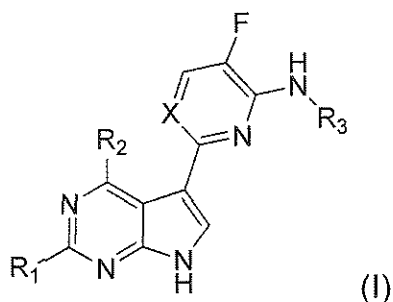


5 of influenza antiviral drugs available on the market: neuraminidase inhibitors
and M2 channel inhibitors. Neuraminidase inhibitors, oseltamivir or zanamivir,
are the primary antiviral agents recommended for the prevention and treatment
of influenza. These are effective against both influenza type A and B viruses.
Development of resistance to these antiviral drugs has been identified during
10 treatment of seasonal influenza and in sporadic oseltamivir-resistant 2009
H1N1 virus, but the public health impact has been limited to date. M2 channel
inhibitors, such as amantadine and rimantadine (amantadanes), are active
against influenza A strains, but not influenza B strains. Amantadane resistance
among circulating influenza A viruses increased rapidly worldwide beginning
15 during 2003-2004. Therefore, amantadine and rimantadine are not
recommended for antiviral treatment or chemoprophylaxis of currently
circulating influenza A virus strains.

In 2009, the novel swine H1N1 strain caused an unexpected influenza
pandemic as a result of reassortment of genes from human, pig, and bird's
20 H1N1 viruses. This past pandemic, together with the ongoing circulation of
highly pathogenic avian H5N1 strains and the recent emergence of the H7N9
virus, a new reassortant of avian origin isolated in China, and associated with
severe respiratory disease with 40% of mortality, which could potentially adapt
for human-to-human transmission, highlighted the vulnerability of the world
25 population to novel influenza strains. Although vaccination remains the main
prophylactic strategy for controlling influenza infection, to bridge the period
before a new vaccine becomes available and to treat the severe influenza
cases, as well as to counter the problem of viral resistance, a wider choice of
anti-influenza drugs is required. Development of new influenza antivirals has
30 therefore again become a high priority and an unmet medical need.

The current ~~invention~~ disclosure relates to a compound of formula (I) which can
be used for the treatment of, or against viral influenza infections:



5 a stereo-isomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof, wherein

X is N or C optionally substituted by $-\text{CN}$, $-\text{CF}_3$, $-\text{C}_{1-3}$ alkyl- $\text{N}-\text{C}(\text{O})-\text{C}_{1-3}$ alkyl, $-\text{C}(\text{O})-\text{NH}_2$, $-\text{C}(\text{O})-\text{NH}-\text{C}_{1-3}$ alkyl, $-\text{C}(\text{O})\text{N}-(\text{dialkyl})$ or $-\text{CH}_2-\text{NC}(\text{O})-\text{CH}_3$;

R_1 is H or CH_3 ;

10 R_2 is H or NH_2 ;

R_3 is C_{1-8} alkyl substituted by carboxylic acid;

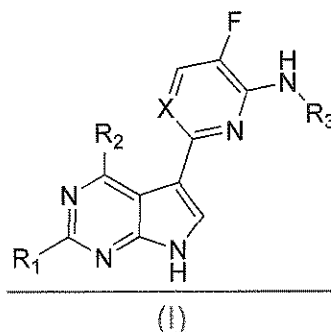
or is C_{3-8} cycloalkyl substituted by carboxylic acid, $-\text{N}-\text{C}_{1-3}$ alkylsulfone,

or

$-\text{N}-\text{C}(\text{O})-\text{C}_{3-6}$ heterocycle optionally substituted by C_{1-6} alkyl;

15 or is C_{3-6} heterocycle substituted by $-\text{N}-\text{C}(\text{O})-\text{C}_{3-6}$ heterocycle.

In one aspect, the present disclosure relates to a compound of formula (I)



20

a stereo-isomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof, wherein

25 X is N or C optionally substituted by $-\text{CN}$, $-\text{CF}_3$, $-\text{C}_{1-3}$ alkyl- $\text{N}-\text{C}(\text{O})-\text{C}_{1-3}$ alkyl,

$-\text{C}(\text{O})-\text{NH}_2$, $-\text{C}(\text{O})-\text{NH}-\text{C}_{1-3}$ alkyl, $-\text{C}(\text{O})\text{N}-(\text{dialkyl})$ or $-\text{CH}_2-\text{NC}(\text{O})-\text{CH}_3$;

R_1 is H or CH_3 ;

R_2 is H or NH_2 ;

R_3 is C_{1-8} alkyl substituted by carboxylic acid;

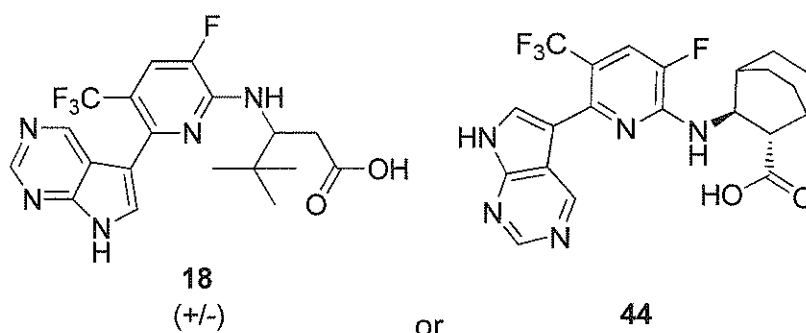
30 or is C_{3-8} cycloalkyl substituted by carboxylic acid, $-\text{N}-\text{C}_{1-3}$ alkylsulfone, or

$-\text{N}-\text{C}(\text{O})-\text{C}_{3-6}$ heterocycle optionally substituted by C_{1-6} alkyl;

or is C_{3-6} heterocycle substituted by $-\text{N}-\text{C}(\text{O})-\text{C}_{3-6}$ heterocycle.

35 Preferably the compound according to the ~~invention~~ disclosure is the compound according to formula (I) wherein R_1 and R_2 are both H.

5 Preferred compounds according to the current ~~invention~~ disclosure have the structural formula



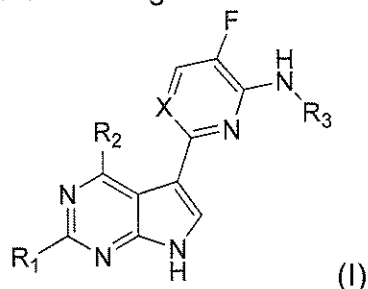
10 In another aspect, ~~Part of the present invention~~ disclosure relates to ~~is~~ also a pharmaceutical composition comprising a compound of formula (I) or a stereo-isomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof as disclosed herein together with one or more pharmaceutically acceptable excipients, diluents or carriers.

15 The pharmaceutical composition may also include additional therapeutic agents, like another antiviral agent or an influenza vaccine, or both.

20 In another aspect, ~~To the present invention~~ disclosure relates to ~~also belongs~~ a compound of formula (I) or a stereo-isomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof as disclosed herein, or a pharmaceutical composition as disclosed herein for use as a medicament.

5 | In another aspect, Additionally the present invention-disclosure relates to a compound of formula (I) or a stereo- isomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof or a pharmaceutical composition for use in the treatment of influenza.

10 | So part of the invention-disclosure is the use of a compound represented by the following structural formula (I)



15 | a stereo-isomeric form , a pharmaceutically acceptable salt, solvate or polymorph thereof, wherein

X is N or C optionally substituted by $-\text{CN}$, $-\text{CF}_3$, $-\text{C}_{1-3}$ alkyl- $\text{N}-\text{C}(\text{O})-\text{C}_{1-3}$ alkyl,

$-\text{C}(\text{O})-\text{NH}_2$, $-\text{C}(\text{O})-\text{NH}-\text{C}_{1-3}$ alkyl, $-\text{C}(\text{O})\text{N}-(\text{dialkyl})$ or $-\text{CH}_2-\text{NC}(\text{O})-\text{CH}_3$;

R_1 is H or CH_3 ;

20 | R_2 is H or NH_2 ;

R_3 is C_{1-8} alkyl substituted by carboxylic acid;

or is C_{3-8} cycloalkyl substituted by carboxylic acid, $-\text{N}-\text{C}_{1-3}$ alkylsulfone,

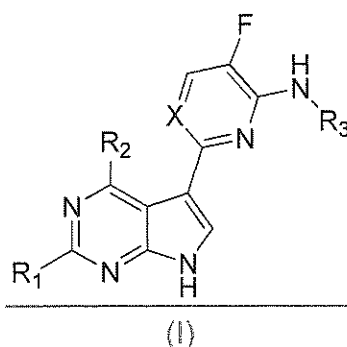
or

$-\text{N}-\text{C}(\text{O})-\text{C}_{3-6}$ heterocycle optionally substituted by C_{1-6} alkyl;

25 | or is C_{3-6} heterocycle substituted by $-\text{N}-\text{C}(\text{O})-\text{C}_{3-6}$ heterocycle

for inhibiting the replication of influenza virus(es) in a biological sample or patient.

30 | In another aspect, the present disclosure relates to a use of a compound represented by the following structural formula (I)



a stereo- isomeric form , a pharmaceutically acceptable salt, solvate or polymorph thereof, wherein

X is N or C optionally substituted by -CN, -CF₃, -C₁₋₃ alkyl-N-C(O)-C₁₋₃ alkyl,

-C(O)-NH₂, -C(O)-NH-C₁₋₃ alkyl, -C(O)N-(dialkyl) or -CH₂-NC(O)-CH₃;

R₁ is H or CH₃;

R₂ is H or NH₂;

R₃ is C₁₋₈ alkyl substituted by carboxylic acid;

or is C₃₋₈ cycloalkyl substituted by carboxylic acid, -N-C₁₋₃ alkyl/sulfone, or

-N-C(O)-C₃₋₆ heterocycle optionally substituted by C₁₋₆ alkyl;

or is C₃₋₆ heterocycle substituted by -N-C(O)-C₃₋₆ heterocycle in the manufacture of a medicament for inhibiting the replication of influenza virus(es) in a biological sample or patient.

Said use may also comprise the co-administration of an additional therapeutic agent, wherein said additional therapeutic agent is selected from an antiviral agent or influenza vaccine, or both.

The term "alkyl" refers to a straight-chain or branched-chain saturated aliphatic hydrocarbon containing the specified number of carbon atoms.

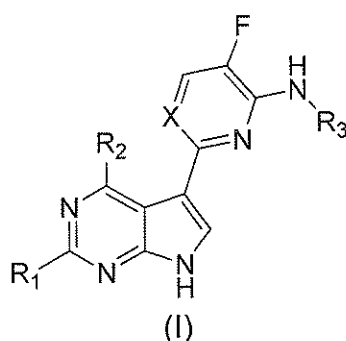
The term "cycloalkyl" refers to a carbo-cyclic ring containing the specified number of carbon atoms.

5 polymorph thereof according to claim 1 together with one or more pharmaceutically acceptable excipients, diluents or carriers.

10 5. A compound of formula (I) or a stereo- isomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof according to claim 1 or a pharmaceutical composition according to claim 4 for use as a medicament.

15 6. A compound of formula (I) or a stereo- isomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof according to claim 1 or a pharmaceutical composition according to claim 4 for use in the treatment of influenza.

7. A use of a compound represented by the following structural formula (I)



25 a stereo- isomeric form , a pharmaceutically acceptable salt, solvate or polymorph thereof, wherein

X is N or C optionally substituted by -CN, -CF₃, -C₁₋₃ alkyl-N-C(O)-C₁₋₃ alkyl,

-C(O)-NH₂, -C(O)-NH-C₁₋₃ alkyl, -C(O)N-(dialkyl) or -CH₂-NC(O)-CH₃;

R₁ is H or CH₃;

30 R₂ is H or NH₂;

R₃ is C₁₋₈ alkyl substituted by carboxylic acid;

or is C₃₋₈ cycloalkyl substituted by carboxylic acid, -N-C₁₋₃ alkylsulfone, or

-N-C(O)-C₃₋₆ heterocycle optionally substituted by C₁₋₆ alkyl;

35 or is C₃₋₆ heterocycle substituted by -N-C(O)-C₃₋₆ heterocycle

for in the manufacture of a medicament for inhibiting the replication of
influenza virus(es) in a biological sample or patient.

5

| 8. The use of claim 7 further comprising ~~co-administering~~ an additional
therapeutic agent.

10

9. The use of claim 8 wherein the additional therapeutic agent is selected
from an antiviral agent or influenza vaccine, or both.

15