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(54) Title: COMBINATION OF A SOMATOSTATIN ANALOGUE AND A RAPAMYCIN

(57) Abstract

A combination of a compound of the somatostatin class and a rapamycin macrolide is useful for the prevention or treatment of cell hyperproliferation.

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COMBINATION OF A SOMATOSTATIN ANALOGUE AND A RAPAMYCIN

The present invention relates to a pharmaceutical combination and its use in the treatment of disorders associated with excess benign and malignant cell proliferation, e.g. tumors or intimal cell proliferation.

There is a continuing need for the development of drugs having increased effectiveness in inhibiting or slowing down undesired cell proliferation, particularly in the cancer field and in vasculopathies.

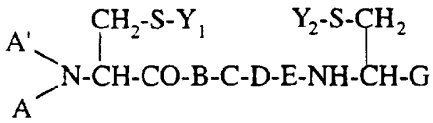
Accordingly, there is provided a pharmaceutical combination comprising a compound of the somatostatin class, and a rapamycin macrolide.

The somatostatin class is a known class of small peptides comprising the naturally occurring somatostatin-14 and analogues having somatostatin related activity, e.g. as disclosed by A.S. Dutta in Small Peptides, Vol.19, Elsevier (1993). By "somatostatin analogue" as used herein is meant any straight-chain or cyclic polypeptide having a structure based on that of the naturally occurring somatostatin-14 wherein one or more amino acid units have been omitted and/or replaced by one or more other amino radical(s) and/or wherein one or more functional groups have been replaced by one or more other functional groups and/or one or more groups have been replaced by one or several other isosteric groups. In general, the term covers all modified derivatives of the native somatostatin-14 which exhibit a somatostatin related activity, e.g. they bind to at least one somatostatin receptor (hSST-1, hSST-2, hSST-3, hSST-4 or hSST-5), preferably in the nMolar range, more preferably to at least the hSST-2 receptor in the nMolar range.

Cyclic, bridge cyclic and straight-chain somatostatin analogues or derivatives are known and have been described together with processes for their production e.g. in US Patent Specifications 4,310,518 and 4,235,886, in European Patent Specifications EP-A-1295; 23,192; 29,310; 29,579; 30,920; 31,303; 63,308; 70,021; 83,305; 215,171; 203,031; 214,872; 143,307; 298,732; 277,419; 389,180; 395,417; 450,480A2; in Belgian Patent Specification BE-A-900,089; and in WO 91/09056; WO 97/01579; WO 97/14715,

the contents thereof, in particular with respect to the compounds, being incorporated herein by reference.

Preferred somatostatin analogues are e. g. compounds of formula I



(I)

wherein

A is C_{1-12}alkyl, C_{7-10}phenylalkyl or a group of formula RCO-,

whereby

i) R is hydrogen, C_{1-11}alkyl, phenyl or C_{7-10}phenylalkyl, or

ii) RCO- is

a) a D-phenylalanine residue optionally ring-substituted by halogen, NO_2, NH_2, OH, C_{1-3}alkyl and/or C_{1-3}alkoxy; or

b) the residue of a natural or a synthetic α-amino-acid other than defined under a) above, or of a corresponding D-amino acid, or

c) a dipeptide residue in which the individual amino acid residues are the same or different and are selected from those defined under a) and/or b) above,

the α-amino group of amino acid residues a) and b) and the N-terminal amino group of dipeptide residues c) being optionally mono- or di-C_{1-12}alkylated or substituted by C_{1-8}alkanoyl;

A' is hydrogen or C_{1-3}alkyl,

Y_1 and Y_2 represent together a direct bond or each of Y_1 and Y_2 is hydrogen

B is -Phe- optionally ring-substituted by halogen, NO_2, NH_2, OH, C_{1-3}alkyl and /or

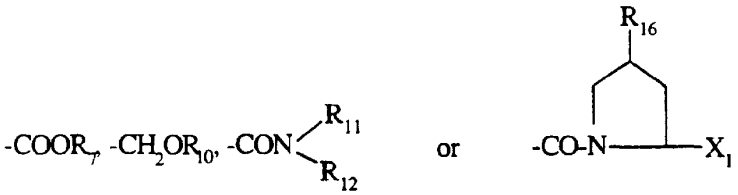
C_{1-3}alkoxy (including pentafluoroalanine), naphthylalanine or pyridylalanine,

C is (L)-Trp- or (D)-Trp- optionally α-N-methylated and optionally benzene-ring-substituted by halogen, NO_2, NH_2, OH, C_{1-3}alkyl and/or C_{1-3}alkoxy,

D is Lys, 4-aminocyclohexylAla or 4-aminocyclohexylGly

E is Thr, Ser, Val, Tyr, Ile, Leu or an aminobutyric or aminoisobutyric acid residue

G is a group of formula



wherein

R_7 is hydrogen or C_{1-3}alkyl,

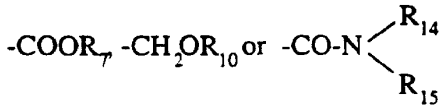
R_{10} is hydrogen or the residue of a physiologically acceptable, physiologically hydrolysable ester, e.g. formyl, C_{2-12}alkylcarbonyl, benzoyl,

R_{11} is hydrogen, C_{1-3}alkyl, phenyl or C_{7-10}phenyl-alkyl,

R_{12} is hydrogen, C_{1-3}alkyl or a group of formula $-CH(R_{13})-X_1$,

R_{13} is CH_2OH, $-(CH_2)_2-OH$, $-(CH_2)_3-OH$, $-CH(CH_3)OH$, isobutyl, butyl, benzyl, naphthyl-methyl or indol-3-yl-methyl, and

X_1 is a group of formula



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