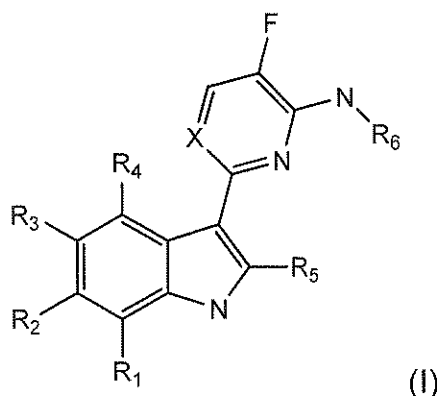


are effective against both influenza type A and B viruses. Development of resistance to these antiviral drugs has been identified during treatment of seasonal influenza and in sporadic oseltamivir-resistant 2009 H1N1 virus, but the public health impact has been limited to date. M2 channel inhibitors, such as amantadine and rimantadine (amantadanes), are active against influenza A strains, but not influenza B strains. Adamantane resistance among circulating influenza A viruses increased rapidly worldwide beginning 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 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 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 therefore again become a high priority and an unmet medical need.

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

In one aspect, there is provided a compound of formula (I):



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- $\text{NH}-\text{C}(\text{O})-\text{C}_{1-3}$  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  $-\text{CH}_2-\text{NH}-\text{C}(\text{O})-\text{CH}_3$ ;

$\text{R}_1$  is F or Cl;

$\text{R}_2$  and  $\text{R}_4$  are each selected from H, halogen, CN,  $\text{CF}_3$ ,  $-\text{O}-\text{alkyl}$  or  $\text{NH}_2$ ;

$\text{R}_3$  is F, Cl, CN,  $\text{CF}_3$ ,  $-\text{C}_{1-3}$  alkyl,  $-\text{O}-\text{alkyl}$ , carboxylic ester or carboxylic amide

$\text{R}_5$  is Br, CN,  $\text{CH}_3$ ,  $\text{CH}_2\text{OH}$ ,  $\text{C}(\text{O})\text{NH}_2$ ,  $\text{NH}_2$  or H;

$\text{R}_6$  is  $\text{C}_{1-8}$  alkyl substituted by carboxylic acid;

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

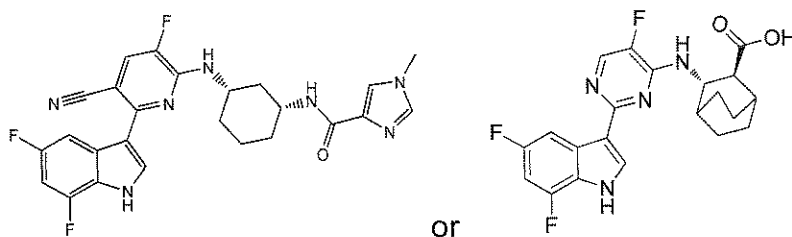
or  $-\text{N}-\text{C}(\text{O})-\text{C}_{3-6}\text{heterocycle}$  optionally substituted by  $\text{C}_{1-6}$  alkyl;

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

or is  $\text{C}_{3-6}$  heterocycle substituted by  $\text{COOH}$ .

Preferably the compound according to the disclosure is the compound according to formula (I) wherein  $\text{R}_1$  and  $\text{R}_3$  are both F.

Preferred compounds according to the current disclosure have the structural formula:



Part of the disclosure, in another aspect, is also a pharmaceutical composition comprising a compound of formula (I) or a stereo- isomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof together with one or more pharmaceutically acceptable excipients, diluents or carriers.

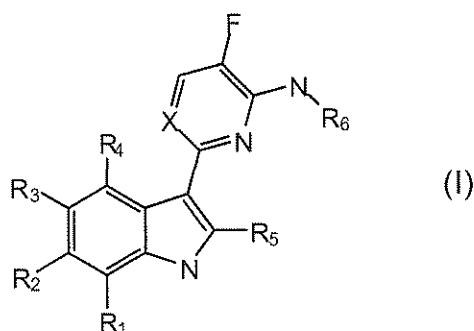
The pharmaceutical composition may also include additional therapeutic agents like another antiviral agent or an influenza vaccine, or both.

In another aspect, there is provided a compound of formula (I) or a stereo- isomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof or a pharmaceutical composition for use as a medicament.

In another aspect, there is provided 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.

- 5 In another aspect, there is provided 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, -CF<sub>3</sub>,

-C<sub>1-3</sub> alkyl-NH-C(O)-C<sub>1-3</sub> alkyl, -C(O)-NH<sub>2</sub>, -C(O)-NH-C<sub>1-3</sub> alkyl, -C(O)-N-(dialkyl)

- 10 or -CH<sub>2</sub>-NH-C(O)-CH<sub>3</sub>;

R<sub>1</sub> is F or Cl;

R<sub>2</sub> and R<sub>4</sub> are each selected from H, halogen, CN, CF<sub>3</sub>, -O-alkyl or NH<sub>2</sub>;

R<sub>3</sub> is F, Cl, CN, CF<sub>3</sub>, -C<sub>1-3</sub> alkyl, -O-alkyl, carboxylic ester or carboxylic amide

R<sub>5</sub> is Br, CN, CH<sub>3</sub>, CH<sub>2</sub>OH, C(O)NH<sub>2</sub>, NH<sub>2</sub> or H;

- 15 R<sub>6</sub> is C<sub>1-8</sub> alkyl substituted by carboxylic acid;

or is C<sub>3-8</sub> cycloalkyl substituted by carboxylic acid, -N-C<sub>1-3</sub>alkylsulfone, or

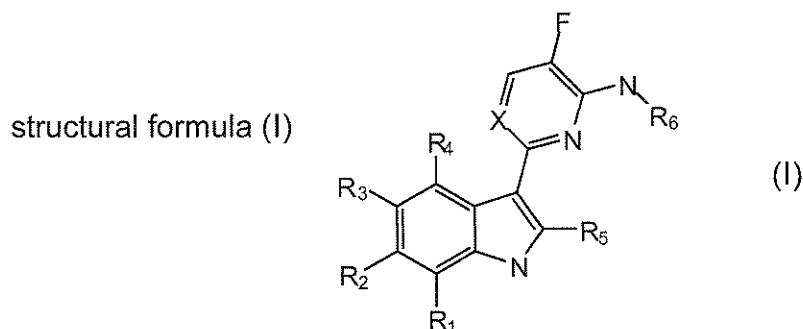
-N-C(O)-C<sub>3-6</sub>heterocycle optionally substituted by C<sub>1-6</sub> alkyl;

or is C<sub>3-6</sub> heterocycle substituted by -N-C(O)-C<sub>3-6</sub> heterocycle;

or is C<sub>3-6</sub> heterocycle substituted by COOH

- 20 in the manufacture of a medicament for inhibiting the replication of influenza virus(es) in a patient.

In another aspect, there is provided use of a compound represented by the following



a stereo- isomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof, wherein X is N or C optionally substituted by -CN, -CF<sub>3</sub>,

5 -C<sub>1-3</sub> alkyl-NH-C(O)-C<sub>1-3</sub> alkyl, -C(O)-NH<sub>2</sub>, -C(O)-NH-C<sub>1-3</sub> alkyl, -C(O)-N-(dialkyl) or -CH<sub>2</sub>-NH-C(O)-CH<sub>3</sub>;

R<sub>1</sub> is F or Cl;

R<sub>2</sub> and R<sub>4</sub> are each selected from H, halogen, CN, CF<sub>3</sub>, -O-alkyl or NH<sub>2</sub>;

R<sub>3</sub> is F, Cl, CN, CF<sub>3</sub>, -C<sub>1-3</sub> alkyl, -O-alkyl, carboxylic ester or carboxylic amide

10 R<sub>5</sub> is Br, CN, CH<sub>3</sub>, CH<sub>2</sub>OH, C(O)NH<sub>2</sub>, NH<sub>2</sub> or H;

R<sub>6</sub> is C<sub>1-8</sub> alkyl substituted by carboxylic acid;

or is C<sub>3-8</sub> cycloalkyl substituted by carboxylic acid, -N-C<sub>1-3</sub>alkylsulfone, or -N-C(O)-C<sub>3-6</sub>heterocycle optionally substituted by C<sub>1-6</sub> alkyl;

or is C<sub>3-6</sub> heterocycle substituted by -N-C(O)-C<sub>3-6</sub> heterocycle;

15 or is C<sub>3-6</sub> heterocycle substituted by COOH

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

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

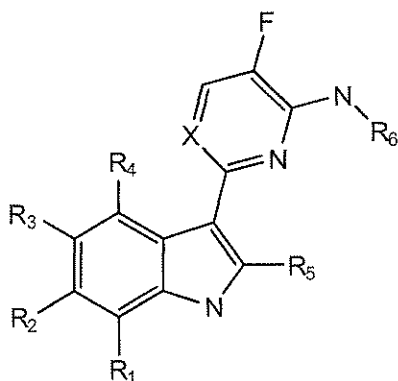
The term "alkyl" refers to a straight-chain or branched-chain saturated aliphatic hydrocarbon containing the specified number of carbon atoms.

25 The term "halogen" refers to F, Cl, Br or I.

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

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

5



(I)

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

10

X is N or C optionally substituted by -CN, -CF<sub>3</sub>, -C<sub>1-3</sub> alkyl-NH-C(O)-C<sub>1-3</sub> alkyl,

-C(O)-NH<sub>2</sub>, -C(O)-NH-C<sub>1-3</sub> alkyl, -C(O)-N(dialkyl) or -CH<sub>2</sub>-NH-C(O)-CH<sub>3</sub>;

R<sub>1</sub> is F or Cl;

R<sub>2</sub> and R<sub>4</sub> are each selected from H, halogen, CN, CF<sub>3</sub>, -O-alkyl or NH<sub>2</sub>;

15

R<sub>3</sub> is F, Cl, CN, CF<sub>3</sub>, -C<sub>1-3</sub> alkyl, -O-alkyl, carboxylic ester or carboxylic amide

R<sub>5</sub> is Br, CN, CH<sub>3</sub>, CH<sub>2</sub>OH, C(O)NH<sub>2</sub>, NH<sub>2</sub> or H;

R<sub>6</sub> is C<sub>1-8</sub> alkyl substituted by carboxylic acid;

or is C<sub>3-8</sub> cycloalkyl substituted by carboxylic acid, -N-C<sub>1-3</sub>alkylsulfone,

or

20

N-C(O)-C<sub>3-6</sub>heterocycle optionally substituted by C<sub>1-6</sub> alkyl;

or is C<sub>3-6</sub> heterocycle substituted by -N-C(O)-C<sub>3-6</sub> heterocycle;

or is C<sub>3-6</sub> heterocycle substituted by COOH

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

25

9. The use of claim 7 or 8 further comprising an additional therapeutic agent.

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