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(54) **DIMERIC COMPOUNDS AND AS INHIBITORS OF NEURAMINIDASE**

DIMERVERBINDUNGEN UND ALS INHIBITOREN DER NEURAMIDINASE

COMPOSES DIMERES EN TANT QU'INHIBITEURS DE LA NEURAMINIDASE

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(73) Proprietor: **BIOTA SCIENTIFIC MANAGEMENT PTY. LTD.**
Melbourne, VIC 3004 (AU)

(72) Inventors:
- **WU, Wen-Yang**
  Mount Waverly, VIC 3149 (AU)
- **JIN, Betty**
  Mount Waverly, VIC 3149 (AU)

(74) Representative: **Beacham, Annabel Rose et al**
Frank B. Dehn & Co.,
European Patent Attorneys,
179 Queen Victoria Street
London EC4V 4EL (GB)

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Remarks:

The file contains technical information submitted after the application was filed and not included in this specification

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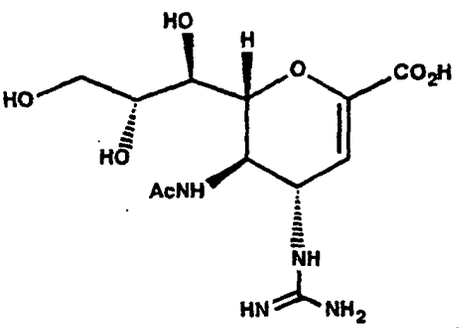
Description

[0001] This invention relates to a new class of chemical compounds and their use in medicine. In particular the invention concerns novel dimeric compounds, methods for their preparation, pharmaceutical formulations thereof and their use as antiviral agents.

BACKGROUND OF THE INVENTION

[0002] Enzymes with the ability to cleave N-acetyl neuraminic acid (NANA), also known as sialic acid, from other carbohydrates are present in many microorganisms. These include bacteria such as *Vibrio cholerae, Clostridium perfringens, Streptococcus pneumoniae* and *Arthrobacter sialophilus,* and viruses such as influenza virus, parainfluenza virus, mumps virus, Newcastle disease virus and Sendai virus. Most of these viruses are of the orthomyxovirus or paramyxovirus groups, and carry a neuraminidase activity on the surface of the virus particles. Many of these neuraminidase-possessing organisms are major pathogens of man and/or animals, and some, such as influenza virus and Newcastle disease virus, cause diseases of enormous importance.

[0003] It has long been thought that inhibitors of neuraminidase might prevent infection by neuraminidase-bearing viruses. Most of the known neuraminidase inhibitors are analogues of neuraminic acid, such as 2-deoxy-2,3-dehydro-N-acetylneuraminic acid (DANA) and some of its derivatives (Meindl *et al*, Virology, 1974 58 457). Our International Patent Publication No. WO 91/16320 describes a number of analogues of DANA which are active against viral neuraminidase, and it has been shown in particular that 4-guanidino-2-deoxy-2,3-dehydro-N-acetylneuraminic acid (Compound (A), code number GG167) is useful in the treatment of influenza A and B (N. Engl. J. Med., 1997 337 874-880). Other patent applications describe various closely-related sialic acid derivatives (*eg.* PCT Publications No. WO 95/18800, No. WO 95/20583 and No. WO 98/06712), and anti-viral macromolecular conjugates of GG167 have also been described (International Patent Application No. PCT/AU97/00771).



Compound (A)

Ac represents acetyl

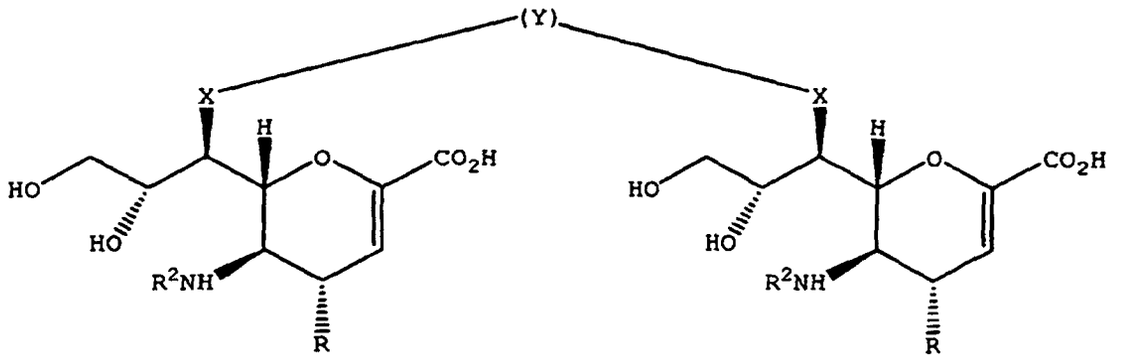
[0004] In addition to the sialic acid based inhibitors mentioned above, other types of highly active inhibitors of influenza virus neuraminidase have also been described, particularly those based on 5- and 6-membered carbocyclic ring systems (*eg.* International Patent Publications No. WO 96/26933 and No. 97/47194).

[0005] Recently, International Patent Publication No. WO 97/06157, No. WO 98/06712 and European Patent Application No. 0823428 have described certain derivatives of compound (A) in which the normal sialic acid 7-hydroxy group is replaced by various other functionalities, which inhibit multiplication of the influenza virus.

[0006] We have now surprisingly found that when two neuraminidase-binding compounds are suitably linked together through a region of the molecule that is not involved in binding to the active site, the resultant dimers show outstanding anti-viral activity. In particular we have found that, although an extra substituent attached to compound (A) at the 7-position generally causes a slight decrease in the anti-influenza activity, when two such 7-substituted molecules of compound (A) are both attached to a suitable spacer moiety, the anti-influenza activity can be greatly improved. Though not wishing to be bound or limited by any proposed mechanism for the observed effect, we believe that the dimeric compounds of the invention have improved anti-influenza activity because they are able to bind to two separate neuraminidase molecules, and thereby cause aggregation of the neuraminidase tetramers and/or the influenza virions.

SUMMARY OF THE INVENTION

[0007] In a first aspect the invention provides a compound of General Formula (I):



(I)

wherein

R is an azido group, a hydroxy group, an unsubstituted or substituted guanidino group, or an unsubstituted or substituted amino group;

R^2 is $COCH_3$, $COCF_3$, SO_2CH_3 or SO_2CF_3;

X is O, O(C=O), NH, NHCO, O(C=O)NH, O(C=S)NH, NH(C=O)NH or NH(C=S)NH;

and spacer group Y is an optionally substituted and/or branched chain of up to 100 atoms in length, with the backbone atoms selected from the group consisting of carbon, nitrogen, oxygen and sulphur;

or a pharmaceutically acceptable salt or derivative thereof.

[0008] Preferably the spacer group is 8 to 100, more preferably 10 to 50, even more preferably 12 to 30 atoms in length.

[0009] Most preferably:

R is an unsubstituted or substituted amino or guanidino group;

R^2 is acetyl or trifluoroacetyl;

X is O(C=O)NH; and

spacer group Y is between 10 and 50 atoms in length.

[0010] Molecular modelling studies indicate that the spacer group could be as short as 18, 15 or 10 atoms long, or may even be shorter than this. The person skilled in the art will readily be able to optimize the spacer length by routine trial and error experimentation.

[0011] In general it is intended that when any variable occurs twice in formula (I), the variable may be the same or different.

[0012] Where R is an amino or guanidino group, suitable substituents include, but are not limited to, alkyl, hydroxyalkyl, allyl, nitrile, alkoxycarbonyl and acyl.

[0013] Suitable spacer groups Y include, but are not limited to, optionally substituted straight or branched hydrocarbon chains, peptides, oligosaccharides, poly amino acids, polyethylene glycol units, alkylamidoalkanes, alkylureidoalkanes, any of which may be used alone, in multiple forms or in combination. The spacer group Y may also optionally have attached to it an extra functionality to improve the pharmaceutical or pharmacokinetic properties of the compound. Such functionalities include lipophilic hydrocarbon groups, polyethylene glycol (PEG) chains and peptides.

[0014] For the purposes of this specification, the terms "hydrocarbon", "alkane" or "alkyl" are intended to include saturated, unsaturated and cyclic hydrocarbon groups, aromatic rings, and combinations of such groups. Suitable substituents on hydrocarbon chains include Br, Cl, F, I, CF_3, NH_2, substituted amino groups such as NHacyl, and alkoxy groups such as methoxy and hydroxy, and are preferably F, Cl, hydroxy, alkoxy, amino, alkylamino or carboxy.

[0015] It will be appreciated by those skilled in the art that the compounds of formula (I) may be modified to provide pharmaceutically acceptable derivatives thereof at any of the functional groups in the compounds of formula (I). Of particular interest as such derivatives are compounds modified at the carboxyl function, hydroxyl functions or at amino groups. Thus compounds of interest include alkyl esters, such as methyl, ethyl, propyl or isopropyl esters, aryl esters, such as phenyl, benzoyl esters, and acetyl esters of the compounds of formula (I).

[0016] It will be appreciated by those skilled in the art that the pharmaceutically acceptable derivatives of the com-

pounds of formula (I) may be derivatised at more than one position.

[0017] The term "pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt, ester or salt of such ester of a compound of formula (I) or any other compound which, upon administration to the recipient, is capable of providing a compound of formula (I) or an antivirally active metabolite or residue thereof. Of particular interest as derivatives are compounds modified at the sialic acid carboxy or glycerol hydroxy groups, or at amino and guanidine groups.

[0018] Pharmaceutically acceptable salts of the compounds of formula (I) include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulphuric, nitric, perchloric, fumaric, maleic, phosphoric, glycollic, lactic, salicylic, succinic, toluene-p-sulphonic, tartaric, acetic, citric, methanesulphonic, formic, benzoic, malonic, naphthalene-2-sulphonic and benzenesulphonic acids. Other acids such as oxalic acid, while not in themselves pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining compounds of the invention and their pharmaceutically acceptable acid addition salts.

[0019] Salts derived from appropriate bases include alkali metal (*eg.* sodium), alkaline earth metal (*eg.* magnesium), ammonium, and NR_4^+ (where R is C_{1-4}alkyl) salts.

[0020] The compounds of formula (I) possesses antiviral activity. In particular these compounds are inhibitors of viral neuraminidase of orthomyxoviruses and paramyxoviruses, for example the viral neuraminidase of influenza A and B, parainfluenza, mumps and Newcastle disease.

[0021] Thus in a second aspect the invention provides a compound of the invention, preferably a compound of formula (I) or a pharmaceutically acceptable derivative thereof, for use as an active therapeutic agent in the treatment of viral infections, for example, orthomyxovirus and paramyxovirus infections.

[0022] In a third aspect the invention provides use of a compound of the invention in the manufacture of a medicament for the treatment of a viral infection, for example, orthomyxovirus and paramyxovirus infections in a mammal. Preferably, the mammal is a human.

[0023] The compound is preferably a compound of General Formula I or Formula Ia.

[0024] In a preferred embodiment of this aspect of the invention the medicament is used to treat infection caused by influenza A or B.

[0025] It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis against infection as well as to the treatment of established infections or symptoms.

[0026] The compounds of the invention may also be used in "in vitro" diagnostic methods, in particular methods for the detection of influenza virus. For use in such methods it may be advantageous to link a compound of the invention to a label.

[0027] It will be further appreciated that the amount of a compound of the invention required for use in treatment will vary not only with the particular compound selected but also with the route of administration, the nature of the condition being treated, and the age and condition of the patient, and will ultimately be at the discretion of the attendant physician or veterinarian. In general however, a suitable dose will be in the range of from about 0.01 to 100 mg/kg of bodyweight per day, preferably in the range of 0.05 to 10 mg/kg/day, most preferably in the range of 0.1 to 1 mg/kg/day.

[0028] Treatment is preferably commenced before or at the time of infection and continued until virus is no longer present in the respiratory tract. However the compounds are also effective when given post-infection, for example after the appearance of established symptoms.

[0029] Suitably treatment is given 1-4 times daily and continued for 3-7 days post-infection, *eg.* 5 days, depending upon the particular compound used.

[0030] The desired dose may be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day.

[0031] The compound is conveniently administered in unit dosage form, for example containing 1 to 1000 mg, conveniently 2 to 200 mg, most conveniently 50 to 100 mg of active ingredient per unit dosage form.

[0032] While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical, it is preferable to present the active ingredient as a pharmaceutical formulation.

[0033] Thus in a fourth aspect the invention provides a pharmaceutical formulation comprising a compound of formula (I) or a pharmaceutically acceptable salt or derivative thereof, together with one or more pharmaceutically acceptable carriers therefor and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not being deleterious to the recipient thereof.

[0034] The compounds of the invention may also be used in combination with other therapeutic agents, for example other anti-infective agents. In particular the compounds of the invention may be employed with other antiviral agents. The invention thus provides in a sixth aspect a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt or derivative thereof together with another therapeutically active agent, in particular an antiviral agent.

[0035] The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical

formulation and thus such formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier therefor comprise a further aspect of the invention.

[0036] Suitable therapeutic agents for use in such combinations include other anti-infective agents, in particular antibacterial and anti-viral agents such as those used to treat respiratory infections. For example, other compounds effective against influenza viruses, such as the sialic acid analogues referred to above, amantadine, rimantadine and ribavirin, may be included in such combinations.

[0037] The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

[0038] When the compounds of the invention are used with a second therapeutic agent active against the same virus, the dose of each compound may either be the same as or different from that employed when each compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

[0039] Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration, or those in a form suitable for administration to the respiratory tract (including the nasal passages) for example by inhalation or insufflation. The formulations may, where appropriate, be conveniently presented in discrete dosage units, and may be prepared by any of the methods well known in the art of pharmacy. These methods include the step of bringing into association the active compound with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired formulation.

[0040] Pharmaceutical formulations suitable for oral administration may conveniently be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution, a suspension or as an emulsion. The active ingredient may also be presented as a bolus, electuary or paste. Tablets and capsules for oral administration may contain conventional excipients such as binding agents, fillers, lubricants, disintegrants, or wetting agents. The tablets may be coated according to methods well known in the art. Oral liquid preparations may for example be in the form of aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles, which may include edible oils, or preservatives.

[0041] The compounds according to the invention may also be formulated for parenteral administration by injection, for example bolus injection, or continuous infusion, and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulating agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilisation from solution, for constitution with a suitable vehicle, *eg.* sterile, pyrogen-free water, before use.

[0042] For topical administration to the epidermis the compounds according to the invention may be formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base, and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents.

[0043] Formulations suitable for topical administration in the mouth include lozenges comprising active ingredient in a flavoured base, usually sucrose and gum acacia or gum tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin or sucrose and gum acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

[0044] Pharmaceutical formulations suitable for rectal administration wherein the carrier is a solid are most preferably presented as unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art, and the suppositories may be conveniently formed by admixture of the active compound with the softened or melted carrier(s) followed by chilling and shaping moulds.

[0045] Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

[0046] For administration to the respiratory tract, including intranasal administration, the neuraminidase inhibitors may be administered by any of the methods and formulations employed in the art for administration to the respiratory tract.

[0047] Thus in general the compounds may be administered in the form of a solution or a suspension or as a dry powder.

[0048] Solutions and suspensions will generally be aqueous, for example prepared from water alone (for example sterile or pyrogen-free water) or water and a physiologically acceptable co-solvent (for example ethanol, propylene glycol or polyethlene glycols such as PEG 400).

[0049] Such solutions or suspensions may additionally contain other excipients for example preservatives (such as benzalkonium chloride), solubilising agents/surfactants such as polysorbates (*eg.* Tween 80, Span 80, benzalkonium chloride), buffering agents, isotonicity-adjusting agents (for example sodium chloride), absorption enhancers and viscosity enhancers. Suspensions may additionally contain suspending agents (for example microcrystalline cellulose, carboxymethyl cellulose sodium).

[0050] Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The formulations may be provided in single or multidose form. In the latter case a means of dose metering is desirably provided. In the case of a dropper or pipette this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray this may be achieved for example by means of a metering atomising spray pump.

[0051] Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the compound is provided in a pressurised pack with a suitable propellant, such as a chlorofluorocarbon (CFC), for example dichlorodifluoromethane, trichlorofluoromethane or dichlorotetrafluoroethane, carbon dioxide or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

[0052] Alternatively the compounds may be provided in the form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidine (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form, for example in capsules or cartridges of *eg*. gelatin, or blister packs from which the powder may be administered by means of an inhaler.

[0053] In formulations intended for administration to the respiratory tract, including intranasal formulations, the compound will generally have a small particle size, for example of the order of 5 microns or less. Such a particle size may be obtained by means known in the art, for example by micronisation.

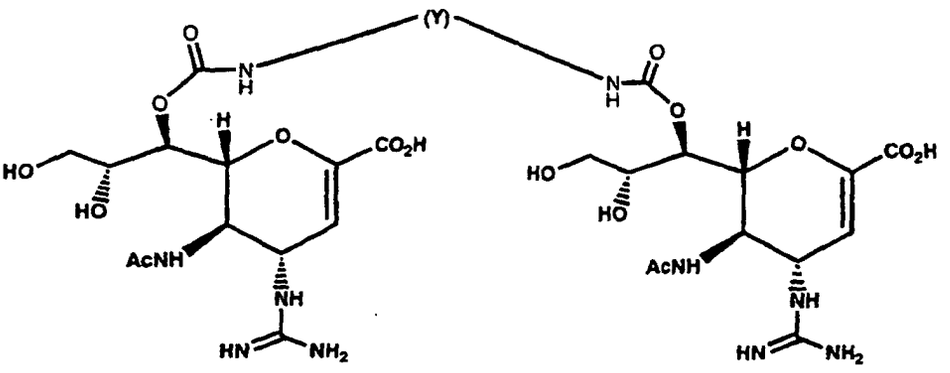
[0054] When desired, formulations adapted to give sustained release of the active ingredient may be employed.

[0055] For the purposes of this specification it will be clearly understood that the word "comprising" means "including but not limited to", and that the word "comprises" has a corresponding meaning.

DETAILED DESCRIPTION OF THE INVENTION

[0056] The invention will now be described in detail by way of reference only to the following non-limiting examples.

[0057] Particular examples of compounds of the invention include those of Formula (Ia), in which the spacer group Y is as shown in Table 1 below.



(Ia)

Table 1

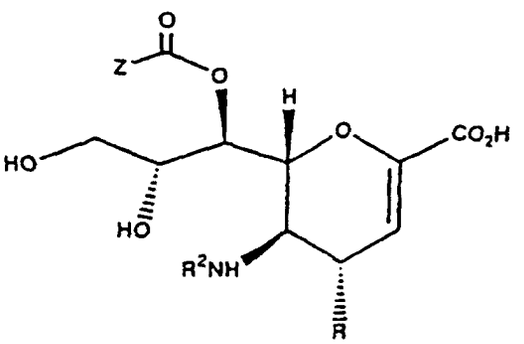
Compound Number	Linking Group Y
(**2**)	$(CH_2)_6NHCONH(CH_2)_4NHCONH(CH_2)_6$
(**3**)	$(CH_2)_6NHCONH(CH_2)_{12}NHCONH(CH_2)_6$

Table 1 (continued)

Compound Number	Linking Group Y
(**4**)	$(CH_2)_6NH[COCH_2NH]_3CONH(CH_2)_6NHCO[NHCH_2CO]_3NH(CH_2)_6$
(**5**)	$(CH_2)_6NH[CO(CH_2)_5NH]_2CONH(CH_2)_{12}NHCO[NH(CH_2)_5CO]_2NH(CH_2)_6$
(**6**)	$(CH_2)_6NH[CO(CH_2)_5NH]_4CONH(CH_2)_6NHCO[NH(CH_2)_5CO]_4NH(CH_2)_6$
(**8**)	$(CH_2)_6NHCOCH_2N[CH_2CO_2H]CH_2CH_2N[CH_2CO_2H]CH_2CONH(CH_2)_6$
(**9**)	$(CH_2)_6NHCO(CH_2)_2CH[NH_2.TFA]CONHCH_2CONH(CH_2)_6$
(**10**)	$CH_2CH_2OCH_2CH_2OCH_2CH_2$

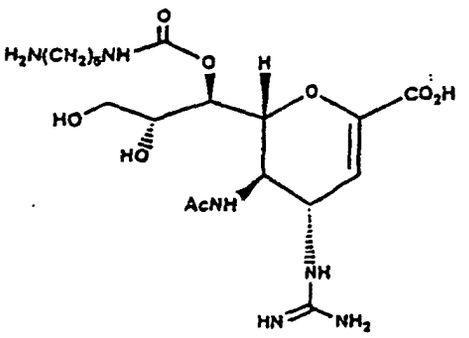
[0058] The compounds of the invention may be prepared by the methods outlined below, in which R and R^2 are as defined for formula (I).

[0059] Suitable monomeric intermediate compounds of general formula (II) can be prepared following methods described in International Patent Publications No. WO 97/06157 and No. WO 97/32214. Thus if the group at position 7 is an arylcarbonate (*eg.* Z = 4-nitrophenoxy), the intermediate can be used to make 7-carbamate derivatives (Z = alkyl-NH) by reaction with various amines (alkyl-NH_2).



(II)

[0060] For example, the (6-aminohexyl)-7-carbamate derivative of GG167, compound (7) below, is a useful precursor to certain compounds of the invention. As will be appreciated by those skilled in the art, it may be necessary or desirable to use protecting groups to protect one or more of the functional groups of the neuraminidase-binding molecule during the process of attaching the monomers to the spacer group. See for example "Protective Groups in Organic Synthesis" by Theodore W. Greene and P.G.M. Wuts (John Wiley & Sons, 1991).



Compound (7)

Example 1 Preparation of Bis-[7-(6'-ethylene-ureidohexyl)-carbamoyloxy-5-acetamido-4-guanidino-2,3,4,5-tetradeoxy-D-*glycero*-D-*galacto*-non-2-enopyranosonic acid] (**2**)

[0061] To a solution of 5-acetamido-7-(6'-aminohexyl)-carbamoyloxy-4-guanidino-2,3,4,5-tetradeoxy-D-*glycero*-D-*galacto*-non-2-enopyranosonic acid (7) (50 mg, 0.1055 mmole) in a mixture of DMSO (1 ml) and pyridine (2.5 ml) were added 1,4-diisocyanatobutane (7.39 mg, 0.0527 mmole) and 4-dimethylaminopyridine (12.87 mg, 0.1055 mmole). The whole mixture was stirred under argon at 50□C for 7 days. The mixture was filtered and the filtrate was evaporated under high vacuum to dryness. The residue was stirred in acetone (2 x 20 ml) at room temperature for 24 hr and filtered. The filter-cake was washed with acetone (5 ml) and recrystallized from a mixture of methanol and water (7:3) to afford the title compound (**2**) as a white solid (18.6 mg, 32%).
MS 1090 $(M+2)^{++}$
^{1}H-nmr (CD_3OD + D_2O) δ (ppm): 1.30-1.70 (m, 20H), 2.01 (br s, 6H), 2.95-3.20 (m, 12H), 3.50-3.65 (m, 2H), 3.70-3.80 (m, 2H), 3.90-4.20 (m, 4H), 4.35-4.70 (m, 6H), 5.70 (br, 2H).

Example 2 Preparation of Bis-[7-(6'-hexyleneureido)-carbamoyloxy-5-acetamido-4-guanidino-2,3,4,5-tetradeoxy-D-*glycero*-D-*galacto*-non-2-enopyranosonic acid) (**3**)

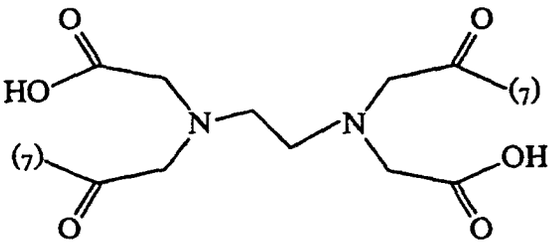
[0062] To a solution of 5-acetamido-7-(6'-aminohexyl)-carbamoyloxy-4-guanidino-2,3,4,5-tetradeoxy-D-*glycero*-D-*galacto*-non-2-enopyranosonic acid (7) (50 mg, 0.1055 mmole) in a mixture of DMSO (1 ml) and pyridine (2.5 ml) were added 4-dimethylaminopyridine (12.87 mg, 0.1055 mmole) and 1,12-diisocyanatododecane (13.31 mg, 0.0527 mmole). The whole mixture was stirred under argon at 50°C for 7 days and then filtered. The filtrate was evaporated under high vacuum to dryness. The residue was taken up in acetone (2 x 30 ml), redissolved in DMSO (1 ml), then diluted with a mixture of acetone and ether (1:1) (100 ml) to afford a white precipitate. After filtration, the filter cake was washed with acetone (20 ml) and air-dried to give a crude product (3), which was then recrystallized from a mixture of methanol and water to afford the title compound (**3**) as a white powder (15 mg, 23.6%).
MS 1202 $(M+2)^{++}$
^{1}H-nmr (CD_3OD + D_2O) δ (ppm): 1.25-1.70 (m, 36H), 1.98 (br, s, 6H), 2.95-3.20 (m, 12H), 3.35-3.70 (m, 4H), 3.80-4.60 (m, 10H), 5.65 (br, 2H).

Example 3 Preparation of amino acid linked Bis-[GG167-7-carbamate]; Compounds No. (**4**), (**5**) and (**6**)

[0063] In a similar manner to that described in Examples 1 and 2, compounds (**4**), (**5**) and (**6**) were each prepared using the 6-aminohexyl-7-carbamate compound (**7**), or protected forms of (**7**), as the key starting material. Each compound was characterised by its mass spectrum and Nmr data.

Example 4 Preparation of Bis-[7-(6'-methyleneamine-N-acetic acid-N-acetamido-hexyl)-carbamoyloxy-5-acetamido-4-guanidino-2,3,4,5-tetradeoxy-*D-glycero-D-galacto*-non-2-enopyranosonic acid] (Compound Number (**8**))

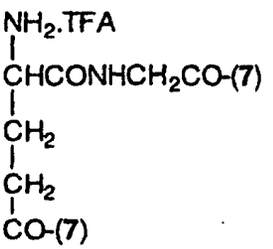
[0064]



[0065] To a solution of 5-acetamido-7-(6'-aminohexyl)-carbamoyloxy-4-guanidino-2,3,4, 5-tetradeoxy-*D-glycero-D-galacto*-non-2-enopyranosonic acid (7) (76 mg, 0.16mmole) in a mixture of DMF (7.5 ml) and pyridine (2.5 ml) were added ethylenediaminetetraacetic dianhydride (20.5 mg, 0.08mmole) and 4-(dimethylamino)pyridine (3.5 mg, 0.028mmole). The whole mixture was stirred at 50°C for 18 hr, then evaporated to dryness under high vacuum. The residue was partitioned between dichloromethane (20 ml) and water (10 ml). The aqueous solution was washed with dichloromethane (10 ml), ethyl acetate (10 ml), then evapotated to dryness under high vacuum. The residue was triturated in acetone (50 ml x 2) and filtered. The solid was dissolved in water (0.5 ml) and chromatographed on a Sephadex G-25 (50 ml) column using water as eluent and the product was freeze-dried, to afford the title compound (**8**) (30 mg, 31%).
MS 1206 (M+2)
^{1}H-nmr (D_2O) δ (ppm): 1.23-1.63 (m, 16H), 1.98 (brs, 6H), 3.00-3.20 (m, 8H), 3.35-3.55 (m, 6H), 3.60-3.92 (m, 10H), 4.08 (m, 4H), 4.43 (dd, 2H), 4.50 (dd, 2H), 4.84 (dd, 2H), 5.66 (br, 2H).

Example 5 Preparation of D-glutam-γ-yl-α-ylamineacetyl, di-[7-(6'-aminohexyl)-carbamoyloxy-5-acetamido-4-guanidino-2,3,4,5-tetradeoxy-*D-glycero-D-galacto*-non-2-enopyranosonic acid] as trifluoroacetic acid salt (Compound Number (**9**))

[0066]



[0067] N-Boc-D-glutam-α-ylamineacetic acid (25 mg, 0.082mmole) was dissolved in water (0.25 ml) containing triethylamine (16.6 mg, 0.164mmole) and N-methylmorpholine (16.6 mg, 0.164mmole). The clear solution was diluted with acetone (3 ml), then cooled to -20°C in a dry ice-acetone bath. Into this solution was added isobutyl chloroformate (26.95 mg, 0.197mmole). The reaction mixture was stirred at -15°±2°C for 12 min., then combined with a solution of 5-acetamido-7-(6'-aminohexyl)carbamoyloxy-4-guanidino-2,3,4,5-tetradeoxy-*D-glycero-D-galacto*-non-2-enopyranosonic acid (7) (116.9 mg, 0.246mmole) and triethylamine (24.9 mg, 0.246 mmole) in water (2.5 ml). The resulting mixture was allowed to agitate at room temperature for 3 hr, then evaporated to dryness under reduced pressure. The residue was subjected to flash column-chromatography (silica gel, 2-propanol:acetic acid:water = 3:1:1 as eluent) to afford the

N-Boc derivative of the title compound (9), which was then treated with trifluoroacetic acid (2 ml) at room temperature for 1 hr, evaporated under vacuum to dryness. The residue was freeze-dried to give the title compound (**9**) as trifluoroacetic acid salt (31 mg, 30.4 %).
MS 1118 (M+2)
^{1}H-nmr (D_2O) δ (ppm): 1.22-1.62 (m, 16H), 1.98 (br., 6H), 2.20 (m, 2H), 2.41 (m, 1H), 2.57 (m, 1H), 2.90-3.25 (m, 8H), 3.59 (br dd, 2H), 3.68 (br dd, 2H), 3.76-4.01 (m, 3H), 4.10 (m, 4H), 4.43 (br dd, 2H), 4.53 (br dd, 2H), 4.95 (br dd, 2H), 5.85 (br., 2H)

Example 6 Inhibition of Influenza Virus Replication by Compounds of the Invention

[0068] Compounds of the invention were tested for their ability to inhibit the replication of influenza A virus, following the standard method that has been described in the literature (see for example Watanabe *et al*, J. Virological Methods, 1994 48 257). The assay was carried out using MDCK cells, and the results are shown in Table 2 below. The results are shown as ID_{50}, the minimum compound concentration that inhibits cytopathic effect by 50% [(μg/ml)], calculated by using a regression analysis program for semi-log curve fitting. The results show that dimeric compounds (**2**), (**3**) and (**4**) are all more active against influenza than the monomeric ligand molecule (**7**), and that compound (**2**) of the invention is even more potent than the highly active compound (**A**) [GG167]. The therapeutic index for the compounds can be calculated by dividing the minimum cytotoxic drug concentration (MTC) by the ID_{50}.

Table 2

Compound No.	Spacer Atoms	ID_{50}	ID_{50}	MTC
	(Number of atoms)	μg/ml	(μM of (A))	μg/ml
(2)	22	0.007	0.013	>10
(3)	30	0.017	0.028	>10
(**4**)	42	0.084	0.11	>10
(5)	58	0.35	0.42	>10
(6)	78	0.63	0.62	>10
(A)	-------	0.0095	0.028	>10
(7)	-------	0.22	0.32	>10

Example 7 Inhibition of Influenza Virus Replication by compounds of the invention

[0069] Compounds of the invention were tested for their ability to inhibit the replication of influenza A/Victoria/3/75 B010 in a standard CPE type assay similar to that described above in Example 6. The results for three separate experiments are shown in Table 3 below.

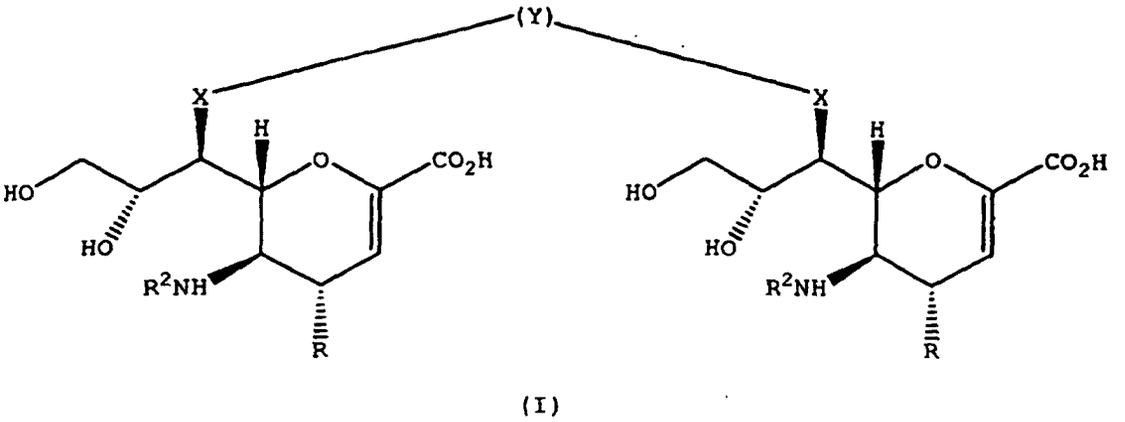
Table 3

Compound No.	EC_{50} (μg/ml)	EC_{90} (μg/ml)	CC_{50} (μg/ml)
8 (test 1)	0.00971	0.0671	> 0.1
9 (test 2)	0.002	-	> 1
9 (test 3)	0.0004	-	> 0.1
Compound (A) (test 2)	0.009	-	> 1
Compound (A) (test 3)	0.009	-	> 0.1

[0070] It will be apparent to the person skilled in the art that while the invention has been described in some detail for the purposes of clarity and understanding, various modifications and alterations to the embodiments and methods described herein may be made without departing from the scope of the inventive concept disclosed in this specification.

Claims

1. A compound of General Formula (I):



(I)

wherein

R is an azido group, a hydroxy group, an unsubstituted or substituted guanidino group, or an unsubstituted or substituted amino group;

R^2 is $COCH_3$, $COCF_3$, SO_2CH_3 or SO_2CF_3;

X is O, O(C=O), NH, NHCO, O(C=O)NH, O(C=S)NH, NH(C=O)NH or NH(C=S)NH;

and spacer group Y is an optionally substituted and/or branched chain of up to 100 atoms in length, with the backbone atoms selected from the group consisting of carbon, nitrogen, oxygen and sulphur;

or a pharmaceutically acceptable salt or derivative thereof.

2. A compound according to claim 1, wherein the spacer group Y is 8 to 100 atoms in length.

3. A compound according to claim 1 or claim 2, wherein the spacer group Y is 10 to 50 atoms in length.

4. A compound according to any one of the preceding claims, wherein the spacer group Y is 12 to 30 atoms in length.

5. A compound according to any one of the preceding claims, in which

R is an unsubstituted or substituted guanidino group, or an unsubstituted or substituted amino group;

R^2 is acetyl or trifluoroacetyl;

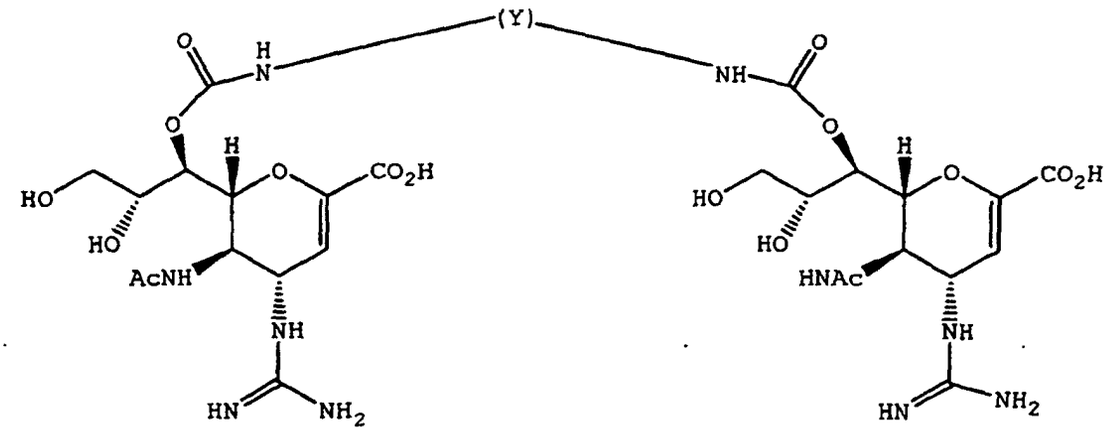
X is O(C=O)NH; and

spacer group Y is between 10 and 50 atoms in length.

6. A compound according to claim 5, in which the substituent on the R group is selected from the group consisting of alkyl, hydroxyalkyl, allyl, nitrile, alkoxycarbonyl and acyl..

7. A compound according to any one of the preceding claims, in which the spacer group Y is selected from the group consisting of optionally substituted straight or branched hydrocarbon chains, peptides, oligosaccharides, polyamino acids, polyethylene glycol units, alkylamidoalkanes, alkylureidoalkanes, any of which may be used alone, in multiple forms or in combination.

8. A compound according to any one of the preceding claims, in which the compound is of Formula (Ia):



(Ia)

wherein

the spacer group Y is selected from the group consisting of:

$(CH_2)_6NHCONH(CH_2)_4NHCONH(CH_2)_6$,
$(CH_2)_6NHCONH(CH_2)_{12}NHCONH(CH_2)_6$,
$(CH_2)_6NH[COCH_2NH]_3CONH(CH_2)_6NHCO[NHCH_2CO]_3NH(CH_2)_6$,
$(CH_2)_6NH[CO(CH_2)_5NH]_2CONH(CH_2)_{12}NHCO[NH(CH_2)_5CO]_2NH(CH_2)_6$,
$(CH_2)_6NH[CO(CH_2)_5NH]_4CONH(CH_2)_6NHCO[NH(CH_2)_5CO]_4NH(CH_2)_6$,
$(CH_2)_6NHCOCH_2N[CH_2CO_2H]CH_2CH_2N[CH_2CO_2H]CH_2CONH(CH_2)_6$,
$(CH_2)_6NHCO(CH_2)_2CH[NH_2.TFA]CONHCH_2CONH(CH_2)_6$, and
$CH_2CH_2OCH_2CH_2OCH_2CH_2$

9. A compound according to any one of the preceding claims, wherein the spacer group Y has attached to it an extra functionality to improve the pharmaceutical or pharmacokinetic properties of the compound, selected from the group consisting of lipophilic hydrocarbon groups, polyethylene glycol (PEG) chains and peptides.

10. A pharmaceutical composition comprising a compound according to any one of claims 1 to 9, together with a pharmaceutically acceptable carrier and, optionally, one or more other therapeutic and/or prophylactic ingredients.

11. A pharmaceutical composition according to claim 10, additionally comprising a second anti-viral agent.

12. A pharmaceutical composition according to claim 11, wherein the second anti-viral agent is selected from the group consisting of sialic acid analogues, amantadine, rimantadine and ribavirin.

13. Use of a compound according to any one of claims 1 to 9 or a pharmaceutical composition according to any one of claims 10 to 12, in the manufacture of a medicament for the treatment or prophylaxis of a viral infection.

14. Use of a compound according to any one of claims 1 to 9 or a pharmaceutical composition according to any one of claims 10 to 12, in the manufacture of a medicament for the treatment or prophylaxis of an orthomyxovirus or paramyxovirus infection in a mammal.

15. Use according to claim 14, wherein the infection is caused by Influenza A or B.

16. Use according to claim 14 or claim 15, wherein the mammal is a human.

17. Use according to any one of claims 14 to 16, wherein the compound is of General Formula I or Formula (Ia).

18. Use according to any one of claims 14 to 17, wherein the dose is in the range of from about 0.01 to 100 mg/kg of bodyweight per day.

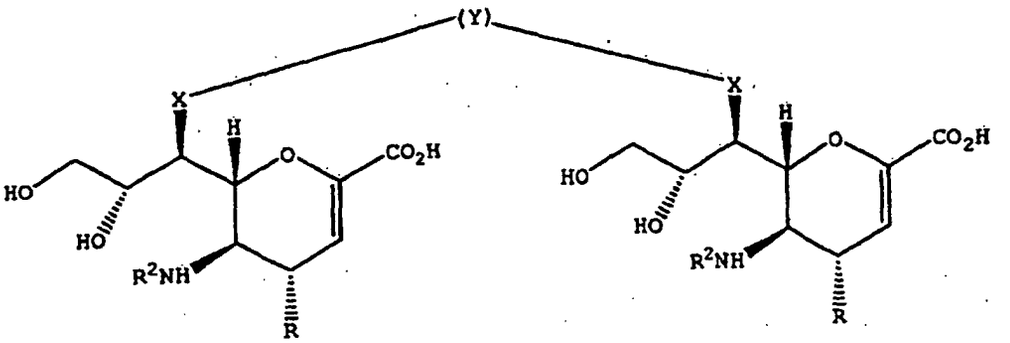
19. A compound according to any one of claims 1 to 9, for use as an active therapeutic agent in the treatment or prophylaxis of viral infections.

20. A compound according to any one of claims 1 to 9, for use as an active therapeutic agent in the treatment or prophylaxis of orthomyxovirus or paramyxovirus infections.

21. An in vitro method for the detection of influenza virus, comprising the step of contacting a compound according to any one of claims 1 to 9 with a sample suspected of comprising the virus.

Patentansprüche

1. Verbindung der allgemeinen Formel (I):



(I)

wobei
R ein Azidorest, eine Hydroxygruppe, ein unsubstituierter oder substituierter Guanidinrest oder eine unsubstituierte oder substituierte Aminogruppe ist;
R^2 gleich $COCH_3$, $COCF_3$, SO_2CH_3 oder SO_2CF_3 ist;
X gleich O, O(C=O), NH, NHCO, O(C=O)NH, O(C=S)NH, NH(C=O)NH oder NH(C=S)NH ist;
und der Spacer Y eine gegebenenfalls substituierte und/oder verzweigte Kette mit einer Länge von bis zu 100 Atomen ist, wobei die Gerüstatome ausgewählt sind aus Kohlenstoff, Stickstoff, Sauerstoff und Schwefel;
oder ein pharmazeutisch verträgliches Salz oder Derivat davon.

2. Verbindung gemäß Anspruch 1, wobei der Spacer Y eine Länge von 8 bis 100 Atomen aufweist.

3. Verbindung gemäß Anspruch 1 oder 2, wobei der Spacer Y eine Länge von 10 bis 50 Atomen aufweist.

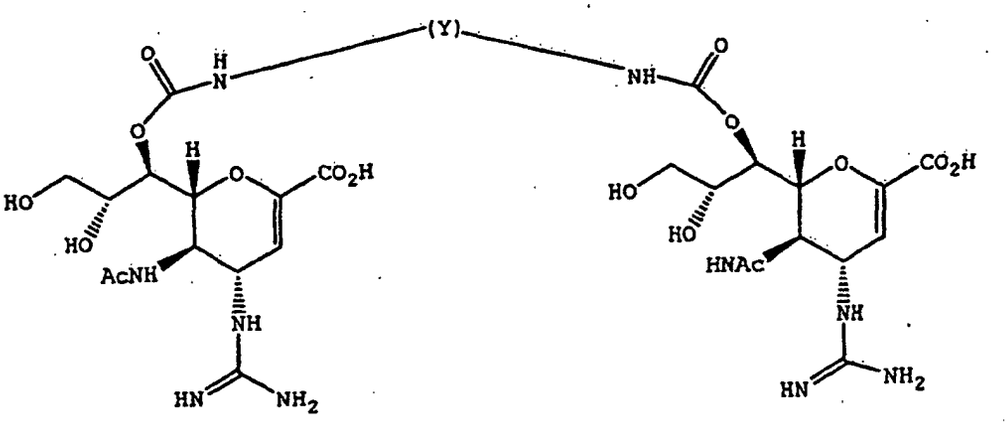
4. Verbindung gemäß einem der vorstehenden Ansprüche, wobei der Spacer Y eine Länge von 12 bis 30 Atomen aufweist.

5. Verbindung gemäß einem der vorstehenden Ansprüche, wobei
R ein unsubstituierter oder substituierter Guanidinrest oder eine unsubstituierte oder substituierte Aminogruppe ist;
R^2 Acetyl oder Trifluoracetyl ist;
X gleich O(C=O)NH ist; und
der Spacer Y eine Länge zwischen 10 und 50 Atomen aufweist.

6. Verbindung gemäß Anspruch 5, wobei der Substituent am Rest R ausgewählt ist aus Alkyl, Hydroxyalkyl, Allyl, Nitril, Alkoxycarbonyl und Acyl.

7. Verbindung gemäß einem der vorstehenden Ansprüche, wobei der Spacer Y ausgewählt ist aus gegebenenfalls substituierten geradkettigen oder verzweigten Kohlenwasserstoffketten, Peptiden, Oligosacchariden, Polyaminosäuren, Polyethylenglycoleinheiten, Alkylamidoalkanen, Alkylureidoalkanen, wobei jedes allein, in verschiedenen Formen oder in Kombination verwendet werden kann.

8. Verbindung gemäß einem der vorstehenden Ansprüche, wobei die Verbindung die Formel (Ia) aufweist:



(Ia)

wobei
der Spacer Y ausgewählt ist aus:

$(CH_2)_6NHCONH(CH_2)_4NHCONH(CH_2)_6$,
$(CH_2)_6NHCONH(CH_2)_{12}NHCONH(CH_2)_6$,
$(CH_2)_6NH[COCH_2NH]_3CONH(CH_2)_6NHCO[NHCH_2CO]_3NH(CH_2)_6$,
$(CH_2)_6NH[CO(CH_2)_5NH]_2CONH(CH_2)_{12}NHCO[NH(CH_2)_5CO]_2NH(CH_2)_6$,
$(CH_2)_6NH[CO(CH_2)_5NH]_4CONH(CH_2)_6NHCO[NH(CH_2)_5CO]_4NH(CH_2)_6$,
$(CH_2)_6NHCOCH_2N[CH_2CO_2H]CH_2CH_2N[CH_2CO_2H]CH_2CONH(CH_2)_6$,
$(CH_2)_6NHCO(CH_2)_2CH[NH_2 \cdot TFA]CONHCH_2CONH(CH_2)_6$, und
$CH_2CH_2OCH_2CH_2OCH_2CH_2$.

9. Verbindung gemäß einem der vorstehenden Ansprüche, wobei der Spacer Y eine zusätzliche Funktionalität an sich gebunden hat, um die pharmazeutischen oder pharmakokinetischen Eigenschaften der Verbindung zu verbessern, ausgewählt aus lipophilen Kohlenwasserstoffresten, Polyethylenglycol(PEG)-Ketten und Peptiden.

10. Arzneimittel, umfassend eine Verbindung gemäß einem der Ansprüche 1 bis 9, zusammen mit einem pharmazeutisch verträglichen Träger und gegebenenfalls einem oder mehreren anderen therapeutischen und/oder prophylaktischen Bestandteilen.

11. Arzneimittel gemäß Anspruch 10, welches zusätzlich ein zweites antivirales Mittel umfasst.

12. Arzneimittel gemäß Anspruch 11, wobei das zweite antivirale Mittel ausgewählt ist aus Sialsäure-Analoga, Amantadin, Rimantadin und Ribavirin.

13. Verwendung einer Verbindung gemäß einem der Ansprüche 1 bis 9 oder eines Arzneimittels gemäß einem der Ansprüche 10 bis 12 zur Herstellung eines Medikaments zur Behandlung oder Prophylaxe einer Virusinfektion.

14. Verwendung einer Verbindung gemäß einem der Ansprüche 1 bis 9 oder eines Arzneimittels gemäß einem der Ansprüche 10 bis 12 zur Herstellung eines Medikaments zur Behandlung oder Prophylaxe einer Orthomyxovirus- oder Paramyxovirusinfektion in einem Säuger.

15. Verwendung gemäß Anspruch 14, wobei die Infektion durch Influenza A oder B hervorgerufen wird.

16. Verwendung gemäß Anspruch 14 oder 15, wobei der Säuger ein Mensch ist.

17. Verwendung gemäß einem der Ansprüche 14 bis 16, wobei die Verbindung die allgemeine Formel I oder Formel (Ia) aufweist.

18. Verwendung gemäß einem der Ansprüche 14 bis 17, wobei die Dosis im Bereich von etwa 0,01 bis 100 mg/kg Körpergewicht pro Tag liegt.

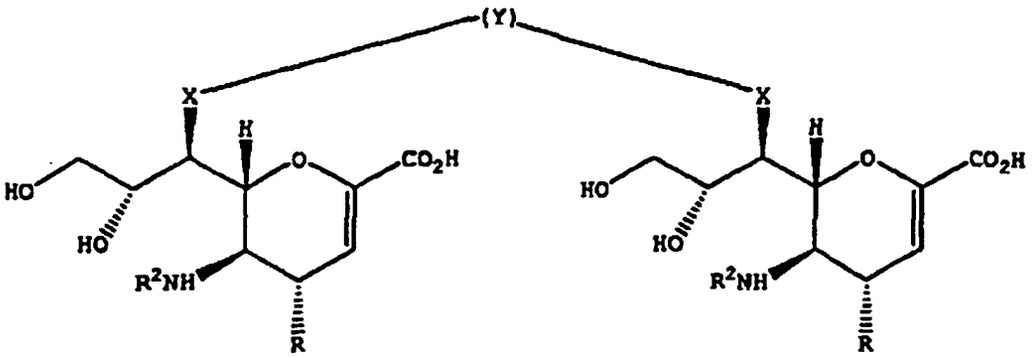
19. Verbindung gemäß einem der Ansprüche 1 bis 9, zur Verwendung als ein therapeutischer Wirkstoff in der Behandlung oder Prophylaxe von Virusinfektionen.

20. Verbindung gemäß einem der Ansprüche 1 bis 9, zur Verwendung als ein therapeutischer Wirkstoff in der Behandlung oder Prophylaxe von Orthomyxovirus- oder Paramyxovirusinfektionen.

21. In-vitro-Verfahren zum Nachweis des Influenzavirus, umfassend den Schritt des Kontaktierens einer Verbindung gemäß einem der Ansprüche 1 bis 9 mit einer Probe, von der angenommen wird, dass sie den Virus umfasst.

Revendications

1. Composé de la formule générale (I) :



(I)

dans laquelle

R est un groupe azido, un groupe hydroxy, un groupe guanidino non substitué ou substitué, ou un groupe amino non substitué ou substitué ;

R^2 est $COCH_3$, $COCF_3$, SO_2CH_3 ou SO_2CF_3 ;

X est O, O(C=O), NH, NHCO, O(C=O)NH, O(C=S)NH, NH(C=O)NH ou NH(C=S)NH ;

et le groupe espaceur Y est une chaîne optionnellement substituée et/ou ramifiée d'une longueur allant jusqu'à 100 atomes, les atomes de l'ossature étant choisis dans le groupe constitué par le carbone, l'azote, l'oxygène et le soufre ;

ou un sel ou dérivé pharmaceutiquement acceptable de ce composé.

2. Composé selon la revendication 1, dans laquelle le groupe espaceur Y a une longueur de 8 à 100 atomes.

3. Composé selon la revendication 1 ou la revendication 2, dans laquelle le groupe espaceur Y a une longueur de 10 à 50 atomes.

4. Composé selon l'une quelconque des revendications précédentes, dans laquelle le groupe espaceur Y a une longueur de 12 à 30 atomes.

5. Composé selon l'une quelconque des revendications précédentes, dans lequel

R est un groupe guanidino non substitué ou substitué, ou un groupe amino non substitué ou substitué ;

R^2 est acétyle ou trifluoroacétyle ;

X est O(C=O) NH ; et

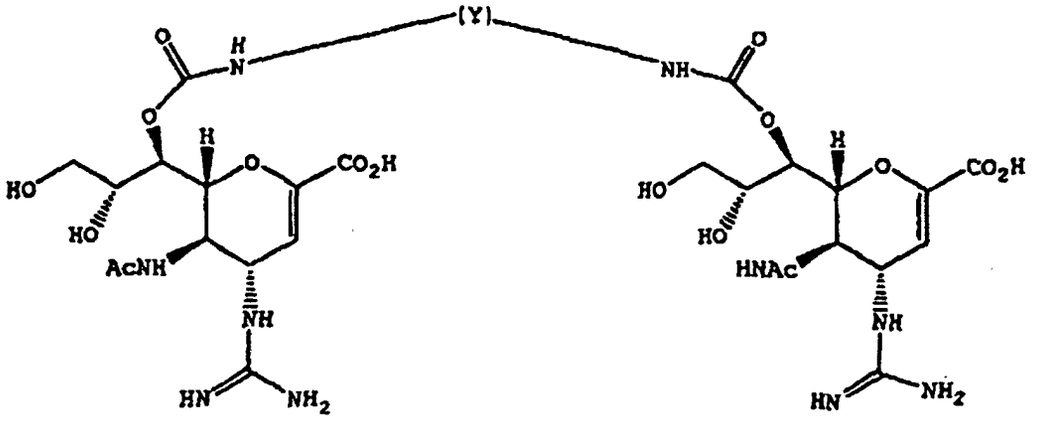
le groupe espaceur Y a une longueur de 10 à 50 atomes.

6. Composé selon la revendication 5, dans lequel le substituant sur le groupe R est choisi dans le groupe constitué

par les radicaux alkyle, hydroxyalkyle, allyle, nitrile, alcoxycarbonyle et acyle.

7. Composé selon l'une quelconque des revendications précédentes, dans lequel le groupe espaceur Y est choisi dans le groupe constitué par des chaînes hydrocarbures linéaires ou ramifiées le cas échéant substitués, des peptides, des oligosaccharides, des polyaminoacides, des motifs polyéthylène glycol, des alkylamidoalcanes, des alkyluréidoalcanes, l'un quelconque d'entre eux pouvant être utilisé seul, sous des formes multiples ou en combinaison.

8. Composé selon l'une quelconque des revendications précédentes, dans lequel le composé est de la formule (Ia) :



(Ia)

dans laquelle

le groupe espaceur Y est choisi dans le groupe constitué par :

$(CH_2)_6NHCONH(CH_2)_4NHCONH(CH_2)_6$,
$(CH_2)_6NHCONH(CH_2)_{12}NHCONH(CH_2)_6$,
$(CH_2)_6NH[COCH_2NH]_3CONH(CH_2)_6NHCO[NHCH_2CO]_3NH(CH_2)_6$,
$(CH_2)_6NH[CO(CH_2)_5NH]_2CONH(CH_2)_{12}NHCO[NH(CH_2)_5CO]_2NH(CH_2)_6$,
$(CH_2)_6NH[CO(CH_2)_5NH]_4CONH(CH_2)_6NHCO[NH(CH_2)_5CO]_4NH(CH_2)_6$,
$(CH_2)_6NHCOCH_2N[CH_2CO_2H]CH_2CH_2N[CH_2CO_2H]CH_2CONH(CH_2)_6$,
$(CH_2)_6NHCO(CH_2)_2CH[NH_2 \cdot TFA]CONHCH_2CONH(CH_2)_6$, et
$CH_2CH_2OCH_2CH_2OCH_2CH_2$

9. Composé selon l'une quelconque des revendications précédentes, dans lequel le groupe espaceur Y possède une fonctionnalité supplémentaire, qui lui est rattachée afin d'améliorer les propriétés pharmaceutiques ou pharmacocinétiques du composé, choisie dans le groupe constitué par des groupes hydrocarbures lipophiles, des chaînes polyéthylène glycol (PEG) et des peptides.

10. Composition pharmaceutique comprenant un composé selon l'une quelconque des revendications 1 à 9 ensemble avec un véhicule pharmaceutiquement acceptable ainsi que, optionnellement, un ou plusieurs autres ingrédients thérapeutiques et/ou prophylactiques.

11. Composition pharmaceutique selon la revendication 10, comprenant en plus un deuxième agent antiviral.

12. Composition pharmaceutique selon la revendication 11, dans laquelle le deuxième agent antiviral est choisi dans le groupe constitué par des analogues de l'acide sialique, l'amantadine, la rimantadine et la ribavirine.

13. Utilisation du composé selon l'une quelconque des revendications 1 à 9 ou d'une composition pharmaceutique selon l'une quelconque des revendications 10 à 12 dans la fabrication d'un médicament destiné au traitement ou à la prophylaxie d'une infection virale.

14. Utilisation du composé selon l'une quelconque des revendications 1 à 9 ou d'une composition pharmaceutique selon l'une quelconque des revendications 10 à 12 dans la fabrication d'un médicament destiné au traitement ou à la prophylaxie d'une infection à orthomyxovirus ou paramyxovirus chez un mammifère.

15. Utilisation selon la revendication 14, dans laquelle l'infection est provoquée par l'influenzavirus A ou B.

16. Utilisation selon la revendication 14 ou la revendication 15, dans laquelle le mammifère est un être humain.

17. Utilisation selon l'une quelconque des revendications 14 à 16, dans laquelle le composé est de la formule générale I ou de la formule (Ia).

18. Utilisation selon l'une quelconque des revendications 14 à 17, dans laquelle la dose se situe dans la plage d'environ 0,01 à 100 mg/kg de masse corporelle par jour.

19. Composé selon l'une quelconque des revendications 1 à 9, destiné à être utilisé comme agent thérapeutique actif dans le traitement ou la prophylaxie d'infections virales.

20. Composé selon l'une quelconque des revendications 1 à 9, destiné à être utilisé comme agent thérapeutique actif dans le traitement ou la prophylaxie d'infections à orthomyxovirus ou paramyxovirus.

21. Procédé *in vitro* pour la détection d'influenzavirus, comprenant l'étape consistant à mettre en contact un composé selon l'une quelconque des revendications 1 à 9 avec un échantillon suspecté de contenir le virus.