for HPLC analysis. HPLC analysis showed three product peaks. The largest peak, accounting for 86% of the product, was **5**. The other two peaks, accounting for 14% of the product, were the two diastereomers of 7-[(*N*-acetyl-L-cysteinyl)thio]-7-deoxydaunomycinone (**11**), as proven by coinjection with authentic samples[36] onto the HPLC and purity analyses with a UV-vis diode array detector. The ratio of the two diastereomers was 1:2. When daunomycin was reduced at pH 7 with 0.4 mol equiv of NADPH and ferredoxin reductase at ambient temperature in the presence of a 60-fold excess of *N*-acetyl-L-cysteine, the ratio of the diastereomers of **11** was 1:2.6.[36]

A similar experiment was run for 20 h using the exact same procedure with deuterated solvents and a 250-fold excess of *N*-acetyl-L-cysteine. HPLC analysis using method B showed 95% **5** and 5% **11**. Additionally, only the isomer formed in the highest proportion above was detected.

Experiment To Trap *N*-Acetyl-L-cysteine with Isomer A of 3 in the Presence of 1a at pH 7.4 under Anaerobic Conditions Using Deuterated Solvents. To a 3-mL volumetric flask were added 0.54 mg of isomer A of **3** (9.36×10^{-7} mol) and deuterium oxide, which had been adjusted to an apparent pH of 3 with DCl. To a 10-mL volumetric flask were added 65.5 mg of *N*-acetyl-L-cysteine (4.01×10^{-4} mol), 0.300 g of Tris-HCl (1.90×10^{-3} mol), 0.0489 g of Tris (4.04×10^{-4} mol), and D_2O. To a 5-mL volumetric flask were added 1.76 mg of daunomycin hydrochloride (3.12×10^{-6} mol) and the Tris-buffered *N*-acetyl-L-cysteine solution. With a syringe, 1.0 mL of the solution of **3** (3.12×10^{-7} mol) was transferred to the center compartment of the three-compartment cell, and 2.0 mL of the pH 7.4 buffered daunomycin-*N*-acetyl-L-cysteine solution (1.25×10^{-6} mol of daunomycin hydrochloride, 8.02×10^{-5} mol of *N*-acetyl-L-cysteine) was transferred to a second compartment. The solutions were freeze-thaw degassed, equilibrated to 25.0 °C, and then mixed. HPLC analysis after 2 h showed three product peaks in addition to unreacted daunomycin. Of the total anthracyclines present, 11% was **5**, 23% was the diastereomers of **11** in a ratio of 1:3.9, and 66% was **1a**.

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9-(Difluorophosphonoalkyl)guanines as a New Class of Multisubstrate Analogue Inhibitors of Purine Nucleoside Phosphorylase

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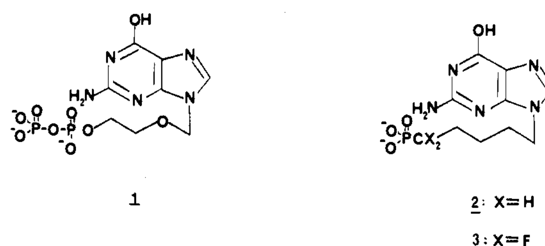
Abstract: 9-(5,5-Difluoro-5-phosphonopentyl)guanine (**3**) was synthesized as a potential multisubstrate analogue inhibitor of purine nucleoside phosphorylase (EC 2.4.2.1, PNP). At pH 7.4, **3** has a K_i value 18-, 26-, 25-, and 5.5-fold lower than that of the nonfluorinated analogue 9-(5-phosphonopentyl)guanine (**2**) regarding PNP from human erythrocyte, rat erythrocyte, calf spleen, and *Escherichia coli*, respectively. Further studies with human erythrocytic PNP show that at pH 6.2 the difference in K_i value is more pronounced (K_{i2}/K_{i3} is 96), and at pH 8.8, where **2** and **3** are both essentially present in the unprotonated form, the ratio is 8. The superiority of the difluorophosphonate **3** over the phosphonate **2** is explained by electronic as well as by steric effects.

Purine nucleoside phosphorylase (EC 2.4.2.1; PNP), a key enzyme in the purine salvage pathway,[1] is believed to be a target for the design of immunosuppresive agents.[2] PNP inhibitors might also be useful in the treatment of T-cell leukemia, gout,[2] and some parasitic diseases.[3] PNP catalyzes the reversible phosphorolysis of guanosine and inosine nucleosides (or deoxynucleosides) to their respective free base and ribose 1-phosphate (or deoxyribose 1-phosphate). This reaction proceeds via a ternary complex of enzyme, nucleoside, and orthophosphate.[1] Based on the finding that the diphosphate derivative of acyclovir (**1**, Chart I) is a very potent inhibitor of the human enzyme[4] (K_i = 8.7 nM, when determined in the presence of 1 mM orthophosphate), metabolically stable "multisubstrate" acyclic nucleotide analogues containing a purine and a phosphate-like moiety such as 9-phosphonoalkyl derivatives of hypoxanthine and guanine have been designed and synthesized.[5,6] The most potent inhibitor of human erythrocytic PNP in this series was 9-(5-phosphonopentyl)guanine

Chart I



Scheme I

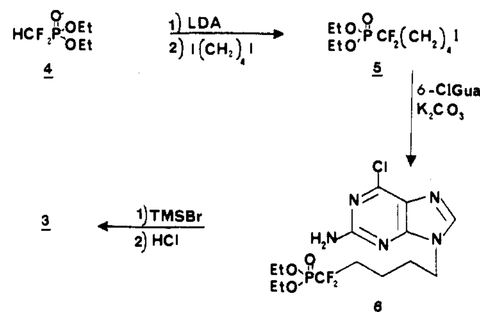


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Table I. Comparison of Inhibition Constants of **2** and **3** for PNP from Various Sources

PNP source	K_i,[a] nM **2**	K_i,[a] nM **3**	K_{i2}/K_{i3}
human erythrocyte	320 ± 15	18 ± 3	18
rat erythrocyte	905 ± 40	35 ± 2	26
calf spleen	400 ± 80	16 ± 2	25
Escherichia coli	82 ± 5	15 ± 2	5.5

[a] K_i was determined at pH 7.4, in the presence of 1 mM P_i.

(**2**) but its K_i value was reported[6] to be 170 nM. Since PNP is not a rate-limiting enzyme and has a very high activity in humans, a biologically active inhibitor requires a K_i value in the 10^{-8}–10^{-9} M range,[2c] and therefore, the previously described inhibitors might not be sufficiently potent in that respect.

Recently, it had been suggested by Blackburn and Kent[7] that α-fluoro- and α,α-difluoroalkanephosphonates should mimic phosphate esters better than the corresponding phosphonates. This assumption was based on both electronic and steric considerations. So far, however, attempts to exploit the potential of fluorophosphonates as substrates or inhibitors of enzymes have not lead to any significant improvement versus nonfluorinated phosphonates.[8]

In this paper, we report the synthesis of 9-(5,5-difluoro-5-phosphonopentyl)guanine (**3**) and compare phosphonates **2** and **3** as inhibitors of PNP from four different origins.

Results and Discussion

The synthetic access to **3** is depicted in Scheme I. 9-(5,5-Difluoro-5-phosphonopentyl)guanine (**3**) was prepared in four steps from diethyl difluorolithiomethanephosphonate (generated by reacting diethyl difluoromethanephosphonate[9] (**4**) with lithium diisopropylamide at −78 °C in THF). Condensation with an excess (2.5 equiv) of 1,4-diiodobutane at −78 °C gave the expected iodo derivative **5** in 40% yield. The purine adduct **6** was regioselectively (>95%) obtained by reacting 2-amino-6-chloropurine (a proguanine derivative) with the intermediate **5** in anhydrous DMF containing potassium carbonate (20 °C, 24 h, 65% yield). The transformation of **6** into the final product **3** was achieved through removal of the phosphonate ethyl groups [(TMS)Br, CH_2Cl_2; H_2O, CH_3CN] and aqueous acid hydrolysis (1 N, HCl, 100 °C, 18 h). The final product **3** was obtained in a pure form after recrystallization from water (60% yield).

9-(5-Phosphonopentyl)guanine (**2**) was prepared from 2-amino-6-chloropurine according to a published method.[5]

The two compounds **2** and **3** were found to inhibit PNP prepared from human erythrocytes, rat erythrocytes, calf spleen, and *Escherichia coli*. Inhibition was competitive with inosine as variable substrate. Apparent inhibition constants (K_i) obtained for **2** and **3** at pH 7.4, with orthophosphate concentration fixed at 1 mM, are listed in Table I. As shown for nonfluorinated phosphonates,[5,6] inhibition decreased with increasing concentrations of orthophosphate. At 50 mM orthophosphate, K_i values of **3** were increased 20- to 40-fold. These results are in agreement with **3** being a multisubstrate analogue inhibitor. The results in Table I demonstrate the importance of fluorine substituents, the fluorinated compound **3** having a K_i value 5- to 26-fold lower than that of the nonfluorinated compound. It is worth noting that similar results were obtained by comparing 9-(7,7-difluoro-7-phosphonoheptyl)guanine (**7**) and 9-(7-phosphonoheptyl)guanine[5] (**8**) as inhibitors of the four PNP; for instance, the K_i values for the human erythrocytic enzyme were found to be 0.1 and 1 μM for compounds **7** and **8**, respectively. The difference between K_i values of **2** and **3** was even more pronounced when the inhibition study was performed at low pH value, as shown in Table II. The marked difference in the K_i value for **2** and **3** at low pH is explained by the second dissociation constant[10] of **3** (pK_{a_2} = 5.3), which is lower than the one of **2** (pK_{a_2} = 7.2). However, these pK_{a_2} values do not explain the difference in K_i values at high pH. For example, at pH 8.8, while both compounds should be essentially present in the unprotonated form, **3** has an 8-times higher affinity than **2** for the human enzyme (Table II). These data, as well as similar results observed with the three other enzymes (data not shown), demonstrate that factors other than acidity are responsible for the higher affinity of **3** toward PNP. Such factors might be the good steric resemblance of the fluorophosphonate moiety to a phosphate ester,[7] the formation of hydrogen bonds between the fluorine atoms and the enzyme,[11] or both.

Table II. Inhibition Constants for Human Erythrocytic PNP. Effect of pH

pH	K_i,[a] nM **2**	K_i,[a] nM **3**	K_{i2}/K_{i3}
6.2	385 ± 15	4 ± 1	96
6.8	270 ± 25	7 ± 1	38
7.4	320 ± 15	18 ± 3	18
8.2	400 ± 40	32 ± 2	12
8.8	410 ± 40	53 ± 7	8

[a] K_i was determined in the presence of 1 mM P_i.

Conclusions

In conclusion, we think that these data represent the first clear evidence of the superiority of a difluorophosphonate derivative over a phosphonate as an enzyme inhibitor and support the theoretical assumptions of Blackburn and co-workers.[7,10] This seems to be a general result since we observed such a superiority for four PNP, which differ in many respects.[1,12] Work is in progress in our laboratories to extend the interesting properties of fluorophosphonates to the design of "multisubstrate" analogue inhibitors of other enzymes accepting phosphate or a phosphate derivative as one of the substrates.

Experimental Section

Reagents. All chemical reagents are from Janssen Chimica (Beerse, Belgium). They were used without further purification.

General Methods. Melting points were obtained on a Buchi SMP-20 melting point apparatus and are uncorrected. Proton and fluorine NMR spectra were recorded on either a Varian EM390 spectrometer (90 MHz) or a Bruker instrument (360 MHz). Chemical shifts are reported in δ units, parts per million (ppm) downfield from TMS for ^1H NMR and from trifluoroacetic acid or hexafluorobenzene for ^{19}F NMR. Mass spectra were recorded on a Finnigan TSQ46 apparatus. Thin-layer chromatography was performed on silica gel 60F-254 plates (Merck; 0.2-mm layer). Flash column chromatography utilized silica gel 60 as the solid phase (230–400 mesh) from E. Merck laboratories.

5-Iodo-1,1-difluoro-1-(diethylphosphono)pentane (5). To a solution of diisopropylamine (12.62 g, 125 mmol) in dry THF (80 mL) was slowly added at 0 °C 76.4 mL of 1.57 N *n*-butyllithium in hexane (120 mmol), and the solution was stirred at 0 °C for 30 min under argon. To this solution was added at −78 °C a solution of diethyl difluoromethanephosphonate (22.56 g, 120 mmol) in 100 ml of THF. After stirring for 40 min at −78 °C, 93 g of cold 1,4-diiodobutane (300 mmol) was rapidly

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added and the mixture was stirred at −78 °C for 4 h and slowly warmed to 20 °C. The reaction mixture was then poured into saturated aqueous ammonium chloride and THF was evaporated under reduced pressure. The residue was extracted three times with ethyl acetate (150 mL × 3). The combined organic phases were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residual oil was purified by flash chromatography using petroleum ether and increasing amounts of ethyl acetate as eluents to give **5** (17.7 g, 40%) as a pale yellow oil ^{1}H NMR ($CDCl_3$) δ 4.30 (m, 4 H), 3.25 (t, 2 H), 1.65–2.4 (m, 6 H), 1.40 (t, 6 H); ^{19}F NMR ($CDCl_3$, C_6H_6 as reference) δ 51 (dt, J_{H-F} = 21 Hz, J_{F-P} = 112 Hz); MS (CI, NH_3) m/z 388 (MNH_4^+), 371 (MH^+), 262.

2-Amino-6-chloro-9-[5,5-difluoro-5-(diethylphosphono)pentyl]purine (6). Anhydrous potassium carbonate (66 mmol, 9.1 g) was added to a stirred suspension of 2-amino-6-chloropurine (6.1 g, 36 mmol) and 5-iodo-1,1-difluoro-1-(diethylphosphono)pentane (**5**; 12.2 g, 33 mmol) in 65 mL of anhydrous DMF at 20 °C under argon. The reaction mixture was stirred at 20 °C for 22 h, filtered over Celite, and evaporated under reduced pressure. The crude residue was purified by flash chromatography on silica gel using ethyl acetate as eluent to give **6** (8.4 g, 62%: ^{1}H NMR (CD_3OD) δ 8.1 (s, H_8), 4.9 (s, NH_2), 4.25 (m, 4 H), 4.15 (t, CH_2N), 2.15 (m, CH_2CF_2), 1.95 (m, CH_2), 1.55 (m, CH_2), 1.3 (t, 6 H, OCH_2CH_3); ^{19}F NMR (CD_3OD; C_6F_6 as reference) δ 52.5 (dt, J_{F-H} = 19 Hz, J_{F-P} = 111 Hz); MS (CI, NH_3) m/z 412 (MH^+). Anal. Calcd for $C_{14}H_2N_5ClF_2PO_3$: C, 40.83; H, 5.14; N, 17.00. Found: C, 40.46; H, 5.21; N, 16.97.

9-(5,5-Difluoro-5-phosphonopentyl)guanine (3). Bromotrimethylsilane (9 g, 59 mmol) was added dropwise to a stirred solution of **6** (6 g, 14.6 mmol) in 80 mL of anhydrous dichloromethane at 20 °C under argon. The reaction mixture was stirred at 20 °C for 44 h and evaporated under reduced pressure. The residue was dissolved in anhydrous acetonitrile, and a pale yellow precipitate was obtained upon addition of 1 mL of water. The solid was collected by filtration giving 5.4 g of product, which was suspended in 50 mL of 1 N HCl and heated at 95 °C for 18 h. The reaction mixture was evaporated under reduced pressure; the residue obtained was dissolved in boiling water and crystallized on cooling, giving 4.6 g of **3** (93% yield from **6**): mp 260 °C; TLC, R_f = 0.44 (EtOH/17% NH_4OH, 60/40); ^{1}H NMR (D_2O, NaOD) δ 8.3 (s, H_8), 4.2 (t, CH_2N), 2.15 (m, CH_2CF_2), 1.95 (m, CH_2), 1.65 (m, CH_2); ^{19}F NMR (D_2O, NaOD, CF_3CO_2H as reference) δ −36.6 (dt, J_{F-P} = 97 Hz, J_{H-F} = 20 Hz); MS (FAB, xenon) m/z 338 (MH^+), 185. Anal. Calcd for $C_{10}H_{14}F_2N_5O_4P\cdot HCl$: C, 32.14; H, 4.04; N, 18.74. Found: C, 31.75; H, 4.39; N, 18.32.

9-(7,7-Difluoro-7-phosphonoheptyl)guanine (7). 9-(7,7-Difluoro-7-phosphonoheptyl)guanine was obtained from diethyl difluoromethanephosphonate, 1,6-diiodohexane, and 6-chloroguanine according to the procedure described for the preparation of **3**. However, in this case, the final product was obtained in a pure form by recrystallization in a 1 M water solution of triethylammonium bicarbonate. **7**: mp 280 °C; TLC, R_f = 0.49 (ETOH/17% NH_4OH, 60/40); ^{1}H NMR (D_2O, NaOD) δ 7.8 (s, H_8), 4.05 (t, CH_2N), 2.03 (m, CH_2CF_2), 1.75 (m, CH_2), 1.45 (m, CH_2), 1.3 (m, 2 CH_2); ^{19}F NMR (D_2O, NaOD, CF_3CO_2– as reference) δ −36.6 (dt, J_{H-F} = 21 Hz, J_{F-P} = 89 Hz); MS (FAB, xenon) m/z 366 (MH^+). Anal. Calcd for $C_{12}H_{18}F_2N_5O_4P$: C, 39.46; H, 4.97; N, 19.17. Found: C, 39.36; H, 5.08; N, 18.64.

Enzymes and Assays. PNP from human erythrocytes, calf spleen, and *E. coli* were purchased from Sigma Chemical Co., St. Louis, MO. PNP from rat erythrocyte was partially purified according to a published method.[13] With inosine as substrate, PNP activity was determined spectrophotometrically by a xanthine oxidase coupled assay.[14] The increase in absorbance at 293 nm was monitored with a Beckman DU-7 spectrophotometer. The typical assay contained 0.1 M HEPES/NaOH buffer, pH 7.4, 0.04 unit of xanthine oxidase (Boehringer Mannheim GmbH, West Germany), 1 mM (or 50 mM) sodium phosphate, appropriate concentrations of inosine (Sigma), and PNP in a total volume of 1.0 mL at 37 °C. Under these conditions, in the presence of 50 mM sodium phosphate, the specific activities of the four PNP, expressed as micromoles per minute per milligram of protein, were found to be 44 (human erythrocytes), 3.5 (rat erythrocytes), 116 (calf spleen), and 24 (*E. coli*).

Inhibition of PNP was measured at five concentrations of inosine and six concentrations of inhibitor. K_i values were determined by using a Dixon plot and a computer program developed in-house for linear regression analysis. It was determined that the inhibitors do not affect xanthine oxidase activity in the assay. For pH dependence studies, a three-component buffer system was used instead of HEPES. This buffer system[15] consisted of 0.052 M MES, 0.051 M TAPSO, 0.1 M diethanolamine, and HCl. The ionic strength of this mixture was 0.1 ± 0.01 M between pH 6.0 and 8.9.[15]

Registry No. **2**, 104495-32-1; **3**, 130434-88-7; **4**, 1478-53-1; **5**, 130434-89-8; **6**, 130434-90-1; **7**, 130434-91-2; **8**, 130434-92-3; PNP, 9030-21-1; $I(CH_2)_4I$, 628-21-7; $I(CH_2)_6I$, 629-09-4; 2-amino-6-chloropurine, 10310-21-1.

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Analysis of the Structures, Infrared Spectra, and Raman Spectra for the Methyl, Ethyl, Isopropyl, and *tert*-Butyl Radicals

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Abstract: Extensive ab initio calculations are reported for the optimized geometries of the methyl, ethyl, isopropyl, and *tert*-butyl radicals. In addition, vibrational frequencies and infrared and Raman intensities are computed and compared with experimental infrared spectra of the series of radicals. The theoretical calculations are used to assign experimental vibrational spectra and elucidate the radical structure.

Introduction

Alkyl radicals are perhaps the simplest but yet some of the most reactive organic radicals. They play a central role in the petroleum industry[1] and are reactive intermediates in the production of many commercial polymers.[2] As reactive intermediates they also play essential roles in polymer degradation,[3] thus determining the stability of many materials such as coatings and lubricants toward heat, light, and high-energy radiation.

Alkyl radicals thus have been the focus of active research in many industrial and academic laboratories. Studies have ranged from gas-phase kinetics for bond fission processes,[4] spectroscopic

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