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(71) Applicant (for all designated States except US): **ANADYS  
PHARMACEUTICALS, INC.** [US/US]; 3115 Merryfield  
Row, San Diego, CA 92121 (US).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **AVERETT, Devron,  
R.** [US/US]; 2529 Newport Avenue, Cardiff By The Sea,  
CA 92007 (US).

(74) Agent: **PINO, Mark, J.**; Connolly Bove Lodge & Hutz  
LLP, 1990 M Street, N.W., Suite 800, Washington, DC  
20036-3425 (US).

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(54) Title: NUCLEOSIDE PHOSPHONATE DERIVATIVES USEFUL IN THE TREATMENT OF HIV INFECTIONS

(57) Abstract: The present invention relates to a method of treating HIV infections by administering a nucleoside phosphonate derivative represented by formula (I).



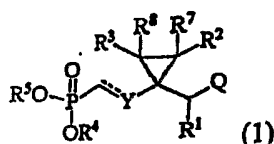
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# Nucleoside Phosphonate Derivatives Useful in the Treatment of HIV Infections

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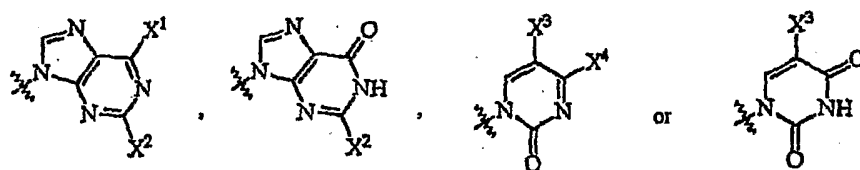
## TECHNICAL FIELD

The present invention relates to a method for treating HIV infections comprising the  
10 administration of a nucleoside phosphonate derivative represented by the following formula (1):



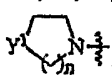
in which

- 15  $\equiv$  represents single bond or double bond,  
 $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^7$  and  $R^8$  independently of one another represent hydrogen, halogen, hydroxy, amino,  $C_1$ - $C_7$ -alkyl,  $C_2$ - $C_6$ -alkenyl,  $C_1$ - $C_5$ -alkylamino,  $C_1$ - $C_5$ -aminoalkyl, or  $C_1$ - $C_5$ -alkoxy,  
 $R^4$  and  $R^5$  independently of one another represent hydrogen, or represent  $C_1$ - $C_4$ -alkyl  
 20 optionally substituted by one or more substituents selected from the group consisting of halogen (particularly, fluorine),  $C_1$ - $C_4$ -alkoxy, phenoxy,  $C_7$ - $C_{10}$ -phenylalkoxy and  $C_2$ - $C_5$ -acyloxy, or represent  $C_1$ - $C_7$ -acyl,  $C_6$ - $C_{12}$ -aryl or optionally substituted carbamoyl, or represent  $-(CH_2)_m-OC(=O)-R^6$  wherein m denotes an integer of 1 to 12 and  $R^6$   
 25 represents  $C_1$ - $C_{12}$ -alkyl,  $C_2$ - $C_7$ -alkenyl,  $C_1$ - $C_5$ -alkoxy,  $C_1$ - $C_7$ -alkylamino, di( $C_1$ - $C_7$ -alkyl)amino,  $C_3$ - $C_6$ -cycloalkyl, or 3 to 6-membered heterocycle having 1 or 2 hetero atoms selected from a group consisting of nitrogen and oxygen,  
 Y represents  $-O-$ ,  $-S-$ ,  $-CH(Z)-$ ,  $=C(Z)-$ ,  $-N(Z)-$ ,  $=N-$ ,  $-SiH(Z)-$ , or  $=Si(Z)-$ , wherein Z represents hydrogen, hydroxy or halogen, or represents  $C_1$ - $C_7$ -alkyl,  $C_1$ - $C_5$ -alkoxy, allyl, hydroxy- $C_1$ - $C_7$ -alkyl,  $C_1$ - $C_7$ -aminoalkyl or phenyl,  
 30 Q represents a group having the following formula:



wherein

$X^1$ ,  $X^2$ ,  $X^3$  and  $X^4$  independently of one another represent hydrogen, amino, hydroxy or halogen, or represent  $C_1$ - $C_7$ -alkyl,  $C_1$ - $C_5$ -alkoxy, allyl, hydroxy- $C_1$ - $C_7$ -alkyl, phenyl or phenoxy each of which is optionally substituted by nitro or  $C_1$ - $C_5$ -alkoxy, or represent  $C_6$ - $C_{10}$ -arylthio which is optionally substituted by nitro, amino,  $C_1$ - $C_6$ -alkyl or  $C_1$ - $C_4$ -alkoxy, or represent  $C_6$ - $C_{12}$ -aryl amino,  $C_1$ - $C_7$ -alkyl amino, di( $C_1$ - $C_7$ -alkyl)amino,  $C_3$ - $C_6$ -

cycloalkyl amino or a structure of  wherein n denotes an integer of 1 or 2 and  $Y^1$  represents O,  $CH_2$  or N-R (R represents  $C_1$ - $C_7$ -alkyl or  $C_6$ - $C_{12}$ -aryl),

pharmaceutically acceptable salts, stereoisomers, and a process for the preparation thereof.

## BACKGROUND ART

Purine or pyrimidine derivatives have anti-cancer and antiviral activities, and more than 10 kinds of the compounds including AZT, 3TC and ACV have already been commercialized. Particularly, since acyclic nucleoside phosphonate derivatives show a potent antiviral effect, cidopovir has been commercialized as an antiviral agent and many compounds including PMEA and PMPA now entered into the step of clinical trials. However, the earlier developed compounds were not perfect in the aspects of toxicity or pharmaceutical activity, and thus, it is still desired to develop a compound having no toxicity as well as a superior activity. The prior researches for purine or pyrimidine derivatives or acyclic nucleoside phosphonate derivatives as reported heretofore are as follows. Patents: US 5817647; US 5977061; US5886179; US 5837871; US 6069249; WO 99/09031; WO96/09307; WO95/22330; US 5935946; US 5877166; US 5792756; Journals: *International Journal of Antimicrobial Agents* 12 (1999), 81-95; *Nature* 323 (1986), 464; *Heterocycles* 31(1990), 1571; *J. Med. Chem.* 42 (1999), 2064; *Pharmacology & Therapeutics* 85 (2000), 251; *Antiviral Chemistry & Chemotherapy* 5 (1994), 57-63.; *Bioorganic & Medicinal Chemistry Letters* 10 (2000) 2687-2690; *Biochemical Pharmacology* 60 (2000), 1907-1913; *Antiviral Chemistry & Chemotherapy* 8 (1997) 557-564; *Antimicrobial Agent and Chemotherapy* 42 (1999) 2885-2892.

## DISCLOSURE OF INVENTION

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Therefore, one object of the present invention is to provide the compound of formula (1) having a good use of antiviral agent, pharmaceutically acceptable salts or isomers thereof.

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It is another object of the present invention to provide a process for the preparation of the compound of formula (1).

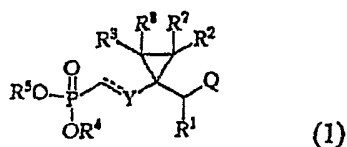
It is still another object of the present invention to provide intermediates which are advantageously used for the preparation of the compound of formula (1).

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## BEST MODE FOR CARRYING OUT THE INVENTION

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The compound of formula (1) according to the present invention, as represented below, is a type of nucleoside phosphonate derivative having a natural base, such as for example, adenine, guanine, uracil, cytosine, thymine or derivatives thereof:



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in which

==== represents single bond or double bond,

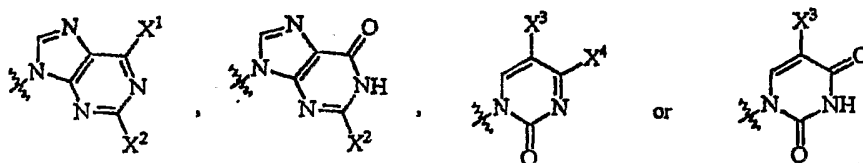
R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>7</sup> and R<sup>8</sup> independently of one another represent hydrogen, halogen, hydroxy,

amino, C<sub>1</sub>-C<sub>7</sub>-alkyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>1</sub>-C<sub>5</sub>-alkylamino, C<sub>1</sub>-C<sub>5</sub>-aminoalkyl, or C<sub>1</sub>-C<sub>5</sub>-alkoxy,

R<sup>4</sup> and R<sup>5</sup> independently of one another represent hydrogen, or represent C<sub>1</sub>-C<sub>4</sub>-alkyl optionally substituted by one or more substituents selected from the group consisting of halogen (particularly, fluorine), C<sub>1</sub>-C<sub>4</sub>-alkoxy, phenoxy, C<sub>7</sub>-C<sub>10</sub>-phenylalkoxy and C<sub>2</sub>-C<sub>5</sub>-acyloxy, or represent C<sub>1</sub>-C<sub>7</sub>-acyl, C<sub>6</sub>-C<sub>12</sub>-aryl or optionally substituted carbamoyl, or represent -(CH<sub>2</sub>)<sub>m</sub>-OC(=O)-R<sup>6</sup> wherein m denotes an integer of 1 to 12 and R<sup>6</sup> represents C<sub>1</sub>-C<sub>12</sub>-alkyl, C<sub>2</sub>-C<sub>7</sub>-alkenyl, C<sub>1</sub>-C<sub>5</sub>-alkoxy, C<sub>1</sub>-C<sub>7</sub>-alkylamino, di(C<sub>1</sub>-C<sub>7</sub>-alkyl)amino, C<sub>3</sub>-C<sub>6</sub>-cycloalkyl, or 3 to 6-membered heterocycle having 1 or 2 hetero atoms selected from a group consisting of nitrogen and oxygen,

Y represents -O-, -S-, -CH(Z)-, =C(Z)-, -N(Z)-, =N-, -SiH(Z)-, or =Si(Z)-, wherein Z represents hydrogen, hydroxy or halogen, or represents C<sub>1</sub>-C<sub>7</sub>-alkyl, C<sub>1</sub>-C<sub>5</sub>-alkoxy, allyl, hydroxy-C<sub>1</sub>-C<sub>7</sub>-alkyl, C<sub>1</sub>-C<sub>7</sub>-aminoalkyl or phenyl,

Q represents a group having the following formula:



wherein

X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup> and X<sup>4</sup> independently of one another represent hydrogen, amino, hydroxy or halogen, or represent C<sub>1</sub>-C<sub>7</sub>-alkyl, C<sub>1</sub>-C<sub>5</sub>-alkoxy, allyl, hydroxy-C<sub>1</sub>-C<sub>7</sub>-alkyl, phenyl or phenoxy each of which is optionally substituted by nitro or C<sub>1</sub>-C<sub>5</sub>-alkoxy, or represent C<sub>6</sub>-C<sub>10</sub>-arylthio which is optionally substituted by nitro, amino, C<sub>1</sub>-C<sub>6</sub>-alkyl or C<sub>1</sub>-C<sub>4</sub>-alkoxy, or represent C<sub>6</sub>-C<sub>12</sub>-aryl amino, C<sub>1</sub>-C<sub>7</sub>-alkylamino, di(C<sub>1</sub>-C<sub>7</sub>-alkyl)amino, C<sub>3</sub>-C<sub>6</sub>-

cycloalkylamino or a structure of wherein n denotes an integer of 1 or 2 and Y<sup>1</sup> represents O, CH<sub>2</sub> or N-R (R represents C<sub>1</sub>-C<sub>7</sub>-alkyl or C<sub>6</sub>-C<sub>12</sub>-aryl).

Since the compound of formula (1) according to the present invention may have one or more asymmetric carbon atoms in the structure depending on the kind of substituents, it can be present in the form of the individual enantiomers, diastereomers, or mixtures thereof including racemate. Further, when a double bond is included in the structure, it can be present in the form of E or Z isomer. Thus, the present invention also includes all of these isomers and their mixtures.

Also, the compound of formula (1) according to the present invention can form a pharmaceutically acceptable salt. Such salt includes non-toxic acid addition salt containing pharmaceutically acceptable anion, for example a salt with inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid, hydrobromic acid, hydriodic acid, etc., a salt with organic carboxylic acids such as tartaric acid, formic acid, citric acid, acetic acid, trichloroacetic acid, trifluoroacetic acid, gluconic acid, benzoic acid, lactic acid, fumaric acid, maleic acid, etc., or a salt with sulfonic acids such as methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalenesulfonic acid, etc., particularly preferably with sulfuric acid, methanesulfonic acid or hydrohalic acid, etc.

Among the compound of formula (1) showing a potent pharmaceutical activity, the preferred compounds are those wherein

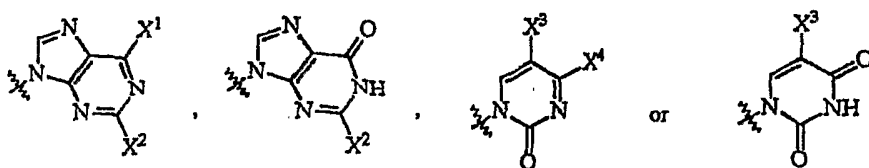
— represents single bond,

$R^1$ ,  $R^2$ ,  $R^3$ ,  $R^7$  and  $R^8$  independently of one another represent hydrogen, fluorine, hydroxy,  $C_1$ - $C_7$ -alkyl,  $C_2$ - $C_6$ -alkenyl,  $C_1$ - $C_5$ -alkylamino,  $C_1$ - $C_5$ -aminoalkyl, or  $C_1$ - $C_5$ -alkoxy,

$R^4$  and  $R^5$  independently of one another represent hydrogen, or represent  $C_1$ - $C_4$ -alkyl optionally substituted by one or more substituents selected from the group consisting of fluorine,  $C_1$ - $C_4$ -alkoxy and phenoxy, or represent carbamoyl substituted by  $C_1$ - $C_5$ -alkyl, or represent  $-(CH_2)_m-OC(=O)-R^6$  wherein m denotes an integer of 1 to 12 and  $R^6$  represents  $C_1$ - $C_{12}$ -alkyl,  $C_2$ - $C_7$ -alkenyl,  $C_1$ - $C_5$ -alkoxy,  $C_1$ - $C_7$ -alkylamino, di( $C_1$ - $C_7$ -alkyl)amino,  $C_3$ - $C_6$ -cycloalkyl, or 3 to 6-membered heterocycle having 1 or 2 hetero atoms selected from a group consisting of nitrogen and oxygen,

Y represents -O-, -S-, or -N(Z)-, wherein Z represents hydrogen, hydroxy,  $C_1$ - $C_7$ -alkyl, or hydroxy- $C_1$ - $C_7$ -alkyl,

Q represents a group having the following formula:



wherein

$X^1$  represents hydrogen, amino, hydroxy or halogen, or represents  $C_1$ - $C_7$ -alkyl,  $C_1$ - $C_5$ -alkoxy, hydroxy- $C_1$ - $C_7$ -alkyl or phenoxy each of which is optionally substituted by nitro or  $C_1$ - $C_5$ -alkoxy, or represents  $C_6$ - $C_{10}$ -arylthio which is optionally substituted by nitro, amino,  $C_1$ - $C_6$ -alkyl or  $C_1$ - $C_4$ -alkoxy, or represents  $C_6$ - $C_{12}$ -aryl amino,  $C_1$ - $C_7$ -alkylamino, di( $C_1$ - $C_7$ -alkyl)amino,  $C_3$ - $C_6$ -cycloalkylamino or a structure of

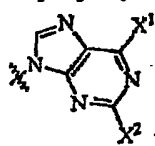


wherein n denotes an integer of 1 or 2 and Y¹ represents O, CH₂ or N-R (R represents C₁-C₇-alkyl), and

X², X³ and X⁴ independently of one another represent hydrogen, amino, hydroxy, halogen, C₁-C₇-alkyl, C₁-C₃-alkoxy, or C₁-C₇-alkylamino.

5

Most preferred compounds are those wherein — represents single bond, R¹, R³, R⁷ and R⁸ independently of one another represent hydrogen, R² represents hydrogen or methyl, R⁴ and R⁵ independently of one another represent t-butylcarbonyloxymethyl, isopropoxycarbonyloxymethyl or 2,2,2-trifluoroethyl, Y represents -O-, Q represents



10 wherein X¹ represents hydrogen, hydroxy, ethoxy, 4-methoxyphenylthio or 4-nitrophenylthio, and X² represents amino.

The compounds of the invention are useful as anti-viral agents, and in particular against

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Human immunodeficiency Virus (HIV).

Typical examples of the compound of formula (1) according to the present invention are described in the following Tables 1 and 7.

Table 1a

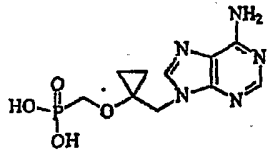
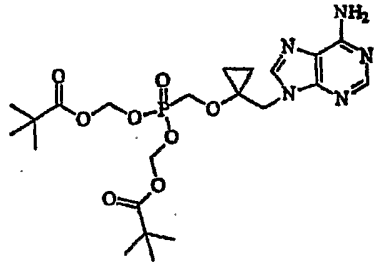
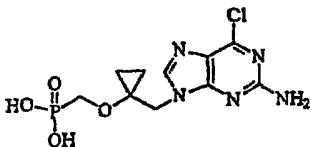
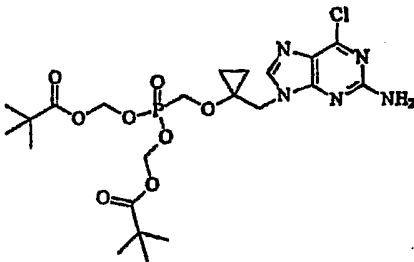
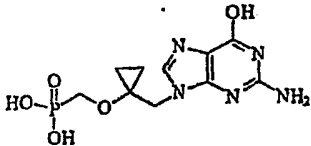
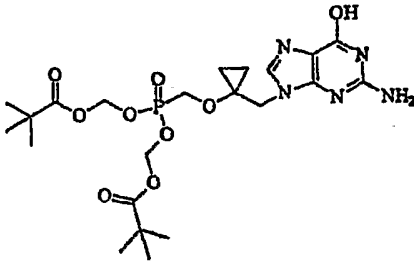
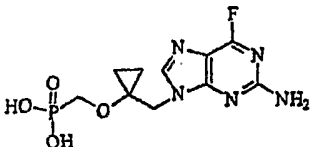
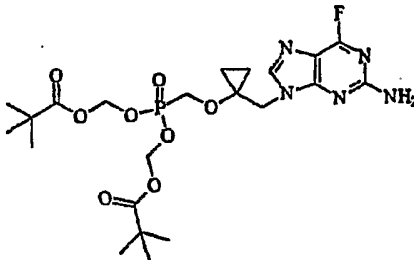
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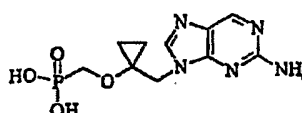
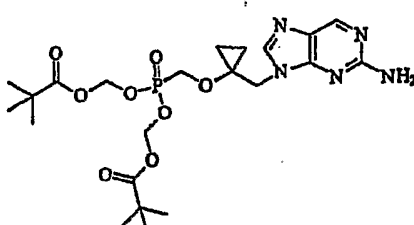
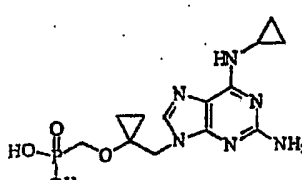
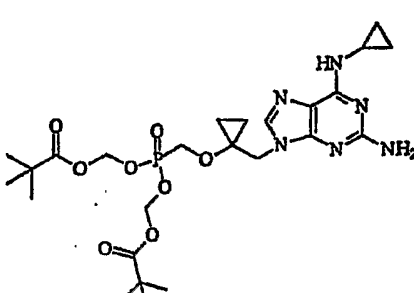
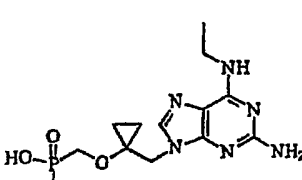
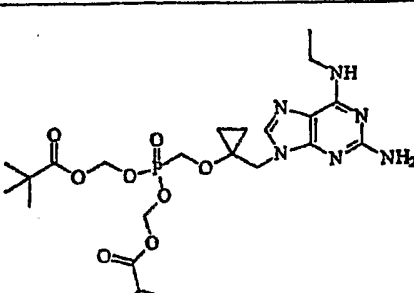
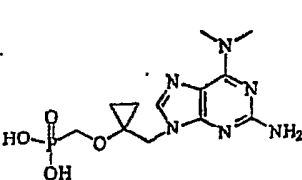
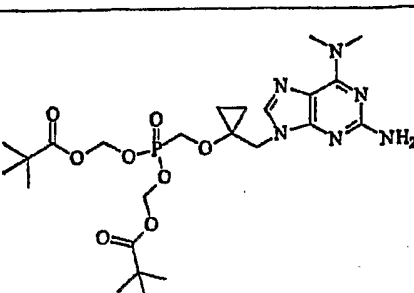
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Table 1c

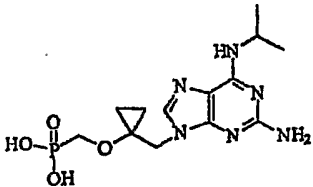
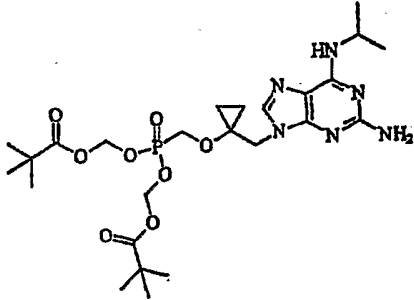
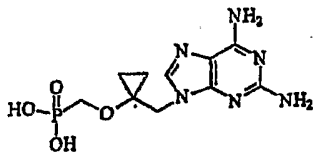
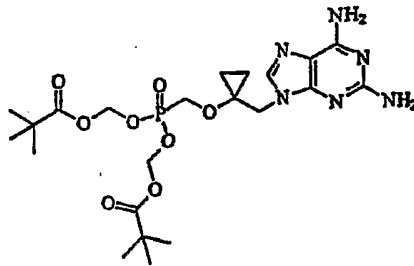
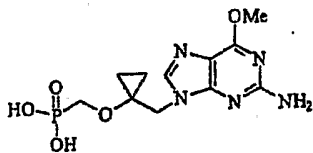
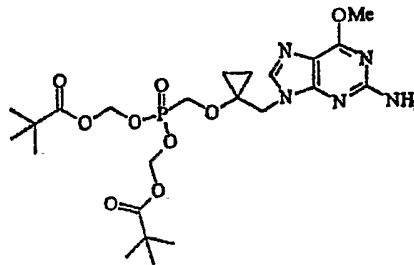
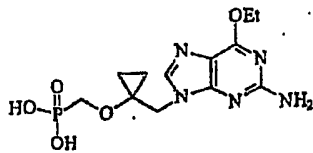
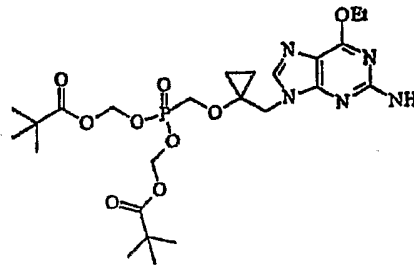
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Table 1d

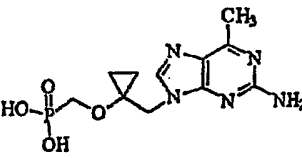
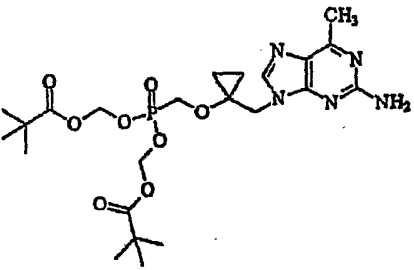
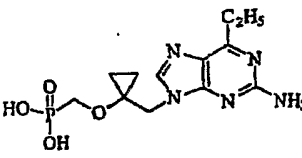
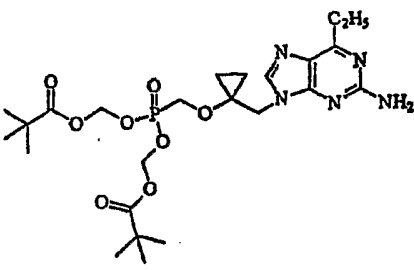
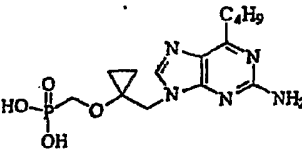
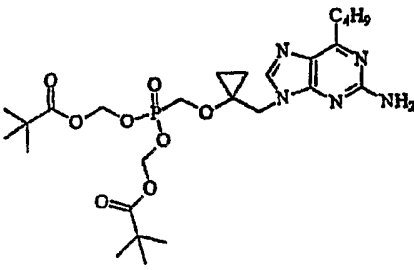
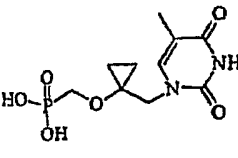
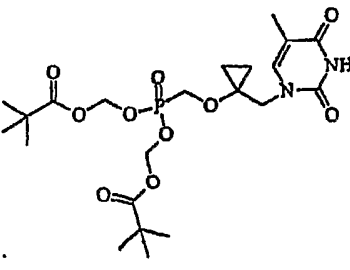
25		26	
27		28	
29		30	
31		32	

Table 1e

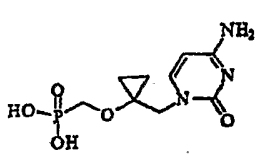
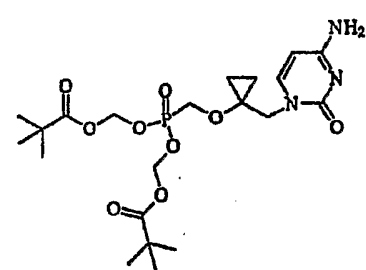
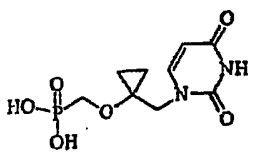
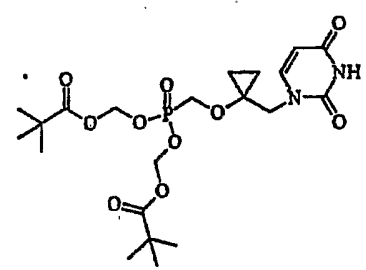
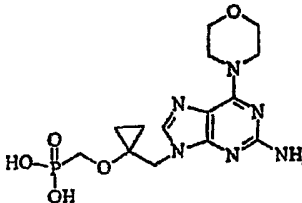
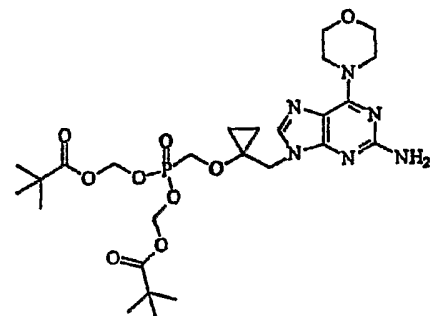
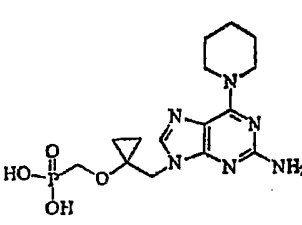
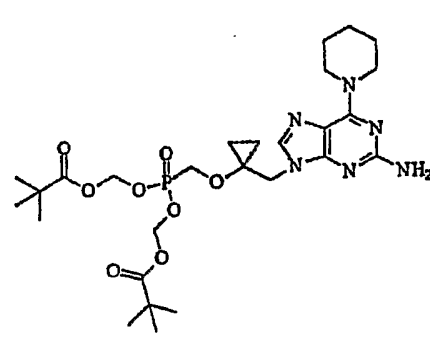
33		34	
35		36	
37		38	
39		40	

Table 1f

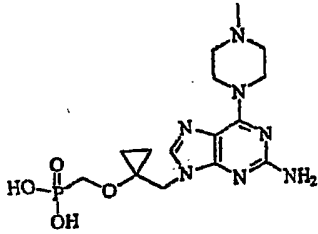
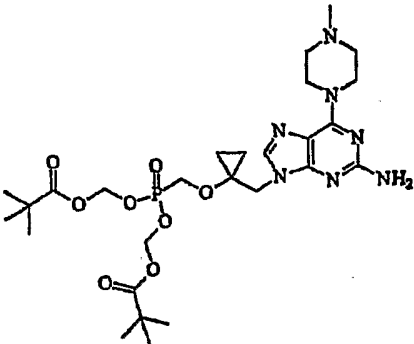
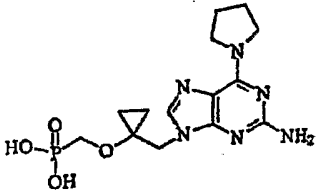
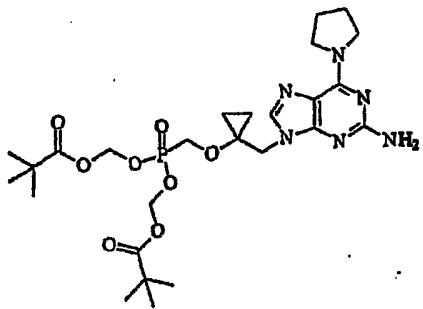
41		42	
43		44	

Table 2a

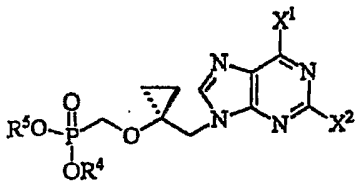
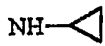
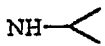
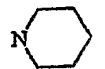
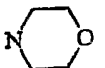
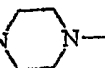
				
COM. NO.	X¹	X²	R⁴	R⁵
45	OH	NH₂	CH₂CF₃	CH₂CF₃
46	Cl	NH₂	CH₂CF₃	CH₂CF₃
47	NH₂	NH₂	CH₂CF₃	CH₂CF₃
48	NH₂	H	CH₂CF₃	CH₂CF₃
49	H	NH₂	CH₂CF₃	CH₂CF₃
50	NH- 	NH₂	CH₂CF₃	CH₂CF₃
51	NHC₂H₅	NH₂	CH₂CF₃	CH₂CF₃
52	N(CH₃)₂	NH₂	CH₂CF₃	CH₂CF₃
53	NH- 	NH₂	CH₂CF₃	CH₂CF₃
54	OCH₃	NH₂	CH₂CF₃	CH₂CF₃
55	CH₃	NH₂	CH₂CF₃	CH₂CF₃
56	C₂H₅	NH₂	CH₂CF₃	CH₂CF₃
57		NH₂	CH₂CF₃	CH₂CF₃
58		NH₂	CH₂CF₃	CH₂CF₃
59		NH₂	CH₂CF₃	CH₂CF₃

Table 2b


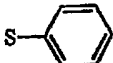
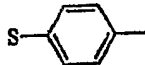
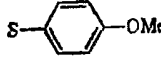
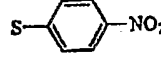
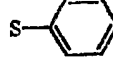
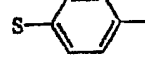
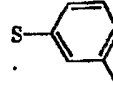
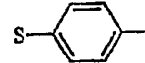
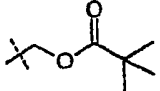
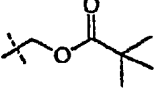
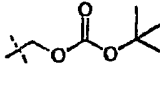
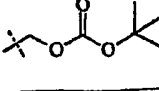
60		NH <sub>2</sub>	CH <sub>2</sub> CF <sub>3</sub>	CH <sub>2</sub> CF <sub>3</sub>
61		NH <sub>2</sub>	CH <sub>2</sub> CF <sub>3</sub>	CH <sub>2</sub> CF <sub>3</sub>
62		NH <sub>2</sub>	CH <sub>2</sub> CF <sub>3</sub>	CH <sub>2</sub> CF <sub>3</sub>
63		NH <sub>2</sub>	CH <sub>2</sub> CF <sub>3</sub>	CH <sub>2</sub> CF <sub>3</sub>
64		NH <sub>2</sub>	CH <sub>2</sub> CF <sub>3</sub>	CH <sub>2</sub> CF <sub>3</sub>
65		NH <sub>2</sub>	H	H
66		NH <sub>2</sub>	H	H
67		NH <sub>2</sub>	H	H
68		NH <sub>2</sub>		
69	H	NH <sub>2</sub>		

Table 2c

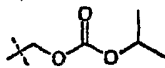
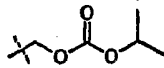
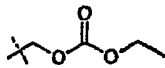
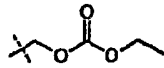
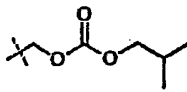
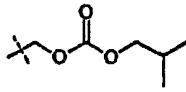
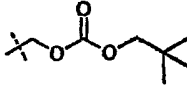
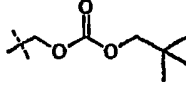
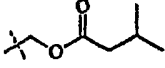
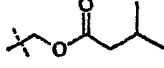
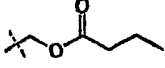
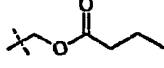
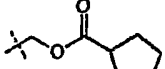
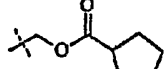
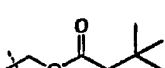
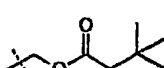
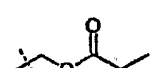
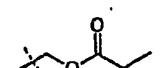
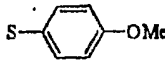
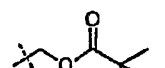
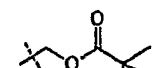
70	H	NH <sub>2</sub>		
71	H	NH <sub>2</sub>		
72	H	NH <sub>2</sub>		
73	H	NH <sub>2</sub>		
74	H	NH <sub>2</sub>		
75	H	NH <sub>2</sub>		
76	H	NH <sub>2</sub>		
77	H	NH <sub>2</sub>		
78	H	NH <sub>2</sub>		
79		NH <sub>2</sub>		



Table 2d

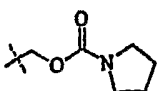
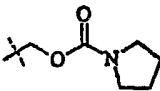
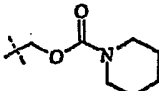
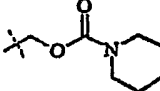
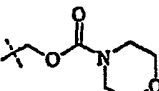
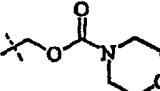
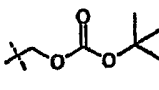
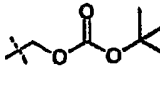
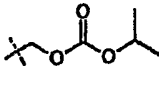
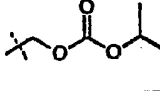
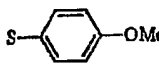
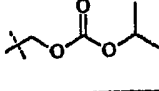
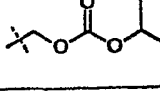
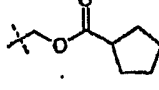
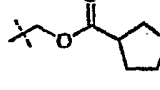
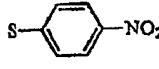
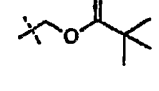
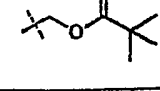
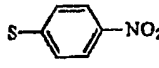
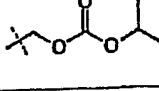
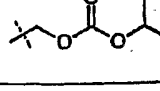
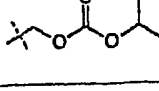
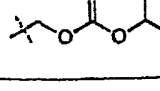
80	H	NH <sub>2</sub>		
81	H	NH <sub>2</sub>		
82	H	NH <sub>2</sub>		
83	OH	NH <sub>2</sub>		
84	OH	NH <sub>2</sub>		
85		NH <sub>2</sub>		
86	OH	NH <sub>2</sub>		
87		NH <sub>2</sub>		
88		NH <sub>2</sub>		
89	NH <sub>2</sub>	H		

Table 2e

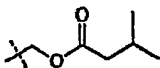
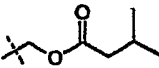
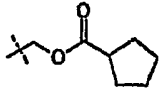
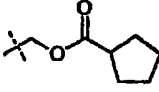
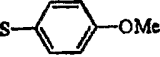
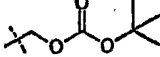
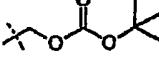
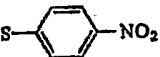
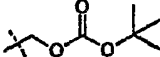
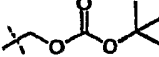
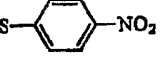
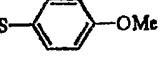
90	NH <sub>2</sub>	H		
91	NH <sub>2</sub>	H		
92		NH <sub>2</sub>		
93		NH <sub>2</sub>		
94	NH <sub>2</sub>	H	H	H
95		NH <sub>2</sub>	H	H
96		NH <sub>2</sub>	H	H

Table 3a

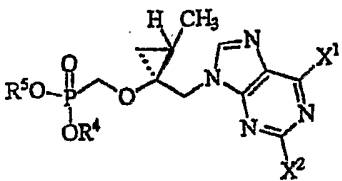
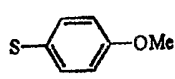
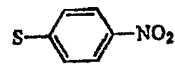
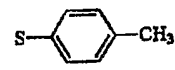
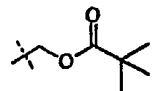
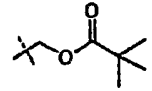
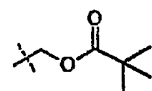
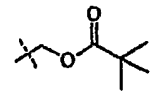
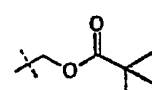
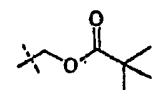
				
COM. NO.	X¹	X²	R⁴	R⁵
97	OH	NH₂	H	H
98	H	NH₂	H	H
99		NH₂	H	H
100		NH₂	H	H
101		NH₂	H	H
102	NH₂	NH₂	H	H
103	NH₂	H	H	H
104	OH	H	H	H
105	OH	NH₂		
106	H	NH₂		
107	NH₂	H		

Table 3b

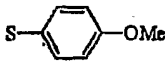
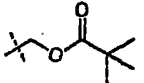
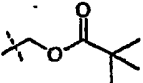
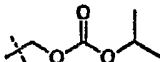
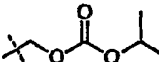
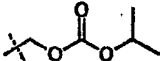
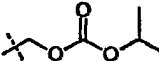
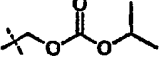
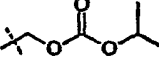
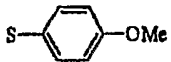
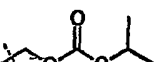
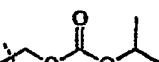
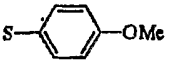
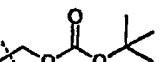
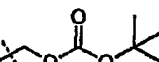
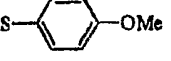
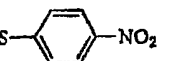
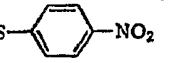
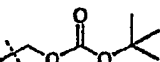
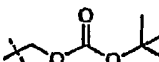
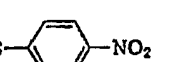
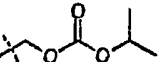
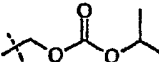
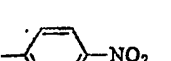
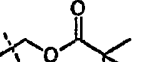
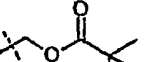
108		NH <sub>2</sub>		
109	OH	NH <sub>2</sub>		
110	H	NH <sub>2</sub>		
111	NH <sub>2</sub>	H		
112		NH <sub>2</sub>		
113		NH <sub>2</sub>		
114		NH <sub>2</sub>	CH <sub>2</sub> CF <sub>3</sub>	CH <sub>2</sub> CF <sub>3</sub>
115		NH <sub>2</sub>	CH <sub>2</sub> CF <sub>3</sub>	CH <sub>2</sub> CF <sub>3</sub>
116		NH <sub>2</sub>		
117		NH <sub>2</sub>		
118		NH <sub>2</sub>		

Table 4

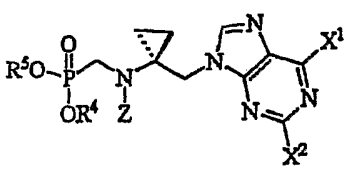
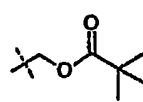
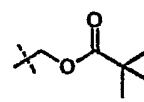
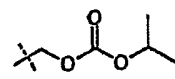
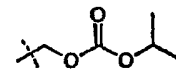
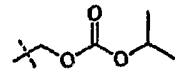
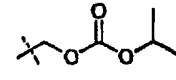
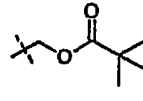
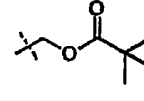
					
COM. NO.	Z	X <sup>1</sup>	X <sup>2</sup>	R <sup>4</sup>	R <sup>5</sup>
119	H	OH	NH <sub>2</sub>	H	H
120	H	H	NH <sub>2</sub>	H	H
121	H	NH <sub>2</sub>	H	H	H
122	CH <sub>3</sub>	OH	NH <sub>2</sub>	H	H
123	CH <sub>3</sub>	H	NH <sub>2</sub>	H	H
124	CH <sub>3</sub>	NH <sub>2</sub>	H	H	H
125	C <sub>2</sub> H <sub>5</sub>	NH <sub>2</sub>	H	H	H
126	CH <sub>3</sub>	NH <sub>2</sub>	H		
127	CH <sub>3</sub>	NH <sub>2</sub>	H		
128	C <sub>2</sub> H <sub>5</sub>	H	NH <sub>2</sub>		
129	C <sub>2</sub> H <sub>5</sub>	H	NH <sub>2</sub>		

Table 5

COM. NO.	Z	X¹	X²	R⁴	R⁵
130	H	OH	NH₂	H	H
131	H	H	NH₂	H	H
132	H	NH₂	H	H	H
133	H	OH	NH₂		
134	H	NH₂	H		
135	CH₃	OH	NH₂	H	H
136	CH₃	H	NH₂	H	H
137	CH₃	NH₂	H	H	H

Table 6

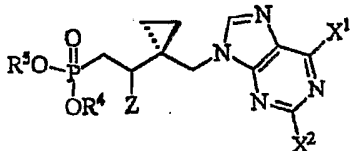
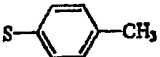
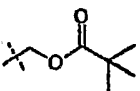
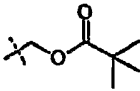
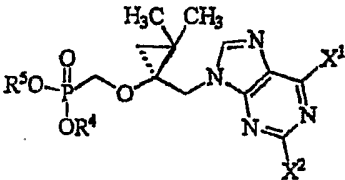
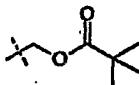
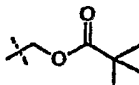
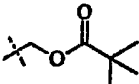
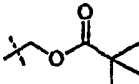
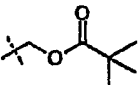
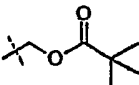
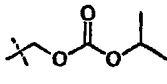
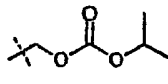
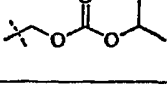
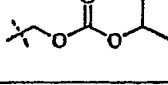
					
COM. NO.	Z	X <sup>1</sup>	X <sup>2</sup>	R <sup>4</sup>	R <sup>5</sup>
138	H	OH	NH <sub>2</sub>	H	H
139	H	H	NH <sub>2</sub>	H	H
140	H	NH <sub>2</sub>	H	H	H
141	H		NH <sub>2</sub>	H	H
142	CH <sub>3</sub>	OH	NH <sub>2</sub>	H	H
143	CH <sub>3</sub>	NH <sub>2</sub>	H	H	H
144	CH <sub>3</sub>	H	NH <sub>2</sub>	H	H
145	CH <sub>3</sub>	NH <sub>2</sub>	H		

Table 7

				
COM. NO.	X¹	X²	R⁴	R²
146	OH	NH₂	H	H
147	H	NH₂	H	H
148	NH₂	H	H	H
149	OH	NH₂		
150	H	NH₂		
151	NH₂	H		
152	NH₂	H		
153	OH	NH₂		

More particularly preferable compounds among the compounds described in the above Tables 1 and 7 are as follows:

- 5     ((1-[(6-amino-9*H*-purin-9-yl)methyl]cyclopropyl)oxy)methylphosphonic acid  
 (Compound 1);  
       3-[(1-[(6-amino-9*H*-purin-9-yl)methyl]cyclopropyl)oxy)methyl]-8,8-dimethyl-  
 3,7-dioxo-2,4,6-trioxa-3λ¹-phosphanon-1-yl pivalate(Compound 2);  
       ((1-[(2-amino-6-chloro-9*H*-purin-9-yl)methyl]cyclopropyl)oxy)methylphosphonic



acid(Compound 3);

3-[(1-[(2-amino-6-chloro-9H-purin-9-yl)methyl]cyclopropyl)oxy)methyl]-8,8-dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate(Compound 4);

((1-[(2-amino-6-hydroxy-9H-purin-9-yl)methyl]cyclopropyl)oxy)methyl  
5 phosphonic acid(Compound 5);

3-[(1-[(2-amino-6-hydroxy-9H-purin-9-yl)methyl]cyclopropyl)oxy)methyl]-8,8-dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate(Compound 6);

((1-[(2-amino-6-fluoro-9H-purin-9-yl)methyl]cyclopropyl)oxy)methylphosphonic  
acid(Compound 7);

3-[(1-[(2-amino-6-fluoro-9H-purin-9-yl)methyl]cyclopropyl)oxy)methyl]-8,8-dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate(Compound 8);

((1-[(2-amino-9H-purin-9-yl)methyl]cyclopropyl)oxy)methylphosphonic acid  
(Compound 9);

3-[(1-[(2-amino-9H-purin-9-yl)methyl]cyclopropyl)oxy)methyl]-8,8-dimethyl-  
15 3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate(Compound 10);

((1-[(2-amino-6-cyclopropylamino-9H-purin-9-yl)methyl]cyclopropyl)oxy) methyl-  
ylphosphonic acid(Compound 11);

3-[(1-[(2-amino-6-cyclopropylamino-9H-purin-9-yl)methyl]cyclopropyl)oxy]  
methyl]-8,8-dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate(Compound

12);

[(1-[(2-amino-6-(dimethylamino)-9H-purin-9-  
yl)methyl]cyclopropyl)oxy)methyl]phosphonic acid(Compound 15);

3-[(1-[(2-amino-6-(dimethylamino)-9H-purin-9-yl)methyl]cyclopropyl)oxy]  
methyl]-8,8-dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate(Compound

16);

[(1-[(2-amino-6-(isopropylamino)-9H-purin-9-  
yl)methyl]cyclopropyl)oxy)methyl]phosphonic acid(Compound 17);

3-[(1-[(2-amino-6-(isopropylamino)-9H-purin-9-yl)methyl]cyclopropyl)oxy]  
methyl]-8,8-dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate(Compound

18);

((1-[(2,6-diamino-9H-purin-9-yl)methyl]cyclopropyl)oxy)methylphosphonic  
acid(Compound 19);

3-[(1-[(2,6-diamino-9H-purin-9-yl)methyl]cyclopropyl)oxy)methyl]-8,8-dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate(Compound 20);

((1-[(2-amino-6-methoxy-9H-purin-9-yl)methyl]cyclopropyl)oxy)methyl  
30 phosphonic acid (Compound 21);

3-[(1-[(2-amino-6-methoxy-9H-purin-9-yl)methyl]cyclopropyl)oxy)methyl]-8,8-

- dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate(Compound 22);  
 ({1-[(2-amino-6-ethoxy-9*H*-purin-9-yl)methyl]cyclopropyl}oxy)methyl  
 phosphonic acid (Compound 23);  
 3-[(1-[(2-amino-6-ethoxy-9*H*-purin-9-yl)methyl]cyclopropyl}oxy)methyl]-8,8-  
 5 dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate(Compound 24);  
 ({1-[(2-amino-6-methyl-9*H*-purin-9-yl)methyl]cyclopropyl}oxy)methyl  
 phosphonic acid(Compound 25);  
 3-[(1-[(2-amino-6-methyl-9*H*-purin-9-yl)methyl]cyclopropyl}oxy)methyl]-8,8-  
 dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate(Compound 26);  
 10 [(1-[(5-methyl-2,4-dioxo-3,4-dihydro-1(2*H*)-  
 pyrimidinyl)methyl]cyclopropyl}oxy)methyl]phosphonic acid(Compound 31);  
 8,8-dimethyl-3-[(1-[(5-methyl-2,4-dioxo-3,4-dihydro-1(2*H*)-  
 pyrimidinyl)methyl]cyclopropyl}oxy)methyl]-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl  
 pivalate (Compound 32);  
 15 [(1-[(2-amino-6-(4-morpholinyl)-9*H*-purin-9-yl)methyl]cyclopropyl}oxy)methyl  
 phosphonic acid(Compound 37);  
 3-[(1-[(2-amino-6-(4-morpholinyl)-9*H*-purin-9-yl)methyl]cyclopropyl}oxy] met-  
 hyl]-8,8-dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate(Compound 38);  
 bis(2,2,2-trifluoroethyl) ({1-[(2-amino-6-hydroxy-9*H*-purin-9-yl)methyl]  
 20 cyclopropyl}oxy)methylphosphonate (Compound 45);  
 bis(2,2,2-trifluoroethyl) ({1-[(2-amino-6-chloro-9*H*-purin-9-yl)methyl]  
 cyclopropyl}oxy)methylphosphonate(Compound 46);  
 bis(2,2,2-trifluoroethyl) ({1-[(2,6-diamino-9*H*-purin-9-yl)methyl]cyclopropyl}  
 oxy)methylphosphonate(Compound 47);  
 25 bis(2,2,2-trifluoroethyl) ({1-[(6-amino-9*H*-purin-9-yl)methyl]cyclopropyl}  
 oxy)methylphosphonate(Compound 48);  
 bis(2,2,2-trifluoroethyl) ({1-[(2-amino-9*H*-purin-9-yl)methyl]cyclopropyl}  
 oxy)methylphosphonate(Compound 49);  
 bis(2,2,2-trifluoroethyl) ({1-[(2-amino-6-dimethylamino-9*H*-purin-9-yl)methyl]  
 30 cyclopropyl}oxy)methylphosphonate(Compound 52);  
 bis(2,2,2-trifluoroethyl) ({1-[(2-amino-6-isopropylamino-9*H*-purin-9-yl)  
 methyl]cyclopropyl}oxy)methylphosphonate(Compound 53);  
 bis(2,2,2-trifluoroethyl) ({1-[(2-amino-6-methoxy-9*H*-purin-9-yl)methyl]  
 cyclopropyl}oxy)methylphosphonate(Compound 54);  
 35 bis(2,2,2-trifluoroethyl) [(1-[(2-amino-6-(4-morpholinyl)-9*H*-purin-9-yl)methyl]  
 cyclopropyl}oxy)methylphosphonate(Compound 58);  
 bis(2,2,2-trifluoroethyl) [(1-[(2-amino-6-(phenylsulfanyl)-9*H*-purin-9-yl]

- methyl}cyclopropyl)oxy]methylphosphonate(Compound 61);  
 bis(2,2,2-trifluoroethyl) {[1-({2-amino-6-[(4-methylphenyl)sulfanyl]-9H-purin-9-yl}methyl)cyclopropyl]oxy}methylphosphonate(Compound 62);  
 bis(2,2,2-trifluoroethyl) {[1-({2-amino-6-[(4-methoxyphenyl)sulfanyl]-9H-purin-9-yl}methyl)cyclopropyl]oxy}methylphosphonate(Compound 63);  
 bis(2,2,2-trifluoroethyl) {[1-({2-amino-6-[(4-nitrophenyl)sulfanyl]-9H-purin-9-yl}methyl)cyclopropyl]oxy}methylphosphonate(Compound 64);  
 [(1-({2-amino-6-(phenylsulfanyl)-9H-purin-9-yl}methyl)cyclopropyl)oxy]methylphosphonic acid(Compound 65);  
 {[1-({2-amino-6-[(4-methylphenyl)sulfanyl]-9H-purin-9-yl}methyl)cyclopropyl]oxy}methylphosphonic acid(Compound 66);  
 3-({[1-({2-amino-6-[(4-methylphenyl)sulfanyl]-9H-purin-9-yl}methyl)cyclopropyl]oxy}methyl)-8,8-dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate(Compound 68);  
 bis{[(*t*-butoxycarbonyl)oxy]methyl}({[1-({2-amino-9H-purin-9-yl}methyl)cyclopropyl]oxy}methylphosphonate(Compound 69);  
 bis{[(isopropoxycarbonyl)oxy]methyl}({[1-({2-amino-9H-purin-9-yl}methyl)cyclopropyl]oxy}methylphosphonate(Compound 70);  
 bis{[(ethoxycarbonyl)oxy]methyl}({[1-({2-amino-9H-purin-9-yl}methyl)cyclopropyl]oxy}methylphosphonate(Compound 71);  
 bis{[(isobutoxycarbonyl)oxy]methyl}({[1-({2-amino-9H-purin-9-yl}methyl)cyclopropyl]oxy}methylphosphonate(Compound 72);  
 3-([1-({2-amino-9H-purin-9-yl}methyl)cyclopropyl]oxy)methyl]-9-methyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphadec-1-yl 3-methylbutanoate(Compound 74);  
 3-([1-({2-amino-9H-purin-9-yl}methyl)cyclopropyl]oxy)methyl]-8-methyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl 2-methylpropanoate(Compound 78);  
 3-({[1-({2-amino-6-[(4-methoxyphenyl)sulfanyl]-9H-purin-9-yl}methyl)cyclopropyl]oxy}methyl)-8,8-dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate(Compound 79);  
 3-([1-({2-amino-9H-purin-9-yl}methyl)cyclopropyl]oxy)methyl]-3,7-dioxo-7-(1-pyrrolidinyl)-2,4,6-trioxa-3 $\lambda^5$ -phosphahept-1-yl 1-pyrrolidinecarboxylate(Compound 80);  
 3-([1-({2-amino-9H-purin-9-yl}methyl)cyclopropyl]oxy)methyl]-3,7-dioxo-7-(1-piperidinyl)-2,4,6-trioxa-3 $\lambda^5$ -phosphahept-1-yl 1-piperidinecarboxylate(Compound 81);  
 3-([1-({2-amino-9H-purin-9-yl}methyl)cyclopropyl]oxy)methyl]-7-(4-morpholinyl)-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphahept-1-yl 4-morpholinecarboxylate(Compound 82);  
 bis{[(*t*-butoxycarbonyl)oxy]methyl}([1-({2-amino-6-hydroxy-9H-purin-9-yl}

- methyl)cyclopropyl]oxy)methylphosphonate(Compound 83);  
 bis{[(isopropoxycarbonyl)oxy)methyl]}{[1-{[2-amino-6-hydroxy-9*H*-purin-9-yl]  
 methyl)cyclopropyl]oxy)methylphosphonate(Compound 84);  
 bis{[(isopropoxycarbonyl)oxy)methyl]}{[1-{[2-amino-[6-(4-methoxyphenyl)  
 5 sulfanyl]-9*H*-purin-9-yl]methyl)cyclopropyl]oxy)methylphosphonate(Compound 85);  
 3-[(1-{[2-amino-6-hydroxy-9*H*-purin-9-yl]methyl)cyclopropyl]oxy)methyl]-7-  
 cyclopentyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphahept-1-yl cyclopentanecarboxylate  
 (Compound 86);  
 3-([1-{[2-amino-[6-(4-nitrophenyl)sulfanyl]-9*H*-purin-9-yl]methyl)cyclopropyl]  
 10 oxy)methyl]-8,8-dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate  
 (Compound 87);  
 bis{[(isopropoxycarbonyl)oxy)methyl]}{[1-{[2-amino-[6-(4-nitrophenyl)sulfanyl]-  
 9*H*-purin-9-yl]methyl)cyclopropyl]oxy)methylphosphonate(Compound 88);  
 bis{[(isopropoxycarbonyl)oxy)methyl]}{[1-{[6-amino-9*H*-purin-9-yl]methyl]cyclo-  
 15 propyl]oxy)methylphosphonate(Compound 89);  
 3-[(1-{[6-amino-9*H*-purin-9-yl]methyl)cyclopropyl]oxy)methyl]-9-methyl-3,7-  
 dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphadec-1-yl 3-methylbutanoate(Compound 90);  
 3-[(1-{[6-amino-9*H*-purin-9-yl]methyl)cyclopropyl]oxy)methyl]-7-cyclopentyl-  
 3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphahept-1-yl cyclopentanecarboxylate(Compound 91);  
 20 bis{[(*t*-butoxycarbonyl)oxy)methyl]}{[1-{[2-amino-[6-(4-  
 methoxyphenyl)sulfanyl]-9*H*-purin-9-  
 yl]methyl)cyclopropyl]oxy)methylphosphonate(Compound 92);  
 bis{[(*t*-butoxycarbonyl)oxy)methyl]}{[1-{[2-amino-[6-(4-nitrophenyl)sulfanyl]-  
 9*H*-purin-9-yl]methyl)cyclopropyl]oxy)methylphosphonate(Compound 93);  
 25 {[1-{[2-amino-[6-(4-nitrophenyl)sulfanyl]-9*H*-purin-9-  
 yl]methyl)cyclopropyl]oxy)methylphosphonic acid(Compound 95);  
 {[1-{[2-amino-[6-(4-methoxyphenyl)sulfanyl]-9*H*-purin-9-  
 yl]methyl)cyclopropyl]oxy)methylphosphonic acid(Compound 96);  
 ((1-{[2-amino-6-hydroxy-9*H*-purin-9-yl]methyl]-2-methylcyclopropyl]oxy)  
 30 methylphosphonic acid(Compound 97);  
 ((1-{[2-amino-9*H*-purin-9-yl]methyl]-2-methylcyclopropyl]oxy)methylphosphonic  
 acid(Compound 98);  
 ([1-{[2-amino-[6-(4-methoxyphenyl)sulfanyl]-9*H*-purin-9-yl]methyl]-2-methyl  
 cyclopropyl]oxy)methylphosphonic acid(Compound 99);  
 35 {[1-{[2-amino-[6-(4-nitrophenyl)sulfanyl]-9*H*-purin-9-yl]methyl]-2-methylcyclo-  
 propyl]oxy)methylphosphonic acid(Compound 100);  
 ([1-{[2-amino-[6-(4-methylphenyl)sulfanyl]-9*H*-purin-9-yl]methyl]-2-methyl

cyclopropyl]oxy)methylphosphonic acid(Compound 101);

((1-[(2,6-diamino-9H-purin-9-yl)methyl]-2-methylcyclopropyl)oxy)methyl  
phosphonic acid(Compound 102);

((1-[(6-amino-9H-purin-9-yl)methyl]-2-methylcyclopropyl)oxy)methylphosphonic  
5 acid(Compound 103);

3-[(1-[(2-amino-6-hydroxy-9H-purin-9-yl)methyl]-2-methylcyclopropyl)oxy]  
methyl]-8,8-dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate(Compound  
105);

3-[(1-[(2-amino-9H-purin-9-yl)methyl]-2-methylcyclopropyl)oxy)methyl]-8,8-  
10 dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate(Compound 106);

3-[(1-[(6-amino-9H-purin-9-yl)methyl]-2-methylcyclopropyl)oxy)methyl]-8,8-  
dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate(Compound 107);

3-[(1-[(2-amino-6-[(4-methoxyphenyl)sulfanyl]-9H-purin-9-yl)methyl]-2-  
methylcyclopropyl]oxy)methyl]-8,8-dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl  
15 pivalate (Compound 108);

bis{[(isopropoxycarbonyl)oxy]methyl}[(1-[(2-amino-6-hydroxy-9H-purin-9-yl]  
methyl]-2-methylcyclopropyl)oxy]methylphosphonate(Compound 109);

bis{[(isopropoxycarbonyl)oxy]methyl}[(1-[(2-amino-9H-purin-9-yl)methyl]-2-  
methylcyclopropyl)oxy]methylphosphonate(Compound 110);

20 bis{[(isopropoxycarbonyl)oxy]methyl}[(1-[(2-amino-[6-(4-methoxyphenyl)  
sulfanyl]-9H-purin-9-yl)methyl]-2-methylcyclopropyl]oxy]methylphosphonate  
(Compound 112);

bis{[(t-butoxycarbonyl)oxy]methyl}[(1-[(2-amino-[6-(4-  
methoxyphenyl)sulfanyl]-9H-purin-9-yl)methyl]-2-  
25 methylcyclopropyl]oxy]methylphosphonate(Compound 113);

bis(2,2,2-trifluoroethyl){[1-[(2-amino-6-[(4-methoxyphenyl)sulfanyl]-9H-purin-9-yl]  
yl)methyl]-2-methylcyclopropyl]oxy]methylphosphonate(Compound 114);

bis(2,2,2-trifluoroethyl){[1-[(2-amino-6-[(4-nitrophenyl)sulfanyl]-9H-purin-9-yl]  
methyl]-2-methylcyclopropyl]oxy]methylphosphonate(Compound 115);

30 bis{[(t-butoxycarbonyl)oxy]methyl}[(1-[(2-amino-[6-(4-nitrophenyl)sulfanyl]-  
9H-purin-9-yl)methyl]-2-methylcyclopropyl]oxy]methylphosphonate(Compound 116);

bis{[(isopropoxycarbonyl)oxy]methyl}[(1-[(2-amino-[6-(4-nitrophenyl)sulfanyl]-  
9H-purin-9-yl)methyl]-2-methylcyclopropyl]oxy]methylphosphonate(Compound 117);

35 3-[(1-[(2-amino-6-[(4-nitrophenyl)sulfanyl]-9H-purin-9-yl)methyl]-2-methyl  
cyclopropyl]oxy)methyl]-8,8-dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl  
pivalate (Compound 118);

((1-[(2-amino-6-hydroxy-9H-purin-9-yl)methyl]cyclopropyl)amino)methyl

phosphonic acid(Compound 119);

((1-[(2-amino-9*H*-purin-9-yl)methyl]cyclopropyl)amino)methylphosphonic acid(Compound 120);

5 ((1-[(6-amino-9*H*-purin-9-yl)methyl]cyclopropyl)amino)methylphosphonic acid(Compound 121);

[[1-[(2-amino-6-hydroxy-9*H*-purin-9-yl)methyl]cyclopropyl](methyl)amino]methylphosphonic acid(Compound 122);

[[1-[(6-amino-9*H*-purin-9-yl)methyl]cyclopropyl](ethyl)amino]methylphosphonic acid(Compound 125);

10 3-[[{1-[(6-amino-9*H*-purin-9-yl)methyl]cyclopropyl}(methyl)amino)methyl]-8,8-dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate(Compound 126);

bis{[(isopropoxycarbonyl)oxy]methyl}[[1-[(6-amino-9*H*-purin-9-yl)methyl]cyclopropyl](methyl)amino]methylphosphonate(Compound 127);

15 3-[[{1-[(2-amino-9*H*-purin-9-yl)methyl]cyclopropyl](ethyl)amino]methyl]-8,8-dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate(Compound 129);

(*E*)-2-{1-[(2-amino-6-hydroxy-9*H*-purin-9-yl)methyl]cyclopropyl}ethenyl phosphonic acid(Compound 130);

(*E*)-2-{1-[(2-amino-9*H*-purin-9-yl)methyl]cyclopropyl}ethenylphosphonic acid (Compound 131);

20 (*E*)-2-{1-[(6-amino-9*H*-purin-9-yl)methyl]cyclopropyl}ethenylphosphonic acid (Compound 132);

3-((*E*)-2-{1-[(2-amino-6-hydroxy-9*H*-purin-9-yl)methyl]cyclopropyl}ethenyl)-8,8-dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate(Compound 133);

25 3-((*E*)-2-{1-[(6-amino-9*H*-purin-9-yl)methyl]cyclopropyl}ethenyl)-8,8-dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate(Compound 134);

(*E*)-2-{1-[(6-amino-9*H*-purin-9-yl)methyl]cyclopropyl}-1-propenylphosphonic acid(Compound 137);

2-{1-[(2-amino-6-hydroxy-9*H*-purin-9-yl)methyl]cyclopropyl}ethylphosphonic acid(Compound 138);

30 2-{1-[(2-amino-9*H*-purin-9-yl)methyl]cyclopropyl}ethylphosphonic acid (Compound 139);

2-{1-[(6-amino-9*H*-purin-9-yl)methyl]cyclopropyl}ethylphosphonic acid (Compound 140);

2-[1-((2-amino-6-[(4-methylphenyl)sulfanyl]-9*H*-purin-9-yl)methyl)cyclopropyl] ethylphosphonic acid(Compound 141);

35 2-{1-[(2-amino-6-hydroxy-9*H*-purin-9-yl)methyl]cyclopropyl}propylphosphonic acid(Compound 142);

2-{1-[(6-amino-9*H*-purin-9-yl)methyl]cyclopropyl}propylphosphonic acid  
(Compound 143);

2-{1-[(2-amino-9*H*-purin-9-yl)methyl]cyclopropyl}propylphosphonic acid  
(Compound 144);

3-(2-{1-[(6-amino-9*H*-purin-9-yl)methyl]cyclopropyl}propyl)-8,8-dimethyl-3,7-  
dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate(Compound 145);

((1-[(2-amino-6-hydroxy-9*H*-purin-9-yl)methyl]-2,2-dimethylcyclopropyl)oxy)  
methylphosphonic acid(Compound 146);

((1-[(2-amino-9*H*-purin-9-yl)methyl]-2,2-dimethylcyclopropyl)oxy)methyl  
phosphonic acid(Compound 147);

((1-[(6-amino-9*H*-purin-9-yl)methyl]-2,2-dimethylcyclopropyl)oxy)methyl  
phosphonic acid(Compound 148);

3-[(1-[(2-amino-6-hydroxy-9*H*-purin-9-yl)methyl]-2,2-  
dimethylcyclopropyl)oxy)methyl]-8,8-dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-  
yl pivalate(Compound 149);

3-[(1-[(2-amino-9*H*-purin-9-yl)methyl]-2,2-dimethylcyclopropyl)oxy)methyl]-  
8,8-dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate(Compound 150);

3-[(1-[(6-amino-9*H*-purin-9-yl)methyl]-2,2-dimethylcyclopropyl)oxy)methyl]-  
8,8-dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate(Compound 151);

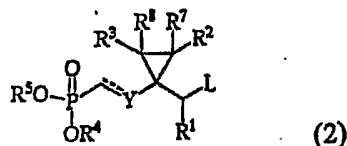
bis{[(isopropoxycarbonyl)oxy)methyl}((1-[(6-amino-9*H*-purin-9-yl)methyl]-2,2-  
dimethylcyclopropyl)oxy)methylphosphonate(Compound 152); and

bis{[(isopropoxycarbonyl)oxy)methyl}[(1-[(2-amino-6-hydroxy-9*H*-purin-9-yl]  
methyl]-2,2-dimethylcyclopropyl)oxy)methylphosphonate(Compound 153).

The compound of formula (1) according to the present invention can be prepared  
by a process as explained below, and thus, it is another object of the present invention to  
provide such a preparation process. However, conditions of the process, such as for  
example, reactants, solvents, bases, amounts of the reactants used, etc. are not restricted to  
those explained below. The compound of the present invention may also be conveniently  
prepared by optionally combining the various synthetic ways described in the present  
specification or known in the arts, and such a combination can be easily performed by one  
of ordinary skill in the art to which the present invention pertains.

The compound of formula (1) of the present invention can be prepared  
characterized in that

(a) a compound represented by the following formula (2):



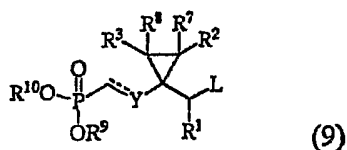
5 in which R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>7</sup>, R<sup>8</sup> and Y are defined as previously described, and L represents a leaving group, preferably methanesulfonyloxy, p-toluenesulfonyloxy or halogen, is reacted with a compound represented by the following formula (3):



10

in which Q is defined as previously described, to produce the compound of formula (1),

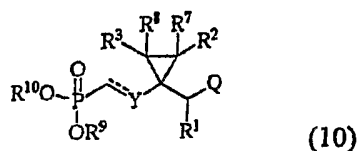
(b) a compound represented by the following formula (9):



15

in which R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>7</sup>, R<sup>8</sup>, Y and L are defined as previously described, and R<sup>9</sup> and R<sup>10</sup> independently of one another represent optionally substituted alkyl, is reacted with the compound of formula (3) to produce a compound represented by the following formula (10):

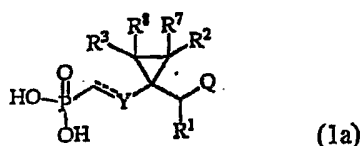
20



25 in which R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>7</sup>, R<sup>8</sup>, Y, Q, R<sup>9</sup> and R<sup>10</sup> are defined as previously described, and the resulting compound of formula (10) is hydrolyzed in the presence of a Lewis acid to

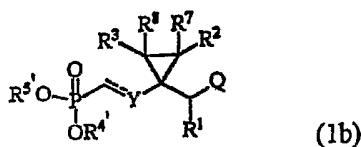


produce a compound represented by the following formula (1a):



5 in which  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^7$ ,  $R^8$ , Y and Q are defined as previously described, or

(c) groups  $R^4$  and  $R^5$  are introduced into the compound of formula (1a) to produce a compound represented by the following formula (1b):



10

in which  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^7$ ,  $R^8$ , Y and Q are defined as previously described, and  $R^4$  and  $R^5$  represent  $R^4$  and  $R^5$  with the exception of hydrogen, respectively, or further the compounds thus obtained are subjected to conventional conversions (see: USP 6,037,335, 5,935,946, and 5,792,756).

15

In the above process variants (a) to (c) for preparing the compound of formula (1), the reactions may be carried out in a solvent and in the presence of a base. As the solvent, one or more selected from a group consisting of dimethylformamide, dichloromethane, tetrahydrofuran, chloroform, 1-methyl-2-pyrrolidinone and dimethylacetamide can be mentioned, and as the base one or more selected from a group consisting of sodium hydride, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, potassium t-butoxide, hydrogen bis(trimethylsilyl)amide, sodium amide, cesium carbonate and potassium bis(trimethylsilyl)amide can be mentioned. The Lewis acid which can be used in the process variant (b) includes trimethylsilylhalide. Further, in the process variant (c) for introducing the groups  $R^4$  and  $R^5$  into the compound of formula (1a), this compound is subjected to an ether-forming reaction with an alkylhalide in the presence of a base, or is treated with thionyl chloride, oxalyl chloride or phosphorus

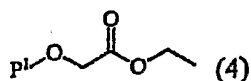
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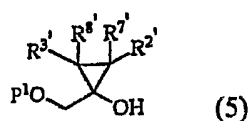
pentachloride to produce a dichlorophosphonate derivative which is then reacted with a suitable alcohol or amine to give the desired compound.

5 The phosphonate compound of formula (2) used as a starting material in the above process is itself a novel compound. Therefore, it is another object of the present invention to provide the compound of formula (2).

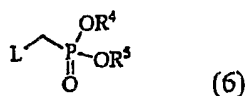
10 The compound of formula (2) wherein Y is O, R<sup>1</sup> is hydrogen, and each of R<sup>2</sup>, R<sup>3</sup>, R<sup>7</sup> and R<sup>8</sup> is hydrogen or alkyl, that is, a compound of the following formula (8), can be prepared characterized in that (i) an ethylglycolate, the alcohol group of which is protected, represented by the following formula (4):



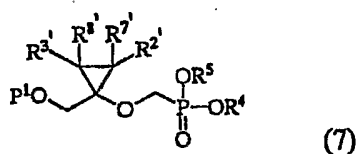
15 in which P<sup>1</sup> represents an alcohol-protecting group, preferably benzyl(Bn), tetrahydropyranyl(THP), t-butyl diphenylsilyl(TBDPS), or t-butyl dimethylsilyl(TBDMS), is reacted with ethyl magnesium bromide[C<sub>2</sub>H<sub>5</sub>MgBr] or the corresponding alkyl magnesium bromide or alkyl magnesium chloride in the presence of titanium tetraisopropoxide[Ti(OiPr)<sub>4</sub>], (ii) the resulting cyclopropanol represented by the following  
20 formula (5):



25 in which P<sup>1</sup> is defined as previously described and each of R<sup>2</sup>, R<sup>3</sup>, R<sup>7</sup> and R<sup>8</sup> represents hydrogen or alkyl, is subjected to an ether-forming reaction in the presence of a base with a compound represented by the following formula (6):

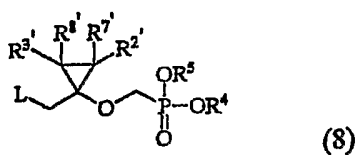


in which L, R<sup>4</sup> and R<sup>5</sup> are defined as previously described, to produce a phosphonate compound represented by the following formula (7):



in which P<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>4</sup> and R<sup>5</sup> are defined as previously described, and (iii) the alcohol-protecting group of the resulting compound of formula (7) is removed and a leaving group(L) is introduced to produce a compound represented by the following formula (8):

10



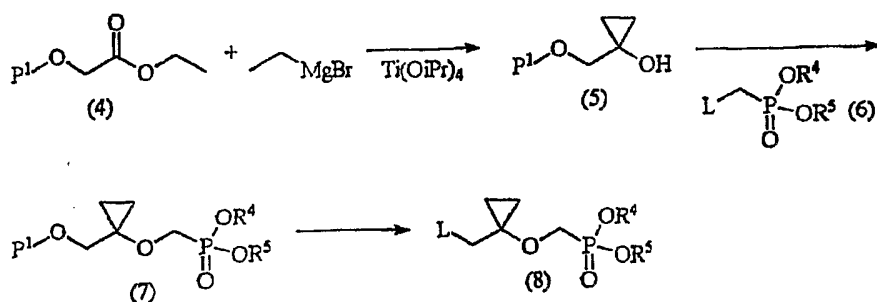
in which L, R<sup>2</sup>, R<sup>3</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>4</sup> and R<sup>5</sup> are defined as previously described.

15

The process for preparing the simplest compound of formula (8) (that is, all of R<sup>2</sup>, R<sup>3</sup>, R<sup>7</sup> and R<sup>8</sup> are hydrogen) is briefly depicted in the following Reaction Scheme 1:

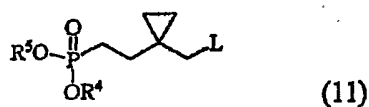
### Reaction Scheme 1

20



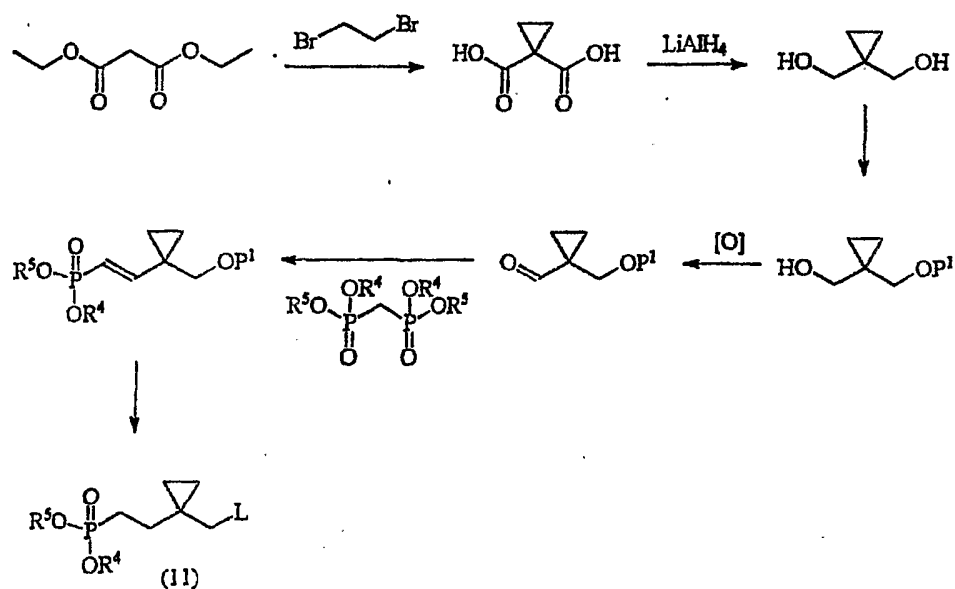
The specific reaction conditions of the above process can be referred to the following Preparations and Examples.

- 5 Further, the compound of formula (2) wherein Y is  $-\text{CH}_2-$ , and each of  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^7$  and  $\text{R}^8$  is hydrogen, that is a compound of the following formula (11):



- 10 in which L,  $\text{R}^4$  and  $\text{R}^5$  are defined as previously described, can be prepared by a process as depicted in the following Reaction Scheme 2:

#### Reaction Scheme 2

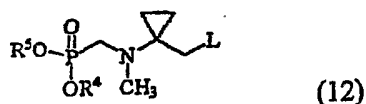


15

- Reaction Scheme 2 is briefly explained below. (i) According to a known method (see: JOC, 1975, Vol.40, 2969-2970), dialkylmalonate is reacted with dihaloethane to give malonic acid wherein cyclopropyl group is introduced into its 2-position. (ii) The malonic acid is reduced to give diol compound, one hydroxy group of which is then
- 20

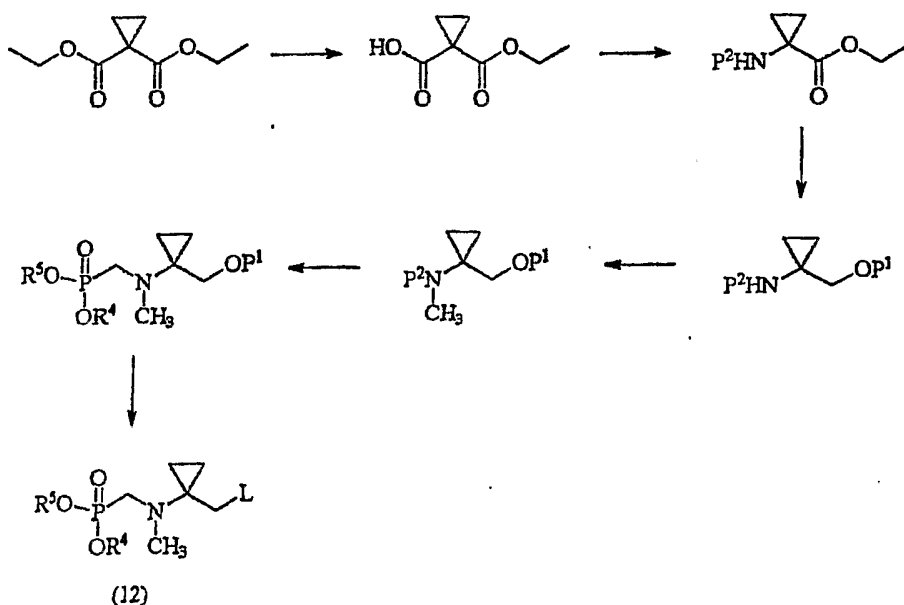
protected with a suitable protecting group ( $P^1$  is defined as previously described). Then, the other hydroxy group is oxidized to an aldehyde group. (iii) The resulting aldehyde compound is reacted with tetraalkylmethylenediphosphonate to give the desired phosphonate compound. (iv) The phosphonate compound thus obtained is reduced to give a compound having no unsaturated bond, alcohol-protecting group ( $P^1$ ) is removed, and a leaving group (L) is introduced to give the compound of formula (11).

Further, the compound of formula (2) wherein Y is  $-N(CH_3)-$  and each of  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^7$  and  $R^8$  is hydrogen, that is a compound of the following formula (12):



in which L,  $R^4$  and  $R^5$  are defined as previously described, can be prepared by a process as depicted in the following Reaction Scheme 3:

### Reaction Scheme 3



Reaction Scheme 3 is briefly explained below. (i) Diethyl 1,1-cyclopropyl

dicarboxylate is selectively hydrolyzed to give a monocarboxylic acid. (ii) An amine group is introduced into the monocarboxylic acid according to the known Curtius Reaction (see: S. Linke, G. T. Tissue and W. Lowowski, *J. Am. Chem. Soc.* 1967, 89, 6308). (iii) The amine group is protected with a suitable protecting group [ $P^2$  may be carbamate or various benzyl protecting groups, or alkyl group (methyl, ethyl, etc.)]. (iv) The opposite ester group is reduced into a hydroxy group, which is then protected ( $P^1$  is defined as previously described). (v) The compound protected with protecting groups is reacted with methyl iodide in the presence of sodium hydride to introduce methyl group into the amine group. (vi) The amine-protecting group is removed and the resulting compound is reacted with dialkylbromomethylphosphonate to give the desired phosphonate compound. (vii) The alcohol-protecting group ( $P^1$ ) is removed from the phosphonate compound thus obtained and then a leaving group (L) is introduced to give the compound of formula (12).

The specific reaction conditions of the above processes can be referred to the following Preparations and Examples.

After the reaction is completed, the resulting product may be further separated and purified by usual work-up processes, such as for example, chromatography, recrystallization, etc.

20

The compound of formula (1) of the present invention can be effectively used as an antiviral agent. Therefore, it is another object of the present invention to provide a composition for the treatment of viral diseases, which comprises as an active ingredient the compound of formula (1), pharmaceutically acceptable salt, hydrate, solvate or isomer thereof together with the pharmaceutically acceptable carrier.

25

When the active compound according to the present invention is used for clinical purpose, it is preferably administered in an amount ranging generally from 0.1 to 10000mg, preferably from 0.5 to 100mg per kg of body weight a day. The total daily dosage may be administered in once or over several times. However, the specific administration dosage for the patient can be varied with the specific compound used, body weight, sex or hygienic condition of the subject patient, diet, time or method of administration, excretion rate, mixing ratio of the agent, severity of the disease to be treated, etc.

30

The compound of the present invention may be administered in the form of injections or oral preparations.

35

5       Injections, for example, sterilized aqueous or oily suspension for injection, can be prepared according to the known procedure using suitable dispersing agent, wetting agent, or suspending agent. Solvents which can be used for preparing injections include water, Ringer's fluid and isotonic NaCl solution, and also sterilized fixing oil may be conveniently used as the solvent or suspending media. Any non-stimulative fixing oil including mono-, di-glyceride may be used for this purpose. Fatty acid such as oleic acid may also be used for injections.

10       As the solid preparation for oral administration, capsules, tablets, pills, powders and granules, etc., preferably capsules and tablets can be mentioned. It is also desirable for tablets and pills to be formulated into enteric-coated preparation. The solid preparations may be prepared by mixing the active compound of formula (1) according to the present invention with at least one carrier selected from a group consisting of inactive diluents  
15       such as sucrose, lactose, starch, etc., lubricants such as magnesium stearate, disintegrating agent and binding agent.

20       When the compound according to the present invention is clinically applied for obtaining the desired antiviral effect, the active compound of formula (1) can be administered in combination with one or more substances selected from the known anti-cancer or antiviral agents.

25       However, preparations comprising the compound of the present invention are not restricted to those explained above, but may contain any substances useful for the treatment or prevention of cancers or viral diseases.

30       The following Preparations (1-35) and Examples (1-52) are disclosed by Choi et al. in International Publication No. WO 02/057288, pgs. 38-82, and are explicitly incorporated herein:

35       **Preparation 1**

**Synthesis of 1-({t-butyl(diphenyl)silyl}oxy)methyl)cyclopropanol**

According to the description in a reference (see: *Syn. Lett.* 07, 1053-1054, 1999), the title compound was prepared as follows. 12g(35 mmole) of ethyl 2-[[t-butyl(diphenyl)silyl]oxy]acetate was dissolved in 200ml of tetrahydrofuran(THF) and 2.2 ml of titaniumtetrakisopropoxide was added thereto. To the mixture was slowly added 29.2ml of ethylmagnesiumbromide(3.0M in THF), and the reaction solution was stirred for 12 hours at room temperature. 20ml of saturated ammonium chloride was added to stop the reaction. About 150ml of tetrahydrofuran (THF) used as a solvent was removed by distillation under reduced pressure, and the reaction mixture was extracted twice with 200ml of ethyl acetate. The ethyl acetate extract was distilled under reduced pressure to give 11.4g(Yield 100%) of the title compound as a white solid.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.44 (q, 2H), 0.78 (q, 2H), 1.09 (s, 9H), 3.67 (s, 2H), 7.41 (m, 6H), 7.70(m, 4H)  
ESI: 344 (M+NH<sub>4</sub>)<sup>+</sup>, C<sub>20</sub>H<sub>26</sub>O<sub>2</sub>Si

#### Preparation 2

Synthesis of diisopropyl {[1-([t-butyl(diphenyl)silyl]oxy)methyl]cyclopropyl}oxy} methylphosphonate

The compound prepared in Preparation 1 (6.5g) was dissolved in 10ml of dimethylformamide(DMF), 32ml of lithium t-butoxide(1.0M in THF) was added thereto, and the resulting mixture was stirred for 10 minutes. To the mixture was added 7.0g of diisopropyl bromomethylphosphonate, and then the temperature was raised to 40 °C and the mixture was stirred for 4 hours. Dimethylformamide(DMF) was removed by distillation under reduced pressure, 40ml of saturated ammonium chloride was added to the residue, which was then extracted with ethyl acetate. The ethyl acetate extract was distilled under reduced pressure and the residue was purified by silica gel column chromatography (eluent: ethyl acetate/n-hexane=1/1, v/v) to give 6.8g(Yield 70%) of the title compound.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.53 (m, 2H), 0.88 (m, 2H), 1.07 (s, 9H), 1.29 (t, 12H), 3.78 (s, 2H), 3.98 (d, 6H), 4.75 (m, 2H), 7.40(m, 6H), 7.67(m, 4H)

#### Preparation 3.



Synthesis of diisopropyl{1-[(hydroxymethyl)cyclopropyl]oxy}methyl phosphonate

The compound prepared in Preparation 2 (8.3g) was dissolved in 100ml of methanol, 3.1g of ammonium fluoride was added thereto, and the resulting mixture was heated under reflux for 2 hours. After the reaction was completed, methanol was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography(eluent: dichloromethane/methanol=20/1, v/v) to give 3.6g(Yield 82%) of the title compound.

$^1\text{H NMR}(\text{CDCl}_3)$   $\delta$  0.60 (t, 2H), 0.87 (t, 2H), 1.28 (d, 12H), 2.5 (br s, 1H), 3.65 (s, 2H), 3.83 (d, 2H), 4.82 (m, 2H)  
ESI: 267 (M+1)<sup>+</sup>, C<sub>11</sub>H<sub>23</sub>O<sub>4</sub>P

Preparation 4

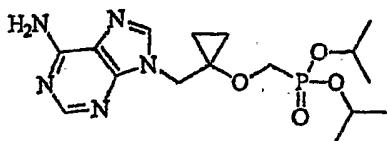
Synthesis of {1-[(diisopropoxyphosphoryl)methoxy]cyclopropyl}methyl methane- sulfonate

The compound prepared in Preparation 3 (1.5g) was dissolved in 50ml of dichloromethane, 0.85ml of triethylamine and 0.84g of methanesulfonylchloride were added thereto, and the resulting mixture was stirred for 30 minutes at room temperature. Saturated ammonium chloride was added to stop the reaction. The product was extracted with dichloromethane and the dichloromethane extract was concentrated by distillation under reduced pressure. The residue was purified by silica gel column chromatography(eluent: ethyl acetate/n-hexane=1/1, v/v) to give 1.63g(Yield 81%) of the title compound.

$^1\text{H NMR}(\text{CDCl}_3)$   $\delta$  0.77 (m, 2H), 1.09 (m, 2H), 1.32 (m, 12H), 3.10 (s, 3H), 3.82 (m, 2H), 4.33 (s, 2H), 4.71 (m, 2H)

Preparation 5

Synthesis of diisopropyl{1-[(6-amino-9H-purin-9-yl)methyl]cyclopropyl}oxy) methylphosphonate

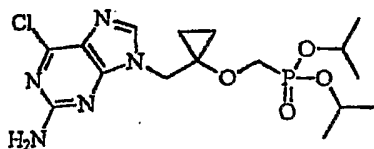


The compound prepared in Preparation 4 (430mg) was dissolved in 18ml of dimethylformamide, 57.6mg (60% purity) of sodium hydride and 162mg of adenine were added thereto, and the resulting mixture was heated under reflux over 4 hours. Saturated ammonium chloride was added to stop the reaction. The product was extracted with ethyl acetate, and the ethyl acetate extract was distilled under reduced pressure. The residue was purified by silica gel column chromatography (eluent: dichloromethane/methanol=20/1, v/v) to give 201mg (Yield 44%) of the title compound.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.86 (t, 2H), 1.01 (t, 2H), 1.24 (d, 6H), 1.34 (d, 6H), 3.86 (d, 2H), 4.34 (s, 2H), 4.71 (m, 2H), 5.97 (br s, 2H), 8.32 (s, 1H), 8.58 (s, 1H)  
ESI: 384 (M+1)<sup>+</sup>, C<sub>16</sub>H<sub>25</sub>N<sub>5</sub>O<sub>4</sub>P

#### Preparation 6

Synthesis of diisopropyl({1-[(2-amino-6-chloro-9H-purin-9-yl)methyl]cyclopropyl} oxy)methylphosphonate



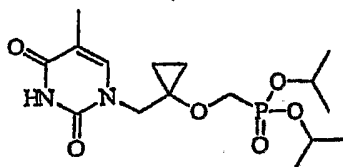
The compound prepared in Preparation 4 (1.64g) was dissolved in 70ml of dimethylformamide, 219mg (60% purity) of sodium hydride and 773mg of 2-amino-6-chloro-9H-purine were added thereto, and the resulting mixture was stirred for 4 hours while heating at a temperature of up to 80 °C. Saturated ammonium chloride was added to stop the reaction. The product was extracted with ethyl acetate, and the ethyl acetate extract was distilled under reduced pressure. The residue was purified by silica gel column chromatography (eluent: dichloromethane/methanol=20/1, v/v) to give 765mg (Yield 40%) of the title compound.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.80 (t, 2H), 1.02 (t, 2H), 1.27 (d, 6H), 1.28 (d, 6H), 3.82 (d, 2H), 4.21 (s, 2H), 4.68 (m, 2H), 5.13 (br s, 2H), 8.15 (s, 1H)

ESI: 418 (M+1)<sup>+</sup>, C<sub>16</sub>H<sub>25</sub>CIN<sub>5</sub>O<sub>4</sub>P

### Preparation 7

Synthesis of diisopropyl[(1{[5-methyl-2,4-dioxo-3,4-dihydro-1(2H)-pyrimidinyl]methyl} cyclopropyl)oxy]methylphosphonate



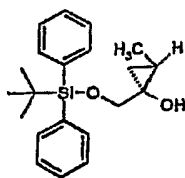
The compound prepared in Preparation 4 (118mg) and thymine were reacted according to the same procedure as Preparation 6 to give 26mg(Yield 21%) of the title compound.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.82 (t, 2H), 0.95 (t, 2H), 1.31 (m, 12H), 1.92 (s, 3H), 3.74 (d, 2H), 3.89 (s, 2H), 4.71 (m, 2H), 7.62 (s, 1H), 9.15 (s, 1H)

ESI: 375 (M+1)<sup>+</sup>, C<sub>16</sub>H<sub>27</sub>N<sub>2</sub>O<sub>6</sub>P

### Preparation 8

Synthesis of 1-([t-butyl(diphenyl)silyl]oxy)methyl)-2-methylcyclopropanol



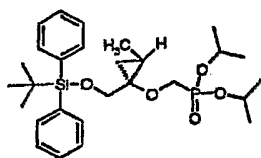
According to the description in a reference (see: *Syn. Lett.* 07, 1053-1054, 1999), the title compound was prepared as follows. 50g(146 mmole) of ethyl 2-([t-butyl(diphenyl)silyl]oxy)acetate was dissolved in 700ml of tetrahydrofuran(THF) and 30.0ml of titaniumtetrakisopropoxide was added thereto. To the mixture was slowly added 290ml of propylmagnesiumchloride(2.0M in THF) at -10°C, and the reaction solution was stirred for 12 hours at room temperature. 200ml of saturated ammonium chloride was added to stop the reaction. The tetrahydrofuran (THF) used as a solvent was removed by distillation under reduced pressure, and the reaction mixture was extracted

twice with 2000ml of n-hexane. The n-hexane extract was distilled under reduced pressure and purified by silica gel column to give 42g of the title compound.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.06 (t, 1H), 0.88 (dd, 2H), 0.97 (d, 3H), 1.09 (s, 9H) 1.1 (m, 1H), 2.78 (s, 1H), 3.70 (d, 1H), 3.86 (d, 1H), 7.41 (m, 6H), 7.70 (m, 4H)  
ESI: 363 (M+Na)<sup>+</sup>, C<sub>21</sub>H<sub>28</sub>O<sub>2</sub>Si

#### Preparation 9

Synthesis of diisopropyl {[1-([t-butyl(diphenyl)silyl]oxy)methyl]-2-methylcyclopropyl]oxy}methylphosphonate

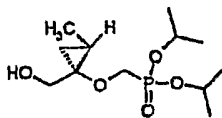


The compound prepared in Preparation 8 (4.2g) was reacted according to the same procedure as Preparation 2 to give 3.3g of the title compound.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.04 (t, 1H), 0.96 (dd, 1H), 0.97 (d, 3H), 1.05 (m, 1H), 1.06 (s, 9H), 1.23 (t, 12H), 3.72 (d, 1H), 3.95 (d, 2H), 3.98 (d, 1H), 4.75 (m, 2H), 7.40 (m, 6H), 7.68 (m, 4H)

#### Preparation 10

Synthesis of diisopropyl{1-[(hydroxymethyl)-2-methylcyclopropyl]oxy}methylphosphonate



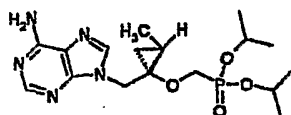
The compound prepared in Preparation 9 (3.3g) was reacted according to the same procedure as Preparation 3 to give 1.7g of the title compound.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.03 (t, 1H), 0.95 (dd, 1H), 0.96 (m, 1H), 1.11 (d, 3H), 1.35 (d, 12H), 2.17 (br s, 1H), 3.80 (d, 2H), 3.96 (d, 1H), 4.80 (m, 2H)

ESI: 303 (M+Na)<sup>+</sup>, C<sub>12</sub>H<sub>22</sub>SO<sub>4</sub>

### Preparation 11

Synthesis of diisopropyl({1-[(6-amino-9H-purin-9-yl)methyl]-2-methylcyclopropyl}oxy)methylphosphonate



The compound prepared in Preparation 10 (1.5g) was dissolved in 50ml of dichloromethane, 0.85ml of triethylamine and 0.84g of methanesulfonylchloride were added thereto, and the resulting mixture was stirred for 30 minutes at room temperature. Saturated ammonium chloride was added to stop the reaction. The product was extracted with dichloromethane and the dichloromethane extract was concentrated by distillation under reduced pressure. The residue was used in the next reaction without any purification.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.42 (m, 1H), 1.12 (d, 3H), 1.25 (m, 1H), 1.32 (m, 12H), 1.33 (m, 1H), 3.10 (s, 3H), 3.76 (m, 2H), 4.31 (d, 1H), 4.71 (d, 1H), 4.76 (m, 2H)

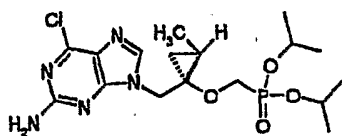
The methanesulfonate thus obtained (430mg) was dissolved in 18ml of dimethylformamide, and 57.6mg (60% purity) of sodium hydride and 162mg of adenine were added thereto. The reaction mixture was refluxed under heating over 4 hours. Saturated ammonium chloride was added to stop the reaction. The product was extracted with ethyl acetate and the ethyl acetate extract was concentrated by distillation under reduced pressure. The residue was purified by silica gel column chromatography (eluent: dichloromethane/methanol=20/1, v/v) to give 201mg(Yield 44%) of the title compound.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.53 (t, 1H), 1.13 (d, 3H), 1.15 (m, 1H), 1.30 (m, 12H), 1.41 (m, 1H), 1.85 (brs, 2H), 3.81 (m, 2H), 4.43 (m, 2H), 4.70 (m, 2H), 5.65 (br s, 2H), 8.26 (s, 1H), 8.34 (s, 1H)

ESI: 398 (M+1)<sup>+</sup>, C<sub>17</sub>H<sub>28</sub>N<sub>5</sub>O<sub>4</sub>P

### Preparation 12

Synthesis of diisopropyl({1-[(2-amino-6-chloro-9H-purin-9-yl)methyl]-2-methylcyclopropyl}oxy)methylphosphonate

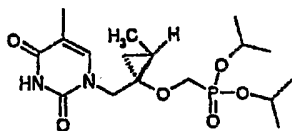


The compound prepared in Preparation 10 was reacted according to the same  
 5 procedure as Preparation 11 except that 6-chloroguanine (2-amino-6-chloro-9H-purine)  
 was used instead of adenine to give the title compound.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.47 (t, J=6.4Hz, 1H), 1.12 (m, 4H), 1.24 (dd, J= 2.8Hz,  
 6.4Hz, 6H), 1.28 (t, J=6.0Hz, 6H), 1.38 (m, 1H), 3.80 (m, 2H), 4.28 (m, 2H), 4.68 (m, 2H),  
 10 5.13 (brs, 2H), 8.15 (s, 1H)  
 ESI: 432 (M+1)<sup>+</sup>, C<sub>17</sub>H<sub>27</sub>ClN<sub>5</sub>O<sub>4</sub>P

### Preparation 13

Synthesis of diisopropyl[(1{[5-methyl-2,4-dioxo-3,4-dihydro-1(2H)-  
 15 pyrimidinyl]methyl}-2-methylcyclopropyl)oxy]methylphosphonate

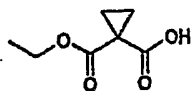


The compound prepared in Preparation 10 was reacted according to the same  
 procedure as Preparation 11 except that thymine was used instead of adenine to give the  
 20 title compound.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.48 (t, 1H), 1.10 (m, 4H), 1.24 (dd, 6H), 1.28 (t, J= 6H),  
 1.38 (m, 1H), 1.92 (s, 3H), 3.80 (m, 2H), 4.28 (m, 2H), 4.68 (m, 2H), 7.62 (s, 1H), 9.15 (s,  
 1H)  
 25 ESI: 389 (M+1)<sup>+</sup>, C<sub>17</sub>H<sub>29</sub>N<sub>2</sub>O<sub>6</sub>P

### Preparation 14

Synthesis of 1-(ethoxycarbonyl)cyclopropanecarboxylic acid



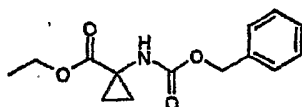
Diethyl 1,1-cyclopropane dicarboxylate (20g) was hydrolyzed in 1N NaOH (107 ml) and ethanol (220ml) for 16 hours, and the ethanol was removed by distillation under reduced pressure. The remaining starting material was removed by using ethyl acetate and the aqueous layer was acidified by 1N HCl. The reaction mixture was extracted with ethyl acetate and distilled under reduced pressure. The residue was purified by silica gel column to give the title compound in a yield of 94%.

$^1\text{H NMR}(\text{CDCl}_3)$   $\delta$  1.06 (t, 3H), 1.53 (m, 2H), 1.62 (m, 2H), 4.21 (q, 2H)

ESI: 159 (M+1) $^+$  C<sub>7</sub>H<sub>10</sub>O<sub>4</sub>

#### Preparation 15

Synthesis of ethyl 1-[[[(benzyloxy)carbonyl]amino]cyclopropanecarboxylate



The carboxylic acid prepared in Preparation 14 (16g) was dissolved in dichloromethane, 10.8ml of oxalyl chloride was added dropwise, and 2 drops of dimethylformamide was added. The reaction mixture was stirred at room temperature for 3 hours and distilled under reduced pressure to give ethoxycarbonyl 1,1-cyclopropane carbonylchloride. This compound, not purified, was dissolved in 30ml of dimethylformamide and the resulting solution was cooled with water-ice. 36g of NaN<sub>3</sub> was added and the reaction was carried out at room temperature for 3 hours. The reaction solution was extracted with 100ml of water and 200ml of diethylether, and the diethylether extract was concentrated to give crude compound which was purified by silica gel column to give an azide compound.

$^1\text{H NMR}(\text{CDCl}_3)$   $\delta$  1.28 (t, 3H), 1.54 (m, 4H), 4.19 (q, 2H)

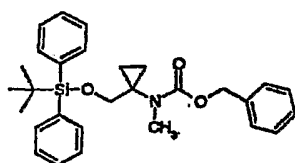
To the azide compound thus obtained (13g) was added dropwise 11ml of benzyl alcohol and the reaction mixture was heated to 100°C, by which the reactants were vigorously reacted with each other with the generation of gas. The reaction mixture was

heated at 100°C for further 1 hour, cooled to room temperature, and distilled under reduced pressure to remove benzyl alcohol. The residue was purified by silica gel column to give the title compound.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 1.19 (m, 5H), 1.54 (m, 2H), 4.11 (m, 2H), 5.15 (br.s, 2H), 7.32 (m, 5H)

#### Preparation 16

Synthesis of benzyl 1-[[t-butyl(diphenylsilyl)oxy]methylcyclopropyl] (methyl)carbamate



The carboxylate prepared in Preparation 15 (13.2g) was dissolved in diethylether, to which 1.3g of LiBH<sub>4</sub> dissolved in diethylether was slowly added dropwise. The reaction mixture was stirred at room temperature for 16 hours, and 50ml of methanol and 5 ml of 1N HCl were added dropwise thereto. The reaction mixture was stirred for 2 hours, the precipitate was removed by suction filtration, and the solvent in the filtrate was removed by distillation under reduced pressure. The residue was purified by silica gel column to give benzyl 1-(hydroxymethyl)cyclopropylcarbamate.

This compound (9.3g) was dissolved in dichloromethane, and 4.2g of imidazole and 13.5ml of t-butyl(diphenyl)silylchloride were added in order. The reaction mixture was stirred at room temperature for 4 hours and the solvent was removed by distillation under reduced pressure. The residue was purified by silica gel column to give benzyl 1-([t-butyl(diphenyl)silyl]oxy)methyl)cyclopropylcarbamate.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.71-1.19 (m, 4H), 1.04 (s, 9H), 3.68 (br.s, 2H), 5.04 (s, 2H), 7.25-7.45 (m, 11H), 7.62 (d, 4H)

The carbamate thus obtained (5.5g) was dissolved in THF, 3.5ml of methane iodide (MeI) was added dropwise and then 1g of NaH was added. The reaction mixture was stirred at room temperature for 4 hours and then extracted with 100ml of diethylether

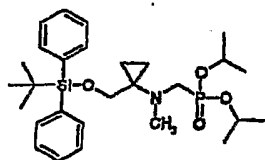


and 100ml of water. The diethylether extract was concentrated by distillation under reduced pressure and the residue was purified by silica gel column to give the title compound.

5  $^1\text{H NMR}(\text{CDCl}_3)$   $\delta$  0.78-0.84 (m, 4H), 1.03 (s, 9H), 3.03 (s, 3H), 3.55- 3.80 (m, 2H), 5.10 (s, 2H), 7.24-7.45 (m, 11H), 7.61 (m, 4H)

#### Preparation 17

10 Synthesis of diisopropyl[1-([t-butyl(diphenyl)silyl]oxy)methyl)cyclopropyl] (methyl)amino]methylphosphonate



15 The carbamate prepared in Preparation 16 (1.0g) was dissolved in ethanol, 100mg of 10% Pd/C was added, and the reaction mixture was subjected to a hydrogenation under hydrogen atmosphere. After the reaction was completed, the solvent was removed by distillation under reduced pressure. The residue was purified by silica gel column to give 1-([t-butyl(diphenyl)silyl]oxy)methyl)-N-methylcyclopropaneamine.

20  $^1\text{H NMR}(\text{CDCl}_3)$   $\delta$  0.36 (m, 2H), 0.65 (m, 2H), 1.05 (s, 9H), 2.36 (s, 3H), 3.57 (s, 2H), 7.37-7.45 (m, 11H), 7.66 (d, 4H)

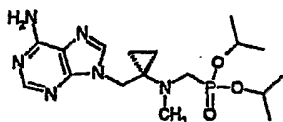
25 The methylcyclopropaneamine thus obtained (1.0g) was dissolved in dichloromethane, to which 1.03ml of diisopropylethylamine and 1.3ml of (diisopropyl phosphoryl)methyl trifluoromethansulfonate were added dropwise. The reaction mixture was reacted under stirring at room temperature for 4 hours, and then extracted with 100ml of diethylether and 100ml of water. The solvent in the diethylether extract was removed by distillation under reduced pressure and the residue was purified by silica gel column to give the title compound.

30  $^1\text{H NMR}(\text{CDCl}_3)$   $\delta$  0.42 (m, 2H), 0.69 (m, 2H), 1.04 (s, 9H), 1.25 (d, 6H), 1.30 (d, 6H), 2.62 (s, 3H), 3.25 (d, 2H), 3.64 (s, 2H), 4.68 (m, 2H), 7.39 (m, 6H), 7.65 (d, 4H)

**Preparation 18**

Synthesis of diisopropyl(1-{[(6-amino-9H-purin-9-yl)methyl]cyclopropyl}  
(methyl)amino)methylphosphonate

5



The compound prepared in Preparation 17 (0.32g) was dissolved in methanol and 1.5g of ammonium fluoride was added dropwise. The reaction mixture was reacted under stirring at 60°C for 24 hours and then the solvent was removed by distillation under  
10 reduced pressure. The residue was purified by silica gel column to give methylaminediisopropylmethylphosphone 1,1-cyclopropane ethyl alcohol.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.56 (m, 2H), 0.73 (m, 2H), 1.31 (m, 12H), 2.56 (s, 3H),  
3.11 (d, 2H), 3.55 (s, 2H), 4.70 (m, 2H)

15

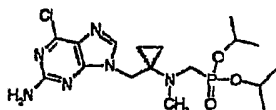
The compound thus obtained was consecutively reacted according to the same procedure as Preparations 4 and 5 to give the title compound.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.78 (m, 2H), 0.86 (m, 2H), 1.25 (m, 12H), 2.35 (s, 3H),  
20 4.10 (s, 2H), 4.68 (m, 2H), 5.13 (m, 2H), 8.32 (s, 1H), 8.58 (s, 1H)

ESI: 397 (M+1)<sup>+</sup>, C<sub>17</sub>H<sub>29</sub>N<sub>6</sub>O<sub>3</sub>P

**Preparation 19**

Synthesis of diisopropyl(1-{[(2-amino-6-chloro-9H-purin-9-yl)methyl]  
25 cyclopropyl}(methyl)amino)methylphosphonate



The compound prepared in Preparation 17 (0.32g) was dissolved in methanol and 1.5g of ammonium fluoride was added dropwise. The reaction mixture was reacted under  
30 stirring at 60°C for 24 hours and then the solvent was removed by distillation under

reduced pressure. The residue was purified by silica gel column to give methylaminediisopropylmethylphosphone 1,1-cyclopropane ethyl alcohol.

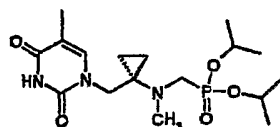
<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.56 (m, 2H), 0.73 (m, 2H), 1.31 (m, 12H), 2.56 (s, 3H),  
5 3.11 (d, 2H), 3.55 (s, 2H), 4.70 (m, 2H)

The compound thus obtained was consecutively reacted according to the same procedure as Preparations 4 and 6 to give the title compound.

10 <sup>1</sup>H NMR(400MHz, CD<sub>3</sub>OD): δ 0.79 (m, 2H), 0.89 (m, 2H), 1.26 (m, 12H), 2.38 (s, 3H), 2.76 (d, 2H, J=7Hz), 4.11 (s, 2H), 4.65 (m, 2H), 5.13 (m, 2H), 8.02 (s, 1H)  
ESI: 431(M+1)<sup>+</sup>, C<sub>17</sub>H<sub>28</sub>CIN<sub>6</sub>O<sub>3</sub>P

#### Preparation 20

15 **Synthesis of diisopropyl[(1-[[5-methyl-2,4-dioxo-3,4-dihydro-1(2H)-pyrimidinyl]methyl]cyclopropyl)(methyl)amino]methylphosphonate**



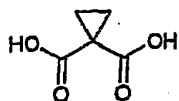
20 The compound prepared in Preparation 17 (0.32g) was dissolved in methanol and 1.5g of ammonium fluoride was added dropwise. The reaction mixture was reacted under stirring at 60 °C for 24 hours and then the solvent was removed by distillation under reduced pressure. The residue was purified by silica gel column to give methylaminediisopropylmethylphosphone 1,1-cyclopropane ethyl alcohol.

25 <sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.56 (m, 2H), 0.73 (m, 2H), 1.31 (m, 12H), 2.56 (s, 3H), 3.11 (d, 2H), 3.55 (s, 2H), 4.70 (m, 2H)

The compound thus obtained was consecutively reacted according to the same procedure as Preparations 4 and 7 to give the title compound.

30

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.79 (m, 2H), 0.90 (m, 2H), 1.31 (m, 12H), 1.92 (s, 3H), 2.38 (s, 3H), 3.75 (d, 2H), 4.10 (s, 2H), 4.65 (m, 2H), 7.62 (s, 1H), 9.15 (s, 1H)

**Preparation 21****Synthesis of 1,1-cyclopropanedicarboxylic acid**

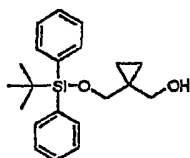
5

In 50% NaOH 187ml was dissolved 15g of diethylmalonate at room temperature. Benzyltriethylammoniumchloride (21.3g) was added and the resulting mixture was stirred for 10 minutes. 1,2-Dibromoethane (12.3g) was added to the reaction solution and the resulting mixture was stirred for more than 18 hours at room temperature. The reaction mixture was neutralized by adding dropwise conc. sulfuric acid and then extracted with ethyl acetate. The extract was distilled under reduced pressure to give 6.2g of the title compound as a white solid.

10

$^1\text{H NMR}(\text{CDCl}_3) \delta$  1.88 (s, 4H)

15

**Preparation 22****Synthesis of [1-({[t-butyl(diphenyl)silyl]oxy}methyl)cyclopropyl]methanol**

20

Lithium aluminum hydride (LAH) 15.3g was dissolved in 39g of tetrahydrofuran, and 11.7g of the carboxylic acid prepared in Preparation 21 was slowly added dropwise at 0°C. The reaction solution was refluxed for 17 hours. The reaction was stopped by adding 10% HCl at room temperature and the mixture was extracted with ethyl acetate. The extract was distilled under reduced pressure and the residue was purified by silica gel column to give 8.2g of diol compound.

25

$^1\text{H NMR}(\text{CDCl}_3) \delta$  0.56 (s, 4H), 2.22 (s, 2H), 3.63 (s, 4H)

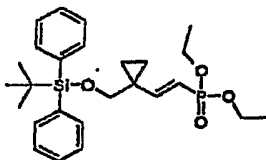
The compound thus obtained (400mg) was dissolved in 12ml of THF, 184mg of

NaH and 1.16g of t-butyl(diphenyl)silylchloride (TBDPSCI) were added, and the resulting mixture was refluxed for 6 hours. The reaction was stopped by adding 10ml of water and the mixture was extracted with ethyl acetate. The extract was distilled under reduced pressure and the residue was purified by silica gel column to give 1.1g of the title compound.

$^1\text{H NMR}(\text{CDCl}_3)$   $\delta$  0.33 (t, 2H), 0.48 (t, 2H), 1.23 (s, 9H), 3.59 (d, 4H), 7.42 (m, 6H), 7.68 (m, 4H)

### Preparation 23

Synthesis of diethyl(E)-2-[1-({t-butyl(diphenyl)silyl}oxy)methyl]cyclopropyl]ethenylphosphonate



The compound prepared in Preparation 22 (2g) was dissolved in 50ml of dichloromethane, and 1.03g of N-methylmorpholine N-oxide and 103mg of tetrapropylammoniumperuthenate (TPAP) were added thereto at room temperature. The reaction mixture was stirred for about 1 hour at room temperature and the reaction was stopped by adding 20ml of water. The reaction solution was extracted with dichloromethane and the extract was concentrated under reduced pressure to give 2.0g of aldehyde compound.

$^1\text{H NMR}(\text{CDCl}_3)$   $\delta$  1.03 (s, 9H), 1.04 (t, 2H), 1.05 (t, 2H), 3.94 (s, 2H), 7.37 (m, 6H), 7.64 (m, 4H), 9.10 (s, 1H)

Tetraethylmethylene diphosphonate (1.7g) was dissolved in 60ml of tetrahydrofuran (THF). At  $-78^\circ\text{C}$ , 264mg of NaH was added, the resulting mixture was stirred for 20 minutes, and then 1.9g of the aldehyde compound as obtained above was added. The reaction solution was stirred at room temperature for 1 hour, and the reaction was stopped by adding 20ml of water. The reaction solution was extracted with ethyl acetate and the extract was concentrated under reduced pressure. The residue was purified

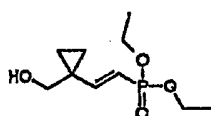
by silica gel column to give 2.32g of the title compound.

$^1\text{H NMR}(\text{CDCl}_3)$   $\delta$  0.76 (t, 2H), 0.81 (t, 2H), 1.04 (s, 9H), 1.31 (t, 6H), 3.71 (s, 2H), 4.05 (m, 4H), 5.70 (m, 1H), 6.42 (m, 1H), 7.43 (m, 6H), 7.64 (d, 4H)

ESI: 501 (M+1) $^+$  C<sub>28</sub>H<sub>41</sub>O<sub>4</sub>PSi

#### Preparation 24

Synthesis of diethyl 2-[1-(hydroxymethyl)cyclopropyl]ethenylphosphonate



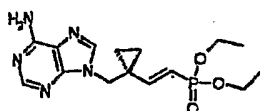
The compound prepared in Preparation 23 was reacted according to the same procedure as Preparation 3 to give the title compound.

$^1\text{H NMR}(\text{CDCl}_3)$   $\delta$  0.76 (t, 2H), 0.81 (t, 2H), 1.04 (s, 9H), 1.31 (t, 6H), 3.71 (s, 2H), 4.05 (m, 4H), 5.70 (m, 1H), 6.42 (m, 1H), 7.43 (m, 6H), 7.64 (d, 4H)

ESI: 501 (M+1) $^+$  C<sub>28</sub>H<sub>41</sub>O<sub>4</sub>PSi

#### Preparation 25

Synthesis of diethyl 2-{1-[(6-amino-9H-purin-9-yl)methyl]cyclopropyl}ethenylphosphonate



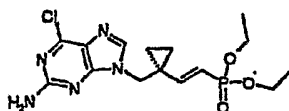
The compound prepared in Preparation 24 was reacted according to the same procedure as Preparations 4 and 5 to give the title compound.

$^1\text{H NMR}(\text{CDCl}_3)$   $\delta$  1.07 (t, 2H), 1.19 (t, 2H), 1.22 (t, 6H), 3.93 (s, 4H), 4.33 (s, 2H), 5.55 (s, 2H), 5.63 (m, 1H), 6.49 (m, 1H), 7.88 (s, 1H), 8.37 (s, 1H)

ESI: 352 (M+1) $^+$  C<sub>15</sub>H<sub>22</sub>N<sub>5</sub>O<sub>3</sub>P

#### Preparation 26

**Synthesis of diethyl 2-{1-[(2-amino-6-chloro-9H-purin-9-yl)methyl]cyclopropyl}ethenylphosphonate**



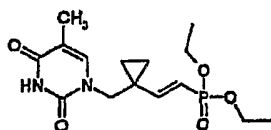
5 The compound prepared in Preparation 24 was reacted according to the same procedure as Preparations 4 and 6 to give the title compound.

$^1\text{H NMR}(\text{CDCl}_3)$   $\delta$  1.06 (t, 2H), 1.15 (t, 2H), 1.23 (t, 6H), 3.93 (s, 4H), 4.18 (s, 2H), 5.12 (s, 2H), 5.59 (m, 1H), 6.58 (m, 1H), 7.81 (s, 1H)

10 ESI:386 (M+1) $^+$  C<sub>15</sub>H<sub>21</sub>ClN<sub>5</sub>O<sub>3</sub>P

**Preparation 27**

**Synthesis of diethyl 2-(1-[[5-methyl-2,4-dioxo-3,4-dihydro-1(2H)-pyrimidinyl]methyl]cyclopropyl)ethenylphosphonate**



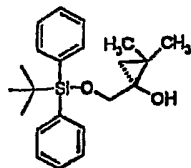
The compound prepared in Preparation 24 was reacted according to the same procedure as Preparations 4 and 7 to give the title compound.

20  $^1\text{H NMR}(\text{CDCl}_3)$   $\delta$  0.93 (t, 2H), 1.01 (t, 2H), 1.24 (t, 6H), 1.92 (s, 3H), 3.91 (s, 2H), 3.96 (m, 4H), 5.49 (m, 1H), 5.87 (m, 1H), 7.62 (s, 1H), 9.15 (s, 1H)

ESI:343 (M+1) $^+$  C<sub>15</sub>H<sub>23</sub>N<sub>2</sub>O<sub>5</sub>P

**Preparation 28**

25 **Synthesis of 1-([t-butyl(diphenyl)silyl]oxy)methyl)-2,2-dimethylcyclopropanol**



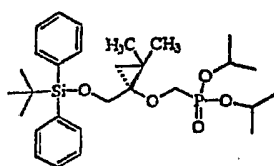
According to the description in a reference (see: *Syn. Lett.* 07, 1053-1054, 1999), the title compound was prepared as follows. 10g(29 mmole) of ethyl 2-[[t-butyl(diphenyl)silyl]oxy]acetate was dissolved in 100ml of tetrahydrofuran (THF) and 6.0 ml of titaniumtetraisopropoxide was added thereto. To the mixture was slowly added 37 ml of isobutylmagnesiumbromide(2.0M in THF) at -10°C, and the reaction solution was stirred for 12 hours at room temperature. 50ml of saturated ammonium chloride was added to stop the reaction. The tetrahydrofuran (THF) used as a solvent was removed by distillation under reduced pressure, and the reaction mixture was extracted twice with 500 ml of n-hexane. The n-hexane extract was distilled under reduced pressure and purified by silica gel column to give 5.0g of the title compound.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.25 (d, 1H), 0.51 (d, 2H), 0.99 (s, 3H), 1.07 (s, 9H), 1.22 (s, 3H), 3.71 (d, 1H), 3.91 (d, 1H), 7.41 (m, 6H), 7.70 (m, 4H)

ESI: 355 (M+1)<sup>+</sup>, C<sub>22</sub>H<sub>30</sub>O<sub>2</sub>Si

#### Preparation 29

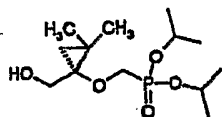
Synthesis of diisopropyl {[1-([t-butyl(diphenyl)silyl]oxy)methyl]-2,2-dimethylcyclopropyl]oxy}methylphosphonate



<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.29 (d, 1H), 0.60 (d, 1H), 1.06 (s, 3H), 1.09 (s, 9H), 1.27 (s, 3H), 1.30 (m, 12H), 3.75 (m, 2H), 3.92 (m, 2H), 4.72 (m, 2H), 7.41 (m, 6H), 7.67 (m, 4H)

ESI: 519 (M+1)<sup>+</sup>, C<sub>28</sub>H<sub>43</sub>O<sub>5</sub>PSi



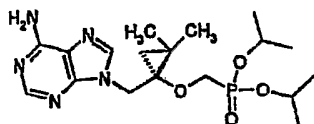
**Preparation 30****Synthesis of diisopropyl{1-[(hydroxymethyl)-2,2-dimethylcyclopropyl]oxy}methylphosphonate**

5

The compound prepared in Preparation 29 was reacted according to the same procedure as Preparation 3 to give the title compound.

$^1\text{H NMR}(\text{CDCl}_3)$   $\delta$  0.39 (d, 1H), 0.59 (d, 1H), 1.13 (s, 3H), 1.21 (s, 3H), 1.33 (d, 12H), 3.76 (m, 2H), 3.86 (m, 2H), 4.76 (m, 2H)

ESI: 295 (M+1)<sup>+</sup>, C<sub>13</sub>H<sub>27</sub>O<sub>4</sub>P

**Preparation 31****Synthesis of diisopropyl({1-[(6-amino-9H-purin-9-yl)methyl]-2,2-dimethylcyclopropyl}oxy)methylphosphonate**

20

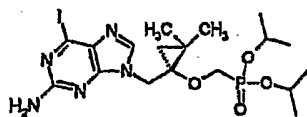
The compound prepared in Preparation 30 was reacted according to the same procedure as Preparation 11 to give the title compound.

$^1\text{H NMR}(500\text{MHz}, \text{CDCl}_3)$ :  $\delta$  0.62 (d, J=5.9Hz, 1H), 0.81 (d, J=5.9Hz, 1H), 1.10 (s, 3H), 1.23 (m, 15H), 3.72 (dd, J=15.1, 11.0Hz, 1H), 3.85 (dd, J=15.1, 5.5Hz, 1H), 4.28 (d, J=15.1Hz, 1H), 4.58 (d, J=15.1Hz, 1H), 4.68 (m, 2H), 5.79 (bs, 2H), 8.19 (s, 1H), 8.32 (s, 1H)

ESI: 412 (M+1)<sup>+</sup>, C<sub>18</sub>H<sub>30</sub>N<sub>5</sub>O<sub>4</sub>P

**Preparation 32****Synthesis of diisopropyl({1-[(2-amino-6-iodo-9H-purin-9-yl)methyl]-2,2-dimethylcyclopropyl}oxy)methylphosphonate**

30

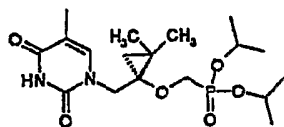


The compound prepared in Preparation 30 was reacted according to the same procedure as Preparation 12 except that 6-iodoguanine was used instead of 6-chloroguanine to give the title compound.

<sup>1</sup>H NMR(500MHz, CDCl<sub>3</sub>): δ 0.58 (d, J=6.4Hz, 1H), 0.80 (d, J=6.4Hz, 1H), 1.10 (s, 3H), 1.24 (m, 8H), 3.72 (dd, J=13.0, 11.0Hz, 1H), 3.88 (dd, J=13.0, 9.3Hz, 1H), 4.08 (d, J=15.1Hz, 1H), 4.47 (d, J=15.1Hz, 1H), 4.67 (m, 2H), 5.05 (bs, 1H), 8.10 (s, 1H)  
ESI: 538 (M+1)<sup>+</sup>, C<sub>18</sub>H<sub>29</sub>N<sub>5</sub>O<sub>4</sub>P

### Preparation 33

Synthesis of diisopropyl[(1{[5-methyl-2,4-dioxo-3,4-dihydro-1(2H)-pyrimidinyl]methyl}-2,2-dimethylcyclopropyl)oxy]methylphosphonate

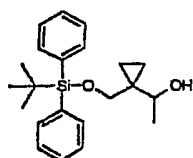


The compound prepared in Preparation 30 was reacted according to the same procedure as Preparation 13 to give the title compound.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.58 (d, 1H), 0.80 (d, 1H), 1.10 (s, 3H), 1.24 (dd, 6H), 1.28 (t, 6H), 1.58 (s, 3H), 1.92 (s, 3H), 3.72 (dd, 1H), 3.88 (dd, 1H), 4.08 (d, 1H), 4.47 (d, 1H), 4.67 (m, 2H), 7.62 (s, 1H), 9.15 (s, 1H)  
ESI: 403 (M+1)<sup>+</sup>, C<sub>18</sub>H<sub>31</sub>N<sub>2</sub>O<sub>6</sub>P

### Preparation 34

Synthesis of 1-[1-([t-butyl(diphenyl)silyl]oxy)methyl]cyclopropyl]-1-methyl alcohol



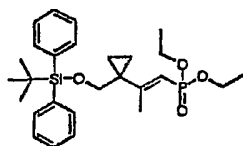
6g of the compound prepared in Preparation 22 was dissolved in 150ml of dichloromethane. 3.0g of N-oxide and 103mg of tetrapropylammoniumperruthenate (TPAP) were added thereto at room temperature. The reaction mixture was stirred for about 1 hour at room temperature and quenched by adding 20ml of water. The reaction mixture was extracted with dichloromethane and the extract was concentrated under reduced pressure to give 6.0g of aldehyde compound which went to next reaction without further purification.

5.23g of the aldehyde was dissolved in 350ml of THF. The solution was cooled to -78 °C and 10.3ml of methylmagnesiumbromide (3.0M solution) was slowly added to the solution and then, stirred for 1 hour at room temperature. The reaction mixture was quenched by 0.5ml of water and 0.5ml of methanol and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate/n-hexane=1/8, v/v) to 3.57g of title compound.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.22 (m, 1H), 0.39 (m, 2H), 0.61 (m, 1H), 1.06 (s, 9H), 1.24 (d, 3H), 3.3 (d, 1H), 3.47 (s, 2H), 3.9 (d, 1H), 7.43 (m, 6H), 7.64 (m, 6H)

#### Preparation 35

Synthesis of diethyl (E)-2-1-[1-({t-butyl(diphenyl)silyl}oxy)methyl]cyclopropyl]-1-propenylphosphonate



4g of the compound prepared in preparation 34 was dissolved in 10ml of dichloromethane. 2.1g of n-morpholine N-oxide and 209mg of tetrapropylammoniumperruthenate (TPAP) were added thereto at room temperature. The reaction mixture was stirred for about 1 hour at room temperature and quenched by adding 20ml of water. The reaction mixture was extracted with dichloromethane and the extract was concentrated under reduced pressure to give 4.0g of compound which went to next reaction without further purification.

Tetraethylmethylenediphosphonate (2.7g) was dissolved in 30ml of tetrahydrofuran (THF) at -78° and 4ml of n-butyllithium was added. The resulting mixture was stirred for 20 minutes, and then 1.0 g of the ketone compound as obtained above was added. The reaction mixture was stirred at room temperature for 1 hour and was stopped by adding 20ml of water. The reaction mixture was extracted with ethyl acetate and concentrated under reduced pressure. The residue was purified by silica gel column to give 654mg of the title compound.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.58 (m, 1H), 0.69 (m, 2H), 1.02 (s, 9H), 1.20 (t, 6H), 2.09 (d, 3H), 3.59 (s, 2H), 4.05 (m, 4H), 5.61 (d, 1H), 7.38 (m, 6H), 7.63 (d, 4H)

#### Example 1

Synthesis of ({1-[(6-amino-9H-purin-9-yl)methyl]cyclopropyl}oxy)methylphosphonic acid (Compound 1)

The compound prepared in Preparation 5 (159mg) was dissolved in 15ml of dichloromethane, 1.27g of trimethylsilylbromide was added thereto, and the resulting mixture was heated under reflux for 18 hours. After the completion of reaction, the reaction mixture was extracted with water, and the water extract was distilled under reduced pressure. The residue was purified by high performance liquid chromatography (HPLC) to give 0.89g (Yield 90%) of the title compound as a white powder.

<sup>1</sup>H NMR(MeOH-d<sub>4</sub>) δ 1.02 (d, 4H), 3.95 (d, 2H), 4.55 (s, 2H), 8.40 (s, 1H), 8.55 (s, 1H)

ESI: 300 (M+1)<sup>+</sup>, C<sub>10</sub>H<sub>14</sub>N<sub>5</sub>O<sub>4</sub>P

#### Example 2

Synthesis of 3-[(1-[(6-amino-9H-purin-9-yl)methyl]cyclopropyl)oxy)methyl]-8,8-dimethyl-3,7-dioxo-2,4,6-trioxo-3λ<sup>5</sup>-phosphanon-1-yl pivalate (Compound 2)

The title compound was prepared according to the method known in a reference(see: J. Med. Chem., 37(12), 1857 (1994)) and USP 5,663,159 (1998).

The compound prepared in Example 1 (1.00g) was dissolved in 150ml of dry dimethylformamide, and 2.08g(7.32 mmol) of N,N'-dicyclohexyl-4-morpholine-

carboxamidine and 2.75g(18.3 mmol) of chloromethyl pivalate were added thereto. When the reaction mixture became homogeneous after about 1 hour, it was stirred for 5 days at room temperature. The reaction solution was filtered, the filtrate was concentrated under reduced pressure, and the residue was fractionated with 50ml of water and 50ml of toluene to separate the organic layer. The aqueous layer was extracted twice with 50ml of toluene. The combined organic layers were concentrated under reduced pressure. The residue was purified by column chromatography(eluent: methanol/dichloromethane= 1/20, v/v) to give 0.59g(Yield 32%) of the title compound as a white solid.

<sup>1</sup>H NMR(500MHz, CDCl<sub>3</sub>) δ 0.91 (m, 2H), 1.12 (m, 2H), 1.20 (m, 18H), 1.90 (br s, 2H), 3.90 (d, 2H), 4.32 (s, 2H), 5.65 (m, 4H), 8.14 (s, 1H), 8.31 (s, 1H)  
ESI: 528 (M+1)<sup>+</sup>, C<sub>22</sub>H<sub>34</sub>N<sub>5</sub>O<sub>8</sub>P

### Example 3

Synthesis of ({1-[(2-amino-6-chloro-9H-purin-9-yl)methyl]cyclopropyl}oxy)methyl phosphonic acid(Compound 3)

The compound prepared in Example 1 (1.00g) was dissolved in 150ml of dry dimethylformamide, and 2.08g(7.32 mmol) of N,N'-dicyclohexyl-4-morpholine-carboxamidine and 2.75g(18.3 mmol) of chloromethyl pivalate were added thereto. When the reaction mixture became homogeneous after about 1 hour, it was stirred for 5 days at room temperature. The reaction solution was filtered, the filtrate was concentrated under reduced pressure, and the residue was fractionated with 50ml of water and 50ml of toluene to separate the organic layer. The aqueous layer was extracted twice with 50ml of toluene. The combined organic layers were concentrated under reduced pressure. The residue was purified by column chromatography (eluent: methanol/dichloromethane=1/20, v/v) to give 0.59g(Yield 32%) of the title compound as a white solid.

<sup>1</sup>H NMR(MeOH-d<sub>4</sub>) δ 1.00 (s, 2H), 1.07 (s, 2H), 3.94 (d, 2H), 4.52 (s, 2H), 9.50 (s, 1H)  
ESI: 334 (M+1)<sup>+</sup>, C<sub>10</sub>H<sub>13</sub>CIN<sub>5</sub>O<sub>4</sub>P

### Example 4

**Synthesis of ({1-[(2-amino-6-hydroxy-9H-purin-9-yl)methyl]cyclopropyl}oxy)methylphosphonic acid(Compound 5)**

The compound prepared in Example 3 (41mg) was dissolved in 5ml of 2N hydrochloric acid and heated under reflux for 6 hours. Water was removed by distillation under reduced pressure to give 37mg(Yield 95%) of the title compound as a white solid.

<sup>1</sup>H NMR(MeOH-d<sub>4</sub>) δ 0.98 (m, 2H), 1.06 (m, 2H), 3.92 (d, 2H), 4.45 (s, 2H), 9.20 (s, 1H)  
ESI: 316 (M+1)<sup>+</sup>, C<sub>10</sub>H<sub>14</sub>N<sub>5</sub>O<sub>5</sub>P

**Example 5**

**Synthesis of ({1-[(2-amino-9H-purin-9-yl)methyl]cyclopropyl}oxy)methylphosphonic acid(Compound 9)**

15

The compound prepared in Preparation 6 (150mg) was dissolved in 15ml of tetrahydrofuran, 15mg of 5% palladium/carbon was added thereto, and the compound was reduced under 1 atm of hydrogen atmosphere for 18 hours. After completion of reaction, palladium/carbon was removed by suction filtration and the filtrate was distilled under reduced pressure. The residue was purified by silica gel column chromatography (eluent: dichloromethane/methanol=20/1, v/v) to give 130mg of diisopropyl compound(ESI: 384(M+1)<sup>+</sup>, C<sub>16</sub>H<sub>26</sub>N<sub>5</sub>O<sub>4</sub>P). This compound was treated with trimethylsilylbromide according to the same procedure as Example 1 to give 91mg(Yield 90%) of the title compound.

25

<sup>1</sup>H NMR(MeOH-d<sub>4</sub>) δ 0.94 (m, 2H), 1.03 (m, 2H), 3.93 (d, 2H), 4.40 (s, 2H), 8.66 (s, 1H), 8.74 (s, 1H)  
ESI: 300 (M+1)<sup>+</sup>, C<sub>10</sub>H<sub>14</sub>N<sub>5</sub>O<sub>4</sub>P

30

**Example 6**

**Synthesis of 3-[(1-[(2-amino-9H-purin-9-yl)methyl]cyclopropyl}oxy)methyl]-8,8-dimethyl-3,7-dioxo-2,4,6-trioxa-3λ<sup>5</sup>-phosphanon-1-yl pivalate(Compound 10)**

The compound prepared in Example 5 was reacted according to the same procedure as Example 2 to give the title compound.

35

<sup>1</sup>H NMR(CDCl<sub>3</sub>-d<sub>4</sub>) δ 0.90 (m, 2H), 1.05 (m, 2H), 1.20 (m, 18H), 3.96 (d, 2H), 4.22 (s, 2H), 5.65 (m, 4H), 8.03 (s, 1H), 8.69 (s, 1H)  
ESI: 528 (M+1)<sup>+</sup>, C<sub>22</sub>H<sub>34</sub>N<sub>5</sub>O<sub>8</sub>P

5

**Example 7**

Synthesis of ({1-[(2-amino-6-cyclopropylamino-9*H*-purin-9-yl)methyl]cyclopropyl}oxy)methylphosphonic acid(Compound 11)

10 The compound prepared in Preparation 6 (200mg) was dissolved in 20ml of ethanol, 53ml of triethylamine and 82mg of cyclopropylamine were added thereto, and the resulting mixture was heated under reflux for 18 hours. Water was added to stop the reaction, and the product was extracted with ethyl acetate. The ethyl acetate extract was concentrated by distillation under reduced pressure and the residue was purified by silica  
15 gel column chromatography(eluent: dichloromethane/methanol=20/1, v/v) to give 178mg(Yield 85%) of the diisopropyl compound.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.59 (t, 2H), 0.83 (m, 4H), 1.00 (t, 2H), 1.24 (d, 6H), 1.29 (d, 6H), 3.0 (brs, 1H), 3.80 (d, 2H), 4.15 (s, 2H), 4.70 (m, 2H), 4.71 (brs, 2H), 5.71 (s, 1H),  
20 7.68 (s, 1H)

The compound thus obtained was treated with trimethylsilylbromide according to the same procedure as Example 1 to give 128mg(Yield 90%) of the title compound.

25 <sup>1</sup>H NMR(MeOH-d<sub>4</sub>) δ 0.86 (m, 2H), 0.94 (m, 2H), 1.02 (m, 2H), 1.07 (m, 2H), 2.90 (br s, 1H), 3.93 (d, 2H), 4.39 (s, 2H), 8.43 (br s, 1H)  
ESI: 355 (M+1)<sup>+</sup>, C<sub>13</sub>H<sub>19</sub>N<sub>6</sub>O<sub>4</sub>P

**Example 8**

30 Synthesis of ({1-[(2-amino-6-ethylamino-9*H*-purin-9-yl)methyl]cyclopropyl}oxy) methylphosphonic acid(Compound 13)

The compound prepared in Preparation 6 (115mg) was dissolved in 20ml of ethanol, 31ml of triethylamine and 0.07ml of ethylamine were added thereto, and the  
35 resulting mixture was heated under reflux for 18 hours. Water was added to stop the

reaction, and the product was extracted with ethyl acetate. The ethyl acetate extract was concentrated by distillation under reduced pressure and the residue was purified by silica gel column chromatography(eluent: dichloromethane/methanol=20/1, v/v) to give 104mg(Yield 89%) of the diisopropyl compound.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.82 (m, 2H), 1.00 (m, 2H), 1.24 (d, 6H), 1.27 (t, 3H), 1.29 (d, 6H), 3.60 (brs, 2H), 3.81 (d, 2H), 4.15 (s, 2H), 4.65 (m, 4H), 5.50 (br s, 1H), 7.78 (s, 1H)

The compound thus obtained was reacted according to the same procedure as Example 1 to give 75mg(Yield 90%) of the title compound.

<sup>1</sup>H NMR(MeOH-d<sub>4</sub>) δ 0.89 (m, 2H), 1.04 (m, 2H), 1.31 (t, 3H), 3.59 (br s, 2H), 3.92 (d, 2H), 4.35 (s, 2H), 9.95 (br s, 1H)

ESI: 343 (M+1)<sup>+</sup>, C<sub>13</sub>H<sub>19</sub>N<sub>6</sub>O<sub>4</sub>P

#### Example 9

Synthesis of [(1-[[2-amino-6-(dimethylamino)-9H-purin-9-yl]methyl]cyclopropyl)oxy]methylphosphonic acid(Compound 15)

The compound prepared in Preparation 6 (115mg) was dissolved in 20ml of ethanol, 38.6ml of triethylamine and 1.74ml of N,N-dimethylamine were added thereto, and the resulting mixture was heated under reflux for 18 hours. Water was added to stop the reaction, and the product was extracted with ethyl acetate. The ethyl acetate extract was concentrated by distillation under reduced pressure and the residue was purified by silica gel column chromatography(eluent: dichloromethane/methanol=20/1, v/v) to give 119mg(Yield 81%) of the diisopropyl compound.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.75 (t, 2H), 0.93 (t, 2H), 1.16 (d, 6H), 1.22 (d, 6H), 3.3 (brs, 6H), 3.74 (d, 2H), 4.09 (s, 2H), 4.60 (m, 2H), 4.69 (brs, 2H), 7.68 (s, 1H)

The compound thus obtained was reacted according to the same procedure as Example 1 to give 86mg(Yield 90%) of the title compound.

<sup>1</sup>H NMR(MeOH-d<sub>4</sub>) δ 0.89 (m, 2H), 1.05 (m, 2H), 3.30 (br s, 6H), 3.90 (d, 2H),



4.37 (s, 2H), 7.92 (br s, 1H)

ESI: 343 (M+1)<sup>+</sup>, C<sub>12</sub>H<sub>19</sub>N<sub>6</sub>O<sub>4</sub>P

#### Example 10

#### 5      Synthesis of [(1-[[2-amino-6-(isopropylamino)-9H-purin-9-yl]methyl]cyclopropyl) oxy]methylphosphonic acid(Compound 17)

10      The compound prepared in Preparation 6 (133mg) was dissolved in 20mL of ethanol, 0.049mL of triethylamine and 0.082mL of isopropylamine were added thereto, and the resulting mixture was heated under reflux for 18 hours. Water was added to stop the reaction, and the product was extracted with ethyl acetate. The ethyl acetate extract was concentrated by distillation under reduced pressure and the residue was purified by silica gel column chromatography(eluent: dichloromethane/methanol=20/1, v/v) to give 95mg(Yield 68%) of the diisopropyl compound.

15

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.83 (m, 2H), 0.98 (m, 2H), 1.28 (m, 18H), 3.79 (d, 2H), 4.15 (s, 2H), 4.60 (br s, 1H), 4.68 (s, 2H), 4.70 (m, 2H), 5.40 (br s, 1H), 7.77 (s, 1H)

20      The compound thus obtained was reacted according to the same procedure as Example 1 to give 72mg(Yield 91%) of the title compound.

<sup>1</sup>H NMR(MeOH-d<sub>4</sub>) δ 0.89 (m, 2H), 1.05 (m, 2H), 1.34 (d, 6H), 3.30 (br s, 1H), 3.90 (d, 2H), 4.36 (s, 2H), 8.01 (br s, 1H)

ESI: 357 (M+1)<sup>+</sup>, C<sub>12</sub>H<sub>19</sub>N<sub>6</sub>O<sub>4</sub>P

25

#### Example 11

#### Synthesis of ({1-[(2,6-diamino-9H-purin-9-yl)methyl]cyclopropyl}oxy)methylphosphonic acid(Compound 19)

30      The compound prepared in Preparation 4 (246mg) and 2,6-diaminopurine were reacted according to the same procedure as Preparation 5 to give 78.5mg(Yield 29%) of the diisopropyl compound.

35      <sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.85 (t, 2H), 1.00 (t, 2H), 1.25 (d, 6H), 1.29 (d, 6H), 1.83 (brs, 2H), 3.82 (d, 2H), 4.15 (s, 2H), 4.68 (m, 2H), 5.39 (d, 2H), 7.85 (s, 1H)

ESI: 399 (M+1)<sup>+</sup>, C<sub>16</sub>H<sub>27</sub>N<sub>6</sub>O<sub>4</sub>P

The compound thus obtained was reacted according to the same procedure as Example 1 to give 72mg(Yield 91%) of the title compound.

<sup>1</sup>H NMR(DMSO-d<sub>6</sub> + CF<sub>3</sub>COOH) δ 0.70 (m, 2H), 0.82 (m, 2H), 3.58 (d, 2H), 4.21 (s, 2H), 8.16 (br s, 1H)

ESI: 315 (M+1)<sup>+</sup>, C<sub>10</sub>H<sub>15</sub>N<sub>6</sub>O<sub>4</sub>P

#### Example 12

Synthesis of ({1-[(2-amino-6-ethoxy-9H-purin-9-yl)methyl]cyclopropyl}oxy) methylphosphonic acid (Compound 23)

6-Chloroguanine derivative prepared in Preparation 6 (100mg) was dissolved in 10 ml of ethanol, 32ml of triethylamine and 53mg of sodium methoxide were added, and the resulting mixture was refluxed for 4 hours. The reaction was stopped by adding 10ml of water. The reaction solution was extracted with dichloromethane and distilled under reduced pressure. The residue was purified by silica gel column to give a compound wherein 6-position of guanine was substituted by ethoxy group.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.83 (t, 2H), 1.00 (t, 2H), 1.24-1.28 (m, 12H), 1.45 (t, 3H), 3.82 (d, 2H), 4.21 (s, 2H), 4.53 (m, 2H), 4.67 (m, 1H), 5.76 (s, 2H), 7.90 (s, 1H)

The compound thus obtained was reacted according to the same procedure as Example 1 to give the title compound.

<sup>1</sup>H NMR(MeOH-d<sub>4</sub>) δ 0.99 (t, 2H), 1.06 (t, 2H), 1.48 (t, 3H), 3.91 (d, 2H), 4.51 (s, 2H), 4.65 (m, 2H), 9.18 (s, 1H)

ESI: 344 (M+1)<sup>+</sup>, C<sub>12</sub>H<sub>18</sub>N<sub>5</sub>O<sub>5</sub>P

#### Example 13

Synthesis of ({1-[(2-amino-6-methyl-9H-purin-9-yl)methyl]cyclopropyl}oxy) methylphosphonic acid(Compound 25)

10ml flask was dried under vacuum and 53mg(0.238mmol) of zinc bromide was

introduced bit by bit under nitrogen atmosphere. 2ml of dry tetrahydrofuran was added dropwise thereto, the temperature was lowered to -78 , 0.08ml(20.238mmol) of methylmagnesium Grignard was added, and the resulting mixture was stirred for 1 hour. After the reaction mixture was warmed to room temperature, about 10mol% of palladiumtetrakis(triphenylphosphine) was added bit by bit. 50mg(0.119mmol) of the compound prepared in Preparation 6 in 1ml of tetrahydrofuran was added to the above reaction solution dropwise. The resulting mixture was heated for 1 hour. The solvent was removed by distillation under reduced pressure, the residue was participated with water and ethyl acetate, and the organic layer was concentrated by distillation under reduced pressure. The residue was purified by silica gel column chromatography(eluent: methylene chloride/methanol=90/10, v/v) to give 20mg(Yield 42%) of the diisopropyl compound.

<sup>1</sup>H NMR(MeOH-d<sub>4</sub>) δ 0.95 (m, 2H), 0.98(m, 2H), 1.17(d, 6H), 1.23 (d, 6H), 2.59(s, 3H), 4.02(s, 1H), 4.10(s, 1H), 4.32(s, 2H), 4.59(m, 2H), 8.12(s, 1H)  
ESI: 398 (M+1)<sup>+</sup>, C<sub>17</sub>H<sub>28</sub>N<sub>5</sub>O<sub>4</sub>P

The compound thus obtained was reacted according to the same procedure as Example 1 to give 8.0mg(Yield 50%) of the title compound.

<sup>1</sup>H NMR(D<sub>2</sub>O) δ 0.87 (m, 2H), 1.02 (m, 2H), 3.79 (s, 1H), 3.81 (s, 1H), 4.53 (s, 2H), 8.25 (s, 1H)  
ESI: 314 (M+1)<sup>+</sup>, C<sub>11</sub>H<sub>16</sub>N<sub>5</sub>O<sub>4</sub>P

#### Example 14

Synthesis of [(1{[5-methyl-2,4-dioxo-3,4-dihydro-1(2H)-pyrimidinyl]methyl} cyclopropyl)oxy]methylphosphonic acid(Compound 31)

The compound prepared in Preparation 7 (19mg) was reacted according to the same procedure as Example 1 to give 14mg(Yield 95%) of the title compound.

ESI: 291 (M+1)<sup>+</sup>, C<sub>10</sub>H<sub>11</sub>N<sub>2</sub>O<sub>6</sub>P  
<sup>1</sup>H NMR(MeOH-d<sub>4</sub>) δ 0.82 (t, 2H), 0.97 (t, 2H), 1.87 (s, 3H), 3.83 (d, 2H), 3.97 (s, 2H), 7.55 (s, 1H)

**Example 15**

**Synthesis of [(1-{[2-amino-6-(4-morpholinyl)-9H-purin-9-yl]methyl} cyclopropyl)oxy]methylphosphonic acid(Compound 37)**

5 The compound prepared in Preparation 6 (134mg) was dissolved in 20ml of ethanol, 0.049ml of triethylamine and 0.085ml of morpholine were added thereto, and the resulting mixture was heated under reflux for 18 hours. Water was added to stop the reaction, and the product was extracted with ethyl acetate. The ethyl acetate extract was concentrated by distillation under reduced pressure and the residue was purified by silica  
10 gel column chromatography(eluent: dichloromethane/methanol=20/1, v/v) to give 66mg(Yield 44%) of the diisopropyl compound.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.83 (m, 2H), 0.99 (m, 2H), 1.24 (d, 6H), 1.30 (d, 6H), 3.79 (m, 6H), 4.18 (s, 2H), 4.21 (br s, 4H), 4.67 (m, 2H), 4.80 (br s, 2H), 7.78 (s, 1H)

15 ESI: 469 (M+1)<sup>+</sup>, C<sub>20</sub>H<sub>33</sub>N<sub>6</sub>O<sub>5</sub>P

The compound thus obtained was treated with trimethylsilylbromide according to the same procedure as Example 1 to give 49mg(Yield 91%) of the title compound.

20 <sup>1</sup>H NMR(MeOH-d<sub>4</sub>) δ 0.89 (m, 2H), 1.07 (m, 2H), 3.81 (m, 4H), 3.92 (d, 2H), 4.40(br s, 6H), 7.87 (s, 1H)

ESI: 384 (M+1)<sup>+</sup>, C<sub>14</sub>H<sub>21</sub>N<sub>6</sub>O<sub>5</sub>P

**Example 16**

25 **Synthesis of [(1-{[2-amino-6-(1-piperidiny)]-9H-purin-9-yl]methyl} cyclopropyl)oxy]methylphosphonic acid(Compound 39)**

The compound prepared in Preparation 6 (154mg) was dissolved in 20ml of ethanol, 0.049ml of triethylamine and 0.11ml of piperidine were added thereto, and the  
30 resulting mixture was heated under reflux for 18 hours. Water was added to stop the reaction, and the product was extracted with ethyl acetate. The ethyl acetate extract was concentrated by distillation under reduced pressure and the residue was purified by silica gel column chromatography(eluent: dichloromethane/methanol=20/1, v/v) to give 123mg (Yield 72%) of the diisopropyl compound.

35

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.80 (m, 2H), 0.99 (m, 2H), 1.22 (d, 6H), 1.26 (d, 6H), 1.63 (m, 4H), 1.67 (m, 2H), 3.78 (d, 2H), 4.14 (s, 6H), 4.54 (br s, 2H), 4.65 (m, 2H), 7.72 (s, 1H)

ESI: 467 (M+1)<sup>+</sup>, C<sub>21</sub>H<sub>35</sub>N<sub>6</sub>O<sub>4</sub>P

5

The compound thus obtained was reacted according to the same procedure as Example 1 to give 87mg(Yield 91%) of the title compound.

<sup>1</sup>H NMR(MeOH-d<sub>4</sub>) δ 0.89 (m, 2H), 1.06 (m, 2H), 1.73 (m, 4H), 1.79 (m, 2H), 3.90 (d, 2H), 4.37 (s, 2H), 4.43(br s, 4H), 7.89 (s, 1H)

10

ESI: 383 (M+1)<sup>+</sup>, C<sub>15</sub>H<sub>23</sub>N<sub>6</sub>O<sub>4</sub>P

#### Example 17

Synthesis of [(1-[[2-amino-6-(4-methyl-1-piperazinyl)-9H-purin-9-yl]methyl] cyclopropyl)oxy]methylphosphonic acid(Compound 41)

15

The compound prepared in Preparation 6 (128mg) was dissolved in 20ml of ethanol, 0.10ml of 4-methyl-1-piperazine was added thereto, and the resulting mixture was heated under reflux for 18 hours. Water was added to stop the reaction, and the product was extracted with ethyl acetate. The ethyl acetate extract was concentrated by distillation under reduced pressure and the residue was purified by silica gel column chromatography (eluent: dichloromethane/methanol=20/1, v/v) to give 123mg(Yield 83%) of the diisopropyl compound.

20

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.80 (m, 2H), 0.98 (m, 2H), 1.21 (d, 6H), 1.27 (d, 6H), 2.30 (s, 3H), 2.48 (m, 4H), 3.78 (d, 2H), 4.13 (s, 2H), 4.22 (br s, 4H), 4.57 (s, 2H), 4.66 (m, 2H), 7.73 (s, 1H)

25

ESI: 482 (M+1)<sup>+</sup>, C<sub>21</sub>H<sub>36</sub>N<sub>7</sub>O<sub>4</sub>P

30

The compound thus obtained was reacted according to the same procedure as Example 1 to give 87mg(Yield 85%) of the title compound.

<sup>1</sup>H NMR(MeOH-d<sub>4</sub>) δ 0.89 (m, 2H), 1.07 (m, 2H), 3.00 (s, 3H), 3.72 (m, 4H), 3.91 (d, 2H), 4.45 (s, 2H), 4.89 (m, 2H), 5.70 (br, 2H), 7.91 (s, 1H)

35

ESI: 398 (M+1)<sup>+</sup>, C<sub>15</sub>H<sub>24</sub>N<sub>7</sub>O<sub>4</sub>P

**Example 18**

**Synthesis of [(1-[[2-amino-6-(1-pyrrolidinyl)-9H-purin-9-yl]methyl]cyclopropyl)oxy]methyl phosphonic acid (Compound 43)**

5

The compound prepared in Preparation 6 (122mg) was dissolved in 20mL of ethanol, 0.07mL of pyrrolidine was added thereto, and the resulting mixture was heated under reflux for 18 hours. Water was added to stop the reaction, and the product was extracted with ethyl acetate. The ethyl acetate extract was concentrated by distillation under reduced pressure and the residue was purified by silica gel column chromatography (eluent: dichloromethane/methanol=20/1, v/v) to give 110mg (Yield 83%) of the diisopropyl compound.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.78 (m, 2H), 0.96 (m, 2H), 1.20 (d, 6H), 1.26 (d, 6H), 2.00 (br s, 4H), 3.60 (br, 3H), 3.78 (d, 2H), 4.09 (br, 2H), 4.12 (s, 2H), 4.63 (m, 2H), 7.69 (s, 1H)

ESI: 453 (M+1)<sup>+</sup>, C<sub>20</sub>H<sub>33</sub>N<sub>6</sub>O<sub>4</sub>P

The compound thus obtained was reacted according to the same procedure as Example 1 to give 76mg (Yield 85%) of the title compound.

<sup>1</sup>H NMR(MeOH-d<sub>4</sub>) δ 0.94 (m, 2H), 1.03 (m, 2H), 2.15 (m, 4H), 3.76 (m, 2H), 3.91 (d, 2H), 4.18 (m, 2H), 4.40 (s, 2H), 5.70 (br, 2H), 8.42 (s, 1H)

ESI: 369 (M+1)<sup>+</sup>, C<sub>14</sub>H<sub>21</sub>N<sub>6</sub>O<sub>4</sub>P

25

**Example 19**

**Synthesis of 3-[(1-[(2-amino-9H-purin-9-yl)methyl]cyclopropyl)oxy] methyl]-9-methyl-3,7-dioxo-2,4,6-trioxa-3λ<sup>5</sup>-phosphadec-1-yl 3-methylbutanoate (Compound 74)**

30

The compound prepared in Example 5 (100mg) was dissolved in dimethylformamide (2mL) and then reacted with chloromethyl 3-methylbutyrate in the presence of triethylamine (3 equivalents) at room temperature for 24 hours. The resulting product was purified by silica gel column to give the title compound in a yield of 41%.

35

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.89 (t, 2H), 0.94 (d, 12H), 1.04 (t, 2H), 2.10 (m, 2H), 2.22 (d, 4H), 3.97 (d, 2H), 4.23 (s, 2H), 5.21 (s, 2H), 5.65 (m, 4H), 8.00 (s, 1H), 8.69 (s, 1H)  
ESI: 527 (M+1)<sup>+</sup>, C<sub>23</sub>H<sub>35</sub>N<sub>4</sub>O<sub>8</sub>P

#### Example 20

Synthesis of 3-[(1-[(2-amino-9H-purin-9-yl)methyl]cyclopropyl)oxy] methyl]-3,7-dioxo-2,4,6-trioxa-3λ<sup>5</sup>-phosphadec-1-yl butyrate(Compound 75)

The compound prepared in Example 5 was reacted with chloromethyl butyrate according to the same procedure as Example 19 at room temperature for 24 hours. The resulting product was purified by silica gel column to give the title compound in a yield of 24%.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.88 (t, 2H), 0.92 (d, 6H), 1.60 (m, 4H), 2.32 (t, 4H), 3.96 (d, 2H), 4.22 (s, 2H), 5.00 (s, 2H), 5.62 (m, 4H), 8.00 (s, 1H), 8.68 (s, 1H)  
ESI: 499 (M+1)<sup>+</sup>, C<sub>21</sub>H<sub>31</sub>N<sub>4</sub>O<sub>8</sub>P

#### Example 21

Synthesis of 3-[(1-[(2-amino-9H-purin-9-yl)methyl]cyclopropyl)oxy] methyl]-8-methyl-3,7-dioxo-2,4,6-trioxa-3λ<sup>5</sup>-phosphanon-1-yl 2-methylpropanoate (Compound 78)

The compound prepared in Example 5 was reacted with chloromethyl isobutyrate according to the same procedure as Example 19 at room temperature for 24 hours. The resulting product was purified by silica gel column to give the title compound in a yield of 21%.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.84 (t, 2H), 0.97 (t, 2H), 1.11 (d, 12H), 2.52 (m, 2H), 3.91 (d, 2H), 4.16 (s, 2H), 5.21 (s, 2H), 5.58 (m, 4H), 7.96 (s, 1H), 8.61 (s, 1H)  
ESI: 499 (M+1)<sup>+</sup>, C<sub>21</sub>H<sub>31</sub>N<sub>4</sub>O<sub>8</sub>P

#### Example 22

Synthesis of 3-[(1-[(2-amino-9H-purin-9-yl)methyl]cyclopropyl)oxy] methyl]-3,7-dioxo-7-(1-pyrrolidiny)-2,4,6-trioxa-3λ<sup>5</sup>-phosphahept-1-yl pyrrolidinecarboxylate (Compound 80)

The compound prepared in Example 5 was reacted with chloromethyl 1-pyrrolidinecarboxylate according to the same procedure as Example 19 at room temperature for 24 hours. The resulting product was purified by silica gel column to give the title compound in a yield of 35%.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.82 (t, 2H), 0.87 (m, 8H), 0.98 (t, 2H), 1.57 (d, 4H), 2.26 (t, 4H), 3.91 (d, 2H), 4.16 (s, 2H), 5.12 (s, 2H), 5.57 (m, 4H), 7.98 (s, 1H), 8.62 (s, 1H)  
ESI: 553 (M+1)<sup>+</sup>, C<sub>23</sub>H<sub>33</sub>N<sub>6</sub>O<sub>8</sub>P

### Example 23

Synthesis of 3-[(1-[(2-amino-9H-purin-9-yl)methyl]cyclopropyl)oxy]methyl]-3,7-dioxo-7-(1-piperidinyl)-2,4,6-trioxa-3λ<sup>6</sup>-phosphahept-1-yl piperidinecarboxylate (Compound 81);

The compound prepared in Example 5 was reacted with chloromethyl 1-piperidinecarboxylate according to the same procedure as Example 19 at room temperature for 24 hours. The resulting product was purified by silica gel column to give the title compound in a yield of 39%.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.86 (t, 2H), 1.02 (t, 2H), 1.47-1.58 (brn, 12H), 3.40 (brn, 8H), 3.99 (d, 2H), 4.22 (s, 2H), 5.00 (s, 2H), 5.69 (m, 4H), 8.00 (s, 1H), 8.67 (s, 1H)  
ESI: 581 (M+1)<sup>+</sup>, C<sub>25</sub>H<sub>37</sub>N<sub>6</sub>O<sub>8</sub>P

### Example 24

Synthesis of 3-[(1-[(2-amino-9H-purin-9-yl)methyl]cyclopropyl)oxy]methyl]-7-(4-morpholinyl)-3,7-dioxo-2,4,6-trioxa-3λ<sup>5</sup>-phosphahept-1-yl morpholinecarboxylate (Compound 82)

The compound prepared in Example 5 was reacted with chloromethyl 4-morpholinecarboxylate according to the same procedure as Example 19 at room temperature for 24 hours. The resulting product was purified by silica gel column to give the title compound in a yield of 40%.



<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.89 (t, 2H), 1.03 (t, 2H), 3.47 (brn, 8H), 3.65 (brn, 8H), 4.00 (d, 2H), 4.24 (s, 2H), 5.04 (s, 2H), 5.70 (m, 4H), 8.07 (s, 1H), 8.69 (s, 1H)

ESI: 586 (M+1)<sup>+</sup>, C<sub>23</sub>H<sub>33</sub>N<sub>6</sub>O<sub>10</sub>P

## 5 Example 25

Synthesis of {[1-({2-amino-6-[(4-methylphenyl)sulfanyl]-9H-purin-9-yl} methyl)cyclopropyl]oxy}methylphosphonic acid(Compound 66)

6-Chloroguanine derivative prepared in Preparation 6 (4.86g) was dissolved in 85  
10 ml of methanol and 1.4g of triethylamine and 2.9g of 4-methylthiocresol were added. The reaction mixture was reacted under reflux condition for 24 hours. The reaction was stopped by adding 20ml of water, and the methanol was removed by distillation under reduced pressure. The reaction mixture was extracted with dichloromethane and purified by silica gel column to give a compound wherein 6-position of guanine was substituted by  
15 4-methylphenylthio group.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.84 (t, 2H), 1.02 (t, 2H), 1.25-1.31 (m, 12H), 2.40 (s, 3H), 4.20 (d, 2H), 4.69 (m, 2H), 4.74 (s, 2H), 7.22 (d, 2H), 7.50 (d, 2H), 8.00 (s, 1H)

20 The compound thus obtained was reacted according to the same procedure as Example 1 and then recrystallized from a mixture of methanol-diethylether (1/20, v/v) to give the title compound.

<sup>1</sup>H NMR(MeOH-d<sub>4</sub>) δ 0.98 (t, 2H), 1.06 (t, 2H), 2.42 (s, 3H), 3.92 (d, 2H), 4.48  
25 (s, 2H), 7.35 (d, 2H), 7.55 (d, 2H), 9.05 (s, 1H)

ESI: 421 (M+1)<sup>+</sup>, C<sub>18</sub>H<sub>21</sub>N<sub>4</sub>O<sub>4</sub>PS

## Example 26

Synthesis of 3-([1-({2-amino-6-[(4-methylphenyl)sulfanyl]-9H-purin-9-yl} methyl)cyclopropyl]oxy)methyl)-8,8-dimethyl-3,7-dioxo-2,4,6-trioxo-3λ<sup>5</sup>-phosphanon-1-yl pivalate(Compound 68)  
30

The methylphosphonic acid prepared in Example 25 was reacted according to the same procedure as Example 2 to give the title compound.

35

<sup>1</sup>H NMR(CDCI<sub>3</sub>) δ 0.82 (t, 2H), 0.98 (t, 2H), 1.18 (s, 18H), 2.36 (s, 3H), 3.93 (d, 2H), 4.15 (s, 2H), 4.93 (s, 2H), 5.60 (m, 4H), 7.18 (d, 2H), 7.48 (d, 2H), 7.88 (s, 1H)

ESI: 649 (M+1)<sup>+</sup>, C<sub>30</sub>H<sub>41</sub>N<sub>4</sub>O<sub>8</sub>PS

#### Example 27

Synthesis of {[1-({2-amino-6-[(4-methoxyphenyl)sulfanyl]-9H-purin-9-yl}methyl)cyclopropyl]oxy}methylphosphonic acid(Compound 96)

6-Chloroguanine derivative prepared in Preparation 6 (4.86g) was dissolved in 85 ml of methanol and 1.4g of triethylamine and 2.9g of 4-methoxythiocresol were added. The reaction mixture was reacted under reflux condition for 24 hours. The reaction was stopped by adding 20ml of water, and the methanol was removed by distillation under reduced pressure. The reaction mixture was extracted with dichloromethane and purified by silica gel column to give a compound wherein 6-position of guanine was substituted by 4-methoxyphenylthio group.

The compound thus obtained was reacted according to the same procedure as Example 1 and then recrystallized from a mixture of methanol-diethylether (1/20, v/v) to give the title compound.

<sup>1</sup>H NMR(MeOH-d<sub>4</sub>) δ 0.77 (m, 2H), 1.05 (m, 2H), 3.87 (s, 3H), 3.92 (d, 2H), 4.45 (s, 2H), 7.10 (d, 2H), 7.59 (d, 2H), 8.09 (s, 1H)

ESI: 438 (M+1)<sup>+</sup>, C<sub>17</sub>H<sub>20</sub>N<sub>5</sub>O<sub>5</sub>PS

#### Example 28

Synthesis of {[1-({2-amino-6-[(4-nitrophenyl)sulfanyl]-9H-purin-9-yl}methyl)cyclopropyl]oxy}methylphosphonic acid(Compound 95)

The compound prepared in Preparation 6 was reacted according to the same procedure as Example 27 except that 4-nitrothiocresol was used instead of 4-methoxythiocresol to give the title compound.

<sup>1</sup>H NMR(MeOH-d<sub>4</sub>) δ 0.86 (m, 2H), 0.95 (m, 2H), 3.82 (d, 2H), 4.35 (s, 2H), 7.81 (d, 2H), 8.22 (d, 2H), 8.72 (s, 1H)

ESI: 453 (M+1)<sup>+</sup>, C<sub>16</sub>H<sub>17</sub>N<sub>6</sub>O<sub>6</sub>PS

**Example 29**

Synthesis of ({1-[(2-amino-6-hydroxy-9*H*-purin-9-yl)methyl]-2-methylcyclopropyl}oxy)methylphosphonic acid(Compound 97)

The 6-chloroguanine derivative prepared in Preparation 12 was consecutively reacted according to the same procedure as Examples 3 and 4 to give the title compound.

<sup>1</sup>H NMR(MeOH-d<sub>4</sub>) δ 0.73 (t, 1H), 1.15 (m, 1H), 1.21(d, 3H), 1.38 (t, 1H), 1.48 (m, 1H), 3.85 (t, 1H), 3.96 (t, 1H), 4.42 (d, 1H), 4.69 (d, 1H), 9.12 (s, 1H)

**Example 30**

Synthesis of {[1-({2-amino-[6-(4-methoxyphenyl)sulfanyl]-9*H*-purin-9-yl}methyl)-2-methylcyclopropyl]oxy}methylphosphonic acid(Compound 99)

The 6-chloroguanine derivative prepared in Preparation 12 was reacted according to the same procedure as Example 27 to give the title compound.

<sup>1</sup>H NMR(MeOH-d<sub>4</sub>) δ 0.67 (t, 1H), 1.13 (m, 2H), 1.20 (d, 3H), 1.45 (m, 1H), 3.85 (m, 1H), 3.86 (s, 3H), 3.94 (m, 1H), 4.42 (d, 1H), 4.68 (d, 1H), 7.09 (d, 2H), 7.59 (d, 2H), 9.00 (s, 1H)

ESI: 452 (M+1)<sup>+</sup>, C<sub>18</sub>H<sub>22</sub>N<sub>5</sub>O<sub>5</sub>PS

**Example 31**

Synthesis of {[1-({2-amino-[6-(4-methylphenyl)sulfanyl]-9*H*-purin-9-yl}methyl)-2-methylcyclopropyl]oxy}methylphosphonic acid(Compound 101)

The 6-chloroguanine derivative prepared in Preparation 12 was reacted according to the same procedure as Example 25 to give the title compound.

<sup>1</sup>H NMR(MeOH-d<sub>4</sub>) δ 0.68 (t, 1H), 1.15 (m, 2H), 1.20 (d, 3H), 1.45 (m, 1H), 2.42 (s, 3H), 3.84 (m, 1H), 3.96 (m, 1H), 4.43 (d, 1H), 4.68 (d, 1H), 7.36 (d, 2H), 7.55 (d, 2H), 9.05 (s, 1H)

ESI: 436 (M+1)<sup>+</sup>, C<sub>18</sub>H<sub>22</sub>N<sub>5</sub>O<sub>4</sub>PS

**Example 32**

Synthesis of {[1-({2-amino-[6-(4-nitrophenyl)sulfanyl]-9H-purin-9-yl)methyl}-2-methylcyclopropyl]oxy}methylphosphonic acid(Compound 100)

5 The 6-chloroguanine derivative prepared in Preparation 12 was reacted according to the same procedure as Example 28 to give the title compound.

<sup>1</sup>H NMR(MeOH-d<sub>4</sub>) δ 0.49 (t, 1H), 0.93 (m, 1H), 1.00 (d, 3H), 1.25 (m, 1H),  
3.64 (m, 1H), 3.76 (m, 1H), 4.28 (d, 1H), 4.53 (d, 1H), 7.72 (d, 2H), 8.14 (d, 2H), 9.10 (s,  
10 1H)  
ESI: 467 (M+1)<sup>+</sup>, C<sub>17</sub>H<sub>19</sub>N<sub>6</sub>O<sub>6</sub>PS

**Example 33**

15 Synthesis of ({1-[(6-amino-9H-purin-9-yl)methyl]-2-methylcyclopropyl}oxy)methylphosphonic acid(Compound 103)

The adenine derivative prepared in Preparation 11 was reacted according to the same procedure as Example 1 to give the title compound.

20 <sup>1</sup>H NMR(MeOH-d<sub>4</sub>) δ 0.64 (t, 1H), 1.09 (m, 1H), 1.20 (d, 3H), 1.43 (m, 1H),  
3.83 (m, 1H), 3.95 (m, 1H), 4.49 (d, 1H), 4.75 (d, 1H), 5.49 (s, 2H), 8.39 (s, 1H), 8.55 (s,  
1H)  
ESI: 314 (M+1)<sup>+</sup>, C<sub>11</sub>H<sub>16</sub>N<sub>5</sub>O<sub>4</sub>P

**Example 34**

25 Synthesis of bis{[(*t*-butoxycarbonyl)oxy]methyl}({1-[(2-amino-9H-purin-9-yl)methyl]cyclopropyl}oxy)methylphosphonate(Compound 69)

30 The compound prepared in Example 5 (187mg) was mixed with 6mL of N-methyl-2-pyrrolidone, and 300mg of triethylamine and 150mg of chloromethyl *t*-butylcarbonate were added. The reaction solution was stirred at room temperature for 4 hours. The reaction was stopped by adding 10mL of water, and the reaction mixture was extracted with ethyl acetate. The extract was distilled under reduced pressure and purified by silica gel column to give the title compound.

35

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.86 (m, 2H), 1.06 (m, 2H), 1.47 (s, 18H), 4.01 (d, 4H), 4.22 (s, 2H), 5.00 (brs, 2H), 5.61 (m, 4H), 7.99 (s, 1H), 8.69 (s, 1H)

ESI: 344 (M+1)<sup>+</sup>, C<sub>22</sub>H<sub>34</sub>N<sub>5</sub>O<sub>10</sub>P

#### Example 35

Synthesis of bis{[(isopropoxycarbonyl)oxy)methyl]}{[1-[(2-amino-9H-purin-9-yl)methyl]cyclopropyl]oxy)methylphosphonate(Compound 70)

The compound prepared in Example 5 (100mg) was mixed with 5ml of N-methyl-2-pyrrolidone, and 110mg of triethylamine and 150mg of chloromethyl isopropylcarbonate were added. The reaction solution was stirred at 50 °C for 4 hours. The reaction was stopped by adding 10ml of water, and the reaction mixture was extracted with ethyl acetate. The extract was distilled under reduced pressure and purified by silica gel column to give the title compound.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.88 (s, 2H), 1.06 (s, 2H), 1.29 (d, 2H), 1.31 (d, 2H), 4.01 (d, 4H), 4.21 (s, 2H), 4.92 (m, 2H), 5.01 (brs, 2H), 5.64 (m, 4H), 7.99 (s, 1H), 8.69 (s, 1H)

ESI: 532 (M+1)<sup>+</sup>, C<sub>20</sub>H<sub>30</sub>N<sub>5</sub>O<sub>10</sub>P

#### Example 36

Synthesis of ({1-[(2-amino-6-hydroxy-9H-purin-9-yl)methyl]-2,2-dimethylcyclopropyl}oxy)methylphosphonic acid(Compound 146)

The compound prepared in Preparation 32 was consecutively reacted according to the same procedure as Examples 1 and 4 to give the title compound.

<sup>1</sup>H NMR(MeOH-d<sub>4</sub>) δ 0.78 (d, 1H), 0.82 (d, 1H), 1.21 (s, 3H), 1.27 (s, 3H), 3.90 (d, 1H), 3.91 (d, 1H), 4.58 (s, 2H), 9.12 (s, 1H)

ESI: 344 (M+1)<sup>+</sup>, C<sub>12</sub>H<sub>18</sub>N<sub>5</sub>O<sub>5</sub>P

#### Example 37

Synthesis of ({1-[(2-amino-9H-purin-9-yl)methyl]-2,2-dimethylcyclopropyl}oxy)methylphosphonic acid(Compound 147)

The compound prepared in Preparation 32 was reacted according to the same

procedure as Example 5 to give a compound wherein 6-position of guanine was reduced by hydrogen.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.60 (d, 1H), 0.82 (d, 1H), 1.21 (s, 3H), 1.22 (s, 3H), 1.22 (m, 15H), 3.73 (m, 1H), 3.87 (m, 1H), 4.13 (d, 1H), 4.49 (d, 1H), 4.67 (m, 2H), 4.98 (brs, 2H), 8.09 (s, 1H), 9.67 (s, 1H)

The compound thus obtained was reacted according to the same procedure as Example 1 to give the title compound.

<sup>1</sup>H NMR(MeOH-d<sub>4</sub>) δ 0.74 (d, 1H), 0.81 (d, 1H), 1.21 (s, 3H), 1.26 (s, 3H), 3.91 (d, 2H), 4.49 (d, 1H), 4.57 (d, 1H), 8.63 (s, 1H), 8.74 (s, 1H)  
ESI: 328 (M+1)<sup>+</sup>, C<sub>12</sub>H<sub>18</sub>N<sub>5</sub>O<sub>4</sub>P

**Example 38**  
Synthesis of ({1-[(6-amino-9H-purin-9-yl)methyl]-2,2-dimethylcyclopropyl} oxy)methylphosphonic acid(Compound 148)

The compound prepared in Preparation 31 was reacted according to the same procedure as Example 1 to give the title compound.

<sup>1</sup>H NMR(MeOH-d<sub>4</sub>) δ 0.77 (d, 1H), 0.79 (d, 1H), 1.25 (s, 3H), 1.28 (s, 3H), 3.90 (d, 2H), 4.61 (d, 1H), 4.70 (d, 1H), 8.38 (s, 1H), 8.51 (s, 1H)  
ESI: 328 (M+1)<sup>+</sup>, C<sub>12</sub>H<sub>18</sub>N<sub>5</sub>O<sub>4</sub>P

**Example 39**  
Synthesis of (E)-2-{1-[(2-amino-6-hydroxy-9H-purin-9-yl)methyl]cyclopropyl} ethenylphosphonic acid(Compound 130)

The compound prepared in Preparation 26 was reacted according to the same procedure as Example 1 to give phosphonic acid derivative.

<sup>1</sup>H NMR(MeOH-d<sub>4</sub>) δ 1.07 (t, 2H), 1.33 (t, 1H), 4.41 (s, 2H), 5.76 (dd, 1H), 6.45 (dd, 1H), 9.18 (s, 1H)

The compound thus obtained was reacted according to the same procedure as Example 4 to give the title compound.

<sup>1</sup>H NMR(MeOH-d<sub>4</sub>) δ 1.08 (t, 2H), 1.34 (t, 1H), 4.38 (s, 2H), 5.78 (dd, 1H),  
6.46 (dd, 1H), 9.11 (s, 1H)  
ESI: 312 (M+1)<sup>+</sup>, C<sub>11</sub>H<sub>14</sub>N<sub>5</sub>O<sub>4</sub>P

#### Example 40

Synthesis of 2-{1-[(2-amino-9H-purin-9-yl)methyl]cyclopropyl}ethyl  
phosphonic acid(Compound 139)

The compound prepared in Preparation 26 was reacted according to the same procedure as Example 5 to give the title compound.

<sup>1</sup>H NMR(MeOH-d<sub>4</sub>) δ 0.58 (t, 2H), 0.85 (t, 2H), 1.42 (m, 2H), 1.95 (m, 2H),  
4.11 (s, 2H), 5.78 (dd, 1H), 8.55 (s, 1H), 8.75(s, 1H)  
ESI: 298 (M+1)<sup>+</sup>, C<sub>11</sub>H<sub>16</sub>N<sub>5</sub>O<sub>3</sub>P

#### Example 41

Synthesis of (E)-2-{1-[(6-amino-9H-purin-9-yl)methyl]cyclopropyl}ethenyl  
phosphonic acid(Compound 132)

The compound prepared in Preparation 25 was reacted according to the same procedure as Example 1 to give the title compound.

<sup>1</sup>H NMR(MeOH-d<sub>4</sub>) δ 0.94 (t, 2H), 1.20 (t, 2H), 4.36 (s, 2H), 5.63 (dd, 1H),  
6.37 (dd, 1H), 8.30 (s, 1H), 8.31 (s, 1H)  
ESI: 296 (M+1)<sup>+</sup>, C<sub>11</sub>H<sub>14</sub>N<sub>5</sub>O<sub>3</sub>P

#### Example 42

Synthesis of 2-{1-[(6-amino-9H-purin-9-yl)methyl]cyclopropyl}ethyl  
phosphonic acid(Compound 140)

The compound prepared in Preparation 25 was reacted according to the same procedure as Example 5 to give the title compound.

<sup>1</sup>H NMR(MeOH-d<sub>4</sub>) δ 0.58 (t, 2H), 0.87 (t, 2H), 1.37 (m, 2H), 1.97 (m, 2H),  
4.24 (s, 2H), 8.31 (s, 1H), 8.42 (s, 1H)  
ESI: 298 (M+1)<sup>+</sup>, C<sub>11</sub>H<sub>16</sub>N<sub>5</sub>O<sub>3</sub>P

5

**Example 43**

Synthesis of 2-{1-[(2-amino-6-hydroxy-9*H*-purin-9-yl)methyl]cyclopropyl}  
ethylphosphonic acid(Compound 138)

10 The compound prepared in Preparation 26 was reacted according to the same  
procedure as Example 12 to give a compound wherein 6-position of guanine was  
substituted by ethoxy group.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 1.00 (t, 2H), 1.10 (t, 2H), 1.16-1.21 (m, 9H), 3.90 (m, 4H),  
15 4.01 (m, 2H), 4.13 (s, 2H), 4.92 (s, 2H), 5.58 (dd, 1H), 6.49 (dd, 1H), 7.62 (s, 1H)

The compound thus obtained (80mg) was dissolved in methanol and reacted under  
hydrogen atmosphere in the presence of 20mg of 10% Pd/C to give a compound wherein  
double bond was reduced.

20

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.49 (t, 2H), 0.66 (t, 2H), 1.21 (t, 6H), 1.42 (m, 2H), 2.01 (m,  
2H), 3.99 (m, 6H), 4.96 (s, 2H), 7.59 (s, 1H)

The compound thus obtained was reacted according to the same procedure as  
25 Example 1 to give the title compound.

<sup>1</sup>H NMR(MeOH-d<sub>4</sub>) δ 0.60 (t, 2H), 0.87 (t, 2H), 1.47 (m, 2H), 1.97 (m, 2H),  
4.16 (s, 2H), 9.12 (s, 1H)  
ESI: 314 (M+1)<sup>+</sup>, C<sub>11</sub>H<sub>16</sub>N<sub>5</sub>O<sub>4</sub>P

30

**Example 44**

Synthesis of 2-{1-[(2-amino-9*H*-purin-9-yl)methyl]cyclopropyl}propyl  
phosphonic acid(Compound 144)

35 The compound prepared in Preparation 35 was consecutively reacted according to



the same procedure as Preparations 24, 26 and Example 5 to give the title compound.

<sup>1</sup>H NMR(MeOH-d<sub>4</sub>) δ 0.62-0.77 (m, 4H), 1.04 (d, 3H), 1.52 (m, 2H), 1.90 (m, 1H), 4.24 (m, 2H), 8.58 (s, 1H), 8.74 (s, 1H)

ESI: 312 (M+1)<sup>+</sup>, C<sub>12</sub>H<sub>18</sub>N<sub>5</sub>O<sub>3</sub>P

#### Example 45

Synthesis of (E)-2-{1-[(6-amino-9H-purin-9-yl)methyl]cyclopropyl}-1-propenylphosphonic acid(Compound 137)

The compound prepared in Preparation 35 was consecutively reacted according to the same procedure as Preparations 24, 25 and Example 1 to give the title compound.

<sup>1</sup>H NMR(MeOH-d<sub>4</sub>) δ 0.86 (t, 2H), 1.10 (t, 2H), 2.19 (d, 3H), 4.38 (s, 2H), 5.23 (d, 1H), 8.34 (s, 1H), 8.37(s, 1H)

ESI: 310 (M+1)<sup>+</sup>, C<sub>12</sub>H<sub>16</sub>N<sub>5</sub>O<sub>3</sub>P

#### Example 46

Synthesis of 2-{1-[(6-amino-9H-purin-9-yl)methyl]cyclopropyl}propyl phosphonic acid(Compound 143)

The compound prepared in Preparation 35 was consecutively reacted according to the same procedure as Preparations 24, 25 and Example 5 to give the title compound.

<sup>1</sup>H NMR(MeOH-d<sub>4</sub>) δ 0.65 (t, 2H), 0.78 (t, 2H), 0.95 (m, 1H), 1.00 (d, 3H), 1.53 (s, 1H), 1.90 (m, 1H), 4.3 (q, 2H), 8.41 (s, 1H), 8.45 (s, 1H)

ESI: 312 (M+1)<sup>+</sup>, C<sub>12</sub>H<sub>18</sub>N<sub>5</sub>O<sub>3</sub>P

#### Example 47

Synthesis of bis(2,2,2-trifluoroethyl) ({1-[(6-amino-9H-purin-9-yl)methyl]cyclopropyl}oxy)methylphosphonate(Compound 48)

To the methylphosphonic acid prepared in Example 1 (150mg) was added dropwise dichloromethane, 0.73ml of *N,N*-diethyltrimethylsilylamine was added dropwise thereto, and the resulting mixture was stirred at room temperature for 2 hours. Oxalyl

chloride (0.15mL) and 2 drops of dimethylformamide were added to the reaction vessel. The mixture was stirred for further 2 hours and the solvent was removed by distillation under reduced pressure. To the residue were added 10mL of pyridine and 2mL of trifluoroethanol, which was then reacted under stirring for 16 hours. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column to give the title compound.

<sup>1</sup>H NMR(CD<sub>3</sub>OD) δ 1.02 (m, 4H), 4.30 (d, 2H), 4.53 (m, 6H), 8.40 (s, 1H), 8.46(s, 1H)

ESI: 464 [M+H]<sup>+</sup>; C<sub>14</sub>H<sub>16</sub>F<sub>6</sub>N<sub>5</sub>O<sub>4</sub>P

#### Example 48

Synthesis of bis(2,2,2-trifluoroethyl) ({1-[(2-amino-9H-purin-9-yl)methyl]cyclopropyl}oxy)methylphosphonate(Compound 49)

The compound prepared in Example 5 was reacted according to the same procedure as Example 47 to give the title compound.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.88 (m, 2H), 1.04 (m, 2H), 4.07 (d, 2H), 4.22 (s, 2H), 4.33 (m, 4H), 5.06 (br.s, 2H), 7.92 (s, 1H), 8.68 (s, 1H)

ESI: 464 [M+H]<sup>+</sup>, C<sub>14</sub>H<sub>16</sub>F<sub>6</sub>N<sub>5</sub>O<sub>4</sub>P

#### Example 49

Synthesis of bis(2,2,2-trifluoroethyl) [1-({2-amino-[6-(4-methylphenyl)sulfanyl]-9H-purin-9-yl)methyl}cyclopropyl]oxy)methylphosphonate(Compound 62)

The compound prepared in Example 25 was reacted according to the same procedure as Example 47 to give the title compound.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.88 (m, 2H), 1.03 (m, 2H), 2.39 (s, 3H), 4.06 (d, 2H), 4.19 (s, 2H), 4.33 (m, 4H), 4.76 (br.s, 2H), 7.22 (d, 2H), 7.50 (d, 2H), 7.82 (s, 1H)

ESI: 586 [M+H]<sup>+</sup>, C<sub>21</sub>H<sub>22</sub>F<sub>6</sub>N<sub>5</sub>O<sub>4</sub>PS

#### Example 50

Synthesis of bis(2,2,2-trifluoroethyl) [(1-[[2-amino-6-hydroxy-9H-purin-9-yl]

methy]cyclopropyl]oxy]methylphosphonate(Compound 45)

The compound prepared in Example 4 was reacted according to the same procedure as Example 47 to give the title compound.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.91 (m, 2H), 1.05 (m, 2H), 4.08 (d, 2H), 4.17 (s, 2H), 4.35 (m, 4H), 4.70 (s, 2H), 7.69 (s, 1H)  
MW=478 [M+H]<sup>+</sup> 479 C<sub>14</sub>H<sub>16</sub>F<sub>6</sub>N<sub>5</sub>O<sub>5</sub>P

#### Example 51

Synthesis of bis(2,2,2-trifluoroethyl)(1-([2-amino-6-cyclopropylamino-9H-purin-9-yl]methyl)cyclopropyl]oxy]methylphosphonate(Compound 50)

The compound prepared in Example 7 was reacted according to the same procedure as Example 47 to give the title compound.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.60 (br.s, 2H), 0.84 (br.s, 4H), 1.01 (m, 2H), 2.98 (br.s, 1H), 4.05 (d, 2H), 4.14 (m, 4H), 4.70 (br.s, 2H), 5.67 (br.s, 1H), 7.60 (s, 1H)  
ESI: 519, [M+H]<sup>+</sup>, C<sub>17</sub>H<sub>21</sub>F<sub>6</sub>N<sub>6</sub>O<sub>4</sub>P

#### Example 52

Synthesis of ({1-[(2-amino-9H-purin-9-yl)methyl]-2-methylcyclopropyl}oxy)methylphosphonic acid(Compound 98)

The 6-chloroguanine derivative prepared in Preparation 12 was reacted according to the same procedure as Example 5 to give the title compound.

<sup>1</sup>H NMR(MeOH-d<sub>4</sub>) δ 0.68 (t, 1H), 1.13 (m, 1H), 1.21 (d, 3H), 1.42 (t, 1H), 3.84 (t, 1H), 3.97 (t, 1H), 4.40 (d, 1H), 4.66 (d, 1H), 8.63 (s, 1H), 8.73 (s, 1H)  
ESI: 314 (M+1)<sup>+</sup>, C<sub>11</sub>H<sub>16</sub>N<sub>5</sub>O<sub>4</sub>P

**Experiment 1****Measurement of Inhibition Effect against Human Immunodeficiency Virus (HIV)**

The compounds of formula 1 protect cells from the cytopathic effects of HIV infection. This activity was demonstrated in the following assay systems and Table 8.

Cells. The T-lymphoblastoid cell line CEM was used in this study to propagate HIV. The cells were maintained in RPMI 1640 growth medium supplemented with 10% fetal bovine serum plus antibiotics. The CD4-expressing cell line used for HIV plaque assays, HT4-6C, was made by transforming HeLa cells with the human CD4 gene as described in Chesebro and Wehrly, *J. Virology*, 62(10), 3779-3788 (1988). These cells were grown in Dulbecco modified eagle medium (DMEM) containing 10% fetal bovine serum plus antibiotics.

Virus propagation. The laboratory strain of HIV-1 (NL4-3) was grown in CEM cells. Virus stocks were prepared from cleared lysates of concentrated infected cells. At peak cytopathic effect (generally 5 days post-infection) culture supernatants were harvested and stored at  $-80^{\circ}\text{C}$ . Viral infectivity titers were determined in threefold endpoint dilution assays conducted in CEM cells (six wells per dilution). The 50% tissue culture infective dose ( $\text{TCID}_{50}$ ) was calculated using the Reed and Muench equation.

Plaque titration using HT4-6C. Cells are seeded into 24-well multiwells at  $5 \times 10^4$  cells per well and incubated overnight at  $37^{\circ}\text{C}$  in growth medium (DMEM containing 10% fetal bovine serum plus antibiotics). Monolayers were infected with 10-fold dilutions of cell-free NL4-3 virus in 0.2 ml of DMEM and were incubated for 1 h at  $37^{\circ}\text{C}$  to allow virus adsorption. Following this, 0.8 ml of DMEM containing 5% fetal bovine serum plus antibiotics was added to each well, and the cultures were incubated at  $37^{\circ}\text{C}$  for 2 to 3 days. The monolayers were fixed with a 10% formaldehyde solution in phosphate-buffered saline and stained with 0.25% crystal violet in order to visualize virus plaques. Individual foci of multinucleated giant cells (plaques) are obvious when this staining procedure was used. Virus titers were evaluated from plaque numbers and were expressed as PFU per milliliter.

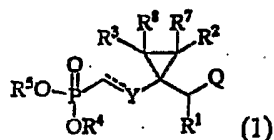
Drug susceptibility assays. Plaque reduction assays were performed by infecting monolayers of HT4-6C cells with 100 to 300 PFU of virus per well in 24-well microdilution plates as described above. Half-log concentrations of inhibitor were added to the culture medium (DMEM containing 5% fetal bovine serum plus antibiotics), and cultures were incubated for 3 days at  $37^{\circ}\text{C}$  prior to fixation and staining as described above.  $\text{ID}_{50}$ s were derived from plots of percentage of plaque reduction versus inhibitor concentration. See Larder *et al.*, *Antimicrob Agents Chemother*, 34(3), 436-41 (March 1990).

Table 8

<u>Compound No.</u>	<u>ID<sub>50</sub> (μM)</u>	<u>ID<sub>25</sub> (μM)</u>
5	≈100	< 10
9	> 100	< 10
10	< 10	< 0.1
98	> 100	< 200
103	> 100	< 10
6	< 10	< 0.1
106	< 100	< 1.0

## CLAIMS

1. A method for treating a HIV infection comprising administering to a patient in need thereof a therapeutically effective amount of a formula 1 compound



in which

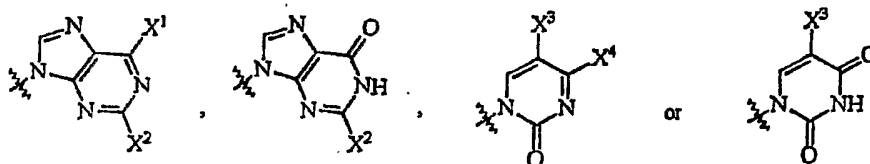
== represents single bond or double bond,

$R^1$ ,  $R^2$ ,  $R^3$ ,  $R^7$  and  $R^8$  independently of one another represent hydrogen, halogen, hydroxy, amino,  $C_1$ - $C_7$ -alkyl,  $C_2$ - $C_6$ -alkenyl,  $C_1$ - $C_5$ -alkylamino,  $C_1$ - $C_5$ -aminoalkyl, or  $C_1$ - $C_5$ -alkoxy,

$R^4$  and  $R^5$  independently of one another represent hydrogen, or represent  $C_1$ - $C_4$ -alkyl optionally substituted by one or more substituents selected from the group consisting of halogen (particularly, fluorine),  $C_1$ - $C_4$ -alkoxy, phenoxy,  $C_7$ - $C_{10}$ -phenylalkoxy and  $C_2$ - $C_5$ -acyloxy, or represent  $C_1$ - $C_7$ -acyl,  $C_6$ - $C_{12}$ -aryl or optionally substituted carbamoyl, or represent  $-(CH_2)_m-OC(=O)-R^6$  wherein m denotes an integer of 1 to 12 and  $R^6$  represents  $C_1$ - $C_{12}$ -alkyl,  $C_2$ - $C_7$ -alkenyl,  $C_1$ - $C_5$ -alkoxy,  $C_1$ - $C_7$ -alkylamino, di( $C_1$ - $C_7$ -alkyl)amino,  $C_3$ - $C_6$ -cycloalkyl, or 3 to 6-membered heterocycle having 1 or 2 hetero atoms selected from a group consisting of nitrogen and oxygen,

Y represents  $-O-$ ,  $-S-$ ,  $-CH(Z)-$ ,  $=C(Z)-$ ,  $-N(Z)-$ ,  $=N-$ ,  $-SiH(Z)-$ , or  $=Si(Z)-$ , wherein Z represents hydrogen, hydroxy or halogen, or represents  $C_1$ - $C_7$ -alkyl,  $C_1$ - $C_5$ -alkoxy, allyl, hydroxy- $C_1$ - $C_7$ -alkyl,  $C_1$ - $C_7$ -aminoalkyl or phenyl,

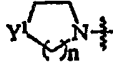
Q represents a group having the following formula:



wherein

$X^1$ ,  $X^2$ ,  $X^3$  and  $X^4$  independently of one another represent hydrogen, amino, hydroxy or halogen, or represent  $C_1$ - $C_7$ -alkyl,  $C_1$ - $C_5$ -alkoxy, allyl, hydroxy- $C_1$ - $C_7$ -alkyl,

phenyl or phenoxy each of which is optionally substituted by nitro or C<sub>1</sub>-C<sub>3</sub>-alkoxy, or represent C<sub>6</sub>-C<sub>10</sub>-arylthio which is optionally substituted by nitro, amino, C<sub>1</sub>-C<sub>6</sub>-alkyl or C<sub>1</sub>-C<sub>4</sub>-alkoxy, or represent C<sub>6</sub>-C<sub>12</sub>-arylamino, C<sub>1</sub>-C<sub>7</sub>-alkylamino, di(C<sub>1</sub>-C<sub>7</sub>-

alkyl)amino, C<sub>3</sub>-C<sub>6</sub>-cycloalkylamino or a structure of  wherein n denotes an integer of 1 or 2 and Y<sup>1</sup> represents O, CH<sub>2</sub> or N-R (R represents C<sub>1</sub>-C<sub>7</sub>-alkyl or C<sub>6</sub>-C<sub>12</sub>-aryl), pharmaceutically acceptable salt, or stereoisomer thereof.

2. The method of claim 1 wherein the pharmaceutically acceptable salt is a salt with sulfuric acid, methanesulfonic acid or hydrohalic acid.

3. The method of claim 1 wherein

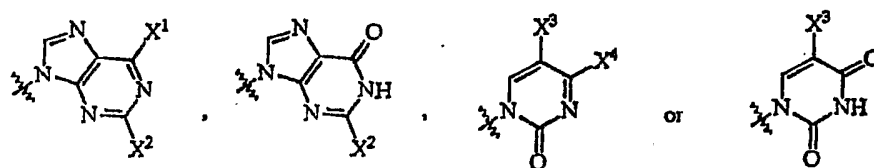
=== represents single bond,

R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>7</sup> and R<sup>8</sup> independently of one another represent hydrogen, fluorine, hydroxy, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>1</sub>-C<sub>3</sub>-alkylamino, C<sub>1</sub>-C<sub>5</sub>-aminoalkyl, or C<sub>1</sub>-C<sub>3</sub>-alkoxy,

R<sup>4</sup> and R<sup>5</sup> independently of one another represent hydrogen, or represent C<sub>1</sub>-C<sub>4</sub>-alkyl optionally substituted by one or more substituents selected from the group consisting of fluorine, C<sub>1</sub>-C<sub>4</sub>-alkoxy and phenoxy, or represent carbamoyl substituted by C<sub>1</sub>-C<sub>5</sub>-alkyl, or represent -(CH<sub>2</sub>)<sub>m</sub>-OC(=O)-R<sup>6</sup> wherein m denotes an integer of 1 to 12 and R<sup>6</sup> represents C<sub>1</sub>-C<sub>12</sub>-alkyl, C<sub>2</sub>-C<sub>7</sub>-alkenyl, C<sub>1</sub>-C<sub>3</sub>-alkoxy, C<sub>1</sub>-C<sub>7</sub>-alkylamino, di(C<sub>1</sub>-C<sub>7</sub>-alkyl)amino, C<sub>3</sub>-C<sub>6</sub>-cycloalkyl, or 3 to 6-membered heterocycle having 1 or 2 hetero atoms selected from a group consisting of nitrogen and oxygen,

Y represents -O-, -S-, or -N(Z)-, wherein Z represents hydrogen, hydroxy, C<sub>1</sub>-C<sub>7</sub>-alkyl, or hydroxy-C<sub>1</sub>-C<sub>7</sub>-alkyl,

Q represents a group having the following formula:



wherein

X<sup>1</sup> represents hydrogen, amino, hydroxy or halogen, or represents C<sub>1</sub>-C<sub>7</sub>-alkyl, C<sub>1</sub>-C<sub>3</sub>-alkoxy, hydroxy-C<sub>1</sub>-C<sub>7</sub>-alkyl or phenoxy each of which is optionally substituted by nitro or C<sub>1</sub>-C<sub>3</sub>-alkoxy, or represents C<sub>6</sub>-C<sub>10</sub>-arylthio which is optionally substituted by nitro, amino, C<sub>1</sub>-C<sub>6</sub>-alkyl or C<sub>1</sub>-C<sub>4</sub>-alkoxy, or represents C<sub>6</sub>-C<sub>12</sub>-arylamino, C<sub>1</sub>-C<sub>7</sub>-alkylamino, di(C<sub>1</sub>-C<sub>7</sub>-alkyl)amino, C<sub>3</sub>-C<sub>6</sub>-cycloalkylamino or a structure of



wherein  $n$  denotes an integer of 1 or 2 and  $Y^1$  represents O,  $CH_2$  or N-R (R represents  $C_1$ - $C_7$ -alkyl), and

$X^2$ ,  $X^3$  and  $X^4$  independently of one another represent hydrogen, amino, hydroxy, halogen,  $C_1$ - $C_7$ -alkyl,  $C_1$ - $C_3$ -alkoxy, or  $C_1$ - $C_7$ -alkylamino.

5,

4. The method of claim 1, wherein the compound is selected from  
 ({1-[(6-amino-9H-purin-9-yl)methyl]cyclopropyl}oxy)methylphosphonic acid  
 (Compound 1);

10 3-[(1-[(6-amino-9H-purin-9-yl)methyl]cyclopropyl}oxy)methyl]-8,8-dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate(Compound 2);

{1-[(2-amino-6-chloro-9H-purin-9-yl)methyl]cyclopropyl}oxy)methylphosphonic acid(Compound 3);

15 3-[(1-[(2-amino-6-chloro-9H-purin-9-yl)methyl]cyclopropyl}oxy)methyl]-8,8-dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate(Compound 4);

{1-[(2-amino-6-hydroxy-9H-purin-9-yl)methyl]cyclopropyl}oxy)methylphosphonic acid(Compound 5);

3-[(1-[(2-amino-6-hydroxy-9H-purin-9-yl)methyl]cyclopropyl}oxy)methyl]-8,8-dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate(Compound 6);

20 {1-[(2-amino-9H-purin-9-yl)methyl]cyclopropyl}oxy)methylphosphonic acid  
 (Compound 9);

3-[(1-[(2-amino-9H-purin-9-yl)methyl]cyclopropyl}oxy)methyl]-8,8-dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate(Compound 10);

{1-[(2-amino-6-cyclopropylamino-9H-purin-9-yl)methyl]cyclopropyl}oxy)methyl phosphonic acid(Compound 11);

25 [(1-[(2-amino-6-(dimethylamino)-9H-purin-9-yl)methyl]cyclopropyl}oxy)methyl phosphonic acid(Compound 15);

3-[(1-[(2-amino-6-(dimethylamino)-9H-purin-9-yl)methyl]cyclopropyl}oxy)methyl]-8,8-dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate(Compound 16);

30 [(1-[(2-amino-6-(isopropylamino)-9H-purin-9-yl)methyl]cyclopropyl}oxy)methyl phosphonic acid(Compound 17);

3-[(1-[(2-amino-6-(isopropylamino)-9H-purin-9-yl)methyl]cyclopropyl}oxy)methyl]-8,8-dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate(Compound 18);

35 {1-[(2,6-diamino-9H-purin-9-yl)methyl]cyclopropyl}oxy)methylphosphonic acid  
 (Compound 19);



- 3-[(1-[(2,6-diamino-9H-purin-9-yl)methyl]cyclopropyl)oxy)methyl]-8,8-dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate(Compound 20);  
 ({1-[(2-amino-6-methoxy-9H-purin-9-yl)methyl]cyclopropyl}oxy)methylphosphonic acid (Compound 21);
- 5 3-[(1-[(2-amino-6-methoxy-9H-purin-9-yl)methyl]cyclopropyl)oxy)methyl]-8,8-dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate(Compound 22);  
 ({1-[(2-amino-6-ethoxy-9H-purin-9-yl)methyl]cyclopropyl}oxy)methylphosphonic acid (Compound 23);
- 10 3-[(1-[(2-amino-6-ethoxy-9H-purin-9-yl)methyl]cyclopropyl)oxy)methyl]-8,8-dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate(Compound 24);  
 [(1-[(5-methyl-2,4-dioxo-3,4-dihydro-1(2H)-pyrimidinyl)methyl]cyclopropyl)oxy]methylphosphonic acid(Compound 31);  
 8,8-dimethyl-3-[(1-[(5-methyl-2,4-dioxo-3,4-dihydro-1(2H)-pyrimidinyl)methyl]cyclopropyl)oxy)methyl]-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate  
 15 (Compound 32);  
 [(1-[(2-amino-6-(4-morpholinyl)-9H-purin-9-yl)methyl]cyclopropyl)oxy)methyl]phosphonic acid(Compound 37);  
 3-[(1-[(2-amino-6-(4-morpholinyl)-9H-purin-9-yl)methyl]cyclopropyl)oxy)methyl]-8,8-dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -  
 20 phosphanon-1-yl pivalate(Compound 38);  
 bis(2,2,2-trifluoroethyl) ((1-[(2-amino-6-hydroxy-9H-purin-9-yl)methyl]cyclopropyl)oxy)methylphosphonate(Compound 45);  
 bis(2,2,2-trifluoroethyl) ((1-[(2-amino-6-chloro-9H-purin-9-yl)methyl]cyclopropyl)oxy)methylphosphonate(Compound 46);  
 25 bis(2,2,2-trifluoroethyl) ((1-[(2,6-diamino-9H-purin-9-yl)methyl]cyclopropyl)oxy)methylphosphonate(Compound 47);  
 bis(2,2,2-trifluoroethyl) ((1-[(6-amino-9H-purin-9-yl)methyl]cyclopropyl)oxy)methylphosphonate(Compound 48);  
 bis(2,2,2-trifluoroethyl) ((1-[(2-amino-9H-purin-9-yl)methyl]cyclopropyl)oxy)methylphosphonate(Compound 49);  
 30 bis(2,2,2-trifluoroethyl) ((1-[(2-amino-6-dimethylamino-9H-purin-9-yl)methyl]cyclopropyl)oxy)methylphosphonate(Compound 52);  
 bis(2,2,2-trifluoroethyl) ((1-[(2-amino-6-isopropylamino-9H-purin-9-yl)methyl]cyclopropyl)oxy)methylphosphonate(Compound 53);  
 35 bis(2,2,2-trifluoroethyl) ((1-[(2-amino-6-methoxy-9H-purin-9-yl)methyl]cyclopropyl)oxy)methylphosphonate(Compound 54);  
 bis(2,2,2-trifluoroethyl) [(1-[(2-amino-6-(4-morpholinyl)-9H-purin-9-yl)methyl]

- cyclopropyl]oxy)methylphosphonate(Compound 58);  
 bis(2,2,2-trifluoroethyl) [(1-{[2-amino-6-(phenylsulfanyl)-9*H*-purin-9-yl]methyl}  
 cyclopropyl]oxy)methylphosphonate(Compound 61);  
 bis(2,2,2-trifluoroethyl) {[1-{[2-amino-6-[(4-methylphenyl)sulfanyl]-9*H*-purin-9-yl]  
 5 methyl]cyclopropyl]oxy}methylphosphonate(Compound 62);  
 bis(2,2,2-trifluoroethyl) {[1-{[2-amino-6-[(4-methoxyphenyl)sulfanyl]-9*H*-purin-9-  
 yl]methyl]cyclopropyl]oxy}methylphosphonate(Compound 63);  
 bis(2,2,2-trifluoroethyl) {[1-{[2-amino-6-[(4-nitrophenyl)sulfanyl]-9*H*-purin-9-yl]  
 methyl]cyclopropyl]oxy}methylphosphonate(Compound 64);  
 10 [(1-{[2-amino-6-(phenylsulfanyl)-9*H*-purin-9-yl]methyl}cyclopropyl]oxy)methyl  
 phosphonic acid(Compound 65);  
 {[1-{[2-amino-6-[(4-methylphenyl)sulfanyl]-9*H*-purin-9-  
 yl]methyl]cyclopropyl]oxy}methylphosphonic acid(Compound 66);  
 3-([1-{[2-amino-6-[(4-methylphenyl)sulfanyl]-9*H*-purin-9-yl]methyl]cyclopropyl]  
 15 oxy)methyl]-8,8-dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate  
 (Compound 68);  
 bis{[(*t*-butoxycarbonyl)oxy)methyl}({1-[2-amino-9*H*-purin-9-yl]methyl]cyclo  
 propyl]oxy)methylphosphonate(Compound 69);  
 bis{[(isopropoxycarbonyl)oxy)methyl}({1-[2-amino-9*H*-purin-9-yl]methyl]cyclo  
 20 propyl]oxy)methylphosphonate (Compound 70);  
 bis{[(ethoxycarbonyl)oxy)methyl}({1-[2-amino-9*H*-purin-9-  
 yl]methyl]cyclopropyl]oxy)methylphosphonate (Compound 71);  
 bis{[(isobutoxycarbonyl)oxy)methyl}({1-[2-amino-9*H*-purin-9-yl]methyl]cyclo  
 propyl]oxy)methylphosphonate (Compound 72);  
 25 3-([1-{[2-amino-9*H*-purin-9-yl]methyl]cyclopropyl]oxy)methyl]-9-methyl-3,7-  
 dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphadec-1-yl 3-methylbutanoate(Compound 74);  
 3-([1-{[2-amino-9*H*-purin-9-yl]methyl]cyclopropyl]oxy)methyl]-8-methyl-3,7-  
 dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl 2-methylpropanoate(Compound 78);  
 3-([1-{[2-amino-6-[(4-methoxyphenyl)sulfanyl]-9*H*-purin-9-  
 30 yl]methyl]cyclopropyl]oxy)methyl]-8,8-dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -  
 phosphanon-1-yl pivalate (Compound 79);  
 3-([1-{[2-amino-9*H*-purin-9-yl]methyl]cyclopropyl]oxy)methyl]-3,7-dioxo-7-(1-  
 pyrrolidinyl)-2,4,6-trioxa-3 $\lambda^5$ -phosphahept-1-yl 1-pyrrolidinecarboxylate(Compound  
 80);  
 35 3-([1-{[2-amino-9*H*-purin-9-yl]methyl]cyclopropyl]oxy)methyl]-3,7-dioxo-7-(1-  
 piperidinyl)-2,4,6-trioxa-3 $\lambda^5$ -phosphahept-1-yl 1-piperidinecarboxylate(Compound  
 81);

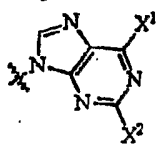
- 3-[(1-[(2-amino-9H-purin-9-yl)methyl]cyclopropyl)oxy)methyl]-7-(4-morpholinyl)-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphahept-1-yl 4-morpholinecarboxylate(Compound 82);
- 5 , bis{[(*t*-butoxycarbonyl)oxy)methyl][(1-[(2-amino-6-hydroxy-9H-purin-9-yl)methyl]cyclopropyl)oxy)methylphosphonate(Compound 83);
- bis{[(isopropoxycarbonyl)oxy)methyl][(1-[(2-amino-6-hydroxy-9H-purin-9-yl)methyl]cyclopropyl)oxy)methylphosphonate(Compound 84);
- 10 bis{[(isopropoxycarbonyl)oxy)methyl}[(1-[(2-amino-[6-(4-methoxyphenyl)sulfanyl]-9H-purin-9-yl)methyl]cyclopropyl)oxy)methylphosphonate(Compound 85);
- 3-[(1-[(2-amino-6-hydroxy-9H-purin-9-yl)methyl]cyclopropyl)oxy)methyl]-7-cyclopentyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphahept-1-yl cyclopentanecarboxylate (Compound 86);
- 15 3-[(1-[(2-amino-[6-(4-nitrophenyl)sulfanyl]-9H-purin-9-yl)methyl]cyclopropyl)oxy)methyl]-8,8-dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate (Compound 87);
- bis{[(isopropoxycarbonyl)oxy)methyl}[(1-[(2-amino-[6-(4-nitrophenyl)sulfanyl]-9H-purin-9-yl)methyl]cyclopropyl)oxy)methylphosphonate(Compound 88);
- 20 , bis{[(isopropoxycarbonyl)oxy)methyl}[(1-[(6-amino-9H-purin-9-yl)methyl]cyclopropyl)oxy)methylphosphonate(Compound 89);
- 3-[(1-[(6-amino-9H-purin-9-yl)methyl]cyclopropyl)oxy)methyl]-9-methyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphadec-1-yl 3-methylbutanoate(Compound 90);
- 3-[(1-[(6-amino-9H-purin-9-yl)methyl]cyclopropyl)oxy)methyl]-7-cyclopentyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphahept-1-yl cyclopentanecarboxylate(Compound 91);
- 25 bis{[(*t*-butoxycarbonyl)oxy)methyl}[(1-[(2-amino-[6-(4-methoxyphenyl)sulfanyl]-9H-purin-9-yl)methyl]cyclopropyl)oxy)methylphosphonate(Compound 92);
- bis{[(*t*-butoxycarbonyl)oxy)methyl}[(1-[(2-amino-[6-(4-nitrophenyl)sulfanyl]-9H-purin-9-yl)methyl]cyclopropyl)oxy)methylphosphonate(Compound 93);
- 30 {[(1-[(2-amino-[6-(4-nitrophenyl)sulfanyl]-9H-purin-9-yl)methyl]cyclopropyl)oxy)methylphosphonic acid(Compound 95);
- {[(1-[(2-amino-[6-(4-methoxyphenyl)sulfanyl]-9H-purin-9-yl)methyl]cyclopropyl)oxy)methylphosphonic acid(Compound 96);
- {[(1-[(2-amino-6-hydroxy-9H-purin-9-yl)methyl]-2-methylcyclopropyl)oxy)methylphosphonic acid(Compound 97);
- 35 , {[(1-[(2-amino-9H-purin-9-yl)methyl]-2-methylcyclopropyl)oxy)methylphosphonic acid(Compound 98);
- {[(1-[(2-amino-[6-(4-methoxyphenyl)sulfanyl]-9H-purin-9-yl)methyl]-2-

- methylcyclopropyl]oxy}methylphosphonic acid(Compound 99);  
 {[1-({2-amino-[6-(4-nitrophenyl)sulfanyl]-9H-purin-9-yl}methyl)-2-methylcyclopropyl]oxy}methylphosphonic acid(Compound 100);  
 {[1-({2-amino-[6-(4-methylphenyl)sulfanyl]-9H-purin-9-yl}methyl)-2-methylcyclopropyl]oxy}methylphosphonic acid(Compound 101);  
 5 ({1-[(2,6-diamino-9H-purin-9-yl)methyl]-2-methylcyclopropyl}oxy)methylphosphonic acid(Compound 102);  
 ({1-[(6-amino-9H-purin-9-yl)methyl]-2-methylcyclopropyl}oxy)methylphosphonic acid(Compound 103);  
 10 3-[(1-[(2-amino-6-hydroxy-9H-purin-9-yl)methyl]-2-methylcyclopropyl]oxy)methyl]-8,8-dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate  
 (Compound 105);  
 3-[(1-[(2-amino-9H-purin-9-yl)methyl]-2-methylcyclopropyl]oxy)methyl]-8,8-dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate(Compound 106);  
 15 3-[(1-[(6-amino-9H-purin-9-yl)methyl]-2-methylcyclopropyl]oxy)methyl]-8,8-dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate(Compound 107);  
 3-[(1-({2-amino-6-[(4-methoxyphenyl)sulfanyl]-9H-purin-9-yl}methyl)-2-methylcyclopropyl]oxy)methyl]-8,8-dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate (Compound 108);  
 20 bis{[(isopropoxycarbonyl)oxy]methyl}[(1-[(2-amino-6-hydroxy-9H-purin-9-yl)methyl]-2-methylcyclopropyl]oxy)methylphosphonate(Compound 109);  
 bis{[(isopropoxycarbonyl)oxy]methyl}[(1-[(2-amino-9H-purin-9-yl)methyl]-2-methylcyclopropyl]oxy)methylphosphonate(Compound 110);  
 25 bis{[(isopropoxycarbonyl)oxy]methyl}[(1-({2-amino-[6-(4-methoxyphenyl)sulfanyl]-9H-purin-9-yl}methyl)-2-methylcyclopropyl]oxy)methylphosphonate(Compound 112);  
 bis{[(t-butoxycarbonyl)oxy]methyl}[(1-({2-amino-[6-(4-methoxyphenyl)sulfanyl]-9H-purin-9-yl}methyl)-2-methylcyclopropyl]oxy)methylphosphonate(Compound 113);  
 30 bis(2,2,2-trifluoroethyl) [(1-({2-amino-6-[(4-methoxyphenyl)sulfanyl]-9H-purin-9-yl}methyl)-2-methylcyclopropyl]oxy)methylphosphonate(Compound 114);  
 bis(2,2,2-trifluoroethyl) [(1-({2-amino-6-[(4-nitrophenyl)sulfanyl]-9H-purin-9-yl}methyl)-2-methylcyclopropyl]oxy)methylphosphonate(Compound 115);  
 bis{[(t-butoxycarbonyl)oxy]methyl}[(1-({2-amino-[6-(4-nitrophenyl)sulfanyl]-9H-purin-9-yl}methyl)-2-methylcyclopropyl]oxy)methylphosphonate(Compound 116);  
 35 bis{[(isopropoxycarbonyl)oxy]methyl}[(1-({2-amino-[6-(4-nitrophenyl)sulfanyl]-9H-purin-9-yl}methyl)-2-methylcyclopropyl]oxy)methylphosphonate(Compound

- 117);  
 3-({1-[(2-amino-6-[(4-nitrophenyl)sulfanyl]-9H-purin-9-yl)methyl]-2-methylcyclopropyl}oxy)methyl)-8,8-dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate(Compound 118);  
 5 ({1-[(2-amino-6-hydroxy-9H-purin-9-yl)methyl]cyclopropyl}amino)methyl phosphonic acid(Compound 119);  
 ({1-[(2-amino-9H-purin-9-yl)methyl]cyclopropyl}amino)methylphosphonic acid(Compound 120);  
 ({1-[(6-amino-9H-purin-9-yl)methyl]cyclopropyl}amino)methylphosphonic acid(Compound 121);  
 10 [{1-[(2-amino-6-hydroxy-9H-purin-9-yl)methyl]cyclopropyl}(methyl)amino]methyl phosphonic acid(Compound 122);  
 [{1-[(6-amino-9H-purin-9-yl)methyl]cyclopropyl}(ethyl)amino]methylphosphonic acid(Compound 125);  
 15 3-{{{1-[(6-amino-9H-purin-9-yl)methyl]cyclopropyl}(methyl)amino}methyl}-8,8-dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate(Compound 126);  
 bis{[(isopropoxycarbonyl)oxy]methyl}[{1-[(6-amino-9H-purin-9-yl)methyl]cyclopropyl}(methyl)amino]methylphosphonate(Compound 127);  
 3-{{{1-[(2-amino-9H-purin-9-yl)methyl]cyclopropyl}(ethyl)amino]methyl}-8,8-dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate(Compound 129);  
 20 2-{1-[(2-amino-6-hydroxy-9H-purin-9-yl)methyl]cyclopropyl}ethylphosphonic acid(Compound 138);  
 2-{1-[(2-amino-9H-purin-9-yl)methyl]cyclopropyl}ethylphosphonic acid(Compound 139);  
 25 2-{1-[(6-amino-9H-purin-9-yl)methyl]cyclopropyl}ethylphosphonic acid(Compound 140);  
 2-[1-[(2-amino-6-[(4-methylphenyl)sulfanyl]-9H-purin-9-yl)methyl]cyclopropyl]ethylphosphonic acid(Compound 141);  
 2-{1-[(2-amino-6-hydroxy-9H-purin-9-yl)methyl]cyclopropyl}propylphosphonic acid(Compound 142);  
 30 2-{1-[(6-amino-9H-purin-9-yl)methyl]cyclopropyl}propylphosphonic acid (Compound 143);  
 2-{1-[(2-amino-9H-purin-9-yl)methyl]cyclopropyl}propylphosphonic acid (Compound 144);  
 35 3-(2-{1-[(6-amino-9H-purin-9-yl)methyl]cyclopropyl}propyl)-8,8-dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate(Compound 145);  
 ({1-[(2-amino-6-hydroxy-9H-purin-9-yl)methyl]-2,2-dimethylcyclopropyl}oxy)

methylphosphonic acid(Compound 146);  
 ({1-[(2-amino-9*H*-purin-9-yl)methyl]-2,2-dimethylcyclopropyl}oxy)methyl  
 phosphonic acid(Compound 147);  
 ({1-[(6-amino-9*H*-purin-9-yl)methyl]-2,2-dimethylcyclopropyl}oxy)methyl  
 phosphonic acid(Compound 148);  
 3-[(1-[(2-amino-6-hydroxy-9*H*-purin-9-yl)methyl]-2,2-dimethylcyclopropyl}oxy)  
 methyl]-8,8-dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate  
 (Compound 149);  
 3-[(1-[(2-amino-9*H*-purin-9-yl)methyl]-2,2-dimethylcyclopropyl}oxy)methyl]-8,8-  
 dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate(Compound 150);  
 3-[(1-[(6-amino-9*H*-purin-9-yl)methyl]-2,2-dimethylcyclopropyl}oxy)methyl]-8,8-  
 dimethyl-3,7-dioxo-2,4,6-trioxa-3 $\lambda^5$ -phosphanon-1-yl pivalate(Compound 151);  
 bis{[(isopropoxycarbonyl)oxy)methyl]}(1-[(6-amino-9*H*-purin-9-yl)methyl]-2,2-  
 dimethylcyclopropyl}oxy)methylphosphonate(Compound 152); and  
 bis{[(isopropoxycarbonyl)oxy)methyl]}(1-[(2-amino-6-hydroxy-9*H*-purin-9-yl)  
 methyl]-2,2-dimethylcyclopropyl}oxy)methylphosphonate(Compound 153).

5. The method of claim 1 wherein  $\equiv$  represents single bond, R<sup>1</sup>, R<sup>3</sup>, R<sup>7</sup> and R<sup>8</sup>  
 independently of one another represent hydrogen, R<sup>2</sup> represents hydrogen or methyl,  
 R<sup>4</sup> and R<sup>5</sup> independently of one another represent t-butylcarbonyloxymethyl,  
 isopropoxycarbonyloxymethyl or 2,2,2-trifluoroethyl, Y represents -O-, Q represents



wherein X<sup>1</sup> represents hydrogen, hydroxy, ethoxy, 4-methoxyphenylthio  
 or 4-nitrophenylthio, and X<sup>2</sup> represents amino.

6. The method of claim 6 wherein R<sup>4</sup> and R<sup>5</sup> are t-butylcarbonyloxymethyl and X<sup>1</sup> is  
 hydrogen or hydroxy.  
 7. The method of claim 1, further comprising at least one additional therapeutic agent.  
 8. The method of claim 7, wherein the additional therapeutic agent is an antiviral agent.  
 9. The method of claim 1, wherein the patient is a mammal.  
 10. The method of claim 9, wherein the mammal is a human.

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US2005/005209

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/675 A61P31/18

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, PAJ, BIOSIS, EMBASE, PASCAL, SCISEARCH

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	CHOI, JONG-RYOO ET AL: "A Novel Class of Phosphonate Nucleosides. 9-(1-Phosphonomethoxycyclopropyl)methylguanine as a Potent and Selective Anti-HBV Agent" JOURNAL OF MEDICINAL CHEMISTRY, 47(11), 2864-2869 CODEN: JMCMAR; ISSN: 0022-2623, 2004, XP002336904 page 2864, column 1, paragraph 1 page 2865, column 2, paragraph 1	1-10
A	WO 02/057288 A (LG CHEM INVESTMENT LTD; CHOI, JONG-RYOO; KIM, JEONG-MIN; ROH, KEE-YOON) 25 July 2002 (2002-07-25) cited in the application	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*Z\* document member of the same patent family

Date of the actual completion of the international search

20 July 2005

Date of mailing of the international search report

03/08/2005

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Friederich, M

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2005/005209

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: —  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claims 1-10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No  
PCT/US2005/005209

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		EP 1358198 A1	05-11-2003
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		US 2004063668 A1	01-04-2004
		ZA 200304181 A	06-10-2004
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