Title (en)

MULTIMERIC MOLECULES, METHOD FOR PREPARING SAME AND USE THEREOF IN THE PREPARATION OF DRUGS

Title (de)

MULTIMERE MOLEKÜLE, VERFAHREN ZU IHRER HERSTELLUNG UND IHRE VERWENDUNG BEI DER HERSTELLUNG VON ARZNEIMITTELN

Title (fr)

MOLÉCULES MULTIMÉRIQUES, LEUR PROCÉDÉ DE PRÉPARATION, ET LEUR UTILISATION POUR LA PRÉPARATION DE MÉDICAMENTS

Publication

EP 2114998 A1 20091111 (FR)

Application

EP 08761833 A 20080204

Priority

- FR 2008000129 W 20080204
- FR 0700809 A 20070205

Abstract (en)

[origin: FR2912147A1] Multimeric compounds with 2, 3 or 4 macrocycles attached to a spacer group and with substituent groups on the macrocycles enabling attachment to a receptor of the TNF super-family are new. Multimeric compounds of formula (I) are new. k, j : 0 or 1; Y' : a macrocycle with 9-36 atoms, functionalised with 3 amino groups (for the attachment of R cvia its terminal carboxylic acid group) and a chain enabling coupling with the spacer Z via a bond X; R ca unit for attachment to a receptor of the THN super-family, preferably corresponding to a sequence derived from a ligand selected from residues forming the interface with the receptor of the ligand (this sequence being able to interact with the receptor), preferably a TNF receptor ligand, especially EDA, CD40L, FasL, OX40L, AITRL, CD30L, VEGI, LIGHT, 4-IBBL, CD27L, LTalpha , TNF, LTbeta , TWEAK, APRIL, BLYS, RANKL or TRAIL; X : a linking group of formula CO-NH (1x), NH-CO (2x), a-CO-NH-CH 2-CO-b (3x), S (4x), NH-CO-NH (8x), S-S (9x), C=N-O (10x), O-N=C (11x), with (a) and (b) as the links to Y'and Z respectively; Z : a bi-, tri- or tetra-functional spacer; if j : k= 0 and X= (1x), (8x), (9x), (5x), (6x), (7x), (13x) or (15x), Z= -CH 2CH 2O-(CH 2CH 2O) m-CH 2CH 2-(Z1) or -(CH 2) m- (Z2); if j : k= 0 and X= (2x), (3x) or (4x), Z= a group of formula NH-CH 2-CH 2-O(CH 2-CH 2-O) m-CH 2-CH 2-NH (Z3), NH-(CH 2) n-NH (Z4), (NH(CH 2) u-CO) n-NH-CH 2-(CH 2) p-NH-(CO-(CH 2) u-NH) (Z5), (Pro) n-NH-(CH 2) p-CH 2-NH-(Pro) n(Z6), (NH(CH 2) u-CO) n-NH-CH 2-CH 2-O(CH 2-CH 2-O) p-CH 2-CH 2-NH-(CO-(CH 2) u-NH) (Z7) or (Pro) n-NH-CH 2-CH 2-O(CH 2-CH 2-O) p-CH 2-CH 2-NH-(Pro) n(Z8); if j : k= 0 and X= (12x) or (14x), Z= a group of formula W'-NH-CH 2-CH 2-O(CH 2-CH 2-O) p-CH 2-CH 2-NH-W'(Z9), W'-NH-(CH 2) p-NH-W'(Z10), W'-(Pro) n-NH-(CH 2) p-NH-(Pro) n-W'(Z11), W'-(NH-(CH 2) uCO) n-NH-CH 2-(CH 2)-NH-(CO-(CH 2) p-NH)-W'(Z12), W'-(NH-(CH 2) uCO) n-CH 2-CH 2-O-(CH 2-CH 2) p-CH 2-CH 2-NH-(CO-(CH 2) p-NH)-W'(Z13) or W'-(Pro) n-NH-CH 2-CH 2-O-(CH 2-CH 2-O) p-CH 2-CH 2-NH-(Pro) n-W'(Z14) with W'= -CH 2NHCO(CH 2) 2CO- (W1) or -CO- (W2); if j : k= 0 and X= 1x, 2x, 8x, 9x, 5x, 6x, 7x, 10x, 11x, 13x or 15x, Z= Z9-Z14 with W'= -(CH 2) rCO- (W3); if j or k : 1 and X= 12x or 14x, Z= a group of Z15-Z19 with W'= W1 or W2; if j or k : 1 and X= 1x, 2x, 8x, 9x, 5x, 6x, 7x, 10x, 11x, 13x or 15x, Z= Z18 or Z19 with W'= W3; Z may also : a group of formula Z20-Z24; m : 1-40; n : 1-10; p : 1-6; u, r : 1-4; if X : 1x, 8x, 9x, 5x, 6x, 7x, 13x or 15x, R (in Z20-Z24)= (CH 2-CH 2-O) m-CH 2-CH 2-COR1 (with m= 3-6), (CH 2) n-COR2 (with n= 1-10) or CH 2-CH 2-O-(CH 2-CH 2-O)-CH 2-CH 2-NH-CO-CH 2-CH 2-COR3 (with m= 1-40); if X : 2x, 3x or 4x, R= NH-CH 2-CH 2-O(CH 2-CH 2-O) m-CH 2-CH 2-NH-CO-CH 2-CH 2-COR4 (with m= 1-40), NH-(CH 2-CH 2-O) m-CH 2-CH 2-COR5 (with m= 3-6), (Pro) nR6, NH-(CH 2) n-COR7 or (NH-(CH 2) u-CO) nR8; if X : 12x or 14x, R= R4-R9 with W as above; if X : 1x, 2x, 8x, 9x, 5x, 6x, 7x, 10x, 11x, 13x or 15x, R= NH-CH 2-CH 2-O-(CH 2-CH 2-O) m-CH 2-CH 2-NH-CO-CH 2-CH 2-CO or W'-NH-(CH 2-CH 2-O) m-CH 2-CH 2-CO with W'= W3. Independent claims are also included for (1) pharmaceutical compositions or vaccine compositions containing (I) as active ingredient together with an acceptable adjuvant (2) a method for the preparation of (I) on a solid support, involving (a) the formation of a linear precursor for (Y) comprising a growing peptide chain by means of successive coupling cycles between N-protected amino-acid residues (3 of which carry an amino group) and the amino group on the growing peptide chain, followed by deprotection, so that the first amino-acid residue is attached to a solid support and the precursor contains at least one D-alanine residue substituted with a D-lysine residue in which the epsilon -NH has been acylated with a carboxylic acid carrying the required function corresponding to group X, (b) cyclisation to form a protected cyclic structure, (c) reaction with a spacer derived from Z to give a dimerised structure, (d) cleavage of protective groups, (e) coupling of the free amino groups with a peptide (already formed or formed in situ by the sequential assembly of amino-acid residues corresponding to groups R cas in (I)), and (f) cleavage of the molecule from the support after removing all protective groups on the functionalised side chains of R c. [Image] [Image] [Image] [Image] [Image] [Image].

IPC 8 full level

C07K 14/705 (2006.01); **A61K 38/17** (2006.01); **A61K 39/00** (2006.01)

CPC (source: EP US)

A61P 29/00 (2017.12 - EP); **A61P 31/00** (2017.12 - EP); **A61P 33/00** (2017.12 - EP); **A61P 35/00** (2017.12 - EP); **A61P 37/00** (2017.12 - EP); **A61P 37/02** (2017.12 - EP); **C07K 14/70575** (2013.01 - EP US); Y02P 20/55 (2015.11 - EP US)

Citation (search report)

See references of WO 2008110695A1

Designated contracting state (EPC)

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MT NL NO PL PT RO SE SI SK TR

DOCDB simple family (publication)

FR 2912147 A1 20080808; **FR 2912147 B1 20121221**; CA 2676083 A1 20080918; EP 2114998 A1 20091111; JP 2010517984 A 20100527; US 2010136034 A1 20100603; WO 2008110695 A1 20080918; WO 2008110695 A8 20090716

DOCDB simple family (application)

FR 0700809 A 20070205; CA 2676083 A 20080204; EP 08761833 A 20080204; FR 2008000129 W 20080204; JP 2009547729 A 20080204; US 52576108 A 20080204