NEW ANTI-VIRAL NUCLEOSIDE ANALOGS

The present invention relates to a series of novel nucleoside analogs which have been shown to possess antiviral activity, in particular against viruses of the family of the Picornaviridae. The invention therefore relates to the new nucleoside analogs, methods for their preparation, pharmaceutical compositions comprising them and to the nucleoside analogs for use as a medicament, more in particular antiviral medicament.
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FIELD OF THE INVENTION

The present invention relates to a series of novel nucleoside analogs which have been shown to possess antiviral activity, in particular against viruses of the family of the Picornaviridae. The invention therefore relates to the new nucleoside analogs, methods for their preparation, pharmaceutical compositions comprising them and to the nucleoside analogs for use as a medicament, more in particular antiviral medicament.

BACKGROUND OF THE INVENTION

Picornaviridae are small, non-enveloped viruses containing a single-stranded (+)-sense RNA genome of 7.5kb, which is covalently linked to a small viral protein (VPg) at its 5' end and polyadenylated at its 3' end. The genomic RNA has a long, highly structured 5' noncoding region that contains the internal ribosome entry site (IRES) necessary for translation initiation, and a shorter 3' noncoding region preceding the poly(A) tract, which are both thought to be involved in RNA replication and translation. The coding region encodes a single polyprotein that will eventually be cleaved to generate 4 structural and 7 non-structural proteins. The icosahedral capsid of the virus is formed by 60 protomers, each one assembled by the 4 structural proteins, designated VP1-4. The non-structural region comprises two proteases, the viral RNA-dependent RNA polymerase (RdRp) and 4 other mature proteins that, either cleaved or as a precursor, are involved in viral replication.

Picornaviruses are a family of small RNA viruses comprising some important pathogens of humans and animals. Transmission usually occurs mechanically. There are ten genera, being Aphthovirus (Foot-and-Mouth Disease Virus), Cardiovirus (Encephalomyocarditis virus + and Theilovirus), Enterovirus (Human Enterovirus A, B, C and D, Bovine Enterovirus, Porcine Enterovirus and Poliovirus), Erbovirus, Duck Hepatitis virus,
Hepatovirus (Avian Encephalomyelitis Virus, Hepatitis A virus +), Kobuvirus, Parecho virus, Rhino virus and Tescho virus.

Enteroviruses and rhinoviruses are implicated in a wide range of infections in humans (and animals). Among the genus of enteroviruses are coxsackieviruses, which are reported to be associated with the development of myocarditis, pancreatitis, meningitis and encephalitis. Other important prototypes amongst the enteroviruses are poliovirus, which can lead to paralytic poliomyelitis, and echo virus, causing aseptic meningitis or encephalomyelitis. Rhinoviruses are the most important etiological factor associated with the common cold, and although often mild and self-limiting, rhinovirus infections have an enormous socio-economical impact. To the genus hepatovirus belongs the hepatitis A virus, a virus that is causing infectious hepatitis in man. The aphantovirus, food and mouth disease virus and the enterovirus swine vesicular virus are important pathogens in livestock.

There is currently no approved antiviral therapy for the treatment of picornaviral infections in man or animals. Therefore, there is still a stringent need in the art for potent inhibitors of Picornaviridae. Therefore a goal of the present invention is to satisfy this urgent need by identifying efficient and non-harmful pharmacetically active ingredients and combination of ingredients for the treatment of Picornaviridae infections in animals and in humans.

The present invention relates to new nucleoside analogs and to their use as anti-viral agents. The prior art, namely by Hrebabecky H. in Collection of Czechoslovak Chemical Communications 2005, 70(1), p 103-123, describes nucleoside analogs being 9-(6-substituted or 6,8-disubstituted or 2,6-disubstituted -9H-purin-9-yl)-5-oxatricyclo[4.2.1.0^3,7]nonane-3-methanols such as the 6-amino-9H-purin-9-yl; the 2,6-diamino-9H-purin-9-yl; 6-(dimethylamino)-9H-purin-9-yl; 6-cyclopropylamino-9H-purin-9-yl; the 6-amino-8-methyl-9H-purin-9-yl derivatives of 5-oxatricyclo[4.2.1.0^3,7]nonane-3-methanols. Also the 6-chloro-8-methyl-9H-purin-9-yl; 6-chloro-9H-purin-9-yl and 2-amino-6-chloro-9H-purin-9-yl derivative of 5-oxatricyclo[4.2.1.0^3,7]nonane-3-methanol are described.
The prior art also describes the compounds 9-[(2-amino-6-chloropyrimidin-4-yl)amino]-5-oxatricyclo[4.2.1.0\(^3\)]nonane-3-methanol, 9-[(5-amino-6-chloropyrimidin-4-yl)amino]-5-oxatricyclo[4.2.1.0\(^3\)]nonane-3-methanol, 9-[(2-amino-6-chloro-5-[(4-chlorophenyl)azo]pyrimidin-4-yl]-amino)-5-oxatricyclo[4.2.1.0\(^3\)]nonane-3-methanol and 9-[(2,5-diamino-6-chloro-pyrimidin-4-yl]-amino)-5-oxatricyclo[4.2.1.0\(^3\)]nonane-3-methanol.

From these prior art 5-oxa-tricyclo[4.2.1.0\(^3\)]nonane-3-methanols no mention is made of any biological activity.

**SUMMARY OF THE INVENTION**

In the present invention, new anti-viral, more in particular anti-Picornaviridae nucleoside analogs are provided. The nucleoside analogs have a substituted or unsubstituted bridged carbocycle and it has been shown that they possess anti-viral activity, more specifically against Picornaviridae. The present invention demonstrates that the nucleoside analogs inhibit the replication of Picornaviridae. Therefore, these nucleoside analogs constitute a new potent class of anti-viral agents that can be used in the treatment and prevention of viral infections in animals, mammals and humans, more specifically for the treatment and prevention of Picornaviridae.

The present invention provides novel nucleoside analogs which have virus replication inhibiting properties. The invention also provides methods for preparation of all such nucleoside analogs and provides pharmaceutical compositions comprising the nucleoside analogs. The invention further relates to the novel nucleoside analogs for use as a medicament and for the prevention and/or treatment of viral infections in subjects (including animals, mammals and humans). The invention also relates to the use of the nucleoside analogs in the manufacture of a medicament for the prevention or treatment of subjects suffering from Picornaviridae infection, as well as for treatment of other viral infections of subjects suffering from such infections. The invention also provides
methods of treatment or prevention of a viral infection in a subject, including animals, mammals and humans.

One aspect of the present invention is the provision of novel nucleoside analogs, said nucleoside analog having a structure according to the formula (A'):

\[
\begin{align*}
R^3 & \quad (3) \\
R^2 & \quad (1) \\
R^1 & \quad (2) \\
R^4 & \\
R^5 & \\
B & \\
W & \\
Z & \\
X & \\
Y & \\
\end{align*}
\]

(A')

wherein:
- \( B \) is selected from an unsubstituted or substituted pyrimidine or purine heterocycle; whereby the purine heterocycle is not substituted with -CF\(_3\) in its 2-position;
- \( W \) is selected from (-CH\(_2\))\(_n\), wherein \( n \) is selected from 0 or 1;
- \( X \) is not present (thereby forming a bond between carbon (2) and carbon (3)) or is selected from -CR\(^6\)R\(^6\)\(^-\) or -CR\(^7\)R\(^7\)\(^-\) C R\(^8\)R\(^8\)\(^-\);
- \( Y \) is not present (thereby forming a bond between carbon (2) and carbon (1)) or is selected from -CR\(^9\)R\(^9\)\(^-\) or -CR\(^{10}\)R\(^{10}\)\(^-\) C R\(^{11}\)R\(^{11}\)\(^-\);
- \( Z \) is selected from -CR\(^{12}\)R\(^{12}\)\(^-\) \(-\)CR\(^{13}\)R\(^{13}\) \(-\)C R\(^{14}\)R\(^{14}\)\(^-\) \(-\)CR\(^{15}\) \(-\)CR\(^{15}\)\(^-\) \(-\)O\(^-\) \(-\) and \(-\)S\(^-\);
- each of \( R^1 \) and \( R^4 \) is independently selected from hydrogen; alkyl; -OH; phosphate; phosphate-alkylene; phosphonate; or phosphonate-alkylene; wherein said alkyl or alkylene can independently be substituted with one or more -OH, aryl or halogen; and wherein said alkyl or alkylene can contain a heteroatom in or at the end of the alkyl chain, said heteroatom selected from O, S and N; and thereby the term phosphate-alkylene includes phosphate-alkoxy and the term phosphonate-alkylene includes phosphonalkyloxy (such as phosphonylmethyl ether);
- each of \( R^2 \) and \( R^3 \) is independently selected from hydrogen; alkyl; -OH; phosphate; phosphate-alkylene; phosphonate; or phosphonate-alkylene- (such as phosphonylmethyl ether); or when taken together with \( R^6 \), \( R^6' \), \( R^7 \) or \( R^7' \) forms a double bond or -O- (thereby forming an epoxy); wherein said alkyl or alkylene can independently be
substituted with one or more -OH; aryl; -OOC-aryl; or halogen; and wherein said alkyl or alkylene can contain a heteroatom in or at the end of the alkyl chain, said heteroatom selected from O, S and N;

- or R² or R³ when taken together with R⁶ or R⁶' is -CH₂-CH₂-CH₂-; -CH₂-CH₂-CH₂-CH₂- or -CHR⁻¹⁶=CHR⁻¹⁷-CHR⁻¹⁸=CHR⁻¹⁹-, wherein each of R⁻¹⁶, R⁻¹⁷, R⁻¹⁸ and R⁻¹⁹ is independently selected from hydrogen; F; Cl; Br or alkyl;

- R⁵ is hydrogen or when taken together with R⁹, R⁹', R¹¹ or R¹¹' forms a double bond;

- each of R⁶ and R⁶' is independently selected from hydrogen; alkyl; or -OH; or taken together with R⁹, R⁹', R¹⁰⁰, R¹⁰⁰', R¹¹ or R¹¹' is -CH₂-O- or -O-CH₂ thereby forming a 5-membered ring; or when taken together with one of R² or R³ forms a double bond or -O- (thereby forming an epoxy); wherein said alkyl can be substituted with one or more -OH; aryl; or halogen;

- each of R⁷ and R⁷' is independently selected from hydrogen; alkyl; or -OH; or when taken together with one of R² or R³ forms a double bond or -O- (thereby forming an epoxy); or when taken together with R⁹, R⁹', R¹⁰⁰, R¹⁰⁰', R¹¹ or R¹¹' is -CH₂-O- or -O-CH₂ thereby forming a 5-membered ring; wherein said alkyl can be substituted with one or more -OH; aryl; or halogen;

- each of R⁸ and R⁸' is independently selected from hydrogen; alkyl; or -OH; or taken together with R⁹, R⁹', R¹⁰⁰, R¹⁰⁰', R¹¹ or R¹¹' is -CH₂-O- or -O-CH₂ thereby forming a 5-membered ring; wherein said alkyl can be substituted with one or more -OH; aryl; or halogen;

- each of R⁹ and R⁹' is independently selected from hydrogen; alkyl; or -OH; or taken together with R⁶, R⁶', R⁷, R⁷', R⁸ or R⁸' is -CH₂-O- or -O-CH₂ thereby forming a 5-membered ring; or when taken together with R⁵ forms a double bond; wherein said alkyl can be substituted with one or more -OH; aryl; or halogen;

- each of R¹⁰ and R¹⁰' is independently selected from hydrogen; alkyl; or -OH; or taken together with R⁶, R⁶', R⁷, R⁷', R⁸ or R⁸' is -CH₂-O- or -O-CH₂ thereby forming a 5-membered ring; or when taken together with R⁵ forms a double bond;

- each of R¹¹ and R¹¹' is independently selected from hydrogen; alkyl; or -OH; or when taken together with R⁵ forms a double bond; or taken together with R⁶, R⁶', R⁷, R⁷', R⁸ or
R^8_I is -CH_2-O- or -O-CH_2- thereby forming a 5-membered ring; wherein said alkyl can be substituted with one or more -OH; aryl; or halogen;
- each of R^{12}, R^{13}, R^{13'}, R^{14}, R^{15}, R^{15'} is independently selected from hydrogen or alkyl; wherein said alkyl can be substituted with one or more -OH; aryl; or halogen;
- the selections for the X, Y and R-groups like -CR_2R_3^- C R^8R^8'-; -CH_2-O- or -CH_2- O- or -O-CH_2- have to be placed in formula (I) from left to right; and isomers (in particular stereo-isomers or tautomers), solvates or pharmaceutically acceptable salts thereof or prodrugs thereof.

Preferably each of R^6 and R^6' is independently selected from hydrogen; alkyl; or -OH; or taken together with R^9, R^9', R^{10}, R^{10'} or R^{11'} is -CH_2-O- or -O-CH_2- thereby forming a 5-membered ring; or when taken together with one of R^2 or R^3 forms a double bond or -O- (thereby forming an epoxy); wherein said alkyl can be substituted with one or more aryl; or halogen.

A particular embodiment of this aspect relates to the nucleoside analogs according to formula (A):

![Diagram](A)

wherein:
- B is selected from an unsubstituted or substituted pyrimidine or purine heterocycle;
- W is selected from (-CH_2-)_n, wherein n is selected from O or 1;
- X is not present (thereby forming a bond between carbon (2) and carbon (3)) or is selected from -CR_6R_6'- or -CR_7R_7'- C R^8R^8';
- Y is not present (thereby forming a bond between carbon (2) and carbon (1)) or is selected from -CR_9R_9'- or -CR_10R_10'- C R_{11}R_{11}';
- Z is selected from -CR_12R_12'; -CR_13R_13'- C R_{14}R_{14}'; -CR_{15}=CR_{15'}'-0'; and -S-;
- each of R¹ and R⁴ is independently selected from hydrogen; alkyl; -OH; phosphate; phosphate-alkylene; phosphonate; or phosphonate-alkylene; wherein said alkyl or alkylene can be substituted with one or more -OH, aryl, halogen; and wherein said alkyl or alkylene can contain a heteroatom in or at the end of the alkyl chain, said heteroatom selected from O, S and N;

- each of R² and R³ is independently selected from hydrogen; alkyl; -OH; phosphate; phosphate-alkylene; phosphonate; or phosphonate-alkylene; or when taken together with R⁶, R⁶', R⁷ or R⁷' forms a double bond or -O- (thereby forming an epoxy); wherein said alkyl or alkylene can be substituted with one or more -OH; aryl; arylalkyl (such as trityl); -OOC-aryl; or halogen; and wherein said alkyl or alkylene can contain a heteroatom in or at the end of the alkyl chain, said heteroatom selected from O, S and N;

- or R² or R³ when taken together with R⁶ or R⁶' is -CH₂⁻CH₂⁻CH₂⁻; -CH₂⁻CH₂⁻CH₂⁻CH₂⁻ or -CHR₁⁶=CHR₁⁷⁻CHR₁⁸=CHR₁⁹⁻, wherein each of R₁⁶, R₁⁷, R₁⁸ and R₁⁹ is independently selected from hydrogen; F; Cl; Br or alkyl;

- R⁵ is hydrogen or when taken together with R⁹, R⁹', R¹¹ or R¹¹' forms a double bond;

- each of R⁶ and R⁶' is independently selected from hydrogen; alkyl; or -OH; or taken together with R⁹, R⁹', R¹⁰ or R¹⁰' is -CH₂⁻O⁻ or -O-CH₂⁻ thereby forming a 5-membered ring; or when taken together with one of R² or R³ forms a double bond or -O- (thereby forming an epoxy); wherein said alkyl can be substituted with one or more -OH; aryl; or halogen;

- each of R⁷ and R⁷' is independently selected from hydrogen; alkyl; or -OH; or when taken together with one of R² or R³ forms a double bond or -O- (thereby forming an epoxy); wherein said alkyl can be substituted with one or more -OH; aryl; or halogen;

- each of R⁸ and R⁸' is independently selected from hydrogen; alkyl; or -OH; or taken together with R⁹, R⁹', R¹⁰ or R¹⁰' is -CH₂⁻O⁻ or -O-CH₂⁻ thereby forming a 5-membered ring; wherein said alkyl can be substituted with one or more -OH; aryl; or halogen;

- each of R⁹ and R⁹' is independently selected from hydrogen; alkyl; or -OH; or taken together with R⁶, R⁶', R⁸ or R⁸' is -CH₂⁻O⁻ or -O-CH₂⁻ thereby forming a 5-membered ring; or when taken together with R⁵ forms a double bond; wherein said alkyl can be substituted with one or more -OH; aryl; or halogen;
- each of $R^{10}$ and $R^{10'}$ is independently selected from hydrogen; alkyl; or -OH; or taken together with $R^6, R^6', R^8$ or $R^8'$ is -CH$_2$O- or -0-CH$_2$- thereby forming a 5-membered ring;
- each of $R^{11}$ and $R^{11'}$ is independently selected from hydrogen; alkyl; or -OH; or when taken together with $R^5$ forms a double bond; wherein said alkyl can be substituted with one or more -OH; aryl; or halogen;

- each of $R^{12}, R^{12'}, R^{13}, R^{14}, R^{14'}, R^{15}, R^{15'}$ is independently selected from hydrogen or alkyl; wherein said alkyl can be substituted with one or more -OH; aryl; or halogen;
- the selections for the $X, Y$ and $R$-groups like -CR$_7$R$_7'$- C R$_8$R$_8'$- ; -CH$_2$O- or -CH$_2$- O- or -0-CH$_2$- have to be placed in formula I from left to right;

and isomers (in particular stereo-isomers or tautomers), solvates or pharmaceutically acceptable salts thereof or prodrugs thereof;

provided that the nucleoside analog is not a 9-(6-substituted or 6,8-disubstituted or 2,6-disubstituted -9H-purin-9-yl)-5-oxa-tricyclo[4.2.1.0$_3^3$]nonane-3-methanol,

more in particular is not the 6-amino-9H-purin-9-yl; 6-(dimethylamino)-9H-purin-9-yl; 6-cyclopropylamino-9H-purin-9-yl; the 2,6-diamino-9H-purin-9-yl; the 6-amino-8-methyl-9H-purin-9-yl; the 6-chloro-8-methyl-9H-purin-9-yl; the 2-amino-6-chloro-9H-purin-9-yl derivative of 5-oxa-tricyclo[4.2.1.0$_3^3$]nonane-3-methanol.

When reference is made to "B is selected from an unsubstituted or substituted pyrimidine or purine heterocycle" this also includes the analogs and derivatives such as the aza and deaza analogs and substituted derivatives.

In a particular embodiment, the nucleoside analogs are not 9-(6-substituted or 6,8-disubstituted or 2,6-disubstituted -9H-purin-9-yl)-5-oxa-tricyclo[4.2.1.0$_3^3$]nonane-3-methanol (according to Formula N), more in particular are not the 6-amino-9H-purin-9-yl; 6-(dimethylamino)-9H-purin-9-yl; 6-cyclopropylamino-9H-purin-9-yl; the 2,6-diamino-9H-purin-9-yl; the 6-amino-8-methyl-9H-purin-9-yl; the 6-chloro-8-methyl-9H-
purin-9-yl; the 6-chloro-9H-purin-9-yl or the 2-amino-6-chloro-9H-purin-9-yl derivative of 5-oxa-tricyclo[4.2.1.0^3 7]nonane-3-methanol.

(in formula (N), "Sub" refers to hydrogen or a substituent, in a particular embodiment selected from -N(CH^3)_2; -NH(cyclopropyl); halogen (more in particular Cl); alkyl (more in particular methyl); or amino.

Particular embodiments of this aspect are described in the claims and relate to subtypes of nucleoside analogs according to formula A' such as the nucleosides according to formulae (A-2), (A-3) including (A-3a) and (A-3b), (A-4), (A-5) or (A-6).

In a particular embodiment, the nucleoside analogs of the present invention are according to formula (A-2), wherein Y is -CR^9R'^9- and X is -CR^6R'^6-:

wherein
- each of B, W, Z, R^1, R^4, R^{12} and R^{12'}, is according to formula (A);
- each of R^2 and R^3 is independently selected from hydrogen; alkyl; -OH; phosphate; phosphate-alkylene; phosphonate; or phosphonate-alkylene; or when taken together with one of R^6 or R^{6'} forms a double bond or -O- (thereby forming an epoxy); wherein said alkyl or alkylene can be substituted with one or more -OH; aryl; -OOC-aryl; or halogen; and wherein said alkyl or alkylene can contain a heteroatom in or at the end of the alkyl chain, said heteroatom selected from O, S and N; or R^2 or R^3 when taken together with
R^6 or R'^6 is -CH₂-CH₂-CH₂-; -CH₂-CH₂-CH₂-CH₂- or -CHR_{16}=CHR_{17}=CHR_{18}=CHR_{19}-,
wherein each of R_{16}, R_{17}, R_{18} and R_{19} is independently selected from hydrogen; F; Cl; Br
or alkyl;
- R^5 is hydrogen or when taken together with one of R^9 or R'^9 forms a double bond;
- each of R^6 and R'^6 is independently selected from hydrogen; alkyl; or -OH; or taken
together with one of R^9 or R'^9 is -CH₂-O- or -0-CH₂ thereby forming a 5-membered
ring; or when taken together with one of R^2 or R^3 forms a double bond or -O-
(thereby forming an epoxy); wherein said alkyl can be substituted with one or more -OH; aryl; or
halogen;
- each of R^9 and R'^9 is independently selected from hydrogen; alkyl; or -OH; or taken
together with one of R^6 or R'^6 is -CH₂-O- or -0-CH₂ thereby forming a 5-membered
ring; or when taken together with R^5 forms a double bond; wherein said alkyl can be
substituted with one or more -OH; aryl; or halogen.

In a more particular embodiment of formula (A-2),
- W is not present whereby B is directly bonded to carbon (1) or is -CH₂=;
- Z is selected from -CR_{12}R_{12}=-;
- R^1 is hydrogen;
- R^4 is selected from hydrogen or alkyl;
- each of R_{12} and R'_{12} is independently selected from hydrogen or alkyl;
- each of R^2 and R^3 is independently selected from hydrogen; alkyl; -OH; phosphate;
phosphate-alkylene; phosphonate; or phosphonate-alkylene; or when taken together with
one of R^6 or R'^6 forms a double bond or -O- (thereby forming an epoxy); wherein said
alkyl or alkylene can be substituted with one or more -OH; aryl; -OOC-aryl; or halogen;
and wherein said alkyl or alkylene can contain a heteroatom in or at the end of the alkyl
chain, said heteroatom selected from O, S and N; or R^2 or R^3 when taken together with
R^6 or R'^6 is -CH₂-CH₂-CH₂-; -CH₂-CH₂-CH₂-CH₂- or -CHR_{16}=CHR_{17}=CHR_{18}=CHR_{19}-,
wherein each of R_{16}, R_{17}, R_{18} and R_{19} is independently selected from hydrogen; F; Cl; Br
or alkyl;
- R^5 is hydrogen or when taken together with one of R^9 or R'^9 forms a double bond;
- each of R⁶ and R⁶' is independently selected from hydrogen; alkyl; or -OH; or when taken together with one of R² or R³ forms a double bond or -O- (thereby forming an epoxy); wherein said alkyl can be substituted with one or more -OH; aryl; or halogen;
- each of R⁹ and R⁹' is independently selected from hydrogen; alkyl; or -OH; or when taken together with R⁵ forms a double bond; wherein said alkyl can be substituted with one or more -OH; aryl; or halogen.

In yet another more particular embodiment of formula (A-2),
- Z is -CH₂⁻;
- each of R⁴, R², R³, R⁵, R⁶, R⁶', R⁹ and R⁹' are hydrogen.

Another embodiment relates to nucleoside analogs according to formula (A-3a) or (A-3b), wherein R⁶' and R⁹' are taken together to form -0-CH₂⁻ or -CH₂-O-:

wherein
- each of B, W, Z, R¹ and R⁴, is according to formula (A);
- each of R² and R³ is independently selected from hydrogen; alkyl; -OH; phosphate; phosphate-alkylene; phosphonate; or phosphonate-alkylene; or when taken together with one of R⁶ or R⁶' forms a double bond or -O- (thereby forming an epoxy); wherein said alkyl or alkylene can be substituted with one or more -OH; aryl; -OOC-aryl; or halogen; and wherein said alkyl or alkylene can contain a heteroatom in or at the end of the alkyl chain, said heteroatom selected from O, S and N;
- R⁵ is hydrogen or when taken together with one of R⁹ or R⁹' forms a double bond;
- R₆ is selected from hydrogen; alkyl; or -OH; or when taken together with one of R² or R³ forms a double bond or -O- (thereby forming an epoxy); wherein said alkyl can be substituted with one or more -OH; aryl; or halogen;

- R⁹ is selected from hydrogen; alkyl; or -OH; or when taken together with R⁵ forms a double bond; wherein said alkyl can be substituted with one or more -OH; aryl; or halogen.

A more particular embodiment of formula (A-3 a and b),

- Z is selected from -CH₂⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻~-~-

- each of R¹, R⁴, R⁵, R⁶ and R⁹ are hydrogen;

- each of R² and R³ is independently selected from hydrogen; -OH; -OCH₃; phosphonylmethylether; benzyloxymethyl; methoxymethyl and chloromethyl.

Another embodiment, the nucleoside analogs are according to formula (A-4), claim 1, wherein Y is not present and thereby the nucleoside analogs are according to the formula IV,

\[
\begin{array}{c}
\text{R}^1 \\
\text{R}^2 \\
\text{R}^3 \\
\text{R}^4 \\
\text{Z} \\
\text{W} \\
\text{B} \\
\text{X} \\
\text{R}^5 \\
\end{array}
\]

(A-4)

wherein

- each of B, W, X, Z, R¹, R², R³ and R⁴, is according to formula (A);

- R⁵ is hydrogen;

- each of R⁶ and R⁶' is independently selected from hydrogen; alkyl; or -OH; or when taken together with R² or R³ forms a double bond or -O- (thereby forming an epoxy); wherein said alkyl can be substituted with one or more -OH; aryl; or halogen.

A more particular embodiment of formula (A-4),
- X is -CH$_2$–;
- Z is selected from -CH$_2$-CH$_2$-; or -CH$_2$=CH$_2$−;
- each of R$^1$, R$^4$ and R$^5$ are hydrogen;
- each of R$^2$ and R$^3$ is independently selected from hydrogen; -OH; or -OCH$_3$.

phosphonomethylether; benzyloxyethyl; methoxymethyl and chloromethyl.

Another particular embodiment relates to nucleoside analogs according to formula (A-5),
wherein Y is -CR$^{10}$R$^{10'}$-CR$^{11}$R$^{11'}$- and X is not present

wherein
- each of B, W, Z, R$^1$ and R$^4$, is according to formula (A);
- each of R$^2$ and R$^3$ is independently selected from hydrogen; alkyl; -OH; phosphate; phosphate-alkylene; phosphonate; or phosphonate-alkylene; wherein said alkyl or alkylene can be substituted with one or more -OH; aryl; -OOC-aryl; or halogen; and

wherein said alkyl or alkyene can contain a heteroatom in or at the end of the alkyl chain, said heteroatom selected from O, S and N;
- R$^5$ is hydrogen or when taken together with R$^{11}$ or R$^{11'}$ forms a double bond;
- each of R$^{10}$ and R$^{10'}$ is independently selected from hydrogen; alkyl; or -OH;
- each of R$^{11}$ and R$^{11'}$ is independently selected from hydrogen; alkyl; or -OH; or when taken together with R$^5$ forms a double bond; wherein said alkyl can be substituted with one or more -OH; aryl; or halogen.

More particularly, the nucleoside analogs can be according to formula (A-6),
wherein
- the dotted line represents a double line which can be present or not present;
- each of $R^2$, $R^3$, $R^{12}$ and $R^{12'}$ is independently selected from hydrogen or alkyl (more in particular methyl).

In a particular embodiment of the different formulae encoded A (A, A', A-2 to A-23) of the invention, the purine and pyrimidine heterocycles of B are coupled directly to carbon (1) (if W is not present) or are coupled to W as following:
- for purines via their $N^9$ or $N^7$, preferably via $N^9$; and
- for pyrimidines via their $N^3$ or $N^1$, preferably via $N^3$.

In a more particular embodiment of the different formulae encoded A (A, A', A-2 to A-23) of the invention, the purine heterocycles of B are coupled directly to carbon (1) (if W is not present) or are coupled to W via their $N^9$ or $N^7$, preferably via $N^9$.

In another particular embodiment of the different formulae of the invention, $R^2$ is hydrogen, while $R^3$ is selected from hydrogen; alkyl; -OH; phosphate; phosphate-alkylene; phosphonate; or phosphonate-alkylene- (such as phosphonylmethyl ether); or when taken together with $R^6$, $R^6'$, $R^7$ or $R^7'$ forms a double bond or -O- (thereby forming an epoxy); wherein said alkyl or alkylene can be substituted with one or more -OH; aryl; -OOC-aryl; halogen; phosphate; phosphate-alkylene; phosphonate; or phosphonate-alkylene- (such as phosphonylmethyl ether); and wherein said alkyl or alkylene can contain a heteroatom in or at the end of the alkyl chain, said heteroatom selected from O, S and N.

In another particular embodiment of the different formulae of the invention, each of $R^1$ and $R^4$ is independently selected from hydrogen; alkyl; or -OH; wherein said alkyl
can be substituted with -OH, aryl, or halogen; and wherein said alkyl can contain a heteroatom in or at the end of the alkyl chain, said heteroatom selected from O, S and N.

In a further embodiment of the invention, the nucleoside analogs are of general formulae (A-2), (A3-a), (A3-b), (A-4), (A-5) and (A-6):
wherein

- W is selected from (-CH₂)ₙ, wherein n is selected from O or 1;
- X is not present (thereby forming a bond between carbon (2) and carbon (3)) or is selected from -CR⁶R⁶⁻ or -CR⁷R⁷⁻ C R⁸R⁸⁻;
- Z is selected from -CR¹²R¹²⁻; -CR¹³R¹³⁻ C R¹⁴R¹⁴⁻; -CR¹⁵=CRC¹⁵⁻ ; -O⁻; and -S⁻;
- each of R¹ and R⁴ is independently selected from hydrogen; alkyl; -OH; phosphate; phosphate-alkylene; phosphonate; or phosphonate-alkylene; wherein said alkyl or alkylene can be substituted with one or more -OH, aryl, halogen; and wherein said alkyl or alkylene can contain a heteroatom in or at the end of the alkyl chain, said heteroatom selected from O, S and N;
- each of R² and R³ is independently selected from hydrogen; alkyl; -OH; phosphate; phosphate-alkylene; phosphonate; or phosphonate-alkylene; or when taken together with R⁶, R⁶', R⁷ or R⁷' forms a double bond or -O⁻ (thereby forming an epoxy); wherein said alkyl or alkylene can be substituted with one or more -OH; aryl; arylalkyl (such as trityl); -OOC-aryl; or halogen; and wherein said alkyl or alkylene can contain a heteroatom in or at the end of the alkyl chain, said heteroatom selected from O, S and N;
- or R² or R³ when taken together with R⁶ or R⁶' is -CH₂-CH₂-CH₂-; -CH₂-CH₂-CH₂-
CH₂- or -CHR ¹⁶=CHR ¹⁷-CHR ¹⁸=CHR ¹⁹-, wherein each of R¹⁶, R¹⁷, R¹⁸ and R¹⁹ is
independently selected from hydrogen; F; Cl; Br or alkyl;
- R⁴ is hydrogen or when taken together with R⁹, R⁹', R¹¹ or R¹¹' forms a double bond;
- each of R⁶ and R⁶' is independently selected from hydrogen; alkyl; or -OH; or taken
together with R⁹, R⁹', R¹⁰ or R¹⁰' is -CH₂-O- or -O-CH₂- thereby forming a 5-
membered ring; or when taken together with one of R² or R³ forms a double bond or -O-
(thereby forming an epoxy); wherein said alkyl can be substituted with one or more -OH;
aryl; or halogen;
- each of R⁷ and R⁷' is independently selected from hydrogen; alkyl; or -OH; or when
taken together with one of R² or R³ forms a double bond or -O- (thereby forming an
epoxy); wherein said alkyl can be substituted with one or more -OH; alkyl; or halogen;
- each of R⁸ and R⁸' is independently selected from hydrogen; alkyl; or -OH; or taken
together with R⁹, R⁹', R¹⁰ or R¹⁰' is -CH₂-O- or -O-CH₂- thereby forming a 5-
membered ring; wherein said alkyl can be substituted with one or more -OH; alkyl; or
halogen;
- each of R⁹ and R⁹' is independently selected from hydrogen; alkyl; or -OH; or taken
together with R⁶, R⁶', R⁸ or R⁸' is -CH₂-O- or -O-CH₂- thereby forming a 5-membered
ring; or when taken together with R⁵ forms a double bond; wherein said alkyl can be
substituted with one or more -OH; alkyl; or halogen;
- each of R¹⁰ and R¹⁰' is independently selected from hydrogen; alkyl; or -OH; or taken
together with R⁶, R⁶', R⁸ or R⁸' is -CH₂-O- or -O-CH₂- thereby forming a 5-membered
ring;
- each of R¹¹ and R¹¹' is independently selected from hydrogen; alkyl; or -OH; or when
taken together with R⁵ forms a double bond; wherein said alkyl can be substituted with
one or more -OH; alkyl; or halogen;
- each of R¹², R¹²', R¹³, R¹⁴, R¹⁴', R¹⁵, R¹⁵' is independently selected from hydrogen
or alkyl; wherein said alkyl can be substituted with one or more -OH; alkyl; or halogen;
- the selections for the X, Y and R-groups like -CR ⁷R⁷'- C R⁸R⁸'-; -CH₂-O- or -CH₂-
O- or -O-CH₂- have to be placed in formula I from left to right;
and isomers (in particular stereo-isomers or tautomers), solvates or pharmaceutically acceptable salts thereof or prodrugs thereof;

provided that the nucleoside analog is not a 9-(6-substituted or 6,8-disubstituted or 2,6-disubstituted -9H-purin-9-yl)-5-oxa-tricyclo[4.2.1.0^3,7]nonane-3-methanol;

and

wherein B is according to formula (P-I),

![Chemical Structure](image)

(P-I)

each of \( R^{20} \) and \( R^{21} \) are independently selected from hydrogen; F; Cl; Br; I; -N\(_3\); -NH\(_2\); -OH; -0-CH\(_3\); -0-C\(_2\)H\(_5\); -0-CH\(_2\)-CH\(_2\)-CH\(_3\); -O-CH(CH\(_3\))\(_2\); -O-C(CH\(_3\))\(_3\); -SH; -S-CH\(_3\); -S-C\(_2\)H\(_5\); -S-CH\(_2\)-CH\(_2\)-CH\(_3\); -S-CH(CH\(_3\))\(_2\); -S-C(CH\(_3\))\(_3\); -CF\(_3\); -NO\(_2\); -COOH; -COO-CH\(_3\); -COO-C\(_2\)H\(_5\); -COO-CH(CH\(_3\))\(_2\); -COO-C(CH\(_3\))\(_3\); -SO\(_2\)-CH\(_3\); -SO\(_2\)-C\(_2\)H\(_5\); -SO\(_2\)-CH\(_2\)-CH\(_2\)-CH\(_3\); -SO\(_2\)-CH(CH\(_3\))\(_2\); -SO\(_2\)-C(CH\(_3\))\(_3\); -CH\(_2\)-CH\(_2\)-OH; -CH\(_3\); -C\(_2\)H\(_5\); -CH\(_2\)-CH\(_2\)-CH\(_3\); -CH(CH\(_3\))\(_2\); -C(CH\(_3\))\(_3\); n-butyl; isobutyl; n-pentyl; sec-pentyl; -(4-chloro)-phenyl; -(4-bromo)-phenyl and -(4-fluoro)-phenyl;

and \( R^{22} \) is selected from hydrogen; F; Cl; Br; I; -COOH; -COO-CH\(_3\); -COO-C\(_2\)H\(_5\); -COO-CH(CH\(_3\))\(_2\); -COO-C(CH\(_3\))\(_3\); n-butyl; isobutyl; n-pentyl; sec-pentyl; -CH\(_2\)-OH; -CH\(_3\); -C\(_2\)H\(_5\); -CH\(_2\)-CH\(_2\)-CH\(_3\); -CH(CH\(_3\))\(_2\); -C(CH\(_3\))\(_3\);
In a particular embodiment, the nucleoside analogs of the present invention are selected from the list of compounds in table 1 (encoded from compound number 1 to 86).

Yet in a more particular embodiment, the nucleoside analogs are selected from the list of:

- 9-[(IR*,2R*,4S*)-bicyclo[2.2.1]hept-2-yl]-6-chloro-9H-purine;
- 9-[(IR*,2R*,4S*)-bicyclo[2.2.1]hept-2-yl]-2,6-dichloro-9H-purine;
- 6-chloro-9-[(IS,2S,4S)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-9H-purine;
- 6-chloro-9-[(1S,2S,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-yl]methyl]-9H-purine;
- 2,6-dichloro-9-[(1S,2S,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-yl]methyl]-9H-purine;
- 6-chloro-9-[(1R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-yl]methyl]-9H-purine;
- 6-chloro-9-[(1S,2R,4R)-3,3-dimethylbicyclo[2.2.1]hept-2-yl]-9H-purine;
- 9-[(IR*,2S*,4R*)-bicyclo[2.2.1]hept-5-en-2-yl]-6-chloro-9H-purine;
- [(li?*,2i?*,45*,65*)-6-(6-chloro-9H-purin-9-yl)bicyclo[2.2.1]hept-2-yl]methyl benzoate;
- [(li?*,2i?*,45*,65*)-6-(6-chloro-9H-purin-9-yl)bicyclo[2.2.1]hept-2-yl]methyl benzoate;
- [(li?*,2i?*,45*,65*)-6-(6-chloro-9H-purin-9-yl)bicyclo[2.2.1]hept-2-yl]methanol;
- 6-chloro-9-[(1R,2S,5R)-6,6-dimethylbicyclo[3.1.1]hept-2-yl]methyl]-9H-purine;
- (IR*,2S*,4R*,7R*)-7-(6-chloro-9H-purin-9-yl)bicyclo[2.2.1]hept-2-ol;
- (IR*,2S*,4S*,7R*)-7-(6-chloro-9H-purin-9-yl)bicyclo[2.2.1]hept-5-en-2-ol;
- 6-chloro-9-[(li?*,2i?*,3i?*,6i?*,75*,9i?*)-9-(methoxymethyl)-4-oxatricyclo[4.2.1.0^3^7] non-2-yl]-9H-purine;
- 6-chloro-9-[(IR*,2S*,4R*,7R*)-2-methoxybicyclo[2.2.1]hept-7-yl]-9H-purine;
- 9-[(IR*,2R*,3R*,6R*,7S*,9S*)-9-(benzyloxy)methyl]-4-oxatricyclo[4.2.1.0^3^7] non-2-yl]-6-chloro-9H-purine;
- (lR*,2R*,3R*,6R*,7S*,9S*)-2-(6-chloro-9H-purin-9-yl)-4-oxatricyclo[4.2.1.0\(^3\)7] nonane-9-methyl [phenyl methoxy-L-alaninyl]-phosphate;
- 6-chloro-9-[(lR*,2R*,3R*,6R*,7S*,9S*)-9-(chloromethyl) - 4-oxatricyclo[4.2. 1.0\(^3\)7] non-2-yl]-9H-purine.

5 - 6-chloro-9-[(lR*,2R*,6i?*,7/S*,85*)-tricyclo[5.2.1.0\(^3\)]non-8-yl]-9H-purine;
- 6-chloro-9-[(lR*,2i?*,4i?*,75')-bicyclo[2.2.1]hept-5-en-2-yl]-9H-purine;
- 6-chloro-9-[(lR*,2i?*,4i?*,55')-bicyclo[2.2.1]heptan-2-ol;
- 6-chloro-9-[\{l?*,25*,4i?*,55*\}-5-fluorobicyclo[2.2.1]hept-2-yl]-9 H-purine;
- 9-(\{I?*,2R*,45*\}-bicyclo[2.2.1]hept-2-yl]-6-(methylsulfanyl)-9 H-purine;
- 9-(\{I?*,2R*,45*\}-bicyclo[2.2.1]hept-2-yl]-6-iodo-9 H-purine;
- 6-azido-9-[\{l?*,2i?*,4,55*,65*\}-3-oxatricyclo[3.2.1.0^24]^3 oct-6-yl]-9 H-purine;
- 6-chloro-9-[\{l?*,2i?*,4,55*,65*\}-3-oxatricyclo[3.2.1.0^24]^3 oct-6-yl]-9 H-purine;
- (I?*,2R*,35*,45*)-2-(2-amino-6-chloro-9 H-purin-9-yl)-4-oxatricyclo[4.2.1.0^24]^3 nonane-9-methanol; and
- (I?*,4i?*,75*)-7-(6-Chloro-9 H-purin-9-yl)bicyclo[2.2.1]hept-5-ene-2,2-dimethanol.

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- 9-(\{I?*,2R*,45*\}-bicyclo[2.2.1]hept-2-yl]-6-iodo-9 H-purine;
- 6-azido-9-[\{l?*,2i?*,4,55*,65*\}-3-oxatricyclo[3.2.1.0^24]^3 oct-6-yl]-9 H-purine;
- 9-(\{I?*,2R*,45*\}-bicyclo[2.2.1]hept-2-yl]-6-methoxy-9 H-purine;
- 9-(\{I?*,2R*,45*\}-bicyclo[2.2.1]hept-2-yl]-6-methyl-9 H-purine;
- 9-(\{I?*,2R*,45*\}-bicyclo[2.2.1]hept-2-yl]-6-chloro-2-nitro-9 H-purine;
- 9-(\{I?*,2R*,45*\}-bicyclo[2.2.1]hept-2-yl]-8-bromo-6-chloro-9 H-purine;
- 9-(\{I?*,2R*,45*\}-bicyclo[2.2.1]hept-2-yl]-6-iodo-9 H-purine;
- 9-(\{I?*,2R*,45*\}-bicyclo[2.2.1]hept-2-yl]-6-methoxy-9 H-purine;
- 9-(\{I?*,2R*,45*\}-bicyclo[2.2.1]hept-2-yl]-6-methyl-9 H-purine;
- 9-(\{I?*,2R*,45*\}-bicyclo[2.2.1]hept-2-yl]-6-chloro-2-nitro-9 H-purine;

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- 6-chloro-9-

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- 9-(\{I?*,2R*,45*\}-bicyclo[2.2.1]hept-2-yl]-6-chloro-8-iodo-9 H-purine;
- 9-(\{I?*,2R*,45*\}-bicyclo[2.2.1]hept-2-yl]-6-chloro-8-iodo-9 H-purine;
- ethyl 9-(\{I?*,2R*,45*\}-bicyclo[2.2.1]hept-2-yl]-6-chloro-9 H-purine-8-carboxylate;
- 9-(\{I?*,2R*,45*\}-bicyclo[2.2.1]hept-2-yl]-6-chloro-9 H-purine-8-carboxylate;
- 6-chloro-9-

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- (I?*,2i?*,35*,45*)-5-(6-chloro-9 H-purin-9-yl)bicyclo[2.2.1]heptane-2,3-diol;
- 7-(\{I?*,2R*,45*\}-bicyclo[2.2.1]hept-2-yl]-4-chloro-7 H-pyrrolo[2,3- J]pyrimidine;
- (I?*,2i?*,3i?*,6i?*,75*,95*)-2-(2-amino-6-chloro-9 H-purin-9-yl)-4-oxatricyclo[4.2.1.0^24]^3 nonane-9-methanol; and
- 6-chloro-9-

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- (I?*,2R*,3S*,4S*)-6-(chloromethyl)-3-(6-chloro-9 H-purin-9-yl)bicyclo[2.2.1]hept-5-en-2-ol;
- (I?*,2R*,35*,45*)-3-(chloro-9 H-purin-9-yl)-5-(hydroxymethyl)bicyclo[2.2.1]hept-5-en-2-ol and
- (I?*,4i?*,75*)-7-(6-Chloro-9 H-purin-9-yl)bicyclo[2.2.1]hept-5-ene-2,2-dimethanol.
According to a second aspect, the invention relates to the nucleoside analogs as described herein for use as a medicament, more in particular for use as an antiviral medicament and for the use in the prevention or treatment of a viral infection in a subject (animal, mammal or human).

The present invention also relates to the use of the nucleoside analogs of the formulae (including but not limited to A', A, A-2, A-3a, A-3b, A-4, A-5 and A-6) and claims herein as antiviral compounds, more particularly as compounds active against Picornaviridae. The invention also relates to the use of nucleoside analogs of the formulae and claims herein for the manufacture of a medicament or as a pharmaceutically active ingredient, especially as a virus replication inhibitor, for instance for the manufacture of a medicament or pharmaceutical composition having antiviral activity for the prevention and/or treatment of viral infections in humans, mammals and animals in general. The present invention further relates to a method of prevention or treatment of a viral infection, preferably a Picornaviridae infection in an animal, including mammals, including a human, comprising administering to the animal in need of such treatment a therapeutically effective amount of a nucleoside analog of formulae and claims herein as an active ingredient, preferably in admixture with at least a pharmaceutically acceptable carrier.

Another aspect of the invention further relates to methods for the preparation of compounds of formulae and claims herein. Also the intermediates (amines and hydroxy bearing derivatives as specified in the examples) used in the preparation methods described herein are aspects of the present invention.

One embodiment relates to a method for the preparation of the nucleoside analogs of the invention, said method comprising the steps of coupling a substituted or unsubstituted pyrimidine or purine heterocycle, preferably a substituted or unsubstituted purine heterocycle, to compounds of the formula (A-7), in particular via the Mitsunobu-reaction:
wherein each of W, X, Y, Z, R₁, R₂, R₃, R₄, R₅, is according to formula (A).

Another particular embodiment relates to a method for the preparation of the nucleoside analogs of the invention, said method comprising the steps of coupling a substituted or unsubstituted pyrimidine or purine heterocycle, preferably a substituted pyrimidine heterocycle, to compounds of the formula (A-8).

wherein each of W, X, Z, Y, R¹, R², R³, R⁴, R⁵, is according to formula (A), said method comprising the steps of
- coupling a substituted 5-amino-pyrimidine, preferably a substituted 4-chloro-5-amino-pyrimidine, to the compounds of formula (A-8); and
- performing a ring-closure in acid trialkyl orthofomate reaction conditions.

Yet another aspect of the present invention relates to pharmaceutical compositions comprising the nucleoside analogs of the invention according to formulae and claims herein in admixture with at least a pharmaceutically acceptable carrier, the active ingredient preferably being in a concentration range of about 0.1 to 100% by weight, and to the use of these derivatives namely as drugs useful for the treatment of subjects suffering from a viral infection, in particular a Picornaviridae infection.
The invention further relates to the use of a composition comprising (a) one or more derivatives of formulae and claims herein, and (b) one or more viral inhibitors as biologically active agents in respective proportions such as to provide a synergistic effect against a viral infection in a mammal, for instance in the form of a combined preparation for simultaneous, separate or sequential use in viral infection therapy. Within the framework of this embodiment of the invention, the viral enzyme inhibitors used as a therapeutically active ingredients (b) may belong to categories already known in the art.

The invention also relates to the nucleoside analogs of the invention according to formulae and claims herein being used for inhibition of the proliferation of other viruses than Picornaviridae, preferably the inhibition of viral activity of other RNA-viruses such as hepatitis B virus, hepatitis C virus or flaviviruses, with in particular yellow fever virus or Dengue virus.

More generally, the invention relates to the compounds of formulae and claims herein being useful as agents having biological activity or as diagnostic agents. Any of the uses mentioned with respect to the present invention may be restricted to a non-medical use, a non-therapeutic use, a non-diagnostic use, or exclusively an in vitro use, or a use related to cells remote from an animal.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

In each of the following definitions, the number of carbon atoms represents the maximum number of carbon atoms generally optimally present in the substituent or linker; it is understood that where otherwise indicated in the present application, the number of carbon atoms represents the optimal maximum number of carbon atoms for that particular substituent or linker.
The term "alkyl" as used herein refers to C\textsubscript{1}-C\textsubscript{18} normal, preferably primary, secondary, or tertiary hydrocarbon chains. Examples are methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-methyl-1-propyl(i-Bu), 2-butyl (s-Bu) 2-methyl-2-propyl (t-Bu), 1-pentyl (n-pentyl), 2-pentyl, 3-pentyl, 2-methyl-2-butyl, 3-methyl-2-butyl, 3-methyl-1-butyl, 2-methyl-1-butyl, 1-hexyl, 2-hexyl, 3-hexyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 3-methyl-3-pentyl, 2-methyl-3-pentyl, 2,3-dimethyl-2-butyl, 3,3-dimethyl-2-butyl, M-pentyl, n-hexyl, M-heptyl, n-octyl, n-nonyl, «-decyl, n-undecyl, n-dodecyl, M-tridecyl, n-tetradecl, w-pentadecyl, n-hexadecyl, rø-heptadecyl, w-octadecyl, n-nonadecyl and n-icosyl.

The term "alkylene" as used herein refers to a saturated, branched or straight chain hydrocarbon radical of C\textsubscript{1,18} carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkane. Typical alkyene radicals include, but are not limited to: methylene (-CH\textsubscript{2}-) 1,2-ethyl (-CH\textsubscript{2}CH\textsubscript{2}H2-), 1,3-propyl (-CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}H2-), 1,4-butyl (-CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}H2-), and the like.

When reference is made to "alkyl can contain a heteroatom in or at the end of the alkyl chain, said heteroatom selected from O, S and N", than any carbon atom of the alkyl can be exchanged for a heteroatom selected from O, S and N when chemically feasible. Examples are CH\textsubscript{3}-CH\textsubscript{2}-O--; CH\textsubscript{3}-O-CH\textsubscript{2}--; and CH\textsubscript{3}-CH\textsubscript{2}-CH\textsubscript{2}-NH-CH\textsubscript{2}-. The same counts for the term "alkylene" whereby the term "phosphonate-alkylene can contain a heteroatom in or at the end of the alkyl chain, said heteroatom selected from O, S and N" also includes phosphonalkyloxy such as phosphonylmethyl ether. As used herein, and unless stated otherwise, the term "phosphonalkyloxy" refers to a phosphonate coupled via an alkylgroup (such as defined herein after) to an oxygen atom which itself can be coupled to another molecule or group.

As used herein and unless otherwise stated, the term "cycloalkyl" means a monocyclic saturated hydrocarbon monovalent radical having from 3 to 10 carbon atoms, such as for instance cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like, or a C\textsubscript{7-10} polycyclic saturated hydrocarbon monovalent radical having from 7 to 10 carbon atoms such as, for instance, norbornyl, fenchyl, trimethyltricycloheptyl or adamantyl.
The terms "alkenyl" and "cycloalkenyl" as used herein is C2-C18 normal, preferably primary, secondary or tertiary and respectively C3-10 cyclic hydrocarbon with at least one site (usually 1 to 3, preferably 1) of unsaturation, i.e. a carbon-carbon, sp2 double bond. Examples include, but are not limited to: ethylene or vinyl (-CH=CH2), allyl (-CH2CH=CH2), cyclopentenyl (-C5H7), and 5-hexenyl (-CH2CH2CH2CH=CH2). The double bond may be in the cis or trans configuration.

The terms "alkynyl" and "cycloalkynyl" as used herein refer respectively C2-C18 normal, preferably primary, secondary, tertiary or the C8-C13 cyclic hydrocarbon with at least one site (usually 1 to 3, preferably 1) of unsaturation, i.e. a carbon-carbon, sp triple bond. Examples include, but are not limited to: acetylenic (-C≡CH) and propargyl (-CH2C≡CH).

The term "aryl" as used herein means a aromatic hydrocarbon radical of 6-20 carbon atoms derived by the removal of hydrogen from a carbon atom of a parent aromatic ring system. Typical aryl groups include, but are not limited to 1 ring, or 2 or 3 rings fused together, radicals derived from benzene, naphthalene, anthracene, biphenyl, and the like.

"Arylalkyl" as used herein refers to an alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp3 carbon atom, is replaced with an aryl radical. Typical arylalkyl groups include, but are not limited to, benzyl, 2-phenylethyl-1-yl, 2-phenylethen-1-yl, naphthylmethyl, 2-naphthylethyl-1-yl, 2-naphthylethen-1-yl, naphthobenzyl, 2-naphthophenylethyl-1-yl and the like. The arylalkyl group comprises 6 to 20 carbon atoms, preferably 7 to 20 carbon atom, e.g. the alkyl moiety, including alkanyl, alkenyl or alkynyl groups, of the arylalkyl group is 1 to 6 carbon atoms and the aryl moiety is 5 to 14 carbon atoms, preferably 6 to 14 carbon atoms. The "arylalkyl" radical may itself be substituted such as but not limited to 4-chlorobenzyl, 4-fluorobenzyl, 2-fluorobenzyl, 3,4-dichlorobenzyl, 2,6-dichlorobenzyl, 3-methylbenzyl, 4-methylbenzyl, 4-ter-butylbenzyl, 1-amino-2-phenylethyl and 1-amino-2-[4-hydroxy-phenyl]ethyl.

As used herein, and unless stated otherwise, the term "purine and pyrimidine heterocycles" include, but are not limited to, adenine, thymine, cytosine, uracil, guanine and (2,6-)diaminopurine such as may be found in naturally-occurring nucleosides. The
term also includes analogs and derivatives thereof. An analog thereof is a heterocycle which mimics such naturally-occurring bases in such a way that its structure (the kinds of atoms present and their arrangement) is similar to the above-listed naturally-occurring heterocycles but is modified by either having additional functional properties with respect to the naturally-occurring bases or lacking certain functional properties of the naturally-occurring bases. Such analogues include, but are not limited to, those derived by replacement of a -CH- moiety by a nitrogen atom ("aza-analogs" e.g. 5-azapyrimidines such as 5-azacytosine) or vice-versa ("deaza-analogs" e.g. 7-deazapurines, such as 7-deaza-adenine or 7-deazaguanine) or both (e.g. 7-deaza, 8-azapurines). The purine and pyrimidine heterocycles can be unsubstituted or substituted and in the last instance can be referred to as a "derivative" of naturally-occurring heterocycles (bases), or analogs thereof. Such substituted derivatives are compounds wherein the heterocyclic ring is substituted with one or more conventional substituents independently selected from the group consisting of halogen; -NH₂; -NH-alkyl; -N(alkyl)₂; -OH; -O-alkyl (such as -OCH₃); -O-aryl; -SH; -S-alkyl (such as -SCH₃); -S-aryl; -CF₃; -NO₂; -COOH; -COO-alkyl; -SO₂alkyl; aryl; halogenoaryl; arylalkyl; or alkyl; wherein each of said alkyl can again be substituted with hydroxy, amino, halogen or -SH. Such purine or pyrimidine heterocycles, analogs and derivatives thereof are well known to those skilled in the art. Specific embodiments of purine and pyrimidine heterocycles B suitable for inclusion into the nucleoside analogs of the present invention include, but are not limited to, hypoxanthine, guanine, adenine, cytosine, inosine, thymine, uracil, xanthine, 8-aza derivatives of 2-aminopurine, 2,6-diaminopurine, 6-chloro-purine, 2,6-dichloro-purine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 7-deaza-8-aza derivatives of adenine, guanine, 2-aminopurine, 2,6-diaminopurine, 6-chloro-purine, 2,6-dichloro-purine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 1-deaza derivatives of 2-aminopurine, 2,6-diaminopurine, 6-chloro-purine, 2,6-dichloro-purine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 7-deaza derivatives of 2-aminopurine, 2,6-diaminopurine, 6-chloro-purine, 2,6-dichloro-purine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 3-deaza derivatives of 2-aminopurine, 2,6-diaminopurine, 6-chloro-purine, 2,6-dichloro-purine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 6-azacytosine; 5-fluorocytosine; 5-chlorocytosine; 5-
iodocytosine; 5-bromocytosine; 5-methylcytosine; 5-bromovinyluracil; 5-fluorouracil; 5-chlorouracil; 5-iodouracil; 5-bromouracil; 5-trifluoromethyluracil; 5-ethynyluracil and 5-propynyluracil.

More in particular, B is a 9-purinyl residue selected from guanyl, 3-deazaguanyl, 1-deazaguanyl, 8-azaguanyl, 7-deazaadenyl, adenyl, 3-deazaadenyl, 1-deazaadenyl, 8-azaadenyl, 7-deazaadenyl, 2,6-diaminopurinyl, 2-aminopurinyl, 6-chloro-2-aminopurinyl and 6-thio-2-aminopurinyl.

In a particular embodiment, the purine heterocycle is according to formula (P-I),

\[
\begin{array}{c}
\text{R}^{20} \\
N \\
\text{R}^{22} \\
N \\
\text{R}^{21} \\
N \\
\text{R}^{20}
\end{array}
\]

wherein each of \(R^{20}\) and \(R^{21}\) are independently selected from hydrogen; halogen; -NH\(_2\); -N\(_3\); -OH; -O-alkyl (such as -OCH\(_3\)); -SH; -S-alkyl (such as -SCH\(_3\)); -CF\(_3\); -NO\(_2\); -COOH; -COO-alkyl; -S0\(_2\)alkyl; aryl; or alkyl; wherein each of said alkyl and aryl can again be substituted with hydroxy, amino, halogen or -SH;

and \(R^{22}\) is selected from hydrogen; halogen; -NH\(_2\); -OH; -O-alkyl (such as -OCH\(_3\)); -SH; -S-alkyl (such as -SCH\(_3\)); -N\(_3\); -NO\(_2\); -COOH; -COO-alkyl; -S0\(_2\)alkyl; aryl; or alkyl; wherein each of said alkyl and aryl can again be substituted with hydroxy, amino or -SH (thereby including the isomers and salts thereof).

In a more particular embodiment, the purine heterocycle is according to formula (P-I), wherein

each of \(R^{20}\) and \(R^{21}\) are independently selected from hydrogen; F; Cl; Br; I; -N\(_3\); -NH\(_2\); -OH; -O-CH\(_3\); -O-C\(_2\)H\(_5\); -O-CH\(_2\)-CH\(_2\)-CH\(_3\); -O-CH(CH\(_3\))\(_2\); -O-C(CH\(_3\))\(_3\); -SH; -S-CH\(_3\); -S-C\(_2\)H\(_5\); -S-CH\(_2\)-CH\(_2\)-CH\(_3\); -S-CH(CH\(_3\))\(_2\); -S-C(CH\(_3\))\(_3\); -CF\(_3\); -NO\(_2\); -COOH; -COO-CH\(_3\); -
COO-C$_2$H$_5$; -COO-CH(CH$_3$)$_2$; -COO-C(CH$_3$)$_3$; -SO$_2$-CH$_3$; -SO$_2$-CH$_2$-CH$_2$-CH$_3$; -SO$_2$-CH(CH$_3$)$_2$; -SO$_2$-C(CH$_3$)$_3$; -CH$_2$F; -CHF$_2$; -CH$_2$Cl; -CHCl$_2$; -CH$_2$OH; -CH$_2$-CH$_2$OH; -CH$_3$; -C$_2$H$_5$; -CH$_2$-CH$_2$-CH$_3$; -CH(CH$_3$)$_2$; -C(CH$_3$)$_3$; n-butyl; isobutyl; n-pentyl; sec-pentyl; -(4-chloro)-phenyl; -(4-bromo)-phenyl and -(4-fluoro)-phenyl;

and R$^{22}$ is selected from hydrogen; F; Cl; Br; I; -COOH; -COO-CH$_3$; -COO-C$_2$H$_5$; -COO-CH(CH$_3$)$_2$; -COO-C(CH$_3$)$_3$; n-butyl; isobutyl; n-pentyl; sec-pentyl; -CH$_2$OH; -CH$_2$-CH$_2$-OH; -CH$_3$; -C$_2$H$_5$; -CH$_2$-CH$_2$-CH$_3$; n-butyl; isobutyl; n-pentyl; sec-pentyl; -CH(CH$_3$)$_2$ and -C(CH$_3$)$_3$.

In an even more particular embodiment, the purine heterocycle is according to formula (P-I), wherein

R$^{20}$ is selected from hydrogen; F; Cl; Br; I; -N$_3$; -NH$_2$; -OH; -0-CH$_3$; -0-C$_2$H$_5$; -0-CH$_2$-CH$_2$-CH$_3$; -0-CH(CH$_3$)$_2$; -O-C(CH$_3$)$_3$; -SH; -S-CH$_3$; -S-C$_2$H$_5$; -S-CH$_2$-CH$_2$-CH$_3$; -S-CH(CH$_3$)$_2$; -S-C(CH$_3$)$_3$; -CF$_3$; -NO$_2$; -COOH; -COO-CH$_3$; -COO-C$_2$H$_5$; -COO-CH(CH$_3$)$_2$; -COO-C(CH$_3$)$_3$; -SO$_2$-CH$_3$; -SO$_2$-C$_2$H$_5$; -SO$_2$-CH$_2$-CH$_2$-CH$_3$; -SO$_2$-CH(CH$_3$)$_2$; -SO$_2$-C(CH$_3$)$_3$; -CH$_2$F; -CHF$_2$; -CH$_2$Cl; -CHCl$_2$; -CH$_2$OH; -CH$_2$-CH$_2$OH; -CH$_3$; -C$_2$H$_5$; -CH$_2$-CH$_2$-CH$_3$; -CH(CH$_3$)$_2$; -C(CH$_3$)$_3$; n-butyl; isobutyl; n-pentyl; sec-pentyl; -(4-chloro)-phenyl; -(4-bromo)-phenyl and -(4-fluoro)-phenyl;

R$^{21}$ is selected from hydrogen; F; Cl; Br; I; -0-CH$_3$; -0-C$_2$H$_5$; -0-CH$_2$-CH$_2$-CH$_3$; -0-CH(CH$_3$)$_2$; -O-C(CH$_3$)$_3$; -CH$_3$; -C$_2$H$_5$; -CH$_2$-CH$_2$-CH$_3$; -CH(CH$_3$)$_2$; -C(CH$_3$)$_3$; n-butyl; isobutyl; n-pentyl and sec-pentyl;

and R$^{22}$ is selected from hydrogen; F; Cl; Br; I; -COOH; -COO-CH$_3$; -COO-C$_2$H$_5$; -COO-CH(CH$_3$)$_2$; -COO-C(CH$_3$)$_3$; n-butyl; isobutyl; n-pentyl; sec-pentyl; -CH$_2$OH; -CH$_2$-CH$_2$-OH; -CH$_3$; -C$_2$H$_5$; -CH$_2$-CH$_2$-CH$_3$; n-butyl; isobutyl; n-pentyl; sec-pentyl; -CH(CH$_3$)$_2$ and -C(CH$_3$)$_3$. 
As used herein with respect to a substituting group, and unless otherwise stated, the terms "arylalkyl", "arylalkenyl" and "heterocyclic-substituted alkyl" refer to an aliphatic saturated or ethylenically unsaturated hydrocarbon monovalent group (preferably a C_{1-18} alkyl or C_{2-18} alkenyl such as defined above) onto which an aryl or heterocyclic group (such as defined herein) is already bonded, and wherein the said aliphatic group and/or the said aryl or heterocyclic group may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, amino, hydroxyl, sulfhydryl, C_{1-7} alkyl, trifluoromethyl and nitro, such as but not limited to 1-amino-2-[indol-2-yl]ethyl, styryl, pyridylmethyl (including all isomers thereof), pyridylethyl, 2-(2-pyridyl)isopropyl, oxazolylbutyl, 2-thienylmethyl, pyrrolylethyl, morpholinyl-ethyl, imidazol-1-yl-ethyl, benzodioxoxylmethyl and 2-furylmethyl.

The term "acyl" as used herein, unless otherwise stated, refers to a carbonyl group directly attached to an alkyl, alkenyl, alkynyl, aryl, heterocyclic, arylalkyl, arylalkenyl, arylalkynyl, heterocyclic-alkyl, heterocyclic-alkenyl or heterocyclic-alkynyl group, such as for example alkanoyl (alkylcarbonyl), aryl (arylcarbonyl), arylalkanoyl or alkylaroyl group, wherein the carbonyl group is coupled to another molecule. As an example, the term "acyloxyalkyl" refers to an acyl group coupled via an oxygen atom to an alkyl group, the latter being further coupled to another molecule or atom.

As an example, "alkylalkenylcarbonate" refers to an alkyl-OC(O)O-alkenyl group, thus a carbonate substituted at one side with an alkyl and on the other side with an alkenyl, one of the alkyl and alkenyl groups being further coupled to another molecule or atom.

As used herein and unless otherwise stated, the terms "alkoxy", "cyclo-alkoxy", "aryloxy", "arylalkoxy", "oxyheterocyclic", "thioalkyl", "thio cycloalkyl", "arylthio", "arylalkylthio" and "thioheterocyclic" refer to substituents wherein an alkyl group, respectively a cycloalkyl, aryl, arylalkyl or heterocyclic group (each of them such as defined herein), are attached to an oxygen atom or a sulfur atom through a single bond, such as but not limited to methoxy, ethoxy, propoxy, butoxy, thioethyl, thiomethyl, phenyloxy, benzylxoy, mercaptobenzyl and the like.
As used herein and unless otherwise stated, the term halogen means any atom selected from the group consisting of fluorine (F), chlorine (Cl), bromine (Br) and iodine (I).

Any substituent designation that is found in more than one site in a compound of this invention shall be independently selected.

Substituents optionally are designated with or without bonds. Regardless of bond indications, if a substituent is polyvalent (based on its position in the structure referred to), then any and all possible orientations of the substituent are intended.

**Detailed description**

The present invention relates to a series of novel nucleoside analogs which have been shown to possess antiviral activity, in particular against viruses of the family of the Picornaviridae. The invention therefore relates to the new nucleoside analogs, methods for their preparation, pharmaceutical compositions comprising them, the use of the nucleoside analogs for the preparation of a medicament and to the nucleoside analogs for use as a medicament, more in particular as antiviral medicament.

The compounds of the invention are employed for the treatment or prophylaxis of viral infections, more particularly Picornaviridae infections.

When using one or more compounds according to the formulae of the application as defined herein:

- the active ingredients of the compound(s) may be administered to the mammal (including a human) to be treated by any means well known in the art, i.e. orally, intranasally, subcutaneously, intramuscularly, intradermally, intravenously, intra-arterially, parenterally or by catheterization.

- the therapeutically effective amount of the preparation of the compound(s), especially for the treatment of viral infections in humans and other mammals, corresponds to an amount which ensures a plasma level of between 1µg/ml and 100 mg/ml, optionally of 10 mg/ml. Depending upon the pathologic condition to be treated and the patient's
condition, the effective amount may be divided into several sub-units per day or may be administered at more than one day intervals.

The present invention further relates to a method for preventing or treating a viral infections in a subject or patient by administering to the patient in need thereof a therapeutically effective amount of the nucleoside analogs of the present invention. The therapeutically effective amount of the preparation of the compound(s), especially for the treatment of viral infections in humans and other mammals, preferably is Picornaviridae protein/enzyme inhibiting amount. More preferably, it is a Picornaviridae replication inhibiting amount or a Picornaviridae enzyme inhibiting amount of the nucleoside analogs of the formulae as defined herein. Depending upon the pathologic condition to be treated and the patient's condition, the effective amount may be divided into several sub-units per day or may be administered at more than one day intervals.

As is conventional in the art, the evaluation of a synergistic effect in a drug combination may be made by analyzing the quantification of the interactions between individual drugs, using the median effect principle described by Chou et al. in *Adv. Enzyme Reg.* (1984) 22:27. Briefly, this principle states that interactions (synergism, additivity, antagonism) between two drugs can be quantified using the combination index (hereinafter referred as CI) defined by the following equation:

\[
CI_x = \frac{ED_1^f}{ED_1^c} + \frac{ED_2^c}{ED_2^f}
\]

wherein ED\(_x\) is the dose of the first or respectively second drug used alone (Ia, 2a), or in combination with the second or respectively first drug (Ic, 2c), which is needed to produce a given effect. The said first and second drug have synergistic or additive or antagonistic effects depending upon CK = 1, CI = 1, or CI > 1, respectively.

Synergistic activity of the pharmaceutical compositions or combined preparations of this invention against viral infection may also be readily determined by means of one or more tests such as, but not limited to, the isobologram method, as previously described by Elion et al. in *J. Biol. Chem.* (1954) 208:477-488 and by Baba et al. in *Antimicrob.*
Agents Chemother. (1984) 25:515-517, using EC\textsubscript{50} for calculating the fractional inhibitory concentration (hereinafter referred as FIC). When the minimum FIC index corresponding to the FIC of combined compounds (e.g., FIC\textsubscript{x} + FIC\textsubscript{y}) is equal to 1.0, the combination is said to be additive; when it is between 1.0 and 0.5, the combination is defined as subsynergistic, and when it is lower than 0.5, the combination is defined as synergistic. When the minimum FIC index is between 1.0 and 2.0, the combination is defined as subantagonistic and, when it is higher than 2.0, the combination is defined as antagonistic.

This principle may be applied to a combination of different antiviral drugs of the invention or to a combination of the antiviral drugs of the invention with other drugs that exhibit anti-Picornaviridae activity.

The invention thus relates to a pharmaceutical composition or combined preparation having synergistic effects against a viral infection and containing:

Either:

A)

(a) a combination of two or more of the nucleoside analogs of the present invention, and
(b) optionally one or more pharmaceutical excipients or pharmaceutically acceptable carriers,

for simultaneous, separate or sequential use in the treatment or prevention of a viral infection

or

B)

(c) one or more anti-viral agents, and
(d) at least one of the nucleoside analogs of the present invention, and
(e) optionally one or more pharmaceutical excipients or pharmaceutically acceptable carriers,

for simultaneous, separate or sequential use in the treatment or prevention of a viral infection.

The pharmaceutical composition or combined preparation with synergistic activity against viral infection according to this invention may contain nucleoside analogs of the present invention, compounds according to the formulae of the application, over a broad
content range depending on the contemplated use and the expected effect of the preparation. Generally, the content of the nucleoside analogs of the present invention of the combined preparation is within the range of 0.1 to 99.9% by weight, preferably from 1 to 99% by weight, more preferably from 5 to 95% by weight.

Hi a particular embodiment, the nucleoside analogs of the invention can be used for the treatment or prevention of Aphthovirus (Foot-and-Mouth Disease Virus), Cardiovirus (Encephalomyocarditis virus + and Theilovirus), Enterovirus (Human Enterovirus A, B, C and D, Bovine Enterovirus, Porcine Enterovirus and Poliovirus), Erbovirus, Duck Hepatitis virus, Hepatovirus (Avian Encephalomyelitis Virus, Hepatitis A virus +), Kobuvirus, Parechovirus, Rhinovirus or Teschovirus.

The invention also relates to the nucleoside analogs of the invention, according to the formulae of the application being used for inhibition of the proliferation of other viruses than Picornaviridae, particularly for the inhibition of other RNA-viruses, including ds and ss RNA viruses and thereby including negative strand and positive strand viruses.

The present invention further provides veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier therefore. Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered orally, parenterally or by any other desired route.

More generally, the invention relates to the compounds according to the formulae of the application being useful as agents having biological activity (particularly antiviral activity) or as diagnostic agents. Any of the uses mentioned with respect to the present invention may be restricted to a non-medical use, a non-therapeutic use, a non-diagnostic use, or exclusively an in vitro use, or a use related to cells remote from an animal.

The compounds of the invention optionally are bonded covalently to an insoluble matrix and used for affinity chromatography (separations, depending on the nature of the groups
of the compounds, for example compounds with aryl are useful in hydrophobic affinity separations.

Those of skill in the art will also recognize that the compounds of the invention may exist in many different protonation states, depending on, among other things, the pH of their environment. While the structural formulae provided herein depict the compounds in only one of several possible protonation states, it will be understood that these structures are illustrative only, and that the invention is not limited to any particular protonation state, any and all protonated forms of the compounds are intended to fall within the scope of the invention.

The term "pharmaceutically acceptable salts" as used herein means the therapeutically active non-toxic salt forms which the compounds according to the formulae of the application are able to form. Therefore, the compounds of this invention optionally comprise salts of the compounds herein, especially pharmaceutically acceptable non-toxic salts containing, for example, Na+, Li+, K+, Ca+2 and Mg+2. Such salts may include those derived by combination of appropriate cations such as alkali and alkaline earth metal ions or ammonium and quaternary amino ions with an acid anion moiety, typically a carboxylic acid. The compounds of the invention may bear multiple positive or negative charges. The net charge of the compounds of the invention may be either positive or negative. Any associated counterions are typically dictated by the synthesis and/or isolation methods by which the compounds are obtained. Typical counterions include, but are not limited to ammonium, sodium, potassium, lithium, halides, acetate, trifluoroacetate, etc., and mixtures thereof. It will be understood that the identity of any associated counter ion is not a critical feature of the invention, and that the invention encompasses the compounds in association with any type of counter ion. Moreover, as the compounds can exist in a variety of different forms, the invention is intended to encompass not only forms of the compounds that are in association with counterions (e.g., dry salts), but also forms that are not in association with counterions (e.g., aqueous or organic solutions). Metal salts typically are prepared by reacting the metal hydroxide with a compound of this invention. Examples of metal salts which are prepared in this
way are salts containing Li+, Na+, and K+. A less soluble metal salt can be precipitated
from the solution of a more soluble salt by addition of the suitable metal compound. In
addition, salts may be formed from acid addition of certain organic and inorganic acids to
basic centers, typically amines, or to acidic groups. Examples of such appropriate acids
include, for instance, inorganic acids such as hydrohalic acids, e.g. hydrochloric or
hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like; or organic acids
such as, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-
oxopropanoic, lactic, pyruvic, oxalic (i.e. ethanedioic), malonic, succinic (i.e. butanedioic
acid), maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic,
benzenesulfonic, p-toluenesulfonic, cyclohexanesulfamic, salicylic (i.e. 2-
hydroxybenzoic), p-aminosalicylic and the like. Furthermore, this term also includes the
solvates which the compounds according to the formulae of the application as well as
their salts are able to form, such as for example hydrates, alcoholates and the like.
Finally, it is to be understood that the compositions herein comprise compounds of the
invention in their unionized, as well as zwitterionic form, and combinations with
stoichiometric amounts of water as in hydrates.
Also included within the scope of this invention are the salts of the parental compounds
with one or more amino acids, especially the naturally-occurring amino acids found as
protein components. The amino acid typically is one bearing a side chain with a basic or
acidic group, e.g., lysine, arginine or glutamic acid, or a neutral group such as glycine,
serine, threonine, alanine, isoleucine, or leucine.
The compounds of the invention also include physiologically acceptable salts thereof.
Examples of physiologically acceptable salts of the compounds of the invention include
salts derived from an appropriate base, such as an alkali metal (for example, sodium), an
alkaline earth (for example, magnesium), ammonium and NX4+ (wherein X is C1-C4
alkyl). Physiologically acceptable salts of an hydrogen atom or an amino group include
salts of organic carboxylic acids such as acetic, benzoic, lactic, fumaric, tartaric, maleic,
malonic, malic, isethionic, lactobionic and succinic acids; organic sulfonic acids, such as
methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids; and
inorganic acids, such as hydrochloric, sulfuric, phosphoric and sulfamic acids.
Physiologically acceptable salts of a compound containing a hydroxy group include the
anion of said compound in combination with a suitable cation such as Na+ and N\textsubscript{X}\textsuperscript{4+} (wherein X typically is independently selected from H or a C\textsubscript{1}–C\textsubscript{4} alkyl group). However, salts of acids or bases which are not physiologically acceptable may also find use, for example, in the preparation or purification of a physiologically acceptable compound. All salts, whether or not derived form a physiologically acceptable acid or base, are within the scope of the present invention.

The nucleoside analogs of the present invention can have different isomeric forms and during the synthesis as provided herein normally one isomeric form is prepared (except for some isomeric impurities). All the atoms in the nucleoside analogs of the present invention can be in the R or S form. For some specific nucleoside analogs of the present invention, the isomeric configuration is given herein.

In a particular embodiment of the different aspects of the invention, the nucleoside analogs of the invention are according to one of the formulae A-10 to A-23 hereunder:
As used herein and unless otherwise stated, the term "enantiomer" means each individual optically active form of a compound of the invention, having an optical purity or enantiomeric excess (as determined by methods standard in the art) of at least 80% (i.e. at least 90% of one enantiomer and at most 10% of the other enantiomer), preferably at least 90% and more preferably at least 98%.

The term "isomers" as used herein means all possible isomeric forms, including tautomeric and sterochemical forms ("stereo-isomers") and including positional isomers, which the compounds according to the formulae of the application may possess. hi a particular embodiment, the term "isomers" excludes positional isomers. Typically, the structures shown herein exemplify only one tautomeric or resonance form of the compounds, but the corresponding alternative configurations are contemplated as well. Unless otherwise stated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, including stereoisomers and tautomers, said mixtures containing all diastereomers and enantiomers (since the compounds according to the formulae of the application may have at least one chiral center) of the basic molecular structure, as well as the stereochemically pure or enriched compounds. More particularly, stereogenic centers may have either the R- or S-configuration, and multiple bonds may have either cis- or trans-configuration.

Pure isomeric forms of the said compounds are defined as isomers substantially free of other enantiomeric or diastereomeric forms of the same basic molecular structure, hi particular, the term "stereoisomerically pure" or "chirally pure" relates to compounds having a stereoisomers excess of at least about 80% (i.e. at least 90% of one isomer and at most 10% of the other possible isomers), preferably at least 90%, more preferably at least 94% and most preferably at least 97%. The terms "enantiomerically pure" and "diastereomerically pure" should be understood in a similar way, having regard to the enantiomeric excess, respectively the diastereomeric excess, of the mixture in question.

Separation of stereoisomers is accomplished by standard methods known to those skilled in the art. One enantiomer of a compound of the invention can be separated substantially free of its opposing enantiomer by a method such as formation of diastereomers using optically active resolving agents ("Stereochemistry of Carbon Compounds," (1962) by E. L. Eliel, McGraw Hill; Lochmuller, C. H., (1975) J. Chromatogr., 113:(3) 283-302).
Separation of isomers in a mixture can be accomplished by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2) formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure enantiomers, or (3) enantiomers can be separated directly under chiral conditions. Under method (1), diastereomeric salts can be formed by reaction of enantiomerically pure chiral bases such as brucine, quinine, ephedrine, strychnine, a-methyl-b-phenylethylamine (amphetamine), and the like with asymmetric compounds bearing acidic functionality, such as carboxylic acid and sulfonic acid. The diastereomeric salts may be induced to separate by fractional crystallization or ionic chromatography. For separation of the optical isomers of amino compounds, addition of chiral carboxylic or sulfonic acids, such as camphorsulfonic acid, tartaric acid, mandelic acid, or lactic acid can result in formation of the diastereomeric salts. Alternatively, by method (2), the substrate to be resolved may be reacted with one enantiomer of a chiral compound to form a diastereomeric pair (Elie, E. and Wilen, S. (1994) Stereochemistry of Organic Compounds, John Wiley & Sons, Inc., p. 322). Diastereomeric compounds can be formed by reacting asymmetric compounds with enantiomerically pure chiral derivatizing reagents, such as menthyl derivatives, followed by separation of the diastereomers and hydrolysis to yield the free, enantiomerically enriched compounds of the invention. A method of determining optical purity involves making chiral esters, such as a menthyl ester or Mosher ester, a-methoxy-a-(trifluoromethyl)phenyl acetate (Jacob III. (1982) J. Org. Chem. 47:4165), of the racemic mixture, and analyzing the NMR spectrum for the presence of the two atropisomeric diastereomers. Stable diastereomers can be separated and isolated by normal- and reverse-phase chromatography following methods for separation of atropisomeric naphthyl-isooquinolines (Hoye, T., WO 96/15 111). Under method (3), a racemic mixture of two asymmetric enantiomers is separated by chromatography using a chiral stationary phase. Suitable chiral stationary phases are, for example, polysaccharides, in particular cellulose or amylose derivatives. Commercially available polysaccharide based chiral stationary phases are ChiralCel™ CA, OA, OB5, OC5, OD, OF, OG, OJ and OK, and ChiralpakTM AD, AS, OP(+) and OT(+). Appropriate eluents or mobile phases for use in combination with said
The terms cis and trans are used herein in accordance with Chemical Abstracts nomenclature and include reference to the position of the substituents on a ring moiety. The absolute stereochemical configuration of the compounds according to the formulae of the application may easily be determined by those skilled in the art while using well-known methods such as, for example, X-ray diffraction or NMR.

Tautomers are organic compounds that are interconvertible by a chemical reaction called tautomerization. As most commonly encountered, this reaction results in the formal migration of a hydrogen atom or proton, accompanied by a switch of a single bond and adjacent double bond. In solutions where tautomerization is possible, a chemical equilibrium of the tautomers will be reached. The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH. For example, the compound 9-(1-benzyl)-1,9-dihydro-6 H-purin-6-one is a tautomer of 9-(1-benzyl)-6-hydroxy-9 H-purine.

The compounds of the invention may be formulated with conventional carriers and excipients, which will be selected in accord with ordinary practice. Tablets will contain excipients, glidants, fillers, binders and the like. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. Formulations optionally contain excipients such as those set forth in the "Handbook of Pharmaceutical Excipients" (1986) and include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like. Subsequently, the term "pharmacologically acceptable carrier" as used herein means any material or substance with which the active ingredient is formulated in order to facilitate its application or dissemination to the locus to be treated, for instance by dissolving,
dispersing or diffusing the said composition, and/or to facilitate its storage, transport or
handling without impairing its effectiveness. The pharmaceutically acceptable carrier
may be a solid or a liquid or a gas which has been compressed to form a liquid, i.e. the
compositions of this invention can suitably be used as concentrates, emulsions, solutions,
granulates, dusts, sprays, aerosols, suspensions, ointments, creams, tablets, pellets or
powders.

Suitable pharmaceutical carriers for use in the said pharmaceutical compositions and their
formulation are well known to those skilled in the art, and there is no particular restriction
to their selection within the present invention. They may also include additives such as
wetting agents, dispersing agents, stickers, adhesives, emulsifying agents, solvents,
coatings, antibacterial and antifungal agents (for example phenol, sorbic acid,
chlorobutanol), isotonic agents (such as sugars or sodium chloride) and the like, provided
the same are consistent with pharmaceutical practice, i.e. carriers and additives which do
not create permanent damage to mammals. The pharmaceutical compositions of the
present invention may be prepared in any known manner, for instance by homogeneously
mixing, coating and/or grinding the active ingredients, in a one-step or multi-steps
procedure, with the selected carrier material and, where appropriate, the other additives
such as surface-active agents may also be prepared by incronisation, for instance in view
to obtain them in the form of microspheres usually having a diameter of about 1 to 10
gm, namely for the manufacture of microcapsules for controlled or sustained release of
the active ingredients.

Suitable surface-active agents, also known as emulgent or emulsifier, to be used in the
pharmaceutical compositions of the present invention are non-ionic, cationic and/or
anionic materials having good emulsifying, dispersing and/or wetting properties. Suitable
anionic surfactants include both water-soluble soaps and water-soluble synthetic surface-
active agents. Suitable soaps are alkaline or alkaline-earth metal salts, unsubstituted or
substituted ammonium salts of higher fatty acids (Ci0-C22), e.g. the sodium or potassium
salts of oleic or stearic acid, or of natural fatty acid mixtures obtainable form coconut oil
or tallow oil. Synthetic surfactants include sodium or calcium salts of polyacrylic acids;
fatty sulphonates and sulphates; sulphonated benzimidazole derivatives and
alkylaryl sulphonates. Fatty sulphonates or sulphates are usually in the form of alkaline or
alkaline-earth metal salts, unsubstituted ammonium salts or ammonium salts substituted with an alkyl or acyl radical having from 8 to 22 carbon atoms, e.g. the sodium or calcium salt of lignosulphonic acid or dodecylsulphonic acid or a mixture of fatty alcohol sulphates obtained from natural fatty acids, alkaline or alkaline-earth metal salts of sulphuric or sulphonic acid esters (such as sodium lauryl sulphate) and sulphonic acids of fatty alcohol/ethylene oxide adducts. Suitable sulphonated benzimidazole derivatives preferably contain 8 to 22 carbon atoms. Examples of alkylarylsulphonates are the sodium, calcium or alcanolamine salts of dodecylbenzene sulphonic acid or dibutyl-naphtalenesulphonic acid or a naphtalene-sulphonic acid/formaldehyde condensation product. Also suitable are the corresponding phosphates, e.g. salts of phosphoric acid ester and an adduct of p-nonylphenol with ethylene and/or propylene oxide, or phospholipids. Suitable phospholipids for this purpose are the natural (originating from animal or plant cells) or synthetic phospholipids of the cephalin or lecithin type such as e.g. phosphatidylethanolamine, phosphatidylserine, phosphatidylglycerine, lysolecithin, cardiolipin, dioctanlyphosphatidyl-choline, dipalmitoylphosphatidyl -choline and their mixtures.

Suitable non-ionic surfactants include polyethoxylated and polypropoxylated derivatives of alkylphenols, fatty alcohols, fatty acids, aliphatic amines or amides containing at least 12 carbon atoms in the molecule, alkylenesulphonates and dialkylsulphosuccinates, such as polyglycol ether derivatives of aliphatic and cycloaliphatic alcohols, saturated and unsaturated fatty acids and alkylphenols, said derivatives preferably containing 3 to 10 glycol ether groups and 8 to 20 carbon atoms in the (aliphatic) hydrocarbon moiety and 6 to 18 carbon atoms in the alkyl moiety of the alkylphenol. Further suitable non-ionic surfactants are water-soluble adducts of polyethylene oxide with polypropylene glycol, ethylenediaminopolypropylene glycol containing 1 to 10 carbon atoms in the alkyl chain, which adducts contain 20 to 250 ethyleneglycol ether groups and/or 10 to 100 propyleneglycol ether groups. Such compounds usually contain from 1 to 5 ethyleneglycol units per propyleneglycol unit. Representative examples of non-ionic surfactants are nonylphenol -polyethoxylethanol, castor oil polyglycolic ethers, polypropylene/polyethylene oxide adducts, tributylphenoxy(polyethoxylethanol, polyethyleneglycol and octylenoxypolyethoxylethanol. Fatty acid esters of polyethylene
sorbitan (such as polyoxyethylene sorbitan trioleate), glycerol, sorbitan, sucrose and pentaerythritol are also suitable non-ionic surfactants.

Suitable cationic surfactants include quaternary ammonium salts, particularly halides, having 4 hydrocarbon radicals optionally substituted with halo, phenyl, substituted phenyl or hydroxy; for instance quaternary ammonium salts containing as N-substituent at least one C8C22 alkyl radical (e.g. cetyl, lauryl, palmityl, myristyl, oleyl and the like) and, as further substituents, unsubstituted or halogenated lower alkyl, benzyl and/or hydroxy-lower alkyl radicals.


Compounds of the invention and their physiologically acceptable salts (hereafter collectively referred to as the active ingredients) may be administered by any route appropriate to the condition to be treated, suitable routes including oral, rectal, nasal, topical (including ocular, buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural). The preferred route of administration may vary with for example the condition of the recipient.

While it is possible for the active ingredients to be administered alone it is preferable to present them as pharmaceutical formulations. The formulations, both for veterinary and for human use, of the present invention comprise at least one active ingredient, as above described, together with one or more pharmaceutically acceptable carriers therefore and optionally other therapeutic ingredients. The carrier(s) optimally are "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. The formulations include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural) administration. The formulations may conveniently be presented in unit dosage form and
may be prepared by any of the methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients, in general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein. For infections of the eye or other external tissues e.g. mouth and skin, the formulations are optionally applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w (including active ingredient(s) in a range between 0.1% and 20% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc), preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, i.e. an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG400) and mixtures thereof. The topical formulations may desirably
include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogs.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Optionally, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus the cream should optionally be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is optionally present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% particularly about 1.5% w/w. Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin
and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate. Formulations suitable for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns (including particle sizes in a range between 20 and 500 microns in increments of 5 microns such as 30 microns, 35 microns, etc), which is administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nasal passage from a container of the powder held close up to the nose.

Suitable formulations wherein the carrier is a liquid, for administration as for example a nasal spray or as nasal drops, include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol administration may be prepared according to conventional methods and may be delivered with other therapeutic agents.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient. It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having
regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

Nucleoside analogs of the invention can be used to provide controlled release pharmaceutical formulations containing as active ingredient one or more compounds of the invention ("controlled release formulations") in which the release of the active ingredient can be controlled and regulated to allow less frequency dosing or to improve the pharmacokinetic or toxicity profile of a given invention compound. Controlled release formulations adapted for oral administration in which discrete units comprising one or more compounds of the invention can be prepared according to conventional methods. Additional ingredients may be included in order to control the duration of action of the active ingredient in the composition. Control release compositions may thus be achieved by selecting appropriate polymer carriers such as for example polyesters, polyamino acids, polyvinyl pyrrolidone, ethylene-vinyl acetate copolymers, methylcellulose, carboxymethylcellulose, protamine sulfate and the like. The rate of drug release and duration of action may also be controlled by incorporating the active ingredient into particles, e.g. microcapsules, of a polymeric substance such as hydrogels, polylactic acid, hydroxyethylcellulose, polyethyl methacrylate and the other above-described polymers. Such methods include colloid drug delivery systems like liposomes, microspheres, microemulsions, nanoparticles, nanocapsules and so on. Depending on the route of administration, the pharmaceutical composition may require protective coatings. Pharmaceutical forms suitable for injectionable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation thereof. Typical carriers for this purpose therefore include biocompatible aqueous buffers, ethanol, glycerol, propylene glycol, polyethylene glycol and the like and mixtures thereof.

In view of the fact that, when several active ingredients are used in combination, they do not necessarily bring out their joint therapeutic effect directly at the same time in the mammal to be treated, the corresponding composition may also be in the form of a medical kit or package containing the two ingredients in separate but adjacent repositories or compartments. In the latter context, each active ingredient may therefore
be formulated in a way suitable for an administration route different from that of the other ingredient, e.g. one of them may be in the form of an oral or parenteral formulation whereas the other is in the form of an ampoule for intravenous injection or an aerosol.

Prodrugs

Another embodiment of this invention relates to various precursor or "pro-drug" forms of the nucleoside analogs of the present invention. It may be desirable to formulate the nucleoside analogs of the present invention in the form of a chemical species which itself is not significantly biologically-active, but which when delivered to the animal or human will undergo a chemical reaction catalysed by the normal function of the body, *inter alia*, enzymes present in the stomach or in blood serum, said chemical reaction having the effect of releasing a nucleoside analog as defined herein. The term "pro-drug" thus relates to these species which are converted *in vivo* into the active pharmaceutical ingredient.

The pro-drugs of the present invention can have any form suitable to the formulator, for example, esters are non-limiting common pro-drug forms. In the present case, however, the pro-drug may necessarily exist in a form wherein a covalent bond is cleaved by the action of an enzyme present at the target *locus*. For example, a C-C covalent bond may be selectively cleaved by one or more enzymes at said target *locus* and, therefore, a pro-drug in a form other than an easily hydrolysable precursor, *inter alia* an ester, an amide, and the like, may be used. The counterpart of the active pharmaceutical ingredient in the pro-drug can have different structures such as an amino acid or peptide structure, alkyl chains, sugar moieties and others as known in the art.

For the purposes of the present invention the term "therapeutically suitable pro-drug" is defined herein as "a nucleoside analog modified in such a way as to be transformed *in vivo* to the therapeutically active form, whether by way of a single or by multiple biological transformations, when in contact with the tissues of the animal or human to which the pro-drug has been administered, and without undue toxicity, irritation, or allergic response, and achieving the intended therapeutic outcome ".
In a particular embodiment, the present invention relates to the phosphate or phosphonate prodrugs of the nucleoside analogs of the invention, thereby including but not limited to phosphate or phosphonate esters, amidates or esteramidates, wherein the phosphate or phosphonate can be mono- or disubstituted. Examples of such esters comprise alkyl esters, alkenyl esters, alkynyl esters, alkoxyalkyl esters, alkoxyalkenyl esters such as octyl, tetracosyl, hexadecyloxypropyl, octadecyloxyethyl, oleyloxypropyl, tetradecyloxypropyl, octadecyloxypropyl, oleyloxyethyl, 1-O-octadecyl-2-O-benzyl-glyceryl and the like as described in the prior art (i.e. Keith K.A. et al. Antimicrobial agents and chemotherapy 2004, 1869-1871; Ciesla, S.L. et al Antiviral Research 2003, 59, 163-171 and are incorporated herein by reference). In a particular embodiment, the esters have at least 16-carbon atoms. Also conversion to the cyclic ester with a lower polarity or neutral hydrophobic cyclic diester are possible. Also the di- or tri-phosphate are included in the nucleoside analogs of the invention.

It should be understood that phosphate or phosphonate prodrugs are very well known in the art as for example described in U.S. Patent No. 6,225,460 and U.S. Patent No. 5,977,089, which are incorporated by reference herein.

In a particular embodiment, the phosphate or phosphonate prodrugs are esters or amidates of alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; aryl; arylalkyl; heterocyclic ring; heterocyclic ring-alkyl; acyloxyalkyl; acyloxyalkenyl; acyloxyalkynyl; acyloxyaryl; acyloxyarylalkyl; acyloxyarylalkenyl; acyloxyarylalkynyl; dialkylcarbonate; alkylarylcarbonate; alkylalkenylcarbonate; alkylalkynylcarbonate; alkenylarylcarbonate; alkenyl-arylcarbonate; alkenylalkynylcarbonate; dialkenylcarbonate; dialkynyl-carbonate; wherein said alkyl, alkenyl and alkynyl can contain a heteroatom in or at the end of the hydrocarbon chain, said heteroatom being selected from the group consisting of oxygen, sulfur and nitrogen; or the prodrugs are further selected from substituents known for phosphates or phosphonates described as anti-viral agents.

In yet another particular embodiment, the phosphates, respectively the phosphonate groups are according to the Formulae (P-2) or (P-3) respectively,
wherein - each $R_{3}^{0}$ and $R_{3}^{1}$ are independently selected from the group consisting of hydrogen; (- $PO_{3}R_{3}^{2}$VPO , $R_{3}^{3}$; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; aryl; arylalkyl; heterocyclic ring; heterocyclic ring-alkyl; acyloxyalkyl; acyloxyalkenyl; acyloxyalkynyl; acyloxaryl; acyloxarylalkyl; acyloxarylalkenyl; acyloxarylalkynyl; dialkylcarbonate; alkylarylcarbonate; alkylalkenylcarbonate; alkylalkynylcarbonate; alkenylarlylcarbonate; alkenylarylcarbonate; alkenylalkynylcarbonate; dialkenylcarbonate; dialkynyl-carbonate; wherein said alkyl, alkenyl and alkynyl can contain a heteroatom in or at the end of the hydrocarbon chain, said heteroatom being selected from the group consisting of oxygen, sulfur and nitrogen; and $R_{3}^{0}$ and $R_{3}^{1}$ are further selected from substituents known for phosphonates described as anti-viral agents; - $R_{3}^{2}$, $R_{3}^{3}$ and $R_{3}^{4}$ are each independently selected from the group consisting of hydrogen; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; aryl; arylalkyl; heterocyclic ring; heterocyclic ring-alkyl; acyloxyalkyl; wherein said alkyl, alkenyl and alkynyl can contain a heteroatom in or at the end of the hydrocarbon chain, said heteroatom being selected from the group consisting of oxygen, sulfur and nitrogen; and $R_{3}^{2}$, $R_{3}^{3}$ and $R_{3}^{4}$ are further selected from substituents known for phosphonates described as anti-viral agents;
- m is 0 or 1;
- q is 1, 2, 3, 4, 5 or 6.

It is understood that the prodrugs can also be in the form of amidates wherein in a particular embodiment the oxygen of each of $OR_{3}^{0}$ and $OR_{3}^{1}$ can be a nitrogen such as NHR$_{3}^{0}$ and NHR$_{3}^{1}$.

Method of preparation
The nucleoside analogs of the invention according to the formulae of the application can be prepared while using a series of chemical reactions known to those skilled in the art, altogether making up the process for preparing said compounds and exemplified further. The processes described further are only meant as examples and by no means are meant to limit the scope of the present invention.

The compound of this invention can be prepared by the following general methods:

**Method A (see Example 3):**

The nucleoside analogs with a structure in analogy with the nucleoside analogs 11, 12, 17, 18, 19, 21, 22, 28, 30, 31, 51, and 52 can be prepared by reaction of 6-chloropurine or 2,6-dichloropurine or any other pyrimidine or purine heterocycle (or their aza or deaza analogs) with compounds of the formulae I to IX and XX and XXI (and analogous structures), performed under Mitsunobu's conditions. The reaction may generally be carried out in tetrahydrofurane or 1,4-dioxane in the presence of triphenylphosphine and diethyl or diisopropyl azodicarboxylate at a temperature from room temperature (about 20 °C) to the boiling point of the solvent used. The compounds thus obtained can be separated from the reaction mixture by chromatography.

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Furthermore, starting from the nucleoside analogs 51 or 52, the nucleoside analogs 35 and 36 can be prepared by the treatment of the benzoates 51 or 52 with a reducing agent such as lithium aluminium hydride or diisobutyl aluminium hydride in tetrahydrofurane at a temperature from -78 °C to 0 °C (Example 4).

**Method B:**

*General Method B*

The nucleoside analogs with a structure in analogy with the nucleoside analog 23 (Example 5) can be prepared from the amine of the formula X and analogous structures like compounds 25, 27 and 57 can for example be prepared with the starting materials XXII, XXIII or XXIV:
by the following two step reaction:
1. Treatment with 5-amino-4,6-dichloropyrimidine can be performed in alcohol (e.g. ethanol, 1-propanol, 2-propanol, 1-butanol) in the presence of triethylamine at a temperature from 100 °C to 110 °C.
2. The next step, ring-closure can be carried out in trimethyl or triethyl orthoformate in the presence of acid such as concentrated hydrochloric acid, sulfuric acid or trifluoroacetic acid. Chromatography or crystallization from aqueous ethanol or aqueous methanol can be used for isolation of thus obtained compounds from the reaction mixture.

The nucleoside analogs with a structure in analogy with the nucleoside analogs 1, 14, 16, 24, 26, 32, 58, 59, 60, 62, 63, 64, 65 and 66 (Example 6) can be prepared from the amines of the formula XI-XXXIII (and analogous structures) by the same procedure as described for 23 followed by hydrolysis which can be performed in the mixture of tetrahydrofurane or dioxane and diluted mineral acid (e.g. hydrochloric acid, sulfuric acid).
Intermediate amines for method $B$:

- The amines of the formulae XI- XIII (and analogous structures) can be prepared from the unsaturated diols having the formulae XVI to XVIII
by the following method (reaction procedure (2)):

(XVI, XVII or XVIII) → (XI, XII or XIII)

(reaction procedure 2, wherein $Z^1$ is a methylene, an ethylene group, an oxygen atom).

The reaction procedure 2 can be effected by reacting XVI, XVII or XVIII with benzyl azidoformate in the presence of a small amount of an inert solvent such as toluene, dioxane at a temperature from around 68 °C to 110 °C. This is followed by hydrogenolysis of the obtained benzyloxycarbonylamine which can be performed in an organic solvent (e.g. methanol, ethanol) in the presence of palladium on carbon at room temperature.

- The unsaturated amine of the formula XIV can be obtained by multistep reaction procedure(1) (Example 7):
Commercially available 5-norbornen-2-yl acetate can be treated with ethyl azidoformate in toluene at 80 °C and then with silica gel. Unsaturated carbamate can be separated from thus obtained mixture by chromatography. Acetyl group can be removed with potassium carbonate in methanol or sodium methoxide in methanol. Conversion of the obtained exo-hydroxy to the endo-hydroxy derivative can be performed by oxidation with pyridinium dichromate followed by reduction thus obtained ketone with sodium borohydride. The free amine (XIV) can be obtained by deprotection with potassium hydroxide in boiling aqueous ethanol.

- The amine of the formula (XV) can be prepared from the unsaturated amine having the formula (XIV) by hydrogenation on palladium catalyst in an alcohol (e.g. methanol, ethanol).

- The nucleoside analogs with a structure in analogy with the nucleoside analogs 2 and 20 (Example 8) can be prepared by the treatment of the compound 1 or 16 respectively, with methyl iodide in dimethylformamide.

- The nucleoside analogs with a structure in analogy with the nucleoside analog 7 (Example 10) can be prepared by the treatment of the compound 1 with benzyl bromide and sodium hydride in dimethylformamide.

- The nucleoside analogs with a structure in analogy with the nucleoside analog 6 (Example 11) can be prepared by the treatment of the compound 1 with phenyl-
(methoxy-L-alaninyl)-phosphorochloridate in the presence of 1-methylimidazole in tetrahydrofurane.

- The nucleoside analogs with a structure in analogy with the nucleoside analogs 8 (Example 12) can be prepared by the treatment of the compound 1 with thionyl chloride in hexamethylphosphortriamide. With the same procedure, for example, compounds 67 and 68 can be prepared from their hydroxy-comprising analogs.

- The compounds as 69, 70, 71 and 72 and analogs thereof can be prepared by the treatment of their hydroxyl-comprising counterparts like compound 14 with (diethylamino)sulfur trifluoride (DAST) in a mixture dichloromethane and pyridine at a temperature from 15 °C to 40 °C.

- Modifications like in compound 42 can be prepared by the treatment of the compound 31 with peracid (e.g. peracetic acid, m-chloroperbenzoic acid) in chlorinated solvent (e.g. chloroform, dichloromethane). Also dihydroxy-substituents like in compound 37 can be introduced starting from compound 31 by the treatment with osmium tetroxide and 4-methylmorpholine-4-oxide in a mixture of water and methanol.

- Deaza-purine analogs like the compound below

![Deaza-purine analog](attachment:image)

can be prepared in analogy with the purine analogs. For example, the compound above can be prepared by the treatment of the compound 1 with 4-chloro-7H-pyrrolo[2,3-c]pyrimidine under conditions of the Mitsunobu reaction.

The purine base of the nucleoside analogs can be modified using the known methods as shown for compound 1 in the Scheme 1.
Scheme 1: Modification of a purine base of compounds of the invention.
All other nucleoside analogs not explicitly mentioned in this general description can be prepared by using the methods as described herein and further combined with the knowledge of a person skilled in the art. This counts for pyrimidines, their aza or deaza analogs or different substituents on the pyrimidine or purine heterocycles.

Examples

The following examples are provided for the purpose of illustrating the present invention and should in no way be interpreted as limiting the scope thereof.

Table 1: Structures of example nucleoside analogs of the invention and their respective codes.

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EXAMPLE 1: ANTIVIRAL SCREENING - ANTI-CBV ASSAY

*Anti-Coxsackie virus assay:* Ninety-six-well cell culture plates can be seeded with Vero cells in DMEM medium containing 10 fetal calf serum (FCS) so that cells reach confluency 24-48 hr later. Medium can then be removed and serial 5-fold dilutions of the test compounds can be added in a total volume of 100 µl, after which the virus inoculum (100 µl) can be added to each well. The virus inoculum used results normally in a 90-100% destruction of the cell monolayer after 5 days incubation at 37°C. Uninfected cells and cells receiving virus without compound can be included in each assay plate. After 5
days, the medium can be removed and 90 µl of DMEM-FCS and 10 µl of MTS/PMS solution (Promega) was added to each well. Following a 2 h incubation period at 37°C, the optical density of the wells can be read at 498 nm in a microplate reader. The 50% effective concentration (EC50) value can then be defined as the concentration of compound that protects 50% of the cell monolayer from virus-induced cytopathic effect.

Cytostatic activity assays: All assays are performed in 96-well microtiter plates. To each well are added 5 - 7.5 x 10⁴ Vero cells and a given amount of the test compound. The cells are allowed to proliferate for 72 h at 37°C in a humidified CO₂-controlled atmosphere. At the end of the incubation period the effect of the compounds on cell proliferation is measured using the MTS/PMS method (Promega). The CC₅₀ (50% cytostatic concentration) was defined as the concentration of the compound that reduced the number of cells by 50%.

Many nucleoside analogs of the invention showed an EC50 of between 5 µM and 50 µM, while the CC50 was always higher than 200 µM. As an example, results of some nucleoside analogs in the anti-Coxsackie virus B3 (CBV) assay are shown in table 2.

Table 2: anti-CBV activity of some nucleoside analogs of the invention

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EXAMPLE 2: MATERIALS AND GENERAL PREPARATION METHODS

For all reactions, analytical grade solvents were used. All moisture sensitive reactions were carried out in oven-dried glassware (135 °C) under a argon atmosphere. All standard equipment was used for the chemical preparation and analysis. For example, a Varian Unity 500 MHz spectrometer or a 200 MHz Varian Gemini apparatus can used for $^1$H NMR and $^{13}$C NMR. Exact mass measurements can be performed on a quadrupole time-of-flight mass spectrometer (Q-Tof-2, Micromass, Manchester, UK) equipped with a standard electrospray-ionization (ESI) interface; samples can be infused in i-PrOH/H$_2$O 1:1 at 3 µL/min.

EXAMPLE 3: SYNTHESIS OF NUCLEOSIDE ANALOGS OF THE INVENTION SUCH AS 17, VIA MITSUNOBU REACTION (METHOD A)

To a mixture of bicyclo[2.2.1]heptan-2-ol (500 mg, 4.45 mmol), triphenylphospine (1.52 g, 5.79 mmol) and 6-chloropurine (757 mg, 4.90 mmol) in THF (35 ml) was dropwise added solution of the diisopropyl azadicarboxylate (1.19 ml, 5.79 mmol) in THF (15 ml). The resulting mixture was stirred overnight (TLC control) and then heated to reflux for 2 hours. The reaction mixture was evaporated and the residue was chromatographed on silica gel column (200 g) in toluene - ethylacetate (6:1 → 4:1) and crystallized from water-methanol. It was obtained 430 mg (39%) of 9-[(lR*,2R*,4S*)-bicyclo[2.2.1]hept-2-yl]-6-chloro-9H-purine (~ example isomeric pure form of 17), m.p. = 104.2 - 104.8 °C. For C$_{12}$H$_{13}$ClN$_4$ (248.7) calculated: 57.95% C, 5.27% H, 14.25% Cl,
22.53% N; found: 57.93% C, 5.32% H, 14.29% Cl, 22.34% N. \(^1\)H NMR (DMSO-(d_6)): 1.27 m, 1 H (H-5'exo); 1.28 m, 1 H (H-7'b); 1.40 ddd, 1 H, \(J_{gem} = 12.1\), \(J(6'ex,5'exo) = 9.1\), \(J(6'ex,5'en) = 4.1\), \(J(6'ex,7'a) = 2.3\) (H-6'exo); 1.54 m, 1 H (H-5'endo); 1.62 tt, 1 H, \(J_{gem} = J(6'en,5'en) = 12.2\), \(J(6'en,5'ex) = J(6'en,1') = 4.5\) (H-6'endo); 1.71 dm, 1 H, \(J_{gem} = 10.3\) (H-7'a); 2.00 ddd, 1 H, \(J_{gem} = 13.4\), \(J(3'ex,2') = 8.5\), \(J(3'ex,7'b) = 2.3\) (H-3'exo); 2.07 m, 1 H (H-3'endo); 2.43 bt, 1 H, \(J(4',3'endo) = J(4',5'en) = 4.2\) (H-4'); 2.55 bd, 1 H, \(J(1',6'en) = 4.6\) (H-I'); 4.56 ddd, 1 H, \(J(2',3'exo) = 8.4\), \(J(2',3'en) = 4.5\), \(J(2',7'bd) = 0.9\) (H-2'); 8.77 s, 1 H (H-2); 8.85 s, 1 H (H-8). \(^{13}\)C NMR (DMSO-(d_6)): 26.94 (C-6'); 27.95 (C-5'); 35.82 (C-7'); 35.93 (C-4'); 37.76 (C-3'); 42.16 (C-1'); 58.37 (C-2'); 131.43 (C-5'); 145.62 (C-8); 149.11 (C-6); 151.45 (C-2); 152.11 (C-4).

According to the same procedure, there were obtained the following compounds:

- **9-[(IR*,2R*,4S*)-Bicyclo[2.2.1]hept-2-yl]-2,6-dichloro-9H-purine** (~ example isomeric pure form of 18), m.p. = 163.3 - 164 °C. For \(\text{C}_{12}\text{H}_{12}\text{Cl}_{2}\text{N}_{4}\) (283.2) calculated: 50.90% C, 4.27% H, 25.04% Cl, 19.79% N; found: 50.96% C, 4.18% H, 24.94% Cl, 19.71% N. \(^1\)H NMR (DMSO-de): 1.28 m, 1 H (H-5'endo); 1.29 dm, 1 H, \(J_{gem} = 10.3\) (H-7'a); 1.40 ddd, 1 H, \(J_{gem} = 12.1\), \(J(6'en,5'endo) = 8.9\), \(J(6'en,5'ex) = 4.2\), \(J(6'en,7'b) = 2.3\) (H-6'endo); 1.53 m, 1 H (H-5'exo); 1.62 tt, 1 H, \(J_{gem} = J(6'ex,5'ex) = 12.2\), \(J(6'ex,5'en) = J(6'ex,1') = 4.5\) (H-6'exo); 1.69 dm, 1 H, \(J_{gem} = 10.4\) (H-7'b); 2.00 m, 2 H (H-3'endo and H-3'exo); 2.42 m, 1 H (H-4'); 2.57 dm, 1 H, \(J(1',6'ex) = 4.6\) (H-I'); 4.49 m, 1 H (H-2'); 8.89 s, 1 H (H-8). \(^{13}\)C NMR (DMSO-d_6): 26.92 (C-6'); 27.89 (C-5'); 35.89 (C-7'); 35.92 (C-4'); 37.90 (C-3'); 41.95 (C-1'); 58.48 (C-2'); 131.05 (C-5); 146.56 (C-8); 149.65 and 150.82 (C-2 and C-6); 153.63 (C-4).

- **6-Chloro-9-[(IS,2S,4S)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-9H-purine** (~ example isomeric pure form of 19), m.p. = 132.3 - 134.5 °C. \([\alpha]_{D} +25.2\) (c 0.352, methanol). For \(\text{C}_{15}\text{H}_{19}\text{Cl}_{4}\) (290.8) calculated: 61.96% C, 6.59% H, 12.19% Cl, 19.27% N; found: 61.89% C, 6.70% H, 12.31% Cl, 19.07% N. \(^1\)H NMR (DMSO-d_6): 0.65 s, 3 H (1'-CH_3); 0.85 s, 3 H and 0.99 s, 3 H (2 x 7'-CH_3); 1.33 ddd, 1 H, \(J_{gem} = 12.3\), \(J(5'en,6'en) = 9.3\), \(J(5'en,6'ex) = 4.9\) (H-5'endo); 1.45 ddd, 1 H, \(J_{gem} = 12.4\), \(J(6'en,5'en) = 9.2\), \(J(6'en,5'ex) = 3.6\) (H-6'endo); 1.66 dt, 1 H, \(J_{gem} =
$J(6'_{ex},5'_{ex}) = 12.2, J(6'_{ex},5'_{en}) = 4.9$ (H-6'exo); $1.82$ m, $1$ H (H-5'exo); $1.95$ t, $1$ 
H, $J(4',3'_{ex}) = J(4',5'_{ex}) = 4.2$ (H-4'); $1.99$ dd, $1$ H, $J_{gem} = 13.2, J(3'_{en},2') = 9.6$
(H-3'endo); $2.77$ dddd, $1$ H, $J_{gem} = 13.3, J(3'_{ex},2') = 6.9, J(3'_{ex},4') = 4.0,$
$J(3'_{ex},5'_{ex}) = 3.2$ (H-3'exo); $4.70$ dd, $1$ H, $J(2',3'_{en}) = 9.5, J(2',3'_{ex}) = 6.9$ (H-2');
$8.79$ s, $1$ H (H-2); $9.00$ s, $1$ H (H-8). $^{13}$C NMR (DMSO-de): $12.06$ (1'-CH$_3$); $19.82$
and $21.13$ (2 x 7'-CH$_3$); $26.55$ (C-5'); $34.31$ (C-3'); $36.64$ (C-6'); $44.59$ (C-4');
$47.24$ (C-7); $50.66$ (C-1'); $63.15$ (C-2'); $131.18$ (C-5); $146.77$ (C-8); $149.28$ (C-6);
$151.41$ (C-2); $153.48$ (C-4).

- 6-Chloro-9-[[1S,2S,5S]-6,6-dimethylbicyclo[3.1.1]hept-2-yl]methyl]-9H-purine

(~ example isomeric pure form of 21), m.p. = 88.5 - 89.8 °C. [α]$_D$ -12.2 (c 0.779,
methanol). For C$_5$H$_9$ClN$_4$ (290.8) calculated: $61.96$% C, $6.59$% H, $12.19$% Cl,
$19.27$% N; found: $61.91$% C, $6.59$% H, $12.29$% Cl, $18.96$% N. $^1$H NMR (DMSO-
de): $0.74$ s, $3$ H and $1.12$ s, $3$ H (2 x 6'-CH$_3$); $1.37$ - $1.48$ m, $3$ H (H-3'a, H-3'b and
H-7'a); $1.62$ dt, $1$ H, $J(1'_{7b}) = J(1'_{5'}) = 5.4, J(1'_{2'}) = 1.0$ (H-I'); $1.70$ m, $2$ H
(H-4'); $1.83$ m, $1$ H (H-5'); $2.06$ dt, $1$ H, $J_{gem} = 10.2, J(7'b_{1''}) = J(7'b_{5'}) = 5.8$
(H-7'b); $2.60$ m, $1$ H (H-2'); $4.13$ m, $2$ H (CH$_2$N); $8.73$ s, $1$ H (H-8); $8.77$ s, $1$ H (H-2).
$^{13}$C NMR (DMSO-d$_6$): $18.89$ (C-3'); $20.08$ (6'-CH$_3$); $23.06$ (C-7'); $23.71$ (C-4');
$26.57$ (6'-CH$_3$); $35.03$ (C-2'); $39.10$ (C-6'); $40.30$ (C-5'); $42.55$ (C-1'); $48.47$
(CH$_2$N); $130.89$ (C-5); $148.00$ (C-8); $149.19$ (C-6); $151.71$ (C-2); $152.37$ (C-4).

- 2,6-Dichloro-9-[[1S,2S,5S]-6,6-dimethylbicyclo[3.1.1]hept-2-yl]methyl]-9H-
purine (~ example isomeric pure form of 22), m.p. = 104.6 - 106.5 °C. [α]$_D$ -11.0 (c
0.504, methanol). For C$_5$H$_9$Cl$_2$N$_4$ (325.3) calculated: $55.39$% C, $5.58$% H, $21.80$%
Cl, $17.23$% N; found: $55.39$% C, $5.49$% H, $22.09$% Cl, $16.96$% N. $^1$H NMR
(DMSO-d$_6$): $0.76$ s, $3$ H and $1.14$ s, $3$ H (2 x 6'-CH$_3$); $1.35$ - $1.50$ m, $3$ H (H-3'a,
H-3'b and H-7'a); $1.64$ t, $1$ H, $J(1'_{7b}) = J(1'_{5'}) = 5.4$ (H-I'); $1.71$ m, $2$ H (H-4');
$1.84$ m, $1$ H (H-5'); $2.06$ dt, $1$ H, $J_{gem} = 10.1, J(7'b_{1''}) = J(7'b_{5'}) = 5.8$ (H-7'b);
$2.56$ m, $1$ H (H-2'); $4.08$ m, $2$ H (CH$_2$N); $8.76$ s, $1$ H (H-8). $^{13}$C NMR (DMSO-
d$_6$): $18.87$ (C-3'); $20.08$ (6'-CH$_3$); $23.04$ (C-7'); $23.70$ (C-4'); $26.57$ (6'-CH$_3$); $34.78$
(C-2'); $39.12$ (C-6'); $40.30$ (C-5'); $42.48$ (C-1'); $48.68$ (CH$_2$N); $130.58$ (C-5); $148.93$
(C-8); $149.76$ and $151.08$ (C-2 and C-6); $153.87$ (C-4).
  (~ example isomeric pure form of 28), m.p. = 83.3 - 84.8 °C. [α]D = -33.0 (c 0.721, methanol). For C15H17ClN4 (288.8) calculated: 62.39% C, 5.93% H, 12.28% Cl, 19.40% N; found: 62.56% C, 6.06% H, 12.07% Cl, 19.22% N. 1H NMR (DMSO-d6): 0.51 s, 3 H (6'-CH3); 1.05 d, 1 H, J gem = 8.6 (H-7'a); 1.13 s, 3 H (6'-CH3); 2.01 m, 1 H (H-5'); 2.07 dt, 1 H, J(1'-7'b) = J(1'-5') = 5.6, J(1'-3') = 1.6 (H-1'); 2.13 dm, 1 H, J gem = 18.0 (H-4'a); 2.25 dm, 1 H, J gem = 18.1 (H-4'b); 2.31 dt, 1 H, J gem = 8.6, J(7'b,1') = J(7'b,5') = 5.6 (H-7'b); 4.83 m, 2 H (CH2N); 5.48 m, 1 H (H-3'); 8.69 s, 1 H (H-8); 8.78 s, 1 H (H-2). 13C NMR (DMSO-d6): 20.83 and 25.93 (2 x 6'-CH3); 30.87 (C-7'); 31.11 (C-4'); 37.76 (C-6'); 40.09 (C-5'); 43.24 (C-1'); 48.20 (CH2N); 121.17 (C-3'); 130.86 (C-5); 142.52 (C-2'); 147.78 (C-8); 149.24 (C-6); 151.85 (C-2); 152.16 (C-4).

- 6-Chloro-9-\{[(lS,2R,4R)-3,3-dimethylbicyclo[2.2.1]hept-2-yl]-9H-purine
  (~ example isomeric pure form of 30), m.p. = 112.3 - 114 °C. [α]D = +3.0 (c 0.231, methanol). For C14H17ClN4 (276.8) calculated: 60.76% C, 6.19% H, 12.81% Cl, 20.24% N; found: 60.48% C, 6.36% H, 12.57% Cl, 19.79% N. 1H NMR (DMSO-d6): 0.39 s, 3 H and 1.27 s, 3 H (2 x 3'-CH3); 1.40 - 1.48 m, 3 H (H-5'ex, H-6'en and H-7'a); 1.73 m, 2 H (H-5'en and H-6'ex); 1.92 dm, 1 H, J(4',5'ex) = 3.6 (H-4'); 2.28 dm, 1 H, J gem = 10.8 (H-7'b); 2.70 dm, 1 H, J(1',6'ex) = 4.8 (H-I'); 4.15 d, 1 H, J(2',7'a) = 1.6 (H-2'); 8.78 s, 1 H (H-8); 8.78 s, 1 H (H-2). 13C NMR (DMSO-Ci6D6): 23.37 (3'-CH3); 23.59 (C-5'); 26.14 (3'-CH3); 28.22 (C-6'); 37.09 (C-T); 42.68 (C-1'); 44.46 (C-3'); 48.03 (C-4'); 68.08 (C-2'); 131.57 (C-5); 145.68 (C-8); 149.22 (C-6); 151.82 (C-2); 152.16 (C-4).

- 9-\{(IR*,2S*,4R*)-Bicyclo[2.2.1]hept-5-en-2-yl\}-6-chloro-9H-purine
  (~ example isomeric pure form of 31), m.p. = 117.5 - 118.5 °C. For C12H11ClN4 (246.7) calculated: 58.42% C, 4.49% H, 14.37% Cl, 22.71% N; found: 58.44% C, 4.38% H, 14.34% Cl, 22.44% N. 1H NMR (DMSO-Cl6D6): 1.56 dm, 1 H, J gem = 9.2 (H-7'a); 1.79 dm, 1 H, J gem = 9.2 (H-7'b); 1.88 ddd, 1 H, J gem = 12.6, J(3en,2) = 8.3, J(3en,7a) = 2.6 (H-3endo); 2.18 dt, 1 H, J gem = 12.6, J(3ex,2) = J(3ex,4) = 3.7 (H-3exo); 3.05 m, 1 H (H-4); 3.21 m, 1 H (H-I); 4.46 ddd, 1 H, J(2,3en) = 8.3, J(2,3ex) = 3.9, J(2,7a) = 1.6 (H-2); 6.26 dd, 1 H, J(6,5) = 5.7, J(6,1) = 3.2 (H-6);
6.37 dd, 1 H, \(J(5,6) = 5.7\), \(J(5,4) = 2.9\) (H-5); 8.78 s, 1 H (H-2'); 8.93 s, 1 H (H-8').

\(^{13}\)C NMR (DMSO\(_d^6\)): 32.14 (C-3); 41.28 (C-4); 46.23 (C-7); 47.55 (C-I); 55.82 (C-2); 131.51 (C-5'); 134.48 (C-6); 140.21 (C-5); 145.96 (C-8'); 149.14 (C-6'); 151.49 (C-2'); 152.60 (C-4').

- \([\text{dd}, 2.00 
  \text{H}, \text{J}(3\text{exo,2}) = 8.5, \text{J}(3\text{exo,7a}) = 2.2, (H-5exo); 2.27 m, 1 H (H-2); 2.3 m, 1 H (H-4); 2.75 bs, 1 H (H-I); 4.16 dd, 1 H, \text{J}_{\text{gem}} = 11.1, J(\text{OCH}_2\text{b},2) = 6.0 (\text{OCH}_2\text{b}); 4.26 dd, 1 H, \text{J}_{\text{gem}} = 11.1, J(\text{OCH}_2\text{a},2) = 9.4 (\text{OCH}_2\text{a}); 4.68 dd 1 H J(6\text{exo}) = 8.5, J(6\text{en}) = 4.0 \text{(H-6); 7.44 m, 2 H (H-3'); 7.57 m, 1 H (H-4')}; 8.04 m, 2 H (H-2'); 8.24 s, 1 H, (H-8'); 8.73 s, 1 H (H-2'). \(^{13}\)C NMR (CDCl\(_3\)): 32.43 (C-3); 33.45 (C-7); 36.02 (C-4); 38.20 (C-5); 39.31 (C-2); 44.36 (C-I); 58.53 (C-6); 66.63 (CH\(_2\)O); 128.38 (C-3'); 129.53 (C-2'); 129.91 (C-I'); 131.95 (C-5'); 133.10 (C-4'); 142.60 (C-8'); 150.94 (C-6'); 151.64 (C-2'); 151.82 (C-4'); 166.48 (C=O).

- \([(\text{IR}*,2\text{S}*,4\text{R}*,55*)-5-(\text{6-Chloro-9 \ H-purin-9-yl})\text{bicyclo}[2.2.1]hept-2-yl]\text{methyl benzoate} \text{(example isomeric pure form of 51), m.p.} 130.5 - 131.5 °C. For C\(_{20}\)H\(_{19}\)ClN\(_4\)O\(_2\) (382.84) calculated: 62.74% C, 5.00% H, 9.26% Cl, 14.63% N; found: 62.77% C, 5.11% H, 9.20% Cl, 14.35% N. \(^1\)H NMR (CDCl\(_3\)): 1.35 dddd, 1 H, \text{J}_{\text{gem}} = 12.7, J(3\text{en},2) = 5.1, J(3\text{en},4) = 4.2, J(3\text{en},5\text{en}) = 3.0 \text{(H-3endo); 1.64-1.72 m, 3 H (H-7a, 7b, 3exo); 2.00 dm, 1H \text{J}_{\text{gem}} = 13.7 \text{(H-5endo); 2.21 ddd, IH}, \text{J}_{\text{gem}} = 13.8, J(5\text{exo},6) = 8.5, j(5\text{exo},7a) = 2.2, (H-5exo); 2.27 m, 1 H (H-2); 2.3 m, 1 H (H-4); 2.75 bs, 1 H (H-I); 4.16 dd, 1 H, \text{J}_{\text{gem}} = 11.1, J(\text{OCH}_2\text{b},2) = 6.0 (\text{OCH}_2\text{b}); 4.26 dd, 1 H, \text{J}_{\text{gem}} = 11.1, J(\text{OCH}_2\text{a},2) = 9.4 (\text{OCH}_2\text{a}); 4.68 dd 1 H J(6\text{exo}) = 8.5, J(6\text{en}) = 4.0 \text{(H-6); 7.44 m, 2 H (H-3'); 7.57 m, 1 H (H-4')}
H, (H-8'); 8.76 s, 1 H (H-2'). 13C NMR (CDCl₃): 31.59 (C-3); 33.48 (C-7); 38.49 (C-1); 39.10 (C-6); 39.91 (C-2); 42.35 (C-4); 57.87 (C-5); 67.29 (CH₂O); 128.40 (C-3''); 129.53 (C-2''); 130.03 (C-1'); 131.89 (C-5'); 133.07 (C-4''); 142.60 (C-8'); 150.98 (C-6'); 151.69 (C-2''); 151.79 (C-4'); 166.54 (C=O).

- (IR,2R,3R,6R,7S,9R)-9-[(6-Chloro-9#-purin-9-yl)methyl]-4-

oxatricyclo[4.2.1.0^3]^3-noreryl-2-ol (11), m.p. 245.5 - 247.5 °C. For C₁₄H₁₃ClN₄O₂ (306.76) calculated: 54.82% C, 4.93% H, 11.56% Cl, 18.26% N; found: 54.93% C, 4.98% H, 11.76% Cl, 18.19% N. ¹H NMR: 1.64 m, 1 H (H-I); 1.80 m, 2 H (H-8); 1.84 td, 1 H, J(9,CH₂) = 8.4, J(9,6) = 2.5 (H-9); 2.03 m, 1 H (H-6); 2.53 m, 1 H (H-7); 3.11 m, 1 H (H-2); 3.45 d, 1 H, J_gem = 8.0 (H-5a); 3.55 dd, 1 H, J_gem = 8.0, J(5b,6) = 3.9 (H-5b); 3.76 dd, 1 H, J(3,7) = 5.0, J(3,1) = 1.4 (H-3); 4.28 m, 2 H (9-CH₂); 4.72 d, 1 H, J(OH,2) = 2.6 (OH); 8.79 s, 1 H (H-8'); 8.80 s, 1 H (H-2'). ¹³C NMR: 30.61 (C-8); 42.34 (C-6); 43.80 (C-I); 44.12 (C-7); 45.69 (C-9); 46.33 (9-CH₂); 73.47 (C-5); 79.88 (C-2); 86.40 (C-3); 130.93 (C-5'); 147.86 (C-8'); 149.26 (C-6'); 151.80 (C-2'); 152.31 (C-4').

- (IR,2R,3R,6R,7S,9R)-9-[(2,6-Dichloro-9 H-purin-9-yl)methyl]-4-

oxatricyclo[4.2.1.0^3]^3-noreryl-2-ol (12), m.p. 260 - 262 °C. For C₁₄H₁₃Cl₂N₄O₂ (341.20) calculated: 49.28% C, 4.14% H, 20.78% Cl, 16.42% N; found: 48.99% C, 4.12% H, 20.77% Cl, 16.20% N.

6-chloro-9-[(li?*,2?*,6?*,7?*,8?*)-tricyclo[5.2.1.0^26]dec-8-yl]-9 H-purine (55), m.p. = 104.3 - 106.5 °C. For C₃₅H₂₅ClN₄ (288.8) calculated: 62.39% C, 5.93% H, 12.28% Cl, 19.40% N; found: 62.25% C, 5.86% H, 12.53% Cl, 19.17% N. ¹H NMR (DMSO, 600.13 MHz): 0.93 - 1.01 m, 2 H (H-3'a and H-5'a); 1.17 - 1.26 m, 2 H (H-4'); 1.44 dm, 1 H, J_gem = 11.1 (H-10'a); 1.47 dm, 1 H, J_gem = 11.1 (H-10'b); 1.65 m, 1 H (H-4'); 1.83 - 1.90 m, 2 H (H-3'b and H-5'b); 1.91 m, 1 H (H-2'); 1.93 m, 1 H (H-9'endo); 2.02 m, 1 H (H-6'); 2.05 dt, 1 H, J_gem = 13.3, J(9'ex,8') = J(9'ex,l') = 4.3 (H-9'exo); 2.15 d, 1 H, J(1',9'ex) = 4.4 (H-I'); 2.33 s, 1 H (H-7'); 4.48 ddd, 1 H, J(8',9'en) = 8.4, J(8',9'ex) = 4.2, J(8',10'a) = 1.0 (H-8'); 8.77 s, 1 H (H-2); 8.86 s, 1 H (H-8). ¹³C NMR (DMSO, 150.92 MHz): 27.46 (C-4'); 29.95 (C-10'); 31.48 (C-3'); 31.87 (C-5'); 36.81 (C-9'); 40.21 (C-I');
• 6-chloro-9-([li?*,8i?*,95*]-tricyclo[6.2.1.0²°]undeca-2,4,6-trien-9-yl)-9 H-purine (56), m.p. = 202.1 - 203.2 °C. For C₁₆H₁₁ClN₄ x Å H₂O (301.3) calculated: 64.76% C, 4.42% H, 11.95% Cl, 18.88% N; found: 63.89% C, 4.21% H, 12.19% Cl, 18.40% N. 'H NMR (DMSO, 499.84 MHz): 1.88 d, 1 H, J<sub>gem</sub> = 9.7 (H-I 1'a); 1.99 ddd, 1 H, J<sub>gem</sub> = 12.9, J(IO 'en, 9') = 8.4, J(10'en,Il 'a) = 2.5 (H-10'endo); 2.20 dt, 1 H, J<sub>gem</sub> = 9.8, J(11'b, l ') = J(11'b,8') = 1.4 (H-I 1'b); 2.52 dt, 1 H, J<sub>gem</sub> = 12.9, J(10'ex,9') = J(10'ex,l ') = 4.0 (H-10'exo); 3.56 m, 1 H (H-I '); 3.73 bs, 1 H (H-8'); 4.53 ddd, 1 H, J(9',10'en) = 8.3, J(9',10'ex) = 4.2, J(9',Il 'a) = 1.0 (H-9'); 7.12 - 7.17 m, 2 H (H-4' and H-5'); 7.28 m, 1 H (H-3'); 7.35 m, 1 H (H-6'); 8.80 s, 1 H (H-2); 9.03 s, 1 H (H-8). 13C NMR (DMSO, 125.70 MHz): 34.91 (C-10'); 43.12 (C-1'); 46.90 (C-2'); 49.36 (C-8'); 57.16 (C-9'); 121.31 (C-3'); 122.10 (C-6'); 126.22 and 126.95 (C-4' and C-5'); 131.56 (C-5); 144.91 (C-7'); 146.07 (C-8); 148.51 (C-2'); 149.23 (C-6); 151.63 (C-2); 152.52 (C-4).
chloropurine (2.27 g, 14.7 mmol) in THF (100 ml). The reaction mixture was stirred overnight and evaporated. Chromatography of the residue on silica gel (400 g) in toluene - ethyl acetate (1 : 1) followed by crystallization from ethanol afforded 2.03 g of white crystals. 1M solution of DIBAL-H in dichloromethane (15.9 ml) was added dropwise to a solution of this product in dichloromethane (85 ml) at -78 °C under argon atmosphere. The reaction mixture was stirred for 45 min, excess of DIBAL-H was decomposed by addition of methanol and the solvent was evaporated. The residue was diluted with methanol and filtered with a Celite pad. Chromatography on silica gel (100 g) in ethyl acetate - toluene - acetone - ethanol (17 : 4 : 3 : 1) afforded 0.97 g (33%) of 35, m.p. 154-155 °C. For C13H15ClN4O (278.74) calculated: 56.02% C, 5.42% H, 12.72% Cl, 20.0% N; found: 55.89% C, 5.29% H, 12.44% Cl, 20.00% N. FAB MS m/z (%): 279/281 (100/37) [M+H], 154.9 (89). 1H NMR (CDCl3): 1.28 dt, 1 H, J gem = 13.0, J(3exo,2) = J(3exo,4) = 4.9, (H-3exo); 1.58 dm, 1 H, J gem = 10.9 (H-7a); 1.67 dm, 1 H, J gem = 10.9 (H-7b); 1.71 ddd, 1 H, J gem = 13.0, J(3endo,2) = 8.6, J(3endo,7b) = 2.4 (H-3endo); 1.82 t, 1 H, J(OH,CH2) = 4.8 (OH); 1.87 m, 1 H (H-2); 1.97 dt, 1 H J gem = 13.5, J(6exo,5) = J(6exo,1) = 4.5 (H-6exo); 2.22 ddd, 1H, J gem = 13.5, J(6endo,5) = 8.5, J(6endo,7a) = 2.5, (H-6endo); 2.56 dm, 1 H, J(1,6ex) = 4.3 (H-I); 2.65 dm, 1 H, J(4,3ex) = 4.5 (H-4); 3.50 m, 2 H, (CH2O); 4.65 ddd 1 H, J(5,6endo) = 8.5, J(5,6exo) = 4.6, J(5,7a) = 1.4 (H-5); 8.25 s, 1 H, (H-8'); 8.76 s, 1 H (H-2'). 13C NMR (CDCl3): 31.45 (C-3); 33.36 (C-7); 38.04 (C-1); 39.33 (C-6); 42.29 (C-4); 43.35 (C-2); 57.98 (C-5); 65.99 (CH2O); 131.84 (C-5'); 142.67 (C-8'); 150.92 (C-6'); 151.66 (C-2'); 151.78 (C-4').

According to the same procedure, there was obtained [(1R*,2R*,4S*,6S*)-6-(6-Chloro-9H-purin-9-yl)bicyclo[2.2.1]heptan-2-yl]methanol (36), yield 1.16 g (35%), m.p. 124-125 °C. For C13H15ClN4O (278.74) calculated: 56.02% C, 5.42% H, 12.72% Cl, 20.10% N; found: 56.00% C, 5.38% H, 12.52% Cl, 19.71% N. FAB MS m/z (%): 279/281 (78/33) [M+H], 154.9 (100). 1H NMR (CDCl3): 1.18 dddd, 1 H, J gem = 12.6, J(3ex,2) = 5.1, J(3ex,4) = 4.1, J(3ex,5ex) = 2.9 (H-3exo); 1.54 ddd, 1 H, J gem = 12.6, J(3endo,2) = 8.6, J(3endo,7b) = 2.3, (H-3endo); 1.56 dm, 1 H, J gem = 11.0 (H-7b); 1.63 dm, 1 H, J gem = 11.0 (H-7a); 1.94 m, 1 H (H-5exo); 1.99 m, 1 H (H-2); 2.12 t, 1 H, J(OH,CH2) = 5.1 (OH); 2.19 ddd, 1H, J gem = 13.8, J(5endo,6) = 8.4, J(5endo,7a) = 2.3, (H-5endo); 2.56 tm,
1 H, J(4,3exo) = J(4,5exo) = 4.1 (H-4); 2.74 bs, 1 H (H-I); 3.49 ddd, 1 H, J(CH'H,H2) = 9.2, J(CH3H,OH) = 5.2 and 3.57 ddd, 1 H, J(CH4H,2) = 6.0, J(CH3H,OH) = 4.1, Jgem = 10.7 (CH2O); 4.64 ddd 1 H J(6,5endo) = 8.4, J(6,5exo) = 4.0, J(6,7a) = 1.4 (H-6); 8.25 s, 1 H, (H-8); 8.75 s, 1 H (H-T). 13C NMR (CDCl3): 32.36 (C-3); 33.30 (C-7); 35.93 (C-4); 38.54 (C-5); 42.71 (C-2); 43.80 (C-I); 58.74 (C-6); 65.39 (CH2O); 131.87 (C-5'); 142.77 (C-8'); 150.88 (C-6'); 151.63 (C-2'); 151.76 (C-4').

EXAMPLE 5: SYNTHESIS OF ISOMERIC PURE 6-CHLORO-9-{[(IR,2S,5R)-6,6-DIMETHYL BICYCLO[3.1.1]HEPT-2-YL]METHYL}-9H-PURINE (23) (Method B)

A mixture of (-)-cis-myrtanylamine (460 mg, 3 mmol), 4,6-dichloropyrimidin-5-amine (984 mg, 6 mmol), and triethylamine (1.8 ml) in ethanol (9 ml) was heated in a pressure vessel at 105 °C for 6 days and, after cooling, was evaporated. The residue was chromatographed on a column of silica gel (200 g). Pyrimidine intermediate was eluted with toluene - ethylacetate (10:1 → 6:1) and this intermediate (730 mg) was immediately used in the next step. Concentrated hydrochloric acid (1 ml) was added to a suspension of pyrimidine intermediate in triethyl orthoformate (80 ml) and the reaction mixture was vigorously stirred for 5 days at room temperature. Reaction mixture was evaporated and the residue was crystallized from water-methanol (95:5) to afford 575 mg (66%) of 6-chloro-9-{[(IR,2S,5R)-6,6-dimethylbicyclo[3.1.1]hept-2-yl]methyl}-9H-purine, m.p. = 121.3 - 122.6. [α]D -11.6 (c 0.368, methanol). For C15H19ClN4 (290.8) calculated: 61.96% C, 6.59% H, 12.19% Cl, 19.27% N; found: 61.91% C, 6.58% H, 11.89% Cl, 18.96% N. ¹H NMR (DMSO, 600.13 MHz): 0.83 d, 1 H, Jgem = 9.6 (H-7a); 1.15 s, 3 H and 1.18 s, 3 H (2 x 6'-CH₃); 1.58 dddd, 1 H, Jgem = 14.9, J(3'a,4'b) = 10.7, J(3'a,2') = 6.4, J(3'a,4'a) = 5.5 (H-3'a); 1.66 ddd, 1 H, J(1',7'b) = 6.4, J(1',5') = 5.1, J(1',T) = 2.1 (H-1'); 1.73 dtt, 1 H, Jgem = 14.9, J(3'b,4'a) = J(3'b,2') = 10.5, J(3'b,4'b) = 2.7 (H-3'b); 1.79 dddd, 1 H, Jgem = 12.8, J(4'a,3'b) = 10.6, J(4'a,3'a) = 5.6, J(4'a,5') = 2.6 (H-4'a); 1.87 m, 1 H (H-5'); 1.91 m, 1 H (H-4'b); 2.27 dtt, 1 H, Jgem = 9.6, J(7'b,1') = J(7'b,5') = 6.3, J(7'b,4'b) = 2.0 (H-7'b); 2.64 m, 1 H (H-2'); 4.27 m, 2 H (CH₂N); 8.78 s, 1 H (H-8); 8.78 s, 1 H (H-2). ¹³C NMR (DMSO, 150.92 MHz): 18.69 (C-3'); 23.13 (6'-CH₃); 25.58
According to the same procedure, there were obtained the following compounds:

- 6-chloro-9-[(1R,4S)-Bicyclo[2.2.1]hept-7-yl]-6-chloro-9H-purine (57), m.p. = 166 - 167 °C. For C_{13}H_{13}ClN_{4}O (276.7) calculated: 56.42% C, 4.74% H, 12.81% Cl, 20.25% N; found: 56.21% C, 4.56% H, 13.08% Cl, 19.96% N. \(^1\)H NMR (DMSO, 600.13 MHz): 1.29 dt, 1 H, \(J_{gem} = 12.8\), \(J(9'\alpha,8'b) = J(9'\beta,8'b) = 2.3\) (H-9'endo); 1.68 dm, 1 H, \(J_{gem} = 11.4\) (H-8'a); 1.85 dm, 1 H, \(J_{gem} = 11.3\) (H-8'b); 2.06 ddd, 1 H, \(J_{gem} = 12.8\), \(J(9'\alpha,6'\alpha) = 10.8\), \(J(9'\alpha,1'\alpha) = 4.5\) (H-9'exo); 2.48 m, 1 H (H-6'); 2.60 m, 1 H (H-I'); 2.74 m, 1 H (FL-T); 3.75 d, 1 H, \(J_{gem} = 8.0\) (H-5'a); 3.80 dd, 1 H, \(J_{gem} = 8.0\), \(J(5'b,6') = 4.2\) (H-5'b); 4.14 d, 1 H, \(J(2',8'a) = 2.1\) (H-2'); 4.76 dd, 1 H, \(J(3',7') = 5.0\), \(J(3',1'\alpha) = 1.4\) (H-3'); 8.77 s, 1 H (H-2); 8.78 s, 1 H (H-8). \(^{13}\)C NMR (DMSO, 150.92 MHz): 35.13 (C-9'); 35.45 (C-8'); 37.16 (C-6'); 39.03 (C-1'); 45.78 (C-7'); 66.85 (C-2'); 74.51 (C-5'); 83.92 (C-3'); 131.30 (C-5); 145.79 (C-8); 149.23 (C-6); 151.57 (C-2); 152.30 (C-4).

- 9-[(7-syn)-Bicyclo[2.2.1]hept-2-en-7-yl]-6-chloro-9H-purine (25), m.p. = 114.5 - 115.5 °C. For C_{18}H_{16}ClN_{4} (246.7) calculated: 58.42% C, 4.49% H, 14.37% Cl, 22.71% N; found: 58.50% C, 4.59% H, 14.63% Cl, 22.43% N. \(^1\)H NMR (DMSO, 600.13 MHz): 1.12 m, 2 H (H-5'endo and H-6'endo); 1.97 m, 2 H (H-5'exo and H-6exo); 3.60 m, 2 H (H-I and H-4); 4.33 m, 1 H (H-7); 6.00 m, 2 H (H-2 and H-3); 8.49 s, 1 H (H-8); 8.76 s, 1 H (H-2'). \(^{13}\)C NMR (DMSO, 150.92 MHz): 22.76, 2 C (C-5 and C-6); 44.81, 2 C (C-I and C-4); 70.73 (C-7); 131.07 (C-5'); 132.07, 2 C (C-2 and C-3); 147.70 (C-8'); 149.10 (C-6'); 151.55 (C-2'); 152.93 (C-4').

- 9-[(IR,4S)-Bicyclo[2.2.1]hept-7-yl]-6-chloro-9H-purine (27), m.p. = 95.5 - 96.7 °C. For C_{18}H_{18}ClN_{4} (248.7) calculated: 57.95% C, 5.27% H, 14.25% Cl, 22.53% N; found: 57.75% C, 5.20% H, 14.41% Cl, 22.33% N. \(^1\)H NMR (DMSO-d\(_6\)) 1.32 m, 2 H (H-5'exo and H-6'exo); 1.42 m, 4 H (H-2'exo, H-3'exo, H-5'endo and H-6'endo); 1.79 m, 2 H (H-2'endo and H-3'endo); 3.19 m, 2 H (H-I' and H-4'); 4.25 bs, 1 H (H-7'); 8.73 s, 1 H (H-8); 8.76 s, 1 H (H-2). \(^{13}\)C NMR (DMSO-d\(_6\)) 26.64, 2 C (C-5' and C-6'); 27.08, 2 C (C-2' and C-3'); 38.55, 2 C (C-I 'and C-

(C-4'); 27.75 (6'-CH\(_3\)); 32.52 (C-7'); 38.49 (C-6'); 40.75 (C-5'); 41.06 (C-2'); 42.93 (C-1'); 49.04 (CH\(_2\)N); 130.86 (C-5); 147.91 (C-8); 149.22 (C-6); 151.72 (C-2); 152.35 (C-4).

A mixture of bicyclo[2.2.1]hept-5-ene-2,3-diyldimethanol (6.17 g, 40 mmol), benzyl azidoformate (8.68 g, 49 mmol), and toluene (10 ml) was stirred at 68 °C (bath temperature). The bath was put off when a spontaneous exothermic reaction had occurred. After termination of the reaction, the mixture was applied on a silica gel column (300 g) and eluted with ethyl acetate. The fractions containing product were evaporated. Palladium(II) hydroxide on carbon (20% Pd, 500 mg) was added to a solution of the residue in methanol (200 ml) and the mixture was stirred under hydrogen atmosphere at room temperature for 7 h. The catalyst was filtered off with a Celite pad, washed with methanol and the filtrates were evaporated. The residue was mixed with ether and resulting crystalline compound (5.41 g) was filtered off. A solution of this compound, 4,6-dichloropyrimidin-5-amine (7.89 g), and triethylamine (9.6 ml) in ethanol (100 ml) was heated in a pressure vessel at 100 °C for 6 days and, after cooling, was taken down. The product obtained by chromatography of the residue on a silica gel column (400 g) in ethyl acetate - acetone - ethanol - water (95 : 15 : 9 : 6) was suspended in triethyl orthoformate (450 ml). Cone, hydrochloric acid (10 ml) was added to this stirred mixture, the resulting solution was left aside at room temperature for 3 days and then evaporated. The residue was dissolved in tetrahydrofuran (125 ml). To the stirred solution, 0.5 M hydrochloric acid (125 ml) was added, the mixture was stirred at room temperature for 3 h and then neutralized with solid sodium hydrogen carbonate. The organic layer was separated and the aqueous layer was extracted with tetrahydrofuran (4 x 100 ml). The combined organic layers were evaporated. Crystallization of the residue from water gave 7.95 g mg (65%) of 1, m.p. 190.5 - 192 °C. For C_{14}H_{15}ClN_{4}O_{2} (306.76)
calculated: 54.82% C, 4.93% H, 11.56% Cl, 18.26% N; found: 54.69% C, 4.94% H, 11.55% Cl, 18.08% N. 

$^1$H NMR (DMSO-de): 1.62 brt, 1 H, $J(9,1) \sim j(9,8a) = 1.0$, $J(9,6) = 2.6$, $J(9,CH_2) = 7.9$ (H-9); 1.72 dm, 1 H, $J_{gem} = 11.7$ (H-8a); 1.82 dq, 1 H, $J(8b,l) \sim J(8b,2) \sim J(X_b J) = 1.4$ (H-8b); 2.07 td, 1 H, $J(6,5a) \sim J(6,7) = 4.0$ (H-6); 2.58 m, 1 H (H-1); 2.69 ddq, 1 H, $J(7,l) \sim J(7,8a) \sim J(7,8b) = 1.2$, $J(7,3) = 5.0$ (R-T); 3.39 dd, 2 H, $J(CH_2OH) = 5.3$ (CH$_2$OH); 3.75 d, 1 H, $J_{gem} = 7.8$ (H-5b); 3.78 dd, 1 H, $J(5a,6) = 3.6$ (H-5a); 4.12 brd, 1 H, $J(2,1) \sim J(2,3) = 1.0$, $J(2,8b) = 1.6$ (H-2); 4.12 t, 1 H (OH); 4.78 brd, 1 H, $J(3,1) = 1.2$, $J(3,8b) = 1.0$ (H-3); 8.77 s, 1 H and 8.78 s, 1 H (H-2', H-8'). $^{13}$C NMR (DMSO-d$_6$): 32.05 (C-8); 41.10 (C-1); 41.35 (C-6); 45.24 (C-7); 50.67 (C-9); 62.75 (CH$_2$O); 67.27 (C-2); 74.16 (C-5); 83.56 (C-3); 131.24 (C-5'); 145.76 (C-8'); 149.18 (C-6'); 151.50 (C-2'); 152.28 (C-4').

According to the same procedure, there were obtained the following compounds:

- [(II *2R *,3R *,6R *,7S *,10*5)-2-(6-Cloro-9H-purin-9-yl)-4-oxatricyclo[4.3.1.0$^3$7]dec-10-yl]methanol (14), m.p. 183.5 - 184.5 °C. For C$_{15}$H$_{17}$ClN$_4$O$_2$ (320.78) calculated: 56.16% C, 5.34% H, 11.05% Cl, 17.47% N; found: 56.88% C, 5.35% H, 11.03% Cl, 17.24% N. FAB MS, m/z (%): 323/321 (39/100) [M + H], 157/155 (35/73).

- [(IR *2R *,3S *,6S *,7S *,9S *)-2-(6-Chloro-9H-purin-9-yl)-4,8-dioxatricyclo[4.2.1.0$^3$7]non-9-yl]methanol (32), m.p. 205.5 - 206.5 °C. For C$_{17}$H$_{13}$ClN$_4$O$_3$ (308.73) calculated: 50.58% C, 4.24% H, 11.48% Cl, 18.15% N; found: 50.43% C, 4.29% H, 11.66% Cl, 18.01% N. FAB MS, m/z (%): 311/309 (37/100) [M + H]. $^4$H NMR (DMSO-(I$_6$): 2.05 ddd, 1 H, $J(9,6) = 2.0$, $J(9,CH_2) = 7.3$ and 8.8 (H-9); 2.16 dt, 1 H, $J(6,7) = J(6,5a) = 4.5$, $J(6,9) = 2.0$ (H-6); 3.33 m, 2 H (CH$_2$O); 3.88 dd, 1 H, $J_{gem} = 8.6$, $J(5a,6) = 4.2$ (H-5a); 3.96 d, 1 H, $J_{gem} = 8.5$ (H-5b); 4.51 dd, 1 H, $J(ZJ) = 4.8$, $J(3,2) = 1.5$ (H-3); 4.59 m, 2 H (H-I and H-2); 4.86 t, 1 H, $J(OH,CH_2) = 5.3$ (OH); 5.18 t, 1 H, $J(7,3) = J(7,6) = 4.8$ (R-T); 8.54 s, 1 H (H-8'); 8.80 s, 1 H (H-2'). $^{13}$C NMR (DMSO-d$_6$): 41.06 (C-6); 50.92 (C-9); 61.66 (CH$_2$O); 64.53 (C-2); 72.29 (C-5); 80.06 (C-1); 81.86 (C-7); 83.25 (C-3); 130.76 (C-5'); 145.24 (C-8'); 149.16 (C-6'); 151.69 (C-2'); 151.85 (C-4').
EXAMPLE 7: SYNTHESIS OF INTERMEDIATE AMINES SUCH AS THE FORMULA XIV FOR METHOD B AND OF COMPOUNDS SUCH AS 24

A solution of bicyclo[2.2.1]hept-5-en-2-yl acetate (mixture of isomers, 10.3 g, 67.7 mmol) and ethyl azidoformate (15.3 g, 133 mmol) in toluene (80 ml) was heated at 80 °C for 10 hours and evaporated. The residue was dissolved in ethyl acetate (80 ml) and silica gel (10 g) was added. After 12 hours of stirring, silica gel was filtered off and filtrate was evaporated. The products were separated by column chromatography on silica gel (400 g). Elution with toluene - ethyl acetate (8:1) afforded 8.3 g (51.2 %) of aziridine as an oil and 5.63 g (34.8 %) of carbamate as an oil. Carbamate (5.63 g, 23.5 mmol) was dissolved in methanol (200 ml) and K₂CO₃ was added (200 mg). The reaction mixture was vigorously stirred for 72 hours and then heated to reflux for 10 hours, K₂CO₃ was removed with DOWEX 50 (H⁺ cycle), the mixture was filtrated and evaporated. The residue was immediately used in next step. A mixture of pyridinium dichromate (13.5 g, 35.9 mmol), molecular sieves (3A, powder, 14 g) and dichloromethane (140 ml) was stirred at room temperature for 15 min. A solution of carbamate (from previous step) in dichloromethane (60 ml) was added to the mixture and reaction mixture was stirred for 12 hours, the insoluble portions were filtered and filtrate was evaporated. Residue was treated with ethylacetate (150 ml) and the mixture was filtrated through a Celite pad and filtrates were taken down. Column chromatography of the residue on silica gel (300 g) with toluene - ethyl acetate (3:1) afforded 1.9 g of keto derivative. Ketocarbamate was dissolved in methanol (70 ml) and solution was immersed in an ice-bath, sodium borohydride (220 mg, 5.84 mmol) was added in small portions during 20 min and the reaction mixture was evaporated, co-distilled with methanol (50 ml) and the residue was partitioned between ethyl acetate (150 ml) and brine (70 ml). The aqueous layer was extracted with ethyl acetate (2 x 150 ml) and combined organic layers were dried over anhydrous sodium sulfate and evaporated. The residue was chromatographed on silica gel (150 g) in ethylacetate - toluene (4:1) to afford 1.7 g of the alcohol. To a solution of alcohol (1.7 g, 8.62 mmol) in ethanol-water (20 ml, 1:1) potassium hydroxide (3.1 g, 55 mmol) was added and the reaction mixture was refluxed for 10 h in argon atmosphere.
Then second portion of potassium hydroxide (0.8 g, 14 mmol) was added and heating was continued for 4 h. The reaction mixture was neutralized with 6 M hydrochloric acid and solution was applied onto a Dowex 50 (H\(^+\) form, 100 ml). The column was eluted with methanol-water (1:1, 300 ml), water (300 ml), methanol (300 ml) and then with 3.5 M methanolic ammonia. Fractions containing the product were evaporated to yield 917 mg (85\%) of (I)\(^{R*}\), 25\%, 45\%, 7\%)-7-aminobicyclo[2.2.1]hept-5-en-2-ol (XIV, total yield from bicyclo[2.2.1]hept-5-en-2-yl acetate 10.8\%). A mixture of the residue (917 mg) and Pd(OH)\(_2\) (20% on charcoal, 300 mg) in methanol (50 ml) was stirred in atmosphere of hydrogen for 15 h. The catalyst was filtered off and washed with methanol and filtrate was evaporated. A mixture of the residue (841 mg, 6.6 mmol), 4,6-dichloropyrimidin-5-amine (1.63 g, 9.9 mmol), and triethylamine (2 ml) in ethanol (20 ml) was heated in a pressure vessel at 100 °C for 6 days and, after cooling, was taken down. The product obtained by chromatography of the residue on a silica gel column (100 g) in ethyl acetate - acetone - ethanol - water (95:15:9:6) was suspended in triethyl orthoformate (90 ml). Cone, hydrochloric acid (2 ml) was added to this stirred mixture, the resulting solution was left aside at room temperature for 3 days and then evaporated. The residue was dissolved in tetrahydrofuran (23 ml). To the stirred solution, 0.5 M hydrochloric acid (23 ml) was added, the mixture was stirred at room temperature for 3 h and then neutralized with solid sodium hydrosuccinate. The organic layer was separated and the aqueous layer was extracted with tetrahydrofuran (4 x 20 ml). The combined organic layers were evaporated. Crystallization of the residue from water gave 1.12 g (6.2\%) of 24, m.p. = 178.7 - 180. °C. For C\(_{12}\)H\(_{13}\)ClN\(_4\)O (264.7) calculated: 54.45% C, 4.95% H, 13.39% Cl, 21.17% N; found: 54.32% C, 5.09% H, 13.40% Cl, 21.00% N. \(^1\)H NMR (DMSO-(I)\(_6\)): 1.01 dd, 1 H, \(J_{gem}\) = 12.8, \(J(3ex,2)\) = 3.8 (H-3exo); 1.28 m, 1 H (H-6endo); 1.34 m, 2 H (H-5exo, 5endo); 2.02 bddd, 1 H, \(J_{gem}\) = 12.8, \(J(6ex,5ex)\) = 9.0, \(J(6ex,5en)\) = 5.2 (H-6exo); 2.12 dddd, 1 H, \(J_{gem}\) = 12.9, \(J(3en,2)\) = 10.1, \(J(3en,4)\) = 4.9, \(J(3en,5en)\) = 2.6 (H-3endo); 3.11 tm, 1 H, \(J(4,3en)\) = \(J(4,5en)\) = 4.5 (H-4); 3.20 tm, 1 H, \(J(1,2)\) = \(J(1,6en)\) = 4.2 (H-I); 4.28 m, 2 H (H-2, H-7); 4.93 d, 1 H, \(J(OH,2)\) = 4.2 (OH); 8.72 s, 1 H (H-8); 8.75 s, 1 H (H-2). \(^1\)C NMR (DMSO-(I)\(_6\)): 17.53 (C-6); 26.79 (C-5); 37.37 (C-3); 39.82 (C-4); 45.23 (C-1); 61.94 (C-7); 67.78 (C-2); 131.17 (C-5'); 147.48 (C-8'); 149.22 (C-6'); 151.49 (C-2'); 152.60 (C-4'). For C\(_{12}\)H\(_{13}\)ClN\(_4\)O (264.7) calculated:
According to the same procedure, excluding the hydrogenation step, there was obtained (IR*,2S*,4S*,7R*)-7-(6-Chloro-9H-purin-9-yl)bicyclo[2.2.1]hept-5-en-2-ol (16), m.p. = 202.6 - 203.5 °C (decomp.). For C_{12}H_{11}ClN_{4}O (262.7) calculated: 54.87% C, 4.22% H, 13.05% Cl, 21.33% N; found: 54.56% C, 4.23% H, 12.96% Cl, 21.05% N. \(^1\)H NMR (DMSO-d_{6}): 0.90 dd, 1 H, J_{gem} = 12.1, J(3ex,2) = 3.0 (H-3exo); 2.27 ddd, 1 H, J_{gem} = 12.1, J(3en,2) = 7.9, J(3en,4) = 3.8 (H-3endo); 3.50 m, 1 H (H-4); 3.67 m, 1 H (H-1); 4.35 bs, 1 H (H-7); 4.55 m, 1 H (H-2); 4.81 d, 1 H, J(OH,2) = 4.6 (OH); 5.91 dd, 1 H, J(6,5) = 5.7, J(6,1) = 2.8 (H-6); 6.20 dd, 1 H, J(5,6) = 5.7, J(5,4) = 2.9 (H-5); 8.48 s, 1 H (H-8'); 8.75 s, 1 H (H-2'). \(^{13}\)C NMR (DMSO-d_{6}): 35.05(C-3); 46.21 (C-4); 51.43 (C-1); 67.74 (C-2); 69.04 (C-7); 129.35 (C-6); 131.04 (C-5); 143.98 (C-5'); 147.56 (C-8'); 149.10 (C-6'); 151.54 (C-2'); 152.74 (C-4').

EXAMPLE 8: SYNTHESIS OF METHYL-ETHER COMPRISING NUCLEOSIDE ANALOGS OF THE INVENTION SUCH AS 2 AND 20

Sodium hydride (60% dispersion in mineral oil, 40 mg, 1 mmol) was added to a mixture of (IR*,2R*,3R*,6R*,7S*,9S*)-2-(6-chloro-9H-purin-9-yl)-4-oxatricyclo[4.2.1.0^26]nonane-9-methanol (1) (153 mg, 0.5 mmol) dimethylformamide (1.5 ml) and methyl iodide (1.5 ml). The mixture was stirred at 0 °C for 0.5 h then at room temperature for 2 h. and evaporated. Solution of the residue in ethyl acetate (15 ml) was washed with water (2 x 5 ml), 10% aqueous sodium thiosulfate, dried over anhydrous sodium sulfate and evaporated. Crystallization of the residue from ethanol afforded 120 mg (75%) of 6-cloro-9-[(1R*,2R*,3R*,6R*,7S*,9S*)-9-(methoxymethyl)-4-oxatricyclo[4.2.1.0^26]non-2-yl]-9H-purine (2), m.p. 147 - 148 °C. For C_{15}H_{17}ClN_{4}O_{2} (320.78) calculated: 56.16% C, 5.34% H, 11.05% Cl, 17.47% N; found: 55.89% C, 5.41% H, 10.86% Cl, 17.20% N. \(^1\)H NMR (DMSO-d_{6}): 1.73 - 1.81 m, 2 H (H-8a, H-9); 1.86 dm, 1 H, J_{gem} = 11.9 (H-8b); 2.09 m, 1 H (H-6); 2.56 m, 1 H (H-1); 2.71 m, 1 H (H-7); 3.28 s, 3 H (CH_{3}O); 3.30 - 3.38 m, 2 H (CH_{2}O); 3.76 - 3.81 m, 2 H (2 x H-5); 4.14 d, 1 H, J(2,8b) = 1.8 (H-2); 4.80 brd,
1 H, J(3,7) = 5.0 (H-3); 8.77 s, 1 H (H-2'); 8.78 s, 1 H (H-8'). \(^{13}\)C NMR (DMSO-d\(_6\)): 32.10 (C-8); 41.22 (C-1); 41.53 (C-6); 45.21 (C-7); 47.52 (C-9); 58.19 (CH\(_3\)O); 67.09 (C-2); 73.63 CH\(_2\)O; 73.93 (C-5); 83.44 (C-3); 131.23 (C-5'); 145.73 (C-8'); 149.15 (C-4'); 151.45 (C-2'); 152.26 (C-6').

According to the same procedure, there was obtained <s-h/oro-9-[(IR*,2S*,4R*,7R*)-2-methoxybicyclo[2.2.1]hept-7-yl]-9H-purine (20), m.p. = 104.2 - 104.8 °C. For C\(_{13}\)H\(_5\)ClN\(_4\)O (264.7) calculated: 56.02% C, 5.42% H, 12.72% Cl, 20.10% N; found: 56.03% C, 5.37% H, 13.40% Cl, 19.82% N. \(^1\)H NMR (DMSO, 600.13 MHz): 1.11 dd, 1 H, J\(_{gem}\) = 13.1, J(3en,2) = 3.6 (H-3endo); 1.24 m, 1 H (H-6exo); 1.34 bddd, 1 H, J\(_{gem}\) = 12.9, J(5en,6en) = 9.5, J(5en,6ex) = 4.4 (H-5endo); 1.44 m, 1 H (H-5exo); 1.79 bddd, 1 H, J\(_{gem}\) = 12.9, J(6en,5en) = 9.5, J(6en,5ex) = 4.7 (H-6endo); 2.14 dddd, 1 H, J\(_{gem}\) = 13.1, J(3ex,2) = 10.0, J(3ex,4) = 4.7, J(3ex,5ex) = 3.0 (H-3exo); 3.15 bt, 1 H, J(4,3ex) = J(4,5ex) = 4.4 (H-4); 3.22 s, 3 H (OMe); 3.50 tm, 1 H, J(l,2) = J(l,6ex) = 4.1 (H-I); 3.93 ddt, 1 H, J(2,3ex) = 10.1, J(2,3en) = J(2,1) = 3.8, J(2,6ex) = 1.5 (H-2); 4.31 bs, 1 H (H-7); 8.74 s, 1 H (H-8'); 8.77 s, 1 H (H-2'). \(^{13}\)C NMR (DMSO, 150.92 MHz): 17.46 (C-6); 26.67 (C-5); 35.08 (C-3); 39.20 (C-4); 42.05 (C-I); 56.45 (OMe); 61.84 (C-7); 77.74 (C-2); 131.19 (C-5'); 147.43 (C-8'); 149.27 (C-6'); 151.55 (C-2'); 152.60 (C-4').

**EXAMPLE 9:** Synthesis of [(li?*,2£*,4i?*,7S*)-7-(6-chloro-9 \(H\)-purin-9-yl)bicyclo[2.2.1]hept-5-en-2-yl]methanol (58) and analogous compounds

A mixture of [(li?*,2£*,4R*,75*)-7-aminobicyclo[2.2.1]hept-5-en-2-yl]methanol (780 mg, 5.60 mmol), 4,6-dichloropyrimidin-5-amine (1.38 g, 8.42), and triethylamine (1.8 ml) in ethanol (9 ml) was heated in a pressure vessel at 105 °C for 6 days and, after cooling, was evaporated. The residue was chromatographed on a column of silica gel (200 g). Pyrimidine intermediate was eluted with ethylacetate \(\rightarrow\) ethylacetate - toluene - acetone - ethanol (17:4:3:1) and this intermediate was immediately used in the next step. Concentrated hydrochloric acid (1.5 ml) was added to a suspension of pyrimidine intermediate in triethyl orthoformate (100 ml) and THF (20 ml) and the reaction mixture was vigorously stirred for 4 days at room temperature. Solution was evaporated and the residue was dissolved in mixture in a mixture of tetrahydrofuran (20 ml) and 0.5 M
hydrochloric acid (20 ml) and stirred at room temperature for 4 hours. After neutralization with solid sodium hydrogen carbonate, mixture was evaporated to a one fourth of original volume and absorbed on silica gel. This silica gel was placed on the top of the silica gel column (200 g). Chromatography with ethylacetate → ethylacetate - toluene - acetone - ethanol (17:4:3:1) afforded product \([(IR^*,2R*AR^*J S^*)-7-(6-chloro-9H-purin-9-yl)bicyclo[2.2.1]hept-5-en-2-yl]methanol \) (58) (900 mg, 58.1%). Compounds were crystallized from ethylacetate-hexanes. M.p. = 133.5 - 133.6 °C. For \(C_{13}H_{13}ClN_4\)O \(C(276.7)\) calculated: 56.42% C, 4.74% H, 12.81% Cl, 20.55% N; found: 56.79% C, 5.02% H, 13.05% Cl, 20.23% N. \(^1\)H NMR (DMSO, 499.84 MHz): 0.60 dd, 1 H, \(J_{\text{gem}} = 11.8, J(3\text{en},2) = 4.7\) (H-3endo); 2.06 ddd, 1 H, \(J_{\text{gem}} = 11.8, J(3\text{ex},2) = 9.0, J(3\text{ex},4) = 3.9\) (H-3exo); 2.49 m, 1 H (H-2); 3.02 ddd, 1 H, \(J_{\text{gem}} = 10.6, J(\text{CH}_2\text{OH}) = 5.5, J(\text{CH}_2\text{2}) = 9.6\) (CH\(_2\)Oa); 3.20 ddd, 1 H, \(J_{\text{gem}} = 10.6, J(\text{CH}_2\text{OH}) = 4.9, J(\text{CH}_2\text{2}) = 6.2\) (CH\(_2\)Ob); 3.55 m, 1 H (H-4); 3.70 m, 1 H (H-1); 4.42 bs, 1 H (H-7); 4.62 t, 1 H, \(J(\text{OH},\text{CH}_2) = 5.2\) (OH); 5.90 dd, 1 H, \(J(6,5) = 5.7, J(6,1) = 2.8\) (H-6); 6.10 bdd, 1 H, \(J(5,6) = 5.7, J(5,4) = 2.9\) (H-5); 8.48 s, 1 H (H-8'); 8.76 s, 1 H (H-2'). \(^{13}\)C NMR (DMSO, 125.70 MHz): 26.84 (C-3); 39.19 (C-2); 45.29 (C-4); 47.06 (C-I); 63.44 (CH\(_2\)O); 71.18 (C-T); 129.66 (C-6); 131.07 (C-5'); 133.48 (C-5); 147.72 (C-8'); 149.11 (C-6'); 151.55 (C-2'); 152.90 (C-4').

According to the same procedure, there were obtained the following compounds:

\[[(IR^*,2R*,4S*,7S^*)-7-(6-Chloro-9H-purin-9-yl)bicyclo[2.2.1]hept-2-en-yl]methanol\] (59), m.p. = 97.6 - 98.7 °C. For \(C_{13}H_{13}ClN_4\)O \(C(278.7)\) calculated: 56.02% C, 5.42% H, 12.72% Cl, 20.10% N; found: 55.99% C, 5.62% H, 12.84% Cl, 19.75% N. \(^1\)H NMR (DMSO, 600.13 MHz): 0.80 dd, 1 H, \(J_{\text{gem}} = 12.4, J(3\text{en},2) = 5.4\) (H-3endo); 1.22 m, 1 H (H-6exo); 1.46 m, 1 H (H-5exo); 1.62 ddd, 1 H, \(J_{\text{gem}} = 13.2, J(6\text{en},5\text{en}) = 9.2, J(6\text{en},5\text{exo}) = 3.9\) (H-6endo); 1.89 tdd, 1 H, \(J_{\text{gem}} = J(3\text{ex},2) = 12.0, J(3\text{ex},4) = 4.5, J(3\text{ex},5\text{ex}) = 3.0\) (H-3exo); 2.26 m, 1 H (H-2); 3.15 m, 1 H (H-4); 3.30 m, 1 H (H-I); 3.38 m, 1 H (CH\(_2\)Oa); 3.48 ddd, 1 H, \(J_{\text{gem}} = 10.8, J(\text{CH}_2\text{OH}) = 4.6, J(\text{CH}_2\text{2}) = 6.5\) (CH\(_2\)Ob); 4.32 bs, 1 H (H-7); 4.59 dd, 1 H, \(J(\text{OH},\text{CH}_2) = 5.4\) and 4.7 (OH); 8.73 s, 1 H (H-8'); 8.76 s, 1 H (H-2'). \(^{13}\)C NMR (DMSO, 150.92 MHz): 19.76 (C-6); 27.01 (C-5); 31.00 (C-3); 38.98 (C-4); 39.28
(C-2); 40.85 (C-I); 62.17 (CH₂O); 64.39 (C-7); 131.19 (C-5'); 147.76 (C-8');
149.24 (C-6'); 151.50 (C-2'); 152.70 (C-4').

- [(Ii? *,2S*,4R*,7S*)-7-(6-Chloro-9 H-purin-9-yl)bicyclo[2.2.1]heptan-2-ol](60), m.p. = 184.5 - 186.3 °C. For C₁₃H₁₃ClN₄O (276.7) calculated:
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56.42% C, 4.74% H, 12.81% Cl, 20.55% N; found: 56.45% C, 4.71% H, 12.93%
Cl, 19.99% N. ¹H NMR (DMSO, 499.84 MHz): 1.35 dd, 1 H, J₆₇ = 12.0,
J(3en,2) = 9.2 (H-3endo); 1.53 ddd, 1 H, J₅₆ = 12.0, J(3ex,2) = 4.4, J(3ex,4) =
3.5 (H-3exo); 1.66 m, 1 H (H-2); 3.53 m, 1 H (H-I); 3.56 m, 1 H (H-4); 3.58 ddd,
1 H, J₆₇ = 10.8, J(CH₂OH) = 5.3, J(CH₂2) = 8.3 (CH₂OA); 3.68 ddd, 1 H, J₃₄ =
10.8, J(CH₂₂OH) = 4.9, J(CH₂2) = 5.7 (CH₂Ob); 4.56 bs, 1 H (R-T); 4.82 t, 1 H,
J(OH,CH₂) = 5.1 (OH); 5.99 bdd, 1 H, J(5,6) = 5.7, J(5,4) = 2.8 (R-S); 6.12 dd, 1
H, J(6,5) = 5.7, J(6,l) = 2.9 (H-6); 8.48 s, 1 H (H-8'); 8.75 s, 1 H (H-2'). ¹³C
NMR (DMSO, 125.70 MHz): 21.78 (C-3); 40.76 (C-2); 44.96 (C-4); 46.78 (C-1);
64.09 (CH₂O); 68.80 (C-7); 131.08 (C-5'); 132.78 (C-5); 133.67 (C-6); 147.81
(C-8'); 149.10 (C-6'); 151.55 (C-2'); 152.98 (C-4').

- [(Ii? *,2S*,4R*,7S*)-6-(6-Chloro-9 H-purin-9-yl)bicyclo[2.2.1]heptan-2-ol](26), m.p. = 154.9 - 156.1 °C (ethylacetate-hexanes). For C₁₂H₁₃ClN₄O (264.7)
calculated: 54.45% C, 4.95% H, 13.39% Cl, 21.17% N; found: 54.28% C, 4.89%
H, 13.83% Cl, 20.92% N. ¹H NMR (DMSO, 499.95 MHz): 1.28 m, 1 H (H-3exo);
1.65 m, 2 H (R-T); 1.68 ddd, 1 H, J₆₇ = 12.9, J(3en,2) = 7.0, J(3en,7) = 1.6 (H-
3endo); 1.87 ddd, 1 H, J₆₇ = 13.1, J(5en,6) = 8.5, J(5en,7) = 1.4 (H-5endo); 1.95
m, 1 H (H-5exo); 2.40 m, 2 H (H-I and H-4); 3.87 m, 1 H (H-2); 4.45 dd, 1 H,
J(6,5en) = 8.4, J(6,5ex) = 4.8 (H-6); 4.84 d, 1 H, J(OH,2) = 3.8 (OH); 8.77 s, 1 H
(H-2'); 8.85 s, 1 H (H-8'). ¹³C NMR (DMSO, 125.73 MHz): 32.42 (C-7); 34.96
(C-4); 37.00 (C-5); 40.51 (C-3); 50.25 (C-I); 54.67 (C-6); 71.00 (C-2); 131.45 (C-
5'); 145.69 (C-8'); 149.15 (C-6'); 151.45 (C-2'); 152.13 (C-4').

C, 4.95% H, 13.39% Cl, 21.17% N; found: 57.75% C, 4.91% H, 13.19% Cl,
21.00% N. ¹H NMR (DMSO, 600.13 MHz): 1.31 dddd, 1 H, J₆₇ = 13.3, J(3ex,4)
= 5.0, J(3ex,2) = 2.4, J(3ex,l) = 1.0 (H-3exo); 1.55 dm, 1 H, J₆₇ = 10.4 (H-7a);
1.65 dm, 1 H, $J_{gem} = 10.5$ (H-7b); 1.78 ddd, 1 H, $J_{gem} = 13.3$, $J(3en,4) = 5.0$, $J(3en,2) = 6.8$, $J(3en,7a) = 2.4$ (H-3endo); 1.83 ddd, 1 H, $J_{gem} = 13.9$, $J(6en,5) = 8.4$, $J(6en,7b) = 2.2$ (H-6endo); 2.02 dddd, 1 H, $J_{gem} = 13.9$, $J(6ex,5) = 3.9$, $J(6ex,1) = 5.0$, $J(6ex,4) = 1.0$ (H-3exo); 2.22 bd, 1 H, $J(1,6ex) = 5.4$ (H-I); 2.54 bd, 1 H, $J(4,3ex) = 5.0$ (H-4); 3.71 m, 1 H (H-2); 4.42 ddd, 1 H, $J(5,6en) = 8.5$, $J(5,6ex) = 3.9$, $J(5,7b) = 1.1$ (H-5); 4.73 d, 1 H, $J(OH,2) = 3.7$ (OH); 8.75 s, 1 H (H-2'); 8.85 s, 1 H (US'). 13C NMR (DMSO, 150.92 MHz): 31.84 (C-7); 32.34 (C-6); 38.98 (C-3); 41.22 (C-4); 43.73 (C-1); 57.65 (C-5); 71.84 (C-2); 131.46 (C-5'); 145.60 (C-8'); 149.11 (C-6'); 151.43 (C-2'); 152.22 (C-4').

10  • (1/?*,2/?*,45/?*,6i/?*)-6-(6-Chloro-9 $H$-purin-9-yl)bicyclo[2.2.1]heptan-2-ol (63), m.p. = 156.2 - 157.2 °C (ether-hexanes). For C_{12}H_{13}ClN_{4}O (264.7) calculated: 54.45% C, 4.95% H, 13.39% Cl, 21.17% N; found: 54.65% C, 5.15% H, 13.67% Cl, 20.87% N. 1H NMR (DMSO, 499.84 MHz): 0.88 dt, 1 H, $J_{gem} = 12.6$, $J(3ex,2) = J(3ex,4) = 3.5$ (H-3exo); 1.42 dm, 1 H, $J_{gem} = 10.7$ (H-7a); 1.85 dm, 1 H, $J_{gem} = 10.7$ (H-7b); 1.91 m, 1 H (H-3endo); 1.96 m, 1 H (H-5exo); 2.12 ddd, 1 H, $J_{gem} = 12.8$, $J(5en,6) = 8.7$, $J(5en,7a) = 2.3$ (H-5endo); 2.34 m, 1 H (H-4); 2.54 m, 1 H (H-I); 4.18 m, 1 H (H-2'); 5.10 d, 1 H, $J(OH,2) = 3.8$ (OH); 5.30 bdd, 1 H, $J(6,5en) = 8.8$, $J(6,5ex) = 4.5$ (H-6); 8.78 s, 1 H (H-2'); 8.86 s, 1 H (H-8'). 13C NMR (DMSO, 125.70 MHz): 39.57 (C-5); 35.28 (C-7); 36.99 (C-4); 37.59 (C-3); 48.50 (C-1'); 50.94 (C-6); 69.49 (C-2'); 131.29 (C-5'); 146.04 (C-8'); 149.13 (C-6'); 151.50 (C-2'); 152.17 (C-4').

25  • (1/?*,2/?*,4i/?*,55/?*)-5-(6-Chloro-9 $H$-purin-9-yl)bicyclo[2.2.1]heptan-2-ol (64), m.p. = 172.5 - 174 °C(ethylacetate). For C_{12}H_{13}ClN_{4}O (264.7) calculated: 54.45% C, 4.95% H, 13.39% Cl, 21.17% N; found: 54.41% C, 4.78% H, 13.20% Cl, 21.05% N. 1H NMR (DMSO, 600.13 MHz): 0.95 dt, 1 H, $J_{gem} = 13.1$, $J(3en,2) = J(3en,7b) = 3.5$ (H-3endo); 1.37 dm, 1 H, $J_{gem} = 10.7$ (H-7a); 1.71 dm, 1 H, $J_{gem} = 10.7$ (H-7b); 1.91 dtt, 1 H, $J_{gem} = 13.5$, $J(6ex,5) = J(6ex,1) = 4.2$, $J(6ex,2) = J(6ex,4) = 1.1$ (H-6exo); 1.98 ddd, 1 H, $J_{gem} = 13.1$, $J(3ex,2) = 10.1$, $J(3ex,4) = 5.2$ (H-3exo); 2.33 m, 1 H (H-I); 2.44 bd, 1 H, $J(4,3ex) = 5.1$ (H-4); 2.63 ddd, 1 H, $J_{gem} = 13.4$, $J(6en,5) = 8.6$, $J(6en,7a) = 2.4$ (H-6endo); 4.09 m, 1 H (H-2); 4.58 ddd, 1 H, $J(5,6en) = 8.6$, $J(5,6ex) = 4.2$, $J(5,7a) = 1.2$ (H-5); 4.83 d, 1 H, $J(OH,2) = 4.0$.
(OH); 8.77 s, 1 H (H-2'); 8.87 s, 1 H (H-8'). $^{13}$C NMR (DMSO, 150.92 MHz):
28.93 (C-6); 34.58 (C-7); 37.44 (C-3); 42.14 (C-I); 42.92 (C-4); 58.28 (C-5);
69.39 (C-2); 131.45 (C-5'); 145.70 (C-8'); 149.14 (C-6'); 151.49 (C-2'); 152.15
(C-4').

- [(ii) *25*,*35*,*45*)-3-(6-Chloro-9 $H$-purin-9-yl)bicyclo[2.2.1]hept-5-en-2-
yl]methanol (65), m.p. = 158 - 159 °C. For C$_{13}$H$_{13}$ClN$_4$O (276.7) calculated:
56.42% C, 4.74% H, 12.81% Cl, 20.25% N; found: 56.42% C, 4.76% H, 12.74%
Cl, 19.96% N. $^1$H NMR: 1.63 dq, 1 H, $J(1b, 1) J(7a, 3) J(7b, 4) = 1.7, J_{gem} =
9.2 (H-7b); 2.03 brdq, 1 H, $J(7a, 3) J(7b, 4) = 1.5 (H-7a); 2.79 dddd, 1 H, $J(2, 1)
= 3.2, J(2, 3) = 4.5, J(2, CHa) = 7.2, J(2, CHa) = 8.2 (H-2); 3.03 ms, 1H (H-I);
3.10 brdq, 1 H, $J(4, 1) J(4, 5) = 3.2 (H-4); 3.33 ddd, 1H, J(CHa, OH) =
4.9, J_{gem} = 10.5 (CHa); 3.44 ddd, 1 H, J(CHb, OH) = 5.5 (CHb); 4.01 dd, 1 H (H-3);
4.65 t, 1 H (OH); 6.30 dd, 1 H, $J(6, 1) = 2.7, J(6, 5) = 5.7 (H-6); 6.34 dd, 1 H
(H-5); 8.78 s, 1 H and 8.96 s, 1 H (H-2', H-8'). $^{13}$C NMR: 43.35 (C-1); 47.09 (C-
7); 48.33 (C-2); 48.53 (C-4); 59.35 (C-5); 63.94 (OCH$_2$); 131.47 (C-7); 135.20
(C-6); 137.38 (C-5); 146.27 (C-8'); 149.16 (C-6'); 151.42 (C-2'); 152.46
(C-4').

- [(IR *2R *,*3R *,*45*)-3-(6-chloro-9 $H$-purin-9-yl)bicyclo[2.2.1]hept-5-en-2-
yl]methanol (66), m.p. = 156 - 157 °C. For C$_{13}$H$_{13}$ClN$_4$O x H$_2$O (281.2)
calculated: 55.52% C, 4.84% H, 12.61% Cl, 19.92% N; found: 55.50% C, 4.69%
H, 12.42% Cl, 19.73% N. $^1$H NMR: 1.63 dq, 1 H, $J(7b, 1) J(7b, 3) J(7b, 4) =
1.7, J_{gem} = 9.2 (H-7b); 2.03 brdq, 1 H, $J(7a, 3) J(7a, 4) = 1.5 (H-7a); 2.79 dddd,
1 H, $J(2, 1) = 3.2, J(2, 3) = 4.5, J(2, CHa) = 7.2, J(2, CHa) = 8.2 (H-2); 3.03 ms,
1H (H-I); 3.10 brdq, 1 H, $J(4, 1) J(4, 5) = 3.2 (H-4); 3.33 ddd, 1H, J(CHa,
OH) = 4.9, J_{gem} = 10.5 (CHa); 3.44 ddd, 1 H, J(CHb, OH) = 5.5 (CHb); 4.01 dd,
1H (H-3); 4.65 t, 1 H (OH); 6.30 dd, 1 H, $J(6, 1) = 2.7, J(6, 5) = 5.7 (H-6); 6.34
dd, 1 H (H-5); 8.78 s, 1 H and 8.96 s, 1 H (H-2’, H-8’). $^{13}$C NMR: 43.35 (C-1);
47.09 (C-7); 48.33 (C-2); 48.53 (C-4); 59.35 (C-5); 63.94 (OCH$_2$); 131.47 (C-7);
135.20 (C-6); 137.38 (C-5); 146.27 (C-8’); 149.16 (C-6’); 151.42 (C-2’); 152.46
(C-4’).
EXAMPLE 10: SYNTHESIS OF BENZYL-ETHER COMPRISING NUCLEOSIDE ANALOGS OF THE INVENTION SUCH AS 7

Sodium hydride (60% dispersion in mineral oil, 40 mg, 1 mmol) was added to a solution of (lR*,2R*,3R*,6R*,7S*,9S*)-2-(6-chloro-9H-purin-9-yl)-4-oxatricyclo[4.2.1.0 3>7 ]nonane-9-methanol (1) (153 mg, 0.5 mmol) and benzyl bromide (0.3 ml) in dimethylformamide (1.5 ml). The mixture was stirred at 0 °C for 0.5 h then at room temperature for 2 h and evaporated. Solution of the residue in ethyl acetate (15 ml) was washed with water (2 x 5 ml), dried over anhydrous sodium sulfate and evaporated.

Chromatography of the residue on silica gel (30 g) in ethyl acetate - toluene (3 : 1) followed by crystallization from ether gave 90 mg (45%) of 9-{(lR*,2R*,3R*,6R*,7S*,9S*)-9-[((benzyloxy)methyl]-4-oxatricyclo[4.2.1.0 7,3]non-2-yl}-6-chloro-9H-purine (7), m.p. 113.5 - 116 °C. For C_{21}H_{21}ClN_{4}O_{2} (396.88) calculated: 63.55% C, 5.33% H, 8.93% Cl, 14.12% N; found: 63.63% C, 5.29% H, 8.72% Cl, 13.89% N. FAB MS, mlz (%): 396/397 (5/8) [M + H], 91(100), 57(31), 52(54). 1H NMR (DMSO-de): 1.76 dm, 1 H, J_{gem} = 11.7 (H-8a'); 1.81-1.87 m, 2 H (H-8b\ H-9'); 2.11 m, 1 H (H-6'); 2.61 m, 1 H (H-T); 2.71 tq, 1 H, J(7,8a) = J(7,8b) = J(7,l) = 1.1, J(7,6) = J(7,3) = 4.7 (H-7'); 3.44 m, 2 H (CH_{2}O); 3.79 m, 2 H (H-5'); 4.15 d, 1 H, J(2,8b) = 1.6 (H-2'); 4.51 m, 2 H (CH_{2}O phenyl); 4.79 dd, 1 H, J(3,7) = 4.9, J(3,l) = 1.2, (H-3'); 7.25-7.37 m, 5 H (phenyl); 8.78 s, 1 H (H-2); 8.79 s, 1 H (H-8). 13C NMR (DMSO-d_{6}): 32.17 (C-8'); 41.31 (C-I'); 41.58 (C-6'); 45.28 (C-7'); 47.71 (C-9'); 67.12 (C-2'); 71.32 (CH_{2}O); 72.20 (CH_{2}O phenyl); 73.99 (C-5'); 83.54 (C-3'); 127.62 (C-4 phenyl); 127.73 (C-2 phenyl); 128.47 (C-3 phenyl); 131.28 (C-5); 138.63 (C-I phenyl); 145.83 (C-8); 149.19 (C-6); 151.52 (C-2); 152.31 (C-4).

EXAMPLE 11: SYNTHESIS OF PHOSPHATE COMPRISING NUCLEOSIDE ANALOGS OF THE INVENTION SUCH AS 6

N-methylimidazole (250 µl, 3 mmol) was added dropwise over 1 min to a stirred solution of phenyl-(methoxy-L-alaninyl)-phosphorochloridate (420 mg, 1.5 mmol) and (lR*,2R*,3R*,6R*,7S*,9S*)-2-(6-chloro-9H-purin-9-yl)-4-oxatricyclo[4.2.1.0 7,3]nonane-
9-methanol (1) (153 mg, 0.5 mmol) in tetrahydrofurane (5 ml). The mixture was stirred under argon at room temperature overnight and then was evaporated. A solution of the residue in chloroform (10 ml) was washed with 1 M HCl (2 x 10 ml), saturated aqueous solution of sodium hydrogencarbonate (10 ml) and water (5 ml). The organic layer was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The residue was chromatographed on a silica gel column (40 g) in ethyl acetate - acetone - ethanol - water (100 : 15 : 6 : 4) to give 205 mg (75%) of (1R*,2R*,3R*,6R*,7S*,9S*)-2-(6-chloro-9H-purin-9-yl)-4-oxatricyclo[4.2.1.0
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| EXAMPLE 12: SYNTHESIS OF NUCLEOSIDE ANALOGS OF THE INVENTION SUCH AS 8 |

Thionyl chloride (0.15 ml) was added dropwise to a solution of (153 mg, 0.5 mmol) in hexamethylphosphortriamide (1 ml), the mixture was stirred at room temperature for 0.5 h and then at 80 °C for 2 h. The mixture was
poured into saturated aqueous sodium hydrgencarbonate (10 ml). The mixture was
extracted with ethyl acetate (2 x 20 ml) and the combined extracts were washed with
water (3 x 10 ml), dried over anhydrous sodium sulfate and evaporated. Crystallization
from ether afforded 158 mg (97%) of 6-chloro-9-[(1R*,2R*,3R*,6R*,7S*,9S*)-9-
(chloromethyl)-4-oxatricyclo[4.2.1.0^37]non-2-yl]-9H-purine (~ example isomeric pure
form of 8), m.p. 156.5 - 158 °C. For C_{14}H_{14}Cl_{2}N_{4}O (325.20) calculated: 51.71% C,
4.34% H, 21.80% Cl, 17.23% N; found: 51.70% C, 4.49% H, 21.59% Cl, 16.93% N.
FAB MS, mlz (%): 327/325 (60/84) [M + H], 241(15), 57(100). ^1^H NMR (DMSO-(I_d):
1.78 dm, 1 H, J_{gem} = 12.0 (H-8a); 1.89 brt, 1 H, J(9,CH_2) = 8.2 (H-9); 1.93 dm, 1 H (H-
8b'); 2.21 m, 1 H (H-6'); 2.64 m, 1 H (H-I'); 2.76 tq, 1 H, J(7,8a) = J(7,8b) = J(7,l) =
1.3, J(7,6) = J(7,3) = 4.7 (H-7'); 3.72 d, 2 H, J(CH_2,9) = 8.2 (CH_2Cl); 3.79-3.83 m, 2 H
(H-5'); 4.18 d, 1 H, J(2,8b) = 1.8 (H-2'); 4.81 dd, 1 H, J(3,7) = 5.0, J(3,l) = 1.0, (H-3');
8.79 s, 1 H (H-2); 8.80 s, 1 H (H-8). ^13^C NMR (DMSO-(I_d): 31.92 (C-8'); 42.19 (C-I');
43.48 (C-6'); 45.48 (C-7'); 46.91 (CH_2Cl); 50.68 (C-9'); 66.85 (C-2'); 73.84 (C-5');
83.32 (C-3'); 131.27 (C-5); 145.78 (C-8); 149.22 (C-6); 151.56 (C-2); 152.30 (C-4).

According to the same procedure, there were obtained the following compounds:
- 6-Chloro-9-[(1L* ,2R*,3R*,6S*,7S*,10S*)-10-(chloromethyl)-4-
oxatricyclo[4.3.1.0^37]dec-2-yl]-9H-purine (67), m.p. 192 - 193.5 °C. For
C_{18}H_{16}Cl_{2}N_{4}O (339.23) calculated: 53.11% C, 4.75% H, 20.90% Cl, 16.52% N;
found: 53.32 %C, 4.82 % H, 21.05 % Cl, 16.25 % N. FAB MS, mlz (%): 337/339
(59/100) [M + H], 157/155 (15/55) [6-chloropurine + H]. ^1^H NMR: 0.67 m, 1 H
(H-9'a); 1.33 m, 1 H (H-9'b); 1.83 m, 1 H (H-8'a); 1.95 - 2.03 m, 3 H (H-6', 8'b
and H-10); 2.14 - 2.18 m, 2 H (H-I' and H-7'); 3.58 d, 1 H, J_{gem} = 7.7 (H-5'a);
3.74 - 3.78 m, 2 H (CH^3Cl and H-5'b); 3.88 dd, 1 H, J_{gem} = 10.9, J(CH,10) = 7.3
(CH^3Cl); 4.53 dd, 1 H, J(2',1') = 4.1, J(2',9'b) = 1.5 (H-2'); 4.73 d, 1 H, J(3',7') =
5.2 (H-3'); 8.79 s, 1 H (H-2); 8.80 s, 1 H (H-8). ^13^C NMR: 11.19 (C-9'); 14.01 (C-
8'); 29.76 (C-I'); 35.15 (C-7'); 39.25 (C-6'); 44.16 (C-10'); 47.44 (CH_2Cl); 62.92
(C-2'); 74.86 (C-5'); 75.91 (C-3'); 131.01 (C-5); 146.30 (C-8); 149.47 (C-6);
151.72 (C-2); 152.19 (C-4).
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6-Chloro-9-[(1R*,2R*,3S*,6S*,1S*,9R*)-9-(chloromethyl)-4,8-dioxatricyclo[4.2.1.03\(^{2}\)7]non-2-yl]-9\(\text{H}\)-purine (68), m.p. 176 - 177 °C. For C\(_{13}\)H\(_{12}\)Cl\(_2\)N\(_4\)O\(_2\) (327.17) calculated: 47.72% C, 3.70% H, 21.67% Cl, 17.12% N; found: 47.67% C, 3.85% H, 21.85% Cl, 16.95% N. FAB MS, \(m/z\) (%): 329/327 (64/100) [M + H], 157/155 (5/15) [6-chloropurine + H]. \(\text{H}^1\) NMR: 2.34 dt, 1 H, \(J(6',7') = J(6',5'a) = 4.7, J(6',9') = 2.0 (H-6'); 2.41 dt, 1 H, \(J(9',6') = 2.1, J(9',CH\(_2\)) = 8.1 (H-9'); 3.61 d, 2 H, \(J(CH\(_2\)9') = 8.1 (CH\(_2\)Cl); 3.92 dd, 1 H, \(J_{\text{gem}} = 8.8, J(5'a,6') = 4.4 (H-5'a); 4.01 d, 1 H, \(J_{\text{gem}} = 8.7 (H-5'b); 4.53 dd, 1 H, \(J(3',7') = 4.7, J(3',1') = 1.4 (H-3'); 4.67 m, 2 H (H-I' and H-2'); 5.25 t, 1 H, \(J(7',3') = J(7',6') = 4.7 (H-T); 8.55 s, 1 H (H-8); 8.80 s, 1 H (H-2). \(\text{C}^{13}\) NMR: 43.43 (C-6'); 45.81 (CH\(_2\)Cl); 50.80 (C-9'); 64.10 (C-2'); 71.96 (C-5'); 80.70 (C-I'); 82.17 (C-7'); 83.07 (C-3'); 130.77 (C-5); 145.25 (C-8); 149.18 (C-6); 151.72 (C-2); 151.89 (C-4).

EXAMPLE 13: Synthesis of 6-Chloro-9-[(1R*,2R*,3R*,6S*,7S*,10S*)-10-(fluororomethyl)-4-oxatricyclo[4.3 .10\(^{10}\)]dec-2-yl]-9\(\text{H}\)-purine (69)

(Diethylamino)sulfur trifluoride (DAST) (0.7 ml, 5 mmol) was added under argon to a stirred solution of chloropurine derivative 14 (321 mg, 1 mmol) and pyridine (1.3 ml) in tetrahydrofuran (12 ml). The mixture was refluxed for 4 h and then was poured under stirring into an aqueous saturated solution of potassium hydrogen carbonate (60 ml). The mixture was extracted with ethyl acetate (2 x 25 ml) and the collected extracts were washed with 10% aqueous solution of potassium hydrogen carbonate (20 ml), 5% hydrochloric acid (10 ml), 10% aqueous potassium hydrogen carbonate (10 ml), dried over anhydrous sodium sulfate and evaporated. Chromatography of the residue on silica gel with ethyl acetate - toluene (22:3) and subsequent crystallization from methanol afforded 101 mg (31%) of fluoro derivative 69. For C\(_{15}\)H\(_{16}\)ClFN\(_4\)O (322.77) calculated: 55.82% C, 5.00% H, 10.98% Cl, 5.89% F, 17.36% N; found: 55.76% C, 5.11% H, 11.14% Cl, 17.21% N. FAB MS, \(m/z\) (%): 325/323 (37/100) [M + H], 157/155 (5/15) [6-chloropurine + H]. \(\text{H}^1\) NMR: 0.69 m, 1 H (H-9'a); 1.36 m, 1 H (H-9'b); 1.80 m, 1 H (H-8'a); 1.92 dt, 1 H, \(J(6',5'b) = J(6',7') = 3.9, J(6',3') = 1.8 (H-6'); 2.00 m, 1 H (H-8'b);
According to the same procedure, there were obtained the following compounds:

- 6-Chloro-9-[(1/?*,2i?*,35 r*,65*,7S*,9R*)]-9-(fluoromethyl)-4,8-dioxatricyclo[4.2.1.0 ^3]non-2-yl-9 H-purine (70), m.p. 176 - 179 °C. For C_{13}H_{12}ClFN_{2}O_{2} (310.72) calculated: 50.25% C, 3.89% H, 11.41% Cl, 6.15% F, 18.03% N; found: 1H NMR: 2.24 dd, 1H, J(6’,7’) = J(6’,5′a) = 4.6, J(6’,9’) = 2.1 (H-6’); 2.47 m, 1H (H-9’); 3.90 ddd, 1H, J_{gem} = 8.7, J(5’a,6’) = 4.3, J(5’a,F) = 1.5 (H-5’a); 4.02 d, 1H, J_{gem} = 8.7 (H-5′b); 4.32 dt, 1H, J_{gem} = J(CH,9’) = 9.3, J(CH,F) = 47.7 (CH^*F); 4.38 ddd, 1H, J_{gem} = 9.1, J(CH,9’) = 6.5, J(CH,F) = 46.8 (CH^*F); 4.53 dd, 1H, J(3’,7’) = 4.8, J(3’,1’) = 1.5 (H-3’); 4.67 s, 1H (H-2’); 4.70 m, 1H (H-1’); 5.23 m, 1H (H-7’); 8.55 s, 1H (H-8’); 8.79 s, 1H (H-2). 13C NMR: 40.06 d, J(6’,F) = 7.2 (C-6’); 48.06 d, J(9’,F) = 19.1 (C-9’); 64.31 (C-2’); 71.85 (C-5’); .79.31 d, J(1’,F) = 4.8 (C-I ’); 81.97 (C-7’); 82.87 d, J(CH_{2},F) = 167.8; 83.19 (C-3’); 130.79 (C-5’); 145.30 (C-8’); 149.16 (C-6’); 151.71 (C-2’); 151.91 (C-4’).

- 6-Chloro-9-[(15*,25*,4i ?,6R *)]-6-fluorobicyclo[2.2.1]hept-2-yl-9i/-purine (71), m.p. = 127.6 - 129 °C. For C_{12}H_{12}ClFN_{4} (266.7) calculated: 54.04% C, 4.54% H, 13.29% Cl, 7.12% F, 21.01% N; found: 53.92% C, 4.31% H, 20.85% N. 1H NMR (DMSO, 499.95 MHz): 1.60 m, 1H (H-5’exo); 1.62 m, 1H (H-7’a); 1.84 m, 1H (H-7b); 1.86 m, 1H (H-5’endo); 1.93 ddd, 1H, J_{gem} = 13.0, J(3’en,2’) = 8.3, J(3’en,7’a) = 2.2 (H-3’endo); 2.00 m, 1H (H-3’exo); 2.52 m, 1H (H-4’); 2.85 bd, 1H, J(1’,F) = 8.8 (H-1’); 4.52 dd, 1H, J(2’,3’en) = 8.3, J(2’,3’ex) = 5.0 (H-2’); 4.98 ddm, 1H, J(6’,F) = 54.5, J(6’,5’en) = 6.4 (H-6’); 8.79 s, 1H (H-2’); 8.87 s, 1H (H-8). 13C NMR (DMSO, 125.73 MHz): 32.90 (C-7’); 34.74 (C-4’); 36.54 (C-
3'); 38.45 d, \(J(5',F) = 19.7\) (C-5'); 48.11 d, \(J(1',F) = 21.9\) (C-1'); 52.85 d, \(J(2',F) = 14.5\) (C-2'); 93.71 d, \(J(6',F) = 181.6\) (C-6'); 131.49 (C-5); 145.79 (C-8); 149.19 (C-6); 151.51 (C-2); 152.15 (C-4).

- 6-Chloro-9-[(l/?*,25*,4i?*,55*)-5-fluorobicyclo[2.2.1]hept-2-yl]-9//-purine (72), m.p. = 110.9 - 112.4 °C. For \(\text{C}_{12}\text{H}_{14}\text{ClF}_{4}\) (266.7) calculated: 54.04% C, 4.54% H, 13.29% Cl, 7.12% F, 21.01% N; found: 53.91% C, 4.31% H, 20.71% N. \(^1\)H NMR (DMSO, 499.95 MHz): 1.60 m, 1 H (H-7’a); 1.64 ddt, 1 H, \(J(6’ex,F) = 39.1, J_{gem} = 14.4, J(6’ex,1’) = 5.1, J(6’ex,5’) = J_Lr = 1.5 (H-6’exo); 1.72 dm, 1 H, \(J_{gem} = 11.0\) (H-7’b); 1.88 ddd, 1 H, \(J_{gem} = 14.4, J(3’en,2’) = 8.3\) (H-3’endo); 1.99 ddd, 1 H, \(J(6’en,F) = 18.2, J_{gem} = 14.4, J(6’en,5’) = 6.3, J(6’en,7’b) = 2.7\) (H-6’endo); 2.16 m, 1 H (H-3’exo); 2.58 m, 1 H (H-4’); 2.69 bd, 1 H, \(J(1’,6’ex) = 5.0\) (H-I ‘); 4.47 ddd, 1 H, \(J(2’,3’en) = 8.5, J(2’,3’ex) = 3.8\) (H-2’); 4.81 ddd, 1 H, \(J(5’,F) = 56.0, J(5’,6’en) = 6.3\) (H-5’); 8.77 s, 1 H (H-2); 8.87 s, 1 H (H-8). \(^{13}\)C NMR (DMSO, 125.73 MHz): 29.96 d, \(J(3’,F) = 11.5\) (C-3’); 32.22 (C-7’); 36.94 d, \(J(6’,F) = 20.7\) (C-6’); 40.75 (C-1’); 41.74 d, \(J(4’,F) = 20.7\) (C-4’); 57.03 (C-2’); 94.46 d, \(J(5’,F) = 180.8\) (C-5’); 131.50 (C-5); 145.68 (C-8); 149.17 (C-6); 151.46 (C-2); 152.26 (C-4).

EXAMPLE 14: Synthesis of 9-[(l/?*,2i?*,45*)-bicyclo[2.2.1]hept-2-yl]-9 H-purine-6-thiol (38)

Mixture of chloropurine (17, 720 mg, 2.9 mmol), thiourea (300 mg, 3.7 mmol) was refluxed in ethanol (15 ml) for 2 hours, cooled to 4 °C in the refrigerator and the crystalline product was filtered off (520 mg, 72.8%). Second crop (110 mg, 15.4%) of the product was obtained after column chromatography on silica gel column (100 g) in ethylacetate. M.p. > 300 °C. For \(\text{C}_{12}\text{H}_{14}\text{N}_{4}\text{S}\) (246.3) calculated: 58.51% C, 5.73% H, 22.74% N, 13.02% S; found: 58.15% C, 5.69% H, 22.47% N, 12.99% S. \(^1\)H NMR (DMSO, 600.13 MHz): 1.25 m, 2 H (H-5’endo and H-7’a); 1.36 dddd, 1 H, \(J_{gem} = 12.0, J(6’en,5’en) = 9.4, J(6’en,5’ex) = 3.8, J(6’en,7’b) = 2.3\) (H-6’endo); 1.53 m, 1 H (H-5’exo); 1.60 tt, 1 H, \(J_{gem} = J(6’ex,5’ex) = 12.2, J(6’ex,5’en) = J(6’ex,1’) = 4.4\) (H-6’exo); 1.66 dm, 1 H, \(J_{gem} = 10.3\) (H-7’b); 1.97 m, 2 H (H-3’endo and H-3’exo); 2.41 tm, 1 H,
\[ J(4',3'\text{ ex}) = J(4',5'\text{ ex}) = 4.2 \text{ (H-4')}; 2.46 \text{ dm}, 1 \text{ H}, J(1',6'\text{ ex}) = 4.5 \text{ (H-1')}; 4.42 \text{ ddd}, 1 \text{ H}, J(2',3'\text{ en}) = 8.4, J(2',3'\text{ ex}) = 4.6, J(2',7'a) = 1.2 \text{ (H-2')}; 8.19 \text{ s}, 1 \text{ H (H-2')}; 8.44 \text{ s}, 1 \text{ H (H-8')}; 13.71 \text{ bs}, 1 \text{ H (SH).} \]

\[ ^{13} \text{C NMR (DMSO, 150.92 MHz):} \]

\[ 26.96 \text{ (C-6')}; 27.94 \text{ (C-5')}; 35.69 \text{ (C-7')}; 35.89 \text{ (C-4')}; 37.82 \text{ (C-3')}; 42.46 \text{ (C-1')}; 57.81 \text{ (C-2')}; 135.53 \text{ (C-5'); 140.99 (C-8'); 144.25 (C-4'); 144.84 (C-2'); 176.02 (C-6').} \]

**EXAMPLE 15:** Synthesis of 9-[(l/?*,2i?*,4S*)-bicyclo[2.2.1]hept-2-yl]-6-(methylsulfanyl)-9\textit{H}-purine (39)

Mixture of purine (44, 270 mg, 1.1 mmol), \( \text{K}_2\text{CO}_3 \) (166 mg, 1.2 mmol) and iodomethane (0.2 ml, 3.2 mmol) was stirred at 0 °C for 4 hours in dimethylformamide (20 ml). Reaction mixture was evaporated, partitioned between ethylacetate (50 ml) and water (20 ml). Organic phase was washed with water (2 x 20 ml), saturated solution of sodium thiosulfate (2 x 25 ml), water (2 x 20 ml) and dried over anhydrous sodium sulfate and evaporated. The pure product (105 mg, 36.7%) was obtained after crystallization from water-methanol. M.p. = 92 - 93.5 °C. For \( \text{C}_{11}\text{H}_{16}\text{N}_4\text{S} \) (246.3) calculated: 59.97% C, 6.19% H, 21.52% N, 12.32% S; found: 60.10% C, 6.21% H, 21.29% N, 12.23% S. \( ^{1} \text{H NMR (DMSO, 600.13 MHz):} \)

\[ 1.26 \text{ m, } 2 \text{ H (H-5'endo and H-7'a'); 1.39 dddd, 1 H, } J_{\text{gem}} = 12.1, J(6'\text{en},5'\text{en}) = 9.0, J(6'\text{en},5'\text{ex}) = 4.0, J(6'\text{en},7'b) = 2.3 \text{ (H-6'endo); 1.49 m, 1 H (H-5'exo); 1.61 tt, 1 H, } J_{\text{gem}} = J(6'\text{ex},5'\text{ex}) = 12.1, J(6'\text{ex},5'\text{en}) = J(6'\text{ex},1') = 5.0 \text{ (H-6'exo); 1.71 dm, 1 H, } J_{\text{gem}} = 10.3 \text{ (H-7'b); 1.97 ddd, 1 H, } J_{\text{gem}} = 13.3, J(3'\text{en},2') = 8.5, J(3'\text{en},7'a) = 0.9 \text{ (H-3'endo); 2.05 m, 1 H (H-3'exo); 2.42 m, 1 H (H-4'); 2.49 m, 1 H (H-1'); 2.65 s, 3 H (SCH\text{\textsubscript{3}}); 4.52 ddd, 1 H, } J(2',3'\text{en}) = 8.5, J(2',3'\text{ex}) = 4.4, J(2',7'a) = 0.9 \text{ (H-2'); 8.60 s, 1 H (H-8'); 8.72 s, 1 H (H-2').} \]

**EXAMPLE 16:** Synthesis of 9-[(l/?*,2i?*,4S*)-bicyclo[2.2.1]hept-2-yl]-6-(methylsulfonyl)-9\textit{H}-purine (45)

S-methylthiopurine (39, 1.2 mmol) was dissolved in chloroform (20 ml). To this mixture was slowly added solution of m-chlorperbenzoic acid (1.46 g, 5.9 mmol, 65%) in
chloroform (25 ml). Reaction mixture was stirred for 2 days, diluted with ethylacetate (100 ml) and washed with saturated solution of sodium thiosulfate (70 ml), saturated solution of NaHCO₃ (2 x 70 ml) and dried over anhydrous sodium sulfate and evaporated. Residue was chromatographed on silica gel column (150 g) in toluene - ethylacetate (1:1). It was obtained 140 mg (40.6%) of the product (crystallized from water-methanol).

M.p. = 126.1 - 128.7 °C. For C₁₃H₁₆N₄O₂S x H₂O (310.4) calculated: 50.31% C, 5.85% H, 18.05% N, 10.33% S; found: 50.25% C, 5.42% H, 17.71% N, 10.37% S. ¹H NMR (DMSO, 600.13 MHz): 1.28 m, 2 H (H-5'endo and H-7'a); 1.41 dddd, 1 H, J₆e'ₐ₁ = 12.1, J(6'e,5'e) = 9.1, J(6'e,5'e) = 4.2, J(6'e,7'b) = 2.3 (H-6'endo); 1.54 m, 1 H (H-5'exo); 1.63 tt, 1 H, J₆e₁ₐ₁ = J(6'e,5'e) = 12.1, J(6'e,5'e) = J(6'e,1') = 4.5 (H-6'exo); 1.73 dm, 1 H, J₆e₁ₐ₁ = 10.3 (H-7'b); 2.01 ddd, 1 H, J₆e₁ₐ₁ = 13.3, J(3'ë,2') = 8.4, J(3'ë,7'a) = 2.3 (H-3'endo); 2.08 m, 1 H (H-3'exo); 2.44 br, 1 H, J(4',3'ex) = J(4',5'ex) = 4.6 (H-4'); 2.56 bd, 1 H, J(1',6'ex) = 4.8 (H-I'); 3.87 s, 3 H (SO₂CH₃); 4.59 ddd, 1 H, J(2',3'ë) = 8.4, J(2',3'ex) = 4.4, J(2',7'a) = 1.2 (H-2'); 8.78 s, 1 H (H-2); 8.85 s, 1 H (H-8). ¹³C NMR (DMSO, 150.92 MHz): 26.95 (C-6'); 27.95 (C-5'); 35.82 (C-V); 35.93 (C-4'); 37.77 (C-3'); 41.65 (SO₂CH₃); 42.19 (C-I'); 58.39 (C-2'); 123.16 (C-5); 145.56 (C-8); 150.95 (C-2); 153.38 (C-6); 154.91 (C-4).

EXAMPLE 17: Synthesis of 9-[(li?*,2i?*,45*)-bicyclo[2.2.1]hept-2-yl]-9'H-purine (43)

Solution of 17 (250 mg, 1.01 mmol) in methanol (20 ml), triethylamine (0.3 ml) was stirred with Pd(OH)₂ (20% on charcoal, 120 mg) in atmosphere of hydrogen for 2 days. The catalyst was filtered off and washed with methanol and filtrate was evaporated. Residue was partitioned between ethylacetate (30 ml) and water (10 ml). Organic phase was dried over anhydrous sodium sulfate and evaporated. Residue was crystallized from petrolether-ether to afford 116 mg (53.6%) of the saturated compound. M.p. = 86.2 - 87.6 °C. For C₁₂H₁₄N₄ (214.3) calculated: 67.27% C, 6.59% H, 26.19% N; found: 67.40% C, 6.51% H, 25.98% N. ¹H NMR (DMSO, 600.13 MHz): 1.27 m, 2 H (H-5'endo and H-7'a); 1.41 dddd, 1 H, J₆e₁ₐ₁ = 12.1, J(6'e,5'e) = 9.0, J(6'e,5'e) = 4.0, J(6'e,7'b) = 2.3 (H-6'endo); 1.54 m, 1 H (H-5'exo); 1.62 tt, 1 H, J₆e₁ₐ₁ = J(6'e,5'e) = 12.2, J(6'e,5'e) = J(6'e,1') = 4.5 (H-6'exo); 1.73 dm, 1 H, J₆e₁ₐ₁ = 10.3 (H-7'b); 2.00 ddd, 1 H, J₆e₁ₐ₁ =
13.3, \( J(3'en,2') = 8.5, J(3'en,7'a) = 2.4 \) (H-3'endo); 2.07 m, 1 H (H-3'exo); 2.43 br, 1 H, \( J(4',3'ex) = J(4',5'ex) = 4.3 \) (H-4'); 2.52 bd, 1 H, \( J(1'6'6'ex) = 4.6 \) (H-I'); 4.57 dddd, 1 H, \( J(2',3'en) = 8.5, J(2'3'ex) = 4.5, J(2',7'a) = 1.4 \) (H-2'); 8.77 s, 1 H (H-8); 8.93 s, 1 H (H-2), 9.14 s, 1 H (H-6). \(^1\)C NMR (DMSO, 150.92 MHz): 27.01 (C-6'); 27.96 (C-5'); 35.85 (C-7'); 35.91 (C-4'); 37.76 (C-3'); 42.24 (C-I'); 57.57 (C-2'); 134.26 (C-5); 145.03 (C-8); 147.99 (C-6); 151.32 (C-4); 151.95 (C-2).

EXAMPLE 18: Synthesis of 9-[(li?*,2i?*,45*)-bicyclo[2.2.1]hept-2-yl]-6-iodo-9 H-purine (44)

The compound 17 (400 mg, 1.61 mmol) was added portionwise into a stirred 57% aqueous HI (5 ml) at 0°C and the resulting suspension was stirred at 0°C for 2 h. Reaction mixture was poured onto water + ice (50 ml) and 35% aqueous NH\(_3\) (15 ml) was added. To this mixture, ethylacetate (150 ml) was added. Organic phase was washed with saturated aqueous Na\(_2\)S\(_2\)O\(_3\) (2 x 70 ml), and water (100 ml). The solvent was evaporated and the residue chromatographed on a silica gel column (150 g, toluene - ethyl acetate 6:1) to give the 6-iodopurine (390 mg, 71.2%) which was recrystallized from water-methanol. M.p. = 164.5 - 166°C. For C\(_{13}\)H\(_{13}\)IN\(_4\) (340.2) calculated: 42.37% C, 3.85% H, 37.31% N; found: 42.49% C, 3.77% H, 36.96% N. \(^1\)H NMR (DMSO, 600.13 MHz): 1.27 m, 2 H (H-5'endo and H-7'a); 1.39 dddd, 1 H, \( J_{gem} = 12.1, J(6'en,5'en) = 9.1, J(6'en,5'ex) = 3.0, J(6'en,7'b) = 2.3 \) (H-6'endo); 1.54 m, 1 H (H-5'exo); 1.61 tt, 1 H, \( J_{gem} = J(6'ex,5'ex) = 12.1, J(6'ex,5'en) = J(6'ex,1') = 4.5 \) (H-6'exo); 1.71 dm, 1 H, \( J_{gem} = 10.3 \) (H-7'b); 1.98 ddd, 1 H, \( J_{gem} = 13.3, J(3'en,2') = 8.5, J(3'en,7'a) = 2.3 \) (H-3'endo); 2.06 m, 1 H (H-3'exo); 2.42 bt, 1 H, \( J(4',3'ex) = J(4',3'ex) = 4.5 \) (H-4'); 2.54 bd, 1 H, \( J(1',6'ex) = 4.7 \) (H-I'); 4.53 ddd, 1 H, \( J(2',3'en) = 8.5, J(2',3'ex) = 4.4, J(2',7'a) = 1.1 \) (H-2'); 8.61 s, 1 H (H-2); 8.81 s, 1 H (H-8). \(^1\)C NMR (DMSO, 150.92 MHz): 26.94 (C-6'); 27.95 (C-5'); 35.81 (C-7'); 35.91 (C-4'); 37.71 (C-3'); 42.15 (C-I'); 58.24 (C-2'); 122.80 (C-6); 138.55 (C-5); 144.56 (C-8); 148.16 (C-4); 151.65 (C-2).
EXAMPLE 19: Synthesis of 6-azido-9-[(lR*,2R*,4S*)-bicyclo[2.2.1]hept-2-yl]-9\(H\)-purine (73)

Solution of 9-[(lR*,2R*,4S*)-bicyclo[2.2.1]hept-2-yl]-6-chloro-9\(H\)-purine (1.29 g, 5.2 mmol), sodium azide (680 mg, 10.4 mmol) in dimethylformamide (40 ml) was heated with stirring under argon atmosphere for 2 hours, evaporated and partitioned between ethylacetate (150 ml) and water (80 ml). Organic phase was washed with brine (2 x 80 ml) and dried over anhydrous sodium sulfate and evaporated (1.24 g, 93%). The pure product (920 mg, 69.3%) was obtained after crystallization from water-methanol. M.p. = 181.0 - 183.3 °C (decomp.). For \(C_{12}H_{13}N_7\) (255.3) calculated: 56.46% C, 5.13% H, 38.41% N; found: 56.24% C, 5.18% H, 38.02% N. \(^1\)H NMR (DMSO, 499.84 MHz): 1.27 - 1.33 m, 1 H (H-5'endo and H-7'a); 1.45 m, 1 H (H-6'endo); 1.56 m, 1 H (H-5'exo); 1.65 tt, 1 H, \(J_{\text{gem}}=J(6'\text{ex},5'\text{ex})=12.0, J(6'\text{ex},5'\text{en})=J(6'\text{ex},1')=4.4 (H-6'exo); 1.71 dm, 1 H, \(J_{\text{gem}}=10.3 (H-7)b); 2.08 m, 2 H (H-3'endo and H-3'exo); 2.46 m, 1 H (H-4'); 2.56 bd, 1 H, \(J(1',6'\text{ex})=4.3 (H-1'); 4.69 m, 1 H (H-2'); 8.80 s, 1 H (H-8); 10.08 s, 1 H (H-2). \(^{13}\)C NMR (DMSO, 125.70 MHz): 26.97 (C-6'); 27.98 (C-5'); 35.78 (C-7'); 36.00 (C-4'); 38.10 (C-3'); 42.61 (C-1'); 58.72 (C-2'); 120.33 (C-5); 135.58 (C-2); 142.32 (C-8); 142.53 (C-4); 145.67 (C-6).

EXAMPLE 20: Synthesis of 9-[(lR*,2R*,4S*)-bicyclo[2.2.1]hept-2-yl]-9\(H\)-purin-6-amine (74)

Solution of the azidopurine 73 (1.14 g, 4.5 mmol) in methanol (20 ml) was stirred with Pd(OH)\(_2\) (20% on charcoal, 200 mg) in atmosphere of hydrogen for 1 day. The catalyst was filtered off and washed with methanol and filtrate was evaporated. Residue was crystallized from ethylacetate to afford 850 mg (82.4%) of the amino compound. M.p. = 212.6 - 214.5 °C (decomp.). For \(C_{12}H_{15}N_5\) (229.3) calculated: 62.86% C, 6.59% H, 30.54% N; found: 62.53% C, 6.56% H, 30.19% N. \(^1\)H NMR (DMSO, 499.84 MHz): 1.22 - 1.27 m, 2 H (H-5'endo and H-7'a); 1.37 m, 1 H (H-6'endo); 1.53 m, 1 H (H-5'exo); 1.59 tt, 1 H, \(J_{\text{gem}}=J(6'\text{ex},5'\text{ex})=12.2, J(6'\text{ex},5'\text{en})=J(6'\text{ex},1')=4.5 (H-6'exo); 1.70 dm, 1 H, \(J_{\text{gem}}=10.2 (H-7)b); 1.93 ddd, 1 H, \(J_{\text{gem}}=13.2, J(3'\text{en},2')=8.5, J(3'\text{en},7'a)=2.2 (H-3'endo); 2.01 m, 1 H (H-3'exo); 2.41 m, 1 H (H-4'); 2.43 bd, 1 H, \(J(1',6'\text{ex})=4.7

To a solution of 17 (205 mg, 0.82 mmol) in toluene (10 ml) was added AgF (750 mg, 5.9 mmol). Reaction mixture was refluxed for 2 hours, inorganic salts were filtered off and filtrate was evaporated. Residue was dissolved in mixture ether-chloroform (25 ml, 9:1) and organic phase was washed with saturated EDTA (15 ml) and water (15 ml), dried over anhydrous sodium sulfate and evaporated. Residue was chromatographed on silica gel (20 g) in toluene-ethylacetate (6:1). It was obtained 136 mg (71.4%) of the fluorour derivative. Compound was crystallized from water-methanol. M.p. = 96 - 97 °C. For C_{12}H_{13}FN_4 (232.3) calculated: 62.06% C, 5.64% H, 8.18% F, 24.12% N; found: 62.07% C, 5.92% H, 8.26% F, 24.12% N. 1H NMR (DMSO, 499.84 MHz): 1.24 - 1.30 m, 2 H (H-5'endo and H-7'a); 1.41 m, 1 H (H-6'endo); 1.54 m, 1 H (H-5'exo); 1.62 tt, 1 H, J_{gem} = J(6' ex, 5' ex) = 12.1, J(6' ex, 5' en) = J(6' ex, 1 ') = 4.5 (H-6'exo); 1.72 dm, 1 H, J_{gem} = 10.3 (H-7'b); 2.00 ddd, 1 H, J_{gem} = 13.3, J(3' en, 2') = 8.4, J(3' en, 7'a) = 2.2 (H-3'endo); 2.07 m, 1 H (H-3'exo); 2.43 m, 1 H (H-4'); 2.55 bd, 1 H, J(l',6' ex) = 4.6 (H-l'); 4.58 ddd, 1 H, J(2',3' en) = 8.4, J(2',3' ex) = 4.5, J(2',7'a) = 0.9 (H-2'); 8.67 d, 1 H, J(2,F) = 0.9 (H-2); 8.83 s, 1 H (H-8). 13C NMR (DMSO, 125.70 MHz): 26.97 (C-6'); 27.95 (C-5'); 35.83 (C-7'); 35.95 (C-4'); 37.83 (C-3'); 42.23 (C-1'); 58.48 (C-2'); 119.84 d, J(5,F) = 29.1 (C-5); 145.35 d, J(8,F) = 2.7 (C-8); 151.15 d, J(2,F) = 14.2 (C-2); 155.92 d, J(4,F) = 11.8 (C-4); 158.94 d, J(6,F) = 255.4 (C-6).
Toluene (12 ml) was added to an argon-purged flask containing 17 (300 mg, 1.21 mmol), K₂CO₃ (242 mg, 1.82 mmol), 4-chlorophenylboronic acid (283 mg, 1.8 mmol) and Pd(PPh₃)₄ (71 mg, 0.07 mmol) and the mixture was stirred under argon at 100 °C for 8 h. After cooling to ambient temperature the mixture was evaporated and the residue was chromatographed on a silica gel column (60 g, ethyl acetate-petroleum ether 1:7). It was obtained 220 mg (56%). Compound was crystallized from water-acetone. M. p. = 167 - 169 °C. For C₁₈H₁₁₇CIN₄ (324.8) calculated: 66.56% C, 5.28% H, 10.92% Cl, 17.25% N; found: 66.61% C, 5.30% H, 11.20% Cl, 16.98% N. ᵃH NMR (DMSO, 499.84 MHz): 1.26 - 1.32 m, 2 H (H-5'endo and H-7'a); 1.43 m, 1 H (H-6'endo); 1.56 m, 1 H (H-5'exo); 1.64 tt, 1 H, ⱽ_gem = ᵃ(J(6'exo,5'exo) = 12.0, ᵃ(J(6'exo,5'en) = ᵃ(J(6'exo,1') = 4.5 (H-6'exo); 1.75 dm, 1 H, ᵃ(J_gem = 10.3 (H-7'b); 2.02 ddd, 1 H, ᵃ(J_gem = 13.3, ᵃ(J(3'en,2') = 8.4, ᵃ(J(3'en,7'a) = 2.2 (H-3'endo); 2.10 m, 1 H (H-3'exo); 2.45 m, 1 H (H-4'); 2.55 bd, 1 H, ᵃ(J(l',6'ex) = 4.9 (H-1'); 4.61 ddd, 1 H, ᵃ(J(2',3'en) = 8.4, ᵃ(J(2',3'ex) = 4.3, ᵃ(J(2',7'a) = 1.0 (H-2'); 7.67 m, 2 H (H-3''); 8.84 s, 1 H (H-8); 8.87 m, 2 H (H-2''); 8.98 s, 1 H (H-2). ᵃ¹C NMR (DMSO, 125.70 MHz): 27.03 (C-6'); 28.02 (C-5'); 35.87 (C-7'); 35.96 (C-4'); 37.80 (C-3'); 42.26 (C-1'); 57.76 (C-2'); 129.07 (C-3''); 130.92 (C-5); 131.21 (C-2''); 134.52 (C-1''); 136.08 (C-4''); 144.81 (C-8); 151.27 (C-6); 151.76 (C-2); 152.77 (C-6).

EXAMPLE 23: Synthesis of 9-[(1R*,2R*,4S*)-bicyclo[2.2.1]hept-2-yl]-6-(trifluoromethyl)-9H-purine (77)

A mixture of the iodopurine derivative (44) (300 mg, 0.94 mmol), CF₃SiMe₃ (206 μl, 1.4 mmol), KF (82 mg, 1.4 mmol), CuI (304 mg, 1.6 mmol), DMF (1 ml) and NMP (1 ml) was stirred and heated at 60 °C for 40 h in an argon atmosphere. After cooling to room temperature the solvents were evaporated and the residue was chromatographed on a column of silica gel (170 g) in toluene - ethylacetate (20:1). It was obtained 215 mg (81%). Compound was crystallized from water-methanol. M. p. = 116.3 - 118 °C. For C₁₃H₁₃FN₄ (282.3) calculated: 55.32% C, 4.64% H, 20.19% F, 19.85% N; found: 55.09% C, 4.53% H, 19.74% Cl, 19.60% N. ᵃH NMR (DMSO, 499.84 MHz): 1.26 - 1.32 m, 2 H (H-5'endo and H-7'a); 1.42 m, 1 H (H-6'endo); 1.56 m, 1 H (H-5'exo); 1.64 tt, 1 H, ᵃ(J_gem = ᵃ(J(6'ex,5'ex) = 12.1, ᵃ(J(6'ex,5'en) = ᵃ(J(6'ex,1') = 4.5 (H-6'exo); 1.74 dm, 1 H, ᵃ(J_gem =
EXAMPLE 24: Synthesis of 9-[(li?*,2i?*,45*)-bicyclo[2.2.1]hept-2-yl]-6-methyl-9
H-purine (79)

To a solution of 17 (490 mg, 1.97 mmol) in methanol (10 ml) was added a solution of
MeONa (prepared from 68 mg Na and 10 ml MeOH). Reaction mixture was stirred
overnight, evaporated and residue was chromatographed on silica gel (40 g) in toluene -
ethylacetate (2:1) to afford 365 mg (76%) of product. Compound was crystallized from
pentane-ether. M.p. = 72 - 74.5 0C. For C_{13}H_{16}N_{4}O (244.3) calculated: 63.91% C, 6.60%
H, 22.93% N; found: 63.73% C, 6.59% H, 22.81% N. 1H NMR (DMSO, 499.84 MHz):
1.22 - 1.28 m, 2 H (H-5'endo and H-7'a); 1.39 m, 1 H (H-6'endo); 1.52 m, 1 H (H-
5'exo); 1.60 tt, 1 H, J_{gem} = J(6'ex,5'ex) = 12.1, J(6'ex,5'en) = J(6'ex,l') = 4.5 (H-6'exo);
1.70 dm, 1 H, J_{gem} = 10.3 (H-7'b); 1.97 dd, 1 H, J_{gem} = 13.2, J(3'en,2') = 8.4, J(3'en,7'a)
= 2.1 (H-3'endo); 2.02 m, 1 H (H-3'exo); 2.41 m, 1 H (H-4'); 2.47 bd, 1 H, J(l',6'ex) =
4.5 (H-I'); 4.08 s, 3 H (OCH$_3$); 4.51 ddd, 1 H, J(2',3'en) = 8.3, J(2',3'ex) = 4.5, J(2',7'a)
= 1.1 (H-2'); 8.51 s, 1 H (H-2); 8.52 s, 1 H (H-8). 13C NMR (DMSO, 125.70 MHz):
27.02 (C-6'); 27.97 (C-5'); 35.78 (C-7'); 35.91 (C-4'); 37.86 (C-3'); 42.38 (C-1'); 54.07
(OCH$_3$); 57.81 (C-2'); 121.19 (C-5); 141.81 (C-8); 151.42 (C-2); 152.24 (C-4); 160.43
(C-6).

EXAMPLE 25: Synthesis of 9-[(li?*,2i?*,45*)-bicyclo[2.2.1]hept-2-yl]-6-methyl-9 H-
purine (79)
A solution of 17 (360 mg, 1.44 mmol) in THF (15 ml) was added to a mixture of methyltriphenylphosphonium iodide (1.14 g, 3.17 mmol) and n-butyllithium (1.6 M in tetrahydrofuran, 1.9 ml). Reaction mixture was refluxed under argon for 5 hours. Sodium carbonate (500 mg) in water (15 ml) was added and refluxing continued an additional 8 h.

The reaction mixture was diluted with ethylacetate (100 ml) and water (20 ml). Organic phase was washed with water (40 ml), dried over anhydrous sodium sulfate and evaporated. Residue was chromatographed on silica gel (150 g) in ethylacetate - toluene (4:1) → ethylacetate. It was obtained 249 mg (75.7%) as a solid foam. For C_{13}H_{16}N_{4}O_{2} (244.3) calculated: 68.39% C, 70.06% H, 24.54% N; found: 68.34% C, 6.97% H, 24.35% N. 1H NMR (DMSO, 499.95 MHz): 1.23 - 1.29 m, 2 H (H-5'endo and H-7a); 1.40 m, 1 H (H-6'endo); 1.53 m, 1 H (H-5'exo); 1.61 tt, 1 H, J_{gem} = J(6'ex,5'ex) = 12.1, J(6'ex,5'en) = J(6'ex,1') = 4.5 (H-6'exo); 1.72 dm, 1 H, J_{gem} = 10.3 (H-7b); 1.98 ddd, 1 H, J_{gem} = 13.3, J(3'en,2') = 8.4, J(3'en,7'a) = 2.2 (H-3'endo); 2.06 m, 1 H (H-3'exo); 2.42 m, 1 H (H-4'); 2.49 m, 1 H (H-I'); 2.70 s, 3 H (CH_{3}); 4.53 ddd, 1 H, J(2',3'en) = 8.4, J(2',3'ex) = 4.4, J(2',7'a) = 1.1 (H-2'); 8.64 s, 1 H (H-8); 8.74 s, 1 H (H-2). 13C NMR (DMSO, 125.73 MHz): 19.19 (CH_{3}); 27.00 (C-6'); 27.96 (C-5'); 35.81 (C-7'); 35.88 (C-4'); 37.73 (C-3'); 42.28 (C-1'); 57.62 (C-2'); 132.95 (C-5); 143.44 (C-8); 150.45 (C-4); 151.50 (C-2); 157.98 (C-6).


Trifluoroaceticacid anhydride (0.37 ml, 2.58 mmol) was added dropwise to a solution of 1 (400 mg, 1.6 mmol) and tetrabutylammonium nitrate (790 mg, 2.6 mmol) in dry CH_{2}Cl_{2} (5 ml) at 0 °C under a argon atmosphere. After stirring for 1 h the solution was poured into 75 ml of sat. aqueous NaHCO_{3}-ice (1:1). The aqueous layer was extracted with 2 portions of 50 ml EtOAc-CHCl_{3} (3:1). The collected organic layers were washed with water (100 ml) and dried over anhydrous sodium sulfate and evaporated. Residue was chromatographed on silica gel (180 g) in toluene - ethylacetate (6:1) to afford 212 mg (45%) of product. Compound was crystallized from water-methanol. M.p. = 147 - 151 °C. For C_{12}H_{12}ClN_{5}O_{2} (244.3) calculated: 49.07% C, 4.12% H, 12.07% Cl, 23.84%
N; found: 48.78% C, 4.03% H, 12.07% Cl, 23.62% N. 1H NMR (DMSO, 600.13 MHz): 1.31 m, 2 H (H-5’endo and H-7’a); 1.44 dddd, 1 H, J$_{gem}$ = 12.2, J(6’en,5’en) = 9.1, J(6’en,5’ex) = 4.2, J(6’en,7b) = 2.3 (H-5’endo); 1.55 m, 1 H (H-5’exo); 1.65 tt, 1 H, J$_{gem}$ = J(6’ex,5’ex) = 12.2, J(6’ex,5’en) = J(6’ex,1’) = 4.6 (H-6’exo); 1.77 dm, 1 H, J$_{gem}$ = 10.4 (H-7’b); 2.06 m, 2 H (H-3’endo and H-3’exo); 2.45 m, 1 H (H-4’); 2.65 dm, 1 H, J(I,6’ex) = 4.6 (H-I’); 4.60 m, 1 H (H-2’); 9.20 s, 1 H (H-8). 13C NMR (DMSO, 150.92 MHz): 26.96 (C-6’); 27.85 (C-5’); 35.96 (C-7’); 35.98 (C-4’); 38.03 (C-3’); 42.02 (C-1’); 59.03 (C-2’); 134.64 (C-5’); 149.27 and 149.92 (C-2 and C-6); 149.92 (C-8); 152.37 (C-4).

**EXAMPLE 27:** Synthesis of 9-[(1R*,2i?*,4S*)-bicyclo[2.2.1]hept-2-yl]-8-bromo-6-chloro-9H-purine (41)

Preparation of lithium salt:

A stirred solution of diisopropylamine (0.24 ml, 2.6 mmol) in dry THF (5 ml) was cooled to -78 °C under argon. n-Butyllithium (1.6 M in hexanes, 1.1 ml, 2.6 mmol) was added dropwise and the mixture stirred for 0.5 hour. A solution of 17 (300 mg, 1.21 mmol) in THF (10 ml) was added slowly and the mixture stirred for 1.5 h at -78 °C. This lithiumated intermediate was used for preparation of 8-substituted-6-chloropurines by quenching with the appropriate reagent.

A solution of dibromotetrachloroethane (790 mg, 2.4 mmol) in dry THF (8 ml) was added to the lithiated intermediate and the mixture was stirred for 2 hour at -78 °C. Saturated aqueous solution of NH$_4$Cl (20 ml) was added. The mixture was allowed to warm to room temperature. Water (60 mL) was added to the mixture and the mixture was extracted with EtOAc (2 x 100 ml). The organic phase was dried over anhydrous sodium sulfate and evaporated. Residue was chromatographed on silica gel (150 g) in toluene - ethylacetate (24:1) to afford 286 mg (72.2%) of product. Compound was crystallized from water-methanol. M.p. = 152 - 154 °C. For C$_{12}$H$_{12}$BrClN$_4$ (327.6) calculated: 43.99% C, 3.69% H, 23.39% Br, 10.82% Cl, 17.10% N; found: 43.80% C, 3.54% H, 16.77% N. 1H NMR (DMSO, 600.13 MHz): 1.28 m, 2 H (H-5’endo and H-7’a); 1.36 dddd, 1 H, J$_{gem}$ = 11.8, J(6’en,5’en) = 8.9, J(6’en,5’ex) = 3.9, J(6’en,7b) = 2.3 (H-
endo); 1.55 m, 1 H (H-5′exo); 1.62 tt, 1 H, $J_{gem} = J(6′ex,5′ex) = 12.2, J(6′ex,5′en) = J(6′ex,1′) = 4.5$ (H-6′exo); 1.89 ddd, 1 H, $J_{gem} = 13.0, J(3′en,2′) = 8.8, J(3′en,7′a) = 2.3$ (H-3′endo); 2.19 dm, 1 H, $J_{gem} = 10.0$ (H-7′b); 2.47 bt, 1 H, $J(4′,3′ex) = J(4′,5′ex) = 4.4$ (H-4′); 2.46 bd, 1 H, $J(1′,6′ex) = 4.6$ (H-I′); 2.85 m, 1 H (H-3′exo); 4.50 ddd, 1 H, $J(2′,3′en) = 8.8, J(2′,3′ex) = 4.7, J(2′,7′a) = 1.3$ (H-2′); 8.73 s, 1 H (H-2). $^{13}$C NMR (DMSO, 150.92 MHz): 27.49 (C-6′); 28.12 (C-5′); 35.59 (C-7′); 35.99 (C-4′); 36.86 (C-3′); 42.60 (C-I′); 63.86 (C-2′); 131.59 (C-5); 137.40 (C-8); 147.95 (C-6); 150.98 (C-2); 152.96 (C-4).


A solution of iodine (615 mg, 2.4 mmol) in dry THF (10 ml) was added to the lithiated intermediate (see Example 27) and the mixture was stirred for 2 hours at -78 °C. A saturated aqueous solution of NH$_4$Cl (20 ml) was added. The mixture was allowed to warm to room temperature. Water (60 ml) was added to the mixture and the mixture was extracted with Et$_2$O (2 x 100 ml). The organic phase was washed with saturated aqueous Na$_2$S$_2$O$_3$ (2 x 80 ml), dried over anhydrous sodium sulfate and evaporated. Residue was chromatographed on silica gel (150 g) in toluene - ethylacetate (24:1) to afford 194 mg (44%) of product. Compound was crystallized from water-methanol. M.p. = 183 - 184 °C. For C$_{12}$H$_{12}$ClIN$_4$ (374.6) calculated: 38.47% C, 3.23% H, 33.88% I, 9.46% Cl, 14.96% N; found: 38.41% C, 3.12% H, 14.65% N. $^1$H NMR (DMSO, 600.13 MHz): 1.29 m, 2 H (H-5′endo and H-7′a); 1.39 dddd, 1 H, $J_{gem} = 11.8, J(6′en,5′en) = 9.0, J(6′en,5′ex) = 3.9, J(6′en,7′b) = 2.3$ (H-6′endo); 1.56 m, 1 H (H-5′exo); 1.62 tt, 1 H, $J_{gem} = J(6′ex,5′ex) = 12.1, J(6′ex,5′en) = J(6′ex,1′) = 4.5$ (H-6′exo); 1.89 ddd, 1 H, $J_{gem} = 12.9, J(3′en,2′) = 8.8, J(3′en,7′a) = 2.2$ (H-3′endo); 2.24 dm, 1 H, $J_{gem} = 9.9$ (H-7′b); 2.49 m, 1 H (H-4′); 2.58 bd, 1 H, $J(1′,6′ex) = 4.6$ (H-I′); 2.96 m, 1 H (H-3′exo); 4.46 ddd, 1 H, $J(2′,3′en) = 8.8, J(2′,3′ex) = 4.8, J(2′,7′a) = 1.2$ (H-2′); 8.66 s, 1 H (H-2). $^{13}$C NMR (DMSO, 150.92 MHz): 27.58 (C-6′); 28.09 (C-5′); 35.15 (C-7′); 36.11 (C-4′); 36.76 (C-3′); 43.19 (C-I′); 65.58 (C-2′); 116.67 (C-8); 133.84 (C-5); 147.68 (C-6); 150.57 (C-2); 152.60 (C-4).
EXAMPLE 29: Synthesis of ethyl 9-[(l/?*,2/?*,4S*)-bicyclo[2.2.1]hept-2-yl]-6-chloro-9H-purine-8-carboxylate (49)

Ethyl chloroformate (0.5 ml, 5.3 mmol) was added to the lithiated intermediate (see Example 27) and the mixture was stirred for 1 hour at -78 °C and for 1 hour at -50 °C. A saturated aqueous solution of NH₄Cl (20 ml) was added. The mixture was allowed to warm to room temperature. Water (60 ml) was added to the mixture and the mixture was extracted with EtOAc (100 ml). The organic phase was washed with water (50 ml), dried over anhydrous sodium sulfate and evaporated. Residue was chromatographed on silica gel (150 g) in toluene - ethylacetate (20:1) to afford 182 mg (43.9%) of product. Compound was crystallized from water-methanol. M.p. = 118 — 120 °C. For C₁₅H₁₁ClN₄O x 1/4 H₂O (325.3) calculated: 55.39% C, 5.42% H, 10.90% Cl, 17.22% N; found: 55.36% C, 5.34% H, 10.85% Cl, 10.85% N. ¹H NMR (DMSO, 600.13 MHz): 1.24 m, 2 H (H-5’endo and H-7’a); 1.37 m, 1 H (H-6’endo); 1.39 t, 3 H, \(J(CH₃,CH₂) = 7.1\) (CH₃); 1.51 - 1.63 m, 2 H (H-5’exo and H-6’exo); 1.83 ddd, 1 H, \(J_{gem} = 12.9, J(3’en,2’) = 8.9, J(3’en,7’a) = 2.2\) (H-3’endo); 2.34 dm, 1 H, \(J_{gem} = 9.9\) (H-7’b); 2.46 bt, 1 H, \(J(4’,3’ex) = J(4’,5’ex) = 4.0\) (H-4’); 2.68 bd, 1 H, \(J(1’,6’ex) = 4.2\) (H-1’); 2.87 m, 1 H (H-3’exo); 4.46 q, 2 H, \(J(CH₂,CH₂) = 7.1\) (CH₂O); 5.07 bdd, 1 H, \(J(2’,3’en) = 8.8, J(2’,3’ex) = 4.9\) (H-2’); 8.86 s, 1 H (H-2’). ¹³C NMR (DMSO, 150.92 MHz): 14.14 (CH₃); 27.69 (C-6’); 28.11 (C-5’); 36.08 (C-7’); 36.23 (C-4’); 36.78 (C-3’); 43.53 (C-1’); 62.81 (C-2’); 62.86 (CH₂O); 130.12 (C-5); 145.36 (C-8); 151.99 (C-6); 152.53 (C-2’); 152.62 (C-4’); 159.05 (C=O).

EXAMPLE 30: Synthesis of \{9-[(l/?*,2/?*,45*)-bicyclo[2.2.1]hept-2-yl]-6-chloro-9 H-purin-8-yl\} methanol (50)

Dimethylformamide (0.3 ml) was added to the lithiated intermediate (see Example 27 - synthesis of compound 41) and the mixture was stirred for 2 hour at -78 °C. A saturated aqueous solution of NH₄Cl (20 ml) was added. The mixture was allowed to warm to room temperature. Water (60 ml) was added to the mixture and the mixture was extracted...
with EtOAc (100 ml). The organic phase was dried over anhydrous sodium sulfate and evaporated. Residue was dissolved in methanol (20 ml) and NaBH₄ (60 mg, 1.59 mmol) was added. Reaction mixture was stirred at 0 °C for 1 hour, evaporated and residue was partitionate between brine (30 ml) and ethylacetate (80 ml). Organic phase was washed with brine (20 ml), dried over anhydrous sodium sulfate and evaporated. Residue was chromatographed on silica gel (150 g) in toluene - ethylacetate (1:1) to afford 120 mg (36%) of product. Compound was crystallized from water-methanol. M.p. = 129 -131 °C. For C₁₃H₁₅ClN₄O (278.7.3) calculated: 56.02% C, 5.42% H, 12.72% Cl, 20.10% N; found: 55.87% C, 5.13% H, 12.89% Cl, 19.90% N. ¹H NMR (DMSO, 600.13 MHz): 1.24 m, 2 H (H-5'endo and H-7'a); 1.40 m, 1 H (H-6'endo); 1.56 m, 2 H (H-5'exo and H-6'exo); 1.86 ddd, 1 H, Jₙₑₑₚₑₚ = 12.7, J(3'en,2') = 8.9, J(3'en,7'a) = 2.2 (H-3'endo); 2.46 dm, 1 H, Jₙₑₑₚₑₚ = 9.7 (H-7'b); 2.48 m, 1 H (H-4'); 2.56 m, 1 H (H-1'); 2.79 ddt, 1 H, Jₙₑₑₚₑₚ = 12.8, J(3'ex,2') = J(3'ex,4') = 4.6, J(3'ex,5'ex) = 2.1 (H-3'exo); 4.63 ddd, 1 H, J(2',3'en) = 8.8, J(2',3'ex) = 5.0 (H-2'); 4.80 m, 2 H (CH₂O); 5.88 t, 1 H, J(OH₂CH₂) = 5.9 (OH); 8.70 s, 1 H (H-2). ¹³C NMR (DMSO, 150.92 MHz): 27.97 and 28.04 (C-6' and C-5'); 35.83 (C-7'); 36.23 (C-4'); 36.83 (C-3'); 43.38 (C-1'); 57.46 (CH₂OH); 60.81 (C-2'); 130.43 (C-5); 148.92 (C-6); 150.77 (C-2); 153.23 (C-4); 158.52 (C-8).

**EXAMPLE 31: Synthesis of 6-chloro-9-[(3'R*,4'R*,6'R*)-6'-exyloct-6-yl]-9H-purine (42)**

To a solution 31 (250 mg, 1.01 mmol) in dichloromethane (45 ml) was added m-chloroperbenzoic acid (400 mg, 1.5 mmol, 65%) and the solution was stirred at r.t. overnight. Reaction mixture was washed with saturated aqueous Na₂S₂O₃ (20 ml), saturated NaHCO₃ (3 x 20 ml), dried over anhydrous sodium sulfate and evaporated. Residue was crystallized from water-methanol to afford 193 mg (72.7%) of the product. M.p. = 159 - 163 °C. For C₁₂H₁₄ClN₄O (262.7) calculated: 54.87% C, 4.22% H, 13.50% Cl, 21.33% N; found: 54.63% C, 4.07% H, 13.79% Cl, 20.59% N. ¹H NMR (DMSO, 600.13 MHz): 1.28 dm, 1 H, Jₙₑₑₚₑₚ = 10.7 (H-7'a); 1.35 dm, 1 H, Jₙₑₑₚₑₚ = 10.6 (H-7'b); 2.06 - 2.14 m, 2 H (H-5'endo and H-5'exo); 2.62 m, 1 H (H-4'); 2.89 m, 1 H (H-1'); 3.34 dd, 1 H, J(3',2') = 3.7, J(3',4') = 1.4 (H-3'); 3.38 dd, 1 H, J(2',3') = 3.8, J(2',4') = 1.7 (H-
2'); 4.60 ddd, 1 H, J(6′,5′en) = 8.0, J(6′,5′ex) = 4.5, J(6′,7′a) = 1.5 (H-6'); 8.79 s, 1 H (H-2); 8.88 s, 1 H (H-8). \(^{13}\)C NMR (DMSO, 150.92 MHz): 23.95 (C-7'); 33.84 (C-5'); 36.88 (C-4'); 42.68 (C-1'); 48.91 (C-2'); 50.83 (C-3'); 54.21 (C-6'); 131.38 (C-5); 145.96 (C-8); 149.18 (C-6); 151.53 (C-2); 152.20 (C-4).

EXAMPLE 32: Synthesis of (li?*,2i?*,35*,45*,55*)-5-(6-chloro-9 \(H\)-purin-9-yl)bicyclo[2.2.1]heptan-2-ol (37)

Compound 31 (250 mg, 1.01 mmol) was dissolved in a mixture of water-methanol (15 ml, 1:1). Solution of NMMO (50% in water, 2 ml) and water solution of osmium tetroxide (50 µl, 100 mg/5 ml) was added and the reaction mixture was stirred at r.t. for 2 days. The reaction mixture was evaporated and the residue was chromatographed on silica gel column (100 g) in ethyl acetate - acetone - ethanol - water (100:15:6:4). It was obtained 224 mg (79%) of the product. Compound was crystallized from water. M.p. = 198 - 200 °C. For C\(_{12}\)H\(_{11}\)ClN\(_4\)O\(_2\) x 3/2 H\(_2\)O (289.7) calculated: 49.57% C, 4.87% H, 12.24% Cl, 19.34% N; found: 49.82% C, 4.55% H, 12.51% Cl, 19.19% N. \(^{1}\)H NMR (DMSO, 600.13 MHz): 1.54 dm, 1 H, J\(_{gem}\) = 10.8 (H-7a); 1.80 dm, 1 H, J\(_{gem}\) = 10.8 (H-7b); 1.89 ddd, 1 H, J\(_{gem}\) = 13.8, J(5en,6) = 8.5, J(5en,7b) = 2.2 (H-5endo); 1.99 m, 1 H (H-5exo); 2.19 dm, 1 H, J(4,5ex) = 4.7 (H-4); 2.40 bs, 1 H (H-I); 3.66 m, 1 H (H-3); 3.78 m, 1 H (H-2); 4.49 dd, 1 H, J(6,5en) = 8.5, J(6,5ex) = 4.3 (H-6); 4.80 d, 1 H, J(OH,2) = 6.1 (2-OH); 4.82 d, 1 H, J(OH-3) = 6.0 (3-OH); 8.76 s, 1 H (H-2'); 8.84 s, 1 H (H-8'). \(^{13}\)C NMR (DMSO, 150.92 MHz): 29.70 (C-7); 32.96 (C-5); 42.77 (C-4); 49.10 (C-I); 54.61 (C-6); 71.28 (C-2); 72.51 (C-3); 131.48 (C-5'); 145.67 (C-8'); 149.13 (C-6'); 151.45 (C-2'); 152.15 (C-4').

EXAMPLE 33: Synthesis of 7-[(li?*,2i?*,35*,45*)]-bicyclo[2.2.1]hept-2-yl]-4-chloro-7 \(H\)-pyrrolo[2,3-rf]pyrimidine (80)

To a mixture of the bicyclo[2.2.1]heptan-ol (550 mg, 4.90 mmol), triphenylphosphate (1.2 g, 4.57 mmol) and 4-chloro-7 \(H\)-pyrrolo[2,3-\(rf\)]pyrimidine (300 mg, 1.95 mmol) in THF (30 ml) was dropwise added solution of the diisopropyl azadicarboxylate (1.0 ml,
4.87 mmol) in THF (15 ml). The resulting mixture was stirred overnight (TLC control) and evaporated. The residue was chromatographed on silica gel column (200 g) in toluene - ethylacetate (15:1) to afford 419 mg (87% based on nucleobase). M.p. = 72 -73 °C. For C_{14}H_{16}ClN_{5} (247.7) calculated: 63.03% C, 5.70% H, 14.31% Cl, 16.96% N; found: 63.15% C, 5.55% H, 14.35% Cl, 16.71% N. 1H NMR (DMSO, 499.84 MHz): 1.20 - 1.28 m, 2 H (H-5'endo and H-7'a); 1.39 m, 1 H (H-6'endo); 1.48 - 1.61 m, 2 H (H-5'exo and H-6'exo); 1.68 dm, 1 H, J_{gem} = 10.2 (H-7b); 1.89 m, 1 H (H-3'exo); 1.97 ddd, 1 H, J_{gem} = 13.2, J(3'en,2') = 8.4, J(3'en,7'a) = 2.1 (H-3'endo); 2.35 bd, 1 H, J(1'6'ex) = 3.9 (H-I'); 2.40 m, 1 H (H-4'); 4.70 bdd, 1 H, J(2',3'en) = 8.2, J(2',3'ex) = 4.6 (H-2'); 6.61 d, 1 H, J(7,8) = 3.7 (H-7); 7.88 d, 1 H, J(8,7) = 3.7 (H-8); 8.61 s, 1 H (H-2). 13C NMR (DMSO, 125.70 MHz): 27.33 (C-6'); 27.92 (C-5'); 35.79 (C-4'); 36.00 (C-7'); 38.28 (C-3'); 42.59 (C-1'); 57.68 (C-2'); 98.46 (C-7); 117.24 (C-5); 128.79 (C-8); 150.21 (C-2); 152.64 and 150.70 (C-4 and C-6).

EXAMLE 34: Synthesis of (li^*,2i^*,3i^*,6i^*,75^*,95*)-2-(2-amino-6-chloro-9 H-purin-9-yl)-4-oxatricyclo[4.2.1.03^7]nonane-9-methanol (9)

A solution of (li^*,2i^*,3i^*,6i^*,75^*,9S^*)-2-amino-4-oxatricyclo[4.2.1.03^7]nonane-9-methanol (508 mg, 3 mmol), 4,6-dichloropyrimidine-2,5-diamine (537 mg, 3 mmol), and triethylamine (1.8 ml) in ethanol (18 ml) was heated in a pressure vessel at 100 °C for 7 days and, after cooling, was evaporated. Chromatography of the residue on a silica gel column (50 g) in ethyl acetate - acetone - ethanol - water (90 : 15 : 11 : 9) followed by crystallization from ethanol afforded 628 mg of a pyrimidinylamino derivative which was dissolved in triethyl orthoformate (32 ml) and Cone, hydrochloric acid (1.5 ml). The resulting solution was left aside at room temperature for 3 days and then evaporated. The residue was dissolved in tetrahydrofuran (18 ml). To the stirred solution, 0.5 M hydrochloric acid (18 ml) was added, the mixture was stirred at room temperature for 3 h and then neutralized with solid sodium hydrogen carbonate. The organic layer was separated and the aqueous layer was extracted with tetrahydrofuran (4 x 16 ml). The combined organic layers were evaporated. The residue was crystallized from water. Yield 460 mg (52%). M.p. 238 - 241 °C. For C_{14}H_{16}ClN_{5}O_{2} (321.77) calculated: 52.26% C,
5.01% H, 11.02% Cl, 21.77% N; found: 52.19% C, 5.10% H, 10.94% Cl, 21.50% N.
FAB MS, mlz (rel. %): 324/322 (35/100) [M + H], 288 (37). 1H NMR: 1.52 brddd, 1 H, J(9,l) ~ J(9,8a) = 1.0, J(9,6) = 2.4, J(9,CH3) = 7.2, J(9,CH3l) = 8.4 (H-9); 1.70 dd, 1 H, Jgem = 11.7 (H-8a); 1.75 dq, 1 H, J(8b,l) ~ J(8b,2) ~ J(8b,7) = 1.4 (H-8b); 2.04 td, 1 H, J(6,5a) ~ J(6,7) = 4.0 (H-6); 2.37 m, 1 H (H-I); 2.67 ddq, 1 H, J(7,l) ~ J(7,8a) ~ J(7,8b) = 1.2, J(7,3) = 5.0, J(7,6) = 4.0 (H-7); 3.35 ddd, 1 H, J(CH5a) = 7.2, J(CH3OH) = 5.4 and 3.38 ddd, 1 H, J(CH5a) = 8.4, J(CH3OH) = 5.0, Jgem = 10.6 (CH2O); 3.72 d, 1 H, Jgem = 7.8 (H-5b); 3.76 dd, 1 H, J(5a,6) = 3.9 (H-5a); 3.88 brd, 1 H, J(2,8b) = 1.6 (H-2); 4.67 dd, 1 H, J(3,l) = 1.2 (H-3); 4.73 t, 1 H, J(OH)CH2 = 5.2 (OH); 6.94 brs, 2 H (NH2); 8.19 s, 1 H (H-8'). 13C NMR: 31.97 (C-8); 41.25 (C-I); 41.33 (C-6); 45.13 (C-7); 50.83 (C-9); 62.80 (CH2O); 66.23 (C-2); 74.09 (C-5); 83.74 (C-3); 123.50 (C-5'); 141.27 (C-8'); 149.61 (C-6'); 154.38 (C-4'); 159.85 (C-2').

EXAMPLE 35: Synthesis of 6-chloro-9-[(li?*,3 R*,6i?*,7i?*,9i?*)-4-oxatricyclo[4.2.1.03-7]non-9-yl]-9H-purine (5)

A mixture of amine (420 mg, 3 mmol), 4,6-dichloropyrimidin-5-amine (900 mg, 5.5 mmol), and triethylamine (1.8 ml) in ethanol (9 ml) was heated in a pressure vessel at 105 °C for 6 days and, after cooling, was evaporated. The residue was chromatographed on a column of silica gel (200 g). Pyrimidine intermediate was eluted with toluene - ethylacetate (5:1 → 1:1) and this intermediate was immediately used in the next step. Concentrated hydrochloric acid (1 ml) was added to a suspension of pyrimidine intermediate in triethyl orthoformate (80 ml) and the reaction mixture was vigorously stirred for 5 days at room temperature. Solution was evaporated and the residue was crystallized from water-methanol (95:5) to afford product (540 mg, 65%). M.p. = 196 - 198 °C. For C13H13ClN4O (276.7) calculated: 56.42% C, 4.74% H, 12.81% Cl, 20.25% N; found: 56.31% C, 4.75% H, 12.72% Cl, 20.04% N. 1H NMR (DMSO, 600.13 MHz): 1.22 dd, 1 H, Jgem = 13.3, J(2'en,8'b) = 3.3 (H-2'endo); 1.50 dm, 1 H, Jgem = 11.2 (H-8'a); 1.73 ddd, 1 H, Jgem = 13.3, J(2'ex,3') = 7.7, J(2'ex,l ') = 4.0 (H-2'exo); 1.96 dm, 1 H, Jgem = 11.2 (H-8'b); 2.58 bd, 1 H, J5,l = J(1',2'ex) = 3.9 (H-l '); 2.74 tq, 1 H, J(7,6') = J(7',3') = 4.8, J(7',8'a) = J(7',8'b) = J(7,l ') = 1.4 (H-7'); 3.04 bt, 1 H, J(6',7') =
J(6',5'b) = 5.2 (H-6'); 3.80 dd, 1 H, J_{gem} = 8.5, J(5'b,6') = 4.6 (H-5'b); 3.94 d, 1 H, J_{gem} = 8.5 (H-5'a); 4.33 ... : 4 ) afforded after crystallization
from ether 1.98 g of diisopropyl ([(l/?*,3S*,6S*,7#*)-2-(5-Methyl-2,4-dioxo-3,4-

EXAMPLE 36: SYNTHESIS OF ([(l/?*,3S*,6S*,7#*)-2-(5-METHYL-2,4-DIOXO-3,4-

A mixture of (IR *,2R *,3S*,4S*)-3-(hydroxymethyl)bicyclo[2.2.1]hept-5-en-2-ol
(4.22 g, 30 mmol), benzyl azidoformate (8.70 g, 37 mmol), and toluene (7 ml) was
stirred at 85 °C (bath temperature) for 2.5 h. The mixture was applied onto a silica gel
column (200 g) and eluted with ethyl acetate. The obtained product (4.58 g, 15.8 mmol)
and diisopropyl (bromomethyl)phosphonate (7.77 g, 30 mmol) was dissolved in
dimethylformamide (50 ml). Sodium hydride (60% dispersion, 1.2 g, 30 mmol) was
added to this stirred solution at 0 °C under argon. The mixture was stirred at 0 °C for 30
min and then at room temperature for 5 h. The mixture was neutralized with acetic acid and
evaporated. The residue was partitioned between ethyl acetate (400 ml) and water (100
ml). The organic phase was separated and washed with 10% aqueous sodium
hydrogencarbonate (100 ml), dried over anhydrous sodium sulfate, and the solvent was
evaporated. Palladium(II) hydroxide on carbon (20% Pd, 200 mg) was added to a solution
of the residue (3.84 g, 8.5 mmol) in methanol (100 ml) and the mixture was stirred under
hydrogen atmosphere at room temperature for 7 h. The catalyst was filtered off with a
Celite pad, washed with methanol and the filtrates were evaporated. A solution of the
residue (2.68 g, 8.4 mmol) and ethyl [(2E)-3-ethoxy-2-methylprop-2-enoyl]carbamate
(1.69 g, 8.4 mmol) in 1,4-dioxane (80 ml) was heated at 100 °C for 2 h. Then 1 M
sulfuric acid (10 ml) was added and the mixture was heated another 4 h. The solid was
filtered off and the filtrates were evaporated. Chromatography on silica gel (250 g) with
ethyl acetate - acetone - ethanol - water (100 : 15 : 6 : 4) afforded after crystallization
from ether 1.98 g of diisopropyl ([(l/?*,3S*,6S*,7 R*)]-2-(5-Methyl-2,4-dioxo-3,4-
dihydropyrimidin-1(2H)-yl)-4-oxatricyclo[4.2.1.037]non-9-yl]oxy)methyl)phosphonate.

For C20H31N2O7P (442.46) calculated: 54.29% C, 7.06% H, 6.33% N, 7.00% P; found: 53.99% C, 7.18% H, 6.17% N, 6.86% P. FAB MS, m/z (%): 443 (27) [M + H], 401 (10), 359 (100). 1H NMR: 1.25 dd, 12 H, J(CH3,CH) = 6.1, J(CH3,P) = 3.5 (CH3 isopropyl); 1.66 brd, 1 H, Jgem = 11.5 (H-8b); 1.78 d, 3 H, J(CH3,6) = 1.1 (CH3); 1.86 dm, 1 H (H-8a); 2.28 m, 1 H (H-6); 2.56 brs, 1 H (H-I); 2.63 m, 1 H, (H-7); 3.46 brs, 1 H (H-9); 3.52 brs, 1 H (H-2); 3.73 - 3.82 m, 4 H (CH2,P, 2 x H-5); 4.34 brd, 1 H, J(3,7) = 4.9 (H-3); 4.61 dh, 2 H, J(CH,P) = 7.7 (CH isopropyl); 7.46 q, 1 H (H-6'); 11.24 brs, 1 H (NH). 13C NMR: 23.89 d, J(CH3,P) = 4.4 (CH3 isopropyliden); 23.99 d, J(CH3,P) = 3.9 (CH3 isopropyliden); 31.59 (C-8); 42.65 (C-I); 44.00 (C-7); 46.83 (C-6); 62.61 d, J(CH2,P) = 166.0 (CH2,P); 63.87 (C-2); 70.33 d, J(CH,P) = 6.4 (CH isopropyl); 70.36 d, J(CH3,P) = 5.9 (CH isopropyl); 71.68 (C-5); 83.71 (C-3); 88.95 d, J(9,P) = 13.7 (C-9); 108.29 (C-5'); 138.13 (C-6'); 151.20 (C-2'); 163.87 (C-4'). A mixture of this protected phosphonate, dichloromethane (25 ml) and bromotrismethylsilane (2 ml) was stirred at room temperature overnight and evaporated. A solution of the residue in methanol (20 ml) and water (10 ml) was after 0.5 h evaporated. Crystallization of the residue from water afforded 1.03 g (9% overall yield) of compound 3. For C14H19N2O7P.H2O (376.31) calculated: 44.68% C, 5.63% H, 7.44% N, 8.23% P; found: 44.64% C, 5.69% H, 7.29% N, 8.01% P.

EXAMPLE 37: SYNTHESIS OF 4-[([i]*,2 R*,4S*)-BICYCLO[2.2.1]HEPT-2-YL OXY]-6-CHLOROPYRIMIDINE (81)

([i]*,2 R*,4S*)-bicyclo[2.2.1]heptan-2-ol (500 mg, 4.46 mmol) was dissolved in dimethylformamide (10 ml) under argon atmosphere. Sodium hydride (196 mg, 4.91 mmol, 60% dispersion in mineral oil) was carraefully added during 20 minutes at 0°C. To this mixture was through septum added 4,6-dichloropyrimidine (731 mg, 4.91 mmol) and reaction mixture was stirred at 0°C for 5 hours and then at r.t. overnight. Reaction mixture was partitioned between ethylacetate (130 ml) and water (80 ml). Organic phase was washed with water (4 x 100 ml), dried over anhydrous sodium sulfate and evaporated. Residue was chromatographed on silica gel (150 g) in toluene - ethylacetate
(30:1) to afford 259 mg (25.8%) of product as an oil. For C₁₁H₁₃ClN₂O (224.7) calculated: 58.80% C, 5.83% H, 15.78% Cl, 12.47% N; found: 59.10% C, 5.98% H, 15.88% Cl, 12.20% N. ¹H NMR (DMSO, 499.84 MHz): 1.08 - 1.20 m, 3 H (H-5'endo, H-6'endo and H-7'a); 1.39 - 1.47 m, 2 H (H-3'exo and H-5'exo); 1.49 - 1.56 m, 2 H (H-6'exo and H-7'b); 1.81 ddd, 1 H, J₆'endo = 13.4, J(3'en,2') = 7.0, J(3'en,7'a) = 2.5 (H-3'endo); 2.28 m, 1 H (H-4'); 2.38 bd, 1 H, J(1'6'ex) = 4.6 (H-1'); 4.86 dm, 1 H, J(2',3'en) = 7.0 (H-2'); 7.10 d, 1 H, J(5,2) = 0.9 (H-5); 8.64 d, 1 H, J(2,5) = 0.9 (H-2).

¹³C NMR (DMSO, 125.70 MHz): 23.87 (C-6'); 27.88 (C-5'); 35.18 (C-7'); 35.18 (C-4'); 39.40 (C-3'); 40.98 (C-1'); 80.37 (C-2'); 108.05 (C-5); 158.66 (C-2); 160.11 (C-4); 169.62 (C-6).

**EXAMPLE 38: SYNTHESIS OF 3-(l/?*,2i?*,35*,45*)-BICYCLO[2.2.1]HEPT-2-YL]-7-CHLORO-3H-[1,2,3]TRIAZOLO[4,5-D]PYRIMIDINE (82)**

A mixture of amine (420 mg, 3 mmol), 4,6-dichloropyrimidin-5-amine (900 mg, 5.5 mmol), and triethylamine (1.8 ml) in ethanol (9 ml) was heated in a pressure vessel at 105°C for 6 days and, after cooling, was evaporated. The residue was chromatographed on a column of silica gel (200 g). Pyrimidine intermediate was eluted with toluene-ethylacetate (5:1 → 2:1) and this intermediate was immediately used in the next step. The intermediate was dissolved in acetic acid (5 ml) and to this mixture was added solution of NaNO₂ (200 mg) in water (10 ml) at 0°C. Reaction mixture was stirred for 2 hours at 0°C. White crystals were filtered off, wash with cold water and ether. It was obtained 450 mg (48%). For C₆H₁₂ClN₅ (249.7) calculated: 52.91% C, 4.84% H, 14.20% Cl, 28.05% N; found: 52.65% C, 4.76% H, 14.41% Cl, 27.72% N.


A solution of azido derivative (l/?*,2i?*,35*,45*)-3-Azido-6-(hydroxymethyl)bicyclo[2.2.1]hept-5-en-2-ol (1.45 g, 8 mmol) in tetrahydrofuran (15 ml) was added dropwise to a stirred 1.0 M solution of lithium aluminium hydride in
tetrahydrofuran (23 ml) at 0 °C under argon atmosphere. The mixture was stirred at 0 °C for 5 h, the excess of hydride was decomposed by slow addition of water. Then solid CO$_2$ was added to adjusted pH of the mixture to ~8. The mixture was filtered with a Celite pad, the filter was washed with methanol (3 x 30 ml) and the combined filtrates were evaporated. The residue was dissolved in ethanol (10 ml), the insoluble portion was filtered off with a Celite pad and the filtrate was evaporated. A solution of amine, obtained in this way, 4,6-dichloropyrimidin-5-amine (1.15 g, 7 mmol), and triethylamine (2.1 ml) in ethanol (21 ml) was heated in a pressure vessel at 100 °C for 6 days and, after cooling, evaporated. The residue was chromatographed on a silica gel column (60 g) in ethyl acetate - acetone - ethanol - water (100 : 15 : 6 : 4) and crystallized from ethyl acetate. It was obtained 501 mg (22%) of (1R*,2R*,3S*,4S*)-3-{(5-Amino-6-chloropyrimidin-4-yl)amino}-6-(hydroxymethyl)bicyclo[2.2.1]hept-5-en-2-ol. Cone. hydrochloric acid (1.4 ml) was added to a stirred mixture of this compound (226 mg, 0.8 mmol) and triethyl orthoformate (14 ml), the resulting solution was stored at room temperature for 3 days and then evaporated. The residue was dissolved in tetrahydrofuran (5 ml). To the stirred solution, 0.5 M hydrochloric acid (5 ml) was added, the mixture was stirred at room temperature for 4 h and then neutralized with solid sodium hydrogen carbonate. The organic layer was separated and the aqueous layer was extracted with tetrahydrofuran (4 x 8 ml). The combined organic phases were dried over anhydrous sodium sulfate and evaporated. The residue was chromatographed on a silica gel column (20 g) in ethyl acetate - toluene and then crystallized from ethanol - ether. Yield 124 mg (50%). M.p. 176 - 177 °C. For Cl$_3$H$_2$Cl$_2$N$_2$O (311.17) calculated: 50.18% C, 3.89% H, 22.79% Cl, 18.01% N; found: 50.06% C, 3.75% H, 22.79% Cl, 17.86% N. FAB MS, mlz (%): 313/311 (71/100) [M + H], 157/155 (36/68) [6-chloropurine + H]. $^1$H NMR: 1.81 dm, 1 H, $J_{gem} = 9.6$ (H-7a); 2.39 dm, 1 H, $J_{gem} = 9.7$ (H-7b); 2.79 m, 1 H (H-1); 3.23 m, 1 H (H-4); 4.15 m, 1 H (H-2); 4.41 m, 2 H (CH$_2$Cl); 4.59 dd, 1 H, $J(3.2) = 6.2$, $J(3.7a) = 1.7$ (H-3); 5.19 d, 1 H, $J(OH,2) = 4.4$ (2-OH); 6.33 m, 1 H (H-5); 8.66 s, 1 H (H-8'); 8.74 s, 1 H (H-2'). $^1$C NMR: 42.76 (CH$_2$Cl); 44.78 (C-7); 46.29 (C-4); 50.89 (C-1); 57.53 (C-3); 68.25 (C-2); 130.54 (C-5'); 135.67 (C-5); 146.51 (C-6); 146.77 (C-8'); 148.74 (C-6'); 151.41 (C-2'); 153.08 (C-4').
According to the same procedure, there were obtained the following compounds:

- (li?*,2i?*,3S*,4S*)-3-(6-Chloro-9H-purin-9-yl)-6-(hydroxymethyl)bicyclo[2.2.1]hept-5-en-2-ol (84), using trifluoroacetic acid instead of hydrochloric acid in the ring-closure step. Yield 250 mg (57%). M.p. 156.5 - 159 °C (decomp.). For C\textsubscript{i}3H\textsubscript{j}ClN\textsubscript{4}O\textsubscript{2} (292.73) calculated: 53.34% C, 4.48% H, 12.11% Cl, 19.14% N; found: 53.19% C, 4.42% H, 12.24% Cl, 18.98% N. FAB MS, m/z (%): 295/293 (33/100) [M + H], 157/155 (74/23) [6-chloropurine + H]. \textsuperscript{1}H NMR: 1.76 dp, 1 H, J\textsubscript{gem} = 9.4, J(7a,2) = J(7a,3) = J(7a,1) = J(7a,4) = 1.6 (H-7a); 2.33 dm, 1 H, J\textsubscript{gem} = 9.3 (H-7b); 2.70 bs, 1 H (H-I); 3.14 m, 1 H (H-4); 4.03 ddd, 1 H, J\textsubscript{gem} = 14.8, J(CH\textsuperscript{a},OH) = 5.5, J(CH\textsuperscript{b},5) = 1.7 (CH\textsuperscript{3}H-O); 4.04 m, 1 H (H-2); 4.10 ddd, 1 H, J\textsubscript{gem} = 14.8, J(CH\textsuperscript{b},OH) = 5.5, J(CH\textsuperscript{b},5) = 1.9 (CH=CH-O); 4.60 dd, 1 H, J(3,2) = 6.2, J(3,7a) = 1.6 (H-3); 4.82 t, 1 H, J(OH\textsubscript{5},CH\textsubscript{2}) = 5.5 (CH\textsubscript{2}OH); 5.08 d, 1 H, J(OH,2) = 4.5 (2-OH); 6.03 m, 1 H (H-5); 8.64 s, 1 H (H-8'); 8.74 s, 1 H (H-2'). \textsuperscript{13}C NMR: 44.14 (C-7); 46.34 (C-4); 44.16 (C-4); 44.89 (C-2); 57.90 (C-3); 59.29 (CH\textsubscript{2}O); 68.46 (C-2); 130.03 (C-5); 130.52 (C-5'); 146.77 (C-8'); 148.68 (C-6'); 151.35 (C-2'); 151.82 (C-6); 153.10 (C-4').

- (li?*,2R*,3S*,4S*)-3-(6-Chloro-9H-purin-9-yl)-5-(hydroxymethyl)bicyclo[2.2.1]hept-5-en-2-ol (85), using (li?*,2i?*,3S*,4S*)-3-Azido-5-(hydroxymethyl)bicyclo[2.2.1]hept-5-en-2-ol as starting compound and using trifluoroacetic acid instead of hydrochloric acid in the ring-closure step. Yield 224 mg (51%). M.p. 179 - 181 °C (decomp.). For C\textsubscript{i}3H\textsubscript{j}ClN\textsubscript{4}O\textsubscript{2} (292.73) calculated: 53.34% C, 4.48% H, 12.11% Cl, 19.14% N; found: 53.01% C, 4.49% H, 12.26% Cl, 18.89% N. FAB MS, m/z (%): 295/293 (30/78) [M + H], 157/155 (37/100) [6-chloropurine + H]. \textsuperscript{1}H NMR: 1.76 dp, 1 H, J\textsubscript{gem} = 9.4, J(7a,1) = J(7a,2) = J(7a,3) = J(7a,4) = 1.7 (H-7a); 2.32 dm, 1 H, J\textsubscript{gem} = 9.3 (H-7b); 2.75 m, 1 H (H-I); 3.11 m, 1 H (H-4); 4.00 m, 1 H (H-2); 4.05 ddd, 1 H, J(CH\textsuperscript{b}H\textsubscript{OH}) = 5.1, J(CH\textsuperscript{b}H\textsubscript{6}) = 1.6 and 4.11 ddd, 1 H, J(CH\textsuperscript{b}H\textsubscript{OH}) = 5.6, J(CH\textsuperscript{b}H\textsubscript{6}) = 1.9, J\textsubscript{gem} = 14.9 (CH\textsubscript{2}O); 4.57 dd, 1 H, J(3,2) = 6.2, J(3,7a) = 1.4 (H-3); 4.89 t, 1 H, J(OH,CH\textsubscript{2}) = 5.4 (CH\textsubscript{2}OH); 5.10 d, 1 H, J(OH,2) = 4.1 (2-OH); 5.89 m, 1 H (H-6); 8.65 s, 1 H (H-8'); 8.75 s, 1 H (H-2'). \textsuperscript{13}C NMR: 44.14 (C-7); 46.34 (C-4);
49.24 (C-I); 57.02 (C-3); 58.99 (CH₂O); 69.98 (C-2); 128.29 (C-6); 130.66 (C-5'); 146.78 (C-8'); 148.78 (C-6'); ... H₂O (311.2) calculated: 54.02% C, 5.02% H, 11.39% Cl, 18.00% N; found: 54.07% C, 4.95% H, 11.32% Cl, 18.05% N.

EXAMPLE 40: (li?*,4i?*,75*)-7-(6-Chloro-9 H-purin-9-yl)bicyclo[2.2.1]hept-5-ene-2,2-
dimethanol (86)

A mixture of amine (510 mg, 3 mmol), 4,6-dichloropyrimidin-5-amine (984 mg, 6 mmol), and triethylamine (2.4 ml) in ethanol (18 ml) was heated in a pressure vessel at 105 °C for 6 days and, after cooling, it was evaporated. The residue was chromatographed on a column of silica gel (200 g) in ethyl acetate - acetone - ethanol - water (100:15:6:4) to afford 866 mg of pyrimidine intermediate as a foam. To a suspension of pyrimidine intermediate in triethyl orthoformate (80 ml) concentrated hydrochloric acid (1.4 ml) was added and the reaction mixture was vigorously stirred for 3 days (suspension dissolved) at room temperature. The solution was evaporated and the residue was redissolved in a mixture of tetrahydrofuran (15 ml) and 0.5 M hydrochloric acid (15 ml) and stirred at room temperature for 4 h. After neutralization with solid sodium hydrougencarbonate, the mixture was evaporated to a fourth of the original volume and adsorbed on silica gel and this silica gel was placed on the top of a silica gel column (200 g). Elution with ethyl acetate - acetone - ethanol - water (100:15:6:4) gave 655 mg (79 %) of the chloropurine nucleoside. M.p. 193.5 - 195 °C (H₂O). ¹H NMR: 0.77 d, 1 H, Jgem = 12.3 (H-3endo); 1.80 dd, 1 H, J(3exo, 4) = 3.8 (H-3exo); 3.43 brdq, 1 H, J(I, 4) ~ J(I, 5) ~ J(I, 7) ~ 1.2, J(I, 6) = 2.8 (H-1); 3.12 dd, 1 H, J(CH₂OH) = 5.2 and 3.28 dd, 1 H, J(CH₂OH) = 4.9, Jgem = 10.4 (CH₂O); 3.56 brt, 1 H, J(4, 1) ~ J(4, 6) ~ J(4, 7) ~ 0.7, J(4, 5) = 2.8 (H-4); 3.70 dd, 1 H, J(CH₂OH) = 5.0 and 3.79 dd, 1 H, J(CH₂OH) = 5.4, Jgem = 10.6 (CH₂O); 4.49 t, 1 H (CH₂OH); 4.78 t, 1 H (CH₂OH); 4.80 m, 1 H (H-7); 6.02 brdd, 1 H, J(5, 7) = 1.0, J(5, 6) = 5.6 (H-5); 6.07 brdd, 1 H, J(6, 7) = 1.0 (H-6); 8.47 s, 1 H and 8.70 s, 1 H (H-2\ H-8'). ¹³C NMR: 30.13 (C-3); 45.55 (C-4); 48.28 (C-2); 49.19 (C-I); 63.81 (CH₂O); 64.82 (CH₂O); 70.03 (C-7); 131.01 (C-5'); 132.53 (C-6); 132.58 (C-5); 147.81 (C-8'); 149.03 (C-6'); 151.49 (C-2'); 152.93 (C-4'). FAB MS, m/z (%): 309/307 (40/100) [M+H]. For C₁₄H₁₅ClN₄O₂ x 1/4 H₂O (311.2) calculated: 54.02% C, 5.02% H, 11.39% Cl, 18.00% N; found: 54.07% C, 4.95% H, 11.32% Cl, 18.05% N.
CLAIMS

1. A nucleoside analog having a structure according to the formula (A):

![](image)

(A)

wherein:

- B is selected from an unsubstituted or substituted pyrimidine or purine heterocycle or aza aza or deaza analogs thereof;

whereby the purine heterocycle is not substituted with -CF₃ in its 2-position;

- W is selected from (-CH₂)ₙ, wherein n is selected from 0 (whereby B is directly bonded to carbon (I)) or 1 or W is -O-;

- X is not present (thereby forming a bond between carbon (2) and carbon (3)) or is selected from -CR⁶R⁶'- or -CR⁷R⁷'- C R⁸R⁸'-;

- Y is not present (thereby forming a bond between carbon (2) and carbon (I)) or is selected from -CR⁹R⁹'- or -CR¹⁰R¹⁰'- C R¹¹R¹¹'-;

- Z is selected from -CR¹²R¹²'-; -CR¹³R¹³'- C R¹⁴R¹⁴'-; -CR¹⁵=CR¹⁵'-; -O-; and -S-;

- each of R¹ and R⁴ is independently selected from hydrogen; alkyl; -OH; phosphate; phosphate-alkylene; phosphonate; or phosphonate-alkylene; wherein said alkyl or alkylene can be substituted with one or more -OH, aryl or halogen; and wherein said alkyl or alkylene can contain a heteroatom in or at the end of the alkyl chain, said heteroatom selected from O, S and N;

- each of R² and R³ is independently selected from hydrogen; alkyl; -OH; phosphate; phosphate-alkylene; phosphonate; or phosphonate-alkylene; or when taken together with R⁵, R⁶, R⁷ or R⁸ forms a double bond or -O- (thereby forming an epoxy); wherein said alkyl or alkylene can be substituted with one or more -OH; aryl; arylalkyl (such as trityl);
-OOC-aryl; or halogen; and wherein said alkyl can contain a heteroatom in or at the end of the alkyl chain; said heteroatom selected from O, S and N;
- or R² or R³ when taken together with R⁶ or R⁵' is -CH₂-CH₂-CH₂-; -CH₂-CH₂-CH₂-CH₂- or -CHR₁⁶=CHR₁⁷-CHR₁⁸=CHR₁⁹-, wherein each of R₁⁶, R₁⁷, R₁⁸ and R₁⁹ is independently selected from hydrogen; F; Cl; Br or alkyl;
- R⁵ is hydrogen or when taken together with R⁹, R⁹', R¹¹ or R¹¹' forms a double bond;
- each of R⁶ and R⁶' is independently selected from hydrogen; alkyl; or -OH; or taken together with R⁹, R⁹', R¹⁰ or R¹⁰' is -CH₂-O- or -O-CH₂- thereby forming a 5-membered ring; or when taken together with one of R² or R³ forms a double bond or -O-
- (thereby forming an epoxy); wherein said alkyl can be substituted with one or more -OH; aryl; or halogen;
- each of R⁷ and R⁷' is independently selected from hydrogen; alkyl; or -OH; or when taken together with one of R² or R³ forms a double bond or -O-
- (thereby forming an epoxy); wherein said alkyl can be substituted with one or more -OH; aryl; or halogen;
- each of R⁸ and R⁸' is independently selected from hydrogen; alkyl; or -OH; or taken together with R⁹, R⁹', R¹⁰ or R¹⁰' is -CH₂-O- or -O-CH₂- thereby forming a 5-membered ring; wherein said alkyl can be substituted with one or more -OH; aryl; or halogen;
- each of R⁹ and R⁹' is independently selected from hydrogen; alkyl; or -OH; or taken together with R⁶, R⁶', R⁸ or R⁸' is -CH₂-O- or -O-CH₂- thereby forming a 5-membered ring; or when taken together with R⁵ forms a double bond; wherein said alkyl can be substituted with one or more -OH; aryl; or halogen;
- each of R¹⁰ and R¹⁰' is independently selected from hydrogen; alkyl; or -OH; or taken together with R⁶, R⁶', R⁸ or R⁸' is -CH₂-O- or -O-CH₂- thereby forming a 5-membered ring;
- each of R¹¹ and R¹¹' is independently selected from hydrogen; alkyl; or -OH; or when taken together with R⁵ forms a double bond; wherein said alkyl can be substituted with one or more -OH; aryl; or halogen;
- each of R¹², R¹²', R¹³, R¹⁴, R¹⁴', R¹⁵, R¹⁵' is independently selected from hydrogen or alkyl; wherein said alkyl can be substituted with one or more -OH; aryl; or halogen;
- the selections for the X, Y and R-groups like -CR\textsubscript{7}R\textsubscript{7}'- C R\textsubscript{8}R\textsubscript{8}'-; -CH\textsubscript{2}O- or -CH\textsubscript{2}O- or -O-CH\textsubscript{2} have to be placed in formula I from left to right;
and isomers (in particular stereo-isomers or tautomers), solvates or pharmaceutically acceptable salts thereof or prodrugs thereof;

provided that the nucleoside analog is not a 9-(6-substituted or 6,8-disubstituted or 2,6-disubstituted 9H-purin-9-yl)-5-oxa-tricyclo[4.2.1.0\textsuperscript{3}7']nonane-3-methanol, more in particular is not the 6-amino-9H-purin-9-yl; 6-(dimethylamino)-9H-purin-9-yl; 6-cyclopropylamino-9H-purin-9-yl; the 2,6-diamino-9H-purin-9-yl; the 6-amino-8-methyl-9H-purin-9-yl; the 6-chloro-8-methyl-9H-purin-9-yl; the 6-chloro-9H-purin-9-yl or the 2-amino-6-chloro-9H-purin-9-yl derivative of 5-oxa-tricyclo[4.2.1.0\textsuperscript{3}7']nonane-3-methanol.

2. The nucleoside analogs according to claim 1, wherein Y is -CR\textsubscript{9k,9'}- and X is -CR\textsubscript{6j,6'}- and thereby the nucleoside analogs are according to the formula (A-2),

\begin{center}
\includegraphics[width=0.5\textwidth]{formula-A2.png}
\end{center}

wherein
- each of B, W, Z, R\textsubscript{1}, R\textsubscript{4}, R\textsubscript{12}, R\textsubscript{13}, R\textsubscript{14}, R\textsubscript{15} and R\textsubscript{15'} is according to formula (A);
- each of R\textsubscript{2} and R\textsubscript{3} is independently selected from hydrogen; alkyl; -OH; phosphate; phosphate-alkylene; phosphonate; or phosphonate-alkylene; or when taken together with one of R\textsubscript{6} or R\textsubscript{6'} forms a double bond or -O- (thereby forming an epoxy); wherein said alkyl or alkylene can be substituted with one or more -OH; aryl; -OOC-aryl; or halogen; and wherein said alkyl or alkylene can contain a heteroatom in or at the end of the alkyl chain, said heteroatom selected from O, S and N;
- or R² or R³ when taken together with R⁶ or R⁶' is -CH₂-CH₂-CH₂-; -CH₂-CH₂-CH₂-CH₂-CH₂- or -CHR=CHR CHplits=CHR ¹⁶=CHR ¹⁷-CHR ¹₈=CHR ¹⁹-, wherein each of R¹⁶, R¹⁷, R¹⁸ and R¹⁹ is independently selected from hydrogen; F; Cl; Br or alkyl;
- R⁵ is hydrogen or when taken together with one of R⁹ or R⁹' forms a double bond;

- each of R⁶ and R⁶' is independently selected from hydrogen; alkyl; or -OH; or taken together with one of R⁹ or R⁹' is -CH₂-O- or -O-CH₂- thereby forming a 5-membered ring; or when taken together with one of R² or R³ forms a double bond or -O- (thereby forming an epoxy); wherein said alkyl can be substituted with one or more -OH; aryl; or halogen;

- each of R⁹ and R⁹' is independently selected from hydrogen; alkyl; or -OH; or taken together with one of R⁶ or R⁶' is -CH₂-O- or -O-CH₂- thereby forming a 5-membered ring; or when taken together with R⁵ forms a double bond; wherein said alkyl can be substituted with one or more -OH; aryl; or halogen.

3. The nucleoside analogs according to claim 2, wherein
- B is according to formula (A);
- W is not present whereby B is directly bonded to carbon (1) or is -CH₂- or W is -O- ;
- Z is selected from -CR ¹²R ¹²' ;
- R ¹ is hydrogen;
- R ⁴ is selected from hydrogen or alkyl;
- each of R ¹² and R ¹²' is independently selected from hydrogen or alkyl;
- each of R² and R³ is independently selected from hydrogen; alkyl; -OH; phosphate; phosphate-alkylene; phosphonate; or phosphonate-alkylene; or R² or R³ when taken together with R⁶ or R⁶' is -CH₂-CH₂-CH₂-; -CH₂-CH₂-CH₂-CH₂- or -CHR=CHR CHplits=CHR ¹⁶=CHR ¹⁷-CHR ¹₈=CHR ¹⁹-, wherein each of R¹⁶, R¹⁷, R¹⁸ and R¹⁹ is independently selected from hydrogen; F; Cl; Br or alkyl; or when taken together with one of R⁶ or R⁶' forms a double bond or -O- (thereby forming an epoxy); wherein said alkyl or alkylene can be substituted with one or more -OH; aryl; -OOC-aryl; or halogen; and wherein said alkyl or alkylene can contain a heteroatom in or at the end of the alkyl chain, said heteroatom selected from O, S and N;
- R⁵ is hydrogen or when taken together with one of R⁹ or R⁹' forms a double bond;
- each of \( R^6 \) and \( R^6' \) is independently selected from hydrogen; alkyl; or -OH; or when taken together with one of \( R^2 \) or \( R^3 \) forms a double bond or -O- (thereby forming an epoxy); wherein said alkyl can be substituted with one or more -OH; aryl; or halogen;
- each of \( R^9 \) and \( R^9' \) is independently selected from hydrogen; alkyl; or -OH; or when taken together with \( R^5 \) forms a double bond; wherein said alkyl can be substituted with one or more -OH; aryl; or halogen.

4. The nucleoside analogs according to claim 3, wherein
- \( Z \) is \(-CH_2-\);
- each of \( R^4, R^2, R^3, R^5, R^6, R^9 \) and \( R^9' \) are hydrogen.

5. The nucleoside analogs according to claim 2, wherein \( R^6' \) and \( R^9' \) are taken together to form \(-O-CH_2-\) or \(-CH_2-O-\) and thereby the nucleoside analogs are according to the formula (A-3a) or (A-3b):

![Diagram](image)

wherein
- each of \( B, W, Z, R^1, R^4, R^{12}, R^{12'}, R^{13}, R^{13'}, R^{14}, R^{14'}, R^{15}, R^{15'} \) is according to formula (A);
- each of \( R^2 \) and \( R^3 \) is independently selected from hydrogen; alkyl; -OH; phosphate; phosphate-alkylene; phosphonate; or phosphonate-alkylene; or when taken together with one of \( R^6 \) or \( R^6' \) forms a double bond or -O- (thereby forming an epoxy); wherein said alkyl or alkylene can be substituted with one or more -OH; aryl; -OOC-aryl; or halogen;
- and wherein said alkyl or alkylene can contain a heteroatom in or at the end of the alkyl chain, said heteroatom selected from O, S and N;
- R5 is hydrogen or when taken together with one of R9 or R9* forms a double bond;
- R6 is selected from hydrogen; alkyl; or -OH; or when taken together with one of R2 or R3 forms a double bond or -O- (thereby forming an epoxy); wherein said alkyl can be substituted with one or more -OH; aryl; or halogen;
- R9 is selected from hydrogen; alkyl; or -OH; or when taken together with R5 forms a double bond; wherein said alkyl can be substituted with one or more -OH; aryl; or halogen.

6. The nucleoside analogs according to claim 5, wherein
- Z is selected from -CH₂-; -O-; or -CH₂-CH₂-;
- each of R1, R4, R5, R6 and R9 are hydrogen;
- each of R2 and R3 is independently selected from hydrogen; -OH; -OCH₃; phosphonomethylether; benzylxoxymethyl; methoxymethyl and chloromethyl.

7. The nucleoside analogs according to claim 1, wherein Y is not present and thereby the nucleoside analogs are according to the formula (A-4),

wherein
- each of B, W, X, Z, R₁, R₂, R₃, R₄, R₇, R₁₂, R₁₂', R₁₃, R₁₃', R₁₄, R₁₅ and R₁₅' is according to formula (A);
- R5 is hydrogen;
- each of R6 and R6' is independently selected from hydrogen; alkyl; or -OH; or when taken together with R2 or R3 forms a double bond or -O- (thereby forming an epoxy);
- wherein said alkyl can be substituted with one or more -OH; aryl; or halogen;
- each of R₈ and R₈' is independently selected from hydrogen; alkyl; or -OH; wherein said alkyl can be substituted with one or more -OH; aryl; or halogen.

8. The nucleoside analogs according to claim 7, wherein
   - B and W are according to formula (A);
   - X is -CH₂⁻;
   - Z is selected from -CH₂CH₂⁻; or -CH₂=CH₂⁻;
   - each of R¹, R⁴ and R⁵ are hydrogen;
   - each of R² and R³ is independently selected from hydrogen; -OH; or -OCH₃.

9. The nucleoside analogs according to claim 1, wherein Y is -CR₁⁰⁻CR₁¹⁻CR¹³⁻ and X is not present and thereby the nucleoside analogs are according to the formula (A-5),

wherein
   - each of B, W, Z, R¹, R⁴, R₁², R₁³, R₁⁵ and R₁⁵' is according to formula (A);
   - each of R² and R³ is independently selected from hydrogen; alkyl; -OH; phosphate; phosphate-alkylene; phosphonate; or phosphonate-alkylene; wherein said alkyl or alkylene can be substituted with one or more -OH; aryl; -OOC-aryl; or halogen; and wherein said alkyl can contain a heteroatom in or at the end of the alkyl chain, said heteroatom selected from O, S and N;
   - R⁵ is hydrogen or when taken together with R¹⁰' or R¹¹' forms a double bond;
   - each of R¹⁰ and R¹⁰' is independently selected from hydrogen; alkyl; or -OH;
- each of $R^{11}$ and $R^{11'}$ is independently selected from hydrogen; alkyl; or -OH; or when taken together with $R^5$ forms a double bond; wherein said alkyl can be substituted with one or more -OH; aryl; or halogen.

10. The nucleoside analogs according to claims 9, said nucleoside analogs having a structure according to formula (A-6),

\[ \text{(A-6)} \]

wherein
- the dotted line represents a double bond which can be present or not present;
- each of $R^2$, $R^3$, $R^{12}$ and $R^{12'}$ is independently selected from hydrogen or alkyl (more in particular methyl).

11. The nucleoside analogs according to claim 1 selected from the list of compounds in table 1 (encoded from compound number 1 to 86).

12. The nucleoside analogs according to claim 1, selected from the list of:
- 9-[(lR*,2R*,4S*)-bicyclo[2.2.1]hept-2-yl]-6-chloro-9H-purine;
- 9-[(lR*,2R*,4S*)-bicyclo[2.2.1]hept-2-yl]-2,6-dichloro-9H-purine;
- 6-chloro-9-[(lS,2S,4S)-l,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-9H-purine;
- (IR*,2R*,3R*,6R*,7S*,9R*)-9-[(2,6-dichloro-9H-purin-9-yl)methyl]-4-oxatricyclo[4.2.1.0^3\text{,}7]nonan-2-ol;
- 6-chloro-9-[(IR,2S,5R)-6,6-dimethylbicyclo[3.1.1]hept-2-yl]methyl]-9H-purine;

- [(IR*,2S*,4R*,7R*)-7-(6-chloro-9H-purin-9-yl)bicyclo[2.2.1]heptan-2-yl];
- 6-chloro-9-[(lR*,2R*,3R*,6R*,7S*,9S*)-9-(methoxymethyl)-4-oxatricyclo[4.2.1.0^3\text{,}7]non-2-yl]-9H-purine;
- 6-chloro-9-[(lR*,2R*,3R*,6R*,7S*,9S*)-9-(chloromethyl)-4-oxatricyclo[4.2.1.0^3\text{,}7]non-2-yl]-9H-purine;
- 6-chloro-9-[(lR*,2R*,4R*,7S*,9S*)-9-(benzyloxy)methyl]-4-oxatricyclo[4.2.1.0^3\text{,}7]non-2-yl]-9H-purine;
- 6-chloro-9-[(lR*,2R*,3R*,6R*,7S*,9S*)-9-(phenylmethoxy-L-alaninyl)-phosphate;
- [(l/?*,2i ?,45*,75*)-7-(6-chloro-9 H-purin-9-yl)bicyclo[2.2.1]hept-2-yl]methanol;
- [(l/?*,25*,4i?*,75*)-7-(6-chloro-9 H-purin-9-yl)bicyclo[2.2.1]hept-5-en-2-yl]methanol;

5
- (IR *,2S *,4R *,55*)-5-(6-chloro-9 H-purin-9-yl)bicyclo[2.2.1]heptan-2-ol;
- (l/?*,2 R *,4S *,6i?*)-6-(6-chloro-9 H-purin-9-yl)bicyclo[2.2.1]heptan-2-ol;
- (l/?*,2i ?,4i?*,55*)-5-(6-chloro-9 H-purin-9-yl)bicyclo[2.2.1]heptan-2-ol;

10
- 6-chloro-9-[(l/?*,2R *,3i?,* ,6S *,7S *,10S*)-10-(chloromethyl)-4-oxatricyclo[4.3.1.0 3>7]dec-2-yl]-9 H-purine;
- 6-chloro-9-[(l/?*,2R *,3S *,6S *,7S *,9R *)-9-(chloromethyl)-4,8-dioxatricyclo[4.2.1.0 3>7]non-2-yl]-9 H-purine;
- 6-chloro-9-[(l/?*,2i?,3i?,* ,6S *,7S *,10S*)-10-(fluoromethyl)-4-oxatricyclo[4.3.1.0 3>7]dec-2-yl]-9 H-purine;

15
- 6-chloro-9-[(l/?*,2i?,* ,3i?,6S *,7S *,9R *)-9-(fluoromethyl)-4,8-dioxatricyclo[4.2.1.0 3>7]non-2-yl]-9 H-purine;
- 6-chloro-9-[(15*,2S *,4i?,6i?*)-6-fluorobicyclo[2.2.1]hept-2-yl]-9 H-purine;
- 6-chloro-9-[(l/?*,25*,4i?,55*)-5-fluorobicyclo[2.2.1]hept-2-yl]-9 H-purine;

20
- 9-[(l/?*,2i?,* ,45*)-bicyclo[2.2.1]hept-2-yl]-9 H-purine-6-thiol;
- 9-[(l/?*,2i?,* ,45*)-bicyclo[2.2.1]hept-2-yl]-6-(methylsulfanyl)-9 H-purine;
- 9-[(l/?*,2i?,45*)-bicyclo[2.2.1]hept-2-yl]-6-(methylsulfonyl)-9 H-purine;
- 9-[(l/?*,2i?*,4S*)-bicyclo[2.2.1]hept-2-yl]-9 H-purine;
- 9-[(l/?*,2i?*,45*)-bicyclo[2.2.1]hept-2-yl]-6-iodo-9 H-purine;

25
- 6-azido-9-[(l/?*,2/?*,45*)-bicyclo[2.2.1]hept-2-yl]-9 H-purine;
- 9-[(l/?*,2R *,45*)-bicyclo[2.2.1]hept-2-yl]-9 H-purine-6-amine;
- 9-[(l/?*,2i?*,4S*)-bicyclo[2.2.1]hept-2-yl]-6-fluoro-9 H-purine;
- 9-[(l/?*,2i?*,45*)-bicyclo[2.2.1]hept-2-yl]-6-(4-chlorophenyl)-9 H-purine;
- 9-[(l/?*,2i?*,45*)-bicyclo[2.2.1]hept-2-yl]-6-(trifluoromethyl)-9 H-purine;

30
- 9-[(l/?*,2i?*,4S*)-bicyclo[2.2.1]hept-2-yl]-6-methoxy-9 H-purine;
- 9-[(l/?*,2i?*,45*)-bicyclo[2.2.1]hept-2-yl]-6-methyl-9 H-purine;
- 9-{(l/?*,2i?*,45*)-bicyclo[2.2.1]hept-2-yl}-6-chloro-2-nitro-9 \( H \)-purine;
- 9-{(l/?*,2i?*,45*)-bicyclo[2.2.1]hept-2-yl}-8-bromo-6-chloro-9 \( H \)-purine;
- 9-{(IR *,2R *,4S*)-bicyclo[2.2.1]hept-2-yl}-6-chloro-8-iodo-9 \( H \)-purine;
- ethyl 9-{(IR *,2R *,4S*)-bicyclo[2.2.1]hept-2-yl}-6-chloro-9 \( H \)-purine-8-carboxylate;
- \{9-{(IR *,2R *,4S*)-bicyclo[2.2.1]hept-2-yl}-purin-8-yl\}methanol;
- 6-chloro-9-{(l/?*,2i?*,45*,55*,6,S*)-3-oxatricyclo[3.2.1.0\( ^{2>4} \)]oct-6-yl}-9 \( H \)-purine;
- (l/?*,2/?*,35*,45*)-5-(6-chloro-9\( H \)-purin-9-yl)bicyclo[2.2.1]heptane-2,3-diol;
- 7-{(l/?*,2i?*,45*)-bicyclo[2.2.1]hept-2-yl}-4-chloro-7 \( H \)-pyrrolo[2,3-flT|pyrimidine;
- (l/?*,2/?*,3i?*,6/?*,75*,95*)-2-(2-amino-6-chloro-9\( H \)-purin-9-yl)-4-oxatricyclo[4.2.1.0\( ^{3>7} \)]nonane-9-methanol;
- 6-chloro-9-{(l/?*,3 R *,6i?*,7i?*,9i?*)-4-oxatricyclo[4.2.1.0\( ^{3>7} \)]non-9-yl}-9 \( H \)-purine
- (IR *,2R *,3S *,4S *)-6-(chloromethyl)-3-(6-chloro-9 \( H \)-purin-9-yl)bicyclo[2.2.1]hept-5-en-2-ol;
- (l/?*,2/?*,35*,45*)-3-(6-chloro-9 \( H \)-purin-9-yl)-6-(hydroxymethyl)bicyclo[2.2.1]hept-5-en-2-ol;
- (1R *,2i?*,35*,4S *)-3-(6-chloro-9\( H \)-purin-9-yl)-5-(hydroxymethyl)bicyclo[2.2.1]hept-5-en-2-ol and
- (IR *,4R *,75*)-7-(6-Chloro-9\( H \)-purin-9-yl)bicyclo[2.2.1]hept-5-ene-2,2-dimethanol.

13. The nucleoside analogs according to claims 1 to 12, wherein B is an unsubstituted purine heterocycle, its aza or deaza analogs or is a purine heterocycle, its aza or deaza analogs substituted with halogen; -NH\(_2\); -NH-alkyl; -N(alkyl), -OH; -O-alkyl (such as -OCH\(_3\)); -SH; -S-alkyl (such as -SCH\(_3\)); -N\(_3\); -CF\(_3\); -NO\(_2\); -COOH; -COO-alkyl; -SO\(_2\)-alkyl; aryl or alkyl; wherein each of said alkyl and aryl can again be substituted with hydroxy, amino, halogen or -SH, whereby the purine heterocycle is not substituted with -CF\(_3\) in its 2-position.

14. The nucleoside analogs according to claim 1 to 13, wherein B is according to formula (P-I),
wherein each of $R^{20}$ and $R^{21}$ are independently selected from hydrogen; halogen; $-\text{NH}_2$; $-\text{N}_3$; $-\text{NH}$-alkyl; $-\text{N}(\text{alkyl})_2$; $-\text{OH}$; $-\text{O}$-alkyl (such as $-\text{OCH}_3$); $-\text{SH}$; $-\text{S}$-alkyl (such as $-\text{SCH}_3$); $-\text{CF}_3$; $-\text{NO}_2$; $-\text{COOH}$; $-\text{COO}$-alkyl; $-\text{SO}_2$-alkyl; aryl or alkyl; wherein each of said alkyl and aryl can again be substituted with hydroxy, amino, halogen or $-\text{SH}$;

and $R^{22}$ is selected from hydrogen; halogen; $-\text{NH}_2$; $-\text{NH}$-alkyl; $-\text{N}(\text{alkyl})_2$; $-\text{OH}$; $-\text{O}$-alkyl (such as $-\text{OCH}_3$); $-\text{SH}$; $-\text{S}$-alkyl (such as $-\text{SCH}_3$); $-\text{N}_3$; $-\text{NO}_2$; $-\text{COOH}$; $-\text{COO}$-alkyl; $-\text{SO}_2$-alkyl; aryl or alkyl; wherein each of said alkyl and aryl can again be substituted with hydroxy, amino or $-\text{SH}$.

15. The nucleoside analogs according to claim 14, wherein each of $R^{20}$ and $R^{21}$ are independently selected from hydrogen; F; Cl; Br; I; $-\text{N}_3$; $-\text{NH}_2$; $-\text{NH}$-alkyl; $-\text{N}(\text{alkyl})_2$; $-\text{OH}$; $-\text{O}$-alkyl; $-\text{O}$-alkyl (such as $-\text{OCH}_3$); $-\text{SH}$; $-\text{S}$-alkyl (such as $-\text{SCH}_3$); $-\text{CF}_3$; $-\text{NO}_2$; $-\text{COOH}$; $-\text{COO}$-alkyl; $-\text{SO}_2$-alkyl; aryl or alkyl; wherein each of said alkyl and aryl can again be substituted with hydroxy, amino, halogen or $-\text{SH}$.

and $R^{22}$ is selected from hydrogen; F; Cl; Br; I; $-\text{COOH}$; $-\text{COO}$-$\text{CH}_3$; $-\text{COO}$-$\text{C}_2\text{H}_5$; $-\text{COO}$-$\text{CH}(\text{CH}_3)_2$; $-\text{COO}$-$\text{C}(\text{CH}_3)_3$; $-\text{SO}_2$-$\text{CH}_3$; $-\text{SO}_2$-$\text{C}_2\text{H}_5$; $-\text{SO}_2$-$\text{CH}_2\text{CH}_2\text{CH}_3$; $-\text{SO}_2$-$\text{CH}(\text{CH}_3)_2$; $-\text{CH}_2\text{F}$; $-\text{CHF}_2$; $-\text{CH}_2\text{Cl}$; $-\text{CHCl}_2$; $-\text{CH}_2\text{OH}$; $-\text{CH}_2\text{CH}_2\text{OH}$; $-\text{CH}_3$; $-\text{C}_2\text{H}_5$; $-\text{CH}_2\text{CH}_2\text{CH}_3$; $-\text{CH}(\text{CH}_3)_2$; $-\text{C}(\text{CH}_3)_3$; n-butyl; isobutyl; n-pentyl; sec-pentyl; -(4-chloro)-phenyl; -(4-bromo)-phenyl and -(4-fluoro)-phenyl;

and $R^{22}$ is selected from hydrogen; F; Cl; Br; I; $-\text{COOH}$; $-\text{COO}$-$\text{CH}_3$; $-\text{COO}$-$\text{C}_2\text{H}_5$; $-\text{COO}$-$\text{CH}(\text{CH}_3)_2$; $-\text{COO}$-$\text{C}(\text{CH}_3)_3$; n-butyl; isobutyl; n-pentyl; sec-pentyl; $-\text{CH}_2\text{OH}$; $-\text{CH}_2\text{CH}_2$-
OH; -CH₃; -C₂H₅; -CH₂-CH₂-CH₃; n-butyl; isobutyl; n-pentyl; sec-pentyl; -CH(CH₃)₂ and -C(CH₃)₃.

16. The nucleoside analogs of general formulae (A-I), (A-2), (A3-a), (A3-b), (A-4), (A-5) and (A-6);
wherein 

$W, Z, X, R_1, R_2, R_3, R_4, R_5, R_6, R_6', R_9, R_9, R_{10}, R_{10}', R_{11}, R_{11}', R_{12}$ and $R_{12}'$ are defined as in claim 1

and

wherein $B$ is according to formula (P-I),

wherein each of $R^{20}$ and $R^{21}$ are independently selected from hydrogen; halogen; $\text{-NH}_2$; $\text{-NH-alkyl}$; $\text{-N(alkyl)}_2$; $\text{-N}_3$; $\text{-OH}$; $\text{-O-alkyl (such as -OCH}_3$; $\text{-SH}$; $\text{-S-alkyl (such as -}$
SCH$_3$; -CF$_3$; -NO$_2$; -COOH; -COO-alkyl; -SO$_2$alkyl; aryl; or alkyl; wherein each of said alkyl and aryl can again be substituted with hydroxy, amino, halogen or -SH;

and R$_{22}$ is selected from hydrogen; halogen; -NH$_2$; -OH; -O-alkyl (such as -OCH$_3$); -SH; -S-alkyl (such as -SCH$_3$); -N$_3$; -NO$_2$; -COOH; -COO-alkyl; -SO$_2$alkyl; aryl; or alkyl; wherein each of said alkyl and aryl can again be substituted with hydroxy, amino or -SH.

17. The nucleoside analogs according to the claims 1 to 16 for use as a medicament.

18. The nucleoside analogs according to the claims 1 to 16 for use as a medicament for the prevention or treatment of a viral infection in an animal or human.

19. The nucleoside analogs according to claim 18, wherein the viral infection is caused by a RNA virus.

20. The nucleoside analogs according to claim 18, wherein the RNA virus is of the Picornaviridae.

21. The nucleoside analogs according to claims 1 to 16 for the treatment of a viral infection in an animal or mammal.

22. The use of a nucleoside analog according to claims 1 to 16 for the manufacture of a medicament.

23. The use of a nucleoside analog according to claim 22 wherein the medicament is for the prevention or treatment of a viral infection in an animal or mammal.

24. The use according to claim 23, wherein the viral infection is caused by a virus of the Picornaviridae.
25. A pharmaceutical composition comprising a nucleoside analog according to any of the claims 1 to 16 as an active ingredient in admixture with at least a pharmaceutically acceptable carrier.

26. A pharmaceutical composition according to claim 25, having antiviral activity.

27. A method of treatment or prevention of a viral infection in an animal or mammal, comprising administering to the animal or mammal in need of such treatment a therapeutically effective amount of a nucleoside analog according to any of the claims 1 to 16.

28. A method for the preparation of the nucleoside analogs according to any of the claims 1 to 16, said method comprising the steps of coupling a substituted or unsubstituted pyrimidine or purine heterocycle or aza or deaza analogs, preferably a substituted purine heterocycle or aza or deaza analogs, to compounds of the formula (A-7), in particular via the Mitsunobu-reaction:

\[
\begin{align*}
W & \quad X & \quad Y & \quad Z & \quad R^1 & \quad R^2 & \quad R^3 & \quad R^4 & \quad R^5 & \quad OH \\
R^6 & \quad R^6' & \quad R^7 & \quad R^7' & \quad R^8 & \quad R^8' & \quad R^9 & \quad R^9' & \quad R^{10} & \quad R^{10'} \\
R^{11} & \quad R^{11'} & \quad R^{12} & \quad R^{12'} & \quad R^{13} & \quad R^{13'} & \quad R^{14} & \quad R^{14'} & \quad R^{15} & \quad R^{15'}
\end{align*}
\]

wherein each of \(W, X, Y, Z, R^1, R^2, R^3, R^4, R^5, R^6, R^6', R^7, R^7', R^8, R^8', R^9, R^9', R^{10}, R^{10'}, \) \(R^{11}, R^{11'}, R^{12}, R^{12'}, R^{13}, R^{13'}, R^{14} R^{14'}, R^{15} \) and \(R^{15'}\) is according to formula (A).

29. A method for the preparation of the nucleoside analogs according to any of the claims 1 to 16, said method comprising the steps of coupling a substituted or unsubstituted pyrimidine or purine heterocycle, preferably a substituted pyrimidine heterocycle, to compounds of the formula (A-8),
wherein each of W, X, Y, Z, R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R₉', R₁₀, R₁₀', R₁₁, R₁₁', R₁₂, R₁₂', R₁₃, R₁₃', R₁₄, R₁₄', R₁₅ and R₁₅' is according to formula (A),

5 said method comprising the steps of
- coupling a substituted 5-amino-pyrimidine, preferably a substituted 4-chloro-5-amino-pyrimidine, to the compounds of formula (A-8); and
- performing a ring-closure in acid trialkyl orthoformate reaction conditions.

30. A method for the preparation of the nucleoside analogs according to any of the claims 1 to 16, said method comprising the steps of
- coupling a unsubstituted or substituted purine heterocycle oraza or deaza analogs with unsubstituted or substituted bicycloalkanylalcohols, bicycloalkenylalcohols, tricycloalkanylalcohols, tricycloalkenylalcohols or hetero analogs thereof via the Mitsunobu reaction; or
- a substituted 5-amino-pyrimidine, preferably a substituted 4-chloro-5-amino-pyrimidine, thereof with unsubstituted or substituted bicycloalkylamines, bicycloalkenylamines, tricycloalkylamines, tricycloalkenylamines or hetero analogs thereof and subsequently performing a ring-closure in an acidic orthoformate; and
- optionally transformation of these compounds obtained as outlined above.