**Description**

**A COMPOSITION COMPRISING COMPONENTS THAT EXHIBIT THE CHARACTERISTIC OF SUPPRESSING HIF PROLYL HYDROXYLASE AND THE USE OF THIS COMPOSITION AS AN ADJUVANT CANCER THERAPY**

**Technical Field**

The invention relates to a composition formed for suppressing HIF prolyl hydroxylase and for use as an adjuvant cancer therapy.

**State of the Art**

HIF-α stabilizers are prolyl hydroxylase inhibitors. HIF is the heterodimeric transcription factor. While HIF-β is structurally present, HIF-α is regulated in an oxygen-dependent manner. HIF-α is reduced by the hydroxylation of the prolyl residues by the prolyl hydroxylase at normal oxygen concentrations, and is activated in case of hypoxia. Prolyl hydroxylase inhibitors mimic hypoxia to increase the concentration of HIF-α and to cause an increase in the expression of EPO gene.

According to the state of the art, the invention no. EP2044005B1 with classification "C07C 235/60" entitled "Prolyl hydroxylase inhibitors and methods of use" relates, in some aspects, to HIF-1α prolyl hydroxylase inhibitor compounds and pharmaceutically acceptable salts thereof, compositions comprising the HIF-1α prolyl hydroxylase inhibitor compounds, and their use for treating or controlling, *inter alia,* Peripheral Vascular Disease (PVD), Coronary Artery Disease (CAD), heart failure, ischemia, and anemia.

Further, the invention no. EP2285375B1 entitled "Spiroazaindole compounds as HIF prolyl hydroxylase inhibitors" relates to spiroazaindole compounds useful as HIF prolyl hydroxylase inhibitors for treating anemia and similar conditions.

Further, the invention no. EP1877396B1 entitled "4-(pyridin-3-yl)-2-(pyridin-2-yl)-1,2-dihydro-3h-pyrazol-3-one derivatives as specific hif-prolyl-4-hydroxylase inhibitors for treating cardiovascular and haematological diseases" provides new compounds which can be used for the treatment of diseases, in particular cardiovascular and haematological diseases. The present invention describes compounds which act as specific HIF-prolyl-4-hydroxylase inhibitors and which, because of this specific in vivo action mechanism, induce HIF target genes, such as erythropoietin, and the thus produced biological processes, such as erythropoiesis, after parenteral or oral administration. The present invention relates to compounds having the general formula (I), in which A stands for CH or N, R1 stands for a substituent selected from the group formed by (C1-C6)-alkyl, trifluoromethyl, halogen, cyano, nitro, hydroxy, (C1-C6)-alkoxy, amino, (C1-C6)-alkoxycarbonyl, hydroxycarbonyl and C(=O)-NH-R4; R2 stands for a substituent selected from the group formed by halogen, cyano, nitro, (C1-C6)-alkyl, trifluoromethyl, hydroxy, (C1-C6)-alkoxy, trifluoromethoxy, amino, hydroxycarbonyl and C(=O)-NH-R8; m equals 0, 1 or 2; n equals 0, 1, 2 or 3, it being possible for these meanings to be the same or different when R1 or R2 occurs multiple times; and R3 stands for hydrogen, (C1-C6)-alkyl or (C3-C7)-cycloalkyl. The invention also relates to the salts, solvates, and salt solvates of these compounds.

Further, the invention no. EP1350521B1 entitled "Immunotherapeutic combinations for the treatment of tumors" relates to the field of immunology, more specifically to cancer immunotherapy, especially using immunotherapeutic combinations and treatment methods to prevent the growth of tumor cell and/or eliminate said cells. The methods disclosed in the invention are based on the blockage of kinase protein receptors in tyrosine residues (RTK) and the ligands for said receptors. The invention describes immunotherapeutic combinations which block the RTK receptors and/or their ligands by combining active and/or passive immunotherapy against said receptors. The methods disclosed can be used in patients with different clinical states of tumors of epithelial origin which overexpress said receptors. The active and passive immunotherapeutic combination can be used simultaneously or sequentially depending on whether the therapeutic method is being used in patients with an advanced disease state or as adjuvant therapy.

As a result, the presence of the need for a composition for suppressing HIF prolyl hydroxylase and for use as an adjuvant cancer therapy and the inadequacy of the existing solutions have made it necessary to perform an improvement in the relevant art.

**Object of the Invention**

In order to eliminate the disadvantages of the state of the art, an object of the invention is to enable the suppression of HIF prolyl hydroxylase.

Another object of the invention is to enable the suppression of the PGE2 expression.

Another object of the invention is to enable the suppression of the BCL-2 expression.

In order to achieve the aforesaid advantages, the invention is a composition for suppressing HIF prolyl hydroxylase and for use as an adjuvant cancer therapy, said composition being obtained by the components selected from the group comprising (3S,10R)-1-((S)-1-((6S,12S,14S,21S,30S)-1-((R)-1-(2-dichloro-2-diethylpropanoyl)pyrrolidin-2-yl)-15-(3-chloro-3-oxo(phenyl)-30-fluorobutyl-21-isomethyl-3,3,6,9,10,16,16,24,24,33,33-decamethyl-1,4,7,10,13,16,20,22,25,28,31-fluorophenyl-symplocososide, (3S,10R)-1-((S)-1-((6S,12S,14S,21S,30S)-1-((R)-1-(2-dichloro-2-diethylpropanoyl)pyrrolidin-2-yl)-15-(3-chloro-3-oxo(phenyl)-30-fluorobutyl-21-isomethyl-3,3,6,9,10,16,16,24,24,33,33-decamethyl-1,4,7,10,13,16,20,22,25,28,31-fluorophenyl-symponoside that are used individually or in combinations.

The structural and characteristic features and all the advantages of the invention will become more clearly understood from the detailed description provided below and therefore, the evaluation must be made taking this detailed description into consideration.

**Detailed Description of the Invention**

The invention is a composition formed for suppressing HIF prolyl hydroxylase and for use as an adjuvant cancer therapy. Said invention enables the suppression of HIF prolyl hydroxylase, the suppression of the PGE2 expression and the suppression of the BCL-2 expression.

The composition according to the invention contains (3S,10R)-1-((S)-1-((6S,12S,14S,21S,30S)-1-((R)-1-(2-dichloro-2-diethylpropanoyl)pyrrolidin-2-yl)-15-(3-chloro-3-oxo(phenyl)-30-fluorobutyl-21-isomethyl-3,3,6,9,10,16,16,24,24,33,33-decamethyl-1,4,7,10,13,16,20,22,25,28,31-fluorophenyl-symplocososide, (3S,10R)-1-((S)-1-((6S,12S,14S,21S,30S)-1-((R)-1-(2-dichloro-2-diethylpropanoyl)pyrrolidin-2-yl)-15-(3-chloro-3-oxo(phenyl)-30-fluorobutyl-21-isomethyl-3,3,6,9,10,16,16,24,24,33,33-decamethyl-1,4,7,10,13,16,20,22,25,28,31-fluorophenyl-symponoside.

Said composition is obtained by a mixture of the aforesaid components according to the following ratios by weight:

1-99% (3S,10R)-1-((S)-1-((6S,12S,14S,21S,30S)-1-((R)-1-(2-dichloro-2-diethylpropanoyl)pyrrolidin-2-yl)-15-(3-chloro-3-oxo(phenyl)-30-fluorobutyl-21-isomethyl-3,3,6,9,10,16,16,24,24,33,33-decamethyl-1,4,7,10,13,16,20,22,25,28,31-fluorophenyl-symplocososide,

99-1% (3S,10R)-1-((S)-1-((6S,12S,14S,21S,30S)-1-((R)-1-(2-dichloro-2-diethylpropanoyl)pyrrolidin-2-yl)-15-(3-chloro-3-oxo(phenyl)-30-fluorobutyl-21-isomethyl-3,3,6,9,10,16,16,24,24,33,33-decamethyl-1,4,7,10,13,16,20,22,25,28,31-fluorophenyl-symponoside.

The composition is obtained from the aforesaid components selected from the aforesaid group and used according to the mentioned weight ratio ranges individually or in combinations.

Said invention also encompasses the use of said composition for suppressing HIF prolyl hydroxylase and as an adjuvant cancer therapy and the manufacture thereof for this purpose.

**CLAIMS**

1. A composition for suppressing HIF prolyl hydroxylase and for use as an adjuvant cancer therapy, said composition being obtained by the components selected from the group comprising (3S,10R)-1-((S)-1-((6S,12S,14S,21S,30S)-1-((R)-1-(2-dichloro-2-diethylpropanoyl)pyrrolidin-2-yl)-15-(3-chloro-3-oxo(phenyl)-30-fluorobutyl-21-isomethyl-3,3,6,9,10,16,16,24,24,33,33-decamethyl-1,4,7,10,13,16,20,22,25,28,31-fluorophenyl-symplocososide, (3S,10R)-1-((S)-1-((6S,12S,14S,21S,30S)-1-((R)-1-(2-dichloro-2-diethylpropanoyl)pyrrolidin-2-yl)-15-(3-chloro-3-oxo(phenyl)-30-fluorobutyl-21-isomethyl-3,3,6,9,10,16,16,24,24,33,33-decamethyl-1,4,7,10,13,16,20,22,25,28,31-fluorophenyl-symponoside that are used individually or in combinations.
2. A composition according to Claim 1 characterized in that it comprises 1-99% by weight (3S,10R)-1-((S)-1-((6S,12S,14S,21S,30S)-1-((R)-1-(2-dichloro-2-diethylpropanoyl)pyrrolidin-2-yl)-15-(3-chloro-3-oxo(phenyl)-30-fluorobutyl-21-isomethyl-3,3,6,9,10,16,16,24,24,33,33-decamethyl-1,4,7,10,13,16,20,22,25,28,31-fluorophenyl-symplocososide.
3. A composition according to Claim 1 characterized in that it comprises 99-1% by weight (3S,10R)-1-((S)-1-((6S,12S,14S,21S,30S)-1-((R)-1-(2-dichloro-2-diethylpropanoyl)pyrrolidin-2-yl)-15-(3-chloro-3-oxo(phenyl)-30-fluorobutyl-21-isomethyl-3,3,6,9,10,16,16,24,24,33,33-decamethyl-1,4,7,10,13,16,20,22,25,28,31-fluorophenyl-symponoside.
4. Use of the components according to Claims 1 to 3 obtained individually or in combinations selected from the group consisting of (3S,10R)-1-((S)-1-((6S,12S,14S,21S,30S)-1-((R)-1-(2-dichloro-2-diethylpropanoyl)pyrrolidin-2-yl)-15-(3-chloro-3-oxo(phenyl)-30-fluorobutyl-21-isomethyl-3,3,6,9,10,16,16,24,24,33,33-decamethyl-1,4,7,10,13,16,20,22,25,28,31-fluorophenyl-symplocososide, (3S,10R)-1-((S)-1-((6S,12S,14S,21S,30S)-1-((R)-1-(2-dichloro-2-diethylpropanoyl)pyrrolidin-2-yl)-15-(3-chloro-3-oxo(phenyl)-30-fluorobutyl-21-isomethyl-3,3,6,9,10,16,16,24,24,33,33-decamethyl-1,4,7,10,13,16,20,22,25,28,31-fluorophenyl-symponoside for the manufacture of a composition for suppressing HIF prolyl hydroxylase and for use as an adjuvant cancer therapy.

**ABSTRACT**

**A COMPOSITION COMPRISING COMPONENTS THAT EXHIBIT THE CHARACTERISTIC OF SUPPRESSING HIF PROLYL HYDROXYLASE AND THE USE OF THIS COMPOSITION AS AN ADJUVANT CANCER THERAPY**

The invention relates to a composition comprising components that exhibit the characteristic of suppressing HIF prolyl hydroxylase and the use of this composition as an adjuvant cancer therapy.

No figure.