

Phosphoric acid derivatives and pharmaceutical use thereof**FIELD OF THE INVENTION**

This invention pertains to phosphoric acid derivatives and their use of preparing an antiviral medicament. In particular, the present invention pertains to the novel phosphoric acid derivatives and their use in prophylaxis or treatment of diseases caused by viral infection, such as human papillomavirus.

BACKGROUND OF THE INVENTION

DNA replication is the fundamental process of duplicating DNA for a daughter cell, which is catalyzed by DNA polymerases. DNA polymerase adds mononucleotides to synthesize a template-specific daughter DNA strand with impressive accuracy, which is essential for maintaining genomic order and thus for the long-term survival of a species. Numerous pathological states, including viral infections and cancer, are attributed to uncontrollable DNA polymerase activity.

Viruses contain either DNA or RNA genome, only produce and replicate in host cells. After entering the host cells, viruses use viral and cellular machineries to complete their life activities, and produce a new generation of viruses. DNA viruses replicate their genomes using DNA polymerases, while RNA viruses replicate and transcribe their genomes using RNA polymerases. Some viruses need to encode their own polymerases for transcription and replication, while many eukaryotic DNA viruses do not encode a viral polymerase, instead relying entirely on host cell machinery for genome replication and mRNA synthesis. (Kyung H. Choi, Viral Polymerases, Adv Exp Med Biol. Author manuscript; available in PMC 2016 Jan 13).

Viral infection may lead to mild to severe illnesses in humans and mammals, and in some instances, can result in death. Examples of pathogenic human DNA viruses are human papillomavirus (HPV), herpes simplex virus (HSV), cytomegalovirus (CMV), hepatitis B virus (HBV), adenovirus, as well as some reverse-transcribing viruses including human immunodeficiency virus (HIV). Viral infection may also lead to neoplasia or cancer in human and other host species, such as human papillomavirus (HPV), hepatitis B viruses and Epstein Barr virus (EBV). Antiviral agents interfere with the integrity of viral life cycle and have been used to prevent or treat viral infection. However, improved antiviral agents are needed for treatment of many common viral diseases.

For example, currently there is no treatment for the HPV virus itself (HPV Treatment | CDC, <https://www.cdc.gov/std/hpv/treatment.htm>, last update July 22, 2021). Human papillomavirus (HPV) belongs to a type of double stranded small DNA virus without an envelope. HPVs do not code for a DNA polymerase, and viral DNA replication relies on host DNA polymerases and other replication proteins. HPV infection has a high degree of strict tissue specificity. It mainly infects human mucosal tissues and epithelial cells, which depends on the differentiated stage of epithelial cells. HPV is commonly classified into low-risk and high-risk types. High risk types of HPV are more likely to lead to human cancer including cervical, rectal, penile, vaginal, and oropharyngeal cancer. The most common cancer-causing HPV types are 16 and 18, which are also the types that the HPV vaccines mainly provide protection. HPV vaccine has been approved for prevention of infection, but not for elimination of the existing HPV infection, genital warts or precancerous lesions. In addition, HPV vaccines only prevent cervical cancer caused by certain subtypes. Therefore, there is a need to develop antiviral treatment for HPV infection.

At present, many marketing antiviral agents are DNA or RNA polymerase substrate (nucleoside or nucleotide) analog, including azidothymidine, acyclovir, ganciclovir, lamivudine, adefovir, tenofovir and cidofovir. For example, cidofovir is a nucleotide analog that resembles cytosine, and is an antiviral agent FDA approved for the management of CMV retinitis in patients with AIDS. After intracellular phosphorylation, the active metabolite cidofovir diphosphate serves as a substrate for viral DNA polymerase and is incorporated into viral DNA, thus terminating further viral DNA replication. It has activity against various DNA viruses, including acyclovir-resistant HSV infections and HPV. Case reports describe the use of cidofovir in the management of recalcitrant warts, however, lack of clinical trials and high cost have limited its utilization (Cook et al, Cidofovir in the Management of Non-Genital Warts: A Review. *J Drugs Dermatol*. 2023 Oct 1;22(10):1009-1016. doi: 10.36849/JDD.7258.)

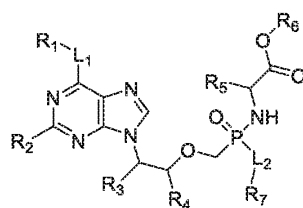
The acyclic nucleotide, 9-(2-phosphonylmethoxyethyl) guanine (PMEG) forms an active phosphorylated metabolite, PMEG diphosphate (PMEG-DP), in cells, which inhibits the growth of various transformed cell lines due to potent inhibition of the nuclear DNA polymerases α , δ and ϵ , resulting in inhibition of DNA synthesis and/or DNA repair. However, the utility of PMEG as an antiproliferative agent is limited by its poor cellular permeability and toxicity due to systemic exposure (Wolfgang et al, *Antimicrobial Agents and Chemotherapy*, 2009, 2777–2784). Gilead has

disclosed a series of phosphonates, monophosphonamidates and bisphosphonamidates that was designed to increase the permeability and accumulation of metabolites (specifically PMEG-DP) into cells for the treatment of DNA viral infections, specifically for treating HPV infections in WO2005066189A1 and WO2009105513A2. the Regents of the University of California has also disclosed a series of nucleotide analogs as HPV inhibitors in WO2014143643A1, WO2016044281A1 and WO2017048956A1.

The present disclosure provides the novel phosphoric acid derivatives and their use of treating diseases caused by human DNA virus and potentially neoplasia.

SUMMARY OF THE INVENTION

The objective of the present invention is to provide a compound of formula (I), a stereoisomer thereof, or a pharmaceutically acceptable salt, solvates and prodrugs thereof:



formula (I)

Wherein,

L₁ is independently selected from -O- or -NH-;

R₁ is independently selected from hydrogen, C₁-C₆ alkyl, deuterated C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₈ cycloalkyl, 4 to 7 membered heterocyclyl, C₆-C₁₀ aryl and 5 to 10 membered heteroaryl, wherein the C₃-C₈ cycloalkyl, 4 to 7 membered heterocyclyl, C₆-C₁₀ aryl and 5 to 10 membered heteroaryl are each optionally further substituted by one or more deuterium, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, halogen, hydroxy, amino, nitro, cyano and ester group;

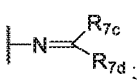
R₂ is independently selected from hydrogen, amino, hydroxy, halogen, cyano, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₂-C₆ alkenyl and C₂-C₆ alkynyl;

R₃ and R₄ are each independently selected from hydrogen, deuterium, halogen, hydroxy, amino, C₁-C₆ alkyl, deuterated C₁-C₆ alkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ haloalkyl and C₁-C₆ alkoxy;

Or R₃ and R₄ together with the atoms to which they are attached can form a 3 to 7 membered heterocycle comprising 1-2 heteroatoms selected from O, N and S;

R₅ and R₆ are each independently selected from hydrogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₃-C₈ cycloalkyl, 4 to 7 membered heterocyclyl, C₆-C₁₀ aryl, benzyl and 5 to 10 membered heteroaryl, wherein the C₃-C₈ cycloalkyl, 4 to 7 membered heterocyclyl, C₆-C₁₀ aryl, benzyl and 5 to 10 membered heteroaryl are each optionally further substituted by one or more deuterium, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, halogen, hydroxy, amino, nitro, cyano and ester group;

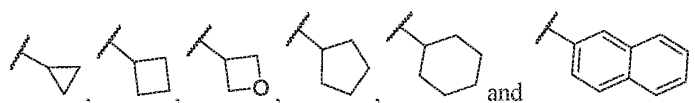
L₂ is independently selected from -O- or -NH-;

R₇ is independently selected from  and ;

R_{7a}, R_{7b}, R_{7c} and R_{7d} are each independently selected from hydrogen, deuterium, C₁-C₆ alkyl, deuterated C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -C(O)O-C₁-C₆ alkyl, -C₃-C₈ cycloalkyl, 4 to 7 membered heterocyclyl, C₆-C₁₀ aryl and 5 to 10 membered heteroaryl, wherein the C₃-C₈ cycloalkyl, 4 to 7 membered heterocyclyl, C₆-C₁₀ aryl and 5 to 10 membered heteroaryl are each optionally further substituted by one or more deuterium, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, halogen, hydroxy, amino, nitro, cyano and ester group;

Or R_{7c} and R_{7d} together with the atom to which they are attached can form a C₃-C₈ carbocycle or a 3 to 7 membered heterocycle comprising 1-2 heteroatoms selected from O, N and S.

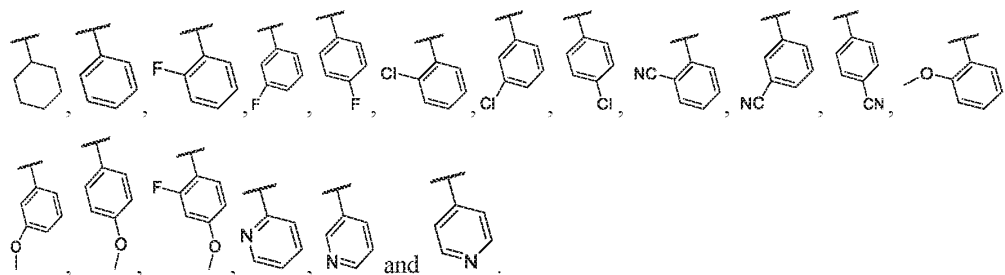
In a more preferred embodiment, in the compound of formula (I), the stereoisomer or the pharmaceutically acceptable salt, solvates and prodrugs thereof, each R₁ is independently selected from hydrogen, C₁-C₆ alkyl (such as methyl, ethyl, propyl and isopropyl), C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ hydroxyalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl,



In a more preferred embodiment, in the compound of formula (I), the stereoisomer or the pharmaceutically acceptable salt, solvates and prodrugs thereof, each R_4 is independently selected from hydrogen, C_1 - C_6 alkyl (such as methyl, ethyl, propyl and isopropyl), C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy and C_1 - C_6 hydroxyalkyl.

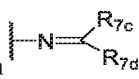
In a more preferred embodiment, in the compound of formula (I), the stereoisomer or the pharmaceutically acceptable salt, solvates and prodrugs thereof, each R_5 is independently selected from hydrogen, C_1 - C_6 alkyl (such as methyl, ethyl, propyl and isopropyl), C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 hydroxyalkyl and benzyl.

In a more preferred embodiment, in the compound of formula (I), the stereoisomer or the pharmaceutically acceptable salt, solvates and prodrugs thereof, each R_{7a} and R_{7b} are independently selected from hydrogen, C_1 - C_6 alkyl (such as methyl, ethyl, propyl and isopropyl), C_1 - C_6 haloalkyl (such as difluoromethyl, trifluoromethyl, 1,1-difluoroethyl, 1,1,2-trifluoroethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, 1,1,2,2-tetrafluoroethyl, 1,1,2,2-tetrafluoropropyl and 1,1,1-trifluoro-2-methylpropan-2-yl), $-C(O)O$ - C_1 - C_6 alkyl,



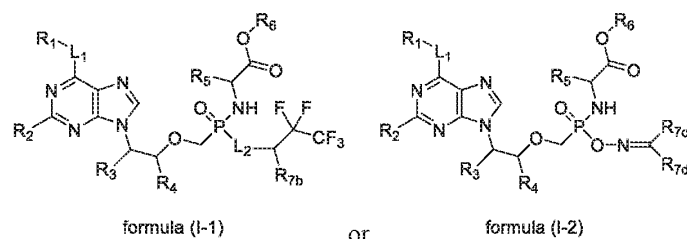
In a more preferred embodiment, in the compound of formula (I), the stereoisomer or the pharmaceutically acceptable salt, solvates and prodrugs thereof, each R_{7c} and R_{7d} are independently selected from hydrogen, C_1 - C_6 alkyl (such as methyl, ethyl, propyl, isopropyl and isobutyl), C_1 - C_6 haloalkyl and phenyl.

In a more preferred embodiment, in the compound of formula (I), the stereoisomer or the

pharmaceutically acceptable salt, solvates and prodrugs thereof, each  is selected

from , , , , ,  and .

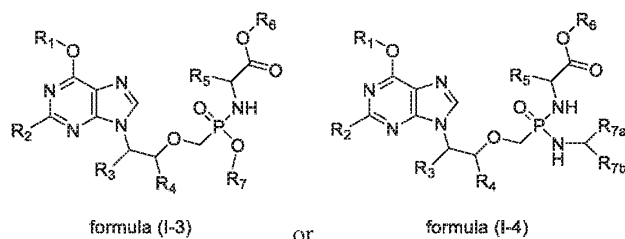
In a more preferred embodiment, the compound of formula (I), the stereoisomer or the pharmaceutically acceptable salt, solvates and prodrugs thereof is the compound of formula (I-1) or formula (I-2), the stereoisomer or the pharmaceutically acceptable salt, solvates and prodrugs thereof:



Wherein:

L₁, L₂, R₁, R₂, R₃, R₄, R₅, R₆, R_{7b}, R_{7c} and R_{7d} are defined as in formula (I).

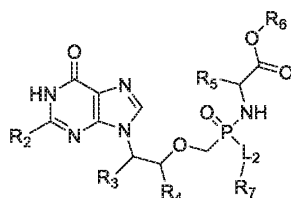
In a more preferred embodiment, the compound of formula (I), the stereoisomer or the pharmaceutically acceptable salt, solvates and prodrugs thereof is the compound of formula (I-3) or formula (I-4), the stereoisomer or the pharmaceutically acceptable salt, solvates and prodrugs thereof:



Wherein:

R₁, R₂, R₃, R₄, R₅, R₆, R₇, R_{7a} and R_{7b} are defined as in formula (I).

In another embodiment, described here are compounds formula (II), a stereoisomer thereof, or a pharmaceutically acceptable salt, solvates and prodrugs thereof:



formula (II)

Wherein,

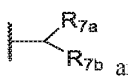
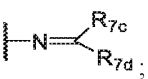
R₂ is independently selected from hydrogen, amino, hydroxy, halogen, cyano, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₂-C₆ alkenyl and C₂-C₆ alkynyl;

R₃ and R₄ are each independently selected from hydrogen, halogen, hydroxy, amino, C₁-C₆ alkyl, deuterated C₁-C₆ alkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ haloalkyl and C₁-C₆ alkoxy;

Or R₃ and R₄ together with the atoms to which they are attached can form a 3 to 7 membered heterocycle comprising 1-2 heteroatoms selected from O, N and S;

R₅ and R₆ are each independently selected from hydrogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₃-C₈ cycloalkyl, 4 to 7 membered heterocyclyl, C₆-C₁₀ aryl, benzyl and 5 to 10 membered heteroaryl, wherein the C₃-C₈ cycloalkyl, 4 to 7 membered heterocyclyl, C₆-C₁₀ aryl, benzyl and 5 to 10 membered heteroaryl are each optionally further substituted by one or more deuterium, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, halogen, hydroxy, amino, nitro, cyano and ester group;

L₂ is independently selected from -O- or -NH-;

R₇ is independently selected from  and ;

R_{7a}, R_{7b}, R_{7c} and R_{7d} are each independently selected from hydrogen, deuterium, C₁-C₆ alkyl, deuterated C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -C(O)O-C₁-C₆ alkyl, -C₃-C₈ cycloalkyl, 4 to 7 membered heterocyclyl, C₆-C₁₀ aryl and 5 to 10 membered heteroaryl, wherein the C₃-C₈ cycloalkyl, 4 to 7

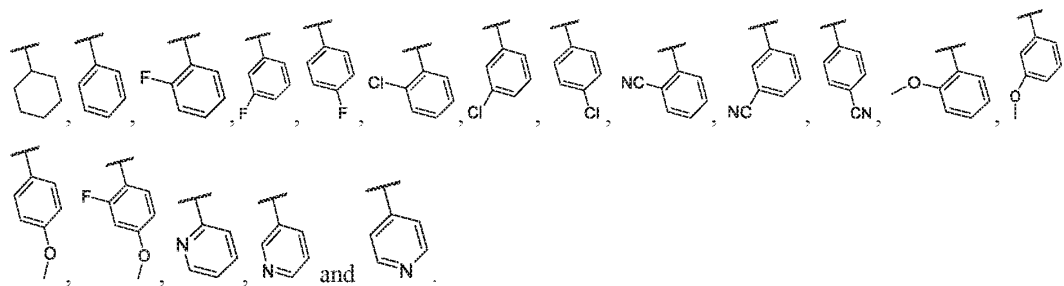
membered heterocyclyl, C₆-C₁₀ aryl and 5 to 10 membered heteroaryl are each optionally further substituted by one or more deuterium, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, halogen, hydroxy, amino, nitro, cyano and ester group;

Or R_{7c} and R_{7d} together with the atom to which they are attached can form a C₃-C₈ carbocycle or a 3 to 7 membered heterocycle comprising 1-2 heteroatoms selected from O, N and S.

In a more preferred embodiment, in the compound of formula (II), the stereoisomer or the pharmaceutically acceptable salt, solvates and prodrugs thereof, each R₄ is independently selected from hydrogen, C₁-C₆ alkyl (such as methyl, ethyl, propyl and isopropyl), C₁-C₆ haloalkyl, C₁-C₆ alkoxy and C₁-C₆ hydroxyalkyl.

In a more preferred embodiment, in the compound of formula (II), the stereoisomer or the pharmaceutically acceptable salt, solvates and prodrugs thereof, each R₅ is independently selected from hydrogen, C₁-C₆ alkyl (such as methyl, ethyl, propyl and isopropyl), C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ hydroxyalkyl and benzyl.

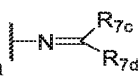
In a more preferred embodiment, in the compound of formula (II), the stereoisomer or the pharmaceutically acceptable salt, solvates and prodrugs thereof, each R_{7a} and R_{7b} are independently selected from hydrogen, C₁-C₆ alkyl (such as methyl, ethyl, propyl and isopropyl), C₁-C₆ haloalkyl (such as difluoromethyl, trifluoromethyl, 1,1-difluoroethyl, 1,1,2-trifluoroethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, 1,1,2,2-tetrafluoroethyl, 1,1,2,2-tetrafluoropropyl and 1,1,1-trifluoro-2-methylpropan-2-yl), -C(O)O-C₁-C₆ alkyl,

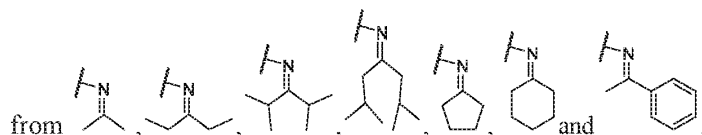


In a more preferred embodiment, in the compound of formula (II), the stereoisomer or the pharmaceutically acceptable salt, solvates and prodrugs thereof, each R_{7c} and R_{7d} are

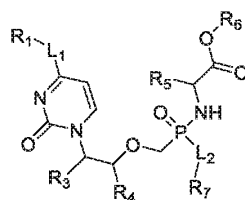
independently selected from hydrogen, C₁-C₆ alkyl (such as methyl, ethyl, propyl, isopropyl and isobutyl), C₁-C₆ haloalkyl and phenyl.

In a more preferred embodiment, in the compound of formula (II), the stereoisomer or the

pharmaceutically acceptable salt, solvates and prodrugs thereof, each  is selected



In another embodiment, described here are compounds formula (III), a stereoisomer thereof, or a pharmaceutically acceptable salt, solvates and prodrugs thereof:



formula (III)

Wherein,

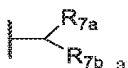
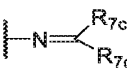
L₁ is independently selected from -O- or -NH-;

R₁ is independently selected from hydrogen, C₁-C₆ alkyl, deuterated C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₈ cycloalkyl, 4 to 7 membered heterocyclyl, C₆-C₁₀ aryl and 5 to 10 membered heteroaryl, wherein the C₃-C₈ cycloalkyl, 4 to 7 membered heterocyclyl, C₆-C₁₀ aryl and 5 to 10 membered heteroaryl are each optionally further substituted by one or more deuterium, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, halogen, hydroxy, amino, nitro, cyano and ester group;

R₃ and R₄ are each independently selected from hydrogen, deuterium, halogen, hydroxy, amino, C₁-C₆ alkyl, deuterated C₁-C₆ alkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ haloalkyl and C₁-C₆ alkoxy;

Or R₃ and R₄ together with the atoms to which they are attached can form a 3 to 7 membered heterocycle comprising 1-2 heteroatoms selected from O, N and S;

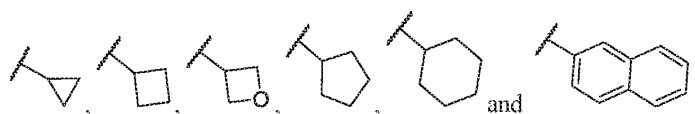
R₅ and R₆ are each independently selected from hydrogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₃-C₈ cycloalkyl, 4 to 7 membered heterocyclyl, C₆-C₁₀ aryl, benzyl and 5 to 10 membered heteroaryl, wherein the C₃-C₈ cycloalkyl, 4 to 7 membered heterocyclyl, C₆-C₁₀ aryl, benzyl and 5 to 10 membered heteroaryl are each optionally further substituted by one or more deuterium, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, halogen, hydroxy, amino, nitro, cyano and ester group; L₂ is independently selected from -O- or -NH-;

R₇ is independently selected from  and .

R_{7a}, R_{7b}, R_{7c} and R_{7d} are each independently selected from hydrogen, deuterium, C₁-C₆ alkyl, deuterated C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -C(O)O-C₁-C₆ alkyl, -C₃-C₈ cycloalkyl, 4 to 7 membered heterocyclyl, C₆-C₁₀ aryl and 5 to 10 membered heteroaryl, wherein the C₃-C₈ cycloalkyl, 4 to 7 membered heterocyclyl, C₆-C₁₀ aryl and 5 to 10 membered heteroaryl are each optionally further substituted by one or more deuterium, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, halogen, hydroxy, amino, nitro, cyano and ester group;

Or R_{7c} and R_{7d} together with the atom to which they are attached can form a C₃-C₈ carbocycle or a 3 to 7 membered heterocycle comprising 1-2 heteroatoms selected from O, N and S.

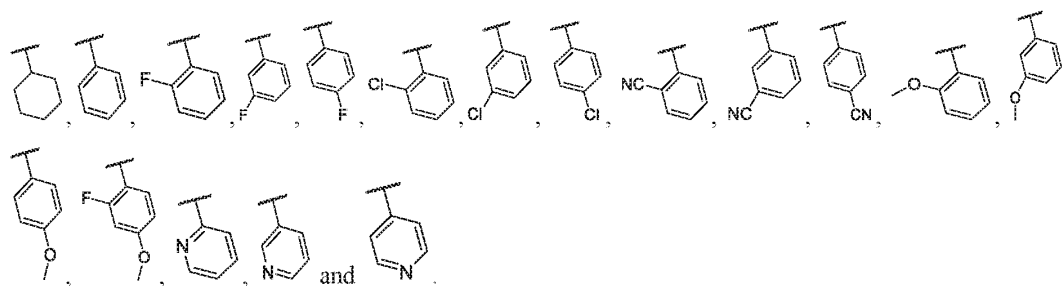
In a more preferred embodiment, in the compound of formula (III), the stereoisomer or the pharmaceutically acceptable salt, solvates and prodrugs thereof, each R₁ is independently selected from hydrogen, C₁-C₆ alkyl (such as methyl, ethyl, propyl and isopropyl), C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ hydroxyalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl,



In a more preferred embodiment, in the compound of formula (III), the stereoisomer or the pharmaceutically acceptable salt, solvates and prodrugs thereof, each R₄ is independently selected from hydrogen, C₁-C₆ alkyl (such as methyl, ethyl, propyl and isopropyl), C₁-C₆ haloalkyl, C₁-C₆ alkoxy and C₁-C₆ hydroxyalkyl.

In a more preferred embodiment, in the compound of formula (III), the stereoisomer or the pharmaceutically acceptable salt, solvates and prodrugs thereof, each R_5 is independently selected from hydrogen, C₁-C₆ alkyl (such as methyl, ethyl, propyl and isopropyl), C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ hydroxyalkyl and benzyl.

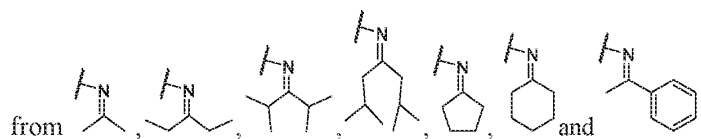
In a more preferred embodiment, in the compound of formula (III), the stereoisomer or the pharmaceutically acceptable salt, solvates and prodrugs thereof, each R_{7a} and R_{7b} are independently selected from hydrogen, C₁-C₆ alkyl (such as methyl, ethyl, propyl and isopropyl), C₁-C₆ haloalkyl (such as difluoromethyl, trifluoromethyl, 1,1-difluoroethyl, 1,1,2-trifluoroethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, 1,1,2,2-tetrafluoroethyl, 1,1,2,2-tetrafluoropropyl and 1,1,1-trifluoro-2-methylpropan-2-yl, -C(O)O-C₁-C₆ alkyl,



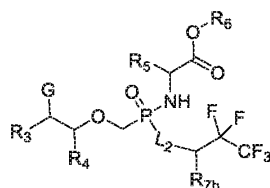
In a more preferred embodiment, in the compound of formula (III), the stereoisomer or the pharmaceutically acceptable salt, solvates and prodrugs thereof, each R_{7c} and R_{7d} are independently selected from hydrogen, C₁-C₆ alkyl (such as methyl, ethyl, propyl, isopropyl and isobutyl), C₁-C₆ haloalkyl and phenyl.

In a more preferred embodiment, in the compound of formula (III), the stereoisomer or the

pharmaceutically acceptable salt, solvates and prodrugs thereof, each $\begin{array}{c} R_{7c} \\ \diagup \\ N \\ \diagdown \\ R_{7d} \end{array}$ is selected



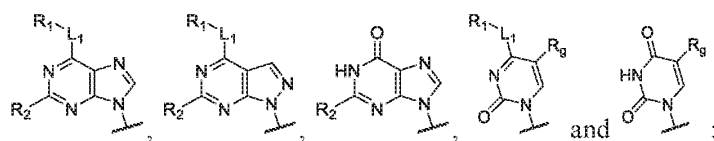
In another embodiment, described here are compounds formula (IV), a stereoisomer thereof, or a pharmaceutically acceptable salt, solvates and prodrugs thereof.



formula (IV)

Wherein,

G is independently selected from



L_1 is independently selected from -O- or -NH-;

R_1 is independently selected from hydrogen, C_1 - C_6 alkyl, deuterated C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_8 cycloalkyl, 4 to 7 membered heterocyclyl, C_6 - C_{10} aryl and 5 to 10 membered heteroaryl, wherein the C_3 - C_8 cycloalkyl, 4 to 7 membered heterocyclyl, C_6 - C_{10} aryl and 5 to 10 membered heteroaryl are each optionally further substituted by one or more deuterium, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, halogen, hydroxy, amino, nitro, cyano and ester group;

R_2 is independently selected from hydrogen, amino, hydroxy, halogen, cyano, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, C_2 - C_6 alkenyl and C_2 - C_6 alkynyl;

R_3 is independently selected from hydrogen, amino, hydroxy, halogen, cyano, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 alkoxy and C_1 - C_6 haloalkoxy;

R_3 and R_4 are each independently selected from hydrogen, deuterium, halogen, hydroxy, amino, C_1 - C_6 alkyl, deuterated C_1 - C_6 alkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 haloalkyl and C_1 - C_6 alkoxy;

Or R_3 and R_4 together with the atoms to which they are attached can form a 3 to 7 membered heterocycle comprising 1-2 heteroatoms selected from O, N and S;

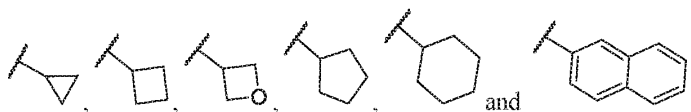
R_5 and R_6 are each independently selected from hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, C_3 - C_8 cycloalkyl, 4 to 7 membered heterocyclyl, C_6 - C_{10} aryl, benzyl and 5 to 10 membered heteroaryl, wherein the C_3 - C_8 cycloalkyl, 4 to 7

membered heterocyclyl, C₆-C₁₀ aryl, benzyl and 5 to 10 membered heteroaryl are each optionally further substituted by one or more deuterium, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, halogen, hydroxy, amino, nitro, cyano and ester group;

L₂ is independently selected from -O- or -NH-;

R_{7b} is independently selected from hydrogen, deuterium, C₁-C₆ alkyl, deuterated C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -C(O)O-C₁-C₆ alkyl, -C₃-C₈ cycloalkyl, 4 to 7 membered heterocyclyl, C₆-C₁₀ aryl and 5 to 10 membered heteroaryl, wherein the C₃-C₈ cycloalkyl, 4 to 7 membered heterocyclyl, C₆-C₁₀ aryl and 5 to 10 membered heteroaryl are each optionally further substituted by one or more deuterium, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, halogen, hydroxy, amino, nitro, cyano and ester group; a 3 to 7 membered heterocycle comprising 1-2 heteroatoms selected from O, N and S.

In a more preferred embodiment, in the compound of formula (IV), the stereoisomer or the pharmaceutically acceptable salt, solvates and prodrugs thereof, each R₁ is independently selected from hydrogen, C₁-C₆ alkyl (such as methyl, ethyl, propyl and isopropyl), C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ hydroxyalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl,

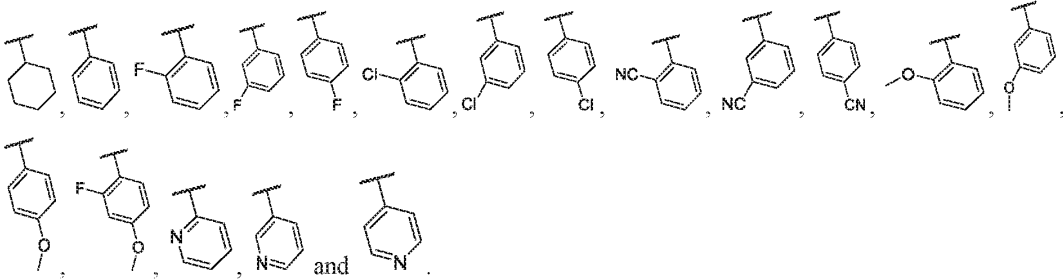


In a more preferred embodiment, in the compound of formula (IV), the stereoisomer or the pharmaceutically acceptable salt, solvates and prodrugs thereof, each R₄ is independently selected from hydrogen, C₁-C₆ alkyl (such as methyl, ethyl, propyl and isopropyl), C₁-C₆ haloalkyl, C₁-C₆ alkoxy and C₁-C₆ hydroxyalkyl.

In a more preferred embodiment, in the compound of formula (IV), the stereoisomer or the pharmaceutically acceptable salt, solvates and prodrugs thereof, each R₅ is independently selected from hydrogen, C₁-C₆ alkyl (such as methyl, ethyl, propyl and isopropyl), C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ hydroxyalkyl and benzyl.

In a more preferred embodiment, in the compound of formula (IV), the stereoisomer or the pharmaceutically acceptable salt, solvates and prodrugs thereof, each R_{7b} is independently selected from hydrogen, C₁-C₆ alkyl (such as methyl, ethyl, propyl and isopropyl), C₁-C₆

haloalkyl (such as difluoromethyl, trifluoromethyl, 1,1-difluoroethyl, 1,1,2-trifluoroethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, 1,1,2,2-tetrafluoroethyl, 1,1,2,2-tetrafluoropropyl and 1,1,1-trifluoro-2-methylpropan-2-yl, -C(O)O-C₁-C₆ alkyl,



In the most preferred embodiment, the compound of formula (I), (I-1), (I-2), (I-3), (I-4), (II), (III) or (IV), the stereoisomer or the pharmaceutically acceptable salt, solvates and prodrugs thereof is selected from the table 1:

Table 1. Representative Compounds of formula (I), (I-1), (I-2), (I-3), (I-4), (II), (III) or (IV).

#	Structure	Name
1		ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3,3-pentafluoropropoxy)phosphoryl)-L-alaninate
2		ethyl (((2-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3,3-pentafluoropropoxy)phosphoryl)-L-alaninate
3		ethyl (((2-(2-amino-6-ethoxy-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3,3-pentafluoropropoxy)phosphoryl)-L-alaninate
4		ethyl (((2-(2-amino-6-isopropoxy-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3,3-pentafluoropropoxy)phosphoryl)-L-alaninate

5		ethyl (((2-(2-amino-6-propoxy-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3,3-pentafluoropropoxy)phosphoryl)-L-alaninate
6		ethyl (((2-(2-amino-6-(2-hydroxyethoxy)-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3,3-pentafluoropropoxy)phosphoryl)-L-alaninate
7		ethyl (((2-(2-amino-6-(2-methoxyethoxy)-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3,3-pentafluoropropoxy)phosphoryl)-L-alaninate
8		ethyl (((2-(2-amino-6-butoxy-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3,3-pentafluoropropoxy)phosphoryl)-L-alaninate
9		ethyl (((2-(2-amino-6-cyclopropoxy-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3,3-pentafluoropropoxy)phosphoryl)-L-alaninate
10		ethyl (((2-(2-amino-6-cyclobutoxy-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3,3-pentafluoropropoxy)phosphoryl)-L-alaninate
11		ethyl (((2-(2-amino-6-(cyclopentyloxy)-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3,3-pentafluoropropoxy)phosphoryl)-L-alaninate
12		ethyl (((2-(2-amino-6-(cyclohexyloxy)-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3,3-pentafluoropropoxy)phosphoryl)-L-alaninate
13		ethyl (((2-(6-(allylamino)-2-amino-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3,3-pentafluoropropoxy)phosphoryl)-L-alaninate

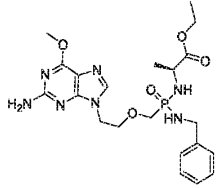
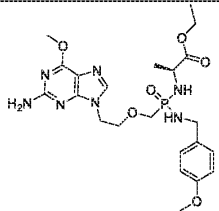
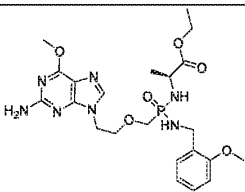
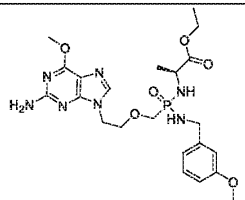
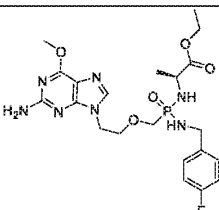
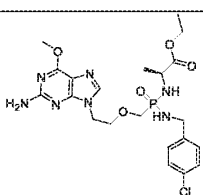
14		ethyl (((2-(2-amino-6-(oxetan-3-ylamino)-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3,3-pentafluoropropoxy)phosphoryl)-L-alaninate
15		ethyl (((2-(2-amino-6-(cyclopropylamino)-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3,3-pentafluoropropoxy)phosphoryl)-L-alaninate
16		ethyl (((2-(2-amino-6-(prop-2-yn-1-ylamino)-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3,3-pentafluoropropoxy)phosphoryl)-L-alaninate
17		ethyl (((2-(2-amino-6-(naphthalen-2-ylamino)-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3,3-pentafluoropropoxy)phosphoryl)-L-alaninate
18		ethyl (((1-(2-amino-6-methoxy-9H-purin-9-yl)propan-2-yl)oxy)methyl)(2,2,3,3,3-pentafluoropropoxy)phosphoryl)-L-alaninate
19		ethyl (((1-(2-amino-6-methoxy-9H-purin-9-yl)-3-hydroxypropan-2-yl)oxy)methyl)(2,2,3,3,3-pentafluoropropoxy)phosphoryl)-L-alaninate
20		ethyl (((1-(2-amino-6-methoxy-9H-purin-9-yl)-3-fluoropropan-2-yl)oxy)methyl)(2,2,3,3,3-pentafluoropropoxy)phosphoryl)-L-alaninate
21		ethyl (((1-(2-amino-6-methoxy-9H-purin-9-yl)-3-methoxypropan-2-yl)oxy)methyl)(2,2,3,3,3-pentafluoropropoxy)phosphoryl)-L-alaninate
22		isopropyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3,3-pentafluoropropoxy)phosphoryl)-L-alaninate

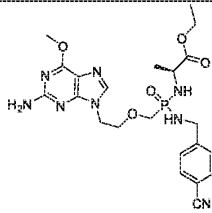
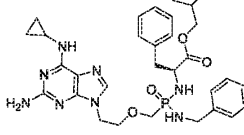
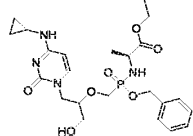
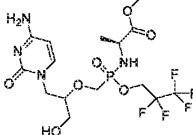
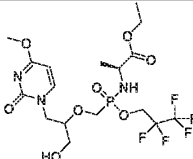
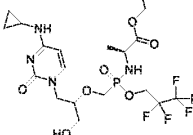
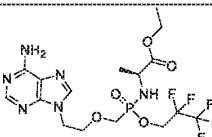
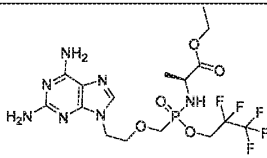
23		pentan-3-yl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3,3-pentafluoropropoxy)phosphoryl)-L-alaninate
24		ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3,3-pentafluoropropoxy)phosphoryl)-L-phenylalaninate
25		ethyl (((2-(2-amino-6-(cyclopropylamino)-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3,3-pentafluoropropoxy)phosphoryl)-L-phenylalaninate
26		ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(2,2,2-trifluoroethoxy)phosphoryl)-L-alaninate
27		ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(3,3,3-trifluoropropoxy)phosphoryl)-L-alaninate
28		ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)((3,3,4,4,4-pentafluorobutan-2-yl)oxy)phosphoryl)-L-alaninate
29		ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3,3-pentafluoro-1-phenylpropoxy)phosphoryl)-L-alaninate
30		ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3,3-pentafluoro-1-(2-fluorophenyl)propoxy)phosphoryl)-L-alaninate

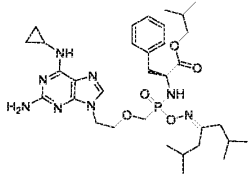
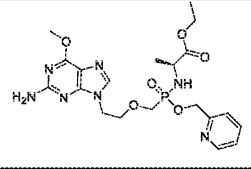
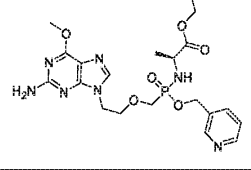
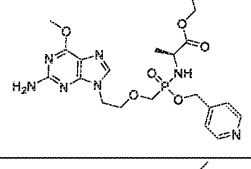
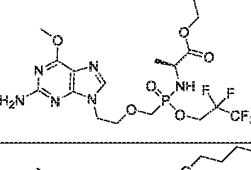
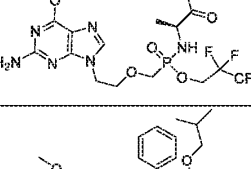
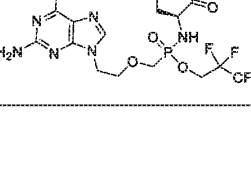
31		ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3,3-pentafluoro-1-(4-fluorophenyl)propoxy)phosphoryl)-L-alaninate
32		ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3,3-pentafluoro-1-(3-fluorophenyl)propoxy)phosphoryl)-L-alaninate
33		ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3,3-pentafluoro-1-(4-methoxyphenyl)propoxy)phosphoryl)-L-alaninate
34		ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3,3-pentafluoro-1-(2-fluoro-4-methoxyphenyl)propoxy)phosphoryl)-L-alaninate
35		ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(1-cyclohexyl-2,2,3,3,3-pentafluoropropoxy)phosphoryl)-L-alaninate
36		ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3-tetrafluorobutoxy)phosphoryl)-L-alaninate
37		ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)((3,3,4,4,4-pentafluorobutan-2-yl)oxy)phosphoryl)-L-alaninate

38		ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3-tetrafluoropropoxy)phosphoryl)-L-alaninate
39		ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(3,3,3-trifluoro-2,2-dimethylpropoxy)phosphoryl)-L-alaninate
40		ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(2,2,3-trifluoropropoxy)phosphoryl)-L-alaninate
41		ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(2,2-difluoroethoxy)phosphoryl)-L-alaninate
42		ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(2,2-difluoropropoxy)phosphoryl)-L-alaninate
43		ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3,3-pentafluoro-1-phenylpropoxy)phosphoryl)-L-alaninate
44		ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)((propan-2-ylideneamino)oxy)phosphoryl)-L-alaninate
45		ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)((2,4-dimethylpentan-3-ylidene)amino)oxy)phosphoryl)-L-alaninate

46		ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)((2,6-dimethylheptan-4-ylidene)amino)oxy)phosphoryl)-L-alaninate
47		ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)((cyclopentylideneamino)oxy)phosphoryl)-L-alaninate
48		ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)((cyclohexylideneamino)oxy)phosphoryl)-L-alaninate
49		ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)((Z)-1-phenylethylidene)amino)oxy)phosphoryl)-L-alaninate
50		ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(1-phenylethoxy)phosphoryl)-L-alaninate
51		ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(2,2,2-trifluoro-1-phenylethoxy)phosphoryl)-L-alaninate
52		ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(2-methoxy-2-oxo-1-phenylethoxy)phosphoryl)-L-alaninate

53		ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(benzylamino)phosphoryl)-L-alaninate
54		ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)((4-methoxybenzyl)amino)phosphoryl)-L-alaninate
55		ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)((2-methoxybenzyl)amino)phosphoryl)-L-alaninate
56		ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)((3-methoxybenzyl)amino)phosphoryl)-L-alaninate
57		ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)((4-fluorobenzyl)amino)phosphoryl)-L-alaninate
58		ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)((4-chlorobenzyl)amino)phosphoryl)-L-alaninate

59		ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)((4-cyanobenzyl)amino)phosphoryl)-L-alaninate
60		isobutyl (((2-(2-amino-6-(cyclopropylamino)-9H-purin-9-yl)ethoxy)methyl)(benzylamino)phosphoryl)-L-phenylalaninate
61		ethyl ((benzyloxy)(((1-(4-(cyclopropylamino)-2-oxopyrimidin-1(2H)-yl)-3-hydroxypropan-2-yl)oxy)methyl)phosphoryl)-L-alaninate
62		ethyl (((((1-(4-amino-2-oxopyrimidin-1(2H)-yl)-3-hydroxypropan-2-yl)oxy)methyl)(2,2,3,3,3-pentafluoropropoxy)phosphoryl)-L-alaninate
63		ethyl (((((1-hydroxy-3-(4-methoxy-2-oxopyrimidin-1(2H)-yl)propan-2-yl)oxy)methyl)(2,2,3,3,3-pentafluoropropoxy)phosphoryl)-L-alaninate
64		ethyl (((((1-(4-(cyclopropylamino)-2-oxopyrimidin-1(2H)-yl)-3-hydroxypropan-2-yl)oxy)methyl)(2,2,3,3,3-pentafluoropropoxy)phosphoryl)-L-alaninate
65		ethyl (((2-(6-amino-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3,3-pentafluoropropoxy)phosphoryl)-L-alaninate
66		ethyl (((2-(2,6-diamino-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3,3-pentafluoropropoxy)phosphoryl)-L-alaninate

67		isobutyl (((2-(2-amino-6-(cyclopropylamino)-9H-purin-9-yl)ethoxy)methyl)((2,6-dimethylheptan-4-ylidene)amino)oxy)phosphoryl)-L-phenylalaninate
68		ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(pyridin-2-ylmethoxy)phosphoryl)-L-alaninate
69		ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(pyridin-3-ylmethoxy)phosphoryl)-L-alaninate
70		ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(pyridin-4-ylmethoxy)phosphoryl)-L-alaninate
71		isobutyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3,3-pentafluoropropoxy)phosphoryl)-L-alaninate
72		butyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3,3-pentafluoropropoxy)phosphoryl)-L-alaninate
73		isobutyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3,3-pentafluoropropoxy)phosphoryl)-L-phenylalaninate

In one embodiment, the present invention provides a pharmaceutical composition comprising a compound of formula (I), (I-1), (I-2), (I-3), (I-4), (II), (III) or (IV), the stereoisomer or a pharmaceutically acceptable salt, prodrug, or solvate salt thereof and one or more pharmaceutically acceptable carriers or excipients.

In one embodiment, the compounds of formula (I), (I-1), (I-2), (I-3), (I-4), (II), (III) or (IV), the stereoisomer or a pharmaceutically acceptable salt, prodrug, or solvate salt thereof described herein may be used in prophylaxis or treatment of diseases caused by viral infection, preferably as an antiviral agent against human papillomavirus (HPV).

In one embodiment, the compounds of formula (I), (I-1), (I-2), (I-3), (I-4), (II), (III) or (IV), the stereoisomer or a pharmaceutically acceptable salt, prodrug, or solvate salt thereof described herein for the preparation of a medicament for the prophylaxis or treatment of the diseases or conditions caused by viral infection, preferably as an antiviral agent against human papillomavirus (HPV).

In some embodiments, the human papillomavirus can be a high-risk human papillomavirus, such as those described herein. For example, the high-risk human papillomavirus can be selected from HPV-16, HPV-18, HPV-31, HPV-33, HPV-35, HPV-39, HPV-45, HPV-51, HPV- 52, HPV-56, HPV-58, HPV-59, HPV-68, HPV-73 and HPV-82. In one embodiment, the human papillomavirus can be HPV-16. In embodiments, the human papillomavirus can be HPV-18. In one embodiment, the human papillomavirus can be one or more of the following high-risk types: HPV-31, HPV-33, HPV-35, HPV-39, HPV-45, HPV-51, HPV-52, HPV-56, HPV-58, HPV-59, HPV-68, HPV-73 and HPV-82.

In some embodiments, the human papillomavirus can be a low-risk human papillomavirus, including those described herein. In one embodiment, the human papillomavirus can be HPV-6. In embodiments, the human papillomavirus can be HPV- 11.

In some embodiments, the diseases or conditions caused by HPV infection can be the result of clinical or sub-clinical papillomavirus infections. Such diseases or conditions, herein sometimes called "HPV associated disorders" or "pathological processes mediated by HPV infection", include, e.g., epithelial malignancies, skin cancer (non-melanoma or melanoma), anogenital malignancies such as cervical cancer, HPV associated precancerous lesions (including LSIL or HSIL cervical tissue), anal carcinoma, malignant lesions, benign lesions, papillomacarcinomas, papilloadenocystomas, papilloma neuropathicum, papillomatosis, cutaneous and mucosal papillomas, condylomas, fibroblastic tumors, and other pathological conditions associated with papillomavirus.

In some embodiments, the diseases or conditions caused by HPV infection can be benign skin warts or common warts. Such warts include, e.g., common warts (*verruca vulgaris*), for example, palmar, plantar, and periungual warts; flat and filiform warts; anal, oral, pharyngeal, laryngeal, and tongue papillomas; and venereal warts (*condyloma accuminata*), also known as genital warts (for example, penile, vulvar, vaginal and cervical warts), which are one of the most serious manifestations of HPV infection.

In one embodiment, a compound of formula (I), (I-1), (I-2), (I-3), (I-4), (II), (III) or (IV), the stereoisomer or a pharmaceutically acceptable salt, prodrug, or solvate may be used in combination with one or more additional therapeutic agents in the prophylaxis or treatment of viral infection.

In one embodiment, methods of the prophylaxis or treatment of a viral infection, especially HPV infection, comprise administering to a subject in need thereof a compound of formula(I), (I-1), (I-2), (I-3), (I-4), (II), (III) or (IV), the stereoisomer or a pharmaceutically acceptable salt, solvate or prodrug thereof, or a pharmaceutical formulation thereof are provided.

DETAILED DESCRIPTION OF THE INVENTION

The present invention may be understood more readily by reference to the following detailed description of the preferred embodiments of the invention and the Examples included herein. It is to be understood that the terminology used herein is for the purpose of describing specific embodiments only and is not intended to be limiting.

Further, one or more hydrogen atoms, carbon atoms or other atoms of the compound of formula (I), (I-1), (I-2), (I-3), (I-4), (II), (III) or (IV), the stereoisomer or a pharmaceutically acceptable salt, prodrug, or solvate salt thereof can be substituted by an isotope of a hydrogen atom, a carbon atom or other atoms, respectively. In addition, the compound of formula (I), (I-1), (I-2), (I-3), (I-4), (II), (III) or (IV), the stereoisomer or a pharmaceutically acceptable salt, prodrug, or solvate salt thereof includes all radioactive labeled bodies thereof. Such the "radioactive labeling" and "radioactive labeled form" of the compound of formula (I), (I-1), (I-2), (I-3), (I-4), (II), (III) or (IV), the stereoisomer or a pharmaceutically acceptable salt, prodrug, or solvate salt thereof are included in the present invention, respectively, and are useful as a study and/or diagnostic tool in metabolized drug dynamic state study and binding assay. Examples of an

isotope which can be incorporated into the compound of the compound of formula (I), (I-1), (I-2), (I-3), (I-4), (II), (III) or (IV), the stereoisomer or a pharmaceutically acceptable salt, prodrug, or solvate salt thereof of the present invention include a hydrogen atom, a carbon atom, a nitrogen atom, an oxygen atom, a phosphorus atom, a sulfur atom, a fluorine atom and a chlorine atom, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl . A particularly preferable example of an isotope which can be incorporated into the compound of formula (I), (I-1), (I-2), (I-3), (I-4), (II), (III) or (IV), the stereoisomer or a pharmaceutically acceptable salt, prodrug, or solvate salt thereof of the present invention is ^2H (i.e., heavy hydrogen atom), and can be prepared by the method shown in Reference examples of the present description, or the method well-known in the art. In addition, a heavy hydrogen atom is expressed as "D" in Reference examples of the present description. The compound of (I), (I-1), (I-2), (I-3), (I-4), (II), (III) or (IV), the stereoisomer or a pharmaceutically acceptable salt, prodrug, or solvate salt thereof of the present invention in which a hydrogen atom has been converted into a heavy hydrogen atom are excellent in respect of bioavailability, metabolism safety, drug efficacy, and toxicity as compared with unconverted forms, in some cases, and can be useful as medicaments.

As used herein, the term "n-membered" where n is an integer typically describes the number of ring-forming atoms in a moiety where the number of ring-forming atoms is n. For example, pyridine is an example of a 6-membered heteroaryl ring and thiophene is an example of a 5-membered heteroaryl ring.

The term "alkyl" refers to a saturated aliphatic hydrocarbon group, which is a straight or branched chain group comprising 1 to 20 carbon atoms, preferably an alkyl having 1 to 8 carbon atoms, more preferably an alkyl having 1 to 6 carbon atoms ($\text{C}_1\text{-C}_6$ alkyl), and most preferably an alkyl having 1 to 3 carbon atoms. Non-limiting examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, sec-butyl, n-pentyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, 1-ethylpropyl, 2-methylbutyl, 3-methylbutyl, n-hexyl, 1-ethyl-2-methylpropyl, 1,1,2-trimethylpropyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1,3-dimethylbutyl, 2-ethylbutyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2,3-dimethylbutyl, n-heptyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 2,3-dimethylpentyl, 2,4-dimethylpentyl, 2,2-dimethylpentyl, 3,3-dimethylpentyl, 2-ethylpentyl, 3-ethylpentyl, n-octyl, 2,3-dimethylhexyl, 2,4-dimethylhexyl, 2,5-dimethylhexyl, 2,2-

dimethylhexyl, 3,3-dimethylhexyl, 4,4-dimethylhexyl, 2-ethylhexyl, 3-ethylhexyl, 4-ethylhexyl, 2-methyl-2-ethylpentyl, 2-methyl-3-ethylpentyl, n-nonyl, 2-methyl-2-ethylhexyl, 2-methyl-3-ethylhexyl, 2,2-diethylpentyl, n-decyl, 3,3-diethylhexyl, 2,2-diethylhexyl, and various branched isomers thereof. For example, the term "C₁₋₄alkyl" means an alkyl group having 1 to 4 carbon atoms. Specifically, C₁₋₄ alkyl is intended to include C₁ alkyl (methyl), C₂ alkyl (ethyl), C₃ alkyl (n-propyl, isopropyl), C₄ alkyl (i.e., n-butyl, t-butyl, isobutyl, sec-butyl). The alkyl group can be substituted or unsubstituted. When substituted, the substituent group(s) can be substituted at any available connection point. The substituent group(s) is preferably one or more groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylamino, halogen, thiol, hydroxy, nitro, cyano, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkoxy, heterocycloxy, cycloalkylthio, heterocyclylthio, oxo, carboxy and carboxylate group, and preferably methyl, ethyl, isopropyl, tert-butyl, haloalkyl, deuterated alkyl, alkoxy-substituted alkyl and hydroxy-substituted alkyl.

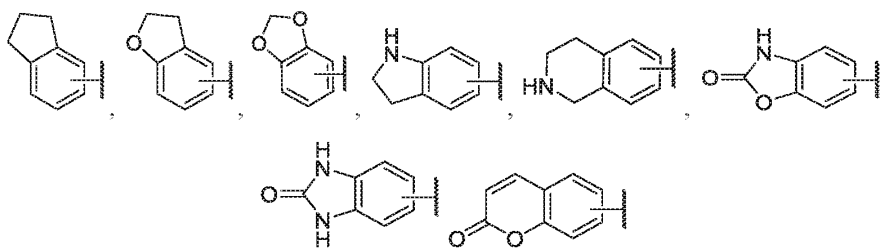
The term "alkenyl" as used herein refers to an unsaturated linear (i.e., unbranched) or branched univalent hydrocarbon chain or combination thereof, having at least one site of olefinic unsaturation (i.e., having at least one moiety of the formula a C=C) and having the number of carbon atoms designated. The alkenyl group may be in "cis" or "trans" configurations, or alternatively in "E" or "Z" configurations. The alkenyl is preferably an alkenyl having 2 to 8 carbon atoms, more preferably an alkenyl having 2 to 6 carbon atoms (C₂-C₆ alkenyl), and most preferably an alkenyl having 2 to 3 carbon atoms. The alkenyl can be further substituted by other related group, for example alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylamino, halogen, thiol, hydroxy, nitro, cyano, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkoxy, heterocycloxy, cycloalkylthio, heterocyclylthio, carboxy or carboxylate group.

The term "alkynyl" as used herein refers to an unsaturated linear (i.e., unbranched) or branched univalent hydrocarbon chain or combination thereof, having at least one site of acetylenic unsaturation (i.e., having at least one moiety of the formula C≡C) having the number of carbon atoms designated. The alkynyl is preferably an alkynyl having 2 to 8 carbon atoms, more preferably an alkynyl having 2 to 6 carbon atoms (C₂-C₆ alkenyl), and most preferably an alkynyl having 2 to 3 carbon atoms. The alkynyl can be further substituted by other related group, for example alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylamino, halogen, thiol,

hydroxy, nitro, cyano, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkoxy, heterocycloxy, cycloalkylthio, heterocyclthio, carboxy or carboxylate group.

The term "cycloalkyl" refers to a saturated or partially unsaturated monocyclic or polycyclic hydrocarbon substituent group having 3 to 20 carbon atoms, preferably 3 to 8 carbon atoms (i.e., (C₃₋₈ cycloalkyl means a cycloalkyl with three to eight carbon atoms), and more preferably 3 to 6 carbon atoms. Non-limiting examples of monocyclic cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, cycloheptyl, cycloheptatrienyl, cyclooctyl and the like. Polycyclic cycloalkyl includes a cycloalkyl having a spiro ring, fused ring or bridged ring. The cycloalkyl is preferably cyclopropyl, cyclobutyl, cyclohexyl, cyclopentyl and cycloheptyl. The cycloalkyl can be further substituted by other related group, for example alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylamino, halogen, thiol, hydroxy, nitro, cyano, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkoxy, heterocycloxy, cycloalkylthio, heterocyclthio, carboxy or carboxylate group.

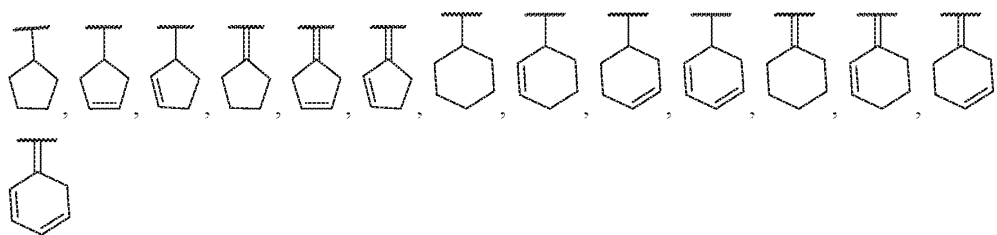
The term "aryl" as used herein refers to an unsaturated aromatic carbocyclic group having a single ring (e.g., phenyl) or multiple condensed rings (e.g., naphthyl or anthryl) which condensed rings may or may not be aromatic. Particular C₆₋₁₀ aryl groups are those having from 6 to 10 annular (i.e., ring) carbon atoms (for example, phenyl and naphthyl). An aryl group having more than one ring where at least one ring is non-aromatic may be connected to the parent structure at either an aromatic ring position or at a non-aromatic ring position. In one variation, an aryl group having more than one ring where at least one ring is non-aromatic is connected to the parent structure at an aromatic ring position. Non-limiting examples thereof include:



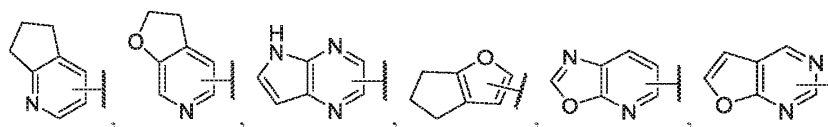
The aryl group can be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylamino, halogen, thiol, hydroxy, nitro, cyano, cycloalkyl,

heterocyclyl, aryl, heteroaryl, cycloalkoxy, heterocyclyloxy, cycloalkylthio, heterocyclthio, carboxy and carboxylate group.

The term "carbocycle" as used herein refers to a non-aromatic carbon only containing ring system which can be saturated or contains one or more units of unsaturation, having three to fourteen ring carbon atoms. In some embodiments, the number of carbon atoms is 3 to 8 (C_3 - C_8 carbocycle). Examples of C_3 - C_8 carbocycle include, but are not limited to, cycloalkyl and cycloalkenyl groups. Non-limiting examples thereof include:



The term "heteroaryl" as used herein refers to an unsaturated aromatic cyclic group having annular (i.e., ring) carbon atoms and at least one annular heteroatom, including but not limited to heteroatoms such as nitrogen, phosphorus, oxygen and sulfur. A heteroaryl group may have a single ring (e.g., pyridyl, furyl) or multiple condensed rings (e.g., indoliziny, benzothienyl) which condensed rings may or may not be aromatic. In some embodiments, the heteroatoms disclosed herein are selected from O, S and N. And the term "a 5- to 10-membered heteroaryl" is specifically intended to include any 5-, 6-, 7-, 8-, 9-, or 10-membered heteroaryl group. The heteroaryl is more preferably 5 or 6 membered heteroaryl, for example, imidazolyl, thienyl, thiazolyl, pyrazolyl, oxazolyl, pyrrolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, thiadiazolyl, pyrazinyl and the like, preferably triazolyl, thienyl, imidazolyl, pyrazolyl or pyrimidinyl, thiazolyl; and more preferably triazolyl, pyrrolyl, thienyl, thiazolyl and pyrimidinyl. Non-limiting examples thereof include:



The heteroaryl group can be optionally substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more groups independently selected from the group

consisting of alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylamino, halogen, thiol, hydroxy, nitro, cyano, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkoxy, heterocycloxy, cycloalkylthio, heterocyclthio, carboxy and carboxylate group.

The term “heterocyclyl” refers to a 3 to 20 membered saturated or partially unsaturated monocyclic or polycyclic hydrocarbon substituent group, wherein one or more ring atoms are heteroatoms selected from the group consisting of N, O and S(O)_m (wherein m is an integer of 0 to 2), but excluding —O—O—, —O—S— or —S—S— in the ring, with the remaining ring atoms being carbon atoms. Preferably, the heterocyclyl has 3 to 12 ring atoms wherein 1 to 4 atoms are heteroatoms; more preferably, the heterocyclyl has 4 to 10 ring atoms; and most preferably 4 to 7 ring atoms. For example, the term “4- to 10-membered heterocyclyl” means the heterocyclyl having 4 to 10 ring atoms. Non-limiting examples of monocyclic heterocyclyl include pyrrolidinyl, imidazolidinyl, tetrahydrofuranyl, tetrahydrothienyl, dihydroimidazolyl, dihydrofuryl, dihydropyrazolyl, dihydropyrrolyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, homopiperazinyl, pyranyl and the like, and preferably tetrahydrofuranyl, and tetrahydropyranyl, pyrazolyl, morpholinyl, piperazinyl and pyranyl. Polycyclic heterocyclyl includes a heterocyclyl having a spiro ring, fused ring or bridged ring. The heterocyclyl having a spiro ring, fused ring or bridged ring is optionally bonded to another group via a single bond, or further bonded to other cycloalkyl, heterocyclyl, aryl and heteroaryl via any two or more atoms on the ring. The heterocyclyl group can be optionally substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylamino, halogen, thiol, hydroxy, nitro, cyano, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkoxy, heterocycloxy, cycloalkylthio, heterocyclthio, oxo, carboxy and carboxylate group.

The term “halo” or “halogen” refers to fluorine, chlorine, bromine or iodine.

The term “haloalkyl” refers to an alkyl group substituted with one or more halogen that may be the same or different, wherein the alkyl is as defined above. For example, “C₁₋₆ haloalkyl” as used herein, refers to a C₁₋₆ alkyl group wherein the alkyl group is substituted with one or more halogen atoms. Examples of C₁₋₆ haloalkyl include, but are not limited to, chloromethyl, dichloromethyl, trichloromethyl, dichloroethyl, dichloropropyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1,1-difluoroethyl, 1,1,2-trifluoroethyl, 2,2,2-trifluoroethyl, 1,1,2,2-

tetrafluoroethyl, pentafluoroethyl, difluoropropyl, 1,1,2,2-tetrafluoropropyl, heptafluoropropyl, 1,1,1-trifluoro-2-methylpropan-2-yl, difluorochloromethyl and dichlorofluoromethyl.

The term “alkoxy” refers to an —O-(alkyl) or an —O- (unsubstituted cycloalkyl) group, wherein the alkyl is as defined above. The alkoxy is preferably an alkoxy having 1 to 8 carbon atoms, more preferably an alkoxy having 1 to 6 carbon atoms (C₁-C₆ alkoxy), and most preferably an alkoxy having 1 to 3 carbon atoms. Non-limiting examples of alkoxy include methoxy, ethoxy, propoxy, butoxy, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy. The alkoxy group can be optionally substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylamino, halogen, thiol, hydroxy, nitro, cyano, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkoxy, heterocyclyloxy, cycloalkylthio, heterocyclylthio, carboxy and carboxylate group.

The term “haloalkoxy” refers to an alkoxy group substituted by one or more halogens, wherein the alkoxy is as defined above.

The term “deuterium” refers to an isotope of hydrogen that has one proton and one neutron in its nucleus and that has twice the mass of ordinary hydrogen, the symbol of deuterium is “D”.

The term “deuterated alkyl” refers to an alkoxy group substituted by one or more deuterium, wherein the alkyl is as defined above.

The term “hydroxyalkyl” refers to an alkoxy group substituted by one or more hydroxy, wherein the alkyl is as defined above.

The term “ester group” refers to an “-C(O)O-” group connected with an alkyl, wherein the alkyl is as defined above, such as “-C(O)O-C₁-C₆ alkyl”.

The term “amino” refers to a —NH₂ group.

The term “nitro” refers to a —NO₂ group.

The term “hydroxy” refers to an —OH group.

The term “cyano” refers to a —CN group.

The term "optionally substituted", as used herein, means that substitution is optional and therefore includes both unsubstituted and substituted atoms and moieties. A "substituted" atom or moiety indicates that any hydrogen on the designated atom or moiety can be replaced with a selection from the indicated substituent group (up to and including that every hydrogen atom on the designated atom or moiety is replaced with a selection from the indicated substituent group), provided that the normal valency of the designated atom or moiety is not exceeded, and that the substitution results in a stable compound. For example, if a methyl group (i.e., -CH₃) is optionally substituted, then up to 3 hydrogen atoms on the carbon atom can be replaced with substituent groups.

A salt or "a pharmaceutically acceptable salt" means a salt prepared by conventional means, and are well known by those skilled in the art. The "pharmacologically acceptable salts" include basic salts of inorganic and organic acids (Berge et al., J. Pharm. Sci. 1977, 66:1).

A "solvate" is formed by treating a compound in a solvent. Solvates of salts of the compounds are also provided. In the case of treating compounds with water, the solvate is hydrates.

A "prodrug" includes any compound that converts into a compound of the present invention, when administered to a subject, e.g., upon metabolic processing of the prodrug.

The term "stereoisomer" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

As used herein, "treat" or "treating" in reference to a disorder means to ameliorate or prevent the disorder or one or more of the biological manifestations of the disorder, to interfere with one or more points in the biological cascade that leads to or is responsible for the disorder, to alleviate one or more of the symptoms or effects associated with the disorder. As indicated above, "treatment" of a disorder includes prevention of the disorder, and "prevention" is understood to refer to the prophylactic administration of a drug to substantially diminish the likelihood or severity of a disorder or biological manifestation thereof, or to delay the onset of such disorder or biological manifestation thereof.

The term "subject" refers to a human (including adults and children) or other animals. In one embodiment, "patient" refers to a human.

As used herein, "safe and effective dose" in reference to a compound or formulas, or a pharmaceutically acceptable salt, prodrug, or solvate thereof an amount sufficient to treat the patient's condition but low enough to avoid serious side effects. A safe and effective dose of a compound will vary with the particular compound chosen (e.g. consider the potency, efficacy, and half-life of the compound); the route of administration chosen; the disorder being treated; the severity of the disorder being treated; the age, size, weight, and physical condition of the patient being treated; the medical history of the patient to be treated; the duration of the treatment; the nature of concurrent therapy; the desired therapeutic effect; and like factors.

The potencies of compounds as inhibitors of an enzyme activity (or other biological activity) can be established by determining the concentrations at which each compound inhibits the activity to a predefined extent and then comparing the results. "IC₅₀" or "IC₉₀" of an inhibitor can be determined by the concentration that inhibits 50% or 90% of the activity in a biochemical assay, which can be accomplished using conventional techniques known in the art, including the techniques described in the examples below.

PREFERRED EMBODIMENTS

The present invention is further described in combination with the following examples, which are not intended to limit the scope of the present invention.

EXAMPLES

The compounds of the present invention may be prepared using the methods disclosed herein and routine modifications thereof, which will be apparent given the disclosure herein and methods are well known in the art. Conventional and well-known synthetic methods may be used in addition to the teachings herein. The synthesis of representative compounds described herein may be accomplished as described in the following examples. If available, reagents may be purchased commercially, e.g., from Sigma Aldrich or other chemical suppliers.

The starting materials used in the examples of the present invention are known and commercially available, or can be synthesized by adopting or according to known methods in the art.

General

The structures of the compounds of the present invention were identified by nuclear magnetic

resonance (NMR) and/or liquid chromatography-mass spectrometry (LC-MS). ¹H-NMR spectra are recorded on a Bruker 400 MHz NMR spectrometer. Significant peaks are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br s, broad singlet), coupling constant(s) in Hertz (Hz) and number of protons. Mass spectrometry results are reported as the ratio of mass over charge, followed by the relative abundance of each ion (in parentheses). Electrospray ionization (ESI) mass spectrometry analysis is conducted on a Shimadzu LC/MSD electrospray mass spectrometer.

The terms “solvent”, “inert organic solvent”, or “inert solvent” refer to a solvent inert under the conditions of the reaction being described in conjunction therewith (including, for example, toluene (“Tol”), acetonitrile, tetrahydrofuran (“THF”), dimethylformamide (“DMF”), ethyl acetate (EA or EtOAc), dichloromethane (DCM), methanol, pyridine and the like. Unless specified to the contrary, the solvents used in the reactions of the present invention are inert organic solvents, and the reactions are carried out under an inert gas, preferably nitrogen and argon.

“SFC” refers to Supercritical Fluid Chromatography, the stereoisomers of example compounds can be prepared with chiral SFC (column: DAICEL CHIRALCEL OD (250mm*30mm,10um).

“DIEA” or “DIPEA” refers to N, N-Diisopropylethylamine.

“TMSBr” refers to Trimethylbromosilane.

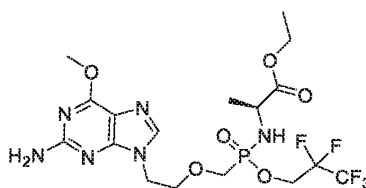
“EDCI” refers to 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide.

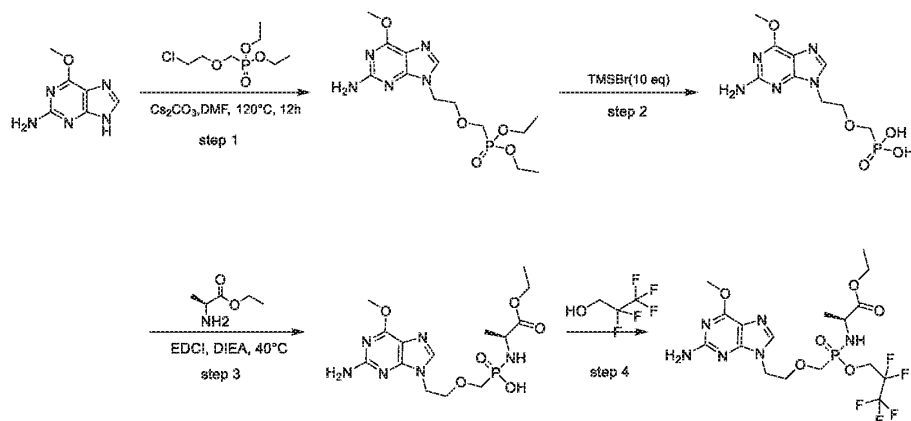
“PYBOP” refers to Benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate.

“DMAP” refers to 4-Dimethylaminopyridine.

Example 1

Ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3,3-pentafluoropropoxy)phosphoryl)-L-alaninate



**Step 1.**

To a solution of 6-methoxy-9H-purin-2-amine (3.00 g, 18.2 mmol, 1 eq) and 2-[2-chloroethoxymethyl(isopropoxy)phosphoryl]oxypropane (5.17 g, 20.0 mmol, 1.1 eq) in DMF (80 mL) was added Cs_2CO_3 (2.96 g, 9.08 mmol, 0.5 eq). The mixture was stirred at 120 °C for 12 hr. The reaction mixture was concentrated under vacuum to give the crude product. The residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~10% Methanol/Dichloromethane gradient @ 60 mL/min). Compound 9-[2-(diisopropoxyphosphorylmethoxy)ethyl]-6-methoxy-purin-2-amine (1.20 g, 3.30 mmol, 12% yield, 75% purity) was obtained as a yellow oil.

MS m/z (ESI):360 $[\text{M}+\text{H}]^+$

Step 2.

To a solution of 9-[2-(diisopropoxyphosphorylmethoxy)ethyl]-6-methoxy-purin-2-amine (1.20 g, 3.30 mmol, 1 eq) in DCM (6 mL) was added TMSBr (4.74 g, 31.0 mmol, 4.01 mL, 10 eq) and 2,6-dimethylpyridine (5.64 g, 52.7 mmol, 6.13 mL, 17 eq) at 0 °C. The mixture was stirred at 25 °C for 6hr. The mixture was quenched by MeOH (10 mL) at 0 °C, and stirred for 1 hour at 25 °C. The mixture was purified by prep-HPLC (column: Welch Xtimate C18 250 * 50mm * 10um; mobile phase: [water(NH_4HCO_3)-ACN]; gradient: 0%-20% B over 20 min). Compound 2-(2-amino-6-methoxy-purin-9-yl)ethoxymethylphosphonic acid (500 mg, 1.65 mmol, 53% yield) was obtained as a white solid.

MS m/z (ESI):304 $[\text{M}+\text{H}]^+$

Step 3.

To a solution of 2-(2-amino-6-methoxy-purin-9-yl)ethoxymethylphosphonic acid (100 mg, 330 μ mol, 1 eq) and ethyl (2S)-2-aminopropanoate (253 mg, 1.65 mmol, 5 eq, HCl salt) in H₂O (3 mL) was added DIEA (213 mg, 1.65 mmol, 287 μ L, 5 eq) and EDCI (316 mg, 1.65 mmol, 5 eq). The mixture was stirred at 40 °C for 12hr. The reaction mixture was filtered to give the filtrate. The residue was purified by prep-HPLC (column: Welch Xtimate C18 40*200 mm 7 μ m; mobile phase: [water(NH₄HCO₃)-ACN]; gradient:0%-30% B over 25 min). Compound 2-(2-amino-6-methoxy-purin-9-yl) ethoxymethyl-N-[(1S)-2-ethoxy-1-methyl-2-oxo-ethyl]phosphonamidic acid (35 mg, 111.85 μ mol, 33% yield) was obtained as a white solid.

MS m/z (ESI): 403[M+H]⁺.

Step 4.

A mixture of 2-(2-amino-6-methoxy-purin-9-yl)ethoxymethyl-N-[rac-(1S)-2-ethoxy-1-methyl-2-oxo-ethyl]phosphonamidic acid (80.0 mg, 199 μ mol, 1 eq), 2,2,3,3,3-pentafluoropropan-1-ol (89.0 mg, 597 μ mol, 59.1 μ L, 3 eq), DIEA (102 mg, 795 μ mol, 138 μ L, 4 eq) and PYBOP (206 mg, 398 μ mol, 2 eq) in DMF was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 25 °C for 16 hr under N₂ atmosphere. The reaction mixture was filtered to remove the insoluble to give the crude product. The residue was purified by flash silica gel chromatography (column: Welch Xtimate C18 40*200mm 7 μ m; mobile phase: [water (NH₄HCO₃)-ACN]; gradient: 12%-52% B over 25 min). Compound ethyl (2S)-2-[[2-(2-amino-6-methoxy-purin-9-yl) ethoxymethyl-(2, 2, 3, 3, 3 pentafluoropropoxy) phosphoryl] amino] propanoate (9.5 mg, 17.07 μ mol, 11% yield, 96% purity) was obtained as a white solid.

¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 7.86 (d, J = 5.38 Hz, 1 H) 4.37 - 4.61 (m, 2 H) 4.26 - 4.34 (m, 2 H) 4.09 - 4.19 (m, 2 H) 4.05 (s, 3 H) 3.95 (br s, 5 H) 1.32 (dd, J = 11.26, 7.13 Hz, 3 H) 1.21 - 1.28 (m, 3 H).

MS m/z (ESI):535 [M+H]⁺

The serial numbers of the exemplary compounds of the present invention are consistent with the serial numbers of the representative compounds in the Table 1. Those skilled in the art can use intermediates similar to Example 1 to synthesize other exemplary compounds. Example 2, 18-43, 50-60, 65-66 are prepared in accordance with the method of Example 1.

Example 22

Isopropyl (2S)-2-[[2-(2-amino-6-methoxy-purin-9-yl) ethoxymethyl-(2, 2, 3, 3, 3-pentafluoro

ropropoxy) phosphoryl] amino] propanoate

¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 7.85 (d, J = 4.25 Hz, 1 H) 4.92 - 5.02 (m, 1 H) 4.39 - 4.57 (m, 2 H) 4.31 (td, J = 5.00, 2.75 Hz, 2 H) 4.05 (s, 3 H) 3.84 - 3.97 (m, 5 H) 1.31 (dd, J = 10.57, 7.19 Hz, 3 H) 1.21 - 1.26 (m, 6 H)

MS m/z (ESI): 548 [M+H]⁺

Example 24

¹H NMR (400 MHz, METHANOL-*d*₄) δ = 7.81 (d, J = 12.1 Hz, 1H), 7.32 - 7.15 (m, 5H), 4.68 - 4.54 (m, 2H), 4.31 - 4.06 (m, 4H), 4.04 (s, 3H), 3.94 - 3.67 (m, 6H), 2.86 - 2.66 (m, 1H), 1.97 - 1.82 (m, 1H), 0.95 - 0.88 (m, 6H)

MS m/z (ESI): 611 [M+H]⁺

Example 25**Isobutyl (2S)-2-[[2-[2-amino-6-(cyclopropylamino) purin-9-yl] ethoxymethyl-(2, 2, 3, 3, 3-pentafluoropropoxy) phosphoryl] amino]-3-phenyl-propanoate**

¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 7.71 (s, 1 H) 7.17 - 7.33 (m, 5 H) 4.14 - 4.26 (m, 3 H) 3.77 - 3.94 (m, 5 H) 3.65 - 3.77 (m, 3 H) 3.18 - 3.25 (m, 1 H) 2.87 - 2.96 (m, 1 H) 2.78 (dd, J = 13.57, 10.44 Hz, 1 H) 1.89 (dt, J = 13.38, 6.69 Hz, 1 H) 0.91 (dd, J = 6.69, 1.94 Hz, 6 H) 0.80 - 0.86 (m, 2 H) 0.54 - 0.63 (m, 2 H)

MS m/z (ESI): 663 [M+H]⁺

Example 26**ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(2,2,2-trifluoroethoxy)phosphoryl)-L-alaninate**

¹H NMR (400 MHz, DMSOL-*d*₆) δ ppm 7.78 - 7.95 (m, 1 H) 6.40 (s, 2 H) 5.59 (dd, J = 12.63, 10.01 Hz, 1 H) 4.33 - 4.48 (m, 2 H) 4.01 - 4.21 (m, 4 H) 3.96 (s, 3 H) 3.73 - 3.90 (m, 5 H) 1.15 - 1.26 (m, 6 H)

MS m/z (ESI): 485 [M+H]⁺

Example 27**ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(3,3,3-**

trifluoropropoxy)phosphoryl)-L-alaninate

¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 7.86 (d, *J* = 6.00 Hz, 1 H) 4.28 - 4.32 (m, 2 H) 4.10 - 4.24 (m, 4 H) 4.05 (s, 3 H) 3.86 - 3.94 (m, 3 H) 3.84 (dd, *J* = 8.19, 5.19 Hz, 1 H) 3.79 (d, *J* = 8.50 Hz, 1 H) 2.43 - 2.59 (m, 2 H) 1.22 - 1.34 (m, 6 H)
MS *m/z* (ESI): 499[M+H]⁺

Example 38**ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3-tetrafluoropropoxy)phosphoryl)-L-alaninate**

¹H NMR (400 MHz, Methanol-*d*₄) δ = 7.86 (d, *J* = 5.6 Hz, 1H), 6.33 - 6.00 (m, 1H), 4.43 - 4.26 (m, 4H), 4.20 - 4.09 (m, 2H), 4.05 (s, 3H), 3.97 - 3.84 (m, 5H), 1.34 - 1.22 (m, 6H)
MS *m/z* (ESI): 517[M+H]⁺

Example 39**ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(3,3,3-trifluoro-2,2-dimethylpropoxy)phosphoryl)-L-alaninate**

¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 7.75 (d, *J* = 4.75 Hz, 1 H) 4.20 (br d, *J* = 4.88 Hz, 2 H) 4.01 - 4.09 (m, 2 H) 3.95 (s, 3 H) 3.81 (dt, *J* = 9.66, 4.61 Hz, 5 H) 3.67 - 3.76 (m, 2 H) 1.20 - 1.24 (m, 3 H) 1.15 (br d, *J* = 4.50 Hz, 3 H) 0.99 (d, *J* = 3.13 Hz, 6 H)
MS *m/z* (ESI): 527[M+H]⁺

Example 41**ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(2,2-difluoroethoxy)phosphoryl)-L-alaninate**

¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 7.89 (d, *J* = 6.38 Hz, 1 H) 5.82 - 6.18 (m, 1 H) 4.30 - 4.35 (m, 2 H) 4.10 - 4.24 (m, 4 H) 4.07 (s, 3 H) 3.84 - 3.96 (m, 5 H) 1.31 - 1.36 (m, 3 H) 1.24 - 1.30 (m, 3 H)
MS *m/z* (ESI): 467[M+H]⁺

Example 42**ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(2,2-**

difluoropropoxy)phosphoryl)-L-alaninate

¹H NMR (400 MHz, Methanol-*d*₄) δ = 7.86 (d, *J* = 5.9 Hz, 1H), 4.35 - 4.27 (m, 2H), 4.19 - 4.07 (m, 3H), 4.05 (s, 3H), 4.03 - 3.81 (m, 6H), 1.68 - 1.49 (m, 3H), 1.34 - 1.22 (m, 6H)

MS *m/z* (ESI): 481 [M+H]⁺

Example 50**ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(1-phenylethoxy)phosphoryl)-L-alaninate**

¹H NMR (400 MHz, Methanol-*d*₄) δ = 7.89 - 7.77 (m, 1H), 7.36 - 7.22 (m, 5H), 5.59 - 5.38 (m, 1H), 4.33 - 4.20 (m, 2H), 4.18 - 4.12 (m, 1H), 4.05 (s, 3H), 3.98 - 3.62 (m, 6H), 1.57 - 1.46 (m, 3H), 1.33 - 1.14 (m, 6H)

MS *m/z* (ESI): 507 [M+H]⁺

Example 51**ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(2,2,2-trifluoro-1-phenylethoxy)phosphoryl)-L-alaninate**

¹H NMR (400 MHz, Methanol-*d*₄) δ = 7.89 - 7.73 (m, 1H), 7.48 - 7.32 (m, 5H), 5.92 - 5.61 (m, 1H), 4.36 - 4.26 (m, 1H), 4.22 - 4.12 (m, 2H), 4.06 (d, *J* = 2.1 Hz, 3H), 4.02 - 3.62 (m, 6H), 1.33 - 1.05 (m, 6H)

MS *m/z* (ESI): 561 [M+H]⁺

Example 52**ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(2-methoxy-2-oxo-1-phenylethoxy)phosphoryl)-L-alaninate**

¹H NMR (400 MHz, Methanol-*d*₄) δ = 7.83 (s, 1H), 7.41 - 7.32 (m, 5H), 5.85 (d, *J* = 10.0 Hz, 1H), 4.27 - 4.14 (m, 6H), 4.06 (s, 3H), 4.03 - 3.97 (m, 1H), 3.86 - 3.80 (m, 4H), 1.33 - 1.25 (m, 6H), 1.19 (t, *J* = 7.2 Hz, 3H)

MS *m/z* (ESI): 551 [M+H]⁺

Example 53**ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(benzylamino)phosphoryl)-L-**

alaninate

¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 7.90 (s, 1 H) 7.17 - 7.34 (m, 5 H) 4.30 (br d, *J* = 3.38 Hz, 2 H) 4.02 - 4.20 (m, 7 H) 3.81 - 3.95 (m, 3 H) 3.73 (br d, *J* = 8.50 Hz, 2 H) 1.21 - 1.35 (m, 6 H)

MS *m/z* (ESI): 492 [M+H]⁺

Example 60**isobutyl (((2-(2-amino-6-(cyclopropylamino)-9H-purin-9-yl)ethoxy)methyl)(benzylamino)phosphoryl)-L-phenylalaninate**

¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 7.73 (d, *J* = 6.13 Hz, 1 H) 7.07 - 7.29 (m, 10 H) 4.17 - 4.23 (m, 2 H) 4.05 - 4.13 (m, 1 H) 3.73 - 3.90 (m, 5 H) 3.66 (t, *J* = 5.00 Hz, 1 H) 3.60 (dd, *J* = 8.76, 2.25 Hz, 1 H) 3.45 (dd, *J* = 13.20, 8.57 Hz, 1 H) 2.97 - 3.07 (m, 1 H) 2.87 (br d, *J* = 3.50 Hz, 1 H) 2.81 (dt, *J* = 13.54, 8.11 Hz, 1 H) 1.82 (dt, *J* = 13.20, 6.54 Hz, 1 H) 0.86 (d, *J* = 6.63 Hz, 6 H) 0.82 (br d, *J* = 6.13 Hz, 2 H) 0.54 - 0.59 (m, 2 H)

MS *m/z* (ESI): 621 [M+H]⁺

Example 71**isobutyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3,3-pentafluoropropoxy)phosphoryl)-L-alaninate**

¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 7.85 (d, *J* = 5.13 Hz, 1 H) 4.43 (br d, *J* = 7.13 Hz, 2 H) 4.31 (td, *J* = 4.78, 2.44 Hz, 2 H) 4.05 (s, 3 H) 3.82 - 3.97 (m, 7 H) 1.92 (br d, *J* = 5.75 Hz, 1 H) 1.34 (dd, *J* = 13.20, 7.19 Hz, 3 H) 0.93 (dd, *J* = 6.57, 4.69 Hz, 6 H)

MS *m/z* (ESI): 563 [M+H]⁺

Example 72**butyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3,3-pentafluoropropoxy)phosphoryl)-L-alaninate**

¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 7.87 (d, *J* = 5.63 Hz, 1 H) 4.41 - 4.57 (m, 2 H) 4.28 - 4.36 (m, 2 H) 4.10 - 4.19 (m, 2 H) 4.07 (s, 3 H) 3.86 - 3.98 (m, 5 H) 1.58 - 1.68 (m, 2 H) 1.32 - 1.43 (m, 5 H) 0.96 (td, *J* = 7.38, 3.63 Hz, 3 H)

MS *m/z* (ESI): 563 [M+H]⁺

Example 73

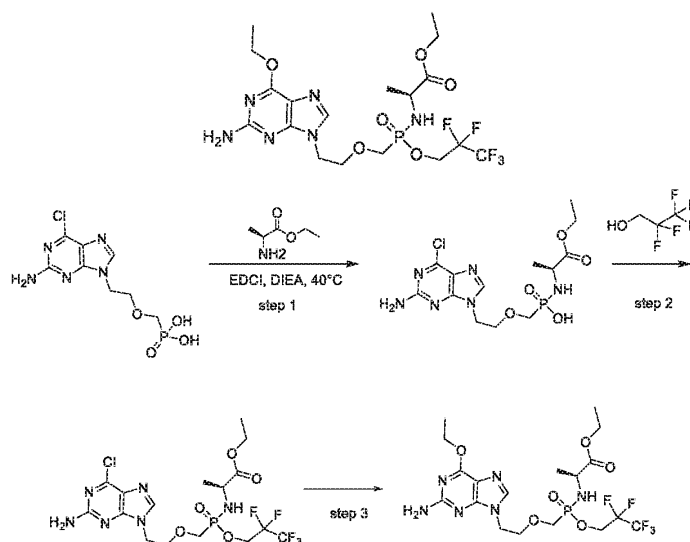
isobutyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3,3-pentafluoropropoxy)phosphoryl)-L-phenylalaninate

^1H NMR (400 MHz, Methanol- d_4) δ = 7.81 (d, J = 12.1 Hz, 1H), 7.32 - 7.15 (m, 5H), 4.68 - 4.54 (m, 2H), 4.31 - 4.06 (m, 4H), 4.04 (s, 3H), 3.94 - 3.67 (m, 6H), 2.86 - 2.66 (m, 1H), 1.97 - 1.82 (m, 1H), 0.95 - 0.88 (m, 6H)

MS m/z (ESI): 639 $[\text{M}+\text{H}]^+$

Example 3

Ethyl (((2-(2-amino-6-ethoxy-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3,3-pentafluoropropoxy)phosphoryl)-L-alaninate



Step 1 and 2 were conducted in the similar manner as those in example 1 to give ethyl (((2-(2-amino-6-chloro-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3,3-pentafluoropropoxy)phosphoryl)-L-alaninate.

MS m/z (ESI): 539 $[\text{M}+\text{H}]^+$

Step 3.

To a solution of ethyl (((2-(2-amino-6-chloro-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3,3-pentafluoropropoxy)phosphoryl)-L-alaninate (1.0 mmol) and ethanol (3 mmol) in Pyridine (1.5 mL) was added DMAP (1.0 mmol, 1 eq). The mixture was stirred at 120°C for 16 hrs. The reaction

mixture was filtered to remove the insoluble and purified by prep-HPLC to give the compound ethyl (((2-(2-amino-6-ethoxy-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3,3-pentafluoropropoxy)phosphoryl)-L-alaninate.

¹H NMR (400 MHz, Methanol-*d*₄) δ = 7.84 (d, *J* = 5.3 Hz, 1H), 4.58 - 4.37 (m, 4H), 4.34 - 4.26 (m, 2H), 4.21 - 4.09 (m, 2H), 3.96 - 3.84 (m, 5H), 1.43 (t, *J* = 7.1 Hz, 3H), 1.35 - 1.30 (m, 3H), 1.28 - 1.22 (m, 3H)

MS *m/z* (ESI): 549 [M+H]⁺

Those skilled in the art can use intermediates similar to Example 3 to synthesize other exemplary compounds. Example 4-12 are prepared in accordance with the method of Example 3.

Example 7

Ethyl (2S)-2-[[2-[2-amino-6-(2-methoxyethoxy)purin-9-yl]ethoxymethyl-(2,2,3,3,3-pentafluoropropoxy)phosphoryl]amino]propanoate

¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 7.76 - 7.91 (m, 1 H) 4.61 (dd, *J* = 5.19, 4.31 Hz, 2 H) 4.44 (td, *J* = 13.04, 7.19 Hz, 2 H) 4.27 - 4.34 (m, 2 H) 4.09 - 4.19 (m, 2 H) 3.85 - 3.98 (m, 5 H) 3.76 - 3.82 (m, 2 H) 3.41 (s, 3 H) 1.30 - 1.37 (m, 3 H) 1.20 - 1.29 (m, 3 H)

MS *m/z* (ESI): 579 [M+H]⁺

Example 13

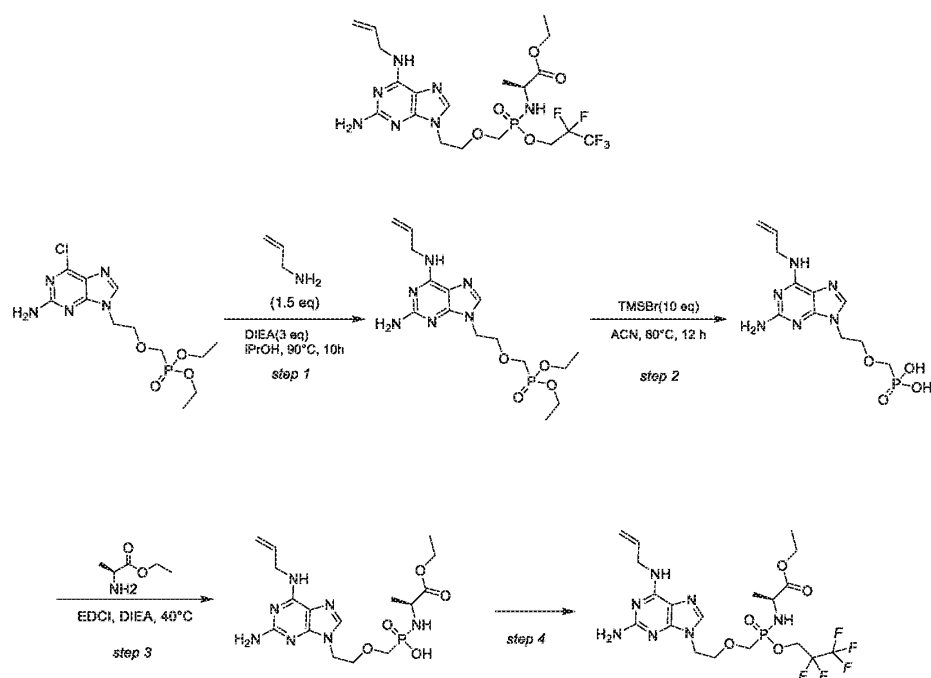
Ethyl (2S)-2-[[2-[6-(allylamino)-2-amino-purin-9-yl]ethoxymethyl-(2,2,3,3,3-pentafluoropropoxy)phosphoryl]amino]propanoate

¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 7.64 (d, *J* = 4.25 Hz, 1 H) 5.81 - 5.97 (m, 1 H) 5.17 (dd, *J* = 17.20, 1.56 Hz, 1 H) 5.03 (dd, *J* = 10.26, 1.50 Hz, 1 H) 4.28 - 4.51 (m, 2 H) 4.13 - 4.21 (m, 2 H) 3.98 - 4.11 (m, 4 H) 3.73 - 3.86 (m, 5 H) 1.21 - 1.26 (m, 3 H) 1.15 (td, *J* = 7.13, 5.13 Hz, 3 H)

MS *m/z* (ESI): 560 [M+H]⁺

Example 13

Ethyl (((2-(6-(allylamino)-2-amino-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3,3-pentafluoropropoxy)phosphoryl)-L-alaninate

**Step 1.**

To a solution of 6-chloro-9-[2-(diisopropoxyphosphorylmethoxy)ethyl]purin-2-amine (200 mg, 510 μmol , 1 eq) and prop-2-en-1-amine hydrochloride (57.3 mg, 613 μmol , 1.2 eq) in i-PrOH (1 mL) was added DIEA (198 mg, 1.53 mmol, 267 μL , 3 eq). The mixture was stirred at 90 °C for 12hr. The reaction mixture was concentrated under vacuum to give the crude product. The residue was purified by flash silica gel chromatography. Compound N6-allyl-9-[2-(diisopropoxyphosphorylmethoxy)ethyl]purine-2,6-diamine (220 mg, crude) was obtained as a yellow oil.

MS m/z (ESI): 385 $[\text{M}+\text{H}]^+$

Step 2.

To a solution of N6-allyl-9-[2-(diisopropoxyphosphorylmethoxy)ethyl]purine-2,6- diamine (210 mg, 509 μmol , 1 eq) in ACN (3 mL) was added TMSBr (779 mg, 5.09 mmol, 658 μL , 10 eq) at 0 °C. The mixture was stirred at 25 °C for 12hr. The reaction mixture was concentrated under vacuum to give the crude product. The mixture was purified by prep-HPLC (column: C18-3 100*30 mm*5 μm ; mobile phase: [water (HCl)-ACN]; gradient: 0%-12% B over 20 min).

Compound 2-[6-(allylamino)-2-amino-purin-9-yl]ethoxymethylphosphonic acid (50 mg, 152.32 μmol , 29% yield) was obtained as a white solid.

MS m/z (ESI): 329 $[\text{M}+\text{H}]^+$

Step 3.

To a solution of 2-[6-(allylamino)-2-amino-purin-9-yl]ethoxymethylphosphonic acid (50 mg, 152 μmol , 1 eq) and ethyl (2S)-2-aminopropanoate (89.2 mg, 762 μmol , 5 eq) in H_2O (1.5 mL) was added EDCI (146 mg, 762 μmol , 5 eq) and DIEA (98.4 mg, 762 μmol , 133 μL , 5 eq). The mixture was stirred at 40 $^\circ\text{C}$ for 12hr. The filtrate was purified by prep-TLC (SiO_2 , DCM: MeOH = 4:1). Compound 2-[6-(allylamino)-2-amino-purin-9-yl] ethoxymethyl-N-[(1S)-2-ethoxy-1-methyl-2-oxo-ethyl]phosphonamidic acid (30 mg, 70.19 μmol , 46% yield) was obtained as a yellow oil.

MS m/z (ESI): 428 $[\text{M}+\text{H}]^+$

Step 4.

Following the similar manner in example 1 to provide ethyl (((2-(6-(allylamino)-2-amino-9H-purin-9-yl)ethoxy)methyl)(2,2,3,3,3-pentafluoropropoxy)phosphoryl)-L-alaninate.

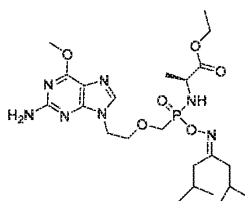
^1H NMR (400 MHz, $\text{METHANOL-}d_4$) δ ppm 7.64 (d, $J = 4.25$ Hz, 1 H) 5.81 - 5.97 (m, 1 H) 5.17 (dd, $J = 17.20, 1.56$ Hz, 1 H) 5.03 (dd, $J = 10.26, 1.50$ Hz, 1 H) 4.28 - 4.51 (m, 2 H) 4.13 - 4.21 (m, 2 H) 3.98 - 4.11 (m, 4 H) 3.73 - 3.86 (m, 5 H) 1.21 - 1.26 (m, 3 H) 1.15 (td, $J = 7.13, 5.13$ Hz, 3 H)

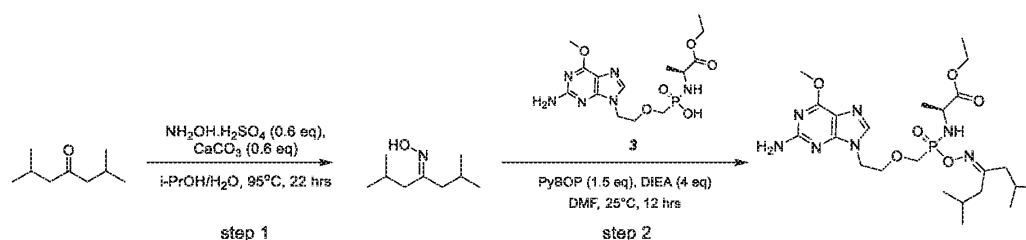
MS m/z (ESI): 560 $[\text{M}+\text{H}]^+$

Those skilled in the art can use intermediates similar to Example 13 to synthesize other exemplary compounds. Example 14-17 are prepared in accordance with the method of Example 13.

Example 44

Ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)((propan-2-ylideneamino)oxy)phosphoryl)-L-alaninate



**Step 1.**

Compound 2,6-dimethylheptan-4-one oxime (875 mg, 5.56 mmol, 79% yield) was obtained as a yellow oil. (Reference, *Chem. Commun.*, **2018**, 54, 12262-12265)

^1H NMR (400 MHz, Chloroform-*d*) δ = 2.29 - 2.02 (m, 4H), 2.02 - 1.84 (m, 2H), 1.02 - 0.83 (m, 12H).

Step 2.

To a solution of 2-((2-amino-6-methoxy-purin-9-yl)ethoxymethyl)-N-((1S)-2-ethoxy-1-methyl-2-oxo-ethyl)phosphonamidic acid (80.0 mg, 199 μmol , 1 eq) and 2,6-dimethylheptan-4-one oxime (94.0 mg, 596 μmol , 3 eq) in DMF (1.50 mL) was added DIEA (103 mg, 795 μmol , 139 μL , 4 eq) and PyBOP (310 mg, 596 μmol , 3 eq). The mixture was stirred at 25°C for 16 hr under N_2 atmosphere. The reaction mixture was filtered to remove the insoluble and concentrated under vacuum to give the crude product. The crude product was purified by prep-HPLC (Neutral condition, column: Welch Xtimate C18 40*200mm 7 μm ; mobile phase: [water(NH_4HCO_3)-ACN]; gradient: 22%-62% B over 25 min). Compound ethyl (2S)-2-[[2-(2-amino-6-methoxy-purin-9-yl)ethoxymethyl-[(1S)-2-ethoxy-1-methyl-2-oxo-ethyl]phosphonamidic acid]]-2,6-dimethylheptan-4-one oxime (17.5 mg, 31.9 μmol , 58% yield, 98% purity) was obtained as a white solid.

^1H NMR (400 MHz, Methanol-*d*₄) δ = 7.96 - 7.72 (m, 1H), 4.32 - 4.25 (m, 2H), 4.21 - 4.10 (m, 2H), 4.05 (s, 3H), 4.03 - 3.84 (m, 5H), 2.27 - 2.10 (m, 2H), 2.10 - 2.04 (m, 2H), 1.99 - 1.81 (m, 2H), 1.38 - 1.32 (m, 3H), 1.26 (t, J = 7.1 Hz, 3H), 0.92 - 0.81 (m, 12H)

MS m/z (ESI): 542 $[\text{M}+\text{H}]^+$

Those skilled in the art can use intermediates similar to Example 44 to synthesize other exemplary compounds. Example 45-49 are prepared in accordance with the method of Example 44.

Example 46

ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)((2,6-dimethylheptan-4-

ylidene)amino)oxy)phosphoryl)-L-alaninate

^1H NMR (400 MHz, Methanol- d_4) δ = 7.85 (s, 1H), 4.31 - 4.23 (m, 2H), 4.21 - 4.11 (m, 2H), 4.05 (s, 3H), 4.00 - 3.84 (m, 5H), 2.43 - 2.27 (m, 4H), 1.80 - 1.72 (m, 4H), 1.34 (d, J = 7.1 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H)

MS m/z (ESI): 484 $[\text{M}+\text{H}]^+$

Example 47

ethyl (((2-(2-amino-6-methoxy-9H-purin-9-

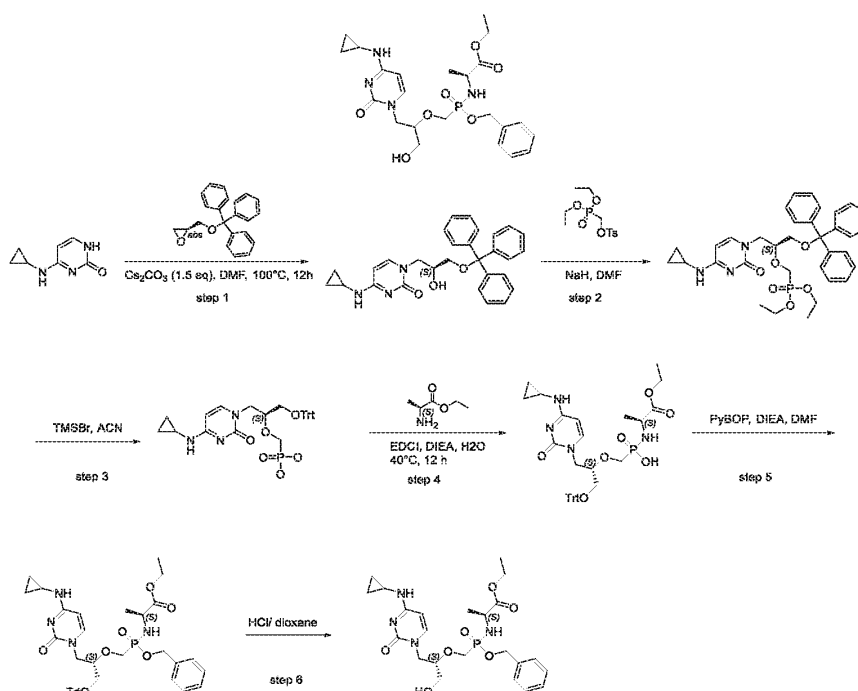
yl)ethoxy)methyl)((cyclopentylideneamino)oxy)phosphoryl)-L-alaninate

^1H NMR (400 MHz, Methanol- d_4) δ = 7.83 (d, J = 8.4 Hz, 1H), 7.59 - 7.34 (m, 5H), 4.32 - 4.24 (m, 2H), 4.18 - 4.00 (m, 5H), 3.96 (d, J = 2.0 Hz, 3H), 3.94 - 3.83 (m, 2H), 2.28 (s, 3H), 1.40 - 1.35 (m, 3H), 1.27 - 1.20 (m, 3H)

MS m/z (ESI): 458 $[\text{M}+\text{H}]^+$

Example 61

ethyl ((benzyloxy)(((1-(4-(cyclopropylamino)-2-oxopyrimidin-1(2H)-yl)-3-hydroxypropan-2-yl)oxy)methyl)phosphoryl)-L-alaninate



Step 1.

To a solution of 4-(cyclopropylamino)pyrimidin-2-ol (1.00 g, 6.62 mmol, 1 *eq*) and (2S)-2-(trityloxymethyl)oxirane (2.09 g, 6.62 mmol, 1 *eq*) in DMF (10.0 mL) was added Cs₂CO₃ (3.23 g, 9.92 mmol, 1.5 *eq*). The mixture was stirred at 100 °C for 3hr. The reaction mixture was filtered to remove the insoluble and concentrated under vacuum to give the crude product. The residue was purified by flash silica gel chromatography to give compound 4-(cyclopropylamino)-1-[rac-(2S)-2-hydroxy-3-trityloxy-propyl]pyrimidin-2-one (1.20 g, 2.57 mmol, 38% yield) as a white solid.

MS m/z (ESI):468 [M+H]⁺

Step 2.

To a solution of 4-(cyclopropylamino)-1-[rac-(2S)-2-hydroxy-3-trityloxy-propyl] pyrimidin-2-one (1.00 g, 2.14 mmol, 1 *eq*) and diethoxyphosphorylmethyl 4- methylbenzenesulfonate (1.03 g, 3.21 mmol, 823 μL, 1.5 *eq*) in THF (10.0 mL) was added NaH (256 mg, 6.42 mmol, 60% purity, 3 *eq*) at -20°C. The mixture was stirred at 50 °C for 12hr. The reaction mixture was filtered to give the filtrate. The residue was purified by prep-HPLC. Compound 4-(cyclopropylamino)-1-[(2S)-2-(diethoxyphosphorylmethoxy)-3-trityloxy-propyl]pyrimidin-2-one (550 mg, 890 μmol, 41% yield) was obtained as a yellow solid.

MS m/z (ESI):618 [M+H]⁺

Step 3.

To a solution of 4-(cyclopropylamino)-1-[(2S)-2-(diethoxyphosphorylmethoxy)-3- trityloxy-propyl]pyrimidin-2-one (540 mg, 874 μmol, 1 *eq*) in DCM (5.00 mL) was added TMSBr (1.34 g, 8.74 mmol, 1.13 mL, 10 *eq*) and 2,6-dimethylpyridine (1.59 g, 14.8 mmol, 1.73 mL, 17 *eq*) at 0°C. The mixture was stirred at 25 °C for 12hr. The reaction mixture was concentrated under vacuum to give the compound [(1S)-1-[[4-(cyclopropylamino)- 2-oxo-pyrimidin-1-yl]methyl]-2-trityloxy-ethoxy]methylphosphonic acid (600 mg, crude) was obtained as a yellow solid.

MS m/z (ESI):562 [M+H]⁺

Step 4.

To a solution of [(1S)-1-[[4-(cyclopropylamino)-2-oxo-pyrimidin-1-yl]methyl]-2- trityloxy-ethoxy]methylphosphonic acid (500 mg, 891 μmol, 1 *eq*) and ethyl (2S)-2-aminopropanoate (683 mg, 4.45 mol, 5 *eq*) in H₂O (1.00 mL) was added EDCI (853 mg, 4.45 mol, 5 *eq*) and DIEA (575 mg, 4.45mol, 77.5 μL, 5 *eq*). The mixture was stirred at 40 °C for 12hr. The reaction mixture was

filtered to give the filtrate. The residue was purified by prep-HPLC. Compound [(1R)-1-[[4-(cyclopropylamino)-2-oxo-pyrimidin-1-yl]methyl]-2-trityloxy-ethoxy]methyl-N-[(1R)-2-ethoxy-1-methyl-2-oxo-ethyl]phosphonamidic acid (210 mg, 317 μ mol, 39% yield) was obtained as a white solid.

MS m/z (ESI): 419 [M+H]⁺

Step 5.

To a solution of [(1S)-1-[[4-(cyclopropylamino)-2-oxo-pyrimidin-1-yl]methyl]-2-trityloxy-ethoxy]methyl-N-[(1S)-2-ethoxy-1-methyl-2-oxo-ethyl]phosphonamidic acid (200 mg, 302 μ mol, 1 *eq*) and phenylmethanol (98.2 mg, 908 μ mol, 94.1 μ L, 3 *eq*) in DMF (4.00 mL) was added PYBOP (315 mg, 605 μ mol, 2 *eq*) and DIEA (156 mg, 1.21 mmol, 210 μ L, 4 *eq*). The reaction mixture was filtered to give the filtrate. The residue was purified by prep-HPLC (column: Welch Xtimate C18 40 * 200 mm 7 μ m; mobile phase: [water (NH₄HCO₃)-ACN]; gradient: 40% - 80% B over 25 min). Compound ethyl (2S)-2-[[benzyloxy-[(1S)-1-[[4-(cyclopropylamino)-2-oxo-pyrimidin-1-yl]methyl]-2-trityloxy-ethoxy]methyl]phosphoryl]amino]propanoate (70.0 mg, 93.2 μ mol, 30% yield) was obtained as a white solid.

MS m/z (ESI): 751 [M+H]⁺

Step 6.

To a solution of ethyl (2S)-2-[[benzyloxy-[(1S)-1-[[4-(cyclopropylamino)-2-oxo-pyrimidin-1-yl]methyl]-2-trityloxy-ethoxy]methyl]phosphoryl]amino]propanoate (40.0 mg, 53.2 μ mol, 1 *eq*) in HOAc (1.00 mL) was stirred at 40 °C for 48hr. The reaction mixture was filtered to give the filtrate. The residue was purified by prep-HPLC (column: Welch Xtimate C18 40 * 200 mm 7 μ m; mobile phase: [water (FA)-ACN]; gradient: 0% - 38% B over 25 min). Compound ethyl (2S)-2-[[benzyloxy-[(1S)-1-[[4-(cyclopropylamino)-2-oxo-pyrimidin-1-yl]methyl]-2-hydroxy-ethoxy]methyl]phosphoryl]amino]propanoate (2.10 mg, 3.98 μ mol, 7% yield, 96% purity) was obtained as a white solid.

¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 7.30 - 7.73 (m, 6 H) 6.10 (br dd, *J* = 8.63, 2.13 Hz, 1 H) 5.68 (br dd, *J* = 10.94, 7.57 Hz, 1 H) 5.02 - 5.08 (m, 2 H) 3.95 - 4.30 (m, 6 H) 3.68 - 3.92 (m, 4 H) 3.52 - 3.66 (m, 1 H) 2.84 (br d, *J* = 2.75 Hz, 1 H) 1.40 (br s, 3 H) 1.27 (q, *J* = 6.96 Hz, 3 H) 0.81 (br d, *J* = 5.38 Hz, 2 H) 0.45 - 0.67 (m, 2 H)

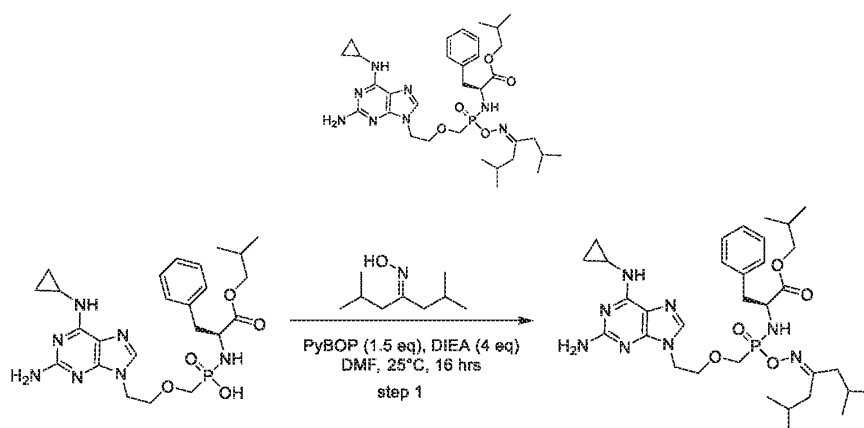
MS m/z (ESI): 509 [M+H]⁺

Those skilled in the art can use intermediates similar to Example 61 to synthesize other exemplary

compounds. Example 62-64 are prepared in accordance with the method of Example 61.

Example 67

Isobutyl (((2-(2-amino-6-(cyclopropylamino)-9H-purin-9-yl)ethoxy)methyl)((2,6-dimethylheptan-4-ylidene)amino)oxy)phosphoryl)-L-phenylalaninate



A mixture of 2,6-dimethylheptan-4-one oxime (35.5 mg, 226 μ mol, 3 eq), 2-[2-amino-6-(cyclopropylamino)purin-9-yl]ethoxymethyl-N-[(1S)-1-benzyl-2-isobutoxy-2-oxoethyl]phosphonamidic acid (40.0 mg, 75.3 μ mol, 1 eq), PYBOP (117 mg, 226 μ mol, 3 eq), DIEA (38.9 mg, 301 μ mol, 52.4 μ L, 4 eq) in DMF (1 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 25 $^{\circ}$ C for 16 hr under N_2 atmosphere. The reaction mixture was concentrated directly. The crude product was purified by reversed-phase HPLC (column: Welch Xtimate C18 40* 200mm 7 μ m; mobile phase: [water(NH_4HCO_3)-ACN]; gradient: 40% -80% B over 25 min). Compound isobutyl (2S)-2-[[2-[2-amino-6-(cyclopropylamino)purin-9-yl]ethoxymethyl-[(1S)-1-isobutyl-3-methyl-butylidene]amino]oxy-phosphoryl]amino]-3-phenylpropanoate (13.9 mg, 20.72 μ mol, 28% yield) was obtained as a white solid.

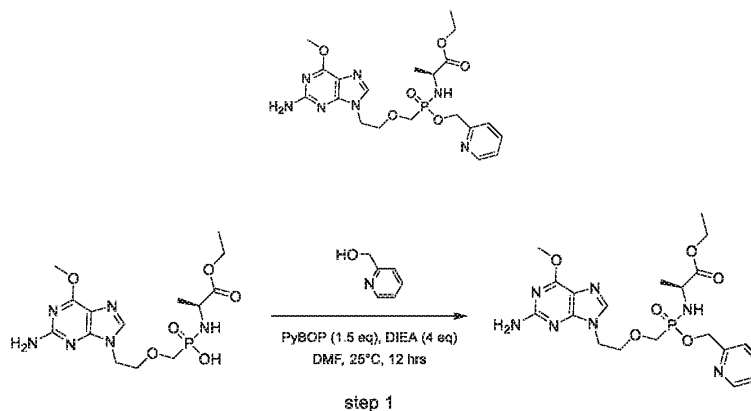
^1H NMR (400 MHz, METHANOL- d_4) δ ppm 7.68 (s, 1 H) 7.15 - 7.28 (m, 5 H) 4.15 - 4.27 (m, 3 H) 3.81 - 3.89 (m, 2 H) 3.66 - 3.78 (m, 3 H) 3.51 (dd, J = 13.20, 7.69 Hz, 1 H) 2.99 - 3.09 (m, 1 H) 2.90 (td, J = 13.29, 8.07 Hz, 2 H) 2.17 - 2.25 (m, 1 H) 2.07 - 2.15 (m, 1 H) 2.02 - 2.06 (m, 2 H) 1.78 - 1.95 (m, 3 H) 0.78 - 0.91 (m, 20 H) 0.55 - 0.61 (m, 2 H)

MS m/z (ESI): 671 $[M+H]^+$

Example 68

ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(pyridin-2-

ylmethoxy)phosphoryl)-L-alaninate

*Step 1.*

To a solution of 2-(2-amino-6-methoxy-purin-9-yl)ethoxymethyl-N-[rac-(1S)-2-ethoxy-1-methyl-2-oxo-ethyl]phosphonamidic acid (50.0 mg, 124 μmol , 1 eq) and 2-pyridyl methanol (27.0 mg, 249 μmol , 24.0 μL , 2 eq) in DMF (1.5 mL) was added DIEA (64.0 mg, 498 μmol , 87.0 μL , 4 eq) and PyBOP (129 mg, 249 μmol , 2 eq). The mixture was stirred at 25°C for 16 hrs. The reaction mixture was filtered and purified by prep-HPLC (Neutral condition, column: Welch Xtimate C18 40*200 mm 7 μm ; mobile phase: [water (NH_4HCO_3)-ACN]; gradient: 0%-40% B over 25 min). Compound ethyl rac-(2S)-2-[[2-(2-amino-6-methoxy-purin-9-yl) ethoxymethyl -(2-pyridylmethoxy)phosphoryl]amino]propanoate (16.4 mg, 32% yield, 97% purity) was obtained as a colorless oil.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.51 (br d, $J = 2.4$ Hz, 1 H), 7.86 - 7.75 (m, 2 H), 7.43 - 7.28 (m, 2 H), 6.39 (s, 2H), 5.47 - 5.32 (m, 1 H), 5.05 - 4.87 (m, 2 H), 4.21 - 4.15 (m, 2 H), 4.08 - 3.99 (m, 2 H), 3.94 (s, 3 H), 3.88 - 3.81 (m, 4 H), 3.78 (d, $J = 8.1$ Hz, 1 H), 1.23 - 1.20 (m, 3 H), 1.18 - 1.11 (m, 3 H)

MS m/z (ESI): 494 $[\text{M}+\text{H}]^+$

Those skilled in the art can use intermediates similar to Example 68 to synthesize other exemplary compounds. Example 69-70 are prepared in accordance with the method of Example 68.

BIOLOGICAL EVALUATION

Exemplary compounds of (I), (I-1), (I-2), (I-3), (I-4), (II), (III) or (IV) were tested to assess biological activity..

1. Antiproliferation assay

Three cervical carcinoma cell lines carrying integrated copies of HPV subtypes (HPV-16 in SiHa and CaSki cells; HPV-18 in HeLa), cultured in Dulbecco's modified Eagle's medium (VivaCell biosciences, Shanghai, China), supplemented with 10% fetal bovine serum (VivaCell biosciences, Shanghai, China), and antibiotics (100 units/ml penicillin, and 100 ug/ml streptomycin [VivaCell biosciences, Shanghai, China]). Cells were detached from culture flasks using trypsin, counted, and plated in 96-well culture plates (750 cells per well). The following day, fourfold serial dilutions of compounds were added in duplicate. No compound was added to control wells to represent 100% proliferation. Seven days after the addition of compounds, cell viability was determined using CellTiter-Glo reagent (Promega) with luminescence quantified on a luminometer (Varioskan LUX, thermoscientific). The IC₅₀ values were calculated by fitting these data to a logistic curve using GraphPad Prism software.

Table 2. Antiproliferative activity of test compounds

Antiproliferative activity (IC ₅₀ , nM)			
Number	CaSki (HPV16)	Hela (HPV18)	SiHa (HPV16)
Example 1	4.9	4.9	0.75
Example 3	40	60	19
Example 7	130	140	30
Example 13	420	360	18
Example 22	90	220	36
Example 25	56	48	1.7
Example 26	230	290	60
Example 27	82	140	18
Example 38	56	350	58
Example 39	99	220	160
Example 41	130	520	75
Example 42	150	140	22
Example 44	8.5	10	1.1
Example 45	290	530	48
Example 47	220	510	62
Example 50	4800	3700	1700

Example 51	43	92	23
Example 52	230	920	250
Example 53	110	300	19
Example 60	36	35	3.2
Example 65	9.5	5.3	1.2
Example 67	8.1	20	1.1
Example 71	13	17	1.5
Example 72	8.3	12	1.5
Example 73	9.5	5.3	1.2

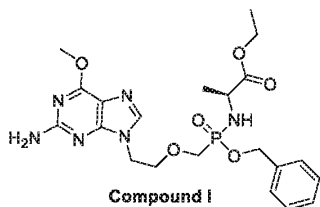
2. Cellular DNA synthesis assay

Cells were detached from culture flasks using trypsin, counted, and plated in 96-well culture plates (5000-10000 cells per well, optimized for each cell type). The following day, four fold serial dilutions of compounds were added in duplicate. No compound was added to control wells to represent 100% signal. After the addition of compounds for 40 h, labeling with 5-bromo-2'-deoxyuridine (BrdU) was performed by adding 20 μ l of 100 μ M BrdU without removing compounds, followed by 4 h of incubation. At the end of incubation, cells were fixed, and the amount of BrdU incorporated into DNA was quantified by an enzyme-linked immunosorbent assay using a Cell Proliferation ELISA and BrdU (colorimetric) Kit (sigma-aldrich). From the experimental data, sigmoidal dose-response curves were generated and the IC₅₀ values were calculated using GraphPad Prism software.

Table 3. Inhibition of cellular DNA synthesis as measured by BrdU labeling in HPV-18-transformed Siha cells.

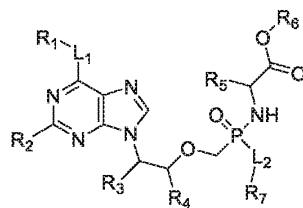
Number	EC ₅₀ (nM)
Example 1	2.88
Example 22	14.6
Example 44	2.4
Example 67	1.5
Example 71	0.96
Example 72	2.8
Example 73	1.8
Compound I	136

Compound I is ethyl (((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)(benzyloxy)phosphoryl)-L-alaninate disclosed in WO2024020127



Claims

1. A compound of formula (I), a stereoisomer thereof, or a pharmaceutically acceptable salt, solvates and prodrugs thereof:



formula (I)

Wherein,

L_1 is independently selected from -O- or -NH-;

R_1 is independently selected from hydrogen, C_1 - C_6 alkyl, deuterated C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_8 cycloalkyl, 4 to 7 membered heterocyclyl, C_6 - C_{10} aryl and 5 to 10 membered heteroaryl, wherein the C_3 - C_8 cycloalkyl, 4 to 7 membered heterocyclyl, C_6 - C_{10} aryl and 5 to 10 membered heteroaryl are each optionally further substituted by one or more deuterium, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, halogen, hydroxy, amino, nitro, cyano and ester group;

R_2 is independently selected from hydrogen, amino, hydroxy, halogen, cyano, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, C_2 - C_6 alkenyl and C_2 - C_6 alkynyl;

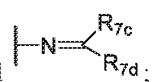
R_3 and R_4 are each independently selected from hydrogen, deuterium, halogen, hydroxy, amino, C_1 - C_6 alkyl, deuterated C_1 - C_6 alkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 haloalkyl and C_1 - C_6 alkoxy;

Or R_3 and R_4 together with the atoms to which they are attached can form a 3 to 7 membered heterocycle comprising 1-2 heteroatoms selected from O, N and S;

R_5 and R_6 are each independently selected from hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, C_3 - C_8 cycloalkyl, 4 to 7 membered heterocyclyl, C_6 - C_{10} aryl, benzyl and 5 to 10 membered heteroaryl, wherein the C_3 - C_8 cycloalkyl, 4 to 7

membered heterocyclyl, C₆-C₁₀ aryl, benzyl and 5 to 10 membered heteroaryl are each optionally further substituted by one or more deuterium, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, halogen, hydroxy, amino, nitro, cyano and ester group;

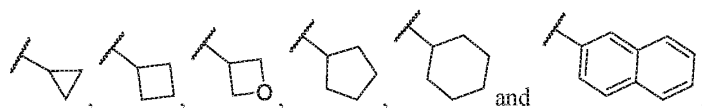
L₂ is independently selected from -O- or -NH-;

R₇ is independently selected from  and ;

R_{7a}, R_{7b}, R_{7c} and R_{7d} are each independently selected from hydrogen, deuterium, C₁-C₆ alkyl, deuterated C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -C(O)O-C₁-C₆ alkyl, -C₃-C₈ cycloalkyl, 4 to 7 membered heterocyclyl, C₆-C₁₀ aryl and 5 to 10 membered heteroaryl, wherein the C₃-C₈ cycloalkyl, 4 to 7 membered heterocyclyl, C₆-C₁₀ aryl and 5 to 10 membered heteroaryl are each optionally further substituted by one or more deuterium, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, halogen, hydroxy, amino, nitro, cyano and ester group;

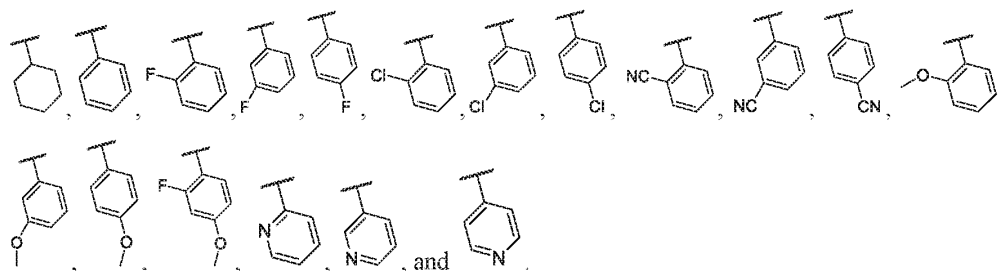
Or R_{7c} and R_{7d} together with the atom to which they are attached can form a C₃-C₈ carbocycle or a 3 to 7 membered heterocycle comprising 1-2 heteroatoms selected from O, N and S.

2. The compound according to claim 1, a stereoisomer thereof, or a pharmaceutically acceptable salt, solvates and prodrugs thereof, wherein each R₁ is independently selected from hydrogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ hydroxyalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl,



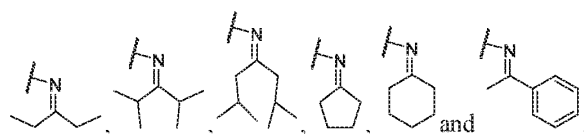
3. The compound according to claim 1, a stereoisomer thereof, or a pharmaceutically acceptable salt, solvates and prodrugs thereof, wherein R₅ is independently selected from hydrogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ hydroxyalkyl and benzyl.

4. The compound according to claim 1, a stereoisomer thereof, or a pharmaceutically acceptable salt, solvates and prodrugs thereof, wherein R_{7a} and R_{7b} are independently selected from hydrogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -C(O)O-C₁-C₆ alkyl,

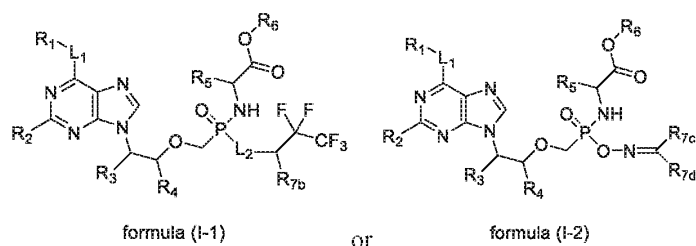


5. The compound according to claim 1, a stereoisomer thereof, or a pharmaceutically acceptable salt, solvates and prodrugs thereof, wherein each R_{7c} and R_{7d} are independently selected from hydrogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl and phenyl.

6. The compound according to claim 1, a stereoisomer thereof, or a pharmaceutically acceptable salt, solvates and prodrugs thereof, wherein $\begin{matrix} R_{7c} \\ | \\ \text{N} \\ | \\ R_{7d} \end{matrix}$ is independently selected from ,



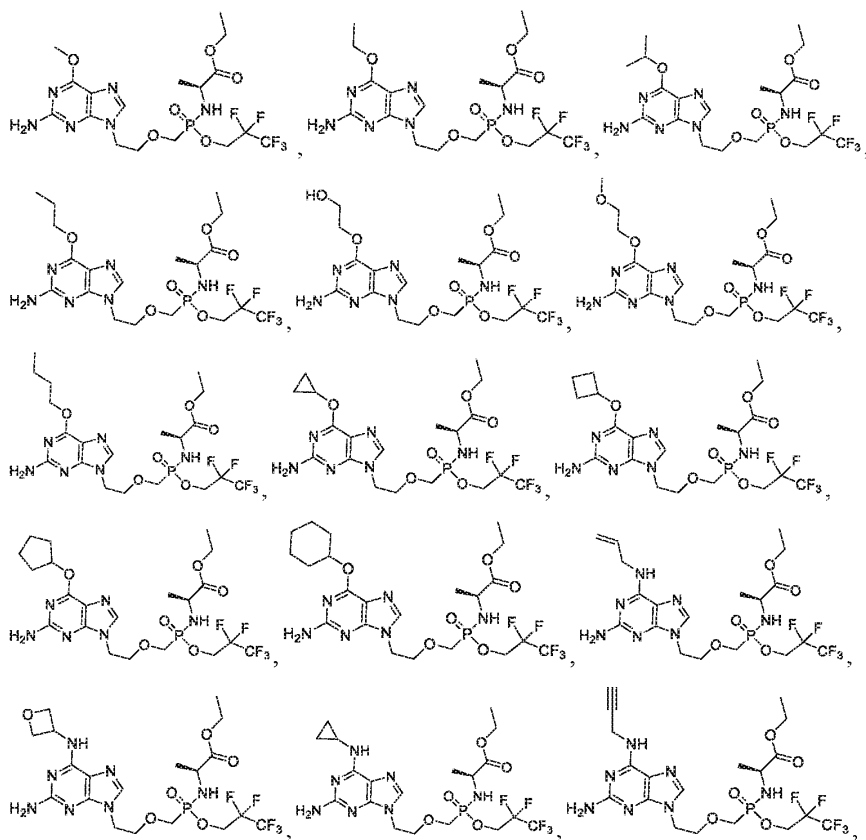
7. The compound according to claim 1, a stereoisomer thereof, or a pharmaceutically acceptable salt, solvates and prodrugs thereof, wherein the compound of formula (I), the stereoisomer or the pharmaceutically acceptable salt, solvates and prodrugs thereof is the compound of formula (I-1) or formula (I-2), the stereoisomer or the pharmaceutically acceptable salt, solvates and prodrugs thereof:

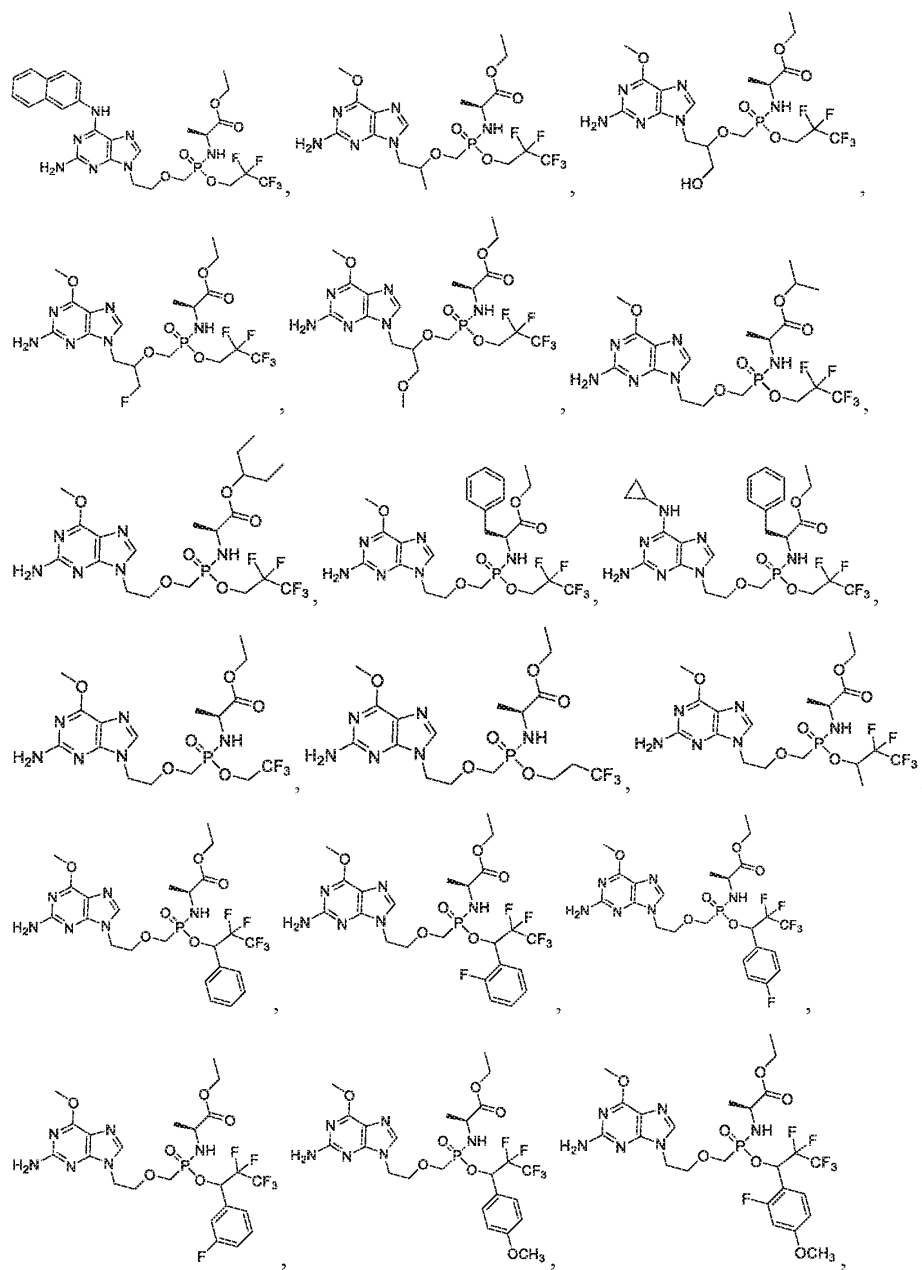


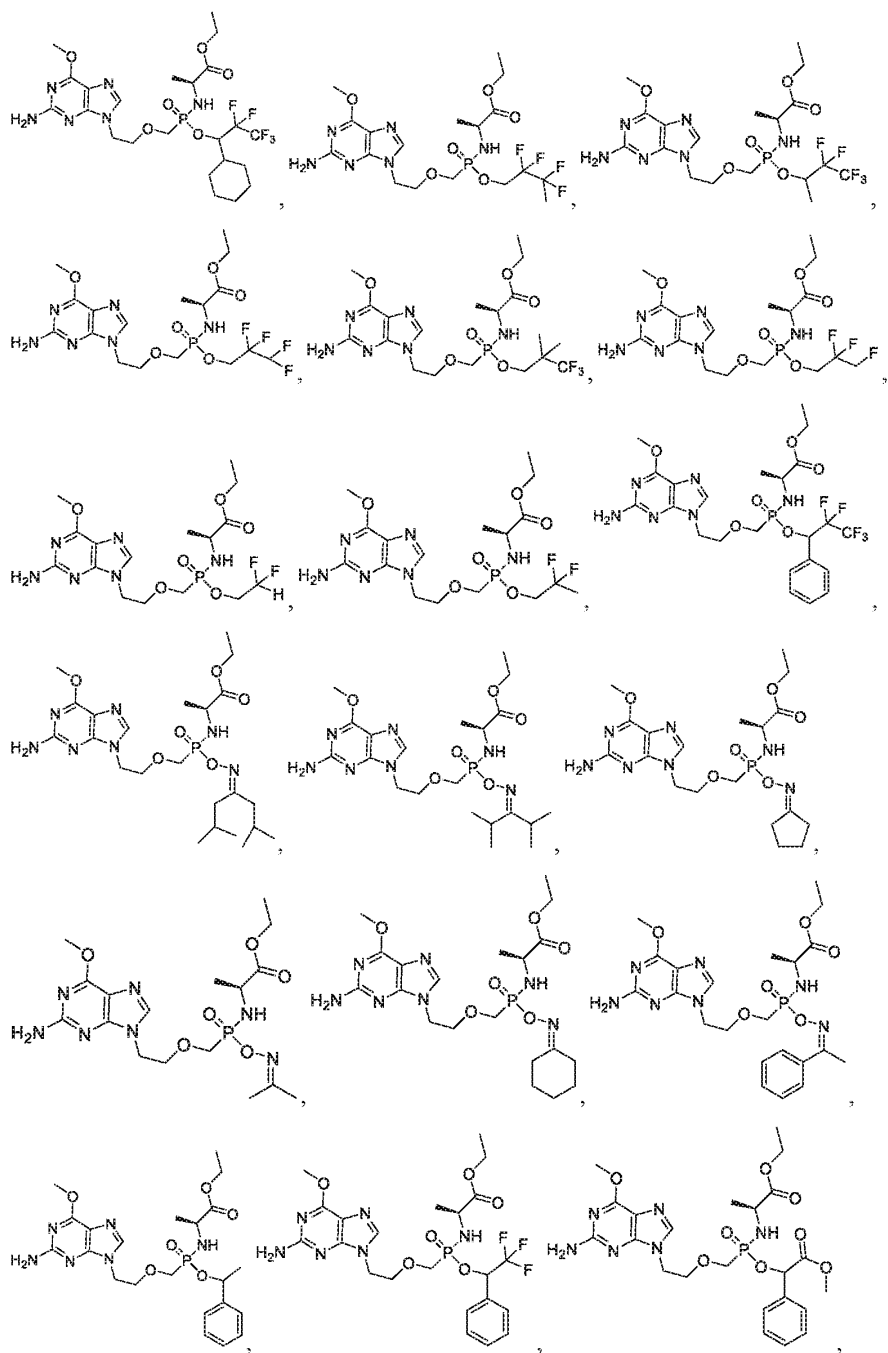
Wherein:

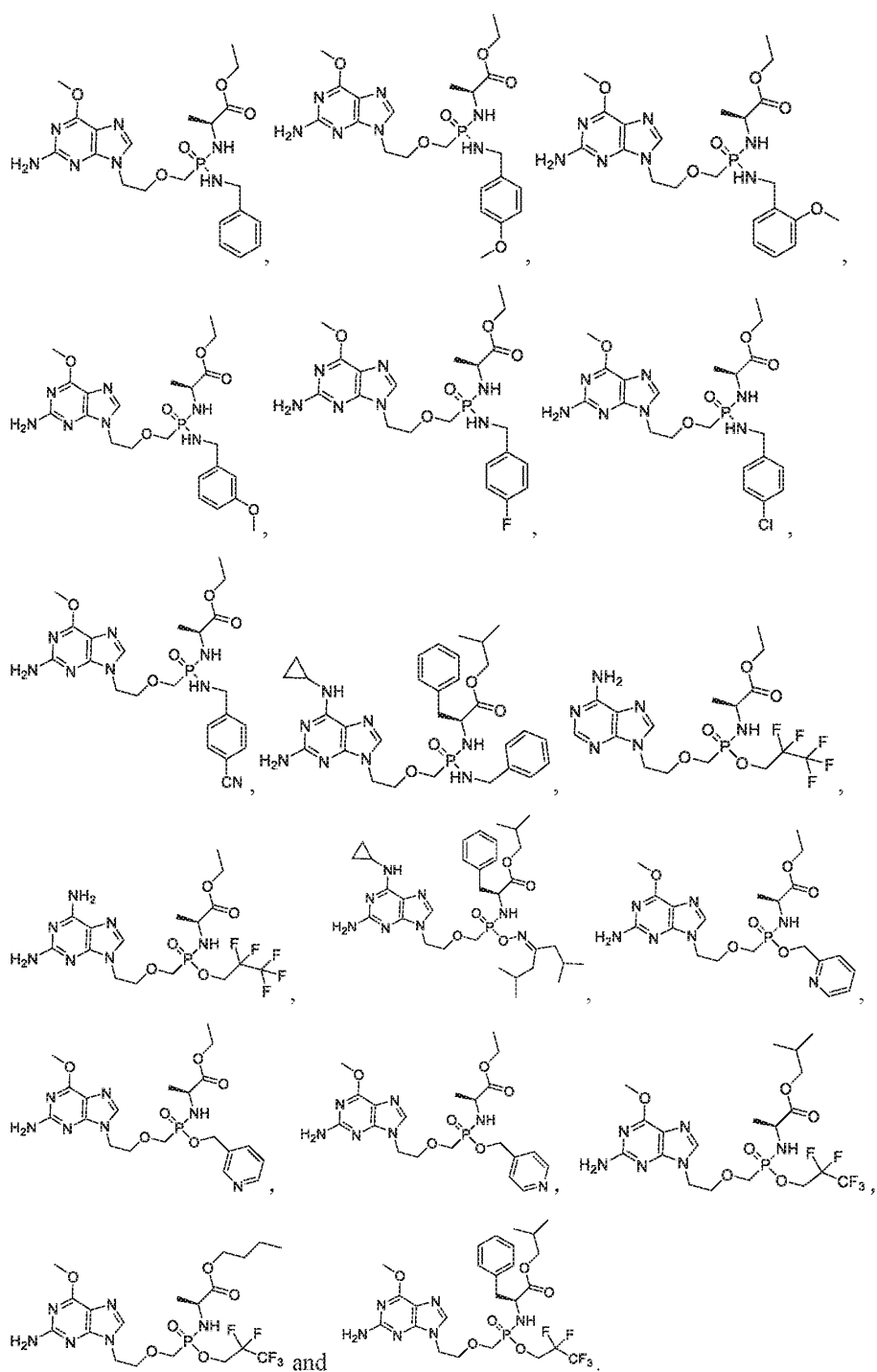
L_1 , L_2 , R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_{7b} , R_{7c} and R_{7d} are defined as in claim 1.

8. The compound according to claim 1, a stereoisomer thereof, or a pharmaceutically acceptable salt, solvates and prodrugs thereof, selected from

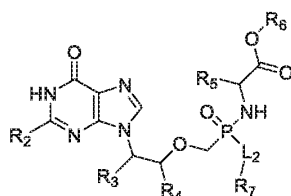








9. A compound formula (II), a stereoisomer thereof, or a pharmaceutically acceptable salt, solvates and prodrugs thereof:



formula (II)

Wherein,

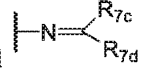
R₂ is independently selected from hydrogen, amino, hydroxy, halogen, cyano, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₂-C₆ alkenyl and C₂-C₆ alkynyl;

R₃ and R₄ are each independently selected from hydrogen, halogen, hydroxy, amino, C₁-C₆ alkyl, deuterated C₁-C₆ alkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ haloalkyl and C₁-C₆ alkoxy;

Or R₃ and R₄ together with the atoms to which they are attached can form a 3 to 7 membered heterocycle comprising 1-2 heteroatoms selected from O, N and S;

R₅ and R₆ are each independently selected from hydrogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₃-C₈ cycloalkyl, 4 to 7 membered heterocyclyl, C₆-C₁₀ aryl, benzyl and 5 to 10 membered heteroaryl, wherein the C₃-C₈ cycloalkyl, 4 to 7 membered heterocyclyl, C₆-C₁₀ aryl, benzyl and 5 to 10 membered heteroaryl are each optionally further substituted by one or more deuterium, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, halogen, hydroxy, amino, nitro, cyano and ester group;

L₂ is independently selected from -O- or -NH-;

R₇ is independently selected from  and ;

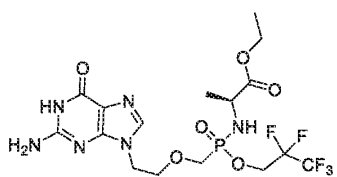
R_{7a}, R_{7b}, R_{7c} and R_{7d} are each independently selected from hydrogen, deuterium, C₁-C₆ alkyl, deuterated C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -C(O)O-C₁-C₆ alkyl, -C₃-C₈ cycloalkyl, 4 to 7 membered heterocyclyl, C₆-C₁₀ aryl and 5 to 10 membered heteroaryl, wherein the C₃-C₈ cycloalkyl, 4 to 7

membered heterocyclyl, C₆-C₁₀ aryl and 5 to 10 membered heteroaryl are each optionally further substituted by one or more deuterium, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, halogen, hydroxy, amino, nitro, cyano and ester group;

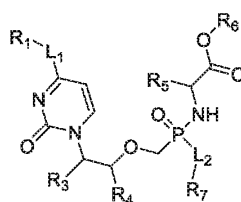
Or R_{7c} and R_{7d} together with the atom to which they are attached can form a C₃-C₈ carbocycle or a 3 to 7 membered heterocycle comprising 1-2 heteroatoms selected from O, N and S.

In a more preferred embodiment, in the compound of formula (II), the stereoisomer or the pharmaceutically acceptable salt, solvates and prodrugs thereof, each R₄ is independently selected from hydrogen, C₁-C₆ alkyl (such as methyl, ethyl, propyl and isopropyl), C₁-C₆ haloalkyl, C₁-C₆ alkoxy and C₁-C₆ hydroxyalkyl.

10. The compound according to claim 9, a stereoisomer thereof, or a pharmaceutically acceptable salt, solvates and prodrugs thereof is



11. A compound formula (III), a stereoisomer thereof, or a pharmaceutically acceptable salt, solvates and prodrugs thereof:



formula (III)

Wherein,

L₁ is independently selected from -O- or -NH-;

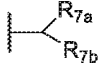
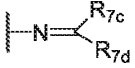
R₁ is independently selected from hydrogen, C₁-C₆ alkyl, deuterated C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₈ cycloalkyl, 4 to 7 membered heterocyclyl, C₆-C₁₀ aryl and 5 to 10 membered heteroaryl, wherein the C₃-C₈ cycloalkyl, 4 to 7 membered heterocyclyl, C₆-C₁₀ aryl and 5 to 10 membered heteroaryl are each optionally further substituted by one or more deuterium, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, halogen, hydroxy, amino, nitro, cyano and ester group;

R₃ and R₄ are each independently selected from hydrogen, deuterium, halogen, hydroxy, amino, C₁-C₆ alkyl, deuterated C₁-C₆ alkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ haloalkyl and C₁-C₆ alkoxy;

Or R₃ and R₄ together with the atoms to which they are attached can form a 3 to 7 membered heterocycle comprising 1-2 heteroatoms selected from O, N and S;

R₅ and R₆ are each independently selected from hydrogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₃-C₈ cycloalkyl, 4 to 7 membered heterocyclyl, C₆-C₁₀ aryl, benzyl and 5 to 10 membered heteroaryl, wherein the C₃-C₈ cycloalkyl, 4 to 7 membered heterocyclyl, C₆-C₁₀ aryl, benzyl and 5 to 10 membered heteroaryl are each optionally further substituted by one or more deuterium, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, halogen, hydroxy, amino, nitro, cyano and ester group;

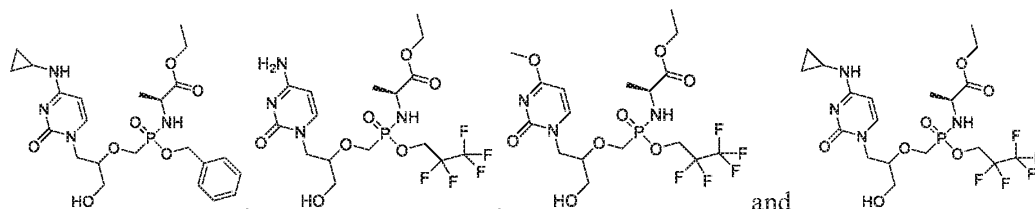
L₂ is independently selected from -O- or -NH-;

R₇ is independently selected from  and .

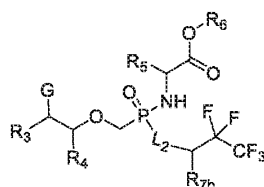
R_{7a}, R_{7b}, R_{7c} and R_{7d} are each independently selected from hydrogen, deuterium, C₁-C₆ alkyl, deuterated C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -C(O)O-C₁-C₆ alkyl, -C₃-C₈ cycloalkyl, 4 to 7 membered heterocyclyl, C₆-C₁₀ aryl and 5 to 10 membered heteroaryl, wherein the C₃-C₈ cycloalkyl, 4 to 7 membered heterocyclyl, C₆-C₁₀ aryl and 5 to 10 membered heteroaryl are each optionally further substituted by one or more deuterium, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, halogen, hydroxy, amino, nitro, cyano and ester group;

Or R_{7c} and R_{7d} together with the atom to which they are attached can form a C₃-C₈ carbocycle or a 3 to 7 membered heterocycle comprising 1-2 heteroatoms selected from O, N and S.

12. The compound according to claim 11, a stereoisomer thereof, or a pharmaceutically acceptable salt, solvates and prodrugs thereof, selected from



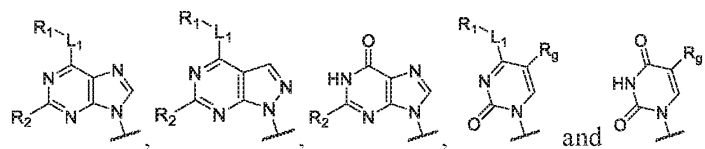
13. A compound formula (IV), a stereoisomer thereof, or a pharmaceutically acceptable salt, solvates and prodrugs thereof:



formula (IV)

Wherein,

G is independently selected from



L₁ is independently selected from -O- or -NH-;

R₁ is independently selected from hydrogen, C₁-C₆ alkyl, deuterated C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₈ cycloalkyl, 4 to 7 membered heterocyclyl, C₆-C₁₀ aryl and 5 to 10 membered heteroaryl, wherein the C₃-C₈ cycloalkyl, 4 to 7 membered heterocyclyl, C₆-C₁₀ aryl and 5 to 10 membered heteroaryl are each optionally further substituted by one or more deuterium, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, halogen, hydroxy, amino, nitro, cyano and ester group;

R₂ is independently selected from hydrogen, amino, hydroxy, halogen, cyano, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₂-C₆ alkenyl and C₂-C₆ alkynyl;

R₆ is independently selected from hydrogen, amino, hydroxy, halogen, cyano, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy and C₁-C₆ haloalkoxy;

R₃ and R₄ are each independently selected from hydrogen, deuterium, halogen, hydroxy, amino, C₁-C₆ alkyl, deuterated C₁-C₆ alkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ haloalkyl and C₁-C₆ alkoxy;

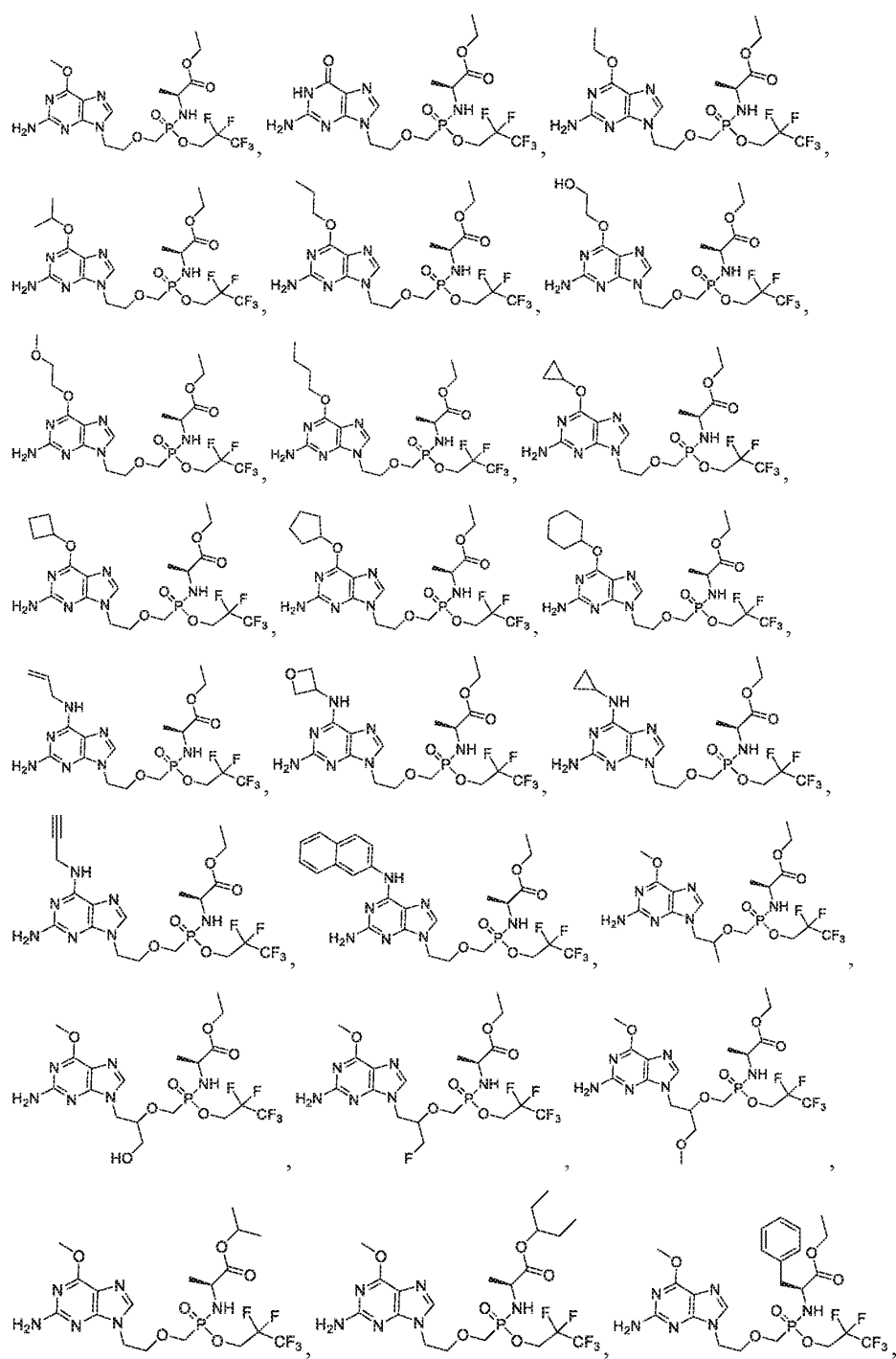
Or R₃ and R₄ together with the atoms to which they are attached can form a 3 to 7 membered heterocycle comprising 1-2 heteroatoms selected from O, N and S;

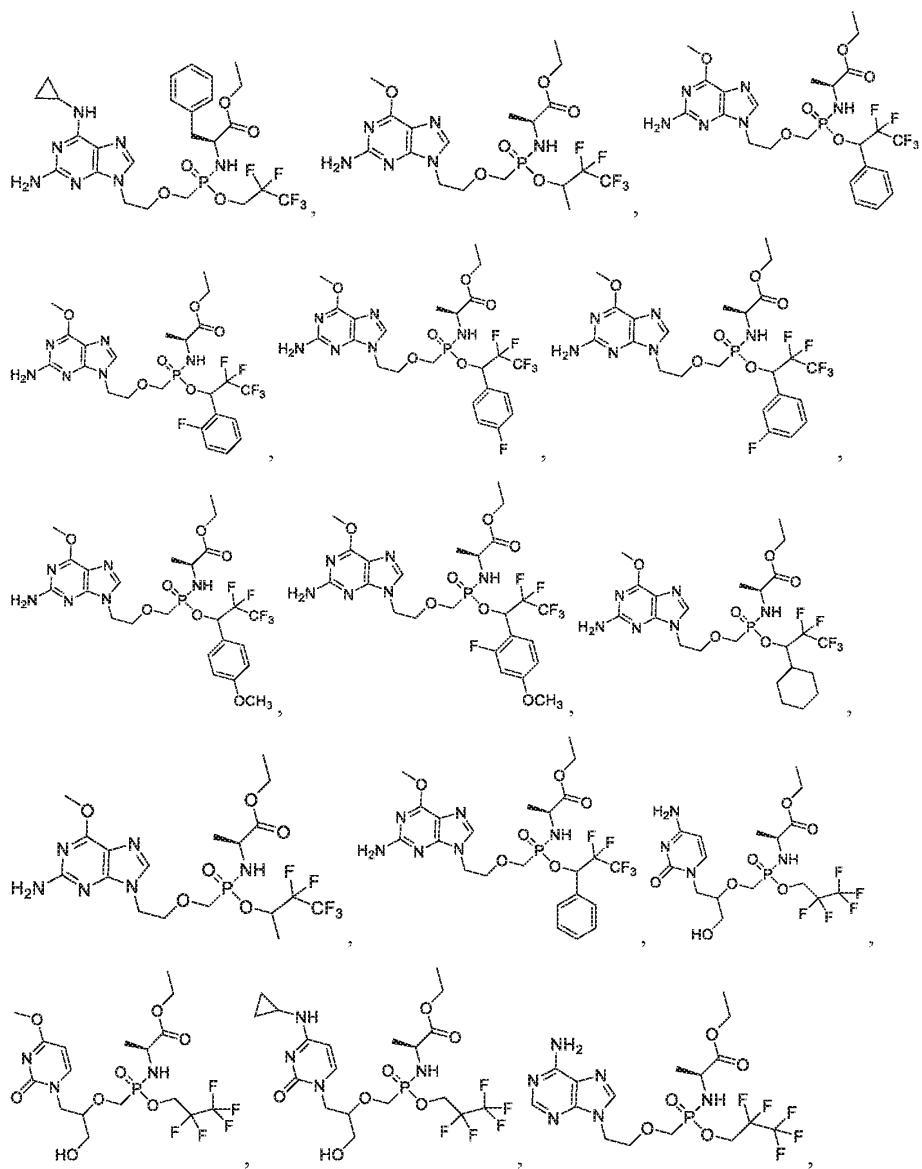
R₅ and R₆ are each independently selected from hydrogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₃-C₈ cycloalkyl, 4 to 7 membered heterocyclyl, C₆-C₁₀ aryl, benzyl and 5 to 10 membered heteroaryl, wherein the C₃-C₈ cycloalkyl, 4 to 7 membered heterocyclyl, C₆-C₁₀ aryl, benzyl and 5 to 10 membered heteroaryl are each optionally further substituted by one or more deuterium, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, halogen, hydroxy, amino, nitro, cyano and ester group;

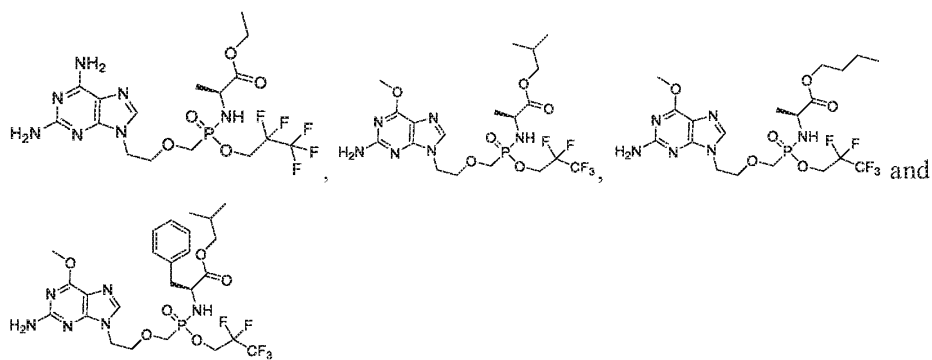
L₂ is independently selected from -O- or -NH-;

R_{7b} is independently selected from hydrogen, deuterium, C₁-C₆ alkyl, deuterated C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -C(O)O-C₁-C₆ alkyl, -C₃-C₈ cycloalkyl, 4 to 7 membered heterocyclyl, C₆-C₁₀ aryl and 5 to 10 membered heteroaryl, wherein the C₃-C₈ cycloalkyl, 4 to 7 membered heterocyclyl, C₆-C₁₀ aryl and 5 to 10 membered heteroaryl are each optionally further substituted by one or more deuterium, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, halogen, hydroxy, amino, nitro, cyano and ester group; a 3 to 7 membered heterocycle comprising 1-2 heteroatoms selected from O, N and S.

14. The compound according to claim 13, a stereoisomer thereof, or a pharmaceutically acceptable salt, solvates and prodrugs thereof, selected from







15. A pharmaceutical composition comprising a compound of any one of claims 1-14, or a stereoisomer thereof, or a pharmaceutically acceptable salt, solvates and prodrugs thereof, and one or more pharmaceutically acceptable carriers.

16. Use of the compound of a compound of any one of claims 1-14, a stereoisomer thereof, or a pharmaceutically acceptable salt, solvates and prodrugs thereof in the preparation of a medicament for the prophylaxis or treatment of the diseases or conditions caused by viral infection, preferably as an antiviral agent against human papillomavirus (HPV).

17. A method of the prophylaxis or treatment of a viral infection, especially HPV infection, comprise administering to a subject in need thereof a compound of any one of claims 1-14, a stereoisomer thereof, or a pharmaceutically acceptable salt, solvates and prodrugs thereof, or a pharmaceutical composition of claim 15.