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(54) **Title**: NOVEL ANTIVIRAL COMPOUNDS

(57) **Abstract**: The present invention relates to a series of novel compounds and derivatives thereof, methods to prevent or treat viral infections by using the novel compounds, processes for their preparation, their use to treat or prevent viral infections and their use to manufacture a medicine to treat or prevent viral infections, preferably infections with viruses belonging to the family of the Togaviridae and more preferably infections with chikungunya virus (CHIKV).

NOVEL ANTIVIRAL COMPOUNDS

FIELD OF THE INVENTION

The present invention relates to a series of novel compounds and derivatives thereof, methods to prevent or treat viral infections by using the novel compounds, processes for their preparation, their use to treat or prevent viral infections and their use to manufacture a medicine to treat or prevent viral infections, preferably infections with viruses belonging to the family of the Togaviridae and more preferably infections with chikungunyavirus (CHIKV). The present invention also relates to the novel compounds and derivatives thereof for use as a medicine, more preferably for use as a medicine for the prevention or treatment of viral infections, preferably infections with viruses belonging to the family of the Togaviridae and more particularly infections with CHIKV. The present invention furthermore relates to pharmaceutical compositions or combination preparations of the novel compounds, to the compositions or preparations for use as a medicine, more preferably for the prevention or treatment of viral infections, preferably infections with viruses belonging to the family of the Togaviridae and more particularly infections with CHIKV.

BACKGROUND OF THE INVENTION

The family of the Togaviridae consists of 2 genera, the Genus Alphavirus including Sindbis virus, Eastern equine encephalitis virus, Western equine encephalitis virus, Venezuelan equine encephalitis virus, Ross River virus, O'nyong'nyong virus, chikungunya, and Semliki Forest virus, and the Genus Rubivirus including Rubella virus.

Chikungunya (CHIKV) is an insect-borne viral disease first described during an outbreak in southern Tanzania in 1952. CHIKV is transmitted to humans by virus-carrying Aedes mosquitoes. CHIKV infection causes an illness with symptoms similar to dengue fever, with an acute febrile phase of the illness lasting two to five days, followed by a prolonged arthralgic disease that affects the joints of the extremities. Most patients recover fully, but in some cases, joint pain may persist for several months, or even years. Occasional cases of eye,

neurological and heart complications have been reported, as well as gastrointestinal complaints. Serious complications are not common, but in older people, the disease can contribute to the cause of death. Often symptoms in infected individuals are mild and the infection may go unrecognized, or be misdiagnosed in areas where dengue occurs. Chikungunya occurs in Africa, Asia and the Indian subcontinent. Human infections in Africa have been at relatively low levels for a number of years, but in 1999-2000, there was a large outbreak in the Democratic Republic of the Congo, and in 2007, there was an outbreak in Gabon. Starting in February 2005, a major outbreak of chikungunya occurred in islands of the Indian Ocean. A large number of imported cases in Europe were associated with this outbreak, mostly in 2006 when the Indian Ocean epidemic was at its peak. A large outbreak of chikungunya in India occurred in 2006 and 2007. Several other countries in South-East Asia were also affected. In 2007, transmission was reported for the first time in Europe, in a localized outbreak in north-eastern Italy. From December 2013 onwards, chikungunya has for the first time been reported to be locally transmitted in the Americas (in the Caribbean). There are no specific drugs to prevent or cure the disease. Treatment is directed primarily at relieving the symptoms, including the joint pain. Although researchers have recently developed a new candidate vaccine to protect against chikungunya virus (Plante et al, 2011. Novel Chikungunya Vaccine Candidate with an IRES-Based Attenuation and Host Range Alteration Mechanism. PLoS Pathogens, 2011; 7 (7)), there is until now no approved commercial chikungunya vaccine available.

There is therefore a clear need in the field for novel, potent, selective compounds with a good activity vs. toxicity profile and this specifically for the viruses of the family of the Togaviridae, more specifically against chikungunya viruses.

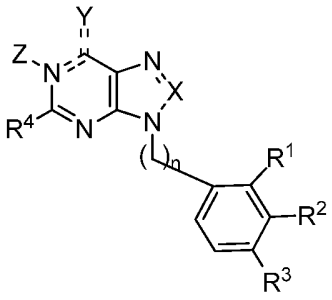
The present invention provides such novel compounds which show activity against Togaviridae, more specifically against CHIKV.

SUMMARY OF THE INVENTION

The invention provides [1,2,3]triazolo[4,5-d]pyrimidin-7(6H)-ones and derivatives thereof as potent viral inhibitors against Togaviridae, preferably against Alphaviruses, and more preferably against chikungunya virus.

The invention relates to [1,2,3]triazolo[4,5-d]pyrimidin-7(6H)-ones and derivatives thereof, which according to the general embodiment of the invention correspond to compounds according to the general formula (I) and (I'), pharmaceutically acceptable salts, solvates, tautomers and isomers (eg. stereoisomers) thereof,

Formula (I)



wherein

(==) is an optional double bond, wherein:

when N==C is a double bond, Z is not present;

when C==Y is a double bond, Y is selected from the group consisting of O, S, and NR^5;

when C==Y is a single bond, Y is selected from the group consisting of OR^5, SR^5, and NR^5R^6;

R^4 is selected from the group consisting of H, C_{1-6} alkyl, aryl, OR^7, SR^7, NR^7R^8, cycloalkyl, $(CH_2)_m$-O-C_{1-3} alkyl, and $(CH_2)_m$-S-C_{1-3} alkyl, and heteroaryl, wherein said alkyl, heteroaryl or aryl groups are optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxyl, sulfhydryl, amino, cyano, and nitro; and wherein m is selected from 0, 1, or 2;

X is selected from the group consisting of N, CR^9, and COH;

n is selected from 0, 1, or 2;

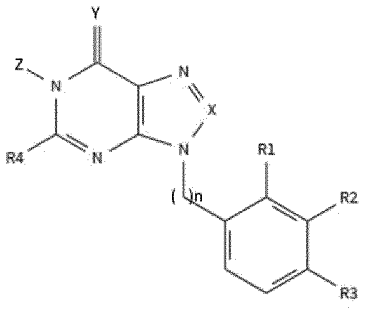
R^1 and R^3 are each independently selected from the group consisting of H, halogen, nitro, C_{1-6} alkyl, OR^{10}, SR^{10}, COR^{10}, and $COOR^{10}$; wherein at least one of R^1 and R^3 is H; R^2 is selected from the group consisting of H, halogen, nitro, CN, C_{1-6} alkyl, OR^{11}, SR^{11}, $NR^{11}R^{12}$, $NR^{11}COR^{12}$, $C=N(OR^{11})R^{12}$, COR^{11}, and $COOR^{11}$, wherein said alkyl group is optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxyl, sulfhydryl, amino, cyano, and nitro; and

R^5, R^6, R^7, R^8 R^9, R^{10}, R^{11}, R^{12} and Z are each independently selected from the group consisting of H and C_{1-6} alkyl, wherein said alkyl groups are optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxyl, sulfhydryl, amino, cyano, and nitro;

with the provisio that 9-[3-(Hydroxymethyl)phenyl]-6-methoxypurine, 6-(Methylamino)-9-[3-(hydroxymethyl)phenyl]purine, and 9-[3-(Hydroxymethyl)phenyl]hypoxanthine are excluded;

and

Formula (I')



wherein

Y is selected from the group consisting of O, S, and NR^5;

R^4 is selected from the group consisting of H, C_{1-6} alkyl, aryl, OR^7, SR^7, NR^7R^8, cycloalkyl, $(CH_2)_m$-O-C_{1-3} alkyl, and $(CH_2)_m$-S-C_{1-3} alkyl, and heteroaryl, wherein said alkyl, heteroaryl or aryl groups are optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxyl, sulfhydryl, amino, cyano, and nitro; and wherein m is selected from 0, 1, or 2;

X is selected from the group consisting of N, CR^9, and COH;

n is selected from 0, 1, or 2;

R^1 and R^3 are each independently selected from the group consisting of H, halogen, nitro, C_{1-6} alkyl, OR^{10}, SR^{10}, COR^{10}, and $COOR^{10}$; wherein at least one of R^1 and R^3 is H;

R^2 is selected from the group consisting of H, halogen, nitro, CN, C_{1-6} alkyl, OR^6, SR^6, $NR^{11}R^{12}$, $NR^{11}COR^{12}$, $C=N(OR^{11})R^{12}$, COR^{11}, and $COOR^{11}$, wherein said alkyl group is optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxyl, sulfhydryl, amino, cyano, and nitro;

R^6 is selected from the group consisting of H and C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-6} heterocycloalkyl, wherein said alkyl- and cycloalkyl-groups are optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxyl, sulfhydryl, amino, cyano, and nitro; and

R^5, R^7, R^8 R^9, R^{10}, R^{11}, R^{12} and Z are each independently selected from the group consisting of H and C_{1-6} alkyl, wherein said alkyl groups are optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxyl, sulfhydryl, amino, cyano, and nitro.

The present invention also concerns a compound having formula I or I', any subgroup thereof, or stereoisomeric forms thereof, for use as a medicine.

The present invention also concerns a compound having formula I or I', any subgroup thereof, or stereoisomeric forms thereof, for use as a medicine for the prevention or treatment of a viral disorder in an animal, preferably in a mammal, said viral disorder being caused by Togaviridae, preferably Alphaviruses, and more preferably chikungunya virus. In a specific embodiment, said viral disorder is an infection with a chikungunya virus. In an embodiment, said mammal is a human being.

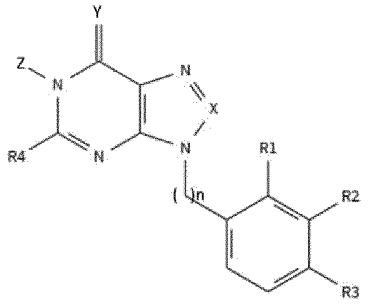
The present invention also concerns a pharmaceutical composition comprising a therapeutically effective amount of a compound having formula I or I', any subgroup thereof, or stereoisomeric forms thereof, and one or more pharmaceutically acceptable exipients. Said composition may further comprise one or more biologically active drugs such as antiviral drugs.

The present invention also concerns a method of prevention or treatment of a viral disorder in an animal, said viral disorder being caused by Togaviridae, preferably Alphaviruses, and more preferably chikungunya virus, comprising the administration of a therapeutically effective amount of a compound having formula I or I', any subgroup thereof, or stereoisomeric forms thereof, optionally in combination with one or more pharmaceutically acceptable excipients. In an embodiment, said animal is a human being.

The present invention also concerns a method for the identification of an agent for the prevention or treatment of a viral disorder in an animal, said viral disorder being caused by Togaviridae, preferably Alphaviruses, and more preferably chikungunya virus, wherein said method comprises screening for agents capable of inhibiting the biological activity of the alphavirus nsP1 protein, more specifically the nsP1 protein of chikungunya virus. In a specific embodiment said agents are capable of inhibiting said nsP1 protein and said agents can inhibit wild type viruses and not nsP1-mutated viruses.

Numbered statements of this invention are:

1. A compound according to formula (I')



(I')

and/or a tautomeric form, and/or a solvate and/or stereoisomer and /or a pharmaceutically acceptable salt thereof, wherein

Y is selected from the group consisting of O, S, and NR^5;

R^4 is selected from the group consisting of H, C_{1-6} alkyl, aryl, OR^7, SR^7, NR^7R^8, cycloalkyl, $(CH_2)_m$-O-C_{1-3} alkyl, and $(CH_2)_m$-S-C_{1-3} alkyl, and heteroaryl, wherein said alkyl, heteroaryl or aryl groups are optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxyl, sulfhydryl, amino, cyano, and nitro; and wherein m is selected from 0, 1, or 2;

X is selected from the group consisting of N, CR^9, and COH;

n is selected from 0, 1, or 2;

R^1 and R^3 are each independently selected from the group consisting of H, halogen, nitro, C_{1-6} alkyl, OR^{10}, SR^{10}, COR^{10}, and $COOR^{10}$; wherein at least one of R^1 and R^3 is H;

R^2 is selected from the group consisting of H, halogen, nitro, CN, C_{1-6} alkyl, OR^6, SR^6, $NR^{11}R^{12}$, $NR^{11}COR^{12}$, $C=N(OR^{11})R^{12}$, COR^{11}, and

$COOR^{11}$, wherein said alkyl group is optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxyl, sulfhydryl, amino, cyano, and nitro;

R^6 is selected from the group consisting of H and C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-6} heterocycloalkyl, wherein said alkyl- and cycloalkyl-groups are optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxyl, sulfhydryl, amino, cyano, and nitro; and

R^5, R^7, R^8 R^9, R^{10}, R^{11}, R^{12} and Z are each independently selected from the group consisting of H and C_{1-6} alkyl, wherein said alkyl groups are optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxyl, sulfhydryl, amino, cyano, and nitro.

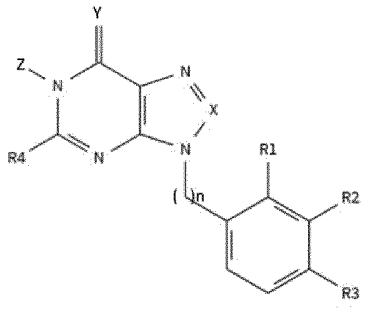
2. The compound according to statement 1, wherein Y is O.
3. The compound according to statement 1 or 2, wherein Z is H.
4. The compound according to any of statements 1 to 3, wherein X is N.
5. The compound according to any of statements 1 to 4, wherein R^4 is methyl or ethyl.
6. The compound according to any of statements 1 to 5, wherein n is 0.
7. The compound according to any of statements 1 to 6, wherein R^1 and R^3 are both H.
8. The compound according to any of statements 1 to 7, wherein R^2 is selected from the group consisting of $COCH_3$, $CH(OH)CH_3$, $C=N(OH)CH_3$, $C=N(OCH_3)CH_3$, CN, $COOCH_2CH_3$, and COOH.
9. The compound according to any of statements 1 to 7, wherein R^2 is selected from the group consisting of OCH_3, $OCH(CH_3)_2$, $N(CH_3)_2$, $NHCOCH_3$, and Cl.
10. The compound according to any of statements 1 to 7, wherein R^2 is $C=N(OCH_3)CH_3$, COCH3 or $OCH(CH_3)_2$.
11. The compound according to statement 1 selected from the group consisting of: 3-(2′-Methoxyphenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-

d]pyrimidin-7(6*H*)-one; 3-(3´-Methoxyphenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 3-(3´-Chlorophenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 3-(3´-Acetylphenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 3-(3´-Benzoylphenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 3-(3´-Isopropoxyphenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; *N*-(3-(5-Methyl-7-oxo-6,7-dihydro-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)phenyl)-acetamide; 3-(4´-Acetylphenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 5-Methyl-3-(4´-propoxyphenyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 3-(3´-Acetylphenyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 3-(Benzo[*d*][1,3]dioxol-5-yl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 3-(5-Methyl-7-oxo-6,7-dihydro-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)benzonitrile; Ethyl 3-(5-methyl-7-oxo-6,7-dihydro-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl) benzoate; 3-(5-Methyl-7-oxo-6,7-dihydro-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)benzoic acid; 3-(3´-Acetylphenyl)-5,6-dimethyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 9-(3´-Acetylphenyl)-2-methyl-1*H*-purin-6(9*H*)-one; 9-(3-Acetylphenyl)-2,8-dimethyl-1*H*-purin-6(9*H*)-one; 3-(3´-(1-Hydroxyethyl)phenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; *(Z/E)*-3-(3´-(1-(Hydroxyimino)ethyl)phenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; (E/*Z*)-3-(3´-(1-(Methoxyimino)ethyl)phenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; (*E/Z*)-Ethyl 2-(((1-(3-(5-methyl-7-oxo-6,7-dihydro-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin -3-yl)phenyl)ethylidene)amino)oxy)acetate; 5-Cyanoethyl-3-(3´-isopropoxyphenyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 3-(3´-Isopropoxyphenyl)-5-phenyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 3-(3´-Isopropoxyphenyl)-5-(4´´-pyridyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 3-(3´-Isopropoxyphenyl)-5-trifluoromethyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 5-Ethyl-3-(3´-isopropoxyphenyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 3-(3´-Isopropoxyphenyl)-5-propyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 3-(3´-Isopropoxyphenyl)-5-isopropyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-

7(6*H*)-one; 3-(3´-Isopropoxyphenyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(6*H*,4*H*)-dione; 3-(3-Isopropoxybenzyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; (E/*Z*)-5-Ethyl-3-(3´-(1-(methoxyimino)ethyl)phenyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; (E/*Z*)-3-(3´-(1-(Methoxyimino)ethyl)phenyl)-5-thioxo-5,6-dihydro-3*H*-[1,2,3]triazolo [4,5-*d*]pyrimidin-7(4*H*)-one; (E/*Z*)-3-(3´-(1-(methoxyimino)ethyl)phenyl)-5-(methylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 3-(3´-Acetylphenyl)-5-ethyl-3*H*-[1,2,3]triazolo[4,5-*d*]pirimidin-7(6*H*)-one; 5-Ethyl-3-(3-(1-hydroxyethyl)phenyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pirimidin-7(6*H*)-one; (*R*) and (S) 3-(3´-(1-Hydroxyethyl)phenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pirimidin-7(6*H*)-one; 5-ethyl-3-(3-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one; and 5-ethyl-3-(3-(piperidin-4-yloxy)phenyl)-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one.

12. A compound according to any of statements 1 to 11 for use as a medicine.

13. A compound according to any of statements 1 to 11, or the compound according to formula (I')



(I')

and/or a tautomeric form, and/or a solvate and/or stereoisomer and /or a pharmaceutically acceptable salt thereof, wherein

Y is selected from the group consisting of O, S, and NR^5;

R^4 is selected from the group consisting of H, C_{1-6} alkyl, aryl, OR^7, SR^7, NR^7R^8, cycloalkyl, $(CH2)_m$-O-C_{1-3} alkyl, $(CH2)_m$-S-C_{1-3} alkyl, and heteroaryl, wherein said alkyl, heteroaryl or aryl groups are optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxyl, sulfhydryl, amino, cyano, and nitro; and wherein m is selected from 0, 1, or 2;

X is selected from the group consisting of N, CR^9, and COH;

n is selected from 0, 1, or 2;

R^1 and R^3 are each independently selected from the group consisting of H, halogen, nitro, C_{1-6} alkyl, OR^{10}, SR^{10}, COR^{10}, and $COOR^{10}$; wherein at least one of R^1 and R^3 is H;

R^2 is selected from the group consisting of H, halogen, nitro, CN, C_{1-6} alkyl, OR^6, SR^6, $NR^{11}R^{12}$, $NR^{11}COR^{12}$, $C=N(OR^{11})R^{12}$, COR^{11}, and $COOR^{11}$, wherein said alkyl group is optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxyl, sulfhydryl, amino, cyano, and nitro;

R^6 is selected from the group consisting of H and C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-6} hetrocycloalkyl, wherein said alkyl- and cycloalkyl-groups are optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxyl, sulfhydryl, amino, cyano, and nitro; and

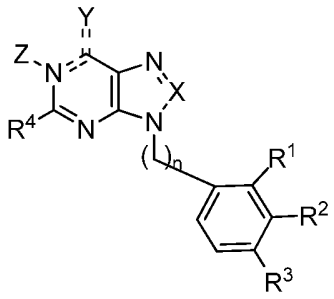
R^5, R^7, R^8 R^9, R^{10}, R^{11}, R^{12} and Z are each independently selected from the group consisting of H and C_{1-6} alkyl, wherein said alkyl groups are optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxyl, sulfhydryl, amino, cyano, and nitro;

for use as a medicine for the prevention or treatment of a viral disorder in a mammal.

14. The compound according to statement 13, wherein said viral disorder is an infection with a virus belonging to the the family of the Togaviridae.
15. The compound according to statement 13 or 14, wherein said viral disorder is a viral infection with an alphavirus.
16. The compound according to any of statements 13 to 15, wherein said viral disorder is a viral infection with chikungunya virus.
17. The compound according to any of statements 13 to 16, wherein said mammal is a human being.
18. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any of statements 1 to 11 and one or more pharmaceutically acceptable carriers.

Further numbered statements of this invention are:

1. A compound according to formula (I)



(I)

and/or a tautomeric form, and/or a solvate and/or stereoisomer and /or a pharmaceutically acceptable salt thereof, wherein

(==) is an optional double bond, wherein:

when N==C is a double bond, Z is not present;

when C==Y is a double bond, Y is selected from the group consisting of O, S, and NR^5;

when C==Y is a single bond, Y is selected from the group consisting of OR^5, SR^5, and NR^5R^6;

R^4 is selected from the group consisting of H, C_{1-6} alkyl, aryl, OR^7, SR^7, NR^7R^8, cycloalkyl, $(CH2)_m$-O-C_{1-3} alkyl, and $(CH2)_m$-S-C_{1-3} alkyl, and heteroaryl, wherein said alkyl, heteroaryl or aryl groups are optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxyl, sulfhydryl, amino, cyano, and nitro; and wherein m is selected from 0, 1, or 2;

X is selected from the group consisting of N, CR^9, and COH;

n is selected from 0, 1, or 2;

R^1 and R^3 are each independently selected from the group consisting of H, halogen, nitro, C_{1-6} alkyl, OR^{10}, SR^{10}, COR^{10}, and $COOR^{10}$; wherein at least one of R^1 and R^3 is H;

R^2 is selected from the group consisting of H, halogen, nitro, CN, C_{1-6} alkyl, OR^{11}, SR^{11}, $NR^{11}R^{12}$, $NR^{11}COR^{12}$, $C=N(OR^{11})R^{12}$, COR^{11}, and $COOR^{11}$, wherein said alkyl group is optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxyl, sulfhydryl, amino, cyano, and nitro; and

R^5, R^6, R^7, R^8 R^9, R^{10}, R^{11}, R^{12} and Z are each independently selected from the group consisting of H and C_{1-6} alkyl, wherein said alkyl groups are optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxyl, sulfhydryl, amino, cyano, and nitro;

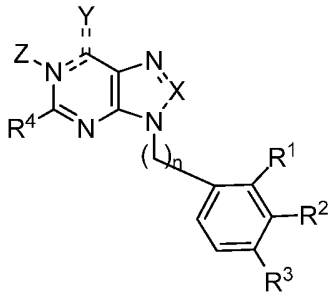
with the provisio that 9-[3-(Hydroxymethyl)phenyl]-6-methoxypurine, 6-(Methylamino)-9-[3-(hydroxymethyl)phenyl]purine, and 9-[3-(Hydroxymethyl)phenyl]hypoxanthine are excluded.

2. The compound according to statement 1, wherein C==Y is a double bond and Y is O.
3. The compound according to statement 1or 2, wherein Z is H.
4. The compound according to any of statements 1 to 3, wherein X is N.

5. The compound according to any of statements 1 to 4, wherein R^4 is methyl or ethyl.
6. The compound according to any of statements 1 to 5, wherein n is 0.
7. The compound according to any of statements 1 to 6, wherein R^1 and R^3 are both H.
8. The compound according to any of statements 1 to 7, wherein R^2 is selected from the group consisting of $COCH_3$, $CH(OH)CH_3$, $C=N(OH)CH_3$, $C=N(OCH_3)CH_3$, CN, $COOCH_2CH_3$, and COOH.
9. The compound according to any of statements 1 to 7, wherein R^2 is selected from the group consisting of OCH_3, $OCH(CH_3)_2$, $N(CH_3)_2$, $NHCOCH_3$, and Cl.
10. The compound according to any of statements 1 to 7, wherein R^2 is $C=N(OCH_3)CH_3$, $COCH_3$ or $OCH(CH_3)_2$.
11. The compound according to statement 1 selected from the group consisting of: 3-(2´-Methoxyphenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 3-(3´-Methoxyphenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 3-(3´-Chlorophenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 3-(3´-Acetylphenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 3-(3´-Benzoylphenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 3-(3´-Isopropoxyphenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; *N*-(3-(5-Methyl-7-oxo-6,7-dihydro-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)phenyl)-acetamide; 3-(4´-Acetylphenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 5-Methyl-3-(4´-propoxyphenyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 3-(3´-Acetylphenyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 3-(Benzo[*d*][1,3]dioxol-5-yl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 3-(5-Methyl-7-oxo-6,7-dihydro-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)benzonitrile; Ethyl 3-(5-methyl-7-oxo-6,7-dihydro-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl) benzoate; 3-(5-Methyl-7-oxo-6,7-dihydro-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)benzoic acid; 3-(3´-Acetylphenyl)-7-amino-5-methyl-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 3-(3´-Acetylphenyl)-5-methyl-7-

methylamino-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 3-(3´-Acetylphenyl)-7-methoxy-5-methyl-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 3-(3´-Acetylphenyl)-5,6-dimethyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 9-(3´-Acetylphenyl)-2-methyl-1*H*-purin-6(9*H*)-one; 9-(3-Acetylphenyl)-2,8-dimethyl-1*H*-purin-6(9*H*)-one; 3-(3´-(1-Hydroxyethyl)phenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; *(Z/E)*-3-(3´-(1-(Hydroxyimino)ethyl)phenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; (E/*Z*)-3-(3´-(1-(Methoxyimino)ethyl)phenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; (*E/Z*)-Ethyl 2-(((1-(3-(5-methyl-7-oxo-6,7-dihydro-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin -3-yl)phenyl)ethylidene)amino)oxy)acetate; 5-Cyanoethyl-3-(3´-isopropoxyphenyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 3-(3´-Isopropoxyphenyl)-5-phenyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 3-(3´-Isopropoxyphenyl)-5-(4´´-pyridyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 3-(3´-Isopropoxyphenyl)-5-trifluoromethyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 5-Ethyl-3-(3´-isopropoxyphenyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 3-(3´-Isopropoxyphenyl)-5-propyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 3-(3´-Isopropoxyphenyl)-5-isopropyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 3-(3´-Isopropoxyphenyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(6*H*,4*H*)-dione; 3-(3-Isopropoxybenzyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; (E/*Z*)-5-Ethyl-3-(3´-(1-(methoxyimino)ethyl)phenyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; (E/*Z*)-3-(3´-(1-(Methoxyimino)ethyl)phenyl)-5-thioxo-5,6-dihydro-3*H*-[1,2,3]triazolo [4,5-*d*]pyrimidin-7(4*H*)-one; and (E/*Z*)-3-(3´-(1-(methoxyimino)ethyl)phenyl)-5-(methylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one.

12. A compound according to any of statements 1 to 11 for use as a medicine.
13. A compound according to any of statements 1 to 11, or the compound according to formula (I)



(I)

and/or a tautomeric form, and/or a solvate and/or stereoisomer and /or a pharmaceutically acceptable salt thereof, wherein

(==) is an optional double bond, wherein:

when N==C is a double bond, Z is not present;

when C==Y is a double bond, Y is selected from the group consisting of O, S, and NR^5;

when C==Y is a single bond, Y is selected from the group consisting of OR^5, SR^5, and NR^5R^6;

R^4 is selected from the group consisting of H, C_{1-6} alkyl, aryl, OR^7, SR^7, NR^7R^8, cycloalkyl, $(CH2)_m$-O-C_{1-3} alkyl, $(CH2)_m$-S-C_{1-3} alkyl, and heteroaryl, wherein said alkyl, heteroaryl or aryl groups are optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxyl, sulfhydryl, amino, cyano, and nitro; and wherein m is selected from 0, 1, or 2;

X is selected from the group consisting of N, CR^9, and COH;

n is selected from 0, 1, or 2;

R^1 and R^3 are each independently selected from the group consisting of H, halogen, nitro, C_{1-6} alkyl, OR^{10}, SR^{10}, COR^{10}, and $COOR^{10}$; wherein at least one of R^1 and R^3 is H;

R^2 is selected from the group consisting of H, halogen, nitro, CN, C_{1-6} alkyl, OR^{11}, SR^{11}, $NR^{11}R^{12}$, $NR^{11}COR^{12}$, $C=N(OR^{11})R^{12}$, COR^{11}, and $COOR^{11}$, wherein said alkyl group is optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxyl, sulfhydryl, amino, cyano, and nitro; and

R^5, R^6, R^7, R^8 R^9, R^{10}, R^{11}, R^{12} and Z are each independently selected from the group consisting of H and C_{1-6} alkyl, wherein said alkyl groups are optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxyl, sulfhydryl, amino, cyano, and nitro;

for use as a medicine for the prevention or treatment of a viral disorder in a mammal.

14. The compound according to statement 13, wherein said viral disorder is an infection with a virus belonging to the the family of the Togaviridae.
15. The compound according to statement 13 or 14, wherein said viral disorder is a viral infection with chikungunya virus.
16. The compound according to any of statements 13 to 15, wherein said mammal is a human being.
17. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any of statements 1 to 11 and one or more pharmaceutically acceptable carriers.

DETAILED DESCRIPTION OF THE INVENTION

Brief description of the figures of the invention

Figure 1. Dose-response effect of compound 5d (MADTP_0314) and a selection of analogues (compound 5f (MADTP_0347), compound 12a (MADTP_0349), and compound 12b (MADTP_0350)), on the replication of wild type virus compared with 5d-resistant CHIKV virus (MADTP_0314-resistant virus). None of the molecules did exert an antiviral effect on the 5d-resistant CHIKV isolates (full resistance was observed) compared to the clear antiviral activity that was observed on the replication of wild-type CHIKV.

Figure 2. Sequence analysis of 5d-resistant virus. One clear mutation was observed in the genome of all 5d-resistant chikungunya virus variants. At position 176 of the nsP1 gene, cytidine was mutated into a thymidine, which at

the protein level translates into a proline-to-serine mutation at position 34 of the nsP1 protein.

Figure 3. Comparative amino acid sequence analysis. Alignment of the amino acid sequence stretch surrounding the nsP1 position 34 of several alphaviruses and rubella virus (RV). A highly conserved amino acid region is observed (grey), in which the histidine of the putative methyltransferase motif is present at position 37. The amino acid that is mutated in MADTP_0314-resistant virus isolates ($P_{34}S$) is also highlighted.

Description

The present invention provides novel [1,2,3]triazolo[4,5-d]pyrimidin-7(6H)-ones with potent antiviral activity against Togaviridae, preferably against Alphaviruses, and more preferably against chikungunya virus. One embodiment of the present invention concerns the compounds and formulations of the present invention, including the compounds of formula I or any subgroup thereof, for human use, such as the antiviral use against Togaviridae, preferably against Alpha viruses, and more preferably against chikungunya virus. In specific embodiments of the present invention, said Alphaviruses are selected from the group consisting of Sindbis virus, Eastern equine encephalitis virus, Western equine encephalitis virus, Venezuelan equine encephalitis virus, Ross River virus, O'nyong'nyong virus, chikungunya, and Semliki Forest virus. In more specific embodiments said Alphaviruses are Sindbis virus, chikungunya, and Semliki Forest virus. In other embodiments of the present invention, said Togaviridae are the viruses from the Genus Rubivirus including Rubella virus. Another embodiment of the present invention concerns the compounds and formulations of the present invention, including the compounds of formula I and I' or any subgroup thereof, for veterinary use such as the antiviral use against Togaviridae, such as the viruses that cause eastern equine encephalitis and western equine encephalitis.

The invention provides several synthetic methodologies for creating [1,2,3]triazolo[4,5-d]pyrimidin-7(6H)-ones derivatives according to the following

general procedures exemplified with some specific [1,2,3]triazolo[4,5-d]pyrimidin-7(6H)-ones. These procedures can however be applied by a person skilled in the art to other compounds of the invention.

One embodiment of the present invention concerns a compound according to the invention, including the compounds of formula I, wherein C---Y is a double bond and Y is O.

A preferred embodiment of the present invention concerns a compound according to the invention, including the compounds of formula I, wherein C---Y is a double bond, more preferably the compounds of formula I'. Another preferred embodiment of the present invention concerns a compound according to the invention including its use, which refers to the compounds of formula I', wherein Y is O.

One embodiment of the present invention concerns a compound according to the invention, including the compounds of formula I, wherein C---Y is a single bond and Y is OH.

One embodiment of the present invention concerns a compound according to the invention, including the compounds of formula I, wherein N---C is a single bond and Z is H. Another embodiment of the present invention concerns a compound according to the invention, including the compounds of formula I', wherein Z is H.

One embodiment of the present invention concerns a compound according to the invention, including the compounds of formula I and I', wherein R^1 and R^3 are both H. One embodiment of the present invention concerns a compound according to the invention, including the compounds of formula I and I', wherein R^2 is selected from the group consisting of $COCH_3$, $CH(OH)CH_3$, $C=N(OH)CH_3$, $C=N(OCH_3)CH_3$, CN, $COOCH_2CH_3$, COOH, OCH_3, $OCH(CH_3)_2$, $N(CH_3)_2$, $NHCOCH_3$, and Cl. In a more specific embodiment R^2 is $OCH(CH_3)_2$. In another specific embodiment R^2 is $COCH_3$. In another specific embodiment R^2 is $C=N(OCH_3)CH_3$. In another specific embodiment, R^1 and R^3 are both H and R^2 is $C=N(OCH_3)CH_3$ or $OCH(CH_3)_2$.

One embodiment of the present invention concerns a compound according to the invention, including the compounds of formula I and I', wherein X is N or CH. In a more specific embodiment X is N. In another specific embodiment X is CH.

One embodiment of the present invention concerns a compound according to the invention, including the compounds of formula I and I', wherein R^4 is methyl or ethyl. In a more specific embodiment R^4 is methyl. In another specific embodiment R^4 is ethyl.

One embodiment of the present invention concerns a compound according to the invention, including the compounds of formula I and I', wherein n is 0.

One embodiment of the present invention concerns a compound according to the invention, including the compounds of formula I and I' wherein R^6 is independently selected from the group consisting of H and C_{1-6} alkyl, wherein said alkyl groups are optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxyl, sulfhydryl, amino, cyano, and nitro.

The present invention also concerns the use of the compound of formula I and I', any subgroup thereof, or stereoisomeric forms thereof, for the manufacture of a medicament for the prevention or treatment of a viral disorder in an animal. In an embodiment, said viral disorder is caused by Togaviridae, preferably Alphaviruses, and more preferably chikungunya virus. In an embodiment, said animal is a mammal, preferably said mammal is a human being. In a specific embodiment, said viral disorder is an infection with an Alphavirus, more specificly said Alphavirus is selected from the group consisting of Sindbis virus, Eastern equine encephalitis virus, Western equine encephalitis virus, Venezuelan equine encephalitis virus, Ross River virus, O'nyong'nyong virus, chikungunya, and Semliki Forest virus. In more specific embodiments said Alphaviruses are Sindbis virus, chikungunya, and Semliki Forest virus. In other embodiments of the present invention, said Togaviridae are the viruses from the

Genus Rubivirus including Rubella virus. In a specific embodiment, said viral disorder is an infection with a chikungunya virus.

Another embodiment of this invention includes the various precursor or "prodrug" forms of the compounds of the present invention, including the compounds of formula I and I' or any subgroup thereof. It may be desirable to formulate the compounds of the present invention in the form of a chemical species which itself is not significantly biologically active, but which when delivered to the body of a human being or higher mammal will undergo a chemical reaction catalyzed by the normal function of the body, inter alia, enzymes present in the stomach or in blood serum, said chemical reaction having the effect of releasing a compound as defined herein. The term "prodrug" or "pro-drug" thus relates to these species which are converted in vivo into the active pharmaceutical ingredient.

The pro-drugs of the present invention can have any form suitable to the formulator, for example, esters are non-limiting common pro-drug forms. In the present case, however, the pro-drug may necessarily exist in a form wherein a covalent bond is cleaved by the action of an enzyme present at the target locus. For example, a C-C covalent bond may be selectively cleaved by one or more enzymes at said target locus and, therefore, a pro-drug in a form other than an easily hydrolysable precursor, inter alia an ester, an amide, and the like, may be used.

For the purposes of the present invention the term "therapeutically suitable pro-drug" is defined herein as a compound modified in such a way as to be transformed in vivo to the therapeutically active form, whether by way of a single or by multiple biological transformations, when in contact with the tissues of humans or mammals to which the pro-drug has been administered, and without undue toxicity, irritation, or allergic response, and achieving the intended therapeutic outcome.

The present invention also concerns a method for the identification of an agent for the prevention or treatment of a viral disorder in an animal, said viral

disorder being caused by Togaviridae, preferably Alphaviruses, and more preferably chikungunya virus, wherein said method comprises screening for agents capable of inhibiting an alphavirus nsP1 protein, more specifically the nsP1 protein of chikungunya virus. In a specific embodiment said agents are capable of inhibiting said nsP1 protein and said agents can inhibit wild type viruses and not nsP1-mutated viruses. In a more specific embodiment of the present invention, said agent is identified by a method comprising the steps of:

(a) Measuring the inhibitory effect of said agent against a wild type virus;
(b) Measuring the inhibitory effect of said agent against nsP1-mutated virus; and
(c) Comparing the inhibitory effect of step (a) to the inhibitory effect of step (b), whereby the inhibitory effect of step (a) is significant larger (at least 2 times, preferably at least 1 log scale) than the inhibitory effect of step (b).

In a more specific embodiment, said wild type virus of step (a) is an alphavirus, more specifically a chikungunya virus and said nsP1 mutated virus is a nsP1 mutated alphavirus, more specifically a nsP1 mutated chikungunya virus, eg. the 5d-resistant CHIKV of Example 4 of the present invention (as described in Figure 2). Another specific embodiment of the present invention relates to the screening method for the identification of agents as described hereabove, wherein said agent is identified when it inhibits the wild type virus, eg. in a replication assay as described in the present invention, whereas it fails to inhibit the nsP1-mutated virus, eg in a replication assay as described in the present invention using a nsP1-mutated alpha virus, more specifically a nsP1-mutated chikungunya virus. In a more specific embodiment of the present invention, said nsP1-mutated virus contains a mutation which modulates any activity associated with nsP1, such as a modulation of its enzymatic activity, eg. methyltransferase or guanylyltransferase.

The present invention also relates to the agents, identified by the screening methods as described in the present invention, and their use for the treatment or prophylaxis of viral infections, preferably Togaviridae infections, more preferably viral infections by Alphaviruses such as chikungunya virus.

DEFINITIONS

In each of the following definitions, the number of carbon atoms represents the maximum number of carbon atoms generally optimally present in the substituent or linker; it is understood that where otherwise indicated in the present application, the number of carbon atoms represents the optimal maximum number of carbon atoms for that particular substituent or linker.

As used herein with respect to a substituting radical, and unless otherwise stated, the term " C_{1-6} alkyl " means straight and branched chain saturated acyclic hydrocarbon monovalent radicals having from 1 to 6 carbon atoms such as, for example, methyl, ethyl, propyl, n-butyl, 1-methylethyl (isopropyl), 2-methylpropyl (isobutyl), 1,1-dimethylethyl (ter-butyl), 2-methylbutyl, n-pentyl, dimethylpropyl, n-hexyl, 2-methylpentyl, 3-methylpentyl and the like. By analogy, the term " C_{1-3} alkyl " refers to such radicals having from 1 to 3 carbon atoms, i.e. up to and including propyl.

As used herein with respect to a substituting radical, and unless otherwise stated, the term " cycloalkyl " means a mono- or polycyclic saturated hydrocarbon monovalent radical having from 3 to 10 carbon atoms), such as for instance cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like, or a C_{7-10} polycyclic saturated hydrocarbon monovalent radical having from 7 to 10 carbon atoms such as, for instance, norbornyl, fenchyl, trimethyltricycloheptyl or adamantyl. (C_{3-6})cycloalkyl refers to a cycloalkyl having from 3 to 6 carbon atoms. (C_{3-6})heterocycloalkyl refers to a (C_{3-6})cycloalkyl wherein at least one carbon atom is replaced by a hetero atom, said heteroatom being independently selected from the group consisting of nitrogen, oxygen, sulfur, selenium and phosphorus. Examples of such (C_{3-6})heterocycloalkyl include but are not limiting to piperidine and tetrahydropyran.As used herein with respect to a substituting radical, and unless otherwise stated, the term " aryl " designate any mono- or polycyclic aromatic monovalent hydrocarbon radical having from 6 up to 30 carbon atoms such as but not limited to phenyl, naphthyl, anthracenyl, phenantracyl, fluoranthenyl, chrysenyl, pyrenyl, biphenylyl, terphenyl, picenyl, indenyl, biphenyl, indacenyl, benzocyclobutenyl,

benzocyclooctenyl and the like, including fused benzo-C4-β cycloalkyl radicals (the latter being as defined above) such as, for instance, indanyl, tetrahydronaphthyl, fluorenyl and the like, all of the said radicals being optionally substituted with one or more substituents independently selected from the group consisting of halogen, amino, trifluoromethyl, hydroxyl, sulfhydryl and nitro, such as for instance 4-fluorophenyl, 4-chlorophenyl, 3,4-dichlorophenyl, 4-cyanophenyl, 2,6-dichlorophenyl, 2-fluorophenyl, 3-chlorophenyl, 3,5-dichlorophenyl and the like.

As used herein with respect to a substituting radical, and unless otherwise stated, the term " heteroaryl " designate an aryl with at least one heteroatom in one or more heterocyclic rings, each of said rings having from 3 to 10 atoms (and optionally further including one or more heteroatoms attached to one or more carbon atoms of said ring, for instance in the form of a carbonyl or thiocarbonyl or selenocarbonyl group, and/or to one or more heteroatoms of said ring, for instance in the form of a sulfone, sulfoxide, N-oxide, phosphate, phosphonate or selenium oxide group), each of said heteroatoms being independently selected from the group consisting of nitrogen, oxygen, sulfur, selenium and phosphorus.

CHEMISTRY

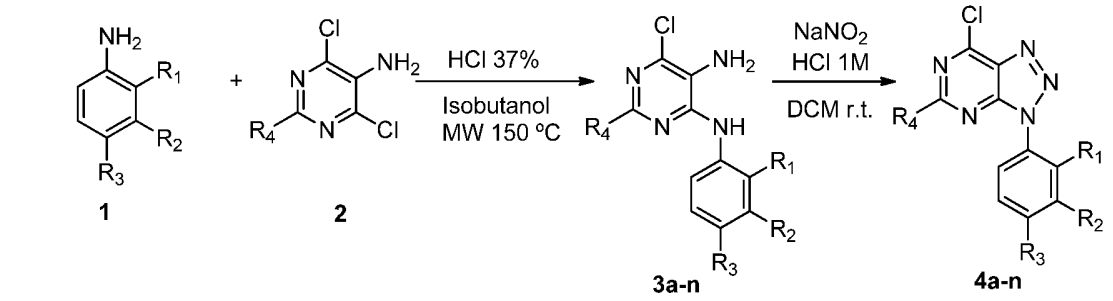
Surprisingly, some [1,2,3]triazolo[4,5-d]pyrimidin-7(6H)-ones have shown selective antiviral activity against the replication of CHIKV in a virus cell based assay.

One aspect of the invention relates to processes for the preparation of the compounds of formula (I) and (I') or structural analogues thereof. Such processes will be explained with reference to the synthetic schemes 1 to 7 hereinafter.

In one embodiment of said aspect of the invention, the synthesis of the [1,2,3]triazolo[4,5-d]pyrimidin-7(6H)-ones is represented in Scheme 1. Reaction of an equimolar amount of differently substituted anilines (**1**) with 4,6-dichloro-5-aminopyrimidines (**2**) in isobutanol in the presence of HCl at 150 °C for 10 min

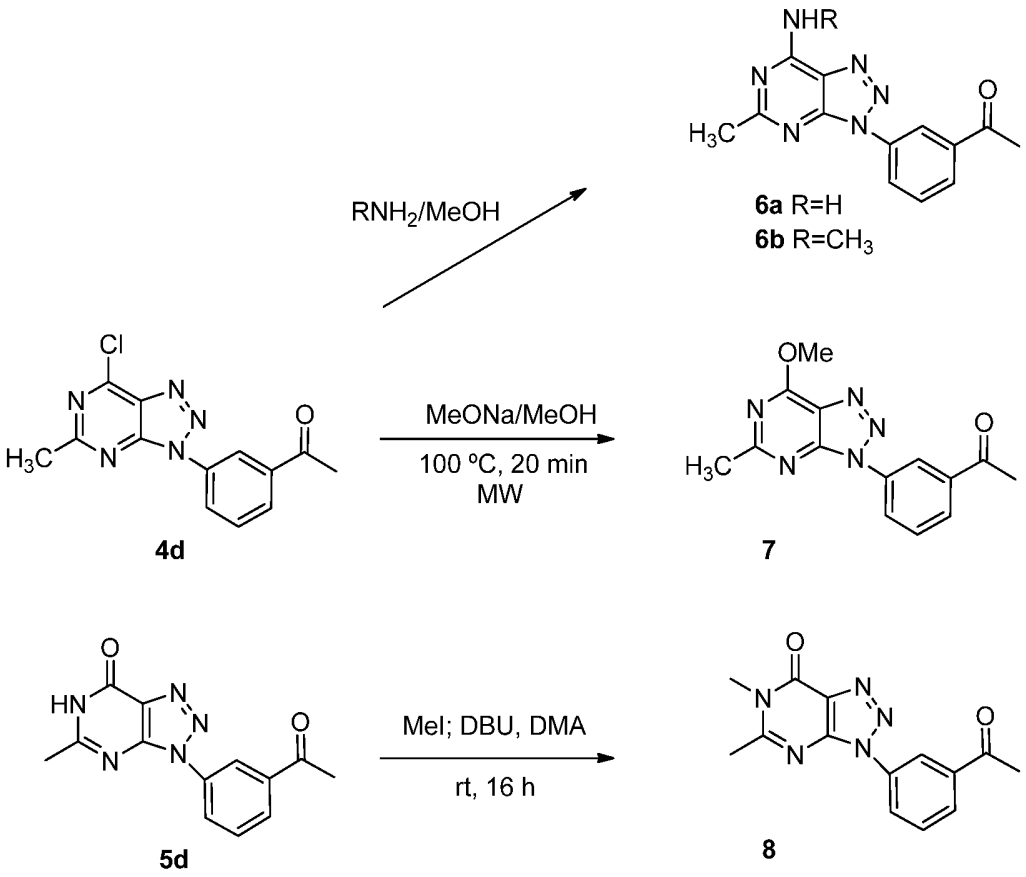
under microwave irradiation afforded the 4-chloro-5,6-diaminopyrimidines **3a-n** in good to excellent yields. The synthesis of compounds **3g**, **3h**, and **3j** has already been reported (Aguado et al. *J. Comb. Chem*, **2009**, *11*, 210-212), as well as the synthesis of **3m** (Aguado et al, *Eur. J Med Chem* **2012**, 49, 279-288). Then reaction of **3a-n** with $NaNO_2$ in CH_2Cl_2 in the presence of HCl at room temperature for 30 min afforded the triazolo derivatives **4a-n.** The synthesis of compounds **4d** and **4j** has already been reported (Aguado et al. *J. Comb. Chem*, **2009**, *11*, 210-212). Finally, treatment of **4a-n** with sodium acetate in DMF in the microwave at 120 ºC afforded the [1,2,3]triazolo[4,5-d]pyrimidin-7(6H)-ones **5a-n**. Hydrolysis of the ethyl ester **5n** afforded the carboxylic acid **5o**.

Scheme 1



a R_1=OMe, R_2=H, R_3=H, R_4=CH_3
b R_1=H, R_2=OMe, R_3=H, R_4=CH_3
c R_1=H, R_2=Cl, R_3=H, R_4=CH_3
d R_1=H, R_2=$COCH_3$, R_3=H, R_4=CH_3
e R_1=H, R_2=COC_6H_5, R_3=H, R_4=CH_3
f R_1=H, R_2=$OCH(CH_3)_2$, R_3=H, R_4=CH_3
g R_1=H, R_2=$NHCOCH_3$, R_3=H, R_4=CH_3
h R_1=H, R_2=H, R_3=$COCH_3$, R_4=CH_3
i R_1=H, R_2=H, R_3=$OCH_2CH_2CH_3$, R_4=CH_3
j R_1=H, R_2=$COCH_3$, R_3=H, R_4=H
k R_1=H, R_2 and R_3= OCH_2O, R_4=CH_3
l R_1=H, R_2=CN, R_3=H, R_4=CH_3
m R_1=H, R_2=$N(CH_3)_2$, R_3=H, R_4=CH_3
n R_1=H, R_2=$COOCH_2CH_3$, R_3=H, R_4=CH_3
o R_1=H, R_2=COOH, R_3=H, R_4=CH_3

The impact of small substituents at positions 6 or/and 7 of the [1,2,3]triazolo[4,5-d]pyrimidine in the activity/toxicity profile was evaluated starting from compounds **4d** and **5d** (Scheme 2).

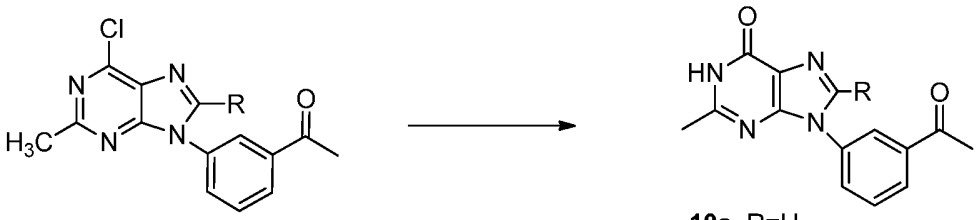


Thus, reaction of **4d** with ammonia or methylamine in MeOH afforded the 7-amino and 7-methylamino derivatives (**6a** and **6b**, respectively) in good yields. Similarly, reaction of **4d** with MeONa in MeOH led to the 7-OMe derivative **7** with 61% yield. On the other hand, reaction of **5d** with DBU and MeI in *N,N*-dimethylacetamide afforded the 6-methyl derivative **8** (88% yield).

[1,2,3]-triazolo[4,5-*d*]pyrimidin-7(6H)-ones may be considered as close structural analogues of hypoxanthines. Therefore, it was considered of interest to obtain the corresponding hypoxanthine analogues of the active hit **5d**. Thus, reaction of the 6-chloropurine derivative **9a** (Aguado et al. *J. Comb. Chem*, **2009**, *11*, 210-212) with sodium acetate in DMF under microwave irradiation at 120 ºC for 1 h afforded the hypoxanthine derivative **10a** (56% yield). On the

other hand, reaction of the 6-chloro-8-methyl derivative (**9b**) (Aguado et al. *J. Comb. Chem*, **2009**, *11*, 210-212) with 1N HCl in dioxane under microwave irradiation for 2h at 100 ºC yielded the purinone derivative **10b** (61%).

Scheme 3

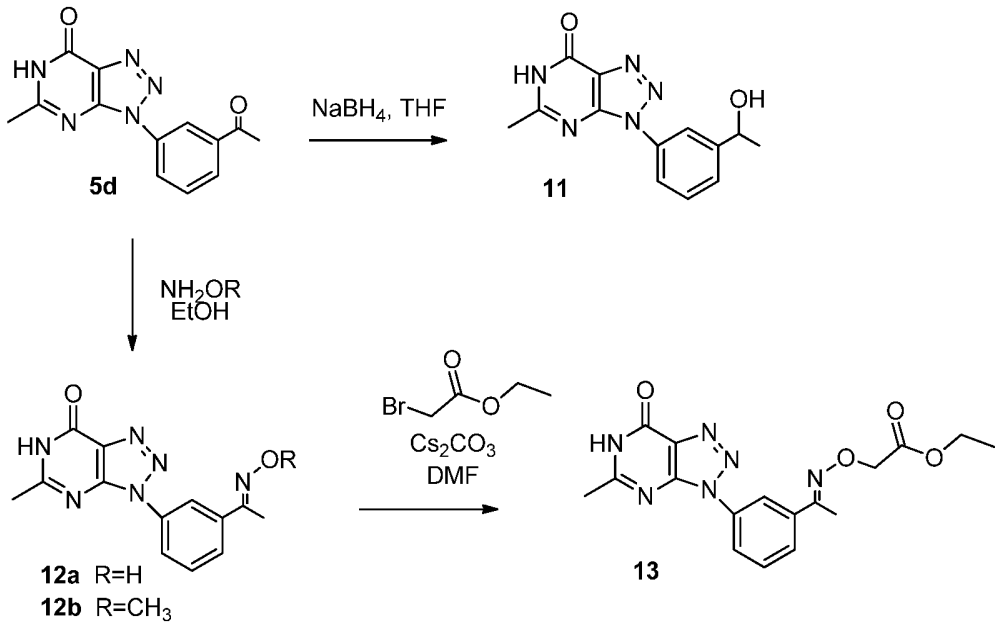


9a R=H
9b R=CH_3

10a R=H
10b R=CH_3

Structural modifications were performed at the ketone **5d** as specified in Scheme 4

Scheme 4

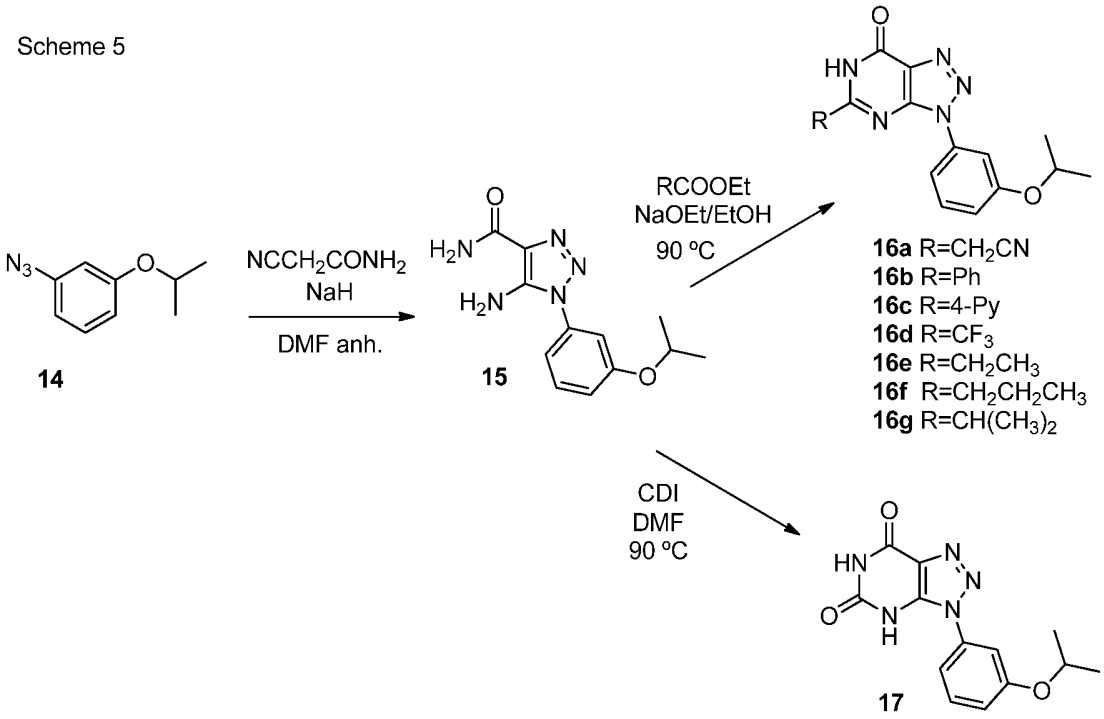


Reaction of **5d** with $NaBH_4$ in THF at 75 ºC overnight allowed the reduction of the ketone function to the corresponding alcohol **11** in 43% yield. Alternatively,

reaction of **5d** with hydroxylamine hydrochloride or methylhydroxylamine a microwave reactor at 80 ºC for 1 hour provided the oxime and methyloxime derivatives **12a** and **12b** in 76 and 77% yield, respectively. Additionally, reaction of **12a** with ethyl bromoacetate in the presence of K_2CO_3 in DMF allowed the selective alkylation of the hydroxyimino group to afford **13** in 46% yield.

In another embodiment of said aspect of the invention, the synthesis of [1,2,3]triazolo[4,5-d]pyrimidin-7(6H)-ones can also be accomplished by reaction of azides with cyanoacetamide and further reaction of the 5-amino-1*H*-1,2,3-triazole-4-carboxamides thus formed with different esters, thus allowing the introduction of different substituents at position 5 of the [1,2,3]triazolo[4,5-d]pyrimidin-7(6H)-ones. (Kuleshov, K,V et al, Chemistry of heterocyclic Compounds 42, 246-260 (2006); Giorgi I, et al Eur. J. Med. Chem 42, 1-9 (2007); Barili P.L et al, J Heterocyclic Chem 22, 1607-1609 (1985) and references therein). While this approach has been extensively applied to 1-alkyl or 1-benzyl derivatives, the described examples of 1-aryl derivatives are much scarcer (Miyashita A et al, Heterocycles, 42, 691-696 (1996); L. Bertelli et al, J Heterocyclic Chem 37, 1169-1176 (2000); J Heteocyclic Chem 33, 1847 (1996); J Heterocyclic Chem 39, 1293 (2002)) partially due to isomerization of the 1-aryl-5-amino-1*H*-1,2,3-triazole-4-carboxamides (L. Bertelli et al, J Heterocyclic Chem 37, 1169-1176 (2000)). This approach was explored starting from 1-azido-3-isopropoxybenzene (**14**) (Organic Letters 10, 5529 – 5531, 2008) (Scheme 5).

Scheme 5

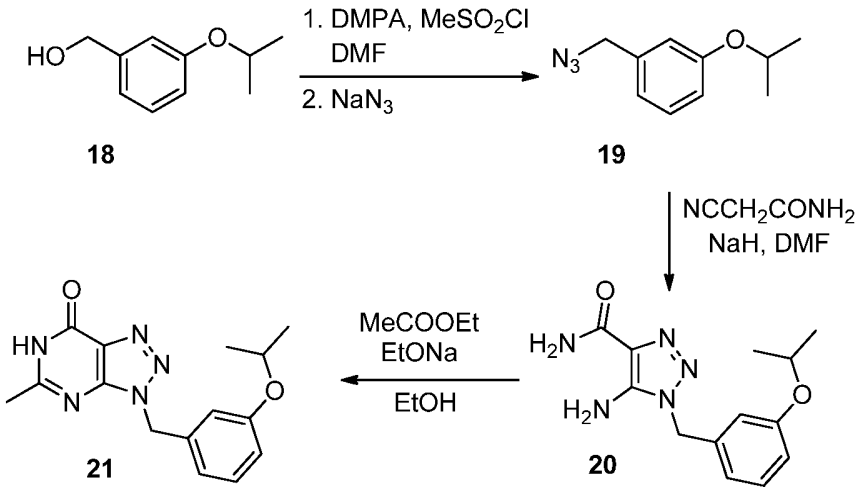


Thus, reaction of **14** with a preformed solution of cyanoacetamide and NaH in dry DMF afforded the key 5-amino-1H-1,2,3-triazole-4-carboxamide (**15**) in 70% yield. The carboxamide **15** reacted with a variety of esters in the presence of sodium ethoxide to afford the differently 5-substituted [1,2,3]triazolo[4,5-*d*]pyrimidin-7(6H)-ones (**16a-g**) in yields varying from 23 to 71%. Alternatively, the cyclization reaction can also be performed by treatment of **15** with the corresponding ester in the presence of tBuOK in THF under microwave-irradiation at 90 ºC for 1 hour.

On the other hand, reaction of the carboxamide **15** with carbonyldiimidazole at 90 ºC overnight afforded the [1,2,3]triazolo[4,5-*d*]pyrimidinedione **17** in 56% yield.

A similar synthetic scheme was used to prepare a benzylic analogue of compound **5f** incorporating a methylene unit between the aryl ring and the [1,2,3]triazolo[4,5-*d*]pyrimidinedione as shown in Scheme 6.

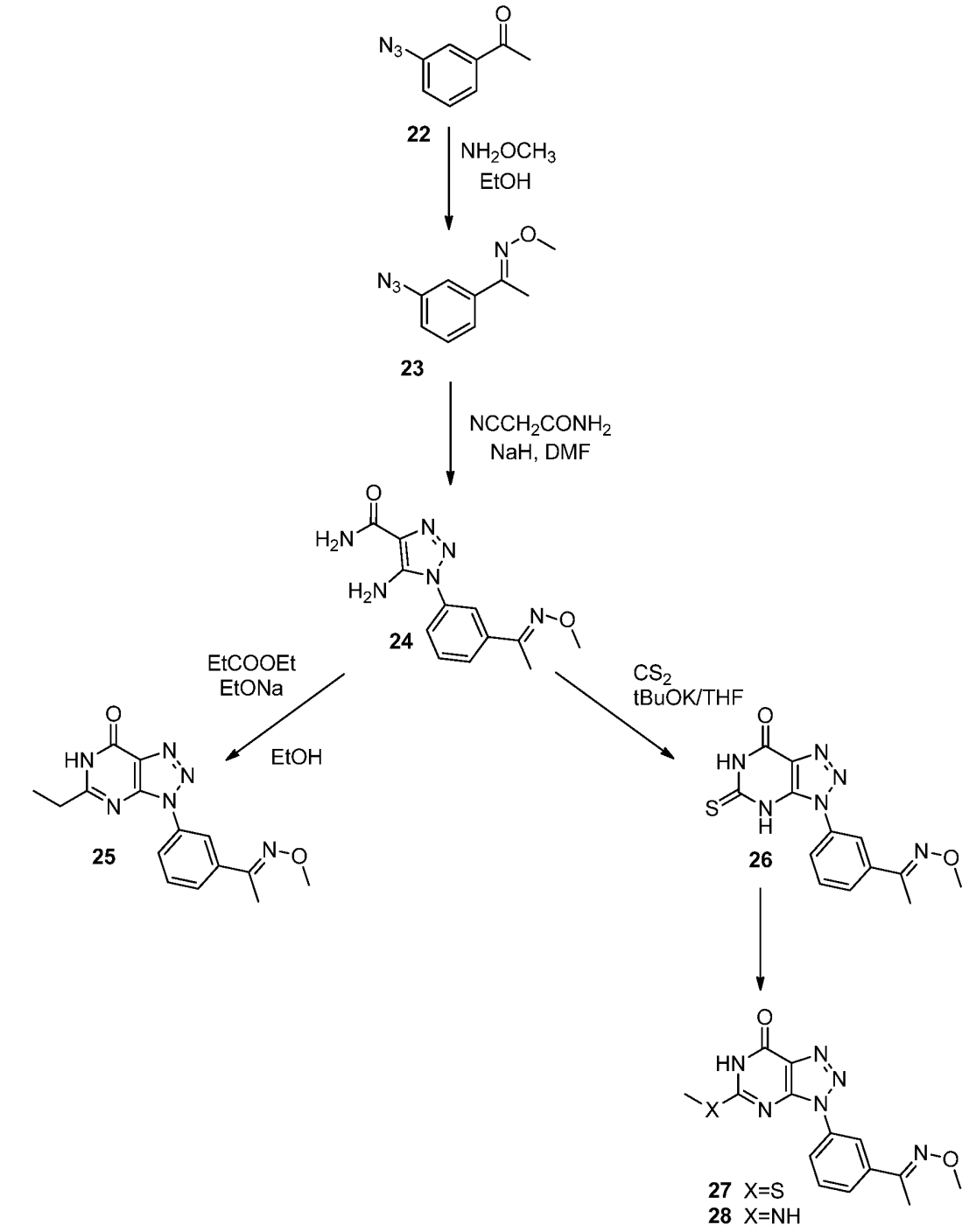
Scheme 6



The starting azide **19** was obtained in 89% yield in two steps by reaction of the alcohol **18** with mesyl chloride and further substitution reaction of the mesyl derivative thus formed with NaN_3. Treatment of **19** with cyanoacetamide in the presence of NaH afforded the 5-amino-1*H*-1,2,3-triazole-4-carboxamide **20** (77% yield). Then reaction of **20** with ethyl acetate in the presence of sodium ethoxide led to the benzylic derivative **21** (75% yield).

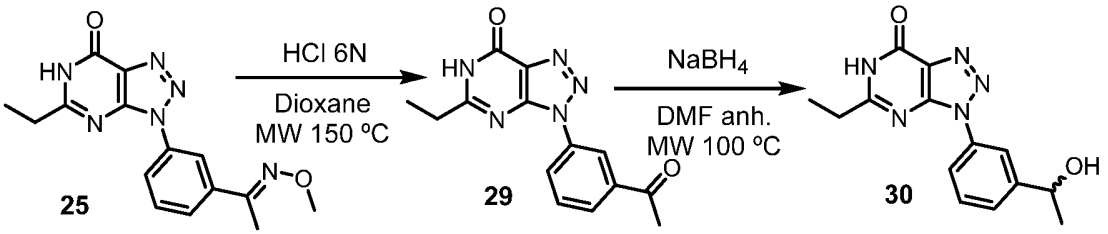
In another embodiment of said aspect of the invention the acetyl derivative **22** (Synlett. 2011,#7, 883-886) reacted with methoxyamine hydrochloride in ethanol in the microwave at 80 ºC for 1 h to afford the methyloxime **23** in 88% yield (Scheme 7). Then reaction with cyanoacetamide in the presence of NaH in DMF afforded the triazolo derivative **24** (79% yield). Reaction of **24** with ethyl propionate in THF in the presence of tBuOK at 90 ºC for 1 h under microwave irradiation yielded the desired 5-ethyl derivative **25** in 85% yield. Alternatively, reaction of **24** with CS_2 in the presence of t-BuOK in THF under microwave-iiradiation at 120 °C for 2h afforded **27** in 86% yield. Further reaction of **28** with iodomethane led to the 5-methylthio derivative **27**. This was transformed into the 5-methylamino **28** by treatment with $MeNH_2$ under microwave conditions (150 °C, 1 h).

Scheme 7


22
NH2OCH3
EtOH
23
NCCH2CONH2
NaH, DMF
24
EtCOOEt
EtONa
EtOH
25
CS2
tBuOK/THF
26
27 X=S
28 X=NH

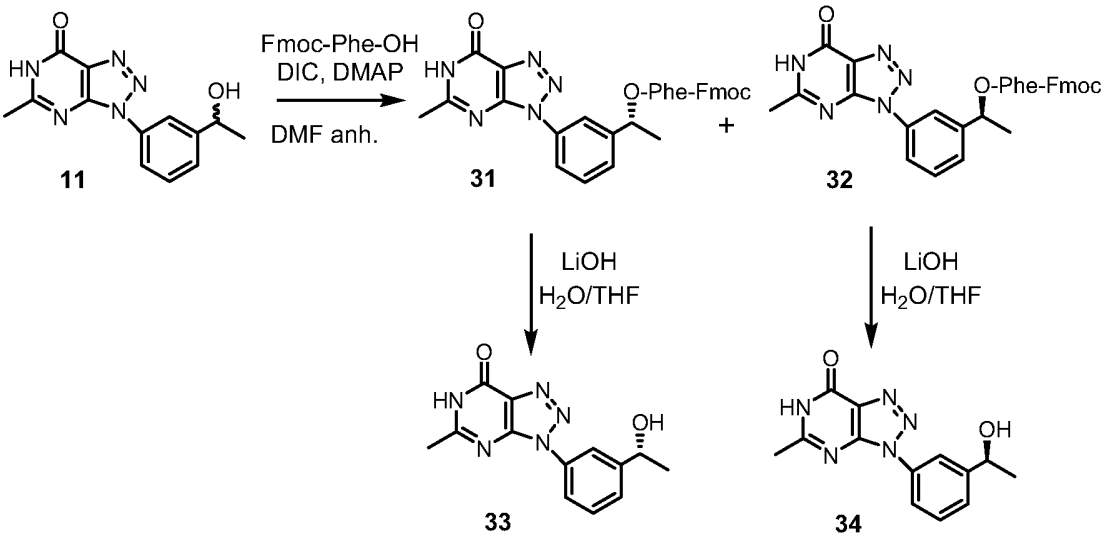
Compound **25** (Scheme 8) was transformed into the corresponding ketone **29** by reaction with HCl 6N in dioxane at 150 °C under microwave irradiation. Moreover, reduction of the ketone by treatment with $NaBH_4$ in DMF at 100 °C also under microwave irradiation afforded the alcohol **30** as a racemic mixture.

Scheme 8



The two enantiomeric alcohols present in compound **11** were obtained as single enantiomers following the procedure described in Scheme 9. Thus, compound **11** reacted with Fmoc-Phe-OH in the presence of diisoproplylcarbodiimide to obtain the esters of Fmoc-Phe **31** and **32** that were isolated by semipreparative HPLC. Each compound (**31** and **32**) was individually treated with LiOH in THF/H_2O to afford the alcohols **33** and **34,** respectively. The assignation of the quiral center as *R* and *S* was performed based on the ^1H NMR data of the Phe esters and of the esters obtained by reaction of the alcohol **34** with *R*-MTA-Cl and *S*-MTA-Cl (*R* and *S* Mosher´s acid chloride)

Scheme 9



The compounds of the invention can be employed for the treatment or prophylaxis of viral infections, preferably Togaviridae infections, more preferably chikungunya virus. When using one or more derivatives of the formula I and/or formula I' as defined herein:

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

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

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

The present invention also relates to a combination of different antiviral drugs of the invention or to a combination of the antiviral drugs of the invention with other drugs that exhibit anti-Togavirus activity, more specifically anti-chikungunya activity.

Certain embodiments of the present invention relate to the treatment or prophylaxis of viral infections, preferably Togaviridae infections. In certain embodiments of the present invention, including the use of the compounds of the present invention for the treatment or prophylaxis of viral infections, said viral infections are caused by Alphaviruses, more specifically said Alphaviruses are selected from the group consisting of Sindbis virus, Eastern equine encephalitis virus, Western equine encephalitis virus, Venezuelan equine encephalitis virus, Ross River virus, O'nyong'nyong virus, chikungunya, and Semliki Forest virus. In more specific embodiments said Alphaviruses are Sindbis virus, chikungunya, and Semliki Forest virus. In other embodiments of the present invention, said Togaviridae infections are caused by the viruses from the Genus Rubivirus including Rubella virus.

The invention also relates to a pharmaceutical composition or combined preparation of antiviral drugs and containing:

either:

A)

(a) a combination of two or more of the [1,2,3]triazolo[4,5-d]pyrimidin-7(6H)-ones or derivatives thereof of the present invention, and

(b) optionally one or more pharmaceutical excipients or pharmaceutically acceptable carriers,

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

or

B)

(a) one or more anti-viral agents, and

(b) at least one of the the [1,2,3]triazolo[4,5-d]pyrimidin-7(6H)-ones or derivatives thereof of the present invention, and

(c) optionally one or more pharmaceutical excipients or pharmaceutically acceptable carriers,

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

The pharmaceutical composition or combined preparation with activity against viral infection according to this invention may contain the [1,2,3]triazolo[4,5-d]pyrimidin-7(6H)-ones or derivatives thereof of the present invention over a broad content range depending on the contemplated use and the expected effect of the preparation. Generally, the content of the [1,2,3]triazolo[4,5-d]pyrimidin-7(6H)-ones or derivatives thereof of the present invention of the combined preparation is within the range of 0.1 to 99.9% by weight, preferably from 1 to 99% by weight, more preferably from 5 to 95% by weight.

When using a pharmaceutical composition of combined preparation:

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

- the therapeutically effective amount of each of the active agents, especially for the treatment of viral infections in humans and other mammals, particularly is a Togaviridae (or chikungunya) enzyme inhibiting amount.

When applying a combined preparation, the active ingredients may be administered simultaneously but it is also beneficial to administer them separately or sequentially, for instance within a relatively short period of time (e.g. within about 24 hours) in order to achieve their functional fusion in the body to be treated.

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

The term "pharmaceutically acceptable salts" as used herein means the therapeutically active non-toxic salt forms which the compounds of formula I or I' are able to form. Therefore, the compounds of this invention optionally comprise salts of the compounds herein, especially pharmaceutically acceptable non-toxic salts containing, for example, Na^+, Li^+, K^+, Ca^{2+} and Mg^{2+}. Such salts may include those derived by combination of appropriate cations such as alkali and alkaline earth metal ions or ammonium and quaternary amino ions with an acid anion moiety, typically a carboxylic acid. The compounds of the invention may bear multiple positive or negative charges. The net charge of the compounds of the invention may be either positive or negative. Any associated counter ions are typically dictated by the synthesis and/or isolation methods by which the compounds are obtained. Typical counter ions include, but are not limited to ammonium, sodium, potassium, lithium, halides, acetate, trifluoroacetate, etc., and mixtures thereof. It will be understood that the identity of any associated counter ion is not a critical feature of the invention, and that the invention encompasses the compounds in association with any type of counter ion. Moreover, as the compounds can exist in a variety of different forms, the invention is intended to encompass not only forms of the compounds that are in association with counter ions (e.g., dry salts), but also forms that are not in association with counter ions (e.g., aqueous or organic solutions). Metal salts typically are prepared by reacting the metal hydroxide with a compound of this invention. Examples of metal salts which are prepared in this way are salts containing Li^+, Na^+, and K^+. A less soluble metal salt can be precipitated from the solution of a more soluble salt by addition of the suitable metal compound.

In addition, salts may be formed from acid addition of certain organic and inorganic acids to basic centers, typically amines, or to acidic groups. Examples of such appropriate acids include, for instance, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, lactic, pyruvic, oxalic (i.e. ethanedioic), malonic, succinic (i.e. butanedioic acid), maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic, cyclohexanesulfamic, salicylic (i.e. 2-hydroxybenzoic), p-aminosalicylic and the like. Furthermore, this term also includes the solvates which the compounds of formula I as well as their salts are able to form, such as for example hydrates, alcoholates and the like. Finally, it is to be understood that the compositions herein comprise compounds of the invention in their unionized, as well as zwitterionic form, and combinations with stoichiometric amounts of water as in hydrates.

Also included within the scope of this invention are the salts of the parental compounds with one or more amino acids, especially the naturally-occurring amino acids found as protein components. The amino acid typically is one bearing a side chain with a basic or acidic group, e.g., lysine, arginine or glutamic acid, or a neutral group such as glycine, serine, threonine, alanine, isoleucine, or leucine.

The compounds of the invention also include physiologically acceptable salts thereof. Examples of physiologically acceptable salts of the compounds of the invention include salts derived from an appropriate base, such as an alkali metal (for example, sodium), an alkaline earth (for example, magnesium), ammonium and NX_4^+ (wherein X is C_1-C_4 alkyl). Physiologically acceptable salts of an hydrogen atom or an amino group include salts of organic carboxylic acids such as acetic, benzoic, lactic, fumaric, tartaric, maleic, malonic, malic, isethionic, lactobionic and succinic acids; organic sulfonic acids, such as methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids; and inorganic acids, such as hydrochloric, sulfuric, phosphoric and sulfamic acids. Physiologically acceptable salts of a compound containing a hydroxy

group include the anion of said compound in combination with a suitable cation such as Na^+ and NX_4^+ (wherein X typically is independently selected from H or a C_1-C_4 alkyl group). However, salts of acids or bases which are not physiologically acceptable may also find use, for example, in the preparation or purification of a physiologically acceptable compound. All salts, whether or not derived form a physiologically acceptable acid or base, are within the scope of the present invention.

As used herein and unless otherwise stated, the term “enantiomer” means each individual optically active form of a compound of the invention, having an optical purity or enantiomeric excess (as determined by methods standard in the art) of at least 80% (i.e. at least 90% of one enantiomer and at most 10% of the other enantiomer), preferably at least 90% and more preferably at least 98%.

The term "isomers" as used herein means all possible isomeric forms, including tautomeric and sterochemical forms, which the compounds of formula I may possess, but not including position isomers. Typically, the structures shown herein exemplify only one tautomeric or resonance form of the compounds, but the corresponding alternative configurations are contemplated as well. Unless otherwise stated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers (since the compounds of formula I may have at least one chiral center) of the basic molecular structure, as wel as the stereochemically pure or enriched compounds. More particularly, stereogenic centers may have either the R- or S-configuration, and multiple bonds may have either cis- or trans-configuration.

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

should be understood in a similar way, having regard to the enantiomeric excess, respectively the diastereomeric excess, of the mixture in question.

Separation of stereoisomers is accomplished by standard methods known to those in the art. One enantiomer of a compound of the invention can be separated substantially free of its opposing enantiomer by a method such as formation of diastereomers using optically active resolving agents ("Stereochemistry of Carbon Compounds," (1962) by E. L. Eliel, McGraw Hill; Lochmuller, C. H., (1975) J. Chromatogr., 113:(3) 283-302). Separation of isomers in a mixture can be accomplished by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2) formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure enantiomers, or (3) enantiomers can be separated directly under chiral conditions. Under method (1), diastereomeric salts can be formed by reaction of enantiomerically pure chiral bases such as brucine, quinine, ephedrine, strychnine, a-methyl-b-phenylethylamine (amphetamine), and the like with asymmetric compounds bearing acidic functionality, such as carboxylic acid and sulfonic acid. The diastereomeric salts may be induced to separate by fractional crystallization or ionic chromatography. For separation of the optical isomers of amino compounds, addition of chiral carboxylic or sulfonic acids, such as camphorsulfonic acid, tartaric acid, mandelic acid, or lactic acid can result in formation of the diastereomeric salts. Alternatively, by method (2), the substrate to be resolved may be reacted with one enantiomer of a chiral compound to form a diastereomeric pair (Eliel, E. and Wilen, S. (1994) Stereochemistry of Organic Compounds, John Wiley & Sons, Inc., p. 322). Diastereomeric compounds can be formed by reacting asymmetric compounds with enantiomerically pure chiral derivatizing reagents, such as menthyl derivatives, followed by separation of the diastereomers and hydrolysis to yield the free, enantiomerically enriched xanthene. A method of determining optical purity involves making chiral esters, such as a menthyl ester or Mosher ester, a-methoxy-a-(trifluoromethyl)phenyl acetate (Jacob III. (1982) J. Org. Chem. 47:4165), of the racemic mixture, and

analyzing the NMR spectrum for the presence of the two atropisomeric diastereomers. Stable diastereomers can be separated and isolated by normal- and reverse-phase chromatography following methods for separation of atropisomeric naphthyl-isoquinolines (Hoye, T., WO96/15111). Under method (3), a racemic mixture of two asymmetric enantiomers is separated by chromatography using a chiral stationary phase. Suitable chiral stationary phases are, for example, polysaccharides, in particular cellulose or amylose derivatives. Commercially available polysaccharide based chiral stationary phases are ChiralCel™ CA, OA, OB5, OC5, OD, OF, OG, OJ and OK, and ChiralpakTM AD, AS, OP(+) and OT(+). Appropriate eluents or mobile phases for use in combination with said polysaccharide chiral stationary phases are hexane and the like, modified with an alcohol such as ethanol, isopropanol and the like. ("Chiral Liquid Chromatography" (1989) W. J. Lough, Ed. Chapman and Hall, New York; Okamoto, (1990) "Optical resolution of dihydropyridine enantiomers by High-performance liquid chromatography using phenylcarbamates of polysaccharides as a chiral stationary phase", J. of Chromatogr. 513:375-378).

The terms cis and trans are used herein in accordance with Chemical Abstracts nomenclature and include reference to the position of the substituents on a ring moiety. The absolute stereochemical configuration of the compounds of formula I may easily be determined by those skilled in the art while using well-known methods such as, for example, X-ray diffraction.

The compounds of the invention may be formulated with conventional carriers and excipients, which will be selected in accord with ordinary practice. Tablets will contain excipients, glidants, fillers, binders and the like. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. Formulations optionally contain excipients such as those set forth in the "Handbook of Pharmaceutical Excipients" (1986) and include ascorbic acid and other antioxidants, chelating

agents such as EDTA, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like.

Subsequently, the term "pharmaceutically acceptable carrier" as used herein means any material or substance with which the active ingredient is formulated in order to facilitate its application or dissemination to the locus to be treated, for instance by dissolving, dispersing or diffusing the said composition, and/or to facilitate its storage, transport or handling without impairing its effectiveness. The pharmaceutically acceptable carrier may be a solid or a liquid or a gas which has been compressed to form a liquid, i.e. the compositions of this invention can suitably be used as concentrates, emulsions, solutions, granulates, dusts, sprays, aerosols, suspensions, ointments, creams, tablets, pellets or powders.

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

Suitable surface-active agents, also known as emulgent or emulsifier, to be used in the pharmaceutical compositions of the present invention are non-ionic, cationic and/or anionic materials having good emulsifying, dispersing and/or

wetting properties. Suitable anionic surfactants include both water-soluble soaps and water-soluble synthetic surface-active agents. Suitable soaps are alkaline or alkaline-earth metal salts, unsubstituted or substituted ammonium salts of higher fatty acids (C_{10}-C_{22}), e.g. the sodium or potassium salts of oleic or stearic acid, or of natural fatty acid mixtures obtainable form coconut oil or tallow oil. Synthetic surfactants include sodium or calcium salts of polyacrylic acids; fatty sulphonates and sulphates; sulphonated benzimidazole derivatives and alkylarylsulphonates. Fatty sulphonates or sulphates are usually in the form of alkaline or alkaline-earth metal salts, unsubstituted ammonium salts or ammonium salts substituted with an alkyl or acyl radical having from 8 to 22 carbon atoms, e.g. the sodium or calcium salt of lignosulphonic acid or dodecylsulphonic acid or a mixture of fatty alcohol sulphates obtained from natural fatty acids, alkaline or alkaline-earth metal salts of sulphuric or sulphonic acid esters (such as sodium lauryl sulphate) and sulphonic acids of fatty alcohol/ethylene oxide adducts. Suitable sulphonated benzimidazole derivatives preferably contain 8 to 22 carbon atoms. Examples of alkylarylsulphonates are the sodium, calcium or alcanolamine salts of dodecylbenzene sulphonic acid or dibutyl-naphtalenesulphonic acid or a naphtalene-sulphonic acid/formaldehyde condensation product. Also suitable are the corresponding phosphates, e.g. salts of phosphoric acid ester and an adduct of p-nonylphenol with ethylene and/or propylene oxide, or phospholipids. Suitable phospholipids for this purpose are the natural (originating from animal or plant cells) or synthetic phospholipids of the cephalin or lecithin type such as e.g. phosphatidylethanolamine, phosphatidylserine, phosphatidylglycerine, lysolecithin, cardiolipin, dioctanylphosphatidyl-choline, dipalmitoylphosphatidyl -choline and their mixtures.

Suitable non-ionic surfactants include polyethoxylated and polypropoxylated derivatives of alkylphenols, fatty alcohols, fatty acids, aliphatic amines or amides containing at least 12 carbon atoms in the molecule, alkylarenesulphonates and dialkylsulphosuccinates, such as polyglycol ether derivatives of aliphatic and cycloaliphatic alcohols, saturated and unsaturated fatty acids and alkylphenols, said derivatives preferably containing 3 to 10 glycol

ether groups and 8 to 20 carbon atoms in the (aliphatic) hydrocarbon moiety and 6 to 18 carbon atoms in the alkyl moiety of the alkylphenol. Further suitable non-ionic surfactants are water-soluble adducts of polyethylene oxide with polypropylene glycol, ethylenediaminopolypropylene glycol containing 1 to 10 carbon atoms in the alkyl chain, which adducts contain 20 to 250 ethyleneglycol ether groups and/or 10 to 100 propyleneglycol ether groups. Such compounds usually contain from 1 to 5 ethyleneglycol units per propyleneglycol unit. Representative examples of non-ionic surfactants are nonylphenol - polyethoxyethanol, castor oil polyglycolic ethers, polypropylene/polyethylene oxide adducts, tributylphenoxypolyethoxyethanol, polyethyleneglycol and octylphenoxypolyethoxyethanol. Fatty acid esters of polyethylene sorbitan (such as polyoxyethylene sorbitan trioleate), glycerol, sorbitan, sucrose and pentaerythritol are also suitable non-ionic surfactants.

Suitable cationic surfactants include quaternary ammonium salts, particularly halides, having 4 hydrocarbon radicals optionally substituted with halo, phenyl, substituted phenyl or hydroxy; for instance quaternary ammonium salts containing as N-substituent at least one C_8-C_{22} alkyl radical (e.g. cetyl, lauryl, palmityl, myristyl, oleyl and the like) and, as further substituents, unsubstituted or halogenated lower alkyl, benzyl and/or hydroxy-lower alkyl radicals.

A more detailed description of surface-active agents suitable for this purpose may be found for instance in "McCutcheon's Detergents and Emulsifiers Annual" (MC Publishing Crop., Ridgewood, New Jersey, 1981), "Tensid-Taschenbucw', 2 d ed. (Hanser Verlag, Vienna, 1981) and "Encyclopaedia of Surfactants" (Chemical Publishing Co., New York, 1981).

While it is possible for the active ingredients to be administered alone, it is preferable to present them as pharmaceutical formulations. The formulations, both for veterinary and for human use, of the present invention comprise at least one active ingredient, as above described, together with one or more pharmaceutically acceptable carriers therefore and optionally other therapeutic ingredients. The carrier(s) optimally are "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to

the recipient thereof. The formulations include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

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

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein. For infections of the eye or other external tissues e.g. mouth and skin, the formulations are optionally applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w (including active ingredient(s) in a range between 0.1% and 20% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc), preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a

cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, i.e. an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG400) and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogs.

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

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

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

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate. Formulations suitable for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns (including particle sizes in a range between 20 and 500 microns in increments of 5 microns such as 30 microns, 35 microns, etc), which is administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as for example a nasal spray or as nasal drops, include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol administration may be prepared according to conventional methods and may be delivered with other therapeutic agents.

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

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations

may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

Compounds of the invention can be used to provide controlled release pharmaceutical formulations containing as active ingredient one or more compounds of the invention ("controlled release formulations") in which the release of the active ingredient can be controlled and regulated to allow less frequency dosing or to improve the pharmacokinetic or toxicity profile of a given invention compound. Controlled release formulations adapted for oral administration in which discrete units comprising one or more compounds of the invention can be prepared according to conventional methods.

Additional ingredients may be included in order to control the duration of action of the active ingredient in the composition. Control release compositions may thus be achieved by selecting appropriate polymer carriers such as for example polyesters, polyamino acids, polyvinyl pyrrolidone, ethylene-vinyl acetate copolymers, methylcellulose, carboxymethylcellulose, protamine sulfate and the like. The rate of drug release and duration of action may also be controlled by incorporating the active ingredient into particles, e.g. microcapsules, of a polymeric substance such as hydrogels, polylactic acid, hydroxymethylcellulose, polyniethyl methacrylate and the other above-described polymers. Such methods include colloid drug delivery systems like liposomes, microspheres, microemulsions, nanoparticles, nanocapsules and so on. Depending on the

route of administration, the pharmaceutical composition may require protective coatings. Pharmaceutical forms suitable for injectionable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation thereof. Typical carriers for this purpose therefore include biocompatible aqueous buffers, ethanol, glycerol, propylene glycol, polyethylene glycol and the like and mixtures thereof.

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

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

EXAMPLES

EXAMPLE 1: Materials and methods

Melting points were obtained on a Reichert-Jung Kofler apparatus and are uncorrected. The elemental analysis was performed with a Heraeus CHN-O-RAPID instrument. The elemental compositions of the compounds agreed to within ± 0.4% of the calculated values. Electrospray mass spectra were measured on a quadrupole mass spectrometer equipped with an electrospray source (Hewlett-Packard, LC/MS HP 1100). 1H and 13C NMR spectra were

recorded on a Varian INNOVA 300 operating at 299 MHz (1H) and 75 MHz (13C), respectively, and Varian INNOVA-400 operating at 399 MHZ (1H) and 99 MHz (13C), respectively.

Analytical TLC was performed on silica gel 60 F254 (Merck) precoated plates (0.2 mm). Spots were detected under UV light (254 nm) and/or charring with ninhydrin. Separations on silica gel were performed by preparative centrifugal circular thin-layer chromatography (CCTLC) on a ChromatotronR (Kiesegel 60 PF254 gipshaltig (Merck)), with layer thickness of 1 and 2 mm and flow rate of 4 or 8 mL/min, respectively. Flash column chromatography was performed in a Biotage Horizon instrument.

Microwave reactions were performed using the Biotage Initiator 2.0 single-mode cavity instrument from Biotage (Uppsala). Experiments were carried out in sealed microwave process vials utilizing the standard absorbance level (400 W maximum power). The temperature was measured with an IR sensor on the outside of the reaction vessel.

Methodology for determination of antiviral and cytostatic activity

Antiviral and cytostatic activity are determined by the methodology described below:

Cells and viruses:

Vero cells were maintained in cell growth medium composed of minimum essential medium (MEM Rega-3, Cat N° 19993-013, Gibco, Belgium) supplemented with 10% Foetal Bovine Serum (FBS, Integro, The Netherlands), 1% L-glutamine (Cat N° 25030024, Gibco), and 1% sodium bicarbonate (Cat N° 25080060, Gibco). chikungunya virus (Indian Ocean strain 899), Sindbis virus (HRsp strain) and Semliki Forest virus (Vietnam strain) were used throughout the experiments.

Antiviral assay:

Vero cells, harvested from confluent, 7-day-old cell culture flasks (Cat N° 90076, TPP), were seeded in 96-well microtiter plates (Cat N° 353072, Becton Dickinson, Aalst, Belgium) at a density of 2.5 × 104 cells/well in 100 µl assay medium and were allowed to adhere overnight in an incubator at (37°C, 5% CO2, 95-99% relative humidity). In a second step, a compound dilution series is prepared in the medium on top of the cells after which the cultures (except for the uninfected control conditions) are infected with 100 CCID50 (i.e., 50 % cell culture infectious dose) virus inoculum in 100 µl assay medium (final assay volume of 200 µl). Following assay setup, the plates are returned as such to the incubator. Each assay was performed in multiplicate (at least in 3-fold) in the same test and assays are repeated independently on different days to assess for inter-experiment variability. On day 7 post-infection (p.i.), the plates are processed using the MTS/PMS method as described by the manufacturer (Promega, The Netherlands). The 50% effective concentration (EC50), which is defined as the compound concentration that is required to inhibit viral RNA replication by 50%, is determined using logarithmic interpolation. Potential cytotoxic/cytostatic effects of the compound are evaluated in uninfected cells by means of the MTS/PMS method. The 50% cytotoxic concentration (CC50; i.e., the concentration that reduces the overall metabolic activity of the cells by 50%) is calculated using logarithmic interpolation. All assay wells are checked microscopically for minor signs of virus-induced CPE or alterations to the cells caused by the compound. A compound is only considered to be a selective inhibitor of virus replication when, at least at one concentration of compound, the cell monolayer resembles the untreated, uninfected cell control conditions.The following examples illustrate the present invention without being limited hereto. Example 2 represents the preparation of the compounds, whereas Example 3 represents the pharmacological examples and the biological activity of certain compounds of this invention.

EXAMPLE 2: Preparation of compounds

Example 2.1

General procedure for the reaction of 4,6-dichloropyrimidines with substituted anilines (3a-n).

A microwave vial was charged with the corresponding aniline (**1**, 1.0 mmol), the 4,6-dichloropyrimidine (**2**, 1.0 mmol), isobutanol (2.5 mL) and 37% aqueous HCl (0.07 mL/mmol). The reaction vessel was sealed and heated in a microwave reactor at 150 ºC for 10-30 min. After cooling, the reaction mixture was worked up as indicated in each case.

Example 2.2

6-Chloro-N^4-(2'-methoxyphenyl)-2-methylpyrimidine-4,5-diamine (3a)

Following the general procedure, a microwave vial was charged with 5-amino-4,6-dichloro-2-methylpyrimidine (200 mg, 1.12 mmol), 2-methoxyaniline (126 µL, 1.12 mmol), isobutanol (2.8 mL) and 37% aqueous HCl (84 µL). After cooling, the product was isolated by filtration and dried to obtain 291 mg (98%) of **3a** as a beige solid. Mp: 241-243 ºC. MS (ES, positive mode): m/z 265 $(M+H)^+$ with a Cl isotopic pattern. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 2.27 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 6.58 (s, 2H, NH_2), 6.96 (m, H-6´), 7.14 (m, 2H, H-4´, H-5´), 7.75 (m, 1H, H-3´), 8.68 (s, 1H, NH).

Example 2.3

6-Chloro-N^4-(3'-methoxyphenyl)-2-methylpyrimidine-4,5-diamine (3b).

Following the general procedure, a microwave vial was charged with 5-amino-4,6-dichloro-2-methylpyrimidine (200 mg, 1.12 mmol), 3-methoxyaniline (126 µL, 1.12 mmol), isobutanol (2.8 mL) and 37% aqueous HCl (84 µL). After cooling, the product was isolated by filtration and dried to obtain 280 mg (95%) of **3b** as a beige solid. Mp: > 250 ºC decomposed. MS (ES, positive mode): m/z 265 $(M+H)^+$ with a Cl isotopic pattern. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.33 (s, 3H, CH_3), 3.74 (s, 3H, OCH_3), 5.49 (s, 2H, NH_2), 6.62 (ddd, J = 8.2, 2.2, 0.8 Hz, 1H, H-4´), 7.21 (pt, J = 8.1 Hz, 1H, H-5´), 7.32 (ddd, J = 8.1, 2.0, 0.8 Hz, 1H, H-6´), 7.53 (pt, J = 2.2 Hz, 1H, H-2´), 9.13 (s, 1H, NH).

Example 2.4

6-Chloro-N^4-(3'-chlorophenyl)-2-methylpyrimidine-4,5-diamine (3c).

Following the general procedure, a microwave vial was charged with 5-amino-4,6-dichloro-2-methylpyrimidine (200 mg, 0.48 mmol), 3-chloroaniline (50 µL, 0.48 mmol), isobutanol (1.2 mL) and 37% aqueous HCl (36 µL). After cooling, the product was isolated by filtration and dried to obtain 120 mg (93%) of **3c** as a brown solid. Mp: 239-241 ºC. MS (ES, positive mode): m/z 269 $(M+H)^+$ with a 2 Cl isotopic pattern. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.33 (s, 3H, CH_3), 6.38 (s, 2H, NH_2), 7.05 (ddd, J = 8.0, 2.0, 0.8 Hz, 1H, H-4´), 7.33 (pt, J = 8.1 Hz, 1H, H-5´), 7.73 (ddd, J = 8.3, 2.0, 0.8 Hz, 1H, H-6´), 7.99 (pt, J = 2.1 Hz, 1H, H-2´), 9.11 (s, 1H, NH).

Compound **3d** has been previously described. (Aguado et al. *J. Comb. Chem*, **2009**, *11*, 210-212).

Example 2.5

6-Chloro-N^4-(3'-benzoylphenyl)-2-methylpyrimidine-4,5-diamine (3e).

Following the general procedure, a microwave vial was charged with 5-amino-4,6-dichloro-2-methylpyrimidine (200 mg, 1.12 mmol), 3´-aminobenzophenone (221 mg, 1.12 mmol), isobutanol (2.8 mL) and 37% aqueous HCl (84 µL). After cooling, the product was isolated by filtration and dried to obtain 338 mg (89%) of **3e** as a dark solid, used as such for the next step. MS (ES, positive mode): m/z 260 $(M+H)^+$ with a Cl isotopic pattern. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.26 (s, 3H, CH_3), 6.23 (s, 2H, NH_2), 7.56 (m, 5H, H-4´, H-5´, H-3´´, H-4´´), 7.78 (d, J = 7.6 Hz, 2H, H-2´´), 8.06 (d, J = 8.0 Hz, 1H, H-6´), 8.26 (s, 1H, H-2´), 9.13 (s, 1H, NH).

Example 2.6

6-Chloro-N^4-(3'-isopropoxyphenyl)-2-methylpyrimidine-4,5-diamine (3f).

Following the general procedure, a microwave vial was charged with 5-amino-4,6-dichloro-2-methylpyrimidine (356 mg, 2.00 mmol), 3-isopropoxyaniline (300 µL, 2.00 mmol), isobutanol (5.0 mL) and 37% aqueous HCl (150 µL). The mixture was washed with saturated aqueous $NaCO_3$. The organic layer was

dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by flash chromatography (dichloromethane/methanol, 30:1) to obtain 417 mg (71%) of **3f** as a solid. Mp: 144-146 ºC. MS (ES, positive mode): m/z 293 $(M+H)^+$ with a Cl isotopic pattern. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.28 (d, *J* = 6.0 Hz, 6H, $CH(C\underline{H}_3)_2$), 2.30 (s, 3H, CH_3), 4.53 (hept, *J* = 6.2 Hz, 1H, CH), 5.18 (s, 2H, NH_2), 6.54 (m, 1H, H-4´), 7.17 (m, 2H, H-5´, H-6´), 7.50 (d, *J* = 1.4 Hz, 1H, H-2´), 8.44 (s, 1H, NH).

Compound **3g** has been previously described (Aguado et al, *Eur. J Med Chem* **2012**, 49, 279-288).

Compound **3h** has been previously described (Aguado et al. *J. Comb. Chem*, **2009**, *11*, 210-212).

Example 2.7

6-Chloro-2-methyl-*N*^{4}-(4'-propoxyphenyl)pyrimidine-4,5-diamine (3i).

Following the general procedure, a microwave vial was charged with 5-amino-4,6-dichloro-2-methylpyrimidine (356 mg, 2.00 mmol), 4-propoxyaniline (297 µL, 2.00 mmol), isobutanol (5.0 mL) and 37% aqueous HCl (150 µL). After cooling, the product was isolated by filtration and dried to obtain 493 mg (84%) of **3i** as a solid. Mp: 208-209 ºC. MS (ES, positive mode): m/z 293 $(M+H)^+$ with a Cl isotopic pattern. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.96 (t, *J* = 7.4 Hz, 3H, $CH_2C\underline{H}_3$), 1.71 (h, *J* = 7.3 Hz, 2H, $C\underline{H}_2CH_3$), 2.30 (s, 3H, CH_3), 3.90 (t, *J* = 6.5 Hz, 2H, OCH_2), 4.38 (s, 2H, NH_2), 6.91 (d, *J* = 9.1 Hz, 2H, H-3´), 7.59 (d, *J* = 9.0 Hz, 2H, H-2´), 9.14 (s, 1H, NH).

Compound **3j** has been previously described (Aguado et al. *J. Comb. Chem*, **2009**, *11*, 210-212).

Example 2.8

6-Chloro-*N*^{4}-[3´,4´-methylenedioxyphenyl]-2-methylpyrimidine-4,5-diamine (3k).

Following the general procedure, a microwave vial was charged with 5-amino-4,6-dichloro-2-methylpyrimidine (200 mg, 1.12 mmol), 3,4-(methylendedioxy)aniline (154 mg, 1.12 mmol), isobutanol (2.8 mL) and HCl conc (84 µL). After cooling, the product was isolated by filtration and dried to obtain 278 mg (89%) of **3k** as a black solid, that was used as such for the next step. MS (ES, positive mode): m/z 279 $(M+H)^+$ with a Cl isotopic pattern. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.32 (s, 3H, CH_3), 6.00 (s, 2H, CH_2), 6.47 (s, 2H, NH_2), 6.88 (d, J = 8.4 Hz, 1H, H-5´), 7.11 (dd, J = 8.4, 2.1 Hz, 1H, H-6´), 7.43 (d, J = 2.1 Hz, 1H, H-2´), 9.38 (s, 1H, NH).

Example 2.9

3-((5-Amino-6-chloro-2-methylpyrimidin-4-yl)amino)benzonitrile (3l).

Following the general procedure, a microwave vial was charged with 5-amino-4,6-dichloro-2-methylpyrimidine (200 mg, 1.12 mmol), 3-aminobenzonitrile (133 mg, 1.12 mmol), isobutanol (2.8 mL) and HCl conc (84 µL). After cooling, the product was isolated by filtration and dried to obtain 264 mg (91%) of **3m** as a brown solid. Mp: 235-237 ºC. MS (ES, positive mode): m/z 260 $(M+H)^+$ with a Cl isotopic pattern. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 2.35 (s, 3H, CH_3), 5.75 (s, 2H, NH_2), 7.50 (m, 2H, H-4´, H-5´), 8.08 (d, J = 7.3 Hz, 1H, H-6´), 8.30 (s, 1H, H-2´), 9.28 (s, 1H, NH).

Compound **3m** has been previously described. (Aguado et al, *Eur. J Med Chem* **2012**, 49, 279-288).

Example 2.10

Ethyl 3-((5-amino-6-chloro-2-methylpyrimidin-4-yl)amino)benzoate (3n).

Following the general procedure, a microwave vial was charged with 5-amino-4,6-dichloro-2-methylpyrimidine (300 mg, 1.69 mmol), ethyl 3-aminobenzoate (247 µL, 1.69 mmol), dioxane (4.2 mL) and HCl conc (127 µL). After cooling, the product was isolated by filtration and dried to obtain 511 mg (98%) of **3n** as a solid used as such for the next step. MS (ES, positive mode): m/z 307 $(M+H)^+$ with a Cl isotopic pattern. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.33 (t, J = 7.1 Hz,

3H, CH_3), 2.34 (s, 3H, CH_3), 4.31 (q, *J* = 7.1 Hz, 2H, CH_2), 5.84 (s, 2H, NH_2), 7.46 (pt, *J* = 7.9 Hz, 1H, H-5´), 7.60 (m, 1H, H-4´), 8.12 (ddd, *J* = 8.0, 2.3, 1.1 Hz, 1H, H-6´), 8.46 (pt, *J* = 1.9 Hz, 1H, H-2´), 9.05 (s, 1H, NH).

Example 2.11

General procedure for the synthesis of 7-chloro-3*H*-[1,2,3]triazolo[4,5-*d*] pyrimidines (4) starting from 4,5-diaminopyrimidines.

To a suspension of the corresponding 4,5-diaminopyrimidine (**3**, 1.00 mmol) in dichloromethane (3.5 mL/mmol), $NaNO_2$ (1.05 mmol) and 1N HCl (3.5 mL/mmol) were added. The mixture was stirred at room temperature for 30 min. The reaction was diluted with dichloromethane. The organic layer was washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, filtered and evaporated to dryness.

Example 2.12

7-Chloro-3-(2´-methoxyphenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine (4a).

Following the general procedure, to a suspension of **3a** (296 mg, 1.12 mmol) in dichloromethane (3.9 mL), $NaNO_2$ (81 mg, 1.17 mmol) and 1N HCl (3.9 mL) were added. After work up 233 mg (75%) of **4a** were obtained as a pale brown solid. Mp: 156-158 ºC. MS (ES, positive mode): m/z 276 $(M+H)^+$ with a Cl isotopic pattern. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.34 (s, 3H, CH_3), 3.74 (s, 3H, OCH_3), 7.15 (ddd, *J* = 7.6, 1.7, 1.1 Hz, 1H, H-5´), 7.32 (dd, *J* = 8.5, 1.1 Hz, 1H, H-3´), 7.47 (dd, *J* = 7.8, 1.7 Hz, 1H, H-6´), 7.62 (ddd, *J* = 8.4, 7.5, 1.7 Hz, 1H, H-4´).

Example 2.13

7-Chloro-3-(3´-methoxyphenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine (4b).

Following the general procedure, to a suspension of **3b** (296 mg, 1.12 mmol) in dichloromethane (3.9 mL), $NaNO_2$ (81 mg, 1.17 mmol) and 1N HCl (3.9 mL) were added. After work up 233 mg (75%) of **4c** were obtained as a solid. Mp: >

110 ºC (decomposed). MS (ES, positive mode): m/z 276 $(M+H)^+$ with a Cl isotopic pattern. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.80 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 7.17 (ddd, *J* = 8.3, 2.4, 1.1 Hz, 1H, H-4´), 7.52-7.70 (m, 3H, H-2´, H-5´, H-6´).

Example 2.14

7-Chloro-3-(3´-chlorophenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-d]pyrimidine (4c).

Following the general procedure, to a suspension of **3c** (300 mg, 1.11 mmol) in dichloromethane (3.9 mL), $NaNO_2$ (81 mg, 1.11 mmol) and 1N HCl (3.9 mL) were added. After work up, 203 mg (65%) of **4b** were obtained as a pale brown solid. Mp: 106-108 ºC. MS (ES, positive mode): m/z 280 $(M+H)^+$ with a Cl isotopic pattern. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 2.45 (s, 3H, CH_3), 7.62 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H, H-4´), 7.68 (pt, *J* = 8.1 Hz, 1H, H-5´), 8.02 (ddd, *J* = 8.1, 2.0, 1.0 Hz, 1H, H-6´), 8.13 (pt, *J* = 2.0 Hz, 1H, H-2´).

Compound **4d** has been previously described (Aguado et al. *J. Med. Chem*, **2010**, *53*, 316-324).

Example 2.15

7-Chloro-3-(3'-benzoylphenyl)- 5-methyl-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidine (4e).

Following the general procedure, to a suspension of **3** (338 mg, 1.00 mmol) in dichloromethane (3.5 mL), $NaNO_2$ (73 mg, 1.05 mmol) and 1N HCl (3.5 mL) were added. After wok up 195 mg (56%) of **4e** were obtained as a pale brown solid. Mp: 136-138 ºC. MS (ES, positive mode): 339 m/z $(M+H)^+$ with a Cl isotopic pattern. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 2.46 (s, 3H, CH_3), 7.78 (m, 7H, H-4´, H-5´, H-2´´, H-3´´, H-4´´), 8.43 (m, 1H, H-6´), 8.50 (s, 1H, H-2´), 9.13 (s, 1H, NH).

Example 2.16

7-Chloro-3-(3´-isopropoxyphenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine (4f).

Following the general procedure, to a suspension of **3f** (150 mg, 0.51 mmol) in dichloromethane (2.0 mL), $NaNO_2$ (69 mg, 0.56 mmol) and 1N HCl (2.0 mL) were added. After work up, the residue was purified by flash chromatography (hexane/ethyl acetate, 1:1) to obtain 152 mg (61%) of **4f** as a solid. Mp: 223-225 ºC. MS (ES, positive mode): m/z 304 $(M+H)^+$ with a Cl isotopic pattern. ^1H NMR (DMSO-d_6, 300 MHz): δ 1.34 (d, J = 6.1 Hz, 6H, $CH(C\underline{H}_3)_2$), 2.82 (s, 3H, CH_3), 4.74 (hept, J = 6.0 Hz, 1H, CH), 7.16 (m, 1H, H-4´), 7.62 (m, 3H, H-2´, H-5´, H-6´).

Example 2.17

***N*-(3-(7-Chloro-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)phenyl)acetamide (4g).**

A flask was charged with **3g** (150 mg, 0.51 mmol), in acetic acid (4 mL) and $NaNO_2$ (35 mg, 0.51 mmol) was slowly added. The vessel was stirred at room temperature for 30 min,dissolved in toluene (15 mL) and evaporated to dryness. The residue was purified by CCTLC in the Chromatothron (dichloromethane/methanol, 20:1) to yield 108 mg (70%) of **4g**, as a pale pink solid. Mp 296-298 ºC. MS (ES, positive mode): m/z 303 $(M+H)^+$ with a Cl isotopic pattern. ^1H NMR (DMSO-d_6, 300 MHz): δ 2.09 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 7.53-8.36 (m, 4H, Ar), 12.75 (br s, 1H, NH).

Example 2.18

7-Chloro-3-(4´-acetylphenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine (4h).

Following the general procedure, to a suspension of **3h** (240 mg, 0.86 mmol) in dichloromethane (2.0 mL), $NaNO_2$ (66 mg, 0.95 mmol) and 1N HCl (2.0 mL) were added. After work up 152 mg (61%) of **4h** were obtained as a solid. Mp: 195-197 ºC. MS (ES, positive mode): m/z 288 $(M+H)^+$ with a Cl isotopic pattern.

^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.45 (s, 3H, CH_3), 2.65 (s, 3H, $COCH_3$), 8.19-8.35 (m, 4H, Ar).

Example 2.19

7-Chloro-3-(4´-propoxyphenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine (4i).

Following the general procedure, to a suspension of **3i** (150 mg, 0.51 mmol) in dichloromethane (2.0 mL), $NaNO_2$ (40 mg, 0.46 mmol) and HCl 1N (2.0 mL) were added. After work up 116 mg (75%) of **4i** were obtained as a solid. Mp: 222-224 ºC. MS (ES, positive mode): m/z 304 $(M+H)^+$ with a Cl isotopic pattern. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.00 (t, *J* = 7.4 Hz, 3H, $CH_2C\underline{H}_3$), 1.77 (h, *J* = 7.3 Hz, 2H, $C\underline{H}_2CH_3$), 2.78 (s, 3H, CH_3), 4.03 (t, *J* = 6.6 Hz, 2H, OCH_2), 7.22 (d, *J* = 9.1 Hz, 2H, H-3´), 7.92 (d, *J* = 9.1 Hz, 2H, H-2´).

Compound **4j** has been previously described (Aguado et al. *J. Med. Chem*, **2010**, *53*, 316-324).

Example 2.20

7-Chloro-3(3´,4´-methylenedioxyphenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine (4k).

Following the general procedure, to a suspension of **3k** (221 mg, 0.79 mmol) in dichloromethane (2.8 mL), $NaNO_2$ (57 mg, 0.83 mmol) and HCl 1N (2.8 mL) were added. After work up 60 mg (26%) of **4k** were obtained as a beige solid. Mp: > 300 ºC decomposed. MS (ES, positive mode): m/z 290 $(M+H)^+$ with a Cl isotopic pattern. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.42 (s, 3H, CH_3), 6.17 (s, 2H, CH_2), 7.17 (d, *J* = 8.3 Hz, 1H, H-5´), 7.42 (dd, *J* = 8.3, 2.0 Hz, 1H, H-6´), 7.49 (d, *J* = 2.0 Hz, 1H, H-2´).

Example 2.21

3-(7-Chloro-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)benzonitrile (4l).

Following the general procedure, to a suspension of **3m** (264 mg, 1.02 mmol) in dichloromethane (3.6 mL), $NaNO_2$ (74 mg, 1.05 mmol) and HCl 1N (3.6 mL) were added. After work up 202 mg (73%) of **4m** were obtained as a brown solid. Mp: 136-138 ºC. MS (ES, positive mode): m/z 271 $(M+H)^+$ with a Cl isotopic pattern. ^1H NMR (DMSO-d_6, 300 MHz): δ 2.83 (s, 3H, CH_3), 7.95 (pt, *J* = 8.0 Hz, 1H, H-5´), 8.09 (m, 1H, H-6´), 8.48 (ddd, *J* = 8.2 Hz, 2.2, 1.1 Hz, 1H, H-4´), 8.59 (pt, *J* = 1.8 Hz, 1H, H-2´).

Example 2.22

3-(7-Chloro-5-methyl-3*H*-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-N,N-dimethylaniline (4m)

Following the general procedure, to a suspension of **3m** (312 mg, 1.12 mmol) in dichloromethane (4 mL), $NaNO_2$ (81 mg, 1.18 mmol) and HCl 1N (4.0 mL) were added. After work-up, 87 mg (27%) of **4m** were obtained as a yellow solid,. Mp 140-141 ºC. MS (ES, positive mode): m/z 289 $(M+H)^+$ with a Cl isotopic pattern. ^1H NMR (DMSO-d_6, 300 MHz): δ 2.83 (s, 3H, CH_3), 7.95 (pt, *J* = 8.0 Hz, 1H, H-5´), 8.09 (m, 1H, H-4´), 8.48 (ddd, *J* = 8.2 Hz, 2.2, 1.1 Hz, 1H, H-6´), 8.59 (pt, *J* = 1.8 Hz, 1H, H-2´).

Example 2.23

Ethyl 3-(7-chloro-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)benzoate (4n).

Following the general procedure, to a suspension of **3n** (511 mg, 1.67 mmol) in dichloromethane (5.8 mL), $NaNO_2$ (121 mg, 1.75 mmol) and HCl 1N (5.8 mL) were added. After work up 367 mg (69%) of **4n** were obtained as a white solid. Mp: 109-110 ºC. MS 318 (ES, positive mode): m/z $(M+H)^+$ with a Cl isotopic pattern. ^1H NMR (DMSO-d_6, 300 MHz): δ 1.36 (t, *J* = 7.1 Hz, 3H, CH_3), 2.82 (s, 3H, CH_3), 4.39 (q, *J* = 7.1 Hz, 2H, CH_2), 7.87 (pt, *J* = 8.0 Hz, 1H, H-5´), 8.15 (m, 1H, H-6´), 8.42 (m, 1H, H-4´), 8.70 (pt, *J* = 1.9 Hz, 1H, H-2´).

Example 2.24

General procedure for the synthesis of [1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-ones (5).

To a solution of the corresponding 7-chloro-3*H*-[1,2,3]triazolo[4,5-d]pyrimidine (**4**) (1.00 mmol) in anhydrous DMF (4.5 mL/mmol), sodium acetate (3.00 mmol) was added. The reaction was microwave-irradiated at 120 ºC for 1 hour. The mixture was dissolved in dichloromethane and washed with brine. The organic layer was dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified as indicated in each case.

Example 2.25

3-(2´-Methoxyphenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one (5a).

Following the general procedure, to a solution of **4a** (170 mg, 0.62 mmol) in anhydrous DMF (2.8 mL), sodium acetate (154 mg, 1.85 mmol) was added. After work-up, the residue was purified by precipitation with dichloromethane/hexane to yield 79 mg (50%) of **5a** as a beige solid. Mp: 235-237 ºC. MS (ES, positive mode): m/z 258 $(M+H)^+$. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.34 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 7.16 (m, 1H, H-5´), 7.33 (d, J = 8.5, 1H, H-3´), 7.48 (dd, J = 7.8, 1.3 Hz, 1H, H-4´), 7.63 (m, 1H, H-6´), 12.63 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 21.8 (CH_3), 56.5 (OCH_3), 113.5, 121.1, 123.3, 127.9 (Ar), 129.2 (C-7a), 132.7 (Ar), 150.8 (C-3a), 154.9 (Ar), 156.3 (C-5), 160.7 (C-7). Anal. calc. for ($C_{12}H_{11}N_5O_2$): C, 56.03; H, 4.31; N, 27.22. Found: C, 55.92; H, 3.97; N, 26.90.

Example 2.26

3-(3´-Methoxyphenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one (5b).

Following the general procedure, to a solution of **4b** (167 mg, 0.61 mmol) in anhydrous DMF (2.7 mL), sodium acetate (151 mg, 1.82 mmol) was added. After work-up, the residue was purified by precipitation with dichloromethane to yield 84 mg (54%) of **5b** as a beige solid. Mp: 280-282 ºC. MS (ES, positive

mode): m/z 258 $(M+H)^+$. ^1H NMR (DMSO-d_6, 400 MHz): δ 2.42 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 7.10 (ddd, *J* = 8.3, 2.3, 1.2 Hz, 1H, H-4´), 7.54 (pt, *J* = 8.3, 1H, H-5´), 7.61 (m, 2H, H-2´, H-6´), 12.74 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 22.4 (CH_3), 56.0 (OCH_3), 108.3, 114.5, 114.7 (Ar), 129.3 (C-7a), 131.0, 136.8 (Ar), 149.3 (C-3a), 156.9 (C-5), 160.3 (C-7), 161.5 (Ar). Anal. calc. for ($C_{12}H_{11}N_5O_2$): C, 56.03; H, 4.31; N, 27.22. Found: C, 55.96; H, 4.10; N, 27.12.

Example 2.27

3-(3´-Chlorophenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one (5c).

Following the general procedure, to a solution of **4c** (150 mg, 0.54 mmol) in anhydrous DMF (2.4 mL), sodium acetate (133 mg, 1.61 mmol) was added. After work-up, the residue was purified by precipitation with dichloromethane/hexane to yield 109 mg (77%) of **5c** as a beige solid. Mp: 255-257 ºC. MS (ES, positive mode): m/z 262 $(M+H)^+$ with a Cl isotopic pattern. ^1H NMR (DMSO-d_6, 400 MHz): δ 2.45 (s, 3H, CH_3), 7.62 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H, H-4´), 7.68 (pt, *J* = 8.1 Hz, 1H, H-5´), 8.03 (ddd, *J* = 8.0, 2.0, 1.1 Hz, 1H, H-6´), 8.13 (pt, *J* = 2.0 Hz, 1H, H-2´), 12.79 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 22.1 (CH_3), 121.1, 122.1, 129.2 (Ar), 129.3 (C-7a), 131.9, 134.3, 136.9 (Ar), 149.3 (C-3a), 156.1 (C-5), 161.4 (C-7). Anal. calc. for ($C_{11}H_8ClN_5O_2$): C, 50.49; H, 3.08; N, 26.76. Found: C, 50.79; H, 2.91; N, 26.58.

Example 2.28

3-(3´-Acetylphenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one (5d).

A microwave vial was charged with **4d** (80 mg, 0.29 mmol) and sodium acetate (70 mg, 0.88 mmol) in anhydrous DMF (1.3 mL) and was irradiated at 120 ºC for 1 h. After work-up, the residue was purified by CCTLC in the Chromatothron (dichloromethane/methanol, 30:1) to yield 65 mg (83%) of **5d** as a yellow solid. Mp 257-259 ºC. MS (ES, positive mode): m/z 270 $(M+H)^+$. ^1H NMR (DMSO-d_6, 300 MHz) δ: 2.45 (s, 3H, CH_3), 2.67 (s, 3H, CH_3), 7.83-8.56 (m, 4H, Ar), 12.79 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 22.1 (CH_3), 27.4 (CH_3), 121.7,

126.9, 129.2 (Ar), 129.3 (C-7a), 136.1, 138.4, 130.8 (Ar), 149.3 (C-3a), 156.2 (C-5), 161.3 (C-7), 197.5 (CO). Anal. calc. for ($C_{13}H_{11}N_5O_2$): C, 57.99; H, 4.12; N, 26.01. Found: C, 57.67; H, 3.98; N, 25.75.

Example 2.29

3-(3´-Benzoylphenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one (5e).

Following the general procedure, to a solution of **4e** (195 mg, 0.56 mmol) in anhydrous DMF (2.5 mL), sodium acetate (139 mg, 1.67 mmol) was added and the mixture was irradiated at 120 ºC for 1 h. The residue was purified by precipitation with dichloromethane and hexane to yield 140 mg (75%) of **5e** as a yellow solid. Mp: 281-283 ºC. MS (ES, positive mode): m/z 332 $(M+H)^+$. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.41 (s, 3H, CH_3), 7.74 (m, 7H, H-4´, H-5´, H-2´´, H-3´´, H-4´´), 8.31 (ddd, *J* = 7.8, 2.1, 1.3 Hz, 1H, H-6´), 8.39 (pt, *J* = 1.6 Hz, 1H, H-2´), 12.76 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 22.3 (CH_3), 123.5, 129.4 (Ar), 129.6 (C-7a), 130.5, 126.4, 130.4, 131.0, 133.8, 136.0, 137.1, 138.7 (Ar), 149.5 (C-3a), 156.4 (C-5), 161.5 (C-7), 195.2 (CO). Anal. calc. for ($C_{18}H_{13}N_5O_2$): C, 65.25; H, 3.95; N, 21.14. Found: C, 64.98; H, 3.81; N, 20.89.

Example 2.30

3-(3´-Isopropoxyphenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one (5f).

Following the general procedure, to a solution of **4f** (60 mg, 0.19 mmol) in anhydrous DMF (1.0 mL) sodium acetate (75 mg, 0.57 mmol) was added. The residue was purified by flash chromatography (dichloromethane/methanol) to yield 38 mg (71%) of **5f** as a solid. Mp: 224-225 ºC. MS (ES, positive mode): m/z 286 $(M+H)^+$. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.33 (d, *J* = 6.0 Hz, 6H, $CH(C\underline{H}_3)_2$), 2.45 (s, 3H, CH_3), 4.71 (hept, *J* = 5.7 Hz, 1H, CH), 7.10 (m, 1H, H-4´), 7.54 (m, 3H, H-2´, H-5´, H-6´), 12.75 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 22.1 ($CH(\underline{C}H_3)_2$), 22.7 (CH_3), 70.2 (CH), 109.5, 114.1, 116.0 (Ar), 129.3 (C-7a), 131.0, 137.0 (Ar), 157.5 (C-5), 158.4 (Ar), 161.8 (C-7). Anal. calc. for ($C_{14}H_{15}N_5O_2$): C, 58.94; H, 5.30; N, 24.55. Found: C, 58.75; H, 5.60; N, 24.25.

Example 2.31

***N*-(3-(5-Methyl-7-oxo-6,7-dihydro-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)phenyl)-acetamide (5g).**

Following the general procedure, a microwave vial was charged with **4g** (90 mg, 0.30 mmol) and sodium acetate (75 mg, 0.90 mmol) in anhydrous DMF (1.5 mL) and was irradiated at 120 ºC for 1 h. After work-up, the residue was purified by CCTLC in the Chromatothron (dichloromethane/methanol, 30:1) to yield 30 mg (35%) of **5g** as a white solid. Mp 287-289 ºC. MS (ES, positive mode): m/z 285 $(M+H)^+$. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.09 (s, 3H, $COCH_3$), 2.45 (s, 3H, CH_3), 7.53-8.35 (m, 4H, Ar), 10.29 (br s, 1H, NH), 12.74 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 22.1 (CH_3), 24.5 (CH_3), 112.9, 117.0, 119.5 (Ar), 129.3 (C-7a), 130.4, 135.9, 140.8 (Ar) 149.1 (C-3a), 156.2 (C-5), 161.0 (C-7) 169.2 (CO). Anal. calc. for ($C_{13}H_{12}N_6O_2$): C, 54.93; H, 4.25; N, 29.56. Found: C, 54.82; H, 4.36; N, 29.65.

Example 2.32

3-(4´-Acetylphenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one (5h).

Following the general procedure, to a solution of **4h** (86 mg, 0.29 mmol) in anhydrous DMF (2.0 mL) sodium acetate (75 mg, 0.87 mmol) was added. After work-up, the residue was purified by flash chromatography (dichloromethane/methanol) to yield 54 mg (62%) of **5h** as a solid. Mp: 286-287 ºC. MS 270 (ES, positive mode): m/z $(M+H)^+$. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.45 (s, 3H, CH_3), 2.64 (s, 3H, $COCH_3$), 8.24 (d, J = 9.0 Hz, 4H, H-2´, H-3´), 12.75 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 22.1 (CH_3), 27.3 (CH_3), 122.0 (Ar), 129.5 (C-7a), 130.2, 136.8, 139.1 (Ar), 149.4 (C-3a), 156.1 (C-5), 161.4 (C-7), 197.5 (CO). Anal. calc. for ($C_{13}H_{11}N_5O_2$): C, 57.99; H, 4.12; N, 26.01. Found: C, 57.84; H, 4.28; N, 25.95.

Example 2.33

5-Methyl-3-(4´-propoxyphenyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one (5i).

Following the general procedure, to a solution of **4i** (60 mg, 0.19 mmol) in anhydrous DMF (2.0 mL), sodium acetate (50 mg, 0.57 mmol) was added. After work-up, the residue was purified by flash cromatography (dichloromethane/methanol) to yield 35 mg (65%) of **5i** as a solid. Mp: 267-268 ºC. MS (ES, positive mode): m/z 286 $(M+H)^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.01 (t, *J* = 7.4 Hz, 3H, $CH_2C\underline{H}_3$), 1.78 (h, *J* = 7.1 Hz, 2H, $C\underline{H}_2CH_3$), 2.43 (s, 3H, CH_3), 4.03 (t, *J* = 6.5 Hz, 2H, OCH_2), 7.18 (d, *J* = 9.0 Hz, 2H, H-3´), 7.85 (d, *J* = 9.0 Hz, 2H, H-2´), 12.69 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 11.1 ($CH_2\underline{C}H_3$), 22.2 (CH_3), 22.6 ($\underline{C}H_2CH_3$), 70.1 (OCH_2), 115.8, 124.8, 128.7 (Ar), 129.2 (C-7a), 149.2 (C-3a), 156.5 (C-5), 159.6 (C-7), 160.9 (Ar) .Anal. calc. for ($C_{14}H_{15}N_5O_2$): C, 58.94; H, 5.30; N, 24.55. Found: C, 58.84; H, 5.55; N, 24.36.

Example 2.34

3-(3´-Acetylphenyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one (5j).

Following the general procedure, to a solution of **4j** (90 mg, 0.33 mmol) in anhydrous DMF (1.5 mL), sodium acetate (82 mg, 0.99 mmol) was added. After work-up, the residue was purified by flash cromatography (dichloromethane/methanol) to yield 50 mg (59%) of **5j** as a beige solid. Mp 262-264 ºC. MS (ES, positive mode): m/z 256 $(M+H)^+$. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.65 (s, 3H, CH_3), 7.80 (pt, *J* = 7.9 Hz, 1H, H-5´), 8.13 (d, *J* = 7.8 Hz, 1H, H-6´), 8.28 (d, *J* = 8.0 Hz, 1H, H-4´), 8.37 (s, 1H, H-5), 8.55 (s, 1H, H-2´), 12.94 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 27.6 (CH_3), 121.7, 127.0 (Ar), 129.6 (C-7a), 131.0, 131.2, 136.2, 138.6 (Ar), 149.1 (C-3a), 151.4 (C-7), 155.9 (C-5), 197.7 (CO). Anal. calc. for ($C_{12}H_9N_5O_2$): C, 56.47; H, 3.55; N, 27.44. Found: C,56.28; H, 3.69; N, 27.25.

Example 2.35

3-(Benzo[*d*][1,3]dioxol-5-yl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one (5k).

Following the general procedure, to a solution of **4k** (32 mg, 0.11 mmol) in anhydrous DMF (0.5 mL), sodium acetate (28 mg, 0.33 mmol) was added. The resulting precipitate was filtered and washed with water to yield 15 mg (50%) of

5k as a beige solid. Mp: > 290 ºC decomposed. MS (ES, positive mode): m/z 272 $(M+H)^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ: 2.30 (s, 3H, CH_3), 6.12 (s, 2H, CH_2), 7.10 (d, *J* = 8.4 Hz, 1H, H-5´), 7.57 (dd, *J* = 8.4, 2.0 Hz, 1H, H-6´), 7.63 (d, *J* = 1.9 Hz, 1H, H-2´).^{13}C NMR (DMSO-d_6, 100 MHz): δ 24.0 (CH_3), 102.3 (CH_2), 103.3, 108.9, 115.3 (Ar), 129.3 (C-7a), 131.1, 147.0, 148.1 (Ar), 150.3 (C-3a), 165.1 (C-5), 173.9 (C-7). Anal. calc. for ($C_{12}H_9N_5O_3$): C, 53.14; H, 3.34; N, 25.82. Found: C, 53.02; H, 3.68; N, 25.77.

Example 2.36

3-(5-Methyl-7-oxo-6,7-dihydro-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)benzonitrile (5l).

Following the general procedure, to a solution of **4l** (170 mg, 0.63 mmol) in anhydrous DMF (2.8 mL), sodium acetate (153 mg, 1.88 mmol) was added. After work-up, the residue was washed with ether and the resulting solid was purified by precipitation with dichloromethane/methanol to yield 104 mg (65%) of **5l** as a beige solid. Mp: > 280 ºC decomposed. MS (ES, positive mode): m/z 253 $(M+H)^+$. ^1H NMR (DMSO-d_6, 400 MHz): δ 2.46 (s, 3H, CH_3), 7.87 (pt, *J* = 8.0 Hz, 1H, H-5´), 8.03 (m, 1H, H-6´), 8.39 (ddd, *J* = 8.3, 2.1, 1.0 Hz, 1H, H-4´), 8.50 (pt, *J* = 1.8 Hz, 1H, H-2´), 12.82 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 22.0 (CH_3), 112.9 (C-3´), 118.3 (CN), 125.7, 127.3 (Ar), 129.2 (C-7a), 131.7, 133.1, 136.1 (Ar), 149.4 (C-3a), 156.3 (C-5), 161.4 (C-7). Anal. calc. for ($C_{12}H_8N_6O$): C, 57.14; H, 3.20; N, 33.32. Found: C, 57.02; H, 3.25; N, 33.45.

Example 2.37

3-(3-(Dimethylamino)phenyl)-5-methyl-3H-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6H)-one (5m)

Following the general procedure, to a solution of **4m** (50 mg, 0.17 mmol) in DMF (0.8 mL), sodium acetate (43 mg, 0.52 mmol) was added. After work-up, the precipitate was isolated by filtration and washed with water to yield 38 mg (81%) of **5m** as a yellow solid. Mp 319-321 ºC. **MS** (ES, positive mode): m/z 272 $(M+H)^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ: 2.42 (s, 3H, CH_3), 2.97 (s, 3H, NMe_2), 6.86 (dd, *J* = 8.4, 2.2 Hz, 1H, H-6´), 7.21 (dd, *J* = 8.0, 1.2 Hz, 1H, H-4´),

7.27 (pt, *J* = 2.2 Hz, 1H, H-2′), 7.40 (pt, *J* = 8.1 Hz, 1H, H-5′), 12.68 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 22.1 (CH_3), 40.4 (NMe_2), 106.2 (C-2′), 110.0 (C-4′), 113.0 (C-6′), 129.2 (C-7a), 130.3 (C-5′), 136.6 (C-1′), 149.1 (C-3a), 151.4 (C-3′), 156.3 (C-5), 160.8 (C-7). Anal. calc. for ($C_{13}H_{14}N_6O$): C, 57.77; H, 5.22; N, 31.09. Found: C, 57.51; H, 5.02; N, 30.78.

Example 2.38

Ethyl 3-(5-methyl-7-oxo-6,7-dihydro-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl) benzoate (5n).

Following the general procedure, to a solution of **4n** (170 mg, 0.63 mmol) in anhydrous DMF (2.8 mL), sodium acetate (153 mg, 1.88 mmol) was added. After work-up, the residue was washed with ether and the resulting solid was purified by precipitation with dichloromethane/methanol to yield 104 mg (65%) of **5n** as a beige solid. Mp: 245-247 ºC. MS (ES, positive mode): m/z 253 $(M+H)^+$. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.46 (s, 3H, CH_3), 7.87 (pt, *J* = 8.0 Hz, 1H, H-5′), 8.03 (m, 1H, H-6′), 8.39 (ddd, *J* = 8.3, 2.1, 1.0 Hz, 1H, H-4′), 8.50 (pt, *J* = 1.8 Hz, 1H, H-2′), 12.82 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 14.6 ($CH_2\underline{C}H_3$), 22.1 (CH_3), 61.8 ($\underline{C}H_2CH_3$), 122.6, 126.7 (Ar), 129.4 (C-7a), 129.7, 130.8, 131.7, 136.1 (Ar), 149.3 (C-3a), 156.2 (C-5), 161.3 (C-7), 165.2 (CO). Anal. calc. for ($C_{14}H_{13}N_5O_3$): C, 56.18; H, 4.38; N, 23.42. Found: C, 56.02; H, 4.62; N, 23.33.

Example 2.39

3-(5-Methyl-7-oxo-6,7-dihydro-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)benzoic acid (5o).

To a solution of **5n** (500 mg, 1.67 mmol) in anhydrous DMF (11.0 mL/mmol), KOH 20% (4.3 mL) was added. The reaction was microwave-irradiated at 100 ºC for 30 min. After cooling, the reaction was concentrated to dryness. The residue was dissolved in water, acidified by addition of HCl 1N and the precipitate thus formed was isolated by filtration to yield 419 mg (92%) of **5o** as a yellow solid. Mp: > 290 ºC decomposed ºC. MS (ES, positive mode): m/z 272

$(M+H)^+$. ^1H NMR (DMSO-d_6, 400 MHz): δ 2.45 (s, 3H, CH_3), 7.79 (pt, J = 8.0 Hz, 1H, H-5´), 8.08 (m, 1H, H-6´), 8.29 (ddd, J = 8.0, 2.2, 1.0 Hz, 1H, H-4´), 8.58 (pt, J = 1.7 Hz, 1H, H-2´), 12.78 (s, 1H, NH), 13.42 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 22.1 (CH_3), 122.9, 126.5 (Ar), 129.4 (C-7a), 129.9, 130.7, 132.7, 136.0 (Ar), 149.3 (C-3a), 156.2 (C-5), 161.3 (C-7), 166.8 (COOH). Anal. calc. for ($C_{12}H_9N_5O_3$): C, 53.14; H, 3.34; N, 25.82. Found: C, 52.95; H, 3.28; N, 25.75.

Example 2.40

3-(3´-Acetylphenyl)-7-amino-5-methyl-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7(6*H*)-one (6a).

A microwave vial containing **4d** (100 mg, 0.34 mmol) in a solution of NH_3 in methanol (2.0 M, 4 mL) was sealed and heated in a microwave reactor at 70 ºC for 30 min. After cooling, the resulting precipitate was filtered and purified by flash column chromatography (dichloromethane/methanol) to yield 60 mg (66%) of **6a** as a solid. Mp: 286-287 ºC. MS (ES, positive mode): m/z 269 $(M+H)^+$. ^1H NMR (DMSO-d_6, 300 MHz): δ 2.50 (s, 3H, CH_3), 2.69 (s, 3H, $COCH_3$), 7.82 (pt, J = 7.9 Hz, 1H, H-5´), 8.10 (d, J = 7.8 Hz, 1H, H-6´), 8.17 (s, 1H, NH), 8.45 (d, J = 8.1 Hz, 1H, H-4´), 8.50 (s, 1H, NH), 8.70 (s, 1H, H-2´). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 26.7 (CH_3), 27.6 ($CO\underline{C}H_3$), 120.9, 123.8, 126.1 (Ar), 128.6 (C-7a), 130.9, 137.1,138.6 (Ar), 150.3 (C-3a), 156.7 (C-7), 168.0 (C-5), 197.9 (CO). Anal. calc. for ($C_{13}H_{12}N_6O$): C, 58.20; H, 4.51; N, 31.33. Found: C, 57.96; H, 4.68; N, 31.09.

Example 2.41

3-(3´-Acetylphenyl)-5-methyl-7-methylamino-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7(6*H*)-one (6b).

A solution of **4d** (100 mg, 0.34 mmol) in methylamine in methanol (2.0 M, 10 mL) was stirred at room temperature for 2 h. After volatiles removal, the residue was purified by flash column chromatography (dichloromethane/methanol) to yield 64 mg (67%) of **6b** as a solid. Mp: 220-221 ºC. MS (ES, positive mode): m/z 283 $(M+H)^+$. ^1H NMR (DMSO-d_6, 300 MHz) δ: 2.55 (s, 3H, CH_3), 2.68 (s,

3H, $COCH_3$), 3.05 (d, *J* = 4.6 Hz, 3H, $NHC\underline{H}_3$), 7.82 (pt, *J* = 7.9 Hz, 1H, H-5´), 8.10 (d, *J* = 7.8 Hz, 1H, H-6´), 8.45 (d, *J* = 8.0 Hz, 1H, H-4´), 8.70 (s, 1H, H-2´), 8.92 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 27.2 (CH_3), 27.6 ($CO\underline{C}H_3$), 27.8 ($NHCH_3$), 120.9, 124.4. 126.1 (Ar), 128.6 (C-7a), 130.9, 137.1, 138.6 (Ar), 150.3 (C-3a), 156.7 (C-7), 168.0 (C-5), 197.9 (CO). Anal. calc. for ($C_{14}H_{14}N_6O$): C, 59.56; H, 5.00; N, 29.77. Found: C, 59.46; H, 4.85; N, 29.58.

Example 2.42

3-(3´-Acetylphenyl)-7-methoxy-5-methyl-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-7(6*H*)-one (7).

A microwave vial was charged with **4d** (100 mg, 0.32 mmol) and sodium methoxide (86 mg, 1.59 mmol) in methanol (4 mL) and was irradiated at 100 ºC for 20 min. After volatiles removal, the residue was purified by CCTLC in the Chromatothron (dichloromethane/methanol, 30:1) to yield 55 mg (61%) of **7** as a white solid. Mp 158-160 ºC. EM (ES, positive mode): m/z 284 $(M+H)^+$. ^1H NMR (DMSO-d_6, 300 MHz): δ 2.69 (s, 3H, CH_3), 2.72 (s, 3H, CH_3), 4.23 (s, 3H, OCH_3), 7.86-8.67 (m, 4H, Ar). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 26.8 (CH_3), 27.6 (CH_3), 55.6 (OCH_3), 125.2, 121.4, 126.6 (Ar), 129.3 (C-7a), 131.1, 136.5, 138.7 (Ar), 151.6 (C-3a), 161.6 (C-7), 168.0 (C-5), 197.8 (CO). Anal. calc. for ($C_{14}H_{13}N_5O_2$): C, 59.36; H, 4.63; N, 24.72. Found: C, 59.60; H, 4.62; N, 24.53.

Example 2.43

3-(3´-Acetylphenyl)-5,6-dimethyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one (8)

To a flask charged with **5d** (90 mg, 0.33 mmol) in N,N-dimethylacetamide (2 mL), iodomethane (27 µL, 0.43 mmol) and DBU (66 µL, 0.44 mmol) were added. The reaction was stirred at room temperature overnight under argon atmosphere. Then, a hexane/diethyl ether (1:1) mixture (10 mL) was added and the resultant suspension was cooled at -20 ºC. The precipitate was dissolved in dichloromethane (20 mL) and washed with saturated aqueous $NaHCO_3$ (15 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by flash chromatography

(dichloromethane/methanol) to yield 80 mg (86%) of **8** as a yellow solid. Mp 166-168 ºC. EM (ES, positive mode): m/z 284 $(M+H)^+$. ^1H NMR (DMSO-d_6, 300 MHz): δ 2.66 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 3.57 (s, 3H, CH_3), 7.80-8.57 (m, 4H, Ar). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 24.2 (CH_3), 26.9 (CH_3), 30.8 (CH_3), 121.0, 126.1, 128.1 (Ar), 128.6 (C-7a), 130.4, 135.6, 138.0 (Ar), 146.8 (C-3a), 155.5 (C-5), 162.1 (C-7), 197.1 (CO). Anal. calc. for ($C_{14}H_{13}N_5O_2$): C, 59.36; H, 4.63; N, 24.72. Found: C, 59.65; H, 4.59; N, 24.68.

Example 2.44

9-(3´-Acetylphenyl)-2-methyl-1*H*-purin-6(9*H*)-one (10a)

To a solution of **9a** (154 mg, 0.54 mmol) in methanol (10.0 mL), sodium methoxide (3.0 mmol) and 2-mercaptoethanol were added. The reaction was heated in a microwave reactor at 100 ºC for 90 min. After cooling, the product was isolated by filtration and dried to obtain 89 mg (62%) of **10b** as a yellowish solid. Mp: 286-287 ºC. MS (ES, positive mode): m/z 269 $(M+H)^+$. ^1H NMR (300 MHz, DMSO-d_6): δ 2.22 (s, 3H, CH_3), 2.64 (s, 3H, CH_3), 7.67 (pt, *J* = 7.8 Hz, 1H, H-5´), 7.91 (d, *J* = 7.8 Hz, 1H, H-6´), 8.18 (m, 2H, H-2´, H-4´), 8.46 (s, 1H, H-8). Anal. calc. for ($C_{14}H_{12}N_4O_2$) C, 62.68; H, 4.51; N, 20.88. Found: C, 62.52; H, 4.85; N, 20.79.

Example 2.45

9-(3-Acetylphenyl)-2,8-dimethyl-1*H*-purin-6(9*H*)-one (10b)

To a solution of **9b** (Aguado et al. *J. Comb. Chem*, **2009**, *11*, 210-212) (63 mg, 0.20 mmol) in dioxane (5.0 mL) a 1N HCl aqueous solution was added. The reaction was heated in a microwave reactor at 100 ºC for 2 hours. The mixture was extracted with ethyl acetate (15 mL) and the organic layer was washed with a saturated aqueous Na_2CO_3 solution (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered and evaporated to dryness in vacuo. The residue was purified by flash column chromatography (dichloromethane/methanol) to yield 35 mg (61%) of **10b** as a solid. Mp: 282-283 ºC. MS (ES, positive mode): m/z 283 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 2.26 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 7.74 (m, 2H, H-5´, H-6´), 8.01 (dd, *J* = 2.4, 1.1 Hz, 1H, H-2´),

8.10 (ddd, *J* = 5.0, 3.5, 1.7 Hz, 1H, H-4´). Anal. calc. for ($C_{15}H_{14}N_4O_2$) C, 63.82; H, 5.00; N, 19.85. Found: C, 63.58; H, 5.06; N, 19.98.

Example 2.46

(+/-) 3-(3´-(1-Hydroxyethyl)phenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one (11)

To a solution of **5d** (100 mg, 0.37 mmol) in THF (1.2 mL), water (60 µL) and $NaBH_4$ (14 mg, 0.37 mmol) were slowly added. The reaction mixture was stirred at 75 ºC overnight. The reaction was extracted with isobutanol. The organic layer was washed with brine and dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by flash chromatography (dichloromethane/methanol) to yield 43 mg (43%) of **11** as a racemic mixture. EM (ES, positive mode): m/z 272 $(M+H)^+$. ^1H NMR (300 MHz, DMSO-d_6): δ 1.39 (d, *J* = 6.4 Hz, 3H, CHC$\underline{H}_3$), 2.45 (s, 3H, CH_3), 4.85 (q, *J* = 6.3 Hz, 1H, CH), 5.40 (d, *J* = 4.3 Hz, 1H, OH), 7.52 (d, *J* = 7.8 Hz, 1H, H-4´), 7.59 (pt, *J* = 7.8 Hz, 1H, H-5´), 7.86 (d, *J* = 7.8 Hz, 1H, H-6´), 7.97 (s, 1H, H-2´), 12.73 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.1 (CH_3), 26.3 (CH$\underline{C}H_3$), 68.1 (CH), 119.7, 121.0, 126.4 (Ar), 129.2 (C-7a), 129.7, 135.5 (Ar), 149.1 (C-3a), 149.8 (Ar), 156.3 (C-5), 160.9 (C-7). Anal. calc. for ($C_{13}H_{13}N_5O_2$): C, 57.56; H, 4.83; N, 25.82. Found: C, 57.56; H, 4.96; N, 25.61.

Example 2.47

***(Z/E)*-3-(3´-(1-(Hydroxyimino)ethyl)phenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one (12a)**

To a solution of **5d** (130 mg, 0.48 mmol) in ethanol (5 mL), hydroxylamine hydrochloride (68 mg, 0.96 mmol) was added. The reaction mixture was heated in a microwave reactor at 80 ºC for 1 hour. After cooling, the reaction was filtered and the solid was purified by flash chromatography (dichloromethane/methanol) to yield 104 mg (76%) of **12a**. Mp: 289-291 ºC. EM (ES, positive mode): m/z 285 $(M+H)^+$. ^1H NMR (300 MHz, DMSO-d_6): δ 2.23 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 7.68 (pt, *J* = 8.0 Hz, 1H, H-5´), 7.82 (d, *J* = 7.0 Hz, 1H, H-6´), 8.01 (d, *J* = 7.1 Hz, 1H, H-4´), 8.30 (s, 1H, H-2´), 11.46 (s, 1H, N-

OH), 12.75 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.2 (C=N(OH)$\underline{C}$H$_3$), 22.3 (CH$_3$), 119.7, 123.0, 126.9 (Ar), 129.5 (C-7a), 130.5, 136.1, 139.0 (Ar), 149.4 (C-3a), 152.7 (C-5), 156.4 ($\underline{C}$=N(OH)CH$_3$), 161.3 (C-7). Anal. calc. for ($C_{13}H_{12}N_6O_2$): C, 54.93; H, 4.25; N, 29.56. Found: C, 54.91; H, 4.19; N, 29.38.

Example 2.48

(E/*Z*)-3-(3´-(1-(Methoxyimino)ethyl)phenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one (12b)

To a solution of **5d** (123 mg, 0.45 mmol) in ethanol (5 mL), *N*-methylhydroxylamine hydrochloride (77 mg, 0.91 mmol) was added. The reaction mixture was heated in a microwave reactor at 80 ºC for 1 hour. After cooling, the reaction was filtered and the solid was purified by flash chromatography (dichloromethane/methanol) to yield 103 mg (77%) of **12b**. Mp: 272-274 ºC. EM (ES, positive mode): m/z 299 $(M+H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.25 (s, 3H, CH$_3$), 2.46 (s, 3H, CH$_3$), 3.96 (s, 3H, OCH$_3$), 7.70 (pt, *J* = 8.0 Hz, 1H, H-5´), 7.83 (d, *J* = 6.9 Hz, 1H, H-6´), 8.07 (d, *J* = 6.0 Hz, 1H, H-4´), 8.32 (s, 1H, H-2´), 12.76 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.0 (C=N(OCH$_3$)$\underline{C}$H$_3$), 22.3 (CH$_3$), 62.5 (OCH$_3$), 119.9, 123.4, 127.0 (Ar), 129.5 (C-7a), 130.6, 136.1, 138.0 (Ar), 149.5 (C-3a), 153.9 (C-5), 156.4 ($\underline{C}$=N(OCH$_3$)$\underline{C}$H$_3$), 161.3 (C-7). Anal. calc. for ($C_{14}H_{14}N_6O_2$): C, 56.37; H, 4.73; N, 28.17. Found: C, 56.31; H, 4.80; N, 28.04.

Example 2.49

(*E/Z*)-Ethyl 2-(((1-(3-(5-methyl-7-oxo-6,7-dihydro-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin -3-yl)phenyl)ethylidene)amino)oxy)acetate (13)

To a solution of **12a** (100 mg, 0.35 mmol) in DMF (2.0 mL), Cs_2CO_3 (230 mg, 0.70 mmol) was added and the mixture was stirred for 10 min. Then, ethyl bromoacetate (117 mg, 1.07 mmol) was slowly added and the reaction was stirred for 2 h. The reaction mixture was evaporated and the residue was purified by flash chromatography (dichloromethane/ethyl acetate) to yield 60 mg (46%) of **13**. Mp: 196-197 ºC. EM (ES, positive mode): m/z 371 $(M+H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.24 (t, *J* = 7.1 Hz, 3H, CH$_2$C$\underline{H}_3$), 2.23 (s, 3H,

CH_3), 2.63 (s, 3H, CH_3), 4.21 (q, *J* = 7.1 Hz, 2H, $C\underline{H}_2CH_3$), 5.01 (s, 2H, OCH_2CO), 7.69 (pt, *J* = 7.9 Hz, 1H, H-5´), 7.84 (d, *J* = 7.9 Hz, 1H, H-6´), 8.03 (d, *J* = 8.0 Hz, 1H, H-4´), 8.30 (s, 1H, H-2´), 11.48 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 12.2 ($CH_2\underline{C}H_3$), 14.7 (C=N(O)$\underline{C}H_3$), 24.4, (CH_3), 46.3 ($\underline{C}H_2CH_3$), 62.3 (CH_2), 120.0, 123.1, 128.4 (Ar), 128.4 (C-7a), 130.5, 135.8, 139.1 (Ar), 147.5 (C-3a), 152.7 (C-5), 155.8 ($\underline{C}$=N(O)$\underline{C}H_3$), 162.1 (C-7), 168.3 (COOEt). Anal. calc. for ($C_{17}H_{18}N_6O_4$): C, 55.13; H, 4.90; N, 22.69. Found: C, 54.97; H, 5.19; N, 22.44.

Example 2.50

5-Amino-1-(3-isopropoxyphenyl)-1*H*-1,2,3-triazole-4-carboxamide (15)

To a suspension of NaH (60% in mineral oil, 152 mg, 6.24 mmol) in anhydrous DMF (5.9 mL), a solution of cyanoacetamide (326 mg, 3.88 mmol) in anhydrous DMF (5.9 mL) was added at 0 ºC. After 1 h a solution of **14** (Organic Letters **2008**, vol. 10, p. 5529 – 5531) (624 mg, 3.52 mmol) in anhydrous DMF (5.9 mL) was slowly added and stirring was continued at room temperature for 1 h. Volatiles were removed. The residue obtained was purified by flash column chromatography (dichloromethane/methanol, 20:1) to yield 641 mg (70%) of **15** as a yellowish solid. Mp: 123-125 ºC. MS (ES, positive mode): m/z 262 $(M+H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.29 (d, *J* = 6.0 Hz, 6H, $CH(C\underline{H}_3)_2$), 4.70 (hept, *J* = 5.7 Hz, 1H, CH), 6.37 (s, 2H, NH_2), 7.08 (m, 3H, H-2´, H-4´, H-6´), 7.26 (s, 1H, $CONH_2$), 7.47 (pt, *J* = 7.9 Hz, 1H, H-5´), 7.62 (s, 1H, $CONH_2$). ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.4 (CH_3), 70.4 (CH), 111.6, 116.5, 116.9 (Ar), 122.3 (C-4), 131.3, 136.6 (Ar), 145.3 (C-5), 158.9 (Ar), 165.0 (CO). Anal. calc. for ($C_{12}H_{15}N_5O_2$): C, 55.16; H, 5.79; N, 26.80. Found: C, 55.30; H, 5.80; N, 26.78.

Example 2.51

General procedure for the synthesis of [1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-ones (16) from 5-amino-1*H*-1,2,3-triazole-4-carboxamides.

To a solution of Na (5.00 mmol) in ethanol (10 mL/mmol), the carboxamide **15** (1.00 mmol) and the appropriate ester (4.00 mmol) were added. The reaction mixture was heated at reflux for 1 to 8 hours. After cooling, the reaction was

concentrated to dryness. The residue was dissolved in water, acidified by addition of acetic acid and the precipitate thus formed was isolated by filtration and purified as specified.

Example 2.52

5-Cyanoethyl-3-(3´-isopropoxyphenyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one (16a)

Following the general procedure, to a solution of Na (38 mg, 1.65 mmol) in ethanol (3.3 mL), **15** (90 mg, 0.33 mmol) and ethyl cyanoacetate (140 µL, 1.31 mmol) were added. The reaction mixture was refluxed for 8 hours. After cooling, a precipitate was obtained that was purified by CCTLC (dichloromethane/methanol, 20:1) to yield 23 mg (23%) of **16a** as a beige solid. Mp: 242-244 ºC. MS (ES, positive mode): m/z 311 $(M+H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.30 (d, J = 6.0 Hz, 6H, $CH(C\underline{H}_3)_2$), 4.31 (s, 2H, CH_2), 4.73 (hept, J = 6.0 Hz, 1H, CH), 7.07 (ddd, J = 8.3, 2.5, 0.9, 1H, H-4´), 7.52 (pt, J = 8.2 Hz, 1H, H-5´), 7.60 (ddd, J = 8.0, 1.9, 0.9 Hz, 1H, H-6´), 7.73 (pt, J = 2.1 Hz, 1H, H-2´), 13.05 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.2 (CH_3), 25.0 (CH_2), 70.4 (CH), 108.8, 113.8 (Ar), 115.6 (CN), 117.2 (Ar), 129.8 (C-7a), 131.2, 136.7 (Ar), 148.3 (C-3a), 154.8 (C-5), 155.7 (C-7), 158.6 (Ar). Anal. calc. for ($C_{15}H_{14}N_6O_2$): C, 58.06; H, 4.55; N, 27.08. Found: C, 57.96; H, 4.52; N, 26.98.

Example 2.53

3-(3´-Isopropoxyphenyl)-5-phenyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one (16b)

Following the general procedure, to a solution of Na (33 mg, 1.45 mmol) in ethanol (2.9 mL), **15** (80 mg, 0.29 mmol) and ethyl phenylacetate (145 µL, 1.16 mmol) were added. The reaction mixture was refluxed for 8 hours to obtain a precipitate that was purified by CCTLC (dichloromethane/methanol, 20:1) to yield 41 mg (41%) of **16b** as a white solid. Mp: 245-246 ºC. MS (ES, positive mode): m/z 348 $(M+H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.33 (d, J = 6.0 Hz, 6H, $CH(C\underline{H}_3)_2$), 4.73 (hept, J = 6.0 Hz, 1H, CH), 7.09 (m, 1H, H-4´), 7.62 (m, 6H, H-3´´, H-4´´, H-2´, H-5´, H-6´), 8.14 (d, J = 7.8 Hz, 2H, H-2´´), 13.05 (s, 1H,

NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.3 (CH_3), 70.6 (CH), 109.5, 114.5, 117.2, 129.2, 129.5 (Ar), 129.8 (C-7a), 131.4, 132.3, 133.1, 137.1 (Ar), 149.3 (C-3a), 156.9 (C-7), 158.4 (Ar), 158.8 (C-5). Anal. calc. for ($C_{19}H_{17}N_5O_2$): C, 65.69; H, 4.93; N, 20.16. Found: C, 64.99; H, 4.95; N, 20.07.

Example 2.54

3-(3´-Isopropoxyphenyl)-5-(4´´-pyridyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one (16c)

Following the general procedure, to a solution of Na (33 mg, 1.45 mmol) in ethanol (2.9 mL), **15** (80 mg, 0.29 mmol) and methyl 4-pyridylacetate (159 µL, 1.16 mmol) were added. The reaction mixture was refluxed for 5 hours to yield 80 mg (79%) of **16c** as a beige solid. Mp: 259-260 ºC. MS (ES, positive mode): m/z 349 $(M+H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.33 (d, J = 6.0 Hz, 6H, $CH(C\underline{H}_3)_2$), 4.73 (hept, J = 6.0 Hz, 1H, CH), 7.11 (d, J = 8.7 Hz, 1H, H-4´), 7.56 (pt, J = 8.3 Hz, 1H, H-5´), 7.66 (m, 2H, H-2´, H-6´), 8.05 (d, J = 5.9 Hz, 2H, H-2´´), 8.83 (d, J = 5.7 Hz, 2H, H-3´´). ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.2 (CH_3), 70.4 (CH), 109.4, 114.4, 117.0, 122.5 (Ar), 130.1 (C-7a), 131.2, 136.7, 139.5 (Ar), 148.7 (C-3a), 150.9, 156.4 (Ar), 156.6 (Ar, C-7), 158.6 (C-5). Anal. calc. for ($C_{18}H_{16}N_6O_2$): C, 62.06; H, 4.63; N, 24.12. Found: C, 61.70; H, 4.61; N, 23.78.

Example 2.55

3-(3´-Isopropoxyphenyl)-5-trifluoromethyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one (16d)

Following the general procedure, to a solution of Na (43 mg, 1.85 mmol) in ethanol (3.7 mL), **15** (96 mg, 0.37 mmol) and ethyl trifluoroacetate (175 µL, 1.47 mmol) were added. The reaction mixture was refluxed for 1 hour. After work-up, **16d** (84 mg, 67%) was isolated as a white solid. Mp: 214-216 ºC. MS (ES, positive mode): m/z 340 $(M+H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.32 (d, J = 6.0 Hz, 6H, $CH(C\underline{H}_3)_2$), 4.69 (hept, J = 6.2 Hz, 1H, CH), 7.13 (ddd, J = 7.8, 2.5, 1.6, 1H, H-4´), 7.55 (m, 3H, H-2´, H-5´, H-6´). ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.0 (CH_3), 70.4 (CH), 109.8, 114.5, 117.1 (Ar), 122.1 (q ap, CF_3), 131.2 (C-7a),

131.3, 136.2 (Ar), 147.5 (C-3a), 148.0 (d, *J* = 39.3 Hz, C-5), 156.7 (C-7), 158.6 (Ar). Anal. calc. for ($C_{14}H_{12}F_3N_5O_2$): C, 49.56; H, 3.57; N, 20.64. Found: C, 49.29; H, 3.33; N, 20.38.

Example 2.56

5-Ethyl-3-(3´-isopropoxyphenyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one (16e)

Procedure 1: Following the general procedure, to a solution of Na (44 mg, 1.90 mmol) in ethanol (3.8 mL), **15** (100 mg, 0.38 mmol) and ethyl propionate (176 µL, 1.52 mmol) were added. The reaction mixture was refluxed for 8 h. After work-up, a precipitate was obtained that was purified by CCTLC (dichloromethane/methanol, 20:1) to yield **16e** (60 mg, 53%) as a white solid.

Procedure 2: To a solution of **15** (30 mg, 0.11 mmol) in anhydrous THF (1.1 mL), tBuOK in THF (1.0 M, 0.17 mmol, 170 µL) and ethyl propionate (53 µL, 0.46 mmol) were added. The reaction was microwave-irradiated at 90 ºC for 1 hour. After cooling, the mixture was diluted with water, acetic acid was added and the reaction was concentrated to dryness. The resulting residue was washed with tBuOH to yield **16e** (26 mg, 79%) as a white solid.

Mp: 242-244 ºC. MS (ES, positive mode): m/z 300 $(M+H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.23 (t, *J* = 7.5 Hz, 3H, CH_3), 1.31 (d, *J* = 6.0 Hz, 6H, $CH(C\underline{H}_3)_2$), 2.71 (q, *J* = 7.5 Hz, 2H, CH_2), 4.69 (hept, *J* = 6.0 Hz, 1H, CH), 7.06 (d, *J* = 8.0, 1H, H-4´), 7.51 (pt, *J* = 8.1 Hz, 1H, H-5´), 7.58 (d, *J* = 8.0 Hz, 1H, H-6´), 7.63 (s, 1H, H-2´), 12.70 (s 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.5 (CH_3), 22.1 ($CH(\underline{C}H_3)_2$), 28.1 (CH_2), 70.3 (CH), 109.2, 114.0, 116.6 (Ar), 129.4 (C-7a), 131.1, 136.9 (Ar), 149.1 (C-3a), 156.3 (C-7), 158.5 (Ar), 165.0 (C-5). Anal. calc. for ($C_{15}H_{17}N_5O_2$): C, 60.19; H, 5.72; N, 23.40. Found: C, 60.21; H, 6.01; N, 23.62.

Example 2.57

3-(3´-Isopropoxyphenyl)-5-propyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one (16f)

Following the general procedure, to a solution of Na (36 mg, 1.55 mmol) in ethanol (3.1 mL), compound **15** (80 mg, 0.31 mmol) and ethyl butyrate (139 µL, 1.22 mmol) were added. The reaction was microwave-irradiated at 90 ºC for 2 hour. After work-up, a precipitate was obtained that was purified by CCTLC (dichloromethane/methanol, 20:1) to yield **16f** (23 mg, 24%) as a white solid. Mp: 216-218 ºC. MS (ES, positive mode): m/z 314 $(M+H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.93 (t, J = 7.4 Hz, 3H, CH_3), 1.31 (d, J = 6.0 Hz, 6H, $CH(C\underline{H}_3)_2$), 1.74 (d, J = 7.4 Hz, 2H, CH_2), 2.66 (h, J = 7.4 Hz, 2H, CH_2), 4.68 (hept, J = 5.6 Hz, 1H, CH), 7.07 (d, J = 8.2 Hz, 1H, H-4´), 7.51 (pt, J = 8.1 Hz, 1H, H-5´), 7.57 (d, J = 8.1 Hz, 1H, H-6´), 7.62 (s, 1H, H-2´), 12.70 (s 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.8 (CH_3), 20.6 (CH_2), 22.1 ($CH(\underline{C}H_3)_2$), 36.5 (CH_2), 70.3 (CH), 109.3, 114.1, 116.6 (Ar), 129.4 (C-7a), 131.1, 136.9 (Ar), 149.1 (C-3a), 156.4 (C-7), 158.5 (Ar), 164.0 (C-5). Anal. calc. for ($C_{16}H_{19}N_5O_2$): C, 61.33; H, 6.11; N, 22.35. Found: C, 61.08; H, 6.23; N, 22.46.

Example 2.58

3-(3´-Isopropoxyphenyl)-5-isopropyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one (16g)

Following the general procedure, to a solution of Na (36 mg, 1.55 mmol) in ethanol (3.1 mL), **15** (80 mg, 0.31 mmol) and ethyl isobutyrate (140 µL, 1.22 mmol) were added. The reaction was microwave-irradiated at 90 ºC for 2 hour. After work-up, a precipitate was obtained that was purified by CCTLC (dichloromethane/methanol, 20:1) to yield **16g** (8 mg, 8%) as a white solid. Mp: 246-247 ºC. MS (ES, positive mode): m/z 314 $(M+H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.25 (d, J = 6.8 Hz, 6H, $CH(C\underline{H}_3)_2$), 1.32 (d, J = 6.0 Hz, 6H, CH_3), 3.00 (hept, J = 6.8 Hz, 1H, CH), 4.69 (hept, J = 6.0 Hz, 1H, OCH), 7.05 (ddd, J = 8.3, 2.5, 0.9 Hz, 1H, H-4´), 7.52 (pt, J = 8.1 Hz, 1H, H-5´), 7.60 (ddd, J = 8.1, 2.0, 0.9 Hz, 1H, H-6´), 7.68 (pt, J = 2.2 Hz, 1H, H-2´), 12.69 (s 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.1 ($CH(\underline{C}H_3)_2$), 22.4 ($CH(\underline{C}H_3)_2$), 33.9 (CH), 70.5 (CH), 109.0, 114.1, 117.1 (Ar), 129.7 (C-7a), 131.4, 137.2 (Ar), 149.2 (C-3a), 156.7 (C-7), 158.7 (Ar), 168.5 (C-5). Anal. calc. for ($C_{16}H_{19}N_5O_2$): C, 61.33; H, 6.11; N, 22.35. Found: C, 61.08; H, 6.23; N, 22.46.

Example 2.59

3-(3´-Isopropoxyphenyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(6*H*,4*H*)-dione (17)

To a solution of **15** (120 mg, 0.50 mmol) in DMF (2.5 mL), *N*,*N*'-diisopropylcarbodiimide (89 mg, 0.55 mmol) was added. The mixture was stirred at 90 ºC overnight. Then, it was concentrated to dryness and the residue was suspended in acetone. The precipitate thus formed was filtered to yield 81 mg (56%) of **17** as a white solid. Mp: 286-288 ºC. MS (ES, positive mode): m/z 288 $(M+ H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.25 (d, *J* = 6.0 Hz, 6H, $CH(C\underline{H}_3)_2$), 4.63 (hept, *J* = 6.1 Hz, 1H, CH), 6.97 (m, 1H, H-4´), 7.31 (s, 1H, H-2´), 7.40 (m, 2H, H-5´, H-6´), 8.34 (s, 1H, N^4H),10.63 (s, 1H, N^6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.2 (CH_3), 70.1 (CH), 110.0, 115.3, 116.2 (Ar), 121.0 (C-7a), 130.8 (Ar), 135.2 (C-3a), 136.5 (Ar), 154.3 (C-5), 157.5 (C-7), 158.3 (Ar). Anal. calc. for ($C_{13}H_{13}N_5O_3$): C, 54.35; H, 4.56; N, 24.38. Found: C, 54.22; H, 4.65; N, 24.21.

Example 2.60

1-(Azidomethyl)-3-isopropoxybenzene (19)

To a solution of **18** (185 mg, 1.11 mmol) in anhydrous DMF (1.4 mL), DMAP (163 mg, 1.34 mmol) and CH_3SO_2Cl (104 µL, 1.34 mmol) were added. The reaction mixture was stirred at room temperature for 5 h. Then, NaN_3 was added and stirring was continued at room temperature for 4 hours. It was diluted with water (20 mL) and extracted with diethyl ether (4 x 10 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to dryness to yield 226 mg (89%) of **19** as an oil. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.25 (d, *J* = 6.1 Hz, 6H, $CH(C\underline{H}_3)_2$), 4.38 (s, 2H, CH_2), 4.61 (hept, *J* = 6.0 Hz, 1H, CH), 6.89 (m, 3H, H-2´, H-4´, H-6´), 7.28 (pt, *J* = 7.7 Hz, 1H, H-5´).

Example 2.61

5-Amino-1-(3´-isopropoxybenzyl)-1*H*-1,2,3-triazole-4-carboxamide (20)

To a suspension of NaH (60% in mineral oil, 37 mg, 1.55 mmol) in anhydrous DMF (1.4 mL) at 0 ºC, a solution of cyanoacetamide (79 mg, 0.94 mmol) in anhydrous DMF (1.4 mL) was added. After 1 h a solution of **19** (196 mg, 0.86 mmol) in anhydrous DMF (1.4 mL) was slowly added and stirring was continued at room temperature for 1 h. Volatiles were removed. The residue obtained was purified by flash column chromatography (dichloromethane/ methanol, 20:1) to yield 183 mg (77%) of **20** as a white solid. Mp: 171-173 ºC. MS (ES, positive mode): m/z 276 $(M+H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.23 (d, J = 6.0 Hz, 6H, $CH(C\underline{H}_3)_2$), 4.54 (hept, J = 6.0 Hz, 1H, CH), 5.35 (s, 2H, CH_2), 6.38 (s, 2H, NH_2), 6.71 (m, 2H, H-2´, H-6´), 6.83 (d, J = 7.9 Hz, 1H, H-4´), 7.08 (s, 1H, $CONH_2$), 7.23 (pt, J = 8.1 Hz, 1H, H-5´), 7.45 (s, 1H, $CONH_2$).

Example 2.62

3-(3-Isopropoxybenzyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one (21)

To a solution of Na (41 mg, 1.80 mmol) in ethanol (3.6 mL), **20** (100 mg, 0.36 mmol) and ethyl acetate (230 µL, 1.45 mmol) were added. The reaction mixture was heated at reflux for 8 hours. After cooling, the reaction was concentrated to dryness. The residue was dissolved in water, acetic acid was added and the precipitate was isolated by filtration to yield 81 mg (75%) of **21** as a white solid. Mp: 186-187 ºC. MS (ES, positive mode): m/z 300 $(M+H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.22 (d, J = 6.0 Hz, 6H, $CH(C\underline{H}_3)_2$), 2.41 (s, 3H, CH_3), 4.56 (hept, J = 6.1 Hz, 1H, CH), 5.65 (s, 2H, CH_2), 6.72 (m, 3H, H-2´, H-4´, H-6´), 7.22 (pt, J = 8.1 Hz, 1H, H-5´).^{13}C NMR (100 MHz, DMSO-d_6): δ 22.1 (CH_3), 22.4 (CH_3), 50.0 (CH_2), 69.8 (CH), 115.6, 115.6, 120.1 (Ar), 128.7 (C-7a), 130.6, 137.7 (Ar), 149.7 (C-3a), 156.6 (C-5), 158.3 (C-7), 160.7 (Ar). Anal. calc. for ($C_{15}H_{17}N_5O_2$): C, 60.19; H, 5.72; N, 23.40. Found: C, 60.24; H, 6.01; N, 23.68.

Example 2.63

(*Z/E*)-1-(3-Azidophenyl)ethanone *O*-methyl oxime (23)

A microwave vial was charged with the methylketone **22**[6] (100 mg, 0.62 mmol) (Chakraborty, A.; Dey, S.; Sawoo, S.; Adarsh, N. N.; Sarkar, A. Organometallics

2010, 29, 6619-6622), methoxyamine hydrochloride (104 mg, 1.24 mmol) and ethanol (5 mL). The reaction vessel was sealed and heated in a microwave reactor at 80 ºC for 1 hour. After cooling, the reaction was concentrated to dryness. The mixture was dissolved in dichloromethane and washed with brine. The organic layer was dried over Na_2SO_4, filtered and evaporated to dryness to yield 336 mg (88%) of **23** as an orange oil, used as such for the next step. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.16 (s, 3H, CH_3), 3.91 (s, 3H, OCH_3), 7.16 (ddd, J = 6.7, 2.2, 2.2 Hz, 1H, H-4), 7.31 (m, 1H, H-5), 7.44 (m, 2H, H-2, H-6).

Example 2.64

(E/*Z*)-5-Amino-1-(3-(1-(methoxyimino)ethyl)phenyl)-1*H*-1,2,3-triazole-4-carboxamide (24)

To a suspension of NaH (60% in mineral oil, 43 mg, 1.78 mmol) in anhydrous DMF (1.7 mL) at 0 ºC, a solution of cyanoacetamide (92 mg, 1.09 mmol) in anhydrous DMF (1.7 mL) was added. After 1 h a solution of **23** (189 mg, 0.99 mmol) in anhydrous DMF (1.7 mL) was slowly added and stirring was continued at room temperature for 1 h. Volatiles were removed. The residue obtained was purified by flash column chromatography (dichloromethane/ methanol, 20:1) to yield 330 mg (79%) of **24** as a white solid. Mp: 155-157 ºC. MS (ES, positive mode): m/z 275 $(M+H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.22 (s, 3H, CH_3), 3.93 (s, 3H, OCH_3), 6.44 (s, 2H, NH_2), 7.22 (s, 1H, $CONH_2$), 7.60 (m, 3H, $CONH_2$, H-5, H-4), 7.78 (m, 2H, H-2, H-6). Anal. calc. for ($C_{12}H_{14}N_6O_2$): C, 52.55; H, 5.14; N, 30.64. Found: C, 52.76; H, 5.40; N, 30.83.

Example 2.65

(E/*Z*)-5-Ethyl-3-(3´-(1-(methoxyimino)ethyl)phenyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one (25)

Procedure 1: To a solution of Na (42 mg, 1.82 mmol) in ethanol (3.6 mL), compound **24** (100 mg, 0.36 mmol) and ethyl propionate (168 µL, 1.46 mmol) were added. The reaction was microwave-irradiated at 90 ºC for 1 hour. After cooling, the reaction was concentrated to dryness. The residue was dissolved in water, acetic acid was added and the precipitate was isolated by filtration. The

crude was purified by CCTLC in the Chromatothron (dichloromethane/methanol, 10:1) to yield 29 mg (26%) of **25** as a white solid.

Procedure 2: To a solution of compound **24** (30 mg, 0.11 mmol) in anhydrous THF (1.1 mL), tBuOK in THF (1.0 M, 0.17 mmol, 170 µL) and ethyl propionate (51 µL, 0.44 mmol) were added. The reaction was microwave-irradiated at 90 ºC for 1 hour. After cooling, the mixture was diluted with water, acetic acid was added and the precipitate thus formed was isolated by filtration to yield 29 mg (85%) of **25** as a white solid.

Mp: 251-252 ºC. MS (ES, positive mode): m/z 313 $(M+H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.26 (t, J = 7.5 Hz, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.73 (q, J = 7.4 Hz, 2H, CH_2), 3.94 (s, 3H, OCH_3), 7.68 (pt, J = 8.0 Hz, 1H, H-5´), 7.80 (m, 1H, H-4´), 8.10 (ddd, J = 7.9, 2.1, 1.0 Hz, 1H, H-6´), 8.49 (pt, J = 1.8 Hz, 1H, H-2´), 12.73 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.4 ($CH_2\underline{C}H_3$), 12.9 (CH_3), 28.2 ($\underline{C}H_2CH_3$), 62.5 (OCH_3), 119.3, 122.7, 126.8 (Ar), 129.7 (C-7a), 130.6, 136.3, 137.8 (Ar), 149.4 (C-3a), 153.8 (C=N), 156.5 (C-5), 165.2 (C-7). Anal. calc. for ($C_{15}H_{16}N_6O_2$): C, 57.68; H, 5.16; N, 26.91. Found: C, 57.48; H, 4.93; N, 27.05.

Example 2.66

(E/*Z*)-3-(3´-(1-(Methoxyimino)ethyl)phenyl)-5-thioxo-5,6-dihydro-3*H*-[1,2,3]triazolo [4,5-*d*]pyrimidin-7(4*H*)-one (26)

To a solution of **24** (30 mg, 0.11 mmol) in anhydrous THF (1.1 mL), tBuOK in THF (1.0 M, 0.17 mmol, 170 µL) and CS_2 (200 µL, 3.32 mmol) were added. The reaction was microwave-irradiated at 120 ºC for 2 hours. After cooling, the mixture was diluted with water, acetic acid was added and the reaction was concentrated to dryness. The resulting residue was washed with tBuOH to yield 31 mg (86%) of **27** as a white solid. Mp: > 300 ºC decomposed. MS (ES, positive mode): m/z 317 $(M+H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.24 (s, 3H, CH_3), 3.95 (s, 3H, OCH_3), 7.68 (pt, J = 7.8 Hz, 1H, H-5´), 7.71 (d, J = 7.7 Hz, 1H, H-4´), 8.20 (d, J = 7.7 Hz, 1H, H-6´), 8.31 (s, 1H, H-2´), 10.95 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.1 (CH_3), 62.5 (OCH_3), 118.8, 122.4, 125.7 (Ar), 127.4 (C-7a), 130.2, 137.2, 137.7 (Ar), 151.7 (C-3a), 154.2 (CH_3C=NO),

156.9 (C-7), 180.7 (C-5). Anal. Calc. for ($C_{13}H_{12}N_6O_2S$): C, 49.36; H, 3.82; N, 26.57; S, 10.14. Found: C, 49.18; H, 3.95; N, 26.54; S, 10.06.

Example 2.67

(E/*Z*)-3-(3´-(1-(Methoxyimino)ethyl)phenyl)-5-(methylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one (27)

To a solution of **27** (228 mg, 0.72 mmol) in DMF (3.6 mL) at rt, iodomethane (54 µL, 0.87 mmol) was added and the mixture was stirred for 30 min at rt. The precipitate thus formed was filtered, and washed with methanol to yield 143 mg (60%) of **28** as a beige solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.24 (s, 3H, CH_3), 2.62 (s, 3H, SCH_3), 3.94 (s, 3H, OCH_3), 7.65 (pt, *J* = 7.7 Hz, 1H, H-5´), 7.77 (d, *J* = 7.6 Hz, 1H, H-4´), 8.13 (d, *J* = 7.6 Hz, 1H, H-6´), 8.59 (s, 1H, H-2´), 10.95 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 12.6 (CH_3), 14.0 (SCH_3), 62.3 (OCH_3), 118.2, 122.0, 126.3 (Ar), 128.6 (C-7a), 130.4, 136.2, 137.6 (Ar), 148.5 (C-3a), 153.6 ($CH_3\underline{C}$=NO), 156.3 (C-7), 164.7 (C-5). Anal. Calc. for ($C_{14}H_{14}N_6O_2S$): C, 50.90; H, 4.27; N, 25.44; S, 9.71. Found: C, 50.75; H, 4.46; N, 25.40, S, 9.81.

Example 2.68

(*E/Z*)-5-(Methylamino)-3-(3´-(1-(methoxyimino)ethyl)phenyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pirimidin-7(6*H*)-one (28)

To a suspensión of **27** (60 mg, 0.18 mmol) in anhydrous DMF (0.4 mL) $MeNH_2$ 2N in MeOH (1.4 mL) was added. The reaction was microwaved-irradiated at 150 ºC for 1h. The reaction was filtered to obtain 21 mg (38%) of **28** as a white solid. Mp 286-288 ºC. EM (ES, positive mode): m/z 314 $(M+H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.24 (s, 3H, CH_3), 2.91 (s, 3H, NCH_3), 3.94 (s, 3H, OCH_3), 7.65 (m, 2H, H-5´, H-6´), 8.18 (d, *J* = 7.7 Hz, 1H, H-4´), 8.70 (s, 1H, H-2´). ^{13}C NMR (100 MHz, DMSO-d_6): δ 12.6 (CH_3), 25.9 (NCH_3), 62.2 (OCH_3), 117.7, 121.0, 125.2, 125.8 (Ar), 130.1 (C-7a), 137.1, 137.4 (Ar), 151.4 (C-3a), 153.7 ($CH_3\underline{C}$=NO), 157.8 (C-5), 159.2 (C-7). Anal. Calc. for ($C_{14}H_{15}N_7O_2$): C, 53.67; H, 4.83; N, 31.29. Found: C, 53.60; H, 4.62; N, 31.36.

Example 2.69

3-(3´-Acetylphenyl)-5-ethyl-3*H*-[1,2,3]triazolo[4,5-*d*]pirimidin-7(6*H*)-one (29)

To a solution of compound **25** (100 mg, 0.32 mmol) in dioxane (1 mL), HCl 6 N (1 mL) was added. The reaction was microwaved irradiated at 120 ºC for 1h. After filtration, the collected solid was dissolved in dichloromethane and treated with hexanes to yield 20 mg (33%) of **29** as a white solid. Pf > 240 ºC (decomp). MS (ES, positive mode): m/z 284 $(M+H)^+$. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.25 (t, J = 7.5 Hz, 3H, CH_3), 2.66 (s, 3H, $COCH_3$), 2.73 (q, J = 7.5 Hz, 2H, CH_2), 7.81 (t, J = 7.9 Hz, 1H, H-5´), 8.11 (d, J = 7.8 Hz, 1H, H-6´), 8.32 (d, J = 7.8 Hz, 1H, H-4´), 8.66 (s, 1H, H-2´), 12.74 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 11.4 (CH_3), 27.3 ($CO\underline{C}H_3$), 28.1 (CH_2), 121.4, 126.4, 128.9 (Ar), 129.5 (C-7a), 130.8, 136.2, 138.4 (Ar), 149.3 (C-3a), 156.3 (C-5), 165.2 (C-7), 197.4 ($\underline{C}OCH_3$). Anal calcd for ($C_{14}H_{13}N_5O_2$): C, 59.36; H, 4.63; N, 24.72. Found: C, 59.16; H, 4.74; N, 24.50.

Example 2.70

(+/-) 5-Ethyl-3-(3-(1-hydroxyethyl)phenyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pirimidin-7(6*H*)-one (30)

To a solution of compound **29** (18 mg, 0.06 mmol) in anhydrous DMF (0.5 mL), $NaBH_4$ (5 mg, 0.13 mmol) was added. The reaction was microwaved heated at 100 ºC for 30 min, and volatiles were removed. The residue obtained was purified by CCTLC (dichloromethane/methanol, 20:1) to yield 15 mg (88%) of **30**. MS (ES, positive mode): m/z 286 $(M+H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.24 (t, J = 7.5 Hz, 3H, $CH_2C\underline{H}_3$), 1.37 (d, J = 6.4 Hz, 3H, $CHC\underline{H}_3$), 2.72 (q, J = 7.5 Hz, 2H, $C\underline{H}_2CH_3$), 4.83 (m, 1H, $CHC\underline{H}_3$), 5.39 (d, J = 4.1 Hz, 1H, OH), 7.49 (d, J = 7.8 Hz, 1H, Ar), 7.58 (t, J = 7.7 Hz, 1H, Ar), 7.89 (d, J = 7.9 Hz, 1H, Ar), 8.05 (s, 1H, Ar), 12.70 (s, 1H, NH). Anal calcd for ($C_{14}H_{15}N_5O_2$): C, 58.94; H, 5.30; N, 24.55. Found: C, 58.66; H, 5.54; N, 24.50.

Example 2.71

(*R,S*)/(*S,S*) 3-(3´-(1-*O*-[*N*-((Fluoren-9-yl)methoxycarbonyl)-L-phenylalanyl]hydroxy ethyl)phenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pirimidin-7(6*H*)-one (31 and 32)

To a solution of Fmoc-Phe-OH (930 mg, 2.41 mmol) in anhydrous DMF (2 mL), diisopropylcarbodiimide (DIC) (180 µl, 1.15 mmol) was added and the mixture was stirred for 30 min at 0 ºC. Then a solution of **11** as a racemate (131 mg, 0.48 mmol) and DMAP (12 mg, 0.10 mmol) in DMF (3 mL) were added and the mixture was further stirred at rt for 1 h. The reaction was treated with dicloromethane (20 mL), washed with 5% citric acid (15 mL), a $NaHCO_3$ solution (15 mL) and brine (15 mL). The organic phase was dried on anhydrous $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography (dichloromethane/methanol, (20:1). Those fractions containing the desired esters (MS (ES, positive mode): m/z 627 $(M+1)^+$) were collected to yield 241 mg. This residue was purified by semipreparative HPLC [column Sunfire C-18 (150 mm x 19 mm x 5 µm); flow: 24 mL/min; isocratic method: 45% CH_3CN (containing 0.1% formic acid) and 55% H_2O for 70 min. The fastest moving fractions (retention time 59.4 min) afforded **31** with a 24% yield; the slowest moving fractions (retention time 62.9 min) afforded **32** in 22% yield. Compound **31**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.55 (d, J = 6.6 Hz, 3H, CH_3), 2.63 (s, 3H, CH_3), 3.16 (t, J = 6.5 Hz, 2H, β-CH_2), 4.16 (t, J = 7.8 Hz, 1H, C<u>H</u>CH_2), 4.36 (m, 2H, CHC<u>H</u>$_2$), 4.70 (q, J = 6.7 Hz, 1H, α-CH), 5.27 (d, J = 8.5 Hz, 1H, NH), 5.96 (q, J = 6.8 Hz, 1H, C<u>H</u>CH_3), 7.12 (m, 2H, Ar), 7.23 (m, 5H, Ar), 7.36 (m, 3H, Ar), 7.52 (m, 3H, Ar), 7.72 (m, 2H, Ar), 8.05 (m, 2H, Ar), 11.96 (s, 1H, NH). Compound **32**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.62 (d, J = 6.6 Hz, 3H, CH_3), 2.64 (s, 3H, CH_3), 3.07 (m, 2H, , β-CH_2), 4.16 (t, J = 7.3 Hz, 1H, C<u>H</u>CH_2), 4.36 (m, 2H, CHC<u>H</u>$_2$), 4.73 (q, J = 6.7 Hz, 1H, α-CH), 5.22 (d, J = 8.4 Hz, 1H, NH), 6.02 (q, J = 6.2 Hz, 1H, C<u>H</u>CH_3), 6.91 (m, 2H, Ar), 7.11 (m, 3H, Ar), 7.28 (m, 2H, Ar), 7.38 (m, 3H, Ar), 7.54 (m, 3H, Ar), 7.73 (m, 2H, Ar), 8.10 (m, 2H, Ar), 12.03 (s, 1H, NH).

Example 2.72

(*R*) 3-(3´-(1-Hydroxyethyl)phenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pirimidin-7(6*H*)-one (33)

To a solution of **31** (36 mg, 0.06 mmol) in THF (1 mL), a solution of LiOH (10 mg, 0.32 mmol) in H_2O (1 mL) was added and the mixture was stirred at rt for 1 h. Volatiles were removed and the residue was purified by CCTLC (dicloromethane/methanol, 20:1) to yield 13 mg of **33** (67%). MS (ES, positive mode): m/z 272 $(M+H)^+$. ^1H NMR data were identical to those of the racemic **11**.

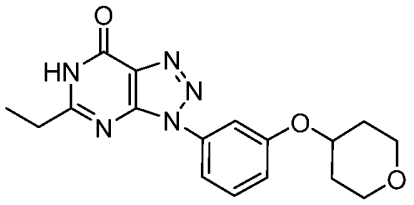
Example 2.73

(*S*) 3-(3´-(1-Hydroxyethyl)phenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pirimidin-7(6*H*)-one (34)

To a solution of **32** (33 mg, 0.05 mmol) in THF (1 mL), a solution of LiOH (10 mg, 0.32 mmol) in H_2O (1 mL) was added and the mixture was stirred at rt for 1 h. Volatiles were removed and the residue was purified by CCTLC (dicloromethane/methanol, 20:1) to yield 8 mg of **34** (57%). MS (ES, positive mode): m/z 272 $(M+H)^+$. ^1H NMR data were identical to those of the racemic **11**.

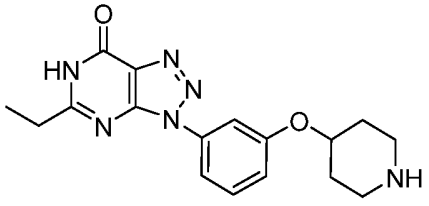
Example 2.74

5-Ethyl-3-(3-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (35)



Example 2.75

5-Ethyl-3-(3-(piperidin-4-yloxy)phenyl)-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (36)



EXAMPLE 3: Biological activity

Table 1. Antiviral evaluation against chikungunya virus of the 3-aryl-[1,2,3]triazolo[4,5-d]pyrimidin-7(6H)-ones in Vero cells.

Compound	EC_{50}(M)	EC_{90}(M)	CC_{50} (M)
5a	348 ± 36	460 ± 13	>777
5b	28 ± 6	179 ± 44	>777
5c	32 ± 11	235 ± 7	>764
5d	19 ± 2	38 ± 16	>743
5e	162 ± 15	>604	>604
5f	12 ± 4	156 ± 43	>701
5l	131 ± 11	187 ± 21	>793
5n	202 ± 38	> 322	322
6a	225 ± 33	309 ± 48	>746
10a	127 ± 10	161 ± 27	491
11	17 ± 7	41 ± 19	>737
12a	56 ± 19	117 ± 46	>704
12b	24 ± 14	87 ± 60	>670
16a	115 ± 16	>296	296
16b	227 ± 21	>372	372
16c	83 ± 5	>113	113

16d	66 ± 1	>118	118
16e	3 ± 1	9 ± 6	>134
21	167 ± 10	232 ± 62	>872
25	4 ± 1	5 ± 1	>274
28	26 ± 3	>84	84
29	41	-	80
30	28 ± 1	-	107± 4
33	38 ± 9		
34	23 ± 15		

Table 2. Antiviral evaluation of the triazolopyrimidine **16e** against SFV and SINV in Vero cells.

Species	Virus (Strain)	**Compound 16e** EC_{50} (M)[a]
Semliki forest virus	Vietnam (lab)	219
Sindbis virus	HRsp (lab)	69 ± 8

[a] 50% effective concentration or calculated concentration of compound that is required to protect 50% of the cells against cytopathic effects caused by the viral infection.

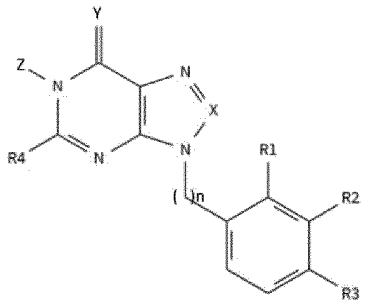
EXAMPLE 4: Identification of the chikungunya virus protein that is involved in the mechanism of action of the compounds of the present invention

Compound **5d** (MADTP_0314) was used for the selection of compound-resistant chikungunya virus variants with the purpose of identifying, by sequencing of the genome and localization of mutations, the viral protein that is involved in the mechanism of action of this compound class. To this end, a clonal selection procedure was used. First, a series of antiviral experiments was performed to determine the lowest concentration of **5d** and the highest input of chikungunya virus for which still 100% inhibition of virus-induced cytopathic effect (CPE) could be observed. This experiment concomitantly yielded information on the MOI-dependency of the activity of the compound. Subsequently, a virus input of 50 $CCID_{50}$ and a **5d** compound concentration of 93 µM were selected to infect Vero cells seeded in three 96-well plates (a total of 144 wells). Assay wells were monitored for the development of CPE (plaque counting at 4 days post-infection (dpi)). Wells with fulminate CPE at 7 dpi were harvested. The 3 virus samples with the lowest plaque count at 4 dpi and full CPE at 7 dpi were used to perform a virus titration in the presence of 93 µM **5d** (each sample was titrated in 6-fold). For each titration, the highest virus dilution showing the lowest plaque count at 4 dpi and full CPE at 7 dpi was harvested, yielding virus populations enriched for replication-competent, compound-resistant virus variants. The best sample of the 6 (lowest plaque count at 4 dpi) was used to infect 25 cm^2 flasks to grow a sufficient large amount of the putative compound-resistant virus for further experiments. At 8 dpi, the supernatant was collected. Finally, initial antiviral experiment with **5d** was repeated with putative compound-resistant virus in parallel with wild-type virus, concomitantly with a comparative analysis of the amount of infecting virus by titration for infectious virus content. Furthermore, the antiviral activity of a selection of analogues of **5d**, found to selectively inhibit CHIKV replication as well, were evaluated for their inhibitory effect on the replication of the **5d**-resistant CHIKV isolates, to confirm cross-resistance and class chemotype. The full genome of the compound-resistant virus variants was sequenced to identify the viral protein that is involved in the mechanism of action of the compound by

localizing the mutations acquired as a consequence of the presence of the compound during the selection procedure. Detailed results are depicted in figure 1, 2, and 3.

CLAIMS

1. A compound according to formula (I')



(I')

and/or a tautomeric form, and/or a solvate and/or stereoisomer and /or a pharmaceutically acceptable salt thereof, wherein

Y is selected from the group consisting of O, S, and NR^5;

R^4 is selected from the group consisting of H, C_{1-6} alkyl, aryl, OR^7, SR^7, NR^7R^8, cycloalkyl, $(CH_2)_m$-O-C_{1-3} alkyl, and $(CH_2)_m$-S-C_{1-3} alkyl, and heteroaryl, wherein said alkyl, heteroaryl or aryl groups are optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxyl, sulfhydryl, amino, cyano, and nitro; and wherein m is selected from 0, 1, or 2;

X is selected from the group consisting of N, CR^9, and COH;

n is selected from 0, 1, or 2;

R^1 and R^3 are each independently selected from the group consisting of H, halogen, nitro, C_{1-6} alkyl, OR^{10}, SR^{10}, COR^{10}, and $COOR^{10}$; wherein at least one of R^1 and R^3 is H;

R^2 is selected from the group consisting of H, halogen, nitro, CN, C_{1-6} alkyl, OR^6, SR^6, $NR^{11}R^{12}$, $NR^{11}COR^{12}$, $C=N(OR^{11})R^{12}$, COR^{11}, and

$COOR^{11}$, wherein said alkyl group is optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxyl, sulfhydryl, amino, cyano, and nitro;

R^6 is selected from the group consisting of H and C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-6} heterocycloalkyl, wherein said alkyl- and cycloalkyl-groups are optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxyl, sulfhydryl, amino, cyano, and nitro; and

R^5, R^7, R^8 R^9, R^{10}, R^{11}, R^{12} and Z are each independently selected from the group consisting of H and C_{1-6} alkyl, wherein said alkyl groups are optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxyl, sulfhydryl, amino, cyano, and nitro.

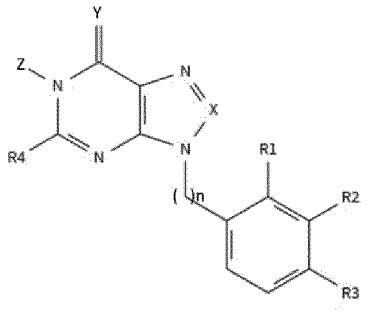
2. The compound according to claim 1, wherein Y is O.
3. The compound according to claim 1 or 2, wherein Z is H.
4. The compound according to any of claims 1 to 3, wherein X is N.
5. The compound according to any of claims 1 to 4, wherein R^4 is methyl or ethyl.
6. The compound according to any of claims 1 to 5, wherein n is 0.
7. The compound according to any of claims 1 to 6, wherein R^1 and R^3 are both H.
8. The compound according to any of claims 1 to 7, wherein R^2 is selected from the group consisting of $COCH_3$, $CH(OH)CH_3$, $C=N(OH)CH_3$, $C=N(OCH_3)CH_3$, CN, $COOCH_2CH_3$, and COOH.
9. The compound according to any of claims 1 to 7, wherein R^2 is selected from the group consisting of OCH_3, $OCH(CH_3)_2$, $N(CH_3)_2$, $NHCOCH_3$, and Cl.
10. The compound according to any of claims 1 to 7, wherein R^2 is $C=N(OCH_3)CH_3$, COCH3 or $OCH(CH_3)_2$.
11. The compound according to claim 1 selected from the group consisting of: 3-(2′-Methoxyphenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-

7(6*H*)-one; 3-(3´-Methoxyphenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 3-(3´-Chlorophenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 3-(3´-Acetylphenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 3-(3´-Benzoylphenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 3-(3´-Isopropoxyphenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; *N*-(3-(5-Methyl-7-oxo-6,7-dihydro-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)phenyl)-acetamide; 3-(4´-Acetylphenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 5-Methyl-3-(4´-propoxyphenyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 3-(3´-Acetylphenyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 3-(Benzo[*d*][1,3]dioxol-5-yl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 3-(5-Methyl-7-oxo-6,7-dihydro-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)benzonitrile; Ethyl 3-(5-methyl-7-oxo-6,7-dihydro-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl) benzoate; 3-(5-Methyl-7-oxo-6,7-dihydro-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)benzoic acid; 3-(3´-Acetylphenyl)-5,6-dimethyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 9-(3´-Acetylphenyl)-2-methyl-1*H*-purin-6(9*H*)-one; 9-(3-Acetylphenyl)-2,8-dimethyl-1*H*-purin-6(9*H*)-one; 3-(3´-(1-Hydroxyethyl)phenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; *(Z/E)*-3-(3´-(1-(Hydroxyimino)ethyl)phenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; (E/*Z*)-3-(3´-(1-(Methoxyimino)ethyl)phenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; (*E/Z*)-Ethyl 2-(((1-(3-(5-methyl-7-oxo-6,7-dihydro-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin -3-yl)phenyl)ethylidene)amino)oxy)acetate; 5-Cyanoethyl-3-(3´-isopropoxyphenyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 3-(3´-Isopropoxyphenyl)-5-phenyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 3-(3´-Isopropoxyphenyl)-5-(4´´-pyridyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 3-(3´-Isopropoxyphenyl)-5-trifluoromethyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 5-Ethyl-3-(3´-isopropoxyphenyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 3-(3´-Isopropoxyphenyl)-5-propyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 3-(3´-Isopropoxyphenyl)-5-isopropyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-

7(6*H*)-one; 3-(3´-Isopropoxyphenyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(6*H*,4*H*)-dione; 3-(3-Isopropoxybenzyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; (E/*Z*)-5-Ethyl-3-(3´-(1-(methoxyimino)ethyl)phenyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; (E/*Z*)-3-(3´-(1-(Methoxyimino)ethyl)phenyl)-5-thioxo-5,6-dihydro-3*H*-[1,2,3]triazolo [4,5-*d*]pyrimidin-7(4*H*)-one; (E/*Z*)-3-(3´-(1-(methoxyimino)ethyl)phenyl)-5-(methylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one; 3-(3´-Acetylphenyl)-5-ethyl-3*H*-[1,2,3]triazolo[4,5-*d*]pirimidin-7(6*H*)-one; 5-Ethyl-3-(3-(1-hydroxyethyl)phenyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pirimidin-7(6*H*)-one; (*R*) and (S) 3-(3´-(1-Hydroxyethyl)phenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pirimidin-7(6*H*)-one; 5-ethyl-3-(3-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one; and 5-ethyl-3-(3-(piperidin-4-yloxy)phenyl)-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one.

12. A compound according to any of claims 1 to 11 for use as a medicine.

13. A compound according to any of claims 1 to 11, or the compound according to formula (I')



(I')

and/or a tautomeric form, and/or a solvate and/or stereoisomer and /or a pharmaceutically acceptable salt thereof, wherein

Y is selected from the group consisting of O, S, and NR^5;

R^4 is selected from the group consisting of H, C_{1-6} alkyl, aryl, OR^7, SR^7, NR^7R^8, cycloalkyl, $(CH2)_m$-O-C_{1-3} alkyl, $(CH2)_m$-S-C_{1-3} alkyl, and

heteroaryl, wherein said alkyl, heteroaryl or aryl groups are optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxyl, sulfhydryl, amino, cyano, and nitro; and wherein m is selected from 0, 1, or 2;

X is selected from the group consisting of N, CR^9, and COH;

n is selected from 0, 1, or 2;

R^1 and R^3 are each independently selected from the group consisting of H, halogen, nitro, C_{1-6} alkyl, OR^{10}, SR^{10}, COR^{10}, and $COOR^{10}$; wherein at least one of R^1 and R^3 is H;

R^2 is selected from the group consisting of H, halogen, nitro, CN, C_{1-6} alkyl, OR^6, SR^6, $NR^{11}R^{12}$, $NR^{11}COR^{12}$, $C=N(OR^{11})R^{12}$, COR^{11}, and $COOR^{11}$, wherein said alkyl group is optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxyl, sulfhydryl, amino, cyano, and nitro;

R^6 is selected from the group consisting of H and C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-6} hetrocycloalkyl, wherein said alkyl- and cycloalkyl-groups are optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxyl, sulfhydryl, amino, cyano, and nitro; and

R^5, R^7, R^8 R^9, R^{10}, R^{11}, R^{12} and Z are each independently selected from the group consisting of H and C_{1-6} alkyl, wherein said alkyl groups are optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxyl, sulfhydryl, amino, cyano, and nitro;

for use as a medicine for the prevention or treatment of a viral disorder in a mammal.

14. The compound according to claim 13, wherein said viral disorder is an infection with a virus belonging to the the family of the Togaviridae.

15. The compound according to claim 13 or 14, wherein said viral disorder is a viral infection with an alphavirus.
16. The compound according to any of claims 13 to 15, wherein said viral disorder is a viral infection with chikungunya virus.
17. The compound according to any of claims 13 to 16, wherein said mammal is a human being.
18. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any of claims 1 to 11 and one or more pharmaceutically acceptable carriers.

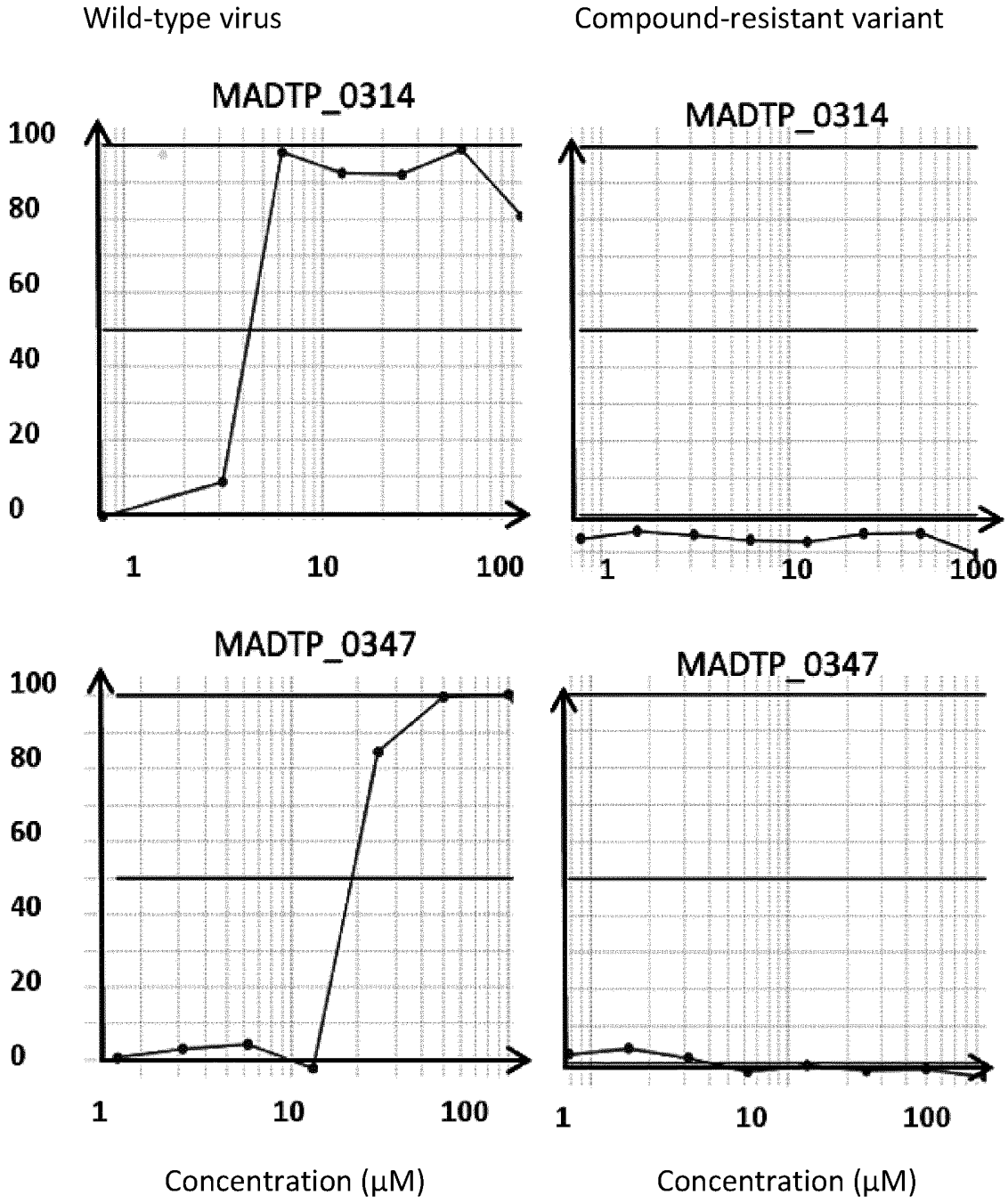

Wild-type virus
Compound-resistant variant
MADTP_0314
MADTP_0314
MADTP_0347
MADTP_0347
100
80
60
40
20
0
1
10
100
Concentration (µM)
Concentration (µM)

FIG. 1

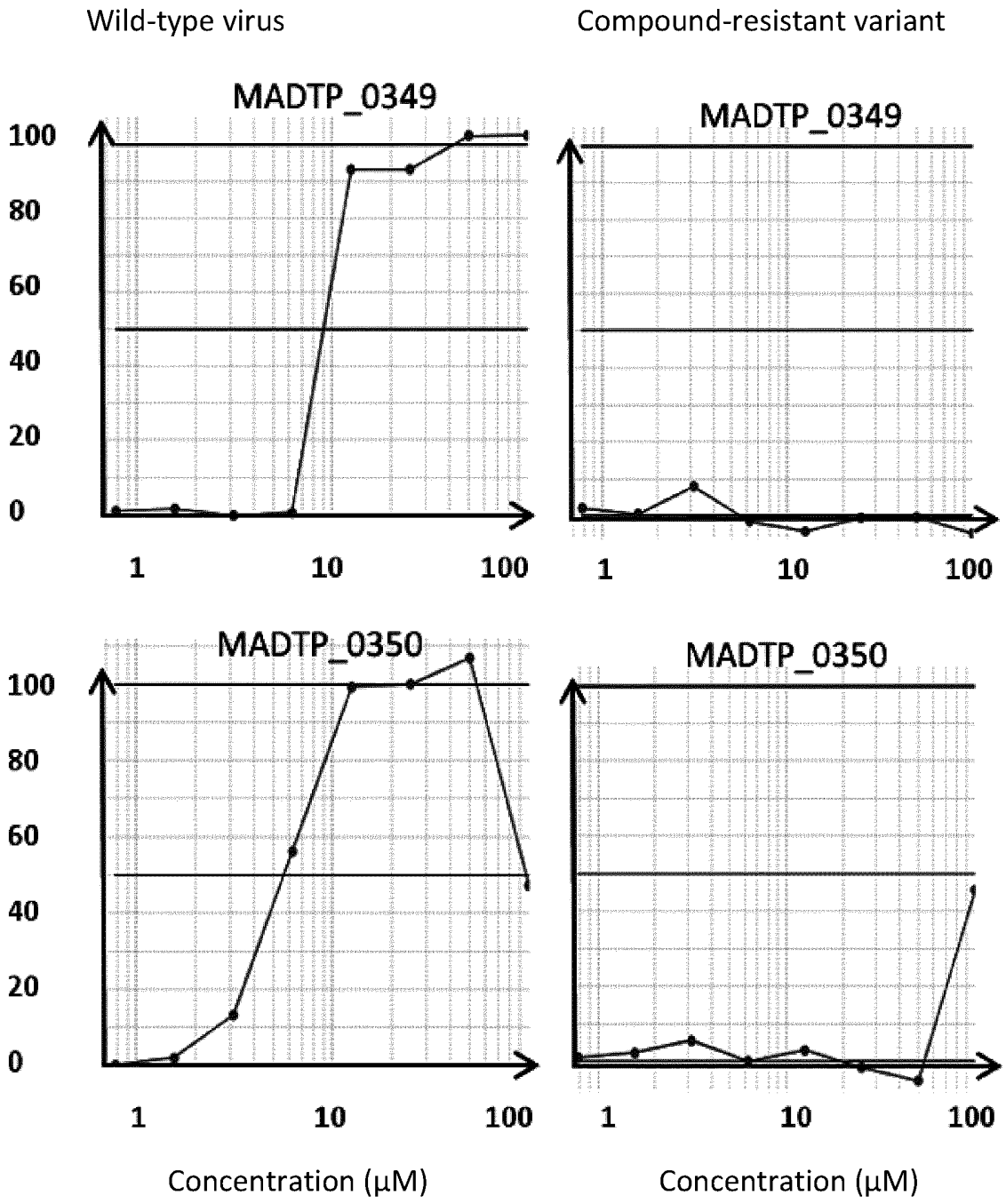

Wild-type virus
Compound-resistant variant
MADTP_0349
MADTP_0349
MADTP_0350
MADTP_0350
100
80
60
40
20
0
1
10
100
Concentration (µM)
Concentration (µM)

FIG. 1 (cont.)

Gene	WT codon	WT AA	Mutant codon			Mutant AA		
			P1	P2	P3	P1	P2	P3
NSp1	CCG	P_{34}	TCG	TCG	TCG	S_{34}	S_{34}	S_{34}

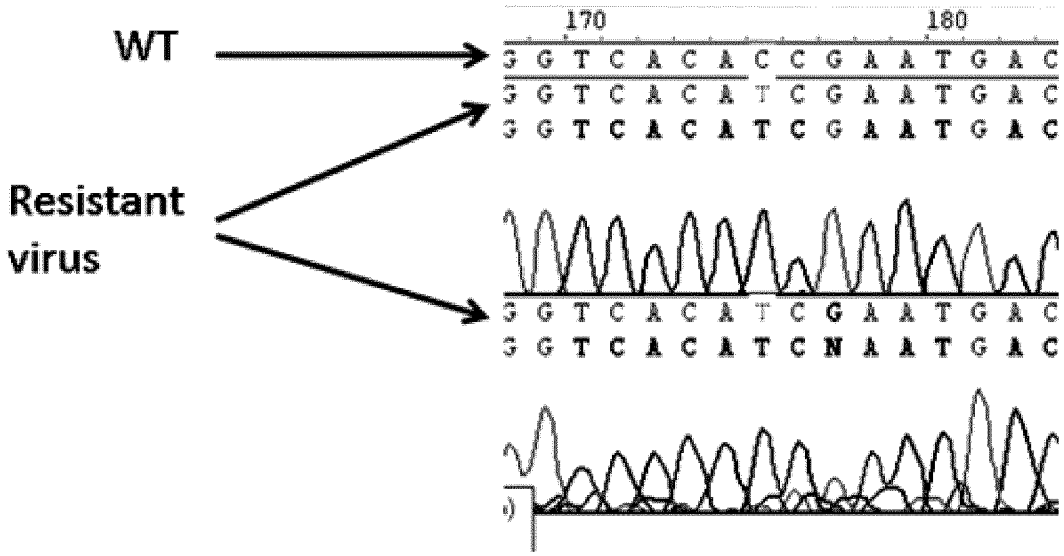


FIG. 2

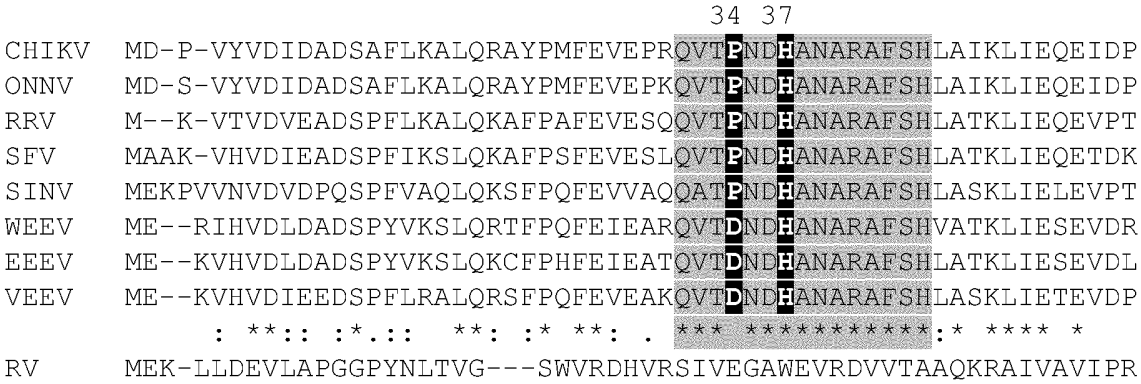

34 37
CHIKV MD-P-VYVDIDADSAFLKALQRAYPMFEVEPRQVTPNDHANARAFSHLAIKLIEQEIDP
ONNV MD-S-VYVDIDADSAFLKALQRAYPMFEVEPKQVTPNDHANARAFSHLAIKLIEQEIDP
RRV M--K-VTVDVEADSPFLKALQKAFPAFEVESQQVTPNDHANARAFSHLATKLIEQEVPT
SFV MAAK-VHVDIEADSPFIKSLQKAFPSFEVESLQVTPNDHANARAFSHLATKLIEQETDK
SINV MEKPVVNVDVDPQSPFVAQLQKSFPQFEVVAQQATPNDHANARAFSHLASKLIELEVPT
WEEV ME--RIHVDLDADSPYVKSLQRTFPQFEIEARQVTDNDHANARAFSHVATKLIESEVDR
EEEV ME--KVHVDLDADSPYVKSLQKCFPHFEIEATQVTDNDHANARAFSHLATKLIESEVDL
VEEV ME--KVHVDIEEDSPFLRALQRSFPQFEVEAKQVTDNDHANARAFSHLASKLIETEVDP
: **:: :*.:: **: :* **: . *** ***********:* **** *
RV MEK-LLDEVLAPGGPYNLTVG---SWVRDHVRSIVEGAWEVRDVVTAAQKRAIVAVIPR

FIG. 3

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/057719

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D473/30 A61K31/519 A61K31/522 C07D487/04 A61P31/12
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KNUD ERIK ANDERSEN ET AL: "Phosphorus Pentoxide in Organic Synthesis. XXXV. Synthesis of Thiazolo[5,4-d]pyrimidin-7-amines and Purine-6-thiones from 5-Acylamino-4-thiazolecarboxamides.", ACTA CHEMICA SCANDINAVICA, vol. 41b, 1 January 1987 (1987-01-01), pages 708-711, XP055116654, DOI: 10.3891/acta.chem.scand.41b-0708 page 709; table 1; compounds a-j	1,3-7,9

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 May 2014	26/05/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Bissmire, Stewart

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	V P KISLYI ET AL: "Synthesis of 66monoo and 5,66disubstituted 1,2,33triazolo[4,55d]pyrimidinn77ones", RUSSIAN CHEMICAL BULLETIN, vol. 52, 1 August 2003 (2003-08-01), pages 1770-1776, XP055116660, ISSN: 1066-5285, DOI: 10.1023/A:1026004720790 page 1771; compound 1a page 1773; compounds 1f-i	1-5,7,8
X	B. R. BAKER ET AL: "Irreversible enzyme inhibitors. 187. Bulk tolerance with inhibitors of guanosine phosphorylase", JOURNAL OF MEDICINAL CHEMISTRY, vol. 14, no. 9, 1 September 1971 (1971-09-01), pages 809-812, XP055116903, ISSN: 0022-2623, DOI: 10.1021/jm00291a008 page 810; table I; compounds 5, 6 page 810; table II; compounds 57-59	1-7,9
X	MIYASHITA A ET AL: "CATALYTIC ACTION OF AZOLIUM SALTS. IX. SYNTHESIS OF 6-AROYL-9H-PURINES AND THEIR ANALOGUES BY NUCLEOPHILIC AROYLATION CATALYZED BY IMIDAZOLIUM OR BENZIMIDAZOLIUM SALT", CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN, JP, vol. 46, no. 3, 1 January 1998 (1998-01-01), pages 390-399, XP001135025, ISSN: 0009-2363 page 392; compounds 25a-c	1-5,7
X	STEPHEN M. GREENBERG ET AL: "Potential Purine Antagonists XXI. Preparation of Some 9-Phenyl-6-substituted Purines 1", THE JOURNAL OF ORGANIC CHEMISTRY, vol. 24, no. 9, 1 September 1959 (1959-09-01), pages 1314-1317, XP055116904, ISSN: 0022-3263, DOI: 10.1021/jo01091a039 page 1315; table I	1-5,7

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BARILI ET AL: "A facile one pot synthesis of 2,9-disubstituted 8-azapurin-6-ones (3,5-disubstituted 7-hydroxy-3H-1,2,3-triazolo[4,5-d]pyrimidines)", JOURNAL OF HETEROCYCLIC CHEMISTRY, WILEY-BLACKWELL PUBLISHING, INC, US, vol. 22, no. 6, 1 November 1985 (1985-11-01), pages 1607-1609, XP002355289, ISSN: 0022-152X, DOI: 10.1002/JHET.5570220628 page 1608; table I	1-5,7
X	HOWARD J. SCHAEFFER ET AL: "Structure-activity relations in adenosine deaminase inhibitors", JOURNAL OF MEDICINAL CHEMISTRY, vol. 13, no. 3, 1 May 1970 (1970-05-01), pages 452-455, XP055117357, ISSN: 0022-2623, DOI: 10.1021/jm00297a026 Table II and page 455, Compound: 9-(m-acetylbenzyl)adenine hydrochloride	1,3,7,8, 10
A	WO 2012/158811 A2 (RFS PHARMA LLC [US]; SCHINAZI RAYMOND F [US]; CHO JONG HYUN [US]; ZHOU) 22 November 2012 (2012-11-22) the whole document	1-18
A	WO 2005/011709 A1 (UNIV YALE [US]; CHENG YUNG-CHI [US]; TANAKA HIROMICHI [JP]; BABA MASAN) 10 February 2005 (2005-02-10) the whole document	1-18
A	US 2005/004144 A1 (CARSON DENNIS A [US] ET AL) 6 January 2005 (2005-01-06) the whole document	1-8

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2014/057719

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		EP 2710023 A2	26-03-2014
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		WO 2005016235 A2	24-02-2005