INTRAVENOUS ANTIVIRAL TREATMENTS

Related Applications

This patent document claims the benefit of priority of U.S. Application No. 60/772,748, filed February 13, 2006, and of International Application No. PCT/US2006/013535, filed April 12, 2006, which applications are herein incorporated by reference.

Background

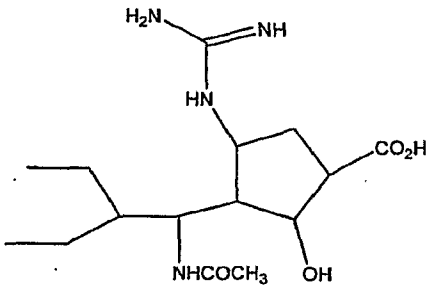
The influenza virus neuraminidase inhibitor peramivir has marked activity against the influenza virus *in vitro* and in experimentally infected mice (Govorkova *et al.*, *Antimicrobial Agents and Chemotherapy, 45(10)*, 2723-2732 (2001); and Smee *et al.*, *Antimicrobial Agents and Chemotherapy, 45(3)*, 743-748 (2001)). Unfortunately, clinical trials using this drug showed a suboptimal therapeutic effect on influenza infection in humans following oral administration over a period of days. Currently there is a need for methods and formulations that are useful for treating viral infections (*e.g.*, influenza infections) in humans.

Summary of the Invention

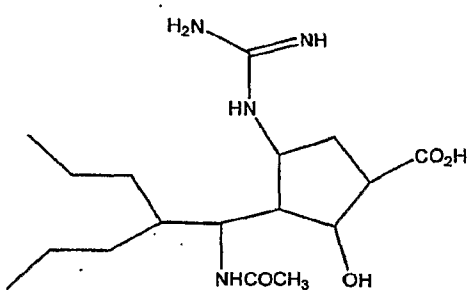
It has unexpectedly been discovered that a single intravenous administration of peramivir to a mouse is effective to treat influenza. These findings are unexpected not only because of the high effectiveness of a single administration of the compound, but also because of the low dose of the compound that was found to provide effective treatment. The ability to obtain therapeutically useful effects with a single administration is important *inter alia* because it minimizes patient compliance issues resulting from the need for multiple administrations. Additionally, the administration of a low dose is important because it minimizes cost and the potential for side-effects. It has also been unexpectedly discovered that intravenous and intramuscular injections of peramivir to humans provides high plasma concentrations of peramivir with an extended half-life.

Accordingly, in one embodiment the invention provides a method for treating a viral infection (*e.g.*, an influenza infection) in a human comprising

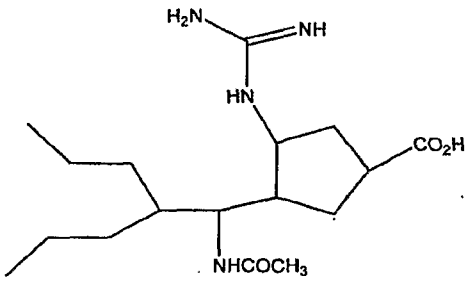
administering an effective anti-viral amount of a compound of formula I, II, III, or IV:



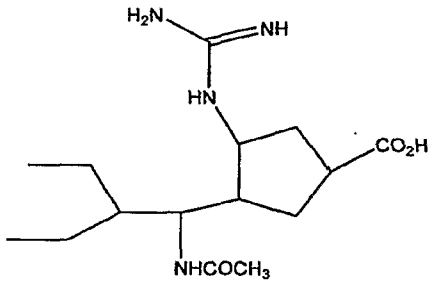
(I)



(II)



(III)



(IV),

or a pharmaceutically acceptable salt thereof, to the human by an intravenous route.

The invention also provides a method for inhibiting a neuraminidase in a human comprising administering an effective inhibitory amount of a compound of formula I, II, III, or IV, or a pharmaceutically acceptable salt thereof, to the human by an intravenous route.

The invention also provides a unit dosage form that is suitable for intravenous administration to a human comprising up to about 400 mg of a compound of formula I, II, III, or IV, or a pharmaceutically acceptable salt thereof.

The invention also provides a unit dosage form that is suitable for intravenous administration to a human comprising up to about 1,000 mg (*e.g.*, up to about 800, 600, 500, 400, 300, 200, 150, 100, or 75 mg) of a compound of formula I, II, III, or IV, or a pharmaceutically acceptable salt thereof.

The invention also provides a kit comprising packaging materials, a compound of formula I, II, III, or IV, or a pharmaceutically acceptable salt

thereof, and instructions for administering the compound to a human by an intravenous route.

The invention also provides the use of a compound of formula I, II, III, or IV, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for intravenous injection for increasing life expectancy or reducing mortality in a group of mammals exposed to a source of an influenza virus, by intravenous injection of a dose of the medicament into each member of the group presenting clinical symptoms of infection.

The invention also provides the use of a compound of formula I, II, III, or IV, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for intravenous injection for increasing life expectancy or reducing mortality in a group of mammals exposed to a source of an influenza virus, by intravenous injection of a dose of the medicament into each member of the group.

Brief Description of the Figures

Figure 1. Figure 1 depicts plasma peramivir concentration time curves after 15 minute intravenous infusions of peramivir to healthy human volunteers.

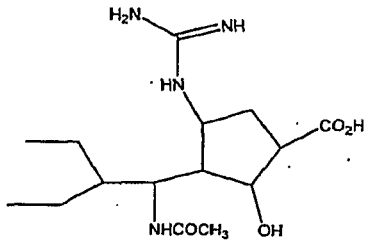
Figure 2. Figure 2 depicts plasma peramivir concentration time curves after intramuscular injections of peramivir to healthy human volunteers.

Detailed Description

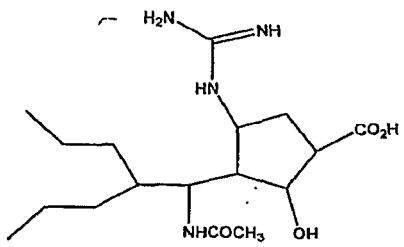
The influenza virus neuraminidase inhibitor peramivir has been previously shown to have marked activity against influenza virus *in vitro* and in experimentally infected mice (Govorkova *et al.*, (2001); and Smee *et al.*, (2001)). Unfortunately, clinical trials using this drug showed an inadequate inhibitory effect on influenza in humans. This effect was attributed to a poor adsorption of the drug when administered once daily orally in patients.

It has been discovered that peramivir is well adsorbed when administered intravenously (i.v.) in mice and that the compound remains at relatively high levels in the plasma for at least 6 hours. A series of experiments presented herein indicates that a single treatment of peramivir given i.v. will protect mice infected with an influenza virus.

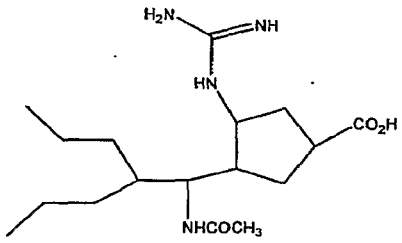
Accordingly, certain embodiments of the present invention provide a method for treating a viral infection in a human comprising administering an effective anti-viral amount of a compound of formula I, II, III, or IV:



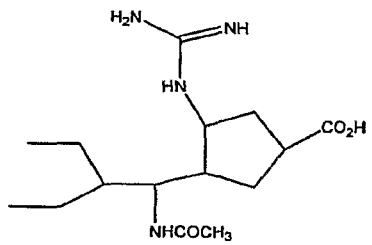
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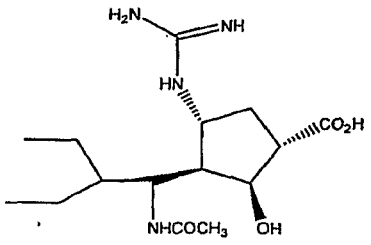
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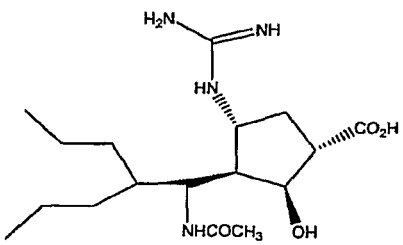
(IV),

or a pharmaceutically acceptable salt thereof, to the human by an intravenous route.

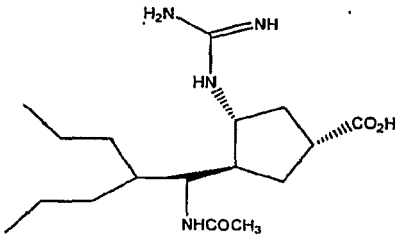
In certain embodiments, the compound of formula I, II, III, or IV is a compound of formula Ia, IIa, IIIa, or IVa:



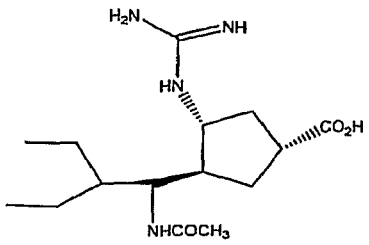
(Ia)



(IIa)



(IIIa)



(IVa),

or a pharmaceutically acceptable salt thereof.

In certain embodiments, the viral infection is an influenza infection. In certain embodiments, the viral infection is an influenza type A or type B infection. In certain embodiments, the viral infection is caused by a strain of virus represented by the formula H_XN_Y wherein X is an integer from 1-16 and Y is an integer from 1-9. In certain embodiments, the influenza is an H3N2, H1N1, H5N1, avian, or seasonal influenza.

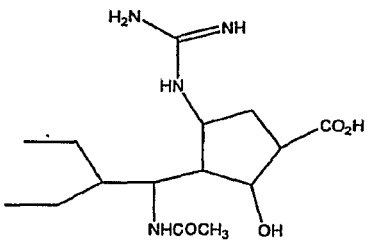
In certain embodiments, the effective anti-viral amount is up to about 800 mg. In certain embodiments, the effective anti-viral amount is up to about 400 mg. In certain embodiments, the effective anti-viral amount is up to about 300 mg. In certain embodiments, the effective anti-viral amount is up to about 200 mg.

In certain embodiments, the entire effective dose is administered in one intravenous administration. In certain embodiments, the entire effective dose is administered in multiple intravenous administrations.

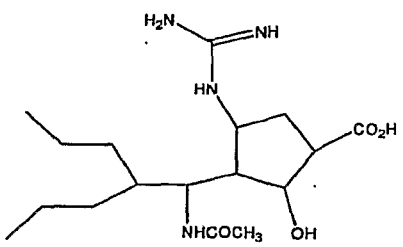
In certain embodiments, a compound or formula Ia, or a pharmaceutically acceptable salt thereof, is administered.

In certain embodiments, the plasma concentration of the compound is higher than the IC_{50} of the virus causing the viral infection 12 hours following administration of the compound.

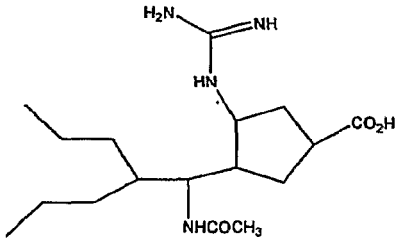
Certain embodiments of the present invention provide a method for inhibiting a neuraminidase in a human comprising administering an effective inhibitory amount of a compound of formula I, II, III, or IV:



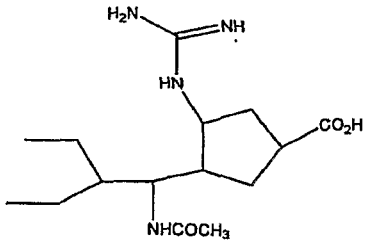
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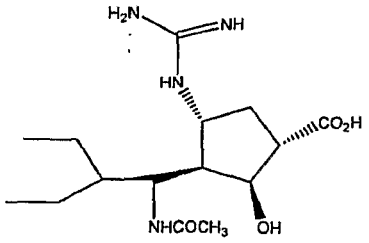
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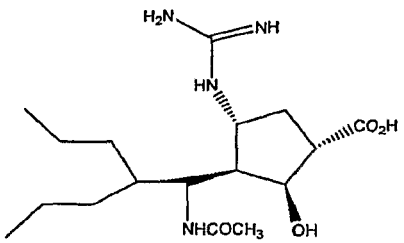
(IV),

or a pharmaceutically acceptable salt thereof, to the human by an intravenous route.

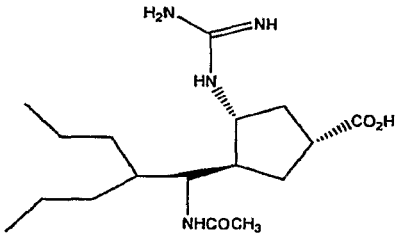
In certain embodiments, the compound of formula I, II, III, or IV is a compound of formula Ia, IIa, IIIa, or IVa:



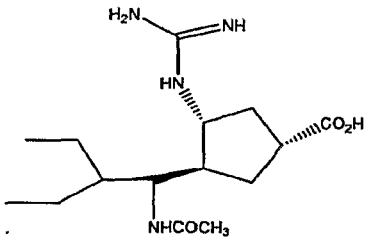
(Ia)



(IIa)



(IIIa)



(IVa),

or a pharmaceutically acceptable salt thereof.

In certain embodiments, the effective inhibitory amount is up to about 800 mg. In certain embodiments, the effective inhibitory amount is up to about 400 mg. In certain embodiments, the effective inhibitory amount is up to about 300 mg. In certain embodiments, the effective inhibitory amount is up to about 200 mg.

In certain embodiments, the entire effective inhibitory dose is administered in one intravenous administration. In certain embodiments, the

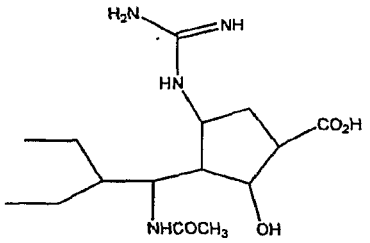
entire effective inhibitory dose is administered in multiple intravenous administrations.

In certain embodiments, a compound of formula Ia, or a pharmaceutically acceptable salt thereof, is administered.

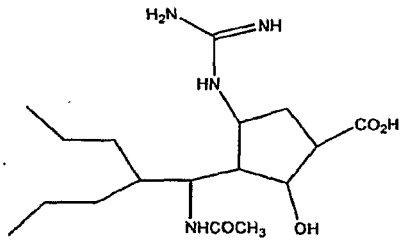
In certain embodiments, the methods may further comprise orally administering a neuraminidase inhibitor to the human.

In certain embodiments, the neuraminidase inhibitor that is administered orally is oseltamivir carboxylate.

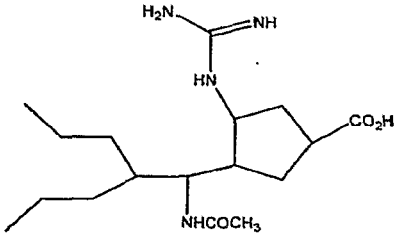
In certain embodiments, the neuraminidase inhibitor that is administered orally is a compound of formula I, II, III, or IV:



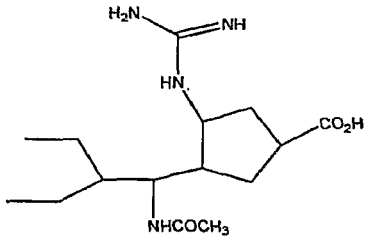
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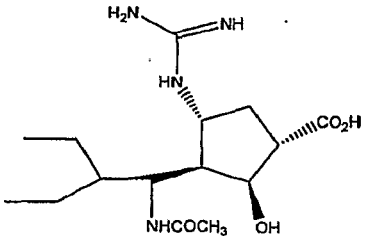
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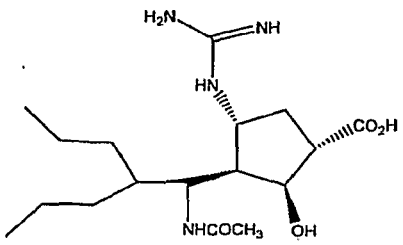
(IV),

or a pharmaceutically acceptable salt thereof.

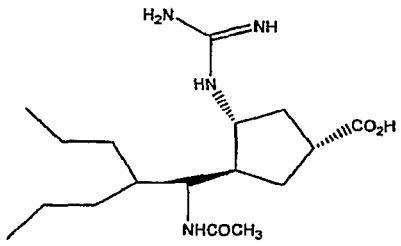
In certain embodiments, the neuraminidase inhibitor that is administered orally is a compound of formula Ia, IIa, IIIa, or IVa:



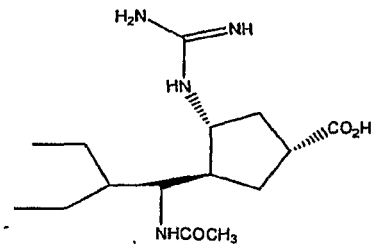
(Ia)



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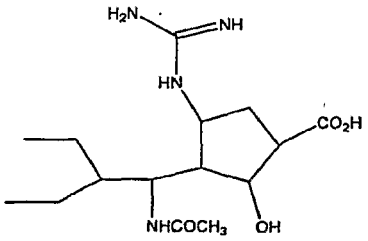
(IVa),

or a pharmaceutically acceptable salt thereof.

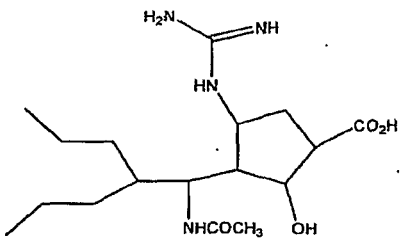
In certain embodiments, the neuraminidase inhibitor that is administered orally is a compound of formula Ia, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the neuraminidase inhibitor that is administered orally is administered for up to 20 days. In certain embodiments, the neuraminidase inhibitor that is administered orally is administered for up to 10 days. In certain embodiments, the neuraminidase inhibitor that is administered orally is administered for up to 5 days.

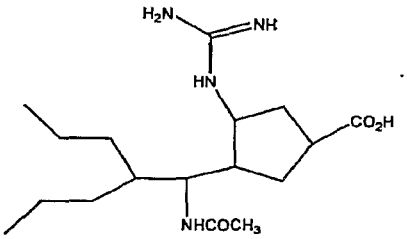
Certain embodiments of the present invention provide a unit dosage form that is suitable for intravenous administration to a human, comprising up to about 800 mg of a compound of formula I, II, III, or IV:



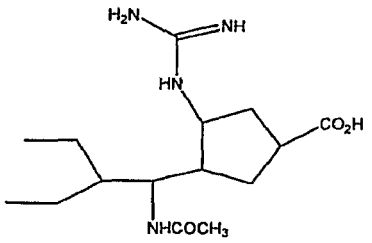
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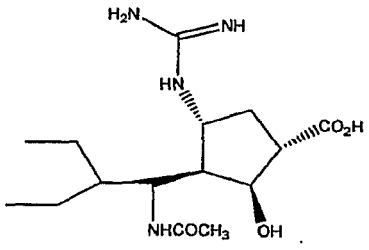
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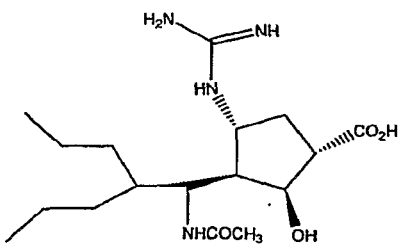
(IV),

or a pharmaceutically acceptable salt thereof.

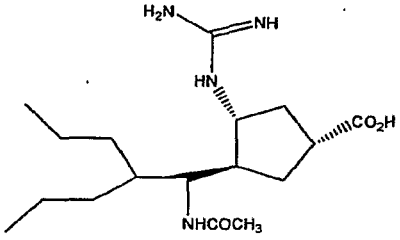
In certain embodiments, the compound of formula I, II, III, or IV is a compound of formula Ia, IIa, IIIa, or IVa:



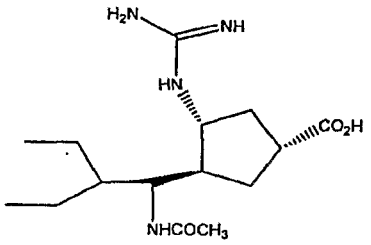
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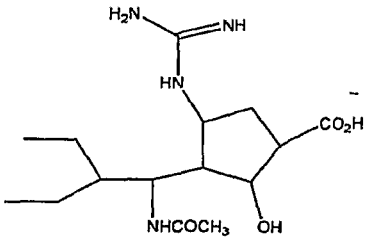


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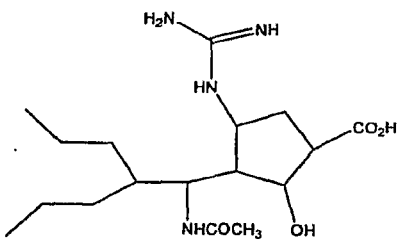
or a pharmaceutically acceptable salt thereof.

In certain embodiments, the unit dosage form comprises up to about 400 mg of the compound or salt. In certain embodiments, the unit dosage form comprises up to about 300 mg of the compound or salt. In certain embodiments, the unit dosage form comprises up to about 200 mg of the compound or salt.

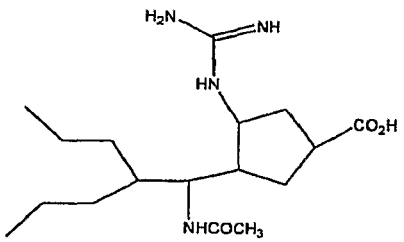
Certain embodiments of the present invention provide a kit, comprising packaging materials, a compound of formula I, II, III, or IV:



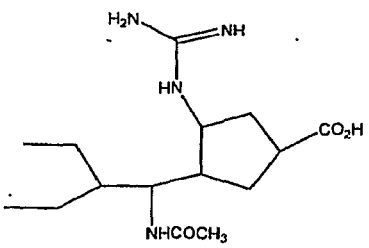
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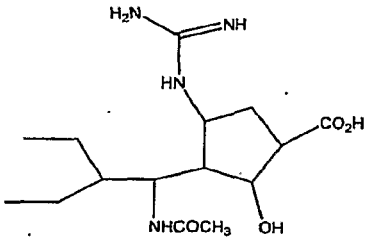
or a pharmaceutically acceptable salt thereof, and instructions for administering the compound to a human by an intravenous route.

In certain embodiments, the compound is provided in a formulation suitable for intravenous administration.

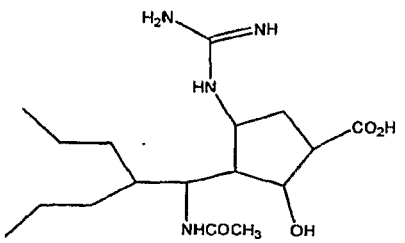
In certain embodiments, the kit comprises up to about 800 mg of the compound or salt. In certain embodiments, the kit comprises up to about 400 mg of the compound or salt. In certain embodiments, the kit comprises up to about 300 mg of the compound or salt. In certain embodiments, the kit comprises up to about 200 mg of the compound or salt.

Certain embodiments of the present invention provide a kit comprising packaging materials, a unit dosage form as described herein, and instructions for administering the compound to a human by an intravenous route.

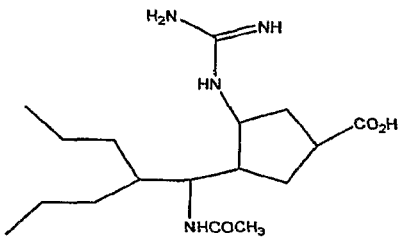
Certain embodiments of the present invention provide a use of a compound of formula I, II, III, or IV:



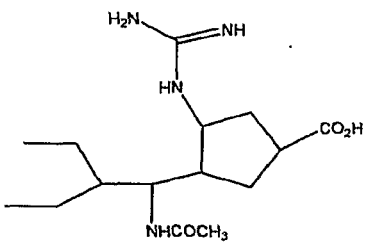
(I)



(II)



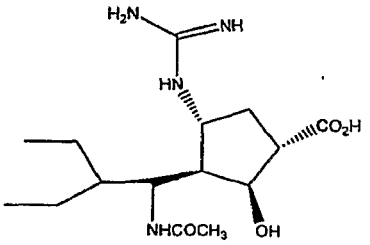
(III)



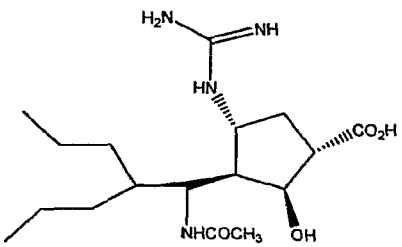
(IV),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for intravenous injection for increasing life expectancy or reducing mortality in a group of mammals exposed to a source of an influenza virus, by intravenous injection of a dose of the medicament into each member of the group presenting clinical symptoms of infection.

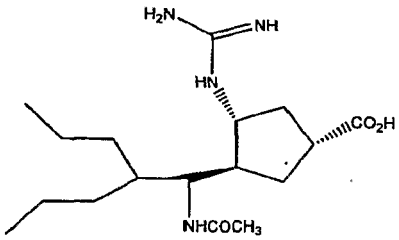
In certain embodiments, the compound of formula I, II, III, or IV is a compound of formula Ia, IIa, IIIa, or IVa:



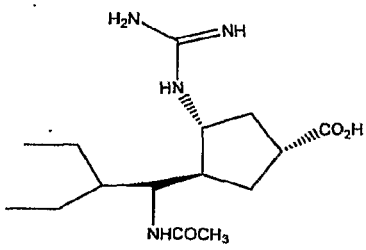
(Ia)



(IIa)



(IIIa)



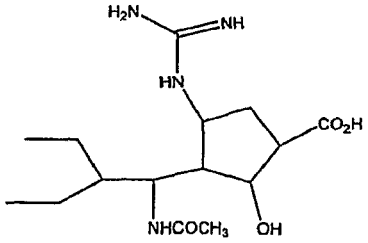
(IVa),

or a pharmaceutically acceptable salt thereof.

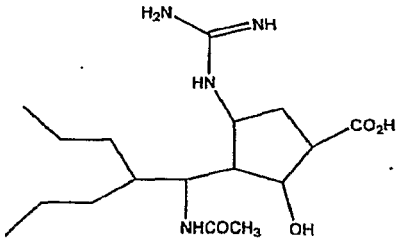
In certain embodiments, the influenza virus is an avian influenza virus. In certain embodiments, the influenza virus is an influenza type A or type B virus. In certain embodiments, the influenza virus is H5N1, or a mutant strain thereof. In certain embodiments, the influenza virus is a strain of virus represented by the formula H_xN_y wherein X is an integer from 1-16 and Y is an integer from 1-9. In certain embodiments, the influenza virus is an H3N2, H1N1, H5N1, avian, or seasonal influenza virus.

In certain embodiments, each member of the group presenting symptoms of infection receives only one intravenous dose of the medicament. In certain embodiments, each member of the group presenting symptoms of infection receives multiple intravenous doses of the medicament.

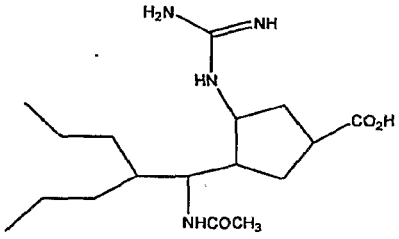
In certain embodiments, the members of the group presenting clinical symptoms of infection are treated orally with a neuraminidase inhibitor. In certain embodiments, the neuraminidase inhibitor is oseltamivir carboxylate. In certain embodiments, the neuraminidase inhibitor is a compound of formula I, II, III, or IV:



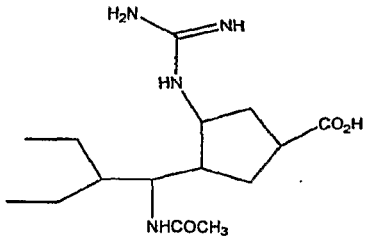
(I)



(II)

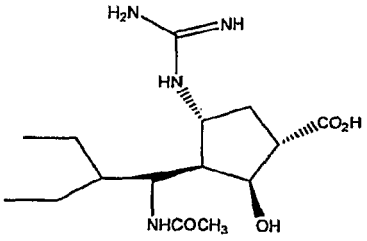


(III)

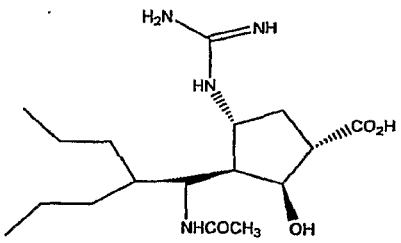


(IV),

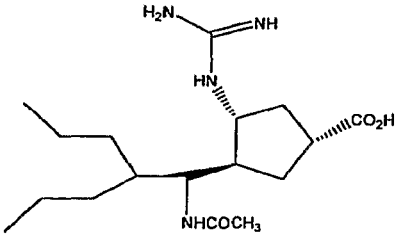
or a pharmaceutically acceptable salt thereof. In certain embodiments, the neuraminidase inhibitor is a compound of formula Ia, IIa, IIIa, or IVa:



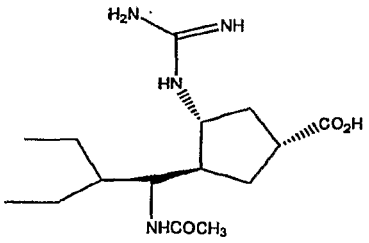
(Ia)



(IIa)



(IIIa)



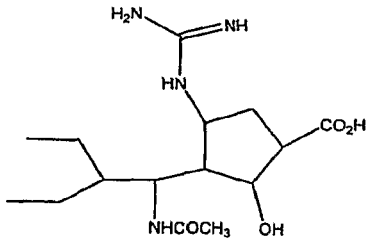
(IVa),

or a pharmaceutically acceptable salt thereof. In certain embodiments, the neuraminidase inhibitor is a compound of formula Ia, or a pharmaceutically acceptable salt thereof.

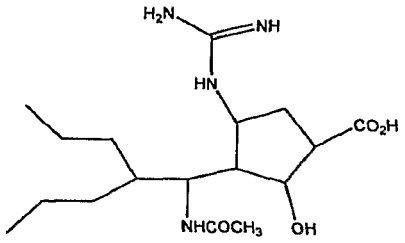
In certain embodiments, the source of the virus is an infected bird. In certain embodiments, the source of the virus is a mammal presenting symptoms of infection.

In certain embodiments, the use is for reducing mortality.

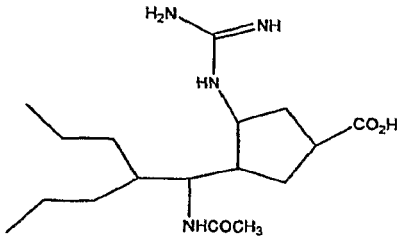
Certain embodiments of the present invention provide a use of a compound of formula I, II, III, or IV:



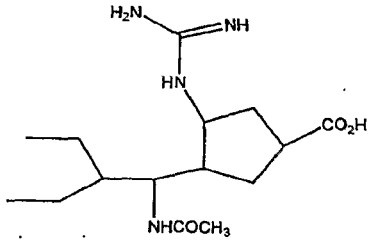
(I)



(II)



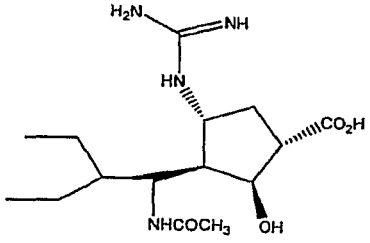
(III)



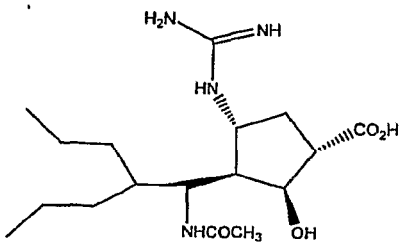
(IV),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for intravenous injection for increasing life expectancy or reducing mortality in a group of mammals exposed to a source of an influenza virus, by intravenous injection of a dose of the medicament into each member of the group.

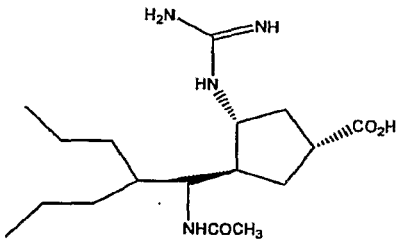
In certain embodiments, the compound of formula I, II, III, or IV is a compound of formula Ia, IIa, IIIa, or IVa:



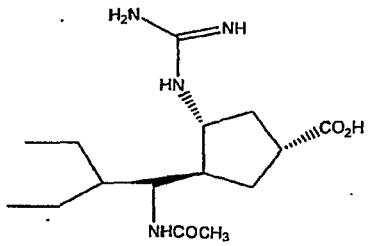
(Ia)



(IIa)



(IIIa)



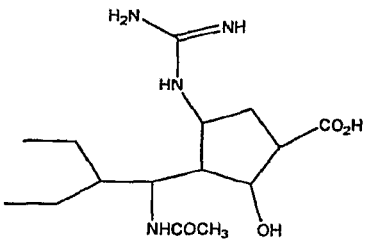
(IVa),

or a pharmaceutically acceptable salt thereof.

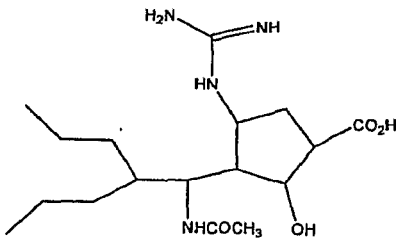
In certain embodiments, the influenza virus is an avian influenza virus. In certain embodiments, the avian influenza virus is H5N1, or a mutant strain thereof. In certain embodiments, the influenza virus is a strain of virus represented by the formula H_xN_y wherein X is an integer from 1-16 and Y is an integer from 1-9. In certain embodiments, the influenza virus is an influenza type A or type B virus. In certain embodiments, the influenza virus is an H3N2, H1N1, H5N1, avian, or seasonal influenza virus.

In certain embodiments, each member of the group receives only one intravenous dose of the medicament. In certain embodiments, each member of the group receives multiple intravenous doses of the medicament.

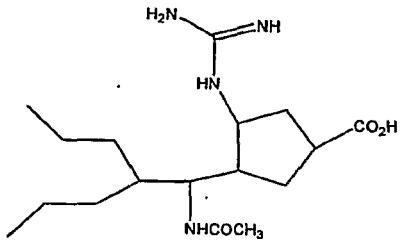
In certain embodiments, the members of the group are treated orally with a neuraminidase inhibitor. In certain embodiments, the neuraminidase inhibitor is oseltamivir carboxylate. In certain embodiments, the neuraminidase inhibitor is a compound of formula I, II, III, or IV:



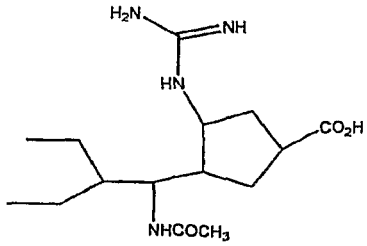
(I)



(II)

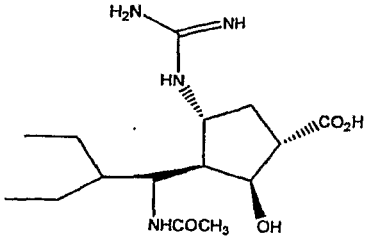


(III)

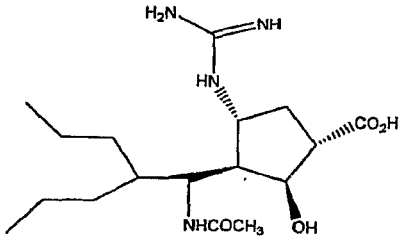


(IV),

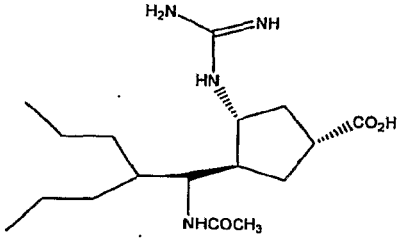
or a pharmaceutically acceptable salt thereof. In certain embodiments, the neuraminidase inhibitor is a compound of formula Ia, IIa, IIIa, or IVa:



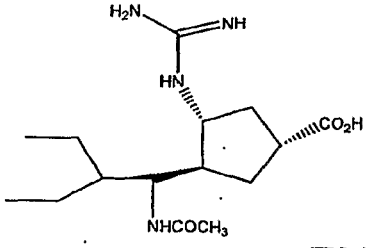
(Ia)



(IIa)



(IIIa)



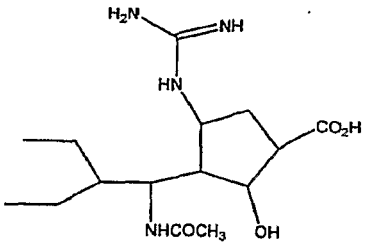
(IVa),

or a pharmaceutically acceptable salt thereof. In certain embodiments, the neuraminidase inhibitor is a compound of formula Ia, or a pharmaceutically acceptable salt thereof.

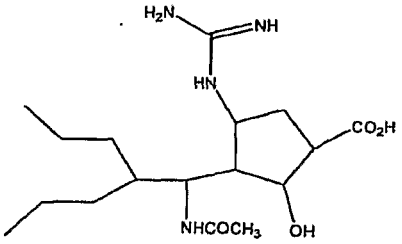
In certain embodiments, the source of the virus is an infected bird. In certain embodiments, the source of the virus is a mammal presenting symptoms of infection.

In certain embodiments, the use is for reducing mortality.

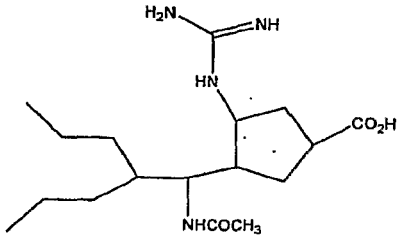
Certain embodiments of the present invention provide a use of a compound of formula I, II, III, or IV:



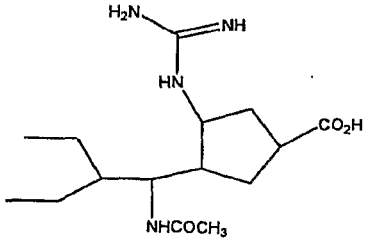
(I)



(II)



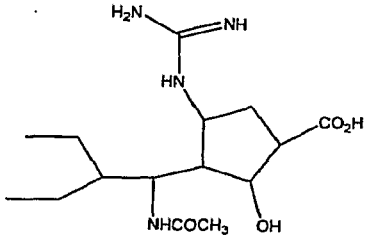
(III)



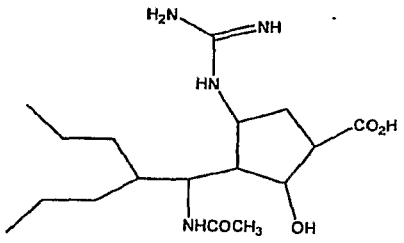
(IV),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for intravenous injection for achieving a plasma concentration in a human of the compound that is effective to treat a virus by intravenous injection of a dose of the medicament into the human.

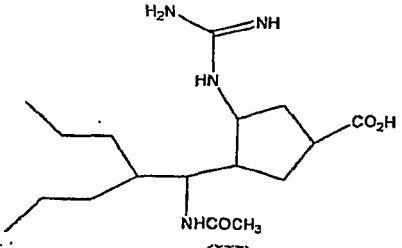
Certain embodiments of the present invention provide a use of a compound of formula I, II, III, or IV:



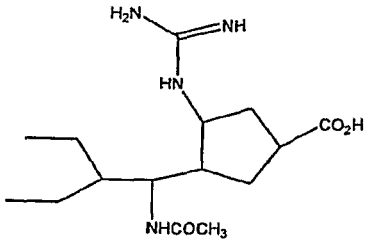
(I)



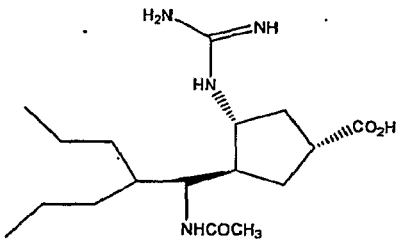
(II)



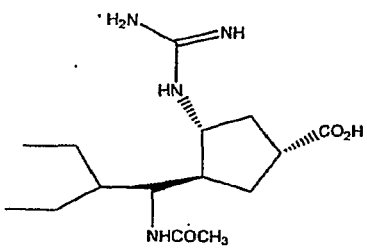
(III)



(IV),



(IIIa)



(IVa),

or a pharmaceutically acceptable salt thereof.

A specific compound of formula I, II, III, or IV is (1*S*,2*S*,3*R*,4*R*)-3-(1-Acetamido-2-ethylbutyl)-4-guanidino-2-hydroxycyclopentane-carboxylic acid; (1*S*,2*S*,3*R*,4*R*)-3-(1-Acetamido-2-propylpentyl)-4-guanidino-2-hydroxycyclopentanecarboxylic acid; (1*R*,3*R*,4*R*)-3-(1-Acetamido-2-propylpentyl)-4-guanidinocyclopentanecarboxylic acid; or (1*R*,3*R*,4*R*)-3-(1-Acetamido-2-ethylbutyl)-4-guanidinocyclopentanecarboxylic acid; or a pharmaceutically acceptable salt thereof.

A specific compound of formula I is a compound of formula Ia, or a pharmaceutically acceptable salt thereof.

It will be appreciated by those skilled in the art that compounds having one or more chiral centers may exist in and be isolated in optically active and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses the use of any racemic, optically-active, polymorphic, or stereoisomeric form, or mixtures thereof, of a compound of formula I, II, III, or IV, which possess the useful properties described herein, it being well known in the art how to prepare optically active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase) and how to determine anti-viral (e.g. anti-influenza) activity using the standard tests described herein, or using other similar tests which are well known in the art.

In cases where compounds are sufficiently basic or acidic to form stable nontoxic acid or base salts, administration of the compounds as salts may be appropriate. Examples of pharmaceutically acceptable salts are organic acid addition salts formed with acids which form a physiological acceptable anion, for

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for intramuscular injection for achieving a plasma concentration in a human of the compound that is effective to treat a virus by intramuscular injection of a dose of the medicament into the human.

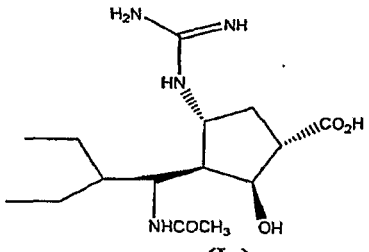
In certain embodiments, the plasma concentration of the compound is higher than the IC_{50} of the virus 12 hours following injection of the compound.

Mice infected with influenza A/Duck/MN/1525/81 (H5N1) virus were treated a single time i.v. 1 hour pre-virus exposure with peramivir at doses of 20, 10 and 3 mg/kg. Peramivir was significantly protective to the mice at the two highest dosages used, as seen by prevention of deaths, lessening of lung consolidation, and inhibition of lung virus titers. The 3 mg/kg dose was moderately inhibitory to lung parameters. The compound appeared well tolerated in concomitantly run toxicity controls. These data indicate that a single i.v. peramivir treatment is efficacious in influenza virus-infected mice.

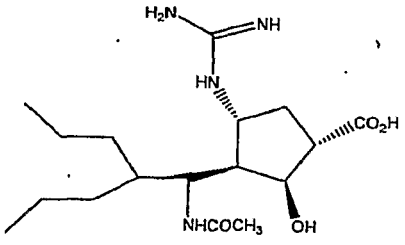
The compounds used in the invention are known in the art and can be synthesized by the art worker using available methods (*see, e.g.*, U.S. Patent No. 6,562,861).

Specific values listed herein for radicals, substituents, and ranges, are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents

A specific compound of formula I, II, III, or IV is a compound of formula Ia, IIa, IIIa, or IVa:



(Ia)



(IIa)

example, tosylate, methanesulfonate, acetate, citrate, malonate, tartarate, succinate, benzoate, ascorbate, α-ketoglutarate, and α-glycerophosphate. Suitable inorganic salts may also be formed, including hydrochloride, sulfate, nitrate, phosphate, bicarbonate, and carbonate salts.

Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound such as an amine with a suitable acid affording a physiologically acceptable anion. Alkali metal (for example, sodium, potassium or lithium) or alkaline earth metal (for example calcium) salts of carboxylic acids can also be made.

The compounds of formula I, II, III, and IV can be formulated as pharmaceutical compositions and administered to a mammalian host, such as a human patient, by intravenous routes. Solutions of the active compound or its salts can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the active ingredient(s) which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form should be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal,

and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound(s) into an appropriate solvent with the other optional ingredients enumerated above, optionally followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

As used herein the terms "treat", "treating" and "treatment" include administering a compound prior to the onset of clinical symptoms of a disease state/condition so as to prevent the development of any symptom, as well as administering a compound after the onset of one or more clinical symptoms of a disease state/condition so as to reduce or eliminate any such symptom, aspect or characteristic of the disease state/condition. Such treating need not be absolute to be useful. As illustrated hereinbelow, the active compounds can be administered prior to exposure to the virus. The agents can also be administered subsequent (*e.g.*, within 1, 2, 3, 4, or 5 days) to exposure to the virus.

As used herein the term "unit dosage form" relates to an intravenous formulation containing a specific amount of a drug, the whole of which is intended to be administered as a single dose. It is distinguished from a supply of an indefinite amount of a medicament, *e.g.*, a bottle of medicine, from which a dose has to be measured out.

In one embodiment the invention provides a method for treating a viral infection in a human comprising administering an effective amount of a compound of formula I, II, III, or IV, or a pharmaceutically acceptable salt thereof, to the human by intravenous administration. Typically, the effective amount is administered in a single intravenous administration. In some embodiments, the effective amount is administered in multiple administrations.

Accordingly, the methods of the invention provide for high patient compliance and they require a low dose of the effective agent.

In one embodiment of the invention, the effective inhibitory amount of the compound of formula I, II, III, or IV is up to about 1,000 mg.

In one embodiment of the invention, the effective inhibitory amount of the compound of formula I, II, III, or IV is up to about 800 mg.

In one embodiment of the invention, the effective inhibitory amount of the compound of formula I, II, III, or IV is up to about 600 mg.

In one embodiment of the invention, the effective inhibitory amount of the compound of formula I, II, III, or IV is up to about 500 mg.

In one embodiment of the invention, the effective inhibitory amount of the compound of formula I, II, III, or IV is up to about 400 mg.

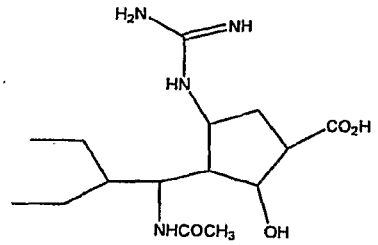
In one embodiment of the invention, the effective inhibitory amount of the compound of formula I, II, III, or IV is up to about 300 mg.

In one embodiment of the invention, the effective inhibitory amount of the compound of formula I, II, III, or IV is up to about 200 mg.

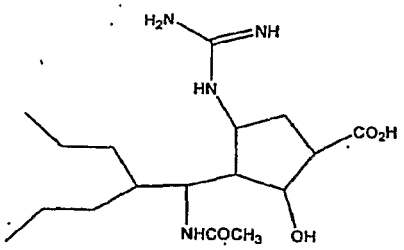
In one embodiment of the invention, the effective inhibitory amount of the compound of formula I, II, III, or IV is up to about 150 mg.

In one embodiment of the invention, the effective inhibitory amount of the compound of formula I, II, III, or IV is up to about 75 mg.

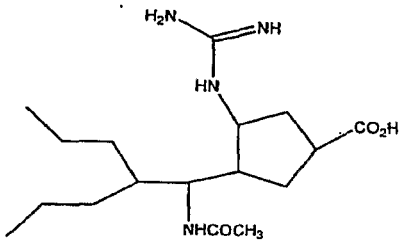
According to the methods of the invention a compound of formula I, II, III, or IV is administered to a human intravenously. In one embodiment of the invention, the compound of formula I, II, III, or IV is administered once to a human intravenously. In another embodiment of the invention, a neuraminidase inhibitor is also administered to the human orally. In one embodiment of the invention, the neuraminidase inhibitor that is administered orally is oseltamivir carboxylate. In one embodiment of the invention, the neuraminidase inhibitor that is administered orally is a compound of formula I, II, III, or IV:



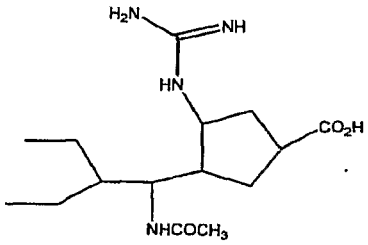
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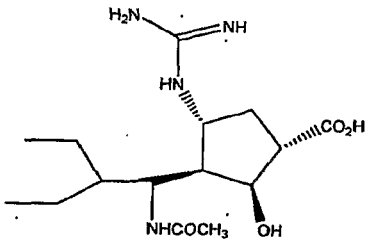


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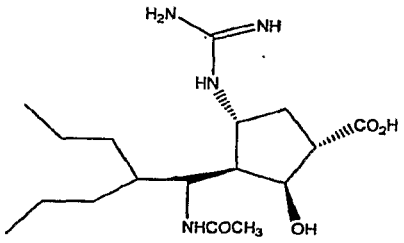


(IV),

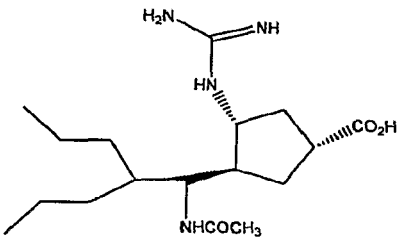
or a pharmaceutically acceptable salt thereof. In one embodiment of the invention, the neuraminidase inhibitor that is administered orally is a compound of formula Ia, IIa, IIIa, or IVa:



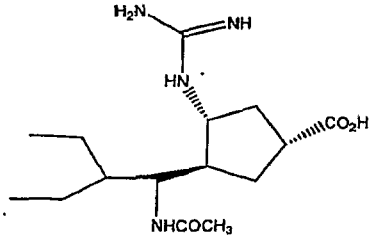
(Ia)



(IIa)



(IIIa)



(IVa),

or a pharmaceutically acceptable salt thereof. In one embodiment of the invention, the neuraminidase inhibitor that is administered orally is a compound of formula Ia, or a pharmaceutically acceptable salt thereof.

According to the methods of the invention, the compound of formula I, II, III, or IV, or a pharmaceutically acceptable salt thereof, can also be administered in combination with one or more additional therapeutic agents, such as anti-viral agents (*e.g.*, agents active against influenza) or antibiotics.

The intravenous formulations of the invention can also comprise one or more additional therapeutic agents, such as anti-viral agents (*e.g.*, agents active against influenza) and antibiotics.

Thus, intravenous administration of peramivir to treat a viral infection is described herein. Intramuscular administration of peramivir to treat a viral infection is also described herein (*see, e.g.*, Example 2), which further exemplifies intramuscular administration of peramivir to treat a viral infection, as is described in International Application No. PCT/US2006/013535, filed April 12, 2006, the disclosure of which is incorporated by reference. Further, as described herein, it has been unexpectedly discovered that intravenous and intramuscular injections of peramivir to humans provides high plasma concentrations of peramivir with an extended plasma half-life.

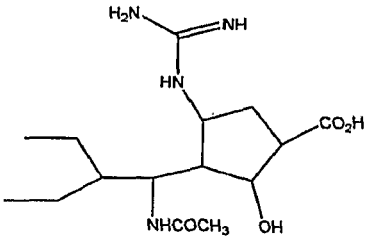
As described herein, the compounds described herein can be used to treat a virus, *e.g.*, an influenza virus. For example, the compounds can be used to treat any one or combination of the following strains. In the table below, the "H" stands for a type of hemagglutinin, and the "N" stands for a type of neuraminidase. The formula H_xN_y wherein X is an integer from 1-16 and Y is an integer from 1-9, can also be used to describe the combinations presented in the table.

Table 1

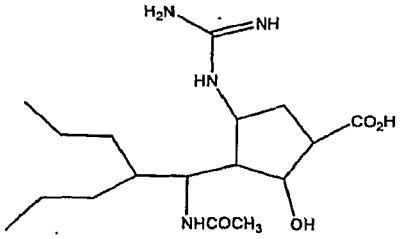
	N1	N2	N3	N4	N5	N6	N7	N8	N9
H1	H1N1	H1N2	H1N3	H1N4	H1N5	H1N6	H1N7	H1N8	H1N9
H2	H2N1	H2N2	H2N3	H2N4	H2N5	H2N6	H2N7	H2N8	H2N9
H3	H3N1	H3N2	H3N3	H3N4	H3N5	H3N6	H3N7	H3N8	H3N9
H4	H4N1	H4N2	H4N3	H4N4	H4N5	H4N6	H4N7	H4N8	H4N9
H5	H5N1	H5N2	H5N3	H5N4	H5N5	H5N6	H5N7	H5N8	H5N9
H6	H6N1	H6N2	H6N3	H6N4	H6N5	H6N6	H6N7	H6N8	H6N9
H7	H7N1	H7N2	H7N3	H7N4	H7N5	H7N6	H7N7	H7N8	H7N9
H8	H8N1	H8N2	H8N3	H8N4	H8N5	H8N6	H8N7	H8N8	H8N9
H9	H9N1	H9N2	H9N3	H9N4	H9N5	H9N6	H9N7	H9N8	H9N9
H10	H10N1	H10N2	H10N3	H10N4	H10N5	H10N6	H10N7	H10N8	H10N9
H11	H11N1	H11N2	H11N3	H11N4	H11N5	H11N6	H11N7	H11N8	H11N9
H12	H12N1	H12N2	H12N3	H12N4	H12N5	H12N6	H12N7	H12N8	H12N9
H13	H13N1	H13N2	H13N3	H13N4	H13N5	H13N6	H13N7	H13N8	H13N9
H14	H14N1	H14N2	H14N3	H14N4	H14N5	H14N6	H14N7	H14N8	H14N9
H15	H15N1	H15N2	H15N3	H15N4	H15N5	H15N6	H15N7	H15N8	H15N9
H16	H16N1	H16N2	H16N3	H16N4	H16N5	H16N6	H16N7	H16N8	H16N9

The virus may be, for example, an avian virus or a humanized avian virus. Thus, the term "avian virus" includes both avian forms of the virus and humanized forms of the avian virus.

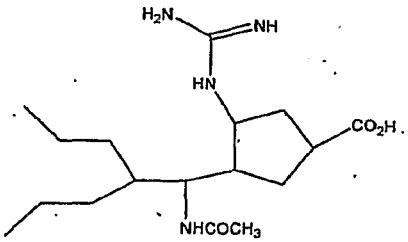
Certain embodiments of the present invention provide the use of a compound of formula I, II, III, or IV:



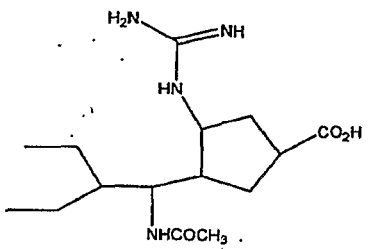
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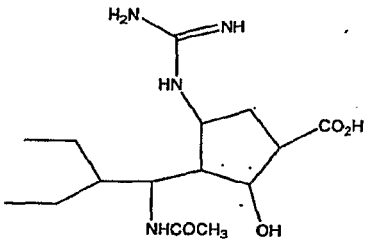
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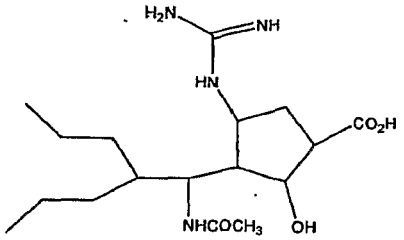
(IV),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for intravenous injection for achieving a plasma concentration in a human of the compound that is effective to treat a virus by intravenous injection of a dose of the medicament into the human.

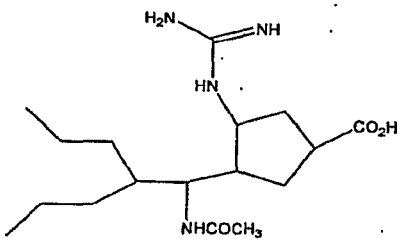
Certain embodiments of the present invention also provide the use of a compound of formula I, II, III, or IV:



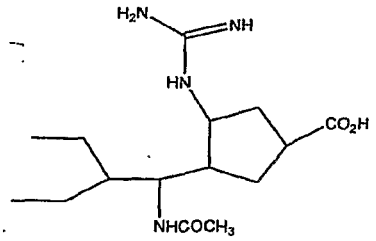
(I)



(II)



(III)



(IV),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for intramuscular injection for achieving a plasma concentration in a human of the compound that is effective to treat a virus by intramuscular injection of a dose of the medicament into the human.

Certain embodiments of the invention also provide compositions comprising peramivir formulated for intravenous administration to a human. Certain embodiments of the invention also provide compositions comprising

peramivir formulated for intravenous administration for use in treating a virus by achieving a plasma concentration in a human of peramivir that is effective to treat the virus.

Certain embodiments of the invention also provide compositions comprising peramivir formulated for intramuscular administration to a human. Certain embodiments of the invention also provide compositions comprising peramivir formulated for intramuscular administration for use in treating a virus by achieving a plasma concentration in a human of peramivir that is effective to treat the virus.

In certain embodiments of the invention, the plasma concentration of the compound is higher than the IC_{50} of the virus at least about 12 hours following the injection.

In certain embodiments of the invention, the plasma concentration of the compound is higher than the IC_{50} of the virus at least about 24 hours following the injection.

In certain embodiments of the invention, the plasma concentration of the compound is higher than the IC_{50} of the virus at least about 36 hours following the injection.

In certain embodiments of the invention, the plasma concentration of the compound is higher than the IC_{50} of the virus at least about 48 hours following the injection.

In certain embodiments of the invention, the plasma concentration of the compound is higher than the IC_{50} of the virus at least about 60 hours following the injection.

In certain embodiments of the invention, the plasma concentration of the compound is higher than the IC_{50} of the virus at least about 72 hours following the injection.

In certain embodiments of the invention, the virus is an influenza virus. In certain embodiments of the invention, the virus is an avian influenza virus. In certain embodiments of the invention, the virus is H5N1, or a mutant strain thereof.

The invention will now be illustrated by the following non-limiting Examples.

Example 1. Effect of IV Treatment with Peramivir on Influenza A Virus Infection

Experiment Design: Mice were infected i.n. with a dose thought to be the LD100 of influenza virus. Groups of 10 mice were treated i.v. with peramivir at dosages of 20, 10 and 3 mg/kg a single time 1 hour pre-virus exposure. Placebo (sterile saline) was administered i.v. in parallel with the above to 20 infected mice. Drug-treated infected mice and placebo-treated controls were observed daily for death through 21 days. As toxicity controls, 3 uninfected mice were treated with the highest dose of the compounds in parallel to the infected animals. All toxicity controls were observed for death through 21 days and were weighed immediately prior to the initial treatment and 18 h after the final treatment. Five normal controls were weighed.

Table 2. Effect of Single I.V. Treatment with Peramivir on an Influenza A Virus Infection in Mice.

Animals: Female 18-21 gram BALB/c mice	*Treatment schedule*: Peramivir,: Single treatment 1 hour pre-virus exposure
Virus: Influenza A/Duck/MN/152518 (H5N1)	*Treatment route*: Peramivir i.v.;
Drug diluent: Sterile Saline	*Expt. duration*: 21 days

		Tox Controls	Infected, Treated Mice	
Treatment	Dose (mg/kg)	Surv/ Total	Surv/ Total	Mean Day to Death[b] ± SD
Peramivir	20	3/3	10/10**	>21.0 ± 0.0***
	10	3/3	10/10**	>21.0 ± 0.0***
	3	3/3	5/10	9.6 ± 1.3
Saline	—	—	9/20	9.1 ± 1.4
Normal Controls	—	5/5	—	—

[b]Mean day to death of mice dying prior to day 21.
**P<0.01; ***P<0.001 compared to saline-treated controls.

The infection induced in this experiment was lethal to 55% of the mice (Table 1), with a mean day to death of 9.1 days. The single i.v. injection with peramivir at 20 and 10 mg/kg was highly protective to the infected animals, with 100% surviving the infection (P<0.01). Toxicity controls run in parallel all survived and gained weight, indicating compound was well tolerated in this experiment.

These data indicate that peramivir is a significant influenza inhibitor when used in a single i.v. injection.

Example 2. Effects of IV and IM Treatment with Peramivir in Humans

Peramivir was studied in a placebo-controlled phase I clinical study in healthy human volunteers to evaluate safety and pharmacokinetic parameters using intravenous and intramuscular administrations. Blood samples were

collected from the subjects at different time points after drug administration to determine the concentration of the drug in plasma. The time course plots are shown in Figure 1 and Figure 2 for intravenous and intramuscular administrations respectively.

In the intravenous study, peramivir concentrations followed linear kinetics with an unusually extended plasma half life of greater than 12 hours. At doses of 2 mg/kg and above, the level of peramivir in plasma at 48 hours post-dose is greater than the IC_{50} for all strains of influenza virus tested, including H5 virus types. For doses greater than 4 mg/kg, even at 72 hours, the levels of the drug are greater than the IC_{50} values.

In the intramuscular study, peramivir concentrations also followed linear kinetics with an unusually extended plasma half life. Even at 72 hours post-dosing, the levels of peramivir are higher than the IC_{50} values for all the influenza virus strains tested.

The long plasma half-life and the high levels of peramivir in human volunteers are unusual and unexpected findings and indicate that intravenous and intramuscular administrations of peramivir are beneficial in the treatment of influenza in humans.

All publications, patents and patent applications cited herein are incorporated herein by reference. While in the foregoing specification this invention has been described in relation to certain embodiments thereof, and many details have been set forth for purposes of illustration, it will be apparent to those skilled in the art that the invention is susceptible to additional embodiments and that certain of the details described herein may be varied considerably without departing from the basic principles of the invention.

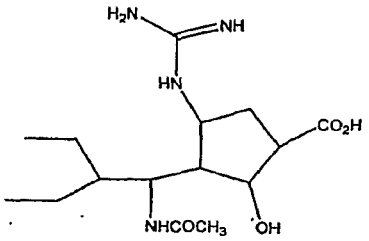
The use of the terms "a" and "an" and "the" and similar referents in the context of describing the invention are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The terms "comprising," "having," "including," and "containing" are to be construed as open-ended terms (*i.e.*, meaning "including, but not limited to") unless otherwise noted. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate

value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (*e.g.*, "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed.

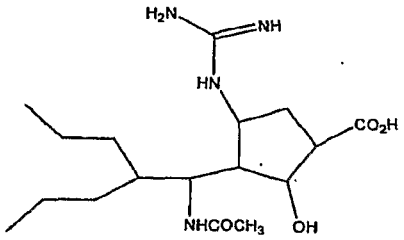
Claims

What is claimed is:

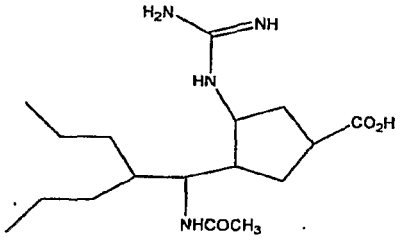
1. A method for treating a viral infection in a human comprising administering an effective anti-viral amount of a compound of formula I, II, III, or IV:



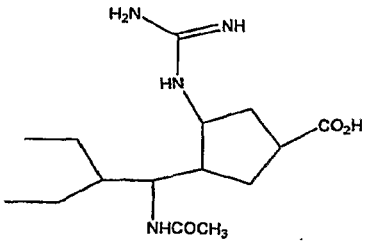
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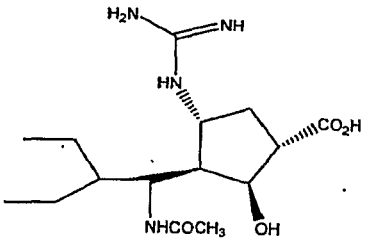
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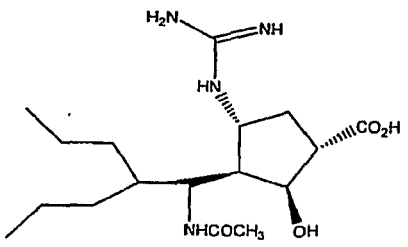
(IV),

or a pharmaceutically acceptable salt thereof, to the human by an intravenous route.

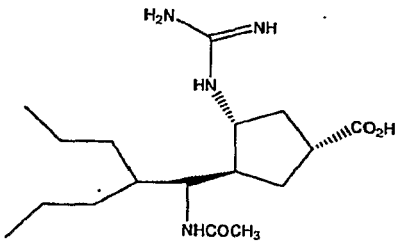
2. The method of claim 1, wherein the compound of formula I, II, III, or IV is a compound of formula Ia, IIa, IIIa, or IVa:



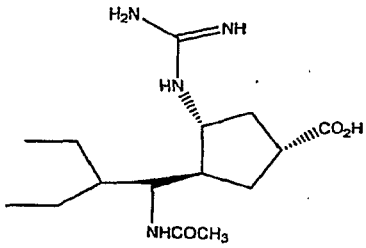
(Ia)



(IIa)



(IIIa)



(IVa),

or a pharmaceutically acceptable salt thereof.

3. The method of claim 1 or 2, wherein the viral infection is an influenza infection.

4. The method of claim 3, wherein the viral infection is an influenza type A or type B infection.

5. The method of claim 1 or 2, wherein the viral infection is caused by a strain of virus represented by the formula H_xN_y wherein X is an integer from 1-16 and Y is an integer from 1-9.

6. The method of claim 3, wherein the influenza is an H3N2, H1N1, H5N1, avian, or seasonal influenza.

7. The method of any one of claims 1-6, wherein the effective anti-viral amount is up to about 800 mg.

8. The method of claim 7, wherein the effective anti-viral amount is up to about 400 mg.

9. The method of claim 8, wherein the effective anti-viral amount is up to about 300 mg.

10. The method of claim 9, wherein the effective anti-viral amount is up to about 200 mg.

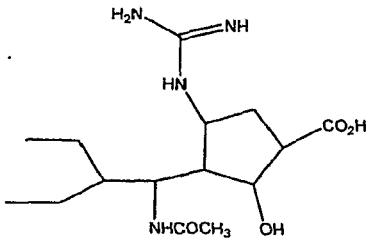
11. The method of any one of claims 1-10, wherein the entire effective dose is administered in one intravenous administration.

12. The method of any one of claims 1-10, wherein the entire effective dose is administered in multiple intravenous administrations.

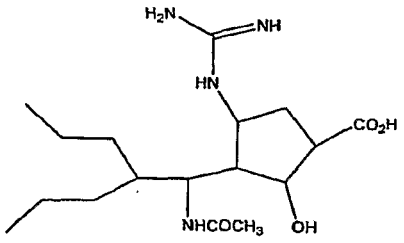
13. The method of any one of claims 2-12, wherein a compound or formula Ia, or a pharmaceutically acceptable salt thereof, is administered.

14. The method of any one of claims 1-13, wherein the plasma concentration of the compound is higher than the IC_{50} of the virus causing the viral infection 12 hours following administration of the compound.

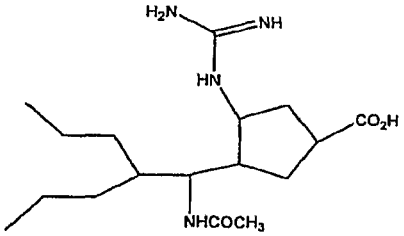
15. A method for inhibiting a neuraminidase in a human comprising administering an effective inhibitory amount of a compound of formula I, II, III, or IV:



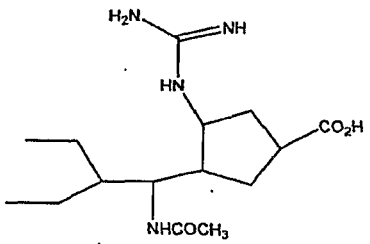
(I)



(II)



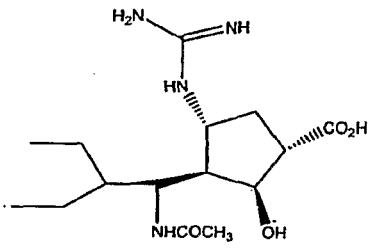
(III)



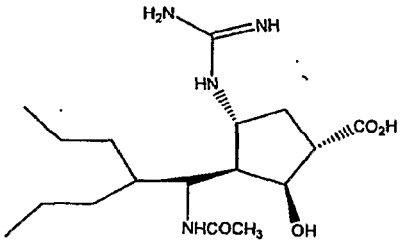
(IV),

or a pharmaceutically acceptable salt thereof, to the human by an intravenous route.

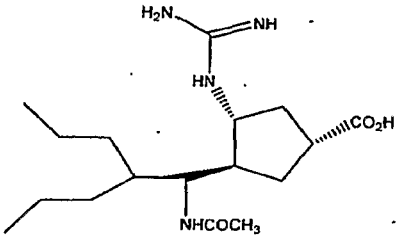
16. The method of claim 15, wherein the compound of formula I, II, III, or IV is a compound of formula Ia, IIa, IIIa, or IVa:



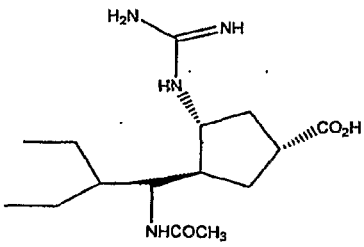
(Ia)



(IIa)



(IIIa)



(IVa),

or a pharmaceutically acceptable salt thereof.

17. The method of claim 15 or 16, wherein the effective inhibitory amount is up to about 800 mg.

18. The method of claim 17, wherein the effective inhibitory amount is up to about 400 mg.

19. The method of claim 18, wherein the effective inhibitory amount is up to about 300 mg.

20. The method of claim 19, wherein the effective inhibitory amount is up to about 200 mg.

21. The method of any one of claims 15-20, wherein the entire effective inhibitory dose is administered in one intravenous administration.

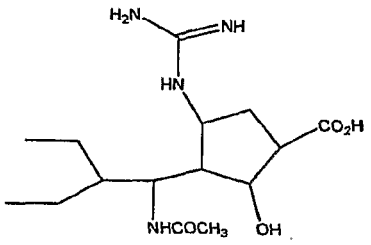
22. The method of any one of claims 15-20, wherein the entire effective inhibitory dose is administered in multiple intravenous administrations.

23. The method of any one of claims 16-22, wherein a compound of formula Ia, or a pharmaceutically acceptable salt thereof, is administered.

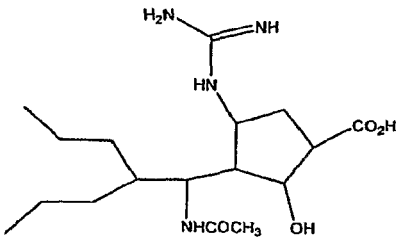
24. The method of any one of claims 1-23, further comprising orally administering a neuraminidase inhibitor to the human.

25. The method of claim 24, wherein the neuraminidase inhibitor that is administered orally is oseltamivir carboxylate.

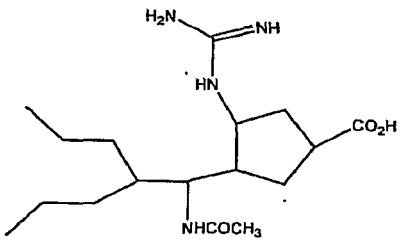
26. The method of claim 24, wherein the neuraminidase inhibitor that is administered orally is a compound of formula I, II, III, or IV:



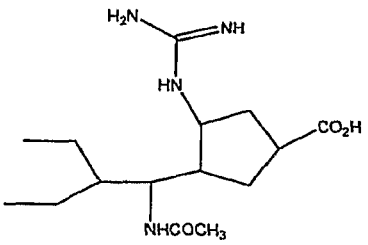
(I)



(II)



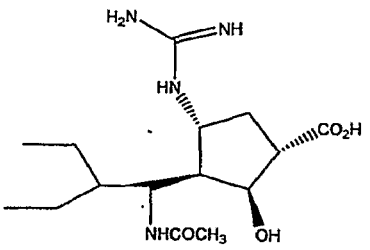
(III)



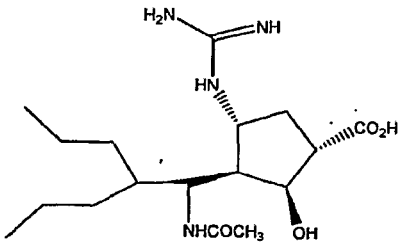
(IV),

or a pharmaceutically acceptable salt thereof.

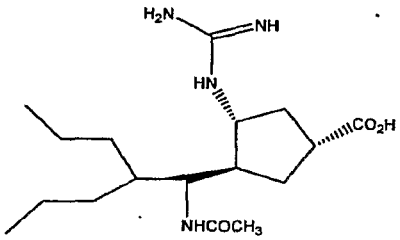
27. The method of claim 24, wherein the neuraminidase inhibitor that is administered orally is a compound of formula Ia, IIa, IIIa, or IVa:



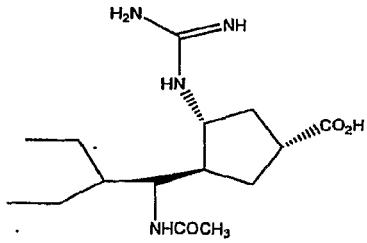
(Ia)



(IIa)



(IIIa)



(IVa),

or a pharmaceutically acceptable salt thereof.

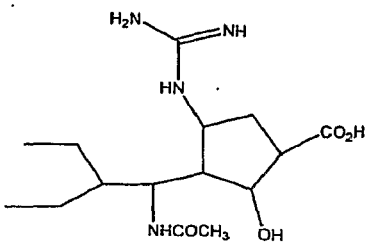
28. The method of claim 27, wherein the neuraminidase inhibitor that is administered orally is a compound of formula Ia, or a pharmaceutically acceptable salt thereof.

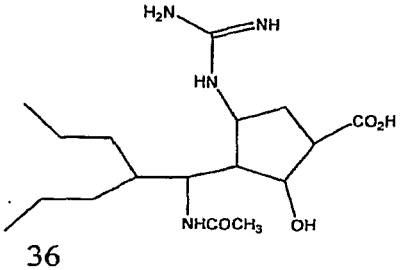
29. The method of any one of claims 24-28, wherein the neuraminidase inhibitor that is administered orally is administered for up to 20 days.

30. The method of claim 29, wherein the neuraminidase inhibitor that is administered orally is administered for up to 10 days.

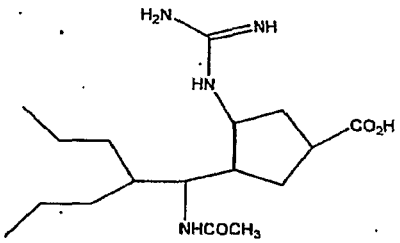
31. The method of claim 30, wherein the neuraminidase inhibitor that is administered orally is administered for up to 5 days.

32. A unit dosage form that is suitable for intravenous administration to a human, comprising up to about 800 mg of a compound of formula I, II, III, or IV:

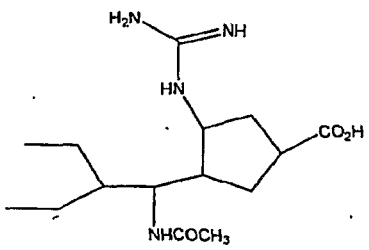




(I)



(II)

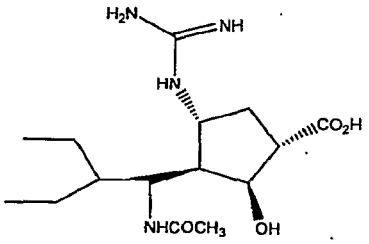


(III)

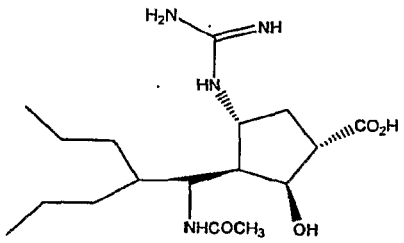
(IV),

or a pharmaceutically acceptable salt thereof.

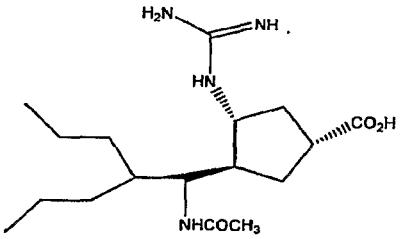
33. The unit dosage form of claim 32, wherein the compound of formula I, II, III, or IV is a compound of formula Ia, IIa, IIIa, or IVa:



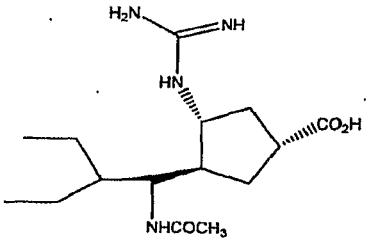
(Ia)



(IIa)



(IIIa)



(IVa),

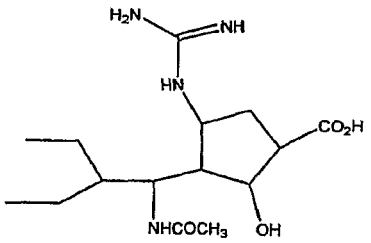
or a pharmaceutically acceptable salt thereof.

34. The unit dosage form of claim 32 or 33 that comprises up to about 400 mg of the compound or salt.

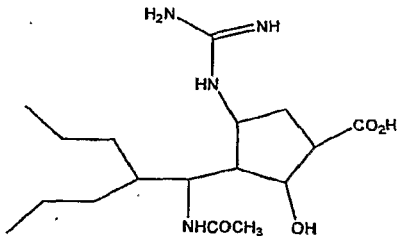
35. The unit dosage form of claim 34 that comprises up to about 300 mg of the compound or salt.

36. The unit dosage form of claim 35 that comprises up to about 200 mg of the compound or salt.

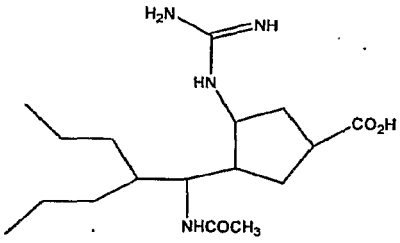
37. A kit, comprising packaging materials, a compound of formula I, II, III, or IV:



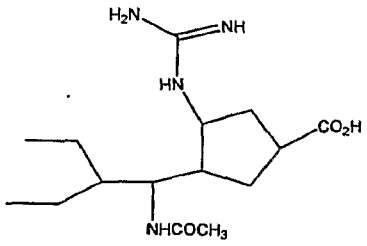
(I)



(II)



(III)



(IV),

or a pharmaceutically acceptable salt thereof, and instructions for administering the compound to a human by an intravenous route.

38. The kit of claim 37, wherein the compound is provided in a formulation suitable for intravenous administration.

39. The kit of claim 37 or 38 that comprises up to about 800 mg of the compound or salt.

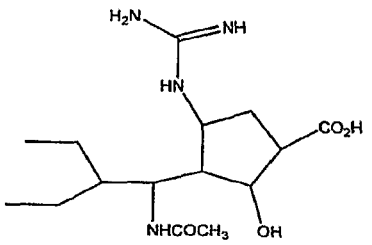
40. The kit of claim 39 that comprises up to about 400 mg of the compound or salt.

41. The kit of claim 40 that comprises up to about 300 mg of the compound or salt.

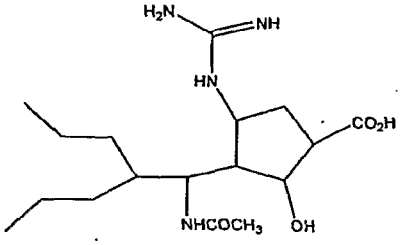
42. The kit of claim 41 that comprises up to about 200 mg of the compound or salt.

43. A kit, comprising packaging materials, a unit dosage form as described in any one of claims 32-36, and instructions for administering the compound to a human by an intravenous route.

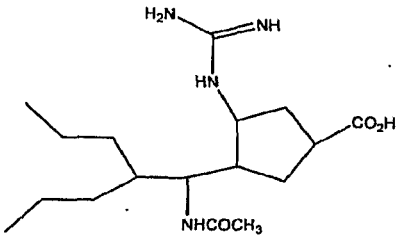
44. Use of a compound of formula I, II, III, or IV:



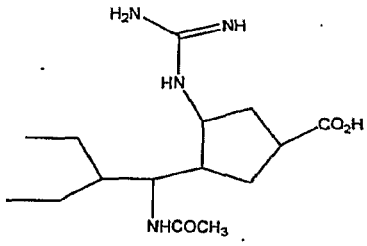
(I)



(II)



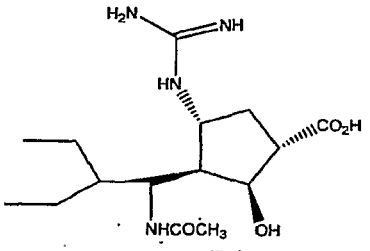
(III)



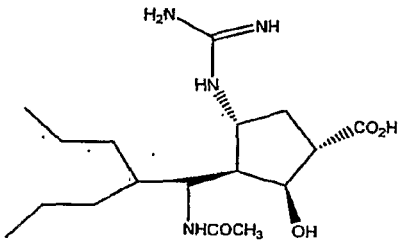
(IV),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for intravenous injection for increasing life expectancy or reducing mortality in a group of mammals exposed to a source of an influenza virus, by intravenous injection of a dose of the medicament into each member of the group presenting clinical symptoms of infection.

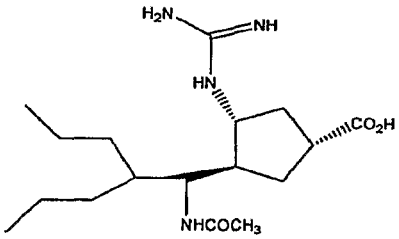
45. Use as in claim 44, wherein the compound of formula I, II, III, or IV is a compound of formula Ia, IIa, IIIa, or IVa:



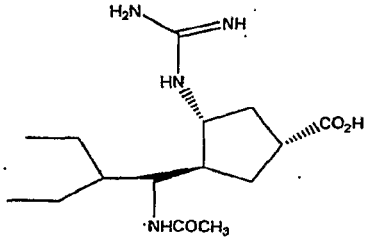
(Ia)



(IIa)



(IIIa)



(IVa),

or a pharmaceutically acceptable salt thereof.

46. Use as claimed in claim 44 or 45, wherein the influenza virus is an avian influenza virus.

47. Use as claimed in claim 44 or 45, wherein the influenza virus is an influenza type A or type B virus.

48. Use as claimed in claim 44 or 45, wherein the influenza virus is H5N1, or a mutant strain thereof.

49. Use as claimed in claim 44 or 45, wherein the influenza virus is a strain of virus represented by the formula H_xN_y wherein X is an integer from 1-16 and Y is an integer from 1-9.

50. Use as claimed in claim 44 or 45, wherein the influenza virus is an H3N2, H1N1, H5N1, avian, or seasonal influenza virus.

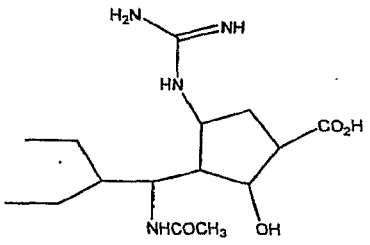
51. Use as claimed in any one of claims 44-50, in which each member of the group presenting symptoms of infection receives only one intravenous dose of the medicament.

52. Use as claimed in any one of claims 44-50, in which each member of the group presenting symptoms of infection receives multiple intravenous doses of the medicament.

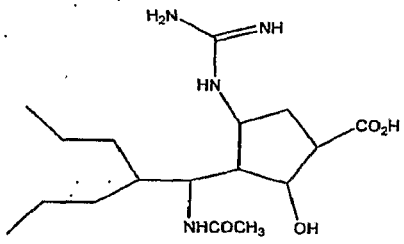
53. Use as claimed in any one of claims 44-52, for increasing life expectancy or reducing mortality in a group of mammals, wherein the members of the group presenting clinical symptoms of infection are treated orally with a neuraminidase inhibitor.

54. Use as claimed in claim 53, in which the neuraminidase inhibitor is oseltamivir carboxylate.

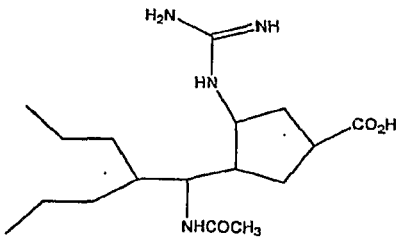
55. Use as claimed in claim 53, in which the neuraminidase inhibitor is a compound of formula I, II, III, or IV:



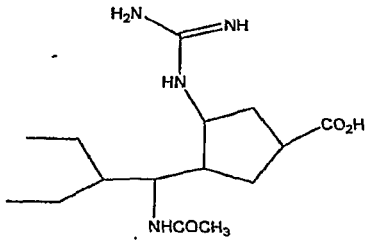
(I)



(II)



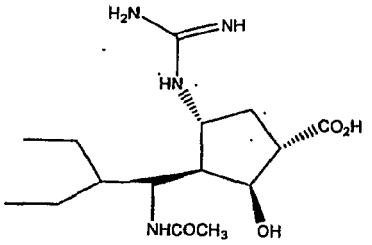
(III)



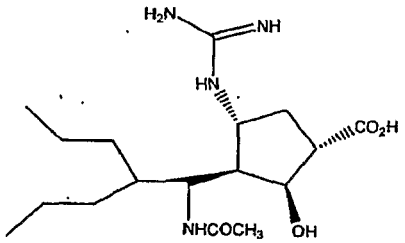
(IV),

or a pharmaceutically acceptable salt thereof.

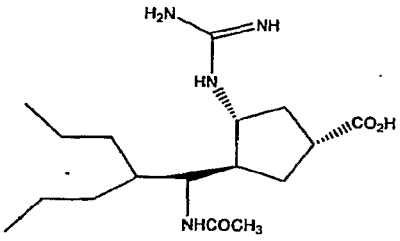
56. Use as claimed in claim 53, in which the neuraminidase inhibitor is a compound of formula Ia, IIa, IIIa, or IVa:



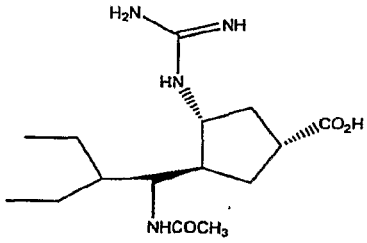
(Ia)



(IIa)



(IIIa)



(IVa),

or a pharmaceutically acceptable salt thereof.

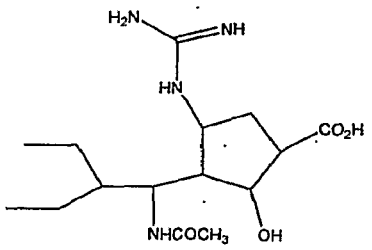
57. Use as claimed in claim 56, in which the neuraminidase inhibitor is a compound of formula Ia, or a pharmaceutically acceptable salt thereof.

58. Use as claimed in any one of claims 44-57, in which the source of the virus is an infected bird.

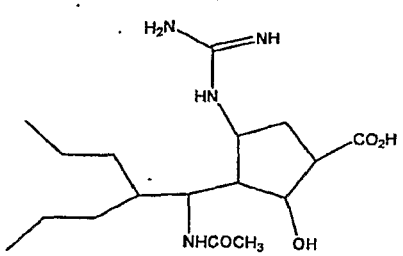
59. Use as claimed in any one of claims 44-57, in which the source of the virus is a mammal presenting symptoms of infection.

60. Use as claimed in any one of claims 44-59, which is for reducing mortality.

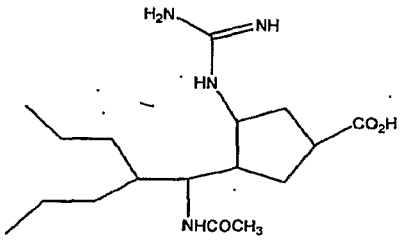
61. Use of a compound of formula I, II, III, or IV:



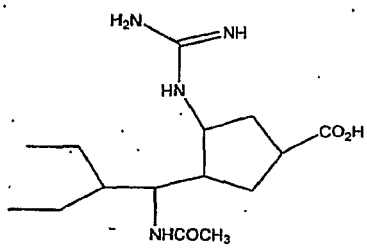
(I)



(II)



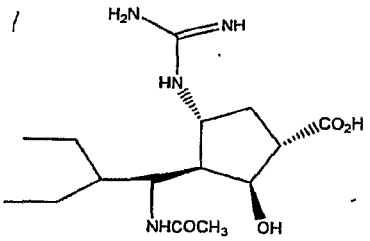
(III)



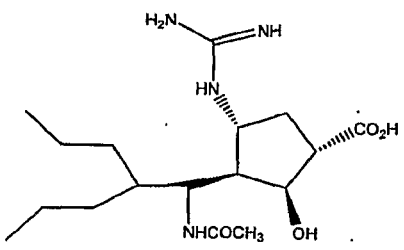
(IV),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for intravenous injection for increasing life expectancy or reducing mortality in a group of mammals exposed to a source of an influenza virus, by intravenous injection of a dose of the medicament into each member of the group.

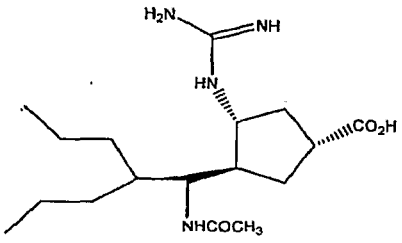
62. Use as in claim 61, wherein the compound of formula I, II, III, or IV is a compound of formula Ia, IIa, IIIa, or IVa:



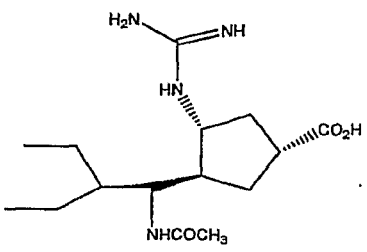
(Ia)



(IIa)



(IIIa)



(IVa),

or a pharmaceutically acceptable salt thereof.

63. Use as claimed in claim 61 or 62, in which the influenza virus is an avian influenza virus.

64. Use as claimed in claim 63, in which the avian influenza virus is H5N1, or a mutant strain thereof.

65. Use as claimed in claim 61 or 62, wherein the influenza virus is a strain of virus represented by the formula H_xN_y wherein X is an integer from 1-16 and Y is an integer from 1-9.

66. Use as claimed in claim 61 or 62, wherein the influenza virus is an influenza type A or type B virus.

67. Use as claimed in claim 61 or 62, wherein the influenza virus is an H3N2, H1N1, H5N1, avian, or seasonal influenza virus.

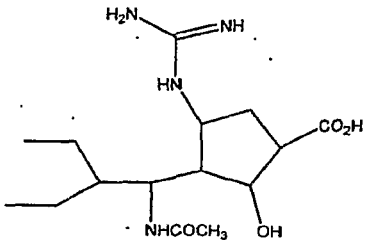
68. Use as claimed in any one of claims 61-67, in which each member of the group receives only one intravenous dose of the medicament.

69. Use as claimed in any one of claims 61-67, in which each member of the group receives multiple intravenous doses of the medicament.

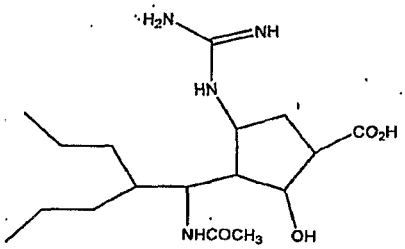
70. Use as claimed in any one of claims 61-69, for increasing life expectancy or reducing mortality in a group of mammals wherein the members of the group are treated orally with a neuraminidase inhibitor.

71. Use as claimed in claim 70, in which the neuraminidase inhibitor is oseltamivir carboxylate.

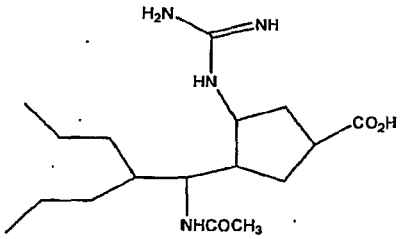
72. Use as claimed in claim 70, in which the neuraminidase inhibitor is a compound of formula I, II, III, or IV:



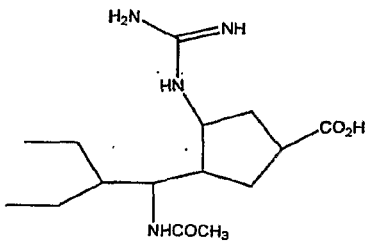
(I)



(II)



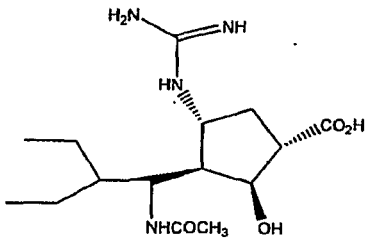
(III)



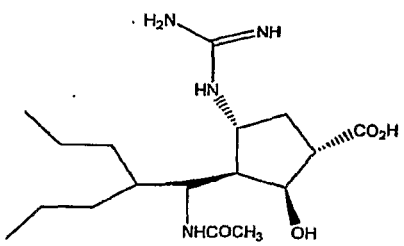
(IV),

or a pharmaceutically acceptable salt thereof.

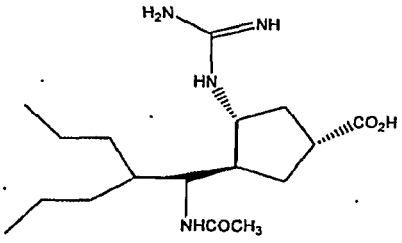
73. Use as claimed in claim 70, in which the neuraminidase inhibitor is a compound of formula Ia, IIa, IIIa, or IVa:



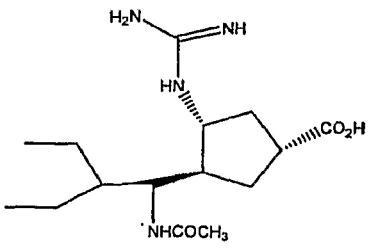
(Ia)



(IIa)



(IIIa)



(IVa),

or a pharmaceutically acceptable salt thereof.

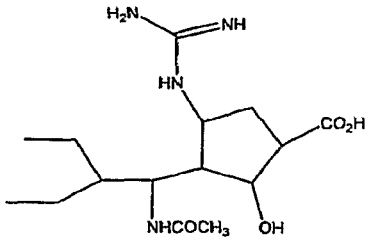
74. Use as claimed in claim 73, in which the neuraminidase inhibitor is a compound of formula Ia, or a pharmaceutically acceptable salt thereof.

75. Use as claimed in any one of claims 61-74, in which the source of the virus is an infected bird.

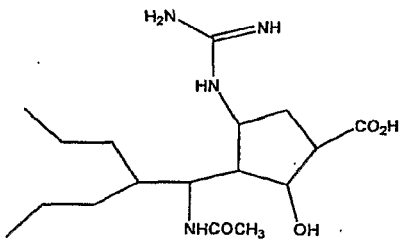
76. Use as claimed in any one of claims 61-74, in which the source of the virus is a mammal presenting symptoms of infection.

77. Use as claimed in any one of claims 61-76, which is for reducing mortality.

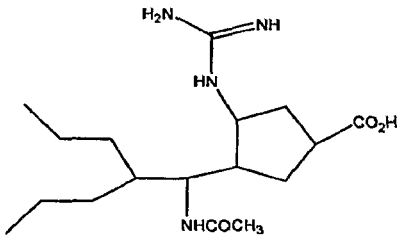
78. Use of a compound of formula I, II, III, or IV:



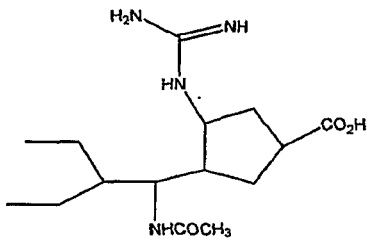
(I)



(II)



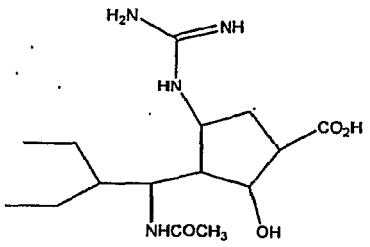
(III)



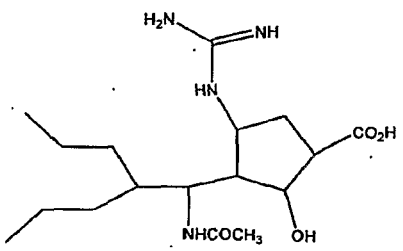
(IV),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for intravenous injection for achieving a plasma concentration in a human of the compound that is effective to treat a virus by intravenous injection of a dose of the medicament into the human.

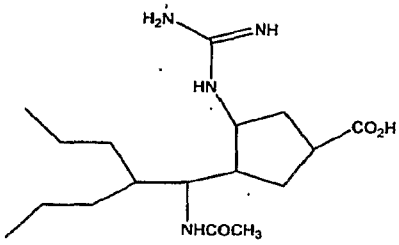
79. Use of a compound of formula I, II, III, or IV:



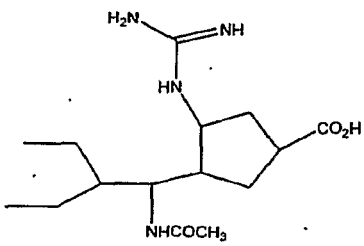
(I)



(II).



(III)



(IV),

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for intramuscular injection for achieving a plasma concentration in a human of the compound that is effective to treat a virus by intramuscular injection of a dose of the medicament into the human.

80. The use of claim 78 or 79, wherein the plasma concentration of the compound is higher than the IC_{50} of the virus 12 hours following injection of the compound.