US 20070117743A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2007/0117743 A1**

Palomera et al. (43) **Pub. Date: May 24, 2007**

(54) **NEW ANTITUMORAL COMPOUNDS**

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(21) Appl. No.: **10/570,734**

(22) PCT Filed: **Sep. 9, 2004**

(86) PCT No.: **PCT/GB04/03847**

§ 371(c)(1),
(2), (4) Date: **Oct. 18, 2006**

(30) **Foreign Application Priority Data**

Sep. 9, 2003 (GB) 0321066.3

Publication Classification

(51) **Int. Cl.**
A61K 38/12 (2006.01)
C07K 7/60 (2006.01)

(52) **U.S. Cl.** **514/9**; 530/317

(57) **ABSTRACT**

New analogues of kahalalide F are provided.

NEW ANTITUMORAL COMPOUNDS

FIELD OF THE INVENTION

[0001] The present invention is directed to new kahalalide antitumoral compounds, in particular to analogues of kahalalide F, pharmaceutical compositions containing them and their use as antitumoral, antiviral, antifungal agents and in the treatment of psoriasis.

BACKGROUND OF THE INVENTION

[0002] The kahalalide compounds are peptides isolated from a Hawaiian herbivorous marine species of mollusc, *Elysia rufescens* and its diet, the green alga *Bryopsis* sp. Kahalalide F is described in Hamann, M et al., J. Am. Chem. Soc., 1993, 115, 5825-5826.

[0003] Kahalalide A-G are described in Hamann, M. et al., J. Org. Chem, 1996, 61, 6594-6600: "Kahalalides: bioactive peptides from a marine mollusk *Elysia rufescens* and its algal diet *Bryopsis* sp.".

[0004] Kahalalide H and J are described in Scheuer P. J. et al., J. Nat. Prod. 1997, 60, 562-567: "Two acyclic kahalalides from the sacoglossan mollusk *Elysia rufescens*".

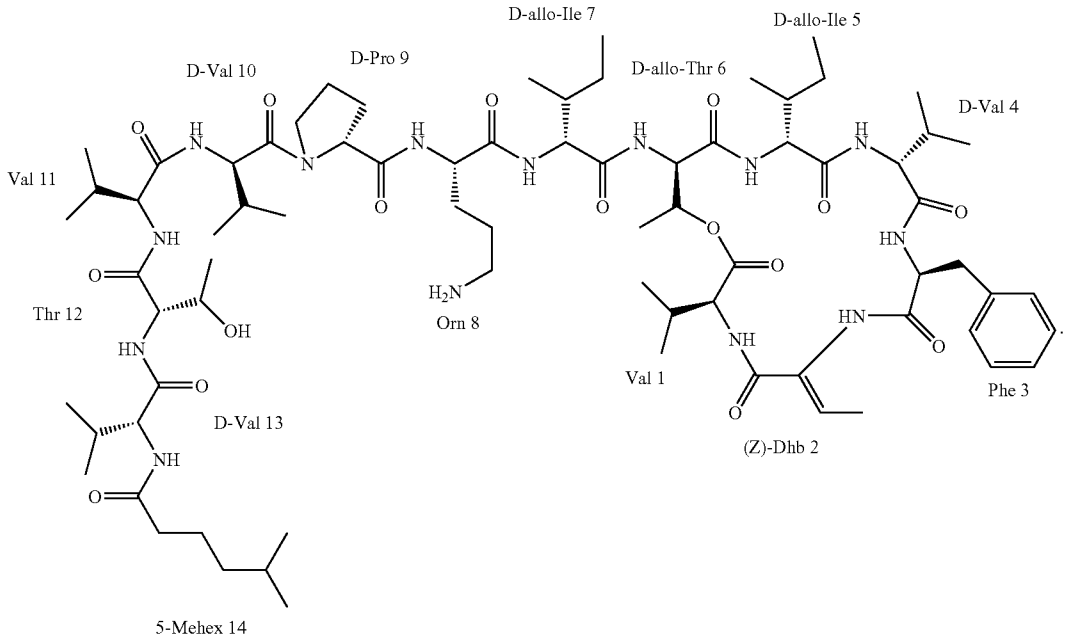
[0005] Kahalalide O is described in Scheuer P. J. et al., J. Nat. Prod. 2000, 63(1) 152-4: "A new depsipeptide from the sacoglossan mollusk *Elysia ornata* and the green alga *Bryopsis* species".

[0006] For kahalalide K, see Kan, Y. et al., J. Nat. Prod. 1999 62(8) 1169-72: "Kahalalide K: A new cyclic depsipeptide from the hawaiian green alga *Bryopsis* species".

[0007] For related reports, see also Goetz et al., Tetrahedron, 1999, 55; 7739-7746: "The absolute stereochemistry of Kahalalide F"; Albericio, F. et al. Tetrahedron Letters, 2000, 41, 9765-9769: "Kahalalide B. Synthesis of a natural cyclodepsipeptide"; Becerro et al. J. Chem. Ecol. 2001, 27(1-1), 2287-99: "Chemical-defenses of the sarcoglossan mollusk *Elysia rufescens* and its host Alga *bryopsis* sp.".

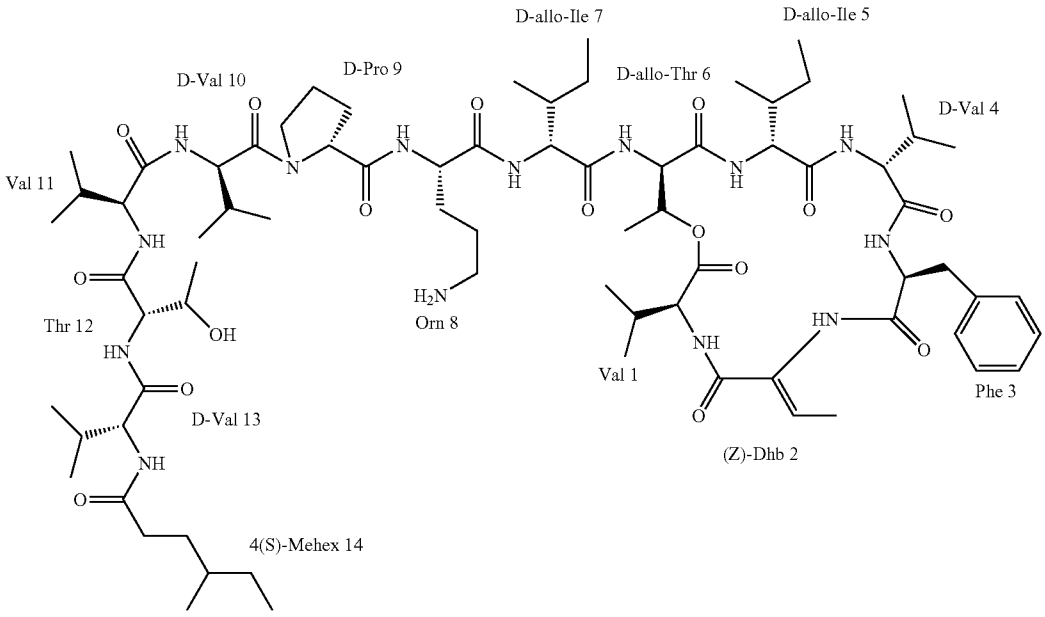
[0008] Of the kahalalide compounds, kahalalide F is the most promising because of its antitumoral activity. Its structure is complex, comprising six amino acids as a cyclic part, and an exocyclic chain of seven amino acids with a terminal fatty acid group. Originally kahalalide F was reported to have the structure (I).

(I)



[0009] In WO 04035613 there is described the 4(S)-methylhexyl compound with the following formula (II). WO 04035613 is incorporated here in full by specific reference.

(II)



[0010] The activity of kahalalide F against in vitro cell cultures of human lung carcinoma A-549 and human colon carcinoma HT-29 were reported in EP 610 078. Kahalalide F has also demonstrated to have antiviral and antifungal properties, as well as to be useful in the treatment of psoriasis.

[0011] WO 02 36145 describes pharmaceutical compositions containing kahalalide F and new uses of this compound in cancer therapy and is incorporated herein by reference in its entirety.

[0012] WO 03 33012 describes the clinical use in oncol-

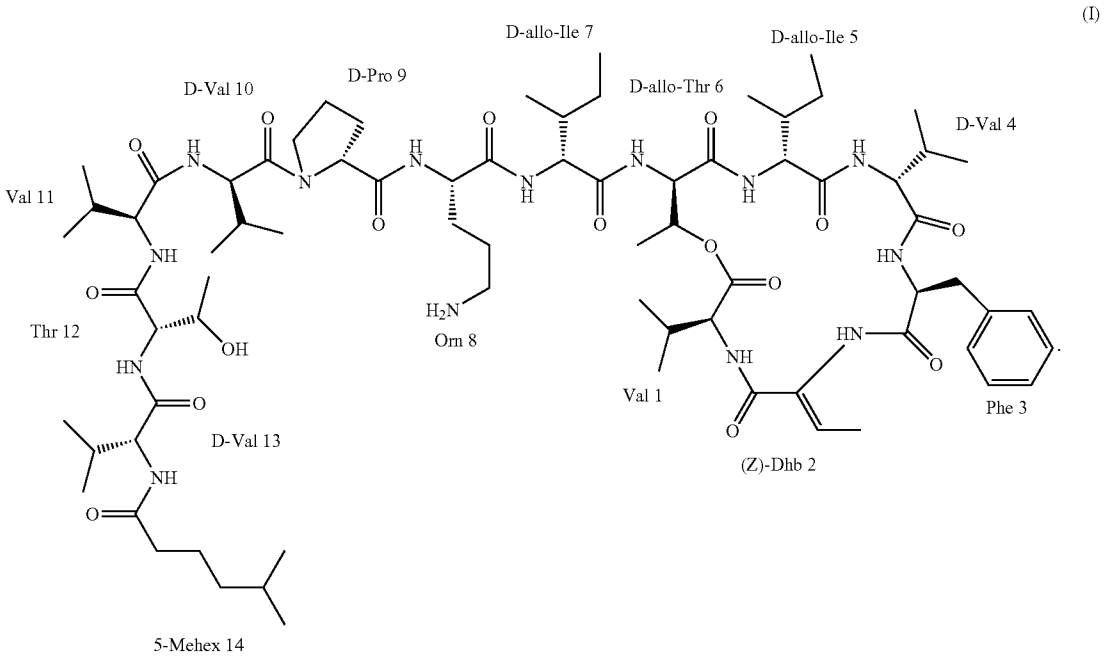
[0013] The synthesis and cytotoxic activities of natural and synthetic kahalalide compounds is described in WO 01 58934, which is incorporated herein by reference in its entirety. WO 01 58934 describes the synthesis of kahalalide F and also of compounds with a similar structure in which the terminal fatty acid chain is replaced by other fatty acids.

[0014] There is still a need to provide further antitumoral compounds, in particular further kahalalide compounds with improved properties.

SUMMARY OF THE INVENTION

[0015] We have found kahalalide analogue compounds

[0016] The present invention is directed to compounds of formula 1



wherein one or more amino acids in the cyclic or exocyclic part have been substituted by other natural or non natural amino acids, have been masked with organic groups or have been removed. The present invention is also directed to compounds of formula 1 wherein the aliphatic terminal acid group has been substituted by other acyl groups or has been removed.

[0017] The present invention is also directed to a pharmaceutical composition comprising a compound as previously defined and a pharmaceutically acceptable carrier, vehicle or diluent.

[0018] The present invention further provides a method of treating any mammal, notably a human, affected by cancer, viral infection, fungal infection or psoriasis which comprises administering to the affected individual a therapeutically effective amount of a compound as defined above.

[0019] The present invention can be employed particularly

compositions of this invention can be employed after other chemotherapy has been tried and not worked.

[0020] The present invention is particularly directed to the treatment of patients affected with prostate cancer, breast cancer, hepatocellular carcinoma, melanoma, colorectal cancer, renal cancer, ovarian cancer, NSCL cancer, epithelial cancer, pancreatic cancer and tumors that overexpress the Her2/neu oncogene.

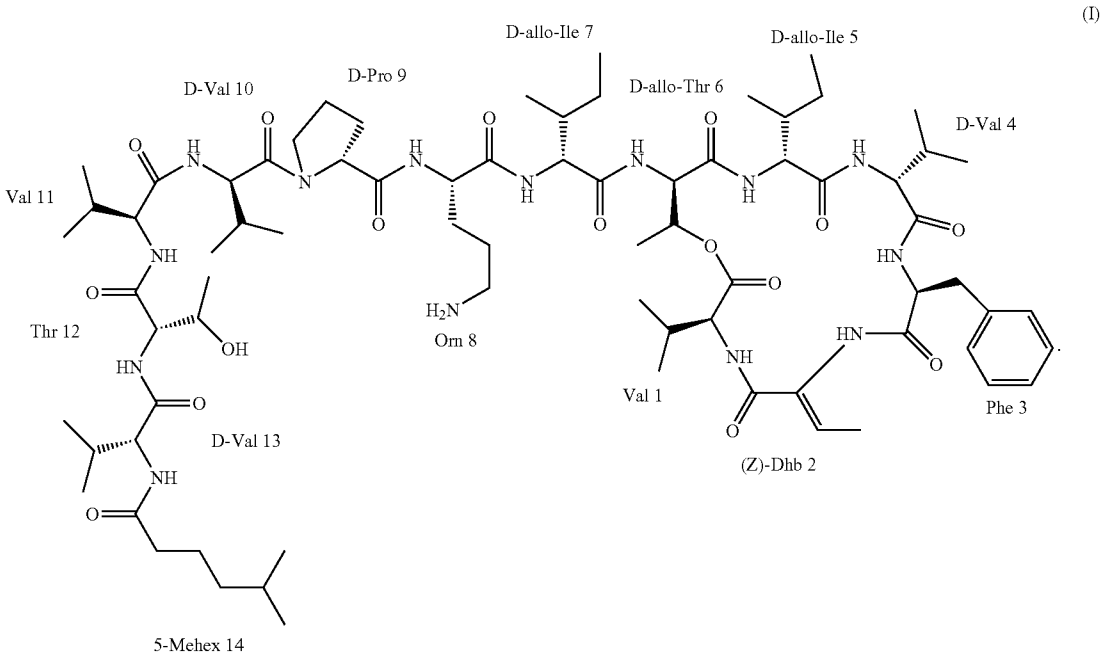
[0021] In another aspect the present invention is directed to the use of a compound as defined above in the manufacture of a medicament. In a preferred embodiment the medicament is for the treatment of cancer, psoriasis, viral infection or fungal infection.

[0022] The invention additionally provides kits comprising separate containers containing a pharmaceutical composition comprising a compound as defined above and a

DETAILED DESCRIPTION OF THE INVENTION

[0023] We have identified analogues of kahalalide F that show significant improvement in activity with respect to kahalalide F.

[0024] The present invention is directed to compounds of formula 1



wherein one or more exocyclic or cyclic amino acids have been substituted by other natural or non natural amino acids, have been masked with organic groups or have been removed. The present invention is also directed to compounds of formula 1 wherein the aliphatic methylhexanoic acyl group has been substituted by other acyl groups or has been removed.

Exocyclic Amino Acids

[0025] Preferred compounds of the invention include those of formula 1 wherein one or more amino acids of the exocyclic chain have been substituted by other natural or non natural amino acids, have been masked with organic groups or have been removed.

[0026] In particular, preferred compounds include those with 1, 2 or 3 replacement amino acids in the exocyclic chain; and those with 1, 2, 3, 4, 5 or 6 removed amino acids in the exocyclic chain.

[0027] Especially preferred are those compounds of formula 1 wherein one exocyclic amino acid has been substituted by another natural or non natural amino acid, and/or has been masked with one or more substituent organic

[0028] Thus, in one aspect of the present invention, there are provided compounds of formula 1 wherein there is not L-Orn at position 8.

[0029] The L-Orn can be replaced by D-Orn, or by another natural or non-natural amino acid. For example, the L-Orn can be replaced by a natural amino acid, such as lysine; or a masked natural amino acid, such as arginine or lysine with one or more alkyl, phenyl or oligomethylene substituents,for example $N(Me)_2$,$N'(Me)_2$-Arg, N(Me,Ph),$N'(Me)_2$-Arg, $N(CH_2)_4$,$N'(Me)_2$-Arg, $N(CH_2)_4$,$N'(CH_2)_4$-Arg, $N^{\varepsilon}(Me)_3$-Lys.

[0030] The L-Orn can be masked. For example, the amino group of the L-Orn may have substituents, notably alkyl substituents that may be further substituted, notably with heterocyclic groups, for example $N^{\delta}(CHN(CH_2)_4$, $N'(CH_2)_4$)-Orn; or more complex substituents as in biotinyl-ornithine or Orn(N^{δ}Tfa).

Cyclic Amino Acids

[0031] Other preferred compounds of the invention include those of formula 1 wherein one or more amino acids of the cyclic chain have been substituted by other natural or non natural amino acids, have been masked with organic groups or have been removed.

[0032] In particular, preferred compounds include those with 1, 2 or 3 replacement amino acids in the cyclic chain.

[0033] Especially preferred are those compounds of formula 1 wherein one or more amino acids have been substituted by other natural or non natural amino acids, and/or

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