Title: ANTIVIRAL COMPOUNDS

ANTIVIRAL COMPOUNDS

Field of the invention
The present invention relates to the use of certain castanospermine esters in the treatment of influenza virus infection.

Background to the invention
Influenza
In normal adults, infection with influenza A viruses can result in a range of clinical effects from asymptomatic infection to primary pneumonia that can progress rapidly to become fatal. Neonates and young children under 5 years of age have the highest rates of hospitalisation after acute viral infection, diagnosed as influenza virus in the laboratory.

Young children are more likely to develop lower respiratory tract disease with various complications. This is generally due to the low level of protective immunity in the very young. During influenza epidemics the death rate in the elderly increases significantly, the main culprit being influenza A strains. Influenza B virus, RSV and other respiratory viruses, including influenza A and B strains, are an increasing problem in transplant recipients and in other immuno-suppressed patients.

While vaccination has proved successful in some circumstances, the approach requires constant change in immunogens to match the current wild-type virus. The benefits of a safe and effective therapy with small molecules has long been sought.

Influenza virus neuraminidase (NA) is a subtype-specific, transmembrane glycoprotein of the class II type and, like haemagglutinin (HA), undergoes antigenic variation. Neuraminidase is also functionally important for the removal of sialic acid residues from various glycoproteins on the host-cell surface that potentially bind viral glycoproteins and hence restrict virion egress. NA activity is necessary to prevent clumping and allow the release of virus progeny from the host cell.

Thus, NA is a potential target in the treatment of influenza virus infection and NA inhibitors have recently found application in the treatment of influenza virus infection.

Recent evidence indicates that resistance to the effects of neuraminidase inhibitors may reside in mutations in haemagglutinin (HA) as well as in the NA gene. This may be due to the reduced affinity of HA mutants for putative cell receptors, thus enabling virus release in the absence of NA activity.
The present inventors have now recognized that the interactions of influenza NA and HA during viral growth indicates that HA inhibitors might interact with NA to benefit future treatment. Moreover, recognizing that the oligosaccharides present on HA play an important role in the activity of this viral glycoprotein in viral growth the present inventors have discovered that the presence of incorrectly configured N-glycans on both HA1 and HA2 interferes with the many functions of HA glycoprotein and/or NA.

**Glycoproteins and viral development**

Glycoproteins are classified into two major classes according to the linkage between sugar and amino acid of the protein. The most common and extensively studied is N-glycosidic linkage between an asparagine of the protein and an N-acetyl-D-glucosamine residue of the oligosaccharide. N-linked oligosaccharides, following attachment to a polypeptide backbone, are processed by a series of specific enzymes in the endoplasmic reticulum (ER) and this processing pathway has been well characterised.

In the ER, α-glucosidase I is responsible for the removal of the terminal α-1,2 glucose residue from the precursor oligosaccharide and α-glucosidase II removes the two remaining α-1,3 linked glucose residues, prior to removal of mannose residues by mannosidases and further processing reactions involving various transferases. These oligosaccharide “trimming” reactions enable glycoproteins to fold correctly and to interact with chaperone proteins such as calnexin and calreticulin for transport through the Golgi apparatus.

**Glucosidase Inhibitors**

Castanospermamine and certain imino sugars, such as deoxyojirimycin (DNJ), are ER α-glucosidase inhibitors and both potently inhibit the early stages of glycoprotein processing. However, their effects differ substantially depending on the system to which they are applied and they may exhibit quite different specificities, castanospermamine being relatively specific for α-glucosidase I.

Castanospermamine is an alkaloid, originally isolated from the seeds of *Castanospermum australe*, having the following formula:

```
\[\text{HO}\]
\[\text{HO}\]
\[\text{N}\]
\[\text{HO}\]
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Systematically, this compound can be named in several ways as follows: [1S-(1α, 6β,7α,8β,8αβ)]-octahydro-1,6,7,8-indoliznetetrol or [1S,(1S,6S,7R,8R,8αR)-1,6,7,8-
tetrahydroxy-indolizidine or 1,2,4,8-tetrahydroxy-1,4,8-nitrilo-L-glycero-D-galacto-octitol. The term "castanospermine" or the first systematic name will be used in the discussion below.

Inhibitors of key enzymes in this biosynthetic pathway, particularly those blocking α-glucosidases and α-mannosidase, have been shown to prevent replication of several enveloped viruses. Such inhibitors may act by interfering with the formation of the viral envelope glycoprotein, so preventing the initial virus-host cell interaction or subsequent fusion. They may also prevent viral duplication by preventing the construction of the proper glycoprotein required for the completion of the viral membrane.

For example, it has been reported that the nonspecific glycosylation inhibitors 2-deoxy-D-glucose and 6-hydroxy-norvaline inhibit expression of HIV glycoproteins and block the formation of syncytia (Blough et al., Biochemical and Biophysical Research Communications, 141(1), 33-38 (1986)). Viral multiplication of HIV-infected cells treated with these agents is stopped, presumably because of the unavailability of glycoprotein required for viral membrane formation.

In another report, the glycosylation inhibitor 2-deoxy-2-fluoro-D-mannose was found to exhibit antiviral activity against influenza infected cells by preventing the glycosylation of viral membrane protein (McDowell et al., Biochemistry, 24(27), 8145-52 (1985)). This report also studied the antiviral activity of 2-deoxyglucose and 2-deoxy-2-fluoroglucose and found that each inhibits viral protein glycosylation by a different mechanism.

Lu et al. (1995) present evidence that N-linked glycosylation is necessary for hepatitis B virus secretion (Virology 213: 660-665) while Block et al. (1994) show that secretion of human hepatitis B virus is inhibited by the imino sugar N-nutyldeoxynojirimycin (PNAS 91: 2235-2239). See also WO9929321.

Taylor et al. (1988) demonstrate the loss of cytomegalovirus infectivity after treatment with castanospermine or other plant alkaloids and relate this to aberrant glycoprotein synthesis (Antiviral Res. 10: 11-26). See also US patent 5,0004,746.

Taylor et al. (1994) show that inhibition of α-glucosidase I of the glycoprotein processing enzymes by 6-0-butanoyl castanospermine has consequences in human immunodeficiency virus-infected T-cells (Antimicrob. Ag. Chemother. 38: 1780-1787) while Sunkara et al. (1989) describe anti-HIV activity of castanospermine analogues (Lancet II 1206). See also US patent 5,0004,746.

Branza-Nichita et al. (2001) J. Virol 75(8): 3527-3536 show that the iminosugar N-butyldexoyojirimycin has an antiviral effect against the pestivirus BVDV. However, the authors make clear that while treatment with α-glucosidase inhibitors may affect the life cycles of this and other enveloped viruses, it is not possible to generalize to other viruses since the effects may depend crucially on the particular folding pathway used by the viral proteins.

Courageot et al. (2000) J. Virol. 74(1): 564-572 report that the α-glucosidase inhibitors castanospermine and DNJ reduce dengue virus production in an in vitro mouse model. However, no substantial difference in activity between the imino sugar inhibitor DNJ and castanospermine was reported.

WO 99/29321 discloses the use of α-glucosidase inhibitors generally (and imino sugars in particular) in the treatment of inter alia HCV infections. However, no reference is made to castanospermine (or esters or derivatives thereof) specifically in this respect. Instead, the document focuses on the activities of various imino sugars.

However, many other known glycosylation inhibitors have been found to have no antiviral activity. Thus the antiviral activity against membraned viruses, in general, and the anti-influenza virus activity, specifically, of glycosylation inhibitors is quite unpredictable.

**Summary of the invention**
According to the present invention there is provided a method for treating an influenza virus infection in a patient in need thereof which comprises administering to the patient an effective amount of a castanospermine ester of the formula:

\[
\text{HO} \quad \begin{array}{c}
\text{N} \\
\text{R_2O} \\
\text{OR_1} \\
\text{OR}
\end{array}
\]

wherein R, R_1 and R_2 are independently hydrogen, C_{1-14} alkanoyl, C_{1-14} alkenoyl, cyclohexanecarbonyl, C_{1-8} alkoxyacetyl,
naphthalenecarbonyl optionally substituted by methyl or halogen; phenyl(C_{2-8} alkanoyl)
wherein the phenyl is optionally substituted by methyl or halogen; cinnamoyl; pyridinecarbonyl
optionally substituted by methyl or halogen; dihydroxyridine carbonyl optionally substituted by
\text{C}_{1-10} \text{ alkyl}; \text{thiophenecarbonyl} optionally substituted by methyl or halogen; \text{or furancarbonyl}
optionally substituted by methyl or halogen; \text{Y} \text{ is hydrogen, C}_{1-4} \text{ alkyl, C}_{1-4} \text{ alkoxy, halogen,}
trifluoromethyl, \text{C}_{1-4} \text{ alkylsulphonyl, C}_{1-4} \text{ alkylmercapto, cyano or dimethylamino}; \text{Y}' \text{ is}
hydrogen, \text{C}_{1-4} \text{ alkyl, C}_{1-4} \text{ alkoxy, halogen or it is combined with Y to give 3,4-methylenedioxy;}
\text{Y}'' \text{ is hydrogen, C}_{1-4} \text{ alkyl, C}_{1-4} \text{ alkoxy or halogen; with R, R}_1 \text{ and R}_2 \text{ being selected in such a}
way that at least one of them, but not more than two of them, is hydrogen; or a
pharmaceutically acceptable salt or derivative thereof.

Preferably, R, R_1 \text{ and R}_2 \text{ are each independently hydrogen, C}_{1-10} \text{ alkanoyl, C}_{1-10} \text{ alkenoyl, C}_{1-8}
alkoxyacetyl, or wherein \text{Y} \text{ is hydrogen, C}_{1-4} \text{ alkyl, C}_{1-4} \text{ alkoxy, halogen, trifluoromethyl, C}_{1-4}
alkylsulphonyl, C}_{1-4} \text{ alkylmercapto, cyano or dimethylamino}; \text{Y}' \text{ is hydrogen, C}_{1-4} \text{ alkyl, C}_{1-4}
alkoxy, halogen or it is combined with Y to give 3,4-methylenedioxy; \text{Y}'' \text{ is hydrogen, C}_{1-4}
alkoxy or halogen; with R, R_1 \text{ and R}_2 \text{ being selected in such a way that at least one of them,}
but not more than two of them, is hydrogen.

R, R_1 \text{ and R}_2 \text{ may each be independently hydrogen, C}_{1-8} \text{ alkanoyl, C}_{1-8} \text{ alkenoyl, C}_{1-8}
alkoxy-acetyl, or a benzoyl optionally substituted with an alkyl or halogen; with R, R_1 \text{ and R}_2
optionally being selected in such a way that at least one of them, but not more than two of
them, is hydrogen.

R, R_1 \text{ and R}_2 \text{ may each be independently hydrogen, C}_{1-8} \text{ alkanoyl, C}_{1-8} \text{ alkenoyl, C}_{1-8}
alkoxy-acetyl, or a benzoyl optionally substituted with a methyl, bromo, chloro, or fluoro group; with
R, R_1 \text{ and R}_2 \text{ optionally being selected in such a way that at least one of them, but not more
than two of them, is hydrogen.}

In preferred embodiments the castanospermine esters have the structures shown in Table 1.
<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
<th>Compound</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAST</td>
<td>H</td>
<td>MDL 29270</td>
<td>H</td>
</tr>
<tr>
<td>MDL 28574</td>
<td>CH₃(CH₂)₆-CO-</td>
<td>MDL 44370</td>
<td>Br-CO⁻</td>
</tr>
<tr>
<td>MDL 43305</td>
<td>CO⁻</td>
<td>MDL 29797</td>
<td>CH₃(CH₂)₆-CO⁻</td>
</tr>
<tr>
<td>MDL 28653</td>
<td>CO⁻</td>
<td>MDL 29710</td>
<td>CH₃(CH₂)₆-CO⁻</td>
</tr>
<tr>
<td>MDL 29435</td>
<td>CO⁻</td>
<td>MDL 29613</td>
<td>CH₃(CH₂)(CH₂)₂CH₂-CO⁻</td>
</tr>
<tr>
<td>MDL 29204</td>
<td>H₂C-CO⁻</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* In MDL 29270 R₁ is H₂C-CO⁻; in all other structures R₁ is H

![Basic Structure](image)

Particularly preferred are castanospermine esters wherein R₁ is a C₁₋₈ alkanoyl, C₁₋₁₀ alkenoyl, C₁₋₅ alkoxy-acetyl, or a benzoyl optionally substituted with an alkyl or halogen group.

R₁ may be a C₁₋₈ alkanoyl, C₁₋₈ alkenoyl, C₁₋₅ alkoxy-acetyl, or a benzoyl optionally substituted with a methyl, bromo, chloro, or fluoro group.

The castanospermine ester may be selected from:

(a) [1S-{1α,6β,7α,8β,8αβ}]-octahydro-1,6,7,8-indolizinetetrol 6-benzoate;
(b) [1S-{1α,6β,7α,8β,8αβ}]-octahydro-1,6,7,8-indolizinetetrol 7-benzoate;
(c) [1S-{1α,6β,7α,8β,8αβ}]-octahydro-1,6,7,8-indolizinetetrol 6-(4-methylenbenzoate);
(d) [1S-{1α,6β,7α,8β,8αβ}]-octahydro-1,6,7,8-indolizinetetrol 7-(4-bromobenzoate);
(e) [1S-{1α,6β,7α,8β,8αβ}]-octahydro-1,6,7,8-indolizinetetrol 6,8-dibutanoate;
(f) \([1S-(1a,6\beta,7a,8\beta,8a\beta)]\)-octahydro-1,6,7,8-indolizin tetrol 6-butanoate;
(g) \([1S-(1a,6\beta,7a,8\beta,8a\beta)]\)-octahydro-1,6,7,8-indolizin tetrol 6-(2-furancarboxylate);
(h) \([1S-(1a,6\beta,7a,8\beta,8a\beta)]\)-octahydro-1,6,7,8-indolizin tetrol 7-(2,4-dichlorob enzoate);
(i) \([1S-(1a,6\beta,7a,8\beta,8a\beta)]\)-octahydro-1,6,7,8-indolizin tetrol 6-(3-hexenoate);
(j) \([1S-(1a,6\beta,7a,8\beta,8a\beta)]\)-octahydro-1,6,7,8-indolizin tetrol 6-octanoate;
(k) \([1S-(1a,6\beta,7a,8\beta,8a\beta)]\)-octahydro-1,6,7,8-indolizin tetrol 6-pentanoate;
(l) an \(O\)-pivaloyl ester;
(m) a 2-ethyl-butyryl ester;
(n) a 3,3-dimethylbutyryl ester;
(o) a cyclopropanoyl ester;
(p) a 4-methoxybenzoate ester;
(q) a 2-aminobenzoate ester; and
(r) a mixture of any or all of (a) - (q).

15 The influenza virus may be any influenza virus, for example influenza A or influenza B.

In another aspect of the invention there is provided the use of a castanospermine ester as described above for the manufacture of a medicament for use in the therapy or prophylaxis of an influenza virus infection.

20 Thus, the invention contemplates a process for the manufacture of a medicament for use in the therapy or prophylaxis of an influenza virus infection, characterized in the use (e.g. as an active ingredient) of the castanospermine esters described above.

25 The therapy or prophylaxis is preferably the treatment or prevention of an infection by an influenza virus as defined above.

The pharmaceuticals of the invention may also comprise the castanospermine esters of the invention in association (e.g. in admixture or co-packaged with) an adjunctive therapeutic.

30 The adjunctive therapeutic may comprise an antiviral compound, for example an anti-influenza drug. Particularly preferred are adjunctive therapeutics comprising an NA inhibitor, for example zanamivir and/or oseltamivir, though other adjunctive therapeutics include influenza vaccines and/or anti-influenza antibodies.

35 Thus, in another aspect, the invention provides a composition comprising a castanospermine ester as defined in any one of the preceding claims in combination with an anti-influenza drug, for example an NA inhibitor. Particularly preferred are compositions comprising the castanospermine esters of the invention in combination with zanamivir and/or oseltamivir. Also contemplated are compositions comprising the castanospermine esters of the invention in combination with an influenza vaccine and/or one or more anti-influenza antibodies.
The composition described above optionally further comprises a pharmaceutically acceptable excipient. Thus, the invention also contemplates a pharmaceutical composition comprising the composition described above.

5

The composition of the invention is preferably for use in therapy or prophylaxis, for example in any of the therapeutic and prophylactic methods described herein.

In another aspect, the invention provides a pharmaceutical kit of parts comprising a castanospermine ester as defined in any one of the preceding claims in combination with an anti-influenza drug, for example an NA inhibitor. Particularly preferred are kits comprising the castanospermine esters of the invention in combination with zanamivir and/or oseltamivir. Also contemplated are kits comprising the castanospermine esters of the invention in combination with an influenza vaccine and/or one or more anti-influenza antibodies. The kit may also further comprise instructions for use in the treatment of an influenza virus infection.

The castanospermine ester and adjunctive anti-influenza drug may be co-packaged in unit dosage form.

20

In the compositions of the invention the castanospermine ester and the adjunctive therapeutic may act in a complementary or synergistic fashion.

In any of the foregoing pharmaceutical compositions, the composition or castanospermine esters of the invention may be present in unit dosage form. Thus the invention also contemplates a kit as defined above in which the castanospermine ester and the adjunctive therapeutic are in unit dosage form.

Also contemplated are pharmaceutical compositions comprising the castanospermine ester of the invention in a form suitable for (or adapted to) delivery to the airways (for example comprising an propellant or aerosol).

Detailed description of the invention

The expression "a pharmaceutically acceptable salt" is intended to cover any non-toxic organic or inorganic acid addition salt of the base compounds.

35

Illustrative inorganic acids which form suitable salts include hydrochloric, hydrobromic, sulphuric, and phosphoric acids and acid metal salts such as sodium monohydrogen orthophosphate and potassium hydrogen sulphate. Illustrative organic acids which form suitable salts include the mono, di, and tricarboxylic acids. Illustrative of such acids are, for example, acetic, glycolic, lactic, pyruvic, malonic, succinic, glutaric, fumaric, malic, tartaric,
citric, ascorbic, maleic, hydroxymaleic, benzoic, hydroxybenzoic, phenylacetic, cinnamic, salicylic, and 2-phenoxybenzoic acids. Other organic acids which form suitable salts are the sulphonic acids such as methane sulphonic acid and 2-hydroxyethane sulphonic acid.

These salts and the base compounds can exist in either a hydrated or a substantially anhydrous form. The acid salts are prepared by standard techniques such as by dissolving the free base in aqueous or aqueous-alcohol solution or other suitable solvent containing the appropriate acid and isolating by evaporating the solution, or by reacting the free base in an organic solvent in which case the salt separates directly or can be obtained by concentration of the solution.

In general the acid addition salts of the compounds of this invention are crystalline materials which are soluble in water and various hydrophilic organic solvents and which in comparison to their free base forms, demonstrate higher melting points and an increased solubility.

The expression "a pharmaceutically acceptable derivative" is intended to cover ester produgs which have greater resistance to hydrolysis and increased lipophilicity. Such produgs exhibit rapid removal from the GI tract when delivered orally whilst providing a "depot effect" which sustains the concentration of the active drug at the target site.

The C<sub>1-14</sub> alkanoyl groups referred to above can be straight- or branched-chain or cyclic and can be exemplified by formyl, acetyl, propionyl, butyryl, isobutyryl, cyclopropanecarbonyl, hexanoyl, octanoyl and decanoyl.

The C<sub>1-14</sub> alkenoyl groups referred to above can be straight- or branched-chain or cyclic but have at least one carbon-carbon double bond. Examples include propenoyl, butenoyl, isobutenoyl, hexenoyl, octenoyl and decenoyl.

The C<sub>1-8</sub> alkoxyacetyl referred to above can be methoxy-acetyl, ethoxyacetyl and butoxyacetyl.

The halogens referred to above can be exemplified by fluorine, chlorine, bromine or iodine.

The C<sub>2-8</sub> alkanoyl groups referred to above can be acetyl, propionyl, butyryl, isobutyryl and hexanoyl.

The C<sub>1-4</sub> alkyl groups referred to above, whether alone or as part of an alkoxy, an alkylsulphonyl or an alkyl-mercapto group, can be straight- or branched-chain alkyl groups containing up to 4 carbon atoms. Examples of various such groups are methyl, ethyl, propyl,
butyl, methoxy, ethoxy, butoxy, methylsulphonyl, ethylsulphonyl, methylmercapto and ethylmercapto.

The phenyl (C$_{2-6}$ alkanoyl) groups referred to above can be benzeneacetyl and benzenepropionyl.

The various naphthalene-carbonyl, pyridine-carbonyl, thiophene-carbonyl and furan-carbonyl groups referred to above include the various position isomers and these can be naphthalene-1-carbonyl, naphthalene-2-carbonyl, nicotinoyl, isonicotinoyl, N-methyl-dihydro-pyridine-3-carbonyl, thiophene-2-carbonyl, thiophene-3-carbonyl, furan-2-carbonyl and furan-3-carbonyl.

The naphthalene, pyridine, thiophene and furan groups can be optionally further substituted as indicated above.

Preferred compounds of the present invention are those wherein R, R$_1$ and R$_2$ are 1 or 2 alkanoyl, alkenoyl or benzoyl groups with the benzoyl substituted by Y, Y' and Y'' as described above, especially a C$_{1-4}$ alkanoyl or a benzoyl optionally substituted with an alkyl or halogen.

More preferred are those compounds of formula 1 wherein one of R, R$_1$ and R$_2$ is alkanoyl or benzoyl, especially a C$_{1-4}$ alkanoyl, C$_{1-6}$ alkenoyl, or a benzoyl optionally substituted with an alkyl or halogen, and the others are hydrogens.

Even more preferred are those compounds of formula 1 wherein one of R, R$_1$ and R$_2$ is a C$_{1-6}$ alkanoyl, C$_{1-6}$ alkenoyl, or a benzoyl optionally substituted with an alkyl or halogen, especially a methyl, bromo, chloro, or fluoro group, and the others are hydrogens.

Most preferred are those compounds of formula 1 wherein R$_1$ is a C$_{1-4}$ alkanoyl, C$_{1-6}$ alkenoyl, or benzoyl optionally substituted with an alkyl or halogen, especially a methyl, bromo, chloro, or fluoro group, most especially a methyl, bromo, chloro, or fluoro group at the para position, and wherein R and R$_2$ are each a hydrogen.

The esters of the present invention are prepared by the reaction of castanospermine with an appropriate acid chloride or anhydride in an inert solvent. The halide can be a chloride or bromide and the anhydride includes mixed anhydrides. The relative amount of the acid halide or anhydride used, the relative amount of solvent, the temperature and the reaction time are all controlled so as to minimize the number of hydroxy groups that will be acylated. Thus, only a limited excess of the acid derivative is used, which means up to about a three-fold excess of the acylating agent.
Use of a solvent in relatively large amounts, serves to dilute the reactants and suppress the amount of higher acylated products that form. The solvent used is preferably one that will dissolve the reactants used without reacting with them.

It is further preferable to carry out the reaction in the presence of a tertiary amine which will react with and remove any acid formed during the course of the reaction. The tertiary amine can be added to the mixture or it can itself be used in excess and serve as the solvent. Pyridine is a preferred solvent in this regard. As indicated above, the time and the temperature are likewise controlled to limit the amount of acylation that takes place.

Preferably, the reaction is carried out with cooling in an ice-bath for a period of about 16 hours to give the monoesters with the reaction time extended to a longer period, such as 7 days, if diesters are desired. The reaction can actually be carried out at higher temperatures and heating can be used as long as the various factors involved are properly controlled.

When the reaction is carried out as described, the final reaction mixture will still contain a considerable amount of unreacted castanospermine. This unreacted material can be recovered from the reaction mixture and recycled in subsequent reactions and thus increase the overall amount of castanospermine converted to ester. This recycling is particularly important when the reaction is carried out under conditions which would favor the isolation of monoesters.

The procedures as described above will generally give 6-or 7-monoesters or 6,7- or 6,8-diesters. Other isomers can be obtained by appropriate use of blocking groups. Thus, for example, castanospermine can be reacted with 2-(dibromomethyl)benzoyl chloride to give the 6,7-diester. This diester is then reacted with an appropriate acid halide or anhydride to give the corresponding 8-ester. The two protecting groups are then readily removed by conversion of the two dibromomethyl groups to formyl (using silver perchlorate and 2,4,6-collidine in aqueous acetone) followed by hydrolysis of the formylbenzoic acid ester obtained using morpholine and hydroxide ion.

The indicated procedure can be used in a similar way to give diester isomers.

With 1,8-O-isopropylidenecastanospermine or 1,8-cyclohexylidenecastanospermine, the reaction with an acid chloride in a standard esterification procedure favors the formation of the 6-ester almost exclusively. The isopropylidene or cyclohexylidene group is then removed by treatment with an acid such as 4-toluene sulphonylic acid. The starting ketal compounds are themselves obtained from castanospermine 6,7-dibenzoate. This dibenzoate is reacted with 2-methoxypropene or 1-methoxycyclohexene and acid to introduce the 1,8-O-isopropylidene or 1,8-O-cyclohexylidene group and the two benzoate ester groups are removed by hydrolysis.
with base such as sodium hydroxide or by transesterification with sodium or potassium
alkoxide as the catalyst.

Medical applications

5 The invention finds application in medicine, for example in methods of therapy and/or
prophylaxis. The methods include veterinary applications.

As used herein, the term "a method of treating influenza virus infection" refers to the
treatment of a patient (human or animal) which has been infected with an influenza virus. The
methods of treatment involve administering to said patient an anti-virally effective amount of
the compositions or medicaments of the invention.

As used herein, the term "influenza infection" refers to any state or condition that involves
(e.g. is caused, exacerbated or characterized by) an influenza virus residing in the cells or
body of said patient.

The term "patient" used herein is taken to mean mammals such as primates, including
humans, sheep, horses, cattle, pigs, dogs, cats, rats and mice.

20 Posology

The medicaments employed in the present invention can be administered by oral or
parenteral routes, including intravenous, intramuscular, intraperitoneal, subcutaneous,
transdermal, airway (aerosol), rectal, vaginal and topical (including buccal and sublingual)
administration.

25 The amount of the castanospermine ester administered can vary widely according to the
particular dosage unit employed, the period of treatment, the age and sex of the patient
treated, the nature and extent of the disorder treated, and the particular castanospermine
ester selected.

30 Moreover, the castanospermine ester can be used in conjunction with other agents known to
be useful in the treatment of influenza infections (as described above) and in such
embodiments the dose may be adjusted accordingly.

35 Lower doses may be used in embodiments that incorporate the castanospermine ester pro-
drug derivatives of the invention which exhibit greater resistance to hydrolysis and increased
lipophilicity. As explained above, such pro-drugs exhibit rapid removal from the GI tract when
delivered orally whilst providing a "depot effect" which sustains the concentration of the active
drug at the target site.
Thus, the effective amount of castanospermine ester to be administered will generally range from about 15 mg/kg to 500 mg/kg. A unit dosage may contain from 25 to 500 mg of the castanospermine ester, and can be taken one or more times per day. The castanospermine ester can be administered with a pharmaceutical carrier using conventional dosage unit forms either orally, parenterally, or topically, as described below.

The preferred route of administration is oral administration. In general a suitable dose will be in the range of 0.1 to 300 mg per kilogram body weight of the recipient per day, preferably in the range of 6 to 150 mg per kilogram body weight per day and most preferably in the range 15 to 100 mg per kilogram body weight per day.

The desired dose is preferably presented as two, three, four, five or six or more sub-doses administered at appropriate intervals throughout the day. These sub-doses may be administered in unit dosage forms, for example, containing 10 to 1500 mg, preferably 20 to 1000 mg, and most preferably 50 to 700 mg of active ingredient per unit dosage form.

Formulation
The compositions of the invention may be provided in combination with a pharmaceutically acceptable excipient. Any suitable excipient may be used, including for example inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavouring agents, colouring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate, and lactose, while corn starch and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin, while the lubricating agent, if present, will generally be magnesium stearate, stearic acid or talc.

The pharmaceutical compositions may take any suitable form, and include for example tablets, elixirs, capsules, solutions, suspensions, powders, granules and aerosols.

The pharmaceutical composition may take the form of a kit of parts, which kit may comprise the composition of the invention together with instructions for use and/or a plurality of different components in unit dosage form.

Tablets for oral use may include the active ingredient mixed with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavouring agents, colouring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate, and lactose, while corn starch and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin, while the lubricating agent, if present, will generally be magnesium
stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as
glycerol monostearate or glyceryl distearate, to delay absorption in the gastrointestinal tract.

Capsules for oral use include hard gelatin capsules in which the active ingredient is mixed
with a solid diluent, and soft gelatin capsules wherein the active ingredient is mixed with water
or an oil such as peanut oil, liquid paraffin or olive oil.

Formulations for rectal administration may be presented as a suppository with a suitable base
comprising for example cocoa butter or a salicylate.

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

For intramuscular, intraperitoneal, subcutaneous and intravenous use, the compounds of the
invention will generally be provided in sterile aqueous solutions or suspensions, buffered to
an appropriate pH and isotonicity.

Suitable aqueous vehicles include Ringer’s solution and isotonic sodium chloride. Aqueous
suspensions according to the invention may include suspending agents such as cellulose
derivatives, sodium alginate, polyvinylpyrrolidone and gum tragacanth, and a wetting agent
such as lecithin. Suitable preservatives for aqueous suspensions include ethyl and n-propyl p-
hydroxybenzoate.

The compounds of the invention may also be presented as liposome formulations.

For oral administration the castanospermine ester can be formulated into solid or liquid
preparations such as capsules, pills, tablets, troches, lozenges, melts, powders, granules,
solutions, suspensions, dispersions or emulsions (which solutions, suspensions dispersions
or emulsions may be aqueous or non-aqueous). The solid unit dosage forms can be a
capsule which can be of the ordinary hard- or soft-shelled gelatin type containing, for
example, surfactants, lubricants, and inert fillers such as lactose, sucrose, calcium phosphate,
and cornstarch.

In another embodiment the compounds of this invention can be tableted with conventional
tablet bases such as lactose, sucrose, and cornstarch in combination with binders such as
acacia, cornstarch, or gelatin, disintegrating agents intended to assist the break-up and
dissolution of the tablet following administration such as potato starch, alginic acid, corn
starch, and guar gum, lubricants intended to improve the flow of tablet granulations and to
prevent the adhesion of tablet material to the surfaces of the tablet dies and punches, for
example, talc, stearic acid, or magnesium, calcium, or zinc stearate, dyes, coloring agents, and flavoring agents intended to enhance the aesthetic qualities of the tablets and make them more acceptable to the patient.

Suitable excipients for use in oral liquid dosage forms include diluents such as water and alcohols, for example, ethanol, benzyl alcohol, and the polyethylene alcohols, either with or without the addition of a pharmaceutically acceptably surfactant, suspending agent or emulsifying agent.

The castanospermine ester derivatives of this invention may also be administered parenterally, that is, subcutaneously, intravenously, intramuscularly, or interperitoneally.

In such embodiments, the medicament is provided as injectable doses of the compound in a physiologically acceptable diluent with a pharmaceutical carrier which can be a sterile liquid or mixture of liquids. Suitable liquids include water, saline, aqueous dextrose and related sugar solutions, an alcohol (such as ethanol, isopropanol, or hexadecyl alcohol), glycols (such as propylene glycol or polyethylene glycol), glycerol ketals (such as 2,2-dimethyl-1,3-dioxolane-4-methanol), ethers (such as poly(ethylene-glycol) 400), an oil, a fatty acid, a fatty acid ester or glyceride, or an acetylated fatty acid glyceride with or without the addition of a pharmaceutically acceptable surfactant (such as a soap or a detergent), suspending agent (such as pectin, carhomers, methylcellulose, hydroxypropylmethylcellulose, or carboxymethylcellulose), or emulsifying agent and other pharmaceutically adjuvants.

Illustrative of oils which can be used in the parenteral formulations of this invention are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, sesame oil, cottonseed oil, corn oil, olive oil, petrolatum, and mineral oil.

Suitable fatty acids include oleic acid, stearic acid, and isostearic acid. Suitable fatty acid esters are, for example, ethyl oleate and isopropyl myristate.

Suitable soaps include fatty alkali metal, ammonium, and triethanolamine salts and suitable detergents include cationic detergents, for example, dimethyl dialkyl ammonium halides, alkyl pyridinium halides, and alkylamines acetates; anionic detergents, for example, alkyl, aryl, and olefin sulphonates, alkyl, olefin, ether, and monoglyceride sulphates, and sulphosuccinates; nonionic detergents, for example, fatty amine oxides, fatty acid alkanolamides, and polyoxyethylenepolypropylene copolymers; and amphoteric detergents, for example, alkyl-beta-aminopropionates, and 2-alkylimidazoline quaternary ammonium salts, as well as mixtures.

The parenteral compositions of this invention will typically contain from about 0.5 to about 25% by weight of the castanospermine ester derivative of formula 1 in solution. Preservatives
and buffers may also be used advantageously. In order to minimize or eliminate irritation at
the site of injection, such compositions may contain a non-ionic surfactant having a
hydrophilic-lipophilic balance (HLB) of from about 12 to about 17. The quantity of surfactant in
such formulations ranges from about 5 to about 15% by weight. The surfactant can be a
single component having the above HLB or can be a mixture of two or more components
having the desired HLB. Illustrative of surfactants used in parenteral formulations are the
class of polyethylene sorbitan fatty acid esters, for example, sorbitan monooleate and the
high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the
condensation of propylene oxide with propylene glycol.

The castanospermine ester derivatives of this invention may also be administered topically,
and when done so the carrier may suitably comprise a solution, ointment or gel base. The
base, for example, may comprise one or more of the following: petrolatum, lanolin,
polyethylene glycols, bee wax, mineral oil, diluents such as water and alcohol, and emulsifiers
and stabilizers. Topical formulations may contain a concentration of the castanospermine
ester or its pharmaceutical salt from about 0.1 to about 10% w/v (weight per unit volume).

The invention will now be described with reference to the following exemplary embodiments,
which are purely illustrative and not intended to be limiting in any way. It will be appreciated
that modifications to detail may be made whilst still falling within the scope of the invention.

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.

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

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 polyethylene glycols such as PEG 400).

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).

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.

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.

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.

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.

**Examplification**

**Methods**

**Plaque Reduction Assay**


Briefly, confluent MDCK cells, seeded at 10^5 cells/well in 24-well culture plates used, infected at a MOI of 0.001, that produced approximately 50-100 plaques per well. Virus was absorbed for 2hrs, at room temperature and removed. Infected cell monolayers were overlaid with 1ml of a 1:1agarose: serum free, double strength medium (supplemented with 0.6% BSA, 0.004% DEAE dextran and 2μg/ml TPCK Trypsin) containing different concentrations of test
compound in triplicate. Likewise, triplicate wells overlaid with compound-free medium, served as untreated controls. Plates were incubated (37°C) for three days, fixed (10% formalin) and stained (3% methylene blue). Plaque number (% of control) was plotted versus compound concentration and IC_{50} values calculated by linear regression analysis.

Results are shown in Table 2. Amantidine, a known drug for influenza infection, was used as the control compound.

**Table 2: Antiviral Activity by plaque reduction assay in MDCK cells against influenza A (strain A/Hong Kong/11/88)**

<table>
<thead>
<tr>
<th>Concentration (μM)</th>
<th>No. Plaques</th>
<th>Mean</th>
<th>% Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>200</td>
<td>3, 1, 1</td>
<td>2</td>
<td>7%</td>
</tr>
<tr>
<td>100</td>
<td>3, 5, 6</td>
<td>5</td>
<td>18%</td>
</tr>
<tr>
<td>50</td>
<td>6, 7, 7</td>
<td>7</td>
<td>26%</td>
</tr>
<tr>
<td>25</td>
<td>6, 7, 10</td>
<td>8</td>
<td>30%</td>
</tr>
<tr>
<td>12</td>
<td>20, 18, 11</td>
<td>16</td>
<td>59%</td>
</tr>
<tr>
<td><strong>Virus control</strong></td>
<td>26, 31, 24</td>
<td>27</td>
<td>100%</td>
</tr>
</tbody>
</table>

**Concamanospermine**

<table>
<thead>
<tr>
<th>Concentration (μM)</th>
<th>No. Plaques</th>
<th>Mean</th>
<th>% Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>0, 0, 0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>25</td>
<td>0, 0, 0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>0, 0, 0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>1, 3, 1</td>
<td>2</td>
<td>4%</td>
</tr>
<tr>
<td><strong>Virus control</strong></td>
<td>14, 14, 26</td>
<td>54</td>
<td>100%</td>
</tr>
</tbody>
</table>

**6-0-Butanoyl Castanospermine (celgosivir)**

<table>
<thead>
<tr>
<th>Concentration (μM)</th>
<th>No. Plaques</th>
<th>Mean</th>
<th>% Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>0, 0, 0</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>25</td>
<td>0, 0, 0</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>12</td>
<td>0, 0, 0</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>6</td>
<td>0, 0, 0</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>6, 3, 6</td>
<td>5</td>
<td>26%</td>
</tr>
<tr>
<td><strong>Virus control</strong></td>
<td>17, 22, 17</td>
<td>19</td>
<td>100%</td>
</tr>
</tbody>
</table>

**Amantadine**

<table>
<thead>
<tr>
<th>Concentration (μM)</th>
<th>No. Plaques</th>
<th>Mean</th>
<th>% Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>0, 0, 0</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>25</td>
<td>0, 0, 0</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>12</td>
<td>0, 0, 0</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>6</td>
<td>0, 0, 0</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>6, 3, 6</td>
<td>5</td>
<td>26%</td>
</tr>
<tr>
<td><strong>Virus control</strong></td>
<td>17, 22, 17</td>
<td>19</td>
<td>100%</td>
</tr>
</tbody>
</table>

**Summary of activities**

<table>
<thead>
<tr>
<th>Drug</th>
<th>IC_{50}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Castanospermine</td>
<td>15μM</td>
</tr>
<tr>
<td>Celgosivir</td>
<td>&lt;6μM</td>
</tr>
<tr>
<td>Amantadine</td>
<td>&lt;3μM</td>
</tr>
</tbody>
</table>
Small animal model/influenza A strain

Briefly, 15-20g female Balb-C mice were inoculated intranasally with 10^2-10^4 pfu of mouse-adapted influenza A/PR8 strain by addition of 25μl of virus to each nostril. Compounds can be administered by the intranasal route. Bucast has been previously shown to have anti-viral activity and to be well tolerated in mice (Bridges, C.G., Ahmed P.S., Kang M.S., Nash R.J., Porter E.A. and Tymns A.S. 1995a. The effect of oral treatment with 6-0-butanoyl castanospermine (MDL 28,574) in the murine zosterform model of HSV-1 infection. Glycobiology 5:249-253).

Mice (5 per group) were treated with compound or PBS 2 hours post inoculation with A/PR/8/34 and twice daily for 72 hours. Animals were sacrificed 8 hrs post-final treatment and the lungs removed for analysis of infectious virus after extraction from tissue. Virus was titrated by plaque assay and referenced by the weight of lungs on removal. Signs of well being, lung pathology and weight losses were also recorded. Results are shown in Table 3.

Treatment with Celgosivir (400mg/kg) reduced the viral load in the respiratory tract ten-fold. The increased lung weight in the placebo animal (up 20% on 400mg 1kg treatment) was considered due to lung consolidation and effects of viral replication. These data show a protective effect of the inhibitor due to control of virus growth infection.

Table 3: Antiviral Effects of 6-0-Butanoyl Castanospermine (Cegosivir) in mice infected with Influenza A virus (strain A/PR/8/34)

<table>
<thead>
<tr>
<th>Treatment mg/kg/day</th>
<th>Mouse</th>
<th>Lung Weight grams</th>
<th>Lung titre p.f.u. x 10^7</th>
</tr>
</thead>
<tbody>
<tr>
<td>200</td>
<td>A</td>
<td>0.331</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>0.279</td>
<td>1.47</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>0.288</td>
<td>11.30</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>0.371</td>
<td>38.70</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>0.289</td>
<td>4.27</td>
</tr>
<tr>
<td>Mean +S.D.</td>
<td></td>
<td>0.312 + 0.038</td>
<td>11.17 + 15.98</td>
</tr>
<tr>
<td>400</td>
<td>A</td>
<td>0.350</td>
<td>6.67</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>0.391</td>
<td>2.00</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>0.313</td>
<td>2.00</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>0.280</td>
<td>1.73</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>0.314</td>
<td>4.00</td>
</tr>
<tr>
<td>Mean +S.D.</td>
<td></td>
<td>0.330 + 0.042</td>
<td>3.28 + 2.10</td>
</tr>
<tr>
<td>PLACEBO</td>
<td>A</td>
<td>0.403</td>
<td>50.60</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>0.369</td>
<td>36.00</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>0.400</td>
<td>37.30</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>0.380</td>
<td>17.30</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>0.409</td>
<td>25.30</td>
</tr>
<tr>
<td>Mean +S.D.</td>
<td></td>
<td>0.392+0.0169</td>
<td>33.30 + 12.87</td>
</tr>
</tbody>
</table>
For further methodological details, see Ryan D.M., Ticehurst J., Dempsey M.H. and Penn C.R. (1994) Inhibition of influenza virus replication in mice by GG167 (4-Guanidino-2,4-dideoxy-2,3-dehydro-N-acetylneuraminic acid) is consistent with extra cellular activity of viral neuraminidase (sialidase): Antimicrobial Agents & Chemother. 38:2270-2275.

**Equivalents**

The foregoing descriptions detail presently preferred embodiments of the present invention.

Numerous modifications and variations in practice thereof are expected to occur to those skilled in the art upon consideration of these descriptions. Those modifications and variations are intended to be encompassed within the claims appended hereto.
CLAIMS:

1. A method of treating an influenza virus infection in a patient in need thereof which comprises administering to the patient an effective amount of a castanospermine ester of the formula:

\[
\begin{align*}
\text{HO} & \\
\text{R}_2\text{O} & \\
\text{OR}_1 & \\
\text{OR} & \\
\text{N} & \\
\end{align*}
\]

wherein \( R, R_1 \) and \( R_2 \) are independently hydrogen, \( C_{1-14} \) alkanoyl, \( C_{1-14} \) alkenoyl, cyclohexanecarbonyl, \( C_{1-4} \) alkoxyacetyl, naphthalenecarbonyl optionally substituted by methyl or halogen; phenyl(\( C_{2-6} \) alkanoyl) wherein the phenyl is optionally substituted by methyl or halogen; cinnamoyl; pyridinecarbonyl optionally substituted by \( C_{1-10} \) alkyl; thiophenecarbonyl optionally substituted by methyl or halogen; or furancarbonyl optionally substituted by methyl or halogen; \( Y \) is hydrogen, \( C_{1-4} \) alkyl, \( C_{1-4} \) alkoxy, halogen, trifluoromethyl, \( C_{1-4} \) alkylsulphonyl, \( C_{1-4} \) alkylmercaptot, cyano or dimethylamino; \( Y' \) is hydrogen, \( C_{1-4} \) alkyl, \( C_{1-4} \) alkoxy, halogen or it is combined with \( Y \) to give 3,4-methylenedioxy; \( Y'' \) is hydrogen, \( C_{1-4} \) alkyl, \( C_{1-4} \) alkoxy or halogen; with \( R, R_1 \) and \( R_2 \) being selected in such a way that at least one of them, but not more than two of them, is hydrogen; or a pharmaceutically acceptable salt or derivative thereof.

2. A method according to claim 1 wherein \( R, R_1 \) and \( R_2 \) are each independently hydrogen, \( C_{1-10} \) alkanoyl, \( C_{1-10} \) alkenoyl, \( C_{1-8} \) alkoxyacetyl, or wherein \( Y \) is hydrogen, \( C_{1-4} \) alkyl, \( C_{1-4} \) alkoxy, halogen, trifluoromethyl, \( C_{1-4} \) alkylsulphonyl, \( C_{1-4} \) alkylmercaptot, cyano or dimethylamino; \( Y' \) is hydrogen, \( C_{1-4} \) alkyl, \( C_{1-4} \) alkoxy, halogen or it is combined with \( Y \) to give 3,4-methylenedioxy; \( Y'' \) is hydrogen, \( C_{1-4} \) alkoxy or halogen; with \( R, R_1 \) and \( R_2 \) being selected in such a way that at least one of them, but not more than two of them, is hydrogen.
3. A method according to claim 1 or claim 2 wherein R, R₁ and R₂ are each independently hydrogen, C₁₈ alkanoyl, C₁₈ alkenoyl, C₁₈ alkoxy-acetyl, or a benzoyl optionally substituted with an alkyl or halogen; with R, R₁ and R₂ being selected in such a way that at least one of them, but not more than two of them, is hydrogen.

4. A method according to claim 1 wherein R, R₁ and R₂ are each independently hydrogen, C₁₈ alkanoyl, C₁₈ alkenoyl, C₁₈ alkoxy-acetyl, or a benzoyl optionally substituted with a methyl, bromo, chloro, or fluoro group; with R, R₁ and R₂ being selected in such a way that at least one of them, but not more than two of them, is hydrogen.

5. A method according to claim 1 wherein R₁ is a C₁₈ alkanoyl, C₁₈ alkenoyl, C₁₈ alkoxy-acetyl, or a benzoyl optionally substituted with an alkyl or halogen group.

6. A method according to claim 1 wherein wherein R₁ is a C₁₈ alkanoyl, C₁₈ alkenoyl, C₁₈ alkoxyacetyl, or a benzoyl optionally substituted with a methyl, bromo, chloro, or fluoro group.

7. A method according to claim 1 wherein the castanospermine ester is selected from:

(a) [1S-(1α,6β,7α,8β,8αβ)]-octahydro-1,6,7,8-indolizinetetrol 6-benzoate;
(b) [1S-(1α,6β,7α,8β,8αβ)]-octahydro-1,6,7,8-indolizinetetrol 7-benzoate;
(c) [1S-(1α,6β,7α,8β,8αβ)]-octahydro-1,6,7,8-indolizinetetrol 6-(4-methylbenzoate);
(d) [1S-(1α,6β,7α,8β,8αβ)]-octahydro-1,6,7,8-indolizinetetrol 7-(4-bromobenzoate);
(e) [1S-(1α,6β,7α,8β,8αβ)]-octahydro-1,6,7,8-indolizinetetrol 6,8-dibutoanote;
(f) [1S-(1α,6β,7α,8β,8αβ)]-octahydro-1,6,7,8-indolizinetetrol 6-butanoate;
(g) [1S-(1α,6β,7α,8β,8αβ)]-octahydro-1,6,7,8-indolizinetetrol 6-(2-furancarbonxylate);
(h) [1S-(1α,6β,7α,8β,8αβ)]-octahydro-1,6,7,8-indolizinetetrol 7-(2,4-dichlorobenzoate);
(i) [1S-(1α,6β,7α,8β,8αβ)]-octahydro-1,6,7,8-indolizinetetrol 6-(3-hexenoate);
(j) [1S-(1α,6β,7α,8β,8αβ)]-octahydro-1,6,7,8-indolizinetetrol 6-octanoate;
(k) [1S-(1α,6β,7α,8β,8αβ)]-octahydro-1,6,7,8-indolizinetetrol 6-pentanoate;
(l) an O-pivaloyl ester;
(m) a 2-ethyl-butryl ester;
(n) a 3,3-dimethylbutyryl ester;
(o) a cyclopropanoyl ester;
(p) a 4-methoxybenzoate ester;
(q) a 2-aminobenzoate ester; and
(r) a mixture of any or all of (a) - (q).

8. A method according to any one of the preceding claims wherein the influenza virus is influenza A or influenza B virus.
9. Use of a castanospermine ester as defined in any one of the preceding claims for the manufacture of a medicament for use in the therapy or prophylaxis of an influenza virus infection.

10. A process for the manufacture of a medicament for use in the therapy or prophylaxis of an influenza virus infection characterized in the use of a castanospermine ester as defined in any one of the preceding claims.

11. The use of claim 9 or process of claim 10 wherein the therapy or prophylaxis is the treatment or prevention an infection by a virus as defined in claim 8.

12. A composition comprising a castanospermine ester as defined in any one of the preceding claims in combination with:
   (a) an anti-influenza drug; and/or
   (b) an influenza vaccine and/or one or more anti-influenza antibodies.

13. The composition of claim 12 wherein the anti-influenza drug is an NA inhibitor, for example zanamivir and/or oseltamivir.

14. The composition of claim 12 or claim 13 further comprising a pharmaceutically acceptable excipient.

15. A pharmaceutical composition comprising the composition of any one of claims 12 to 14.

16. The composition of any one of claims 12 to 15 for use in therapy or prophylaxis.

17. A pharmaceutical kit of parts comprising a castanospermine ester as defined in any one of the preceding claims in combination with:
   (a) an anti-influenza drug; and/or
   (b) an influenza vaccine and/or one or more anti-influenza antibodies.

18. The kit of claim 17 further comprising instructions for use in the treatment of an influenza infection.

19. The kit of claim 17 or claim 18 wherein the castanospermine ester and/or anti-influenza drug and/or an influenza vaccine and/or one or more anti-influenza antibodies are in unit dosage form.
20. A pharmaceutical composition comprising the castanospermine ester as defined in any one of the preceding claims in a form suitable for (or adapted to) delivery to the respiratory tract.

21. The pharmaceutical composition of claim 20 wherein the composition:
   (a) is in a dropper or pipette; and/or
   (b) is in an atomising spray pump; and/or
   (c) takes the form of an aerosol formulation comprising the castanospermine ester in a pressurised pack with a propellant; and/or
   (d) is in an inhaler; and/or
   (e) is particulate, each particle having a size of about 5 microns or less.