

inhibitors of this activity in influenza viruses (Tomassini, J. et al., (1994), Antimicrob. Agents Chemother., 38, pp. 2827-2837). In addition, flutimide, a substituted 2,6-diketopiperazine, identified in extracts of *Delitschia confertasporea*, a fungal species, has been shown to inhibit the endonuclease of influenza virus (Tomassini, J. et al., (1996), Antimicrob. Agents Chemother., 40, pp. 1189-1193). Moreover, there have been attempts to interfere with viral transcription by nucleoside analogs, such as 2'-deoxy-2'-fluoroguanosine (Tisdale, M. et al., (1995), Antimicrob. Agents Chemother., 39, pp. 2454-2458).

WO 2005/087766 discloses certain pyridopyrazine- and pyrimidopyrazine-dione compounds which are stated to be inhibitors of HIV integrase and inhibitors of HIV replication. The compounds are described as being useful in the prevention and treatment of infection by HIV and in the prevention, delay in the onset, and treatment of AIDS.

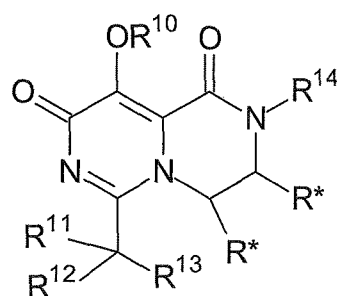
WO 2012/039414 describes compounds which are described as having antiviral effects, particularly having growth inhibitory activity on influenza viruses.

EP-A-2 444 400 also discloses compounds which allegedly have antiviral activities, especially inhibiting activity for influenza viruses.

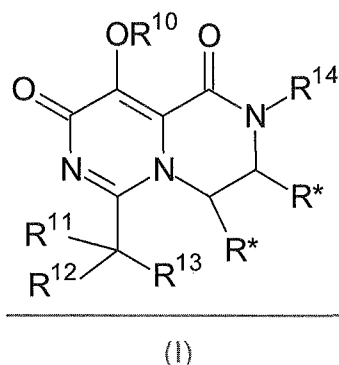
It is an object of the present invention to identify further compounds which are effective against viral diseases and which have improved pharmacological properties.

Summary of the invention

Accordingly, in a first embodiment one example, the present invention disclosure provides a compound having the general formula (I).



In one aspect, there is provided a compound having the general formula (I), optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, prodrug, codrug, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof,



wherein

X^{10} is NR^{15} , $N(R^{15})C(O)$, $C(O)NR^{15}$, O , $C(O)$, $C(O)O$, $OC(O)$; $N(R^{15})SO_2$, $SO_2N(R^{15})$, S , SO , or SO_2 ;

R^{10} is $-H$, a $-C_{1-6}$ alkyl group or a $-C(O)-C_{1-6}$ alkyl group;

R^{11} is $-H$, a $-C_{1-6}$ alkyl group, or a $-C_{1-6}$ alkyl group which is substituted by one or more halogen atoms;

R^{12} is $-H$, a $-C_{1-6}$ alkyl group, or a $-C_{1-6}$ alkyl group which is substituted by one or more halogen atoms;

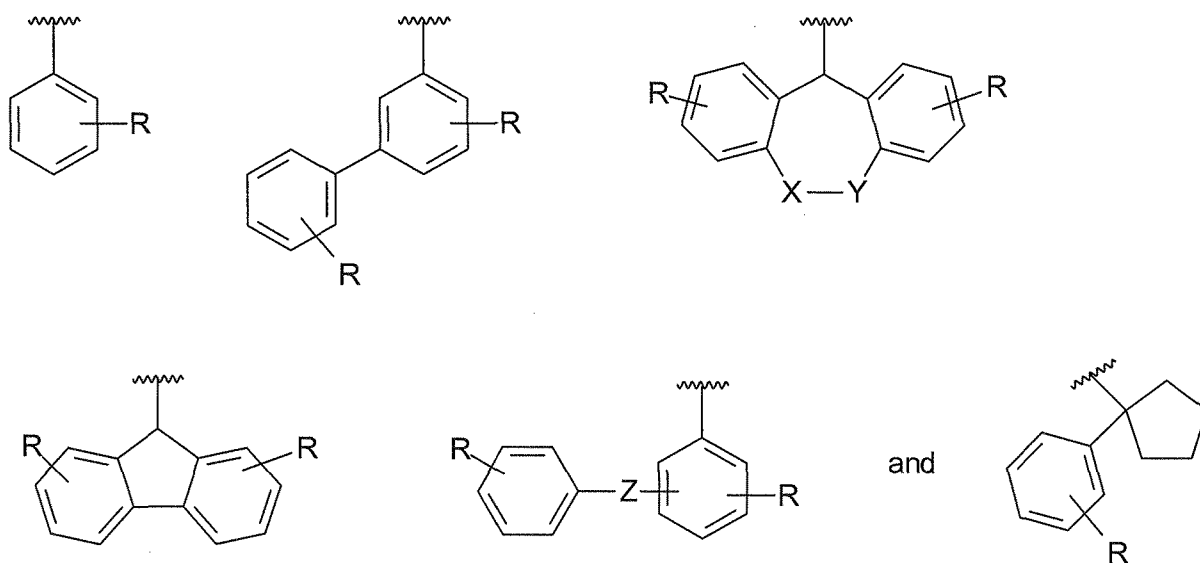
or wherein R^{11} and R^{12} can be joined together to form a 3- to 7-membered carbo- or heterocyclic ring;

R^{13} is $-R^{16}$, or $-X^{10}-R^{16}$;

R^{14} is $-H$, $-(\text{optionally substituted } C_{1-6} \text{ alkyl})$, $-(\text{optionally substituted } C_{3-7} \text{ cycloalkyl})$, $-(\text{optionally substituted aryl})$, $-C_{1-4} \text{ alkyl}-(\text{optionally substituted } C_{3-7} \text{ cycloalkyl})$, or $-C_{1-4} \text{ alkyl}-(\text{optionally substituted aryl})$;

R¹⁵ is -H, -(optionally substituted C₁₋₆ alkyl), -(optionally substituted C₃₋₇ cycloalkyl), -(optionally substituted aryl), -C₁₋₄ alkyl-(optionally substituted C₃₋₇ cycloalkyl), or -C₁₋₄ alkyl-(optionally substituted aryl);

5 R¹⁶ is selected from



wherein

X is absent, CH₂, NH, C(O)NH, S or O;

Y is CH₂;

Z is O or S; and

R is independently selected from -H, -C₁₋₆ alkyl, -CF₃, -Hal, -CN, -OH, and -O-C₁₋₆ alkyl;

R¹⁷ is -H, -C₁₋₆ alkyl, or -(CH₂CH₂O)_rH;

R¹⁸ is -H, or -C₁₋₆ alkyl;

R^{**} is independently selected from -C₁₋₆ alkyl, -C(O)-C₁₋₆ alkyl, -Hal, -CF₃, -CN, -COOR¹⁷, -OR¹⁷, -(CH₂)_qNR¹⁷R¹⁸, -C(O)-NR¹⁷R¹⁸, and -NR¹⁷-C(O)-C₁₋₆ alkyl;

R^{*} is independently selected from -H, -C₁₋₆ alkyl, and -C₃₋₇ cycloalkyl;

q is 0 to 4; and

r is 1 to 3;

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wherein the alkyl group, aryl group and/or cycloalkyl group in R^{14} and R^{15} can be optionally substituted with one or more substituents R^{**} .

It is understood that throughout the present specification the term "a compound having the general formula (I)" encompasses pharmaceutically acceptable salts, solvates, polymorphs, prodrugs, codrugs, cocrystals, tautomers, racemates, enantiomers, or diastereomers or mixtures thereof unless mentioned otherwise.

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A further embodiment of the present invention relates to a pharmaceutical composition comprising a compound having the general formula (I) and optionally one or more pharmaceutically acceptable excipient(s) and/or carrier(s).

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Thus, in another aspect, there is provided a pharmaceutical composition comprising:
a compound having the general formula (I) as defined herein, optionally in the form of a
pharmaceutically acceptable salt, solvate, polymorph, prodrug, codrug, cocrystal, tautomer,
racemate, enantiomer, or diastereomer or mixture thereof,
and optionally one or more pharmaceutically acceptable excipient(s) and/or carrier(s).

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The compounds having the general formula (I) are useful for treating, ameliorating or preventing viral diseases.

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Thus, in another aspect, there is provided a compound having the general formula (I) as
defined herein, optionally in the form of a pharmaceutically acceptable salt, solvate,
polymorph, prodrug, codrug, cocrystal, tautomer, racemate, enantiomer, or diastereomer or
mixture thereof,

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wherein the compound is for use in the treatment, amelioration or prevention of a viral disease
caused by Herpesviridae, Filoviridae, Paramyxoviridae, Rhabdoviridae, Orthomyxoviridae,
Bunyaviridae, Arenaviridae, Coronaviridae, Picornaviridae, Togaviridae, or Flaviviridae.

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In yet another aspect, there is also provided use of a compound having the general formula (I)
as defined herein, optionally in the form of a pharmaceutically acceptable salt, solvate,
polymorph, prodrug, codrug, cocrystal, tautomer, racemate, enantiomer, or diastereomer or
mixture thereof in the manufacture of a medicament for treating, ameliorating or preventing a
viral disease caused by Herpesviridae, Filoviridae, Paramyxoviridae, Rhabdoviridae,
Orthomyxoviridae, Bunyaviridae, Arenaviridae, Coronaviridae, Picornaviridae, Togaviridae, or
Flaviviridae.

In yet another aspect, there is also provided a compound having the general formula (I) as defined herein, optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, prodrug, codrug, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof,

wherein the compound is for use in the treatment, amelioration or prevention of influenza.

In yet another aspect, there is also provided use of a compound having the general formula (I) as defined herein, optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, prodrug, codrug, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof in the manufacture of a medicament for treating, ameliorating or preventing influenza.

It has been surprisingly found that the compounds according to the present invention which have the bulky group on the left hand ring have improved properties compared to the compounds disclosed in EP-A-2 444 400. In particular, the interaction with protein could be optimized resulting in better binding properties. Furthermore, shifting of the bulky group should avoid problems due to a chiral center and due to the planarization through shift from sp³ to sp². In addition, the crucial vector for additional hydrophobic interactions may be stabilized and improved.

Detailed description of the invention

Before the present invention is described in detail below, it is to be understood that this invention is not limited to the particular methodology, protocols and reagents described herein as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims. Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art.

Preferably, the terms used herein are defined as described in "A multilingual glossary of biotechnological terms: (IUPAC Recommendations)", Leuenberger, H.G.W, Nagel, B. and Kölbl, H. eds. (1995), Helvetica Chimica Acta, CH-4010 Basel, Switzerland.

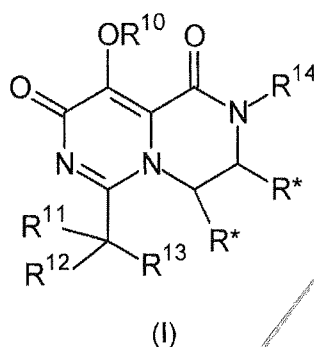
PCT/EP2014/050165

Savira pharmaceuticals GmbH et al.
Our ref.: U2797 PCT

30. Jan. 2015

CLAIMS

1. A compound having the general formula (I), optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, prodrug, codrug, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof,



wherein

X^{10} is NR^{15} , $N(R^{15})C(O)$, $C(O)NR^{15}$, O , $C(O)$, $C(O)O$, $OC(O)$; $N(R^{15})SO_2$, $SO_2N(R^{15})$, S , SO , or SO_2 ;

R^{10} is $-H$, a $-C_{1-6}$ alkyl group or a $-C(O)-C_{1-6}$ alkyl group;

R^{11} is $-H$, a $-C_{1-6}$ alkyl group, or a $-C_{1-6}$ alkyl group which is substituted by one or more halogen atoms;

R^{12} is $-H$, a $-C_{1-6}$ alkyl group, or a $-C_{1-6}$ alkyl group which is substituted by one or more halogen atoms;

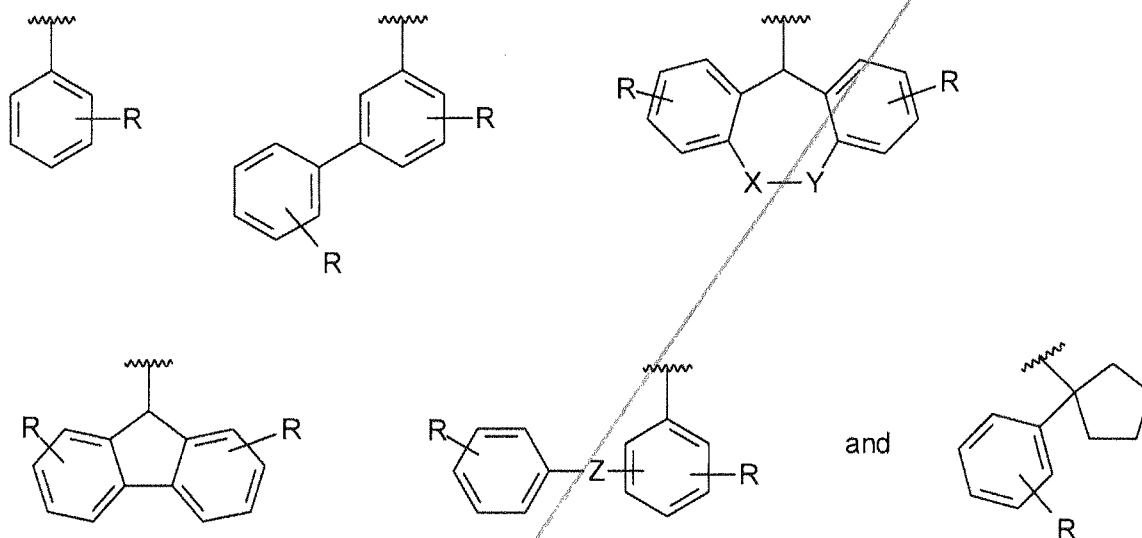
or wherein R^{11} and R^{12} can be joined together to form a 3- to 7-membered carbocyclic or heterocyclic ring;

R^{13} is $-R^{16}$, or $-X^{10}-R^{16}$;

R^{14} is $-H$, $-(\text{optionally substituted } C_{1-6} \text{ alkyl})$, $-(\text{optionally substituted } C_{3-7} \text{ cycloalkyl})$, $-(\text{optionally substituted aryl})$, $-C_{1-4} \text{ alkyl}-(\text{optionally substituted } C_{3-7} \text{ cycloalkyl})$, or $-C_{1-4} \text{ alkyl}-(\text{optionally substituted aryl})$;

R^{15} is $-H$, $-(\text{optionally substituted } C_{1-6} \text{ alkyl})$, $-(\text{optionally substituted } C_{3-7} \text{ cycloalkyl})$, $-(\text{optionally substituted aryl})$, $-C_{1-4} \text{ alkyl}-(\text{optionally substituted } C_{3-7} \text{ cycloalkyl})$, or $-C_{1-4} \text{ alkyl}-(\text{optionally substituted aryl})$;

R^{16} is selected from



wherein

X is absent, CH_2 , NH , $C(O)NH$, S or O ;

Y is CH_2 ;

Z is O or S ; and

R is independently selected from $-H$, $-C_{1-6} \text{ alkyl}$, $-CF_3$, $-Hal$, $-CN$, $-OH$, and $-O-C_{1-6} \text{ alkyl}$;

R^{17} is $-H$, $-C_{1-6} \text{ alkyl}$, or $-(CH_2CH_2O)_iH$;

R^{18} is $-H$, or $-C_{1-6} \text{ alkyl}$;

R^{**} is independently selected from $-C_{1-6} \text{ alkyl}$, $-C(O)-C_{1-6} \text{ alkyl}$, $-Hal$, $-CF_3$, $-CN$, $-COOR^{17}$, $-OR^{17}$, $-(CH_2)_qNR^{17}R^{18}$, $-C(O)-NR^{17}R^{18}$, and $-NR^{17}-C(O)-C_{1-6} \text{ alkyl}$;

R^* is independently selected from $-H$, $-C_{1-6} \text{ alkyl}$, and $-C_{3-7} \text{ cycloalkyl}$;

q is 0 to 4; and

r is 1 to 3;

wherein the alkyl group, aryl group and/or cycloalkyl group in R^{14} and R^{15} can be optionally substituted with one or more substituents R^{**} .

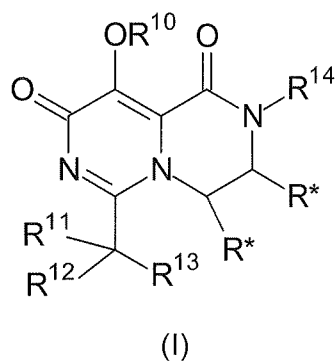
2. The compound according to claim 1, wherein R^{13} is $-R^{16}$.
3. The compound according to claim 1, wherein R^{13} is $-X^{10}-R^{16}$ and X^{10} is $N(R^{15})SO_2$.
4. The compound according to any of claims 1 to 3, wherein R^{11} and R^{12} are $-H$.
5. The compound according to any of claims 1 to 4, wherein R^{10} is $-H$, or $-(\text{optionally substituted } C_{1-6} \text{ alkyl})$.
6. The compound according to any of claims 1 to 5, wherein R^{14} is $-H$, $-(\text{optionally substituted } C_{1-6} \text{ alkyl})$, or $-(\text{optionally substituted aryl})$.
7. A pharmaceutical composition comprising:
a compound having the general formula (I) as defined in any of claims 1 to 6, optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, prodrug, codrug, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof, and optionally one or more pharmaceutically acceptable excipient(s) and/or carrier(s).
8. The pharmaceutical composition according to claim 7, which additionally comprises at least one further medicament which is selected from the group consisting of a polymerase inhibitor which is different from the compound having the general formula (I); neuramidase inhibitor; M2 channel inhibitor; alpha glucosidase inhibitor; ligand of another influenza target; antibiotics, anti-inflammatory agents, lipoxxygenase inhibitors, EP ligands, bradykinin ligands, and cannabinoid ligands.
9. A compound having the general formula (I) as defined in any of claims 1 to 6, optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, prodrug, codrug, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof,

wherein the compound is for use in the treatment, amelioration or prevention of a viral disease caused by Herpesviridae, Filoviridae, Paramyxoviridae, Rhabdoviridae, Orthomyxoviridae, Bunyaviridae, Arenaviridae, Coronaviridae, Picornaviridae, Togaviridae, or Flaviviridae.

10. A method of treating, ameliorating or preventing a viral disease caused by Herpesviridae, Filoviridae, Paramyxoviridae, Rhabdoviridae, Orthomyxoviridae, Bunyaviridae, Arenaviridae, Coronaviridae, Picornaviridae, Togaviridae, or Flaviviridae; the method comprising administering to a patient in need thereof an effective amount of a compound having the general formula (I) as defined in any of claims 1 to 6, optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, prodrug, codrug, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof.
11. A compound having the general formula (I) as defined in any of claims 1 to 6, optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, prodrug, codrug, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof, wherein the compound is for use in the treatment, amelioration or prevention of influenza.
12. A method of treating, ameliorating or preventing influenza; the method comprising administering to a patient in need thereof an effective amount of a compound having the general formula (I) as defined in any of claims 1 to 6, optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, prodrug, codrug, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof.
13. The compound or method according to claim 9 or 10, wherein at least one further medicament which is selected from the group consisting of a polymerase inhibitor which is different from the compound having the general formula (I); neuramidase inhibitor; M2 channel inhibitor; alpha glucosidase inhibitor; ligand of another influenza target; antibiotics, anti-inflammatory agents, lipoxigenase inhibitors, EP ligands, bradykinin ligands, and cannabinoid ligands is administered concurrently with, sequentially with or separately from the compound having the general formula (I).
14. The compound, pharmaceutical composition or method according to any of claims 1 to 13, wherein the compound having the general formula (I) exhibits an IC_{50} of less than about 40 μM in the FRET endonuclease activity assay disclosed herein.

CLAIMS

1. A compound having the general formula (I), optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, prodrug, codrug, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof,



wherein

R^{10} is NR^{15} , $N(R^{15})C(O)$, $C(O)NR^{15}$, O, $C(O)$, $C(O)O$, $OC(O)$; $N(R^{15})SO_2$, $SO_2N(R^{15})$, S, SO , or SO_2 ;

R^{10} is $-H$, a $-C_{1-6}$ alkyl group or a $-C(O)-C_{1-6}$ alkyl group;

R^{11} is $-H$, a $-C_{1-6}$ alkyl group, or a $-C_{1-6}$ alkyl group which is substituted by one or more halogen atoms;

R^{12} is $-H$, a $-C_{1-6}$ alkyl group, or a $-C_{1-6}$ alkyl group which is substituted by one or more halogen atoms;

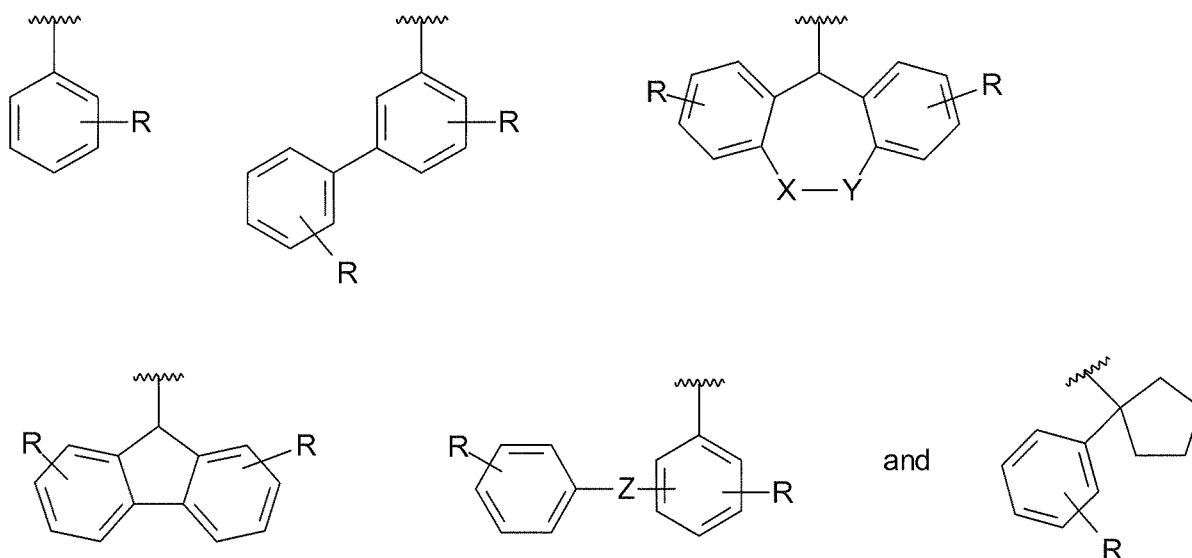
or wherein R^{11} and R^{12} can be joined together to form a 3- to 7-membered carbocyclic or heterocyclic ring;

R^{13} is $-R^{16}$, or $-X^{10}-R^{16}$;

R^{14} is $-H$, $-(\text{optionally substituted } C_{1-6} \text{ alkyl})$, $-(\text{optionally substituted } C_{3-7} \text{ cycloalkyl})$, $-(\text{optionally substituted aryl})$, $-C_{1-4} \text{ alkyl}-(\text{optionally substituted } C_{3-7} \text{ cycloalkyl})$, or $-C_{1-4} \text{ alkyl}-(\text{optionally substituted aryl})$;

R¹⁵ is -H, -(optionally substituted C₁₋₆ alkyl), -(optionally substituted C₃₋₇ cycloalkyl), -(optionally substituted aryl), -C₁₋₄ alkyl-(optionally substituted C₃₋₇ cycloalkyl), or -C₁₋₄ alkyl-(optionally substituted aryl);

R¹⁶ is selected from



wherein

X is absent, CH₂, NH, C(O)NH, S or O;

Y is CH₂;

Z is O or S; and

R is independently selected from -H, -C₁₋₆ alkyl, -CF₃, -Hal, -CN, -OH, and -O-C₁₋₆ alkyl;

R¹⁷ is -H, -C₁₋₆ alkyl, or -(CH₂CH₂O)_rH;

R¹⁸ is -H, or -C₁₋₆ alkyl;

R^{}** is independently selected from -C₁₋₆ alkyl, -C(O)-C₁₋₆ alkyl, -Hal, -CF₃, -CN, -COOR¹⁷, -OR¹⁷, -(CH₂)_qNR¹⁷R¹⁸, -C(O)-NR¹⁷R¹⁸, and -NR¹⁷-C(O)-C₁₋₆ alkyl;

R^{*} is independently selected from -H, -C₁₋₆ alkyl, and -C₃₋₇ cycloalkyl;

q is 0 to 4; and

r is 1 to 3;

wherein the alkyl group, aryl group and/or cycloalkyl group in R^{14} and R^{15} can be optionally substituted with one or more substituents R^{**} .

2. The compound according to claim 1, wherein R^{13} is $-R^{16}$.
3. The compound according to claim 1, wherein R^{13} is $-X^{10}-R^{16}$ and X^{10} is $N(R^{15})SO_2$.
4. The compound according to any of claims 1 to 3, wherein R^{11} and R^{12} are $-H$.
5. The compound according to any of claims 1 to 4, wherein R^{10} is $-H$, or $-(\text{optionally substituted } C_{1-6} \text{ alkyl})$.
6. The compound according to any of claims 1 to 5, wherein R^{14} is $-H$, $-(\text{optionally substituted } C_{1-6} \text{ alkyl})$, or $-(\text{optionally substituted aryl})$.
7. A pharmaceutical composition comprising:
a compound having the general formula (I) as defined in any of claims 1 to 6, optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, prodrug, codrug, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof, and optionally one or more pharmaceutically acceptable excipient(s) and/or carrier(s).
8. The pharmaceutical composition according to claim 7, which additionally comprises at least one further medicament which is selected from the group consisting of a polymerase inhibitor which is different from the compound having the general formula (I); neuramidase inhibitor; M2 channel inhibitor; alpha glucosidase inhibitor; ligand of another influenza target; antibiotics, anti-inflammatory agents, lipoxxygenase inhibitors, EP ligands, bradykinin ligands, and cannabinoid ligands.
9. A compound having the general formula (I) as defined in any of claims 1 to 6, optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, prodrug, codrug, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof, wherein the compound is for use in the treatment, amelioration or prevention of a viral disease caused by Herpesviridae, Filoviridae, Paramyxoviridae, Rhabdoviridae, Orthomyxoviridae, Bunyaviridae, Arenaviridae, Coronaviridae, Picornaviridae, Togaviridae, or Flaviviridae.

10. ; Use of a compound having the general formula (I) as defined in any of claims 1 to 6, optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, prodrug, codrug, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof in the manufacture of a medicament for treating, ameliorating or preventing a viral disease caused by Herpesviridae, Filoviridae, Paramyxoviridae, Rhabdoviridae, Orthomyxoviridae, Bunyaviridae, Arenaviridae, Coronaviridae, Picornaviridae, Togaviridae, or Flaviviridae.
11. A compound having the general formula (I) as defined in any of claims 1 to 6, optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, prodrug, codrug, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof, wherein the compound is for use in the treatment, amelioration or prevention of influenza.
12. Use of a compound having the general formula (I) as defined in any of claims 1 to 6, optionally in the form of a pharmaceutically acceptable salt, solvate, polymorph, prodrug, codrug, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof in the manufacture of a medicament for treating, ameliorating or preventing influenza.
13. The compound or use according to claim 9 or 10, wherein at least one further medicament which is selected from the group consisting of a polymerase inhibitor which is different from the compound having the general formula (I); neuramidase inhibitor; M2 channel inhibitor; alpha glucosidase inhibitor; ligand of another influenza target; antibiotics, anti-inflammatory agents, lipoxygenase inhibitors, EP ligands, bradykinin ligands, and cannabinoid ligands is to be administered concurrently with, sequentially with or separately from the compound having the general formula (I).
14. The compound, pharmaceutical composition or use according to any of claims 1 to 13, wherein the compound having the general formula (I) exhibits an IC_{50} of less than about 40 μ M in the FRET endonuclease activity assay disclosed herein.