxy-3-{4-[(3,7-dimethyl-2,6-dioxopurin-1-yl)methyl]-1*H*-1,2,3-triazol-1-yl}-1-hydroxypropylphosphonate (1*R*,2*S*)-16g

Yield: 80%; white powder [chromatographed on a silica gel column with chloroform–methanol (50:1, 20:1, 10:1, v/v)]; $[\alpha]_D^{20}$ +9.9 (*c* 0.91 in $CHCl_3$); mp: 72–74 °C; IR (KBr): = 3260, 3011, 2951, 2894, 1707, 1663, 1223, 1022, 753, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.61 (s, 1H, HC5′), 7.48 (s, 1H), 7.32–7.24 (m, 10H, H_{aromat}), 7.22–7.19 (m, 3H, H_{aromat}), 7.14–7.09 (m, 2H, H_{aromat}), 5.29 (s, 2H, CH_2), 5.02 (dd, *J* = 13.2 Hz, *J* = 8.4 Hz, 4H, 2 × $POCH_2Ph$), 4.67 (dd, *J* = 14.7 Hz, *J* = 3.6 Hz, 1H, H-3a), 4.58 (dd, *J* = 14.7 Hz, *J* = 6.3 Hz, 1H, H-3b), 4.40 (d, *J* = 11.1 Hz, 1H, OC$H_a$$H_b$Ph), 4.29 (d, *J* = 11.1 Hz, 1H, OCH_aH_bPh), 4.16 (dddd, *J* = 9.6 Hz, *J* = 6.6 Hz, *J* = 6.3 Hz, *J* = 3.6 Hz, 1H, H-2), 3.95 (dd, *J* = 9.6 Hz, *J* = 6.0 Hz, 1H, H-1), 3.94 (s, 3H, CH_3), 3.52 (s, 3H, CH_3), 1.93 (br s, 1H, OH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 154.6, 151.1, 148.8, 143.2, 141.6, 137.0, 136.0 (d, *J* = 6.0 Hz, C_{ipso}), 135.8 (d, *J* = 6.0 Hz, C_{ipso}), 128.6, 128.5, 128.3, 128.2, 128.1, 128.0, 127.8, 125.0, 107.5, 78.1 (d, *J* = 5.2 Hz, C-2), 72.8, 68.5 (d, *J* = 6.9 Hz, POC), 68.4 (d, *J* = 6.9 Hz, POC), 67.9 (d, *J* = 161.8 Hz, PC), 50.4 (d, *J* = 4.7 Hz, C-3), 36.1, 33.7, 29.8; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 24.09 ppm. Anal. Calcd for $C_{34}H_{36}N_7O_7P \times H_2O$: C, 58.03; H, 5.44; N, 13.93. Found: C, 58.35; H, 5.26; N, 13.87.

4.2.20. (1*R*,2*S*)-Dibenzyl 2-benzyloxy-3-{4-[(1,3-dimethyl-2,6-dioxopurin-7-yl)methyl]-1*H*-1,2,3-triazol-1-yl}-1-hydroxypropylphosphonate (1*R*,2*S*)-16h

Yield: 91%; colorless oil [chromatographed on a silica gel column with chloroform–methanol (50:1, 20:1, 10:1, v/v)]; $[\alpha]_D^{20}$ +2.8 (*c* 1.05 in $CHCl_3$); IR (film): ν = 3243, 2953, 2893, 1703, 1660, 1212, 998, 746, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.80 (s, 1H, HC5′), 7.47 (s, 1H), 7.35–7.25 (m, 10H, H_{aromat}), 7.23–7.15 (m, 3H, H_{aromat}), 7.06–7.02 (m, 2H, H_{aromat}), 5.52 (s, 2H, CH_2), 5.09–4.97 (m, 4H, 2 × $POCH_2Ph$), 4.70 (dd, *J* = 14.1 Hz, *J* = 3.3 Hz, 1H, H-3a), 4.61 (dd, *J* = 14.1 Hz, *J* = 6.6 Hz, 1H, H-3b), 4.44 (d, *J* = 11.4 Hz, 1H, OC$H_a$$H_b$Ph), 4.25 (d, *J* = 11.4 Hz, 1H, OCH_aH_bPh), 4.14 (dddd, *J* = 9.3 Hz, *J* = 6.6 Hz, *J* = 5.7 Hz, *J* = 3.3 Hz, 1H, H-2), 3.97 (dd, *J* = 8.4 Hz, *J* = 5.7 Hz, 1H, H-1); 3.60 (br s, 1H, OH), 3.54 (s, 3H, CH_3), 3.33 (s, 3H, CH_3), ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 155.2; 151.4; 148.7; 141.9; 141.4, 136.8, 135.8 (d, *J* = 5.4 Hz, C_{ipso}), 135.6 (d, *J* = 5.4 Hz, C_{ipso}), 128.6, 128.5, 128.4, 128.2, 128.0, 127.9, 127.8, 125.1, 106.4, 77.4 (s, C-2), 72.6, 68.6 (d, *J* = 7.0 Hz, POC), 68.4 (d, *J* = 7.0 Hz, POC), 67.4 (d, *J* = 147.2 Hz, PC), 50.4 (d, *J* = 6.0 Hz, C-3), 41.5, 29.9, 28.1; ^{31}P NMR (121.5 MHz, $CDCl_3$):

δ = 23.91 ppm. Anal. Calcd for $C_{34}H_{36}N_7O_7P$: C, 59.56; H, 5.29; N, 14.30. Found: C, 59.82; H, 5.13; N, 14.22.

4.2.21. (1*R*,2*S*)-Dibenzyl 2-benzyloxy-3-{4-[(8-chloro-1,3-dimethyl-2,6-dioxopurin-7-yl)methyl]-1*H*-1,2,3-triazol-1-yl}-1-hydroxypropylphosphonate (1R,2S)-16i

Yield: 85%; white powder [chromatographed on a silica gel column with chloroform–methanol (50:1, 20:1, 10:1, v/v)]; $[\alpha]_D^{20}$ +3.3 (*c* 1.35 in $CHCl_3$); mp: 69–71 °C; IR (KBr): ν = 32662, 3010, 2952, 2863, 1706, 1663, 1214, 994, 744, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.77 (s, 1H, HC5′), 7.34–7.25 (m, 10H, H_{aromat}), 7.24–7.14 (m, 3H, H_{aromat}), 7.07–7.01 (m, 2H, H_{aromat}), 5.58 (s, 2H, CH_2), 5.09–4.96 (m, 4H, 2 × $POCH_2Ph$), 4.70 (dd, *J* = 14.4 Hz, *J* = 3.3 Hz, 1H, H-3a), 4.59 (dd, *J* = 14.4 Hz, *J* = 6.6 Hz, 1H, H-3b), 4.40 (d, *J* = 11.1 Hz, 1H, OCH_aH_bPh), 4.24 (d, *J* = 11.1 Hz, 1H, OCH_aH_bPh), 4.19–4.09 (m, 1H, H-2), 3.97 (dd, *J* = 9.0 Hz, *J* = 6.0 Hz, 1H, H-1), 3.67 (br s, 1H, OH), 3.51 (s, 3H, CH_3), 3.32 (s, 3H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 154.2, 151.0, 147.0, 141.3, 138.8, 136.7, 135.6 (d, *J* = 6.0 Hz, C_{ipso}), 135.6 (d, *J* = 6.0 Hz, C_{ipso}), 128.6, 128.5, 128.2, 128.0, 127.9, 127.8, 127.7, 125.1, 107.2, 77.4 (s, C-2), 72.8, 68.5 (d, *J* = 6.0 Hz, POC), 68.4 (d, *J* = 6.0 Hz, POC), 67.8 (d, *J* = 161.4 Hz, PC), 50.8 (d, *J* = 5.9 Hz, C-3), 41.0, 29.8, 28.0; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 23.85 ppm. Anal. Calcd for $C_{34}H_{35}ClN_7O_7P$: C, 56.71; H, 4.90; N, 13.62. Found: C, 56.72; H, 4.72; N, 13.53.

4.2.22. (1*R*,2*S*)-Dibenzyl 2-benzyloxy-1-hydroxy-3-{4-[(2-oxopyridin-1-yl)methyl]-1*H*-1,2,3-triazol-1-yl}propylphosphonate (1*R*,2*S*)-16j

Yield: 81%; brown oil [chromatographed on a silica gel column with chloroform–methanol (50:1, 20:1, 10:1, v/v)]; $[\alpha]_D^{20}$ +4.5 (*c* 0.78 in $CHCl_3$); IR (film): ν = 3267, 3067, 2953, 2890, 1657, 1216, 1024, 751, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.77 (s, 1H, HC5′), 7.60–7.54 (m, 1H, H_{aromat}), 7.31–7.23 (m, 11H, H_{aromat}), 7.22–7.13 (m, 3H, H_{aromat}), 7.07–7.02 (m, 2H, H_{aromat}), 6.53–5.58 (m, 1H, H_{aromat}), 6.14 (dt, *J* = 6.9 Hz, *J* = 1.2 Hz, 1H, H_{aromat}), 5.17 (br s, 1H, OH), 5.12 (s, 2H, CH_2), 5.06–4.98 (m, 4H, 2×$POCH_2Ph$), 4.72 (dd, *J* = 14.4 Hz, *J* = 3.3 Hz, 1H, H-3a), 4.59 (dd, *J* = 14.4 Hz, *J* = 6.6 Hz, 1H, H-3b), 4.42 (d, *J* = 11.1 Hz, 1H, OCH_aH_bPh), 4.26 (d, *J* = 11.1 Hz, 1H, OCH_aH_bPh), 4.14 (dddd, *J* = 9.3 Hz, *J* = 6.6 Hz, *J* = 5.4 Hz, *J* = 3.3 Hz, 1H, H-2), 4.06–4.01 (m, 1H, H-1); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 162.2, 142.3, 139.9, 137.8, 136.0, 135.9 (d, *J* = 6.0 Hz, C_{ipso}), 135.8 (d, *J* = 6.0 Hz, C_{ipso}), 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 125.4, 106.2, 77.6 (s, C-2), 72.9, 68.5 (d, *J* = 6.9 Hz, POC), 68.4 (d, *J* = 6.9 Hz, POC), 67.7 (d, *J* = 162.3 Hz, PC), 50.4 (d, *J* = 6.9 Hz, C-3), 44.3; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 24.51 ppm. Anal. Calcd for $C_{32}H_{33}N_4O_6P$: C, 63.99; H, 5.54; N, 9.33. Found: C, 63.75; H, 5.33; N, 9.46.

4.2.23. (1*R*,2*S*)-Dibenzyl 2-benzyloxy-3-{4-[(3-benzoyl-2,4-dioxopyrimidin-1-yl)methyl]-1*H*-1,2,3-triazol-1-yl}-1-hydroxypropylphosphonate (1*R*,2*S*)-16k

Yield: 81%; colorless oil [chromatographed on a silica gel column with chloroform–methanol (50:1, 20:1, 10:1, v/v)]; $[\alpha]_D^{20}$ +3.4 (*c* 3.77 in $CHCl_3$); IR (film): ν = 3410, 3260, 2924, 2853, 1748, 1705, 1664, 1237, 740, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.90–7.86 (m, 2H), 7.68–7.56 (m, 3H), 7.47–7.42 (m, 2H, H_{aromat}), 7.33–7.26 (m, 11H, H_{aromat}), 7.24–7.18 (m, 2H, H_{aromat}), 7.08–7.05 (m, 2H, H_{aromat}), 5.78 (d, *J* = 7.7 Hz, 1H, *H*C=CH), 5.08–5.00 (m, 4H, 2 × $POCH_2Ph$), 4.96 (s, 2H, CH_2), 4.67–4.62 (m, 2H, H-3b, H-3a), 4.42 (AB, J_{AB} = 11.3 Hz, 1H, OCH_aH_bPh), 4.28 (AB, J_{AB} = 11.3 Hz, 1H, OCH_aH_bPh), 4.17–4.07 (m, 1H, H-2), 3.91 (dd, *J* = 8.7 Hz, *J* = 5.8 Hz, 1H, H-1), 1.80 (br s, 1H, OH); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 168.7 (s, C=O), 162.3 (s, C=O), 149.8 (s, C=O), 144.2, 136.7, 135.9 (d, *J* = 5.4 Hz, C_{ipso}), 135.8 (d, *J* = 5.4 Hz, C_{ipso}), 135.1, 131.5, 130,5, 129.2, 128.7, 128.7, 128.6, 128.5, 128.2, 128.2, 102.7, 75.5 (d, *J* = 4.4 Hz, C-2), 68.6 (d, *J* = 6.7 Hz, POC), 68.5 (d, *J* = 6.7 Hz, POC), 67.7 (d, *J* = 161.8 Hz, PC), 50.5 (d, *J* = 3.9 Hz, C-3), 43.1; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 23.31 ppm. Anal. Calcd for $C_{38}H_{36}N_5O_8P$: C, 63.24; H, 5.03; N, 9.70. Found: C, 63.17; H, 5.33; N, 9.57.

4.2.24. (1*R*,2*S*)-Dibenzyl 2-benzyloxy-3-{4-[(3-benzoyl-2,4-dioxoquinazolin-1-yl)methyl]-1*H*-1,2,3-triazol-1-yl}-1-hydroxypropylphosphonate (1*R*,2*S*)-16l

Yield: 88%; white solid [chromatographed on a silica gel column with chloroform–methanol (50:1, 20:1, 10:1, v/v)]; $[\alpha]_D^{20}$ +2.9 (*c* 2.34 in $CHCl_3$); mp: 145–147 °C; IR (KBr): ν = 3418, 3277, 2925, 2855, 1749, 1702, 1665, 1608, 1480, 1391, 1249, 754, 691 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.17 (dd, *J* = 8.0 Hz, *J* = 1.6 Hz, 1H), 7.95–7.91 (m, 2H, 2 × *o*-CH), 7.86 (br d, *J* = 8.5 Hz, 1H), 7.71 (ddd, *J* = 8.8 Hz, *J* = 7.3 Hz, *J* = 1.6 Hz, 1H), 7.61 (s, 1H, *H*C5′), 7.64–7.38 (m, 1H, *p*-CH), 7.47–7.41 (m, 2H, 2 × *m*-CH), 7.30–7.23 (m, 11H), 7.16–7.08 (m, 3H), 7.00–6.96 (m, 2H), 5.34 (s, 2H, CH_2), 5.00 (t, 4H, *J* = 8.3 Hz, 2 × $POCH_2Ph$), 4.67 (dd, *J* = 14.5 Hz, *J* = 3.1 Hz, 1H, H-3b), 4.54 (dd, *J* = 14.5 Hz, *J* = 6.9 Hz, 1H, H-3b), 4.37 (AB, J_{AB} = 11.2 Hz, 1H, OCH_aH_bPh), 4.17 (AB, J_{AB} = 11.2 Hz, 1H, OCH_aH_b Ph), 4.14–4.06 (m, 1H, H-2), 3.98 (dd, *J* = 8.9 Hz, *J* = 5.7 Hz, 1H, H-1), 1.85 (br s, 1H, OH); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 168.6 (s, C=O); 161.1 (s, C=O); 149.5 (s, C=O); 142.4 (s, HC=C); 140.3; 136.7; 136.2; 135.9 (d, *J* = 5.4 Hz, C_{ipso}), 135.8 (d, *J* = 5.4 Hz, C_{ipso}), 135.0, 131.7, 130.5, 129.2, 128.9, 128.7, 128.6, 128.4, 128.2, 128.1, 128.1, 125.3, 123.8, 115.6, 115.3, 77.6 (d, *J* = 4.8 Hz), 72.9, 68.5 (d, *J* = 6.8 Hz, POC), 68.4 (d, *J* = 6.8 Hz, POC), 68.0 (d, *J* = 161.4 Hz, PC), 50.4 (d, *J* = 6.0 Hz, C-3), 38.9; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 23.37 ppm. Anal. Calcd for $C_{42}H_{38}N_5O_8P$: C, 65.36; H, 4.96; N, 9.07. Found: C, 65.17; H, 5.18; N, 8.87.

4.2.25. (1*S*,2*R*,3*S*)-Dibenzyl 4-{[4-(6-amino-purin-9-yl)methyl]-1*H*-1,2,3-triazol-1-yl}-1,2,3-trihydroxy-2,3-*O*-isopropylidenebutylphosphonate (1*S*,2*R*,3*S*)-17a

Yield: 83%; white powder [chromatographed on a silica gel column with chloroform–methanol (50:1, 20:1, 10:1, v/v)]; $[\alpha]_D^{20}$ 21.7 (*c* 1.12 in DMSO); mp: 193–195 °C; IR (KBr): ν = 3233, 3187, 2957, 2925, 1646, 1216, 1047, 996, 777, 698 cm^{-1}; ^1H NMR (CD_3 OD, 600 MHz): δ = 8.25 (s, 1H, N=C*H*), 8.21 (s, 1H, *H*CN), 8.00 (s 1H, *H*C5′), 7.407.32 (m, 10H, 2xC_6H_5), 5.55 (s, 2H, HC=CCH_2), 5.185.08 (m, 4H, 2 × $POCH_2Ph$), 4.74 (dd, *J* = 14.5 Hz, *J* = 2.9 Hz, 1H, H-4b), 4.64 (dd, *J* = 14.5 Hz, *J* = 6.8 Hz, 1H, H-4b), 4.50 (dt, *J* = 6.8 Hz, *J* = 2.9 Hz, 1H, H-3), 4.17 (dd, *J* = 8.9 Hz, *J* = 5.7 Hz, 1H, H-1), 4.06 (dt, *J* = 6.8 Hz, *J* = 5.7 Hz, 1H, H-2), 1.32 (s, 3H, CH_3), 1.14 (s, 3H, CH_3); ^{13}C NMR (151 MHz, CD_3OD): δ = 156.4, 153.0, 149.8, 142.9, 141.1, 137.1 (d, *J* = 5.7 Hz, C_{ipso}), 137.0 (d, *J* = 5.5 Hz, C_{ipso}), 128.8, 128.6, 128.6, 128.2, 128.1, 125.1, 119.1, 110.1 (s, *C*$(CH_3)_2$), 77.5 (d, *J* = 8.5 Hz, C-3), 76.8 (d, *J* = 8.2 Hz, C-2), 67.9 (d, *J* = 162.7 Hz, C-1), 67.9 (d, *J* = 6.6 Hz, COP), 67.4 (d, *J* = 6.6 Hz, COP), 52.3 (s, C-4), 38.4 (s, HC=C—CH_2—N), 27.2 (s, CH_3), 27.2 (s, CH_3); ^{31}P NMR (CD_3OD, 242 MHz): δ = 22.57 ppm. Anal. Calcd for $C_{29}H_{33}N_8O_6P$: C, 56.13; H, 5.36; N, 18.06. Found: C, 55.87; H, 5.24; N, 17.85.

4.2.26. (1*S*,2*R*,3*S*)-Dibenzyl 4-{[4-(5-methyl-2,4-dioxopyrimidin-1-yl)methyl]-1*H*-1,2,3-triazol-1-yl}-1,2,3-trihydroxy-2,3-*O*-isopropylidenebutylphosphonate (1*S*,2*R*,3*S*)-17b

Yield: 83%; white powder [chromatographed on a silica gel column with chloroform–methanol (50:1, 20:1, 10:1, v/v)]; $[\alpha]_D^{20}$ 11.5 (*c* 1.12 in DMSO); mp: 194–195 °C; IR (KBr): ν = 3238, 3034, 2957, 2823, 1682, 1214, 1057, 745, 695 cm^{-1}; ^1H NMR ($CDCl_3$,

600 MHz): δ = 8.58 (br s, 1H, NH), 7.80 (s 1H, *H*C5′), 7.427.38 (m, 11H, 2 × C_6H_5, *H*C═C), 5.155.08 (m, 4H, 2 × POCH_2Ph), 4.96 (AB, J_{AB} = 15.0 Hz, 1H, CH_aH$_b$), 4.94 (AB, J_{AB} = 15.0 Hz, 1H, CH$_a$$H_b$), 4.75 (dd, *J* = 14.4 Hz, *J* = 2.6 Hz, 1H, H-4b), 4.58 (dd, *J* = 14.4 Hz, *J* = 6.4 Hz, 1H, H-4a), 4.50 (dt, *J* = 2.6 Hz, *J* = 6.4 Hz, 1H, H-3), 4.15 (dt, *J* = 7.6 Hz, *J* = 6.4 Hz, 1H, H-2), 4.05 (dt, *J* = 7.6 Hz, *J* = 5.3 Hz, 1H, H-1), 3.40 (dd, *J* = 12.6 Hz, *J* = 5.3 Hz, 1H), 1.95 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.22 (s, 3H, CH_3); ^{13}C NMR (151 MHz, DMSO-d_6): δ = 164.7 (s, C═O), 151.2 (s, C═O), 142.8 (s, HC═*C*—CH_3), 141.6, 137.1 (d, *J* = 5.6 Hz, C_{ipso}), 137.0 (d, *J* = 5.6 Hz, C_{ipso}), 128.9, 128.6, 128.6, 128.2, 128.1 (C_{aromat}), 125.1, 110.1 (s, *C*(CH_3)$_2$), 109.4 (s, HC═*C*CH_3), 77.4 (d, *J* = 8.0 Hz), 76.8 (d, *J* = 8.0 Hz), 68.0 (d, *J* = 6.7 Hz, POC), 67.9 (d, *J* = 162.7 Hz, PC), 67.5 (d, *J* = 6.7 Hz, POC), 52.3 (s, C-4), 42.6, 27.2, 12.4; ^{31}P NMR ($CDCl_3$, 242 MHz): δ = 21.48 ppm. Anal. Calcd for $C_{29}H_{34}N_5O_8P$: C, 56.95; H, 5.60; N, 11.45. Found: C, 56.92; H, 5.53; N, 11.28.

4.2.27. (1*S*,2*R*,3*S*)-Dibenzyl 4-{[4-(2,4-dioxopyrimidin-1-yl)methyl]-1*H*-1,2,3-triazol-1-yl}-1,2,3-trihydroxy-2,3-*O*-isopropylidenebutylphosphonate (1*S*,2*R*,3*S*)-17c

Yield: 85%; yellow pale powder [chromatographed on a silica gel column with chloroform–methanol (50:1, 20:1, 10:1, v/v)]; $[\alpha]_D^{20}$ 28.3 (*c* 1.07 in CH_3OH); mp: 157–159 °C; IR (KBr): ν = 3231, 3061, 2891, 2826, 1675, 1226, 1052, 996, 737, 696 cm^{-1}; ^{1}H NMR (CD_3OD, 600 MHz): δ = 7.95 (s 1H, *H*C5′), 7.70 (d, *J* = 7.9 Hz, 1H, HC═C*H*), 7.427.32 (m, 10H, 2 × C_6H_5), 5.68 (d, *J* = 7.6 Hz, 1H, *H*C═CH), 5.175.09 (m, 4H, 2 × POCH_2Ph), 5.06 (AB, J_{AB} = 15.3 Hz, 1H, CH_aH$_b$), 5.03 (AB, J_{AB} = 15.3 Hz, 1H, CH$_a$$H_b$), 4.76 (dd, *J* = 14.5 Hz, *J* = 2.9 Hz, 1H, H-4b), 4.65 (dd, *J* = 14.5 Hz, *J* = 6.3 Hz, 1H, H-4b), 4.52 (ddd, *J* = 7.2 Hz, *J* = 6.3 Hz, *J* = 2.9 Hz, 1H, H-3), 4.20 (dt, *J* = 8.8 Hz, *J* = 5.7 Hz, 1H, H-1), 4.10 (dt, *J* = 7.3 Hz, *J* = 5.7 Hz, 1H, H-2), 1.35 (s, 3H, CH_3), 1.24 (s, 3H, CH_3); ^{13}C NMR (151 MHz, CD_3OD): δ = 165.2 (s, C═O), 151.2 (s, C═O), 145.4 (s, N-CH═*C*H) 142.2, 136.3 (d, *J* = 5.6 Hz, C_{ipso}), 136.2 (d, *J* = 5.6 Hz, C_{ipso}), 128.2, 128.2, 128.2, 127.9, 127.8 (C_{aromat}), 125.1, 110.3 (s, *C*(CH_3)$_2$), 101.3 (s, N*C*H═CH), 77.0 (d, *J* = 8.4 Hz), 76.6 (d, *J* = 8.6 Hz), 68.5 (d, *J* = 7.3 Hz, COP), 68.2 (d, *J* = 7.3 Hz, COP), 67.9 (d, *J* = 165.3 Hz, C-1), 52.0 (s, C-4), 42.5 (s, HC═C—*C*H_2—N), 25.9 (s, CH_3), 25.7 (s, CH_3); ^{31}P NMR (CD_3OD, 242 MHz): δ = 22.60 ppm. Anal. Calcd for $C_{28}H_{32}N_5O_8P$: C, 56.28; H, 5.40; N, 11.72. Found: C, 56.42; H, 5.21; N, 11.70.

4.2.28. (1*S*,2*R*,3*S*)-Dibenzyl 4-{[4-(*N*^{4}-acetylamino-2-oxopyrimidin-1-yl)methyl]-1*H*-1,2,3-triazol-1-yl}-1,2,3-trihydroxy-2,3-*O*-isopropylidenebutylphosphonate (1*S*,2*R*,3*S*)-17d

Yield: 89%; white powder [chromatographed on a silica gel column with chloroform–methanol (50:1, 20:1, 10:1, v/v)]; $[\alpha]_D^{20}$ 18.7 (*c* 0.92 in DMSO); mp: 167–168 °C; IR (KBr): ν = 3395, 3306, 3136, 3065, 2999, 1714, 1672, 1223, 1059, 966, 797, 742 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 10.15 (br s, 1H, NH), 8.48 (s 1H, *H*C5′), 8.15 (d, *J* = 7.6 Hz, 1H, HC═C*H*), 7.51 (d, *J* = 7.6 Hz, *H*C═CH), 7.467.32 (m, 10H, 2 × C_6H_5), 6.64 (br s, 1H), 5.32–5.10 (m, 6H, 2 × $POCH_2Ph$, HC═CCH_2), 4.86 (dd, *J* = 14.1 Hz, *J* = 1,9 Hz, 1H, H-4b), 4.60 (dd, *J* = 14,1 Hz, *J* = 8.8 Hz, 1H, H-4a), 4.52 (dt, *J* = 8.8 Hz, *J* = 1.9 Hz, 1H, H-3), 4.184.11 (br m, 1H), 4.023.98 (m, 1H), 2.25 (s, 3H, NHC(O)CH_3), 1.45 (s, 3H, CH_3), 1.40 (s, 3H, CH_3); ^{13}C NMR (151 MHz, DMSO-d_6): δ = 171.4 (s, C═O), 163.0, 155.5 (s, C═O), 150.5, 142.4, 137.1 (d, *J* = 5.6 Hz, C_{ipso}), 137.0 (d, *J* = 5.6 Hz, C_{ipso}), 128.9, 128.6, 128.6, 128.2 (C_{aromat}), 125.4, 110.2 (s, *C*(CH_3)$_2$), 95.9, 77.5 (d, *J* = 8.3 Hz), 76.9 (d, *J* = 8.3 Hz), 68.0 (d, *J* = 6.5 Hz, POC), 67.9 (d, *J* = 162.6 Hz, CP), 67.5 (d, *J* = 6.5 Hz, POC), 52.3 (s, C-4), 44.9 (s, HC═C—*C*H_2—N), 27.3 (s, C-*C*H_3), 27.2 (s, C-*C*H_3), 24.8 (s,*C*H_3C(O)); ^{31}P NMR ($CDCl_3$, 242 MHz): δ = 23.14 ppm. Anal. Calcd for $C_{30}H_{35}N_6O_8P$: C, 56.42; H, 5.52; N, 13.16. Found: C, 56.62; H, 5.53; N, 12.97.

4.2.29. (1*S*,2*R*,3*S*)-Dibenzyl 4-{[4-(3,7-dimethyl-2,6-dioxopurin-1-yl)methyl]-1*H*-1,2,3-triazol-1-yl}-1,2,3-trihydroxy-2,3-*O*-isopropylidenebutylphosphonate (1*S*,2*R*,3*S*)-17g

Yield: 88%; white powder [chromatographed on a silica gel column with chloroform–methanol (50:1, 20:1, 10:1, v/v)]; $[\alpha]_D^{20}$ 9.3 (*c* 1.96 in $CHCl_3$); mp: 187–188 °C; IR (KBr): ν = 3275, 3012, 2998, 2965, 1708, 1663, 1218, 1023, 757, 693 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.70 (s 1H, *H*C5′), 7.48 (s, 1H, NC*H*═N), 7.407.25 (m, 10H, 2 × C_6H_5), 5.35 (AB, J_{AB} = 14.5 Hz, 1H, CH_aH$_b$), 5.33 (AB, J_{AB} = 14.5 Hz, 1H, CH$_a$$H_b$), 5.185.05 (m, 4H, 2 × POCH_2Ph), 4.69 (dd, *J* = 14.5 Hz, *J* = 2.9 Hz, 1H, H-4a), 4.60 (dd, *J* = 14.5 Hz, *J* = 5.8 Hz, 1H, H-4b), 4.50 (ddd, *J* = 7.6 Hz, *J* = 5.8 Hz, *J* = 2.9 Hz, 1H, H-3), 4.13 (dt, *J* = 10.6 Hz, *J* = 5.5 Hz, 1H, H-1), 4.05 (dt, *J* = 7.6 Hz, *J* = 5.5 Hz, 1H, H-2), 4.00 (s, 3H, NCH_3), 3.58 (s, 3H, NCH_3), 3.29 (dd, *J* = 12.9 Hz, *J* = 5.5 Hz, 1H), 1.36 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), ^{13}C NMR (151 MHz, $CDCl_3$): δ = 154.8 (s, C═O), 151.3 (s, C═O), 148.9, 143.3, 141.6, 136.0 (d, *J* = 5.3 Hz, C_{ipso}), 135.9 (d, *J* = 6.0 Hz, C_{ipso}), 128.6, 128.6, 128.5, 128.5, 128.2, 128.0 (C_{aromat}), 124.9, 110.3 (s, *C*(CH_3)$_2$), 107.7, 76.7 (d, *J* = 7.8 Hz), 76.6 (d, *J* = 3.9 Hz), 68.6 (d, *J* = 7.1 Hz, COP), 68.6 (d, *J* = 162.3 Hz, C-1), 68.5 (d, *J* = 7.1 Hz, COP), 51.9 (s, C-4), 35.9 (s, HC═C—*C*H_2), 35.9 (s, CH_3), 33.6 (s, CH_3), 29.7 (s, CH_3), 26.9 (s, CH_3), 26.8(s, CH_3); ^{31}P NMR ($CDCl_3$, 242 MHz): δ = 21.64 ppm. Anal. Calcd for $C_{31}H_{36}N_7O_8P$: C, 55.94; H, 5.45; N, 14.73. Found: C, 55.73; H, 5.43; N, 14.69.

4.2.30. (1*S*,2*R*,3*S*)-Dibenzyl 4-{[4-(8-chloro-1,3-dimethyl-2,6-dioxopurin-7-yl)methyl]-1*H*-1,2,3-triazol-1-yl}-1,2,3-trihydroxy-2,3-*O*-isopropylidenebutylphosphonate (1*S*,2*R*,3*S*)-17i

Yield: 92%; white powder [chromatographed on a silica gel column with chloroform–methanol (50:1, 20:1, 10:1, v/v)]; $[\alpha]_D^{20}$ 22.8 (*c* 1.09 in $CHCl_3$); mp: 208–209 °C; IR (KBr): ν = 3229, 3010, 2998, 2982, 1704, 1667, 1236, 1063, 778, 693 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.82 (s 1H, *H*C5′), 7.387.26 (m, 10H, 2 × C_6H_5), 5.67 (AB, J_{AB} = 14.5 Hz, 1H, CH_aH$_b$), 5.64 (AB, J_{AB} = 14.5 Hz, 1H, CH$_a$$H_b$), 5.185.06 (m, 4H, 2 × POCH_2Ph), 4.70 (dd, *J* = 14.5 Hz, *J* = 2.9 Hz, 1H, H-4b), 4.64 (dd, *J* = 14.5 Hz, *J* = 5.7 Hz, 1H, H-4b), 4.50 (ddd, *J* = 8.0 Hz, *J* = 5.8 Hz, *J* = 2.9 Hz, 1H, H-3), 4.13 (dt, *J* = 8.0 Hz, *J* = 5.2 Hz, 1H, H-1), 4.03 (dt, *J* = 7.6 Hz, *J* = 5.2 Hz, 1H, H-2), 3.56 (s, 3H, NCH_3), 3.41 (s, 3H, NCH_3), 3.14 (dd, *J* = 13.0 Hz, *J* = 5.2 Hz, 1H), 1.36 (s, 3H, CH_3), 1.21 (s, 3H, CH_3); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 154.4 (s, C═O), 151.3, 147.4, 141.5, 139.1, 135.9 (d, *J* = 5.6 Hz, C_{ipso}), 128.6, 128.6, 128.3, 128.0 (s, C_{aromat}), 125.1, 110.3 (s, *C*(CH_3)$_2$), 107.4, 76.4 (d, *J* = 5.7 Hz), 76.3 (d, *J* = 8.5 Hz), 68.7 (d, *J* = 6.9 Hz, COP), 68.6 (d, *J* = 6.9 Hz, COP), 68.5 (d, *J* = 162.0 Hz, C-1), 51.9 (s, C-4), 41.0 (s, HC═C—*C*H_2), 29.9 (s, CH_3), 28.0 (s, CH_3), 26.9 (s, CH_3), 26.8 (s, CH_3); ^{31}P NMR ($CDCl_3$, 242 MHz): δ = 21.35 ppm. Anal. Calcd for $C_{31}H_{35}ClN_7O_8P$: C, 53.18; H, 5.04; N, 14.01. Found: C, 53.15; H, 4.83; N, 13.90.

4.2.31. (1*S*,2*R*,3*R*)-Dibenzyl 4-{[4-(6-amino-purin-9-yl)methyl]-1*H*-1,2,3-triazol-1-yl}-1,2,3-trihydroxy-2,3-*O*-isopropylidenebutylphosphonate (1*S*,2*R*,3*R*)-17a

Yield: 81%; white powder [chromatographed on a silica gel column with chloroform–methanol (50:1, 20:1, 10:1, v/v)]; $[\alpha]_D^{20}$ +21.8 (*c* 1.43 in DMSO); mp: 100–102 °C; IR (KBr): ν = 3324, 3185, 2987, 1646, 1602, 1219, 1053, 1009 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.31 (s, 1H, *H*C═N), 8.02 (s, 1H, N═C*H*), 7.79 (s, 1H, *H*C5′), 7.37–7.23 (m, 10H, 2 × C_6H_5), 6.48 (s, 2H, NH_2), 5.44 (s, 2H, HC—C—*C*H_2), 5.19–5.08 (m, 4H, 2 × $POCH_2Ph$), 4.99 (dd, *J* = 14.2 Hz, *J* = 1.5 Hz, 1H, H-4b), 4.54–4.50 (m, 2H), 4.42–4.36 (m, 1H), 4.20 (dt, *J* = 8.0 Hz, *J* = 6.1 Hz, 1H, H-1), 3.33 (br s, 1H, OH), 1.41 (s, 3H, CH_3), 1.27 (s, 3H, CH_3); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 155.6, 152.7, 149.6, 141.9, 140.6, 136.1 (d, *J* = 5.5 Hz, C_{ipso}), 135.0 (d, *J* = 5.5 Hz, C_{ipso}), 128.6, 128.5, 128.5,

128.5, 128.0, 128.0 (C_{aromat}), 124.1, 119.1, 110.1 (s, $C(CH_3)_2$), 76.4 (d, J = 11.9 Hz, C-3), 75.6 (s, C-2), 68.5 (d, J = 6.8 Hz, COP), 68.4 (d, J = 6.8 Hz, COP), 66.3 (d, J = 163.0 Hz, C-1), 50.9 (s, C-4), 38.6 (s, HC═C—CH_2—N), 27.9 (s, CH_3), 25.5 (s, CH_3); ^{31}P NMR (243 MHz, $CDCl_3$): δ = 23.84 ppm. Anal. Calcd for $C_{29}H_{33}N_8O_8P$: C, 56.13; H, 5.36; N, 18.06. Found: C, 56.15; H, 5.34; N, 17.97.

4.2.32. (1*S*,2*R*,3*R*)-Dibenzyl 4-{[4-(5-methyl-2,4-dioxopyrimidin-1-yl)methyl]-1*H*-1,2,3-triazol-1-yl}-1,2,3-trihydroxy-2,3-*O*-isopropylidenebutylphosphonate (1*S*,2*R*,3*R*)-17b

Yield: 89%; white powder [chromatographed on a silica gel column with chloroform–methanol (50:1, 20:1, 10:1, v/v)]; $[\alpha]_D^{20}$ +10.2 (*c* 1.02 in $CHCl_3$); mp: 126–127 °C; IR (KBr): ν = 3225, 3063, 2988, 2819, 1680, 1456, 1218, 1051, 966 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.94 (s, 1H, NH), 7.76 (s, 1H, *H*C5′), 7.40–7.29 (m, 11H, 2 × C_6H_5, *H*C═C), 5.18–5.07 (m, 4H, 2 × POCH_2Ph), 5.00 (dd, J = 14.2 Hz, J = 2.6 Hz, 1H, H-4b), 4.98 (AB, J_{AB} = 15.0 Hz, 1H, CH_aH$_b$), 4.94 (AB, J_{AB} = 15.0 Hz, 1H, CH$_a$$H_b$), 4.58–4.52 (m, 1H, H-3), 4.46 (dt, J = 8.7 Hz, J = 6.1 Hz, 1H, H-2), 4.42 (dd, J = 14.2 Hz, J = 9.7 Hz, 1H, H-4a), 4.24 (br s, 1H, OH), 4, 13 (dt, J = 8.7 Hz, J = 5.5 Hz, 1H, H-1), 1.63 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.25 (s, 3H, CH_3); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 164.3 (s, C═O), 151.2 (s, C═O), 141.9 (s, HC═*C*—CH_3), 140.3, 136.1 (d, J = 5.6 Hz, C_{ipso}), 136.0 (d, J = 5.6 Hz, C_{ipso}), 128.6, 128.6, 128.6, 128.5, 128.1, 128.0 (C_{aromat}), 124.7, 111.2 (s, $C(CH_3)_2$), 110.1 (s, H*C*═CCH_3), 76.5 (d, J = 12.3 Hz, C-3), 75.5 (s, C-2), 68.6 (d, J = 7.1 Hz, POC), 68.4 (d, J = 7.1 Hz, POC), 66.5 (d, J = 162.2 Hz, PC), 50.9 (s, C-4), 42.8, 27.9, 25.5, 12.2; ^{31}P NMR (243 MHz, $CDCl_3$): δ = 23.36 ppm. Anal. Calcd for $C_{29}H_{34}N_5O_8P$: C, 56.95; H, 5.60; N, 11.45. Found: C, 57.10; H, 5.51; N, 11.33.

4.2.33. (1*S*,2*R*,3*R*)-Dibenzyl 4-{[4-(2,4-dioxopyrimidin-1-yl)methyl]-1*H*-1,2,3-triazol-1-yl}-1,2,3-trihydroxy-2,3-*O*-isopropylidenebutylphosphonate (1*S*,2*R*,3*R*)-17c

Yield: 93%; white powder [chromatographed on a silica gel column with chloroform–methanol (50:1, 20:1, 10:1, v/v)]; $[\alpha]_D^{20}$ +29.4 (*c* 1.18 in $CHCl_3$); mp: 155–156 °C; IR (KBr): ν = 3221, 3012, 2825, 1688, 1241, 1052 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.23 (s, 1H, NH), 7.78 (s, 1H, *H*C5′), 7.57 (d, J = 7.8 Hz, 1H, HC═C—*H*), 7.40–7.33 (m, 10H, 2 × C_6H_5), 5.70 (d, J = 7.8 Hz, 1H, *H*C═C—H), 5.18–5.08 (m, 5H, 2 × POCH_2Ph, OH), 5.10 (AB, J_{AB} = 15.0 Hz, 1H, CH_aH$_b$), 4.90 (AB, J_{AB} = 15.0 Hz, 1H, CH$_a$$H_b$), 4.98 (dd, J = 14.2 Hz, J = 2.5 Hz, 1H, H-4b), 4.58–4.52 (m, 1H, H-3), 4.46 (dt, J = 8.9 Hz, J = 6.2 Hz, 1H, H-2), 4.42 (dd, J = 14.2 Hz, J = 9.8 Hz, 1H, H-4a), 4,14 (dt, J = 8,9 Hz, J = 5,5 Hz, 1H, H-1), 1.44 (s, 3H, CH_3), 1.30 (s, 3H, CH_3); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 164.0 (s, C═O), 151.2 (s, C═O), 144.5 (s, N—CH═*C*H), 141.6, 136.1 (d, J = 6.3 Hz, C_{ipso}), 136.0 (d, J = 6.3 Hz, C_{ipso}), 128.6, 128.6, 128.5, 128.5, 128.1, 128.0 (C_{aromat}), 124.8, 110.1 (s, $C(CH_3)_2$), 102.6 (s, NC*H*=CH), 76.4 (d, J = 12.4 Hz, C-3), 75.5 (s, C-2), 68.6 (d, J = 6.9 Hz, COP), 68.4 (d, J = 6.9 Hz, COP), 66.4 (d, J = 162.6 Hz, C-1), 50.9 (s, C-4), 43.0 (s, HC═C—CH_2—N), 28.0 (s, CH_3), 25.5 (s, CH_3); ^{31}P NMR (243 MHz, $CDCl_3$): δ = 23.43 ppm. Anal. Calcd for $C_{28}H_{32}N_5O_8P$: C, 56.28; H, 5.40; N, 11.72. Found: C, 56.42; H, 5.23; N, 11.91.

4.2.34. (1*S*,2*R*,3*R*)-Dibenzyl 4-{[4-(N^4-acetylamino-2-oxopyrimidin-1-yl)methyl]-1*H*-1,2,3-triazol-1-yl}-1,2,3-trihydroxy-2,3-*O*-isopropylidenebutylphosphonate (1*S*,2*R*,3*R*)-17d

Yield: 95%; white powder [chromatographed on a silica gel column with chloroform–methanol (50:1, 20:1, 10:1, v/v)]; $[\alpha]_D^{20}$ +30.7 (*c* 0.75 in $CHCl_3$); mp: 107–108 °C; IR (KBr): ν = 3227, 2986, 2936, 1721, 1663, 1494, 1219, 1051, 966 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.30 (s, 1H, *H*C5′), 8.08 (d, J = 7.6 Hz, 1H, *H*-C=CH), 7.55 (d, J = 7.6 Hz, 1H, HC═C—*H*), 7.45–7.30 (m, 10H, 2 × C_6H_5), 6.70 (br s, 1H, N—H), 5.25 (dd, J = 14.1 Hz, J = 2.2 Hz, 1H, H-4b), 5.19–5.07 (m, 6H, 2 × POCH_2Ph, HC═C—CH_2), 4.98–4.95 (m, 2H, H-3, OH), 4.84 (dd, J = 14.1 Hz, J = 10.2 Hz, 1H, H-4a), 4.63 (ddd, J = 10.3 Hz, J = 7.7 Hz, J = 5.6 Hz, 1H, H-2), 4.20 (dt, J = 10.3 Hz, J = 3.6 Hz, 1H, H-1), 2.26 (s, 3H, C(O)CH_3), 1.49 (s, 3H, CH_3), 1.38 (s, 3H, CH_3); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 171.6 (s, C═O), 163.4, 155.5 (s, C═O), 149.4, 140.9, 136.3 (d, J = 5.5 Hz, C_{ipso}), 136.1 (d, J = 5.5 Hz, C_{ipso}), 128.5, 128.4, 127.8, 127.6 (C_{aromat}), 125.4, 110.4 (s, $C(CH_3)_2$), 97.1, 77.1 (d, J = 14.5 Hz, C-3), 75.1 (s, C-2), 68.8 (d, J = 7.5 Hz, POC), 68.4 (d, J = 7.5 Hz, POC), 66.4 (d, J = 163.0 Hz, C-1), 50.3 (s, C-4), 45.4 (s, HC═C—CH_2—N), 28.1 (s, C—CH_3), 25.8 (s, C—CH_3), 24.7 (s,CH_3C(O)); ^{31}P NMR (243 MHz, $CDCl_3$): δ = 25.31 ppm. Anal. Calcd for $C_{30}H_{35}N_6O_8P$: C, 56.42; H, 5.52; N, 13.16 Found: C, 56.33; H, 5.44; N, 13.02.

4.2.35. (1*S*,2*R*,3*R*)-Dibenzyl 4-{[4-(3,7-dimethyl-2,6-dioxopurin-1-yl)methyl]-1*H*-1,2,3-triazol-1-yl}-1,2,3-trihydroxy-2,3-*O*-isopropylidenebutylphosphonate (1*S*,2*R*,3*R*)-17g

Yield: 96%; white powder [chromatographed on a silica gel column with chloroform–methanol (50:1, 20:1, 10:1, v/v)]; $[\alpha]_D^{20}$ +7.7 (*c* 0.95 in $CHCl_3$); mp: 93–95 °C; IR (KBr): ν = 3418, 3287, 2938, 1708, 1662, 1455, 1220, 1039, 997 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.78 (s, 1H, *H*C5′), 7.48 (s, 1H, N = CH—N), 7.38–7.21 (m, 10H, 2 × C_6H_5), 5.41 (br s, 1H, OH), 5.30 (AB, J_{AB} = 14.5 Hz, 1H, CH_aH$_b$), 5.27 (AB, J_{AB} = 14.5 Hz, 1H, CH$_a$$H_b$), 5.12–5.03 (m, 4H, 2 × POCH_2Ph), 4.95 (dd, J = 14.2 Hz, J = 2.5 Hz, 1H, H-4b), 4.57–4.52 (m, 1H, H-3), 4.49 (dt, J = 9.1 Hz, J = 6.1 Hz, 1H, H-2), 4.36 (dd, J = 14.2 Hz, J = 9.6 Hz, 1H, H-4a), 4.17 (dt, J = 9.1 Hz, J = 5.9 Hz, 1H, H-1), 3.93 (s, 3H, N—CH_3), 3.52 (s, 3H, N—CH_3), 1.39 (s, 3H, CH_3), 1.26 (s, 3H, CH_3); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 154.8 (s, C═O), 151.3 (s, C═O), 148.3, 143.3, 141.6, 136.1 (d, J = 6.3 Hz, C_{ipso}), 136.0 (d, J = 6,3 Hz, C_{ipso}), 128.6, 128.5, 128.5, 128.4, 128.0, 127.9 (C_{aromat}), 124.4, 109.9 (s, $C(CH_3)_2$), 107.7, 76.5 (d, J = 12.4 Hz, C-3), 75.6 (s, C-2), 68.4 (d, J = 7.1 Hz, COP), 68.3 (d, J = 6.9 Hz, COP), 66.5 (d, J = 161.8 Hz, C-1), 50.4 (s, C-4), 36.0 (s, HC═C—CH_2), 33.6 (s, CH_3), 29.7 (s, CH_3), 27.9 (s, CH_3), 25.5 (s, CH_3); ^{31}P NMR (243 MHz, $CDCl_3$): δ = 23.73 ppm. Anal. Calcd for $C_{31}H_{36}N_7O_8P$: C, 55.94; H, 5.45; N, 14.73 Found: C, 56.07; H, 5.20; N, 15.02.

4.2.36. (1*S*,2*R*,3*R*)-Dibenzyl 4-{[4-(1,3-dimethyl-2,6-dioxopurin-7-yl)methyl]-1*H*-1,2,3-triazol-1-yl}-1,2,3-trihydroxy-2,3-*O*-isopropylidenebutylphosphonate (1*S*,2*R*,3*R*)-17h

Yield: 94%; colorless oil [chromatographed on a silica gel column with chloroform–methanol (50:1, 20:1, 10:1, v/v)]; $[\alpha]_D^{20}$ +122.1 (*c* 1.70 in $CHCl_3$); IR (film): ν = 3097, 2948, 2865, 1707, 1664, 1222, 1029, 997, 745, 644 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.91 (s, 1H, *H*C5′), 7.83 (s, 1H, N═CH—N), 7.38–7.30 (m, 10H, 2 × C_6H_5), 5.63 (AB, J_{AB} = 15.0 Hz, 1H, CH_aH$_b$), 5.60 (AB, J_{AB} = 15.0 - Hz, 1H, CH$_a$$H_b$), 5.17–5.06 (m, 4H, 2 × POCH_2Ph), 4.96 (dd, J = 14.2 Hz, J = 2.7 Hz, 1H, H-4b), 4.55–4.52 (m, 1H, H-3), 4.45 (dt, J = 8.6 Hz, J = 6.1 Hz, 1H, H-2), 4.38 (dd, J = 14.2 Hz, J = 9.7 Hz, 1H, H-4a), 4.11 (dt, J = 8.7 Hz, J = 5.6 Hz, 1H, H-1), 3.66 (br s, 1H, OH), 3.59 (s, 3H, N—CH_3), 3.43 (s, 3H, N—CH_3), 1.45 (s, 3H, CH_3), 1.30 (s, 3H, CH_3); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 155.4 (s, C═O), 151.6 (s, C═O), 148.9, 141.9, 141.5, 135.9 (d, J = 5.9 Hz, C_{ipso}), 135.9 (d, J = 5.9 Hz, C_{ipso}), 128.6, 128.6, 128.6, 128.0, 127.9 (C_{aromat}), 124.7, 110.1 (s, $C(CH_3)_2$), 106.5, 76.4 (d, J = 12.2 Hz, C-3), 75.5 (s, C-2), 68.6 (d, J = 7.3 Hz, COP), 68.4 (d, J = 7.3 Hz, COP), 65.5 (d, J = 162.0 Hz, CP), 50.8 (s, C-4), 41.5, 29.8 (s, CH_3), 27.9 (s, CH_3), 27.9 (s, CH_3), 25.5 (s, CH_3); ^{31}P NMR (242 MHz, $CDCl_3$): δ = 23.14 ppm. Anal. Calcd for $C_{31}H_{36}N_7O_8P$: C, 55.94; H, 5.45; N, 14.73 Found: C, 55.75; H, 5.68; N, 14.55.

4.2.37. (1*S*,2*R*,3*R*)-Dibenzyl 4-{[4-(8-chloro-1,3-dimethyl-2,6-dioxopurin-7-yl)methyl]-1*H*-1,2,3-triazol-1-yl}-1,2,3-trihydroxy-2,3-*O*-isopropylidenebutylphosphonate (1*S*,2*R*,3*R*)-17i

Yield: 94%; white powder [chromatographed on a silica gel column with chloroform–methanol (50:1, 20:1, 10:1, v/v)]; $[\alpha]_D^{20}$ +17.0 (*c* 1.37 in $CHCl_3$); mp: 194–196 °C; IR (KBr): ν = 3279, 2992, 2954, 2895, 1706, 1663, 1541, 1378, 1217, 997 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 7.89 (s, 1H, *H*C5′), 7.37–7.29 (m, 10H, 2 × C_6H_5), 5.65 (AB, J_{AB} = 15.2 Hz, 1H, CH_aH_b), 5.62 (AB, J_{AB} = 15.2 Hz, 1H, CH_aH_b), 5.15–5.04 (m, 4H, 2 × POCH_2Ph), 4.96 (dd, *J* = 14.2 Hz, *J* = 2.5 Hz, 1H, H-4b), 4.91 (br s, 1H, OH), 4.57–4.52 (m, 1H, H-3), 4.49 (dt, *J* = 8.9 Hz, *J* = 6.4 Hz, 1H, H-2), 4.37 (dd, *J* = 14.2 Hz, *J* = 9.8 Hz, 1H, H-4a), 4.12 (dt, *J* = 9.1 Hz, *J* = 5.8 Hz, 1H, H-1), 3.54 (s, 3H, N—CH_3), 3.39 (s, 3H, N—CH_3), 1.41 (s, 3H, CH_3), 1.28 (s, 3H, CH_3); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 154.5 (s, C=O), 159.3, 147.4 (s, C=O), 141.5, 139.1, 135.9 (C_{ipso}), 128.6, 128.6, 128.5, 128.1, 127.9 (s, C_{aromat}), 124.7, 110.0 (s, $C(CH_3)_2$), 107.4, 76.3 (d, *J* = 12,2 Hz, C-3), 75.6 (s, C-2), 68.6 (d, *J* = 7.3 Hz, COP), 68.4 (d, *J* = 7.3 Hz, COP), 66.5 (d, *J* = 161.6 Hz, C-1), 50.6 (s, C-4), 41.0 (s, HC=C—CH_2), 29.8 (s, CH_3), 28.0 (s, CH_3), 27.9 (s, CH_3), 25.5 (s, CH_3); ^{31}P NMR (243 MHz, $CDCl_3$): δ = 23.46 ppm. Anal. Calcd for $C_{31}H_{35}ClN_7O_8P$: C, 53.18; H, 5.04; N, 14.01. Found: C, 53.28; H, 4.81; N, 14.28.

4.3. Synthesis of phosphonic acid 21b and 21k (general procedure)

The dibenzyl phosphonates (1*S*,2*S*)-**16b** and (1*S*,2*S*)-**16k** (1 mmol) were dissolved in methanol (10 mL) and water (2 mL) and 10% Pd–C (10 mg) was added. The suspension was stirred under hydrogen atmosphere at room temperature for 48 h. The catalyst was filtered through a layer of Celite and the aqueous solution was concentrated in vacuo to give pure phosphonic acids **21b** and **21k**.

4.3.1. (1*S*,2*S*)-3-{4-[(5-Methyl-2,4-dioxopyrimidin-1-yl)methyl]-1*H*-1,2,3-triazol-1-yl}-1,2-dihydroxypropylphosphonic acid (1*S*,2*S*)-21b

Yield: 87%; white powder; $[\alpha]_D^{20}$ 18.3 (*c* 1.85 in DMSO); mp: 240–243 °C; IR (KBr): ν = 3290, 2833, 1680, 1614, 1225, 1020 cm^{-1}; ^1H NMR (300 MHz, CD_3OD): δ = 8.05 (s, 1H, HC5′), 7.55 (d, *J* = 1.1 Hz, 1H, CH_3C=C*H*), 5.02 (s, 2H, CH_2), 4.67 (dd, *J* = 14.4 Hz, *J* = 3.8 Hz, 1H, H-3a), 4.52 (dd, *J* = 14.4 Hz, *J* = 9.6 Hz, 1H, H-3b), 4.32–4.25 (m, 1H, H-2), 3.76 (dd, *J* = 10.8 Hz, *J* = 4.1 Hz, 1H, H-1), 1.84 (d, *J* = 1.1 Hz, 3H, CH_3); ^{13}C NMR (151 MHz, DMSO-d_6): δ = 164.7, 151.2, 142.5, 141.6, 124.8, 109.3, 70.6, 68.6 (d, *J* = 164.2 Hz, PC), 53.2 (d, *J* = 5.6 Hz), 42.6, 12.4; ^{31}P NMR (121.5 MHz, CD_3OD): δ = 18.47 ppm. Anal. Calcd for $C_{11}H_{16}N_5O_7P \times H_2O$: C, 34.84; H, 4.78; N, 18.47. Found: C, 35.02; H, 5.00; N, 14.20.

4.3.2. (1*S*,2*S*)-3-{4-[(3-benzoyl-2,4-dioxopyrimidin-1-yl)methyl]-1*H*-1,2,3-triazol-1-yl}-1,2-dihydroxypropylphosphonic acid (1*S*,2*S*)-21k

Yield: 89%; white powder; $[\alpha]_D^{20}$ 17.6 (*c* 3.42 in DMSO); mp: 130–132 °C; IR (KBr): ν = 3323, 2830, 1701, 1698,1230, 1025, 762, 689 cm^{-1}; ^1H NMR (300 MHz, CD_3OD): δ = 8.03 (s, 1H, HC5′), 7.97–7.95 (m, 2H, H_{aromat}), 7.85 (d, *J* = 8.0 Hz, 1H, *H*C=CH), 7.75–7.68 (m, 1H, H_{aromat}), 7.60–7.54 (m, 2H, H_{aromat}), 5.84 (d, *J* = 8.0 Hz, 1H, *H*C=CH), 5.15 (s, 2H, CH_2), 4.72 (dd, *J* = 13.9 Hz, *J* = 3.8 Hz, 1H, H-3a), 4.50 (dd, *J* = 13.9 Hz, *J* = 8.9 Hz, 1H, H-3b), 4.31–4.22 (m, 1H, H-2), 3.78 (dd, *J* = 10.5 Hz, *J* = 4.1 Hz, 1H, H-1); ^{13}C NMR (151 MHz, CD_3OD): δ = 170.0 (s, C=O), 162.7 (s, C=O), 149.9 (s, C=O), 147.0, 141.8, 136.0, 131.6, 130.5, 125.0, 101.4, 70.6 (d, *J* = 4.4 Hz, C-2), 68.9 (d, *J* = 157.7 Hz, PC), 53.3 (d, *J* = 9.0 Hz, C-3), 43.4; ^{31}P NMR (121.5 MHz, CD_3OD): δ = 21.53 ppm. Anal. Calcd for $C_{17}H_{18}N_5O_8P \times H_2O$: C, 43.50; H, 4.30; N, 14.92. Found: C, 43.72; H, 4.55; N, 15.16.

4.4. Antiviral activity assays

The compounds were evaluated against the following viruses: herpes simplex virus type 1 (HSV-1) strain KOS, thymidine kinase-deficient (TK^-) HSV-1 KOS strain resistant to ACV (ACV^r), herpes simplex virus type 2 (HSV-2) strains Lyons and G, varicella-zoster virus (VZV) strain Oka, TK^- VZV strain 07−1, human cytomegalovirus (HCMV) strains AD-169 and Davis, vaccinia virus Lederle strain, respiratory syncytial virus (RSV) strain Long, vesicular stomatitis virus (VSV), Coxsackie B4, Parainfluenza 3, Influenza virus A (subtypes H1N1, H3N2), influenza virus B, Reovirus-1, Sindbis, Reovirus-1, Punta Toro, human immunodeficiency virus type 1 strain III_B and human immunodeficiency virus type 2 strain ROD. The antiviral, other than anti-HIV, assays were based on inhibition of virus-induced cytopathicity or plaque formation in human embryonic lung (HEL) fibroblasts, African green monkey cells (Vero), human epithelial cells (HeLa) or Madin-Darby canine kidney cells (MDCK). Confluent cell cultures in microtiter 96-well plates were inoculated with 100 $CCID_{50}$ of virus (1 $CCID_{50}$ being the virus dose to infect 50% of the cell cultures) or with 20 plaque forming units (PFU) (VZV) in the presence of varying concentrations of the test compounds. Viral cytopathicity or plaque formation was recorded as soon as it reached completion in the control virus-infected cell cultures that were not treated with the test compounds. Antiviral activity was expressed as the EC_{50} or compound concentration required to reduce virus-induced cytopathogenicity or viral plaque formation by 50%.

4.5. Anti-HIV activity assays

Inhibition of HIV-1(III_B)- and HIV-2(ROD)-induced cytopathicity in CEM cell cultures was measured in microtiter 96-well plates containing ~3 × 10^5 CEM cells/mL infected with 100 CCID50 of HIV per milliliter and containing appropriate dilutions of the test compounds. After 4–5 days of incubation at 37 °C in a CO_2-controlled humidified atmosphere, CEM giant (syncytium) cell formation was examined microscopically. The EC_{50} (50% effective concentration) was defined as the compound concentration required to inhibit HIV-induced giant cell formation by 50%.

4.6. Cytostatic activity assays

All assays were performed in 96-well microtiter plates. To each well were added (5–7.5) × 10^4 tumor cells and a given amount of the test compound. The cells were allowed to proliferate for 48 h (murine leukemia L1210 cells) or 72 h (human lymphocytic CEM and human cervix carcinoma HeLa cells) at 37 °C in a humidified CO_2-controlled atmosphere. At the end of the incubation period, the cells were counted in a Coulter counter. The IC_{50} (50% inhibitory concentration) was defined as the concentration of the compound that inhibited cell proliferation by 50%.

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References and notes

1. Herdewijn, P. *Modified Nucleosides in Biochemistry, Biotechnology and Medicine*; Wiley-VCH: Weinheim, 2008.
2. Chu, C. K. *Antiviral Nucleosides: Chiral Synthesis and Chemotherapy*; Elsevier B.V: Amsterdam, 2003.
3. Schaeffer, H. J.; Beauchamp, L.; De Miranda, P.; Elion, G. B.; Bauer, D. J.; Collins, P. *Nature* **1978**, *272*, 583.
4. Martin, J. C.; Smee, D. F.; Verheyden, J. P. H. *J. Org. Chem.* **1985**, *50*, 755.
5. De Clercq, E. *Med. Res. Rev.* **2013**, *33*, 1278.
6. Lin, T.-S.; Liu, M.-C. h. *Tetrahedron Lett.* **1984**, *25*, 905.
7. Kamiya, T.; Saito, Y.; Hashimoto, M.; Seki, H. *Tetrahedron Lett.* **1969**, *10*, 4729.
8. Kamiya, T.; Saito, Y.; Hashimoto, M.; Seki, H. *Tetrahedron* **1972**, *28*, 899.
9. Votruba, I.; Holý, A. *Collect. Czech. Chem. Commun.* **1982**, *47*, 167.
10. De Clercq, E.; Descamps, J.; De Somer, P.; Holý, A. *Science* **1978**, *200*, 563.
11. De Clercq, P.; Holý, A. *J. Med. Chem.* **1979**, *22*, 510.
12. Holý, A.; Votruba, I.; De Clercq, E. *Collect. Czech. Chem. Commun.* **1985**, *50*, 245.
13. Slama, K.; Holý, A. *Acta Entomol. Bohemoslav.* **1988**, *85*, 94.
14. Wróblewski, A. E.; Karolczak, W. *Tetrahedron* **2003**, *59*, 6075.
15. Wolfe, M. S.; Borchardt, R. T. *J. Med. Chem.* **1991**, *34*, 1521.
16. De Clercq, E. *Adv. Virus Res.* **1993**, *42*, 1.
17. Amblard, F.; Cho, J. H.; Schinazi, R. F. *Chem. Rev.* **2009**, *109*, 4207.
18. Nájera, C.; Sansano, J. M. *Org. Biomol. Chem.* **2009**, *7*, 4567.
19. Tron, G. C.; Pirali, T.; Bilington, R. A.; Canonico, P. L.; Sorba, G.; Genazzani, A. A. *Med. Res. Rev.* **2008**, *28*, 278.
20. Saito, Y.; Escuret, V.; Durantel, D.; Zoulim, F.; Schinazi, R. F.; Agrofoglio, L. A. *Bioorg. Med. Chem.* **2003**, *11*, 3633.
21. Holý, A.; Dvořáková, H.; Jindřich, J.; Masojídková, M.; Budějínský, M.; Balzarini, J.; Andrei, G.; De Clercq, E. *J. Med. Chem.* **1996**, *39*, 4073.
22. Lazrek, H. B.; Taourirte, M.; Oulih, T.; Lebtoumi, M.; Barascut, J. L.; Imbach, J. L. *Nucleosides Nucleotides* **1997**, *16*, 1115.
23. Lazrek, H. B.; Taourirte, M.; Oulih, T.; Barascut, J. L.; Imbach, J. L.; Pannecouque, C.; Witrouw, M.; De Clercq, E. *Nucleosides, Nucleotides Nucleic Acids* **1949**, *2001*, 20.
24. Diab, S. A.; Hienzch, A.; Lebargy, C.; Guillarme, S.; Pfund, E.; Lequeux, T. *Org. Biomol. Chem.* **2009**, *7*, 4481.
25. Elayadi, H.; Smietana, M.; Pannecouque, Ch.; Leyssen, P.; Neyts, J.; Vasseur, J.-J.; Lazrek, H. B. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7365.
26. Ganesan, M.; Muraleedharan, K. M. *Nucleosides, Nucleotides Nucleic Acids* **2010**, *29*, 91.
27. Koszytkowska-Stawińska, M.; Mironiuk-Puchalska, E.; Rowicki, T. *Tetrahedron* **2012**, *68*, 214.
28. Koszytkowska-Stawińska, M.; Sas, W. *Tetrahedron* **2013**, *69*, 2619.
29. Głowacka, I. E.; Balzarini, J.; Wróblewski, A. E. *Nucleosides, Nucleotides Nucleic Acids* **2012**, *31*, 293.
30. Głowacka, I. E.; Balzarini, J.; Wróblewski, A. E. *Arch. Pharm. Chem. Life Sci.* **2013**, *346*, 278.
31. Głowacka, I. E.; Balzarini, J.; Wróblewski, A. E. *Arch. Pharm. Chem. Life Sci.* **2013**, *346*, 677.
32. Piotrowska, D. G.; Balzarini, J.; Głowacka, I. E. *Eur. J. Med. Chem.* **2012**, *47*, 501.
33. Głowacka, I. E.; Balzarini, J.; Wróblewski, A. E. *Eur. J. Med. Chem.* **2013**, *70C*, 703.
34. Głowacka, I. E.; Balzarini, J.; Wróblewski, A. E. *Arch. Pharm. Chem. Life Sci.* **2014**. http://dx.doi.org/10.1002/ardp.201300468.
35. Głowacka, I. E.; Balzarini, J.; Piotrowska, D. G. *Arch. Pharm. Chem. Life Sci.* **2014**. http://dx.doi.org/10.1002/ardp.201300471.
36. Wróblewski, A. E.; Głowacka, I. E *Tetrahedron: Asymmetry* **2002**, *13*, 989.
37. Wróblewski, A. E.; Głowacka, I. E. *Pol. J. Chem.* **1895**, *2005*, 79.
38. Wróblewski, A. E.; Głowacka, I. E. *Tetrahedron* **2005**, *61*, 11930.
39. Alvarez, R.; Velázquez, S.; San-Félix, A.; Aquaro, S.; De Clercq, E.; Perno, C.-F.; Karlsson, A.; Balzarini, J.; Camarasa, M. J. *J. Med. Chem.* **1994**, *37*, 4185.
40. Lindsell, W. E.; Murray, Ch.; Preston, P. N.; Woodman, T. A. J. *Tetrahedron* **2000**, *56*, 1233.
41. Krim, J.; Taourirte, M.; Engels, J. W. *Molecules* **2012**, *17*, 179.
42. Pérez-Serrano, L.; Casarrubios, L.; Dominguez, G.; González-Pérez, P.; Pérez-Castells, J. *Synthesis* **1810**, *2002*, 13.
43. Waer, M. J. A.; Herdewijn, P. A. M. M.; Pfleiderer, W. E. Immunosupressive effects of 8-substituted xanthine derivatives. US7, 253, 176 B1 2007.
44. Casaschi, A.; Grigg, R.; Sansano, J. M. *Tetrahedron* **2000**, *56*, 7553.
45. Daly, J. W.; Padgett, W. L.; Shamim, M. T. *J. Med. Chem.* **1986**, *29*, 1305.
46. Himmelsbacg, F.; Mark, M.; Eckhardt, M.; Langkopf, E.; Maier, R. Xanthine derivatives, the preparation thereof and use as pharmaceutical compositions. US2002/198205; 2002 (A1).
47. Casaschi, A.; Grigg, R.; Sansano, J. M. *Tetrahedron* **2001**, *57*, 607.
48. Lee, Y.-S.; Kim, B. H. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1395.
49. Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057.
50. Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596.