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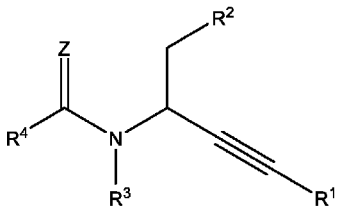
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(54) Title: MAIN PROTEASE INHIBITORS



(I)

(57) Abstract: The invention relates to compounds of formula (I) wherein R^1, R^2, R^3 and R^4 are as defined herein, pharmaceutical compositions comprising the compounds and methods for synthesising compounds according to formula I. This invention further relates to methods of treating COVID-19 in a patient by administering therapeutically effective amounts of the compounds and methods of inhibiting or preventing replication of SARS-CoV-2 with the compounds on the invention and uses of the compounds of the invention in the these methods and in the manufacturing of a medicament.

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MAIN PROTEASE INHIBITORS

FIELD OF THE INVENTION

The invention relates to compounds, pharmaceutical compositions and methods capable of inhibiting or preventing replication of a virus expressing Main Protease (M^{pro}). The invention also relates to the use of these compounds and pharmaceutical compositions in the treatment or prevention of a disease or condition caused by infection with a virus expressing Main Protease (M^{pro}). The invention further relates to the use of these compounds and pharmaceutical compositions in the manufacture of a medicament for treating infection by a virus expressing Main Protease (M^{pro}) and/or treating or preventing a disease or condition caused by infection by a virus expressing Main Protease (M^{pro}), in a subject in need thereof.

BACKGROUND OF THE INVENTION

Coronaviruses (CoVs) belong to the Nidovirales order of enveloped positive-sense single-stranded RNA viruses (Anirudhan et al. J Med Virol. 2021, 93, 2722). Before 2002, there were only two known human CoV species, HCoV-229E and HCoV-OC43, with infections exhibiting symptoms similar to those of the common cold caused by rhinovirus. These two coronaviruses were identified in 1965 and have been extensively studied for the following 20 years. There are now seven known species of human CoVs (HCoVs): HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, MERS-CoV, SARS-CoV, and SARS-CoV-2 belonging to alpha- and beta-coronaviruses. About 30% of mild upper respiratory diseases are caused by HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1. SARS-CoV and MERS-CoV, which first appeared in China in 2002 and in Saudi Arabia in 2012, respectively, caused severe health and economic crisis at the global level. Even though its infection rate is slow, MERS-CoV infections are still ongoing. More recently, a novel coronavirus emerged (SARS-CoV-2), which has a higher infection rate causing a worldwide outbreak of the coronavirus disease 2019 (COVID-19). It is therefore desirable to have new compounds, pharmaceutical compositions and methods of inhibiting SARS-CoV-2 viral replication and of treating COVID-19 in patients.

SARS-CoV-2 is a close cousin of SARS-CoV, sharing an overall amino-acid sequence identity of 82%. Based on this similarity it is reasonable to assume that

knowledge of the molecular pathogenesis of SARS-CoV and SARS-CoV-2 could result in treatment strategies for coronavirus diseases.

Coronavirus replication and transcription function is encoded by the so-called "replicase" gene (Ziebuhr et al., J. Gen. Virol. 2000, 81, 853), which consists of two overlapping polyproteins that are extensively processed by viral proteases. The C-proximal region is processed at eleven conserved interdomain junctions by the coronavirus "3C-like" or main protease (M^{Pro}). The name "3C-like" protease derives from certain similarities between the coronavirus enzyme and the well-known picornavirus 3C proteases. M^{pro} is a 33.8-kDa cysteine protease which mediates the maturation of functional polypeptides involved in the assembly of replication-transcription machinery. M^{pro} digests the polyprotein at no less than 11 conserved sites, starting with the autolytic cleavage of this enzyme itself. The structure of SARS-CoV-2 M^{Pro} was established using high resolution X-ray (Zhang et al. Science. 2020, 368, 409). This study revealed that the SARS-CoV M^{Pro} and SARS-CoV-2 M^{Pro} have a high degree of similarity and identified a couple of differences between both SARS-CoV M^{Pro} and SARS-CoV-2 M^{Pro}. In addition, since M^{Pro} has no human homolog and is highly conserved among all coronaviruses (Yang et al. Curr. Pharm. Des. 2006, 12, 4573), it represents an attractive drug target against coronaviruses.

In WO 2021/207409 A2, WO 2021/205298 A1, WO 2021/205296 A1, WO 2021/205290 A1, WO 2021/250648 A1, WO 2022/040186 A1 and WO 2022/013684 A1 compounds and methods were disclosed aimed at treating COVID-19 by targeting the SARS-Cov-2 M^{Pro}.

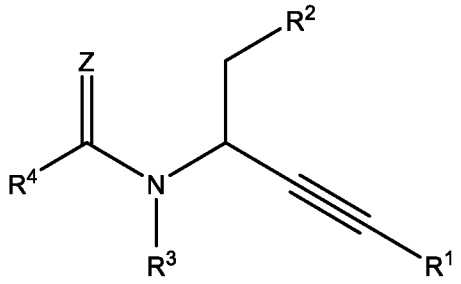
In view of the ongoing worldwide outbreak of the coronavirus disease 2019 (COVID-19) and future coronavirus diseases, there is a need for new compounds, pharmaceutical compositions, methods of inhibiting coronavirus replication and methods of treating COVID-19 in patients.

Accordingly, it is an object of the invention to provide compounds, pharmaceutical compositions and methods, which have a better affinity and/or reduced off-target reactivity compared to the prior art M^{Pro} inhibitors. It is a further object of the invention to provide compounds, pharmaceutical compositions and methods with improved pharmacokinetics compared to the prior art.

SUMMARY OF THE INVENTION

The inventors have found that one or more of these objectives of the invention can be realized with the compounds, pharmaceutical compositions and methods described herein.

Thus, in a first aspect, the present invention provides a compound of formula I



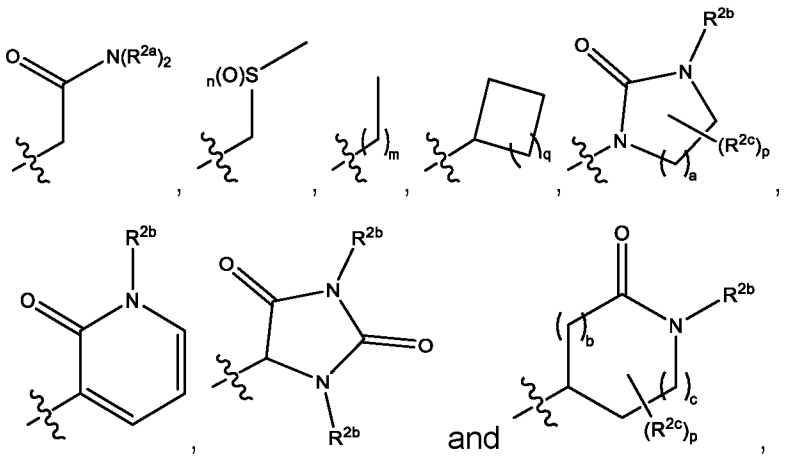
I

or a pharmaceutically acceptable salt, solvate and/or hydrate thereof, wherein:

Z is either a oxygen or a sulphur atom;

R^1 is selected from the group consisting of hydrogen, methyl optionally substituted with one to three halo, phenyl optionally substituted with one to five halo.

R^2 is selected from the group consisting of:



wherein each R^{2a} is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl;

wherein each R^{2b} is independently selected from the group consisting of hydrogen, halo, hydroxy, trifluoromethyl, C_1-C_6 alkyl-C(O)-, C_1-C_6 alkyl-OC(O)- and C_1-C_6 alkoxy

Wherein each R^{2c} is independently selected from the group consisting of hydrogen, halo, hydroxy, oxo, trifluoromethyl, C_1-C_6 alkyl ; C_1-C_6 alkoxy

wherein n, a, b and c are at each occurrence independently selected from 0, 1 and 2;

wherein q is at each occurrence independently selected from 0, 1, 2, 3 and 4;

wherein p is at each occurrence independently selected from 0, 1, 2 and 3;

wherein m is at each occurrence independently selected from 0 to 5;

R^3 is selected from the group consisting of hydrogen and methyl;

R^4 is selected from the group consisting of C_1-C_8 alkyl, C_3-C_{12} cycloalkyl, 4- to 12-membered heterocycloalkyl, C_6-C_{10} aryl and 5- to 10-membered heteroaryl;

wherein each R4 group is optionally substituted with one to two R^{4a};

or R^3 and R^4, taken together with the nitrogen and carbon atoms to which they are attached, form a 4- to 12-membered heterocycloalkyl or a 5- to 10-membered heteroaryl, which can be optionally substituted with one to two R^{4a};

R^{4a} is at each occurrence independently selected from the group consisting of R^{4b}, R^{4b}-O-, R^{4b}-NH-, $(R^{4b})_2$-N-, R^{4b}-C(O)NH- and R^{4b}-OC(O)NH-;

Wherein each R^{4b} is at each occurrence independently selected from the group consisting of C_1-C_8 alkyl, C_3-C_{12} cycloalkyl, 4- to 12-membered heterocycloalkyl, C_6-C_{10} aryl and 5- to 10-membered heteroaryl;

wherein each R^{4b} group is optionally substituted with one to two R^{4c};

R^{4c} is at each occurrence independently selected from the group consisting of R^{4d}, R^{4d}-O-, R^{4d}-NH-, $(R^{4d})_2$-N-, R^{4d}-C(O)NH- and R^{4d}-OC(O)NH-;

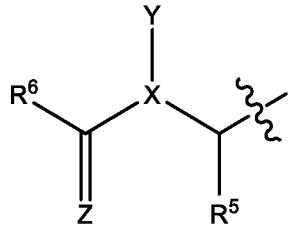
Wherein each R^{4d} is at each occurrence is independently selected from the group consisting of C_1-C_8 alkyl, C_3-C_{12} cycloalkyl, 4- to 12-membered heterocycloalkyl, C_6-C_{10} aryl and 5- to 10-membered heteroaryl;

wherein each R^4, R^{4b} and R^{4d} is optionally substituted with one to five substituents at each occurrence independently selected from the group consisting of methyl, halo, hydroxy, oxo, imino and sulfanylidene.

As shown in the examples, compounds of the invention are potent inhibitors of SARS-CoV2 and MERS-CoV. The alkyne group of the compounds according to the invention covalently interacts with the catalytic cysteine residue of M^{Pro} thereby preventing viral replication. Without wishing to be bound by any theory, the inventors believe that this is a proximity-driven activity-based reaction and that the present compounds are non-reactive against other thiols. This is indicative of reduced off-

target effects, compared to the M^{Pro} known from the prior art discussed herein elsewhere.

In a preferred embodiment of the present invention, a compound as defined herein is provided, wherein R^4 is:



wherein:

Z is either an oxygen or a sulphur atom;

X is either a nitrogen or a carbon atom;

Y is hydrogen or, when X is a nitrogen atom, Y and R^5 or R^6, taken together with the nitrogen and carbon atoms to which they are attached, form a 4- to 12-membered heterocycloalkyl or a 5- to 10-membered heteroaryl;

R^5 is selected from the group consisting of C_1-C_6 alkyl, (C_3-C_6 cycloalkyl)-C_1-C_3 alkyl and (phenyl)-C_1-C_3 alkyl;

wherein each R^5 group is optionally substituted with one to five substituents at each occurrence independently selected from the group consisting of C_1-C_3 alkyl, halo, -CF_3;

R^6 is selected from the group consisting of C_1-C_8 alkyl, C_1-C_8 alkoxy, (C_1-C_8 alkoxy)-C_1-C_8 alkyl, C_3-C_{12} cycloalkyl, (C_3-C_{12} cycloalkyl)-C_1-C_8 alkyl, (C_3-C_{12} cycloalkyl)-C_1-C_8 alkoxy, C_3-C_{12} cycloalkoxy, (C_3-C_{12} cycloalkoxy)-C_1-C_8 alkyl, (C_3-C_{12} cycloalkoxy)-C_1-C_8 alkoxy, 4- to 12-membered heterocycloalkyl, (4- to 12-membered heterocycloalkyl)-C_1-C_8 alkyl, (4- to 12-membered heterocycloalkyl)-C_1-C_8 alkoxy, 4- to 12-membered heterocycloalkoxy, (4- to 12-membered heterocycloalkoxy)-C_1-C_8 alkyl, (4- to 12-membered heterocycloalkoxy)-C_1-C_8 alkoxy, C_6-C_{10} aryl, (C_6-C_{10} aryl)-C_1-C_8 alkyl, (C_6-C_{10} aryl)-C_1-C_8 alkoxy, 5- to 10-membered heteroaryl, (5- to 10-membered heteroaryl)-C_1-C_8 alkyl and (5- to 10-membered heteroaryl)-C_1-C_8 alkoxy;

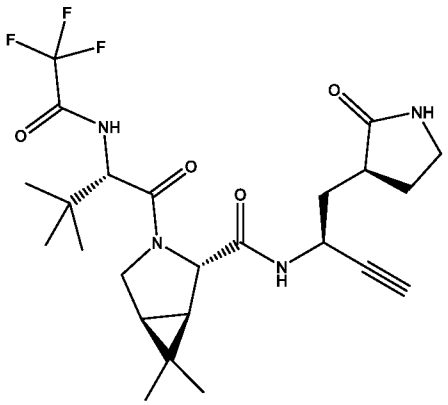
wherein each R^6 group is optionally substituted with one to five R^{6a};

R^{6a} at each occurrence is independently selected from the group consisting of C_1-C_3 alkyl, C_1-C_3 alkoxy, halo, hydroxy, oxo, phenyl, benzyl, C_1-C_6 alkyl-C(O)NH-, C_1-C_6

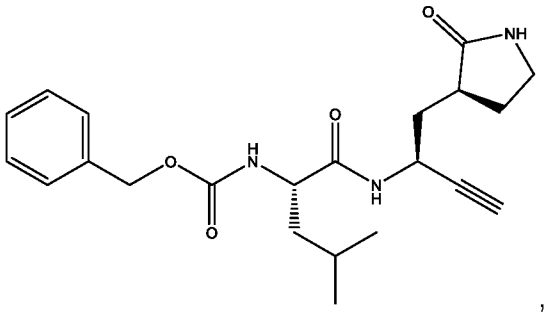
cycloalkyl-C(O)NH-, 5- to 6-membered heterocycloalkyl-C(O)NH, phenyl-C(O)NH-, 5- to 6-membered heteroaryl-C(O)NH-, C_1-C_6 alkyl-OC(O)NH-;

wherein each R^{6a} group is optionally substituted with one to five fluoro or one substituent selected from the group consisting of C_1-C_3 alkyl, C_1-C_3 alkoxy, chloro, hydroxy, oxo, trifluoromethyl.

In a particularly preferred embodiment of the present invention, a compound as defined herein is provided, selected from the group consisting of



and

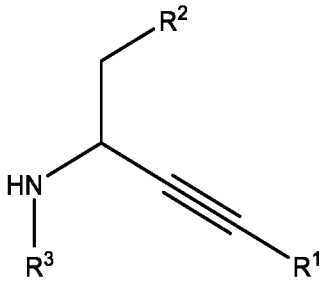


,

and pharmaceutically acceptable salts, solvates and hydrates thereof

In a second aspect, the invention provides a method for preparing a compound as defined herein, or a pharmaceutically acceptable salt thereof, said method comprising the steps of:

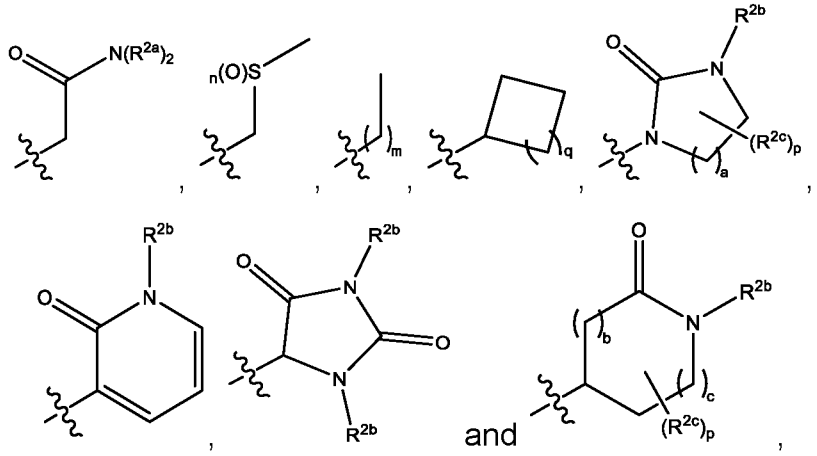
a) providing a first compound according to formula (X)



(X)

wherein R^1 is selected from the group consisting of hydrogen, methyl optionally substituted with one to three halo, phenyl optionally substituted with one to five halo.

R^2 is selected from the group consisting of:



wherein each R^{2a} is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl;

wherein each R^{2b} is independently selected from the group consisting of hydrogen, halo, hydroxy, trifluoromethyl, C_1-C_6 alkyl-C(O)-, C_1-C_6 alkyl-OC(O)- and C_1-C_6 alkoxy

Wherein each R^{2c} is independently selected from the group consisting of hydrogen, halo, hydroxy, oxo, trifluoromethyl, C_1-C_6 alkyl ; C_1-C_6 alkoxy

wherein n, a, b and c are at each occurrence independently selected from 0, 1 and 2;

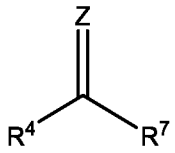
wherein q is at each occurrence independently selected from 0, 1, 2, 3 and 4;

wherein p is at each occurrence independently selected from 0, 1, 2 and 3;

wherein m is at each occurrence independently selected from 0 to 5;

R^3 is selected from the group consisting of hydrogen and methyl;

b) providing a second compound according to formula (Y)



(Y)

wherein Z is either an oxygen or a sulphur atom;

R^7 is selected from the group consisting of hydroxy, halo and carboxylate

R^4 is selected from the group consisting of C_1-C_8 alkyl, C_3-C_{12} cycloalkyl, 4- to 12-membered heterocycloalkyl, C_6-C_{10} aryl and 5- to 10-membered heteroaryl;

wherein each R4 group is optionally substituted with one to two R^{4a};

or R^3 and R^4, taken together with the nitrogen and carbon atoms to which they are attached, form a 4- to 12-membered heterocycloalkyl or a 5- to 10-membered heteroaryl, which can be optionally substituted with one to two R^{4a};

R^{4a} is at each occurrence independently selected from the group consisting of R^{4b}, R^{4b}-O-, R^{4b}-NH-, $(R^{4b})_2$-N-, R^{4b}-C(O)NH- and R^{4b}-OC(O)NH-;

Wherein each R^{4b} is at each occurrence independently selected from the group consisting of C_1-C_8 alkyl, C_3-C_{12} cycloalkyl, 4- to 12-membered heterocycloalkyl, C_6-C_{10} aryl and 5- to 10-membered heteroaryl;

wherein each R^{4b} group is optionally substituted with one to two R^{4c};

R^{4c} is at each occurrence independently selected from the group consisting of R^{4d}, R^{4d}-O-, R^{4d}-NH-, $(R^{4d})_2$-N-, R^{4d}-C(O)NH- and R^{4d}-OC(O)NH-;

Wherein each R^{4d} is at each occurrence is independently selected from the group consisting of C_1-C_8 alkyl, C_3-C_{12} cycloalkyl, 4- to 12-membered heterocycloalkyl, C_6-C_{10} aryl and 5- to 10-membered heteroaryl;

wherein each R^4, R^{4b} and R^{4d} is optionally substituted with one to five substituents at each occurrence independently selected from the group consisting of methyl, halo, hydroxy, oxo, imino and sulfanylidene.

c) reacting said first compound with said second compound under conditions that result in the formation of a compound of any one of the embodiments of the first aspect.

A third aspect of the present invention provides pharmaceutical compositions comprising a compound as defined herein or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent. In a preferred embodiment, said pharmaceutical composition is provided in a unit dosage form suitable for oral administration, preferably in the form of a tablet or capsule.

A fourth aspect of the present invention, provides a method for treating a viral infection and/or treating or preventing a disease or condition caused by infection with a virus expressing Main Protease (M^{pro}), in a subject in need thereof, the method comprising administering to said subject a therapeutically effective amount of a compound as defined herein.

A fifth aspect of the present invention, provides a method for inhibiting or preventing replication of a virus expressing Main Protease (M^{pro}), the method comprising contacting the viruses with an inhibitory amount of a compound as defined herein.

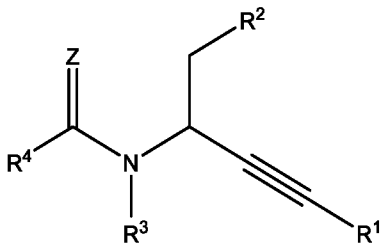
In a sixth aspect, a use is provided of a compound as defined herein in a method of treating infection by a virus expressing Main Protease (M^{pro}) and/or treating or preventing a disease or condition caused by infection by a virus expressing Main Protease (M^{pro}).

In a seventh aspect of the present invention, a use is provided of a compound as defined herein, in the manufacture of a medicament for treating infection by a virus expressing Main Protease (M^{pro}) and/or treating or preventing a disease or condition caused by infection by a virus expressing Main Protease (M^{pro}).

These and other aspects of the invention, will become apparent to those of average skill in the art, based on the following description and examples

DETAILED DESCRIPTION

As indicated above, the first aspect of the invention concerns a compound of formula I:



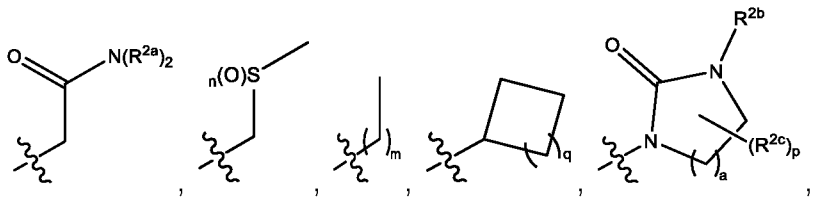
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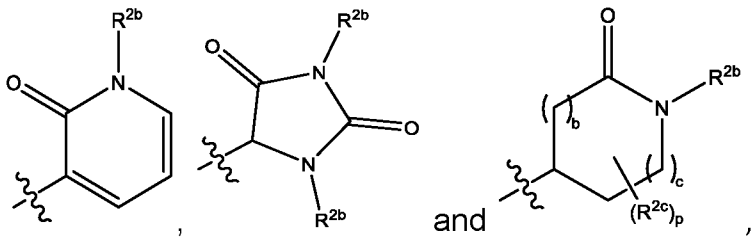
or a pharmaceutically acceptable salt, solvate and/or hydrate thereof, wherein:

Z is either a oxygen or a sulphur atom;

R^1 is selected from the group consisting of hydrogen, methyl optionally substituted with one to three halo, phenyl optionally substituted with one to five halo.

R^2 is selected from the group consisting of:





wherein each R^{2a} is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl;

wherein each R^{2b} is independently selected from the group consisting of hydrogen, halo, hydroxy, trifluoromethyl, C_1-C_6 alkyl-C(O)-, C_1-C_6 alkyl-OC(O)- and C_1-C_6 alkoxy

Wherein each R^{2c} is independently selected from the group consisting of hydrogen, halo, hydroxy, oxo, trifluoromethyl, C_1-C_6 alkyl ; C_1-C_6 alkoxy

wherein n, a, b and c are at each occurrence independently selected from 0, 1 and 2;

wherein q is at each occurrence independently selected from 0, 1, 2, 3 and 4;

wherein p is at each occurrence independently selected from 0, 1, 2 and 3;

wherein m is at each occurrence independently selected from 0 to 5;

R^3 is selected from the group consisting of hydrogen and methyl;

R^4 is selected from the group consisting of C_1-C_8 alkyl, C_3-C_{12} cycloalkyl, 4- to 12-membered heterocycloalkyl, C_6-C_{10} aryl and 5- to 10-membered heteroaryl;

wherein each R4 group is optionally substituted with one to two R^{4a};

or R^3 and R^4, taken together with the nitrogen and carbon atoms to which they are attached, form a 4- to 12-membered heterocycloalkyl or a 5- to 10-membered heteroaryl, which can be optionally substituted with one to two R^{4a};

R^{4a} is at each occurrence independently selected from the group consisting of R^{4b}, R^{4b}-O-, R^{4b}-NH-, $(R^{4b})_2$-N-, R^{4b}-C(O)NH- and R^{4b}-OC(O)NH-;

Wherein each R^{4b} is at each occurrence independently selected from the group consisting of C_1-C_8 alkyl, C_3-C_{12} cycloalkyl, 4- to 12-membered heterocycloalkyl, C_6-C_{10} aryl and 5- to 10-membered heteroaryl;

wherein each R^{4b} group is optionally substituted with one to two R^{4c};

R^{4c} is at each occurrence independently selected from the group consisting of R^{4d}, R^{4d}-O-, R^{4d}-NH-, $(R^{4d})_2$-N-, R^{4d}-C(O)NH- and R^{4d}-OC(O)NH-;

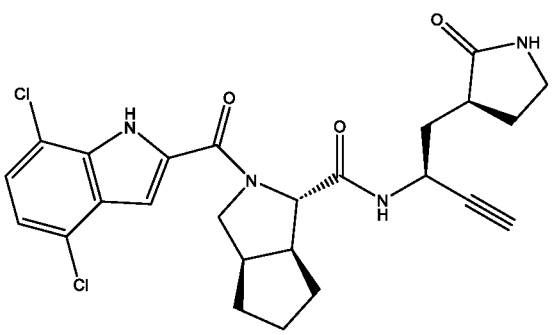
Wherein each R^{4d} is at each occurrence is independently selected from the group consisting of C_1-C_8 alkyl, C_3-C_{12} cycloalkyl, 4- to 12-membered heterocycloalkyl, C_6-C_{10} aryl and 5- to 10-membered heteroaryl;

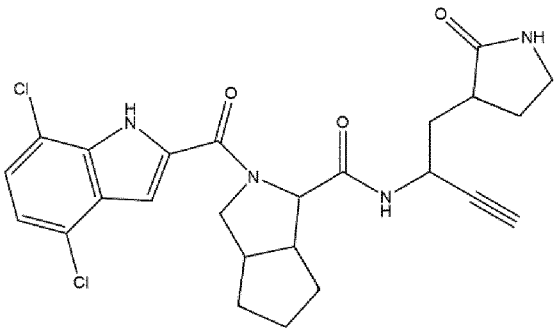
wherein each R^4, R^{4b} and R^{4d} is optionally substituted with one to five substituents at each occurrence independently selected from the group consisting of methyl, halo, hydroxy, oxo, imino and sulfanylidene.

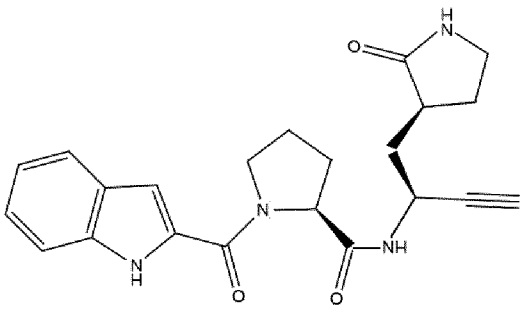
In certain preferred embodiments the compound of the invention is a compound according to formula I, with the proviso that R^4 comprises not more than one moiety selected from the group consisting of heterocycloalkyl and heteroaryl, where the term heterocycloalkyl includes mono- as well as polycyclic heterocycloalkyl and the term heteroaryl includes mono- as well as polycyclic heteroary.

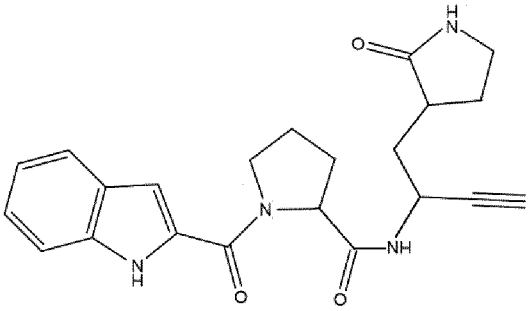
In certain preferred embodiments, the compound of the invention is a compound according to formula I with the proviso that said compound according to formula (I) is not (1S,3aR,6aS)-2-(4,7-dichloro-1H-indole-2-carbonyl)-N-[(2S)-1-[(3S)-2-oxopyrrolidin-3-yl]but-3-yn-2-yl]-hexahydro-1H-cyclopenta[c]pyrrole-1-carboxamide.

In preferred embodiments, the compound of the invention is a compound according to formula I with the proviso that said compound according to formula (I) is not any of the following compounds:

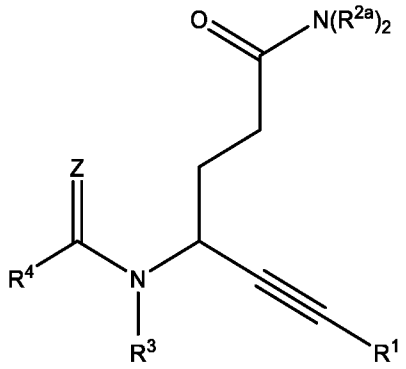








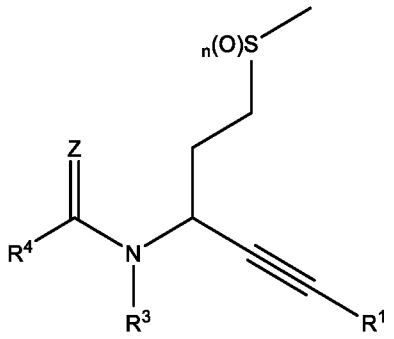
In certain embodiments, the compound of the invention is a compound according to formula I(a), or a pharmaceutically acceptable salt, solvate and/or hydrate thereof.



I(a)

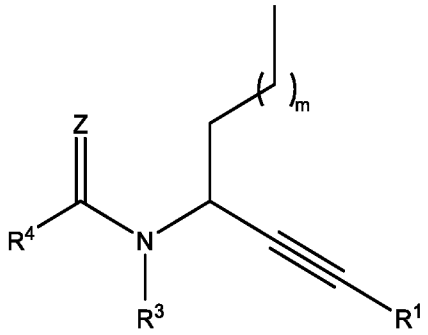
In preferred embodiments, the compound of the invention is a compound according to formula I(a), or a pharmaceutically acceptable salt, solvate and/or hydrate thereof, wherein R^{2a} is selected from the group comprising hydrogen.

In certain embodiments, the compound of invention is a compound according to formula I(b), or a pharmaceutically acceptable salt, solvate and/or hydrate thereof.



I(b)

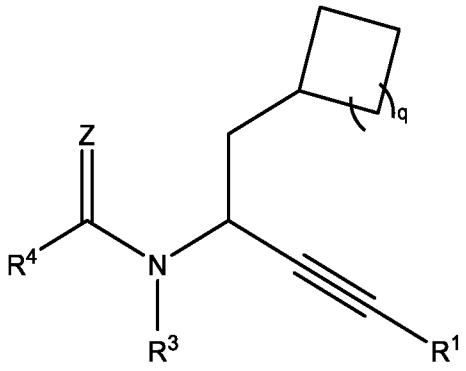
In certain embodiments, the compound of the invention is a compound according to formula I(c), or a pharmaceutically acceptable salt, solvate and/or hydrate thereof.



I(c)

In preferred embodiments, the compound of the invention is a compound according to formula I(c), or a pharmaceutically acceptable salt, solvate and/or hydrate thereof, wherein m is selected from 0 and 1.

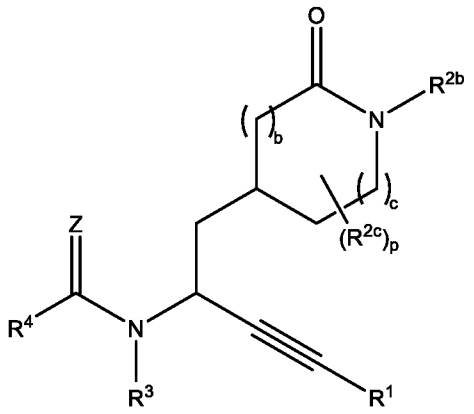
In certain embodiments, the compound the invention is a compound according to formula I(d), or a pharmaceutically acceptable salt, solvate and/or hydrate thereof.



I(d)

In preferred embodiments, the compound of the invention is a compound according to formula I(d), or a pharmaceutically acceptable salt, solvate and/or hydrate thereof, wherein q is 1.

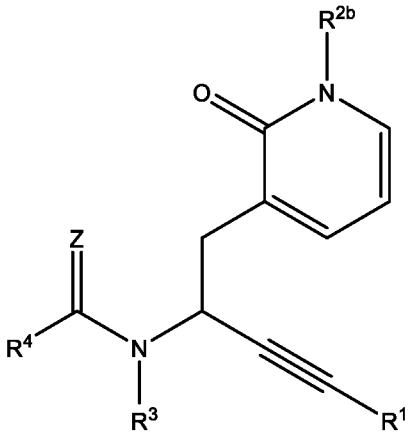
In certain embodiments, the compound of the invention is a compound according to formula I(e), or a pharmaceutically acceptable salt, solvate and/or hydrate thereof.



I(e)

In preferred embodiments, the compound of the invention is a compound according to formula I(e), or a pharmaceutically acceptable salt, solvate and/or hydrate thereof, wherein R^{2b} is hydrogen, b is 0, c is 1 and p is 0.

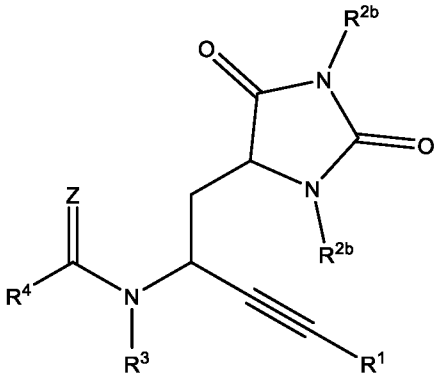
In certain embodiments, the compound of the invention is a compound according to formula I(f), or a pharmaceutically acceptable salt, solvate and/or hydrate thereof.



I(f)

In preferred embodiments, the compound the invention is a compound according to formula I(f), or a pharmaceutically acceptable salt, solvate and/or hydrate thereof, wherein R^{2b} is hydrogen.

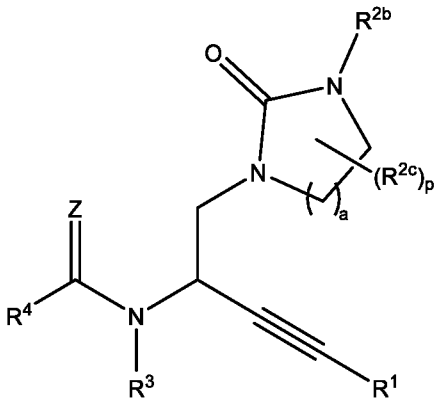
In certain embodiments, the compound of the invention is a compound according to formula I(g), or a pharmaceutically acceptable salt, solvate and/or hydrate thereof.



I(g)

In preferred embodiments, the compound of the invention is compound according to formula I(g), or a pharmaceutically acceptable salt, solvate and/or hydrate thereof, wherein R^{2b} is hydrogen.

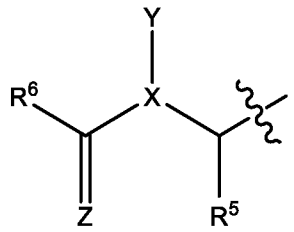
In certain embodiments, the compound of the invention is a compound according to formula I(h), or a pharmaceutically acceptable salt, solvate and/or hydrate thereof.



I(h)

In preferred embodiments, the compound of the invention is a compound according to formula I(h), or a pharmaceutically acceptable salt, solvate and/or hydrate thereof, wherein R^{2b} is hydrogen, a is 1 and p is 0.

In particularly preferred embodiments, the compound of the invention is a compound of any one of formulae I and I(a) to I(h), or a pharmaceutically acceptable salt, solvate and/or hydrate thereof, wherein R^4 is:



wherein:

Z is at each occurrence independently selected from either an oxygen or a sulphur atom;

X is either a nitrogen or a carbon atom;

Y is hydrogen or, when X is a nitrogen atom, Y and R^5 or R^6, taken together with the nitrogen and carbon atoms to which they are attached, form a 4- to 12-membered heterocycloalkyl or a 5- to 10-membered heteroaryl; preferably a 4- to 7-membered or 9-12 membered heterocycloalkyl or a 5- to 10-membered heteroaryl;

R^5 is selected from the group consisting of C_1-C_6 alkyl, (C_3-C_6 cycloalkyl)-C_1-C_3 alkyl and (phenyl)-C_1-C_3 alkyl;

wherein each R^5 group is optionally substituted with one to five substituents at each occurrence independently selected from the group consisting of C_1-C_3 alkyl, halo, -CF_3;

R^6 is selected from the group consisting of C_1-C_8 alkyl, C_1-C_8 alkoxy, (C_1-C_8 alkoxy)-C_1-C_8 alkyl, C_3-C_{12} cycloalkyl, (C_3-C_{12} cycloalkyl)-C_1-C_8 alkyl, (C_3-C_{12} cycloalkyl)-C_1-C_8 alkoxy, C_3-C_{12} cycloalkoxy, (C_3-C_{12} cycloalkoxy)-C_1-C_8 alkyl, (C_3-C_{12} cycloalkoxy)-C_1-C_8 alkoxy, 4- to 12-membered heterocycloalkyl, (4- to 12-membered heterocycloalkyl)-C_1-C_8 alkyl, (4- to 12-membered heterocycloalkyl)-C_1-C_8 alkoxy, 4- to 12-membered heterocycloalkoxy, (4- to 12-membered heterocycloalkoxy)-C_1-C_8 alkyl, (4- to 12-membered heterocycloalkoxy)-C_1-C_8 alkoxy, C_6-C_{10} aryl, (C_6-C_{10} aryl)-C_1-C_8 alkyl, (C_6-C_{10} aryl)-C_1-C_8 alkoxy, 5- to 10-membered heteroaryl, (5- to 10-membered heteroaryl)-C_1-C_8 alkyl and (5- to 10-membered heteroaryl)-C_1-C_8 alkoxy;

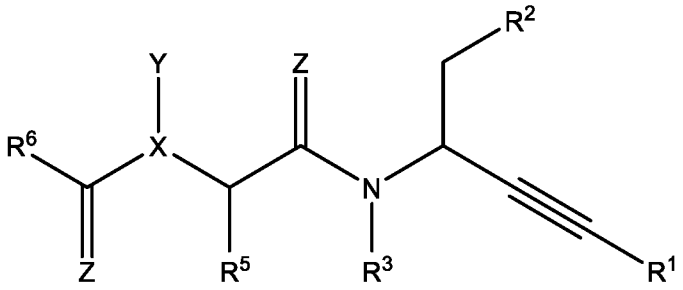
wherein each R^6 group is optionally substituted with one to five R^{6a};

R^{6a} at each occurrence is independently selected from the group consisting of C_1-C_3 alkyl, C_1-C_3 alkoxy, halo, hydroxy, oxo, phenyl, benzyl, C_1-C_6 alkyl-C(O)NH-, C_1-C_6 cycloalkyl-C(O)NH-, 5- to 6-membered heterocycloalkyl-C(O)NH, phenyl-C(O)NH-, 5- to 6-membered heteroaryl-C(O)NH-, C_1-C_6 alkyl-OC(O)NH-, preferably selected from the group consisting of C_1-C_3 alkyl, C_1-C_3 alkoxy, fluoro, hydroxy, oxo, phenyl, benzyl,

C_1-C_6 alkyl-C(O)NH-, C_1-C_6 cycloalkyl-C(O)NH-, 5- to 6-membered heterocycloalkyl-C(O)NH, phenyl-C(O)NH-, 5- to 6-membered heteroaryl-C(O)NH-, C_1-C_6 alkyl-OC(O)NH-;

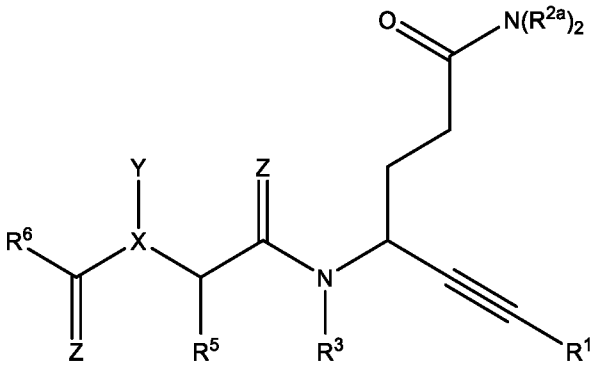
wherein each R^{6a} group is optionally substituted with one to five fluoro or one substituents selected from the group consisting of C_1-C_3 alkyl, C_1-C_3 alkoxy, chloro, hydroxy, oxo, trifluoromethyl, preferably substituted with one to five fluoro or one substituents selected from the group consisting of C_1-C_3 alkyl, C_1-C_3 alkoxy, hydroxy, oxo, trifluoromethyl,

Hence, in particularly preferred embodiments, the compound of the invention is a compound according to general formula (II), or a pharmaceutically acceptable salt, solvate and/or hydrate thereof.



(II)

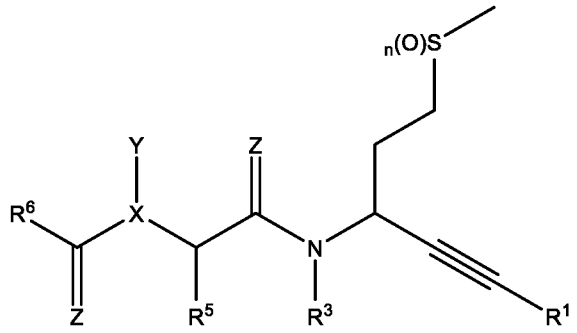
In certain embodiments, the compound of the invention is a compound according to formula II(a), or a pharmaceutically acceptable salt, solvate and/or hydrate thereof.



II(a)

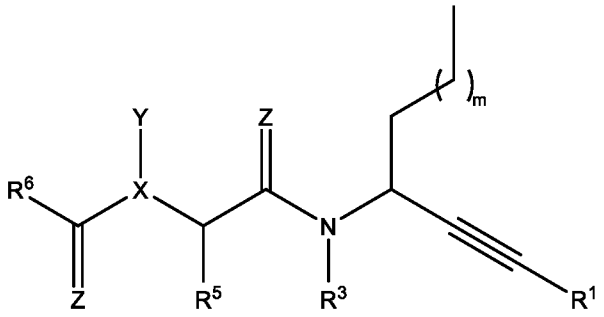
In preferred embodiments, the compound of the invention is a compound according to formula II(a), or a pharmaceutically acceptable salt, solvate and/or hydrate thereof, wherein R^{2a} is selected from the group comprising hydrogen.

In embodiments, the compound of the invention is a compound according to formula II(b), or a pharmaceutically acceptable salt, solvate and/or hydrate thereof.



II(b)

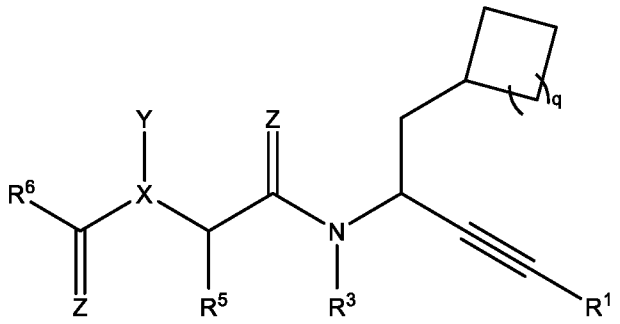
In certain embodiments, the compound of the invention is a compound according to formula II(c), or a pharmaceutically acceptable salt, solvate and/or hydrate thereof.



II(c)

In preferred embodiments, the compound of the invention is a compound according to formula II(c), or a pharmaceutically acceptable salt, solvate and/or hydrate thereof, wherein m is selected from 0 and 1.

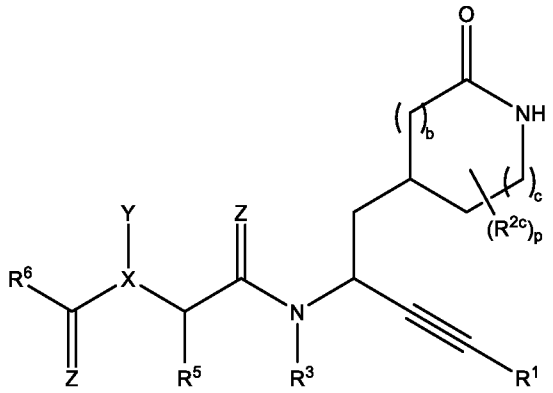
In certain embodiments, the compound of the invention is a compound according to formula II(d), or a pharmaceutically acceptable salt, solvate and/or hydrate thereof.



II(d)

In preferred embodiments, the compound of the invention is a compound according to formula II(d), or a pharmaceutically acceptable salt, solvate and/or hydrate thereof, wherein q is 1.

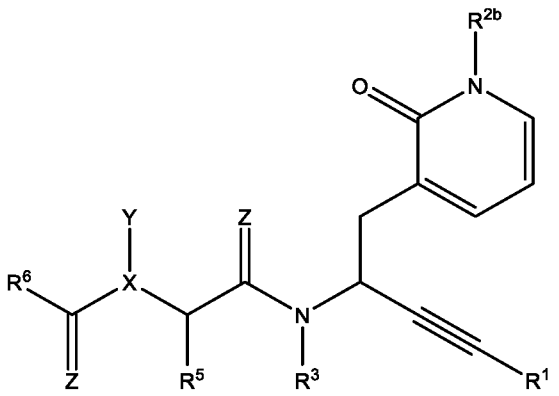
In certain embodiments, the compound of the invention is a compound according to formula II(e), or a pharmaceutically acceptable salt, solvate and/or hydrate thereof.



II(e)

In preferred embodiments, the compound of the invention is a compound according to formula II(e), or a pharmaceutically acceptable salt, solvate and/or hydrate thereof, wherein R^{2b} is hydrogen, b is 0, c is 1 and p is 0.

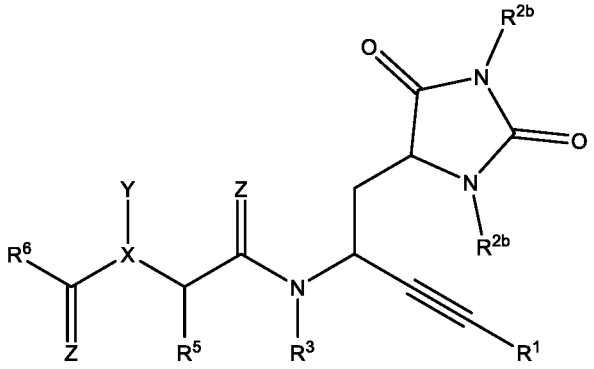
In certain embodiments, the compound of the invention is a compound according to formula II(f), or a pharmaceutically acceptable salt, solvate and/or hydrate thereof.



II(f)

In preferred embodiments, the compound of the invention is a compound according to formula II(f), or a pharmaceutically acceptable salt, solvate and/or hydrate thereof, wherein R^{2b} is hydrogen.

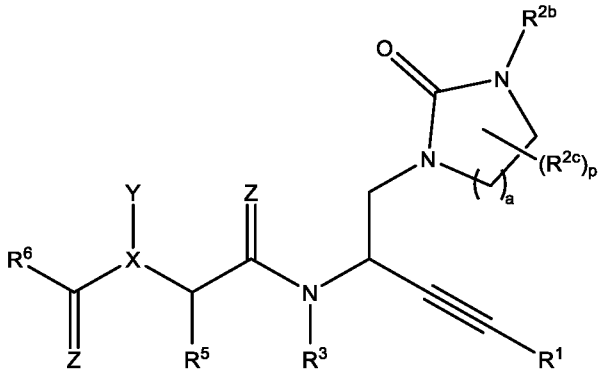
In embodiments, the compound of the invention is a compound according to formula II(g), or a pharmaceutically acceptable salt, solvate and/or hydrate thereof.



II(g)

In preferred embodiments, the compound of the invention is a compound according to formula II(g), or a pharmaceutically acceptable salt, solvate and/or hydrate thereof, wherein R^{2b} is hydrogen.

In certain embodiments, the compound of the invention is a compound according to formula II(h), or a pharmaceutically acceptable salt, solvate and/or hydrate thereof.



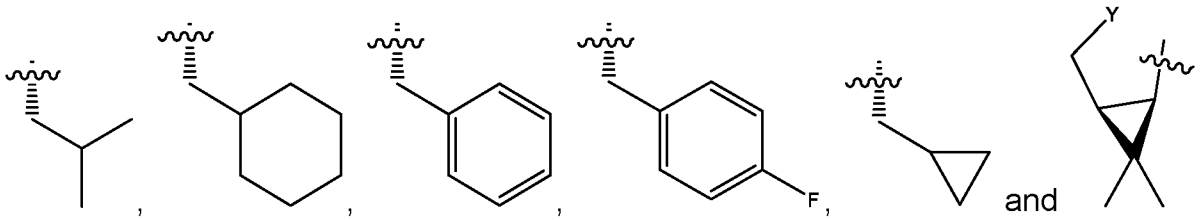
II(h)

In preferred embodiments, the compound of the invention is a compound according to formula II(h), or a pharmaceutically acceptable salt, solvate and/or hydrate thereof, wherein R^{2b} is hydrogen, a is 1 and p is 0.

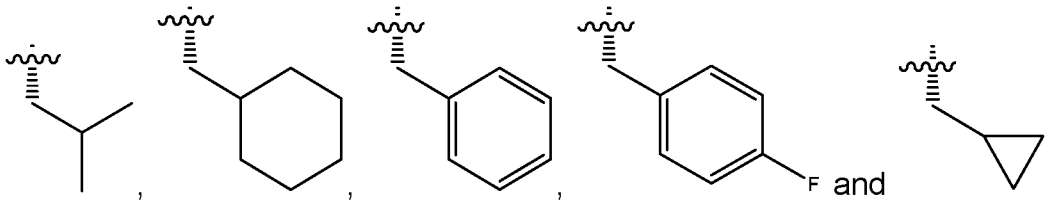
In the above formulae (I), (Ia-Ih), (II) and (IIa-IIh), R^3 preferably represents hydrogen.

In the above formulae (I), (Ia-Ih), (II) and (IIa-IIh), R^1 preferably represents hydrogen, fluoro or trimethylfluoro, most preferably hydrogen.

In the above formulae (II) and (IIa-IIh), R^5 is preferably selected from the group consisting of:



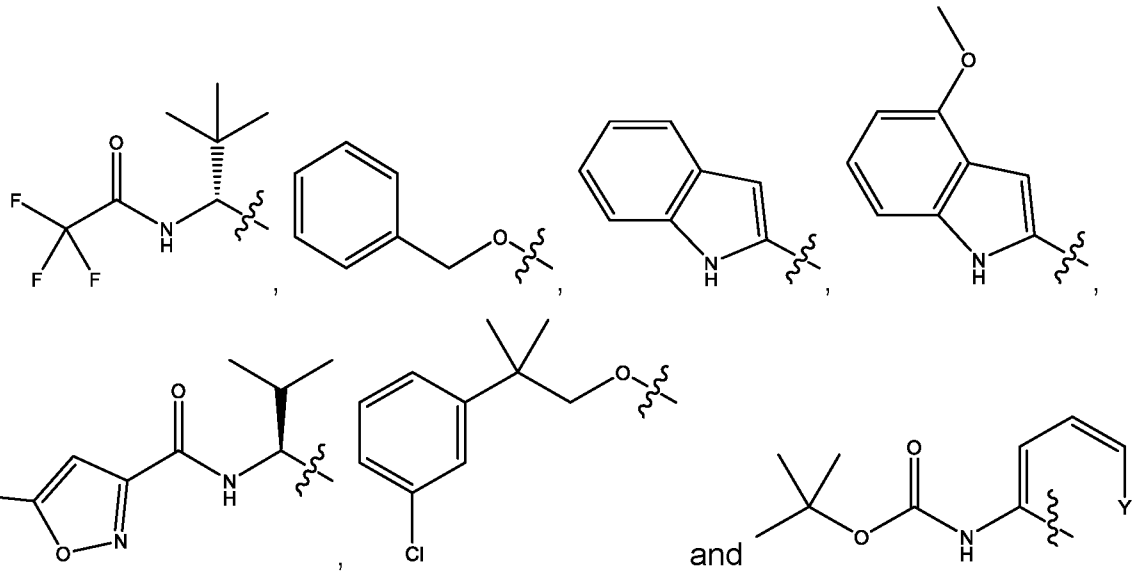
In the above formulae (II) and (IIa-IIh), when X is nitrogen and Y is hydrogen, R^5 is preferably selected from the group consisting of:



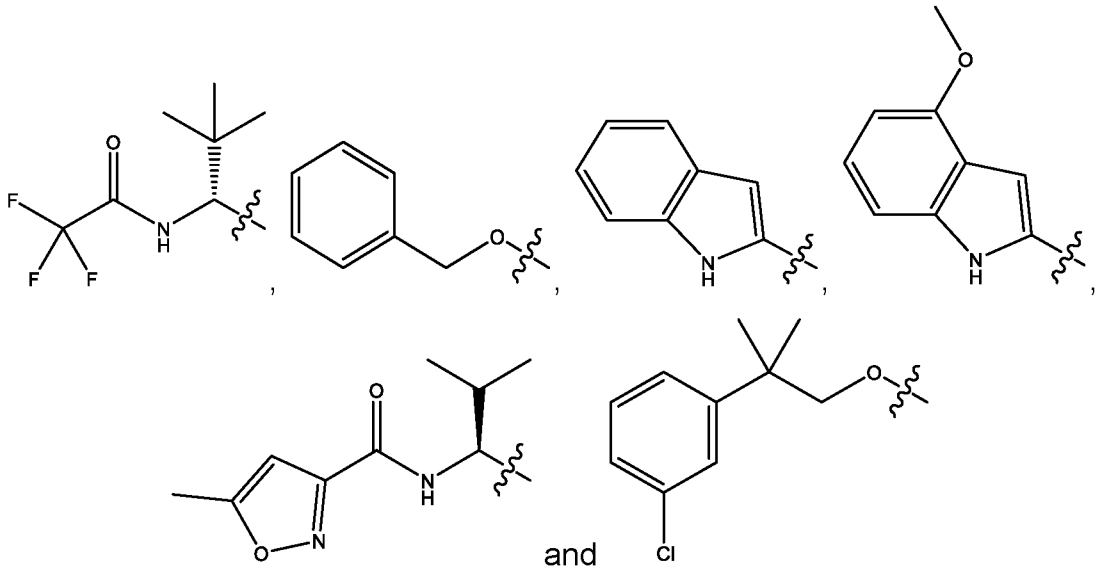
In the above formulae (II) and (IIa-IIh) when X is nitrogen, Y and R^5, taken together with the nitrogen and carbon atoms to which they are attached, preferably selected from



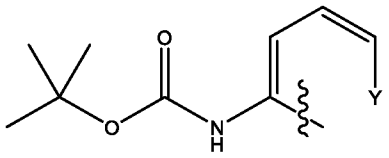
In the above formulae (II) and (IIa-IIh), R^6 is preferably is selected from the group consisting of:



In the above formulae (II) and (IIa-IIh), when X is nitrogen and Y is hydrogen, R^6 is preferably is selected from the group consisting of:



In the above formulae (II) and (IIa-IIh) when X is nitrogen, Y and R^6, taken together with the nitrogen and carbon atoms to which they are attached, form



Compounds of the invention contain at least one chiral centre and, therefore, exist as stereoisomers, such as enantiomers and diastereomers. According to the invention, the chemical structures depicted herein, and therefore the compounds of the invention, encompass all of the corresponding compound's stereoisomers.

Thus, in accordance with the invention the chemical structures depicted herein by structural formula not indicating a specific stereochemistry, and therefore the compounds of the invention, encompass both a stereochemically pure form and mixtures of different stereoisomers, such as enantiomers and/or diastereomers. Thus, the invention encompasses compounds of formulae (I), (Ia-Ih), (II) and (IIa-IIh), in enantiomerically pure form, enantiomerically-enriched form, diastereomerically pure form, diastereomerically enriched form, as racemic mixture or as diastereomeric mixture.

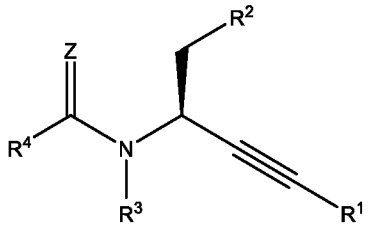
In highly preferred embodiments, compounds of formulae (I), (Ia-Ih), (II) and (IIa-IIh), are provided wherein one of the stereoisomers makes up more than 60 mol%, more than 80 mol%, more than 90 mol%, more than 95 mol%, more than 97 mol%, more than 98.5 mol%, more than 99 mol% of the compound. In accordance with the invention, generally stated, a compound is considered stereochemically pure when one of the stereoisomers makes up more than more than 90 mol%, more than 95 mol%, more than 97 mol%, more than 98.5 mol%, more than 99 mol% of the compound.

Enantiomeric mixtures can be resolved into their component enantiomers or stereoisomers by well-known methods, such as chiral-phase gas chromatography, chiral-phase high performance liquid chromatography, or crystallizing the compound in a chiral solvent.

Diastereomeric mixtures can be resolved into their component diastereomers by well-known methods for separating two chemical compounds, for example based on their different melting points, boiling points etc.

Stereochemically pure compounds can also be obtained from stereochemically pure intermediates, reagents, and catalysts by well-known asymmetric synthetic methods.

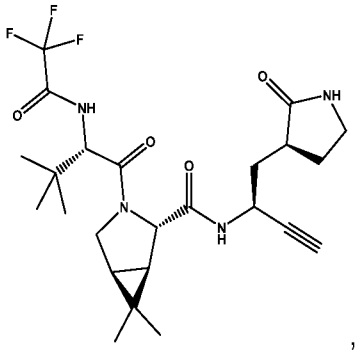
In a preferred embodiments, the compound of the invention has the absolute configuration as represented by formula (Ix).



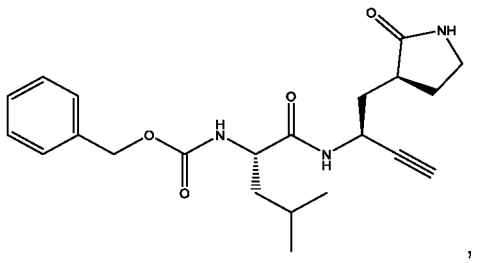
(Ix)

In a preferred embodiments of the invention, the above formulae (Ia-Ih), (II) and (IIa-IIh), have the same absolute configuration as represents represented by formula (Ix).

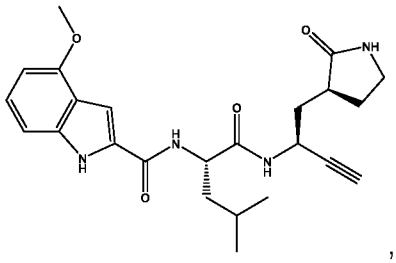
In particularly preferred embodiments, the compound of the invention is compound selected from the group consisting of:



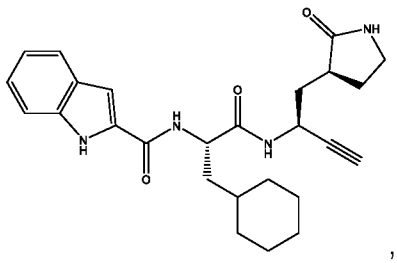
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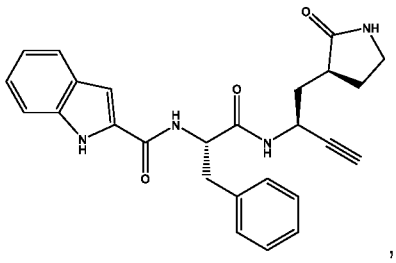
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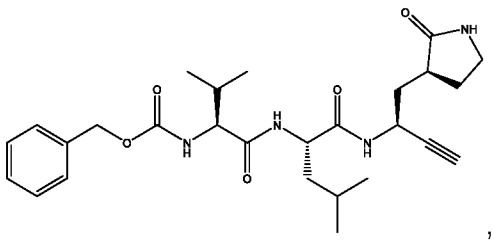
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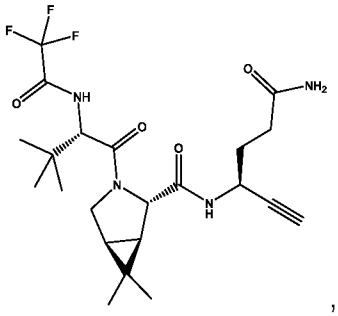
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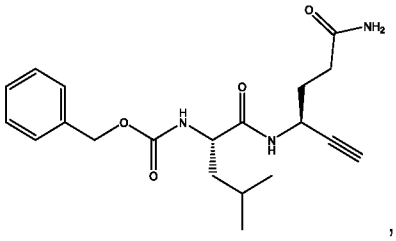
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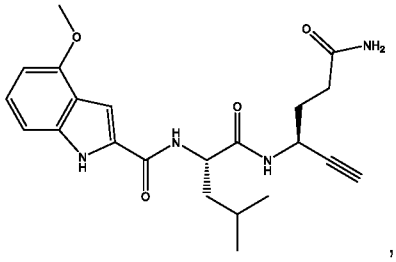
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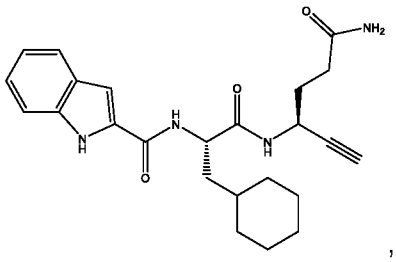
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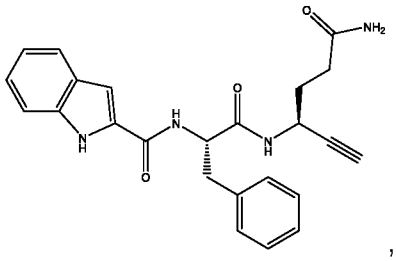
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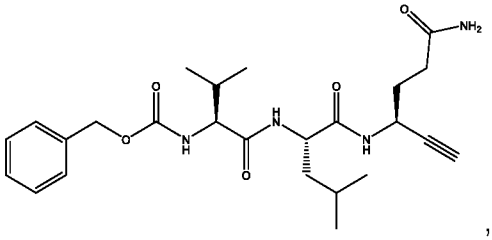
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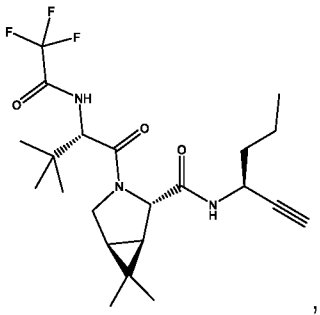
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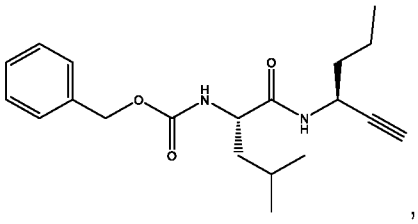
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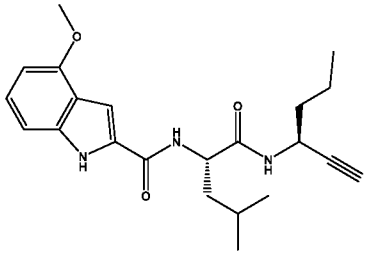
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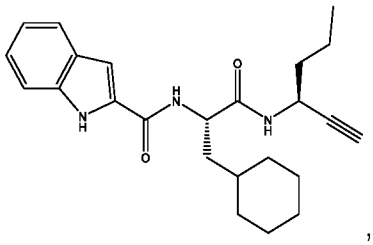
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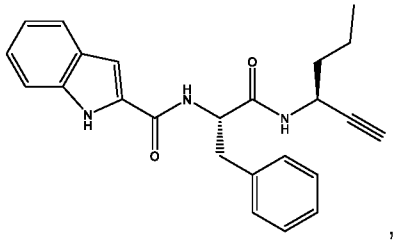
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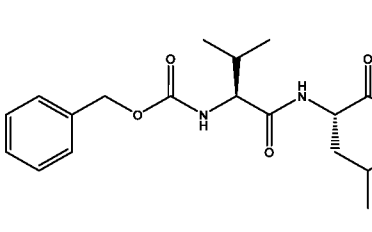
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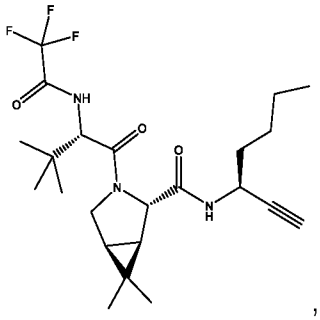
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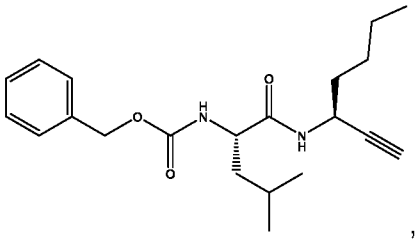
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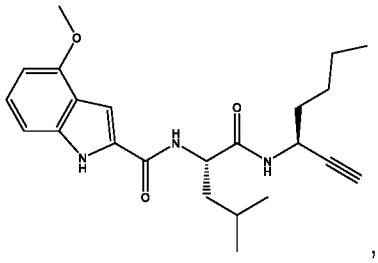
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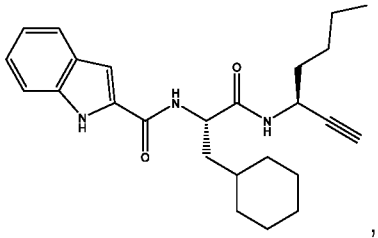
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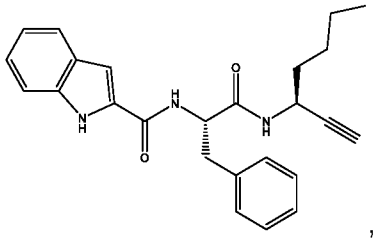
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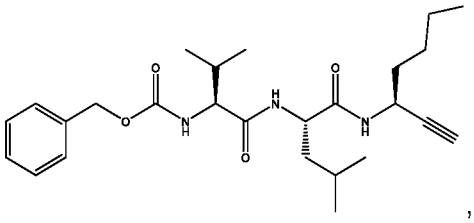
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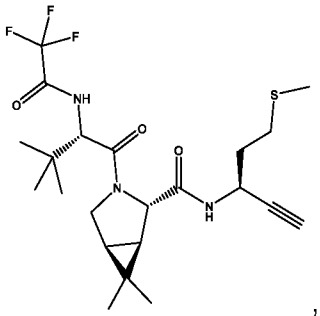
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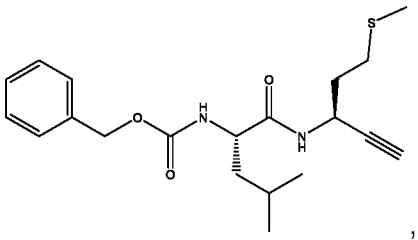
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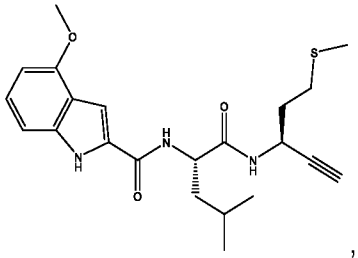
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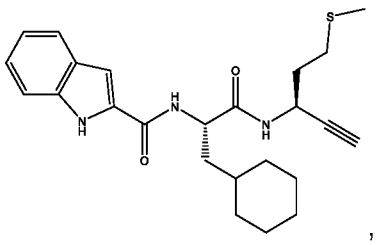
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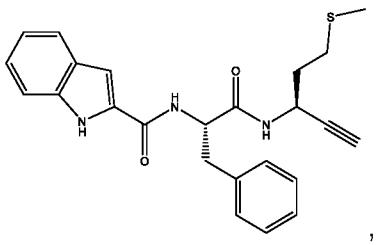
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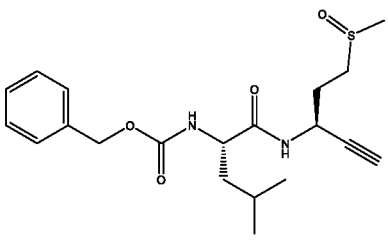
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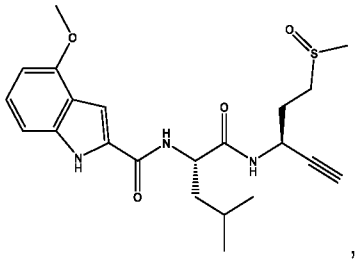
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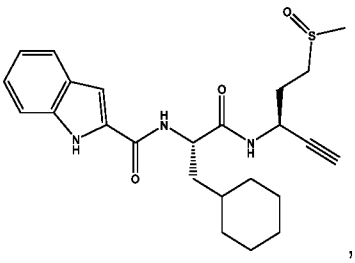
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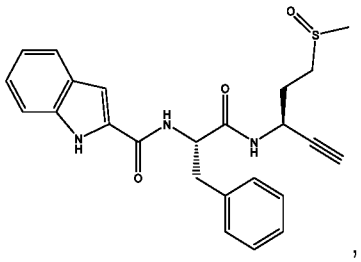
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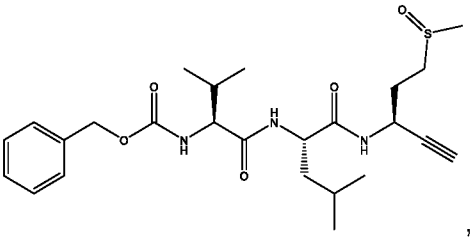
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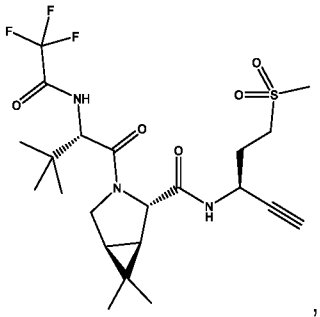
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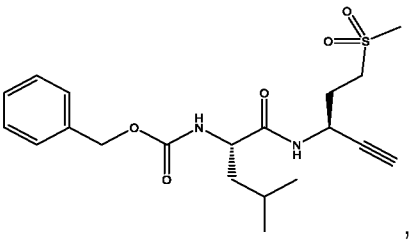
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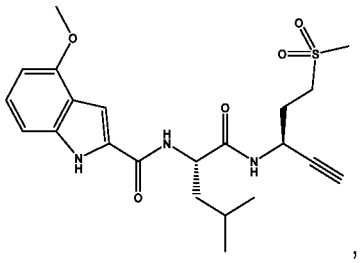
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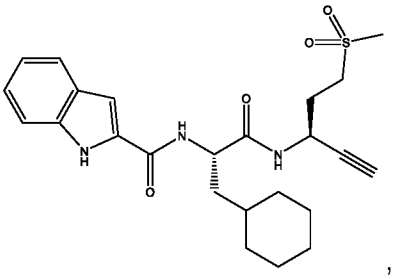
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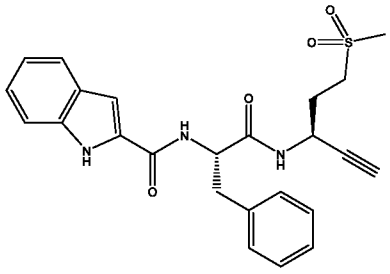
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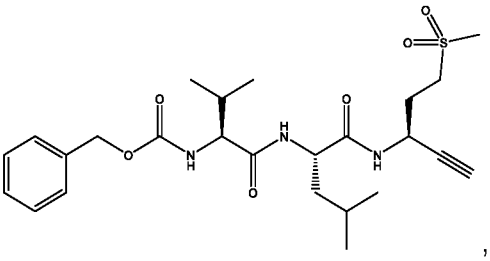
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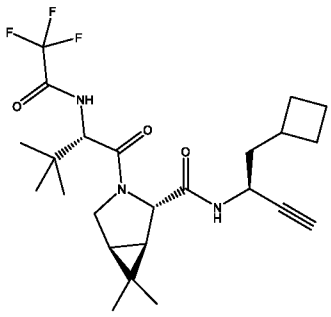
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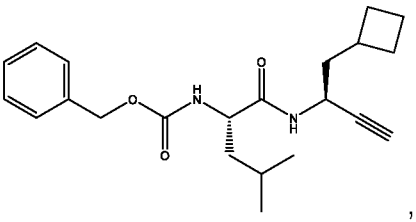
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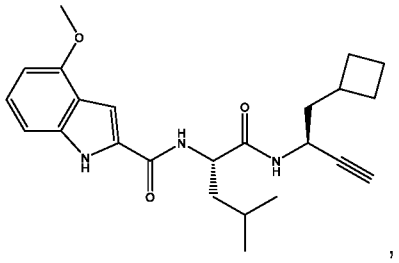
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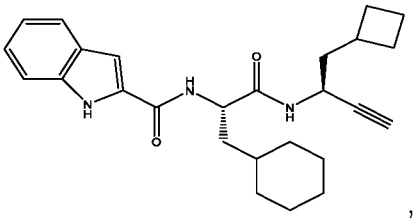
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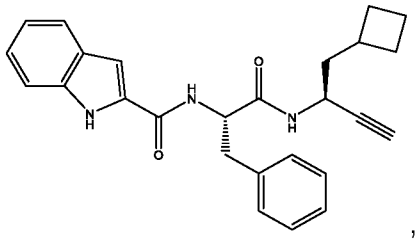
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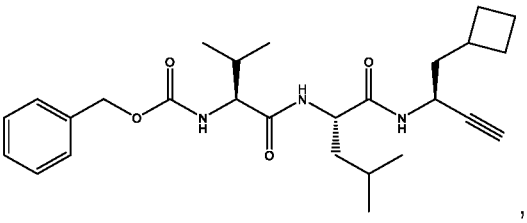
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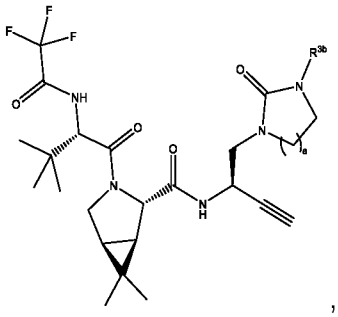
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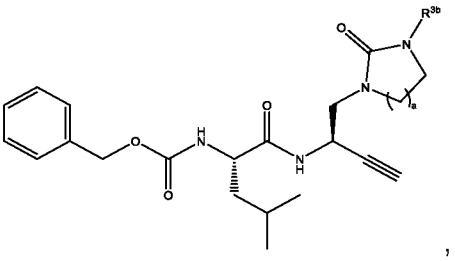
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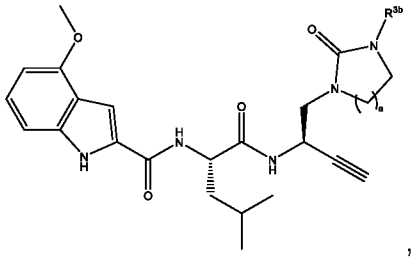
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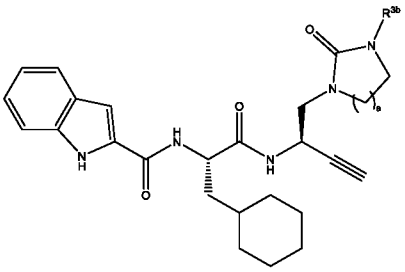
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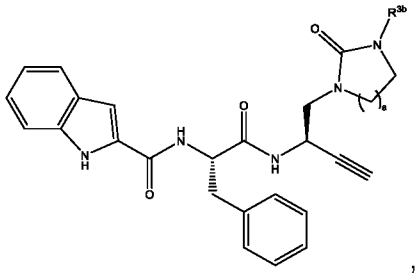
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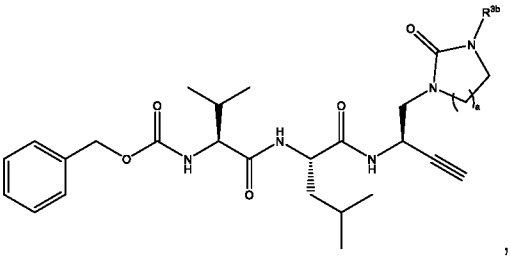
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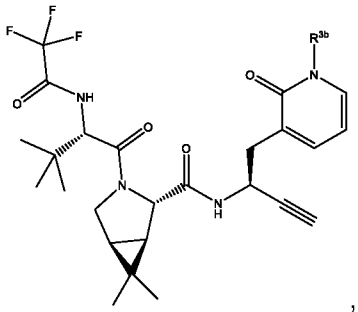
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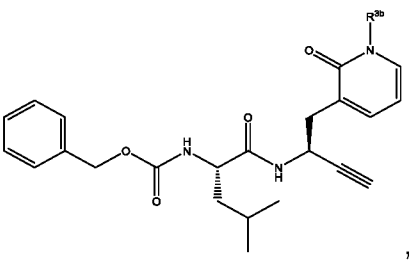
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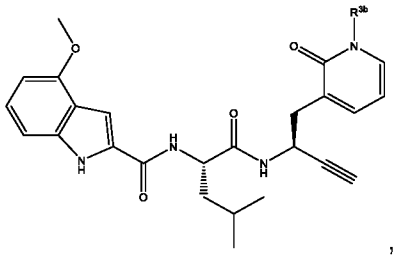
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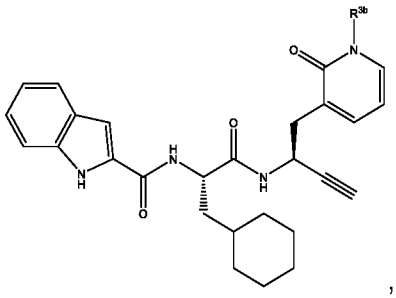


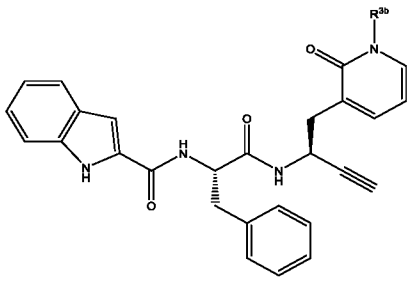
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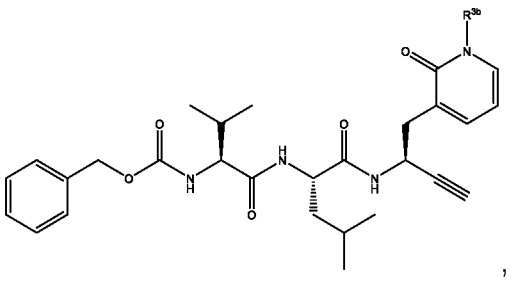


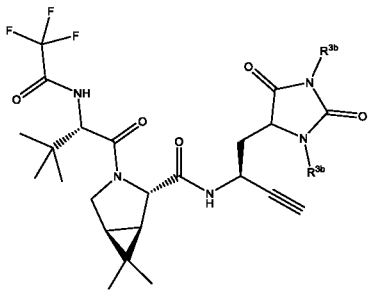
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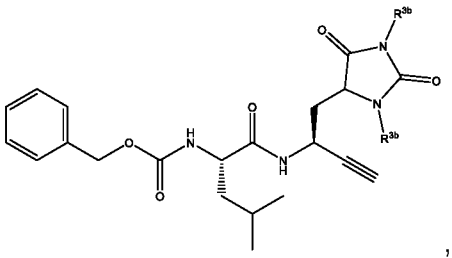

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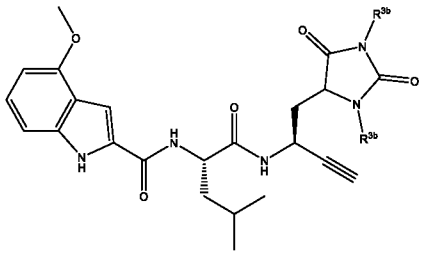

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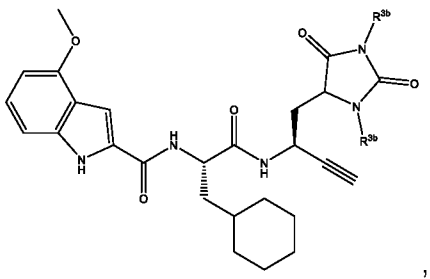

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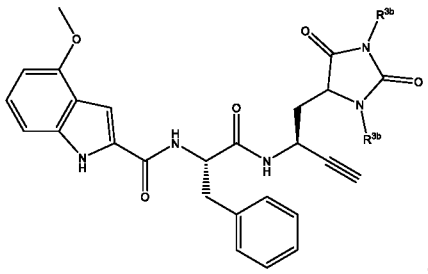

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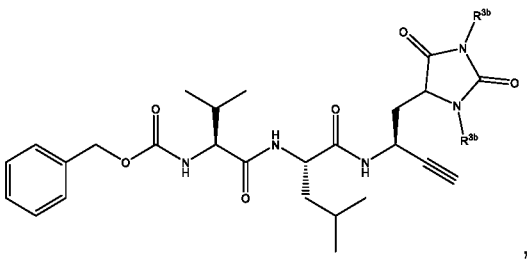

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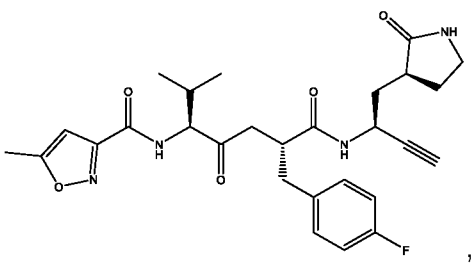

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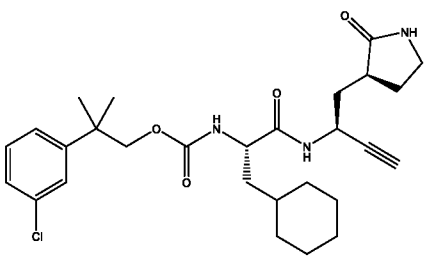

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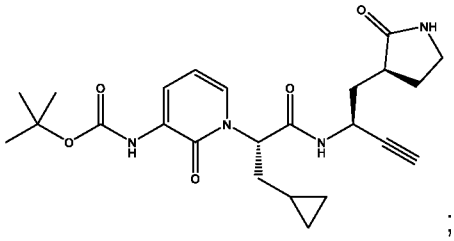

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and



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and pharmaceutically acceptable salts, solvates and hydrates thereof,

Wherein each R^{3b} is independently selected from the group consisting of hydrogen, halo, hydroxy, trifluoromethyl, -C(O)C_1-C_6 alkyl, -C(O)OC_1-C_6 alkyl and C_1-C_6 alkoxy; wherein a is at each occurrence independently selected from 0, 1 and 2.

In preferred embodiments, the compound of the invention is compound selected from the group consisting of:

(1*R*,2*S*,5*S*)-3-((*S*)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-6,6-dimethyl-*N*-((*S*)-1-((*S*)-2-oxopyrrolidin-3-yl)but-3-yn-2-yl)-3-azabicyclo[3.1.0]hexane-2-carboxamide,

benzyl ((*S*)-4-methyl-1-oxo-1-(((*S*)-1-((*S*)-2-oxopyrrolidin-3-yl)but-3-yn-2-yl)amino)pentan-2-yl)carbamate,

4-methoxy-*N*-((*S*)-4-methyl-1-oxo-1-(((*S*)-1-((*S*)-2-oxopyrrolidin-3-yl)but-3-yn-2-yl)amino)pentan-2-yl)-1*H*-indole-2-carboxamide,

N-((*S*)-3-cyclohexyl-1-oxo-1-(((*S*)-1-((*S*)-2-oxopyrrolidin-3-yl)but-3-yn-2-yl)amino)propan-2-yl)-1*H*-indole-2-carboxamide,

N-((*S*)-1-oxo-1-(((*S*)-1-((*S*)-2-oxopyrrolidin-3-yl)but-3-yn-2-yl)amino)-3-phenylpropan-2-yl)-1*H*-indole-2-carboxamide,

benzyl ((*S*)-3-methyl-1-(((*S*)-4-methyl-1-oxo-1-(((*S*)-1-((*S*)-2-oxopyrrolidin-3-yl)but-3-yn-2-yl)amino)pentan-2-yl)amino)-1-oxobutan-2-yl)carbamate,

(1*R*,2*S*,5*S*)-*N*-((*S*)-6-amino-6-oxohex-1-yn-3-yl)-3-((*S*)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide,

benzyl ((*S*)-1-(((*S*)-6-amino-6-oxohex-1-yn-3-yl)amino)-4-methyl-1-oxopentan-2-yl)carbamate,

N-((*S*)-1-(((*S*)-6-amino-6-oxohex-1-yn-3-yl)amino)-4-methyl-1-oxopentan-2-yl)-4-methoxy-1*H*-indole-2-carboxamide,

N-((*S*)-1-(((*S*)-6-amino-6-oxohex-1-yn-3-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)-1*H*-indole-2-carboxamide,

N-((*S*)-1-(((*S*)-6-amino-6-oxohex-1-yn-3-yl)amino)-1-oxo-3-phenylpropan-2-yl)-1*H*-indole-2-carboxamide,
benzyl ((*S*)-1-(((*S*)-1-(((*S*)-6-amino-6-oxohex-1-yn-3-yl)amino)-4-methyl-1-oxopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate,
(1*R*,2*S*,5*S*)-3-((*S*)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-*N*-((*S*)-hex-1-yn-3-yl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide,
benzyl ((*S*)-1-(((*S*)-hex-1-yn-3-yl)amino)-4-methyl-1-oxopentan-2-yl)carbamate,
N-((*S*)-1-(((*S*)-hex-1-yn-3-yl)amino)-4-methyl-1-oxopentan-2-yl)-4-methoxy-1*H*-indole-2-carboxamide,
N-((*S*)-3-cyclohexyl-1-(((*S*)-hex-1-yn-3-yl)amino)-1-oxopropan-2-yl)-1*H*-indole-2-carboxamide,
N-((*S*)-1-(((*S*)-hex-1-yn-3-yl)amino)-1-oxo-3-phenylpropan-2-yl)-1*H*-indole-2-carboxamide,
benzyl ((*S*)-1-(((*S*)-1-(((*S*)-hex-1-yn-3-yl)amino)-4-methyl-1-oxopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate,
(1*R*,2*S*,5*S*)-3-((*S*)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-*N*-((*S*)-hept-1-yn-3-yl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide,
benzyl ((*S*)-1-(((*S*)-hept-1-yn-3-yl)amino)-4-methyl-1-oxopentan-2-yl)carbamate,
N-((*S*)-1-(((*S*)-hept-1-yn-3-yl)amino)-4-methyl-1-oxopentan-2-yl)-4-methoxy-1*H*-indole-2-carboxamide,
N-((*S*)-3-cyclohexyl-1-(((*S*)-hept-1-yn-3-yl)amino)-1-oxopropan-2-yl)-1*H*-indole-2-carboxamide,
N-((*S*)-1-(((*S*)-hept-1-yn-3-yl)amino)-1-oxo-3-phenylpropan-2-yl)-1*H*-indole-2-carboxamide,
benzyl ((*S*)-1-(((*S*)-1-(((*S*)-hept-1-yn-3-yl)amino)-4-methyl-1-oxopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate,
(1*R*,2*S*,5*S*)-3-((*S*)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-6,6-dimethyl-*N*-((*S*)-5-(methylthio)pent-1-yn-3-yl)-3-azabicyclo[3.1.0]hexane-2-carboxamide,
benzyl ((*S*)-4-methyl-1-(((*S*)-5-(methylthio)pent-1-yn-3-yl)amino)-1-oxopentan-2-yl)carbamate,
4-methoxy-*N*-((*S*)-4-methyl-1-(((*S*)-5-(methylthio)pent-1-yn-3-yl)amino)-1-oxopentan-2-yl)-1*H*-indole-2-carboxamide,

N-((*S*)-3-cyclohexyl-1-(((*S*)-5-(methylthio)pent-1-yn-3-yl)amino)-1-oxopropan-2-yl)-1*H*-indole-2-carboxamide,
N-((*S*)-1-(((*S*)-5-(methylthio)pent-1-yn-3-yl)amino)-1-oxo-3-phenylpropan-2-yl)-1*H*-indole-2-carboxamide,
benzyl ((*S*)-3-methyl-1-(((*S*)-4-methyl-1-(((*S*)-5-(methylthio)pent-1-yn-3-yl)amino)-1-oxopentan-2-yl)amino)-1-oxobutan-2-yl)carbamate,
(1*R*,2*S*,5*S*)-3-((*S*)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-6,6-dimethyl-*N*-((3*S*)-5-(methylsulfinyl)pent-1-yn-3-yl)-3-azabicyclo[3.1.0]hexane-2-carboxamide,
benzyl ((2*S*)-4-methyl-1-(((3*S*)-5-(methylsulfinyl)pent-1-yn-3-yl)amino)-1-oxopentan-2-yl)carbamate,
4-methoxy-*N*-((2*S*)-4-methyl-1-(((3*S*)-5-(methylsulfinyl)pent-1-yn-3-yl)amino)-1-oxopentan-2-yl)-1*H*-indole-2-carboxamide,
N-((2*S*)-3-cyclohexyl-1-(((3*S*)-5-(methylsulfinyl)pent-1-yn-3-yl)amino)-1-oxopropan-2-yl)-1*H*-indole-2-carboxamide,
N-((2*S*)-1-(((3*S*)-5-(methylsulfinyl)pent-1-yn-3-yl)amino)-1-oxo-3-phenylpropan-2-yl)-1*H*-indole-2-carboxamide,
benzyl ((2*S*)-3-methyl-1-(((2*S*)-4-methyl-1-(((3*S*)-5-(methylsulfinyl)pent-1-yn-3-yl)amino)-1-oxopentan-2-yl)amino)-1-oxobutan-2-yl)carbamate,
(1*R*,2*S*,5*S*)-3-((*S*)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-6,6-dimethyl-*N*-((*S*)-5-(methylsulfonyl)pent-1-yn-3-yl)-3-azabicyclo[3.1.0]hexane-2-carboxamide,
benzyl ((*S*)-4-methyl-1-(((*S*)-5-(methylsulfonyl)pent-1-yn-3-yl)amino)-1-oxopentan-2-yl)carbamate,
4-methoxy-*N*-((*S*)-4-methyl-1-(((*S*)-5-(methylsulfonyl)pent-1-yn-3-yl)amino)-1-oxopentan-2-yl)-1*H*-indole-2-carboxamide,
N-((*S*)-3-cyclohexyl-1-(((*S*)-5-(methylsulfonyl)pent-1-yn-3-yl)amino)-1-oxopropan-2-yl)-1*H*-indole-2-carboxamide,
N-((*S*)-1-(((*S*)-5-(methylsulfonyl)pent-1-yn-3-yl)amino)-1-oxo-3-phenylpropan-2-yl)-1*H*-indole-2-carboxamide,
benzyl ((*S*)-3-methyl-1-(((*S*)-4-methyl-1-(((*S*)-5-(methylsulfonyl)pent-1-yn-3-yl)amino)-1-oxopentan-2-yl)amino)-1-oxobutan-2-yl)carbamate,
(1*R*,2*S*,5*S*)-*N*-((*S*)-1-cyclobutylbut-3-yn-2-yl)-3-((*S*)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide,

benzyl ((*S*)-1-(((*S*)-1-cyclobutylbut-3-yn-2-yl)amino)-4-methyl-1-oxopentan-2-yl)carbamate,

N-((*S*)-1-(((*S*)-1-cyclobutylbut-3-yn-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-4-methoxy-1*H*-indole-2-carboxamide,

N-((*S*)-1-(((*S*)-1-cyclobutylbut-3-yn-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)-1*H*-indole-2-carboxamide,

N-((*S*)-1-(((*S*)-1-cyclobutylbut-3-yn-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)-1*H*-indole-2-carboxamide,

benzyl ((*S*)-1-(((*S*)-1-(((*S*)-1-cyclobutylbut-3-yn-2-yl)amino)-4-methyl-1-oxopentan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate,

N-((3*S*,6*R*)-6-(4-fluorobenzyl)-2-methyl-4,7-dioxo-7-(((*S*)-1-((*S*)-2-oxopyrrolidin-3-yl)but-3-yn-2-yl)amino)heptan-3-yl)-5-methylisoxazole-3-carboxamide,

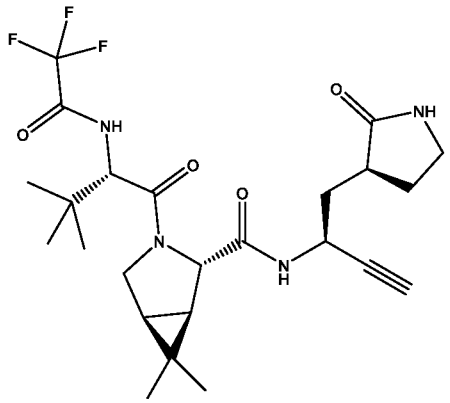
2-(3-chlorophenyl)-2-methylpropyl ((*S*)-3-cyclohexyl-1-oxo-1-(((*S*)-1-((*S*)-2-oxopyrrolidin-3-yl)but-3-yn-2-yl)amino)propan-2-yl)carbamate;

tert-butyl (1-((*S*)-3-cyclopropyl-1-oxo-1-(((*S*)-1-((*S*)-2-oxopyrrolidin-3-yl)but-3-yn-2-yl)amino)propan-2-yl)-2-oxo-1,2-dihydropyridin-3-yl)carbamate;

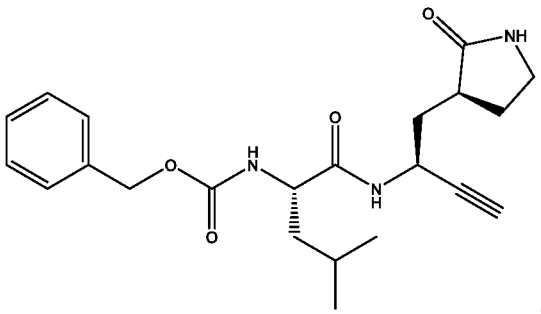
and the pharmaceutically acceptable salts, esters and solvates thereof.

The IUPAC names proposed herein for the compounds (and intermediates) of the invention were generated using Chemdraw, level: Professional, version 20.0.0.38 (PerkinElmer Informatics, Inc., Waltham, Massachusetts, United States). To the extent that the generated IUPAC names and the structures provided herein do not fully correspond, the structures are correct and leading.

In preferred embodiments, the compound of formula I is compound selected from the group consisting of



and



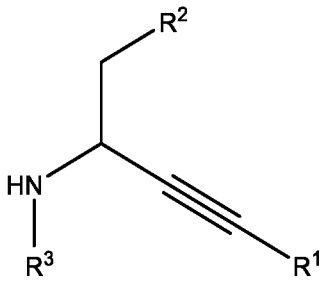
,

and pharmaceutically acceptable salts, solvates and hydrates thereof.

The term "pharmaceutically acceptable" as used herein has its conventional meaning and refers to compounds, material, compositions and/or dosage forms, which are, within the scope of sound medical judgment suitable for contact with the tissues of mammals, especially humans, without excessive toxicity, irritation, allergic response and other problem complications commensurate with a reasonable benefit/risk ratio. Suitable examples of pharmaceutically acceptable salts of the compounds of the present invention include the acid addition salts formed with inorganic acids (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like), as well as salts formed with organic acids such as acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, fumaric acid, maleic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalene sulfonic acid, naphthalene disulfonic acid, methane sulfonic acid, p-toluene sulfonic acid and polygalacturonic acid.

In a second aspect, the invention concerns a method for preparing a compound as defined herein, said method comprising the steps of:

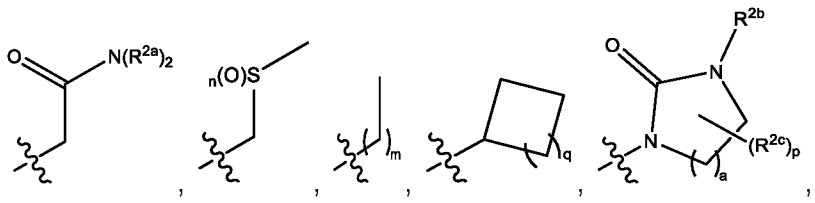
a) providing a first compound according to formula (X)

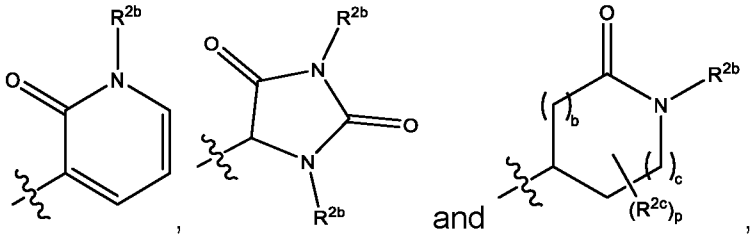


(X)

wherein R^1 is selected from the group consisting of hydrogen, methyl optionally substituted with one to three halo, phenyl optionally substituted with one to five halo.

R^2 is selected from the group consisting of:





wherein each R^{2a} is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl;

wherein each R^{2b} is independently selected from the group consisting of hydrogen, halo, hydroxy, trifluoromethyl, C_1-C_6 alkyl-C(O)-, C_1-C_6 alkyl-OC(O)- and C_1-C_6 alkoxy

Wherein each R^{2c} is independently selected from the group consisting of hydrogen, halo, hydroxy, oxo, trifluoromethyl, C_1-C_6 alkyl ; C_1-C_6 alkoxy

wherein n, a, b and c are at each occurrence independently selected from 0, 1 and 2;

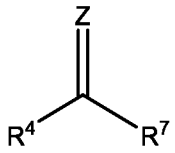
wherein q is at each occurrence independently selected from 0, 1, 2, 3 and 4;

wherein p is at each occurrence independently selected from 0, 1, 2 and 3;

wherein m is at each occurrence independently selected from 0 to 5;

R^3 is selected from the group consisting of hydrogen and methyl;

b) providing a second compound according to formula (Y)



(Y)

wherein Z is either a oxygen or a sulphur atom;

R^7 is selected from the group consisting of hydroxy, halo and carboxylate

R^4 is selected from the group consisting of C_1-C_8 alkyl, C_3-C_{12} cycloalkyl, 4- to 12-membered heterocycloalkyl, C_6-C_{10} aryl and 5- to 10-membered heteroaryl;

wherein each R4 group is optionally substituted with one to two R^{4a};

or R^3 and R^4, taken together with the nitrogen and carbon atoms to which they are attached, form a 4- to 12-membered heterocycloalkyl or a 5- to 10-membered heteroaryl, which can be optionally substituted with one to two R^{4a};

R^{4a} is at each occurrence independently selected from the group consisting of R^{4b}, R^{4b}-O-, R^{4b}-NH-, $(R^{4b})_2$-N-, R^{4b}-C(O)NH- and R^{4b}-OC(O)NH-;

Wherein each R^{4b} is at each occurrence independently selected from the group consisting of C_1-C_8 alkyl, C_3-C_{12} cycloalkyl, 4- to 12-membered heterocycloalkyl, C_6-C_{10} aryl and 5- to 10-membered heteroaryl;

wherein each R^{4b} group is optionally substituted with one to two R^{4c};

R^{4c} is at each occurrence independently selected from the group consisting of R^{4d}, R^{4d}-O-, R^{4d}-NH-, $(R^{4d})_2$-N-, R^{4d}-C(O)NH- and R^{4d}-OC(O)NH-;

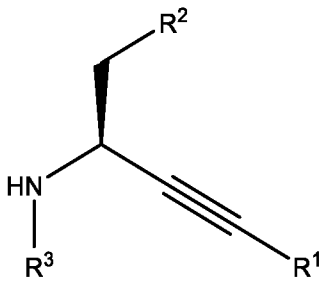
Wherein each R^{4d} is at each occurrence is independently selected from the group consisting of C_1-C_8 alkyl, C_3-C_{12} cycloalkyl, 4- to 12-membered heterocycloalkyl, C_6-C_{10} aryl and 5- to 10-membered heteroaryl;

wherein each R^4, R^{4b} and R^{4d} is optionally substituted with one to five substituents at each occurrence independently selected from the group consisting of methyl, halo, hydroxy, oxo, imino and sulfanylidene.

c) reacting said first compound with said second compound under conditions that result in the formation of a compound of the invention.

In the above formulae (Y), R^7 preferably represents hydroxy, iodo, bromo, chloro or fluoro, most preferably hydroxy.

In preferred embodiments, more than 60 mol%, more than 80 mol%, more than 90 mol%, more than 95 mol%, more than 97 mol%, more than 98.5 mol%, more than 99 mol% of the compound of formula (X) provided in step a) is a compound with absolute configuration as represented by formula (Xa).



(Xa)

In preferred embodiments the reaction is performed in a suitable solvent, such as a chloroalkane, e.g. dichloromethane.

In preferred embodiments the reaction is performed at a suitable temperature, e.g. at room temperature.

In preferred embodiments the reaction is performed in the presence of a base, preferably a sterically hindered base, more preferably a sterically hindered amine base, such as triethylamine or N,N-Diisopropylethylamine, preferably N,N-Diisopropylethylamine.

In preferred embodiments, the reaction is performed in the presence of one or more coupling reagents, such as hydroxybenzotriazole, 6-Chloro-1-hydroxybenzotriazole, 1-Hydroxy-7-azabenzotriazole, N,N-Diisopropylethylamine, N,N′-Dicyclohexylcarbodiimide or 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide, (Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate, (Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate, (7-Azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate, Bromotripyrrolidinophosphonium hexafluorophosphate, Bis(2-oxo-3-oxazolidinyl)phosphinic chloride, preferably hydroxybenzotriazole and 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide.

In preferred embodiments, the reaction is performed in the presence of one or more racemization supressing agents, such as such as hydroxybenzotriazole, 6-Chloro-1-hydroxybenzotriazole, 1-Hydroxy-7-azabenzotriazole, (Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate, (Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate, (7-Azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate, Bromotripyrrolidinophosphonium hexafluorophosphate, Bis(2-oxo-3-oxazolidinyl)phosphinic chloride, preferably hydroxybenzotriazole.

In a third aspect, the invention concerns pharmaceutical composition comprising a compound of the invention and a pharmaceutically acceptable carrier or diluent.

In preferred embodiments the pharmaceutical composition is provided in a unit dosage form suitable for oral administration, preferably in the form of a tablet or capsule.

Another aspect of the invention concerns a method of treating infection by a virus expressing Main Protease (Mpro) and/or treating or preventing a disease or condition caused by infection by a virus expressing Main Protease (Mpro), in a subject in need thereof, the method comprising administering to said subject a therapeutically effective amount of a compound or a pharmaceutical composition of the invention.

Another aspect of the invention concerns a method of inhibiting or preventing replication of a virus expressing Main Protease (M^{pro}), the method comprising contacting the viruses with an inhibitory amount of a compound according to the invention.

Another aspect of the invention concerns the use of a compound according to the invention, in a method of treating infection by a virus expressing Main Protease (M^{pro}) and/or treating or preventing a disease or condition caused by infection by a virus expressing Main Protease (M^{pro}), in a subject in need thereof.

Another aspect of the invention concerns the use of a compound according to the invention, in the manufacture of a medicament for treating infection by a virus expressing Main Protease (M^{pro}) and/or treating or preventing a disease or condition caused by infection by a virus expressing Main Protease (M^{pro}), in a subject in need thereof.

The terms "treat", "treating" or "treatment", when used in conjunction with a specific disease or symptom (for example: “method of treating disease …”) refers to curing, alleviating or abrogating said disease and/or accompanying symptoms, diminishing extent of disease, stabilizing (i.e. not worsening) the state of disease, delaying or slowing of disease progression, ameliorating the disease state, prolonging survival (as compared to expected survival without treatment), etc. The terms "prevent", "preventing" or "prevention", as used herein, refer to reducing the risk for a subject to acquire a disease and/or accompanying symptoms, delaying the moment a subject acquires disease, etc. The terms “treat”, “treating” or “treatment”, when used in relation to a patient or subject (for example: “method of treating a subject”), typically refers to the act of administering a therapeutic compound to said patient or subject for whatever therapeutic and/or prophylactic purpose.

The term ‘main protease’, abbreviated by M^{Pro}, as used herein relates to an enzyme that is essential for the replication and transcription function of viruses expressing Main Protease (M^{pro}), such as coronavirus. Alterative names for M^{Pro} include 3C-like protease, 3CL or $3CL^{pro}$.

In preferred embodiments, the viral infection is infection with a coronavirus, preferably a coronavirus selected from the group consisting of HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, MERS-CoV, SARS-CoV, and SARS-CoV-2.

In preferred embodiments, the disease or condition caused by a viral infection is a respiratory illness, such as acute respiratory distress syndrome (ARDS), Middle East respiratory syndrome (MERS) and COVID-19.

The term a "therapeutically effective amount", "effective amount" or a "sufficient amount" of a compound of the present invention is a quantity sufficient to, when administered to the subject, including a mammal, for example a human, effect beneficial or desired results, including clinical results, and, as such, an "effective amount" or synonym thereto depends upon the context in which it is being applied. In the context of disease, therapeutically effective amounts of the compounds of the present invention are used to treat, modulate, attenuate, reverse, or effect viral infection in a mammal. An "effective amount" is intended to mean that amount of a compound that is sufficient to treat, prevent or inhibit viral infections and/or diseases associated with such viral infections.

It is to be understood that many or most of the pharmacologically and/or physiologically active ingredients contained in the compositions as defined herein can exist in the form of a pharmaceutically acceptable salt or solvate. Such forms will typically be equally suitable for use in the present invention although, is as immediately apparent to those skilled in the art, the amount of such a salt, hydrate or solvate to be administered and/or to be incorporated into a unit dose form needs to be adjusted to take account of the molecular weight difference between the free base and salt form.

Unless otherwise defined, all terms used in disclosing the invention, including technical and scientific terms, have the meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. By means of further guidance, term definitions are included to better appreciate the teaching of the present invention.

"A", "an", and "the" as used herein refer to both singular and plural forms unless the context clearly dictates otherwise. By way of example, "a compartment" refers to one or more than one compartment.

"About" as used herein referring to a measurable value such as a parameter, an amount, a temporal duration, and the like, is meant to encompass variations of +/- 10% or less, more preferably +/-5% or less, even more preferably +/-1% or less of and from the specified value, in so far such variations are appropriate to perform in the disclosed invention. However, it is to be understood that the value to which the modifier "about" refers is itself also specifically disclosed.

"Comprise", "comprising", "comprises" and "comprised of" as used herein are synonymous with "include", "including", "includes" or "contain", "containing", "contains" and are inclusive or open-ended terms that specify the presence of what follows, e.g. a component, and do not exclude or preclude the presence of additional, non-recited components, features, element, members, steps, known in the art or disclosed therein.

The recitation of numerical ranges by endpoints includes all numbers and fractions subsumed within that range, as well as the recited endpoints. The skilled person will appreciate that the present invention can incorporate any number of the specific features described above.

DESCRIPTION OF THE FIGURES

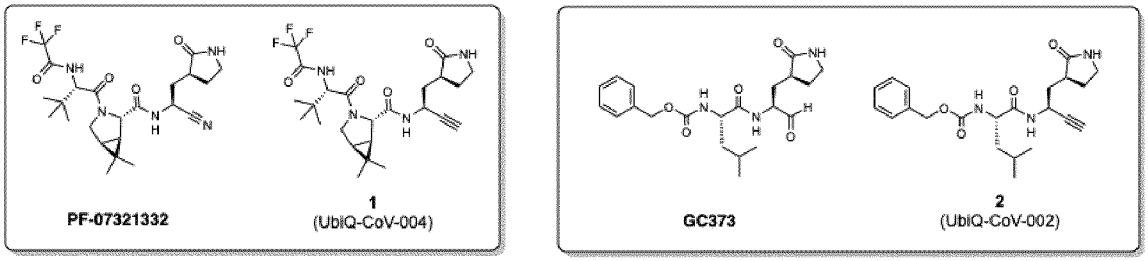
Figure 1 depicts the antiviral activity against SARS-CoV-2 of UbiQ-CoV-002 compared to control compound GC376 and of UbiQ-CoV-004 compared to control compound PF-07321332.

Figure 2 depicts the antiviral activity against MERS-CoV of UbiQ-CoV-004 compared to control compound PF-07321332.

EXAMPLES

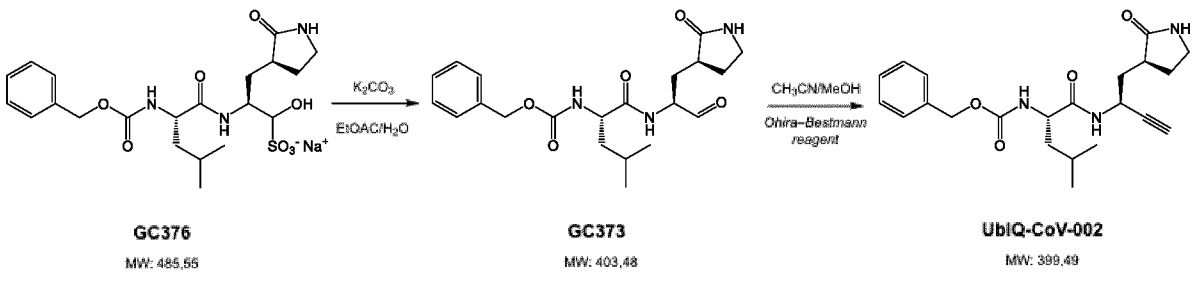
General

The concept of this invention was demonstrated by selecting two potent and representative M^{pro} inhibitors, PF-07321332 (Owen et al. Science 2021, 374, 1586) and GC373 (Kim et al. J. Virol. 2012, 86, 11754), (Kim et al. PLoS Pathog. 2016, 12, e1005531), (Pedersen et al. J. Feline Med. Surg. 2018, 20, 378) and comparing them with their alkyne based variants according to the invention, denominated UbiQ-CoV-004 and UbiQ-CoV-002, respectively. Results were generated and described for UbiQ-CoV-002 and UbiQ-CoV-004 (against their prior art counterparts) in a cytopathic effect reduction assay with SARS-CoV-2, and for UbiQ-CoV-004 (against its prior art counterpart) in a cytopathic effect reduction assay with MERS-CoV.



General reagents were used as received. Solvents were purchased from Biosolve or Aldrich. Peptide synthesis reagents were purchased from Novabiochem or ChemImpex. Analytical thin layer chromatography was performed on aluminium sheets precoated with silica gel 60 F254. Staining with ninhydrin (3 gr in 100 mL ethanol) and heating on a stirrer plate (±120°C), or $KMnO_4$ (3 gr $KMnO_4$, 20 g K_2CO_3 and 5 mL 5% aqueous NaOH in 300 mL H_2O). Column chromatography was carried out on silica gel (0.035-0.070 mm, 90Å). LC-MS measurements were performed on a Micromass LCT Premier (Waters) equipped with a 2795 separation module (Alliance HT). Mobile phases: A= 1% CH_3CN, 0.1% formic acid in milliQ water. B= 1% milliQ water and 0.1% formic acid in CH_3CN. Column: XBridge BEH300 C18 3.5 µm 4.6x100mm. column T= 40°C; flow= 0.8 mL/min. Gradient: 30-80%B over 6.5 min. Data processing was performed using Waters MassLynx Mass Spectrometry Software 4.1.

Example 1 – Synthesis of benzyl ((S)-4-methyl-1-oxo-1-(((S)-1-((S)-2-oxopyrrolidin-3-yl)but-3-yn-2-yl)amino)pentan-2-yl)carbamate (UbiQ-CoV-002) (Scheme 1).



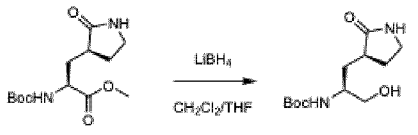
Scheme 1.

GC-376 was obtained according to the method previously described by Kim et al. (J. Virol. 2012, 86, 11754). To a solution of potassium carbonate (0.3 g, 2.1 mmol)

in water (5 mL) was added GC-376 (225 mg, 0.44 mmol, Ambeed A1003140, CAS nr. 1416992-39-6) and ethyl acetate (5 mL). After stirring the mixture at 20°C for 2 h, the organic phase was separated and dried with sodium sulfate. Aldehyde GC-373 was obtained as an oil after evaporation of ethyl acetate. Next, Ohira-Bestmann reagent (dimethyl (1-diazo-2-oxopropyl)phosphonate, 84 µL, 0.53 mmol) was dissolved in CH_3CN (5 mL) and potassium carbonate (146 mg, 1.06 mmol) was added. After stirring this suspension at room temperature for 10 minutes, the crude GC-373 (0.44 mmol) was dissolved in methanol (2 mL) and added to the reaction mixture. After stirring overnight, analysis by TLC and LC-MS showed complete consumption of starting material and formation of UbiQ-CoV-002 (Rf in CH2Cl2/methanol 95/5: 0.5). Solvents were removed in vacuo and the residue was dissolved in a 1:1 mixture of ethyl acetate/water. After separating the organic and aqueous layer, the organic layer was washed with water and Brine, and dried with sodium sulfate. Purification by silica gel chromatography (0 - 3% methanol in CH_2Cl_2) afforded UbiQ-CoV-002 (135 mg, 0.34 mmol, 77%) as an oil. When carefully subjected to high vacuum, the oil formed a glassy foam, allowing isolation of the product as a powder. LC-MS (ESI+): m/z 399.9 $[M-H]^+$, 421.9 $[M-Na]^+$. 1H NMR (300 MHz, $CDCl_3$) δ 7.55 (1H, d, *J*= 9 Hz), 7.26 (5H, m), 6.58 (1H, s), 5.66 (1H, d, *J*= 9 Hz), 5.03 (2H, s), 4.72–4.61 (1H, m), 4.20–4.28 (1H, m), 3.27–3.14 (2H, m), 2.38–2.17 (4H, m), 1.79–1.41 (5H, m), 0.86 (6H, m).

Example 2 – Synthesis of ((1R,2S,5S)-3-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-6,6-dimethyl-N-((S)-1-((S)-2-oxopyrrolidin-3-yl)but-3-yn-2-yl)-3-azabicyclo[3.1.0]hexane-2-carboxamide) (UbiQ-CoV-004)

Example 2.1 – synthesis of alcohol 2 from methyl ester 1 (Scheme 2).

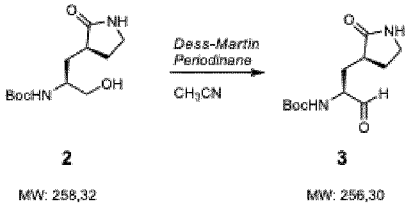


1 MW: 286,33 2 MW: 258,32

Scheme 2.

Methyl ester 1 ((S)-Methyl 2-((tert-butoxycarbonyl)amino)-3-((S)-2-oxopyrrolidin-3-yl)propanoate, CAS nr. 328086-60-8, 10 g, 35 mmol, Rf= 0.3 in CH_2Cl_2/methanol 95/5) was dissolved in CH_2Cl_2 (120 mL) and cooled in an ice-bath. Next, 50 mmol $LiBH_4$ (25 mL of a 2M solution in THF) was added slowly. The reaction mixture was allowed to warm to room temperature and stirring was continued for 2 hrs, upon which analysis by TLC and LC-MS showed completion. The reaction was quenched by slow addition of 200 mL of a saturated aqueous NH_4Cl solution. The CH_2Cl_2 layer was separated, dried over sodium sulfate and concentrated under reduced pressure. Purification by silica gel chromatography (petroleum ether 40-60/ethyl acetate 1/1→ ethyl acetate→ ethyl acetate/methanol 95/5 → 90/10) afforded Alcohol 2 (*tert*-butyl ((*S*)-1-hydroxy-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamate) as a white powder. Rf in CH_2Cl_2/methanol 95/5: ±0.15. Yield: 4.0 gr, 15.5 mmol, 44%. LC-MS (ESI+): m/z 281 $[M-Na]^+$, 539 $[M-M-Na]^+$.

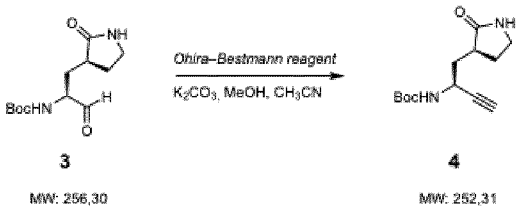
Example 2.2 – synthesis of aldehyde 3 from alcohol 2 (Scheme 3).



Scheme 3.

Under a blanket of N_2, 50 mL CH_3CN was added to Alcohol 2 (2.18 gr, 8.45 mmol) and the mixture was cooled in an ice-bath. Next, Dess-Martin periodinane (1,1,1-Tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1H)-one, CAS nr. 87413-09-0, 1.5 equiv, 12.7 mmol, 5.4 gr) was added and the reaction mixture was allowed to warm to room temperature (under a blanket of N_2). The reaction mixture was then allowed to stir for 3 hrs, after which TLC analysis showed completion. Reaction mixture was then quenched with 10% $Na_2S_2O_3$ followed with stirring for 15 min. The layers were separated and the CH_2Cl_2 layer was washed with 10% $Na_2S_2O_3$, saturated $NaHCO_3$, water and Brine. The CH_2Cl_2 layer was dried over sodium sulfate and concentrated to furnish Aldehyde 3 (*tert*-butyl ((*S*)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamate) as a yellowish foam, Rf in CH_2Cl_2/methanol 95/5: ±0.3. Crude yield: 1.0 gr, 3.90 mmol, 46%. LC-MS (ESI+): m/z 279 $[M-Na]^+$, 297 $[M-Na]^+$-hydrate.

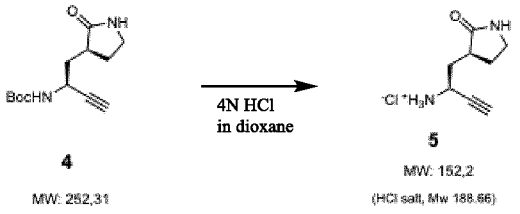
Example 2.3 – synthesis of Alkyne 4 from Aldehyde 3 (Scheme 4).



Scheme 4.

To a solution of Ohira-Bestmann reagent (dimethyl (1-diazo-2-oxopropyl)phosphonate, 1.65 mL, 10.3 mmol) in CH_3CN (100 mL) was added potassium carbonate (2.9 gr, 2.3 mmol). After the suspension was stirred at room temperature for 10 minutes, a solution of crude Aldehyde 3 (8.6 mmol) in methanol (40 mL) was added. After stirring overnight, the solvents were removed in vacuo and the residue was dissolved in a 1:1 mixture of ethyl acetate/water. The organic and aqueous layer were separated and the organic layer was washed with water and dried with sodium sulfate. The organic layer was dried under high vacuum affording crude Alkyne 4 (*tert*-butyl ((*S*)-1-((*S*)-2-oxopyrrolidin-3-yl)but-3-yn-2-yl)carbamate) as a white foam (crude yield: 1.8 gr, 7.1 mmol, 83%). LC-MS (ESI+): m/z 275 $[M\text{-}Na]^+$, 527 $[M\text{-}M\text{-}Na]^+$.

Example 2.4 – deprotection of Alkyne 4 to form alkyne amine 5 (Scheme 5).

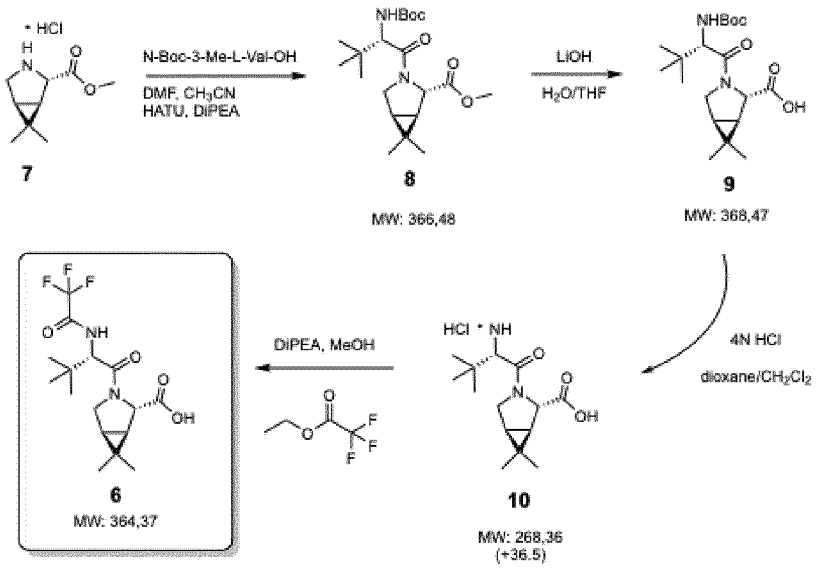


Scheme 5.

The crude of Alkyne 4 was dissolved in 20 mL 4N HCl in dioxane and stirred at room temperature for 2 hrs, when analysis by TLC showed completion. 20 mL CH_2Cl_2 and 20 mL methanol were added and the solvents were removed in vacuo. Crude yield

alkyne amine 5 ((*S*)-3-((*S*)-2-aminobut-3-yn-1-yl)pyrrolidin-2-one, HCl salt): 1.50 gr, 8.0 mmol, 92%. Rf= 0.25 in ethyl acetate/methanol/acetic acid 80/20/1.

Example 2.5 – synthesis of building block 6 (Scheme 6).



Scheme 6.

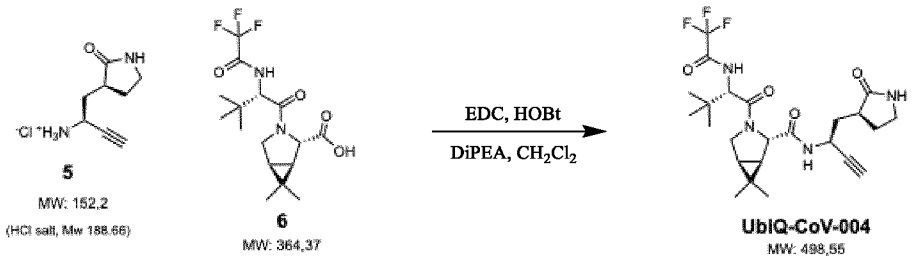
Methyl (1R,2S,5S)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylate, HCl salt (compound 7, CAS nr. 565456-77-1, 5.00 g, 24.3 mmol) and N-tert-butoxycarbonyl-L-tert-leucine (CAS nr. 62965-35-9, 6.18 g, 26.7 mmol) were dissolved N,N-dimethylformamide (10 mL) and acetonitrile (90 mL). After cooling this solution in an ice-bath, 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU, CAS nr. 148893-10-1, 10.2 g, 26.7 mmol) was added, followed by N,N-diisopropylethylamine (DiPEA, 12.7 mL, 72.9 mmol). The reaction mixture was allowed to warm to room temperature and stirred overnight. TLC analysis showed complete consumption of compound 7, where upon it was concentrated *in vacuo*. The resulting residue was dissolved in ethyl acetate (200 mL) and washed with water (200 mL). The separated aqueous layer was extracted with ethyl acetate (2 x 100 mL). The combined organic phases were washed with water (100 mL), 1N HCl (100 mL), Brine (100 mL), dried over sodium sulfate, filtered and concentrated. Purification by silica gel chromatography (30-50% ethyl acetate in petroleum ether 40-60) afforded compound 8 (Methyl (1R,2S,5S)-3-[N-(tert-

butoxycarbonyl)-3-methyl-L-valyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylate) as a colorless oil. Yield: 9.4 g, 24.3 mmol, >99%. LC-MS (ESI+): m/z 405 $[M+Na]^+$.

Next, to a solution of compound 8 (9.4 g, 24 mmol) in tetrahydrofuran (24 mL) was added LiOH monohydrate (3 g, 72 mmol) and 5 mL water. After the reaction mixture had been stirred at room temperature for 2 h, TLC analysis (CH_2Cl_2/methanol 95/5) showed complete consumption of compound 8. Most of the tetrahydrofuran was removed in vacuo and the residue adjusted with 1N HCl to pH ±2. The resulting mixture was extracted with ethyl acetate (2 x 150 mL) and the combined organic layers were washed with Brine (500 mL), dried over sodium sulfate, filtered and concentrated to provide compound 9 ((1R,2S,5S)-3-[N-(tert-Butoxycarbonyl)-3-methyl-L-valyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylic acid) as a white solid (8.6 gr, 23.3 mmol, 96%). LC-MS (ESI+): m/z 369 $[M+H]^+$, m/z 391 $[M+Na]^+$.

Next, a solution of 4N HCl in 1,4-dioxane (10 mL) was added to a solution of compound 9 (2.0 g, 5.4 mmol) in CH_2Cl_2 (10 mL) and the reaction mixture was stirred overnight at room temperature. TLC analysis showed complete consumption of compound 9. Removal of solvents afforded Compound 10 ((1R,2S,5S)-6,6-Dimethyl-3-(3-methyl-L-valyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid, HCl salt) as a white solid that was used directly in the following step. LC-MS (ESI+): m/z 269 $[M+H]^+$. To a solution of compound 10 (5.4 mmol) in methanol (10 mL) is added triethylamine (1.0 mL, 8.7 mmol) and ethyl trifluoroacetate (2.8 mL, 20 mmol). The reaction mixture was stirred for 4 hrs at 50°C and overnight at room temperature. TLC analysis (CH_2Cl_2/methanol 90/10) showed starting material; additional triethylamine (1.4 mL, 8.7 mmol) and ethyl trifluoroacetate (0.6 mL, 5.4 mmol) were added and the reaction mixture was stirred for 4 hrs at 50°C and overnight at room temperature. The reaction mixture was concentrated *in vacuo* at 50°C and the residue diluted with water (25 mL). After adding 1N HCl (25 mL), a white precipitate was formed. Upon adding ethyl acetate (200 mL), the solid dissolved in the organic layer. This was washed with Brine (200 mL), dried over sodium sulfate, filtered, and concentrated to afford Building Block 6 ((1R,2S,5S)-6,6-Dimethyl-3-[3-methyl-N-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxylic acid) as a white solid (1.7 gr, 4.7 mmol, crude yield= 86%). Rf= 0.15 in ethyl acetate/methanol/acetic acid 80/20/1. LC-MS (ESI+): m/z 365 $[M+H]^+$.

Example 2.6 – synthesis of UbiQ-CoV-004 from Building Block 6 and alkyne amine 5 (Scheme 7).



Scheme 7.

Amino alkyne 5 (0.45 gr, 2.4 mmol) and building block 6 (1.04 gr, 2.88 mmol) were dissolved in 50 mL CH_2Cl_2 followed by addition of Hydroxybenzotriazole (HOBt, 0.48 mmol, 63 mg), N,N-diispropylethylamine (DiPEA, 7.2 mmol, 1.25 mL) and 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide·HCl (EDC, 0.45 gr, 2.88 mmol). After stirring overnight at room temperature, TLC analysis with $KMnO_4$ staining showed complete consumption of 5. The reaction mixture was washed with 1N $KHSO_4$ and the CH_2Cl_2 layer dried with sodium sulfate. Purification by silica gel chromatography (petroleum ether 40-60/ethyl acetate 1/1 → ethyl acetate) afforded UbiQ-CoV-004 ((1*R*,2*S*,5*S*)-3-((*S*)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-6,6-dimethyl-*N*-((*S*)-1-((*S*)-2-oxopyrrolidin-3-yl)but-3-yn-2-yl)-3-azabicyclo[3.1.0]hexane-2-carboxamide) as an oil. Rf= 0.5 in ethyl acetate. When carefully subjected to high vacuum, the oil formed a glassy foam, allowing isolation of the product as a powder. Yield: 684 mg, 1.37 mmol, 57%. LC-MS (ESI+): m/z 499 $[M-H]^+$, 521 $[M-Na]^+$. 1H NMR (300 MHz, DMSO-*d*6) δ 9.39 (1H, d, *J*= 6 Hz), 8.58 (1H, d, *J*= 9 Hz), 7.54 (1H, s), 4.68 (1H, m), 4.41 (1H, d, *J*= 8.4 Hz), 4.15 (1H, s), 3.91 (1H, dd, *J*= 10.3 and 5.3 Hz), 3.69 (1H, d, *J*= 10.3 Hz), 3.21 (1H, d, *J*= 2.3 Hz), 3.11 (1H, t, *J*= 8.9 and 9.2 Hz), 3.00 (2H, m), 2.36 (1H, m), 2.02–2.16 (2H, m), 1,65–1.44 (3H, m), 1.25 (1H, d, *J*= 7.8 Hz), 1.03 (s, 3H), 0.98 (s, 9H), 0.85 (s, 3H).

Example 3 - Evaluation of inhibitory potency in cytopathic effect reduction assay with SARS-CoV-2

Starting with a 20 mM DMSO stock of compound, a 2-fold serial dilution was made starting with 3 µM in EMEM + 2% FCS containing 0.38 µM of the P-Gp inhibitor

CP-100356 (at this stage all compounds are concentrated 1.5 times). Next, 100 µl of the compound dilutions were added to wells from a 96 wells cluster containing 1.0E+4 VeroE6 cells. To the wells 150 PFU SARS-CoV-2 L0002 strain (Wuhan strain) in 50 µL EMEM + 2% FCS or only medium was added. After incubating the plates for 4 days at 37°C, MTS reagent was added and the plates were incubated further at 37°C. Absorption was measured using Envion multiplate reader at a wavelength of 495 nm. Percentage viable cells were calculated against untreated/no compound control. The EC50 was calculated using GraphPad. All points are done in 4-fold.

The results of this test are represented in figure 1, which reveals that both UbiQ-CoV-002 (EC50= 1.0 µM) and UbiQ-CoV-004 (EC50= 832 nM) show potent inhibition of SARS-CoV-2.

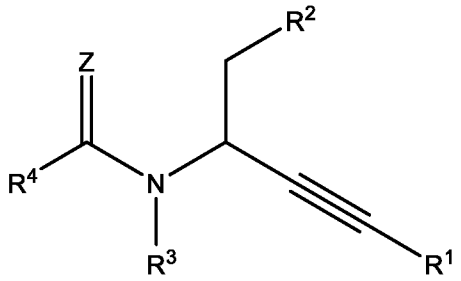
Example 4 Evaluation of inhibitory potency in cytopathic effect reduction assay with MERS-CoV-2

Starting with a 20 mM DMSO stock of compound, a 2-fold serial dilution was made starting with 3 µM in EMEM + 2% FCS (at this stage all compounds are concentrated 1.5 times). Next, 100 µl of the compound dilutions were added to wells from a 96 wells cluster containing 1.5E+4 Huh7 cells. To the wells 225 PFU MERS-CoV N3 Jordan strain in 50 µL EMEM + 2% FCS or only medium was added. Plates were incubated for 2 days at 37°C. Next, MTS reagent was added and the plates were incubated further at 37°C. Absorption was measured using Envion multiplate reader at a wavelength of 495 nm. Percentage viable cells were calculated against untreated/no compound control. The EC50 was calculated using GraphPad. All points are done in 4-fold.

The results of this test are represented in figure 2, which reveals that UbiQ-CoV-004 shows potent inhibition of MERS-CoV (EC50= 566 nM).

Claims

1. A compound of formula I



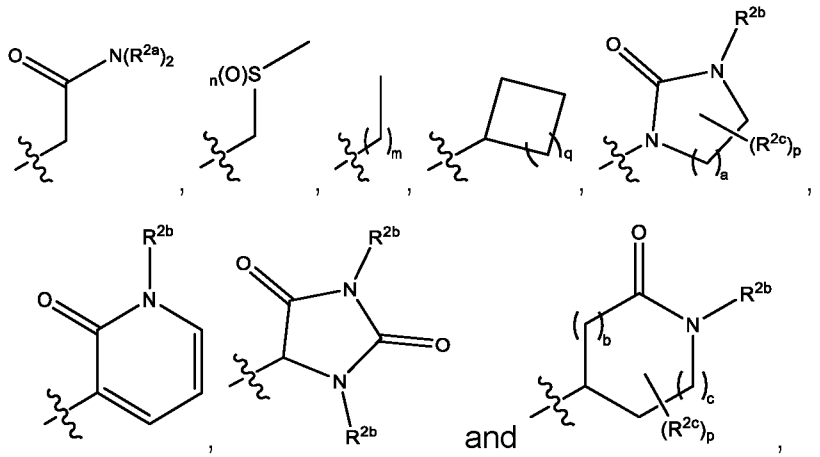
I

or a pharmaceutically acceptable salt, solvate and/or hydrate thereof, wherein:

Z is either a oxygen or a sulphur atom;

R^1 is selected from the group consisting of hydrogen, methyl optionally substituted with one to three halo, phenyl optionally substituted with one to five halo.

R^2 is selected from the group consisting of:



wherein each R^{2a} is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl;

wherein each R^{2b} is independently selected from the group consisting of hydrogen, halo, hydroxy, trifluoromethyl, C_1-C_6 alkyl-C(O)-, C_1-C_6 alkyl-OC(O)- and C_1-C_6 alkoxy

Wherein each R^{2c} is independently selected from the group consisting of hydrogen, halo, hydroxy, oxo, trifluoromethyl, C_1-C_6 alkyl ; C_1-C_6 alkoxy

wherein n, a, b and c are at each occurrence independently selected from 0, 1 and 2;

wherein q is at each occurrence independently selected from 0, 1, 2, 3 and 4;

wherein p is at each occurrence independently selected from 0, 1, 2 and 3;

wherein m is at each occurrence independently selected from 0 to 5;

R^3 is selected from the group consisting of hydrogen and methyl;

R^4 is selected from the group consisting of C_1-C_8 alkyl, C_3-C_{12} cycloalkyl, 4- to 12-membered heterocycloalkyl, C_6-C_{10} aryl and 5- to 10-membered heteroaryl;

wherein each R4 group is optionally substituted with one to two R^{4a};

or R^3 and R^4, taken together with the nitrogen and carbon atoms to which they are attached, form a 4- to 12-membered heterocycloalkyl or a 5- to 10-membered heteroaryl, which can be optionally substituted with one to two R^{4a};

R^{4a} is at each occurrence independently selected from the group consisting of R^{4b}, R^{4b}-O-, R^{4b}-NH-, $(R^{4b})_2$-N-, R^{4b}-C(O)NH- and R^{4b}-OC(O)NH-;

Wherein each R^{4b} is at each occurrence independently selected from the group consisting of C_1-C_8 alkyl, C_3-C_{12} cycloalkyl, 4- to 12-membered heterocycloalkyl, C_6-C_{10} aryl and 5- to 10-membered heteroaryl;

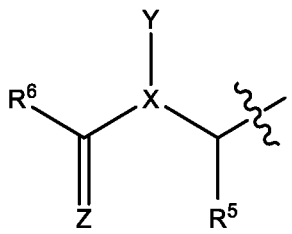
wherein each R^{4b} group is optionally substituted with one to two R^{4c};

R^{4c} is at each occurrence independently selected from the group consisting of R^{4d}, R^{4d}-O-, R^{4d}-NH-, $(R^{4d})_2$-N-, R^{4d}-C(O)NH- and R^{4d}-OC(O)NH-;

Wherein each R^{4d} is at each occurrence is independently selected from the group consisting of C_1-C_8 alkyl, C_3-C_{12} cycloalkyl, 4- to 12-membered heterocycloalkyl, C_6-C_{10} aryl and 5- to 10-membered heteroaryl;

wherein each R^4, R^{4b} and R^{4d} is optionally substituted with one to five substituents at each occurrence independently selected from the group consisting of methyl, halo, hydroxy, oxo, imino and sulfanylidene.

2. A compound according to claim 1, wherein R^4 is:



Wherein:

Z is at each occurrence independently selected from either an oxygen or a sulphur atom;

X is either a nitrogen or a carbon atom;

Y is hydrogen or, when X is a nitrogen atom, Y and R^5 or R^6, taken together with the nitrogen and carbon atoms to which they are attached, form a 4- to 12-membered heterocycloalkyl or a 5- to 10-membered heteroaryl;

R^5 is selected from the group consisting of C_1-C_6 alkyl, (C_3-C_6 cycloalkyl)-C_1-C_3 alkyl and (phenyl)-C_1-C_3 alkyl;

wherein each R^5 group is optionally substituted with one to five substituents at each occurrence independently selected from the group consisting of C_1-C_3 alkyl, halo, -CF_3 ;

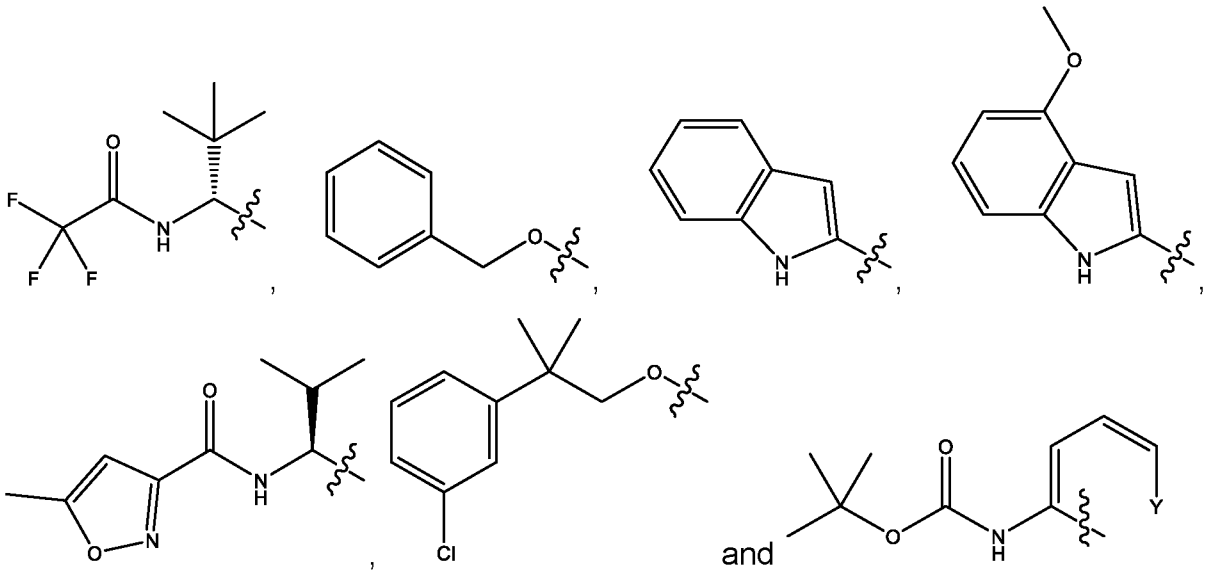
R^6 is selected from the group consisting of C_1-C_8 alkyl, C_1-C_8 alkoxy, (C_1-C_8 alkoxy)-C_1-C_8 alkyl, C_3-C_{12} cycloalkyl, (C_3-C_{12} cycloalkyl)-C_1-C_8 alkyl, (C_3-C_{12} cycloalkyl)-C_1-C_8 alkoxy, C_3-C_{12} cycloalkoxy, (C_3-C_{12} cycloalkoxy)-C_1-C_8 alkyl, (C_3-C_{12} cycloalkoxy)-C_1-C_8 alkoxy, 4- to 12-membered heterocycloalkyl, (4- to 12-membered heterocycloalkyl)-C_1-C_8 alkyl, (4- to 12-membered heterocycloalkyl)-C_1-C_8 alkoxy, 4- to 12-membered heterocycloalkoxy, (4- to 12-membered heterocycloalkoxy)-C_1-C_8 alkyl, (4- to 12-membered heterocycloalkoxy)-C_1-C_8 alkoxy, C_6-C_{10} aryl, (C_6-C_{10} aryl)-C_1-C_8 alkyl, (C_6-C_{10} aryl)-C_1-C_8 alkoxy, 5- to 10-membered heteroaryl, (5- to 10-membered heteroaryl)-C_1-C_8 alkyl and (5- to 10-membered heteroaryl)-C_1-C_8 alkoxy;

wherein each R^6 group is optionally substituted with one to five R^{6a};

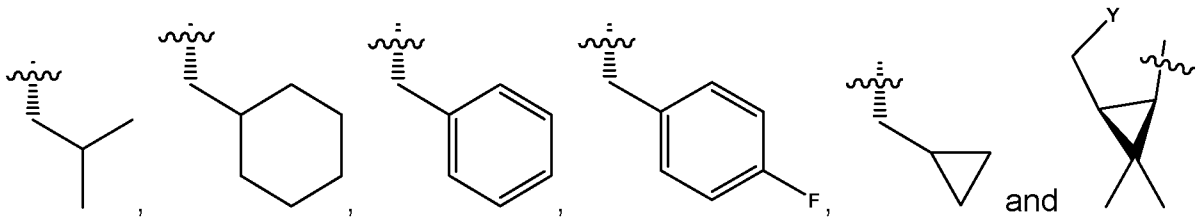
R^{6a} at each occurrence is independently selected from the group consisting of C_1-C_3 alkyl, C_1-C_3 alkoxy, halo, hydroxy, oxo, phenyl, benzyl, C_1-C_6 alkyl-C(O)NH-, C_1-C_6 cycloalkyl-C(O)NH-, 5- to 6-membered heterocycloalkyl-C(O)NH, phenyl-C(O)NH-, 5- to 6-membered heteroaryl-C(O)NH-, C_1-C_6 alkyl-OC(O)NH-;

wherein each R^{6a} group is optionally substituted with one to five fluoro or one substituents selected from the group consisting of C_1-C_3 alkyl, C_1-C_3 alkoxy, chloro, hydroxy, oxo, trifluoromethyl.

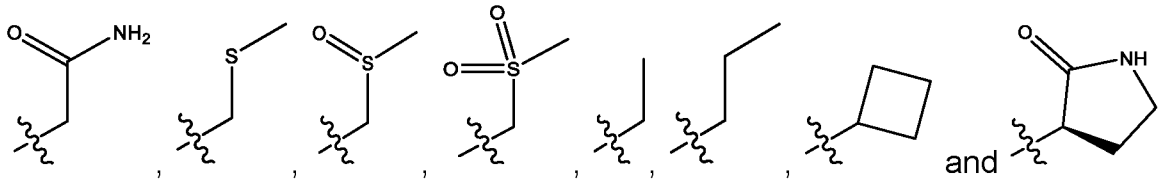
3. A compound according to claim 2, wherein R^6 is selected from the group consisting of:



4. A compound according to claim 2 or 3, wherein R^5 is selected from the group consisting of:

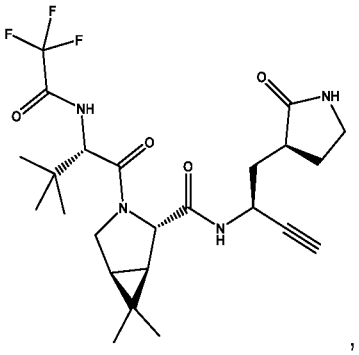
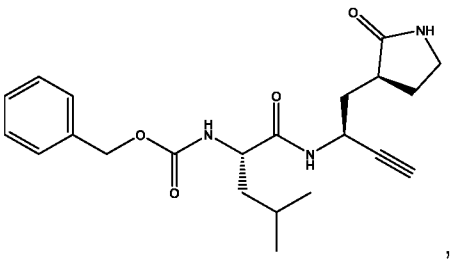
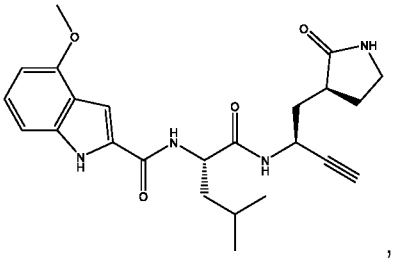
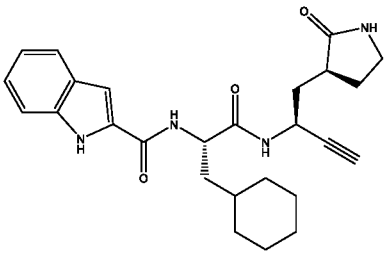
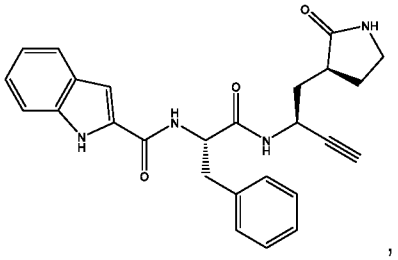
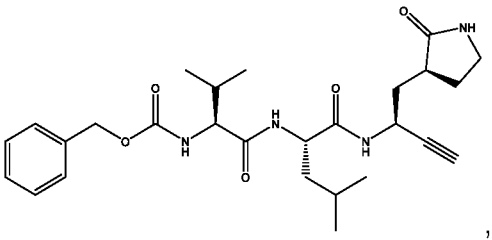
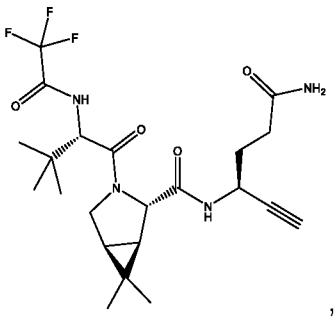
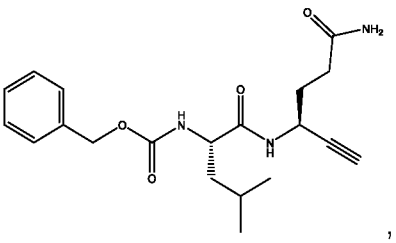
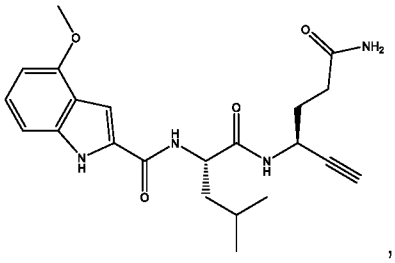
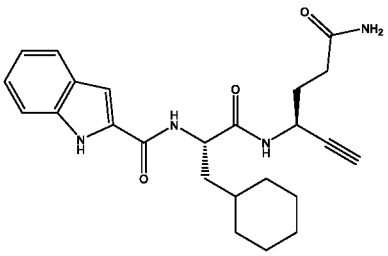
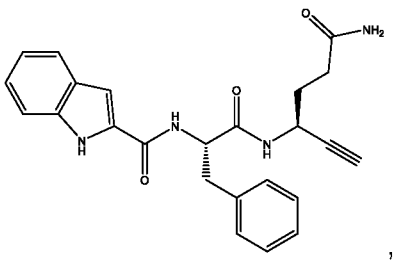
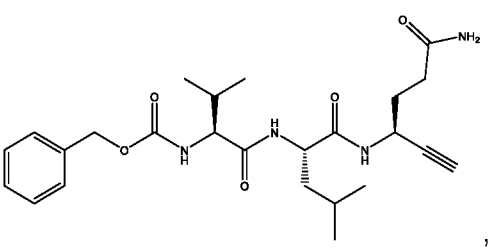


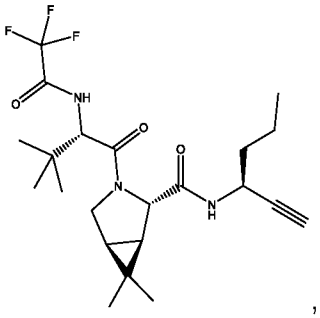
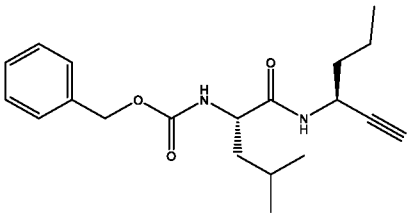
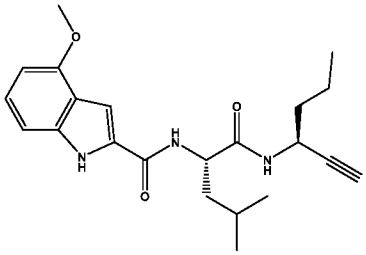
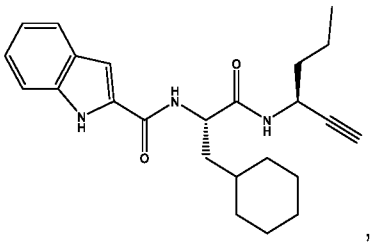
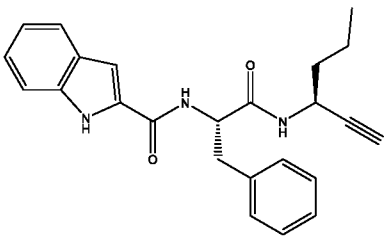
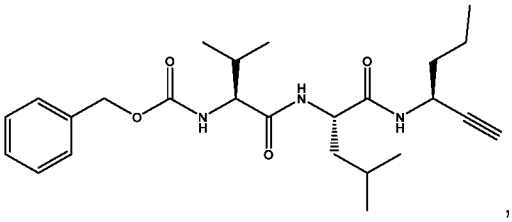
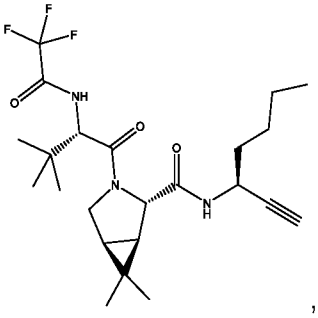
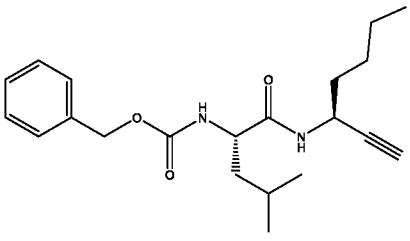
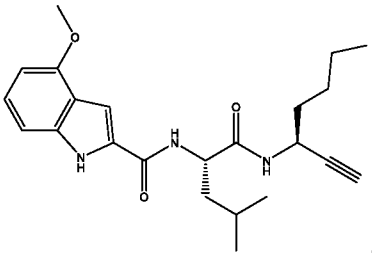
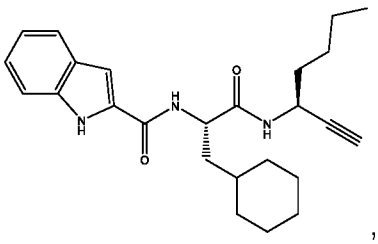
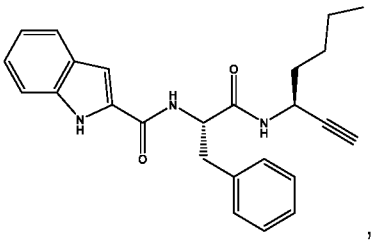
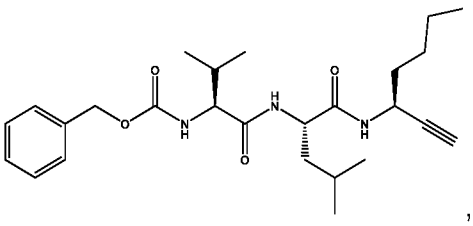
5. A compound according to any one of claims 1-4, wherein R^2 is selected from the group consisting of:

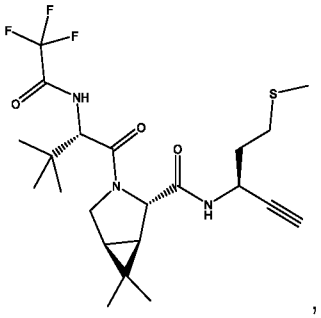
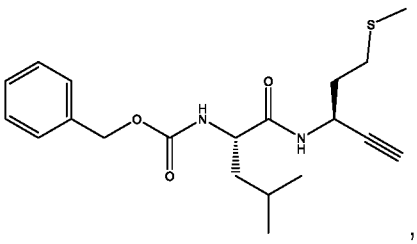
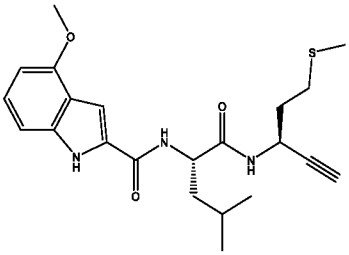
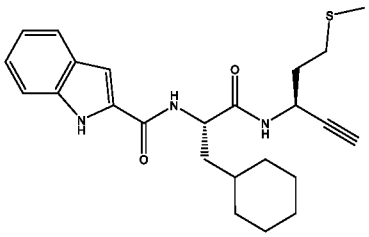
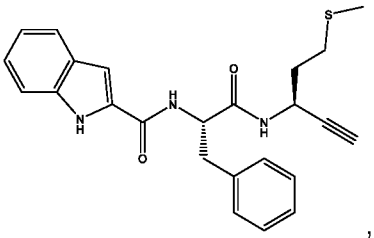
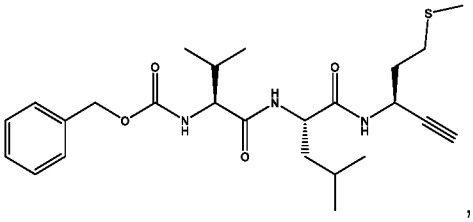
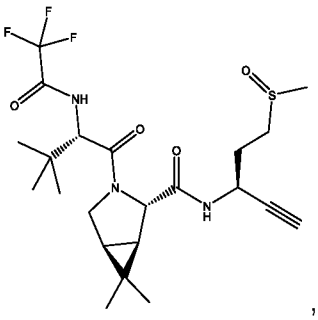
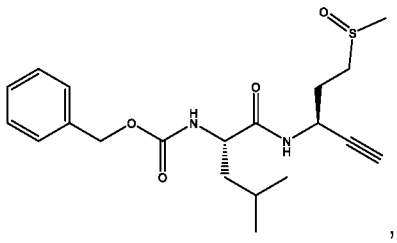
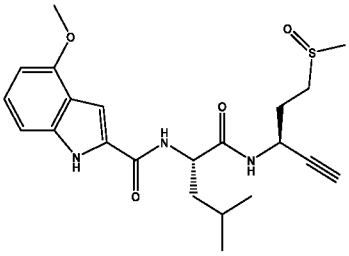
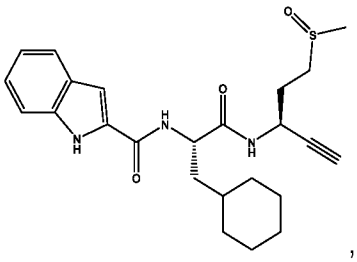
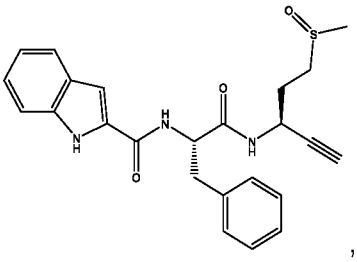
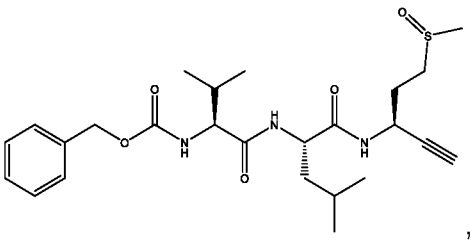


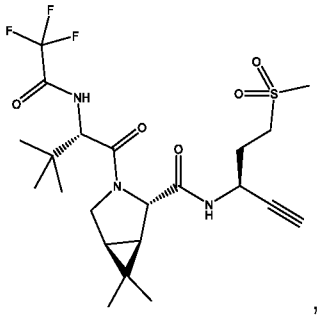
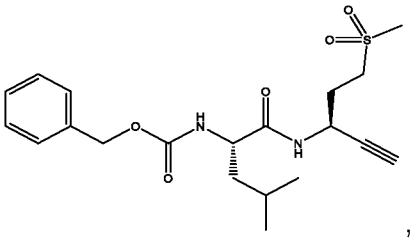
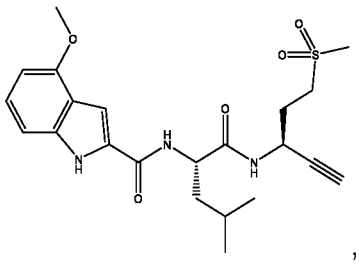
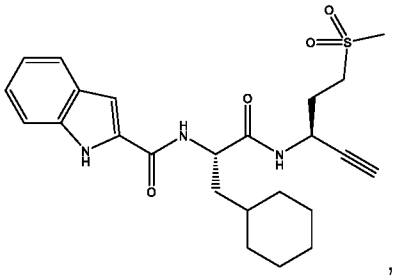
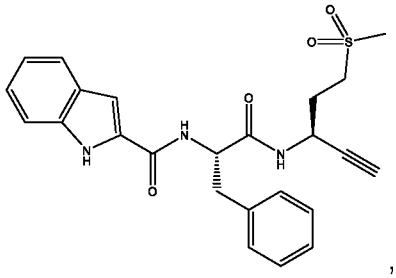
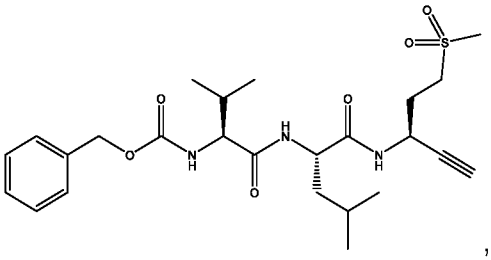
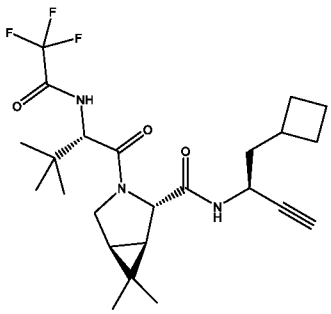
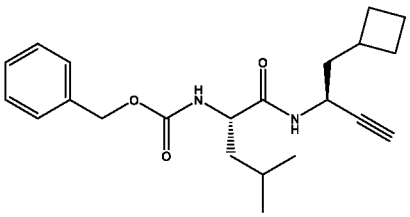
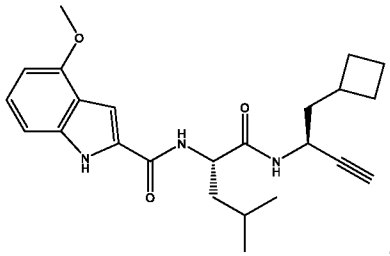
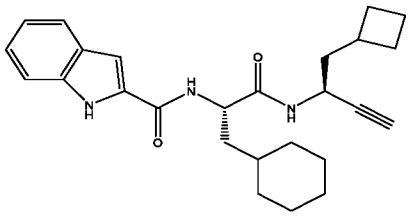
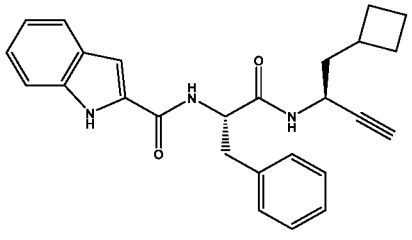
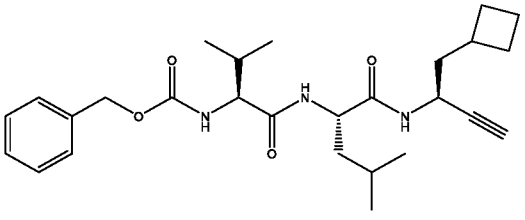
6. A compound according to any one of claims 1-5, wherein R^1 is selected from the group consisting of -H, $-CH_3$, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CCl_3$, $-CHCl_2$ and $-CH_2Cl$,

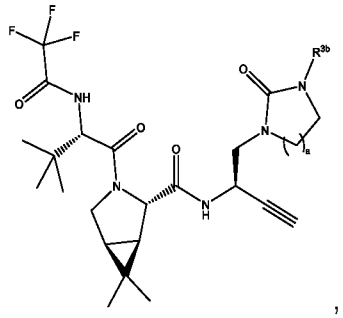
7. A compound according to claim 1, which is selected from the group consisting of:

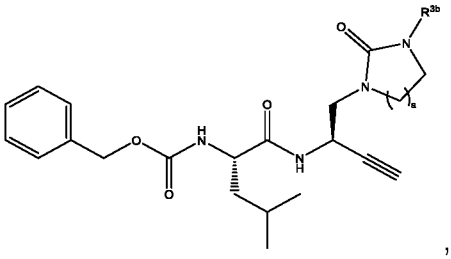

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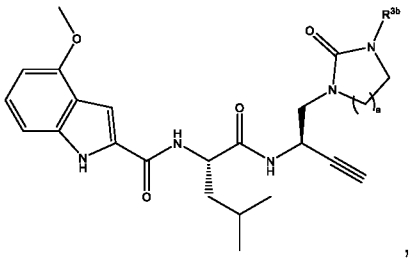

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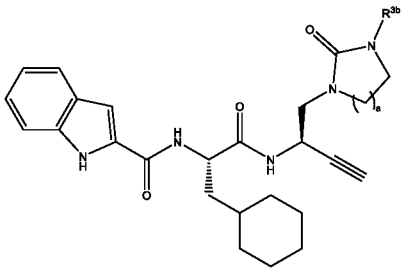

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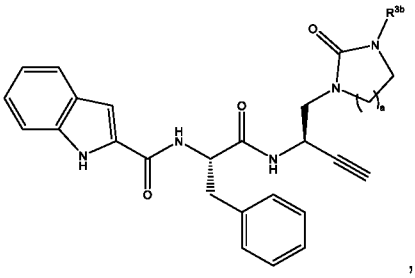

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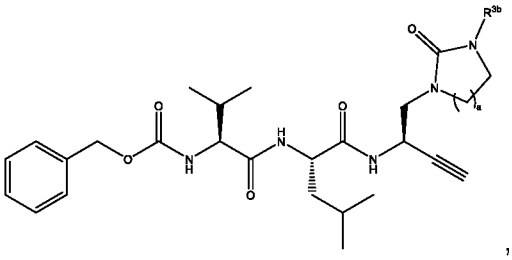

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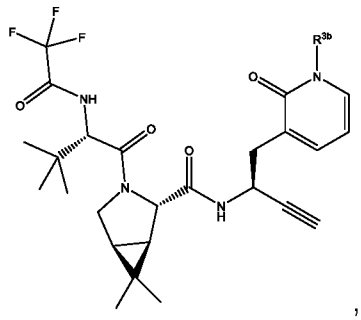

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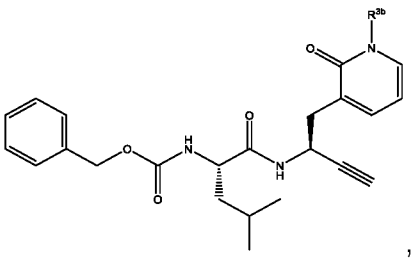

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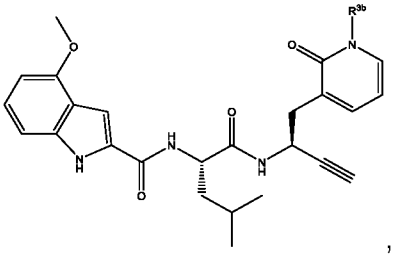

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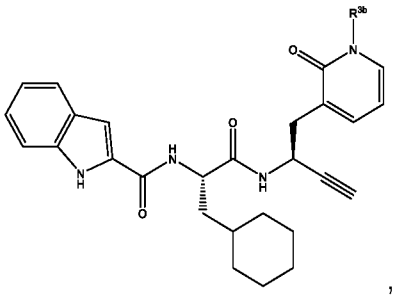

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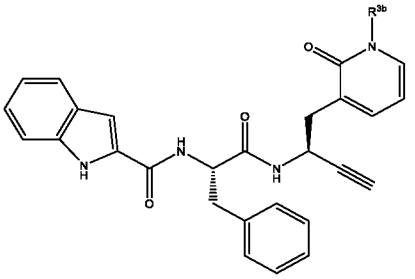

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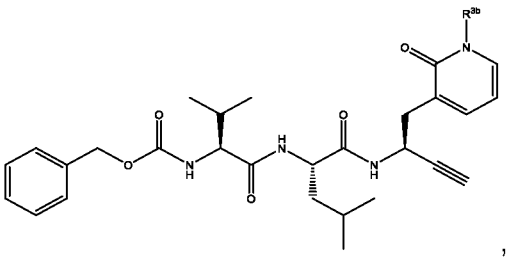

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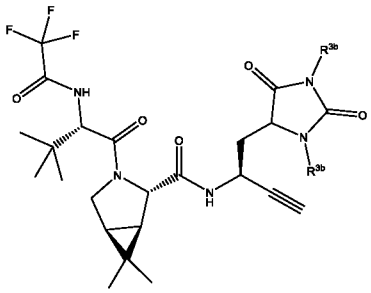
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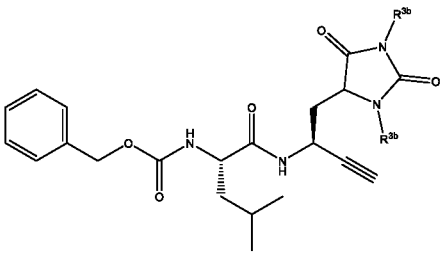
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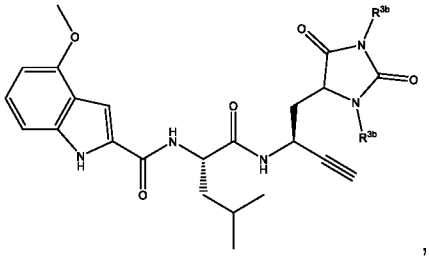
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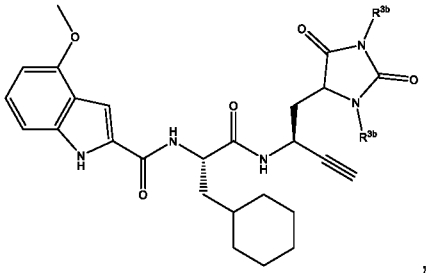
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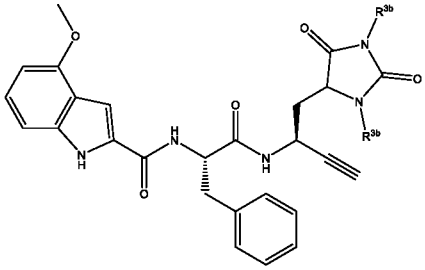
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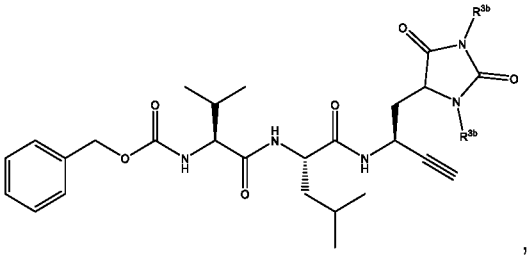
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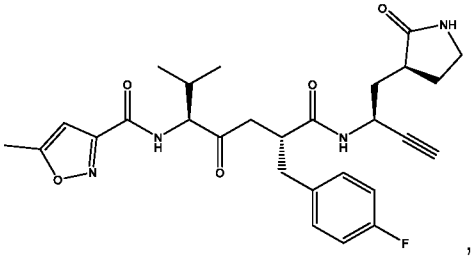
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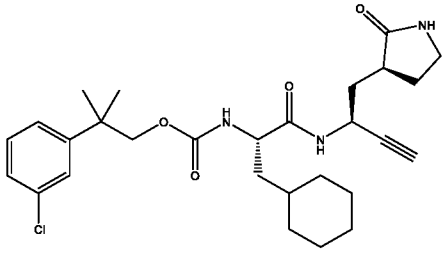
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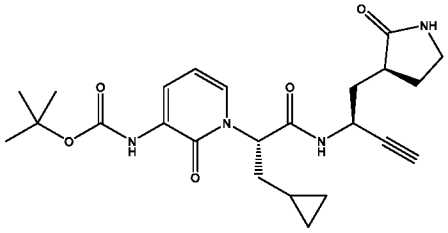
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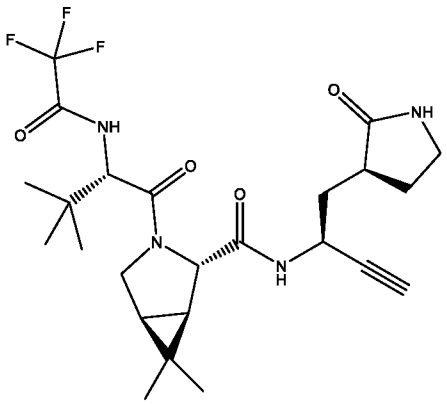
;

and pharmaceutically acceptable salts, solvates and hydrates thereof,

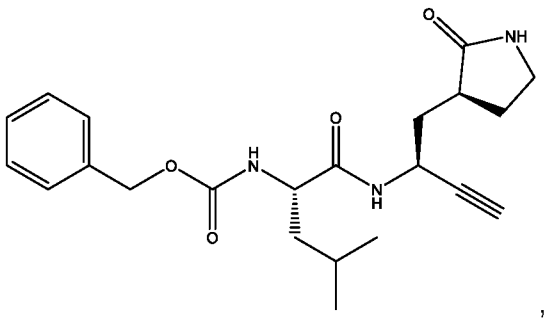
Wherein each R^{3b} is independently selected from the group consisting of hydrogen, halo, hydroxy, trifluoromethyl, -C(O)C_1-C_6 alkyl, -C(O)OC_1-C_6 alkyl and C_1-C_6 alkoxy;

wherein a is at each occurrence independently selected from 0, 1 and 2.

8. The compound of claim 1, which is selected from the group consisting of



and

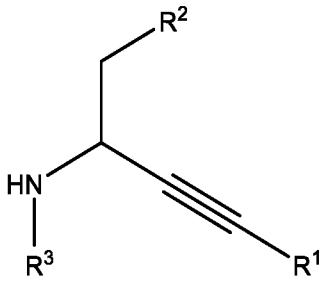


,

and pharmaceutically acceptable salts, solvates and hydrates thereof

9. Method for preparing a compound of any one of the preceding claims, said method comprising the steps of:

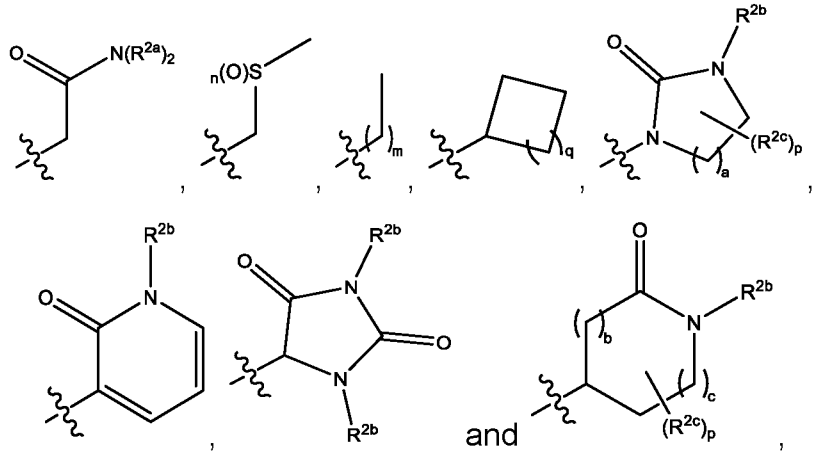
a) providing a first compound according to formula (X)



(X)

wherein R^1 is selected from the group consisting of hydrogen, methyl optionally substituted with one to three halo, phenyl optionally substituted with one to five halo.

R^2 is selected from the group consisting of:



wherein each R^{2a} is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl;

wherein each R^{2b} is independently selected from the group consisting of hydrogen, halo, hydroxy, trifluoromethyl, C_1-C_6 alkyl-C(O)-, C_1-C_6 alkyl-OC(O)- and C_1-C_6 alkoxy

Wherein each R^{2c} is independently selected from the group consisting of hydrogen, halo, hydroxy, oxo, trifluoromethyl, C_1-C_6 alkyl ; C_1-C_6 alkoxy

wherein n, a, b and c are at each occurrence independently selected from 0, 1 and 2;

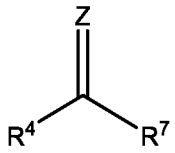
wherein q is at each occurrence independently selected from 0, 1, 2, 3 and 4;

wherein p is at each occurrence independently selected from 0, 1, 2 and 3;

wherein m is at each occurrence independently selected from 0 to 5;

R^3 is selected from the group consisting of hydrogen and methyl;

b) providing a second compound according to formula (Y)



(Y)

wherein Z is either a oxygen or a sulphur atom;

R^7 is selected from the group consisting of hydroxy, halo and carboxylate

R^4 is selected from the group consisting of C_1-C_8 alkyl, C_3-C_{12} cycloalkyl, 4- to 12-membered heterocycloalkyl, C_6-C_{10} aryl and 5- to 10-membered heteroaryl;

wherein each R4 group is optionally substituted with one to two R^{4a};

or R^3 and R^4, taken together with the nitrogen and carbon atoms to which they are attached, form a 4- to 12-membered heterocycloalkyl or a 5- to 10-membered heteroaryl, which can be optionally substituted with one to two R^{4a};

R^{4a} is at each occurrence independently selected from the group consisting of R^{4b}, R^{4b}-O-, R^{4b}-NH-, $(R^{4b})_2$-N-, R^{4b}-C(O)NH- and R^{4b}-OC(O)NH-;

Wherein each R^{4b} is at each occurrence independently selected from the group consisting of C_1-C_8 alkyl, C_3-C_{12} cycloalkyl, 4- to 12-membered heterocycloalkyl, C_6-C_{10} aryl and 5- to 10-membered heteroaryl;

wherein each R^{4b} group is optionally substituted with one to two R^{4c};

R^{4c} is at each occurrence independently selected from the group consisting of R^{4d}, R^{4d}-O-, R^{4d}-NH-, $(R^{4d})_2$-N-, R^{4d}-C(O)NH- and R^{4d}-OC(O)NH-;

Wherein each R^{4d} is at each occurrence is independently selected from the group consisting of C_1-C_8 alkyl, C_3-C_{12} cycloalkyl, 4- to 12-membered heterocycloalkyl, C_6-C_{10} aryl and 5- to 10-membered heteroaryl;

wherein each R^4, R^{4b} and R^{4d} is optionally substituted with one to five substituents at each occurrence independently selected from the group consisting of methyl, halo, hydroxy, oxo, imino and sulfanylidene.

c) reacting said first compound with said second compound under conditions that result in the formation of a compound of any one of the claims 1-8.

10. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 8 and a pharmaceutically acceptable carrier or diluent.

11. A pharmaceutical composition according to claim 10, provided in a unit dosage form suitable for oral administration, preferably in the form of a tablet or capsule.

12. Method of treating a viral infection and/or treating or preventing a disease or condition caused by infection with a virus expressing Main Protease (M^{pro}), in a subject in need thereof, the method comprising administering to said subject a therapeutically effective amount of a compound of any one of claims 1-8 or of a composition according to claim 10 or 11.

13. Method according to claim 12, wherein the viral infection is infection with a coronavirus, preferably a coronavirus selected from the group consisting of HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, MERS-CoV, SARS-CoV, and SARS-CoV-2

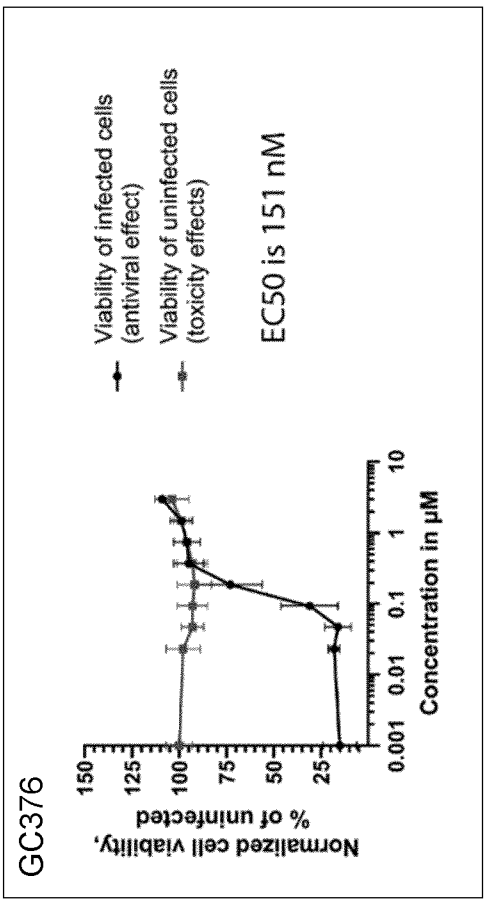
14. Method according to claim 12 or 13, wherein the disease or condition caused by a viral infection is a respiratory illness, such as acute respiratory distress syndrome (ARDS), Middle East respiratory syndrome (MERS) and COVID-19.

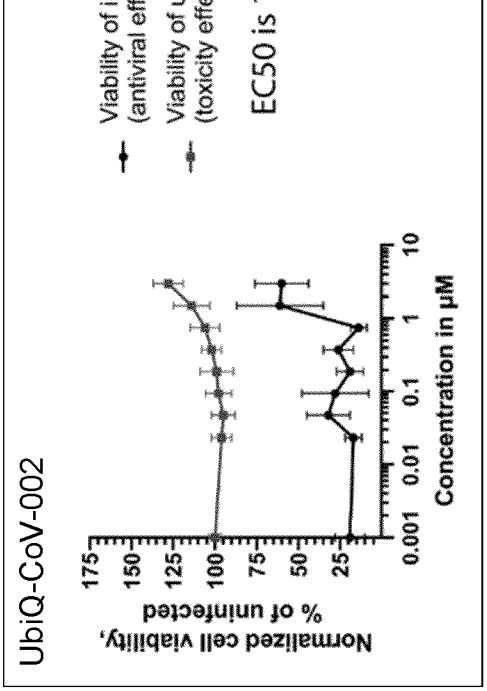
15. Method of inhibiting or preventing replication of a virus expressing Main Protease (M^{pro}), the method comprising contacting the viruses with an inhibitory amount of a compound according to any one of claims 1-8.

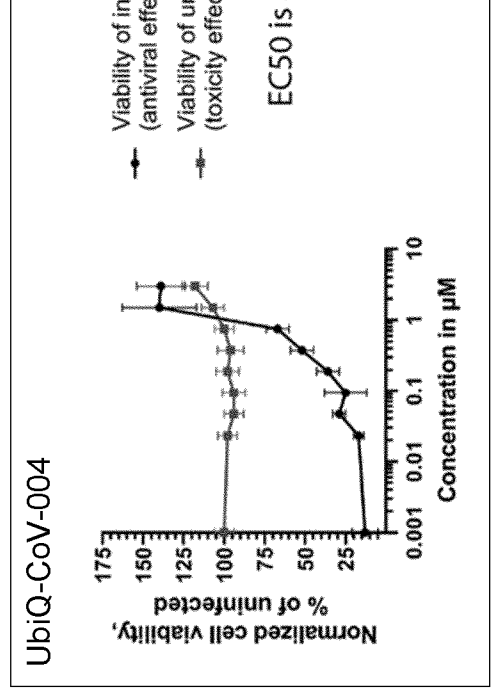
16. Compound according to any one of claims 1-8, for use in a method of treating infection by a virus expressing Main Protease (M^{pro}) and/or treating or preventing a disease or condition caused by infection by a virus expressing Main Protease (M^{pro}), in a subject in need thereof.

17. Use of a compound according to any one of claims 1-8, in the manufacture of a medicament for treating infection by a virus expressing Main Protease (M^{pro}) and/or treating or preventing a disease or condition caused by infection by a virus expressing Main Protease (M^{pro}), in a subject in need thereof.

Figure 1


GC376
Viability of infected cells (antiviral effect)
Viability of uninfected cells (toxicity effects)
EC50 is 151 nM
Normalized cell viability, % of uninfected
Concentration in µM
150
125
100
75
50
25
0.001
0.01
0.1
1
10


UbiQ-CoV-002
Viability of infected cells (antiviral effect)
Viability of uninfected cells (toxicity effects)
EC50 is 1.0 µM
Normalized cell viability, % of uninfected
Concentration in µM
175
150
125
100
75
50
25
0.001
0.01
0.1
1
10


UbiQ-CoV-004
Viability of infected cells (antiviral effect)
Viability of uninfected cells (toxicity effects)
EC50 is 832 nM
Normalized cell viability, % of uninfected
Concentration in µM
175
150
125
100
75
50
25
0.001
0.01
0.1
1
10

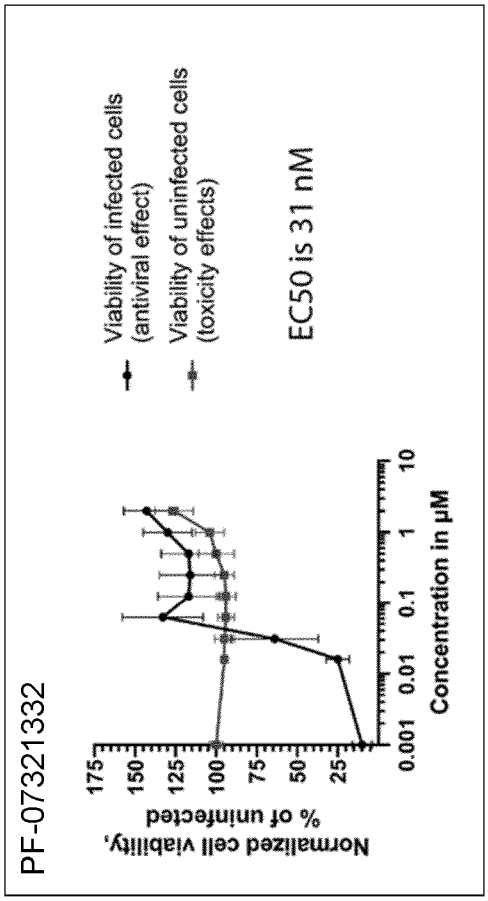
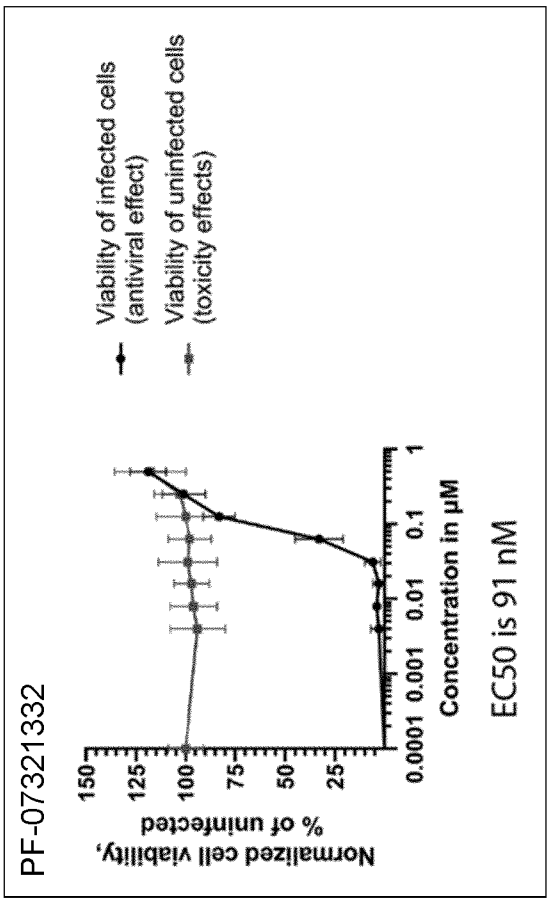
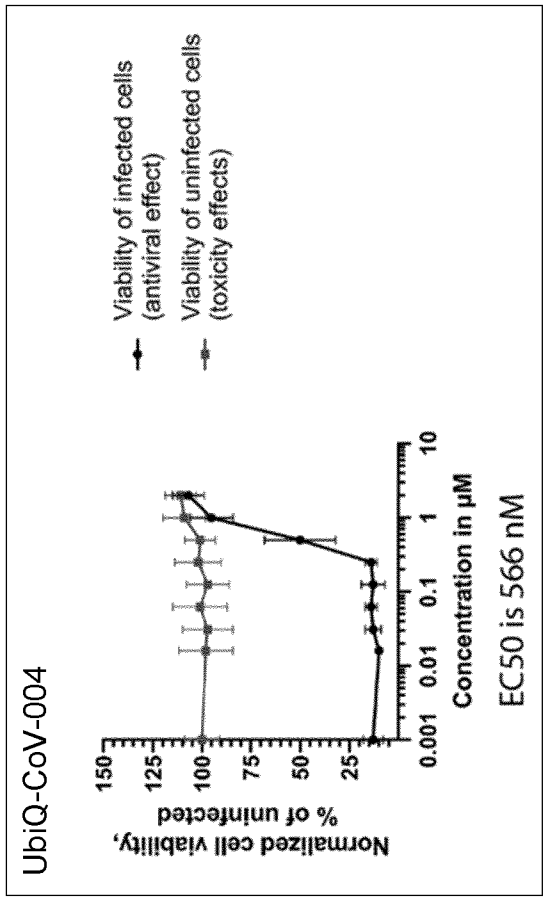

PF-07321332
Viability of infected cells (antiviral effect)
Viability of uninfected cells (toxicity effects)
EC50 is 31 nM
Normalized cell viability, % of uninfected
Concentration in µM
175
150
125
100
75
50
25
0.001
0.01
0.1
1
10

Figure 2


PF-07321332
Viability of infected cells (antiviral effect)
Viability of uninfected cells (toxicity effects)
Normalized cell viability, % of uninfected
150
125
100
75
50
25
0.0001 0.001 0.01 0.1 1
Concentration in µM
EC50 is 91 nM


UbiQ-CoV-004
Viability of infected cells (antiviral effect)
Viability of uninfected cells (toxicity effects)
Normalized cell viability, % of uninfected
150
125
100
75
50
25
0.001 0.01 0.1 1 10
Concentration in µM
EC50 is 566 nM

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2023/079898

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims;; it is covered by claims Nos.:

1-7, 9-17(all partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2023/079898

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/12 C07D207/26 C07D209/02 C07D209/42 A61K31/4015
A61P31/14 C07C271/00
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 A61P C07C

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, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2021/252491 A1 (ALIGOS THERAPEUTICS INC [US]; UNIV LEUVEN KATH [BE]) 16 December 2021 (2021-12-16) Scheme A on page 104, page 425, compound 177; page 450, eighth compound; claims -----	1-7,9-17
X	MARION GARREAU ET AL: "C-Terminal Bioconjugation of Peptides through Photoredox Catalyzed Decarboxylative Alkynylation", ANGEWANDTE CHEMIE INTERNATIONAL EDITION, VERLAG CHEMIE, HOBOKEN, USA, vol. 58, no. 24, 8 May 2019 (2019-05-08), pages 8182-8186, XP072087686, ISSN: 1433-7851, DOI: 10.1002/ANIE.201901922 scheme 4, compound 111 -----	1,5
	-/--	

[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
31 January 2024	09/04/2024

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	Guspanová, Jana

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2023/079898

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2020/244970 A1 (BASF SE [DE]) 10 December 2020 (2020-12-10) page 23, table 7a, compounds I.A-1.7a.B-1 to I.A-6.7a.B-1, I.B-1.7a.B-1 to I.B-1.7a.B-1	1,5
X	KOLLETH AMANDINE ET AL: "Kinetic resolution of propargylamines via a highly enantioselective non-enzymatic N-acylation process", CHEMICAL COMMUNICATIONS, vol. 48, no. 85, 1 January 2012 (2012-01-01), page 10511, XP093040295, UK ISSN: 1359-7345, DOI: 10.1039/c2cc35719d scheme 1, compounds 3c, 3d	1,5
X	KLAUBER ERIC G. ET AL: "Merging Nucleophilic and Hydrogen Bonding Catalysis: An Anion Binding Approach to the Kinetic Resolution of Propargylic Amines", JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 132, no. 39, 15 September 2010 (2010-09-15), pages 13624-13626, XP093040298, ISSN: 0002-7863, DOI: 10.1021/ja105337h chart 1	1,5
X	KATRITZKY ALAN R ET AL: "A Conceptually New Approach to the Synthesis of Secondary Amides and Thioamides1", J. ORG. CHEM, vol. 53, 1 January 1988 (1988-01-01), pages 5854-5856, XP093040301, table 1, compound 1j	1,5

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2023/079898

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2021252491 A1	16-12-2021	AU 2021289665 A1	15-12-2022
		BR 112022025037 A2	14-02-2023
		CA 3183740 A1	16-12-2021
		CN 116096714 A	09-05-2023
		EP 4165037 A1	19-04-2023
		IL 298324 A	01-01-2023
		JP 2023530267 A	14-07-2023
		KR 20230038457 A	20-03-2023
		TW 202216679 A	01-05-2022
		US 2022009903 A1	13-01-2022
		WO 2021252491 A1	16-12-2021
WO 2020244970 A1	10-12-2020	NONE	

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-7, 9-17(all partially)

Compound of formula I wherein R2 means a linear moiety

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2. claims: 1-7, 9-17(all partially)

Compound of formula I wherein R2 means a cycloalkyl moiety

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3. claims: 8(completely); 1-7, 9-17(partially)

Compound of formula I wherein R2 means a heterocyclic moiety
