SUPPLEMENTAL DATA

Cellular influx, efflux, and anabolism of 3-carboranyl thymidine analogs: Potential boron delivery agents for neutron capture therapy.

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S.1. Chemistry

S.1.1. General Experimental Part

^{1}H-, ^{13}C-, and ^{31}P NMR spectra were obtained on a Bruker DRX 400 at The Ohio State University College of Pharmacy (400 MHz for ^{1}H, 100 MHz for ^{13}C, and 161 MHz for ^{31}P). Chemical shifts (δ) are reported in ppm from internal deuterated chloroform or methanol. Coupling constants are reported in Hz. ^{13}C and ^{31}P nuclear magnetic resonance (NMR) spectra are fully decoupled. High resolution–electrospray ionization (HR-ESI) mass spectra (MS) were obtained on a Micromass LCT spectrometer at The Ohio State University Campus Chemical Instrumentation Center.

Silica gel 60 (0.063-0.200 mm), used for gravity column chromatography, and silica gel 60 (0.015-0.049 mm), used for flash column chromatography, were purchased from Dynamic Adsorbents Inc. (Norcross, GA). Reagent-grade solvents were used for column chromatography. Precoated glass-backed thin layer chromatography (TLC) plates with silica gel 60 F254 (0.25 mm layer thickness) from Dynamic Adsorbents Inc. were used for TLC. General compound visualization for TLC was achieved by UV light. Carborane-containing compounds were selectively visualized by spraying the plate with a 0.06% $PdCl_2$/1% HCl solution and heating at 120°C, which caused the slow (15-45 s) formation of a gray spot due to the reduction of Pd^{2+} to Pd^{0}.

Anhydrous solvents were purchased directly either from Acros Organics (Morris Plains, NJ) or from Sigma Aldrich (Milwaukee, WI). Tetrahydrofuran (THF) was distilled from sodium and benzophenone indicator under argon. All reactions were carried out under argon.

Preparative high pressure liquid chromatography (HPLC) was performed with a Gemini 5µ C18 column (21.20 mm x 250 mm, 5 µm particle size) supplied by Phenomenex Inc. (Torrance,

CA) on a Hitachi HPLC system (L-2130) with a Windows based data acquisition and Hitachi Diode array detector (L-2455). Analytical HPLC was carried out with a Gemini 5μ C18 110A Column (250 x 4.6 mm) supplied by Phenomenex Inc. using the HPLC system mentioned above. Radiometer HPLC was performed with Beckman System Gold HPLC system with 166 UV/Vis detector and 127 solvent module.

S.1.2. Solvent systems for HPLC analysis

S.1.2.1 Preparative HPLC

Method A:

Time (min)	**Triethylammonium hydrogen carbonate buffer (100 mM)**	**Acetonitrile (0.1 % TFA) Concentration**	**Flow rate (ml/min)**
	A (%)	**B (%)**	
0	100	0	1
1	100	0	7
110	40	60	7
111	100	0	7
120	100	0	1

S.1.2.2. Analytical HPLC

Method B:

Time (min)	Water (0.1 % TFA) Concentration A (%)	Acetonitrile (0.1 % TFA) Concentration B (%)	Flow rate (ml/min)
0	55	45	1
25	55	45	1
34	0	100	1
35	55	45	1
45	55	45	1

Method C:

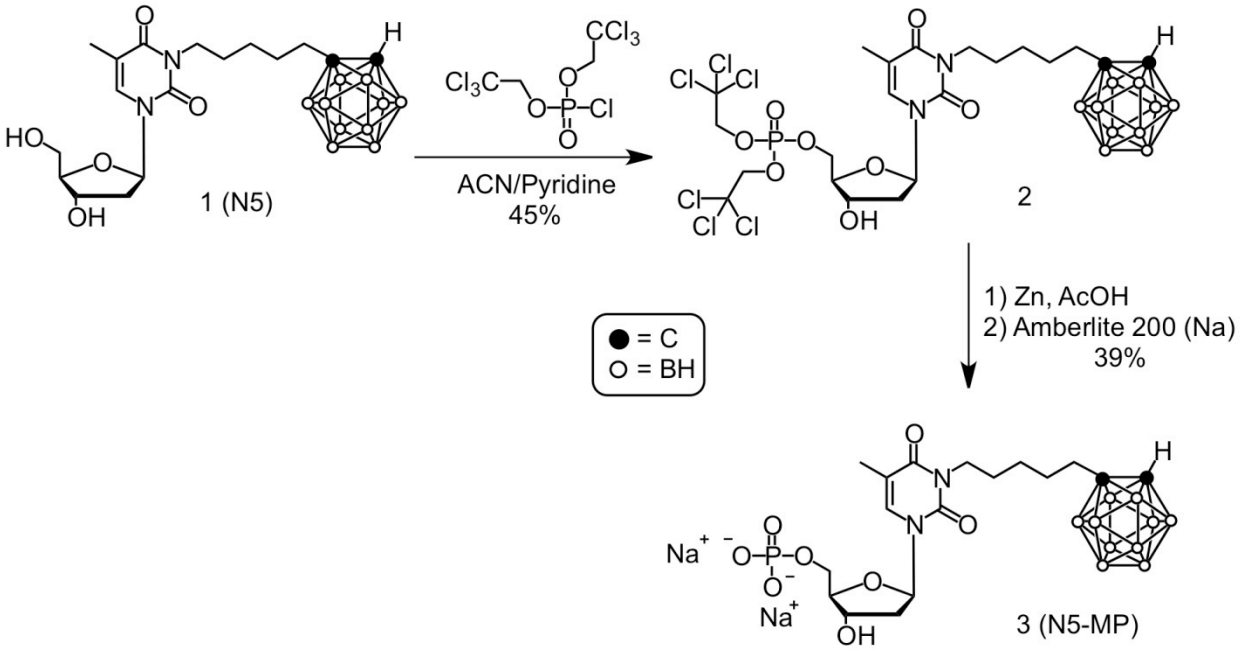
Time (min)	Water (0.1 % TFA) Concentration A (%)	Acetonitrile (0.1 % TFA) Concentration B (%)	Flow rate (ml/min)
0.00	65.0	35.0	1.0
27.0	30.0	70.0	1.0
28.0	65.0	35.0	1.0
40.0	65.0	35.0	1.0

S.1.3. Detailed synthetic procedures

S.1.3.1. Previously described compounds

N5-2OH (Hasabelnaby et al. 2012), N5-2OH monophosphate (Al-Madhoun et al., 2004), N5 (Lunato et al., 1999) as well as compounds 5 (Hasabelnaby et al. 2012) and 6 (Davisson et al., 1987) (see below) were synthesized as described previously. HPLC retention times for N5 (Method B), N5-2OH (Method C), and N5-2OH-MP (Method C) were 33.04, 16.45 and 13.87, respectively.

S.1.3.2. Synthesis of N5-MP



Scheme S1: Synthesis of N5-monophosphate

S.1.3.2.1. 5'-Bis(2,2,2-trichloroethyl) ester of N5 (2).

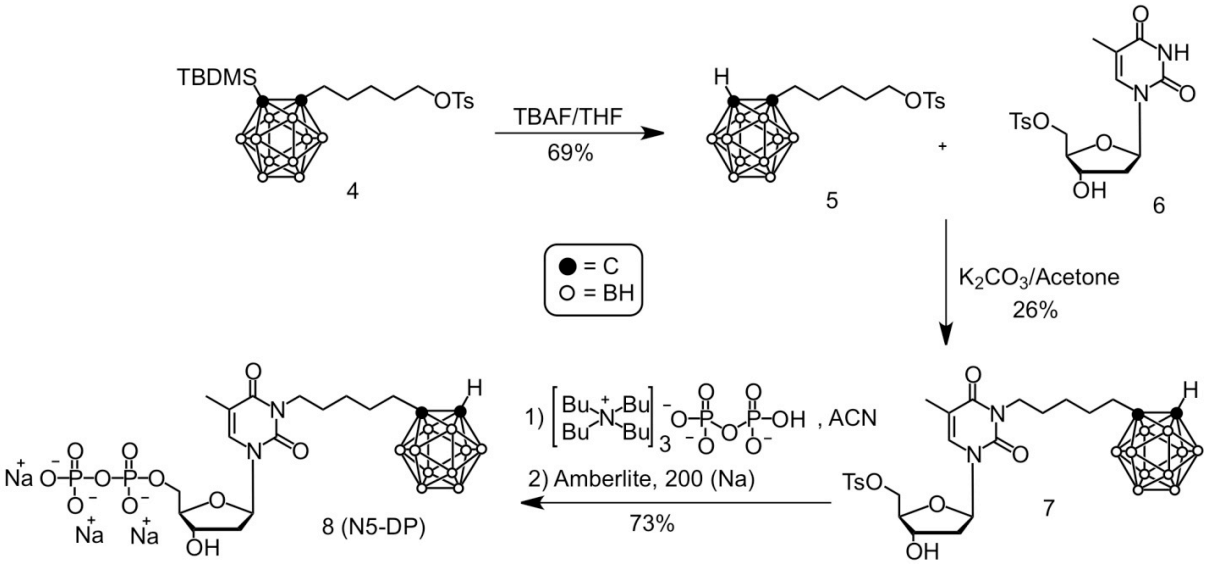
A mixture of N5 (compound **1**, 340 mg, 0.75 mmol), bis(2,2,2-trichoroethyl) phosphorochloridate (330 mg, 0.87 mmol), anhydrous pyridine (50 µL, 1.04 mmol) in 10 ml of

acetonitrile was stirred at 0°C for 5 days. The reaction was quenched by adding 5 ml of MeOH and stirred for additional 30 min at room temperature. Following solvent evaporation, the residue was extracted with 20 ml of diethylether and washed with 10 ml of 0.1 M HCl. The organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography using hexanes: ethyl acetate (9:1) to give compound **2** (0.27 g, 45%). ^{1}H NMR (MeOH-d4) δ: 7.55 (s, 1H), 6.30 (t, *J* = 6.8, 1H), 4.8 (ds, 4H), 4.44-4.51 (m, 4H), 4.11 (m, 1H), 3.88 (t, *J* = 7.1, 2H), 2.24-2.32 (m, 4H), 2.93 (s, 3H), 1.50-1.61 (s, 4H), 1.30 (m, 2H). ^{13}C NMR (MeOH-d4) δ: 164.53, 151.45, 135.57, 110.41, 95.26, 86.90, 85.32, 77.77, 76.53, 71.00, 69.34, 62.88, 41.25, 39.82, 37.83, 29.24, 27.27, 26.45, 12.66. MS (HR-ESI) for $C_{21}H_{36}B_{10}Cl_2N_2NaO_8P$ [$(M+Na)^+$]. Calcd: m/z 819.1290 Found: m/z 819.1309. HPLC retention time (Method B): 21.71.

S.1.3.2.2. Disodium salt of the 5'-monophosphate of N5 (3).

To a solution of 20 mg (0.31 mmol) of zinc powder in 10 ml of acetic acid, compound **2** (30 mg, 0.04 mmol) was added and the resulting suspension was stirred for 10 h. The reaction mixture was filtered and evaporated. The residue was purified by HPLC (Method A) and the desired compound was passed through a column containing Amberlite 200 (sodium form) to furnish the disodium salt of the 5'-monophosphates of N5 (**3**, 8.5 mg, 39%). ^{1}H NMR (MeOH-d4, 400 MHz) δ: 7.91 (s, 1H), 6.36 (t, J= 6.74, 1H), 4.52 (m, 2H), 4.04 (m, 3H), 3.9 (t, *J* = 6.94, 2H), 2.20-2.31 (m, 4H), 1.96 (s, 3H), 1.47-1.64 (m, 4H), 1.31 (m, 2H). ^{13}C NMR (MeOH-d4, 100 MHz) δ: 165.50, 152.38, 136.70, 111.14, 88.04, 87.14, 77.27, 73.17, 63.62, 61.96, 41.89, 38.56, 30.73, 29.95, 27.96, 27.15, 13.43. ^{31}P NMR (MeOH-d4, 161 MHz) δ: 4.31. MS (HR-ESI) for $C_{17}H_{34}B_{10}N_2O_8PNa$ [$(M+Na)^+$]. Calcd: m/z 556.2954 Found: m/z 556.2939.

S.1.3.3. Synthesis of N5-DP



Scheme S2: Synthesis of N5-Diphosphate

S.1.3.3.1. 5-(*o*-Carboran-1-yl)pentyl tosylate (5).

To a solution of compound **4** (0.3 g, 0.6 mmol) in THF (30 ml) was added a 1 M solution of TBAF (0.9 ml, 0.9 mmol) in THF at -78ºC. The reaction mixture was stirred at room temperature for 1 h. Distilled water (10 ml) was added and excess THF was removed under reduced pressure. The residue was extracted with ethyl acetate, the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and filtered. The residue was purified by silica gel column chromatography using hexanes: ethyl acetate (8:2) to give compound **5** (158 mg, 69%). ^{1}H NMR ($CDCl_3$) δ: 7.77 (d, *J* = 8.26, 2H), 7.35 (d, *J*= 8.26, 2H), 4.00 (t, *J* = 6.1, 2H), 3.45 (s, 1H), 2.46 (s, 3H), 2.15 (t, *J* = 8.1, 2H), 1.64 (m, 2H), 1.41 (m, 2H), 1.31 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 145.07, 133.07, 130.05, 127.99, 75.04, 69.96, 61.24, 37.84, 28.60, 28.43, 24.96, 21.80.

S.1.3.3.2. 3-(*o*-Carboranylpentyl)-5'-tosyl-thymidine (7).

A mixture of compound **5** (130 mg, 0.34 mmol), compound **6** (122 mg, 0.31 mmol), and K_2CO_3 (85 mg, 0.62 mmol) in 10 ml of DMF/acetone (50/50) was stirred for 2 days at 50°C. The solvent was evaporated and the residue was purified by silica gel column chromatography using DCM: acetone (85: 15) to give compound **7** (50 mg, 27%). ^{1}H NMR ($CDCl_3$) δ: 7.79 (d, *J* = 8.6, 2H), 7.38 (m, 3H), 6.37 (t, *J* = 7.2, 1H), 4.53 (m, 1H), 4.26 (d, *J* = 2.51, 1H), 4.09 (m, 1H), 3.88 (m, 2H), 3.59 (br s, 1H), 2.47 (s, 3H), 2.33-2.39 (m, 2H), 2.16-2.24 (m, 4H), 1.94 (s, 3H), 1.59 (m, 2H), 1.49 (m, 2H), 1.32 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 163.44, 151.00, 145.82, 133.42, 132.34, 130.34, 127.98, 110.95, 85.43, 83.70, 75.39, 71.42, 68.85, 61.13, 41.04, 40.50, 37.92, 28.82, 27.07, 26.26, 21.86, 13.33. MS (HR-ESI) for $C_{24}H_{39}B_{10}N_2O_7SNa$ [$(M+Na)^+$]. Calcd: m/z 631.3452 Found: m/z 631.3487.

S.1.3.3.3. Trisodium salt of the 5'-diphosphate of N5 (8).

To a solution of compound **7** (10 mg, 0.016 mmol) in anhydrous CH_3CN (16 µL, 1M), tris(tetra-*n*-butylammonium) hydrogen pyrophosphate (22 mg, 0.24 mmol) was added. The mixture was stirred for 2 days and methanol (0.5 ml) was added. Following filtration, the resulting solution was purified by HPLC (Method A) to give the 5'-diphosphate of N5. The obtained material was dissolved in methanol and passed through an ion exchange column [Amberlite 200 (sodium form)] to give the trisodium salt of the 5'-diphosphate of N5 (compound **8**, 8 mg, 73%). ^{1}H NMR (MeOH-d4) δ: 7.83 (s, 1H), 6.33 (t, *J*=6.71, 1H), 4.60 (m, 1H), 4.23 (m, 1H), 4.17 (m, 1H), 4.02 (br s, 1H), 3.90 (t, J= 7.23, 2H), 3.19 (m, 1H), 2.83 (m, 2H), 2.27 (m, 2H), 1.97 (s, 3H), 1.52-1.65 (m, 2H), 1.49 (m, 2H), 1.28 (m, 2H). ^{13}C NMR (MeOH-d4) δ: 165.58, 152.43, 136.46, 111.15, 87.57, 86.91, 72.03, 66.38, 66.34, 60.05, 42.48, 40.76, 32.15,

28.67, 28.29, 24.83, 13.42. ^{31}P NMR (MeOH-d4, 161 MHz) δ: -6.30, -8.36. MS (HR-ESI) for $C_{17}H_{36}B_{10}N_2O_{11}P_2$ $[M]^+$. Calcd: m/z 616.2846 Found: m/z 616.2840. HPLC retention time (Method B): 16.67.

Additional Comments: The mono- and diphosphate of N5 (3 & 8) were used in studies with recombinant kinases (see main manuscript) as surrogate systems for the corresponding phosphates of N5-2OH. The synthesis of the diphosphate of N5-2OH would have required a relatively complex synthetic procedure involving an acetonide-protected form of N5-2OH (Hasabelnaby et al., 2012). We noticed that the diphosphate of N5 was unstable under slightly acidic conditions resulting in the cleavage of the phosphate moieties. The necessary acidic removal of an acetonide group from the diphosphate of an acetonide-protected form of N5-2OH most likely would have resulted in simultaneous cleavage of phosphate moieties. Synthesis of the diphosphate of N5 does not require acidic conditions and N5 and N5-2OH appear to have generally similar enzymatic properties (Hasabelnaby et al., 2012; Lunato et al., 1999) Thus, the use of N5-phosphates as surrogates for the corresponding N5-2OH phosphates is warranted.

S.2. HPLC analysis of intracellular N5-2OH metabolites

S.2.1. General comments

Procedures for cell culture experiments and protocols for the enzymatic production of N5-2OH-MP are described in the *Materials and Methods* section of the main article.

S.2.2. Figure legends

Figure S1: Reverse-phase (C18) HPLC analysis of intracellular N5-2OH metabolites in L929 $TK1^+$ and L929 $TK1^-$ cells.

A. N5-2OH [red] and its monophosphate product [blue] in a control assay using TK1 protein with 100 μM N5-2OH (100 μM N5-2OH and 0.1 μM [^{3}H]N5-2OH) as described in *Materials and Methods*. **B**. Intracellular metabolites of N5-2OH in L929-$TK1^+$ cells [red] and L929 $TK1^-$ cells [blue] incubated for 60 min with 1 μM [^{3}H]N5-2OH. The ^{3}[H]-radiolabeled products were identified by HPLC using a reversed-phase-18 Discovery® C18 column (250 x4.6 mm; 5 μm particles). The mobile phase was A = 0.1% TFA in Water, B = 0.1% TFA in acetonitrile at a flow rate of 1 ml/min. The gradient used was as follows: 0–27 min, 35-70% B; 27–28 min, 70-35% B; 28–40 min, 35% B.

Additional comments: As shown in the chromatograms there was a significant amount of N52OH-MP found in extracts from $TK1^+$ cells (red). Both L929 $TK1^+$ and L929 $TK1^-$ cells contained substantial and similar levels of non-phosphorylated [^{3}H]N5-2OH. On the other hand, there were no detectable levels of di and/or tri-phosphates in cell extracts from L929 $TK1^+$ or $TK1^-$ cells. In a separate HPLC analysis (data not shown) it was established that synthetically and enzymatically produced N5-DP and N5-TP eluted in fractions 7 and 2, respectively, using the same solvent system. In chromatogram B, the signal for [^{3}H]N5-2OH in L929 $TK1^-$ cells [blue] is distributed both into fraction 18 and 19.

Figure S2. Partisil SAX HPLC analysis of intracellular N5-2OH metabolites in L929 $TK1^+$ and of enzymatically produced N5-2OH-MP.

A: Radio-HPLC of ^{3}H-materials in L929 $TK1^+$ cells following 2 h-incubation with 0.1 µM [^{3}H]N5-2OH / 0.9 µM N5-2OH. **B**: Enzymatically produced [^{3}H]N5-2OH-MP. **C**: Enzymatically produced non-radiactive N5-2OH-MP. The ^{3}[H]-radiolabeled products were identified by HPLC on a Partisil SAX Column (250 x 4.6 mm, Whatman/GE Healthcare, Piscataway, NJ) using Beckmann analytical HPLC system with radioflow detector (500TR, Packard, San Diego, CA). The mobile phase was A = 20% acetonitrile in water, B = phosphate buffer pH 7.2 (sodium phosphate dibasic, 0.5 M) at a flow rate of 1 ml/min. The gradient used was as follows: 0–5 min, 100-0% B; 5–20 min, 0-100% B; 20–40 min, 100-0% B.

Additional comments: In addition to signals for [^{3}H]N5-2OH, radio-HPLC did not show significant signals for metabolites other than [^{3}H]N5-2OH-MP in cell extracts from L929 $TK1^+$ cells that were exposed to [^{3}H]N5-2OH (Figure S2). One additional signal for an unidentified tritiated cellular component was detected (Figure S2 A), which eluted with the solvent front. It did not seem to be nucleos(t)ide material. It could have been [^{3}H]H_2O produced during cell culturing. HPLC-retention times for N5-2OH-MP produced both enzymatically (Figure S2 B & C) and during cell culture (Figure S2 A) were 12.5-12.7 min. Formation of enzymatically produced non-radioactive N5-2OH-MP (Figure S2 C) was confirmed by HR-MS (ESI-MS) for $C_{20}H_{42}B_{10}N_2O_{10}P$. Calcd: 609.3580. Found: m/z 609.3612].

S.3. Computational studies

Figure S3: Docked poses of dTMP (A) and N5-2OH-MP (B) in TMPK (PDB ID # 1E2D). In docked poses, carbon atoms are shown in cyan. In co-crystalized dTMP carbon atoms are shown in grey.

Studies were carried out on a Optiplex GX 270 desktop computer/workstation with Windows operating system using PyMoL (DeLano Scientific LLC., San Francisco, CA), Surflex version 2.11 (Biopharmics LLC, San Francisco, CA), and SYBYL-X 1.3 (Tripos International, St. Louis, MO). Human TMPK (PDB ID # 1E2D) complexed with dTMP, adenosine diphosphate (ADP), and Mg^{2+} was used for docking. N5-2OH was constructed as described previously (Tiwari et al. 2009). N5-2OH-MP was prepared by adding a phosphate group to 5'-OH of N5-2OH using Sybyl. N5-2OH-MP was aligned to co-crystalized dTMP prior to docking. The protein structure in mol2 format was prepared with the structure preparation tool of Sybyl. The blocking groups AMI and CXC were added to the N- and C-termini, respectively, for neutralization. Water molecules were removed, hydrogen atoms were added, and side chain amides and side chain bumps were fixed. Both dTMP and ADP were deleted from the crystal structure prior to docking. For docking, the protomol file was generated using the "none" command from the protein mol2 file. Docking was carried out with Surflex using the default method. The root-mean-square deviations (RMSDs) of the docked poses were obtained using the "rms" command. For the calculation of the RMSD of N52OH-MP, only the dThd scaffold was considered using co-crystalized dTMP as a reference molecule.

S.4. Autoradiographic studies

Figure S4. Autoradiogram of a TLC analysis of diphosphate products in TMPK enzyme reactions with dTMP, N5-MP, and N5-2OH-MP.

The assays were performed for 20, 40, and 60 min, as described in *Materials and Methods*. Products of the enzyme reactions were separated by TLC using a running buffer of 0.2 M Na H_2PO_4.

Additional comments: Several sets of experiments were carried out with reaction times ranging from 20 and 60 min. No diphosphate products of N5 and N5-2OH were generated.

Figure S5. Autoradiogram of a TLC analysis of mono- and diphosphate products in the TK1-, UMP-CMPK-, and TMPK enzyme reactions with dThd (A) and AZT (B).

The reaction was initiated by adding either 100 ng of TK1 alone (1, 4); or a mixture of TK1 & UMP-CMPK (2, 5); or a mixture of TK1 & TMPK (3, 6) to the assay followed by incubation at 37 °C for 30 min and subsequent termination by boiling. For the separation of nucleoside mono- and diphosphates in the coupled reactions, chromatography was performed for 8-12 hr using isobutyric acid:NH_4OH:H_2O (66:1:33) (v/v) as the mobile phase. The products were detected by autoradiography as described in *Materials and Methods.*

Additional comments: As a control for the coupled synthesis for each enzyme step, assays were carried out using either TK1 alone or combinations of TK1 with TMPK or UMP-CMPK. An autoradiogram of a TLC analysis of mono and diphosphate products for enzyme reactions with dThd and AZT is shown in Fig. S5. dTMP and AZT-MP are not substrates for UMP-CMPK and only one monophosphate product with TK1 and UMP-CMPK was observed. However, dTMP and AZT-MP are good substrates for TMPK resulting in the formation of dTDP and AZT-DP, respectively, using the TK1/TMPK combination (Fig. S5).

S.5. Figures

Fig. S1

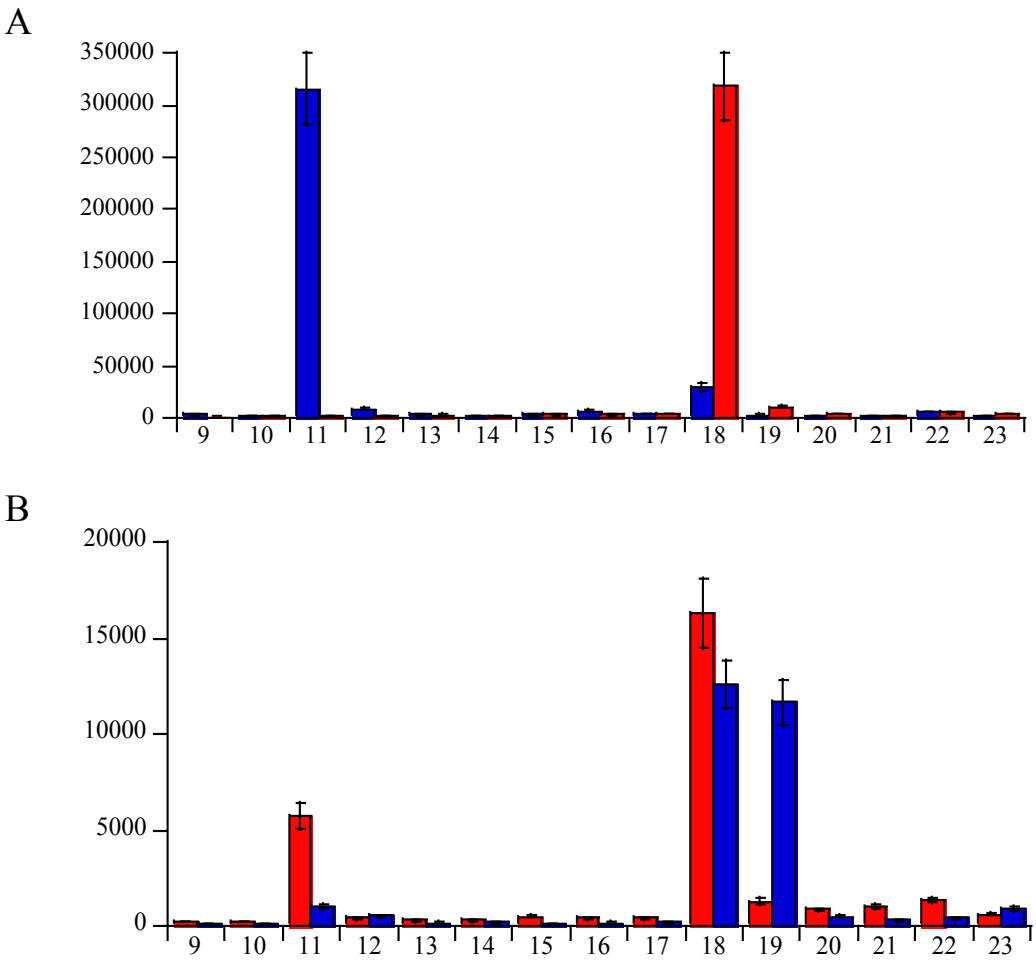


Fig. S2

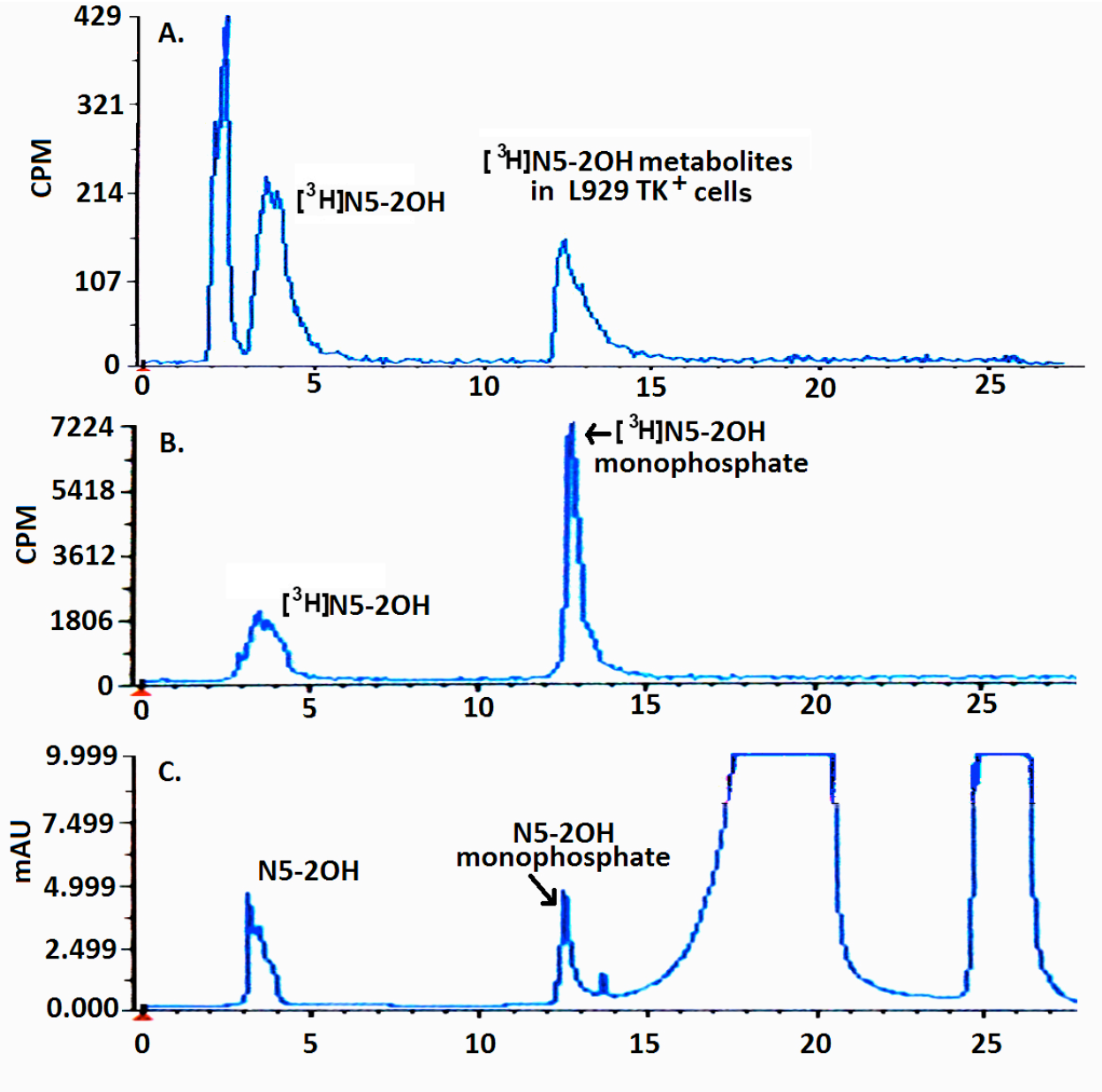

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Fig. S3

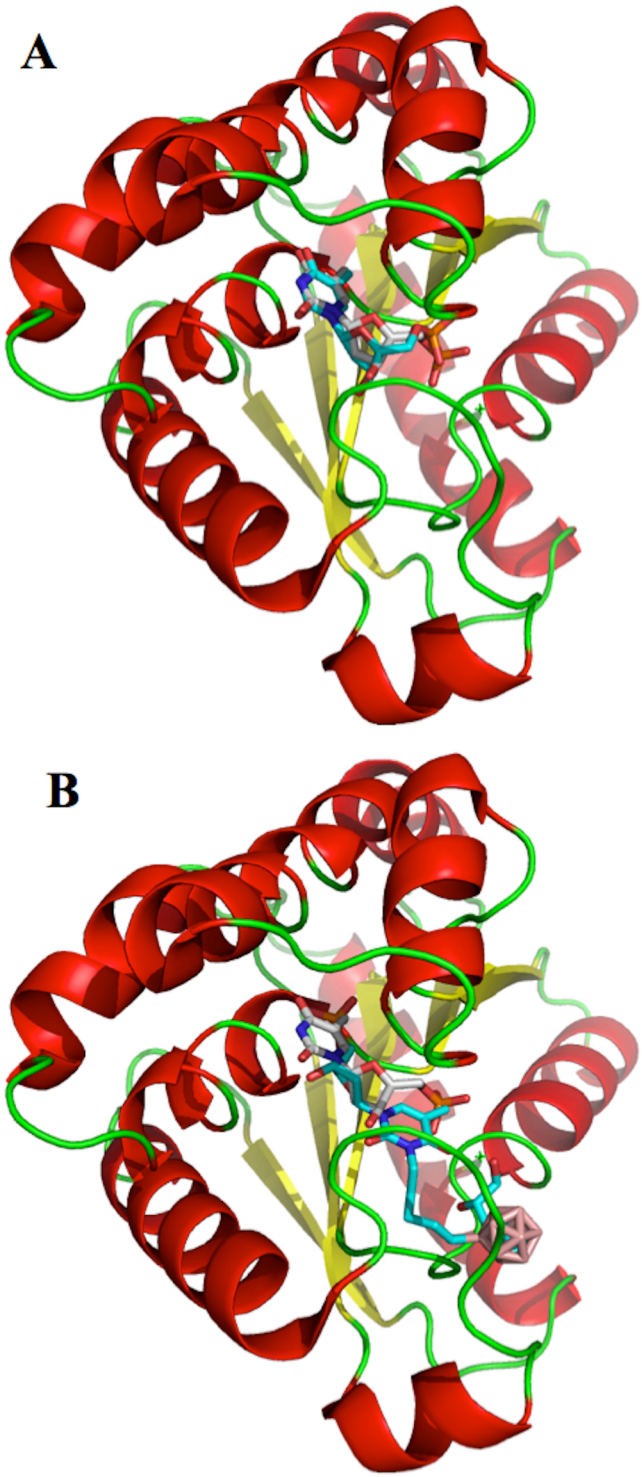
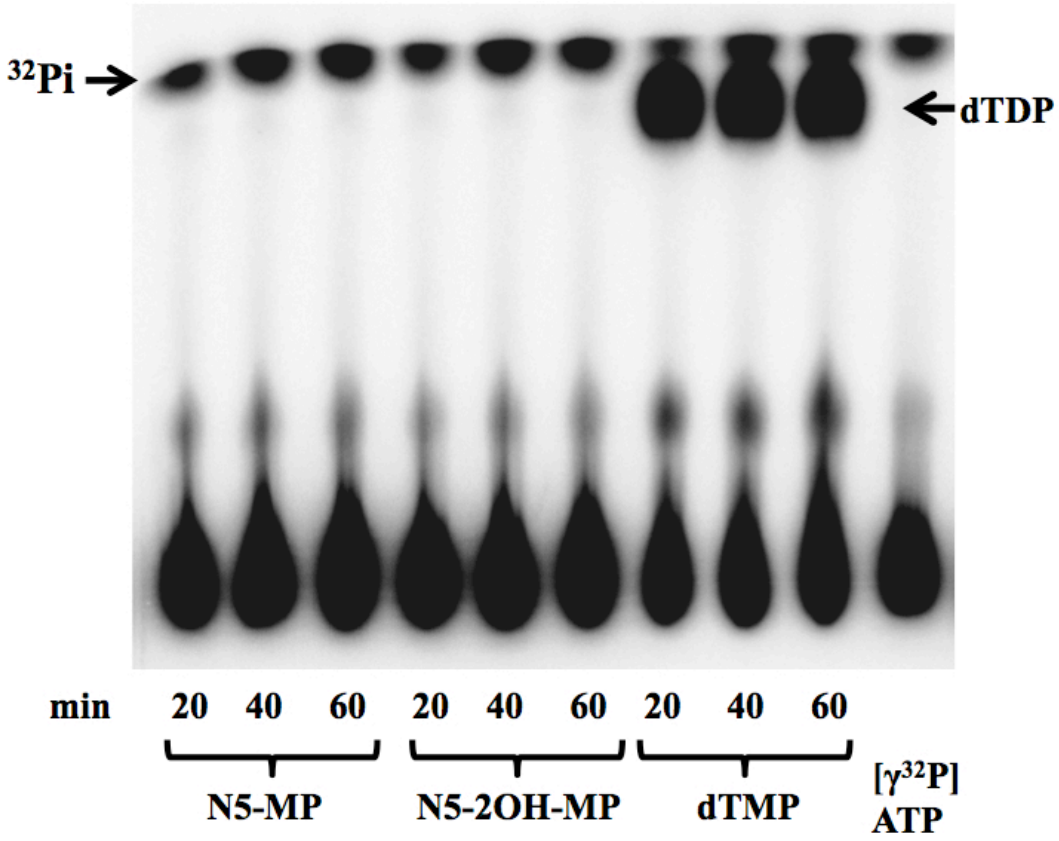


Fig. S4


32Pi
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min
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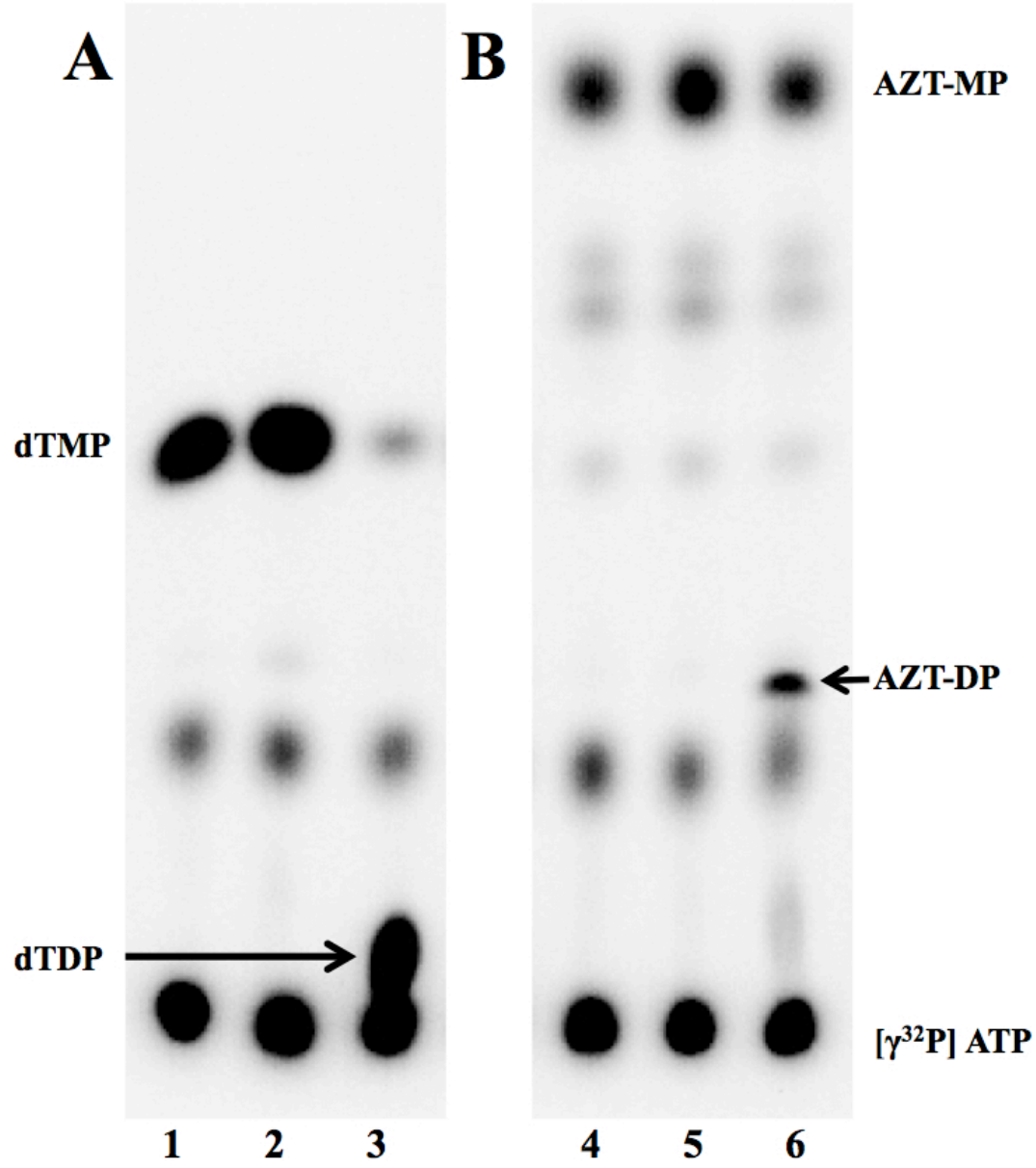
N5-MP
N5-2OH-MP
dTMP
[γ32P]
ATP

Fig. S5



S.6. List of Abbreviations

AcOH, acetic acid; ACN, acetonitrile; AZT, zidovudine; AZT-MP, AZT monophosphate; AZT-DP, AZT diphosphate; $CDCl_3$, deuterated chloroform; DCM, dichloromethane; DMF, dimethylformamide; dThd, thymidine; HPLC, high-performance liquid chromatography; HR-ESI, high resolution–electrospray ionization; MeOH, methanol; MeOH-d4, deuterated methanol; MS, mass spectra; N5, 3-[5-(*o*-carboran-1-yl)pentan-1-yl]thymidine; N5-DP, N5-diphosphate; N5-MP, N5-monophosphate; N5-TP, N5-triphosphate; N5-2OH, 3-[5-{2-(2,3-dihydroxyprop-1-yl)-*o*-carboran-1-yl}pentan-1-yl]thymidine; N5-2OH-MP, N5-2OH monophosphate; TBAF, tetrabutyl ammonium fluoride; TFA, trifluoroacetic acid; THF; tetrahydrofurane; TLC, thin layer chromatography; TK1, thymidine kinase 1; TMPK, thymidine monophosphate kinase; RMSD, root-mean-square deviations; UMP-CMPK, uridine monophosphate-cytidine monophosphate kinase.

S.7. References

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