[0005] Compound B, *i.e.* (1S,2S)-2-[4-[7-cyclopropyl-5-[(1R)-1-methyl-3,4-dihydro-1*H*-isoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl]-3-fluoro-phenyl]cyclopropane-carboxylic acid, is disclosed in WO-2016/174079 as compound O5.

[0006] WO-2017/134133 discloses combinations of 3-({5-chloro-1-[3-(methylsulfonyl)-propyl]-1*H*-indol-2-yl}methyl)-1-(2,2,2-trifluoroethyl)-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one, and one or more RSV inhibiting compounds for use in the treatment of RSV infection.

[0007] It has now been found that the combination of 3-({5-chloro-1-[3-(methylsulfonyl)-propyl]-1*H*-indol-2-yl}methyl)-1-(2,2,2-trifluoroethyl)-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one (hereinafter referred to as Compound A) and (1S,2S)-2-[4-[7-cyclopropyl-5-[(1R)-1-methyl-3,4-dihydro-1*H*-isoquinoline-2-carbonyl]pyrazolo[1,5-a]pyrimidin-2-yl]-3-fluoro-phenyl]cyclopropanecarboxylic acid (hereinafter referred to as Compound B), provides an improved therapy in the treatment of RSV infection.

[0008] Disclosed herein is a combination of Compound A and Compound B and the use of this combination for preventing, treating or ameliorating RSV infection in a subject in need thereof.

[0008a] In one aspect, disclosed herein is a combination comprising 3-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-indol-2-yl}methyl)-1-(2,2,2-trifluoroethyl)-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one, or a pharmaceutically acceptable salt thereof, as Compound A, and
(1S,2S)-2-[4-[7-cyclopropyl-5-[(1R)-1-methyl-3,4-dihydro-1*H*-isoquinoline-2-carbonyl]-pyrazolo[1,5-a]pyrimidin-2-yl]-3-fluoro-phenyl]cyclopropanecarboxylic acid, or a pharmaceutically acceptable salt thereof, as Compound B;
for use in preventing, treating or ameliorating respiratory syncytial virus (RSV) infection.

[0009] Other examples relate to a pharmaceutical product comprising the combination of Compound A and Compound B and the use of said pharmaceutical product for preventing, treating or ameliorating RSV infection.

[0009a] In another aspect, disclosed herein is a pharmaceutical composition comprising a combination as described herein, and a pharmaceutically acceptable carrier.

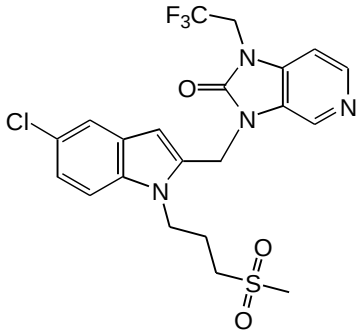
[0009b] In another aspect, disclosed herein is a pharmaceutical composition for use in the treatment or amelioration of RSV infection wherein said composition comprises a combination as described herein, and a pharmaceutically acceptable carrier.

[0009c] In another aspect, disclosed herein is a pharmaceutical composition for use in the prevention of RSV infection wherein said composition comprises a combination as described herein, and a pharmaceutically acceptable carrier.

[0009d] In another aspect, disclosed herein is use of a combination as described herein in the manufacture of a medicament for use in the prevention, treatment or amelioration of RSV infection.

[0010] Still other examples relate to a method of preventing, treating or ameliorating RSV infection in a subject in need thereof comprising administering the combination of Compound A and Compound B in an effective amount to said subject.

[0011] Compound A is 3-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-indol-2-yl}methyl)-1-(2,2,2-trifluoroethyl)-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one disclosed in WO-2012/080447 as compound P55 having the following structure :



methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic, cyclamic, salicylic, p-aminosalicylic, pamoic and the like acids. The Compound A or Compound B may also be converted into the pharmaceutically acceptable metal or amine addition salt forms by treatment with appropriate organic or inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium or potassium salts; or the magnesium or calcium salts; salts with organic bases, e.g. the benzathine, N-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine, and the like. The term addition salt form is meant to also comprise any solvates that Compound A or Compound B, as well as the salts thereof, may form. Such solvates are, for example, hydrates, alcoholates, e.g. ethanolates, and the like.

[0015] In an example the amount of Compound A and the amount of Compound B in the combinations according to the present disclosure is such that a synergistic antiviral effect against RSV is obtained.

[0016] The amounts of the Compound A in the combinations of the disclosure that are administered on a daily basis may vary from about 10 mg to about 2500 mg, about 50 mg to about 1000 mg, or from about 50 mg to about 500 mg.

[0017] The amounts of the Compound B in the combinations of the disclosure that are administered on a daily basis may vary from about 10 mg to about 2500 mg, about 50 mg to about 1000 mg, or from about 50 mg to about 500 mg for the total amount of the Compound B.

[0018] All amounts mentioned in this and the following paragraphs refer to the free form (*i.e.* non-salt form). The above values represent free-form equivalents, *i.e.* quantities as if the free form would be administered. If salts are administered the amounts need to be calculated in function of the molecular weight ratio between the salt and the free form.

[0019] The above mentioned daily doses are calculated for an average body weight of about 70 kg and should be recalculated in case of paediatric applications, or when used with patients with a substantially diverting body weight.

[0020] The dosages may be presented as one, two, three or four or more sub-doses administered at appropriate intervals throughout the day. The dosage used preferably corresponds to the daily amount of Compound A and Compound B mentioned above, or a sub-dose thereof, such as 1/2, 1/3, or 1/4 thereof. A dosage form may contain the

Compound A and Compound B, in an amount equal to the ranges or quantities mentioned in the previous paragraphs, either in separate formulations or in a combined formulation. Such combined formulation is preferred.

[0021] In the instance where Compound A and Compound B are to be administered once daily, this can be accomplished by administering a combined fixed dose combination containing Compound A and Compound B. Dosage forms that can be administered are described hereinafter, oral dosage forms, in particular oral solutions being preferred.

[0022] Active ingredients may be formulated in pharmaceutical compositions either separately or as a combined pharmaceutical composition. In the latter instance, there is provided a pharmaceutical composition comprising a therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, and the Compound B, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. A therapeutically effective amount in this context is an amount sufficient to stabilize or to reduce RSV infection, in infected subjects. Therapeutically effective amounts may in particular correspond to the amounts mentioned above for administration on a daily base or of the subdoses thereof in ease of multiple daily administrations.

[0023] In a further example, this disclosure relates to a process of preparing a pharmaceutical composition as specified herein, which comprises intimately mixing a pharmaceutically acceptable carrier with a therapeutically effective amount of the Compound A, or a pharmaceutically acceptable salt thereof, and an effective amount of the Compound B, or a pharmaceutically acceptable salt thereof.

[0024] The combinations provided herein may also be formulated as a combined preparation for simultaneous or sequential use in RSV therapy. In such a case, the Compound A is formulated in a pharmaceutical composition containing other pharmaceutically acceptable excipients, and the Compound B is formulated separately in a pharmaceutical composition containing other pharmaceutically acceptable excipients. Conveniently, these separate pharmaceutical compositions can be part of a kit for simultaneous or sequential use.

[0025] The individual components of the combination of the present disclosure can be administered simultaneously or separately at different times during the course of therapy or concurrently in divided or single combination forms.

[0026] Therefore, the Compound A and Compound B, individually or combined, may be formulated into various pharmaceutical compositions suitable for administration purposes. In these, a therapeutically effective amount of each of the particular compounds A and B is combined with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. Pharmaceutical compositions may be prepared as medicaments to be administered orally, parenterally (including subcutaneously, intramuscularly, and intravenously), rectally, bucally, or nasally. Suitable compositions for oral administration include powders, granulates, aggregates, tablets, compressed or coated pills, dragees, sachets, hard or gelatin capsules, syrups and suspensions. Suitable compositions for parenteral administration include aqueous or non-aqueous solutions or emulsions, while for rectal administration suitable compositions for administration include suppositories with a hydrophilic or hydrophobic vehicle. For nasal delivery there can be used suitable aerosol delivery systems.

[0027] For example, in preparing the compositions for oral administration, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid compositions such as suspensions, syrups, elixirs, emulsions and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of solid compositions. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, such as solubilizers, emulsifiers or further auxiliaries may be added thereto. Injectable solutions may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of both. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Also included are solid form preparations intended to be converted, shortly before use, to liquid form preparations such as powders for reconstitution.

[0028] The pharmaceutical compositions may be conveniently presented in unit dosage form for ease of administration and uniformity of dosage. Examples include tablets (including scored or coated tablets), capsules, pills, suppositories, powder packets, wafers, injectable solutions or suspensions and the like, and segregated multiples thereof.

[0029] The combination of Compound A and Compound B, as specified herein, is useful in the treatment of warm-blooded animals, in particular humans, infected with RSV.

[0030] The present disclosure also relates to a method for treating or ameliorating RSV infection in a subject in need thereof comprising administering the combination of Compound A and Compound B, or a pharmaceutically acceptable salt of any of the

foregoing, in a therapeutically effective amount to said subject. The amount of Compound A can range from 1 mg/kg to 50 mg/kg or 5 mg/kg to 50 mg/kg and the amount of Compound B can range from 1 mg/kg to 50 mg/kg or 5 mg/kg to 50 mg/kg.

[0031] In an example the present disclosure further relates to a method for treating or ameliorating RSV infection in a subject in need thereof comprising administering the combination of Compound A and Compound B, or a pharmaceutically acceptable salt of any of the foregoing, wherein the amount of Compound A and the amount of Compound is such that a synergistic antiviral effect against RSV is obtained.

[0032] Other examples relate to a method for treating or ameliorating a RSV infection comprising contacting a cell infected with the RSV virus with an effective amount of a combination of Compound A and of Compound B, or a pharmaceutically acceptable salt of any of the foregoing.

[0033] As used herein, the terms "treat," "treating," "treatment," "therapeutic," and "therapy" do not necessarily mean total cure or abolition of the disease or condition. Any reduction of viral load or alleviation of any undesired signs or symptoms of a disease or condition, to any extent can be considered treatment and/or therapy.

[0034] The terms "therapeutically effective amount" and "effective amount" are used to indicate an amount of an active compound, or pharmaceutical agent, that elicits the biological or medicinal response indicated. For example, a therapeutically effective amount of compound can be the amount needed to prevent, alleviate or ameliorate symptoms of disease, reduce viral load, or prolong the survival of the subject being treated. This response may occur in a tissue, system, animal or human and includes reduction of viral load, alleviation of the signs or symptoms of the disease being treated. Determination of an effective amount is well within the capability of those skilled in the art, in view of the disclosure provided herein. The therapeutically effective amount of the compounds disclosed herein required as a dose will depend on the route of administration, the type of animal, including human, being treated, and the physical characteristics of the specific animal under consideration. The dose can be tailored to achieve a desired effect, but will depend on such factors as weight, diet, concurrent medication and other factors which those skilled in the medical arts will recognize.

[0035] Various indicators for determining the effectiveness of a method for treating a respiratory syncytial virus (RSV) infection are known to those skilled in the art. Example of suitable indicators include, but are not limited to, a reduction in viral load, a reduction in

Claims

1. A combination comprising
3-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-indol-2-yl}methyl)-1-(2,2,2-trifluoroethyl)-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one, or a pharmaceutically acceptable salt thereof, as Compound A, and
(1S,2S)-2-[4-[7-cyclopropyl-5-[(1R)-1-methyl-3,4-dihydro-1*H*-isoquinoline-2-carbonyl]-pyrazolo[1,5-a]pyrimidin-2-yl]-3-fluoro-phenyl]cyclopropanecarboxylic acid, or a pharmaceutically acceptable salt thereof, as Compound B;
for use in preventing, treating or ameliorating respiratory syncytial virus (RSV) infection.

2. The combination for use according to claim 1 wherein the amount of Compound A and the amount of Compound B is such that a synergistic antiviral effect against RSV is obtained.

3. The combination for use according to claim 1 or claim 2 wherein the amount of Compound A ranges from 10 mg to 2500 mg and the amount of Compound B ranges from 10 mg to 2500 mg.

4. A pharmaceutical composition comprising a combination as claimed in any one of claims 1 to 3, and a pharmaceutically acceptable carrier.

5. A pharmaceutical composition for use in the treatment or amelioration of RSV infection wherein said composition comprises a combination as claimed in any one of claims 1 to 3, and a pharmaceutically acceptable carrier.

6. A pharmaceutical composition for use in the prevention of RSV infection wherein said composition comprises a combination as claimed in any one of claims 1 to 3, and a pharmaceutically acceptable carrier.

7. Use of a combination as described in any one of claims 1 to 3 in the manufacture of a medicament for use in the prevention, treatment or amelioration of RSV infection.

8. Use of a pharmaceutical composition as claimed in claim 6 in the manufacture of a medicament for use in the prevention, treatment or amelioration of RSV infection.

9. The use as claimed in claim 7 wherein the combination of Compound A and Compound B is formulated in a single pharmaceutical composition.

10. The use as claimed in claim 7 wherein the combination of Compound A and Compound B is formulated as a separate pharmaceutical composition comprising Compound A and a separate pharmaceutical composition comprising Compound B whereby the pharmaceutical compositions are to be administered simultaneously or sequentially.