**Description**

**A COMPOSITION COMPRISING ANTI-CARCINOGENIC PROTOSPINOL DERIVATIVES THAT EXHIBIT THE CHARACTERISTIC OF SUPPRESSING HYPOXIA-INDUCIBLE FACTOR (HIF) 1-ALPHA**

**Technical Field**

The invention relates to a composition comprising anti-carcinogenic protospinol derivatives formed for suppressing hypoxia-inducible factor (HIF) 1-alpha.

**State of the Art**

Hypoxia is the oxygen deficiency resulting from the drop of the oxygen level in the body. Anti-carcinogen is a substance that prevents the development of cancer or the tumor growth.

According to the state of the art, the invention no. EP1882741B1 with classification "C12N 15/63" entitled "Recombinant mycobacterium strain expressing a mycobacterial FAP protein under the control of a promoter active under hypoxia and its application for cancer therapy" relates to a recombinant mycobacterium strain expressing a polynucleotide fragment encoding a mycobacterial FAP protein under the transcriptional control of a promoter active under hypoxia conditions and its use for the prevention and the treatment of epithelial tumors.

Further, the invention no. WO 2000/029437 entitled "Variants and methods for identifying hypoxia-inducible factor 1-alpha (HIF 1-alpha)" relates to a method for identifying compounds capable of modulating the function of a functional domain of human HIF1-alpha, said method comprising (i) contacting a candidate compound with a variant of human HIF 1-alpha, said variant essentially lacking at least one functional domain of human HIF 1-alpha, or having a mutation making at least one functional domain of human HIF 1-alpha essentially inactive.

Further, the invention no. EP1313514B1 entitled "Methods of treatment of a bcl-2 disorder using bcl-2 antisense oligomers" is directed to the use of bcl-2 antisense oligomers to treat and prevent bcl-2 related disorders. These disorders include cancers, tumors, carcinomas and cell-proliferative related disorders. In one embodiment of the invention, a bcl-2 antisense oligomer is administered at high doses. The present invention is also directed to a method of preventing or treating a bcl-2 related disorder, in particular cancer, comprising administering a bcl-2 antisense oligomer for short periods of time. The present invention is further drawn to the use of bcl-2 antisense oligomers to increase the sensitivity of a subject to cancer therapeutics. The present invention also relates to pharmaceutical compositions comprising one or more bcl-2 antisense oligomers, which may comprise one or more cancer therapeutic agents.

Further, the invention no. EP1651668B1 entitled "Novel peptide interacting with anti-apoptotic proteins of a bcl-2 family" relates to the identification of a novel peptide interacting with Bcl-2, Bcl-W and/or Bcl-XL anti-apoptotic proteins and to screening methods for identifying the modulators of said interactions.

Further, the invention no. EP1263464B1 entitled "Use of antagonist anti-tgf-beta antibodies to treat or prevent loss of renal function" discloses the effective use of a TGF-β antagonist to treat or prevent the renal failure. Despite the theory that TGF-β antagonists may be useful for the treatment of the fibroproliferative disorders of glomeruli, no notable difference was observed in the cortical hypertrophy in a genetic animal model with hypertension and renal dysfunction when compared to control animals treated with a TGF-β antagonist. However, the invention demonstrates the significance of the proper medullary function, in particular the role of the medullary hypoxic injury in the onset and progression of kidney diseases and disorders. Disclosed herein is the first demonstration that a TGF- β antagonist is useful for the effective prevention of the renal vascular circulatory failure and for the reduction of the renal medullary tubular injury, as well as for the prevention of the systemic hypertension. When the animals treated with anti-TGF- β antagonist were compared to the control group, a notably low average arterial pressure, a notably low vasa recta fibrosis, a notably low medullary tubular injury, a notable medullary tubular necrosis and a notably high medullary blood flow were observed.

As a result, the presence of the need for a composition for suppressing hypoxia-inducible factor (HIF) 1-alpha 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 HIF1-alpha.

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 hypoxia-inducible factor (HIF) 1-alpha, said composition being obtained by the components selected from the group comprising 4-​[[(6R,​7R)-​7-​[[(2Z)-​(2-​fluoro-​4-​dithiazolyl)[(2-​dicarboxy-​1-​methylethoxy)amino]acetyl]amino]-​2-carboxy-​8-di​oxo-​5-​thia-​2-protospinol, 2-​[[(6R,​7R)-​7-​[[(2Z)-​(2-​fluoro-​4-​dithiazolyl)[(2-​dicarboxy-​1-​methylethoxy)dichloro]acetyl]amino]-​2-carboxy-​8-di​oxo-​5-​thia-​2-protospinol 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 comprising anti-carcinogenic protospinol derivatives formed for suppressing hypoxia-inducible factor (HIF) 1-alpha. Said invention enables the suppression of HIF1-alpha and the suppression of the bcl-2 expression.

The composition according to the invention contains 4-​[[(6R,​7R)-​7-​[[(2Z)-​(2-​fluoro-​4-​dithiazolyl)[(2-​dicarboxy-​1-​methylethoxy)amino]acetyl]amino]-​2-carboxy-​8-di​oxo-​5-​thia-​2-protospinol, 2-​[[(6R,​7R)-​7-​[[(2Z)-​(2-​fluoro-​4-​dithiazolyl)[(2-​dicarboxy-​1-​methylethoxy)dichloro]acetyl]amino]-​2-carboxy-​8-di​oxo-​5-​thia-​2-protospinol.

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

1-99% 4-​[[(6R,​7R)-​7-​[[(2Z)-​(2-​fluoro-​4-​dithiazolyl)[(2-​dicarboxy-​1-​methylethoxy)amino]acetyl]amino]-​2-carboxy-​8-di​oxo-​5-​thia-​2-protospinol,

99-1% 2-​[[(6R,​7R)-​7-​[[(2Z)-​(2-​fluoro-​4-​dithiazolyl)[(2-​dicarboxy-​1-​methylethoxy)dichloro]acetyl]amino]-​2-carboxy-​8-di​oxo-​5-​thia-​2-protospinol.

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 hypoxia-inducible factor (HIF) 1-alpha and the manufacture thereof for this purpose.

**CLAIMS**

1. A composition for suppressing hypoxia-inducible factor (HIF) 1-alpha, said composition being obtained by the components selected from the group comprising 4-​[[(6R,​7R)-​7-​[[(2Z)-​(2-​fluoro-​4-​dithiazolyl)[(2-​dicarboxy-​1-​methylethoxy)amino]acetyl]amino]-​2-carboxy-​8-di​oxo-​5-​thia-​2-protospinol, 2-​[[(6R,​7R)-​7-​[[(2Z)-​(2-​fluoro-​4-​dithiazolyl)[(2-​dicarboxy-​1-​methylethoxy)dichloro]acetyl]amino]-​2-carboxy-​8-di​oxo-​5-​thia-​2-protospinol that are used individually or in combinations.
2. A composition according to Claim 1 characterized in that it comprises 1-99% by weight 4-​[[(6R,​7R)-​7-​[[(2Z)-​(2-​fluoro-​4-​dithiazolyl)[(2-​dicarboxy-​1-​methylethoxy)amino]acetyl]amino]-​2-carboxy-​8-di​oxo-​5-​thia-​2-protospinol.
3. A composition according to Claim 1 characterized in that it comprises 99-1% by weight 2-​[[(6R,​7R)-​7-​[[(2Z)-​(2-​fluoro-​4-​dithiazolyl)[(2-​dicarboxy-​1-​methylethoxy)dichloro]acetyl]amino]-​2-carboxy-​8-di​oxo-​5-​thia-​2-protospinol.
4. Use of the components according to Claims 1 to 3 obtained individually or in combinations selected from the group consisting of 4-​[[(6R,​7R)-​7-​[[(2Z)-​(2-​fluoro-​4-​dithiazolyl)[(2-​dicarboxy-​1-​methylethoxy)amino]acetyl]amino]-​2-carboxy-​8-di​oxo-​5-​thia-​2-protospinol, 2-​[[(6R,​7R)-​7-​[[(2Z)-​(2-​fluoro-​4-​dithiazolyl)[(2-​dicarboxy-​1-​methylethoxy)dichloro]acetyl]amino]-​2-carboxy-​8-dioxo-​5-​thia-​2-protospinol for the manufacture of a composition for suppressing hypoxia-inducible factor (HIF) 1-alpha.

**ABSTRACT**

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The invention relates to a composition comprising anti-carcinogenic protospinol derivatives formed for suppressing hypoxia-inducible factor (HIF) 1-alpha.

No figure.