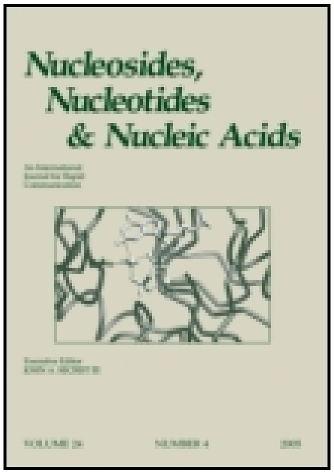

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Synthesis of N^6-Substituted 9-[3-(Phosphonomethoxy)Propyl]Adenine Derivatives As Possible Antiviral Agents

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SYNTHESIS OF N^6-SUBSTITUTED 9-[3-(PHOSPHONOMETHOXY)PROPYL]ADENINE DERIVATIVES AS POSSIBLE ANTIVIRAL AGENTS

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□ *A number of N^6-substituted 9-[3-(phosphonomethoxy)propyl]adenine derivatives having hydroxymethyl at C-1′-position were prepared from the appropriate 6-chloroadenine derivative. The syntheses of the corresponding prodrugs of these compounds are also reported. These compounds showed poor activity against HCV in replicon assay.*

Keywords Acyclic nucleosides; Prodrugs; Antiviral

INTRODUCTION

Extensive studies have been done on 9-[2-(phosphonomethoxy)ethyl] adenine and guanine derivatives.[1–7] A number of lead compounds (Chart 1), such as PMEA (**1a**), PMEDAP (**1g**), and PMEG (**2a**) evolved from those studies and adefovir dipivoxil (**1b**), the prodrug of PMEA, was approved by FDA for HBV infections. All these compounds are unsubstituted acyclic nucleoside derivatives. Substituting the C-2′-position by methyl, hydroxymethyl, fluoromethyl resulted in some more lead compounds (Chart 1), such as PMPA (**1c**), HPMPA (**1e**), FPMPA (**1f**), HPMPDAP (**1h**), PMPG (**2b**), and HPMPG (**2c**). These studies resulted in a FDA-approved compound, tenofovir disoproxil (**1b**), the prodrug of PMPA for HIV infections.

Various N^6-substituted adenosine derivatives as agonists and partial agonists of adenosine receptors have been reported.[8–10] Recently, a number of

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1a, R=H, R'=H, R"=H (PMEA)
1b, R=H, R'=H, R"=$CH_2OC(O)C(CH_3)_3$ (adefovir dipivoxil)
1c, R=H, R'=CH_3, R"=H (PMPA)
1d, R=H, R'=CH_3, R"=$CH_2OC(O)OCH(CH_3)_2$ (tenofovir disoproxil)
1e, R=H, R'-CH_2OH, R"=H (HPMPA)
1f, R=H, R'=CH_2F, R"=H (FPMPA)
1g, R=NH_2, R'=H, R"=H (PMEDAP)
1h, R=NH_2, R'=CH_2OH, R"=H (HPMPDAP)

2a, R=H (PMEG)
2b, R=CH_3 (PMPG)
2c, R=CH_2OH (HPMPG)

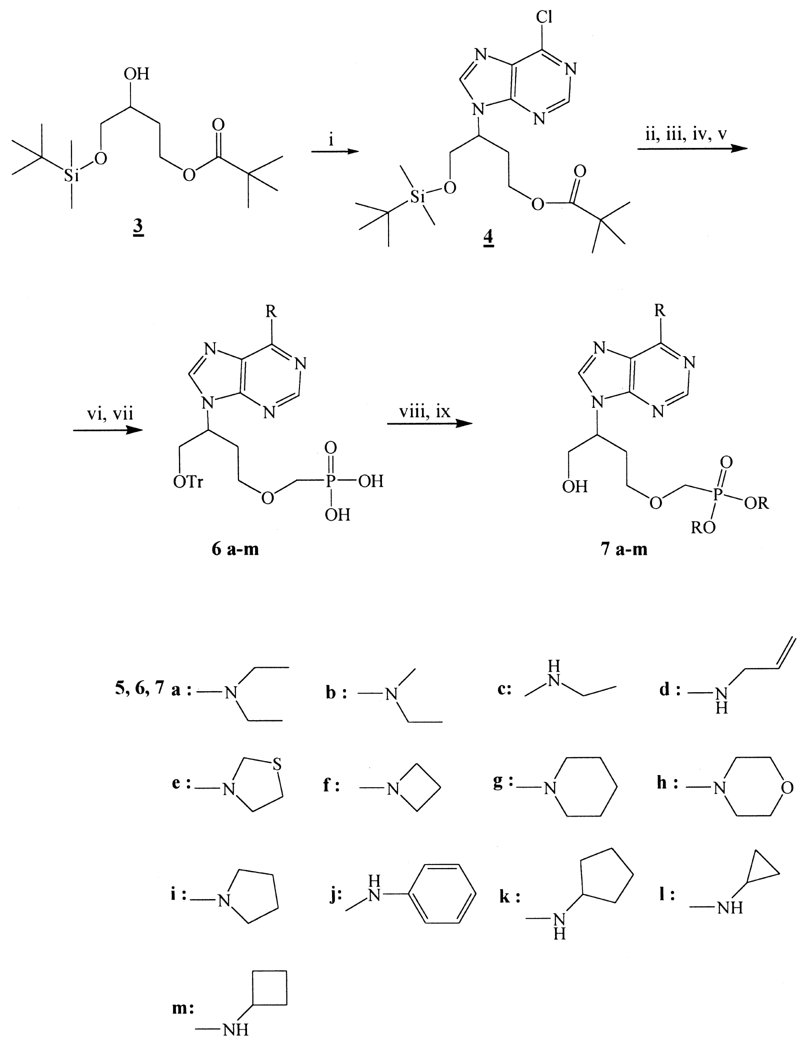
CHART 1

adenosine analogs, where ribose has been replaced by 2′-methylribose have been reported as potent hepatitis C viral (HCV) polymerase inhibitors. Further replacement of 6-amino of adenosine by thiophene; 6-thiomethyl; hydrazine derivatives, such as methylhydrazino, acetylhydrazino, hydroxyethylhydrazino, methylsulphonylhydrazino; amine derivatives, such as hydroxylamino, methoxylamino, aminoethylamino; and hydroxy derivatives, such as *tert*-butyloxycarbonylaminohydroxyl, and benzyloxycarbonylaminohydroxyl have been studied for HCV inhibitory activity and found to have HCV replication EC_{50} values less than 10 μM.[11–16]

In one of the preceding papers, we have described the synthesis of 9-[3-(phosphonomethoxy)propyl]adenine derivatives substituted at C-1′-position with hydroxymethyl, fluoromethyl, aminomethyl, azidomethyl, etc., as possible antiviral agents. We now wish to report the synthesis of N^6-substituted 9-[3-(phosphonomethoxy)propyl]adenine derivatives, having the hydroxymethyl group at the C-1′-position.

RESULTS AND DISCUSSION

The synthesis of all the compounds reported here started from racemic 1-*tert*-butyldimethylsilyl-4-pivaloylbutan-1,2,4-triol (**3**) reported in the preceding papers. Compound **3** under Mitsunobu reaction conditions with 6-chloropurine, triphenylphosphine (TPP) and diisopropylazodicarboxylate (DIAD) in dioxane gave desired nucleoside **4** (Scheme 1). The displacement of the chloro group in **4** by substituted amino at the 6-position was achieved by heating the mixture of **4** with corresponding amine in ethanol at 60°C. Since the TBDMS group was not found compatible for the phosphonomethylation reaction, it became necessary to replace TBDMS with



7c, d, k: R = $CH_2OC(O)C(CH_3)_3$

7a-b, e-j, l, m: R = $CH_2OC(O)OCH(CH_3)_2$

SCHEME 1 Reagents: i) 6-chloropurine, Ph_3P, DIAD; ii) amine, EtOH, Et_3N; iii) Bu_4NF, THF; iv) TrCl, pyridine; v) NaOMe; vi) NaH, TsO-CH_2-P(O)(O-iPr)$_2$; vii) TMSI, Et_3N; viii) $ClCH_2OC(O)C(CH_3)_3$ or $ClCH_2OC(O)OCH(CH_3)_2$, Et_3N; ix) HCl, CH_3CN.

trityl, which was achieved by deprotection of TBDMS, with tetrabutylammonium fluoride (TBAF) and treating the resultant free hydroxyl with tritylchloride. Further basic hydrolysis of the pivaloyl group resulted in the desired nucleosides, **5a-m**. The phosphonomethylation of **5a-m** was obtained by reacting with p-toluenesulfonyloxymethylphosphonate using sodium hydride as base to give the phosphonomethoxy derivatives, which upon hydrolysis of ester with TMS-iodide in the presence of triethylamine gave the desired phosphonic acid derivatives **6a-m**. The use of triethylamine was essential to keep the trityl protecting group intact. The reaction of phosphonic acids **6a-m** with an appropriate chloromethyl pivalate or chloromethyl-2-propylcarbonate in the presence of triethylamine gave diprotected prodrugs, which upon deprotection of trityl under mild acidic conditions with HCl in acetonitrile yielded the targets **7a-m**. In the case of the secondary amine, the yield of the formation of the prodrugs was low due to the formation of a side product corresponding to a coupling of the amine with chloromethyl pivalate.

BIOLOGICAL ACTIVITY

These compounds showed poor activity against HCV in replicon assay.[17]

EXPERIMENTAL

All reagents and solvents were purchased from Aldrich and used as received. ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR were recorded on a Bruker 300 MHz instrument. Chemical shifts (δ) are reported in parts per million (ppm) referenced to TMS at 0.00 or respective deuterated solvent peak. ^{31}P NMR chemical shifts are reported with respect to D_3PO_4 in D_2O as the external standard. Coupling constants (J) are reported in hertz. IR spectra were obtained from films on NaCl plates for oils or KBr pellets for solids with a scan range of 4000–500 cm^{-1} on a FT-IR spectrometer (BioRad FTS-3500GX). Mass spectra data were acquired on a Waters ZMD mass spectrometer coupled with a Waters System 2695 for loading of the samples in ES positive or negative mode. HRMS data were recorded on Bruker Bioapex 4.7E. The elemental analysis (C, H, and N) were performed by Atlantic Microlab in Norcross, Georgia. The TLC solvent system CMA-80 and CMA-50 refers to chloroform:methanol:conc. NH_4OH (80:18:2) and chloroform:methanol:conc. NH_4OH (50:40:10), respectively. The non-UV active compounds were visualized by charring the TLC plate sprayed with ammonium molybdate/cesium sulfate spray prepared by dissolving conc. H_2SO_4 (22.4 mL), $CeSO_4$ (45 mg), $(NH_4)_6Mo_7O_{24}\bullet 4\ H_2O$ (7 g) in 100 mL water. The olefin compounds were visualized by using $KMnO_4$ spray.

(±)-9-[(1-*tert*-Butyldimethylsilyloxymethyl)(3-pivaloyloxy)propyl]-6-chloropurine (4). To a mixture of **3** (92 g, 0.302 mol), triphenylphosphine (158 g, 0.60 mol) and 6-chloropurine (95 g, 0.60 mol) in anhydrous dioxane (1.5 L) was added a solution of DIAD (0.6 mol) in dioxane (60 mL) over a period of 3.5 h at room temperature and the mixture stirred further for 16 h. The reaction mixture was filtered through a short pad of Celite to remove insoluble materials and the residue purified on a column of silica gel eluting with $CHCl_3$:MeOH (100:0 to 95:5) to provide 95 g (72%) of **3** as a gum. ^{1}H NMR ($CDCl_3$): δ 8.87 (s, 1H), 8.27 (s, 1H), 4.85 (m, 1H), 4.18–4.02 (m, 2H), 3.95–3.82 (m, 2H), 2.42–2.28 (m, 2H), 1.15 (s, 9H), 0.82 (s, 9H), 0.0 (m, 6H). IR (KBr, cm^{-1}) 3019, 2400, 1724, 1592, 1215, 765. MS (ES^+) 463.38 $(M+Na)^+$. Anal. Calcd for $C_{20}H_{33}ClN_4O_3Si$: C, 55.04; H, 7.66; N, 12.46. Found: C, 54.72; H, 7.53; N, 12.19.

General Procedure for the Conversion of 4 to 5a-m

To a solution of **4** in EtOH (15 mL/mmol) was added 10 eq. of Et_3N and 6 eq. of the corresponding amine. The resulting solution was stirred at 60°C for 16 h, evaporated to dryness and partitioned between chloroform and water. The organic layer was collected, washed 3 times with water, dried over $MgSO_4$ and evaporated to dryness to give an oil. The resulting oil was dissolved in THF (10 mL/mmol) and a solution of 1 M TBAF in THF added (1.1 eq.). The reaction was stirred at room temperature for 30 min, evaporated to dryness, then adsorbed on silica gel and chromatographed using chloroform:methanol as eluent to give the desilylated derivative.

To the latter were added pyridine (10 mL/mmol) and trityl chloride (2 eq.) and the reaction mixture stirred at 70°C for 16 h. The reaction mixture was then evaporated to dryness, the residue was dissolved in ethyl acetate and washed with water 3 times. The organic layer on concentration and purification on a silica gel column using hexanes:ethyl acetate (100:0 to 90:10) as eluent gave tritylated product, which was dissolved in MeOH (10 mL/mmol) and treated with 5.4 N NaOMe in MeOH (2 eq.). The reaction mixture was stirred at room temperature for 16 h and neutralized with acetic acid. The resulting mixture was then evaporated to dryness, the residue was dissolved in $CHCl_3$ and washed with water. The organic layer was dried over $MgSO_4$, filtered, and the filtrate was concentrated and the residue was purified on a silica gel column eluting with $CHCl_3$:MeOH (100:0 to 95:5) to provide the desired compounds **5a-m**.

(±)-9-[(1-Trityloxymethyl)(3-hydroxy)propyl]-6-diethylaminopurine (5a). Using the general procedure, **4** gave **5a** (80%). ^{1}H NMR (DMSO-d_6): δ 8.30 (s, 1H), 8.12 (s, 1H), 7.30–7.00 (m, 15H), 4.85 (m, 1H), 4.56 (t, 1H,

J = 4.9 Hz), 3.99 (m, 4H), 3.39 (m, 1H), 3.30 (m, 1H partially masked by water peak in DMSO-d_6), 3.19 (m, 2H), 2.33 (m, 1H), 2.02 (m, 1H), 1.22 (t, 6H, J = 6.7 Hz). IR (KBr, cm^{-1}) 2927, 1583, 1442, 1282, 1031. HRMS Calcd for $C_{32}H_{35}N_5O_2$ $(M+H)^+$ 522.2868. Found 522.2854.

(±)-9-[(1-Trityloxymethyl)(3-hydroxy)propyl]-6-(N-methyl-N-ethyl) aminopurine (5b). Using the general procedure, **4** gave **5b** (73%). ^{1}H NMR (DMSO-d_6): δ 8.30 (s, 1H), 8.13 (s, 1H), 7.30–7.00 (m, 15H), 4.87 (m, 1H), 4.56 (t, 1H, J = 4.9 Hz), 4.10 (m, 2H), 3.49–3.25 (m, 5H), 3.20 (m, 2H), 2.32 (m, 1H), 2.01 (m, 1H), 1.19 (t, 3H, J = 6.9 Hz). IR (KBr, cm^{-1}) 2870, 1586, 1284, 1025, 898. HRMS Calcd for $C_{31}H_{33}N_5O_2$ $(M+H)^+$ 508.2712. Found 508.2689.

(±)-9-[(1-Trityloxymethyl)(3-hydroxy)propyl]-6-ethylaminopurine (5c). Using the general procedure, **4** gave **5c** (90%). ^{1}H NMR (DMSO-d_6): δ 8.88 (br s, 1H), 8.26 (s, 1H), 8.11 (s, 1H), 7.30–7.00 (m, 15H), 4.84 (m, 1H), 4.55 (t, 1H, J = 5.0 Hz), 3.53 (m, 2H), 3.40 (m, 1H), 3.29 (m, 1H, partially masked by water peak in DMSO-d_6), 3.19 (m, 2H), 2.32 (m, 1H), 1.99 (m, 1H), 1.22 (m, 3H). IR (KBr, cm^{-1}) 2978, 2878, 1710, 1615, 1446, 1221, 1105, 1043. HRMS Calcd for $C_{30}H_{31}N_5O_2$ $(M+H)^+$ 494.2555. Found 494.2552.

(±)-9-[(1-Trityloxymethyl)(3-hydroxy)propyl]-6-allylaminopurine (5d). Using the general procedure, **4** gave **5d** (90%). ^{1}H NMR (DMSO-d_6): δ 8.88 (br s, 1H), 8.29 (s, 1H), 8.12 (s, 1H), 7.30–7.00 (m, 15H), 5.99 (m, 1H), 5.18 (dd, 1H, J = 1.6 and 15.4 Hz), 5.05 (dd, 1H, J = 1.6 and 11.8 Hz), 4.85 (m, 1H), 4.56 (t, 1H, J = 5.0 Hz), 4.13 (m, 2H), 3.40 (m, 1H), 3.29 (m, 1H, partially masked by water peak in DMSO-d_6), 3.19 (m, 2H), 2.32 (m, 1H), 2.00 (m, 1H). IR (KBr, cm^{-1}) 3284, 2980, 1710, 1615, 1448, 1221, 1105, 1041. HRMS Calcd for $C_{31}H_{31}N_5O_2$ $(M+H)^+$ 506.2555. Found 506.2547.

(±)-9-[(1-Trityloxymethyl)(3-hydroxy)propyl]-6-N-thiazolidinopurine (5e). Using the general procedure, **4** gave **5e** (40%). ^{1}H NMR (DMSO-d_6): δ 8.39 (s, 1H), 8.22 (s, 1H), 7.30–7.00 (m, 15H), 5.12 (m, 1H), 4.91 (m, 1H), 4.31 (m, 2H), 3.50–3.10 (m, 8H), 2.34 (m, 1H), 2.02 (m, 1H). IR (KBr, cm^{-1}) 2931, 2877, 1691, 1582, 1456, 1218, 1032. HRMS Calcd for $C_{31}H_{31}N_5O_2S$ $(M+H)^+$ 538.2276. Found 538.2262.

(±)-9-[(1-Trityloxymethyl)(3-hydroxy)propyl]-6-N-azetidinopurine (5f). Using the general procedure, **4** gave **5f** (88%). ^{1}H NMR (DMSO-d_6): δ 8.26 (s, 1H), 8.12 (s, 1H), 7.30–7.00 (m, 15H), 4.85 (m, 1H), 4.54 (t, 1H, J = 4.9 Hz), 4.36 (m, 4H), 3.41 (m, 1H), 3.28 (m, 1H), 3.19 (m, 2H), 2.44 (m, 2H, partially masked by DMSO), 2.30 (m, 1H), 2.00 (m, 1H). IR (KBr, cm^{-1})

2934, 1589, 1465, 1296, 1221, 1072, 1049, 896. HRMS Calcd for $C_{31}H_{31}N_5O_2$ $(M+H)^+$ 506.2555. Found 506.2531.

(±)-9-[(1-Trityloxymethyl)(3-hydroxy)propyl]-6-N-piperidinopurine (5g). Using the general procedure, **4** gave **5g** (22%). ^{1}H NMR (DMSO-d_6): δ 8.32 (s, 1H), 8.13 (s, 1H), 7.30–7.00 (m, 15H), 4.87 (m, 1H), 4.55 (t, 1H, J = 5.0 Hz), 4.22 (m, 4H), 3.39 (m, 1H), 3.29 (m, 1H), 3.20 (m, 2H), 2.32 (m, 1H), 2.01 (m, 1H), 1.63 (m, 6H). IR (KBr, cm^{-1}) 2849, 1584, 1444, 1338, 1248, 1048, 982. HRMS Calcd for $C_{33}H_{35}N_5O_2$ $(M+H)^+$ 534.2868. Found 534.2842.

(±)-9-[(1-Trityloxymethyl)(3-hydroxy)propyl]-6-N-morpholinopurine (5h). Using the general procedure, **4** gave **5h** (22%). ^{1}H NMR (DMSO-d_6): δ 8.34 (s, 1H), 8.19 (s, 1H), 7.30–7.00 (m, 15H), 4.90 (m, 1H), 4.55 (t, 1H, J = 4.9 Hz), 4.23 (m, 4H), 3.73 (m, 4H), 3.41 (m, 1H), 3.30 (m, 1H), 3.20 (m, 2H), 2.31 (m, 1H), 2.00 (m, 1H). IR (KBr, cm^{-1}) 2853, 1580, 1444, 1251, 1111, 1066, 995. HRMS Calcd for $C_{32}H_{33}N_5O_3$ $(M+H)^+$ 536.2661. Found 536.2639.

(±)-9-[(1-Trityloxymethyl)(3-hydroxy)propyl]-6-N-pyrrolidinopurine (5i). Using the general procedure, **4** gave **5i** (20%). ^{1}H NMR (DMSO-d_6): δ 8.32 (s, 1H), 8.14 (s, 1H), 7.30–7.00 (m, 15H), 4.86 (m, 1H), 4.55 (t, 1H, J = 5.0 Hz), 4.09 (m, 2H), 3.66 (m, 2H), 3.43 (m, 1H), 3.28 (m, 1H), 3.18 (m, 2H), 2.30 (m, 1H), 1.95 (m, 5H). IR (KBr, cm^{-1}) 2925, 1588, 1467, 1323, 1220, 972. HRMS Calcd for $C_{32}H_{33}N_5O_2$ $(M+H)^+$ 520.2712. Found 520.2689.

(±)-9-[(1-Trityloxymethyl)(3-hydroxy)propyl]-6-N-phenylaminopurine (5j). Using the general procedure, **4** gave **5j** (22%). ^{1}H NMR (DMSO-d_6): δ 9.90 (s, 1H), 8.40 (s, 1H), 8.00 (s, 1H), 7.40–7.00 (m, 20H), 4.90 (m, 1H), 4.60 (t, 1H, J = 4.8 Hz), 3.46 (m, 1H), 3.36 (m, 1H), 3.25 (m, 2H), 2.37 (m, 1H), 2.02 (m, 1H). IR (KBr, cm^{-1}) 2926, 1615, 1576, 1468, 1437, 1364, 1218, 1050, 898. HRMS Calcd for $C_{34}H_{31}N_5O_2$ $(M+H)^+$ 542.2555. Found 542.2543.

(±)-9-[(1-Trityloxymethyl)(3-hydroxy)propyl]-6-cyclopentylaminopurine (5k). Using the general procedure, **4** gave **5k** (80%). ^{1}H NMR (DMSO-d_6): δ 8.27 (s, 1H), 8.10 (s, 1H), 7.30–7.00 (m, 15H), 4.83 (m, 1H), 4.55 (t, 1H, J = 4.9 Hz), 3.40 (m, 1H), 3.29 (m, 1H, partially masked by D_2O), 3.19 (m, 2H), 3.00 (m, 1H), 2.43 (m, 1H partially masked by DMSO), 2.32 (m, 1H), 2.00-41.97 (m, 2H), 1.63 (m, 6H). IR (KBr, cm^{-1}) 2938, 1710, 1614, 1476, 1222, 1105, 1039. HRMS Calcd for $C_{33}H_{35}N_5O_2$ $(M+H)^+$ 534.2868. Found 534.2851.

(±)-9-[(1-Trityloxymethyl)(3-hydroxy)propyl]-6-cyclopropylaminopurine (5l). Using the general procedure, **4** gave **5l** (88%). ^{1}H NMR (DMSO-d_6): δ 8.28 (s, 1H), 8.16 (s, 1H), 7.88 (br s, 1H), 7.30–7.00 (m, 15H), 4.86 (m, 1H), 4.56 (t, 1H, J = 4.9 Hz), 3.41 (m, 1H), 3.30 (m, 1H, partially masked water peak in DMSO-d_6), 3.17 (m, 3H), 2.32 (m, 1H), 2.00 (m, 1H), 0.95 (m, 2H), 0.80 (m, 2H). IR (KBr, cm^{-1}) 1615, 1575, 1473, 1353, 1214, 1050. HRMS Calcd for $C_{31}H_{31}N_5O_2$ $(M+H)^+$ 506.2555. Found 506.2539.

(±)-9-[(1-Trityloxymethyl)(3-hydroxy)propyl]-6-cyclobutylaminopurine (5m). Using the general procedure, **4** gave **5m** (78%). ^{1}H NMR (DMSO-d_6): δ 8.27 (s, 1H), 8.10 (s, 1H), 7.94 (m, 1H), 7.30–7.00 (m, 15H), 4.80 (m, 2H), 4.54 (t, 1H, J = 5.0 Hz), 3.40 (m, 1H), 3.30 (m, 1H, partially masked by water peak in DMSO-d_6), 3.20 (m, 2H), 2.16 (m, 6H), 1.66 (m, 2H). IR (KBr, cm^{-1}) 2929, 1612, 1575, 1471, 1219, 1048, 896. HRMS Calcd for $C_{32}H_{33}N_5O_2$ $(M+H)^+$ 520.2712. Found 520.2690.

General Procedure for the Conversion of 5a-m to 6a-m

A solution of **5a-m** in DMF (7.5 mL/mmol) was treated with sodium hydride (4 eq.) at room temperature and the mixture stirred for 1 h. To this solution was then added a solution of p-toluenesulfonyloxymethylphosphonate (1.2 eq.) in DMF (5 mL) and the mixture stirred at room temperature for 24 h. The reaction mixture was diluted with ethyl acetate, neutralized with acetic acid and washed with water and brine and the organic layer was dried over $MgSO_4$. After filtration, the filtrate was concentrated and the residue was purified on a silica gel column using ethyl acetate: hexanes:methanol (1:1:0 to 1:1:0.05) as an eluent to give the desired phosphonomethoxy derivatives.

The phosphonomethoxy derivative was taken in DMF (10 mL/mmol) and treated with triethylamine (1 mL/mmol) followed by trimethylsilyliodide (1.5 mL/mmol) and the reaction mixture flask covered with aluminum foil to protect from light and stirred for 14 h at room temperature. It was then diluted with 1 N tetraethylammonium bicarbonate buffer (10 mL/mmol), water (30 mL/mmol) and chloroform (40 mL/mmol) and was stirred for 1 h. The organic phase was collected and the aqueous phase was re-extracted with chloroform and the combined organic phases were dried over $MgSO_4$. After filtration, the filtrate was concentrated and the residue was purified on a silica gel column using chloroform:methanol (1:0 to 85:15), then CMA-80:CMA-50 (1:0 to 0:1), as eluent to give the free phosphonates **6a-m**.

(±)-9-[(1-Trityloxymethyl)(3-phosphonomethoxy)propyl]-6-diethylaminopurine (6a). Using the general procedure, **5a** gave **6a** (6%). ^{1}H NMR

(DMSO-d_6): δ 8.29 (s, 1H), 8.08 (s, 1H), 7.30–7.00 (m, 15H), 4.80 (m, 1H), 3.95 (m, 4H), 3.50–3.10 (m, 6H), 2.33 (m, 1H), 2.04 (m, 1H), 1.22 (t, 6H, J = 6.7 Hz). ^{31}P NMR: 13.20. HRMS Calcd for $C_{33}H_{38}N_5O_5P$ (M+H)$^+$ 616.2688. Found 616.2690.

(±)-9-[(1-Trityloxymethyl)(3-phosphonomethoxy)propyl]-6-N-methyl-N-ethylaminopurine (6b). Using the general procedure, **5b** gave **6b** (6.5%). ^{1}H NMR (DMSO-d_6): δ 8.30 (s, 1H), 8.11 (s, 1H), 7.30–7.00 (m, 15H), 6.10 (br s, 2H), 4.82 (m, 1H), 4.07 (m, 2H), 3.50–3.10 (m, 9H), 2.35 (m, 1H, partially masked by DMSO-d_6), 2.07 (m, 1H), 1.19 (t, 3H, J = 6.8 Hz). ^{31}P NMR: 13.20. HRMS Calcd for $C_{32}H_{36}N_5O_5P$ (M+H)$^+$ 602.2532. Found 602.2518.

(±)-9-[(1-Trityloxymethyl)(3-phosphonomethoxy)propyl]-6-ethylamino-purine (6c). Using the general procedure, **5c** gave **6c** (11%). ^{1}H NMR (DMSO-d_6): δ 8.29 (s, 1H), 8.08 (s, 1H), 7.87 (br s, 1H), 7.3–7.0 (m, 15H), 5.99 (m, 1H), 5.16 (dd, 1H, J = 1.7 and 17.1 Hz), 5.07 (dd, 1H, J = 1.7 and 17.0 Hz), 4.80 (m, 1H), 4.17 (m, 2H), 3.77 (m, 2H), 3.50–3.00 (m, 6H), 2.35 (m, 1H), 2.04 (m, 1H). ^{31}P NMR: 13.19. HRMS Calcd for $C_{32}H_{34}N_5O_5P$ (M+H)$^+$ 600.2375. Found 600.2370.

(±)-9-[(1-Trityloxymethyl)(3-phosphonomethoxy)propyl]-6-allylamino-purine (6d). Using the general procedure, **5d** gave **6d** (5.5%). ^{1}H NMR (DMSO-d_6): δ 8.26 (s, 1H), 8.10 (s, 1H), 7.30–7.00 (m, 15H), 4.83 (m, 1H), 4.60 (br s, 2H), 4.08 (m, 2H), 3.65 (m, 2H), 3.48 (m, 1H), 3.30–3.00 (m, 5H), 2.30 (m, 1H), 1.93 (m, 5H). ^{31}P NMR: 13.38. HRMS Calcd for $C_{33}H_{36}N_5O_5P$ (M+H)$^+$ 614.2532. Found 614.2551.

(±)-9-[(1-Trityloxymethyl)(3-phosphonomethoxy)propyl]-6-N-thiazoli-dinopurine (6e). Using the general procedure, **5e** gave **6e** (6%). ^{1}H NMR (DMSO-d_6): δ 8.39 (s, 1H), 8.18 (s, 1H), 7.30–7.00 (m, 15H), 5.12 (m, 2H), 4.88 (m, 1H),4.60 (br s, 2H), 4.30 (m, 2H), 3.50 (m, 1H), 3.18 (m, 7H), 2.35 (m, 1H, partially masked by DMSO-d_6), 2.07 (m, 1H). ^{31}P NMR: 13.03. HRMS Calcd for $C_{32}H_{34}N_5O_5SP$ (M+H)$^+$ 632.2096. Found 632.2094.

(±)-9-[(1-Trityloxymethyl)(3-phosphonomethoxy)propyl]-6-N-azetidi-nopurine (6f). Using the general procedure, **5f** gave **6f** (6.5%). ^{1}H NMR (DMSO-d_6): δ 8.35 (s, 1H), 8.15 (s, 1H), 7.30–7.00 (m, 15H), 5.30 (br s, 2H), 4.86 (m, 1H), 4.23 (m, 4H), 3.72 (m, 4H), 3.48 (m, 1H), 3.40–3.10 (m, 5H), 2.35 (m, 1H), 2.05 (m, 1H). ^{31}P NMR: 13.19. HRMS Calcd for $C_{33}H_{36}N_5O_6P$ (M+H)$^+$ 630.2481. Found 630.2507.

(±)-9-[(1-Trityloxymethyl)(3-phosphonomethoxy)propyl]-6-N-piperidinopurine (6g). Using the general procedure, **5g** gave **6g** (9%). ^{1}H NMR (DMSO-d_6): δ 8.30 (s, 1H), 8.10 (s, 1H), 7.30–7.00 (m, 15H), 4.83 (m, 1H), 4.60 (br s, 2H), 4.21 (m, 4H), 3.46 (m, 1H), 3.40–3.00 (m, 5H), 2.35 (m, 1H), 2.06 (m, 1H), 1.64 (m, 6H). ^{31}P NMR: 13.15. HRMS Calcd for $C_{34}H_{38}N_5O_5P$ $(M+H)^+$ 628.2688. Found 628.2685.

(±)-9-[(1-Trityloxymethyl)(3-phosphonomethoxy)propyl]-6-N-morpholinopurine (6h). Using the general procedure, **5h** gave **6h** (6%). ^{1}H NMR (DMSO-d_6): δ 8.28 (s, 1H), 8.09 (s, 1H), 7.30–7.00 (m, 15H), 4.82 (m, 1H), 4.60 (br s, 2H), 4.37 (m, 2H), 3.48 (m, 1H), 3.28 (m, 1H), 3.14 (m, 4H), 2.46 (m, 2H, partially masked by DMSO-d_6), 2.30 (m, 1H), 2.04 (m, 1H). ^{31}P NMR: 13.05. HRMS Calcd for $C_{32}H_{34}N_5O_5P$ $(M+H)^+$ 600.2375. Found 600.2369.

(±)-9-[(1-Trityloxymethyl)(3-phosphonomethoxy)propyl]-6-N-pyrrolidinopurine (6i). Using the general procedure, **5i** gave **6i** (10%). ^{1}H NMR (DMSO-d_6): δ 8.27 (s, 1H), 8.15 (s, 1H), 7.3–7.0 (m, 15H), 4.83 (m, 1H), 4.51 (br s, 2H), 4.10 (m, 2H), 3.65 (m, 2H), 3.52 (m, 1H), 3.3–3.0 (m, 5H), 2.38 (m, 1H), 2.0 (m, 5H). ^{31}P NMR: 13.64. HRMS Calcd for $C_{33}H_{36}N_5O_5P$ $(M+H)^+$ 614.2532. Found 614.2551.

(±)-9-[(1-Trityloxymethyl)(3-phosphonomethoxy)propyl]-6-N-phenylaminopurine (6j). Using the general procedure, **5j** gave **6j** (5.5%). ^{1}H NMR (DMSO-d_6): δ 9.86 (br s, 1H), 8.48 (s, 1H), 8.28 (s, 1H), 7.40–7.00 (m, 20H), 5.20 (br s, 2H), 4.91 (m, 1H), 3.51 (m, 1H), 3.21 (m, 5H), 2.36 (m, 1H), 2.08 (m, 1H). ^{31}P NMR: 13.27. HRMS Calcd for $C_{35}H_{34}N_5O_5P$ $(M+H)^+$ 636.2375. Found 636.2364.

(±)-9-[(1-Trityloxymethyl)(3-phosphonomethoxy)propyl]-6-cyclopentylaminopurine (6k). Using the general procedure, **5k** gave **6k** (10%) δ in ppm (DMSO-d_6): 8.26 (s, 1H), 8.05 (s, 1H), 7.58 (br s, 1H), 7.30–7.00 (m, 15H), 4.81 (m, 1H), 4.53 (m, 2H), 3.50–3.00 (m, 6H), 2.35 (m, 2H), 1.95 (m, 2H), 1.63 (m, 6H). ^{31}P NMR: 13.91.

(±)-9-[(1-Trityloxymethyl)(3-phosphonomethoxy)propyl]-6-cyclopropylaminopurine (6l). Using the general procedure, **5l** gave **6l** (6.5%). ^{1}H NMR (DMSO-d_6): δ 8.29 (s, 1H), 8.13 (1H), 7.80 (br s, 1H), 7.30–7.00 (m, 15H), 4.82 (m, 1H), 4.50 (br s, 2H), 3.46 (m, 3H), 3.30–3.10 (m, 4H), 2.35 (m, 1H, partially masked by DMSO-d_6), 2.05 (m, 1H), 0.70 (m, 4H). ^{31}P NMR: 12.75. HRMS Calcd for $C_{32}H_{34}N_5O_5P$ $(M+H)^+$ 600.2373. Found 600.2378.

(±)-9-[(1-Trityloxymethyl)(3-phosphonomethoxy)propyl]-6-cyclobutylaminopurine (6m). Using the general procedure, **5m** gave **6m** (6.5%). ^{1}H NMR (DMSO-d_6): δ 8.29 (s, 1H), 8.07 (s, 1H), 7.96 (br s, 1H), 7.30–7.00 (m, 15H), 5.00 (br s, 2H), 4.79 (m, 2H), 3.45 (m, 1H), 3.30 (m, 1H), 3.15 (m, 4H), 2.36–2.00 (m, 6H), 1.66 (m, 2H). ^{31}P NMR: 12.94. HRMS Calcd for $C_{33}H_{36}N_5O_5P$ $(M+H)^+$ 614.2532. Found 614.2538.

General Procedure for the Conversion of 6a-m to 7a-m

A solution of **6a-m** in DMF (10 mL/mmol) was treated with triethylamine (12 mL/mmol) followed by chloromethyl pivalate or chloromethyl-2-propylcarbonate (25 eq.) and stirred for 2 days at room temperature. The mixture was then diluted with ethyl acetate and washed with water and the organic layer was dried over $MgSO_4$. After filtration, the filtrate was concentrated and the residue purified on a silica gel column using chloroform: methanol (100:0 to 95:5) as eluent to give diprotected prodrugs of phosphonic acids. The resultant prodrugs were taken in acetonitrile:0.2 M HCl (1:1, 10 mL/mmol) and stirred for 14 h at room temperature. The solution was then very carefully neutralized with Et_3N to pH 6.0, diluted with water, and concentrated to remove most of the organic solvent. The residual material was again diluted with water and extracted with chloroform and the organic layer was dried over $MgSO_4$. After filtration, the filtrate was concentrated and the residue purified on a silica gel column using chloroform:methanol (1:0 to 9:1) as eluent to give the desired targets **7a-m** as colorless oil.

(±)-9-[(1-Hydroxymethyl)(3-(di-isopropyloxycarbonyloxymethylphosphono)methoxy)propyl]-6-diethylaminopurine (7a). Using the general procedure, **6a** gave **7a** (46%). ^{1}H NMR (DMSO-d_6): δ 8.16 (s, 1H), 8.10 (s, 1H), 5.56 (m, 4H), 5.04 (t, 1H, J = 5.3 Hz), 4.80 (m, 2H), 4.58 (m, 1H), 4.10 (m, 4H), 3.83 (m, 3H), 3.66 (m, 1H), 3.45 (m, 1H), 3.30 (m, 1H partially masked by water in DMSO-d_6), 2.17 (m, 2H), 1.21 (m, 18H). ^{31}P NMR: 22.83. MS (ES$^+$) 606.66 $(M+H)^+$. Anal. Calcd for $C_{24}H_{40}N_5O_{11}P \bullet 0.25\ H_2O$: C, 47.25; H, 6.69; N, 11.47. Found: C, 47.10; H, 6.85; N, 11.28.

(±)-9-[(1-Hydroxymethyl)(3-(di-isopropyloxycarbonyloxymethylphosphono)methoxy)propyl]-6-N-methyl-N-ethylaminopurine (7b). Using the general procedure, **6b** gave **7b** (20%). ^{1}H NMR (DMSO-d_6): δ 8.17 (s, 1H), 8.11 (s, 1H), 5.59 (m, 4H), 5.05 (t, 1H, J = 5.4 Hz), 4.80 (m, 2H), 4.59 (m, 1H), 4.05 (m, 2H), 3.82 (m, 3H), 3.66 (m, 1H), 3.40 (m, 2H), 2.49 (s, 3H, partially masked by DMSO-d_6), 2.17 (m, 2H), 1.24 (m, 15H). ^{31}P NMR: 22.80. MS (ES$^+$) 592.08 $(M+H)^+$. Anal. Calcd for $C_{23}H_{38}N_5O_{11}P \bullet 0.5\ H_2O$: C, 45.99; H, 6.54; N, 11.66. Found: C, 46.22; H, 6.57; N, 11.36.

(±)-9-[(1-Hydroxymethyl)(3-(di-*tert*-butylcarbonyloxymethylphosphono)methoxy)propyl]-6-ethylaminopurine (7c). Using the general procedure, **6c** gave **7c** (31%).[1]H NMR (DMSO-d_6): δ 8.14 (s, 1H), 8.08 (s, 1H), 7.71 (br s, 1H), 5.60 (m, 4H), 5.04 (t, 1H, $J = 5.4$ Hz), 4.55 (m, 1H), 3.82 (m, 3H), 3.70 (m, 1H), 3.48 (m, 3H), 3.29 (m, 1H partially masked by water peak in DMSO-d_6), 2.18 (m, 2H), 1.13 (m, 21H). ^{31}P NMR: 22.87. MS (ES$^+$) 596.31 (M + Na)$^+$.

(±)-9-[(1-Hydroxymethyl)(3-(di-*tert*-butylcarbonyloxymethylphosphono)methoxy)propyl]-6-allylaminopurine (7d). Using the general procedure, **6d** gave **7d** (32%). ^{1}H NMR (DMSO-d_6): δ 8.15 (s, 1H), 8.10 (s, 1H), 7.89 (br s, 1H), 5.93 (m, 1H), 5.59 (m, 4H), 5.14 (m, 1H), 5.05 (m, 2H), 4.56 (m, 1H), 4.10 (m, 2H), 3.82 (m, 3H), 3.69 (m, 1H), 3.45 (m, 1H), 3.29 (m, 1H partially masked by water peak in DMSO-d_6), 2.19 (m, 2H), 1.17 (m, 18H). ^{31}P NMR: 22.87. MS (ES$^+$) 608.33 (M + Na)$^+$. Anal. Calcd for $C_{25}H_{40}N_5O_9P$: C, 50.45; H, 6.76; N, 11.72. Found: C, 50.45; H, 7.14; N, 11.03.

(±)-9-[(1-Hydroxymethyl)(3-(di-isopropyloxycarbonyloxymethylphosphono)methoxy)propyl]-6-N-thiazolidinopurine (7e). Using the general procedure, **6e** gave **7e** (27%). ^{1}H NMR (DMSO-d_6): δ 8.26 (s, 1H), 8.21 (s, 1H), 5.57 (m, 4H), 5.05 (m, 2H), 4.81 (m, 2H), 4.61 (m, 1H), 4.28 (m, 2H), 3.83 (m, 3H), 3.70 (m, 1H), 3.45 (m, 1H), 3.29 (m, 2H partially masked by water peak in DMSO-d_6), 3.12 (m, 2H), 2.20 (m, 2H), 1.22 (m, 12H). ^{31}P NMR: 22.80. MS (ES$^+$) 622.08 (M+H)$^+$. Anal. Calcd for $C_{23}H_{36}N_5O_{11}PS \bullet 0.5\ H_2O$: C, 43.80; H, 5.91; N, 11.10. Found: C, 44.58; H, 6.10; N, 10.67.

(±)-9-[(1-Hydroxymethyl)(3-(di-isopropyloxycarbonyloxymethylphosphono)methoxy)propyl]-6-N-azetidinopurine (7f). Using the general procedure, **6f** gave **7f** (24%). ^{1}H NMR (DMSO-d_6): δ 8.15 (s, 1H), 8.09 (s, 1H), 5.58 (m, 4H), 5.04 (t, 1H, $J = 5.4$ Hz), 4.81 (m, 2H), 4.56 (m, 1H), 4.33 (m, 4H), 3.83 (m, 3H), 3.70 (m, 1H), 3.43 (m, 1H), 3.27 (m, 1H partially masked by water in DMSO-d_6), 2.42 (m, 2H), 2.16 (m, 2H), 1.23 (m, 12H). ^{31}P NMR: 22.79. MS (ES$^+$) 590.04 (M+H)$^+$. Anal. Calcd for $C_{23}H_{36}N_5O_{11}P \bullet 0.75\ H_2O$: C, 45.80; H, 6.26; N, 11.61. Found: C, 45.96; H, 6.44; N, 11.25.

(±)-9-[(1-Hydroxymethyl)(3-(di-isopropyloxycarbonyloxymethylphosphono)methoxy)propyl]-6-N-piperidinopurine (7g). Using the general procedure, **6g** gave **7g** (43%). ^{1}H NMR (DMSO-d_6): δ 8.16 (s, 1H), 8.11 (s, 1H), 5.57 (m, 4H), 5.04 (t, 1H, $J = 5.4$ Hz), 4.81 (m, 2H), 4.59 (m, 1H), 4.19 (m, 4H), 3.83 (m, 3H), 3.68 (m, 1H), 3.43 (m, 1H), 3.29 (m, 1H partially masked by water in DMSO-d_6), 2.19 (m, 2H), 1.70–1.30 (m, 6H), 1.23 (m, 12H). ^{31}P NMR: 22.81. MS (ES$^+$) 618.34 (M+H)$^+$. Anal. Calcd for

$C_{25}H_{40}N_5O_{11}P \bullet 0.75\ H_2O$: C, 47.57; H, 6.62; N, 11.09. Found: C, 47.86; H, 6.56; N, 10.62.

(±)-9-[(1-Hydroxymethyl)(3-(di-isopropyloxycarbonyloxymethylphosphono)methoxy)propyl]-6-N-morpholinopurine (7h). Using the general procedure, **6h** gave **7h** (18%). ^{1}H NMR (DMSO-d_6): δ 8.22 (s, 1H), 8.17 (s, 1H), 5.57 (m, 4H), 5.04 (t, 1H, J = 5.3 Hz), 4.81 (m, 2H), 4.60 (m, 1H), 4.19 (m, 4H), 3.83 (m, 3H), 3.71 (m, 5H), 3.43 (m, 1H), 3.29 (m, 1H partially masked by water in DMSO-d_6), 2.18 (m, 2H), 1.23 (m, 12H). ^{31}P NMR: 22.79. MS (ES$^+$) 620.29 (M+H)$^+$. Anal. Calcd for $C_{24}H_{38}N_5O_{12}P \bullet 0.5\ H_2O$: C, 45.85; H, 6.25; N, 11.14. Found: C, 46.05; H, 6.21; N, 10.42.

(±)-9-[(1-Hydroxymethyl)(3-(di-isopropyloxycarbonyloxymethylphosphono)methoxy)propyl]-6-N-pyrrolidinopurine (7i). Using the general procedure, **6i** gave **7i** (28%). ^{1}H NMR (DMSO-d_6): δ 8.16 (s, 1H), 8.08 (s, 1H), 5.58 (m, 4H), 5.05 (t, 1H, J = 5.4 Hz), 4.81 (m, 2H), 4.58 (m, 1H), 4.05 (m, 2H), 3.83 (m, 3H), 3.67 (m, 3H), 3.43 (1H), 3.28 (m, 1H partially masked by water peak in DMSO-d_6), 2.19 (m, 2H), 1.94 (m, 4H), 1.22 (m, 12H). ^{31}P NMR: 22.78. MS (ES$^+$) 604.29 (M+H)$^+$. Anal. Calcd for $C_{24}H_{38}N_5O_{11}P \bullet 0.5\ CHCl_3$: C, 44.99; H, 5.94; N, 10.75. Found: C, 45.09; H, 6.03; N, 10.16.

(±)-9-[(1-Hydroxymethyl)(3-(di-isopropyloxycarbonyloxymethylphosphono)methoxy)propyl]-6-N-phenylaminopurine (7j). Using the general procedure, **6j** gave **7j** (31%). ^{1}H NMR (DMSO-d_6): δ 9.84 (br s, 1H), 8.32 (s, 1H), 8.30 (s, 1H), 7.94 (m, 2H), 7.31 (m, 2H), 7.02 (m, 1H), 5.58 (m, 4H), 5.07 (t, 1H, J = 5.3 Hz), 4.80 (m, 2H), 4.63 (m, 1H), 3.84 (m, 3H), 3.73 (m, 1H), 3.46 (m, 1H), 3.29 (m, 1H partially masked by water peak in DMSO-d_6), 2.21 (m, 2H), 1.21 (m, 12H). ^{31}P NMR: 22.81. MS (ES$^+$) 626.23 (M+H)$^+$. Anal. Calcd for $C_{26}H_{36}N_5O_{11}P \bullet H_2O$: C, 48.52; H, 5.95; N, 10.88. Found: C, 48.66; H, 5.89; N, 10.39.

(±)-9-[(1-Hydroxymethyl)(3-(di-*tert*-butylcarbonyloxymethylphosphono)methoxy)propyl]-6-cyclopentylaminopurine (7k). Using the general procedure, **6k** gave **7k** (45%). ^{1}H NMR (DMSO-d_6): δ 8.14 (s, 1H), 8.08 (s, 1H), 7.60 (br s, 1H), 5.58 (m, 4H), 5.04 (t, 1H, J = 5.4 Hz), 4.54 (m, 2H), 3.78 (m, 3H), 3.68 (m, 1H), 3.42 (m, 1H), 3.29 (m, 1H partially masked by water in DMSO-d_6), 2.17 (m, 2H), 1.90 (m, 2H), 1.80–1.50 (m, 6H), 1.12 (m, 18H). ^{31}P NMR: 22.88. MS (ES$^+$) 614.44 (M+H)$^+$. Anal. Calcd for $C_{27}H_{44}N_5O_9P$: C, 50.53; H, 7.04; N, 10.83. Found: C, 50.64; H, 7.12; N, 10.44.

(±)-9-[(1-Hydroxymethyl)(3-(di-isopropyloxycarbonyloxymethylphosphono)methoxy)propyl]-6-cyclopropylaminopurine (7l). Using the general procedure, **6l** gave **7l** (7%). ^{1}H NMR ($CDCl_3$): δ 8.38 (s, 1H), 7.89 (s, 1H), 6.20 (br s, 1H), 5.71 (m, 5H), 4.92 (m, 2H), 4.71 (m, 1H), 4.08 (m, 2H), 3.84 (m, 2H), 3.65 (m, 1H), 3.23 (m, 1H), 3.02 (br s, 1H), 2.27 (m, 2H), 1.29 (m, 12H), 0.94 (m, 2H), 0.66 (m, 2H). ^{31}P NMR: 22.69. MS (ES$^+$) 590.19 $(M+H)^+$.

(±)-9-[(1-Hydroxymethyl)(3-(di-isopropyloxycarbonyloxymethylphosphono)methoxy)propyl]-6-cyclobutylaminopurine (7m). Using the general procedure, **6m** gave **7m** (29%). ^{1}H NMR (DMSO-d_6): δ 8.14 (s, 1H), 8.10 (s, 1H), 7.95 (br s, 1H), 5.58 (m, 4H), 5.04 (t, 1H, J = 5.3 Hz), 4.80 (m, 2H), 4.60 (m, 2H), 3.84 (m, 3H), 3.68 (m, 1H), 3.44 (m, 1H), 3.27 (m, 1H partially masked by water peak in DMSO-d_6), 2.15 (m, 6H), 1.64 (m, 2H), 1.24 (m, 12H). ^{31}P NMR: 22.81. MS (ES$^+$) 604.13 $(M+H)^+$. Anal. Calcd for $C_{24}H_{38}N_5O_{11}P \bullet 0.75\ H_2O$: C, 46.71; H, 6.45; N, 11.34. Found: C, 47.14; H, 6.65; N, 11.04.

REFERENCES

1. Holy, A.; Dvorakova, H.; Jindrich, J.; Masojidkova, M.; Budesinsky, M.; Balzarini, J.; Andrei, G.; De Clercq, E. Acyclic nucleotide analogs derived from 8-azapurines: Synthesis and antiviral activity. J. Med. Chem. **1996**, 39, 4073–4088.
2. Balzarini, J.; Pannecouque, C.; De Clercq, E.; Aquaro, S.; Perno, C.-F.; Egberink, H.; Holy, A. Antiretrovirus activity of a novel class of acyclic pyrimidine nucleoside phosphonates. Antimicrob. Agents Chemother. **2002**, 46, 2185–2193.
3. Balzarini, J.; Perno, C.F.; Schols, D.; De Clercq, E. Activity of acyclic nucleoside phosphonate analogues against human immunodeficiency virus in monocyte/macrophages and peripheral blood lymphocytes. Biochem. Biophys. Res. Commun. **1991**, 178, 329–335.
4. De Clercq, E.; Holy, A.; Rosenberg, I.; Sakuma, T.; Balzarini, J.; Maudgal, P.C. A novel selective broad-spectrum anti-DNA virus agent. Nature **1986**, 323, 464–467.
5. Naesens, L.; De Clercq, E. Therapeutic potential of HPMPC (cidofovir), PMEA (adefovir) and related acyclic nucleoside phosphonate analogues as broad-spectrum antiviral agents. Nucleosides Nucleotides **1997**, 16, 983–992.
6. Balzarini, J.; Holy, A.; Jindrich, J.; Naesens, L.; Snoeck, R.; Schols, D.; De Clercq, E. Differential antiherpesvirus and antiretrovirus effects of the (S) and (R) enantiomers of acyclic nucleoside phosphonates: Potent and selective in vitro and in vivo antiretrovirus activities of (R)-9-(2-phosphonomethoxypropyl)-2,6-diaminopurine. Antimicrob. Agents Chemother. **1993**, 37, 332–338.
7. Balzarini, J.; Aquaro, S.; Perno, C.-F.; Holy, A.; De Clercq, E. Activity of the (R)-enantiomers of 9-(2-phosphonyl-methoxypropyl)adenine and 9-(2-phosphonyl-methoxypropyl)-2,6-diaminopurine against human immunodeficiency virus in different human cell systems. Biochem. Biophys. Res. Commun. **1996**, 219, 337–341.
8. Vittori, S.; Lorenzen, A.; Stannek, C.; Costanzi, S.; Volpini, R.; IJzerman, A.P.; Von Frijtag Drabbe Kunzel, J. K.; Cristalli, G. N-cycloalkyl derivatives of adenosine and 1-deazaadenine as agonists and partial agonists of the A_1 adenosine receptor. J. Med. Chem. **2000**, 43, 250–260.
9. Hamilton, H.W.; Bristo, J.A. C_4 Substituted 1-β-D-ribofuranosylpyrazolo[3,4-d]pyrimidines as adenosine agonist analogues. J. Med. Chem. **1983**, 26, 1601–1606.
10. Angeli, P.; Brasili, L.; Brancia, E.; Giardina, D.; Quaglia, W.; Melchiorre, C. Structure-activity relationships among benextramine-related tetraamine disulfides at peripheral α-adrenoreceptors. J. Med. Chem. **1985**, 28, 1643–1647.
11. Carroll, S.S.; Tomassini, J.E.; Bosserman, M.; Getty, K.; Stahlhut, M.W.; Eldrup, A.B.; Bhat, B.; Hall, D.; Simcoe, A.L.; LaFemina, R.; Rutkowski, C.A.; Wolanski, B.; Yang, Z.; Migliaccio, G.;

De Francesco, R.; Kuo, L.C.; MacCoss, M.; Olsen, D.B. Inhibition of hepatitis C virus RNA replication by 2′-modified nucleoside analogues. J. Biol. Chem. **2003**, 278(14), 11979–11984.

12. Carroll, S.S.; LaFemina, R.; Hall, D.; Himmelberger, A.L.; Kuo, L.C.; MacCoss, M.; Olsen, D.B.; Rutkowski, C.A.; Tomassini, J.E.; An, H.; Bhat, B.; Bhat, N.; Cook, P.D.; Eldrup, A.B.; Guinosso C.J.; Prhavc, M.; Prakash, T.P. Nucleoside derivatives as inhibitors of RNA-dependent RNA viral polymerase. PCT Patent Appl. WO 02/057425 A2, 2002.
13. Ding, Y.; An, H. Deazapurine nucleoside analogs and their use as therapeutic agents. PCT Patent Appl. WO 03/061576 A2, 2003.
14. An, H.; Ding, Y.; Shaw, S.; Hong, Z. 2′-beta-modified-6-substituted adenosine analogs and their use as antiviral agents. PCT Patent Appl. WO 03/062256 A1, 2003.
15. Hong, Z.; An, H.; Ding, Y.; Girardet, J.L.; Zhong, W. Sugar modified nucleosides as viral replication inhibitors. PCT Patent Appl. WO 03/062255 A2, 2003.
16. An, H.; Hong, Z.; Smith, K.; Ding, Y.; Girardet, J.L. Tricyclic nucleoside library compounds, synthesis, and use as antiviral agents. PCT Patent Appl. WO 03/061385 A1, 2003.
17. Carroll, S.S.; Tomassini, J.E.; Bosserman, M.; Getty, K.; Stahlhut, M.W.; Eldrup, A.B.; Bhat, B.; Hall, D.; Simcoe, A.L.; LaFemina, R.; Rutkowski, C.A.; Wolanski, B.; Yang, Z.; Migliaccio, G.; De Francesco, R.; Kuo, L.C.; MacCoss, M.; Olsen, D.B. Inhibition of hepatitis C virus RNA replication by 2′-modified nucleoside analogs. J. Biol. Chem. **2003**, 278, 11979–11984.