US 20130122024A1

(19) **United States**

(12) **Patent Application Publication**

LERCHEN et al.

(10) **Pub. No.: US 2013/0122024 A1**

(43) **Pub. Date: May 16, 2013**

(54) **NEW BINDER-DRUG CONJUGATES (ADCS) AND USE THEREOF**

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(21) Appl. No.: **13/451,916**

(22) Filed: **Apr. 20, 2012**

(30) **Foreign Application Priority Data**

Apr. 21, 2011	(EP)	11163467.1
Apr. 21, 2011	(EP)	11163470.5
Apr. 21, 2011	(EP)	11163472.1
Apr. 21, 2011	(EP)	11163474.7
Jun. 1, 2011	(EP)	11168556.6
Jun. 1, 2011	(EP)	11168557.4
Jun. 1, 2011	(EP)	11168558.2
Jun. 1, 2011	(EP)	11168559.0
Dec. 14, 2011	(EP)	11193609.2
Dec. 14, 2011	(EP)	11193618.3
Dec. 14, 2011	(EP)	11193621.7
Dec. 14, 2011	(EP)	11193623.3

Publication Classification

(51) **Int. Cl.**

C07K 16/18	(2006.01)
A61K 39/395	(2006.01)
A61K 45/06	(2006.01)
C07K 7/06	(2006.01)

(52) **U.S. Cl.**

CPC . ***C07K 16/18*** (2013.01); ***C07K 7/06*** (2013.01); ***A61K 39/3955*** (2013.01); ***A61K 45/06*** (2013.01)

USPC ... **424/179.1**; 530/391.9; 530/330; 530/389.1

(57) **ABSTRACT**

The present application relates to new binder-drug conjugates (ADCs) of N,N-dialkylauristatins that are directed against the target mesothelin, to active metabolites of these ADCs, to processes for preparing these ADCs, to the use of these ADCs for treating and/or preventing illnesses, and also to the use of these ADCs for producing medicaments for treating and/or preventing illnesses, more particularly hyperproliferative and/or angiogenic diseases such as, for example, cancer diseases. Such treatments may be practised as a monotherapy or else in combination with other medicaments or further therapeutic measures.

NEW BINDER-DRUG CONJUGATES (ADCS) AND USE THEREOF

[0001] The file named SEQUENCE-LISTING.txt submitted herewith that is 327 kilobytes and was created on Apr. 20, 2012 is hereby incorporated by reference herein in its entirety.

[0002] The present application relates to new binder-drug conjugates (ADCs) of N,N-dialkylauristatins that are directed against the target mesothelin, to active metabolites of these ADCs, to processes for preparing these ADCs, to the use of these ADCs for treating and/or preventing illnesses, and also to the use of these ADCs for producing medicaments for treating and/or preventing illnesses, more particularly hyperproliferative and/or angiogenic diseases such as, for example, cancer diseases. Such treatments may be practised as a monotherapy or else in combination with other medicaments or further therapeutic measures.

[0003] Cancer diseases are the consequence of uncontrolled cell growth in a wide variety of tissues. In many cases the new cells penetrate existing tissue (invasive growth), or they metastase into remote organs. Cancer diseases occur in a wide variety of organs, and the illnesses often progress in a tissue-specific manner. The designation "cancer disease" as a generic term therefore describes a large group of defined diseases of different organs, tissues and cell types.

[0004] Early-stage tumours may be able to be removed by surgical and radiotherapeutic measures. Metastasized tumours can generally only be given palliative therapy by means of chemotherapeutic agents. The objective in that case is to achieve the optimum combination of improving quality of life and prolonging remaining lifetime.

[0005] The majority of the chemotherapeutic agents which are presently administered parenterally are often not target-directed at the tumour tissue or the tumour cells, but instead, as a result of their systemic administration, are distributed non-specifically within the body, hence including at locations at which exposure to the drug is undesirable, such as in healthy cells, tissues and organs, for example. This may lead to unwanted side-effects and even to serious effects of general toxicity, which then often greatly limit the therapeutically useful dose range of the drug, or necessitate complete cessation of medication.

[0006] The improved and selective availability of these chemotherapeutic agents in the tumour cell or the immediately surrounding tissue, and the associated boost in effect, on the one hand, and minimization of toxic side-effects, on the other hand, have therefore been a focal point for a number of years in the development of new chemotherapeutic agents. Many attempts have been made to date to develop efficient methods of introducing the drug into the target cell. Optimizing the association between drug and intracellular target and minimizing the intercellular distribution of drug, to adjacent cells, for example, nevertheless continue to constitute a difficult problem.

[0007] Monoclonal antibodies, for example, are suitable for the target-directed addressing of tumour tissue and tumour cells. The significance of such antibodies for the clinical treatment of cancer diseases has seen a considerable general increase in recent years, based on the activity of such agents as trastuzumab (Herceptin), rituximab (Rituxan), cetuximab (Erbitux) and bevacizumab (Avastin), which have since been approved for the therapy of individual, specific tumour diseases [see e.g. G. P. Adams and L. M. Weiner, *Nat. Biotechnol.* 23, 1147-1157 (2005)]. Consequently there has also been a marked increase in interest in so-called immunoconjugates such as, for example, the aforementioned ADCs, in which an internalizing antibody directed against a tumour-associated antigen is joined covalently via a linking unit ("linker") to a cytotoxic agent. Following introduction of the ADC into the tumour cell and subsequent cleavage of the conjugate, either the cytotoxic agent itself or another metabolite with cytotoxic activity, formed from the cytotoxic agent, is released within the tumour cell, where it is able to develop its effect directly and selectively. In this way it would be possible to keep the damage to normal tissue within significantly closer limits in comparison to a conventional chemotherapy of the cancer disease [see e.g. J. M. Lambert, *Curr. Opin. Pharmacol.* 5, 543-549 (2005); A. M. Wu and P. D. Senter, *Nat. Biotechnol.* 23, 1137-1146 (2005); P. D. Senter, *Curr. Opin. Chem. Biol.* 13, 235-244 (2009); L. Ducry and B. Stump, *Bioconjugate Chem.* 21, 5-13 (2010)].

[0008] Instead of antibodies, it is also possible for binders from the small-molecule drug sphere to be used as binders which bind selectively to a specific target location ("target"), such as to a receptor, for example [see e.g. E. Ruoslahti et al., *Science* 279, 377-380 (1998); D. Karkan et al., PLoS ONE 3 (6), e2469 (Jun. 25, 2008)]. Also known are conjugates of cytotoxic drug and addressing ligand that exhibit a defined cleavage point between ligand and drug for the release of the drug. A "predetermined break point" of this kind may exist, for example, within a peptide chain which can be cleaved selectively at a particular site by a specific enzyme at the location of action [see e.g. R. A. Firestone and L. A. Telan, US Patent Application US 2002/0147138].

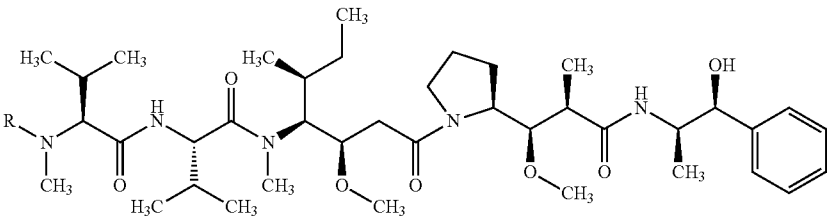
[0009] The activity of monoclonal antibodies is demonstrated in various types of cancer. Thus HERCEPTIN® and Erbitux® are used successfully in the treatment of HER2-positive breast cancer and EGFR-positive colorectal cancer, respectively.

[0010] The coupling of cytotoxic compounds to antibodies forms an extended possibility for additionally improving cancer therapy, since these conjugates allow tumour-specific toxophore accumulation and at the same time reduce the systemic toxicity. With respect to activity and tolerance, clinical studies with brentuximab vedotin in Hodgkin's lymphoma and with trastuzumab-DM1 in breast cancer have yielded highly promising results, which support the development of new antibodies and new ADCs against other tumour antigens.

[0011] The mesothelin precursor polypeptide is a glycophosphatidylinositol (GPI) anchored glycosylated cell surface protein which is cleaved proteolytically into a 30 kDa N-terminal secreted polypeptide (megakaryocyte potentiating factor, MPF) and a 40 kDa C-terminal polypeptide which is present on the cell membrane predominantly with GPI anchoring (mesothelin) (Chang, K. and I. Pastan, Proc. Natl. Acad. Sci. USA, (1996) 93(1):136).

[0012] On account of this surface expression and of the overexpression in a number of types of tumour, more particularly in ovarian carcinoma, in carcinoma of the pancreas and in mesotheliomes, and also on account of the highly limited expression in normal tissue, mesothelin represents a suitable antigen for monoclonal antibody therapy (Argani, P. et al., Clin. Cancer Res. (2001) 7(12): 3862; Hassan, R., et al., Clin. Cancer Res. (2004) 10(12 Pt 1):3937). The precise function of mesothelin is unknown to date; mesothelin gene-deficient mice do not exhibit any instantaneous anatomical, haematological or reproduction-restricting peculiarities (Bera, T. K. and I. Pastan, Mol. Cell. Biol. (2000) 20(8):2902). Mesothelin, however, is a highly variable protein, which is subject to posttranslational modifications such as proteolytic digestion and glycosylations (Hassan, R., et al., Clin. Cancer Res. (2004) 10(12 Pt 1): 3937). Therapeutic antibodies ought therefore to recognize an invariant epitope independently of the individual mesothelin modifications. Antibodies can be selected according to their desired properties, such as invariant affinity or internalization, for example, with the use of monoclonal antibodies guaranteeing that these properties on the one hand apply in respect of all antibodies and on the other hand can also be produced with long-term consistency.

[0013] Auristatin E (AE) and monomethylauristatin E (MMAE) are synthetic analogues of the dola-statins, a specific group of linear pseudopeptides which were originally isolated from marine sources and which have in some cases very potent cytotoxic activity with respect to tumour cells [for a review see e.g. G. R. Pettit, *Prog. Chem. org. Nat. Prod.* 70, 1-79 (1997); G. R. Pettit et al., *Anti-Cancer Drug Design* 10, 529-544 (1995); G. R. Pettit et al., *Anti-Cancer Drug Design* 13, 243-277 (1998)].



Auristatin (AE): R = CH_3
Monomethylauristatin E (MMAE): R = H

[0014] MMAE, however, possesses the disadvantage of a comparatively high systemic toxicity. For improving tumour selectivity, MMAE is used more particularly in conjunction with enzymatically cleavable valine-citrulline linkers in the ADC setting for more targeted tumour therapy [WO 2005/081711-A2; S. O. Doronina et al., *Bioconjugate Chem.* 17, 114-124 (2006)]. Following proteolytic cleavage, MMAE is released preferably intracellularly from corresponding ADCs.

[0015] When employed in the form of binder-drug conjugates (ADCs), however, MMAE is not compatible with linking units (linkers) between binder and drug that do not have an enzymatically cleavable predetermined break point [S. O. Doronina et al., *Bioconjugate Chem.* 17, 114-124 (2006)].

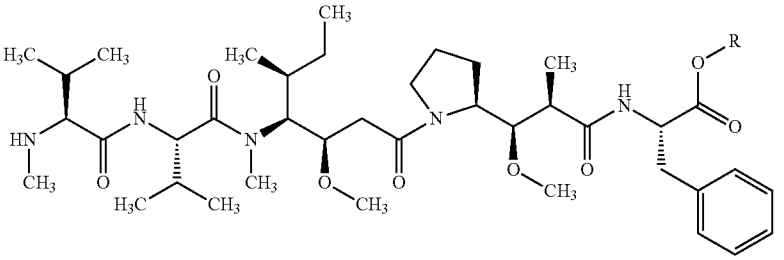
[0016] Monomethylauristatin F (MMAF) is an auristatin derivative having a C-terminal phenylalanine unit which exhibits only moderate antiproliferative activity in comparison to MMAE. This fact is very probably attributable to the free carboxyl group, whose polarity and charge adversely affect the capacity of this compound to access cells. In this connection, the methyl ester of MMAF (MMAF-OMe) has been described, as a neutral-charged prodrug derivative with cell access capability, which, in comparison to MMAF, has an in vitro cytotoxicity for various carcinoma cell lines that is increased by a number of orders of magnitude [S. O. Doronina et al., *Bioconjugate Chem.* 17, 114-124 (2006)]. It can be assumed that this effect is brought about by MMAF itself, which, following uptake of the prodrug into the cells, is rapidly released by intracellular ester hydrolysis.

[0017] However, drug compounds based on simple ester derivatives are generally subject to the risk of chemical instability on account of non-specific ester hydrolysis, independent of the intended site of action, by means, for example, of esterases that are present in the blood plasma; this non-specific hydrolysis may significantly restrict the usefulness of such compounds in therapy.

[0018] Monomethylauristatin F (MMAF) and also various ester derivatives and amide derivatives thereof have been disclosed in WO 2005/081711-A2. Further auristatin analogues with a C-terminal, amidically substituted phenylalanine unit are described in WO 01/18032-A2. WO 02/088172-A2 and WO 2007/008603-A1 claim MMAF analogues which relate to side-chain modifications of the phenylalanine, while WO 2007/008848-A2 claims those in which the carboxyl group of the phenylalanine has been modified. Auristatin conjugates linked via the C-terminus have been recently described in WO 2009/117531-A1 [see also S. O. Doronina et al., *Bioconjugate Chem.* 19, 1960-1963 (2008)].

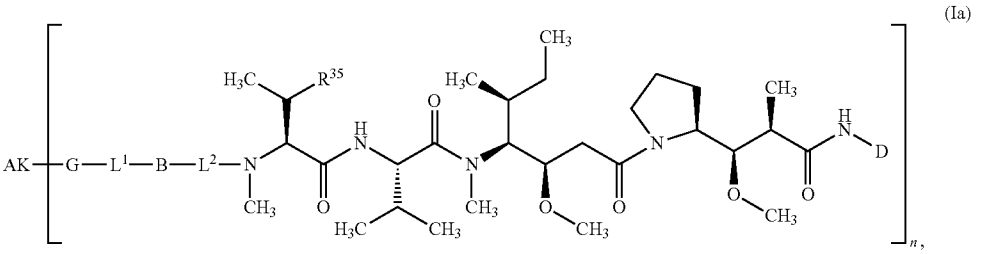
[0019] Furthermore, auristatin derivatives such as MMAE and MMAF are also substrates for transporter proteins which are expressed by many tumour cells, and this may lead to the development of resistance to these drugs.

[0020] The problem addressed with the present invention was that of providing new binder-drug conjugates (ADCs) which, through combination of new N,N-dialkylauristatin derivatives with innovative, suitable linkers and binder, exhibit a very attractive activity profile, such as, for example, in terms of their specific tumour effect and/or the reduced potential of the metabolites formed intracellularly to be a substrate with respect to transporter proteins, and which are therefore suitable for the treatment and/or prophylaxis of hyperproliferative and/or angiogenic diseases, such as cancer diseases, for example.



Monomethylauristatin F (MMAF): R = H
Monomethylauristatin F methyl ester (MMAF—OMe): R = CH_3

[0021] The present invention provides binder-drug conjugates of the general formula (Ia)



(Ia)

in which

[0022] n is a number from 1 to 50,

[0023] AK is a binder,

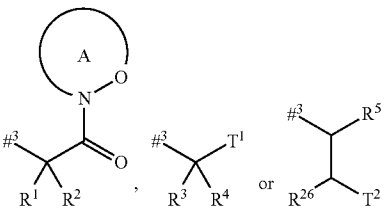
[0024] the group §-G-L^1-B-L^2-§§ is a linker,

[0025] where

[0026] § marks the linkage site with the group AK and

[0027] §§ marks the linkage site with the nitrogen atom,

[0028] D is a group of the formula



[0029] where

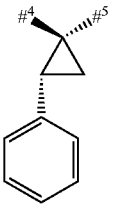
[0030] #3 marks the linkage site with the nitrogen atom,

[0031] R^1 is hydrogen or methyl,

[0032] R^2 is isopropyl, isobutyl, sec-butyl, tert-butyl, phenyl, benzyl, 1-hydroxyethyl, 4-hydroxybenzyl, 4-hydroxy-3-nitrobenzyl, 4-hydroxy-3-aminobenzyl, 1-phenylethyl, diphenylmethyl, 1H-imidazol-4-ylmethyl or 1H-indol-3-ylmethyl,

[0033] or

[0034] R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula

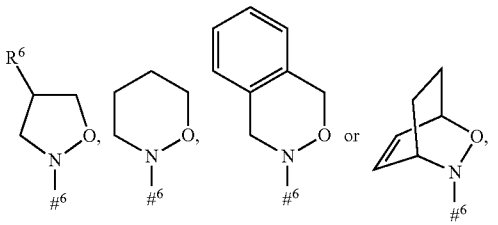


[0035] in which

[0036] #4 marks the linkage site with the adjacent nitrogen atom,

[0037] #5 marks the linkage site with the carbonyl group,

[0038] the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



[0039] in which

[0040] #6 marks the linkage site with the carbonyl group,

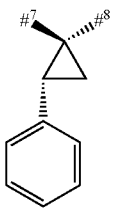
[0041] R^6 is hydrogen, hydroxy or benzyloxy,

[0042] R^3 is hydrogen or methyl,

[0043] R^4 is isopropyl, isobutyl, sec-butyl, tert-butyl, phenyl, benzyl, 1-hydroxyethyl, 4-hydroxybenzyl, 4-hydroxy-3-nitrobenzyl, 4-hydroxy-3-aminobenzyl, 1-phenylethyl, diphenylmethyl, 1H-imidazol-4-ylmethyl or 1H-indol-3-ylmethyl,

[0044] or

[0045] R^3 and R^4 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula



[0046] in which

[0047] #7 marks the linkage site with the adjacent nitrogen atom,

[0048] #8 marks the linkage site with the group T^1,

[0049] T^1 is a group of the formula —C(═O)—OR^7, —C(═O)—NR^8R^9, —C(═O)—NH—NH—R^{10} or —CH_2—O—R^{11},

[0050] in which

[0051] R^7 is hydrogen, methyl, ethyl, n-propyl, tert-butyl, benzyl or adamantylmethyl,

[0052] R^8 is hydrogen or methyl,

[0053] R^9 is hydrogen, methyl, ethyl, n-propyl or benzyl,

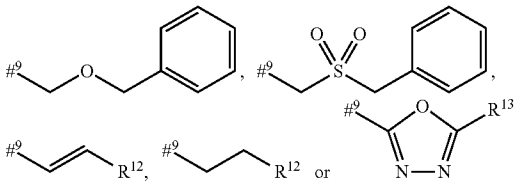
[0054] or

[0055] R^8 and R^9 together with the nitrogen atom to which they are bonded form a 4- to 7-membered heterocycle,

[0056] R^{10} is benzoyl,

[0057] R^{11} is benzyl, which may be substituted in the phenyl group by methoxycarbonyl or carboxyl,

[0058] R^5 is hydrogen, methyl or a group of the formula



[0059] in which

[0060] #9 marks the linkage site with —CHC(R^{26})-T^2,

[0061] R^{12} is phenyl which may be substituted by methoxycarbonyl, carboxyl or a group of the formula —S(O)$_2$OH,

[0062] R^{13} is phenyl which may be substituted by methoxycarbonyl or carboxyl,

[0063] R^{26} is hydrogen or hydroxy,

[0064] T^2 is phenyl, benzyl, 1H-indol-3-yl or 1H-indol-3-ylmethyl,

[0065] R^{35} is methyl or hydroxy,

and also their salts, solvates and solvates of the salts.

[0066] Compounds of the invention are the compounds of the formula (Ia) and (I) and their salts, solvates and solvates of the salts, the compounds of the formulae identified below and encompassed by formula (Ia) and (I), and their salts, solvates and solvates of the salts, and also the compounds identified below as working examples and encompassed by formula (Ia) and (I), and their salts, solvates and solvates of the salts, to the extent that the compounds identified below and encompassed by formula (Ia) and (I) are not already salts, solvates and solvates of the salts.

[0067] Depending on their structure, the compounds of the invention may exist in different stereoisomeric forms, i.e. in the form of configurational isomers or else where appropriate as conformational isomers (enantiomers and/or diastereoisomers, including those in the case of atropisomers). The present invention therefore encompasses the enantiomers and diastereomers and their respective mixtures. The stereoisomerically homogeneous constituents can be isolated from such mixtures of enantiomers and/or diastereomers in a known way; for this purpose it is preferred to use chromatographic processes, more particularly HPLC chromatography on an achiral or chiral phase.

[0068] Where the compounds of the invention can occur in tautomeric forms, the present invention encompasses all of the tautomeric forms.

[0069] The present invention also encompasses all suitable isotopic variants of the compounds of the invention. An isotopic variant of a compound of the invention is understood here to mean a compound in which at least one atom within the compound of the invention has been exchanged for another atom of the same atomic number but with a different atomic mass from the atomic mass which occurs commonly or predominantly in nature. Examples of isotopes which can be incorporated into an inventive compound are those of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulphur, fluorine, chlorine, bromine and iodine such as ^{2}H (deuterium), ^{3}H (tritium), ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{32}P, ^{33}P, ^{33}S, ^{34}S, ^{36}S, ^{18}F, ^{36}Cl, ^{82}Br, ^{123}I, ^{124}I, ^{129}I and ^{131}I. Particular isotope variants of a compound of the invention, such as more particularly those in which one or more radioactive isotopes are incorporated, may be of benefit, for example, for investigating the mechanism of action or the distribution of drug in the body; owing to the comparative ease of preparation and detectability, compounds labelled with ^{3}H or ^{14}C isotopes are especially suitable for these purposes. Furthermore, the incorporation of isotopes, such as of deuterium, for example, may lead to certain therapeutic advantages as a consequence of greater metabolic stability of the compound, such as an extension to the half-life in the body or a reduction in the active dose required, for example; such modifications of the compounds of the invention may therefore, where appropriate, also constitute a preferred embodiment of the present invention. Isotopic variants of the compounds of the invention can be prepared by the processes known to the skilled person, as for example in accordance with the methods described later on below and the procedures reproduced in the working examples, by using corresponding isotopic modifications of the respective reagents and/or starting compounds.

[0070] Preferred salts in the context of the present invention are physiologically acceptable salts of the compounds of the invention. Also encompassed are salts which although themselves not suitable for pharmaceutical applications may nevertheless be used, for example, for isolating or purifying the compounds of the invention.

[0071] Physiologically acceptable salts of the compounds of the invention encompass acid addition salts of mineral acids, carboxylic acids and sulphonic acids, examples being salts of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanesulphonic acid, benzenesulphonic acid, toluenesulphonic acid, naphthalenedisulphonic acid, acetic acid, trifluoroacetic acid, propionic acid, lactic acid, tartaric acid, malic acid, citric acid, fumaric acid, maleic acid and benzoic acid.

[0072] Physiologically acceptable salts of the compounds of the invention also encompass salts of customary bases, such as, by way of example and preferably, alkali metal salts (e.g. sodium and potassium salts), alkaline earth metal salts (e.g. calcium and magnesium salts) and ammonium salts, derived from ammonia or organic amines having 1 to 16 C atoms, such as, by way of example and preferably, ethylamine, diethylamine, triethylamine, ethyldiisopropylamine, monoethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, dimethylaminoethanol, procaine, dibenzylamine, N-methylpiperidine, N-methylmorpholine, arginine, lysine and 1,2-ethylenediamine.

[0073] Solvates in the context of the invention are those forms of the compounds of the invention that form a complex in the solid or liquid state through coordination with solvent molecules. Hydrates are one specific form of solvates, in which the coordination takes place with water. Preferred solvates in the context of the present invention are hydrates.

[0074] Furthermore, the present invention also encompasses prodrugs of the compounds of the invention. The term "prodrugs" here identifies compounds which may themselves be biologically active or inactive but are converted during

their residence in the body into compounds of the invention (by metabolism or hydrolysis, for example).

[0075] In the context of the present invention the definitions of the substituents, unless otherwise specified, are as follows:

$(C_1$-$C_4)$-Alkyl in the context of the invention is a linear or branched alkyl radical having 1 to 4 carbon atoms. By way of example and with preference, the following may be mentioned: methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, 1-methylpropyl and tert-butyl.

$(C_1$-$C_4)$-Alkylcarbonyl in the context of the invention is a linear or branched alkyl radical having 1 to 4 carbon atoms which is linked via a carbonyl group. By way of example and with preference, the following may be mentioned: methylcarbonyl, ethylcarbonyl, n-propylcarbonyl, isopropylcarbonyl, n-butylcarbonyl, isobutylcarbonyl, 1-methylpropylcarbonyl and tert-butylcarbonyl.

Alkanediyl in the context of the invention is a linear, α,ω-divalent alkyl radical having the particular number of carbon atoms indicated. By way of example and of preference, the following may be mentioned: methylene, ethane-1,2-diyl (1,2-ethylene), propane-1,3-diyl (1,3-propylene), butane-1,4-diyl (1,4-butylene), pentane-1,5-diyl (1,5-pentylene), hexane-1,6-diyl (1,6-hexylene), heptane-1,7-diyl (1,7-hexylene), octane-1,8-diyl (1,8-octylene), nonane-1,9-diyl (1,9-nonylene), decane-1,10-diyl(1,10-decylene).

$(C_3$-$C_7)$-Cycloalkyl and 3- to 7-membered carbocycle respectively in the context of the invention is a monocyclic, saturated cycloalkyl group having 3 to 7 carbon atoms. By way of example and of preference, the following may be mentioned: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

[0076] The side group of an α-amino acid in the definition of R^{19} encompasses not only the side groups of the naturally occurring α-amino acids but also the side groups of homologues and isomers of these α-amino acids. The α-amino acid here may be in the L or D configuration or else may be present as a mixture of the L and D forms. Examples that may be given of side groups are as follows: methyl (alanine), propan-2-yl (valine), propan-1-yl (norvaline), 2-methylpropan-1-yl (leucine), 1-methylpropan-1-yl (isoleucine), butan-1-yl (norleucine), tert-butyl (2-tert-butylglycine), phenyl (2-phenylglycine), benzyl (phenylalanine), p-hydroxy-benzyl (tyrosine), indol-3-ylmethyl (tryptophan), imidazol-4-ylmethyl (histidine), hydroxymethyl (serine), 2-hydroxyethyl (homoserine), 1-hydroxyethyl (threonine), mercaptomethyl (cysteine), methylthiomethyl (S-methylcysteine), 2-mercaptoethyl (homocysteine), 2-methylthio ethyl (methionine), carbamoylmethyl (asparagine), 2-carbamoylethyl (glutamine), carboxymethyl (aspartic acid), 2-carboxyethyl (glutamic acid), 4-aminobutan-1-yl (lysine), 4-amino-3-hydroxybutan-1-yl (hydroxylysine), 3-aminopropan-1-yl (ornithine), 2-aminoethyl (2,4-diaminobutyric acid), aminomethyl (2,3-diaminopropionic acid), 3-guanidinopropan-1-yl (arginine), 3-ureidopropan-1-yl (citrulline). Preferred α-amino acid side groups in the definition of R^{19} are methyl (alanine), propan-2-yl (valine), 2-methylpropan-1-yl (leucine), benzyl (phenylalanine), imidazol-4-ylmethyl (histidine), hydroxymethyl (serine), 1-hydroxyethyl (threonine), 4-aminobutan-1-yl (lysine), 3-aminopropan-1-yl (ornithine), 2-aminoethyl (2,4-diaminobutyric acid), aminomethyl (2,3-diaminopropionic acid), 3-guanidinopropan-1-yl (arginine). The L configuration is preferred in each case.

[0077] A 4- to 7-membered heterocycle in the context of the invention is a monocyclic, saturated heterocycle having a total of 4 to 7 ring atoms, which contains one or two ring heteroatoms from the series N, O, S, SO and/or SO_2 and is linked via a ring carbon atom or optionally a ring nitrogen atom. Preference is given to a 5- to 7-membered heterocycle having one or two ring heteroatoms from the series N, O and/or S, more preferably a 5- or 6-membered heterocycle having one or two ring heteroatoms from the series N and/or O. By way of example, the following may be mentioned: azetidinyl, oxetanyl, pyrrolidinyl, pyrazolidinyl, tetrahydrofuranyl, thiolanyl, piperidinyl, piperazinyl, tetrahydropyranyl, tetrahydrothiopyranyl, morpholinyl, thiomorpholinyl, hexahydroazepinyl and hexahydro-1,4-diazepinyl. Preference is given to pyrrolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, tetrahydropyranyl and morpholinyl.

[0078] In the formula of the group which may be represented by A, B, B^1, D, G, L^1, L^2, L^4, L^6, R^1, R^2, R^3, R^4 and R^5, respectively, the end point of the line at which the symbol $\#^6$, *, **, $\#^3$, $\#^1$, $\#^2$, $\#\#^1$, $\#\#^2$, $\#\#^3$, $\#\#^4$, $\#\#^5$, $\#\#^6$, $\#\#^7$, $\#\#^8$, ***, ****, $\#^4$, $\#^5$, $\#^6$, $\#^7$, $\#^8$ or $\#^9$ is located is not a carbon atom or a CH_2 group, but instead is part of the bond to the atom designated in each case, to which the A, B, B^1, D, G, L^1, L^2, L^4, L^6, R^1, R^2, R^3, R^4 or R^5 is bonded.

[0079] In the context of the present invention, all radicals which occur multiply have their definition independently of one another. If radicals in the compounds of the invention are substituted, the radicals, unless otherwise specified, may be substituted one or more times. Substitution by one or by two identical or different substituent(s) is preferred. Particularly preferred is substitution by one substituent.

[0080] In the context of the present invention the terms used, unless otherwise specified, have the following definitions:

[0081] The term "linker" is understood in the broadest sense as a chemical unit which comprises a covalent bond or a series of atoms that links a binder covalently to a drug. The term "linker" is understood preferably as a series of atoms in the sense of the present invention that links a binder covalently to a drug. Furthermore, linkers may be represented, for example, by divalent chemical units, such as alkyldiyls, aryldiyls, heteroaryldiyls, heterocyclyldiyls, dicarbonyl acid esters, dicarbonyl acid amides.

[0082] The term "binder" is understood in the broadest sense as a molecule which binds to a target molecule which is present on a particular target cell population to be addressed with the binder-drug conjugate. The term "binder" should be understood in its broadest interpretation and encompasses, for example, lectins, proteins which are able to bind particular sugar chains, or phospholipid-binding proteins. Such binders comprise, for example, high molecular mass proteins (binding proteins), polypeptides or peptides (binding peptides), non-peptidic (e.g. aptamers (U.S. Pat. No. 5,270,163) review article by Keefe A D., et al., Nat. Rev. Drug Discov. 2010; 9:537-550), or vitamins) and all other cell-binding molecules or substances. Binding proteins are, for example, antibodies and antibody fragments or antibody mimetics such as, for example, affibodies, adnectins, anticalins, DARPins, avimers, nanobodies (review articles by Gebauer M. et al., Curr. Opinion in Chem. Biol. 2009; 13:245-255; Nuttall S. D. et al., Curr. Opinion in Pharmacology 2008; 8:608-617). Binding peptides are, for example, ligands of a ligand-receptor pair, such as VEGF in the ligand-receptor pair VEGF/KDR, such as transferrin of the ligand-receptor pair transfer-

rin/transferrin receptor, or cytokines/cytokine receptor, such as TNFalpha in the ligand receptor pair TNFalpha/TNFalpha receptor.

[0083] Preferred binders in accordance with the invention are (more particularly human, monoclonal) antibodies or antigen-binding antibody fragments which bind to mesothelin. In the case of anti-mesothelin antibodies, n, in other words the number of toxophore molecules per antibody molecule, is preferably in the range from 1 to 10, more preferably 2 to 8.

[0084] A "target molecule" is understood in the broadest sense to be a molecule which is present in the target cell population, and may be a protein (e.g. a receptor of a growth factor) or a non-peptidic molecule (e.g. a sugar or phospholipid). Preferably it is a receptor or an antigen.

[0085] The term "extracellular" target molecule describes a target molecule which is attached to the cell and which is located on the outside of a cell or the part of a target molecule which is located on the outside of a cell, i.e. a binder may bind to an intact cell at its extracellular target molecule. An extracellular target molecule may be anchored in the cell membrane or may be part of the cell membrane. The skilled person knows of methods for identifying extracellular target molecules. For proteins this may be done via determination of the transmembrane domain(s) and the orientation of the protein in the membrane. This data is generally recorded in protein databases (e.g. SwissProt).

[0086] The term "cancer target molecule" describes a target molecule which is multiply present on one or more cancer cell types in comparison to non-cancer cells of the same tissue type. The cancer target molecule is preferably present selectively on one or more cancer cell types in comparison to non-cancer cells of the same tissue type, with "selectively" describing an at least twofold accumulation on cancer cells in comparison to non-cancer cells of the same tissue type (a "selective cancer target molecule"). The use of cancer target molecules allows selective therapy of cancer cells with the conjugates of the invention.

[0087] The binder may be linked via a bond to the linker. Known from the literature are various possibilities of covalent coupling (conjugation) of organic molecules to antibody. The linking of the binder may take place by means of a heteroatom of the binder. Inventive heteroatoms of the binder that may be used for linking are sulphur (in one embodiment via a sulphhydryl group of the binder), oxygen (in accordance with the invention by means of a carboxyl or hydroxy group of the binder) and nitrogen (in one embodiment via a primary or secondary amine group or amide group of the binder). Preferred in accordance with the invention is the conjugation of the toxophores to the antibody via one or more sulphur atoms of cysteine residues of the antibody and/or via one or more NH groups of lysine residues of the antibody. These heteroatoms may be present in the natural binder or may be introduced by means of methods of chemistry or molecular biology. In accordance with the invention, the linking of the binder to the toxophore has little influence over the binding activity of the binder to the target molecule. In a preferred embodiment the linking has no influence on the binding activity of the binder to the target molecule.

[0088] The term "antibody" is understood in accordance with the present invention in its broadest sense and encompasses immunoglobulin molecules, examples being intact or modified monoclonal antibodies, polyclonal antibodies or multispecific antibodies (e.g. bispecific antibodies). An immunoglobulin molecule preferably comprises a molecule having four polypeptide chains, two heavy chains (H chains) and two light chains (L chains), which are linked typically by disulphide bridges. Each heavy chain comprises a variable domain of the heavy chain (abbreviated to VH) and a constant domain of the heavy chain. The constant domain of the heavy chain may encompass, for example, three domains CH1, CH2 and CH3. Each light chain comprises a variable domain (abbreviated to VL) and a constant domain. The constant domain of the light chain comprises one domain (abbreviated to CL). The VH and VL domains may be further subdivided into regions having hypervariability, also called complementarity-determining regions (abbreviated to CDR), and regions having a low sequence variability ("framework region", abbreviated to FR). Each VH and VL region is typically composed of three CDRs and up to four FRs. For example, in the following order from the amino terminus to the carboxy terminus: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. An antibody may be obtained from any species suitable for the antibody, such as, for example, rabbit, lama, camel, mouse or rat. In one embodiment the antibody is of human or murine origin. An antibody may for example be human, humanized or chimeric.

[0089] The term "monoclonal" antibody identifies antibodies which have been obtained from a population of substantially homogeneous antibodies, i.e. individual antibodies of the population are identical except for naturally occurring mutations which may occur in small numbers. Monoclonal antibodies recognize a single antigenic binding site with a high specificity. The term "monoclonal antibody" does not refer to a particular production method.

[0090] The term "intact" antibody refers to antibodies which comprise not only an antigen-binding domain but also the constant domain of the light and heavy chain. The constant domain may be a naturally occurring domain, or a variant thereof in which a plurality of amino acid positions have been altered.

[0091] The term "modified intact" antibody refers to intact antibodies which have been fused with another polypeptide or protein, not originating from an antibody, via the amino terminus or carboxyl terminus thereof, by means of a covalent bond (e.g. a peptide linkage). Furthermore, antibodies may be modified by introducing reactive cysteines at defined locations, in order to facilitate coupling to a toxophore (see Junutula et al. Nat. Biotechnol. 2008 August; 26(8):925-32).

[0092] The term "human" antibody identifies antibodies which can be obtained from a human being or are synthetic human antibodies. A "synthetic" human antibody is an antibody which in parts or as a whole is obtainable from synthetic sequences in silico which are based on the analysis of human antibody sequences. A human antibody may be encoded, for example, by a nucleic acid which has been isolated from a library of antibody sequences which are of human origin. One example of such antibodies can be found in Soderlind et al., Nature Biotech. 2000, 18:853-856.

[0093] The term "humanized" or "chimeric" antibody describes antibodies which consist of a non-human and of a human sequence component. In these antibodies, part of the sequences of the human immunoglobulin (recipient) is replaced by sequence components of a non-human immunoglobulin (donor). In many cases the donor is a murine immunoglobulin. With humanized antibodies, amino acids of the CDR in the recipient are replaced by amino acids of the donor. In some cases, amino acids of the framework as well are

replaced by corresponding amino acids of the donor. In some cases the humanized antibody contains amino acids which were present neither in the recipient nor in the donor and which were inserted during the optimization of the antibody. In the case of chimeric antibodies, the variable domains of the donor immunoglobulin are fused with the constant regions of a human antibody.

[0094] The term complementarity-determining region (CDR) as used here refers to those amino acids in a variable antibody domain that are necessary for binding to the antigen. Every variable region typically has three CDR regions, identified as CDR1, CDR2 and CDR3. Each CDR region may comprise amino acids according to the definition of Kabat and/or amino acids of a hypervariable loop, defined according to Chotia. The definition according to Kabat encompasses, for example, the region of approximately amino acid position 24-34 (CDR1), 50-56 (CDR2) and 89-97 (CDR3) of the variable light chain and 31-35 (CDR1), 50-65 (CDR2) and 95-102 (CDR3) of the variable heavy chain (Kabat et al., Sequences of Proteins of Immulological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991)). The definition according to Chotia encompasses, for example, the region of approximately amino acid position 26-32 (CDR1), 50-52 (CDR2) and 91-96 (CDR3) of the variable light chain and 26-32 (CDR1), 53-55 (CDR2) and 96-101 (CDR3) of the variable heavy chain Chothia and Lesk; J Mol Biol 196: 901-917 (1987)). In some cases a CDR may comprise amino acids from one CDR region as defined by Kabat and Chotia.

[0095] Depending on the amino acid sequence of the constant domain of the heavy chain, antibodies may be divided into different classes. There are five main classes of intact antibodies: IgA, IgD, IgE, IgG and IgM, and a number of them may be broken down into further subclasses (isotypes), e.g. IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2. The constant domains of the heavy chain that correspond to the different classes are identified as [alpha/α], [delta/δ], [epsilon/ϵ], [gamma/γ] and [mu/μ]. Both the three-dimensional structure and the subunit structure of antibodies are known.

[0096] The term "functional fragment" or "antigen-binding antibody fragments" of a antibody/immunoglobulin is defined as a fragment of an antibody/immunoglobulin (e.g. the variable domains of an IgG) which further encompasses the antigen binding domains of the antibody/immunoglobulin. The "antigen binding domain" of an antibody typically encompasses one or more hypervariable regions of an antibody, e.g. the CDR, CDR2 and/or CDR3 region. However, the "framework" or "scaffold" region of an antibody may also play a part with regard to the binding of the antibody to the antigen. The framework region forms the scaffold for the CDRs. The antigen-binding domain preferably encompasses at least amino acids 4 to 103 of the variable light chain and amino acid 5 to 109 of the variable heavy chain, more preferably amino acid 3 to 107 of the variable light chain and 4 to 111 of the variable heavy chain, particular preference being given to the complete variable light and heavy chains, i.e. amino acid 1-109 of the VL and 1 to 113 of the VH (numbering according to WO97/08320).

[0097] "Functional fragments" or "antigen-binding antibody fragments" of the invention encompass, non-conclusively, Fab, Fab', $F(ab')_2$ and Fv fragments, diabodies, Single Domain Antibodies (DAbs), linear antibodies, individual chains of antibodies (single-chain Fv, abbreviated to ScFv); and multispecific antibodies, such as bi and tri-specific antibodies, for example, formed from antibody fragments C. A. K Borrebaeck, editor (1995) Antibody Engineering (Breakthroughs in Molecular Biology), Oxford University Press; R. Kontermann & S. Duebel, editors (2001) Antibody Engineering (Springer Laboratory Manual), Springer Verlag). Antibodies other than "multispecific" or "multifunctional" antibodies are those having identical binding sites. Multispecific antibodies may be specific for different epitopes of an antigen or may be specific for epitopes of more than one antigen (see, for example WO 93/17715; WO 92/08802; WO 91/00360; WO 92/05793; Tutt, et al., 1991, J. Immunol. 147:60 69; U.S. Pat. Nos. 4,474,893; 4,714,681; 4,925,648; 5,573,920; 5,601,819; or Kostelny et al., 1992, J. Immunol. 148: 1547 1553). An $F(ab')_2$ or Fab molecule may be constructed such that the number of intermolecular disulphide interactions occurring between the Ch1 and the CL domains can be reduced or else completely prevented.

[0098] "Functional fragments" or "antigen-binding antibody fragments" may be fused with another polypeptide or protein, not originating from an antibody, via the amino terminus or carboxyl terminus thereof, by means of a covalent bond (e.g. a peptide linkage). Furthermore, antibodies and antigen-binding fragments may be modified by introducing reactive cysteines at defined locations, in order to facilitate coupling to a toxophore (see Junutula et al. Nat. Biotechnol. 2008 August; 26(8):925-32).

[0099] Polyclonal antibodies can be prepared by methods known to a person of ordinary skill in the art. Monoclonal antibodies may be prepared by methods known to a person of ordinary skill in the art (Köhler and Milstein, Nature, 256, 495-497, 1975). Human and humanized monoclonal antibodies may be prepared by methods known to a person of ordinary skill in the art (Olsson et al., Meth Enzymol. 92, 3-16 or Cabilly et al U.S. Pat. No. 4,816,567 or Boss et al U.S. Pat. No. 4,816,397).

[0100] A person of ordinary skill in the art is aware of diverse methods for preparing human antibodies and fragments thereof, such as, for example, by means of transgenic mice (N Lonberg and D Huszar, Int Rev Immunol. 1995; 13(1):65-93) or Phage Display Technologies (Clackson et al., Nature. 1991 Aug. 15; 352(6336):624-8). Antibodies of the invention may be obtained from recombinant antibody libraries consisting for example of the amino acid sequences of a multiplicity of antibodies compiled from a large number of healthy volunteers. Antibodies may also be produced by means of known recombinant DNA technologies. The nucleic acid sequence of an antibody can be obtained by routine sequencing or is available from publically accessible databases.

[0101] An "isolated" antibody or binder has been purified to remove other constituents of the cell. Contaminating constituents of a cell which may interfere with a diagnostic or therapeutic use are, for example, enzymes, hormones, or other peptidic or non-peptidic constituents of the cell. A preferred antibody or binder is one which has been purified to an extent of more than 95%, relative to the antibody or binder (determined for example by Lowry method, UV-Vis spectroscopy or by SDS capillary gel electrophoresis). Furthermore an antibody which has been purified to such an extent that it is possible to determine at least 15 amino acids of the amino terminus or of an internal amino acid sequence, or which has been purified to homogeneity, the homogeneity being determined by SDS-PAGE under reducing or non-reducing conditions (detection may be determined by means of Coomassie

Blau staining or preferably by silver coloration). However, an antibody is normally prepared by one or more purification steps.

[0102] The term "specific binding" or "binds specifically" refers to an antibody or binder which binds to a predetermined antigen/target molecule. Specific binding of an antibody or binder typically describes an antibody or binder having an affinity of at least 10^{-7} M (as Kd value; i.e. preferably those with smaller Kd values than 10^{-7} M), with the antibody or binder having an at least two times higher affinity for the predetermined antigen/target molecule than for a non-specific antigen/target molecule (e.g. bovine serum albumin, or casein) which is not the predetermined antigen/target molecule or a closely related antigen/target molecule.

[0103] Antibodies which are specific against a cancer cell antigen can be prepared by a person of ordinary skill in the art by means of methods with which he or she is familiar (such as recombinant expression, for example) or may be acquired commercially (as for example from Merck KGaA, Germany). Examples of known commercially available antibodies in cancer therapy are Erbitux® (cetuximab, Merck KGaA), Avastin® (bevacizumab, Roche) and Herceptin® (trastuzumab, Genentech). Trastuzumab is a recombinant humanized monoclonal antibody of the IgG1kappa type which in a cell-based assay (Kd=5 nM) binds the extracellular domains of the human epidermal growth receptor with high affinity. The antibody is produced recombinantly in CHO cells.

[0104] The compounds of the formula (I) represent a subgroup of the compounds of the formula (Ia).

[0105] A preferred subject of the invention are binder-drug conjugates of the general formula (Ia) in which

[0106] n is a number from 1 to 50,

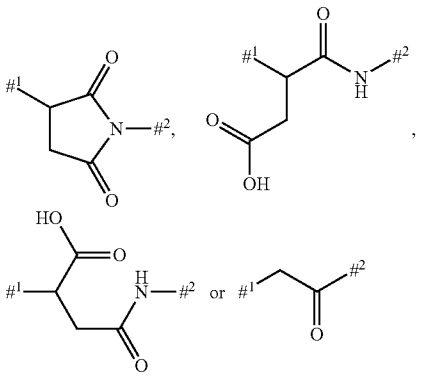
[0107] AK is AK_1 or AK_2

[0108] where

[0109] AK_1 is a binder (preferably an anti-mesothelin antibody) which is bonded via a sulphur atom of the binder to the group G,

[0110] AK_2 is a binder (preferably an anti-mesothelin antibody) which is bonded via a nitrogen atom of the binder to the group G,

[0111] G when $AK=AK_1$, is a group of the formula



[0112] where

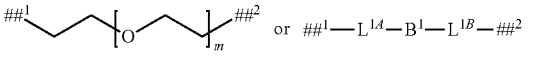
[0113] $\#^1$ marks the linkage site with the sulphur atom of the binder,

[0114] $\#^2$ marks the linkage site with the group L^1,

[0115] or

[0116] when $AK=AK_2$, is carbonyl,

[0117] L^1 is a bond, linear (C_1-C_{10})-alkanediyl, a group of the formula



[0118] where

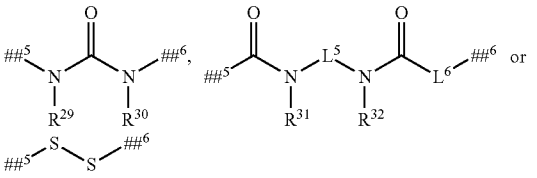
[0119] m is a number from 2 to 6,

[0120] $\#^1$ marks the linkage site with the group G,

[0121] $\#^2$ marks the linkage site with the group B,

[0122] L^{1A} is linear (C_2-C_{10})-alkanediyl,

[0123] B^1 is a group of the formula



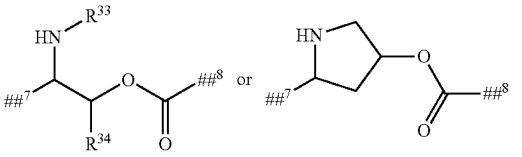
[0124] in which

[0125] $\#^5$ marks the linkage site with the group L^{1A},

[0126] $\#^6$ marks the linkage site with the group L^{1B},

[0127] L^5 is a bond or (C_2-C_4)-alkanediyl,

[0128] L^6 is a bond or a group of the formula



[0129] in which

[0130] $\#^7$ marks the linkage site with the carbonyl group,

[0131] $\#^8$ marks the linkage site with L^{1B},

[0132] R^{33} is hydrogen, (C_1-C_4)-alkylcarbonyl, tert-butyloxycarbonyl or benzyloxycarbonyl,

[0133] R^{34} is hydrogen or methyl,

[0134] R^{29} is hydrogen or (C_1-C_4)-alkyl,

[0135] R^{30} is hydrogen or (C_1-C_4)-alkyl,

[0136] or

[0137] R^{29} and R^{30} together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

[0138] R^{31} is hydrogen or (C_1-C_4)-alkyl,

[0139] R^{32} is hydrogen or (C_1-C_4)-alkyl,

[0140] or

[0141] R^{31} and R^{32} together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

[0142] L^{1B} is linear (C_2-C_{10})-alkanediyl,

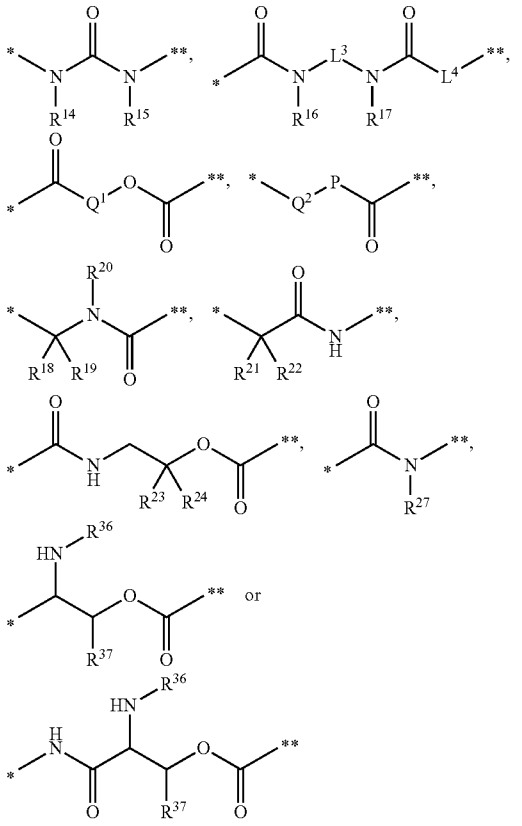
[0143] and

[0144] where (C_1-C_{10})-alkanediyl may be substituted by 1 to 4 substituents selected independently of one another from the group consisting of methyl, hydroxy and benzyl,

[0145] and

[0146] where two carbon atoms of the alkanediyl chain in 1,2, 1,3 or 1,4 relation to one another, with inclusion of any carbon atoms situated between them, may be bridged to form a (C_3-C_6)-cycloalkyl ring or a phenyl ring,

[0147] B is a bond or a group of the formula



[0148] where

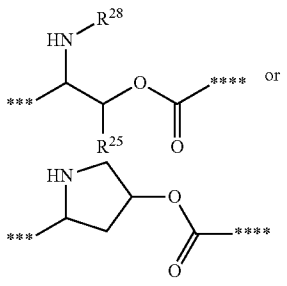
[0149] * marks the linkage site with L^1,

[0150] ** marks the linkage site with L^2,

[0151] P is O or NH,

[0152] L^3 is a bond or (C_2-C_4)-alkanediyl,

[0153] L^4 is a bond or a group of the formula



[0154] in which

[0155] *** marks the linkage site with the carbonyl group,

[0156] **** marks the linkage site with L^2,

[0157] R^{25} is hydrogen or methyl,

[0158] R^{28} is hydrogen, (C_1-C_4)-alkylcarbonyl, tert-butyloxycarbonyl or benzyloxycarbonyl,

[0159] Q^1 is a 4- to 7-membered heterocycle,

[0160] Q^2 is a 3- to 7-membered carbocycle or a 4- to 7-membered heterocycle,

[0161] R^{14} is hydrogen or (C_1-C_4)-alkyl,

[0162] R^{15} is hydrogen or (C_1-C_4)-alkyl,

[0163] or

[0164] R^{14} and R^{15} together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

[0165] R^{16} is hydrogen or (C_1-C_4)-alkyl,

[0166] R^{17} is hydrogen or (C_1-C_4)-alkyl,

[0167] or

[0168] R^{16} and R^{17} together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

[0169] R^{18} is hydrogen or (C_1-C_4)-alkyl,

[0170] R^{19} is hydrogen or the side group of a natural α-amino acid or of its homologues or isomers,

[0171] R^{20} is hydrogen or (C_1-C_4)-alkyl,

[0172] or

[0173] R^{19} and R^{20} together with the atoms to which they are bonded form a pyrrolidinyl ring,

[0174] R^{21} is hydrogen or (C_1-C_4)-alkyl,

[0175] R^{22} is hydrogen or (C_1-C_4)-alkyl,

[0176] or

[0177] R^{21} and R^{22} together with the atoms to which they are bonded form a 3- to 7-membered carbocycle,

[0178] R^{23} is (C_1-C_4)-alkyl,

[0179] R^{24} is hydrogen or (C_1-C_4)-alkyl,

[0180] R^{27} is hydrogen or (C_1-C_4)-alkyl,

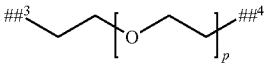
[0181] R^{36} is hydrogen, (C_1-C_4)-alkylcarbonyl, tert-butyloxycarbonyl or benzyloxycarbonyl,

[0182] R^{37} is hydrogen or methyl,

[0183] or

[0184] R^{36} and R^{37} together with the atoms to which they are bonded form a pyrrolidine ring,

[0185] L^2 is linear (C_2-C_{10})-alkanediyl or is a group of the formula



[0186] where

[0187] p is a number from 2 to 6,

[0188] ##^{3} marks the linkage site with the group B,

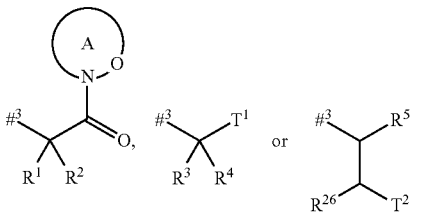
[0189] ##^{4} marks the linkage site with the nitrogen atom,

[0190] where (C_2-C_{10})-alkanediyl may be substituted by 1 to 4 substituents selected independently of one another from the group consisting of methyl, hydroxy and benzyl,

[0191] and

[0192] where two carbon atoms of the alkanediyl chain in 1,2, 1,3 or 1,4 relation to one another, with inclusion of any carbon atoms situated between them, may be bridged to form a (C_3-C_6)-cycloalkyl ring or a phenyl ring,

[0193] D is a group of the formula



[0194] in which

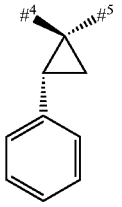
[0195] $\#^3$ marks the linkage site with the nitrogen atom,

[0196] R^1 is hydrogen or methyl,

[0197] R^2 is isopropyl, isobutyl, sec-butyl, tert-butyl, phenyl, benzyl, 1-hydroxyethyl, 4-hydroxybenzyl, 4-hydroxy-3-nitrobenzyl, 4-hydroxy-3-aminobenzyl, 1-phenylethyl, diphenylmethyl, 1H-imidazol-4-ylmethyl or 1H-indol-3-ylmethyl,

[0198] or

[0199] R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula

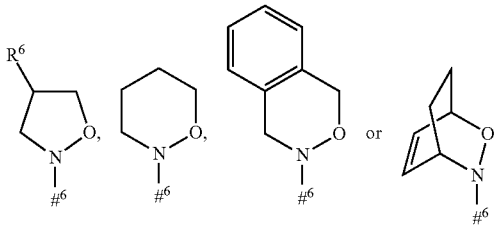


[0200] in which

[0201] $\#^4$ marks the linkage site with the adjacent nitrogen atom,

[0202] $\#^5$ marks the linkage site with the carbonyl group,

[0203] the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



[0204] in which

[0205] $\#^6$ marks the linkage site with the carbonyl group,

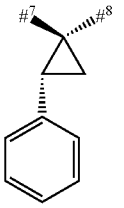
[0206] R^6 is hydrogen, hydroxy or benzyloxy,

[0207] R^3 is hydrogen or methyl,

[0208] R^4 is isopropyl, isobutyl, sec-butyl, tert-butyl, phenyl, benzyl, 1-hydroxyethyl, 4-hydroxybenzyl, 4-hydroxy-3-nitrobenzyl, 4-hydroxy-3-aminobenzyl, 1-phenylethyl, diphenylmethyl, 1H-imidazol-4-ylmethyl or 1H-indol-3-ylmethyl,

[0209] or

[0210] R^3 and R^4 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula



[0211] in which

[0212] $\#^7$ marks the linkage site with the adjacent nitrogen atom,

[0213] $\#^8$ marks the linkage site with the group T^1,

[0214] T^1 is a group of the formula —C(═O)—OR^7, —C(═O)—NR^8R^9, —C(═O)—NH—NH—R^{10} or —CH_2—O—R^{11},

[0215] in which

[0216] R^7 is hydrogen, methyl, ethyl, n-propyl, tert-butyl, benzyl or adamantylmethyl,

[0217] R^8 is hydrogen or methyl,

[0218] R^9 is hydrogen, methyl, ethyl, n-propyl or benzyl,

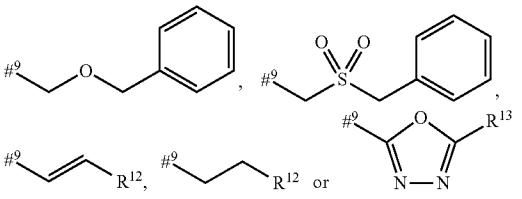
[0219] or

[0220] R^8 and R^9 together with the nitrogen atom to which they are bonded form a 4- to 7-membered heterocycle,

[0221] R^{10} is benzoyl,

[0222] R^{11} is benzyl, which may be substituted in the phenyl group by methoxycarbonyl or carboxyl,

[0223] R^5 is hydrogen, methyl or a group of the formula



[0224] in which

[0225] $\#^9$ marks the linkage site with —CHC(R^{26})-T^2,

[0226] R^{12} is phenyl which may be substituted by methoxycarbonyl, carboxyl or a group of the formula —$S(O)_2OH$,

[0227] R^{13} is phenyl which may be substituted by methoxycarbonyl or carboxyl,

[0228] R^{26} is hydrogen or hydroxy,

[0229] T^2 is phenyl, benzyl, 1H-indol-3-yl or 1H-indol-3-ylmethyl,

[0230] R^{35} is methyl or hydroxy,

and also their salts, solvates and solvates of the salts. A preferred subject of the invention are binder-drug conjugates of the general formula (Ia) in which

[0231] n is a number from 1 to 50,

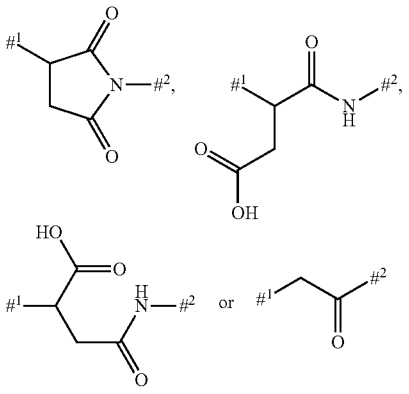
[0232] AK is AK_1 or AK_2

[0233] where

[0234] AK_1 is a binder which is bonded via a sulphur atom of the binder to the group G,

[0235] AK_2 is a binder which is bonded via a nitrogen atom of the binder to the group G,

[0236] G when $AK=AK_1$, is a group of the formula



[0237] in which

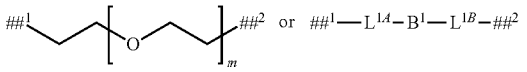
[0238] $\#^1$ marks the linkage site with the sulphur atom of the binder,

[0239] $\#^2$ marks the linkage site with the group L^1,

[0240] or

[0241] when $AK=AK_2$, is carbonyl,

[0242] L^1 is a bond, linear $(C_1\text{-}C_{10})$-alkanediyl, a group of the formula



[0243] where

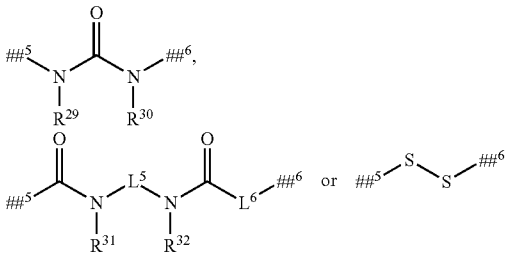
[0244] m is a number from 2 to 6,

[0245] $\#\#^1$ marks the linkage site with the group G,

[0246] $\#\#^2$ marks the linkage site with the group B,

[0247] L^{1A} is linear $(C_2\text{-}C_{10})$-alkanediyl,

[0248] B^1 is a group of the formula



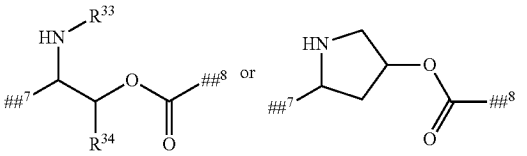
[0249] in which

[0250] $\#\#^5$ marks the linkage site with the group L^{1A},

[0251] $\#\#^6$ marks the linkage site with the group L^{1B},

[0252] L^5 is a bond or $(C_2\text{-}C_4)$-alkanediyl,

[0253] L^6 is a bond or a group of the formula



[0254] in which

[0255] $\#\#^7$ marks the linkage site with the carbonyl group,

[0256] $\#\#^8$ marks the linkage site with L^{1B},

[0257] R^{33} is hydrogen $(C_1\text{-}C_4)$-alkylcarbonyl, tert-butyloxycarbonyl or benzyloxycarbonyl,

[0258] R^{34} is hydrogen or methyl,

[0259] R^{29} is hydrogen or $(C_1\text{-}C_4)$-alkyl,

[0260] R^{30} is hydrogen or $(C_1\text{-}C_4)$-alkyl,

[0261] or

[0262] R^{29} and R^{30} together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

[0263] R^{31} is hydrogen or $(C_1\text{-}C_4)$-alkyl,

[0264] R^{32} is hydrogen or $(C_1\text{-}C_4)$-alkyl,

[0265] or

[0266] R^{31} and R^{32} together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

[0267] L^{1B} is linear $(C_2\text{-}C_{10})$-alkanediyl,

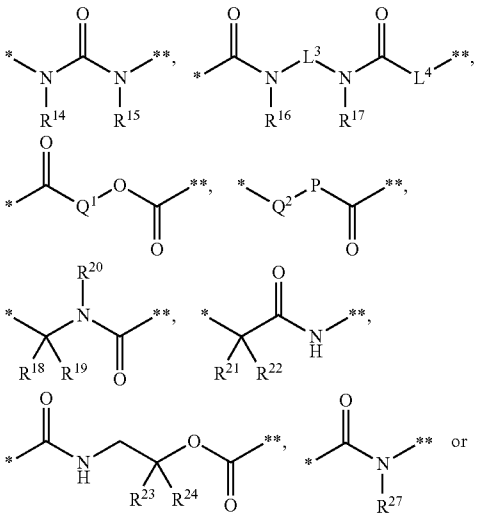
[0268] and

[0269] where $(C_1\text{-}C_{10})$-alkanediyl may be substituted by 1 to 4 substituents selected independently of one another from the group consisting of methyl, hydroxy and benzyl,

[0270] and

[0271] where two carbon atoms of the alkanediyl chain in 1,2, 1,3 or 1,4 relation to one another, with inclusion of any carbon atoms situated between them, may be bridged to form a $(C_3\text{-}C_6)$-cycloalkyl ring or a phenyl ring,

[0272] B is a bond or a group of the formula



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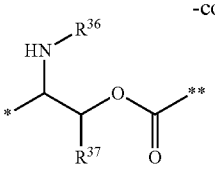


[0273] where

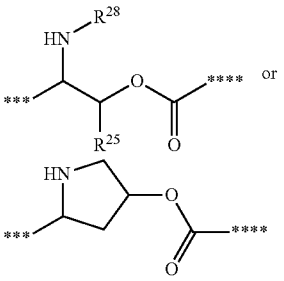
[0274] * marks the linkage site with L^1,

[0275] ** marks the linkage site with L^2,

[0276] P is O or NH,

[0277] L^3 is a bond or $(C_2$-$C_4)$-alkanediyl,

[0278] L^4 is a bond or a group of the formula



[0279] in which

[0280] *** marks the linkage site with the carbonyl group,

[0281] **** marks the linkage site with L^2,

[0282] R^{25} is hydrogen or methyl,

[0283] R^{28} is hydrogen, $(C_1$-$C_4)$-alkylcarbonyl, tert-butyloxycarbonyl or benzyloxycarbonyl,

[0284] Q^1 is a 4- to 7-membered heterocycle,

[0285] Q^2 is a 3- to 7-membered carbocycle or a 4- to 7-membered heterocycle,

[0286] R^{14} is hydrogen or $(C_1$-$C_4)$-alkyl,

[0287] R^{15} is hydrogen or $(C_1$-$C_4)$-alkyl,

[0288] or

[0289] R^{14} and R^{15} together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

[0290] R^{16} is hydrogen or $(C_1$-$C_4)$-alkyl,

[0291] R^{17} is hydrogen or $(C_1$-$C_4)$-alkyl,

[0292] or

[0293] R^{16} and R^{17} together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

[0294] R^{18} is hydrogen or $(C_1$-$C_4)$-alkyl,

[0295] R^{19} is hydrogen or the side group of a natural α-amino acid or of its homologues or isomers,

[0296] R^{20} is hydrogen or $(C_1$-$C_4)$-alkyl,

[0297] or

[0298] R^{19} and R^{20} together with the atoms to which they are bonded form a pyrrolidinyl ring,

[0299] R^{21} is hydrogen or $(C_1$-$C_4)$-alkyl,

[0300] R^{22} is hydrogen or $(C_1$-$C_4)$-alkyl,

[0301] or

[0302] R^{21} and R^{22} together with the atoms to which they are bonded form a 3- to 7-membered carbocycle,

[0303] R^{23} is $(C_1$-$C_4)$-alkyl,

[0304] R^{24} is hydrogen or $(C_1$-$C_4)$-alkyl,

[0305] R^{27} is hydrogen or $(C_1$-$C_4)$-alkyl,

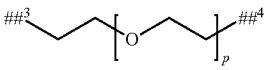
[0306] R^{36} is hydrogen, $(C_1$-$C_4)$-alkylcarbonyl, tert-butyloxycarbonyl or benzyloxycarbonyl,

[0307] R^{37} is hydrogen or methyl,

[0308] or

[0309] R^{36} and R^{37} together with the atoms to which they are bonded form a pyrrolidine ring,

[0310] L^2 is linear $(C_2$-$C_{10})$-alkanediyl or is a group of the formula



[0311] where

[0312] p is a number from 2 to 6,

[0313] ##3 marks the linkage site with the group B,

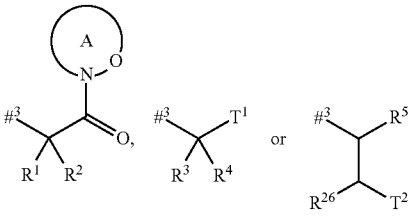
[0314] ##4 marks the linkage site with the nitrogen atom,

[0315] where $(C_2$-$C_{10})$-alkanediyl may be substituted by 1 to 4 substituents selected independently of one another from the group consisting of methyl, hydroxy and benzyl,

[0316] and

[0317] where two carbon atoms of the alkanediyl chain in 1,2, 1,3 or 1,4 relation to one another, with inclusion of any carbon atoms situated between them, may be bridged to form a $(C_3$-$C_6)$-cycloalkyl ring or a phenyl ring,

[0318] D is a group of the formula



[0319] in which

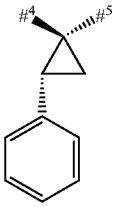
[0320] #3 marks the linkage site with the nitrogen atom,

[0321] R^1 is hydrogen or methyl,

[0322] R^2 is isopropyl, isobutyl, sec-butyl, tert-butyl, phenyl, benzyl, 1-hydroxyethyl, 4-hydroxybenzyl, 4-hydroxy-3-nitrobenzyl, 4-hydroxy-3-aminobenzyl, 1-phenylethyl, diphenylmethyl, 1H-imidazol-4-ylmethyl or 1H-indol-3-ylmethyl,

[0323] or

[0324] R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula

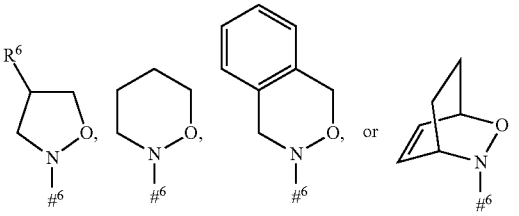


[0325] in which

[0326] #4 marks the linkage site with the adjacent nitrogen atom,

[0327] #5 marks the linkage site with the carbonyl group,

[0328] the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



[0329] in which

[0330] #6 marks the linkage site with the carbonyl group,

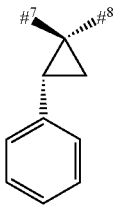
[0331] R^6 is hydrogen, hydroxy or benzyloxy,

[0332] R^3 is hydrogen or methyl,

[0333] R^4 is isopropyl, isobutyl, sec-butyl, tert-butyl, phenyl, benzyl, 1-hydroxyethyl, 4-hydroxybenzyl, 4-hydroxy-3-nitrobenzyl, 4-hydroxy-3-aminobenzyl, 1-phenylethyl, diphenylmethyl, 1H-imidazol-4-ylmethyl or 1H-indol-3-ylmethyl,

[0334] or

[0335] R^3 and R^4 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula



[0336] in which

[0337] #7 marks the linkage site with the adjacent nitrogen atom,

[0338] #8 marks the linkage site with the group T^1,

[0339] T^1 is a group of the formula —C(═O)—OR^7, —C(═O)—NR^8R^9, —C(═O)—NH—NH—R^{10} or —CH_2—O—R^{11},

[0340] in which

[0341] R^7 is hydrogen, methyl, ethyl, n-propyl, tert-butyl, benzyl or adamantylmethyl,

[0342] R^8 is hydrogen or methyl,

[0343] R^9 is hydrogen, methyl, ethyl, n-propyl or benzyl,

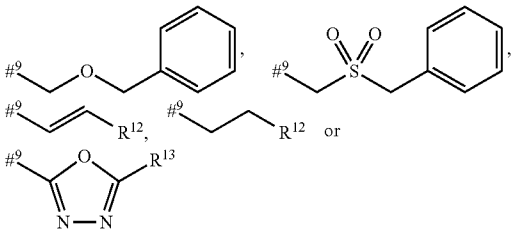
[0344] or

[0345] R^8 and R^9 together with the nitrogen atom to which they are bonded form a 4- to 7-membered heterocycle,

[0346] R^{10} is benzoyl,

[0347] R^{11} is benzyl, which may be substituted in the phenyl group by methoxycarbonyl or carboxyl,

[0348] R^5 is hydrogen, methyl or a group of the formula



[0349] in which

[0350] #9 marks the linkage site with —CHC(R^{26})-T^2,

[0351] R^{12} is phenyl which may be substituted by methoxycarbonyl, carboxyl or a group of the formula —$S(O)_2OH$,

[0352] R^{13} is phenyl which may be substituted by methoxycarbonyl or carboxyl,

[0353] R^{26} is hydrogen or hydroxy,

[0354] T^2 is phenyl, benzyl, 1H-indol-3-yl or 1H-indol-3-ylmethyl,

[0355] R^{35} is methyl or hydroxy,

and also their salts, solvates and solvates of the salts.

[0356] Preferred subject of the invention are binder-drug conjugates of the general formula (Ia) in which

[0357] n is a number from 1 to 20,

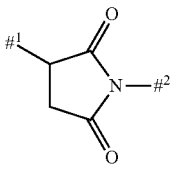
[0358] AK is AK_1 or AK_2

[0359] where

[0360] AK_1 is an antibody or an antigen-binding antibody fragment which binds to mesothelin and is bonded via the sulphur atom of a cysteine residue of the binder to the group G,

[0361] AK_2 is an antibody or an antigen-binding antibody fragment which binds to mesothelin and is bonded via the NH side group of a lysine residue of the binder to the group G,

[0362] G when AK=AK_1, is a group of the formula



[0363] in which

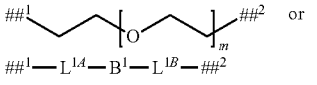
[0364] #1 marks the linkage site with the cysteine residue of the binder,

[0365] #2 marks the linkage site with the group L^1,

[0366] or

[0367] when AK=AK_2, is carbonyl,

[0368] L^1 is a bond, linear (C_2-C_6)-alkanediyl, a group of the formula



[0369] where

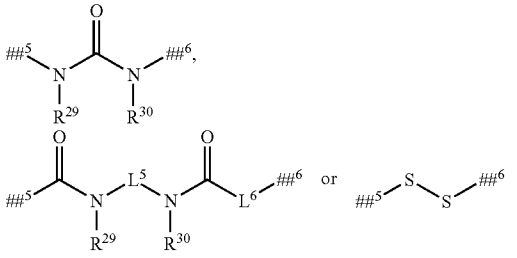
[0370] m is a number from 2 to 6,

[0371] ##1 marks the linkage site with the group G,

[0372] ##[2] marks the linkage site with the group B,

[0373] L^{1A} is linear (C_2-C_6)-alkanediyl,

[0374] B^1 is a group of the formula



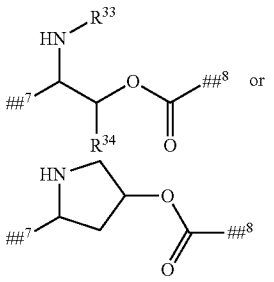
[0375] in which

[0376] ##[5] marks the linkage site with the group L^{1A},

[0377] ##[6] marks the linkage site with the group L^{1B},

[0378] L^5 is a bond,

[0379] L^6 is a bond or a group of the formula



[0380] in which

[0381] ##[7] marks the linkage site with the carbonyl group,

[0382] ##[8] marks the linkage site with L^{1B},

[0383] R^{33} is hydrogen, methylcarbonyl or tert-butyloxycarbonyl,

[0384] R^{34} is hydrogen or methyl,

[0385] R^{29} is hydrogen,

[0386] R^{30} is hydrogen,

[0387] R^{31} is hydrogen or methyl,

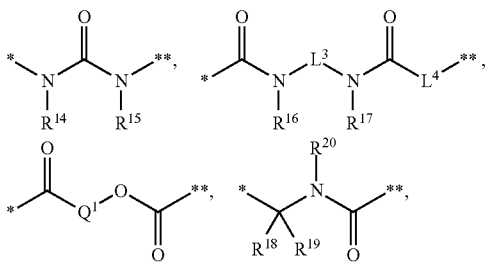
[0388] R^{32} is hydrogen or methyl,

[0389] L^{1B} is linear (C_2-C_6)-alkanediyl,

[0390] and

[0391] where (C_2-C_6)-alkanediyl may be substituted by 1 or 2 methyl substituents,

[0392] B is a bond or a group of the formula



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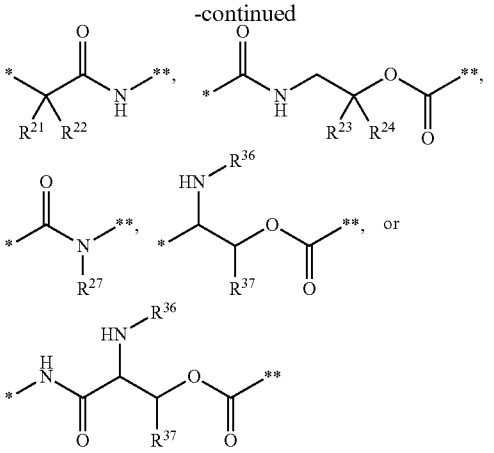


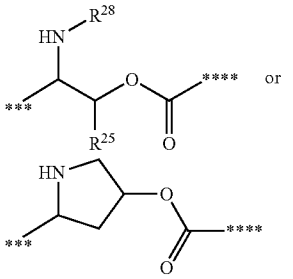
[0393] where

[0394] * marks the linkage site with L^1,

[0395] ** marks the linkage site with L^2,

[0396] L^3 is a bond or ethane-1,2-diyl,

[0397] L^4 is a bond or a group of the formula



[0398] in which

[0399] *** marks the linkage site with the carbonyl group,

[0400] **** marks the linkage site with L^2,

[0401] R^{25} is hydrogen or methyl,

[0402] R^{28} is hydrogen, methylcarbonyl or tert-butyloxycarbonyl,

[0403] Q^1 is a 4- to 7-membered heterocycle,

[0404] R^{14} is hydrogen,

[0405] R^{15} is hydrogen,

[0406] R^{16} is hydrogen or methyl,

[0407] R^{17} is hydrogen or methyl,

[0408] or

[0409] R^{16} and R^{17} together with the atoms to which they are bonded form a piperazinyl ring,

[0410] R^{18} is hydrogen,

[0411] R^{19} is hydrogen, methyl, propan-2-yl, 2-methylpropan-1-yl or 1-methylpropan-1-yl,

[0412] R^{20} is hydrogen or methyl,

[0413] or

[0414] R^{19} and R^{20} together with the atoms to which they are bonded form a pyrrolidinyl ring,

[0415] R^{21} is hydrogen or methyl,

[0416] R^{22} is hydrogen or methyl,

[0417] or

[0418] R^{21} and R^{22} together with the atoms to which they are bonded form a cyclopropyl ring,

[0419] R^{23} is methyl,

[0420] R^{24} is hydrogen or methyl,

[0421] R^{27} is hydrogen,

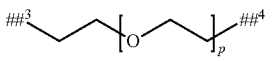
[0422] R^{36} is hydrogen, methylcarbonyl or tert-butyloxycarbonyl,

[0423] R^{37} is hydrogen or methyl,

[0424] or

[0425] R^{36} and R^{37} together with the atoms to which they are bonded form a pyrrolidine ring,

[0426] L^2 is linear (C_2-C_6)-alkanediyl or is a group of the formula



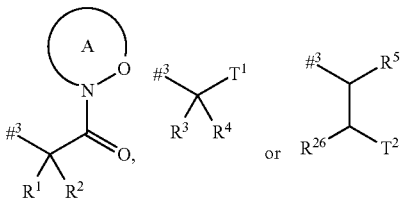
[0427] where

[0428] p is a number from 2 to 6,

[0429] $\#\#^3$ marks the linkage site with the group B,

[0430] $\#\#^4$ marks the linkage site with the nitrogen atom, where (C_2-C_{10})-alkanediyl may be substituted by 1 or 2 methyl substituents,

[0431] D is a group of the formula



[0432] where

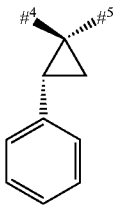
[0433] $\#^3$ marks the linkage site with the nitrogen atom,

[0434] R^1 is hydrogen,

[0435] R^2 is 1-hydroxyethyl, benzyl, 4-hydroxybenzyl, 1-phenylethyl or 1H-indol-3-ylmethyl,

[0436] or

[0437] R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula

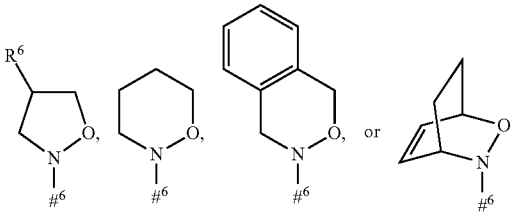


[0438] in which

[0439] $\#^4$ marks the linkage site with the adjacent nitrogen atom,

[0440] $\#^5$ marks the linkage site with the carbonyl group,

[0441] the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



[0442] in which

[0443] $\#^6$ marks the linkage site with the carbonyl group,

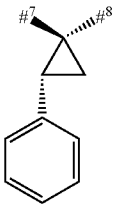
[0444] R^6 is hydrogen, hydroxy or benzyloxy,

[0445] R^3 is hydrogen,

[0446] R^4 is 1-hydroxyethyl, benzyl, 4-hydroxybenzyl, 1-phenylethyl or 1H-indol-3-ylmethyl,

[0447] or

[0448] R^3 and R^4 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula



[0449] in which

[0450] $\#^7$ marks the linkage site with the adjacent nitrogen atom,

[0451] $\#^8$ marks the linkage site with the group T^1,

[0452] T^1 is a group of the formula —C(═O)—OR^7, —C(═O)—NR^8R^9, —C(═O)—NH—NH—R^{10} or —CH_2—O—R^{11},

[0453] in which

[0454] R^7 is hydrogen, methyl, ethyl, n-propyl, tert-butyl, benzyl or adamantylmethyl,

[0455] R^8 is hydrogen or methyl,

[0456] R^9 is hydrogen, methyl, ethyl, n-propyl or benzyl,

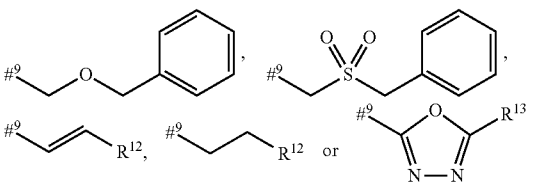
[0457] or

[0458] R^8 and R^9 together with the nitrogen atom to which they are bonded form a 4- to 7-membered heterocycle,

[0459] R^{10} is benzoyl,

[0460] R^{11} is benzyl, which may be substituted in the phenyl group by methoxycarbonyl or carboxyl,

[0461] R^5 is hydrogen, methyl or a group of the formula



[0462] in which

[0463] $\#^9$ marks the linkage site with —CHC(R^{26})-T^2,

[0464] R^{12} is phenyl which may be substituted by methoxycarbonyl, carboxyl or a group of the formula —S(O)$_2$OH,

[0465] R^{13} is phenyl which may be substituted by methoxycarbonyl or carboxyl,

[0466] R^{26} is hydrogen or hydroxy,

[0467] T^2 is phenyl, benzyl, 1H-indol-3-yl or 1H-indol-3-ylmethyl,

[0468] R^{35} is methyl or hydroxy,

and also their salts, solvates and solvates of the salts.

[0469] Preferred subject matter of the invention are binder-drug conjugates of the general formula (Ia) in which

[0470] n is a number from 1 to 20,

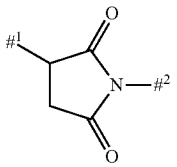
[0471] AK is AK_1 or AK_2

[0472] where

[0473] AK_1 is an antibody or an antigen-binding antibody fragment which binds to mesothelin and is bonded via the sulphur atom of a cysteine residue of the binder to the group G,

[0474] AK_2 is an antibody or an antigen-binding antibody fragment which binds to mesothelin and is bonded via the NH side group of a lysine residue of the binder to the group G,

[0475] G when AK=AK_1, is a group of the formula



[0476] in which

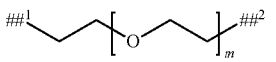
[0477] $\#^1$ marks the linkage site with the cysteine residue of the binder,

[0478] $\#^2$ marks the linkage site with the group L^1,

[0479] or

[0480] when AK=AK_2, is carbonyl,

[0481] L^1 is a bond, linear (C_2-C_6)-alkanediyl, a group of the formula



or $\#\#^1—L^{1A}—B^1—L^{1B}—\#\#^2$

[0482] where

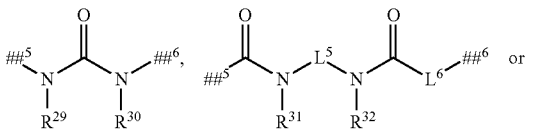
[0483] m is a number from 2 to 6,

[0484] $\#\#^1$ marks the linkage site with the group G,

[0485] $\#\#^2$ marks the linkage site with the group B,

[0486] L^{1A} is linear (C_2-C_6)-alkanediyl,

[0487] B^1 is a group of the formula



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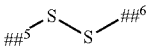


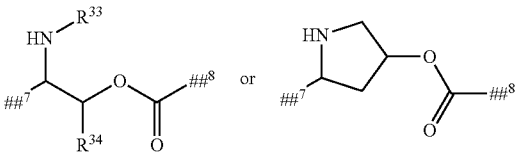
[0488] in which

[0489] $\#\#^5$ marks the linkage site with the group L^{1A},

[0490] $\#\#^6$ marks the linkage site with the group L^{1B},

[0491] L^5 is a bond,

[0492] L^6 is a bond or a group of the formula



[0493] in which

[0494] $\#\#^7$ marks the linkage site with the carbonyl group,

[0495] $\#\#^8$ marks the linkage site with L^{1B},

[0496] R^{33} is hydrogen, methylcarbonyl or tert-butyloxycarbonyl,

[0497] R^{34} is hydrogen or methyl,

[0498] R^{29} is hydrogen,

[0499] R^{30} is hydrogen,

[0500] R^{31} is hydrogen or methyl,

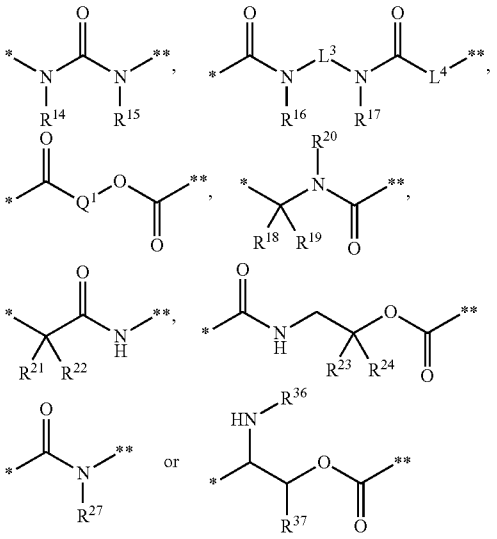
[0501] R^{32} is hydrogen or methyl,

[0502] L^{1B} is linear (C_2-C_6)-alkanediyl,

[0503] and

[0504] where (C_2-C_6)-alkanediyl may be substituted by 1 or 2 methyl substituents,

[0505] B is a bond or a group of the formula



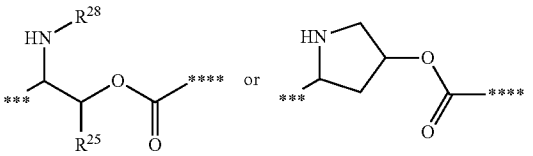
[0506] where

[0507] * marks the linkage site with L^1,

[0508] ** marks the linkage site with L^2,

[0509] L^3 is a bond or ethane-1,2-diyl,

[0510] L^4 is a bond or a group of the formula



[0511] in which

[0512] *** marks the linkage site with the carbonyl group,

[0513] **** marks the linkage site with L^2,

[0514] R^{25} is hydrogen or methyl,

[0515] R^{28} is hydrogen, methylcarbonyl or tert-butyloxycarbonyl,

[0516] Q^1 is a 4- to 7-membered heterocycle,

[0517] R^{14} is hydrogen,

[0518] R^{15} is hydrogen,

[0519] R^{16} is hydrogen or methyl,

[0520] R^{17} is hydrogen or methyl,

[0521] or

[0522] R^{16} and R^{17} together with the atoms to which they are bonded form a piperazinyl ring,

[0523] R^{18} is hydrogen,

[0524] R^{19} is hydrogen, methyl, propan-2-yl, 2-methylpropan-1-yl or 1-methylpropan-1-yl,

[0525] R^{20} is hydrogen or methyl,

[0526] or

[0527] R^{19} and R^{20} together with the atoms to which they are bonded form a pyrrolidinyl ring,

[0528] R^{21} is hydrogen or methyl,

[0529] R^{22} is hydrogen or methyl,

[0530] or

[0531] R^{21} and R^{22} together with the atoms to which they are bonded form a cyclopropyl ring,

[0532] R^{23} is methyl,

[0533] R^{24} is hydrogen or methyl,

[0534] R^{27} is hydrogen,

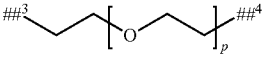
[0535] R^{36} is hydrogen, methylcarbonyl or tert-butyloxycarbonyl,

[0536] R^{37} is hydrogen or methyl,

[0537] or

[0538] R^{36} and R^{37} together with the atoms to which they are bonded form a pyrrolidine ring,

[0539] L^2 is linear (C_2-C_6)-alkanediyl or is a group of the formula



[0540] where

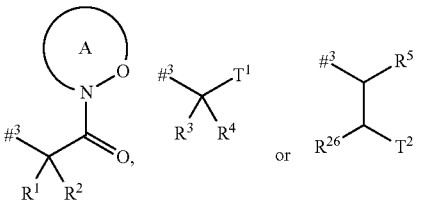
[0541] p is a number from 2 to 6,

[0542] $\#\#^3$ marks the linkage site with the group B,

[0543] $\#\#^4$ marks the linkage site with the nitrogen atom,

[0544] where (C_2-C_{10})-alkanediyl may be substituted by 1 or 2 methyl substituents,

[0545] D is a group of the formula



[0546] where

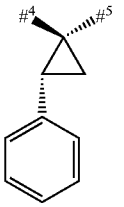
[0547] $\#^3$ marks the linkage site with the nitrogen atom,

[0548] R^1 is hydrogen,

[0549] R^2 is 1-hydroxyethyl, benzyl, 4-hydroxybenzyl, 1-phenylethyl or 1H-indol-3-yl-methyl,

[0550] or

[0551] R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula

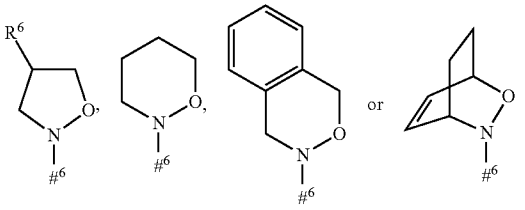


[0552] in which

[0553] $\#^4$ marks the linkage site with the adjacent nitrogen atom,

[0554] $\#^5$ marks the linkage site with the carbonyl group,

[0555] the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



[0556] in which

[0557] $\#^6$ marks the linkage site with the carbonyl group,

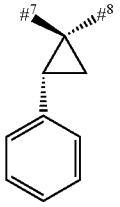
[0558] R^6 is hydrogen, hydroxy or benzyloxy,

[0559] R^3 is hydrogen,

[0560] R^4 is 1-hydroxyethyl, benzyl, 4-hydroxybenzyl, 1-phenylethyl or 1H-indol-3-yl-methyl,

[0561] or

[0562] R^3 and R^4 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula



[0563] in which

[0564] #7 marks the linkage site with the adjacent nitrogen atom,

[0565] #8 marks the linkage site with the group T^1,

[0566] T^1 is a group of the formula —C(═O)—OR^7, —C(═O)—NR^8R^9, —C(═O)—NH—NH—R^{10} or —CH_2—O—R^{11},

[0567] in which

[0568] R^7 is hydrogen, methyl, ethyl, n-propyl, tert-butyl, benzyl or adamantylmethyl,

[0569] R^8 is hydrogen or methyl,

[0570] R^9 is hydrogen, methyl, ethyl, n-propyl or benzyl,

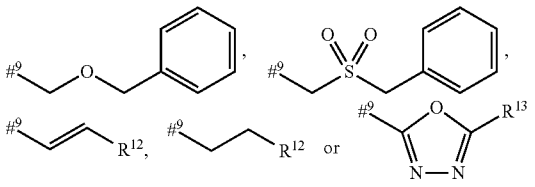
[0571] or

[0572] R^8 and R^9 together with the nitrogen atom to which they are bonded form a 4- to 7-membered heterocycle,

[0573] R^{10} is benzoyl,

[0574] R^{11} is benzyl, which may be substituted in the phenyl group by methoxycarbonyl or carboxyl,

[0575] R^5 is hydrogen, methyl or a group of the formula



[0576] in which

[0577] #9 marks the linkage site with —CHC(R^{26})-T^2,

[0578] R^{12} is phenyl which may be substituted by methoxycarbonyl, carboxyl or a group of the formula —$S(O)_2OH$,

[0579] R^{13} is phenyl which may be substituted by methoxycarbonyl or carboxyl,

[0580] R^{26} is hydrogen or hydroxy,

[0581] T^2 is phenyl, benzyl, 1H-indol-3-yl or 1H-indol-3-ylmethyl,

[0582] R^{35} is methyl or hydroxy,

and also their salts, solvates and solvates of the salts.

[0583] Preferred subject matter of the invention are binder-drug conjugates of the general formula (Ia), in which

[0584] n is a number from 1 to 10,

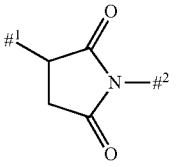
[0585] AK is AK_1 or AK_2

[0586] where

[0587] AK_1 is an antibody which comprises the six CDR sequences of the antibody MF-Ta, the variable light and variable heavy chain of the antibody MF-Ta or the light and heavy chain of the antibody MF-Ta, and is bonded via the sulphur atom of a cysteine residue of the binder to the group G,

[0588] AK_2 is an antibody which comprises the six CDR sequences of the antibody MF-Ta, the variable light and variable heavy chain of the antibody MF-Ta or the light and heavy chain of the antibody MF-Ta, and is bonded via the NH side group of a lysine residue of the binder to the group G,

[0589] G when AK=AK_1, is a group of the formula



[0590] in which

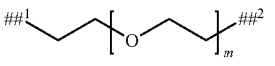
[0591] #1 marks the linkage site with the cysteine residue of the binder,

[0592] #2 marks the linkage site with the group L^1,

[0593] or

[0594] when AK=AK_2, is carbonyl,

[0595] L^1 is a bond, linear (C_2-C_6)-alkanediyl, a group of the formula



[0596] where

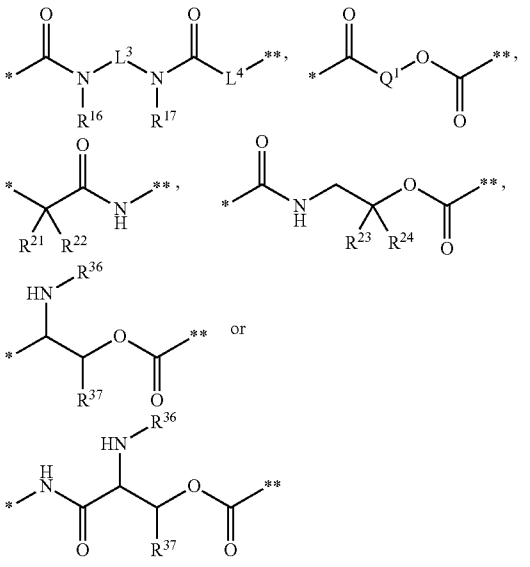
[0597] m is a number 2 or 3,

[0598] ##1 marks the linkage site with the group G,

[0599] ##2 marks the linkage site with the group B,

[0600] where (C_2-C_6)-alkanediyl may be substituted by 1 or 2 methyl substituents,

[0601] B is a bond or a group of the formula



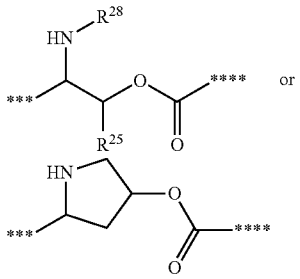
[0602] where

[0603] * marks the linkage site with L^1,

[0604] ** marks the linkage site with L^2,

[0605] L^3 is a bond or ethane-1,2-diyl,

[0606] L^4 is a bond or a group of the formula



[0607] in which

[0608] *** marks the linkage site with the carbonyl group,

[0609] **** marks the linkage site with L^2,

[0610] R^{25} is methyl,

[0611] R^{28} is hydrogen, methylcarbonyl or tert-butyloxycarbonyl,

[0612] Q^1 is piperidine-1,4-diyl,

[0613] R^{16} is hydrogen or methyl,

[0614] R^{17} is hydrogen or methyl,

[0615] or

[0616] R^{16} and R^{17} together with the atoms to which they are bonded form a piperazinyl ring,

[0617] R^{21} is hydrogen or methyl,

[0618] R^{22} is hydrogen or methyl,

[0619] or

[0620] R^{21} and R^{22} together with the atoms to which they are bonded form a cyclopropyl ring,

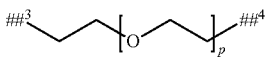
[0621] R^{23} is methyl,

[0622] R^{24} is hydrogen,

[0623] R^{36} is hydrogen, methylcarbonyl or tert-butyloxycarbonyl,

[0624] R^{37} is hydrogen or methyl,

[0625] L^2 is linear (C_2-C_6)-alkanediyl or is a group of the formula



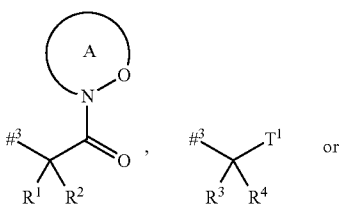
[0626] where

[0627] p is a number from 2 to 6,

[0628] $\#\#^3$ marks the linkage site with the group B,

[0629] $\#\#^4$ marks the linkage site with the nitrogen atom,

[0630] D is a group of the formula



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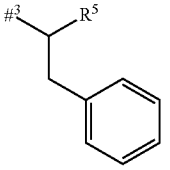


[0631] where

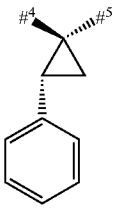
[0632] $\#^3$ marks the linkage site with the nitrogen atom,

[0633] R^1 is hydrogen,

[0634] R^2 is 1-hydroxyethyl, benzyl, 4-hydroxybenzyl, 1-phenylethyl or 1H-indol-3-yl-methyl,

[0635] or

[0636] R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula

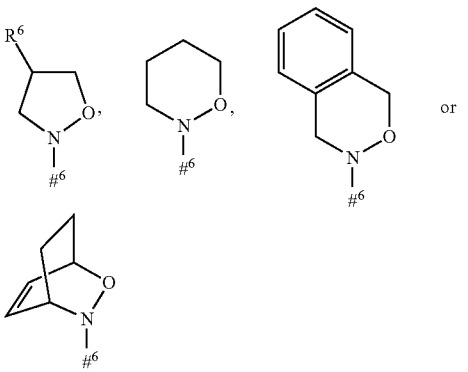


[0637] in which

[0638] $\#^4$ marks the linkage site with the adjacent nitrogen atom,

[0639] $\#^5$ marks the linkage site with the carbonyl group,

[0640] the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



[0641] in which

[0642] $\#^6$ marks the linkage site with the carbonyl group,

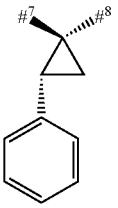
[0643] R^6 is hydrogen, hydroxy or benzyloxy,

[0644] R^3 is hydrogen,

[0645] R^4 is benzyl, 4-hydroxybenzyl, 1-phenylethyl or 1H-indol-3-ylmethyl,

[0646] or

[0647] R^3 and R^4 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula



[0648] in which

[0649] $\#^7$ marks the linkage site with the adjacent nitrogen atom,

[0650] $\#^8$ marks the linkage site with the group T^1,

[0651] T^1 is a group of the formula —C(═O)—OR^7, —C(═O)—NR^8R^9 or —CH_2—O—R^{11}, in which

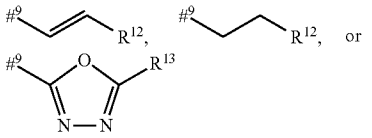
[0652] R^7 is hydrogen, methyl, ethyl, n-propyl, tert-butyl, benzyl or adamantylmethyl,

[0653] R^8 is hydrogen or methyl,

[0654] R^9 is hydrogen, methyl, ethyl, n-propyl or benzyl,

[0655] R^{11} is benzyl, which may be substituted in the phenyl group by methoxycarbonyl or carboxyl,

[0656] R^5 is hydrogen, methyl or a group of the formula



[0657] in which

[0658] $\#^9$ marks the linkage site with —$CHCH_2$phenyl,

[0659] R^{12} is phenyl which may be substituted by methoxycarbonyl, carboxyl or a group of the formula —$S(O)_2OH$,

[0660] R^{13} is phenyl which may be substituted by methoxycarbonyl or carboxyl,

[0661] R^{35} is methyl or hydroxy,

and also their salts, solvates and solvates of the salts.

[0662] Preferred subject matter of the invention are binder-drug conjugates of the general formula (Ia) in which

[0663] n is a number from 1 to 10,

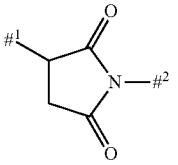
[0664] AK is AK_1 or AK_2

[0665] where

[0666] AK_1 is an antibody which comprises the six CDR sequences of the antibody MF-Ta, the variable light and variable heavy chain of the antibody MF-Ta or the light and heavy chain of the antibody MF-Ta, and is bonded via the sulphur atom of a cysteine residue of the binder to the group G,

[0667] AK_2 is an antibody which comprises the six CDR sequences of the antibody MF-Ta, the variable light and variable heavy chain of the antibody MF-Ta or the light and heavy chain of the antibody MF-Ta, and is bonded via the NH side group of a lysine residue of the binder to the group G,

[0668] G when AK=AK_1, is a group of the formula



[0669] in which

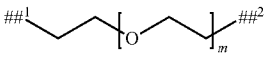
[0670] $\#^1$ marks the linkage site with the cysteine residue of the binder,

[0671] $\#^2$ marks the linkage site with the group L^1,

[0672] or

[0673] when AK=AK_2, is carbonyl,

[0674] L^1 is a bond, linear (C_2-C_6)-alkanediyl, a group of the formula



[0675] where

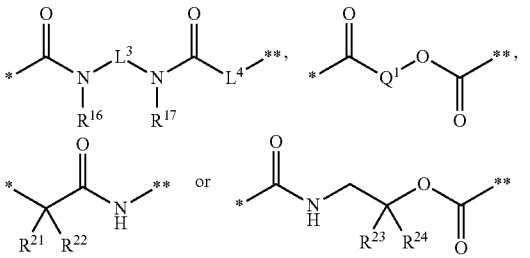
[0676] m is a number 2 or 3,

[0677] $\#\#^1$ marks the linkage site with the group G,

[0678] $\#\#^2$ marks the linkage site with the group B,

[0679] where (C_2-C_6)-alkanediyl may be substituted by 1 or 2 methyl substituents,

[0680] B is a bond or a group of the formula



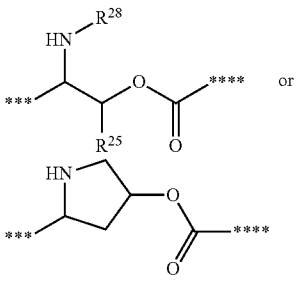
[0681] where

[0682] * marks the linkage site with L^1,

[0683] ** marks the linkage site with L^2,

[0684] L^3 is a bond or ethane-1,2-diyl,

[0685] L^4 is a bond or a group of the formula



[0686] in which

[0687] *** marks the linkage site with the carbonyl group,

[0688] **** marks the linkage site with L^2,

[0689] R^{25} is methyl,

[0690] R^{28} is hydrogen, methylcarbonyl or tert-butyloxycarbonyl,

[0691] Q^1 is piperidine-1,4-diyl,

[0692] R^{16} is hydrogen or methyl,

[0693] R^{17} is hydrogen or methyl,

[0694] or

[0695] R^{16} and R^{17} together with the atoms to which they are bonded form a piperazinyl ring,

[0696] R^{21} is hydrogen or methyl,

[0697] R^{22} is hydrogen or methyl,

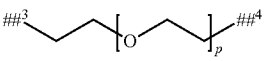
[0698] or

[0699] R^{21} and R^{22} together with the atoms to which they are bonded form a cyclopropyl ring,

[0700] R^{23} is methyl,

[0701] R^{24} is hydrogen,

[0702] L^2 is linear (C_2-C_6)-alkanediyl or is a group of the formula



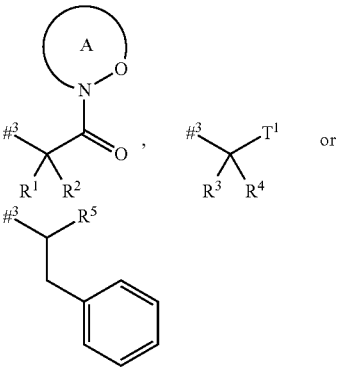
[0703] where

[0704] p is a number from 2 to 6,

[0705] $\#\#^3$ marks the linkage site with the group B,

[0706] $\#\#^4$ marks the linkage site with the nitrogen atom,

[0707] D is a group of the formula



[0708] where

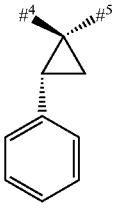
[0709] $\#^3$ marks the linkage site with the nitrogen atom,

[0710] R^1 is hydrogen,

[0711] R^2 is 1-hydroxyethyl, benzyl, 4-hydroxybenzyl, 1-phenylethyl or 1H-indol-3-yl-methyl,

[0712] or

[0713] R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula

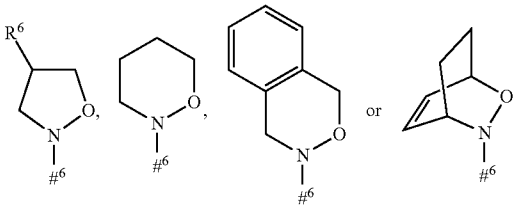


[0714] in which

[0715] $\#^4$ marks the linkage site with the adjacent nitrogen atom,

[0716] $\#^5$ marks the linkage site with the carbonyl group,

[0717] the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



[0718] in which

[0719] $\#^6$ marks the linkage site with the carbonyl group,

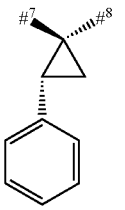
[0720] R^6 is hydrogen, hydroxy or benzyloxy,

[0721] R^3 is hydrogen,

[0722] R^4 is benzyl, 4-hydroxybenzyl, 1-phenylethyl or 1H-indol-3-ylmethyl,

[0723] or

[0724] R^3 and R^4 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula



[0725] in which

[0726] $\#^7$ marks the linkage site with the adjacent nitrogen atom,

[0727] $\#^8$ marks the linkage site with the group T^1,

[0728] T^1 is a group of the formula —C(═O)—OR^7, —C(═O)—NR^8R^9 or —CH_2—O—R^{11}, in which

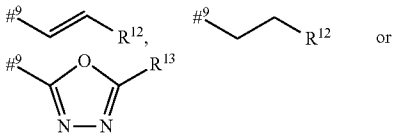
[0729] R^7 is hydrogen, methyl, ethyl, n-propyl, tert-butyl, benzyl or adamantylmethyl,

[0730] R^8 is hydrogen or methyl,

[0731] R^9 is hydrogen, methyl, ethyl, n-propyl or benzyl,

[0732] R^{11} is benzyl, which may be substituted in the phenyl group by methoxycarbonyl or carboxyl,

[0733] R^5 is hydrogen, methyl or a group of the formula



[0734] in which

[0735] #9 marks the linkage site with —$CHCH_2$phenyl,

[0736] R^{12} is phenyl which may be substituted by methoxycarbonyl, carboxyl or a group of the formula —$S(O)_2OH$,

[0737] R^{13} is phenyl which may be substituted by methoxycarbonyl or carboxyl,

[0738] R^{35} is methyl or hydroxy,

[0739] and also their salts, solvates and solvates of the salts.

[0740] Preferred subject matter of the present invention are binder-drug conjugates of the general formula (Ia) as indicated above, in which

[0741] n is a number from 1 to 10,

[0742] AK is AK_2,

[0743] where

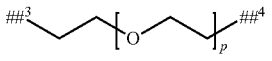
[0744] AK_2 is an antibody which comprises the six CDR sequences of the antibody MF-Ta, the variable light and variable heavy chain of the antibody MF-Ta or the light and heavy chain of the antibody MF-Ta, and is bonded via the NH side group of a lysine residue of the binder to the group G,

[0745] G is carbonyl,

[0746] L^1 is a bond,

[0747] B is a bond,

[0748] L^2 is linear (C_3-C_6)-alkanediyl or is a group of the formula



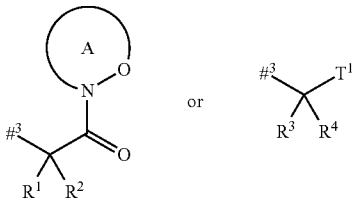
[0749] where

[0750] p is a number 2 or 3,

[0751] ##3 marks the linkage site with the group B,

[0752] ##4 marks the linkage site with the nitrogen atom,

[0753] D is a group of the formula



[0754] where

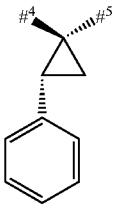
[0755] #3 marks the linkage site with the nitrogen atom,

[0756] R^1 is hydrogen,

[0757] R^2 is benzyl, 4-hydroxybenzyl or 1H-indol-3-ylmethyl,

[0758] or

[0759] R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula

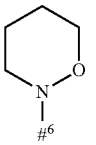


[0760] in which

[0761] #4 marks the linkage site with the adjacent nitrogen atom,

[0762] #5 marks the linkage site with the carbonyl group,

[0763] the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



[0764] in which

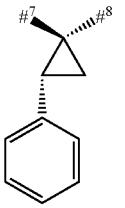
[0765] #6 marks the linkage site with the carbonyl group,

[0766] R^3 is hydrogen,

[0767] R^4 is benzyl, 4-hydroxybenzyl or 1H-indol-3-ylmethyl,

[0768] or

[0769] R^3 and R^4 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula



[0770] in which

[0771] #7 marks the linkage site with the adjacent nitrogen atom,

[0772] #8 marks the linkage site with the group T^1,

[0773] T^1 is a group of the formula —C(═O)—OR^7 or —C(═O)—NR^8R^9

[0774] in which

[0775] R^7 is hydrogen, methyl, ethyl, n-propyl, tert-butyl, benzyl or adamantylmethyl,

[0776] R^8 is hydrogen,

[0777] R^9 is hydrogen or benzyl,

[0778] R^{35} is methyl,

and also their salts, solvates and solvates of the salts.

[0779] Preferred subject matter of the invention are binder-drug conjugates of the general formula (Ia), in which

[0780] n is a number from 1 to 10,

[0781] AK is AK_2,

[0782] where

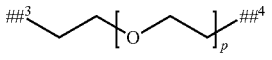
[0783] AK_2 is an antibody which comprises the six CDR sequences of the antibody MF-Ta, the variable light and variable heavy chain of the antibody MF-Ta or the light and heavy chain of the antibody MF-Ta, and is bonded via the NH side group of a lysine residue of the binder to the group G,

[0784] G is carbonyl,

[0785] L^1 is a bond,

[0786] B is a bond,

[0787] L^2 is linear (C_3-C_6)-alkanediyl or is a group of the formula



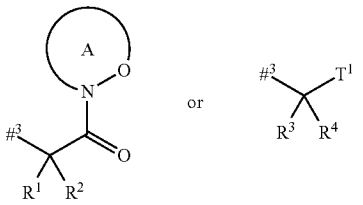
[0788] where

[0789] p is a number 2 or 3,

[0790] $\#\#^3$ marks the linkage site with the group B,

[0791] $\#\#^4$ marks the linkage site with the nitrogen atom,

[0792] D is a group of the formula



[0793] where

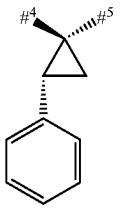
[0794] $\#^3$ marks the linkage site with the nitrogen atom,

[0795] R^1 is hydrogen,

[0796] R^2 is benzyl or 1H-indol-3-ylmethyl,

[0797] or

[0798] R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula

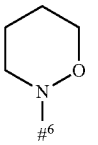


[0799] in which

[0800] $\#^4$ marks the linkage site with the adjacent nitrogen atom,

[0801] $\#^5$ marks the linkage site with the carbonyl group,

[0802] the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



[0803] in which

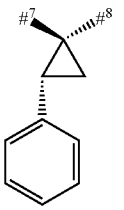
[0804] $\#^6$ marks the linkage site with the carbonyl group,

[0805] R^3 is hydrogen,

[0806] R^4 is benzyl or 1H-indol-3-ylmethyl,

[0807] or

[0808] R^3 and R^4 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula



[0809] in which

[0810] $\#^7$ marks the linkage site with the adjacent nitrogen atom,

[0811] $\#^8$ marks the linkage site with the group T^1,

[0812] T^1 is a group of the formula —C(═O)—OR^7 or —C(═O)—NR^8R^9

[0813] in which

[0814] R^7 is hydrogen, methyl, ethyl, n-propyl, tert-butyl, benzyl or adamantylmethyl,

[0815] R^8 is hydrogen,

[0816] R^9 is hydrogen or benzyl,

[0817] R^{35} is methyl,

and also their salts, solvates and solvates of the salts.

[0818] Preferred subject matter of the present invention are binder-drug conjugates of the general formula (Ia) as indicated above, in which

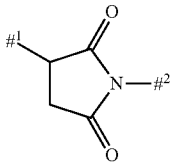
[0819] n is a number from 1 to 10,

[0820] AK is AK_1,

[0821] where

[0822] AK_1 is an antibody which comprises the six CDR sequences of the antibody MF-Ta, the variable light and variable heavy chain of the antibody MF-Ta or the light and heavy chain of the antibody MF-Ta, and is bonded via the sulphur atom of a cysteine residue of the binder to the group G,

[0823] G is a group of the formula

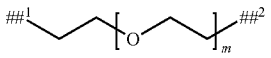


[0824] where

[0825] $\#^1$ marks the linkage site with the cysteine residue of the binder,

[0826] $\#^2$ marks the linkage site with the group L^1,

[0827] L^1 is a bond, linear (C_3-C_5)-alkanediyl or a group of the formula



[0828] where

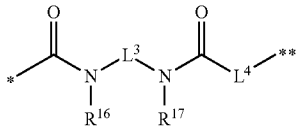
[0829] m is a number 2 or 3,

[0830] $\#\#^1$ marks the linkage site with the group G,

[0831] $\#\#^2$ marks the linkage site with the group B,

[0832] where (C_3-C_5)-alkanediyl may be substituted by 1 or 2 methyl substituents,

[0833] B is a bond or a group of the formula



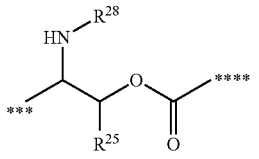
[0834] where

[0835] * marks the linkage site with L^1,

[0836] ** marks the linkage site with L^2,

[0837] L^3 is a bond or ethane-1,2-diyl,

[0838] L^4 is a bond or a group of the formula



[0839] in which

[0840] *** marks the linkage site with the carbonyl group,

[0841] **** marks the linkage site with L^2,

[0842] R^{25} is methyl,

[0843] R^{28} is hydrogen, methylcarbonyl or tert-butyloxycarbonyl,

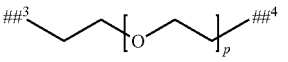
[0844] R^{16} is hydrogen or methyl,

[0845] R^{17} is hydrogen or methyl,

[0846] or

[0847] R^{16} and R^{17} together with the atoms to which they are bonded form a piperazinyl ring,

[0848] L^2 is linear (C_3-C_5)-alkanediyl or is a group of the formula



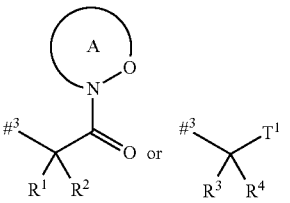
[0849] where

[0850] p is a number 2 or 3,

[0851] $\#\#^3$ marks the linkage site with the group B,

[0852] $\#\#^4$ marks the linkage site with the nitrogen atom,

[0853] D is a group of the formula



[0854] where

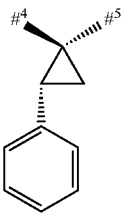
[0855] $\#^3$ marks the linkage site with the nitrogen atom,

[0856] R^1 is hydrogen,

[0857] R^2 is benzyl, 4-hydroxybenzyl or 1H-indol-3-ylmethyl,

[0858] or

[0859] R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula

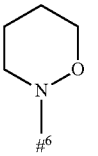


[0860] in which

[0861] $\#^4$ marks the linkage site with the adjacent nitrogen atom,

[0862] $\#^5$ marks the linkage site with the carbonyl group,

[0863] the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



[0864] in which

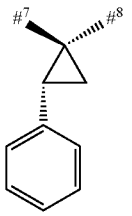
[0865] $\#^6$ marks the linkage site with the carbonyl group,

[0866] R^3 is hydrogen,

[0867] R^4 is benzyl, 4-hydroxybenzyl or 1H-indol-3-ylmethyl,

[0868] or

[0869] R^3 and R^4 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula



[0870] in which

[0871] $\#^7$ marks the linkage site with the adjacent nitrogen atom,

[0872] $\#^8$ marks the linkage site with the group T^1,

[0873] T^1 is a group of the formula —C(═O)—OR^7 or —C(═O)—NR^8R^9, in which

[0874] R^7 is hydrogen, methyl, ethyl, n-propyl, tert-butyl, benzyl or adamantylmethyl,

[0875] R^8 is hydrogen,

[0876] R^9 is hydrogen or benzyl,

[0877] R^{35} is methyl,

and also their salts, solvates and solvates of the salts.

[0878] Preferred subject matter of the invention are binder-drug conjugates of the general formula (Ia), in which

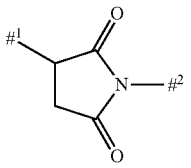
[0879] n is a number from 1 to 10,

[0880] AK is AK_1,

[0881] where

[0882] AK_1 is an antibody which comprises the six CDR sequences of the antibody MF-Ta, the variable light and variable heavy chain of the antibody MF-Ta or the light and heavy chain of the antibody MF-Ta, and is bonded via the sulphur atom of a cysteine residue of the binder to the group G,

[0883] G is a group of the formula

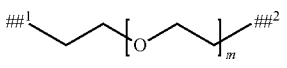


[0884] where

[0885] $\#^1$ marks the linkage site with the cysteine residue of the binder,

[0886] $\#^2$ marks the linkage site with the group L^1,

[0887] L^1 is a bond, linear (C_3-C_5)-alkanediyl or a group of the formula



[0888] where

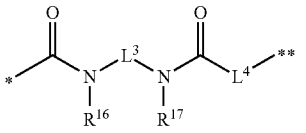
[0889] m is a number 2 or 3,

[0890] $\#\#^1$ marks the linkage site with the group G,

[0891] $\#\#^2$ marks the linkage site with the group B,

[0892] where (C_3-C_5)-alkanediyl may be substituted by 1 or 2 methyl substituents,

[0893] B is a bond or a group of the formula



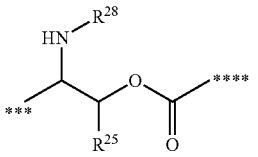
[0894] where

[0895] * marks the linkage site with L^1,

[0896] ** marks the linkage site with L^2,

[0897] L^3 is a bond or ethane-1,2-diyl,

[0898] L^4 is a bond or a group of the formula



[0899] in which

[0900] *** marks the linkage site with the carbonyl group,

[0901] **** marks the linkage site with L^2,

[0902] R^{25} is methyl,

[0903] R^{28} is hydrogen, methylcarbonyl or tert-butyloxycarbonyl,

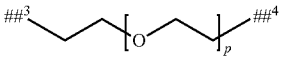
[0904] R^{16} is hydrogen or methyl,

[0905] R^{17} is hydrogen or methyl,

[0906] or

[0907] R^{16} and R^{17} together with the atoms to which they are bonded form a piperazinyl ring,

[0908] L^2 is linear (C_3-C_5)-alkanediyl or is a group of the formula



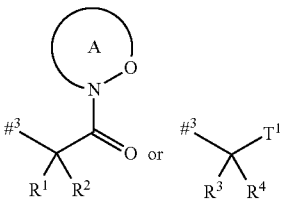
[0909] where

[0910] p is a number 2 or 3,

[0911] $\#\#^3$ marks the linkage site with the group B,

[0912] $\#\#^4$ marks the linkage site with the nitrogen atom,

[0913] D is a group of the formula



[0914] where

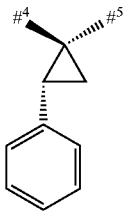
[0915] #3 marks the linkage site with the nitrogen atom,

[0916] R^1 is hydrogen,

[0917] R^2 is benzyl or 1H-indol-3-ylmethyl,

[0918] or

[0919] R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula

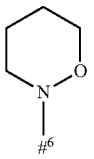


[0920] in which

[0921] #4 marks the linkage site with the adjacent nitrogen atom,

[0922] #5 marks the linkage site with the carbonyl group,

[0923] the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



[0924] in which

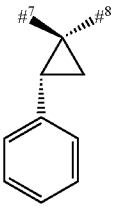
[0925] #6 marks the linkage site with the carbonyl group,

[0926] R^3 is hydrogen,

[0927] R^4 is benzyl or 1H-indol-3-ylmethyl,

[0928] or

[0929] R^3 and R^4 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula



[0930] in which

[0931] #7 marks the linkage site with the adjacent nitrogen atom,

[0932] #8 marks the linkage site with the group T^1,

[0933] T^1 is a group of the formula —C(═O)—OR^7 or —C(═O)—NR^8R^9,

[0934] in which

[0935] R^7 is hydrogen, methyl, ethyl, n-propyl, tert-butyl, benzyl or adamantylmethyl,

[0936] R^8 is hydrogen,

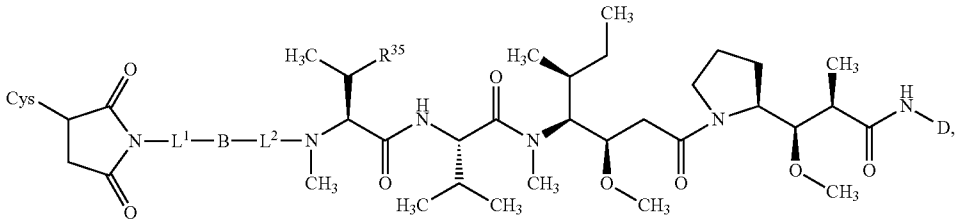
[0937] R^9 is hydrogen or benzyl,

[0938] R^{35} is methyl,

and also their salts, solvates and solvates of the salts.

[0939] Additionally provided by the present invention are compounds of the formula (XXXa)

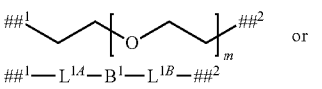
(XXXa)



in which

[0940] Cys is a cysteine residue which is bonded via the sulphur atom of the side chain to a carbon atom of the succinimide,

[0941] L^1 is a bond, linear (C_1-C_{10})-alkanediyl, a group of the formula



or

[0942] where

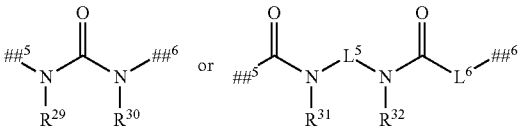
[0943] m is a number from 2 to 6,

[0944] ##1 marks the linkage site with the group G,

[0945] ##2 marks the linkage site with the group B,

[0946] L^{1A} is linear (C_2-C_{10})-alkanediyl,

[0947] B^1 is a group of the formula



[0948] in which

[0949] ##5 marks the linkage site with the group L^{1A},

[0950] ##6 marks the linkage site with the group L^{1B},

[0951] L^5 is a bond or $(C_2$-$C_4)$-alkanediyl,

[0952] L^6 is a bond,

[0953] R^{29} is hydrogen or $(C_1$-$C_4)$-alkyl,

[0954] R^{30} is hydrogen or $(C_1$-$C_4)$-alkyl,

[0955] or

[0956] R^{29} and R^{30} together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

[0957] R^{31} is hydrogen or $(C_1$-$C_4)$-alkyl,

[0958] R^{32} is hydrogen or $(C_1$-$C_4)$-alkyl,

[0959] or

[0960] R^{31} and R^{32} together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

[0961] L^{1B} is linear $(C_2$-$C_{10})$-alkanediyl,

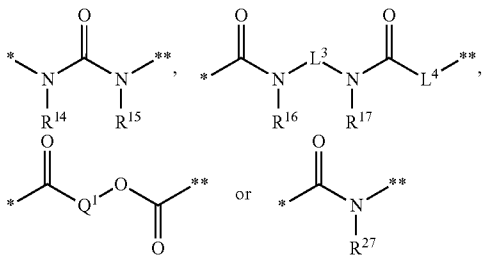
[0962] and

[0963] where $(C_1$-$C_{10})$-alkanediyl may be substituted by 1 to 4 substituents selected independently of one another from the group consisting of methyl, hydroxy and benzyl,

[0964] and

[0965] where two carbon atoms of the alkanediyl chain in 1,2, 1,3 or 1,4 relation to one another, with inclusion of any carbon atoms situated between them, may be bridged to form a $(C_3$-$C_6)$-cycloalkyl ring or a phenyl ring,

[0966] B is a bond or a group of the formula



[0967] where

[0968] * marks the linkage site with L^1,

[0969] ** marks the linkage site with L^2,

[0970] P is O or NH,

[0971] L^3 is a bond or $(C_2$-$C_4)$-alkanediyl,

[0972] L^4 is a bond,

[0973] Q^1 is a 4- to 7-membered heterocycle,

[0974] Q^2 is a 3- to 7-membered carbocycle or a 4- to 7-membered heterocycle,

[0975] R^{14} is hydrogen or $(C_1$-$C_4)$-alkyl,

[0976] R^{15} is hydrogen or $(C_1$-$C_4)$-alkyl,

[0977] or

[0978] R^{14} and R^{15} together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

[0979] R^{16} is hydrogen or $(C_1$-$C_4)$-alkyl,

[0980] R^{17} is hydrogen or $(C_1$-$C_4)$-alkyl,

[0981] or

[0982] R^{16} and R^{17} together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

[0983] R^{18} is hydrogen or $(C_1$-$C_4)$-alkyl,

[0984] R^{19} is hydrogen or the side group of a natural α-amino acid or of its homologues or isomers,

[0985] R^{20} is hydrogen or $(C_1$-$C_4)$-alkyl,

[0986] or

[0987] R^{19} and R^{20} together with the atoms to which they are bonded form a pyrrolidinyl ring,

[0988] R^{21} is hydrogen or $(C_1$-$C_4)$-alkyl,

[0989] R^{22} is hydrogen or $(C_1$-$C_4)$-alkyl,

[0990] or

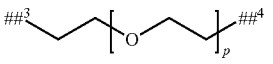
[0991] R^{21} and R^{22} together with the atoms to which they are bonded form a 3- to 7-membered carbocycle,

[0992] R^{23} is $(C_1$-$C_4)$-alkyl,

[0993] R^{24} is hydrogen or $(C_1$-$C_4)$-alkyl,

[0994] R^{27} is hydrogen or $(C_1$-$C_4)$-alkyl,

[0995] L^2 is linear $(C_2$-$C_{10})$-alkanediyl or is a group of the formula



[0996] where

[0997] p is a number from 2 to 6,

[0998] ##3 marks the linkage site with the group B,

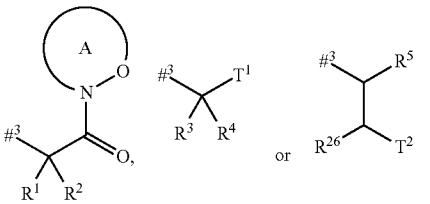
[0999] ##4 marks the linkage site with the nitrogen atom,

[1000] where $(C_2$-$C_{10})$-alkanediyl may be substituted by 1 to 4 substituents selected independently of one another from the group consisting of methyl, hydroxy and benzyl,

[1001] and

[1002] where two carbon atoms of the alkanediyl chain in 1,2, 1,3 or 1,4 relation to one another, with inclusion of any carbon atoms situated between them, may be bridged to form a $(C_3$-$C_6)$-cycloalkyl ring or a phenyl ring,

[1003] D is a group of the formula



[1004] where

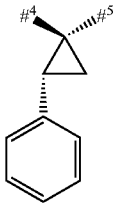
[1005] #3 marks the linkage site with the nitrogen atom,

[1006] R^1 is hydrogen or methyl,

[1007] R^2 is isopropyl, isobutyl, sec-butyl, tert-butyl, phenyl, benzyl, 1-hydroxyethyl, 4-hydroxybenzyl, 4-hydroxy-3-nitrobenzyl, 4-hydroxy-3-aminobenzyl, 1-phenylethyl, diphenylmethyl, 1H-imidazol-4-ylmethyl or 1H-indol-3-ylmethyl,

[1008] or

[1009] R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula

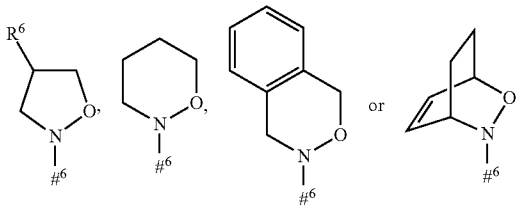


[1010] in which

[1011] #4 marks the linkage site with the adjacent nitrogen atom,

[1012] #5 marks the linkage site with the carbonyl group,

[1013] the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



[1014] in which

[1015] #6 marks the linkage site with the carbonyl group,

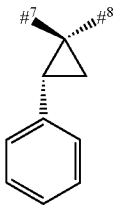
[1016] R^6 is hydrogen, hydroxy or benzyloxy,

[1017] R^3 is hydrogen or methyl,

[1018] R^4 is isopropyl, isobutyl, sec-butyl, tert-butyl, phenyl, benzyl, 1-hydroxyethyl, 4-hydroxybenzyl, 4-hydroxy-3-nitrobenzyl, 4-hydroxy-3-aminobenzyl, 1-phenylethyl, diphenylmethyl, 1H-imidazol-4-ylmethyl or 1H-indol-3-ylmethyl,

[1019] or

[1020] R^3 and R^4 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula



[1021] in which

[1022] #7 marks the linkage site with the adjacent nitrogen atom,

[1023] #8 marks the linkage site with the group T^1,

[1024] T^1 is a group of the formula —C(=O)—OR^7, —C(=O)—NR^8R^9, —C(=O)—NH—NH—R^{10} or —CH_2—O—R^{11},

[1025] in which

[1026] R^7 is hydrogen, methyl, ethyl, n-propyl, tert-butyl, benzyl or adamantylmethyl,

[1027] R^8 is hydrogen or methyl,

[1028] R^9 is hydrogen, methyl, ethyl, n-propyl or benzyl,

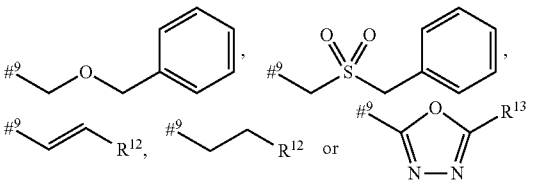
[1029] or

[1030] R^8 and R^9 together with the nitrogen atom to which they are bonded form a 4- to 7-membered heterocycle,

[1031] R^{10} is benzoyl,

[1032] R^{11} is benzyl, which may be substituted in the phenyl group by methoxycarbonyl or carboxyl,

[1033] R^5 is hydrogen, methyl or a group of the formula



[1034] in which

[1035] #9 marks the linkage site with —CHC(R^{26})-T^2,

[1036] R^{12} is phenyl which may be substituted by methoxycarbonyl, carboxyl or a group of the formula —$S(O)_2OH$,

[1037] R^{13} is phenyl which may be substituted by methoxycarbonyl or carboxyl,

[1038] R^{26} is hydrogen or hydroxy,

[1039] T^2 is phenyl, benzyl, 1H-indol-3-yl or 1H-indol-3-ylmethyl,

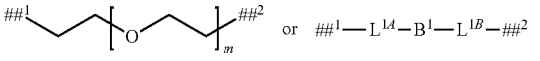
[1040] R^{35} is methyl or hydroxy,

and also their salts, solvates and solvates of the salts.

[1041] Preferred in the context of the present invention are additionally also compounds of the formula (XXXa) in which

[1042] Cys is a cysteine residue which is bonded via the sulphur atom of the side chain via a carbon atom of the succinimide,

[1043] L^1 is a bond, linear (C_2-C_6)-alkanediyl, a group of the formula



[1044] where

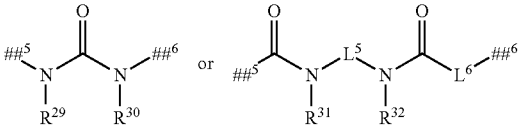
[1045] m is a number 2 or 3,

[1046] ##1 marks the linkage site with the group G,

[1047] ##2 marks the linkage site with the group B,

[1048] L^{1A} is linear (C_2-C_6)-alkanediyl,

[1049] B^1 is a group of the formula



[1050] in which

[1051] ##5 marks the linkage site with the group L^{1A},

[1052] ##6 marks the linkage site with the group L^{1B},

[1053] L^5 is a bond,

[1054] L^6 is a bond,

[1055] R^{29} is hydrogen,

[1056] R^{30} is hydrogen,

[1057] R^{31} is hydrogen or methyl,

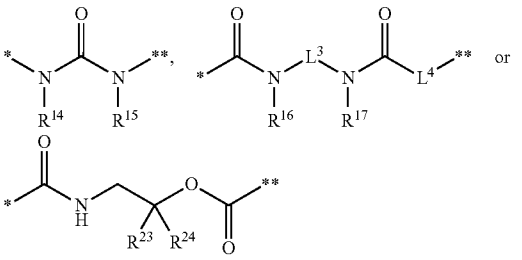
[1058] R^{32} is hydrogen or methyl,

[1059] L^{1B} is linear (C_2-C_6)-alkanediyl,

[1060] and

[1061] where (C_2-C_6)-alkanediyl may be substituted by 1 or 2 methyl substituents,

[1062] B is a bond or a group of the formula



or

[1063] where

[1064] * marks the linkage site with L^1,

[1065] ** marks the linkage site with L^2,

[1066] L^3 is a bond or ethane-1,2-diyl,

[1067] L^4 is a bond,

[1068] R^{14} is hydrogen,

[1069] R^{15} is hydrogen,

[1070] R^{16} is hydrogen or methyl,

[1071] R^{17} is hydrogen or methyl,

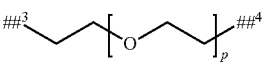
[1072] or

[1073] R^{16} and R^{17} together with the atoms to which they are bonded form piperazinyl ring,

[1074] R^{23} is methyl,

[1075] R^{24} is hydrogen or methyl,

[1076] L^2 is linear (C_2-C_6)-alkanediyl or is a group of the formula



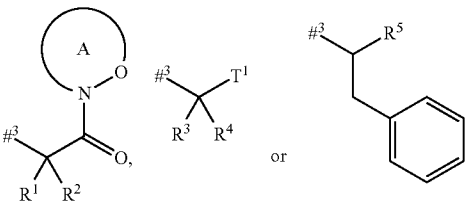
[1077] where

[1078] p is a number 2 or 3,

[1079] $\#\#^3$ marks the linkage site with the group B,

[1080] $\#\#^4$ marks the linkage site with the nitrogen atom,

[1081] D is a group of the formula



or

[1082] where

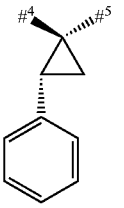
[1083] $\#^3$ marks the linkage site with the nitrogen atom,

[1084] R^1 is hydrogen,

[1085] R^2 is 1-hydroxyethyl, benzyl, 4-hydroxybenzyl, 1-phenylethyl or 1H-indol-3-yl-methyl,

[1086] or

[1087] R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula

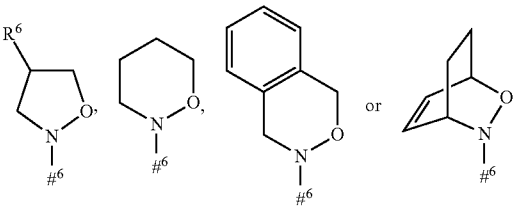


[1088] in which

[1089] $\#^4$ marks the linkage site with the adjacent nitrogen atom,

[1090] $\#^5$ marks the linkage site with the carbonyl group,

[1091] the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



or

[1092] in which

[1093] $\#^6$ marks the linkage site with the carbonyl group,

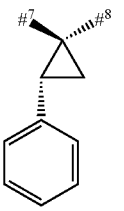
[1094] R^6 is hydrogen, hydroxy or benzyloxy,

[1095] R^3 is hydrogen,

[1096] R^4 is 1-hydroxyethyl, benzyl, 4-hydroxybenzyl, 1-phenylethyl or 1H-indol-3-yl-methyl,

[1097] or

[1098] R^3 and R^4 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula



[1099] in which

[1100] $\#^7$ marks the linkage site with the adjacent nitrogen atom,

[1101] $\#^8$ marks the linkage site with the group T^1,

[1102] T^1 is a group of the formula —C(═O)—OR^7, —C(═O)—NR^8R^9, —C(═O)—NH—NH—R^{10} or —CH_2—O—R^{11},

[1103] in which

[1104] R^7 is hydrogen, methyl, ethyl, n-propyl, tert-butyl, benzyl or adamantylmethyl,

[1105] R^8 is hydrogen or methyl,

[1106] R^9 is hydrogen, methyl, ethyl, n-propyl or benzyl,

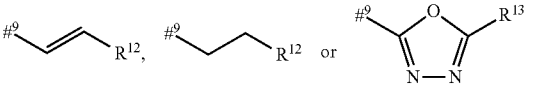
[1107] or

[1108] R^8 and R^9 together with the nitrogen atom to which they are bonded form a 4- to 7-membered heterocycle,

[1109] R^{10} is benzoyl,

[1110] R^{11} is benzyl which may be substituted in the phenyl group by methoxycarbonyl or carboxyl,

[1111] R^5 is hydrogen, methyl or a group of the formula



[1112] in which

[1113] #9 marks the linkage site with —$CHCH_2$phenyl,

[1114] R^{12} is phenyl which may be substituted by methoxycarbonyl, carboxyl or a group of the formula —$S(O)_2OH$,

[1115] R^{13} is phenyl which may be substituted by methoxycarbonyl or carboxyl,

[1116] R^{35} is methyl or hydroxy,

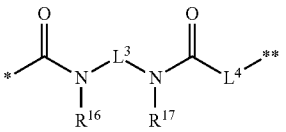
and also their salts, solvates and solvates of the salts.

[1117] Particularly preferred in the context of the present invention are additionally also compounds of the formula (XXXa) in which

[1118] Cys is a cysteine residue which is bonded via the sulphur atom of the side chain via a carbon atom of the succinimide,

[1119] L^1 is a bond or linear (C_2-C_6)-alkanediyl,

[1120] B is a bond or a group of the formula



[1121] where

[1122] * marks the linkage site with L^1,

[1123] ** marks the linkage site with L^2,

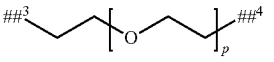
[1124] L^3 is a bond,

[1125] L^4 is a bond,

[1126] R^{16} is hydrogen or methyl,

[1127] R^{17} is hydrogen or methyl,

[1128] L^2 is linear (C_2-C_6)-alkanediyl or is a group of the formula



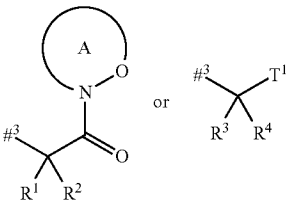
[1129] where

[1130] p is a number 2 or 3,

[1131] ##3 marks the linkage site with the group B,

[1132] ##4 marks the linkage site with the nitrogen atom,

[1133] D is a group of the formula



[1134] where

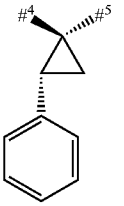
[1135] #3 marks the linkage site with the nitrogen atom,

[1136] R^1 is hydrogen,

[1137] R^2 is benzyl or 1H-indol-3-ylmethyl,

[1138] or

[1139] R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula

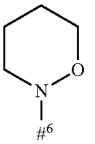


[1140] in which

[1141] #4 marks the linkage site with the adjacent nitrogen atom,

[1142] #5 marks the linkage site with the carbonyl group,

[1143] the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



[1144] in which

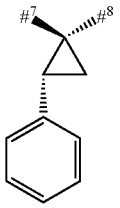
[1145] #6 marks the linkage site with the carbonyl group,

[1146] R^3 is hydrogen,

[1147] R^4 is benzyl or 1H-indol-3-ylmethyl,

[1148] or

[1149] R^3 and R^4 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula



[1150] in which

[1151] $\#^7$ marks the linkage site with the adjacent nitrogen atom,

[1152] $\#^8$ marks the linkage site with the group T^1,

[1153] T^1 is a group of the formula —C(=O)—OR^7 or —C(=O)—NR^8R^9,

[1154] in which

[1155] R^7 is hydrogen,

[1156] R^8 is hydrogen,

[1157] R^9 is hydrogen,

[1158] R^{35} is methyl,

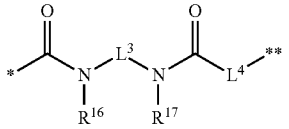
and also their salts, solvates and solvates of the salts.

[1159] Preferred subject matter of the present invention are compounds of the formula (XXXa) as indicated above, in which

[1160] Cys is a cysteine residue which is bonded via the sulphur atom of the side chain via a carbon atom of the succinimide,

[1161] L^1 is a bond or linear (C_2-C_6)-alkanediyl,

[1162] B is a bond or a group of the formula



[1163] where

[1164] * marks the linkage site with L^1,

[1165] ** marks the linkage site with L^2,

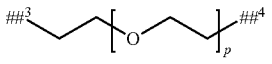
[1166] L^3 is a bond,

[1167] L^4 is a bond,

[1168] R^{16} is hydrogen or methyl,

[1169] R^{17} is hydrogen or methyl,

[1170] L^2 is linear (C_2-C_6)-alkanediyl or is a group of the formula



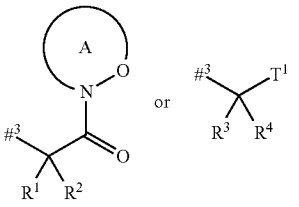
[1171] where

[1172] p is a number 2 or 3,

[1173] $\#\#^3$ marks the linkage site with the group B,

[1174] $\#\#^4$ marks the linkage site with the nitrogen atom,

[1175] D is a group of the formula

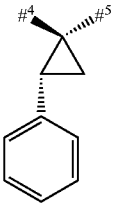


[1176] where $\#^3$ marks the linkage site with the nitrogen atom, R^1 is hydrogen,

[1177] R^2 is benzyl, 4-hydroxybenzyl or 1H-indol-3-yl-methyl,

[1178] or

[1179] R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula

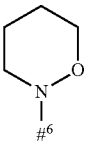


[1180] in which

[1181] $\#^4$ marks the linkage site with the adjacent nitrogen atom,

[1182] $\#^5$ marks the linkage site with the carbonyl group,

[1183] the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



[1184] in which

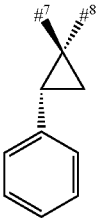
[1185] $\#^6$ marks the linkage site with the carbonyl group,

[1186] R^3 is hydrogen,

[1187] R^4 is benzyl, 4-hydroxybenzyl or 1H-indol-3-yl-methyl,

[1188] or

[1189] R^3 and R^4 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula



[1190] in which

[1191] $\#^7$ marks the linkage site with the adjacent nitrogen atom,

[1192] $\#^8$ marks the linkage site with the group T^1,

[1193] T^1 is a group of the formula —C(=O)—OR^7 or —C(=O)—NR^8R^9,

[1194] in which

[1195] R^7 is hydrogen,

[1196] R^8 is hydrogen,

[1197] R^9 is hydrogen,

[1198] R^{35} is methyl,

and also their salts, solvates and solvates of the salts.

[1199] The present invention additionally provides compounds of the formula (XXXI)

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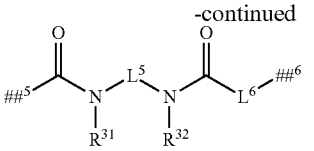


[1207] in which

[1208] $\#^5$ marks the linkage site with the group L^{1A},

[1209] $\#^6$ marks the linkage site with the group L^{1B},

[1210] L^5 is a bond or $(C_2$-$C_4)$-alkanediyl,

[1211] L^6 is a bond,

[1212] R^{29} is hydrogen or $(C_1$-$C_4)$-alkyl,

[1213] R^{30} is hydrogen or $(C_1$-$C_4)$-alkyl,

[1214] or

[1215] R^{29} and R^{30} together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

[1216] R^{31} is hydrogen or $(C_1$-$C_4)$-alkyl,

[1217] R^{32} is hydrogen or $(C_1$-$C_4)$-alkyl,

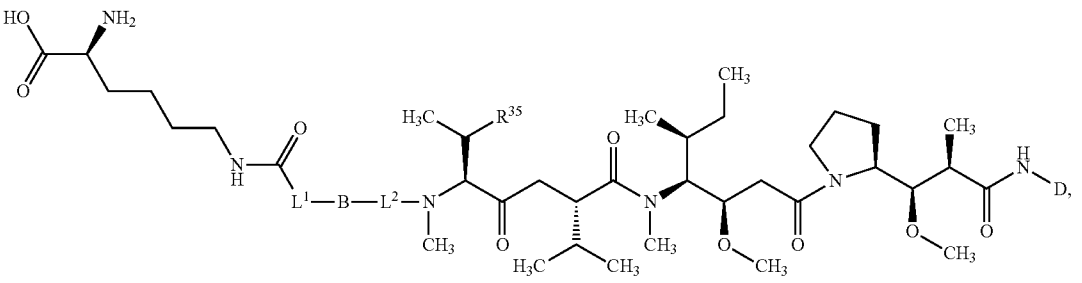
[1218] or

[1219] R^{31} and R^{32} together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

[1220] L^{1B} is linear $(C_2$-$C_{10})$-alkanediyl,

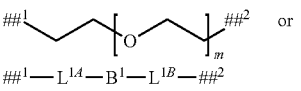
[1221] and

(XXXI)



in which

[1200] L^1 is a bond, linear $(C_1$-$C_{10})$-alkanediyl, a group of the formula



or

[1201] where

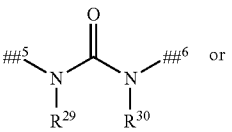
[1202] m is a number from 2 to 6,

[1203] $\#^1$ marks the linkage site with the group G,

[1204] $\#^2$ marks the linkage site with the group B,

[1205] L^{1A} is linear $(C_2$-$C_{10})$-alkanediyl,

[1206] B^1 is a group of the formula



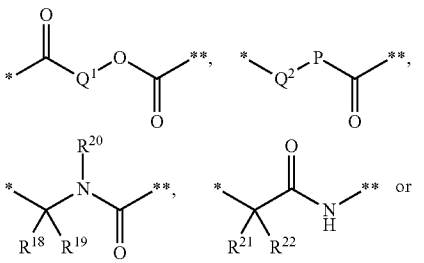
or

[1222] where $(C_1$-$C_{10})$-alkanediyl may be substituted by 1 to 4 substituents selected independently of one another from the group consisting of methyl, hydroxy and benzyl,

[1223] and

[1224] where two carbon atoms of the alkanediyl chain in 1,2, 1,3 or 1,4 relation to one another, with inclusion of any carbon atoms situated between them, may be bridged to form a $(C_3$-$C_6)$-cycloalkyl ring or a phenyl ring,

[1225] B is a bond or a group of the formula



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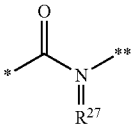


[1226] where

[1227] * marks the linkage site with L^1,

[1228] ** marks the linkage site with L^2,

[1229] P is O or NH,

[1230] Q^1 is a 4- to 7-membered heterocycle,

[1231] Q^2 is a 3- to 7-membered carbocycle or a 4- to 7-membered heterocycle,

[1232] R^{18} is hydrogen or $(C_1$-$C_4)$-alkyl,

[1233] R^{19} is hydrogen or the side group of a natural α-amino acid or of its homologues or isomers,

[1234] R^{20} is hydrogen or $(C_1$-$C_4)$-alkyl,

[1235] or

[1236] R^{19} and R^{20} together with the atoms to which they are bonded form a pyrrolidinyl ring,

[1237] R^{21} is hydrogen or $(C_1$-$C_4)$-alkyl,

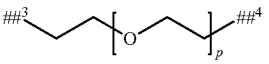
[1238] R^{22} is hydrogen or $(C_1$-$C_4)$-alkyl,

[1239] or

[1240] R^{21} and R^{22} together with the atoms to which they are bonded form a 3- to 7-membered carbocycle,

[1241] R^{27} is hydrogen or $(C_1$-$C_4)$-alkyl,

[1242] L^2 is linear $(C_2$-$C_{10})$-alkanediyl or is a group of the formula



[1243] where

[1244] p is a number from 2 to 6,

[1245] ##^{3} marks the linkage site with the group B,

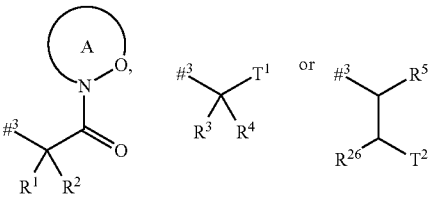
[1246] ##^{4} marks the linkage site with the nitrogen atom,

[1247] where $(C_2$-$C_{10})$-alkanediyl may be substituted by 1 to 4 substituents selected independently of one another from the group consisting of methyl, hydroxy and benzyl,

[1248] and

[1249] where two carbon atoms of the alkanediyl chain in 1,2, 1,3 or 1,4 relation to one another, with inclusion of any carbon atoms situated between them, may be bridged to form a $(C_3$-$C_6)$-cycloalkyl ring or a phenyl ring,

[1250] D is a group of the formula



[1251] in which

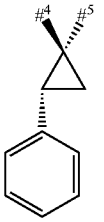
[1252] #^{3} marks the linkage site with the nitrogen atom,

[1253] R^1 is hydrogen or methyl,

[1254] R^2 is isopropyl, isobutyl, sec-butyl, tert-butyl, phenyl, benzyl, 1-hydroxyethyl, 4-hydroxybenzyl, 4-hydroxy-3-nitrobenzyl, 4-hydroxy-3-aminobenzyl, 1-phenylethyl, diphenylmethyl, 1H-imidazol-4-ylmethyl or 1H-indol-3-ylmethyl,

[1255] or

[1256] R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula

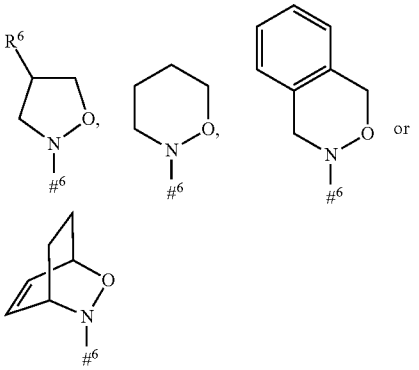


[1257] in which

[1258] #^{4} marks the linkage site with the adjacent nitrogen atom,

[1259] #^{5} marks the linkage site with the carbonyl group,

[1260] the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



[1261] in which

[1262] #^{6} marks the linkage site with the carbonyl group,

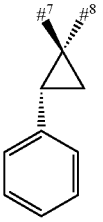
[1263] R^6 is hydrogen, hydroxy or benzyloxy,

[1264] R^3 is hydrogen or methyl,

[1265] R^4 is isopropyl, isobutyl, sec-butyl, tert-butyl, phenyl, benzyl, 1-hydroxyethyl, 4-hydroxybenzyl, 4-hydroxy-3-nitrobenzyl, 4-hydroxy-3-aminobenzyl, 1-phenylethyl, diphenylmethyl, 1H-imidazol-4-ylmethyl or 1H-indol-3-ylmethyl,

[1266] or

[1267] R^3 and R^4 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula



[1268] in which

[1269] #7 marks the linkage site with the adjacent nitrogen atom,

[1270] #8 marks the linkage site with the group T^1,

[1271] T^1 is a group of the formula —C(═O)—OR^7, —C(═O)—NR^8R^9, —C(═O)—NH—NH—R^{10} or —CH_2—O—R^{11},

[1272] in which

[1273] R^7 is hydrogen, methyl, ethyl, n-propyl, tert-butyl, benzyl or adamantylmethyl,

[1274] R^8 is hydrogen or methyl,

[1275] R^9 is hydrogen, methyl, ethyl, n-propyl or benzyl,

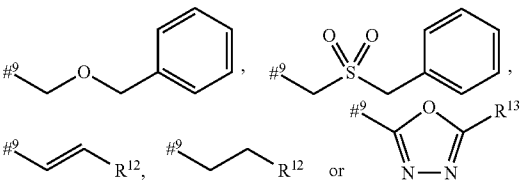
[1276] or

[1277] R^8 and R^9 together with the nitrogen atom to which they are bonded form a 4- to 7-membered heterocycle,

[1278] R^{10} is benzoyl,

[1279] R^{11} is benzyl, which may be substituted in the phenyl group by methoxycarbonyl or carboxyl,

[1280] R^5 is hydrogen, methyl or a group of the formula



[1281] in which

[1282] #9 marks the linkage site with —CHC(R^{26})-T^2,

[1283] R^{12} is phenyl which may be substituted by methoxycarbonyl, carboxyl or a group of the formula —$S(O)_2OH$,

[1284] R^{13} is phenyl which may be substituted by methoxycarbonyl or carboxyl,

[1285] R^{26} is hydrogen or hydroxy,

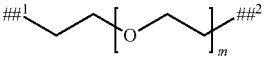
[1286] T^2 is phenyl, benzyl, 1H-indol-3-yl or 1H-indol-3-ylmethyl,

[1287] R^{35} is methyl or hydroxy,

and also their salts, solvates and solvates of the salts.

[1288] Preferred in the context of the present invention are also compounds of the formula (XXXI) in which

[1289] L^1 is a bond, linear (C_2-C_6)-alkanediyl or a group of the formula



[1290] where

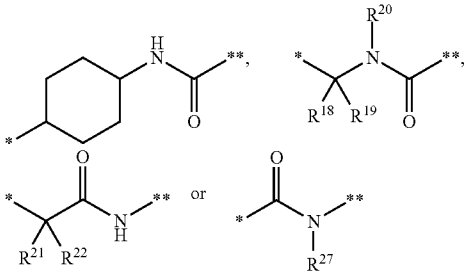
[1291] m is a number 2 or 3,

[1292] ##1 marks the linkage site with the group G,

[1293] ##2 marks the linkage site with the group B,

[1294] where (C_2-C_6)-alkanediyl may be substituted by 1 or 2 methyl substituents,

[1295] B is a bond or a group of the formula



[1296] where

[1297] * marks the linkage site with L^1,

[1298] ** marks the linkage site with L^2,

[1299] R^{18} is hydrogen,

[1300] R^{19} is methyl, propan-2-yl, 2-methylpropan-1-yl or 1-methylpropan-1-yl,

[1301] R^{20} is hydrogen or (C_1-C_4)-alkyl,

[1302] or

[1303] R^{19} and R^{20} together with the atoms to which they are bonded form a pyrrolidinyl ring,

[1304] R^{21} is hydrogen or methyl,

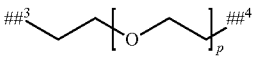
[1305] R^{22} is hydrogen or methyl,

[1306] or

[1307] R^{21} and R^{22} together with the atoms to which they are bonded form a cyclopropyl ring,

[1308] R^{27} is hydrogen or methyl,

[1309] L^2 is linear (C_2-C_6)-alkanediyl or is a group of the formula



[1310] where

[1311] p is a number 2 or 3,

[1312] ##3 marks the linkage site with the group B,

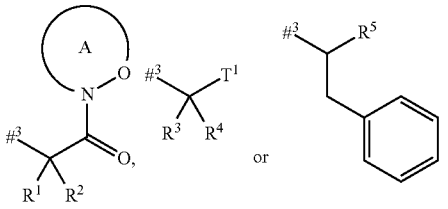
[1313] ##4 marks the linkage site with the nitrogen atom,

[1314] where (C_2-C_{10})-alkanediyl may be substituted by 1 or 2 methyl substituents,

[1315] and

[1316] where two carbon atoms of the alkanediyl chain in 1,4 relation to one another, with inclusion of any carbon atoms situated between them, may be bridged to form a phenyl ring,

[1317] D is a group of the formula



[1318] in which

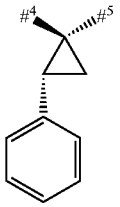
[1319] $\#^3$ marks the linkage site with the nitrogen atom,

[1320] R^1 is hydrogen,

[1321] R^2 is 1-hydroxyethyl, benzyl, 4-hydroxybenzyl, 1-phenylethyl or 1H-indol-3-yl-methyl,

[1322] or

[1323] R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula

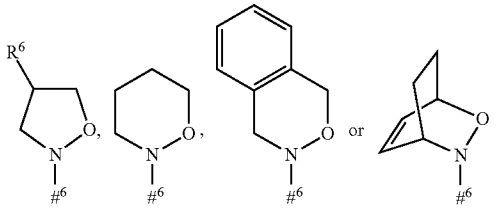


[1324] in which

[1325] $\#^4$ marks the linkage site with the adjacent nitrogen atom,

[1326] $\#^5$ marks the linkage site with the carbonyl group,

[1327] the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



[1328] in which

[1329] $\#^6$ marks the linkage site with the carbonyl group,

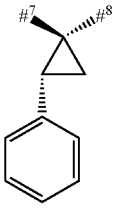
[1330] R^6 is hydrogen, hydroxy or benzyloxy,

[1331] R^3 is hydrogen,

[1332] R^4 is 1-hydroxyethyl, benzyl, 4-hydroxybenzyl, 1-phenylethyl or 1H-indol-3-yl-methyl,

[1333] or

[1334] R^3 and R^4 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropan-1,1-diyl group of the formula



[1335] in which

[1336] $\#^7$ marks the linkage site with the adjacent nitrogen atom,

[1337] $\#^8$ marks the linkage site with the group T^1,

[1338] T^1 is a group of the formula —C(═O)—OR^7, —C(═O)—NR^8R^9, —C(═O)—NH—NH—R^{10} or —CH_2—O—R^{11},

[1339] in which

[1340] R^7 is hydrogen, methyl, ethyl, n-propyl, tert-butyl, benzyl or adamantylmethyl,

[1341] R^8 is hydrogen or methyl,

[1342] R^9 is hydrogen, methyl, ethyl, n-propyl or benzyl,

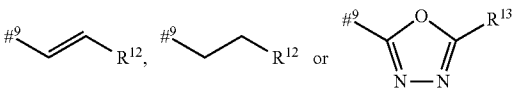
[1343] or

[1344] R^8 and R^9 together with the nitrogen atom to which they are bonded form a 4- to 7-membered heterocycle,

[1345] R^{10} is benzoyl,

[1346] R^{11} is benzyl, which may be substituted in the phenyl group by methoxycarbonyl or carboxyl,

[1347] R^5 is hydrogen, methyl or a group of the formula



[1348] in which

[1349] $\#^9$ marks the linkage site with —$CHCH_2$phenyl,

[1350] R^{12} is phenyl which may be substituted by methoxycarbonyl, carboxyl or a group of the formula —$S(O)_2OH$,

[1351] R^{13} is phenyl which may be substituted by methoxycarbonyl or carboxyl,

[1352] R^{35} is methyl or hydroxy,

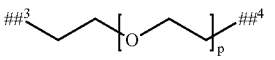
and also their salts, solvates and solvates of the salts.

[1353] Particularly preferred in the context of the present invention are also compounds of the formula (XXXI) in which

[1354] L^1 is a bond,

[1355] B is a bond,

[1356] L^2 is linear (C_2-C_6)-alkanediyl or is a group of the formula



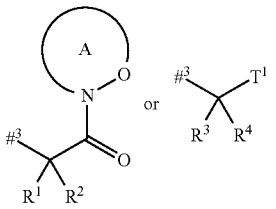
[1357] where

[1358] p is a number 2 or 3,

[1359] $\#\#^3$ marks the linkage site with the group B,

[1360] $\#\#^4$ marks the linkage site with the nitrogen atom,

[1361] D is the group of the formula



[1362] where

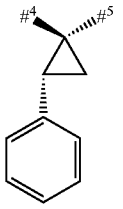
[1363] $\#^3$ marks the linkage site with the nitrogen atom,

[1364] R^1 is hydrogen,

[1365] R^2 is benzyl or 1H-indol-3-ylmethyl,

[1366] or

[1367] R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula

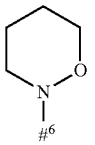


[1368] in which

[1369] $\#^4$ marks the linkage site with the adjacent nitrogen atom,

[1370] $\#^5$ marks the linkage site with the carbonyl group,

[1371] the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



[1372] in which

[1373] $\#^6$ marks the linkage site with the carbonyl group,

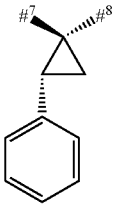
[1374] R^6 is hydrogen, hydroxy or benzyloxy,

[1375] R^3 is hydrogen,

[1376] R^4 is benzyl or 1H-indol-3-ylmethyl,

[1377] or

[1378] R^3 and R^4 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula



[1379] in which

[1380] $\#^7$ marks the linkage site with the adjacent nitrogen atom,

[1381] $\#^8$ marks the linkage site with the group T^1,

[1382] T^1 is a group of the formula —C(═O)—OR^7 or —C(═O)—NR^8R^9,

[1383] in which

[1384] R^7 is hydrogen,

[1385] R^8 is hydrogen,

[1386] R^9 is hydrogen,

[1387] R^{35} is methyl,

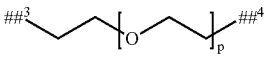
and also their salts, solvates and solvates of the salts.

[1388] Preferred subject matter of the present invention are compounds of the formula (XXXI) as indicated above, in which

[1389] L^1 is a bond,

[1390] B is a bond,

[1391] L^2 is linear (C_2-C_6)-alkanediyl or is a group of the formula



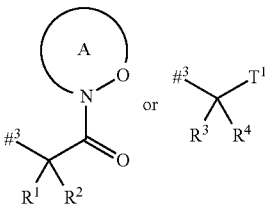
[1392] where

[1393] p is a number 2 or 3,

[1394] $\#\#^3$ marks the linkage site with the group B,

[1395] $\#\#^4$ marks the linkage site with the nitrogen atom,

[1396] D is a group of the formula



[1397] where

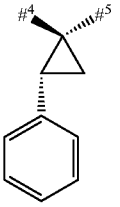
[1398] $\#^3$ marks the linkage site with the nitrogen atom,

[1399] R^1 is hydrogen,

[1400] R^2 is benzyl, 4-hydroxybenzyl or 1H-indol-3-ylmethyl,

[1401] or

[1402] R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula

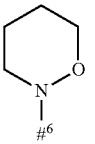


[1403] in which

[1404] #4 marks the linkage site with the adjacent nitrogen atom,

[1405] #5 marks the linkage site with the carbonyl group,

[1406] the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



[1407] in which

[1408] #6 marks the linkage site with the carbonyl group,

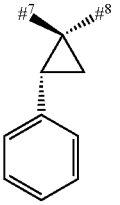
[1409] R^6 is hydrogen, hydroxy or benzyloxy,

[1410] R^3 is hydrogen,

[1411] R^4 is benzyl, 4-hydroxybenzyl or 1H-indol-3-ylmethyl,

[1412] or

[1413] R^3 and R^4 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula



[1414] in which

[1415] #7 marks the linkage site with the adjacent nitrogen atom,

[1416] #8 marks the linkage site with the group T^1,

[1417] T^1 is a group of the formula —C(═O)—OR^7 or —C(═O)—NR^8R^9,

[1418] in which

[1419] R^7 is hydrogen,

[1420] R^8 is hydrogen,

[1421] R^9 is hydrogen,

[1422] R^{35} is methyl,

and also their salts, solvates and solvates of the salts.

[1423] Particularly preferred are the following compounds of the formulae (XXXa) and (XXXI) selected from the following group:

[1424] N-[6-(3-{[(2R)-2-amino-2-carboxyethyl]sulphanyl}-2,5-dioxopyrrolidin-1-yl)hexyl]-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(1S)-1-carboxy-2-(1H-indol-3-yl)ethyl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide,

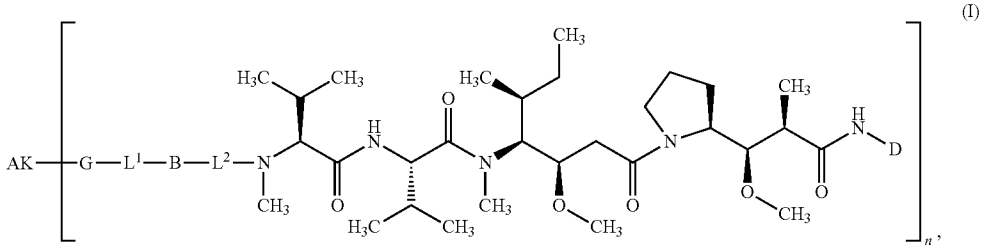
[1425] N-[6-(3-{[(2R)-2-amino-2-carboxyethyl]sulphanyl}-2,5-dioxopyrrolidin-1-yl)hexyl]-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide,

[1426] N-(6-{[(5S)-5-amino-5-carboxypentyl]amino}-6-oxohexyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide trifluoroacetate,

[1427] N-(6-{[(5S)-5-amino-5-carboxypentyl]amino}-6-oxohexyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(1S)-1-carboxy-2-(1H-indol-3-yl)ethyl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide,

and also their salts, solvates and solvates of the salts.

[1428] The present invention additionally provides binder-drug conjugates of the general formula (I)



in which

[1429] n is a number from 1 to 50,

[1430] AK is a binder,

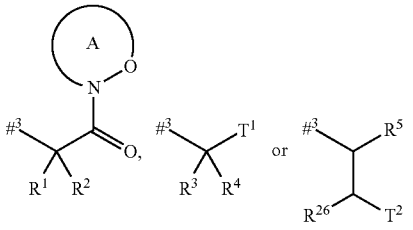
[1431] the group §-G-L^1-B-L^2-§§ is a linker,

[1432] where

[1433] § marks the linkage site with the group AK and

[1434] §§ marks the linkage site with the nitrogen atom,

[1435] D is a group of the formula



[1436] where

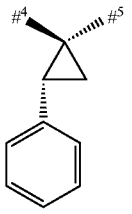
[1437] #3 marks the linkage site with the nitrogen atom,

[1438] R^1 is hydrogen,

[1439] R^2 is 1-hydroxyethyl, benzyl, 1-phenylethyl or 1H-indol-3-ylmethyl,

[1440] or

[1441] R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula

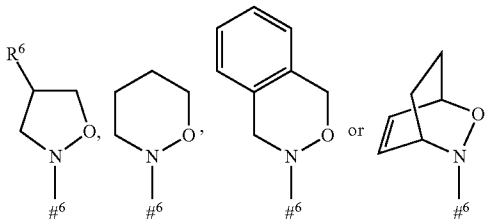


[1442] in which

[1443] #4 marks the linkage site with the adjacent nitrogen atom,

[1444] #5 marks the linkage site with the carbonyl group,

[1445] the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



[1446] in which

[1447] #6 marks the linkage site with the carbonyl group,

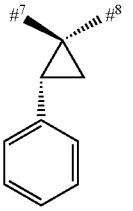
[1448] R^6 is hydrogen, hydroxy or benzyloxy,

[1449] R^3 is hydrogen,

[1450] R^4 1-hydroxyethyl, benzyl, 1-phenylethyl or 1H-indol-3-ylmethyl,

[1451] or

[1452] R^3 and R^4 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula



[1453] in which

[1454] #7 marks the linkage site with the adjacent nitrogen atom,

[1455] #8 marks the linkage site with the group T^1,

[1456] T^1 is a group of the formula —C(═O)—OR^7, —C(═O)—NR^8R^9, —C(═O)—NH—NH—R^{10} or —CH_2—O—R^{11},

[1457] in which

[1458] R^7 is hydrogen, methyl, ethyl, n-propyl, tert-butyl, benzyl or adamantylmethyl,

[1459] R^8 is hydrogen or methyl,

[1460] R^9 is hydrogen, methyl, ethyl, n-propyl or benzyl,

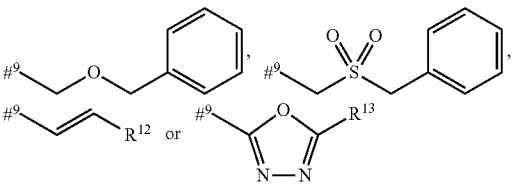
[1461] or

[1462] R^8 and R^9 together with the nitrogen atom to which they are bonded form a 4- to 7-membered heterocycle,

[1463] R^{10} is benzoyl,

[1464] R^{11} is benzyl, which may be substituted in the phenyl group by methoxycarbonyl or carboxyl,

[1465] R^5 is hydrogen, methyl or a group of the formula



[1466] in which

[1467] #9 marks the linkage site with —CHC(R^{26})-T^2,

[1468] R^{12} is phenyl which may be substituted by methoxycarbonyl, carboxyl or a group of the formula —$S(O)_2OH$,

[1469] R^{13} is phenyl which may be substituted by methoxycarbonyl or carboxyl,

[1470] R^{26} is hydrogen or hydroxy,

[1471] T^2 is phenyl, benzyl, 1H-indol-3-yl or 1H-indol-3-ylmethyl,

and also their salts, solvates and solvates of the salts.

[1472] Preferred subject matter of the invention are binder-drug conjugates of the general formula (I), in which

[1473] n is a number from 1 to 50,

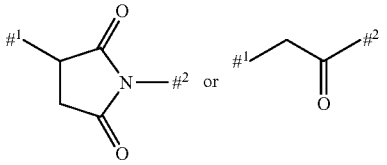
[1474] AK is AK_1 or AK_2

[1475] where

[1476] AK_1 is a binder which is bonded via a sulphur atom of the binder to the group G,

[1477] AK_2 is a binder which is bonded via a nitrogen atom of the binder to the group G,

[1478] G when $AK=AK_1$, is a group of the formula



[1479] where

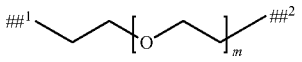
[1480] $\#^1$ marks the linkage site with the sulphur atom of the binder,

[1481] $\#^2$ marks the linkage site with the group L^1,

[1482] or

[1483] when $AK=AK_2$, is carbonyl,

[1484] L^1 is a bond, linear $(C_1\text{-}C_{10})$-alkanediyl or is a group of the formula



[1485] where

[1486] m is a number from 2 to 6,

[1487] $\#\#^1$ marks the linkage site with the group G,

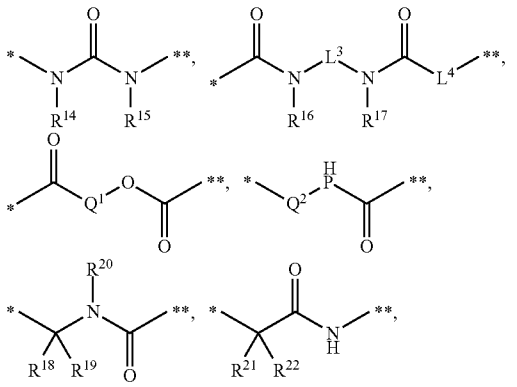
[1488] $\#\#^2$ marks the linkage site with the group B,

[1489] where $(C_1\text{-}C_{10})$-alkanediyl may be substituted by 1 to 4 methyl substituents,

[1490] and

[1491] where two carbon atoms of the alkanediyl chain in 1,2, 1,3 or 1,4 relation to one another, with inclusion of any carbon atoms situated between them, may be bridged to form a $(C_3\text{-}C_6)$-cycloalkyl ring or a phenyl ring,

[1492] B is a bond or a group of the formula



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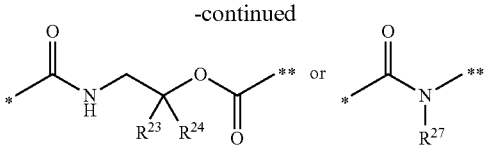


[1493] where

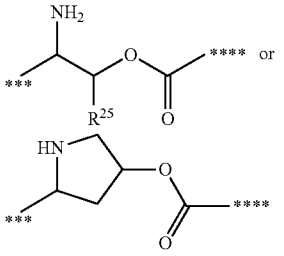
[1494] * marks the linkage site with L^1,

[1495] ** marks the linkage site with L^2,

[1496] P is O or NH,

[1497] L^3 is a bond or $(C_2\text{-}C_4)$-alkanediyl,

[1498] L^4 is a bond or a group of the formula



[1499] in which

[1500] *** marks the linkage site with the carbonyl group,

[1501] **** marks the linkage site with L^2,

[1502] R^{25} is hydrogen or methyl,

[1503] Q^1 is a 4- to 7-membered heterocycle,

[1504] Q^2 is a 3- to 7-membered carbocycle or a 4- to 7-membered heterocycle,

[1505] R^{14} is hydrogen or $(C_1\text{-}C_4)$-alkyl,

[1506] R^{15} is hydrogen or $(C_1\text{-}C_4)$-alkyl,

[1507] or

[1508] R^{14} and R^{15} together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

[1509] R^{16} is hydrogen or $(C_1\text{-}C_4)$-alkyl,

[1510] R^{17} is hydrogen or $(C_1\text{-}C_4)$-alkyl,

[1511] or

[1512] R^{16} and R^{17} together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

[1513] R^{18} is hydrogen or $(C_1\text{-}C_4)$-alkyl,

[1514] R^{19} is hydrogen or the side group of a natural α-amino acid or of its homologues or isomers,

[1515] R^{20} is hydrogen or $(C_1\text{-}C_4)$-alkyl,

[1516] or

[1517] R^{19} and R^{20} together with the atoms to which they are bonded form a pyrrolidinyl ring,

[1518] R^{21} is hydrogen or $(C_1\text{-}C_4)$-alkyl,

[1519] R^{22} is hydrogen or $(C_1\text{-}C_4)$-alkyl,

[1520] or

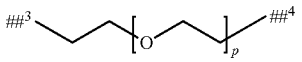
[1521] R^{21} and R^{22} together with the atoms to which they are bonded form a 3- to 7-membered carbocycle,

[1522] R^{23} is $(C_1\text{-}C_4)$-alkyl,

[1523] R^{24} is hydrogen or $(C_1\text{-}C_4)$-alkyl,

[1524] R^{27} is hydrogen or $(C_1\text{-}C_4)$-alkyl,

[1525] L^2 is linear $(C_2\text{-}C_{10})$-alkanediyl or is a group of the formula



[1526] where

[1527] p is a number from 2 to 6,

[1528] ##3 marks the linkage site with the group B,

[1529] ##4 marks the linkage site with the nitrogen atom,

[1530] where (C_2-C_{10})-alkanediyl may be substituted by 1 to 4 methyl substituents, and

[1531] where two carbon atoms of the alkanediyl chain in 1,2, 1,3 or 1,4 relation to one another, with inclusion of any carbon atoms situated between them, may be bridged to form a (C_3-C_6)-cycloalkyl ring or a phenyl ring,

[1532] D has the definitions indicated above,

and also their salts, solvates and solvates of the salts.

[1533] Preferred subject matter of the invention are binder-drug conjugates of the general formula (I),

in which

[1534] n is a number from 1 to 50,

[1535] AK is AK_1 or AK_2

[1536] where

[1537] AK_1 is an antibody or an antigen-binding antibody fragment and are bonded via a sulphur atom to the group G,

[1538] AK_2 is an antibody or an antigen-binding antibody fragment and are bonded via a nitrogen atom to the group G,

[1539] G, L^1, B, L^2 and D have the definitions indicated above,

and also their salts, solvates and solvates of the salts.

[1540] Preferred subject matter of the present invention are binder-drug conjugates of the general formula (I), in which

[1541] n is a number from 1 to 20,

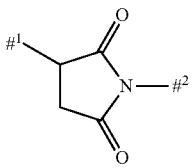
[1542] AK is AK_1 or AK_2

[1543] where

[1544] AK_1 is an antibody or an antigen-binding antibody fragment which binds to mesothelin and is bonded via the sulphur atom of a cysteine residue of the binder to the group G,

[1545] AK_2 is an antibody or an antigen-binding antibody fragment which binds to mesothelin and is bonded via the NH side group of a lysine residue of the binder to the group G,

[1546] G when $AK=AK_1$, is a group of the formula



[1547] in which

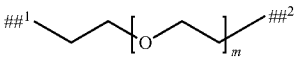
[1548] #1 marks the linkage site with the cysteine residue of the binder,

[1549] #2 marks the linkage site with the group L^1,

[1550] or

[1551] when $AK=AK_2$, is carbonyl,

[1552] L^1 is a bond, linear (C_2-C_6)-alkanediyl or is a group of the formula



[1553] where

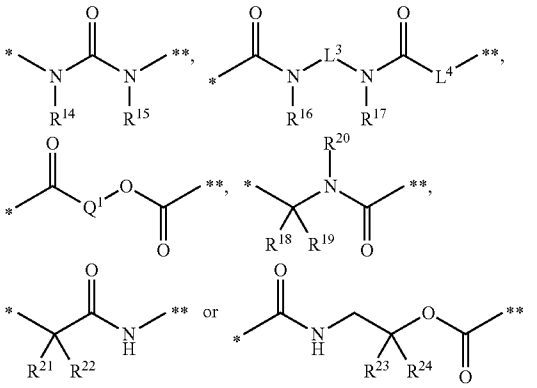
[1554] m is a number from 2 to 6,

[1555] ##1 marks the linkage site with the group G,

[1556] ##2 marks the linkage site with the group B,

[1557] where (C_2-C_6)-alkanediyl may be substituted by 1 or 2 methyl substituents,

[1558] B is a bond or a group of the formula



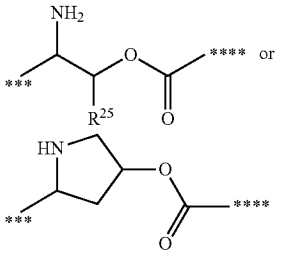
[1559] where

[1560] * marks the linkage site with L^1,

[1561] ** marks the linkage site with L^2,

[1562] L^3 is a bond or ethane-1,2-diyl,

[1563] L^4 is a bond or a group of the formula



[1564] in which

[1565] *** marks the linkage site with the carbonyl group,

[1566] **** marks the linkage site with L^2,

[1567] R^{25} is methyl,

[1568] Q^1 is a 4- to 6-membered carbocycle or piperidine-1,4-diyl,

[1569] R^{14} is hydrogen,

[1570] R^{15} is hydrogen,

[1571] R^{16} is hydrogen or methyl,

[1572] R^{17} is hydrogen or methyl,

[1573] or

[1574] R^{16} and R^{17} together with the atoms to which they are bonded form a piperazinyl ring,

[1575] R^{18} is hydrogen,

[1576] R^{19} is hydrogen, methyl, propan-2-yl, 2-methylpropan-1-yl or 1-methylpropan-1-yl,

[1577] R^{20} is hydrogen or methyl,

[1578] or

[1579] R^{19} and R^{20} together with the atoms to which they are bonded form a pyrrolidinyl ring,

[1580] R^{21} is hydrogen or methyl,

[1581] R^{22} is hydrogen or methyl,

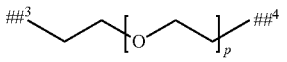
[1582] or

[1583] R^{21} and R^{22} together with the atoms to which they are bonded form a cyclopropyl ring,

[1584] R^{23} is methyl,

[1585] R^{24} is hydrogen or methyl,

[1586] L^2 is linear (C_2-C_6)-alkanediyl or is a group of the formula



[1587] where

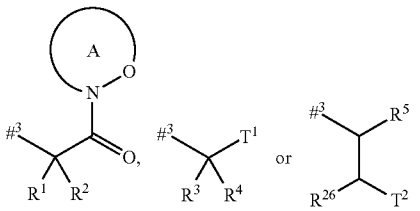
[1588] p is a number from 2 to 6,

[1589] $\#\#^3$ marks the linkage site with the group B,

[1590] $\#\#^4$ marks the linkage site with the nitrogen atom,

[1591] where (C_2-C_6)-alkanediyl may be substituted by 1 or 2 methyl substituents,

[1592] D is a group of the formula



[1593] where

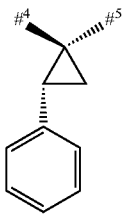
[1594] $\#^3$ marks the linkage site with the nitrogen atom,

[1595] R^1 is hydrogen,

[1596] R^2 is 1-hydroxyethyl, benzyl, 1-phenylethyl or 1H-indol-3-ylmethyl,

[1597] or

[1598] R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula

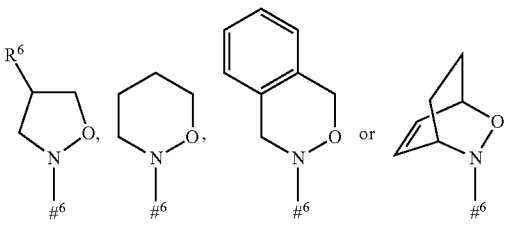


[1599] in which

[1600] $\#^4$ marks the linkage site with the adjacent nitrogen atom,

[1601] $\#^5$ marks the linkage site with the carbonyl group,

[1602] the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



[1603] in which

[1604] $\#^6$ marks the linkage site with the carbonyl group,

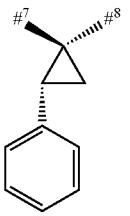
[1605] R^6 is hydrogen, hydroxy or benzyloxy,

[1606] R^3 is hydrogen,

[1607] R^4 is 1-hydroxyethyl, benzyl, 1-phenylethyl or 1H-indol-3-ylmethyl,

[1608] or

[1609] R^3 and R^4 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula



[1610] in which

[1611] $\#^7$ marks the linkage site with the adjacent nitrogen atom,

[1612] $\#^8$ marks the linkage site with the group T^1,

[1613] T^1 is a group of the formula —C(=O)—OR^7, —C(=O)—NR^8R^9, —C(=O)—NH—NH—R^{10} or —CH_2—O—R^{11},

[1614] in which

[1615] R^7 is hydrogen, methyl, ethyl, n-propyl, tert-butyl, benzyl or adamantylmethyl,

[1616] R^8 is hydrogen or methyl,

[1617] R^9 is hydrogen, methyl, ethyl, n-propyl or benzyl,

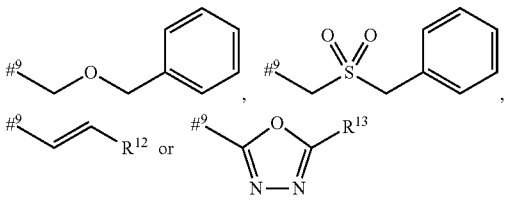
[1618] or

[1619] R^8 and R^9 together with the nitrogen atom to which they are bonded form a 4- to 7-membered heterocycle,

[1620] R^{10} is benzoyl,

[1621] R^{11} is benzyl, which may be substituted in the phenyl group by methoxycarbonyl or carboxyl,

[1622] R^5 is hydrogen, methyl or a group of the formula



[1623] in which

[1624] $\#^9$ marks the linkage site with —CHC(R^{26})-T^2,

[1625] R^{12} is phenyl which may be substituted by methoxycarbonyl, carboxyl or a group of the formula —$S(O)_2OH$,

[1626] R^{13} is phenyl which may be substituted by methoxycarbonyl or carboxyl,

[1627] R^{26} is hydrogen or hydroxy,

[1628] T^2 is phenyl, benzyl, 1H-indol-3-yl or 1H-indol-3-ylmethyl,

and also their salts, solvates and solvates of the salts.

[1629] Particularly preferred subject matter of the present invention are binder-drug conjugates of the general formula (I), in which

[1630] n is a number from 1 to 10,

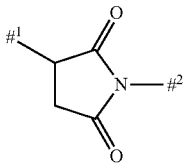
[1631] AK is AK_1 or AK_2

[1632] where

[1633] AK_1 is an antibody which comprises the six CDR sequences of the antibody MF-Ta, the variable light and variable heavy chain of the antibody MF-Ta or the light and heavy chain of the antibody MF-Ta, and is bonded via the sulphur atom of a cysteine residue of the binder to the group G,

[1634] AK_2 is an antibody which comprises the six CDR sequences of the antibody MF-Ta, the variable light and variable heavy chain of the antibody MF-Ta or the light and heavy chain of the antibody MF-Ta, and is bonded via the NH side group of a lysine residue of the binder to the group G,

[1635] G when AK=AK_1, is a group of the formula



[1636] in which

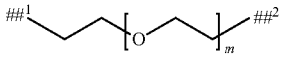
[1637] $\#^1$ marks the linkage site with the cysteine residue of the binder,

[1638] $\#^2$ marks the linkage site with the group L^1,

[1639] or

[1640] when AK=AK_2, is carbonyl,

[1641] L^1 is a bond, linear (C_2-C_6)-alkanediyl or is a group of the formula



[1642] where

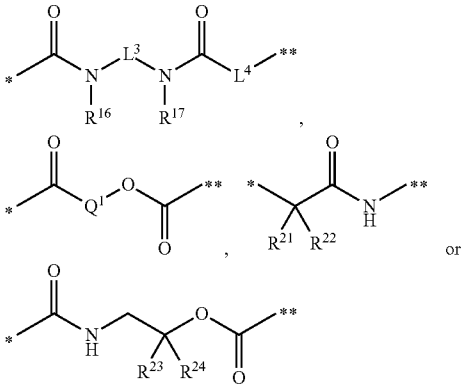
[1643] m is a number 2 or 3,

[1644] $\#\#^1$ marks the linkage site with the group G,

[1645] $\#\#^2$ marks the linkage site with the group B,

[1646] where (C_2-C_6)-alkanediyl may be substituted by 1 or 2 methyl substituents,

[1647] B is a bond or a group of the formula



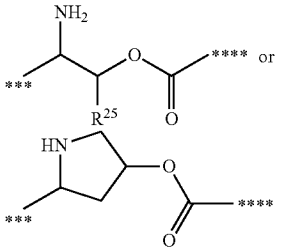
[1648] where

[1649] * marks the linkage site with L^1,

[1650] ** marks the linkage site with L^2,

[1651] L^3 is a bond or ethane-1,2-diyl,

[1652] L^4 is a bond or a group of the formula



[1653] where

[1654] *** marks the linkage site with the carbonyl group,

[1655] **** marks the linkage site with L^2,

[1656] R^{25} is methyl,

[1657] Q^1 is piperidine-1,4-diyl,

[1658] R^{16} is hydrogen or methyl,

[1659] R^{17} is hydrogen or methyl,

[1660] or

[1661] R^{16} and R^{17} together with the atoms to which they are bonded form a piperazinyl ring,

[1662] R^{21} is hydrogen or methyl,

[1663] R^{22} is hydrogen or methyl,

[1664] or

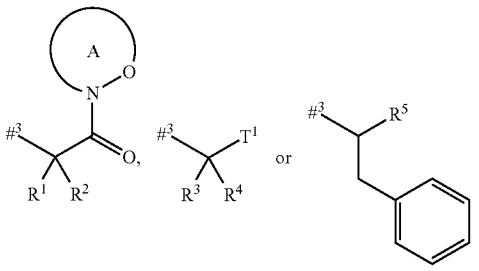
[1665] R^{21} and R^{22} together with the atoms to which they are bonded form a cyclopropyl ring,

[1666] R^{23} is methyl,

[1667] R^{24} is hydrogen,

[1668] L^2 is linear (C_2-C_6)-alkanediyl,

[1669] D is a group of the formula



[1670] where

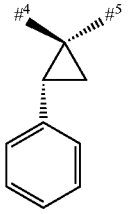
[1671] $\#^3$ marks the linkage site with the nitrogen atom,

[1672] R^1 is hydrogen,

[1673] R^2 is 1-hydroxyethyl, benzyl, 1-phenylethyl or 1H-indol-3-ylmethyl,

[1674] or

[1675] R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula

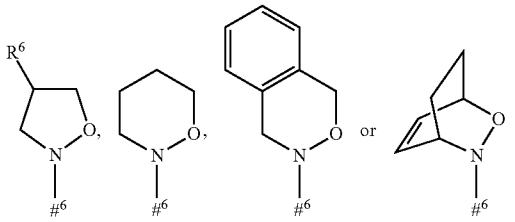


[1676] in which

[1677] $\#^4$ marks the linkage site with the adjacent nitrogen atom,

[1678] $\#^5$ marks the linkage site with the carbonyl group,

[1679] the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



[1680] in which

[1681] $\#^6$ marks the linkage site with the carbonyl group,

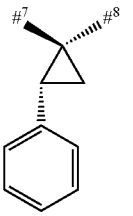
[1682] R^6 is hydrogen, hydroxy or benzyloxy,

[1683] R^3 is hydrogen,

[1684] R^4 is benzyl, 1-phenylethyl or 1H-indol-3-ylmethyl,

[1685] or

[1686] R^3 and R^4 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula



[1687] in which

[1688] $\#^7$ marks the linkage site with the adjacent nitrogen atom,

[1689] $\#^8$ marks the linkage site with the group T,

[1690] T^1 is a group of the formula —C(═O)—OR^7, —C(═O)—NR^8R^9 or —CH_2—O—R^{11}, in which

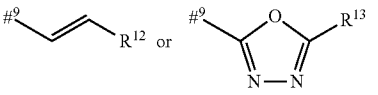
[1691] R^7 is hydrogen, methyl, ethyl, n-propyl, benzyl or adamantylmethyl,

[1692] R^8 is hydrogen or methyl,

[1693] R^9 is hydrogen, methyl, ethyl, n-propyl or benzyl,

[1694] R^{11} is benzyl, which may be substituted in the phenyl group by methoxycarbonyl or carboxyl,

[1695] R^5 is hydrogen or a group of the formula



[1696] in which

[1697] $\#^9$ marks the linkage site with —CHC(R^{26}) phenyl,

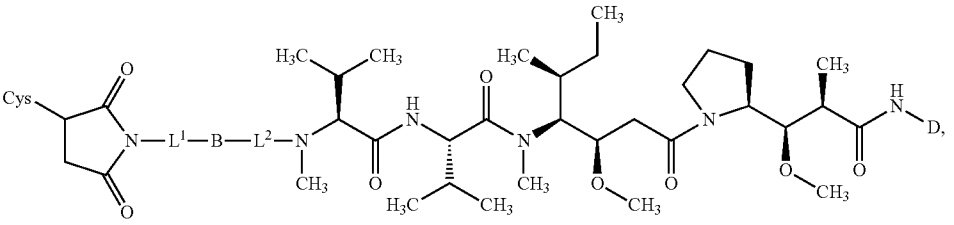
[1698] R^{12} is phenyl which may be substituted by methoxycarbonyl, carboxyl or a group of the formula —$S(O)_2OH$,

[1699] R^{13} is phenyl which may be substituted by methoxycarbonyl or carboxyl,

and also their salts, solvates and solvates of the salts.

[1700] The present invention additionally provides compounds of the formula (XXX)

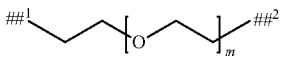
(XXX)



in which

[1701] Cys is a cysteine residue which is bonded via the sulphur atom of the side chain to a carbon atom of the succinimide.

[1702] L^1 is a bond, linear (C_1-C_{10})-alkanediyl or is a group of the formula



[1703] in which

[1704] m is a number from 2 to 6,

[1705] $\#\#^1$ marks the linkage site with the group G,

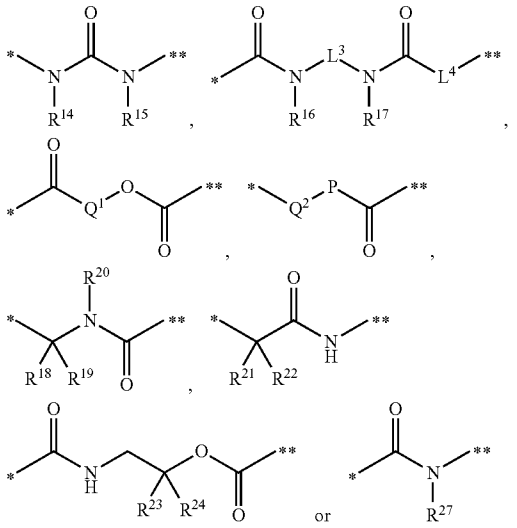
[1706] $\#\#^2$ marks the linkage site with the group B,

[1707] where (C_1-C_{10})-alkandiyl may be substituted by 1 to 4 methyl substituents,

[1708] and

[1709] where two carbon atoms of the alkanediyl chain in 1,2, 1,3 or 1,4 relation to one another, with inclusion of any carbon atoms situated between them, may be bridged to form a (C_3-C_6)-cycloalkyl ring or a phenyl ring,

[1710] B is a bond or a group of the formula



[1711] where

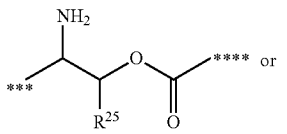
[1712] * marks the linkage site with L^1,

[1713] ** marks the linkage site with L^2,

[1714] P is O or NH,

[1715] L^3 is a bond or (C_2-C_4)-alkanediyl,

[1716] L^4 is a bond or a group of the formula



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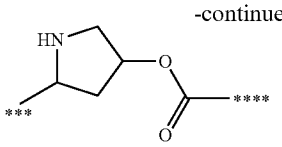


[1717] in which

[1718] *** marks the linkage site with the carbonyl group,

[1719] **** marks the linkage site with L^2,

[1720] R^{25} is hydrogen or methyl

[1721] Q^1 is a 3- to 7-membered carbocycle or a 4- to 7-membered aza heterocycle,

[1722] Q^2 is a 3- to 7-membered carbocycle or a 4- to 7-membered aza heterocycle,

[1723] R^{14} is hydrogen or (C_1-C_4)-alkyl,

[1724] R^{15} is hydrogen or (C_1-C_4)-alkyl,

[1725] or

[1726] R^{14} and R^{15} together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

[1727] R^{16} is hydrogen or (C_1-C_4)-alkyl,

[1728] R^{17} is hydrogen or (C_1-C_4)-alkyl,

[1729] or

[1730] R^{16} and R^{17} together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

[1731] R^{18} is hydrogen or (C_1-C_4)-alkyl,

[1732] R^{19} is hydrogen or the side group of a natural α-amino acid or of its homologues or isomers,

[1733] R^{20} is hydrogen or (C_1-C_4)-alkyl,

[1734] or

[1735] R^{19} and R^{20} together with the atoms to which they are bonded form a pyrrolidinyl ring,

[1736] R^{21} is hydrogen or (C_1-C_4)-alkyl,

[1737] R^{22} is hydrogen or (C_1-C_4)-alkyl,

[1738] or

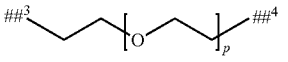
[1739] R^{21} and R^{22} together with the atoms to which they are bonded form a 3- to 7-membered carbocycle,

[1740] R^{23} is (C_1-C_4)-alkyl,

[1741] R^{24} is hydrogen or (C_1-C_4)-alkyl,

[1742] R^{27} is hydrogen or (C_1-C_4)-alkyl,

[1743] L^2 is linear (C_2-C_{10})-alkanediyl or is a group of the formula



[1744] where

[1745] p is a number from 2 to 6,

[1746] $\#\#^3$ marks the linkage site with the group B,

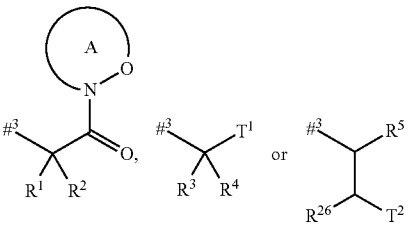
[1747] $\#\#^4$ marks the linkage site with the nitrogen atom,

[1748] where (C_2-C_{10})-alkanediyl may be substituted by 1 to 4 substituents,

[1749] and

[1750] where two carbon atoms of the alkanediyl chain in 1,2, 1,3 or 1,4 relation to one another, with inclusion of any carbon atoms situated between them, may be bridged to form a (C_3-C_6)-cycloalkyl ring or a phenyl ring,

[1751] D is a group of the formula



[1752] in which

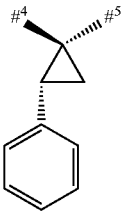
[1753] #3 marks the linkage site with the nitrogen atom,

[1754] R1 is hydrogen,

[1755] R2 is 1-hydroxyethyl, benzyl, 1-phenylethyl or 1H-indol-3-ylmethyl,

[1756] or

[1757] R1 and R2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula

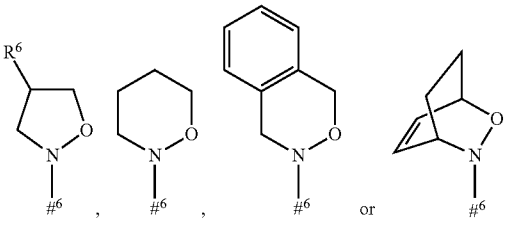


[1758] in which

[1759] #4 marks the linkage site with the adjacent nitrogen atom,

[1760] #5 marks the linkage site with the carbonyl group,

[1761] the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



[1762] in which

[1763] #6 marks the linkage site with the carbonyl group,

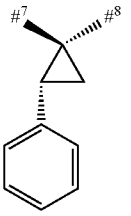
[1764] R6 is hydrogen, hydroxy or benzyloxy,

[1765] R3 is hydrogen,

[1766] R4 is 1-hydroxyethyl, benzyl, 1-phenylethyl or 1H-indol-3-ylmethyl,

[1767] or

[1768] R3 and R4 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula



[1769] in which

[1770] #7 marks the linkage site with the adjacent nitrogen atom,

[1771] #8 marks the linkage site with the group T1,

[1772] T1 is a group of the formula —C(═O)—OR7, —C(═O)—NR8R9, —C(═O)—NH—NH—R10 or —CH2—O—R11, in which

[1773] R7 is hydrogen, methyl, ethyl, n-propyl, tert-butyl, benzyl or adamantylmethyl,

[1774] R8 is hydrogen or methyl,

[1775] R9 is hydrogen, methyl, ethyl, n-propyl or benzyl,

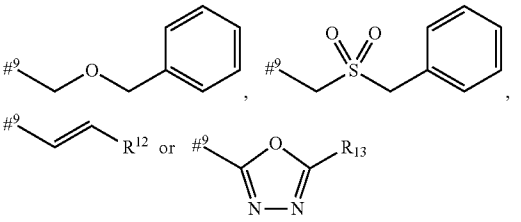
[1776] or

[1777] R8 and R9 together with the nitrogen atom to which they are bonded form a 4- to 7-membered heterocycle,

[1778] R10 is benzoyl,

[1779] R11 is benzyl, which may be substituted in the phenyl group by methoxycarbonyl or carboxyl,

[1780] R5 is hydrogen, methyl or a group of the formula



[1781] in which

[1782] #9 marks the linkage site with —CHC(R26)-T2,

[1783] R12 is phenyl which may be substituted by methoxycarbonyl, carboxyl or a group of the formula —S(O)2OH,

[1784] R13 is phenyl which may be substituted by methoxycarbonyl or carboxyl,

[1785] R26 is hydrogen or hydroxy,

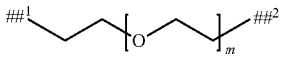
[1786] T2 is phenyl, benzyl, 1H-indol-3-yl or 1H-indol-3-ylmethyl,

and also their salts, solvates and solvates of the salts.

[1787] Particularly preferred in the context of the present invention in addition are also compounds of the formula (XXX), in which

[1788] Cys is a cysteine residue which is bonded via the sulphur atom of the side chain via a carbon atom of the succinimide,

[1789] L1 is a bond, linear (C2-C6)-alkanediyl or is a group of the formula



[1790] in which

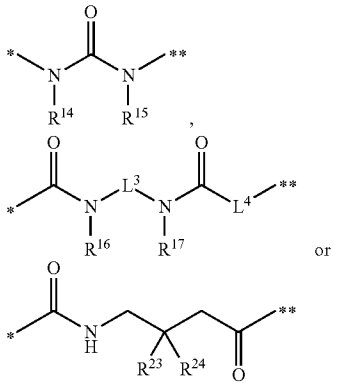
[1791] m is a number from 2 to 6,

[1792] ##[1] marks the linkage site with the group G,

[1793] ##[2] marks the linkage site with the group B,

[1794] where (C_2-C_6)-alkandiyl may be substituted by 1 or 2 methyl substituents,

[1795] B is a bond or a group of the formula



[1796] where

[1797] * marks the linkage site with L^1,

[1798] ** marks the linkage site with L^2,

[1799] L^3 is a bond or ethane-1,2-diyl,

[1800] L^4 is a bond,

[1801] R^{14} is hydrogen,

[1802] R^{15} is hydrogen,

[1803] R^{16} is hydrogen or methyl,

[1804] R^{17} is hydrogen or methyl,

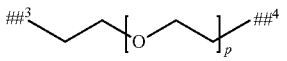
[1805] or

[1806] R^{16} and R^{17} together with the atoms to which they are bonded form a piperazinyl ring,

[1807] R^{23} is methyl,

[1808] R^{24} is hydrogen or methyl,

[1809] L^2 is linear (C_2-C_6)-alkanediyl or is a group of the formula



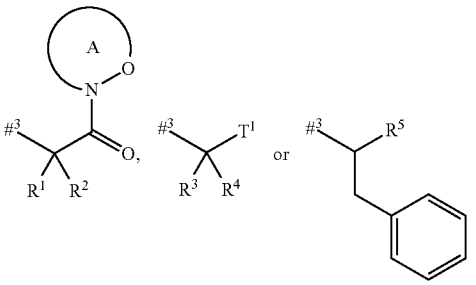
[1810] where

[1811] p is a number 2 or 3,

[1812] ##[3] marks the linkage site with the group B,

[1813] ##[4] marks the linkage site with the nitrogen atom,

[1814] D is a group of the formula



[1815] in which

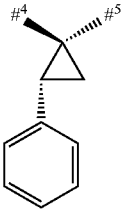
[1816] #[3] marks the linkage site with the nitrogen atom,

[1817] R^1 is hydrogen,

[1818] R^2 is 1-hydroxyethyl, benzyl, 1-phenylethyl or 1H-indol-3-ylmethyl,

[1819] or

[1820] R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula

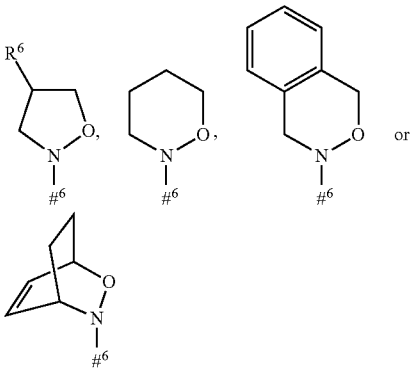


[1821] in which

[1822] #[4] marks the linkage site with the adjacent nitrogen atom,

[1823] #[5] marks the linkage site with the carbonyl group,

[1824] the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



[1825] in which

[1826] #6 marks the linkage site with the carbonyl group,

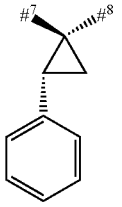
[1827] R^6 is hydrogen, hydroxy or benzyloxy,

[1828] R^3 is hydrogen,

[1829] R^4 is benzyl, 1-phenylethyl or 1H-indol-3-ylmethyl,

[1830] or

[1831] R^3 and R^4 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula



[1832] in which

[1833] #7 marks the linkage site with the adjacent nitrogen atom,

[1834] #8 marks the linkage site with the group T,

[1835] T^1 is a group of the formula —C(═O)—OR^7, —C(═O)—NR^8R^9, —C(═O)—NH—NH—R^{10} or —CH_2—O—R^{11},

[1836] in which

[1837] R^7 is hydrogen, methyl, ethyl, n-propyl, benzyl or adamantylmethyl,

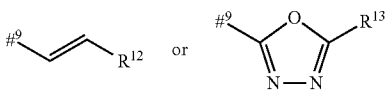
[1838] R^8 is hydrogen or methyl,

[1839] R^9 is hydrogen, methyl, ethyl, n-propyl or benzyl,

[1840] R^{10} is benzoyl,

[1841] R^{11} is benzyl, which may be substituted in the phenyl group by methoxycarbonyl or carboxyl,

[1842] R^5 is hydrogen or a group of the formula



[1843] in which

[1844] #9 marks the linkage site with —CHC(R^{26})phenyl,

[1845] R^{12} is phenyl which may be substituted by methoxycarbonyl, carboxyl or a group of the formula —$S(O)_2OH$,

[1846] R^{13} is phenyl which may be substituted by methoxycarbonyl or carboxyl,

and also their salts, solvates and solvates of the salts.

[1847] Preferred in the context of the present invention are also compounds of the formula (Ia), in which

n=1-20, more preferably n=1-10 and very preferably n=2-8.

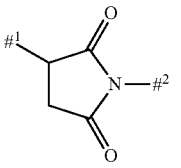
[1848] Preferred in the context of the present invention are also compounds of the formula (Ia), in which

[1849] AK is AK_1

[1850] where

[1851] AK_1 is an antibody or an antigen-binding antibody fragment which binds to mesothelin and is bonded via the sulphur atom of a cysteine residue of the binder to the group G,

[1852] G is a group of the formula



[1853] where

[1854] #1 marks the linkage site with the cysteine residue of the binder,

[1855] #2 marks the linkage site with the group L^1,

and

[1856] n, L^1, B, L^2, D and R^{35} have the definitions indicated above,

and also their salts, solvates and solvates of the salts.

[1857] Preferred in the context of the present invention are also compounds of the formula (Ia), in which

[1858] AK is AK_2

[1859] where

[1860] AK_2 is an antibody or an antigen-binding antibody fragment which binds to mesothelin and is bonded via the NH side group of a lysine residue of the binder to the group G,

[1861] G is carbonyl,

and

[1862] n, L^1, B, L^2, D and R^{35} have the definitions indicated above,

and also their salts, solvates and solvates of the salts.

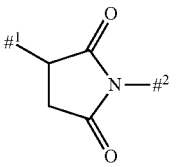
[1863] Preference in the context of the present invention is also given to compounds of the formula (Ia), in which

[1864] AK is AK_1

[1865] where

[1866] AK_1 is an antibody which comprises the six CDR sequences of the antibody MF-Ta, the variable light and variable heavy chain of the antibody MF-Ta or the light and heavy chain of the antibody MF-Ta, and which is attached via the sulphur atom of a cysteine residue of the binder to the group G,

[1867] G is a group of the formula



[1868] where

[1869] #1 marks the linkage site with the cysteine residue of the binder,

[1870] #2 marks the linkage site with the group L^1,

and

[1871] n, L^1, B, L^2, D and R^{35} have the definitions indicated above,

and also their salts, solvates and solvates of the salts.

[1872] Preference in the context of the present invention is also given to compounds of the formula (Ia), in which

[1873] AK is AK_2

[1874] where

[1875] AK_2 is an antibody which comprises the six CDR sequences of the antibody MF-Ta, the variable light and variable heavy chain of the antibody MF-Ta or the light and heavy chain of the antibody MF-Ta, and which is bonded via the NH side group of a lysine residue of the binder to the group G,

[1876] G is carbonyl,

and

[1877] n, L^1, B, L^2, D and R^{35} have the definitions indicated above,

and also their salts, solvates and solvates of the salts.

[1878] Preference in the context of the present invention is also given to compounds of the general formula (Ia), in which

[1879] AK is AK_2

[1880] where

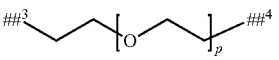
[1881] AK_2 is an antibody which comprises the six CDR sequences of the antibody MF-Ta, the variable light and variable heavy chain of the antibody MF-Ta or the light and heavy chain of the antibody MF-Ta, and which is bonded via the NH side group of a lysine residue of the binder to the group G,

[1882] G is carbonyl,

[1883] L^1 is a bond,

[1884] B is a bond,

[1885] L^2 is linear $(C_3$-$C_6)$-alkanediyl or is a group of the formula



[1886] where

[1887] p is a number 2 or 3,

[1888] $\#\#^3$ marks the linkage site with the group B,

[1889] $\#\#^4$ marks the linkage site with the nitrogen atom,

[1890] n, D and R^{35} have the definitions indicated above,

and also their salts, solvates and solvates of the salts.

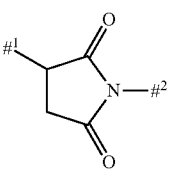
[1891] Preference in the context of the present invention is also given to compounds of the general formula (Ia), in which

[1892] AK is AK_1

[1893] where

[1894] AK_1 is an antibody which comprises the six CDR sequences of the antibody MF-Ta, the variable light and variable heavy chain of the antibody MF-Ta or the light and heavy chain of the antibody MF-Ta, and which is attached via the sulphur atom of a cysteine residue of the binder to the group G,

[1895] G is a group of the formula

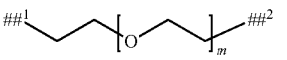


[1896] where

[1897] $\#^1$ marks the linkage site with the cysteine residue of the binder,

[1898] $\#^2$ marks the linkage site with the group L^1,

[1899] L^1 is a bond, linear $(C_3$-$C_5)$-alkanediyl or a group of the formula



[1900] where

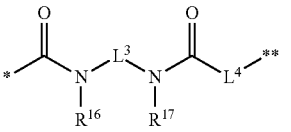
[1901] m is a number 2 or 3,

[1902] $\#\#^1$ marks the linkage site with the group G,

[1903] $\#\#^2$ marks the linkage site with the group B,

[1904] where $(C_3$-$C_5)$-alkanediyl may be substituted by 1 or 2 methyl substituents,

[1905] B is a bond or a group of the formula



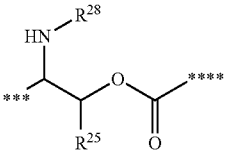
[1906] where

[1907] * marks the linkage site with L^1,

[1908] ** marks the linkage site with L^2,

[1909] L^3 is a bond or ethane-1,2-diyl,

[1910] L^4 is a bond or a group of the formula



[1911] in which

[1912] *** marks the linkage site with the carbonyl group,

[1913] **** marks the linkage site with L^2,

[1914] R^{25} is methyl,

[1915] R^{28} is hydrogen, methylcarbonyl or tert-butyloxycarbonyl,

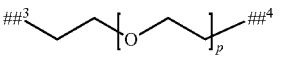
[1916] R^{16} is hydrogen or methyl,

[1917] R^{17} is hydrogen or methyl,

[1918] or

[1919] R^{16} and R^{17} together with the atoms to which they are bonded form a piperazinyl ring,

[1920] L^2 is linear $(C_3$-$C_5)$-alkanediyl or is a group of the formula



[1921] where

[1922] p is a number 2 or 3,

[1923] $\#\#^3$ marks the linkage site with the group B,

[1924] $\#\#^4$ marks the linkage site with the nitrogen atom,

and

[1925] n, D and R^{35} have the definitions indicated above,

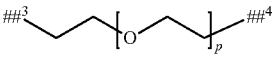
and also their salts, solvates and solvates of the salts.

[1926] Preferred in the context of the present invention are also compounds of the formula (Ia), (XXXa) and (XXXI), in which

[1927] L^1 is a bond,

[1928] B is a bond,

[1929] L^2 is linear $(C_3\text{-}C_6)$-alkanediyl or is a group of the formula



[1930] where

[1931] p is a number 2 or 3,

[1932] $\#\#^3$ marks the linkage site with the group B,

[1933] $\#\#^4$ marks the linkage site with the nitrogen atom,

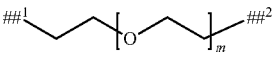
and

[1934] n, AK, Cys, G, D and R^{35} have the definitions indicated above,

and also their salts, solvates and solvates of the salts.

[1935] Preferred in the context of the present invention are also compounds of the formula (Ia), in which

[1936] L^1 is linear $(C_1\text{-}C_{10})$-alkanediyl or a group of the formula



[1937] where

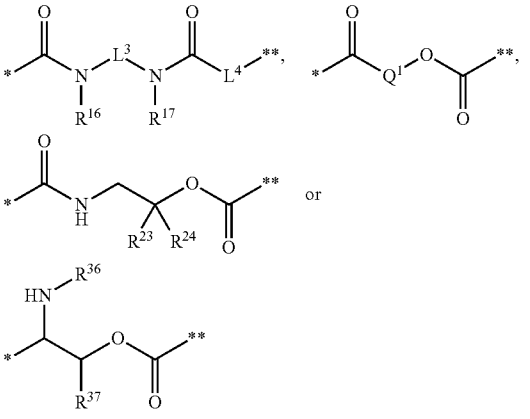
[1938] m is a number from 2 to 6,

[1939] $\#\#^1$ marks the linkage site with the group G,

[1940] $\#\#^2$ marks the linkage site with the group B,

[1941] where $(C_1\text{-}C_{10})$-alkanediyl may be substituted by 1 to 4 substituents selected independently of one another from the group consisting of methyl, hydroxyl and benzyl,

[1942] B is a bond or a group of the formula



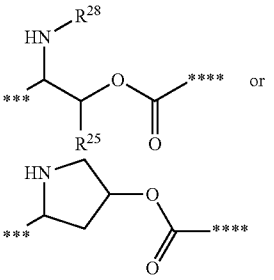
[1943] where

[1944] * marks the linkage site with L^1,

[1945] ** marks the linkage site with L^2,

[1946] L^3 is a bond or $(C_2\text{-}C_4)$-alkanediyl,

[1947] L^4 is a group of the formula



[1948] in which

[1949] *** marks the linkage site with the carbonyl group,

[1950] **** marks the linkage site with L^2,

[1951] R^{25} is hydrogen or methyl,

[1952] R^{28} is hydrogen, $(C_1\text{-}C_4)$-alkylcarbonyl, tert-butyloxycarbonyl or benzyloxycarbonyl,

[1953] Q^1 is a 4- to 7-membered heterocycle,

[1954] R^{16} is hydrogen or $(C_1\text{-}C_4)$-alkyl,

[1955] R^{17} is hydrogen or $(C_1\text{-}C_4)$-alkyl,

[1956] or

[1957] R^{16} and R^{17} together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

[1958] R^{23} is $(C_1\text{-}C_4)$-alkyl,

[1959] R^{24} is hydrogen or $(C_1\text{-}C_4)$-alkyl,

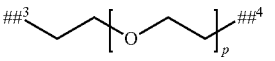
[1960] R^{36} is hydrogen, $(C_1\text{-}C_4)$-alkylcarbonyl, tert-butyloxycarbonyl or benzyloxycarbonyl,

[1961] R^{37} is hydrogen or methyl,

[1962] or

[1963] R^{36} and R^{37} together with the atoms to which they are bonded form a pyrrolidine ring,

[1964] L^2 is linear $(C_2\text{-}C_{10})$-alkanediyl or is a group of the formula



[1965] where

[1966] p is a number from 2 to 6,

[1967] $\#\#^3$ marks the linkage site with the group B,

[1968] $\#\#^4$ marks the linkage site with the nitrogen atom,

[1969] where $(C_2\text{-}C_{10})$-alkanediyl may be substituted by 1 to 4 substituents selected independently of one another from the group consisting of methyl, hydroxyl and benzyl,

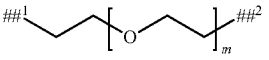
and

[1970] n, AK, G, D and R^{35} have the definitions indicated above,

and also their salts, solvates and solvates of the salts.

[1971] Preferred in the context of the present invention are also compounds of the formula (Ia), in which

[1972] L^1 is linear $(C_2\text{-}C_6)$-alkanediyl or a group of the formula



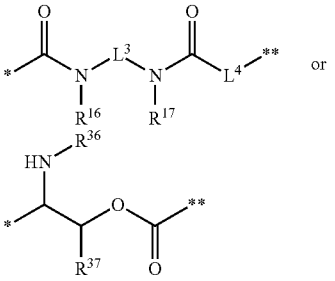
[1973] where

[1974] m is a number 2 or 3,

[1975] ##[1] marks the linkage site with the group G,

[1976] ##[2] marks the linkage site with the group B,

[1977] B is a bond or a group of the formula



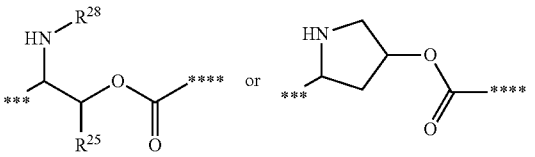
[1978] where

[1979] * marks the linkage site with L^1,

[1980] ** marks the linkage site with L^2,

[1981] L^3 is a bond or ethane-1,2-diyl,

[1982] L^4 is a group of the formula



[1983] where

[1984] *** marks the linkage site with the carbonyl group,

[1985] **** marks the linkage site with L^2,

[1986] R^{25} is hydrogen or methyl,

[1987] R^{28} is hydrogen, methylcarbonyl or tert-butyloxycarbonyl,

[1988] R^{16} is hydrogen or methyl,

[1989] R^{17} is hydrogen or methyl,

[1990] or

[1991] R^{16} and R^{17} together with the atoms to which they are bonded form a piperazinyl ring,

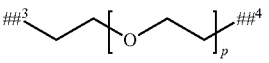
[1992] R^{36} is hydrogen, methylcarbonyl or tert-butyloxycarbonyl,

[1993] R^{37} is hydrogen or methyl,

[1994] or

[1995] R^{36} and R^{37} together with the atoms to which they are bonded form a pyrrolidine ring,

[1996] L^2 is linear (C_2-C_6)-alkanediyl or is a group of the formula



[1997] where

[1998] p is a number 2 or 3,

[1999] ##[3] marks the linkage site with the group B,

[2000] ##[4] marks the linkage site with the nitrogen atom,

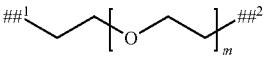
and

[2001] n, AK, G, D and R^{35} have the definitions indicated above,

and also their salts, solvates and solvates of the salts.

[2002] Preferred in the context of the present invention are also compounds of the formula (Ia) in which

[2003] L^1 is a bond, linear (C_2-C_6)-alkanediyl or a group of the formula



[2004] where

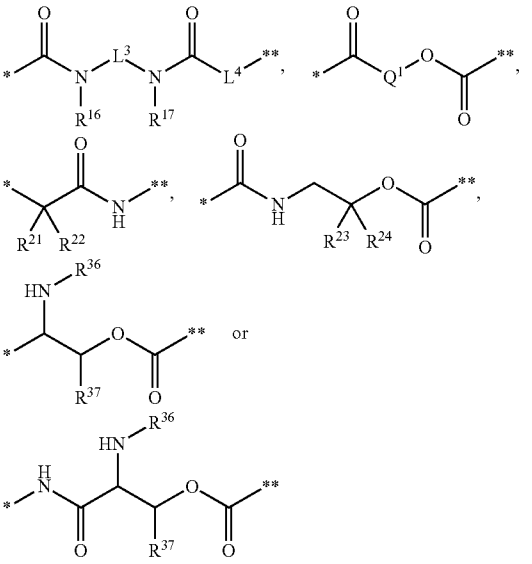
[2005] m is a number 2 or 3,

[2006] ##[1] marks the linkage site with the group G,

[2007] ##[2] marks the linkage site with the group B,

[2008] where (C_2-C_6)-alkanediyl may be substituted by 1 or 2 methyl substituents,

[2009] B is a bond or a group of the formula



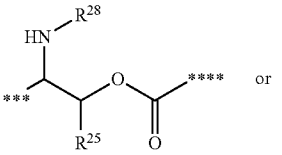
[2010] where

[2011] * marks the linkage site with L^1,

[2012] ** marks the linkage site with L^2,

[2013] L^3 is a bond or ethane-1,2-diyl,

[2014] L^4 is a group of the formula



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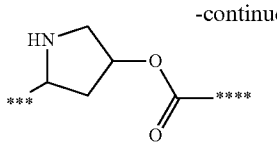


[2015] in which

[2016] *** marks the linkage site with the carbonyl group,

[2017] **** marks the linkage site with L^2,

[2018] R^{25} is methyl,

[2019] R^{28} is hydrogen, methylcarbonyl or tert-butyloxycarbonyl,

[2020] Q^1 is piperidine-1,4-diyl,

[2021] R^{16} is hydrogen or methyl,

[2022] R^{17} is hydrogen or methyl,

[2023] or

[2024] R^{16} and R^{17} together with the atoms to which they are bonded form a piperazinyl ring,

[2025] R^{21} is hydrogen or methyl,

[2026] R^{22} is hydrogen or methyl,

[2027] or

[2028] R^{21} and R^{22} together with the atoms to which they are bonded form a cyclopropyl ring,

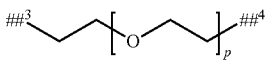
[2029] R^{23} is methyl,

[2030] R^{24} is hydrogen,

[2031] R^{36} is hydrogen, methylcarbonyl or tert-butyloxycarbonyl,

[2032] R^{37} is hydrogen or methyl,

[2033] L^2 is linear (C_2-C_6)-alkanediyl or is a group of the formula



[2034] where

[2035] p is a number from 2 to 6,

[2036] $\#\#^3$ marks the linkage site with the group B,

[2037] $\#\#^4$ marks the linkage site with the nitrogen atom,

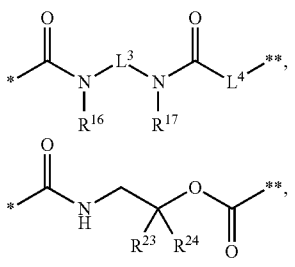
and also their salts, solvates and solvates of the salts.

[2038] Preferred in the context of the present invention are also compounds of the formula (Ia) in which

[2039] L^1 is linear (C_2-C_6)-alkanediyl,

[2040] where (C_2-C_6)-alkanediyl may be substituted by 1 or 2 methyl substituents,

[2041] B is a bond or a group of the formula



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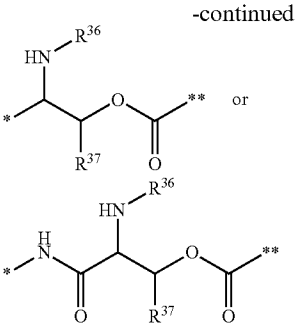


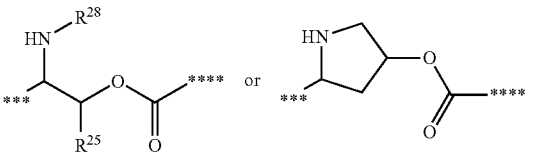
[2042] where

[2043] * marks the linkage site with L^1,

[2044] ** marks the linkage site with L^2,

[2045] L^3 is a bond,

[2046] L^4 is a group of the formula



[2047] in which

[2048] *** marks the linkage site with the carbonyl group,

[2049] **** marks the linkage site with L^2,

[2050] R^{25} is methyl,

[2051] R^{28} is hydrogen, methylcarbonyl or tert-butyloxycarbonyl,

[2052] R^{16} is hydrogen or methyl,

[2053] R^{17} is hydrogen or methyl,

[2054] R^{23} is methyl,

[2055] R^{24} is hydrogen,

[2056] R^{36} is hydrogen, methylcarbonyl or tert-butyloxycarbonyl,

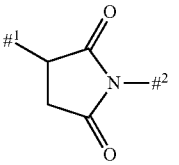
[2057] R^{37} is hydrogen or methyl,

[2058] L^2 is linear (C_2-C_6)-alkanediyl,

and also their salts, solvates and solvates of the salts.

[2059] Preferred in the context of the present invention are also compounds of the formula (Ia) and (XXXa), in which

[2060] G is a group of the formula

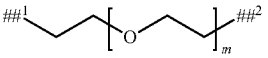


[2061] in which

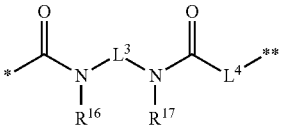
[2062] $\#^1$ marks the linkage site with the cysteine residue of the binder,

[2063] $\#^2$ marks the linkage site with the group L^1,

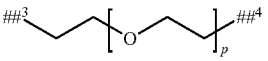
[2064] L^1 is linear (C_3-C_5)-alkanediyl or a group of the formula



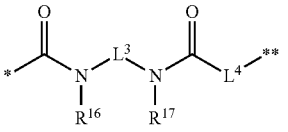
[2065] in which
[2066] m is a number 2 or 3,
[2067] ##[1] marks the linkage site with the group G,
[2068] ##[2] marks the linkage site with the group B,
[2069] where (C_3-C_5)-alkanediyl may be substituted by 1 or 2 methyl substituents,
[2070] B is a bond or a group of the formula



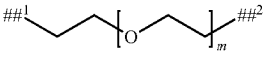
[2071] where
[2072] * marks the linkage site with L^1,
[2073] ** marks the linkage site with L^2,
[2074] L^3 is a bond or ethane-1,2-diyl,
[2075] L^4 is a bond,
[2076] L^2 is linear (C_3-C_5)-alkanediyl or is a group of the formula



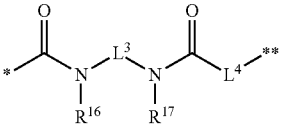
[2077] where
[2078] p is a number 2 or 3,
[2079] ##[3] marks the linkage site with the group B,
[2080] ##[4] marks the linkage site with the nitrogen atom,
and
[2081] n, AK_1, Cys, D, R^{16} and R^{17} have the definitions indicated above,
and also their salts, solvates and solvates of the salts.
[2082] Preferred in the context of the present invention are also compounds of the formula (Ia) and (XXXa), in which
[2083] B is a bond or a group of the formula



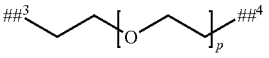
[2084] where
[2085] * marks the linkage site with L^1,
[2086] ** marks the linkage site with L^2,
[2087] L^3 is a bond or ethane-1,2-diyl,
[2088] L^4 is a bond,
[2089] n, AK, Cys, G, L^1, L^2, D, R^{16}, R^{17} and R^{35} have the definitions indicated above,
and also their salts, solvates and solvates of the salts.
[2090] Preferred in the context of the present invention are also compounds of the formula (Ia), (XXXa) and (XXXI), in which
[2091] L^1 is a bond, linear (C_3-C_5)-alkanediyl or a group of the formula



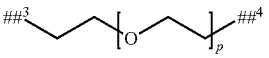
[2092] where
[2093] m is a number 2 or 3,
[2094] ##[1] marks the linkage site with the group G,
[2095] ##[2] marks the linkage site with the group B,
[2096] where (C_3-C_5)-alkanediyl may be substituted by 1 or 2 methyl substituents,
[2097] B is a bond or a group of the formula



[2098] where
[2099] * marks the linkage site with L^1,
[2100] ** marks the linkage site with L^2,
[2101] L^3 is a bond,
[2102] L^4 is a bond
[2103] R^{16} is hydrogen,
[2104] R^{17} is hydrogen,
[2105] L^2 is linear (C_3-C_6)-alkanediyl or is a group of the formula

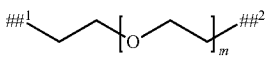


[2106] where
[2107] p is a number 2 or 3,
[2108] ##[3] marks the linkage site with the group B,
[2109] ##[4] marks the linkage site with the nitrogen atom,
[2110] n, AK, Cys, G, D and R^{35} have the definitions indicated above,
and also their salts, solvates and solvates of the salts.
[2111] Preferred in the context of the present invention are also compounds of the formula (Ia), (XXXa) and (XXXI), in which
[2112] L^1 is a bond,
[2113] B is a bond,
[2114] L^2 is linear (C_3-C_6)-alkanediyl or is a group of the formula



[2115] where
[2116] p is a number 2 or 3,
[2117] ##[3] marks the linkage site with the group B,
[2118] ##[4] marks the linkage site with the nitrogen atom,
[2119] n, AK, Cys, G, D and R^{35} have the definitions indicated above,
and also their salts, solvates and solvates of the salts.
[2120] Preferred in the context of the present invention are also compounds of the formula (Ia), (XXXa) and (XXXI), in which

[2121] L^1 is linear (C_3-C_5)-alkanediyl or a group of the formula



[2122] where

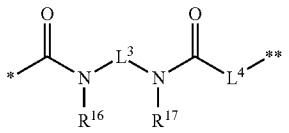
[2123] m is a number 2 or 3,

[2124] $\#\#^1$ marks the linkage site with the group G,

[2125] $\#\#^2$ marks the linkage site with the group B,

[2126] where (C_3-C_5)-alkanediyl may be substituted by 1 or 2 methyl substituents,

[2127] B is a group of the formula



[2128] where

[2129] * marks the linkage site with L^1,

[2130] ** marks the linkage site with L^2,

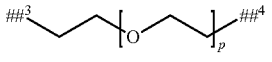
[2131] L^3 is a bond,

[2132] L^4 is a bond,

[2133] R^{16} is hydrogen,

[2134] R^{17} is hydrogen,

[2135] L^2 is linear (C_3-C_6)-alkanediyl or is a group of the formula



[2136] where

[2137] p is a number 2 or 3,

[2138] $\#\#^3$ marks the linkage site with the group B,

[2139] $\#\#^4$ marks the linkage site with the nitrogen atom,

[2140] n, AK, Cys, G, D and R^{35} have the definitions indicated above,

and also their salts, solvates and solvates of the salts.

[2141] Preferred in the context of the present invention are also compounds of the formula (Ia), in which

[2142] n is a number from 2 to 8, preferably 2 to 5,

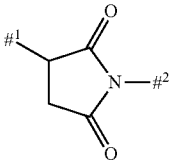
[2143] AK is AK_1 or AK_2

[2144] where

[2145] AK_1 is an antibody or an antigen-binding antibody fragment which binds to mesothelin and is bonded via the sulphur atom of a cysteine residue of the binder to the group G,

[2146] AK_2 is an antibody or an antigen-binding antibody fragment which binds to mesothelin and is bonded via the NH side group of a lysine residue of the binder to the group G,

[2147] G when $AK=AK_1$, is a group of the formula



[2148] in which

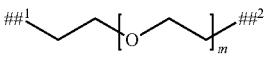
[2149] $\#^1$ marks the linkage site with the cysteine residue of the binder,

[2150] $\#^2$ marks the linkage site with the group L^1,

[2151] or

[2152] when $AK=AK_2$, is carbonyl,

[2153] L^1 is a bond, linear (C_3-C_5)-alkanediyl or a group of the formula



[2154] where

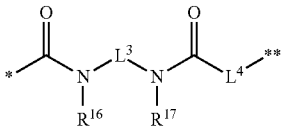
[2155] m is a number 2 or 3,

[2156] $\#\#^1$ marks the linkage site with the group G,

[2157] $\#\#^2$ marks the linkage site with the group B,

[2158] where (C_3-C_5)-alkanediyl may be substituted by 1 or 2 methyl substituents,

[2159] B is a bond or a group of the formula



[2160] where

[2161] * marks the linkage site with L^1,

[2162] ** marks the linkage site with L^2,

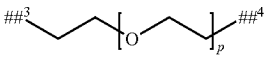
[2163] L^3 is a bond,

[2164] L^4 is a bond,

[2165] R^{16} is hydrogen,

[2166] R^{17} is hydrogen,

[2167] L^2 is linear (C_3-C_6)-alkanediyl or is a group of the formula



[2168] where

[2169] p is a number 2 or 3,

[2170] $\#\#^3$ marks the linkage site with the group B,

[2171] $\#\#^4$ marks the linkage site with the nitrogen atom, and

[2172] D and R^{35} have the definitions indicated above,

and also their salts, solvates and solvates of the salts.

[2173] Preferred in the context of the present invention are also compounds of the formula (Ia), in which

[2174] n is a number from 2 to 8, preferably 2 to 5,

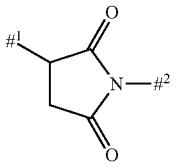
[2175] AK is AK_1 or AK_2,

[2176] where

[2177] AK_1 is an antibody or an antigen-binding antibody fragment which binds to mesothelin and is bonded via the sulphur atom of a cysteine residue of the binder to the group G,

[2178] AK_2 is an antibody or an antigen-binding antibody fragment which binds to mesothelin and is bonded via the NH side group of a lysine residue of the binder to the group G,

[2179] G when $AK=AK_1$, is a group of the formula



[2180] in which

[2181] $\#^1$ marks the linkage site with the cysteine residue of the binder,

[2182] $\#^2$ marks the linkage site with the group L^1,

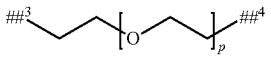
[2183] or

[2184] when $AK=AK_2$, is carbonyl,

[2185] L^1 is a bond,

[2186] B is a bond,

[2187] L^2 is linear $(C_3\text{-}C_6)$-alkanediyl or is a group of the formula



[2188] where

[2189] p is a number 2 or 3,

[2190] $\#\#^3$ marks the linkage site with the group B,

[2191] $\#\#^4$ marks the linkage site with the nitrogen atom,

[2192] D and R^{35} have the definitions indicated above, and also their salts, solvates and solvates of the salts.

[2193] Preferred in the context of the present invention are also compounds of the formula (Ia), in which

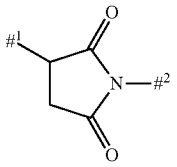
[2194] n is a number from 2 to 8, preferably 2 to 5,

[2195] AK is AK_1,

[2196] where

[2197] AK_1 is an antibody or an antigen-binding antibody fragment which binds to mesothelin and is bonded via the sulphur atom of a cysteine residue of the binder to the group G,

[2198] G is a group of the formula

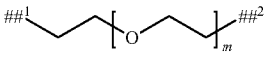


[2199] where

[2200] $\#^1$ marks the linkage site with the cysteine residue of the binder,

[2201] $\#^2$ marks the linkage site with the group L^1,

[2202] L^1 is linear $(C_3\text{-}C_5)$-alkanediyl or a group of the formula



[2203] where

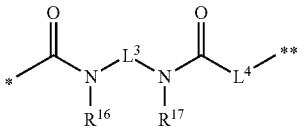
[2204] m is a number 2 or 3,

[2205] $\#\#^1$ marks the linkage site with the group G,

[2206] $\#\#^2$ marks the linkage site with the group B,

[2207] where $(C_3\text{-}C_5)$-alkanediyl may be substituted by 1 or 2 methyl substituents,

[2208] B is a group of the formula



[2209] where

[2210] * marks the linkage site with L^1,

[2211] ** marks the linkage site with L^2,

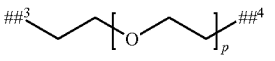
[2212] L^3 is a bond,

[2213] L^4 is a bond,

[2214] R^{16} is hydrogen,

[2215] R^{17} is hydrogen,

[2216] L^2 is linear $(C_3\text{-}C_6)$-alkanediyl or is a group of the formula



[2217] where

[2218] p is a number 2 or 3,

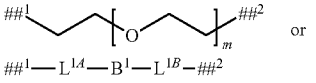
[2219] $\#\#^3$ marks the linkage site with the group B,

[2220] $\#\#^4$ marks the linkage site with the nitrogen atom,

[2221] D and R^{35} have the definitions indicated above, and also their salts, solvates and solvates of the salts.

[2222] Preferred in the context of the present invention are also compounds of the formula (Ia), in which

[2223] L^1 is a bond, linear $(C_3\text{-}C_5)$-alkanediyl, a group of the formula



[2224] where

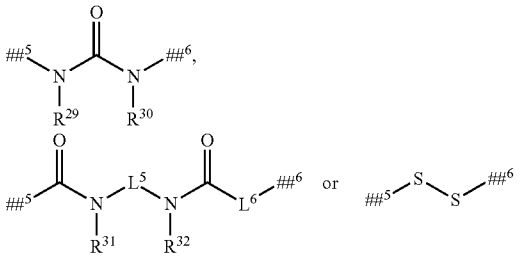
[2225] m is a number 2 or 3,

[2226] $\#\#^1$ marks the linkage site with the group G,

[2227] $\#\#^2$ marks the linkage site with the group B,

[2228] L^{1A} is linear $(C_3\text{-}C_6)$-alkanediyl,

[2229] B^1 is a group of the formula



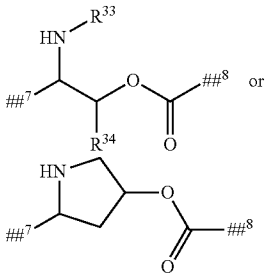
[2230] in which

[2231] $\#\#^5$ marks the linkage site with the group L^{1A},

[2232] $\#\#^6$ marks the linkage site with the group L^{1B},

[2233] L^5 is a bond or ethane-1,2-diyl,

[2234] L^6 is a bond or a group of the formula



[2235] in which

[2236] $\#\#^7$ marks the linkage site with the carbonyl group,

[2237] $\#\#^8$ marks the linkage site with L^{1B},

[2238] R^{33} is hydrogen, $(C_1$-$C_4)$-alkylcarbonyl or tert-butyloxycarbonyl,

[2239] R^{34} is hydrogen or methyl,

[2240] R^{29} is hydrogen or methyl,

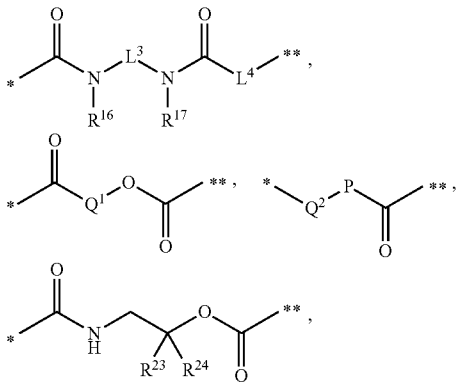
[2241] R^{30} is hydrogen or methyl,

[2242] R^{31} is hydrogen or methyl,

[2243] R^{32} is hydrogen or methyl,

[2244] L^{1B} is linear $(C_3$-$C_6)$-alkanediyl,

[2245] B is a bond or a group of the formula



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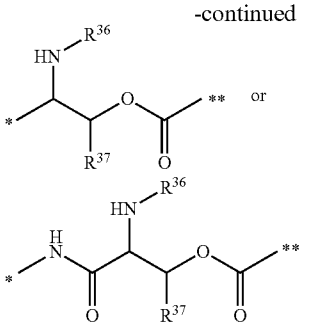


[2246] where

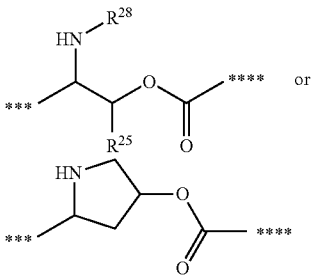
[2247] * marks the linkage site with L^1,

[2248] ** marks the linkage site with L^2,

[2249] P is O,

[2250] L^3 is a bond or ethane-1,2-diyl,

[2251] L^4 is a group of the formula



[2252] in which

[2253] *** marks the linkage site with the carbonyl group,

[2254] **** marks the linkage site with L^2,

[2255] R^{25} is hydrogen or methyl,

[2256] R^{28} is hydrogen, $(C_1$-$C_4)$-alkylcarbonyl or tert-butyloxycarbonyl,

[2257] Q^1 is a 4- to 7-membered heterocycle,

[2258] Q^2 is a 3- to 7-membered carbocycle or a 4- to 7-membered heterocycle,

[2259] R^{16} is hydrogen or methyl,

[2260] R^{17} is hydrogen or methyl,

[2261] R^{23} is $(C_1$-$C_4)$-alkyl,

[2262] R^{24} is hydrogen or $(C_1$-$C_4)$-alkyl,

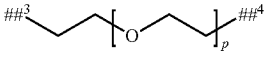
[2263] R^{36} is hydrogen, $(C_1$-$C_4)$-alkylcarbonyl or tert-butyloxycarbonyl,

[2264] R^{37} is hydrogen or methyl,

[2265] or

[2266] R^{36} and R^{37} together with the atoms to which they are bonded form a pyrrolidine ring,

[2267] L^2 is linear $(C_2$-$C_6)$-alkanediyl or is a group of the formula



[2268] where

[2269] p is a number 2 or 3,

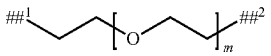
[2270] ##[3] marks the linkage site with the group B,

[2271] ##[4] marks the linkage site with the nitrogen atom,

and also their salts, solvates and solvates of the salts.

[2272] Preferred in the context of the present invention are also compounds of the formula (Ia), in which

[2273] L^1 is linear (C_3-C_5)-alkanediyl or a group of the formula



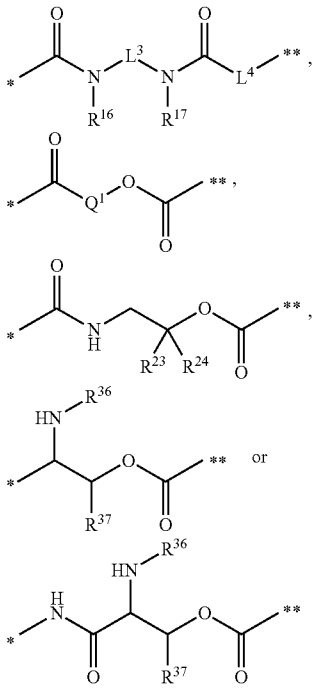
[2274] where

[2275] m is a number 2 or 3,

[2276] ##[1] marks the linkage site with the group G,

[2277] ##[2] marks the linkage site with the group B,

[2278] B is a group of the formula



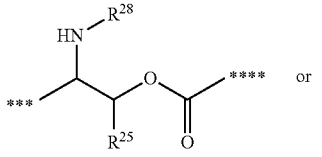
[2279] where

[2280] * marks the linkage site with L^1,

[2281] ** marks the linkage site with L^2,

[2282] L^3 is a bond or ethane-1,2-diyl,

[2283] L^4 is a group of the formula



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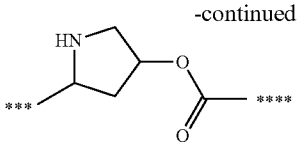


[2284] in which

[2285] *** marks the linkage site with the carbonyl group,

[2286] **** marks the linkage site with L^2,

[2287] R^{25} is methyl,

[2288] R^{28} is hydrogen, methylcarbonyl or tert-butyloxycarbonyl,

[2289] Q^1 is piperidine-1,4-diyl,

[2290] R^{16} is hydrogen or methyl,

[2291] R^{17} is hydrogen or methyl,

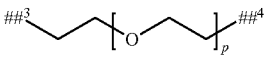
[2292] R^{23} is methyl,

[2293] R^{24} is hydrogen,

[2294] R^{36} is hydrogen, methylcarbonyl or tert-butyloxycarbonyl,

[2295] R^{37} is hydrogen or methyl,

[2296] L^2 is linear (C_2-C_6)-alkanediyl or is a group of the formula



[2297] where

[2298] p is a number 2 or 3,

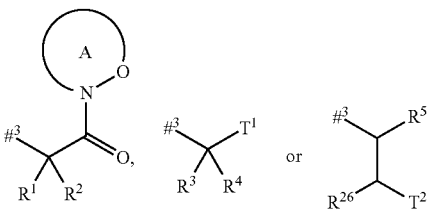
[2299] ##[3] marks the linkage site with the group B,

[2300] ##[4] marks the linkage site with the nitrogen atom,

and also their salts, solvates and solvates of the salts.

[2301] Preferred in the context of the present invention are also compounds of the formula (Ia), (XXXa) and (XXXI), in which

[2302] D is a group of the formula



[2303] where

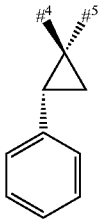
[2304] #[3] marks the linkage site with the nitrogen atom,

[2305] R^1 is hydrogen or methyl,

[2306] R^2 is isopropyl, isobutyl, sec-butyl, tert-butyl, phenyl, benzyl, 1-hydroxyethyl, 4-hydroxybenzyl, 4-hydroxy-3-nitrobenzyl, 4-hydroxy-3-aminobenzyl, 1-phenylethyl, diphenylmethyl, 1H-imidazol-4-ylmethyl or 1H-indol-3-ylmethyl,

[2307] or

[2308] R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula

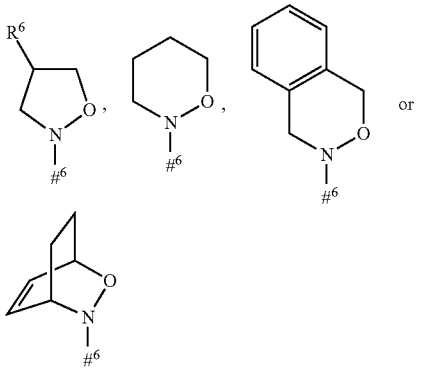


[2309] in which

[2310] #4 marks the linkage site with the adjacent nitrogen atom,

[2311] #5 marks the linkage site with the carbonyl group,

[2312] the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



[2313] in which

[2314] #6 marks the linkage site with the carbonyl group,

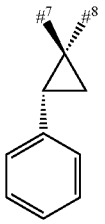
[2315] R^6 is hydrogen, hydroxy or benzyloxy,

[2316] R^3 is hydrogen or methyl,

[2317] R^4 is isopropyl, isobutyl, sec-butyl, tert-butyl, phenyl, benzyl, 1-hydroxyethyl, 4-hydroxybenzyl, 4-hydroxy-3-nitrobenzyl, 4-hydroxy-3-aminobenzyl, 1-phenylethyl, diphenylmethyl, 1H-imidazol-4-ylmethyl or 1H-indol-3-ylmethyl,

[2318] or

[2319] R^3 and R^4 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula



[2320] in which

[2321] #7 marks the linkage site with the adjacent nitrogen atom,

[2322] #8 marks the linkage site with the group T^1,

[2323] T^1 is a group of the formula —C(═O)—OR^7, —C(═O)—NR^8R^9, —C(═O)—NH—NH—R^{10} or —CH_2—O—R^{11},

[2324] in which

[2325] R^7 is hydrogen, methyl, ethyl, n-propyl, tert-butyl, benzyl or adamantylmethyl,

[2326] R^8 is hydrogen or methyl,

[2327] R^9 is hydrogen, methyl, ethyl, n-propyl or benzyl,

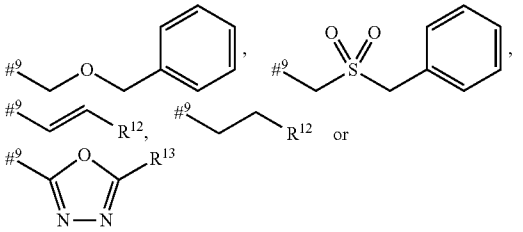
[2328] or

[2329] R^8 and R^9 together with the nitrogen atom to which they are bonded form a 4- to 7-membered heterocycle,

[2330] R^{10} is benzoyl,

[2331] R^{11} is benzyl, which may be substituted in the phenyl group by methoxycarbonyl or carboxyl

[2332] R^5 is hydrogen, methyl or a group of the formula



[2333] in which

[2334] #9 marks the linkage site with —CHC(R^{26})-T^2,

[2335] R^{12} is phenyl which may be substituted by methoxycarbonyl, carboxyl or a group of the formula —$S(O)_2OH$,

[2336] R^{13} is phenyl which may be substituted by methoxycarbonyl or carboxyl,

[2337] R^{26} is hydrogen,

[2338] T^2 is phenyl, benzyl, 1H-indol-3-yl or 1H-indol-3-ylmethyl,

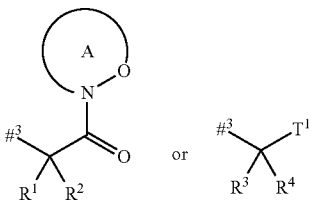
and

[2339] n, AK, Cys, G, L^1, B, L^2, D and R^{35} have the definitions indicated above,

and also their salts, solvates and solvates of the salts.

[2340] Preferred in the context of the present invention are also compounds of the formula (Ia), (XXXa) and (XXXI), in which

[2341] D is a group of the formula



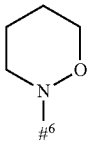
[2342] where

[2343] #3 marks the linkage site with the nitrogen atom,

[2344] R1 is hydrogen,

[2345] R2 is benzyl, 4-hydroxybenzyl, 1-phenylethyl or 1H-indol-3-ylmethyl,

[2346] the ring A with the N—O moiety present therein is a heterocycle of formula



[2347] in which

[2348] #6 marks the linkage site with the carbonyl group,

[2349] R3 is hydrogen,

[2350] R4 is benzyl, 4-hydroxybenzyl, 1-phenylethyl or 1H-indol-3-ylmethyl,

[2351] T1 is a group of the formula —C(═O)—OR7 or —C(═O)—NR8R9,

[2352] in which

[2353] R7 is hydrogen,

[2354] R8 is hydrogen,

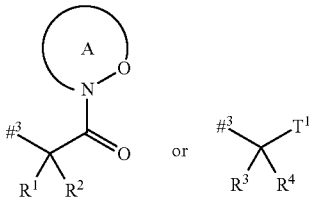
[2355] R9 is hydrogen,

[2356] n, AK, Cys, G, L1, B, L2, D and R35 have the definitions indicated above,

and also their salts, solvates and solvates of the salts.

[2357] Preferred in the context of the present invention are also compounds of the formula (Ia), (XXXa) and (XXXI), in which

[2358] D is a group of the formula



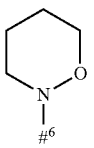
[2359] where

[2360] #3 marks the linkage site with the nitrogen atom,

[2361] R1 is hydrogen,

[2362] R2 is benzyl, 4-hydroxybenzyl, 1-phenylethyl or 1H-indol-3-ylmethyl,

[2363] the ring A with the N—O moiety present therein is a heterocycle of the formula



[2364] in which

[2365] #6 marks the linkage site with the carbonyl group,

[2366] R3 is hydrogen,

[2367] R4 is benzyl, 4-hydroxybenzyl, 1-phenylethyl or 1H-indol-3-ylmethyl,

[2368] T1 is a group of the formula —C(═O)—NR8R9,

[2369] in which

[2370] R8 is hydrogen,

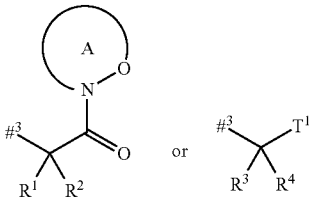
[2371] R9 is hydrogen,

[2372] n, AK, Cys, G, L1, B, L2, D and R35 have the definitions indicated above,

and also their salts, solvates and solvates of the salts.

[2373] Preferred in the context of the present invention are also compounds of the formula (Ia), (XXXa) and (XXXI), in which

[2374] D is a group of the formula



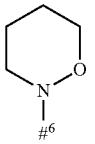
[2375] where

[2376] #3 marks the linkage site with the nitrogen atom,

[2377] R1 is hydrogen,

[2378] R2 is 4-hydroxybenzyl or 1H-indol-3-ylmethyl,

[2379] the ring A with the N—O moiety present therein is a heterocycle of the formula



[2380] in which

[2381] #6 marks the linkage site with the carbonyl group,

[2382] R3 is hydrogen,

[2383] R4 is 4-hydroxybenzyl or 1H-indol-3-ylmethyl,

[2384] T1 is a group of the formula —C(═O)—NR8R9,

[2385] in which

[2386] R8 is hydrogen,

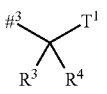
[2387] R9 is hydrogen,

[2388] n, AK, Cys, G, L1, B, L2, D and R35 have the definitions indicated above,

and also their salts, solvates and solvates of the salts.

[2389] Preferred in the context of the present invention are also compounds of the formula (Ia), (XXXa) and (XXXI), in which

[2390] D is a group of the formula



[2391] where

[2392] #3 marks the linkage site with the nitrogen atom,

[2393] R3 is hydrogen,

[2394] R4 is 4-hydroxybenzyl or 1H-indol-3-ylmethyl,

[2395] T^1 is a group of the formula —C(=O)—OR^7 or —C(=O)—NR^8R^9,

[2396] in which

[2397] R^7 is hydrogen,

[2398] R^8 is hydrogen,

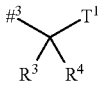
[2399] R^9 is hydrogen,

[2400] n, AK, Cys, G, L^1, B, L^2, D and R^{35} have the definitions indicated above,

and also their salts, solvates and solvates of the salts.

[2401] Preferred in the context of the present invention are also compounds of the formula (Ia), (XXXa) and (XXXI), in which

[2402] D is a group of the formula



[2403] where

[2404] #3 marks the linkage site with the nitrogen atom,

[2405] R^3 is hydrogen,

[2406] R^4 is 4-hydroxybenzyl or 1H-indol-3-ylmethyl,

[2407] T^1 is a group of the formula —C(=O)—NR^8R^9,

[2408] in which

[2409] R^8 is hydrogen,

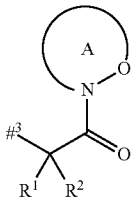
[2410] R^9 is hydrogen,

[2411] n, AK, Cys, G, L^1, B, L^2, D and R^{35} have the definitions indicated above,

and also their salts, solvates and solvates of the salts.

[2412] Preferred in the context of the present invention are also compounds of the formula (Ia), (XXXa) and (XXXI), in which

[2413] D is a group of the formula



[2414] where

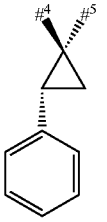
[2415] #3 marks the linkage site with the nitrogen atom,

[2416] R^1 is hydrogen or methyl,

[2417] R^2 is isopropyl, isobutyl, sec-butyl, tert-butyl, phenyl, benzyl, 1-hydroxyethyl, 4-hydroxybenzyl, 4-hydroxy-3-nitrobenzyl, 4-hydroxy-3-aminobenzyl, 1-phenylethyl, diphenylmethyl, 1H-imidazol-4-ylmethyl or 1H-indol-3-ylmethyl,

[2418] or

[2419] R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula

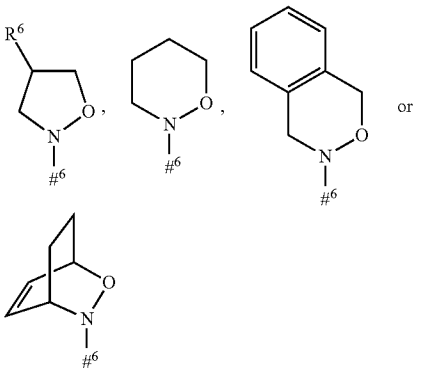


[2420] in which

[2421] #4 marks the linkage site with the adjacent nitrogen atom,

[2422] #5 marks the linkage site with the carbonyl group,

[2423] the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



[2424] in which

[2425] #6 marks the linkage site with the carbonyl group,

[2426] R^6 is hydrogen, hydroxy or benzyloxy,

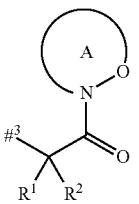
and

[2427] n, AK, Cys, G, L^1, B, L^2 and R^{35} have the definitions indicated above,

and also their salts, solvates and solvates of the salts.

[2428] Preferred in the context of the present invention are also compounds of the formula (Ia), (XXXa) and (XXXI), in which

[2429] D is a group of the formula



[2430] where

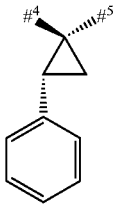
[2431] #3 marks the linkage site with the nitrogen atom,

[2432] R^1 is hydrogen,

[2433] R^2 is benzyl, 4-hydroxybenzyl, 1-phenylethyl or 1H-indol-3-ylmethyl,

[2434] or

[2435] R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula

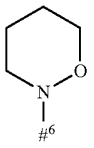


[2436] in which

[2437] $\#^4$ marks the linkage site with the adjacent nitrogen atom,

[2438] $\#^5$ marks the linkage site with the carbonyl group,

[2439] the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



[2440] in which

[2441] $\#^6$ marks the linkage site with the carbonyl group,

and

[2442] n, AK, Cys, G, L^1, B, L^2 and R^{35} have the definitions indicated above,

and also their salts, solvates and solvates of the salts.

[2443] Preferred in the context of the present invention are also compounds of the formula (Ia), (XXXa) and (XXXI), in which

[2444] R^{35} is hydroxyl,

and

[2445] n, AK, Cys, G, L^1, B, L^2, D and R^{35} have the definitions indicated above,

and also their salts, solvates and solvates of the salts.

[2446] Preferred in the context of the present invention are also compounds of the formula (Ia), (XXXa) and (XXXI), in which

[2447] R^{35} is methyl,

and

[2448] n, AK, Cys, G, L^1, B, L^2, D and R^{35} have the definitions indicated above,

and also their salts, solvates and solvates of the salts.

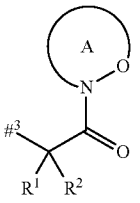
[2449] Particularly preferred in the context of the present invention are, furthermore, also compounds of the formula (XXXa), in which

[2450] Cys is an L-cysteine residue which is bonded via the sulphur atom of the side chain via a carbon atom of the succinimide,

and also their salts, solvates and solvates of the salts.

[2451] Preferred in the context of the present invention are also compounds of the formula (I) and (XXX), in which

[2452] D is a group of the formula



[2453] where

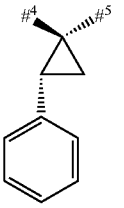
[2454] $\#^3$ marks the linkage site with the nitrogen atom,

[2455] R^1 is hydrogen,

[2456] R^2 is benzyl, 1-phenylethyl or 1H-indol-3-ylmethyl,

[2457] or

[2458] R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula

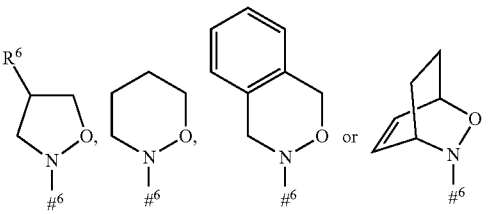


[2459] in which

[2460] $\#^4$ marks the linkage site with the adjacent nitrogen atom,

[2461] $\#^5$ marks the linkage site with the carbonyl group,

[2462] the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



[2463] in which

[2464] $\#^6$ marks the linkage site with the carbonyl group,

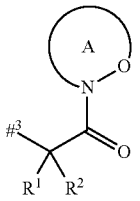
[2465] R^6 is hydrogen, hydroxy or benzyloxy,

[2466] n, AK, Cys, G, L^1, L^2 and B have the definitions indicated above,

and also their salts, solvates and solvates of the salts.

[2467] Particularly preferred in the context of the present invention are also compounds of the formula (I) and (XXX), in which

[2468] D is a group of the formula



[2469] where

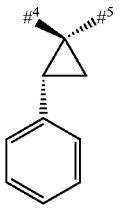
[2470] $\#^3$ marks the linkage site with the nitrogen atom,

[2471] R^1 is hydrogen,

[2472] R^2 is benzyl or 1H-indol-3-ylmethyl,

[2473] or

[2474] R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula

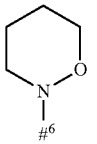


[2475] in which

[2476] $\#^4$ marks the linkage site with the adjacent nitrogen atom,

[2477] $\#^5$ marks the linkage site with the carbonyl group,

[2478] the ring A with the N—O moiety present therein is a heterocycle of the formula



[2479] in which

[2480] $\#^6$ marks the linkage site with the carbonyl group,

[2481] n, AK, Cys, G, L^1, L^2 and B have the definitions indicated above,

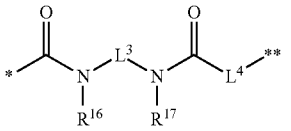
and also their salts, solvates and solvates of the salts.

[2482] Preferred in the context of the present invention are also compounds of the formula (I), in which

[2483] n=1-20, more preferably n=1-10 and very preferably n=2-8.

[2484] Preferred in the context of the present invention are also compounds of the formula (I) and (XXX), in which

[2485] B is a bond or a group of the formula



[2486] where

[2487] * marks the linkage site with L^1,

[2488] ** marks the linkage site with L^2,

[2489] L^3 is a bond or ethane-1,2-diyl,

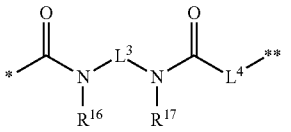
[2490] L^4 is a bond,

[2491] n, AK, Cys, G, L^1, L^2, D, R^{16} and R^{17} have the definitions indicated above,

and also their salts, solvates and solvates of the salts.

[2492] Particularly preferred in the context of the present invention are also compounds of the formula (I) and (XXX), in which

[2493] B is a bond or a group of the formula



[2494] where

[2495] * marks the linkage site with L^1,

[2496] ** marks the linkage site with L^2,

[2497] L^3 and L^4 is a bond,

[2498] n, AK, Cys, G, L^1, L^2, D, R^{16} and R^{17} have the definitions indicated above,

and also their salts, solvates and solvates of the salts.

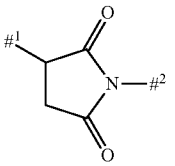
[2499] Preferred in the context of the present invention are also binder-drug conjugates of the general formula (I), in which

[2500] AK is AK_1,

[2501] where

[2502] AK_1 is a binder which is bonded via the sulphur atom of a cysteine residue of the binder to the group G,

[2503] G is a group of the formula

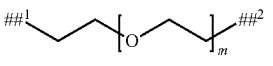


[2504] where

[2505] $\#^1$ marks the linkage site with the cysteine residue of the binder,

[2506] $\#^2$ marks the linkage site with the group L^1,

[2507] L^1 is a bond, linear (C_1-C_{10})-alkanediyl or is a group of the formula



[2508] where

[2509] m is a number from 2 to 6,

[2510] ##[1] marks the linkage site with the group G,

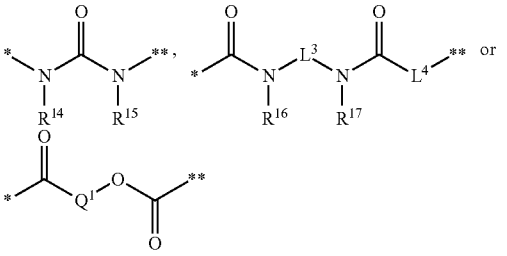
[2511] ##[2] marks the linkage site with the group B,

[2512] where (C_1-C_{10})-alkanediyl may be substituted by 1 to 4 methyl substituents,

[2513] and

[2514] where two carbon atoms of the alkanediyl chain in 1,2, 1,3 or 1,4 relation to one another, with inclusion of any carbon atoms situated between them, may be bridged to form a (C_3-C_6)-cycloalkyl ring or a phenyl ring,

[2515] B is a bond or a group of the formula



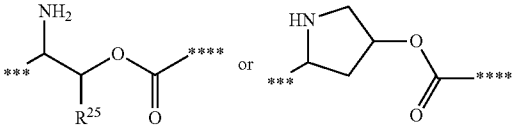
[2516] where

[2517] * marks the linkage site with L^1,

[2518] ** marks the linkage site with L^2,

[2519] L^3 is a bond or (C_2-C_4)-alkanediyl,

[2520] L^4 is a bond or a group of the formula



[2521] in which

[2522] *** marks the linkage site with the carbonyl group,

[2523] **** marks the linkage site with L^2,

[2524] R^{25} is hydrogen or methyl,

[2525] Q^1 is a 4- to 7-membered heterocycle,

[2526] R^{14} is hydrogen or (C_1-C_4)-alkyl,

[2527] R^{15} is hydrogen or (C_1-C_4)-alkyl,

[2528] or

[2529] R^{14} and R^{15} together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

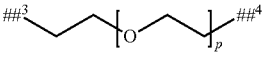
[2530] R^{16} is hydrogen or (C_1-C_4)-alkyl,

[2531] R^{17} is hydrogen or (C_1-C_4)-alkyl,

[2532] or

[2533] R^{16} and R^{17} together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

[2534] L^2 is linear (C_2-C_{10})-alkanediyl or is a group of the formula



[2535] where

[2536] p is a number from 2 to 6,

[2537] ##[3] marks the linkage site with the group B,

[2538] ##[4] marks the linkage site with the nitrogen atom,

[2539] where (C_2-C_{10})-alkanediyl may be substituted by 1 to 4 methyl substituents,

[2540] and

[2541] where two carbon atoms of the alkanediyl chain in 1,2, 1,3 or 1,4 relation to one another, with inclusion of any carbon atoms situated between them, may be bridged to form a (C_3-C_6)-cycloalkyl ring or a phenyl ring,

and also their salts, solvates and solvates of the salts.

[2542] Preferred in the context of the present invention are also binder-drug conjugates of the general formula (I), in which

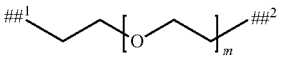
[2543] AK is AK_2,

[2544] where

[2545] AK_2 is a binder which is bonded via the NH side group of a lysine residue of the binder to the group G,

[2546] G is carbonyl,

[2547] L^1 is a bond, linear (C_1-C_{10})-alkanediyl or is a group of the formula



[2548] where

[2549] m is a number from 2 to 6,

[2550] ##[1] marks the linkage site with the group G,

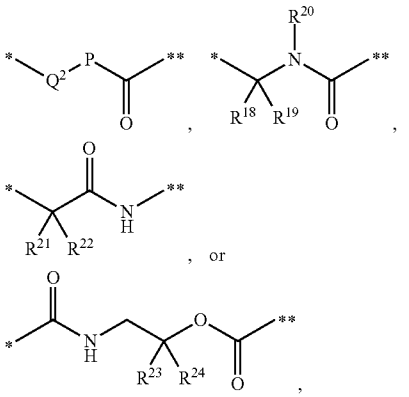
[2551] ##[2] marks the linkage site with the group B,

[2552] where (C_1-C_{10})-alkanediyl may be substituted by 1 to 4 methyl substituents,

[2553] and

[2554] where two carbon atoms of the alkanediyl chain in 1,2, 1,3 or 1,4 relation to one another, with inclusion of any carbon atoms situated between them, may be bridged to form a (C_3-C_6)-cycloalkyl ring or a phenyl ring,

[2555] B is a bond or a group of the formula



[2556] where

[2557] * marks the linkage site with L^1,

[2558] ** marks the linkage site with L^2,

[2559] P is O or NH,

[2560] Q^2 is a 3- to 7-membered carbocycle or a 4- to 7-membered heterocycle,

[2561] R^{18} is hydrogen or $(C_1$-$C_4)$-alkyl,

[2562] R^{19} is hydrogen or the side group of a natural α-amino acid or of its homologues or isomers,

[2563] R^{20} is hydrogen or $(C_1$-$C_4)$-alkyl,

[2564] or

[2565] R^{19} and R^{20} together with the atoms to which they are bonded form a pyrrolidinyl ring,

[2566] R^{21} is hydrogen or $(C_1$-$C_4)$-alkyl,

[2567] R^{22} is hydrogen or $(C_1$-$C_4)$-alkyl,

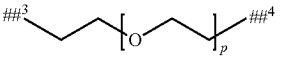
[2568] or

[2569] R^{21} and R^{22} together with the atoms to which they are bonded form a 3- to 7-membered carbocycle,

[2570] R^{23} is $(C_1$-$C_4)$-alkyl,

[2571] R^{24} is hydrogen or $(C_1$-$C_4)$-alkyl,

[2572] L^2 is linear $(C_2$-$C_{10})$-alkanediyl or is a group of the formula



[2573] where

[2574] p is a number from 2 to 6,

[2575] $\#\#^3$ marks the linkage site with the group B,

[2576] $\#\#^4$ marks the linkage site with the nitrogen atom,

[2577] where $(C_2$-$C_{10})$-alkanediyl may be substituted by 1 to 4 methyl substituents,

[2578] and

[2579] where two carbon atoms of the alkanediyl chain in 1,2, 1,3 or 1,4 relation to one another, with inclusion of any carbon atoms situated between them, may be bridged to form a $(C_3$-$C_6)$-cycloalkyl ring or a phenyl ring, and also their salts, solvates and solvates of the salts.

[2580] Particularly preferred in the context of the present invention are binder-drug conjugates of the formula (Ia), in which

[2581] n is a number from 2 to 8,

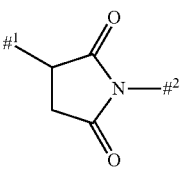
[2582] AK is AK_1 or AK_2,

[2583] where

[2584] AK_1 is a human or humanized antibody or an antigen-binding antibody fragment which binds to mesothelin and is bonded via the sulphur atom of a cysteine residue of the binder to the group G,

[2585] AK_2 is a human or humanized antibody or an antigen-binding antibody fragment which binds to mesothelin and is bonded via the NH side group of a lysine residue of the binder to the group G,

[2586] G when $AK=AK_1$, is a group of the formula



[2587] in which

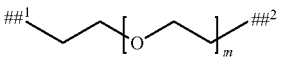
[2588] $\#^1$ marks the linkage site with the cysteine residue of the binder,

[2589] $\#^2$ marks the linkage site with the group L^1,

[2590] or

[2591] when $AK=AK_2$, is carbonyl,

[2592] L^1 is a bond, linear $(C_2$-$C_6)$-alkanediyl or is a group of the formula



[2593] where

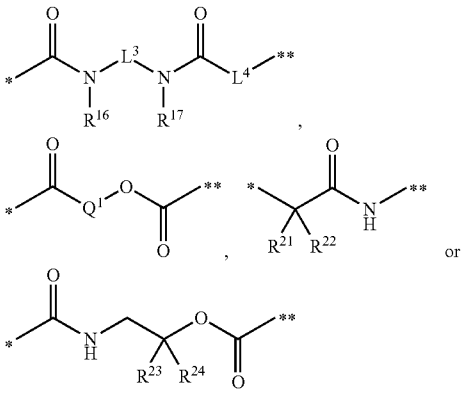
[2594] m is a number 2 or 3,

[2595] $\#\#^1$ marks the linkage site with the group G,

[2596] $\#\#^2$ marks the linkage site with the group B,

[2597] where $(C_2$-$C_6)$-alkanediyl may be substituted by 1 or 2 methyl substituents,

[2598] B is a bond or a group of the formula



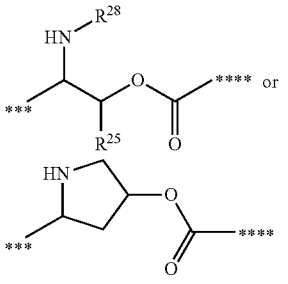
[2599] where

[2600] * marks the linkage site with L^1,

[2601] ** marks the linkage site with L^2,

[2602] L^3 is a bond or ethane-1,2-diyl,

[2603] L^4 is a bond or a group of the formula



[2604] in which

[2605] *** marks the linkage site with the carbonyl group,

[2606] **** marks the linkage site with L^2,

[2607] R^{25} is methyl,

[2608] R^{28} is hydrogen, methylcarbonyl or tert-butyloxycarbonyl,

[2609] Q^1 is piperidine-1,4-diyl,

[2610] R^{16} is hydrogen or methyl,

[2611] R^{17} is hydrogen or methyl,

[2612] or

[2613] R^{16} and R^{17} together with the atoms to which they are bonded form a piperazinyl ring,

[2614] R^{21} is hydrogen or methyl,

[2615] R^{22} is hydrogen or methyl,

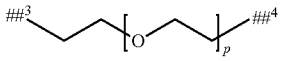
[2616] or

[2617] R^{21} and R^{22} together with the atoms to which they are bonded form a cyclopropyl ring,

[2618] R^{23} is methyl,

[2619] R^{24} is hydrogen,

[2620] L^2 is linear (C_2-C_6)-alkanediyl or is a group of the formula



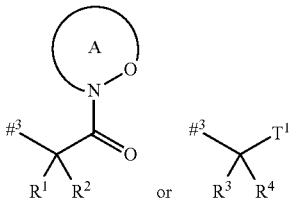
[2621] where

[2622] p is a number from 2 to 6,

[2623] $\#\#^3$ marks the linkage site with the group B,

[2624] $\#\#^4$ marks the linkage site with the nitrogen atom,

[2625] D is a group of the formula



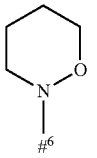
[2626] where

[2627] $\#^3$ marks the linkage site with the nitrogen atom,

[2628] R^1 is hydrogen,

[2629] R^2 is 4-hydroxybenzyl or 1H-indol-3-ylmethyl,

[2630] the ring A with the N—O moiety present therein is



[2631] in which

[2632] $\#^6$ marks the linkage site with the carbonyl group,

[2633] R^3 is hydrogen,

[2634] R^4 is 4-hydroxybenzyl or 1H-indol-3-ylmethyl,

[2635] T^1 is a group of the formula —C(═O)—NR^8R^9,

[2636] R^8 is hydrogen or methyl,

[2637] R^9 is hydrogen, methyl, or ethyl,

[2638] R^{35} is methyl,

and also their salts, solvates and solvates of the salts.

[2639] Particularly preferred in the context of the present invention are binder-drug conjugates of the formula (Ia), in which

[2640] n is a number from 2 to 8, preferably from 2 to 5,

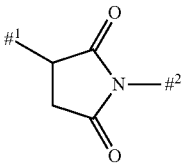
[2641] AK is AK_1 or AK_2,

[2642] where

[2643] AK_1 is a human or humanized antibody or an antigen-binding antibody fragment which binds to mesothelin and is bonded via the sulphur atom of a cysteine residue of the binder to the group G,

[2644] AK_2 is a human or humanized antibody or an antigen-binding antibody fragment which binds to mesothelin and is bonded via the NH side group of a lysine residue of the binder to the group G,

[2645] G when AK=AK_1 is a group of the formula



[2646] where

[2647] $\#^1$ marks the linkage site with the cysteine residue of the binder,

[2648] $\#^2$ marks the linkage site with the group L^1,

[2649] or

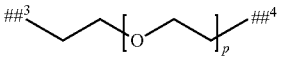
[2650] when AK=AK_2, is carbonyl,

[2651] L^1 is a bond,

[2652] B is a bond

[2653] R^{17} is hydrogen,

[2654] L^2 is pentane-1,5-diyl, hexane-1,6-diyl or is a group of the formula



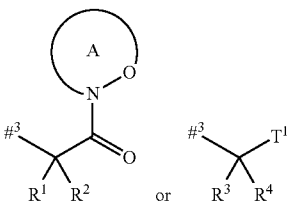
[2655] where

[2656] p is a number 2 or 3,

[2657] $\#\#^3$ marks the linkage site with the group B,

[2658] $\#\#^4$ marks the linkage site with the nitrogen atom,

[2659] D is a group of the formula



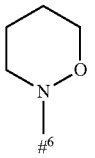
[2660] where

[2661] $\#^3$ marks the linkage site with the nitrogen atom,

[2662] R^1 is hydrogen,

[2663] R^2 is 4-hydroxybenzyl or 1H-indol-3-ylmethyl,

[2664] the ring A with the N—O moiety present therein is



[2665] in which

[2666] #6 marks the linkage site with the carbonyl group,

[2667] R^3 is hydrogen,

[2668] R^4 is 4-hydroxybenzyl or 1H-indol-3-ylmethyl,

[2669] T^1 is a group of the formula —C(═O)—NR^8R^9,

[2670] R^8 is hydrogen,

[2671] R^9 is hydrogen,

[2672] R^{35} is methyl,

and also their salts, solvates and solvates of the salts.

[2673] Preferred subject matter of the invention are binder-drug conjugates of the general formula (Ia), in which

[2674] n is a number from 2 to 8, preferably from 2 to 5,

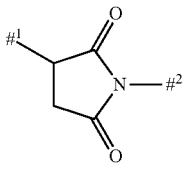
[2675] AK is AK_1 or AK_2,

[2676] where

[2677] AK_1 is a human or humanized antibody or an antigen-binding antibody fragment which binds to mesothelin and is bonded via the sulphur atom of a cysteine residue of the binder to the group G,

[2678] AK_2 is a human or humanized antibody or an antigen-binding antibody fragment which binds to mesothelin and is bonded via the NH side group of a lysine residue of the binder to the group G,

[2679] G when AK=AK_1, is a group of the formula



[2680] where

[2681] #1 marks the linkage site with the cysteine residue of the binder,

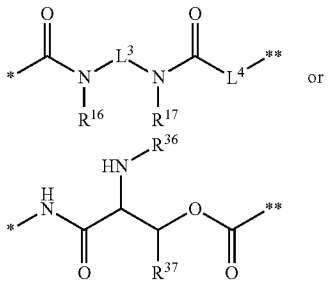
[2682] #2 marks the linkage site with the group L^1,

[2683] or

[2684] when AK=AK_2, is carbonyl,

[2685] L^1 is linear (C_2-C_6)-alkanediyl,

[2686] B is a group of the formula



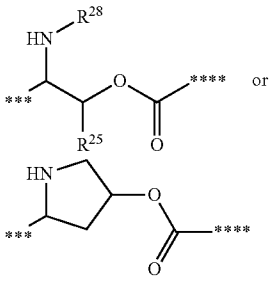
[2687] where

[2688] * marks the linkage site with L^1,

[2689] ** marks the linkage site with L^2,

[2690] L^3 is a bond,

[2691] L^4 is a group of the formula



[2692] in which

[2693] *** marks the linkage site with the carbonyl group,

[2694] **** marks the linkage site with L^2,

[2695] R^{25} is methyl,

[2696] R^{28} is hydrogen, methylcarbonyl or tert-butyloxycarbonyl,

[2697] R^{16} is hydrogen,

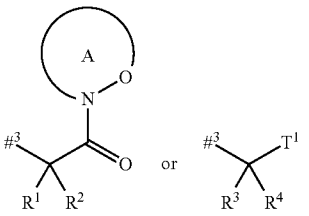
[2698] R^{17} is hydrogen,

[2699] R^{36} is hydrogen, methylcarbonyl or tert-butyloxycarbonyl,

[2700] R^{37} is methyl,

[2701] L^2 is linear (C_2-C_4)-alkanediyl,

[2702] D is a group of the formula



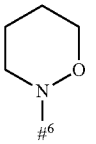
[2703] where

[2704] #3 marks the linkage site with the nitrogen atom,

[2705] R^1 is hydrogen,

[2706] R^2 is 4-hydroxybenzyl or 1H-indol-3-ylmethyl,

[2707] the ring A with the N—O moiety present therein is



[2708] in which

[2709] #6 marks the linkage site with the carbonyl group,

[2710] R^3 is hydrogen,

[2711] R^4 is 4-hydroxybenzyl or 1H-indol-3-ylmethyl,

[2712] T^1 is a group of the formula —C(═O)—NR^8R^9,

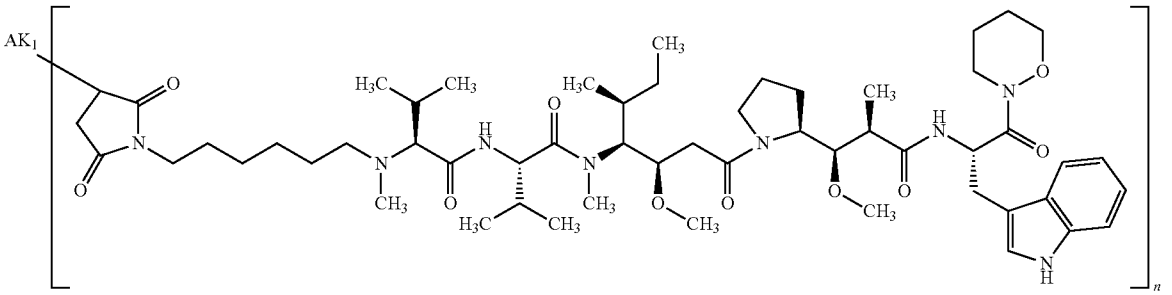
[2713] R^8 is hydrogen,

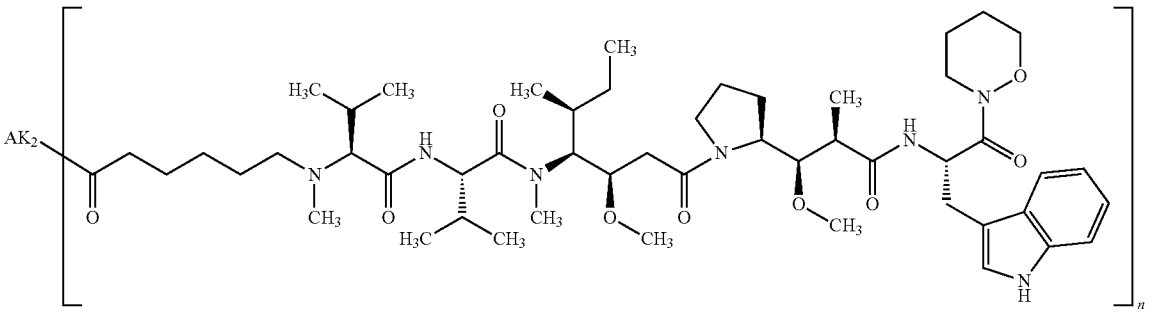
[2714] R^9 is hydrogen,

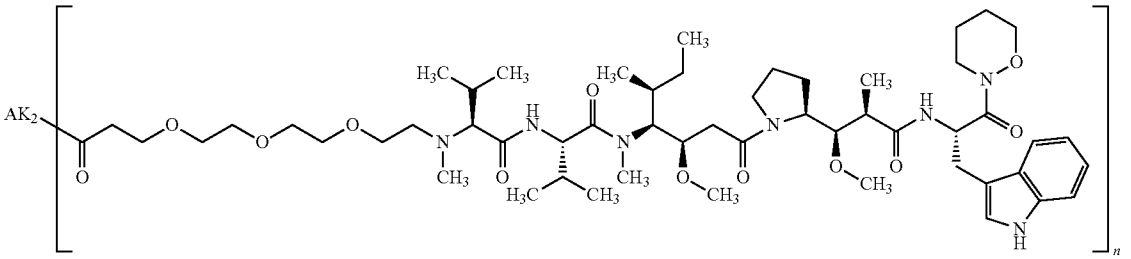
[2715] R^{35} is methyl or hydroxy,

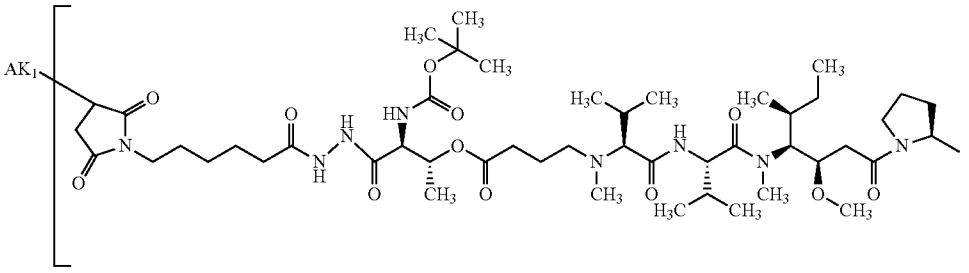
and also their salts, solvates and solvates of the salts.

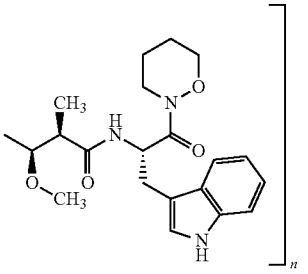
[2716] Particularly preferred in the context of the present invention are also drug-binder conjugates selected from the following compounds:











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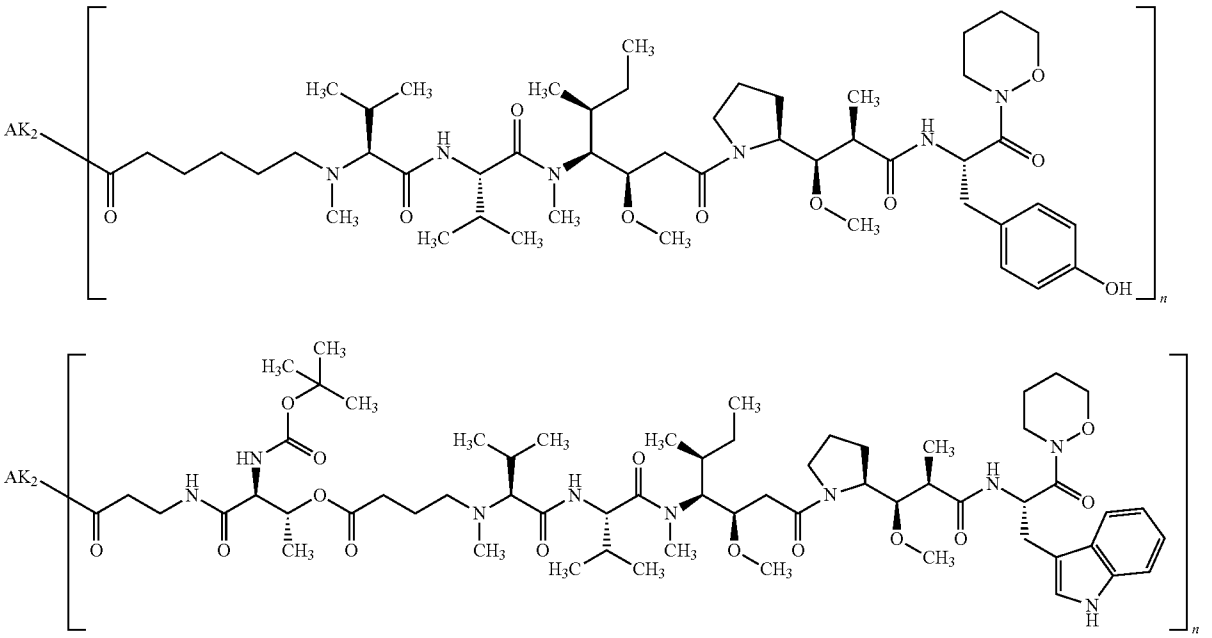


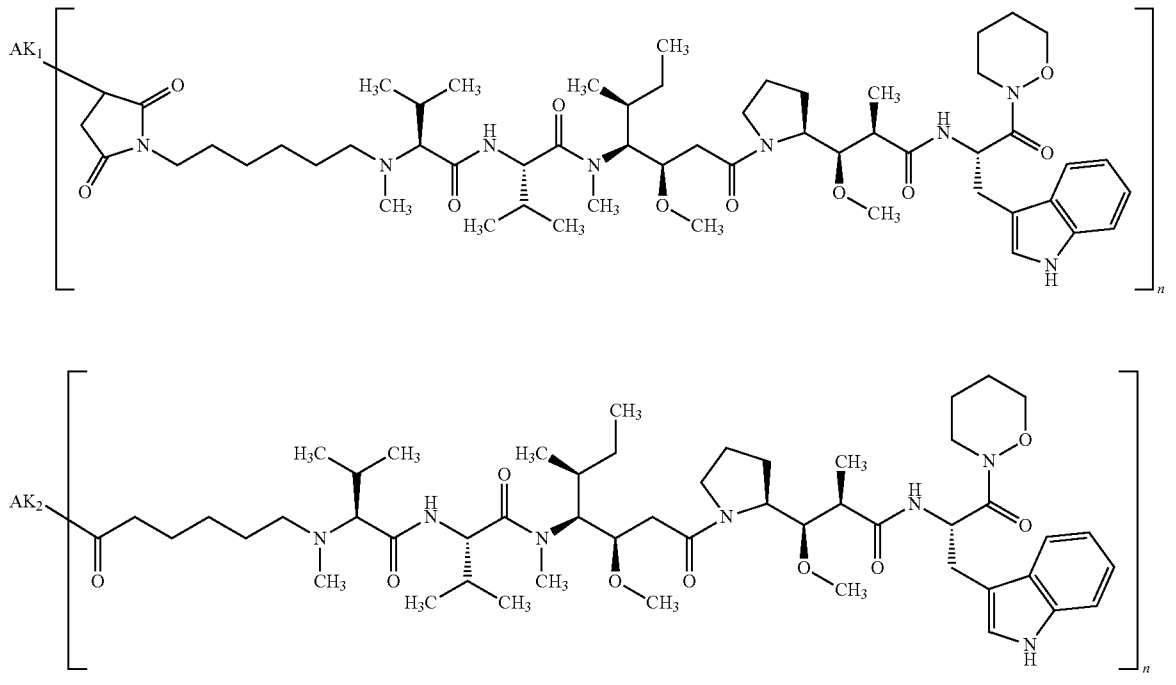
[2717] where in each case

[2718] n is a number from 2 to 8, preferably 2 to 5,

[2719] AK_1 is a human or humanized antibody or an antigen-binding antibody fragment which binds to mesothelin and is bonded via the sulphur atom of a cysteine residue of the binder to the group G,

[2720] AK_2 is a human or humanized antibody or an antigen-binding antibody fragment which binds to mesothelin and is bonded via the NH side group of a lysine residue of the binder to the group G.

[2721] More particularly preferred in the context of the present invention are also binder-drug conjugates selected from the following compounds:



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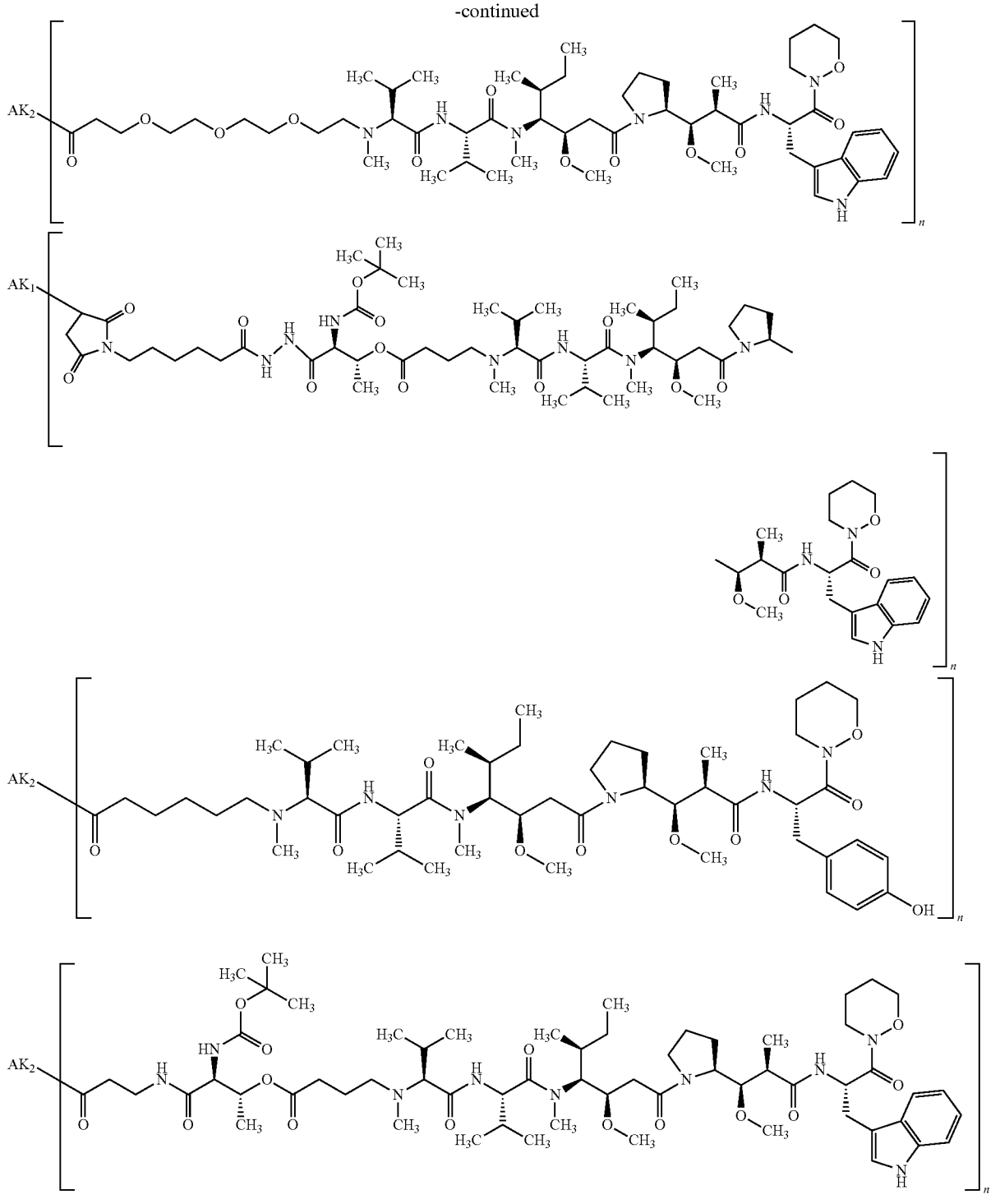


[2722] where in each case

[2723] n is a number from 2 to 8, preferably 2 to 5,

[2724] AK_1 is an antibody which comprises the six CDR sequences of the antibody MF-Ta, the variable light and variable heavy chain of the antibody MF-Ta or the light and heavy chain of the antibody MF-Ta, and is bonded via the sulphur atom of a cysteine residue of the binder to the group G,

[2725] AK_2 is an antibody which comprises the six CDR sequences of the antibody MF-Ta, the variable light and variable heavy chain of the antibody MF-Ta or the light and heavy chain of the antibody MF-Ta, and is bonded via the NH side chain of a lysine residue of the binder to the group G.

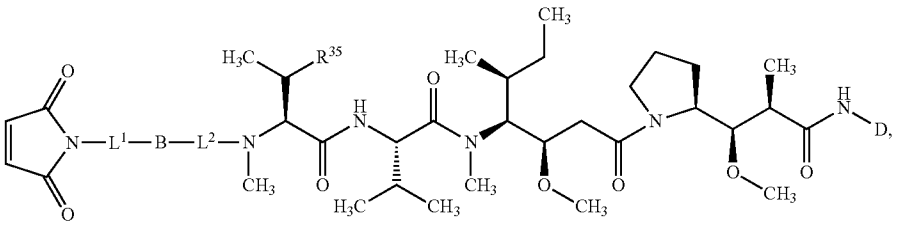
[2726] The definitions of radicals that are indicated individually in the respective combinations and preferred combinations of radicals are also replaced arbitrarily by radical definitions of other combinations, independently of the respective combinations of radicals that are indicated.

[2727] Especially preferred are combinations of two or more of the abovementioned preference ranges.

[2728] Further provided by the invention is a process for preparing the compounds of the invention of the formula (Ia), characterized in that a solution of the binder in PBS buffer

[2729] [A] is admixed with a suitable reducing agent, such as, for example, dithiothreitol or tris(2-carboxyethyl)phosphine hydrochloride, and is subsequently reacted with a compound of the formula (IIa)

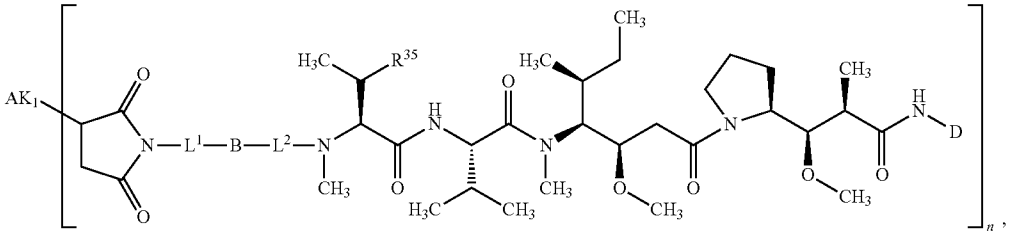
(IIa)



[2730] in which D, L^1, B, L^2 and R^{35} each have the definitions indicated above,

[2731] to give a compound of the formula (I-A)

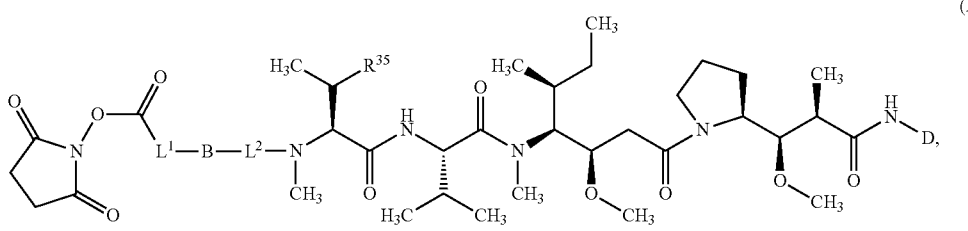
(Ia-A)



[2732] in which n, AK_2, D, L^1, B, L^2 and R^{35} each have the definitions indicated above, or

[2733] [B] is reacted with a compound of formula (IIIa)

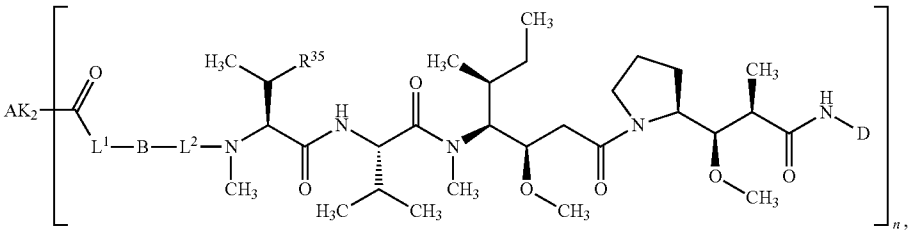
(IIIa)



[2734] in which D, L^1, B, L^2 and R^{35} each have the definitions indicated above,

[2735] to give a compound of the formula (Ia-B)

(Ia-B)

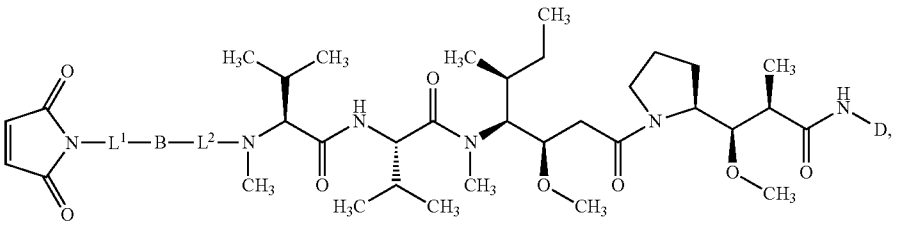


[2736] in which n, AK_2, D, L^1, B, L^2 and R^{35} each have the definitions indicated above.

[2737] Further provided by the invention is a process for preparing the compounds of the invention of the formula (I), characterized in that a solution of the binder in PBS buffer

[2738] [A] is admixed with a suitable reducing agent, such as, for example, dithiothreitol or tris(2-carboxyethyl)phosphine hydrochloride, and is subsequently reacted with a compound of the formula (II)

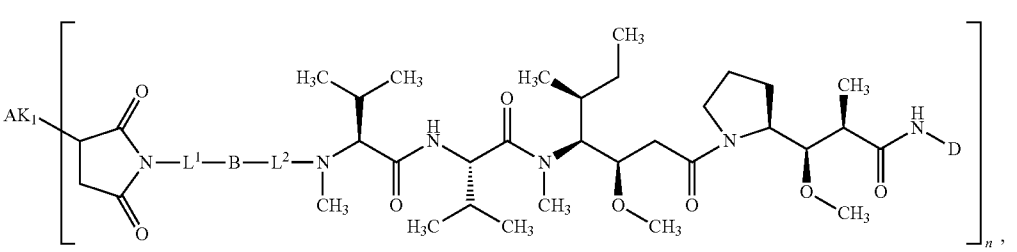
(II)



[2739] in which D, L^1, B and L^2 each have the definitions indicated above,

[2740] to give a compound of the formula (I-A)

(I-A)

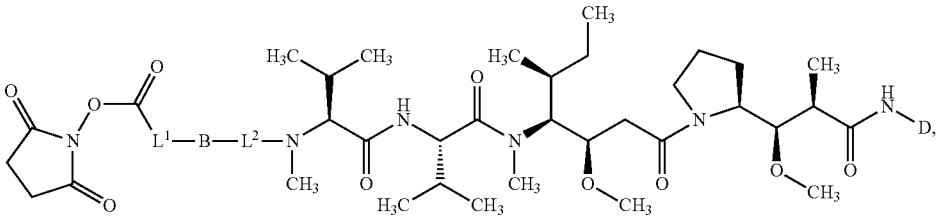


[2741] in which n, AK_1, D, L^1, B and L^2 each have the definitions indicated above,

or

[2742] [B] is reacted with a compound of the formula (III)

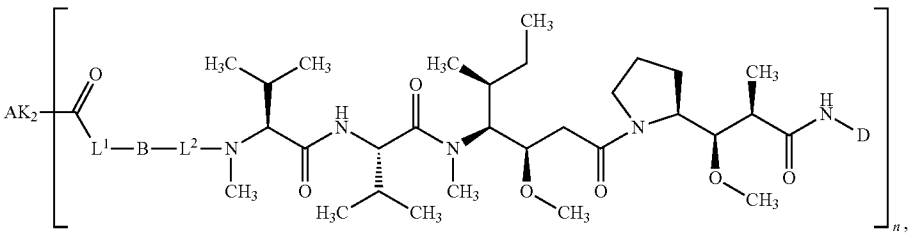
(III)



[2743] in which D, L^1, B and L^2 each have the definitions indicated above,

[2744] to give a compound of the formula (I-B)

(I-B)



[2745] in which n, AK_2, D, L^1, B and L^2 each have the definitions indicated above.

Cysteine Coupling:

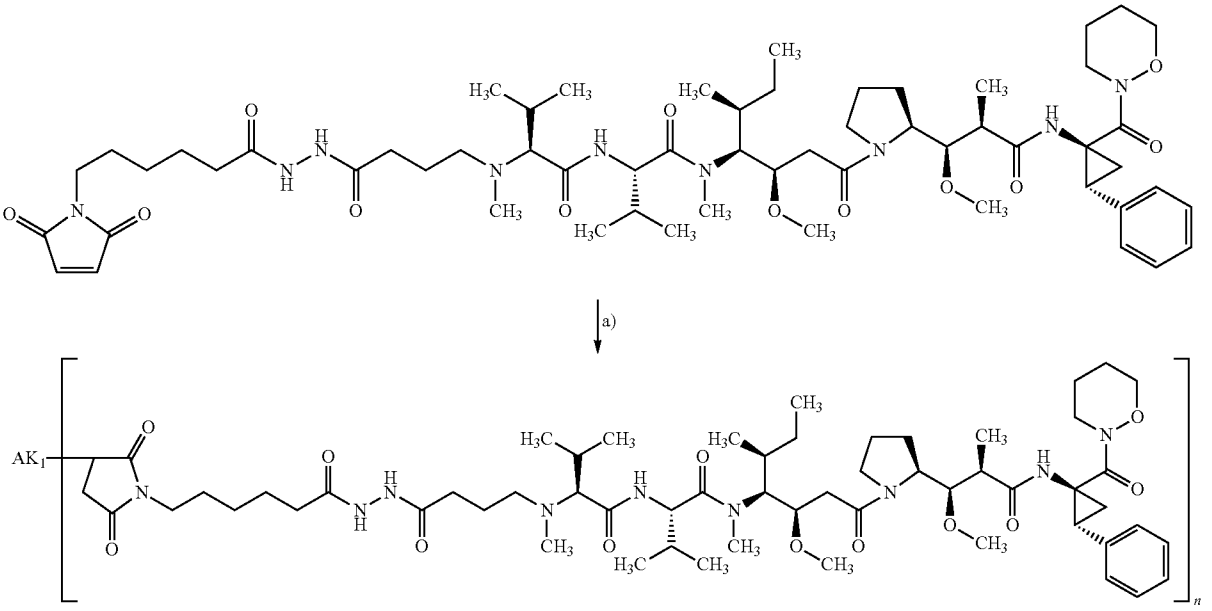
[2746] The partial reduction of the antibody and also the subsequent conjugation of the (partially) reduced antibody with a compound of the formula (II) or (IIa) takes place in accordance with the methods known to the skilled person, see e.g. Ducry et. al., Bioconj. Chem. 2010, 21, 5 and references herein, Klussman et. al., Bioconj. Chem. 2004, 15(4), 765-773. The mild reduction of the antibody is accomplished preferably by addition of 2-6 equivalents of TCEP to the antibody, which is present in a suitable buffer solution, preferably phosphate buffer, and by stirring for 30-180 minutes at temperatures between 15 and 40° C., preferably at RT. This is followed by the conjugation, by addition of a solution of a compound of the formula (II) or (IIa) in DMSO, acetonitrile or DMF to the solution of the (partially) reduced antibody in PBS buffer, and subsequent reaction at a temperature of 0° C. to +40° C., more particularly of +10° C. to +30° C., for a period of 30 minutes to 6 hours, more particularly 1 to 2 hours.

Lysine Coupling:

[2747] First of all the compounds of the formula (III) or (IIa) or comparable activated carboxyl components are prepared by conventional methods of peptide chemistry. They are then taken up in inert solvents such as DMSO or DMF, for example, and added to the antibody, which is preferably present in phosphate buffer at a neutral pH. The solution is stirred for 1-16 h at a temperature between 15 and 40° C., preferably RT.

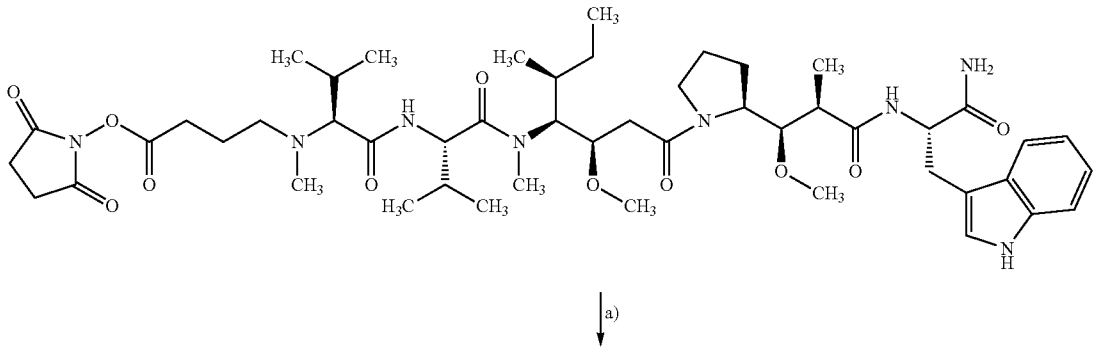
[2748] The preparation processes described above are elucidated by way of example using the schemes below (Scheme 1 and 2):

Scheme 1



[a): 1. AK (antibody), TCEP, PBS buffer, RT; 2. Addition of the maleimide derivative in DMSO, RT].

Scheme 2



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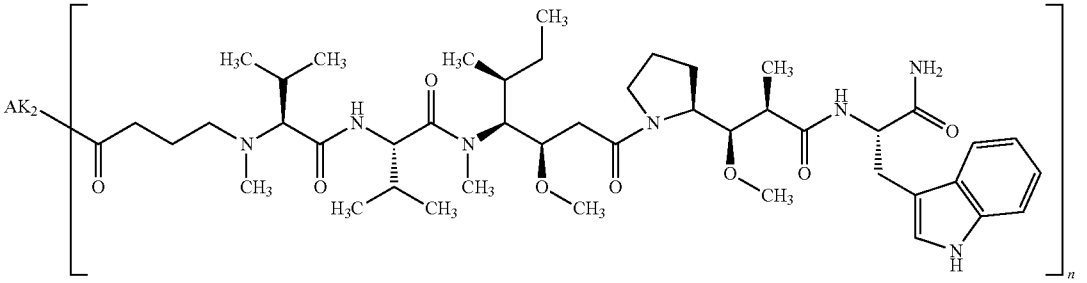
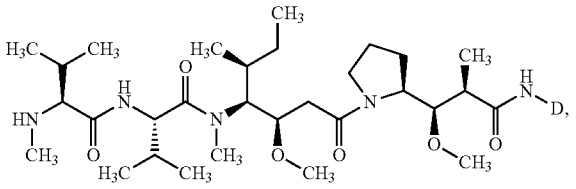
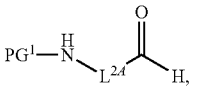


[a]: AK (antibody), PBS buffer, RT admix with activated carboxyl derivative of the linker-drug components].

[2749] The compounds of the formula (II) in which L^1 and B are a bond can be prepared by subjecting a compound of the formula (IV)



in which D has the definition indicated above,
to reductive amination in an inert solvent with a compound of the formula (V)



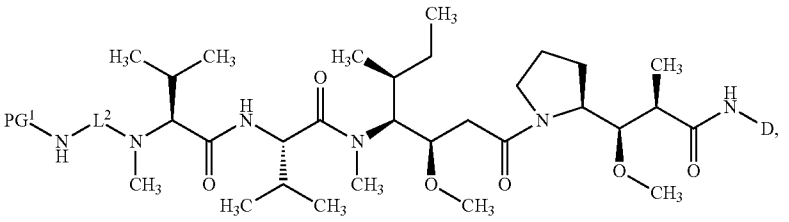
(V)

in which

[2750] L^{2A} has the above-defined definition of L^2, but is shortened by one carbon atom in the alkyl chain length,

[2751] PG^1 is an amino-protective group such as, for example, (9H-fluoren-9-ylmethoxy)carbonyl, tert-butoxycarbonyl or benzyloxycarbonyl,

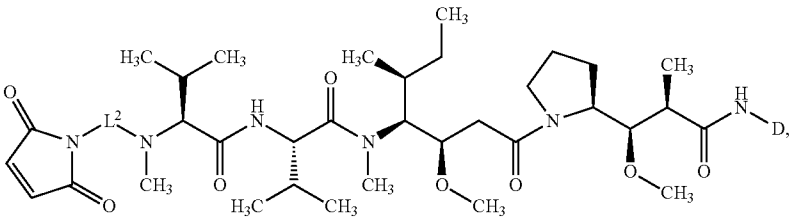
[2752] to give a compound of the formula (VI)



(VI)

in which D, L^2 and PG^1 have the definition indicated above,

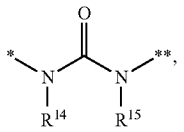
[2753] eliminating the protective group PG^1 from this compound by methods known to the skilled person, and reacting the deprotected compound in an inert solvent in the presence of a suitable base with methyl 2,5-dioxo-2,5-dihydro-1H-pyrrole-1-carboxylate to give a compound of the formula (II-A)



(II-A)

in which D and L^2 each have the definitions indicated above.

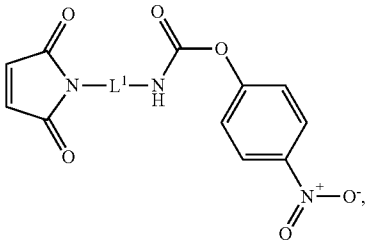
[2754] The compounds of the formula (II) in which B is a group of the formula (B^1)



(B^1)

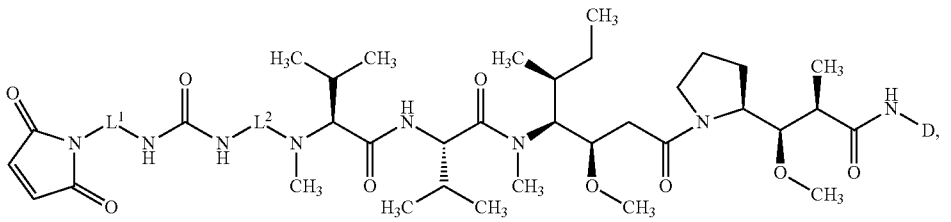
in which *, **, R^{14} and R^{15} each have the conditions indicated above,

can be prepared by eliminating the protective group PG^1 from a compound of the formula (VI) by methods known to the skilled person, and reacting the deprotected compound in an inert solvent in the presence of a suitable base with a compound of the formula (VII)



(VII)

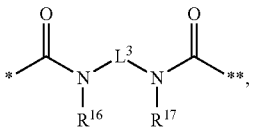
in which L^1 has the definition indicated above,
to give a compound of the formula (II-B)



(II-B)

in which D, L^1 and L^2 each have the definitions indicated above.

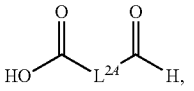
[2755] The compounds of the formula (II) in which B is a group of the formula (B^2)



(B^2)

in which *, **, L^3, R^{16} and R^{17} each have the conditions indicated above can be prepared by subjecting a compound of the formula (IV)

to reductive amination in an inert solvent with a compound of the formula (VIII)

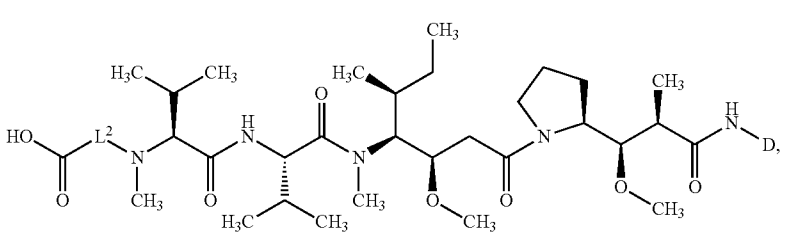


(VIII)

in which

[2756] L^{2A} has the above-defined definition of L^2, but is shortened by one carbon atom in the alkyl chain length,

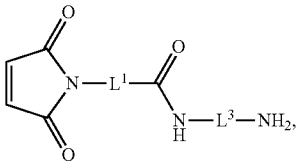
to give a compound of the formula (IX)



(IX)

in which D and L^2 have the definitions indicated above,

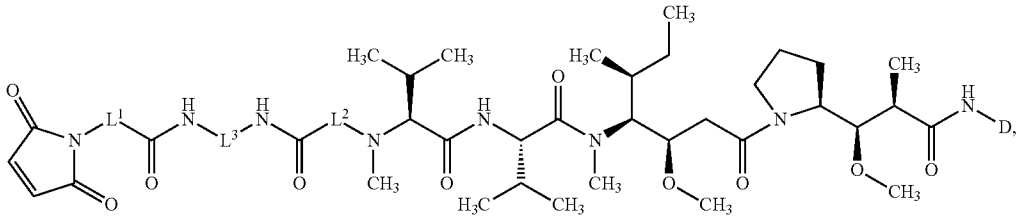
and reacting this compound in an inert solvent in the presence of a suitable coupling reagent and a suitable base with a compound of the formula (X)



(X)

in which L^1 and L^3 each have the definitions indicated above,

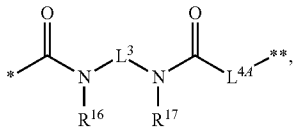
to give a compound of the formula (II-C)



(II-C)

in which D, L^1, L^2 and L^3 each have the definitions indicated above.

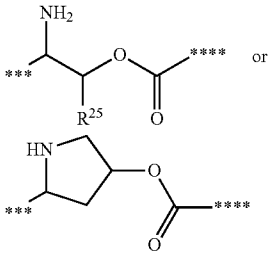
[2757] Compound of the formula (II), in which B is a group of the formula (B^3)



(B^3)

in which *, **, L^3, R^{16} and R^{17} each have the conditions indicated above and

[2758] L^{4A} is a group of the formula



or

[2759] in which

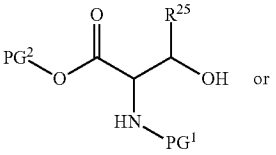
[2760] *** marks the linkage site with the carbonyl group,

[2761] **** marks the linkage site with L^2,

[2762] R^{25} is hydrogen or methyl,

can be prepared by reacting a compound of the formula (IX) in an inert solvent in the presence of a suitable base and a suitable coupling reagent with a compound of the formula (XI-A) or (XI-B)

(XI-A)



or

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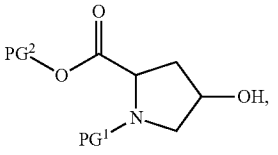
(XI-B)

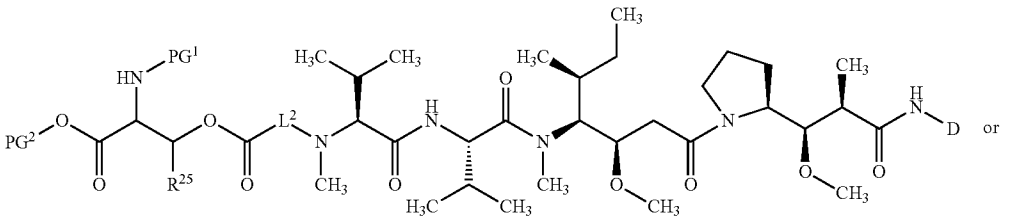


in which R^{25} and PG^1 each have the definitions indicated above and

PG^2 is a suitable carboxyl-protective group, more particularly benzyl,

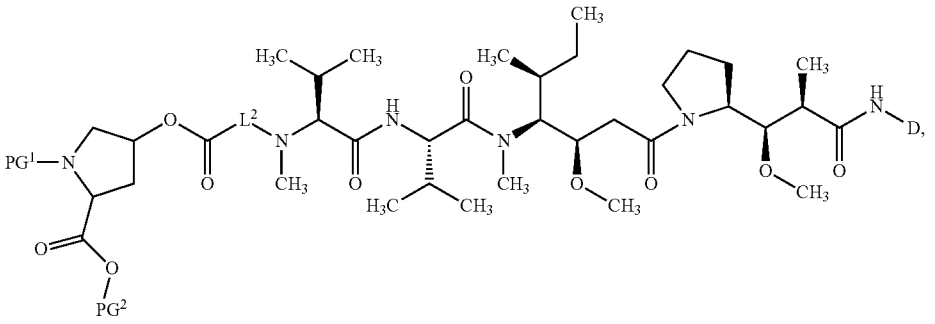
to give a compound (XII-A) or (XII-B)

(XII-A)



or

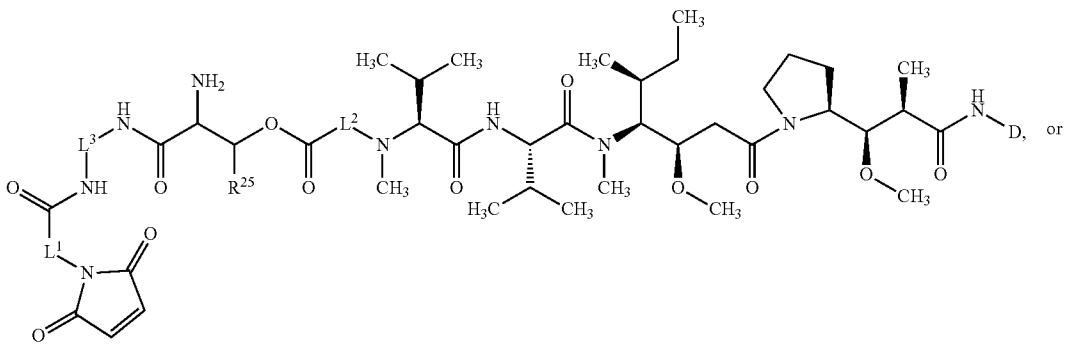
(XII-B)



in which D, PG', PG^2 and L^2 have the definitions indicated above,

eliminating the protective group PG^2 from this compound subsequently, by methods known to the skilled person, and reacting the deprotected compound in an inert solvent in the presence of a suitable coupling reagent and a suitable base with a compound of the formula (X), and finally, eliminating the protective group PG1 from this compound, by methods known to the skilled person, to give a compound of the formula (II-D-A) or (II-D-B)

(II-D-A)



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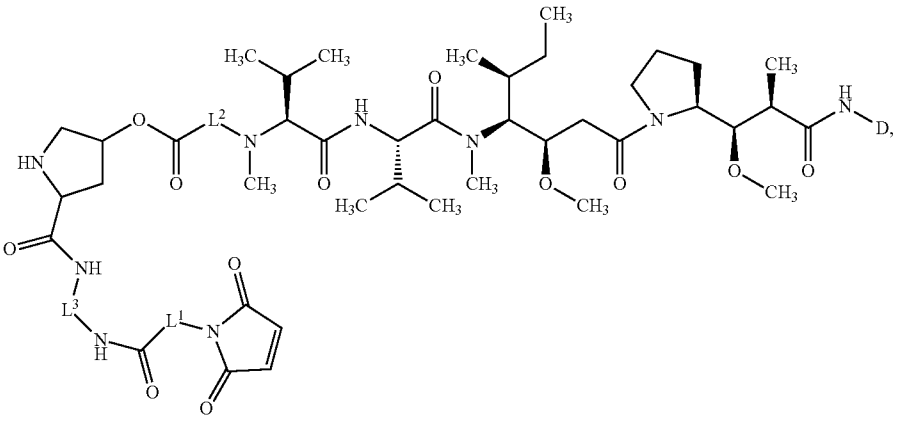
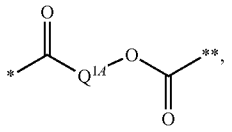
(II-D-B)



in which D, L^1, L^2 and L^3 have the definitions indicated above.

[2763] Compound of the formula (II), in which B is a group of the formula (B^4)

(B^4)

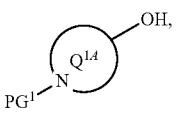


in which *, ** each have the conditions indicated above and

[2764] Q^{1A} is an N-linked 4- to 7-membered heterocycle,

can be prepared by reacting a compound of the formula (IX) in an inert solvent in the presence of a suitable base and a suitable coupling reagent with a compound of the formula (XXI)

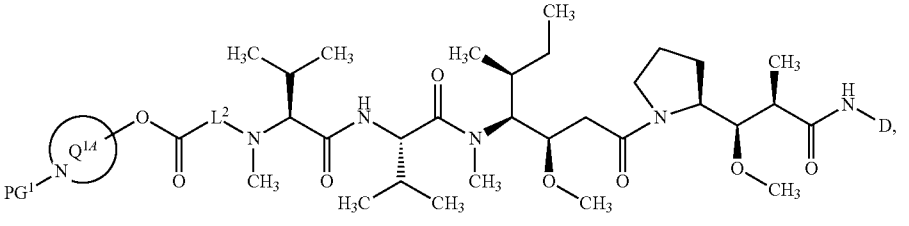
(XXI)



in which PG^1 and Q^{1A} each have the definitions indicated above,

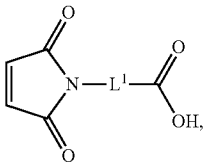
to give a compound of the formula (XXII)

(XXII)



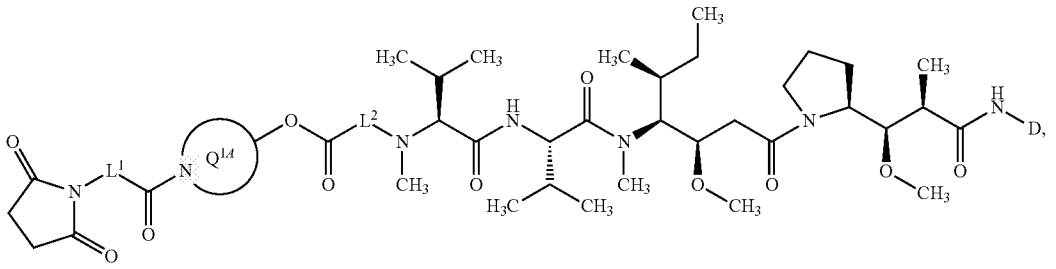
in which PG^1, Q^{1A}, D and L^2 have the definitions indicated above,
eliminating the protective group PG^1 from this compound, by methods known to the skilled person, and subsequently reacting the deprotected compound in an inert solvent in the presence of a suitable coupling reagent and a suitable base with a compound of the formula (XXIII)

(XXIII)



in which L^1 has the definition indicated above,
to give a compound of the formula (II-D)

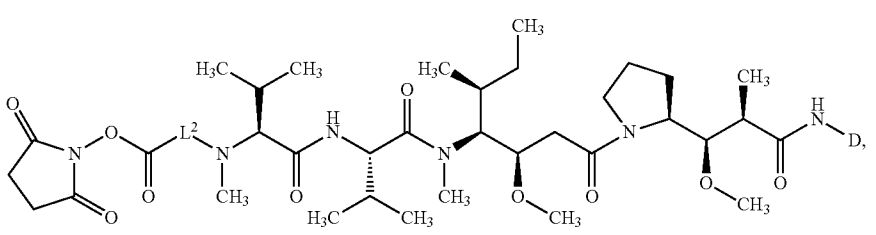
(II-D)



in which Q^{1A}, D, L^1 and L^2 have the definitions indicated above.

[2765] The compounds of the formula (III), in which L^1 and B are a bond can be prepared by reacting a compound of the formula (IX) in an inert solvent in the presence of a suitable coupling reagent and a suitable base with N-hydroxysuccinimide to give a compound of the formula (III-A)

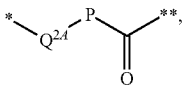
(III-A)



in which D and L^2 each have the definitions indicated above.

[2766] The compounds of the formula (III), in which L^1 is a bond and B is a group of the formula (B^{5A})

(B^{5A})

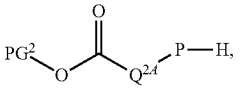


in which *, ** and P each have the definitions indicated above and

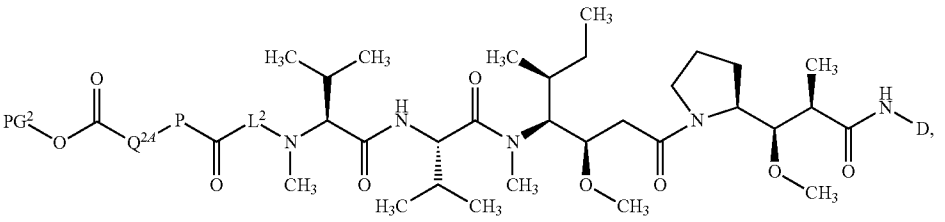
[2767] Q^{2A} is a 3- to 7-membered carbocycle,

can be prepared by reacting a compound of the formula (IX) in an inert solvent in the presence of a suitable coupling reagent and a suitable base with a compound of the formula (XIII)

(XIII)

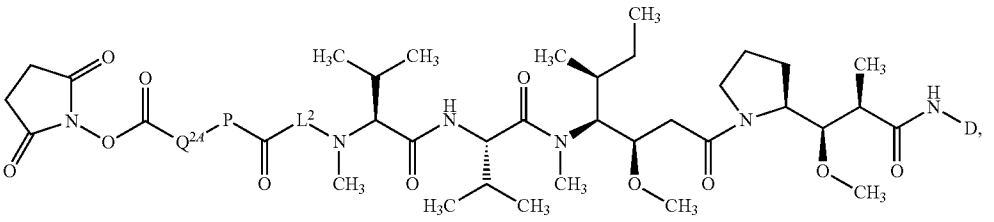


in which P, Q^{2A} and PG^2 each have the definitions indicated above,
to give a compound of the formula (XIV)



(XIV)

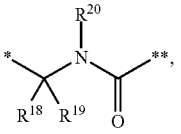
in which D, P, Q^{2A}, L^2 and PG^2 each have the definitions indicated above,
eliminating the protective group PG^2 from this compound by methods known to the skilled person, and subsequently reacting the deprotected compound in an inert solvent in the presence of a suitable base with N-hydroxysuccinimide to give a compound of the formula (III-B)



(III-B)

in which D, P, Q^{2A} and L^2 each have the definitions indicated above.

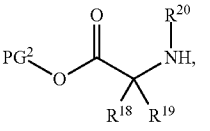
[2768] The compounds of the formula (III), in which L^1 is a bond and B is a group of the formula (B^6)



(B^6)

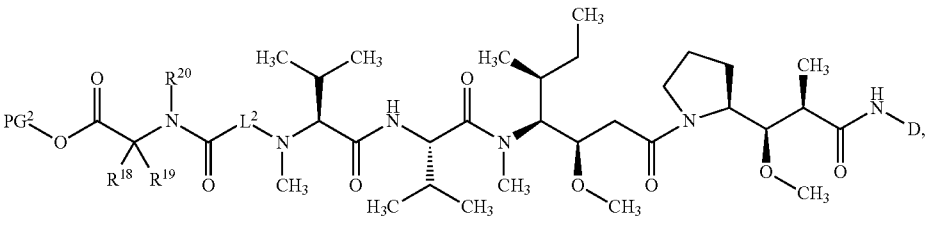
in which *, **, R^{18}, R^{19} and R^{20} each have the definitions indicated above,

can be prepared by reacting a compound of the formula (IX) in an inert solvent in the presence of a suitable coupling reagent and a suitable base with a compound of the formula (XV)



(XV)

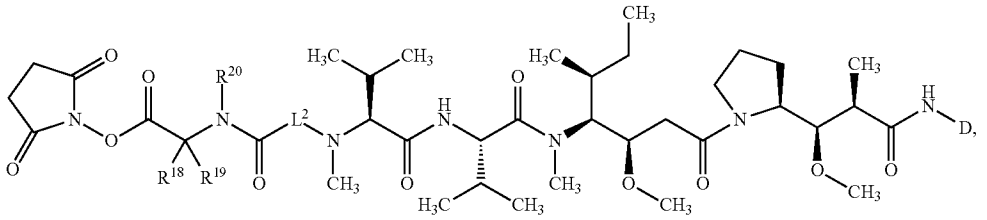
in which R^{18}, R^{19}, R^{20} and PG^2 each have the definitions indicated above,
to give a compound of the formula (XVI)



(XVI)

in which D, R^{18}, R^{19}, R^{20}, L^2 and PG^2 each have the definitions indicated above,

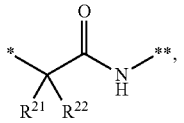
eliminating the protective group PG^2 from this compound by methods known to the skilled person, and subsequently reacting the deprotected compound in an inert solvent in the presence of a suitable coupling reagent and a suitable base with N-hydroxysuccinimide to give a compound of the formula (III-C)



(III-C)

in which D, R^{18}, R^{19}, R^{20} and L^2 each have the definitions indicated above.

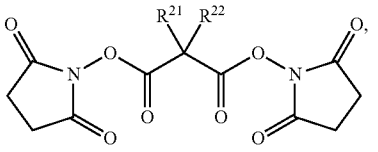
[2769] The compounds of the formula (III), in which L^1 is a bond and B is a group of the formula (B^7)



(B^7)

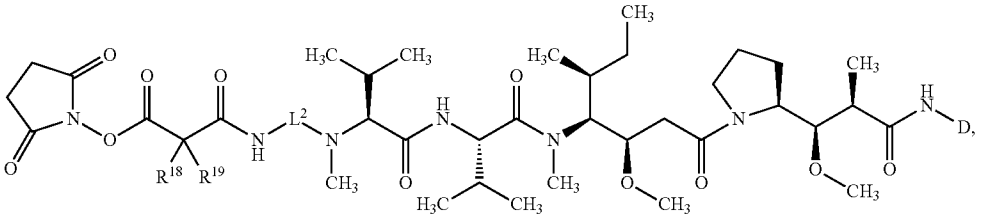
in which *, **, R^{21} and R^{22} each have the definitions indicated above,

can be prepared by eliminating the protective group PG^1 from a compound of the formula (VI) by methods known to the skilled person, and reacting the resultant deprotected compound in an inert solvent in the presence of a suitable base with a compound of the formula (XVII)



(XVII)

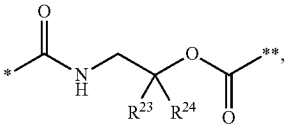
in which R^{21} and R^{22} each have the definitions indicated above,
to give a compound of the formula (III-D)



(III-D)

in which D, R^{21}, R^{22} and L^2 each have the definitions indicated above.

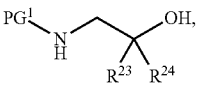
[2770] The compounds of the formula (III), in which B is a group of the formula (B^8)



(B^8)

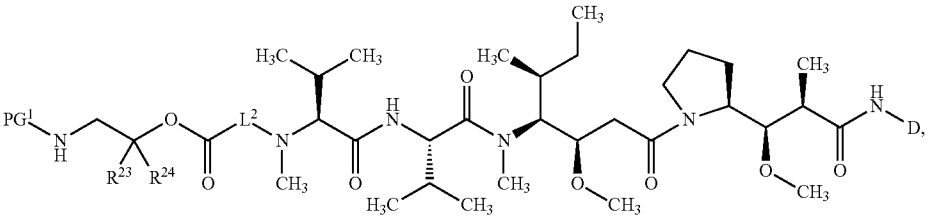
in which *, **, R^{23} and R^{24} each have the definitions indicated above,

can be prepared by reacting a compound of the formula (IX) in an inert solvent in the presence of a suitable coupling reagent and a suitable base with a compound of the formula (XVIII)



(XVIII)

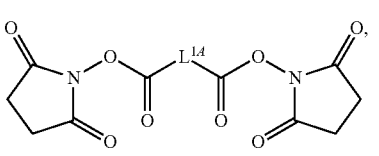
in which R^{23}, R^{24} and PG^1 each have the definitions indicated above, to give a compound of the formula (XIX)



(XIX)

in which D, R^{23}, R^{24}, L^2 and PG^1 each have the definitions indicated above,

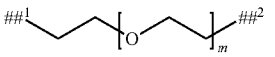
eliminating the protective group PG^1 from this compound by methods known to the skilled person, and subsequently reacting the deprotected compound in an inert solvent in the presence of a suitable coupling reagent and a suitable base with a compound of the formula (XX)



(XX)

in which

L^{1A} is linear (C_1-C_{10})-alkanediyl or is a group of the formula



[2771] where

[2772] m is a number from 2 to 6,

[2773] $##^1$ marks the linkage site with the group G,

[2774] $##^2$ marks the linkage site with the group B,

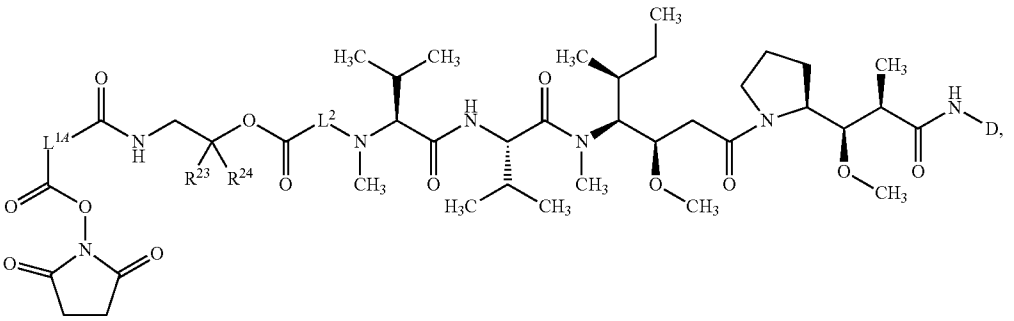
[2775] where (C_1-C_{10})-alkanediyl may be substituted by 1 to 4 methyl substituents,

[2776] and

[2777] where two carbon atoms of the alkanediyl chain in 1,2, 1,3 or 1,4 relation to one another, with inclusion of any carbon atoms situated between them, may be bridged to form a (C_3-C_6)-cycloalkyl ring or a phenyl ring,

to give a compound of the formula (III-E)

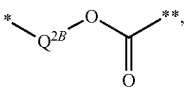
(III-E)



in which D, R^{23}, R^{24}, L^{1A} and L^2 each have the definitions indicated above.

[2778] The compounds of the formula (III), in which B is a group of the formula (B^{5B})

(B^{5B})

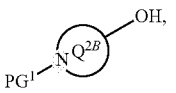


in which * and ** each have the definitions indicated above and

[2779] Q^{2B} is an N-linked 4- to 7-membered heterocycle,

can be prepared by reacting a compound of the formula (IX) in an inert solvent in the presence of a suitable base and a suitable coupling reagent with a compound of the formula (XXIV)

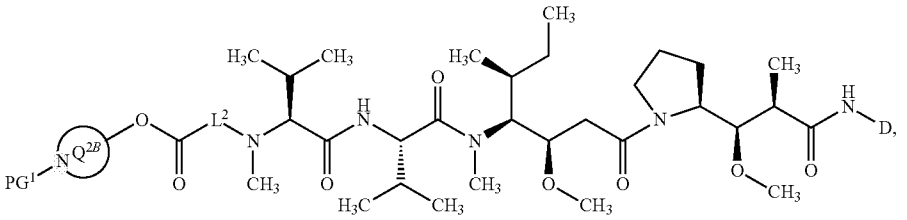
(XXIV)



in which PG^1 and Q^{2B} each have the definitions indicated above,

to give a compound of the formula (XXV)

(XXV)

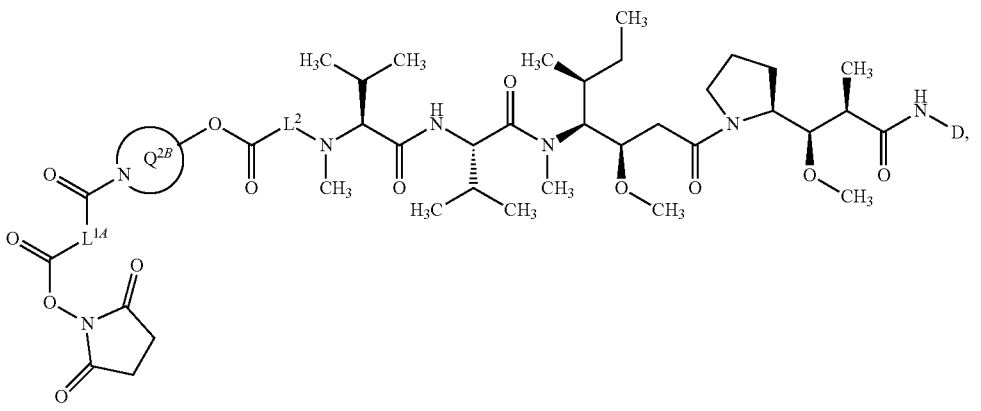


in which PG^1, Q^{2B}, D and L^2 have the definitions indicated above,

eliminating the protective group PG^1 from this compound by methods known to the skilled person,

and subsequently converting the deprotected compound in an inert solvent in the presence of a suitable base with a compound of the formula (XX) into a compound of the formula (III-F)

(III-F)



in which Q^{2B}, D, L^{1A} and L^2 have the definitions indicated above.

[2780] The reactions (IV)+(V)→(VI) and (IV)+(VIII)→(IX) take place in the solvents which are customary for a reductive amination and are inert under the reaction conditions, optionally in the presence of an acid and/or of a water-removing agent as catalyst. Such solvents include, for example, alcohols such as methanol, ethanol, n-propanol, isopropanol, n-butanol or tert-butanol, ethers such as tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane or bis(2-methoxyethyl)ether, or other solvents such as dichloromethane, 1,2-dichloroethane, N,N-dimethylformamide or else water. It is also possible to use mixtures of these solvents. As solvent it is preferred to use a 1,4-dioxane/water mixture, with addition of acetic acid or dilute hydrochloric acid as catalyst.

[2781] Reducing agents suitable for this reaction are, in particular, complex borohydrides, such as, for example, sodium borohydride, sodium cyanoborohydride, sodium triacetoxyborohydride, tetra-n-butylammonium borohydride or borane-pyridine complex. It is preferred to use sodium cyanoborohydride or borane-pyridine complex.

[2782] The reactions (IV)+(V)→(VI) and (IV)+(VIII)→(IX) take place in general in a temperature range from 0° C. to +120° C., preferably at +50° C. to +100° C. The reactions may be carried out under atmospheric, increased or reduced pressure (e.g. from 0.5 to 5 bar); it is usual to operate at atmospheric pressure.

[2783] The above-described coupling reactions (IX)+(X)→(II-C), (XII-A) or (XII-B)+(X)→(II-D-A) or (II-D-B), (IX)+(XIII)→(XIV), (IX)+(XV)→(XVI) and (XXII)+(XXIII)→(II-D) (amide formation from amine component and carboxylic acid component respectively) are carried out by standard methods of peptide chemistry [see e.g. M. Bodanszky, *Principles of Peptide Synthesis*, Springer-Verlag, Berlin, 1993; M. Bodanszky and A. Bodanszky, *The Practice of Peptide Synthesis*, Springer-Verlag, Berlin, 1984; H.-D. Jakubke and H. Jeschkeit, *Aminosäuren, Peptide, Proteine*, Verlag Chemie, Weinheim, 1982].

[2784] Examples of inert solvents for these coupling reactions are ethers such as diethyl ether, diisopropyl ether, tert-butyl methyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane or bis(2-methoxyethyl)ether, hydrocarbons such as benzene, toluene, xylene, pentane, hexane, heptane, cyclohexane or petroleum fractions, halogenated hydrocarbons such as dichloromethane, trichloromethane, tetrachloromethane, 1,2-dichloroethane, trichloroethylene or chlorobenzene, or dipolar-aprotic solvents such as acetone, methyl ethyl ketone, acetonitrile, ethyl acetate, pyridine, dimethyl sulphoxide (DMSO), N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA), N,N'-dimethylpropyleneurea (DMPU) or N-methylpyrrolidinone (NMP). It is also possible to use mixtures of such solvents. Preference is given to using N,N-dimethylformamide.

[2785] Examples of suitable activating/condensing agents for these couplings include carbodiimides such as N,N'-diethyl-, N,N'-dipropyl-, N,N'-diisopropyl-, N,N'-dicyclohexylcarbodiimide (DCC) or N-(3-dimethylaminoisopropyl)-N'-ethylcarbodiimide hydrochloride (EDC), phosgene derivatives such as N,N'-carbonyldiimidazole (CDI) or isobutyl chloroformate, 1,2-oxazolium compounds such as 2-ethyl-5-phenyl-1,2-oxazolium 3-sulphate or 2-tert-butyl-5-methylisoxazolium perchlorate, acylamino compounds such as 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline, phosphorus compounds such as propanephosphonic anhydride, diethyl cyanophosphonate, bis(2-oxo-3-oxazolidinyl)phosphoryl chloride, benzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate or benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (PyBOP), or uronium compounds such as O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU), 2-(2-oxo-1-(2H)-pyridyl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TPTU), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) or O-(1H-6-chlorobenzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate (TCTU), optionally in combination with further auxiliaries such as 1-hydroxybenzotriazole (HOBt) or N-hydroxysuccinimide (HOSu), and also, as bases, alkali metal carbonates, e.g. sodium or potassium carbonate, or tertiary amine bases such as triethylamine, N-methylmorpholine, N-methylpiperidine, N,N-diisopropylethylamine, pyridine or 4-N,N-dimethylaminopyridine.

[2786] In the context of the present invention, as activating/condensing agents for such coupling reactions, it is preferred to use N-(3-dimethylaminoisopropyl)-N'-ethylcarbodiimide hydrochloride (EDC) in combination with 1-hydroxybenzotriazole (HOBt) and N,N-diisopropylethylamine, or O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) likewise in conjunction with N,N-diisopropylethylamine.

[2787] The coupling reactions (IX)+(X)→(II-C), (XII-A) or (XII-B)+(X)→(II-D-A) or (II-D-B), (IX)+(XIII)→(XIV), (IX)+(XV)→(XVI) and (XXII)+(XXIII)→(II-D) are carried out in general in a temperature range from −20° C. to +60° C., preferably at 0° C. to +40° C. The reactions may take place under atmospheric, at increased or at reduced pressure (e.g. from 0.5 to 5 bar); it is usual to operate under atmospheric pressure.

[2788] The esterifications (IX)+(XVIII)→(XII) and (IX)+(XI-A) or (XI-B)→(XII-A) or (XII-B), (IX)+(XXIV)→(XXV) and also (IX)+(XXI)→(XXII) take place in analogy to the above-described amide coupling reactions. These reactions take place preferably in dichloromethane, using N-(3-dimethylaminoisopropyl)-N'-ethylcarbodiimide hydrochloride (EDC) and 4-dimethylaminopyridine at a temperature of +50° C. to 100° C. under atmospheric pressure.

[2789] The functional groups optionally present in the compounds—such as amino, hydroxyl and carboxyl groups in particular—may also be present in a temporarily protected form during the above-described process steps, if useful or necessary. In these cases, such protective groups are introduced and removed in accordance with customary methods known from peptide chemistry [see, for example, T. W. Greene and P. G. M. Wuts, *Protective Groups in organic Synthesis*, Wiley, New York, 1999; M. Bodanszky and A. Bodanszky, *The Practice of Peptide Synthesis*, Springer-Verlag, Berlin, 1984]. Where two or more protected groups are present, they can be liberated again optionally simultaneously in a one-pot reaction, or else liberated again in separate reaction steps.

[2790] As an amino-protective group PG^1 it is preferred to use tert-butoxycarbonyl (Boc), benzyloxycarbonyl (Z) or (9H-fluoren-9-ylmethoxy)carbonyl (Fmoc); for a hydroxyl or carboxyl function it is preferred to use tert-butyl or benzyl as protective group PG^2. The elimination of a tert-butyl or tert-butoxycarbonyl group is typically accomplished by treatment with a strong acid, such as hydrogen chloride, hydrogen bromide or trifluoroacetic acid, in an inert solvent such as diethyl ether, 1,4-dioxane, dichloromethane or acetic acid; this reaction may optionally also be carried out without addition of an inert solvent. In the case of benzyl or benzyloxycarbonyl as protective group, this group is removed preferably by hydrogenolysis in the presence of a suitable palladium catalyst, such as palladium on activated carbon, for example. The

(9H-fluoren-9-ylmethoxy)carbonyl group is generally eliminated using a secondary amine base such as diethylamine or piperidine.

[2791] The reaction (VI)→(II-A) takes place in a solvent which is inert under the reaction conditions, such as, for example, ethers such as tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane or bis(2-methoxyethyl)ether, alcohols such as methanol, ethanol, isopropanol, n-butanol or tert-butanol, or dipolar-aprotic solvents such as acetone, methyl ethyl ketone, acetonitrile, ethyl acetate, pyridine, dimethyl sulphoxide (DMSO), N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA), N,N'-dimethylpropyleneurea (DMPU) or N-methylpyrrolidinone (NMP) or water. It is also possible to use mixtures of such solvents. Preference is given to using a mixture of 1,4-dioxane and water.

[2792] Suitable bases for the reaction (VI)→(II-A) are, for example, alkali metal carbonates such as potassium carbonate, sodium carbonate or lithium carbonate, alkali metal hydrogencarbonates such as sodium or potassium hydrogencarbonate or alkali metal alkoxides such as sodium methoxide, sodium ethoxide or potassium tert-butoxide. It is preferred to use sodium hydrogencarbonate.

[2793] The reaction (VI)→(II-A) takes place in a temperature range from 0° C. to +50° C., preferably at +10° C. to +30° C. The reaction may take place under atmospheric, under elevated or under reduced pressure (e.g. from 0.5 to 5 bar); it is usual to operate under atmospheric pressure.

[2794] The reaction (VI)+(VII)→(II-B) takes place in a solvent which is inert under the reaction conditions, such as, for example, ethers such as tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane or bis(2-methoxyethyl)ether, alcohols such as methanol, ethanol, isopropanol, n-butanol or tert-butanol, or dipolar-aprotic solvents such as acetone, methyl ethyl ketone, acetonitrile, ethyl acetate, pyridine, dimethyl sulphoxide (DMSO), N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA), N,N'-dimethylpropyleneurea (DMPU) or N-methylpyrrolidinone (NMP) or water. It is also possible to use mixtures of such solvents. Preference is given to using DMF.

[2795] Suitable bases for the reaction (VI)+(VII)→(II-B) are, for example, tertiary amine bases such as triethylamine, N-methylmorpholine, N-methylpiperidine, N,N-diisopropylethylamine, pyridine or 4-N,N-dimethylaminopyridine. Preference is given to using N,N-diisopropylethylamine.

[2796] The reaction (VI)+(VII)→(II-B) takes place in a temperature range from 0° C. to +50° C., preferably at +10° C. to +30° C. The reaction may take place under atmospheric, under elevated or under reduced pressure (e.g. from 0.5 to 5 bar); it is usual to operate under atmospheric pressure.

[2797] The reactions (IX)→(III-A), (XIV)→(III-B) and (XVI)→(III-C) and also (VI)+(XVII)→(III-D), (XIX)+(XX)→(III-E) and (XXV)+(XX)→(III-F) take place in a solvent which is inert under the reaction conditions. Examples of suitable solvents are ethers such as diethyl ether, diisopropyl ether, tert-butyl methyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane or bis(2-methoxyethyl)ether, hydrocarbons such as benzene, toluene, xylene, pentane, hexane, heptane, cyclohexane or petroleum fractions, halogenated hydrocarbons such as dichloromethane, trichloromethane, tetrachloromethane, 1,2-dichloroethane, trichloroethylene or chlorobenzene, or dipolar-aprotic solvents such as acetone, methyl ethyl ketone, acetonitrile, ethyl acetate, pyridine, dimethyl sulphoxide (DMSO), N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA), N,N'-dimethylpropyleneurea (DMPU) or N-methylpyrrolidinone (NMP). It is also possible to use mixtures of such solvents. Preference is given to using N,N-dimethylformamide.

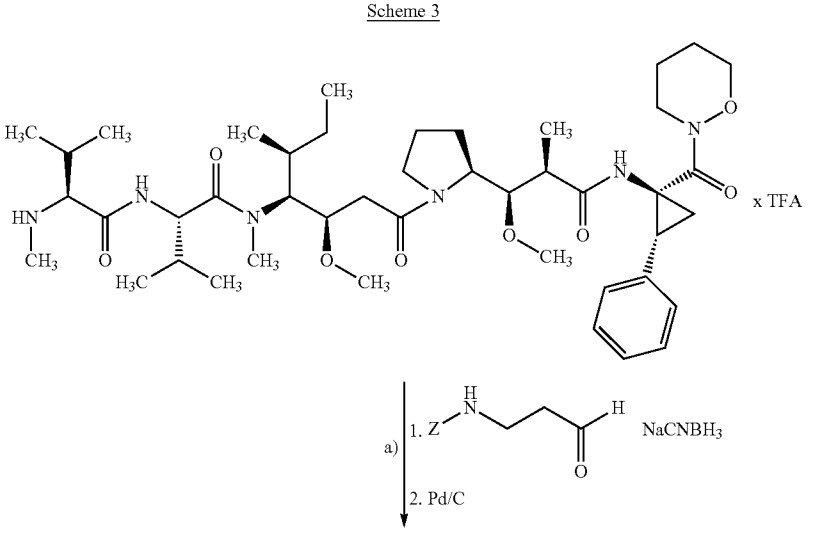
[2798] Suitable bases for these reactions are, for example, tertiary amines such as triethylamine, N-methylmorpholine, N-methylpiperidine, N,N-diisopropylethylamine, pyridine or 4-N,N-dimethylaminopyridine. Preference is given to using N,N-diisopropylethylamine, optionally with addition of 4-N,N-dimethylaminopyridine.

[2799] The reactions (IX)→(III-A), (XIV)→(III-B) and (XVI)→(III-C) and also (VI)+(XVII)→(III-D) and (XIX)+(XX)→(III-E) take place in a temperature range from 0° C. to +50° C., preferably at +10° C. to +30° C. The reaction may take place under atmospheric, under elevated or under reduced pressure (e.g. from 0.5 to 5 bar); it is usual to operate under atmospheric pressure.

[2800] The compounds of the formulae (II), (III), (I-A) and (I-B) are sub-quantities of the compounds of the formulae (IIa), (IIIa), (Ia-A) and (Ia-B), respectively, where R^{35} is methyl. The preparation of the compounds (IIa) and (IIIa) takes place in analogy to the preparation of the compound of the formulae (II) and (III) as described above.

[2801] The above-described processes are illustrated by way of example by the following synthesis schemes (Scheme 3 to 13, 18):

Scheme 3



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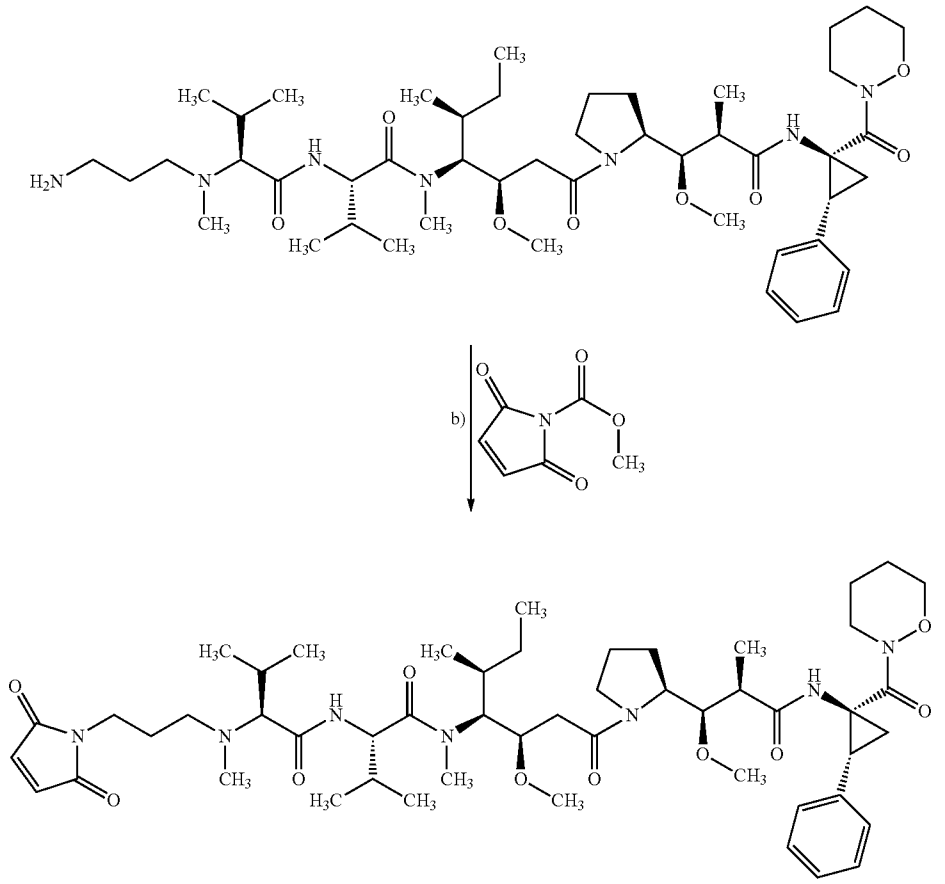
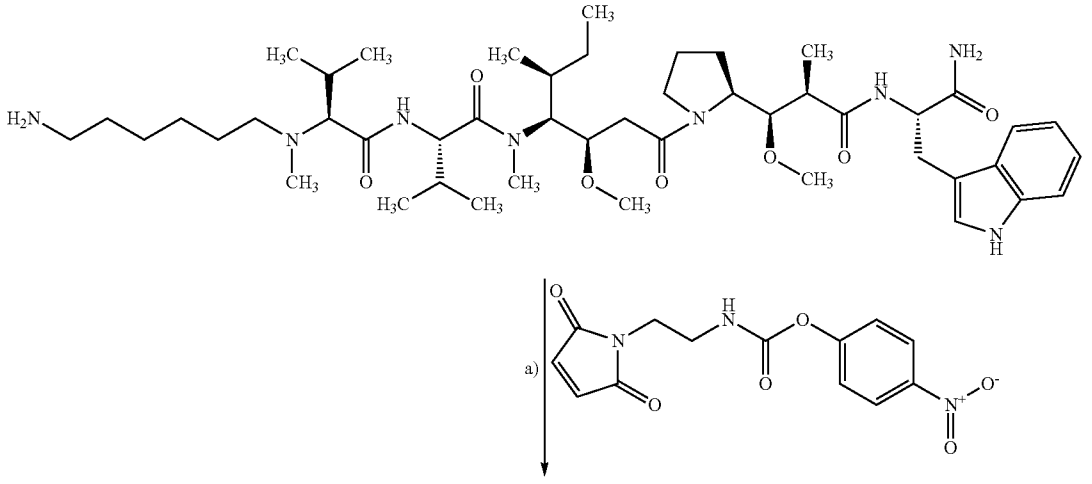


[a): 1. Water/dioxane, 1 N HCl, 100° C.; 2. H_2, Pd/C, methanol, RT; b): $NaHCO_3$, H_2O, dioxane, RT].

Scheme 4



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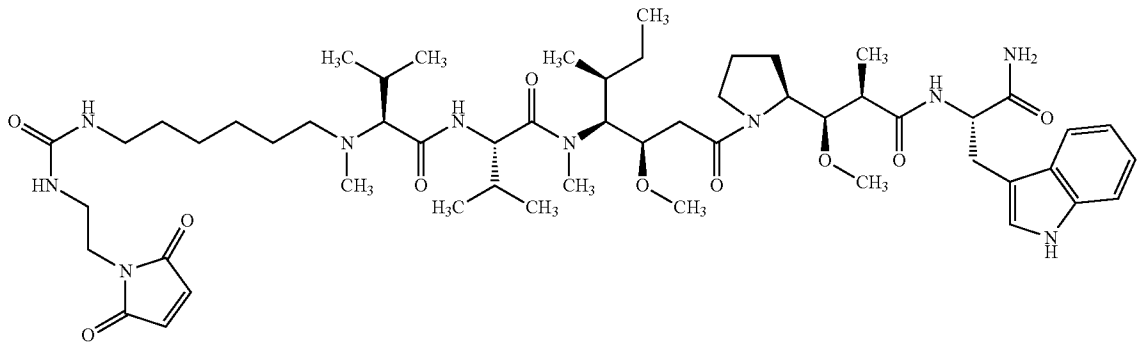
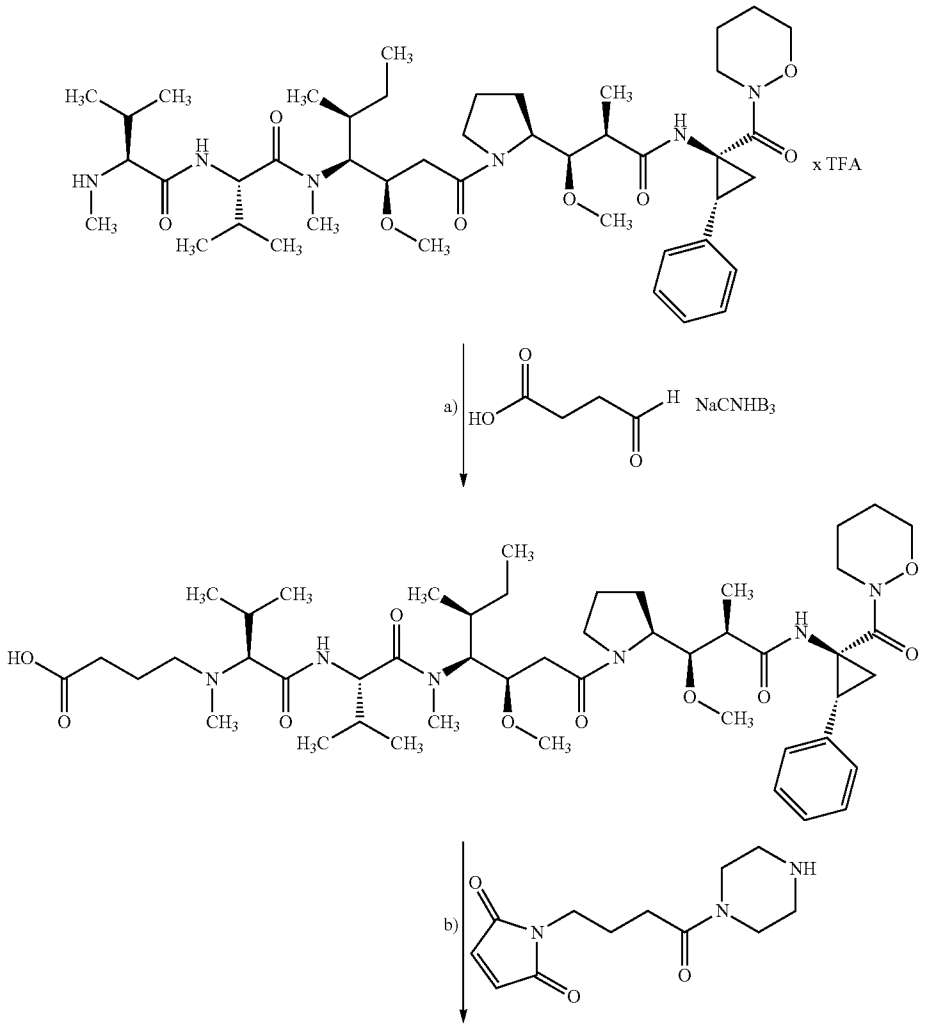


[a): Diisopropylethylamine, DMF, RT].

Scheme 5



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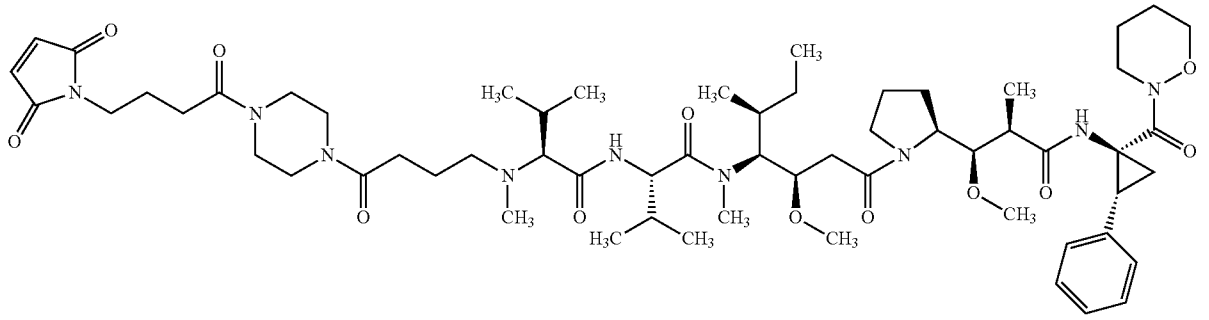
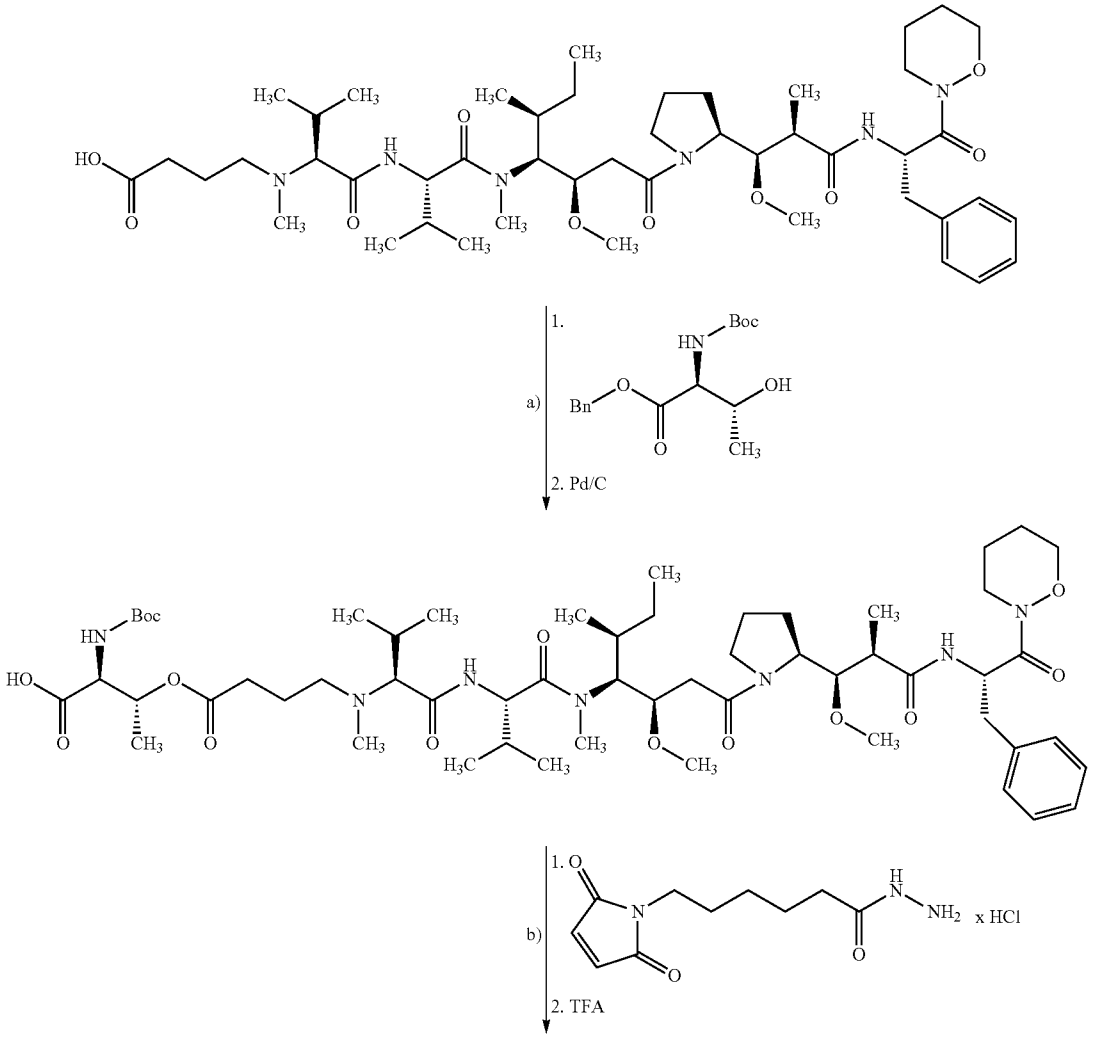


[a): Water/dioxane, 1 N HCl, 100° C.; b): HATU, diisopropylamine, DMF, RT].

Scheme 6



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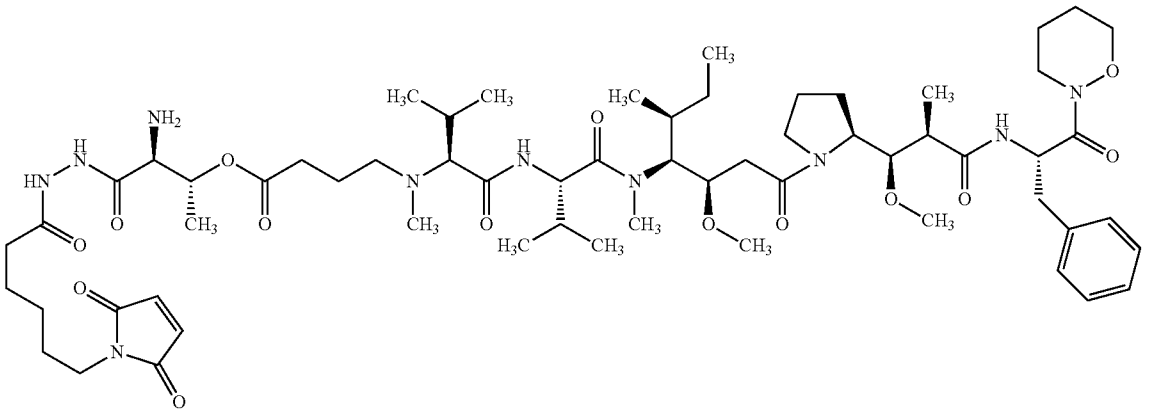
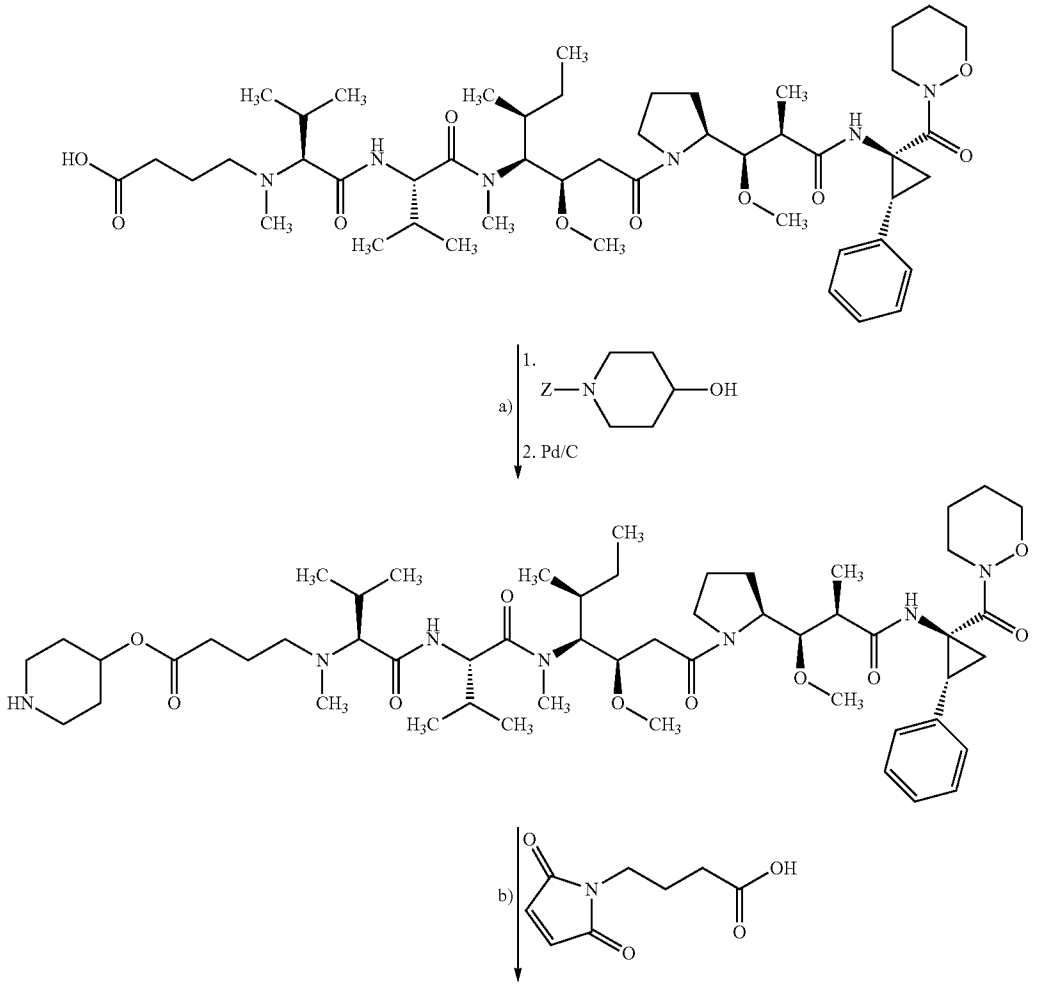


[a): 1. EDCI, DMAP, dichloromethane, RT; 2. H_2, methanol, RT; b): 1. EDCI, HOBt, diisopropylamine, DMF, RT; 2. dichloromethane, RT].

Scheme 7



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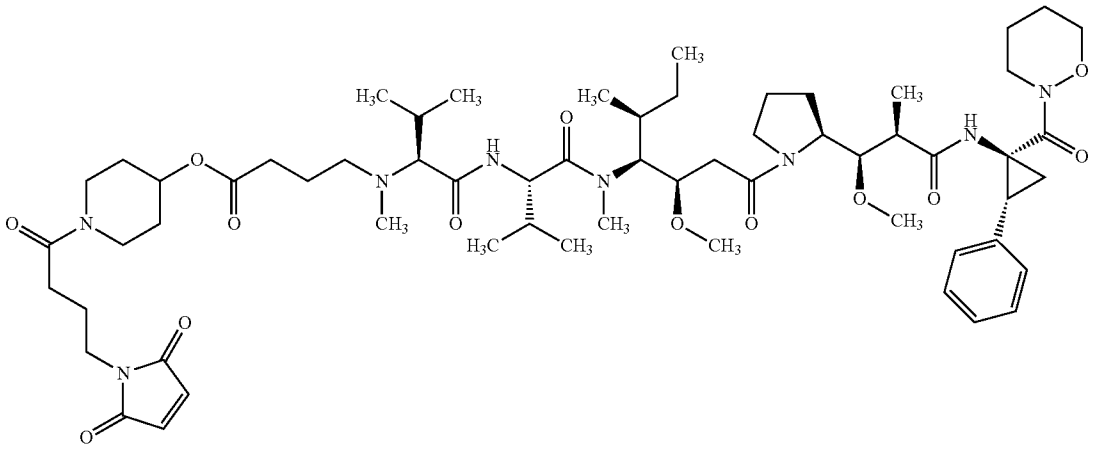
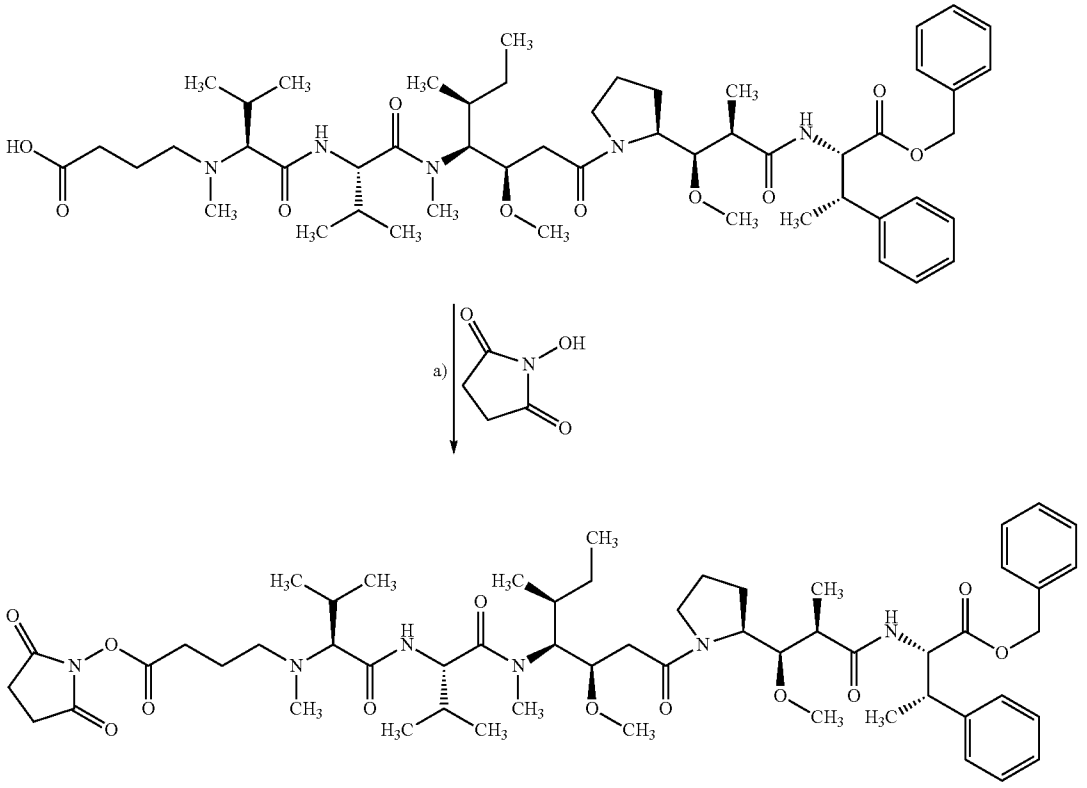


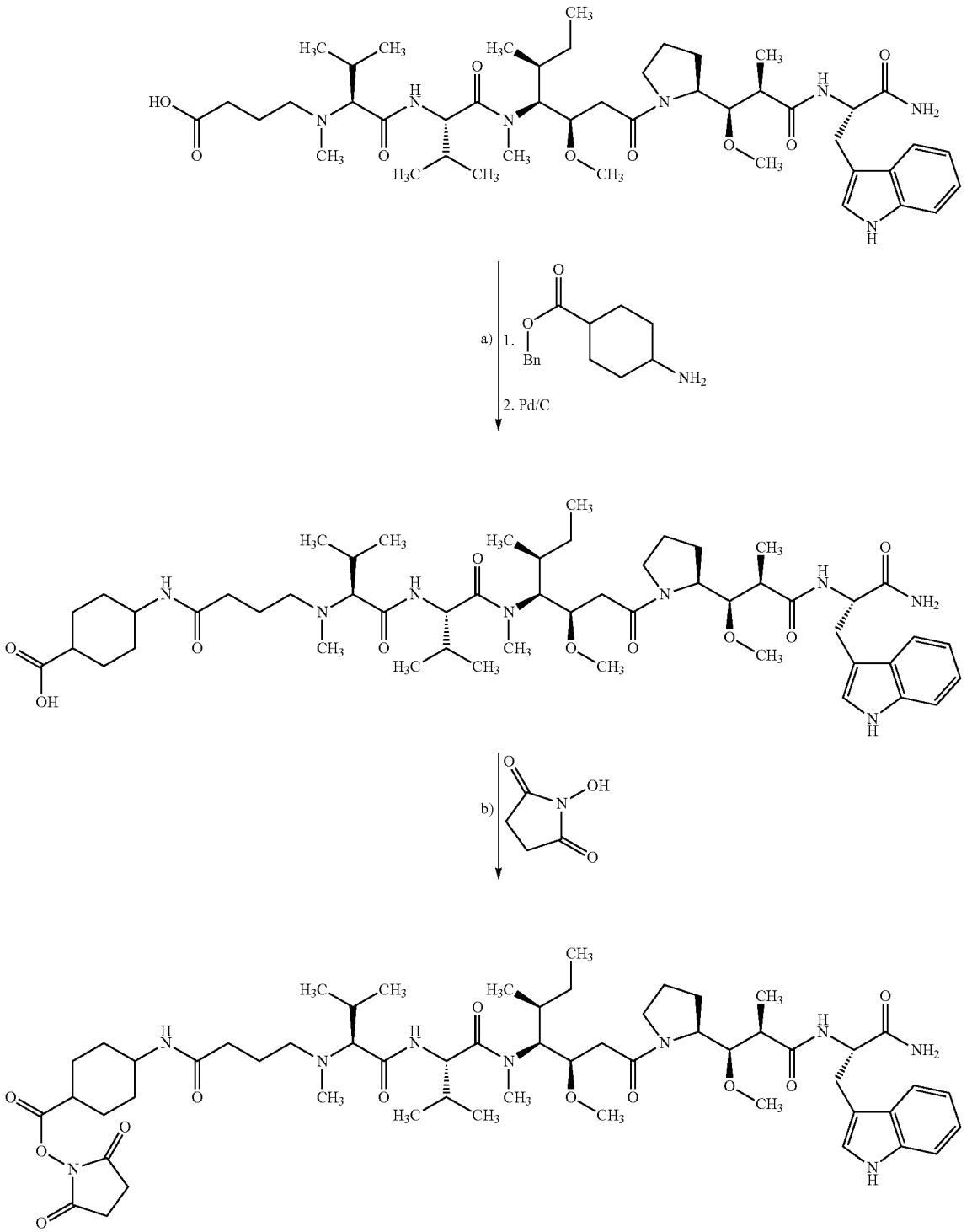
[a): 1. EDCI, DMAP, dichloromethane, RT; 2. H_2, methanol, RT; b): HATU, diisopropylamine, DMF, RT].

Scheme 8



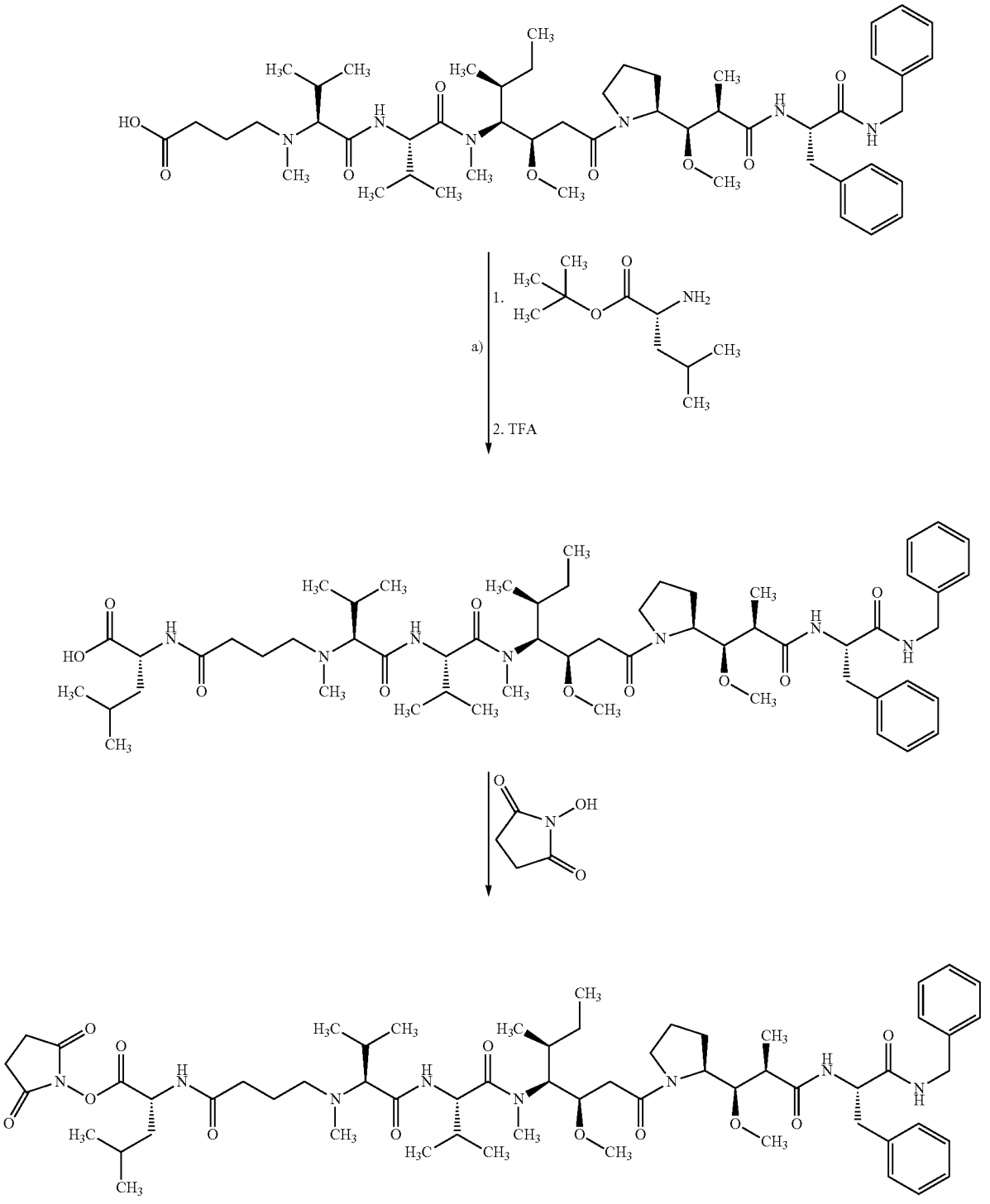
[a): EDCI, dichloromethane, RT].

Scheme 9



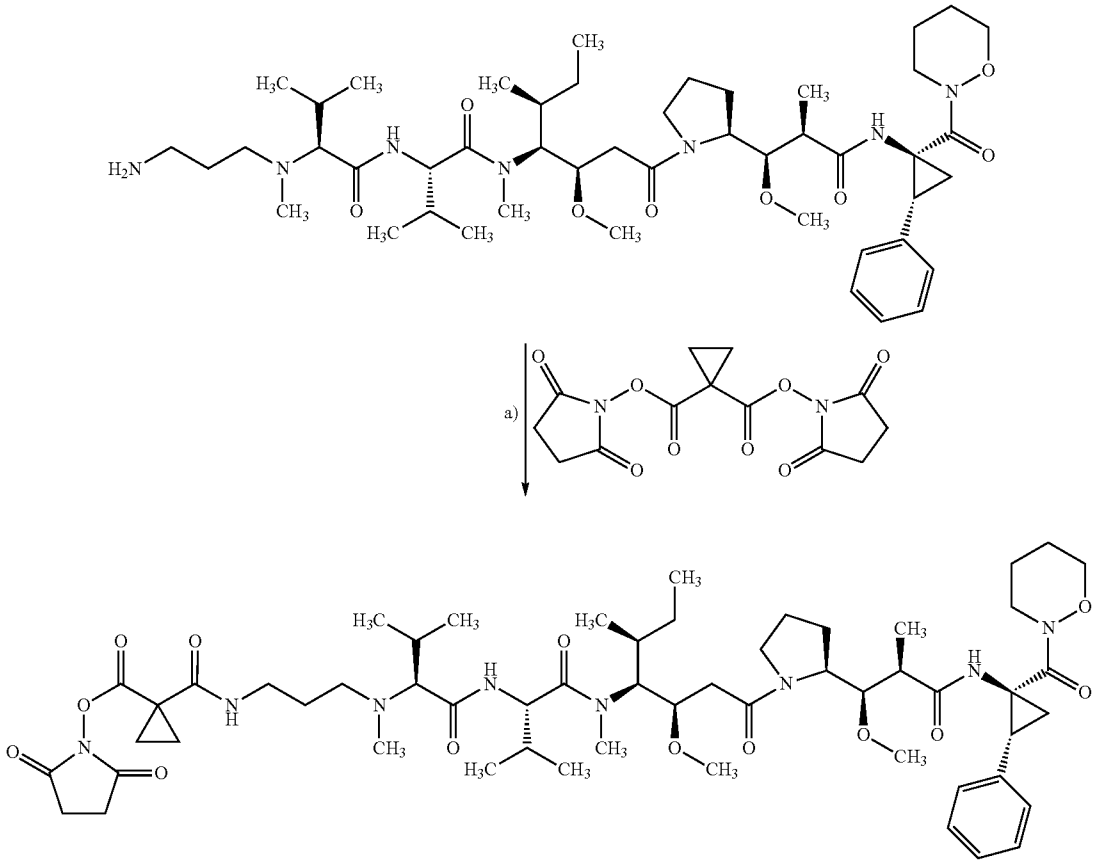
[a): HATU, diisopropylethylamine, DMF, RT; 2. H_2, methanol, RT; b): EDCI, DMAP, dichloromethane, RT].

Scheme 10



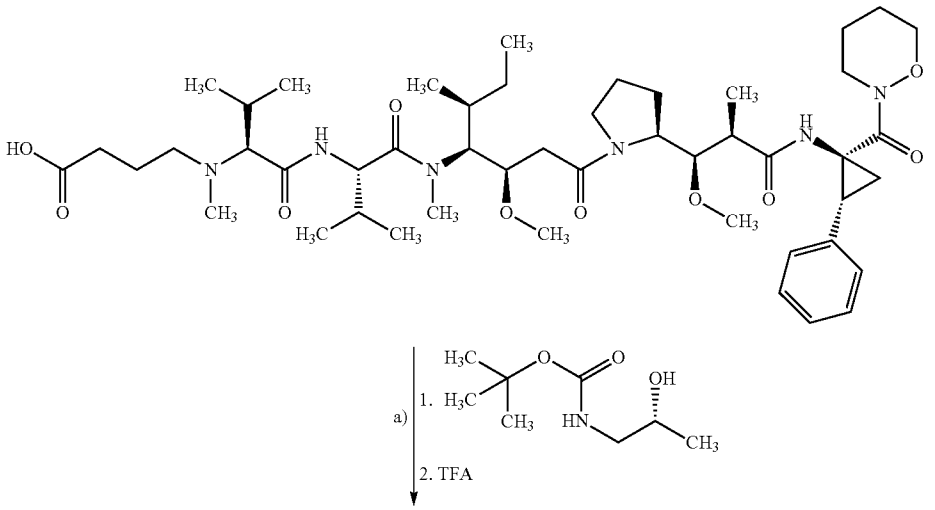
[a): 1. HATU, diisopropylethylamine, DMF, RT; 2. dichloromethane, RT; b): EDCI, DMAP, dichloromethane, RT].

Scheme 11



[a): Diisopropylethylamine, DMF, RT].

Scheme 12



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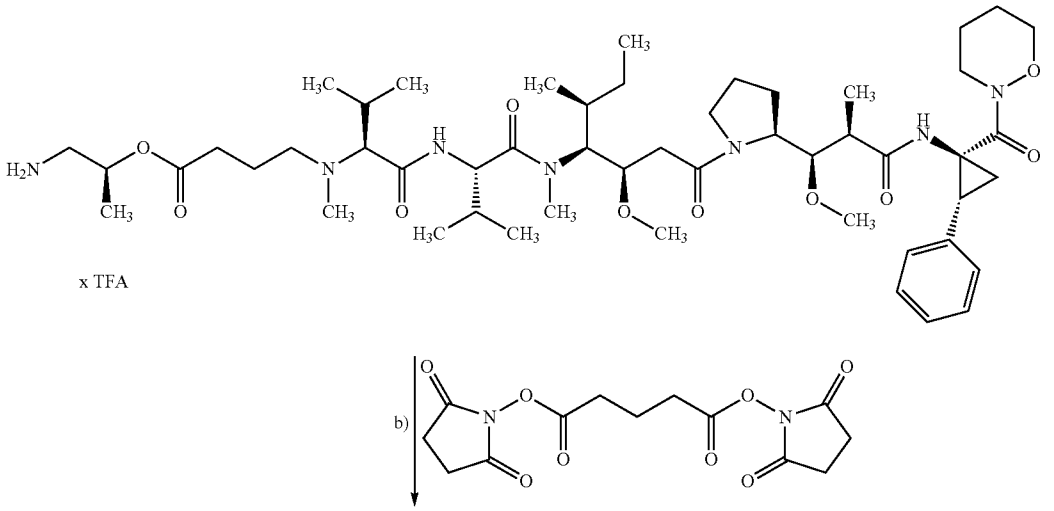
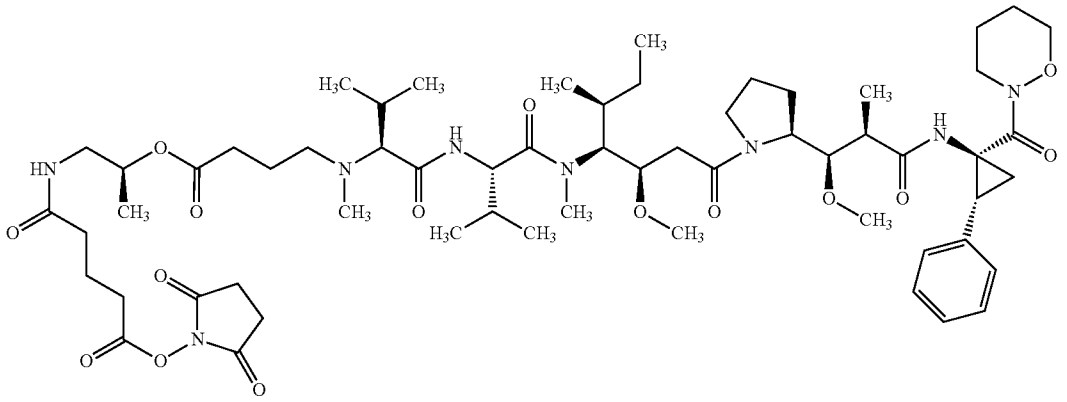
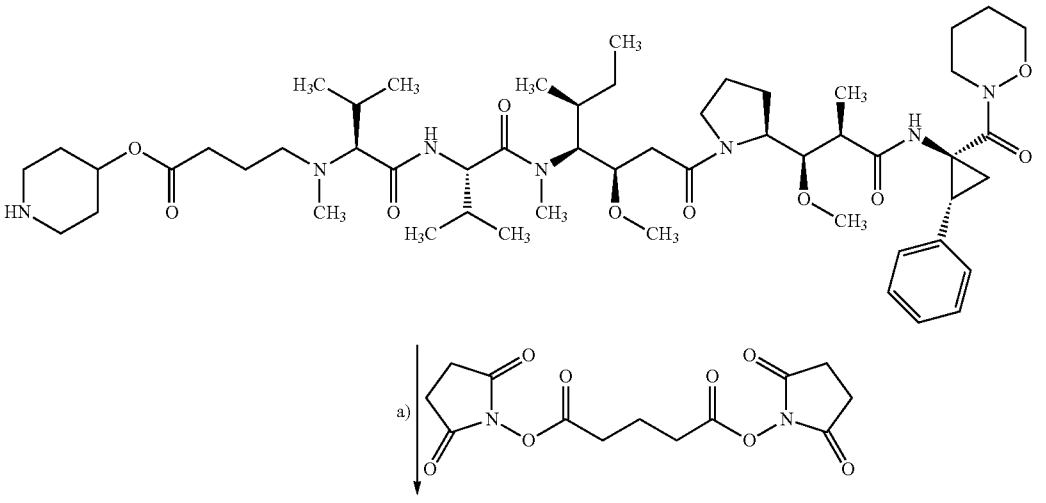


x TFA



[a): 1. EDCI, DMAP, dichloromethane, RT; 2. dichloromethane, RT; b) diisopropylamine, DMAP, dichloromethane, RT].

Scheme 13



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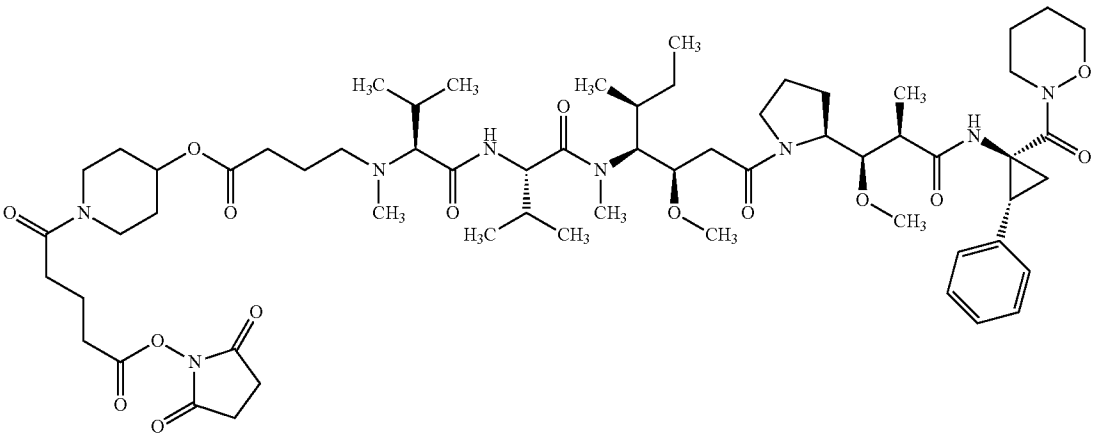
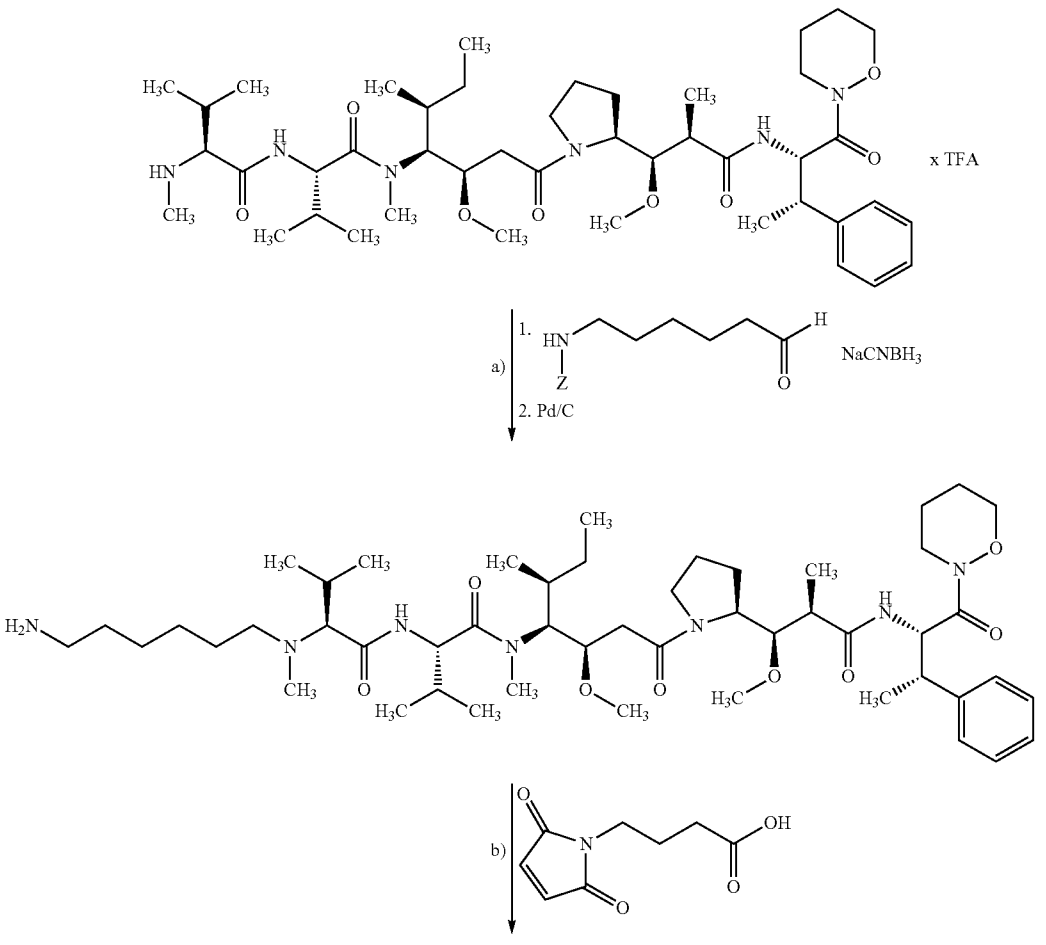


[a): DMAP diisopropylamine, dichloromethane, RT].

Scheme 18



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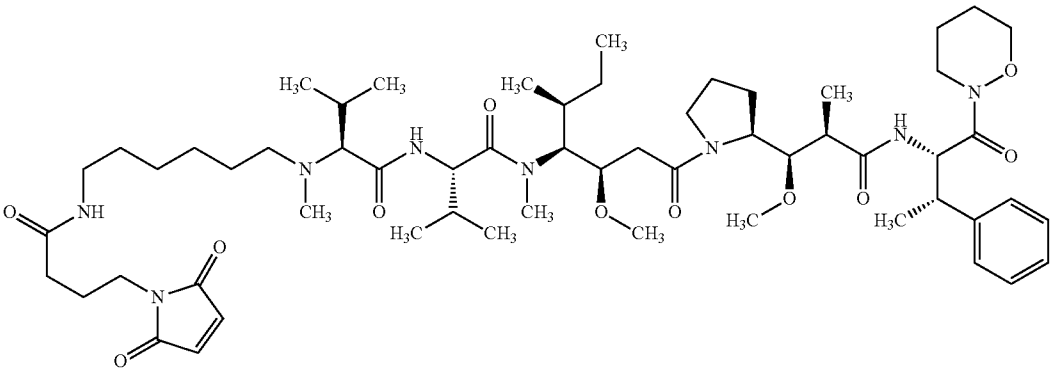
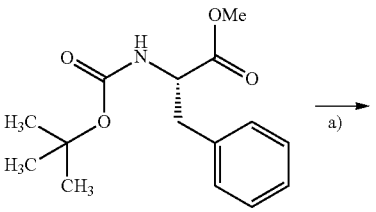


[a): 1. Water/dioxane, 1N HCl, 100° C.; 2. H_2, Pd/C, methanol, RT; b): HATU, diisopropylethylamine, RT].

[2802] The compounds of the formula (IV) can be prepared from commercially available amino acid building blocks or those known from the literature (see, for example, Pettit et al., *Synthesis* 1996, 719; Shioiri et al., *Tetrahedron Lett.* 1991, 32, 931; Shioiri et al., *Tetrahedron* 1993, 49, 1913; Koga et al., *Tetrahedron Lett.* 1991, 32, 2395; Vidal et al., *Tetrahedron* 2004, 60, 9715; Poncet et al., *Tetrahedron* 1994, 50, 5345. Pettit et al., *J. org. Chem.* 1994, 59, 1796) in analogy to processes known from the literature, in accordance with customary methods of peptide chemistry, and as described in the present experimental section. The synthesis schemes below (Scheme 14 to 16) illustrate the preparation by way of example.

Scheme 14



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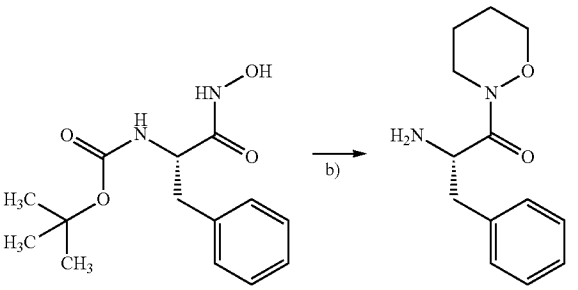
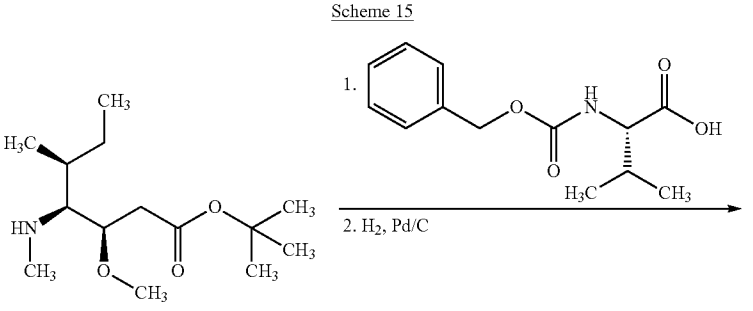


[a): Hydroxylamine hydrochloride, KOH, MeOH, 0° C. → RT; b): $BrCH_2(CH_2)_2CH_2Br$, K_2CO_3, acetone, reflux].

Scheme 15



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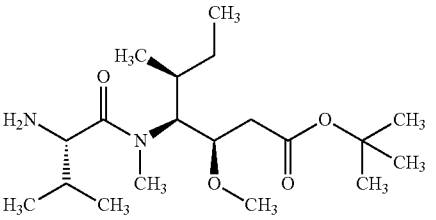
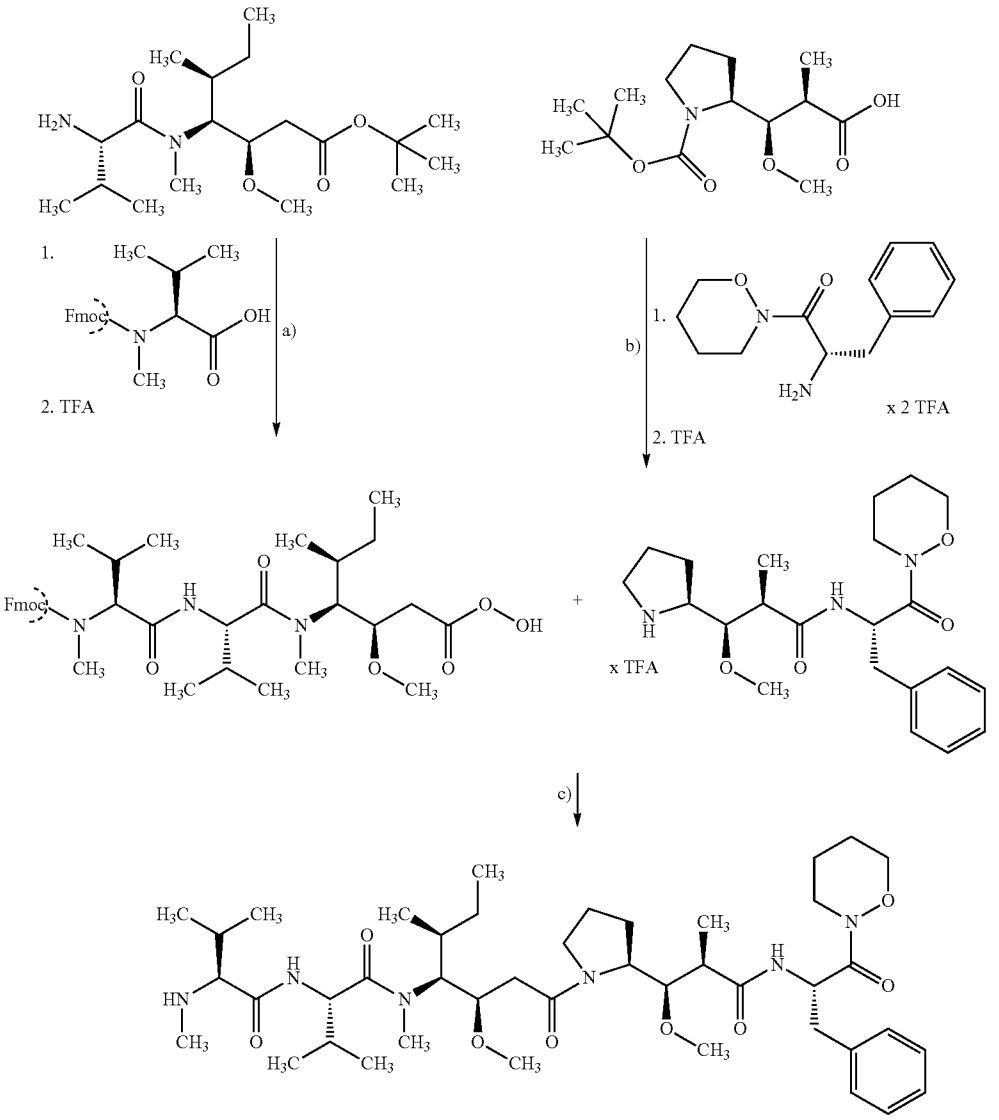


[a): 1. Diisopropylethylamine, BEP, dichloromethane, -10° C. → RT; 2. MeOH].

Scheme 16



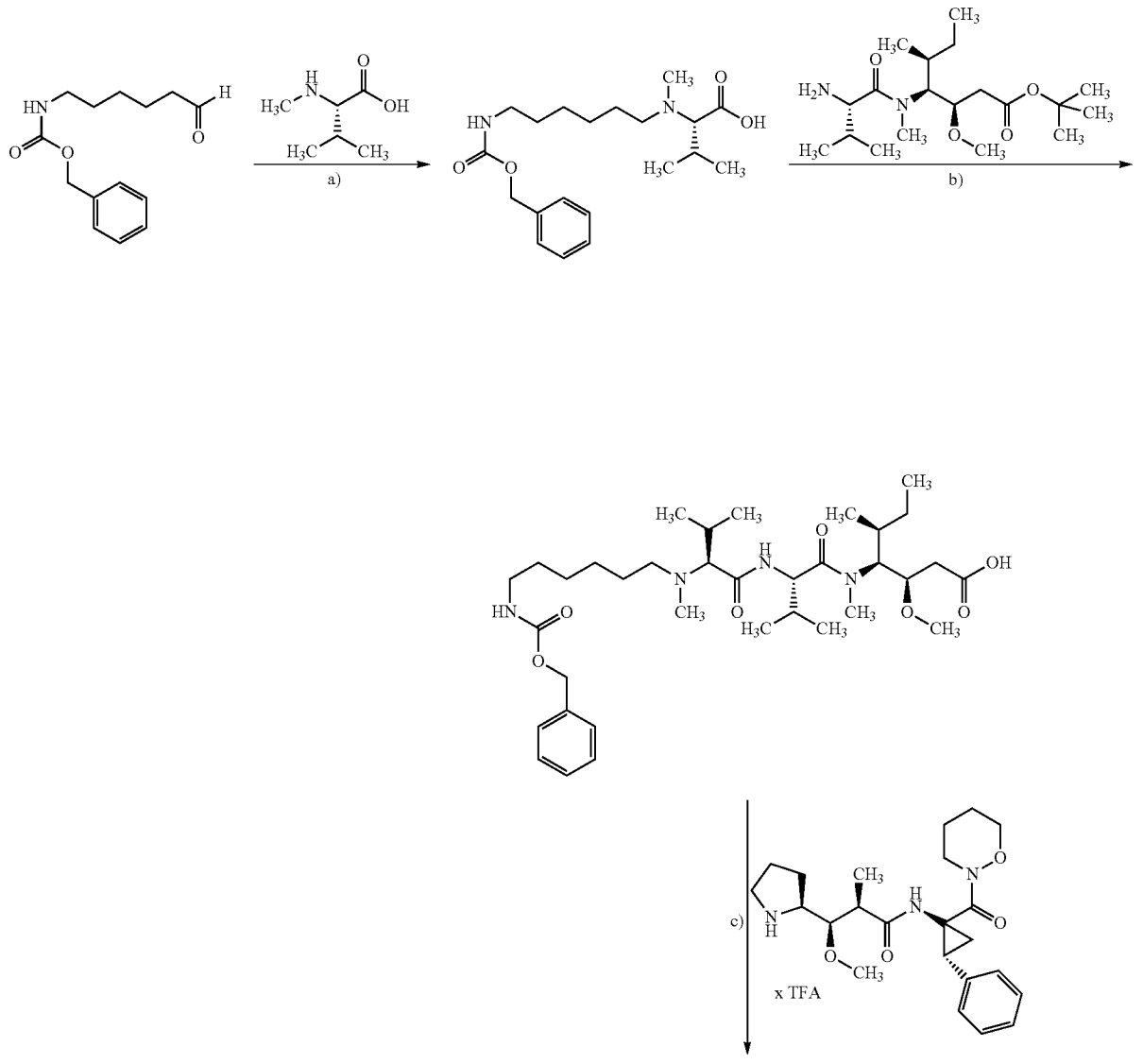
[a): 1. Diisopropylethylamine, BEP, DMF, RT; 2. dichloromethane; b): 1. HATU, diisopropylethylamine, DMF, RT; 2. dichloromethane, RT; c): 1. HATU, diisopropylethylamine, DMF, RT; 2. piperidine, DMF, RT].

[2803] The compounds of the formulae (XI), (XIII), (XV), (XVII) and (XXI), including, where appropriate, chiral or diastereomeric forms thereof, are available commercially or are described as such in the literature, or they can be prepared by routes that are obvious to the skilled person, in analogy to methods published in the literature. Numerous comprehensive instructions and also literature information on the preparation of the starting materials are also given in the experimental section, in the section relating to the preparation of the starting compounds and intermediates.

[2804] The compounds of the formulae (V), (VII), (VIII), (X), (XVIII), (XX) and (XXIII), including, where appropriate, chiral or diastereomeric forms thereof, are known from the literature, or can be prepared by routes which are obvious to the skilled person, in analogy to methods published in the literature. Numerous comprehensive instructions and also literature information on the preparation of the starting materials are also given in the experimental section, in the section relating to the preparation of the starting compounds and intermediates.

[2805] Alternatively, individual steps of the preparation sequence may be carried out in a different order. This approach is illustrated by way of example in the synthesis schemes below (Scheme 17, 19 and 20).

Scheme 17



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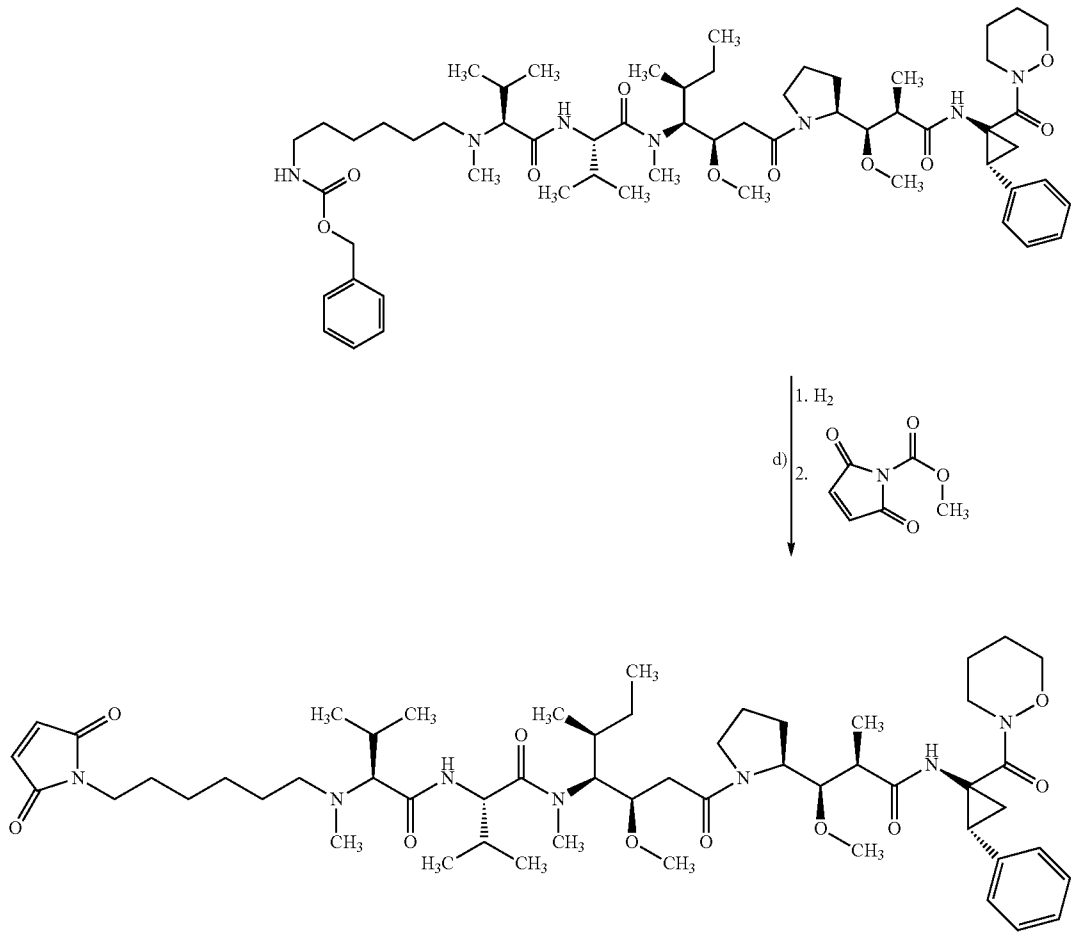
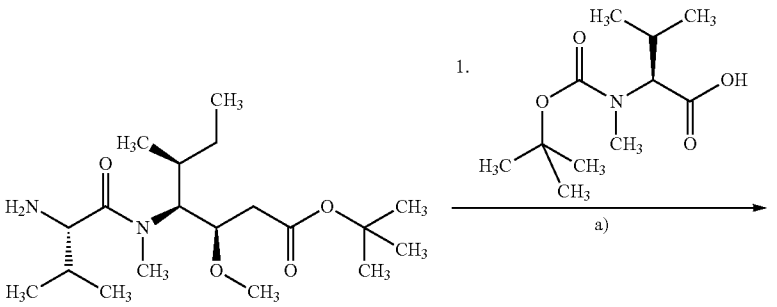


[a): Borane-pyridine complex, acetic acid, MeOH; b): 1. HOBt, EDCI, diisopropylethylamine, DMF, RT; 2. TFA, dichloromethane, RT; c): HATU, diisopropylethylamine, DMF, RT; d) 1. Pd/C, MeOH, RT; 2. $NaHCO_3$, dioxane, water].

Scheme 19



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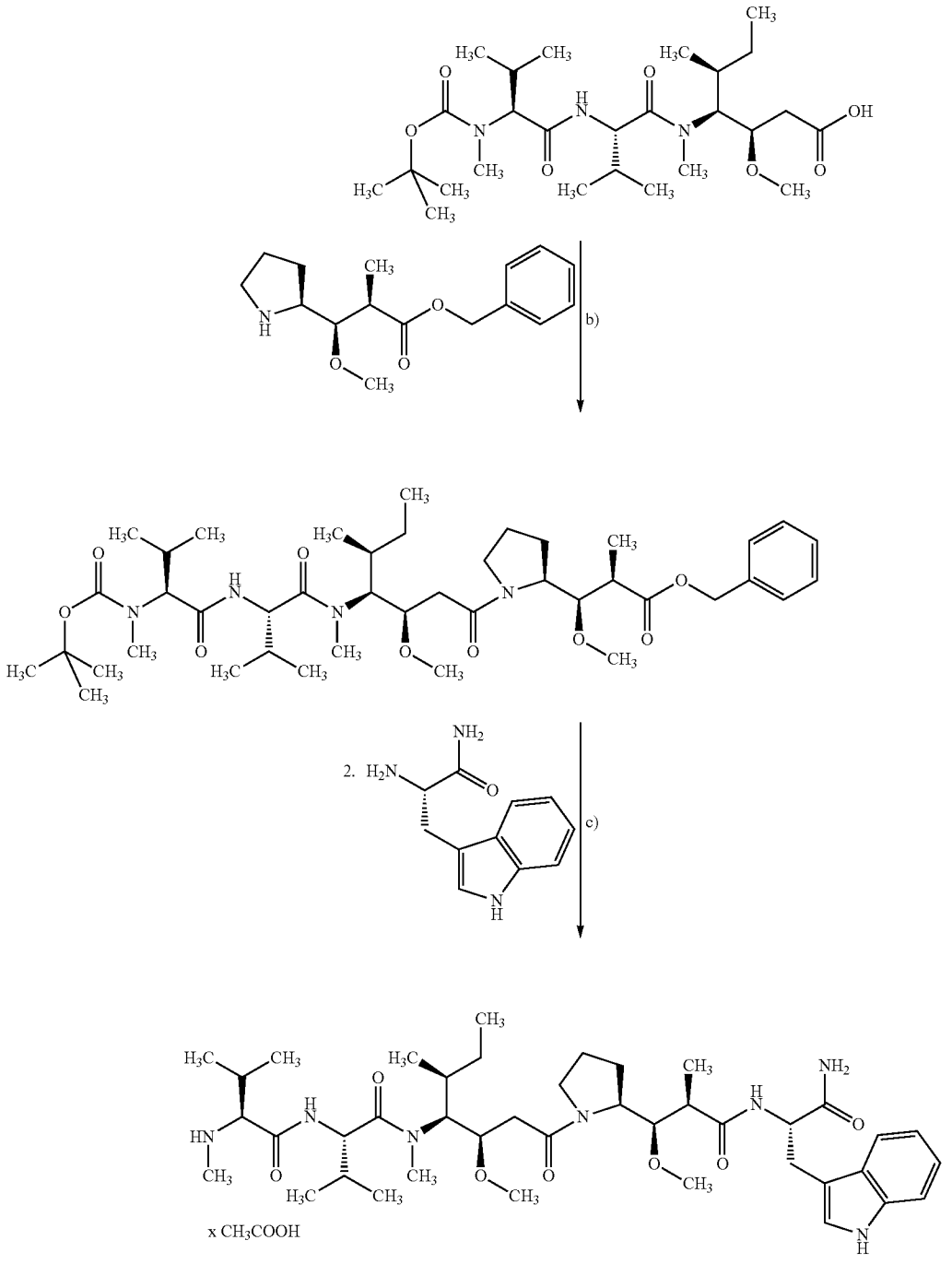
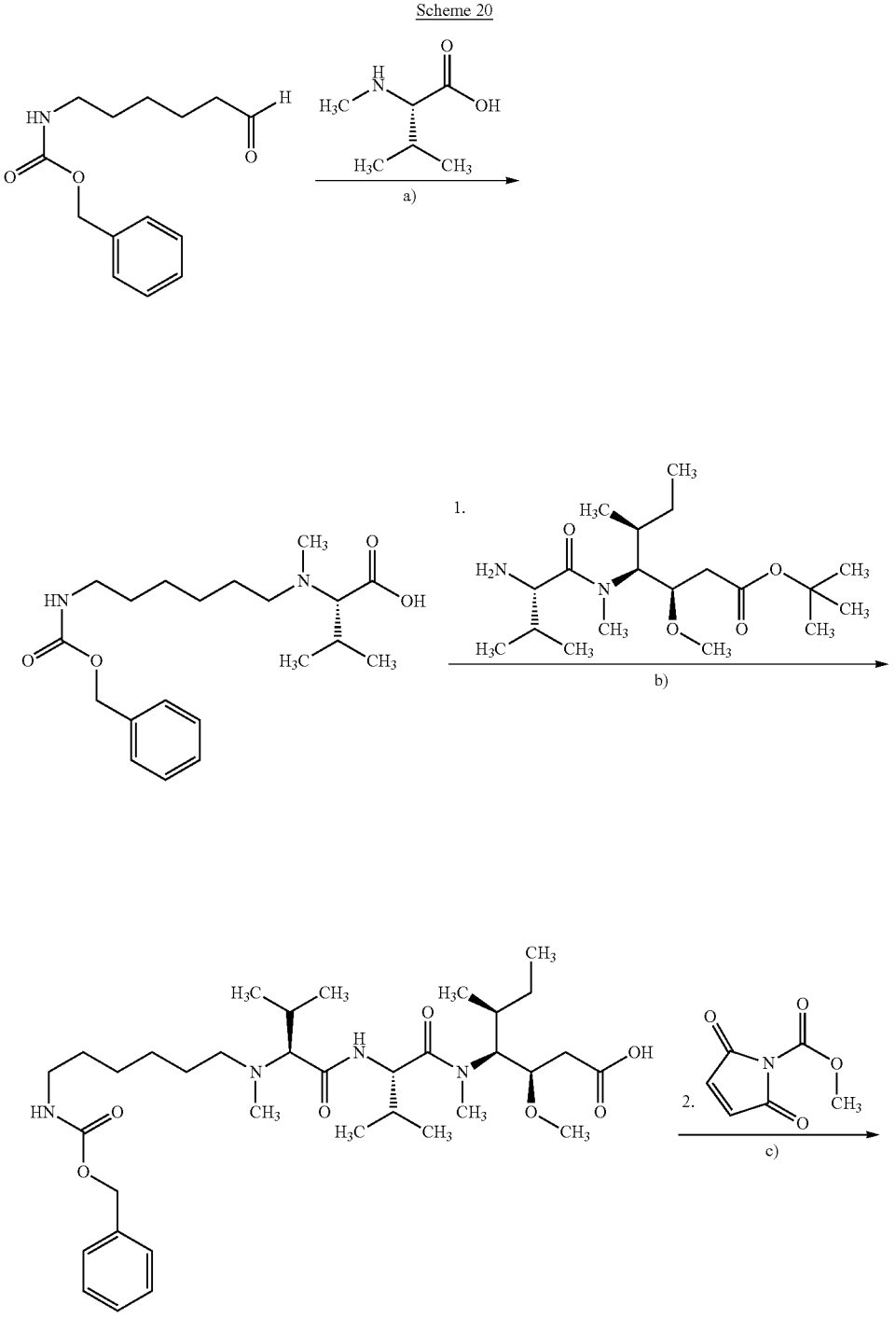


[a): 1. HATU, diisopropylethylamine, DMF, RT; 2. TFA, dichloromethane, RT; 3. $((H_3C)_3C(C{=}O))_2O$, DMF, diisopropylethylamine; b) diisopropylethylamine, BEP, DMF, RT; c) 1. H_2, Pd/C (10%) methanol, RT; 2. HATU, diisopropylethylamine, DMF, RT; 3. TFA, dichloromethane, RT].

Scheme 20



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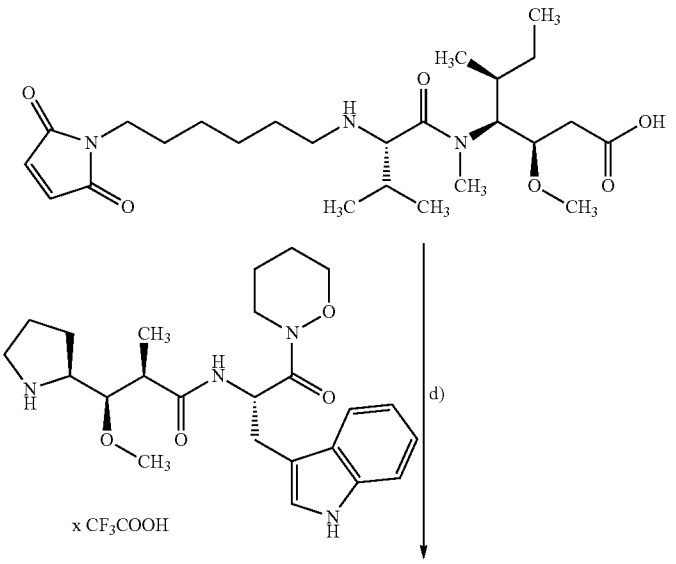
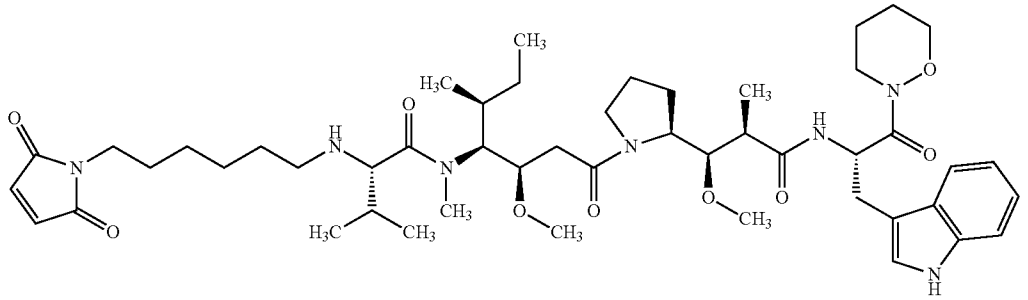


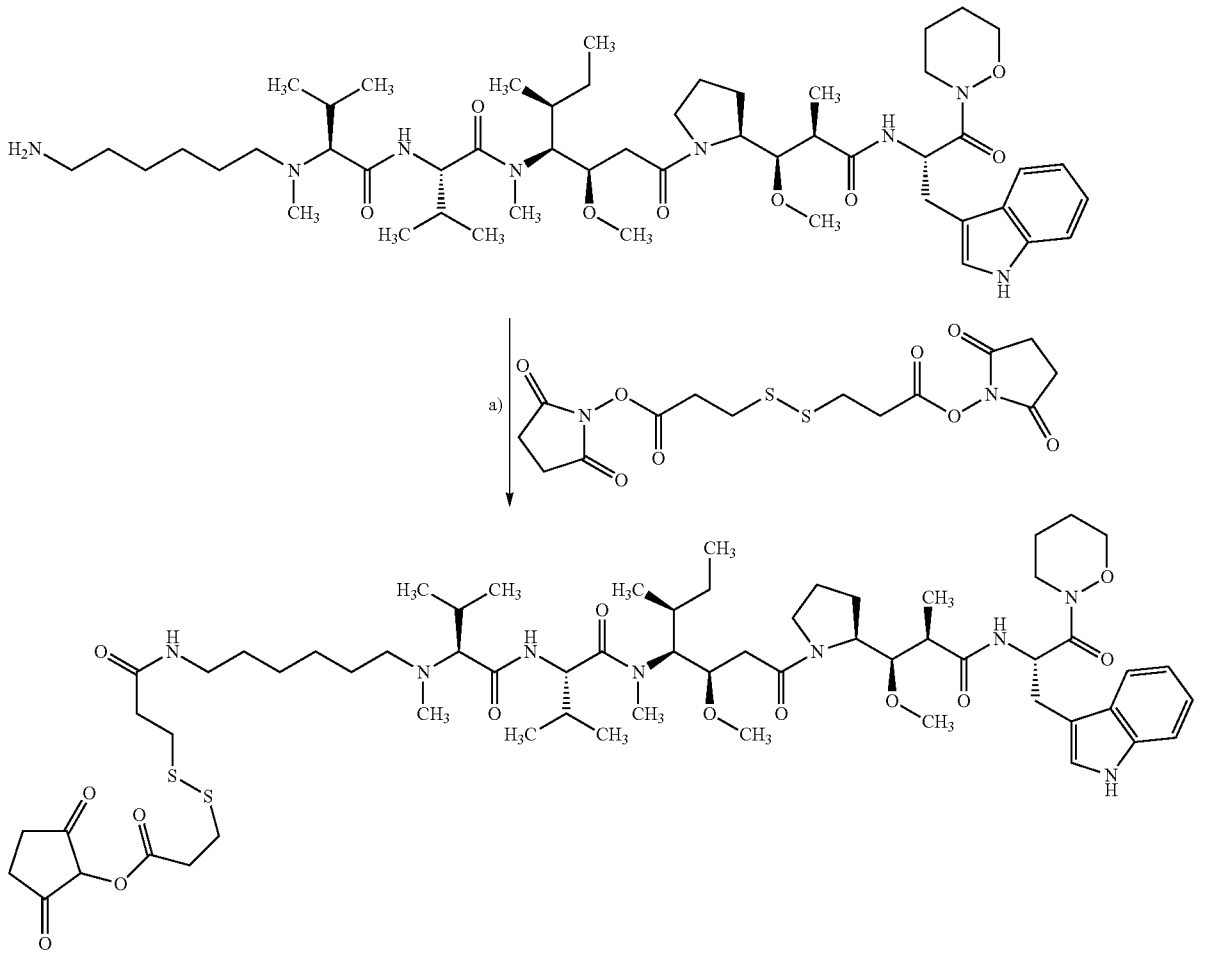
O



[a): Borane-pyridine complex, acetic acid, MeOH; b): 1. HOBt, EDCI, diisopropylethylamine, DMF, RT; 2. TFA, dichloromethane, RT; c): 1. H_2, Pd/C, MeOH, RT; 2. $NaHCO_3$, dioxane, water; d) HATU, diisopropylethylamine, DMF, RT;].

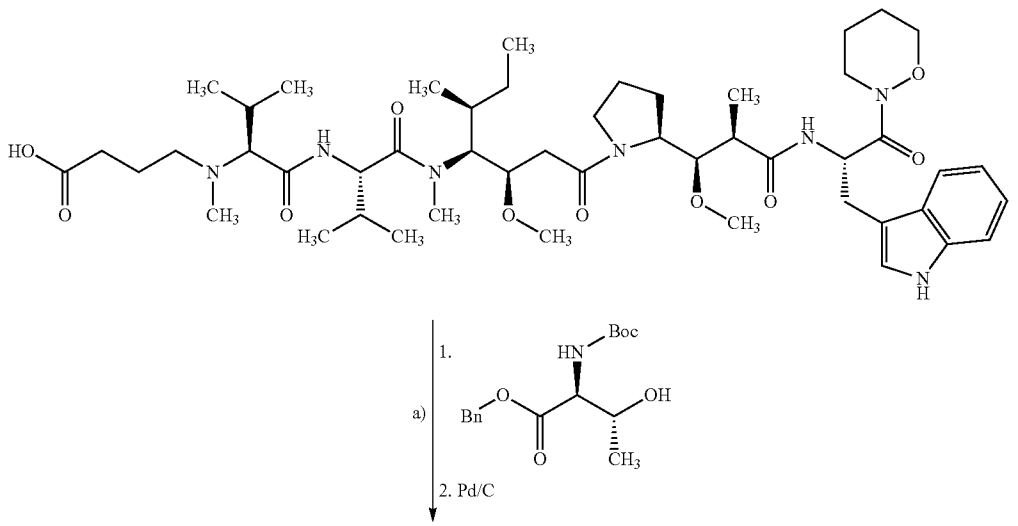
[2806] Further ADCs may be prepared by way of example in accordance with the following methods:

Scheme 21



[a): Diisopropylethylamine, DMF, RT].

Scheme 22



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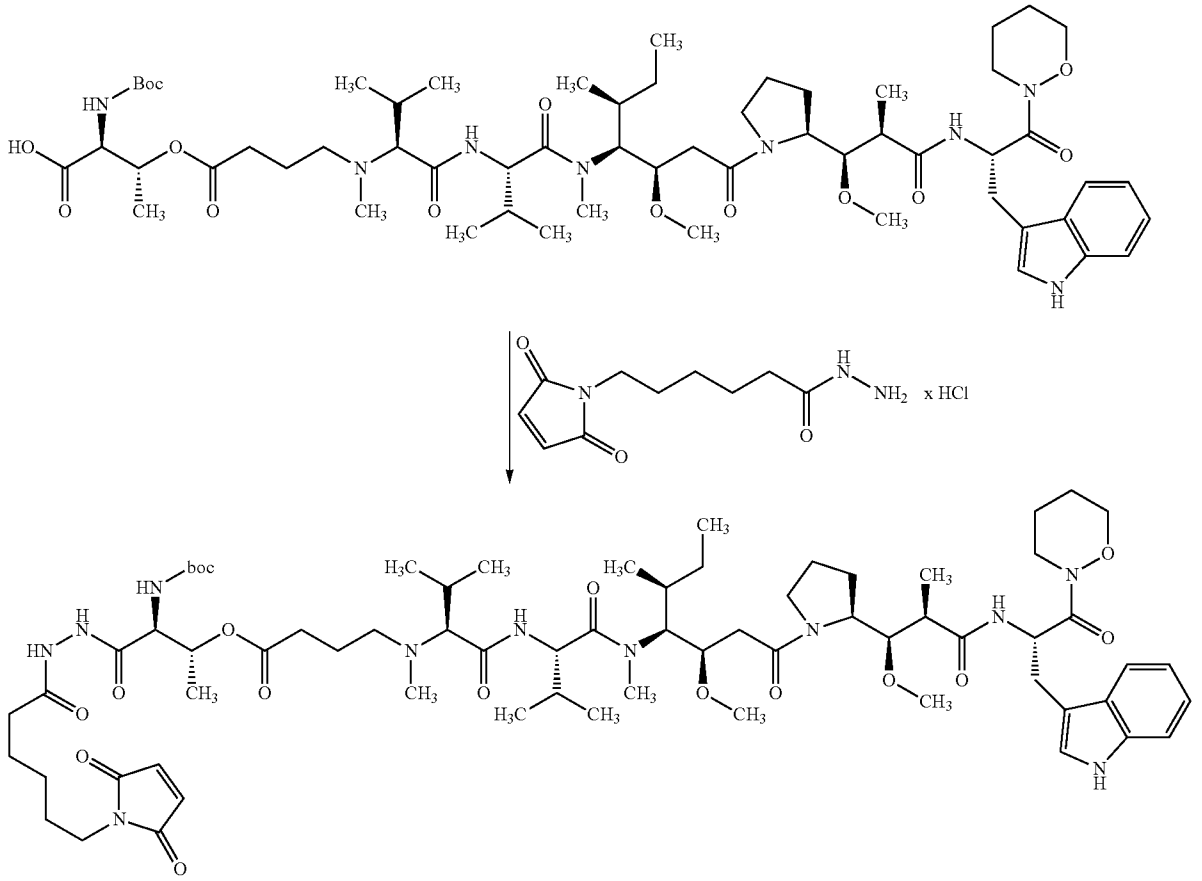

[a): 1. EDCI, DMAP, dichloromethane, RT; 2. H_2, methanol, RT; b): HATU, diisopropylethylamine, DMF, RT;

[2807] In one embodiment the binder binds to a target molecule which is present on a cancer cell. In one preferred embodiment the binder binds to a cancer target molecule.

[2808] In another preferred embodiment the target molecule is a selective cancer target molecule.

[2809] In one particularly preferred embodiment the target molecule is a protein.

[2810] In one embodiment the target molecule is an extracellular target molecule. In one preferred embodiment the extracellular target molecule is a protein.

[2811] Cancer target molecules are known to the skilled person. Examples thereof are listed below.

[2812] Examples of cancer target molecules are as follows: (1) EGF receptor (NCBI reference sequence NP_005219.2) Sequence (1210 amino acids):

>gi|29725609|ref|NP_005219.21 epidermal growth factor receptor isoform a precursor [*Homo sapiens*]
MRPSGTAGAALLALLAALCPASRALEEKKVCQGTSNKLTQLGTFEDHFLSLQRMFN

NCEVVLGNLEITYVQRNYDLSFLKTIQEVAGYVLIALNTVERIPLENLQIIRGNMYYE

NSYALAVLSNYDANKTGLKELPMRNLQEILHGAVRFSNNPALCNVESIQWRDIVSSD

FLSNMSMDFQNHLGSCQKCDPSCPNGSCWGAGEENCQKLTKIICAQQCSGRCRGKS

PSDCCHNQCAAGCTGPRESDCLVCRKFRDEATCKDTCPPLMLYNPTTYQMDVNPEG

KYSFGATCVKKCPRNYVVTDHGSCVRACGADSYEMEEDGVRKCKKCEGPCRKVCN

GIGIGEFKDSLSINATNIKHFKNCTSISGDLHILPVAFRGDSFTHTPPLDPQELDILKTVK

EITGFLLIQAWPENRTDLHAFENLEIIRGRTKQHGQFSLAVVSLNITSLGLRSLKEISDG

DVIISGNKNLCYANTINWKKLFGTSGQKTKIISNRGENSCKATGQVCHALCSPEGCW

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GPEPRDCVSCRNVSRGRECVDKCNLLEGEPREFVENSECIQCHPECLPQAMNITCTGR

GPDNCIQCAHYIDGPHCVKTCPAGVMGENNTLVWKYADAGHVCHLCHPNCTYGCT

GPGLEGCPTNGPKIPSIATGMVGALLLLLVVALGIGLFMRRRHIVRKRTLRRLLQERE

LVEPLTPSGEAPNQALLRILKETEFKKIKVLGSGAFGTVYKGLWIPEGEKVKIPVAIKE

LREATSPKANKEILDEAYVMASVDNPHVCRLLGICLTSTVQLITQLMPFGCLLDYVRE

HKDNIGSQYLLNWCVQIAKGMNYLEDRRLVHRDLAARNVLVKTPQHVKITDFGLA

KLLGAEEKEYHAEGGKVPIKWMALESILHRIYTHQSDVWSYGVTVWELMTFGSKPY

DGIPASEISSILEKGERLPQPPICTIDVYMIMVKCWMIDADSRPKFRELIIEFSKMARDP

QRYLVIQGDERMHLPSPTDSNFYRALMDEEDMDDVVDADEYLIPQQGFFSSPSTSRT

PLLSSLSATSNNSTVACIDRNGLQSCPIKEDSFLQRYSSDPTGALTEDSIDDTFLPVPEY

INQSVPKRPAGSVQNPVYHNQPLNPAPSRDPHYQDPHSTAVGNPEYLNTVQPTCVNS

TFDSPAHWAQKGSHQISLDNPDYQQDFFPKEAKPNGIFKGSTAENAEYLRVAPQSSE

FIGA

[2813] The extracellular domain is marked by underlining.
(2) Mesothelin (SwissProt reference Q^{13421}-3)
Sequence (622 amino acids):

>sp|Q13421-3|MSLN_HUMAN Isoform 2 of Mesothelin OS = *Homo sapiens*
GN = MSLN
MALPTARPLLGSCGTPALGSLLFLLFSLGWVQPSRTLAGETGQEAAPLDGVLANPPNISS

LSPRQLLGFPCAEVSGLSTERVRELAVALAQKNVKLSTEQLRCLAHRLSEPPEDLDALPL

DLLLFLNPDAFSGPQACTRFFSRITKANVDLLPRGAPERQRLLPAALACWGVRGSLLSEA

DVRALGGLACDLPGRFVAESAEVLLPRLVSCPGPLDQDQQEAARAALQGGGPPYGPPSTW

SVSTMDALRGLLPVLGQPIIRSIPQGIVAAWRQRSSRDPSWRQPERTILRPRFRREVEKT

ACPSGKKAREIDESLIFYKKWELEACVDAALLATQMDRVNAIPFTYEQLDVLKHKLDELY

PQGYPESVIQHLGYLFLKMSPEDIRKWNVTSLETLKALLEVNKGHEMSPQVATLIDRFVK

GRGQLDKDTLDTLTAFYPGYLCSLSPEELSSVPPSSIWAVRPQDLDTCDPRQLDVLYPKA

RLAFQNMNGSEYFVKIQSFLGGAPTEDLKALSQQNVSMDLATFMKLRTDAVLPLTVAEVQ

KLLGPHVEGLKAEERHRPVRDWILRQRQDDLDTLGLGLQGGIPNGYLVLDLSMQEALSGT

PCLLGPGPVLTVLALLLASTLA

[2814] Mesothelin is encoded by amino acids 296-598. Amino acids 37-286 code for "megakaryocyte-potentiating factor". Mesothelin is anchored in the cell membrane by a GPI anchor and is localized extracellularly.
(3) Carboanhydrase IX (SwissProt reference Q^{16790})
Sequence (459 amino acids):

>sp|Q16790|CAH9_HUMAN Carbonic anhydrase 9 OS = *Homo sapiens*
GN = CA9 PE = 1 SV = 2
MAPLCPSPWLPLLIPAPAPGLTVQLLLSLLLLVPVHPQRLPRMQEDSPLGGGSSGEDDPL

GEEDLPSEEDSPREEDPPGEEDLPGEEDLPGEEDLPEVKPKSEEEGSLKLEDLPTVEAPG

DPQEPQNNAHRDKEGDDQSHWRYGGDPPWPRVSPACAGRFQSPVDIRPQLAAFCPALRPL

ELLGFQLPPLPELRLRNNGHSVQLTLPPGLEMALGPGREYRALQLHLHWGAAGRPGSEHT

-continued

VEGHRFPAEIHVVHLSTAFARVDEALGRPGGLAVLAAFLEEGPEENSAYEQLLSRLEEIA

EEGSETQVPGLDISALLPSDFSRYFQYEGSLTTPPCAQGVIWTVFNQTVMLSAKQLHTLS

DTLWGPGDSRLQLNFRATQPLNGRVIEASFPAGVDSSPRAAEPVQLNSCLAAGDILALVF

GLLFAVTSVAFLVQMRRQHRRGTKGGVSYRPAEVAETGA

[2815] The extracellular domain is marked by underlining.

(4) C4.4a (NCBI reference sequence NP_055215.2; Synonym LYPD3)

Sequence (346 amino acids):

>gi|93004088|ref|NP_055215.2| ly6/PLAUR domain-containing protein 3 precursor [*Homo sapiens*]
MDPARKAGAQAMIWTAGWLLLLLLRGGAQALECYSCVQKADDGCSPNKMKTVKC

APGVDVCTEAVGAVETIHGQFSLAVRGCGSGLPGKNDRGLDLHGLLAFIQLQQCAQ

DRCNAKLNLTSRALDPAGNESAYPPNGVECYSCVGLSREACQGTSPPVVSCYNASD

HVYKGCFDGNVTLTAANVTVSLPVRGCVQDEFCTRDGVTGPGFTLSGSCCQGSRCN

SDLRNKTYFSPRIPPLVRLPPPEPTTVASTTSVTTSTSAPVRPTSTTKPMPAPTSQTPRQ

GVEHEASRDEEPRLTGGAAGHQDRSNSGQYPAKGGPQQPHNKGCVAPTAGLAALLL

AVAAGVLL

[2816] The matured, extracellular domain is marked by underlining (SEQ ID NO:1).

(5) CD52 (NCBI reference sequence NP_001794.2)

>gi|68342030|ref|NP_001794.2|CAMPATH-1 antigen precursor [*Homo sapiens*]
MKRFLFLLLTISLLVMVQIQTGLSGQNDTSQTSSPSASSNISGGIFLFFVANAIIHLFCFS

(6) Her2 (NCBI reference sequence NP_004439.2)

>gi|54792096|ref|NP_004439.2|receptor tyrosine-protein kinase erbB-2 isoform a [*Homo sapiens*]
MELAALCRWGLLLALLPPGAASTQVCTGTDMKLRLPASPETHLDMLRHLYQGCQV

VQGNLELTYLPTNASLSFLQDIQEVQGYVLIAHNQVRQVPLQRLRIVRGTQLFEDNY

ALAVLDNGDPLNNTTPVTGASPGGLRELQLRSLTEILKGGVLIQRNPQLCYQDTILW

KDIFHKNNQLALTLIDTNRSRACHPCSPMCKGSRCWGESSEDCQSLTRTVCAGGCAR

CKGPLPTDCCHEQCAAGCTGPKHSDCLACLHFNHSGICELHCPALVTYNTDTFESMP

NPEGRYTFGASCVTACPYNYLSTDVGSCTLVCPLHNQEVTAEDGTQRCEKCSKPCAR

VCYGLGMEHLREVRAVTSANIQEFAGCKKIFGSLAFLPESFDGDPASNTAPLQPEQLQ

VFETLEEITGYLYISAWPDSLPDLSVFQNLQVIRGRILHNGAYSLTLQGLGISWLGLRS

LRELGSGLALIHHNTHLCFVHTVPWDQLFRNPHQALLHTANRPEDECVGEGLACHQ

LCARGHCWGPGPTQCVNCSQFLRGQECVEECRVLQGLPREYVNARHCLPCHPECQP

QNGSVTCFGPEADQCVACAHYKDPPFCVARCPSGVKPDLSYMPIWKFPDEEGACQP

CPINCTHSCVDLDDKGCPAEQRASPLTSIISAVVGILLVVVLGVVFGILIKRRQQKIRK

YTMRRLLQETELVEPLTPSGAMPNQAQMRILKETELRKVKVLGSGAFGTVYKGIWIP

DGENVKIPVAIKVLRENTSPKANKEILDEAYVMAGVGSPYVSRLLGICLTSTVQLVTQ

LMPYGCLLDHVRENRGRLGSQDLLNWCMQIAKGMSYLEDVRLVHRDLAARNVLV

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KSPNHVKITDFGLARLLDIDETEYHADGGKVPIKWMALESILRRRFTHQSDVWSYGV

TVWELMTFGAKPYDGIPAREIPDLLEKGERLPQPPICTIDVYMIMVKCWMIDSECRPR

FRELVSEFSRMARDPQRFVVIQNEDLGPASPLDSTFYRSLLEDDDMGDLVDAEEYLV

PQQGFFCPDPAPGAGGMVHHRHRSSSTRSGGGDLTLGLEPSEEEAPRSPLAPSEGAGS

DVFDGDLGMGAAKGLQSLPTHDPSPLQRYSEDPTVPLPSETDGYVAPLTCSPQPEYV

NQPDVRPQPPSPREGPLPAARPAGATLERPKTLSPGKNGVVKDVFAFGGAVENPEYL

TPQGGAAPQPHPPPAFSPAFDNLYYWDQDPPERGAPPSTFKGTPTAENPEYLGLDVPV

(7) CD20 (NCBI reference sequence NP_068769.2)

>gi|23110987|ref|NP_068769.2| B-lymphocyte antigen CD20 [*Homo sapiens*]
MTTPRNSVNGTFPAEPMKGPIAMQSGPKPLFRRMSSLVGPTQSFFMRESKTLGAVQI

MNGLFHIALGGLLMIPAGIYAPICVTVWYPLWGGIMYIISGSLLAATEKNSRKCLVKG

KMIMNSLSLFAAISGMILSIMDILNIKISHFLKMESLNFIRAHTPYINIYNCEPANPSEKN

SPSTQYCYSIQSLFLGILSVMLIFAFFQELVIAGIVENEWKRTCSRPKSNIVLLSAEEKK

EQTIEIKEEVVGLTETSSQPKNEEDIEIIPIQEEEEEETETNFPEPPQDQESSPIENDSSP

(8) The lymphocyte-activating antigen CD30 (SwissProt ID P28908)

>gi|68348711|ref|NP_001234.2| tumor necrosis factor receptor superfamily member 8 isoform 1 precursor [*Homo sapiens*]
MRVLLAALGLLFLGALRAFPQDRPFEDTCHGNPSHYYDKAVRRCCYRCPMGLFPTQ

QCPQRPTDCRKQCEPDYYLDEADRCTACVTCSRDDLVEKTPCAWNSSRVCECRPGM

FCSTSAVNSCARCFFHSVCPAGMIVKFPGTAQKNTVCEPASPGVSPACASPENCKEPS

SGTIPQAKPTPVSPATSSASTMPVRGGTRLAQEAASKLTRAPDSPSSVGRPSSDPGLSP

TQPCPEGSGDCRKQCEPDYYLDEAGRCTACVSCSRDDLVEKTPCAWNSSRTCECRP

GMICATSATNSRARCVPYPICAAETVTKPQDMAEKDTTFEAPPLGTQPDCNPTPENG

EAPASTSPTQSLLVDSQASKTLPIPTSAPVALSSTGKPVLDAGPVLFWVILVLVVVVGS

SAFLLCHRRACRKRIRQKLHLCYPVQTSQPKLELVDSRPRRSSTQLRSGASVTEPVAE

ERGLMSQPLMETCHSVGAAYLESLPLQDASPAGGPSSPRDLPEPRVSTEHTNNKIEKI

YIMKADTVIVGTVKAELPEGRGLAGPAEPELEEELEADHTPHYPEQETEPPLGSCSDV

MLSVEEEGKEDPLPTAASGK

(9) The lymphocyte adhesion molecule CD22 (SwissProt ID P20273)

>gi|157168355|ref|NP_001762.2| B-cell receptor CD22 isoform 1 precursor [*Homo sapiens*]
MHLLGPWLLLLVLEYLAFSDSSKWVFEHPETLYAWEGACVWIPCTYRALDGDLESFI

LFHNPEYNKNTSKFDGTRLYESTKDGKVPSEQKRVQFLGDKNKNCTLSIHPVHLNDS

GQLGLRMESKTEKWMERIHLNVSERPFPPHIQLPPEIQESQEVTLTCLLNFSCYGYPIQ

LQWLLEGVPMRQAAVTSTSLTIKSVFTRSELKFSPQWSHHGKIVTCQLQDADGKFLS

NDTVQLNVKHTPKLEIKVTPSDAIVREGDSVTMTCEVSSSNPEYTTVSWLKDGTSLK

KQNTFTLNLREVTKDQSGKYCCQVSNDVGPGRSEEVFLQVQYAPEPSTVQILHSPAV

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EGSQVEFLCMSLANPLPTNYTWYHNGKEMQGRTEEKVHIPKILPWHAGTYSCVAEN

ILGTGQRGPGAELDVQYPPKKVTTVIQNPMPIREGDTVTLSCNYNSSNPSVTRYEWK

PHGAWEEPSLGVLKIQNVGWDNTTIACAACNSWCSWASPVALNVQYAPRDVRVRKI

KPLSEIHSGNSVSLQCDFSSSHPKEVQFFWEKNGRLLGKESQLNFDSISPEDAGSYSC

WVNNSIGQTASKAWTLEVLYAPRRLRVSMSPGDQVMEGKSATLTCESDANPPVSHY

TWFDWNNQSLPYHSQKLRLEPVKVQHSGAYWCQGTNSVGKGRSPLSTLTVYYSPET

IGRRVAVGLGSCLAILILAICGLKLQRRWKRTQSQQGLQENSSGQSFFVRNKKVRRAP

LSEGPHSLGCYNPMMEDGISYTTLRFPEMNIPRTGDAESSEMQRPPPDCDDTVTYSAL

HKRQVGDYENVIPDFPEDEGIHYSELIQFGVGERPQAQENVDYVILKH

(10) The myloid cell surface antigen CD33 (SwissProt ID P20138)

>gi|130979981|ref|NP_001763.3| myeloid cell surface antigen CD33 isoform 1 precursor [*Homo sapiens*]
MPLLLLLPLLWAGALAMDPNFWLQVQESVTVQEGLCVLVPCTFFHPIPYYDKNSPV

HGYWFREGAIISRDSPVATNKLDQEVQEETQGRFRLLGDPSRNNCSLSIVDARRRDN

GSYFFRMERGSTKYSYKSPQLSVHVTDLTHRPKILIPGTLEPGHSKNLTCSVSWACEQ

GTPPIFSWLSAAPTSLGPRTTHSSVLIITPRPQDHGTNLTCQVKFAGAGVTTERTIQLN

VTYVPQNPTTGIFPGDGSGKQETRAGVVHGAIGGAGVTALLALCLCLIFFIVKTHRRK

AARTAVGRNDTHPTTGSASPKHQKKSKLHGPTETSSCSGAAPTVEMDEELHYASLNF

HGMNPSKDTSTEYSEVRTQ

(11) The transmembrane glycoprotein NMB (SwissProt ID Q[14956])

>gi|52694752|ref|NP_001005340.1| transmembrane glycoprotein NMB isoform a precursor [*Homo sapiens*]
MECLYYFLGFLLLAARLPLDAAKRFHDVLGNERPSAYMREHNQLNGWSSDENDWN

EKLYPVWKRGDMRWKNSWKGGRVQAVLTSDSPALVGSNITFAVNLIFPRCQKEDA

NGNIVYEKNCRNEAGLSADPYVYNWTAWSEDSDGENGTGQSHHNVFPDGKPFPHH

PGWRRWNFIYVFHTLGQYFQKLGRCSVRVSVNTANVTLGPQLMEVTVYRRHGRAY

VPIAQVKDVYVVTDQIPVFVTMFQKNDRNSSDETFLKDLPIMFDVLIHDPSHFLNYST

INYKWSFGDNTGLFVSTNHTVNHTYVLNGTFSLNLTVKAAAPGPCPPPPPPPRPSKPT

PSLATTLKSYDSNTPGPAGDNPLELSRIPDENCQINRYGHFQATITIVEGILEVNIIQMT

DVLMPVPWPESSLIDFVVTCQGSIPTEVCTIISDPTCEITQNTVCSPVDVDEMCLLTVR

RTFNGSGTYCVNLTLGDDTSLALTSTLISVPDRDPASPLRMANSALISVGCLAIFVTVI

SLLVYKKHKEYNPIENSPGNVVRSKGLSVFLNRAKAVFFPGNQEKDPLLKNQEFKGVS

(12) The adhesion molecule CD56 (SwissProt ID P13591)

>gi|94420689|ref|NP_000606.3| neural cell adhesion molecule 1 isoform 1 [*Homo sapiens*]
MLQTKDLIWTLFFLGTAVSLQVDIVPSQGEISVGESKFFLCQVAGDAKDKDISWFSPN

GEKLTPNQQRISVVWNDDSSSTLTIYNANIDDAGIYKCVVTGEDGSESEATVNVKIFQ

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KLMFKNAPTPQEFREGEDAVIVCDVVSSLPPTIIWKHKGRDVILKKDVRFIVLSNNYL

QIRGIKKTDEGTYRCEGRILARGEINFKDIQVIVNVPPTIQARQNIVNATANLGQSVTL

VCDAEGFPEPTMSWTKDGEQIEQEEDDEKYIFSDDSSQLTIKKVDKNDEAEYICIAEN

KAGEQDATIHLKVFAKPKITYVENQTAMELEEQVTLTCEASGDPIPSITWRTSTRNISS

EEKTLDGHMVVRSHARVSSLTLKSIQYTDAGEYICTASNTIGQDSQSMYLEVQYAPK

LQGPVAVYTWEGNQVNITCEVFAYPSATISWFRDGQLLPSSNYSNIKIYNTPSASYLEV

TPDSENDFGNYNCTAVNRIGQESLEFILVQADTPSSPSIDQVEPYSSTAQVQFDEPEAT

GGVPILKYKAEWRAVGEEVWHSKWYDAKEASMEGIVTIVGLKPETTYAVRLAALNGKGL

GEISAASEFKTQPVQGEPSAPKLEGQMGEDGNSIKVNLIKQDDGGSPIRHYLVRYRAL

SSEWKPEIRLPSGSDHVMLKSLDWNAEYEVYVVAENQQGKSKAAHFVFRTSAQPTAIP

ANGSPTSGLSTGAIVGILIVIFVLLLVVVDITCYFLNKCGLFMCIAVNLCGKAGPGAK

GKDMEEGKAAFSKDESKEPIVEVRTEEERTPNHDGGKHTEPNETTPLTEPEKGPVEAK

PECQETETKPAPAEVKTVPNDATQTKENESKA

(13) The surface molecule CD70 (SwissProt ID P32970)

>gi|4507605|ref|NP_001243.1| CD70 antigen [*Homo sapiens*]
MPEEGSGCSVRRRPYGCVLRAALVPLVAGLVICLVVCIQRFAQAQQQLPLESLGWD

VAELQLNHTGPQQDPRLYWQGGPALGRSFLHGPELDKGQLRIHRDGIYMVHIQVTL

AICSSTTASRHHPTTLAVGICSPASRSISLLRLSFHQGCTIASQRLTPLARGDTLCTNLT

GTLLPSRNTDETFFGVQWVRP

(14) The surface molecule CD74 (SwissProt ID P04233)

>gi|10835071|ref|NP_004346.1| HLA class II histocompatibility antigen
gamma chain isoform b [*Homo sapiens*]
MHRRRSRSCREDQKPVMDDQRDLISNNEQLPMLGRRPGAPESKCSRGALYTGFSILV

TLLLAGQATTAYFLYQQQGRLDKLTVTSQNLQLENLRMKLPKPPKPVSKMRMATPL

LMQALPMGALPQGPMQNATKYGNMTEDHVMHLLQNADPLKVYPPLKGSFPENLRH

LKNTMETIDWKVFESWMHHWLLFEMSRHSLEQKPTDAPPKESLELEDPSSGLGVTK

QDLGPVPM

(15) The B-lymphocyte antigen CD19 (SwissProt ID P15391)

>gi|296010921|ref|NP_001171569.1| B-lymphocyte antigen CD19 isoform 1
precursor [*Homo sapiens*]
MPPPRLLFFLLFLTPMEVRPEEPLVVKVEEGDNAVLQCLKGTSDGPTQQLTWSRESPL

KPFLKLSLGLPGLGIHMRPLAIWLFIFNVSQQMGGFYLCQPGPPSEKAWQPGWTVNV

EGSGELFRWNVSDLGGLGCGLKNRSSEGPSSPSGKLMSPKLYVWAKDRPEIWEGEPP

CLPPRDSLNQSLSQDLTMAPGSTLWLSCGVPPDSVSRGPLSWTHVHPKGPKSLLSLEL

KDDRPARDMWVMETGLLLPRATAQDAGKYYCHRGNLTMSFHLEITARPVLWHWL

LRTGGWKVSAVTLAYLIFCLCSLVGILHLQRALVLRRKRKRMTDPTRRFFKVTPPPG

SGPQNQYGNVLSLPTPTSGLGRAQRWAAGLGGTAPSYGNPSSDVQADGALGSRSPP

GVGPEEEEGEGYEEPDSEEDSEFYENDSNLGQDQLSQDGSGYENPEDEPLGPEDEDSF

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SNAESYENEDEELTQPVARTMDFLSPHGSAWDPSREATSLAGSQSYEDMRGILYAAP

QLRSIRGQPGPNHEEDADSYENMDNPDGPDPAWGGGGRMGTWSTR

(16) The surface protein mucin-1 (SwissProt ID P15941)

>gi|65301117|ref|NP_002447.4| mucin-1 isoform 1 precursor [*Homo sapiens*]
MTPGTQSPFFLLLLLTVLTVVTGSGHASSTPGGEKETSATQRSSVPSSTEKNALSTGVS

FFFLSFHISNLQFNSSLEDPSTDYYQELQRDISEMFLQIYKQGGFLGLSNIKFRPGSVVV

QLTLAFREGTINVHDVETQFNQYKTEAASRYNLTISDVSVSDVPFPFSAQSGAGVPG

WGIALLVLVCVLVALAIVYLIALAVCQCRRKNYGQLDIFPARDTYHPMSEYPTYHTH

GRYVPPSSTDRSPYEKVSAGNGGSSLSYTNPAVAATSANL

(17) The surface protein CD138 (SwissProt ID P18827)

>gi|29568086|ref|NP_002988.3| syndecan-1 precursor [*Homo sapiens*]
MRRAALWLWLCALALSLQPALPQIVATNLPPEDQDGSGDDSDNFSGSGAGALQDIT

LSQQTPSTWKDTQLLTAIPTSPEPTGLEATAASTSTLPAGEGPKEGEAVVLPEVEPGLT

AREQEATPRPRETTQLPTTHQASTTTATTAQEPATSHPHRDMQPGHHETSTPAGPSQ

ADLHTPHTEDGGPSATERAAEDGASSQLPAAEGSGEQDFTFETSGENTAVVAVEPDR

RNQSPVDQGATGASQGLLDRKEVLGGVIAGGLVGLIFAVCLVGFMLYRMKKKDEGS

YSLEEPKQANGGAYQKPTKQEEFYA

(18) The integrin alphaV (Genbank Accession No.: NP_002201.1)

>gi|4504763|ref|NP_002201.1| integrin alpha-V isoform 1 precursor
[*Homo sapiens*]
MAFPPRRRLRLGPRGLPLLLSGLLLPLCRAFNLDVDSPAEYSGPEGSYFGFAVDFFVP

SASSRMFLLVGAPKANTTQPGIVEGGQVLKCDWSSTRRCQPIEFDATGNRDYAKDDP

LEFKSHQWFGASVRSKQDKILACAPLYHWRTEMKQEREPVGTCFLQDGTKTVEYAP

CRSQDIDADGQGFCQGGFSIDFTKADRVLLGGPGSFYWQGQLISDQVAEIVSKYDPN

VYSIKYNNQLATRTAQAIFDDSYLGYSVAVGDFNGDGIDDFVSGVPRAARTLGMVYI

YDGKNMSSLYNFTGEQMAAYFGFSVAATDINGDDYADVFIGAPLFMDRGSDGKLQE

VGQVSVSLQRASGDFQTTKLNGFEVFARFGSAIAPLGDLDQDGFNDIAIAAPYGGED

KKGIVYIFNGRSTGLNAVPSQILEGQWAARSMPPSFGYSMKGATDIDKNGYPDLIVG

AFGVDRAILYRARPVITVNAGLEVYPSILNQDNKTCSLPGTALKVSCFNVRFCLKAD

GKGVLPRKLNFQVELLLDKLKQKGAIRRALFLYSRSPSHSKNMTISRGGLMQCEELIA

YLRDESEFRDKLTPITIFMEYRLDYRTAADTTGLQPILNQFTPANISRQAHILLDCGED

NVCKPKLEVSVDSDQKKIYIGDDNPLTLIVKAQNQGEGAYEAELIVSIPLQADFIGVV

RNNEALARLSCAFKTENQTRQVVCDLGNPMKAGTQLLAGLRFSVHQQSEMDTSVKF

DLQIQSSNLFDKVSPVVSHKVDLAVLAAVEIRGVSSPDHIFLPIPNWEHKENPETEED

VGPVVQHIYELRNNGPSSFSKAMLHLQWPYKYNNNTLLYILHYDIDGPMNCTSDMEI

NPLRIKISSLQTTEKNDTVAGQGERDHLITKRDLALSEGDIHTLGCGVAQCLKIVCQV

GRLDRGKSAILYVKSLLWTETFMNKENQNHSYSLKSSASFNVIEFPYKNLPIEDITNST

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LVTTNVTWGIQPAPMPVPVWVIILAVLAGLLLLAVLVFVMYRMGFFKRVRPPQEEQ

EREQLQPHENGEGNSET

(19) The teratocarcinoma-derived growth factor 1 protein TDGF1 (Genbank Accession No.: NP_003203.1)

>gi|4507425|ref|NP_003203.1| teratocarcinoma-derived growth factor 1 isoform 1 precursor [*Homo sapiens*]
MDCRKMARFSYSVIWIMAISKVFELGLVAGLGHQEFARPSRGYLAFRDDSIWPQEEP

AIRPRSSQRVPPMGIQHSKELNRTCCLNGGTCMLGSFCACPPSFYGRNCEHDVRKEN

CGSVPHDTWLPKKCSLCKCWHGQLRCFPQAFLPGCDGLVMDEHLVASRTPELPPSA

RTTTFMLVGICLSIQSYY

(20) The prostate-specific membrane antigen PSMA (Swiss Prot ID: Q04609)

>gi|4758398|ref|NP_004467.1| glutamate carboxypeptidase 2 isoform 1 [*Homo sapiens*]
MWNLLHETDSAVATARRPRWLCAGALVLAGGFFLLGFLFGWFIKSSNEATNITPKH

NMKAFLDELKAENIKKFLYNFTQIPHLAGTEQNFQLAKQIQSQWKEFGLDSVELAHY

DVLLSYPNKTHPNYISIINEDGNEIFNTSLFEPPPPGYENVSDIVPPFSAFSPQGMPEGD

LVYVNYARTEDFFKLERDMKINCSGKIVIARYGKVFRGNKVKNAQLAGAKGVILYS

DPADYFAPGVKSYPDGWNLPGGGVQRGNILNLNGAGDPLTPGYPANEYAYRRGIAE

AVGLPSIPVHPIGYYDAQKLLEKMGGSAPPDSSWRGSLKVPYNVGPGFTGNFSTQKV

KMHIHSTNEVTRIYNVIGTLRGAVEPDRYVILGGHRDSWVFGGIDPQSGAAVVHEIV

RSFGTLKKEGWRPRRTILFASWDAEEFGLLGSTEWAEENSRLLQERGVAYINADSSIE

GNYTLRVDCTPLMYSLVHNLTKELKSPDEGFEGKSLYESWTKKSPSPEFSGMPRISKL

GSGNDFEVFFQRLGIASGRARYTKNWETNKFSGYPLYHSVYETYELVEKFYDPMFK

YHLTVAQVRGGMVFELANSIVLPFDCRDYAVVLRKYADKIYSISMKHPQEMKTYSV

SFDSLFSAVKNFTEIASKFSERLQDFDKSNPIVLRMMNDQLMFLERAFIDPLGLPDRPF

YRHVIYAPSSHNKYAGESFPGIYDALFDIESKVDPSKAWGEVKRQIYVAAFTVQAAA

ETLSEVA

(21) The tyrosine protein kinase EPHA2 (Swiss Prot ID: P29317)

>gi|32967311|ref|NP_004422.2| ephrin type-A receptor 2 precursor [*Homo sapiens*]
MELQAARACFALLWGCALAAAAAAQGKEVVLLDFAAAGGELGWLTHPYGKGWDL

MQNIMNDMPIYMYSVCNVMSGDQDNWLRTNWVYRGEAERIFIELKFTVRDCNSFP

GGASSCKETFNLYYAESDLDYGTNFQKRLFTKIDTIAPDEITVSSDFEARHVKLNVEE

RSVGPLTRKGFYLAFQDIGACVALLSVRVYYKKCPELLQGLAHFPETIAGSDAPSLAT

VAGTCVDHAVVPPGGEEPRMHCAVDGEWLVPIGQCLCQAGYEKVEDACQACSPGF

FKFEASESPCLECPEHTLPSPEGATSCECEEGFFRAPQDPASMPCTRPPSAPHYLTAVG

MGAKVELRWTPPQDSGGREDIVYSVTCEQCWPESGECGPCEASVRYSEPPHGLTRTS

VTVSDLEPHMNYTFTVEARNGVSGLVTSRSFRTASVSINQTEPPKVRLEGRSTTSLSV

-continued

SWSIPPPQQSRVWKYEVTYRKKGDSNSYNVRRTEGFSVTLDDLAPDTTYLVQVQAL

TQEGQGAGSKVHEFQTLSPEGSGNLAVIGGVAVGVVLLLVLAGVGFFIHRRRKNQR

ARQSPEDVYFSKSEQLKPLKTYVDPHTYEDPNQAVLKFTTEIHPSCVTRQKVIGAGEF

GEVYKGMLKTSSGKKEVPVAIKTLKAGYTEKQRVDFLGEAGIMGQFSHHNIIRLEGV

ISKYKPMMIITEYMENGALDKFLREKDGEFSVLQLVGMLRGIAAGMKYLANMNYV

HRDLAARNILVNSNLVCKVSDFGLSRVLEDDPEATYTTSGGKIPIRWTAPEAISYRKF

TSASDVWSFGIVMWEVMTYGERPYWELSNHEVMKAINDGFRLPTPMDCPSAIYQLM

MQCWQQERARRPKFADIVSILDKLIRAPDSLKTLADFDPRVSIRLPSTSGSEGVPFRTV

SEWLESIKMQQYTEHFMAAGYTAIEKVVQMTNDDIKRIGVRLPGHQKRIAYSLLGLK

DQVNTVGIPI

(22) The surface protein SLC44A4 (Genbank Accession No: NP_001171515)

>gi|295849282|ref|NP_001171515.1| choline transporter-like protein 4 isoform 2 [*Homo sapiens*]
MGGKQRDEDDEAYGKPVKYDPSFRGPIKNRSCTDVICCVLFLLFILGYIVVGIVAWL

YGDPRQVLYPRNSTGAYCGMGENKDKPYLLYFNIFSCILSSNIISVAENGLQCPTPQT

VITSLQQELCPSFLLPSAPALGRCFPWTNVTPPALPGITNDTTIQQGISGLIDSLNARDIS

VKIFEDFAQSWYWILVALGVALVLSLLFILLLRLVAGPLVLVLILGVLGVLAYGIYYC

WEEYRVLRDKGASISQLGFTTNLSAYQSVQETWLAALIVLAVLEAILLLMLIFLRQRI

RIAIALLKEASKAVGQMMSTMFYPLVTFVLLLICIAYWAMTALYLATSGQPQYVLW

ASNISSPGCEKVPINTSCNPTAHLVNSSCPGLMCVFQGYSSKGLIQRSVFNLQIYGVLG

LFWTLNWVLALGQCVLAGAFASFYWAFHKPQDIPTFPLISAFIRTLRYHTGSLAFGAL

ILTLVQIARVILEYIDHKLRGVQNPVARCIMCCFKCCLWCLEKFIKFLNRNAYIMIAIY

GKNFCVSAKNAFMLLMRNIVRVVVLDKVTDLLLFFGKLLVVGGVGVLSFFFFSGRIP

GLGKDFKSPHLNYYWLPIMTSILGAYVIASGFFSVFGMCVDTLFLCFLEDLERNNGSL

DRPYYMSKSLLKILGKKNEAPPDNKKRKK

(23) The surface protein BMPR1B (SwissProt: O00238)

(24) The transport protein SLC7A5 (SwissProt: Q01650)

(25) The epithelial prostate antigen STEAP1 (SwissProt: Q9UHE8)

(26) The ovarian carcinoma antigen MUC16 (SwissProt: Q8WXI7)

(27) The transport protein SLC34A2 (SwissProt: O95436)

(28) The surface protein SEMA5b (SwissProt: Q9P283)

(29) The surface protein LYPD1 (SwissProt: Q8N2G4)

(30) The endothelin receptor type B EDNRB (SwissProt: P24530)

(31) The ring finger protein RNF43 (SwissProt: Q68DV7)

(32) The prostate carcinoma-associated protein STEAP2 (SwissProt: Q8NFT2)

(33) The cation channel TRPM4 (SwissProt: Q8TD43)

(34) The complement receptor CD21 (SwissProt: P20023)

(35) The B-cell antigen receptor complex-associated protein CD79b (SwissProt: P40259)

(36) The cell adhesion antigen CEACAM6 (SwissProt: P40199)

(37) The dipeptidase DPEP1 (SwissProt: P16444)

(38) The interleukin receptor IL20Ralpha (SwissProt: Q9UHF4)

(39) The proteoglycan BCAN (SwissProt: Q96GW7)

(40) The ephrin receptor EPHB2 (SwissProt: P29323)

(41) The prostate stem cell-associated protein PSCA (Genbank Accession No: NP_005663.2)

(42) The surface protein LHFPL3 (SwissProt: Q86UP9)

(43) The receptor protein TNFRSF13C (SwissProt: Q96RJ3)

(44) The B-cell antigen receptor complex-associated protein CD79a (SwissProt: P11912)

(45) The receptor protein CXCR5 (SwissProt: P32302)

(46) The ion channel P2X5 (SwissProt: Q93086)

(47) The lymphocyte antigen CD180 (SwissProt: Q99467)

(48) The receptor protein FCRL1 (SwissProt: Q96LA6)

(49) The receptor protein FCRL5 (SwissProt: Q96RD9)

(50) The MHC class II molecule Ia antigen HLA-DOB (Genbank Accession No: NP_002111.1)

(51) The T-cell protein VTCN1 (SwissProt: Q7Z7D3).

[2817] In one preferred subject of the invention the cancer target molecule is selected from the group consisting of the cancer target molecules (1)-(51).

[2818] In another particularly preferred subject of the invention the binder binds to an extracellular cancer target molecule which is selected from the group consisting of the cancer target molecules (1)-(51).

[2819] In another particularly preferred subject of the invention the binder binds specifically to an extracellular cancer target molecule which is selected from the group consisting of the cancer target molecules (1)-(51).

[2820] In one particularly preferred subject of the invention the cancer target molecule is selected from the group consisting of EGF receptor (NP_005219.2), mesothelin (Q^{13421}-3), C4.4a (NP_055215.2) and carboanhydrase IX (CA IX; NP_001207.2).

[2821] In another particularly preferred subject of the invention the binder binds to an extracellular cancer target molecule which is selected from the group consisting of EGF receptor (NP_005219.2), mesothelin (Q^{13421}-3), C4.4a (NP_055215.2) and carboanhydrase IX (CA IX; Q^{16790}).

[2822] In another particularly preferred subject of the invention the binder binds specifically to an extracellular cancer target molecule which is selected from the group consisting of EGF receptor (NP_005219.2), mesothelin (Q^{13421}-3), C4.4a (NP_055215.2) and carboanhydrase IX (CA IX; Q^{16790}).

[2823] In one preferred embodiment the binder, after binding to its extracellular target molecule on the target cell, is internalized by the target cell as a result of the binding. The effect of this is that the binder-drug conjugate, which may be an immunoconjugate or an ADC, is taken up by the target cell.

[2824] In one embodiment the binder is a binding protein. In one preferred embodiment the binder is an antibody, an antigen-binding antibody fragment, a multispecific antibody or an antibody mimetic.

[2825] Preferred antibody mimetics are affibodies, adnectins, anticalins, DARPins, avimers, or nanobodies. Preferred multispecific antibodies are bispecific and trispecific antibodies.

[2826] In one preferred embodiment the binder is an antibody or an antigen-binding antibody fragment, more preferably an isolated antibody or an isolated antigen-binding antibody fragment.

[2827] Preferred antigen-binding antibody fragments are Fab, Fab', $F(ab')_2$ and Fv fragments, diabodies, DAbs, linear antibodies and scFv. Particularly preferred are Fab, diabodies and scFv.

[2828] In one particularly preferred embodiment the binder is an antibody. Particularly preferred are monoclonal antibodies or antigen-binding antibody fragments thereof. Further particularly preferred are human, humanized or chimeric antibodies or antigen-binding antibody fragments thereof.

[2829] Antibodies or antigen-binding antibody fragments which bind cancer target molecules may be prepared by a person of ordinary skill in the art using known processes, such as, for example, chemical synthesis or recombinant expression. Binders for cancer target molecules may be acquired commercially or may be prepared by a person of ordinary skill in the art using known processes, such as, for example, chemical synthesis or recombinant expression. Further processes for preparing antibodies or antigen-binding antibody fragments are described in WO 2007/070538 (see page 22 "Antibodies"). The skilled person knows how processes such as phage display libraries (e.g. Morphosys HuCAL Gold) can be compiled and used for discovering antibodies or antigen-binding antibody fragments (see WO 2007/070538, page 24 ff and Example 1 on page 70, Example 2 on page 72). Further processes for preparing antibodies that use DNA libraries from B-cells are described for example on page 26 (WO 2007/070538). Processes for humanizing antibodies are described on page 30-32 of WO2007070538 and in detail in Queen, et al., Pros. Natl. Acad. Sci. USA 86:10029-10033, 1989 or in WO 90/0786. Furthermore, processes for the recombinant expression of proteins in general and of antibodies in particular are known to the skilled person (see, for example, in Berger and Kimmel (Guide to Molecular Cloning Techniques, Methods in Enzymology, Vol. 152, Academic Press, Inc.); Sambrook, et al., (Molecular Cloning: A Laboratory Manual, (Second Edition, Cold Spring Harbor Laboratory Press; Cold Spring Harbor, N.Y.; 1989) Vol. 1-3); Current Protocols in Molecular Biolony, (F. M. Ausabel et al. [Eds.], Current Protocols, Green Publishing Associates, Inc./John Wiley & Sons, Inc.); Harlow et al., (Monoclonal Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory Press (19881, Paul [Ed.]); Fundamental Immunology, (Lippincott Williams & Wilkins (1998)); and Harlow, et al., (Using Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory Press (1998)). The skilled person knows the corresponding vectors, promoters and signal peptides which are necessary for the expression of a protein/antibody. Commonplace processes are also described in WO 2007/070538 on pages 41-45. Processes for preparing an IgG1 antibody are described for example in WO 2007/070538 in Example 6 on page 74 ff. Processes which allow the determination of the internalization of an antibody after binding to its antigen are known to the skilled person and are described for example in WO 2007/070538 on page 80. The skilled person is able to use the processes described in WO 2007/070538 that have been used for preparing carboanhydrase IX (Mn) antibodies in analogy for the preparation of antibodies with different target molecule specificity.

EGFR Antibodies

[2830] Examples of antibodies which bind the cancer target molecules EGFR are cetuximab (INN number 7906), panitumumab (INN number 8499) and nimotuzumab (INN number 8545). Cetuximab (Drug Bank Accession Number DB00002) is a chimeric anti-EGFR1 antibody which is produced in SP2/0 mouse myeloma cells and is sold by ImClone Systems Inc/Merck KgaA/Bristol-Myers Squibb Co. Cetuximab is indicated for the treatment of metastasizing, EGFR expressing, colorectal carcinoma with wild type K-Ras gene. It has an affinity of 10^{-10}M

Sequence:

Cetuximab Light Chain (Kappa):

[2831]

DILLTQSPVILSVSPGERVSFSCRASQSIGTNIHWYQQRTNGSPRLLIKY

ASESISGIPSRFSGSGSGTDFTLSINSVESEDIADYYCQQNNNWPTTFGA

GTKLELKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV

-continued

DNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG

LSSPVTKSFNRGEC

Cetuximab Heavy Chain:

[2832]

QVQLKQSGPGLVQPSQSLSITCTVSGFSLTNYGVHWVRQSPGKGLEWLGV

IWSGGNTDYNTPFTSRLSINKDNSKSQVFFKMNSLQSNDTAIYYCARALT

YYDYEFAYWGQGTLVTVSAASTKGPSVFPLAPSSKSTSGGTAALGCLVKD

YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY

ICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPK

DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS

TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV

YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL

DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[2833] Panitumumab (INN number 8499) (Drug Bank Accession Number DB01269) is a recombinant monoclonal human IgG2 antibody which binds specifically to the human EGF receptor 1 and is sold by Abgenix/Amgen. Panitumumab originates from the immunization of transgenic mice (XenoMouse). These mice are capable of producing human immunoglobulin (light and heavy chains). A specific B-cell clone was selected which produces antibodies against EGFR, and this clone was immortalized with CHO cells (Chinese hamster ovary cells). These cells are now used for the production of a 100% human antibody. Panitumumab is indicated for the treatment of EGFR-expressing, metastasizing colorectal carcinoma, which is resistant to chemotherapeutic treatment with fluoropyrimidine, oxaliplatin and irinotecan. It has an affinity of 10^{-11}M.

Sequence:

Panitumumab Light Chain (Kappa):

[2834]

DIQMTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPGKAPKLLIYD

ASNLETGVPSRFSGSGSGTDFTFTISSLQPEDIATYFCQHFDHLPLAFGG

GTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV

DNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG

LSSPVTKSFNRGEC

Panitumumab Heavy Chain:

[2835]

QVQLQESGPGLVKPSETLSLTCTVSGGSVSSGDYYWTWIRQSPGKGLEWI

GHIYYSGNTNYNPSLKSRLTISIDTSKTQFSLKLSSVTAADTAIYYCVRD

RVTGAFDIWGQGTMVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKD

-continued

YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTY

TCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLM

ISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRV

VSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLP

PSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDG

SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[2836] Nimotuzumab (INN number 8545) (EP 00586002, EP 00712863) is a humanized monoclonal IgG1 antibody which binds specifically to the human EGF receptor 1 and is sold by YM BioScienecs Inc. (Mississauga Canada). It is produced in non-secreting NSO cells (mammalian cell line). Nimotuzumab is approved for the treatment of head-and-neck tumours, highly malignant astrocytoma and glioblastoma multiforms (not in EU and US) and pancreatic carcinoma (orphan drug, EMA). It has an affinity of 10^{-8}M.

[2837] Further embodiments of EGFR antibodies are as follows:

[2838] Zalutumumab/2F8/HuMax-EGFr, from Genmab A/S (WO 02/100348, WO 2004/056847, INN number 8605)

[2839] Necitumumab/11F8, ImClone/IMC-11F8, from ImClone Systems Inc. [Eli Lilly & Co] (WO 2005/090407 (EP 01735348-A1, US 2007/0264253-A1, U.S. Pat. No. 7,598,350, WO 2005/090407-A1), INN number 9083)

[2840] Matuzumab/anti-EGFR MAb, Merck KGaA/anti-EGFR MAb, Takeda/EMD 72000/EMD-6200/EMD-72000 and EMD-55900/MAb 425/monoclonal antibody 425, from Merck KGaA/Takeda (WO 92/15683, INN number 8103 (Matuzumab))

[2841] RG-7160/GA-201/GA201/R-7160/R7160/RG7160/RO-4858696/RO-5083945/R04858696/R05083945, from Glycart Biotechnology AG (Roche Holding AG) (WO 2010/112413-A1, WO 2010/115554)

[2842] GT-MAB 5.2-GEX/CetuGEX, from Glycotope GmbH (WO 2008/028686-A2 (EP 01900750-A1, EP 01911766-A1, EP 02073842-A2, US 2010/0028947-A1)

[2843] ISU-101, from Isu Abxis Inc (ISU Chemical Co Ltd)/Scancell (WO 2008/004834-A1)

[2844] ABT-806/mAb-806/ch-806/anti-EGFR monoc. antibody 806, from Ludwig Institute for Cancer Research/Abbott/Life Science Pharmaceuticals (WO 02/092771, WO 2005/081854 and WO 2009/023265)

[2845] SYM-004 (consists of two chimeric IgG1 antibodies (992 and 1024)), from Symphogen A/S (WO 2010/022736-A2)

[2846] MR1-1/MR1-1 KDEL, from IVAX Corp (Teva Pharmaceutical Industries Ltd) (Duke University), (Patent: WO2001/062931-A2)

[2847] Antibody against the deletion mutant, EGFRvIII, from Amgen/Abgenix (WO 2005/010151, U.S. Pat. No. 7,628,986)

[2848] SC-100, from Scancell Ltd (WO 01/088138-A1)

[2849] MDX-447/EMD 82633/BAB-447/H 447/MAb, EGFR, Medarex/Merck KgaA, from Bristol-Myers Squibb (US)/Merck KGaA (DE)/Takeda (JP), (WO 91/05871, WO 92/15683)

[2850] Anti-EGFR-Mab, from Xencor (WO 2005/056606)

[2851] DXL-1218/anti-EGFR monoclonal antibody (cancer), InNexus, from InNexus Biotechnology Inc., Pharmaprojects PH048638

[2852] In one preferred embodiment the anti-EGFR antibodies are selected from the group consisting of cetuximab, panitumumab, nimotuzumab, zalutumumab, necitumumab, matuzumab, RG-716, GT-MAB 5.2-GEX, ISU-101, ABT-806, SYM-004, MR1-1, SC-100, MDX-447, and DXL-1218.

[2853] In one particularly preferred embodiment the anti-EGFR antibodies are selected from the group consisting of cetuximab, panitumumab, nimotuzumab, zalutumumab, necitumumab and matuzumab.

[2854] The skilled person knows of processes which can be used to prepare further antibodies, from the CDR regions of the abovementioned antibodies by means of sequence variations, these further antibodies having a similar or better affinity and/or specificity for the target molecule.

[2855] In a further embodiment, the anti-EGFR antibodies or antigen-binding antibody fragments are selected from the group consisting of

antibodies or antigen-binding antibody fragments comprising the three CDR regions of the light chain and the three CDR regions of the heavy chain of one of the following antibodies: cetuximab, panitumumab, nimotuzumab, zalutumumab, necitumumab, matuzumab, RG-716, GT-MAB 5.2-GEX, ISU-101, ABT-806, SYM-004, MR1-1, SC-100, MDX-447, and DXL-1218.

[2856] In another embodiment the anti-EGFR antibodies or antigen-binding antibody fragments are selected from the group consisting of

antibodies or antigen-binding antibody fragments comprising the three CDR regions of the light chain and the three CDR regions of the heavy chain of one of the following antibodies: cetuximab, panitumumab, nimotuzumab, zalutumumab, necitumumab, matuzumab.

Carboanhydrase IX Antibodies

[2857] Examples of antibodies which bind the cancer target molecule carbonahydrase IX are described in WO 2007/070538-A2 (e.g. Claims 1-16).

[2858] In one preferred embodiment the anti-carboanhydrase IX antibodies or antigen-binding antibody fragments are selected from the group consisting of anti-carboanhydrase IX antibodies or antigen-binding antibody fragments 3ee9 (Claim 4 (a) in WO 2007/070538-A2), 3ef2 (Claim 4 (b) in WO2007/070538-A2), 1e4 (Claim 4 (c) in WO 2007/070538-A2), 3a4 (Claim 4 (d) in WO 2007/070538-A2), 3ab4 (Claim 4 (e) in WO 2007/070538-A2), 3ah10 (Claim 4 (f) in WO 2007/070538-A2), 3bb2 (Claim 4 (g) in WO 2007/070538-A2), 1aa1 (Claim 4 (h) in WO 2007/070538-A2), 5a6 (Claim 4 (i) in WO 2007/070538-A2) and 5aa3 (Claim 4 (j) in WO 2007/070538-A2).

[2859] In one preferred embodiment the anti-carboanhydrase IX antibodies or antigen-binding antibody fragments are selected from the group consisting of:

anti-carboanhydrase IX antibodies or antigen-binding antibody fragments thereof which comprise the sequences of the three CDR regions of the light chain and the sequences of the three CDR regions of the heavy chain of the antibody 3ee9 (from WO 2007/070538-A2),

anti-carboanhydrase IX antibodies or antigen-binding antibody fragments thereof which comprise the sequences of the three CDR regions of the light chain and the sequences of the three CDR regions of the heavy chain of the antibody 3ef2 (from WO 2007/070538-A2),

anti-carboanhydrase IX antibodies or antigen-binding antibody fragments thereof which comprise the sequences of the three CDR regions of the light chain and the sequences of the three CDR regions of the heavy chain of the antibody 1e4 (from WO 2007/070538-A2),

anti-carboanhydrase IX antibodies or antigen-binding antibody fragments thereof which comprise the sequences of the three CDR regions of the light chain and the sequences of the three CDR regions of the heavy chain of the antibody 3a4 (from WO 2007/070538-A2),

anti-carboanhydrase IX antibodies or antigen-binding antibody fragments thereof which comprise the sequences of the three CDR regions of the light chain and the sequences of the three CDR regions of the heavy chain of the antibody 3ab4 (from WO 2007/070538-A2),

anti-carboanhydrase IX antibodies or antigen-binding antibody fragments thereof which comprise the sequences of the three CDR regions of the light chain and the sequences of the three CDR regions of the heavy chain of the antibody 3ah10 (from WO 2007/070538-A2),

anti-carboanhydrase IX antibodies or antigen-binding antibody fragments thereof which comprise the sequences of the three CDR regions of the light chain and the sequences of the three CDR regions of the heavy chain of the antibody 3bb2 (from WO 2007/070538-A2),

anti-carboanhydrase IX antibodies or antigen-binding antibody fragments thereof which comprise the sequences of the three CDR regions of the light chain and the sequences of the three CDR regions of the heavy chain of the antibody 1aa1 (from WO 2007/070538-A2),

anti-carboanhydrase IX antibodies or antigen-binding antibody fragments thereof which comprise the sequences of the three CDR regions of the light chain and the sequences of the three CDR regions of the heavy chain of the antibody 5a6 (from WO 2007/070538-A2), and

anti-carboanhydrase IX antibodies or antigen-binding antibody fragments thereof which comprise the sequences of the three CDR regions of the light chain and the sequences of the three CDR regions of the heavy chain of the antibody 5aa3 (from WO 2007/070538-A2).

[2860] The here-indicated sequences of the CDR regions are disclosed in FIGS. 2a-2c, page 128-130 in WO 2007/070538-A2.

[2861] In one preferred embodiment the anti-carboanhydrase IX antibodies or antigen-binding antibody fragments are selected from the group consisting of:

an antibody or antigen-binding fragment which comprises the amino acid sequence of the variable light and variable heavy chains of the antibody 3ee9, as indicated in WO 2007/070538-A2 in FIG. 4b on page 137,

an antibody or antigen-binding fragment which comprises the amino acid sequence of the variable light and variable heavy chains of the antibody 3ef2, as indicated in WO 2007/070538-A2 in FIG. 4c on page 138 and in FIG. 4b on page 137, an antibody or antigen-binding fragment which comprises the amino acid sequence of the variable light and variable heavy chains of the antibody 1e4, as indicated in WO 2007/070538-A2 in FIG. 4a on page 136,

an antibody or antigen-binding fragment which comprises the amino acid sequence of the variable light and variable heavy chains of the antibody 3a4, as indicated in WO 2007/070538-A2 in FIG. 4a on page 136,

an antibody or antigen-binding fragment which comprises the amino acid sequence of the variable light and variable heavy chains of the antibody 3ab4, as indicated in WO 2007/070538-A2 in FIG. 4a on page 136,

an antibody or antigen-binding fragment which comprises the amino acid sequence of the variable light and variable heavy chains of the antibody 3ah10, as indicated in WO 2007/070538-A2 in FIG. 4a on page 136,

an antibody or antigen-binding fragment which comprises the amino acid sequence of the variable light and variable heavy chains of the antibody 3bb2, as indicated in WO 2007/070538-A2 in FIG. 4b on page 137,

an antibody or antigen-binding fragment which comprises the amino acid sequence of the variable light and variable heavy chains of the antibody 1aa1, as indicated in WO 2007/070538-A2 in FIG. 4a on page 136,

an antibody or antigen-binding fragment which comprises the amino acid sequence of the variable light and variable heavy chains of the antibody 5a6, as indicated in WO 2007/070538-A2 in FIG. 4b on page 137, and

an antibody or antigen-binding fragment which comprises the amino acid sequence of the variable light and variable heavy chains of the antibody 5aa3, as indicated in WO 2007/070538-A2 in FIG. 4b on page 137.

[2862] In one particularly preferred embodiment the anti-carboanhydrase IX antibody is antibody 3ee9 from WO 2007/070538-A2.

[2863] In one particularly preferred embodiment the anti-carboanhydrase IX antibody or the antigen-binding antibody fragment comprises the amino acid sequences of the CDR regions of the variable heavy chain of the antibody 3ee9 (VH3-CDR1: GFTFSSYGMS; VH3-CDR2: GISSLGSTTYYADSVKG; VH3-CDR3: TGSPGTFMHGDH, see FIG. 2a, page 128 in WO2007070538-A2) and the amino acid sequences of the CDR regions of the variable light chain of the antibody 3ee9 (VLk1-CDR1: RASQDINNYLS; VLk1-CDR2: YGASNLQS; VLk1-CDR3: QQYYGRPT, see FIG. 2b, page 129 in WO 2007/070538-A2).

[2864] In one particularly preferred embodiment the anti-carboanhydrase IX antibody or the antigen-binding antibody fragment comprises the amino acid sequences of a variable heavy chain of the antibody 3ee9

(VH3:ELVESGGGLVQPGGSLRLSCAASGFTF-SSYGMSWVRQAPGKGLEWVSGISSLG STTYYADS-VKGRFTISRDNSKNTLYLQMNSLRAED-TAVYYCARTGSPGTFMHGDHW GQGTLVTVSS, see FIG. 4b, page 137 in WO 2007070538-A2) and the amino acid sequences of the variable light chain of the antibody 3ee9

(VLk1:DIQMTQSPSSLSASVGDRVTIT-CRaSQDINNYLSWYQQKPGKAPKLLIYGASNL QSGVPSRFSGSGSGTDFTLTISSLQPED-FAVYYCQQYYGRPTTFGQGTKVEIKRT, see FIG. 4b, page 137 in WO 2007070538-A2).

[2865] In one preferred embodiment the anti-carboanhydrase IX antibody 3ee9 is an IgG antibody.

[2866] In one particularly preferred embodiment the anti-carboanhydrase IX antibody 3 ee9 is an IgG1 antibody (3ee9-IgG1),

where the amino acid sequence of the heavy chain comprises the following sequence:

```
QVELVESGGGLVQPGGSLRLSCAASGFTFSSYGMSWVRQAPGKGLEWVSG
ISSLGSTTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARTG
SPGTFMHGDHWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV
KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ
TYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK
PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY
NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP
QVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP
VLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP
GK
```

and the amino acid sequences of the light chain comprises the following sequence:

```
DIQMTQSPSSLSASVGDRVTITCRASQDINNYLSWYQQKPGKAPKLLIYG
ASNLQSGVPSRFSGSGSGTDFTLTISSLQPEDFAVYYCQQYYGRPTTFGQ
GTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV
DNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC
```

anti-carboanhydrase IX antibody 3ee9-IgG1:

[2867] A further aspect of the present invention is the provision of the anti-carboanhydrase IX antibody 3ee9-IgG1.

C4.4a Antibodies:

[2868] Examples of C4.4a antibodies and antigen-binding fragments are described below. The sequences of the antibodies are indicated in Table 1, with each line reproducing the respective CDR amino acid sequences of the variable light chain and of the variable heavy chain, respectively of the antibody listed in column 1. The amino acid sequences of the variable light chain and of the variable heavy chain, and the nucleic acid sequence of the antibody indicated in column 1 in each case, are also indicated.

[2869] In one embodiment the anti-C4.4a antibodies or antigen-binding antibody fragments bind to the S1 domain S1 (amino acid position 1-85 of SEQ ID NO: 1) of C4.4a.

[2870] In one embodiment the anti-C4.4a antibodies or antigen-binding antibody fragments are cross-reactive with human C4.4a (SEQ ID NO:1) and with murine C4.4a (SEQ ID NO:2).

[2871] In one embodiment the anti-C4.4a antibodies or antigen-binding antibody fragments thereof, after binding to a cell which expresses C4.4a, are internalized by the cell.

[2872] In another embodiment the anti-C4.4a antibodies or antigen-binding antibody fragments compete with the antibody M31-B01 and/or with the antibody M20-D02-S-A for binding to C4.4a. Antibodies M31-B01 and M20-D02-S-A compete for binding to C4.4a. The antibodies B01-1 to B01-12 were prepared from M31-B01 by means of affinity maturation and compete with M31-B01 for binding to C4.4a. The antibodies D02-1 to D02-13 were prepared from M20-D02-S-A by means of affinity maturation and compete with M20-D02-S-A for binding to C4.4a.

[2873] In a further embodiment the anti-C4.4a antibodies or antigen-binding antibody fragments comprise at least one, two or three of the CDR amino acid sequences given in Table 1 or Table 2.

[2874] In another embodiment the anti-C4.4a antibodies or antigen-binding antibody fragments comprise at least one, two or three CDR amino acid sequences of an antibody given in Table 1 or Table 2.

[2875] In a further embodiment the anti-C4.4a antibodies or antigen-binding antibody fragments comprise at least one, two or three CDR amino acid sequences of the variable light chain and at least one, two or three CDR amino acid sequences of the variable heavy chain of an antibody given in Table 1 or Table 2.

[2876] In another embodiment the anti-C4.4a antibodies or antigen-binding antibody fragments comprise which are at least 50%, 60%, 70%, 80%, 90% or 95% identical with the CDR amino acid sequences of the variable light chain and with the CDR amino acid sequences of the variable heavy chain, of an antibody given in Table 1 or Table 2.

[2877] In another embodiment the CDR sequences of the anti-C4.4a antibodies or antigen-binding antibody fragments comprise

CDR sequences of the heavy chain which conform to the CDR sequences SEQ ID NO: 297 (CDR H1), SEQ ID NO: 298 (CDR H2) and SEQ ID NO: 299 (CDR H3) and CDR sequences of the light chain which conform to the CDR sequences SEQ ID NO: 300 (CDR L1), SEQ ID NO: 22 (CDR L2) and SEQ ID NO: 301 (CDR L3), or

CDR sequences of the heavy chain which conform to the CDR sequences SEQ ID NO: 302 (CDR H1), SEQ ID NO: 303 (CDR H2) and SEQ ID NO: 304 (CDR H3) and CDR sequences of the light chain which conform to the CDR sequences SEQ ID NO: 305 (CDR L1), SEQ ID NO: 306 (CDR L2) and SEQ ID NO: 307 (CDR L3).

[2878] In another embodiment the anti-C4.4a antibodies or antigen-binding antibody fragments comprise which are at least 50%, 60%, 70%, 80%, 90% or 95% identical with the variable light chain and with the variable heavy chain, of an antibody given in Table 1 or Table 2.

[2879] In another embodiment the anti-C4.4a antibodies or antigen-binding antibody fragments comprise the three CDR amino acid sequences of the variable light chain and the three CDR amino acid sequences of the variable heavy chain of an antibody given in Table 1 or Table 2.

[2880] In another embodiment the anti-C4.4a antibodies or antigen-binding antibody fragments comprise a variable light chain and/or a variable heavy chain of an antibody given in Table 1 or Table 2.

[2881] In another embodiment the anti-C4.4a antibodies or antigen-binding antibody fragments comprise the variable light chain and the variable heavy chain of an antibody given in Table 1 or Table 2.

[2882] In one preferred embodiment the C4.4a antibodies and the antigen-binding antibody fragments are selected from the group consisting of

antibody which comprises the CDR sequences of the variable heavy chain represented by the sequences SEQ ID NO: 75-77 and which comprises the CDR sequences of the variable light chain represented by the sequences SEQ ID NO: 78-80 (B01-10),

antibody which comprises the CDR sequences of the variable heavy chain represented by the sequences SEQ ID NO: 5, 9 and 13 and which comprises the CDR sequences of the variable light chain represented by the sequences SEQ ID NO: 17, 21 and 25 (M31-B01),

antibody which comprises the CDR sequences of the variable heavy chain represented by the sequences SEQ ID NO: 6, 10 and 14 an which comprises the CDR sequences of the variable light chain represented by the sequences SEQ ID NO: 18, 22 and 26 (M20-D02-S-A),

antibody which comprises the CDR sequences of the variable heavy chain represented by the sequences SEQ ID NO: 7, 11 and 15 and which comprises the CDR sequences of the variable light chain represented by the sequences SEQ ID NO: 19, 23 and 27 (M60-G03),

antibody which comprises the CDR sequences of the variable heavy chain represented by the sequences SEQ ID NO: 8, 12 and 16 and which comprise the CDR sequences of the variable light chain represented by the sequences SEQ ID NO: 20, 24 and 28 (36-H02),

antibody which comprises the CDR sequences of the variable heavy chain represented by the sequences SEQ ID NO: 45-47 and which comprises the CDR sequences of the variable light chain represented by the sequences SEQ ID NO: 48-50 (B01-3),

antibody which comprises the CDR sequences of the variable heavy chain represented by the sequences SEQ ID NO: 55-57 and which comprises the CDR sequences of the variable light chain represented by the sequences SEQ ID NO: 58-60 (B01-5),

antibody which comprises the CDR sequences of the variable heavy chain represented by the sequences SEQ ID NO: 65-67 and which comprises the CDR sequences of variable light chain represented by the sequences SEQ ID NO: 68-70 (B01-7),

antibody which comprises the CDR sequences of the variable heavy chain represented by the sequences SEQ ID NO: 85-87 and which comprises the CDR sequences of the variable light chain represented by the sequences SEQ ID NO: 88-90 (B01-12),

antibody which comprises the CDR sequences of the variable heavy chain represented by the sequences SEQ ID NO: 95-97 and which comprises the CDR sequences of the variable light chain represented by the sequences SEQ ID NO: 98-100 (D02-4),

antibody which comprises the CDR sequences of the variable heavy chain represented by the sequences SEQ ID NO: 105-107 and which comprises CDR sequences of the variable light chain represented by the sequences SEQ ID NO: 108-110 (D02-6),

antibody which comprises the CDR sequences of the variable heavy chain represented by the sequences SEQ ID NO: 115-117 and which comprises the CDR sequences of the variable light chain represented by the sequences SEQ ID NO: 118-120 (D02-7),

antibody which comprises the CDR sequences of the variable heavy chain represented by the sequences SEQ ID NO: 125-127 and which comprises the CDR sequences of the variable light chain represented by the sequences SEQ ID NO: 128-130 (D02-11),

and antibody which comprises the CDR sequences of the variable heavy chain represented by the sequences SEQ ID NO: 135-137 which comprises the CDR sequences of the variable light chain represented by the sequences SEQ ID NO: 138-140 (D02-13).

[2883] In one preferred embodiment the C4.4a antibodies and the antigen-binding antibody fragments are selected from the group consisting of

antibodies which comprise the amino acid sequence of the variable heavy chain represented by the sequence SEQ ID NO: 81 and which comprise the amino acid sequence of the variable light chain represented by the sequence SEQ ID NO: 82 (B01-7),

antibodies which comprise the amino acid sequence of the variable heavy chain represented by the sequence SEQ ID NO: 33 and which comprise the amino acid sequence of the variable light chain represented by the sequence SEQ ID NO: 29 (M31-B01),

antibodies which comprise the amino acid sequence of the variable heavy chain represented by the sequence SEQ ID NO: 34 and which comprise the amino acid sequence of the variable light chain represented by the sequence SEQ ID NO: 30 (M20-D02 S-A),

antibodies which comprise the amino acid sequence of the variable heavy chain represented by the sequence SEQ ID NO: 35 and which comprise the amino acid sequence of the variable light chain represented by the sequence SEQ ID NO: 31 (M60-G03),

antibodies which comprise the amino acid sequence of the variable heavy chain represented by the sequence SEQ ID NO: 36 and which comprise the amino acid sequence of the variable light chain represented by the sequence SEQ ID NO: 32 (M36-H02),

antibodies which comprise the amino acid sequence of the variable heavy chain represented by the sequence SEQ ID NO: 51 and which comprise the amino acid sequence of the variable light chain represented by the sequence SEQ ID NO: 52 (B01-3),

antibodies which comprise the amino acid sequence of the variable heavy chain represented by the sequence SEQ ID NO: 61 and which comprise the amino acid sequence of the variable light chain represented by the sequence SEQ ID NO: 62 (B01-5),

antibodies which comprise the amino acid sequence of the variable heavy chain represented by the sequence SEQ ID NO: 71 and which comprise the amino acid sequence of the variable light chain represented by the sequence SEQ ID NO: 72 (B01-7)

antibodies which comprise the amino acid sequence of the variable heavy chain represented by the sequence SEQ ID NO: 91 and which comprise the amino acid sequence of the variable light chain represented by the sequence SEQ ID NO: 92 (B01-12),

antibodies which comprise the amino acid sequence of the variable heavy chain represented by the sequence SEQ ID NO: 101 and which comprise the amino acid sequence of the variable light chain represented by the sequence SEQ ID NO: 102 (D02-4),

antibodies which comprise the amino acid sequence of the variable heavy chain represented by the sequence SEQ ID NO: 111 and which comprise the amino acid sequence of the variable light chain represented by the sequence SEQ ID NO: 112 (D02-6),

antibodies which comprise the amino acid sequence of the variable heavy chain represented by the sequence SEQ ID NO: 121 and which comprise the amino acid sequence of the variable light chain represented by the sequence SEQ ID NO: 122 (D02-7),

antibodies which comprise the amino acid sequence of the variable heavy chain represented by the sequence SEQ ID NO: 131 and which comprise the amino acid sequence of the variable light chain represented by the sequence SEQ ID NO: 132 (D02-11),

and antibodies which comprise the amino acid sequence of the variable heavy chain represented by the sequence SEQ ID NO: 141 and which comprise the amino acid sequence of the variable light chain represented by the sequence SEQ ID NO: 142 (D02-13).

[2884] In another embodiment the anti-C4.4a antibodies comprise the light chain and the heavy chain of an antibody given in Table 2.

[2885] In one preferred embodiment the anti-C4.4a antibodies comprise the light chain and the heavy chain of an antibody given in Table 2.

[2886] In one particularly preferred embodiment the C4.4a antibody is selected from the group consisting of

antibody which comprises the amino acid sequence of the light chain represented by SEQ ID NO: 346 and which comprises the amino acid sequence of the heavy chain represented by SEQ ID NO: 347 (M31-B01),

antibody which comprises the amino acid sequence of the light chain represented by SEQ ID NO: 352 and which comprises the amino acid sequence of the heavy chain represented by SEQ ID NO: 353 (B01-3),

antibody which comprises the amino acid sequence of the light chain represented by SEQ ID NO: 364 and which comprises the amino acid sequence of the heavy chain represented by SEQ ID NO: 365 (B01-10), and

antibody which comprises the amino acid sequence of the light chain represented by SEQ ID NO: 382 and which comprises the amino acid sequence of the heavy chain represented by SEQ ID NO: 383 (D02-6).

TABLE 1

Sequences of the C4.4a antibodies

Antibody	SEQ ID NO: HCDR1	SEQ ID NO: HCDR2	SEQ ID NO: HCDR3	SEQ ID NO: LCDR1	SEQ ID NO: LCDR2	SEQ ID NO: LCDR3
M31-B01	5	9	13	17	21	25
M20-D02 S-A	6	10	14	18	22	26
M60-G03	7	11	15	19	23	27
M36-H02	8	12	16	20	24	28
B01-3	45	46	47	48	49	50
B01-5	55	56	57	58	59	60
B01-7	65	66	67	68	69	70
B01-10	75	76	77	78	79	80
B01-12	85	86	87	88	89	90
D02-4	95	96	97	98	99	100
D02-6	105	106	107	108	109	110
D02-7	115	116	117	118	119	120
D02-11	125	126	127	128	129	130
D02-13	135	136	137	138	139	140
B01-nn1	145	146	147	148	149	150
B01-nn2	153	154	155	156	157	158
B01-nn3	161	162	163	164	165	166
B01-nn4	169	170	171	172	173	174
B01-nn5	177	178	179	180	181	182
B01-2	185	186	187	188	189	190
B01-4	193	194	195	196	197	198
B01-6	201	202	203	204	205	206
B01-8	209	210	211	212	213	214
B01-9	217	218	219	220	221	222
B01-11	225	226	227	228	229	230
B01-12	233	234	235	236	237	238

TABLE 1-continued

Sequences of the C4.4a antibodies

D02-ogl	241	242	243	244	245	246
D02-5	249	250	251	252	253	254
D02-8	257	258	259	260	261	262
D02-9	265	266	267	268	269	270
D02-10	273	274	275	276	277	278
D02-11	281	282	283	284	285	286
D02-12	289	290	291	292	293	294

Antibody	SEQ ID NO: VH Protein	SEQ ID NO: VL Protein	SEQ ID NO: VH Nucleotide	SEQ ID NO: VL Nucleotide
M31-B01	33	29	41	37
M20-D02 S-A	34	30	42	38
M60-G03	35	31	43	39
M36-H02	36	32	44	40
B01-3	51	52	53	54
B01-5	61	62	63	64
B01-7	71	72	73	74
B01-10	81	82	83	84
B01-12	91	92	93	94
D02-4	101	102	103	104
D02-6	111	112	113	114
D02-7	121	122	123	124
D02-11	131	132	133	134
D02-13	141	142	143	144
B01-nn1	151	152	308	309
B01-nn2	159	160	310	311
B01-nn3	167	168	312	313
B01-nn4	175	176	314	315
B01-nn5	183	184	316	317
B01-2	191	192	318	319
B01-4	199	200	320	321
B01-6	207	208	322	323
B01-8	215	216	324	325
B01-9	223	224	326	327
B01-11	231	232	328	329
B01-12	239	240	330	331
D02-ogl	247	248	332	333
D02-5	255	256	334	335
D02-8	263	264	336	337
D02-9	271	272	338	339
D02-10	279	280	340	341
D02-11	287	288	342	343
D02-12	295	296	344	345

TABLE 2

Sequences of the light and heavy chain of the C4.4a antibodies

Antibody	Light chain SEQ ID NO:	Heavy chain SEQ ID NO:
M31-B01	346	347
B01-1	348	349
B01-2	350	351
B01-3	352	353
B01-4	354	355
B01-5	356	357
B01-6	358	359
B01-7	360	361
B01-8	362	363
B01-10	364	365
B01-11	366	367
B01-12	368	369
M20-D02 S-A	370	371
D02-1	372	373
D02-2	374	375
D02-3	376	377
D02-4	378	379
D02-5	380	381
D02-6	382	383

TABLE 2-continued

Sequences of the light and heavy chain of the C4.4a antibodies

Antibody	Light chain SEQ ID NO:	Heavy chain SEQ ID NO:
D02-7	384	385
D02-8	386	387
D02-9	388	389
D02-10	390	391
D02-11	392	393
D02-12	394	395
D02-13	396	397

Anti-C4.4a Antibody IgG:

[2887] A further aspect of the present invention is the provision of an anti-C4.4a IgG1 antibody which comprises the amino acid sequence of the light chain and of the heavy chain of an antibody given in Table 2.

[2888] One example of an antibody which binds the cancer target molecule Her2 is trastuzumab (Genentech). Trastuzumab is a humanized antibody which is used for the treatment among other things of breast cancer. One example of an antibody which binds the cancer target molecule CD20 is rituximab (Genentech). Rituximab (CAS number: 174722-31-7) is a chimeric antibody which is used for the treatment of Non-Hodgkin's Lymphoma. One example of an antibody which binds the cancer target molecule CD52 is alemtuzumab (Genzyme). Alemtuzumab (CAS number: 216503-57-0) is a humanized antibody which is used for the treatment of chronic lymphatic leukaemia.

Mesothelin Antibody

[2889] Binders particularly preferred in accordance with the invention are anti-mesothelin antibodies, more particularly human or humanized anti-mesothelin antibodies. The antibodies preferably have an affinity of at least 10^{-7} M (as Kd value; in other words preferably those with smaller Kd values than 10^{-7} M), preferably of at least 10^{-8} M, more preferably in the range from 10^{-9} M to 10^{-11} M. The Kd values may be determined, for example, by means of surface plasmon resonance spectroscopy.

[2890] The antibody-drug conjugates of the invention likewise exhibit affinities in these ranges. The affinity is preferably not substantially affected by the conjugation of the drugs (in general, the affinity is reduced by less than one order of magnitude, in other words, for example, at most from 10^{-8} M to 10^{-7} M).

[2891] The antibodies used in accordance with the invention are also notable preferably for a high selectivity. A high selectivity exists when the antibody of the invention exhibits an affinity for the target protein which is better by a factor of at least 2, preferably by a factor of 5 or more preferably by a factor of 10, than for an independent other antigen, e.g. human serum albumin (the affinity may be determined, for example, by means of surface plasmon resonance spectroscopy).

[2892] Furthermore, the antibodies of the invention that are used are preferably cross-reactive. In order to be able to facilitate and better interpret preclinical studies, for example toxicological or activity studies (e.g. in xenograft mice), it is advantageous if the antibody used in accordance with the invention not only binds the human target protein but also

binds the species target protein in the species used for the studies. In one embodiment the antibody used in accordance with the invention, in addition to the human target protein, is cross-reactive to the target protein of at least one further species. For toxicological and activity studies it is preferred to use species of the families of rodents, dogs and non-human primates. Preferred rodent species are mouse and rat. Preferred non-human primates are rhesus monkeys, chimpanzees and long-tailed macaques.

[2893] In one embodiment the antibody used in accordance with the invention, in addition to the human target protein, is cross-reactive to the target protein of at least one further species selected from the group of species consisting of mouse, rat and long-tailed macaque (*Macaca fascicularis*). Especially preferred are antibodies used in accordance with the invention which in addition to the human target protein are at least cross-reactive to the mouse target protein. Preference is given to cross-reactive antibodies whose affinity for the target protein of the further non-human species differs by a factor of not more than 50, more particularly by a factor of not more than ten, from the affinity for the human target protein.

[2894] The antibodies of the invention that are used are additionally notable preferably for invariant binding to mesothelin. Invariant binding is notable, for example, by the fact that the antibody of the invention that is used binds to an epitope of mesothelin which cannot be masked by a further extracellular protein. Such a further extracellular protein is, for example, the protein Ovarian Cancer Antigen 125 (CA125). Antibodies used with preference are notable for the fact that their binding to mesothelin is not blocked by CA125.

[2895] Anti-mesothelin antibodies are described for example in WO 2009/068204. These antibodies can be used in accordance with the invention.

[2896] A further aspect of the present invention is the provision of a new anti-mesothelin antibody (MF-Ta) whose amino acid sequence comprises the CDR sequences of the variable heavy chain represented by the sequences SEQ ID NO:398 (HCDR1), SEQ ID NO:399 (HCDR2) and SEQ ID NO:400 (HCDR3) and the CDR sequences of the variable light chain represented by the sequences SEQ ID NO:401 (LCDR1), SEQ ID NO:402 (LCDR2) and SEQ ID NO:403 (LCDR3).

[2897] In one preferred embodiment the amino acid sequence of the anti-mesothelin antibody MF-Ta or antigen-binding antibody fragments comprises the sequence of the variable heavy chain represented by the sequences SEQ ID NO:404 and the sequence of the variable light chain represented by the sequence SEQ ID NO:405. In one preferred embodiment the amino acid sequence of the anti-mesothelin antibody MF-Ta or antigen-binding antibody fragments comprises the sequence of the variable heavy chain which is encoded by the nucleic acid sequence SEQ ID NO:406, and the sequence of the variable light chain which is encoded by the nucleic acid sequence SEQ ID NO:407.

[2898] In one particularly preferred embodiment the amino acid sequence of the anti-mesothelin antibody MF-Ta comprises the sequence of the heavy chain represented by the sequences SEQ ID NO:408 and the sequence of the light chain represented by the sequence SEQ ID NO:409.

[2899] In one particularly preferred embodiment the amino acid sequence of the anti-mesothelin antibody MF-Ta comprises the sequence of the heavy chain which is encoded with a nucleic acid sequence SEQ ID NO:410, and the sequence of the light chain with is encoded with a nucleic acid sequence SEQ ID NO: 411.

[2900] Further examples of antibodies which bind the cancer target molecule mesothelin are known to the skilled person and are described for example in WO 2009/068204 and can be used for the binder-drug conjugates of the invention.

[2901] In one embodiment of the binder-drug conjugates, the binder is an anti-mesothelin antibody or antigen-binding antibody fragment, where the antibody binds to mesothelin and exhibits invariant binding.

[2902] In one embodiment of the binder-drug conjugates, an anti-mesothelin antibody or antigen-binding antibody fragment comprises the amino acid sequences of the three CDR regions of the light chain and the amino acid sequences of the three CDR regions of the heavy chain of an antibody described in WOv2009/068204-A1 (Table 7; page 61-63).

[2903] In one preferred embodiment the mesothelin antibodies or antigen-binding antibody fragments are selected from the group consisting of

anti-mesothelin antibodies or antigen-binding antibody fragments thereof which comprise the sequences of the three CDR regions of the light chain and the sequences of the three CDR regions of the heavy chain of the antibody MF-Ta,

anti-mesothelin antibodies or antigen-binding antibody fragments thereof which comprise the sequences of the three CDR regions of the light chain and the sequences of the three CDR regions of the heavy chain of the antibody MF-J (WO2009068204-A1; Table 7; page 61),

anti-mesothelin antibodies or antigen-binding antibody fragments thereof which comprise the sequences of the three CDR regions of the light chain and the sequences of the three CDR regions of the heavy chain of the antibody MOR06640 (WO 2009/068204-A1; Table 7; page 61),

anti-mesothelin antibodies or antigen-binding antibody fragments thereof which comprise the sequences of the three CDR regions of the light chain and the sequences of the three CDR regions of the heavy chain of the antibody MF-226 (WO 2009/068204-A1; Table 7; page 61) and

anti-mesothelin antibodies or antigen-binding antibody fragments thereof which comprise the sequences of the three CDR regions of the light chain and the sequences of the three CDR regions of the heavy chain of the antibody MOR06626 (WO 2009/068204-A1; Table 7; page 61).

[2904] In one particularly preferred embodiment the mesothelin antibodies or antigen-binding antibody fragments are selected from the group consisting of

anti-mesothelin antibodies or antigen-binding antibody fragments thereof which comprise the sequence of the variable light chain and the sequence of the variable heavy chain of the antibody MF-Ta,

anti-mesothelin antibodies or antigen-binding antibody fragments thereof which comprise the sequence of the variable light chain and the sequence of the variable heavy chain of the antibody MF-J (WO 2009/068204-A1; Table 7; page 61),

anti-mesothelin antibodies or antigen-binding antibody fragments thereof which comprise the sequence of the variable light chain and the sequence of the variable heavy chain of the antibody MOR06640 (WO 2009/068204-A1; Table 7; page 61),

anti-mesothelin antibodies or antigen-binding antibody fragments thereof which comprise the sequence of the variable light chain and the sequence of the variable heavy chain of the antibody MF-226 (WO 2009/068204-A1; Table 7; page 61),

anti-mesothelin antibodies or antigen-binding antibody fragments thereof which comprise the sequence of the variable light chain and the sequence of the variable heavy chain of the antibody MOR06626 (WO 2009/068204-A1; Table 7; page 61).

Further Antibodies:

[2905] An example of an antibody which binds the cancer target molecule Her2 is trastuzumab (Genentech). Trastuzumab is a humanized antibody which is used for the treatment inter alia of breast cancer. One example of an antibody which binds the cancer target molecule CD20 is rituximab (Genentech). Rituximab (CAS number: 174722-31-7) is a chimeric antibody which is used for the treatment of non-Hodgkin's lymphoma. One example of an antibody which binds the cancer target molecule CD52 is alemtuzumab (Genzyme). Alemtuzumab (CAS number: 216503-57-0) is a humanized antibody which is used for the treatment of chronic lymphatic leukaemia.

[2906] Other examples of antibodies which bind to HER2, besides trastuzumab (INN 7637, CAS No: RN: 180288-69-1) and pertuzumab (Cas No: 380610-27-5), are antibodies as disclosed in WO 2009/123894-A2, WO 200/8140603-A2, or in WO 2011/044368-A2. An example of an anti-HER2 conjugate is trastuzumab-emtansine (INN No. 9295).

[2907] Examples of antibodies which bind the cancer target molecule CD30 and can be used for the treatment of cancer, e.g. Hodgkin's lymphoma, are brentuximab, iratumumab and antibodies as disclosed in WO 2008/092117, WO 2008/036688 or WO 2006/089232. An example of an anti-CD30 conjugate is brentuximab vedotine (INN No. 9144).

[2908] Examples of antibodies which bind the cancer target molecule CD22 and can be used for the treatment of cancer, e.g. lymphoma, are inotuzumab or epratuzumab. Examples of anti-CD22 conjugates are inotuzumab ozagamycin (INN No. 8574), or anti-CD22-MMAE and anti-CD22-MC-MMAE (CAS RN: 139504-50-0 and 474645-27-7).

[2909] Examples of antibodies which bind the cancer target molecule CD33 and can be used for the treatment of cancer, e.g. leukaemia, are gemtuzumab or lintuzumab (INN 7580). An example of an anti-CD33 conjugate is gemtuzumab-ozagamycin.

[2910] An example of an antibody which binds the cancer target molecule NMB and can be used for the treatment of cancer, e.g. melanoma or breast cancer, is glembatumumab (INN 9199). An example of an anti-NMB conjugate is glembatumumab vedotine (CAS RN: 474645-27-7).

[2911] An example of an antibody which binds the cancer target molecule CD56 and can be used for the treatment of cancer, e.g. multiple myeloma, small-cell carcinoma of the lung, MCC or ovarian carcinoma, is lorvotuzumab. An example of an anti-CD56 conjugate is lorvotuzumab mertansine (CAS RN: 139504-50-0).

[2912] Examples of antibodies which bind the cancer target molecule CD70 and can be used for the treatment of cancer, e.g. non-Hodgkin's lymphoma or kidney cell cancer, are disclosed in WO 2007/038637-A2 or WO 2008/070593-A2. An example of an anti-CD70 conjugate is SGN-75 (CD70 MMAF).

[2913] An example of an antibody which binds the cancer target molecule CD74 and can be used for the treatment of cancer, e.g. multiple myeloma, is milatuzumab. An example of an anti-CD74 conjugate is milatuzumab-doxorubicin (CAS RN: 23214-92-8).

[2914] An example of an antibody which binds the cancer target molecule CD 19 and can be used for the treatment of cancer, e.g. non-Hodgkin's lymphoma, is disclosed in WO 2008/031056-A2. Further antibodies and examples of an anti-CD19 conjugate (SAR3419) are disclosed in WO 2008/047242-A2.

[2915] Examples of antibodies which bind the cancer target molecule mucin-1 and can be used for the treatment of cancer, e.g. non-Hodgkin's lymphoma, are clivatuzumab or the antibodies disclosed in WO 2003/106495-A2, WO 2008/028686-A2. Examples of anti-mucin conjugates are disclosed in WO 2005/009369-A2.

[2916] Examples of antibodies which bind the cancer target molecule CD138 and conjugates thereof which can be used for the treatment of cancer, e.g. multiple myeloma, are disclosed in WO 2009/080829-A1, WO 2009/080830-A1.

[2917] Examples of antibodies which bind the cancer target molecule integrin alphaV and can be used for the treatment of cancer, e.g. melanoma, sarcoma or carcinoma, are intetumumab (Cas RN: 725735-28-4), abciximab (Cas-RN: 143653-53-6), etaracizumab (Cas-RN: 892553-42-3) or the antibodies disclosed in U.S. Pat. No. 7,465,449, EP 19859-A1, WO 2002/012501-A1 or WO 2006/062779-A2. Examples of anti-integrin alphaV conjugates are intetumumab-DM4 and other ADCs disclosed in WO 2007/024536-A2.

[2918] Examples of antibodies which bind the cancer target molecule TDGF1 and can be used for the treatment of cancer are the antibodies disclosed in WO 02/077033-A1, U.S. Pat. No. 7,318,924, WO 2003/083041-A2 and WO 2002/088170-A2. Examples of anti-TDGF1 conjugates are disclosed in WO 2002/088170-A2.

[2919] Examples of antibodies which bind the cancer target molecule PSMA and can be used for the treatment of cancer, e.g. prostate carcinoma, are the antibodies disclosed in WO 97/35616-A1, WO 99/47554-A1, and WO 01/009192-A1. Examples of anti-PSMA conjugates are disclosed in WO 2009/026274-A1.

[2920] Examples of antibodies which bind the cancer target molecule EPHA2, can be used for preparing a conjugate and can be used for the treatment of cancer are disclosed in WO 2004/091375-A2.

[2921] Examples of antibodies which bind the cancer target molecule SLC44A4, can be used for preparing a conjugate and can be used for the treatment of cancer, e.g. pancreatic or prostate carcinoma, are disclosed in WO 2009/033094-A2 and US 2009/0175796-A1.

[2922] An example of an antibody which binds the cancer target molecule HLA-DOB is the antibody lym-1 (Cas-RN: 301344-99-0), which can be used for the treatment of cancer, e.g. non-Hodgkin's lymphoma. Examples of anti-HLA-DOB conjugates are disclosed for example in WO 2005/081711-A2.

[2923] Examples of antibodies which bind the cancer target molecule VTCN1, can be used for preparing a conjugate and can be used for the treatment of cancer, e.g. ovarian carcinoma, pancreatic, lung or breast cancer, are disclosed in WO 2006/074418-A2.

[2924] The compounds of the invention possess valuable pharmacological properties and can be used for the prevention and treatment of diseases in humans and animals.

[2925] The binder-drug conjugates (ADCs) of the invention, of the formula (Ia), exhibit a high and specific cytotoxic activity with regard to tumour cells, as may be shown on the

basis of the assays set out in the present experimental section (C-1. to C-7e.). This high and specific cytotoxic activity on the part of the binder-drug conjugates (ADCs) of the invention, of the formula (Ia), is achieved through the appropriate combination of the new N,N-dialkylauristatin derivative and binder with linkers which exhibit not only an enzymatically, hydrolytically or reductively cleavable predetermined break point, for the release of the toxophores, but also no such predetermined break point. More particularly, through the use of stable linkers which have no enzymatically, hydrolytically or reductively cleavable predetermined break point for the release of the toxophores, and which, following uptake of the ADCs into the tumour cell and following complete intracellular, enzymatic breakdown of the antibody, still remain wholly or partly intact, the activity is confined very specifically to the tumour cell. Compatibility between ADCs and stable linkers presupposes, among other things, that the metabolites formed intracellularly can be formed with sufficient efficacy, are able to reach their target and are able there to develop their anti-proliferative activity on the target with sufficient potency, without being carried out of the tumour cell again beforehand by transporter proteins. The metabolites formed intracellularly after the compounds of the formula (Ia) of the invention have been taken up exhibit a reduced potential as a substrate with respect to transporter proteins, thereby suppressing their redistribution into the systemic circulation and hence the triggering of potential side effects by the toxophore itself. Furthermore, the innovative N-alkyl attachment maintains the basic character at the amino end of the monomethyl-auristatin peptide. Especially in the case of the binder-drug conjugates (ADCs) of the formula (Ia) of the invention that are linked via lysine side chains, the overall charge of the antibody remains constant, irrespective of the number of toxophore-linker loadings.

[2926] The compatibility of the ADCs with a stabile linker chemistry and with the target in question, in conjunction with metabolites which represent a substrate for transporter proteins to a relatively low degree, offers an enlarged therapeutic window.

[2927] More particularly, the binder-drug conjugates of the invention, of the formula (Ia), exhibit a high and specific cytotoxic activity with respect to tumour cells which express mesothelin. The activity with respect to tumour cells which do not express mesothelin is significantly weaker at the same time.

[2928] On the basis of this profile of properties, the compounds of the invention are therefore suitable to a particular degree for the treatment of hyperproliferative diseases in humans and in mammals generally. The compounds are able on the one hand to inhibit, block, reduce or lower cell proliferation and cell division, and on the other hand to increase apoptosis.

[2929] The hyperproliferative diseases for the treatment of which the compounds of the invention can be employed include in particular the group of cancer and tumour diseases. In the context of the present invention, these are understood as meaning, in particular, the following diseases, but without being limited to them: mammary carcinomas and mammary tumours (ductal and lobular forms, also in situ), tumours of the respiratory tract (parvicellular and non-parvicellular carcinoma, bronchial carcinoma), cerebral tumours (e.g. of the brain stem and of the hypothalamus, astrocytoma, medulloblastoma, ependymoma and neuro-ectodermal and pineal tumours), tumours of the digestive organs (oesophagus, stomach, gall bladder, small intestine, large intestine, rectum), liver tumours (including hepatocellular carcinoma, cholangiocellular carcinoma and mixed hepatocellular and cholangiocellular carcinoma), tumours of the head and neck region (larynx, hypopharynx, nasopharynx, oropharynx, lips and oral cavity), skin tumours (squamous epithelial carcinoma, Kaposi sarcoma, malignant melanoma, Merkel cell skin cancer and non-melanomatous skin cancer), tumours of soft tissue (including soft tissue sarcomas, osteosarcomas, malignant fibrous histiocytomas, lymphosarcomas and rhabdomyosarcomas), tumours of the eyes (including intraocular melanoma and retinoblastoma), tumours of the endocrine and exocrine glands (e.g. thyroid and parathyroid glands, pancreas and salivary gland), tumours of the urinary tract (tumours of the bladder, penis, kidney, renal pelvis and ureter) and tumours of the reproductive organs (carcinomas of the endometrium, cervix, ovary, vagina, vulva and uterus in women and carcinomas of the prostate and testicles in men). These also include proliferative blood diseases in solid form and as circulating blood cells, such as lymphomas, leukaemias and myeloproliferative diseases, e.g. acute myeloid, acute lymphoblastic, chronic lymphocytic, chronic myelogenic and hair cell leukaemia, and also AIDS-correlated lymphomas, Hodgkin's lymphomas, non-Hodgkin's lymphomas, cutaneous T-cell lymphomas, Burkitt's lymphomas and lymphomas in the central nervous system.

Preferred Hyperproliferative Diseases for Anti-CA9 Binder-Drug Conjugates

[2930] Hyperproliferative diseases for the treatment of which the compounds of the invention can be preferably employed are CA9-overexpressing tumours, mammary carcinomas and mammary tumours (e.g. ductal and lobular forms, also in situ); tumours of the respiratory tract (e.g. parvicellular and non-parvicellular carcinoma, bronchial carcinoma), including preferably non-parvicellular carcinoma of the lung; cerebral tumours (e.g. of the brain stem and of the hypothalamus, astrocytoma, medulloblastoma, ependymoma and/or neuro-ectodermal and pineal tumours); tumours of the digestive organs (oesophagus, stomach, gall bladder, small intestine, large intestine, rectum), including more preferably stomach tumours and intestinal tumours; liver tumours (including hepatocellular carcinoma, cholangiocellular carcinoma and mixed hepatocellular and cholangiocellular carcinoma); tumours of the head and neck region (e.g. larynx, hypopharynx, nasopharynx, oropharynx, lips, oral cavity, tongue and oesophagus); tumours of the urinary tract (tumours of the bladder, penis, kidney, renal pelvis and ureter), including more preferably tumours of the kidneys and of the bladder; and/or tumours of the reproductive organs (carcinomas of the endometrium, cervix, ovary, vagina, vulva and uterus in women and/or carcinomas of the prostate and testicles in men), including more preferably carcinomas of the cervix and uterus.

Preferred Hyperproliferative Diseases for Anti-EGFR Binder-Drug Conjugates

[2931] Hyperproliferative diseases for the treatment of which the compounds of the invention can be preferably employed are EGFR-overexpressing tumours, respiratory tract tumours (e.g. parvicellular and non-pavicellular carcinomas, bronchial carcinoma), including preferably non-parvicellular carcinoma of the lung; tumours of the digestive

organs (e.g. oesophagus, stomach, gall bladder, small intestine, large intestine, rectum), including especially intestinal tumours; tumours of the endocrine and exocrine glands (e.g. thyroid and parathyroid glands, pancreas and salivary gland), including preferably pancreas; tumours of the head and neck region (e.g. larynx, hypopharynx, nasopharynx, oropharynx, lips, oral cavity, tongue and oesophagus); and/or gliomas.

Preferred Hyperproliferative Diseases for Anti-Mesothelin Binder-Drug Conjugates

[2932] Hyperproliferative diseases for the treatment of which the compounds of the invention can be preferably employed are mesothelin-overexpressing tumours, tumours of the reproductive organs (carcinomas of the endometrium, cervix, ovary, vagina, vulva and uterus in women and/or carcinomas of the prostate and testicles in men), including preferably ovarian carcinomas; tumours of the endocrine and exocrine glands (e.g. thyroid and parathyroid glands, pancreas and salivary gland), including preferably pancreas; respiratory tract tumours (e.g. parvicellular and non-parvicellular carcinoma, bronchial carcinoma), including preferably non-parvicellular carcinoma of the lung; and/or mesotheliomas.

Preferred Hyperproliferative Diseases for Anti-C4.4a Binder-Drug Conjugates

[2933] Hyperproliferative diseases for the treatment of which the compounds of the invention can be preferably employed are C4.4a-overexpressing tumours, squamous epithelial carcinomas (e.g. of the cervix, vulva, vagina, of the anal duct, endometrium, fallopian tube, penis, scrotum, of the oesophagus, breast, of the bladder, of the bile duct, endometrium, uterus and ovary); mammary carcinomas and mammary tumours (e.g. ductal and lobular forms, also in situ); tumours of the respiratory tract (e.g. parvicellular and non-parvicellular carcinoma, bronchial carcinoma), including preferably non-parvicellular carcinoma of the lung, squamous epithelial carcinoma and adenocarcinoma of the lung; tumours of the head and neck region (e.g. larynx, hypopharynx, nasopharynx, oropharynx, lips, oral cavity, tongue and oesophagus, squamous epithelial carcinomas of the head and neck region); tumours of the urinary tract (tumours of the bladder, penis, kidney, renal pelvis and ureter, squamous epithelial carcinomas of the bladder), including more preferably tumours of the kidneys and of the bladder; skin tumours (squamous epithelial carcinoma, Kaposi sarcoma, malignant melanoma, Merkel cell skin cancer and non-melanomatous skin cancer), including more preferably melanomas; tumours of the endocrine and exocrine glands (e.g. thyroid and parathyroid glands, pancreas and salivary gland), including preferably pancreas; tumours of the digestive organs (e.g. oesophagus, stomach, gall bladder, small intestine, large intestine, rectum), including especially colorectal carcinomas; and/or tumours of the reproductive organs (carcinomas of the endometrium, cervix, ovary, vagina, vulva and uterus in women and/or carcinomas of the prostate and testicles in men), including more preferably uterine carcinomas.

[2934] These well-described diseases in humans can also occur with a comparable aetiology in other mammals and can be treated there with the compounds of the present invention.

[2935] In the context of the present invention, the term "treatment" or "treat" encompasses an inhibiting, delaying, stemming, alleviating, attenuating, restricting, reducing, suppressing, repressing or healing of an illness, a complaint, a disease, an injury or a disruption to health, the development, course or progress of such conditions and/or the symptoms of such conditions. The term "therapy" is understood here to be synonymous with the term "treatment".

[2936] The terms "prevention", "prophylaxis" or "preclusion" are used synonymously in the context of the present invention, and refer to the avoidance or reduction in the risk of acquiring, experiencing, suffering or having an illness, a complaint, a disease, an injury or a disruption to health, a development or progress of such conditions and/or the symptoms of such conditions.

[2937] The treatment or prevention of an illness, complaint, disease, injury or disruption to health may be partial or complete.

[2938] The present invention thus further provides the use of the compounds of the invention for the treatment and/or prevention of diseases, in particular the abovementioned diseases.

[2939] The present invention furthermore provides the use of the compounds of the invention for the preparation of a medicament for the treatment and/or prevention of diseases, in particular the abovementioned diseases.

[2940] The present invention furthermore provides the use of the compounds of the invention in a method for the treatment and/or prevention of diseases, in particular the abovementioned diseases.

[2941] The present invention furthermore provides a method for the treatment and/or prevention of diseases, in particular the abovementioned diseases, using an effective amount of at least one of the compounds of the invention.

[2942] The anti-mesothelin binder-drug conjugate of the invention is used preferably for treating cancer in a patient, where the cancer cells of the patient that are to be treated have mesothelin expression. Treatment is administered more preferably to patients whose mesothelin expression in cancer cells is higher than in healthy cells.

[2943] One method of identifying patients who respond advantageously to an anti-mesothelin binder-drug conjugate for the treatment of cancer involves determining the mesothelin expression in cancer cells of the patient. In one embodiment the mesothelin expression is determined by mesothelin gene expression analysis. The skilled person knows of methods for gene expression analysis such as, for example, RNA detection, quantitative or qualitative polymerase chain reaction or fluorescence in situ hybridization (FISH). In another preferred embodiment the mesothelin expression is determined by means of immunohistochemistry with an anti-mesothelin antibody. The immunohistochemistry is carried out preferably on formaldehyde-fixed tissue. The antibody for use in the immunohistochemistry is the same antibody which is also used in the conjugate. The antibody for use in the immunohistochemistry is a second antibody which—preferably specifically—recognizes the mesothelin target protein.

[2944] The compounds according to the invention can be employed by themselves or, if required, in combination with one or more other pharmacologically active substances, as long as this combination does not lead to undesirable and unacceptable side effects. The present invention furthermore therefore provides medicaments comprising at least one of the compounds of the invention and one or more further drugs, in particular for the treatment and/or prevention of the abovementioned diseases.

[2945] For example, the compounds of the present invention can be combined with known antihyperproliferative, cytostatic or cytotoxic substances for the treatment of cancer diseases. Suitable drugs in the combination which may be mentioned by way of example are as follows:

aldesleukin, alendronic acid, alfaferone, alitretinoin, allopurinol, aloprim, aloxi, altretamine, aminoglutethimide, amifostine, amrubicin, amsacrine, anastrozole, anzmet, aranesp, arglabin, arsenic trioxide, aromasin, 5-azacytidine, azathioprine, BCG or tice-BCG, bestatin, betamethasone acetate, betamethasone sodium phosphate, bexarotene, bleomycin sulphate, broxuridine, bortezomib, busulfan, calcitonin, campath, capecitabine, carboplatin, casodex, cefesone, celmoleukin, cerubidin, chlorambucil, cisplatin, cladribin, clodronic acid, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunoxome, decadron, decadron phosphate, delestrogen, denileukin diftitox, depomedrol, deslorelin, dexrazoxane, diethylstilbestrol, diflucan, docetaxel, doxifluridine, doxorubicin, dronabinol, DW-166HC, eligard, elitek, ellence, emend, epirubicin, epoetin-alfa, epogen, eptaplatin, ergamisol, estrace, estradiol, estramustine sodium phosphate, ethinylestradiol, ethyol, etidronic acid, etopophos, etoposide, fadrozole, farstone, filgrastim, finasteride, fligrastim, floxuridine, fluconazole, fludarabin, 5-fluorodeoxyuridine monophosphate, 5-fluorouracil (5-FU), fluoxymesterone, flutamide, formestane, fosteabine, fotemustine, fulvestrant, gammagard, gemcitabine, gemtuzumab, gleevec, gliadel, goserelin, granisetron hydrochloride, histrelin, hycamtin, hydrocortone, erythro-hydroxynonyladenine, hydroxyurea, ibritumomab tiuxetan, idarubicin, ifosfamide, interferon-alpha, interferon-alpha-2, interferon-alpha-2α, interferon-alpha-2β, interferon-alpha-n1, interferon-alpha-n3, interferon-beta, interferon-gamma-1α, interleukin-2, intron A, iressa, irinotecan, kytril, lentinan sulphate, letrozole, leucovorin, leuprolide, leuprolide acetate, levamisole, levofolic acid calcium salt, levothroid, levoxyl, lomustine, lonidamine, marinol, mechlorethamine, mecobalamin, medroxyprogesterone acetate, megestrol acetate, melphalan, menest, 6-mercaptopurine, mesna, methotrexate, metvix, miltefosine, minocycline, mitomycin C, mitotane, mitoxantrone, modrenal, myocet, nedaplatin, neulasta, neumega, neupogen, nilutamide, nolvadex, NSC-631570, OCT-43, octreotide, ondansetron hydrochloride, orapred, oxaliplatin, paclitaxel, pediapred, pegaspargase, pegasys, pentostatin, picibanil, pilocarpine hydrochloride, pirarubicin, plicamycin, porfimer sodium, prednimustine, prednisolone, prednisone, premarin, procarbazine, procrit, raltitrexed, rebif, rhenium-186 etidronate, rituximab, roferon-A, romurtide, salagen, sandostatin, sargramostim, semustine, sizofuran, sobuzoxane, solumedrol, streptozocin, strontium-89 chloride, Synthroid, tamoxifen, tamsulosin, tasonermin, tastolactone, taxoter, teceleukin, temozolomide, teniposide, testosterone propionate, testred, thioguanine, thiotepa, thyrotropin, tiludronic acid, topotecan, toremifen, tositumomab, tastuzumab, teosulfan, tretinoin, trexall, trimethylmelamine, trimetrexate, triptorelin acetate, triptorelin pamoate, UFT, uridine, valrubicin, vesnarinone, vinblastine, vincristine, vindesine, vinorelbine, virulizin, zinecard, zinostatin-stimalamer, zofran; ABI-007, acolbifen, actimmune, affinitak, aminopterin, arzoxifen, asoprisnil, atamestane, atrasentan, avastin, BAY 43-9006 (sorafenib), CCI-779, CDC-501, celebrex, cetuximab, crisnatol, cyproterone acetate, decitabine, DN-101, doxorubicin-MTC, dSLIM, dutasteride, edotecarin, eflornithine, exatecan, fenretinide, histamine dihydrochloride, histrelin hydrogel implant, holmium-166 DOTMP, ibandronic acid, interferon-gamma, intron-PEG, ixabepilone, keyhole limpet hemocyanine, L-651582, lanreotide, lasofoxifen, libra, lonafarnib, miproxifen, minodronate, MS-209, liposomal MTP-PE, MX-6, nafarelin, nemorubicin, neovastat, nolatrexed, oblimersen, onko-TCS, osidem, paclitaxel polyglutamate, pamidronate disodium, PN-401, QS-21, quazepam, R-1549, raloxifen, ranpirnas, 13-cis-retic acid, satraplatin, seocalcitol, T-138067, tarceva, taxoprexin, thymosin-alpha-1, tiazofurin, tipifarnib, tirapazamine, TLK-286, toremifen, transMID-107R, valspodar, vapreotide, vatalanib, verteporfin, vinflunin, Z-100, zoledronic acid and combinations of these.

[2946] In a preferred embodiment, the compounds of the present invention can be combined with antihyperproliferative agents, which can be, by way of example—without this list being conclusive as follows:

aminoglutethimide, L-asparaginase, azathioprine, 5-azacytidine, bleomycin, busulfan, carboplatin, carmustine, chlorambucil, cisplatin, colaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, diethylstilbestrol, 2',2'-difluorodeoxycytidine, docetaxel, doxorubicin (adriamycin), epirubicin, epothilone and its derivatives, erythrohydroxynonyladenin, ethinylestradiol, etoposide, fludarabin phosphate, 5-fluorodeoxyuridine, 5-fluorodeoxyuridine monophosphate, 5-fluorouracil, fluoxymesterone, flutamide, hexamethylmelamine, hydroxyurea, hydroxyprogesterone caproate, idarubicin, ifosfamide, interferon, irinotecan, leucovorin, lomustine, mechlorethamine, medroxyprogesterone acetate, megestrol acetate, melphalan, 6-mercaptopurine, mesna, methotrexate, mitomycin C, mitotane, mitoxantrone, paclitaxel, pentostatin, N-phosphonoacetyl L-aspartate (PALA), plicamycin, prednisolone, prednisone, procarbazine, raloxifen, semustine, streptozocin, tamoxifen, teniposide, testosterone propionate, thioguanine, thiotepa, topotecan, trimethylmelamine, uridine, vinblastine, vincristine, vindesine and vinorelbine.

[2947] The compounds of the invention can also be combined in a very promising manner with biological therapeutics such as antibodies (e.g. avastin, rituxan, erbitux, herceptin). The compounds of the invention can also achieve positive effects in combination with therapies directed against angiogenesis, such as, for example, with avastin, axitinib, recentin, regorafenib, sorafenib or sunitinib. Combinations with inhibitors of the proteasome and of mTOR and also with antihormones and steroidal metabolic enzyme inhibitors are likewise particularly suitable because of their favourable profile of side effects.

[2948] Generally, the following aims can be pursued with the combination of compounds of the present invention with other agents having a cytostatic or cytotoxic action:

[2949] an improved activity in slowing down the growth of a tumour, in reducing its size or even in its complete elimination compared with treatment with an individual drug;

[2950] the possibility of employing the chemotherapeutics used in a lower dosage than in monotherapy;

[2951] the possibility of a more tolerable therapy with few side effects compared with individual administration;

[2952] the possibility of treatment of a broader spectrum of tumour diseases;

[2953] the achievement of a higher rate of response to the therapy;

[2954] a longer survival time of the patient compared with present-day standard therapy.

[2955] The compounds according to the invention can moreover also be employed in combination with radiotherapy and/or surgical intervention.

[2956] The present invention furthermore provides medicaments which comprise at least one compound of the invention, conventionally together with one or more inert, non-toxic, pharmaceutically suitable excipients, and the use thereof for the abovementioned purposes.

[2957] The compounds of the invention can act systemically and/or locally. They can be administered in a suitable manner for this purpose, such as for example parenterally, possibly by means of inhalation, or as an implant or stent.

[2958] The compounds of the invention can be administered in suitable administration forms for these administration routes.

[2959] Parenteral administration can be effected with bypassing of an absorption step (e.g. intravenously, intraarterially, intracardially, intraspinally or intralumbally) or with inclusion of an absorption (e.g. intramuscularly, subcutaneously, intracutaneously, percutaneously or intraperitoneally). Administration forms which are suitable for parenteral administration include injection and infusion formulations in the form of solutions, suspensions, emulsions or lyophilizates. Parenteral administration is preferred, in particular intravenous administration.

[2960] In general, it has proved advantageous in the case of parenteral administration to administer amounts of from about 0.001 to 1 mg/kg, preferably about 0.01 to 0.5 mg/kg of body weight to achieve effective results.

[2961] Nevertheless it may be necessary to deviate from the amounts mentioned, and in particular depending on the body weight, administration route, individual behaviour towards the active compound, nature of the formulation and point of time or interval at which administration takes place. Thus in some cases it may be sufficient to manage with less than the abovementioned minimum amount, while in other cases the upper limit mentioned must be exceeded. In the case where relatively large amounts are administered, it may be advisable to distribute these into several individual doses over the day.

[2962] The following examples illustrate the invention. The invention is not limited to the examples.

[2963] The percentage figures in the following tests and examples are percentages by weight, unless stated otherwise; parts are parts by weight. Solvent ratios, dilution ratios and concentration data of liquid/liquid solutions in each case relate to the volume.

A. EXAMPLES

Abbreviations and Acronyms

[2964] A431NS human tumour cell line

[2965] A549 human tumour cell line

[2966] ABCB1 ATP-binding cassette sub-family B member 1 (synonym for P-gp and MDR1)

[2967] abs. absolute

[2968] ADC antibody-drug-conjugate

[2969] Ac acetyl

[2970] aq. aqueous, aqueous solution

[2971] ATP adenosine triphosphate

[2972] BCRP breast cancer resistance protein, an efflux transporter

[2973] Boc tert-butoxycarbonyl

[2974] br. broad (in NMR)

[2975] Ex. example

[2976] ca. circa, approximately

[2977] CAIX carboanhydrase IX

[2978] CI chemical ionization (in MS)

[2979] d doublet (in NMR)

[2980] d day(s)

[2981] TLC thin-layer chromatography

[2982] DCI direct chemical ionization (in MS)

[2983] dd doublet of a doublet (in NMR)

[2984] DMAP 4-N,N-dimethylaminopyridine

[2985] DME 1,2-dimethoxyethane

[2986] DMEM Dulbecco's modified eagle medium (standardized nutrient medium for cell culture)

[2987] DMF N,N-dimethylformamide

[2988] DMSO dimethyl sulphoxide

[2989] DPBS, D-PBS, Dulbecco's phosphate-buffered saline solution

[2990] PBS PBS=DPBS=D-PBS, pH 7.4, from Sigma, No. D8537

[2991] Composition:

[2992] 0.2 g KCl

[2993] 0.2 g KH_2PO_4 (anhydrous)

[2994] 8.0 g NaCl

[2995] 1.15 g Na_2HPO_4 (anhydrous)

[2996] make up to 1 l with H_2O

[2997] dt doublet of a triplet (in NMR)

[2998] DTT DL-dithiothreitol

[2999] EDC N'-(3-dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride

[3000] EGFR epidermal growth factor receptor

[3001] EI electron impact ionization (in MS)

[3002] ELISA enzyme-linked immunosorbent assay

[3003] eq. equivalent(s)

[3004] ESI electrospray ionization (in MS)

[3005] ESI-MicroTofq ESI-MicroTofq (name of the mass spectrometer, with Tof=time of flight and q=quadrupole)

[3006] FCS foetal calf serum

[3007] Fmoc (9H-fluoren-9-ylmethoxy)carbonyl

[3008] sat. saturated

[3009] GTP guanosine 5'-triphosphate

[3010] h hour(s)

[3011] HATU O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate

[3012] HCT-116 human tumour cell line

[3013] HEPES 4-(2-hydroxyethyl)piperazine-1-ethanesulphonic acid

[3014] HOAc acetic acid

[3015] HOBt 1-hydroxy-1H-benzotriazole hydrate

[3016] HOSu N-hydroxysuccinimide

[3017] HPLC high-pressure, high-performance liquid chromatography

[3018] HT29 human tumour cell line

[3019] IC_{50} half-maximum inhibitory concentration

[3020] i.m. intramuscular, administration into the muscle

[3021] i.v. intravenous, administration into the vein

[3022] conc. concentrated

[3023] LC-MS liquid chromatography-coupled mass spectrometry

[3024] LLC-PK1 cells Lewis lung carcinoma pork kidney cell line

[3025] L-MDR human MDR1 transfected LLC-PK1 cells

[3026] m multiplet (in NMR)

[3027] MDR1 multidrug resistance protein 1

[3028] min minute(s)
[3029] MS mass spectrometry
[3030] MTT 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide
[3031] NCI-H292 human tumour cell line
[3032] NCI-H520 human tumour cell line
[3033] NMM N-methylmorpholine
[3034] NMP N-methyl-2-pyrrolidinone
[3035] NMR nuclear magnetic resonance spectrometry
[3036] NMRI mouse strain, originating from Naval Medical Research Institute (NMRI)
[3037] Nude mice experimental animals
[3038] NSCLC non-small cell lung cancer (non-parvicellular bronchial carcinoma)
[3039] PBS phosphate-buffered saline solution
[3040] Pd/C palladium on activated carbon
[3041] P-gp P-glycoprotein, a transporter protein
[3042] PNGaseF enzyme for sugar elimination
[3043] quant. quantitative (for yield)
[3044] quart quartet (in NMR)
[3045] quint quintet (in NMR)
[3046] R_f retention index (for TLC)
[3047] RT room temperature
[3048] R_t retention time (for HPLC)
[3049] s singlet (in NMR)
[3050] s.c. subcutaneous, administration beneath the skin
[3051] SCC-4 human tumour cell line
[3052] SCC-9 human tumour cell line
[3053] SCID mice experimental mice with a severe combined immunodeficiency
[3054] t triplet (in NMR)
[3055] tert tertiary
[3056] TFA trifluoroacetic acid
[3057] THF tetrahydrofuran
[3058] UV ultraviolet spectrometry
[3059] v/v volume to volume ratio (of a solution)
[3060] Z benzyloxycarbonyl

HPLC and LC-MS Methods:

Method 1 (LC-MS):

[3061] Instrument: Waters Acquity SQD UPLC System; column: Waters Acquity UPLC HSS T3 1.8µ 50 mm×1 mm; eluent A: 1 l water+0.25 ml 99% strength formic acid, eluent B: 1 l acetonitrile+0.25 ml 99% strength formic acid; gradient: 0.0 min 90% A→1.2 min 5% A→2.0 min 5% A; flow rate: 0.40 ml/min; oven: 50° C.; UV detection: 210-400 nm.

Method 2 (LC-MS):

[3062] Instrument: Micromass QuattroPremier with Waters UPLC Acquity; column: Thermo Hypersil GOLD 1.9µ 50 mm×1 mm; eluent A: 1 l water+0.5 ml 50% strength formic acid, eluent B: 1 l acetonitrile+0.5 ml 50% strength formic acid; gradient: 0.0 min 90% A→0.1 min 90% A→1.5 min 10% A→2.2 min 10% A; flow rate: 0.33 ml/min; oven: 50° C.; UV detection: 210 nm.

Method 3 (LC-MS):

[3063] Instrument: Micromass Quattro Micro MS with HPLC Agilent Series 1100; column: Thermo Hypersil GOLD 3µ 20 mm×4 mm; eluent A: 1 l water+0.5 ml 50% strength formic acid, eluent B: 1 l acetonitrile+0.5 ml 50% strength formic acid; gradient: 0.0 min 100% A→3.0 min 10% A→4.0 min 10% A→4.01 min 100% A (flow rate 2.5 ml/min)->5.00 min 100% A; oven: 50° C.; flow rate: 2 ml/min; UV detection: 210 nm.

Method 4 (LC-MS):

[3064] MS instrument: Micromass ZQ; HPLC instrument: HP 1100 Series; UV DAD; column: Phenomenex Gemini 3µ 30 mm×3.00 mm; eluent A: 1 l water+0.5 ml 50% strength formic acid, eluent B: 1 l acetonitrile+0.5 ml 50% strength formic acid; gradient: 0.0 min 90% A→2.5 min 30% A→3.0 min 5% A→4.5 min 5% A; flow rate: 0.0 min 1 ml/min→2.5 min/3.0 min/4.5 min 2 ml/min; oven: 50° C.; UV detection: 210 nm.

Method 5 (HPLC):

[3065] Instrument: HP 1090 Series II; column: Merck Chromolith SpeedROD RP-18e, 50 mm×4.6 mm; preliminary column: Merck Chromolith Guard Cartridge Kit RP-18e, 5 mm×4.6 mm; injection volume: 5 µl; eluent A: 70% $HClO_4$ in water (4 ml/litre), eluent B: acetonitrile; gradient: 0.00 min 20% B→0.50 min 20% B→3.00 min 90% B→3.50 min 90% B→3.51 min 20% B→4.00 min 20% B; flow rate: 5 ml/min; column temperature: 40° C.

Method 6 (HPLC):

[3066] Instrument: Waters 2695 with DAD 996; column: Merck Chromolith SpeedROD RP-18e, 50 mm×4.6 mm; ord. No.: 1.51450.0001, preliminary column: Merck Chromolith Guard Cartridge Kit RP-18e, 5 mm×4.6 mm; ord. No.: 1.51470.0001, eluent A: 70% $HClO_4$ in water (4 ml/litre), eluent B: acetonitrile; gradient: 0.00 min 5% B→0.50 min 5% B→3.00 min 95% B→4.00 min 95% B; flow rate: 5 ml/min.

Method 7 (LC-MS):

[3067] MS instrument: Waters ZQ; HPLC instrument: Agilent 1100 Series; UV DAD; column: Thermo Hypersil GOLD 3µ 20 mm×4 mm; eluent A: 1 l water+0.5 ml 50% strength formic acid, eluent B: 1 l acetonitrile+0.5 ml 50% strength formic acid; gradient: 0.0 min 100% A→3.0 min 10% A→4.0 min 10% A→4.1 min 100% A (flow rate 2.5 ml/min); oven: 55° C.; flow rate: 2 ml/min; UV detection: 210 nm.

Method 8 (LC-MS):

[3068] MS instrument: Waters ZQ; HPLC instrument: Agilent 1100 Series; UV DAD; column: Thermo Hypersil GOLD 3µ 20 mm×4 mm; eluent A: 1 l water+0.5 ml 50% strength formic acid, eluent B: 1 l acetonitrile+0.5 ml 50% strength formic acid; gradient: 0.0 min 100% A→2.0 min 60% A→2.3 min 40% A→3.0 min 20% A→4.0 min 10% A→4.2 min 100% A (flow rate 2.5 ml/min); oven: 55° C.; flow rate: 2 ml/min; UV detection: 210 nm.

Method 9 (LC-MS):

[3069] Instrument: Waters Acquity SQD UPLC System; column: Waters Acquity UPLC HSS T3 1.8µ 50 mm×1 mm; eluent A: 1 l water+0.25 ml 99% strength formic acid, eluent B: 1 l acetonitrile+0.25 ml 99% strength formic acid; gradient: 0.0 min 95% A→6.0 min 5% A→7.5 min 5% A; oven: 50° C.; flow rate: 0.35 ml/min; UV detection: 210-400 nm.

Method 10 (HPLC):

[3070] Instrument: Agilent 1200 Series; column: Agilent Eclipse XDB-C18 5μ 4.6 mm×150 mm; preliminary column: Phenomenex KrudKatcher Disposable Pre-Column; injection volume: 5 μl; eluent A: 1 l water+0.01% trifluoroacetic acid; eluent B: 1 l acetonitrile+0.01% trifluoroacetic acid; gradient: 0.00 min 10% B→1.00 min 10% B→1.50 min 90% B→5.5 min 10% B; flow rate: 2 ml/min; column temperature: 30° C.

[3071] For all reactants or reagents whose preparation is not explicitly described below, they were obtained commercially from generally available sources. For all other reactants or reacents whose preparation is likewise not described below, and which were not available commercially or were obtained from sources which are not generally available, a reference is given to the published literature in which their preparation is described.

Method 11 (LC-MS):

[3072] Instrument: Waters ACQUITY SQD UPLC System; column: Waters Acquity UPLC HSS T3 1.8μ 130×2 mm; eluent A: 1 l water+0.25 ml 99% strength formic acid, eluent B: 1 l acetonitrile+0.25 ml 99% strength formic acid; gradient: 0.0 min 90% A→1.2 min 5% A→2.0 min 5% A oven: 50° C.; flow rate: 0.60 ml/min; UV detection: 208-400 nm.

Method 12 (HPLC):

[3073] Instrument: Agilent 1200 Series with column oven and DAD; column: Merck Chromolith SpeedROD RP-18e, 50 mm×4.6 mm; ord. No.: 1.51450.0001; preliminary column: Merck Chromolith Guard Cartridge Kit RP-18e, 5 mm×4.6 mm; ord. No.: 1.51470.0001; eluent A: 70% $HClO_4$ in water (4 ml/litre), eluent B: acetonitrile; gradient: 0.00 min 5% B→0.50 min 5% B→3.00 min 95% B→4.00 min 95% B; flow rate: 5 ml/min; column temperature: 30° C.

Method 13 (LC-MS):

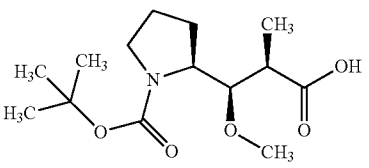
[3074] MS instrument: Waters (Micromass) Quattro Micro; Instrument HPLC: Agilent 1100 Series; column: YMC-Triart C18 3μ 50×3 mm; eluent A: 1 l water+0.01 mol ammonium carbonate, eluent B: 1 l acetonitrile; gradient: 0.0 min 100% A→2.75 min 5% A→4.5 min 5% A; oven: 40° C.; flow rate: 1.25 ml/min; UV detection: 210 nm.

Starting Compounds and Intermediates

Starting Compound 1

(2R,3R)-3-[(2S)-1-(tert-butoxycarbonyl)pyrrolidin-2-yl]-3-methoxy-2-methylpropanoic acid (Boc-dolaproine)

[3075]

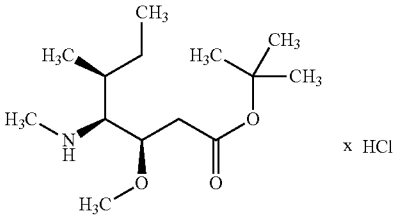


[3076] The title compound can be prepared in various ways according to literature methods; see, for example, Pettit et al., *Synthesis* 1996, 719; Shioiri et al., *Tetrahedron Lett.* 1991, 32, 931; Shioiri et al., *Tetrahedron* 1993, 49, 1913; Koga et al., *Tetrahedron Lett.* 1991, 32, 2395; Vidal et al., *Tetrahedron* 2004, 60, 9715; Poncet et al., *Tetrahedron* 1994, 50, 5345. It was prepared either as the free acid or as a 1:1 salt with dicyclohexylamine.

Starting Compound 2a

tert-butyl (3R,4S,5S)-3-methoxy-5-methyl-4-(methylamino)heptanoate hydrochloride (dolaisoleucine-OtBu×HCl)

[3077]

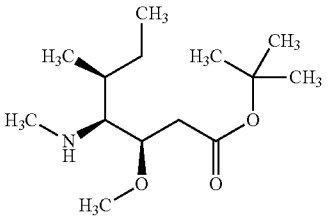


[3078] The title compound can be prepared in various ways according to literature methods; see, for example, Pettit et al., *J. org. Chem.* 1994, 59, 1796; Koga et al., *Tetrahedron Lett.* 1991, 32, 2395; Shioiri et al., *Tetrahedron Lett.* 1991, 32, 931; Shioiri et al., *Tetrahedron* 1993, 49, 1913.

Starting Compound 2b

tert-butyl (3R,4S,5S)-3-methoxy-5-methyl-4-(methylamino)heptanoate (dolaisoleucine-O^{t}Bu)

[3079]

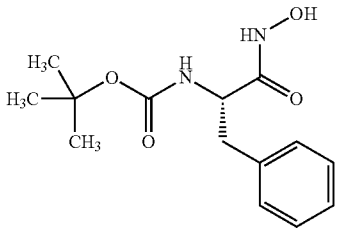


[3080] The compound was prepared in analogy to starting compound 2a, except that the hydrogenation was performed without addition of 1N hydrochloric acid.

Starting Compound 3

Nα-(tert-butoxycarbonyl)-N-hydroxy-L-phenylalaninamide

[3081]



[3082] The title compound was prepared by the literature method (A. Ritter et al., *J. org. Chem.* 1994, 59, 4602).

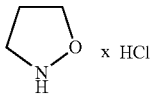
[3083] Yield: 750 mg (75% of theory)

[3084] LC-MS (Method 3): R_t=1.67 min; MS (ESIpos): m/z=281 $(M+H)^+$.

Starting Compound 4

1,2-oxazolidine hydrochloride

[3085]

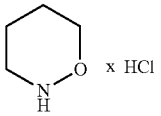


[3086] The title compound can be prepared by literature methods (see, for example, H. King, *J. Chem. Soc.* 1942, 432); it is also commercially available.

Starting Compound 5

1,2-oxazinane hydrochloride

[3087]

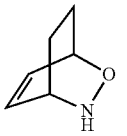


[3088] The title compound can be prepared by literature methods (see, for example, H. King, *J. Chem. Soc.* 1942, 432).

Starting Compound 6

2-oxa-3-azabicyclo[2.2.2]oct-5-ene

[3089]



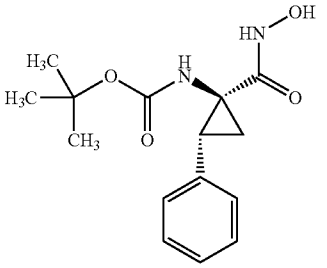
[3090] The title compound can be prepared in Boc-protected form by the literature method (see, for example, C. Johnson et al., *Tetrahedron Lett.* 1998, 39, 2059); the deprotection was effected in a customary manner by treatment with trifluoroacetic acid and subsequent neutralization.

[3091] Yield: 149 mg (89% of theory)

Starting Compound 7

tert-butyl (1S,2R)-1-(hydroxycarbamoyl)-2-phenylcyclopropylcarbamate

[3092]



[3093] The title compound was prepared by a literature method (A. Ritter et al., *J. org. Chem.* 1994, 59, 4602) proceeding from commercially available (1S,2R)-1-[(tert-butoxycarbonyl)amino]-2-phenylcyclopropanecarboxylic acid (C. Cativiela et al., *Chirality* 1999, 11, 583).

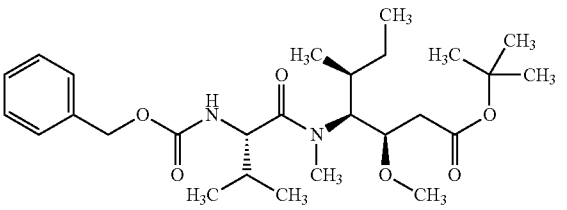
[3094] Yield: 339 mg (59% of theory)

[3095] LC-MS (Method 1): R_t=0.82 min; MS (ESIpos): m/z=293 $(M+H)^+$.

Intermediate 1

tert-butyl (3R,4S,5S)-4-[{N-[(benzyloxy)carbonyl]-valyl}(methyl)amino]-3-methoxy-5-methylheptanoate

[3096]



[3097] 10.65 g (41.058 mmol) of tert-butyl (3R,4S,5S)-3-methoxy-5-methyl-4-(methylamino)heptanoate (starting compound 2b) were taken up in 250 ml of dichloromethane and the solution was cooled to −10° C. Then, while stirring, 10.317 g (41.058 mmol) of N-[(benzyloxy)carbonyl]-L-valine, 16.866 g (61.586 mmol) of 2-bromo-1-ethylpyridinium tetrafluoroborate (BEP) and 28.6 ml of N,N-diisopropylethylamine were added, and the mixture was subsequently stirred at RT for 20 h. The reaction mixture was then diluted with dichloromethane and shaken twice with saturated sodium chloride solution, dried over sodium sulphate, filtered and concentrated. The residue was purified by flash chromatography on silica gel with 4:1 petroleum ether/ethyl acetate as the eluent. The corresponding fractions were concentrated and the residue was dried under high vacuum overnight. 10.22 g (51% of theory) of the title compound were obtained as a yellowish oil.

[3098] HPLC (Method 5): R_t=2.3 min;

[3099] LC-MS (Method 2): R_t=1.59 min; MS (ESIpos): m/z=493 $(M+H)^+$.

[3101] 500 mg (1 mmol) of tert-butyl (3R,4S,5S)-4-[{N-[(benzyloxy)carbonyl]-L-valyl}(methyl)amino]-3-methoxy-5-methylheptanoate (intermediate 1) were dissolved in 50 ml of methanol and, after addition of 100 mg of 10% palladium on activated carbon, hydrogenated under standard hydrogen pressure at RT for 1 h. The catalyst was then filtered off and the solvent was removed under reduced pressure. This gave 370 mg (quant.) of the title compound as a virtually colourless oil.

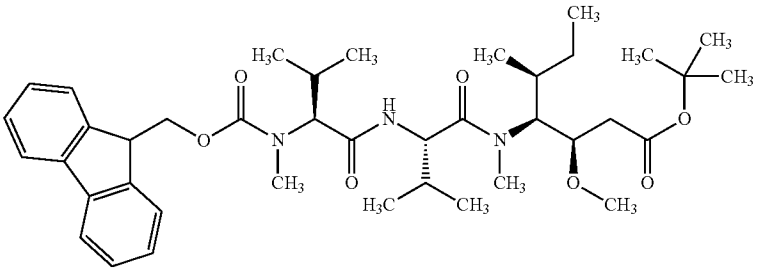
[3102] HPLC (Method 5): R_t=1.59 min;

[3103] LC-MS (Method 1): R_t=0.74 min; MS (ESIpos): m/z=359 $(M+H)^+$.

Intermediate 3

N-[(9H-fluoren-9-ylmethoxy)carbonyl]-N-methyl-L-valyl-N-[(3R,4S,5S)-1-tert-butoxy-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

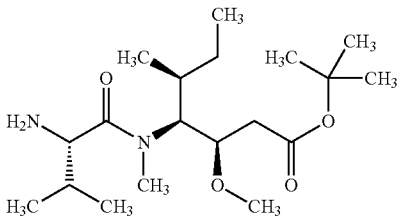
[3104]



Intermediate 2

tert-butyl (3R,4S,5S)-3-methoxy-5-methyl-4-[methyl(L-valyl)amino]heptanoate

[3100]



[3105] 4.64 g (13.13 mmol) of N-[(9H-fluoren-9-ylmethoxy)carbonyl]-N-methyl-L-valine were dissolved in 20 ml of DMF and admixed successively with 4.28 g (11.94 mmol) of tert-butyl (3R,4S,5S)-3-methoxy-5-methyl-4-[methyl(L-valyl)amino]heptanoate (Intermediate 2), 2.75 g (14.33 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 2.2 g (14.33 mmol) of 1-hydroxy-1H-benzotriazole hydrate. The mixture was stirred at RT overnight. The reaction mixture was then poured into a mixture of semisaturated aqueous ammonium chloride solution and ethyl acetate. The organic phase was removed, washed successively with saturated sodium hydrogencarbonate solution and saturated sodium chloride solution, dried over magnesium sulphate, filtered and concentrated. The residue was used directly in the next stage, without further purification.

[3106] Yield: 9.1 g (quant., 60% purity)

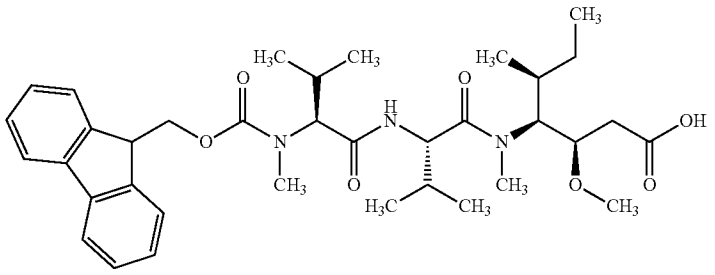
[3107] HPLC (Method 5): R_t=2.7 min;

[3108] LC-MS (Method 2): R_t=1.99 min; MS (ESIpos): m/z=694 $(M+H)^+$.

Intermediate 4

N-[(9H-fluoren-9-ylmethoxy)carbonyl]-N-methyl-L-valyl-N-[(2R,3S,4S)-1-carboxy-2-methoxy-4-methylhexan-3-yl]-N-methyl-L-valinamide

[3109]



[3110] 9.1 g of the crude product N-[(9H-fluoren-9-ylmethoxy)carbonyl]-N-methyl-L-valyl-N-[(3R,4S,5S)-1-tert-butoxy-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Intermediate 3) were taken up in 56.6 ml of dichloromethane, 56.6 ml of trifluoroacetic acid were added, and the mixture was stirred at RT for 2 h. Subsequently, the reaction mixture was concentrated under reduced pressure and the remaining residue was purified by flash chromatography, using dichloromethane, 3:1 dichloromethane/ethyl acetate and 15:5:0.5 dichloromethane/ethyl acetate/methanol as eluent. After purification of the corresponding fractions and concentration, 5.8 g (86% of theory) of the title compound were obtained as a colourless foam.

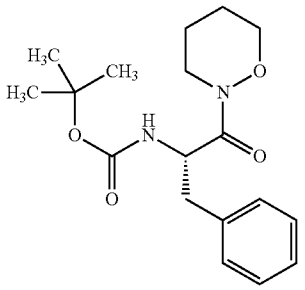
[3111] HPLC (Method 5): R_t=2.2 min;

[3112] LC-MS (Method 1): R_t=1.3 min; MS (ESIpos): m/z=638 $(M+H)^+$.

Intermediate 5

tert-butyl (2S)-1-(1,2-oxazinan-2-yl)-1-oxo-3-phenylpropan-2-yl carbamate

[3113]



[3114] 500 mg (1.9 mmol) of N-(tert-butoxycarbonyl)-L-phenylalanine were dissolved in 10 ml of DMF and admixed successively with 466 mg (3.8 mmol) of 1,2-oxazinane hydrochloride (Starting Compound 5), 433 mg (2.3 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 382 mg (2.8 mmol) of 1-hydroxy-1H-benzotriazole hydrate and 731 mg (5.7 mmol) of N,N-diisopropylethylamine. The mixture was stirred at RT overnight. The reaction mixture was then poured into a mixture of semisaturated aqueous ammonium chloride solution and ethyl acetate. The organic phase was removed, washed successively with saturated sodium hydrogencarbonate solution and saturated sodium chloride solution, dried over magnesium sulphate, filtered and concentrated. 620 mg (98% of theory) of the title compound were obtained.

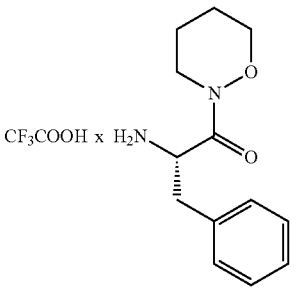
[3115] HPLC (Method 5): R_t=1.8 min;

[3116] LC-MS (Method 2): R_t=1.62 min; MS (ESIpos): m/z=235 $(M-C_4H_8—CO_2+H)^+$.

Intermediate 6

(2S)-2-amino-1-(1,2-oxazinan-2-yl)-3-phenylpropan-1-one trifluoroacetate

[3117]



[3118] 620 mg (1.85 mmol) of tert-butyl (2S)-1-(1,2-oxazinan-2-yl)-1-oxo-3-phenylpropan-2-yl carbamate (Intermediate 5) were taken up in 5 ml of dichloromethane, 10 ml of trifluoroacetic acid were added and the mixture was stirred at RT for 30 min. Subsequently, the reaction mixture was concentrated under reduced pressure and the remaining residue was lyophilized from water/acetonitrile. In this way, 779 mg (91% of theory) of the title compound were obtained as a colourless foam.

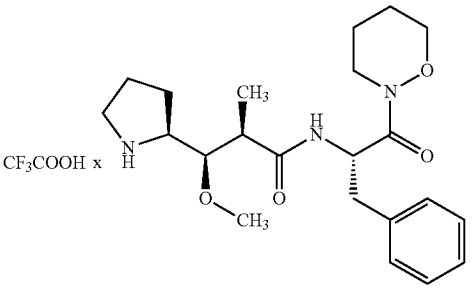
[3119] HPLC (Method 5): R_t=0.45 min;

[3120] LC-MS (Method 3): R_t=1.09 min; MS (ESIpos): m/z=235 $(M+H)^+$.

Intermediate 7

(2R,3R)-3-methoxy-2-methyl-N-[(2S)-1-(1,2-oxazinan-2-yl)-1-oxo-3-phenylpropan-2-yl]-3-[(2S)-pyrrolidin-2-yl]propanamide trifluoroacetate

[3121]



[3122] 360 mg (1.25 mmol) of (2R,3R)-3-[(2S)-1-(tert-butoxycarbonyl)pyrrolidin-2-yl]-3-methoxy-2-methylpropanoic acid (Starting Compound 1) were taken up in 10 ml of DMF and admixed successively with 579.2 mg (1.25 mmol) of (2S)-2-amino-1-(1,2-oxazinan-2-yl)-3-phenylpropan-1-one trifluoroacetate (Intermediate 6), 714.5 mg (1.88 mmol) of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) and 655 μl of N,N-diisopropylethylamine. The mixture was stirred at RT for 16 h. The reaction mixture was then concentrated, and the residue was taken up in ethyl acetate and extracted by shaking first with 5% aqueous citric acid solution, then with 5% aqueous sodium hydrogencarbonate solution and subsequently with saturated sodium chloride solution. The organic phase was concentrated and the residue was purified by flash chromatography on silica gel with 16:4 dichloromethane/methanol as the eluent. The corresponding fractions were combined and the solvent was removed under reduced pressure. After the residue had been dried under high vacuum, 503.5 mg (74% of theory) of the Boc-protected intermediate tert-butyl (2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(2S)-1-(1,2-oxazinan-2-yl)-1-oxo-3-phenylpropan-2-yl]amino}-3-oxopropyl]pyrrolidine-1-carboxylate were obtained.

[3123] HPLC (Method 12): R_t=2.0 min;

[3124] LC-MS (Method 1): R_t=1.12 min; MS (ESIpos): m/z=504 $(M+H)^+$.

[3125] 503 mg (1 mmol) of this intermediate were taken up in 20 ml of dichloromethane, 10 ml of trifluoroacetic acid were added, and the mixture was stirred at RT for 30 min. Subsequently, the reaction mixture was concentrated under reduced pressure and redistilled with dichloromethane. The remaining residue was precipitated from ethyl acetate with n-pentane, and the solvent was decanted off. The residue thus obtained was dissolved in water and extracted by shaking with ethyl acetate, and the aqueous phase was subsequently lyophilized. In this way, 462 mg (89% of theory) of the title compound were obtained as a colourless foam.

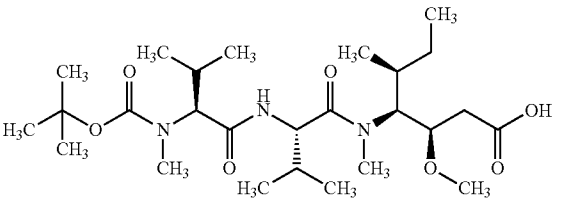
[3126] HPLC (Method 12): R_t=1.53 min;

[3127] LC-MS (Method 11): R_t=0.57 min; MS (ESIpos): m/z=404 $(M+H)^+$.

Intermediate 8

N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(2R,3S,4S)-1-carboxy-2-methoxy-4-methylhexan-3-yl]-N-methyl-L-valinamide

[3128]



[3129] 51 mg (0.08 mmol) of N-[(9H-fluoren-9-ylmethoxy)carbonyl]-N-methyl-L-valyl-N-[(2R,3S,4S)-1-carboxy-2-methoxy-4-methylhexan-3-yl]-N-methyl-L-valinamide (Intermediate 4) were dissolved in 10 ml of DMF, and 0.5 ml of piperidine was added. After stirring at RT for 10 min, the reaction mixture was concentrated under reduced pressure and the residue was stirred with diethyl ether. The insoluble constituents were filtered off and washed repeatedly with diethyl ether. Then the filter residue was taken up in 5 ml of dioxane/water and the solution was adjusted to pH 11 with 1 N sodium hydroxide solution. Under ultrasound treatment, a total of 349 mg (1.6 mmol) of di-tert-butyl dicarbonate were added in several portions, in the course of which the pH of the solution was kept at 11. After the reaction had ended, the dioxane was evaporated off and the aqueous solution was adjusted to a pH of 2-3 with citric acid. The mixture was extracted twice with 50 ml each time of ethyl acetate. The organic phases were combined, dried over magnesium sulphate and concentrated under reduced pressure. The residue was taken up in diethyl ether and the of the title compound was precipitated with pentane. The solvent was removed by decantation. The residue was digested several times more with pentane and finally dried under high vacuum. 40 mg (97% of theory) of the title compound were thus obtained.

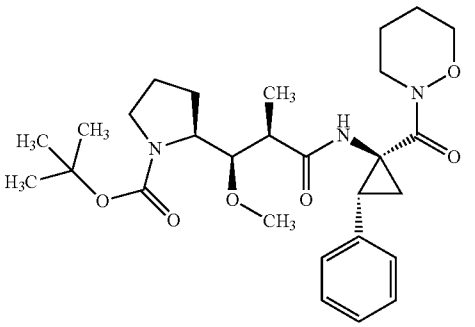
[3130] HPLC (Method 6): R_t=2.2 min;

[3131] LC-MS (Method 2): R_t=1.32 min; MS (ESIpos): m/z=516 $(M+H)^+$.

Intermediate 9

tert-butyl (2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidine-1-carboxylate

[3132]



[3133] The title compound was prepared in analogy to the synthesis of Intermediates 5, 6 and 7 over three stages, by coupling of commercially available (1S,2R)-1-[(tert-butoxycarbonyl)amino]-2-phenylcyclopropanecarboxylic acid with 1,2-oxazinane hydrochloride (Starting Compound 5), subsequent deprotection with trifluoroacetic acid and coupling with Starting Compound 1. The end product was purified by preparative HPLC.

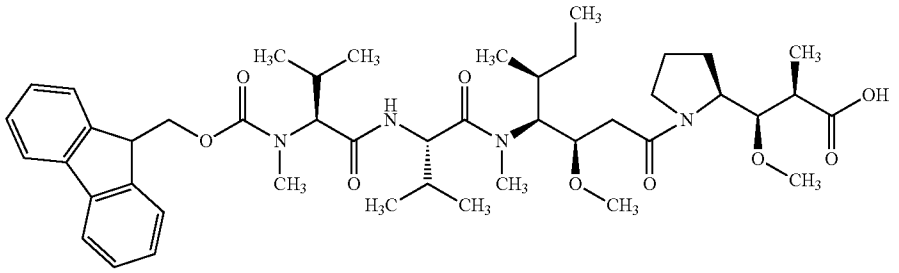
[3134] HPLC (Method 5): R_t=2.12 min;

[3135] LC-MS (Method 2): R_t=1.25 min; MS (ESIpos): m/z=516 $(M+H)^+$.

Intermediate 10

N-[(9H-fluoren-9-ylmethoxy)carbonyl]-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-2-carboxy-1-methoxypropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3136]



[3137] 315 mg (0.494 mmol) of N-[(9H-fluoren-9-ylmethoxy)carbonyl]-N-methyl-L-valyl-N-[(2R,3S,4S)-1-carboxy-2-methoxy-4-methylhexan-3-yl]-N-methyl-L-valinamide (Intermediate 4) were dissolved in 12 ml of DMF, and admixed with 104 mg (0.543 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 83 mg (0.543 mmol) of 1-hydroxy-1H-benzotriazole hydrate, and the mixture was stirred at RT for 90 min. Subsequently, 112 µl of N,N-diisopropylethylamine and 149 mg (0.494 mmol) of (2R,3R)-3-methoxy-2-methyl-3-[(2S)-pyrrolidin-2-yl]propanoic acid trifluoroacetate, which had been prepared beforehand from Starting Compound 1 by elimination of the Boc protecting group by means of trifluoroacetic acid, were added. The mixture was stirred at RT for 2 h and then concentrated under high vacuum. The remaining residue was purified twice by preparative HPLC. 140 mg (35% of theory) of the title compound were obtained in the form of a colourless foam.

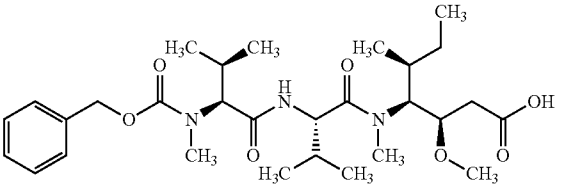
[3138] HPLC (Method 5): R_t=2.40 min;

[3139] LC-MS (Method 1): R_t=1.38 min; MS (ESIpos): m/z=807 $(M+H)^+$.

Intermediate 11

N-[(benzyloxy)carbonyl]-N-methyl-L-threonyl-N-[(2R,3S,4S)-1-carboxy-2-methoxy-4-methylhexan-3-yl]-N-methyl-L-valinamide

[3140]



[3141] First, N-[(benzyloxy)carbonyl]-N-methyl-L-threonine was released from 237 mg (0.887 mmol) of its dicyclohexylamine salt thereof by taking it up in ethyl acetate and extractive shaking with 5% aqueous sulphuric acid. The organic phase was dried over magnesium sulphate, filtered and concentrated. The residue was taken up in 16 ml of DMF and admixed successively with 365 mg (1 mmol) of tert-butyl (3R,4S,5S)-3-methoxy-5-methyl-4-[methyl(L-valyl)amino]heptanoate (Intermediate 2), 185 mg (0.967 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 148 mg (0.967 mmol) of 1-hydroxy-1H-benzotriazole hydrate. The mixture was stirred at RT for 2 h. The reaction mixture was then poured into a mixture of semisaturated aqueous ammonium chloride solution and ethyl acetate. The organic phase was removed, washed successively with saturated sodium hydrogencarbonate solution and saturated sodium chloride solution, dried over magnesium sulphate, filtered and concentrated. The residue was purified by preparative HPLC. 283 mg (53% of theory) of the tert-butyl ester intermediate N-[(benzyloxy)carbonyl]-N-methyl-L-threonyl-N-[(3R,4S,5S)-1-tert-butoxy-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide were thus obtained.

[3142] HPLC (Method 5): R_t=2.17 min.

[3143] 283 mg (0.466 mmol) of this intermediate were taken up in 5 ml of dichloromethane, 5 ml of anhydrous trifluoroacetic acid were added, and the mixture was stirred at RT for 2 h. Subsequently, the reaction mixture was concentrated under high vacuum and the remaining residue was purified by means of preparative HPLC. This gave 156 mg (61% of theory) of the title compound as a colourless foam.

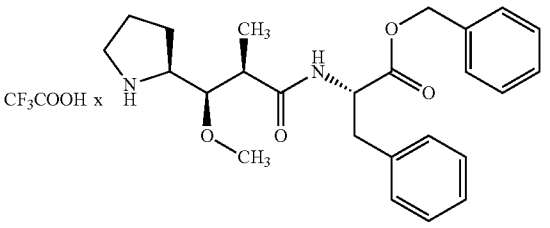
[3144] HPLC (Method 5): R_t=1.50 min;

[3145] LC-MS (Method 2): R_t=1.09 min; MS (ESIpos): m/z=552 $(M+H)^+$.

Intermediate 12

benzyl N-{(2R,3R)-3-methoxy-2-methyl-3-[(2S)-pyrrolidin-2-yl]propanoyl}-L-phenylalaninate trifluoroacetate

[3146]



[3147] In the first step, Starting Compound 1 was released from 600 mg (1.28 mmol) of the corresponding dicyclohexylammonium salt by dissolving the salt in 100 ml of ethyl acetate and extractive shaking, first with 50 ml of 0.5% sulphuric acid and then with saturated sodium chloride solution. Then the organic phase was dried over magnesium sulphate, filtered, concentrated and reacted immediately with benzyl L-phenylalaninate in analogy to the synthesis of Intermediate 7, and then deprotected.

[3148] Yield: 650 mg (94% over 2 stages)

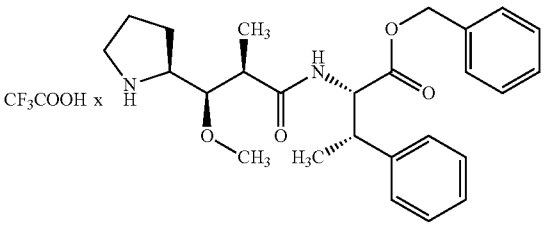
[3149] HPLC (Method 6): R_t=1.76 min;

[3150] LC-MS (Method 2): R_t=1.68 min; MS (ESIpos): m/z=425 $(M+H)^+$.

Intermediate 13

benzyl (βS)—N-{(2R,3R)-3-methoxy-2-methyl-3-[(2S)-pyrrolidin-2-yl]propanoyl}-β-methyl-L-phenylalaninate trifluoroacetate

[3151]



[3152] First, (2R,3R)-3-[(2S)-1-(tert-butoxycarbonyl)pyrrolidin-2-yl]-3-methoxy-2-methylpropanoic acid was released from 351 mg (0.75 mmol) of the dicyclohexylamine salt (Starting Compound 1) by taking it up in ethyl acetate and extractive shaking with aqueous 5% potassium hydrogensulphate solution. The organic phase was dried over magnesium sulphate, filtered and concentrated. The residue was taken up in 10 ml of DMF and admixed successively with 373 mg (0.75 mmol) of benzyl (βS)-β-methyl-L-phenylalaninate trifluoroacetate [prepared from commercially available (βS)—N-(tert-butoxycarbonyl)-β-methyl-L-phenylalanine by EDC/DMAP-mediated esterification with benzyl alcohol and subsequent detachment of the Boc protecting group with trifluoroacetic acid], 428 mg (1.125 mmol) of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) and 392 µl of N,N-diisopropylethylamine. The mixture was stirred at RT for 20 h. The reaction mixture was then poured onto a mixture of semisaturated aqueous ammonium chloride solution and ethyl acetate. The organic phase was removed, washed successively with saturated sodium hydrogencarbonate solution and saturated sodium chloride solution, and subsequently concentrated. The residue was purified by means of preparative HPLC. This gave 230 mg (57% of theory) of the Boc-protected intermediate benzyl (βS)—N-{(2R,3R)-3-[(2S)-1-(tert-butoxycarbonyl)pyrrolidin-2-yl]-3-methoxy-2-methylpropanoyl}-β-methyl-L-phenylalaninate.

[3153] HPLC (Method 6): R_t=2.3 min;

[3154] LC-MS (Method 1): R_t=1.36 min; MS (ESIpos): m/z=539 $(M+H)^+$.

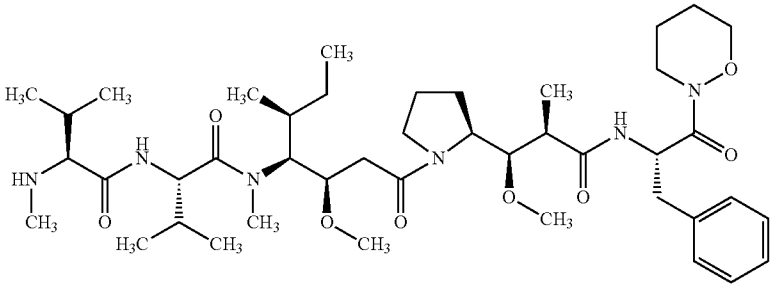
[3155] 230 mg (0.42 mmol) of this intermediate were taken up in 5 ml of dichloromethane, 5 ml of trifluoroacetic acid were added, and the mixture was stirred at RT for 30 min. Subsequently, the reaction mixture was concentrated under reduced pressure. The remaining residue was the reaction mixture dried further under reduced pressure and then lyophilized from acetonitrile/water. In this way, 230 mg (quant.) of the title compound were obtained.

[3156] HPLC (Method 6): R_t=1.6 min.

Intermediate 14

N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(2S)-1-(1,2-oxazinan-2-yl)-1-oxo-3-phenylpropan-2-yl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide trifluoroacetate

[3157]



x CF_3COOH

[3158] 143 mg (0.223 mmol) of N-[(9H-fluoren-9-ylmethoxy)carbonyl]-N-methyl-L-valyl-N-[(2R,3S,4S)-1-carboxy-2-methoxy-4-methylhexan-3-yl]-N-methyl-L-valinamide (Intermediate 4) were taken up in 15 ml of DMF and admixed successively with 141 mg (0.22 mmol) of (2R,3R)-3-methoxy-2-methyl-N-[(2S)-1-(1,2-oxazinan-2-yl)-1-oxo-3-phenylpropan-2-yl]-3-[(2S)-pyrrolidin-2-yl]propanamide trifluoroacetate (Intermediate 7), 102 mg (0.27 mmol) of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) and 128 µl (0.74 mmol) of N,N-diisopropylethylamine. The mixture was stirred at RT for 3 h. The reaction mixture was then poured into a mixture of semisaturated aqueous ammonium chloride solution and ethyl acetate. The organic phase was removed, washed successively with saturated sodium hydrogencarbonate solution and saturated sodium chloride solution, dried over magnesium sulphate, filtered and concentrated. This gave 275 mg (quant.) of the Fmoc-protected intermediate N-[(9H-fluoren-9-ylmethoxy)carbonyl]-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(2S)-1-(1,2-oxazinan-2-yl)-1-oxo-3-phenylpropan-2-yl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide.

[3159] HPLC (Method 5): R_t=2.73 min;

[3160] LC-MS (Method 4): R_t=3.19 min; MS (ESIpos): m/z=1023 $(M+H)^+$.

[3161] 46 mg (0.045 mmol) of this intermediate were dissolved in 4 ml of DMF. After 1 ml of piperidine had been added, the reaction mixture was stirred at RT for 1 h. Subsequently, the reaction mixture was concentrated under reduced pressure and the residue was purified by means of preparative HPLC (eluent: acetonitrile+0.01% TFA/water+0.01% TFA). 22 mg (54% of theory) of the title compound were obtained as a colourless foam.

[3162] HPLC (Method 5): R_t=1.68 min;

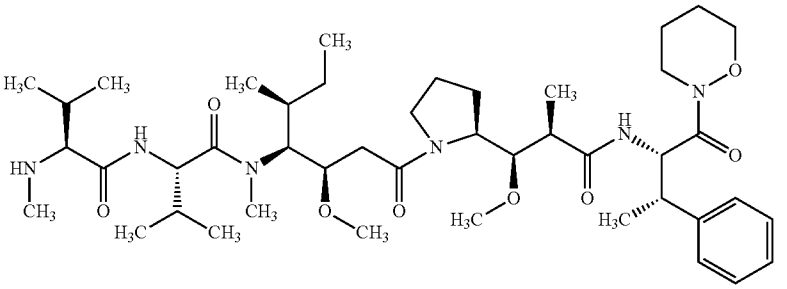
[3163] LC-MS (Method 2): R_t=1.03 min; MS (ESIpos): m/z=801 $(M+H)^+$

[3164] ^{1}H NMR (600 MHz, DMSO-d_6): δ=8.8 (m, 2H), 8.7 (m, 1H), 8.42 and 8.15 (2d, 1H), 7.3-7.1 (m, 5H), 5.12 and 4.95 (2m, 1H), 4.70 and 4.62 (2m, 1H), 4.62 and 4.50 (2t, 1H), 4.1-3.9 (m, 3H), 3.85 (m, 1H), 3.75-3.6 (m, 2H), 3.23, 3.18, 3.17, 3.14, 3.02 and 2.96 (6s, 9H), 3.1-2.9 and 2.75 (2m, 2H), 2.46 (m, 3H), 2.4-2.1 (m, 2H), 2.05 (br. m, 2H), 1.85-1.55 (br. m, 6H), 1.5-1.2 (br. m, 3H), 1.1-0.8 (m, 18H), 0.75 (t, 3H) [further signals hidden under H_2O peak].

Intermediate 15

N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(2S,3S)-1-(1,2-oxazinan-2-yl)-1-oxo-3-phenylbutan-2-yl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide trifluoroacetate

[3165]



x CF_3COOH

[3166] 126 mg (0.198 mmol) of N-[(9H-fluoren-9-ylmethoxy)carbonyl]-N-methyl-L-valyl-N-[(2R,3S,4S)-1-carboxy-2-methoxy-4-methylhexan-3-yl]-N-methyl-L-valinamide (Intermediate 4) were taken up in 10 ml of DMF and admixed successively with 105 mg (0.198 mmol) of (2R,3R)-3-methoxy-2-methyl-N-[(2S,3S)-1-(1,2-oxazinan-2-yl)-1-oxo-3-phenylbutan-2-yl]-3-[(2S)-pyrrolidin-2-yl]propanamide trifluoroacetate (Intermediate 17), 41.6 mg (0.217 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 33 mg (0.217 mmol) of 1-hydroxy-1H-benzotriazole hydrate and 79 µl (0.454 mmol) of N,N-diisopropylethylamine. The mixture was stirred at RT overnight. The reaction mixture was then poured into a mixture of semisaturated aqueous ammonium chloride solution and ethyl acetate. The organic phase was removed, washed successively with saturated sodium hydrogencarbonate solution and saturated sodium chloride solution, dried over magnesium sulphate, filtered and concentrated. This gave 220 mg (quant.) of the Fmoc-protected intermediate N-[(9H-fluoren-9-ylmethoxy)carbonyl]-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(2S,3S)-1-(1,2-oxazinan-2-yl)-1-oxo-3-phenylbutan-2-yl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide.

[3167] HPLC (Method 5): R_t=2.77 min;

[3168] LC-MS (Method 1): R_t=1.5 min; MS (ESIpos): m/z=1037 $(M+H)^+$.

[3169] 220 mg (0.212 mmol) of this intermediate were dissolved in 5 ml of DMF. After 1 ml of piperidine had been added, the reaction mixture was stirred at RT for 1 h. Subsequently, the reaction mixture was concentrated under reduced pressure and the residue was purified by means of preparative HPLC (eluent: acetonitrile+0.01% TFA/water+0.01% TFA). 91 mg (46% of theory) of the title compound were obtained as a colourless foam.

[3170] HPLC (Method 5): R_t=1.71 min;

[3171] LC-MS (Method 1): R_t=0.9 min; MS (ESIpos): m/z=815 $(M+H)^+$

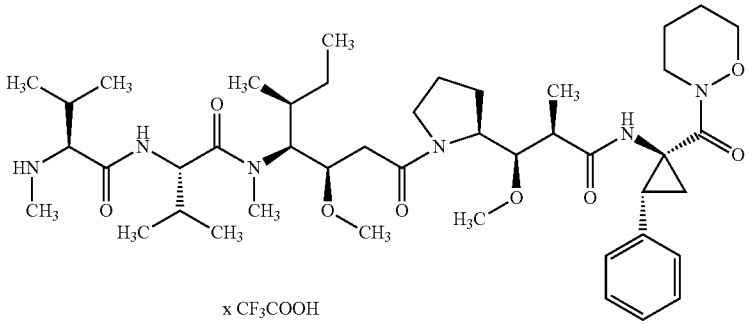
[3172] ^{1}H NMR (600 MHz, DMSO-d_6): δ=8.87 and 8.80 (2d, 2H), 8.75 (m, 1H), 8.40 and 7.98 (2d, 1H), 7.3-7.1 (m,

5H), 5.45 and 5.2 (2t, 1H), 4.78 and 4.62 (2m, 1H), 4.73 and 4.58 (2t, 1H), 4.2-4.0 (m, 3H), 3.7-3.6 (m, 1H), 3.35, 3.20, 3.18, 3.14, 3.12 and 3.00 (6s, 9H), 3.1 and 2.95 (2m, 2H), 2.46 (m, 3H), 2.4-2.0 (m, 4H), 1.9-1.6 (m, 4H), 1.6-1.2 (m, 5H), 1.1-0.75 (m, 21H), 0.80 (t, 3H) [further signals hidden under H_2O peak].

Intermediate 16

N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide trifluoroacetate

[3173]



x CF_3COOH

[3174] 617 mg (1.2 mmol) of tert-butyl (2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidine-1-carboxylate (Intermediate 24) were taken up in 44 ml of dichloromethane, 4.4 ml of trifluoroacetic acid were added and the mixture was stirred at RT for 30 min. Subsequently, the reaction mixture was concentrated under reduced pressure and the remaining residue was lyophilized from dioxane/water. 702 mg (quant.) of the deprotected compound (2R,3R)-3-methoxy-2-methyl-N-[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]-3-[(2S)-pyrrolidin-2-yl]propanamide trifluoroacetate were obtained as a crude product, which was used in the following stage without further purification.

[3175] 470 mg (0.74 mmol) of N-[(9H-fluoren-9-ylmethoxy)carbonyl]-N-methyl-L-valyl-N-[(2R,3S,4S)-1-carboxy-2-methoxy-4-methylhexan-3-yl]-N-methyl-L-valinamide (Intermediate 4) were taken up in 57 ml of DMF and admixed successively with 390 mg (approx. 0.74 mmol) of the above-obtained (2R,3R)-3-methoxy-2-methyl-N-[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]-3-[(2S)-pyrrolidin-2-yl]propanamide trifluoroacetate, 336 mg (0.88 mmol) of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) and 423 µl (2.4 mmol) of N,N-diisopropylethylamine. The mixture was stirred at RT for 2 h. The reaction mixture was then poured into a mixture of semisaturated aqueous ammonium chloride solution and ethyl acetate. The organic phase was removed, washed successively with saturated sodium hydrogencarbonate solution and saturated sodium chloride solution, dried over sodium sulphate, filtered and concentrated. The residue was purified by preparative HPLC. This gave 453 mg (59% of theory) of the Fmoc-protected intermediate N-[(9H-fluoren-9-ylmethoxy)carbonyl]-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide.

[3176] HPLC (Method 5): R_t=2.58 min;

[3177] LC-MS (Method 1): R_t=3.10 min; MS (ESIpos): m/z=1035 $(M+H)^+$.

[3178] 453 mg (0.438 mmol) of this intermediate were dissolved in 24 ml of DMF. After 2.4 ml of piperidine had been added, the reaction mixture was stirred at RT for 30 min. Subsequently, the reaction mixture was concentrated under reduced pressure and the residue was purified by preparative HPLC (eluent: acetonitrile/0.1% TFA in water). 260 mg (64% of theory) of the title compound were obtained as a colourless foam.

[3179] HPLC (Method 5): R_t=1.64 min;

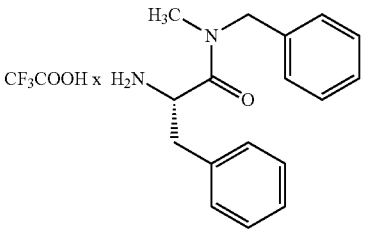
[3180] LC-MS (Method 1): R_t=0.86 min; MS (ESIpos): m/z=813 $(M+H)^+$

[3181] ^1H NMR (400 MHz, DMSO-d_6): δ=8.8 (m, 2H), 8.65 (m, 2H), 7.3-7.1 (m, 5H), 4.8-4.05 (m, 2H), 4.0 and 3.82 (2m, 2H), 3.8-3.5 (m, 8H), 3.32, 3.29, 3.20, 3.19, 3.12 and 3.00 (6s, 9H), 2.65 (t, 1H), 2.5-2.45 (m, 3H), 2.4-1.3 (m, 15H), 1.15-0.85 (m, 18H), 0.8 and 0.75 (2d, 3H) [further signals hidden under H_2O peak].

Intermediate 17

N-benzyl-N-methyl-L-phenylalaninamide trifluoroacetate

[3182]



[3183] 1000 mg (3.77 mmol) of N-(tert-butoxycarbonyl)-L-phenylalanine were dissolved in 10 ml of DMF and admixed with 457 mg (3.77 mmol) of N-methylbenzylamine, 2150 mg (5.65 mmol) of O-(7-azabenzotriazol-1-yl)-N,N,N',

N'-tetramethyluronium hexafluorophosphate and 657 μl of N,N-diisopropylethylamine. The reaction mixture was stirred at RT for 30 min and then concentrated under reduced pressure. The residue was taken up in dichloromethane and extracted by shaking three times with water. The organic phase was dried over magnesium sulphate and concentrated. The residue was purified by flash chromatography on silica gel with 3:1 petroleum ether/ethyl acetate as the eluent. The product fractions were concentrated and the residue was dried under high vacuum. This gave 1110 mg (75% of theory) of the Boc-protected intermediate N-benzyl-N^{α}-(tert-butoxycarbonyl)-N-methyl-L-phenylalaninamide.

[3184] HPLC (Method 6): R_t=2.1 min;

[3185] LC-MS (Method 1): R_t=1.14 min; MS (ESIpos): m/z=369 $(M+H)^+$.

[3186] 1108 mg (3.007 mmol) of this intermediate were taken up in 30 ml of dichloromethane, 10 ml of trifluoroacetic acid were added, and the mixture was stirred at RT for 30 min. Subsequently, the reaction mixture was concentrated under reduced pressure, the remaining residue was stirred with dichloromethane and the solvent was distilled off. The residue was stirred twice more with pentane, the solvent was decanted off again each time and the of the title compound was finally dried under high vacuum. 1075 mg (93% of theory) of the title compound were thus obtained as a resin.

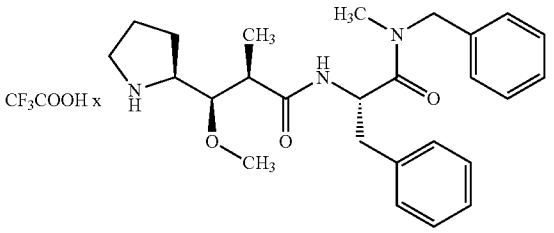
[3187] HPLC (Method 6): R_t=1.6 min;

[3188] LC-MS (Method 1): R_t=0.6 min; MS (ESIpos): m/z=269 $(M+H)^+$.

Intermediate 18

N-benzyl-N^{α}-{(2R,3R)-3-methoxy-2-methyl-3-[(2S)-pyrrolidin-2-yl]propanoyl}-N-methyl-L-phenylalaninamide trifluoroacetate

[3189]



[3190] First, (2R,3R)-3-[(2S)-1-(tert-butoxycarbonyl)pyrrolidin-2-yl]-3-methoxy-2-methylpropanoic acid (Starting Compound 1) was released from 141 mg (0.491 mmol) of its dicyclohexylamine salt by taking it up in ethyl acetate and extractive shaking with 5% aqueous sulphuric acid. The organic phase was dried over magnesium sulphate, filtered and concentrated. The residue was taken up in 10 ml of DMF and 187.6 mg (0.49 mmol) of N-benzyl-N-methyl-L-phenylalaninamide trifluoroacetate (Intermediate 9), 190.3 mg (1.47 mmol) of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) and 256 μl of N,N-diisopropylethylamine were added. The mixture was stirred at RT for 1 h. The reaction mixture was then concentrated, the residue was taken up in ethyl acetate and the solution was subsequently extracted by shaking successively with saturated ammonium chloride solution, saturated sodium hydrogencarbonate solution and water. The organic phase was dried over magnesium sulphate and concentrated. The residue was purified by flash chromatography on silica gel with 30:1 acetonitrile/water as the eluent. The product fractions were concentrated and the residue was dried under high vacuum. This gave 168 mg (64% of theory) of the Boc-protected intermediate tert-butyl (2S)-2-[(1R,2R)-3-({(2S)-1-[benzyl(methyl)amino]-1-oxo-3-phenylpropan-2-yl}amino)-1-methoxy-2-methyl-3-oxopropyl]pyrrolidine-1-carboxylate.

[3191] HPLC (Method 6): R_t=2.2 min;

[3192] LC-MS (Method 2): R_t=1.22 min; MS (ESIpos): m/z=538 $(M+H)^+$.

[3193] 168 mg (0.312 mmol) of this intermediate were taken up in 15 ml of dichloromethane, 3 ml of trifluoroacetic acid were added, and the mixture was stirred at RT for 30 min. Subsequently, the reaction mixture was concentrated under reduced pressure. The remaining residue was stirred first with dichloromethane, then with diethyl ether, and the solvent was distilled off again each time. After drying under high vacuum, 170 mg (99% of theory) of the title compound were obtained as a resin.

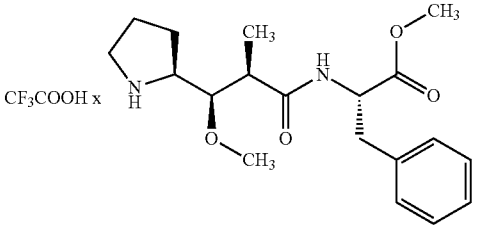
[3194] HPLC (Method 6): R_t=1.7 min;

[3195] LC-MS (Method 1): R_t=0.73 min; MS (ESIpos): m/z=438 $(M+H)^+$.

Intermediate 19

methyl N-{(2R,3R)-3-methoxy-2-methyl-3-[(2S)-pyrrolidin-2-yl]propanoyl}-L-phenylalaninate trifluoroacetate

[3196]



[3197] The title compound was prepared in analogy to the synthesis of Intermediate 18, proceeding from (2R,3R)-3-[(2S)-1-(tert-butoxycarbonyl)pyrrolidin-2-yl]-3-methoxy-2-methylpropanoic acid (Starting Compound 1), which was released from the dicyclohexylamine salt, and methyl L-phenylalaninate hydrochloride.

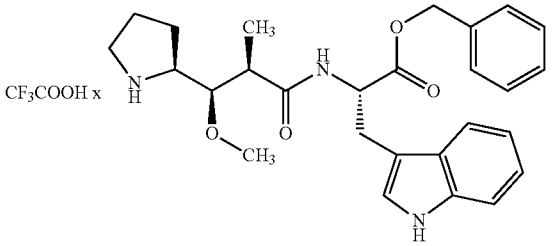
[3198] HPLC (Method 5): R_t=0.6 min;

[3199] LC-MS (Method 3): R_t=1.17 min; MS (ESIpos): m/z=349 $(M+H)^+$.

Intermediate 20

benzyl N-{(2R,3R)-3-methoxy-2-methyl-3-[(2S)-pyrrolidin-2-yl]propanoyl}-L-tryptophanate trifluoroacetate

[3200]



[3201] The title compound was prepared in analogy to the synthesis of Intermediate 18, proceeding from (2R,3R)-3-[(2S)-1-(tert-butoxycarbonyl)pyrrolidin-2-yl]-3-methoxy-2-methylpropanoic acid (Starting Compound 1), which was released from the dicyclohexylamine salt, and benzyl L-tryptophanate.

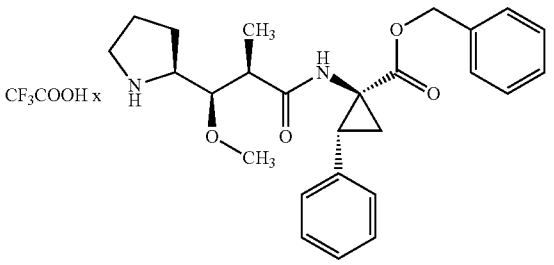
[3202] HPLC (Method 6): R_t=2.0 min;

[3203] LC-MS (Method 1): R_t=0.8 min; MS (ESIpos): m/z=464 $(M+H)^+$.

Intermediate 21

benzyl (1S,2R)-1-({(2R,3R)-3-methoxy-2-methyl-3-[(2S)-pyrrolidin-2-yl]propanoyl}amino)-2-phenylcyclopropanecarboxylate trifluoroacetate

[3204]



[3205] The title compound was prepared in analogy to the synthesis of Intermediate 18, proceeding from (2R,3R)-3-[(2S)-1-(tert-butoxycarbonyl)pyrrolidin-2-yl]-3-methoxy-2-methylpropanoic acid (Starting Compound 1), which was released from the dicyclohexylamine salt, and benzyl (1S,2R)-1-amino-2-phenylcyclopropanecarboxylate. Benzyl (1S,2R)-1-amino-2-phenylcyclopropanecarboxylate had been prepared beforehand by standard methods, by esterifying commercially available (1S,2R)-1-[(tert-butoxycarbonyl)amino]-2-phenylcyclopropanecarboxylic acid with benzyl alcohol and subsequent Boc detachment with trifluoroacetic acid.

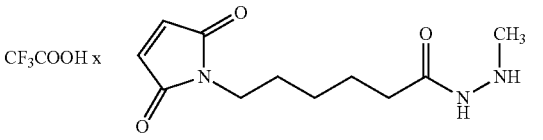
[3206] HPLC (Method 5): R_t=1.5 min;

[3207] LC-MS (Method 2): R_t=0.93 min; MS (ESIpos): m/z=437 $(M+H)^+$.

Intermediate 22

6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-N'-methylhexanehydrazide trifluoroacetate

[3208]



[3209] 100 mg (473 μmol) of 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoic acid were dissolved in 71 μl of DMF and then admixed with 139 mg (947 μmol) of tert-butyl 1-methylhydrazinecarboxylate, 182 mg (947 μmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 145 mg (947 μmol) of 1-hydroxy-1H-benzotriazole hydrate. The mixture was stirred at RT overnight and then concentrated under reduced pressure. The remaining residue was purified by means of preparative HPLC. After lyophilization from dioxane/water, 129 mg (80% of theory) of the protected intermediate were obtained as a colourless foam.

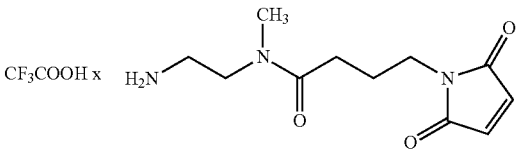
[3210] Subsequently, the 129 mg (380 μmol) were deblocked with 2 ml of trifluoroacetic acid in 8 ml of dichloromethane. After stirring at RT for 1 h, the reaction mixture was concentrated under reduced pressure. The residue was lyophilized from acetonitrile/water, which left 125 mg (83% of theory) of the title compound as a colourless foam.

[3211] LC-MS (Method 1): R_t=0.38 min; MS (ESIpos): m/z=240 $(M+H)^+$

Intermediate 23

N-(2-aminoethyl)-4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-N-methylbutanamide trifluoroacetate

[3212]



[3213] First, 35 mg (164 μmol) of tert-butyl 2-(methylamino)ethyl carbamate hydrochloride trifluoroacetate, 30 mg (164 μmol) of 4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl) butanoic acid, mg (197 μmol) of O-(7-azabenzotriazol-1-yl)-N, N,N',N'-tetramethyluronium hexafluorophosphate and 57 μl of N,N-diisopropylethylamine were combined in 5 ml of DMF and stirred at RT overnight. Subsequently, the solvent was removed under reduced pressure and the remaining residue was purified by means of preparative HPLC. The corresponding fractions were concentrated and, by lyophilization from dioxane/water, 35 mg (63% of theory) of the protected intermediate were obtained.

[3214] HPLC (Method 12): R_t=1.6 min;

[3215] LC-MS (Method 1): R_t=0.71 min; MS (ESIpos): m/z=340 $(M+H)^+$.

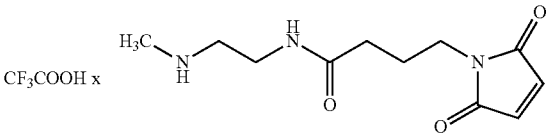
[3216] Subsequently, the entire amount of the protected intermediate was deblocked with 1 ml of trifluoroacetic acid in 5 ml of dichloromethane to obtain 28 mg (77% of theory) of the title compound.

[3217] LC-MS (Method 3): R_t=0.75 min; MS (ESIpos): m/z=240 $(M+H)^+$.

Intermediate 24

4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-N-[2-(methylamino)ethyl]butanamide trifluoroacetate

[3218]



[3219] First, 35 mg (164 μmol) of tert-butyl (2-aminoethyl) methyl carbamate hydrochloride trifluoroacetate, 30 mg (164 μmol) of 4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)butanoic acid, mg (197 μmol) of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and 57 μl of N,N-diisopropylethylamine were combined in 5 ml of DMF and stirred at RT for 30 min. Subsequently, the solvent was removed under reduced pressure and the remaining residue was purified by means of preparative HPLC. The corresponding fractions were concentrated and, by lyophilization from dioxane/water, 51 mg (91% of theory) of the protected intermediate were obtained.

[3220] HPLC (Method 12): R_t=1.6 min;

[3221] LC-MS (Method 1): R_t=0.77 min; MS (ESIpos): m/z=340 $(M+H)^+$.

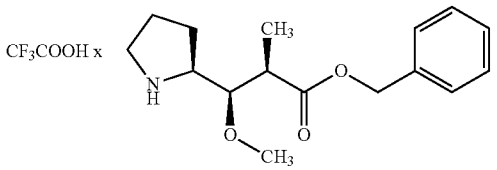
[3222] Subsequently, the entire amount was deprotected with 1 ml of trifluoroacetic acid in 5 ml of dichloromethane to obtain 45 mg (69% of theory) of the title compound.

[3223] LC-MS (Method 1): R_t=0.19 min; MS (ESIpos): m/z=240 $(M+H)^+$.

Intermediate 25

benzyl (2R,3R)-3-methoxy-2-methyl-3-[(2S)-pyrrolidin-2-yl]propanoate trifluoroacetate

[3224]



[3225] First, (2R,3R)-3-[(2S)-1-(tert-butoxycarbonyl)pyrrolidin-2-yl]-3-methoxy-2-methylpropanoic acid was released from 1.82 g (388 mmol) of its dicyclohexylamine salt by taking it up in ethyl acetate and extractive shaking with 100 ml of 0.5% sulphuric acid. The organic phase was dried over magnesium sulphate, filtered and concentrated. The residue was taken up in 10 ml of dioxane and 10 ml of water, 1517 mg (4.66 mmol) of caesium carbonate were added, and the mixture was treated in an ultrasound bath for 5 min and concentrated under reduced pressure and redistilled once with DMF. The residue was then taken up in 15 ml of dichloromethane, and 1990 mg (11.64 mmol) of benzyl bromide were added. The mixture was treated in an ultrasound bath for 15 min and then concentrated under reduced pressure. The residue was partitioned between ethyl acetate and water, and the organic phase was removed and extracted by shaking with saturated sodium chloride solution and then concentrated. The residue was then purified by preparative HPLC. This gave 1170 mg (80% of theory) of the Boc-protected intermediate.

[3226] Subsequently, these 1170 mg were deprotected immediately with 5 ml of trifluoroacetic acid in 15 ml of dichloromethane. After stirring at RT for 15 min, the reaction mixture was concentrated under reduced pressure. The residue was lyophilized from dioxane. After drying under high vacuum, there remained 1333 mg (84% of theory) of the title compound as a yellow oil.

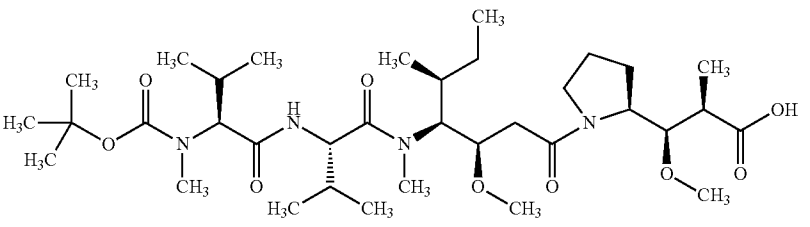
[3227] HPLC (Method 6): R_t=1.5 min;

[3228] LC-MS (Method 1): R_t=0.59 min; MS (ESIpos): m/z=278 $(M+H)^+$.

Intermediate 26

N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-2-carboxy-1-methoxypropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3229]



[3230] 1200 mg (2.33 mmol) of N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(2R,3S,4S)-1-carboxy-2-methoxy-4-methylhexan-3-yl]-N-methyl-L-valinamide (Intermediate 5) were combined with 910.8 mg (2.33 mmol) of benzyl (2R,3R)-3-methoxy-2-methyl-3-[(2S)-pyrrolidin-2-yl]propanoate trifluoroacetate (Intermediate 14), 1327 mg (3.49 mmol) of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and 2027 µl of N,N-diisopropylethylamine in 50 ml of DMF, and the mixture was stirred at RT for 5 min. Thereafter, the solvent was removed under reduced pressure. The remaining residue was taken up in ethyl acetate and extracted by shaking successively with 5% aqueous citric acid solution and saturated sodium hydrogencarbonate solution. The organic phase was removed and concentrated. The residue was purified by means of preparative HPLC. The product fractions were combined and concentrated, and the residue was dried under high vacuum. This gave 1000 mg (55% of theory) of the benzyl ester intermediate N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-(benzyloxy)-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide as a resin.

[3231] LC-MS (Method 1): R_t=1.56 min; MS (ESIpos): m/z=775 $(M+H)^+$.

[3232] The entire amount of this intermediate obtained was taken up in 25 ml of a mixture of methanol and dichloromethane (20:1), and the benzyl ester group was removed by hydrogenation under standard hydrogen pressure with 10% palladium on activated carbon as a catalyst. After stirring at RT for 30 min, the catalyst was filtered off and the filtrate was concentrated under reduced pressure. This gave 803 mg (91% of theory) of the title compound as a white solid.

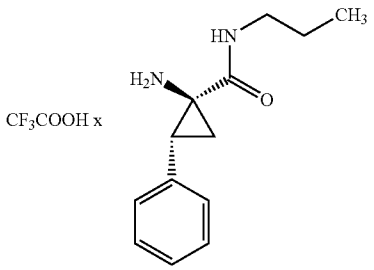
[3233] HPLC (Method 6): R_t=2.1 min;

[3234] LC-MS (Method 1): R_t=1.24 min; MS (ESIpos): m/z=685 $(M+H)^+$.

Intermediate 27

(1S,2R)-1-amino-2-phenyl-N-propylcyclopropanecarboxamide trifluoroacetate

[3235]



[3236] The title compound was prepared by coupling commercially available (1S,2R)-1-[(tert-butoxycarbonyl)amino]-2-phenylcyclopropanecarboxylic acid with n-propylamine in the presence of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) and subsequent Boc detachment with trifluoroacetic acid (yield: 85% of theory over both stages).

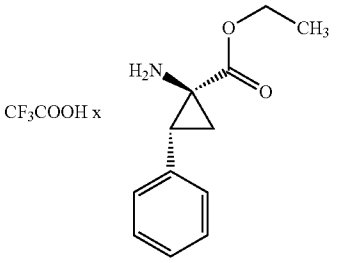
[3237] HPLC (Method 6): R_t=1.2 min;

[3238] LC-MS (Method 1): R_t=0.52 min; MS (ESIpos): m/z=219 $(M+H)^+$.

Intermediate 28

ethyl (1S,2R)-1-amino-2-phenylcyclopropanecarboxylate trifluoroacetate

[3239]



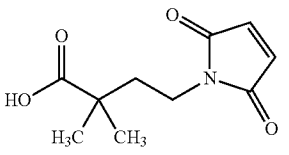
[3240] The title compound was prepared by standard methods, by esterifying commercially available (1S,2R)-1-[(tert-butoxycarbonyl)amino]-2-phenylcyclopropanecarboxylic acid with ethanol and subsequent Boc detachment with trifluoroacetic acid.

[3241] LC-MS (Method 1): R_t=0.50 min; MS (ESIpos): m/z=206 $(M+H)^+$.

Intermediate 29

4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-2,2-dimethylbutanoic acid

[3242]



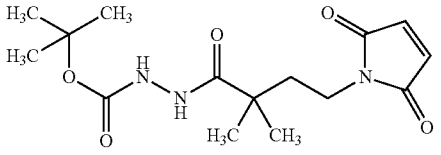
[3243] To a solution of 1.39 g (8.95 mmol) of N-methoxycarbonylmaleimide in 44 ml of saturated sodium hydrogencarbonate solution were added, at 0° C., 1.5 g (8.95 mmol) of 4-amino-2,2-dimethylbutyric acid, and the mixture was stirred for 40 min. Subsequently, the cooling bath was removed and the reaction mixture was stirred for a further 1 h. While cooling with ice, the reaction mixture was then adjusted to pH 3 by adding sulphuric acid, and extracted with ethyl acetate. The combined organic phases were dried over magnesium sulphate and concentrated. 1.17 g (79% purity, 49% of theory) of the title compound were obtained.

[3244] LC-MS (Method 1): R_t=0.64 min; m/z=212 $(M+H)^+$.

Intermediate 30

tert-butyl 2-[4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-2,2-dimethylbutanoyl]hydrazinecarboxylate

[3245]



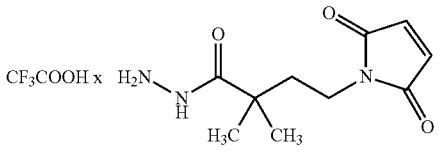
[3246] To a solution of 50 mg (237 μmol) of 4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-2,2-dimethylbutanoic acid in 2 ml of THF were added, at 0° C., first 26 μl (237 μmol) of 4-methylmorpholine and then 31 μl (237 μmol) of isobutyl chloroformate. After removing the cooling bath and stirring at RT for a further 15 min, 31.3 mg (237 μmol) of tert-butyloxycarbonyl hydrazide were added. The reaction mixture was stirred overnight and then concentrated. The residue was purified by preparative HPLC. 50.8 mg (66% of theory) of the title compound were obtained.

[3247] LC-MS (Method 1): R_t=0.71 min; m/z=324 $(M-H)^-$.

Intermediate 31

4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-2,2-dimethylbutanehydrazide trifluoroacetate

[3248]



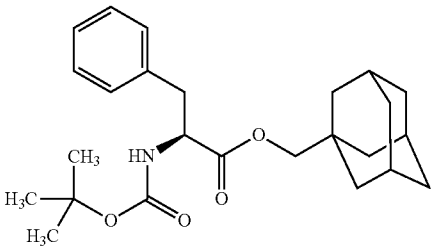
[3249] 50 mg (154 mmol) of tert-butyl 2-[4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-2,2-dimethylbutanoyl]hydrazinecarboxylate were dissolved in 2 ml of dichloromethane, and 0.4 ml of trifluoroacetic acid was added. The reaction mixture was stirred at RT for 30 min and then concentrated. 55.2 mg (93% purity, 99% of theory) of the title compound were obtained.

[3250] LC-MS (Method 1): R_t=0.36 min; m/z=226 $(M+H)^+$.

Intermediate 32

adamantan-1-ylmethyl N-(tert-butoxycarbonyl)-L-phenylalaninate

[3251]



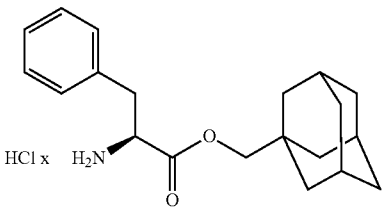
[3252] To a solution of 500 mg (1.89 mmol) of N-Boc-L-phenylalanine in 25 ml of dichloromethane were added, at RT, 1192 mg (6.2 mmol) of EDC, 578 μl (4.1 mmol) of triethylamine, 345 mg (2.8 mmol) of DMAP and 345 mg (2.1 mmol) of 1-adamantylmethanol. The reaction mixture was stirred overnight, then diluted with 50 ml of dichloromethane, and was successively washed with 10% aqueous citric acid solution, water and saturated sodium chloride solution. The organic phase was dried over magnesium sulphate, then concentrated, and the residue was purified by preparative HPLC. 769 mg (90% of theory) of the title compound were obtained.

[3253] LC-MS (Method 2): R_t=1.84 min; m/z=414 $(M+H)^+$.

Intermediate 33

adamantan-1-ylmethyl L-phenylalaninate hydrochloride

[3254]



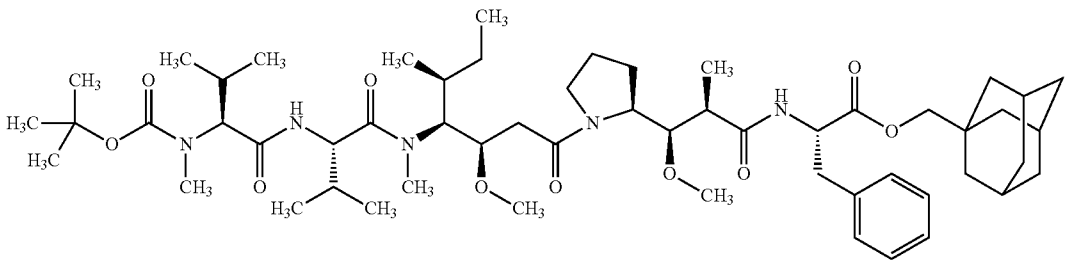
[3255] 769 mg (1.86 mmol) of adamantan-1-ylmethyl N-(tert-butoxycarbonyl)-L-phenylalaninate (Intermediate 13) were dissolved in 25 ml of a 4 N solution of hydrogen chloride in dioxane and stirred at RT for 1 h. Subsequently, the reaction mixture was concentrated and the residue was dried under reduced pressure. 619 mg (95% of theory) of the title compound were obtained.

[3256] LC-MS (Method 1): R_t=0.82 min; m/z=314 $(M+H)^+$.

Intermediate 34

N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(adamantan-1-ylmethoxy)-1-oxo-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3257]



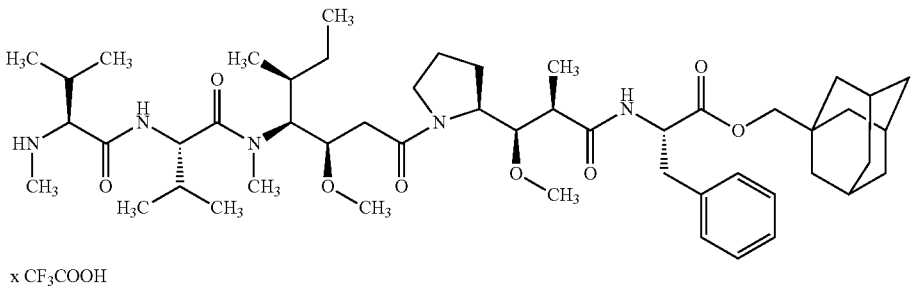
[3258] To a solution of 20 mg (29 μmol) of N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-2-carboxy-1-methoxypropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide in 1 ml of DMF were added, at RT, 15.3 μl (88 μmol) of N,N-diisopropylethylamine, 6.7 mg (44 μmol) of HOBt and 6.7 mg (35 mmol) of EDC, and the mixture was stirred for 30 min. Subsequently, 10.1 mg (32 μmol) of adamantan-1-yl L-phenylalaninate hydrochloride were added. After stirring overnight, the reaction mixture was separated directly into its components via preparative HPLC. 27.5 mg (93% of theory) of the title compound were obtained.

[3259] LC-MS (Method 1): R_t=1.70 min; m/z=980 $(M+H)^+$.

Intermediate 35

N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(adamantan-1-ylmethoxy)-1-oxo-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide trifluoroacetate

[3260]



x CF_3COOH

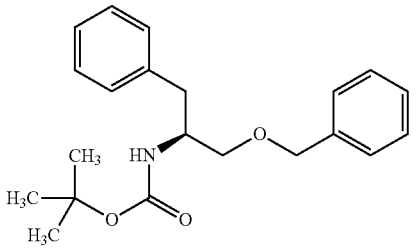
[3261] 27.5 mg (28 μmol) of N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(adamantan-1-ylmethoxy)-1-oxo-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide were dissolved in 1.8 ml of dichloromethane, and 361 μl of TFA were added. The reaction mixture was stirred for 30 min and then concentrated. The residue was taken up in water and lyophilized. 22.7 mg (81% of theory) of the title compound were obtained.

[3262] LC-MS (Method 1): R_t=1.14 min; m/z=880 $(M+H)^+$.

Intermediate 36

tert-butyl (2S)-1-(benzyloxy)-3-phenylpropan-2-yl carbamate

[3263]



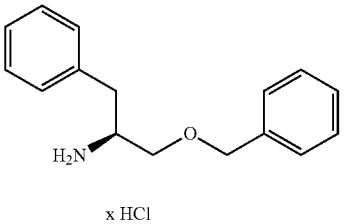
[3264] Under an argon atmosphere, 500 mg (1.99 mmol) of N-Boc-L-phenylalaninol were dissolved in 5 ml of DMF and cooled to 0° C. Subsequently, 159 mg (3.98 mmol) of a 60% suspension of sodium hydride in paraffin oil were added. The reaction mixture was stirred until the evolution of gas had ended and then 260 μl (2.19 mmol) of benzyl bromide were added. The cooling bath was removed and the reaction mixture was stirred at RT for 2 h. Thereafter, the reaction mixture was concentrated, the residue was taken up in ice-water and the mixture was extracted with dichloromethane. The organic phase was washed with saturated sodium chloride solution, dried over magnesium sulphate and concentrated. The residue was purified by means of preparative HPLC. 226 mg (33% of theory) of the title compound were obtained.

[3265] LC-MS (Method 1): R_t=1.28 min; m/z=342 $(M+H)^+$.

Intermediate 37

(2S)-1-(benzyloxy)-3-phenylpropan-2-amine hydrochloride

[3266]



x HCl

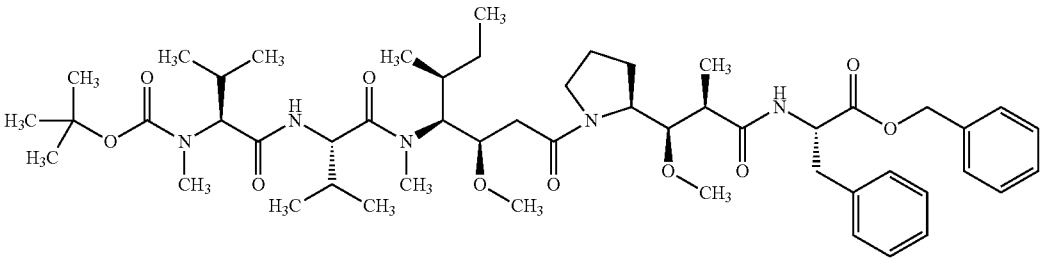
[3267] 220 mg (644 μmol) of tert-butyl (2S)-1-(benzyloxy)-3-phenylpropan-2-yl carbamate were dissolved in 11 ml of a 4 N solution of hydrogen chloride in dioxane and stirred at RT for 1 h. Then the reaction mixture was concentrated and the residue was dried under reduced pressure. 138 mg (77% of theory) of the title compound were obtained.

[3268] LC-MS (Method 1): R_t=0.65 min; m/z=242 $(M+H)^+$.

Intermediate 38

N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(benzyloxy)-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3269]



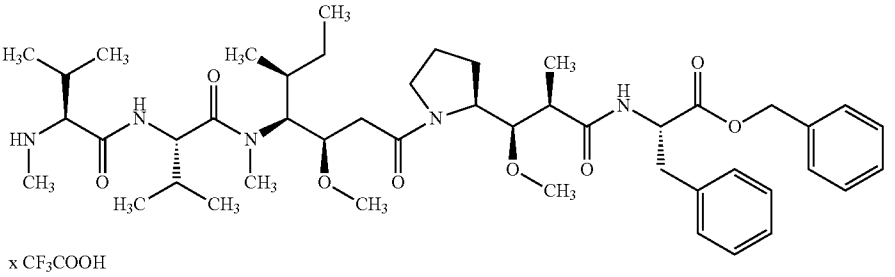
[3270] To a solution of 20 mg (29 μmol) of N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-2-carboxy-1-methoxypropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide in 1 ml of DMF were added, at RT, 15.3 μl (88 μmol) of N,N-diisopropylethylamine, 6.7 mg (44 μmol) of HOBt and 6.7 mg (35 mmol) of EDC, and the mixture was stirred for 30 min. Subsequently, 7.8 mg (32 μmol) of (2S)-1-(benzyloxy)-3-phenylpropan-2-amine hydrochloride were added. After stirring overnight, the reaction mixture was separated directly into its components via preparative HPLC. 26 mg (98% of theory) of the title compound were obtained.

[3271] LC-MS (Method 1): R_t=1.51 min; m/z=909 (M+H)+.

Intermediate 39

N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(benzyloxy)-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide trifluoroacetate

[3272]



x CF_3COOH

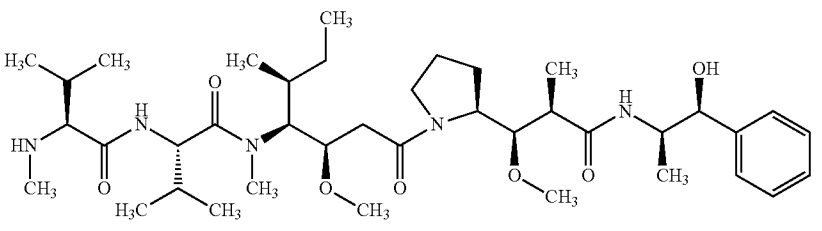
[3273] 26 mg (29 μmol) of N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(benzyloxy)-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide were dissolved in 1.8 ml of dichloromethane, and 370 μl of TFA were added. The reaction mixture was stirred at RT for 30 min and then concentrated. The residue was taken up in water and lyophilized. 26.4 mg (quant.) of the title compound were obtained.

[3274] LC-MS (Method 1): R_t=0.97 min; m/z=809 $(M+H)^+$.

Intermediate 40

N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(1S,2R)-1-hydroxy-1-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3275]



[3276] 50 mg (70 μmol) of Intermediate 26 and 11 mg (70 μmol) of (1S,2R)-2-amino-1-phenylpropan-1-ol in 10 ml of DMF were admixed with 42 mg (0.11 μmol) of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and 25 μl of N,N-diisopropylethylamine, and the reaction mixture was stirred at RT for 5 min. This was followed by concentration and purification of the residue by means of preparative HPLC. After combining the corresponding fractions, concentrating and drying under high vacuum, 49 mg (81%) of the protected intermediate were obtained. Subsequently, the Boc group was detached by known conditions with trifluoroacetic acid in dichloromethane. Concentration was followed by the purification of the title compound by preparative HPLC, and 26 mg (52%) of the title compound were obtained.

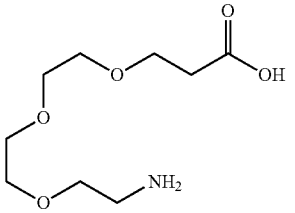
[3277] HPLC (Method 12): R_t=1.65 min;

[3278] LC-MS (Method 1): R_t=0.77 min; MS (ESIpos): m/z=718 $(M+H)^+$.

Intermediate 41

3-{2-[2-(2-aminoethoxy)ethoxy]ethoxy}propanoic acid trifluoroacetate

[3279]



x CF_3COOH

[3280] 150 mg (541 μmol) of tert-butyl 3-{2-[2-(2-aminoethoxy)ethoxy]ethoxy}propanoate were dissolved in 3 ml of dichloromethane, 1.5 ml of trifluoroacetic acid were added, and the reaction mixture was stirred at RT for 1 h, then concentrated.

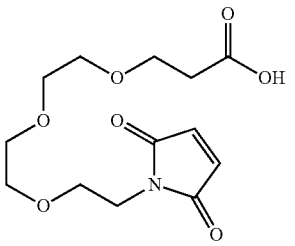
[3281] 181 mg (100% of theory) of the title compound were obtained.

[3282] MS (EI): m/z 222 $(M+H)^+$

Intermediate 42

3-(2-{2-[2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethoxy]ethoxy}ethoxy)propanoic acid

[3283]



[3284] 186 mg (555 μmol) of 3-{2-[2-(2-aminoethoxy)ethoxy]ethoxy}propanoic acid trifluoroacetate were dissolved in 2.6 ml of saturated sodium hydrogencarbonate solution and admixed at 0° C. with 86 mg (555 μmol) of N-methoxycarbonylmaleimide. The reaction mixture was stirred at 0° C. for 40 min and at RT for 1 h, then cooled again to 0° C., adjusted to pH 3 with sulphuric acid and extracted 3× with 25 ml of ethyl acetate. The combined organic phases were dried over magnesium sulphate and concentrated.

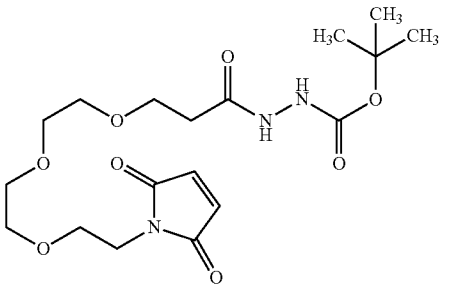
[3285] 126 mg (75% of theory) of the title compound were obtained.

[3286] LC-MS (Method 1): R_t=0.53 min; m/z=302 $(M+H)^+$.

Intermediate 43

tert-butyl 15-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-4-oxo-7,10,13-trioxa-2,3-diazapentadecan-1-oate

[3287]



[3288] 125 mg (417 μmol) of 3-(2-{2-[2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethoxy]ethoxy}ethoxy) propanoic acid were dissolved at 0° C. in 2.1 ml of THF and admixed with 46 μl (417 mmol) of 4-methylmorpholine and 54.5 μl (417 μmol) of isobutyl chloroformate. The ice bath was removed and the reaction mixture was stirred at RT for 30 min. Subsequently, at 0° C., 55 mg (417 μmol) of tert-butyloxycarbonyl hydrazide were added. The reaction mixture was warmed to RT overnight, concentrated and purified by preparative HPLC.

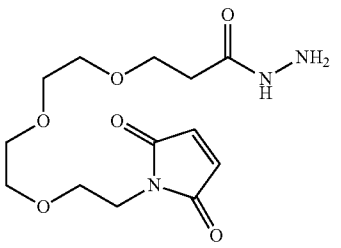
[3289] 60 mg (33% of theory) of the title compound were obtained.

[3290] LC-MS (Method 1): R_t=0.66 min; m/z=416 $(M+H)^+$.

Intermediate 44

3-(2-{2-[2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethoxy]ethoxy}ethoxy)propanehydrazide trifluoroacetate

[3291]



x CF_3COOH

[3292] 60 mg (145 μmol) of tert-butyl 15-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-4-oxo-7,10,13-trioxa-2,3-diazapentadecan-1-oate were dissolved in 1 ml of dichloromethane, and 0.2 ml of trifluoroacetic acid was added. The reaction mixture was stirred at RT for 30 min and then concentrated.

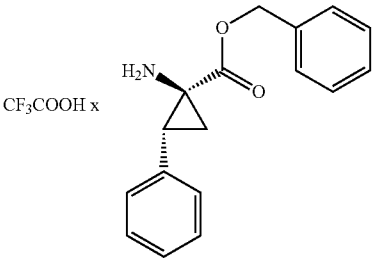
[3293] 62 mg (100% of theory) of the title compound were obtained.

[3294] LC-MS (Method 1): R_t=0.35 min; m/z=316 $(M+H)^+$.

Intermediate 45

benzyl (1S,2R)-1-amino-2-phenylcyclopropanecarboxylate trifluoroacetate

[3295]



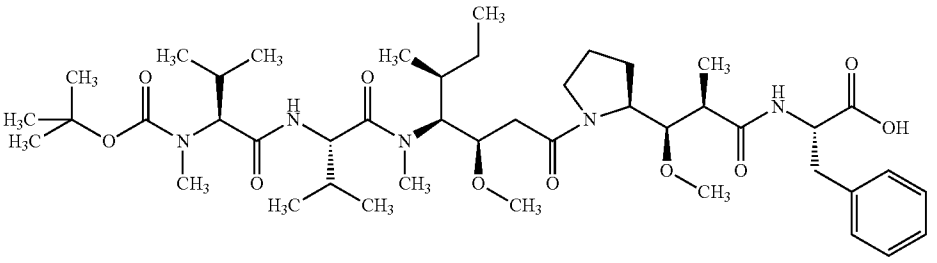
[3296] The title compound was prepared by standard methods, by esterifying commercially available (1S,2R)-1-[(tert-butoxycarbonyl)amino]-2-phenylcyclopropanecarboxylic acid with benzyl alcohol and subsequent Boc detachment with trifluoroacetic acid.

[3297] LC-MS (Method 1): R_t=0.72 min; MS (ESIpos): m/z=268 $(M+H)^+$.

Intermediate 46

N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(1S)-1-carboxy-2-phenylethyl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3298]



[3299] 383 mg (0.743 mmol) of N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(2R,3S,4S)-1-carboxy-2-methoxy-4-methylhexan-3-yl]-N-methyl-L-valinamide (Intermediate 8) were combined with 485 mg (0.743 mmol) of benzyl N-{(2R,3R)-3-methoxy-2-methyl-3-[(2S)-pyrrolidin-2-yl]propanoyl}-L-phenylalaninate trifluoroacetate (Intermediate 12), 424 mg (1.114 mmol) of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and 388 μl of N,N-diisopropylethylamine in 15 ml of DMF, and the mixture was stirred at RT for 10 min. Subsequently, the solvent was removed under reduced pressure. The remaining residue was taken up in ethyl acetate and extracted by shaking successively with 5% aqueous citric acid solution and saturated sodium hydrogencarbonate solution. The organic phase was removed and concentrated, and the residue was purified by means of preparative HPLC. The product fractions were combined and concentrated, and the residue was dried under high vacuum. 335 mg (48% of theory) of the benzyl ester intermediate were obtained as a foam.

[3300] LC-MS (Method 1): R_t=1.49 min; MS (ESIpos): m/z=922 $(M+H)^+$.

[3301] 100 mg (0.11 mmol) of this intermediate were taken up in 15 ml of methanol and the benzyl ester group was removed by hydrogenation under standard hydrogen pressure with 10% palladium on activated carbon as a catalyst. After stirring at RT for 1 h, the catalyst was filtered off and the filtrate was concentrated under reduced pressure. After lyophilization from dioxane, 85 mg (94% of theory) of the title compound were obtained as a solid.

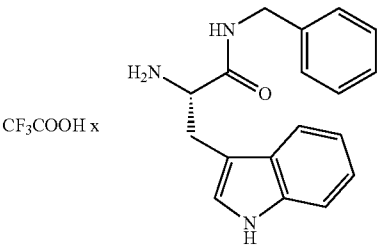
[3302] HPLC (Method 12): R_t=2.4 min;

[3303] LC-MS (Method 1): R_t=1.24 min; MS (ESIpos): m/z=832 $(M+H)^+$.

Intermediate 47

N-benzyl-L-tryptophanamide trifluoroacetate

[3304]



[3305] 202 mg (0.5 mmol) of 2,5-dioxopyrrolidin-1-yl N-(tert-butoxycarbonyl)-L-tryptophanate and 45 mg (0.42 mmol) of benzylamine were dissolved in 10 ml of DMF, and 110 μl (630 μmol) of N,N-diisopropylethylamine were added. The reaction mixture was stirred at RT for 3 h. Subsequently,

the reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (eluent: 20:0.5:0.05 dichloromethane/methanol/17% aq. ammonia). The corresponding fractions were combined and concentrated. The resulting residue was digested with diethyl ether and then dried under high vacuum. Subsequently, this residue was taken up in 10 ml of dichloromethane, and 3 ml of anhydrous trifluoroacetic acid were added. After stirring at RT for 45 minutes, the mixture was concentrated and the residue was purified by preparative HPLC. After drying under high vacuum, 117 mg (57% of theory over both stages) of the title compound were obtained.

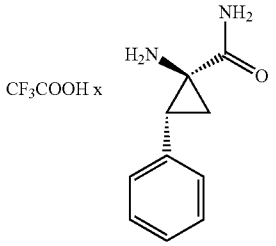
[3306] HPLC (Method 12): R_t=1.6 min;

[3307] LC-MS (Method 1): R_t=0.66 min; MS (ESIpos): m/z=294 $(M+H)^+$.

Intermediate 48

(1S,2R)-1-amino-2-phenylcyclopropanecarboxamide trifluoroacetate

[3308]



[3309] 50 mg (180 μmol) of commercially available (1S,2R)-1-[(tert-butoxycarbonyl)amino]-2-phenylcyclopropanecarboxylic acid were dissolved in 5 ml of DMF, 94 μl (541 μmol) of N,N-diisopropylethylamine, 31 mg (270 μmol) of N-hydroxysuccinimide and 41.5 mg (216 μmol) of EDC were added, and then the mixture was stirred at RT overnight. The reaction mixture was then concentrated, the residue was taken up in dioxane, 71 mg (901 μmol) of ammonium hydrogencarbonate were added, and the reaction mixture was then left to stand at RT for 3 days. The reaction mixture was then diluted with a 1:1 mixture of ethyl acetate and water. The organic phase was removed, dried over magnesium sulphate and concentrated. The resulting residue was subsequently taken up in 3 ml of dichloromethane, and 3 ml of anhydrous trifluoroacetic acid were added. Stirring at RT for 1 h was followed by concentration. The residue was stirred with pentane, filtered off with suction and lyophilized from dioxane. In this way, 32 mg (62% of theory over both stages) of the title compound were obtained.

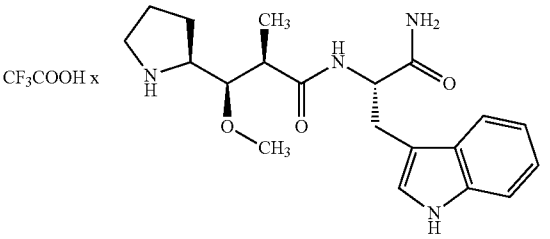
[3310] HPLC (Method 6): R_t=0.38 min;

[3311] LC-MS (Method 1): R_t=0.20 min; MS (ESIpos): m/z=177 $(M+H)^+$.

Intermediate 49

N^{α}-{(2R,3R)-3-methoxy-2-methyl-3-[(2S)-pyrrolidin-2-yl]propanoyl}-L-tryptophanamide trifluoroacetate

[3312]



[3313] The title compound was prepared in analogy to the synthesis of Intermediate 13 from Starting Compound 1 and L-tryptophanamide hydrochloride.

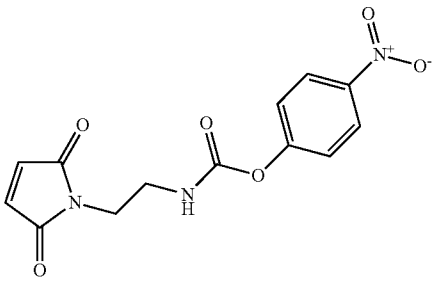
[3314] HPLC (Method 5): R_t=1.4 min;

[3315] LC-MS (Method 1): R_t=0.92 min; MS (ESIpos): m/z=473 $(M+H)^+$.

Intermediate 50

4-nitrophenyl 2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethyl carbamate

[3316]



[3317] 813 mg (3.1 mmol) of triphenylphosphine were dissolved in 25 ml of THF and cooled to −70° C. under argon. After dropwise addition of 627 mg (3.1 mmol) of diisopropyl azodicarboxylate, the mixture was stirred for 5 min. Subsequently, 500 mg (3.1 mmol) of tert-butyl 2-aminoethyl carbamate dissolved in 5 ml of THF were added dropwise, and the reaction mixture was stirred at −70° C. for a further 5 min. Then 136.6 mg (1.55 mmol) of 2,2-dimethyl-1-propanol dissolved in 1 ml of THF and 301 mg (3.1 mmol) of maleimide were added, the reaction mixture was stirred at −70° C. for a further 10 min and then the mixture was warmed to RT. After stirring at RT for a further 16 h, the solvent was removed under reduced pressure and the residue was purified by means of preparative HPLC. This gave 463 mg (62%) of the protected intermediate.

[3318] After removing the Boc protecting group under standard conditions, 652 mg of 1-(2-aminoethyl)-1H-pyrrole-2,5-dione were obtained as the trifluoroacetate.

[3319] 112.9 mg (543 μmol) of nitrophenyl chloroformate were dissolved in 30 ml of THF and, after addition of 100 mg (271.6 μmol) of 1-(2-aminoethyl)-1H-pyrrole-2,5-dione trifluoroacetate, the mixture was stirred at RT for 30 min. The mixture was filtered and the filtrate was concentrated to dryness and then slurried with diethyl ether. After filtration with suction and drying, 60 mg (95% of theory) of the title compound were obtained.

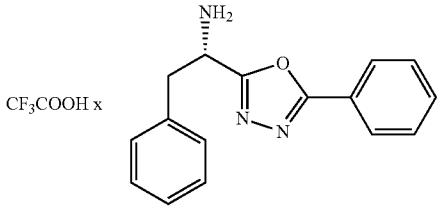
[3320] HPLC (Method 5): R_t=0.65 min;

[3321] LC-MS (Method 1): R_t=0.74 min; MS (ESIpos): m/z=306 $(M+H)^+$.

Intermediate 51

(1S)-2-phenyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl) ethanamine trifluoroacetate

[3322]



[3323] 200 mg (0.75 mmol) of N-(tert-butoxycarbonyl)-L-phenylalanine were initially charged at 0° C. in 5.5 ml of dichloromethane, and 128 mg (0.79 mmol) of 1,1'-carbonyldiimidazole were added. After 30 min, 103 mg (0.75 mmol) of benzoyl hydrazide were added. After a further 45 min at 0° C., 500 mg (1.5 mmol) of carbon tetrabromide and 395 mg (1.5 mmol) of triphenylphosphine were finally added. The reaction mixture was stirred first at 0° C. for 2 h and then at RT overnight. The mixture was subsequently concentrated on a rotary evaporator, and the residue was dried under high vacuum. The crude product thus obtained was purified by means of preparative HPLC. 217 mg (78% of theory) of the Boc-protected intermediate tert-butyl (1S)-2-phenyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl carbamate were obtained.

[3324] LC-MS (Method 12): R_t=1.15 min; MS (ESIpos): m/z=366 $(M+H)^+$

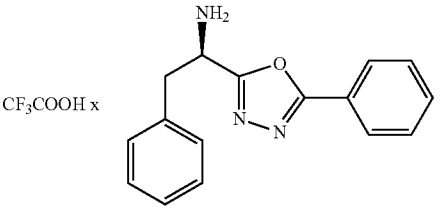
[3325] 217 mg (0.59 mmol) of this intermediate were taken up in 3 ml of dichloromethane, 0.6 ml of trifluoroacetic acid were added, and the mixture was stirred at RT for 30 min. Subsequently, the reaction mixture was concentrated under reduced pressure. The remaining residue was the reaction mixture dried further under reduced pressure and then lyophilized from dioxane. In this way, 214 mg (90% of theory) of the title compound were obtained.

[3326] LC-MS (Method 11): R_t=0.62 min; MS (ESIpos): m/z=266 $(M+H)^+$

Intermediate 52

(1R)-2-phenyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl) ethanamine trifluoroacetate

[3327]



[3328] 200 mg (0.75 mmol) of N-(tert-butoxycarbonyl)-D-phenylalanine were initially charged at 0° C. in 5.5 ml of dichloromethane, and 128.3 mg (0.79 mmol) of 1,1'-carbonyldiimidazole were added. After 30 min, 103 mg (0.75 mmol) of benzoyl hydrazide were added. After a further 45 min at 0° C., 500 mg (1.5 mmol) of carbon tetrabromide and 395 mg (1.5 mmol) of triphenylphosphine were finally added. The reaction mixture was stirred first at 0° C. for 2 h and then at RT overnight. The mixture was subsequently concentrated on a rotary evaporator, and the residue was dried under high vacuum. The crude product thus obtained was purified by means of preparative HPLC. 219 mg (80% of theory) of the Boc-protected intermediate tert-butyl (1R)-2-phenyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl carbamate were obtained.

[3329] LC-MS (Method 2): R_t=1.36 min; MS (ESIpos): m/z=366 $(M+H)^+$

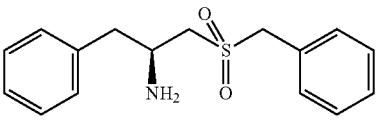
[3330] 219 mg (0.6 mmol) of this intermediate were taken up in 3 ml of dichloromethane, 0.6 ml of trifluoroacetic acid were added, and the mixture was stirred at RT for 30 min. Subsequently, the reaction mixture was concentrated under reduced pressure. The remaining residue was the reaction mixture dried further under reduced pressure and then lyophilized from dioxane. In this way, 196 mg (86% of theory) of the title compound were obtained as a solid.

[3331] HPLC (Method 10): R_t=2.41 min

Intermediate 53

(2S)-1-(benzylsulphonyl)-3-phenylpropan-2-amine

[3332]



[3333] 200 mg (1.13 mmol) of (4S)-4-benzyl-1,3-oxazolidin-2-one were initially charged in 3 ml of tert-butanol, and 280 mg (2.26 mmol) of benzyl mercaptan were added. The mixture was subsequently heated under reflux for 2 days. Thereafter, the reaction mixture was concentrated on a rotary evaporator and the resulting (2S)-1-(benzylsulphanyl)-3-phenylpropan-2-amine intermediate was converted further directly, without workup.

[3334] HPLC (Method 10): R_t=2.63 min

[3335] LC-MS (Method 1): R_t=0.67 min; MS (ESIpos): m/z=258 (M+H)+

[3336] The crude intermediate obtained above was dissolved in a solution of 2 ml of 30% hydrogen peroxide and 5 ml of formic acid, and the mixture was stirred at RT for 12 h. Then the reaction mixture was added to saturated sodium sulphate solution and extracted three times with ethyl acetate. The organic phase was dried over magnesium sulphate and concentrated under reduced pressure. The crude product obtained was purified by means of preparative HPLC. 343 mg (61% of theory) of the title compound were thus obtained.

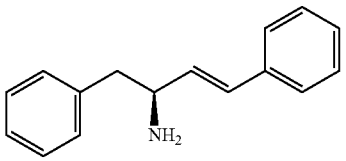
[3337] HPLC (Method 10): R_t=2.40 min;

[3338] LC-MS (Method 12): R_t=0.65 min; MS (ESIpos): m/z=290 (M+H)+

Intermediate 54

(2S,3E)-1,4-diphenylbut-3-en-2-amine

[3339]



[3340] 552.7 mg (9.85 mmol) of potassium hydroxide were dissolved in methanol, adsorbed onto 1.1 g of neutral aluminium oxide and then dried under high vacuum. To a solution of 240 mg (0.82 mmol) of (2S)-1-(benzylsulphonyl)-3-phenylpropan-2-amine and 1.56 g of the potassium hydroxide on aluminium oxide thus prepared in 6.2 ml of n-butanol were added dropwise, at 5-10° C., 307 μl (3.3 mmol) of dibromodifluoromethane. The reaction mixture was stirred at RT for 2 h, then filtered through Celite, and the residue was washed thoroughly with dichloromethane. The filtrate was concentrated and the resulting residue was dried under reduced pressure. The crude product thus obtained was purified by means of preparative HPLC. 98 mg (35% of theory) of the title compound were obtained with an E/Z diastereomer ratio of 4:1.

[3341] HPLC (Method 10): R_t=2.46 min;

[3342] LC-MS (Method 12): R_t=0.75 min; MS (ESIpos): m/z=224 $(M+H)^+$

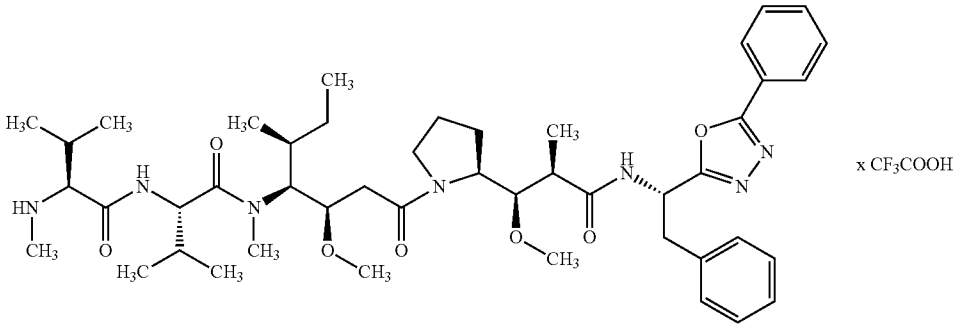
[3343] The E/Z diastereomer mixture obtained above was dissolved in 2 ml of ethanol and 0.2 ml of N,N-diisopropylethylamine, and separated by means of HPLC on chiral phase [column: Daicel Chiralpak AD-H, 5 μm 250 mm×20 mm, eluent: hexane/(ethanol+0.2% diethylamine) 50:50 v/v; UV detection: 220 nm; temperature: 30° C.]. The appropriate fractions were concentrated on a rotary evaporator, and the residue was dried under reduced pressure. 45 mg of the title compound were obtained.

[3344] ^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]=2.62-2.83 (m, 2H) 3.52-3.71 (m, 1H) 6.18-6.30 (m, 1H) 6.34-6.46 (m, 1H) 6.98-7.57 (m, 10H) [further signals hidden under solvent peaks].

Intermediate 55

N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(1S)-2-phenyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide trifluoroacetate

[3345]



[3346] 20 mg (29 μmol) of N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-2-carboxy-1-methoxypropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide were dissolved in 1 ml of DMF, 13.3 mg (35 μmol) of HATU and 15.3 μl (88 μmol) of N,N-diisopropylethylamine were added, and the mixture was stirred at RT for 30 min. Subsequently, 12.2 mg (32 μmol) of (1S)-2-phenyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethanamine trifluoroacetate were added. The reaction mixture was stirred at RT overnight and then separated by preparative HPLC. This gave 22 mg (81% of theory) of N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(1S)-2-phenyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide.

[3347] LC-MS (Method 12): R_t=1.45 min; MS (ESIpos): m/z=933 $(M+H)^+$

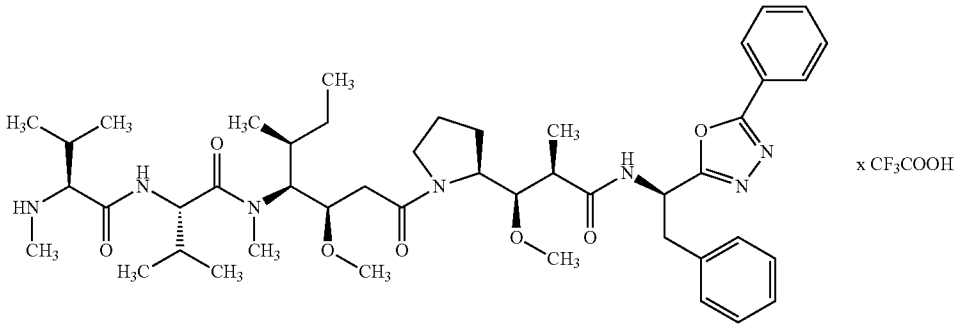
[3348] By subsequently detaching the BOC protecting group with trifluoroacetic acid, 22.4 mg (98% of theory) of the title compound were then obtained.

[3349] LC-MS (Method 11): R_t=0.85 min; MS (ESIpos): m/z=833 $(M+H)^+$

Intermediate 56

N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(1R)-2-phenyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide trifluoroacetate

[3350]



[3351] N-(tert-Butoxycarbonyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(1R)-2-phenyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide was prepared in analogy to the synthesis of Intermediate 55, by reaction of 20 mg (29 µmol) of N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-2-carboxy-1-methoxypropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide with 12.2 mg (32 µmol) of (1R)-2-phenyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethanamine trifluoroacetate.

[3352] Yield: 17 mg (64% of theory)

[3353] HPLC (Method 10): R_t=3.74 min;

[3354] LC-MS (Method 1): R_t=1.45 min; MS (ESIpos): m/z=933 $(M+H)^+$

[3355] By subsequently detaching the BOC protecting group with trifluoroacetic acid, 17.1 mg (99% of theory) of the title compound were then obtained.

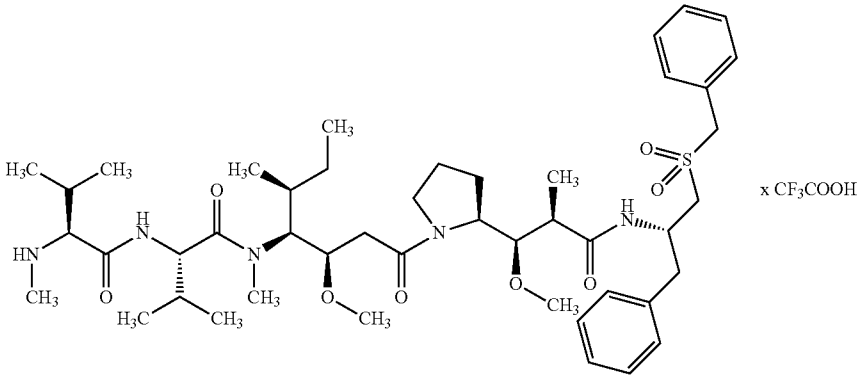
[3356] HPLC (Method 10): R_t=2.55 min;

[3357] LC-MS (Method 11): R_t=0.85 min; MS (ESIpos): m/z=833 $(M+H)^+$

Intermediate 57

N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(benzylsulphonyl)-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide trifluoroacetate

[3358]



[3359] N-(tert-Butoxycarbonyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(benzylsulphonyl)-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide was prepared in analogy to the synthesis of Intermediate 55, by reaction of 20 mg (29 μmol) of N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-2-carboxy-1-methoxypropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide with 9.3 mg (20 μmol) of (2S)-1-(benzylsulphonyl)-3-phenylpropan-2-amine.

[3360] Yield: 19.2 mg (68% of theory)

[3361] HPLC (Method 10): R_t=3.5 min;

[3362] LC-MS (Method 12): R_t=1.41 min; MS (ESIpos): m/z=957 $(M+H)^+$

[3363] By subsequently detaching the BOC protecting group with trifluoroacetic acid, 19.3 mg (99% of theory) of the title compound were then obtained.

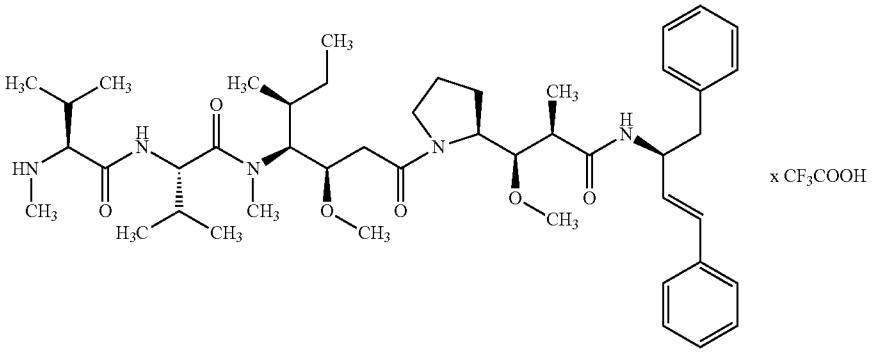
[3364] HPLC (Method 10): R_t=2.52 min;

[3365] LC-MS (Method 1): R_t=0.86 min; MS (ESIpos): m/z=857 (M+H)+

Intermediate 58

N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S,3E)-1,4-diphenylbut-3-en-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide trifluoroacetate

[3366]



[3367] N-(tert-Butoxycarbonyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S,3E)-1,4-diphenylbut-3-en-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide was prepared in analogy to the synthesis of Intermediate 55, by reaction of 20 mg (29 μmol) N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-2-carboxy-1-methoxypropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide with 7.1 mg (32 μmol) of (2S,3E)-1,4-diphenylbut-3-en-2-amine.

[3368] Yield: 15.1 mg (58% of theory)

[3369] HPLC (Method 10): R_t=4.2 min;

[3370] LC-MS (Method 12): R_t=1.51 min; MS (ESIpos): m/z=891 (M+H)+

[3371] By subsequently detaching the BOC protecting group with trifluoroacetic acid, 15.7 mg (99% of theory) of the title compound were then obtained.

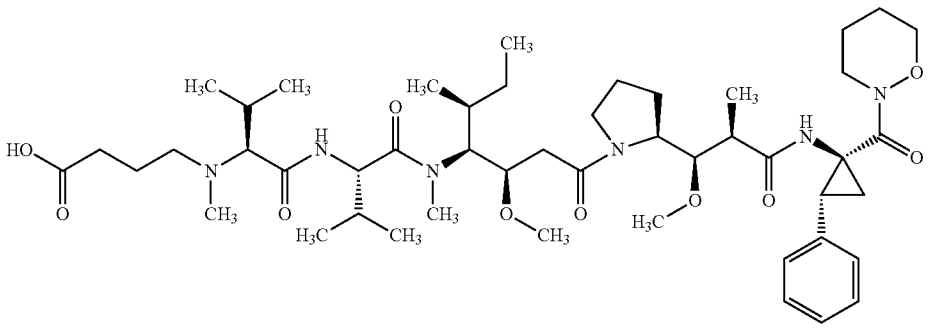
[3372] HPLC (Method 10): R_t=2.62 min;

[3373] LC-MS (Method 12): R_t=0.97 min; MS (ESIpos): m/z=791 (M+H)+

Intermediate 61

N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3374]



[3375] 50 mg (0.054 mmol) of N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide trifluoroacetate (Intermediate 16) were dissolved in 8 ml of dioxane/water, and 70 ml (0.108 mmol) of a 15% solution of 4-oxobutanoic acid in water were added. The reaction mixture was subsequently stirred at 100° C. for 1 h. After cooling to RT, 3.7 mg (0.059 mmol) of sodium cyanoborohydride were added and the mixture was adjusted to a pH of 3 by adding about 300 μl of 0.1 N hydrochloric acid. The reaction mixture was then stirred at 100° C. for a further 2 h. After cooling, another 70 ml (0.108 mmol) of the 15% 4-oxobutanoic acid solution were added and the reaction mixture was again stirred at 100° C. for 1 h. Then a further 3.7 mg (0.059 mmol) of sodium cyanoborohydride were added and about 300 μl of 0.1 N hydrochloric acid were subsequently used to adjust the pH back to 3. The reaction mixture was then stirred at 100° C. for another 2 h. In the event of conversion still being incomplete, this procedure was repeated for a third time. The reaction mixture was finally concentrated and the residue was purified by means of preparative HPLC. In this way, 32 mg (65% of theory) of the title compound were obtained in the form of a colourless foam.

[3376] HPLC (Method 5): R_t=1.64 min;

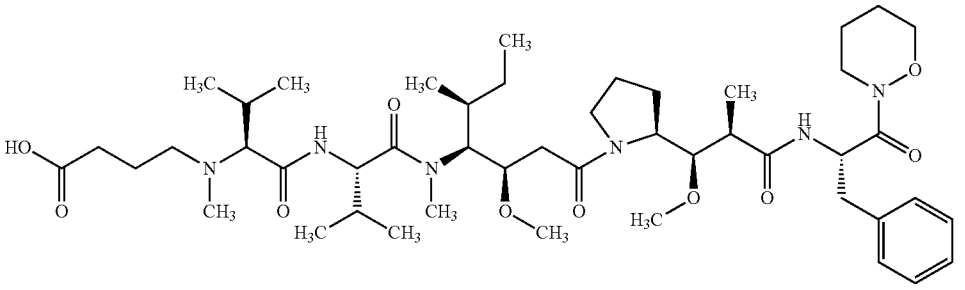
[3377] LC-MS (Method 9): R_t=4.76 min; MS (ESIpos): m/z=899 $(M+H)^+$

[3378] ^{1}H NMR (500 MHz, DMSO-d_6): δ=8.95 and 8.8 (2m, 1H), 8.88 and 8.65 (2s, 1H), 7.4-7.1 (m, 5H), 5.0, 4.78, 4.65 and 4.55 (4m, 2H), 4.1-3.7 (m, 5H), 3.32, 3.29, 3.20, 3.12, 3.1 and 3.0 (6s, 9H), 2.75 (m, 2H), 2.63 (t, 1H), 2.4-2.2 (m, 4H), 2.1-1.2 (m, 12H), 1.2-0.8 (m, 16H), 0.75 (m, 3H) [further signals hidden under H_2O and DMSO peaks].

Intermediate 62

N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(2S)-1-(1,2-oxazinan-2-yl)-1-oxo-3-phenylpropan-2-yl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3379]



[3380] The title compound was prepared in analogy to the synthesis of Intermediate 61, by reaction of 50 mg of N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(2S)-1-(1,2-oxazinan-2-yl)-1-oxo-3-phenylpropan-2-yl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide trifluoroacetate (Intermediate 14) with 4-oxobutanoic acid.

[3381] Yield: 34 mg (70% of theory)

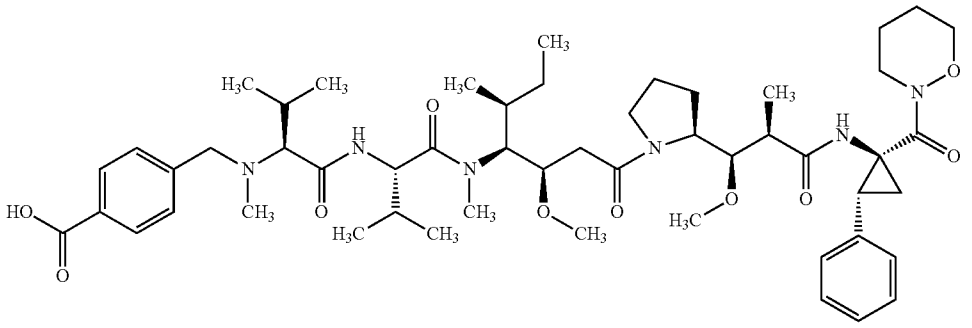
[3382] HPLC (Method 5): R_t=1.64 min;

[3383] LC-MS (Method 9): R_t=4.77 min; MS (ESIpos): m/z=887 $(M+H)^+$.

Intermediate 63

N-(4-carboxybenzyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3384]



[3385] The title compound was prepared in analogy to the synthesis of Intermediate 61, by reaction of 15 mg of N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide trifluoroacetate (Intermediate 16) with 4-formylbenzoic acid.

[3386] Yield: 7.5 mg (48% of theory)

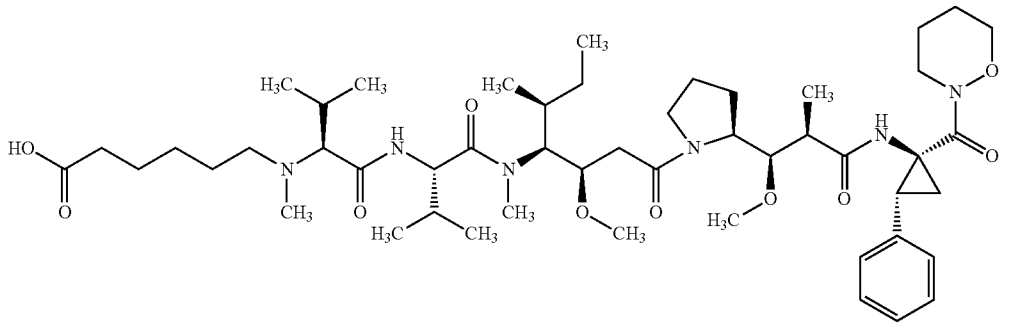
[3387] HPLC (Method 5): R_t=1.75 min;

[3388] LC-MS (Method 1): R_t=0.97 min; MS (ESIpos): m/z=947 $(M+H)^+$.

Intermediate 64

N-(5-carboxypentyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3389]



[3390] 10 mg (0.011 mmol) of N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide trifluoroacetate (Intermediate 16) were dissolved in 2 ml of dioxane/water, and 2.8 mg (0.022 mmol) of 6-oxohexanoic acid were added. The reaction mixture was subsequently stirred at 100° C. for 1 h. After cooling to RT, 0.75 mg (0.012 mmol) of sodium cyanoborohydride was added and the mixture was adjusted to a pH of 3 by adding 0.1 N hydrochloric acid. The reaction mixture was then stirred at 100° C. for a further hour. After cooling, another 2.8 mg (0.022 mmol) of 6-oxohexanoic acid were added and the reaction mixture was again stirred at 100° C. for 1 h. A further 0.75 mg (0.012 mmol) of sodium cyanoborohydride was added and 0.1 N hydrochloric acid was subsequently used to adjust the pH back to 3. The reaction mixture was then stirred at 100° C. for another 1 h. This procedure was then repeated for a third time. The reaction mixture was finally concentrated and the crude product was purified by means of preparative HPLC. This gave 6.4 mg (64% of theory) of the title compound in the form of a colourless foam.

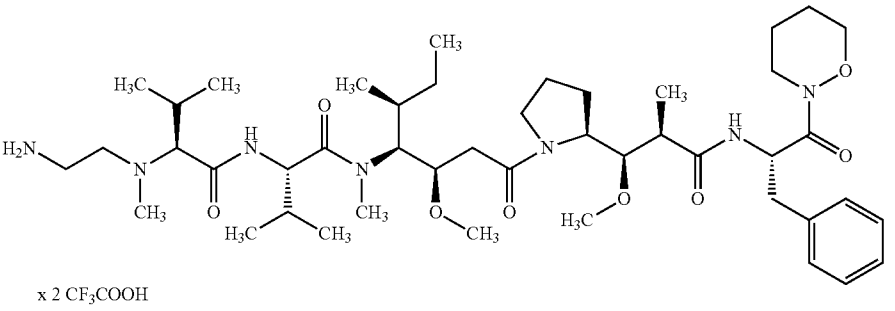
[3391] HPLC (Method 5): R_t=1.68 min;

[3392] LC-MS (Method 9): R_t=4.86 min; MS (ESIpos): m/z=927 $(M+H)^+$.

Intermediate 65

N-(2-aminoethyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(2S)-1-(1,2-oxazinan-2-yl)-1-oxo-3-phenylpropan-2-yl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide bistrifluoroacetate

[3393]



[3394] The title compound was prepared by reaction of 68 mg of N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(2S)-1-(1,2-oxazinan-2-yl)-1-oxo-3-phenylpropan-2-yl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide trifluoroacetate (Intermediate 14) with tert-butyl 2-oxoethyl carbamate and subsequent detachment of the Boc protecting group with trifluoroacetic acid.

[3395] Yield: 49 mg (62% of theory over two stages)

[3396] HPLC (Method 5): R_t=1.58 min;

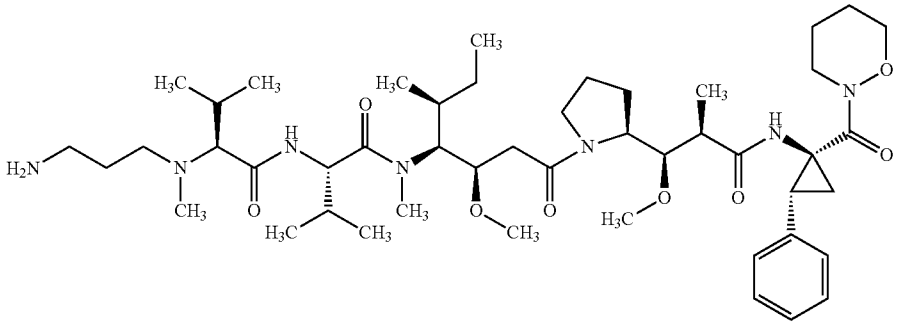
[3397] LC-MS (Method 2): R_t=1.05 min; MS (ESIpos): m/z=844 $(M+H)^+$

[3398] ^{1}H NMR (600 MHz, DMSO-d_6): δ=8.25 (m, 1H), 8.45 and 8.15 (2d, 1H), 7.65-7.55 (m, 3H), 7.23-7.1 (m, 5H), 5.12 and 4.95 (2m, 1H), 4.72 and 4.62 (2m, 1H), 4.6 and 4.52 (2t, 1H), 4.2-3.8 (m, 4H), 3.7 (d, 1H), 3.23, 3.20, 3.19, 3.18, 3.03 and 2.98 (6s, 9H), 3.0-2.7 (m, 6H), 2.4-1.2 (m, 15H), 1.05, 1.0, 0.88 and 0.82 (4d, 6H), 0.92 (m, 6H), 0.73 (m, 6H) [further signals hidden under H_2O peak].

Intermediate 66

N-(3-aminopropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3399]



[3400] The title compound was prepared in analogy to the synthesis of Intermediate 65, by reaction of 25 mg (0.027 mmol) of N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide trifluoroacetate (Intermediate 16) with benzyl 3-oxopropyl carbamate and subsequent hydrogenolytic detachment of the Z protecting group (with 10% palladium on charcoal as a catalyst, in ethanol as a solvent).

[3401] Yield: 11 mg (41% of theory over two stages)

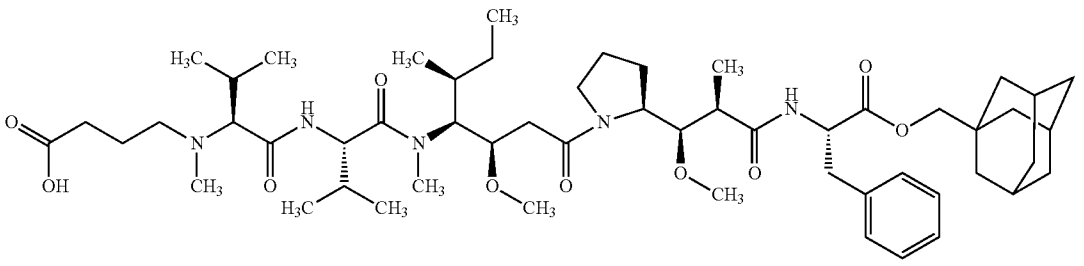
[3402] HPLC (Method 5): R_t=1.53 min;

[3403] LC-MS (Method 1): R_t=0.72 min; MS (ESIpos): m/z=870 $(M+H)^+$.

Intermediate 67

N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(adamantan-1-ylmethoxy)-1-oxo-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3404]



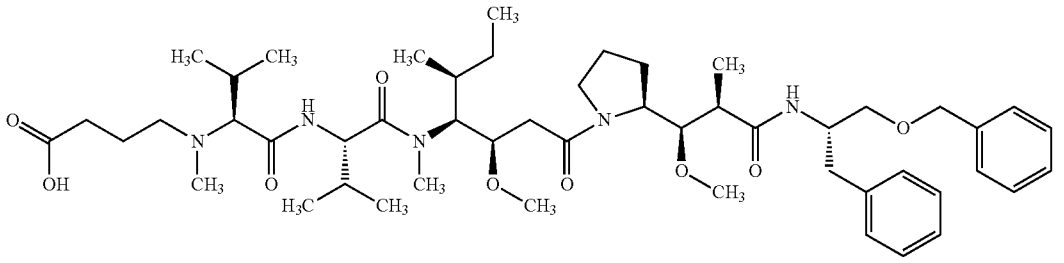
[3405] 26 mg (26 μmol) of N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(adamantan-1-ylmethoxy)-1-oxo-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide trifluoroacetate and 33.9 μl of a 15% aqueous succinaldehydic acid solution (53 μmol) were dissolved in 957 μl of a 1:1-dioxane/water mixture and heated to 100° C. for 1 h. After brief cooling, 1.81 mg (29 μmol) of sodium cyanoborohydride were added. The reaction mixture was adjusted to pH 3 by adding 0.1 N hydrochloric acid and the mixture was heated to 100° C. for a further 2 h. After again adding the same amounts of succinaldehydic acid solution, sodium cyanoborohydride and hydrochloric acid, the mixture was heated once again to 100° C. for 2 h. The reaction mixture was then separated directly into its components by means of preparative HPLC. 18.5 mg (73% of theory) of the title compound were thus obtained.

[3406] LC-MS (Method 1): R_t=1.17 min; m/z=967 $(M+H)^+$.

Intermediate 68

N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(benzyloxy)-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3407]



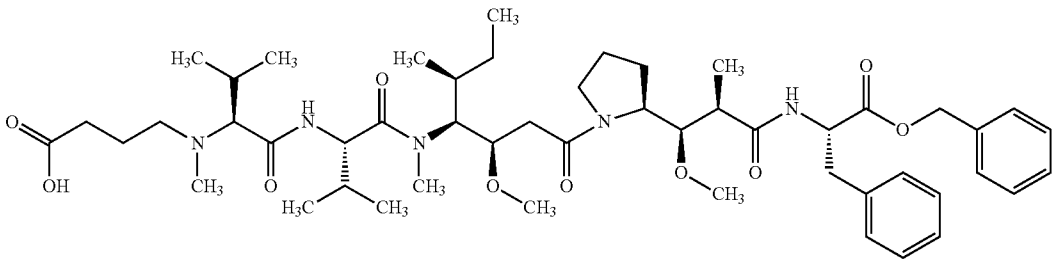
[3408] mg (26 μmol) of N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(benzyloxy)-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide trifluoroacetate and 33.7 μl of a 15% aqueous succinaldehydic acid solution (52 μmol) were dissolved in 953 μl of a 1:1-dioxane/water mixture and heated to 100° C. for 1 h. After brief cooling, 1.80 mg (29 mmol) of sodium cyanoborohydride were added. The reaction mixture was adjusted to pH 3 by adding 0.1 N hydrochloric acid and the mixture was heated to 100° C. for a further 2 h. After again adding the same amounts of succinaldehydic acid solution, sodium cyanoborohydride and hydrochloric acid, the mixture was heated once again to 100° C. for 2 h. The reaction mixture was then separated directly into its components by means of preparative HPLC. 15.2 mg (65% of theory) of the title compound were thus obtained.

[3409] LC-MS (Method 1): R_t=1.01 min; m/z=895 $(M+H)^+$

Intermediate 69

N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(benzyloxy)-1-oxo-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3410]



[3411] 53 mg (84 μmol) of N-[(9H-fluoren-9-ylmethoxy) carbonyl]-N-methyl-L-valyl-N-[(2R,3S,4S)-1-carboxy-2-methoxy-4-methylhexan-3-yl]-N-methyl-L-valinamide (Intermediate 4) and 45 mg (84 μmol) of benzyl N-{(2R,3R)-3-methoxy-2-methyl-3-[(2S)-pyrrolidin-2-yl]propanoyl}-L-phenylalaninate trifluoroacetate (Intermediate 12) were taken up in 2 ml of DMF, 19 μl of N,N-diisopropylethylamine, 14 mg (92 μmol) of HOBt and 17.6 mg (92 μmol) of EDC were added and then the mixture was stirred at RT overnight. Subsequently, the reaction mixture was concentrated and the residue was purified by means of preparative HPLC. This gave 59 mg (68% of theory) of the Fmoc-protected intermediate N-[(9H-fluoren-9-ylmethoxy)carbonyl]-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(benzyloxy)-1-oxo-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide.

[3412] LC-MS (Method 1): R_t=1.55 min; m/z=1044 $(M+H)^+$.

[3413] 57 mg (0.055 mmol) of this intermediate were treated with 1.2 ml of piperidine in 5 ml of DMF to detach the Fmoc protecting group. After concentration and purification by means of preparative HPLC, 39 mg (76% of theory) of the free amine intermediate N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(benzyloxy)-1-oxo-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide were obtained as the trifluoroacetate.

[3414] HPLC (Method 5): R_t=1.9 min;

[3415] LC-MS (Method 1): R_t=1.01 min; m/z=822 $(M+H)^+$.

[3416] 37 mg (0.045 mmol) of this intermediate were dissolved in 5 ml of dioxane/water and, analogously to the preparation of the compound in Intermediate 66, reacted with a 15% aqueous solution of 4-oxobutanoic acid in the presence of sodium cyanoborohydride. 16 mg (39% of theory) of the title compound were obtained in the form of a colourless foam.

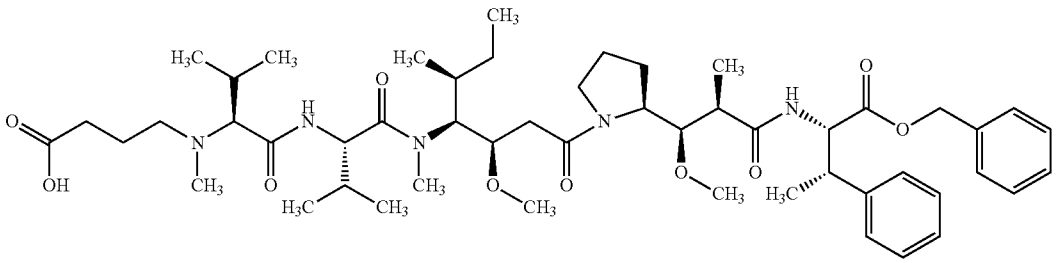
[3417] HPLC (Method 6): R_t=2.1 min;

[3418] LC-MS (Method 1): R_t=1.01 min; MS (ESIpos): m/z=908 $(M+H)^+$.

Intermediate 70

N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S,3S)-1-(benzyloxy)-1-oxo-3-phenylbutan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3419]



[3420] First, in analogy to the synthesis described in Intermediate 14, proceeding from Intermediates 4 and 26, the amine compound N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S,3S)-1-(benzyloxy)-1-oxo-3-phenylbutan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide was prepared.

[3421] 30 mg (0.032 mmol) of this compound were dissolved in 6 ml of dioxane/water, and 41 μl (0.063 mmol) of a 15% aqueous solution of 4-oxobutanoic acid were added. The reaction mixture was subsequently stirred at 100° C. for 1 h. After cooling to RT, 2.2 mg (0.035 mmol) of sodium cyanoborohydride were added and the mixture was adjusted to a pH of 3 by adding about 300 μl of 0.1 N hydrochloric acid. The reaction mixture was then stirred at 100° C. for a further 2 h. After cooling, another 41 μl (0.063 mmol) of the 15% 4-oxobutanoic acid solution were added and the reaction mixture was again stirred at 100° C. for 1 h. Then a further 2.2 mg (0.035 mmol) of sodium cyanoborohydride were added and about 300 μl of 0.1 N hydrochloric acid were subsequently used to adjust the pH back to 3. The reaction mixture was then stirred at 100° C. for another 2 h. In the event of conversion still being incomplete, this procedure was repeated for a third time. The reaction mixture was finally concentrated and the crude product was purified by means of preparative HPLC. This gave 24 mg (82% of theory) of the title compound in the form of a colourless foam.

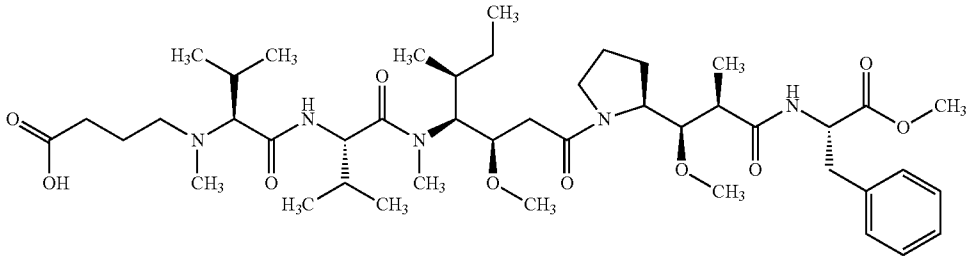
[3422] HPLC (Method 5): R_t=1.9 min;

[3423] LC-MS (Method 9): R_t=5.15 min; MS (ESIpos): m/z=922 $(M+H)^+$.

Intermediate 71

N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-3-{[(2S)-1-methoxy-1-oxo-3-phenylpropan-2-yl]amino}-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3424]



[3425] First, in analogy to the synthesis described in Intermediate 14, proceeding from Intermediates 4 and 39, the amine compound N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-3-{[(2S)-1-methoxy-1-oxo-3-phenylpropan-2-yl]amino}-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide was prepared. 7 mg (0.009 mmol) of this compound were then used, in analogy to the preparation of Intermediate 61, by reaction with 4-oxobutanoic acid in the presence of sodium cyanoborohydride, to obtain 2 mg (22% of theory) of the title compound in the form of a colourless foam.

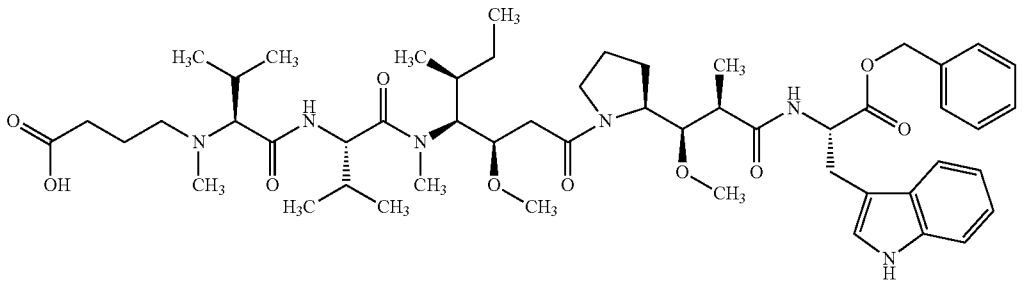
[3426] HPLC (Method 6): R_t=1.9 min;

[3427] LC-MS (Method 2): R_t=1.06 min; MS (ESIpos): m/z=832 $(M+H)^+$.

Intermediate 72

N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(benzyloxy)-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3428]



[3429] 212 mg (411 μmol) of N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(2R,3S,4S)-1-carboxy-2-methoxy-4-methylhexan-3-yl]-N-methyl-L-valinamide (Intermediate 8) and 237 mg (411 mmol) of benzyl-N-{(2R,3R)-3-methoxy-2-methyl-3-[(2S)-pyrrolidin-2-yl]propanoyl}-L-tryptophanate trifluoroacetate (Intermediate 20) were taken up in 30 ml of DMF, and 188 mg (493 μmol) of O-(7-azabenzotriazol-1-yl)-N, N,N',N'-tetramethyluronium hexafluorophosphate and 215 μl N,N-diisopropylethylamine were added. The reaction mixture was stirred at RT for 20 h, then concentrated under reduced pressure, and the residue was purified by means of preparative HPLC. The product fractions were combined and concentrated, and the residue was dried under high vacuum. This gave 315 mg (80% of theory) of the Boc-protected intermediate N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(benzyloxy)-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide as a colourless foam.

[3430] LC-MS (Method 1): R_t=1.45 min; m/z=961 $(M+H)^+$.

[3431] 50 mg (52 μmol) of this intermediate were treated with 1 ml of trifluoroacetic acid in 9 ml of dichloromethane to detach the Boc protecting group. After concentration and purification by means of preparative HPLC, 29 mg (57% of theory) of the free amine intermediate N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{R25)-1-(benzyloxy)-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide were obtained as the trifluoroacetate.

[3432] LC-MS (Method 1): R_t=0.99 min; m/z=861 $(M+H)^+$.

[3433] 29 mg (0.03 mmol) of this intermediate were dissolved in 6 ml of dioxane/water, and 39 μl (0.059 mmol) of a 15% aqueous solution of 4-oxobutanoic acid were added. The reaction mixture was subsequently stirred at 100° C. for 1 h. After cooling to RT, 2 mg (0.033 mmol) of sodium cyanoborohydride were added and the mixture was adjusted to a pH of 3 by adding about 300 μl of 0.1 N hydrochloric acid. The reaction mixture was then stirred at 100° C. for a further 2 h. After cooling, another 39 μl (0.059 mmol) of the 15% 4-oxobutanoic acid solution were added and the reaction mixture was again stirred at 100° C. for 1 h. Then a further 2 mg (0.033 mmol) of sodium cyanoborohydride were added and about 300 μl of 0.1 N hydrochloric acid were subsequently used to adjust the pH back to 3. The mixture was then stirred at 100° C. for another 2 h. Thereafter, the reaction mixture was poured onto a 1:1 mixture of semisaturated aqueous ammonium chloride solution and ethyl acetate. The organic phase was removed, washed with saturated sodium chloride solution, dried over sodium sulphate and concentrated. The residue was freeze-dried from water/acetonitrile. This gave 27 mg (94% of theory) of the title compound in the form of a colourless foam.

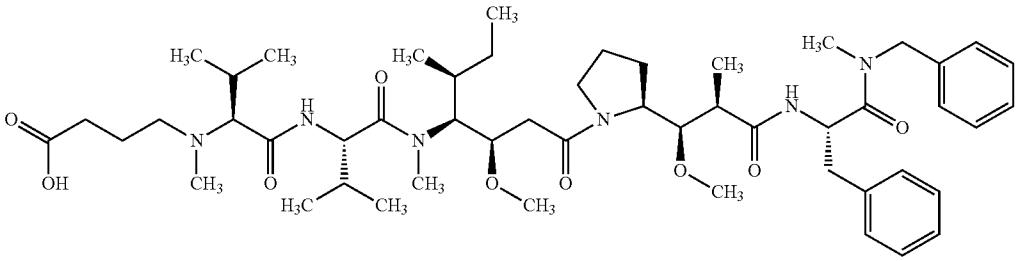
[3434] HPLC (Method 5): R_t=2.2 min;

[3435] LC-MS (Method 9): R_t=5.04 min; MS (ESIpos): m/z=947 $(M+H)^+$.

Intermediate 73

N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-({(2S)-1-[benzyl(methyl)amino]-1-oxo-3-phenylpropan-2-yl}amino)-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3436]



[3437] First, in analogy to the synthesis described in Intermediate 14, proceeding from Intermediates 4 and 38, the amine compound N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-({(2S)-1-[benzyl(methyl)amino]-1-oxo-3-phenylpropan-2-yl}amino)-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide was prepared. 25 mg (0.026 mmol) of this compound were then used, in analogy to the preparation of Intermediate 61, by reaction with 4-oxobutanoic acid in the presence of sodium cyanoborohydride, to obtain 13 mg (54% of theory) of the title compound in the form of a colourless foam.

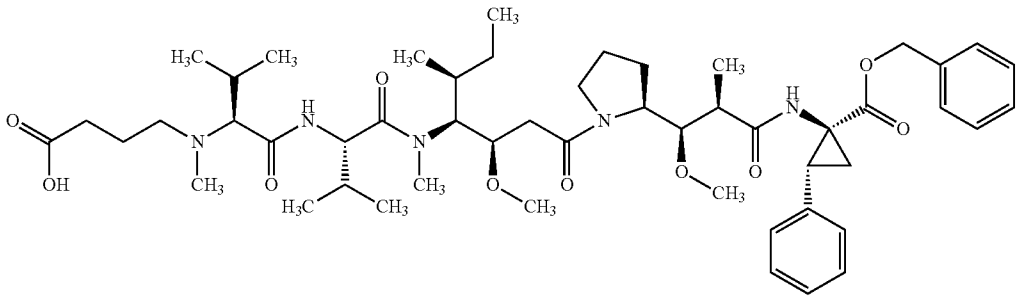
[3438] HPLC (Method 12): R_t=2.2 min;

[3439] LC-MS (Method 9): R_t=5.01 min; MS (ESIpos): m/z=921 $(M+H)^+$.

Intermediate 74

N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-({(1S,2R)-1-[(benzyloxy)carbonyl]-2-phenylcyclopropyl}amino)-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3440]



[3441] 50 mg (73 μmol) of N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-2-carboxy-1-methoxypropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Intermediate 26) and 28 mg (73 μmol) of benzyl (1S,2R)-1-amino-2-phenylcyclopropanecarboxylate trifluoroacetate (Intermediate 45) were taken up in ml of DMF, and 42 mg (110 μmol) of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and 38 μl of N,N-diisopropylethylamine were added. The reaction mixture was stirred at RT for 5 h, then concentrated under reduced pressure, and the residue was purified by means of preparative HPLC. The product fractions were combined and concentrated. After lyophilization from dioxane/water, 35 mg (51% of theory) of the Boc-protected intermediate N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-({(1S,2R)-1-[(benzyloxy)carbonyl]-2-phenylcyclopropyl}amino)-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide were obtained as a colourless foam.

[3442] LC-MS (Method 1): R_t=1.52 min; m/z=934 $(M+H)^+$.

[3443] 35 mg of this intermediate were treated with 1 ml of trifluoroacetic acid in 5 ml of dichloromethane to detach the Boc protecting group. After concentration and lyophilization from dioxane/water, 34 mg (97% of theory) of the free amine intermediate N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-({(1S,2R)-1-[(benzyloxy)carbonyl]-2-phenylcyclopropyl}amino)-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide were obtained as the trifluoroacetate.

[3444] LC-MS (Method 1): R_t=0.91 min; m/z=834 $(M+H)^+$.

[3445] 11 mg (0.011 mmol) of this intermediate were then used, in analogy to the preparation of Intermediate 66, by reaction with 4-oxobutanoic acid in the presence of sodium cyanoborohydride, to obtain 2.5 mg (24% of theory) of the title compound in the form of a colourless foam.

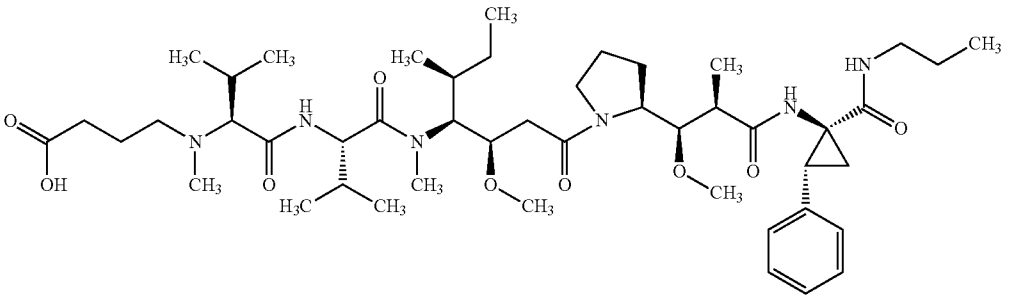
[3446] HPLC (Method 12): R_t=2.2 min;

[3447] LC-MS (Method 9): R_t=5.1 min; MS (ESIpos): m/z=920 $(M+H)^+$.

Intermediate 75

N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(1S,2R)-2-phenyl-1-(propylcarbamoyl)cyclopropyl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3448]



[3449] First, in analogy to the synthesis described in Intermediate 74, by coupling of N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-2-carboxy-1-methoxypropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Intermediate 26) and (1S,2R)-1-amino-2-phenyl-N-propylcyclopropanecarboxamide trifluoroacetate (Intermediate 27) in the presence of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and subsequent detachment of the Boc protecting group by means of trifluoroacetic acid, the amine compound N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(1S,2R)-2-phenyl-1-(propylcarbamoyl)cyclopropyl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide was prepared as the trifluoroacetate. 14 mg (0.016 mmol) of this compound were then used, in analogy to the preparation of Intermediate 61, by reaction with 4-oxobutanoic acid in the presence of sodium cyanoborohydride, to obtain 11.3 mg (83% of theory) of the title compound.

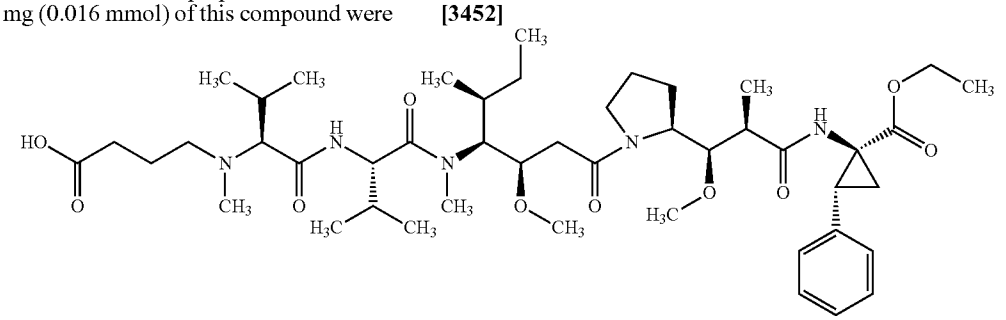
[3450] HPLC (Method 6): R_t=1.9 min;

[3451] LC-MS (Method 2): R_t=1.27 min; MS (ESIpos): m/z=871 $(M+H)^+$.

Intermediate 76

N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(1S,2R)-1-(ethoxycarbonyl)-2-phenylcyclopropyl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3452]



[3453] First, by coupling of Intermediate 46 (N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-2-carboxy-1-methoxypropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide) with Intermediate 48 (ethyl (1S,2R)-1-amino-2-phenylcyclopropanecarboxylate trifluoroacetate) in the presence of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and subsequent Boc detachment, the starting compound N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(1S,2R)-1-(ethoxycarbonyl)-2-phenylcyclopropyl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide trifluoroacetate was prepared. 70 mg (0.079 mmol) of this starting material were then used, by reaction with 4-oxobutanoic acid, in analogy to Intermediate 61, to obtain 46 mg (68% of theory) of the title compound.

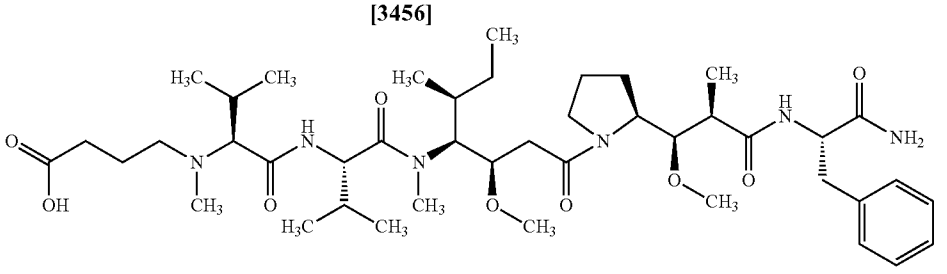
[3454] HPLC (Method 6): R_t=1.9 min;

[3455] LC-MS (Method 2): R_t=1.28 min; MS (ESIpos): m/z=858 (M+H)+

Intermediate 77

N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-amino-1-oxo-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3456]



[3457] First, in analogy to the synthesis described in Intermediate 75, by coupling of N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-2-carboxy-1-methoxypropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Intermediate 26) and L-phenylalaninamide hydrochloride in the presence of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and subsequent detachment of the Boc protecting group by means of trifluoroacetic acid, the amine compound N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-amino-1-oxo-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide was prepared as the trifluoroacetate. 47 mg (0.049 mmol) of this compound were then used, in analogy to the preparation of Intermediate 61, by reaction with 4-oxobutanoic acid in the presence of sodium cyanoborohydride, to obtain 39 mg (96% of theory) of the title compound.

[3458] HPLC (Method 6): R_t=1.7 min;

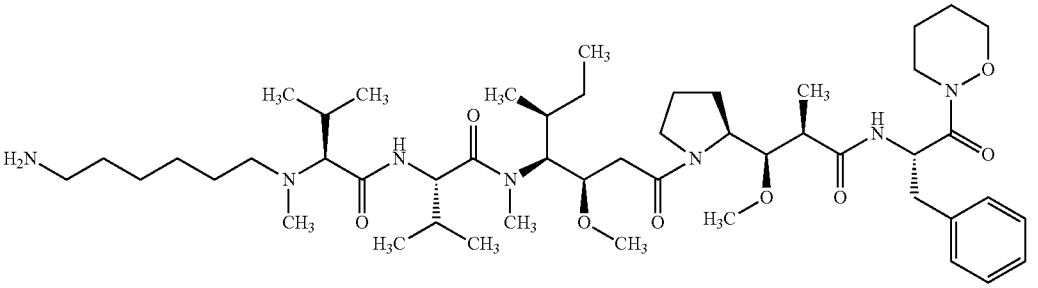
[3459] LC-MS (Method 9): R_t=4.44 min; MS (ESIpos): m/z=817 $(M+H)^{-1}$

[3460] ^{1}H NMR (500 MHz, DMSO-d_6): δ=8.95 and 8.8 (2m, 1H), 8.25 and 8.0 (2d, 1H), 7.45, 7.35 and 7.0 (3s, broad, 2H), 7.3-7.1 (m, 5H), 4.8-4.4 (2m, 3H), 3.95 (m, 1H), 3.82 (m, 1H), 3.72 (d, 1H), 3.22, 3.18, 3.15, 3.05 and 3.00 (5s, 9H), 2.85-2.7 (m, 4H), 2.45-1.6 (m, 12H), 1.5-1.2 (m, 3H), 1.1-0.7 (m, 21H) [further signals hidden under solvent peaks].

Intermediate 78

N-(6-aminohexyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(2S)-1-(1,2-oxazinan-2-yl)-1-oxo-3-phenylpropan-2-yl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3461]



[3462] This compound was prepared in analogy to Intermediate 66 over 2 stages, proceeding from 20 mg (16 μmol) of the compound from Intermediate 14 and benzyl 6-oxohexyl carbamate, and the hydrogenation was performed in methanol as the solvent.

[3463] Yield: 7.6 mg (55% of theory over 2 stages)

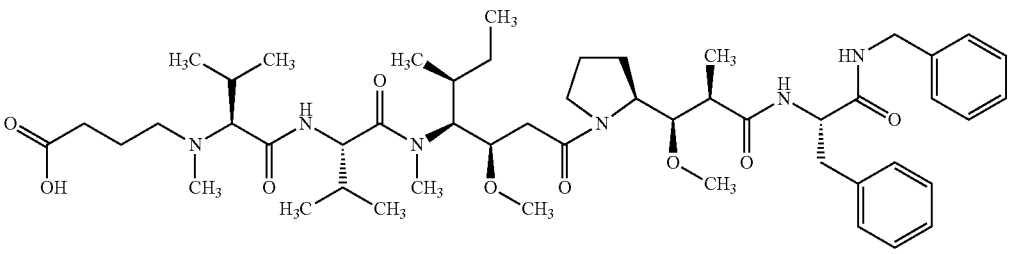
[3464] HPLC (Method 6): R_t=1.8 min;

[3465] LC-MS (Method 1): R_t=0.7 min; MS (ESIpos): m/z=901 $(M+H)^+$.

Intermediate 79

N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(benzylamino)-1-oxo-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3466]



[3467] 36 mg (43 μmol) of N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(1S)-1-carboxy-2-phenylethyl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Intermediate 46) and 4.6 mg (43 μmol) of benzylamine were taken up in 5 ml of DMF, 7.5 μl (88 μmol) of N,N-diisopropylethylamine, 10 mg (65 μmol) of HOBt and 10 mg (52 μmol) of EDC were added, and then the mixture was stirred at RT overnight. Subsequently, the reaction mixture was concentrated and the residue was purified by means of preparative HPLC. 29 mg (73% of theory) of the Boc-protected intermediate N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(benzylamino)-1-oxo-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide were obtained.

[3468] LC-MS (Method 1): R_t=1.43 min; m/z=921 $(M+H)^+$.

[3469] 29 mg of this intermediate were treated with 1 ml of trifluoroacetic acid in 6 ml of dichloromethane to detach the Boc protecting group. After concentration and lyophilization from dioxane/water, 30 mg (quant.) of the free amine intermediate N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(benzylamino)-1-oxo-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide were obtained as the trifluoroacetate.

[3470] LC-MS (Method 1): R_t=0.95 min; m/z=821 $(M+H)^+$.

[3471] 17 mg (0.018 mmol) of this intermediate were then used, in analogy to the preparation of Intermediate 61, by reaction with 4-oxobutanoic acid in the presence of sodium cyanoborohydride, to obtain 13 mg (80% of theory) of the title compound in the form of a colourless foam.

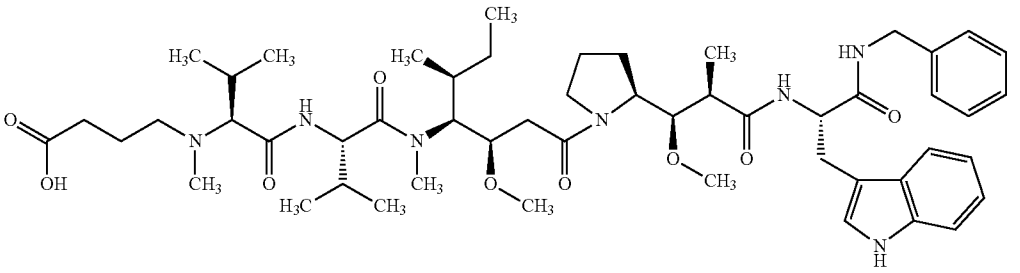
[3472] HPLC (Method 5): R_t=1.7 min;

[3473] LC-MS (Method 9): R_t=4.97 min; MS (ESIpos): m/z=907 $(M+H)^+$.

Intermediate 80

N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(benzylamino)-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3474]



[3475] First, in analogy to the synthesis described in Intermediate 74, by coupling of N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-2-carboxy-1-methoxypropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Intermediate 26) and N-benzyl-L-tryptophanamide trifluoroacetate (Intermediate 47) in the presence of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and subsequent detachment of the Boc protecting group by means of trifluoroacetic acid, the amine compound N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(benzylamino)-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide was prepared as the trifluoroacetate. 10 mg (0.01 mmol) of this compound were then used, in analogy to the preparation of Intermediate 61, by reaction with 4-oxobutanoic acid in the presence of sodium cyanoborohydride, to obtain 2.5 mg (26% of theory) of the title compound.

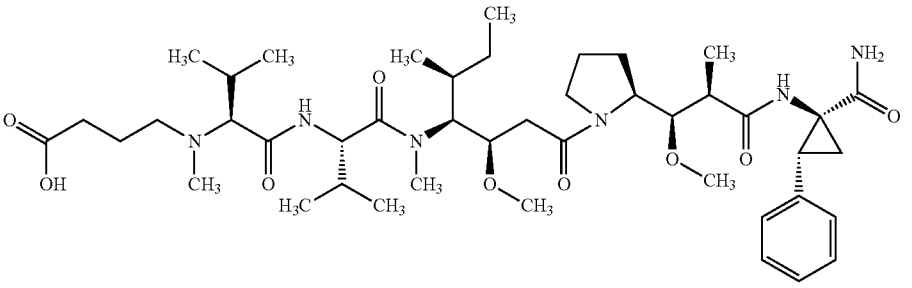
[3476] HPLC (Method 5): R_t=1.7 min;

[3477] LC-MS (Method 2): R_t=1.13 min; MS (ESIpos): m/z=946 $(M+H)^+$.

Intermediate 81

N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(1S,2R)-1-carbamoyl-2-phenylcyclopropyl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3478]



[3479] First, in analogy to the synthesis described in Intermediate 74, by coupling of N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-2-carboxy-1-methoxypropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Intermediate 26) and (1S,2R)-1-amino-2-phenylcyclopropanecarboxamide trifluoroacetate (Intermediate 48) in the presence of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and subsequent detachment of the Boc protecting group by means of trifluoroacetic acid, the amine compound N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(1S,2R)-1-carbamoyl-2-phenylcyclopropyl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide was prepared as the trifluoroacetate. 14 mg (0.0163 mmol) of this compound were then used, in analogy to the preparation of Intermediate 61, by reaction with 4-oxobutanoic acid in the presence of sodium cyanoborohydride, to obtain 8 mg (57% of theory) of the title compound.

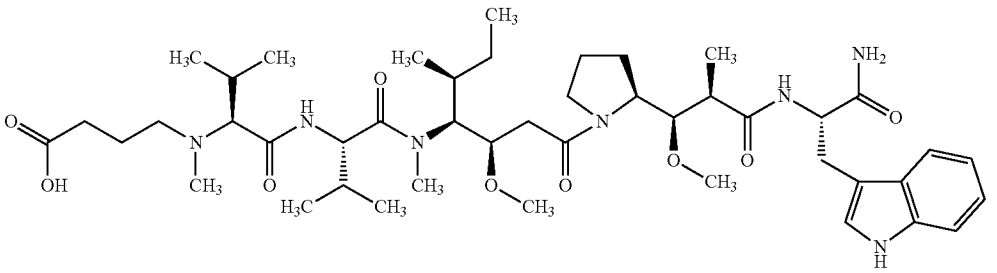
[3480] HPLC (Method 5): R_t=1.6 min;

[3481] LC-MS (Method 9): R_t=4.64 min; MS (ESIpos): m/z=829 $(M+H)^+$.

Intermediate 82

N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-amino-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3482]



[3483] First, in analogy to the synthesis described in Intermediate 69, by coupling of N-[(9H-fluoren-9-ylmethoxy)carbonyl]-N-methyl-L-valyl-N-[(2R,3S,4S)-1-carboxy-2-methoxy-4-methylhexan-3-yl]-N-methyl-L-valinamide (Intermediate 4) and N^{α}-{(2R,3R)-3-methoxy-2-methyl-3-[(2S)-pyrrolidin-2-yl]propanoyl}-L-tryptophanamide trifluoroacetate (Intermediate 49) in the presence of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and subsequent detachment of the Fmoc protecting group by means of piperidine, the amine compound N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-amino-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide was prepared as the trifluoroacetate. 78 mg (0.088 mmol) of this compound were then used, in analogy to the preparation of Intermediate 61, by reaction with 4-oxobutanoic acid in the presence of sodium cyanoborohydride, to obtain 68 mg (90% of theory) of the title compound.

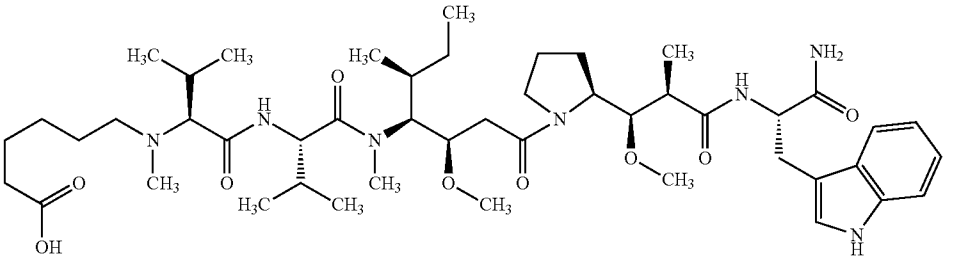
[3484] HPLC (Method 5): R_t=1.8 min;

[3485] LC-MS (Method 9): R_t=4.49 min; MS (ESIpos): m/z=856 $(M+H)^+$.

Intermediate 83

N-(5-carboxypentyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-amino-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3486]



[3487] This compound was prepared in analogy to the compound in Intermediate 82, proceeding from 20 mg (26 μmol) of N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-amino-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide trifluoroacetate, by reaction with 4-oxobutanoic acid in the presence of sodium cyanoborohydride prepared.

[3488] Yield: 5 mg (25% of theory)

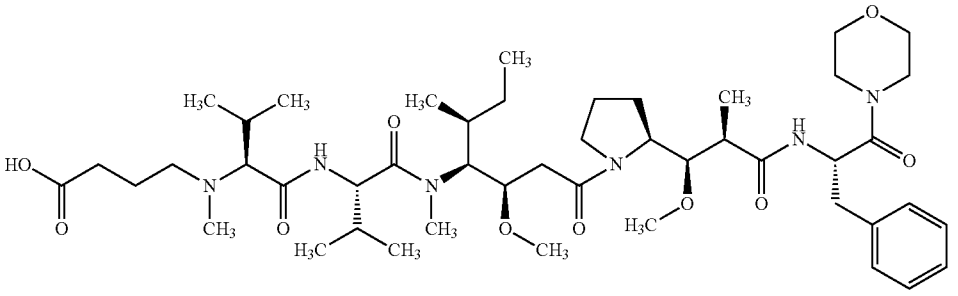
[3489] HPLC (Method 5): R_t=1.6 min;

[3490] LC-MS (Method 11): R_t=0.72 min; MS (ESIpos): m/z=884 $(M+H)^+$.

Intermediate 84

N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(2S)-1-(morpholin-4-yl)-1-oxo-3-phenylpropan-2-yl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3491]



[3492] First, in analogy to the synthesis described in Intermediate 79, by coupling of N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(1S)-1-carboxy-2-phenylethyl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Intermediate 46) and morpholine in the presence of EDC and HOBT and subsequent detachment of the Boc protecting group by means of trifluoroacetic acid, the amine compound N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(2S)-1-(morpholin-4-yl)-1-oxo-3-phenylpropan-2-yl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide was prepared as the trifluoroacetate. 30 mg (0.033 mmol) of this compound were then used, in analogy to the preparation of Intermediate 61, by reaction with 4-oxobutanoic acid in the presence of sodium cyanoborohydride, to obtain 22 mg (76% of theory) of the title compound.

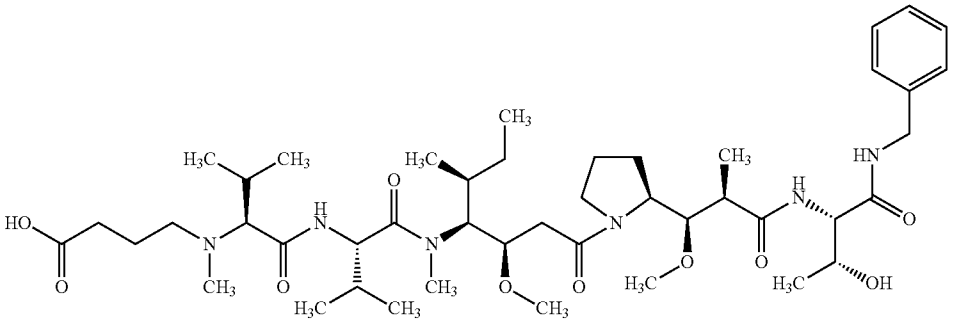
[3493] HPLC (Method 5): R_t=1.6 min;

[3494] LC-MS (Method 9): R_t=4.58 min; MS (ESIpos): m/z=887 $(M+H)^+$.

Intermediate 85

N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S,3R)-1-(benzylamino)-3-hydroxy-1-oxobutan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3495]



[3496] First, in analogy to the synthesis described in Intermediate 79, by coupling of N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(1S)-1-carboxy-2-phenylethyl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Intermediate 46) and N-benzyl-L-threoninamide trifluoroacetate in the presence of HATU and subsequent detachment of the Boc protecting group by means of trifluoroacetic acid, the amine compound N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S,3R)-1-(benzylamino)-3-hydroxy-1-oxobutan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide was prepared as the trifluoroacetate. 21 mg (0.024 mmol) of this compound were then used, in analogy to the preparation of Intermediate 61, by reaction with 4-oxobutanoic acid in the presence of sodium cyanoborohydride, to obtain 20 mg (97% of theory) of the title compound.

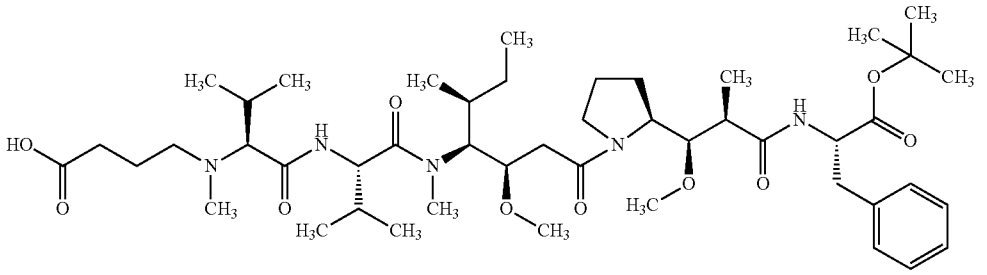
[3497] HPLC (Method 5): R_t=1.54 min;

[3498] LC-MS (Method 9): R_t=4.49 min; MS (ESIpos): m/z=861 $(M+H)^+$.

Intermediate 86

N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-tert-butoxy-1-oxo-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3499]



[3500] First, in analogy to the synthesis described in Intermediate 74, by coupling of N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-2-carboxy-1-methoxypropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Intermediate 26) and tert-butyl-L-phenylalaninate hydrochloride in the presence of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and subsequent detachment of the Boc protecting group by means of trifluoroacetic acid to obtain the tert-butyl ester (stirring with trifluoroacetic acid in dichloromethane for 40 minutes), the amine compound N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-tert-butoxy-1-oxo-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide was prepared as the trifluoroacetate. 22 mg (0.02 mmol) of this compound were then used, in analogy to the preparation of Intermediate 61, by reaction with 4-oxobutanoic acid in the presence of sodium cyanoborohydride, to obtain 16 mg (94% of theory) of the title compound.

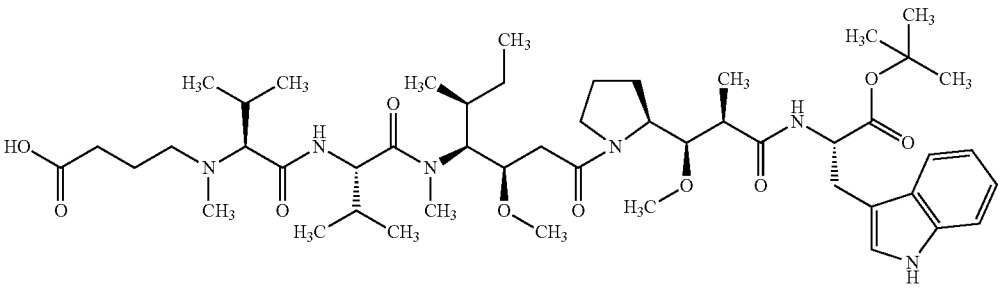
[3501] HPLC (Method 5): R_t=2.0 min;

[3502] LC-MS (Method 9): R_t=5.05 min; MS (ESIpos): m/z=874 $(M+H)^+$.

Intermediate 87

N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-tert-butoxy-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3503]



[3504] This compound was prepared in analogy to the synthesis described in Intermediate 86, proceeding from 230 mg (336 μmol) of N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-2-carboxy-1-methoxypropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Intermediate 26) and tert-butyl-L-tryptophanate hydrochloride over 3 stages.

[3505] Yield: 95 mg (31% of theory over 3 stages)

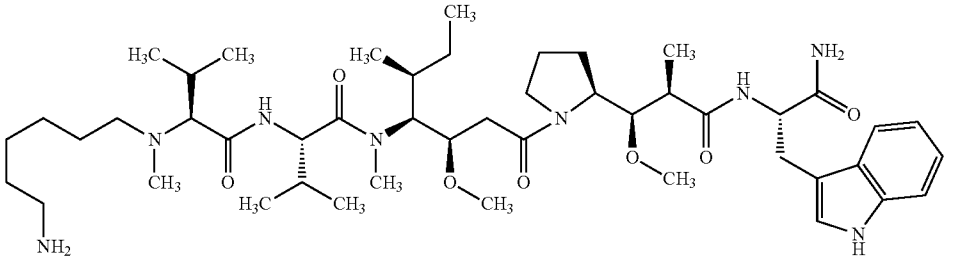
[3506] HPLC (Method 5): R_t=2.0 min;

[3507] LC-MS (Method 9): R_t=5.05 min; MS (ESIpos): m/z=913 $(M+H)^+$.

Intermediate 88

N-(6-aminohexyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-amino-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3508]



[3509] First, in analogy to the syntheses described in Intermediate 69, by coupling of N-[(9H-fluoren-9-ylmethoxy)carbonyl]-N-methyl-L-valyl-N-[(2R,3S,4S)-1-carboxy-2-methoxy-4-methylhexan-3-yl]-N-methyl-L-valinamide (Intermediate 4) and N^{α}-{(2R,3R)-3-methoxy-2-methyl-3-[(2S)-pyrrolidin-2-yl]propanoyl}-L-tryptophanamide trifluoroacetate (Intermediate 49) in the presence of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and subsequent detachment of the Fmoc protecting group by means of piperidine, the amine compound N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-amino-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide was prepared as the trifluoroacetate. 30 mg (0.03 mmol) of this compound were then used, in analogy to the preparation of the compound of Intermediate 61, by reaction with benzyl 6-oxohexyl carbamate, which had been obtained beforehand by oxidation of benzyl 6-hydroxyhexyl carbamate, in the presence of sodium cyanoborohydride, to obtain 17 mg (45% of theory) of the Z-protected compound. Subsequently, hydrogenolysis in methanol over 10% palladium/activated carbon afforded the title compound.

[3510] Yield: 14 mg (95% of theory)

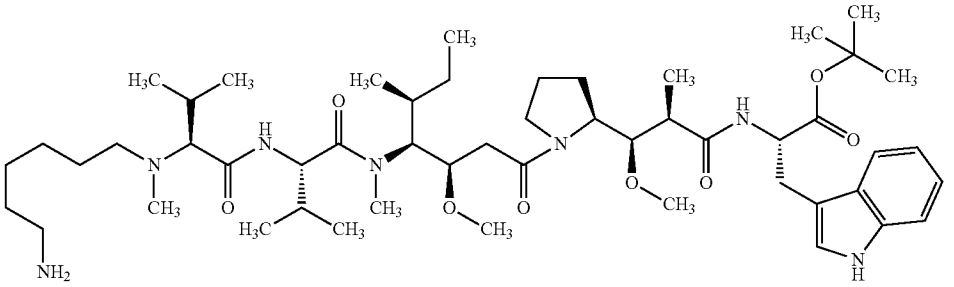
[3511] HPLC (Method 5): R_t=1.5 min;

[3512] LC-MS (Method 1): R_t=0.73 min; MS (ESIpos): m/z=869 $(M+H)^+$.

Intermediate 89

N-(6-aminohexyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-tert-butoxy-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3513]



[3514] First, in analogy to the synthesis described in Intermediate 86, by coupling of N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-2-carboxy-1-methoxypropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Intermediate 26) and tert-butyl-L-tryptophanate hydrochloride in the presence of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and subsequent detachment of the Boc protecting group by means of trifluoroacetic acid to obtain the tert-butyl ester (stirring with 1:10 trifluoroacetic acid/dichloromethane for 30 min), the amine compound N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-tert-butoxy-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide was prepared as the trifluoroacetate. 71 mg (0.075 mmol) of this compound were then used, in analogy to the preparation of the compound of Intermediate 61, by reaction with benzyl 6-oxohexyl carbamate, which had been obtained beforehand by oxidation of benzyl 6-hydroxyhexyl carbamate, in the presence of sodium cyanoborohydride, to obtain 35 mg (44% of theory) of the Z-protected compound. Subsequently, hydrogenolysis in methanol over 10% palladium/activated carbon afforded the title compound.

[3515] Yield: 30 mg (98% of theory)

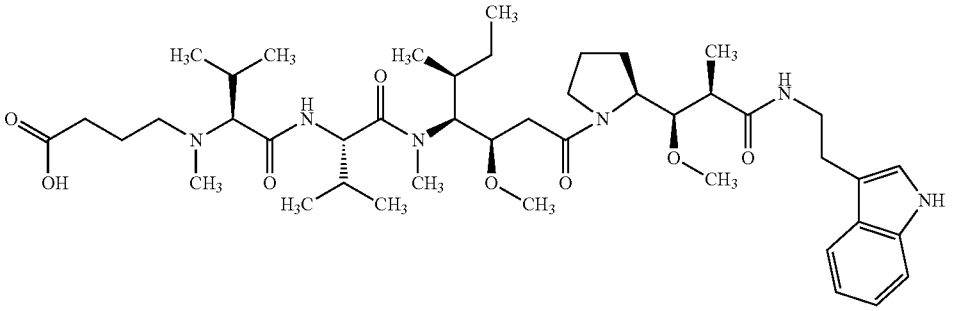
[3516] HPLC (Method 5): Rt=1.9 min;

[3517] LC-MS (Method 1): Rt=0.77 min; MS (ESIpos): m/z=926 $(M+H)^+$.

Intermediate 90

N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[2-(1H-indol-3-yl)ethyl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3518]



[3519] First, in analogy to the synthesis described in Intermediate 74, by coupling of N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-2-carboxy-1-methoxypropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Intermediate 26) and 2-(1H-indol-3-yl)ethanamine in the presence of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and subsequent detachment of the Boc protecting group by means of trifluoroacetic acid, the amine compound N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[2-(1H-indol-3-yl)ethyl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide was prepared as the trifluoroacetate. 100 mg (0.119 mmol) of this compound were then used, in analogy to the preparation of Intermediate 61, by reaction with 4-oxobutanoic acid in the presence of sodium cyanoborohydride, to obtain 50 mg (49% of theory) of the title compound. The title compound was purified here by flash chromatography on silica gel with dichloromethane/methanol/17% ammonia as the eluent, in the course of which the mixing ratio was switched from initially 15/2/02 to 15/4/0.5.

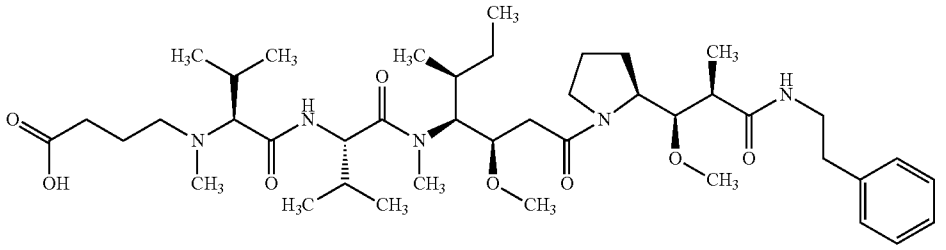
[3520] HPLC (Method 6): R_t=1.8 min;

[3521] LC-MS (Method 1): R_t=0.87 min; MS (ESIpos): m/z=813 $(M+H)^+$.

Intermediate 91

N-(3-carboxypropyl)-N-methyl-L-valyl-N-{(3R,4S,5S)-3-methoxy-1-[(2S)-2-{(1R,2R)-1-methoxy-2-methyl-3-oxo-3-[(2-phenylethyl)amino]propyl}pyrrolidin-1-yl]-5-methyl-1-oxoheptan-4-yl}-N-methyl-L-valinamide

[3522]



[3523] First, in analogy to the synthesis described in Intermediate 74, by coupling of N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-2-carboxy-1-methoxypropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Intermediate 26) and phenylethylamine in the presence of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and subsequent detachment of the Boc protecting group by means of trifluoroacetic acid, the amine compound N-methyl-L-valyl-N-{(3R,4S,5S)-3-methoxy-1-[(2S)-2-{(1R,2R)-1-methoxy-2-methyl-3-oxo-3-[(2-phenylethyl)amino]propyl}pyrrolidin-1-yl]-5-methyl-1-oxoheptan-4-yl}-N-methyl-L-valinamide was prepared as the trifluoroacetate. 57 mg (0.071 mmol) of this compound were then used, in analogy to the preparation of Intermediate 61, by reaction with 4-oxobutanoic acid in the presence of sodium cyanoborohydride, to obtain 44 mg (80% of theory) of the title compound. The title compound can also be purified here by flash chromatography on silica gel with dichloromethane/methanol/17% ammonia as the eluent (15/2/02->15/4/0.5).

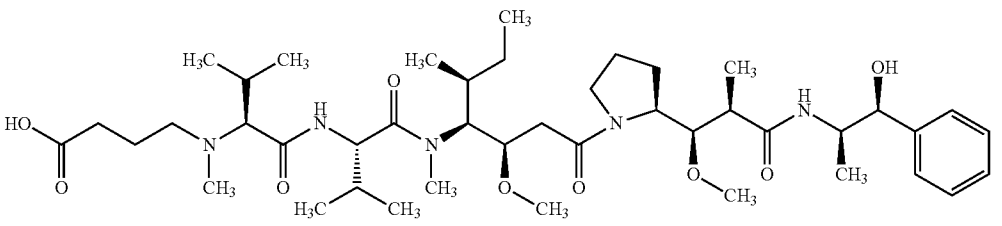
[3524] HPLC (Method 5): R_t=1.7 min;

[3525] LC-MS (Method 9): R_t=4.64 min; MS (ESIpos): m/z=774 $(M+H)^+$.

Intermediate 92

N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(1S,2R)-1-hydroxy-1-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3526]



[3527] 100 mg (0.139 mmol) of N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(1S,2R)-1-hydroxy-1-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Intermediate 40) were used, in analogy to the preparation of Intermediate 61, by reaction with 4-oxobutanoic acid in the presence of sodium cyanoborohydride, to obtain 94 mg (84% of theory) of the title compound. The title compound was purified by preparative HPLC.

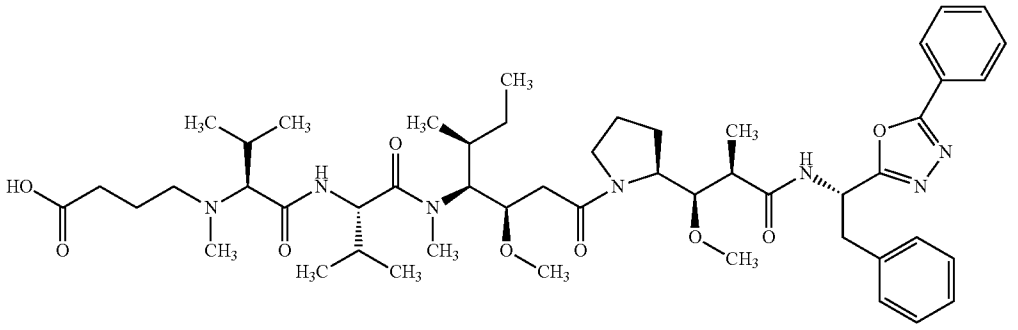
[3528] HPLC (Method 5): R_t=1.5 min;

[3529] LC-MS (Method 9): R_t=4.46 min; MS (ESIpos): m/z=804 $(M+H)^+$.

Intermediate 93

N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(1S)-2-phenyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3530]



[3531] 22.4 mg (24 μmol) of N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(1S)-2-phenyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide trifluoroacetate were dissolved in 1.4 ml of dioxane/water and, analogously to the preparation of Intermediate 61, reacted with 15% aqueous solution of 4-oxobutanoic acid in the presence of sodium cyanoborohydride. After lyophilization from dioxane, 8.2 mg (38% of theory) of the title compound were obtained in the form of a white solid.

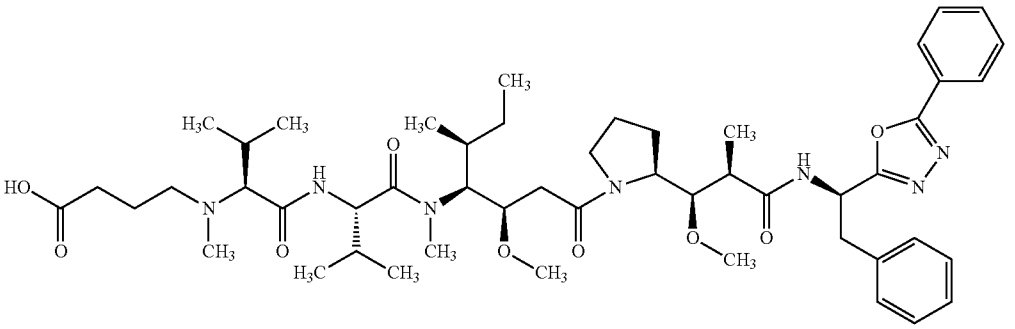
[3532] HPLC (Method 10): R_t=2.54 min

[3533] LC-MS (Method 12): R_t=0.94 min; MS (ESIpos): m/z=919 $(M+H)^+$

Intermediate 94

N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(1R)-2-phenyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3534]



[3535] 17.1 mg (18 μmol) of N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(1R)-2-phenyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide trifluoroacetate were dissolved in 1.1 ml of dioxane/water and, analogously to the preparation of Intermediate 61, reacted with 15% aqueous solution of 4-oxobutanoic acid in the presence of sodium cyanoborohydride. After lyophilization from dioxane, 14.8 mg (89% of theory) of the title compound were obtained in the form of a white solid.

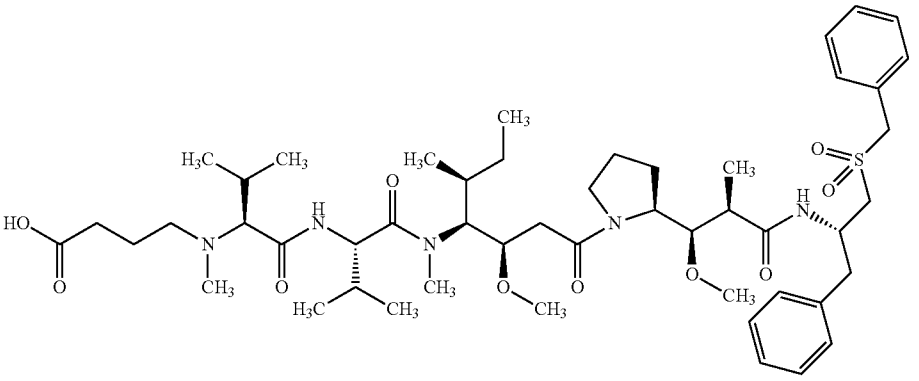
[3536] HPLC (Method 10): R_t=2.54 min;

[3537] LC-MS (Method 12): R_t=0.92 min; MS (ESIpos): m/z=919 (M+H)+

Intermediate 95

N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(benzylsulphonyl)-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3538]



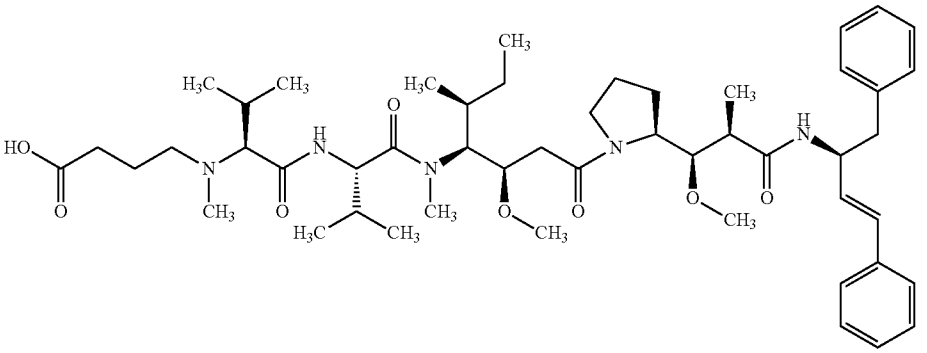
[3539] 19.3 mg (20 μmol) N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(benzylsulphonyl)-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide trifluoroacetate were dissolved in 1.2 ml of dioxane/water and, analogously to the preparation of Intermediate 61, reacted with 15% aqueous solution of 4-oxobutanoic acid in the presence of sodium cyanoborohydride. After lyophilization from dioxane, 8.6 mg (45% of theory) of the title compound were obtained in the form of a solid.

[3540] LC-MS (Method 11): R_t=0.85 min; MS (ESIpos): m/z=943 (M+H)+

Intermediate 96

N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S,3E)-1,4-diphenylbut-3-en-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3541]



[3542] 15.5 mg (10 μmol) of N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S,3E)-1,4-diphenylbut-3-en-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide trifluoroacetate were dissolved in 1.0 ml of dioxane/water and, analogously to the preparation of Intermediate 61, reacted with 15% aqueous solution of 4-oxobutanoic acid in the presence of sodium cyanoborohydride. After lyophilization from dioxane, 10.3 mg (68% of theory) of the title compound were obtained in the form of a white solid.

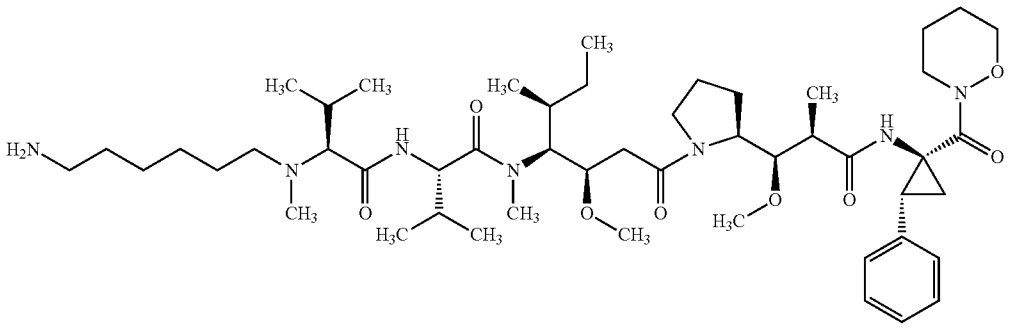
[3543] HPLC (Method 10): R_t=2.59 min;

[3544] LC-MS (Method 11): R_t=0.94 min; MS (ESIpos): m/z=877 (M+H)+

Intermediate 97

N-(6-aminohexyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3545]



[3546] The title compound was prepared in analogy to the synthesis of Intermediate 66, by reaction of 200 mg (0.108 mmol) of N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide trifluoroacetate (Intermediate 16) with benzyl 6-oxohexyl carbamate and subsequent hydrogenolytic detachment of the Z protecting group (with 5% palladium on charcoal as a catalyst, in methanol as a solvent).

[3547] Yield: 69 mg (65% of theory over two stages)

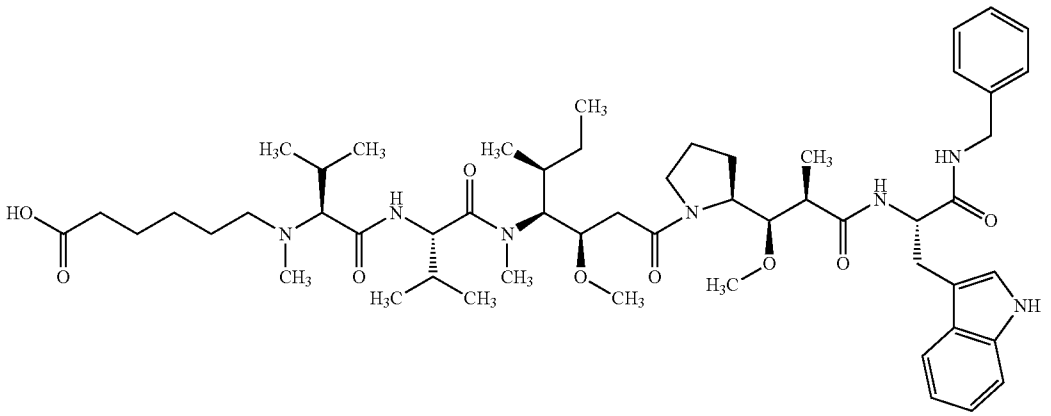
[3548] HPLC (Method 5): R_t=1.7 min;

[3549] LC-MS (Method 1): R_t=0.76 min; MS (ESIpos): m/z=912 $(M+H)^+$.

Intermediate 98

N-(5-carboxypentyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(benzylamino)-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3550]



[3551] This compound was prepared in analogy to the synthesis described in Intermediate 80. The purification was effected by preparative HPLC.

[3552] Yield: 40 mg (29% of theory over 3 stages)

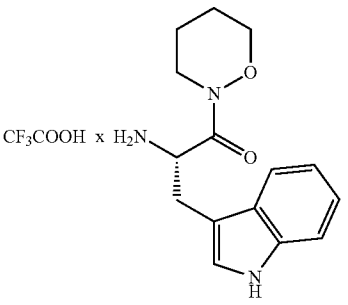
[3553] HPLC (Method 5): R_t=1.9 min;

[3554] LC-MS (Method 1): R_t=0.92 min; MS (ESIpos): m/z=974 $(M+H)^+$.

Intermediate 99

(2S)-2-amino-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)propan-1-one trifluoroacetate

[3555]



[3557] HPLC (Method 12): R_t=1.9 min;

[3558] LC-MS (Method 1): R_t=1.03 min; MS (ESIpos): m/z=374 $(M+H)^+$.

[3559] Using 166 mg (444.5 μmol) of this intermediate, under standard conditions with 3 ml of trifluoroacetic acid in 20 ml of dichloromethane, the Boc protecting group was detached and, after HPLC purification, 155 mg (86% of theory) of the title compound were obtained.

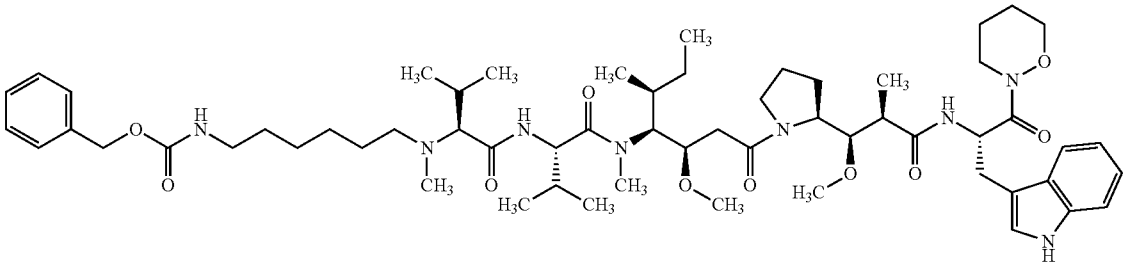
[3560] HPLC (Method 12): R_t=1.43 min;

[3561] LC-MS (Method 11): R_t=0.56 min; MS (ESIpos): m/z=274 $(M+H)^+$.

Intermediate 100

N-(6-{[(benzyloxy)carbonyl]amino}hexyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3562]



[3563] 177 mg (260 μmol) of N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-2-carboxy-1-methoxypropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Intermediate 26) and 100 mg (260 μmol) of (2S)-2-amino-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)propan-1-one trifluoroacetate (Intermediate 99) were taken up in 15 ml of DMF, and 118 mg (310 μmol) of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and 140 μl of N,N-diisopropylethylamine were added. The reaction mixture was stirred at RT for 30 min, then concentrated under reduced pressure, and the residue was purified by means of preparative HPLC. The product fractions were combined and concentrated. After lyophilization from dioxane, 170 mg (68% of theory) of the Boc-protected intermediate were obtained.

[3564] LC-MS (Method 1): R_t=1.36 min; m/z=940 $(M+H)^+$.

[3565] 170 mg of this intermediate were treated with 3 ml of trifluoroacetic acid in 30 ml of dichloromethane for 30 min

to detach the Boc protecting group. Then the reaction mixture was concentrated under reduced pressure and the residue was purified by means of preparative HPLC to obtain 155 mg (86% of theory) of the deprotected N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide intermediate.

[3566] HPLC (Method 12): R_t=1.85 min;

[3567] LC-MS (Method 1): R_t=0.86 min; MS (ESIpos): m/z=840 $(M+H)^+$.

[3568] 50 mg (0.052 mmol) of this intermediate were then used, in analogy to the preparation of Intermediate 97, with benzyl 6-oxohexyl carbamate in the presence of sodium cyanoborohydride and subsequent hydrogenolytic detachment of the Z protecting group (with 5% palladium on charcoal as a catalyst, in methanol as a solvent), prepared to prepare the title compound.

[3569] Yield: 21 mg (37% of theory)

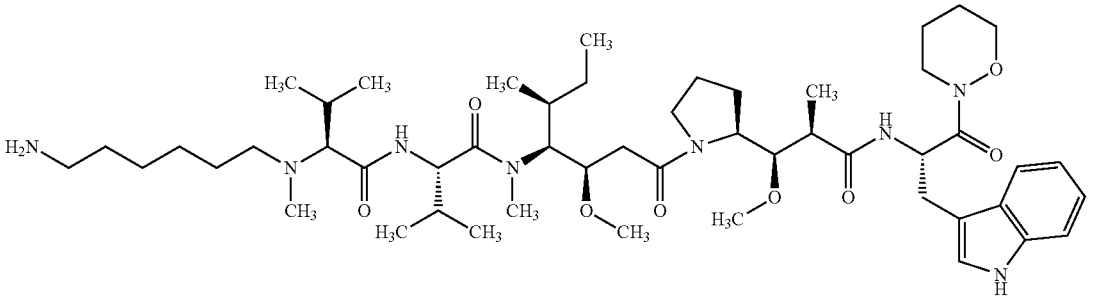
[3570] HPLC (Method 12): R_t=2.1 min;

[3571] LC-MS (Method 1): R_t=1.02 min; MS (ESIpos): m/z=1073 $(M+H)^+$.

Intermediate 101

N-(6-aminohexyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3572]



[3573] 26.7 mg (24.87 μmol) of Intermediate 100 were dissolved in 10 ml of methanol and hydrogenated over palladium/activated carbon (5%) under standard hydrogen pressure for 30 min. The catalyst was filtered off and the solvent was evaporated off under reduced pressure. After the residue had been dried under high vacuum, 22.5 mg (96% of theory) of the title compound were obtained.

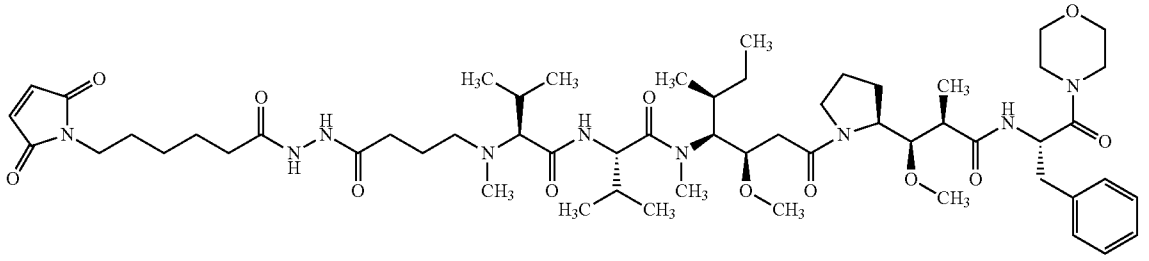
[3574] HPLC (Method 5): R_t=1.7 min;

[3575] LC-MS (Method 1): R_t=0.76 min; MS (ESIpos): m/z=939 $(M+H)^+$.

Intermediate 102

N-(4-{2-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(2S)-1-(morpholin-4-yl)-1-oxo-3-phenylpropan-2-yl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3576]



[3577] This compound was prepared in analogy to the synthesis described in Intermediate 157 from N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(2S)-1-(morpholin-4-yl)-1-oxo-3-phenylpropan-2-yl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide and commercially available 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanehydrazide.

[3578] Yield: 8 mg (71% of theory)

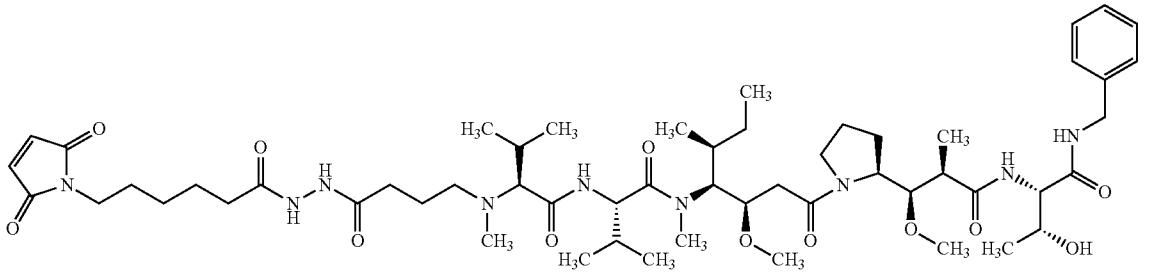
[3579] HPLC (Method 12): R_t=1.9 min;

[3580] LC-MS (Method 1): R_t=0.87 min; MS (ESIpos): m/z=1094 $(M+H)^+$.

Intermediate 103

N-(4-{2-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S,3R)-1-(benzylamino)-3-hydroxy-1-oxobutan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3581]



[3582] This compound was prepared in analogy to the synthesis described in Intermediate 157 from N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S,3R)-1-(benzylamino)-3-hydroxy-1-oxobutan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide and commercially available 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanehydrazide.

[3583] Yield: 3 mg (22% of theory)

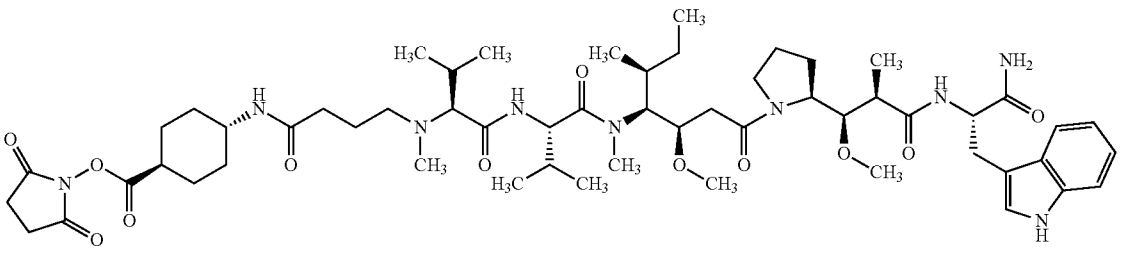
[3584] HPLC (Method 5): R_t=1.6 min;

[3585] LC-MS (Method 1): R_t=0.78 min; MS (ESIpos): m/z=1069 $(M+H)^+$.

Intermediate 104

N-{4-[(trans-4-{[(2,5-dioxopyrrolidin-1-yl)oxy]carbonyl}cyclohexyl)amino]-4-oxobutyl}-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-amino-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3586]



[3587] First, benzyl trans-4-aminocyclohexanecarboxylate trifluoroacetate was prepared from trans-4-aminocyclohexanecarboxylic acid by introducing the Boc protecting group, then introducing the benzyl ester protecting group and subsequently detaching the Boc protecting group by conventional peptide chemistry methods.

[3588] 15 mg (18 μmol) of N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-amino-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide were then dissolved in 5 ml of dimethylformamide and subsequently admixed with 13 mg (35 μmol) of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, 9 μl of N,N-diisopropylethylamine and with 15 mg (44 μmol) of benzyl trans-4-aminocyclohexanecarboxylate trifluoroacetate. The mixture was stirred at RT for 1 h and then concentrated under reduced pressure. The remaining residue was purified by means of preparative HPLC. The corresponding fractions were combined and the solvent was evaporated off under reduced pressure. After the residue had been dried under high vacuum, 14.7 mg (78% of theory) of the protected intermediate were obtained as a colourless foam.

[3589] HPLC (Method 6): R_t=2.0 min;

[3590] LC-MS (Method 1): R_t=0.95 min; MS (ESIpos): m/z=1072 $(M+H)^+$.

[3591] From this protected intermediate, the benzyl ester was first removed by hydrogenolytic means and the free carboxyl component was obtained in quantitative yield. 14 mg (14 μmol; 1 equiv.) of the deprotected compound were taken up in 5 ml of DMF and admixed with 3.3 mg (29 μmol; 2.1 equiv.) of N-hydroxysuccinimide in the presence of 4.1 mg (21 μmol; 1.5 equiv.) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 7.5 μl (44 μmol; 3.1 equiv.) of N,N-diisopropylethylamine and 0.9 mg (7 μmol; 0.5 equiv.) of 4-dimethylaminopyridine, and the mixture was stirred at RT overnight. Then another 10 equiv. of N-hydroxysuccinimide, 5 equiv. of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 5 equiv. of N,N-diisopropylethylamine and 0.5 equiv. of 4-dimethylaminopyridine were added and the reaction mixture was treated in an ultrasound bath for 5 h. Subsequently, the solvent was evaporated off, the residue was purified by means of preparative HPLC and the corresponding fractions were combined and concentrated. After lyophilization of the residue from dioxane, 9.7 mg (62% of theory) of the title compound were obtained as a colourless foam.

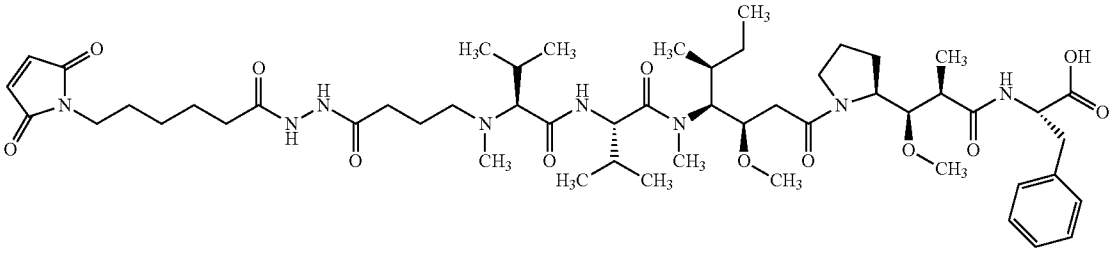
[3592] HPLC (Method 6): R_t=1.8 min;

[3593] LC-MS (Method 11): R_t=0.77 min; MS (ESIpos): m/z=1078 $(M+H)^+$.

Intermediate 105

N-(4-{2-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(1S)-1-carboxy-2-phenylethyl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3594]



[3595] This compound was prepared in analogy to the synthesis described in Intermediate 157, proceeding from 4-{[(2S)-1-{[(2S)-1-{[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-tert-butoxy-1-oxo-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)amino}-3-methylbutan-2-yl]amino}-3-methyl-1-oxobutan-2-yl](methyl)amino}butanoic acid and commercially available 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanehydrazide. The ester intermediate was obtained in 42% yield. In a second step, 6 mg (6 μmol) of this intermediate were cleaved with trifluoroacetic acid the tert-butyl ester. After HPLC purification, 3.4 mg (48% of theory) of the title compound were obtained.

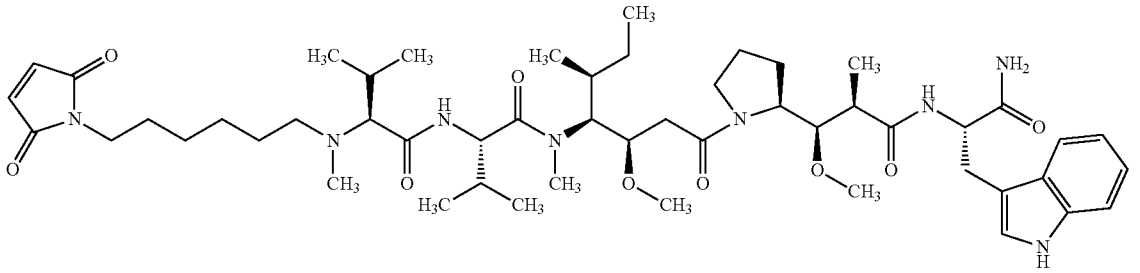
[3596] HPLC (Method 5): R_t=1.66 min;

[3597] LC-MS (Method 2): R_t=1.04 min; MS (ESIpos): m/z=1025 $(M+H)^+$.

Intermediate 106

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexyl]-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-amino-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3598]



[3599] 14 mg (16 μmol) of N-(6-aminohexyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-amino-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Intermediate 88) were taken up in 750 μl of dioxane and admixed with 1.5 ml of saturated sodium hydrogencarbonate solution and then with 3.2 mg (21 μmol) of methyl 2,5-dioxo-2,5-dihydro-1H-pyrrole-1-carboxylate. The reaction mixture was stirred at RT for 1 h and then concentrated under reduced pressure. The remaining residue was purified by means of preparative HPLC. After lyophilization, 5.5 mg (36% of theory) of the title compound were obtained.

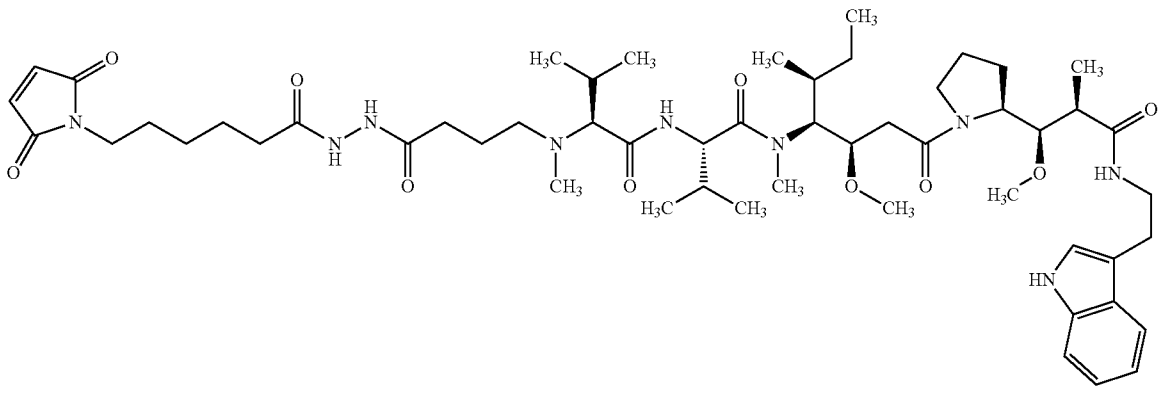
[3600] HPLC (Method 5): R_t=1.7 min;

[3601] LC-MS (Method 1): R_t=0.84 min; MS (ESIpos): m/z=949 $(M+H)^+$.

Intermediate 107

N-(4-{2-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[2-(1H-indol-3-yl)ethyl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3602]



[3603] 38 mg (47 μmol) of N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[2-(1H-indol-3-yl)ethyl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide were dissolved in 37 ml of DMF and then admixed with 71 mg (187 μmol) of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, 33 μl of N,N-diisopropylethylamine and with 37 mg (140 μmol) of commercially available 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanehydrazide. The mixture was stirred at RT for 1 h. This was followed by concentration under high vacuum and purification of the remaining residue by means of preparative HPLC. Thus, 12.2 mg (26% of theory) of the title compound were obtained as a colourless foam.

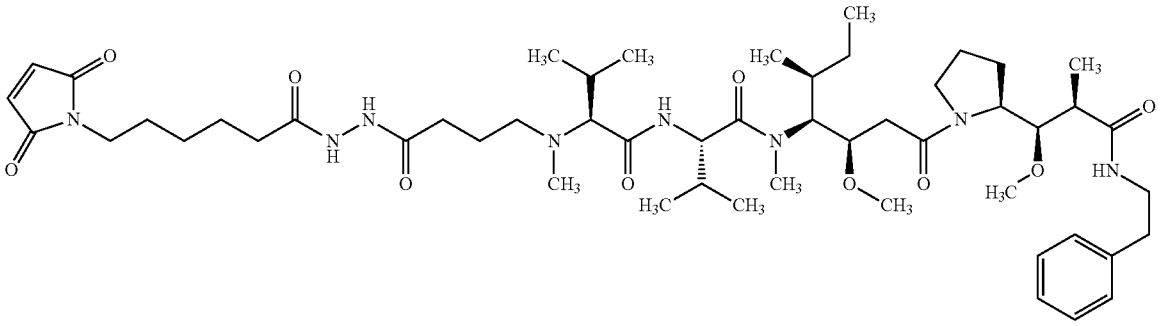
[3604] HPLC (Method 5): R_t=1.6 min;

[3605] LC-MS (Method 1): R_t=0.85 min; MS (ESIpos): m/z=1020 $(M+H)^+$.

Intermediate 108

N-(4-{2-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-N-methyl-L-valyl-N-{(3R,4S,5S)-3-methoxy-1-[(2S)-2-{(1R,2R)-1-methoxy-2-methyl-3-oxo-3-[(2-phenylethyl)amino]propyl}pyrrolidin-1-yl]-5-methyl-1-oxoheptan-4-yl}-N-methyl-L-valinamide

[3606]



[3607] The compound was prepared in analogy to Intermediate 107.

Yield: 2.5 mg (30% of theory)

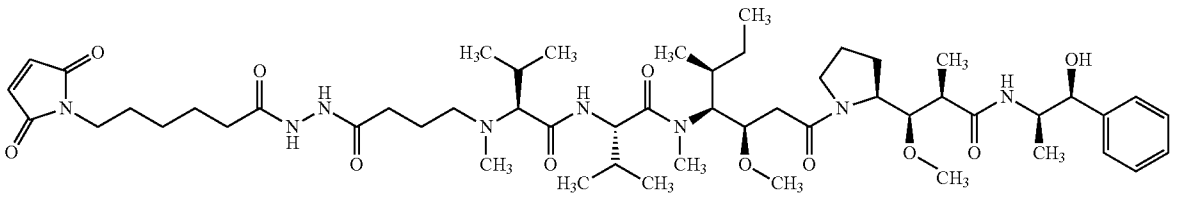
[3608] HPLC (Method 12): R_t=1.9 min;

[3609] LC-MS (Method 1): R_t=0.9 min; MS (ESIpos): m/z=981 $(M+H)^+$.

Intermediate 109

N-(4-{2-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(1S,2R)-1-hydroxy-1-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3610]



[3611] The compound was prepared in analogy to Intermediate 107 from the compound in Intermediate 92.

[3612] Yield: 35 mg (65% of theory)

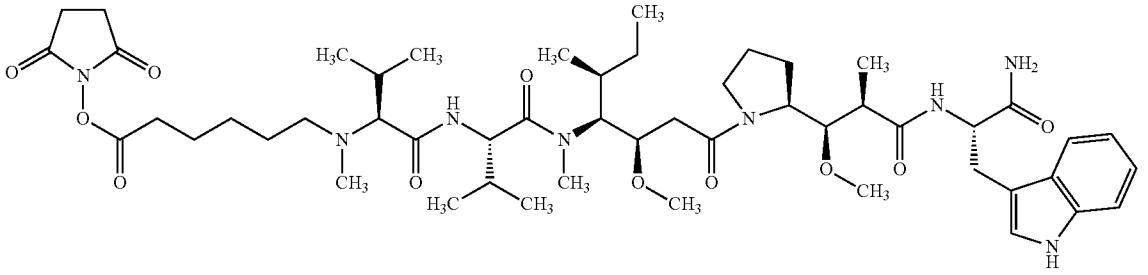
[3613] HPLC (Method 5): R_t=1.9 min;

[3614] LC-MS (Method 11): R_t=0.76 min; MS (ESIpos): m/z=1011 $(M+H)^+$.

Intermediate 110

N-{6-[(2,5-dioxopyrrolidin-1-yl)oxy]-6-oxohexyl}-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-amino-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3615]



[3616] This compound was prepared in analogy to Intermediate 147 from the compound in Intermediate 83.

[3617] Yield: 2.4 mg (24% of theory)

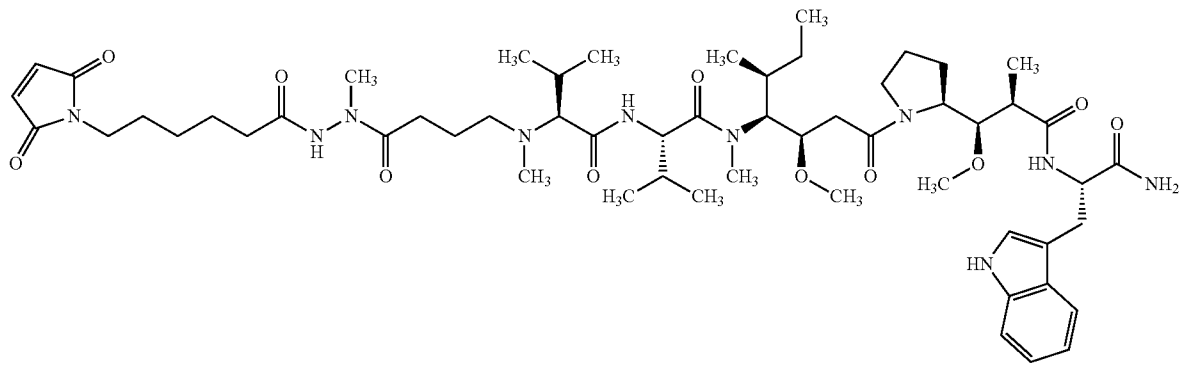
[3618] HPLC (Method 6): R_t=1.8 min;

[3619] LC-MS (Method 1): R_t=0.87 min; MS (ESIpos): m/z=981 $(M+H)^+$.

Intermediate 111

N-(4-{2-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-1-methylhydrazino}-4-oxobutyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-amino-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3620]



[3621] This compound was prepared in analogy to Intermediate 140 from Intermediate 82 and Intermediate 22.

[3622] Yield: 6.5 mg (51% of theory)

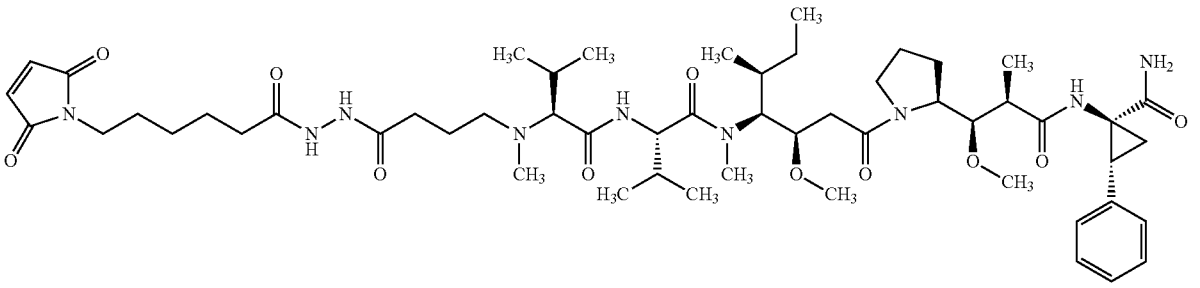
[3623] HPLC (Method 6): R_t=1.8 min;

[3624] LC-MS (Method 1): R_t=4.71 min; MS (ESIpos): m/z=1077 $(M+H)^+$.

Intermediate 112

N-(4-{2-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl) hexanoyl]hydrazino}-4-oxobutyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(1S,2R)-1-carbamoyl-2-phenylcyclopropyl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3625]



[3626] This compound was prepared in analogy to Intermediate 157 from the compound in Intermediate 81.

[3627] Yield: 5.7 mg (57% of theory)

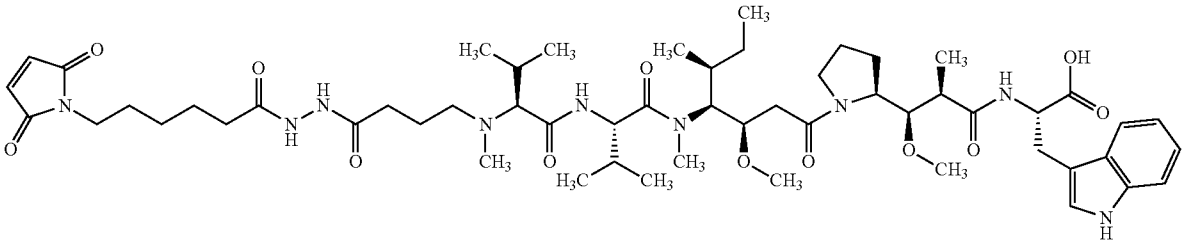
[3628] HPLC (Method 5): R_t=1.6 min;

[3629] LC-MS (Method 1): R_t=0.87 min; MS (ESIpos): m/z=1036 $(M+H)^+$.

Intermediate 113

N-(4-{2-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl) hexanoyl]hydrazino}-4-oxobutyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(1S)-1-carboxy-2-(1H-indol-3-yl)ethyl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3630]



[3631] 95 mg (104 μmol) of 4-{[(2S)-1-{[(2S)-1-{[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-tert-butoxy-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)amino}-3-methylbutan-2-yl]amino}-3-methyl-1-oxobutan-2-yl](methyl)amino}butanoic acid were dissolved in DMF and then admixed with 79.5 mg (209 μmol) of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, 73 μl of N,N-diisopropylethylamine and with 68 mg (261 μmol) of commercially available 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanehydrazide. The mixture was stirred at RT for 2 h. This was followed by concentration under high vacuum and purification of the remaining residue by means of preparative HPLC. Thus, 104 mg (89% of theory) of the tert-butyl ester of the title compound were obtained as a colourless foam.

[3632] HPLC (Method 5): R_t=2.0 min;

[3633] LC-MS (Method 1): R_t=0.93 min; MS (ESIpos): m/z=1121 $(M+H)^+$.

[3634] The intermediate was taken up in 33.4 ml of dichloromethane, 17 ml of trifluoroacetic acid were added, and the mixture was stirred at RT for 1 h. Subsequently, the reaction mixture was concentrated under reduced pressure and the residue was purified by preparative HPLC.

[3635] Thus, 61 mg (62% of theory) of the title compound were obtained as a colourless foam.

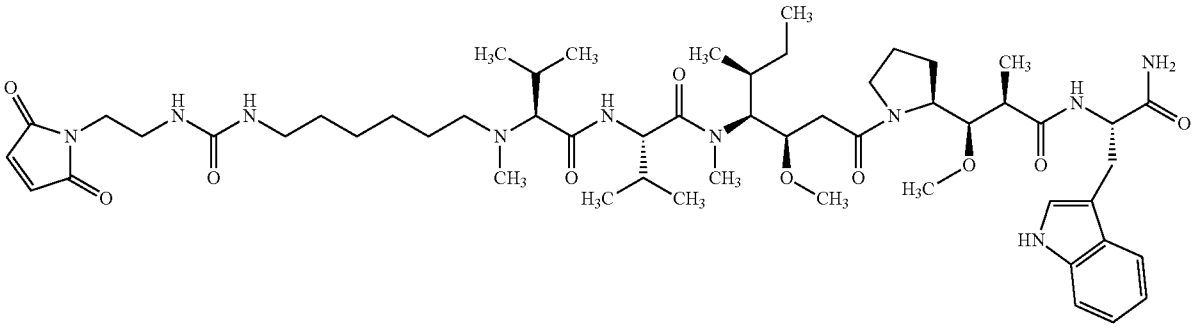
[3636] HPLC (Method 5): R_t=1.7 min;

[3637] LC-MS (Method 1): R_t=0.86 min; MS (ESIpos): m/z=1064 $(M+H)^+$.

Intermediate 114

N-[6-({[2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethyl]carbamoyl}amino)hexyl]-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-amino-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3638]



[3639] 5 mg (5 μmol) of N-(6-aminohexyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-amino-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide were taken up in 885 μl of DMF and admixed with 5.3 mg (8 μmol) of 4-nitrophenyl 2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethyl carbamate and 2.8 μl of N,N-diisopropylethylamine. The reaction mixture was stirred at RT for 2 h and then concentrated to dryness. The residue was purified by means of preparative HPLC.

[3640] Yield: 0.58 mg (11% of theory) of a colourless foam

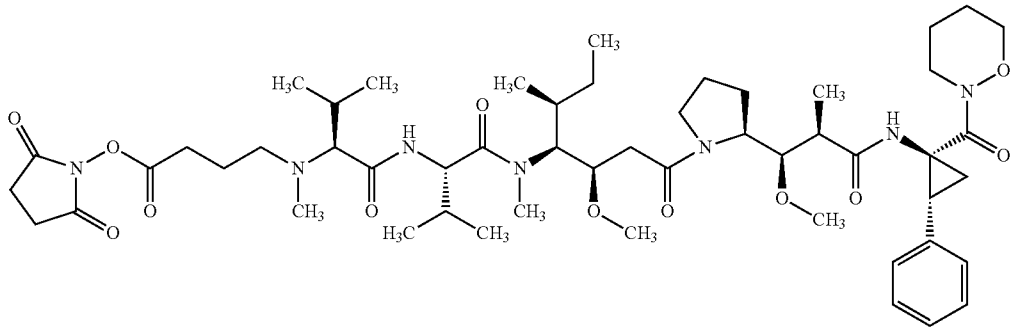
[3641] HPLC (Method 5): R_t=1.6 min;

[3642] LC-MS (Method 1): R_t=0.83 min; MS (ESIpos): m/z=1035 $(M+H)^+$.

Intermediate 115

N-{4-[(2,5-dioxopyrrolidin-1-yl)oxy]-4-oxobutyl}-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3643]



[3644] This compound was prepared in analogy to the compound in Intermediate 147, proceeding from 8 mg (9 μmol) of N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide. After concentration, the activated ester was purified by means of preparative HPLC and, after removal of the solvent under reduced pressure, reacted immediately with the antibody.

[3645] Yield: 3 mg (27% of theory) (hydrolysis-sensitive)

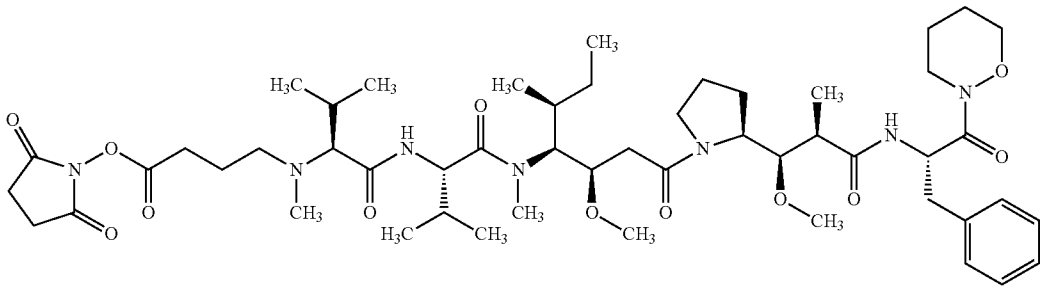
[3646] HPLC (Method 5): R_t=1.7 min;

[3647] LC-MS (Method 1): R_t=0.87 min; MS (ESIpos): m/z=996 $(M+H)^+$.

Intermediate 116

N-{4-[(2,5-dioxopyrrolidin-1-yl)oxy]-4-oxobutyl}-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(2S)-1-(1,2-oxazinan-2-yl)-1-oxo-3-phenylpropan-2-yl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3648]



[3649] This compound was prepared in analogy to the compound in Intermediate 147, proceeding from 5 mg (6 μmol) of N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(2S)-1-(1,2-oxazinan-2-yl)-1-oxo-3-phenylpropan-2-yl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide. After concentration, the activated ester was purified by means of preparative HPLC and, after removal of the solvent under reduced pressure, reacted immediately with the antibody.

[3650] Yield: 3.2 mg (43% of theory) (hydrolysis-sensitive)

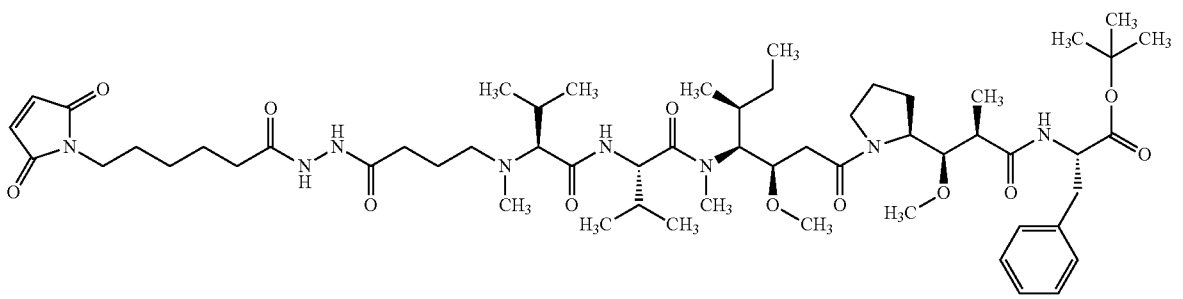
[3651] HPLC (Method 5): R_t=1.7 min;

[3652] LC-MS (Method 1): R_t=0.92 min; MS (ESIpos): m/z=984 $(M+H)^+$.

Intermediate 117

N-(4-{2-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-tert-butoxy-1-oxo-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3653]



[3654] This compound was prepared in analogy to Intermediate 157 from the compound in Intermediate 86.

[3655] Yield: 7 mg (42% of theory)

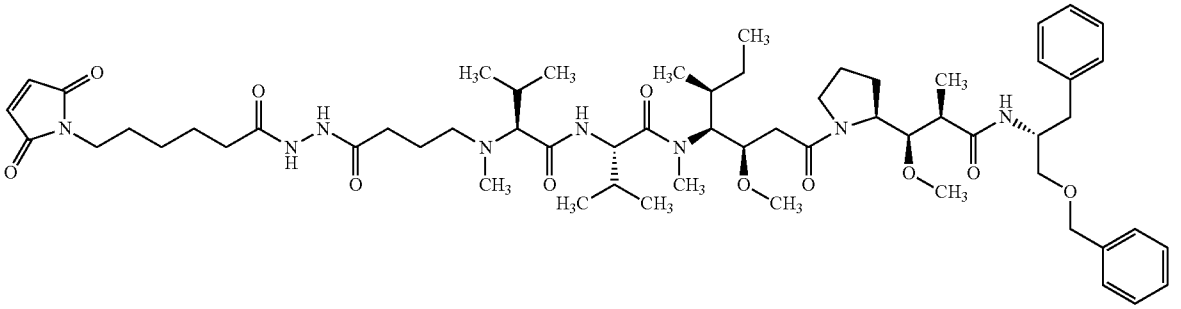
[3656] HPLC (Method 5): R_t=1.6 min;

[3657] LC-MS (Method 1): R_t=0.94 min; MS (ESIpos): m/z=1081 $(M+H)^+$.

Intermediate 118

N-(4-{2-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl) hexanoyl]hydrazino}-4-oxobutyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2R)-1-(benzyloxy)-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3658]



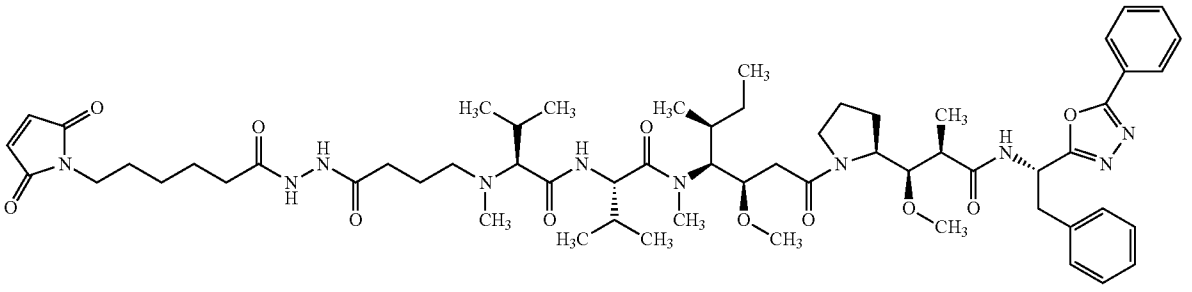
[3659] The target compound was prepared analogously to Intermediate 157 from 7 mg (7.8 μmol) of the compound in Intermediate 68. Yield: 6.3 mg (53% of theory)

[3660] LC-MS (Method 1): R_t=1.00 min; MS (ESIpos): m/z=1102 $(M+H)^+$.

Intermediate 119

N-(4-{2-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl) hexanoyl]hydrazino}-4-oxobutyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(1S)-2-phenyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl]amino}propyl] pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3661]



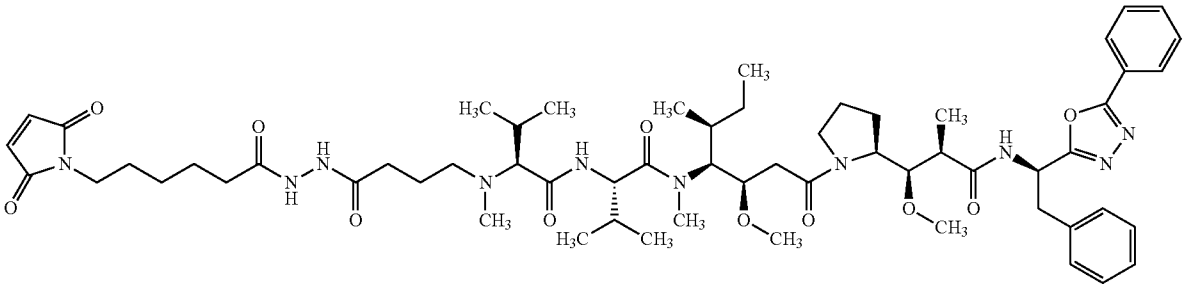
[3662] 7.4 mg (8.1 mmol) of N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(1S)-2-phenyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl]amino}propyl] pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide and 6.3 mg (24.2 mmol) of 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanehydrazide hydrochloride were coupled and worked up in analogy to Intermediate 157. 1.6 mg (13% of theory) of the title compound were obtained as a solid.

[3663] LC-MS (Method 11): R_t=0.89 min; MS (ESIpos): m/z=1126 $(M+H)^+$

Intermediate 120

N-(4-{2-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl) hexanoyl]hydrazino}-4-oxobutyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(1R)-2-phenyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl]amino}propyl] pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3664]



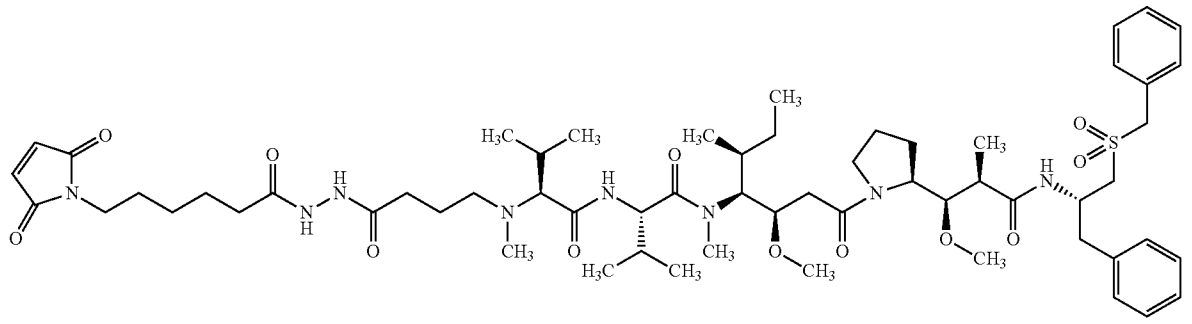
[3665] 12.8 mg (13.9 mmol) of N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(1R)-2-phenyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl]amino}propyl] pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide and 10.9 mg (41.8 mmol) of 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanehydrazide hydrochloride were coupled and worked up in analogy to Intermediate 157. 10.8 mg (59% of theory) of the title compound were obtained as a solid.

[3666] LC-MS (Method 11): R_t=0.90 min; MS (ESIpos): m/z=1126 $(M+H)^+$

Intermediate 121

N-(4-{2-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl) hexanoyl]hydrazino}-4-oxobutyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(benzylsulphonyl)-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3667]



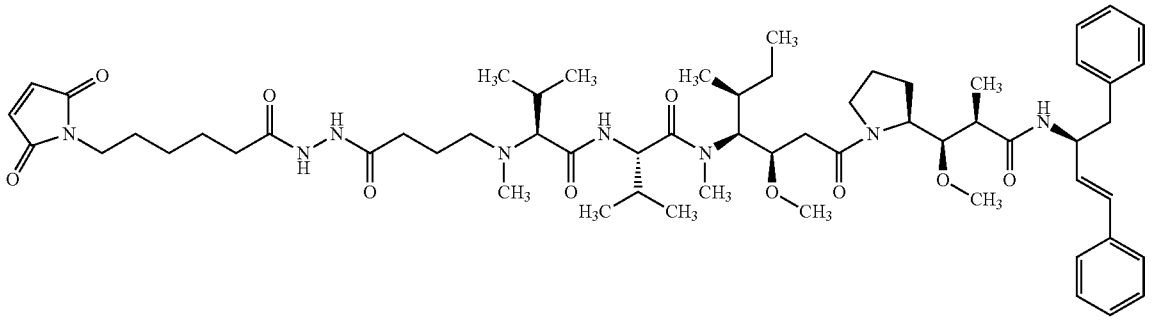
[3668] 7.4 mg (7.9 mmol) of N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(benzylsulphonyl)-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide and 6.2 mg (23.5 mmol) of 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanehydrazide hydrochloride were coupled and worked up in analogy to Intermediate 157. 6.9 mg (74% of theory) of the title compound were obtained as a solid.

[3669] LC-MS (Method 11): R_t=0.87 min; MS (ESIpos): m/z=1150 (M+H)+

Intermediate 122

N-(4-{2-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S,3E)-1,4-diphenylbut-3-en-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3670]



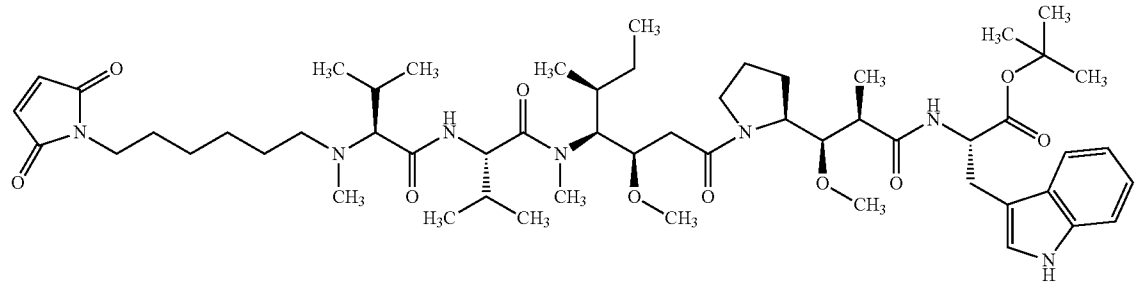
[3671] 8 mg (9.1 mmol) of N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S,3E)-1,4-diphenylbut-3-en-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide and 7.2 mg (27.4 mmol) of 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanehydrazide hydrochloride were coupled and worked up in analogy to Intermediate 157. 8.2 mg (82% of theory) of the title compound were obtained as a white solid.

[3672] LC-MS (Method 11): R_t=0.95 min; MS (ESIpos): m/z=1083 (M+H)+

Intermediate 123

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexyl]-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-tert-butoxy-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3673]



[3674] 30 mg (30 μmol) of Intermediate 89 were taken up in 2 ml of 1,4-dioxane and admixed with 4 ml of saturated sodium hydrogencarbonate solution and then with 7.5 mg (50 μmol) of methyl 2,5-dioxo-2,5-dihydro-1H-pyrrole-1-carboxylate. The reaction mixture was stirred at RT for 1 h and then concentrated under reduced pressure. The remaining residue was purified by means of preparative HPLC. After lyophilization, 24 mg (74% of theory) of the title compound were obtained.

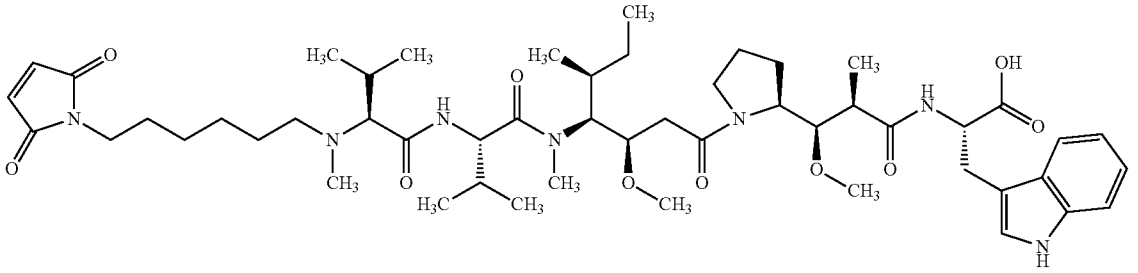
[3675] HPLC (Method 5): R_t=2.2 min;

[3676] LC-MS (Method 1): R_t=1.01 min; MS (ESIpos): m/z=1006 $(M+H)^+$.

Intermediate 124

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexyl]-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(1S)-1-carboxy-2-(1H-indol-3-yl)ethyl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3677]



[3678] 22 mg (20 μmol) of Intermediate 123 were reacted with 4 ml of trifluoroacetic acid in 8 ml of dichloromethane at RT for 1 h. Thereafter, the reaction mixture was concentrated under reduced pressure. The remaining residue was purified by means of preparative HPLC. After lyophilization, 11 mg (54% of theory) of the title compound were obtained.

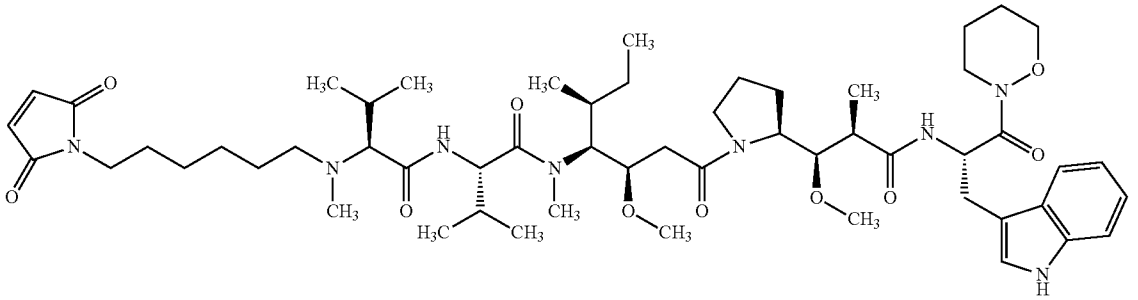
[3679] HPLC (Method 5): R_t=1.8 min;

[3680] LC-MS (Method 11): R_t=0.85 min; MS (ESIpos): m/z=950 $(M+H)^+$.

Intermediate 125

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexyl]-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3681]



[3682] 22.5 mg (20 μmol) of Intermediate 101 were taken up in 2 ml of 1:1 dioxane/water and then admixed with 5.6 mg (40 μmol) of methyl 2,5-dioxo-2,5-dihydro-1H-pyrrole-1-carboxylate and with 0.25 ml of saturated sodium hydrogencarbonate solution. The reaction mixture was stirred at RT for 30 min. Then another 0.25 ml of the saturated sodium hydrogencarbonate solution was added and the reaction mixture was stirred at RT for a further 15 min and then concentrated under reduced pressure. The remaining residue was purified by means of preparative HPLC. After lyophilization, 12.8 mg (50% of theory) of the title compound were obtained as a colourless foam.

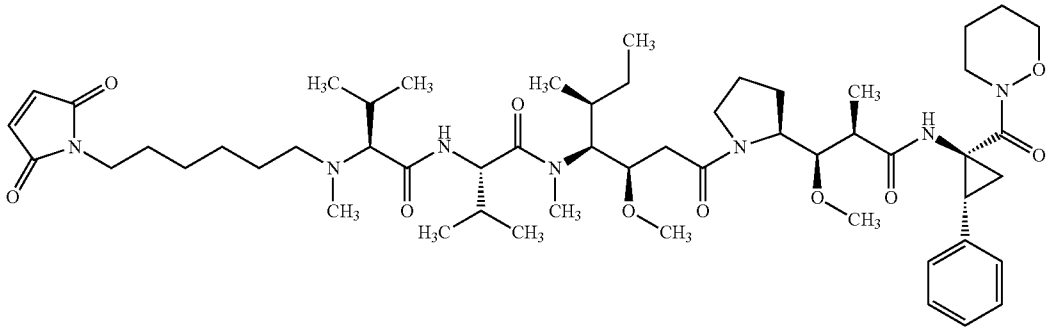
[3683] HPLC (Method 5): R_t=1.9 min;

[3684] LC-MS (Method 1): R_t=0.95 min; MS (ESIpos): m/z=1019 $(M+H)^+$.

Intermediate 126

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexyl]-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3685]



[3686] 64 mg (70 μmol) of N-(6-aminohexyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Intermediate 97) were taken up in 3 ml of 1:1 dioxane/water, then adjusted to pH 9 with 4 ml of saturated sodium hydrogencarbonate solution and subsequently admixed with 16.3 mg (110 μmol) of methyl 2,5-dioxo-2,5-dihydro-1H-pyrrole-1-carboxylate. The reaction mixture was stirred at RT for 1 h and then concentrated under reduced pressure. Then another 8 mg (55 μmol) of methyl 2,5-dioxo-2,5-dihydro-1H-pyrrole-1-carboxylate were added, and the reaction mixture was adjusted again to pH 9 and stirred at RT for a further hour. This was followed by concentration and purification of the remaining residue by means of preparative HPLC. At first, 31 mg of an as yet uncyclized intermediate were obtained. 27 mg of this intermediate were taken up again in 2 ml of 1:1 dioxane/water and then admixed with 250 μl of saturated sodium hydrogencarbonate solution. After stirring at RT for 2 hours, the reaction mixture was concentrated and the residue was purified by means of preparative HPLC. After lyophilization, 20 mg (29% of theory) of the title compound were obtained.

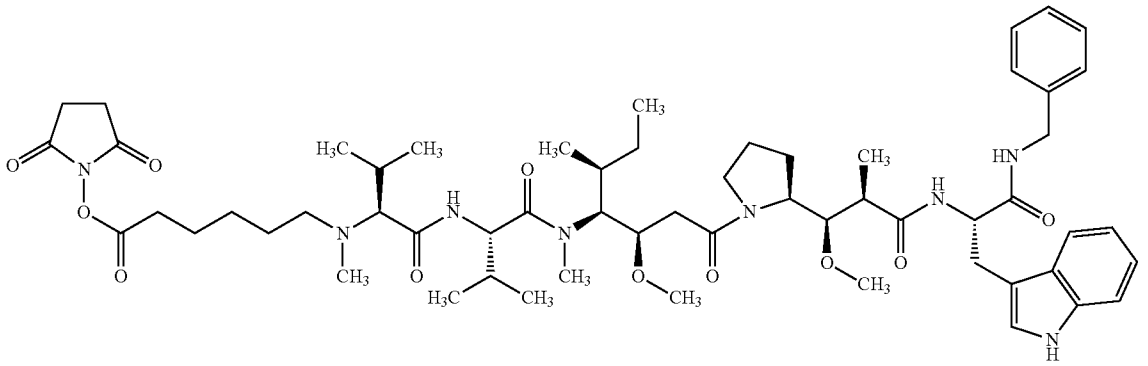
[3687] HPLC (Method 5): R_t=1.96 min;

[3688] LC-MS (Method 1): R_t=0.97 min; MS (ESIpos): m/z=992 $(M+H)^+$.

Intermediate 127

N-{6-[(2,5-dioxopyrrolidin-1-yl)oxy]-6-oxohexyl}-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(benzylamino)-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3689]



[3690] 17 mg (18 μmol) of N-(5-carboxypentyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(benzylamino)-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Intermediate 98) were dissolved in 2.8 ml of dichloromethane and admixed with 20 mg (174 mmol) of 1-hydroxypyrrolidine-2,5-dione and then with 10 mg (52 μmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 0.21 mg (0.17 μmol) of DMAP. After stirring at RT for 4 h, the reaction mixture was concentrated under reduced pressure. The remaining residue was purified by means of preparative HPLC. After lyophilization, 8.2 mg (43% of theory) of the title compound were obtained.

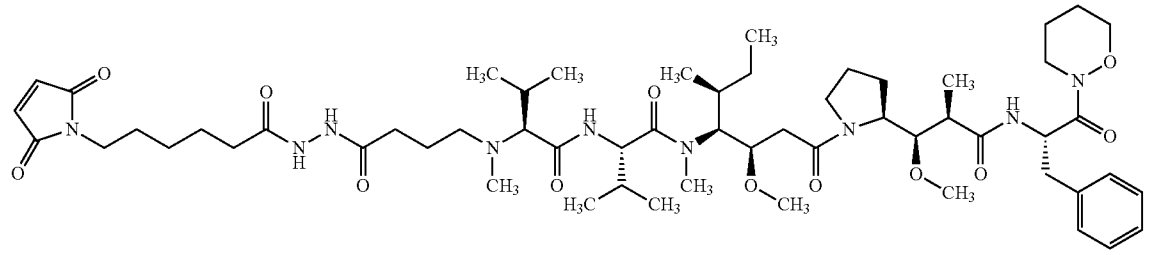
[3691] HPLC (Method 5): R_t=2.0 min;

[3692] LC-MS (Method 1): R_t=0.98 min; MS (ESIpos): m/z=1071 $(M+H)^+$.

Intermediate 128

N-(4-{2-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(2S)-1-(1,2-oxazinan-2-yl)-1-oxo-3-phenylpropan-2-yl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3693]



[3694] 5 mg (5.6 μmol) of N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(2S)-1-(1,2-oxazinan-2-yl)-1-oxo-3-phenylpropan-2-yl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide were dissolved in 845 μl of DMF and then admixed with 3.2 mg (17 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 2.6 mg (17 μmol) of 1-hydroxy-1H-benzotriazole hydrate, 1.96 μl of N,N-diisopropylethylamine and with 5.9 mg (22.5 μmol) of commercially available 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanehydrazide. The mixture was stirred at RT overnight and then concentrated under high vacuum. The remaining residue was purified by means of preparative HPLC. Thus, 2.2 mg (36% of theory) of the title compound were obtained as a colourless foam.

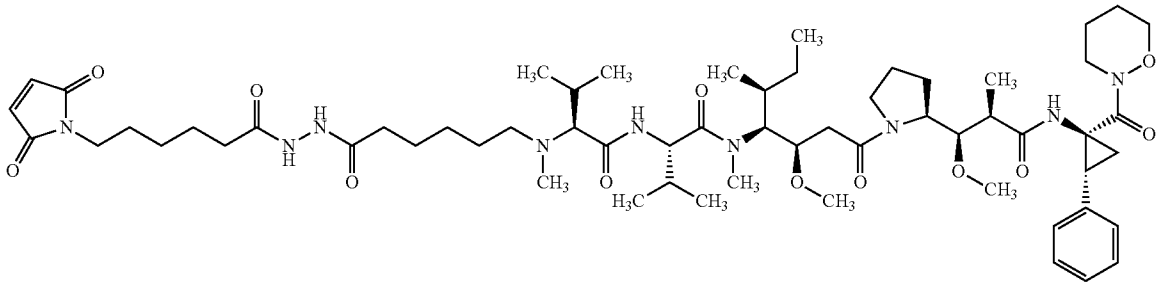
[3695] HPLC (Method 5): R_t=1.7 min;

[3696] LC-MS (Method 1): R_t=0.88 min; MS (ESIpos): m/z=1094 $(M+H)^+$.

Intermediate 129

N-(6-{2-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]hydrazino}-6-oxohexyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3697]



[3698] 4 mg (4.3 μmol) of N-(5-carboxypentyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide were dissolved in 646 μl of DMF and then admixed with 2.5 mg (13 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 2.0 mg (13 μmol) of 1-hydroxy-1H-benzotriazole hydrate, 2.25 μl of N,N-diisopropylethylamine and with 4.5 mg (17 μmol) of commercially available 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanehydrazide. The mixture was stirred at RT for 3 h and then concentrated under high vacuum. The remaining residue was purified by means of preparative HPLC. Thus, 1.9 mg (39% of theory) of the title compound were obtained as a colourless foam.

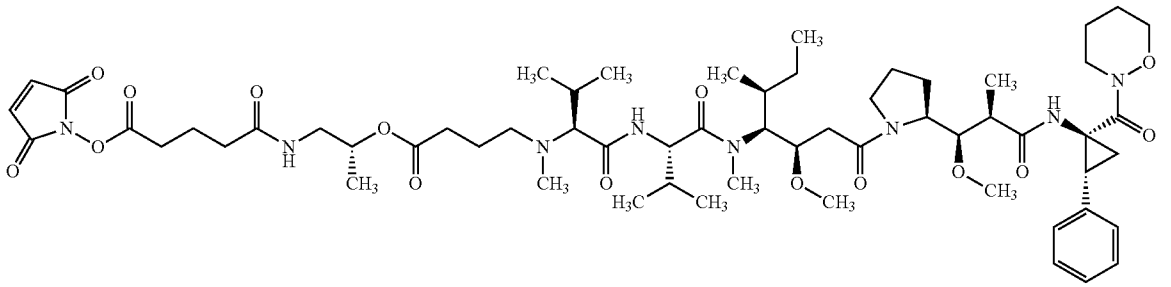
[3699] HPLC (Method 5): R_t=1.7 min;

[3700] LC-MS (Method 9): R_t=4.9 min; MS (ESIpos): m/z=1134 $(M+H)^+$.

Intermediate 130

N-(4-{[(2R)-1-({5-[(2,5-dioxopyrrolidin-1-yl)oxy]-5-oxopentanoyl}amino)propan-2-yl]oxy}-4-oxobutyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3701]



[3702] 10.5 mg (11.7 μmol) of N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide were dissolved in 3.7 ml of dichloromethane and then admixed with 6.7 mg (35 μmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 0.7 mg (5.8 mmol) of 4-dimethylaminopyridine and with 8.2 mg (47 μmol) of commercially available tert-butyl (2R)-2-hydroxypropyl carbamate. The mixture was stirred at RT overnight and then concentrated under high vacuum. The remaining residue was purified by means of preparative HPLC. Thus, 7.5 mg (61% of theory) of the Boc-protected intermediate were obtained as a colourless foam.

[3703] HPLC (Method 5): R_t=2.0 min;

[3704] LC-MS (Method 1): R_t=1.03 min; MS (ESIpos): m/z=1056 $(M+H)^+$.

[3705] Subsequently, the Boc protecting group was detached with trifluoroacetic acid. 4.9 mg (0.005 mmol) of the deprotected crude product were then, without further purification, taken up in 1.8 ml of dichloromethane and admixed with 3.7 mg (0.011 mmol) of 1,1'-[(1,5-dioxopentane-1,5-diyl)bis(oxy)]dipyrrolidine-2,5-dione, 2.4 μl (0.014 mmol) of N,N-diisopropylethylamine and 0.6 mg (5 μmol) of 4-dimethylaminopyridine. The mixture was stirred at RT for 2 h and then concentrated under high vacuum. The remaining residue was purified by means of preparative HPLC. Thus, 0.77 mg (15% of theory) of the title compound were obtained as a colourless foam.

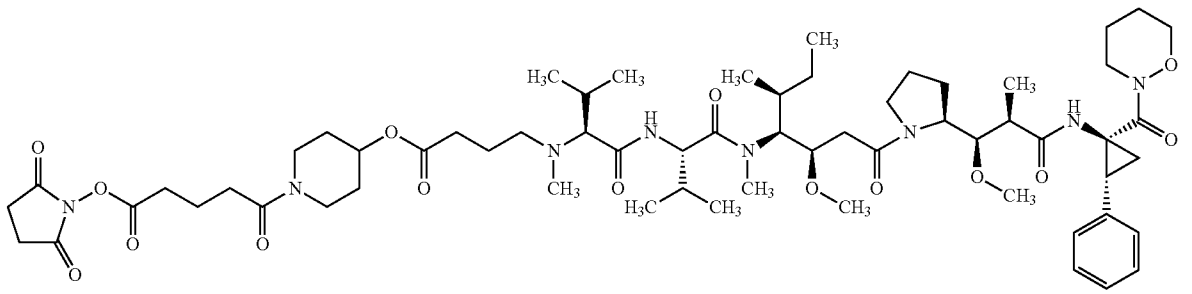
[3706] HPLC (Method 5): R_t=1.8 min;

[3707] LC-MS (Method 1): R_t=0.93 min; MS (ESIpos): m/z=1167 $(M+H)^+$.

Intermediate 131

N-{4-[(1-{5-[(2,5-dioxopyrrolidin-1-yl)oxy]-5-oxopentanoyl}piperidin-4-yl)oxy]-4-oxobutyl}-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3708]



[3709] 10 mg (11 μmol) of N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide were dissolved in 2 ml of dichloromethane and then admixed with 4.3 mg (22 μmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 0.88 mg (6 mmol) of 4-dimethylaminopyridine and with 5.2 mg (22 μmol) of commercially available benzyl 4-hydroxypiperidine-1-carboxylate. The mixture was stirred at RT overnight and then concentrated under high vacuum. The remaining residue was purified by means of preparative HPLC. Thus, 5 mg (40% of theory) of the Z-protected intermediate were obtained as a colourless foam.

[3710] HPLC (Method 5): R_t=2.1 min;

[3711] LC-MS (Method 1): R_t=1.04 min; MS (ESIpos): m/z=1116 $(M+H)^+$.

[3712] Subsequently, the Z protecting group was detached by hydrogenolytic means in ethanol over palladium/activated carbon. 4.6 mg (0.005 mmol) of the deprotected crude product were then, without further purification, taken up in 1.8 ml of dichloromethane and admixed with 3.8 mg (0.012 mmol) of 1,1'-[(1,5-dioxopentane-1,5-diyl)bis(oxy)]dipyrrolidine-2,5-dione, 0.8 μl (0.005 mmol) of N,N-diisopropylethylamine and 0.6 mg (5 μmol) of 4-dimethylaminopyridine. The mixture was stirred at RT overnight and then concentrated under high vacuum. The remaining residue was purified by means of preparative HPLC. Thus, 0.96 mg (16% of theory) of the title compound were obtained as a colourless foam.

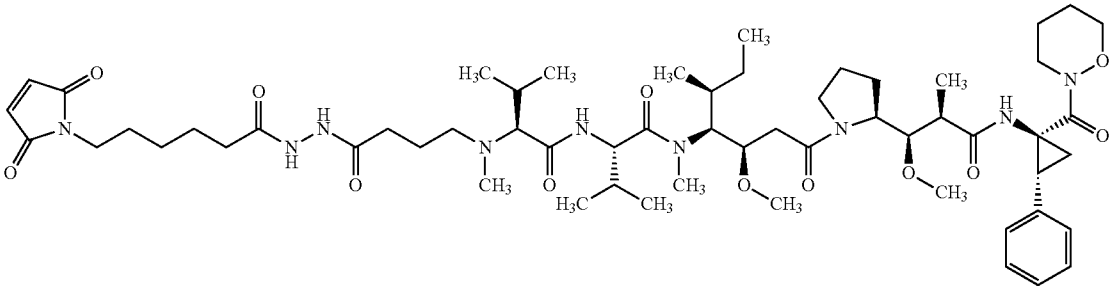
[3713] HPLC (Method 5): R_t=1.8 min;

[3714] LC-MS (Method 1): R_t=0.94 min; MS (ESIpos): m/z=1193 $(M+H)^+$.

Intermediate 132

N-(4-{2-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]hydrazinyl}-4-oxobutyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3715]



[3716] 15 mg (16.7 μmol) of N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide were dissolved in 2500 μl of DMF and then admixed with 9.6 mg (50 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 7.6 mg (50 μmol) of 1-hydroxy-1H-benzotriazole hydrate, 5.8 μl of N,N-diisopropylethylamine and with 17.4 mg (67 μmol) of commercially available 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanehydrazide. The mixture was stirred at RT overnight and then concentrated under high vacuum. The remaining residue was purified by means of preparative HPLC. Thus, 11.2 mg (52% of theory) of the title compound were obtained as a colourless foam.

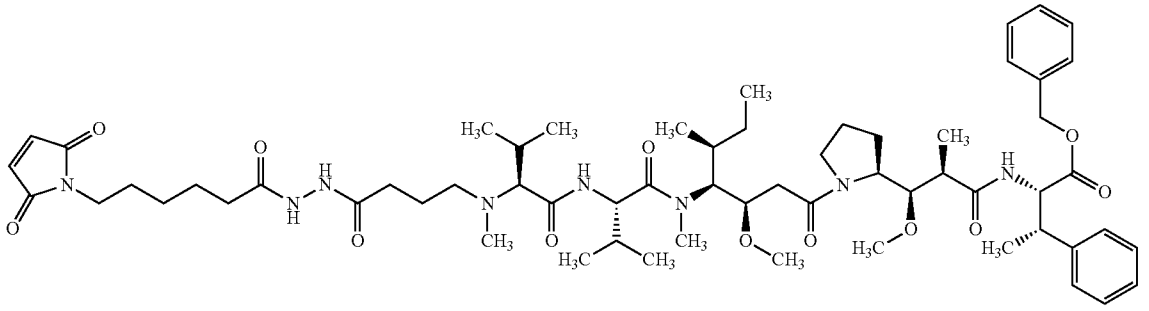
[3717] HPLC (Method 5): R_t=1.7 min;

[3718] LC-MS (Method 2): R_t=1.09 min; MS (ESIpos): m/z=1106 $(M+H)^+$.

Intermediate 133

N-(4-{2-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl) hexanoyl]hydrazinyl}-4-oxobutyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S,3S)-1-(benzyloxy)-1-oxo-3-phenylbutan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3719]



[3720] 5.8 mg (6.3 μmol) of N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S,3S)-1-(benzyloxy)-1-oxo-3-phenylbutan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide were dissolved in 943 μl of DMF and then admixed with 3.6 mg (19 μmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 2.9 mg (19 μmol) of 1-hydroxy-1H-benzotriazole hydrate, 2.2 μl of N,N-diisopropylethylamine and with 6.6 mg (25 μmol) of commercially available 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanehydrazide. The mixture was stirred at RT overnight and then concentrated under high vacuum. The remaining residue was purified by means of preparative HPLC. Thus, 4.5 mg (64% of theory) of the title compound were obtained as a colourless foam.

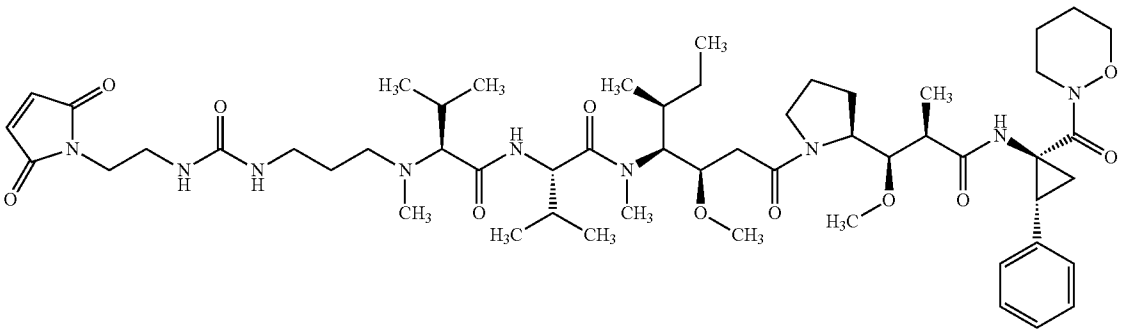
[3721] HPLC (Method 5): R_t=2.0 min;

[3722] LC-MS (Method 1): R_t=1.03 min; MS (ESIpos): m/z=1129 $(M+H)^+$.

Intermediate 134

N-[3-({[2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl) ethyl]carbamoyl}amino)propyl]-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3723]



[3724] First, 4-nitrophenyl 2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethyl carbamate was prepared under standard conditions, proceeding from commercially available 1-(2-aminoethyl)-1H-pyrrole-2,5-dione trifluoroacetate and 4-nitrophenyl chlorocarbonate.

[3725] 5 mg (6 μmol) of N-(3-aminopropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide were dissolved in 1000 μl of DMF and then admixed with 2 μl of N,N-diisopropylethylamine and with 2.2 mg (9 μmol) of 4-nitrophenyl 2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl) ethyl carbamate. The mixture was stirred at RT for 1 h and then concentrated under high vacuum. The remaining residue was purified by means of preparative HPLC. Thus, 1.6 mg (23% of theory) of the title compound were obtained as a colourless foam.

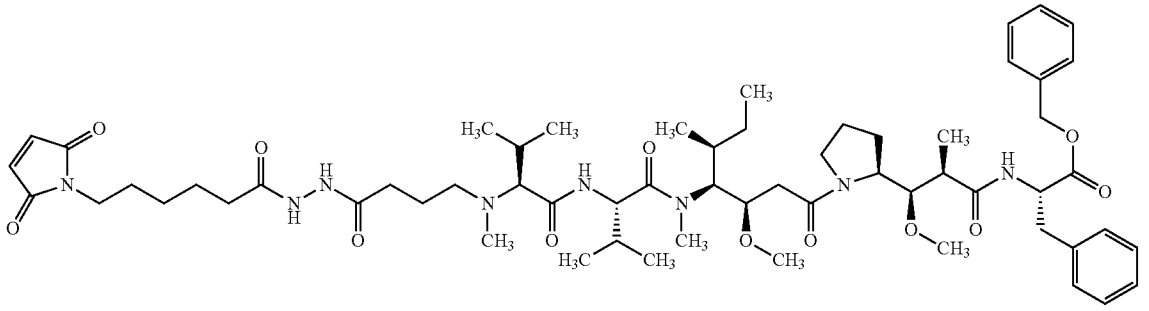
[3726] HPLC (Method 5): R_t=1.7 min;

[3727] LC-MS (Method 2): R_t=1.09 min; MS (ESIpos): m/z=1036 $(M+H)^+$.

Intermediate 135

N-(4-{2-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl) hexanoyl]hydrazino}-4-oxobutyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(benzyloxy)-1-oxo-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3728]



[3729] 10 mg (11 μmol) of N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(benzyloxy)-1-oxo-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide were dissolved in 4000 μl of DMF and then admixed with 6.3 mg (33 μmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 4.5 mg (33 μmol) of 1-hydroxy-1H-benzotriazole hydrate, 5.7 μl of N,N-diisopropylethylamine and with 11.5 mg (44 μmol) of commercially available 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanehydrazide. The mixture was stirred at RT overnight and then concentrated under high vacuum. The remaining residue was purified by means of preparative HPLC. Thus, 2.6 mg (14% of theory) of the title compound were obtained as a colourless foam.

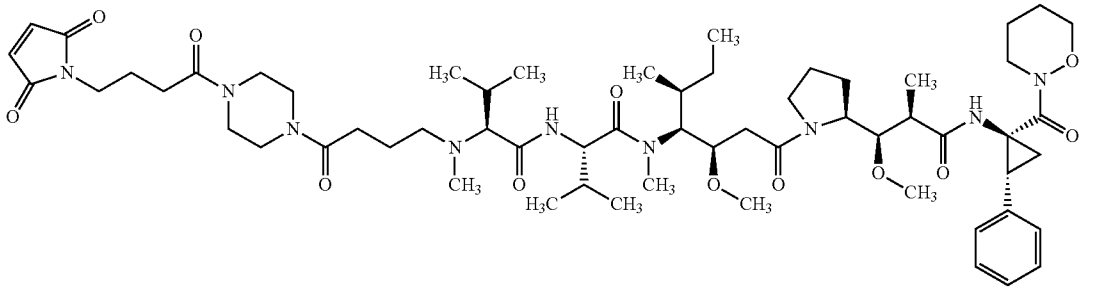
[3730] HPLC (Method 6): R_t=2.1 min;

[3731] LC-MS (Method 1): R_t=1.01 min; MS (ESIpos): m/z=1115 $(M+H)^+$.

Intermediate 136

N-(4-{4-[4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl) butanoyl]piperazin-1-yl}-4-oxobutyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3732]



[3733] First, 1-[4-oxo-4-(piperazin-1-yl)butyl]-1H-pyrrole-2,5-dione trifluoroacetate was prepared under standard conditions, proceeding from tert-butyl piperazine-1-carboxylate and 4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)butanoic acid over 2 stages.

[3734] 5 mg (5.6 μmol) of N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide were dissolved in 1000 μl of DMF and then admixed with 2.1 mg (11 μmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 1.7 mg (11 μmol) of 1-hydroxy-1H-benzotriazole hydrate, 2 μl of N,N-diisopropylethylamine and with 3.5 mg (5.6 μmol) of 1-[4-oxo-4-(piperazin-1-yl) butyl]-1H-pyrrole-2,5-dione trifluoroacetate. The mixture was stirred at RT overnight. Then 2.1 mg (5.6 μmol) of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate were added and the reaction mixture was stirred at RT for a further 3 h. Subsequently, the solvent was removed under reduced pressure and the remaining residue was purified by means of preparative HPLC. The corresponding fractions were concentrated and, by lyophilization from water, 0.6 mg (10% of theory) of the title compound was obtained as a colourless foam.

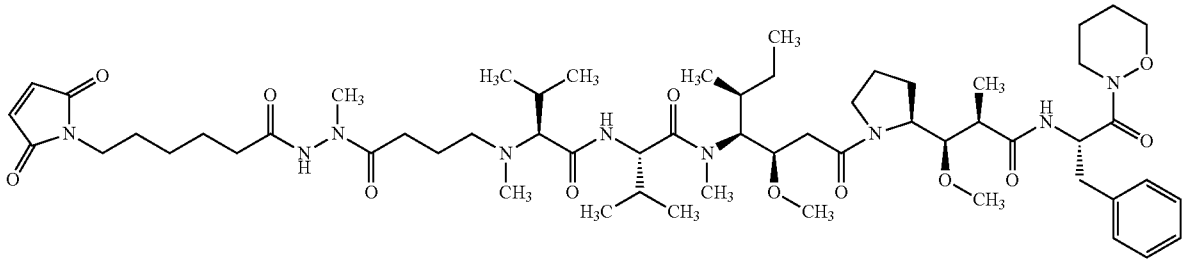
[3735] HPLC (Method 6): R_t=1.9 min;

[3736] LC-MS (Method 1): R_t=0.9 min; MS (ESIpos): m/z=1132 $(M+H)^+$.

Intermediate 137

N-(4-{2-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl) hexanoyl]-1-methylhydrazino}-4-oxobutyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(2S)-1-(1,2-oxazinan-2-yl)-1-oxo-3-phenylpropan-2-yl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3737]



[3738] First, 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-N-methylhexanehydrazide trifluoroacetate was prepared under standard conditions, proceeding from commercially available 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoic acid and tert-butyl 1-methylhydrazinecarboxylate over 2 stages.

[3739] 6.9 mg (8 μmol) of N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(2S)-1-(1,2-oxazinan-2-yl)-1-oxo-3-phenylpropan-2-yl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide were dissolved in 2540 μl of DMF and then admixed with 3.6 mg (9 mmol) of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, 3 μl of N,N-diisopropylethylamine and with 4.1 mg (12 μmol) of 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-N-methylhexanehydrazide trifluoroacetate. The mixture was stirred at RT overnight. Subsequently, the solvent was removed under reduced pressure and the remaining residue was purified by means of preparative HPLC. Thus, 3.9 mg (45% of theory) of the title compound were obtained as a colourless foam.

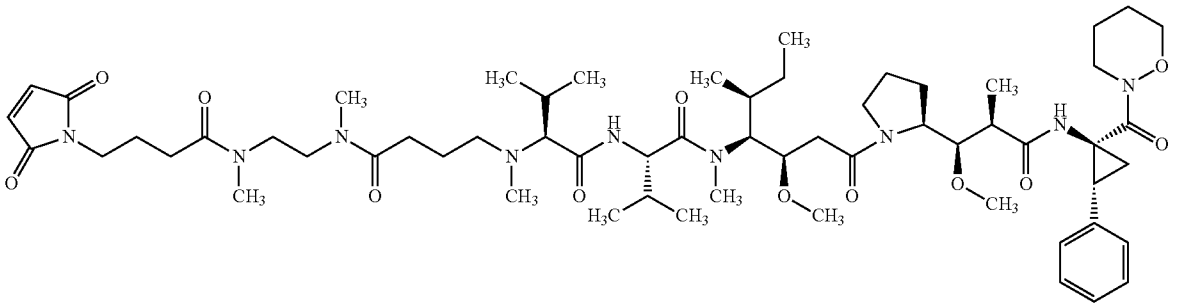
[3740] HPLC (Method 5): R_t=1.8 min;

[3741] LC-MS (Method 1): R_t=0.93 min; MS (ESIpos): m/z=1108 $(M+H)^+$.

Intermediate 138

N-{4-[(2-{[4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)butanoyl](methyl)amino}ethyl)(methyl)amino]-4-oxobutyl}-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3742]



[3743] Proceeding from tert-butylmethyl 2-(methylamino) ethyl carbamate and 4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)butanoic acid, over 2 stages, 4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-N-methyl-N-[2-(methylamino)ethyl] butanamide trifluoroacetate was first prepared by.

[3744] 6.6 mg (7.3 μmol) of N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl] pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide were dissolved in 2000 μl of DMF and then admixed with 5.6 mg (14.7 mmol) of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, 2.6 μl of N,N-diisopropylethylamine and with 4.1 mg (9 μmol) of 4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-N-methyl-N-[2-(methylamino)ethyl]butanamide trifluoroacetate. After stirring at RT for 3 h, the same amounts of HATU and N,N-diisopropylethylamine were added once again, and the reaction mixture was then stirred at RT overnight. Subsequently, the solvent was removed under reduced pressure and the remaining residue was purified by means of preparative HPLC. Thus, 4 mg (44% of theory) of the title compound were obtained as a colourless foam.

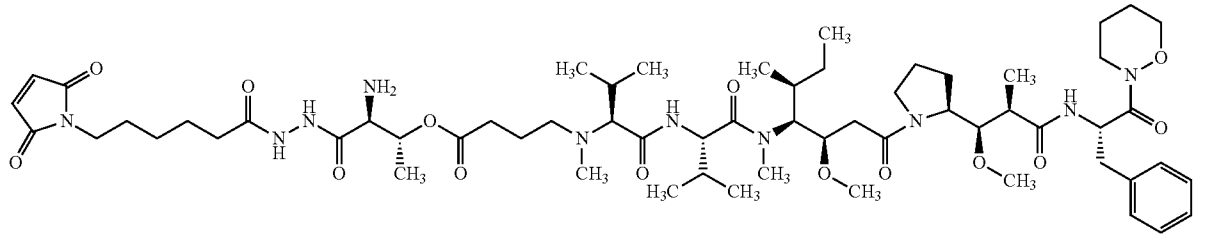
[3745] HPLC (Method 6): R_t=2.0 min;

[3746] LC-MS (Method 1): R_t=0.91 min; MS (ESIpos): m/z=1134 $(M+H)^+$.

Intermediate 139

(2R,3S)-3-amino-4-{2-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutan-2-yl (3R,4S,7S,10S)-4-[(2S)-butan-2-yl]-7,10-diisopropyl-3-(2-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(2S)-1-(1,2-oxazinan-2-yl)-1-oxo-3-phenylpropan-2-yl]amino}-3-oxopropyl]pyrrolidin-1-yl}-2-oxoethyl)-5,11-dimethyl-6,9-dioxo-2-oxa-5,8,11-triazapentadecan-15-oate

[3747]



[3748] 13 mg (14.7 μmol) of N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(2S)-1-(1,2-oxazinan-2-yl)-1-oxo-3-phenylpropan-2-yl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide were dissolved in 10 ml of dichloromethane and then admixed with 8.4 mg (44 μmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 5.4 mg (44 mmol) of 4-dimethylaminopyridine and with 9 mg (29.3 μmol) of commercially available benzyl N-(tert-butoxycarbonyl)-L-threoninate. The mixture was stirred at RT for 5 h. Subsequently, the reaction mixture was twice extracted by shaking with water and the organic phase was dried over sodium sulphate and concentrated under reduced pressure. The remaining residue was purified by means of preparative HPLC. After lyophilization from dioxane/water, 14 mg (81% of theory) of the protected intermediate were obtained as a colourless foam.

[3749] HPLC (Method 12): R_t=2.3 min;

[3750] LC-MS (Method 1): R_t=1.13 min; MS (ESIpos): m/z=1178 $(M+H)^+$.

[3751] Subsequently, the Z protecting group was detached by hydrogenolytic means in methanol over 10% palladium/activated carbon. 9.5 mg (0.0087 mmol) of the deprotected crude product were then, without further purification, taken up in 5 ml of DMF, and admixed 5 mg (26.2 μmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 4 mg (26.2 μmol) of 1-hydroxy-1H-benzotriazole hydrate, 54.6 μl of N,N-diisopropylethylamine and with 9.1 mg (34.9 μmol) of commercially available 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanehydrazide. The mixture was stirred at RT for 1 h and then concentrated under high vacuum. The remaining residue was purified by means of preparative HPLC. After lyophilization from dioxane, 9.5 mg (84% of theory) of the Boc-protected intermediate were obtained.

[3752] HPLC (Method 12): R_t=2.1 min;

[3753] LC-MS (Method 1): R_t=0.97 min; MS (ESIpos): m/z=1295 $(M+H)^+$.

[3754] Subsequently, 9.5 mg (7.3 μmol) were deprotected with 0.5 ml of trifluoroacetic acid in 2 ml of dichloromethane of the Boc-protected intermediate and, after lyophilization from dioxane, 9 mg (82% of theory) of the title compound were obtained as a colourless foam.

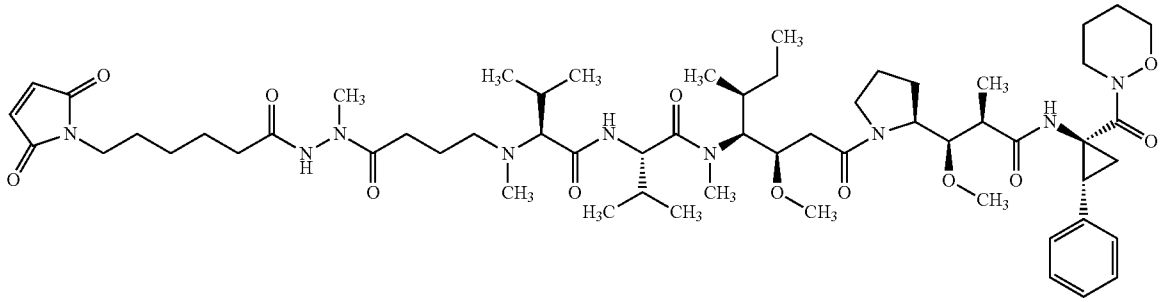
[3755] HPLC (Method 12): R_t=2.1 min;

[3756] LC-MS (Method 1): R_t=0.84 min; MS (ESIpos): m/z=1195 $(M+H)^+$.

Intermediate 140

N-(4-{2-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]-1-methylhydrazino}-4-oxobutyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3757]



[3758] 4.1 mg (12 μmol) of 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-N-methylhexanehydrazide trifluoroacetate (Intermediate 22) were dissolved together with 6.9 mg (8 μmol) of the compound from Intermediate 61 in 2.5 ml of DMF and then admixed with 3.5 mg (9 μmol) of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and 3 μl of N,N-diisopropylethylamine. The mixture was stirred at RT overnight and then concentrated under high vacuum. The remaining residue was purified by means of preparative HPLC. After lyophilization from dioxane, 2.6 mg (30% of theory) of the title compound were obtained.

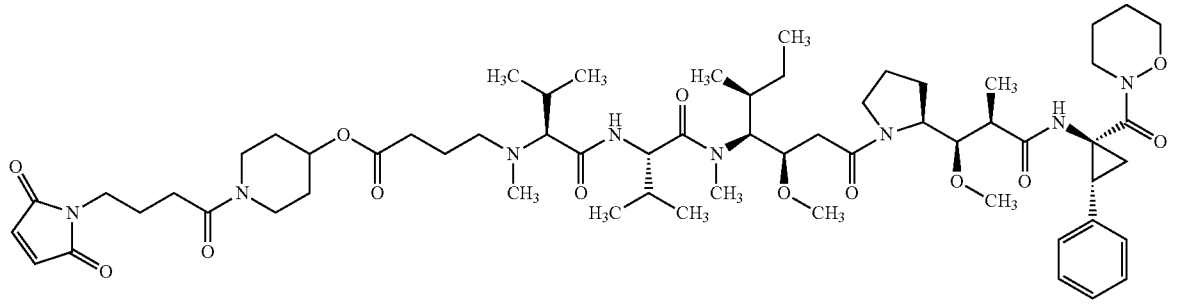
[3759] HPLC (Method 5): R_t=1.8 min;

[3760] LC-MS (Method 1): R_t=0.90 and 0.91 min; MS (ESIpos): m/z=1120 $(M+H)^+$.

Intermediate 141

N-[4-({1-[4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl) butanoyl]piperidin-4-yl}oxy)-4-oxobutyl]-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R, 2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl] amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3761]



[3762] 44 mg (49 μmol) of N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R, 2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl] pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide were dissolved in 2 ml of dichloromethane and then admixed with 18.8 mg (98 μmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 3.8 mg (24 mmol) of 4-dimethylaminopyridine and with 23 mg (98 μmol) of commercially available benzyl 4-hydroxypiperidine-1-carboxylate. The mixture was stirred at RT overnight and then concentrated under high vacuum. The remaining residue was purified by means of preparative HPLC. Thus, 22 mg (40% of theory) of the Z-protected intermediate were obtained as a colourless foam.

[3763] HPLC (Method 5): R_t=2.1 min;

[3764] LC-MS (Method 1): R_t=1.04 min; MS (ESIpos): m/z=1116 $(M+H)^+$.

[3765] Subsequently, the Z protecting group was detached by hydrogenolytic means in ethanol over palladium/activated carbon.

[3766] 19 mg (19 μmol) of the deprotected crude product were then, without further purification, taken up in 4 ml of DMF and admixed with 7 mg (39 μmol) of 4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)butanoic acid, 11 mg (29 μmol) of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and 5 μl of N,N-diisopropylethylamine. The mixture was stirred at RT for 1 h and then concentrated under high vacuum. The remaining residue was purified by means of preparative HPLC. After lyophilization from dioxane, 7.5 mg (34% of theory) of the title compound were obtained.

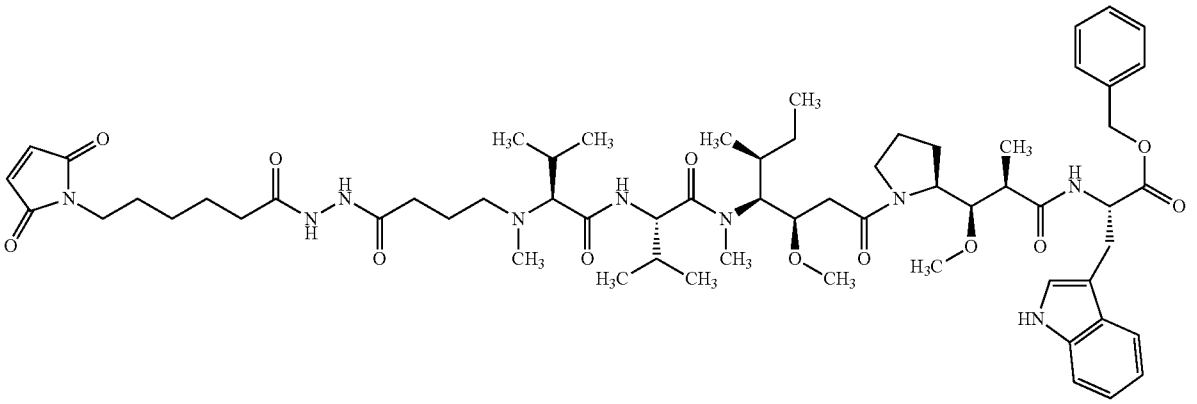
[3767] HPLC (Method 5): R_t=1.8 min;

[3768] LC-MS (Method 1): R_t=0.94 min; MS (ESIpos): m/z=1147 $(M+H)^+$.

Intermediate 142

N-(4-{2-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl) hexanoyl]hydrazino}-4-oxobutyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(benzyloxy)-3-(1H-indol-3-yl)-1-oxopropan-2-yl] amino}-1-methoxy-2-methyl-3-oxopropyl] pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3769]



[3770] 9 mg (9.5 μmol) of N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(benzyloxy)-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Intermediate 72) were dissolved in 1000 μl of DMF and then admixed with 10 mg (38 μmol) of commercially available 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl) hexanehydrazide, 7.2 mg (19 μmol) of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and 8 μl of N,N-diisopropylethylamine, and the reaction mixture was stirred at RT for 1 h. Subsequently, the solvent was removed under reduced pressure and the remaining residue was purified by means of preparative HPLC. The corresponding fractions were concentrated and, by lyophilization, 6.4 mg (58% of theory) of the title compound were obtained as a colourless foam.

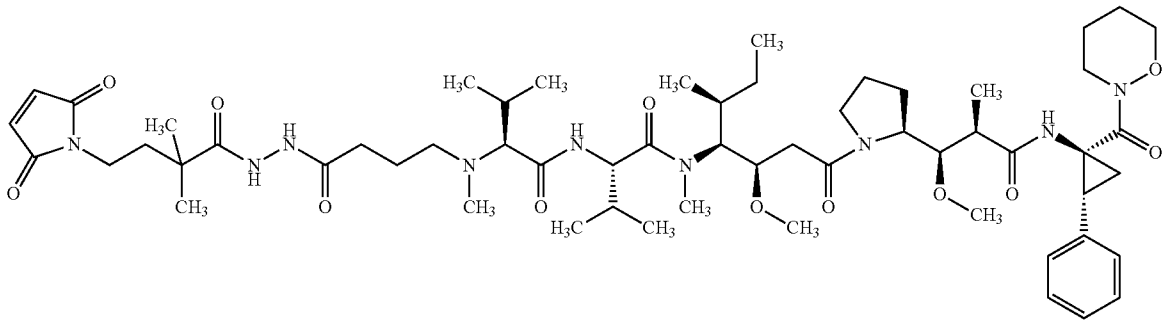
[3771] HPLC (Method 5): R_t=1.9 min;

[3772] LC-MS (Method 1): R_t=0.99 min; MS (ESIpos): m/z=1154 $(M+H)^+$.

Intermediate 143

N-(4-{2-[4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-2,2-dimethylbutanoyl]hydrazino}-4-oxobutyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl] amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3773]



[3774] 6 mg (6.7 μmol) of N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Intermediate 61) were reacted with 3 mg (8.7 μmol) of 4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-2,2-dimethylbutanehydrazide trifluoroacetate in analogy to Intermediate 142 to give 2 mg (27% of theory) of the title compound.

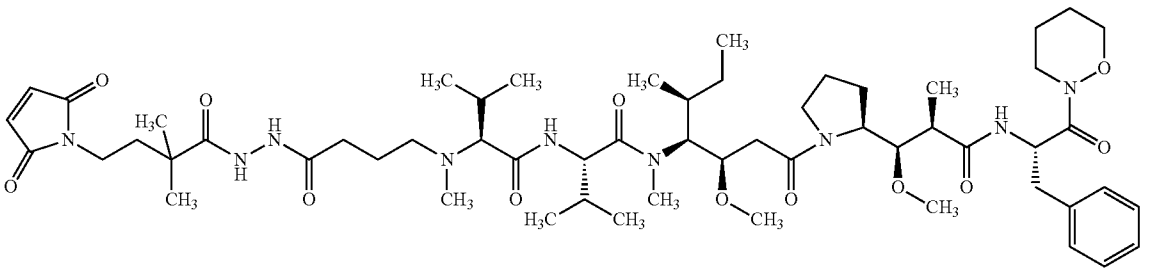
[3775] HPLC (Method 12): R_t=2.1 min;

[3776] LC-MS (Method 3): R_t=1.92 min; MS (ESIpos): m/z=1106 $(M+H)^+$.

Intermediate 144

N-(4-{2-[4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-2,2-dimethylbutanoyl]hydrazino}-4-oxobutyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(2S)-1-(1,2-oxazinan-2-yl)-1-oxo-3-phenylpropan-2-yl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3777]



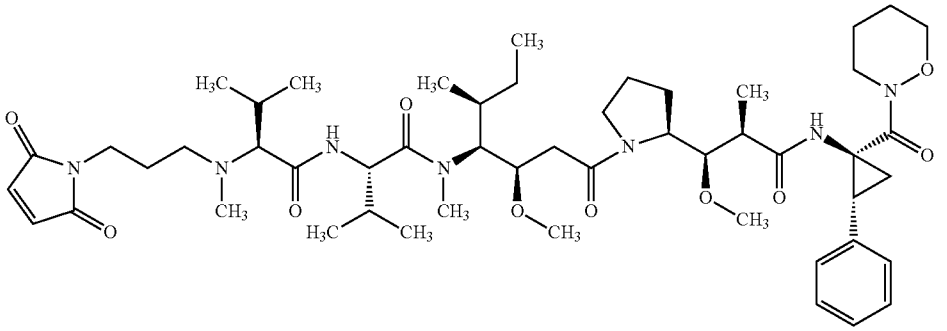
[3778] To a solution of 5 mg (5.6 μmol) of N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(2S)-1-(1,2-oxazinan-2-yl)-1-oxo-3-phenylpropan-2-yl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide in 1 ml of DMF were added 7.65 mg (22.5 μmol) of 4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-2,2-dimethylbutanehydrazide trifluoroacetate, 3.2 mg (16.9 μmol) of EDC, 1.96 μl (11.3 μmol) of diisopropylethylamine and 2.6 mg (16.9 μmol) of HOBT. The reaction mixture was stirred at RT for 3 h. Subsequently, a further 0.95 mg (2.8 μmol) of 4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-2,2-dimethylbutanehydrazide trifluoroacetate was added. After stirring overnight, the reaction mixture was concentrated and purified by preparative HPLC. 3.5 mg (85% purity, 48% of theory) of the title compound were obtained.

[3779] LC-MS (Method 3): R_t=1.86 min; m/z=1094 $(M+H)^+$.

Intermediate 145

N-[3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propyl]-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenyl cyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3780]



[3781] 12 mg (14 μmol) of N-(3-aminopropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Intermediate 66) were taken up in 750 μl of dioxane and admixed with 1.5 ml of saturated sodium hydrogencarbonate solution and then with 3.2 mg (21 μmol) of methyl 2,5-dioxo-2,5-dihydro-1H-pyrrole-1-carboxylate. The reaction mixture was stirred at RT for 1 h and then concentrated under reduced pressure. The remaining residue was purified by means of preparative HPLC. After lyophilization, 4.2 mg (32% of theory) of the title compound were obtained.

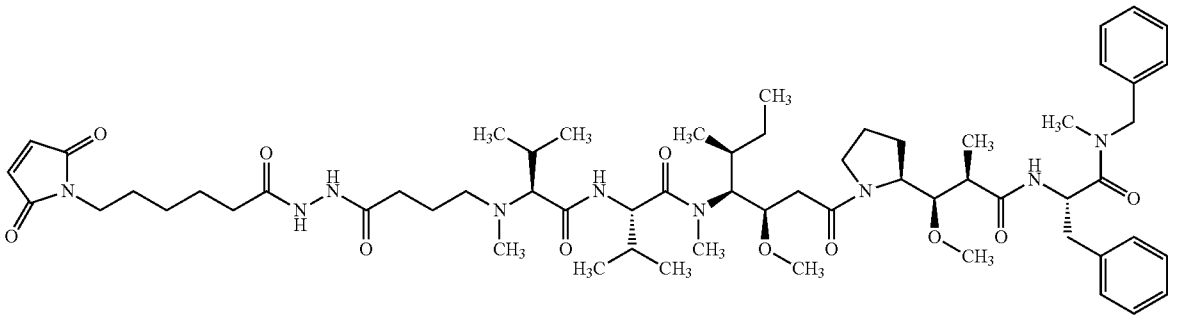
[3782] HPLC (Method 5): R_t=1.7 min;

[3783] LC-MS (Method 1): R_t=0.94 min; MS (ESIpos): m/z=950 $(M+H)^+$.

Intermediate 146

N-(4-{2-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-({(2S)-1-[benzyl(methyl)amino]-1-oxo-3-phenylpropan-2-yl}amino)-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3784]



[3785] 9 mg (9.8 μmol) of N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-({(2S)-1-[benzyl(methyl)amino]-1-oxo-3-phenylpropan-2-yl}amino)-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Intermediate 73) were reacted in analogy to Intermediate 133 with 10 mg (39 μmol) of 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanehydrazide to give 1.8 mg (15% of theory) of the title compound.

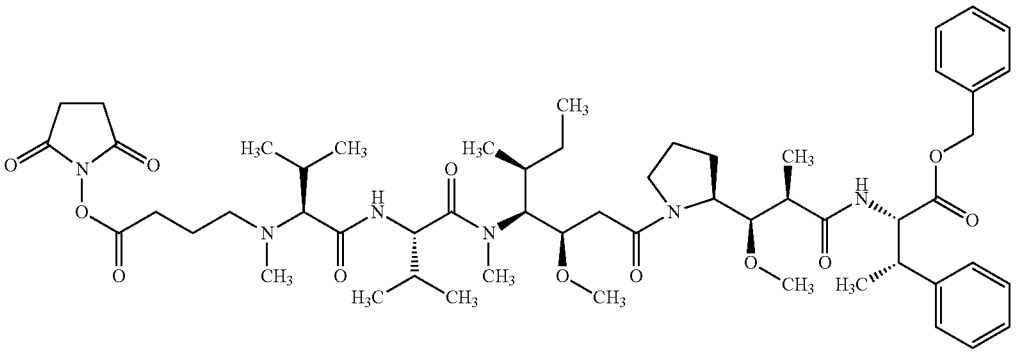
[3786] HPLC (Method 12): R_t=2.2 min;

[3787] LC-MS (Method 9): R_t=5.11 min; MS (ESIpos): m/z=1128 $(M+H)^+$.

Intermediate 147

N-{4-[(2,5-dioxopyrrolidin-1-yl)oxy]-4-oxobutyl}-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S,3S)-1-(benzyloxy)-1-oxo-3-phenylbutan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3788]



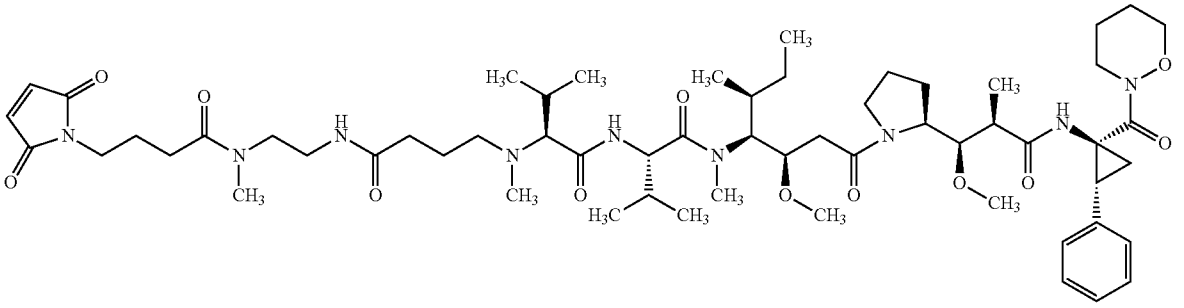
[3789] 16 mg (17 μmol) of N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S,3S)-1-(benzyloxy)-1-oxo-3-phenylbutan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Intermediate 70) were dissolved in 2 ml of dichloromethane and admixed with 2.6 mg (23 mmol) of 1-hydroxypyrrolidine-2,5-dione and then with 4 mg (21 μmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. After stirring at RT for 2 h, the same amounts of 1-hydroxypyrrolidine-2,5-dione and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added once again. Then stirring at RT overnight, the reaction mixture was concentrated under reduced pressure. The remaining residue was purified by means of preparative HPLC. After lyophilization, 10 mg (56% of theory) of the title compound were obtained.

[3790] HPLC (Method 5): R_t=2.0 min;

Intermediate 148

N-{4-[(2-{[4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)butanoyl](methyl)amino}ethyl)amino]-4-oxobutyl}-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3791]



[3792] 6 mg (7 μmol) of N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Intermediate 61) were combined with 2.8 mg (8 μmol) of N-(2-aminoethyl)-4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-N-methylbutanamide trifluoroacetate, 10.1 mg (27 μmol) of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and 5 μl of N,N-diisopropylethylamine in 2 ml of DMF and stirred at RT overnight. Then another 5 mg (23.5 μmol) of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and 3 μl of N,N-diisopropylethylamine were added. After stirring at RT for a further 5 h, the solvent was removed under reduced pressure and the remaining residue was purified by means of preparative HPLC. The corresponding fractions were concentrated and, by lyophilization from dioxane, 1.3 mg (15% of theory) of the title compound were obtained.

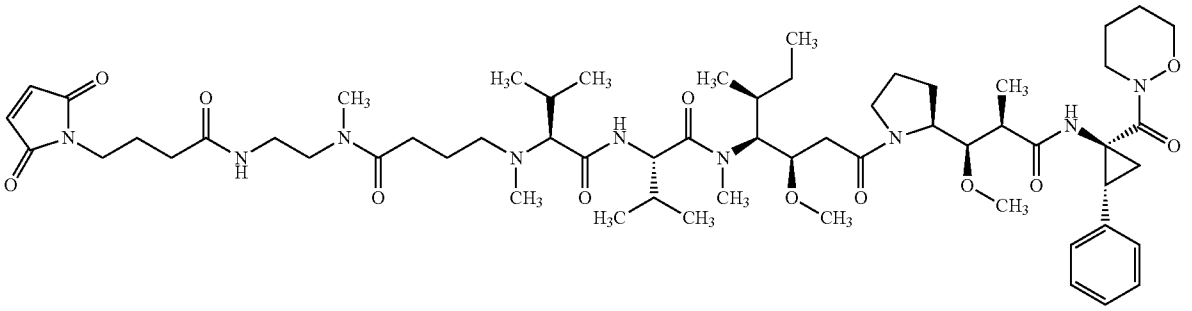
[3793] HPLC (Method 12): R_t=2.1 min;

[3794] LC-MS (Method 2): R_t=1.21 min; MS (ESIpos): m/z=1120 $(M+H)^+$.

Intermediate 149

N-{4-[(2-{[4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl) butanoyl]amino}ethyl)(methyl)amino]-4-oxobutyl}-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl] amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3795]



[3796] 6 mg (7 μmol) of N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Intermediate 61) were combined with 3.1 mg (9 μmol) of 4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-N-[2-(methylamino) ethyl]butanamide trifluoroacetate, 10.1 mg (27 μmol) of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and 5 μl of N,N-diisopropylethylamine in 2 ml of DMF, and the mixture was stirred at RT for 4 h. Then the solvent was removed under reduced pressure and the remaining residue was purified by means of preparative HPLC. The corresponding fractions were concentrated and, by lyophilization from dioxane, 1 mg (13.4% of theory) of the title compound were obtained.

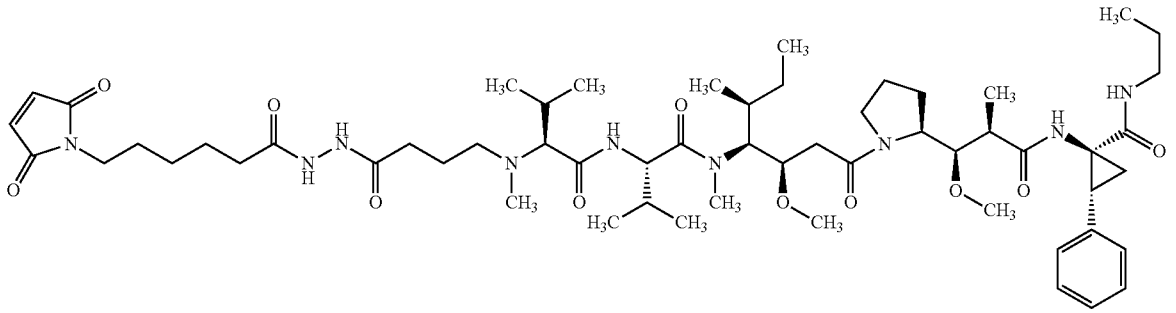
[3797] HPLC (Method 12): R_t=2.1 min;

[3798] LC-MS (Method 1): R_t=0.89 min; MS (ESIpos): m/z=1121 $(M+H)^+$.

Intermediate 150

N-(4-{2-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl) hexanoyl]hydrazino}-4-oxobutyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(1S,2R)-2-phenyl-1-(propylcarbamoyl)cyclopropyl]amino}propyl] pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3799]



[3800] 7.9 mg (9 μmol) of N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[1S,2R)-2-phenyl-1-(propylcarbamoyl)cyclopropyl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide were dissolved in 3 ml of DMF and then admixed with 10.4 mg (54 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 8.3 mg (54 μmol) of 1-hydroxy-1H-benzotriazole hydrate, 9 μl of N,N-diisopropylethylamine and with 9.5 mg (36 μmol) of commercially available 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanehydrazide. The mixture was stirred at RT overnight and then concentrated under high vacuum. The remaining residue was purified by means of preparative HPLC. Thus, 4.3 mg (22% of theory) of the title compound were obtained as a colourless foam.

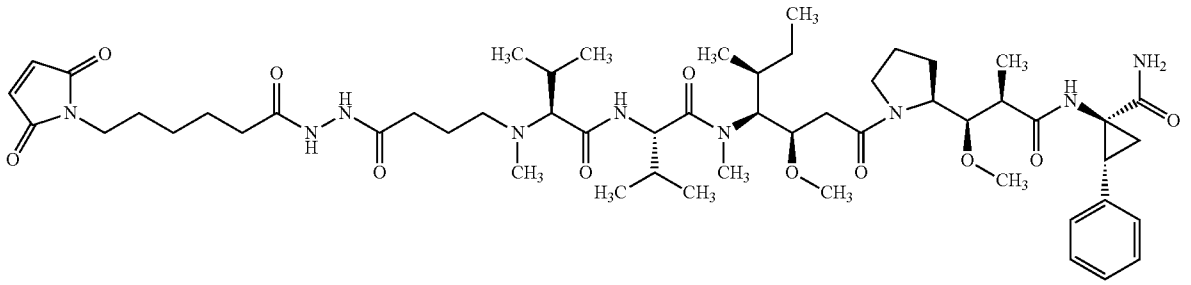
[3801] HPLC (Method 6): R_t=1.9 min;

[3802] LC-MS (Method 9): R_t=4.93 min; MS (ESIpos): m/z=1078 $(M+H)^+$.

Intermediate 151

N-(4-{2-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(1S,2R)-1-carbamoyl-2-phenylcyclopropyl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3803]



[3804] The compound was prepared analogously to Intermediate 150, proceeding from the compound in Intermediate 81.

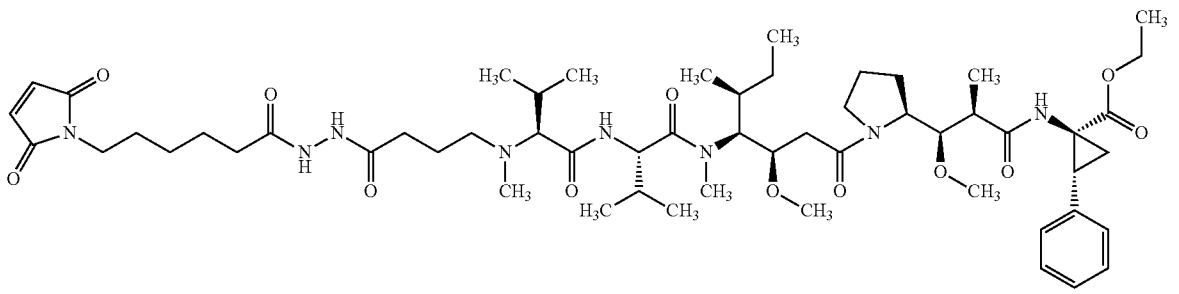
[3805] HPLC (Method 5): R_t=1.7 min;

[3806] LC-MS (Method 1): R_t=0.87 min; MS (ESIpos): m/z=1036 $(M+H)^+$.

Intermediate 152

N-(4-{2-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(1S,2R)-1-(ethoxycarbonyl)-2-phenylcyclopropyl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3807]



[3808] 10 mg (12 μmol) of N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(1S,2R)-1-(ethoxycarbonyl)-2-phenylcyclopropyl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide were dissolved in 3 ml of DMF and then admixed with 8.9 mg (23 μmol) of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, 10 μl of N,N-diisopropylethylamine and with 12 mg (47 μmol) of commercially available 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl) hexanehydrazide. The mixture was stirred at RT for 1 h. This was followed by concentration under high vacuum and purification of the remaining residue by means of preparative HPLC. Thus, 5.8 mg (37% of theory) of the title compound were obtained as a colourless foam.

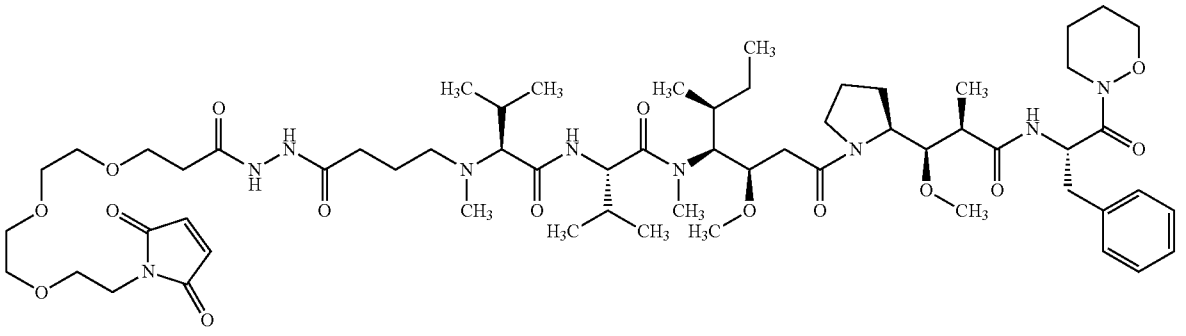
[3809] HPLC (Method 6): R_t=2.0 min;

[3810] LC-MS (Method 9): R_t=4.99 min; MS (ESIpos): m/z=1066 $(M+H)^+$.

Intermediate 153

N-[1-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-12,15-dioxo-3,6,9-trioxa-13,14-diazaoctadecan-18-yl]-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(2S)-1-(1,2-oxazinan-2-yl)-1-oxo-3-phenylpropan-2-yl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3811]



[3812] To a solution of 5 mg (5.6 μmol) of N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(2S)-1-(1,2-oxazinan-2-yl)-1-oxo-3-phenylpropan-2-yl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide in 1 ml of DMF were added 9.7 mg (22.5 μmol) of 3-(2-{2-[2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethoxy]ethoxy}ethoxy)propanehydrazide trifluoroacetate, 3.2 mg (16.9 μmol) of EDC, 1.96 μl (11.3 μmol) of N,N-diisopropylethylamine and 2.6 mg (16.9 μmol) of HOBT. The reaction mixture was stirred at RT for 3 h. Subsequently, a further 1.2 mg (2.8 μmol) of 3-(2-{2-[2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethoxy]ethoxy}ethoxy) propanehydrazide trifluoroacetate were added. The reaction mixture was stirred at RT overnight and then purified by preparative HPLC.

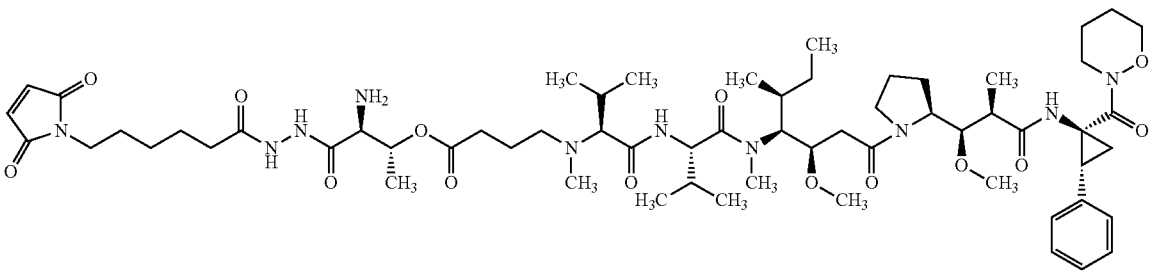
[3813] 3.6 mg (51% of theory) of the title compound were obtained.

[3814] LC-MS (Method 1): R_t=0.90 min; m/z=1185 $(M+H)^+$.

Intermediate 154

(2R,3S)-3-amino-4-{2-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutan-2-yl (3R,4S,7S,10S)-4-[(2S)-butan-2-yl]-7,10-diisopropyl-3-(2-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-2-oxoethyl)-5,11-dimethyl-6,9-dioxo-2-oxa-5,8,11-triazapentadecan-15-oate

[3815]



[3816] 15 mg (17 μmol) of N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(15)-1-(1,2-oxazinan-2-yl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide were dissolved in 10 ml of dichloromethane and then admixed with 12.8 mg (67 μmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 10 mg (83 μmol) of 4-dimethylaminopyridine and with 10.3 mg (33 μmol) of commercially available benzyl N-(tert-butoxycarbonyl)-L-threoninate. The mixture was heated to reflux for 4 h. Then the same amounts of coupling reagent and 4-dimethylaminopyridine were added again and the reaction mixture was heated under reflux overnight. Subsequently, the reaction mixture was diluted with dichloromethane and extracted by shaking once with water, and the organic phase was removed and concentrated under high vacuum. The remaining residue was purified by means of preparative HPLC. Thus, 7.7 mg (37% of theory) of the protected intermediate were obtained as a colourless foam.

[3817] HPLC (Method 12): R_t=2.5 min;

[3818] LC-MS (Method 1): R_t=1.13 min; MS (ESIpos): m/z=1190 $(M+H)^+$.

[3819] Subsequently, the benzyl ester protecting group was removed by hydrogenation under standard hydrogen pressure in methanol over 10% palladium/activated carbon, and the acid thus obtained, as described in Intermediate 151, was joined to 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanehydrazide. In a last step, the Boc protecting group was detached with trifluoroacetic acid. The remaining residue was purified by means of preparative HPLC. Thus, 0.22 mg (2.5% of theory over 3 stages) of the title compound was obtained as a colourless foam.

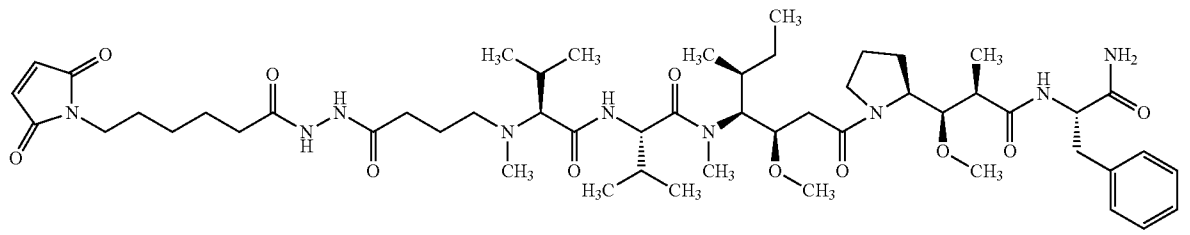
[3820] HPLC (Method 12): R_t=2.0 min;

[3821] LC-MS (Method 1): R_t=0.81 min; MS (ESIpos): m/z=1207 $(M+H)^+$.

Intermediate 155

N-(4-{2-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-amino-1-oxo-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3822]



[3823] This compound was prepared in analogy to the synthesis described in Intermediate 152, from N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-amino-1-oxo-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide and commercially available 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanehydrazide.

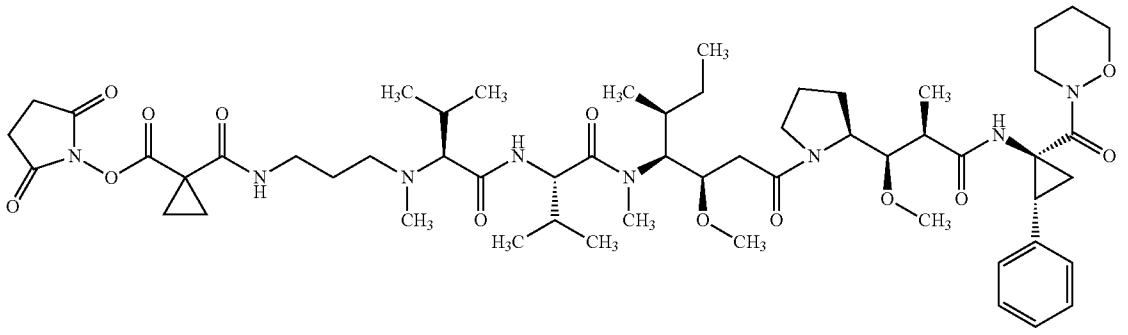
[3824] HPLC (Method 5): R_t=1.6 min;

[3825] LC-MS (Method 1): R_t=0.82 min; MS (ESIpos): m/z=1024 $(M+H)^+$.

Intermediate 156

N-(3-{[(1-{[(2,5-dioxopyrrolidin-1-yl)oxy]carbonyl}cyclopropyl)carbonyl]amino}propyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3826]



[3827] This compound was prepared in analogy to the synthesis described in the last stage of Intermediate 131, from N-(3-aminopropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide and 1,1'-[cyclopropane-1,1-diylbis(carbonyloxy)]dipyrrolidine-2,5-dione, which had been obtained from the corresponding dicarboxylic acid beforehand.

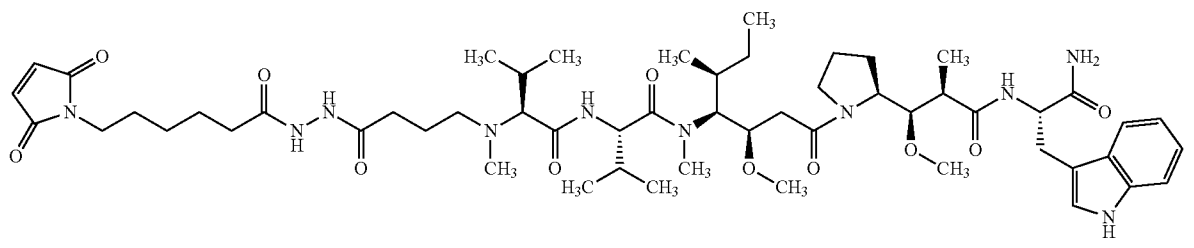
[3828] HPLC (Method 12): R_t=2.0 min;

[3829] LC-MS (Method 1): R_t=0.92 min; MS (ESIpos): m/z=1080 $(M+H)^+$.

Intermediate 157

N-(4-{2-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-amino-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3830]



[3831] 15 mg (18 μmol) of (N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-amino-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide were dissolved in 3.8 ml of DMF and then admixed with 27 mg (70 μmol) of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, 12 μl of N,N-diisopropylethylamine and with 14 mg (53 μmol) of commercially available 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanehydrazide. The reaction mixture was stirred at RT for 1 h. This was followed by concentration under high vacuum and purification of the remaining residue by means of preparative HPLC. Thus, 6.2 mg (33% of theory) of the title compound were obtained as a colourless foam.

[3832] HPLC (Method 5): R_t=1.6 min;

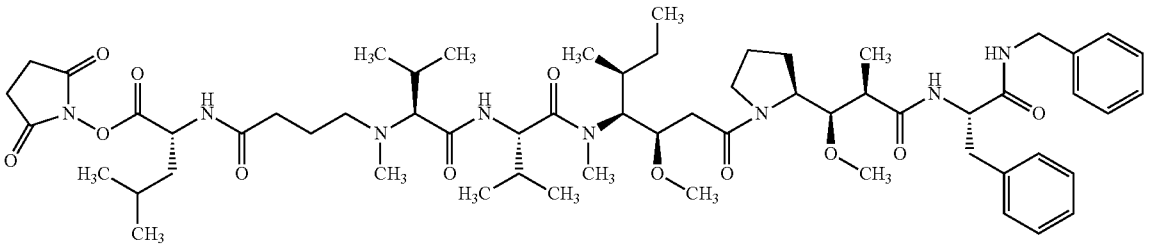
[3833] LC-MS (Method 1): R_t=0.85 min; MS (ESIpos): m/z=1063 $(M+H)^+$.

[3834] ^{1}H-NMR (500 MHz, DMSO-d_6, characteristic signals): δ=10.8 (d, 1H), 9.8-9.7 (m, 2H), 9.6 and 9.4 (2m, 1H), 8.9, 8.88, 8.78 and 8.75 (4d, 1H), 8.08 and 7.85 (2d, 1H), 7.6-6.9 (m, 9H), 4.7-4.4 (m, 3H), 3.4 (t, 2H), 3.23, 3.2, 3.18, 3.0, and 2.99 (5s, 9H), 2.8 (m, 3H), 2.1 (t, 2H), 1.06 and 1.01 (2d, 3H), 0.95-0.8 (m, 15H), 0.8-0.75 (dd, 3H).

Intermediate 158

N-[4-({(2R)-1-[(2,5-dioxopyrrolidin-1-yl)oxy]-4-methyl-1-oxopentan-2-yl}amino)-4-oxobutyl]-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(benzylamino)-1-oxo-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3835]



[3836] 13 mg (14.7 μmol) of N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(benzylamino)-1-oxo-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide were dissolved in 4 ml of dimethylformamide and then admixed with 9.4 mg (25 mmol) of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, 6 μl of N,N-diisopropylethylamine and with 7 mg (31 μmol) of commercially available tert-butyl D-leucinate hydrochloride. The mixture was stirred at RT for 5 h and then concentrated under reduced pressure. The remaining residue was purified by means of preparative HPLC. After lyophilization from dioxane/water, 6.5 mg (49% of theory) of the protected intermediate were obtained as a colourless foam.

[3837] HPLC (Method 5): R_t=2.2 min;

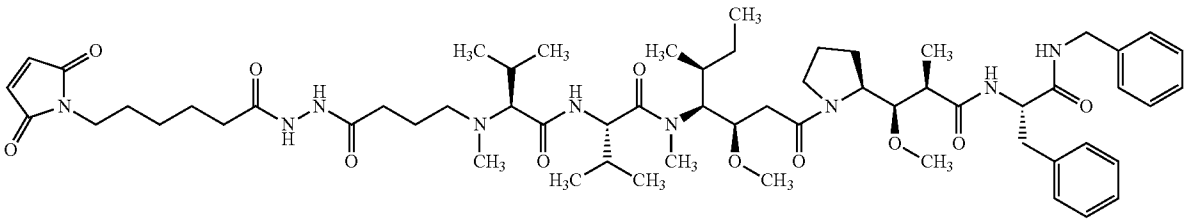
[3838] LC-MS (Method 1): R_t=1.21 min; MS (ESIpos): m/z=1076 $(M+H)^+$.

[3839] Trifluoroacetic acid in dichloromethane was first used to detach the Boc protecting group from this protected intermediate, giving 6.2 mg (99% of theory) of the deprotected compound. 5.2 mg (5 μmol) of this intermediate were taken up in 1.5 ml of dichloromethane and reacted with 0.8 mg (7 μmol) of N-hydroxysuccinimide in the presence of 1.2 mg (6 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 0.16 mg (1 mmol) of 4-dimethylaminopyridine. After stirring at RT for 2 h, the reaction mixture was concentrated and purified by means of preparative HPLC. 1.3 mg of the title compound were obtained, some of which was hydrolysed to the reactant.

Intermediate 159

N-(4-{2-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl) hexanoyl]hydrazino}-4-oxobutyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(benzylamino)-1-oxo-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3840]



[3841] This compound was prepared in analogy to the synthesis described in Intermediate 157, from N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(benzylamino)-1-oxo-3-phenylpropan-2-yl] amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide and commercially available 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanehydrazide.

[3842] Yield: 6 mg (53% of theory)

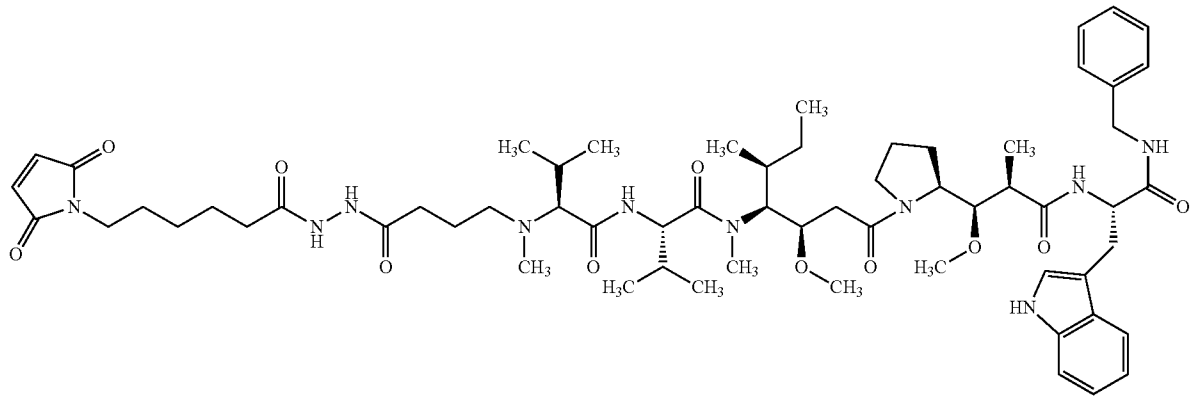
[3843] HPLC (Method 5): R_t=1.9 min;

[3844] LC-MS (Method 1): R_t=0.94 min; MS (ESIpos): m/z=1114 $(M+H)^+$.

Intermediate 160

N-(4-{2-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl) hexanoyl]hydrazino}-4-oxobutyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(benzylamino)-3-(1H-indol-3-yl)-1-oxopropan-2-yl] amino}-1-methoxy-2-methyl-3-oxopropyl] pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3845]



[3846] This compound was prepared in analogy to the synthesis described in Intermediate 157, from 20 mg (21 μmol) of N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(benzylamino)-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide and commercially available 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanehydrazide.

[3847] Yield: 13 mg (52% of theory)

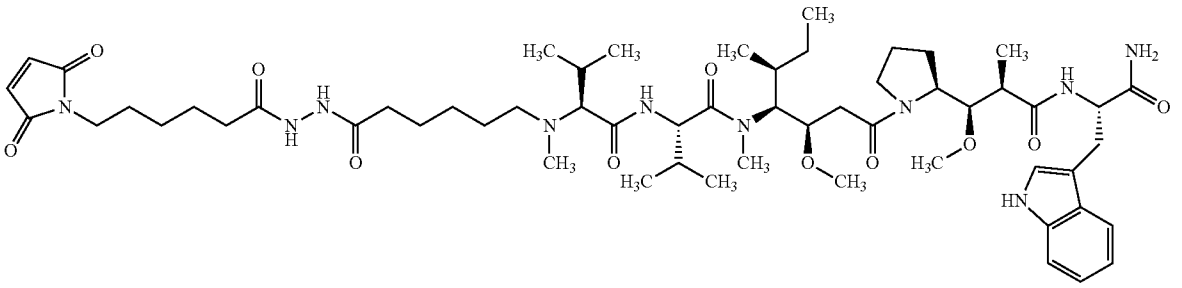
[3848] HPLC (Method 5): R_t=1.9 min;

[3849] LC-MS (Method 1): R_t=0.92 min; MS (ESIpos): m/z=1153 $(M+H)^+$.

Intermediate 161

N-(6-{2-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]hydrazino}-6-oxohexyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-amino-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3850]



[3851] This compound was prepared in analogy to the synthesis described in Intermediate 157, from N-(5-carboxypentyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-amino-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide and commercially available 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanehydrazide.

[3852] Yield: 0.8 mg (16% of theory)

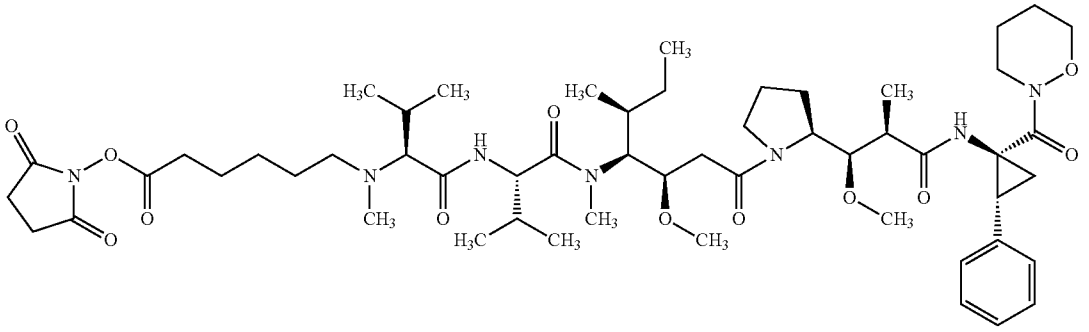
[3853] HPLC (Method 5): R_t=1.6 min;

[3854] LC-MS (Method 1): R_t=0.78 min; MS (ESIpos): m/z=1092 $(M+H)^+$.

Intermediate 162

N-{6-[(2,5-dioxopyrrolidin-1-yl)oxy]-6-oxohexyl}-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3855]



[3856] 18 mg (20 μmol) of N-(5-carboxypentyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Intermediate 64) were dissolved in 3.2 ml of dichloromethane and admixed with 22 mg (190 mmol) of 1-hydroxypyrrolidine-2,5-dione and then with 11 mg (60 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 0.24 mg (0.17 mmol) of DMAP. After stirring at RT for 2 h, another 22 mg (190 mmol) of 1-hydroxypyrrolidine-2,5-dione, 11 mg (60 μmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 0.24 mg (0.17 μmol) of DMAP were added and the reaction mixture was stirred at RT for a further hour. This was followed by concentration under reduced pressure. The remaining residue was purified by means of preparative HPLC. After lyophilization, 8.2 mg (41% of theory) of the title compound were obtained.

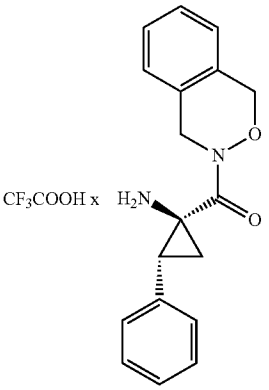
[3857] HPLC (Method 5): R_t=2.0 min;

[3858] LC-MS (Method 11): R_t=0.9 min; MS (ESIpos): m/z=1024 $(M+H)^+$.

Intermediate 163

[(1S,2R)-1-amino-2-phenylcyclopropyl](1,4-dihydro-3H-2,3-benzoxazin-3-yl)methanone trifluoroacetate

[3859]



[3860] First, proceeding from 265 mg (0.82 mmol) of tert-butyl (1S,2R)-1-(hydroxycarbamoyl)-2-phenylcyclopropyl carbamate (Starting Compound 7), by reaction with 1,2-bis(bromomethyl)benzene, analogously to a literature method (see H. King, *J. Chem. Soc.* 1942, 432), the Boc-protected tert-butyl (1S,2R)-1-(1,4-dihydro-3H-2,3-benzoxazin-3-ylcarbonyl)-2-phenylcyclopropyl carbamate intermediate was prepared.

[3861] Yield: 108 mg (34% of theory)

[3862] LC-MS (Method 2): R_t=1.3 min; MS (ESIpos): m/z=395 $(M+H)^+$.

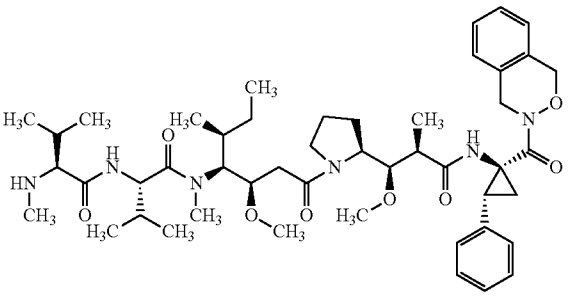
[3863] 108 mg (0.27 mmol) of this intermediate were taken up in 3.7 ml of dichloromethane, 1.8 ml of trifluoroacetic acid were added, and the mixture was stirred at RT for 15 min. This was followed by concentration under reduced pressure and lyophilization of the remaining residue from dioxane. 112 mg of the title compound were obtained in quantitative yield as a colourless foam.

[3864] LC-MS (Method 1): R_t=0.7 min; MS (ESIpos): m/z=295 $(M+H)^+$.

Intermediate 164

N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(1S,2R)-1-(1,4-dihydro-3H-2,3-benzoxazin-3-ylcarbonyl)-2-phenylcyclopropyl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide trifluoroacetate

[3865]



[3866] 166 mg (0.196 mmol) of N-[(9H-fluoren-9-ylmethoxy)carbonyl]-N-methyl-L-valyl-N-[3R,4S,5S)-1-{(2S)-2-[(1R,2R)-2-carboxy-1-methoxypropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Intermediate 10) were taken up in 40 ml of DMF and admixed successively with 80 mg (0.196 mmol) of [(1S,2R)-1-amino-2-phenylcyclopropyl](1,4-dihydro-3H-2,3-benzoxazin-3-yl)methanone trifluoroacetate (Intermediate 163), 112 mg (0.294 mmol) of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) and 682 μl (3.9 mmol) of N,N-diisopropylethylamine. The mixture was subsequently stirred at RT overnight. The reaction mixture was then concentrated under reduced pressure, the residue was taken up in ethyl acetate and the solution was washed with saturated aqueous sodium chloride solution. The organic phase was dried over magnesium sulphate, filtered and concentrated. The residue was finally purified by preparative HPLC. In this way, 19 mg (9% of theory) of the Fmoc-protected intermediate N-[(9H-fluoren-9-ylmethoxy)carbonyl]-N-methyl-L-valyl-N-[3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(1S,2R)-1-(1,4-dihydro-3H-2,3-benzoxazin-3-ylcarbonyl)-2-phenylcyclopropyl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide were obtained.

[3867] HPLC (Method 5): R_t=1.68 min;

[3868] LC-MS (Method 1): R_t=1.51 min; MS (ESIpos): m/z=1083 $(M+H)^+$.

[3869] 19 mg (0.015 mmol) of this intermediate were dissolved in 4 ml of DMF. After 817 μl of piperidine had been added, the reaction mixture was stirred at RT for 5 min. This was followed by concentration under reduced pressure, and the residue was first digested with diethyl ether and then

purified by means of preparative HPLC (eluent: acetonitrile+0.1% TFA/0.1% aq. TFA). The corresponding fractions were combined, the solvent was removed under reduced pressure and then the residue was lyophilized from dioxane/water. 12 mg (92% of theory) of the title compound were obtained as a colourless foam.

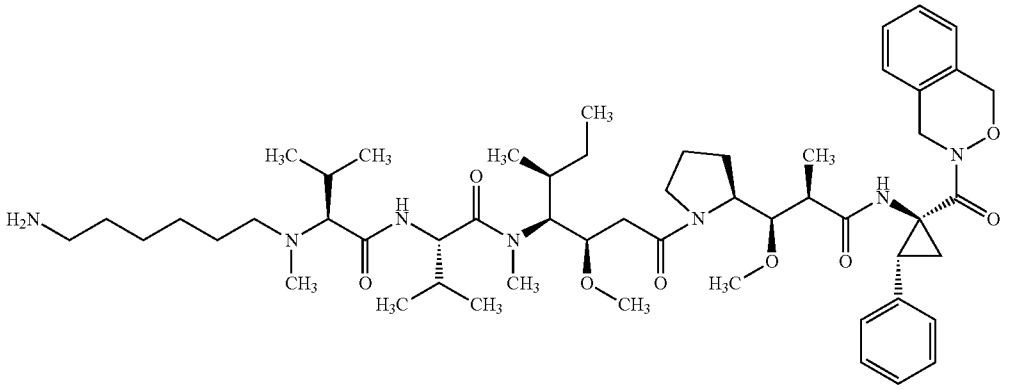
[3870] HPLC (Method 6): R_t=2.0 min;

[3871] LC-MS (Method 1): R_t=0.94 min; MS (ESIpos): m/z=861 $(M+H)^+$.

Intermediate 165

N-(6-aminohexyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(1S,2R)-1-(1,4-dihydro-3H-2,3-benzoxazin-3-ylcarbonyl)-2-phenylcyclopropyl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3872]



[3873] 20 mg (0.021 mmol) of Intermediate 164 were used, in analogy to the preparation of Intermediate 97, with benzyl 6-oxohexyl carbamate in the presence of sodium cyanoborohydride and subsequent hydrogenolytic detachment of the Z protecting group (with 5% palladium on charcoal as a catalyst, in methanol as a solvent), to prepare the title compound.

[3874] Yield: 4.5 mg (23% of theory over 2 stages)

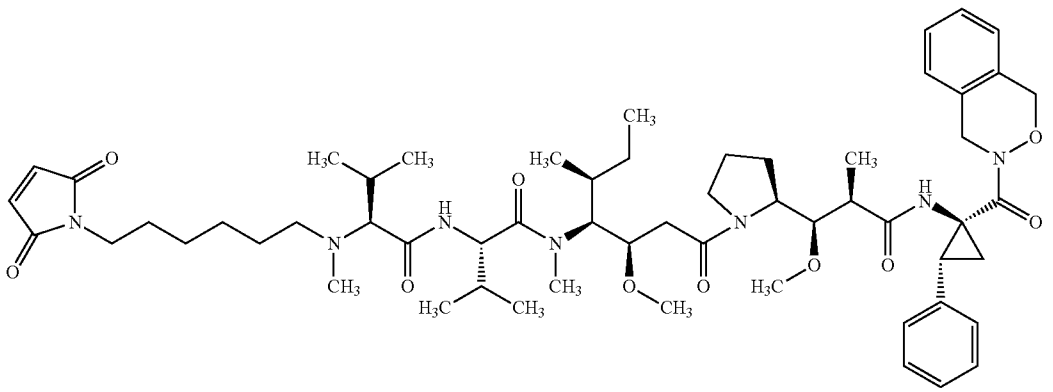
[3875] HPLC (Method 12): R_t=1.9 min;

[3876] LC-MS (Method 1): R_t=0.9 min; MS (ESIpos): m/z=960 $(M+H)^+$.

Intermediate 166

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexyl]-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(1S,2R)-1-(1,4-dihydro-3H-2,3-benzoxazin-3-ylcarbonyl)-2-phenylcyclopropyl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3877]



[3878] 4.4 mg (4.5 μmol) of Intermediate 165 were taken up in 1 ml of 1:1 dioxane/water and then admixed with 1 mg (6.8 μmol) of methyl 2,5-dioxo-2,5-dihydro-1H-pyrrole-1-carboxylate and with 50 μl of saturated aqueous sodium hydrogencarbonate solution. The reaction mixture was stirred at RT for 30 min. Then another 50 μl of the saturated aqueous sodium hydrogencarbonate solution were added and the reaction mixture was stirred at RT for a further 15 min and then concentrated under reduced pressure. The remaining residue was purified by means of preparative HPLC. After lyophilization, 1 mg (21% of theory) of the title compound were obtained as a colourless foam.

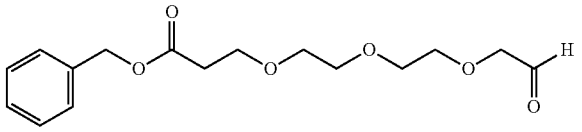
[3879] HPLC (Method 12): R_t=2.1 min;

[3880] LC-MS (Method 1): R_t=1.08 min; MS (ESIpos): m/z=1040 $(M+H)^+$.

Intermediate 167

benzyl 3-{2-[2-(2-oxoethoxy)ethoxy]ethoxy}propanoate

[3881]



[3882] The title compound was prepared from 6 g (21.55 mmol) of commercially available 3-{2-[2-(2-hydroxyethoxy)ethoxy]ethoxy}propanoic acid under standard conditions, first by esterification with benzyl chloride and caesium carbonate and subsequent oxidation with sulphur trioxide-pyridine complex.

[3883] Yield: 611 mg (10% of theory over 2 stages)

[3884] LC-MS (Method 2): R_t=1.69 min; MS (ESIpos): m/z=311 $(M+H)^+$.

Intermediate 168

N-(2-{2-[2-(2-carboxyethoxy)ethoxy]ethoxy}ethyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-amino-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3885]

[3886] First, in analogy to the synthesis described in Intermediate 69, by coupling of N-[(9H-fluoren-9-ylmethoxy)carbonyl]-N-methyl-L-valyl-N-[(2R,3S,4S)-1-carboxy-2-methoxy-4-methylhexan-3-yl]-N-methyl-L-valinamide (Intermediate 4) and N^{α}-{(2R,3R)-3-methoxy-2-methyl-3-[(2S)-pyrrolidin-2-yl]propanoyl}-L-tryptophanamide trifluoroacetate (Intermediate 49) in the presence of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and subsequent detachment of the Fmoc protecting group by means of piperidine, the amine compound N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-amino-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide was prepared as the trifluoroacetate.

[3887] 25 mg (0.028 mmol) of this compound and 17.5 mg (0.06 mmol) of Intermediate 167 were combined in 2 ml of methanol and admixed with 12.6 mg (0.14 mmol) of borane-pyridine complex and 2.5 ml of acetic acid. The reaction mixture was stirred at RT overnight. Then the same amounts of borane-pyridine complex and acetic acid were added once again and the reaction mixture was stirred at RT for a further 24 h. This was followed by concentration under reduced pressure, and the residue was purified by means of preparative HPLC. After concentration of the corresponding fractions and lyophilization from 1:1 dioxane/water, 26.5 mg (88% of theory) of the Z-protected title compound were obtained.

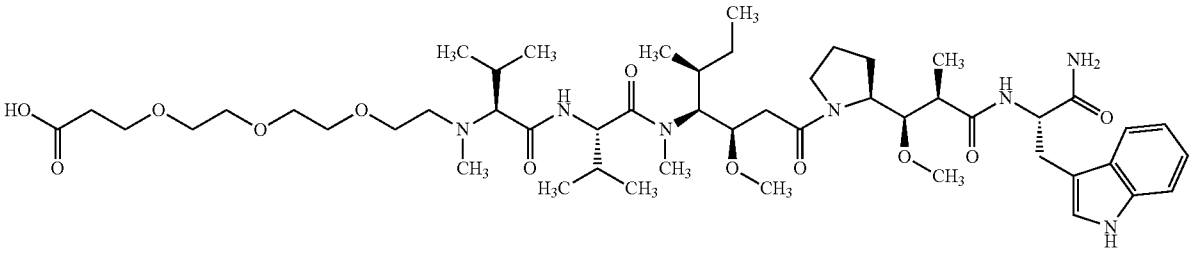
[3888] HPLC (Method 12): R_t=2.04 min;

[3889] LC-MS (Method 1): R_t=0.97 min; MS (ESIpos): m/z=1064 $(M+H)^+$.

[3890] 25 mg (0.024 mmol) of this intermediate were taken up in 10 ml of methanol and hydrogenated over 10% palladium on activated carbon under standard hydrogen pressure at RT for 45 min. The catalyst was then filtered off and the solvent was removed under reduced pressure. After lyophilization from dioxane, 19.7 mg (85% of theory) of the title compound were obtained.

[3891] HPLC (Method 12): R_t=1.8 min;

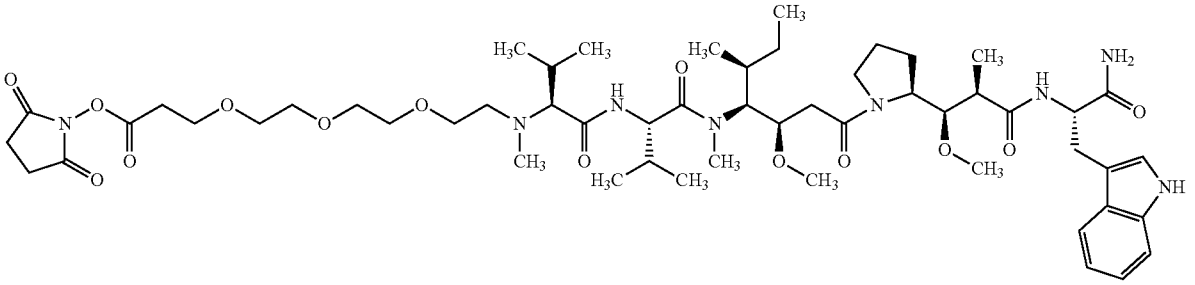
[3892] LC-MS (Method 1): R_t=0.83 min; MS (ESIpos): m/z=974 $(M+H)^+$.



Intermediate 169

N-{2-[2-(2-{3-[(2,5-dioxopyrrolidin-1-yl)oxy]-3-oxopropoxy}ethoxy)ethoxy]ethyl}-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-amino-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3893]



[3894] 10 mg (10 μmol) of Intermediate 168 were dissolved in 3 ml of DMF and admixed with 3.5 mg (30 mmol) of 1-hydroxypyrrolidine-2,5-dione and then with 2.4 mg (10 μmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 5 μl of N,N-diisopropylethylamine. After stirring at RT for 20 h, 8 mg (0.02 mmol) of HATU were added and the reaction mixture was stirred once again at RT overnight and then concentrated under reduced pressure. The remaining residue was purified by means of preparative HPLC. After lyophilization from dioxane, 8.6 mg (64% of theory) of the title compound were obtained.

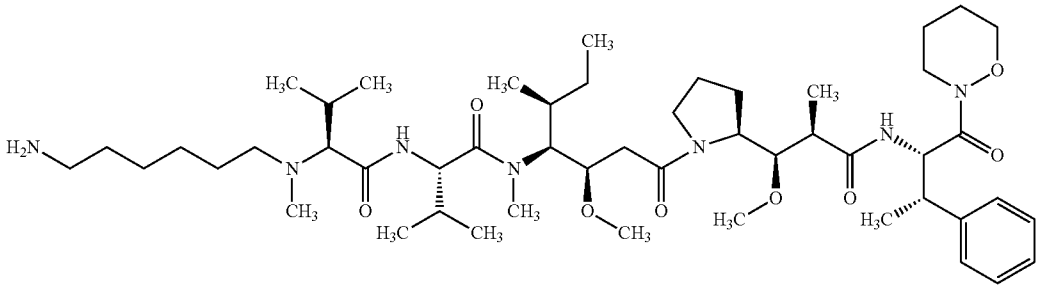
[3895] HPLC (Method 12): R_t=1.9 min;

[3896] LC-MS (Method 11): R_t=0.81 min; MS (ESIpos): m/z=1071 $(M+H)^+$.

Intermediate 170

N-(6-aminohexyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(2S,3S)-1-(1,2-oxazinan-2-yl)-1-oxo-3-phenylbutan-2-yl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3897]



[3898] This compound was prepared in analogy to Intermediate 101 over 2 stages, proceeding from 26 mg (0.028 mmol) of Intermediate 15.

[3899] Yield: 16.7 mg (63% of theory over 2 stages)

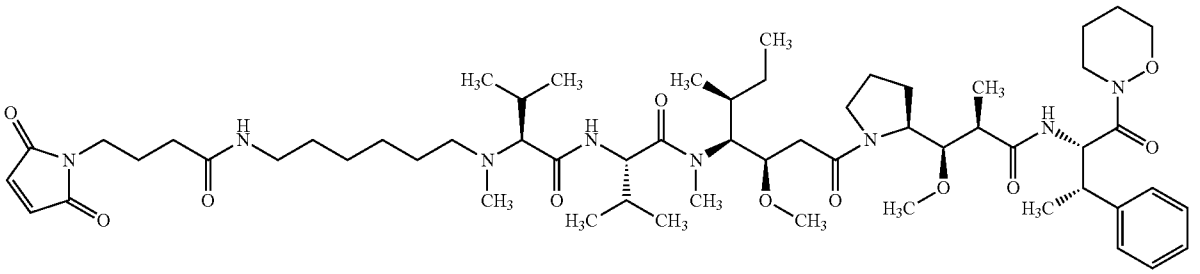
[3900] HPLC (Method 12): R_t=1.9 min;

[3901] LC-MS (Method 1): R_t=0.81 min; MS (ESIpos): m/z=914 $(M+H)^+$.

Intermediate 171

N-(6-{[4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl) butanoyl]amino}hexyl)-N-methyl-L-valyl-N-[(3R, 4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(2S,3S)-1-(1,2-oxazinan-2-yl)-1-oxo-3-phenylbutan-2-yl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3902]



[3903] 6.7 mg (7.3 μmol) of the compound formed from Intermediate 170 and 3 mg (14.7 μmol) of commercially available 4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)butanoic acid were taken up in 2 ml of DMF and admixed with 5.6 mg (14.7 μmol) of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) and 2 μl of N,N-diisopropylethylamine. The mixture was stirred at RT for 30 min. The reaction mixture was concentrated and the residue was purified by means of preparative HPLC. The corresponding fractions were combined, the solvent was removed under reduced pressure and then the residue was lyophilized from dioxane. Thus, 4.5 mg (56% of theory) of the title compound were obtained.

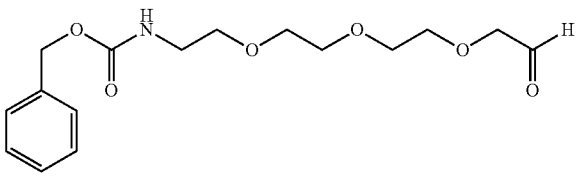
[3904] HPLC (Method 12): R_t=2.0 min;

[3905] LC-MS (Method 1): R_t=1.12 min; MS (ESIpos): m/z=1079 $(M+H)^+$.

Intermediate 172

benzyl 2-{2-[2-(2-oxoethoxy)ethoxy]ethoxy}ethyl carbamate

[3906]



[3907] The title compound was prepared from commercially available 2-{2-[2-(2-aminoethoxy)ethoxy] ethoxy}ethanol under standard conditions, by first introducing the Z protecting group and then oxidizing with sulphur trioxide-pyridine complex.

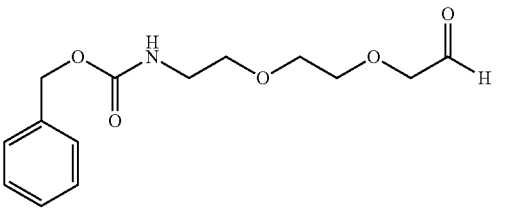
[3908] HPLC (Method 12): R_t=1.4 min;

[3909] LC-MS (Method 11): R_t=0.65 min; MS (ESIpos): m/z=326 $(M+H)^+$.

Intermediate 173

benzyl {2-[2-(2-oxoethoxy)ethoxy]ethyl carbamate

[3910]



[3911] The title compound was prepared analogously to Intermediate 172 from commercially available 2-[2-(2-aminoethoxy)ethoxy]ethanol under standard conditions, by first introducing the Z protecting group and then oxidizing with sulphur trioxide-pyridine complex.

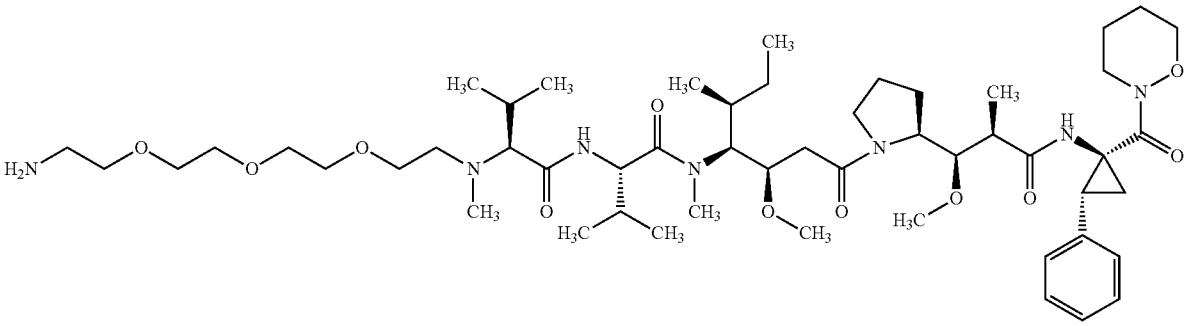
[3912] HPLC (Method 12): R_t=1.3 min;

[3913] LC-MS (Method 11): R_t=0.68 min; MS (ESIpos): m/z=282 $(M+H)^+$.

Intermediate 174

N-(2-{2-[2-(2-aminoethoxy)ethoxy]ethoxy}ethyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenyl cyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3914]



[3915] 47 mg (0.05 mmol) of Intermediate 16 were reductively aminated in analogy to the preparation of Intermediate 167 with benzyl 2-{2-[2-(2-oxoethoxy)ethoxy]ethoxy}ethyl carbamate in the presence of borane-pyridine complex. Subsequently, the Z protecting group was removed by hydrogenolytic means with 5% palladium on charcoal as a catalyst and in methanol as a solvent, and 38 mg (66% of theory over 2 stages) of the title compound were prepared.

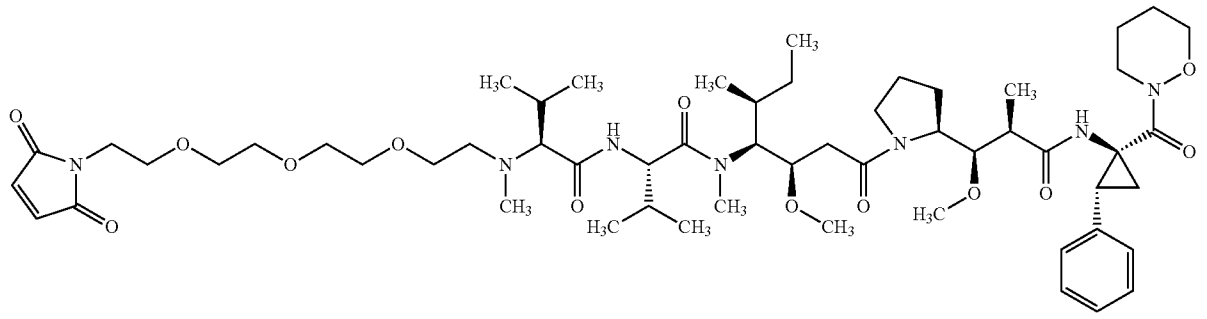
[3916] HPLC (Method 5): R_t=1.7 min;

[3917] LC-MS (Method 1): R_t=0.8 min; MS (ESIpos): m/z=988 $(M+H)^+$.

Intermediate 175

N-[2-(2-{2-[2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethoxy]ethoxy}ethoxy)ethyl]-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3918]



[3919] The preparation was effected in analogy zu Intermediate 166, proceeding from 34 mg (0.03 mmol) of Intermediate 174.

[3920] Yield: 8.3 mg (23% of theory)

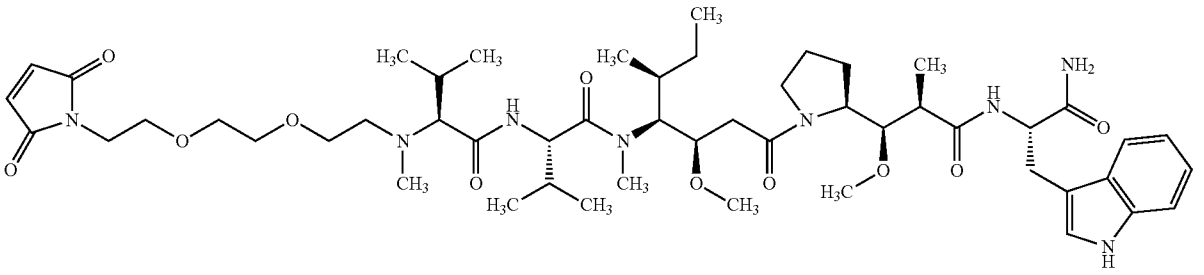
[3921] HPLC (Method 5): R_t=1.9 min;

[3922] LC-MS (Method 1): R_t=0.97 min; MS (ESIpos): m/z=1068 $(M+H)^+$.

Intermediate 176

N-(2-{2-[2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethoxy]ethoxy}ethyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-amino-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3923]



[3924] The preparation was effected in analogy to Intermediates 174 and 175, commencing with the reductive amination of Intermediate 16 with Intermediate 173, subsequent deprotection and formation of the maleimide.

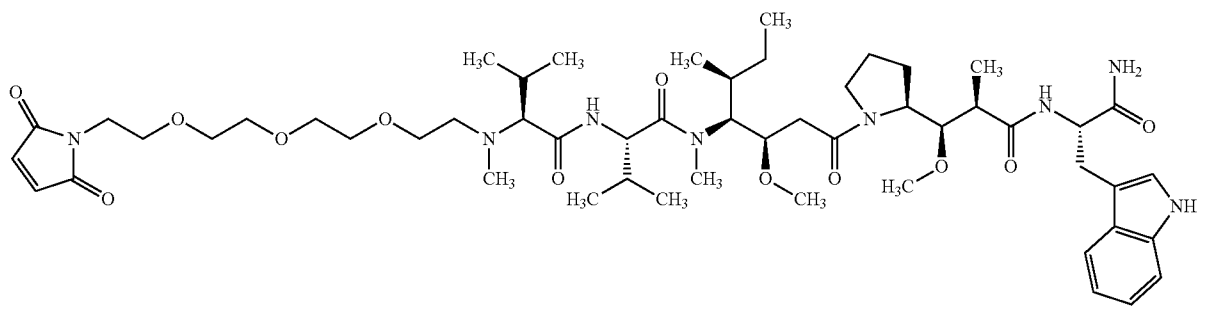
[3925] HPLC (Method 12): R_t=1.8 min;

[3926] LC-MS (Method 11): R_t=0.8 min; MS (ESIpos): m/z=981 $(M+H)^+$.

Intermediate 177

N-[2-(2-{2-[2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethoxy]ethoxy}ethoxy)ethyl]-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-amino-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3927]



[3928] The preparation was effected in analogy to Intermediates 174 and 175, commencing with the reductive amination of Intermediate 16 with Intermediate 172, subsequent deprotection and formation of the maleimide.

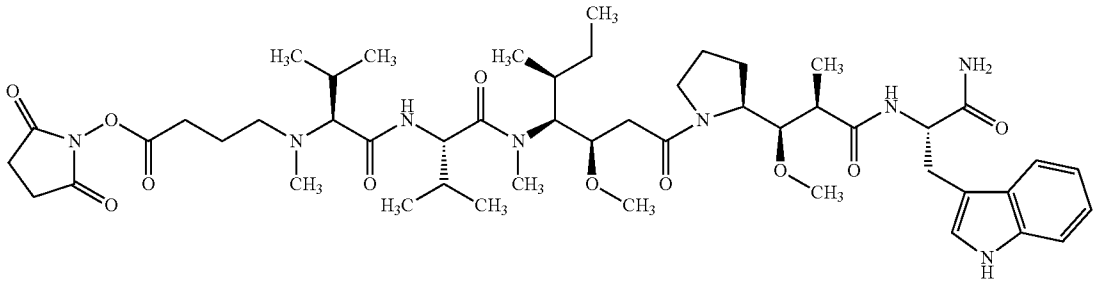
[3929] HPLC (Method 12): R_t=1.9 min;

[3930] LC-MS (Method 1): R_t=0.86 min; MS (ESIpos): m/z=1025 $(M+H)^+$.

Intermediate 178

N-{4-[(2,5-dioxopyrrolidin-1-yl)oxy]-4-oxobutyl}-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-amino-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3931]



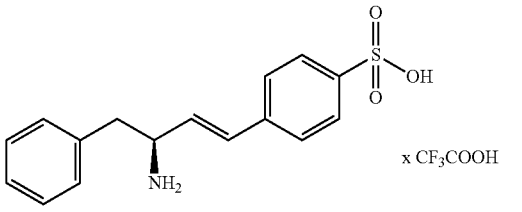
[3932] The preparation was effected in analogy to Intermediates 162, proceeding from 6 mg of Intermediate 82.

[3933] LC-MS (Method 1): R_t=0.82 min; MS (ESIpos): m/z=953 $(M+H)^+$.

Intermediate 179

4-[(1E,3S)-3-amino-4-phenylbut-1-en-1-yl]benzenesulphonic acid trifluoroacetate

[3934]



[3935] A mixture of 13.6 mg (0.06 mmol) of palladium(II) acetate, 469 mg (1.46 mmol) of potassium 4-iodobenzenesulphonate, 300 mg (1.21 mmol) of (S)-tert-butyl 1-phenylbut-3-en-2-yl carbamate, 16.5 mg (0.12 mmol) of phenylurea and 167.6 mg (1.21 mmol) of potassium carbonate in 7.5 ml of DMF was heated to 160° C. in a microwave for 15 min. The crude product was subsequently purified directly by preparative HPLC. This gave 312 mg of a mixture of 31% of the BOC-protected compound and 69% of the free amine.

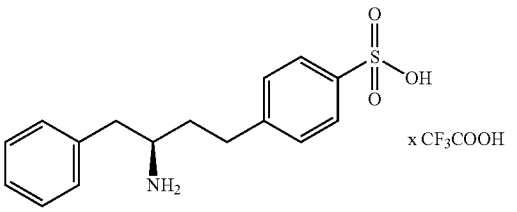
[3936] This mixture was subsequently taken up in 30 ml of dichloromethane, admixed with 1 ml of trifluoroacetic acid and stirred at RT for 20 h. After concentrating under reduced pressure, the residue was stirred with diethyl ether, and the precipitate formed was filtered off with suction and washed with diethyl ether. This gave 200 mg (62% of theory) of the title compound.

[3937] LC-MS (Method 11): R_t=0.44 min; MS (ESIpos): m/z=304 $(M+H)^+$.

Intermediate 180

4-[(3R)-3-amino-4-phenylbutyl]benzenesulphonic acid

[3938]



[3939] 100 mg (0.25 mmol) of 4-[(1E,3S)-3-amino-4-phenylbut-1-en-1-yl]benzenesulphonic acid trifluoroacetate were suspended in 10 ml of acetic acid and a few drops of DMF and water, admixed with 70 mg (0.07 mmol) of palladium on charcoal (10%) and hydrogenated at hydrogen pressure 2.2 bar for 24 h. The solution was filtered and the filtrate purified by prep. HPLC.

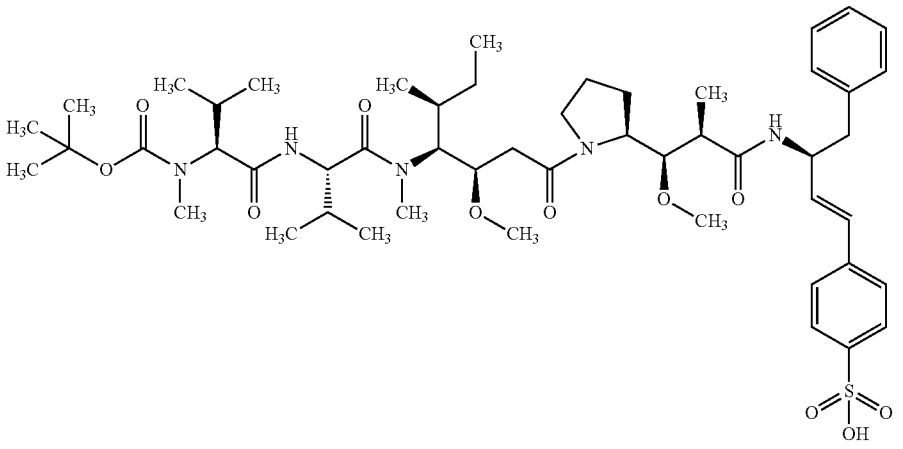
[3940] 29 mg (76% purity, 21% of theory) of product were obtained.

[3941] LC-MS (Method 1): R_t=0.46 min; MS (ESIpos): m/z=306 $(M+H)^+$.

Intermediate 181

N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(2S,3E)-1-phenyl-4-(4-sulphophenyl)but-3-en-2-yl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3942]



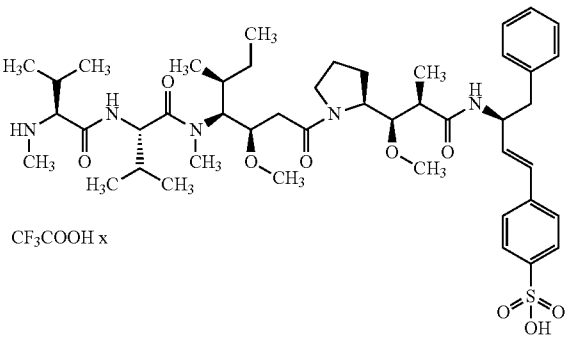
[3943] To a solution of 90 mg (0.13 mmol) of N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-2-carboxy-1-methoxypropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide in 4 ml of DMF were added 60 mg (0.16 mmol) of HATU and 69 μl of (0.39 mmol) Hünig's base. The reaction mixture was stirred at RT for 30 min and then admixed with 60 mg (0.15 mmol) 60.3 mg (0.13 mmol) of 4-[(1E,3S)-3-amino-4-phenylbut-1-en-1-yl]benzenesulphonic acid trifluoroacetate. After stirring overnight, the reaction mixture was purified by prep. HPLC. This gave 127 mg of a 44:56 mixture of the title compound and of the already deprotected amine.

[3944] LC-MS (Method 1): R_t=1.21 min; MS (ESIpos): m/z=971 $(M+H)^+$; R_t=0.84 min; MS (ESIpos): m/z=871 $(M+H)^+$ for the deprotected compound.

Intermediate 182

N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(2S,3E)-1-phenyl-4-(4-sulphophenyl)but-3-en-2-yl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide trifluoroacetate

[3945]



[3946] 90 mg of Intermediate 180 were dissolved in 4.6 ml of dichloromethane, and 0.92 ml of trifluoroacetic acid was added. The reaction mixture was stirred at RT for 30 min and then concentrated. The crude product obtained was purified by prep. HPLC.

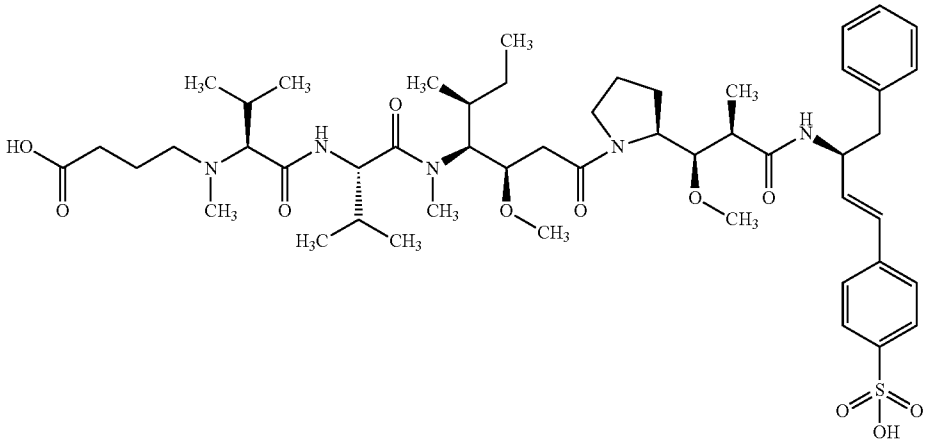
[3947] 91 mg (98% of theory) of the target compound were obtained.

[3948] LC-MS (Method 1): R_t=0.85 min; MS (ESIpos): m/z=871 $(M+H)^+$

Intermediate 183

N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(2S,3E)-1-phenyl-4-(4-sulphophenyl)but-3-en-2-yl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3949]



[3950] 16.7 μl (0.03 mmol) of a 15% aqueous succinaldehyde solution were initially charged in 943 μl of methanol and admixed with 17 mg (0.02 mmol) of N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(2 S,3E)-1-phenyl-4-(4-sulphophenyl)but-3-en-2-yl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide trifluoroacetate (Intermediate 181) and 1.1 μl (0.02 mmol) of acetic acid. The reaction mixture was stirred for 5 min at RT and then 2.9 μl (0.02 mmol) of borane-pyridine complex were added. After 1 h, a further 2 equivalents each of succinaldehyde, acetic acid and borane-pyridine complex were added and the mixture was stirred at RT for 20 h. The reaction mixture was then purified by prep. HPLC.

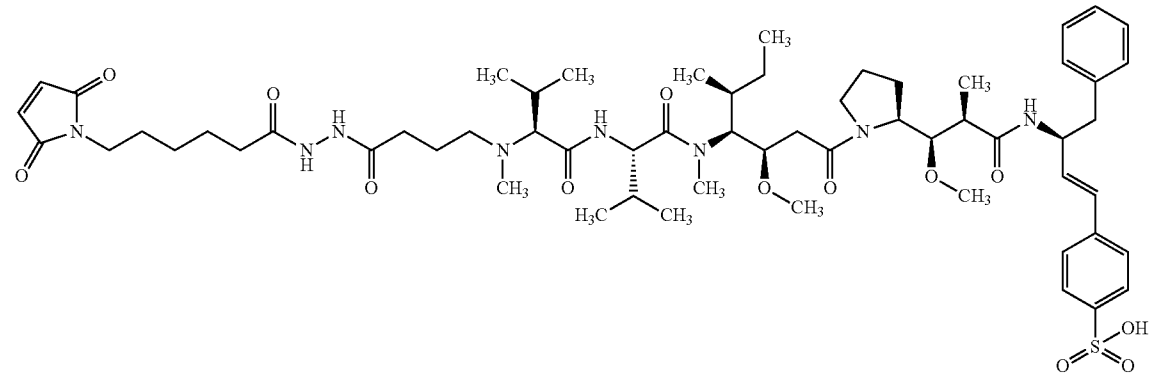
[3951] This gave 20 mg (83% purity, 80% of theory) of the title compound.

[3952] LC-MS (Method 1): R_t=0.87 min; MS (ESIpos): m/z=957 $(M+H)^+$

Intermediate 184

N-(4-{2-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(2S,3E)-1-phenyl-4-(4-sulphophenyl)but-3-en-2-yl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3953]



[3954] 8 mg (7.5 μmol) of N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(2S,3E)-1-phenyl-4-(4-sulphophenyl)but-3-en-2-yl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide, 2.8 mg (8.2 μmol) of 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanehydrazide trifluoroacetate, 3.4 mg (9 μmol) of HATU and 3.9 μl of Hünig's base were stirred in 0.77 ml of DMF at RT for 20 h. Subsequently, the reaction mixture was purified by prep. HPLC.

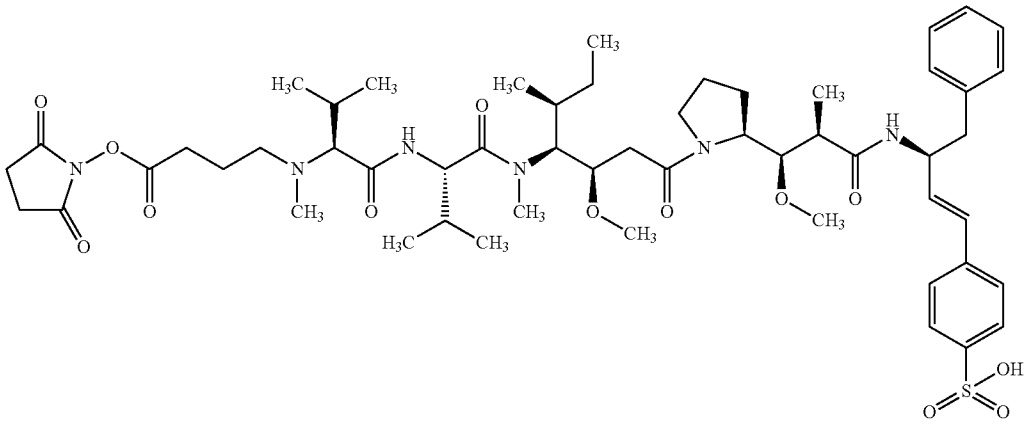
[3955] 3 mg (31% of theory) of the title compound were obtained.

[3956] LC-MS (Method 1): R_t=0.90 min; MS (ESIpos): m/z=1164 $(M+H)^+$

Intermediate 185

N-{4-[(2,5-dioxopyrrolidin-1-yl)oxy]-4-oxobutyl}-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(2S,3E)-1-phenyl-4-(4-sulphophenyl)but-3-en-2-yl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3957]



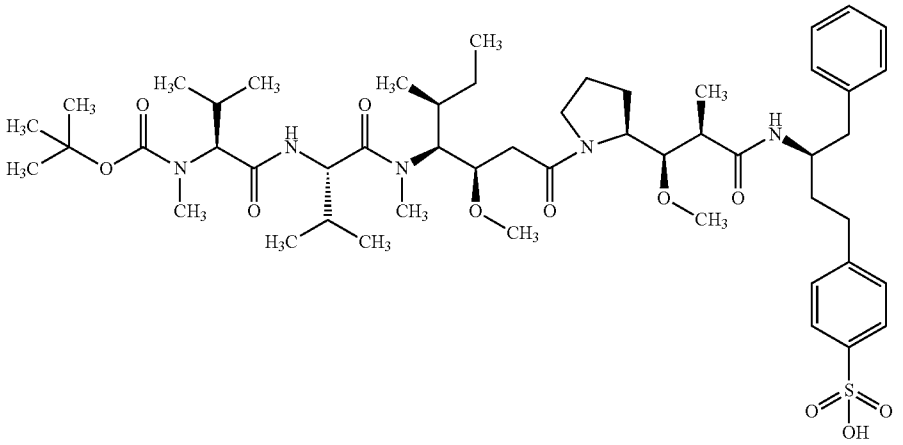
[3958] To a solution of 8 mg (7.5 μmol) of N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(2S,3E)-1-phenyl-4-(4-sulphophenyl)but-3-en-2-yl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide in 2 ml of DMF were added 8.6 mg (74.8 μmol) of N-hydroxysuccinimide, 8.5 mg (22.4 μmol) of EDCI and 0.1 mg (0.75 μmol) of DMAP. The reaction mixture was stirred at RT for 20 h. Subsequently, 1.3 μl (7.5 μmol) of Hünig's base were added and the mixture was stirred for 1 h. The reaction mixture was then purified by prep. HPLC. 2.6 mg (72% purity, 21% of theory) of the title compound were obtained.

[3959] LC-MS (Method 1): R_t=0.89 min; MS (ESIpos): m/z=1054 $(M+H)^+$

Intermediate 186

N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(2R)-1-phenyl-4-(4-sulphophenyl)butan-2-yl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3960]



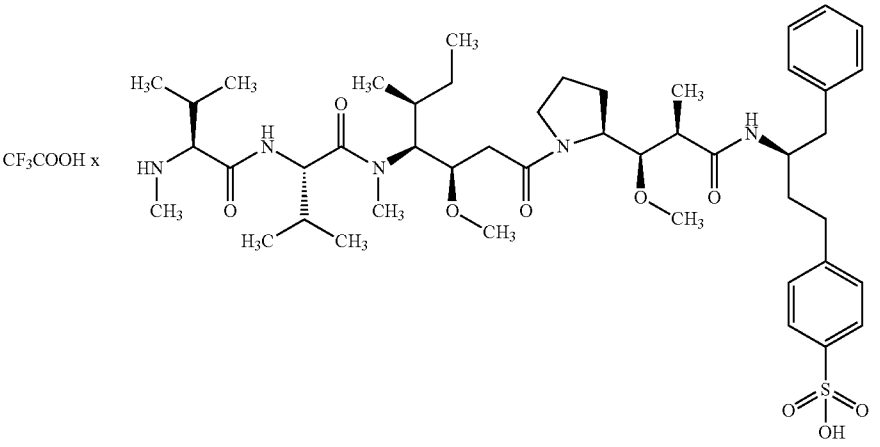
[3961] To a solution of 43 mg (0.06 mmol) of N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-2-carboxy-1-methoxypropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide in 1.9 ml of DMF were added 29 mg (0.07 mmol) of HATU and 33 μl (0.19 mmol) of Hünig's base. The reaction mixture was stirred at RT for 30 min and then admixed with 29 mg (0.07 mmol) of 4-[(3R)-3-amino-4-phenylbutyl]benzenesulphonic acid trifluoroacetate. After stirring overnight, the reaction mixture was purified by prep. HPLC. This gave 58 mg of a 45:55 mixture of the title compound and of the already deprotected amine.

[3962] LC-MS (Method 1): R_t=1.09 min; MS (ESIpos): m/z=973 $(M+H)^+$; R_t=0.87 min; MS (ESIpos): m/z=873 $(M+H)^+$ for the deprotected compound.

Intermediate 187

N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(2R)-1-phenyl-4-(4-sulphophenyl)butan-2-yl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide trifluoro acetate

[3963]



[3964] 58 mg of Intermediate 186 were dissolved in 4.1 ml of dichloromethane, 0.41 ml of trifluoroacetic acid was added and the mixture was stirred at RT for 30 min. After concentration under reduced pressure, the crude product was purified by prep. HPLC.

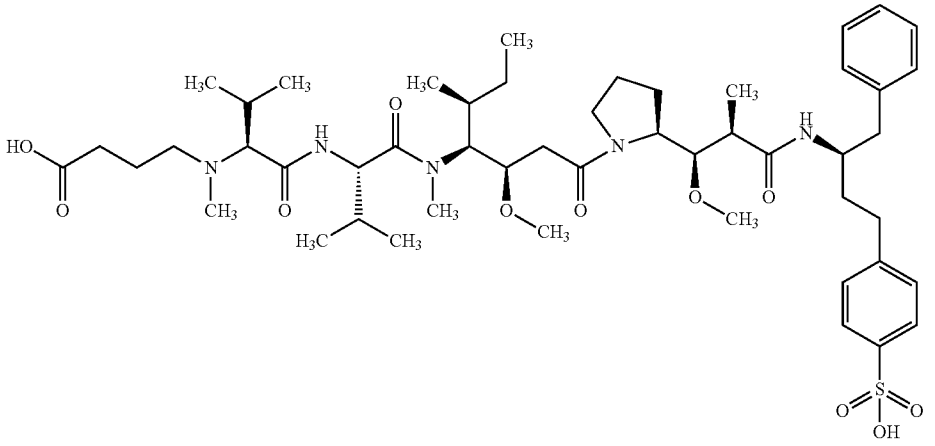
[3965] 50 mg (90% purity, 85% of theory) of the title compound were obtained.

[3966] LC-MS (Method 1): R_t=0.87 min; MS (ESIpos): m/z=873 $(M+H)^+$

Intermediate 188

N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S, 5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(2R)-1-phenyl-4-(4-sulphophenyl) butan-2-yl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3967]



[3968] 171 µl (0.26 mmol) of a 15% aqueous succinaldehyde solution were initially charged in 2.5 ml of methanol and admixed with 50 mg (0.05 mmol) of N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(2R)-1-phenyl-4-(4-sulphophenyl)butan-2-yl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide trifluoroacetate and 11.6 µl (0.2 mmol) of acetic acid. The reaction mixture was stirred for 5 min at RT and then 30 µl (0.24 mmol) of borane-pyridine complex were added. After stirring for 24 hours, a further equivalent of borane-pyridine complex was added and the mixture was stirred for a further 2 h. The reaction mixture was then purified by prep. HPLC.

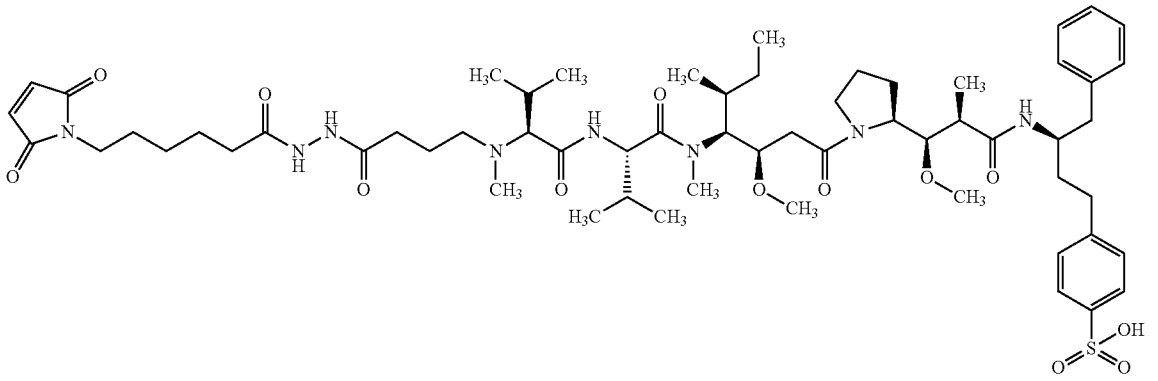
[3969] 40 mg (90% purity, 66% of theory) of the title compound were obtained.

[3970] LC-MS (Method 1): R_t=0.91 min; MS (ESIpos): m/z=959 $(M+H)^+$

Intermediate 189

N-(4-{2-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl) hexanoyl]hydrazino}-4-oxobutyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(2R)-1-phenyl-4-(4-sulphophenyl)butan-2-yl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3971]



[3972] 10 mg (9.3 μmol) of N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(2R)-1-phenyl-4-(4-sulphophenyl)butan-2-yl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide, 3.5 mg (10.3 μmol) of 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl) hexanehydrazide trifluoroacetate, 4.3 mg (11.2 μmol) of HATU and 4.9 μl (28 μmol) of Hünig's base were stirred in 1 ml of DMF at RT for 20 h. Subsequently, the reaction mixture was purified by prep. HPLC.

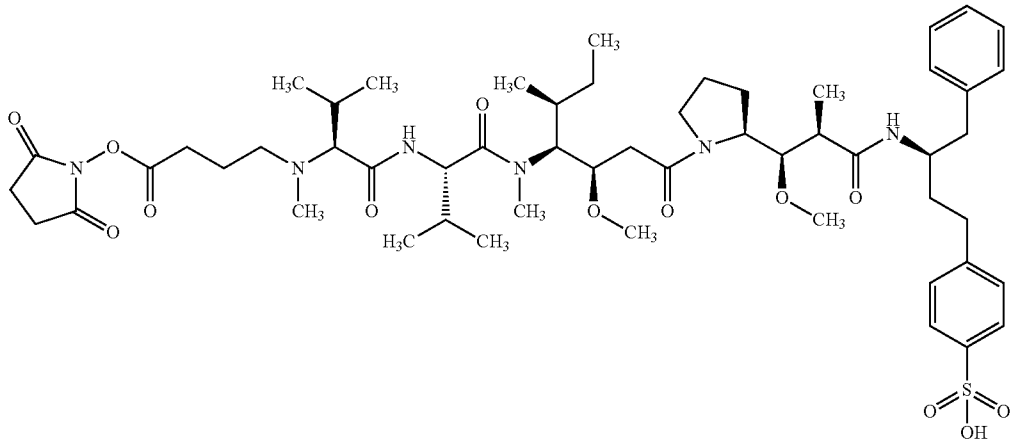
[3973] 4.2 mg (92% purity, 33% of theory) of the title compound were obtained.

[3974] LC-MS (Method 1): R_t=0.91 min; MS (ESIpos): m/z=1166 $(M+H)^+$

Intermediate 190

N-{4-[(2,5-dioxopyrrolidin-1-yl)oxy]-4-oxobutyl}-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(2R)-1-phenyl-4-(4-sulphophenyl)butan-2-yl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3975]



[3976] To a solution of 10 mg (9.3 μmol) of N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(2R)-1-phenyl-4-(4-sulphophenyl)butan-2-yl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide in 2.5 ml of DMF were added 10.7 mg (93 μmol) of N-hydroxysuccinimide, 10.6 mg (28 μmol) of EDCI and 0.12 mg (0.9 μmol) of DMAP. The reaction mixture was stirred at RT for 20 h and then purified by prep. HPLC.

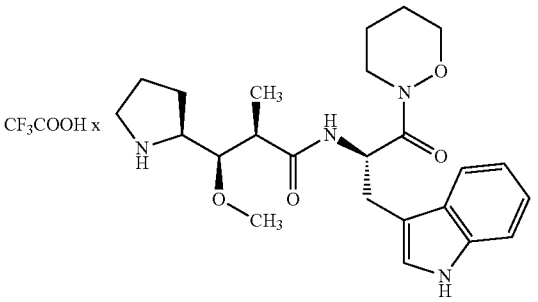
[3977] 3.8 mg (72% purity, 25% of theory) of the title compound were obtained.

[3978] LC-MS (Method 1): R_t=0.90 min; MS (ESIpos): m/z=1055 $(M+H)^+$

Intermediate 191

(2R,3R)—N-[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]-3-methoxy-2-methyl-3-[(2S)-pyrrolidin-2-yl]propanamide trifluoroacetate

[3979]



[3980] The title compound was prepared in analogy to the synthesis of Intermediate 7 over two stages from Starting Compound 1 and (2S)-2-amino-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)propan-1-one trifluoroacetate (Intermediate 99).

[3981] Yield over 2 stages: 62 mg (67% of theory)

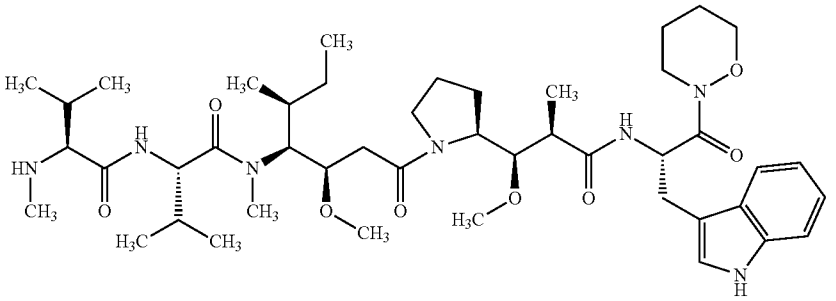
[3982] HPLC (Method 6): R_t=1.65 min;

[3983] LC-MS (Method 1): R_t=0.7 min; MS (ESIpos): m/z=443 $(M+H)^+$.

Intermediate 192

N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3984]



[3985] 1015 mg (1.59 mmol) of N-[(9H-fluoren-9-ylmethoxy)carbonyl]-N-methyl-L-valyl-N-[(2R,3S,4S)-1-carboxy-2-methoxy-4-methylhexan-3-yl]-N-methyl-L-valinamide (Intermediate 4) were taken up in 50 ml of DMF, admixed with 654 mg (2.39 mmol) of 2-bromo-1-ethylpyridinium tetrafluoroborate (BEP) and 2.8 ml of N,N-diisopropylethylamine, and stirred at RT for 10 min. Then 1083 mg (1.75 mmol) of (2R,3R)—N-[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]-3-methoxy-2-methyl-3-[(2S)-pyrrolidin-2-yl]propanamide trifluoroacetate (Intermediate 191) were added and then the mixture was treated in an ultrasound bath at RT for 30 min. The reaction mixture was then concentrated under reduced pressure and the residue was taken up in 300 ml of ethyl acetate. The organic phase was washed successively with 5% aqueous citric acid solution and 5% aqueous sodium hydrogencarbonate solution, dried over magnesium sulphate, filtered and concentrated. The crude product thus obtained (1684 mg), without further purification, was taken up in 20 ml of acetonitrile, 2 ml of piperidine were added and the reaction mixture was then stirred at RT for 10 min. Then the mixture was concentrated under reduced pressure and the residue was admixed with diethyl ether. The solvent was concentrated by evaporation again and the residue was purified by flash chromatography on silica gel (eluent: 15:1:0.1->15:2:0.2 dichloromethane/methanol/17% aqueous ammonia solution). The corresponding fractions were combined, the solvent was removed under reduced pressure and the residue was lyophilized from acetonitrile/water. Thus, 895 mg (67% over 2 stages) of the title compound were obtained.

[3986] HPLC (Method 12): R_t=1.8 min;

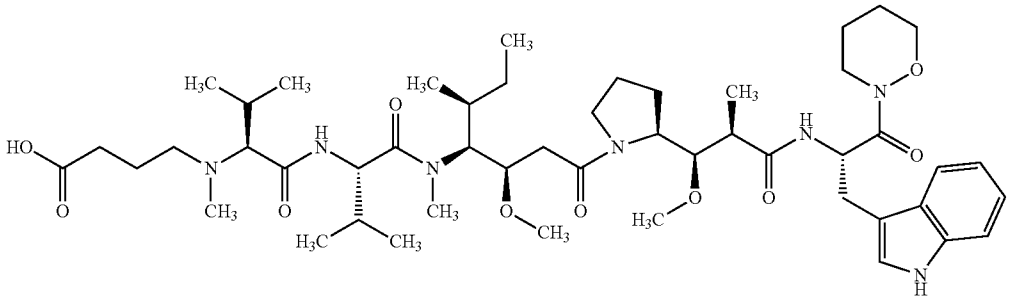
[3987] LC-MS (Method 1): R_t=0.84 min; MS (ESIpos): m/z=840 $(M+H)^+$.

[3988] ^{1}H NMR (500 MHz, DMSO-d_6): δ=10.8 (d, 1H), 8.3 and 8.05 (2d, 1H), 8.0 (d, 1H), 7.5 (m, 1H), 7.3 (m, 1H), 7.15 and 7.08 (2s, 1H) 7.05-6.9 (m, 2H), 5.12 and 4.95 (2m, 1H), 4.65 (m, 1H), 4.55 (m, 1H), 4.1-3.8 (m, 4H), 3.75 (d, 1H), 3.23, 3.18, 3.17, 3.12, 2.95 and 2.88 (6s, 9H), 3.1-3.0 and 2.85 (2m, 2H), 2.65 (d, 1H), 2.4-2.2 (m, 3H), 2.15 (m, 3H), 1.95 (br. m, 2H), 1.85-0.8 (br. m, 11H), 1.08 and 1.04 (2d, 3H), 0.9-0.75 (m, 15H), 0.75-0.65 (dd, 3H) [further signals hidden under H_2O peak].

Intermediate 193

N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3989]



[3990] 50 mg (0.052 mmol) of N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Intermediate 192) and 204 μl einer of a 15% aqueous solution of 4-oxobutanoic acid were combined in 2 ml of methanol and admixed with 23.4 mg (0.252 mmol) of borane-pyridine complex and 6 μl of acetic acid. The reaction mixture was stirred at RT overnight. This was followed by concentration under reduced pressure, and the residue was purified by means of preparative HPLC. After concentration of the corresponding fractions, 38 mg (78% of theory) of the title compound were obtained.

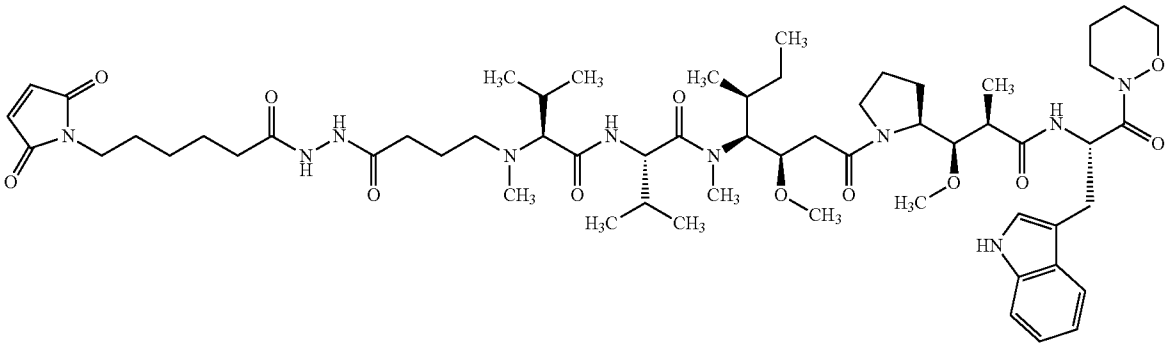
[3991] HPLC (Method 5): R_t=1.7 min;

[3992] LC-MS (Method 9): R_t=4.7 min; MS (ESIpos): m/z=926 $(M+H)^+$.

Intermediate 194

N-(4-{2-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3993]



[3994] This compound was prepared in analogy to the synthesis described in Intermediate 157 from 10 mg (11 μmol) of N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methylpropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide and commercially available 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanehydrazide.

[3995] Yield: 4.4 mg (35% of theory)

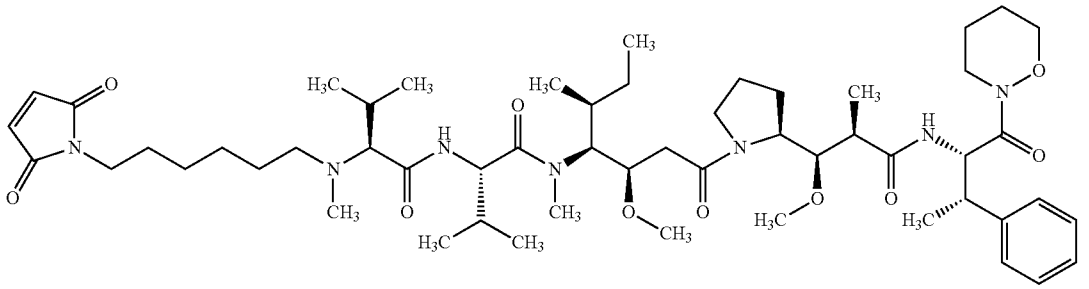
[3996] HPLC (Method 5): R_t=1.8 min;

[3997] LC-MS (Method 1): R_t=0.90 min; MS (ESIpos): m/z=1133 $(M+H)^+$.

Intermediate 195

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexyl]-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(2S,3S)-1-(1,2-oxazinan-2-yl)-1-oxo-3-phenylbutan-2-yl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[3998]



[3999] This compound was prepared in analogy to Intermediate 166, proceeding from 9 mg (0.010 mmol) of Intermediate 170.

[4000] Yield: 1.1 mg (10% of theory)

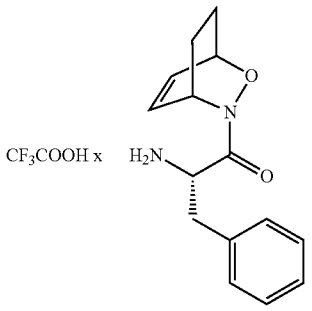
[4001] HPLC (Method 12): R_t=2.0 min;

[4002] LC-MS (Method 1): R_t=0.99 min; MS (ESIpos): m/z=994 $(M+H)^+$.

Intermediate 196

(2S)-2-amino-1-(2-oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl)-3-phenylpropan-1-one trifluoroacetate

[4003]



[4004] 41 mg (0.37 mmol) of 2,5-dioxopyrrolidin-1-yl N-(tert-butoxycarbonyl)-L-phenylalaninate were taken up in 10 ml of DMF and admixed with 149 mg (0.41 mmol) of 2-oxa-3-azabicyclo[2.2.2]oct-5-ene (Starting Compound 6) and 72 μl (0.41 mmol) of N,N-diisopropylethylamine. The mixture was stirred at RT for 1 h. The solvent was removed under reduced pressure, and the residue was taken up in ethyl acetate and extracted by shaking with 5% aqueous citric acid solution and then with 5% aqueous sodium hydrogencarbonate solution. The organic phase was concentrated and the residue was purified by flash chromatography on silica gel with 10:1 toluene/ethanol as the eluent. The corresponding fractions were combined and the solvent was removed under reduced pressure. After the residue had been dried under high vacuum, 69 mg (47% of theory) of the Boc-protected intermediate tert-butyl (2S)-1-(2-oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl)-1-oxo-3-phenylpropan-2-yl carbamate were thus obtained as a diastereomer mixture.

[4005] LC-MS (Method 1): R_t=1.1 min; MS (ESIpos): m/z=359 $(M+H)^+$.

[4006] 64 mg (0.18 mmol) of this intermediate were taken up in 10 ml of dichloromethane, 1 ml of trifluoroacetic acid was added, and the mixture was stirred at RT for 30 min. This was followed by concentration under reduced pressure and lyophilization of the remaining residue from water/dioxane. In this way, 66 mg (quant.) of the title compound were obtained as a foam.

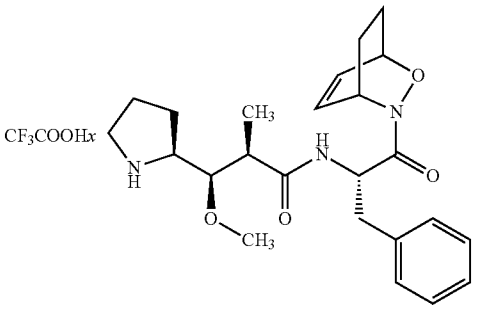
[4007] HPLC (Method 6): R_t=1.45 min;

[4008] LC-MS (Method 3): R_t=1.12 min; MS (ESIpos): m/z=259 $(M+H)^+$.

Intermediate 197

(2R,3R)-3-methoxy-2-methyl-N-[(2S)-1-(2-oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl)-1-oxo-3-phenylpropan-2-yl]-3-[(2S)-pyrrolidin-2-yl]propanamide trifluoroacetate

[4009]



[4010] First, (2R,3R)-3-[(2S)-1-(tert-butoxycarbonyl)pyrrolidin-2-yl]-3-methoxy-2-methylpropanoic acid (Starting Compound 1) was released from 83 mg (0.18 mmol) of its dicyclohexylamine salt by taking it up in ethyl acetate and extractive shaking with 5% aqueous potassium hydrogensulphate solution. The organic phase was dried over magnesium sulphate, filtered and concentrated. The residue was taken up in 10 ml of DMF and admixed successively with mg (0.18 mmol) of (2S)-2-amino-1-(2-oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl)-3-phenylpropan-1-one trifluoroacetate (Intermediate 196), 101 mg (0.266 mmol) of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) and 93 µl (0.53 mmol) of N,N-diisopropylethylamine. The mixture was stirred at RT for 30 min. The reaction mixture was then concentrated and the residue was purified by preparative HPLC. This gave 52 mg (56% of theory) of the Boc-protected intermediate tert-butyl (2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(2S)-1-(2-oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl)-1-oxo-3-phenylpropan-2-yl]amino}-3-oxopropyl]pyrrolidine-1-carboxylate.

[4011] HPLC (Method 6): R_t=2.13 min;

[4012] LC-MS (Method 1): R_t=1.13 min; MS (ESIpos): m/z=528 $(M+H)^+$.

[4013] 52 mg (0.1 mmol) of this intermediate were taken up in 10 ml of dichloromethane, 1 ml of trifluoroacetic acid was added, and the mixture was stirred at RT for 20 min. This was followed by concentration under reduced pressure and stirring of the remaining residue with 20 ml of diethyl ether. After 10 min, the mixture was filtered and the filter residue was dried under high vacuum. In this way, 39 mg (72% of theory) of the title compound were obtained.

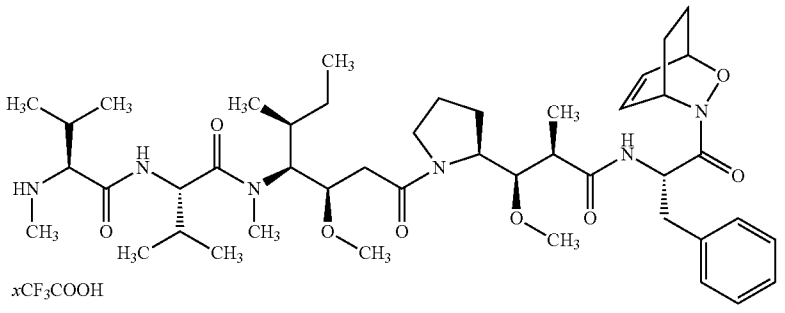
[4014] HPLC (Method 6): R_t=1.62 min;

[4015] LC-MS (Method 1): R_t=0.68 min; MS (ESIpos): m/z=428 $(M+H)^+$.

Intermediate 198

N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(2S)-1-(2-oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl)-1-oxo-3-phenylpropan-2-yl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide trifluoroacetate

[4016]



[4017] 44.5 mg (0.071 mmol) of N-[(9H-fluoren-9-ylmethoxy)carbonyl]-N-methyl-L-valyl-N-[(2R,3S,4S)-1-carboxy-2-methoxy-4-methylhexan-3-yl]-N-methyl-L-valinamide (Intermediate 4) were taken up in 10 ml of DMF and admixed successively with 38.6 mg (0.071 mmol) of (2R,3R)-3-methoxy-2-methyl-N-[(2S)-1-(2-oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl)-1-oxo-3-phenylpropan-2-yl]-3-[(2S)-pyrrolidin-2-yl]propanamide trifluoroacetate (Intermediate 197), 32.5 mg (0.086 mmol) of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) and 41 µl (0.235 mmol) of N,N-diisopropylethylamine. The mixture was stirred at RT for 1 h. The reaction mixture was then concentrated under reduced pressure and the residue was taken up in ethyl acetate. The organic phase was washed successively with 5% aqueous citric acid solution and 5% aqueous sodium hydrogencarbonate solution, dried over magnesium sulphate, filtered and concentrated. This gave 73 mg (98% of theory) of the Fmoc-protected intermediate N-[(9H-fluoren-9-ylmethoxy)carbonyl]-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(2S)-1-(2-oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl)-1-oxo-3-phenylpropan-2-yl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide.

[4018] HPLC (Method 6): R_t=2.78 min;

[4019] LC-MS (Method 3): R_t=2.96 min; MS (ESIpos): m/z=1047 $(M+H)^+$.

[4020] 73 mg (0.071 mmol) of this intermediate were dissolved in 5 ml of DMF. After 0.5 ml of piperidine had been added, the reaction mixture was stirred at RT for 10 min. This was followed by concentration under reduced pressure, and the residue was digested repeatedly with diethyl ether. After the diethyl ether had been decanted off, the residue was purified by preparative HPLC (eluent: acetonitrile/0.1% aq. TFA). 16 mg (26% of theory) of the title compound were obtained as a foam.

[4021] HPLC (Method 6): R_t=1.94 min;

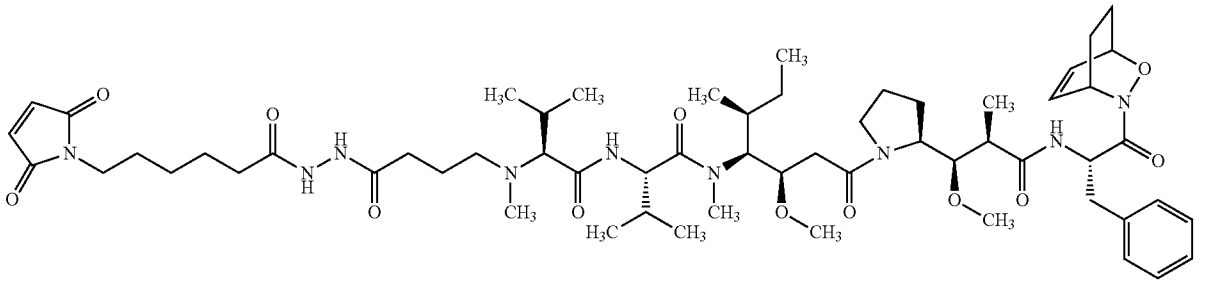
[4022] LC-MS (Method 3): R_t=1.71 min; MS (ESIpos): m/z=825 $(M+H)^+$

[4023] ^{1}H NMR (400 MHz, DMSO-d_6): δ=8.9-8.6 (m, 3H), 8.4, 8.3, 8.1 and 8.0 (4d, 1H), 7.3-7.1 (m, 5H), 6.7-6.5 (m, 2H), 5.2-4.8 (m, 3H), 4.75-4.55 (m, 3H), 4.05-3.95 (m, 1H), 3.7-3.4 (m, 4H), 3.22, 3.17, 3.15, 3.05, 3.02 and 2.95 (6s, 9H), 3.0 and 2.7 (2 br. m, 2H), 2.46 (m, 3H), 2.4-1.2 (br. m, 13H), 1.1-0.85 (m, 18H), 0.75 (m, 3H) [further signals hidden under H_2O peak].

Intermediate 199

N-(4-{2-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl) hexanoyl]hydrazino}-4-oxobutyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(2S)-1-(2-oxa-3-azabicyclo [2.2.2]oct-5-en-3-yl)-1-oxo-3-phenylpropan-2-yl] amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[4024]



[4025] The title compound was prepared in analogy to Intermediates 193 and 194, proceeding from 23 mg (24 μmol) of N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(2S)-1-(2-oxa-3-azabi-cyclo[2.2.2]oct-5-en-3-yl)-1-oxo-3-phenylpropan-2-yl] amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide trifluoroacetate (Intermediate 198).

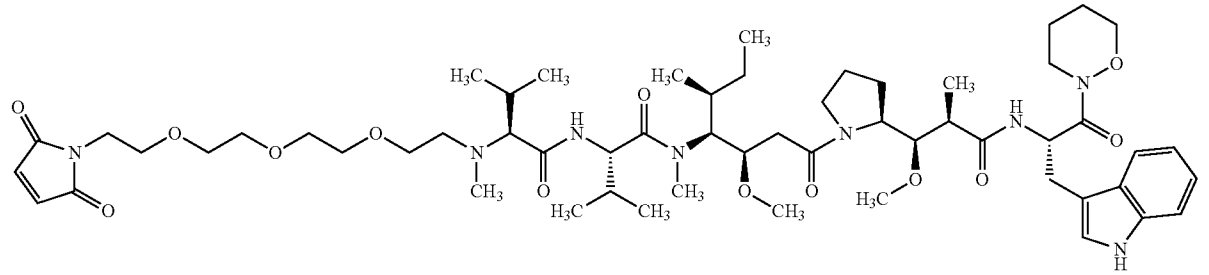
[4026] HPLC (Method 12): R_t=1.9 min;

[4027] LC-MS (Method 2): R_t=2.1 min; MS (ESIpos): m/z=1118 $(M+H)^+$.

Intermediate 200

N-[2-(2-{2-[2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethoxy]ethoxy}ethoxy)ethyl]-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl] amino}-1-methoxy-2-methyl-3-oxopropyl] pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[4028]



[4029] The preparation was effected in analogy to Intermediates 174 and 175, commencing with the reductive alkylation of Intermediate 192 with Intermediate 172, subsequent deprotection and formation of the maleimide.

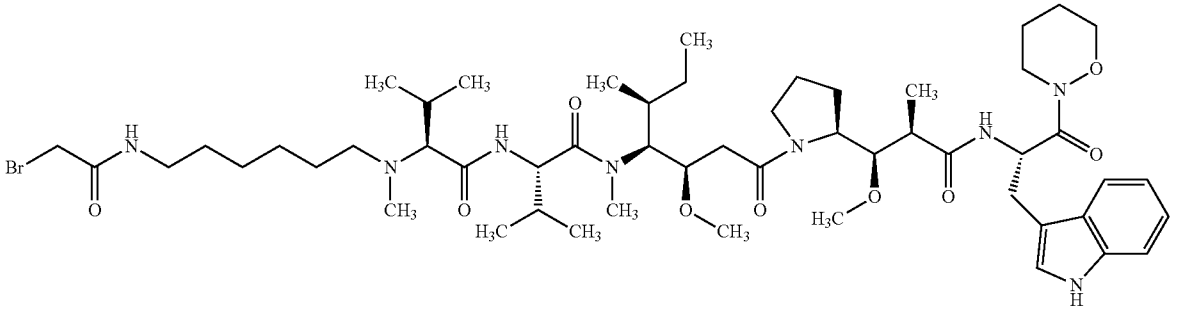
[4030] HPLC (Method 12): R_t=1.9 min;

[4031] LC-MS (Method 1): R_t=0.86 min; MS (ESIpos): m/z=1025 $(M+H)^+$.

Intermediate 201

N-{6-[(bromoacetyl)amino]hexyl}-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[4032]



[4033] 22 mg (0.023 mmol) of N-(6-aminohexyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Intermediate 101) were dissolved in 9.5 ml of THF and admixed at 0° C. with 4.2 μl of triethylamine. A solution of bromoacetyl chloride in THF was added dropwise and the reaction mixture was stirred at 0° C. for 30 min. The reaction mixture was concentrated and the residue was purified by preparative HPLC. Thus, 6.9 mg (26% of theory) of the title compound were obtained as a foam.

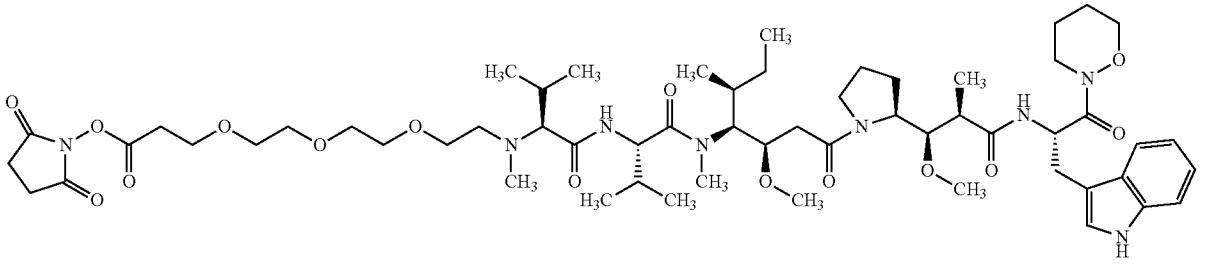
[4034] HPLC (Method 5): R_t=1.8 min;

[4035] LC-MS (Method 11): R_t=0.9 min; MS (ESIpos): m/z=1059 and 1061 $(M+H)^+$.

Intermediate 202

N-{2-[2-(2-{3-[(2,5-dioxopyrrolidin-1-yl)oxy]-3-oxopropoxy}ethoxy)ethoxy]ethyl}-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[4036]



[4037] The preparation was at first effected in analogy to Intermediate 168, commencing with the reductive alkylation of Intermediate 192 with Intermediate 167 and subsequent hydrogenolytic cleavage of the benzyl ester of N-(2-{2-[2-(2-carboxyethoxy)ethoxy]ethoxy}ethyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide.

[4038] 13 mg (10 μmol) of this intermediate were dissolved in 5 ml of DMF and admixed with 2.1 mg (20 mmol) of 1-hydroxypyrrolidine-2,5-dione, 6.5 μl of N,N-diisopropylethylamine and 7.1 mg (0.02 mmol) of HATU. The reaction mixture was stirred at RT overnight and then concentrated under reduced pressure. The remaining residue was purified by means of preparative HPLC. After lyophilization from acetonitrile/water, 9.2 mg (62% of theory) of the title compound were obtained.

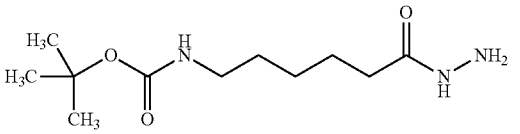
[4039] HPLC (Method 12): R_t=2.0 min;

[4040] LC-MS (Method 2): R_t=2.1 min; MS (ESIpos): m/z=1141 $(M+H)^+$.

Intermediate 203

tert-butyl 6-hydrazino-6-oxohexyl carbamate

[4041]



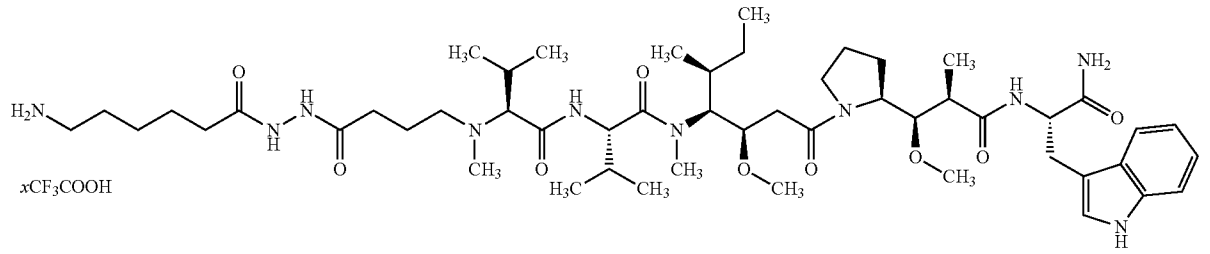
[4042] This compound was prepared by standard peptide chemistry methods, by coupling of 6-[(tert-butoxycarbonyl)amino]hexanoic acid with benzyl hydrazinecarboxylate in the presence of EDCI and HOBT, and subsequent hydrogenolytic cleavage of the benzyloxycarbonyl protecting group.

[4043] LC-MS (Method 11): R_t=0.59 min; MS (ESIpos): m/z=246 $(M+H)^+$.

Intermediate 204

N-{4-[2-(6-aminohexanoyl)hydrazino]-4-oxobutyl}-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-amino-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide trifluoroacetate

[4044]



[4045] 146 mg (50 μmol) of (N-(3-carboxypropyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-amino-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide were dissolved in 5 ml of DMF and then admixed with 30.6 mg (80 μmol) of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, 19 μl of N,N-diisopropylethylamine and with 22.4 mg (60 μmol) of tert-butyl 6-hydrazino-6-oxohexyl carbamate. The reaction mixture was stirred at RT for 1.5 h. This was followed by concentration under high vacuum and purification of the remaining residue by means of preparative HPLC. Thus, 43 mg (68% of theory) of the protected intermediate were obtained, which were then taken up in 10 ml of dichloromethane and deprotected with 1 ml of trifluoroacetic acid. The reaction mixture was concentrated and the residue was stirred with dichloromethane, and the solvent was removed again under reduced pressure. Thus, 45 mg (68% of theory over 2 stages) of the title compound were obtained.

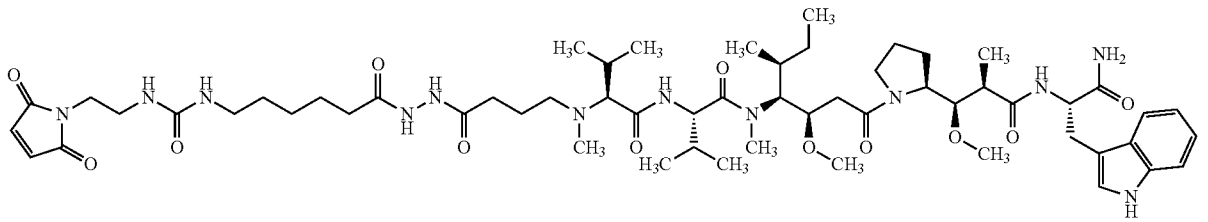
[4046] HPLC (Method 12): R_t=1.6 min;

[4047] LC-MS (Method 11): R_t=0.66 min; MS (ESIpos): m/z=983 $(M+H)^+$.

Intermediate 205

N-(4-{2-[6-({[2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethyl]carbamoyl}amino)hexanoyl]hydrazino}-4-oxobutyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-amino-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[4048]



[4049] This compound was prepared in analogy to Intermediate 114, proceeding from Intermediates 50 and 204.

[4050] Yield: 4 mg (78% of theory)

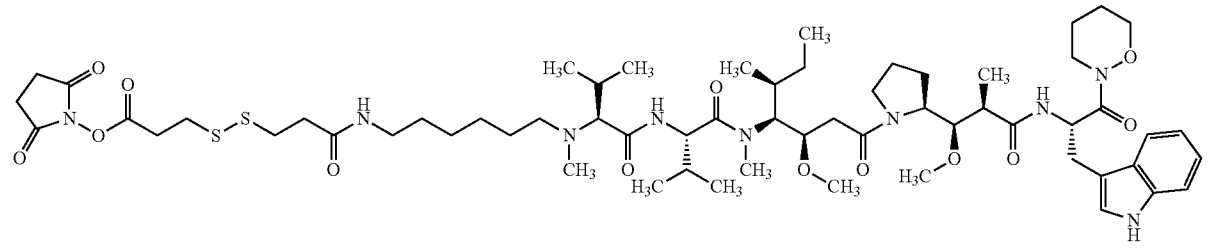
[4051] HPLC (Method 12): R_t=1.7 min;

[4052] LC-MS (Method 11): R_t=0.73 min; MS (ESIpos): m/z=1149 $(M+H)^+$.

Intermediate 206

N-(6-{[3-({3-[(2,5-dioxopyrrolidin-1-yl)oxy]-3-oxopropyl}disulphanyl)propanoyl]amino}hexyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[4053]



[4054] 8 mg (10 μmol) of Intermediate 101 were dissolved in 2 ml of DMF and admixed with 8.6 mg (20 μmol) of 1,1'-{disulphanediylbis[(1-oxopropane-3,1-diyl)oxy]}dipyrrolidine-2,5-dione and 3.7 μl of N,N-diisopropylethylamine. The reaction mixture was stirred at RT for 2 h and then the solvent was evaporated off under reduced pressure and the residue was purified by preparative HPLC. 7.2 mg (68% of theory) of the title compound were obtained.

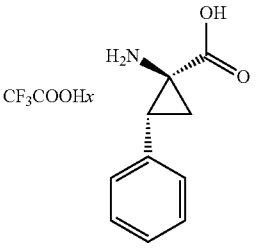
[4055] HPLC (Method 5): R_t=1.9 min;

[4056] LC-MS (Method 11): R_t=0.94 min; MS (ESIpos): m/z=615 [½ $(M+2H^+]$

Intermediate 207

(1S,2R)-1-amino-2-phenylcyclopropanecarboxylic acid trifluoroacetate

[4057]



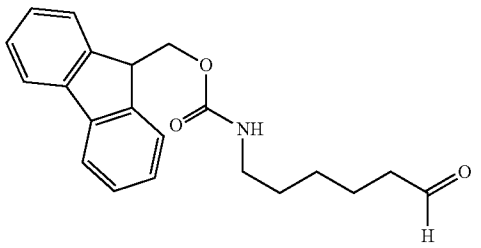
[4058] The title compound was obtained in quantitative yield by deprotecting 210 mg (0.76 mmol) of commercially available (1S,2R)-1-[(tert-butoxycarbonyl)amino]-2-phenylcyclopropanecarboxylic acid with trifluoroacetic acid.

[4059] LC-MS (Method 1): R_t=0.23 min; MS (ESIpos): m/z=178 $(M+H)^+$.

Intermediate 208

9H-fluoren-9-ylmethyl 6-oxohexyl carbamate

[4060]



[4061] The title compound was prepared from 1 g (2.95 mmol) of commercially available 9H-fluoren-9-ylmethyl 6-hydroxyhexyl carbamate under standard conditions, by oxidation with sulphur trioxide-pyridine complex. 840 mg (85% of theory) of the title compound were obtained.

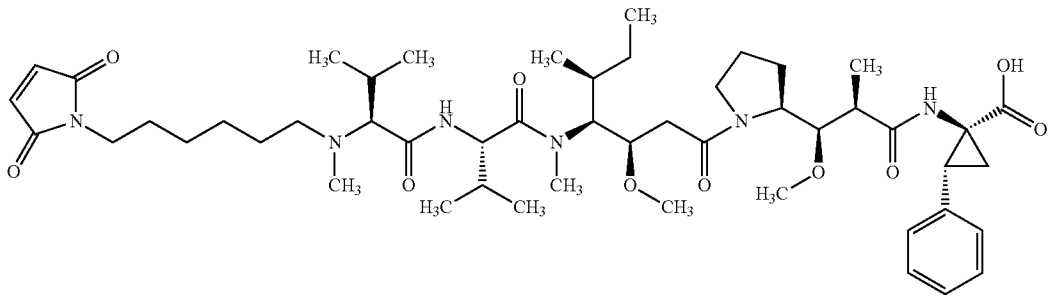
[4062] HPLC (Method 12): R_t=2.0 min;

[4063] LC-MS (Method 1): R_t=1.1 min; MS (ESIpos): m/z=338 $(M+H)^+$.

Intermediate 209

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexyl]-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(1S,2R)-1-carboxy-2-phenylcyclopropyl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[4064]



[4065] First, in analogy to the synthesis described in Intermediate 75, by coupling of N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-2-carboxy-1-methoxypropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Intermediate 26) and (1S,2R)-1-amino-2-phenylcyclopropanecarboxylic acid trifluoroacetate (Intermediate 207) in the presence of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and subsequent detachment of the Boc protecting group by means of trifluoroacetic acid, the amine compound N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(1S,2R)-1-carboxy-2-phenylcyclopropyl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide was prepared as the trifluoroacetate.

[4066] To 22 mg (0.026 mmol) of this compound in 10 ml of methanol were then added 17 mg (0.05 mmol) of 9H-fluoren-9-ylmethyl 6-oxohexyl carbamate (Intermediate 208) and 2.3 mg of acetic acid, and also 11.4 mg (0.12 mmol) of borane-pyridine complex. The reaction mixture was stirred at RT overnight. Then the same amounts of borane-pyridine complex and acetic acid, and also 8 mg of fluoren-9-ylmethyl 6-oxohexyl carbamate, were added once again and the reaction mixture was stirred at RT for a further 24 h. This was followed by concentration under reduced pressure, and the residue was purified by means of preparative HPLC. After concentration of the corresponding fractions, the product was used immediately in the next stage.

[4067] 33 mg of the still contaminated intermediate were taken up in 5 ml of DMF, and 1 ml of piperidine was added. After stirring at RT for 15 min, the reaction mixture was concentrated and the resulting residue was purified by preparative HPLC. Thus, 11 mg (55% of theory over 2 stages) of the aminocarboxylic acid intermediate were obtained.

[4068] HPLC (Method 12): R_t=1.7 min;

[4069] LC-MS (Method 11): R_t=0.7 min; MS (ESIpos): m/z=843 $(M+H)^+$.

[4070] 6 mg (7.12 μmol) of this intermediate were taken up in 1 ml of dioxane and then admixed with 6.6 mg (42.7 μmol) of methyl 2,5-dioxo-2,5-dihydro-1H-pyrrole-1-carboxylate and with 5 μl of saturated aqueous sodium hydrogencarbonate solution. The reaction mixture was stirred at RT for 1 h. Then another 3 portions each of 50 μl of the saturated aqueous sodium hydrogencarbonate solution were added and the reaction mixture was stirred at RT for a further 30 min. Then the reaction mixture was acidified to pH 2 with trifluoroacetic acid and subsequently concentrated under reduced pressure. The remaining residue was purified by means of preparative HPLC. After lyophilization from acetonitrile/water, 4 mg (60% of theory) of the title compound were obtained as a foam.

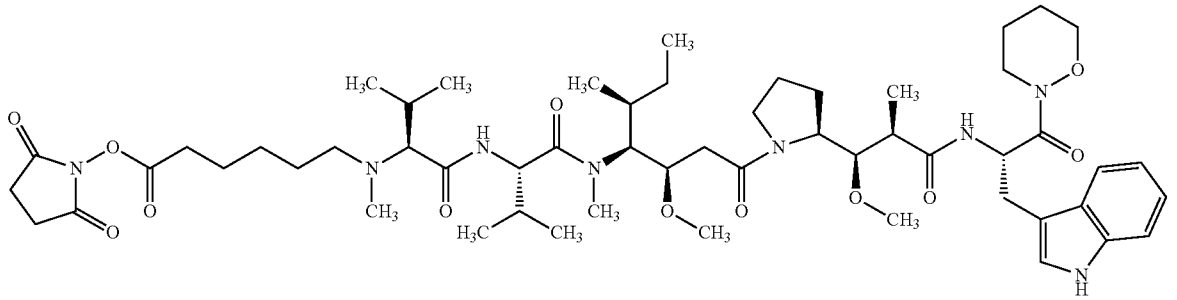
[4071] HPLC (Method 12): R_t=1.9 min;

[4072] LC-MS (Method 11): R_t=0.88 min; MS (ESIpos): m/z=923 $(M+H)^+$.

Intermediate 210

N-{6-[(2,5-dioxopyrrolidin-1-yl)oxy]-6-oxohexyl}-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[4073]



[4074] First, 6-oxohexanoic acid was prepared by a literature method (J. org. Chem. 58, 1993, 2196-2200).

[4075] 80 mg (0.08 mmol) of N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Intermediate 192) and 65.4 mg (0.5 mmol) of 6-oxohexanoic acid were combined in 9 ml of methanol and admixed with 10 μl of acetic acid and 37.4 mg (0.4 mmol) of borane-pyridine complex. The reaction mixture was stirred at RT overnight. This was followed by concentration under reduced pressure, and the residue was taken up in 1:1 acetonitrile/water and adjusted to pH 2 with trifluoroacetic acid. The reaction mixture was concentrated again and the residue was purified by means of preparative HPLC. After concentration of the corresponding fractions, 70 mg (86% of theory) of N-(5-carboxypentyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide were obtained as the trifluoroacetate.

[4076] HPLC (Method 12): R_t=1.9 min;

[4077] LC-MS (Method 1): R_t=0.87 min; MS (ESIpos): m/z=955 $(M+H)^+$.

[4078] ^{1}H NMR (500 MHz, DMSO-d_6, characteristic signals): δ=12.0 (br. M, 1H), 10.8 (s, 1H), 9.4 (m, 1H), 8.9 and 8.8 (2d, 1H), 8.3 and 8.02 (2d, 1H), 7.5 (m, 1H), 7.3 (m, 1H), 7.15 and 7.1 (2s, 1H) 7.05-6.9 (m, 2H), 5.12 and 4.95 (2m, 1H), 4.7-4.5 (m, 2H), 4.1-3.8 (m, 4H), 3.75 (d, 1H), 3.25, 3.2, 3.18, 3.13, 2.98 and 2.88 (6s, 9H), 2.8 (m, 3H), 1.08 and 1.04 (2d, 3H), 0.95-0.8 (m, 15H), 0.8-0.65 (dd, 3H).

[4079] 22 mg (23 μmol) of this intermediate were dissolved in 1.8 ml of dichloromethane and admixed with 13.2 mg (70 μmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 26.5 mg (230 μmol) of 1-hydroxypyrrolidine-2,5-dione and 0.28 mg (2 μmol) of dimethylaminopyridine, and the reaction mixture was stirred at RT for 2 h. Subsequently, the reaction mixture was concentrated under reduced pressure and the remaining residue was purified by means of preparative HPLC. After lyophilization from acetonitrile/water, 21.3 mg (88% of theory) of the title compound were obtained.

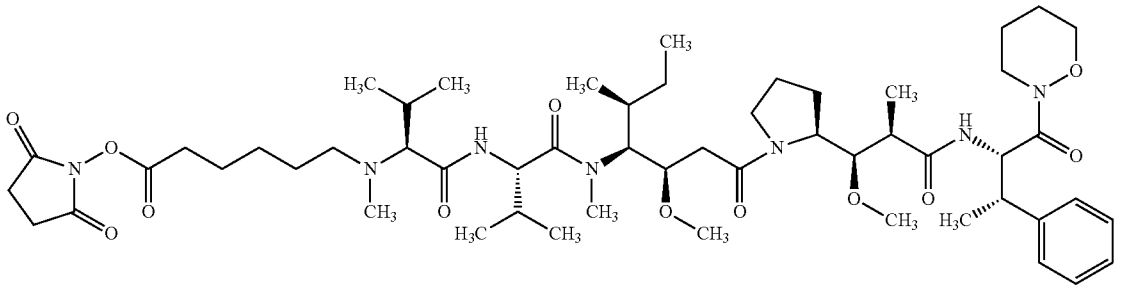
[4080] HPLC (Method 12): R_t=1.9 min;

[4081] LC-MS (Method 1): R_t=0.94 min; MS (ESIpos): m/z=1052 $(M+H)^+$.

Intermediate 211

N-{6-[(2,5-dioxopyrrolidin-1-yl)oxy]-6-oxohexyl}-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(2S,3S)-1-(1,2-oxazinan-2-yl)-1-oxo-3-phenylbutan-2-yl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[4082]



[4083] 15 mg (20 μmol) of N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(2S,3S)-1-(1,2-oxazinan-2-yl)-1-oxo-3-phenylbutan-2-yl]amino}-3-oxopropyl]pyrrolidin-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide trifluoroacetate (Intermediate 15) were reductively alkylated with 6-oxohexanoic acid, in analogy to Intermediate 210.

[4084] Yield: 9.2 mg (61% of theory)

[4085] HPLC (Method 12): R_t=1.9 min;

[4086] LC-MS (Method 1): R_t=0.87 min; MS (ESIpos): m/z=929 $(M+H)^+$.

[4087] 9 mg (10 μmol) of this intermediate were dissolved in 3 ml of DMF and admixed with 5.6 mg (48 μmol) of 1-hydroxypyrrolidine-2,5-dione, 5 μl of N,N-diisopropylethylamine and 5.5 mg (0.015 mmol) of HATU, and the reaction mixture was treated in an ultrasound bath for 6 h. In the course of this, 5.5 mg of HATU were added every hour. Subsequently, the reaction mixture was concentrated under reduced pressure, and the residue was taken up in acetonitrile/water and adjusted to pH 2 with trifluoroacetic acid. After concentrating again under reduced pressure, the remaining residue was purified by means of preparative HPLC. After lyophilization from acetonitrile/water, 5.8 mg (57% of theory) of the title compound were obtained.

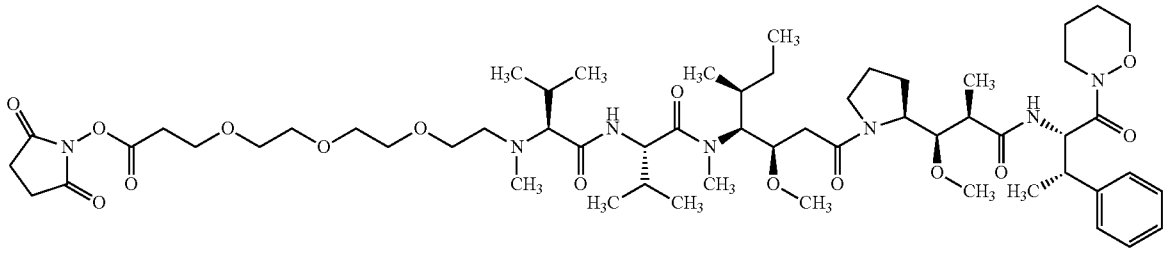
[4088] HPLC (Method 12): R_t=2.0 min;

[4089] LC-MS (Method 1): R_t=0.95 min; MS (ESIpos): m/z=1027 $(M+H)^+$.

Intermediate 212

N-{2-[2-(2-{3-[(2,5-dioxopyrrolidin-1-yl)oxy]-3-oxopropoxy}ethoxy)ethoxy]ethyl}-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(2S,3S)-1-(1,2-oxazinan-2-yl)-1-oxo-3-phenylbutan-2-yl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[4090]



[4091] The preparation was at first effected in analogy to Intermediate 168, commencing with the reductive alkylation of Intermediate 15 with Intermediate 167 and subsequent hydrogenolytic cleavage of the benzyl ester of N-(2-{2-[2-(2-carboxyethoxy)ethoxy]ethoxy}ethyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(2S,3S)-1-(1,2-oxazinan-2-yl)-1-oxo-3-phenylbutan-2-yl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide.

[4092] 8.4 mg (8 μmol) of this intermediate were dissolved in 3 ml of DMF and admixed with 9.5 mg (80 μmol) of 1-hydroxypyrrolidine-2,5-dione, 10 μl of N,N-diisopropylethylamine and 9.4 mg (25 μmol) of HATU, and the reaction mixture was stirred at RT overnight and then concentrated under reduced pressure. Subsequently, the reaction mixture was concentrated under reduced pressure, and the residue was taken up in acetonitrile/water and adjusted to pH 2 with trifluoroacetic acid. After concentrating again under reduced pressure, the remaining residue was purified by means of preparative HPLC. After lyophilization from acetonitrile/water, 4 mg (32% of theory) of the title compound were obtained.

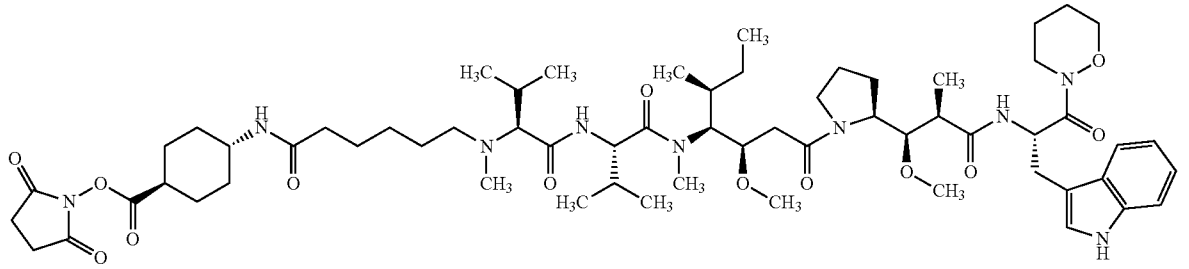
[4093] HPLC (Method 12): R_t=2.0 min;

[4094] LC-MS (Method 1): R_t=0.96 min; MS (ESIpos): m/z=1117 $(M+H)^+$.

Intermediate 213

N-{6-[(trans-4-{[(2,5-dioxopyrrolidin-1-yl)oxy]carbonyl}cyclohexyl)amino]-6-oxohexyl}-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[4095]



[4096] This compound was prepared in analogy to Intermediate 104, proceeding from N-(5-carboxypentyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide, the synthesis of which was described under Intermediate 210. 9.3 mg of the title compound (37% of theory over 3 stages) were obtained.

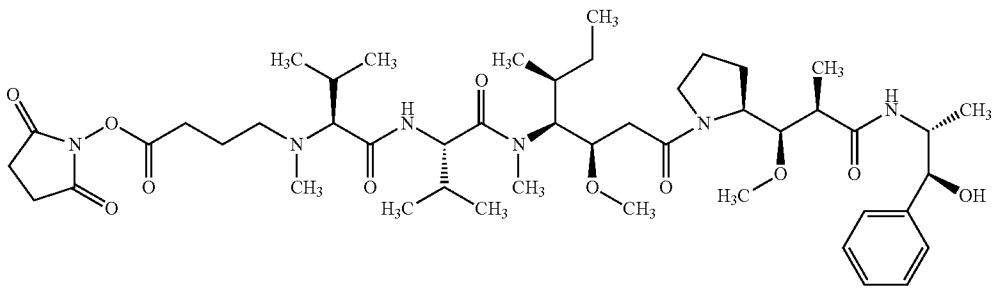
[4097] HPLC (Method 12): R_t=1.9 min;

[4098] LC-MS (Method 1): R_t=0.9 min; MS (ESIpos): m/z=1177 $(M+H)^+$.

Intermediate 214

N-{4-[(2,5-dioxopyrrolidin-1-yl)oxy]-4-oxobutyl}-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(1S,2R)-1-hydroxy-1-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[4099]



[4100] This compound was prepared in analogy to Intermediate 210, by conversion of Intermediate 92 to the active ester.

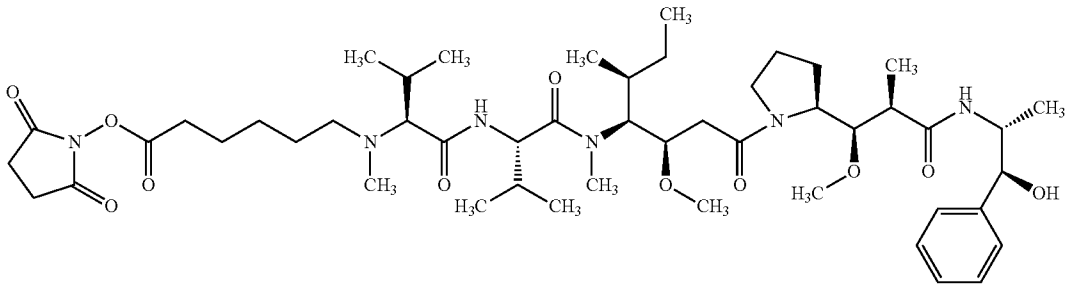
[4101] HPLC (Method 5): R_t=1.6 min;

[4102] LC-MS (Method 11): R_t=0.82 min; MS (ESIpos): m/z=901 $(M+H)^+$.

Intermediate 215

N-{6-[(2,5-dioxopyrrolidin-1-yl)oxy]-6-oxohexyl}-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(1S,2R)-1-hydroxy-1-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[4103]



[4104] First, Intermediate 40, in analogy to Intermediate 183, was used with borane-pyridine complex to prepare N-(5-carboxypentyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(1S,2R)-1-hydroxy-1-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide. From this compound, in analogy to Intermediate 210, the active ester was then generated. 34 mg (36% of theory over 2 stages) of the title compound were obtained.

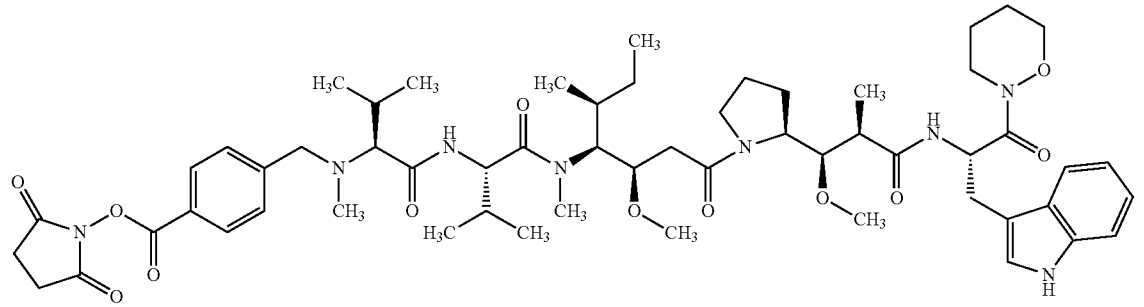
[4105] HPLC (Method 5): R_t=1.6 min;

[4106] LC-MS (Method 1): R_t=0.85 min; MS (ESIpos): m/z=930 $(M+H)^+$.

Intermediate 216

N-(4-{[(2,5-dioxopyrrolidin-1-yl)oxy]carbonyl}benzyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[4107]



[4108] First, in analogy to the preparation of Intermediate 183, Intermediate 192 was reacted with 4-formylbenzoic acid with borane-pyridine complex to give N-(4-carboxybenzyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide. This compound was then used, in analogy to Intermediate 210, to generate 11 mg (68% of theory) of the title compound.

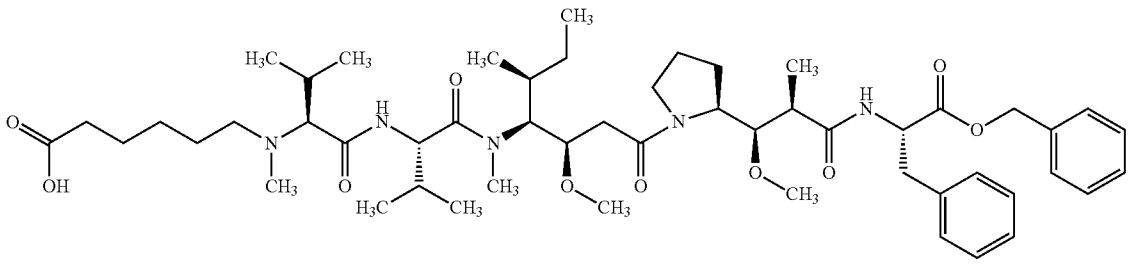
[4109] HPLC (Method 5): R_t=1.8 min;

[4110] LC-MS (Method 1): R_t=1.13 min; MS (ESIpos): m/z=1072 $(M+H)^+$.

Intermediate 217

N-(5-carboxypentyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(benzyloxy)-1-oxo-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[4111]



[4112] 53 mg (84 μmol) of N-[(9H-fluoren-9-ylmethoxy)carbonyl]-N-methyl-L-valyl-N-[(2R,3S,4S)-1-carboxy-2-methoxy-4-methylhexan-3-yl]-N-methyl-L-valinamide (Intermediate 4) and 45 mg (84 μmol) of benzyl N-{(2R,3R)-3-methoxy-2-methyl-3-[(2S)-pyrrolidin-2-yl]propanoyl}-L-phenylalaninate trifluoroacetate (Intermediate 12) were taken up in 2 ml of DMF, 19 μl of N,N-diisopropylethylamine, 14 mg (92 μmol) of HOBt and 17.6 mg (92 μmol) of EDC were added and then the mixture was stirred at RT overnight. Subsequently, the reaction mixture was concentrated and the residue was purified by means of preparative HPLC. This gave 59 mg (68% of theory) of the Fmoc-protected intermediate N-[(9H-fluoren-9-ylmethoxy)carbonyl]-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(benzyloxy)-1-oxo-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide.

[4113] LC-MS (Method 1): R_t=1.55 min; m/z=1044 $(M+H)^+$.

[4114] 57 mg (0.055 mmol) of this intermediate were treated with 1.2 ml of piperidine in 5 ml of DMF to detach the Fmoc protecting group. After concentration and purification by means of preparative HPLC, 39 mg (76% of theory) of the free amine intermediate N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(benzyloxy)-1-oxo-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide were obtained as the trifluoroacetate.

[4115] HPLC (Method 5): R_t=1.9 min;

[4116] LC-MS (Method 1): R_t=1.01 min; m/z=822 $(M+H)^+$.

[4117] 60 mg (0.06 mmol) of this intermediate were reacted, in analogy to Intermediate 210, with 6-oxohexanoic acid in the presence of borane-pyridine complex. 45 mg (75% of theory) of the title compound were obtained as a foam.

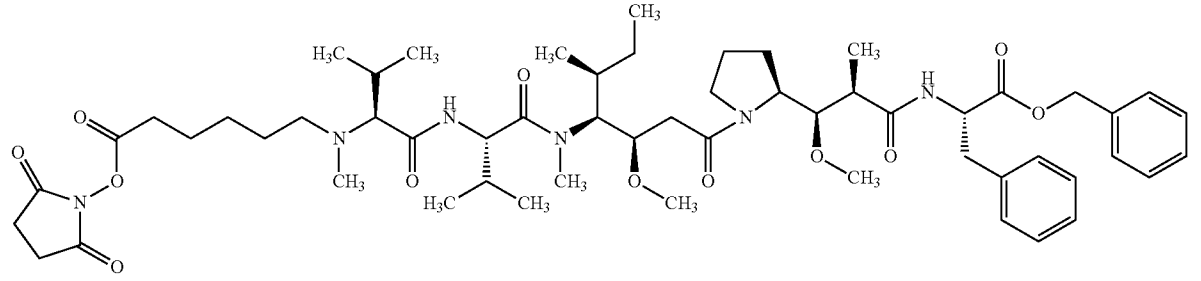
[4118] HPLC (Method 5): R_t=1.9 min;

[4119] LC-MS (Method 1): R_t=0.97 min; MS (ESIpos): m/z=9936 $(M+H)^+$.

Intermediate 218

N-{6-[(2,5-dioxopyrrolidin-1-yl)oxy]-6-oxohexyl}-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(benzyloxy)-1-oxo-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[4120]



[4121] This compound was prepared by conversion of 42 mg (0.05 mmol) of Intermediate 217 to the active ester.

[4122] Yield: 26 mg (54%)

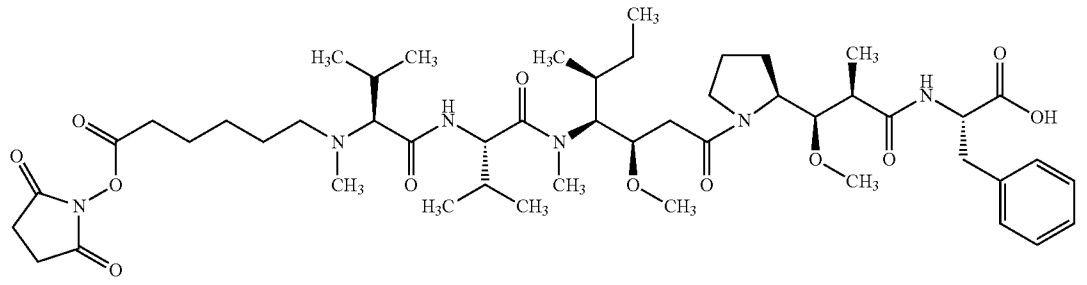
[4123] HPLC (Method 5): R_t=2.1 min;

[4124] LC-MS (Method 1): R_t=1.01 min; MS (ESIpos): m/z=1034 $(M+H)^+$.

Intermediate 219

N-{6-[(2,5-dioxopyrrolidin-1-yl)oxy]-6-oxohexyl}-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(1S)-1-carboxy-2-phenylethyl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[4125]



[4126] 20 mg (0.02 mol) of the compound from Intermediate 218 were taken up in 2.4 ml of methanol and hydrogenated over 5% palladium on activated carbon under standard hydrogen pressure at RT for 30 min. The catalyst was then filtered off and the solvent was removed under reduced pressure. The residue was lyophilized from 1:1 acetonitrile/water. This gave 14 mg (92% of theory) of the title compound as a colourless foam.

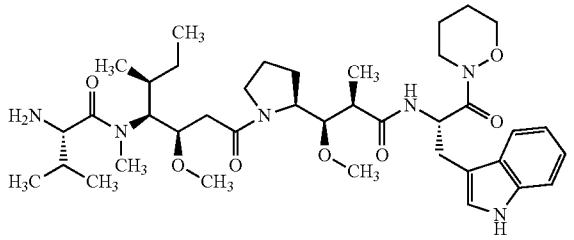
[4127] HPLC (Method 5): R_t=1.7 min;

[4128] LC-MS (Method 1): R_t=0.86 min; MS (ESIpos): m/z=944 $(M+H)^+$.

Intermediate 220

N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[4129]



[4130] 0.5 g (1.01 mmol) of Intermediate 1 in 10 ml of dichloromethane were admixed with 1 ml of trifluoroacetic acid. After treatment in an ultrasound bath for 30 min, the mixture was concentrated and redistilled first with DCM and then with diethyl ether, and dried under high vacuum. The oily residue was used in the next stage, without further purification.

[4131] 500 mg of this intermediate were dissolved in 20 ml of DMF and admixed with 466 mg (3.8 mmol) of Intermediate 191, 382 mg (1.01 mmol) of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) and 440 µl (2.5 mmol) of N,N-diisopropylethylamine. The mixture was stirred at RT for 1 h and then concentrated. The residue was taken up in dichloromethane and extracted by shaking first twice with 5% aqueous citric acid solution and then with saturated aqueous sodium hydrogencarbonate solution. The organic phase was concentrated and the residue was purified by flash chromatography on silica gel with 95:5 dichloromethane/methanol as the eluent. The corresponding fractions were combined and the solvent was removed under reduced pressure. After the residue had been dried under high vacuum, 562 mg (65% of theory over both stages) of the Z-protected intermediate were obtained.

[4132] 562 mg (0.57 mmol) of this intermediate were taken up in 50 ml of methanol and hydrogenated with 155 mg of 10% palladium on activated carbon under standard hydrogen pressure at RT for 20 min. The catalyst was then filtered off and the solvent was removed under reduced pressure. The residue was purified by preparative HPLC. The corresponding fractions were combined, the solvent was evaporated off under reduced pressure and the residue was lyophilized from dioxane. This gave 361 mg (87% of theory) of the title compound as a foam.

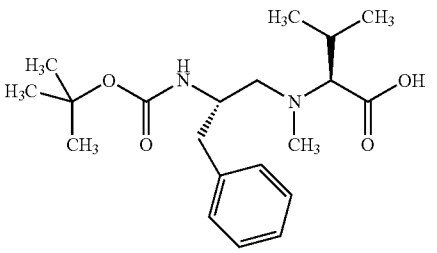
[4133] HPLC (Method 5): double peak with R_t=1.75 and 1.86 min;

[4134] LC-MS (Method 1): double peak at R_t=0.84 min and 0.91 min with the same mass; MS (ESIpos): m/z=944 $(M+H)^+$.

Intermediate 221

N-{(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropyl}-N-methyl-L-valine

[4135]



[4136] 100 mg (0.76 mmol) of commercially available N-methyl-L-valine and 285 mg (1.14 mmol) of commercially available tert-butyl (2S)-1-oxo-3-phenylpropan-2-yl carbamate were combined in 22 ml of methanol and admixed with 340 mg (3.66 mmol) of borane-pyridine complex and 70 µl of acetic acid. The reaction mixture was stirred at RT overnight. This was followed by concentration under reduced pressure, and the residue was purified by flash chromatography on silica gel with dichloromethane/methanol/17% aqueous ammonia solution as the eluent. After concentration of the corresponding fractions and lyophilization from 1:1 dioxane/water, 259 mg (93% of theory) of the title compound were obtained.

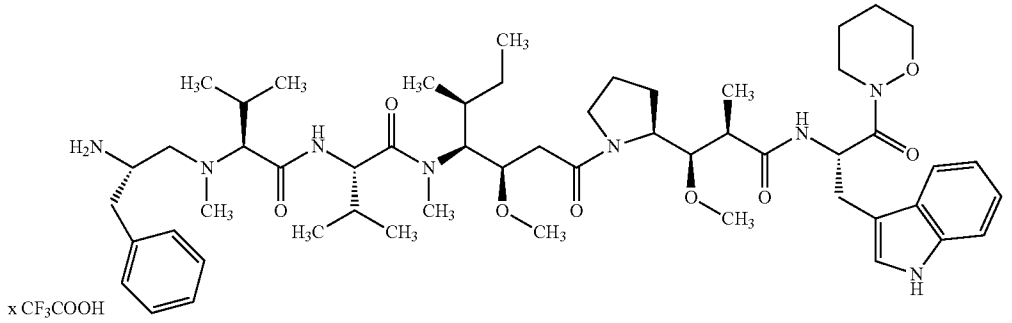
[4137] HPLC (Method 12): R_t=1.6 min;

[4138] LC-MS (Method 11): R_t=0.76 min; MS (ESIpos): m/z=365 $(M+H)^+$.

Intermediate 222

N-[(2S)-2-amino-3-phenylpropyl]-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide trifluoroacetate

[4139]



[4140] 40 mg (0.11 mmol) of N-{(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropyl}-N-methyl-L-valine (Intermediate 221) were dissolved in 5 ml of DMF and admixed with 80 mg (0.11 mmol) of N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Intermediate 220), 50 mg (0.13 mmol) of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) and 57 µl (2.5 mmol) of N,N-diisopropylethylamine. The mixture was stirred at RT for 1 h and then concentrated. The residue was taken up in ethyl acetate and washed first with 5% aqueous citric acid solution and then with water. The organic phase was concentrated and the residue was purified by means of preparative HPLC. The corresponding fractions were combined and the solvent was removed under reduced pressure. After lyophilization from dioxane, 60 mg (50% of theory) of the protected intermediate were obtained.

[4141] HPLC (Method 12): R_t=2.2 min;

[4142] LC-MS (Method 1): R_t=1.17 min; MS (ESIpos): m/z=1073 $(M+H)^+$.

[4143] 60 mg (0.05 mmol) of this intermediate were taken up in 10 ml of dichloromethane, 2 ml of trifluoroacetic acid were added, and the reaction mixture was stirred at RT for 1.5 h. Subsequently, the reaction mixture was concentrated under reduced pressure and the remaining residue was purified by means of preparative HPLC. The corresponding fractions were combined, the solvent was removed under reduced pressure and the residue was lyophilized from dioxane/water. In this way, 25 mg (42% of theory) of the title compound were obtained as a foam.

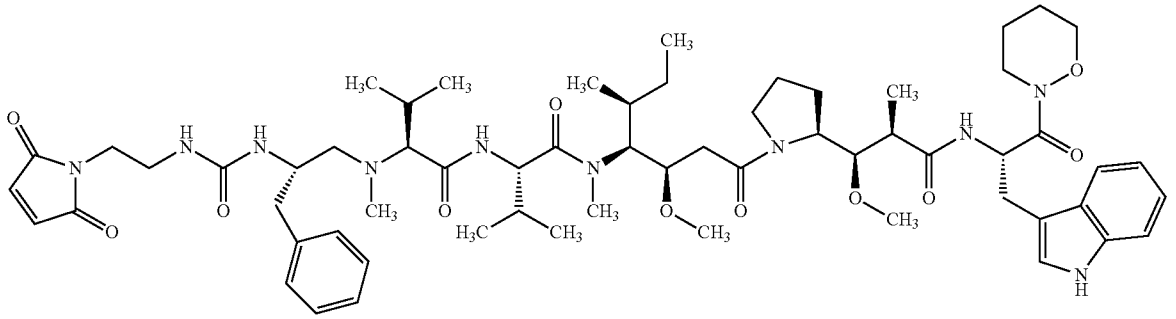
[4144] HPLC (Method 12): R_t=1.9 min;

[4145] LC-MS (Method 1): R_t=0.95 min; MS (ESIpos): m/z=974 $(M+H)^+$.

Intermediate 223

N-[(2S)-2-({[2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethyl]carbamoyl}amino)-3-phenylpropyl]-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[4146]



[4147] The preparation was effected in analogy to Intermediate 134, proceeding from 5 mg (4.6 mmol) of Intermediate 222. 3.4 mg (65% of theory) of the title compound were obtained.

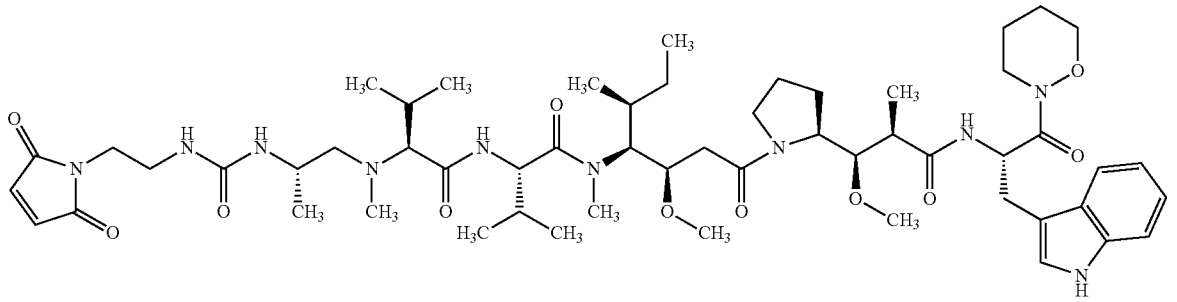
[4148] HPLC (Method 12): R_t=2.0 min;

[4149] LC-MS (Method 1): R_t=0.99 min; MS (ESIpos): m/z=1140 $(M+H)^+$.

Intermediate 224

N-[(2S)-2-({[2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethyl]carbamoyl}amino)propyl]-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[4150]



[4151] The preparation was effected in analogy to the synthesis of Intermediate 223.

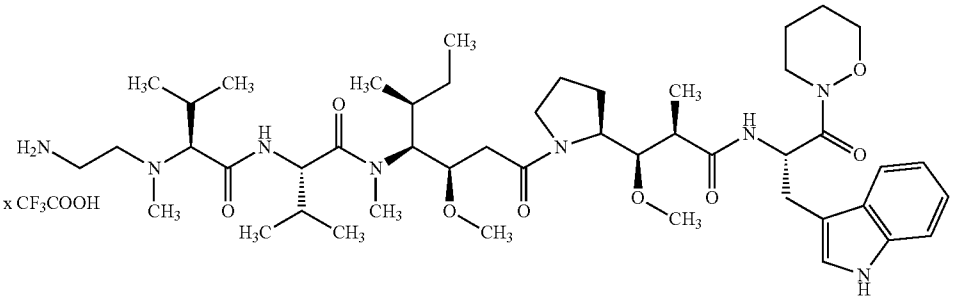
[4152] HPLC (Method 12): R_t=1.9 min;

[4153] LC-MS (Method 1): R_t=0.92 min; MS (ESIpos): m/z=1064 $(M+H)^+$.

Intermediate 225

N-(2-aminoethyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide trifluoroacetate

[4154]



[4155] 100 mg (0.76 mmol) of commercially available N-methyl-L-valine and 182 mg (1.14 mmol) of commercially available tert-butyl 2-oxoethyl carbamate were combined in 20 ml of methanol and admixed with 340 mg (3.66 mmol) of borane-pyridine complex and 65 μl of acetic acid. The reaction mixture was stirred at RT overnight. This was followed by concentration under reduced pressure, and the residue was purified by flash chromatography on silica gel with dichloromethane/methanol/17% aqueous ammonia solution (15/4/0.5) as the eluent. After concentration of the corresponding fractions and lyophilization from 1:1 dioxane/water, 190 mg in 39% purity (35% of theory) of the intermediate were obtained, which were converted further without further purification.

[4156] 50 mg (0.07 mmol) of this intermediate were dissolved in 10 ml of DMF and admixed with 52 mg (0.07 mmol) of N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Intermediate 220), 32 mg (0.09 mmol) of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophos-

phate (HATU) and 37 μl (0.2 mmol) of N,N-diisopropylethylamine. The mixture was stirred at RT overnight and then concentrated. The residue was taken up in ethyl acetate and extracted by shaking first with 5% aqueous citric acid solution and then with water. The organic phase was concentrated and the residue was purified by means of preparative HPLC. The corresponding fractions were combined and the solvent was removed under reduced pressure. After lyophilization from dioxane, 53 mg (76% of theory) of the protected intermediate were obtained.

[4157] HPLC (Method 12): R_t=2.0 min;

[4158] LC-MS (Method 1): R_t=1.02 min; MS (ESIpos): m/z=984 $(M+H)^+$.

[4159] 53 mg (0.05 mmol) of this intermediate were taken up in 10 ml of dichloromethane, 2 ml of trifluoroacetic acid were added, and the reaction mixture was stirred at RT for 30 min. Subsequently, the reaction mixture was concentrated under reduced pressure and the remaining residue was purified by means of preparative HPLC. The corresponding fractions were combined, the solvent was removed under reduced pressure and the residue was lyophilized from dioxane/water. In this way, 21 mg (40% of theory) of the title compound were obtained in 65% purity.

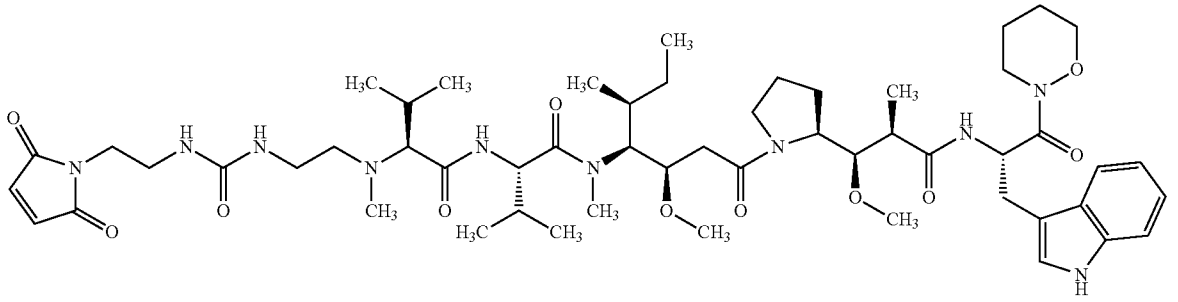
[4160] HPLC (Method 12): R_t=1.7 min;

[4161] LC-MS (Method 1): R_t=0.87 min; MS (ESIpos): m/z=884 $(M+H)^+$.

Intermediate 226

N-[2-({[2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethyl]carbamoyl}amino)ethyl]-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[4162]



[4163] The preparation was effected proceeding from Intermediate 225, in analogy to the synthesis of Intermediate 134. 11.6 mg (59% of theory) of the title compound were obtained.

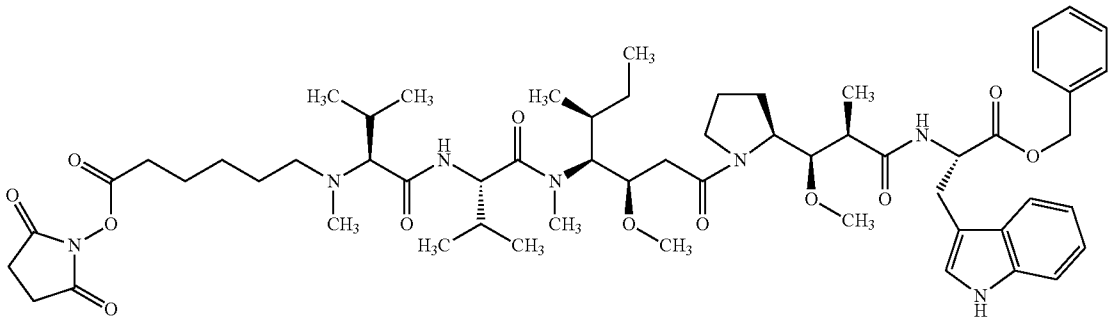
[4164] HPLC (Method 12): R_t=1.9 min;

[4165] LC-MS (Method 1): R_t=0.90 min; MS (ESIpos): m/z=1050 $(M+H)^+$.

Intermediate 227

N-{6-[(2,5-dioxopyrrolidin-1-yl)oxy]-6-oxohexyl}-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(benzyloxy)-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[4166]



[4167] This compound was prepared analogously to Intermediate 218, by conversion to the active ester.

[4168] Yield: 18 mg (51% of theory)

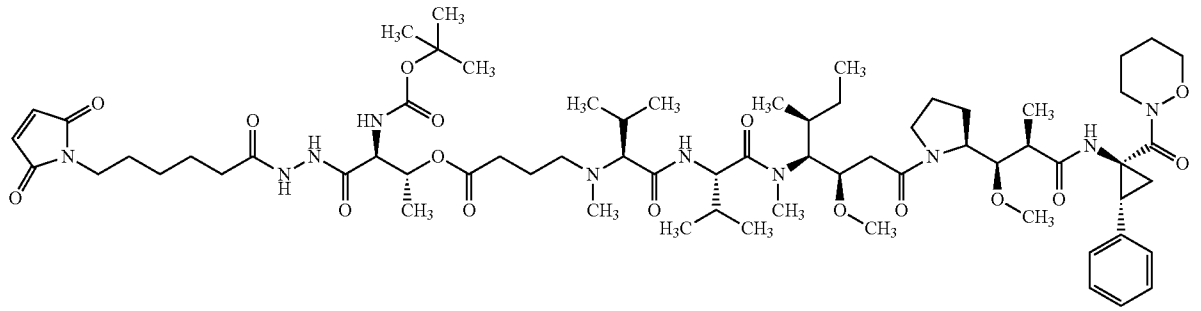
[4169] HPLC (Method 5): R_t=2.1 min;

[4170] LC-MS (Method 1): R_t=0.98 min; MS (ESIpos): m/z=1073 $(M+H)^+$.

Intermediate 228

(2R,3S)-3-[(tert-butoxycarbonyl)amino]-4-{2-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutan-2-yl(3R,4S,7S,10S)-4-[(2S)-butan-2-yl]-7,10-diisopropyl-3-(2-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-2-oxoethyl)-5,11-dimethyl-6,9-dioxo-2-oxa-5,8,11-triazapentadecan-15-oate

[4171]



[4172] The title compound was prepared by coupling the Boc-protected intermediate obtained in the synthesis of Intermediate 154 with commercially available 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanehydrazide.

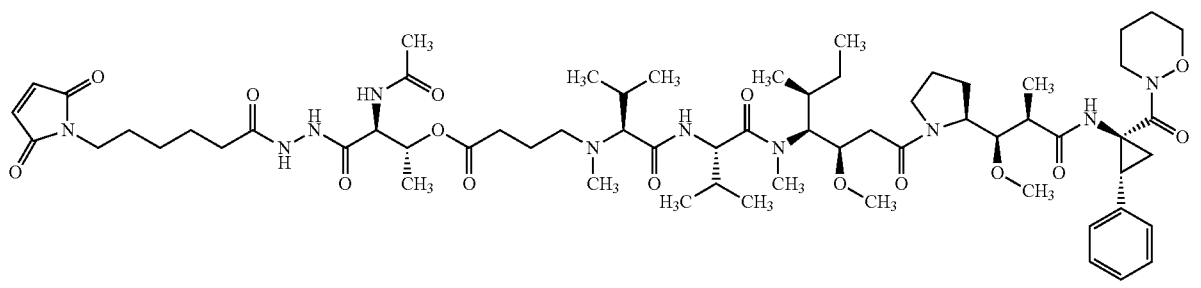
[4173] HPLC (Method 12): R_t=2.1 min;

[4174] LC-MS (Method 1): R_t=0.97 min; MS (ESIpos): m/z=1308 $(M+H)^+$.

Intermediate 229

(2R,3S)-3-acetamido-4-{2-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutan-2-yl (3R,4S,7S,10S)-4-[(2S)-butan-2-yl]-7,10-diisopropyl-3-(2-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-2-oxoethyl)-5,11-dimethyl-6,9-dioxo-2-oxa-5,8,11-triazapentadecan-15-oate

[4175]



[4176] The title compound was prepared from 7.5 mg (2.5 μmol) of Intermediate 154 by acetylation with 2.3 μl of acetic anhydride in 1 ml of DMF in the presence of 0.4 μl of N,N-diisopropylethylamine.

[4177] Yield: 1.4 mg (40% of theory)

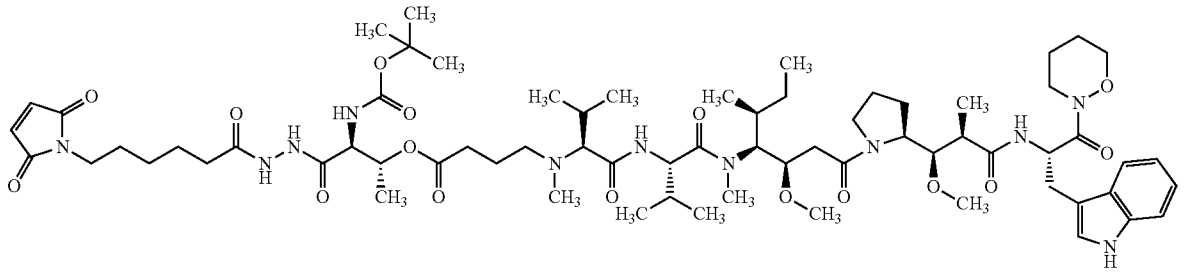
[4178] HPLC (Method 12): R_t=1.9 min;

[4179] LC-MS (Method 1): R_t=0.86 min; MS (ESIpos): m/z=1250 $(M+H)^+$.

Intermediate 230

(2R,3S)-3-[(tert-butoxycarbonyl)amino]-4-{2-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutan-2-yl (3R,4S,7S,10S)-4-[(2S)-butan-2-yl]-3-(2-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-2-oxoethyl)-7,10-diisopropyl-5,11-dimethyl-6,9-dioxo-2-oxa-5,8,11-triazapentadecan-15-oate

[4180]



[4181] This compound was prepared in analogy to Intermediate 228, proceeding from Intermediate 193. 16 mg (30% of theory over 3 stages) of the title compound were obtained.

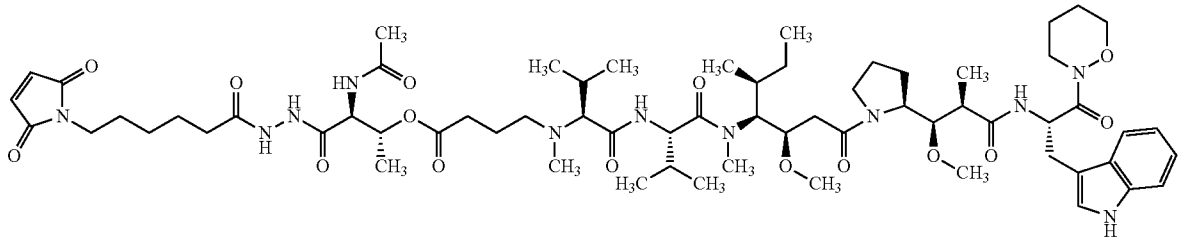
[4182] HPLC (Method 12): R_t=2.0 min;

[4183] LC-MS (Method 1): R_t=1.02 min; MS (ESIpos): m/z=1335 $(M+H)^+$.

Intermediate 231

(2R,3S)-3-acetamido-4-{2-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]hydrazino}-4-oxobutan-2-yl (3R,4S,7S,10S)-4-[(2S)-butan-2-yl]-3-(2-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-2-oxoethyl)-7,10-diisopropyl-5,11-dimethyl-6,9-dioxo-2-oxa-5,8,11-triazapentadecan-15-oate

[4184]



[4185] This compound was prepared from 8 mg (6 μmol) of Intermediate 230, first by deprotection with trifluoroacetic acid and subsequent acetylation with acetic anhydride in DMF in the presence of N,N-diisopropylethylamine. 2 mg (37% of theory over 2 stages) of the title compound were obtained.

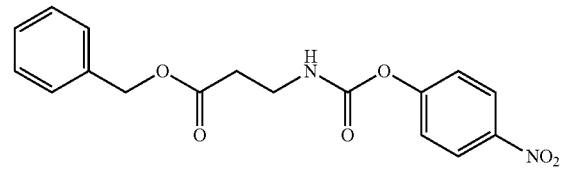
[4186] HPLC (Method 12): R_t=1.9 min;

[4187] LC-MS (Method 1): R_t=0.88 min; MS (ESIpos): m/z=1277 $(M+H)^+$.

Intermediate 232

benzyl N-[(4-nitrophenoxy)carbonyl]-beta-alaninate

[4188]



[4189] 200 mg (0.57 mmol) of commercially available 4-methylbenzenesulphonic acid-benzyl beta-alaninate and 229 mg (1.14 mmol) of 4-nitrophenyl chlorocarbonate were taken up in 15 ml of tetrahydrofuran and the reaction mixture was then heated to reflux for 30 min. Subsequently, the reaction mixture was concentrated under reduced pressure and the residue was purified by means of preparative HPLC. After concentration of the corresponding fractions and drying of the residue under high vacuum, 86 mg (44% of theory) of the title compound were obtained.

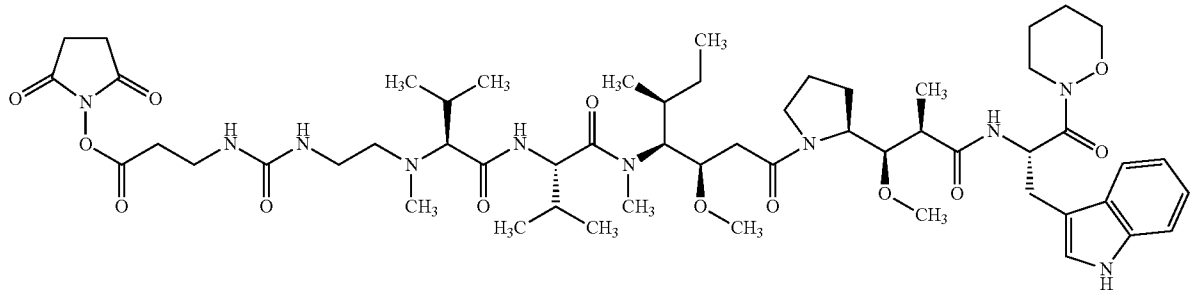
[4190] HPLC (Method 12): R_t=1.8 min;

[4191] LC-MS (Method 1): R_t=1.07 min; MS (ESIpos): m/z=345 $(M+H)^+$.

Intermediate 233

N-{2-[({3-[(2,5-dioxopyrrolidin-1-yl)oxy]-3-oxopropyl}carbamoyl)amino]ethyl}-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[4192]



[4193] 13 mg (10 μmol) of Intermediate 225 and 6.7 mg (20 μmol) of Intermediate 232 were dissolved in 3 ml of DMF, and then 7 μl of N,N-diisopropylethylamine were added. The mixture was stirred at RT overnight and then concentrated under high vacuum. The remaining residue was purified by means of preparative HPLC. After concentration of the corresponding fractions and drying of the residue under high vacuum, 5.4 mg (38% of theory) of the protected intermediate were obtained.

[4194] HPLC (Method 5): R_t=2.1 min;

[4195] LC-MS (Method 1): R_t=0.6 in; MS (ESIpos): m/z=1089 $(M+H)^+$.

[4196] 5.4 mg (5 μmol) of this intermediate were dissolved in 5 ml of methanol and, after addition of 2 mg of 10% palladium on activated carbon, hydrogenated under standard hydrogen pressure at RT for 20 min. The catalyst was then filtered off and the solvent was removed under reduced pressure. After the residue had been dried under high vacuum, 5 mg (quant.) of the acid intermediate were obtained.

[4197] HPLC (Method 12): R_t=1.8 min;

[4198] LC-MS (Method 1): R_t=0.84 min; MS (ESIpos): m/z=999 $(M+H)^+$.

[4199] 5 mg (10 μmol) of this intermediate were dissolved in 1 ml of DMF and admixed with 5.8 mg (50 mmol) of 1-hydroxypyrrolidine-2,5-dione and then with 2.6 μl of N,N-diisopropylethylamine and 3.8 mg (10 μmol) of HATU. After stirring at RT for 20 h, the reaction mixture was concentrated under reduced pressure. The remaining residue was purified by means of preparative HPLC. After lyophilization from 1:1 dioxane/water, 1.1 mg (20% of theory) of the title compound were obtained.

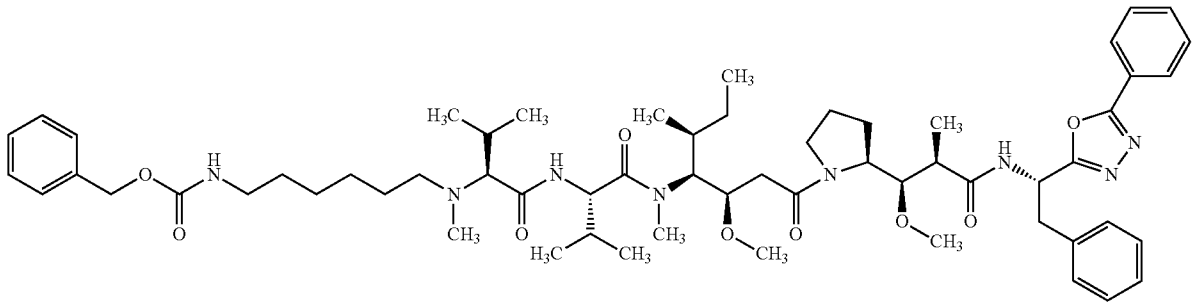
[4200] HPLC (Method 12): R_t=1.9 min;

[4201] LC-MS (Method 1): R_t=0.87 min; MS (ESIpos): m/z=1096 $(M+H)^+$.

Intermediate 234

N-(6-{[(benzyloxy)carbonyl]amino}hexyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(1S)-2-phenyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[4202]



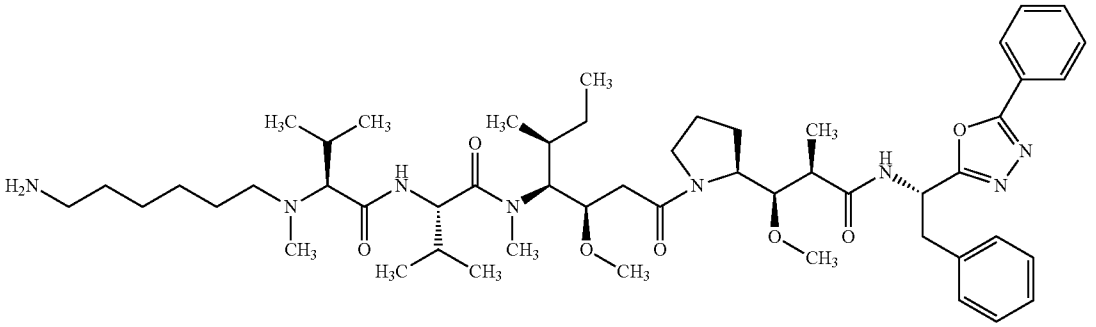
[4203] 25 mg (30 μmol) of N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(1S)-2-phenyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Intermediate 55) and 45 mg (180 μmol) of benzyl 6-oxohexyl carbamate were taken up in 3 ml of methanol and acidified with acetic acid. At room temperature, 15 μl (144 μmol; 9.4M) of borane-pyridine complex were subsequently added. The mixture was subsequently stirred at RT for 24 h, and acetic acid and 15 μl (144 μmol; 9.4M) of borane-pyridine complex were added again after 8 h. The reaction mixture was subsequently adjusted to pH 2 with TFA and purified by means of preparative HPLC. The product fractions were combined and concentrated, and the residue was dried under high vacuum. This gave 15 mg (46% of theory) of the title compound as a foam.

[4204] LC-MS (Method 1): R_t=1.03 min; m/z=1066 $(M+H)^+$.

Intermediate 235

N-(6-aminohexyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(1S)-2-phenyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[4205]



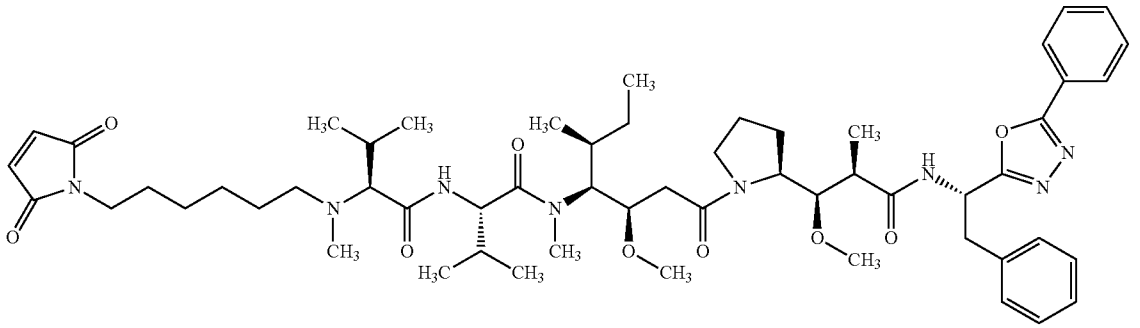
[4206] 15 mg (14 μmol) of N-(6-{[(benzyloxy)carbonyl]amino}hexyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(1S)-2-phenyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Intermediate 234) were taken up in 3 ml of methanol, and 1.8 mg of palladium on charcoal (5%) were added. The reaction mixture was subsequently hydrogenated under standard hydrogen pressure at RT for 2 h. The catalyst was then filtered off and the solvent was removed under reduced pressure. The residue was lyophilized from 1:1 acetonitrile/water. 11 mg (86% of theory) of the title compound were obtained as a foam.

[4207] LC-MS (Method 1): R_t=0.81 min; m/z=932 $(M+H)^+$.

Intermediate 236

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexyl]-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(1S)-2-phenyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[4208]



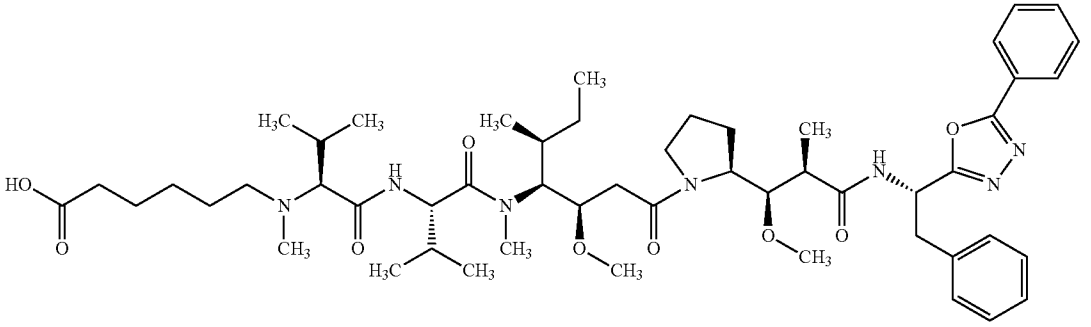
[4209] 11 mg (12 μmol) of N-(6-aminohexyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(1S)-2-phenyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Intermediate 235) were taken up in 500 μl of 1:1 dioxane/water and admixed with 253 μl of 1M aqueous sodium hydrogencarbonate solution and then with 2.8 mg (18 μmol) of methyl 2,5-dioxo-2,5-dihydro-1H-pyrrole-1-carboxylate. The reaction mixture was stirred at RT for 30 min and then acidified with trifluoroacetic acid. The reaction mixture was purified by means of preparative HPLC. After lyophilization, 0.8 mg (7% of theory) of the title compound was obtained.

[4210] LC-MS (Method 1): R_t=1.01 min; m/z=1012 $(M+H)^+$.

Intermediate 237

N-(5-carboxypentyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(1S)-2-phenyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[4211]



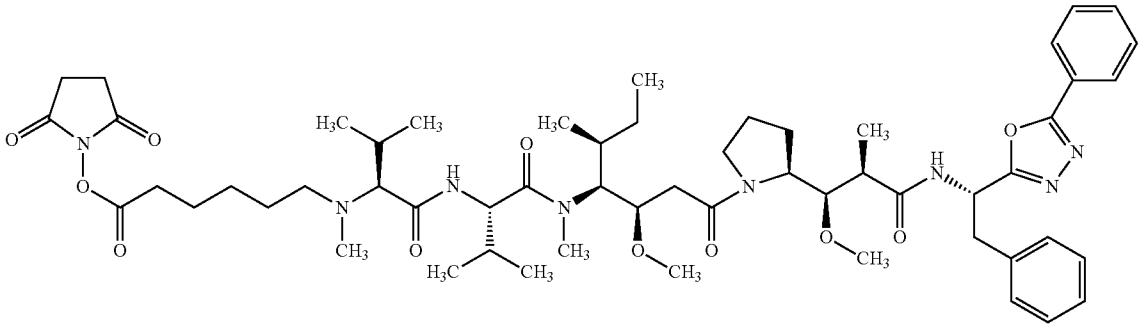
[4212] 25 mg (30 μmol) of N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(1S)-2-phenyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Intermediate 55) and 23 mg (180 μmol) of 6-oxohexanoic acid were taken up in 3 ml of methanol and acidified with acetic acid. At room temperature, 15 μl (144 μmol; 9.4M) of borane-pyridine complex were subsequently added. The reaction mixture was subsequently stirred at RT for 20 h, and acetic acid and 15 μl (144 μmol; 9.4M) of borane-pyridine complex were added again after 8 h. The reaction mixture was subsequently adjusted to pH 2 with trifluoroacetic acid and purified by means of preparative HPLC. The product fractions were combined and concentrated, and the residue was lyophilized. 21 mg (74% of theory) of the title compound were thus obtained as a foam.

[4213] LC-MS (Method 1): R_t=0.91 min; m/z=947 $(M+H)^+$.

Intermediate 238

N-{6-[(2,5-dioxopyrrolidin-1-yl)oxy]-6-oxohexyl}-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(1S)-2-phenyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[4214]



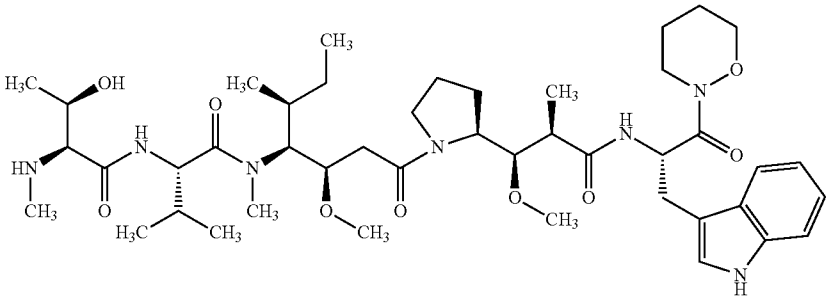
[4215] 21 mg (22 μmol) of Intermediate 237 were dissolved in 1 ml of DMF and admixed with 38 mg (333 μmol) of 1-hydroxypyrrolidine-2,5-dione and then with 2.4 mg (10 μmol) of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) and 19 μl of N,N-diisopropylethylamine. After stirring at RT for 2 h, the reaction mixture was purified by means of preparative HPLC. After lyophilization from dioxane, 22 mg (96% of theory) of the title compound were obtained.

[4216] LC-MS (Method 1): R_t=0.95 min; m/z=1044 $(M+H)^+$.

Intermediate 239

N-methyl-L-threonyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide trifluoroacetate

[4217]



[4218] First, N-[(benzyloxy)carbonyl]-N-methyl-L-threonine was released from 237 mg (0.887 mmol) of its dicyclohexylamine salt by taking it up in ethyl acetate and extractive shaking with 5% aqueous sulphuric acid. The organic phase was dried over magnesium sulphate, filtered and concentrated. 14.7 mg (0.055 mmol) of N-[(benzyloxy)carbonyl]-N-methyl-L-threonine were taken up in 3 ml of DMF and admixed successively with 40 mg (0.055 mmol) of Intermediate 220, 12.7 mg (0.066 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 10 mg (0.066 mmol) of 1-hydroxy-1H-benzotriazole hydrate. The mixture was subsequently stirred at RT for 2 h. The solvent was then removed under reduced pressure and the residue purified by preparative HPLC. 29 mg (54% of theory) of the Z-protected intermediate were thus obtained.

[4219] LC-MS (Method 1): R_t=1.15 min; MS (ESIpos): m/z=976 $(M+H)^+$.

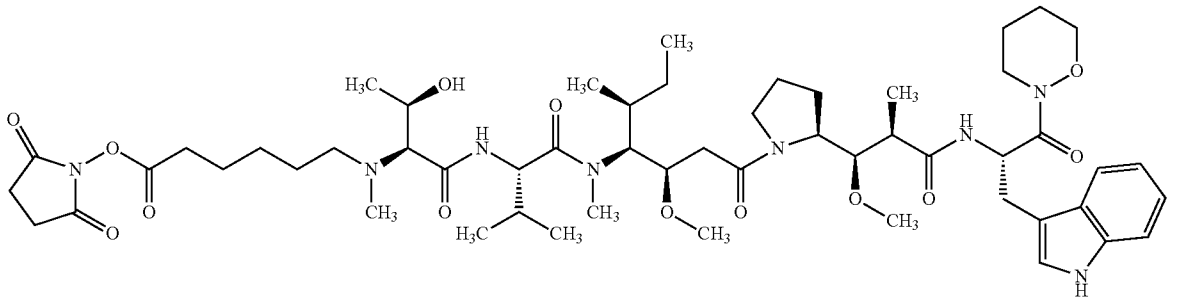
[4220] 29 mg (0.003 mmol) of this intermediate were dissolved in 5 ml of methanol and hydrogenated over 5 mg of 5% palladium/charcoal at RT and standard pressure for 1 h. The catalyst was subsequently filtered off and the solvent was evaporated off. The remaining residue was purified by preparative HPLC. 17 mg (54% of theory) of the title compound were obtained.

[4221] LC-MS (Method 1): R_t=0.77 min; MS (ESIpos): m/z=842 $(M+H)^+$.

Intermediate 240

N-{6-[(2,5-dioxopyrrolidin-1-yl)oxy]-6-oxohexyl}-N-methyl-L-threonyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[4222]



[4223] This compound was prepared in analogy to Intermediate 210 from 15.6 mg (0.016 mmol) of Intermediate 239. 10.8 mg (67% of theory over 2 stages) of the title compound were obtained.

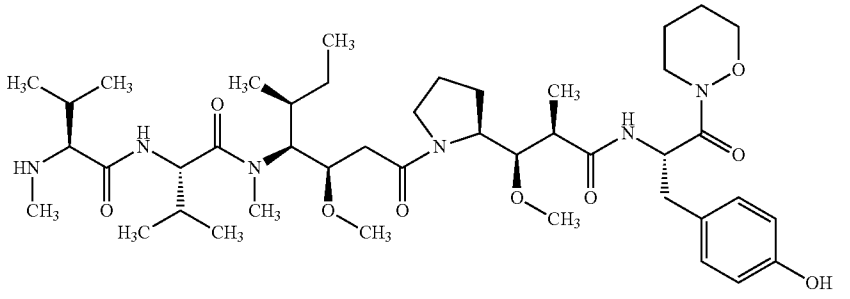
[4224] HPLC (Method 5): R_t=1.7 min;

[4225] LC-MS (Method 1): R_t=0.85 min; MS (ESIpos): m/z=1053 $(M+H)^+$.

Intermediate 241

N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(4-hydroxyphenyl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide trifluoroacetate

[4226]



[4227] First, in analogy to Intermediate 5, trifluoroacetic acid-(2S)-2-amino-3-(4-hydroxyphenyl)-1-(1,2-oxazinan-2-yl)propan-1-one (1:1) was prepared. This reagent was then used, in analogy to the synthesis described in Intermediate 75, by coupling with N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-2-carboxy-1-methoxypropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Intermediate 26) in the presence of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and subsequent detachment of the Boc protecting group by means of trifluoroacetic acid, to prepare the title compound.

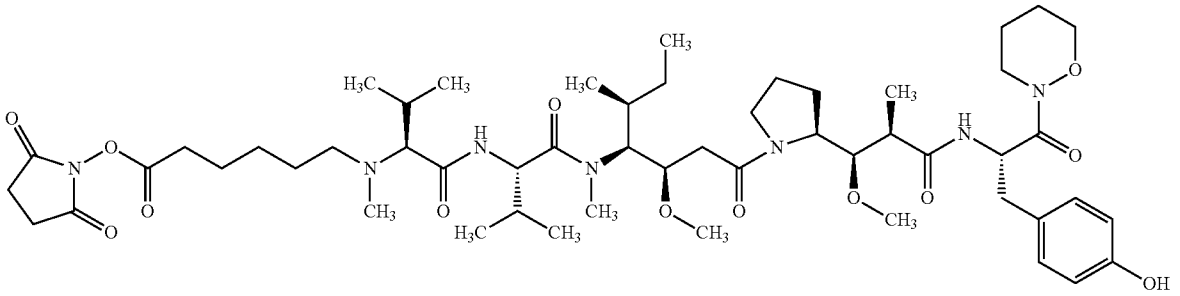
[4228] HPLC (Method 12): R_t=1.7 min;

[4229] LC-MS (Method 1): R_t=0.85 min; MS (ESIpos): m/z=817 $(M+H)^+$.

Intermediate 242

N-{6-[(2,5-dioxopyrrolidin-1-yl)oxy]-6-oxohexyl}-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(4-hydroxyphenyl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[4230]



[4231] 50 mg (0.05 mmol) of Intermediate 241 were reacted, in analogy to Intermediate 210, with 6-oxohexanoic acid in the presence of borane-pyridine complex. Subsequently, 22.5 mg (0.02 mmol) of the resulting acid were converted to the activated ester. 13.5 mg (36% of theory over 2 stages) of the title compound were obtained.

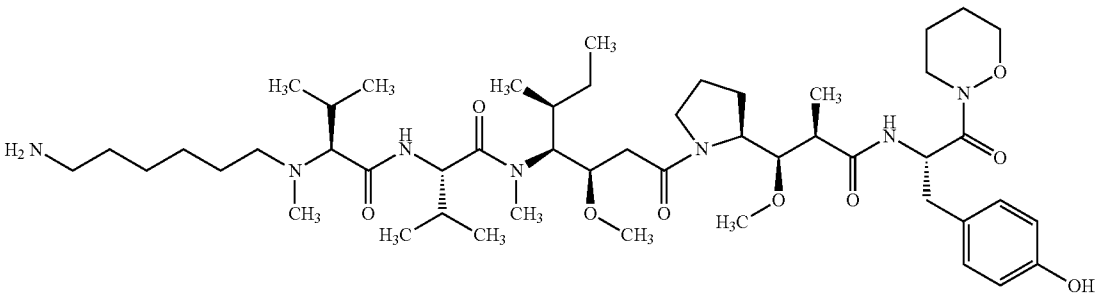
[4232] HPLC (Method 12): R_t=1.8 min;

[4233] LC-MS (Method 1): R_t=0.86 min; MS (ESIpos): m/z=1028 $(M+H)^+$.

Intermediate 243

N-(6-aminohexyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(4-hydroxyphenyl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[4234]



[4235] The preparation was effected in analogy to Intermediate 78, by reductive alkylation of Intermediate 241 with benzyl 6-oxohexyl carbamate and borane-pyridine complex and subsequent hydrogenation in methanol as the solvent.

[4236] Yield: 17.5 mg (34% of theory over 2 stages)

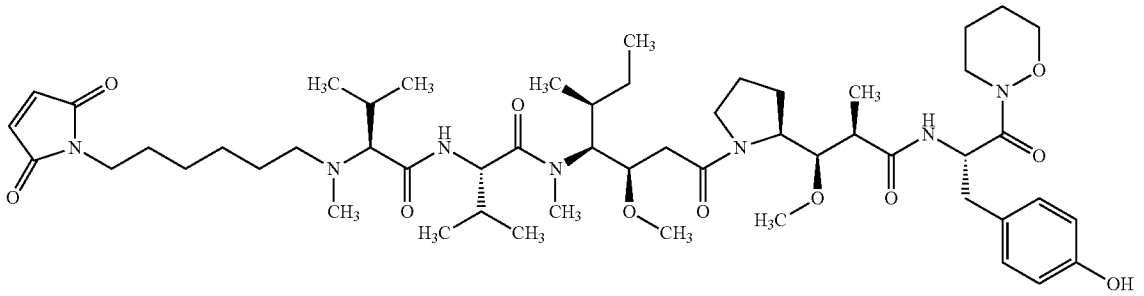
[4237] HPLC (Method 12): R_t=1.7 min;

[4238] LC-MS (Method 1): R_t=0.63 min; MS (ESIpos): m/z=916 $(M+H)^+$.

Intermediate 244

N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexyl]-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(4-hydroxyphenyl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[4239]



[4240] The preparation was effected in analogy to Intermediate 166, proceeding from Intermediate 243.

[4241] Yield: 1.3 mg (12% of theory)

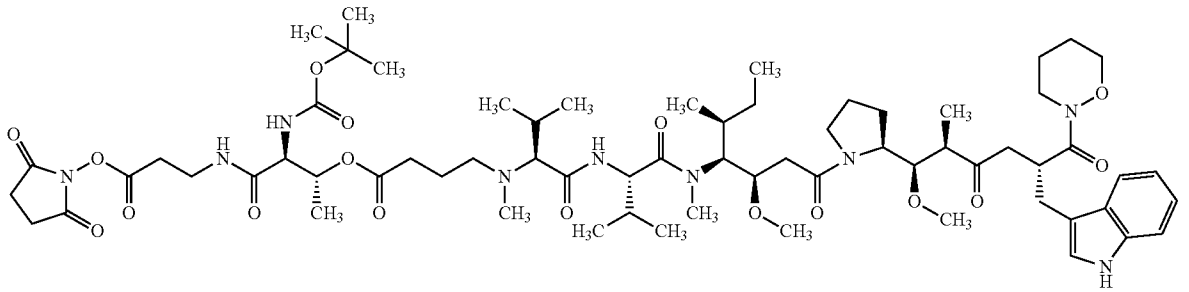
[4242] HPLC (Method 12): R_t=1.9 min;

[4243] LC-MS (Method 1): R_t=0.89 min; MS (ESIpos): m/z=996 $(M+H)^+$.

Intermediate 245

2,5-dioxopyrrolidin-1-yl O-[(3R,4S,7S,10S)-4-[(2S)-butan-2-yl]-3-(2-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-2-oxoethyl)-7,10-diisopropyl-5,11-dimethyl-6,9,15-trioxo-2-oxa-5,8,11-triazapentadecan-15-yl]-N-(tert-butoxycarbonyl)-L-threonyl-beta-alaninate

[4244]



[4245] First, Intermediate 193, as described for Intermediate 154, was reacted with benzyl N-(tert-butoxycarbonyl)-L-threoninate and then the benzyl ester was removed by hydrogenolysis. 30 mg (0.027 mmol) of the N-[4-({(1S,2R)-1-[(tert-butoxycarbonyl)amino]-1-carboxypropan-2-yl}oxy)-4-oxobutyl]-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide thus obtained were then coupled with 4-methylbenzenesulphonic acid-benzyl beta-alaninate in the presence of HATU and the benzyl ester was removed again by hydrogenolysis (yield: 24 mg (71% of theory over 2 stages)). Finally, 10 mg (0.008 mmol) of the resulting acid were converted to the activated ester. After HPLC purification, 2.7 mg (23% of theory) of the title compound were obtained.

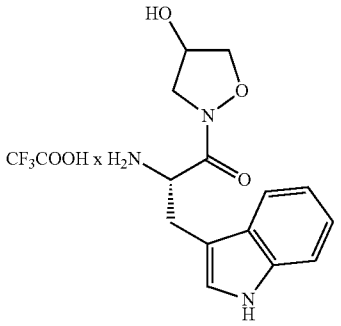
[4246] HPLC (Method 5): R_t=1.9 min;

[4247] LC-MS (Method 1): R_t=1.01 min; MS (ESIpos): m/z=1295 $(M+H)^+$

Intermediate 246a

(2S)-2-amino-1-(4-hydroxy-1,2-oxazolidin-2-yl)-3-(1H-indol-3-yl)propan-1-one trifluoroacetate (Diastereomer 1)

[4248]



[4249] 1.6 g (3.982 mmol) of 2,5-dioxopyrrolidin-1-yl N-(tert-butoxycarbonyl)-L-tryptophanate were dissolved in 15 ml of DMF and admixed with 500 mg (3.982 mmol) of 1,2-oxazolidin-4-ol and 100 μl of N,N-diisopropylethylamine. The reaction mixture was stirred at RT overnight. Then another 100 μl of N,N-diisopropylethylamine were added, and the mixture was first treated in an ultrasound bath for 5 h, then stirred at RT overnight, and subsequently concentrated under reduced pressure. The remaining residue was taken up in ethyl acetate and extracted first twice with 5% aqueous citric acid solution, then with saturated aqueous sodium hydrogencarbonate solution and finally with water. The organic phase was concentrated and the residue was separated into the diastereomers by flash chromatography on silica gel with 95:5 dichloromethane/methanol as the eluent. The corresponding fractions of both diastereomers were combined and the solvent was removed under reduced pressure. After the residues had been dried under high vacuum, 272 mg (18% of theory) of Diastereomer 1 (R_f=0.18 (95:5 dichloromethane/methanol) and 236 mg (16% of theory) of Diastereomer 2 (R_f=0.13 (95:5 dichloromethane/methanol), and also 333 mg (22% of theory) of a mixed fraction of the Boc-protected intermediates were obtained.

[4250] Under standard conditions, 5 ml of trifluoroacetic acid in 20 ml of dichloromethane were used to detach the Boc protecting group from 272 mg (725 μmol) of Diastereomer 1 of this intermediate and, after lyophilization from dioxane/water, 290 mg (quant) of the title compound were obtained in 75% purity and used in the next stage without further purification.

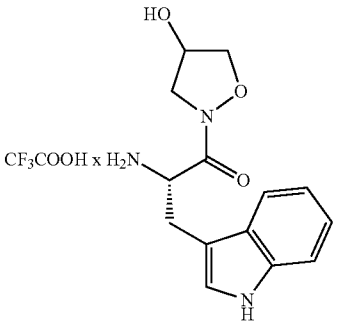
[4251] HPLC (Method 12): R_t=1.1 min;

[4252] LC-MS (Method 13): R_t=1.80 min; MS (ESIpos): m/z=276 $(M+H)^+$

Intermediate 246b

(2S)-2-amino-1-(4-hydroxy-1,2-oxazolidin-2-yl)-3-(1H-indol-3-yl)propan-1-one trifluoroacetate (Diastereomer 2)

[4253]



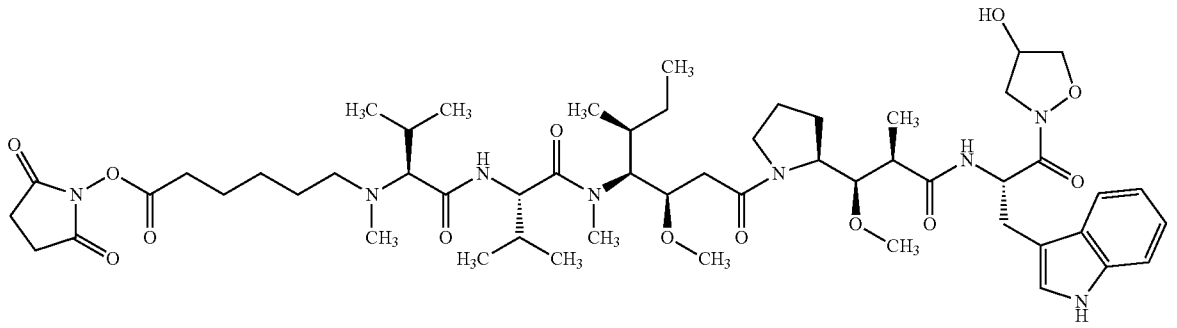
[4254] Under standard conditions, 5 ml of trifluoroacetic acid in 20 ml of dichloromethane were used to detach the Boc protecting group from 236 mg (630 μmol) of Diastereomer 2 of the intermediate described in 246a and, after concentration, stirring with diethyl ether and drying of the residue under high vacuum, 214 mg (76%) of the title compound were obtained.

[4255] LC-MS (Method 13): R_t=1.84 min; MS (ESIpos): m/z=276 $(M+H)^+$

Intermediate 247a

N-{6-[(2,5-dioxopyrrolidin-1-yl)oxy]-6-oxohexyl}-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(4-hydroxy-1,2-oxazolidin-2-yl)-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Diastereomer 1)

[4256]



[4257] To synthesize this compound, the coupling of Intermediates 26 and 246a with subsequent detachment of the Boc protecting group was first performed as described for Intermediate 74. Subsequently, the alkylation with 6-oxohexanoic acid in the presence of borane-pyridine complex and subsequent conversion of the acid to the active ester were performed as described for Intermediate 210. The title compound was purified by preparative HPLC.

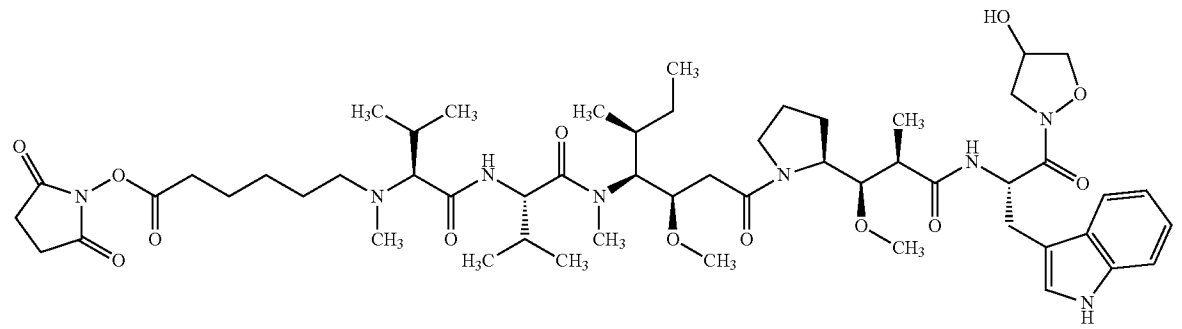
[4258] HPLC (Method 12): R_t=1.8 min;

[4259] LC-MS (Method 1): R_t=0.86 min; MS (ESIpos): m/z=1053 $(M+H)^+$

Intermediate 247b

N-{6-[(2,5-dioxopyrrolidin-1-yl)oxy]-6-oxohexyl}-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(4-hydroxy-1,2-oxazolidin-2-yl)-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Diastereomer 2)

[4260]



[4261] To synthesize this compound, the coupling of Intermediates 26 and 246b with subsequent detachment of the Boc protecting group was first performed as described for Intermediate 74. Subsequently, the alkylation with 6-oxohexanoic acid in the presence of borane-pyridine complex and subsequent conversion of the acid to the active ester were performed as described for Intermediate 210. The title compound was purified by preparative HPLC.

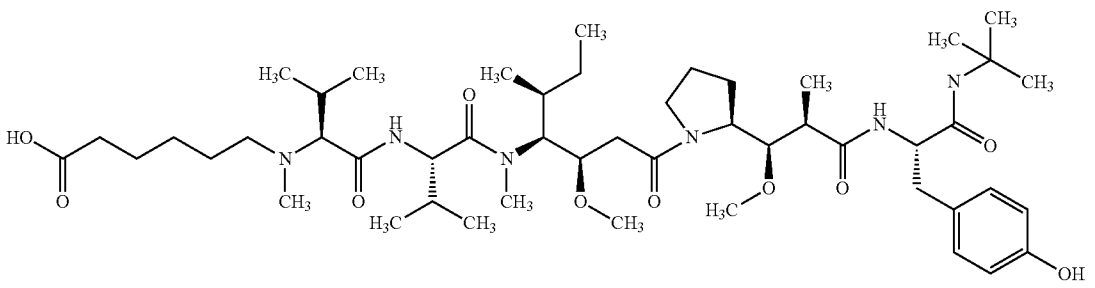
[4262] HPLC (Method 12): R_t=1.8 min;

[4263] LC-MS (Method 1): R_t=0.86 min; MS (ESIpos): m/z=1053 $(M+H)^+$

Intermediate 248

N-(5-carboxypentyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-tert-butoxy-3-(4-hydroxyphenyl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[4264]



[4265] First, in analogy to the synthesis described in Intermediate 86, by coupling N-(tert-butoxycarbonyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-2-carboxy-1-methoxypropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide (Intermediate 26) and tert-butyl L-tyrosinate in the presence of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and subsequent detachment of the Boc protecting group by means of trifluoroacetic acid to obtain the tert-butyl ester (stirring with trifluoroacetic acid in dichloromethane for 40 min), the amine compound tert-butyl N-[(2R,3R)-3-methoxy-3-{(2S)-1-[(3R,4S,5S)-3-methoxy-5-methyl-4-(methyl{(2S)-3-methyl-2-[(N-methyl-L-valyl)amino]butyl}amino)heptanoyl]pyrrolidin-2-yl}-2-methylpropanoyl]-tyrosinate was prepared as the trifluoroacetate. 38 mg (0.04 mmol) of this compound were then used, in analogy to the preparation of Intermediate 210, by reaction with 6-oxohexanoic acid in the presence of borane-pyridine complex, to obtain 31 mg (99% of theory) of the title compound.

[4266] HPLC (Method 12): R_t=1.8 min;

[4267] LC-MS (Method 1): R_t=0.88 min; MS (ESIpos): m/z=918 $(M+H)^+$.

B: PREPARATION OF ANTIBODY-DRUG CONJUGATES (ADCs)

[4268] The intermediates described above were linked, for example, to the anti-mesothelin antibody MF-Ta, with the linkage having taken place in accordance with the methods set out below, via cysteine or lysine side chains, alternatively, of the antibody protein. The anti-mesothelin antibody MF-Ta was prepared in analogy to the methods described in WO 2009/068204-A1. The antibody MF-Ta was expressed in eukaryotic CHO cells (stable cell line) and purified via protein A and gel filtration before it was subjected to the conjugation in D-PBS buffer.

B-1. General Procedure 1 (Coupling Via Cysteine):

[4269] Added to a solution of the corresponding antibody in PBS buffer in the concentration range between 1 mg/ml and 15 mg/ml were 3 equivalents of tris(2-carboxyethyl) phosphine hydrochloride (TCEP), in solution in PBS buffer, and the mixture was stirred at RT for 1 hour. Subsequently, depending on the desired loading, between 2 and 10 equivalents of the maleimide precursor compound or halide precursor compound for coupling (Intermediate 102, 103, 105-109, 111-114, 117-126, 128, 129, 132-146, 148-155, 157, 159-161, 166, 171, 175-177, 184, 189, 194-195, 199-201, 205, 209, 223-224, 226, 228-231, 236 and 244) were added as a solution in DMSO. The amount of DMSO here ought not to exceed 10% of the overall volume. The batch was stirred at RT for 60-120 minutes and then applied to PD 10 columns (Sephadex® G-25, GE Healthcare) equilibrated with PBS, and eluted with PBS buffer. Optionally a concentration procedure was carried out additionally by means of ultracentrifugation. If necessary, for more effective removal of low molecular mass constituents, the concentration by ultrafiltration was repeated after re-dilution with PBS buffer.

[4270] Normally, unless otherwise indicated, 5 mg of the corresponding antibody in PBS buffer were used for the reduction and the subsequent coupling. Following purification via the PD10 column, this gave, in each case, solutions of the corresponding ADC in 3.5 ml of PBS buffer. The particular protein concentration indicated was then determined for these solutions. Furthermore, the loading of the antibody (drug/mAb ratio) was determined in accordance with the methods described in B-4.

[4271] This process was used to prepare the immunoconjugates represented in Examples 1, 2, 5-19, 21-28, 30, 31, 33-37, 39-46, 48, 51-57, 59, 60, 71, 73-76, 78-80, 82-84, 86-87, 96, 98-103, 108 and 112.

[4272] In the structural formulae illustrated, the definition of AK_1 is as follows

AK_1=MF-Ta(partially reduced)-S§1

where

[4273] §1 denotes the link with the succinimide group,

[4274] MF-Ta (partially reduced) is the partially reduced MF-Ta antibody (heavy chain SEQ ID NO: 408 and light chain SEQ ID NO: 409)

and

[4275] S stands for the sulphur atom of a cysteine residue of the partially reduced antibody.

B-2. General Operating Procedure 2 (Coupling Via Lysine Side Chains):

[4276] Added to a solution of the corresponding antibody in PBS buffer in the concentration range between 1 mg/ml and 15 mg/ml were, depending on the desired loading, between 2 and 5 equivalents of the precursor compound for coupling (Intermediate 104, 110, 115, 116, 127, 130, 131, 147, 156, 158, 162, 169, 178, 185, 190, 202, 206, 210-216, 218, 219, 227, 233, 238, 240, 242, 245, 247a and 247b) as a solution in DMSO. After 30 minutes of stirring at RT, the same amount of precursor compound in DMSO was added again. Alternatively it was possible to add 4-10 equivalents of the precursor compound for coupling, in one go. The amount of DMSO here ought not to exceed 10% of the overall volume. After a further 30 minutes of stirring at RT, the batch was applied to PD 10 columns (Sephadex® G-25, GE Healthcare) equilibrated with PBS, and eluted with PBS buffer. Optionally a concentration procedure was carried out additionally by means of ultracentrifugation. If necessary, for more effective removal of low molecular mass constituents, the concentration by ultrafiltration was repeated after re-dilution with PBS buffer.

[4277] Normally, unless otherwise indicated, 5 mg of the corresponding antibody in PBS buffer were used for the coupling. Following purification via the PD10 column, this gave, in each case, solutions of the corresponding ADC in 3.5 ml of PBS buffer. The particular protein concentration indicated was then determined for these solutions and the loading of the antibody (drug/mAb ratio) was determined in accordance with the methods described in B-4.

[4278] This process was used to prepare the immunoconjugates represented in Examples 3, 4, 20, 29, 32, 38, 47, 49, 50, 58, 61, 72, 77, 81, 85, 88-95, 97, 104, 109-111 and 113-115.

[4279] In the structural formulae illustrated, the definition of AK_2 is as follows

AK_2=MF-Ta-NH§^{2}

where

[4280] §^{2} denotes the link with the carbonyl group,

MF-Ta is the non-reduced MF-Ta antibody (heavy chain SEQ ID NO: 408 and light chain SEQ ID NO: 409)

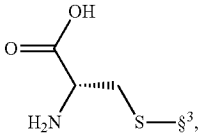
and

NH stands for the side chain amino group of a lysine residue of the antibody.

B-3a. General Process for Preparing Cysteine Adducts:

[4281] 10 μmol of the above-described maleimide precursor compounds were taken up in 3 ml of DMF and admixed with 2.1 mg (20 μmol) of L-cysteine. The reaction mixture was stirred at RT for 2 hours, then concentrated under reduced pressure and subsequently purified by preparative HPLC.

[4282] In the structural formulae illustrated, the definition of Cys is as follows



where

§^{3} denotes the link with the linker-toxophore unit.

B-3b. General Process for Preparing Lysine Adducts:

[4283] 10 μmol of the above-described active ester precursor compounds were taken up in 5 ml of DMF and admixed, in the presence of 30 μmol of N,N-diisopropylethylamine, with α-amino-protected L-lysine. The reaction mixture was stirred at RT for 2 hours, then concentrated under reduced pressure and subsequently purified by preparative HPLC. The protective group was then removed by known methods.

Further Purification and Characterization of the Conjugates of the Invention

[4284] After reaction had taken place, in certain cases the reaction mixture was concentrated, by ultrafiltration, for example, and then desalted and purified by means of chromatography, for example using a Sephadex® G-25. Elution took place with, for example, phosphate-buffered saline (PBS). The solution was subsequently subjected to sterile filtration and freezing. An alternative option is to lyophilize the conjugate.

[4285] B-4. Determination of the toxophore loading

[4286] The toxophore loading of the resultant solutions of the conjugates described in the working examples, in PBS buffer, was determined as follows:

[4287] The toxophore loading of lysine-linked ADCs was determined by mass-spectrometric determination of the molecular weights of the individual conjugate species. In this case, to start with, the antibody conjugates were deglycosylated by means of PNGaseF, and the sample was acidified and, following HPLC separation, was analysed by mass spectrometry using an ESI-MicroTofQ (Bruker Daltonik). All of the spectra were added via the signal in the TIC (Total Ion Chromatogram), and the molecular weight of the various conjugate species was calculated on the basis of MaxEnt Deconvolution. Following signal integration of the different species, the DAR (Drug/Antibody Ratio) was then calculated.

[4288] For protein identification, in addition to the molecular weight determination, a tryptic digestion was carried out after deglycosylation and/or denaturing, and this digestion, after denaturing, reduction and derivatization, confirmed the identity of the protein on the basis of the tryptic peptides detected.

[4289] The toxophore loading of cysteine-linked conjugates was determined via reversed-phase chromatography of the reduced and denatured ADC. The ADC solution (1 mg/mL, 50 μL) was admixed with guanidinium hydrochloride (GuHCl) (28.6 mg) and with a solution of DL-dithiothreitol (DTT) (500 mM, 3 μL). The mixture was incubated at 55° C. for an hour and analysed by HPLC.

[4290] The HPLC analysis was carried out on an Agilent 1260 HPLC System with detection at 220 nm. The column used was a Polymer Laboratories PLRP-S Polymeric Reversed Phase column (catalogue number PL1912-3802) (2.1×150 mm, 8 μm particle size, 1000 Å) with a flow rate of 1 mL/min, using the following gradient: 0 min, 25% B; 3 min, 25% B; 28 min, 50% B. Eluent A consisted of 0.05% trifluoroacetic acid (TFA) in water, eluent B of 0.05% trifluoroacetic acid in acetonitrile.

[4291] The peaks detected were assigned by retention time comparison with the light chain (L0) and the heavy chain (H0) of the unconjugated antibody. Peaks which were detected exclusively in the conjugated sample were assigned to the light chain, with a toxophore (L1), and to the heavy chains, with one, two and three toxophores (H1, H2, H3).

[4292] The average loading of the antibody with toxophores was calculated as follows: first of all, the light-chain loading was calculated from the peak areas—determined by integration—of the peaks L0 and L1 belonging to the light chains, as the sum of the toxophore number weighted integration results of L0 and L1, divided by the sum of the singularly weighted integration results of L0 and L1. In the same way, the heavy-chain loading was calculated from the peak areas—determined by integration—of the peaks H0, H1, H2 and H3, belonging to the heavy chains, as the sum of the toxophore number weighted integration results of H0, H1, H2 and H3, divided by the sum of the singularly weighted integration results of H0, H1, H2 and H3. The DAR is given by the light-chain loading and the heavy-chain loading, as the twofold sum of light-chain loading and heavy-chain loading. The factor 2 takes account of the fact that an antibody consists of two light chains and two heavy chains. In certain individual cases it may be impossible exactly to determine the toxophore loading, owing to co-elutions of certain peaks.

B-5. Testing of the Antigen Binding of the ADC

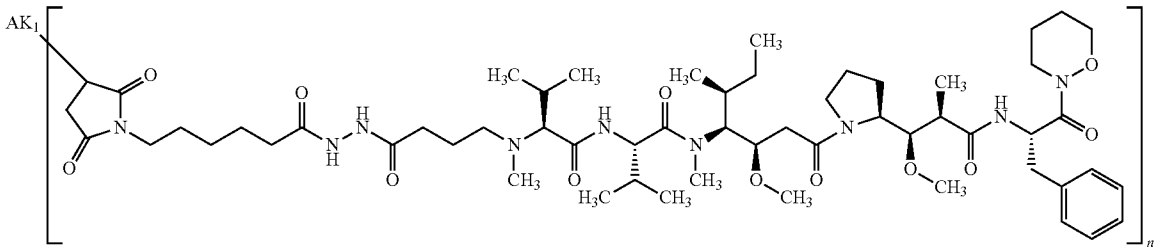
[4293] The binding capacity of the binder to the target molecule was tested after coupling had taken place. The skilled worker knows of diverse methods for achieving this—for example, the affinity of the conjugate can be tested by means of ELISA technology or surface plasmon resonance analysis (BIAcore™ measurements). The conjugate concentration can be measured by the skilled person using common methods—for example, for antibody conjugates, by means of protein determination (see also Doronina et al.; Nature Biotechnol. 2003; 21:778-784 and Polson et al., Blood 2007; 1102:616-623).

Working Examples

Immunoconjugates

Example 1

[4294]

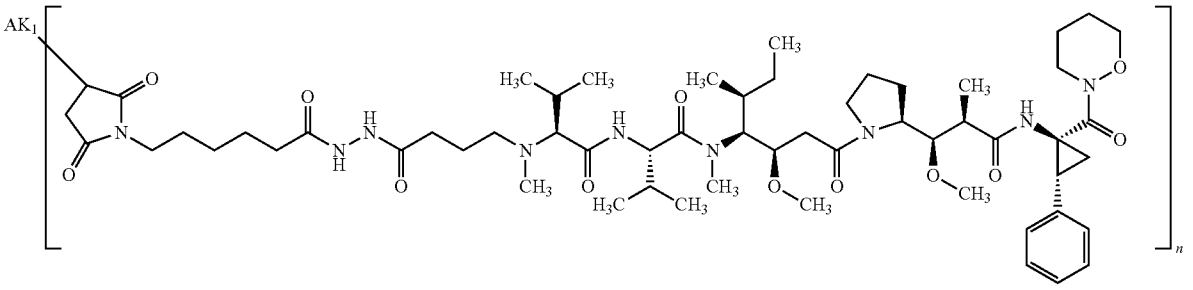


[4295] Protein concentration: 0.96 mg/ml

[4296] Drug/mAb Ratio: 3.1

Example 2

[4297]

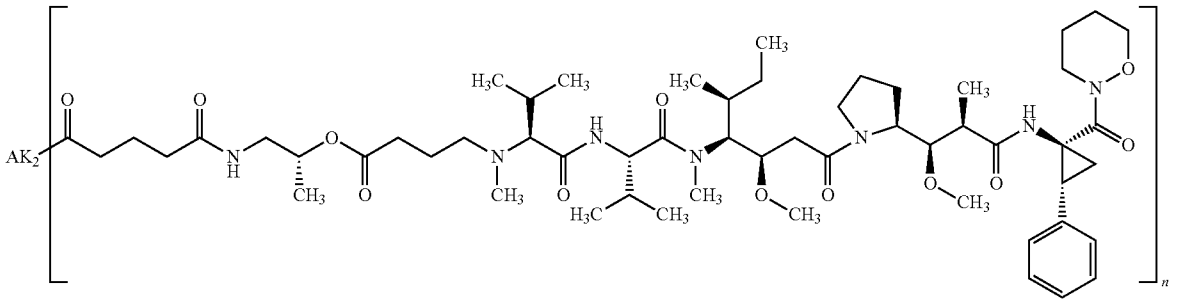


[4298] Protein concentration: 0.44 mg/ml

[4299] Drug/mAb Ratio: 4.6

Example 3

[4300]

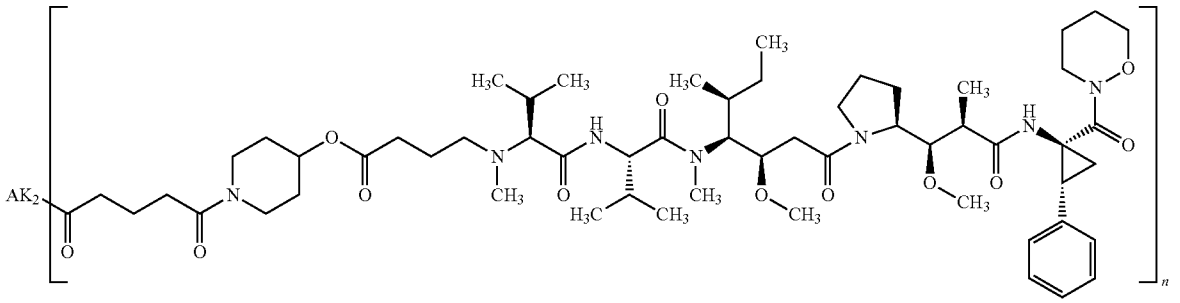


[4301] Protein concentration: 1.09 mg/ml

[4302] Drug/mAb Ratio: 2.1

Example 4

[4303]

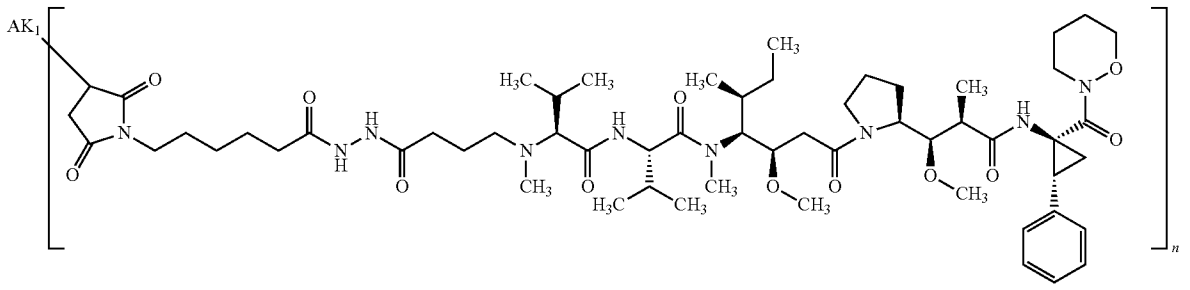


[4304] Protein concentration: 0.87 mg/ml

[4305] Drug/mAb Ratio: 3.8

Example 5

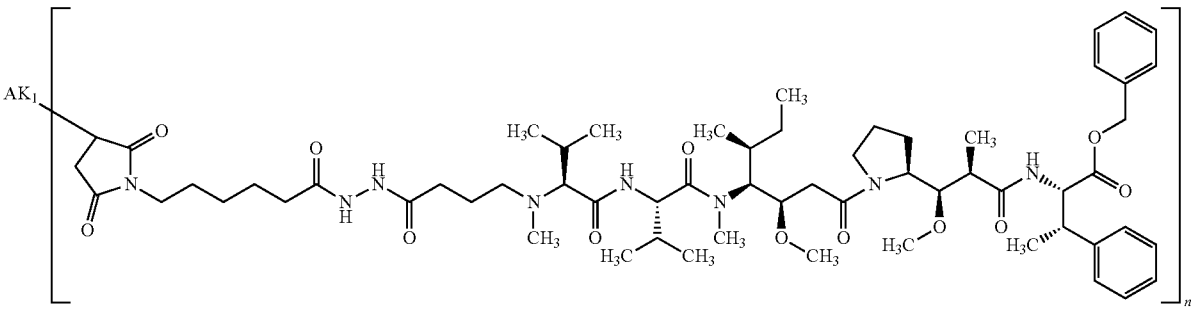
[4306]



[4307] Protein concentration: 0.45 mg/ml
[4308] Drug/mAb Ratio: 6.5

Example 6

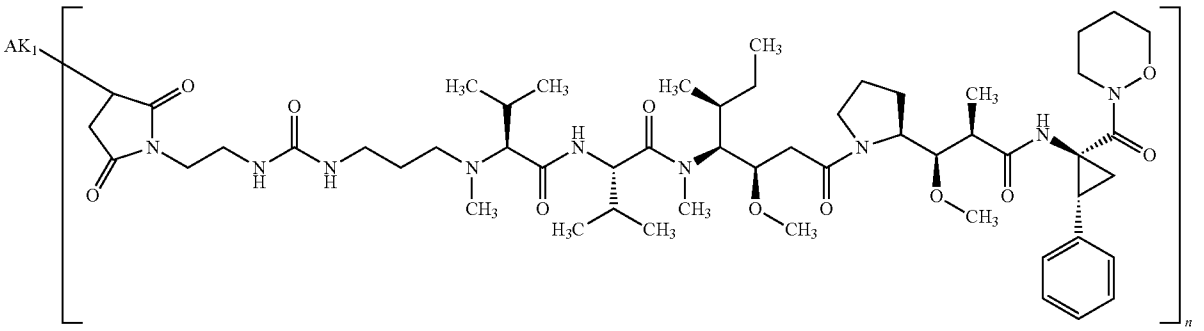
[4309]



[4310] Protein concentration: 0.15 mg/ml
[4311] Drug/mAb Ratio: 3.1

Example 7

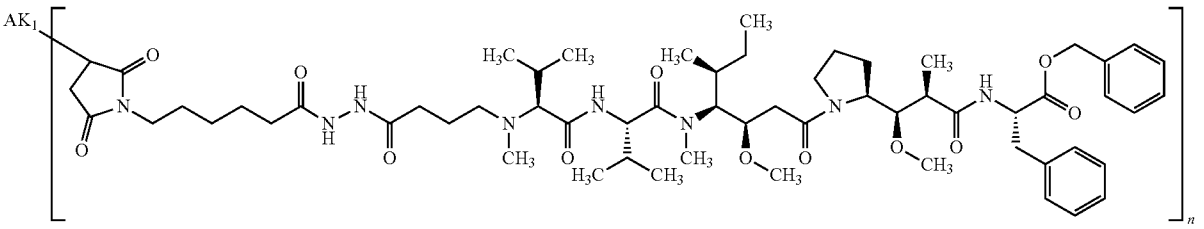
[4312]



[4313] Protein concentration: 0.94 mg/ml
[4314] Drug/mAb Ratio: 2.8

Example 8

[4315]

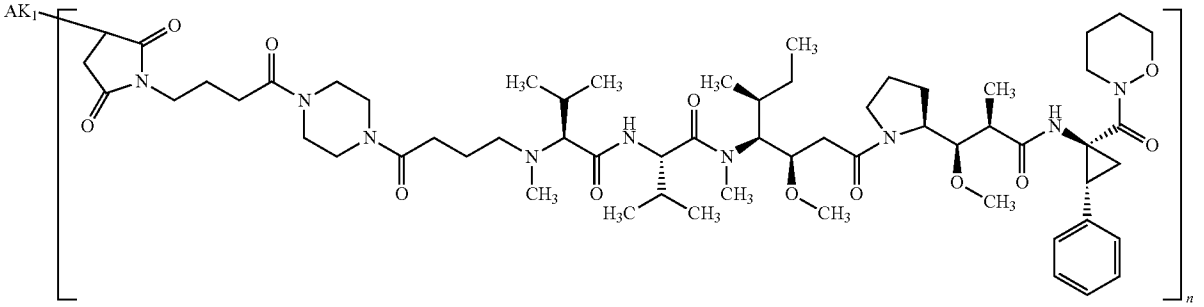


[4316] Protein concentration: 0.45 mg/ml

[4317] Drug/mAb Ratio: 0.9

Example 9

[4318]

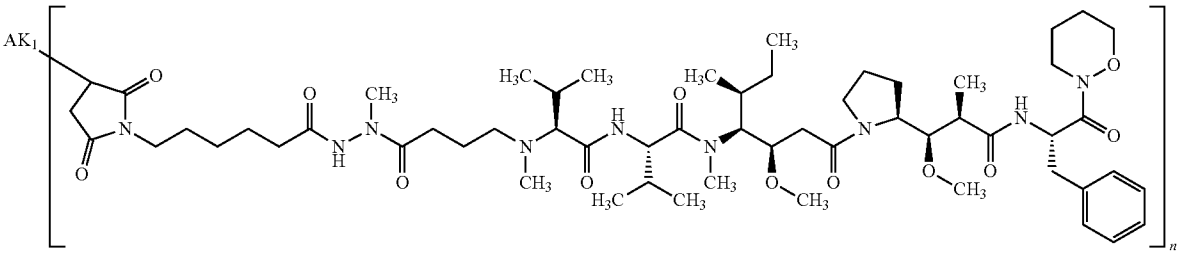


[4319] Protein concentration: 0.51 mg/ml

[4320] Drug/mAb Ratio: 6.6

Example 10

[4321]

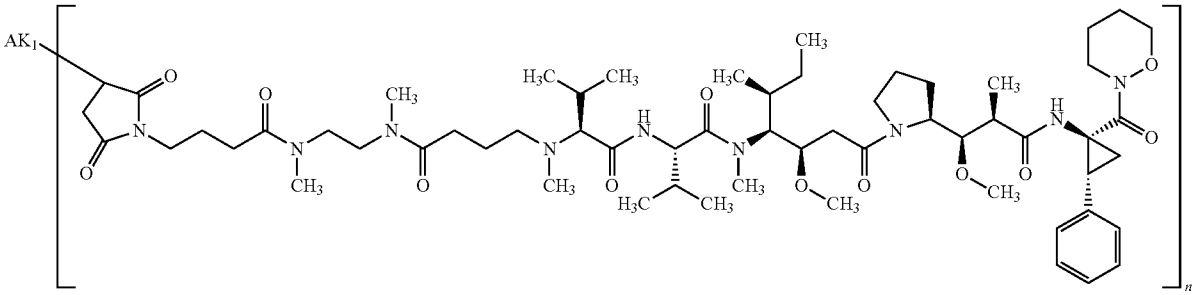


[4322] Protein concentration: 0.47 mg/ml

[4323] Drug/mAb Ratio: 4.2

Example 11

[4324]

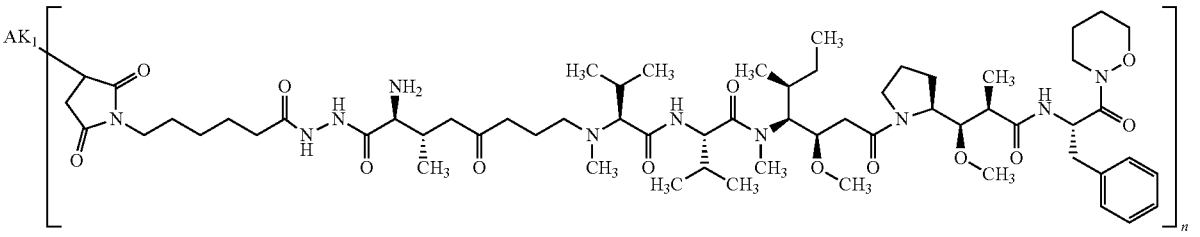


[4325] Protein concentration: 0.45 mg/ml

[4326] Drug/mAb Ratio: 5.9

Example 12

[4327]

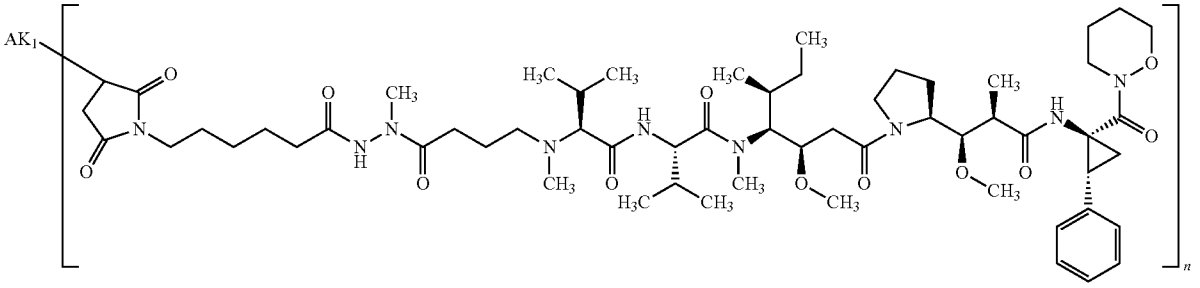


[4328] Protein concentration: 0.47 mg/ml

[4329] Drug/mAb Ratio: 3.3

Example 13

[4330]

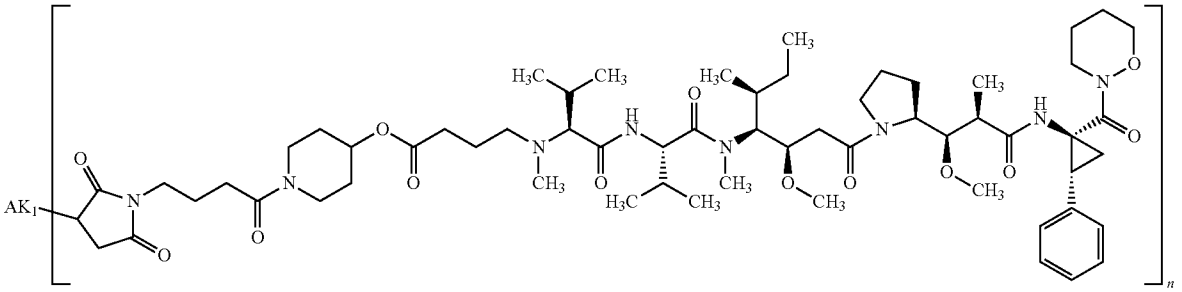


[4331] Protein concentration: 0.53 mg/ml

[4332] Drug/mAb Ratio: 2.8

Example 14

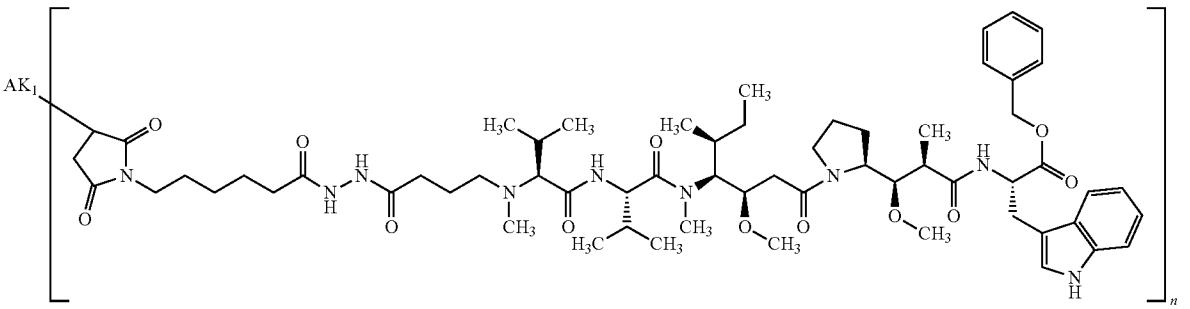
[4333]



[4334] Protein concentration: 0.92 mg/ml
[4335] Drug/mAb Ratio: 3.5

Example 15

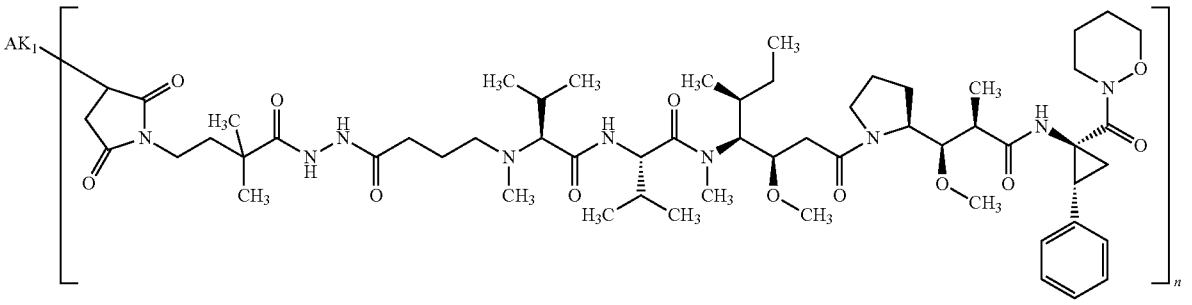
[4336]



[4337] Protein concentration: 0.09 mg/ml
[4338] Drug/mAb Ratio: nd

Example 16

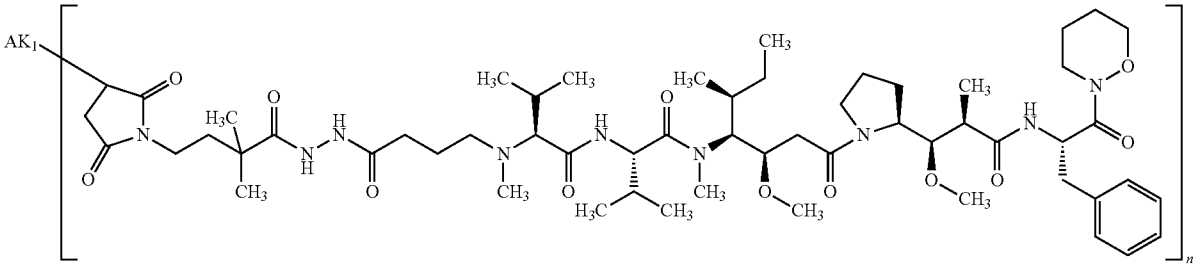
[4339]



[4340] Protein concentration: 0.62 mg/ml
[4341] Drug/mAb Ratio: 1.8

Example 17

[4342]

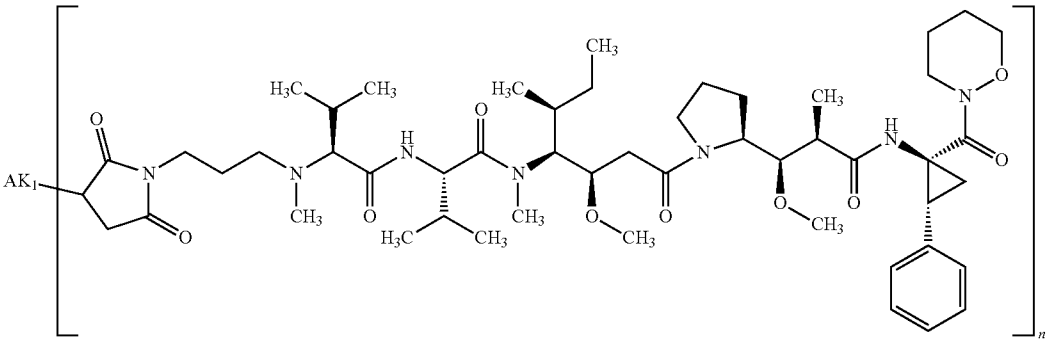


[4343] Protein concentration: 0.55 mg/ml

[4344] Drug/mAb Ratio: 3.8

Example 18

[4345]

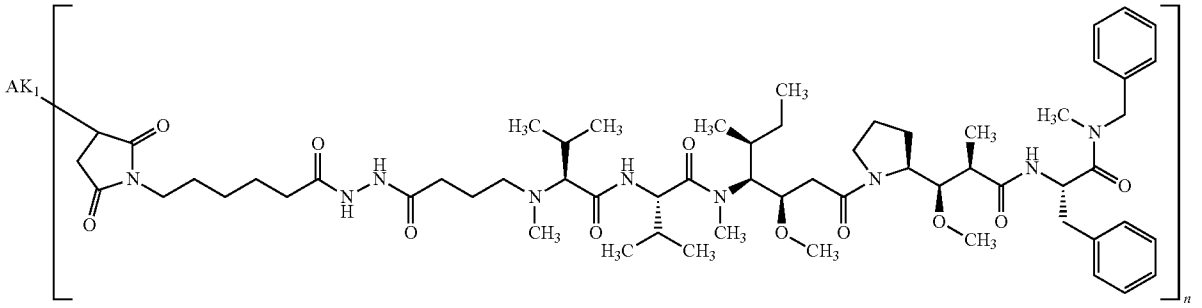


[4346] Protein concentration: 0.54 mg/ml

[4347] Drug/mAb Ratio: 4.4

Example 19

[4348]

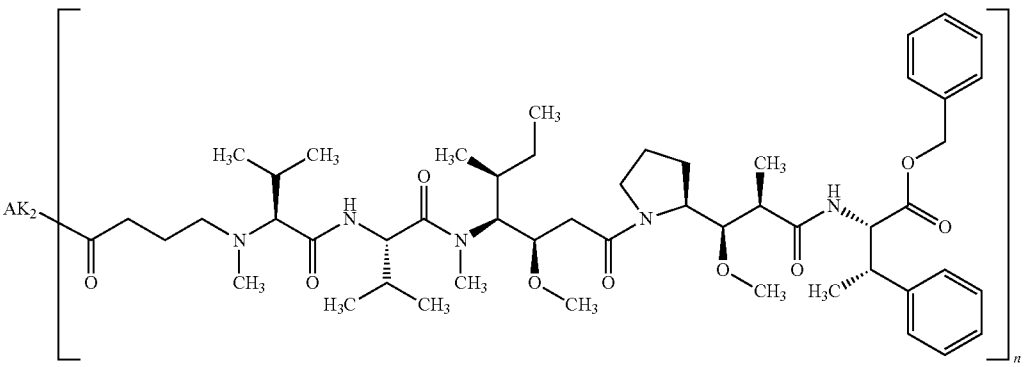


[4349] Protein concentration: 0.56 mg/ml

[4350] Drug/mAb Ratio: 4.0

Example 20

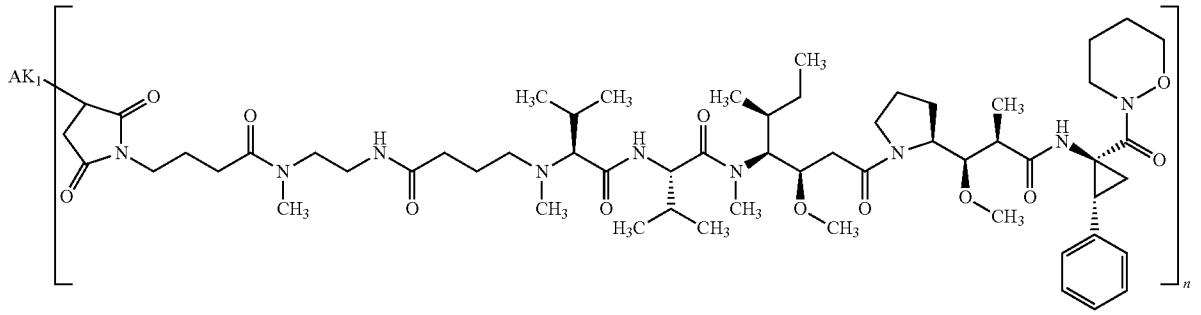
[4351]



[4352] Protein concentration: 1.1 mg/ml
[4353] Drug/mAb Ratio: 0.3

Example 21

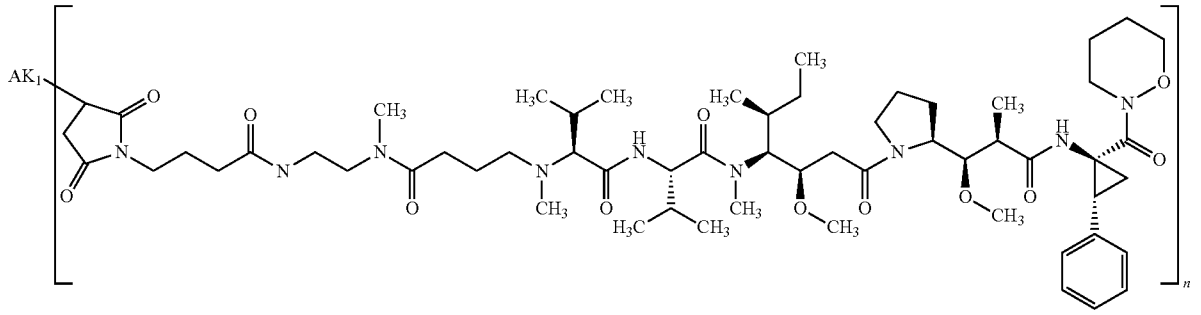
[4354]



[4355] Protein concentration: 0.61 mg/ml
[4356] Drug/mAb Ratio: 0.9

Example 22

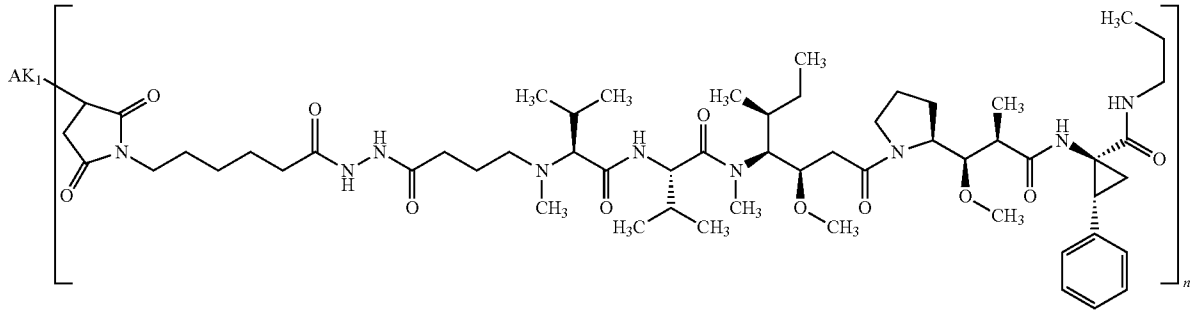
[4357]



[4358] Protein concentration: 0.57 mg/ml
[4359] Drug/mAb Ratio: 1.2

Example 23

[4360]



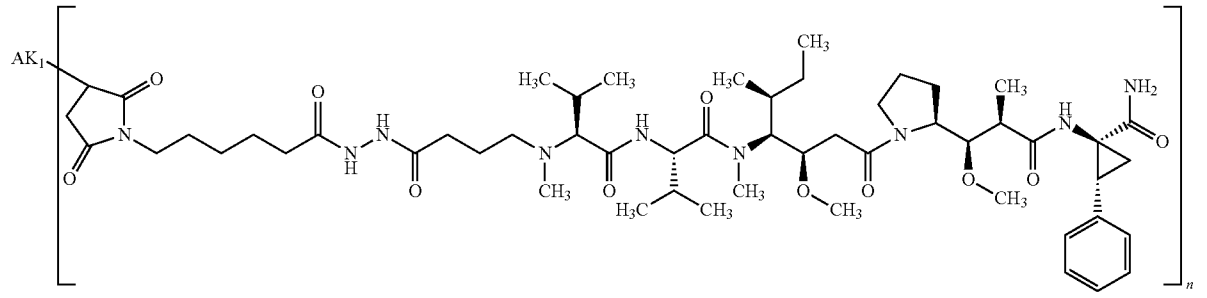
[4361] Coupling here was carried out using 100 mg of MF-Ta in PBS and following the Sephadex purification the reaction mixture was concentrated by ultracentrifugation.

[4362] Protein concentration: 11.2 mg/ml

[4363] Drug/mAb Ratio: 3.4

Example 24

[4364]

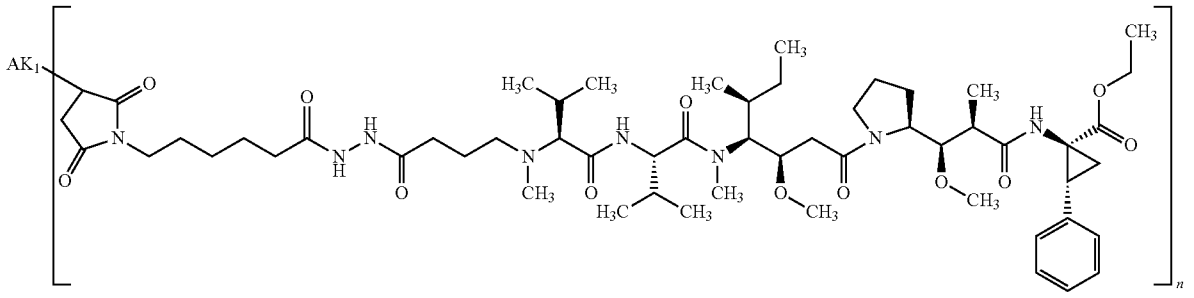


[4365] Protein concentration: 1.56

[4366] Drug/mAb Ratio: 2.8

Example 25

[4367]

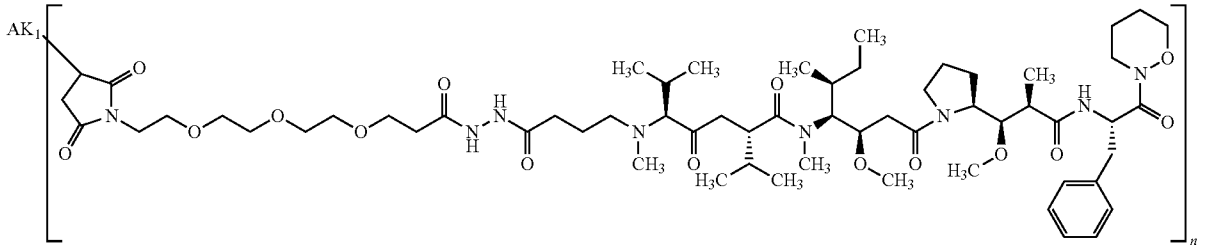


[4368] Protein concentration: 0.60 mg/ml

[4369] Drug/mAb Ratio: 2.4

Example 26

[4370]

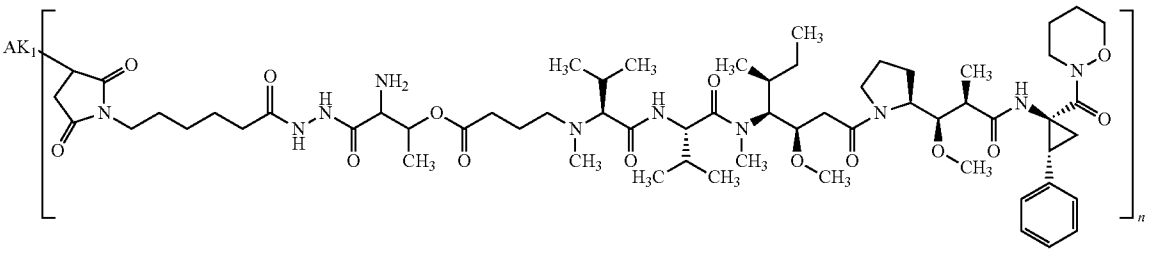


[4371] Protein concentration: 0.58 mg/ml

Drug/mAb-Ratio: 2.6

Example 27

[4372]

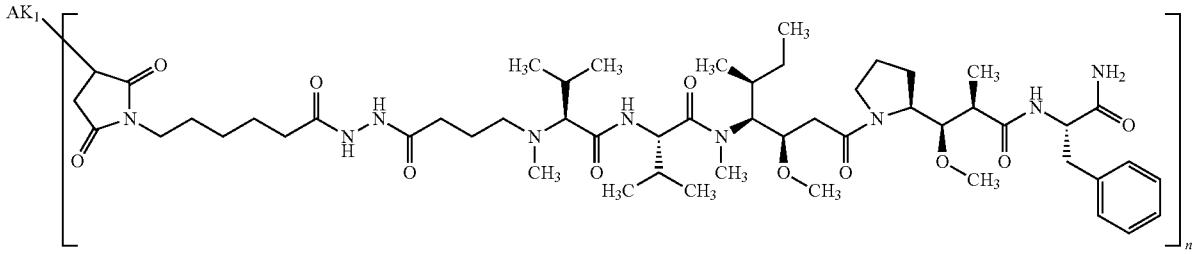


[4373] Protein concentration: 0.39 mg/ml

Drug/mAb-Ratio: 0.8

Example 28

[4374]



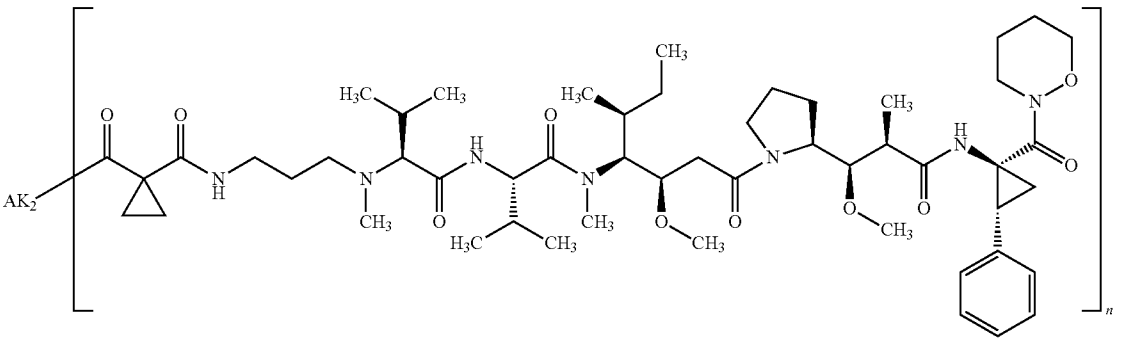
[4375] Coupling here was carried out using 70 mg of MF-Ta in PBS and following the Sephadex purification the reaction mixture was concentrated by ultracentifugation.

[4376] Protein concentration: 13.2 mg/ml

[4377] Drug/mAb Ratio: 4.6

Example 29

[4378]

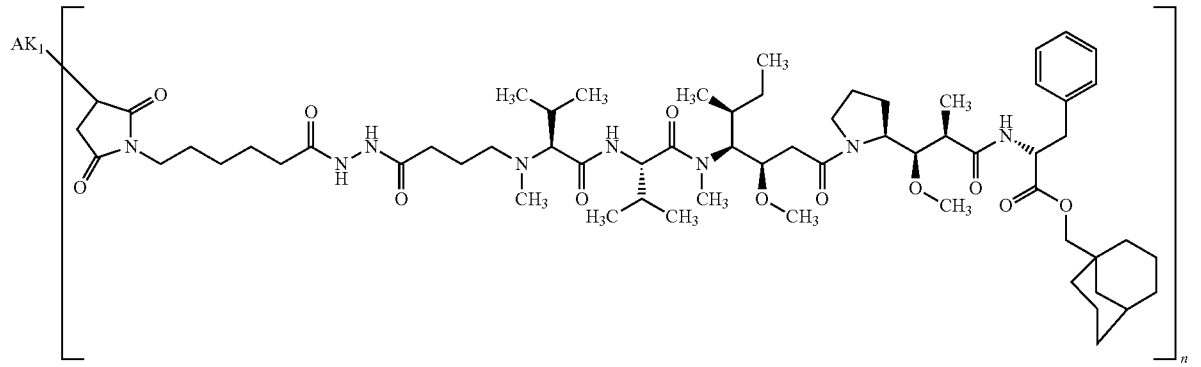


[4379] Protein concentration: 0.98 mg/ml

[4380] Drug/mAb Ratio: 1.1

Example 30

[4381]

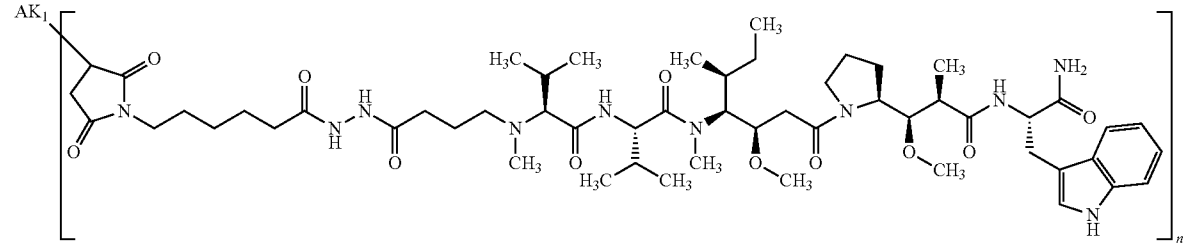


[4382] Protein concentration: 0.55 mg/ml

[4383] Drug/mAb Ratio: not determinable

Example 31

[4384]



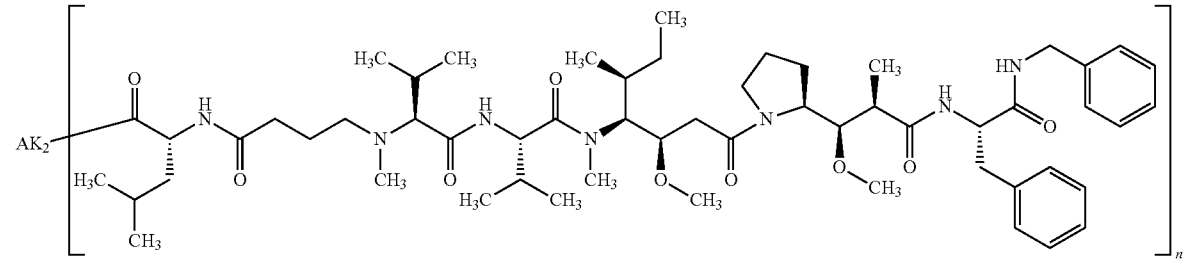
[4385] Coupling here was carried out using 40 mg of MF-Ta in PBS and following the Sephadex purification the reaction mixture was concentrated by ultracentrifugation.

[4386] Protein concentration: 10.6 mg/ml

[4387] Drug/mAb Ratio: 4.1

Example 32

[4388]

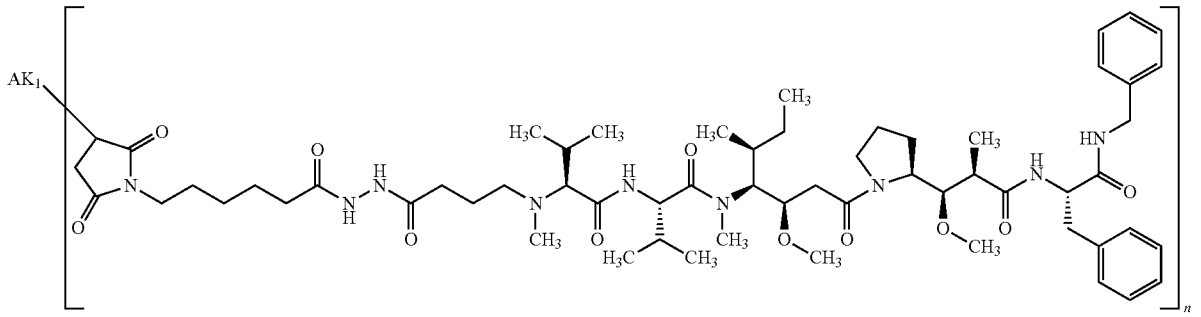


[4389] Protein concentration: 0.96 mg/ml

[4390] Drug/mAb Ratio: 0.4

Example 33

[4391]



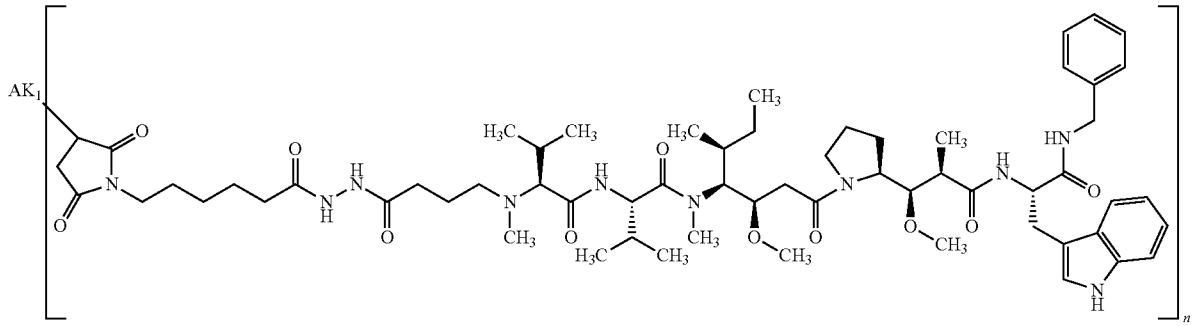
[4392] Coupling here was carried out using 70 mg of MF-Ta in PBS and following the Sephadex purification the reaction mixture was concentrated by ultracentifugation.

[4393] Protein concentration: 12.7 mg/ml

[4394] Drug/mAb Ratio: 3.6

Example 34

[4395]

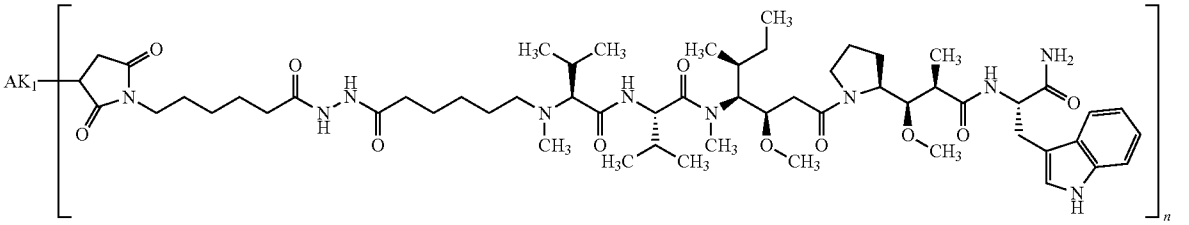


[4396] Protein concentration: 1.1 mg/ml

[4397] Drug/mAb Ratio: 2.7

Example 35

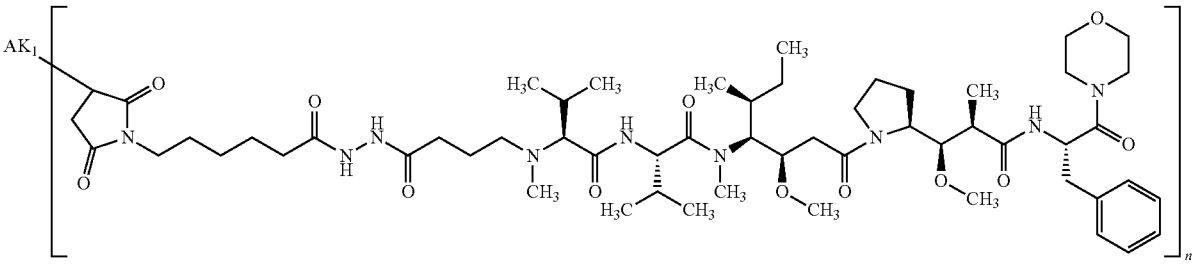
[4398]



[4399] Protein concentration: 1.24 mg/ml
[4400] Drug/mAb Ratio: 2.6

Example 36

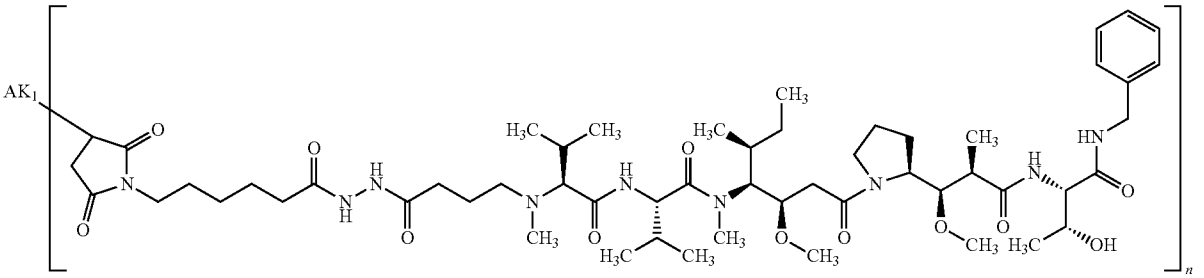
[4401]



[4402] Protein concentration: 0.99 mg/ml
[4403] Drug/mAb Ratio: 2.3

Example 37

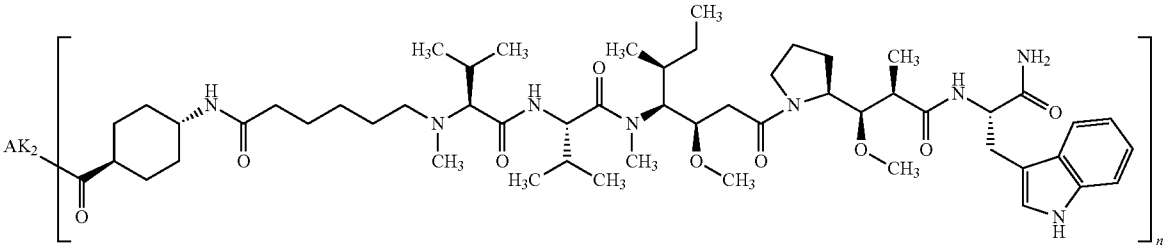
[4404]



[4405] Protein concentration: 1.22 mg/ml
[4406] Drug/mAb Ratio: 3.3

Example 38

[4407]

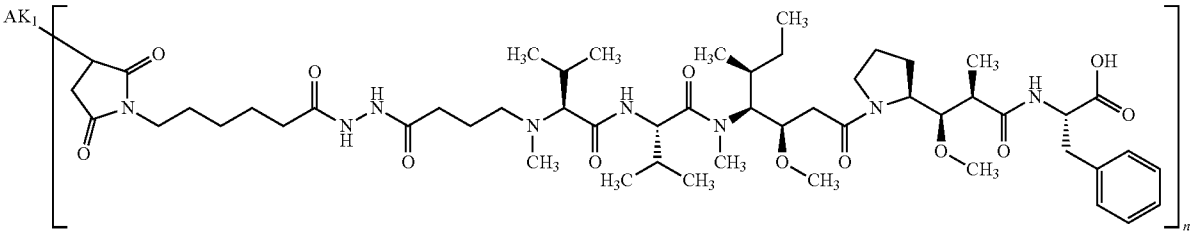


[4408] Protein concentration: 1.34 mg/ml

[4409] Drug/mAb Ratio: 1.2

Example 39

[4410]

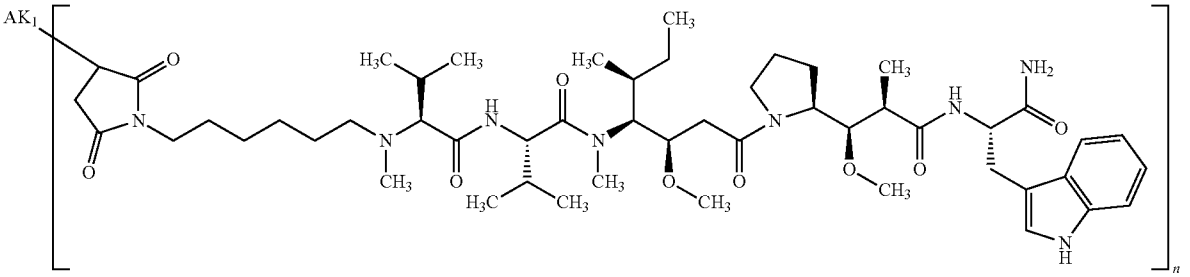


[4411] Protein concentration: 1.28 mg/ml

[4412] Drug/mAb Ratio: 3.2

Example 40

[4413]



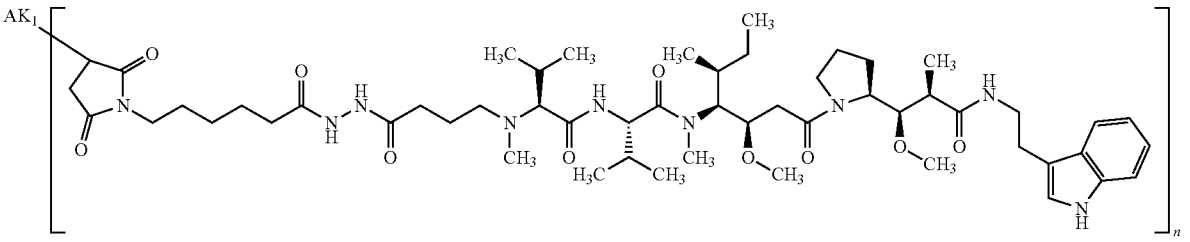
[4414] Coupling here was carried out using 70 mg of MF-Ta in PBS and following the Sephadex purification the reaction mixture was concentrated by ultracentrifugation.

[4415] Protein concentration: 10.9 mg/ml

[4416] Drug/mAb Ratio: 5.1

Example 41

[4417]



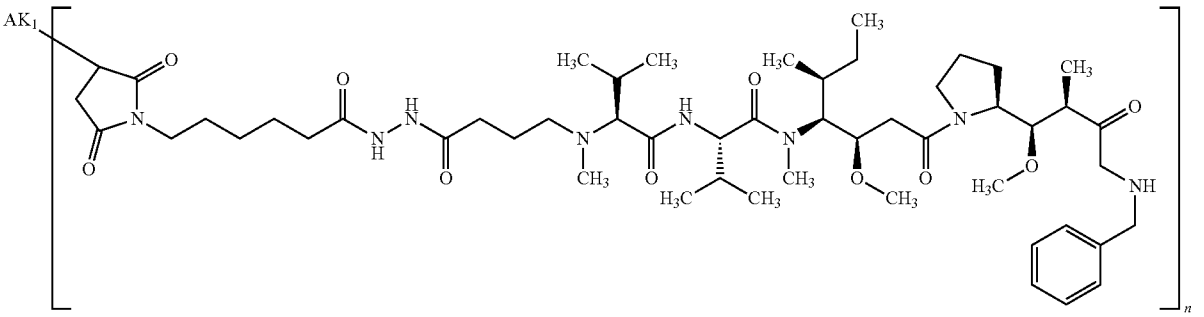
[4418] Coupling here was carried out using 100 mg of MF-Ta in PBS and following the Sephadex purification the reaction mixture was concentrated by ultracentrifugation.

[4419] Protein concentration: 10.3 mg/ml

[4420] Drug/mAb Ratio: 4.3

Example 42

[4421]

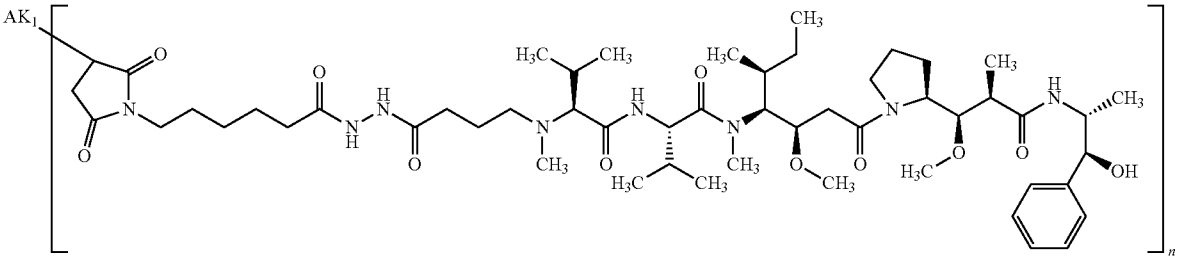


[4422] Protein concentration: 1.08 mg/ml

[4423] Drug/mAb Ratio: 2.8

Example 43

[4424]

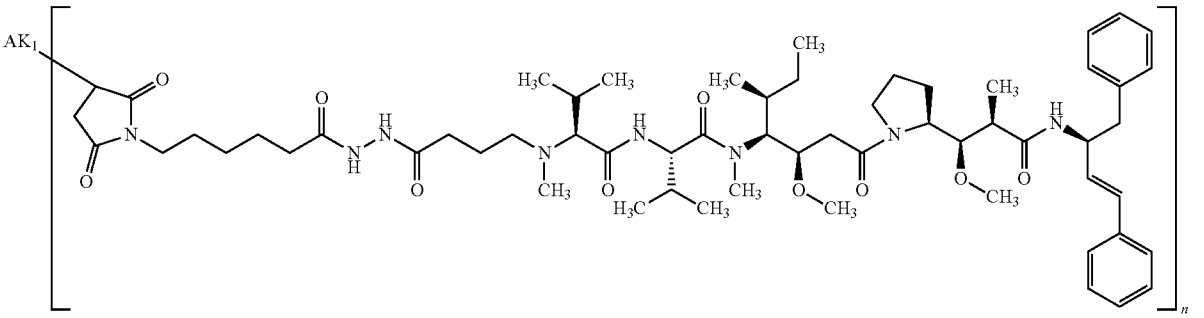


[4425] Protein concentration: 1.24 mg/ml

[4426] Drug/mAb Ratio: 2.8

Example 44

[4427]

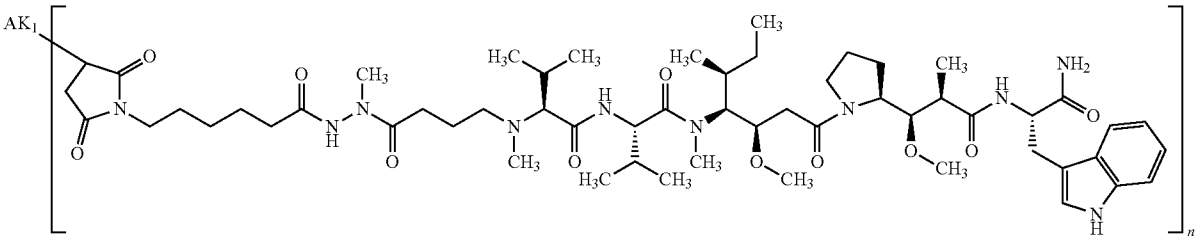


[4428] Protein concentration: 1.28 mg/ml

[4429] Drug/mAb Ratio: 3.8

Example 45

[4430]

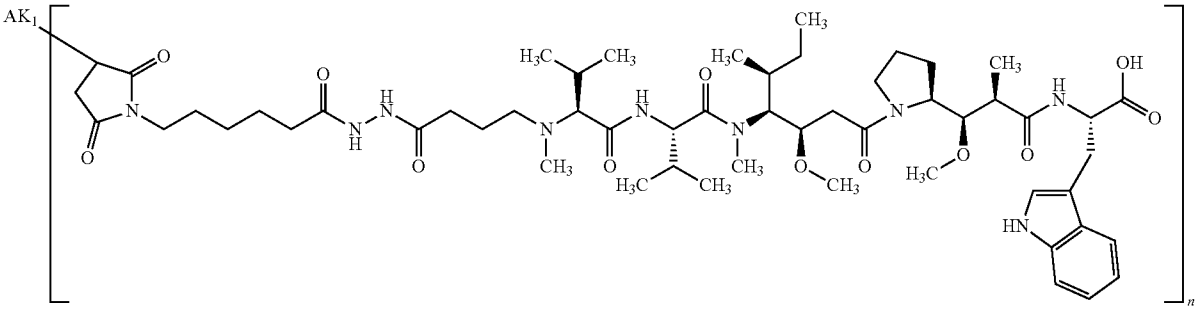


[4431] Protein concentration: 1.07 mg/ml

[4432] Drug/mAb Ratio: 3.0

Example 46

[4433]

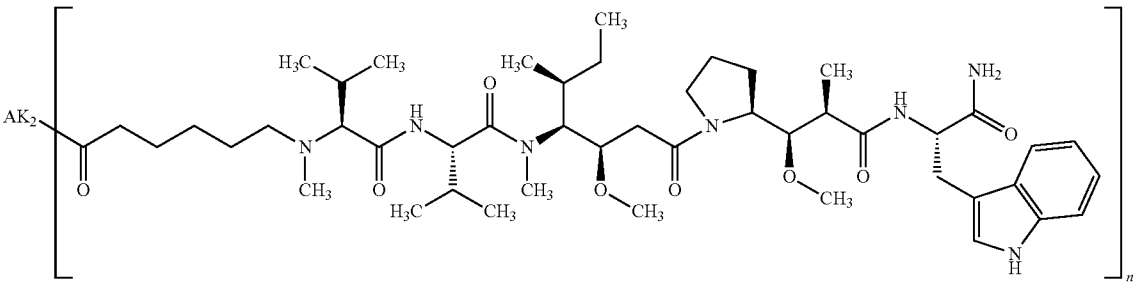


[4434] Protein concentration: 1.35 mg/ml

[4435] Drug/mAb Ratio: 4.0

Example 47

[4436]



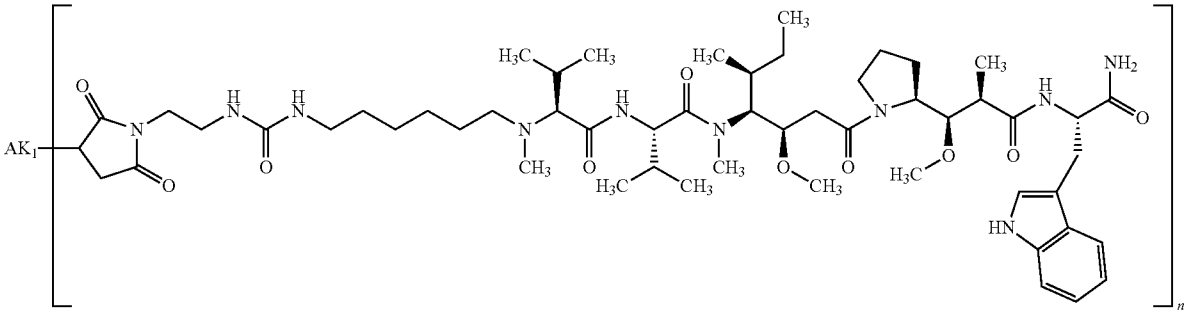
[4437] Coupling here was carried out using 100 mg of MF-Ta in PBS and following the Sephadex purification the reaction mixture was concentrated by ultracentrifugation.

[4438] Protein concentration: 12.2 mg/ml

[4439] Drug/mAb Ratio: 5.6

Example 48

[4440]

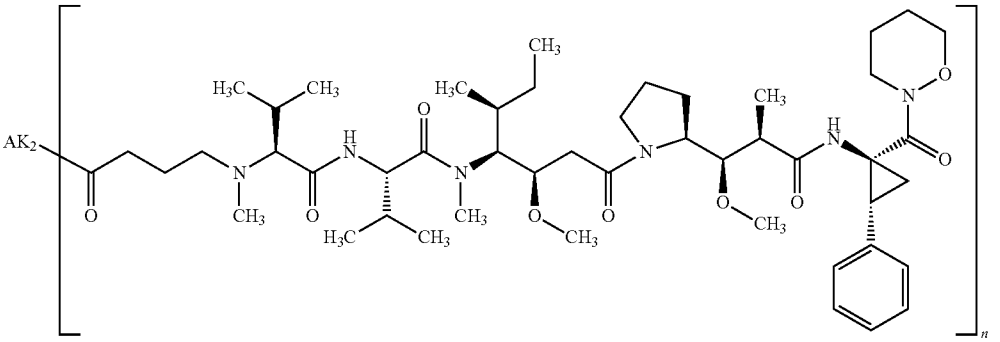


[4441] Protein concentration: 1.32 mg/ml

[4442] Drug/mAb Ratio: 3.2

Example 49

[4443]

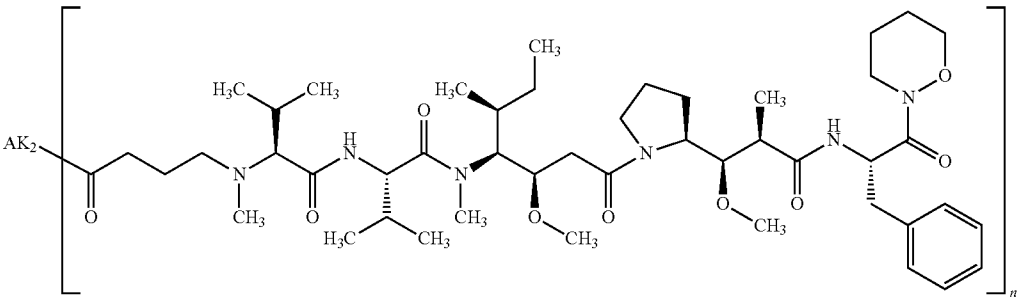


[4444] Protein concentration: 1.01 mg/ml

[4445] Drug/mAb Ratio: 0.9

Example 50

[4446]

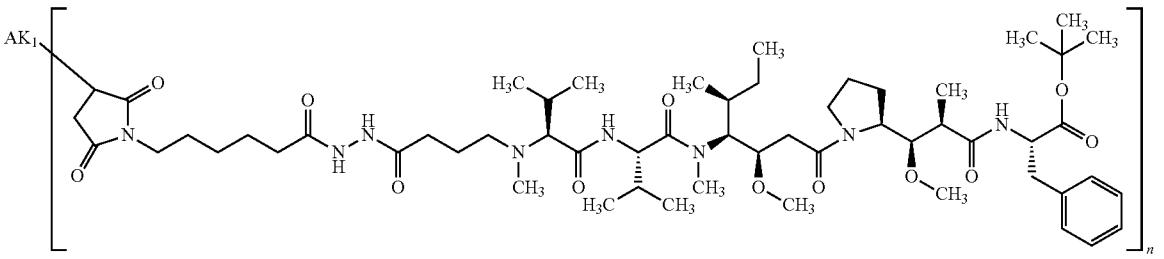


[4447] Protein concentration: 1.03 mg/ml

[4448] Drug/mAb Ratio: 0.3

Example 51

[4449]



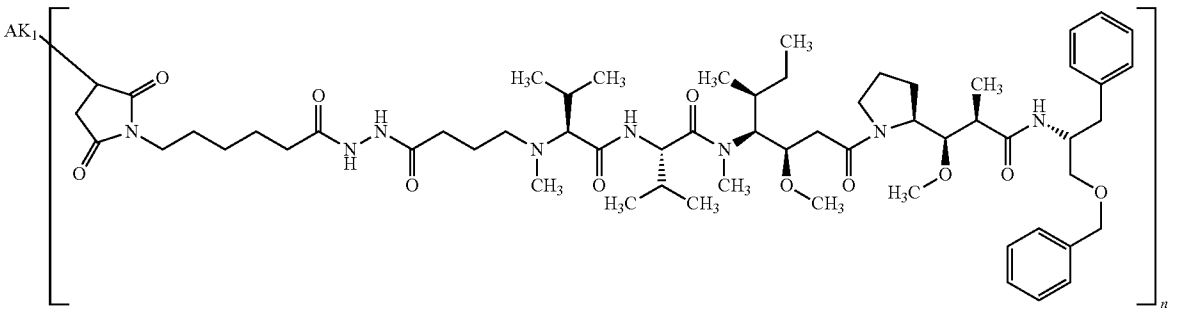
[4450] Protein concentration: 0.62 mg/ml

[4451] Drug/mAb Ratio: 3.1

[4452] This ADC was concentrated by means of vivaspin centrifugation, re-diluted, and concentrated and re-diluted again.

Example 52

[4453]

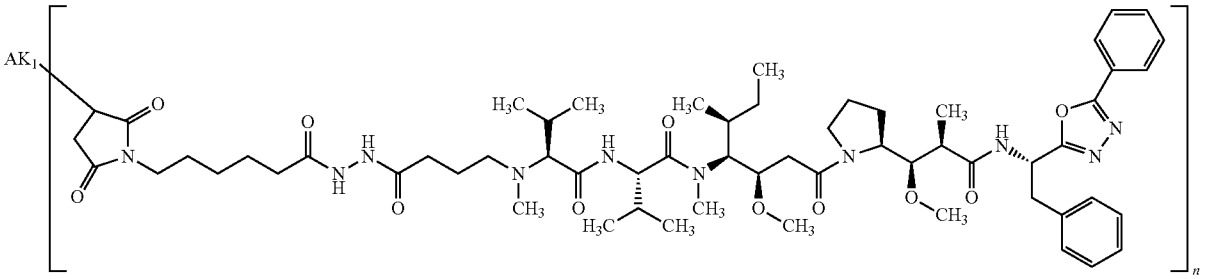


[4454] Protein concentration: 1.26 mg/ml

[4455] Drug/mAb Ratio: not determinable

Example 53

[4456]



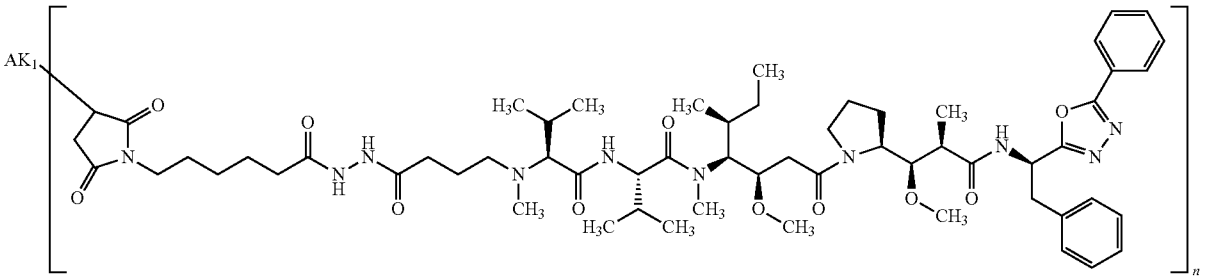
[4457] Coupling here was carried out using 5 mg of MF-Ta in PBS and following the Sephadex purification the batch was concentrated by ultracentifugation and re-diluted.

[4458] Protein concentration: 1.21 mg/ml

[4459] Drug/mAb Ratio: not determinable exactly

Example 54

[4460]



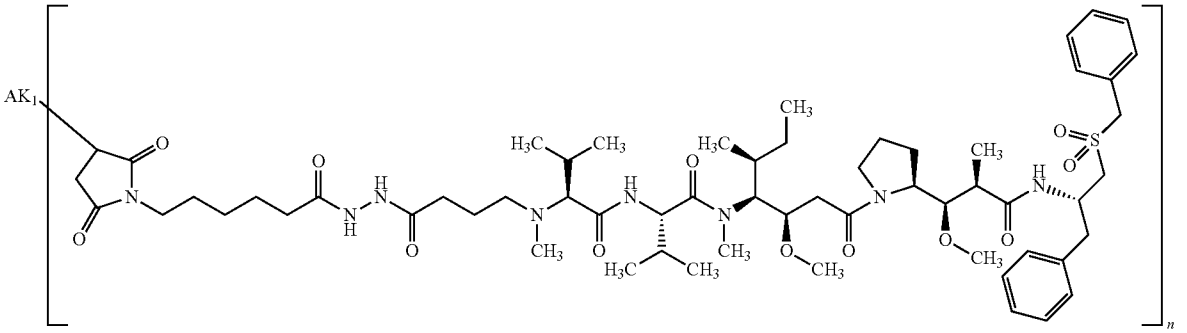
[4461] Coupling here was carried out using 5 mg of MF-Ta in PBS and following the Sephadex purification the batch was concentrated by ultracentifugation and re-diluted.

[4462] Protein concentration: 0.8 mg/ml

[4463] Drug/mAb Ratio: 2.8

Example 55

[4464]

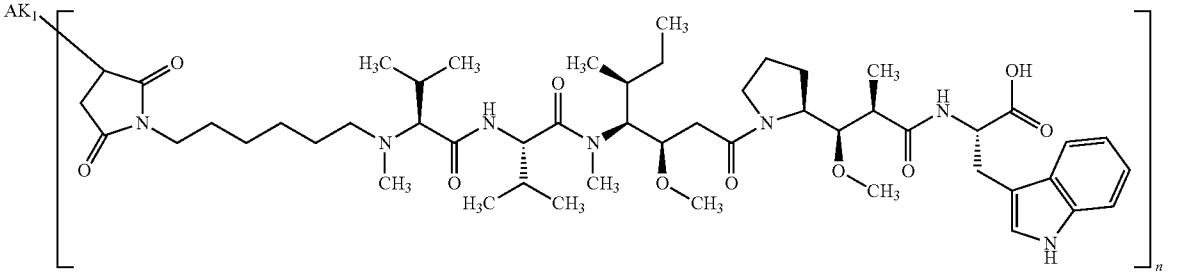


[4465] Protein concentration: 1.44 mg/ml

[4466] Drug/mAb Ratio: 4.1

Example 56

[4467]

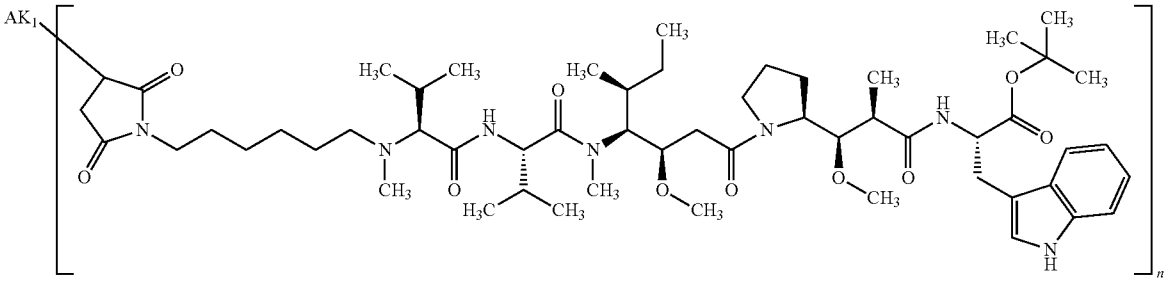


[4468] Protein concentration: 0.92 mg/ml

[4469] Drug/mAb Ratio: 3.5

Example 57

[4470]



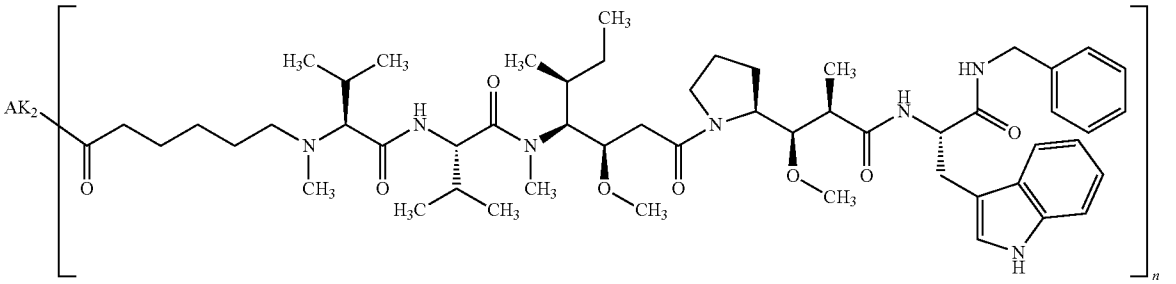
[4471] Coupling here was carried out using 5 mg of MF-Ta in PBS and following the Sephadex purification the batch was concentrated by ultracentrifugation and re-diluted.

[4472] Protein concentration: 0.77 mg/ml

[4473] Drug/mAb Ratio: >1.5 (not determinable exactly)

Example 58

[4474]

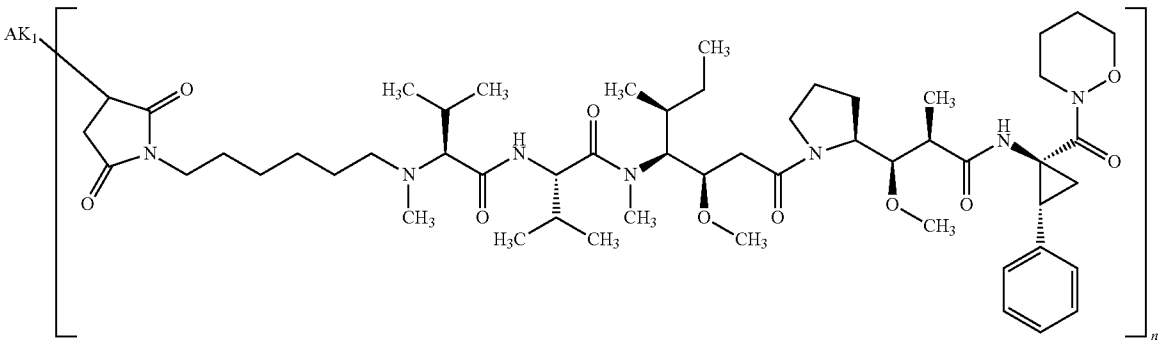


[4475] Protein concentration: 1.3 mg/ml

[4476] Drug/mAb Ratio: 2.0

Example 59

[4477]



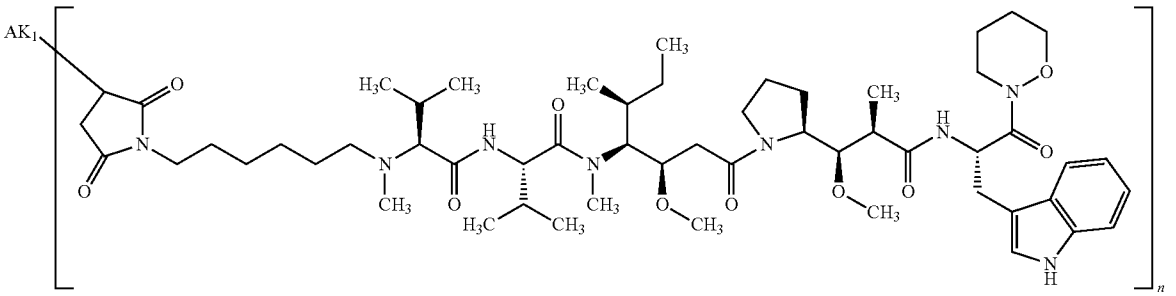
[4478] Coupling here was carried out using 150 mg of MF-Ta in PBS and following the Sephadex purification the reaction mixture was concentrated by ultracentrifugation.

[4479] Protein concentration: 11.2 mg/ml

[4480] Drug/mAb Ratio: 3.7

Example 60

[4481]



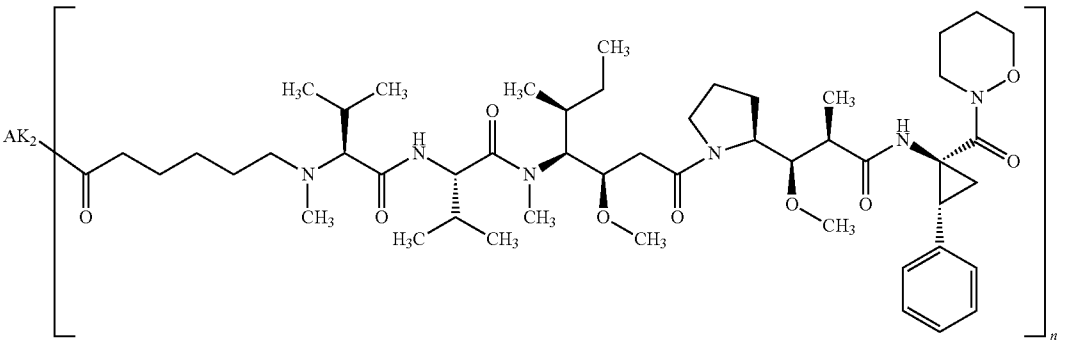
[4482] Coupling here was carried out using 100 mg of MF-Ta in PBS and following the Sephadex purification the reaction mixture was concentrated by ultracentrifugation.

[4483] Protein concentration: 11.4 mg/ml

[4484] Drug/mAb Ratio: 3.9

Example 61

[4485]



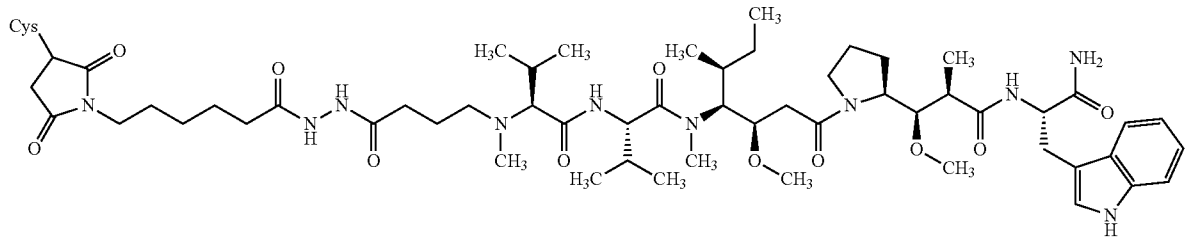
[4486] Coupling here was carried out using 60 mg of MF-Ta in PBS and following the Sephadex purification the reaction mixture was concentrated by ultracentrifugation.

[4487] Protein concentration: 10.5 mg/ml

[4488] Drug/mAb Ratio: 4.4

Example 62

[4489] N-(4-{2-[6-(3-{[(2R)-2-Amino-2-carboxyethyl] sulphanyl}-2,5-dioxopyrrolidin-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-amino-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl] pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide



[4490] 10 mg (10 μmol) of Intermediate 157 were taken up in 5.2 ml of DMF and admixed with 2.28 mg (20 μmol) of L-cysteine. The reaction mixture was stirred at RT for 2 hours, then concentrated under reduced pressure and subsequently purified by preparative HPLC. This gave 5.8 mg (48% of theory) of the title compound.

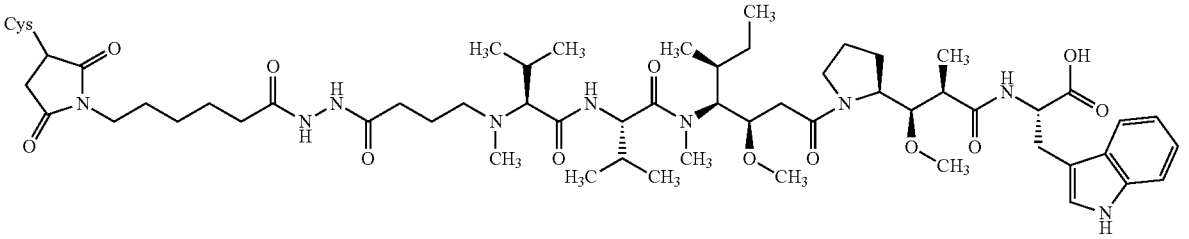
[4491] HPLC (Method 5): R_t=1.45 min;

[4492] LC-MS (Method 1): R_t=0.74 min; MS (ESIpos): m/z=1184 $(M+H)^+$.

Example 63

N-(4-{2-[6-(3-{[(2R)-2-Amino-2-carboxyethyl]sulphanyl}-2,5-dioxopyrrolidin-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(1S)-1-carboxy-2-(1H-indol-3-yl)ethyl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[4493]



[4494] 10 mg (10 μmol) of Intermediate 113 were taken up in 5.2 ml of DMF and admixed with 2.28 mg (20 μmol) of L-cysteine. The reaction mixture was stirred at RT for 2 hours, then concentrated under reduced pressure and subsequently purified by preparative HPLC. This gave 6 mg (54% of theory) of the title compound.

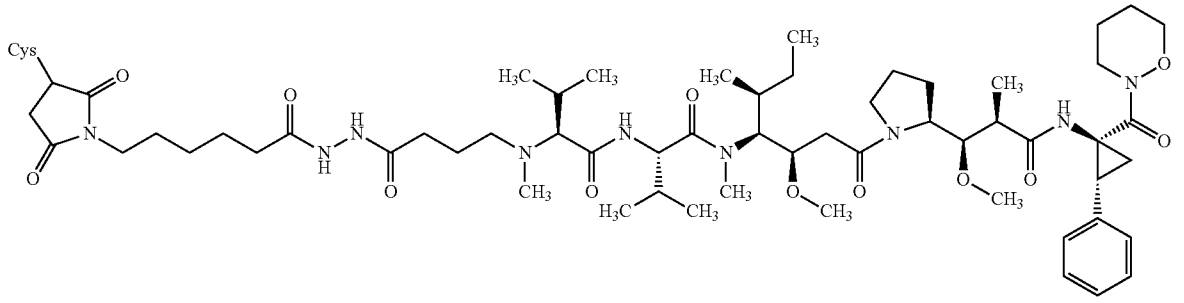
[4495] HPLC (Method 5): R_t=1.5 min;

[4496] LC-MS (Method 1): R_t=0.77 min; MS (ESIpos): m/z=1185 $(M+H)^+$.

Example 64

N-(4-{2-[6-(3-{[(2R)-2-Amino-2-carboxyethyl]sulphanyl}-2,5-dioxopyrrolidin-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[4497]



[4498] 9 mg (8.3 μmol) of Intermediate 132 were taken up in 4 ml of DMF and admixed with 3 mg (24.4 μmol) of L-cysteine. The reaction mixture was stirred at RT overnight, then concentrated under reduced pressure and subsequently purified by preparative HPLC. This gave 6.8 mg (68% of theory) of the title compound.

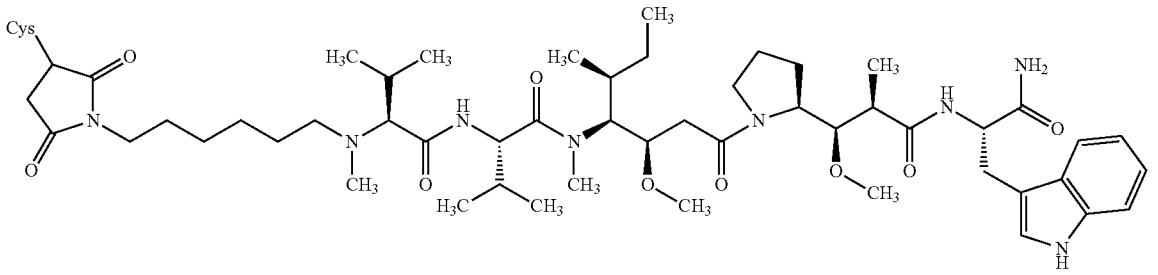
[4499] HPLC (Method 12): R_t=1.8 min;

[4500] LC-MS (Method 1): R_t=0.78 min; MS (ESIpos): m/z=1227 $(M+H)^+$.

Example 65

N-[6-(3-{[(2R)-2-Amino-2-carboxyethyl]sulphanyl}-2,5-dioxopyrrolidin-1-yl)hexyl]-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-amino-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[4501]



[4502] 10 mg (10 μmol) of Intermediate 106 were taken up in 5.8 ml of DMF and admixed with 2.5 mg (20 μmol) of L-cysteine. The reaction mixture was stirred at RT for 2 hours, then concentrated under reduced pressure and subsequently purified by preparative HPLC. This gave 5.2 mg (46% of theory of the title compound.

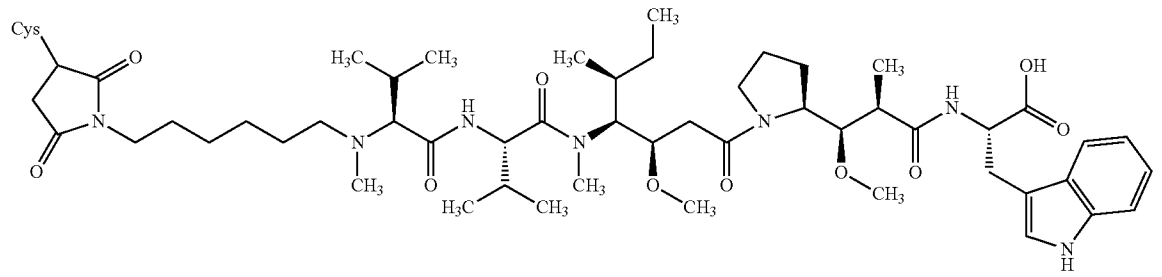
[4503] HPLC (Method 5): R_t=1.5 min;

[4504] LC-MS (Method 11): R_t=0.71 min; MS (ESIpos): m/z=1070 $(M+H)^+$.

Example 66

N-[6-(3-{[(2R)-2-Amino-2-carboxyethyl]sulphanyl}-2,5-dioxopyrrolidin-1-yl)hexyl]-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(1S)-1-carboxy-2-(1H-indol-3-yl)ethyl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[4505]



[4506] 10 mg (10 μmol) of Intermediate 124 were taken up in 4 ml of DMF and admixed with 2.5 mg (20 μmol) of L-cysteine. The reaction mixture was stirred at RT for 2 hours, then concentrated under reduced pressure and subsequently purified by preparative HPLC. This gave 7.2 mg (64% of theory of the title compound.

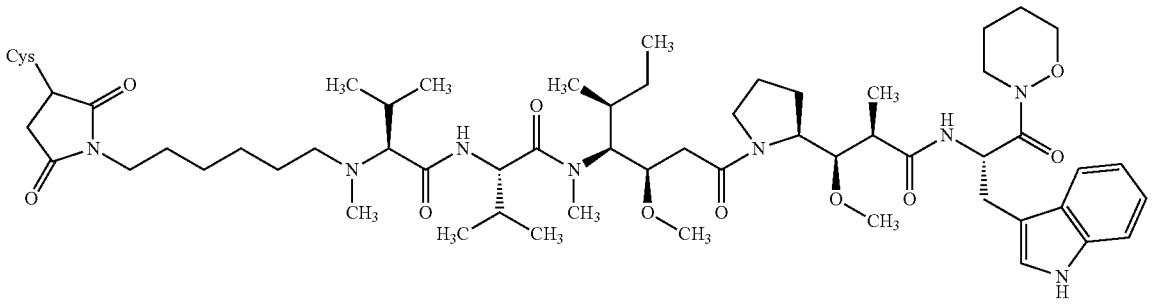
[4507] HPLC (Method 5): R_t=1.6 min;

[4508] LC-MS (Method 1): R_t=0.8 min; MS (ESIpos): m/z=1071 $(M+H)^+$.

Example 67

N-[6-(3-{[(2R)-2-Amino-2-carboxyethyl]sulphanyl}-2,5-dioxopyrrolidin-1-yl)hexyl]-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[4509]



[4510] 10 mg (10 μmol) of Intermediate 125 were taken up in 4 ml of DMF and admixed with 2.4 mg (20 μmol) of L-cysteine. The reaction mixture was stirred at RT for 2 hours, then concentrated under reduced pressure and subsequently purified by preparative HPLC. This gave 7.7 mg (69% of theory of the title compound.

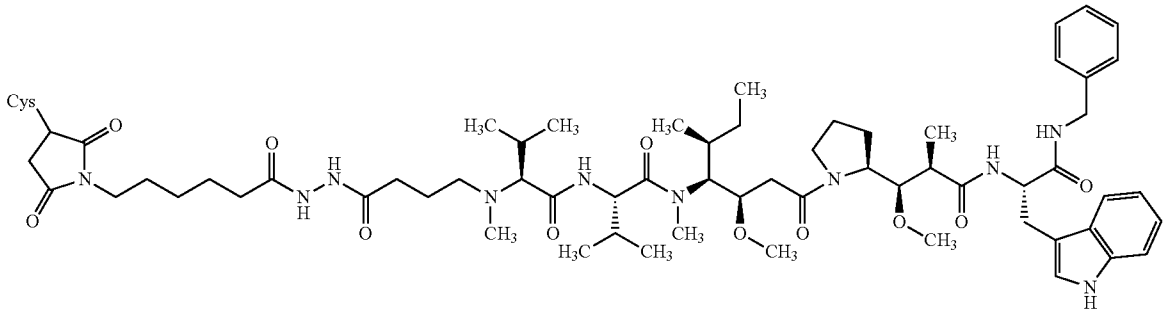
[4511] HPLC (Method 5): R_t=1.7 min;

[4512] LC-MS (Method 2): R_t=1.91 min; MS (ESIpos): m/z=1140 $(M+H)^+$.

Example 68

N-(4-{2-[6-(3-{[(2R)-2-Amino-2-carboxyethyl]sulphanyl}-2,5-dioxopyrrolidin-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(benzylamino)-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[4513]



[4514] 10 mg (10 μmol) of Intermediate 160 were taken up in 3 ml of DMF and admixed with 2.1 mg (20 μmol) of L-cysteine. The reaction mixture was stirred at RT for 2 hours, then concentrated under reduced pressure and subsequently purified by preparative HPLC. This gave 8.1 mg (73% of theory of the title compound.

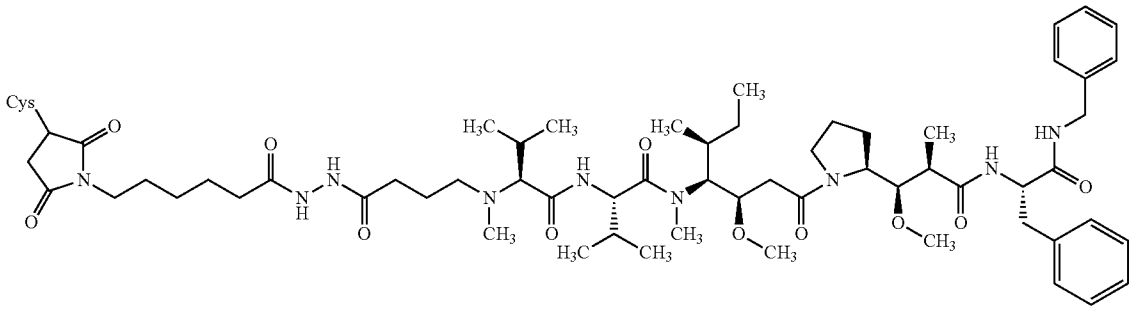
[4515] HPLC (Method 5): R_t=1.7 min;

[4516] LC-MS (Method 1): R_t=0.86 min; MS (ESIpos): m/z=1274 $(M+H)^+$.

Example 69

N-(4-{2-[6-(3-{[(2R)-2-Amino-2-carboxyethyl]sulphanyl}-2,5-dioxopyrrolidin-1-yl)hexanoyl]hydrazino}-4-oxobutyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-(benzylamino)-1-oxo-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[4517]



[4518] 3.5 mg (3 μmol) of Intermediate 159 were taken up in 1 ml of DMF and admixed with 0.76 mg (6 μmol) of L-cysteine. The reaction mixture was stirred at RT for 2 hours, then concentrated under reduced pressure and subsequently purified by preparative HPLC. This gave 2.6 mg (65% of theory of the title compound.

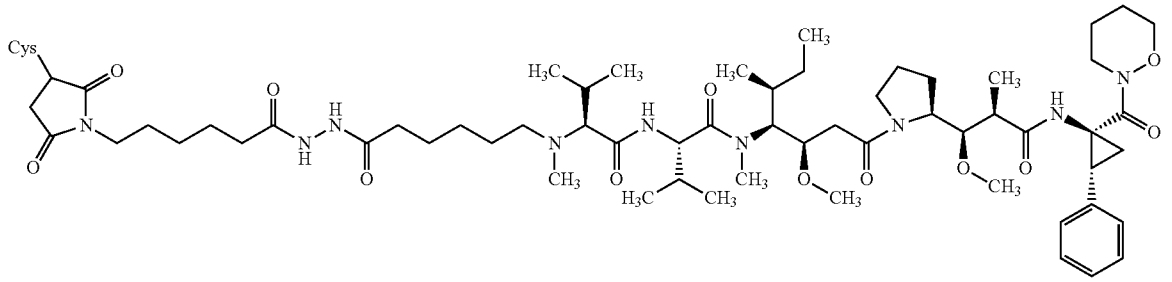
[4519] HPLC (Method 5): R_t=1.75 min;

[4520] LC-MS (Method 1): R_t=0.85 min; MS (ESIpos): m/z=1235 $(M+H)^+$.

Example 70

N-(6-{2-[6-(3-{[(2R)-2-Amino-2-carboxyethyl]sulphanyl}-2,5-dioxopyrrolidin-1-yl)hexanoyl]hydrazino}-6-oxohexyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-{[(1S,2R)-1-(1,2-oxazinan-2-ylcarbonyl)-2-phenylcyclopropyl]amino}-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[4521]



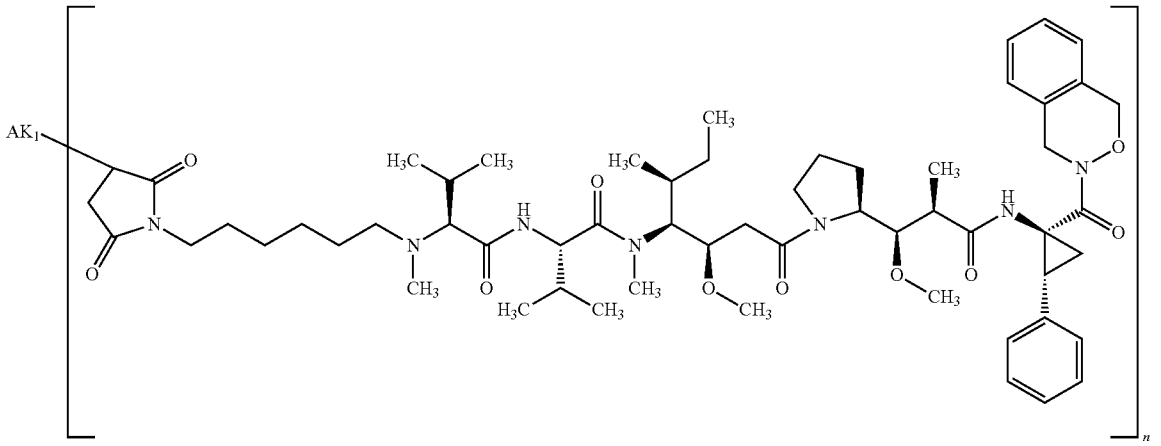
[4522] 3.6 mg (3 μmol) of Intermediate 129 were taken up in 1 ml of DMF and admixed with 0.77 mg (6 μmol) of L-cysteine. The reaction mixture was stirred at RT for 2 hours, then concentrated under reduced pressure and subsequently purified by preparative HPLC. This gave 1.55 mg (39% of theory of the title compound.

[4523] HPLC (Method 5): R_t=1.6 min;

[4524] LC-MS (Method 1): R_t=0.87 min; MS (ESIpos): m/z=1255 $(M+H)^+$.

Example 71

[4525]



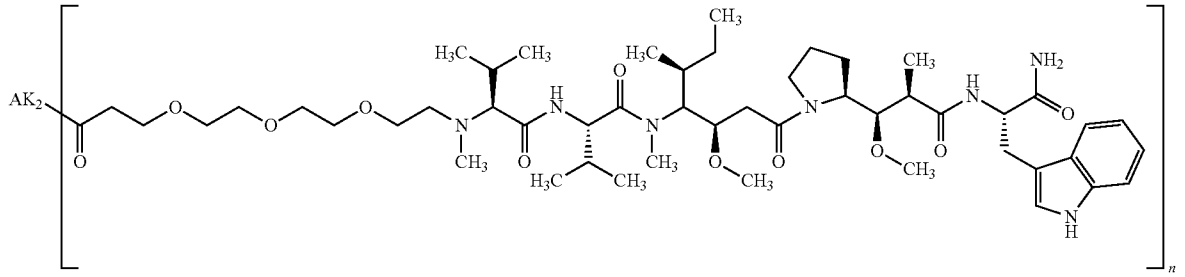
[4526] Coupling here was carried out using 5 mg of MF-Ta in PBS and the reaction mixture, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

[4527] Protein concentration: 0.9 mg/ml

[4528] Drug/mAb Ratio: 1

Example 72

[4529]



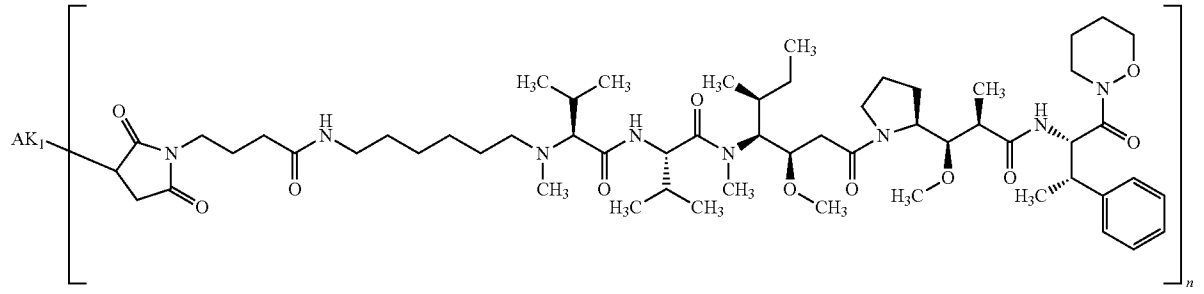
[4530] Coupling here was carried out using 5 mg of MF-Ta in PBS and the reaction mixture, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

[4531] Protein concentration: 1.86 mg/ml

[4532] Drug/mAb Ratio: 2.9

Example 73

[4533]



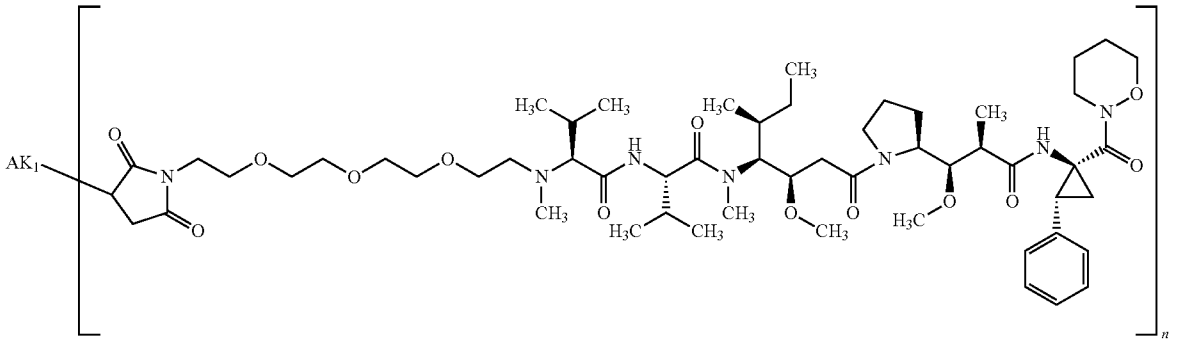
[4534] Coupling here was carried out using 5 mg of MF-Ta in PBS and the reaction mixture, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

[4535] Protein concentration: 1.05 mg/ml

[4536] Drug/mAb Ratio: 4.4

Example 74

[4537]



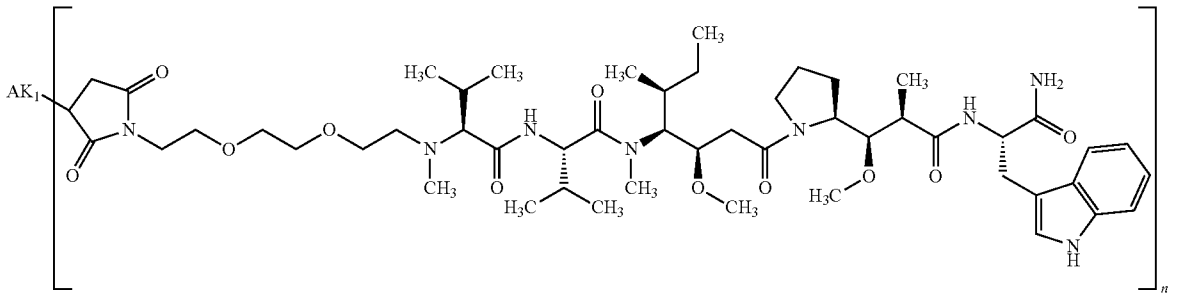
[4538] Coupling here was carried out using 5 mg of MF-Ta in PBS and the reaction mixture, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

[4539] Protein concentration: 1.13 mg/ml

[4540] Drug/mAb Ratio: 2.8

Example 75

[4541]



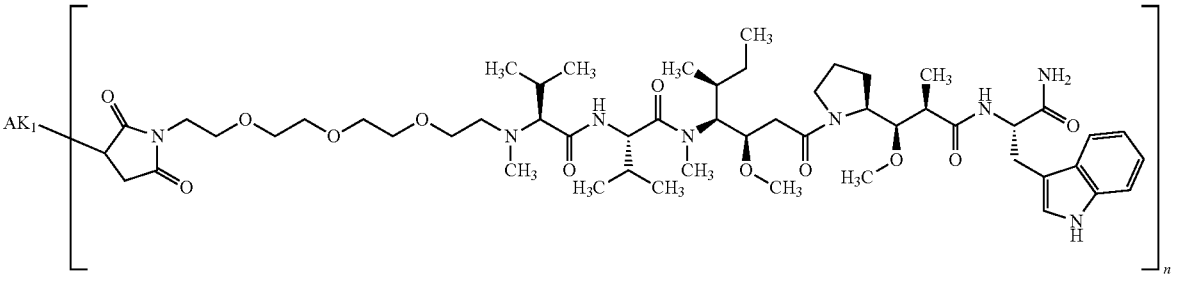
[4542] Coupling here was carried out using 5 mg of MF-Ta in PBS and the reaction mixture, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

[4543] Protein concentration: 1.41 mg/ml

[4544] Drug/mAb Ratio: 3.9

Example 76

[4545]



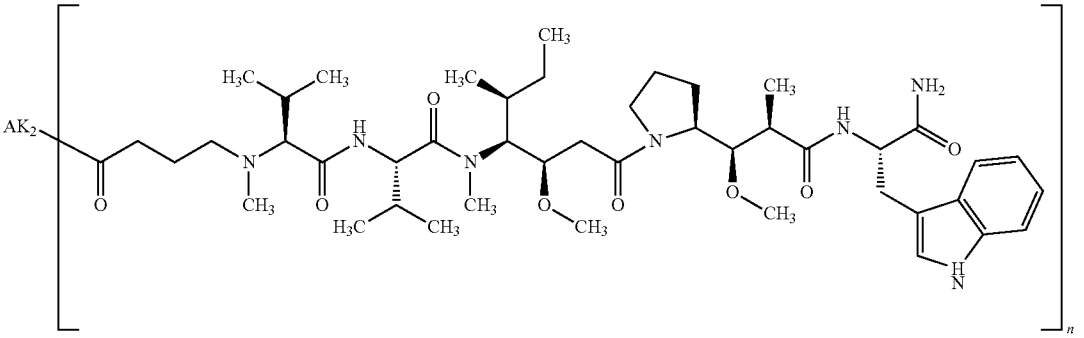
[4546] Coupling here was carried out using 5 mg of MF-Ta in PBS and the reaction mixture, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

[4547] Protein concentration: 1.38 mg/ml

[4548] Drug/mAb Ratio: 4.3

Example 77

[4549]



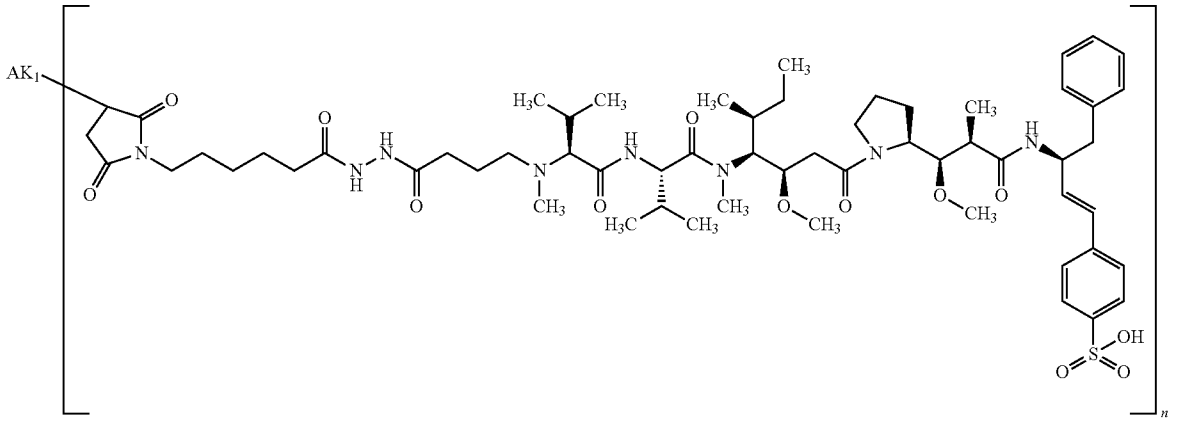
[4550] Coupling here was carried out using 5 mg of MF-Ta in PBS and the reaction mixture, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

[4551] Protein concentration: 1.32 mg/ml

[4552] Drug/mAb Ratio: 1

Example 78

[4553]



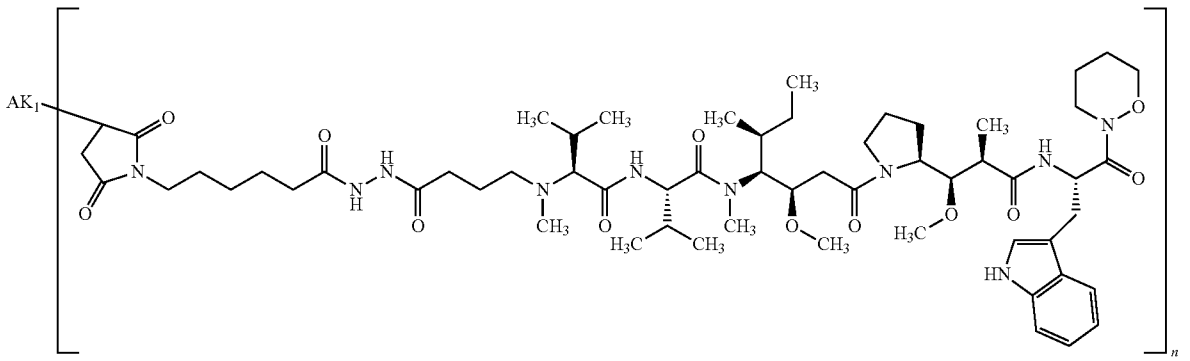
[4554] Coupling here was carried out using 5 mg of MF-Ta in PBS and the reaction mixture, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

[4555] Protein concentration: 1.14 mg/ml

[4556] Drug/mAb Ratio: 5.3

Example 79

[4557]



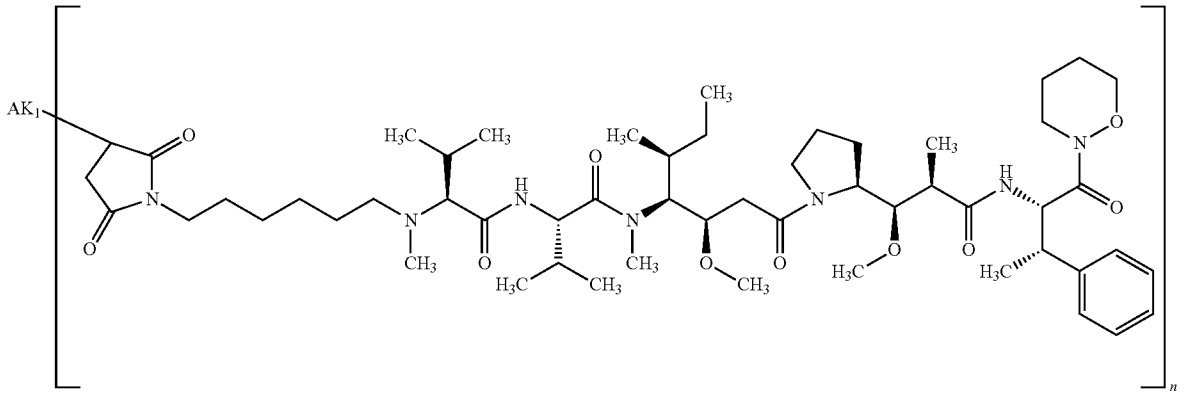
[4558] Coupling here was carried out using 5 mg of MF-Ta in PBS and the reaction mixture, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

[4559] Protein concentration: 1.25 mg/ml

[4560] Drug/mAb Ratio: 4.8

Example 80

[4561]



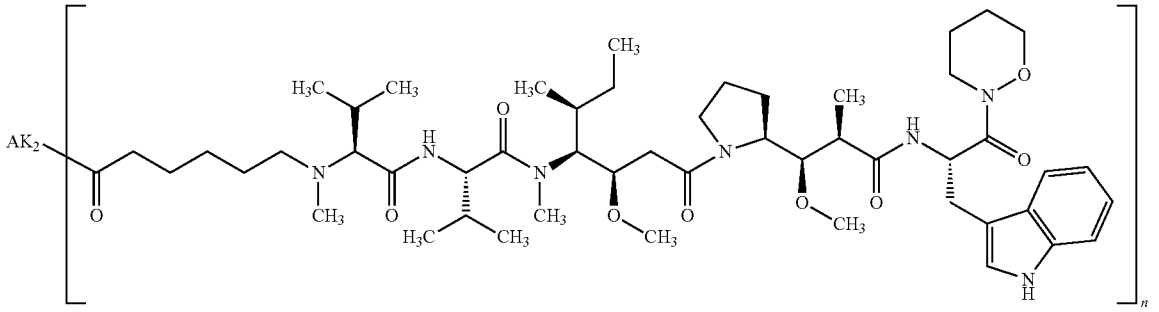
[4562] Coupling here was carried out using 5 mg of MF-Ta in PBS and the reaction mixture, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

[4563] Protein concentration: 1.12 mg/ml

[4564] Drug/mAb Ratio: 1.7

Example 81

[4565]



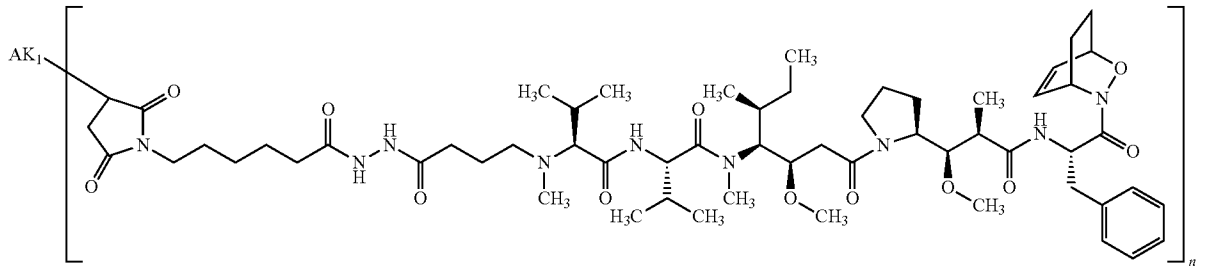
[4566] Coupling here was carried out using 150 mg of MF-Ta in PBS and the reaction mixture, following Sephadex purification, was concentrated by ultracentrifugation, re-diluted with PBS and concentrated again.

[4567] Protein concentration: 12.2 mg/ml

[4568] Drug/mAb Ratio: 4.1

Example 82

[4569]



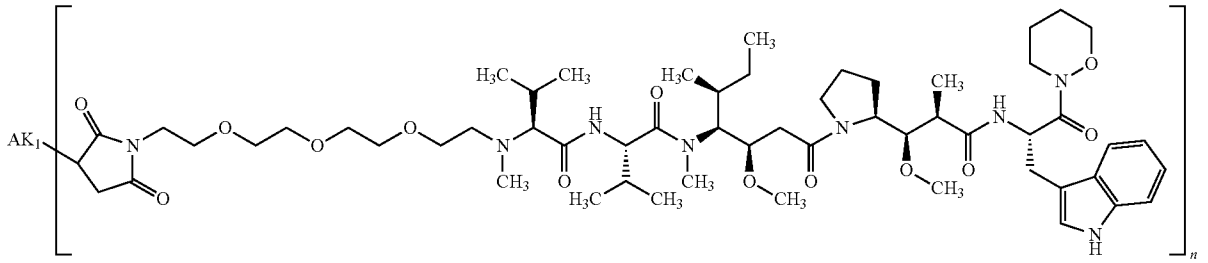
[4570] Coupling here was carried out using 5 mg of MF-Ta in PBS and the reaction mixture, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

[4571] Protein concentration: 0.86 mg/ml

[4572] Drug/mAb Ratio: 3.4

Example 83

[4573]



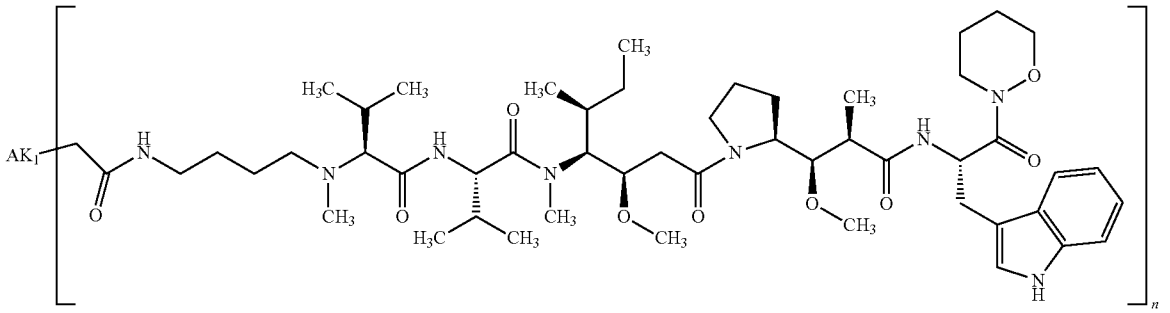
[4574] Coupling here was carried out using 5 mg of MF-Ta in PBS and the reaction mixture, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

[4575] Protein concentration: 1.43 mg/ml

[4576] Drug/mAb Ratio: 3.7

Example 84

[4577]



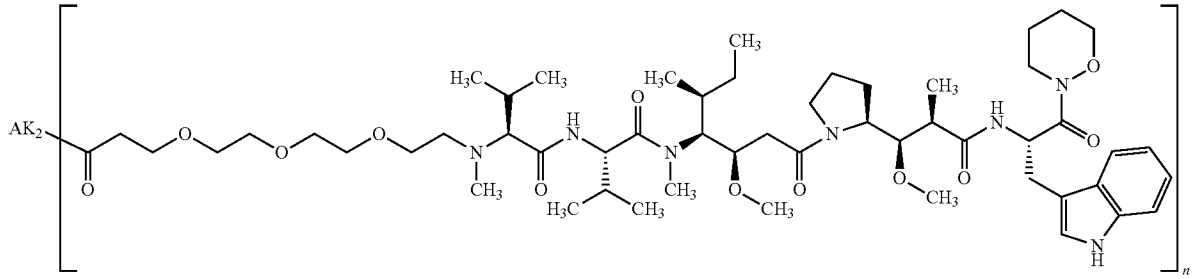
[4578] Coupling here was carried out using 5 mg of MF-Ta in PBS and the reaction mixture, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

[4579] Protein concentration: 0.8 mg/ml

[4580] Drug/mAb Ratio: 0.7

Example 85

[4581]



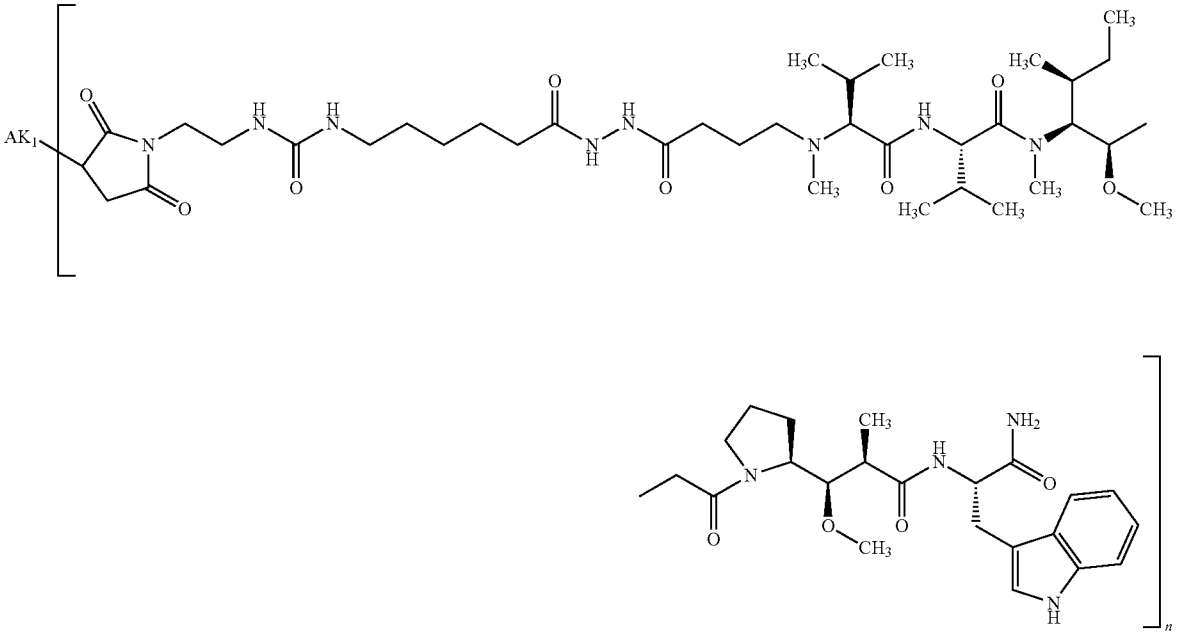
[4582] Coupling here was carried out using 50 mg of MF-Ta in PBS and the reaction mixture, following Sephadex purification, was concentrated by ultracentrifugation, re-diluted with PBS and concentrated again.

[4583] Protein concentration: 9.5 mg/ml

[4584] Drug/mAb Ratio: 2.9

Example 86

[4585]



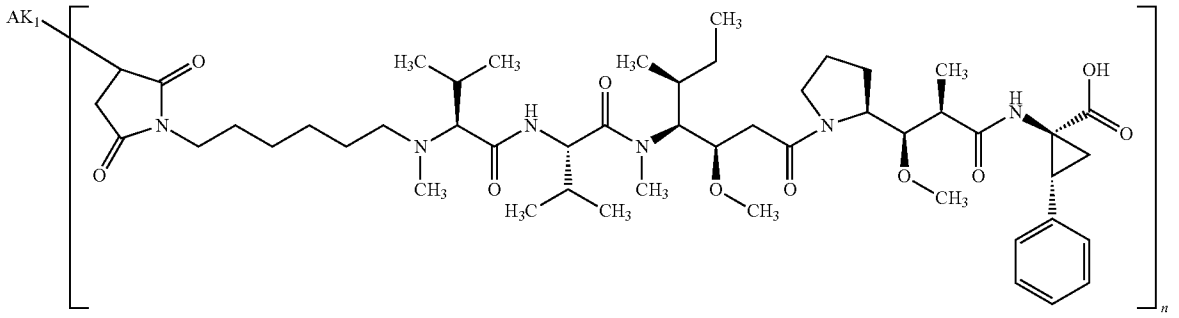
[4586] Coupling here was carried out using 5 mg of MF-Ta in PBS and the reaction mixture, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

[4587] Protein concentration: 1.52 mg/ml

[4588] Drug/mAb Ratio: 3.2

Example 87

[4589]



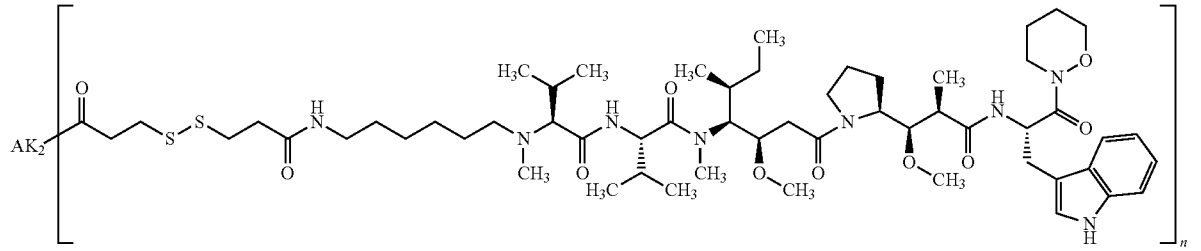
[4590] Coupling here was carried out using 5 mg of MF-Ta in PBS and the reaction mixture, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

[4591] Protein concentration: 1.25 mg/ml

[4592] Drug/mAb Ratio: 4.6

Example 88

[4593]



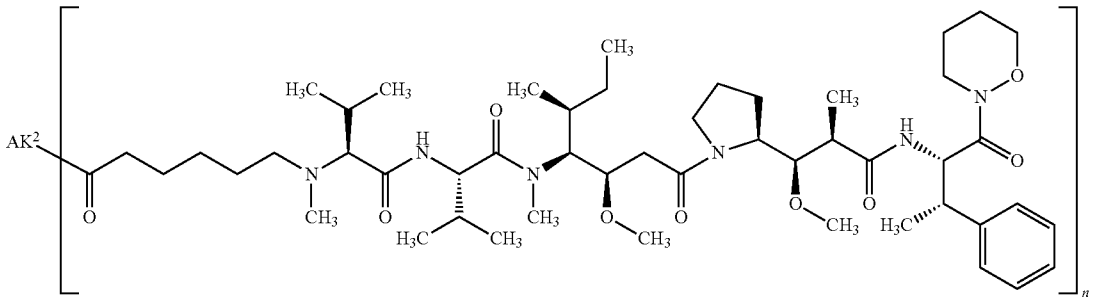
[4594] Coupling here was carried out using 5 mg of MF-Ta in PBS and the reaction mixture, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

[4595] Protein concentration: 1.47 mg/ml

[4596] Drug/mAb Ratio: 1.6

Example 89

[4597]



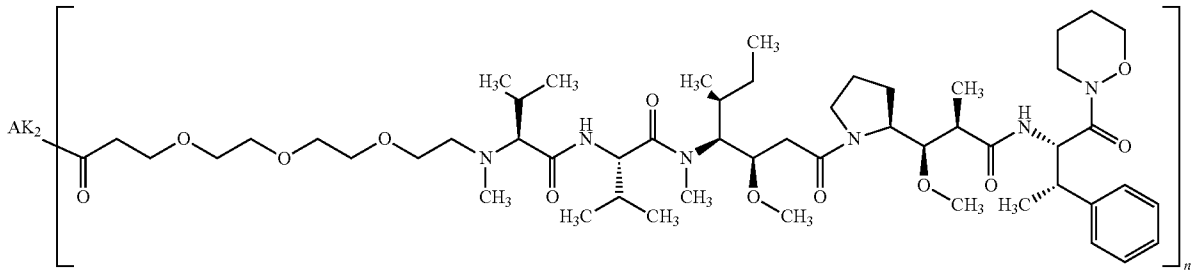
[4598] Coupling here was carried out using 5 mg of MF-Ta in PBS and the reaction mixture, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

[4599] Protein concentration: 0.99 mg/ml

[4600] Drug/mAb Ratio: 5.5

Example 90

[4601]



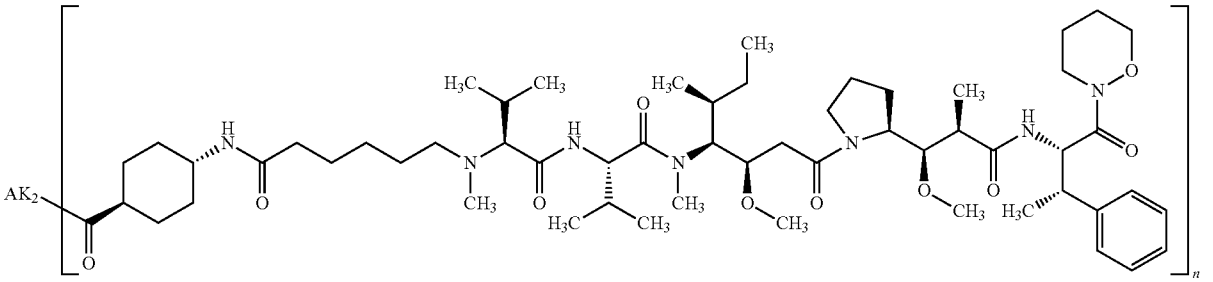
[4602] Coupling here was carried out using 5 mg of MF-Ta in PBS and the reaction mixture, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

[4603] Protein concentration: 1.02 mg/ml

[4604] Drug/mAb Ratio: 4.0

Example 91

[4605]



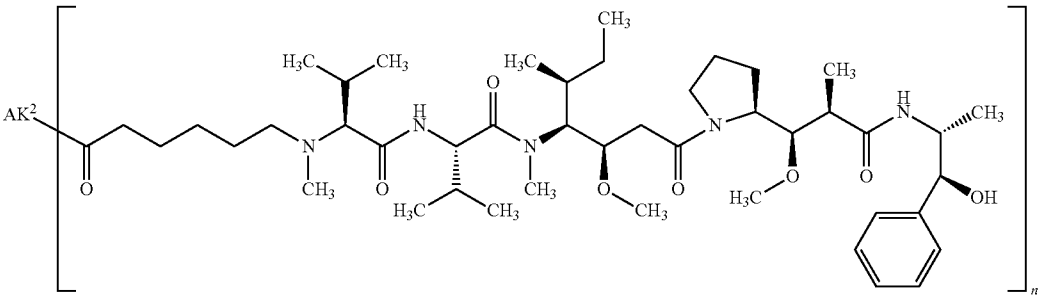
[4606] Coupling here was carried out using 5 mg of MF-Ta in PBS and the reaction mixture, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

[4607] Protein concentration: 1.63 mg/ml

[4608] Drug/mAb Ratio: 3.8

Example 92

[4609]



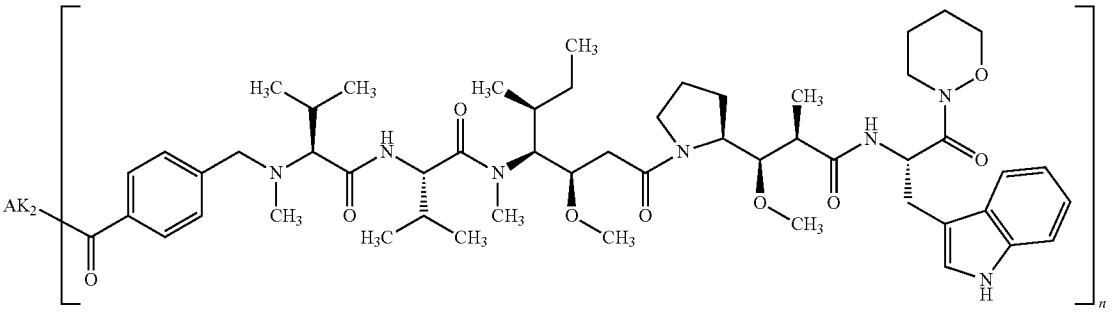
[4610] Coupling here was carried out using 5 mg of MF-Ta in PBS and the reaction mixture, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

[4611] Protein concentration: 1.27 mg/ml

[4612] Drug/mAb Ratio: 3.0

Example 93

[4613]



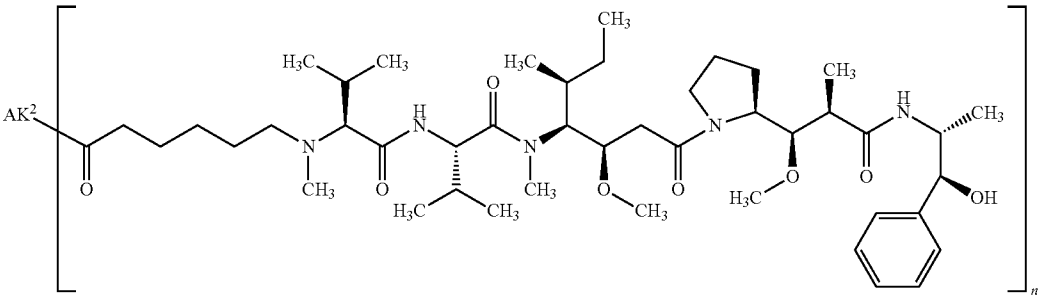
[4614] Coupling here was carried out using 5 mg of MF-Ta in PBS and the reaction mixture, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

[4615] Protein concentration: 1.58 mg/ml

[4616] Drug/mAb-Ratio: 0.6

Example 94

[4617]



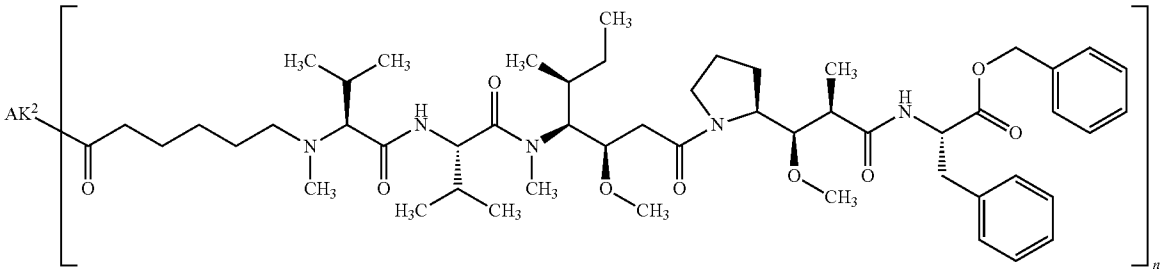
[4618] Coupling here was carried out using 5 mg of MF-Ta in PBS and the reaction mixture, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

[4619] Protein concentration: 1.31 mg/ml

[4620] Drug/mAb Ratio: 6.6

Example 95

[4621]



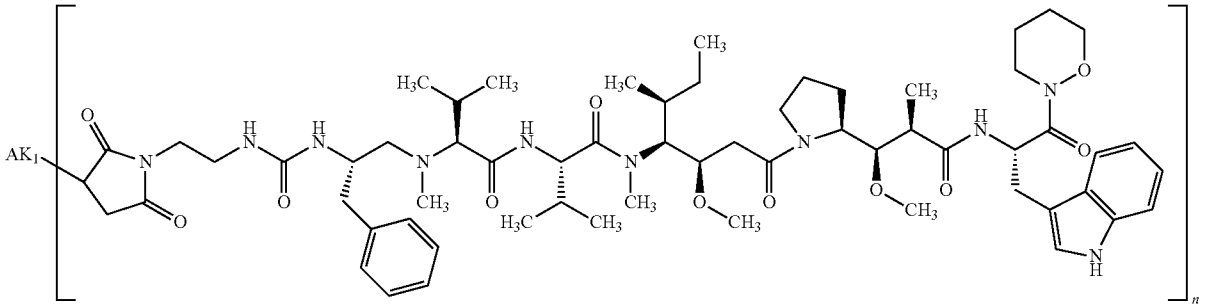
[4622] Coupling here was carried out using 5 mg of MF-Ta in PBS and the reaction mixture, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

[4623] Protein concentration: 1.75 mg/ml

[4624] Drug/mAb Ratio: 1.8

Example 96

[4625]



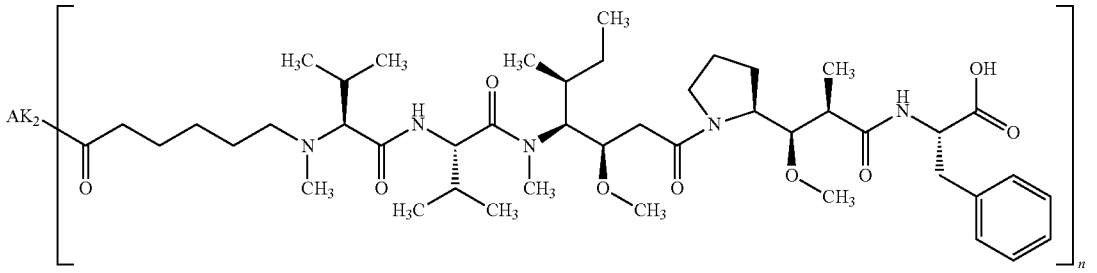
[4626] Coupling here was carried out using 5 mg of MF-Ta in PBS and the reaction mixture, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

[4627] Protein concentration: 1.44 mg/ml

[4628] Drug/mAb Ratio: 2.5

Example 97

[4629]



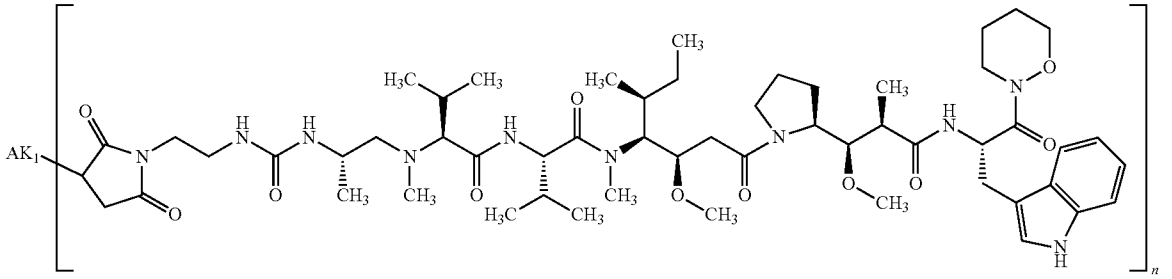
[4630] Coupling here was carried out using 5 mg of MF-Ta in PBS and the reaction mixture, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

[4631] Protein concentration: 1.96 mg/ml

[4632] Drug/mAb Ratio: 5.6

Example 98

[4633]



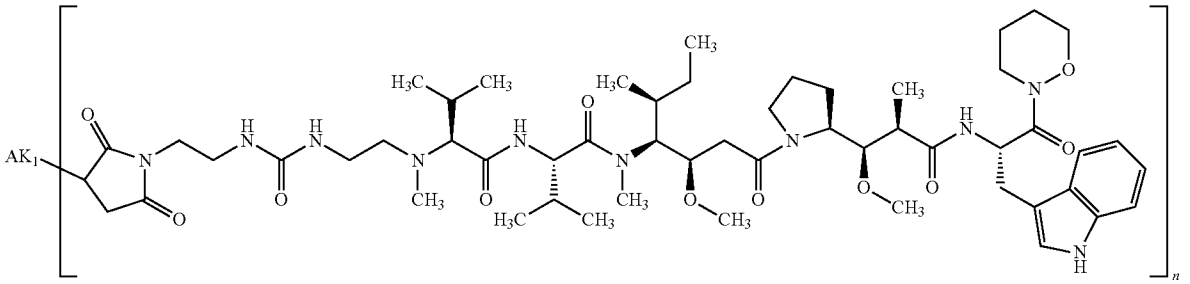
[4634] Coupling here was carried out using 5 mg of MF-Ta in PBS and the reaction mixture, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

[4635] Protein concentration: 1.58 mg/ml

[4636] Drug/mAb Ratio: 4.2

Example 99

[4637]



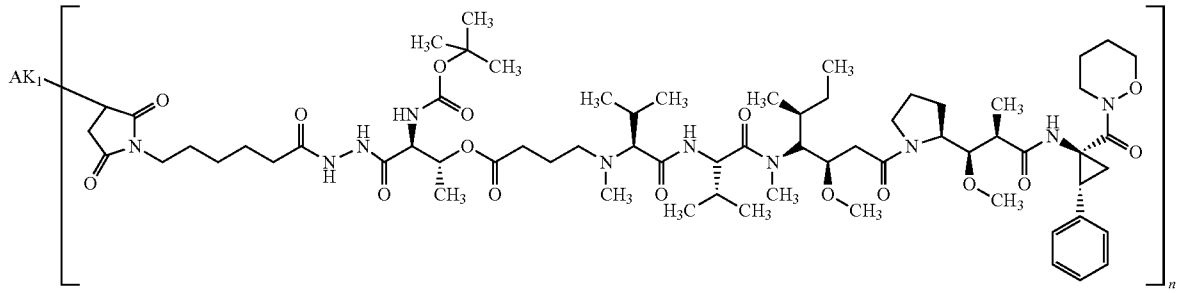
[4638] Coupling here was carried out using 5 mg of MF-Ta in PBS and the reaction mixture, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

[4639] Protein concentration: 1.48 mg/ml

[4640] Drug/mAb Ratio: 4.6

Example 100

[4641]



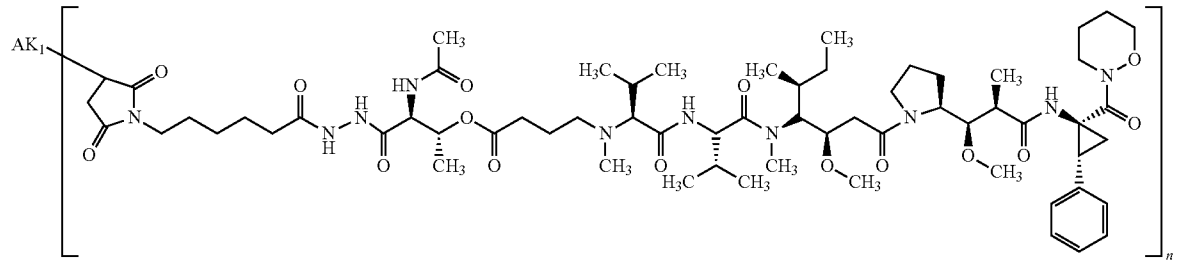
[4642] Coupling here was carried out using 5 mg of MF-Ta in PBS and the reaction mixture, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

[4643] Protein concentration: 1.5 mg/ml

[4644] Drug/mAb Ratio: 3.1

Example 101

[4645]



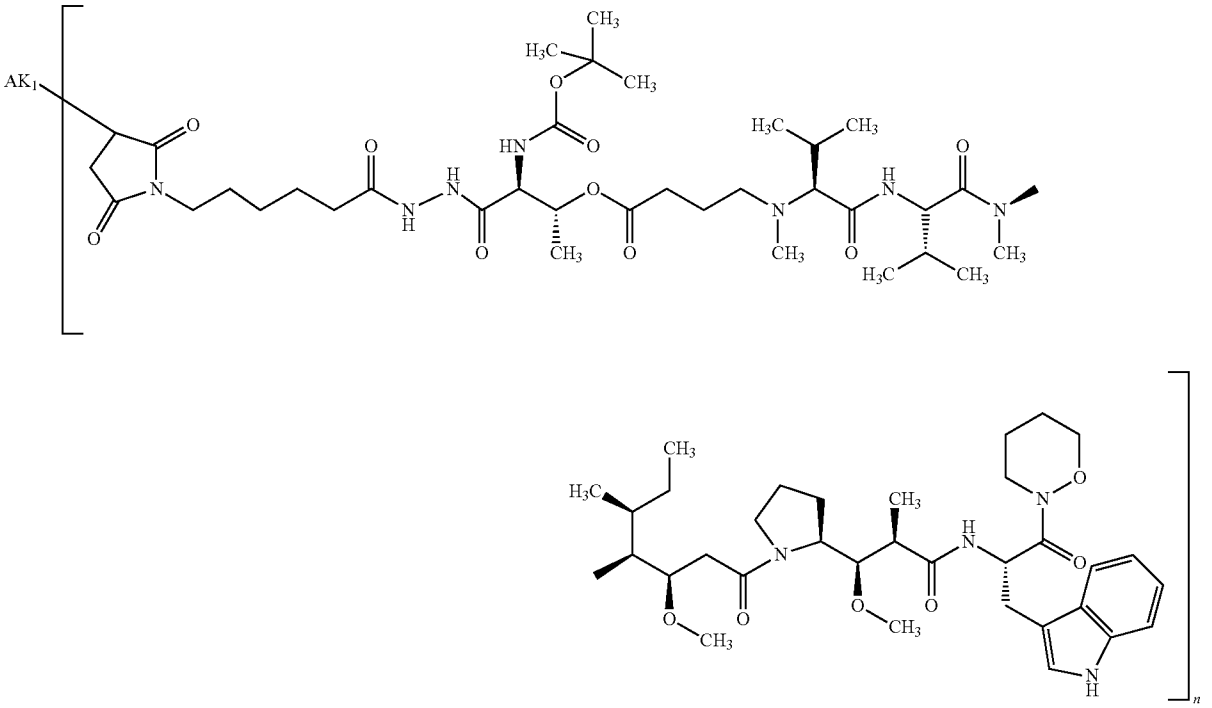
[4646] Coupling here was carried out using 5 mg of MF-Ta in PBS and the reaction mixture, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

[4647] Protein concentration: 1.3 mg/ml

[4648] Drug/mAb Ratio: 4.3

Example 102

[4649]



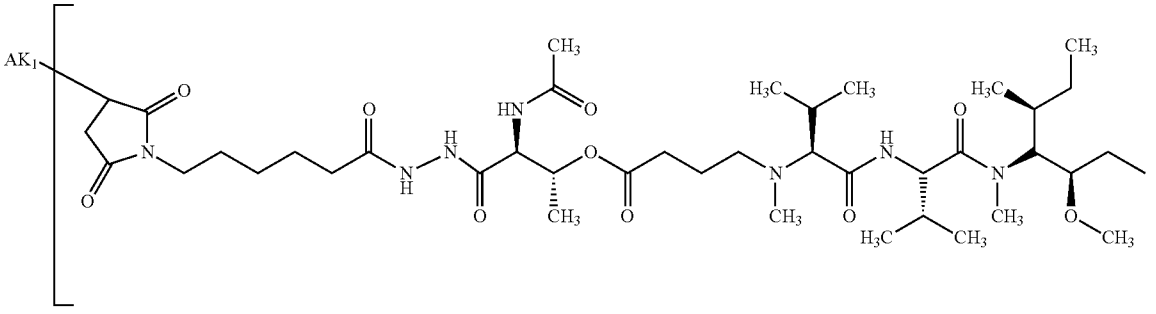
[4650] Coupling here was carried out using 5 mg of MF-Ta in PBS and the reaction mixture, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

[4651] Protein concentration: 1.62 mg/ml

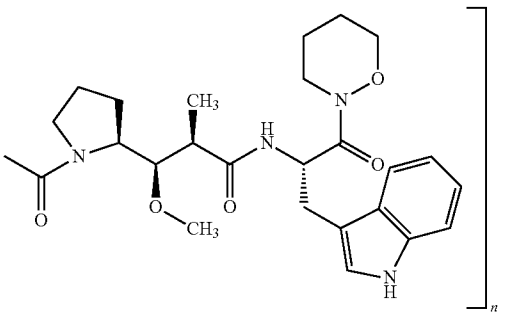
[4652] Drug/mAb Ratio: 2.2

Example 103

[4653]



-continued



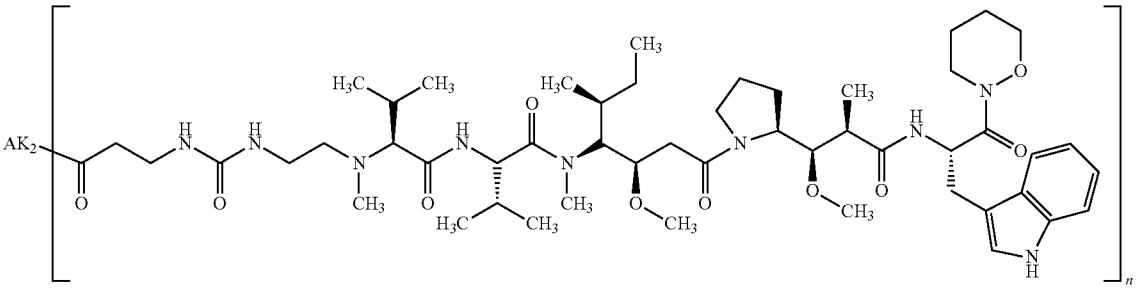
[4654] Coupling here was carried out using 5 mg of MF-Ta in PBS and the reaction mixture, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

[4655] Protein concentration: 1.37 mg/ml

[4656] Drug/mAb Ratio: 2.8

Example 104

[4657]



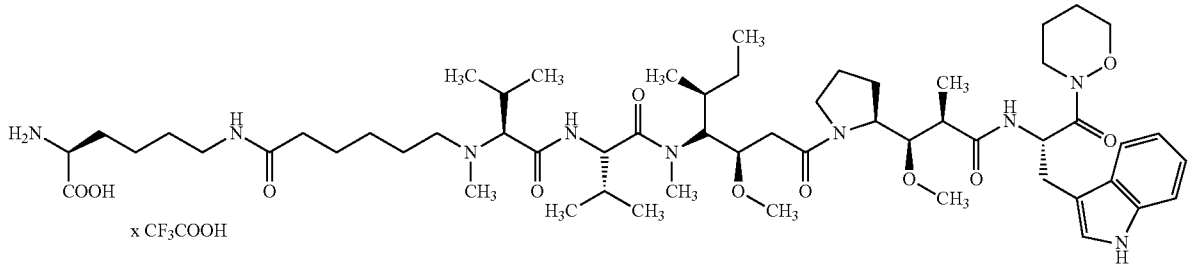
[4658] Coupling here was carried out using 5 mg of MF-Ta in PBS and the reaction mixture, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

[4659] Protein concentration: 1.43 mg/ml

[4660] Drug/mAb Ratio: 4.0

Example 105

[4661] N-(6-{[(5S)-5-Amino-5-carboxypentyl]amino}-6-oxohexyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide trifluoroacetate



[4662] 15.5 mg (15 μmol) of Intermediate 210 were taken up in 5 ml of DMF and admixed with 4.4 mg (18 μmol) of N^2-(tert-butoxycarbonyl)-L-lysine and also 7.7 μL (44 μmol) of N,N-diisopropylethylamine. The reaction mixture was stirred at RT overnight and then concentrated under reduced pressure. The residue was subsequently purified by preparative HPLC. This gave 14 mg (81% of theory) of the protected intermediate of the title compound, which was subsequently taken up in 1 ml of dichloromethane and deprotected with 1 ml of trifluoroacetic acid. The reaction mixture was concentrated and, following lyophilization of the residue from acetonitrile/water 1:1, 15 mg (97% of theory) of the title compound were obtained.

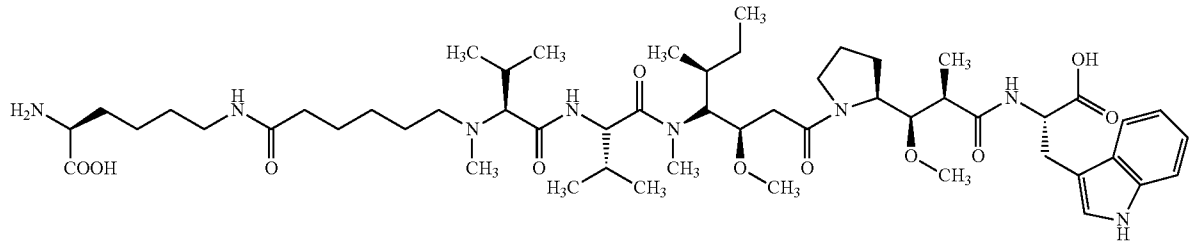
[4663] HPLC (Method 12): R_t=1.8 min;

[4664] LC-MS (Method 1): R_t=0.79 min; MS (ESIpos): m/z=1083 $(M+H)^+$.

Example 106

N-(6-{[(5S)-5-Amino-5-carboxypentyl]amino}-6-oxohexyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(1S)-1-carboxy-2-(1H-indol-3-yl)ethyl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide

[4665]



[4666] 40 mg (40 μmol) of Intermediate 227 were taken up in 5 ml of DMF and admixed with 11.5 mg (40 μmol) of N^2-[(benzyloxy)carbonyl]-L-lysine and also 13 μL (80 μmol) of N,N-diisopropylethylamine. The reaction mixture was stirred at RT overnight, then concentrated under reduced pressure and subsequently purified by preparative HPLC. This gave 32.5 mg (70% of theory) of the protected intermediate of the title compound.

[4667] This 32.5 mg of the intermediate were dissolved in 10 ml of methanol and, following addition of 2 mg of 10% palladium on activated carbon, were hydrogenated under standard hydrogen pressure at RT for 30 minutes. The catalyst was then removed by filtration and the solvent was removed under reduced pressure. Lyophilization of the residue from dioxane/water 1:1 gave 26 mg (99% of theory) of the title compound.

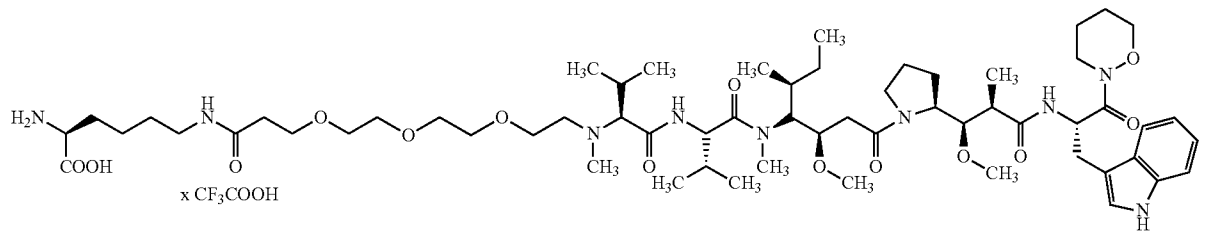
[4668] HPLC (Method 12): R_t=1.7 min;

[4669] LC-MS (Method 1): R_t=0.76 min; MS (ESIpos): m/z=1014 $(M+H)^+$.

Example 107

N-[(18S)-18-Amino-18-carboxy-12-oxo-3,6,9-trioxa-13-azaoctadec-1-yl]-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide trifluoroacetate

[4670]



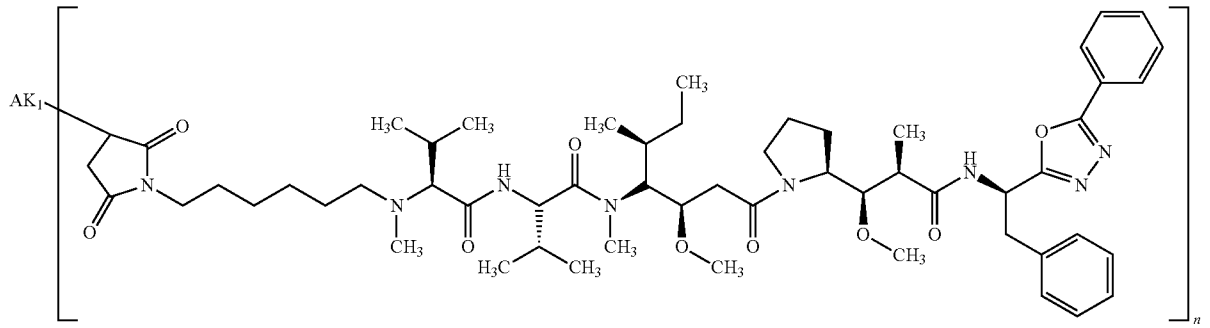
[4671] 3.5 mg (3 μmol) of Intermediate 202 were taken up in 2 ml of DMF and admixed with 0.8 mg (3 μmol) of N^2-(tert-butoxycarbonyl)-L-lysine and also 1.6 μL (10 μmol) of N,N-diisopropylethylamine. The reaction mixture was stirred at RT overnight and then concentrated under reduced pressure. The residue was taken up in acetonitrile/water: 1:1, brought to a pH of 2 with trifluoroacetic acid and then purified by preparative HPLC. This gave 1 mg (25% of theory) of the protected intermediate of the title compound, which was subsequently taken up in 500 μl of dichloromethane and deprotected with 500 μl of trifluoroacetic acid. The reaction mixture was concentrated and, following lyophilization of the residue from acetonitrile/water 1:1, 1 mg (89% of theory) of the title compound was obtained.

[4672] HPLC (Method 12): R_t=1.9 min;

[4673] LC-MS (Method 1): R_t=0.82 min; MS (ESIpos): m/z=1173 $(M+H)^+$.

Example 108

[4674]



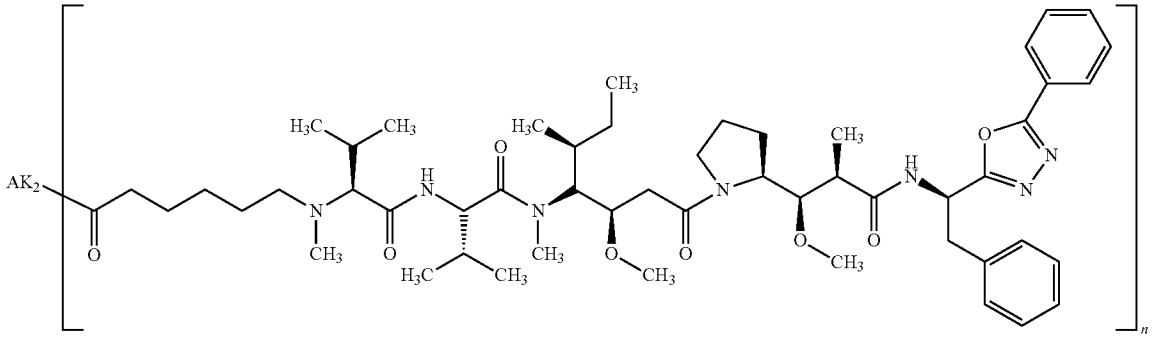
[4675] Coupling here was carried out using 5 mg of MF-Ta in PBS, and the batch, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

[4676] Protein concentration: 0.81 mg/ml

[4677] Drug/mAb Ratio: 2.5

Example 109

[4678]



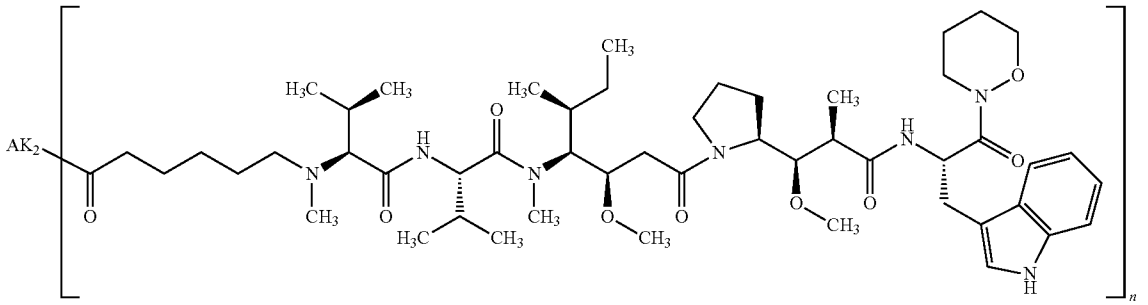
[4679] Coupling here was carried out using 5 mg of MF-Ta and the batch, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

[4680] Protein concentration: 1.06 mg/ml

[4681] Drug/mAb Ratio: 1.8

Example 110

[4682]



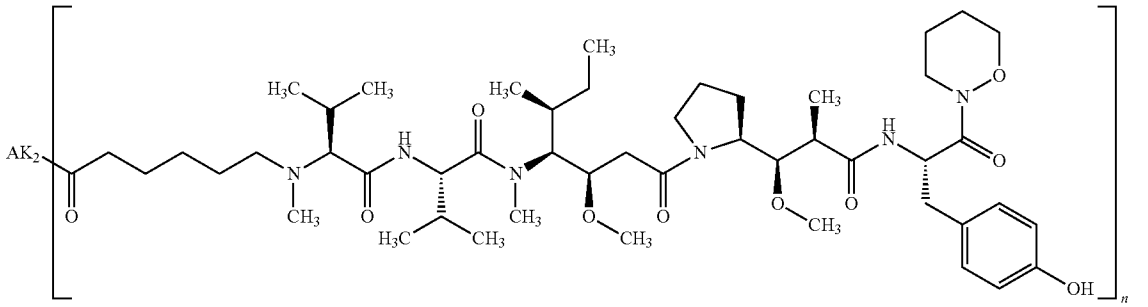
[4683] Coupling here was carried out using 5 mg of MF-Ta and the reaction mixture, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted with PBS.

[4684] Protein concentration: 1.36 mg/ml

[4685] Drug/mAb Ratio: 7.2

Example 111

[4686]



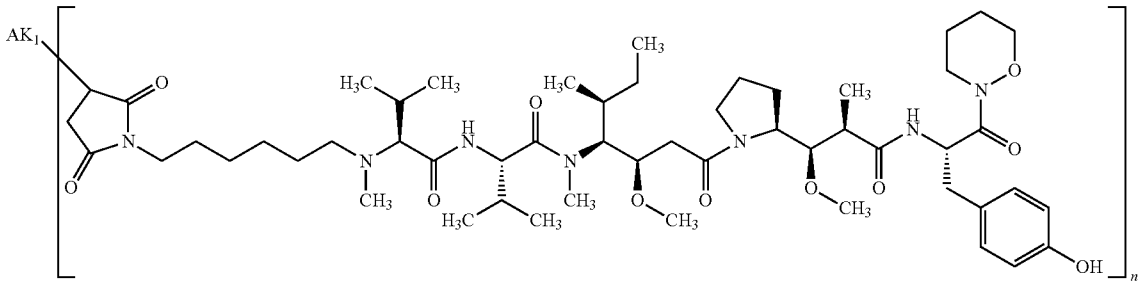
[4687] Coupling here was carried out using 5 mg of MF-Ta and the reaction mixture, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted with PBS.

[4688] Protein concentration: 1.57 mg/ml

[4689] Drug/mAb Ratio: 2.9

Example 112

[4690]



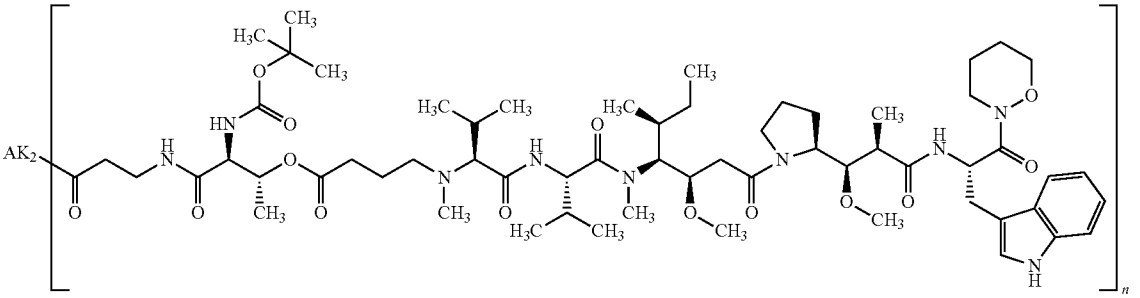
[4691] Coupling here was carried out using 5 mg of MF-Ta in PBS, and the batch, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

[4692] Protein concentration: 1.44 mg/ml

[4693] Drug/mAb Ratio: 2.5

Example 113

[4694]



[4695] Coupling here was carried out using 5 mg of MF-Ta in PBS, and the batch, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted.

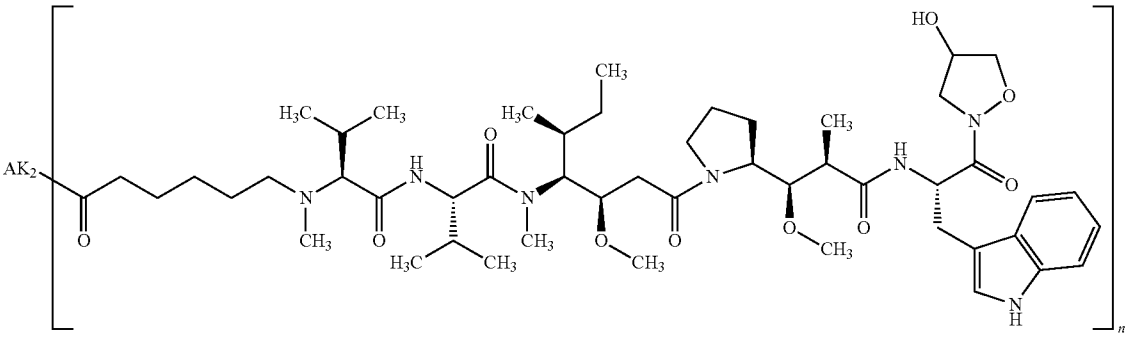
[4696] Protein concentration: 1.74 mg/ml

[4697] Drug/mAb Ratio: 3.6

Example 114

Diastereomer 1

[4698]



[4699] Coupling here was carried out using Intermediate 247a and 5 mg of MF-Ta in PBS and the batch, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted with PBS.

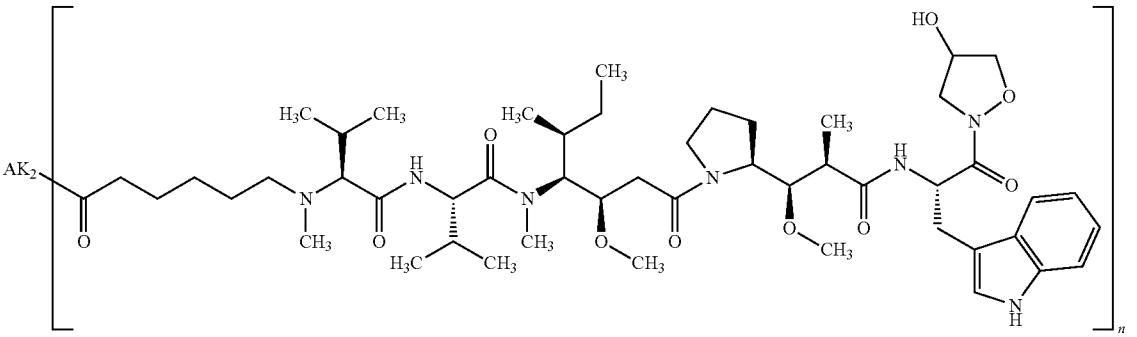
[4700] Protein concentration: 1.57 mg/ml

[4701] Drug/mAb Ratio: 4.2

Example 115

Diastereomer 2

[4702]



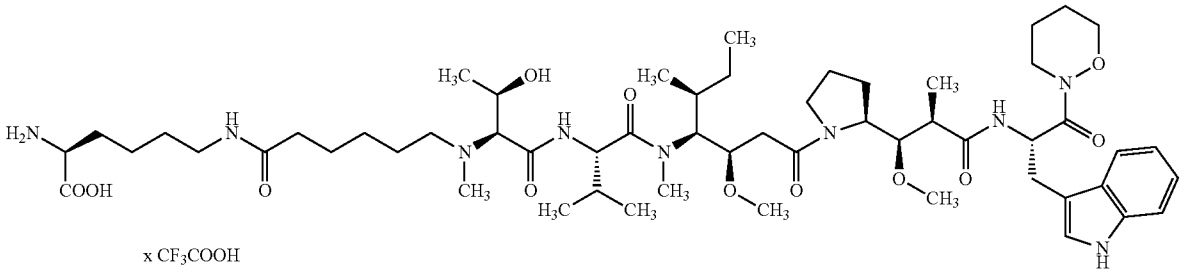
[4703] Coupling here was carried out using Intermediate 247b and 5 mg of MF-Ta in PBS and the batch, following Sephadex purification, was concentrated by ultracentrifugation and re-diluted with PBS.

[4704] Protein concentration: 1.42 mg/ml

[4705] Drug/mAb Ratio: 4.0

Example 116

[4706] N-(6-{[(5S)-5-Amino-5-carboxypentyl]amino}-6-oxohexyl)-N-methyl-L-threonyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide trifluoroacetate



[4707] 8.6 mg (8 μmol) of Intermediate 240 were taken up in 5 ml of DMF and admixed with 4.0 mg (16 μmol) of N^2-(tert-butoxycarbonyl)-L-lysine and also 2 μL (16 μmol) of N,N-diisopropylethylamine. The reaction mixture was stirred at RT for 4 hours, then admixed again with the same amounts of N^2-(tert-butoxycarbonyl)-L-lysine and N,N-diisopropylethylamine, and stirred at RT overnight. The batch was subsequently concentrated under reduced pressure. The residue was then purified by preparative HPLC. This gave 7 mg (72% of theory) of the protected intermediate of the title compound, which was subsequently taken up in 1 ml of dichloromethane and deprotected with 0.5 ml of trifluoroacetic acid. The batch was concentrated and the residue was purified by preparative HPLC. Drying under a high vacuum gave 3.3 mg (47% of theory) of the title compound.

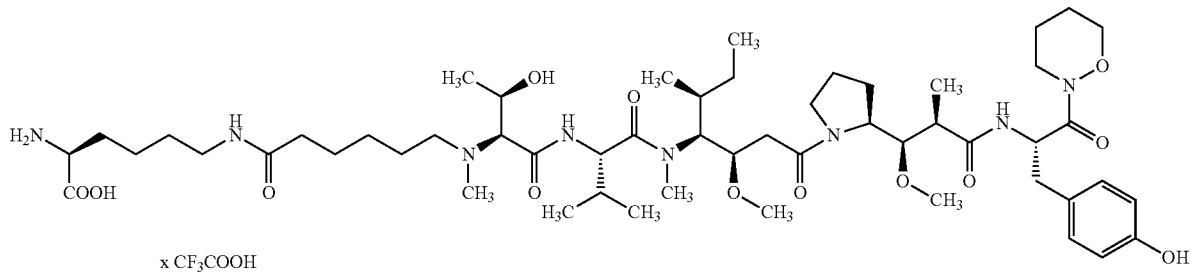
[4708] HPLC (Method 5): R_t=1.5 min;

[4709] LC-MS (Method 1): R_t=0.8 min; MS (ESIpos): m/z=1084 $(M+H)^+$.

Example 117

N-(6-{[(5S)-5-Amino-5-carboxypentyl]amino}-6-oxohexyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(4-hydroxyphenyl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide trifluoroacetate

[4710]



x CF_3COOH

[4711] 8 mg (8 μmol) of Intermediate 242 were taken up in 3 ml of DMF and admixed with 2.9 mg (12 μmol) of N^2-(tert-butoxycarbonyl)-L-lysine and also 2.7 μL (16 μmol) of N,N-diisopropylethylamine. The reaction mixture was stirred at RT overnight, then admixed again with the same amounts of N^2-(tert-butoxycarbonyl)-L-lysine and N,N-diisopropylethylamine, and stirred at RT for a further 4 hours. The batch was subsequently concentrated under reduced pressure. The residue was then purified by preparative HPLC. Lyophilization from acetonitrile/water gave 6.5 mg (72% of theory) of the protected intermediate of the title compound, which was subsequently taken up in 5 ml of dichloromethane and deprotected with 0.75 ml of trifluoroacetic acid. The batch was concentrated, and lyophilization of the residue from dioxane/water gave 5 mg (76% of theory) of the title compound.

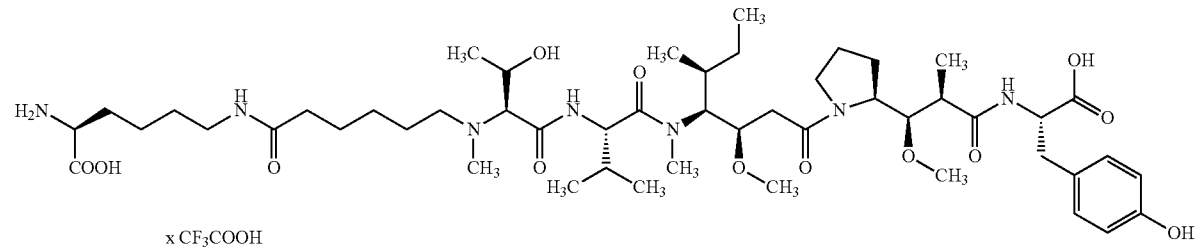
[4712] HPLC (Method 12): R_t=1.7 min;

[4713] LC-MS (Method 1): R_t=0.69 min; MS (ESIpos): m/z=1059 $(M+H)^+$.

Example 118

N-(6-{[(5S)-5-Amino-5-carboxypentyl]amino}-6-oxohexyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(1S)-1-carboxy-2-(4-hydroxyphenyl)ethyl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide trifluoroacetate

[4714]



x CF_3COOH

[4715] 38 mg (41 μmol) of Intermediate 248 were first converted into the N-hydroxysuccinimide ester. 72 mg of the crude product obtained were taken up in 5 ml of DMF and admixed with 24 mg (100 μmol) of N^2-(tert-butoxycarbonyl)-L-lysine and 23 μL of N,N-diisopropylethylamine. The reaction mixture was stirred at RT overnight, and then admixed again with 16 mg of N^2-(tert-butoxycarbonyl)-L-lysine and 12 μL of N,N-diisopropylethylamine, and subsequently treated in an ultrasound bath for a further 2 hours. The batch was then concentrated under reduced pressure and the residue was purified by preparative HPLC. Lyophilization from acetonitrile/water gave 20 mg (50% of theory) of the protected intermediate of the title compound.

[4716] 15 mg (12 μmol) of this intermediate were subsequently taken up in 3 ml of dichloromethane and admixed with 1 ml of trifluoroacetic acid. After 40 minutes of stirring at RT, a further 1.5 ml of trifluoroacetic acid were added and the batch was treated in an ultrasound bath for 1 hour. Thereafter the batch was concentrated, and lyophilization of the residue from dioxane/water gave 13 mg (90% of theory) of the title compound.

[4717] HPLC (Method 12): R_t=1.5 min;

[4718] LC-MS (Method 1): R_t=0.68 min; MS (ESIpos): m/z=990 $(M+H)^+$.

C: EVALUATION OF BIOLOGICAL ACTIVITY

[4719] The biological effect of the compounds of the invention can be demonstrated by the assays described below

C-1. In Vitro Cell Proliferation Tests

[4720] The cytotoxic activity of the conjugates of the invention was tested in an in vitro cell proliferation test. For this purpose, a mammalian cell which expresses either the target molecule of the binder endogenously or recombinantly was incubated with the conjugate of the invention. Cell proliferation was determined after an incubation time of several hours to several days, on the basis of the cell count in comparison to a control to which no conjugate was added. As further controls it is possible to add the unconjugated toxophore alone, or to use cells which do not express the target molecule of the binder. The cell count was determined by methods known to the skilled person, as for example by counting or through the use of an assay kit which allows the cell count to be determined via an ATP measurement (e.g. ATPlite™, Perkin-Elmer). In this way the IC_{50} of the conjugates of the invention was ascertained. By comparing the IC_{50} of the conjugate in measurements on cells which carry the target molecule of the binder, and non-carrying cells, it was possible to determine the selectivity of the conjugate.

C-2. Determination of the Antiproliferative Activity of Anti-Mesothelin ADC in the Human Colonic Carcinoma Cell Line HT29

[4721] A defined number of cells from the human colonic carcinoma cell line HT29 wt (2500 c/well, wildtype) was seeded out into a 96-well MTP in complete medium (10% FCS-RPMI) and incubated overnight at 37° C./5% carbon dioxide. In parallel to this, transfected HT29 cells which stably express mesothelin were plated out in complete medium in a 96-well MTP and incubated overnight (2500c/well; 37° C./5% carbon dioxide).

[4722] After 18 hours, the seeding medium was replaced by fresh medium with 10% FCS. Treatment commenced with the addition of the compounds of the invention. The transfected cells and the HT29 wt cells were treated identically here.

[4723] For the substances under investigation, dose-effect curves were determined in a concentration range of 10^{-5} M-10^{-14} M (1:10 dilution series).

[4724] Incubation times of 48 h-96 h were selected.

[4725] Proliferation was detected using the MTT assay (ATCC, Manassas, Va., USA, Catalogue No. 30-1010K). At the end of the selected incubation time, the HT29 wt cells were incubated with MTT for 4 h, followed by lysis of the cells overnight by addition of the detergent.

[4726] The dye formed was detected at 570 nm.

[4727] The proliferation of cells which were not treated with test substance but were otherwise identically treated was defined as the 100% figure. The data obtained from this test represents triplicate determinations, and at least two independent experiments were carried out.

[4728] Table 3 lists the IC_{50} values') of representative working examples from this assay:

[1]) The activity data reported relate to the working examples described in the present experimental section, with the drug/mAB ratios indicated. The values may possibly deviate for different drug/mAB ratios.

TABLE 3

Example	HT29 meso$^+$ IC_{50} [nM]	HT29 wt IC_{50} [nM]
1	0.17	5.3
2	0.4	162
3	5	22
4	1	13
5	0.06	8
5	0.16	5.4
6	0.019	0.27
7	20	>300
8	0.03	1
9	0.11	1.4
10	0.14	3.3
11	1.5	8.6
12	0.015	11
13	2	9
14	0.07	20
15	0.02	2
16	0.6	11
17	0.05	8
18	25	221
19	9	>50
20	0.2	0.29
21	0.35	3
22	0.8	3.6
23	1.1	6
24	0.5	5
25	4.4	14
26	0.02	1.4
27	24	>1000
28	0.3	31
29	6	14
30	0.2	2
31	0.45	>500
32	0.9	3
33	0.01	0.2
34	0.06	3.1
35	2.6	60
36	0.35	1.1
37	38	167
38	52	89
39	0.6	>500
40	0.013	4.9
41	25	>500
42	0.2	0.2
43	1.7	6.3
44	0.27	1.6
45	2	44

TABLE 3-continued

Example	HT29 meso+ IC_{50} [nM]	HT29 wt IC_{50} [nM]
46	3	500
47	7.2	294
48	10	32
49	1.8	0.9
50	0.6	1.4
51	0.8	15
52	3	2
53	0.74	9.2
54	0.09	1.1
55	0.002	0.28
56	0.7	162
57	0.018	4
58	0.4	2.5
59	0.6	4.1
60	0.06	10
61	9.2	46
71	22	90
72	1.5	>1000
73	2	227
74	5.3	57
75	0.13	672
76	0.09	769
77	3.3	>1000
78	2.1	219
79	0.03	199
80	0.25	317
81	1.6	3000
82	0.04	10
83	0.3	>1000
84	70	>1000
85	6.8	>1000
86	43	>1000
87	0.27	554
88	0.3	54
89	2.7	74
90	7.4	135
91	13	>1000
92	5.6	18
93	425	>1000
94	3.1	33
95	<0.1	0.15
96	>1000	>1000
97	4.1	>1000
98	30	>1000
99	2.2	>1000
100	0.5	>500
101	4.6	>500
102	0.09	839
103	0.18	602
104	177	>500
108	1.3	16
109	0.06	10
110	3.1	>500
111	0.02	14
112	1.6	>500
113	0.04	>500
114	7	>500
115	15	>500

C-3. Determination of the Effect on Tubulin Polymerization

[4729] Cancer cells are denatured cells which frequently lead to the formation of tumours also as a result of increased cell division. Microtubuli form the spindle fibres of the spindle apparatus and are an essential constituent of the cell cycle. The regulated construction and breakdown of microtubuli allows the precise division of the chromosomes among the daughter cells, and constitutes a continuously dynamic process. Disruption to this dynamic process results in incorrect cell division and ultimately in cell death. The increased cell division of cancer cells, however, also makes them particularly sensitive towards spindle fibre poisons, which constitute a fixed constituent of chemotherapy. Spindle fibre poisons such as paclitaxel or epothilone lead to a sharply increased polymerization rate of the microtubuli, while vinca alkaloids or else monomethylauristatin E (MMAE) lead to a sharply reduced polymerization rate of the microtubuli. In both cases, the necessary dynamism of the cell cycle is critically disrupted. The compounds investigated in the context of the present invention result in a reduced polymerization rate of the microtubuli.

[4730] Tubulin polymerization was investigated using the "Fluorescence-based Microtubule Polymerisation Assay Kit" from Cytoskeleton (Denver, Colo., USA; order number: BK011). With this assay, GTP is added to unpolymerized tubulin, allowing polymerization to take place spontaneously. The assay is based on the binding of the fluorophore 4',6-diamidino-2-phenylindole (DAPI) to tubulin. Free and bound DAPI can be differentiated on the basis of different emission spectra. Since DAPI exhibits a significantly high affinity for polymerized tubulin in comparison to non-polymerized tubulin, the tubulin polymerization can be followed via the increase in the fluorescence of bound DAPI fluorophores.

[4731] For the implementation of this assay, the compounds of the invention, in solution in DMSO, were diluted from their initial concentration of 10 mM to 1 μM in water. In addition to the buffer control, paclitaxel, with a polymerization-increasing effect, and vinblastin, with a polymerization inhibiting effect, were run additionally as assay controls. Measurement was carried out using 96-well plates with a half base area. The kinetics of the tubulin polymerization were monitored in a Fluorimeter at 37° C. for 1 hour. The excitation wavelength was 355 nm, and emission was monitored at 460 nm. For the region of linear increase within the first 10 minutes, a calculation was made of the change in fluorescence per minute (ΔF/min), which represents the polymerization rate of the microtubuli. The potency of the test substances was quantified on the basis of their respective reduction of the polymerization rate.

[4732] The reduction in the tubulin polymerization rate occurs in dependence on the concentration of the test substance added. Whereas the addition of 100 μM MMAF causes complete cessation of polymerization, the addition of 1 μM MMAF leads to a reduction in the polymerization rate of 40-45%, where a comparison of the activity of different substances is shown at best. The compound from Example 64 inhibited the polymerization rate to an extent of 41% at 1 μM. The compounds from Examples 62-70 and 105-107 exhibited a level of tubulin polymerization inhibition comparable with MMAF.

[4733] The value for the inhibition of MMAF at a concentration of 1 μM is set as being 100%.

[4734] Table 6 gives data for the inhibition of tubulin polymerization by representative working examples.

TABLE 6

Working example	Concentration of toxophore [μM]	Tubulin polymerization in the presence of toxophore in [%]. Tubulin polymerization rate at 1 μM MMAF set at 100%
MMAF	1	100
MMAF	10	34
MMAF	100	0

TABLE 6-continued

Working example	Concentration of toxophore [μM]	Tubulin polymerization in the presence of toxophore in [%]. Tubulin polymerization rate at 1 μM MMAF set at 100%
105	1	45
105	10	1
106	1	80
106	10	14
107	1	60
107	10	0
62	1	88
62	10	25
63	1	109
63	10	27
64	1	120
65	1	117
65	10	64
66	1	107
66	10	25
67	1	121
67	10	35
68	1	111
68	10	45
69	1	110
107	1	78
107	10	24
116	1	102
116	10	31
117	1	88
117	10	21
118	1	90
118	10	17

[4735] The MMAF toxophore and the working examples inhibit tubulin polymerization as a function of their concentration. At 100 μM MMAF, the tubulin polymerization is inhibited completely. Working Example 105 inhibits the tubulin polymerization rate at 1 μM to 45% of the value measured for 1 μM MMAF.

C-4. In Vitro Tests for Determining Cell Permeability

[4736] The cell permeability of a substance can be investigated by means of in vitro testing in a flux assay using Caco-2 cells [M. D. Troutman and D. R. Thakker, *Pharm. Res.* 20 (8), 1210-1224 (2003)]. For this purpose, the cells were cultured for 15-16 days on 24-well filter plates. For the determination of permeation, the respective working example was applied in a HEPES buffer to the cells either apically (A) or basally (B) and incubated for 2 hours. After 0 hours and after 2 hours, samples were taken from the cis and trans compartments. The samples were separated by HPLC (Agilent 1200, Böblingen, Germany) using reverse phase columns. The HPLC system was coupled via a Turbo Ion Spray Interface to a Triple Quadropol mass spectrometer API 4000 (Applied Biosystems Applera, Darmstadt, Germany). The permeability was evaluated on the basis of a P_{app} value, which was calculated using the formula published by Schwab et al. [D. Schwab et al., *J. Med. Chem.* 46, 1716-1725 (2003)].

[4737] Of critical importance for toxophores which are released intracellularly is the permeability from B to A [P_{app} (B-A)]: the lower this permeability, the longer the residence time of the working example in the cell following intracellular release, and hence also the longer the time available for interaction with the biochemical target (in this case: tubulin).

[4738] Table 4 below sets out permeability data for representative working examples from this assay:

TABLE 4

Working example	P_{app} (B-A) [nm/s]
62	2
63	1.6
64	2.5
65	5
66	1
68	7
105	2
106	1
116	1.8
117	1.5

[4739] The working examples exhibit a low permeability from B to A [P_{app} (B-A) and therefore have a long residence time in the CaCo-2 cells. In comparison, monomethylauristatin E (MMAE) and monomethylauristatin F (MMAF) in this test exhibit a P_{app} (B-A) value of 73 nm/s, and therefore have a significantly shorter residence time in the Caco-2 cells.

C-5. In Vitro Tests for Determining the Substrate Properties for P-Glycoprotein (P-gp)

[4740] Many tumour cells express transporter proteins for drugs, and this frequently accompanies the development of resistance towards cytostatics. Substances which are not substrates of such transporter proteins, such as P-glycoprotein (P-gp) or BCRP, for example, could therefore exhibit an improved activity profile.

[4741] The substrate properties of a substance for P-gp (ABCB1) were determined by means of a flux assay using LLC-PK1 cells which overexpress P-gp (L-MDR1 cells) [A. H. Schinkel et al., *J. Clin. Invest.* 96, 1698-1705 (1995)]. For this purpose, the LLC-PK1 cells or L-MDR1 cells were cultured on 96-well filter plates for 3-4 days. For determination of the permeation, the respective test substance, alone or in the presence of an inhibitor (such as Ivermectin or Verapamil, for example), was applied in a HEPES buffer to the cells either apically (A) or basally (B) and incubated for 2 hours. After 0 hours and after 2 hours, samples were taken from the cis and trans compartments. The samples were separated by HPLC using reverse phase columns. The HPLC system was coupled via a Turbo Ion Spray Interface to a Triple Quadropol mass spectrometer API 3000 (Applied Biosystems Applera, Darmstadt, Germany). The permeability was evaluated on the basis of a P_{app} value which was calculated using the formula published by Schwab et al. [D. Schwab et al., *J. Med. Chem.* 46, 1716-1725 (2003)].

[4742] Of critical importance for toxophores which are released intracellularly is the permeability from B to A [P_{app} (B-A)]: the lower this permeability, the longer the residence time of the working example in the cell following intracellular release, and hence also the longer the time available for interaction with the biochemical target (in this case: tubulin).

[4743] Table 5 below lists permeability data for representative working examples from this assay, which was carried out in L-MDR1 cells:

TABLE 5

Working example	P_{app} (B-A) [nm/s]
62	3
63	3.6

TABLE 5-continued

Working example	P_{app} (B-A) [nm/s]
64	2.1
65	3.6
66	4
68	2
105	6
106	4

[4744] The working examples exhibit a low permeability from B to A [P_{app} (B-A) and therefore have a long residence time in the L-MDR1 cells.

C-6. Pharmacokinetics in the HT29 Tumour Model with Mesothelin-Transfected and Non-Transfected HT29 Cells

[4745] Following intravenous administration of 16 mg/kg of Example 5, the plasma concentrations and tumour concentrations of Example 5 and also of potential metabolites such as, for example, of Example 64 were measured. In the animals with mesothelin-transfected tumours, the area under the curve (AUC) for the compound from Example 64 in plasma was about 0.50 mg*h/l; in the tumour, the exposure of the compound from Example 64 was about 400 times higher (AUC=203 mg*h/L). In the animals with nontransfected tumour animals, the exposure of Example 64 in plasma was identical to the exposure in plasma in animals with transfected tumours. In contrast, the AUC in the tumour in the nontransfected animals was about 8 times lower than in the transfected animals. This shows a distinct targeting effect in the tumour in the presence of the antigen.

Analysis for Quantifying the Compound from Example 64

[4746] The measurement of the compound from Example 64 in plasma and tumour took place following precipitation of the proteins with methanol, by means of high-pressure liquid chromatography (HPLC) coupled to a tandem mass spectrometer (MS).

[4747] For the processing of 100 μL of plasma, it was admixed with 400 μL of methanol and 10 μL of internal standard (ISTD, 50 ng/mL in methanol) and shaken for 10 seconds. After centrifuging for 5 minutes at 16 000 g, 250 μL of supernatant were transferred to an autosampler vial, which was made up with 250 μL of ammonium acetate buffer (AAC, 10 mM, pH 6.8) and shaken again.

[4748] For the processing of a tumour, it was admixed with 4 times the amount of methanol. In a Tissuelyser II (Quiagen), the sample was comminuted at 30 impacts per minute for 6 minutes and then centrifuged off at 16 000 g for 5 minutes. 50 μL of the supernatant were transferred to an autosampler vial and made up with 50 μL of ammonium acetate buffer (10 mM, pH 6.8) and with 5 μL of ISTD. After again being shaken, the tumour sample was ready for measurement.

[4749] The measurement of both matrix samples took place, lastly, on the HPLC-coupled, atmospheric pressure ionization/tandem mass spectrometer by means of a Turbo Ion Spray Interface (TISP) on an API4000 instrument from SCIEX. The m/z transitions measured were as follows:

Example 64 (quantifier) 614.652→570.9

Example 64 (qualifier 1) 614.652→555.0

Example 64 (qualifier 2) 614.652→500.4

Internal standard (ISTD) 726.665→694.5

[4750] HPLC/LC-MSMS (TISP) analysis ran on an HP1100 pump (Agilent) with a Gemini column (5 μm C18 110 A, 50×3 mm, Phenomenex). Under the following gradient conditions: flow rate 0.4 mL/min; gradient: 0.0 min-1.0 min 10% acetonitrile/90% AAC, 1.0 min-3.0 min 10% acetonitrile/90% AAC→50% acetonitrile/50% AAC, 3.0 min-5.5 min 50% acetonitrile/50% AAC, 5.5 min-5.6 min 50% acetonitrile/50% AAC→10% acetonitrile/90% AAC, 5.6 min-6.0 min 10% acetonitrile/90% AAC.

[4751] For calibration, plasma samples were admixed with concentrations of 0.5-2000 μg/L. The detection limit (LOQ) was 2 μg/L. The linear range extended from 2 to 1000 μg/L

[4752] For the calibration of the tumour samples, the supernatant of untreated tumours was admixed with concentrations of 0.5-200 μg/L. The detection limit was 5 μg/L. The linear range extended from 5 to 200 μg/L.

[4753] Quality controls for validity testing contained 5 and 50 μg/L, with an additional 500 μg/L in plasma. The concentrations found for these samples deviated by up to 20% from the intended value (data not attached).

C-7. Activity Test In Vivo

[4754] The activity of the conjugates of the invention was tested in vivo by means for example of xenograft models. The skilled person knows of methods in the prior art for testing the activity of the compounds of the invention (see, for example, WO 2005/081711; Polson et al., Cancer Res. 2009 Mar. 15; 69(6):2358-64). For this purpose, for example, rodents (e.g. mice) were implanted with a tumour cell line which expresses the target molecule of the binder. The implanted animals were subsequently administered either a conjugate of the invention or a control antibody, or isotonic salt solution. Administration took place singly or more often. Tumour size was determined after an incubation time of several days, in a comparison of conjugate-treated animals and the control group. The conjugate-treated animals showed a lower tumour size.

C-7a. Testing of Anti-Mesothelin ADCs in Experimental Tumours in the Mouse

[4755] Human tumour cells which express mesothelin are injected subcutaneously into the flank of immunosuppressed mice, such as nude mice or SCID mice. 1-10 million cells are detached from the cell culture, centrifuged and resuspended with 100 μl of medium or 1:1 medium/Matrigel. The cell suspension is injected beneath the skin of the mouse.

[4756] Within a few days, a tumour grows. Treatment begins no earlier than at a tumour size of 20 mm^2. In order to investigate the effect on tumours that are already established, the treatment may also be commenced only at a tumour size of 50-100 mm^2.

[4757] Treatment with ADCs takes place via the intravenous route into the caudal vein of the mouse. The ADC is dissolved in PBS and is administered with a volume of 5 ml/kg.

[4758] The treatment scheme is governed by the pharmacokinetics of the antibody. As a standard, treatment takes place three times following every fourth day. Treatment, however, may also be continued further, or a second cycle with three days of treatment may follow at a later point in time.

[4759] As a standard basis, 8 animals are used per treatment group. This number may be higher if particularly strong fluctuations in tumour growth or after treatment are anticipated. As well as the groups which receive the active substances, one group, as a control group, is treated only with the buffer, in accordance with the same scheme.

[4760] In the course of the experiment, the area of the tumour is measured regularly using a sliding caliper in two dimensions (length/width).

[4761] At the end of the experiment, the tumours are removed and weighed. The ratio of the average tumour weights for the therapy group (T) to the control group (C) is expressed as T/C.

C-7b. Activity in the HT29 Colonic Carcinoma Tumour Model with Mesothelin-Transfected HT29 Cells

[4762] One million HT29 cells (stably transfected with mesothelin) are inoculated subcutaneously into the flank of NMRI nude mice. Treatment begins intravenously with an average tumour size of 30 mm^2 on day 6 (day 6, 10, 14). Following the treatment, the tumour growth is monitored up to day 26. For reasons of animal protection law, the animals of the control group must be properly sacrificed on day 26, owing to the large tumours.

[4763] The ADCs bring about a distinct inhibition of tumour growth. On day 26, the experiment is ended and the tumours of all the animals are weighed. From this, T/C is calculated, as the tumour weight of the treatment group in relation to the control group.

TABLE 7

ADC	Dose	T/C
Vehicle	—	1
Example 60	5 mg/kg	0.32
Example 81	5 mg/kg	0.33

C-7c. Activity in the Ovcar3 Ovarian Carcinoma Tumour Model

[4764] Three million Ovcar3 cells are inoculated subcutaneously into the flank of NMRI nude mice.

[4765] Treatment begins intravenously at a dose of 5 mg/kg with an average tumour size of 40 mm^2 on day 49 (day 38, 42, 46 and day 70, 74). Following the treatment, the tumour growth is monitored up to day 78. At the end of the experiment, the tumours are removed and weighed.

[4766] The ADCs bring about a marked inhibition of tumour growth. On day 78, the experiment is ended and the tumours of all of the animals are weighed. From this, T/C is calculated, as the tumour weight of the treatment group in relation to the control group.

TABLE 8

ADC	Dose	T/C
Vehicle	—	1
Example 60	5 mg/kg	0.3
Example 81	5 mg/kg	0.23
Example 60	10 mg/kg	0.32
Example 81	10 mg/kg	0.16

C-7D. Activity in the NCI-H322 Pulmonary Carcinoma Tumour Model, which Expresses Mesothelin Endogenously. Treatment Scheme q4dx3.

[4767] Five million NCI-H322 cells are inoculated subcutaneously into the flank of NMRI nude mice. Treatment begins intravenously with a tumour size of about 50 mm^2 on day 21 (day 21, 25, 29). Following the treatment, the tumour growth is monitored up to day 42. For reasons of animal protection law, the animals of the control group must be properly sacrificed on day 42, owing to the large tumours.

[4768] The ADCs bring about a distinct inhibition of tumour growth. On day 42, the experiment is ended and the tumours of all the animals are weighed. From this, T/C is calculated, as the tumour weight of the treatment group in relation to the control group.

TABLE 9

ADC	Dose	T/C
Vehicle	—	1
Example 60	5 mg/kg	0.31
Example 60	15 mg/kg	0.09
Example 81	5 mg/kg	0.09

C-7e. Activity in the NCI-H322 Pulmonary Carcinoma Tumour Model which Expresses Mesothelin Endogenously. Treatment Scheme: Single Administration.

[4769] Five million NCI-H322 cells are inoculated subcutaneously into the flank of NMRI nude mice. Treatment with the ADCs or vehicle takes place intravenously once at a tumour size of about 45 mm^2 on day 22. Following the treatment, the tumour growth is monitored. For reasons of animal protection law, the animals of the control group must be properly sacrificed on day 50, owing to the large tumours.

[4770] The ADCs bring about a marked inhibition of tumour growth. The tumour areas (length×width) on day 50 are used in order to determine the T/C.

TABLE 10

ADC	Dose	T/C
Vehicle	—	1
Example 60	5 mg/kg 1x	0.73
Example 81	5 mg/kg 1x	0.33
Example 60	15 mg/kg 1x	0.32
Example 81	15 mg/kg 1x	0.23

D. WORKING EXAMPLES FOR PHARMACEUTICAL COMPOSITIONS

[4771] The compounds of the invention can be converted as follows into pharmaceutical preparations:

i.v. Solution:

[4772] The compound of the invention is dissolved at a concentration below the saturation solubility in a physiologically tolerated solvent (e.g. isotonic saline solution, D-PBS, or a formulation with glycine and sodium chloride in citrate buffer with addition of polysorbate 80). The solution is subjected to sterile filtration and dispensed into sterile and pyrogen-free injection containers.

i.v. Solution:

[4773] The compounds of the invention can be converted into the administration forms cited. This can be accomplished in a known way by "mixing with" or "dissolving in" inert, non-toxic, pharmaceutically suitable excipients (e.g. buffer substances, stabilizers, solubilizers, preservatives). The following, for example, may be present: amino acids (glycine, histidine, methionine, arginine, lysine, leucine, isoleucine, threonine, glutamic acid, phenylalanine and others), sugars and related compounds (glucose, saccharose, mannitol, trehalose, sucrose, mannose, lactose, sorbitol), glycerol, sodium salts, potassium, ammonium salts and calcium salts (e.g. sodium chloride, potassium chloride or disodiumhydrogenphosphate and many others), acetate/acetic acid buffer sys-

tems, phosphate buffer systems, citric acid and citrate buffer systems, trometamol (TRIS and TRIS salts), Polysorbates (e.g. Polysorbate 80 and Polysorbate 20), Poloxamers (e.g. Poloxamer 188 and Poloxamer 171), Macrogols (PEG derivatives, e.g. 3350), Triton X-100, EDTA salts, glutathione, albumins (e.g. human), urea, benzyl alcohol, phenol, chlorocresol, metacresol, benzalkonium chloride and many others.

Lyophilizate for Subsequent Conversion into an i.v., s.c. or i.m. Solution:

[4774] Alternatively the compounds of the invention may be converted into a stable lyophilizate (possibly with the aid of abovementioned excipients) and, before being administered, reconstituted with a suitable solvent (e.g. injection-grade water, isotonic saline solution) and administered.

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 411

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<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 1

Leu Glu Cys Tyr Ser Cys Val Gln Lys Ala Asp Asp Gly Cys Ser Pro
1 5 10 15

Asn Lys Met Lys Thr Val Lys Cys Ala Pro Gly Val Asp Val Cys Thr
20 25 30

Glu Ala Val Gly Ala Val Glu Thr Ile His Gly Gln Phe Ser Leu Ala
35 40 45

Val Arg Gly Cys Gly Ser Gly Leu Pro Gly Lys Asn Asp Arg Gly Leu
50 55 60

Asp Leu His Gly Leu Leu Ala Phe Ile Gln Leu Gln Gln Cys Ala Gln
65 70 75 80

Asp Arg Cys Asn Ala Lys Leu Asn Leu Thr Ser Arg Ala Leu Asp Pro
85 90 95

Ala Gly Asn Glu Ser Ala Tyr Pro Pro Asn Gly Val Glu Cys Tyr Ser
100 105 110

Cys Val Gly Leu Ser Arg Glu Ala Cys Gln Gly Thr Ser Pro Pro Val
115 120 125

Val Ser Cys Tyr Asn Ala Ser Asp His Val Tyr Lys Gly Cys Phe Asp
130 135 140

Gly Asn Val Thr Leu Thr Ala Ala Asn Val Thr Val Ser Leu Pro Val
145 150 155 160

Arg Gly Cys Val Gln Asp Glu Phe Cys Thr Arg Asp Gly Val Thr Gly
165 170 175

Pro Gly Phe Thr Leu Ser Gly Ser Cys Cys Gln Gly Ser Arg Cys Asn
180 185 190

Ser Asp Leu Arg Asn Lys Thr Tyr Phe Ser Pro Arg Ile Pro Pro Leu
195 200 205

Val Arg Leu Pro Pro Pro Glu Pro Thr Thr Val Ala Ser Thr Thr Ser
210 215 220

Val Thr Thr Ser Thr Ser Ala Pro Val Arg Pro Thr Ser Thr Thr Lys
225 230 235 240

Pro Met Pro Ala Pro Thr Ser Gln Thr Pro Arg Gln Gly Val Glu His
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Glu Ala Ser Arg Asp Glu Glu Pro Arg Leu Thr Gly Gly Ala Ala Gly
260 265 270

His Gln Asp Arg Ser Asn
275

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<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 2

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1 5 10 15

His Arg Met Lys Thr Val Lys Cys Gly Pro Gly Val Asp Val Cys Thr
20 25 30

Glu Ala Val Gly Ala Val Glu Thr Ile His Gly Gln Phe Ser Val Ala
35 40 45

Val Arg Gly Cys Gly Ser Gly Ile Pro Gly Lys Asn Asp Arg Gly Leu
50 55 60

Asp Leu His Gly Leu Leu Ala Phe Phe Gln Leu Gln Gln Cys Ser Glu
65 70 75 80

Asp Arg Cys Asn Ala Lys Leu Asn Leu Thr Leu Arg Gly Leu Asn Pro
85 90 95

Ala Gly Asn Glu Ser Ala Tyr Glu Pro Asn Gly Ala Glu Cys Tyr Ser
100 105 110

Cys Val Gly Leu Ser Arg Glu Lys Cys Gln Gly Ser Met Pro Pro Val
115 120 125

Val Asn Cys Tyr Asn Ala Ser Gly Arg Val Tyr Lys Gly Cys Phe Asp
130 135 140

Gly Asn Val Thr Leu Thr Ala Ala Asn Val Thr Val Ser Leu Pro Val
145 150 155 160

Arg Gly Cys Val Gln Asp Glu Thr Cys Thr Arg Asp Gly Val Thr Gly
165 170 175

Pro Gly Phe Thr Leu Ser Gly Ser Cys Cys Gln Gly Pro Arg Cys Asn
180 185 190

Ala Asp Leu Arg Asn Lys Thr Tyr Phe Ser Pro Arg Ile Pro Pro Leu
195 200 205

Val Leu Leu Pro Pro Pro Thr Thr Ala Ala Pro Ser Thr Arg Ala Gln
210 215 220

Asn Ser Ser Ser Thr Thr Ser Thr Ala Ala Pro Thr Thr Thr Thr Ser
225 230 235 240

Ile Ile Lys Pro Thr Thr Ala Gln Ala Ser His Thr Ser Pro His Glu
245 250 255

Met Asp Leu Glu Val Ile Gln Glu Glu Gly Ala Ser Leu Ser Gly Gly
260 265 270

Ala Ala Gly His Gly Gly Thr Ala Gly His Gly Gly Ala Ala Gly His
275 280 285

Gln Asp Arg Ser Asn
290

<210> SEQ ID NO 3
<211> LENGTH: 346
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 3

Met Asp Pro Ala Arg Lys Ala Gly Ala Gln Ala Met Ile Trp Thr Ala
1 5 10 15

Gly Trp Leu Leu Leu Leu Leu Leu Arg Gly Gly Ala Gln Ala Leu Glu

-continued

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            20                  25                  30

Cys Tyr Ser Cys Val Gln Lys Ala Asp Asp Gly Cys Ser Pro Asn Lys
        35                  40                  45

Met Lys Thr Val Lys Cys Ala Pro Gly Val Asp Val Cys Thr Glu Ala
    50                  55                  60

Val Gly Ala Val Glu Thr Ile His Gly Gln Phe Ser Leu Ala Val Arg
65                  70                  75                  80

Gly Cys Gly Ser Gly Leu Pro Gly Lys Asn Asp Arg Gly Leu Asp Leu
                85                  90                  95

His Gly Leu Leu Ala Phe Ile Gln Leu Gln Gln Cys Ala Gln Asp Arg
            100                 105                 110

Cys Asn Ala Lys Leu Asn Leu Thr Ser Arg Ala Leu Asp Pro Ala Gly
        115                 120                 125

Asn Glu Ser Ala Tyr Pro Pro Asn Gly Val Glu Cys Tyr Ser Cys Val
    130                 135                 140

Gly Leu Ser Arg Glu Ala Cys Gln Gly Thr Ser Pro Pro Val Val Ser
145                 150                 155                 160

Cys Tyr Asn Ala Ser Asp His Val Tyr Lys Gly Cys Phe Asp Gly Asn
                165                 170                 175

Val Thr Leu Thr Ala Ala Asn Val Thr Val Ser Leu Pro Val Arg Gly
            180                 185                 190

Cys Val Gln Asp Glu Phe Cys Thr Arg Asp Gly Val Thr Gly Pro Gly
        195                 200                 205

Phe Thr Leu Ser Gly Ser Cys Cys Gln Gly Ser Arg Cys Asn Ser Asp
    210                 215                 220

Leu Arg Asn Lys Thr Tyr Phe Ser Pro Arg Ile Pro Pro Leu Val Arg
225                 230                 235                 240

Leu Pro Pro Pro Glu Pro Thr Thr Val Ala Ser Thr Thr Ser Val Thr
                245                 250                 255

Thr Ser Thr Ser Ala Pro Val Arg Pro Thr Ser Thr Thr Lys Pro Met
            260                 265                 270

Pro Ala Pro Thr Ser Gln Thr Pro Arg Gln Gly Val Glu His Glu Ala
        275                 280                 285

Ser Arg Asp Glu Glu Pro Arg Leu Thr Gly Gly Ala Ala Gly His Gln
    290                 295                 300

Asp Arg Ser Asn Ser Gly Gln Tyr Pro Ala Lys Gly Gly Pro Gln Gln
305                 310                 315                 320

Pro His Asn Lys Gly Cys Val Ala Pro Thr Ala Gly Leu Ala Ala Leu
                325                 330                 335

Leu Leu Ala Val Ala Ala Gly Val Leu Leu
            340                 345


<210> SEQ ID NO 4
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<213> ORGANISM: Mus musculus

<400> SEQUENCE: 4

Met Asp Ala Ala Arg Arg Gly Asp Thr Gln Pro Val Met Trp Thr Thr
1               5                   10                  15

Gly Trp Leu Leu Leu Leu Pro Leu Leu Leu Cys Glu Gly Ala Gln Ala
            20                  25                  30

Leu Glu Cys Tyr Ser Cys Val Gln Lys Ala Asp Asp Gly Cys Ser Pro
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-continued

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        35                  40                  45

His Arg Met Lys Thr Val Lys Cys Gly Pro Gly Val Asp Val Cys Thr
    50                  55                  60

Glu Ala Val Gly Ala Val Glu Thr Ile His Gly Gln Phe Ser Val Ala
65                  70                  75                  80

Val Arg Gly Cys Gly Ser Gly Ile Pro Gly Lys Asn Asp Arg Gly Leu
                85                  90                  95

Asp Leu His Gly Leu Leu Ala Phe Phe Gln Leu Gln Gln Cys Ser Glu
            100                 105                 110

Asp Arg Cys Asn Ala Lys Leu Asn Leu Thr Leu Arg Gly Leu Asn Pro
        115                 120                 125

Ala Gly Asn Glu Ser Ala Tyr Glu Pro Asn Gly Ala Glu Cys Tyr Ser
    130                 135                 140

Cys Val Gly Leu Ser Arg Glu Lys Cys Gln Gly Ser Met Pro Pro Val
145                 150                 155                 160

Val Asn Cys Tyr Asn Ala Ser Gly Arg Val Tyr Lys Gly Cys Phe Asp
                165                 170                 175

Gly Asn Val Thr Leu Thr Ala Ala Asn Val Thr Val Ser Leu Pro Val
            180                 185                 190

Arg Gly Cys Val Gln Asp Glu Thr Cys Thr Arg Asp Gly Val Thr Gly
        195                 200                 205

Pro Gly Phe Thr Leu Ser Gly Ser Cys Cys Gln Gly Pro Arg Cys Asn
    210                 215                 220

Ala Asp Leu Arg Asn Lys Thr Tyr Phe Ser Pro Arg Ile Pro Pro Leu
225                 230                 235                 240

Val Leu Leu Pro Pro Pro Thr Thr Ala Ala Pro Ser Thr Arg Ala Gln
                245                 250                 255

Asn Ser Ser Ser Thr Thr Ser Thr Ala Ala Pro Thr Thr Thr Thr Ser
            260                 265                 270

Ile Ile Lys Pro Thr Thr Ala Gln Ala Ser His Thr Ser Pro His Glu
        275                 280                 285

Met Asp Leu Glu Val Ile Gln Glu Glu Gly Ala Ser Leu Ser Gly Gly
    290                 295                 300

Ala Ala Gly His Gly Gly Thr Ala Gly His Gly Gly Ala Ala Gly His
305                 310                 315                 320

Gln Asp Arg Ser Asn Met Glu Lys Tyr Pro Gly Lys Gly Gly Ala Gln
                325                 330                 335

Ile Pro Ala Lys Gly Gly Ser Gly Thr Leu Gly Ser Trp Leu Ser Ala
            340                 345                 350

Val Leu Leu Thr Val Val Ala Gly Ala Met Leu
        355                 360


<210> SEQ ID NO 5
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 5

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<210> SEQ ID NO 6
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<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

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<210> SEQ ID NO 7
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 7

Phe Gly His Tyr Tyr Met Phe Trp Ile
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<210> SEQ ID NO 8
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 8

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1 5

<210> SEQ ID NO 9
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 9

Val Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser
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Val Lys Gly Arg
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<210> SEQ ID NO 10
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 10

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Val Lys Gly Arg
20

<210> SEQ ID NO 11
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<212> TYPE: PRT
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<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

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<400> SEQUENCE: 11

Val Ser Ala Ile Ser Gly Ser Gly Tyr Ser Thr His Tyr Ala Asp Ser
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Val Lys Gly Arg
20

<210> SEQ ID NO 12
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 12

Val Ser Ala Ile Ser Ser Ser Gly Ser Ser Thr Tyr Tyr Ala Asp Ser
1 5 10 15

Val Lys Gly Arg
20

<210> SEQ ID NO 13
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 13

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<210> SEQ ID NO 14
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

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Ala Lys Gly Asp Tyr Leu Val Tyr Ser Ala Tyr Tyr Phe Asp Ser
1 5 10 15

<210> SEQ ID NO 15
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 15

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<210> SEQ ID NO 16
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 16

Ala Arg Glu Ser Gly Gly Ser Gly Pro Asn Tyr Tyr Tyr Gly Met Asp
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Val

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<210> SEQ ID NO 17
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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 17

Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Val Val His
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<210> SEQ ID NO 18
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 18

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<210> SEQ ID NO 19
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 19

Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Val Val His
1 5 10

<210> SEQ ID NO 20
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 20

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1 5 10

<210> SEQ ID NO 21
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 21

Asp Asn Asn Lys Arg Pro Ser
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<210> SEQ ID NO 22
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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 22

Arg Asn Asn Gln Arg Pro Ser

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1 5

<210> SEQ ID NO 23
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 23

Ser Asn Asn Gln Arg Pro Ser
1 5

<210> SEQ ID NO 24
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 24

Ser Asn Asn Gln Arg Pro Ser
1 5

<210> SEQ ID NO 25
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 25

Cys Ala Ala Trp Asp Asp Arg Leu Asn Gly Pro Val
1 5 10

<210> SEQ ID NO 26
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 26

Cys Ala Ala Trp Asp Asp Arg Leu Asn Gly Trp Val
1 5 10

<210> SEQ ID NO 27
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 27

Cys Gln Ser Tyr Asp Ser Ser His Val Leu
1 5 10

<210> SEQ ID NO 28
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 28

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Cys Gln Ser Tyr Asp Arg Ser Leu Arg Gly Trp Val
1               5                   10


<210> SEQ ID NO 29
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 29

Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1               5                   10                  15

Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
            20                  25                  30

Tyr Val Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
        35                  40                  45

Leu Ile Tyr Asp Asn Asn Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
    50                  55                  60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu
65                  70                  75                  80

Arg Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Arg
                85                  90                  95

Leu Asn Gly Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110

Gln


<210> SEQ ID NO 30
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 30

Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1               5                   10                  15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Val Gly Ser Asn
            20                  25                  30

Pro Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35                  40                  45

Ile Tyr Arg Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50                  55                  60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65                  70                  75                  80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Arg Leu
                85                  90                  95

Asn Gly Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110


<210> SEQ ID NO 31
<211> LENGTH: 111
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 31
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Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1               5                   10                  15

Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
            20                  25                  30

Tyr Val Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
        35                  40                  45

Leu Ile Tyr Ser Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe
    50                  55                  60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu
65                  70                  75                  80

Arg Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser Ser
                85                  90                  95

His Val Leu Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110


<210> SEQ ID NO 32
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 32

Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1               5                   10                  15

Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
            20                  25                  30

Tyr Val Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
        35                  40                  45

Leu Ile Tyr Ser Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe
    50                  55                  60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu
65                  70                  75                  80

Arg Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Arg Ser
                85                  90                  95

Leu Arg Gly Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110

Gln


<210> SEQ ID NO 33
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 33

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
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65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Leu Trp Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Thr Ser
115

<210> SEQ ID NO 34
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 34

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Gln Met Thr Trp Ile Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Val Ser Trp Asn Gly Ala Arg Thr His Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Gly Asp Tyr Leu Val Tyr Ser Ala Tyr Tyr Phe Asp Ser Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Thr Ser
115 120

<210> SEQ ID NO 35
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 35

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Gly His Tyr
20 25 30

Tyr Met Phe Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Gly Ser Gly Tyr Ser Thr His Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Leu Pro Tyr Gly Ser Gln Ser Gly Val Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Thr Ser

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115 120

<210> SEQ ID NO 36
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 36

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Asn
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Ser Ser Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Ser Gly Gly Ser Gly Pro Asn Tyr Tyr Tyr Gly Met Asp
100 105 110

Val Trp Gly Gln Gly Thr Leu Val Thr Val Thr Ser
115 120

<210> SEQ ID NO 37
<211> LENGTH: 339
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 37

cagtctgtgc tgactcagcc accctcagcg tctgggaccc ctgggcagag ggtcaccatc 60

tcctgcactg ggagcagctc caacattggg gcgggttatg ttgtacattg gtatcagcag 120

ctcccaggaa cggcccccaa actcctcatc tatgacaata ataagcgacc ctcaggggtc 180

cctgaccgat tctctggctc caagtctggc acctcagcct ccctggccat cagtgggctc 240

cggtccgagg atgaggctga ttattactgt gcagcatggg atgacaggct gaatggtccg 300

gtgttcggcg gaggaaccaa gttaaccgtc ctaggtcag 339

<210> SEQ ID NO 38
<211> LENGTH: 336
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 38

cagtctgtgc tgactcagcc accctcagcg tctgggaccc ccgggcagag ggtcaccatc 60

tcttgttctg gaagcagctc caacgtcggg agtaatcctg taaactggta tcagcagctc 120

ccaggaacgg cccccaaact cctcatctat aggaataatc agcggccctc aggggtccct 180

gaccgattct ctggctccaa gtctggcacc tcagcctccc tggccatcag tgggctccgg 240

tccgaggatg aggctgatta ttactgtgca gcatgggatg acaggctgaa tggttgggtg 300

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ttcggcggag gaaccaagct gacggtccta ggtcag 336

<210> SEQ ID NO 39
<211> LENGTH: 333
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 39

cagtctgtgc tgactcagcc accctcagcg tctgggaccc ccgggcagag ggtcaccatc 60

tcctgcactg ggagcagctc caacattggg gcgggttatg ttgtacattg gtatcagcag 120

ctcccaggaa cggcccccaa actcctcatc tatagtaata atcagcggcc ctcaggagtc 180

cctgaccgat tctctggctc caagtctggc acctcagcct ccctggccat cagtgggctc 240

cggtccgagg atgaggctga ttattactgc cagtcctatg acagcagcca tgttttattc 300

ggcggaggaa ccaagctgac ggtcctaggt cag 333

<210> SEQ ID NO 40
<211> LENGTH: 339
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 40

cagtctgtgc tgactcagcc accctcagcg tctgggaccc ccgggcagag ggtcaccatc 60

tcctgcactg ggagcagctc caacattggg gcgggttatg ttgtacattg gtatcagcag 120

ctcccaggaa cggcccccaa actcctcatc tatagtaata atcagcggcc ctcaggggtc 180

cctgaccgat tctctggctc caagtctggc acctcagcct ccctggccat cagtgggctc 240

cggtccgagg atgaggctga ttattactgc cagtcctatg acagaagcct gcgtggttgg 300

gtgttcggcg gaggaaccaa gctgacggtc ctaggtcag 339

<210> SEQ ID NO 41
<211> LENGTH: 351
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 41

gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggggtc cctgagactc 60

tcctgtgcag cctctggatt caccttcagt aacgcctgga tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtttcatac attagtagta gtggtagtac catatactac 180

gcagactctg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agccgaggac actgccgtgt attactgtgc gagagaaggg 300

ttatgggcct ttgactactg gggccagggt accctggtca ccgtgactag t 351

<210> SEQ ID NO 42
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

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<400> SEQUENCE: 42

gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgagactc 60

tcctgtgcag cctctggatt caccttcagt gactatcaga tgacctggat ccgccagact 120

ccagggaagg ggctggagtg ggtatcgggt gttagttgga atggcgctag gacgcactat 180

gcagactctg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240

ctacaaatga acagcctgag agccgaggac actgccgtgt attactgtgc gaagggcgac 300

tacctggttt actccgcata ctactttgac tcctggggcc agggtaccct ggtcaccgtg 360

actagt 366

<210> SEQ ID NO 43
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 43

gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgagactc 60

tcctgtgcag cctctggatt caccttcggt cactactata tgttctggat ccgtcaggct 120

ccagggaagg ggctggagtg ggtctcagct attagtggta gtggttatag cacacactac 180

gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agccgaggac actgccgtgt attactgtgc gagactgcca 300

tatggttcgc agagtggcgt tgactactgg ggccagggta ccctggtcac cgtgactagt 360

<210> SEQ ID NO 44
<211> LENGTH: 372
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 44

gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgagactc 60

tcctgtgcag cctctggatt caccttcagt agcaactaca tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtctcagct attagtagta gtggtagtag cacatactac 180

gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agccgaggac actgccgtgt attactgtgc gagagaatct 300

ggtgggagcg gaccgaacta ctactacggt atggacgtct ggggccaagg taccctggtc 360

accgtgacta gt 372

<210> SEQ ID NO 45
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 45

Phe Ser Asn Ala Trp Met Ser Trp Val
1 5

<210> SEQ ID NO 46

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<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 46

Val Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser
1 5 10 15

Val Lys Gly Arg
20

<210> SEQ ID NO 47
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 47

Ala Arg Glu Gly Leu Trp Ala Phe Asp Tyr
1 5 10

<210> SEQ ID NO 48
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 48

Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Val Val His
1 5 10

<210> SEQ ID NO 49
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 49

Asp Asn Asn Lys Arg Pro Ser
1 5

<210> SEQ ID NO 50
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 50

Cys Ala Ala Trp Asp Asp Arg Leu Asn Gly Pro Val
1 5 10

<210> SEQ ID NO 51
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 51

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

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1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Leu Trp Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser
        115


<210> SEQ ID NO 52
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 52

Glu Ser Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1               5                   10                  15

Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
            20                  25                  30

Tyr Val Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
        35                  40                  45

Leu Ile Tyr Asp Asn Asn Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
    50                  55                  60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu
65                  70                  75                  80

Arg Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Arg
                85                  90                  95

Leu Asn Gly Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110

Gln


<210> SEQ ID NO 53
<211> LENGTH: 351
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 53

gaggtgcagc tgctggaaag cggcggagga ctggtgcagc ctggaggcag cctgagactg     60

tcttgcgccg ccagcggctt caccttcagc aacgcctgga tgagctgggt ccgacaggct    120

cctggcaagg gcctggaatg ggtgtcctac atcagcagca gcggcagcac catctactac    180

gccgacagcg tgaagggccg gttcaccatc agccgggaca acagcaagaa caccctgtac    240

ctgcagatga acagcctgcg ggccgaggac accgccgtgt actactgcgc cagagaaggc    300

ctgtgggcct tcgactactg gggccagggc accctggtca ccgtgtctag c             351
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<210> SEQ ID NO 54
<211> LENGTH: 339
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 54

gagagcgtgc tgacccagcc tcctagcgtg tccggcgctc ctggccagag agtgaccatc 60

agctgcaccg gcagcagcag caacatcgga gccggctacg tggtgcactg gtatcagcag 120

ctgcccggca ccgcccccaa gctgctgatc tacgacaaca acaagcggcc tagcggcgtg 180

cccgacagat tcagcggcag caagagcggc accagcgcca gcctggccat cagcggcctg 240

agaagcgagg acgaggccga ctactactgc gccgcctggg acgacagact gaacggccct 300

gtgttcggcg gaggcaccaa gctgaccgtg ctgggacag 339

<210> SEQ ID NO 55
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 55

Phe Ser Asn Ala Trp Met Ser Trp Val
1 5

<210> SEQ ID NO 56
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 56

Val Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser
1 5 10 15

Val Lys Gly Arg
20

<210> SEQ ID NO 57
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 57

Ala Arg Glu Gly Leu Trp Ala Phe Asp Tyr
1 5 10

<210> SEQ ID NO 58
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 58

Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Val Val His
1 5 10

-continued

<210> SEQ ID NO 59
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 59

Asp Asn Asn Lys Arg Pro Ser
1 5

<210> SEQ ID NO 60
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 60

Cys Ala Ala Tyr Asp Asp Ser Leu Ser Gly Pro Val
1 5 10

<210> SEQ ID NO 61
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 61

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Leu Trp Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 62
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 62

Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
20 25 30

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Tyr Val Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
35 40 45

Leu Ile Tyr Asp Asn Asn Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu
65 70 75 80

Arg Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Tyr Asp Asp Ser
85 90 95

Leu Ser Gly Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

Gln

<210> SEQ ID NO 63
<211> LENGTH: 351
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 63

gaggtgcagc tgctggaatc cggcggaggc ctggtgcagc ctggcggatc tctgagactg 60

tcctgcgccg ccagcggctt taccttctcc aacgcctgga tgtcctgggt ccgacaggcc 120

cctggcaagg gactggaatg ggtgtcctac atctcctcct ccggctccac catctactac 180

gccgactccg tgaagggccg gttcaccatc tcccgggaca actccaagaa caccctgtac 240

ctgcagatga actccctgcg ggccgaggac accgccgtgt actactgcgc ccgagagggc 300

ctgtgggcct tcgattattg gggccagggc accctggtca ccgtcagctc a 351

<210> SEQ ID NO 64
<211> LENGTH: 339
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 64

cagtccgtgc tgacccagcc cccttctgtg tctggcgccc ctggccagag agtgaccatc 60

tcttgcaccg gctcctccag caacatcggc gctggctacg tggtgcactg gtatcagcag 120

ctgcccggca ccgcccccaa gctgctgatc tacgacaaca acaagcggcc ctccggcgtg 180

cccgacagat tctccggctc caagtccggc acctccgcct ccctggccat ctccggcctg 240

agatctgagg acgaggccga ctactactgc gccgcctacg acgactccct gtccggccct 300

gtgttcggcg gaggcacaaa gttaaccgtg ctgggccag 339

<210> SEQ ID NO 65
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 65

Phe Ser Asn Ala Trp Met Ser Trp Val
1 5

<210> SEQ ID NO 66
<211> LENGTH: 20

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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 66

Val Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser
1 5 10 15

Val Lys Gly Arg
20

<210> SEQ ID NO 67
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 67

Ala Arg Glu Gly Leu Trp Ala Phe Asp Tyr
1 5 10

<210> SEQ ID NO 68
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 68

Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Val Val His
1 5 10

<210> SEQ ID NO 69
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 69

Asp Asn Asn Lys Arg Pro Ser
1 5

<210> SEQ ID NO 70
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 70

Cys Ala Ala Phe Asp Asp Ser Leu Asn Gly Pro Val
1 5 10

<210> SEQ ID NO 71
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 71

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

-continued

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Leu Trp Ala Phe Asp Lys Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser
        115


<210> SEQ ID NO 72
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 72

Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1               5                   10                  15

Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
            20                  25                  30

Tyr Val Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
        35                  40                  45

Leu Ile Tyr Asp Asn Asn Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
    50                  55                  60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu
65                  70                  75                  80

Arg Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Phe Asp Asp Arg
                85                  90                  95

Leu Asn Gly Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110

Gln


<210> SEQ ID NO 73
<211> LENGTH: 351
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 73

gaggtgcagc tgctggaatc cggcggaggc ctggtgcagc ctggcggatc tctgagactg     60

tcctgcgccg cctccggctt taccttctcc aacgcctgga tgtcctgggt ccgacaggct    120

cctggcaagg gcctggaatg ggtgtcctac atctcctcct ccggctccac catctactac    180

gccgactccg tgaagggccg gttcaccatc tcccgggaca actccaagaa caccctgtac    240

ctgcagatga actccctgcg ggccgaggac accgccgtgt actactgcgc ccgagagggc    300

ctgtgggcct tcgataagtg gggccagggc accctggtca ccgtcagctc a             351
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-continued

<210> SEQ ID NO 74
<211> LENGTH: 339
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 74

cagtccgtgc tgacccagcc tccttccgcc tctggcaccc ctggccagag agtgaccatc 60

tcctgcaccg gctcctccag caacatcggc gctggctacg tggtgcactg gtatcagcag 120

ctgcccggca ccgcccccaa gctgctgatc tacgacaaca acaagcggcc ctccggcgtg 180

cccgacagat tctccggctc caagtccggc acctccgcct ccctggccat ctccggcctg 240

agatctgagg acgaggccga ctactactgc gccgccttcg acgaccggct gaacggccct 300

gtgttcggcg gaggcacaaa gttaaccgtg ctgggccag 339

<210> SEQ ID NO 75
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 75

Phe Ser Ser Ala Trp Met Ser Trp Val
1 5

<210> SEQ ID NO 76
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 76

Val Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser
1 5 10 15

Val Lys Gly Arg
20

<210> SEQ ID NO 77
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 77

Ala Arg Glu Gly Leu Trp Ala Phe Asp Tyr
1 5 10

<210> SEQ ID NO 78
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 78

Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Val Val His
1 5 10

-continued

<210> SEQ ID NO 79
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 79

Asp Asn Asn Lys Arg Pro Ser
1 5

<210> SEQ ID NO 80
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 80

Cys Ala Ala Tyr Asp Asp Ser Leu Ser Gly Pro Val
1 5 10

<210> SEQ ID NO 81
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 81

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Ala
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Leu Trp Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 82
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 82

Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
20 25 30

Tyr Val Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu

-continued

```
        35                  40                  45

Leu Ile Tyr Asp Asn Asn Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
    50                  55                  60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu
65                  70                  75                  80

Arg Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Tyr Asp Asp Ser
                85                  90                  95

Leu Ser Gly Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110

Gln
```

<210> SEQ ID NO 83
<211> LENGTH: 351
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 83

```
gaggtgcagc tgctggaatc cggcggaggc ctggtgcagc ctggcggatc tctgagactg     60

tcctgcgccg ccagcggctt taccttctcc agcgcctgga tgtcctgggt ccgacaggcc    120

cctggcaagg gactggaatg ggtgtcctac atctcctcct ccggctccac catctactac    180

gccgactccg tgaagggccg gttcaccatc tcccgggaca actccaagaa caccctgtac    240

ctgcagatga actccctgcg ggccgaggac accgccgtgt actactgcgc ccgagagggc    300

ctgtgggcct tcgattattg gggccagggc accctggtca ccgtcagctc a             351
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<210> SEQ ID NO 84
<211> LENGTH: 339
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 84

```
cagtccgtgc tgacccagcc cccttctgtg tctggcgccc ctggccagag agtgaccatc     60

tcttgcaccg gctcctccag caacatcggc gctggctacg tggtgcactg gtatcagcag    120

ctgcccggca ccgcccccaa gctgctgatc tacgacaaca acaagcggcc ctccggcgtg    180

cccgacagat tctccggctc caagtccggc acctccgcct ccctggccat ctccggcctg    240

agatctgagg acgaggccga ctactactgc gccgcctacg acgactccct gtccggccct    300

gtgttcggcg gaggcacaaa gttaaccgtg ctgggccag                           339
```

<210> SEQ ID NO 85
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 85

```
Phe Ser Ser Ala Trp Met Ser Trp Val
1               5
```

<210> SEQ ID NO 86
<211> LENGTH: 20
<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 86

Val Ser Tyr Ile Ser Ser Ser Gly Ser Ser Thr Tyr Tyr Ala Asp Ser
1 5 10 15

Val Lys Gly Arg
20

<210> SEQ ID NO 87
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 87

Ala Arg Glu Gly Leu Trp Ala Phe Asp Lys
1 5 10

<210> SEQ ID NO 88
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 88

Ser Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Val Val His
1 5 10

<210> SEQ ID NO 89
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 89

Asp Asn Asn Gln Arg Pro Ser
1 5

<210> SEQ ID NO 90
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 90

Cys Ala Ala Phe Asp Asp Arg Leu Ser Gly Pro Val
1 5 10

<210> SEQ ID NO 91
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 91

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

-continued

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Ala
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Tyr Ile Ser Ser Ser Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Leu Trp Ala Phe Asp Lys Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser
        115


<210> SEQ ID NO 92
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 92

Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1               5                   10                  15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ala Gly
            20                  25                  30

Tyr Val Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
        35                  40                  45

Leu Ile Tyr Asp Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe
    50                  55                  60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu
65                  70                  75                  80

Arg Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Phe Asp Asp Arg
                85                  90                  95

Leu Ser Gly Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110

Gln


<210> SEQ ID NO 93
<211> LENGTH: 351
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 93

gaggtgcagc tgctggaaag cggcggaggc ctggtgcagc ctggcggaag cctgagactg     60

agctgtgccg ccagcggctt caccttcagc agcgcctgga tgagctgggt ccgacaggcc    120

cctggcaagg gcctggaatg ggtgtcctac atcagcagca gcggcagcag cacctactac    180

gccgacagcg tgaagggccg gttcaccatc agccgggaca acagcaagaa caccctgtac    240

ctgcagatga acagcctgcg ggccgaggac accgccgtgt actactgcgc cagagaaggc    300

ctgtgggcct tcgataagtg gggccagggc accctggtca ccgtcagctc a             351
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<210> SEQ ID NO 94
<211> LENGTH: 339
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 94

cagagcgtgc tgacccagcc tcctagcgcc tctggcaccc ctggccagag agtgaccatc 60

agctgcagcg gcagcagcag caacatcgga gccggctacg tggtgcactg gtatcagcag 120

ctgcccggca ccgcccccaa gctgctgatc tacgacaaca accagcggcc cagcggcgtg 180

cccgacagat tttccggcag caagagcggc accagcgcca gcctggccat cagcggcctg 240

agaagcgagg acgaggccga ctactactgc gccgccttcg acgacagact gagcggccct 300

gtgttcggcg gaggcacaaa gttaaccgtg ctgggccag 339

<210> SEQ ID NO 95
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 95

Phe Ser Asp Tyr Gln Met Thr Trp Ile
1 5

<210> SEQ ID NO 96
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 96

Val Ser Gly Val Ser Trp Asn Gly Ala Arg Thr His Tyr Ala Asp Ser
1 5 10 15

Val Lys Gly Arg
20

<210> SEQ ID NO 97
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 97

Ala Lys Gly Asp Tyr Leu Val Tyr Ser Ala Tyr Tyr Phe Asp Ser
1 5 10 15

<210> SEQ ID NO 98
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 98

Ser Gly Ser Ser Ser Asn Val Gly Ser Asn Pro Val Asn
1 5 10

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<210> SEQ ID NO 99
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 99

Arg Asn Asn Gln Arg Pro Ser
1 5

<210> SEQ ID NO 100
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 100

Cys Ala Ala Trp Asp Asp Arg Leu Asn Gly Trp Val
1 5 10

<210> SEQ ID NO 101
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 101

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Gln Met Thr Trp Ile Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Trp Asn Gly Gly Ser Thr His Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Gly Asp Tyr Leu Val Tyr Ser Ala Tyr Tyr Phe Asp Ser Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 102
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 102

Glu Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30

Pro Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

-continued

Ile Tyr Arg Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Arg Leu
85 90 95

Asn Gly Trp Gly Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110

<210> SEQ ID NO 103
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 103

gaggtgcagc tgctggaaag cggcggagga ctggtgcagc ctggaggcag cctgagactg 60

tcttgcgccg ccagcggctt caccttcagc gactaccaga tgacctggat ccgacagacc 120

cctggcaagg gcctggaatg ggtgtccggc atcagctgga acggaggcag cacccactac 180

gccgacagcg tgaagggccg gttcaccatc agccgggaca acagcaagaa caccctgtac 240

ctgcagatga acagcctgcg ggccgaggac accgccgtgt actactgcgc caagggcgac 300

tacctggtgt acagcgccta ctacttcgac agctggggcc agggcaccct ggtcaccgtg 360

tctagc 366

<210> SEQ ID NO 104
<211> LENGTH: 336
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 104

gagagcgtgc tgacccagcc tcctagcgcc tctggcaccc ctggccagag agtgaccatc 60

agctgctctg gcagcagcag caacatcgga agcaaccccg tgaactggta tcagcagctg 120

cccggcaccg cccccaagct gctgatctac cggaacaacc agcggcctag cggcgtgccc 180

gacagattca gcggcagcaa gagcggcacc agcgccagcc tggccatcag cggcctgaga 240

agcgaggacg aggccgacta ctactgcgcc gcctgggacg acagactgaa cggctggggc 300

ttcggcggag gcaccaagct gaccgtgctg ggacag 336

<210> SEQ ID NO 105
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 105

Phe Ser Asp Tyr Gln Met Thr Trp Ile
1 5

<210> SEQ ID NO 106
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

-continued

<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 106

Val Ser Gly Ile Ser Trp Asn Gly Gly Ser Thr His Tyr Ala Asp Ser
1 5 10 15

Val Lys Gly Arg
20

<210> SEQ ID NO 107
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 107

Ala Lys Gly Asp Tyr Leu Val Tyr Ser Ser Tyr Tyr Phe Lys Ser
1 5 10 15

<210> SEQ ID NO 108
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 108

Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn Pro Val Asn
1 5 10

<210> SEQ ID NO 109
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 109

Arg Asn Asn Gln Arg Pro Ser
1 5

<210> SEQ ID NO 110
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 110

Cys Ala Ala Trp Asp Asp Arg Leu Ser Gly Trp Ala
1 5 10

<210> SEQ ID NO 111
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 111

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr

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```
            20                  25                  30

Gln Met Thr Trp Ile Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Gly Ile Ser Trp Asn Gly Gly Ser Thr His Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Lys Gly Asp Tyr Leu Val Tyr Ser Ser Tyr Tyr Phe Lys Ser Trp
            100                 105                 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 112
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 112

Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1               5                   10                  15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
            20                  25                  30

Pro Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35                  40                  45

Ile Tyr Arg Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50                  55                  60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65                  70                  75                  80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Arg Leu
                85                  90                  95

Ser Gly Trp Ala Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110


<210> SEQ ID NO 113
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 113

gaggtgcagc tgctggaatc cggcggaggc ctggtgcagc ctggcggatc tctgagactg     60

tcctgcgccg cctccggctt caccttctcc gactaccaga tgacctggat cagacagacc    120

cccggcaagg gcctggaatg ggtgtccggc atctcctgga acggcggctc cacccactac    180

gccgactctg tgaagggccg gttcaccatc tcccgggaca actccaagaa caccctgtac    240

ctgcagatga actccctgcg ggccgaggac accgccgtgt actactgcgc caagggcgac    300

tacctggtgt actcctccta ctacttcaag tcctggggcc agggcaccct ggtcaccgtc    360

agctca                                                               366


<210> SEQ ID NO 114
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<211> LENGTH: 336
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 114

cagtccgtgc tgacccagcc tccttccgcc tctggcaccc ctggccagag agtgaccatc 60

tcctgctccg gctcctcctc caacatcggc tccaaccccg tgaactggta tcagcagctg 120

cccggcaccg cccccaagct gctgatctac cggaacaacc agcggccctc cggcgtgccc 180

gacagattct ccggctccaa gtccggcacc tccgcctccc tggccatctc cggcctgaga 240

tctgaggacg aggccgacta ctactgcgcc gcctgggacg accggctgtc tggctgggct 300

tttggcggcg gaacaaagtt aaccgtgctg ggccag 336

<210> SEQ ID NO 115
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 115

Phe Ser Asp Tyr Gln Met Thr Trp Ile
1 5

<210> SEQ ID NO 116
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 116

Val Ser Gly Ile Ser Trp Asn Gly Gly Ser Thr His Tyr Ala Asp Ser
1 5 10 15

Val Lys Gly Arg
20

<210> SEQ ID NO 117
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 117

Ala Lys Gly Asp Tyr Leu Val Tyr Lys Ser Tyr Tyr Phe Lys Ser
1 5 10 15

<210> SEQ ID NO 118
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 118

Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn Pro Val Asn
1 5 10

<210> SEQ ID NO 119

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<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 119

Arg Asn Asn Gln Arg Pro Ser
1 5

<210> SEQ ID NO 120
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 120

Cys Ala Ala Trp Asp Asp Ser Leu Ser Gly Trp Ala
1 5 10

<210> SEQ ID NO 121
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 121

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Gln Met Thr Trp Ile Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Trp Asn Gly Gly Ser Thr His Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Gly Asp Tyr Leu Val Tyr Lys Ser Tyr Tyr Phe Lys Ser Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 122
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 122

Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30

Pro Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

-continued

Ile Tyr Arg Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Leu
85 90 95

Ser Gly Trp Ala Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110

<210> SEQ ID NO 123
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 123

gaggtgcagc tgctggaatc cggcggaggc ctggtgcagc ctggcggatc tctgagactg 60

tcctgcgccg cctccggctt caccttctcc gactaccaga tgacctggat cagacagacc 120

cccggcaagg gcctggaatg ggtgtccggc atctcctgga acggcggctc cacccactac 180

gccgactctg tgaagggccg gttcaccatc tcccgggaca actccaagaa caccctgtac 240

ctgcagatga actccctgcg ggccgaggac accgccgtgt actactgcgc caagggcgac 300

tacctggtgt acaagtccta ctacttcaag tcctggggcc agggcaccct ggtcaccgtc 360

agctca 366

<210> SEQ ID NO 124
<211> LENGTH: 336
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 124

cagtccgtgc tgacccagcc tccttccgcc tctggcaccc ctggccagag agtgaccatc 60

tcctgctccg gctcctcctc caacatcggc tccaaccccg tgaactggta tcagcagctg 120

cccggcaccg cccccaagct gctgatctac cggaacaacc agcggccctc cggcgtgccc 180

gacagattct ccggctccaa gtccggcacc tccgcctccc tggccatctc cggcctgaga 240

tctgaggacg aggccgacta ctactgcgcc gcctgggacg actccctgtc tggctgggct 300

tttggcggcg gaacaaagtt aaccgtgctg ggccag 336

<210> SEQ ID NO 125
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 125

Phe Ser Asp Tyr Gln Met Thr Trp Ile
1 5

<210> SEQ ID NO 126
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 126

Val Ser Gly Ile Ser Trp Asn Gly Gly Ser Thr His Tyr Ala Asp Ser
1 5 10 15

Val Lys Gly Arg
20

<210> SEQ ID NO 127
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 127

Ala Lys Gly Asp Tyr Leu Val Tyr Ser Ser Tyr Tyr Phe Lys Ser
1 5 10 15

<210> SEQ ID NO 128
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 128

Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn Pro Val Asn
1 5 10

<210> SEQ ID NO 129
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 129

Arg Asn Asn Gln Arg Pro Ser
1 5

<210> SEQ ID NO 130
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 130

Cys Ala Ala Trp Asp Asp Arg Leu Ser Gly Trp Gly
1 5 10

<210> SEQ ID NO 131
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 131

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

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Gln Met Thr Trp Ile Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Gly Ile Ser Trp Asn Gly Gly Ser Thr His Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Lys Gly Asp Tyr Leu Val Tyr Ser Ser Tyr Tyr Phe Lys Ser Trp
            100                 105                 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 132
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 132

Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1               5                   10                  15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
            20                  25                  30

Pro Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35                  40                  45

Ile Tyr Arg Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50                  55                  60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65                  70                  75                  80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Arg Leu
                85                  90                  95

Ser Gly Trp Gly Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110


<210> SEQ ID NO 133
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 133

gaggtgcagc tgctggaatc cggcggaggc ctggtgcagc ctggcggatc tctgagactg     60

tcctgcgccg cctccggctt caccttctcc gactaccaga tgacctggat cagacagacc    120

cccggcaagg gcctggaatg ggtgtccggc atctcctgga acggcggctc cacccactac    180

gccgactctg tgaagggccg gttcaccatc tcccgggaca actccaagaa caccctgtac    240

ctgcagatga actccctgcg ggccgaggac accgccgtgt actactgcgc caagggcgac    300

tacctggtgt actcctccta ctacttcaag tcctggggcc agggcaccct ggtcaccgtc    360

agctca                                                               366


<210> SEQ ID NO 134
<211> LENGTH: 336
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 134

cagtccgtgc tgacccagcc tccttccgcc tctggcaccc ctggccagag agtgaccatc 60

tcctgctccg gctcctcctc caacatcggc tccaaccccg tgaactggta tcagcagctg 120

cccggcaccg cccccaagct gctgatctac cggaacaacc agcggccctc cggcgtgccc 180

gacagattct ccggctccaa gtccggcacc tccgcctccc tggccatctc cggcctgaga 240

tctgaggacg aggccgacta ctactgcgcc gcctgggacg accggctgtc tggctgggga 300

tttggcggcg gaacaaagtt aaccgtgctg ggccag 336

<210> SEQ ID NO 135
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 135

Phe Ser Ser Tyr Gln Met Thr Trp Ile
1 5

<210> SEQ ID NO 136
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 136

Val Ser Gly Ile Ser Trp Asn Gly Gly Ser Thr His Tyr Ala Asp Ser
1 5 10 15

Val Lys Gly Arg
20

<210> SEQ ID NO 137
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 137

Ala Lys Gly Asp Tyr Leu Val Tyr Lys Ser Tyr Tyr Phe Lys Ser
1 5 10 15

<210> SEQ ID NO 138
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 138

Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn Pro Val Asn
1 5 10

<210> SEQ ID NO 139
<211> LENGTH: 7

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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 139

Arg Asn Asn Gln Arg Pro Ser
1 5

<210> SEQ ID NO 140
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 140

Cys Ala Ala Trp Asp Asp Ser Leu Ser Gly Trp Ala
1 5 10

<210> SEQ ID NO 141
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 141

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gln Met Thr Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Trp Asn Gly Gly Ser Thr His Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Gly Asp Tyr Leu Val Tyr Lys Ser Tyr Tyr Phe Lys Ser Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 142
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 142

Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30

Pro Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Arg Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser

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```
    50                  55                  60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65                  70                  75                  80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Leu
                85                  90                  95

Ser Gly Trp Ala Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110


<210> SEQ ID NO 143
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 143

gaggtgcagc tgctggaaag cggcggaggc ctggtgcagc ctggcggaag cctgagactg     60

agctgtgccg ccagcggctt caccttcagc agctaccaga tgacctggat cagacaggcc    120

cctggcaagg gcctggaatg ggtgtccggc atcagctgga acggcggcag cacccactac    180

gccgacagcg tgaagggccg gttcaccatc agccgggaca acagcaagaa caccctgtac    240

ctgcagatga acagcctgcg ggccgaggac accgccgtgt actactgcgc caagggcgac    300

tacctggtgt acaagagcta ctacttcaag agctggggcc agggcacact ggtcaccgtc    360

agctca                                                               366


<210> SEQ ID NO 144
<211> LENGTH: 336
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 144

cagagcgtgc tgacccagcc tcctagcgcc tctggcaccc ctggccagag agtgaccatc     60

agctgcagcg gcagcagcag caacatcggc agcaaccccg tgaactggta tcagcagctg    120

cccggcaccg cccccaagct gctgatctac cggaacaacc agcggcccag cggcgtgccc    180

gacagatttt ccggcagcaa gagcggcacc agcgccagcc tggccatcag cggcctgaga    240

agcgaggacg aggccgacta ctactgcgcc gcctgggacg atagcctgag cggctgggcc    300

tttggcggcg gaacaaagtt aaccgtgctg ggccag                               336


<210> SEQ ID NO 145
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 145

Phe Ser Asn Ala Trp Met Ser Trp Val
1               5


<210> SEQ ID NO 146
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder
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<400> SEQUENCE: 146

Val Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser
1 5 10 15

Val Lys Gly Arg
20

<210> SEQ ID NO 147
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 147

Ala Arg Glu Gly Leu Trp Ala Phe Asp Lys
1 5 10

<210> SEQ ID NO 148
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 148

Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Val Val His
1 5 10

<210> SEQ ID NO 149
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 149

Asp Asn Asn Lys Arg Pro Ser
1 5

<210> SEQ ID NO 150
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 150

Cys Ala Ala Tyr Asp Asp Ser Leu Lys Gly Pro Val
1 5 10

<210> SEQ ID NO 151
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 151

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

-continued

```
Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Leu Trp Ala Phe Asp Lys Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Thr Ser
        115


<210> SEQ ID NO 152
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 152

Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1               5                   10                  15

Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
            20                  25                  30

Tyr Val Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
        35                  40                  45

Leu Ile Tyr Asp Asn Asn Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
    50                  55                  60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu
65                  70                  75                  80

Arg Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Tyr Asp Asp Ser
                85                  90                  95

Leu Lys Gly Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110

Gln


<210> SEQ ID NO 153
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 153

Phe Ser Asn Ala Trp Met Ser Trp Val
1               5


<210> SEQ ID NO 154
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 154

Val Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser
1               5                   10                  15
```

-continued

Val Lys Gly Arg
20

<210> SEQ ID NO 155
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 155

Ala Arg Glu Gly Leu Trp Ala Phe Asp Lys
1 5 10

<210> SEQ ID NO 156
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 156

Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Val Val His
1 5 10

<210> SEQ ID NO 157
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 157

Asp Asn Asn Lys Arg Pro Ser
1 5

<210> SEQ ID NO 158
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 158

Cys Ala Ala Phe Asp Asp Ser Leu Asn Gly Pro Val
1 5 10

<210> SEQ ID NO 159
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 159

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

-continued

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Leu Trp Ala Phe Asp Lys Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Thr Ser
115

<210> SEQ ID NO 160
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 160

Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
20 25 30

Tyr Val Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
35 40 45

Leu Ile Tyr Asp Asn Asn Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu
65 70 75 80

Arg Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Phe Asp Asp Ser
85 90 95

Leu Asn Gly Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

Gln

<210> SEQ ID NO 161
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 161

Phe Ser Asn Ala Trp Met Ser Trp Val
1 5

<210> SEQ ID NO 162
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 162

Val Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser
1 5 10 15

Val Lys Gly Arg
20

<210> SEQ ID NO 163
<211> LENGTH: 10

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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 163

Ala Arg Glu Gly Leu Trp Ala Phe Asp Lys
1 5 10

<210> SEQ ID NO 164
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 164

Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Val Val His
1 5 10

<210> SEQ ID NO 165
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 165

Asp Asn Asn Lys Arg Pro Ser
1 5

<210> SEQ ID NO 166
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 166

Cys Ala Ala Tyr Asp Asp Ser Leu Ser Gly Pro Val
1 5 10

<210> SEQ ID NO 167
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 167

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

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Ala Arg Glu Gly Leu Trp Ala Phe Asp Lys Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Thr Ser
115

<210> SEQ ID NO 168
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 168

Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
20 25 30

Tyr Val Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
35 40 45

Leu Ile Tyr Asp Asn Asn Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu
65 70 75 80

Arg Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Phe Asp Asp Ser
85 90 95

Leu Asn Gly Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

Gln

<210> SEQ ID NO 169
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 169

Phe Ser Ser Ala Trp Met Ser Trp Val
1 5

<210> SEQ ID NO 170
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 170

Val Ser Tyr Ile Ser Ser Ser Gly Ser Ser Thr Tyr Tyr Ala Asp Ser
1 5 10 15

Val Lys Gly Arg
20

<210> SEQ ID NO 171
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 171

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Ala Arg Glu Gly Leu Trp Ala Phe Asp Trp
1               5                   10


<210> SEQ ID NO 172
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 172

Ser Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Val Val His
1               5                   10


<210> SEQ ID NO 173
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 173

Asp Asn Asn Gln Arg Pro Ser
1               5


<210> SEQ ID NO 174
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 174

Cys Ala Ala Tyr Asp Asp Ser Leu Ser Gly Pro Val
1               5                   10


<210> SEQ ID NO 175
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 175

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Ala
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Tyr Ile Ser Ser Ser Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Leu Trp Ala Phe Asp Trp Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Thr Ser
        115
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<210> SEQ ID NO 176
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 176

Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ala Gly
20 25 30

Tyr Val Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
35 40 45

Leu Ile Tyr Asp Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu
65 70 75 80

Arg Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Tyr Asp Asp Ser
85 90 95

Leu Ser Gly Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

Gln

<210> SEQ ID NO 177
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 177

Phe Ser Ser Ala Trp Met Ser Trp Val
1 5

<210> SEQ ID NO 178
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 178

Val Ser Tyr Ile Ser Ser Ser Gly Ser Ser Thr Tyr Tyr Ala Asp Ser
1 5 10 15

Val Lys Gly Arg
20

<210> SEQ ID NO 179
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 179

Ala Arg Glu Gly Leu Trp Ala Phe Asp Asn
1 5 10

<210> SEQ ID NO 180

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<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 180

Ser Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Val Val His
1 5 10

<210> SEQ ID NO 181
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 181

Asp Asn Asn Gln Arg Pro Ser
1 5

<210> SEQ ID NO 182
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 182

Cys Ala Ala Tyr Asp Asp Ser Leu Asn Gly Pro Val
1 5 10

<210> SEQ ID NO 183
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 183

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Leu Trp Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Thr Ser
115

<210> SEQ ID NO 184
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 184

Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ala Gly
20 25 30

Tyr Val Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
35 40 45

Leu Ile Tyr Asp Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu
65 70 75 80

Arg Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Tyr Asp Asp Ser
85 90 95

Leu Asn Gly Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

Gln

<210> SEQ ID NO 185
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 185

Phe Ser Ser Ala Trp Met Ser Trp Val
1 5

<210> SEQ ID NO 186
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 186

Val Ser Tyr Ile Ser Ser Ser Gly Ser Ser Thr Tyr Tyr Ala Asp Ser
1 5 10 15

Val Lys Gly Arg
20

<210> SEQ ID NO 187
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 187

Ala Arg Glu Gly Leu Trp Ala Phe Asp Tyr
1 5 10

<210> SEQ ID NO 188
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

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<400> SEQUENCE: 188

Ser Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Val Val His
1 5 10

<210> SEQ ID NO 189
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 189

Asp Asn Asn Gln Arg Pro Ser
1 5

<210> SEQ ID NO 190
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 190

Cys Ala Ala Trp Asp Asp Arg Leu Asn Gly Pro Val
1 5 10

<210> SEQ ID NO 191
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 191

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Ala
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Ser Ser Ser Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Leu Trp Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 192
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 192

Glu Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

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Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ala Gly
20 25 30

Tyr Val Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
35 40 45

Leu Ile Tyr Asp Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu
65 70 75 80

Arg Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Arg
85 90 95

Leu Asn Gly Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

Gln

<210> SEQ ID NO 193
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 193

Phe Thr Phe Ser Asn Ala Trp Met Ser Trp Val
1 5 10

<210> SEQ ID NO 194
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 194

Val Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser
1 5 10 15

Val Lys Gly Arg
20

<210> SEQ ID NO 195
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 195

Ala Arg Glu Gly Leu Trp Ala Phe Asp Tyr
1 5 10

<210> SEQ ID NO 196
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 196

Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Val Val His
1 5 10

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<210> SEQ ID NO 197
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 197

Asp Asn Asn Lys Arg Pro Ser
1 5

<210> SEQ ID NO 198
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 198

Cys Ala Ala Tyr Asp Asp Arg Leu Asn Gly Pro Val
1 5 10

<210> SEQ ID NO 199
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 199

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Leu Trp Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 200
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 200

Glu Ser Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
20 25 30

Tyr Val Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
35 40 45

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Leu Ile Tyr Asp Asn Asn Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
    50                  55                  60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu
65                  70                  75                  80

Arg Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Tyr Asp Asp Arg
                85                  90                  95

Leu Asn Gly Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110

Gln
```

<210> SEQ ID NO 201
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 201

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Phe Thr Phe Ser Ser Ala Trp Met Ser Trp Val
1               5                   10
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<210> SEQ ID NO 202
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 202

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Val Ser Tyr Ile Ser Ser Ser Gly Ser Ser Thr Tyr Tyr Ala Asp Ser
1               5                   10                  15

Val Lys Gly Arg
            20
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<210> SEQ ID NO 203
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 203

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Ala Arg Glu Gly Leu Trp Ala Phe Asp Gly
1               5                   10
```

<210> SEQ ID NO 204
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 204

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Ser Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Val Val His
1               5                   10
```

<210> SEQ ID NO 205
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

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<400> SEQUENCE: 205

Asp Asn Asn Gln Arg Pro Ser
1 5

<210> SEQ ID NO 206
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 206

Cys Ala Ala Tyr Asp Asp Ser Leu Asn Arg Pro Val
1 5 10

<210> SEQ ID NO 207
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 207

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Ala
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Ser Ser Ser Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Leu Trp Ala Phe Asp Gly Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 208
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 208

Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ala Gly
20 25 30

Tyr Val Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
35 40 45

Leu Ile Tyr Asp Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu
65 70 75 80

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Arg Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Tyr Asp Asp Ser
85 90 95

Leu Asn Arg Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

Gln

<210> SEQ ID NO 209
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 209

Phe Thr Phe Ser Asn Ala Trp Met Ser Trp Val
1 5 10

<210> SEQ ID NO 210
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 210

Val Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser
1 5 10 15

Val Lys Gly Arg
20

<210> SEQ ID NO 211
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 211

Ala Arg Glu Gly Leu Trp Ala Phe Asp Tyr
1 5 10

<210> SEQ ID NO 212
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 212

Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Val Val His
1 5 10

<210> SEQ ID NO 213
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 213

Asp Asn Asn Lys Arg Pro Ser
1 5

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<210> SEQ ID NO 214
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 214

Cys Ala Ala Phe Asp Asp Ser Leu Asn Gly Pro Val
1 5 10

<210> SEQ ID NO 215
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 215

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Leu Trp Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 216
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 216

Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
20 25 30

Tyr Val Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
35 40 45

Leu Ile Tyr Asp Asn Asn Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu
65 70 75 80

Arg Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Phe Asp Asp Ser
85 90 95

Leu Asn Gly Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

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Gln

<210> SEQ ID NO 217
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 217

Phe Ser Ser Ala Trp Met Ser Trp Val
1 5

<210> SEQ ID NO 218
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 218

Val Ser Tyr Ile Ser Ser Ser Gly Ser Ser Thr Tyr Tyr Ala Asp Ser
1 5 10 15

Val Lys Gly Arg
20

<210> SEQ ID NO 219
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 219

Ala Arg Glu Gly Leu Trp Ala Phe Asp Lys
1 5 10

<210> SEQ ID NO 220
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 220

Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Val Val His
1 5 10

<210> SEQ ID NO 221
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 221

Asp Asn Asn Lys Arg Pro Ser
1 5

<210> SEQ ID NO 222
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 222

Cys Ala Ala Phe Asp Asp Ser Leu Asn Gly Pro Val
1 5 10

<210> SEQ ID NO 223
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 223

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Ala
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Ser Ser Ser Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Leu Trp Ala Phe Asp Lys Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Thr Ser
115

<210> SEQ ID NO 224
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 224

Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
20 25 30

Tyr Val Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
35 40 45

Leu Ile Tyr Asp Asn Asn Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu
65 70 75 80

Arg Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Phe Asp Asp Ser
85 90 95

Leu Asn Gly Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

Gln

<210> SEQ ID NO 225
<211> LENGTH: 11

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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 225

Phe Thr Phe Ser Ser Ala Trp Met Ser Trp Val
1 5 10

<210> SEQ ID NO 226
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 226

Val Ser Tyr Ile Ser Ser Ser Gly Ser Ser Thr Tyr Tyr Ala Asp Ser
1 5 10 15

Val Lys Gly Arg
20

<210> SEQ ID NO 227
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 227

Ala Arg Glu Gly Leu Trp Ala Phe Asp Lys
1 5 10

<210> SEQ ID NO 228
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 228

Ser Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Val Val His
1 5 10

<210> SEQ ID NO 229
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 229

Asp Asn Asn Gln Arg Pro Ser
1 5

<210> SEQ ID NO 230
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 230

Cys Ala Ala Phe Asp Asp Ser Leu Asn Gly Pro Val
1 5 10

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<210> SEQ ID NO 231
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 231

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Ala
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Ser Ser Ser Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Leu Trp Ala Phe Asp Lys Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 232
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 232

Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ala Gly
20 25 30

Tyr Val Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
35 40 45

Leu Ile Tyr Asp Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu
65 70 75 80

Arg Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Phe Asp Asp Ser
85 90 95

Leu Asn Gly Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

Gln

<210> SEQ ID NO 233
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 233

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Phe Thr Phe Ser Ser Ala Trp Met Ser Trp Val
1 5 10

<210> SEQ ID NO 234
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 234

Val Ser Tyr Ile Ser Ser Ser Gly Ser Ser Thr Tyr Tyr Ala Asp Ser
1 5 10 15

Val Lys Gly Arg
20

<210> SEQ ID NO 235
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 235

Ala Arg Glu Gly Leu Trp Ala Phe Asp Lys
1 5 10

<210> SEQ ID NO 236
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 236

Ser Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Val Val His
1 5 10

<210> SEQ ID NO 237
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 237

Asp Asn Asn Gln Arg Pro Ser
1 5

<210> SEQ ID NO 238
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 238

Cys Ala Ala Phe Asp Asp Arg Leu Ser Gly Pro Val
1 5 10

<210> SEQ ID NO 239
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 239

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Ala
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Ser Ser Ser Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Leu Trp Ala Phe Asp Lys Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 240
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 240

Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ala Gly
20 25 30

Tyr Val Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
35 40 45

Leu Ile Tyr Asp Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu
65 70 75 80

Arg Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Phe Asp Asp Arg
85 90 95

Leu Ser Gly Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

Gln

<210> SEQ ID NO 241
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 241

Phe Ser Asp Tyr Gln Met Thr Trp Ile
1 5

<210> SEQ ID NO 242

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<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 242

Val Ser Gly Val Ser Trp Asn Gly Ala Arg Thr His Tyr Ala Asp Ser
1 5 10 15

Val Lys Gly Arg
20

<210> SEQ ID NO 243
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 243

Ala Lys Gly Asp Tyr Leu Val Tyr Ser Ser Tyr Tyr Phe Lys Ser
1 5 10 15

<210> SEQ ID NO 244
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 244

Ser Gly Ser Ser Ser Asn Val Gly Ser Asn Pro Val Asn
1 5 10

<210> SEQ ID NO 245
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 245

Arg Asn Asn Gln Arg Pro Ser
1 5

<210> SEQ ID NO 246
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 246

Cys Ala Ala Trp Asp Asp Arg Leu Asn Gly Trp Thr Gly
1 5 10

<210> SEQ ID NO 247
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 247

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

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1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20                  25                  30

Gln Met Thr Trp Ile Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Gly Val Ser Trp Asn Gly Ala Arg Thr His Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Lys Gly Asp Tyr Leu Val Tyr Ser Ser Tyr Tyr Phe Lys Ser Trp
            100                 105                 110

Gly Gln Gly Thr Leu Val Thr Val Thr Ser
        115                 120


<210> SEQ ID NO 248
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 248

Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1               5                   10                  15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Val Gly Ser Asn
            20                  25                  30

Pro Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35                  40                  45

Ile Tyr Arg Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50                  55                  60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65                  70                  75                  80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Arg Leu
                85                  90                  95

Asn Gly Trp Gly Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110


<210> SEQ ID NO 249
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 249

Phe Thr Phe Ser Ser Tyr Gln Met Thr Trp Ile
1               5                   10


<210> SEQ ID NO 250
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 250
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Val Ser Gly Ile Ser Trp Asn Gly Gly Ser Thr His Tyr Ala Asp Ser
1 5 10 15

Val Lys Gly Arg
20

<210> SEQ ID NO 251
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 251

Ala Lys Gly Asp Tyr Leu Val Tyr Ser Ala Tyr Tyr Phe Asp Ser
1 5 10 15

<210> SEQ ID NO 252
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 252

Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn Pro Val Asn
1 5 10

<210> SEQ ID NO 253
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 253

Arg Asn Asn Gln Arg Pro Ser
1 5

<210> SEQ ID NO 254
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 254

Cys Ala Ala Trp Asp Asp Arg Leu Asn Gly Trp Gly
1 5 10

<210> SEQ ID NO 255
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 255

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gln Met Thr Trp Ile Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

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Ser Gly Ile Ser Trp Asn Gly Gly Ser Thr His Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Lys Gly Asp Tyr Leu Val Tyr Ser Ala Tyr Tyr Phe Asp Ser Trp
            100                 105                 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 256
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 256

Glu Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1               5                   10                  15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
            20                  25                  30

Pro Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35                  40                  45

Ile Tyr Arg Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50                  55                  60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65                  70                  75                  80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Arg Leu
                85                  90                  95

Asn Gly Trp Gly Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110


<210> SEQ ID NO 257
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 257

Phe Thr Phe Ser Asp Tyr Gln Met Thr Trp Ile
1               5                   10


<210> SEQ ID NO 258
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 258

Val Ser Gly Ile Ser Trp Asn Gly Gly Ser Thr His Tyr Ala Asp Ser
1               5                   10                  15

Val Lys Gly Arg
            20


<210> SEQ ID NO 259
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<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 259

Ala Lys Gly Asp Tyr Leu Val Tyr Ser Ser Tyr Tyr Phe Lys Tyr
1 5 10 15

<210> SEQ ID NO 260
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 260

Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn Pro Val Asn
1 5 10

<210> SEQ ID NO 261
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 261

Arg Asn Asn Gln Arg Pro Ser
1 5

<210> SEQ ID NO 262
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 262

Cys Ala Ala Trp Asp Asp Arg Leu Asn Gly Trp Ala
1 5 10

<210> SEQ ID NO 263
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 263

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Gln Met Thr Trp Ile Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Trp Asn Gly Gly Ser Thr His Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

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Ala Lys Gly Asp Tyr Leu Val Tyr Ser Ser Tyr Tyr Phe Lys Tyr Trp
            100                 105                 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 264
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 264

Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1               5                   10                  15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
            20                  25                  30

Pro Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35                  40                  45

Ile Tyr Arg Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50                  55                  60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65                  70                  75                  80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Arg Leu
                85                  90                  95

Asn Gly Trp Ala Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110


<210> SEQ ID NO 265
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 265

Phe Thr Phe Ser Asp Tyr Gln Met Thr Trp Ile
1               5                   10


<210> SEQ ID NO 266
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 266

Val Ser Gly Ile Ser Trp Asn Gly Gly Ser Thr His Tyr Ala Asp Ser
1               5                   10                  15

Val Lys Gly Arg
            20


<210> SEQ ID NO 267
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 267
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Ala Lys Gly Asp Tyr Leu Val Tyr Ser Ser Tyr Tyr Phe Lys Ser
1               5                   10                  15


<210> SEQ ID NO 268
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 268

Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn Pro Val Asn
1               5                   10


<210> SEQ ID NO 269
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 269

Arg Asn Asn Gln Arg Pro Ser
1               5


<210> SEQ ID NO 270
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 270

Cys Ala Ala Trp Asp Asp Ser Leu Asn Gly Trp Gly
1               5                   10


<210> SEQ ID NO 271
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 271

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20                  25                  30

Gln Met Thr Trp Ile Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Gly Ile Ser Trp Asn Gly Gly Ser Thr His Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Lys Gly Asp Tyr Leu Val Tyr Ser Ser Tyr Tyr Phe Lys Ser Trp
            100                 105                 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120
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<210> SEQ ID NO 272
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 272

Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30

Pro Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Arg Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Leu
85 90 95

Asn Gly Trp Gly Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110

<210> SEQ ID NO 273
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 273

Phe Thr Phe Ser Asp Tyr Gln Met Thr Trp Ile
1 5 10

<210> SEQ ID NO 274
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 274

Val Ser Gly Ile Ser Trp Asn Gly Gly Ser Thr His Tyr Ala Asp Ser
1 5 10 15

Val Lys Gly Arg
20

<210> SEQ ID NO 275
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 275

Ala Lys Gly Asp Tyr Leu Val Tyr Lys Ser Tyr Tyr Phe Lys Ser
1 5 10 15

<210> SEQ ID NO 276
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 276

Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn Pro Val Asn
1 5 10

<210> SEQ ID NO 277
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 277

Arg Asn Asn Gln Arg Pro Ser
1 5

<210> SEQ ID NO 278
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 278

Cys Ala Ala Trp Asp Asp Arg Leu Ser Gly Trp Gly
1 5 10

<210> SEQ ID NO 279
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 279

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Gln Met Thr Trp Ile Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Trp Asn Gly Gly Ser Thr His Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Gly Asp Tyr Leu Val Tyr Lys Ser Tyr Tyr Phe Lys Ser Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 280
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 280

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Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1               5                   10                  15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
            20                  25                  30

Pro Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35                  40                  45

Ile Tyr Arg Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50                  55                  60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65                  70                  75                  80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Arg Leu
                85                  90                  95

Ser Gly Trp Gly Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110


<210> SEQ ID NO 281
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 281

Phe Thr Phe Ser Asp Tyr Gln Met Thr Trp Ile
1               5                   10


<210> SEQ ID NO 282
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 282

Val Ser Gly Ile Ser Trp Asn Gly Gly Ser Thr His Tyr Ala Asp Ser
1               5                   10                  15

Val Lys Gly Arg
            20


<210> SEQ ID NO 283
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 283

Ala Lys Gly Asp Tyr Leu Val Tyr Ser Ser Tyr Tyr Phe Lys Ser
1               5                   10                  15


<210> SEQ ID NO 284
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 284

Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn Pro Val Asn
1               5                   10
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<210> SEQ ID NO 285
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 285

Arg Asn Asn Gln Arg Pro Ser
1 5

<210> SEQ ID NO 286
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 286

Cys Ala Ala Trp Asp Asp Arg Leu Ser Gly Trp Gly
1 5 10

<210> SEQ ID NO 287
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 287

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Gln Met Thr Trp Ile Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Trp Asn Gly Gly Ser Thr His Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Gly Asp Tyr Leu Val Tyr Ser Ser Tyr Tyr Phe Lys Ser Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 288
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 288

Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30

Pro Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu

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        35                  40                  45

Ile Tyr Arg Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50                  55                  60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65                  70                  75                  80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Arg Leu
                85                  90                  95

Ser Gly Trp Gly Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110


<210> SEQ ID NO 289
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 289

Phe Thr Phe Ser Asp Tyr Gln Met Thr Trp Ile
1               5                   10


<210> SEQ ID NO 290
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 290

Val Ser Gly Ile Ser Trp Asn Gly Gly Ser Thr His Tyr Ala Asp Ser
1               5                   10                  15

Val Lys Gly Arg
            20


<210> SEQ ID NO 291
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 291

Ala Lys Gly Asp Tyr Leu Val Tyr Lys Ser Tyr Tyr Phe Lys Ser
1               5                   10                  15


<210> SEQ ID NO 292
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 292

Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn Pro Val Asn
1               5                   10


<210> SEQ ID NO 293
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder
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<400> SEQUENCE: 293

Arg Asn Asn Gln Arg Pro Ser
1 5

<210> SEQ ID NO 294
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 294

Cys Ala Ala Trp Asp Asp Ser Leu Asn Gly Trp Gly
1 5 10

<210> SEQ ID NO 295
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 295

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Gln Met Thr Trp Ile Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Trp Asn Gly Gly Ser Thr His Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Gly Asp Tyr Leu Val Tyr Lys Ser Tyr Tyr Phe Lys Ser Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 296
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 296

Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30

Pro Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Arg Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65 70 75 80

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Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Leu
85 90 95

Asn Gly Trp Gly Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110

<210> SEQ ID NO 297
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: consensus sequence for M20 D02 S-A derived CDR H1
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: X = D or S

<400> SEQUENCE: 297

Phe Ser Xaa Tyr Gln Met Thr Trp Ile
1 5

<210> SEQ ID NO 298
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: consensus sequence for M20 D02 S-A derived CDRH2
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: X = V or I
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: X = A or G
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (10)..(10)
<223> OTHER INFORMATION: X = R or S

<400> SEQUENCE: 298

Val Ser Gly Xaa Ser Trp Asn Gly Xaa Xaa Thr His Tyr Ala Asp Ser
1 5 10 15

Val Lys Gly Arg
20

<210> SEQ ID NO 299
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: consensus for M20 D02 S-A derived CDRH3
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: X = S, K, or R
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (10)..(10)
<223> OTHER INFORMATION: X = A, S or R
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (14)..(14)
<223> OTHER INFORMATION: X = D, K, E or R
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (15)..(15)
<223> OTHER INFORMATION: X = S or Y

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<400> SEQUENCE: 299

Ala Lys Gly Asp Tyr Leu Val Tyr Xaa Xaa Tyr Tyr Phe Xaa Xaa
1 5 10 15

<210> SEQ ID NO 300
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: consensus seqeunce derived from M20 D02 S-A CDRL1
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: X = V or I

<400> SEQUENCE: 300

Ser Gly Ser Ser Ser Asn Xaa Gly Ser Asn Pro Val Asn
1 5 10

<210> SEQ ID NO 301
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: consensus sequence derived from M20 D02 S-A derived CDR L3
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: X = A, Q or R
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: X = D or G
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: X = R or S
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: X = N, W or S
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: X = V, A or G

<400> SEQUENCE: 301

Cys Ala Xaa Trp Xaa Asp Xaa Leu Xaa Gly Trp Xaa
1 5 10

<210> SEQ ID NO 302
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: consensus sequence derived from M31 B01 CDR H1
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: X = N or S
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: X = A or Y

<400> SEQUENCE: 302

Phe Ser Xaa Xaa Trp Met Ser Trp Val
1 5

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<210> SEQ ID NO 303
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: consensus sequence derived from M31 B01 CDR H2
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (10)..(10)
<223> OTHER INFORMATION: X = T or S
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (11)..(11)
<223> OTHER INFORMATION: X = I or T

<400> SEQUENCE: 303

Val Ser Tyr Ile Ser Ser Ser Gly Ser Xaa Xaa Tyr Tyr Ala Asp Ser
1 5 10 15

Val Lys Gly Arg
20

<210> SEQ ID NO 304
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: consensus sequence derived from M31 B01 CDR H3
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (10)..(10)
<223> OTHER INFORMATION: X = Y, K, G, W or N

<400> SEQUENCE: 304

Ala Arg Glu Gly Leu Trp Ala Phe Asp Xaa
1 5 10

<210> SEQ ID NO 305
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: consensus sequence derived from M31 B01 CDR L1
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: X = T or S

<400> SEQUENCE: 305

Xaa Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Val Val His
1 5 10

<210> SEQ ID NO 306
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: consensus sequence derived from M31 B01 CDR L2
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: X = K or Q

<400> SEQUENCE: 306

Asp Asn Asn Xaa Arg Pro Ser
1 5

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<210> SEQ ID NO 307
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: consensus sequence derived from M31 B01 CDR L3
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: X = W, E, F or Y
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: X = R, S or M
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: X = N, K or S
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (10)..(10)
<223> OTHER INFORMATION: X = G or R
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (11)..(11)
<223> OTHER INFORMATION: X = P or A

<400> SEQUENCE: 307

Cys Ala Ala Xaa Asp Asp Xaa Leu Xaa Xaa Xaa Val
1 5 10

<210> SEQ ID NO 308
<211> LENGTH: 351
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 308

gaggtgcagc tgctggagag cgggggggg ctggtgcagc cgggggggag cctgcgcctg 60

agctgcgcgg cgagcgggtt tacctttagc aacgcgtgga tgagctgggt gcgccaggcg 120

ccggggaaag ggctggagtg ggtgagctat attagcagca gcgggagcac catttattat 180

gcggatagcg tgaaagggcg ctttaccatt agccgcgata acagcaaaaa caccctgtat 240

ctgcagatga acagcctgcg cgcggaggat accgcggtgt attattgcgc gcgcgagggg 300

ctgtgggcgt ttgataaatg ggggcagggg accctggtga ccgtgaccag c 351

<210> SEQ ID NO 309
<211> LENGTH: 339
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 309

cagagcgtgc tgacccagcc gccgagcgcg agcgggaccc cggggcagcg cgtgaccatt 60

agctgcaccg ggagcagcag caacattggg gcggggtatg tggtgcattg gtatcagcag 120

ctgccgggga ccgcgccgaa actgctgatt tatgataaca acaaacgccc gagcggggtg 180

ccggatcgct ttagcgggag caaaagcggg accagcgcga gcctggcgat tagcgggctg 240

cgcagcgagg atgaggcgga ttattattgc gcggcgtatg atgatagcct gaaagggccg 300

gtgtttgggg gggggaccaa actgaccgtg ctggggcag 339

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<210> SEQ ID NO 310
<211> LENGTH: 351
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 310

gaggtgcagc tgctggagag cgggggggggg ctggtgcagc cgggggggag cctgcgcctg 60

agctgcgcgg cgagcgggtt tacctttagc aacgcgtgga tgagctgggt gcgccaggcg 120

ccggggaaag ggctggagtg ggtgagctat attagcagca gcgggagcac catttattat 180

gcggatagcg tgaaagggcg ctttaccatt agccgcgata acagcaaaaa caccctgtat 240

ctgcagatga acagcctgcg cgcggaggat accgcggtgt attattgcgc gcgcgagggg 300

ctgtgggcgt ttgataaatg ggggcagggg accctggtga ccgtgaccag c 351

<210> SEQ ID NO 311
<211> LENGTH: 339
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 311

cagagcgtgc tgacccagcc gccgagcgtg agcggggcgc cggggcagcg cgtgaccatt 60

agctgcaccg ggagcagcag caacattggg gcggggtatg tggtgcattg gtatcagcag 120

ctgccgggga ccgcgccgaa actgctgatt tatgataaca acaaacgccc gagcggggtg 180

ccggatcgct ttagcgggag caaaagcggg accagcgcga gcctggcgat tagcgggctg 240

cgcagcgagg atgaggcgga ttattattgc gcggcgtttg atgatagcct gaacgggccg 300

gtgtttgggg gggggaccaa actgaccgtg ctggggcag 339

<210> SEQ ID NO 312
<211> LENGTH: 351
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 312

gaggtgcagc tgctggagag cgggggggggg ctggtgcagc cgggggggag cctgcgcctg 60

agctgcgcgg cgagcgggtt tacctttagc aacgcgtgga tgagctgggt gcgccaggcg 120

ccggggaaag ggctggagtg ggtgagctat attagcagca gcgggagcac catttattat 180

gcggatagcg tgaaagggcg ctttaccatt agccgcgata acagcaaaaa caccctgtat 240

ctgcagatga acagcctgcg cgcggaggat accgcggtgt attattgcgc gcgcgagggg 300

ctgtgggcgt ttgataaatg ggggcagggg accctggtga ccgtgaccag c 351

<210> SEQ ID NO 313
<211> LENGTH: 339
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 313

cagagcgtgc tgacccagcc gccgagcgtg agcggggcgc cggggcagcg cgtgaccatt 60

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agctgcaccg ggagcagcag caacattggg gcggggtatg tggtgcattg gtatcagcag 120

ctgccgggga ccgcgccgaa actgctgatt tatgataaca acaaacgccc gagcggggtg 180

ccggatcgct ttagcgggag caaaagcggg accagcgcga gcctggcgat tagcgggctg 240

cgcagcgagg atgaggcgga ttattattgc gcggcgtttg atgatagcct gaacgggccg 300

gtgtttgggg gggggaccaa actgaccgtg ctggggcag 339

<210> SEQ ID NO 314
<211> LENGTH: 351
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 314

gaggtgcagc tgctggagag cgggggggggg ctggtgcagc cgggggggag cctgcgcctg 60

agctgcgcgg cgagcgggtt tacctttagc agcgcgtgga tgagctgggt gcgccaggcg 120

ccggggaaag ggctggagtg ggtgagctat attagcagca gcgggagcag cacctattat 180

gcggatagcg tgaaagggcg ctttaccatt agccgcgata acagcaaaaa caccctgtat 240

ctgcagatga acagcctgcg cgcggaggat accgcggtgt attattgcgc gcgcgagggg 300

ctgtgggcgt ttgattggtg ggggcagggg accctggtga ccgtgaccag c 351

<210> SEQ ID NO 315
<211> LENGTH: 339
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 315

cagagcgtgc tgacccagcc gccgagcgcg agcgggaccc cggggcagcg cgtgaccatt 60

agctgcagcg ggagcagcag caacattggg gcggggtatg tggtgcattg gtatcagcag 120

ctgccgggga ccgcgccgaa actgctgatt tatgataaca accagcgccc gagcggggtg 180

ccggatcgct ttagcgggag caaaagcggg accagcgcga gcctggcgat tagcgggctg 240

cgcagcgagg atgaggcgga ttattattgc gcggcgtatg atgatagcct gagcgggccg 300

gtgtttgggg gggggaccaa actgaccgtg ctggggcag 339

<210> SEQ ID NO 316
<211> LENGTH: 351
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 316

gaggtgcagc tgctggagag cgggggggggg ctggtgcagc cgggggggag cctgcgcctg 60

agctgcgcgg cgagcgggtt tacctttagc aacgcgtgga tgagctgggt gcgccaggcg 120

ccggggaaag ggctggagtg ggtgagctat attagcagca gcgggagcac catttattat 180

gcggatagcg tgaaagggcg ctttaccatt agccgcgata acagcaaaaa caccctgtat 240

ctgcagatga acagcctgcg cgcggaggat accgcggtgt attattgcgc gcgcgagggg 300

ctgtgggcgt ttgattattg ggggcagggg accctggtga ccgtgaccag c 351

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<210> SEQ ID NO 317
<211> LENGTH: 339
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 317

cagagcgtgc tgacccagcc gccgagcgcg agcgggaccc cggggcagcg cgtgaccatt 60

agctgcagcg ggagcagcag caacattggg gcggggtatg tggtgcattg gtatcagcag 120

ctgccgggga ccgcgccgaa actgctgatt tatgataaca accagcgccc gagcggggtg 180

ccggatcgct ttagcgggag caaaagcggg accagcgcga gcctggcgat tagcgggctg 240

cgcagcgagg atgaggcgga ttattattgc gcggcgtatg atgatagcct gaacgggccg 300

gtgtttgggg gggggaccaa actgaccgtg ctggggcag 339

<210> SEQ ID NO 318
<211> LENGTH: 351
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 318

gaggtgcagc tgctggagag cgggggggg ctggtgcagc cgggggggag cctgcgcctg 60

agctgcgcgg cgagcgggtt tacctttagc agcgcgtgga tgagctgggt gcgccaggcg 120

ccggggaaag ggctggagtg ggtgagctat attagcagca gcgggagcag cacctattat 180

gcggatagcg tgaaagggcg ctttaccatt agccgcgata acagcaaaaa caccctgtat 240

ctgcagatga acagcctgcg cgcggaggat accgcggtgt attattgcgc gcgcgagggg 300

ctgtgggcgt ttgattattg ggggcagggg accctggtga ccgtgagcag c 351

<210> SEQ ID NO 319
<211> LENGTH: 339
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 319

gagagcgtgc tgacccagcc gccgagcgcg agcgggaccc cggggcagcg cgtgaccatt 60

agctgcagcg ggagcagcag caacattggg gcggggtatg tggtgcattg gtatcagcag 120

ctgccgggga ccgcgccgaa actgctgatt tatgataaca accagcgccc gagcggggtg 180

ccggatcgct ttagcgggag caaaagcggg accagcgcga gcctggcgat tagcgggctg 240

cgcagcgagg atgaggcgga ttattattgc gcggcgtggg atgatcgcct gaacgggccg 300

gtgtttgggg gggggaccaa actgaccgtg ctggggcag 339

<210> SEQ ID NO 320
<211> LENGTH: 351
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 320

gaggtgcagc tgctggagag cgggggggg ctggtgcagc cgggggggag cctgcgcctg 60

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agctgcgcgg cgagcgggtt tacctttagc aacgcgtgga tgagctgggt gcgccaggcg 120

ccggggaaag ggctggagtg ggtgagctat attagcagca gcgggagcac catttattat 180

gcggatagcg tgaaagggcg ctttaccatt agccgcgata acagcaaaaa caccctgtat 240

ctgcagatga acagcctgcg cgcggaggat accgcggtgt attattgcgc gcgcgagggg 300

ctgtgggcgt ttgattattg ggggcagggg accctggtga ccgtgagcag c 351

<210> SEQ ID NO 321
<211> LENGTH: 339
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 321

gagagcgtgc tgacccagcc gccgagcgtg agcggggcgc cggggcagcg cgtgaccatt 60

agctgcaccg ggagcagcag caacattggg gcggggtatg tggtgcattg gtatcagcag 120

ctgccgggga ccgcgccgaa actgctgatt tatgataaca acaaacgccc gagcggggtg 180

ccggatcgct ttagcgggag caaaagcggg accagcgcga gcctggcgat tagcgggctg 240

cgcagcgagg atgaggcgga ttattattgc gcggcgtatg atgatcgcct gaacgggccg 300

gtgtttgggg gggggaccaa actgaccgtg ctggggcag 339

<210> SEQ ID NO 322
<211> LENGTH: 351
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 322

gaggtgcagc tgctggagag cgggggggg ctggtgcagc cgggggggag cctgcgcctg 60

agctgcgcgg cgagcgggtt tacctttagc agcgcgtgga tgagctgggt gcgccaggcg 120

ccggggaaag ggctggagtg ggtgagctat attagcagca gcgggagcag cacctattat 180

gcggatagcg tgaaagggcg ctttaccatt agccgcgata acagcaaaaa caccctgtat 240

ctgcagatga acagcctgcg cgcggaggat accgcggtgt attattgcgc gcgcgagggg 300

ctgtgggcgt ttgatgggtg ggggcagggg accctggtga ccgtgagcag c 351

<210> SEQ ID NO 323
<211> LENGTH: 339
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 323

cagagcgtgc tgacccagcc gccgagcgcg agcgggaccc cggggcagcg cgtgaccatt 60

agctgcagcg ggagcagcag caacattggg gcggggtatg tggtgcattg gtatcagcag 120

ctgccgggga ccgcgccgaa actgctgatt tatgataaca accagcgccc gagcggggtg 180

ccggatcgct ttagcgggag caaaagcggg accagcgcga gcctggcgat tagcgggctg 240

cgcagcgagg atgaggcgga ttattattgc gcggcgtatg atgatagcct gaaccgcccg 300

gtgtttgggg gggggaccaa actgaccgtg ctggggcag 339

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<210> SEQ ID NO 324
<211> LENGTH: 351
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 324

gaggtgcagc tgctggagag cgggggggggg ctggtgcagc cgggggggag cctgcgcctg 60

agctgcgcgg cgagcgggtt tacctttagc aacgcgtgga tgagctgggt gcgccaggcg 120

ccggggaaag ggctggagtg ggtgagctat attagcagca gcgggagcac catttattat 180

gcggatagcg tgaaagggcg ctttaccatt agccgcgata acagcaaaaa caccctgtat 240

ctgcagatga acagcctgcg cgcggaggat accgcggtgt attattgcgc gcgcgagggg 300

ctgtgggcgt ttgattattg ggggcagggg accctggtga ccgtgagcag c 351

<210> SEQ ID NO 325
<211> LENGTH: 339
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 325

cagagcgtgc tgacccagcc gccgagcgtg agcggggcgc cggggcagcg cgtgaccatt 60

agctgcaccg ggagcagcag caacattggg gcggggtatg tggtgcattg gtatcagcag 120

ctgccgggga ccgcgccgaa actgctgatt tatgataaca acaaacgccc gagcggggtg 180

ccggatcgct ttagcgggag caaaagcggg accagcgcga gcctggcgat tagcgggctg 240

cgcagcgagg atgaggcgga ttattattgc gcggcgtttg atgatagcct gaacgggccg 300

gtgtttgggg gggggaccaa actgaccgtg ctggggcag 339

<210> SEQ ID NO 326
<211> LENGTH: 351
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 326

gaggtgcagc tgctggagag cgggggggggg ctggtgcagc cgggggggag cctgcgcctg 60

agctgcgcgg cgagcgggtt tacctttagc agcgcgtgga tgagctgggt gcgccaggcg 120

ccggggaaag ggctggagtg ggtgagctat attagcagca gcgggagcag cacctattat 180

gcggatagcg tgaaagggcg ctttaccatt agccgcgata acagcaaaaa caccctgtat 240

ctgcagatga acagcctgcg cgcggaggat accgcggtgt attattgcgc gcgcgagggg 300

ctgtgggcgt ttgataaatg ggggcagggg accctggtga ccgtgaccag c 351

<210> SEQ ID NO 327
<211> LENGTH: 339
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 327

cagagcgtgc tgacccagcc gccgagcgcg agcgggaccc cggggcagcg cgtgaccatt 60

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agctgcaccg ggagcagcag caacattggg gcggggtatg tggtgcattg gtatcagcag 120

ctgccgggga ccgcgccgaa actgctgatt tatgataaca acaaacgccc gagcggggtg 180

ccggatcgct ttagcgggag caaaagcggg accagcgcga gcctggcgat tagcgggctg 240

cgcagcgagg atgaggcgga ttattattgc gcggcgtttg atgatagcct gaacgggccg 300

gtgtttgggg gggggaccaa actgaccgtg ctggggcag 339

<210> SEQ ID NO 328
<211> LENGTH: 351
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 328

gaggtgcagc tgctggagag cgggggggg ctggtgcagc cgggggggag cctgcgcctg 60

agctgcgcgg cgagcgggtt tacctttagc agcgcgtgga tgagctgggt gcgccaggcg 120

ccggggaaag ggctggagtg ggtgagctat attagcagca gcgggagcag cacctattat 180

gcggatagcg tgaaagggcg ctttaccatt agccgcgata acagcaaaaa caccctgtat 240

ctgcagatga acagcctgcg cgcggaggat accgcggtgt attattgcgc gcgcgagggg 300

ctgtgggcgt ttgataaatg ggggcagggg accctggtga ccgtgagcag c 351

<210> SEQ ID NO 329
<211> LENGTH: 339
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a

<400> SEQUENCE: 329

cagagcgtgc tgacccagcc gccgagcgcg agcgggaccc cggggcagcg cgtgaccatt 60

agctgcagcg ggagcagcag caacattggg gcggggtatg tggtgcattg gtatcagcag 120

ctgccgggga ccgcgccgaa actgctgatt tatgataaca accagcgccc gagcggggtg 180

ccggatcgct ttagcgggag caaaagcggg accagcgcga gcctggcgat tagcgggctg 240

cgcagcgagg atgaggcgga ttattattgc gcggcgtttg atgatagcct gaacgggccg 300

gtgtttgggg gggggaccaa actgaccgtg ctggggcag 339

<210> SEQ ID NO 330
<211> LENGTH: 351
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 330

gaggtgcagc tgctggagag cgggggggg ctggtgcagc cgggggggag cctgcgcctg 60

agctgcgcgg cgagcgggtt tacctttagc agcgcgtgga tgagctgggt gcgccaggcg 120

ccggggaaag ggctggagtg ggtgagctat attagcagca gcgggagcag cacctattat 180

gcggatagcg tgaaagggcg ctttaccatt agccgcgata acagcaaaaa caccctgtat 240

ctgcagatga acagcctgcg cgcggaggat accgcggtgt attattgcgc gcgcgagggg 300

ctgtgggcgt ttgataaatg ggggcagggg accctggtga ccgtgagcag c 351

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<210> SEQ ID NO 331
<211> LENGTH: 339
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 331

cagagcgtgc tgacccagcc gccgagcgcg agcgggaccc cggggcagcg cgtgaccatt 60

agctgcagcg ggagcagcag caacattggg gcggggtatg tggtgcattg gtatcagcag 120

ctgccgggga ccgcgccgaa actgctgatt tatgataaca accagcgccc gagcggggtg 180

ccggatcgct ttagcgggag caaaagcggg accagcgcga gcctggcgat tagcgggctg 240

cgcagcgagg atgaggcgga ttattattgc gcggcgtttg atgatcgcct gagcgggccg 300

gtgtttgggg gggggaccaa actgaccgtg ctggggcag 339

<210> SEQ ID NO 332
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 332

gaggtgcagc tgctggagag cgggggggag ctggtgcagc cgggggggag cctgcgcctg 60

agctgcgcgg cgagcgggtt tacctttagc gattatcaga tgacctggat tcgccagacc 120

ccggggaaag ggctggagtg ggtgagcggg gtgagctgga acggggcgcg cacccattat 180

gcggatagcg tgaaagggcg ctttaccatt agccgcgata acagcaaaaa caccctgtat 240

ctgcagatga acagcctgcg cgcggaggat accgcggtgt attattgcgc gaaaggggat 300

tatctggtgt atagcagcta ttattttaaa agctgggggc aggggaccct ggtgaccgtg 360

accagc 366

<210> SEQ ID NO 333
<211> LENGTH: 336
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 333

cagagcgtgc tgacccagcc gccgagcgcg agcgggaccc cggggcagcg cgtgaccatt 60

agctgcagcg ggagcagcag caacgtgggg agcaacccgg tgaactggta tcagcagctg 120

ccggggaccg cgccgaaact gctgatttat cgcaacaacc agcgcccgag cggggtgccg 180

gatcgcttta gcgggagcaa aagcgggacc agcgcgagcc tggcgattag cgggctgcgc 240

agcgaggatg aggcggatta ttattgcgcg gcgtgggatg atcgcctgaa cgggtggggg 300

tttgggggg ggaccaaact gaccgtgctg gggcag 336

<210> SEQ ID NO 334
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 334

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gagcagctgc tggagagcgg ggggggggctg gtgcagccgg gggggagcct gcgcctgagc 60

tgcgcggcga gcgggtttac ctttagcagc tatcagatga cctggattcg ccagaccccg 120

gggaaagggc tggagtgggt gagcgggatt agctggaacg gggggagcac ccattatgcg 180

gatagcgtga aagggcgctt taccattagc cgcgataaca gcaaaaacac cctgtatctg 240

cagatgaaca gcctgcgcgc ggaggatacc gcggtgtatt attgcgcgaa aggggattat 300

ctggtgtata gcgcgtatta ttttgatagc tgggggcagg ggaccctggt gaccgtgagc 360

agc 363

<210> SEQ ID NO 335
<211> LENGTH: 333
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 335

caggtgctga cccagccgcc gagcgcgagc gggaccccgg ggcagcgcgt gaccattagc 60

tgcagcggga gcagcagcaa cattgggagc aacccggtga actggtatca gcagctgccg 120

gggaccgcgc cgaaactgct gatttatcgc aacaaccagc gcccgagcgg ggtgccggat 180

cgctttagcg ggagcaaaag cgggaccagc gcgagcctgg cgattagcgg gctgcgcagc 240

gaggatgagg cggattatta ttgcgcggcg tgggatgatc gcctgaacgg gtgggggttt 300

gggggggga ccaaactgac cgtgctgggg cag 333

<210> SEQ ID NO 336
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 336

gaggtgcagc tgctggagag cgggggggg ctggtgcagc cgggggggag cctgcgcctg 60

agctgcgcgg cgagcgggtt tacctttagc gattatcaga tgacctggat tcgccagacc 120

ccggggaaag ggctggagtg ggtgagcggg attagctgga acgggggggag cacccattat 180

gcggatagcg tgaaagggcg ctttaccatt agccgcgata acagcaaaaa caccctgtat 240

ctgcagatga acagcctgcg cgcggaggat accgcggtgt attattgcgc gaaaggggat 300

tatctggtgt atagcagcta ttattttaaa tattgggggc aggggaccct ggtgaccgtg 360

agcagc 366

<210> SEQ ID NO 337
<211> LENGTH: 336
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 337

cagagcgtgc tgacccagcc gccgagcgcg agcgggaccc cggggcagcg cgtgaccatt 60

agctgcagcg ggagcagcag caacattggg agcaacccgg tgaactggta tcagcagctg 120

ccggggaccg cgccgaaact gctgatttat cgcaacaacc agcgcccgag cggggtgccg 180

gatcgcttta gcgggagcaa aagcgggacc agcgcgagcc tggcgattag cgggctgcgc 240

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agcgaggatg aggcggatta ttattgcgcg gcgtgggatg atcgcctgaa cgggtgggcg 300

tttgggggg ggaccaaact gaccgtgctg gggcag 336

<210> SEQ ID NO 338
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 338

gaggtgcagc tgctggagag cgggggggg ctggtgcagc cgggggggag cctgcgcctg 60

agctgcgcgg cgagcgggtt tacctttagc gattatcaga tgacctggat tcgccagacc 120

ccggggaaag ggctggagtg ggtgagcggg attagctgga acgggggggag cacccattat 180

gcggatagcg tgaaagggcg ctttaccatt agccgcgata acagcaaaaa caccctgtat 240

ctgcagatga acagcctgcg cgcggaggat accgcggtgt attattgcgc gaaaggggat 300

tatctggtgt atagcagcta ttattttaaa agctgggggc aggggaccct ggtgaccgtg 360

agcagc 366

<210> SEQ ID NO 339
<211> LENGTH: 336
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 339

cagagcgtgc tgacccagcc gccgagcgcg agcgggaccc cggggcagcg cgtgaccatt 60

agctgcagcg ggagcagcag caacattggg agcaacccgg tgaactggta tcagcagctg 120

ccggggaccg cgccgaaact gctgatttat cgcaacaacc agcgcccgag cggggtgccg 180

gatcgcttta gcgggagcaa aagcgggacc agcgcgagcc tggcgattag cgggctgcgc 240

agcgaggatg aggcggatta ttattgcgcg gcgtgggatg atagcctgaa cgggtggggg 300

tttgggggg ggaccaaact gaccgtgctg gggcag 336

<210> SEQ ID NO 340
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 340

gaggtgcagc tgctggagag cgggggggg ctggtgcagc cgggggggag cctgcgcctg 60

agctgcgcgg cgagcgggtt tacctttagc gattatcaga tgacctggat tcgccagacc 120

ccggggaaag ggctggagtg ggtgagcggg attagctgga acgggggggag cacccattat 180

gcggatagcg tgaaagggcg ctttaccatt agccgcgata acagcaaaaa caccctgtat 240

ctgcagatga acagcctgcg cgcggaggat accgcggtgt attattgcgc gaaaggggat 300

tatctggtgt ataaaagcta ttattttaaa agctgggggc aggggaccct ggtgaccgtg 360

agcagc 366

<210> SEQ ID NO 341

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<211> LENGTH: 336
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 341

cagagcgtgc tgacccagcc gccgagcgcg agcgggaccc cggggcagcg cgtgaccatt 60

agctgcagcg ggagcagcag caacattggg agcaacccgg tgaactggta tcagcagctg 120

ccggggaccg cgccgaaact gctgatttat cgcaacaacc agcgcccgag cggggtgccg 180

gatcgcttta gcgggagcaa aagcgggacc agcgcgagcc tggcgattag cgggctgcgc 240

agcgaggatg aggcggatta ttattgcgcg gcgtgggatg atcgcctgag cgggtggggg 300

tttgggggggg ggaccaaact gaccgtgctg gggcag 336

<210> SEQ ID NO 342
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 342

gaggtgcagc tgctggagag cgggggggggg ctggtgcagc cgggggggag cctgcgcctg 60

agctgcgcgg cgagcgggtt tacctttagc gattatcaga tgacctggat tcgccagacc 120

ccggggaaag ggctggagtg ggtgagcggg attagctgga acgggggggag cacccattat 180

gcggatagcg tgaaagggcg ctttaccatt agccgcgata acagcaaaaa caccctgtat 240

ctgcagatga acagcctgcg cgcggaggat accgcggtgt attattgcgc gaaaggggat 300

tatctggtgt atagcagcta ttattttaaa agctgggggc aggggaccct ggtgaccgtg 360

agcagc 366

<210> SEQ ID NO 343
<211> LENGTH: 336
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 343

cagagcgtgc tgacccagcc gccgagcgcg agcgggaccc cggggcagcg cgtgaccatt 60

agctgcagcg ggagcagcag caacattggg agcaacccgg tgaactggta tcagcagctg 120

ccggggaccg cgccgaaact gctgatttat cgcaacaacc agcgcccgag cggggtgccg 180

gatcgcttta gcgggagcaa aagcgggacc agcgcgagcc tggcgattag cgggctgcgc 240

agcgaggatg aggcggatta ttattgcgcg gcgtgggatg atcgcctgag cgggtggggg 300

tttgggggggg ggaccaaact gaccgtgctg gggcag 336

<210> SEQ ID NO 344
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 344

gaggtgcagc tgctggagag cgggggggggg ctggtgcagc cgggggggag cctgcgcctg 60

-continued

agctgcgcgg cgagcgggtt tacctttagc gattatcaga tgacctggat tcgccagacc 120

ccggggaaag ggctggagtg ggtgagcggg attagctgga acgggggggag cacccattat 180

gcggatagcg tgaaagggcg ctttaccatt agccgcgata acagcaaaaa caccctgtat 240

ctgcagatga acagcctgcg cgcggaggat accgcggtgt attattgcgc gaaaggggat 300

tatctggtgt ataaaagcta ttattttaaa agctgggggc aggggaccct ggtgaccgtg 360

agcagc 366

<210> SEQ ID NO 345
<211> LENGTH: 336
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C4.4a binder

<400> SEQUENCE: 345

cagagcgtgc tgacccagcc gccgagcgcg agcgggaccc cggggcagcg cgtgaccatt 60

agctgcagcg ggagcagcag caacattggg agcaacccgg tgaactggta tcagcagctg 120

ccggggaccg cgccgaaact gctgatttat cgcaacaacc agcgcccgag cggggtgccg 180

gatcgcttta gcgggagcaa aagcgggacc agcgcgagcc tggcgattag cgggctgcgc 240

agcgaggatg aggcggatta ttattgcgcg gcgtgggatg atagcctgaa cgggtggggg 300

tttgggggggg ggaccaaact gaccgtgctg gggcag 336

<210> SEQ ID NO 346
<211> LENGTH: 217
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 346

Asp Ile Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
20 25 30

Tyr Val Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
35 40 45

Leu Ile Tyr Asp Asn Asn Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu
65 70 75 80

Arg Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Arg
85 90 95

Leu Asn Gly Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
115 120 125

Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
130 135 140

Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Gly Asp Ser Ser Pro Val
145 150 155 160

Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
165 170 175

Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser

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            180                 185                 190

His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
        195                 200                 205

Lys Thr Val Ala Pro Thr Glu Cys Ser
    210                 215


<210> SEQ ID NO 347
<211> LENGTH: 447
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 347

Gln Val Glu Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Leu Trp Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
        115                 120                 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
    130                 135                 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145                 150                 155                 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
                165                 170                 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
            180                 185                 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
        195                 200                 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
    210                 215                 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225                 230                 235                 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
                245                 250                 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
            260                 265                 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
        275                 280                 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
    290                 295                 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305                 310                 315                 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
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                325                 330                 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
            340                 345                 350

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
        355                 360                 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
    370                 375                 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385                 390                 395                 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
                405                 410                 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
            420                 425                 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445


<210> SEQ ID NO 348
<211> LENGTH: 217
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 348

Glu Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1               5                   10                  15

Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
            20                  25                  30

Tyr Val Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
        35                  40                  45

Leu Ile Tyr Asp Asn Asn Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
    50                  55                  60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu
65                  70                  75                  80

Arg Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Arg
                85                  90                  95

Leu Asn Gly Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110

Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
        115                 120                 125

Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
    130                 135                 140

Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
145                 150                 155                 160

Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
                165                 170                 175

Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
            180                 185                 190

His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
        195                 200                 205

Lys Thr Val Ala Pro Thr Glu Cys Ser
    210                 215


<210> SEQ ID NO 349
<211> LENGTH: 446
<212> TYPE: PRT
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<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 349

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Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                  10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Leu Trp Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
        115                 120                 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
    130                 135                 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145                 150                 155                 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
                165                 170                 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
            180                 185                 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
        195                 200                 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
    210                 215                 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225                 230                 235                 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
                245                 250                 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
            260                 265                 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
        275                 280                 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
    290                 295                 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305                 310                 315                 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
                325                 330                 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
            340                 345                 350

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
        355                 360                 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
    370                 375                 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
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385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> SEQ ID NO 350
<211> LENGTH: 217
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 350

Glu Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ala Gly
20 25 30

Tyr Val Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
35 40 45

Leu Ile Tyr Asp Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu
65 70 75 80

Arg Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Arg
85 90 95

Leu Asn Gly Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
115 120 125

Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
130 135 140

Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
145 150 155 160

Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
165 170 175

Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
180 185 190

His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
195 200 205

Lys Thr Val Ala Pro Thr Glu Cys Ser
210 215

<210> SEQ ID NO 351
<211> LENGTH: 446
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 351

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Ala
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

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Ser Tyr Ile Ser Ser Ser Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Leu Trp Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
        115                 120                 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
    130                 135                 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145                 150                 155                 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
                165                 170                 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
            180                 185                 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
        195                 200                 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
    210                 215                 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225                 230                 235                 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
                245                 250                 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
            260                 265                 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
        275                 280                 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
    290                 295                 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305                 310                 315                 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
                325                 330                 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
            340                 345                 350

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
        355                 360                 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
    370                 375                 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385                 390                 395                 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
                405                 410                 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
            420                 425                 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440                 445
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<210> SEQ ID NO 352
<211> LENGTH: 217
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 352

Glu Ser Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
20 25 30

Tyr Val Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
35 40 45

Leu Ile Tyr Asp Asn Asn Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu
65 70 75 80

Arg Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Arg
85 90 95

Leu Asn Gly Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
115 120 125

Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
130 135 140

Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
145 150 155 160

Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
165 170 175

Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
180 185 190

His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
195 200 205

Lys Thr Val Ala Pro Thr Glu Cys Ser
210 215

<210> SEQ ID NO 353
<211> LENGTH: 446
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 353

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Leu Trp Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

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```
Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
        115                 120                 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
    130                 135                 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145                 150                 155                 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
                165                 170                 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
            180                 185                 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
        195                 200                 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
    210                 215                 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225                 230                 235                 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
                245                 250                 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
            260                 265                 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
        275                 280                 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
    290                 295                 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305                 310                 315                 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
                325                 330                 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
            340                 345                 350

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
        355                 360                 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
    370                 375                 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385                 390                 395                 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
                405                 410                 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
            420                 425                 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440                 445


<210> SEQ ID NO 354
<211> LENGTH: 217
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 354

Glu Ser Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1               5                   10                  15

Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
            20                  25                  30
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```
Tyr Val Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
        35                  40                  45

Leu Ile Tyr Asp Asn Asn Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
    50                  55                  60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu
65                  70                  75                  80

Arg Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Tyr Asp Asp Arg
                85                  90                  95

Leu Asn Gly Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110

Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
        115                 120                 125

Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
    130                 135                 140

Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
145                 150                 155                 160

Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
                165                 170                 175

Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
            180                 185                 190

His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
        195                 200                 205

Lys Thr Val Ala Pro Thr Glu Cys Ser
    210                 215


<210> SEQ ID NO 355
<211> LENGTH: 446
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 355

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Leu Trp Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
        115                 120                 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
    130                 135                 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145                 150                 155                 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
                165                 170                 175
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```
Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
            180                 185                 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
        195                 200                 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
    210                 215                 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225                 230                 235                 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
                245                 250                 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
            260                 265                 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
        275                 280                 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
    290                 295                 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305                 310                 315                 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
                325                 330                 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
            340                 345                 350

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
        355                 360                 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
    370                 375                 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385                 390                 395                 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
                405                 410                 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
            420                 425                 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440                 445


<210> SEQ ID NO 356
<211> LENGTH: 217
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 356

Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1               5                   10                  15

Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
            20                  25                  30

Tyr Val Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
        35                  40                  45

Leu Ile Tyr Asp Asn Asn Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
    50                  55                  60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu
65                  70                  75                  80

Arg Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Tyr Asp Asp Ser
                85                  90                  95
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```
Leu Ser Gly Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110

Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
        115                 120                 125

Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
    130                 135                 140

Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
145                 150                 155                 160

Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
                165                 170                 175

Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
            180                 185                 190

His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
        195                 200                 205

Lys Thr Val Ala Pro Thr Glu Cys Ser
    210                 215


<210> SEQ ID NO 357
<211> LENGTH: 446
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 357

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Leu Trp Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
        115                 120                 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
    130                 135                 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145                 150                 155                 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
                165                 170                 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
            180                 185                 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
        195                 200                 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
    210                 215                 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225                 230                 235                 240
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Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
                245                 250                 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
            260                 265                 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
        275                 280                 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
    290                 295                 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305                 310                 315                 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
                325                 330                 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
            340                 345                 350

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
        355                 360                 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
    370                 375                 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385                 390                 395                 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
                405                 410                 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
            420                 425                 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440                 445


<210> SEQ ID NO 358
<211> LENGTH: 217
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 358

Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1               5                   10                  15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ala Gly
            20                  25                  30

Tyr Val Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
        35                  40                  45

Leu Ile Tyr Asp Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe
    50                  55                  60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu
65                  70                  75                  80

Arg Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Tyr Asp Asp Ser
                85                  90                  95

Leu Asn Arg Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110

Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
        115                 120                 125

Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
    130                 135                 140

Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
145                 150                 155                 160
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Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
                165                 170                 175

Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
            180                 185                 190

His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
        195                 200                 205

Lys Thr Val Ala Pro Thr Glu Cys Ser
    210                 215


<210> SEQ ID NO 359
<211> LENGTH: 446
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 359

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Ala
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Tyr Ile Ser Ser Ser Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Leu Trp Ala Phe Asp Gly Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
        115                 120                 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
    130                 135                 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145                 150                 155                 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
                165                 170                 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
            180                 185                 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
        195                 200                 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
    210                 215                 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225                 230                 235                 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
                245                 250                 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
            260                 265                 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
        275                 280                 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
    290                 295                 300
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Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305                 310                 315                 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
                325                 330                 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
            340                 345                 350

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
        355                 360                 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
    370                 375                 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385                 390                 395                 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
                405                 410                 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
            420                 425                 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440                 445


<210> SEQ ID NO 360
<211> LENGTH: 217
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 360

Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1               5                   10                  15

Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
            20                  25                  30

Tyr Val Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
        35                  40                  45

Leu Ile Tyr Asp Asn Asn Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
    50                  55                  60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu
65                  70                  75                  80

Arg Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Phe Asp Asp Arg
                85                  90                  95

Leu Asn Gly Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110

Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
        115                 120                 125

Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
    130                 135                 140

Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
145                 150                 155                 160

Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
                165                 170                 175

Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
            180                 185                 190

His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
        195                 200                 205

Lys Thr Val Ala Pro Thr Glu Cys Ser
    210                 215
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<210> SEQ ID NO 361
<211> LENGTH: 446
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 361

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Leu Trp Ala Phe Asp Lys Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
210 215 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

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Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
    370                 375                 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385                 390                 395                 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
                405                 410                 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
            420                 425                 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440                 445


<210> SEQ ID NO 362
<211> LENGTH: 217
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 362

Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1               5                   10                  15

Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
            20                  25                  30

Tyr Val Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
        35                  40                  45

Leu Ile Tyr Asp Asn Asn Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
    50                  55                  60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu
65                  70                  75                  80

Arg Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Phe Asp Asp Ser
                85                  90                  95

Leu Asn Gly Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110

Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
        115                 120                 125

Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
    130                 135                 140

Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
145                 150                 155                 160

Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
                165                 170                 175

Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
            180                 185                 190

His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
        195                 200                 205

Lys Thr Val Ala Pro Thr Glu Cys Ser
    210                 215


<210> SEQ ID NO 363
<211> LENGTH: 446
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 363

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15
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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Leu Trp Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
        115                 120                 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
    130                 135                 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145                 150                 155                 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
                165                 170                 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
            180                 185                 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
        195                 200                 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
    210                 215                 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225                 230                 235                 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
                245                 250                 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
            260                 265                 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
        275                 280                 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
    290                 295                 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305                 310                 315                 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
                325                 330                 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
            340                 345                 350

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
        355                 360                 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
    370                 375                 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385                 390                 395                 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
                405                 410                 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
            420                 425                 430
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His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440                 445


<210> SEQ ID NO 364
<211> LENGTH: 217
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 364

Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1               5                   10                  15

Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
            20                  25                  30

Tyr Val Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
        35                  40                  45

Leu Ile Tyr Asp Asn Asn Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
    50                  55                  60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu
65                  70                  75                  80

Arg Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Tyr Asp Asp Ser
                85                  90                  95

Leu Ser Gly Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110

Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
        115                 120                 125

Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
    130                 135                 140

Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
145                 150                 155                 160

Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
                165                 170                 175

Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
            180                 185                 190

His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
        195                 200                 205

Lys Thr Val Ala Pro Thr Glu Cys Ser
    210                 215


<210> SEQ ID NO 365
<211> LENGTH: 446
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 365

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Ala
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
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Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Leu Trp Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
        115                 120                 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
    130                 135                 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145                 150                 155                 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
                165                 170                 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
            180                 185                 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
        195                 200                 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
    210                 215                 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225                 230                 235                 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
                245                 250                 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
            260                 265                 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
        275                 280                 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
    290                 295                 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305                 310                 315                 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
                325                 330                 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
            340                 345                 350

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
        355                 360                 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
    370                 375                 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385                 390                 395                 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
                405                 410                 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
            420                 425                 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440                 445


<210> SEQ ID NO 366
<211> LENGTH: 217
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 366
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```
Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1               5                  10                  15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ala Gly
            20                  25                  30

Tyr Val Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
        35                  40                  45

Leu Ile Tyr Asp Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe
    50                  55                  60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu
65                  70                  75                  80

Arg Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Phe Asp Asp Ser
                85                  90                  95

Leu Asn Gly Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110

Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
        115                 120                 125

Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
    130                 135                 140

Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
145                 150                 155                 160

Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
                165                 170                 175

Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
            180                 185                 190

His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
        195                 200                 205

Lys Thr Val Ala Pro Thr Glu Cys Ser
    210                 215


<210> SEQ ID NO 367
<211> LENGTH: 446
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 367

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                  10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Ala
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Tyr Ile Ser Ser Ser Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Leu Trp Ala Phe Asp Lys Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
        115                 120                 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
    130                 135                 140
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```
Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145                 150                 155                 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
                165                 170                 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
            180                 185                 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
        195                 200                 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
    210                 215                 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225                 230                 235                 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
                245                 250                 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
            260                 265                 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
        275                 280                 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
    290                 295                 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305                 310                 315                 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
                325                 330                 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
            340                 345                 350

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
        355                 360                 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
    370                 375                 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385                 390                 395                 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
                405                 410                 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
            420                 425                 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440                 445


<210> SEQ ID NO 368
<211> LENGTH: 217
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 368

Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1               5                   10                  15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ala Gly
            20                  25                  30

Tyr Val Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
        35                  40                  45

Leu Ile Tyr Asp Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe
    50                  55                  60
```

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```
Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu
65                  70                  75                  80

Arg Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Phe Asp Asp Arg
                85                  90                  95

Leu Ser Gly Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110

Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
        115                 120                 125

Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
    130                 135                 140

Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
145                 150                 155                 160

Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
                165                 170                 175

Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
            180                 185                 190

His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
        195                 200                 205

Lys Thr Val Ala Pro Thr Glu Cys Ser
    210                 215


<210> SEQ ID NO 369
<211> LENGTH: 446
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 369

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Ala
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Tyr Ile Ser Ser Ser Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Leu Trp Ala Phe Asp Lys Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
        115                 120                 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
    130                 135                 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145                 150                 155                 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
                165                 170                 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
            180                 185                 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
        195                 200                 205
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Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
    210                 215                 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225                 230                 235                 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
                245                 250                 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
            260                 265                 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
        275                 280                 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
    290                 295                 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305                 310                 315                 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
                325                 330                 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
            340                 345                 350

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
        355                 360                 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
    370                 375                 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385                 390                 395                 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
                405                 410                 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
            420                 425                 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440                 445


<210> SEQ ID NO 370
<211> LENGTH: 216
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 370

Asp Ile Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1               5                   10                  15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Val Gly Ser Asn
            20                  25                  30

Pro Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35                  40                  45

Ile Tyr Arg Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50                  55                  60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65                  70                  75                  80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Arg Leu
                85                  90                  95

Asn Gly Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115                 120                 125
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Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130                 135                 140

Pro Gly Ala Val Thr Val Ala Trp Lys Gly Asp Ser Ser Pro Val Lys
145                 150                 155                 160

Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                165                 170                 175

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195                 200                 205

Thr Val Ala Pro Thr Glu Cys Ser
    210                 215


<210> SEQ ID NO 371
<211> LENGTH: 452
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 371

Gln Val Glu Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20                  25                  30

Gln Met Thr Trp Ile Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Gly Val Ser Trp Asn Gly Ala Arg Thr His Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Lys Gly Asp Tyr Leu Val Tyr Ser Ala Tyr Tyr Phe Asp Ser Trp
            100                 105                 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
    130                 135                 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
    210                 215                 220

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
225                 230                 235                 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
                245                 250                 255

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
            260                 265                 270
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```
His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
        275                 280                 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
    290                 295                 300

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305                 310                 315                 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
                325                 330                 335

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
            340                 345                 350

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
        355                 360                 365

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
    370                 375                 380

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
385                 390                 395                 400

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
                405                 410                 415

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
            420                 425                 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
        435                 440                 445

Ser Pro Gly Lys
    450


<210> SEQ ID NO 372
<211> LENGTH: 216
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 372

Glu Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1               5                   10                  15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Val Gly Ser Asn
            20                  25                  30

Pro Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35                  40                  45

Ile Tyr Arg Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50                  55                  60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65                  70                  75                  80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Arg Leu
                85                  90                  95

Asn Gly Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115                 120                 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130                 135                 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145                 150                 155                 160

Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                165                 170                 175
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```
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195                 200                 205

Thr Val Ala Pro Thr Glu Cys Ser
    210                 215


<210> SEQ ID NO 373
<211> LENGTH: 451
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 373

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20                  25                  30

Gln Met Thr Trp Ile Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Gly Val Ser Trp Asn Gly Ala Arg Thr His Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Lys Gly Asp Tyr Leu Val Tyr Ser Ala Tyr Tyr Phe Asp Ser Trp
            100                 105                 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
    130                 135                 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
    210                 215                 220

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
225                 230                 235                 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
                245                 250                 255

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
            260                 265                 270

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
        275                 280                 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
    290                 295                 300

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305                 310                 315                 320
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Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
                325                 330                 335

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
            340                 345                 350

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
        355                 360                 365

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
    370                 375                 380

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
385                 390                 395                 400

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
                405                 410                 415

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
            420                 425                 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
        435                 440                 445

Ser Pro Gly
    450


<210> SEQ ID NO 374
<211> LENGTH: 216
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 374

Glu Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1               5                   10                  15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
            20                  25                  30

Pro Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35                  40                  45

Ile Tyr Arg Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50                  55                  60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65                  70                  75                  80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Arg Leu
                85                  90                  95

Asn Gly Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115                 120                 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130                 135                 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145                 150                 155                 160

Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                165                 170                 175

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195                 200                 205

Thr Val Ala Pro Thr Glu Cys Ser
    210                 215
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<210> SEQ ID NO 375
<211> LENGTH: 451
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 375

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Gln Met Thr Trp Ile Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Trp Asn Gly Gly Ser Thr His Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Gly Asp Tyr Leu Val Tyr Ser Ala Tyr Tyr Phe Asp Ser Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
115 120 125

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
130 135 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145 150 155 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
165 170 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
180 185 190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
195 200 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
210 215 220

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
225 230 235 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
245 250 255

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
260 265 270

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
275 280 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
290 295 300

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305 310 315 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
325 330 335

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
340 345 350

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
355 360 365

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```
Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
    370                 375                 380

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
385                 390                 395                 400

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
                405                 410                 415

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
            420                 425                 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
        435                 440                 445

Ser Pro Gly
    450


<210> SEQ ID NO 376
<211> LENGTH: 216
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 376

Glu Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1               5                   10                  15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
            20                  25                  30

Pro Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35                  40                  45

Ile Tyr Arg Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50                  55                  60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65                  70                  75                  80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Arg Leu
                85                  90                  95

Asn Gly Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115                 120                 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130                 135                 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145                 150                 155                 160

Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                165                 170                 175

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195                 200                 205

Thr Val Ala Pro Thr Glu Cys Ser
    210                 215


<210> SEQ ID NO 377
<211> LENGTH: 451
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 377

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
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```
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30

Gln Met Thr Trp Ile Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Gly Ile Ser Trp Asn Gly Gly Ser Thr His Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Lys Gly Asp Tyr Leu Val Tyr Ser Ala Tyr Tyr Phe Asp Ser Trp
            100                 105                 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
    130                 135                 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
    210                 215                 220

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
225                 230                 235                 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
                245                 250                 255

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
            260                 265                 270

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
        275                 280                 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
    290                 295                 300

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305                 310                 315                 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
                325                 330                 335

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
            340                 345                 350

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
        355                 360                 365

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
    370                 375                 380

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
385                 390                 395                 400

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
                405                 410                 415
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```
Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
            420                 425                 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
        435                 440                 445

Ser Pro Gly
    450
```

<210> SEQ ID NO 378
<211> LENGTH: 216
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 378

```
Glu Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1               5                   10                  15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
            20                  25                  30

Pro Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35                  40                  45

Ile Tyr Arg Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50                  55                  60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65                  70                  75                  80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Arg Leu
                85                  90                  95

Asn Gly Trp Gly Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115                 120                 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130                 135                 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145                 150                 155                 160

Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                165                 170                 175

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195                 200                 205

Thr Val Ala Pro Thr Glu Cys Ser
    210                 215
```

<210> SEQ ID NO 379
<211> LENGTH: 451
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 379

```
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20                  25                  30

Gln Met Thr Trp Ile Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Gly Ile Ser Trp Asn Gly Gly Ser Thr His Tyr Ala Asp Ser Val
```

-continued

```
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Lys Gly Asp Tyr Leu Val Tyr Ser Ala Tyr Tyr Phe Asp Ser Trp
            100                 105                 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
    130                 135                 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
    210                 215                 220

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
225                 230                 235                 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
                245                 250                 255

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
            260                 265                 270

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
        275                 280                 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
    290                 295                 300

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305                 310                 315                 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
                325                 330                 335

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
            340                 345                 350

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
        355                 360                 365

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
    370                 375                 380

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
385                 390                 395                 400

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
                405                 410                 415

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
            420                 425                 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
        435                 440                 445

Ser Pro Gly
    450
```

-continued

<210> SEQ ID NO 380
<211> LENGTH: 216
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 380

Glu Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30

Pro Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Arg Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Arg Leu
85 90 95

Asn Gly Trp Gly Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
115 120 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
130 135 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145 150 155 160

Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
165 170 175

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
180 185 190

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
195 200 205

Thr Val Ala Pro Thr Glu Cys Ser
210 215

<210> SEQ ID NO 381
<211> LENGTH: 451
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 381

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gln Met Thr Trp Ile Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Trp Asn Gly Gly Ser Thr His Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Gly Asp Tyr Leu Val Tyr Ser Ala Tyr Tyr Phe Asp Ser Trp

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```
           100                 105                 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
    130                 135                 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
    210                 215                 220

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
225                 230                 235                 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
                245                 250                 255

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
            260                 265                 270

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
        275                 280                 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
    290                 295                 300

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305                 310                 315                 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
                325                 330                 335

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
            340                 345                 350

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
        355                 360                 365

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
    370                 375                 380

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
385                 390                 395                 400

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
                405                 410                 415

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
            420                 425                 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
        435                 440                 445

Ser Pro Gly
    450


<210> SEQ ID NO 382
<211> LENGTH: 216
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 382

Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
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1               5                   10                  15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
            20                  25                  30

Pro Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35                  40                  45

Ile Tyr Arg Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50                  55                  60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65                  70                  75                  80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Arg Leu
                85                  90                  95

Ser Gly Trp Ala Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115                 120                 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130                 135                 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145                 150                 155                 160

Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                165                 170                 175

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195                 200                 205

Thr Val Ala Pro Thr Glu Cys Ser
    210                 215


<210> SEQ ID NO 383
<211> LENGTH: 451
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 383

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20                  25                  30

Gln Met Thr Trp Ile Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Gly Ile Ser Trp Asn Gly Gly Ser Thr His Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Lys Gly Asp Tyr Leu Val Tyr Ser Ser Tyr Tyr Phe Lys Ser Trp
            100                 105                 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
    130                 135                 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
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145                 150                 155                 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
    210                 215                 220

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
225                 230                 235                 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
                245                 250                 255

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
            260                 265                 270

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
        275                 280                 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
    290                 295                 300

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305                 310                 315                 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
                325                 330                 335

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
            340                 345                 350

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
        355                 360                 365

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
    370                 375                 380

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
385                 390                 395                 400

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
                405                 410                 415

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
            420                 425                 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
        435                 440                 445

Ser Pro Gly
    450


<210> SEQ ID NO 384
<211> LENGTH: 216
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 384

Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1               5                   10                  15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
            20                  25                  30

Pro Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35                  40                  45

Ile Tyr Arg Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
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    50                  55                  60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65                  70                  75                  80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Leu
                85                  90                  95

Ser Gly Trp Ala Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115                 120                 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130                 135                 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145                 150                 155                 160

Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                165                 170                 175

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195                 200                 205

Thr Val Ala Pro Thr Glu Cys Ser
    210                 215


<210> SEQ ID NO 385
<211> LENGTH: 451
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 385

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20                  25                  30

Gln Met Thr Trp Ile Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Gly Ile Ser Trp Asn Gly Gly Ser Thr His Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Lys Gly Asp Tyr Leu Val Tyr Lys Ser Tyr Tyr Phe Lys Ser Trp
            100                 105                 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
    130                 135                 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
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        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
    210                 215                 220

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
225                 230                 235                 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
                245                 250                 255

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
            260                 265                 270

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
        275                 280                 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
    290                 295                 300

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305                 310                 315                 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
                325                 330                 335

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
            340                 345                 350

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
        355                 360                 365

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
    370                 375                 380

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
385                 390                 395                 400

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
                405                 410                 415

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
            420                 425                 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
        435                 440                 445

Ser Pro Gly
    450


<210> SEQ ID NO 386
<211> LENGTH: 216
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 386

Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1               5                   10                  15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
            20                  25                  30

Pro Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35                  40                  45

Ile Tyr Arg Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50                  55                  60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65                  70                  75                  80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Arg Leu
                85                  90                  95

Asn Gly Trp Ala Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
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            100                 105                 110

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115                 120                 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130                 135                 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145                 150                 155                 160

Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                165                 170                 175

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195                 200                 205

Thr Val Ala Pro Thr Glu Cys Ser
    210                 215


<210> SEQ ID NO 387
<211> LENGTH: 451
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 387

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20                  25                  30

Gln Met Thr Trp Ile Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Gly Ile Ser Trp Asn Gly Gly Ser Thr His Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Lys Gly Asp Tyr Leu Val Tyr Ser Ser Tyr Tyr Phe Lys Tyr Trp
            100                 105                 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
    130                 135                 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
    210                 215                 220

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
225                 230                 235                 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
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               245                 250                 255

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
            260                 265                 270

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
        275                 280                 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
    290                 295                 300

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305                 310                 315                 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
                325                 330                 335

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
            340                 345                 350

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
        355                 360                 365

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
    370                 375                 380

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
385                 390                 395                 400

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
                405                 410                 415

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
            420                 425                 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
        435                 440                 445

Ser Pro Gly
    450


<210> SEQ ID NO 388
<211> LENGTH: 216
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 388

Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1               5                   10                  15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
            20                  25                  30

Pro Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35                  40                  45

Ile Tyr Arg Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50                  55                  60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65                  70                  75                  80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Leu
                85                  90                  95

Asn Gly Trp Gly Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115                 120                 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130                 135                 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
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145                 150                 155                 160

Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                165                 170                 175

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195                 200                 205

Thr Val Ala Pro Thr Glu Cys Ser
    210                 215


<210> SEQ ID NO 389
<211> LENGTH: 451
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 389

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20                  25                  30

Gln Met Thr Trp Ile Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Gly Ile Ser Trp Asn Gly Gly Ser Thr His Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Lys Gly Asp Tyr Leu Val Tyr Ser Ser Tyr Tyr Phe Lys Ser Trp
            100                 105                 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
    130                 135                 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
    210                 215                 220

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
225                 230                 235                 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
                245                 250                 255

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
            260                 265                 270

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
        275                 280                 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
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    290                 295                 300

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305                 310                 315                 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
                325                 330                 335

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
            340                 345                 350

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
        355                 360                 365

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
    370                 375                 380

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
385                 390                 395                 400

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
                405                 410                 415

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
            420                 425                 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
        435                 440                 445

Ser Pro Gly
    450


<210> SEQ ID NO 390
<211> LENGTH: 216
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 390

Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1               5                   10                  15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
            20                  25                  30

Pro Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35                  40                  45

Ile Tyr Arg Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50                  55                  60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65                  70                  75                  80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Arg Leu
                85                  90                  95

Ser Gly Trp Gly Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115                 120                 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130                 135                 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145                 150                 155                 160

Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                165                 170                 175

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
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        195                 200                 205

Thr Val Ala Pro Thr Glu Cys Ser
    210                 215


<210> SEQ ID NO 391
<211> LENGTH: 451
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 391

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20                  25                  30

Gln Met Thr Trp Ile Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Gly Ile Ser Trp Asn Gly Gly Ser Thr His Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Lys Gly Asp Tyr Leu Val Tyr Lys Ser Tyr Tyr Phe Lys Ser Trp
            100                 105                 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
    130                 135                 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
    210                 215                 220

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
225                 230                 235                 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
                245                 250                 255

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
            260                 265                 270

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
        275                 280                 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
    290                 295                 300

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305                 310                 315                 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
                325                 330                 335

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
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            340                 345                 350

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
        355                 360                 365

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
    370                 375                 380

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
385                 390                 395                 400

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
                405                 410                 415

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
            420                 425                 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
        435                 440                 445

Ser Pro Gly
    450


<210> SEQ ID NO 392
<211> LENGTH: 216
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 392

Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1               5                   10                  15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
            20                  25                  30

Pro Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35                  40                  45

Ile Tyr Arg Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50                  55                  60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65                  70                  75                  80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Arg Leu
                85                  90                  95

Ser Gly Trp Gly Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115                 120                 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130                 135                 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145                 150                 155                 160

Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                165                 170                 175

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195                 200                 205

Thr Val Ala Pro Thr Glu Cys Ser
    210                 215


<210> SEQ ID NO 393
<211> LENGTH: 451
<212> TYPE: PRT
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<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 393

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Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                  10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20                  25                  30

Gln Met Thr Trp Ile Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Gly Ile Ser Trp Asn Gly Gly Ser Thr His Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Lys Gly Asp Tyr Leu Val Tyr Ser Ser Tyr Tyr Phe Lys Ser Trp
            100                 105                 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
    130                 135                 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
    210                 215                 220

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
225                 230                 235                 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
                245                 250                 255

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
            260                 265                 270

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
        275                 280                 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
    290                 295                 300

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305                 310                 315                 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
                325                 330                 335

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
            340                 345                 350

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
        355                 360                 365

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
    370                 375                 380

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
```

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385 390 395 400

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
405 410 415

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
420 425 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
435 440 445

Ser Pro Gly
450

<210> SEQ ID NO 394
<211> LENGTH: 216
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 394

Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30

Pro Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Arg Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Leu
85 90 95

Asn Gly Trp Gly Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
115 120 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
130 135 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145 150 155 160

Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
165 170 175

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
180 185 190

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
195 200 205

Thr Val Ala Pro Thr Glu Cys Ser
210 215

<210> SEQ ID NO 395
<211> LENGTH: 451
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 395

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

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Gln Met Thr Trp Ile Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Gly Ile Ser Trp Asn Gly Gly Ser Thr His Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Lys Gly Asp Tyr Leu Val Tyr Lys Ser Tyr Tyr Phe Lys Ser Trp
            100                 105                 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
    130                 135                 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
    210                 215                 220

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
225                 230                 235                 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
                245                 250                 255

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
            260                 265                 270

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
        275                 280                 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
    290                 295                 300

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305                 310                 315                 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
                325                 330                 335

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
            340                 345                 350

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
        355                 360                 365

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
    370                 375                 380

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
385                 390                 395                 400

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
                405                 410                 415

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
            420                 425                 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
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        435                 440                 445

Ser Pro Gly
    450


<210> SEQ ID NO 396
<211> LENGTH: 216
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 396

Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1               5                   10                  15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
            20                  25                  30

Pro Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35                  40                  45

Ile Tyr Arg Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50                  55                  60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65                  70                  75                  80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Leu
                85                  90                  95

Ser Gly Trp Ala Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115                 120                 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130                 135                 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145                 150                 155                 160

Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                165                 170                 175

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195                 200                 205

Thr Val Ala Pro Thr Glu Cys Ser
    210                 215


<210> SEQ ID NO 397
<211> LENGTH: 451
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 397

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30

Gln Met Thr Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Gly Ile Ser Trp Asn Gly Gly Ser Thr His Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
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Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Lys Gly Asp Tyr Leu Val Tyr Lys Ser Tyr Tyr Phe Lys Ser Trp
            100                 105                 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
    130                 135                 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
    210                 215                 220

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
225                 230                 235                 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
                245                 250                 255

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
            260                 265                 270

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
        275                 280                 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
    290                 295                 300

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305                 310                 315                 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
                325                 330                 335

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
            340                 345                 350

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
        355                 360                 365

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
    370                 375                 380

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
385                 390                 395                 400

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
                405                 410                 415

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
            420                 425                 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
        435                 440                 445

Ser Pro Gly
    450


<210> SEQ ID NO 398
<211> LENGTH: 10
<212> TYPE: PRT
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-continued

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 398

Gly Tyr Ser Phe Thr Ser Tyr Trp Ile Gly
1 5 10

<210> SEQ ID NO 399
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 399

Trp Met Gly Ile Ile Asp Pro Gly Asp Ser Arg Thr Arg Tyr Ser Pro
1 5 10 15

Ser Phe Gln Gly
20

<210> SEQ ID NO 400
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 400

Gly Gln Leu Tyr Gly Gly Thr Tyr Met Asp Gly
1 5 10

<210> SEQ ID NO 401
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 401

Thr Gly Thr Ser Ser Asp Ile Gly Gly Tyr Asn Ser Val Ser
1 5 10

<210> SEQ ID NO 402
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 402

Leu Met Ile Tyr Gly Val Asn Asn Arg Pro Ser
1 5 10

<210> SEQ ID NO 403
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 403

Ser Ser Tyr Asp Ile Glu Ser Ala Thr Pro
1 5 10

<210> SEQ ID NO 404
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 404

Gln Val Glu Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr

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            20                  25                  30

Trp Ile Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45

Gly Ile Ile Asp Pro Gly Asp Ser Arg Thr Arg Tyr Ser Pro Ser Phe
    50                  55                  60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Gln Leu Tyr Gly Gly Thr Tyr Met Asp Gly Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 405
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 405

Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1               5                   10                  15

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Ile Gly Gly Tyr
            20                  25                  30

Asn Ser Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45

Met Ile Tyr Gly Val Asn Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Asp Ile Glu
                85                  90                  95

Ser Ala Thr Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110

Gln


<210> SEQ ID NO 406
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 406

caggtggaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt     60

agctgcaaag gttccggata ttcctttact tcttattgga ttggttgggt gcgccaggcc    120

cctgggaagg gtctcgagtg gatgggcatt atcgatccgg gtgatagccg tacccgttat    180

tctccgagct ttcagggcca ggtgaccatt agcgcggata aaagcattag caccgcgtat    240

cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgtggtcag    300

ctttatggtg gtacttatat ggatggttgg ggccaaggca ccctggtgac ggttagctca    360


<210> SEQ ID NO 407
<211> LENGTH: 339
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
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<400> SEQUENCE: 407

gatatcgcac tgacccagcc agcttcagtg agcggctcac caggtcagag cattaccatc 60

tcgtgtacgg gtactagcag cgatattggt ggttataatt ctgtgtcttg gtaccagcag 120

catcccggga aggcgccgaa acttatgatt tatggtgtta ataatcgtcc ctcaggcgtg 180

agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240

caagcggaag acgaagcgga ttattattgc tcttcttatg atattgagtc tgctactcct 300

gtgtttggcg gcggcacgaa gttaaccgtc ctaggtcag 339

<210> SEQ ID NO 408
<211> LENGTH: 450
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 408

Gln Val Glu Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

Trp Ile Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asp Pro Gly Asp Ser Arg Thr Arg Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Gly Gln Leu Tyr Gly Gly Thr Tyr Met Asp Gly Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg

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    290                 295                 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                 330                 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
        355                 360                 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                 390                 395                 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                405                 410                 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            420                 425                 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        435                 440                 445

Gly Lys
    450


<210> SEQ ID NO 409
<211> LENGTH: 217
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 409

Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1               5                   10                  15

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Ile Gly Gly Tyr
            20                  25                  30

Asn Ser Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45

Met Ile Tyr Gly Val Asn Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Asp Ile Glu
                85                  90                  95

Ser Ala Thr Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110

Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
        115                 120                 125

Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
    130                 135                 140

Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Gly Asp Ser Ser Pro Val
145                 150                 155                 160

Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
                165                 170                 175

Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
            180                 185                 190

His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
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195 200 205

Lys Thr Val Ala Pro Thr Glu Cys Ser
210 215

<210> SEQ ID NO 410
<211> LENGTH: 1353
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 410

caggtggaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact tcttattgga ttggttgggt gcgccaggcc 120

cctgggaagg gtctcgagtg gatgggcatt atcgatccgg gtgatagccg tacccgttat 180

tctccgagct ttcagggcca ggtgaccatt agcgcggata aaagcattag caccgcgtat 240

cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgtggtcag 300

ctttatggtg gtacttatat ggatggttgg ggccaaggca ccctggtgac ggttagctca 360

gcctccacca agggtccatc ggtcttcccc ctggcaccct cctccaagag cacctctggg 420

ggcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg 480

tggaactcag gcgccctgac cagcggcgtg cacaccttcc cggctgtcct acagtcctca 540

ggactctact ccctcagcag cgtggtgacc gtgccctcca gcagcttggg cacccagacc 600

tacatctgca acgtgaatca caagcccagc aacaccaagg tggacaagaa agttgagccc 660

aaatcttgtg acaaaactca cacatgccca ccgtgcccag cacctgaact cctgggggga 720

ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggaccccct 780

gaggtcacat gcgtggtggt ggacgtgagc cacgaagacc ctgaggtcaa gttcaactgg 840

tacgtggacg gcgtggaggt gcataatgcc aagacaaagc cgcgggagga gcagtacaac 900

agcacgtacc gggtggtcag cgtcctcacc gtcctgcacc aggactggct gaatggcaag 960

gagtacaagt gcaaggtctc caacaaagcc ctcccagccc ccatcgagaa aaccatctcc 1020

aaagccaaag ggcagccccg agaaccacag gtgtacaccc tgccccatc ccgggatgag 1080

ctgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctatcc cagcgacatc 1140

gccgtggagt gggagagcaa tgggcagccg gagaacaact acaagaccac gcctcccgtg 1200

ctggactccg acggctcctt cttcctctac agcaagctca ccgtggacaa gagcaggtgg 1260

cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg 1320

cagaagagcc tctccctgtc tccgggtaaa tga 1353

<210> SEQ ID NO 411
<211> LENGTH: 654
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 411

gatatcgcac tgacccagcc agcttcagtg agcggctcac caggtcagag cattaccatc 60

tcgtgtacgg gtactagcag cgatattggt ggttataatt ctgtgtcttg gtaccagcag 120

catcccggga aggcgccgaa acttatgatt tatggtgtta ataatcgtcc ctcaggcgtg 180

agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240

caagcggaag acgaagcgga ttattattgc tcttcttatg atattgagtc tgctactcct 300

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gtgtttggcg gcggcacgaa gttaaccgtc ctaggtcagc ccaaggctgc cccctcggtc    360

actctgttcc cgccctcctc tgaggagctt caagccaaca aggccacact ggtgtgtctc    420

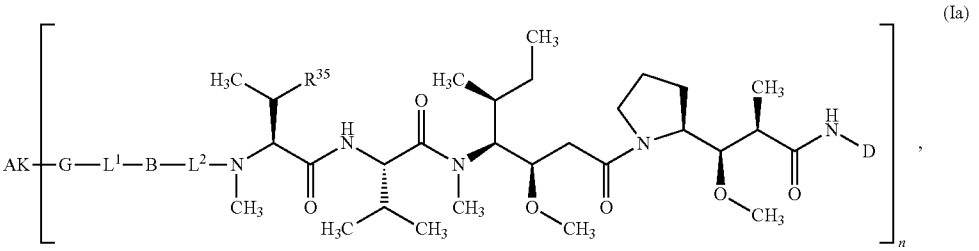
ataagtgact tctacccggg agccgtgaca gtggcctgga agggagatag cagccccgtc    480

aaggcgggag tggagaccac cacaccctcc aaacaaagca acaacaagta cgcggccagc    540

agctatctga gcctgacgcc tgagcagtgg aagtcccaca gaagctacag ctgccaggtc    600

acgcatgaag ggagcaccgt ggagaagaca gtggccccta cagaatgttc atag          654
```

1. Binder-drug conjugates of the general formula (Ia)



(Ia)

in which

n is a number from 1 to 50,

AK is a binder,

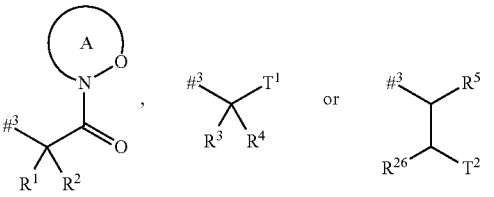
the group §-G-L^1-B-L^2-§§ is a linker,

where

§ marks the linkage site with the group AK and

§§ marks the linkage site with the nitrogen atom,

D is a group of the formula



where

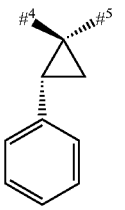
$\#^3$ marks the linkage site with the nitrogen atom,

R^1 is hydrogen or methyl,

R^2 is isopropyl, isobutyl, sec-butyl, tert-butyl, phenyl, benzyl, 1-hydroxyethyl, 4-hydroxybenzyl, 4-hydroxy-3-nitrobenzyl, 4-hydroxy-3-aminobenzyl, 1-phenylethyl, diphenylmethyl, 1H-imidazol-4-ylmethyl or 1H-indol-3-ylmethyl,

or

R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula

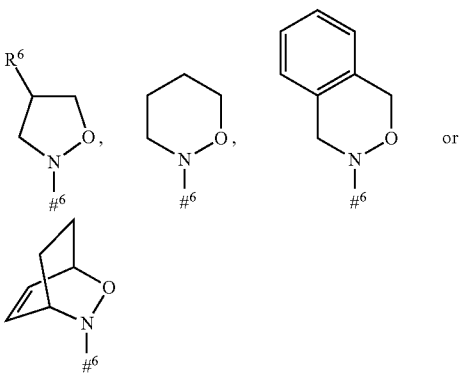


in which

$\#^4$ marks the linkage site with the adjacent nitrogen atom,

$\#^5$ marks the linkage site with the carbonyl group,

the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



in which

$\#^6$ marks the linkage site with the carbonyl group,

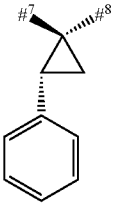
R^6 is hydrogen, hydroxy or benzyloxy,

R^3 is hydrogen or methyl,

R^4 is isopropyl, isobutyl, sec-butyl, tert-butyl, phenyl, benzyl, 1-hydroxyethyl, 4-hydroxybenzyl, 4-hydroxy-3-nitrobenzyl, 4-hydroxy-3-aminobenzyl, 1-phenylethyl, diphenylmethyl, 1H-imidazol-4-ylmethyl or 1H-indol-3-ylmethyl,

or

R^3 and R^4 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula



in which

$\#^7$ marks the linkage site with the adjacent nitrogen atom,

$\#^8$ marks the linkage site with the group T^1,

T^1 is a group of the formula —C(=O)—OR^7, —C(=O)—NR^8R^9, —C(=O)—NH—NH—R^{10} or —CH_2—O—R^{11},

in which

R^7 is hydrogen, methyl, ethyl, n-propyl, tert-butyl, benzyl or adamantylmethyl,

R^8 is hydrogen or methyl,

R^9 is hydrogen, methyl, ethyl, n-propyl or benzyl,

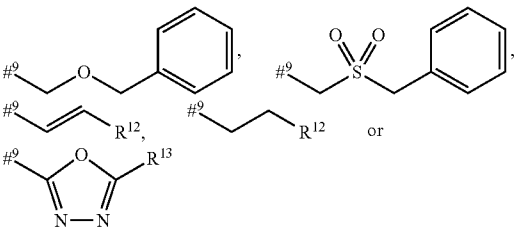
or

R^8 and R^9 together with the nitrogen atom to which they are bonded form a 4- to 7-membered heterocycle,

R^{10} is benzoyl,

R^{11} is benzyl, which may be substituted in the phenyl group by methoxycarbonyl or carboxyl,

R^5 is hydrogen, methyl or a group of the formula



in which

$\#^9$ marks the linkage site with —CHC(R^{26})-T^2,

R^{12} is phenyl which may be substituted by methoxycarbonyl, carboxyl or a group of the formula —$S(O)_2OH$,

R^{13} is phenyl which may be substituted by methoxycarbonyl or carboxyl,

R^{26} is hydrogen or hydroxy,

T^2 is phenyl, benzyl, 1H-indol-3-yl or 1H-indol-3-ylmethyl,

R^{35} is methyl or hydroxy,

and also their salts, solvates and solvates of the salts.

2. Binder-drug conjugates of the general formula (Ia) according to claim **1**, in which

n is a number from 1 to 50,

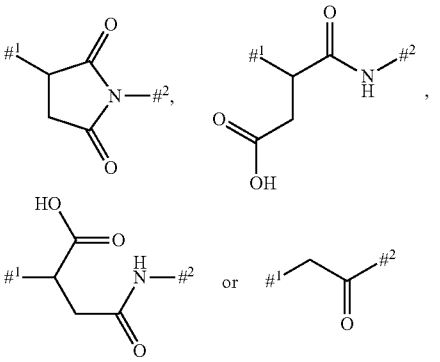
AK is AK_1 or AK_2

where

AK_1 is a binder which is bonded via a sulphur atom of the binder to the group G,

AK_2 is a binder which is bonded via a nitrogen atom of the binder to the group G,

G when $AK=AK_1$, is a group of the formula



where

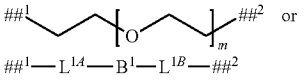
$\#^1$ marks the linkage site with the sulphur atom of the binder,

$\#^2$ marks the linkage site with the group L^1,

or

when $AK=AK_2$, is carbonyl,

L^1 is a bond, linear (C_1-C_{10})-alkanediyl, a group of the formula



where

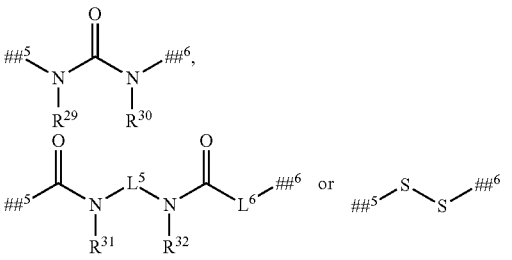
m is a number from 2 to 6,

$\#\#^1$ marks the linkage site with the group G,

$\#\#^2$ marks the linkage site with the group B,

L^{1A} is linear (C_2-C_{10})-alkanediyl,

B^1 is a group of the formula



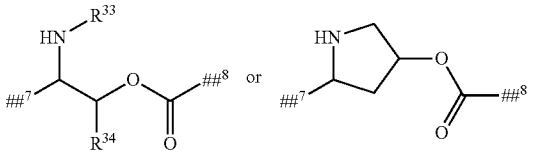
in which

##[5] marks the linkage site with the group L^{1A},

##[6] marks the linkage site with the group L^{1B},

L^5 is a bond or $(C_2$-$C_4)$-alkanediyl,

L^6 is a bond or a group of the formula



in which

##[7] marks the linkage site with the carbonyl group,

##[8] marks the linkage site with L^{1B},

R^{33} is hydrogen, $(C_1$-$C_4)$-alkylcarbonyl, tert-butyloxycarbonyl or benzyloxycarbonyl,

R^{34} is hydrogen or methyl,

R^{29} is hydrogen or $(C_1$-$C_4)$-alkyl,

R^{30} is hydrogen or $(C_1$-$C_4)$-alkyl,

or

R^{29} and R^{30} together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

R^{31} is hydrogen or $(C_1$-$C_4)$-alkyl,

R^{32} is hydrogen or $(C_1$-$C_4)$-alkyl,

or

R^{31} and R^{32} together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

L^{1B} is linear $(C_2$-$C_{10})$-alkanediyl,

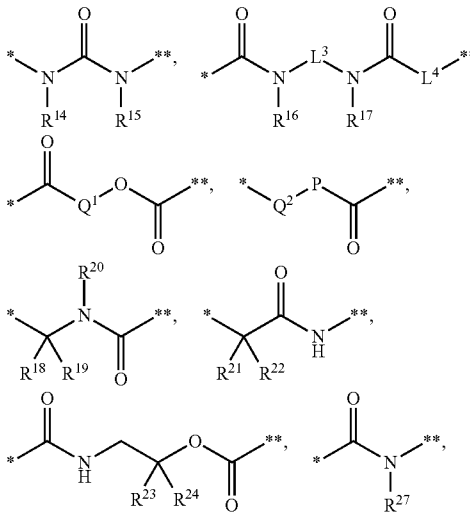
and

where $(C_1$-$C_{10})$-alkanediyl may be substituted by 1 to 4 substituents selected independently of one another from the group consisting of methyl, hydroxy and benzyl,

and

where two carbon atoms of the alkanediyl chain in 1,2, 1,3 or 1,4 relation to one another, with inclusion of any carbon atoms situated between them, may be bridged to form a $(C_3$-$C_6)$-cycloalkyl ring or a phenyl ring,

B is a bond or a group of the formula



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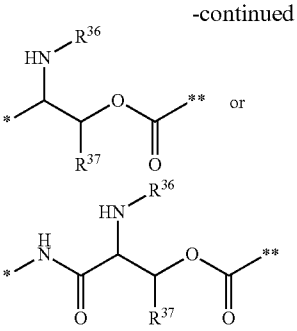


where

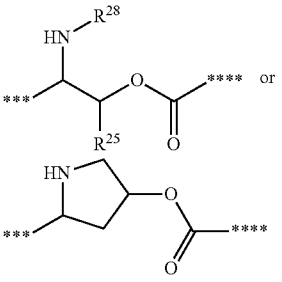
* marks the linkage site with L^1,

** marks the linkage site with L^2,

P is O or NH,

L^3 is a bond or $(C_2$-$C_4)$-alkanediyl,

L^4 is a bond or a group of the formula



in which

*** marks the linkage site with the carbonyl group,

**** marks the linkage site with L^2,

R^{25} is hydrogen or methyl,

R^{28} is hydrogen, $(C_1$-$C_4)$-alkylcarbonyl, tert-butyloxycarbonyl or benzyloxycarbonyl,

Q^1 is a 4- to 7-membered heterocycle,

Q^2 is a 3- to 7-membered carbocycle or a 4- to 7-membered heterocycle,

R^{14} is hydrogen or $(C_1$-$C_4)$-alkyl,

R^{15} is hydrogen or $(C_1$-$C_4)$-alkyl,

or

R^{14} and R^{15} together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

R^{16} is hydrogen or $(C_1$-$C_4)$-alkyl,

R^{17} is hydrogen or $(C_1$-$C_4)$-alkyl,

or

R^{16} and R^{17} together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

R^{18} is hydrogen or $(C_1$-$C_4)$-alkyl,

R^{19} is hydrogen or the side group of a natural α-amino acid or of its homologues or isomers,

R^{20} is hydrogen or $(C_1$-$C_4)$-alkyl,

or

R^{19} and R^{20} together with the atoms to which they are bonded form a pyrrolidinyl ring,

R^{21} is hydrogen or $(C_1$-$C_4)$-alkyl,

R^{22} is hydrogen or $(C_1$-$C_4)$-alkyl,

or

R^{21} and R^{22} together with the atoms to which they are bonded form a 3- to 7-membered carbocycle,

R^{23} is $(C_1$-$C_4)$-alkyl,

R^{24} is hydrogen or $(C_1$-$C_4)$-alkyl,

R^{27} is hydrogen or $(C_1$-$C_4)$-alkyl,

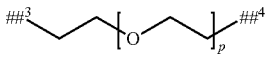
R^{36} is hydrogen, $(C_1$-$C_4)$-alkylcarbonyl, tert-butyloxycarbonyl or benzyloxycarbonyl,

R^{37} is hydrogen or methyl,

or

R^{36} and R^{37} together with the atoms to which they are bonded form a pyrrolidine ring,

L^2 is linear $(C_2$-$C_{10})$-alkanediyl or is a group of the formula



where

p is a number from 2 to 6,

$\#\#^3$ marks the linkage site with the group B,

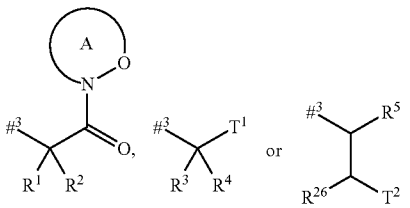
$\#\#^4$ marks the linkage site with the nitrogen atom,

where $(C_2$-$C_{10})$-alkanediyl may be substituted by 1 to 4 substituents selected independently of one another from the group consisting of methyl, hydroxy and benzyl,

and

where two carbon atoms of the alkanediyl chain in 1,2-, 1,3- or 1,4 relation to one another, with inclusion of any carbon atoms situated between them, may be bridged to form a $(C_3$-$C_6)$-cycloalkyl ring or a phenyl ring,

D is a group of the formula



in which

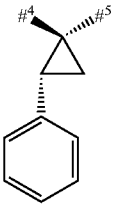
$\#^3$ marks the linkage site with the nitrogen atom,

R^1 is hydrogen or methyl,

R^2 is isopropyl, isobutyl, sec-butyl, tert-butyl, phenyl, benzyl, 1-hydroxyethyl, 4-hydroxybenzyl, 4-hydroxy-3-nitrobenzyl, 4-hydroxy-3-aminobenzyl, 1-phenylethyl, diphenylmethyl, 1H-imidazol-4-ylmethyl or 1H-indol-3-ylmethyl,

or

R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula

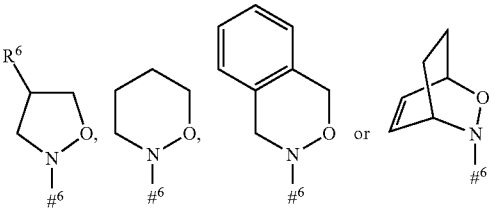


in which

$\#^4$ marks the linkage site with the adjacent nitrogen atom,

$\#^5$ marks the linkage site with the carbonyl group,

the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



in which

$\#^6$ marks the linkage site with the carbonyl group,

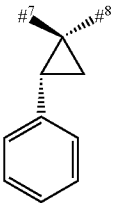
R^6 is hydrogen, hydroxy or benzyloxy,

R^3 is hydrogen or methyl,

R^4 is isopropyl, isobutyl, sec-butyl, tert-butyl, phenyl, benzyl, 1-hydroxyethyl, 4-hydroxybenzyl, 4-hydroxy-3-nitrobenzyl, 4-hydroxy-3-aminobenzyl, 1-phenylethyl, diphenylmethyl, 1H-imidazol-4-ylmethyl or 1H-indol-3-ylmethyl,

or

R^3 and R^4 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula



in which

$\#^7$ marks the linkage site with the adjacent nitrogen atom,

$\#^8$ marks the linkage site with the group T^1,

T^1 is a group of the formula —C(═O)—OR^7, —C(═O)—NR^8R^9, —C(═O)—NH—NH—R^{10} or —CH_2—O—R^{11},

in which

R^7 is hydrogen, methyl, ethyl, n-propyl, tert-butyl, benzyl or adamantylmethyl,

R^8 is hydrogen or methyl,

R^9 is hydrogen, methyl, ethyl, n-propyl or benzyl,

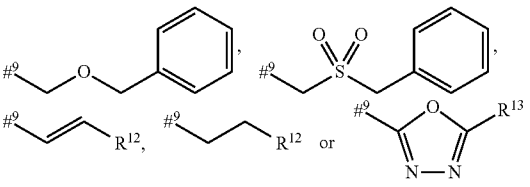
or

R^8 and R^9 together with the nitrogen atom to which they are bonded form a 4- to 7-membered heterocycle,

R^{10} is benzoyl,

R^{11} is benzyl, which may be substituted in the phenyl group by methoxycarbonyl or carboxyl,

R^5 is hydrogen, methyl or a group of the formula



in which

$\#^9$ marks the linkage site with —CHC(R^{26})-T^2,

R^{12} is phenyl which may be substituted by methoxycarbonyl, carboxyl or a group of the formula —$S(O)_2OH$,

R^{13} is phenyl which may be substituted by methoxycarbonyl or carboxyl,

R^{26} is hydrogen or hydroxy,

T^2 is phenyl, benzyl, 1H-indol-3-yl or 1H-indol-3-ylmethyl,

R^{35} is methyl or hydroxy,

and also their salts, solvates and solvates of the salts.

3. Binder-drug conjugates of the general formula (Ia) according to claim **1** or **2**, in which

n is a number from 1 to 20,

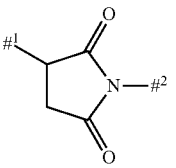
AK is AK_1 or AK_2

where

AK_1 is an antibody or an antigen-binding antibody fragment which binds to mesothelin and is bonded via the sulphur atom of a cysteine residue of the binder to the group G,

AK_2 is an antibody or an antigen-binding antibody fragment which binds to mesothelin and is bonded via the NH side group of a lysine residue of the binder to the group G,

G when $AK=AK_1$, is a group of the formula



in which

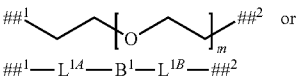
$\#^1$ marks the linkage site with the cysteine residue of the binder,

$\#^2$ marks the linkage site with the group L^1,

or

when $AK=AK_2$, is carbonyl,

L^1 is a bond, linear (C_2-C_6)-alkanediyl, a group of the formula



where

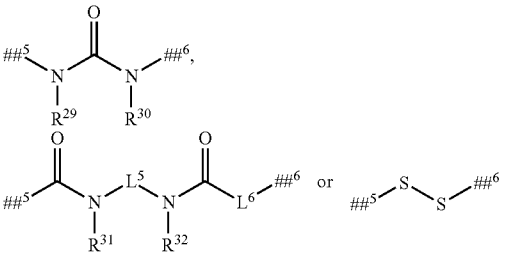
m is a number from 2 to 6,

$\#\#^1$ marks the linkage site with the group G,

$\#\#^2$ marks the linkage site with the group B,

L^{1A} is linear (C_2-C_6)-alkanediyl,

B^1 is a group of the formula



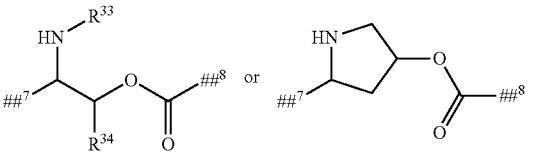
in which

$\#\#^5$ marks the linkage site with the group L^{1A},

$\#\#^6$ marks the linkage site with the group L^{1B},

L^5 is a bond,

L^6 is a bond or a group of the formula



in which

$\#\#^7$ marks the linkage site with the carbonyl group,

$\#\#^8$ marks the linkage site with L^{1B},

R^{33} is hydrogen, methylcarbonyl or tert-butyloxycarbonyl,

R^{34} is hydrogen or methyl,

R^{29} is hydrogen,

R^{30} is hydrogen,

R^{31} is hydrogen or methyl,

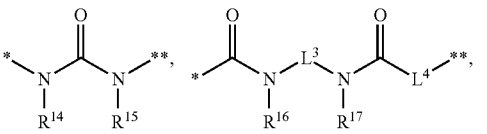
R^{32} is hydrogen or methyl,

L^{1B} is linear (C_2-C_6)-alkanediyl,

and

where (C_2-C_6)-alkanediyl may be substituted by 1 or 2 methyl substituents,

B is a bond or a group of the formula



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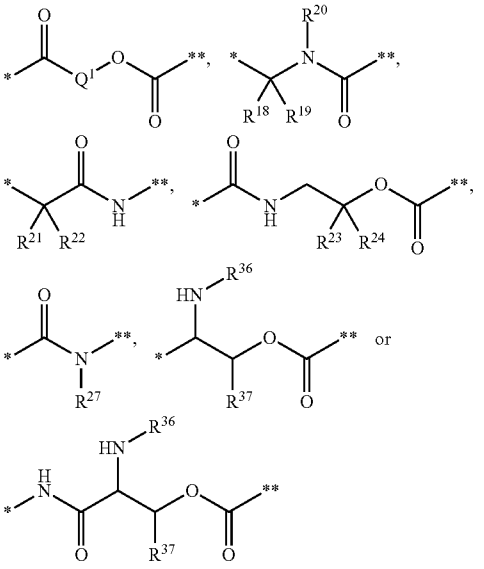
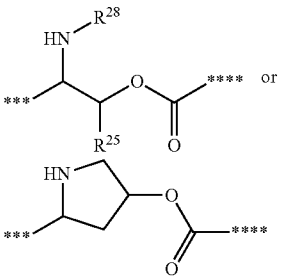
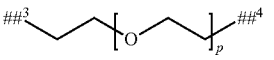


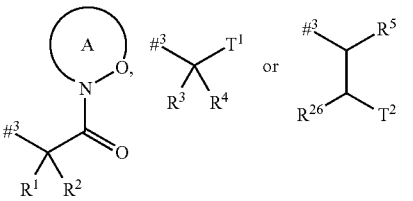
where
* marks the linkage site with L^1,
** marks the linkage site with L^2,
L^3 is a bond or ethane-1,2-diyl,
L^4 is a bond or a group of the formula



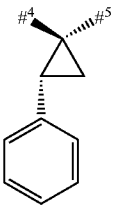
in which
*** marks the linkage site with the carbonyl group,
**** marks the linkage site with L^2,
R^{25} is hydrogen or methyl,
R^{28} is hydrogen, methylcarbonyl or tert-butyloxycarbonyl,
Q^1 is a 4- to 7-membered heterocycle,
R^{14} is hydrogen,
R^{15} is hydrogen,
R^{16} is hydrogen or methyl,
R^{17} is hydrogen or methyl,
or
R^{16} and R^{17} together with the atoms to which they are bonded form a piperazinyl ring,
R^{18} is hydrogen,
R^{19} is hydrogen, methyl, propan-2-yl, 2-methylpropan-1-yl or 1-methylpropan-1-yl,
R^{20} is hydrogen or methyl,
or
R^{19} and R^{20} together with the atoms to which they are bonded form a pyrrolidinyl ring,
R^{21} is hydrogen or methyl,
R^{22} is hydrogen or methyl,
or
R^{21} and R^{22} together with the atoms to which they are bonded form a cyclopropyl ring,
R^{23} is methyl,
R^{24} is hydrogen or methyl,
R^{27} is hydrogen,
R^{36} is hydrogen, methylcarbonyl or tert-butyloxycarbonyl,
R^{37} is hydrogen or methyl,
or
R^{36} and R^{37} together with the atoms to which they are bonded form a pyrrolidine ring,
L^2 is linear (C_2-C_6)-alkanediyl or is a group of the formula



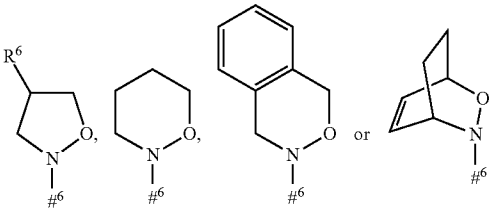
where
p is a number from 2 to 6,
##3 marks the linkage site with the group B,
##4 marks the linkage site with the nitrogen atom,
where (C_2-C_{10})-alkanediyl may be substituted by 1 or 2 methyl substituents,
D is a group of the formula



where
#3 marks the linkage site with the nitrogen atom,
R^1 is hydrogen,
R^2 is 1-hydroxyethyl, benzyl, 4-hydroxybenzyl, 1-phenylethyl or 1H-indol-3-ylmethyl,
or
R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula



in which
#4 marks the linkage site with the adjacent nitrogen atom,
#5 marks the linkage site with the carbonyl group,
the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



in which

$\#^6$ marks the linkage site with the carbonyl group,

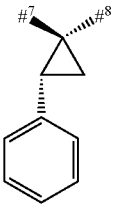
R^6 is hydrogen, hydroxy or benzyloxy,

R^3 is hydrogen,

R^4 is 1-hydroxyethyl, benzyl, 4-hydroxybenzyl, 1-phenylethyl or 1H-indol-3-ylmethyl,

or

R^3 and R^4 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula



in which

$\#^7$ marks the linkage site with the adjacent nitrogen atom,

$\#^8$ marks the linkage site with the group T^1,

T^1 is a group of the formula —C(═O)—OR^7, —C(═O)—NR^8R^9, —C(═O)—NH—NH—R^{10} or —CH_2—O—R^{11},

in which

R^7 is hydrogen, methyl, ethyl, n-propyl, tert-butyl, benzyl or adamantylmethyl,

R^8 is hydrogen or methyl,

R^9 is hydrogen, methyl, ethyl, n-propyl or benzyl,

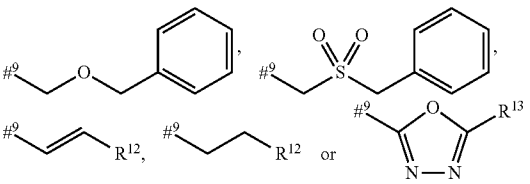
or

R^8 and R^9 together with the nitrogen atom to which they are bonded form a 4- to 7-membered heterocycle,

R^{10} is benzoyl,

R^{11} is benzyl, which may be substituted in the phenyl group by methoxycarbonyl or carboxyl,

R^5 is hydrogen, methyl or a group of the formula



in which

$\#^9$ marks the linkage site with —CHC(R^{26})-T^2,

R^{12} is phenyl which may be substituted by methoxycarbonyl, carboxyl or a group of the formula —$S(O)_2OH$,

R^{13} is phenyl which may be substituted by methoxycarbonyl or carboxyl,

R^{26} is hydrogen or hydroxy,

T^2 is phenyl, benzyl, 1H-indol-3-yl or 1H-indol-3-ylmethyl,

R^{35} is methyl or hydroxy,

and also their salts, solvates and solvates of the salts.

4. Binder-drug conjugates of the general formula (Ia) according to any of claims **1** to **3**, in which

n is a number from 1 to 10,

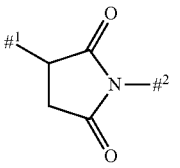
AK is AK_1 or AK_2

where

AK_1 is an antibody which comprises the six CDR sequences of the antibody MF-Ta, the variable light and variable heavy chain of the antibody MF-Ta or the light and heavy chain of the antibody MF-Ta, and is bonded via the sulphur atom of a cysteine residue of the binder to the group G,

AK_2 is an antibody which comprises the six CDR sequences of the antibody B01-3, B01-10, M31-B01 or D02-6, the variable light and variable heavy chain of the antibody B01-3, B01-10, M31-B01 or D02-6 or the light and heavy chain of the antibody B01-3, B01-10, M31-B01 or D02-6, and is bonded via the NH side group of a lysine residue of the binder to the group G,

G when AK=AK_1, is a group of the formula



in which

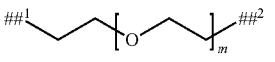
$\#^1$ marks the linkage site with the cysteine residue of the binder,

$\#^2$ marks the linkage site with the group L^1,

or

when AK=AK_2, is carbonyl,

L^1 is a bond, linear (C_2-C_6)-alkanediyl, a group of the formula



where

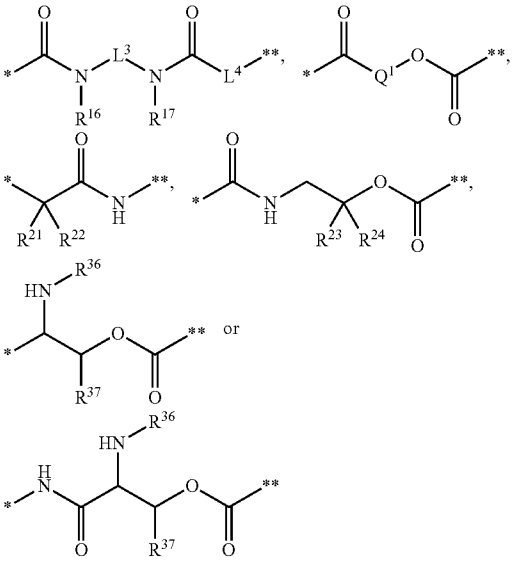
m is a number 2 or 3,

$\#\#^1$ marks the linkage site with the group G,

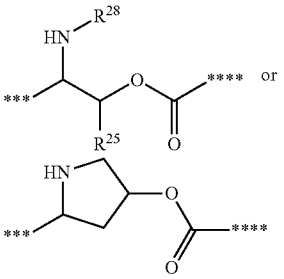
$\#\#^2$ marks the linkage site with the group B,

where (C_2-C_6)-alkanediyl may be substituted by 1 or 2 methyl substituents,

B is a bond or a group of the formula

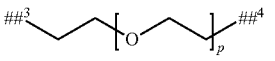


* marks the linkage site with L^1,
** marks the linkage site with L^2,
L^3 is a bond or ethane-1,2-diyl,
L^4 is a bond or a group of the formula

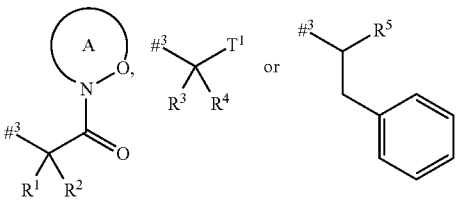


in which
*** marks the linkage site with the carbonyl group,
**** marks the linkage site with L^2,
R^{25} is methyl,
R^{28} is hydrogen, methylcarbonyl or tert-butyloxycarbonyl,
Q^1 is piperidine-1,4-diyl,
R^{16} is hydrogen or methyl,
R^{17} is hydrogen or methyl,
or
R^{16} and R^{17} together with the atoms to which they are bonded form a piperazinyl ring,
R^{21} is hydrogen or methyl,
R^{22} is hydrogen or methyl,
or
R^{21} and R^{22} together with the atoms to which they are bonded form a cyclopropyl ring,
R^{23} is methyl,
R^{24} is hydrogen,
R^{36} is hydrogen, methylcarbonyl or tert-butyloxycarbonyl,
R^{37} is hydrogen or methyl,

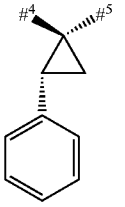
L^2 is linear (C_2-C_6)-alkanediyl or is a group of the formula



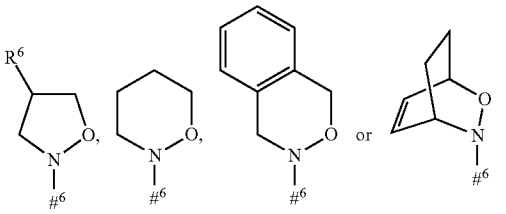
where
p is a number from 2 to 6,
$\#\#^3$ marks the linkage site with the group B,
$\#\#^4$ marks the linkage site with the nitrogen atom,
D is a group of the formula



where
$\#^3$ marks the linkage site with the nitrogen atom,
R^1 is hydrogen,
R^2 is 1-hydroxyethyl, benzyl, 4-hydroxybenzyl, 1-phenylethyl or 1H-indol-3-ylmethyl,
or
R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula



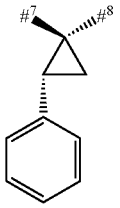
in which
$\#^4$ marks the linkage site with the adjacent nitrogen atom,
$\#^5$ marks the linkage site with the carbonyl group,
the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



in which
$\#^6$ marks the linkage site with the carbonyl group,
R^6 is hydrogen, hydroxy or benzyloxy,
R^3 is hydrogen,
R^4 is benzyl, 4-hydroxybenzyl, 1-phenylethyl or 1H-indol-3-ylmethyl,

or

R^3 and R^4 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1, 1-diyl group of the formula



in which

$\#^7$ marks the linkage site with the adjacent nitrogen atom,

$\#^8$ marks the linkage site with the group T^1,

T^1 is a group of the formula —C(═O)—OR^7, —C(═O)—NR^8R^9, or —CH_2—O—R^{11},

in which

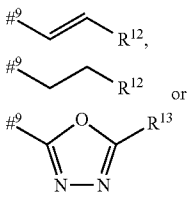
R^7 is hydrogen, methyl, ethyl, n-propyl, tert-butyl, benzyl or adamantylmethyl,

R^8 is hydrogen or methyl,

R^9 is hydrogen, methyl, ethyl, n-propyl or benzyl,

R^{11} is benzyl, which may be substituted in the phenyl group by methoxycarbonyl or carboxyl,

R^5 is hydrogen, methyl or a group of the formula



in which

$\#^9$ marks the linkage site with —$CHCH_2$phenyl,

R^{12} is phenyl which may be substituted by methoxycarbonyl, carboxyl or a group of the formula —$S(O)_2OH$,

R^{13} is phenyl which may be substituted by methoxycarbonyl or carboxyl,

R^{35} is methyl or hydroxy,

and also their salts, solvates and solvates of the salts.

5. Binder-drug conjugates of the general formula (Ia) according to any of claims **1** to **4**, in which

n is a number from 1 to 10,

AK is AK_2

where

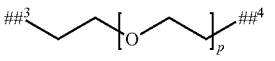
AK_2 is an antibody which comprises the six CDR sequences of the antibody MF-Ta, the variable light and variable heavy chain of the antibody MF-Ta or the light and heavy chain of the antibody MF-Ta, and is bonded via the NH side group of a lysine residue of the binder to the group G,

G is carbonyl,

L^1 is a bond,

B is a bond,

L^2 is linear (C_3-C_6)-alkanediyl or is a group of the formula



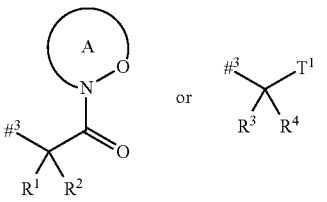
where

p is a number 2 or 3,

$\#\#^3$ marks the linkage site with the group B,

$\#\#^4$ marks the linkage site with the nitrogen atom,

D is a group of the formula



where

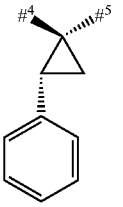
$\#^3$ marks the linkage site with the nitrogen atom,

R^1 is hydrogen,

R^2 is benzyl, 4-hydroxybenzyl or 1H-indol-3-ylmethyl,

or

R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1, 1-diyl group of the formula

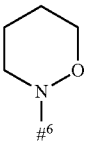


in which

$\#^4$ marks the linkage site with the adjacent nitrogen atom,

$\#^5$ marks the linkage site with the carbonyl group,

the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



in which

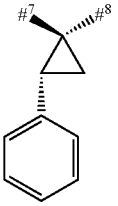
$\#^6$ marks the linkage site with the carbonyl group,

R^3 is hydrogen,

R^4 is benzyl, 4-hydroxybenzyl or 1H-indol-3-ylmethyl,

or

R^3 and R^4 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1, 1-diyl group of the formula



in which

$\#^7$ marks the linkage site with the adjacent nitrogen atom,

$\#^8$ marks the linkage site with the group T^1,

T^1 is a group of the formula —C(═O)—OR^7 or —C(═O)—NR^8R^9

in which

R^7 is hydrogen, methyl, ethyl, n-propyl, tert-butyl, benzyl or adamantylmethyl,

R^8 is hydrogen,

R^9 is hydrogen or benzyl,

R^{35} is methyl,

and also their salts, solvates and solvates of the salts.

6. Binder-drug conjugates of the general formula (Ia) according to any of claims **1** to **4**, in which

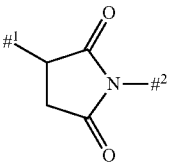
n is a number from 1 to 10,

AK is AK_1,

where

AK_1 is an antibody which comprises the six CDR sequences of the antibody MF-Ta, the variable light and variable heavy chain of the antibody MF-Ta or the light and heavy chain of the antibody MF-Ta, and is bonded via the sulphur atom of a cysteine residue of the binder to the group G,

G is a group of the formula

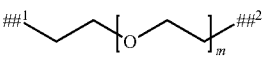


where

$\#^1$ marks the linkage site with the cysteine residue of the binder,

$\#^2$ marks the linkage site with the group L^1,

L^1 is a bond, linear (C_3-C_5)-alkanediyl or a group of the formula



where

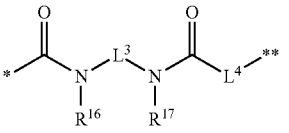
m is a number 2 or 3,

$\#\#^1$ marks the linkage site with the group G,

$\#\#^2$ marks the linkage site with the group B,

where (C_3-C_5)-alkanediyl may be substituted by 1 or 2 methyl substituents,

B is a bond or a group of the formula



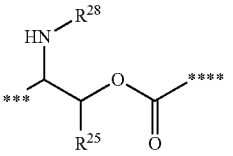
where

* marks the linkage site with L^1,

** marks the linkage site with L^2,

L^3 is a bond or ethane-1,2-diyl,

L^4 is a bond or a group of the formula



in which

*** marks the linkage site with the carbonyl group,

**** marks the linkage site with L^2,

R^{25} is methyl,

R^{28} is hydrogen, methylcarbonyl or tert-butyloxycarbonyl,

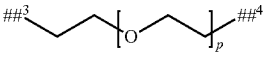
R^{16} is hydrogen or methyl,

R^{17} is hydrogen or methyl,

or

R^{16} and R^{17} together with the atoms to which they are bonded form a piperazinyl ring,

L^2 is linear (C_3-C_5)-alkanediyl or is a group of the formula



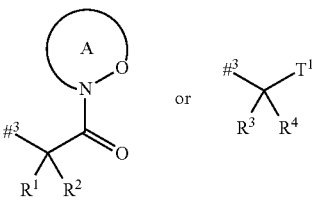
where

p is a number 2 or 3,

$\#\#^3$ marks the linkage site with the group B,

$\#\#^4$ marks the linkage site with the nitrogen atom,

D is a group of the formula



where

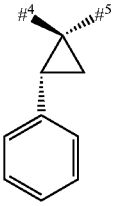
$\#^3$ marks the linkage site with the nitrogen atom,

R^1 is hydrogen,

R^2 is benzyl, 4-hydroxybenzyl or 1H-indol-3-ylmethyl,

or

R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1, 1-diyl group of the formula

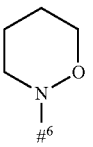


in which

$\#^4$ marks the linkage site with the adjacent nitrogen atom,

$\#^5$ marks the linkage site with the carbonyl group,

the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



in which

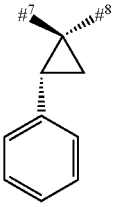
$\#^6$ marks the linkage site with the carbonyl group,

R^3 is hydrogen,

R^4 is benzyl, 4-hydroxybenzyl or 1H-indol-3-ylmethyl,

or

R^3 and R^4 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1, 1-diyl group of the formula



in which

$\#^7$ marks the linkage site with the adjacent nitrogen atom,

$\#^8$ marks the linkage site with the group T^1,

T^1 is a group of the formula —C(═O)—OR^7 or —C(═O)—NR^8R^9,

in which

R^7 is hydrogen, methyl, ethyl, n-propyl, tert-butyl, benzyl or adamantylmethyl,

R^8 is hydrogen,

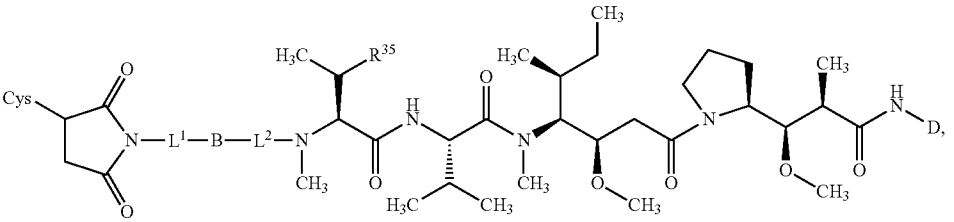
R^9 is hydrogen or benzyl,

R^{35} is methyl,

and also their salts, solvates and solvates of the salts.

7. Compounds of the formula (XXXa)

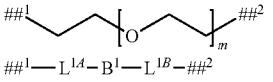
(XXXa)



in which

Cys is a cysteine residue which is bonded via the sulphur atom of the side chain to a carbon atom of the succinimide,

L^1 is a bond, linear (C_1-C_{10})-alkanediyl, a group of the formula



or

where

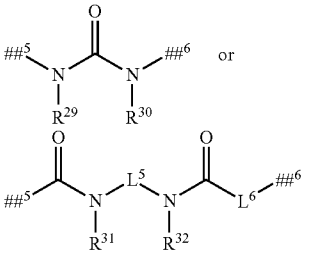
m is a number from 2 to 6,

$\#\#^1$ marks the linkage site with the group G,

$\#\#^2$ marks the linkage site with the group B,

L^{1A} is linear (C_2-C_{10})-alkanediyl,

B^1 is a group of the formula

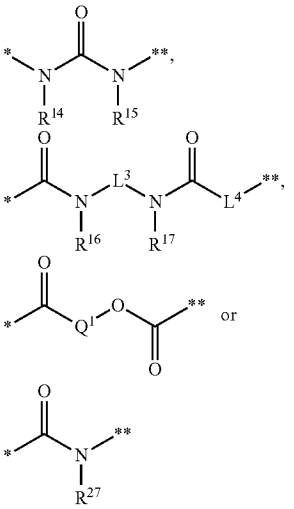


in which

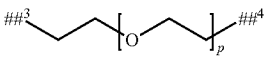
$\#\#^5$ marks the linkage site with the group L^{1A},

$\#\#^6$ marks the linkage site with the group L^{1B},

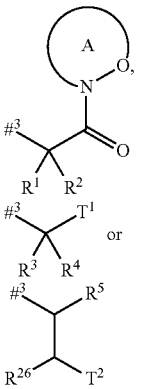
L^5 is a bond or $(C_2$-$C_4)$-alkanediyl,
L^6 is a bond,
R^{29} is hydrogen or $(C_1$-$C_4)$-alkyl,
R^{30} is hydrogen or $(C_1$-$C_4)$-alkyl,
or
R^{29} and R^{30} together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,
R^{31} is hydrogen or $(C_1$-$C_4)$-alkyl,
R^{32} is hydrogen or $(C_1$-$C_4)$-alkyl,
or
R^{31} and R^{32} together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,
L^{1B} is linear $(C_2$-$C_{10})$-alkanediyl,
and
where $(C_1$-$C_{10})$-alkanediyl may be substituted by 1 to 4 substituents selected independently of one another from the group consisting of methyl, hydroxy and benzyl,
and
where two carbon atoms of the alkanediyl chain in 1,2, 1,3 or 1,4 relation to one another, with inclusion of any carbon atoms situated between them, may be bridged to form a $(C_3$-$C_6)$-cycloalkyl ring or a phenyl ring,
B is a bond or a group of the formula



where
* marks the linkage site with L^1,
** marks the linkage site with L^2,
P is O or NH,
L^3 is a bond or $(C_2$-$C_4)$-alkanediyl,
L^4 is a bond,
Q^1 is a 4- to 7-membered heterocycle,
Q^2 is a 3- to 7-membered carbocycle or a 4- to 7-membered heterocycle,
R^{14} is hydrogen or $(C_1$-$C_4)$-alkyl,
R^{15} is hydrogen or $(C_1$-$C_4)$-alkyl,
or
R^{14} and R^{15} together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,
R^{16} is hydrogen or $(C_1$-$C_4)$-alkyl,
R^{17} is hydrogen or $(C_1$-$C_4)$-alkyl,
or
R^{16} and R^{17} together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,
R^{18} is hydrogen or $(C_1$-$C_4)$-alkyl,
R^{19} is hydrogen or the side group of a natural α-amino acid or of its homologues or isomers,
R^{20} hydrogen or $(C_1$-$C_4)$-alkyl,
or
R^{19} and R^{20} together with the atoms to which they are bonded form a pyrrolidinyl ring,
R^{21} is hydrogen or $(C_1$-$C_4)$-alkyl,
R^{22} is hydrogen or $(C_1$-$C_4)$-alkyl,
or
R^{21} and R^{22} together with the atoms to which they are bonded form a 3- to 7-membered carbocycle,
R^{23} is $(C_1$-$C_4)$-alkyl,
R^{24} is hydrogen or $(C_1$-$C_4)$-alkyl,
R^{27} is hydrogen or $(C_1$-$C_4)$-alkyl,
L^2 is linear $(C_2$-$C_{10})$-alkanediyl or is a group of the formula



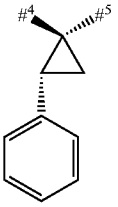
where
p is a number from 2 to 6,
##3 marks the linkage site with the group B,
##4 marks the linkage site with the nitrogen atom,
where $(C_2$-$C_{10})$-alkanediyl may be substituted by 1 to 4 substituents selected independently of one another from the group consisting of methyl, hydroxy and benzyl,
and
where two carbon atoms of the alkanediyl chain in 1,2-, 1,3- or 1,4 relation to one another, with inclusion of any carbon atoms situated between them, may be bridged to form a $(C_3$-$C_6)$-cycloalkyl ring or a phenyl ring,
D is a group of the formula



where
#3 marks the linkage site with the nitrogen atom,
R^1 is hydrogen or methyl,
R^2 is isopropyl, isobutyl, sec-butyl, tert-butyl, phenyl, benzyl, 1-hydroxyethyl, 4-hydroxybenzyl, 4-hydroxy-3-nitrobenzyl, 4-hydroxy-3-aminobenzyl, 1-phenylethyl, diphenylmethyl, 1H-imidazol-4-ylmethyl or 1H-indol-3-ylmethyl,

or

R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula

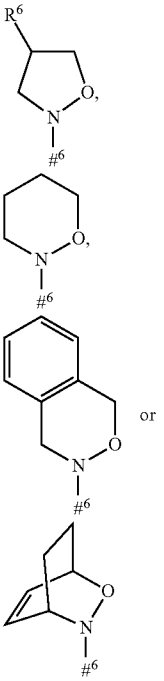


in which

$\#^4$ marks the linkage site with the adjacent nitrogen atom,

$\#^5$ marks the linkage site with the carbonyl group,

the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



in which

$\#^6$ marks the linkage site with the carbonyl group,

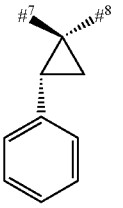
R^6 is hydrogen, hydroxy or benzyloxy,

R^3 is hydrogen or methyl,

R^4 is isopropyl, isobutyl, sec-butyl, tert-butyl, phenyl, benzyl, 1-hydroxyethyl, 4-hydroxybenzyl, 4-hydroxy-3-nitrobenzyl, 4-hydroxy-3-aminobenzyl, 1-phenylethyl, diphenylmethyl, 1H-imidazol-4-ylmethyl or 1H-indol-3-ylmethyl,

or

R^3 and R^4 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula



in which

$\#^7$ marks the linkage site with the adjacent nitrogen atom,

$\#^8$ marks the linkage site with the group T^1,

T^1 is a group of the formula —C(═O)—OR^7, —C(═O)—NR^8R^9, —C(═O)—NH—NH—R^{10} or —CH_2—O—R^{11},

in which

R^7 is hydrogen, methyl, ethyl, n-propyl, tert-butyl, benzyl or adamantylmethyl,

R^8 is hydrogen or methyl,

R^9 is hydrogen, methyl, ethyl, n-propyl or benzyl,

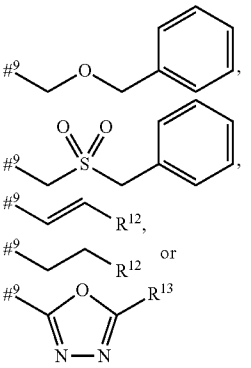
or

R^8 and R^9 together with the nitrogen atom to which they are bonded form a 4- to 7-membered heterocycle,

R^{10} is benzoyl,

R^{11} is benzyl, which may be substituted in the phenyl group by methoxycarbonyl or carboxyl,

R^5 is hydrogen, methyl or a group of the formula



in which

$\#^9$ marks the linkage site with —CHC(R^{26})-T2,

R^{12} is phenyl which may be substituted by methoxycarbonyl, carboxyl or a group of the formula —$S(O)_2OH$,

R^{13} is phenyl which may be substituted by methoxycarbonyl or carboxyl,

R^{26} is hydrogen or hydroxy,

T^2 is phenyl, benzyl, 1H-indol-3-yl or 1H-indol-3-ylmethyl,

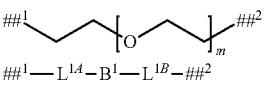
R^{35} is methyl or hydroxy,

and also their salts, solvates and solvates of the salts.

8. Compounds of the formula (XXXa) according to claim **7**, in which

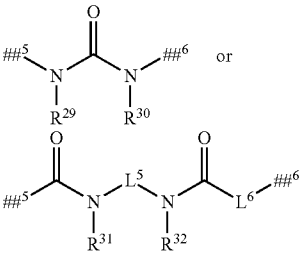
Cys is a cysteine residue which is bonded via the sulphur atom of the side chain via a carbon atom of the succinimide,

L^1 is a bond, linear (C_2-C_6)-alkanediyl, a group of the formula

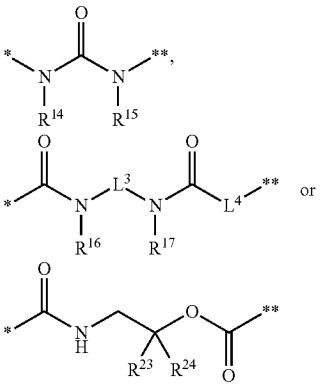


or

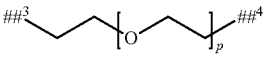
where
m is a number 2 or 3,
$##^1$ marks the linkage site with the group G,
$##^2$ marks the linkage site with the group B,
L^{1A} is linear (C_2-C_6)-alkanediyl,
B^1 is a group of the formula



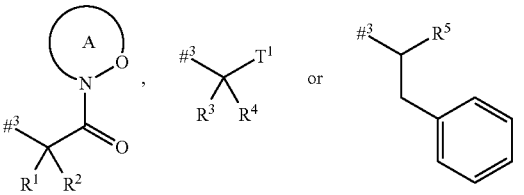
in which
$##^5$ marks the linkage site with the group L^{1A},
$##^6$ marks the linkage site with the group L^{1B},
L^5 is a bond,
L^6 is a bond,
R^{29} is hydrogen,
R^{30} is hydrogen,
R^{31} is hydrogen or methyl,
R^{32} is hydrogen or methyl,
L^{1B} is linear (C_2-C_6)-alkanediyl,
and
where (C_2-C_6)-alkanediyl may be substituted by 1 or 2 methyl substituents,
B is a bond or a group of the formula



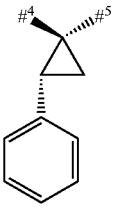
where
* marks the linkage site with L^1,
** marks the linkage site with L^2,
L^3 is a bond or ethane-1,2-diyl,
L^4 is a bond,
R^{14} is hydrogen,
R^{15} is hydrogen,
R^{16} is hydrogen or methyl,
R^{17} is hydrogen or methyl,
or
R^{16} and R^{17} together with the atoms to which they are bonded form piperazinyl ring,
R^{23} is methyl,
R^{24} is hydrogen or methyl,
L^2 is linear (C_2-C_6)-alkanediyl or is a group of the formula



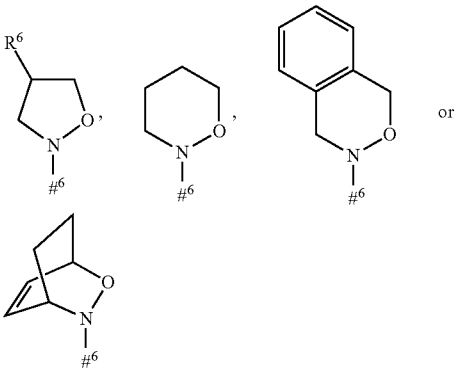
where
p is a number 2 or 3,
$##^3$ marks the linkage site with the group B,
$##^4$ marks the linkage site with the nitrogen atom,
D is a group of the formula



where
$#^3$ marks the linkage site with the nitrogen atom,
R^1 is hydrogen,
R^2 is 1-hydroxyethyl, benzyl, 4-hydroxybenzyl, 1-phenylethyl or 1H-indol-3-ylmethyl,
or
R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula



in which
$#^4$ marks the linkage site with the adjacent nitrogen atom,
$#^5$ marks the linkage site with the carbonyl group,
the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



or

in which

$\#^6$ marks the linkage site with the carbonyl group,

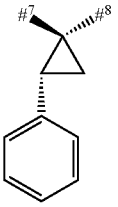
R^6 is hydrogen, hydroxy or benzyloxy,

R^3 is hydrogen,

R^4 is 1-hydroxyethyl, benzyl, 4-hydroxybenzyl, 1-phenylethyl or 1H-indol-3-ylmethyl,

or

R^3 and R^4 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula



in which

$\#^7$ marks the linkage site with the adjacent nitrogen atom,

$\#^8$ marks the linkage site with the group T^1,

T^1 is a group of the formula —C(═O)—OR^7, —C(═O)—NR^8R^9, —C(═O)—NH—NH—R^{10} or —CH_2—O—R^{11},

in which

R^7 is hydrogen, methyl, ethyl, n-propyl, tert-butyl, benzyl or adamantylmethyl,

R^8 is hydrogen or methyl,

R^9 is hydrogen, methyl, ethyl, n-propyl or benzyl,

or

R^8 and R^9 together with the nitrogen atom to which they are bonded form a 4- to 7-membered heterocycle,

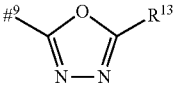
R^{10} is benzoyl,

R^{11} is benzyl which may be substituted in the phenyl group by methoxycarbonyl or carboxyl,

R^5 is hydrogen, methyl or a group of the formula

or

-continued



in which

$\#^9$ marks the linkage site to —$CHCH_2$phenyl,

R^{12} is phenyl which may be substituted by methoxycarbonyl, carboxyl or a group of the formula —$S(O)_2OH$,

R^{13} is phenyl which may be substituted by methoxycarbonyl or carboxyl,

R^{35} is methyl or hydroxy,

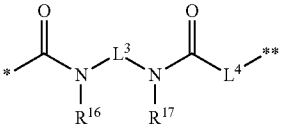
and also their salts, solvates and solvates of the salts.

9. Compounds of the formula (XXXa) according to either of claim **7** or **8**, in which

Cys is a cysteine residue which is bonded via the sulphur atom of the side chain via a carbon atom of the succinimide,

L^1 is a bond or linear (C_2-C_6)-alkanediyl,

B is a bond or a group of the formula



where

* marks the linkage site with L^1,

** marks the linkage site with L^2,

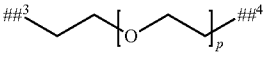
L^3 is a bond,

L^4 is a bond,

R^{16} is hydrogen or methyl,

R^{17} is hydrogen or methyl,

L^2 is linear (C_2-C_6)-alkanediyl or is a group of the formula



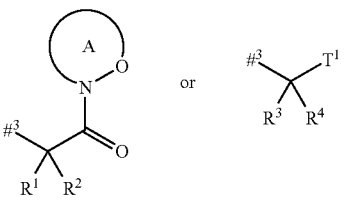
where

p is a number 2 or 3,

$\#\#^3$ marks the linkage site with the group B,

$\#\#^4$ marks the linkage site with the nitrogen atom,

D is a group of the formula



or

where

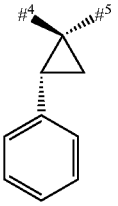
$\#^3$ marks the linkage site with the nitrogen atom,

R^1 is hydrogen,

R^2 is benzyl or 1H-indol-3-ylmethyl,

or

R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1, 1-diyl group of the formula

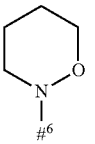


in which

$\#^4$ marks the linkage site with the adjacent nitrogen atom,

$\#^5$ marks the linkage site with the carbonyl group,

the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



in which

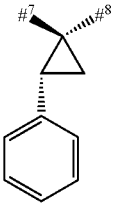
$\#^6$ marks the linkage site with the carbonyl group,

R^3 is hydrogen,

R^4 is benzyl or 1H-indol-3-ylmethyl,

or

R^3 and R^4 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1, 1-diyl group of the formula



in which

$\#^7$ marks the linkage site with the adjacent nitrogen atom,

$\#^8$ marks the linkage site with the group T^1,

T^1 is a group of the formula —C(═O)—OR^7 or —C(═O)—NR^8R^9,

in which

R^7 is hydrogen,

R^8 is hydrogen,

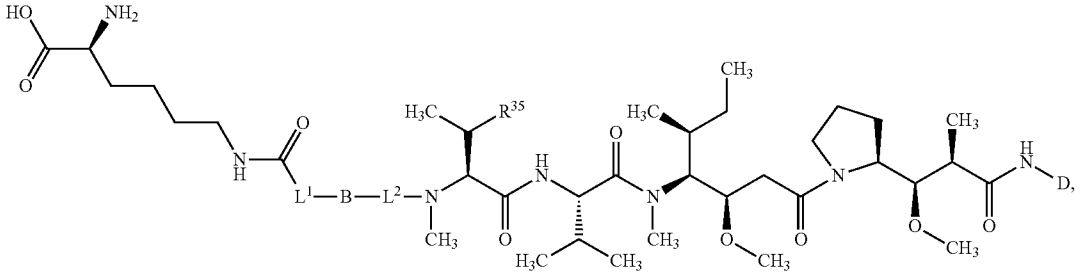
R^9 is hydrogen,

R^{35} is methyl,

and also their salts, solvates and solvates of the salts.

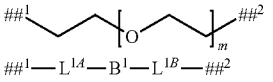
10. Compounds of the formula (XXXI)

(XXXI)



in which

L^1 is a bond, linear (C_1-C_{10})-alkanediyl, a group of the formula



or

where

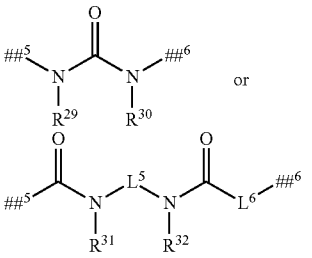
m is a number from 2 to 6,

$\#\#^1$ marks the linkage site with the group G,

$\#\#^2$ marks the linkage site with the group B,

L^{1A} is linear (C_2-C_{10})-alkanediyl,

B^1 is a group of the formula



or

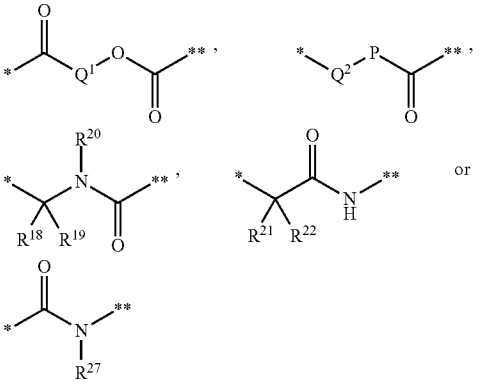
in which

$\#\#^5$ marks the linkage site with the group L^{1A},

$\#\#^6$ marks the linkage site with the group L^{1B},

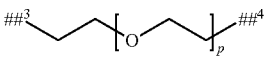
L^5 is a bond or (C_2-C_4)-alkanediyl,
L^6 is a bond,
R^{29} is hydrogen or (C_1-C_4)-alkyl,
R^{30} is hydrogen or (C_1-C_4)-alkyl,
or
R^{29} and R^{30} together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,
R^{31} is hydrogen or (C_1-C_4)-alkyl,
R^{32} is hydrogen or (C_1-C_4)-alkyl,
or
R^{31} and R^{32} together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,
L^{1B} is linear (C_2-C_{10})-alkanediyl,
and
where (C_1-C_{10})-alkanediyl may be substituted by 1 to 4 substituents selected independently of one another from the group consisting of methyl, hydroxy and benzyl,
and
where two carbon atoms of the alkanediyl chain in 1,2, 1,3 or 1,4 relation to one another, with inclusion of any carbon atoms situated between them, may be bridged to form a (C_3-C_6)-cycloalkyl ring or a phenyl ring,

B is a bond or a group of the formula



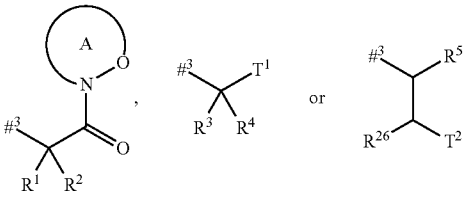
where
* marks the linkage site with L^1,
** marks the linkage site with L^2,
P is O or NH,
Q^1 is a 4- to 7-membered heterocycle,
Q^2 is a 3- to 7-membered carbocycle or a 4- to 7-membered heterocycle,
R^{18} is hydrogen or (C_1-C_4)-alkyl,
R^{19} is hydrogen or the side group of a natural α-amino acid or of its homologues or isomers,
R^{20} is hydrogen or (C_1-C_4)-alkyl,
or
R^{19} and R^{20} together with the atoms to which they are bonded form a pyrrolidinyl ring,
R^{21} is hydrogen or (C_1-C_4)-alkyl,
R^{22} is hydrogen or (C_1-C_4)-alkyl,
or
R^{21} and R^{22} together with the atoms to which they are bonded form a 3- to 7-membered carbocycle,
R^{27} is hydrogen or (C_1-C_4)-alkyl,

L^2 is linear (C_2-C_{10})-alkanediyl or is a group of the formula

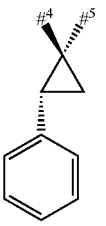


where
p is a number from 2 to 6,
##3 marks the linkage site with the group B,
##4 marks the linkage site with the nitrogen atom,
where (C_2-C_{10})-alkanediyl may be substituted by 1 to 4 substituents selected independently of one another from the group consisting of methyl, hydroxy and benzyl,
and
where two carbon atoms of the alkanediyl chain in 1,2, 1,3 or 1,4 relation to one another, with inclusion of any carbon atoms situated between them, may be bridged to form a (C_3-C_6)-cycloalkyl ring or a phenyl ring,

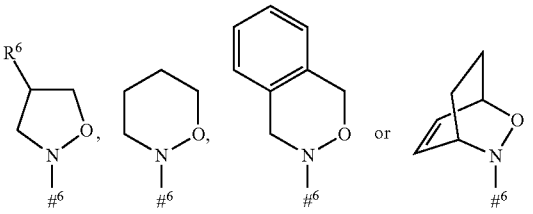
D is a group of the formula



in which
#3 marks the linkage site with the nitrogen atom,
R^1 is hydrogen or methyl,
R^2 is isopropyl, isobutyl, sec-butyl, tert-butyl, phenyl, benzyl, 1-hydroxyethyl, 4-hydroxybenzyl, 4-hydroxy-3-nitrobenzyl, 4-hydroxy-3-aminobenzyl, 1-phenylethyl, diphenylmethyl, 1H-imidazol-4-ylmethyl or 1H-indol-3-ylmethyl,
or
R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula



in which
#4 marks the linkage site with the adjacent nitrogen atom,
#5 marks the linkage site with the carbonyl group,
the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



in which

$\#^6$ marks the linkage site with the carbonyl group,

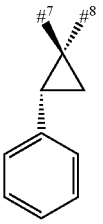
R^6 is hydrogen, hydroxy or benzyloxy,

R^3 is hydrogen or methyl,

R^4 is isopropyl, isobutyl, sec-butyl, tert-butyl, phenyl, benzyl, 1-hydroxyethyl, 4-hydroxybenzyl, 4-hydroxy-3-nitrobenzyl, 4-hydroxy-3-aminobenzyl, 1-phenylethyl, diphenylmethyl, 1H-imidazol-4-ylmethyl or 1H-indol-3-ylmethyl,

or

R^3 and R^4 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula



in which

$\#^7$ marks the linkage site with the adjacent nitrogen atom,

$\#^8$ marks the linkage site with the group T^1,

T^1 is a group of the formula —C(═O)—OR^7, —C(═O)—NR^8R^9, —C(═O)—NH—NH—R^{10} or —CH_2—O—R^{11},

in which

R^7 is hydrogen, methyl, ethyl, n-propyl, tert-butyl, benzyl or adamantylmethyl,

R^8 is hydrogen or methyl,

R^9 is hydrogen, methyl, ethyl, n-propyl or benzyl,

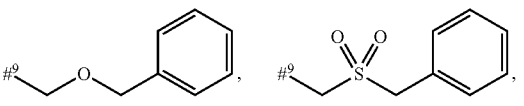
or

R^8 and R^9 together with the nitrogen atom to which they are bonded form a 4- to 7-membered heterocycle,

R^{10} is benzoyl,

R^{11} is benzyl, which may be substituted in the phenyl group by methoxycarbonyl or carboxyl,

R^5 is hydrogen, methyl or a group of the formula



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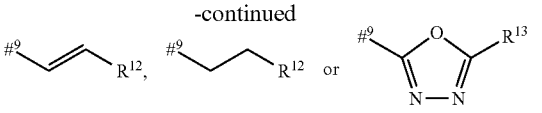


$\#^9$ marks the linkage site with —CHC(R^{26})-T^2,

R^{12} is phenyl which may be substituted by methoxycarbonyl, carboxyl or a group of the formula —$S(O)_2OH$,

R^{13} is phenyl which may be substituted by methoxycarbonyl or carboxyl,

R^{26} is hydrogen or hydroxy,

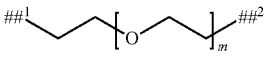
T^2 is phenyl, benzyl, 1H-indol-3-yl or 1H-indol-3-ylmethyl,

R^{35} is methyl or hydroxy,

and also their salts, solvates and solvates of the salts.

11. Compounds of the formula (XXXI) according to claim **10**, in which

L^1 is a bond, linear (C_2-C_6)-alkanediyl or a group of the formula



where

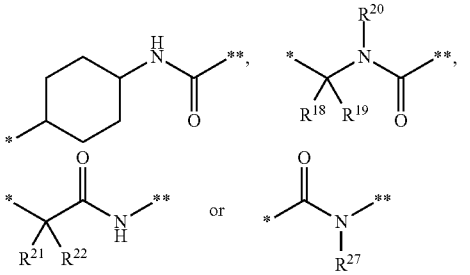
m is a number 2 or 3,

$\#\#^1$ marks the linkage site with the group G,

$\#\#^2$ marks the linkage site with the group B,

where (C_2-C_6)-alkanediyl may be substituted by 1 or 2 methyl substituents,

B is a bond or a group of the formula



where

* marks the linkage site with L^1,

** marks the linkage site with L^2,

R^{18} is hydrogen,

R^{19} is methyl, propan-2-yl, 2-methylpropan-1-yl or 1-methylpropan-1-yl,

R^{20} is hydrogen or (C_1-C_4)-alkyl,

or

R^{19} and R^{20} together with the atoms to which they are bonded form a pyrrolidinyl ring,

R^{21} is hydrogen or methyl,

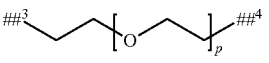
R^{22} is hydrogen or methyl,

or

R^{21} and R^{22} together with the atoms to which they are bonded form a cyclopropyl ring,

R^{27} is hydrogen or methyl,

L^2 is linear (C_2-C_6)-alkanediyl or is a group of the formula



where

p is a number 2 or 3,

$\#\#^3$ marks the linkage site with the group B,

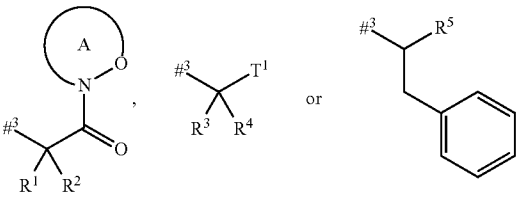
$\#\#^4$ marks the linkage site with the nitrogen atom,

where (C_2-C_{10})-alkanediyl may be substituted by 1 or 2 methyl substituents,

and

where two carbon atoms of the alkanediyl chain in 1,4 relation to one another, with inclusion of any carbon atoms situated between them, may be bridged to form a phenyl ring,

D is a group of the formula



in which

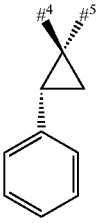
$\#^3$ marks the linkage site with the nitrogen atom,

R^1 is hydrogen,

R^2 is 1-hydroxyethyl, benzyl, 4-hydroxybenzyl, 1-phenylethyl or 1H-indol-3-ylmethyl,

or

R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1, 1-diyl group of the formula

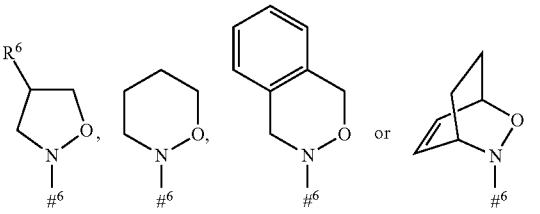


in which

$\#^4$ marks the linkage site with the adjacent nitrogen atom,

$\#^5$ marks the linkage site with the carbonyl group,

the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



in which

$\#^6$ marks the linkage site with the carbonyl group,

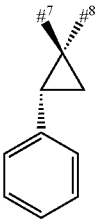
R^6 is hydrogen, hydroxy or benzyloxy,

R^3 is hydrogen,

R^4 is 1-hydroxyethyl, benzyl, 4-hydroxybenzyl, 1-phenylethyl or 1H-indol-3-ylmethyl,

or

R^3 and R^4 together with the carbon atoms to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1, 1-diyl group of the formula



in which

$\#^7$ marks the linkage site with the adjacent nitrogen atom,

$\#^8$ marks the linkage site with the group T^1,

T^1 is a group of the formula —C(═O)—OR^7, —C(═O)—NR^8R^9, —C(═O)—NH—NH—R^{10} or —CH_2—O—R^{11},

in which

R^7 is hydrogen, methyl, ethyl, n-propyl, tert-butyl, benzyl or adamantylmethyl,

R^8 is hydrogen or methyl,

R^9 is hydrogen, methyl, ethyl, n-propyl or benzyl,

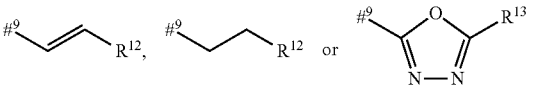
or

R^8 and R^9 together with the nitrogen atom to which they are bonded form a 4- to 7-membered heterocycle,

R^{10} is benzoyl,

R^{11} is benzyl, which may be substituted in the phenyl group by methoxycarbonyl or carboxyl,

R^5 is hydrogen, methyl or a group of the formula



in which

$\#^9$ marks the linkage site with —$CHCH_2$phenyl,

R^{12} is phenyl which may be substituted by methoxycarbonyl, carboxyl or a group of the formula —$S(O)_2OH$,

R^{13} is phenyl which may be substituted by methoxycarbonyl or carboxyl,

R^{35} is methyl or hydroxy,

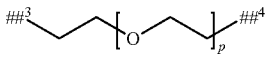
and also their salts, solvates and solvates of the salts.

12. Compounds of the formula (XXXI) according to either of claim **10** or **11**, in which

L^1 is a bond,

B is a bond,

L^2 is linear (C_2-C_6)-alkanediyl or is a group of the formula



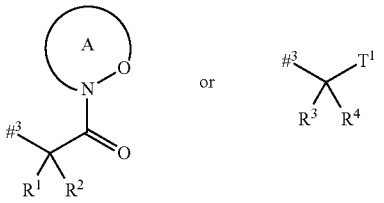
where

p is a number 2 or 3,

$\#\#^3$ marks the linkage site with the group B,

$\#\#^4$ marks the linkage site with the nitrogen atom,

D is a group of the formula



where

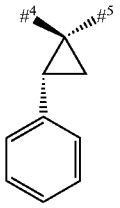
$\#^3$ marks the linkage site with the nitrogen atom,

R^1 is hydrogen,

R^2 is benzyl or 1H-indol-3-ylmethyl,

or

R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula

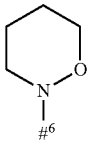


in which

$\#^4$ marks the linkage site with the adjacent nitrogen atom,

$\#^5$ marks the linkage site with the carbonyl group,

the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



in which

$\#^6$ marks the linkage site with the carbonyl group,

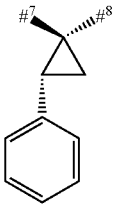
R^6 is hydrogen, hydroxy or benzyloxy,

R^3 is hydrogen,

R^4 is benzyl or 1H-indol-3-ylmethyl,

or

R^3 and R^4 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula



in which

$\#^7$ marks the linkage site with the adjacent nitrogen atom,

$\#^8$ marks the linkage site with the group T^1,

T^1 is a group of the formula —C(═O)—OR^7 or —C(═O)—NR^8R^9,

in which

R^7 is hydrogen,

R^8 is hydrogen,

R^9 is hydrogen,

R^{35} is methyl,

and also their salts, solvates and solvates of the salts.

13. Compounds of the formulae (XXXa) and (XXXI) selected from the following group:

N-[6-(3-{[(2R)-2-amino-2-carboxyethyl]sulphanyl}-2,5-dioxopyrrolidin-1-yl)hexyl]-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(1S)-1-carboxy-2-(1H-indol-3-yl)ethyl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide,

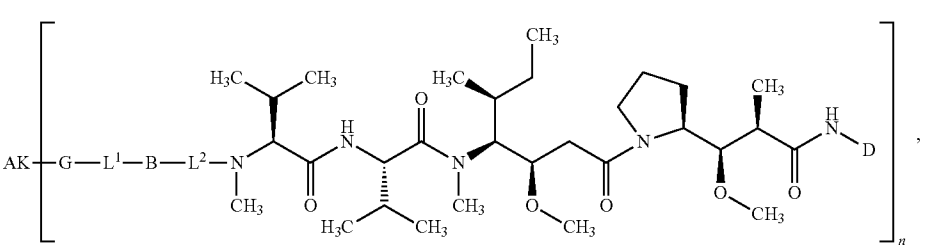
N-[6-(3-{[(2R)-2-amino-2-carboxyethyl]sulphanyl}-2,5-dioxopyrrolidin-1-yl)hexyl]-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide,

N-(6-{[(5S)-5-amino-5-carboxypentyl]amino}-6-oxohexyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-3-(1H-indol-3-yl)-1-(1,2-oxazinan-2-yl)-1-oxopropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide trifluoroacetate,

N-(6-{[(5S)-5-amino-5-carboxypentyl]amino}-6-oxohexyl)-N-methyl-L-valyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(1S)-1-carboxy-2-(1H-indol-3-yl)ethyl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide,

and also their salts, solvates and solvates of the salts.

14. Binder-drug conjugates of the general formula (I)



(I)

in which

n is a number from 1 to 50,

AK is a binder,

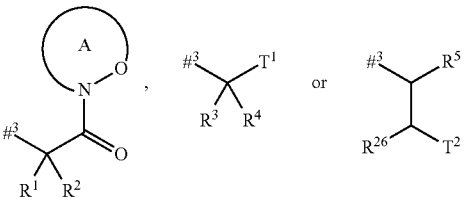
the group §-G-L^1-B-L^2-§§ is a linker,

where

§ marks the linkage site with the group AK and

§§ marks the linkage site with the nitrogen atom,

D is a group of the formula



where

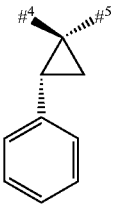
$\#^3$ marks the linkage site with the nitrogen atom,

R^1 is hydrogen,

R^2 is 1-hydroxyethyl, benzyl, 1-phenylethyl or 1H-indol-3-ylmethyl,

or

R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1, 1-diyl group of the formula

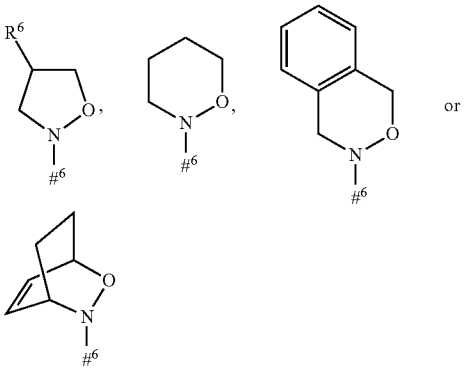


in which

$\#^4$ marks the linkage site with the adjacent nitrogen atom,

$\#^5$ marks the linkage site with the carbonyl group,

the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



in which

$\#^6$ marks the linkage site with the carbonyl group,

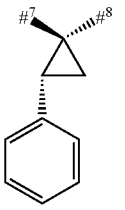
R^6 is hydrogen, hydroxy or benzyloxy,

R^3 is hydrogen,

R^4 1-hydroxyethyl, benzyl, 1-phenylethyl or 1H-indol-3-ylmethyl,

or

R^3 and R^4 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1, 1-diyl group of the formula



in which

$\#^7$ marks the linkage site with the adjacent nitrogen atom,

$\#^8$ marks the linkage site with the group T^1,

T^1 is a group of the formula —C(=O)—OR^7, —C(=O)—NR^8R^9, —C(=O)—NH—NH—R^{10} or —CH_2—O—R^{11},

in which

R^7 is hydrogen, methyl, ethyl, n-propyl, tert-butyl, benzyl or adamantylmethyl,

R^8 is hydrogen or methyl,

R^9 is hydrogen, methyl, ethyl, n-propyl or benzyl,

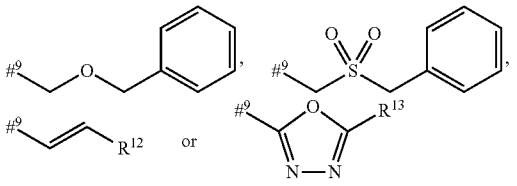
or

R^8 and R^9 together with the nitrogen atom to which they are bonded form a 4- to 7-membered heterocycle,

R^{10} is benzoyl,

R^{11} is benzyl, which may be substituted in the phenyl group by methoxycarbonyl or carboxyl,

R^5 is hydrogen, methyl or a group of the formula



in which

$\#^9$ marks the linkage site with —CHC(R^{26})-T^2,

R^{12} is phenyl which may be substituted by methoxycarbonyl, carboxyl or a group of the formula —$S(O)_2OH$,

R^{13} is phenyl which may be substituted by methoxycarbonyl or carboxyl,

R^{26} is hydrogen or hydroxy,

T^2 is phenyl, benzyl, 1H-indol-3-yl or 1H-indol-3-ylmethyl,

and also their salts, solvates and solvates of the salts.

15. Binder-drug conjugates according to claim **14** with the general formula (I),

in which

n is a number from 1 to 50,

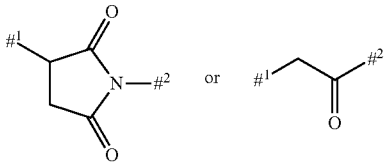
AK is AK_1 or AK_2

where

AK_1 is a binder which is bonded via a sulphur atom of the binder to the group G,

AK_2 is a binder which is bonded via a nitrogen atom of the binder to the group G,

G when $AK=AK_1$, is a group of the formula



where

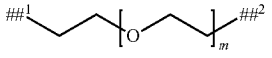
$\#^1$ marks the linkage site with the sulphur atom of the binder,

$\#^2$ marks the linkage site with the group L^1,

or

when $AK=AK_2$, is carbonyl,

L^1 is a bond, linear (C_1-C_{10})-alkanediyl or is a group of the formula



where

m is a number from 2 to 6,

$\#\#^1$ marks the linkage site with the group G,

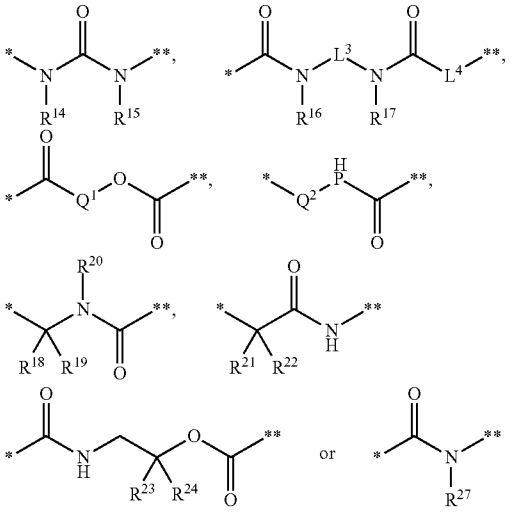
$\#\#^2$ marks the linkage site with the group B,

where (C_1-C_{10})-alkanediyl may be substituted by 1 to 4 methyl substituents,

and

where two carbon atoms of the alkanediyl chain in 1,2, 1,3 or 1,4 relation to one another, with inclusion of any carbon atoms situated between them, may be bridged to form a (C_3-C_6)-cycloalkyl ring or a phenyl ring,

B is a bond or a group of the formula



where

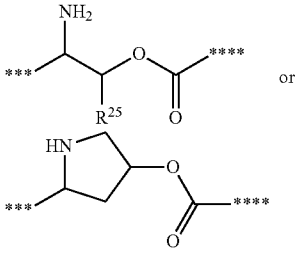
* marks the linkage site with L^1,

** marks the linkage site with L^2,

P is O or NH,

L^3 is a bond or (C_2-C_4)-alkanediyl,

L^4 is a bond or a group of the formula



in which

*** marks the linkage site with the carbonyl group,

**** marks the linkage site with L^2,

R^{25} is hydrogen or methyl,

Q^1 is a 4- to 7-membered heterocycle,

Q^2 is a 3- to 7-membered carbocycle or a 4- to 7-membered heterocycle,

R^{14} is hydrogen or (C_1-C_4)-alkyl,

R^{15} is hydrogen or (C_1-C_4)-alkyl,

or

R^{14} and R^{15} together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

R^{16} is hydrogen or (C_1-C_4)-alkyl,

R^{17} is hydrogen or (C_1-C_4)-alkyl,

or

R^{16} and R^{17} together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

R^{18} is hydrogen or (C_1-C_4)-alkyl,

R^{19} is hydrogen or the side group of a natural α-amino acid or of its homologues or isomers,

R^{20} is hydrogen or (C_1-C_4)-alkyl,

or

R^{19} and R^{20} together with the atoms to which they are bonded form a pyrrolidinyl ring,

R^{21} is hydrogen or (C_1-C_4)-alkyl,

R^{22} is hydrogen or (C_1-C_4)-alkyl,

or

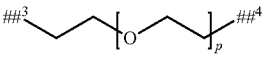
R^{21} and R^{22} together with the atoms to which they are bonded form a 3- to 7-membered carbocycle,

R^{23} is (C_1-C_4)-alkyl,

R^{24} is hydrogen or (C_1-C_4)-alkyl,

R^{27} is hydrogen or (C_1-C_4)-alkyl,

L^2 is linear (C_2-C_{10})-alkanediyl or is a group of the formula



where

p is a number from 2 to 6,

$##^3$ marks the linkage site with the group B,

$##^4$ marks the linkage site with the nitrogen atom,

where (C_2-C_{10})-alkanediyl may be substituted by 1 to 4 methyl substituents, and

where two carbon atoms of the alkanediyl chain in 1,2, 1,3 or 1,4 relation to one another, with inclusion of any carbon atoms situated between them, may be bridged to form a (C_3-C_6)-cycloalkyl ring or a phenyl ring,

D has the definitions indicated in claim **14**,

and also their salts, solvates and solvates of the salts.

16. Binder-drug conjugates according to claim **14** or **15** of the general formula (I),

in which

n is a number from 1 to 50,

AK is AK_1 or AK_2

where

AK_1 is an antibody or an antigen-binding antibody fragment and are bonded via a sulphur atom to the group G,

AK_2 is an antibody or an antigen-binding antibody fragment and are bonded via a nitrogen atom to the group G,

G, L^1, B, L^2 and D have the definitions indicated in the claim **14** or **15**,

and also their salts, solvates and solvates of the salts.

17. Binder-drug conjugates according to any of claims **14** to **16** of the general formula (I), in which

n is a number from 1 to 20,

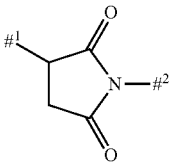
AK is AK_1 or AK_2

where

AK_1 is an antibody or an antigen-binding antibody fragment which binds to mesothelin and is bonded via the sulphur atom of a cysteine residue of the binder to the group G,

AK_2 is an antibody or an antigen-binding antibody fragment which binds to mesothelin and is bonded via the NH side group of a lysine residue of the binder to the group G,

G when $AK=AK_1$, is a group of the formula



in which

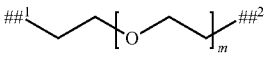
$\#^1$ marks the linkage site with the cysteine residue of the binder,

$\#^2$ marks the linkage site with the group L^1,

or

when $AK=AK_2$, is carbonyl,

L^1 is a bond, linear (C_2-C_6)-alkanediyl or is a group of the formula



where

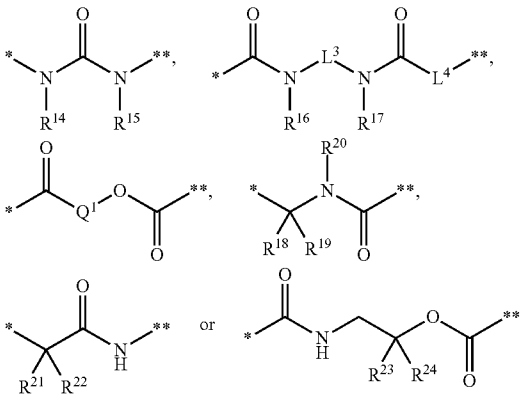
m is a number from 2 to 6,

$##^1$ marks the linkage site with the group G,

$##^2$ marks the linkage site with the group B,

where (C_2-C_6)-alkanediyl may be substituted by 1 or 2 methyl substituents,

B is a bond or a group of the formula



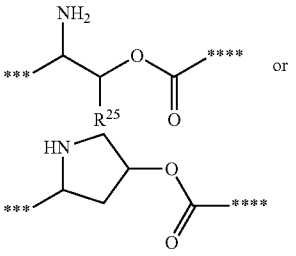
where

* marks the linkage site with L^1,

** marks the linkage site with L^2,

L^3 is a bond or ethane-1,2-diyl,

L^4 is a bond or a group of the formula



in which

*** marks the linkage site with the carbonyl group,

**** marks the linkage site with L^2,

R^{25} is methyl,

Q^1 is a 4- to 6-membered carbocycle or piperidine-1,4-diyl,

R^{14} is hydrogen,

R^{15} is hydrogen,

R^{16} is hydrogen or methyl,

R^{17} is hydrogen or methyl,

or

R^{16} and R^{17} together with the atoms to which they are bonded form a piperazinyl ring,

R^{18} is hydrogen,

R^{19} is hydrogen, methyl, propan-2-yl, 2-methylpropan-1-yl or 1-methylpropan-1-yl,

R^{20} is hydrogen or methyl,

or

R^{19} and R^{20} together with the atoms to which they are bonded form a pyrrolidinyl ring,

R^{21} is hydrogen or methyl,

R^{22} is hydrogen or methyl,

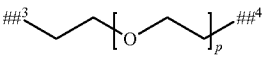
or

R^{21} and R^{22} together with the atoms to which they are bonded form a cyclopropyl ring,

R^{23} is methyl,

R^{24} is hydrogen or methyl,

L^2 is linear $(C_2\text{-}C_6)$-alkanediyl or is a group of the formula



where

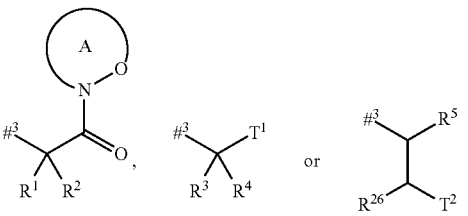
p is a number from 2 to 6,

##^{3} marks the linkage site with the group B,

##^{4} marks the linkage site with the nitrogen atom,

where $(C_2\text{-}C_6)$-alkanediyl may be substituted by 1 or 2 methyl substituents,

D is a group of the formula



where

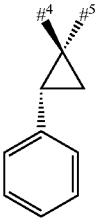
#^{3} marks the linkage site with the nitrogen atom,

R^1 is hydrogen,

R^2 is 1-hydroxyethyl, benzyl, 1-phenylethyl or 1H-indol-3-ylmethyl,

or

R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula

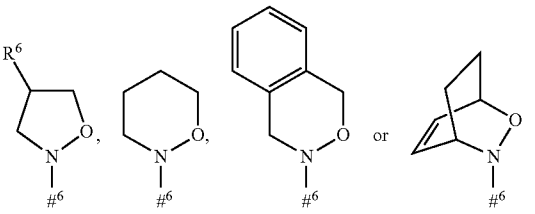


in which

#^{4} marks the linkage site with the adjacent nitrogen atom,

#^{5} marks the linkage site with the carbonyl group,

the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



in which

#^{6} marks the linkage site with the carbonyl group,

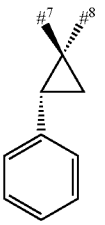
R^6 is hydrogen, hydroxy or benzyloxy,

R^3 is hydrogen,

R^4 is 1-hydroxyethyl, benzyl, 1-phenylethyl or 1H-indol-3-ylmethyl,

or

R^3 and R^4 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula



in which

#^{7} marks the linkage site with the adjacent nitrogen atom,

#^{8} marks the linkage site with the group T^1,

T^1 is a group of the formula —C(═O)—OR^7, —C(═O)—NR^8R^9, —C(═O)—NH—NH—R^{10} or —CH_2—O—R^{11},

in which

R^7 is hydrogen, methyl, ethyl, n-propyl, tert-butyl, benzyl or adamantylmethyl,

R^8 is hydrogen or methyl,

R^9 is hydrogen, methyl, ethyl, n-propyl or benzyl,

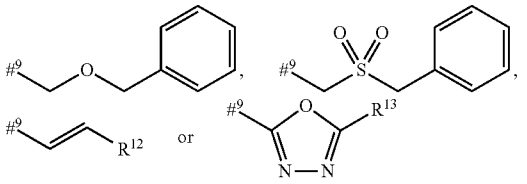
or

R^8 and R^9 together with the nitrogen atom to which they are bonded form a 4- to 7-membered heterocycle,

R^{10} is benzoyl,

R^{11} is benzyl, which may be substituted in the phenyl group by methoxycarbonyl or carboxyl,

R^5 is hydrogen, methyl or a group of the formula



in which

#9 marks the linkage site with —CHC(R^{26})-T^2,

R^{12} is phenyl which may be substituted by methoxycarbonyl, carboxyl or a group of the formula —$S(O)_2OH$,

R^{13} is phenyl which may be substituted by methoxycarbonyl or carboxyl,

R^{26} is hydrogen or hydroxy,

T^2 is phenyl, benzyl, 1H-indol-3-yl or 1H-indol-3-ylmethyl,

and also their salts, solvates and solvates of the salts.

18. Binder-drug conjugates according to any of claims **14** to **17** of the general formula (I)

in which

n is a number from 1 to 10,

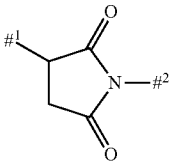
AK is AK_1 or AK_2

where

AK_1 is an antibody which comprises the six CDR sequences of the antibody MF-Ta, the variable light and variable heavy chain of the antibody MF-Ta or the light and heavy chain of the antibody MF-Ta, and is bonded via the sulphur atom of a cysteine residue of the binder to the group G,

AK_2 is an antibody which comprises the six CDR sequences of the antibody MF-Ta, the variable light and variable heavy chain of the antibody MF-Ta or the light and heavy chain of the antibody MF-Ta, and is bonded via the NH side group of a lysine residue of the binder to the group G,

G when $AK=AK_1$, is a group of the formula



in which

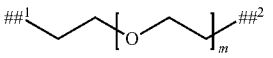
#1 marks the linkage site with the cysteine residue of the binder,

#2 marks the linkage site with the group L^1,

or

when $AK=AK_2$, is carbonyl,

L^1 is a bond, linear (C_2-C_6)-alkanediyl or is a group of the formula



where

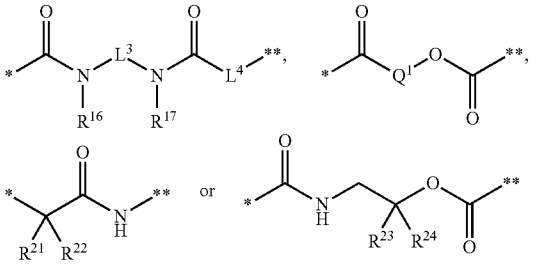
m is a number 2 or 3,

##1 marks the linkage site with the group G,

##2 marks the linkage site with the group B,

where (C_2-C_6)-alkanediyl may be substituted by 1 or 2 methyl substituents,

B is a bond or a group of the formula



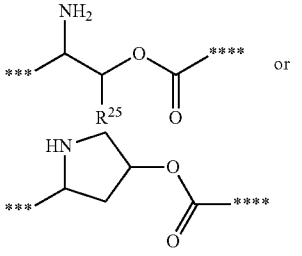
where

* marks the linkage site with L^1,

** marks the linkage site with L^2,

L^3 is a bond or ethane-1,2-diyl,

L^4 is a bond or a group of the formula



in which

*** marks the linkage site with the carbonyl group,

**** marks the linkage site with L^2,

R^{25} is methyl,

Q^1 is piperidine-1,4-diyl,

R^{16} is hydrogen or methyl,

R^{17} is hydrogen or methyl,

or

R^{16} and R^{17} together with the atoms to which they are bonded form a piperazinyl ring,

R^{21} is hydrogen or methyl,

R^{22} is hydrogen or methyl,

or

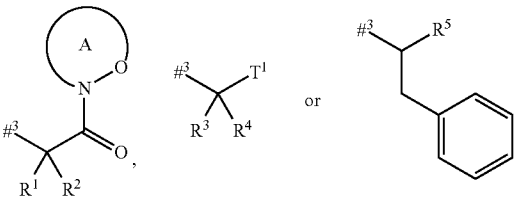
R^{21} and R^{22} together with the atoms to which they are bonded form a cyclopropyl ring,

R^{23} is methyl,

R^{24} is hydrogen,

L^2 is linear (C_2-C_6)-alkanediyl,

D is a group of the formula



where

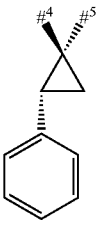
#3 marks the linkage site with the nitrogen atom,

R^1 is hydrogen,

R^2 is 1-hydroxyethyl, benzyl, 1-phenylethyl or 1H-indol-3-ylmethyl,

or

R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula

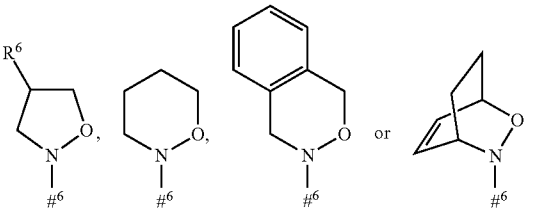


in which

#4 marks the linkage site with the adjacent nitrogen atom,

#5 marks the linkage site with the carbonyl group,

the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



in which

#6 marks the linkage site with the carbonyl group,

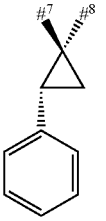
R^6 is hydrogen, hydroxy or benzyloxy,

R^3 is hydrogen,

R^4 is benzyl, 1-phenylethyl or 1H-indol-3-ylmethyl,

or

R^3 and R^4 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1,1-diyl group of the formula



in which

#7 marks the linkage site with the adjacent nitrogen atom,

#8 marks the linkage site with the group T^1,

T^1 is a group of the formula —C(═O)—OR^7, —C(═O)—NR^8R^9 or —CH_2—O—R^{11},

in which

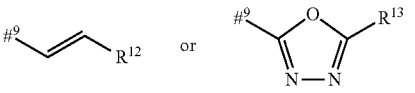
R^7 is hydrogen, methyl, ethyl, n-propyl, benzyl or adamantylmethyl,

R^8 is hydrogen or methyl,

R^9 is hydrogen, methyl, ethyl, n-propyl or benzyl,

R^{11} is benzyl, which may be substituted in the phenyl group by methoxycarbonyl or carboxyl,

R^5 is hydrogen or a group of the formula



in which

#9 marks the linkage site with —CHC(R^{26})phenyl,

R^{12} is phenyl which may be substituted by methoxycarbonyl, carboxyl or a group of the formula —$S(O)_2OH$,

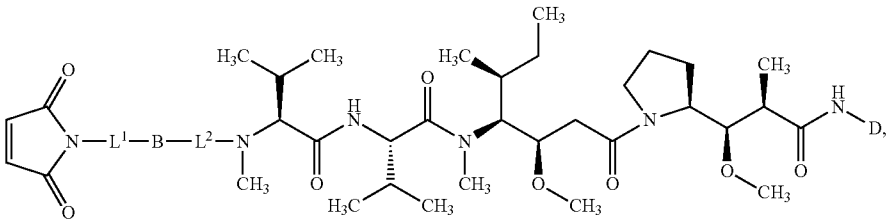
R^{13} is phenyl which may be substituted by methoxycarbonyl or carboxyl,

and also their salts, solvates and solvates of the salts.

19. Process for preparing the compounds of the invention according to any of claims **14** to **18**, of the general formula (I), characterized in that a solution of the binder in a buffer

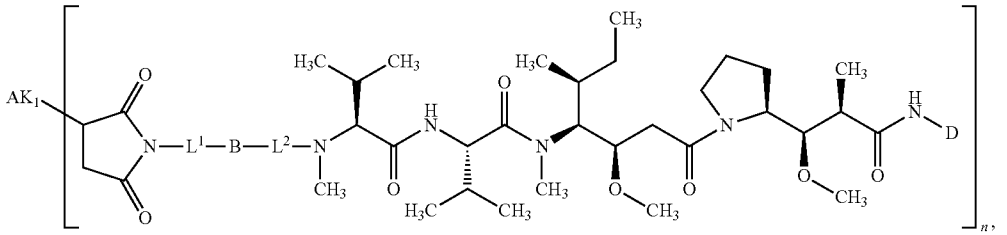
[A] is admixed with a suitable reducing agent, such as, for example, dithiothreitol or tris(2-carboxyethyl)phosphine hydrochloride, and is subsequently reacted with a compound of the formula (II)

(II)



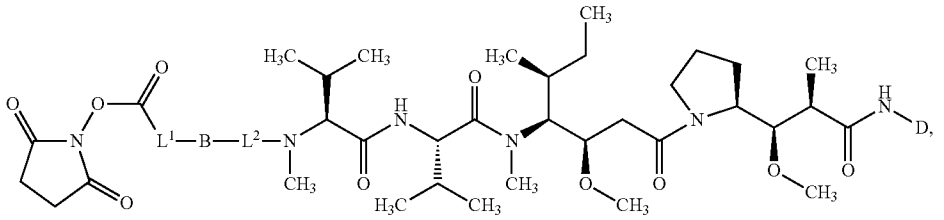
in which D, L^1, B and L^2 each have the definitions indicated in claims **1** to **5**,
to give a compound of the formula (I-A)

(I-A)



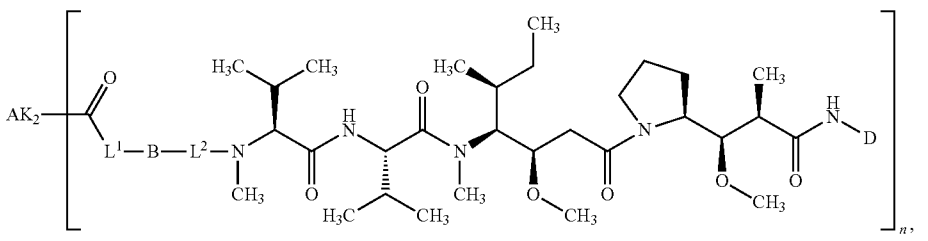
in which n, AK_1, D, L^1, B and L^2 each have the definitions indicated in claims **1** to **5**,
or
[B] is reacted with a compound of the formula (III)

(III)



in which D, L^1, B and L^2 each have the definitions indicated in claims **1** to **5**,
to give a compound of the formula (I-B)

(I-B)

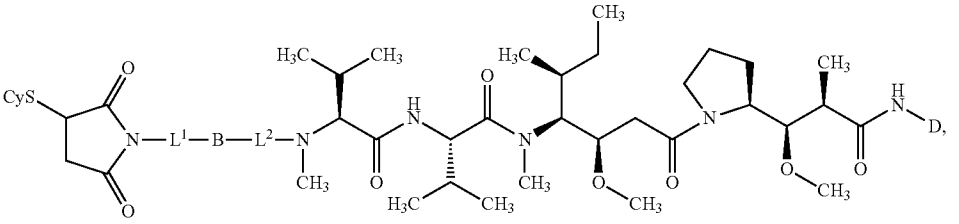


in which n, AK_2, D, L^1, B and L^2 each have the definitions indicated in claims **1** to **5**.

20. Compounds prepared by the process according to claim **19** or **54**, where AK_1 and AK_2 is an antibody which comprises the six CDR sequences of the antibody MF-Ta, the variable light and variable heavy chain of the antibody MF-Ta or the light and heavy chain of the antibody MF-Ta,

and also their salts, solvates and solvates of the salts.

21. Compounds of the formula (XXX)

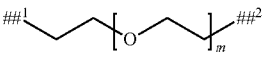


(XXX)

in which

Cys is a cysteine residue which is bonded via the sulphur atom of the side chain to a carbon atom of the succinimide,

L^1 is a bond, linear (C_1-C_{10})-alkanediyl or is a group of the formula



where

m is a number from 2 to 6,

##[1] marks the linkage site with the group G,

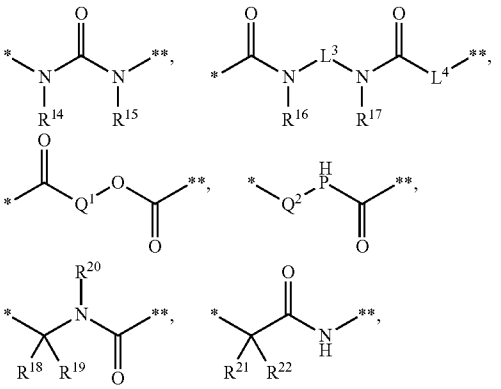
##[2] marks the linkage site with the group B,

where (C_1-C_{10})-alkandiyl may be substituted by 1 to 4 methyl substituents,

and

where two carbon atoms of the alkanediyl chain in 1,2, 1,3 or 1,4 relation to one another, with inclusion of any carbon atoms situated between them, may be bridged to form a (C_3-C_6)-cycloalkyl ring or a phenyl ring,

B is a bond or a group of the formula



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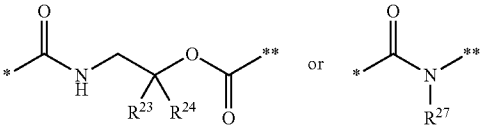


where

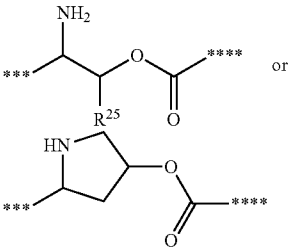
* marks the linkage site with L^1,

** marks the linkage site with L^2,

P is O or NH,

L^3 is a bond or (C_2-C_4)-alkanediyl,

L^4 is a bond or a group of the formula



in which

*** marks the linkage site with the carbonyl group,

**** marks the linkage site with L^2,

R^{25} is hydrogen or methyl,

Q^1 is a 3- to 7-membered carbocycle or a 4- to 7-membered aza heterocycle,

Q^2 is a 3- to 7-membered carbocycle or a 4- to 7-membered aza heterocycle,

R^{14} is hydrogen or (C_1-C_4)-alkyl,

R^{15} is hydrogen or (C_1-C_4)-alkyl,

or

R^{14} and R^{15} together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

R^{16} is hydrogen or (C_1-C_4)-alkyl,

R^{17} is hydrogen or (C_1-C_4)-alkyl,

or

R^{16} and R^{17} together with the atoms to which they are bonded form a 5- or 6-membered heterocycle,

R^{18} is hydrogen or (C_1-C_4)-alkyl,

R^{19} is hydrogen or the side group of a natural α-amino acid or of its homologues or isomers,

R^{20} is hydrogen or (C_1-C_4)-alkyl,

or

R^{19} and R^{20} together with the atoms to which they are bonded form a pyrrolidinyl ring,

R^{21} is hydrogen or $(C_1$-$C_4)$-alkyl,

R^{22} is hydrogen or $(C_1$-$C_4)$-alkyl,

or

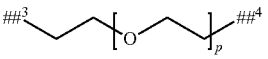
R^{21} and R^{22} together with the atoms to which they are bonded form a 3- to 7-membered carbocycle,

R^{23} is $(C_1$-$C_4)$-alkyl,

R^{24} is hydrogen or $(C_1$-$C_4)$-alkyl,

R^{27} is hydrogen or $(C_1$-$C_4)$-alkyl,

L^2 is linear $(C_2$-$C_{10})$-alkanediyl or is a group of the formula



where

p is a number from 2 to 6,

$\#\#^3$ marks the linkage site with the group B,

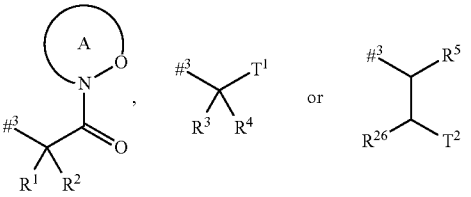
$\#\#^4$ marks the linkage site with the nitrogen atom,

where $(C_2$-$C_{10})$-alkanediyl may be substituted by 1 to 4 methyl substituents,

and

where two carbon atoms of the alkanediyl chain in 1,2, 1,3 or 1,4 relation to one another, with inclusion of any carbon atoms situated between them, may be bridged to form a $(C_3$-$C_6)$-cycloalkyl ring or a phenyl ring,

D is a group of the formula



in which

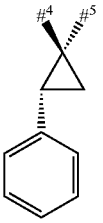
$\#^3$ marks the linkage site with the nitrogen atom,

R^1 is hydrogen,

R^2 is 1-hydroxyethyl, benzyl, 1-phenylethyl or 1H-indol-3-ylmethyl,

or

R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1, 1-diyl group of the formula

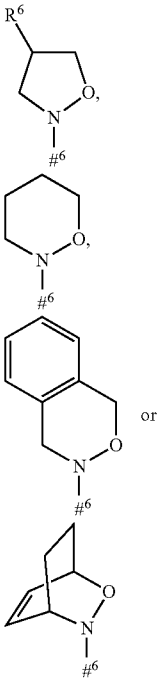


in which

$\#^4$ marks the linkage site with the adjacent nitrogen atom,

$\#^5$ marks the linkage site with the carbonyl group,

the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



in which

$\#^6$ marks the linkage site with the carbonyl group,

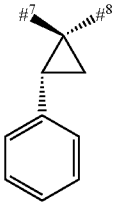
R^6 is hydrogen, hydroxy or benzyloxy,

R^3 is hydrogen,

R^4 is 1-hydroxyethyl, benzyl, 1-phenylethyl or 1H-indol-3-ylmethyl,

or

R^3 and R^4 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1, 1-diyl group of the formula



in which

$\#^7$ marks the linkage site with the adjacent nitrogen atom,

$\#^8$ marks the linkage site with the group T^1,

T^1 is a group of the formula —C(═O)—OR^7, —C(═O)—NR^8R^9, —C(═O)—NH—NH—R^{10} or —CH_2—O—R^{11},

in which

R^7 is hydrogen, methyl, ethyl, n-propyl, tert-butyl, benzyl or adamantylmethyl,

R^8 is hydrogen or methyl,

R^9 is hydrogen, methyl, ethyl, n-propyl or benzyl,

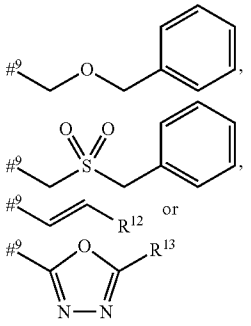
or

R^8 and R^9 together with the nitrogen atom to which they are bonded form a 4- to 7-membered heterocycle,

R^{10} is benzoyl

R^{11} is benzyl, which may be substituted in the phenyl group by methoxycarbonyl or carboxyl,

R^5 is hydrogen, methyl or a group of the formula



in which

$\#^9$ marks the linkage site with —CHC(R^{26})-T^2,

R^{12} is phenyl which may be substituted by methoxycarbonyl, carboxyl or a group of the formula —S(O)$_2$OH,

R^{13} is phenyl which may be substituted by methoxycarbonyl or carboxyl,

R^{26} is hydrogen or hydroxy,

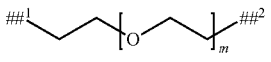
T^2 is phenyl, benzyl, 1H-indol-3-yl or 1H-indol-3-ylmethyl,

and also their salts, solvates and solvates of the salts.

22. Compounds of the formula (XXX) according to claim **21**, in which

Cys is a cysteine residue which is bonded via the sulphur atom of the side chain to a carbon atom of the succinimide,

L^1 is a bond, linear (C_2-C_6)-alkanediyl or is a group of the formula



where

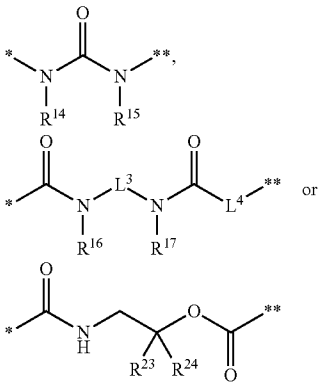
m is a number from 2 to 6,

$\#\#^1$ marks the linkage site with the group G,

$\#\#^2$ marks the linkage site with the group B,

where (C_2-C_6)-alkandiyl may be substituted by 1 or 2 methyl substituents,

B is a bond or a group of the formula



where

* marks the linkage site with L^1,

** marks the linkage site with L^2,

L^3 is a bond or ethane-1,2-diyl,

L^4 is a bond,

R^{14} is hydrogen,

R^{15} is hydrogen,

R^{16} is hydrogen or methyl,

R^{17} is hydrogen or methyl,

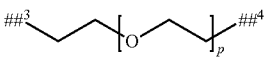
or

R^{16} and R^{17} together with the atoms to which they are bonded form a piperazinyl ring,

R^{23} is methyl,

R^{24} is hydrogen or methyl,

L^2 is linear (C_2-C_6)-alkanediyl or is a group of the formula



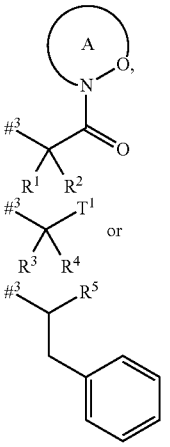
where

p is a number 2 or 3,

$\#\#^3$ marks the linkage site with the group B,

$\#\#^4$ marks the linkage site with the nitrogen atom,

D is a group of the formula



in which

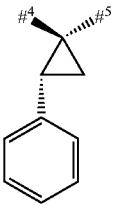
$\#^3$ marks the linkage site with the nitrogen atom,

R^1 is hydrogen,

R^2 is 1-hydroxyethyl, benzyl, 1-phenylethyl or 1H-indol-3-ylmethyl,

or

R^1 and R^2 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1, 1-diyl group of the formula

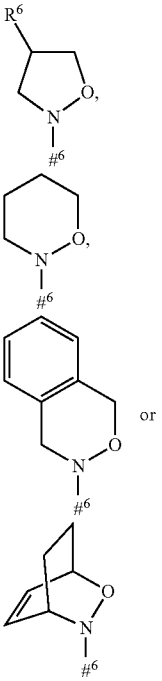


in which

$\#^4$ marks the linkage site with the adjacent nitrogen atom,

$\#^5$ marks the linkage site with the carbonyl group,

the ring A with the N—O moiety present therein is a mono- or bicyclic, optionally substituted heterocycle of the formula



in which

$\#^6$ marks the linkage site with the carbonyl group,

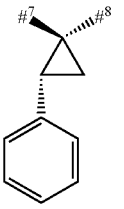
R^6 is hydrogen, hydroxy or benzyloxy,

R^3 is hydrogen,

R^4 is benzyl, 1-phenylethyl or 1H-indol-3-ylmethyl,

or

R^3 and R^4 together with the carbon atom to which they are bonded form a (1S,2R)-2-phenylcyclopropane-1, 1-diyl group of the formula



in which

$\#^7$ marks the linkage site with the adjacent nitrogen atom,

$\#^8$ marks the linkage site with the group T^1,

T^1 is a group of the formula —C(═O)—OR^7, —C(═O)—NR^8R^9, —C(═O)—NH—NH—R^{10} or —CH_2—O—R^{11},

in which

R^7 is hydrogen, methyl, ethyl, n-propyl, benzyl or adamantylmethyl,

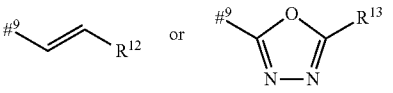
R^8 is hydrogen or methyl,

R^9 is hydrogen, methyl, ethyl, n-propyl or benzyl,

R^{10} is benzoyl,

R^{11} is benzyl, which may be substituted in the phenyl group by methoxycarbonyl or carboxyl,

R^5 is hydrogen or a group of the formula



in which

$\#^9$ marks the linkage site with —CHC(R^{26})phenyl,

R^{12} is phenyl which may be substituted by methoxycarbonyl, carboxyl or a group of the formula —$S(O)_2OH$,

R^{13} is phenyl which may be substituted by methoxycarbonyl or carboxyl,

and also their salts, solvates and solvates of the salts.

23. Binder-drug conjugate according to any of claims **1** to **6** or **14** to **18** where the binder binds to a cancer target molecule.

24. Binder-drug conjugate according to any of claim **1** to **6**, **14** to **18** or **23**, where the binder binds to an extracellular target molecule.

25. Binder-drug conjugate according to any of claims **1** to **6**, **14** to **18** or **23** to **24**, where the binder binds to an extracellular cancer target molecule.

26. Binder-drug conjugate according to any of claims **1** to **6**, **14** to **18** or **23** to **25**, where the target molecule, extracellular target molecule, cancer target molecule or extracellular cancer target molecule is a protein.

27. Binder-drug conjugate according to any of claims **1** to **6**, **14** to **18** or **23** to **26**, where the binder after binding to the extracellular target molecule is internalized by the cell expressing the target molecule.

28. Binder-drug conjugate according to any of claims **1** to **6**, **14** to **18** or **23** to **27**, where the binder is a binder protein.

29. Binder-drug conjugate according to any of claims **1**, **2**, **14**, **15**, **20** or **23** to **28**, where the binder is an antibody or an antigen-binding antibody fragment thereof or an antibody mimetic.

30. Binder-drug conjugate according to any of claims **1** to **6**, **14** to **18** or **23** to **29**, **10** where the antibody is a monoclonal antibody.

31. Binder-drug conjugate according to any of claims **1** to **6**, **14** to **18** and **23** to **30**, where the antibody is a human, humanized or chimeric antibody.

32. Binder-drug conjugate according to any of claims **1** to **6**, **14** to **18** or **23** to **31**, where the antibody is an intact or a modified intact antibody.

33. Binder-drug conjugate according to any of claims **1** to **6**, **14** to **18** or **23** to **32**, where the antibody is an antibody of the IgG class.

34. Binder-drug conjugate according to any of claims **1** to **6**, **14** to **18** or **23** to **33**, where the binder binds to an extracellular cancer target molecule which is selected from the group consisting of EGF receptor (NP_005219.2), mesothelin (Q13421-3), C4.4a (NP_055215.2) and carboanhydrase IX (CA IX; NP_001207.2).

35. Binder-drug conjugate according to any of claims **1** to **6**, **14** to **18** or **23** to **34**, where the binder binds specifically to an extracellular cancer target molecule which is selected from the group consisting of EGF receptor (NP_005219.2), mesothelin (Q13421-3), C4.4a (NP_055215.2) and carboanhydrase IX (CA IX; NP_001207.2).

36. Binder-drug conjugate according to any of claims **1** to **6**, **14** to **18** or **23** to **35**, where the antibody binds to C4.4a.

37. Binder-drug conjugate according to any of claims **1** to **6**, **14** to **18** or **23** to **36**, where the antibody binds to mesothelin and exhibits invariant binding.

38. Binder-drug conjugate according to any of claims **1** to **6**, **14** to **18** or **23** to **37**, where the antibody binds specifically to mesothelin.

39. Binder-drug conjugate according to any of claims **1** to **6**, **14** to **18** or **23** to **38**, where the binder is an anti-mesothelin antibody or antigen-binding antibody fragment which comprises the amino acid sequences of the three CDR regions of the light chain and the amino acid sequences of the three CDR regions of the heavy chain of an antibody described in WO 2009068204-A1 (Table 7; pages 61-63).

40. Binder-drug conjugate according to any of claims **1** to **3**, **14** to **17** or **23** to **39**, where the antimesothelin antibody or antigen-binding antibody fragment is selected from the group consisting of

- anti-mesothelin antibodies or antigen-binding antibody fragments thereof which comprise the sequences of the three CDR regions of the light chain and the sequences of the three CDR regions of the heavy chain of the antibody MF-Ta,
- anti-mesothelin antibodies or antigen-binding antibody fragments thereof which comprise the sequences of the three CDR regions of the light chain and the sequences of the three CDR regions of the heavy chain of the antibody MF-J,
- anti-mesothelin antibodies or antigen-binding antibody fragments thereof which comprise the sequences of the three CDR regions of the light chain and the sequences of the three CDR regions of the heavy chain of the antibody MOR06640,
- anti-mesothelin antibodies or antigen-binding antibody fragments thereof which comprise the sequences of the three CDR regions of the light chain and the sequences of the three CDR regions of the heavy chain of the antibody MF-226, and
- anti-mesothelin antibodies or antigen-binding antibody fragments thereof which comprise the sequences of the three CDR regions of the light chain and the sequences of the three CDR regions of the heavy chain of the antibody MOR06626.

41. Binder-drug conjugate according to any of claims **1** to **3**, **14** to **17** or **23** to **40**, where the antimesothelin antibody or antigen-binding antibody fragment is selected from the group consisting of

- anti-mesothelin antibodies or antigen-binding antibody fragments thereof which comprise the sequence of the variable light chain and the sequence of the variable heavy chain of the antibody MF-Ta,
- anti-mesothelin antibodies or antigen-binding antibody fragments thereof which comprise the sequence of the variable light chain and the sequence of the variable heavy chain of the antibody MF-J,
- anti-mesothelin antibodies or antigen-binding antibody fragments thereof which comprise the sequence of the variable light chain and the sequence of the variable heavy chain of the antibody MOR06640,
- anti-mesothelin antibodies or antigen-binding antibody fragments thereof which comprise the sequence of the variable light chain and the sequence of the variable heavy chain of the antibody MF-226, and
- anti-mesothelin antibodies or antigen-binding antibody fragments thereof which comprise the sequence of the variable light chain and the sequence of the variable heavy chain of the antibody MOR06626.

42. Antibodies or antigen-binding antibody fragments which bind to mesothelin, where the antibody sequence comprises the amino acid sequence of the variable heavy chain represented by the sequences SEQ ID NO:404 and the amino acid sequence of the variable light chain represented by the sequence SEQ ID NO:405.

43. Antibodies or antigen-binding antibody fragments which bind to mesothelin, where the antibody sequence comprises the amino acid sequence of the variable heavy chain which is encoded by the nucleic acid sequence SEQ ID NO:406, and the amino acid sequence of the variable light chain which is encoded by the nucleic acid sequence SEQ ID NO:407.

44. Antibodies which bind to mesothelin, where the antibody sequence comprises the amino acid sequence of the heavy chain represented by the sequences SEQ ID NO:408 and the amino acid sequence of the light chain represented by the sequence SEQ ID NO:409.

45. Antibodies or antigen-binding antibody fragments according to any of claims **42** to **44**, which bind specifically to mesothelin.

46. Binder-drug conjugate according to any of claims **1** to **3**, **14** to **17** or **23** to **38**, where the anti-mesothelin antibody comprises the amino acid sequence of the heavy chain represented by the sequences SEQ ID NO:408 and the amino acid sequence of the light chain represented by the sequence SEQ ID NO:409.

47. Binder-drug conjugate or compounds according to any of claim **1** to **18**, **21** to **41** or **46** for the treatment and/or prophylaxis of illnesses.

48. Binder-drug conjugate or a compound according to any of claim **1** to **18**, **21** to **41** or **46** for use in a method for the treatment and/or prophylaxis of hyperproliferative and/or angiogenic diseases.

49. Binder-drug conjugate or a compound according to any of claim **1** to **18**, **21** to **41** or **46** for producing a medicament for the treatment and/or prophylaxis of hyperproliferative and/or angiogenic diseases.

50. Medicament comprising a binder-drug conjugate or a compound according to any of claims **1** to **18**, **21** to **41** or **46** to **48**, in combination with an inert, non-toxic, pharmaceutically suitable excipient.

51. Medicament comprising a binder-drug conjugate or a compound according to any of claims **1** to **18**, **21** to **41** or **46** to **48**, in combination with one or more anti-hyperproliferative, cytostatic or cytotoxic substances.

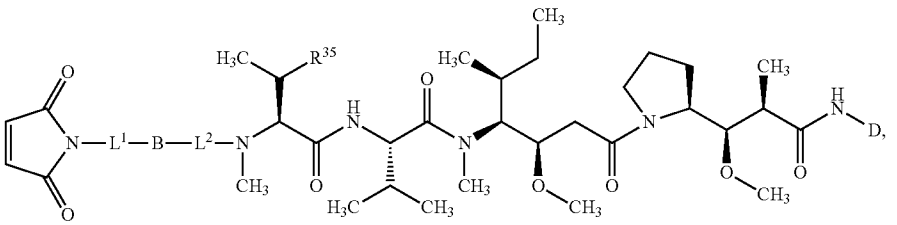
52. Medicament according to claim **50** or **51** for the treatment and/or prophylaxis of hyperproliferative and/or angiogenic diseases.

53. Method for the treatment and/or prophylaxis of hyperproliferative and/or angiogenic diseases in humans and animals, using an effective amount of at least one binder-drug conjugate or a compound according to any of claims **1** to **18** or **21** to **41**, or of a medicament as defined in either of claims **50** and **51**.

54. Process for preparing the compounds of the invention according to any of claims **1** to **6**, of the general formula (Ia), characterized in that a solution of the binder in a buffer

[A] is admixed with a suitable reducing agent, such as, for example, dithiothreitol or tris(2-carboxyethyl)phosphine hydrochloride, and is subsequently reacted with a compound of the formula (IIa)

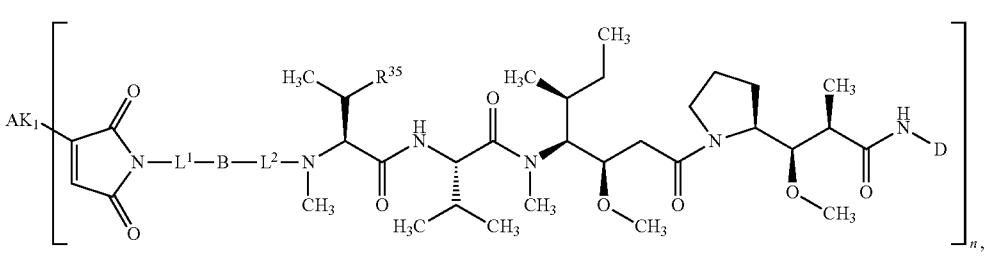
(IIa)



in which D, L^1, B, L^2 and R^{35} each have the definitions indicated in claims **1** to **6**,

to give a compound of the formula (Ia-A)

(Ia-A)

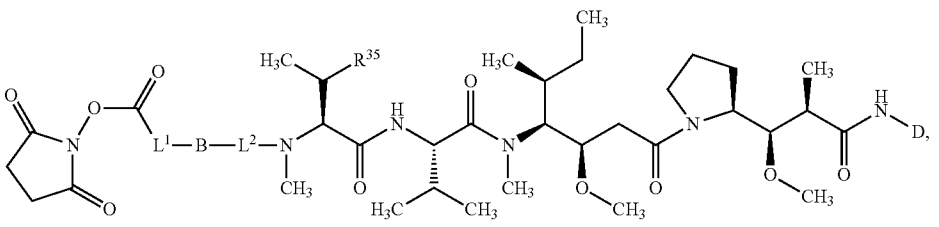


in which n, AK_1, D, L^1, B, L^2 and R^{35} each have the definitions indicated in claims **1** to **6**.

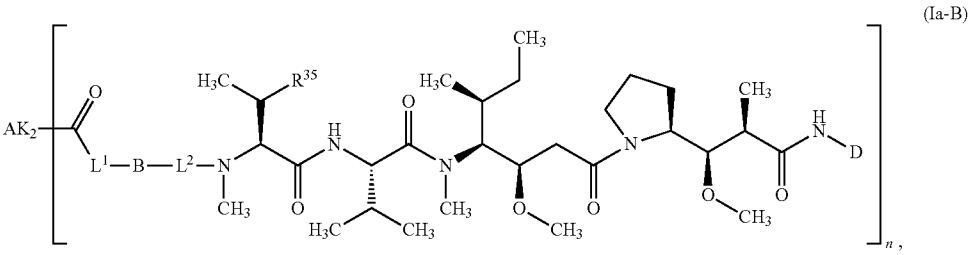
or

[B] is reacted with a compound of the formula (IIIa)

(IIIa)



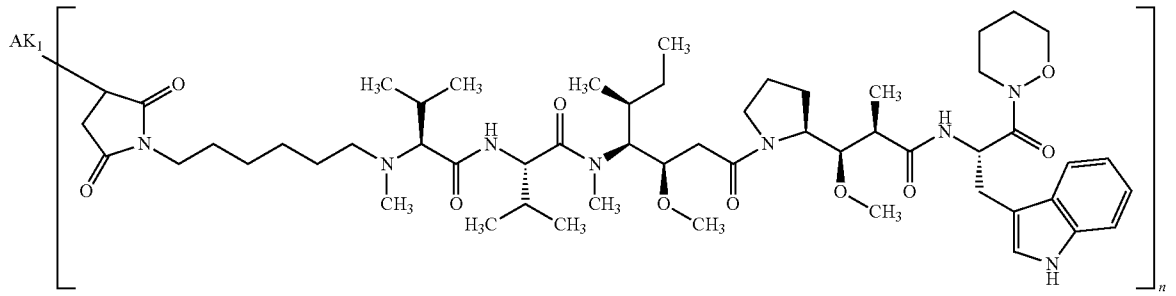
in which D, L^1, B, L^2 and R^{35} each have the definitions indicated in claims **1** to **6**,
to give a compound of the formula (Ia-B)

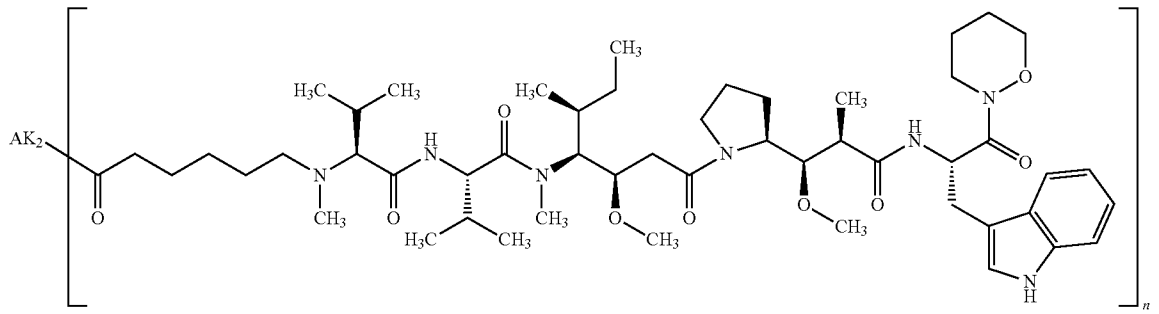


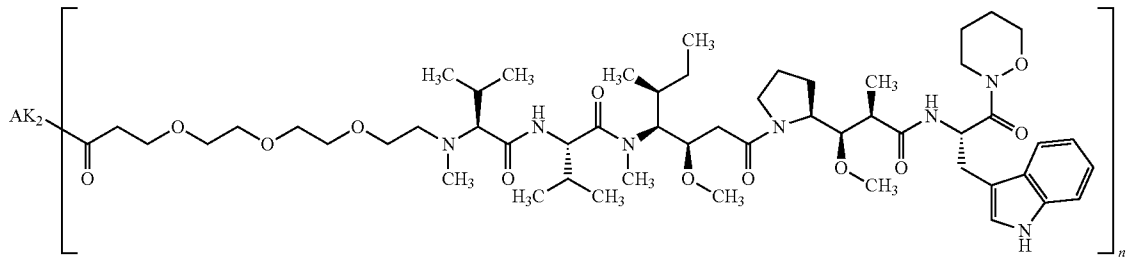
(Ia-B)

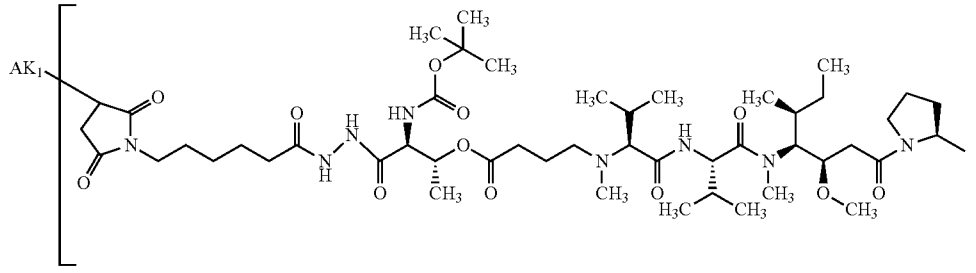
in which n, AK_2, D, L^1, B, L^2 and R^{35} each have the definitions indicated in claims **1** to **6**.

55. Binder-drug conjugates selected from the following compounds:









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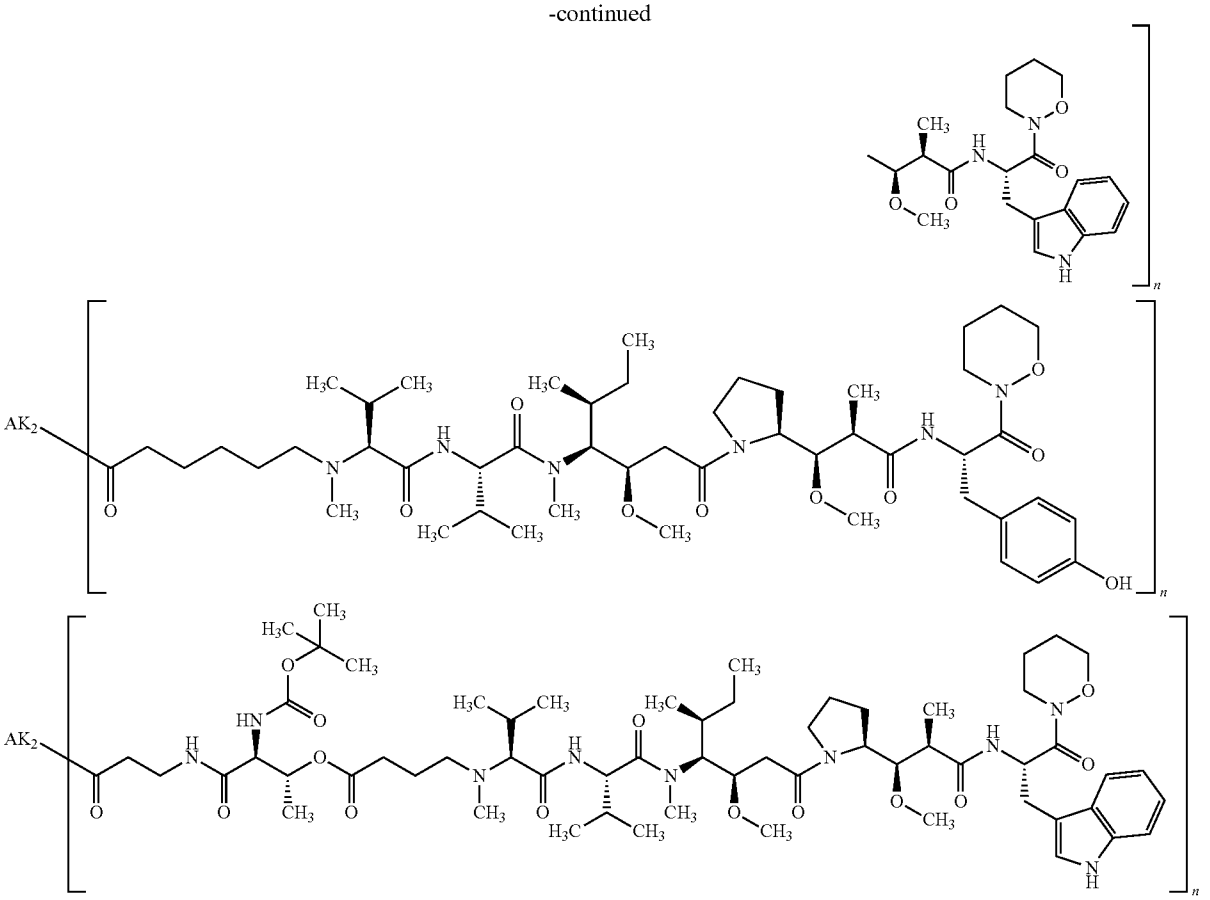

where in each case

n is a number from 2 to 8, preferably 2 to 5,

AK_1 is a human or humanized antibody or an antigen-binding antibody fragment which binds to mesothelin and is bonded via the sulphur atom of a cysteine residue of the binder to the group G,

AK_2 is a human or humanized antibody or an antigen-binding antibody fragment which binds to mesothelin and is bonded via the NH side group of a lysine residue of the binder to the group G.

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